Application of pharmacokinetic models to projection data in positron emission tomography

Ralph Paul Maguire

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Abstract

In positron emission tomography (PET), coincidence detection of annihilation photons enables the measurement of Radon transforms of the instantaneous activity concentration of labelled tracers in the human body. Using reconstruction algorithms, spatial maps of the activity distribution can be created and analysed to reveal the pharmacokinetics of the labelled tracer. This thesis considers the possibility of applying pharmacokinetic modelling to the count rate data measured by the detectors, rather than reconstructed images. A new concept is proposed - parameter projections - Radon transforms of the spatial distribution of the parameters of the model, which simplifies the problem considerably. Using this idea, a general linear least squares GLLS framework is developed and applied to the one and two tissue-compartment models for [O-15]water and [F-18]FDG. Simulation models are developed from first principles to demonstrate the accuracy of the GLLS approach to parameter estimation. This requires the validation of the whole body distribution of each of the tracers, using pharmacokinetic techniques, leading to novel compartment based whole body models for [O-15]water and [F-18]FDG. A simplified Monte-Carlo framework for error estimation of the tissue models is developed, based on system parameters. It is also shown that the variances of maps of the spatial variance of the parameters of the model - parametric images - can be calculated in projection space. It is clearly demonstrated that the precision of the variance estimates is higher than that obtained from estimates based on reconstructed images. Using the methods, it is shown how statistical parametric maps of the difference between two neuronal activation conditions can be calculated from projection data. The methods developed allow faster results analysis, avoiding lengthy reconstruction of large data sets, and allow access to robust statistical techniques for activation analysis through use of the known, Poisson distributed nature, of the measured projection data.
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Acknowledgements

This work, as with all memetic replicators (Dawkins, 1998), this work is a transient concentrator of a set of memes, the origin of which is difficult to trace. Perhaps the most objective method to assess their roots is the reference section. However, since this work was completed by an individual, experiences and influences, sometimes beyond the scope of the subject matter, have helped influence the environment in which those ideas were nurtured and flourished.

I would firstly like to thank Prof. Nico Leenders for the opportunity which he provided for this work to be carried out, for his scientific support, and above all the 'air cover' which he provided for me to pursue my own ideas.

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Thankfully the objective scientific method allows the scientist to accept memes of which he may be initially sceptical. In this regard I would like to thank Prof. Wolfgang Müller-Schauenburg and Dr. Jörg van den Hoff for their ideas on the application of linear pharmacokinetic models and for open and lively discussion.

Most constantly, consistently and importantly I have enjoyed and am grateful for, the support of my family; Tina, Tim and James.
Preface

Positron emission tomography was established in the 1960's and promised imaging of the living human body and high time resolution. As the positron decays it emits two gamma rays and it was recognised that there was a potential to detect these events in coincidence. It was foreseen that positron labelled tracers might be used to study physiology, and provide an in-vivo equivalent of the autoradiographic studies of the previous decade.

Retrospectively, many of the early developments in the field appear to have been haphazard or irrational. The first PET camera had its detectors arranged in a pattern that violates one of the fundamental laws of image recovery. There was no practical reconstruction algorithm until many years later. Although the number of substances that can be labelled with positron emitters is high, only a few of these are metabolised in a time frame that is suitable for practical PET measurement. In this complex of problems, physicists, radiochemists, mathematicians and statisticians started to develop their own interests, and the fields diverged.

Through the pioneering work of a few centres, which recognised the need to confront physical scientists working in this field with the practical measurement requirements in order to use PET as a medical research tool, milestones were achieved. For example, the development of fully 3D measurement, which increased the sensitivity of the instrumentation; simpler pharmacokinetic models such as that for [C-11]flumazenil, which recognise the trade-off between accuracy and precision in the measurement, and image statistical analysis techniques, which allow multi-study comparisons.

Slowly, the research fields have converged. Understanding of the whole measurement process, in terms of the research hypothesis has become mature. In some cases the challenge has been to simplify the problem, and make it communicable to others outside the immediate research community. As the
communication between the disciplines has become faster, and the understanding of the individual elements required for data analysis has become greater, the impact of results has increased dramatically. In the field of neurology, PET has arguably been able to make the biggest contribution in the 'decade of the brain', declared in 1990 by the president of the United States.

This thesis is concerned with the interface between the reconstruction algorithm, and the pharmacokinetic models that explain the measured data. By clearly reconsidering the challenge of applying the models to the raw measured data, rather than reconstructed activity concentration images, a new formalism was derived - parameter projections. This simple idea clarifies which models can be applied to the raw data directly, and figuratively illuminates the path from the detectors through the models to image statistics. Hopefully it is a contribution to the 'language of PET', which increases understanding and advances the communication necessary for the challenges of the future.

Units:

SI units are preferred throughout this document and the nomenclature follows guidelines from the United States National Institute of Standards and Technology. One exception is the use of min (1 min = 60 s) and min\(^{-1}\) instead of s and s\(^{-1}\), and ml (1 ml = 1 cm\(^3\)) for physiological rate constants. Although they are not SI units min and l are accepted by the international committee for weights and measures for use with SI. Within the recommendations of NIST, older units have been given in brackets. 'Counts per second' has been given its proper SI unit Hz.
### Table of symbols

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Quantity</th>
<th>Units</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\mu$</td>
<td>Linear attenuation coefficient</td>
<td>cm$^{-1}$</td>
</tr>
<tr>
<td>$V$</td>
<td>Volume of tissue or space</td>
<td>ml</td>
</tr>
<tr>
<td>$\eta$</td>
<td>Crystal efficiency</td>
<td>Unitless</td>
</tr>
<tr>
<td>$F$</td>
<td>Perfusion</td>
<td>ml·100g$^{-1}$·min$^{-1}$</td>
</tr>
<tr>
<td>$b$</td>
<td>General binominal variable</td>
<td></td>
</tr>
<tr>
<td>$\sigma_x^2$</td>
<td>Variance of random variable $x$</td>
<td></td>
</tr>
<tr>
<td>$T$</td>
<td>True coincidence count rate</td>
<td>Hz</td>
</tr>
<tr>
<td>$S$</td>
<td>Count rate (scattered photons)</td>
<td>Hz</td>
</tr>
<tr>
<td>$R$</td>
<td>Count rate (Random events)</td>
<td>Hz</td>
</tr>
<tr>
<td>$C_{sec}$</td>
<td>Noise equivalent count rate</td>
<td>Hz</td>
</tr>
<tr>
<td>$K$</td>
<td>Total coincidence counts attributable to a</td>
<td>Unitless</td>
</tr>
<tr>
<td></td>
<td>volume</td>
<td></td>
</tr>
<tr>
<td>$r; [r, \theta]$</td>
<td>Spatial vector and its polar coordinate pair</td>
<td></td>
</tr>
<tr>
<td></td>
<td>representation</td>
<td></td>
</tr>
<tr>
<td>$[x, y]$</td>
<td>Cartesian coordinate pair</td>
<td>cm</td>
</tr>
<tr>
<td>$[x', y']$</td>
<td>Cartesian coordinate pair in a rotated system</td>
<td>cm</td>
</tr>
<tr>
<td>$\phi$</td>
<td>Rotated coordinate angle</td>
<td>rad</td>
</tr>
<tr>
<td>$\lambda_\phi(x_r)$</td>
<td>Radon transform at rotated coordinate $x_r$</td>
<td>Units of transformed quantity (Here typically Bq ml$^{-1}$ cm$^{-1}$)</td>
</tr>
<tr>
<td>$\nu$</td>
<td>Spatial frequency</td>
<td>cm$^{-1}$</td>
</tr>
<tr>
<td>$H(v)$</td>
<td>Apodising filter function in frequency space</td>
<td></td>
</tr>
<tr>
<td>$u(r)$</td>
<td>Point average of radon transforms through a</td>
<td>Units of transform point in $\mathbb{R}$</td>
</tr>
<tr>
<td>$U(r)$</td>
<td>Point average of radon transforms through a</td>
<td>Units of transform point in $\mathbb{R}$</td>
</tr>
<tr>
<td>$c(r)$</td>
<td>Activity concentration at point located by</td>
<td>Bq ml$^{-1}$</td>
</tr>
<tr>
<td></td>
<td>vector $r$</td>
<td></td>
</tr>
<tr>
<td>$c_f$</td>
<td>Free activity concentration of tracer in</td>
<td>Bq ml$^{-1}$</td>
</tr>
</tbody>
</table>
\[ c_b \] Bound activity concentration of tracer in Bq/ml
\[ c_p \] Concentration of tracer in plasma Bq/ml
\[ c_t \] Total concentration of tracer in tissue Bq/ml
\[ c_s \] Plasma concentration of glucose mol/l
\[ c \] Concentration, which will generally be a mol/l or Bq/ml function of spatial position and time
\[ A_s \] Specific Activity Bq/mol
\[ c^* \] Concentration of labelled species. In mol/l or Bq/ml derivations where there are both labelled and unlabelled tracers present.
\[ c \] Vector of regional activity concentrations at Bq/ml one position, at various times
\[ \Phi \] Flow ml/min
\[ j \] Point mass flux mol/min
\[ \mathbb{R}^2 \] Set of all points on a 2-D plane
\[ \mathbb{R}^3 \] Set of all points in 3-D space
\[ K_m \] Michaelis-Menten half saturation mol/l concentration.
\[ V_m \] Reaction rate mol/l
\[ K_d \] Dissociation constant mol/l or Bq/ml
\[ K_e \] Reaction equilibrium constant Unitless
\[ B_m \] Total concentration of receptors mol/l or Bq/ml
\[ V_b \] Regional blood volume, a percentage of the Unitless local tissue volume
\[ \varepsilon \] Sensitivity Hz/ml-Bq
\[ \varepsilon_{20} \] Scanner sensitivity referred to a 20 cm Hz/ml-Bq uniform source.
\[ W \] Augmented design matrix
\[ X \] Design matrix of basis functions in GLLS
\[ \rho \] Partition coefficient of water in brain Unitless (0.8) tissue
\[ p \] Fraction of relative free volume which will Unitless not be bound
\( K_i \) Metabolic rate of glucose \( \mu mol\cdot 100 g^{-1}\cdot min^{-1} \)

\( K_i \) Uptake rate constant \( Min^{-1} \)

\( k_i \) Activity concentration injection rate \( Bq\cdot ml^{-1}\cdot min^{-1} \)

\( k_n (i, 2, 3, 4) \) Rate constant in a compartmental model \( min^{-1} \)

\( k \) Vector of rate constants above.

\( \Lambda \) Vector of radon transforms at constant \( x \), all acquisition times

\( \kappa \) Vector of parameter projections.

\( \kappa_n \) Radon transform of rate constant \( n \). A \( cm\cdot min^{-1} \) parameter projection

\( \alpha_k \) Parameter of spectral analysis equation \( Bq\cdot ml^{-1} \)

\( \beta_k \) Exponent parameter in spectral analysis equation \( min^{-1} \)

\( A \) Transition matrix defining reconstruction

\( y \) Vector of activity concentrations at each position in an image at a fixed time.

\( K \) Parametric image matrix with rows corresponding to rate constants, and columns to position in space

\( L \) Dynamic radon transform matrix. Rows are equal to all projections in a projection set at a fixed time.

\( Y \) Dynamic image data matrix. Rows correspond to a position in the image, and columns to acquisition time.

\( \tau \) Dispersion time constant \( min \)

\( \lambda \) Vector of all Radon transforms in one projection set, at a fixed time.

\( t \) Time \( min \)
1. Positron Emission Tomography

Positron emission tomography is well established as a quantitative tracer methodology used to study the uptake and washout of pharmacologically active substances in the living human body. The spatial resolution of the instrumentation allows simultaneous independent measurements of spatially remote tissues samples, and its temporal resolution is well matched to the rate of change of metabolic processes affected by delivery of energy metabolism substrates, such as O₂ and glucose, from the systemic circulation.

The measurement relies on the detection of photons from the annihilation of positrons emitted by radiolabelled tracer substances. As a tracer method, high sensitivity is essential, since the aim is to introduce only small concentrations of a compound into the body, and still have a measurable signal. Using radiolabelling techniques, PET is able to measure, and image, concentrations in the femto- to pico-molar range, far below that which would produce a pharmacological effect. In contrast to other medical imaging modalities, the technique is also quantitative.

By detecting emitted photons in coincidence in a ring of detectors surrounding the subject, an estimate of the spatial distribution of the tracer's concentration can be calculated. This result is usually presented as a set of two-dimensional cross-sectional images. By making a rapid succession of acquisitions after injection, the time course of the tracer can be measured simultaneously in different tissues.

The application of PET in the medical field can be classified into three major areas:

- Determination of in-vivo physiology, e.g. quantitative flow and metabolism and pharmacodynamics.
- In-vivo pharmacology of radiolabelled drugs and receptor studies.
Measurement of local changes in neuronal energy metabolism which may be invoked by a cognitive task or as a result of pathology. The most common tracers here are [0-15]water and [F-18]fluorodeoxyglucose.

Its success as a physiological measurement method can be attributed to three characteristics of the method; electronic collimation (section 1.4), potentially exact correction for attenuation (section 1.5) and the availability of pharmacologically interesting tracer substances - PET tracers (section 1.12).

1.1 Positron decay

For some neutron deficient isotopes, the decay of the nucleus results in the emission of a positron (a positively charged anti-matter electron) and a neutrino. The positron loses energy to the surrounding matter and eventually combines with an electron to form a very short-lived particle (positronium) which decays with a half-life of 10^{-10} s (Evans, 1955). The decay of positronium results in the emission of two 511 keV photons, the energy of which sums to twice the rest mass of the electron. There is also a small probability that either, a three-gamma decay will occur or that decay will occur, while the positronium has high momentum. If the momentum is high, then the photons may have energies in excess of 511 keV. In order to conserve momentum in the decay process the two photons assume trajectories that are approximately 180° apart. The small residual centre of mass momentum of the positronium at the time of decay results in a small (6 μsr) uncertainty in the collinearity.

1.2 Detector blocks

Since the development of the earliest PET camera at Brookhaven National Laboratory, USA in 1962 (Rankowitz et al. 1962), a construction of a ring of scintillating crystals has been the basis of nearly all instruments including the currently available commercial machines, such as shown in figure 1.
Figure 1 Cut-away view of a modern PET scanner partially showing the ring of crystal blocks and their associated photomultiplier readout tubes, which surround the patient-port.

Modern PET scanners are based on the concept of a block detector of Bismuth Germanate ($\text{Bi}_4\text{Ge}_3\text{O}_{12}$) crystals and photomultiplier readouts as shown in figure 2.

Large crystals of BGO detector material are sawn into individual elements of dimensions circa $4.05 \times 4.39 \times 30$ mm (Grootoonk et al. 1996)) with an integral light guide (Casey
and Nutt, 1985). The dimensions of the crystal and the ring diameter impose a limit on the angular sampling, which in turn limits the resolution of the reconstructed images. For a machine with 32 rings of 576 crystals each, and an acceptance angle of 1 rad, then the total number of possible coincidence channels is $8.4 \times 10^3$.

The high density of BGO itself represents a consensus for efficiency as the most important crystal characteristic, since the linear attenuation coefficient is proportional to density at 511 keV (mass attenuation coefficient: 0.11 cm$^2$/g (Turner, 1986)). BGO is also relatively easy to grow, non-hygroscopic and inexpensive; the raw cost of the material is currently (1999) around EUR 20.00 cm$^{-3}$.

As the data in Table 1 indicate, BGO is not optimal in all characteristics. Other cerium doped crystals offer better performance in different respects, and a lot of interest has been shown in the application of LSO, which has a comparable density to BGO, but a shorter decay time and a higher light yield. The improvement of these characteristics could yield a better overall efficiency, especially at high count-rates, and a higher energy resolution, which could be used to improve discrimination of scattered events.

By careful selection of LSO crystals during the manufacturing process, two different forms can be identified, which differ in their decay times (Schmand et al. 1998). This characteristic has been exploited to allow determination of the depth of interaction of the photon with the crystal. By forming a stacked sandwich of crystals with different decay times, the crystal in which the interaction took place can be identified by the decay time of the event. This extra information can, in principle, be incorporated into the reconstruction algorithm to avoid the assumption that the photon’s trajectory is parallel to the side of the crystal, and that the photon is totally absorbed in one crystal. In practice this method remains to be proven.
### Table 1 Characteristics of scintillating crystals, based on data from (van Eijk, 1995)

<table>
<thead>
<tr>
<th>Crystal</th>
<th>Decay time (ns)</th>
<th>Density (g/cm³)</th>
<th>Photon yield (x 10⁴/MeV)</th>
<th>Emission (nm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NaI(Tl)</td>
<td>230</td>
<td>3.67</td>
<td>4.1</td>
<td>410</td>
</tr>
<tr>
<td>CsI(Tl)</td>
<td>800</td>
<td>4.51</td>
<td>5.5</td>
<td>565</td>
</tr>
<tr>
<td>BGO</td>
<td>300</td>
<td>7.13</td>
<td>0.9</td>
<td>480</td>
</tr>
<tr>
<td>BaF₂(Ce)</td>
<td>600</td>
<td>4.88</td>
<td>1.0</td>
<td>310</td>
</tr>
<tr>
<td>CdWO₄(Ce)</td>
<td>3000</td>
<td>7.9</td>
<td>2.8</td>
<td>500</td>
</tr>
<tr>
<td>Gd₂SiO₅(Ce) (GSO)</td>
<td>60</td>
<td>6.71</td>
<td>.11</td>
<td>440</td>
</tr>
<tr>
<td>Lu₂SiO₅(Ce) (LSO)</td>
<td>40</td>
<td>7.4</td>
<td>2.5</td>
<td>420</td>
</tr>
<tr>
<td>Y₃Al₅O₁₂(Ce) (YAG)</td>
<td>65</td>
<td>4.6</td>
<td>0.9</td>
<td>550</td>
</tr>
</tbody>
</table>

#### 1.3 Photomultiplier arrays and dead time

In modern commercial devices, each of the arrays of e.g. 64 crystals is machined to include its own integral light guide, connecting it to one of 4 photomultiplier tubes (PMT). The length of the light guides is deliberately shortened to introduce a light loss, which depends on the crystal’s location in the block. Using Anger logic (Anger, 1959), enhanced by this light modulation, events from any of the crystals can be uniquely identified. However, this light
modulation compromises the energy resolution, which is around 20% for the block as a whole.

The BGO crystal has a relaxation time of around 300 ns, but the combined response time of the photomultiplier tubes (PMT) and Anger logic increases the total dead time to 2500 ns. Total system coincidence counts (ECAT EXACT HR+ 30.4 Hz·ml·Bq⁻¹, [1.1 MHz·ml·μCi⁻¹]) (Grootoonk et al. 1996; Adam et al. 1996) will be around 2% of the total count rate, including photons which are not counted in coincidence (typically 2.3 kHz·ml·kBq⁻¹, [85 MHz·ml·μCi⁻¹]) contributing to a crystal dead time of the order of 7% at 1 kBq·ml⁻¹. The most important component of this at low count rates is the Anger logic used in the crystal readout, which contributes 90% of the dead time. Although new crystal materials offer one method to reduce this effect, new crystal readout methods are also being explored.

In this respect there are a number of methods, which are presently being investigated. The application of optical fibre (Qi et al. 1998) to couple each crystal to an individual readout PMT, obviating the need for Anger logic position decoding, is one possibility. The advantages of this method have, however, currently been applied to the problem of packing smaller crystal arrays rather than as a dead time reduction scheme. Multi-anode PMTs have also been tested (Pawelke et al. 1996), and their specifications in other respects match those of block detectors well. Solid state avalanche photo-diodes (APD) (Renker, 1995), which can be attached to individual crystals, are also an interesting development and larger area devices may be practical for PET detector application.

1.4 Electronic collimation and time resolution

The crystals in modern PET instruments are arranged in a series of rings to form a cylindrical geometry, and until recently (see section 1.6), only acquisition between crystals on the same ring of the instrument were considered. Defined pairs of these crystals in each ring form individual
coincidence channels - there are typically 31000 of these. Valid events in the separate crystals of one channel are registered when they fall within a defined energy window (250 - 600 keV). Events that are registered by the separate crystals of a coincidence channel within a 12 ns time window are recorded as a valid coincidence event ('Prompt' event). This energy window is deliberately chosen to include photon events scattered in the object under study, in order to increase the efficiency of the system, and also because the energy resolution of the crystal is poor (20 %). This choice does, however, compromise absolute quantification, without correction for these scattered events. In normal tissue, the Klein-Nishina (Evans, 1955) reference scattering distribution predicts that scattered events will be scattered into a small solid angle, about the original trajectory, thus they do not lose much of their initial directional information. This is another justification for retaining scattered events. Commercial PET instruments also record events in a delayed 30 ns coincidence window, in order to estimate the number of events which are recorded as coincidences, but which come from different annihilation events ('Random' events). The probability of more than one coincidence event being detected in the 12 ns window ('Multiple' event) is in fact rather small, so that these events may be rejected without altering counting statistics significantly. The measured count rate, corrected for random, multiple and scattered events, is commonly referred to as the 'true' count rate.

The line in space between two coincidence channel detector pairs is termed a "line of response" (LOR). As a consequence of the collinearity of the annihilation photons it can be assumed, to a first approximation, that the positron decay event occurred in the space subtended by this line. This assumption is in fact violated because of photon scattering, non-collinearity of the emitted photons and the finite range of positrons. The latter of these factors limits the theoretical limit of resolution for PET to around 2 mm, depending on the positron energy of the radionuclide.
The advantage of the coincidence acquisition approach is that there is no requirement for a mechanical collimator to determine the acquisition ray direction and there is also no requirement that such a collimator be moved, in order to acquire projections of the activity from all directions. Since the crystals are arranged in a ring round the patient it is necessary to define the coincidence channels electronically and to store the acquired data appropriately. It is therefore possible to acquire a sequence of images very rapidly with PET, such that it is not the minimum acquisition time of the instrument that limits the time between measurements, but rather considerations of patient dose and image statistics. In fact it is possible to record individual coincidence events as they occur and to store them, along with the event timing, to be processed into sequences of images with timing intervals determined post-acquisition. This *list mode* acquisition method is available on some prototype instruments, but analysis techniques to fully exploit the method are still under development.

1.5 Attenuation correction

Photons emitted in an object under study will be attenuated on their trajectory to the detectors. Consider a uniform cylinder, filled with activity, located centrally in a PET system with the axis of the cylinder perpendicular to the plane through one ring of detectors. Figure 3 shows two lines of response for a cylindrical object in the centre of the scanner. For points near the edge of the cylinder LORs will have a much shorter chord length intersecting the cylinder than for central points, and consequently fewer photons will be attenuated on their trajectory out of the object. Line of response acquisition allows a simple correction for the spatial variation in attenuation to be performed.
If an event occurs anywhere in the scanner field of view, the probability that it will be detected using coincidence measurement of the individual photons is (Barrett and Swindell, 1982):

$$P = \left[ \eta_1 e^{-\mu_1} \eta_2 e^{-\mu_2} \right]$$  \hspace{1cm} (1.1)

where $l_1$ and $l_2$ are the path lengths for the individual photons in the attenuating medium, and $\eta_1$ and $\eta_2$ are the quantum efficiencies of the detectors. The probability of a coincidence event being registered is then:

$$P = \eta_1 \eta_2 e^{-\mu L}$$  \hspace{1cm} (1.2)

where $L$ is the sum of $l_1$ and $l_2$.

The practical implication of this result is that the detection probability for an event is independent of its position along a LOR. In fact the measurement source can be placed outside the object; this is the basis of the transmission source...
method, used to determine this attenuation correction for each line of response before or after the emission measurement.

If the transmission count rate for photons along a line of response can be measured with and without the attenuating object in place, then the attenuation coefficient can be determined from the ratio of the two count rates. These rates can be measured by placing a source close enough to one detector that the probability of detection is approximately 1, and measuring the count rate in the detector at the other end of the LOR, in the two conditions. The ratio of the two count rates can be used to correct the emission data directly, without explicitly estimating the attenuation coefficient.

It is interesting to note the meaning of attenuation in this context, since coefficients quoted and used by the commercial manufacturers will differ from the values found in standard reference works. Coefficients of attenuation and absorption for a sample of material of thickness \( I \) are properly defined with reference to the Beer-Lambert model:

\[
\frac{I}{I_0} = e^{-\mu d}
\]

where \( I_0 \) and \( I \) are the incident and exit intensities of a beam traversing the sample. The linear attenuation coefficient is the value of \( \mu \) determined using narrow beam geometry, where scattered radiation is not detected. The linear absorption coefficient is that value of \( \mu \) determined when the detector registers scattered, as well as transmitted radiation. The mass attenuation coefficient is the linear attenuation constant divided by the density of the material.

For many common materials (air, concrete, water, tissue, lead glass) the mass attenuation coefficients at 511 keV are very similar (range 0.08 - 0.1 \text{ cm}^2\text{g}^{-1}). The mass absorption coefficients for most materials are also similar. (range: 0.028 - 0.035 \text{ cm}^2\text{g}^{-1}).
However the geometry of the detectors and sources during transmission and emission acquisition in PET lies somewhere between the idealised attenuation and absorption conditions described above. Consequently, the coefficient in equation (1.2), for data including scatter, has a value of (0.086 cm$^{-1}$) - somewhere between the linear attenuation coefficient for tissue at 511 keV (0.1 cm$^{-1}$) and the linear absorption coefficient for soft tissue at 511 keV (0.034 cm$^{-1}$) (density of tissue assumed to be 1 g ml$^{-1}$).

### 1.6 Fully 3D PET acquisition

In the earliest research PET instruments the crystals were arranged regularly, but sparsely on the surface of a sphere surrounding the sensitive volume. In order to reduce the complexity of the acquisition electronics, and because of a lack of a full mathematical description for the reconstruction of data, on the first commercially successful instruments, only the coincidences between crystals on the same ring were acquired. Heavy lead septa were mounted between the individual rings to collimate the acquisition in the axial direction and to reduce the amount of axial scattered radiation recorded by the crystals. However, the efficiency of a scanner is directly related to its acceptance angle.

In a state-of-the-art machine with a ring diameter of 83 cm, an axial extent of 12.8 cm (32 rings) and crystals of axial dimension 0.4 cm, the total solid angle subtended by one crystal ring is 0.061 sr or 0.5% of the total possible solid angle. If all the rings are considered simultaneously, then this solid angle rises to 2.35 sr, i.e. 18% of the maximum angle, with a consequent increase in efficiency for the system.

Efficiency is normally measured using a standard 20 cm diameter polypropylene liquid or solid source - a compromise between two clinical measurement conditions, brain and body. The 'camera sensitivity' $\varepsilon_{\mu}$ is then quoted, usually in units of Hz ml $\mu$Ci$^{-1}$, which might be rendered in SI units: Hz ml Bq$^{-1}$.
terms of an absolute efficiency measurement, this method has obvious disadvantages, since there will be attenuation and scatter effects within the object. The camera sensitivity will also be proportional to the axial length of the field of view for fixed detector efficiency. In this text, the sensitivity will be retained, since it provides a measure of the average system count rate, including the effects named above, for a given activity concentration in an object which approximates the conditions in a human subject.

In fact commercial machines have long been exploiting increased angle of acceptance by assigning the coincidence counts from adjacent rings to a virtual plane which is located between the rings (cross-plane acquisition). This technique requires the approximation that the small angle between the virtual plane and the centre of the ring can be ignored. The exploration of the possibility with higher acceptance angle - albeit with increased number of measured scatter events and more complex reconstruction methodologies - has enjoyed a recent revival (Townsend et al. 1989; Dahlbohm et al. 1989) and has lead to a new generation of fully 3D instruments.

One of the most challenging practical aspects of 3D imaging is data handling, since the number of LORs and hence data sizes have increased dramatically. For a single ring of crystals with 576 crystals and a 2.35 sr solid angle of acceptance there are 46080 possible LORs. For a 24 ring system with 576 crystals per ring, allowing coincidences between all rings and the same acceptance angle there are a possible $2.6 \times 10^7$ LORs.

1.7 Rotating Positron Camera

If the acceptance angle can be increased, then it should be possible to reduce the total number of detectors, and yet retain the overall efficiency. This is the principle that was used in the design of the rotating camera system, PRT-2 (Townsend et al. 1993). The scanner consists of two arrays of $10 \times 3$ detector blocks, with 64 crystals of dimensions $6.35 \times 6.35 \times 20$ mm, yielding a total of $80 \times 24$ crystals in each
array. Thus the two partial arrays of crystals complete only 40% of a total ring.

In table 2 PRT-2 is compared with other prototype and commercial scanners, using a signal to noise characteristic, noise equivalent counts (NEC), which is defined with reference to the count rates for true (T), scatter (S) and random (R) coincidences (see also section 1.4), measured:

\[ C_{\text{neq}} = \frac{T^2}{(T + S + 2fR)} \]  

where \( f \) is the fraction of the field of view subtended by the object.
Table 2. A comparative list of NEC count rates for commercial and prototype PET instruments, using 3D acquisition.

<table>
<thead>
<tr>
<th>Scanner</th>
<th>Sensitivity $\varepsilon_{30}$ Hz·ml·Bq$^{-1}$</th>
<th>Maximum NEC Activity conc. at Maximum NEC (kBq·ml$^{-1}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Siemens-CTI PRT-1</td>
<td>2.4</td>
<td>17</td>
</tr>
<tr>
<td>Siemens-CTI PRT-2</td>
<td>6.1</td>
<td>24</td>
</tr>
<tr>
<td>Siemens-CTI ART</td>
<td>8.1</td>
<td>30</td>
</tr>
<tr>
<td>Siemens-CTI 953B</td>
<td>13.8</td>
<td>52</td>
</tr>
<tr>
<td>Siemens-CTI EXACT</td>
<td>21.1</td>
<td>48</td>
</tr>
<tr>
<td>Siemens-CTI HR+</td>
<td>30.4</td>
<td>110</td>
</tr>
<tr>
<td>GE Quest</td>
<td>12.2</td>
<td>30</td>
</tr>
<tr>
<td>GE ADVANCE</td>
<td>30.4</td>
<td>159</td>
</tr>
</tbody>
</table>

(Personal communication 1999 D.W. Townsend UPMC PET centre, Pittsburgh, USA.)

The Siemens-CTI EXACT scanner contains a factor 2.6 times more detector blocks than PRT-2, however they are arranged in a full ring, rather than as partial rings. The table shows that the maximum NEC for PRT-2 is only a factor 2 less than that for the EXACT. This is because of the reduced rate of random coincidences in the partial ring scanner, which leads to an increased 'count efficiency' when compared to the full ring arrangement.

1.8 2D and 3D reconstruction

The acquired data, that is a set of counts for each detector pair, can be assigned two spatial co-ordinates $x$, and $\phi$, in a
co-ordinate system rotated with respect to the polar co-ordinate system defining the image space, as illustrated in Figure 4.

![Co-ordinate system for the projection of a 2D object](image)

Figure 4 Co-ordinate system for the projection of a 2D object. \([x_r,y_r]\) is a co-ordinate frame rotated by angle \(\phi\) about the stationary co-ordinate system \([x,y]\). The Radon transform (projection) is the integral of the distribution \(c(r)\) along a line of constant \(x_r\). An example projection is given as a dot-dash line, which can be located with the polar co-ordinate pair \([x_r,\phi]\). On the right hand side of the diagram is a sinogram in which each point is a radon transform. The radon transform of the distribution of \(c(r)\) at angle \(\phi\), i.e. \(\lambda_\phi(x_r)\), is shown.

If it is assumed that the data can be ideally corrected for attenuation correction as described in section 1.5, then the counts for each line of response are directly proportional to the line integral of activity along that LOR:

\[
\lambda_\phi(x_r) = \int c(r)dy,
\]

where \(\lambda_\phi(x_r)\) is the (attenuation corrected) projection of the object \(c(r)\) along a line \(l\) in the direction \(y\). \(r\) is a vector locating a point in the object space. The individual projections can be neatly ordered into a \([x_r,\phi]\) 'sinogram' space.

The problem of reconstruction of a function in space from its line integrals, i.e. the inverse of the transform defined above, is closely related to potential theory. In his paper, Radon (Radon, 1917) pointed out the analogy of the potential
field, which leads to solutions for both two ($\mathbb{R}^2$) and three ($\mathbb{R}^3$) dimensional space.

Consider again the line integral of a general function $c(r)$ as defined for $\mathbb{R}^2$ in equation (1.5). The point average of the Radon transform at that point is:

$$u(r) = u(x, y) = \frac{1}{\pi} \int_{-\pi/2}^{\pi/2} \lambda_\phi(x\cos(\phi) + y\sin(\phi)) \, d\phi$$  \hspace{1cm} (1.6)

Radon noticed the analogy with the solution to the problem of reconstruction of mass density from the Newtonian potential at a point in the plane, for which Gustav Herglotz had proposed the solution:

$$c(r) = \frac{1}{\pi} \int_0^\infty \frac{d\alpha(q)}{q}$$  \hspace{1cm} (1.7)

Where $u(q)$ is the average of $u(q)$ around a circle of radius $q$, surrounding the function $c$ at the point defined by vector $r$. The mathematical notation here has been taken directly from Radon's original paper. It prescribes an integral summation of the $u(q)$, divided by the radius $q$ at which the average is determined. It is important that the summation be done using infinitesimal step changes in $u(q)$, rather than small changes in $q$.

For $\mathbb{R}^3$, a very elegant solution can be found by considering the analogy with the Newtonian potential of the mass density in space. Using Poisson's equation, the solution can simply be written:

$$c(r) = -\frac{\nabla^2 U(r)}{2\pi}$$  \hspace{1cm} (1.8)

Here $U$ is analogous to $u$ above, but is defined for $\mathbb{R}^3$. 
1.9 Filtered back projection implementation in 2D

Referring back to figure 4, equation (1.8) can be expanded to the following operational equation (Barrett and Swindell, 1982; Kouris et al. 1982):

\[
C(r,\alpha) = -\frac{1}{\pi} \int_0^\pi d\phi \int dx \frac{\partial}{\partial x} \lambda_r(x_r) \frac{1}{(x_r - r \cos(\alpha - \phi))}
\]

where \( C(r,\alpha) \) is an estimate of the activity concentration at the point with polar co-ordinates \([r,\theta]\).

This equation can be interpreted as a two step process, involving the formation of an image of point averages of the Radon transforms, as defined by equation (1.6), and a subsequent deconvolution with the function \( \frac{1}{r} \). This \( \mathbb{R}^2 \) deconvolution can be carried out using the convolution theorem of Fourier transforms, i.e. Fourier transform of the convolution of two functions \( f \) and \( g \) is equivalent to the product of the Fourier transforms of the two functions:

\[
h = f \otimes g = F(h) = F(f).F(g)
\]

where operator \( F \) is the Fourier transform, and function \( h \) is the convolution of \( f \) and \( g \).

Also the central slice theorem states that the 1-D Fourier transform of a projection is equal to a section of the 2-D Fourier transform of the object, meaning that the deconvolution can be implemented in 1-D, on a line by line basis in sinogram space.

As a result of the inherent noise in the measurement data and because sampling is discrete, this method is inadequate in practice and the Fourier transform of the PSF of the scanner must be filtered with an apodising filter in order to suppress high frequency noise (Ramachandian and Lakshminarayanan, 1971). Typically a Hann filter is used with a high frequency
cut-off around the Nyquist limit, defined by the scanner geometry.

1.10 3D reconstruction

Consider again the equation (1.9). It can be extended using the co-ordinate system in Figure 5 to its equivalent in \( \mathbb{R}' \) (Barrett and Swindell, 1982):

\[
c(r) = -\frac{1}{4\pi} \nabla^2 \int_{2\pi} d\Omega \lambda_n(r \cdot \mathbf{n})
\]

where \( \Omega \) is the angle of a rotated plane with normal \( \mathbf{n} \), and \( r \cdot \mathbf{n} \) defines the direction of a 1D plane integral.

Similarly to 2D projections where it is only necessary to have a set of projections over 180°, Orlov's condition (Orlov, 1976) states that it is only necessary that \( \mathbf{n} \) trace out one-half of a great circle, in order to reconstruct a three dimensional object. This is only true in the case where there are no statistical fluctuations in the projection data. In PET, the
limited counting statistics impressed by low patient dose mean that it is desirable to use as many independent projections as are available. However, the number of available projections through a point is a function of the axial position of the point. So, the PSF varies with position - is said to be shift variant.

One solution (Kinahan and Rogers, 1990) is to use a set of projections, parallel to the axis of the PET instrument, to create a low statistics back projection of the object. This can then be used to fill in missing projections before filtered back projection, and filtering in image space (Kinahan et al. 1988).

1.11 Rebinning techniques

As a result of the long reconstruction times required, the direct application of the 3D extension of filtered back projection has been superseded by the application of rebinning techniques. These allow a set of 2D projections of the activity distribution to be calculated from the acquired data set and reprojected using the standard 2D filtered back projection algorithm.

The single slice rebinning (SSRB) technique is an extrapolation of the cross-plane acquisition technique discussed in section 1.6. If the angle of a projection plane that passes through the centre of a virtual projection plane parallel to the crystal rings is ignored then all such planes can be summed to form a 2-D projection. Fourier rebinning (FORE) (Defrise et al. 1995) is a mathematically rigorous extension of this technique using the frequency-distance approximation (Edholm et al. 1986) to calculate a 2-D Fourier transform of the 2D-projection set.

1.12 Tracers

As important to the PET technique as instrumentation are radiotracers. Although there is a wide range of pharmaceuticals available commercially and for research, only a limited number of those are interesting as PET tracers. That
is tracers which will result in a high signal (count rate) per unit injected activity, and a signal which is very sensitive to changes in the physiological variable under study. As has been discussed the resolution of the PET instrument in time and space is not ideal and the statistical quality of the data is limited by the dose given to the patient. The spatial and temporal signal measured after injection, and hence measurement sensitivity, will depend heavily on the pharmacokinetics of the tracer.

A simple example of this is the difference in the metabolic pathways of [C-11]D-glucose and [F-18]FDG. Although labelled glucose can be synthesised, it is rapidly metabolised in the citric acid cycle to water and [C-11]CO₂, which are washed out into the peripheral blood stream (Blomqvist et al. 1990). The tracer does not remain in any metabolic compartment for a long enough time to allow accurate in-vivo measurement. In contrast, [F-18]FDG is transported across the blood-brain barrier like glucose, but becomes trapped after phosphorylation. In this way the [F-18]FDG concentration in tissue at any time is proportional to the total integral of labelled [F-18] supplied to the tissue times the uptake rate of glucose.

At another extreme, the cocaine analogue ligand [C-11]Beta-CIT (Mueller et al. 1993) is extracted very quickly from the periphery and binds strongly to non-specific and specific neuro-receptors. It is, however, a very poor PET tracer of receptor density since the signal detected by the PET scanner is mainly dependent on the rate of delivery to tissue i.e. regional cerebral blood flow, rather than receptor density. This tracer has been modified (Halldin et al. 1996) to [C-11]Beta-CIT-FP, a similar compound, which exhibits reversible binding. With this variant, the signal, although now temporally more complex, can be analysed to gain information about the neuro-receptors under study.

The following table indicates some of the common tracer compounds that have found application in studying various physiological systems.
Table 3 A selection of PET tracers, their function and application.

<table>
<thead>
<tr>
<th>Radiochemical form</th>
<th>Function</th>
<th>Application</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-[F-18]fluoro-2-deoxy-D-glucose (FDG)</td>
<td>Glucose analogue tracer</td>
<td>Energy metabolism</td>
</tr>
<tr>
<td>[F-18]Fluorodopa</td>
<td>Catecholamine substrate</td>
<td>Dopaminergic synthesis</td>
</tr>
<tr>
<td>[O-15]Water</td>
<td>Freely diffusible blood flow tracer</td>
<td>Cerebral and myocardial perfusion</td>
</tr>
<tr>
<td>[C-11]Acetate</td>
<td>Fatty acid metabolism</td>
<td>Cardiac metabolism</td>
</tr>
<tr>
<td>[C-11]Raclopride</td>
<td>D2 receptor ligand</td>
<td>Post synaptic dopaminergic binding</td>
</tr>
<tr>
<td>[C-11]Flumazenil</td>
<td>Benzodiazepine receptor ligand</td>
<td>Epilepsy research.</td>
</tr>
</tbody>
</table>

1.13 Pharmacokinetic modelling

Gibaldi and Perrier (Gibaldi and Perrier, 1975) define pharmacokinetics as "the study of the time course of drug and metabolite levels in different fluids, tissues and excreta of the body and of the mathematical relationships required to develop models to interpret such data."

One element that is missing from this definition is instrumentation. Models, which are to be used for the analysis of experimental data, should be able to explain the measured data, and must therefore take into account the limitations of the instrumentation. The models that are used in PET are very much simpler than those used to explain the known biological processes contributing to tracer delivery and metabolism. This
is a direct result of the limitations of spatial and temporal resolution.

The examples of [F-18]FDG and [C-11]Beta-CIT, used in section 1.12, illustrate the interdependence of tracer, model and instrumentation. The aim of optimisation of each of these components is to achieve a measurement system which is most sensitive to change in the biological system, and which allows measurement of those changes with the highest statistical power.

Using model-building (Landaw and DiStefano III, 1984) allows the significance of increases in model complexity to be assessed in a rational way, thus constraining the models to explain only the underlying signal, and reject noise. Even with a minimal model configuration, estimation of individual parameters can be difficult. Because of this, data analysis models, which seek to maximise precision (repeatability), sometimes to the detriment of accuracy (absolute measurement), can be better metrics of the physiological differences between different populations (Koepppe et al. 1992). The corollary to this is that in order to measure with good accuracy, it may be necessary to accept lower precision, e.g. when exploring the detailed kinetics of a new tracer or patient group it may be necessary to estimate the rate constant of one step of the pharmacokinetic model.

In the following three subsections, the basic model equations will be derived for the three most common processes in the exchange of substances between physiological compartments will be derived in using a fresh approach; diffusion (leading to the Kety-Schmidt model), facilitated binding (leading to the Michaelis-Menten model) and Ligand binding (which can also be seen as a Michaelis-Menten type model). Through this exploration of the three processes, it will be shown how these three different situations lead to similar compartmental model equations. It will also be shown how the models relate to fundamental physical and physiological quantities, which aids in their interpretation and an understanding of their limitations.
1.14 Diffusion processes

The transport of substances from the peripheral bloodstream to tissue and their accumulation and excretion are moderated by two main mechanisms i.e.

1. Aqueous or lipid diffusion, which is movement of ions in solution across a boundary from a higher to a lower concentration, or

2. Transport by special carriers (facilitated diffusion). Both of these diffusion methods can be modelled by the first Fick diffusion equation (Ganong, 1991):

\[ J = -DA \frac{\Delta c}{\Delta x} \]  

(1.12)

where \( J \) is the flux of molecules (mol·min\(^{-1}\))

\( A \) is the area of the diffusion surface (cm\(^2\))

\( D \) is the permeability coefficient, (cm\(^2\)·min\(^{-1}\))

and \( \Delta x \) and \( \Delta c \) are the membrane thickness and concentration difference respectively.

Consider the flux across a membrane, separating two compartments, 't' and 'b', with concentrations \( c_t \) and \( c_b \) respectively. Dividing by the compartments' respective volumes, and treating \( D, A \) and \( \Delta x \) as a single constant, \( K \) (min\(^{-1}\)), the following equation can be derived:

\[ \frac{dc_t}{dt} = K(c_b - c_t) \]  

(1.13)

Note that \( K \) in this equation is positive, to indicate flux into compartment 't' and negative to indicate loss.

It is also possible to treat the influx and efflux processes in an equation set with separate rate constants describing these processes:
\[
\frac{dc}{dt} = k_1c_b - k_2c_i
\]

(1.14)

1.15 Kety-Schmidt model

The simple membrane barrier discussed above can in fact be quite a complicated structure, but as long as the assumptions of concentration independent transport rates hold, the same model and equations can be used. The most important example of this in neurological PET measurement is the blood brain barrier, which physically separates the brain from the circulation.

Nutrients are supplied to the brain by the cerebral vasculature, which consists of a branching network of arteries (4 mm diameter) and arterioles (30 μm diameter, total cross-sectional area 400 cm²), ending at small capillaries of diameter 5 μm, with a wall thickness of 1 μm (Ganong, 1991). The entire network of capillaries has a cross-sectional area of 4500 cm², which allows rapid exchange, during the blood’s passage. The capillaries’ path is very tortuous, and, on the scale of its diameter, the barrier is an inhomogeneous structure containing tightly bound epithelial cells, connected to astrocytes. There are also differences in the concentration of substances in blood, along the length of the capillary, due to the exchanges taking place. Washout and drainage of the tissues, is accomplished using a network of vessels with a larger total cross-sectional area, venules (20 μm diameter, total cross-sectional area 4000 cm²) and veins (5 mm diameter).

Early studies (Kety and Schmidt, 1948) Kety-Schmidt of global brain metabolism and blood flow proposed a simple model for the uptake of freely diffusible tracers into tissue:
Figure 6. A compartment model showing the local arterial supply \( (c_a) \) and venous drainage \( (c_v) \) of a tissue element with a concentration \( (c) \). The blood flow \( \Phi \) is equal in the arteries and veins.

This model leads to the following set of equations, which are an expression of mass balance:

\[
\frac{dq_t}{dt} = \Phi c_p - \Phi c_v \tag{1.15}
\]

Note that in a more general form this can be expressed as:

\[
j = \Phi \cdot \nabla c \tag{1.16}
\]

where \( j \) is the point mass flux, a vector, \( \Phi \) is the local flow and \( c \) is the point activity concentration in space. A positive \( j \) indicates a source of material and negative is a sink.

The spatial resolution of the PET measurement is not high enough to be able to measure the gradient of \( c \). However the activity concentration in arterial blood is measured using an arterial canula, and it is supposed that the activity in the periphery is the same as that in the capillaries. Also for a tracer with an extraction of \( 1 \), at the venous end of the capillaries, the blood and tissue will be in equilibrium. Thus \( c_v \), which is not measured, must be approximated from a knowledge of the tissue concentration \( c \) and the partition coefficient \( \rho \):
Using (1.17) and dividing (1.15) by the tissue volume, the following differential equation and solution set can be found for the relationship between the arterial plasma and tissue concentration of [O-15]water:

\[
\frac{dc_t}{dt} = Fc_p - \frac{F}{\rho}c_t
\]

\[
c_t = Fe\left(\frac{F}{\rho}\right) \otimes c_p
\]  

This equation set is expressed in the diagram in figure 7. Using the assumptions stated it has been possible to move from a microscopic description of perfusion where all the elements are not measured, to a macroscopic one in terms of the concentrations measured by the PET camera and arterial blood sampling.

![Diagram](https://via.placeholder.com/150)

**Figure 7.** Single tissue compartment model for the uptake of a freely diffusible tracer. The plasma compartment \((c_p)\) supplies the tissue compartment \((c_t)\) with perfusion \(F\). \(\rho\) is the partition coefficient between plasma and tissue.

### 1.16 Facilitated transport

A substrate of a biochemical reaction may also be transported across a membrane by a carrier substance. Such reactions are characterised by the reaction rate equation (Michaelis and Menten, 1913).

\[
A + B \leftrightarrow AB \leftrightarrow A + B
\]
where $V$ is the reaction rate (rate of concentration change of 'A' in the distal membrane compartment) (mol/(ml·min))

$V_m$ is the maximum reaction rate. (mol/(ml·min))

c is the concentration of substrate 'A' (mol·ml⁻¹)

and $K_m$ is the concentration (mol·ml⁻¹) at which half of the maximum rate (when the enzyme is 'saturated') is achieved.

If concentration of the substrate $c$ is much higher than $K_m$ (i.e. the enzyme is saturated), then according to equation (1.20) the reaction proceeds at its maximum rate $V_m$, which is then approximately constant and concentration independent. In the PET experiment a tracer - i.e. a radiolabelled version of 'A' or an analogue substance -, with concentration $c^*$ is introduced and follows the same pathway as the natural substrate 'A'.

\[ c^* = fc \tag{1.21} \]

where fraction $f$ is a number of orders of magnitudes smaller than one.

However, the rate of the reaction is not disturbed by the low concentration $c^*$ of the radiolabelled substance, so, by the product rule, its concentration change is:

\[
\frac{dc^*}{dt} = \frac{dc^*}{dc} \cdot \frac{dc}{dt} = f \frac{dc}{dt} \tag{1.22}
\]

Substituting for $V_m$ and $f$ from (1.20) and (1.21).

\[
\frac{dc^*}{dt} = \frac{c^*}{c} V_m = \left( \frac{V_m}{c} \right) c^* = k c^* \bigg|_{c=K_m} \tag{1.23}
\]
In fact it can be shown (Phelps et al. 1986), that this general equation form also holds when an enzyme is not saturated, and is central to the tracer principal.

1.17 Ligand Binding

Communication in the central nervous system has two distinct aspects, with very different temporal characteristics. Firstly, there are the electro-ionic and action potential changes in the polarisation across membrane boundaries. These action potentials are propagated rapidly (4 ms⁻¹) from the nerve cell body to the synapses - nerve endings, which contain chemical substances (neurotransmitters) and which, in turn, are secreted to stimulate the connected neurone. Modulation of this transmission by changes in the concentration of substances at the synapse results in changes of network behaviour, which have a higher organisational level than the electrical signals.

At the synaptic junctions, neurotransmitter substances are stored in the pre-synaptic terminal, and upon release cross the synaptic cleft, to bind with receptors on the post-synaptic side. There may also be binding on the pre-synaptic terminal itself, offering a means for negative feedback of signal transmission.

The binding of transmitter substance \((T)\) with receptor \((R)\) can be considered as a chemical reaction:

\[
T + R \leftrightarrow TR
\]

Let the concentration of the reactants and products be schematically represented thus:

\[
c + F \leftrightarrow c_b
\]

where \(c_b\) is the concentration of the ligand-receptor complex, \(c\) is the concentration of the ligand, which is equal to the concentration of bound receptors. \(F\) is the concentration of the unbound (free) receptor. This chemical reaction would have
an equilibrium constant (Atkins and Clugston, 1982) given by the following equation:

\[ K_c = \frac{c_b}{c_f F} \]  \hspace{1cm} (1.24)

Noting that the total concentration of receptors \( B_m \) is given by

\[ B_m = c_b + F \]  \hspace{1cm} (1.25)

equation (1.24) can be rearranged to yield:

\[ B = \frac{B_m c_f}{1 + \frac{c_f}{K_c}} \]  \hspace{1cm} (1.26)

\( K_d \) is defined as the concentration at which \( B = F = 0.5B_m \) and is from (1.24):

\[ K_d = \frac{1}{K_c} \]  \hspace{1cm} (1.27)

Substituting into equation (1.26) yields:

\[ B = \frac{B_m c_f}{c_f + K_d} \]  \hspace{1cm} (1.28)

By comparison with equation (1.20) it can be seen that this reaction is analogous to the 'Michaelis-Menten' kinetic model.

Note however the important distinction between (1.20) and (1.28). In the first equation, the reaction rate is on the left hand side, in the second it is the concentration of ligand receptor complex, i.e. the concentration in the second compartment. From (1.28) it can be seen that at low ligand concentrations, the concentration of bound receptors is proportional to the ligand concentration.
If a compartment model for binding is proposed, with one compartment containing the concentration of free ligand and the other the concentration of bound ligand-receptor complex. The rate of change of the concentration of ligand-receptor complex can be described by a differential equation with two components. An increase due to the association (binding) of ligand and free receptors, described by a rate constant $k_{on}$ and a dissociation of ligand-receptor complex, described by the rate constant $k_{off}$ (Clark, 1933):

$$\frac{dc_b}{dt} = k_{on} F c_f - k_{off} c_b$$  \hspace{1cm} (1.29)

Using equation (1.25) this can be rewritten:

$$\frac{dc_b}{dt} = k_{on} c_f (B_m - c_b) - k_{off} c_b$$ \hspace{1cm} (1.30)

Note that for a true tracer experiment $B_m >> B$, implying also that $B_m = F$ yielding:

$$\frac{dc_b}{dt} = k_{on} B_m c_f - k_{off} c_b$$ \hspace{1cm} (1.31)

At equilibrium, the left hand side of (1.31) is equal to zero, yielding:

$$\frac{k_{off}}{k_{on}} = \frac{B_m c_f}{c_b} \bigg|_{dc_b=0}$$ \hspace{1cm} (1.32)

using this equation, $B_m = F$, (1.27), and (1.24) the following equation can be derived:

$$c_b = \frac{B_m c_f}{K_d} \bigg|_{dc_b=0}$$ \hspace{1cm} (1.33)

which is in agreement with the limit of small $c_f$ in equation (1.28).
The ratio of the constants $B_m$ and $K_d$ in equation (1.33) is called the binding potential (BP), the ratio of the bound and free ligand concentrations, at equilibrium.

Referring back to equation (1.29), the PET experiment, using radiolabelled ligand with a concentration $c^*$, forming a ligand-receptor complex, with concentration $B^*$, which can be described:

$$\frac{dc^*_b}{dt} = k_{on} F c_f^* - k_{off} c_b^*$$  \hspace{1cm} (1.34)

For the case with $B_m >> c_v$, the further derivation for the non-labelled ligand and complex is identical. However, in the case where this is not true, it is important that a distinction is made between the labelled and unlabelled ligand complex. In order to do this, the specific activity $A_s$ - the ratio of radiolabelled substance to unlabelled substance, is introduced:

$$A_s = \frac{c_f^*}{c_f} = \frac{c_b^*}{c_b}$$  \hspace{1cm} (1.35)

Equation (1.25) can now be modified, for the radiolabelled species:

$$B_m = \frac{c_b^*}{A_s} + F$$  \hspace{1cm} (1.36)

Substituting this equation into (1.34), a general non-linear differential equation for receptor binding can be derived:

$$\frac{dc_b^*}{dt} = k_{on} \left( B_m - \frac{c_b^*}{A_s} \right) c_f^* - k_{off} c_b^*$$  \hspace{1cm} (1.37)

1.18 Compartment models

The equations defined in the section 1.16 and 1.17 above for the transport and binding of substances lead to differential equations for concentration changes in individual compartments. However as mentioned previously, the sensitivity and hence temporal resolution limit the number of identifiable
metabolic steps. In practice, the model shown below for receptor tracers has proven to be on the limit of complexity (Cunningham and Lammertsma, 1995).

![Diagram of a general compartment model for the uptake of PET tracers. (Cunningham and Lammertsma, 1995)](image)

Figure 4 General compartment model for the uptake of PET tracers. (Cunningham and Lammertsma, 1995)

The model shows four basic compartments, a blood compartment split into three components, and three tissue compartments. The PET instrument measures the activity concentration in tissue, with a specific spatial and temporal resolution. By identifying the image elements that are spatially associated with specific organs (region of interest (ROI) analysis), their activity time course during the measurement can be determined.

The blood compartment forms the input to the model and is normally measured using a series of blood samples during the study. Depending on the possible peripheral metabolic pathways of the tracer substance it may be necessary to separate the plasma component of the blood from the other components. An additional activity component due to the small (circa 5%) volume of intra-capillary blood in $V_b$ is always measured in the tissue data.

As has been seen in previous sections, models of tissue perfusion, facilitated transport and binding lead to similar
equations, and, in general, exchange between compartments is well described using those equations. It is also possible to solve the equations and derive an operational equation in terms of the rate constants, which can be used to explain the PET data.

Using non-linear parameter estimation, the values of each rate constant in an appropriate model can then be estimated, however, correlations within the model mean that the variance of the estimated parameters is often poor. Within the context of medical research using PET, it is often better to use a combination of parameters as an index for changes in pathology, rather than the individual rate constants themselves. In this way a lower variance of the index, and hence a higher sensitivity, in the sense of statistical power can be achieved. An excellent example of this is the use of partition coefficient to reflect receptor occupancy (Kooppe et al. 1992).

1.19 Non-linear parameter estimation

The optimum estimate of the model variables for a given data set is determined by minimising the sum of the squared differences between the model prediction and the measured data. This can be shown rigorously (Press et al. 1992; Beck and Arnold, 1977) to be a reasonable definition in terms of a maximum likelihood estimation. If the expected variance for each of the data points is known, then the normalised statistic $\chi^2$, which is the variance weighted sum of squares can be minimised. The $\chi^2$ sum of squared difference or other functions, used to determine the goodness of fit are termed 'cost functions'. Generally, algorithms for solving the non-linear least squares problem start with an initial estimate of the solution, and iteratively seek the parameter set which minimises the cost function.

There are two main methods of determining the modification to the parameters. The method of steepest descent increments parameters by an amount which depends on the local gradient of
the cost function. Taylor series methods model the local variation of the cost function as a linear function and solve for a local solution using linear regression. The latter of these two methods is also called Gauss-Newton minimisation. The Marquardt-Levenberg algorithm (Marquardt, 1963; Levenberg, 1944), which represents a compromise between steepest descent and Taylor series methods has been shown to perform well.

The simplex algorithm (Nelder and Mead, 1965) considers the problem from a geometrical perspective, in a space with dimensions $P$ as there are variables in the problem. Each of the $(P+1)$ vertices of a simplex in this space, is an estimate of the solution. The algorithm proceeds by wandering the simplex through parameter space, exchanging the poorest vertex (estimate) for a new estimate, at each iteration. One of three methods, reflection, expansion, or contraction, of the poor estimate about the hyper-plane passing through the remaining points, chooses the next estimate. Experience shows this method to be adaptable and therefore robust in estimation.

It is essential to consider the results of non-linear parameter estimation critically. One of the simplest verifications is to plot a simulated curve, based on the estimated parameters and to compare it with the data. If there it appears that there is a consistent pattern in the distribution of the measured data points around the simulated curve, then this is indicative of a poor solution. However this may be because of a number of reasons.

Firstly, at the optimum solution a small perturbation in the parameters will result in an increase in the residual sum of squares. However there are other parameter sets in the universe of all parameters for which this is also true (local minima). In order to avoid finding a local, rather than the global solution, it is important to start the iterative search close to the optimum solution, where the solution space is smooth and well conditioned, and non-linear optimisation algorithms perform best. Lower order models, with fewer parameters may not be optimal for a given data set, however
the solution space is often much better conditioned over a larger range of parameters. Parameter estimates from these lower order models can be used to estimate optimal solution for the higher model, and provide a way to estimate starting parameters.

Secondly, the model itself may not be optimal. Later in this thesis the technique of model building using a hierarchical set of models, to determine the best model to explain the data is introduced. Examining trends in the residuals is one way to view this process qualitatively.

1.20 General linear regression and basis functions

Non-linear estimation methods are essential if the operational equation is indeed non-linear, however if the model can be reformulated so that there is linearity, then general linear regression allows the optimal solution to be found without iteration.

Consider a general linear pharmacokinetic model for use to explain PET data. It can be written in matrix form:

\[ \mathbf{c} = \mathbf{Xk} \] (1.38)

where \( \mathbf{c} \) is a vector of dimension \( N \), and \( N \) is the number of measured data points. Each element of the vector \( c_i \) is given by \( c_i(r, t_i) \), the activity concentration in tissue at a position located by vector \( r \) at time \( t_i \). \( \mathbf{k} \) is also a vector of dimension \( M \), the number of model parameters, and has elements \( k_j(r) \), the value of the \( j \)th parameter at spatial location \( r \). \( \mathbf{X} \) is a matrix of functions with elements:

\[ X_{ij} = f_j(t_i) \] (1.39)

\( f_j \) are functions of time, which must be independent of space, typically they are functions of \( c_p \), the activity concentration in plasma.
The functions $f(t)$ are called basis functions of the model, and may be non-linear. Because general linear regression does not require iteration it is a fast estimation procedure and has been used with multiple basis functions to determine the characteristic spectrum of a tracer's time activity course (Cunningham and Jones, 1993).

1.21 Parametric images

It is appropriate that this overview of PET instrumentation, pharmacokinetics and parameter estimation should conclude with a section about parametric images, since they provide perhaps the most succinct summary of the PET measurement. As has been seen, the measured coincidence events are reconstructed to an image of activity concentration, and many measurements may be made, resulting in a time sequence of images. The activity time course of regions can be analysed by applying pharmacokinetic models to explain the data, and by parameter estimation techniques the characteristics of the model can be determined.

PET is able to measure both the temporal and spatial aspects of pharmacokinetics, in its application to measure human physiology, the pharmacokinetics is indicative of a certain state, which is considered to be invariable throughout the measurement time. In this sense, the temporal component is only necessary for measurement, and the results are a spatial map of the physiological variable of interest.

The spatial elements of one image in the measurement are quantified in a discrete matrix, which can be viewed as an image. In these terms a matrix element is a picture element or pixel. It is also possible to imagine an independent application of pharmacokinetic analysis on an element-by-element level. That is, applying time activity course analysis, and parameter estimation at each pixel, to determine a physiological variable e.g. perfusion (regional cerebral blood flow - rCBF). Seen as an image, the matrix of perfusion values would form a parametric image.
Practically, as the ROI size is reduced, the precision of the local activity concentration determination diminishes proportionally to the area of the ROI, for an object of constant activity concentration. Non-linear parameter estimation in this limit of poor statistics is practically very difficult, both slow, and subject to bias and poor precision in parameter estimates.

Linear models, such as that expressed in equation (1.39), have major advantages. There is no bias introduced into the method, as the precision of the measured data decreases. If the average of the parameter estimates from activity time courses of individual pixels is compared with the parameter estimate derived from an average activity time course of the same pixels, the results are identical. This is because linear least squares parameter estimation has a deterministic solution, which also leads to another advantage, calculation efficiency and speed. Since a full PET data set will typically contain \(10^6\) pixels, computational expense is also an important factor, and non-iterative linear methods are fast, and can be implemented using vectorised and parallel processing techniques.

Linear techniques are also central to this thesis, since using the linear properties of the Radon transform, and the analysis techniques, it is possible to consider the application of these methods to the estimation of parametric images directly from the projection data of the measurement. This could potentially allow access to the predictable statistical distribution of the projection counting data, allowing more robust statistical analysis of the precision of the data.
2. Parameter projections

2.1 Introduction

This chapter introduces the concept of parameter projections, a new concept which shows which pharmacokinetic models can be applied to projection data. Since linear pharmacokinetic methods are necessary for this method, a discussion of the merits of those models, with specific examples is given. The general linear least squares matrix framework for linear models is explained, and used to develop the general matrix notation of the parameter projection derivation. Applications are then discussed to demonstrate independence from reconstruction and pharmacokinetic analysis methods.

2.2 Precision of pharmacokinetic estimates

The compartment models in section 1.18 lead to sets of ordinary differential equations that can be solved to reveal non-linear operational equations in terms of the model rate constants. Using these equations, and non-linear parameter estimation techniques, the multidimensional space, describing the universe of all solutions, can be searched for an optimal solution in the least squares sense (Bard, 1974).

As well as imposing a limitation on the total number of identifiable compartments, the statistical nature of the PET measurement also limits the precision with which individual rate constants in the model can be measured. Consider the widest application of PET, in medical research where the aim is to address a specific hypothesis. Typically the experimental design will involve the comparison of a control group and another group with the hypothesis that a certain aspect of a physiological function differs. This hypothesis is to be examined by using a specific PET experiment - PET tracer, instrumentation and model - designed to be sensitive to changes in that aspect of physiology under study. The aim will often be to perform spatial multivariate statistical testing to identify loci of significant change. The instrumentalational element of the experiment contains many
different aspects of measurement and analysis, e.g. the spatial resolution, which might be defined by ROI analysis.

Experimental design should consider all aspects of the experiment, and the data analysis model should reflect a choice, which yields the highest statistical power for the hypothesis under consideration. The precision of the estimated rate parameters in PET is often poor, as a result of the statistical fluctuations in the count rate and the inter-correlations between parameters. Therefore single rate constants of the pharmacokinetic models, outlined up to this point, may not provide a measure of change with the highest power. There is a trade-off between the precision of estimation of the parameters and the total number of parameters estimated. In many cases combinations of the individual rate constants (the microparameters) to form macroparameters, which reflect an essential aspect of the measurement, such as an overall uptake rate for a particular substance, might be more appropriate.

In this chapter, the theory concept of application of pharmacokinetic models to projection data will be examined. Firstly however, some of the techniques, using the concept of macroparameters, and linearisation will be reviewed. An understanding of the concepts of these analytical methods, and their power to reduce the model, and thus data, to an essential summary is necessary to grasp the motivation.

2.3 Sokoloff technique

A good example of a model where macroparameters can be applied is the two tissue-compartment model for FDG (Sokoloff, 1978), with four rate constants \([k_i, k_2, k_p, k_j]\) shown in figure 8.
Figure 8. The two tissue-compartment Sokoloff model of FDG uptake in tissue. $c_p$ is the concentration of FDG in the plasma pool, supplying the free FDG concentration in tissue ($c_f$). FDG is phosphorylated to FDG-6-PO4, which is bound - concentration $c_b$. The dotted line indicates the blood brain barrier. Rate constants $[k_1, k_2, k_3, k_4]$ quantify the exchange between the compartments. De-phosphorylation is a very slow process, in relation to the length of the scan, and $k_4$ is often assumed to be zero.

If $k_4$ in this model can be assumed to be zero, the model leads to the following differential equations describing the uptake and binding of FDG, and more generally any substance that can be described with this model configuration:

$$\frac{dc_f}{dt} = k_1 c_p - (k_2 + k_3) c_f$$  \quad (2.1)

$$\frac{dc_b}{dt} = k_3 c_f$$  \quad (2.2)

Including the small blood volume component $V_b$, the analytical solution for $c_i$, the total activity concentration measured by the tomograph is:

$$c_i = k_1 \left\{ \frac{k_2}{(k_2 + k_3)} e^{-(k_2+k_3)t} + \frac{k_1}{(k_2 + k_3)} \right\} \otimes c_p + V_b c_p$$  \quad (2.3)

where $\otimes$ denotes the convolution operation. The left-hand term in braces represents the time course of the fractional component of activity, delivered to tissue, but which will not be metabolised. The right-hand component in braces is the fraction that is eventually metabolised and bound in tissue. This equation can be rearranged (Mueller-Schauenberg, 1999):
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\[ c_i = k_i \left[ e^{-k_2 T} + \frac{k_3}{k_2 + k_3} \left( 1 - e^{-k_2 T} \right) \right] \otimes c_p + V_p c_p \quad (2.4) \]

into a form in which the left and right components in braces describe the time courses in the free and bound compartments \((c_f\) and \(c_b\)), respectively.

Since \(k_t\) and \(k_i\) both describe loss from the free compartment, changing either of their values in a model simulation will have a similar effect on the shape of the simulated uptake activity time course. If parameter estimation is performed on perfect data, with no measurement error then \(k_t\) and \(k_i\) can be determined accurately. If a number of estimations of \(k_t\) and \(k_i\) from measured data sets with random experimental error, but the same underlying parameters, then the estimates of \(k_t\) and \(k_i\) will be correlated. Although it is possible to determine estimates of the three rate constants from a PET measurement, \(k_t\) and \(k_i\) are highly correlated, because they both describe loss from the free compartment. When equilibrium has been established between \(c_f\) and the activity concentration in plasma \(c_p\), at a time \(T\) then:

\[ \frac{dc_f(T)}{dt} = 0 \quad (2.5) \]

Therefore from (2.1):

\[ \frac{k_i}{(k_2 + k_3)} c_p = c_f \quad (2.6) \]

\[ \Rightarrow \frac{dc_f(T)}{dt} = \frac{k_i k_3}{(k_2 + k_3)} c_p(T) = K_t c_p(T) \quad (2.7) \]

\(K_t\) is the total influx rate of FDG at equilibrium; a macro-parameter.
Since FDG and glucose are analogues, their influx rate constants are proportional; the empirical constant of proportionality $L$ is called the 'lumped constant'

$$L = \frac{K_i}{K_0^G} \quad (2.8)$$

In text the abbreviation 'LC' will be used. If the concentration of glucose in plasma is $c_p^G$ and the influx rate constant $K_i^G$, the rate of glucose utilisation for a tissue sample (rCMRGlux) FDG technique can be calculated:

$$\frac{dc_p^G}{dt} = K_i^G c_p^G = \frac{K_i}{L} c_p^G \quad (2.9)$$

Using equation (2.3) it is possible to fit time activity data from a PET [F-18]FDG experiment, to recover estimates for $k_i$, $k_o$, and $k_p$, and to estimate $K_i$, allowing the rCMRGlux to be estimated. $K_i$ can also be calculated using linear least squares, as will be seen in a later section of this chapter.

### 2.4 Weighted integration

[0-15]water has been shown to be a very useful tracer for the measurement of regional cerebral perfusion (rCBF). It is extracted from blood plasma during one transit of the cerebral capillaries (1 sec.) and distributes in the tissue in a comparable time. Its uptake can be described using a simple 'one tissue-compartment model' which is equivalent to that in figure 8, with $k_j$ equal to zero, i.e. within the experimental limitations of the [0-15]water experiment there is no binding of water in tissue. The model can then be expressed by one differential equation:

$$\frac{dc_i}{dt} = k_1 c_p - k_2 c_i \quad (2.10)$$

The approach of weighted integration (Carson et al. 1986) is to multiply this equation by two functions $[x_i(t), x_j(t)]$, which
express weightings dependent on time. These weighting functions determine the, time varying, contribution of the effects governed by $k_i$ and $k_j$ to the tissue signal.

\[
\begin{pmatrix}
\int x_1 c_\phi dt - \int x_1 c_\phi dt \\
\int x_2 c_\phi dt - \int x_2 c_\phi dt
\end{pmatrix}
\begin{pmatrix}
k_i \\
k_j
\end{pmatrix}
= 
\begin{pmatrix}
-\int \frac{d}{dt} x_1 c_\phi dt \\
-\int \frac{d}{dt} x_2 c_\phi dt
\end{pmatrix}
\tag{2.11}
\]

Using maximum likelihood analysis the weighting functions are chosen to minimise the variance in estimations of $[k_i, k_j]$ for a range of simulated values. With known weighting functions all the integrals in equation (2.11) can be calculated for a given data set $[c_i, c_j]$. The weighting functions do not depend on any spatial elements and it is therefore possible to use the parameter projection concept to apply the method to the projection data to calculate the parameter projections of $[k_i, k_j]$. Verification of this is clear by comparing the matrix expression of a linear model in the general derivation, later in this chapter.

The two weighting functions for the [0-15]water model, suitable for measured data which has not been corrected for decay, are shown in figure 9, i.e. they are appropriate for analysis of [0-15]water data which has not been corrected for decay.
Figure 9 (Carson et al. 1986) Curves describing the optimal weighting functions \([x_1, x_2]\) for the one-tissue compartment model of \([0-15]\)water uptake, over the normal range of human brain perfusion values, the model here includes effects of decay.

By ignoring the model and simply integrating the total counts per projection, a parameter projection of a function that is monotonically related to flow can be generated. It has been shown that a range of integration times from 0 to 120 s is optimal (Kanno, I et al. 1991) to calculate this index; integrating for a shorter period reduces the signal to noise ratio, and with a longer integration period, the index becomes increasingly dependent on partition coefficient effects. The weighted integration method performs this optimisation implicitly.

2.5 Multiple time graphical analysis (MTGA)

The compartment model in figure 8 can be generalised to many different tracers, which have intermediate equilibrating compartments and a final irreversible compartment. The final step might be related, as with FDG, to an enzyme catalysed biochemical transformation, or to ligand binding, which section 1.17 showed to be analogous to a chemical reaction.
Considering equation (2.3) again, the convolution operation can be expanded:

\[ c_i = \frac{k_3}{(k_2 + k_3)} \int c_p dt + \frac{k_1 k_2}{(k_2 + k_3)} e^{-(k_2 + k_3)t} \otimes c_p + V_b c_p \]  

(2.12)

The term in the middle of the right hand side of the above equation is derived from the left hand term in braces of equation (2.3). It expresses the time course in tissue of that fraction of the delivered activity, which is not metabolised, and is eventually washed out. If \( c_p \) is constant or varying very slowly in comparison to the rate \((k_2 + k_3)\), then the convolution term can be expanded, to yield:

\[ c_i = \frac{k_1 k_3}{(k_2 + k_3)} \int c_p dt + \frac{k_1 k_2}{(k_2 + k_3)^2} c_p + V_b c_p \]  

(2.13)

\[ c_i = \frac{k_1 k_3}{(k_2 + k_3)} \int c_p dt + \left( \frac{k_1 k_2}{(k_2 + k_3)^2} + V_b \right) c_p \]  

(2.14)

\[ c_i = \frac{k_1 k_3}{(k_2 + k_3)} \int c_p dt + \left( \frac{k_1 k_2}{(k_2 + k_3)^2} + V_b \right) c_p \]  

(2.15)

The following variables are defined:

\[ K_i = \frac{k_1 k_3}{(k_2 + k_3)} \]  

(2.16)

\[ p = \frac{k_1 k_2}{(k_2 + k_3)^2} \]  

(2.17)

The term \( K_i \) is the uptake influx constant. Note that in this thesis, there is a possible cause of confusion between matrix element subscripts and this nomenclature. It should however be clear in each case whether a subscript or the naming convention is meant. Substituting these variables into (2.15) yields:
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\[
\frac{c_t}{c_p} = K_i \int c_p \, dt + p \tag{2.18}
\]

\[
\frac{c_t}{c_p} = K \theta + p \tag{2.19}
\]

where \( \theta \) is termed the exposure (Gjedde, 1982), and has units of time. If at any time \( T \), when the plasma concentration is \( c_p \), the integral of plasma up to that time is say \( \int_0^T c_p \, dt \), then the exposure can be thought of as the equivalent time yielding the same total integral with an input activity concentration of \( \int_0^T c_p \, dt \). This method has variously been referred to as the Gjedde-Patlak, or Patlak plot (Patlak et al. 1983) in the literature. In the original sources the nomenclature multiple time graphical analysis was used, which will be abbreviated here to MTGA.

2.6 Linear methods

Linear analysis methods such as MTGA are not only desirable because they are more precise; they are also computationally much less expensive than non-linear analysis. If general least squares (GLLS) parameter estimation is thought of as an operator, then the linearity properties are very desirable for PET parameter estimation. Since the PET measurement consists of a multivariate data set, containing many spatial elements (pixels) then direct, deterministic methods are available to estimate the precision of estimates derived from data with known statistical properties (Fischer and van Belle, 1993). This makes linear methods not only appealing for the analysis of activity time course data from region of interest analysis, but also for the calculation of parametric images. Whether regional averages are calculated before or after parameter estimation is immaterial when using the linear least squares operator on the image data. This means that the ROI analysis
can be performed after the calculation of a parametric image, and the result will be the same as that estimated from an activity time course generated from the same ROI.

Lastly, and for this work, most importantly, it should be possible to combine the GLLS linear operator with the linear operator describing reconstruction. By reversing the order of application of the operators, PET-pharmacokinetic parameter estimation can be applied first to the raw projection data of the measurement, with subsequent reconstruction of parametric images. This approach would have the advantage of being efficient, since the reconstruction operator is costly, and would allow the known (Poisson) nature of the raw data to be exploited for variance estimation during pharmacokinetic analysis.

2.7 Decomposition of filtered back projection

One method of applying a linear pharmacokinetic model directly to the projection data might be to consider the mathematical details of particular reconstruction and linear pharmacokinetic analysis, algorithms. This approach has previously been studied (Tsui and Budinger, 1978), in connection with the estimation of organ clearance. Expressing the analysis method for organ clearance and the filtered back projection algorithm as sums and exchanging the order of summation, it was shown that the linear analysis method, could be applied to the projection data. As will be seen later, the condition of linearity on its own is not sufficient, and this method is dependent on an analytical reduction of both the particular back projection algorithm and the pharmacokinetic analysis method. Clearly a method which is more general and does not require a detailed analysis for each model would be more desirable.

2.8 MTGA expressed as a parameter projection

Recalling equation (2.19), the variation of the parameters with spatial location with PET can be introduced:
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\[
\frac{c_i(r,t)}{c_p(t)} = K(r)\theta + p(r) \tag{2.20}
\]

where \(K(r)\) and \(p(r)\) are the values of the influx rate and the partition coefficient, respectively, at points located by the vector \(r\). \(\theta\) is the exposure as previously defined.

If time is now considered as a variable in the Radon transform, equation (1.5):

\[
\lambda_p(x_r,t) = \int c_i(r,t) dy_r \tag{2.21}
\]

Rearranging (2.20) and substituting for \(c_i(r,t)\) in this equation the following is obtained:

\[
\lambda_p(x_r,t) = \int (K(r)\theta + p(r))c_p(t)dy_r \tag{2.22}
\]

Since \(c_p(t)\) and \(\theta\) are independent of \(r\):

\[
\frac{\lambda_p(x_r,t)}{c_p(t)} = \theta \int K(r)dy_r + \int p(r)dy_r \tag{2.23}
\]

This is a linear equation in terms of the projection data, the plasma data, the exposure \(\theta\), and two terms:

\[
K_\theta(x_r) = \int K(r)dy_r \tag{2.24}
\]

and

\[
\pi_\theta(x_r) = \int p(r)dy_r \tag{2.25}
\]

By comparison with (1.5), \(K_\theta(x_r)\) and \(\pi_\theta(x_r)\) can be seen to be the \(R^2\) projections of the uptake rate constant and partition coefficient in equation (2.20), respectively. These equations define what have been termed as (Maguire, 1997) 'parameter projections' or 'parameter transforms'. Note that parameter
projection has a special meaning in parameter estimation associated with process control, which has no association with the meaning here.

2.9 Parameter projections generalised.

Consider again the general linear pharmacokinetic model (1.38)

with basis functions in the columns of in matrix $X$, which must be independent of space. If equation (1.38) is integrated with respect to $y$, and the left hand side is substituted from the left hand side of (2.21), the result is:

$$\Lambda = X\kappa$$

(2.26)

Here, $\Lambda$ is a vector of dimension $N$ (see above), with elements:

$$\Lambda_i = \lambda(x_i, t_i)$$

(2.27)

and $\kappa$, of dimension $M$ (see above), contains elements:

$$\kappa_j(x_r) = \int k_j(t)dy$$

(2.28)

Comparing the right hand side of this equation with that in (1.5) it can be seen that the $\kappa_j(x_r)$ are parameter projections of the $'j'$th parameter of the model, $k_j(r)$.

Equation (2.26) can be solved on a projection-by-projection basis, using general linear least squares regression of $\Lambda$ on $X$, yielding estimates of $\kappa(x_r)$ at each projection:

$$\kappa = (X^TX)^{-1}X^T\Lambda$$

(2.29)

In this equation 'T' represents the matrix transpose operator. The estimates can then be reconstructed to form parametric images of the model parameters.
In contrast to techniques based on decomposition of the reconstruction algorithm, the concept of parameter projections allows the model to be applied to the raw data quite independently of the subsequent reconstruction algorithm.

Using this formulation also clarifies which models and analysis methods can be applied to the raw projection data, namely those which can be expressed in terms of basis functions which do not contain a spatial element. Again, the reconstruction algorithm need not be considered at all, and indeed it is fruitless to attempt application of any method which cannot be written in those terms.

As will be shown later, consideration of the variance also becomes much simpler using parameter projections, since methods are described in the literature to derive the individual (parametric image) pixel variance, based on the variance of its (parameter) projections (Maguire et al. 2000). Since the distribution of the projection value can be expected to be close to a Poisson distribution, statistical analysis should be more straightforward.

Although the equations above have been written for application to $\mathbb{R}^2$ projections, the technique has obvious computational advantages in the calculation of parametric images for $\mathbb{R}^3$ PET. Instead of reconstructing each time sequences of a set of data, an equation such as (2.26) can be used to fit the measured projection and plasma data to calculate parameter projections. Only one reconstruction per parameter is then necessary to reconstruct the parametric images.

2.10 Blomqvist's method

Recall the model in figure 8, and its associated differential equations. By directly integrating them, and rearranging, the following operational equation can be derived (Blomqvist, 1984):\begin{equation}
c(r,T) = k_1 \int_0^T c_p(t) dt + k_2 \int_0^T c_p(v) dv dt - (k_2 + k_3) \int_0^T c(r,t) dt \tag{2.30}
\end{equation}
Although this equation is linear in the rate constants of the model, the last term contains a spatial dependency, violating the conditions of equation (2.26) and it is therefore not possible to derive separate parameter transforms as in the previous case.

This method can however be successfully applied to the calculation of maps of the rate constants in reconstructed images, albeit with the same restrictions on precision for $k_2$ and $k_3$ due to their high correlation.

2.11 Application to spectral analysis

In this text, models for the explanation of PET data have been described which are derived from rationale, drawn from biochemistry and tempered with the resolution constraints of the instrumentation. It is possible to consider the PET data first, and to determine a possible model configuration from the data. Solutions to this approach are degenerate without some prior knowledge of possible model configurations. However the concept of any PET pharmacokinetic model being composed of a sum of exponential functions (Mueller-Schauenburg, 1976) can be invoked to restrict the description of the signal to:

$$c_i(t) = \sum_{k=1}^{N} c_{i_k}(t) \otimes \alpha_k e^{-\beta_k}$$  \hspace{1cm} (2.31)

where the $\alpha_k$ are coefficients of the exponential basis functions which are characterised by clearance rates $\beta_k$ (In practice these are restricted to be greater than the minimum possible clearance rate and less than 1).

The technique was originally (Cunningham and Jones, 1993) applied to region of interest and image data, by fixing the basis functions, i.e. choosing around 100 values of $\beta_k$ and then performing linear least squares regression to generate 100 estimates of $\alpha_k$. This results in a characteristic 'spectrum' for a particular activity time course; large values of $\alpha_k$ indicate a strong component of the corresponding $\beta_k$ in the data.
Using the following relationships, estimates of $K_i$ and the partition coefficient between total tissue and plasma ($P$) can in theory be estimated:

\begin{align}
K_i &= \sum_{k=1}^{N} \alpha_k \\
P &= \sum_{k=1}^{N} \frac{\alpha_k}{\beta_k}
\end{align}

Effectively these estimates imply extrapolating the impulse to $t=0$ and $t=\infty$, respectively, and the macroparameters are in fact better estimated from the impulse response function calculated at times within the scan protocol (Meikle et al. 1998).

Note however that equation (2.31) for known $\beta_k$, conforms to the requirements of the basis functions for equation (2.38) - and spectral analysis can therefore be written in those terms. Consequently the derivation can be pursued to derive parameter projections of the $\alpha_i$, and parametric images of selected components of the spectrum can be calculated.

Research on the application of spectral methods to projection data has been done (Meikle et al. 1998), however an error of 5% in the accuracy of the estimates was found, which is not explained by the theory. In order to restrict the possible values for the $\alpha_i$, to the positive domain, the authors chose a non-negative least squares estimation algorithm (Lawson and Hanson, 1974), which they point out is non-linear. Nevertheless, the combination of spectral analysis and parameter projections, allowed the authors to select any reconstruction algorithm, and in particular to explore the coupling of maximum likelihood estimation methods and spectral analysis.
2.12 MLEM and kinetic a-priori information

An alternative to filtered back projection is maximum likelihood reconstruction, which does not consider the analytical solution to the problem of back projection. Instead, the problem is restated in a discrete form, based on the following equation:

\[ \lambda = Ay \quad (2.34) \]

\( \lambda \) is a vector of dimension \( n_p \), the number of projection elements in the discrete sinogram, containing the projection counts. \( y \) is a vector of dimension \( n_p \), the number of pixels in the reconstructed image, containing the reconstructed image pixel values, and \( A \) is a matrix of dimensions \([ n_p, n_p] \), each element \( A_{ij} \) is the probability of an emission from image pixel 'i', being registered by detector pair 'j'.

The problem is then to estimate \( y \), which is done iteratively, from a starting estimate. At each iteration, \( \lambda \) is calculated from (2.34) and compared with the measured values, resulting in an adjustment.

It is the reconstruction of parametric images, however, which is of real interest. To incorporate kinetic models into the discrete reconstruction process, equation (2.38), which expresses a general kinetic model is modified to a matrix expression which describes the time course in each pixel, and the associated kinetic parameters:

\[ Y = KX^T \quad (2.35) \]

\( Y \) is a matrix with elements \( Y_{ij} \) equal to \( (c_i)_j \), the activity concentration in pixel 'i' at time 'j'. Superscript T again denotes the transpose matrix operation. The rows of \( Y \) are equal to \( C^i \), as defined in equation (2.38). \( K \) has elements \( K_{ij} \) equal to \( k_{ij} \), the value of the 'i'th pixel in a parametric image of parameter 'j' (The rows of \( K \) are equal to \( k^j \) as defined in equation
(2.38) $X^T$ is the transpose of the matrix $X$, as previously defined.

In an analogous way, time variation is now introduced into equation (2.34):

$$L = AY$$

(2.36)

where $L$ is a matrix with columns $L_j$ equal to $\lambda_j$, the activity concentration image at time $'j'$. $Y$ and $A$ are as defined in the previous two equations.

Substituting equation (2.35) into (2.36) and rearranging yields:

$$L = (AX)K^T$$

(2.37)

This equation can be solved similarly to equation (2.34), to allow direct calculation of parametric images from the full time sequence of images $L$. It has been shown to be practically applicable (Matthews et al. 1997) for a number of specific cases.

2.13 List mode

As PET systems become more complex in terms of the number of active coincidence channels, attention is returning to acquisition protocol methods that do not require the definition of a predetermined time protocol, but rather store events in a sequential list with high resolution time information - 'List mode'. The data is rebinned, post-acquisition, into ordered sinograms, which may have any time length within the original scan duration. Thus analysis methods can be used which might make use of the whole dynamic series to estimate some parameters, before subsequently reanalysing the data with a lower time resolution to estimate the parameters of interest with high precision (Lammertsma et al. 1990).

Equation (2.26) does not contain any restrictions on the timing of acquisition and can be applied to high time
resolution list mode data, in order to estimate parametric images, without the necessity of reconstructing large numbers of images. In fact it is possible to consider replacing $\Lambda$ with the instantaneous estimate $\frac{1}{T}$ where $T$ is the period measured between two events in the same channel, allowing on-line estimation of the parameter projection.

2.14 FORE reconstruction method

A main motivation for exploring the concept of parameter projections, was the long reconstruction times which are to be expected for fully $\mathbb{R}^3$ acquisition in PET, however as computing power increases, this issue should diminish in importance.

It is not in fact necessary to invoke fully three dimensional reconstruction algorithms since it has been shown that the $\mathbb{R}^3$ data set can be reordered into an equivalent $\mathbb{R}^2$ data set requiring $\mathbb{R}^2$ methods for reconstruction (Defrise et al. 1997). The simplest method to achieve this is using the cross-plane reconstruction, described in section 1.6, increasing the axial extent to include the entire available axial field of view. However this method is inexact, since the oblique angle of the acquisition is ignored.

Consider again figure 4, and let the co-ordinates extend to $\mathbb{R}^3$, using the system in figure 10.
By an ingenious insight (Edholm et al. 1986) it has been shown that there is an approximate equivalence between the Fourier transform of a $\mathbb{R}^2$ sinogram located at $z$, and the Fourier transform of any oblique sinogram passing through its plane:

$$P(\omega, k, z, t) = P(\omega, k, z - \left\lfloor \frac{k}{\omega} \right\rfloor 0)$$

(2.38)

where $\omega$ is a continuous frequency corresponding to $x$, and $k$ is an integer Fourier index corresponding to $\phi$. This method has been shown to be the current best-choice reconstruction algorithm in terms of a best estimate of the true activity distribution (Defrise et al. 1997), and in terms of computational efficiency (Egger and Morel, 1998).

Effectively this result means that $\mathbb{R}^1$ acquisitions can, for all practical purposes be reconstructed using the $\mathbb{R}^2$ algorithms, after rebinning, and computational burden is no longer an important issue. Parameter projections, however, still allow exploitation of the particular statistical properties of the projection data, as will be seen in a later section.
3. Parameter projections and MTGA

3.1 Introduction

As was explained in section 2.8 it is possible to express the MTGA method in terms of parameter projections to allow calculation on the raw sinogram data. In this chapter a validation of that assertion is discussed, using the tracer [F-18]FDG, one of the most commonly applied tracer substances (Maguire et al. 1997). Firstly an outline of the FDG experimental technique will be presented that outlines and criticises specific aspects of the method, and secondly, a validation of the technique when compared to non-linear estimation will be shown, through Monte-Carlo simulation. Finally an application of the parameter projection method is given with an analysis of the associated error.

3.2 FDG experimental method

In order to apply [F-18]FDG experimentally in humans, the subject has a catheter inserted into the radial artery, for the continuous withdrawal of blood during the scanning period. At the same time, a catheter is inserted into an arm vein in order to deliver the tracer. F-18 is prepared by the \(^{0-18}(p,n)F-18\) reaction using an \([0-18]H_2O\) target, and the extracted isotope is used to label FDG (Hamacher et al. 1986). Like many PET tracer substances FDG is a poison, but is used in such low (tracer) concentrations that there is no physiological effect.

The subject lies on the tomograph bed with eyes and ears covered, to reduce extraneous brain activation. The head is fixed, using an individually fitted polyurethane head mould, in a shell attached to the bed. A transmission measurement is then made. In fact the brain has an approximately constant attenuation coefficient (see section 1.5), and it is possible to estimate the resultant attenuation along each LOR. By determining the outer contours of the brain from data which is not corrected, the chord of intersection of each LOR can be determined. An additional correction can be made for denser
bone, by assuming a constant thickness of the skull round the contour's perimeter. The attenuation of any head support is often ignored. Injection of the tracer is by infusion of a 100 ml physiological saline solution of the tracer into the arm vein over 3 min. This slow infusion reduces inaccuracy in the determination of the activity course in plasma, which is necessary for accurate quantification. Typically 200 MBq is infused, resulting in a whole body effective dose equivalent of 3 mSv.

If perfusion tissue and extraction of FDG across the blood brain barrier are similar in all active brain regions, then the parameter $p$ will be a function of the total active tissue in a given region of interest. It should, therefore also be expected that in regions with more atrophy, or where CSF infiltration is greater, there would be less free FDG in tissue relative to blood, and hence $p$ will be smaller.

### 3.3 Healthy human ageing and glucose utilisation

Variation in resting rCMRGlut in healthy human subjects has been observed to be around 10% within and 13% between individuals (Camargo et al. 1990). This has been variously explained by instrumental factors (Herzog et al. 1991), physiological variance due to subject state (Szabo et al. 1992), and also due to ageing (Wang et al. 1994; Petit Taboue et al. 1998).

The issue of whether rCMRGlut was a function of age has been debated in the literature, and it is interesting to follow the interplay between the definition and measurement of rCMRGlut and the instrumentation. Initially, studies on small groups of normal volunteers failed to find any effect of change of rCMRGlut with age (Hawkins et al. 1983), but with larger numbers of volunteers and higher resolution instrumentation, differences were observed. These differences were attributed to atrophy (de Leon et al. 1987; Schlageter et al. 1987), however, it is known that as the brain ages, CSF will infiltrate grey matter regions as neurones die (Pfefferbaum et al. 1994).
From the following definition it can be seen that the unit rCMRGlu, implies concentration measurement:

\[
\frac{dc^G}{dt} = \frac{1}{V} \frac{dm^G_s}{dt}
\]  

where \( m^G_s \) is the mass of glucose in the measured volume \( V \). In the PET experiment, with current spatial resolutions, this volume will always be heterogeneous, containing CSF and grey and white matter. The model of the brain as being composed of one type of grey or white matter breaks down at this resolution and the variations in the numbers of neurones, synapses, and especially mitochondria should be considered in a more complete model of brain tissue types. Variation on a regional basis, as a result of pathophysiology, or atrophy in the composition of grey matter will introduce variability into the metabolically active portion of \( V \), and in turn into the measured rCMRGlu. Similarly, the interplay between resolution and tissue metabolism spatial distribution will introduce an uncontrolled variation into the measured rCMRGlu.

In the light of this discussion, it can be seen that it is important to clarify the definition of rCMRGlu before proceeding to discuss measured values. If the operational definition in equation (3.1) is used, where \( V \) is simply the measurement volume, then it is clear that effects such as atrophy and infiltration of CSF into cortical areas will cause changes in the measured rCMRGlu. Recent literature data (Petit Taboue et al. 1998) and the data presented here (see figure 11) show that there is a slow decrease in rCMRGlu, so defined, with age, which is especially pronounced in the frontal lobes.
3.4 Validation of the MTGA applied to sinogram data

3.4.1 Methods

Five studies were performed on normal subjects. Each was catheterised in a radial artery and received a 183 MBq dose of FDG infused over 3 min into a vein in the contralateral arm. A time sequence of 16 acquisitions, (3 × 1 min, 10 × 3 min, 3 × 5 min) was recorded for 48 min using a tomograph (Siemens-CTI ECAT 933/04-16, Knoxville, USA), which records data from 7 contiguous slices, each 8 mm thick. 19 blood samples were also obtained at 0.3, 0.6, 1, 1.3, 1.6, 2, 2.5, 3, 4, 5, 7, 10, 15, 20, 25, 30, 41, 48 and 55 min. after injection, from the indwelling arterial catheter, using a protocol of rapid 10 s measurements at the beginning and less frequent measurements later. These were centrifuged, and plasma concentrations of [F-18]FDG were determined.

Blood samples were measured using a well-counter (Berthold LB 95 G, Regensburg, Switzerland), which was based on a single NaI(Tl) crystal 50.3 mm (2 inches) in diameter, with efficiencies of 20% at 660 keV and 75% at 300 keV.
In Figure 12 the results of an experiment to determine the count rate performance determined over a range of measurement activities is shown. The experiment involved the measurement of a sample of C-11 over 4 hr. The results were decay corrected to the start of the sequence of measurements. The 4th measurement in the series, which was well within the working range of the detector, was used with the predetermined efficiency (0.177) to determine the actual activity concentration of the sample. Using the half-life of C-11 (20.3 min) (Lederer et al. 1978), the actual activities of the sample at other times were calculated. The experiment was repeated with samples of different volume, and figure 13 shows that there is no extra detectable effect of sample volume on efficiency.

At high count rates the dead time in the crystals caused a non-linearity in the response, and over compensation using a fixed background correction was responsible for the non-linearity of the detector at low count rates. By carefully measuring the background activity before, during and after the experiment, this effect can be minimised. Sample volume did not have an impact on the measurement accuracy, except where a larger sample size resulted in a higher total measured activity. The results should be compared with those for the coincidence-based detector, which are given later in this work. Clearly the performance of the coincidence detector is better at both these extremes of measurement.
Figure 12. Plot of detector efficiency vs. total sample activity. Decreased measured activity at lower sample activities, < 1 kBq, was due to a fixed background activity correction in the device. At count rates above 100 kBq·ml⁻¹ the dead time of the device had a significant effect on calibration.
A determination of the blood glucose level was also made. Subjects had their eyes open, and ears unplugged during the scanning period. Prior to the emission scan, a transmission scan was acquired using a ring source of Ge-68/Ga-69, with a total activity of approx. 60 MBq. The scan duration of approx. 20 min assured $1 \times 10^6$ counts per plane in the transmission sinograms.

An implementation of the method described in section 2.8 was used to apply the MTGA method on an element-by-element basis to the projection data. Parameter projections of $K^o_i$ and $p$ were estimated. These were subsequently reconstructed into parametric images, using Fourier filtered back projection (Hann filter, cut-off at the Nyquist limit of 0.5 cycles/pixel.). The $K^o_i$ images were scaled using $c_i$ to images of rCMRGlut in order to assess the influence of the study protocol on estimates of rCMRGlut. The range of data used for the analysis was varied, by excluding earlier time frames. Each of the ranges ended at 47.5 min, but the starting times
were varied between 4.5 and 35.5, resulting in 11 separate estimates.

For comparison, the 16 time frames were also reconstructed resulting in sequential images of activity concentration, using the same reconstruction algorithm and filter as for the parametric images. MTGA was then applied on a pixel-by-pixel basis to these images in order to calculate parametric images of $K^g$, and $p$. Note that this method requires many more reconstruction steps, than the projection method. Each time point of the sequence must be reconstructed separately, in 3D imaging the computational cost of reconstruction is high, making this method less efficient than using parameter projections.

After estimation, the following brain regions of interest (ROI) were identified for further analysis: Frontal, insular and occipital cortex, cerebellum and white matter, on both the left and right hemispheres of the brain. The regions were defined using standard software tools (ECAT 6 software; Siemens-CTI; Knoxville; USA), that required operator interaction to define regions identified directly from the rCMRGlus parametric images calculated by both the image and the projection methods.

In order to assess the component of the variance of the estimated rCMRGlus values, which was not accounted for by the inter-subject variation, a ratio between the left and right hemisphere regions of interest was defined on an individual region and subject basis. Since, it was expected that this value should be close to 1 in all regions of interest (Cherry et al. 1993), and for all subjects, it gives a direct measure of repeatability of the measurement.

3.4.2 Results

The results for both techniques were found to be identical, (to within 1%) for both parameters ($K^g$, rCMRGlus) and $p$, for all the data ranges which were examined. This of course implies that the mean and standard deviation and hence the accuracy
and precision of the methods is identical. In table 4 the estimates from 5 of these analyses is given:

Table 4 Results of the estimation of rCMRGlu (µmol/100g/min) performed on the projection data for five regions of interest, and 5 fitting ranges. L and R indicate left and right hemisphere ROI respectively.

<table>
<thead>
<tr>
<th>Range (min.)</th>
<th>White Matter</th>
<th>Frontal Cortex</th>
<th>Cerebellum</th>
<th>Insular Cortex</th>
<th>Occipital Cortex</th>
</tr>
</thead>
<tbody>
<tr>
<td>L R</td>
<td>L R</td>
<td>L R</td>
<td>L R</td>
<td>L R</td>
<td>L R</td>
</tr>
<tr>
<td>4.5-47.5</td>
<td>16.9 16.7</td>
<td>42.0 42.2</td>
<td>34.2 34.5</td>
<td>42.6 41.2</td>
<td>37.9 40.7</td>
</tr>
<tr>
<td>10.5-47.5</td>
<td>16.1 15.6</td>
<td>40.5 40.6</td>
<td>32.2 32.8</td>
<td>40.9 40.1</td>
<td>36.4 39.4</td>
</tr>
<tr>
<td>19.5-47.5</td>
<td>15.6 14.7</td>
<td>39.1 39.1</td>
<td>30.3 31.8</td>
<td>39.2 38.6</td>
<td>34.6 38.0</td>
</tr>
<tr>
<td>28.5-47.5</td>
<td>15.1 13.0</td>
<td>37.4 38.3</td>
<td>27.5 30.5</td>
<td>37.4 37.8</td>
<td>33.3 35.8</td>
</tr>
<tr>
<td>35.5-47.5</td>
<td>13.7 11.9</td>
<td>37.8 39.5</td>
<td>27.7 27.7</td>
<td>33.9 37.2</td>
<td>31.0 35.1</td>
</tr>
</tbody>
</table>

The observed values for rCMRGlu are in good agreement with published values (Wang et al. 1994; Szabo et al. 1992; Herzog et al. 1991; Camargo et al. 1990), within the wide range of uncertainty given by differences in instrumentation, resting state and age of the subjects. As the starting time for the estimation is increased, thus including fewer time points, rCMRGlu estimations decrease in each region. This is illustrated graphically in figure 14 with the associated increase in $p$ in figure 15. The correlation coefficient between the estimated $p$ and rCMRGlu across starting times, for each
individual ROI was less than -0.99 in each case, indicating a very high negative correlation.

Figure 14. Decrease in the estimated glucose utilisation as the estimation starting time is increased in 11 steps. The starting point of the estimation is plotted on the independent axis - later starting points imply a shorter fitting range. Five regions are shown [white matter: '.', frontal: '.', insular cortex: '--', occipital cortex: '...', cerebellum: '-']
Figure 15. Increase in the estimated 'p' value as the estimation starting time is increased in 11 steps. The starting point of the estimation is plotted on the independent axis - later starting points imply a shorter fitting range. Five regions are shown [white matter: '.', frontal: '-', insular cortex: '--', occipital cortex: '...', cerebellum: '-']

The greatest decrease was observed in the right hemisphere white matter region (28.4 %). Estimates from opposite hemispheres are in good agreement for the range 4.5 - 47.5 min differences in the occipital cortex are the greatest (6.8 %). The coefficient of variation for the estimates, calculated by comparing estimates between subjects, is given in table 5.
Table 5. Associated coefficient of variation (%) of the results of the estimation of rCMRGl existence for five regions of interest. L and R indicate left and right hemisphere ROI respectively.

<table>
<thead>
<tr>
<th>Range (min.)</th>
<th>White Matter</th>
<th>Frontal Cortex</th>
<th>Cerebellum</th>
<th>Insular Cortex</th>
<th>Occipital Cortex</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>L</td>
<td>R</td>
<td>L</td>
<td>R</td>
<td>L</td>
</tr>
<tr>
<td>4.5 - 47.5</td>
<td>36.9</td>
<td>31.6</td>
<td>15.9</td>
<td>16.0</td>
<td>20.4</td>
</tr>
<tr>
<td></td>
<td>20.4</td>
<td>16.3</td>
<td>24.1</td>
<td>19.7</td>
<td>18.7</td>
</tr>
<tr>
<td>35.5 - 47.5</td>
<td>48.4</td>
<td>30.3</td>
<td>24.2</td>
<td>24.0</td>
<td>34.4</td>
</tr>
<tr>
<td></td>
<td>34.4</td>
<td>36.6</td>
<td>28.7</td>
<td>46.5</td>
<td>18.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>29.1</td>
</tr>
</tbody>
</table>

The coefficient of variation (CV) is greatest in the left and right white matter regions, and least for the frontal cortex, for both estimation ranges given in the table. The CV in this table includes the inter-subject variance, which is expected to be the largest component, and is expected to be 13.8% and 7.1% (sample size 12) for inter- and intra-personal rCMRGl existence, respectively (Camargo et al. 1990). The CV is least in the frontal cortex, indicating that this area has the most precision. As the estimation range decreases the CV increases although there are differences in this increase in each ROI.

Tables analogous to those for rCMRGl existence are given below for the parameter 'p', which was found to be smallest in the white matter, and greatest in the cerebellum. As the estimation range was shortened, the estimated p increased in all regions, with a maximum difference in the right white matter ROI (142 %). The inter-hemispheric differences were smaller than for rCMRGl existence, using the estimation range 4.5-47.5 min, but again the consistency between the hemispheres decreased as the estimation range was shortened.
Table 6. Estimated p parameter as determined by regression on the projection data. L and R indicate left and right hemispherical ROI.

<table>
<thead>
<tr>
<th>Range (min.)</th>
<th>White Matter</th>
<th>Frontal Cortex</th>
<th>Cerebellum</th>
<th>Insular Cortex</th>
<th>Occipital Cortex</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>L</td>
<td>R</td>
<td>L</td>
<td>R</td>
<td>L</td>
</tr>
<tr>
<td>4.5 - 47.5</td>
<td>0.16</td>
<td>0.19</td>
<td>0.32</td>
<td>0.32</td>
<td>0.44</td>
</tr>
<tr>
<td>10.5 - 47.5</td>
<td>0.21</td>
<td>0.24</td>
<td>0.40</td>
<td>0.40</td>
<td>0.54</td>
</tr>
<tr>
<td>19.5 - 47.5</td>
<td>0.24</td>
<td>0.29</td>
<td>0.48</td>
<td>0.48</td>
<td>0.64</td>
</tr>
<tr>
<td>28.5 - 47.5</td>
<td>0.27</td>
<td>0.39</td>
<td>0.60</td>
<td>0.52</td>
<td>0.81</td>
</tr>
<tr>
<td>35.5 - 47.5</td>
<td>0.36</td>
<td>0.46</td>
<td>0.57</td>
<td>0.45</td>
<td>0.78</td>
</tr>
</tbody>
</table>
Table 7. Associated coefficient of variation (%) of the results of the estimation of $p'$ for five regions of interest. L and R indicate left and right hemisphere ROIs respectively.

<table>
<thead>
<tr>
<th>Parameter projections and MTGA 83</th>
</tr>
</thead>
<tbody>
<tr>
<td>Table 7. Associated coefficient of variation (%) of the results of the estimation of $p'$ for five regions of interest. L and R indicate left and right hemisphere ROIs respectively.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Range (min.)</th>
<th>White Matter</th>
<th>Frontal Cortex</th>
<th>Cerebellum Cortex</th>
<th>Insular Cortex</th>
<th>Occipital Cortex</th>
</tr>
</thead>
<tbody>
<tr>
<td>L</td>
<td>R</td>
<td>L</td>
<td>R</td>
<td>L</td>
<td>R</td>
</tr>
<tr>
<td>4.5 - 47.5</td>
<td>24.5</td>
<td>33.9</td>
<td>14.6</td>
<td>10.8</td>
<td>14.3</td>
</tr>
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<td></td>
<td>15.2</td>
<td>14.8</td>
<td>12.3</td>
<td>17.6</td>
<td>4.0</td>
</tr>
<tr>
<td>35.5 - 47.5</td>
<td>45.2</td>
<td>38.0</td>
<td>58.5</td>
<td>55.6</td>
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<td>55.5</td>
<td>74.6</td>
<td>12.6</td>
<td>37.1</td>
<td>40.7</td>
</tr>
</tbody>
</table>

In table 8, the results of the right / left hemisphere region of interest ratio are given. Inter-hemispheric ratios for rCMRGl and $p$ are close to 1.0, and the standard deviation of rCMRGl, for the range 4.5-47.5 min, is approximately the same as that expected from the intra-subject variation. The standard deviation of the $p$ ratio is more sensitive to the estimation time range than that for the rCMRGl estimate. For starting times up to 20 min the standard deviation of the inter-hemispheric rCMRGl ratio is less than 8%.
Table 8. Inter-hemispheric ratios for rCMRGlu and $p$, for 5 MTGA estimation ranges, together with associated standard deviations.

<table>
<thead>
<tr>
<th>Estimation range</th>
<th>time</th>
<th>Inter-hemispheric ratio of rCMRGlu</th>
<th>Standard deviation</th>
<th>Inter-hemispheric ratio of $p$</th>
<th>Standard deviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.5 - 47.5</td>
<td>0.99</td>
<td>0.080</td>
<td>1.04</td>
<td>0.14</td>
<td></td>
</tr>
<tr>
<td>10.5 - 47.5</td>
<td>0.99</td>
<td>0.083</td>
<td>1.05</td>
<td>0.15</td>
<td></td>
</tr>
<tr>
<td>19.5 - 47.5</td>
<td>0.99</td>
<td>0.085</td>
<td>1.05</td>
<td>0.26</td>
<td></td>
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<tr>
<td>28.5 - 47.5</td>
<td>0.99</td>
<td>0.11</td>
<td>1.18</td>
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<td></td>
</tr>
<tr>
<td>35.5 - 47.5</td>
<td>1.00</td>
<td>0.24</td>
<td>1.11</td>
<td>1.15</td>
<td></td>
</tr>
</tbody>
</table>

3.4.3 Discussion

The expected identity between the parameter projection based calculation of both rCMRGlu and $p$ was found. Both the absolute values of the parameters and their precision were the same. The variance in the original raw data is therefore propagated through both analysis methods - image and sinogram - in the same way.

The results of the rCMRGlu calculations varied regionally, as expected from the literature, and there was no increased discrepancy between the results from regions with slower kinetics - white matter. This shows that the condition of equilibrium of the free tissue compartment with plasma, which is required for the calculation of rCMRGlu in the MTGA analysis method, is not a prerequisite of parameter projections. Any bias in the final rCMRGlu value resulting from incomplete equilibration will be present in both methods.

In this study, a decrease in rCMRGlu was observed for later starting points of the MTGA analysis. In a typical protocol, a
time series of 20 acquisitions might be made over 48 min. Studies by (Lucignani et al. 1993) have shown that there are systematic differences in the quantification of FDG depending on the experimental protocol. Regional cerebral glucose utilisation (rCMRGlut) will decline with increasing study duration. There are a number of issues here, firstly the complete equilibrium of the plasma activity concentration with blood, secondly the irreversibility of the phosphorylation step of FDG, and thirdly tissue inhomogeneity within the measured volume.

As previously explained, the application of MTGA to [F-18]FDG studies relies on the assumption that any reversible compartments are in equilibrium with plasma over the time range of the linear regression. This equilibrium is an asymptotic process, with a time constant determined by the two rate constants for clearance from the first tissue compartment:

\[ \tau = \frac{1}{(k_2 + k_3)} \]  

Typically this time constant will be around 7.1 min, which means that a full equilibrium, to within 5%, will occur at around 5\( \tau \), i.e. 35 min. If linear regression includes data from earlier times then there will be a bias in the estimate, although the precision of the estimate may be higher than if the estimation range is shortened, by beginning later.

Although the assumption has been made that the phosphorylation step is irreversible, this assumption may not be completely true. Lastly there is the issue of homogeneity in the measured region. Brain tissue can be broadly segmented into three components, grey matter, white matter and CSF. Metabolism of FDG occurs mainly in the mitochondria of the grey matter, which contains the neurone bodies and the synapses. In the neocortex, regions that are very rich in pure grey or white matter can be determined, but here an infiltration of and
mixing with CSF can be detected as a result of normal ageing (Pfefferbaum et al. 1994). A clear example is the cerebellum, which is very heterogeneous, within the resolution of the PET camera - the cerebellum contains more neurones than the rest of the brain. This means that a spatial sample of the uptake tissue time course of [F-18]FDG from this area must contain a mixture of white and grey matter (Schmidt et al. 1992). If a model such as that described in section 2.3, which explains only data from homogeneous tissue, then an apparent $k_4$ can be found which is simply due to the mixture of measured signals from different tissues in the region.

The increase in the estimated value of $p$ with increase in the starting point of the MTGA estimation appeared linear with increase in the starting time of the estimation. The proportion of the free [F-18]FDG in tissue that will not be metabolised should vary in direct proportion to the free [F-18]FDG concentration itself. This means that after equilibrium of the free tracer, $p$ will be constant. However, the estimation of $p$ will be very sensitive to the effects discussed above in connection with the issue of decreasing rCMRGlux with increasing starting times. As will be seen later in the simulation studies, the value of $p$ is also sensitive to the rate of change of the plasma activity concentration, which is assumed to be constant, for MTGA.

The inter-hemispheric ratios (Table 8) provide an interesting method to examine the repeatability of the MTGA method, that is the variance associated only with the measurement. It assumes that rCMRGlux and $p$ should be similar on opposite hemispheres, and this is borne out by the absolute values. Since the ratio is made separately for each subject and region, the components of inter-subject and inter-region variability are not present in the standard deviation.

In conclusion, it is clear that MTGA can be applied using the parameter projection method. In the assessment of human metabolic function with PET, [F-18]FDG is a very important tracer method, but there are a number of important
methodological issues, surrounding the PET model, which need to be taken into consideration when using the tracer. It is important that comparisons of measured rCMRGluc between subject groups should only be made when the same measurement protocol has been made. The $p$ value has to be interpreted with care, since it is likely to depend even more heavily on protocol issues than rCMRGluc.

3.5 Comparison of Non-linear and linear methods - introduction

The advantages of applying linear methods to projection data are clear, however as has been shown, the solutions to differential equations based on compartment models are intrinsically non-linear. In order to address the question of whether using macroparameters and linear methods introduces any bias or decreases the precision of estimation Monte-Carlo simulation studies were performed.

To be able to perform the Monte-Carlo studies, normal values for the plasma input to the tissue uptake model for $[F-18]$FDG had to be established. To achieve this a novel model of the whole body distribution of FDG was established, which allows simulation of the arterial plasma activity time course. Secondly a new Monte-Carlo framework for simulation of tissue activity concentration time curves, based on scanner system parameters was built up and subsequently used to examine the properties of the linear and non-linear operators.

3.6 Plasma models

3.6.1 Introduction

This section introduces a new plasma model for the whole body distribution of FDG. In contrast to previous models in the literature, the model has been constructed rationally from a consideration of possible body compartments for the distribution of the tracer. The appropriateness of the model to explain measured data is determined using statistical methods. The final model and parameters determined form a large subject group allow simulation of the arterial time
course in plasma, which supplies the brain. This data will be used as an input in establishing the accuracy of parameter determination in the tissue model in a later section.

3.6.2 Methods

A series of 74 blood activity time courses was obtained from normal subjects using the same protocol previously described in section 3.2. Two compartment models were proposed for analysing the data, as shown in figures 16 and 17. Both of these were implemented in the MATLAB 5.3 matrix algebra package (Mathworks, Natick, USA).

Figure 16 Proposed one tissue compartment model explaining the measured distribution of FDG in the body after injection.
In both these models the parameter $k_i$ is equivalent to the activity concentration injection rate of the infusate in Bq/(ml-min) - i.e. the contribution to the plasma activity concentration per unit time. In the model in figure 16 parameters $k_3$ and $k_4$ represent clearance to, and washout from, fast equilibrating tissue, and $k_5$ represents clearance from plasma unexplained by the tissue compartment. The delay between the plasma compartment and the measured compartment was also considered, this is simply an origin shift and should not be confused with the delay between the measured PET tissue signal and plasma signal, which will be discussed later. In the more complex model shown in figure 17, a second compartment was added. Although this introduces two extra parameters, it is in fact the next highest order model differing from the simpler model in figure 16.

Non-linear optimisation was used to determine the model parameters for each of the data sets, and an F-test (Landaw
and DiStefano III, 1984) was used to assess the most appropriate model to explain the measured data.

3.6.3 Results

All data sets were fitted using both models. The results of the F-test were inconclusive. The F-tests showed a significant improvement in explanation of the data by the more complex model in 42 cases out of 71 blood curves, at the 95% confidence level. In tables 9 and 10, the median values and coefficient of variation for each of the models is given.

Table 9. Fitted values and coefficient of variation for the simpler - one tissue compartment - FDG plasma model.

<table>
<thead>
<tr>
<th>Parameter</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>$k_1$ (Bq/(ml·min))</td>
<td>$k_2$</td>
<td>$k_3$</td>
<td>$k_4$</td>
<td>Delay</td>
<td></td>
</tr>
<tr>
<td>(min⁻¹)</td>
<td>(min⁻¹)</td>
<td>(min⁻¹)</td>
<td>(min)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>$1.14 \times 10^4$</td>
<td>0.034</td>
<td>0.18</td>
<td>0.090</td>
<td>0.010</td>
</tr>
<tr>
<td>COV %</td>
<td>30</td>
<td>70</td>
<td>70</td>
<td>60</td>
<td>130</td>
</tr>
</tbody>
</table>

Table 10. Fitted values and coefficient of variation for the more complex - two tissue compartment - FDG plasma model

<table>
<thead>
<tr>
<th>Parameter</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>$k_1$ (Bq/(ml·min))</td>
<td>$k_2$</td>
<td>$k_3$</td>
<td>$k_4$</td>
<td>$k_5$</td>
<td>$k_6$</td>
<td>Delay</td>
</tr>
<tr>
<td>(min⁻¹)</td>
<td>(min⁻¹)</td>
<td>(min⁻¹)</td>
<td>(min⁻¹)</td>
<td>(min⁻¹)</td>
<td>(min)</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>$1.66 \times 10^4$</td>
<td>0.058</td>
<td>0.46</td>
<td>0.25</td>
<td>0.047</td>
<td>0.020</td>
</tr>
<tr>
<td>COV %</td>
<td>40</td>
<td>30</td>
<td>50</td>
<td>20</td>
<td>40</td>
<td>50</td>
</tr>
</tbody>
</table>
An estimate of the average plasma volume $V_p$ of the subjects from the fitted $k_t$, the infusion time $T = 3$ min and the total infused activity $A$, can be calculated from the following equation:

$$V_p = \frac{A}{k_t T} \quad (3.3)$$

Assuming an average 185 MBq input activity, as required by the measurement protocol, this volume was calculated to be 3.71 +/- 1.5 l, which is in agreement with the expected average value of 3.5 l (Ganong, 1991). The ratio of $k_s$ and $k_t$ suggests a 1.84 partition coefficient with plasma for this compartment, which is equivalent to a notional volume of 6.44 l. The other compartment has a notional volume of 8.33 l, however it's time constant ($l/k_t$) is 50.8 min as compared with ($l/k_t$) 3.94 min for the first compartment.

Since the variance in the parameters [$k_2, k_3, k_4, \text{delay}$], which are included in both models was significantly lower for the more complex model, and using the F-test data, it was used in preference to the simpler model. In figure 18, a typical data set with fitted curves for both models is given.
3.6.4 Discussion

The aim of this experiment was to determine an optimal model for the explanation of the data which was measured. This optimal model depends not only on the underlying physiological processes, but also on the measurement instrumentation and protocol. By adding parameters to an existing model, it is always possible to improve a model fit and reduce the residual sum of squares. The question is whether the extra parameter is in fact associated with a real aspect of data or whether the new fit is explaining the noise in a particular data set. By using the F-test, as has been done here, the optimal model can be found. That is, one that describes all relevant processes that can be observed above the noise, but which does not fit the idiosyncrasies of individual data sets, which are there because of random fluctuations.

The F-test indicated that the more complex model was appropriate in a little less than half of the 71 data sets.
However, the variance of the individual parameters of the model was lower, with the exception of $k_t$, the activity concentration injection rate. This gives confidence in the necessity of the more complex model. Adding more compartments to this model would reduce the significance of any improvement, as determined by the F-test. For these reasons it was decided to accept the more complex model as a sound basis for the simulation studies in the following sections.

The input to both models was discontinuous - a constant infusion up to 3 min followed by no input for the rest of the study. This means that most of the information about $k_i$, is from the early portion of the curve, little or no information about $k_i$ is contained in the earlier part of the curve. One possible strategy to tease the models apart would be to fit only portions of the curve with each model.

The results of parameter estimation have been given here with an indication of their spread, using the coefficient of variation. The standard error of the mean, which is an estimate of the accuracy of the estimate of each of the parameters as a population parameter would be very much smaller. It is thought that the imprecision observed is mainly due to the physiological variation in individual subjects. This can come from a variety of sources, for [F-18]FDG, it will to some extent depend on the subjects fasting state, since the heart's metabolism may switch from glucose to fatty acid metabolism. This decreases the uptake of [F-18]FDG. Variability in body mass is also an important factor in this variation.

Given the imprecision in the estimates, it is possible that the second compartment identified is a mixture of reversible and irreversible binding of [F-18]FDG, as might be expected from the pharmacokinetics of brain and heart tissue, the main organs using glucose.

Models of the plasma distribution of the whole body distribution of FDG have been proposed previously (Feng et al.)
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1993), but the authors chose to fit generic exponential function models to their proposed compartment models, which makes determination of the exchange rate constants difficult. Since the units of the fitted parameters are also unclear, a comparison of the direct physiological meaning of the compartment volumes is impossible. It is clear however that the authors found that a four compartment model was necessary to explain data measured over 140 min, much longer than the time course in the current experiment. The authors also found that the multi-exponential model was unable to account for the slow increase of the plasma time activity course at the beginning of the study. The value of $k_t$ in the experiment presented here is very much dependent on the peak value of the early part of the curve, in relation to the washout constants. This perhaps illustrates the need to consider the possible physiological meaning of model variables (rate constants) when designing models.

Of course it has to be remembered that the models explain the measurement on the underlying physiology, and are therefore at the same time restricted and determined by the instrumentation. With higher sensitivity, and higher time resolution an even more complex model might be appropriate to explain the data. The main purpose here was to model the plasma curve in order to simulate, realistically, the time course of the tissue activity, and the model is certainly adequate for that purpose. Only the $k_t$ parameter was varied to simulate different injected activities, during the subsequent simulations, and all other parameters were held constant.

3.7 Accuracy of the MTGA and non-linear methods

3.7.1 Non-linear parameter estimation (Ralston’s algorithm)

The non-linear parameter estimation problem can be posed as (Jennrich and Sampson, 1968):

$$ Q(\theta) = \sum_{i \in D} (y_i - f_i(\theta))^2 $$  

(3.4)
where the function $Q$ is known as the cost function - which determines the goodness of fit - $\theta$ is a vector of parameters of the model function$f$.

Most non-linear parameter estimation algorithms have taken one of two approaches (Marquardt, 1963) to estimate the local gradient in the cost function: Taylor series, or steepest decent. Each step of the steepest descent method can be written:

$$\theta_{n+1} = \theta_n - \left(\frac{dQ}{d\theta}\right)$$  \hspace{1cm} (3.5)

where $n$ is the iteration index. The Taylor's series (Gauss or Gauss-Newton) method, on the other hand, approximates the local model function $f$ using a first order Taylor's series expansion, allowing a general linear least squares solution for the change in the parameters $\Delta\theta$:

$$f(\theta + \Delta\theta) \approx f(\theta) + \left(\frac{df}{d\theta}\right)\Delta\theta$$ \hspace{1cm} (3.6)

$$\therefore (y - f(\theta)) = \left(\frac{df}{d\theta}\right)\Delta\theta$$ \hspace{1cm} (3.7)

which can be solved:

$$\Delta\theta = -\frac{1}{2} \left(\frac{df}{d\theta}\right)^T \left(\frac{df}{d\theta}\right)^{-1} dQ(\theta) \frac{dQ}{d\theta}$$ \hspace{1cm} (3.8)

A superscript $T$ indicates the transpose function. In general the step $\Delta\theta$ will be modified by a fraction $K$: $0 \leq K < 1$, which ensures that the step is interpolated rather than extrapolated from the data.

The asymptotic covariance matrix for a single data set can be estimated by:
\[ \Sigma = s^2 \left( \frac{df}{d\theta} \frac{df}{d\theta}^T \right)^{-1} \]  
\[ s^2 = Q(\theta)/n - p \]

\(n\) and \(p\) are the number of data points and the number of parameters of the problem respectively.

A modified version of this algorithm has been proposed (Ralston, L and Jennrich, I, 1978; Jennrich and Sampson, 1968), which introduces a numerical approximation for the differentials given above, and implements stepwise inversion of the matrix on the right hand side of equation (3.8):

### 3.7.2 Linear least squares and pivoting

Consider the general least squares problem again, which can be written in terms of equation (2.38) and its solution:

\[ b = (X'X)^{-1} X'C \]  

(3.11)

The inversion step of the solution can be accomplished using Gauss-Jordan pivots on the diagonals of the matrix, which is to be inverted. The corresponding matrix element \(z_{ij}\) resulting from a pivot on the \(x_{ij}\)th element of matrix \(X\) with elements \(x_{ij}\) is given by:

\[ z_{ij} = x_{ij} - x_{ik} x_{ik} / x_{kk} \quad i \neq k, j \neq k \]
\[ z_{ij} = -x_{ik} / x_{kk} \quad i \neq k, j = k \]
\[ z_{ij} = x_{ik} / x_{kk} \quad i = k, j \neq k \]
\[ z_{ij} = 1 / x_{kk} \quad i = k, j = k \]

Further, if the matrix \(X\) is augmented to form matrix \(W\):

\[ W = \begin{pmatrix} X'X & X'Y \\ Y'X & Y'Y \end{pmatrix} \]

(3.13)

then:
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\[ W^{-1} = \begin{pmatrix} (XX)^{-1} & b \\ -b & S \end{pmatrix} \quad (3.14) \]

where \( b \) is the result of regressing \( c \) on \( X \) in equation (2.38), and \( S \) is the residual sum of squares. This step can be accomplished by a set of Gauss-Jordan pivots. At each pivot step, the element is chosen which achieves the largest reduction in the residual sum of squares. Pivoting is only carried out if the current pivot is large enough to retain the numerical accuracy of the matrix; in the case of a partially inverted matrix then estimates of the parameters in \( b \) corresponding to the pivoted elements are used.

Jennrich and Sampson (Jennrich and Sampson, 1968) proposed these modifications and their use in first order Taylor series approach to non-linear parameter estimation outlined above. Instead of an analytical expression for the local gradient of the function an approximation was proposed, based on a history of previous solutions. At the \( 'i' \)th iteration, the local gradient is estimated by calculating the difference between the current parameter estimations and the previous \( p+1 \), where \( p \) is the number of parameters in the problem.

3.7.3 Noise models

For both the linear and non-linear parameter estimation methods, it is possible to estimate the inaccuracy of determined parameters from an estimate of the covariance matrix, which can be obtained from the matrix description of the model (see section 4.6). However, this is a point estimate of the population variance, a random variable, which may or may not be close to the true population covariance / variance description.

An elegant and accurate method to obtain good error estimates (Press et al. 1992) is Monte-Carlo simulation. If a good description of the contributions to the noise from the instrumentation is available, then this can be used to assess
how changes could contribute to increased precision in the measurement.

Full geometrical descriptions of PET instrumentation, including the effects of light transport have been reported in the literature (Thompson et al. 1992). In parallel, Monte Carlo error estimation has been performed using model simulations and data noise estimates obtained from measured data (Coxson et al. 1997). But in order to gain a better insight into the impact of instrumentation on parameter estimates, it is necessary to combine these two approaches.

Considering a scanner as a counter, with a uniform and known scanner sensitivity, then the number of counts within a volume of interest, for a given activity concentration $c(t)$ (Bq.ml⁻¹) can be calculated:

$$K = c(t) \varepsilon T$$

(3.15)

where $\varepsilon$ is a sensitivity (Hz.ml.Bq⁻¹) which is a function of volume of interest size and the scanner efficiency, $T$ is the counting time in seconds.

Sensitivity $\varepsilon$ can be calculated from the size of the volume of interest and the sensitivity $\varepsilon_{20}$ measured using a 20 cm uniform phantom (Hz.ml.Bq⁻¹) [historical units Hz.ml.µCi⁻¹]. The historical units have been maintained, since these are quoted in the literature on scanners. It is defined using the count rate obtained from a 20 cm diameter calibration phantom occupying the whole axial dimension, with a known activity concentration. Thus the count rate is reduced by attenuation in the object, and represents a typical expected count rate in a uniformly attenuating and active object, which is slightly larger than the head, and smaller than the torso. The efficiency $\varepsilon$, which is similarly dependent on the attenuation, can be calculated from $\varepsilon_{20}$:

$$\varepsilon = \frac{r^2 \varepsilon_{20}}{R^2 N}$$

(3.16)
where \( R \) and \( r \) are the radii of the ROI and the calibration phantom (20 cm), and \( N \) is the number of measurement planes.

In this way the size of the region of interest and the sensitivity of the scanner can be varied. Note that the equation is an approximation as it ignores attenuation, so that \( \varepsilon \) will be underestimated for regions on the edge of an object and overestimated for those in the centre. The value will also be underestimated due to the overall difference in the attenuation of and scatter in the 20 cm phantom when compared to the human head.

3.7.4 Method

The model described in section 2.3 was implemented with parameters to take account of the dephosphorylation of FDG - rate constant \( k_i \) - and with a parameter to take the delay between the measured tissue and plasma activity time courses. Using the input model shown in the previous section, different blood time activity time courses were generated, with appropriate noise characteristics depending on measurement parameters such as the scanner sensitivity. The rate constants for the standard FDG model previously determined using the data from normal volunteers in Table 11, were used along with equation (2.7) yielding an ideal \( K_i \) of 0.032 min\(^{-1}\).

<table>
<thead>
<tr>
<th>Delay (min)</th>
<th>( k_1 ) (min(^{-1}))</th>
<th>( k_2 ) (min(^{-1}))</th>
<th>( k_3 ) (min(^{-1}))</th>
<th>( k_4 ) (min(^{-1}))</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.1</td>
<td>0.09</td>
<td>0.09</td>
<td>0.05</td>
<td>0.001</td>
</tr>
</tbody>
</table>

A series of 400 blood curves was generated and appropriate noise was added using a Poisson noise process. 4 x 100 tissue curves were also generated for each of 4 different scanner sensitivity values (10^0, 10^1, 10^2 Hz-ml-Bq\(^{-1}\)). Care was taken to ensure that the noise associated with each measurement point
was also appropriate for a scanner with 15 planes in the axial direction and a 1 cm ROI radius. Thus, for comparison with the ECAT EXACT HR+ (sensitivity 30.4 Hz·ml·Bq⁻¹), the effective volume measured would be 3.14 ml. The measurement durations were chosen according to the normal FDG measurement protocol implemented at Paul Scherrer Institute.

Using the implementation of Ralston's algorithm each of these curves was individually fitted to the FDG compartment model with 5 parameters, \([k_1, k_2, k_3, k_4, \text{delay}]\) with ideal values \([0.09, 0.09, 0.05, 0.0001, 0]\). From (2.17) \(K_t\) was therefore 0.0321.

In order to investigate the effect of parameter value on the precision of the macroparameter estimates, \(k_1\) was varied from 0 min⁻¹ to 0.1 min⁻¹, and non-linear and MTGA parameter estimation was performed on the simulated curves.

\(V_f\), the relative volume of the free tracer in tissue compartment was determined using the relationships:

\[
V_f = \frac{k_1}{(k_1 + k_t)}
\]

(3.18)

The ideal value for \(p\) was calculated from (2.17)

3.7.5 Results

In figures 19 and 20, the results of varying the sensitivity on the precision of determination of \(K_t\) are shown.
Figure 19. Boxplots of the $K_t$ estimated using non-linear regression (ideal value 0.321) at various scanner sensitivities (ECAT EXACT HR+ 30.4 Hz·ml·Bq⁻¹) (Grootoonk et al. 1996; Adam et al. 1996) (ECAT 933 scanner (Siemens-CTI user’s manual, Knoxville, USA) [extrapolated to 15 cm axial field of view] 8.1 Hz·ml·Bq⁻¹. Crosses outlier data points - as in all boxplots these are 1.5 times QR greater than the 75% quartile, or 1.5 times QR less than the 25% quartile, where QR is the range between the 25% and 75% quartiles.

The results show that the precision of the MTGA analysis is higher in the determination of $K_t$, than non-linear fitting, when all 5 parameters of the model, including $k_i$ and the delay are determined. For each of the sensitivities [1, 10, 100] Hz·ml·Bq⁻¹, the precision (Coefficient of variation %) of the $K_t$ estimates for non-linear fitting and MTGA were [8%, 3%, 2%] and [3%, 1%, 0.5%], respectively. Clearly the precision increases with camera sensitivity, and the limiting precision of the plasma activity concentration determination does not affect the precision of the high camera sensitivity estimates appreciably.
Figure 20. Boxplots of $K_t$ estimated using MTGA, (ideal value 0.321) at various scanner sensitivities (ECAT EXACT HR+ 30.4 Hz·ml·Bq⁻¹) (Grootoont et al. 1996; Adam et al. 1996) (ECAT 933 scanner [extrapolated to 15 cm axial field of view] 8.1 Hz·ml·Bq⁻¹ (User’s manual Siemens-CTI, Knoxville, USA)

Figure 21 shows the variation in the $K_t$ parameter over a wide range of $k_j$ values. $K_t$ varies non-linearly over the range, with an almost linear variation for small $k_j$, this can be predicted from equation (2.16). The precision of the $K_t$ in absolute units is good across the range of $k_j$ values for both methods. The accuracy of both methods also seems to be comparable - the correlation coefficients of the ideal value vs. the estimates from MTGA and non-linear estimation were both 0.99. At lower $k_j$ values, there is an offset in the estimated $k_j$, which decreases for the non-linear estimation method. The MTGA method, however, slightly underestimates $K_t$ when $k_j$ is high.
Figure 21. Graph of $K_n$ determined by both MTGA (x) and non-linear parameter estimation '"', for 10 different $k_3$ values. Error bars are +/- 1 standard deviation. The solid line is the ideal $K_n$ calculated from the simulation parameters.

The variation in the estimated $p$ and $V_f$ values is given in figure 22, for various $k_3$ values. The relationship between $V_f$ and $p$ can clearly be seen from this figure. At low $k_3$ both parameters are identical, and equal to the simple ratio of $k_1$ to $k_4$. At higher $k_3$, the two values diverge as the proportion of the activity which will be metabolised in the free compartment, increases, thus decreasing the proportion which will not be metabolised.
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Figure 22. Graph of estimated $p$ ('x') and $V_f$ (') as a function of $k_3$. The ideal value of $p$ was calculated from the simulation parameter values and is given as a solid line. The calculated $V_f$ is shown as a dot-dash line.

$V_f$ is underestimated by maximally 5% across the range of $k_3$ values. $p$ on the other hand is consistently overestimated by the MTGA method. As $k_3$ increases, this overestimation becomes smaller. At a $k_3$ value of zero, $p$ is estimated to be 1.1, i.e. 10% higher than the ideal value.

3.7.6 Discussion

The MTGA and non-linear methods were both able to determine $K_t$ with good accuracy, although the precision of the MTGA method was higher. The precision of the estimates from both methods was affected by the camera sensitivity, which was to be expected, since this has a direct effect on the variances of the measured activity concentration data.

In this work, dephosphorylation was included in the simulation model, which may account for the difference in accuracy of the MTGA, and non-linear methods. However this also meant that the non-linear method was required to estimate an extra parameter which is not included in the $K_t$ macroparameter, namely $k_3$. This
would be expected to have an influence on the accuracy of the other parameters, and it would be interesting to examine the performance of the non-linear method without \( k_4 \), although this may not be physiologically realistic.

The total time required for establishment of equilibrium between the free FDG in tissue compartment and the plasma pool will increase as \( k_3 \) decreased. The MTGA analysis was always started at the same time point (20 min) after infusion of the tracer, thus at lower \( k_3 \), \( K_t \) may be overestimated and \( p \) underestimated, due to this effect.

In section 2.8, the assumption of a slowly varying plasma activity concentration was made as part of the MTGA derivation. As \( k_3 \) decreases this assumption also becomes less appropriate. It is thought that this is the main reason for the over estimation of \( p \), shown graphically in figure 22. If the derivation is reviewed, it can be seen that if \( c_p \) is not constant, but slowly decreasing, then the convolution in equation (2.12) will be underestimated in equation (2.13). Thus for a given set of parameters, and a given measured blood time activity course, equation (2.13), would underestimate the tissue time activity course. Conversely, during GLLS estimation, using (2.13) as the operational equation, \( p \) is overestimated.

Nevertheless, in the range of \( k_3 \) values from 0.7 to 0.1 \( K_t \) is estimated with good accuracy and precision by the MTGA technique, and it can be coupled with GLLS and parameter projections, to provide fast and precise parametric images. In the next chapter it will be shown how MTGA and the GLLS approach can also allow a better estimation of the imprecision of parametric images on a pixel by pixel basis.
4. Estimating the pixel variance of parametric images

4.1 Introduction

In previous sections some of the reasons for the difficulty in performing absolute measurements - that is in comparing the in-vivo measured data from subjects and in-vitro data have been discussed. This might seem to be a real impediment to its practical application, but there are many important research papers in neuroscience literature, which prove its unique applications. It is not the ability to compare with in-vitro results which has made PET attractive to researchers, but rather its sensitivity to, and specificity for, (definitions in the medical field) physiological and patho-physiological change.

Seen in this light, the main aim of PET methodology research should be to increase the precision of the measurement. Indeed, any changes to the instrumentation or to analytical methods that improve the absolute accuracy, at the cost of increasing the measurement uncertainty will have a reduced applicability. Improved methodology should increase the statistical power of any investigation performed with the instrument, by improving its repeatability, i.e. reducing the variance associated with the measured variables. It follows that it is equally important to be able to estimate the variance associated with those variables, in order to understand the sensitivity of the experiment.

Parametric images provide an excellent summary of the measurement, embodying both the temporal information content and the spatial resolution. The discussion of statistical power in the measurement can also be reduced to a consideration of the pixel-by-pixel variance in relevant parametric images. These images are dependent on the reconstruction and pharmacokinetic analysis methods. The variance of parametric images can be used as a good indicator of the quality of the measurement. By observing the change in the variance, as a result of changes in the methodology, the
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degree of improvement can immediately be gauged.

In this section, methods for the description of signal to noise for the system will be reviewed. The variance reconstruction equation which allows image pixel variance to be estimated from a variance estimate of the projection data will be derived, since there is no explicit derivation in the literature. A justification for the assumption that the count data have a Poisson probability distribution is also given. Using these results, this thesis shows how the variance of parameter projections, which can be calculated from the known variance of the raw projection data can be used to calculate the variance of the pixels in a reconstructed parametric image (Maguire et al. 1999).

Toward the end of the section, results of pixel variance estimation are given for some extreme activity concentration distributions, to illustrate the power of the variance reconstruction equation. Finally a simulation study is used to prove that the estimates of the individual pixel variance which can be gained from a parameter projection based method are more precise than estimates from either analysis of reconstructed images, or comparison of multiple parametric images.

4.2 System estimates of variance and noise.

The issue of the individual pixel variance was addressed early in the development of Emission Computed Tomography, with the aim of deriving system estimates of the uncertainty of the measured pixel values (Budinger et al. 1977). This culminated in the definition of the system parameter 'noise equivalent counts' (NEC), which has been described in a previous section.

Models used to estimate the pixel noise used to estimate the pixel variances and NEC were constructed based on considerations of the number of reconstructed elements - pixels, and the number of acquired counts per acquisition plane. This effectively means that the point spread function PSF, which describes the smoothness - a measure of the inter-
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Pixel correlation - in the final image, is fixed. Following from this assumption, a 'rule of thumb' was empirically derived (Budinger et al. 1978) for the signal to noise ratio of each pixel in the image $S$, using the total number of events detected $K$, and the total number of image elements $N$:

$$S = 0.83 \frac{K^{1/4}}{N^{1/2}}$$

(4.1)

Further work however, took a more direct approach to calculating the individual pixel variance (Alpert et al. 1982), by decomposing the reconstruction algorithm, and considering the propagation of variance from the coincidence measurements, to the images. Using direct variance combination rules for a linear function of $x$, $f(x)$, namely:

$$\sigma_{f(x)}^2 = f^2(\sigma_x)$$

(4.2)

the reconstruction equation (1.9) was modified to yield a new variance reconstruction operator. Assuming that the projection values had a Poisson distribution, and further that the projection value itself was a good estimate of the mean value of the population, an equation for the individual pixel error was derived. In the next section, a full derivation of the reconstruction function is described, based on that for transmission tomography.

4.3 Derivation of the emission tomography variance reconstruction equation.

The following derivation of the rigorous expression for signal to noise ratio follows the derivation by (Barrett and Swindell, 1982) (their section 10.5.2). In their text they refer to a radiological image such as in computerised tomography. In that case a measurement very similar to a PET transmission scan is performed with an external source. Transmitted photons are detected by a detector or array of detectors on the distal side of the patient. The Radon transform of the attenuation can be calculated:
where $\lambda_y$ is the Radon transform for a discrete detector in the imaging system with co-ordinates $[l,j]$.

$N_y$ are the counts recorded during an acquisition and $N_0$ is the source strength in counts (during the acquisition).

In the PET imaging system the Radon transform in 2D is measured by one coincidence channel, similarly with co-ordinates $[l,j]$ in the imaging system. The equivalent Radon transform is then simply:

$$\lambda_y = K_y$$

where $\lambda_y$ is, as above and $K_y$ are the counts recorded during an acquisition.

Since the logarithmic term is not present in this equation system, the derivation of expression for SNR is simplified.

A random variable $\Delta N_y$ is defined:

$$\Delta N_y = N_y - \bar{N}_y$$

where $\bar{N}_y$ is the mean of the counts per channel over all channels. Following from the Poisson nature of the distribution of the counts, the expected value of the product of this variable for two statistically independent channels is:

$$\langle \Delta N_y \Delta N_{y'} \rangle = N_y \delta_{y' y}$$

where $\delta_{y_y}$ is the Kronecker symbol, as defined in the original text. So the expectation value is equal to the mean of the counts when $l=l'$ and $j=j'$ and is zero everywhere else. From (4.3) then:
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\[ \langle \Delta \lambda_y \Delta \lambda_{y'} \rangle = N_y \delta_{y'y} \] (4.7)

Using these equations and shifting from the discrete detector space \([l,j]\) to the continuous 2D image space \([x,\phi]\) with the following definitions:

\[ \delta_{y'y} = \delta((x_j) - (x_i),) \Delta x \] (4.8)

\[ \delta_{y'y} = \delta(\phi_i - \phi_j) \Delta \phi \] (4.9)

\[ \Delta \phi = \frac{\pi}{M} \] (4.10)

where \(M\) is the number of projection angles, expression (4.6) above is rewritten:

\[ \langle \Delta \lambda_y(x_r) \Delta \lambda_y(x_r + X) \rangle = \frac{\pi}{M} \pi_0(x_r) \delta(X) \delta(\phi - \phi') \] (4.11)

\(X\) is a linear distance in the \(x\), dimension

\(\phi\) and \(\Delta \phi\) are the projection angle and angular sampling, respectively.

\(\pi_0(x_r)\) is defined by the following expression,

\[ \pi_0(x_r) = \frac{N_y}{\Delta x} \] (4.12)

where \(\Delta x\) is the sampling width, i.e. the coverage of one channel in the \(x\), direction.

The normally operational equation for filtered back projection is restated:

\[ \langle c(r,\theta) \rangle = \frac{M}{\pi} \int_0^\pi d\phi \pi_0(x_r) \otimes q_i(x_r) \] (4.13)
where \( c(r,\theta) \) is the estimate of the activity at point \((r,\theta)\) in the image space and

\[ q_i(x_r) \] is a 1D back projection filter, which may also contain scaling factors and may, in the case of PET include a normalisation for acquisition time. As above a zero mean random variable for the activity estimate can be defined as follows:

\[
\Delta c(r,\theta) = c(r,\theta) - \langle c(r,\theta) \rangle
\]

\[
= \frac{M}{\pi} \int_0^\pi d\phi \{ \Delta \lambda_\phi(x_r) \otimes q_i(x_r) \}_{x_r = \cos(\theta - \phi)}
\]

\[
= \frac{M}{\pi} \int_0^\pi d\phi \int_{-\infty}^\infty dx \Delta \lambda_\phi(x_r) q_i[r \cos(\theta - \phi) - x_r]
\]

The variance of this random variable is defined as:

\[
\sigma^2_c(r,\theta) = \langle [c(r,\theta)]^2 \rangle
\]

Substituting (4.13) into this expression, rearranging and simplifying:

\[
\sigma^2_c(r,\theta) = \frac{M}{\pi} \int_0^\pi d\phi \int_{-\infty}^\infty dx \left[ q_i[r \cos(\theta - \phi) - x_r]\right]^2
\]

\[
= \frac{M}{\pi} \int_0^\pi d\phi \int_{-\infty}^\infty dx \left[ q_i[r \cos(\theta - \phi) - x_r]\right]^2
\]

\[
= \frac{M}{\pi} \int_0^\pi d\phi \int_{-\infty}^\infty dx \left[ q_i[r \cos(\theta - \phi) - x_r]\right]^2
\]

Note this expression deviates from 10.178 (Barrett and Swindell) in the respect that the variance at a point is now
directly related to the number of counts in a channel. This is exactly the same result as previously shown, without derivation, in the literature (Alpert et al. 1982), where the expected value of each projection element is approximated by the actual measured value.

4.4 Correlations between pixels

The derivation given in the last section is valid for individual pixels. In PET it is often the aim to examine a large measurement volume in a subject, which is expected to exhibit homogeneous pharmacokinetic properties since it contains similar tissue e.g. a region of cerebral cortex or an organ such as the liver. This is done by calculating an average value of all the pixels within that region. The variance of this mean is difficult to calculate, since there is a co-variance between each of the individual pixel values that contribute to it.

It can be seen that this correlation arises by considering the estimation of a pixel's value from the projection measurements, as seen in the last derivation. Since each projection measurement value will contribute to more than one pixel - it will contribute to all the pixels along the line over which it is back projected. The correlation of pixels will depend on their distance from one another, such that pixels that are closer will have a higher correlation coefficient than those further away will, with the effect decreasing in proportion to the PSF of reconstruction. Thus if an image is reconstructed with a broader - smoother - filter, the PSF will be broader and covariance between a pixel and its neighbours will be present over larger radius. Indeed the variance and covariance depend on the object and are non-stationary within the image plane, over the object as a whole, and also locally near boundaries in the object distribution - at the edges (Wilson et al. 1991).

However, the projections themselves, are independent measurements of the tracer distribution, thus if the original projections, corresponding to any region can be identified,
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Then it should be possible to evaluate the variance for a region, starting using an equation similar to (4.20) variance reconstruction. In fact it has been shown (Huesman, 1984) that it is possible to pre-compute the constant variance magnification factor due to the convolution filter and any other constants of reconstruction and apply them to the projections, identified with the region of interest to estimate the variance very efficiently. This technique has also been extended to 3D PET measurement (Klein et al. 1997), and by carefully considering the contribution of the elements of reconstruction such as randoms, scatter and dead time, a close approximation, which does not require the projection data has been proposed (Carson et al. 1999).

In a later section, significance testing in the context of parametric imaging will be discussed, but it should be pointed out here that this method uses the concept of a region of interest driven data analysis. An alternative is the application of image statistical analysis that takes into account the inter-pixel correlation. This approach compensates for the covariance between pixels by altering the variance of the expected distribution of pixel values, depending on the smoothness of the reconstruction methods, and hence, of the final images. Prerequisites for these analyses are parametric images, and some assessment of their individual pixel variance.

4.5 Distribution of count values in projections

One of the underlying principles of radioactive decay is that the probability \( P \) of a given atomic nucleus decaying in a given time period is a constant. Now consider the random variable \( k \), which results from a sequence of \( n \) Bernoulli trials, with individual outcome probabilities \( P \) and \( (1-P) \) the probability of exactly \( k \) successes is (Goodman and Ratti, 1979):

\[
b(k,n,P) = \frac{n!}{(n-k)!k!} n^k (1-P)^{n-k} \quad (4.21)
\]
If \( n \) is large, and \( P \) is small then the probability of observing \( c \) successes can be approximated by the Poisson probability distribution:

\[
c(k, nP) = \left( \frac{(nP)^k}{k!} \right) e^{-nP}
\]  

(4.22)

Consider observing radioactive decay, by counting the number of observed events in a fixed time interval \( t \). This is analogous to performing a series of \( n \) Bernoulli trials, where \( n \) is the number of time intervals and \( P \) is the probability of a decay in a given time interval. The number of time intervals can be made arbitrarily large, so that \( P \) is arbitrarily small. If \( nP \) is large, then the probability distribution can be approximated by a normal (Gaussian) distribution with mean \( nP \) and variance \( nP \).

From this discussion, it is expected that the number of counts observed in one projection should also be governed by a Poisson probability distribution, and indeed this is the case for most situations. However, in the limit of very high or very low count rates there may be deviations from the theoretical distribution, because of corrections applied for the observed random coincidences and instrumental dead time.

### 4.6 Using parameter projections to estimate variance

Returning to equation (4.20), it is clear from this general form that the individual pixel variance of an image pixel in a parametric image might be calculated from knowledge of the variance of the projection of that parameter. Since it has been shown that such parameter projections might be calculated by general linear least squares (GLLS), then it is clear that the inaccuracy of the parameter estimates might also be estimated during regression. Referring to the equations in section 2.9 it can be shown that the errors in the parameters can be estimated from a knowledge of the (Johnson and Witchern, 1998):
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\[ \text{Cov}(k) = \sigma^2 (X'X)^{-1} \]  \hspace{1cm} (4.23)

\[ \sigma^2 = \frac{(C - Xk)(C - Xk)}{n} \]  \hspace{1cm} (4.24)

The variances of the parameter projections are now the diagonal elements of the left-hand side of equation (4.23).

It should also be noted that the general model expression previously used could also be applied to very simple models of tracer uptake, such as is generally used for the uptake of [0-15]Water. In that case, a simple integral of the observed activity concentration is used, between a time when the radioactivity reaches the capillary bed, and a time approximately 100 s later (Kanno, I et al. 1991). The pixel value of this integral is an index that is monotonically related to rCBF, for a fixed injection protocol and which can be normalised to account of the injected activity concentration. The integration can be performed on a reconstructed time sequence of images, or on the projection sinograms, with subsequent reconstruction. This can be formulated in terms of equation (2.38) by setting \( X \) as a scalar equal to one, \( k = k(r) \) is then an index that monotonically increases with increasing regional cerebral perfusion, and \( c(r,t) = c(r) \) is an integral:

\[ \sigma^2 = \frac{(C - Xk)(C - Xk)}{n} \]  \hspace{1cm} (4.25)

where \( c(r,t) \) is the activity concentration at a point in space and the integral is taken between a time point \( T_i \), a short time after injection of the tracer, and a time \( T_j \), typically 100 s after injection. Performing the integration numerically, the variance of the numerical integral can be estimated from the individual time points.
4.7 Implementation of individual pixel variance equation

Equation (4.20) can be used to estimate the individual pixel variance for a single PET reconstruction, by assuming that the measured projections, considered as random variables, are in fact good estimates of their own mean. As with all counting, governed by an underlying Poisson distribution. Since the population variance is equal to the mean, it is expected that the coefficient of variation will be:

\[ \frac{\sigma}{\mu} = \frac{\sqrt{K}}{K} = \frac{1}{\sqrt{K}} \]  (4.26)

Also, even at low total counts, the pixel estimate of variance required is estimated from a composite of projection elements, it is therefore to be expected that this coefficient of variation of this estimation will be lower than that of the projections themselves.

The attenuation correction is also often a measured variable see section 1.5, so the variance of the attenuation correction map can be calculated from the measured projections during the transmission scan and the blank scan (transmission without the object in place). However, in PET equipment, it is standard practise to smooth the transmission images, prior to the calculation of an attenuation matrix, complicating the estimation. In the case of an attenuation correction calculated from the assumption of a constant attenuation correction for brain tissue and skull, and knowledge of the contours of the head there is no variance associated with the estimate.

In implementing equation (4.20) it is noted that a convolution of each plane parallel projection with the square of the filter function is required. The filter functions which are used in PET are most easily, and accurately defined in frequency space. e.g. for the tomographic (ramp) filter:

\[ H(\nu) = \nu \]  (4.27)

and for the Hann apodising filter:
where \( H(v) \) is a function describing the filter at a particular frequency and \( v_c \) is the cut-off frequency of the filter. In computer assisted tomography, the filter functions are invariably defined in frequency space, and the convolution function is achieved by multiplying the Fourier transform of the plane parallel projection with the filter \( H(v) \).

\[
H(v) = F(h(x))
\]  

(4.29)

where \( F \) denotes the real Fourier transform operation, therefore

\[
F(h^2(x)) = H(v) \otimes H(v)
\]  

(4.30)

Due to the efficiency of the fast Fourier transform (Press et al. 1992), this equation is best implemented as a computer algorithm based on:

\[
F(h^2(x)) = H(v) \otimes H(v) = F^{-1}((F(H(v))^2)
\]  

(4.31)

In figures 23 and 24 the Hann filter and squared Hann filter are given in image space for comparison.
Figure 23 Form of the Hann filter for three different filter cut-offs, 0.2 (dotted line), 0.5 (dash-dot) and 1 (line) times the Nyquist frequency, with a projection sampling interveal of 0.31 cm.

Figure 24 Form of the squared Hann filter for three different filter cut-offs, 0.2 (dotted line), 0.5 (dash-dot) and 1 (line) times the Nyquist frequency, with projection sampling interval of 0.31 cm. Note the logarithmic scale on the dependent axis.
The form of these filters is the point spread function of the reconstructed object. Often this point spread function is approximated with a Gaussian curve, and described with a full width at half maximum, which, as can be seen from the figures above, may not be entirely appropriate.

4.8 General results.

By simulating sinogram data and adding Poisson noise, the general characteristics of the individual pixel variance, for different object configurations can be calculated. For illustration take firstly a slice through a very thin radioactive rod, with a 0.31 cm diameter at the centre of the field of view, and a similar slice through a hollow cylinder, 20 cm in diameter, with a wall of thickness 5 mm, containing a constant activity concentration. Figure 25 shows normalised profiles through the reconstructed images from both these configurations, along with normalised calculated variances, along the same profile.

Figure 25 Profiles of the normalised reconstructed image pixel values and associated variances through two object configurations - a thin rod (diameter 0.31 cm i.e. 1 reconstructed pixel) at the centre of the field of view [Image dashed line, and variance dotted line], and a hollow cylinder (20 cm in diameter with a 5 mm wall thickness) [Image dot-dash, variance solid line].
The variance estimates are smoother than the images. The point source contributes to the variance at all points along the diameter, similarly the variance at the centre of the image of the hollow cylinder due to contributions from the active wall. For these extreme conditions there is a dependence of the variance pattern on the object distribution.

The pixel variance will also be dependent on the filter used. As a lower cut-off frequency is used, the resolution of the image will degrade, but the signal to noise ratio of an individual pixel will improve. Since the filter is broader and the reconstructed image smoother, there will also be a stronger dependence between neighbouring pixels in the reconstructed image. Again, careful consideration of the hypothesis that is to be examined, and the requirement for spatial resolution should guide the choice of filter for a particular application. It may in fact be appropriate to analyse the data with different reconstruction filters, in order to obtain the best balance between signal to noise ratio and resolution.

The following series of images shows the reconstructed signal to noise ratio for a slice through a cylindrical phantom of diameter 20 cm, with two inserts - a 1 cm wide wall at the rim, and a 2.5 cm tube in the centre. The inserts have 1.2 times the activity concentration in the rest of the phantom. The activity concentration was chosen so that the simulated sinograms contained $1 \times 10^6$ events.
Figure 26. Slice through a reconstructed signal to noise ratio image of a cylindrical phantom with inserts at rim and centre (see text); reconstructed with a Hann filter cut-off at the Nyquist limit (0.5 cycles/pix).

Figure 27. Slice through a reconstructed signal to noise ratio image of a cylindrical phantom with inserts at rim and centre (see text); reconstructed with a Hann filter cut-off at 0.5 Nyquist limit.
Figure 28. Slice through a reconstructed signal to noise ratio image of a cylindrical phantom with inserts at rim and centre (see text); reconstructed with a Hann filter cut-off at 0.2 Nyquist limit.

In the last figure, a profile through the horizontal diameter of the reconstructed signal to noise image of the phantom is shown, for each of the three reconstruction cut-off frequencies.

Figure 29. Profile through three reconstructed signal to noise ratio image of a cylindrical phantom with inserts at rim and centre. The solid line represents the results for a reconstruction cut-off frequency at the Nyquist limit, and the dots and dot-dash lines at 0.2 and 0.5 times the Nyquist frequency, respectively.
As the resolution of the reconstruction is decreased, so the signal to noise ratio in individual pixels is increased along with statistical power in that region. Clearly the correlation between pixels increases, however this is simply a restatement that the resolution decreases, i.e. the number of independently measured resolution elements - RESELS - is decreased. Each pixel is a member of one or more RESELS.

In the field of positron emission tomography, this method to determine individual pixel variance has not been widely enough applied, and should be incorporated into every experimental design. Similarly, appropriate choice of filter is essential to maximisation of statistical power, indeed within the same experiment it may be necessary to reconstruct the data with multiple filter cut-offs in order to achieve the maximum statistical power for each activated region size. An analysis methodology incorporating multi-resolution reconstruction techniques would be a significant advance.

4.9 Validation of application to parameter projections

4.9.1 Method

A comparison was made between estimates of the individual pixel variance of parametric images calculated using three different methods. Firstly, calculation of the variance with subsequent back projection - projection method - secondly reconstruction of a time series of activity images and subsequent regression for each pixel independently and lastly, estimation by comparison of a series of 30 simulated parametric images. This is shown schematically in figure 30.
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Figure 30, Schematic diagram of the simulations and analyses in the validation of parameter projection variance analysis. The data sets $N_1$ to $N_{30}$ were alternatively reconstructed to sets of activity concentration images $I_1$ to $I_{30}$ or analysed to calculate sinograms containing parameter projections $P_1$ to $P_{30}$ and their variances $Z_1$ to $Z_{30}$. The images 'I' were then analysed to produce parametric images $K_1$ to $K_{30}$ and estimates of their variance $S_1^p$ to $S_{30}^p$.

Similarly, the parameter projections and variance projections 'P' and 'Z' were reconstructed to parametric images and associated variances $S_1^f$ to $S_{30}^f$. $S_1^p$ is estimated by calculating the variance between pixels of the sets of parametric images 'K'.

The simulated object was a slice through a 20 cm phantom containing two inserts, centred on one diameter of the phantom
and 5 cm from the centre, one 8 cm and the other 2 cm in diameter, as shown in figure 31.

Two configurations were used, one in which the mean activity concentration in the inserts was the same as the central compartment, and one where the inserts had an activity concentration which was 20% higher. The activity concentration in the central compartment $c(r,t)$ was governed by the following equation:

$$c(r,t) = k_1(r,t)t_1c_p + k_2(r,t)c_p$$  \hspace{1cm} (4.32)

$k_1$ and $k_2$ can be thought of as uptake and distribution parameters, similar to $K_t$ and $p$ for the Patlak model, $t_1$ is the measurement time. The other functions are - conventionally in this text - $c$, the total activity in tissue, $c_p$ the activity concentration in plasma. One simulation consisted of a full set of projections estimated using the object configuration and equation (4.32) at 10 distinct times $t_i=1..10$. $c_p$ was chosen such that the total number of counts in the sinogram was $1 \times 10^6$ for $t_i$.

Reconstructions of the images and the variance were made using a Hann filter with the cut-off set to half the Nyquist
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frequency, into a $128 \times 128$ matrix, the variances were reconstructed using equation (4.20). Signal to noise ratio images were defined as the ratio of the image to its standard deviation, as calculated by each of the three methods.

To assess the impact of differences in the technique on significance testing in image space, maps of $Z_i$, a test $Z$ statistic for the difference between contrast and no-contrast image, calculated independently for each pixel, were estimated from:

$$Z_i = \frac{k_i^c + k_i^n}{\sqrt{\sigma_{k_i^c}^2 + \sigma_{k_i^n}^2}} \sqrt{N} \tag{4.33}$$

$k_i^c$ is the estimate of the uptake rate constant at pixel 'i' in the contrast condition. $k_i^n$ is the analogous estimate for the non-contrast condition. The respective variances of these two terms appear in the denominator: $\sigma_{k_i^c}^2$ and $\sigma_{k_i^n}^2$. $N$ is the number of simulations - measurements. The $Z$-maps were calculated for two different reconstruction filters, with the cut-off frequency at the Nyquist limit and 0.2 times the Nyquist limit.

4.9.2 Results

Figure 32 shows a profile through resulting variance images from both the sinogram and image method, along a horizontal diameter through the cylinder in figure 32. The results from the projection method can be modelled as a smoothly varying function, whereas the image method estimates have much more variability.
Figure 32. Plot of the estimated pixel variance along a 0.31 cm wide profile through the horizontal diameter of a phantom containing two inserts with increased activity from one simulation. Estimates from the parameter projection method ('o') and those from the image method ('x').

In figure 33, the same profiles are shown for the images of the mean estimated variance for all three methods; projection, image and group. The estimates from the projection method are smoother than the other two methods. In central pixels there is a difference of up to 25% between the projection and the group method, but the maximum difference between the projection and image methods is 7% - this is in a single pixel which appears to be an outlier.
In figures 34 and 35 the local signal noise ratio images, calculated using standard deviation estimates from each of the three methods, are given. There is a variation of the signal to noise ratio, from the outside toward the centre of the main compartment, and from the side of the insert closest to the edge of the cylinder, toward the centre. Projection method images are smoother than the other two. The group method shows most fluctuation between neighbouring pixels. In the experiment based on only two runs the signal to noise ratio image from the group method is very difficult to interpret.

Figure 33. Plot of the average variance calculated by the projection method ('o'), image method ('x') and group method ('triangles'). Averages were made over 100 simulation sets.

Figure 34. Images of the signal to noise ratio for each of the three methods, [projection, image, group] [left, centre, right], as calculated from a set of 15 simulations.
Figure 35. Images of the signal to noise ratio for each of the three methods, [projection, image, group] [left, centre, right], as calculated from a set of two simulations.

The Z-maps for the difference between the mean pixel values in the contrast and non-contrast simulations are given in figures 36 and 37, using a reconstruction filter at the Nyquist filter and 0.2 times the Nyquist limit respectively.

Figure 36. Student's 't' maps for the difference between the contrast and no-contrast simulations, for each of the three methods, [projection, image, group] [left, centre, right], reconstructed with a filter set to a cut-off frequency at the Nyquist frequency.

Figure 37. Student's 't' maps for the difference between the contrast and no-contrast simulations, for each of the three methods, [projection, image, group] [left, centre, right], reconstructed with a filter set to a cut-off frequency of 0.2 times the Nyquist frequency.
4.9.3 Discussion

The estimations of pixel variance by each of the methods; image, projection and group have the same mean value, but differ in the precision of the estimates. The projection method is computationally more efficient than the other two methods and shows the highest precision of estimation.

By using the projection data population the projection method uses the most fundamental and complete statistical description in the variance estimation. The other image and group methods use the derived random variables, pixel activity concentration and pixel uptake variable respectively.

To see this, define a matrix $\mathbf{M}(I,J)$ containing random variables $m_{ij}$ with variance $s^2$. Now calculate the variance of the mean of the columns by two different methods.

Method a.) A mean of the columns is calculated and the estimated variance of this new random variable ($s^2_\mu$) calculated from the $J$ estimates. The expected variance $S^2_\mu$ of this variance estimate is:

$$S^2_\mu = \frac{2(s^2/(I-1))^2}{(J-1)}$$  \hspace{1cm} (4.34)

Method b.) An estimate of the variance of $m_{ij}$ is made from the columns ($s^2_\mu$) and used to calculate the expected value of the variance of the mean of the columns $s^2_\mu$:

$$s^2_\mu = \frac{s^2}{(I-1)}$$  \hspace{1cm} (4.35)

The variance $S^2_\mu$ of this random variable is predicted to be:

$$S^2_\mu = \frac{2\left(\frac{s^4}{(I-1)^2}\right)/ (I-1)/(J-1)}{(J-1)}$$  \hspace{1cm} (4.36)
Although the estimated variance of the mean $s_{\mu}^2$ of a column is identical for both methods a.) and b.), $S_o^2$ is a factor $(I-1)$ smaller than $S_u^2$; Method b. is $(I-1)$ times more precise.
5. Linear models for [0-15]Water

5.1 Introduction

This section examines the application of a linear pharmacokinetic model to the one-tissue compartment model for [0-15]water. To do this a simulation framework is built up, similar to section 2. Special attributes of the [0-15]water model are reviewed; delay, dispersion and the vascular component. An on-line plasma device, developed for quantitative measurement of [0-15]water in humans is described, as well as the rCBF measurement protocol. Using data from a large cohort of volunteers, a whole body model of rCBF is developed. This is then used as the input to a simulation of the tissue activity time course of [0-15]water in brain.

Using this simulation environment, the accuracy and precision of non-linear and linear methods to estimate rCBF are investigated and it is shown that they are very similar (Maguire et al. 1999). This means that the linear estimator has distinct advantages with respect to calculation efficiency, and the deterministic nature of linear estimation, and is therefore to be recommended.

5.2 Perfusion measurement with [0-15]Water

The time resolution of PET allows measurement of metabolic processes with time constants in the range of seconds. Coupled with the non-invasive nature of the measurement, this makes it possible to study changes in metabolic processes in real time in the living human brain. If a localised brain region associated with a certain functional task is activated then the neurones consume more energy. The increased energy demand might be met in the short term from anaerobic glycolysis, however within seconds homeostatic changes occur to increase the supply of oxygen and glucose to those regions. In fact the perfusion is increased by more than the change in the oxygen consumption, and this effect is presently not fully understood (Fox et al. 1988). This is achieved through the blood supply
to the brain, which is arranged to ensure that every volume element of the brain is constantly provided with enough oxygen and glucose. An increase in demand is reflected in a local increase in this circulation, through small (1 μm) diameter capillaries. The supply depends not only on the flow of blood through the capillaries, but also on the number of capillaries in a volume element, leading to the definition of 'perfusion' as blood flow per unit tissue mass (ml/(min·g)).

Measurement of regional cerebral perfusion, often misnamed blood flow and which will be given the abbreviation rCBF here, has been the basis of many experiments examining the function of the human brain. Since [0-15]water, a positron labelled substance, exchanges rapidly with tissue, it can be injected and its concentration change in tissue used as an indicator of local perfusion. The half-life of 0-15 is well matched to the characteristic time constant of the uptake process, which is described by a mono-exponential system response. This means that the tracer decays rapidly in comparison with the time it takes to measure perfusion, and thus repeat experiments can be performed in rapid succession. Using multiple measurements with different paradigms it is possible to identify brain areas associated with specific cognitive tasks. Since it is chemically easy to produce, [0-15]water has become the tracer of choice, although its extraction into tissue is somewhat limited (Votaw et al. 1999).

5.3 Delay and dispersion

Since the measurement time is short, the effects of delay discussed in section (3.6) are very important. The typical delay of around 20 s, may represent 20% of the total scan time. Of this delay the most important component is the difference in time between blood reaching the detector, through the radial artery, and it reaching the brain via the carotid artery.

Injection of [0-15]water is typically into an arm vein, where it travels in the blood stream via the right atrium and ventricle of the heart to the capillary bed of the lungs, to
the left atrium and ventricle, from there it is pumped into the arterial system. During this transit, the initially sharply shaped bolus pulse undergoes dispersion to a more broadly shaped activity time course, which is presented to the arteries. Since it reaches the brain some time before the radial artery, where the blood is sampled, it can undergo further dispersion, resulting in a difference in the time course measured and that in the brain.

Perhaps more importantly, blood is often sampled using a pump and detector system (see later in section 5.5). This allows a further opportunity for dispersion of the signal, especially in connectors with a large dead volume. It has been shown (Iida et al. 1988) that, within the limitations of the PET measurement, this dispersion can be modelled using a simple mono-exponential model:

\[ \frac{dc_p^*}{dt} = \frac{1}{\tau} c_p - \frac{1}{\tau} c_p^* \] (5.37)

where \( c_p \) is the activity concentration in arterial blood, and \( c_p^* \) is the dispersed activity concentration time course, measured in the detector. \( \tau \) is the dispersion time constant.

It can be seen that this model is closely related to the compartment model of the \([0-15]\)water uptake, and indeed it leads to a similar solution:

\[ c_p^* = \frac{1}{\tau} e^{-\frac{t}{\tau}} \otimes c_p \] (5.38)

If the dispersion is known, or determined by parameter estimation, then equation (5.37) can be used to correct the data, using an approximation to the differential equation's solution:

\[ c_p = \tau \frac{dc_p^*}{dt} + c_p^* \] (5.39)
5.4 Vascular component

The volume of the arterial components of the vascular system as a whole, are much smaller than the venous - 54% of the blood volume is found in the venous circulation (Ganong, 1991), 9% in the arteries, arterioles and capillaries, and the rest is in the heart, lungs and aorta. On a microscopic level, the total cross-sectional area of arterioles is 4 times smaller than that of the venules, mainly due to the thicker walls of the arterioles. For a tracer with high extraction the venous and tissue activity concentrations will be in constant equilibrium, and it will be impossible to distinguish these compartments from one another. The residual intra-vesicular blood component of the PET signal in the arterioles, which can be distinguished because of the difference in its kinetics is only around 1% of the total tissue volume, and its signal contribution is often neglected. Its inclusion has been proposed (Fujita et al. 1993), however its presence as an extra parameter reduces the precision of the flow determination.

5.5 On-line plasma measurement device

Because of the short half-life of O-15, and the relatively fast pharmacokinetics of water, accuracy of timing in the experiment is essential, as is a high temporal resolution. Unlike the [F-18]FDG experiment, where adequate timing can be accomplished, by manually sampling blood, every few minutes, blood sampling is done using an automatic sampling pump. A number of devices have been proposed for this task (Eriksson et al. 1999; Graham and Lewellen, 1993; Votaw and Shulman, 1998; Ranicar et al. 1991), those which exploit coincidence counting have a very low background counting rate.

In the experiments that will be described, the COIN-422 automatic counting device (MAGEN scientific, New York, USA) was used. This device is based around two 5 cm BGO devices switched in coincidence. It can be connected to an indwelling catheter, inserted in the radial artery, using 1 mm internal diameter PVC tubing. A peristaltic pump is connected to the
tubing on the distal side of the detector, and used to maintain a flow of sampled blood of 3 ml min⁻¹, through the sensitive volume (60 μl). This ensures that the sensitive volume is flushed once in every counting period (1 s). The device's efficiency is constant up to 1.1 MBq ml⁻¹, and its total efficiency is estimated to be 21%.

The use of a coincidence counting device for blood sampling is recommended, especially for studies with neuro-receptor ligands, which often require accurate measurement of low activity concentrations at the end of the study. In PET there are three requirements for blood counting. Continuous on-line withdrawal and measurement, the counting of samples and measurement of separated metabolites, which may also be on-line, for example by high-pressure liquid chromatography (HPLC). Since PET uses positron labelled tracers, it is most natural that a coincidence positron detection system be used as the detection method.

5.6 [0-15]water experimental

0-15 can easily be produced in a cyclotron using the N-14(d,n)0-15 reaction (Clark and Buckingham, 1975). The radioactive 0-15 can subsequently be used to oxidise Hydrogen in a burning reaction, producing a few pl of [0-15]water which are then trapped by bubbling through physiological saline solution, and injected. For the experiments described here, deuterons were not available from the 70 MeV cyclotron, and an O-16(p,pn)0-15 reaction was used to produce the oxygen. This method is rarely used, because of the availability of dedicated cyclotrons and complicates the water production, because of the low specific activity of radioactive oxygen produced. Effectively all of the target gas (18 l at STP) must be used up in a burning reaction with Hydrogen, to produce 2.5 ml of water.

In 2D tomography 1 GBq is a typical applied dose of [0-15]water, per experiment, with 6 experiments in a session, for one subject. This results in a total 'whole body effective
dose equivalent' (EDE) of 7.2 mSv per subject (Smith et al. 1994), which is substantially above the expected annual background EDE of 2 mSv. At that effective dose the incidence of long term stochastic effects is expected to be $2.8 \times 10^{-2}$ % (ICRP-60, Nov 1990), which has to be considered in the ethical context of the experiment. Using 3D tomography the same statistical power in the experiment can be achieved, using a 3 fold lower applied dose per experiment, and 3 fold decreased total EDE.

The PET measurement can be performed using 'list' mode (section 1.4) where available; because of the large variation in count rates during the study, it provides a very effective means of compressing the data at times when the count rate is low, at the start of the study. High time resolution can also be optimally used in calculating flow, delay and dispersion, without creating unnecessary large sparse spatial data sets. An alternative to this is to trigger measurement of a single integrated 120 s measurement from the point where the injected activity reaches the brain (Kanno, I et al. 1991). This is most commonly used in protocols that avoid quantification, by relying on normalisation of the data.

The experiments described here have used a high time resolution ($18 \times 10^3$ s) acquisition mode, and a longer protocol, allowing more accurate measurement of the partition coefficient component of the signal. Measurement of the blood signal was extended by 30 s, in order to account for the delay between the tomograph and blood detector measured signals.

5.7 Linear model of [O-15]Water uptake

Equation (1.19) expresses a non-linear equation which is a solution to the differential equation (1.18), however an alternative approach (Van den Hoff et al. 1993), is to integrate the differential equation:

$$c_i(T) = F \cdot \int_0^T c_p \, dt - \frac{F}{\rho_0} \int_0^T c_i \, dt$$  \hspace{1cm} (5.40)
substituting for $c_p$ in equation (5.40), from (5.39), and adding a term to account for delay:

$$c_p(T) = F \cdot \tau \cdot c_p^*(T + \Delta t) + F \int_0^t c_p^*(t + \Delta t) \, dt - \frac{F}{\rho} \int_0^t c_p(t + \Delta t) \, dt$$  \hfill (5.41)

This equation has also been derived independently (Toussaint and Meyer, 1998) and has been shown to be a special case of the analysis described by Logan (Logan et al. 1990) for receptor binding.

Since equation (5.41) is linear, a GLLS approach with the integrals and plasma term on the right hand side of the equation as basis functions can be adopted in order to estimate the flow, dispersion and partition coefficient. As with all linear methods, this has the advantage of being computationally efficient, and can be used to generate parametric images on a pixel-by-pixel basis. It can be written in the form of (2.38), however parameter projections cannot be derived, since one of the basis functions contains the tissue signal and hence has a spatial dependency. The issue of parameter variance and covariance is also unclear, and so it was decided to investigate the relative merits of direct non-linear parameter estimation, or application of equation (5.41), to parameter determination.

5.8 Plasma model

A number of plasma models for [O-15]water uptake have been proposed in the literature, mostly in order to evaluate the dosimetry of the radiotracer. Early descriptions (Bigler et al. 1981), were extrapolated from data from long lived isotopes (C-14), and included three compartments, a central pool, and slow and fast exchanging tissue pools. More recent work, in adult humans (Smith et al. 1994) and infants (Powers et al. 1988), have proposed models based on broader sources on physiological constants in man, and the latter of these has measured the biological half-life in the peripheral circulation in man as an extra variable.
The purpose of this experiment was to determine whether the two tissue-compartment model of water clearance from plasma was indeed appropriate to explain the measured data, and to determine the physiological constants associated with it, allowing simulation.

5.8.1 Methods

Twelve healthy volunteers were recruited to a study into the functional expression of reward in humans. Each was studied 6 times with slightly varying paradigms, the activity time course in whole blood was automatically sampled in each case, (MAGEN COIN 422 detector, MAGEN scientific, New York, USA) with a time resolution of 1 s. One data set was rejected because of technical difficulties in recording. Each of the model configurations in figure 38 was implemented in MATLAB 5.3, using the ordinary differential equation integrator, which implements the Runge-Kutta algorithm (Press et al. 1992).

Figure 38. The most complex [O-15]water plasma model configuration (CM+). $k_1$ represents the rate of activity concentration injection, $k_1$ and $k_2$ are the uptake and washout from the fast exchanging compartment, $k_3$ and $k_4$ are the uptake and washout from a second, slower exchanging compartment. Delay and dispersion are included between the plasma pool and the measuring instrument.
The model in figure 38 is the most complex in a hierarchical set. The simplest model (SM) has $k_j$ and $k_s$ set to zero, that is there is no further route of sequestration of [O-15]water from plasma, except the fast exchanging compartment. A more complex model (CM), which is identical to SM, but has a $k_i$, allowing another path for loss of activity from the central compartment, and the most complex model (CM+), which has two tissue-compartment, and thus $k_j$ and $k_s$. For all the models, $k_i$ is defined, just as for [F-18]FDG (section 3.6).

The input was modelled as a constant 5 s infusion, although it was delivered as a bolus injection each time. The simplex algorithm (Nelder and Mead, 1965) was used to fit each of the models to the data sets. Early parts of the curve, up to the arrival of the activity at the detector were not included in the estimation. The fitting procedure was repeated for both the full 3.5 min of data and a subset of only 2 min that is more representative of a more commonly applied measurement protocol.

Only time points after the point where the activity concentration exceeded 20% of the peak were included in the parameter estimation.

5.8.2 Results

The results of fitting the 3.5 min and 2 min data sets are given in Tables 12 and 13. Note that the coefficient of variation is a measure of the population spread. The medians were derived from 71 data sets, thus the standard error of each mean is expected to be around 8 times smaller than the coefficient of variation.
Table 12. Medians of the parameters determined using each of the models, using the whole (3.5 min) time set of data. Coefficients of variation COV (%) are given in brackets.

<table>
<thead>
<tr>
<th>Model</th>
<th>$k_i$</th>
<th>$k_j$</th>
<th>$k_2$</th>
<th>$k_3$</th>
<th>$k_4$</th>
<th>Delay ($\Delta t$)</th>
<th>Disp. ($\tau$)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$X \times 10^4$</td>
<td>(min$^{-1}$)</td>
<td>(min$^{-1}$)</td>
<td>(min$^{-1}$)</td>
<td>(min$^{-1}$)</td>
<td>(min)</td>
<td>(min)</td>
</tr>
<tr>
<td>CM+</td>
<td>4.0</td>
<td>2.6</td>
<td>0.80</td>
<td>1.0</td>
<td>0.092</td>
<td>0.56</td>
<td>0.12</td>
</tr>
<tr>
<td>COV%</td>
<td>(40)</td>
<td>(30)</td>
<td>(20)</td>
<td>(40)</td>
<td>(50)</td>
<td>(20)</td>
<td>(10)</td>
</tr>
<tr>
<td>CM</td>
<td>4.3</td>
<td>3.0</td>
<td>0.73</td>
<td>0.82</td>
<td>-</td>
<td>0.56</td>
<td>0.12</td>
</tr>
<tr>
<td>COV%</td>
<td>(40)</td>
<td>(30)</td>
<td>(30)</td>
<td>(40)</td>
<td>-</td>
<td>(20)</td>
<td>(30)</td>
</tr>
<tr>
<td>SM</td>
<td>3.4</td>
<td>2.8</td>
<td>0.41</td>
<td>-</td>
<td>-</td>
<td>0.58</td>
<td>0.084</td>
</tr>
<tr>
<td>COV%</td>
<td>(40)</td>
<td>(30)</td>
<td>(20)</td>
<td>-</td>
<td>-</td>
<td>(20)</td>
<td>(40)</td>
</tr>
</tbody>
</table>
Table 13. Medians of the parameters determined using each of the models, using the whole (2 min) time set of data. Coefficients of variation COV (%) are given in brackets.

<table>
<thead>
<tr>
<th>Model</th>
<th>$k_1$</th>
<th>$k_2$</th>
<th>$k_3$</th>
<th>$k_4$</th>
<th>Delay ($\Delta t$)</th>
<th>Disp. ($\tau$)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>X 10$^6$</td>
<td>(min$^{-1}$)</td>
<td>(min$^{-1}$)</td>
<td>(min$^{-1}$)</td>
<td>(min)</td>
<td>(min)</td>
</tr>
<tr>
<td></td>
<td>(Bq/(ml.min))</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CM+</td>
<td>4.1</td>
<td>2.6</td>
<td>0.81</td>
<td>1.2</td>
<td>0.092</td>
<td>0.56</td>
</tr>
<tr>
<td>COV%</td>
<td>(30)</td>
<td>(40)</td>
<td>(30)</td>
<td>(40)</td>
<td>(100)</td>
<td>(20)</td>
</tr>
<tr>
<td>CM</td>
<td>4.4</td>
<td>3.0</td>
<td>0.84</td>
<td>0.93</td>
<td>-</td>
<td>0.56</td>
</tr>
<tr>
<td>COV%</td>
<td>(30)</td>
<td>(30)</td>
<td>(50)</td>
<td>(60)</td>
<td>(20)</td>
<td>(20)</td>
</tr>
<tr>
<td>SM</td>
<td>3.5</td>
<td>2.9</td>
<td>0.46</td>
<td>-</td>
<td>-</td>
<td>0.58</td>
</tr>
<tr>
<td>COV%</td>
<td>(40)</td>
<td>(30)</td>
<td>(20)</td>
<td></td>
<td>(20)</td>
<td>(20)</td>
</tr>
</tbody>
</table>

Analysis of the residual sum of squares, using the F-test showed that CM was superior to SM in 89% of the data sets, and that CM+ was superior to CM in only 17% of cases. Using reference values for the plasma volume of 3500 ml (Ganong, 1991), and the injection time of 5 s, the injected activity for CM was calculated from equation (3.3) to be $1.2 \times 10^9$ Bq. This is in good agreement with the target injected activity of $1 \times 10^9$ Bq. From $k_1$ and $k_2$, the partition coefficient of the volume of distribution of the (fast exchanging) tissue compartment, was estimated to be 12.5 l. The volumes for the fast and slow exchanging compartment volumes of model CM+ were estimated to be 2.4 and 45 l respectively. Figures 39 shows a comparison of the fits using a typical blood curve.
Figure 39. Typical measured plasma curve, and fitted curves, for the SM(−), CM(−), and CM+(...) models are shown.

At the start of the experiment there is still some residual activity in plasma - up to around 30 s. This is the reason for restricting the data used for parameter estimation to later times. On the scale of figure 39, all three curves can be seen to explain the measured data quite well, although deviation of the SM model is apparent even at this level of detail.
Figure 40. Activation concentration peak of the data shown in figure 39, between 0.4 and 1.1 min. Fitted curves, for the SM(-), CM(-), and CM+(...) models are shown.

The peak is located after the phase of infusion, and represents the transition between infusion, and the washout phase. In both the infusion and washout phases around the peak, the data in this example are well explained by all three models. Especially in the washout phase there appear to be trends in the residual differences between the fitted and measured curves for SM. Figure 40 shows a larger scale graph of the data and model estimations around the time course peak. For this data set, the model functions pass below the maximum measured activity concentration.
At late time points there are marked differences between the time courses of the fitted curves for CM and CM+, and that for SM. CM and CM+ seem to explain the data well for these times.

There is good agreement between the estimated delay and dispersion components between the CM and CM+ models, for both the 2 min and 3 min data. The dispersion estimation of the SM model was much lower, indicating that the missing $k_3$ component when comparing with CM, was partially compensated for in the dispersion.

Both CM and CM+ exhibited similar fitted $k_1$ values, and the extra (spurious) $k_1$ fitted in the CM+ model was an order of magnitude smaller.

5.8.3 Discussion

The results of the F-tests show that CM is a more appropriate model to explain the measured data than SM, in the majority of cases. This means that CM is really necessary to explain the data. However CM+ was only more appropriate in a small
minority of cases when compared to CM. It can therefore be concluded, from the normal interpretation of the F-test in this context, that in the majority of cases extra parameters in CM+ are associated with the noise in the data, rather than underlying physical processes. CM is therefore the model of choice for the experimental set up and data sets which have been measured.

Comparison of the plasma volume, derived from the median $k_i$ values, with the expected value in human controls, gives confidence in the interpretation of the model parameters. Since SM did not include a $k_3$ component, it was unable to explain the later time points in the data set. The differences between the SM and CM models can be seen in figure 41. The value for $k_3$, estimated by the CM model, is very much higher than the expected blood clearance through the kidneys (0.005 min$^{-1}$), which indicates that this clearance is not only via this pathway. More likely is clearance to a slower equilibrating compartment.

The coefficient of variation was high for all the parameters, however this can be expected because of the large variation between individuals. Subject weight, which was not controlled, will have a direct effect on all the parameters. As mentioned previously, the delay parameter includes the time between starting instrument measurement and the injection, therefore part of the standard deviation is due to non-physiological effects. $k_4$ in the CM+ model shows the largest variation in the 2 min. data sets. This is also an indication that it is a spurious parameter in the model, which will fluctuate with each idiosyncratic data set.

The deviations of all three models at the peak might be further explained by an imperfect input function. Although it was given using an infusion pump, mixing with the saline chaser may result in imperfect delivery. In order to correct for this, the infusion delivery could be monitored using a calibrated detector.
The volume of the fast equilibrating compartment found to be around 12.5 l, is slightly higher than the 9.8 l suggested for all high blood flow organs (Smith et al. 1994). Interestingly, the extracellular water volume in man is around 14 l. However if we explain the data in terms of a two compartment model, of extra- and inter-cellular water, then it should also be possible to detect these two compartments in tissue data. The Kety-Schmidt model of perfusion has always been considered sufficient to explain measured PET data, and the fractional water volume (space) seen is much larger than that expected from the extracellular water alone (Go, 1997).

In the original study, whole brain time activity courses were compared with the arterial plasma time activity curves to determine the delay and dispersion due to the measurement method. Although the delay component here also accounts for the delay between start of measurement and the injection, and is thus not comparable, the dispersion value is similar to the previously determined dispersion constant. This suggests that using the plasma model described here it might be possible to identify the dispersion component from the blood curve alone.

5.9 Accuracy of [0-15]Water linear and non-linear methods

5.9.1 Methods

The results of plasma model determination were used to generate plasma time activity courses, which were used as the input to an implementation of the Kety-Schmidt, one tissue-compartment model, with delay and dispersion implemented (sections 1.15 and 0). The noise model previously described (section 3.7.3) was used to simulate PET scanner measured data. Ideal values of perfusion and partition coefficient of water of 0.400 min⁻¹ and 0.500 respectively. The delay and dispersion parameters were both set to 10 s for the simulations, and were fitted along with the flow and partition coefficient parameters. Decay of the blood data during delay was incorporated into the simulation model and parameter estimation methods.
Two simulation studies were done, one to investigate the relative merits of the non-linear and linear fitting methods in with different noise characteristics, representative of those encountered when using both 2D and 3D PET instruments. Three sensitivities were used 1, 10 and 100 Hz/ml·Bq⁻¹.

The second simulation experiment investigated the effects of the sampling protocol on the determination of the perfusion and partition coefficient parameters. Blood sampling was assumed to consist of a series of blood samples, intervals fixed at [1, 2.5, 5, 7, 10 and 15 s]. Since the injected activity was fixed the total number of counts per sampling interval was then calculated from equation (3.15). This means that the total number of counts was proportional to the counting interval. Indeed this is the case if the sampling pump runs continuously, and the longer sampling period represents a longer integral. It is equivalent to a running average, or convolution of the blood time activity course with a constant function of width 12 s.

5.9.2 Results

Tables 14 and 15 show the results of the determination of the effects of sensitivity on the estimated parameters. The precision of both the perfusion and partition coefficient was similar for both the linear and non-linear methods, although the linear method was slightly more sensitive to increased noise at very low sensitivities.
Table 14. Non-linear estimates of the model parameters. The ideal values for Δt, τ, F, F/ρ, were 10 s, 10 s, 0.4 min⁻¹, and 0.5, respectively. The results are the medians of 50 simulations, standard deviations are given in brackets.

<table>
<thead>
<tr>
<th>Sensitivity Hz·ml·Bq⁻¹</th>
<th>Δt (min)</th>
<th>τ (min)</th>
<th>F min⁻¹</th>
<th>F/ρ min⁻¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>10.0 (0.2)</td>
<td>10.1 (0.3)</td>
<td>0.40 (0.002)</td>
<td>0.50 (0.006)</td>
</tr>
<tr>
<td>10</td>
<td>10.0 (0.2)</td>
<td>10.2 (0.2)</td>
<td>0.40 (0.002)</td>
<td>0.50 (0.005)</td>
</tr>
<tr>
<td>100</td>
<td>10.0 (0.1)</td>
<td>10.0 (0.2)</td>
<td>0.40 (0.002)</td>
<td>0.50 (0.006)</td>
</tr>
</tbody>
</table>

Both methods also showed good accuracy across all the sensitivities that were simulated. Modern commercial 3D scanners have a sensitivity that is between the highest two sensitivity measurements shown here.

Table 15. Linear (van den Hoff) estimates of the model parameters. The ideal values for Δt, τ, F, F/ρ, were 10 s, 10 s, 0.4 min⁻¹, and 0.5, respectively. The results are the medians of 50 simulations, standard deviations are given in brackets.

<table>
<thead>
<tr>
<th>Sensitivity Hz·ml·Bq⁻¹</th>
<th>Δt (min)</th>
<th>τ (min)</th>
<th>F min⁻¹</th>
<th>F/ρ min⁻¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>10.0 (0.7)</td>
<td>9.9 (0.4)</td>
<td>0.40 (0.003)</td>
<td>0.50 (0.009)</td>
</tr>
<tr>
<td>10</td>
<td>10.0 (0.1)</td>
<td>9.9 (0.3)</td>
<td>0.40 (0.003)</td>
<td>0.50 (0.006)</td>
</tr>
<tr>
<td>100</td>
<td>10.0 (0.1)</td>
<td>10.0 (0.3)</td>
<td>0.40 (0.003)</td>
<td>0.50 (0.006)</td>
</tr>
</tbody>
</table>

Tables 16 and 17 show the results of the estimation of the effect of the blood timing are given. The delay and dispersion
parameters varied strongly as the sampling interval was increased. However the perfusion and perfusion/partition coefficient ratios were not affected strongly by the change in the protocol. There was less than 1% difference in their values throughout the range of sampling intervals.

Table 16. Results of non-linear fitting of data simulated with varying plasma sampling times at a sensitivity of 50 Hz ml-Bq⁻¹. Ideal values are as in the previous table.

<table>
<thead>
<tr>
<th>Blood timing s (min)</th>
<th>Δτ (min)</th>
<th>τ (min)</th>
<th>F (min⁻¹)</th>
<th>F/ρ (min⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>10.0 (0.2)</td>
<td>10.0 (0.2)</td>
<td>0.40 (0.003)</td>
<td>0.50 (0.005)</td>
</tr>
<tr>
<td>2.5</td>
<td>10.0 (0.1)</td>
<td>10.0 (0.1)</td>
<td>0.40 (0.002)</td>
<td>0.50 (0.004)</td>
</tr>
<tr>
<td>5</td>
<td>10.0 (0.1)</td>
<td>10.0 (0.2)</td>
<td>0.40 (0.001)</td>
<td>0.50 (0.002)</td>
</tr>
<tr>
<td>7</td>
<td>10.0 (0.3)</td>
<td>10.0 (0.2)</td>
<td>0.40 (0.002)</td>
<td>0.50 (0.005)</td>
</tr>
<tr>
<td>10</td>
<td>10.0 (0.2)</td>
<td>10.4 (0.2)</td>
<td>0.40 (0.002)</td>
<td>0.50 (0.003)</td>
</tr>
<tr>
<td>15</td>
<td>10.0 (0.6)</td>
<td>10.5 (0.8)</td>
<td>0.40 (0.003)</td>
<td>0.50 (0.007)</td>
</tr>
</tbody>
</table>
Table 17. Results of linear fitting of data simulated with varying plasma sampling times at a sensitivity of 50 Hz·ml·Bq⁻¹. Ideal values are as in the previous table.

<table>
<thead>
<tr>
<th>Blood timing</th>
<th>$\Delta t$ (min)</th>
<th>$\Delta t$ (min)</th>
<th>$F$ min⁻¹</th>
<th>$F/\rho$ min⁻¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>10.0 (0.0)</td>
<td>10.0 (0.2)</td>
<td>0.40 (0.003)</td>
<td>0.50 (0.006)</td>
</tr>
<tr>
<td>2.5</td>
<td>10.0 (0.0)</td>
<td>10.0 (0.2)</td>
<td>0.40 (0.003)</td>
<td>0.50 (0.006)</td>
</tr>
<tr>
<td>5</td>
<td>10.0 (0.2)</td>
<td>10.0 (0.3)</td>
<td>0.40 (0.002)</td>
<td>0.50 (0.006)</td>
</tr>
<tr>
<td>7</td>
<td>9.0 (0.0)</td>
<td>11.3 (0.2)</td>
<td>0.40 (0.003)</td>
<td>0.49 (0.006)</td>
</tr>
<tr>
<td>10</td>
<td>9.0 (0.5)</td>
<td>11.5 (0.7)</td>
<td>0.40 (0.003)</td>
<td>0.50 (0.007)</td>
</tr>
<tr>
<td>15</td>
<td>7.5 (0.5)</td>
<td>13.3 (0.7)</td>
<td>0.40 (0.003)</td>
<td>0.50 (0.008)</td>
</tr>
</tbody>
</table>

Table 18 shows the correlation coefficients between the parameters, determined by varying the plasma measurement protocol, giving an indication of the correlations in the model. High correlations were found between delay and dispersion in the linear (−0.98) non-linear (−0.73), cases. Although the median values of the flow and partition coefficient parameters were very similar, there was only a poor correlation between individual estimates.
### Table 18. Correlation coefficients between the estimated parameters.

<table>
<thead>
<tr>
<th></th>
<th>$F'$</th>
<th>$(F/\rho)^a$</th>
<th>$\Delta t^d$</th>
<th>$\tau^d$</th>
<th>$F^i$</th>
<th>$(F/\rho)^i$</th>
<th>$\Delta t^i$</th>
<th>$\tau^i$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$F'$</td>
<td>1.00</td>
<td>0.64</td>
<td>-0.41</td>
<td>0.53</td>
<td>0.45</td>
<td>0.15</td>
<td>-0.50</td>
<td>0.47</td>
</tr>
<tr>
<td>$(F/\rho)^a$</td>
<td>0.64</td>
<td>1.00</td>
<td>-0.38</td>
<td>0.46</td>
<td>0.18</td>
<td>0.12</td>
<td>-0.27</td>
<td>0.26</td>
</tr>
<tr>
<td>$\Delta t^d$</td>
<td>-0.41</td>
<td>-0.38</td>
<td>1.00</td>
<td>-0.73</td>
<td>-0.10</td>
<td>-0.04</td>
<td>0.18</td>
<td>-0.15</td>
</tr>
<tr>
<td>$\tau^d$</td>
<td>0.53</td>
<td>0.46</td>
<td>-0.73</td>
<td>1.00</td>
<td>0.26</td>
<td>-0.02</td>
<td>-0.53</td>
<td>0.51</td>
</tr>
<tr>
<td>$F^i$</td>
<td>0.45</td>
<td>0.18</td>
<td>-0.10</td>
<td>0.26</td>
<td>1.00</td>
<td>-0.12</td>
<td>0.04</td>
<td></td>
</tr>
<tr>
<td>$(F/\rho)^i$</td>
<td>0.15</td>
<td>0.12</td>
<td>-0.04</td>
<td>-0.02</td>
<td>0.71</td>
<td>1.00</td>
<td>0.48</td>
<td>-0.56</td>
</tr>
<tr>
<td>$\Delta t^i$</td>
<td>-0.50</td>
<td>-0.27</td>
<td>-0.18</td>
<td>-0.53</td>
<td>-0.12</td>
<td>0.48</td>
<td>1.00</td>
<td>-0.98</td>
</tr>
<tr>
<td>$\tau^i$</td>
<td>0.47</td>
<td>0.26</td>
<td>-0.15</td>
<td>0.51</td>
<td>0.04</td>
<td>-0.56</td>
<td>-0.98</td>
<td>1.00</td>
</tr>
</tbody>
</table>

### 5.9.3 Discussion

Both methods are precise in the determination of perfusion and flow/perfusion ratio, although the linear method is faster and has the desirable properties of the GLLS operator. The linear method does show some bias in the estimation of perfusion.

The estimations of flow and flow partition coefficient ratio for both methods were not affected dramatically by the sensitivity of the simulated scanner. At both the higher sensitivities the accuracy was essentially the same, indicating that the noise on the plasma input curve is perhaps the limiting factor in absolute determination of cerebral perfusion, rather than the sensitivity of the camera.

When the interval between sampling was long, the delay and dispersion parameters showed coupled, positive and negative
biases, respectively. This coupling was seen to some extent during the lower sensitivity simulation experiments. Although the individual estimates of the delay and dispersion were not accurate at higher inter-sample intervals, the biases on the individual parameters cancelled. This can be seen by reference to equation (5.39), which can be written in the following discrete form:

\[ c(t) = \tau \frac{\Delta c^*(t+T)}{\Delta t} + c^*(t+T) \quad (5.42) \]

where \( T \) represents the delay. By approximating \( c^*(t+T) \):

\[ c^*(t+T) = \frac{\Delta c^*(t)}{\Delta t} T + c^*(t) \quad (5.43) \]

Substituting into (5.42) following is obtained:

\[
\Delta \left( \frac{\Delta c^*(t)}{\Delta t} T + c^*(t) \right) \\

\Rightarrow c(t) = \tau \left[ \Delta \left( \frac{\Delta c^*(t)}{\Delta t} \right) \frac{1}{\Delta t} \right] + \frac{\Delta c^*(t)}{\Delta t} T + c^*(t) \quad (5.44)
\]

\[
\Rightarrow c(t) = \tau T \left[ \frac{\Delta c^*(t)}{\Delta t} \frac{1}{\Delta t} \right] + \frac{\Delta c^*(t)}{\Delta t} + \left( \frac{\Delta c^*(t)}{\Delta t} T + c^*(t) \right) \quad (5.45)
\]

The term in braces in this equation is the numerical approximation to the second derivative of the capillary activity concentration. If this is small with respect to the other terms then:

\[ c(t) = \frac{\Delta c^*(t)}{\Delta t} (\tau + T) + c^*(t) \quad (5.46) \]

From this equation it is clear why the dispersion constant and delay are correlated.

The observed poor correlation of the estimates of flow and partition coefficient between the two methods is at first surprising. However the correlation does depend on the range
of potential values; the flow and partition coefficient were constant for all of the measurements. This means that the estimates were randomly distributed around the ideal value. Had the flow and partition coefficient values been varied over a wider range, a higher correlation might have been observed. Within the range bounds which were used, correlations between flow or partition coefficient and delay and dispersion were also observed, indicating extra degrees of freedom in the non-linear and linear solutions which help to explain the poor correlation.

The precision and accuracy of the linear method encourages its use. Since the method is linear it can easily be applied to make pixel by pixel estimates of these parameters, and hence parametric images.
6. Statistical mapping in projection space

In previous chapters it has been shown that the concept of parameter projections provides a simple conceptual basis for the combination of the Radon transform and particular pharmacokinetic models. It has also been shown that the precision of estimation of parameters of the model, which are of physiological interest, is comparable to the non-linear methods, and that there are circumstances where the estimation in parameter space shows distinct advantages in computational speed and in calculation of raw pixel-wise Z-maps of differences between conditions.

In this chapter, the application of a parameter projection based method to the estimation of perfusion using [0-15]water will be given. This combines the theoretical issues already discussed in the previous chapters, with the practical issues of data analysis, and the restrictions of inter-subject variability in PET. It is shown how the concepts previously introduced can be extended to the domain of statistical parametric mapping, allowing the assessment of significant change due to neuronal activation.

6.1 Measured [0-15]water tissue data

The data previously mentioned in section 5.8.1 were used. Of the twelve subjects in the original study, only 10 tissue data sets were usable, due to technical problems with the tomograph during the study. The subjects were all healthy males in the age range 22-37. They were introduced into the scanner and positioned as for the FDG experiment, described in 3.2. Transmission scans were performed in order to correct for the attenuation.

In the experimental design, the subjects were asked to perform a task, where they reacted to a random image, presented on a screen in front of them, by pressing a button. An appropriate response was reinforced either with a simple acknowledgement of success, or with a monetary reward. Images were presented in pairs, and the subject had to learn the appropriate
response (pressing the button, or no response), which was coupled to each of the pair of images. In this way, the difference in the reward activation pattern, between acknowledgement and monetary reward could be examined (Thut et al. 1997).

[0-15] water (1 GBq) was introduced into an arm vein, shortly before the task began, and a series of $18 \times 10$ s acquisitions were performed. The plasma activity concentration level was determined, using an on-line plasma sampling detector (section 5.5).

The current data sets were measured on a scanner with a limited 5.6 cm field of view in the axial direction. Since the brain is some 14 cm from its most apical to basal point, this means that the entire brain cannot be measured with a single study. In the current experiment, each condition was measured twice, once with the lower half of the subject's brain in the scanner field of view. The second measurement was made with the subject translated approximately 5.6 cm in the direction of the feet (this distance was measured accurately each time with a scale fixed to the patient bed, and recorded with the scan).

A separate set of parametric images was generated for the two data sets gathered at the different positions, using the same task, and protocol. The translational data and knowledge of the orientation of the scanner's field of view with respect to the bed were used to re-interpolate the data to a single data set with $14 \times 8$ mm slices, which incorporated the whole brain.

6.2 Van den Hoff method applied to parameter projections

As has been stated 2.9, the parameter projection concept requires that the functions of the design matrix of the GLLS expression of the model should not contain any dependence on space. This is unfortunately the case in equation (5.41), thus precluding its translation into a form which will allow GLLS estimation of parameter projections.
Statistical mapping in projection space 157

One approach to this challenge is to use an approximation. If the operational equation excluding corrections for delay and dispersion is considered:

\[ c_i(T) = F \cdot \int_0^T c_a \, dt - \frac{F}{\rho} \int_0^T c_i \, dt \quad (6.1) \]

and the \( c_i \) term on the right hand side is substituted from the equation itself, then:

\[ c_i(T) = F \cdot \int_0^T c_a \, dt - \frac{F}{\rho} \int_0^T \left\{ F \cdot \int_0^T c_a \, ds - \frac{F}{\rho} \int_0^T c_i \, ds \right\} \, dt \quad (6.2) \]

rearranging:

\[ c_i(T) = F \cdot \int_0^T c_a \, dt - \frac{F^2}{\rho} \int_0^T \int_0^T c_a \, dts + \left( \frac{F}{\rho} \right)^2 \int_0^T \int_0^T \int_0^T c_i \, dsdt \quad (6.3) \]

It is possible to continue this substitution to yield a series of nested integrals in terms of powers of \( \left( \frac{F}{\rho^{-1}} \right)^n \) where \( n=2,3,... \)

thus:

\[ c_i(T) = \sum_{n=1}^{N} \left( \frac{F}{\rho^{-1}} \right)^n \int_0^t c_a \, dt + \left( \frac{F}{\rho} \right)^n \int_0^t c_i \, dt \quad (6.4) \]

where the symbolism \( \int_0^t \) represents the 'n-fold' integral with respect to time of \( c_a \) or \( c_i \).

Tissue activity time courses were calculated for the parameter combination \( F=0.4 \) and \( \rho=0.8 \), typical values in the [0-15] water experiment. In figure 42, the simulated capillary arterial activity time course is shown with a noise free tissue activity time course, along with approximations using equation (6.4) truncated at \( n=1 \) to 4.
Figure 42. Time activity course of equation (6.4) truncated at different 'n' (-). The time course of the capillary arterial activity time course is also given (...), and the ideal tissue time course for perfusion and washout constant of 0.4 min⁻¹ and 0.8 min⁻¹.

If equation (6.4) is truncated at the first member i.e. \( n=1 \), the following is obtained:

\[
c_1(T) = F \int_0^T c_a \, dt - \frac{F^2}{\rho} \int_0^T \int_0^t c_a \, dt \, ds
\]

(6.5)

If considered in the GLLS model representation, it can be seen that the design matrix functions are now independent of space, so that the model can be applied to projections, using the previous formalism. Using GLLS and this truncation to estimate the parameters of the simulated time course in figure 42 gave the result, which is plotted in figure 43.
Figure 43. Estimated time tissue time course from equation (6.5) using GLLS (-). The time course of the capillary arterial activity time course is also given (...), and the ideal tissue time course for perfusion and washout constant of 0.4 min⁻¹ and 0.8 min⁻¹.

If the equation (6.5) including delay and dispersion components is integrated over a set of volume elements V, within which the dispersion and delay are constant the following is obtained:

\[
\int_{V} c_{r}(r,T) dv = \int_{V} \left\{ F \cdot r \cdot c_{a}^{*}(T + \Delta t) + F \cdot \int_{0}^{T} c_{a}(t + \Delta t) dt - \frac{F^2}{\rho} \int_{V} \int_{0}^{T} c_{a}(t + \Delta t) dtds \right\} dv \quad (6.6)
\]

where \( r \) is a vector locating an activity concentration \( c_{r} \) in space. Rearranging yields:

\[
\int_{V} c_{r}(r,T) dv = \tau \cdot c_{a}^{*}(T + \Delta t) \int_{V} F dv + \int_{V} c_{a}(t + \Delta t) dt \int_{V} F dv - \frac{F^2}{\rho} \int_{V} \int_{0}^{T} c_{a}(t + \Delta t) dtds \int_{V} dv \quad (6.7)
\]

This equation can immediately be cast in the GLLS form and used to solve for the constant \( \tau \) and \( \Delta t \) in the volume \( V \). Note that \( V \) might also be the set of volume elements subtended by a LOR, if the integration is carried out along a LOR then the term on the left hand side are the projection data. Since the
delay might be expected to depend on the distance of a tissue volume element from the heart, it was decided to assume constant delay and dispersion throughout a plane.

Equation (6.7) was applied on a plane by plane basis, regressing the total integral of all counts in the projections of a plane, against the plasma integrals on the right hand side of the equation. The delay and dispersion constants were then estimated from the regression coefficients, for each plane.

6.3 Spatial normalisation

Since each individual subject has unique brain morphology, it is necessary to spatially transform images, before they can be compared on a pixel-by-pixel basis. The transformation involves determining a new location for each element in a standardised space, in which the relationship between position and neuro-anatomy is fixed.

Spatial normalisation was achieved in this study using rigid body geometry translations and rotations, and scaling along 3 axes (Woods et al. 1998; Ashburner and Friston, 1997). Parametric images of flow, were compared with a standard template, normalised in the space of the stereotactic atlas of Talairach and Tournoux (Talairach and Tournoux, 1988), and using an iterative procedure, a best estimator of the rigid body transforms was obtained. This mapping between the measurement geometry and the stereotactic space allowed resampling of the measured data matrix, to a matrix representing standard space. Likewise, the estimated variance of a parameter projection can be spatially normalised, observing that any fractions and scaling factors employed in interpolation steps should be squared, when calculating variances.

For the current study, nearest neighbour interpolation was used, simplifying the calculations for the variances. This results in a final volume, in which large differences between pixels can be observed. The intrinsic smoothing of other
window functions may result in a normalised volume, in which each voxel element has been more optimally sampled from the original space.

6.4 Statistical maps

In PET activation studies using [0-15]water, one of the main aims is to locate the loci of change of neuronal activation through changes in flow between two separate measurements, or groups of measurements.

One of the most important developments in PET in the last 15 years has been the introduction of image statistical techniques into the assessment of the significance of differences between parametric images acquired in different states of neuronal activation or pathology.

Early work considered local signal to noise ratio images (Z-maps), formed by calculating the difference between sets of parametric images acquired in different conditions. Repetitions were performed in single subjects allowing individual pixel variances to be calculated and hence local signal to noise ratio images for the difference between conditions. At points where there is a neuronal activation, this signal to noise ratio will be larger than in areas without activation. However pixels in the parametric images and hence signal to noise images are not independent, because of the filtering discussed in section 4.7. This means that at a given statistical threshold, clusters of pixels will be observed. The aim of statistical image analysis is to assess the statistical significance of these excursion sets.

Correction for multiple comparisons in the signal to noise ratio images (Friston et al. 1991) can be achieved by modifying the threshold of significance based on the number of independent regions in the image. This method, although conservative, provided enough statistical power to yield interesting results. Further research in the early 1990's led to the development of more sensitive and general analyses based on the concept of Gaussian random fields (Worsley et al.)
Statistical mapping in projection space

If a description of the smoothness of the image (the inter-pixel correlation / the resolution of the image) then the distribution of number of pixels which might be expected to exceed a certain threshold can be calculated. Similarly, the highest pixel value in an excursion cluster can also be described statistically. Using this information, significance can be assigned to the number of clusters, the cluster sizes and the maximum SNR values, found above a certain threshold.

Concurrently with the development of the image statistical methods necessary to assess the significance of excursion sets in Z-maps, a general linear framework for the testing of significant differences was established. Both of these developments, combined with normalisation of the co-ordinate systems have resulted in the MATLAB application SPM (Functional Imaging Lab., Welcome Institute, London, UK), which has become a standard in the field (Frackowiak et al. 1997).

As has been seen in chapter 4, variances of parameter projections can be calculated and reprojected to form accurate and precise estimates of the individual pixel variances. Using the estimates of the variance of the parameter projections, it would be possible to calculate an estimate of the ratio of the mean to the standard deviation for each of the sinogram elements. This would potentially allow statistical testing in projection space. However it is the real space location of significant differences that is the real goal. In order to construct an image space map of the observed mean to standard deviation ratio for the differences between two observations, the means and the standard deviations of that difference need to be known. It is in fact not useful to construct statistical maps in sinogram space as has previously been done (Cherry et al. 1993), unless the proposed statistical test is designed to test for differences along LORs.
6.5 Comparison of statistical maps

6.5.1 Methods

Equation (6.7) was applied on a plane by plane basis, regressing the total integral of all counts in the projections of a plane, against the plasma integrals on the right hand side of the equation. The delay and dispersion constants were then estimated from the regression coefficients, for each plane. Using equation (6.5) flow parameter projections were estimated on a element-by-element basis in the sinogram sets of the data described in section 6.1, and reconstructed using a Hann filter with the cut-off at 0.8 times the Nyquist frequency. The variances of the flow parameter were also estimated, and back projected appropriately in order to estimate the individual pixel variances in the final image. Only the measured data from the time of injection to 120 s was considered.

For comparison, each of the 18 images of the time sequence was also back projected using the same reconstruction parameters, and equation (5.40) was used to estimate the flow on a pixel-by-pixel basis. Similarly estimations based on the projections, the delay and dispersion parameters were determined from the total counts independently for each tomographic slice.

The images were then spatially normalised using the SPM96 software (Welcome trust functional imaging laboratory, London, UK). Variance images were also normalised using extensions to handle the pixel-by-pixel variances.

From these normalised images, two variance estimates analogous to the image and projection methods in chapter 4 were used to calculate pixel-by-pixel difference images between the activation condition ('monetary reward') and the control condition ('acknowledgement'). The signal-to-noise ratio of these images (uncorrected Z-maps) were then calculated using the estimations of the variance from the two methods.
The flow estimations from the image based calculation were compared with the sinogram approximation, by plotting individual pixel values from each method. Their covariance was assessed by estimating the centroid of the data, and a set of ellipses, enclosing proportions of the data, with their major and minor axes aligned along the regression line and a line perpendicular to it.

6.5.2 Results

In figure 44 a comparison between the estimated flow values using the sinogram method, which involves the approximation of equation (6.5), and the image method, which avoids the approximation is shown.

![Figure 44. Comparison of the estimated blood flows. Individual points are a subset of each 300° point in the data matrix. Only those points with blood flows > 0 were considered. The regression line (...) is also given, along with confidence intervals containing 50 % and 90 % of the data.](image)

The estimated flows using the approximation correlate well with those from the exact method, and exhibit similar precision. The regression line indicates that there is a 52 % difference in the mean values, although there is no offset. The range of the exact image method is similar to that in the
published literature, and the projection approximation is thus lower than expected. The correlation contours show that the standard deviations of the individual estimates is similar. In figure 45, normalised variance images are shown from the projection method. A barred pattern is clearly visible, due to the alternating high and low variance of the individual acquisition planes of the camera.

In figure 46, the analogous variance pattern is shown for the exact image method. These images show patterns that indicate the underlying functional images, i.e. they show higher variance in the cortex where there is high uptake. On the most basal images in the set, in the bottom right hand corner, high variance is apparent around large blood vessels supplying the brain. This patterning can be traced in more apical images, indicating the pathway of the vessels. The barred pattern, due to interpolation, is not as apparent in these images.
Figure 45. Variance maps from the sinogram approximation method. The variance images have been normalised to $2 \times 10^4$. From the top of the brain, the slices read left to right, top to bottom in the figure, each is an 8 mm slice from the Montreal Neurological Institute Standard Brain, based on the Talairach atlas.
Finally, in figures 47 and 48, maps of the mean difference to standard deviation statistical maps are given. Activated regions coincide in the frontal regions of slices 8 to 11, however there is a marked difference in the extent of the activation on slice 9. The image method also shows activation in the thalamus, which the projection method did not reveal, and the projection method shows activations on slices 13-15, which were not confirmed by the exact image method.

Figure 46. Variance maps from the exact image method. The variance images have been normalised to $2 \times 10^4$. 
Figure 47. Pixelwise maps of the mean to standard deviation ratio overlaid on the mean rCBF for the activation condition. The rCBF images have been rescaled by a factor 5. Black areas are ratios above 35.
Figure 48. Pixelwise maps of the mean to standard deviation ratio overlaid on the mean rCBF for the exact image method. The rCBF values have been rescaled by a factor 8. Black areas are ratios above 35.

6.5.3 Discussion

The projection approximation is less precise than the exact image method, when calculating regional cerebral blood flow. Rather than an absolute measure of perfusion, it is an index, which correlates well with the actual measured perfusion, as estimated by the image method. The advantage of the projection approximation is that it provides access to the projection data using the one tissue-compartment model, which is suitable
for [0-15] water, and thus has the advantage of calculation speed.

The variance maps showed different characteristics, and in the image variance maps the inability of the model to explain the data in regions of high blood volume (the large arteries) was clear. Since this effect is a deviation from the linear assumptions of the model, it is possible that the projection method is unable to spatially locate the areas where the rCBV differs. That is the concept of parameter projection breaks down for a non-linear analysis, which is effectively true in those regions where the blood volume is very high.

All subjects were measured with similar 'pitch angle', that is the rotation between the atlas and measurement co-ordinate systems, about the mid-hemispheric plane of the brain. This was ensured by aligning the subjects with the camera field of view using an in-built LASER positioning system. The barred pattern on the projection method estimates would therefore be expected, and it is surprising that it is not seen on the images calculated using the image method. The previous results on simulated data have shown that random variance components can be accurately estimated by both methods, albeit with an increased accuracy for the sinogram estimation. This would suggest that there are differences in the way in which systematic errors, and inadequacies in the model are handled by both methods.

Without a gold standard it is difficult to assess which of the two mean to standard deviation images represents the most true pattern of activation. Both show similar areas in the frontal cortex already identified as being associated with reward in humans, but there are also differences in the patterns. Based on the results of the simulation experiments it is tempting to assume that the projection method would produce fewer false positives, since random fluctuations in the image are smaller. However the current data may not be sufficiently precise to draw those conclusions. The results do however encourage the exploration of the technique of variance calculation using
projection data as a means to improve statistical testing in the image domain.
The central theme of this thesis has been to examine the possibility of the application of pharmacokinetic models to projection data. The most important contribution has been to establish the concept of parameter projections, a simple tool, which reduces the complexity of the problem. Using this concept, it becomes clear that in order to apply an analysis method, based on a pharmacokinetic model, to projection data, it should fulfil two criteria.

1. The model and analysis method should be expressed in terms of:

\[ c = Xk \]  

(2.38)

where the individual terms are explained in section 2.9.

2. The basis functions in this equation should be independent of space.

The construction decouples the model application from the reconstruction algorithm, a satisfying result since it embodies the physics of the problem rather than implementation considerations. The second constraint also qualifies the notion that linear methods should be applicable to projections, a statement which is incomplete.

Experience has shown that the number of pharmacokinetic tissue compartments that can be identified within the radiation dose constraints and instrumentation of the PET measurement in humans is two, the one-tissue and two-tissue compartment models. This thesis has carefully examined both of these conditions.

For the latter of these two models it has been shown that multiple time graphical analysis (MTGA) can be applied to projection data using the parameter projection technique. This method is exact and reduces the number of reconstructions that are required by a factor equal to the number of acquisitions in the time series. The one-tissue model is however less
accessible, and published basis function solutions do not fulfil condition 2. above. Parameter projections show that the solution is to find an analytical expression of the model in which the spatial dependence is removed.

The basis function solution to the one-compartment model that has been presented here is an approximation, indeed the estimates of flow obtained are significantly different using an exact method. As has been discussed in previous chapters this may not be important for PET, and indeed it may be better to have an index of a physiological variable which is sensitive to change and precise but inaccurate, than a more accurate measure. In this sense one obvious extension to this work would be to investigate the application of a simple integral to [0-15]water data - one of the most common analysis methods.

Again, starting from the principle of parameter projections, it has been shown that the variance of parametric images is best calculated using the raw count data, rather than reconstructed time series of images. This method leads to estimates of the variance, which in the limits of high signal to noise ratio - smooth images - and a small number of repetition measurements, have a higher precision than either estimates based the reconstructed images, or that calculated by comparison between the pixels of parametric images.

The consequence of this is that statistical parametric maps (SPM) and signal to noise ratio images, calculated by this method are very close to the asymptotic values which could be calculated by many repetitions of the experiment or by high count rate acquisitions. Thus the SPM generated using the variance projection method are less sensitive to the total number of measurements made.

The application of the calculation of individual pixel variance in activity concentration images has not been explored here. In this thesis, previous methods (Alpert et al. 1982) were extended to the calculation of the variances in parametric images. However the previous authors did not
clearly point out the advantages of calculation based on the raw count data for activity concentration images, in the limit of low count rate. In fact the same conclusions about higher precision apply here also and it is clear that good estimations for each pixel and frame are important for non-linear as well as linear estimation. Good estimations of the individual pixel variance are essential for weighted parameter estimation and if non-linear models are to be applied in image space, then this variance can be used in assessment of the appropriateness of a model, and the precision of estimated parameters on a pixel-by-pixel basis.

Although it has been shown here that SPM calculation, based on projection data is feasible, the contribution of individual subject variability has not been assessed. By normalising the data, one of the major components in the variability can be removed, whilst retaining estimates of the individual variance of the normalised values, based on the raw pixel data. This may not however be the most appropriate approach. A more rigorous investigation of this topic and the partitioning of the total variance into appropriate components is a research project in its own right.

One of the most satisfying aspects of the entire project has been to see how the concept of parameter projections has been able to contribute to the reasoning and application of both analysis methods to projection data (Meikle et al. 1998) and the integration of models into special reconstruction methods (Matthews et al. 1997). PET is an instrumentation method that is used to address medical hypotheses. As such, it is necessary to understand the whole acquisition chain, from the injection and pharmacokinetics, to the statistical parametric images. Parameter projections aid researchers working in the field of pharmacokinetic modelling and in reconstruction to incorporate aspects of each others work and to clarify the contribution of each component of data analysis to the statistical power with which the hypothesis is assessed.

As can be seen through the simulation studies which have been done as part of this thesis, the hypothesis and
pharmacokinetic model have to be taken into account when optimising the hardware of instrumentation - e.g. crystal characteristics, detector acceptance angles. Parameter projections allow the impact in changes in experimental design to be clearly understood in terms of the precision of model estimates.

In concluding one aspect of the analysis chain which has an impact on all the others should be highlighted - spatial scale. In the selection of the most appropriate pharmacokinetic model, the signal-to-noise ratio of the data is important. Filtering, as has been seen in chapter 4, has a direct effect on both the signal-to-noise ratio and the resolution of the data. In turn, this affects the results of statistical analyses. Choice of appropriate filtering, and hence scale is of central importance to the application of PET. If methods can be found to locally adjust the resolution of the data to the most appropriate resolution for local hypothesis testing in the image then the instrumentation can be tuned for the hypothesis yet further.
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