SPATIOTEMPORAL IMAGE RECONSTRUCTION WITH RESOLUTION RECOVERY FOR DYNAMIC PET/CT IN ONCOLOGY

A THESIS SUBMITTED TO THE UNIVERSITY OF MANCHESTER FOR THE DEGREE OF DOCTOR OF PHILOSOPHY IN THE FACULTY OF MEDICAL AND HUMAN SCIENCES

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1. Molecular imaging using Positron Emission Tomography ........................................ 19
  1.1 Principles of PET ............................................................................................................ 20
  1.2 From PET to PET/CT ....................................................................................................... 21
  1.3 PET/CT imaging in oncology .......................................................................................... 22
  1.4 Measuring metabolism and perfusion in oncology studies ........................................... 23
    1.4.1 Metabolic imaging ................................................................................................... 23
    1.4.2 Perfusion imaging .................................................................................................. 24
  1.5 Parameter estimation in dynamic Positron Emission Tomography – A two step approach ....................................................................................................................... 25
  1.6 ROI Vs Parametric imaging .......................................................................................... 27
  1.7 Limitations of the current methodology ...................................................................... 28
  1.8 About this Thesis ......................................................................................................... 30

2. Image reconstruction from projections ............................................................................ 32
  2.1. Introduction .................................................................................................................. 33
  2.2. Analytical methods to image reconstruction ................................................................. 34
  2.3. Statistical methods in image reconstruction ................................................................ 36
    2.3.1. A model for the image ............................................................................................ 36
    2.3.2. A model for the system ......................................................................................... 37
    2.3.3. A model for the data ............................................................................................. 38

3.1. Introduction

3.2. Measuring perfusion with Positron Emission Tomography
   3.2.1 Perfusion and the Renkin–Crone model
   3.2.2 The Kety–Schmidt model and perfusion kinetics
   3.2.3 Delay and Dispersion in the 1-tissue compartment model
   3.2.4 Partial volume and vascular effects
   3.2.5 Parameter estimation schemes
   3.2.6 Summary of ongoing research in Oncology perfusion studies

3.3. Evaluation of basis function, linear least squares and generalized linear least squares methods for 1-tissue compartment model
   3.3.1 Introduction
   3.3.2 Materials and methods
   3.3.3 Results
   3.3.4 Discussion
   3.3.5 Conclusion

4. Image reconstruction and associated software on the Biograph 6 B-HiRez and TruePoint TrueV PET/CT

4.1 Introduction

4.2 The Biograph-6 Barrel HiRez and TruePoint TrueV PET/CT

4.3 Data acquisition
4.4 List-mode rebinning, histogramming and sinogram formation ...................... 97
  4.4.1 Methods ................................................................................................... 99
  4.4.2 Results .................................................................................................... 101
  4.4.3 Discussion ............................................................................................ 102
4.5 Data corrections – quantitative methods ..................................................... 103
  4.5.1 Data generation on the scanners ............................................................ 103
  4.5.2 Data preparation .................................................................................... 104
  4.5.3 Sinogram generation ............................................................................. 105
4.6 Deriving the geometric system matrix ......................................................... 110
  4.6.1 Methods ................................................................................................. 113
  4.6.2 Results ................................................................................................... 114
  4.6.3 Discussion ............................................................................................ 117
4.7 Image reconstruction .................................................................................... 118
  4.7.1 Methods ................................................................................................. 118
  4.7.2 Results ................................................................................................... 122
  4.7.3 Discussion ............................................................................................ 123
4.8 Conclusion ................................................................................................... 124

5. Space-variant image based PSF parameterization and resolution recovery
image reconstruction ............................................................................................ 125
5.1 Introduction .................................................................................................. 126
5.2 Materials and methods .................................................................................. 129
  5.2.1 Space-variant and count rate dependent PSF parameterization in image
  space via a printed array .................................................................................. 129
  5.2.2 Resolution recovery based image reconstruction on the HiRez and
  TruePoint TrueV PET/CT .................................................................................. 139
5.3 Results .......................................................................................................... 144
  5.3.1 Space-variant and count rate dependent PSF parameterization in image
  space via a printed array .................................................................................. 144
  5.3.2 Resolution recovery based image reconstruction on the HiRez and
  TruePoint TrueV PET/CT .................................................................................. 155
5.4 Discussion ..................................................................................................... 163
  5.4.1 Experimental design and methodology .................................................. 164
5.4.2 Reconstruction performance evaluation and image versus projection based resolution modelling comparison ................................................................. 167
5.5 Conclusion ........................................................................................................ 168

6. Implementation and evaluation of direct 4-D parametric image reconstruction in perfusion [$^{15}$O]H$_2$O PET/CT imaging .................................................. 171
6.1 Introduction ...................................................................................................... 172
6.2 Theory .............................................................................................................. 175
   6.2.1 3-D maximum likelihood problem .......................................................... 176
   6.2.2 4-D maximum likelihood problem .......................................................... 177
   6.2.3 Using weighted least squares to solve the ML image based problem .... 179
6.3 Materials and methods .................................................................................. 180
   6.3.1 Implementation and optimization of direct and post-reconstruction kinetic analysis algorithms .............................................................. 180
   6.3.2 Evaluating parameter estimation precision and accuracy in abdominal [$^{15}$O]H$_2$O PET imaging with direct 4-D image reconstruction ............... 185
6.4 Results ............................................................................................................ 191
   6.4.1 Implementation and optimization of direct and post-reconstruction kinetic analysis algorithms .............................................................. 191
   6.4.2 Evaluating parameter estimation reproducibility and accuracy in abdominal [$^{15}$O]H$_2$O PET imaging with direct 4-D image reconstruction ............... 195
6.5 Discussion ..................................................................................................... 210
   6.5.1 Implementation and optimization of direct and post-reconstruction kinetic analysis algorithms .............................................................. 210
   6.5.2 Evaluating parameter estimation reproducibility and accuracy in abdominal [$^{15}$O]H$_2$O PET imaging with direct 4-D image reconstruction ............... 211
6.6 Conclusion .................................................................................................... 213

7. Impact of erroneous kinetic model formulation in direct 4-D image reconstruction ........................................................................................................... 214
7.1 Introduction .................................................................................................... 215
7.2 Theory ............................................................................................................ 216
7.3 Materials and methods ................................................................................ 218
   7.3.1 Data generation ........................................................................................ 218
7.3.2 Kinetic modelling ................................................................. 223
7.3.3 Image reconstruction and analysis ........................................ 223
7.4 Results .................................................................................... 225
7.4.1 Noiseless data ................................................................. 225
7.4.2 Noisy data ................................................................. 231
7.5 Discussion .............................................................................. 237
7.6 Conclusion .............................................................................. 239

8. Research outcome and future prospects ...................................... 240
8.1 Thesis summary ...................................................................... 241
8.2 Research outcome and future work ............................................ 243
List of Figures

Figure 1.1 Diagram showing the 2-step kinetic modelling methodology ......................... 28
Figure 1.2 Diagram showing the direct 4-D methodology ............................................. 29
Figure 2.1 Image based on non-uniform mesh elements. ............................................. 37
Figure 2.2 Simulated positron tracks (^{18}F) in water ................................................. 45
Figure 2.3 Three of the resolution limiting effects in a PET system ............................ 46
Figure 2.4 4-D Gibbs spatiotemporal prior ................................................................. 52
Figure 2.5 Set of b-spline basis functions ................................................................. 54
Figure 2.6 PCA in sinogram space ........................................................... 55
Figure 2.7 Image decomposion based on wavelets ..................................................... 55
Figure 2.8 Principle of wavelet denoising ................................................................. 56
Figure 2.9 Direct parametric reconstruction through sinogram wavelet denoising ......... 58
Figure 3.1 The fick principle for blood flow ............................................................... 64
Figure 3.2 The Fick principle for perfusion ................................................................. 64
Figure 3.3 The steady state method ......................................................................... 68
Figure 3.4 Estimated parameters vs BF I ................................................................. 77
Figure 3.5 Estimated parameters vs BF II ................................................................. 78
Figure 3.6 Estimated parameters vs BF III ............................................................... 79
Figure 3.7 Estimated parameters vs noise level I ....................................................... 81
Figure 3.8 Estimated parameters vs noise level II ...................................................... 82
Figure 3.9 Box-whisker plots of estimated parameters vs noise level ......................... 83
Figure 3.10 Estimated parameters MSE vs noise level I ............................................. 84
Figure 3.11 Estimated parameters MSE vs noise level II .......................................... 85
Figure 4.1 PET/CT data proacessing .......................................................................... 91
Figure 4.2 The Biograph 6 B-HiRez and the TruePoint TrueV PET/CT ....................... 92
Figure 4.3 The Biograph 6 B-Hi-Rez (left) and the TruePoint TrueV PET/CT .......... 93
Figure 4.4 Data acquisition in PET/CT ....................................................................... 95
Figure 4.5 ‘Michelogram’ diagrams for the PET/CT .................................................. 96
Figure 4.6 The PDR card to perform LOR-to-projection bin mapping ......................... 97
Figure 4.7 The 32 list-mode decoding scheme based on the PETLink protocol .......... 98
Figure 4.8 A 2-D PET/CT sinogram mask ................................................................. 100
Figure 4.9  Sinograms as generated by the matlab based list-mode histogrammer. ..... 101
Figure 4.10  Summed sinograms across planes with 2 histogrammers......................... 102
Figure 4.11  Axial zoom factors for on the HiRez PET/CT....................................... 107
Figure 4.12  Sinogram before and after arc correction .............................................. 108
Figure 4.13  Representative sinograms ................................................................. 109
Figure 4.14  Different geometric system matric methodologies.................................. 112
Figure 4.15  LOR axial profileson the TrueV and HiRez............................................ 115
Figure 4.16  Representation of the HiRez scanner overlaid with axial LORs .............. 116
Figure 4.17  LORs at varying radial distance from a single projection view ............. 116
Figure 4.18  LOR passing through image space along with the probability matrix ....... 117
Figure 4.19  Image reconstruction data flow using an UW-OSEM algorithms.......... 119
Figure 4.20  Sensitivity images from a patient study................................................ 121
Figure 4.21  Representative reconstructed planes from the IQ phantom.................. 122
Figure 4.22  1-D radial profile through the reconstructed the IQ phantom .............. 123
Figure 4.24  Representative reconstructed planes from the Cologne phantom ......... 123
Figure 5.1  Picture of printed point sources ............................................................ 131
Figure 5.2  Picture of a Perspex phantom used on the PET/CT ................................ 132
Figure 5.3  Alignment of the Perspex phantom ...................................................... 133
Figure 5.4  PSF sampling scheme for the HiRez ...................................................... 134
Figure 5.5  PSF sampling scheme for the HRRT ..................................................... 135
Figure 5.6  Segment zero sinograms on the PET/CT .............................................. 137
Figure 5.7  Fitted PSFs on the PET/CT ................................................................. 139
Figure 5.8  Reconstructed optimization array on the HRRT and PET/CT ............... 144
Figure 5.9  PSF parameterization on the PET/CT I ............................................... 146
Figure 5.10  PSF parameterization on the PET/CT II ............................................. 147
Figure 5.11  Spatial resolution on the HRRT I ....................................................... 149
Figure 5.12  Spatial resolution on the HRRT II ..................................................... 150
Figure 5.13  Spatial resolution on the HRRT III ................................................... 151
Figure 5.14  Radial assymetry on the HRRT ....................................................... 152
Figure 5.15  Spatial resolution on the HRRT IV .................................................. 153
Figure 5.16  Spatial resolution on the HRRT V ................................................... 154
Figure 5.17  Spatial resolution vs count rate on the HRRT ..................................... 155
Figure 5.18  Reconstructed point sources with various algorithm.......................... 157
Figure 5.19  Profiles from Reconstructed point sources with various algorithm........ 157
Figure 5.20  Spatial resolution on the PET/CT .......................................................... 158
Figure 5.21  Reconstructed images using the NEMA phantom on PET/CT.............. 159
Figure 5.22  Contrast recovery coefficient vs image roughness ................................ 159
Figure 5.23  Reconstructed images from the Cologne phantom on the PET/CT ...... 160
Figure 5.24  Reconstructed clinical images on the PET/CT I .................................... 161
Figure 5.25  Reconstructed clinical images on the PET/CT II .................................... 162
Figure 5.26  Profiles through reconstructed clinical images on the PET/CT .......... 163
Figure 6.1  Events curve from an [15O]H2O scan ...................................................... 180
Figure 6.2  Graph showing different input function methods .................................. 181
Figure 6.3  Graph showing the 6 measured input function from repeated scans .... 186
Figure 6.4  Schematic diagram of bootstrap re-sampling scheme .............................. 187
Figure 6.5  Simulated parametric images ................................................................. 189
Figure 6.6  Graph showing the simulated time-activity curves (TACs) .................... 190
Figure 6.7  Parametric images I .............................................................................. 192
Figure 6.8  Mean perfusion vs image roughness as a function of iterations .......... 193
Figure 6.9  Parametric images II ............................................................................ 194
Figure 6.10  Parametric images IIII ........................................................................ 196
Figure 6.11  Mean parameter estimates vs CoV across the 6 repeated scans ......... 198
Figure 6.12  Scatter plots of mean kinetic parameters versus CoV across 6 scans ..... 199
Figure 6.13  CoV parametric maps across 6 bootstrap realizations ....................... 201
Figure 6.14  Scatter plots of mean kinetic parameters versus CoV across 6 bootstrap 202
Figure 6.15  CoV parametric maps across 100 simulated noisy realizations I ........ 204
Figure 6.16  CoV parametric maps across 100 simulated noisy realizations II ........ 205
Figure 6.17  Mean ROI kinetic parameter CoV vs (true) kinetic parameters ............ 206
Figure 6.18  Percentage bias parametric maps across the 100 noisy realizations ...... 207
Figure 6.19  Mean ROI kinetic parameter bias vs (true) kinetic parameters .......... 208
Figure 6.20  Mean ROI Parameter percentage bias vs CoV for up to 15 iterations ...... 209
Figure 7.1  Emission and residual images from a dynamic [15O]H2O scan .............. 217
Figure 7.2  Schematic diagram showing the dual input model in liver ..................... 217
Figure 7.3  Simulated parametric images for a plane in the digital 4-D phantom .... 219
Figure 7.4  Graphs showing simulated TACs in the digital phantom ..................... 221
Figure 7.5  Representative simulated emission images from 4 representative frames .223
List of Tables

Table 2.1 Isotope positron energy and the corresponding PSF FWHM ......................... 44
Table 3.1 Perfusion studies in oncology PET ............................................................... 71
Table 4.1 Characteristics of the PET component on the HiRez and TrueV scanners..... 93
Table 6.1 Simulated kinetic parameters used on the dynamic 4-D digital phantom I .189
Table 6.2 Parameter mean and standard deviation within the tumour and spleen I ....203
Table 6.3 Parameter mean and standard deviation within the tumour and spleen II ...203
Table 7.1 Simulated kinetic parameters used on the dynamic 4-D digital phantom I .220
Table 7.2 Tables showing the different simulated combinations................................. 224
Table 7.3 Mean ROI parameter bias for the noiseless data........................................... 230
Table 7.4 Mean ROI parameter bias for the noisy data. ................................................. 230
### List of Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>3DRP</td>
<td>3D-reprojection</td>
</tr>
<tr>
<td>AC</td>
<td>Attenuation correction</td>
</tr>
<tr>
<td>ACF</td>
<td>Attenuation correction factor</td>
</tr>
<tr>
<td>AIF</td>
<td>Arterial input function</td>
</tr>
<tr>
<td>ANW</td>
<td>Attenuation normalization weighted</td>
</tr>
<tr>
<td>API</td>
<td>Axial projection index</td>
</tr>
<tr>
<td>APS</td>
<td>Axial projection size</td>
</tr>
<tr>
<td>ART</td>
<td>Algebraic reconstruction technique</td>
</tr>
<tr>
<td>ASI</td>
<td>Axial sinogram index</td>
</tr>
<tr>
<td>ASO</td>
<td>Antisense oligonucleotide</td>
</tr>
<tr>
<td>AW</td>
<td>Attenuation weighted</td>
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<tr>
<td>BA</td>
<td>Bin address</td>
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<tr>
<td>BFM</td>
<td>Basis functions method</td>
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<tr>
<td>BGO</td>
<td>Bismuth germanate</td>
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<tr>
<td>B-HR</td>
<td>Barrel-HiRez</td>
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<tr>
<td>CAMM</td>
<td>Content adaptive mesh model</td>
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<tr>
<td>CBF</td>
<td>Cerebral blood flow</td>
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<tr>
<td>CIC</td>
<td>Clinical imaging centre</td>
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<tr>
<td>COV</td>
<td>Coefficient of variation</td>
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<td>CRC</td>
<td>Contrast recovery coefficient</td>
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<tr>
<td>CT</td>
<td>Computed tomography</td>
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<tr>
<td>DICOM</td>
<td>Digital imaging and communications in medicine</td>
</tr>
<tr>
<td>DIFT</td>
<td>Direct inverse Fourier transform</td>
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<tr>
<td>DOI</td>
<td>Depth of interaction</td>
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<tr>
<td>EM</td>
<td>Expectation maximization</td>
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<tr>
<td>FBP</td>
<td>Filtered backprojection</td>
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<tr>
<td>FDG</td>
<td>Fluoro-2-deoxy-D-glucose</td>
</tr>
<tr>
<td>FLT</td>
<td>Fluoro-3'-deoxy-3'-L-fluorothymidine</td>
</tr>
<tr>
<td>FORE</td>
<td>Fourier rebinning</td>
</tr>
<tr>
<td>FOV</td>
<td>Field of view</td>
</tr>
<tr>
<td>FPGA</td>
<td>Flash programmable gate array</td>
</tr>
<tr>
<td>FWHM</td>
<td>Full width at half maximum</td>
</tr>
<tr>
<td>GLLS</td>
<td>Generalized linear least squares</td>
</tr>
<tr>
<td>GSK</td>
<td>Glaxosmithkline</td>
</tr>
<tr>
<td>GSO</td>
<td>Gadolinium oxyorthosilicate</td>
</tr>
<tr>
<td>GUI</td>
<td>Graphical user interface</td>
</tr>
<tr>
<td>HCC</td>
<td>Hepatocellular carcinoma</td>
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<tr>
<td>HRRT</td>
<td>High resolution research tomograph</td>
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<tr>
<td>HU</td>
<td>Hounsfield Units</td>
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<tr>
<td>IDIF</td>
<td>Image derived input function</td>
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<tr>
<td>IF</td>
<td>Input function</td>
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<tr>
<td>IQ</td>
<td>Image quality</td>
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<tr>
<td>IR</td>
<td>Image roughness</td>
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<tr>
<td>IRF</td>
<td>Impulse response function</td>
</tr>
<tr>
<td>KL</td>
<td>Karhunen loeve</td>
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<td>Abbreviation</td>
<td>Description</td>
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<tr>
<td>LLS</td>
<td>Linear least squares</td>
</tr>
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<td>LOR</td>
<td>Line of response</td>
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<td>LS</td>
<td>Least squares</td>
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<td>LSB</td>
<td>Less significant bit</td>
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<td>LSF</td>
<td>Line spread function</td>
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<td>LSO</td>
<td>Cerium-doped lutetium oxyorthosilicate</td>
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<td>Lookup table</td>
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<td>LYSO</td>
<td>Cerium-doped lutetium-yttrium oxyorthosilicate</td>
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<td>MAP</td>
<td>Maximum a posteriori</td>
</tr>
<tr>
<td>ML</td>
<td>Maximum likelihood</td>
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<td>MLEM</td>
<td>Maximum likelihood expectation maximization</td>
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<tr>
<td>MRI</td>
<td>Magnetic resonance imaging</td>
</tr>
<tr>
<td>MSB</td>
<td>Most significant bit</td>
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<td>MSE</td>
<td>Mean square error</td>
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<td>NEC</td>
<td>Noise-equivalent counts</td>
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<td>NEMA</td>
<td>National electrical manufacturers association</td>
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<td>NLS</td>
<td>Nonlinear least squares</td>
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<td>NNLS</td>
<td>Non negative least squares</td>
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<td>OP</td>
<td>Ordinary Poisson</td>
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<td>OSEM</td>
<td>Ordered subsets expectation maximization</td>
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<td>PCA</td>
<td>Principal component analysis</td>
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<td>Petlink DMA rebinner</td>
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<td>PET</td>
<td>Positron emission tomography</td>
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<td>PHS</td>
<td>Patient handling system</td>
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<td>PMT</td>
<td>Photomultiplier tube</td>
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<td>PS</td>
<td>Permeability surface</td>
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<td>PSF</td>
<td>Point spread function</td>
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<td>PVC</td>
<td>Partial volume correction</td>
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<tr>
<td>PVE</td>
<td>Partial volume effect</td>
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<tr>
<td>QC</td>
<td>Quality control</td>
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<tr>
<td>RC</td>
<td>Resolution recovery</td>
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<td>RCBF</td>
<td>Regional cerebral blood flow</td>
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<td>Resolution modeling</td>
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<td>ROI</td>
<td>Region of interest</td>
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<td>RPI</td>
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<td>Radial projection size</td>
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<td>RSS</td>
<td>Residual sum of squares</td>
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<td>SD</td>
<td>Standard deviation</td>
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<td>SNR</td>
<td>Signal to noise ratio</td>
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<td>SP</td>
<td>Shifted Poisson</td>
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<td>SPECT</td>
<td>Single photon emission computed tomography</td>
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<td>SS</td>
<td>Sinogram size</td>
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<td>SSRB</td>
<td>Single slice rebinning</td>
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<td>SUV</td>
<td>Standardized uptake value</td>
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<td>TAC</td>
<td>Time activity curve</td>
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<td>TBF</td>
<td>Temporal basis functions</td>
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<td>TBF</td>
<td>Tumor blood flow</td>
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<td>TPTV</td>
<td>Truepoint trueV</td>
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<tr>
<td>Acronym</td>
<td>Description</td>
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<td>TSI</td>
<td>Transaxial sinogram index</td>
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<tr>
<td>UW</td>
<td>Unweighted</td>
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<tr>
<td>Vd</td>
<td>Volume of distribution</td>
</tr>
<tr>
<td>WLS</td>
<td>Weighted least squares</td>
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Abstract

SPATIOTEMPORAL IMAGE RECONSTRUCTION WITH RESOLUTION RECOVERY FOR DYNAMIC PET/CT IN ONCOLOGY

A thesis for the degree of PhD
Fotis Kotasidis
The University of Manchester

September 2011

Positron emission tomography (PET) is a powerful and highly specialised imaging modality that has the inherent ability to detect and quantify changes in the biodistribution of an intravenously administered radio-labelled tracer, through dynamic image acquisition of the system under study. By modelling the temporal distribution of the tracer, parameters of interest regarding specific biological processes can be derived. Traditionally parameter estimation is done by first reconstructing a set of dynamic images independently, followed by kinetic modelling, leading to parameters of reduced accuracy and precision. Furthermore only simple geometrical models are used during image reconstruction to model the mapping between the image space and the data space, leading to images of reduced resolution. This thesis attempts to address some of the problems associated with the current methodology, by implementing and evaluating new spatiotemporal image reconstruction strategies in oncology PET/CT imaging, with simulated, phantom and real data. More specifically this thesis is concerned with iterative reconstruction techniques, the incorporation of resolution recovery and kinetic modelling strategies within the image reconstruction process and the application of such methods in perfusion $[^{15}O]H_2O$ imaging. This work is mainly based upon 2 whole body PET/CT scanners, the Siemens Biograph 6 B-HiRez and TruePoint TrueV, but some aspects of this work were also implemented for the High resolution research tomograph (HRRT).
Declaration

No portion of the work referred to in this thesis has been submitted in support of an application for another degree or qualification of this or any other university or other institute of learning. The implementation of the GLLS algorithm in chapter 3 was provided by Dr Julian Matthews. In chapter 5 reconstructions on the HRRT were provided by Giorgos Angelis, while list-mode data histogramming to assess the effect of DOI on the HRRT was provided by Jose Anton-Rodriguez.
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CHAPTER 1

Molecular imaging using Positron Emission Tomography
1.1 Principles of PET

Positron emission tomography (PET) is a powerful and highly specialised imaging modality for non-invasive measurements of different physiological and biological processes at a molecular level. PET is a quantitative method used nowadays mainly but not exclusively in oncology, as opposed to the early days when it was used mainly in neurology and cardiology.

The theory of emission tomography applies to PET, but the data acquisition is significantly different from the well-known single photon emission tomography (SPECT). The principles of PET are based on the fact that by labelling a compound with a positron emitting isotope and intravenously injecting it in the patient in tracer quantities, one can detect its bio-distribution inside the body and investigate a number of physiological and biochemical processes such as perfusion, proliferation and glucose metabolism. Following administration of the radio-labelled compound and nucleus decay, positrons travels a short distance in the tissue prior to thermalization and annihilation with atomic electrons. As opposed to SPECT, were a single photon is emitted, in PET a pair of 2 almost co-linear photons are emitted at opposite directions and rings of detectors surrounding the patient with a 360 ° coverage, collect the events. The hypothetical line connecting the 2 detectors that detected the photons is called Line Of Response (LOR). This provides an electronic collimation as opposed to physical collimation in SPECT. The 2 photons needs to be detected within a time window to be considered in coincidence and coming from the same annihilation, which in modern scanners is in the order of 4-7 nanoseconds. During the course of a scan, several million events are detected along several projection angles and stored for further processing after the end of the data acquisition. The timing uncertainty in the detection process and the lack of accurate localization of the annihilation point along the LOR results in the need to use a mathematical image reconstruction procedure to calculate the spatial distribution of the radioactivity concentration from the measured projection data. Due to the imperfect nature of the imaging system and the attenuation by the patient, a number of corrections need to be taken into account during the image reconstruction process, in order to produce quantitative parameters.
1.2 From PET to PET/CT

As opposed to CT which is used for structural imaging, PET is referred to as functional imaging due to its ability to measure functional characteristics of tissue and their changes for instance with different pathologies. Despite the fact that these 2 modalities have different sensitivities and specificities, their combined acquisition can be highly advantageous. As it is often the case, functional changes process structural changes and using structural information can help localize the origin of these functional abnormalities and correlate their position with respect to anatomical structures in the body. As such, combining the structural information derived from a CT with the functional information from PET appears to be a logical approach. Prior to the advent of PET/CT, acquisition of a separate CT and PET scan on a different day was used to be the standard approach. Subsequently, co-registered anatomical and functional images would be generated, using software based techniques (Woods et al 1993). This technique works well in the brain, being a single organ with rigid motion, but performs poorly in body applications due to the complex nature of motion from different organs, such as the heart, the lungs and intestines to name a few (Wahl et al 1993). By combining the 2 imaging modalities within a single gantry, such problems no longer exist, with the patient staying on the same bed during the PET and CT acquisition. Although such a combined approach was first implemented in SPECT in the early 90s (Hasegawa et al 1991), it was another decade until the first commercial PET/CT was introduced in clinical practice (Beyer et al 2000). Despite the fact that having a single frame for both modalities, providing simultaneous acquisition, could be advantageous, it is very challenging from an engineering point of view. This is one of the reasons why a sequential design is used by all 3 major manufacturers, which is only a small compromise due to the rapid CT acquisition.

Apart from the benefit of having inherently co-registered anatomical and functional images in one scanning session, another benefit from such a design is the ability to perform almost noise free attenuation correction, based on the information from the CT data (Kinahan et al 1998). This avoids the noisy and time consuming transmission scan with a rotating source, normally used in stand alone PET scanners. On the other hand, due to the fact that the PET signal is averaged due to respiratory motion compared to the relatively motionless signal in the CT (the speed of acquisition means that it is relatively...
motionless, but motion can and does occur), errors in the attenuation can be introduced (Mavi et al 2005). Nevertheless PET/CT is now the standard design in PET imaging as multi-modality imaging can help in improved patient diagnosis and disease monitoring in oncology.

1.3 PET/CT imaging in oncology

PET is an establish modality in Oncology, as for the last 2 decades PET imaging has been used for numerous studies involving many benign and malignant abnormalities. It was the advent of [18F]FDG however which helped in the widespread use of PET that can be seen today. The main applications in Oncology includes the differentiation between malignant and benign tumours, the quantitative metabolic activity of malignant tumours using the Warburg principle of increased glucose consumption by the tumoral cells and the measurement of blood flow in the abnormal tumoral vascular network which is triggered by angiogenesis. Many of these applications are often utilized for staging newly diagnosed tumours, restaging in the event of disease recurrence and for treatment response monitoring protocols.

Accurate extent of the disease is essential in order to provide the most effective treatment regime. Mavi et al (2005) found that 30% of the patients participated in the study and diagnosed with lung cancer in the initial staging, were found to have metastasis using PET altering the treatment decisions. PET can also differentiate stage N3 from potentially resectable stage N1 and N2 disease.

Restaging, following chemotherapy, radiotherapy or surgery, for any disease recurrence using PET, has been proven to overcome the shortcomings of anatomical based modalities, having increased sensitivity but reduced specificity due to tissue inflammatory response after treatment.

Response monitoring is essential for patient management, as positive and early response to a specific therapeutic regime may provide prognostic information regarding overall treatment. On the other hand, early negative response can help in treatment escalation or even in alternative treatment strategies. To date, response monitoring is mainly assessed using information derived from anatomical imaging modalities, which do not provide early response, as functional changes are likely to precede structural changes. When functional imaging is used, there is a variety of analytical methods to
quantify these changes (Hoekstra et al 2000). In order to accurately access response monitoring in a reproducible way, quantitative analysis is preferred, which due to its complexity is not routinely used in clinical response monitoring protocols. To simplify the procedures but still maintain a level of quantitation, semi-quantitative parameters are often used. Kinetic modelling though is the only approach when tumour specific drug trials are in early phases (Tseng et al 2004, Hentschel et al 2007, Krak et al 2008).

1.4 Measuring metabolism and perfusion in oncology studies

1.4.1 Metabolic imaging

One of the radiopharmaceuticals that is extensively used in oncology studies to provide measures of metabolic activity, is [$^{18}$F]FDG or Fluorine-18 labelled 2 deoxy-2-D-glucose in which the hydroxyl group of glucose has been replaced by a positron emitter fluorine isotope. Although the molecule is qualitatively similar to glucose, the altered hydroxyl group prevents the FDG from going further down the glucoytic pathway. [$^{18}$F]FDG is transported from plasma into the cell by the same glucose transporters namely GLUT1 and GLUT4. As FDG and glucose are similar, they are competing in the phosphorylation step. The 2 by-products, FDG-6-phosphate and glucose-6-phosphate follow different routes at this point. Glucose is further metabolized into fructose-6-phosphate by phosphohexoseisomerase, while [$^{18}$F]FDG is trapped due to the lack of the hydroxyl atom (Phelps et al 1979). Although metabolically trapped, FDG-6-phosphate can be slowly dephosphorylated with a rate described by rate constant $k_4$ and then either rephosphorylated, or cleared to the plasma with a $k_2$ rate constant. In plasma, FDG unlike glucose is not reabsorbed after glomerular filtration, but is rapidly cleared from blood circulation through urine excretion (Buerkle et al 2008).

The basis of using [$^{18}$F]FDG PET for tumour imaging is the elevated levels of glucose consumption in malignant cells. Increased expression of glucose transporters and enzymes responsible for metabolism can contribute to this glucose accumulation and consumption. [$^{18}$F]FDG uptake is also regulated by the hypoxic nature of the tumour, as well as the cellular proliferation and reduced tumour suppressing mechanisms (Buerkle et al 2008). This multi-factorial relation embraces possible correlation of [$^{18}$F]FDG uptake with other tumour specific physiologic measurement. Functional imaging with
PET is highly sensitive to changes in glucose consumption, due to abnormal physiologic behaviour. This increased sensitivity is accompanied though by a reduced specificity, due to the fact that other non-malignant physiologic processes can contribute to increased glucose levels, such as inflammatory disorders as well as benign lesions (Cook et al 1996).

PET \([^{18}\text{F}]\text{FDG}\) has been used repeatedly over the last years to differentiate between malignant and benign tumours. The differentiation is based on qualitative and quantitative criteria. Uptake values as a semi-quantitative marker are being used extensively and a threshold of 2.5 is applied for differentiation, with a significant overlap though at some occasions. Although big tumours in a late stage can be easily spotted, there is an ever increasing demand to use PET and PET/CT for disease staging protocols. Early detection of metastatic tumours is important and motivates the development of even better scanners, as well as more efficient analysis techniques. One of the inherent problems is signal-to-noise ratio (SNR) in the reconstructed images, which makes qualitative and quantitative interpretation and analysis a challenging task. An important parameter which results in noisy images is the limited counting statistics. The effect is even more pronounced in dynamic studies, where the division of the overall counts into time frames further deteriorates the image quality.

1.4.2 Perfusion imaging

Another important application of PET is the ability to measure blood flow in different tissues and by this mean to assess their functionality and viability. As blood flow is the way for cellular nutritive supply and waste disposal, imaging of vascular physiology can provide valuable information for the region of interest.

Chemotherapeutic agents as well as conventional radiotherapy are relying on adequate vascular blood supply to the tumour. Tumours having highly vascular network, can help in delivery of the necessary drug in treatment quantities, while highly oxygenated tumours can enhance the radiation induced results. On the other hand, low oxygenation can lead to hypoxia and accurate staging of tumoral vascular physiology can assist in better treatment management. Apart from assisting these more conventional anticancer treatments which target the malignancy itself, perfusion imaging can provide insights into angiogenesis and anti-angiogenic treatment response monitoring protocols (Kotz et al 2009).
Tumours are characterized by a growth in demand for nutrients and as the cells multiply there is a need for neo-vascularisation. This phenomenon is triggered by growth factors which are over-expressed under hypoxic conditions. Under these factors endothelial cells which make up old vessel, proliferate and migrate to new sites forming a new vascular network. This network is chaotic, incomplete with arterio-venous shunts and leaky vessels. The interstitial pressure in the tumours is elevated and despite the increased flow, perfusion is limited leading to anaerobic metabolism. New anti-angiogenic treatments target this highly irregular vascular structure, to inhibit the formation of new vessels. An early in vivo tumour response is important to assess treatment efficacy of these new therapeutic agents and imaging of blood flow with freely diffusible tracers can provide prognostic information. For instance there is increased interest in anti-vascular and anti-angiogenic response monitoring protocols (Jennings et al 2008).

In physical sciences, flow is quantity as volume of fluid over time (ml/min). In medical sciences, as blood flow is used to supply a viable tissue, this is typically normalised by the tissue volume (ml/sec/ml), with perfusion, the portion of blood flow which is able to supply nutrients, of most interest. An example of non-perfusive blood flow is a shunt, which is a direct connection between an artery and a vein bypassing the capillary bed. Another parameter of interest when assessing the vascular physiology of a tissue, apart from perfusion is the volume of distribution (Vd). It is a physiologic concept which applies in equilibrium conditions between tissue and plasma. It is defined as the ratio of tissue concentration over plasma concentration and the physiologic meaning is that it represents the proportion of tissue volume which exchanges substances or any tracer with blood or plasma.

1.5 Parameter estimation in dynamic Positron Emission Tomography – A two step approach

PET scanners are very specialized cameras and in principle they work in a similar way to normal digital cameras, by collecting photons over a period of time, to produce a static image from the integrated measurements. This mode of imaging is almost exclusively used in clinical practice, in order to provide quantitative estimates related to the accumulation of a radio-labelled compound and reconstruct its spatial distribution. Images produced in that way can provide valuable information regarding the system
under study and can help to estimate semi-quantitative indices such as the standardized uptake value (SUV). Such indices are frequently used in oncology to provide a simple method of basic quantification and provide differentiation between malignant and benign lesions as mentioned before. However a lot more information can be derived by splitting the time course of a scan into a number of time frames and measuring the spatiotemporal distribution of the activity concentration. The measured PET signal can then be modelled using a mathematical formula that relates the delivery of radioactivity to tissue, to the changing concentrations within tissue, through a number of parameters which are related, but not necessary equal to real physiological parameters. Given then an input function (time course of the radioactivity concentration in blood or plasma), which determines the delivery of the radio-labelled compound to the tissue and known model parameters, that describes the fate of the tracer after it passes the capillary bed and enters the tissue, one can predict the spatiotemporal radioactivity concentration of the target region. In dynamic PET, the task of kinetic modelling is an inverse problem of the above model, where these parameters which relate to physiological indices, are estimated given the measured tissue spatiotemporal radioactivity concentration and an input function.

Choosing the correct model is very important and is dependant upon the administered tracer, the target region and the scanner characteristics. In most cases the actual underlying model is too complicated to be identified due to the statistical variations of the measured data and the limitations introduced by the instrumentation. A simplified version of the model is then chosen in most cases as a trade off between statistical reliability of the derived parameters and error due to using a simplified model. As such, their is always a need for improving the statistical quality of the measured data and reducing the noise in the reconstructed images, to allow more complex models to be used with less variable and more accurate kinetic parameters. Despite the fact that fully quantitative analysis based on kinetic modelling can provide more meaningful parameters compared to semi-quantitative indices from static imaging in term of their relation with the true physiological parameters that one is trying to infer, it is not regularly used in clinical practice. This is mainly due to the time the subject needs to be scanned and the need for having an input function, with the continuous online measurements of arterial blood after arterial cannulation being the gold standard.
Conventionally, parameter estimation in PET is performed using a 2-step approach. Following dynamic acquisition of the emission data and histogramming into a number of time frames depending upon the required temporal sampling, each time frame is individually reconstructed, resulting in a sequence of dynamic images. Traditionally, simple analytical methods have been used for image reconstruction, producing images of low resolution and increased noise. On the other hand, iterative methods have gained increased popularity, due to a better handling of statistical noise and the physical processes during emission and detection, but suffer from bias due to incomplete convergence and low counts within the frames. Even so, when iterative methods are used in dynamic studies, a simplistic detection model is normally used. Following reconstruction of the independent emission images, kinetic modelling is then performed on the independently reconstructed temporal frames to estimate the kinetic parameters.

1.6 ROI Vs Parametric Imaging

Usually parameter estimation is performed on a regional level, after delineating an ROI using anatomical information when available and applying the kinetic model to calculate parameters representing the average TAC. This method is attractive as many voxels are summed together, improving the statistics and resulting in reliable parameters. However, as the underlying tissue contains heterogeneous kinetics, the average that is calculated when estimating regional kinetics, inherently results in biased estimates. Additionally, the spatial average limits the spatial information that PET data can potentially give. To overcome these problems one should model the kinetics at the scanner’s finest image discretization element, which is the voxel. In this way parametric images are obtained, allowing spatial heterogeneity of physiologic parameters to be assessed. However, despite the benefits of parametric imaging compared to regional analysis, it suffers from increased noise due to reduced counting statistics at the voxel level. This results in bias and non-statistically reliable parameter estimates. Also computational time becomes an important parameter. To address the excess noise, while maintaining the spatial information, different post reconstruction methods have been applied in the reconstructed images to improve signal-to-noise ratio (SNR), such as spatial and temporal filtering, Fourier transformations, ridge regression methods, spatial
Figure 1.1 Schematic diagram showing the 2-step methodology where emission images are first independently reconstructed followed by kinetic modelling given an input function and a model.

constraints and voxel clustering. These methods are expected to improve parameters but still kinetic parameter estimation is performed using a 2 step approach.

1.7 Limitations of the current methodology

Using the current image reconstruction and kinetic modelling methodology, there are a number of problems both in the spatial and the temporal dimension. As the image reconstruction does not usually take into account the complex physics phenomena taking place during emission and detection, images are severely affected both quantitatively and qualitatively, with reduced resolution and increased variance. This effect is not specific to dynamic imaging, but applies also to static imaging. In the context of dynamic imaging, it has however and added importance when performing parameter estimation, as the lack of accurate mapping between the image and the projection space can exacerbate the already increased statistical noise in the data from splitting the complete dataset into time frames. Apart from reduced statistical reliability in the parameter estimates due to the increased variance, lack of an accurate system
Figure 1.2 Schematic diagram showing an improved methodology where parametric images are derived directly in one step with kinetic modelling being part of the image reconstruction process.

matrix can result in bias due to partial volume effects and activity within nearby regions. This is especially true when assessing the kinetics for a small hot tumour in a cold background, as the activity spilling in cannot compensate for the activity spilling out and if parametric imaging is used, the tumour will appear larger and less active (Soret et al 2007).

In the temporal dimension, there are different problems with the established methodology in dynamic studies. Using analytical reconstruction methods, like FBP, for parameter estimation from independently reconstructed images, results in very noisy images and subsequently in kinetic parameters with reduced precision if voxel wise parameter estimation is performed. On the other hand, using non-linear iterative reconstruction algorithms based on statistical methods, improved handling of statistical noise is achieved, but the differential convergence rate for different temporal frames (having different number of counts), can lead to independently reconstructed images with differential variance properties.
Another problem is associated with the fact that for accurate parameter fitting, knowledge of the noise distribution in the images is essential (Qi 2003). However, within iterative reconstruction schemes, such distribution is difficult to be calculated when independently reconstructing images and usually the spatial variant characteristics of the noise structure and noise correlations are not taken into account during the kinetic modelling step. Figure 1.1 illustrates the 2-step methodology predominantly being used in dynamic PET studies to derive kinetic parameters, while Figure 1.2 shows a potential improvement over the established methodology, by directly reconstructing parametric images avoiding independent frame reconstruction.

1.8 About this Thesis

It is the aim of this thesis to address some of the problems associated with the current methodology, by implementing and evaluating new spatiotemporal image reconstruction strategies in oncology PET/CT imaging, with simulated, phantom and real data. More specifically this thesis is concerned with iterative reconstruction techniques, the incorporation of resolution recovery and kinetic modelling strategies within the image reconstruction process and the application of such methods in perfusion $[^{15}\text{O}]\text{H}_2\text{O}$ imaging. This work is mainly based upon 2 whole body PET/CT scanners, the Siemens Biograph 6 B-HiRez and TruePoint TrueV, which were installed at the Wolfson Molecular Imaging Centre (WMIC) during the time that this research took place, but some aspects of this work were also implemented for the High resolution research tomograph (HRRT) also installed at the WMIC. The rest of the thesis proceeds as follows.

In chapters 2 a review of some of the most pertinent aspects regarding statistical image reconstruction in PET imaging is presented, while chapter 3 reviews the kinetic modelling in perfusion imaging including a comparative evaluation of current parameter estimation schemes in dynamic perfusion studies using simulated data. In chapter 4 technical information regarding the 2 PET/CT scanners, mainly used in this thesis, are presented, along with information regarding the implementation of an image reconstruction platform applicable to both scanners. Chapter 5 describes the implementation of a novel method for measuring the spatial variant resolution blurring component on a PET/CT scanner and the incorporation of such a component within
image reconstruction using image based techniques. Chapter 6 is concerned with the implementation of a newly proposed spatio-temporal 4-D algorithm on a PET/CT scanner and the application and evaluation of such an approach in perfusion $[^{15}\text{O}]\text{H}_2\text{O}$ imaging. Finally chapter 7 investigates potential artefacts in direct parametric imaging from using a suboptimal kinetic model within a 4-D image reconstruction algorithm.
CHAPTER 2

Image reconstruction from projections
2.1. Introduction

For all the different applications and kinetic modelling strategies discussed in the 1st chapter, the image reconstruction problem is common. As in many other fields, one has to reconstruct the image from a set of measured data. In PET more specifically one has to estimate the coefficients of the spatial basis functions in static imaging or the coefficients of a set of spatiotemporal basis functions in dynamic studies, based on a set of measured projections. This is the case where data acquisition is done with the traditional way of sinogram formation. In the case of list mode data acquisition, one can reconstruct the data directly, without having first to histogram the data into projections. In both cases, the outcome is the need to solve a similar inverse problem. Two general classes of image reconstruction methods exist: analytical and iterative reconstruction methods. The choice of the reconstruction algorithm has a profound effect on the resolution and noise properties of the image, and accurate modelling of the statistical nature of the photon emission detection process, the physical emission and detection effects and the temporal distribution of the radioactivity concentration during image reconstruction can result in images of improved quality. In this thesis, EM based iterative reconstruction methods were used exclusively, but an overview of the analytic and other iterative algorithms is also presented.

This chapter does not attempt to produce a rigorous mathematical derivation of the different methods, but excellent reviews exist in the literature (Leahy and Qi 2000, Qi and Leahy 2006). Rather this chapter will provide an overview of the image reconstruction problem and set the scene for the research undertaken during this project (presented in chapters 5, 6 and 7).

The chapter proceeds as follows: first an overview of the analytical and iterative methods is presented, along with their strengths and weaknesses. Then the spatial resolution based partial volume effects (PVEs) in the context of PET are discussed, along with image reconstruction based resolution recovery approaches to enhance spatial resolution in the reconstructed images. Finally spatiotemporal image reconstruction methods which take into account a temporal model for the data are discussed, for reduced variance in parameter estimates in dynamic PET imaging.
2.2. Analytical methods to image reconstruction

Considering PET detection as a linear process, the number of photon pairs detected in the absence of attenuation, scattered and accidental coincidences is proportional to the integral of the radioactivity distribution along a line of response (LOR).

\[
E\{\text{photons}\} = \iiint_{\text{LOR}} S(x,y,z)F(x,y,z)\,dx\,dy\,dz \quad (2.1)
\]

where \( E\{\} \) is the expected value, \( S \) is the sensitivity within the tube and \( F \) is the radioactivity distribution. Analytic methods are based on the inversion of the integral model to recover the activity distribution. They are formulated with several assumptions, including continuous sampling, no statistical noise leading exact solutions, the volume integral model is transformed into a line integral with the sensitivity being a delta function and physical effects such as positron range, non-colinearity, intercrystal scatter and crystal penetration amongst others are ignored (Wernick and Aarsvold 2004). The cornerstone of analytic image reconstruction is the central section theorem. The 2 dimensional central section theorem states that a profile at angle \( \phi \) crossing the centre of the 2-D Fourier transform of an object, is equal to the 1-D Fourier transform of the projection of the object along the same angle \( \phi \)

\[
G(u_x,\phi) = F(u_x,u_y) = F_z\{f(x,y)\} \quad (2.2)
\]

where \( G(u_x,\phi) \) is the 1-D Fourier transform of a projection \( g(x,\phi) \) and \( F(u_x,u_y) \) is the 2-D Fourier transform of the object. To reconstruct the data, one must back-project the projected data into the image space along the appropriate LORs, but since the spatial information was lost during integration, a constant value is placed along the LOR. The 2-D Fourier transform of a back-projection, equals the Fourier transform of the object weighted by the inverse distance from the origin. This inverse distance weighting due to angular oversampling, accentuates low frequencies resulting in a blurred image and filtering is needed.

\[
B(u_x,u_y) = \frac{F(u_x,u_y)}{u} \quad (2.3)
\]
where \( B(u_x, u_y) \) is the Fourier transform of the back-projection. One option to recover the image is to back-project the data, filter in Fourier space and then inverse Fourier transform.

\[
f(x, y) = F_2^{-1}\{uF_2\{b(x, y) = \int_0^\pi g(x_r, \varphi) d\varphi\} \} \quad (2.4)
\]

where \( F_2 \) denotes the 2-D Fourier transform, \( b(x, y) \) is the back-projected image, and \( u \) is the filtering in Fourier space. A better approach is to first filter the projections and then back-project.

\[
p^f (x_r, \varphi) = F_1^{-1}\{u_{x_r}F_1\{p(x_r, \varphi)\}\} \quad (2.5)
\]

\[
f(x, y) = b(x, y) = \int_0^\pi (p^f (x_r, \varphi) = F_1^{-1}\{u_{x_r}F_1\{p(x_r, \varphi)\}\}) d\varphi \quad (2.6)
\]

where \( u_{x_r} \) is a section through the 2-D filter \( u \). Using septa and 2-D imaging, in order to reconstruct the original tracer distribution, all the line integrals from the different projection angles within the specific image plane are needed. In the case of 3-D imaging, the line integrals along oblique LORs are also needed. For 3-D filtered back-projection one has to fill the truncated oblique sinograms due to limited detector coverage. The 3DRP algorithm of Kinahan and Rogers (1989) can be used for that purpose to first reconstruct an initial low quality image using the direct planes, which is then forward projected to fill the missing projections. Instead of using 3-D image reconstruction, one can compress the data into equivalent 2-D sinograms and then use 2-D filtered back-projection. This rebinning process, e.g. single slice and multi-slice rebinning, results in resolution degradation away from the central axis (Daube-Witherspoon and Muehllehner 1987). More advanced methods like Fourier rebinning can partially compensate for this effect, achieving a compromise between computational time and accuracy (Defrise et al 1997).

Although computationally efficient and simple, analytic methods fail to account for the complex physical emission and detection phenomena during the imaging process and the line integral model is an idealization, producing images of reduced accuracy. As will be more thoroughly discussed later, positron range, photon non-collinearity,
intercrystal scatter and crystal penetration degrade spatial resolution and result in the measured projection data to deviate from the line integral model. On top of that, the statistical nature of the photon generation and detection processes is not accounted for in analytical methods and as such the statistical variation in the data is not properly modelled (Qi and Leahy 2000). This results in noisy images and usually filtering of the projection data is used as a way to cut off the high frequency components, at the cost of reduced spatial resolution.

2.3. Statistical methods in image reconstruction

Using statistical reconstruction methods, the physical effects during the imaging process can be modelled with a variable level of complexity, based on the balance of computational load and modelling accuracy. This opens the road for resolution recovery based image reconstruction methods, which have the potential to improve spatial resolution. Although in the past such methods were difficult to be applied in clinical practice, recent advancements in computational power and efficient algorithm implementations, using matrix factorizations and fast projector operations, have resulted in their gradually increasing utilization. Also assigning a probabilistic model for the data a more comprehensive approach towards modelling the noise properties in the data is achieved. Generally iterative algorithms are based on 5 components for each of which one can choose based on the individual properties of each solution.

2.3.1. A model for the image

The first component is a model for the image. This is the discretization of the image domain using a set of spatial basis functions. The most common basis function is the voxel or the pixel, which has a unit value within the cubic area and zero outside of it. The activity within the voxel is given by the coefficients and is proportional to the underlying activity distribution. It is the purpose of the reconstruction process to recover the spatial distribution of these coefficients.

\[
f_j = \iiint f(x,y,z)b_j(x,y,z)dx dy dz \quad (2.7)
\]
where \( b_j(x,y,z) \) is the \( j^{th} \) basis function and \( f_j \) is the coefficient. Apart from voxels, other spatial basis functions have been proposed. Lewitt (1992) proposed spherically symmetric volume elements (blobs) with a bell-shaped profile similar to a Gaussian function. These blobs, due to overlapping, produce a smoothed representation of the image, similar to a regularized image. Brankov et al (2004) proposed a mesh modelling of an image, which involves partitioning the image domain into a collection of non-overlapping (generally polygonal) patches, called mesh elements, defined by their vertices called nodes. In a mesh model, the image function is determined over each element by interpolation based on the values at the nodes. The content-adaptive mesh model (CAMM), is an image representation based on non-uniform sampling, in which the samples (mesh nodes) are placed automatically, so that their spatial density varies in relation to the degree of local image detail (Figure 2.1). One of the advantages of this approach is that an image can be represented by fewer mesh nodes than pixels.

![Figure 2.1](image.png)  
**Figure 2.1** A myocardium image based on non-uniform mesh elements (Brankov et al 2004).

### 2.3.2. A model for the system

The second component is a system model, which relates the image domain and the projection domain through a matrix which is called the system matrix.

\[
\bar{g}_i = \sum_j h_{ij} f_j \quad (2.8)
\]
where $\bar{g}_i$ is the mean of the $i^{th}$ projection ($\bar{g}_i \in G$), $f_j$ refers to the $j^{th}$ image voxel ($f_j \in F$) and $h_{ij}$ is the system matrix, mapping voxel $j^{th}$ to the $i^{th}$ projection bin. In mathematical terms the system matrix represents the probability of an event originating from the $j^{th}$ image voxel, being detected in the $i^{th}$ projection bin. In the case of raw data the forward model includes two additive noise terms from random ($r_i$) and scattered ($s_i$) coincidences.

$$\bar{g}_i = \sum_j h_{ij} f_j + r_i + s_i \quad (2.9)$$

### 2.3.3. A model for the data

The third component is a model for the data. This is a way to describe how the projection data vary around their expected value. The model is chosen based on the nature of the emission and detection process and is represented by a Poisson probability distribution. This is true for uncorrected data and neglecting the detector dead time. In this case, the Poisson probability law for $P$ projections states that the probability of obtaining the random vector of Poisson distributed photon counts $G$ (as related to vector $F$ from equation (2.8) or (2.9)) is:

$$L(G|F) = \prod_{i=1}^{p} \frac{g_i^{g_i} e^{-g_i}}{g_i!} \quad (2.10)$$

When corrections are applied to the data, the model is not Poisson anymore and a shifted Poisson model has been proposed by Yavuz et al (1996). Another model is the Gaussian in the case where the mean number of events in the projection bins is high enough.

$$L(G|F) = k \exp \left[ -\frac{1}{2} \sum_{i=1}^{p} \left( \frac{g_i - \bar{g}_i}{\bar{g}_i} \right)^2 \right] \quad (2.11)$$

where $k$ is a normalizing constant. One difference when considering a Gaussian model for the data is the fact that negative values in $g_i$ have non-zero probability compared to the Poisson model, where negatives have zero probability. As the average number of
counts per sinogram bin though is less than unity in modern scanners, Poisson statistics is a valid consideration.

### 2.3.4 Objective functions

After making a choice for each of the 3 components mentioned, one has to establish a criterion so as to decide which of the all the possible images should be the one that matches the true image. The objective function is often the key component in iterative methods, as often different algorithms used to optimize the objective function can arrive to the same solution. This is though complicated by the fact that algorithms are often prematurely terminated before reaching convergence and as such the reconstructed image would also depend on the optimization algorithm. There are a number of criteria which are going to be mentioned briefly with emphasis on the ML criterion.

**a) Constraint satisfaction**

This criterion can be viewed as one in which the image should be the solution based on constraints imposed by the projection data and any prior knowledge like the non-negativity in the image. The reconstruction problem in this context is analogous to solving a set of simultaneous equations. If the number of equations (projection bins) is larger than the number of unknowns (pixels), then a unique solution exists in the interception point (for consistent data). When there is noise in the data, the intersection point is shifted to a possible zero value point (non-existing for inconsistent data). This criterion is the base for the Algebraic Reconstruction techniques (ART) and it has the disadvantage that it doesn’t include any modelling for the statistical nature of the data emission and detection processes (Gordon et al 1970).

**b) Maximum Likelihood**

In this criterion, first introduced by Rockmore and Macovski (1976), the Poisson probability stated above is the likelihood function of the image vector \( F \). In this context the criterion states that amongst all possible image vectors \( F \), choose the one \( \hat{F} \) that maximizes the likelihood function.
\[ \hat{F} = \text{argmax}_f L(G|F) \] (2.12)

ML estimators tend to produce an unbiased solution as the number of counts increases but exhibit the least variance among unbiased objectives. A problem in ML estimators is the ill-conditioning, whereby a small perturbation in the data results in parameter estimates with disproportionately increased variance. To avoid this increased variance, usually the optimization algorithm is prematurely terminated prior to the ML estimate. Another approach is the inclusion of a penalty term in the objective function, which represents our prior knowledge about the reconstructed image.

c) Least Squares and Weighted Least Squares

The Least Squares criterion also tries to minimize the inconsistency between the measured projections and the mapping of the image estimate through the system matrix (Fessler et al 1994).

\[ \hat{F} = \text{argmin}_f \| G - HF \|^2 \] (2.13)

As different projection data might have different variance properties, weighting can be introduced to control the significance of these projections in the solution. Least square estimators are similar to ML estimators when a Gaussian model is assumed for the data. Both LS and ML estimators enforce maximum consistency with the projections and as the data are dominated by noise so also do the image estimates.

d) Bayesian methods – The Maximum a Posteriori criterion

Similar to the ML criterion is the MAP criterion, having an additive term called the prior, which enforces smoothness.

\[ \hat{F} = \text{argmax}_f [\ln L(G|F) + \ln L(F)] \] (2.14)
This smoothing is based on prior knowledge that the imaging system is low-pass and so any higher frequency components will likely be attributed to noise. To model such a smoothing function, the Markov random field is usually chosen, which can be described by the Gibbs probability density function.

\[
L(F) = \frac{1}{Z} e^{-\beta U(F)} \tag{2.15}
\]

where \(Z\) is a normalizing constant, \(\beta\) is the weighting factor which balances the PDF contribution to the solution and \(U(F)\) is called the energy function and is based on correlations between neighbouring pixels. The MAP criterion is often called a penalized ML criterion, as it imposes a penalty on noisy estimates. This penalty term can also be imposed in the LS and WLS criteria. Instead of using the Gibbs PDF to impose image smoothness, one can use anatomical priors from MRI or CT data as the Gibbs PDF suppresses the contrast from true sharp edges in the image (Gindi et al 1993). On the other hand, anatomical priors may lead to inaccuracies as the anatomical boundaries may not coincide with the functional boundaries.

2.3.5 Iterative reconstruction algorithms

The fifth and last component of an iterative method is the algorithm that seeks the reconstructed image which minimises or maximises the objective function. Most of the algorithms follow some common steps. First an initial estimate is forward projected and compared with the measured projections. Then the error term from the comparison is back-projected and is used to update the initial image. It is the specific way of completing these tasks that distinguishes the different reconstruction algorithms. The first algorithm used in emission tomography was the Algebraic Reconstruction Technique (ART) along with the constraint satisfaction criterion. An initial image is projected in an algebraic sense in every plane defined by each projection bin, adding a correction term in every update. An extension of the method is the multiplicative ART, where the initial image is updated by multiplying with the correction term (Gordon et al 1970).

The most common algorithm which is being used for over 2 decades with great success is the expectation maximization (EM) algorithm, which is used to solve
maximum likelihood problems (ML-EM). Although known earlier (Dempster et al 1977) it was first introduced in Emission tomography by Shepp and Vardi (1982). The algorithm is similar to MART with the difference that all the pixels are updated simultaneously to produce an image within 30-50 iteration. The EM algorithm is a special case of a more general category of reconstruction methods called optimization transfer methods. In these more general methods, the cost function is replaced by another one (one can choose from a whole series of surrogate function), the optimization of which results in the optimization of the original cost function. The method is applicable both to ML as well as MAP objective functions. Since for each EM iteration one forward and one back-projection is needed, the process is considerably slower than FBP, where only a back-projection is needed. To address the slow convergence, Hudson and Larkin (1994) introduced the ordered-subsets EM (OSEM), where the projections are grouped into subsets and each subset is separately used in each sub-iteration to update the image. The number of subsets governs the degree of acceleration, while the projections of each subset should ideally have maximum angular differences. For example if we consider having 336 angular views and 21 subsets, then each subset has 16 projections with 22.5º angular difference between them, considering a 360º coverage. Although computationally efficient, OSEM does not converge to the ML estimate when noisy data are considered. Since the original algorithm by Hudson and Larkin (1994), different variations leading to convergence have been introduced. Another two algorithms, trying to accelerate convergence, are worth mentioning. The first is the space alternating generalized EM by Fessler and Hero (1994), where each pixel is updated individually using an alternate approach to the complete data space. The second one is the row action ML algorithm by Browne and De Pierro (1996), which is similar to OS-EM with the addition of a step-size adjustment factor. This is decreasing in every iteration, until convergence is reached.

To solve the LS criterion, there are a number of methods, all of which follow the same pattern. The initial image is updated via a search direction (such as the gradient), using a step size in a specified direction. It is the way the direction is chosen that differentiates the algorithm. In the steepest ascent algorithm, the algorithm makes a step in the direction the objective function changes the fastest (Lewitt and Muehllehner 1986). Conjugate gradient algorithms are more effective, achieve convergence in fewer iterations and a step in one direction is not affected by a previous step in another
direction (Kaufman et al 1993). Further speedup in both steepest ascent and conjugate gradient methods can be achieved using a pre-conditioner. Another algorithm is the coordinate descent, where each pixel is updated individually, with the direction vector being 1 in the updating pixel and zero everywhere else (Fessler et al 1994). Finally there are a number of algorithms which solve the MAP criterion and are similar to the ML-EM algorithms. The main one is called MAP-EM and has a form similar to ML-EM, with the addition of a prior term. An extension is the generalized EM MAP, where the pixels are updated sequentially. An excellent and extensive review in image reconstruction from projections can be found in Leahy and Qi (2000) and Qi and Leahy (2006).

2.4 Image reconstruction based resolution recovery

PET is a highly quantitative imaging technique but despite advancements in correcting for the physical effects which introduce bias in parameter estimates, such as scatter and attenuation, biases introduced from the limited spatial resolution and finite image sampling, collectively referred to as partial volume effects (PVE), are usually overlooked. Here we discuss the spatial resolution related PVE due to physical and detector spatial resolution limiting effects and its correction using image reconstruction based resolution recovery techniques.

2.4.1 Spatial resolution in PET

As mentioned in the 1st chapter, spatial resolution in oncology PET is of high importance as it affects both the quantitative as well as qualitative accuracy of the reconstructed images, due to apparent changes in the tumour uptake from activity spilling in and out as well as in the tumour size and shape.

Spatial resolution in PET can be characterized using a point or a line source sufficiently smaller than the intrinsic spatial resolution of the system, to measure the FWHM of a profile along the axial, radial and tangential direction. The blurring introduced to the point/line source by the imaging process is referred to as the system’s point/line spread function (PSF/LSF). This PSF is the product of a number of resolution limiting effects which can be categorized into emission and detection effects.
**Emission effects**

There are 2 main physical factors dictating the intrinsic spatial resolution of a PET system. The first is the distance between the point of positron emission and annihilation, referred to as positron range (Levin et al 1999). Positrons from different isotopes are emitted with different maximum energy and different energy distributions, which has a profound effect on the positron range. After emission, positrons lose energy through elastic and inelastic interactions, mainly with atomic electrons, exciting or ionizing them along their path. The PSF distribution resulting from positron range has a sharp spike with small FWHM, but with long exponential tails, resulting in a larger effective FWHM. Apart from the positron energy, positron range depends on the medium it traverses, which results in a further complication. If a spatially-variant positron range model is to be considered, a tissue density map is needed in which case a CT can be used to guide the process (Alessio and Macdonald 2008). Table 2.1 shows the spatial resolution degradation for a number of positron emitting isotopes caused by the positron range, while in Figure 2.2 simulated positron tracks are shown for $^{18}\text{F}$ in water. The second limiting physical factor is the photon non-collinearity and its origin is the residual momentum in the electron-positron system prior to annihilation causing a small deviation of $0.25^\circ$ FWHM in the photon angle due to conservation of momentum (Shibuya et al 2007).

<table>
<thead>
<tr>
<th>Isotope</th>
<th>Maximum positron energy (MeV)</th>
<th>FWHM (mm)</th>
<th>Effective FWHM (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$^{18}\text{F}$</td>
<td>0.64</td>
<td>0.13</td>
<td>0.54</td>
</tr>
<tr>
<td>$^{11}\text{C}$</td>
<td>0.96</td>
<td>0.13</td>
<td>0.92</td>
</tr>
<tr>
<td>$^{13}\text{N}$</td>
<td>1.2</td>
<td>0.17</td>
<td>1.35</td>
</tr>
<tr>
<td>$^{15}\text{O}$</td>
<td>1.7</td>
<td>0.28</td>
<td>2.4</td>
</tr>
<tr>
<td>$^{68}\text{Ga}$</td>
<td>1.9</td>
<td>0.31</td>
<td>2.8</td>
</tr>
<tr>
<td>$^{82}\text{Rb}$</td>
<td>3.4</td>
<td>0.42</td>
<td>6.1</td>
</tr>
</tbody>
</table>

*Table 2.1* Table showing the positron energy and the corresponding PSF FWHM caused by the positron range. (adapted from Lecomte 2004)
The spatial resolution degradation can be estimated as:

$$FWHM \approx \left(0.25 \times \frac{\pi}{180}\right) \times \frac{D}{2} \quad (2.16)$$

with $D$ being the scanner’s diameter. For a whole body scanner with a ~850 mm diameter, such as the HiRez PET/CT, the FWHM would be ~1.87 mm.

Detection effects

These effects include the detector size, inter-crystal Compton scatter, crystal penetration or parallax error as well as positioning mis-identification due to light sharing, pulse pile up and PMT effects. Detector size plays an important role in the system’s spatial resolution, as it dictates the sampling distance during data acquisition, with a FWHM equal to half the detector width. The inter-crystal scatter is closely linked with the resolution degradation, caused by the light sharing and the scintillator – PMT coupling. Although reducing the amount of light shared between adjacent crystals using improved scintillator – PMT coupling can improve resolution, multiple Compton scatter interactions are still a source of spatial resolution degradation. Their overall effect on the FWHM is however small due to their exponential distribution (Lecomte 2004).
Figure 2.3 Three of the resolution limiting effects in a PET system: positron range (i), photon non-collinearity (ii) and angular dependent crystal penetration (iii)

So far all the described emission and detection effects produce an almost Gaussian symmetrically distributed PSF in the centre of the scanner’s FOV, with a FWHM analytically calculated by the following equation (Moses and Derenzo 1993)

\[
FWHM = \sqrt{\left(\frac{d}{2}\right)^2 + b^2 + r^2 + (0.0022D)^2}
\]  (2.17)

where d is the detector width, b is the accuracy from the position identification in the detector, r is the positron range, while the parameter 0.0022D accounts for the photon non-collinearity as mentioned before. The most significant effect contributing to the spatial resolution degradation comes from the radially dependent crystal penetration and the lack of depth of interaction (DOI) information. At the centre of the FOV the photons hit the detector surface with no angle and the LORs are correctly registered. Further away from the centre, due to the angle of incidence progressively increasing, the probability of a photon penetrating an adjacent detector increases and together increases the mis-positioning of the registered LOR. This effect causes the spatial resolution to be radially dependent. Apart from the radial parallax error, scanners acquiring in 3D mode, suffer from axial parallax errors due to the oblique sinograms. Although in the early scanners with small axial FOV and maximum ring difference (small polar angle) this axial effect was small, in modern scanners with larger axial FOVs, which acquire data with a large polar angle, such parallax error effects can be significant. To minimize
axial parallax errors in the centre of the axial FOV, geometries other than the conventional cylindrical ones have been explored, such as the barrel geometry on the Siemens HiRez PET/CT. Furthermore dual layer phoswich detectors have been used to measure the DOI and reduce the parallax error, such as the ones used on the High Resolution Research Tomograph (HRRT).

Apart from these effects, other data acquisition and reconstruction effects can also affect spatial resolution, such as the axial under-sampling (span), the angular mashing, the projection interleaving, the sinogram rebinning, the image discretization scheme, the post-reconstruction filtering and the number of iterations. All these software related effects can be adjusted to control the trade-off between spatial resolution and statistical noise.

2.4.2 Partial volume correction using image reconstruction based resolution recovery

There are a number of partial volume correction (PVC) methods, some of which attempt to improve only the regional quantitative accuracy, while others attempt to produce PVC images tackling both quantitative and qualitative accuracy.

The simplest way of correcting for PVE is to delineate the structure/tumour of interest and apply a pre-calculated recovery coefficient (RC), which is unique for different tumour sizes and shapes, background contrast, reconstruction parameters and scanner model (Geworski et al 2000). For more complex structures, were the ROI is close to many different uptake regions of varying intensity, the geometric transfer matrix (GTM) approach maybe more suitable, which is a generalization of the RC method (Rousset et al 1998). These methods work well for regional PVC, but for parametric imaging at the voxel level, PVC images are needed.

As mentioned in the introduction, PVEs are a combination of spatial resolution effects and tissue fraction effects from reduced image sampling. As such a number of PVC methods exist in the literature which attempt to correct for either of the 2 effects and produce PVC parametric images, such as partition and multi-resolution based methods, deconvolution techniques as well as kinetic model based PVC, many of which use some sort of anatomical information based on MRI data (Iida et al 1988b, Labbe et al 1998, Boussion et al 2006). Here we are interested in the methods which attempt to correct for
PVE by recovering the spatial resolution during the image reconstruction process. All of these methods take into account the scanner’s PSF from one or more of the spatial resolution degrading effects mentioned before.

One of the benefits of statistical image reconstruction algorithms is the ability to model the emission and detection effects which cause the spatial resolution to degrade and the imaging process to deviate from the line integral model. Strictly speaking image reconstruction methods, modelling the different resolution degrading effects, should not be considered as resolution recovery methods, as opposed to the other post-reconstruction strategies which are trying to ‘recover’ the spatial resolution lost during the image reconstruction, but as a natural extension of the statistical model-based iterative reconstruction methods. The accuracy with which these degrading effects are modelled, directly affects the accuracy and spatial resolution of the reconstructed image. They can be factored independently with a separate PSF for each of the blurring effects, but a more sound approach is to consider a combined PSF encompassing all the resolution degrading effects. These effects can be modelled as of being effects acting either in sinogram space or in image space.

**Sinogram space modelling**

This approach seems logical as in $^{18}$F applications for example, were the positron range is small (and considered as acting on the image space), spatial resolution degradation comes primarily from the detector related effects. As such the system matrix, as defined in section 2.3.2, can be factorized into separate probabilities to reduce the storage (Mumcuoglu et al 1996, Qi et al 1998).

$$\bar{G}_m = \sum_i h_{im}^B \sum_j h_i^{At} h_i^{No} \bar{h}_{ji}^{Ge} f_j \quad (2.18)$$

Where $h_{ji}^{Ge}$ is a matrix holding the geometric probabilities mapping from image space to projection space ($F \mapsto G$), $h_i^{No}$ is the matrix holding the detector sensitivities ($G \mapsto G$), $h_i^{At}$ is a matrix holding the attenuation probabilities ($G \mapsto G$) and $h_{im}^B$ is a matrix holding the sinogram blurring components that limit the spatial resolution ($G \mapsto G$).

**Image space modelling**

Measuring the projection based PSF results in a 4-dimensional function which is difficult to measure and store and usually symmetries and simplifications are taken into account along directions and dimensions were the PSF is minimally variable. To avoid measuring such a multi-dimensional function the system’s PSF can be measured and applied in image space, where the blurring is a 3-D operation rather than a 4-D one. With this in mind the forward model becomes

\[

g_i = \sum_k h_i^{At} h_i^{No} h_i^{Ge} \sum_j h_{ij}^{Bl} f_j
\]  

(2.19)

Where now \( h_{ij}^{Bl} \) is a matrix holding the image blurring components that limit the spatial resolution, mapping from image space to image space (\( F \rightarrow F \)) and representing the probability of a positron emission in \( j^{th} \) voxel resulting in an event being reconstructed in the \( k^{th} \) voxel. Furthermore this approach can also be implemented using list-mode reconstruction, as projection space modelling is only applicable when reconstructing from projections.

Despite the reduced complexity of the image based modelling compared to sinogram based modelling, until recently only limited studies existed in the literature (Reader et al 2001, 2002, 2003, Rahmim 2003, Sureau et al 2008, Rapisadra et al 2010, Cloquet et al 2010, Kotasidis et al 2011). Nevertheless image based methods are only approximating the resolution limiting effects and as such in theory are expected to be less accurate compared to sinogram based resolution modelling methods.
2.4.3 Deriving the PSF

Although image based and projection based methods are different in terms of their implementation within the image reconstruction, both require estimation of the PSF model. This is done either by analytic derivation (Rahmim et al 2008b, Moehrs et al 2008), Monte Carlo simulations (Alessio et al 2006, Ortuno et al 2006), or by measuring the scanner response to a point source at different points in the field-of-view (FOV) (Panin et al 2006, 2007, Wiant et al 2009, Tohme et al 2009, Cloquet et al 2010, Alessio et al 2010, Rapisadra et al 2010, Kotasidis et al 2011). Simulations provide the most flexible approach as the geometric and the blurring components can be separated, but again such calculations needs to be validated with real data. Scanning a collimated point source at every voxel in the FOV can provide the most accurate results, but such an experimental approach is difficult to set up due to collimation.

Deriving the PSF from real point source measurements is a very laborious process. Conventionally this method requires a point source positioned and scanned at different but known locations in the FOV. In addition, for projection space resolution modelling (RM), in order to derive the angular blurring component in projection space, the point source needs to be collimated to avoid crosstalk from adjacent LORs. For that reason, typically measurements with an un-collimated point source are used, assuming no blurring in the angular direction. This also enables the use of ordered subsets type reconstruction algorithms, since there is no blurring across LORs within different subsets. Using a point source, at the location of each image voxel, the blurring kernels can in theory be derived. However in practice this involves a huge number of measurements and restricts the reconstructed image grid to be the same as the one used for the PSF measurement. For that reason, interpolation and extrapolation of a limited number of measurements is typically performed, using a parameterized model of the blurring.

2.5 Spatiotemporal 4-D image reconstruction

So far we have considered the image reconstruction problem as the one of recovering the coefficients of the spatial basis functions, which in the case of static imaging are the voxel intensities. The task of PET image reconstruction in the context of dynamic
imaging can be thought as of recovering the temporally varying voxel-wise activity concentration, which when mapped through a temporal model describing our expectation of the temporal distribution of the administered radio-labelled tracer, can result in parameters regarding underlying physiological and biochemical functions.

Due to the aforementioned problems associated with this conventional 2 step approach, as analyzed in chapter 1, a number of authors have attempted to tackle these by introducing reconstruction methods which address some or all of them. All these methods, one way or another, are trying to incorporate the temporal dimension within the reconstruction process and as such can be considered as fully 4-D image reconstruction methods. A differentiation can be made, as some of these methods make use of a non-physiologically based temporal model, as a means of temporal regularization prior to parameter estimation. These methods are referred to by many researchers as ‘indirect’ 4-D methods, as although they use a model as a temporal constraint between the frames, they deliver parameter estimates via a 2 step route. In a second group of methods, a joint approach to parameter estimation is used, where kinetic parameters are estimated directly during or before the reconstruction process in a single step. These methods are often referred to as ‘direct’ 4-D methods as they use physiologically meaningful kinetic models. As such, the task of image reconstruction can be thought as of reconstructing parameter estimates directly from measured projections, without any intermediate step. In the rest of the chapter, an overview of the different 4-D image reconstruction techniques that can be found in the literature is presented, with an emphasis on direct 4-D image reconstruction strategies.

2.5.1 4-D image reconstruction methods for temporal regularization

2.5.1.1 Temporal smoothing

Temporal smoothing is based on the similar behaviour neighbouring time frames have. Walledge et al (2004) exploiting this concept, applied a filtered image of the previous frame as the initializing image for the next frame. In this way, high frequency details that are retained after filtering, force the current estimate to estimate them with less iterations. In this way a temporal correlation is achieved. On the other hand, the method also introduces noise early in the estimation, along with the signal high
Figure 2.4 The 3 left figures show the 3-D spatial domain clique in the Gibbs prior while the right one is the 1-D temporal domain clique (Lee et al 2005a)

Another approach to enforce temporal smoothing is to apply it as a penalty term within a MAP framework (Lalush et al 1996, Lee et al 2005a). The algorithm they implemented is an extension of the 3D MAP RBI EM to 4D MAP RBI EM using a spatiotemporal 4-D Gibbs prior. Figure 2.4 illustrated the concept behind a 4-D prior. A similar method was used by Jonsson et al (2000), where the prior is proportional to the square value difference between adjacent pixels. An extension of the method by Lalush et al (1996) was proposed by Kadrmas and Gullberg (2001), as they used a compartmental model based temporal smoothing prior. The prior is calculated based on the voxel wise fitted TAC, which is updated in every iteration. In this way the parameter estimates change in each iteration, along with the prior term. At the extreme end of this method, Reader et al (2007a) interchanged the reconstructed intensity in the intermediate images with the intensity after fitting the model first. In this way a smoothing is performed due to the fitting and omits the need for any prior term.

2.5.1.2. Temporal basis functions

Another way to tackle the SNR problem is to consider an intermediate state between reconstructing separate frames and a static summed image. In the first case, the temporal basis functions (TBF) used are top hat functions, denoting frame independence. In this way, only a fraction of the data are used for each frame, while using more complex TBF, data before or after the current frame are considered. The use of TBF is based either on the data itself or the physiologic model under study. In the former case a smoothing is achieved while in the latter the basis coefficients have physiologic meaning. Asma et al (2000) and Nichols et al (2002) in PET and Reutter et al (2000) in SPECT, used a set of b-spline TBF, with the reconstruction having to recover the basis coefficients. They used a penalized ML criterion with a conjugate
gradient algorithm and with the coefficient images having no physiological meaning. The b-splines are defined by knots which are placed non-uniformly to better model the rate of change of the TAC at different time points. They have the advantage that they are well conditioned and small changes in the coefficients create small changes in the image. A careful knot optimization though is needed. Nichols et al (2002) used information from the head curve to optimize spline order and knot density, while Verhaeghe et al (2004) used the inter-iterations TACs. A higher order b-spline was found to better smooth the data, while denser knots better represent fast kinetics with the expense of noisier TACs. Figure 2.5 shows different b-spline basis functions that can be used to enforce temporal correlation. In an extension of the method, Verhaeghe et al (2006, 2007a, 2007b) proposed joint estimation of coefficients and b-spline TBF. Knots are not defined a priori, but are optimized within the ML-EM. This approach has similarities to the method of Reader et al (2006) where a more general approach was used. The TBF are not specified a priori but are left to be jointly estimated with the coefficients. First the TBF are optimized for fixed iterations keeping the coefficients constant and then the TBF are fixed while the coefficients are optimized. This method though increased the computation time an order of magnitude. Some level of acceleration was achieved (Reader et al 2007b) by simultaneously updating the coefficients and the basis functions. The method reduced the reconstruction time to half, omitting the need to specify the iterations for each cycle. On the other hand a relaxation term on the EM algorithm is needed to avoid instabilities.

2.5.1.3. Karhunen – Loeve transformations and Principal Component Analysis

Another approach in 4-D reconstruction is the Karhunen – Loeve (KL) transformation of the entire dynamic sequence. The theory behind the KL transformation is based on the fact that a temporally correlated spatial imaging sequence can be transformed into a number of un-correlated components. Wernick et al (1997, 1999) proposed a penalized weighted least squares (PWLS) algorithm were the entire spatiotemporally distributed data are KL transformed based on principal component analysis (PCA). If the penalty term is separable in space and time, the un-correlated components can be reconstructed independently.
Using inverse KL transforms the entire 4-D set is obtained. As the signal is contained in the first 2-3 components according to the authors, the rest of the components can be discarded and not reconstructed as they contain only noise. This strategy further reduces the reconstruction time. KL transforms have also been used in CT (Lu et al 2002), as well as in SPECT (Narayanan et al 1999, Fan et al 2007). Although PCA provides a set of smoothed TACs, it is difficult to be used within an ML-EM algorithm as the non-negativity constraint cannot be imposed in KL space. In the aforementioned methods, PCA is applied without a sinogram noise normalization step while Chen et al (2004) include a noise normalization, to account for the variable noise properties in each frame (Figure 2.6). Also all the methods use the high order component truncation to further smooth the data but an optimal truncation scheme is still left to be optimized.

2.5.1.4. Wavelet transformations

In the last decade, wavelets have brought increasing interest in their use in PET and imaging generally. Wavelets transform a signal into a sum of translations and dilations of a band-pass function called the mother wavelet.
The signal decomposition is in space and frequency, compared to a Fourier transform (frequency only) (Figure 2.7). This decomposition gives a set of coefficients for a set of basis functions. By thresholding the coefficients, a signal denoising is achieved (Figure 2.8). In static image reconstruction wavelets have been used both with analytic and statistical methods. Donoho et al (1995) used the so called wavelet-vaguelette decomposition with FBP. In statistical image reconstruction, wavelets can be used to denoise the data (Kisilev et al 2000) or to serve as a prior term within a MAP framework. Figueiredo and Nowak (2003) and Lee et al (2007) using a wavelet MAP algorithm, modelled the data using wavelets and reconstructed the wavelet coefficients. Wavelets have also extensively been applied to de-noise dynamic PET data post-reconstruction, both in the spatial and the temporal dimension (Millet et al 2000, Lin et al 2001a, 2001b). Turkheimer et al (2000) pioneered the field by applying kinetic modelling in the wavelet space.
All the aforementioned wavelet methods either apply wavelet decomposition in the temporal and spatial dimension post reconstruction, or apply a spatial decomposition during frame by frame reconstruction. A better approach though is to de-noise the data during reconstruction. Verhaeghe et al (2008) used a spatiotemporal wavelet basis function within a fully 4-D reconstruction. They used the PLS criterion and maximized it using the iterative thresholding algorithm (Daubechies et al 2004). A b-spline wavelet was used for the spatial dimension and an e-spline for the temporal.

2.5.2 4-D image reconstruction methods for direct parameter estimation

All the aforementioned methods are trying to improve SNR, without though considering the parameter estimation problem, which is the endpoint of image reconstruction in dynamic imaging. In order to simplify the parameter estimation sequence and directly reconstruct parameters of interest in a single step, a joint approach can be used to create parametric images by modelling the data before or during reconstruction.
2.5.2.1. Parametric Sinograms

One approach is to apply the kinetic modelling directly on the projection data, so as to reconstruct a single set of parametric sinograms. The concept was first conceived by Tsui and Budinger (1978) as they tried to calculate the mean clearance time of a tracer in projection space. The methods can be categorized based on the applied model. Limber et al (1995) used 2 exponential basis functions to model the projection data. It was Meikle et al (1998) who first derived a set of parameters (Vd and Ki) directly from projection data. To model the data, a spectral analysis method was used. This modelling approach is particularly advantageous in oncology, where the in vivo radiotracer distribution is not known for new anticancer drugs. The impulse response function (IRF) is directly reconstructed from the summed IRFs over a specific LOR in the projection domain. The method provides 2 orders of magnitude improved SNR compared to the conventional approach, but with expense of bias, especially at the IRF extremes. This can be attributed to the noisy data and the fact that the projection data contain heterogeneous dynamics from different tissues along a given LOR, causing adjacent coefficients to merge. Also as the NNLS algorithm is used, it breaks down when negative bin values are used after subtraction of scatter or randoms. A similar approach to Meikle et al (1998) was also used by Bentourkia (2002). The technique has also been used in SPECT to directly estimate macro-parameters of interest (Maltz et al 2000). Matthews et al (1997) proposed a method based on singular value decomposition (SVD) to derive a set of basis functions. Then, based on these BF, spectral analysis was performed. Maguire et al (1996) also derived a set of macro-parameters by exploiting the fact that data transformation, based on Patlak graphical analysis, can yield a set of 2 basis functions. Reconstructing the coefficients, 2 parametric images are obtained. Arhjoul et al (2007) wavelet transformed the projection data, applied a Patlak model on the transform data and inverse wavelet transformed the coefficients prior to reconstruction (Figure 2.9). The method produces superior images as further denoising is applied using wavelets. Although the direct sinogram methods result in reconstructing parametric images, they can only be applied with linear models which can be extended to projection space as the projections are linearly related with the pixels along a given LOR. Also after modelling the data the Poisson distribution is no longer a valid assumption.
2.5.2.2. Direct parameter estimation during image reconstruction

A problem encountered in kinetic modelling is the accurate knowledge of the variance distribution in every frame, in order to weight the data contribution during the fitting procedure. While analytic and approximate formulae for the weighting can be calculated for FBP reconstructed data, in iterative reconstruction methods such a formula is not straightforward. This is due to pixel correlations and algorithm non-linearity. Including the parameter estimation within the reconstruction, a better estimate can be used for the variance as the raw data are considered to follow the Poisson distribution. The parameter estimation can follow 2 routes: ROI imaging and parametric imaging.

2.5.2.2.1. Direct ROI reconstruction

When modelling a regional TAC, ROI delineation is done either manually or using one of the many automatic methods. In order to directly reconstruct a regional parameter of interest, prior knowledge about the ROI is needed. Zeng et al (1995) and Huesman et al (1998) applied one and two tissue models in the forward model to derive regional kinetics. To obtain the regional boundaries, an initial reconstruction was obtained from the summed data to calculate ROI information. As this is impractical...
Chiao et al (1994a) used a joint estimation method to derive the kinetics and the boundaries simultaneously. In an extension and when ROI boundaries are difficult to be obtained from noisy images Chiao et al (1994b) used prior information from MRI and CT, which were incorporated within a penalized ML framework. An intermediate state between ROI and voxel imaging is cluster imaging. Clusters are formed from voxels having similar kinetics and thus resolution in the image is retained, improving SNR (Kimura et al 1999). Kamasak et al (2007, 2009) used clustering directly in projection data for Poisson and Gaussian (pre-corrected) distributed data.

2.5.2.2.2. Direct parametric reconstruction

The ROI approach suffers from all the aforementioned problems analyzed in chapter 1 (section 1.6). As such, direct parametric imaging is the obvious way to calculate parameters, while maintaining the spatial resolution of the emission image. It was Snyder et al (1984) and Carson and Lange (1985) who first proposed such a scheme within an EM algorithm, without though implementing it. A plethora of direct parametric reconstruction methods have been implemented since then, both for linear and non-linear kinetic models.

Kamasak et al (2005) was one of the first to directly derive a set of micro-parameters of interest, using the 2-tissue compartmental model with a MAP criterion and a coordinate descent algorithm. Since the model is nonlinear in its parameters, the algorithm has nested optimization sub-algorithms to decouple the non-linearity from the system model. The method as expected is slower, but less biased estimates are calculated. Using an EM based direct reconstruction algorithm Yan et al (2008, 2010) derived a set of micro-parameters for the 1-tissue compartment model.

Although with 4-D algorithms incorporating nonlinear compartmental models all the rate constants are directly estimated, these are time consuming, complex and usually slow to converge. As such, algorithms have also been implemented for linear kinetic models. Wang et al (2008a) incorporated a Patlak graphical analysis model with a MAP criterion. In a similar manner Tsoumpas et al (2008) also used Patlak analysis using the parametric iterative reconstruction algorithm of Matthews et al (1997). The algorithm improved SNR and mean square error (MSE), but introduced small bias in small objects. Moreover, reduced convergence in heterogeneous areas was seen along with increased reconstruction time. Rahmim et al (2010) applied a similar 4-D algorithm for
direct Patlak parameter estimation in oncology FDG patients, showing reduced noise compared to conventional Patlak parametric images. Similar algorithms have been implemented for reversible kinetics by Rahmim et al (2009), who incorporated a Logan graphical analysis method within a 4-D algorithm and demonstrated its applicability in plasma as well as reference tissue models.

Apart from graphical analysis models, data driven models have also been used within a 4-D framework. Reader et al (2007c) advanced the field by simultaneously estimating a system IF and the spectral coefficients. In a first step, the coefficients are optimized keeping the IF constant, while in a second step the coefficients are kept constant optimizing the IF. The method has been used by the authors as a means to regularize the data and as such it belongs to the TBF approaches. In the case of a true IF though, it can return the true BF coefficients and in this sense is a direct method. A similar concept has also been attempted in SPECT (Reutter et al 2005). Wang and Qi (2009a) used a similar approach to include spectral analysis within a MAP reconstruction, using a Laplacian prior as sparsity regularization, similar to the one used by Gunn et al (2002) in the basis pursuit approach to spectral analysis.

As mentioned above, one problem when non-linear compartmental models are used within a 4-D framework is that the resulting algorithms can be more complicated than their post-reconstruction counterparts and exhibit slow convergence. To tackle these issues due to the coupling between the emission image reconstruction problem and the kinetic parameter estimation problem, Wang and Qi (2009b) proposed an algorithm to decouple these 2 components using the optimization transfer principle and paraboloidal surrogate functions. In an extension of this work, they used linear Patlak and spectral analysis models within a nested EM algorithm (Wang and Qi 2010), while similar is the work of Matthews et al (2010) in which following separation between the image and projection space problems, the ML image based problem is transformed into a LS problem for which many existing methods can be used. Using the same optimization transfer approach also Wang and Qi (2009c) developed a minorization-maximization algorithm to include a simplified reference tissue model within a 4-D framework. Finally, along similar lines with the work of Wang and Qi (2009b, 2010) is the work of Rahmim et al (2011), who also used a decoupling technique and a surrogate function with a single compartment model to directly estimate myocardial perfusion in $^{82}$Rb imaging.
CHAPTER 3

Pharmacokinetic modelling in $^{15}\text{O}]\text{H}_2\text{O}$ perfusion imaging
3.1. Introduction

Spatiotemporal 4-D image reconstruction methods have the potential to improve quantification and signal to noise ratio, by incorporating temporal information in the reconstruction process. In the previous chapter, a number of 4-D spatiotemporal image reconstruction strategies were reviewed, with an emphasis on direct estimation of kinetic parameters from projection data. In this chapter we review the theory and the different parameter estimation schemes in PET perfusion imaging, with an emphasis on methods applicable in dynamic imaging.

Combining traditional 3-D image reconstruction and pharmacokinetic modelling into one step, is a challenging task and 4-D methods are expected to behave differently, depending upon the tracer and application. However, the behaviour of the kinetic modelling as independent process is expected to be similar to when applied to 4-D methods and as such one can draw conclusions about the accuracy and precision of different kinetic modelling parameter estimation schemes by, investigating these processes at reduced dimensions. For that purpose, 1-D simulations were used to investigate a variety of kinetic modelling strategies applied to perfusion imaging and separate from image reconstruction. Different methods were implemented and assessed using simulated \[^{15}\text{O}] \text{H}_2\text{O}\) time-activity curves at varying noise levels. More specifically the linear least square (LLS), generalized linear least squares (GLLS) and basis function (BF) parameter estimation methods were evaluated using a number of simulations to optimize individual parameters in each method, as well as to compared the different methods between them (Boellard et al 2005).

3.2. Measuring perfusion with Positron Emission Tomography

3.2.1 Perfusion and the Renkin–Crone model

The Renkin–Crone model (Renkin 1959, Crone 1963), describes how 3 distinct quantities, namely the perfusion (F), the permeability (P) and the surface area (S) affect the Extraction Fraction from plasma to tissue (E) of a radiotracer such as \[^{15}\text{O}] \text{H}_2\text{O}\). Only the product of the last two is required and is called the permeability surface area product.

\[
E = 1 - e^{-\frac{PS}{F}} \quad (3.1)
\]
At a specific perfusion, it is up to the permeability surface area product whether or not the substance or the specific tracer will be completely extracted or whether some will pass into venous blood. The permeability is tracer specific for a given tissue, while the surface area has to do with the available capillary bed surface for the tracer to exchange. If the combination of P and S is high compared to perfusive flow, the extraction fraction will be independent of perfusion, resulting in a complete extraction fraction (unity). If PS is low, then the extraction fraction is influenced by perfusion. Considering the exchange rates between blood and a single tissue compartment, the influx rate \( K_1 \) is the product of extraction fraction and perfusion

\[
K_1 = EF \quad (3.2)
\]

It can be seen that in the case of tracers with high PS compared to perfusive flow (extraction fraction equals to unity), one can measure perfusion (F) by calculating the kinetic rate constant \( K_1 \), assuming complete exchange between plasma and tissue. For tumour perfusion imaging with \(^{15}\text{O}]\text{H}_2\text{O} \), as the normal values are below 100 ml/min/100g, the above model is valid and complete extraction can be hypothesized Laking et al (2006). \(^{15}\text{O}]\text{H}_2\text{O} \) is a chemically inert, freely diffusible tracer, which has almost 100% first pass extraction and is suitable for perfusion measurements. It has been used for the first time at the early 80’s to measure cerebral blood flow (CBF) by Frackowiak et al (1980) and Herscovitch et al (1983) among others. The \(^{15}\text{O}]\text{H}_2\text{O} \) can either be injected using a bolus, or inhaled in the form of \(^{15}\text{O}]\text{CO}_2 \) and subsequently converted to \(^{15}\text{O}]\text{H}_2\text{O} \) in the lungs. As this sequence is more time consuming, the scan lasts longer, requiring larger doses and the rate of increase of radioactivity in blood is less sharp (which is undesirable for modelling) with only a fraction of the administered dose is absorbed, although radioactivity exposure occurs to the patient and in particular the lungs. Also due to accumulating activity in the lungs, spill over effects to abnormal thoracic uptake might be possible and bolus injection is the preferred choice in many cases (Anderson et al 2002).

### 3.2.2 The Kety – Schmidt model and perfusion kinetics

In 1951 Kety et al formulated a model for the measurement of CBF. This model is based on the mass equilibrium law (Fick’s principle) which states that the rate of change
of a quantity in a tissue, equals the difference between arterial and venous concentration multiplied by the flow

\[
\frac{dq(t)}{dt} = \Phi(C_A(t) - C_V(t)) \quad (3.3)
\]

where \( q(t) \) is the molecular equivalent of the tissue quantity in the original formulation, while it is equal to activity (kBq) using the tracer principle in PET, \( \Phi \) is the blood flow, \( C_A(t) \) is the arterial concentration and \( C_V(t) \) the venous concentration (Figure 3.1).

\[\Phi[ml/min] \quad Q(t)[Bq] \quad \Phi[ml/min] \]
\[C_a(t)[Bq/ml] \quad M[g] \quad C_v(t)[Bq/ml]\]

Figure 3.1 The fick principle for blood flow

However perfusion in medical sciences is the nutritive flow over a tissue volume and so dividing with the perfusive tissue, the model becomes:

\[
\frac{dC_{PET}(t)}{dt} = f(C_A(t) - C_V(t)) \quad (3.4)
\]

where \( C_{PET}(t) \) is the measured tissue concentration by the scanner and \( f \) is the blood flow per unit volume of tissue (Figure 3.2). Assuming all the blood flow \( (f) \) is perfusive blood flow (i.e. it travels through capillary bed) and the PS product is large relative to flow, then venous blood equilibrates with the concentration in tissue.

\[f[ml/min/g] \quad Q(t)[Bq] \quad f[ml/min/g] \]
\[C_a(t)[Bq/ml] \quad M[g] \quad C_v(t)[Bq/ml]\]

Figure 3.2 The Fick principle for perfusion
However there is only a certain fraction of the tissue the water can enter (i.e. not into lipid deposits) and hence the concentration in tissue is the concentration in the tissue region divided by this fractional volume ($V_d$) that water occupies.

$$\frac{dC_{PET}(t)}{dt} = f\left(C_A(t) - \frac{C_{PET}(t)}{V_d}\right) \quad (3.5)$$

This is equivalent to a single tissue compartmental model, with the $K_1$ being equal to perfusion ($f$) and $k_2$ being equal to ($\frac{f}{V_d}$). The operational equation using the impulse response function (IRF) convolved with the input function (IF) is given by:

$$C_{PET}(t) = C_A(t) \otimes f e^{-\left(\frac{f}{V_d}\right)t} \quad (3.6)$$

### 3.2.3 Delay and Dispersion in the 1-tissue compartment model

As the IF is needed for the 1-tissue model, it is usually measured in a peripheral sampling point. Due to the fact that the measured IF suffers from delay and dispersion due the peripheral location of the sampling artery and the apparatus used for measurement, corrections are needed. The delay is due to the difference in tracer arrival time between the sampling point and the tissue of interest, while the dispersion refers to the differential blurring of the input function due to heterogeneity of flow rates through arteries and tubing used to withdraw and sample the blood. Iida et al (1986) modelled dispersion using a mono-exponential function. The measured and the dispersion corrected IF is given by:

$$C_A(t) = C_A'(t) \otimes \frac{1}{\tau} e^{-\frac{t}{\tau}} \quad (3.7)$$

where $\tau$ is the dispersion time constant, $C_A(t)$ is the measured IF and $C_A'(t)$ the delay and dispersion corrected IF. Including the delay $\Delta t$:

$$C_A'(t) = C_A(t - \Delta t) + \tau \frac{dC_A(t - \Delta t)}{dt} \quad (3.8)$$

Van Den Hoff et al (1993) used a dynamic protocol to fit the delay and dispersion as well as perfusion and $Vd$, to the measured data, with the last being constant in Meyer’s implementation. After linearizing the operational equation (Blomqvist et al 1984) he derived a graphical approach similar to the graphical approaches used in the 2 tissue model (Patlak et al 1983), to evaluate delay and dispersion. Although the method fits delay and dispersion together, it suffers from noise correlation due to the integration in the linearization process. Hinz et al (2006) using a spectral analysis approach calculated a global delay parameter for the brain in neuroreceptor studies. They used the total counts in the FOV to fit a predetermined set of delay BF. On a second step having a constant delay they fitted the ROI TAC’s to calculate perfusion and $Vd$.

When the heart or the aorta is in the FOV, especially in thoracic imaging, then image derived IF (IDIF) can be used omitting the need for corrections, but such an approach suffers from PVE due to reduced resolution and sampling. Watabe et al (2001) first used IDIF from the aorta in a [$^{15}$O]H$_2$O study. For accurate delineation of the aorta, they used a [$^{15}$O]CO scan and measure the diameter of the aorta from reconstructed image profiles.

3.2.4 Partial volume and vascular effects

As it was mentioned in chapter 1, small tumours can be affected by PVE. This phenomenon is more obvious during the influx phase where there is no equilibrium between the blood and tissues and the activity only spills out. To compensate for this effect, a partial volume correction term ($p \leq 1$) is added in the model, which can either be constant or allow to be fitted simultaneously with the parameters of interest. This parameter takes into account the fact that perfusion is artificially reduced due to the activity concentration affected by PVE. Adding such a term and fitting for it instead of fixing it, results in only being able to estimating the combined term ($pf$). If $Vd$ then is not fixed, perfusion cannot be measured neither from the influx nor from the efflux part of the TAC.

$$C_{PET}(t) = C_A(t) \otimes pf e^{-\frac{t}{Vd}}$$  \hspace{1cm} (3.9)

Another addition to this model originates from the fact that even in parametric imaging, where the region of interest is the smallest possible, portion of the signal includes a
vascular contribution from adjacent arteries. The ROI or pixel TAC then is a summation of the true uncontaminated tissue TAC and the arterial blood TAC. The model then is formulated as:

\[
C_{\text{PET}}(t) = C_A(t) \otimes p f e^{-k_{\text{vid}} t} + V_a C_A(t) \tag{3.10}
\]

where \( V_a \) is the fractional blood volume. When the tumour is surrounded by venous blood, such a modification is not necessary, as for \([^{15}\text{O}]\text{H}_2\text{O}\) it is assumed that venous blood and tissue concentrations equilibrate (Bacharach et al 2000). With too many parameters to fit, strategies to omit the fractional blood volume term can be applied as a pre-correction step. One strategy is to use a \([^{15}\text{O}]\text{CO}\) scan, to visualize the blood pool and subtract it from the \([^{15}\text{O}]\text{H}_2\text{O}\) scan (Iida et al 1988b). This technique has problems associated with accurate registration and subsequent bias in the model, as well as the need for a second scan adding dose to the patient. Another method involves factor analysis of dynamic images, omitting the need for a CO scan. Factor analysis was proposed by Lee et al (2000) and is based on principal component analysis. It has the advantage of calculating the IF directly from the \([^{15}\text{O}]\text{H}_2\text{O}\) scan and can be used for pixel wise imaging due to reduced parameterization of the model. In cases though where \([^{15}\text{O}]\text{H}_2\text{O}\) is slowly infused and perfusion is elevated, factor analysis is unable to separate tissue from plasma TAC.

### 3.2.5 Parameter estimation schemes

Once the model had been formulated, there are a number of methods and techniques to calculate the parameters of interest. These methods are based either on alternative acquisition protocols, or on mathematical manipulation of the operational equation.

#### 3.2.5.1 The steady state method

The steady state (SS) method was first implemented by Jones et al (1976) and is based on tracer constant infusion to achieve equilibrium conditions between the uptake, the combination of washout and the decay of the isotope. After equilibrium, the operational equation is simplified and flow can easily be extracted with only one measurement (Figure 3.3). The method assumes a constant \( V_d \) and requires stable and continuous tracer supply from the cyclotron which results in a challenging protocol.
3.2.5.2 Auto-radiographic method

Autoradiography was used for the first time for CBF measurements by Herscovitch et al (1983). The method requires continuing blood sampling with only one PET measurement. To solve the operational equation a look-up table is used where perfusion is related to a number of counts. As in the SS, a fixed $Vd$ value is assumed.

3.2.5.3 Dynamic methods

3.2.5.3.1 Integration projection

Huang et al (1982) proposed a method based on the SS approach and applied it to calculate CBF in human Huang et al (1983). Time activity curves from the tissue and plasma are needed. The method assumes that after time $T$, the $C_{PET}(t)$ is zero and perfusion and $Vd$ can be calculated integrating the operational equation from the beginning of the scan until time $(T)$, using decay corrected and non-decay corrected data. Instead of reconstructing the data and then integrating, the technique allows the integration to be done in projection space, reconstructing the integrated image. One has to wait long enough for the equality to be valid or extrapolate, using data of reducing statistical quality towards the end of the scan.

3.2.5.3.2 Weighted Integration

Weighted integration was proposed by Carson et al (1986) and is an optimized version of the integration projection method. The weighting factors are optimized to minimize
the errors in the parameter estimates. Non-linear least squares (NLS) is used to iteratively solve the cost function which minimizes the mean square error for a specific parameter range and distribution, as well as for a specific IF. The method is based on standard template IF and the optimization is impractical for individual IF. Also using NLS for every IF will compromise the computational efficiency of the method.

### 3.2.5.3.3 Linearizations

Instead of using non-linear optimization techniques for parameter estimation, the operational equation can be linearized and parameters can be easily estimated using linear regression. The direct linearization was first applied by Blomqvist et al (1984) in the FDG model and was subsequently implemented for the flow model by Van Den Hoff et al (1993). Yokoi et al (1993) after linearizing and rearranging the data, obtain a graphical method for calculating both perfusion and $V_d$. Using linear regression the $x$ intercept gives the $V_d$ while the y intercept gives the perfusion. Feng and Ho (1993a) proposed the linear least square method (LLS) by directly integrating the operation equation, but the method, despite its attractive computational properties, suffers from bias in the parameter estimates due to noise and correlation of noise between frames. The bias problem can be partially solved using a generalized version of the LLS method (GLLS) (Feng and Ho 1993a). A number of studies in the literature have made use of the LLS and GLLS methods to generate parametric images of perfusion (Chen et al 1998, Lee et al 2005b, Boellaard et al 2005, Wen et al 2009).

### 3.2.5.3.4 Basis functions

The BF approach was first introduced by Gunn et al (1997) to linearize the non-linear terms in the operational equation. Watabe et al (2005) used the BF method to calculate myocardial blood flow (MBF) in pigs. They used 300 BF to calculate F, $V_a$ and perfusive tissue fraction (PTF) keeping $V_d$ as constant. The method showed good correlation with the NLS method but the constant $V_d$ value that was used clearly introduced bias. Lodge et al (2000) used 2561 BF with flow intervals of 0.0035 ml/min/g between adjacent BF. They tested various formulations of the original flow model, but no attempt was made to compare the result using other fitting methods.
Boellaard et al (2005) compared the BF, the LLS and the GLLS methods in clinical data to calculate MBF, tumour blood flow (TBF) and CBF parametric images using a standard formulation of the models. A positive bias using BF at low perfusion values was observed as in Lodge et al (2000), although in a smaller degree due to reduced parameterization. At high perfusion values, the LLS and GLLS methods systematically underestimated perfusion up to 20% with GLLS failing to improve the noise induced bias compared to the LLS method, possibly due to the reduced model complexity in the 1-tissue model. This trend was also seen in Lee et al (2005b).

### 3.2.6 Summary of ongoing research in Oncology perfusion studies

To date, there is a limited number of research papers measuring perfusion in oncology, using quantitative PET analysis. Most of the work is concentrated into assessing drug efficacy after neo-adjuvant of primary chemotherapy. In Table 3.1 studies involving tumour perfusion imaging with PET are summarized. From the table it is seen that with the exception of 2 studies, most of the analysis has been based on deriving regional kinetic parameters using noisy FBP images. The combination of FBP reconstruction along with regional kinetic analysis is likely to be suboptimal in assessing heterogeneous regions. As perfusion in tumours is expected to be highly heterogeneous, parametric imaging of perfusion has the potential to offer substantial benefits to measure this heterogeneity and for that reason strategies to improve the SNR of parametric maps are important. Sophisticated direct 4-D image reconstruction methods can help reducing SNR in parameter estimates, making parametric imaging of perfusion a feasible task. A number of dynamic parameter estimation methods have the potential to be incorporated with a 4-D algorithm, with different characteristics in terms of the accuracy and precision in the parameter estimates they deliver. In the remaining half of the chapter 3 fast parameter estimation methods are individually optimized and compared to each other for generating parametric image of perfusion, using simulated data.
<table>
<thead>
<tr>
<th>Author</th>
<th>Method and Tracer</th>
<th>IF</th>
<th>Application</th>
<th>Tracer administration</th>
<th>Patients</th>
<th>Method</th>
<th>Analysis</th>
<th>Reconstruction</th>
</tr>
</thead>
</table>

Table 3.1 Perfusion studies with PET involving different types of cancer in the literature
3.3 Evaluation of basis function, linear least squares and generalized linear least squares methods for 1-tissue compartment model.

3.3.1 Introduction

Based on the review presented above, a number of parameter estimation schemes exist which are capable of delivering parametric images of perfusion, volume of distribution and blood volume. In this thesis only dynamic methods are of interest and in order to decide what would be the optimal scheme to use within a 4-D image reconstruction algorithm, both in terms of performance and computational efficiency, a comparison study was performed. Noiseless and noisy 1-D TACs were simulated in Matlab (Mathworks) corresponding to $[^{15}\text{O}]\text{H}_2\text{O}$ kinetics. Then 3 main parameter estimation schemes were first individually optimized and evaluated and then compared to each other, to assess their relative performance in terms of bias and standard deviation in the parameter estimates they deliver. In the rest of the chapter the BF, the LLS and the GLLS methods are compared. First the simulation methodology is presented, followed by representative results and conclusions.

3.3.2 Materials and methods

All simulated TACs represented $[^{15}\text{O}]\text{H}_2\text{O}$ kinetics from a 6-minute scan in different tissues, having different perfusion ($K_1$), efflux rate ($k_2$) and fractional blood volume ($V_a$) values. The frame definition was taken from a typical clinical scan (14x5sec, 5x10sec, 3x20sec, 6x30sec) with 28 time frames. As already mentioned $[^{15}\text{O}]\text{H}_2\text{O}$ is freely diffusible tracer with its temporal distribution described by a 1-tissue compartment model (Kety 1951). As the measured PET signal often includes contributions both from the tissue and the arterial vasculature, a blood volume component was also included in the model. As such the following model was used to simulate the TACs.

$$fC_A(t)\otimes e^{-(k_2+\lambda)t} + V_aC_A(t)$$ (3.11)

where $C_A(t)$ is the arterial input function activity concentration over the time respectively, $f$ is the perfusion ($f = K_1$), $k_2$ is the efflux rate, $V_a$ is the fractional blood volume and $\lambda$ is the decay constant of $[^{15}\text{O}]$ ($\lambda = 0.00567 \text{ sec}^{-1}$). To study the different
parameter estimation schemes under a variety of noisy conditions, Poisson noise was introduced in the TACs and 20 different noise levels were considered. The different noise levels were obtained by simulating TACs with exponentially spaced count levels. For the optimization procedure, different TACs were simulated in each method to assess their individual performance, using a common IF and a variety of kinetics, while for the comparison between them, common TACs were used. As the BF and GLLS methods have a number of free parameters, the optimization was performed individually for each parameter, varying the parameter of interest while keeping the others fixed.

3.3.2.1 Basis function method

The BF as mentioned above was first introduced by Gunn et al (1997) as an alternative to nonlinear least square parameter estimation, to generate parametric images in $^{11}$C-Raclopride PET imaging. The method linearizes the kinetic modelling operational equation by pre-calculating the nonlinear term for a range of physiologically plausible kinetics (set of BF). Then parameter estimation is performed using linear regression for each of the BF, to estimate the respective coefficient. Parameters are selected based on the BF which gives the minimum residual sum of squares (RSS) amongst the set of BF. Throughout the simulations, the range of the parameter ($\theta$) in the nonlinear term was set to $\lambda = 0.0056 \text{ sec}^{-1} < \theta < 0.2 \text{ sec}^{-1}$.

Noiseless data

An important and free parameter in the BF method is the number of BF. Increasing the number of basis functions, improves the accuracy of the parameter estimates, but at the same time increases the computation time as the parameter estimation is performed for each BF. As such, a minimum number of BF should be used to provide sufficient accuracy in the parameters, with the minimum possible computation load. This optimization is also a function of the spacing between the kinetics represented by the BF within the set range of possible kinetics, as well as a function of the kinetic parameters (perfusion) themselves. As such 2 sets of simulations were conducted to optimize the number of BF and evaluate its dependency on other parameters.

In the 1st simulation, a TAC representing regions with medium to low perfusion was used and 2 BF spacing schemes were evaluated within a BF framework: one
representing a linear spacing and one representing a logarithmic spacing within the predefined range of kinetics. The number of BF varied between 1 and 300 and parameters were estimated for each number of BF.

In the 2\textsuperscript{nd} simulation, 3 TACs were used to simulate regions with different perfusion levels, in order to assess any dependency between the kinetic parameters and the number of BF needed. In this simulation a logarithmic spacing between the BF was used, with the number of BF again ranging between 1 and 300.

**Noisy data**

Under noisy conditions a single simulation was conducted using 4000 noisy realizations. Similar to the noiseless data, the minimum number of BF necessary was evaluated for 2 extreme levels of noise. The BF were logarithmically spaced, ranging between 1 and 100.

### 3.3.2.2 Linear least square method

The LLS method was introduced for rapid parameter estimation in CBF imaging and generalized to N compartment models (Feng and Ho 1993a). The method can be derived easily by directly integrating both sides of the differential equation (3.5), including a blood volume component (see section 3.1.2). A number of macro-parameters can then be estimated by linear regression, with the kinetic micro-parameters then derived as a combination of these macro-parameters. A rigorous derivation of the original method can be found in Feng and Ho (1993a) and Lee et al (2005b) using a blood volume component. The LLS method is very straightforward with no internal parameters to control during parameter estimation and as such no optimization was needed.

### 3.3.2.3 Generalized linear least square method

Despite its simplicity the LLS method can result in biased parameter estimates as it does not handle noise in the measurements in an optimal way. This occurs as in every frame the integration from zero to the frame time results in error terms, including measurement errors from previous time frames. Therefore the errors are not statistically independent, which can result in biased parameters, especially in 2\textsuperscript{nd} or higher order models (Feng et al 1993b). The GLLS method uses an original set of estimated
parameters to calculate an autoregressive filter, which is then applied in the model in order to whiten the correlated noise and deliver unbiased estimates (Feng and Ho 1993a). Parameter estimation is performed using an iterative scheme and an initial estimate for the parameters is needed. In this simulation study, an existing implementation of the GLLS method was used (Matthews et al 2010) as opposed to the other 2 methods which were implemented for comparison purposes. In the GLLS method only noisy simulations were considered and a number of parameters were evaluated.

In the 1st simulation, the number of internal iterations was optimized. Iterations ranged from 1 to 4 and mean and standard deviation parameters over 4000 noisy realizations were estimated using TACs at 2 perfusion levels. Initial values were provided using the LLS method.

Similar to the 1st simulation was the 2nd simulation, were instead of evaluating the iteration number, 3 different initialization schemes were tested. Parameter estimation was performed using 2 internal iterations.

<table>
<thead>
<tr>
<th></th>
<th>BF method</th>
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<th>GLLS method</th>
<th></th>
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<td></td>
<td></td>
<td>Noiseless simulations</td>
<td></td>
<td>noisy simulations</td>
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<tr>
<td></td>
<td></td>
<td>K\textsubscript{1} (ml/sec/ml)</td>
<td>Vd (ml/ml)</td>
<td>V\textsubscript{a} (ml/ml)</td>
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<td>0.9</td>
<td>0.05</td>
<td>0.009</td>
</tr>
<tr>
<td>2\textsuperscript{nd} simulation</td>
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<td>0.9</td>
<td>0.05</td>
<td>0.0667</td>
</tr>
<tr>
<td>0.0333</td>
<td>0.9</td>
<td>0.05</td>
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<tr>
<td>0.0667</td>
<td>0.9</td>
<td>0.05</td>
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</tr>
<tr>
<td>2\textsuperscript{nd} simulation</td>
<td>0.0667</td>
<td>0.9</td>
<td>0.05</td>
<td>0.0667</td>
</tr>
</tbody>
</table>

*Table 3.2* Table summarizing the kinetics that were simulated for the optimization of each method and the comparison between them.
3.3.2.4 Comparing the BF, LLS and GLLS methods

After optimizing the methods individually, the methods were compared. Mean and standard deviation parameters over 10000 noisy realizations were estimated at 20 different noise levels for the 3 methods, as well as mean square error estimates at the same noise levels. In the BF method 200 BF were used, while in the GLLS method parameters were estimated with 2 internal iterations and initialization provided by the LLS method. Parameter estimation in all methods was performed using a non-negative least squares (NNLS) objective function, which enforces a non-negativity constrain in the parameters based on prior knowledge that negative estimates are non-physiologically plausible. Table 3.2 summarizes the kinetic parameters used to simulate the TACs both in the optimization of the individual methods, as well as in the comparison between them.

3.3.3 Results

3.3.3.1 Parameter estimation optimization

3.3.3.1.1 BF method

In the BF method, choosing the optimum number of BF is important as mentioned above. One of the parameters directly related with the number of BF, is the spacing of the kinetics represented and Figure 3.4 shows the estimated perfusion, $V_d$ and $V_a$ as a function of the number of basis functions, using a linear spacing of the kinetics within the predetermined range, as well as using a logarithmic spacing. Comparing the 2 schemes it can be seen that using a logarithmic sampling, a better coverage of the kinetics can be achieved with reduced variance in the parameter estimates at increasing number of BF. In both sampling schemes, as the number of BF increases, the accuracy of the parameter estimates improves. When only a small number of BF is used, the estimated parameters oscillate quite substantially due to the coarse sampling. In the linear sampling the oscillations are more pronounced with sudden discontinuities happening when the addition of one more BF results from having $|θ_{left} - θ_{sim}| < |θ_{right} - θ_{sim}|$ to having $|θ_{left} - θ_{sim}| > |θ_{right} - θ_{sim}|$ where $θ_{sim}$ is the simulated parameter and $θ_{right}$, $θ_{left}$ are the closest parameters to the simulated parameter from the left and right side in the spectrum. As the number of BF increases, the sampling increases as well and after a
Figure 3.4 Estimated perfusion (i), volume of distribution (ii) and fractional blood volume (iii) using the BF method as a function of BF number using 2 BF spacing schemes.
Figure 3.5 Estimated perfusion (i), volume of distribution (ii) and fractional blood volume (iii) using the BF method as a function of BF number for TACs simulating 3 different perfusion levels.
Figure 3.6 Estimated mean perfusion (i), volume of distribution (ii) and fractional blood volume (iii) over 4000 noisy realizations using the BF method as a function of BF number for TACs with 2 different noise levels.
certain number of BF the parameters seem to have converged with minimal oscillations. The larger oscillations occur in $V_a$ for both sampling schemes, which increases the number of BF needed, despite perfusion and $Vd$ almost reaching a plateau at a smaller number of BF. This threshold appears to be between 100 and 150 BF for the logarithmic spacing with mean percentage bias less than 1.2% for perfusion, 0.06% for $Vd$ and 5.5% for $V_a$, while for linear spacing even after 250-300 BF, substantial oscillations can be seen with mean percentage bias equal to 2.2% for perfusion, 0.13% for $Vd$ and 11.1% for $V_a$.

To assess any correlation between the number of BF and the kinetic parameters, in Figure 3.5 the estimated parameters from 3 TACs simulating different perfusion levels, are plotted again as a function of the BF number. The graphs reveal a dependency between the perfusion and the required minimum number of BF. For regions with high perfusion, the estimated perfusion and $V_a$ appear to vary more for the same number of BF compared to lower perfusion regions. Consequently more BF are needed at increased perfusion regions for the parameters to converge. As these simulations were under noiseless condition and to test whether noise has any effect on the BF number, in Figure 3.6 parameters were estimated for 2 noise levels, for a TAC representing a medium to low perfusion region. What is seen is that under noisy conditions, increasing the number of BF doesn’t change the estimated parameters even after as little as 10 BF. At the same time though, $Vd$ and $V_a$ appear biased compared to the parameters estimated from the high statistics TAC, even at the highest number of BF.

### 3.3.3.1.2 GLLS method

Similar to the BF method, a number of free parameters are available for optimization in the GLLS method. In Figure 3.7 the mean and standard deviation perfusion over 4000 noisy realizations is plotted for 20 different noise levels for increasing internal GLLS iterations. To evaluate the effect of increasing iterations at varying perfusion levels in Figure 3.7 (i) the simulated TAC represented a medium to low perfusion region while in Figure 3.7 (ii) the simulated TAC represented a high perfusion region. At medium to low perfusion (Figure 3.7 (i)) and at high statistics, increasing the iterations has no obvious effect and even one iteration is sufficient. At the other extreme and at very noisy TACs, the mean perfusion appears to oscillate after the 2nd iteration as if there are
more than one local minima. This effect is more pronounced in the high perfusion TAC (Figure 3.7 (ii)) and it appears that 2 iterations are sufficient, with further iterations offering no improvement. Ho and Feng (1999) and Boellard et al (2005) concluded that even one iteration is sufficient, which can be the case for low noise levels, but the data suggest that at high noise levels a 2nd iteration offers improvements. Finally it can be seen as expected that the mean perfusion is negatively biased with the bias being more pronounced in the high perfusion regions compared to low perfusion.

Another free parameter that was assessed was the initialization of the parameters and in Figure 3.8 three initialization schemes were used. In the 1st scheme the true parameters were used, in the 2nd scheme parameters were initialized to unity, while in

![Figure 3.7 Estimated mean (x) and standard deviation (+ = 1sd) perfusion over 4000 noisy realizations versus noise level (TAC counts with Poisson noise) using different number of internal GLLS iterations. Results from TACs simulating region with both low (i) and high (ii) perfusion levels are shown.](image)
Figure 3.8 Estimated mean (x) and standard deviation (+ = 1sd) perfusion over 4000 noisy realizations versus noise level (TAC counts with Poisson noise) using different initialization scheme in the GLLS method. Results from TACs simulating region with both low (i) and high (ii) perfusion levels are shown.

the 3rd scheme the LLS method, which requires no initialization, was used to provide an initial estimate. Similarly, the initialization was tested at medium to low and high perfusion values.

From both graphs it can be seen that using the LLS method to provide an initial estimate results in almost identical mean and standard deviation perfusion estimates compared to when the true parameters were given as an initial estimate. As such, the LLS methods can provide a very good initial estimate and was used as the standard methods for GLLS initialization.
Figure 3.9 Box-whisker plots showing the estimated mean and standard deviation perfusion (i), efflux rate (ii) and fractional blood volume (iii) over 10000 noisy realizations as a function of noise level (TAC counts with Poisson noise) for the BF, LLS and GLLS methods and for medium perfusion levels (0.009 ml/sec/ml).
Figure 3.10 MSE plots of perfusion (i), efflux rate (ii) and fractional blood volume (iii) over 10000 noisy realizations as a function of noise level (TAC counts with Poisson noise) for the BF, LLS and GLLS methods and for medium perfusion levels (0.009 ml/sec/ml).
Figure 3.11 MSE plots of perfusion (i), efflux rate (ii) and fractional blood volume (iii) over 10000 noisy realizations as a function of noise level (TAC counts with Poisson noise) for the BF, LLS and GLLS methods and for high perfusion levels (0.667 ml/sec/ml).
3.3.3.2 Comparing the methods

Having optimized the methods individually, the 3 methods were compared to each other. In Figure 3.9 box-whisker plots of estimated parameter mean and standard deviation using 10000 noisy TACs realizations (representing medium perfusion regions) is shown for 20 noise levels. The central point in the box represents the medium of the distribution, with the edges representing the 25th and 75th percentiles and with whiskers showing the outliers. Looking at the outliers, as well as the percentile box for the 3 methods (in the zoomed inlet), as the noise level increases the BF method appears to suffer from increased standard deviation in the perfusion and $k_2$, compared to the other methods, with the GLLS method giving the least variant distributions. In the $V_a$ all methods gave similar results, both in terms of bias and standard deviation. To take into account both the bias and standard deviation in the parameters, the MSE is finally plotted in Figure 3.10 (medium to low perfusion) and Figure 3.11 (high perfusion) again using 10000 realization in each of the 20 noise levels. From the graphs it can be concluded that under medium to low perfusion conditions the GLLS method delivers parameter estimate with the least MSE amongst the 3 methods, even under very noisy conditions. Conversely going from medium to high flow regions it can also be seen that the GLLS is no longer consistently the best method, as each method behaves differently at varying perfusion levels.

3.3.4 Discussion

A 1-D simulation study was conducted with TACs representing $[^{15}\text{O}]\text{H}_2\text{O}$ kinetics, in order to compare parameter estimation schemes for generating parametric images of perfusion in $[^{15}\text{O}]\text{H}_2\text{O}$ PET imaging. The purpose of the simulations was to study the parameter estimation problem separate from the image reconstruction problem, in order to evaluate which method would be more suitable to be used within a 4-D image reconstruction algorithm for direct estimation of perfusion, volume of distribution and fractional blood volume. The BF, LLS and GLLS methods were individually optimized were nesseccary and evaluated in a comparative study.

Based on the results presented, the GLLS methods was found to give the least MSE at perfusion levels most commonly encountered within the body. At the same time, the
performance of GLLS was found to be dependent on the true kinetic parameters, with the MSE deteriorating faster compared to the other methods as perfusion levels increase. This MSE deterioration under high perfusion conditions, reflects the effect of bias being dependent on the kinetic parameters particularly on the GLLS, with increasing negative bias in high perfusion regions. This is in agreement with Boellard et al (2005) who also compared the 3 methods, leading to the conclusion that although the GLLS was introduced to reduce bias in the LLS, such improvements are minimal in the 1-tissue model (Feng and Ho 1993a). Critically though such high perfusion levels doesn’t represent the perfusion levels typically observed in $[^{15}O]H_2O$ scans (although such high perfusion levels can still be encountered), with most organs having perfusion levels in the low to medium range (Figure 3.10). Overall then the GLLS appears to be the best amongst the methods for generating parametric images of perfusion, volume of distribution and fractional blood volume, with the least MSE in the perfusion range most likely to be observed in clinical scans.

Apart from the accuracy and precision of the methods, the purpose of the simulations was also to evaluate their potential incorporation within a 4-D image reconstruction algorithm. From the implementation point of view the BF method is completely impractical within a direct parameter estimation algorithm, as based on the results presented at least 150-200 BF are necessary. With voxel wise parameter estimation performed for every BF, it is extremely computationally demanding, as also parameter estimation needs to be performed in every image update if used within an iterative based image reconstruction algorithm such as OSEM. One of course can limit the range of kinetics represented in the BF, which results in requiring less BF to obtain a good sampling. Here we used a maximum value of 0.2 sec$^{-1}$ and the optimization for the necessary number of BF was done based on this range. Conversely the LLS method is very simple with a better MSE, compared to the BF method, under a wide range of perfusion levels. Most importantly is computationally efficient, producing parametric maps very fast, making it suitable for voxel wise fitting in scanners having in excess of 10 million voxels in image space. The GLLS method is more computationally expensive compared to the LLS method, but still within acceptable limits time wise so as to be used within a 4-D reconstruction algorithm. If further speedup in the parameter estimation is needed, other methods can be use, such as masking the patient contour to limit parameter estimation to physiologically important regions and using parallel
computing techniques. Finally, the iterative scheme of the GLLS method can be integrated within iterative image reconstruction algorithms, as initial parameters in the GLLS can be provided using a one step late approach from the previous iteration, with LLS initialization only in the 1st iteration.

3.3.5 Conclusion

Based on the 1-D simulations presented, the GLLS method was found to produce the best MSE at low to medium perfusion levels compared to other perfusion parameter estimation schemes, with minimal demands in computational time, thus making it compatible to be used within a 4-D image reconstruction framework. Care should be taken when interpreting results from high perfusion regions as MSE in all methods appears to deteriorate substantially, with the GLLS method being the most susceptible.
CHAPTER 4

Image reconstruction and associated software on the Biograph 6 B-HiRez and TruePoint TrueV PET/CT
4.1 Introduction

In the 1st chapter, it was emphasized that the aim of this thesis is to implement current and new 3-D and 4-D advanced image reconstruction algorithms in whole-body PET/CT oncology studies, while the next 2 chapters focused on the image reconstruction and kinetic modelling steps as 2 separate processes and from an algorithmic perspective. The aim of this chapter is to describe the research undertaken in the early stages of this project, with respect to the implementation of an image reconstruction software package for two PET/CT scanners and provide insights into the image reconstruction problem from a practical point of view.

The development of existing and new image reconstruction algorithms throughout the rest of the thesis was based on 2 whole-body PET/CT scanners, the Biograph 6 Barrel HiRez (B-HR) and the TruePoint TrueV PET/CT (TPTV) (Siemens Molecular Imaging Inc., TN, USA). At the beginning of this project, research was initially focussed on studies conducted on the B-HiRez PET/CT scanner which was installed at the Wolfson Molecular Imaging Centre (Bercier et al 2004, Brambilla et al 2005, Panin et al 2006). At a later stage, the scanner was replaced by the TruePoint TrueV PET/CT (Jakoby et al 2006, Panin et al 2007, Jakoby et al 2009). For such clinical PET/CT systems, access to image reconstruction software is restricted, with minimal access to low level raw and intermediate sinogram data. With only the scanner’s data inputs (list-mode data) and outputs (reconstructed images) being known and with the intermediate processes being a ‘black box’, developing novel image reconstruction strategies is a daunting task (Figure 4.1). A completely independent image reconstruction platform from the one the scanner is using, is required before undertaking any research. As such, a lot of time was invested in developing image reconstruction software, which at the first stage could match and later surpass the scanner’s image reconstruction capabilities through implementation on novel reconstruction algorithms, both for 3-D and dynamic 4-D imaging. First, in order to independently generate sinograms for static and dynamic studies, software was written to histogram the raw list-mode data into sinograms, based on the list-mode protocol that both scanners are using. Then, using existing software provided by Siemens, correction sinograms (attenuation, scatter, normalization) were generated to be used by the image reconstruction software.
One of the cornerstones of image reconstruction is the forward and backward projectors, which are based on an estimate of the scanner’s geometric system matrix. Software was developed, to implement a 3D version of the ‘Siddon’s algorithm’, in order to calculate and store the system matrix for both PET/CT scanners. Finally, completely independent software from the one the scanner is using was written in Matlab to perform 2-D, 3-D and 4-D image reconstruction for both scanners.

The chapter attempts to give an overview of the technical rather than mathematical aspects of the image reconstruction process on the 2 PET/CT scanners based on existing and newly developed software and follows the data flow from list-mode acquisition to image reconstruction. First, some technical information regarding the 2 PET/CT scanners are described, with an emphasis on data acquisition and organization. Then, existing (sinogram generation) and new (list-mode histogramming, system matrix calculation and image reconstruction) software is presented, along with brief theory, methodology and representative results in each of the steps.

4.2 The Biograph-6 Barrel HiRez and TruePoint TrueV PET/CT

The Biograph 6 Barrel - HiRez PET/CT (Siemens Molecular Imaging Inc., TN, USA) is a whole body scanner used in oncology studies mainly (Brambilla et al 2005, Panin et al 2006). The scanner has 3 axial block rings and in every ring 13 axial crystal rings. The gaps between the block rings are equal to one crystal and as such there are another
2 axial rings corresponding to these gaps. The axial extent of the scanner is 162 mm and it has 81 direct and cross planes resulting in an axial sampling distance of 2 mm. Transaxially, the scanner has a 700 mm patient port with a 585 mm reconstructed FOV and a 854.8 mm detector diameter (427.4 mm radius). Contrary to the mainstream design of a cylindrical geometry, axially and between the outer and the central block rings, there is an angle of 7.5 °, giving it a barrel shape. Due to this curvature, the transaxial FOV as such is a function of the axial distance. The block design is made of 13×13 LSO crystals with every crystal being 4x4x20mm. Each block ring has 48 blocks (144 in total) resulting in 624 crystals and 48 gaps per crystal ring, 8112 crystals per block ring and 24336 overall. When this block design was introduced in the scanner, (marketed as the HiRez), it was an improvement over its predecessor, the LSO PET/CT pico 3-D, in which the crystal dimensions were 6.45×6.45×25 mm arranged in an 8×8 block, which results in only 9216 crystals overall and with only 47 planes, 3.375 mm in thickness (Bercier et al 2004). There are 12 detector electronic assemblies (DEA) or buckets, with each one serving 12 blocks and consisting of 6 dual channels analog subsections (Puterbaugh et al 2003). The gaps between the blocks are not equal in all directions (axially and transaxially) but are considered to be equal to the dimensions of a crystal elements. The pico electronics, along with the fast decay time of the LSO, result in a 4.5 ns time coincidence window, with a 425-650 keV energy window typically used (Table 4.1).

Figure 4.2 The Biograph 6 B-HiRez (left) and the TruePoint TrueV PET/CT (centre) without the external gantry covers. The addition of a 4th crystal ring (right) extends the FOV from 16.2cm to 21.6cm.
<table>
<thead>
<tr>
<th></th>
<th>B- HR</th>
<th>TPTV</th>
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<tbody>
<tr>
<td>Detector ring diameter (mm)</td>
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<td>830</td>
</tr>
<tr>
<td>No of detector rings (crystals + gaps)</td>
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<td>52+3</td>
</tr>
<tr>
<td>No of blocks rings</td>
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<td>4</td>
</tr>
<tr>
<td>No of detectors/block</td>
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<td>169</td>
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<tr>
<td>No of block/ring</td>
<td>48</td>
<td>48</td>
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<tr>
<td>No of detectors/ring</td>
<td>624+48</td>
<td>624+48</td>
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<tr>
<td>No of crystal overall</td>
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</tr>
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</tr>
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<tr>
<td>Axial block ring angle (º)</td>
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</tr>
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</table>

**Table 4.1** The table summarizes the main characteristics of the PET component on the HiRez and TrueV scanners.

**Figure 4.3** The Biograph 6 B-Hi-Rez (left) and the TruePoint TrueV PET/CT (right) geometric design and block rings.
The Biograph 6 TruePoint TrueV PET/CT (Siemens Molecular Imaging Inc., TN, USA) is an improvement over the Hi-Rez (Jakoby et al. 2006, 2009) and features 2 important additions compared to its predecessor. In order to increase the sensitivity, the scanner has an additional block ring, which extends its axial FOV to 216 mm. As it utilizes the same HiRez block design, this results in 192 blocks with 32448 crystal elements overall and with 109 image planes. Secondly, the spherical design of the scanner has been replaced with a more conventional cylindrical one. A comparison between the characteristics of the 2 scanners can be seen in Table 4.1 while Figure 4.3 shows a schematic representation of the geometric features on the 2 scanners with additional detector ring on the TrueV and the axial curvature on the HiRez standing out.

### 4.3 Data acquisition

Both scanners acquire data in fully 3-D mode, which results in a large number on LORs. Considering first a 2-D plane of detectors which coincides to a 2-D detector ring, data are collected having $\theta = 0^\circ$ where $\theta$ is the polar angle a 2-D plane has with respect to the z-axis of the scanner and a single projection view is formed by collecting data with opposing detectors. Under normal conditions the sinogram would have $N_d/2$ radial elements and $N_d$ angular samples in the range $0<\varphi<180^\circ$ where $\varphi$ is the azimuthal angle and $N_d = 672$ is the number of detectors in the ring including the gaps (the same for both scanners). Usually radial elements are reduced, depending on the scanner-to-FOV ratio, by not taking into account the LORs at the edge of the transaxial FOV as these LORs do not pass through object being scanned and in order to minimize the parallax error. As such, in both scanners a projection in the sinogram has only $N_d/4$ radial elements. To increase the radial sampling, adjacent rows in the sinogram (representing projections from 2 consecutive azimuthal angles) are interleaved, as they have a $D_x/2$ offset, where $D_x$ is the LOR-to-LOR sampling distance. This is the reason for having almost parallel projections, with the error though being relatively small. After interleaving the projections, there are $N_d/2=336$ angular samples with an azimuthal sampling distance $180^\circ/(N_d/2) = 0.5357^\circ$ and $(N_d/4)\times2 = N_d/2 = 336$ radial samples. At the centre of the radial FOV, after projection interleaving and at a specific azimuthal angle, the radial sampling distance ($D_x$) is equal to half the detector spacing.
(\(D_x = D_d/2 = 4 \text{ mm}/2 = 2 \text{ mm}\)), where \(D_d\) is the detector-to-detector spacing. Due to the curvature of the detector ring though, the radial sampling is changing towards the edge of the FOV and the non-uniform sampling interval is calculated using the following equation

\[
D_x = \frac{D_d \sqrt{1 - \left(\frac{x}{R}\right)^2}}{2} \tag{4.1}
\]

where \(x\) is the radial position of the LOR and \(R\) is the scanner radius (Buchert et al 2000). This radially dependent radial sampling can be seen in Figure 4.4, with the sampling interval gradually decreasing towards the edge of the FOV.

In the axial direction, the axial sampling is dictated again by the axial detector width (\(D_d = 4 \text{ mm}\)), with the number of planes (direct planes) equal to the number of detector rings including the gaps (\(N_z = 41\)), where \(N_z\) is the number of detector rings. Increased sampling and plane sensitivity is achieved by combining detectors in neighboring rings (cross planes). This results in \(N_z + (N_z-1) = 55+54 = 109\), direct and cross planes when acquiring in 2-D on the TrueV PET/CT, with a sampling interval \(D_d/2 = 2 \text{ mm}\). On the HiRez, \(N_z + (N_z-1) = 41+40 = 81\) planes are obtained but due to the curvature of the scanner in the axial direction (barrel shape), the sampling distance is also calculated using an equation similar to Equation 4.1. This translates to the axial sampling distance decreasing towards the edge of the axial FOV.

**Figure 4.4** In the axial direction 5 and 6 detector planes are combined in each sinogram plane in both scanners (span =11). Depending on the polar angle, span and ring difference, the planes are sorted in different segments. In the transaxial direction, the projections are interleaved to increase radial sampling, with the variable radial sampling distance generating non-uniformly sampled sinograms.
Increasing span, reduces the number of reconstructed sinograms and improves the statistics in the combined sinograms, but at the same time deteriorates axial resolution. Considering now the 3-D case for planes having $\theta \neq 0^\circ$ and in order to maintain a relative large portion of the axial FOV with relatively constant sensitivity, the maximum allowed extent of axial coincidences (ring difference) is restricted to 27 and 38 for the HiRez and TrueV PET/CT respectively. This ring difference, along with the span configuration, results in 5 (seg 0 [81 planes], seg ±1 [69 planes/seg], seg ±2 [47 planes/seg]) for the HiRez and 7 (seg 0 [109 planes], seg ±1 [97 planes/seg], seg ±2 [75 planes/seg], seg ±3 [53 planes/seg]) segments for the TrueV PET/CT, with each segment containing planes with ever increasing polar angles. In reality not all planes in an oblique segment share the same polar angle. In each segment, the combination of ever increasing/decreasing oblique planes results in oblique direct and cross planes with slightly different polar angles between them. Nevertheless, certain groups of planes within a segment do share the same polar angle, a feature very important to establish axial translation and mirror symmetries when calculating the scanner’s system matrix. The combination of the planes axially can be visually assessed by generating a Michelogram (Figure 4.5). An excellent introduction to PET data acquisition schemes can be found in Fahey (2002).

Figure 4.5 ‘Michelogram’ diagrams used to visualize the axial compression scheme with 5 segments on the Hirez (i) and the 7 segments on the TrueV (ii). The white strips indicate gaps between the block rings which are inserted are ‘pseudo-planes’. Segments are indicated by different colour shading and within each segment, elements having the same average detector location are combined (5 and 6 axial planes are combined in a span 11 configuration) and given an axial plane location each to their average value.
4.4 List-mode rebinning, histogramming and sinogram formation

In both scanners during data acquisition, detector–pair packets containing the axial and transaxial detector indexes from coincidence events, along with other information such as the nature of the event (prompt or random), are transmitted from the scanner’s coincidence controller, to the ACS data acquisition PC in 64-bit words. Instead of saving the data in that 64-bit format, typically the list-mode stream is rebinned on-line during the acquisition process to record sinogram address instead of detector addresses. This enables the data to be ‘replayed’ (rebinned +histogrammed) during post processing, to generate sinograms of any desired duration. However, due to the many-to-one mapping of detector addresses to sinogram addresses, the original 64 bit listmode data can not be exactly reproduced or use different sinogram construction, such as smaller axial compression. This functionality is provided by the PDR (PETLINK DMA Rebinner) card (Jones et al 1996, 2000, 2002, 2004, 2007). This is a PCI card which performs rapid 64 to 32 bit conversion for online detector-to-sinogram bin address mapping. The 64-bit packets arrive in the FPGA router via fiber channel. Inside the PDR, the 2 logic FPGAs are connected to programmable flash memory chips. These chips hold look up tables (LUT), based on which the mapping between the detector space and the native LOR projection space takes place (Figure 4.6). These LUTs take into account information such as the span, the ring difference and the projection interleaving, to correctly allocate each LOR to a specific sinogram bin address (axial, angular and radial sinogram index).

Figure 4.6 64-bit list-mode events are sorted on-line using the PDR card to perform LOR-to-projection bin mapping using programmable flash memory chips. The PDR can also perform on-line arc correction and has been tested for TOF rebinning as well as for rebinning data from continuous bed movement.
For each incoming event, first a transaxial sinogram index (TSI) is encoded based on the transaxial detector pair indexes. Then, for the maximum ring difference specified and based on the span selected (different LUTs for different span) and the axial detector pair indexes, plane and segment sinogram indexes are encoded. Using the plane and segment sinogram indexes then, an axial sinogram index (ASI) is created, which is an index through the 3-D sinogram space. Finally, the overall bin address (BA) is calculated based on the following equation:

\[ BA = (ASI \times SS) + TSI = (ASI \times (RPS \times APS)) + (API \times RPS) + RPI \quad (4.2) \]

where SS stands for the sinogram size, RPS is the radial projection size, APS is the angular projection size. In the case of the HiRez and the TrueV PET/CT SS = RPS×APS = 336×336 = 112896. API is the angular projection index (API = \{1…336\}) and RPI the radial projection index (RPI = \{1…336\}). On the HiRez ASI = \{1…313\} as there are 313 sinograms in all 5 segments, while on the TrueV ASI = \{1…559\} due to the longer axial FOV and the extra 2 segments. The BA decimal number is converted into binary and occupies the last 29 bit in the 32-bit word. The 4 most significant bits (MSB) are reserved to indicate whether the word is an emission (prompt or random) or transmission event or whether the word belongs to a time marker/block singles event. The different binary words that can be encountered in a 32-bit list-mode file are seen in Figure 4.7. During the mapping process, the non-uniform radial sampling, as well as axial sampling in the case of the HiRez, that the LOR might

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**Figure 4.7** Figure showing the 32 list-mode decoding scheme based on the PETLink protocol.
have, is not taken into account. As such, the 32-bit projection address corresponds to a non-uniformly sampled intermediate sinogram, were each bin corresponds to a single LOR (Jones et al 2007). At the start of the data acquisition, the option of either storing the 32-bit list-mode for post-processing or directly performing histogramming of the 32-bit list mode into sinograms is provided. If the option to save the 32-bit list-mode is selected at the beginning of the acquisition process, then the original list-mode can be replayed to create either static or dynamic sinograms using the LMreplay software which is a plug-and-play functionality under license on the scanner’s GUI.

4.4.1 Methods

As it will be analyzed more thoroughly in the image reconstruction section, the HiRez PET/CT scanner can only reconstructed in 2D using an attenuation-weighed ordered subsets expectation maximization (AW-OSEM) algorithm, as opposed to the TrueV PET/CT which allows 3-D reconstruction with an ordinary Poisson OSEM algorithm (OP-OSEM). As such, there is no need to store the prompts and randoms sinograms separately. Although capable of list-mode acquisition, the scanner is only allowing list-mode replaying into a net-trues sinogram by directly subtracting the randoms from the prompts sinogram internally. This automatically forbids any independent algorithm development which requires the prompts and randoms sinograms separately (as these are not available by the scanner), such as the OP-OSEM. Another complication is that list-mode histogramming is directly followed by image reconstruction, with no option to perform these 2 processes in 2 separate steps. Due to these reasons, an independent software package was developed in Matlab to process the 32-bit list-mode data for both PET/CT scanners and perform histogramming into prompts, randoms and net-trues sinograms using the PETLink protocol (Jones et al 1999). The software accepts list-mode files, both in DICOM and interfile formats and generates dynamic or static sinograms in interfile format. Before execution, the user can select the frame definition required by specifying the duration of each frame, as well as the buffer size which effectively allocates the memory size during binary reading. At the beginning the user is prompted to select the list-mode file along with the directory to save the sinograms. The code loops through the frames and the buffers needed to read the entire list-mode file.
At the heart of the code exists a series of flags, which based on the time tags, the frame duration and the buffer size, control the whole process. If the buffer is too small for the current frame, then a new buffer is read to complete the frame. If the buffer holds more data than the frame definition permits, then the portion of the buffer needed to complete the frame is identified and read, the sinograms for the current frame are closed and saved, and the rest of the buffer is made available to the next frame. Based on the above, a part or the complete data in the buffer are passed for further processing sequentially. First the 4 MSBs are decoded based on the PETLink protocol as seen in Figure 4.7. Based on the identity of the word (prompts, randoms, singles, and time tags) the events are separated. If the word belongs to an emission event, the 29 LSBs which hold the actual bin address are converted to a decimal number. Then using the decoding scheme given by Equation (4.2), the ASI, API and RPI indexes are derived and the corresponding address in the 3-D sinogram is incremented. In Figure 4.8 a transaxial sinogram mask is shown with the rhomboid block-block pattern and the gaps between the blocks. Tags words are treated separately, to decode the elapsed time from the time tags and the singles per block. The software also generates interfile sinogram headers (.hdr) from the DICOM or interfile list-mode headers, which are identical to the ones generated by both scanners. At the end, a log file is generated and saved automatically in the sinogram folder, which contains information and statistics for each frame during the histogramming. A post-histogramming quality check can be done then to identify any problems during the process.

**Figure 4.8** A 2-D mask calculated using scanner specific equations taking into account the gaps between the blocks.
To validate that the histogramming is done according to the transfer protocol and no counts are lost during histogramming or mis-positioned in neighbour sinogram bin, list-mode data corresponding to a scanned array of point sources were histogrammed using the LMreplay utility in the HiRez scanner and using the developed Matlab software to create net-trues sinograms. The two 3D sinograms were then subtracted one by one and the absolute difference was summed across all the 313 3-D sinograms to verify any inconsistencies between them.

### 4.4.2 Results

In Figure 4.9 the prompts, the randoms and the net-trues sinograms for a specific plane generated using the list-mode histogrammer written in Matlab, are plotted. The sinograms, as mention before, are in LOR space, not corrected for non-uniformity of sampling.

![Figure 4.9](image)

**Figure 4.9** Prompts (i), randoms (ii) and net-trues (iii) sinograms as generated by the Matlab based list-mode histogrammer based on the PETLink data acquisition protocol.

Figure 4.10 shows the sinograms generated both by the scanner and using the matlab based code. The sinograms in the figure, are the summed sinogram across all the 313 3-D sinograms, while the difference is just the subtraction between the 2, one-by-one and summed also across all 313 3-D sinograms. After performing the subtraction the difference as seen in Figure 4.10 (iii) was found to be zero, meaning that the histogramming is performed consistently and no counts are lost during the process.
Figure 4.10 Summed sinograms across the 313 planes using the scanner’s LM replay (i) and the Matlab based histogrammer (ii) along with the summed difference between them (iii). No difference was found between the 2 histogrammers.

4.4.3 Discussion

A list-mode histogrammer was developed in Matlab to generate static and dynamic sinograms from 32-bit binary list-mode data and enable access to prompts, randoms in addition to net-trues projection data. The histogrammer generates data identical to the ones generated by both the HiRez and the TrueV PET/CT scanners. As the sinograms correspond to non-uniformly sampled data, a geometric correction needs to be applied prior to being used by the image reconstruction software. This is done in a process called ‘arc correction’ which geometrically transforms the non-uniformly sampled sinograms caused by the arc shape scanner (Figure 4.4), into uniform ones. As such the system matrix used in the image reconstruction would correspond to the geometry of a virtual scanner with uniform spaced LORs. This process will be more extensively described in the next section. Alternatively the sinograms can be used by the image reconstruction software without arc-correction, using a system matrix corresponding to the native geometry of the scanner. In this case the exact scanner geometry is needed, while in the former case only the geometry of the arc-corrected sinogram is needed.

To avoid arc-correction during the reconstruction process, the PDR card described above has the ability to perform on-line nearest neighbor LOR-to-projection bin mapping or rebinning. In that way, uniformly sampled sinograms are created on-line by nearest neighbor interpolation, thus avoiding the need for post-histogramming geometric arc correction, but such functionality was not used on the specific scanners. This architecture has previously been tested for a number of different PET scanner designs (Jones et al 2002, 2004, 2007). The PDR card can also be used to pass the 64-bit
packet to be written in disk. Then using an emulator with similar functionality to the PDR, the packets can be rebinned to 32-bit words before being histogrammed. However this functionality is not directly accessible using the scanners graphical users interface.

4.5 Data corrections – quantitative methods

After rebinning and histogramming the emission data, and before image reconstruction, a number of quantitative corrections need to take place, with the estimation of erroneous scatter and random events and corrections for attenuation and differentiate LOR sensitivity, to either enable emission data correction or incorporation of these estimations within the image reconstruction software. As such, a number of sinograms need to be generated and for that purpose existing software from Siemens was used. The sinogram correction and generation software accepts a combination of data obtained both from the scanners (attenuation correction factors and normalization components), as well as from the in-house list-mode histogrammer (emission sinograms). Although existing software is used, as this has an impact on subsequent image reconstruction and its required steps, some details with respect to the generation of the correction sinograms are provided.

4.5.1 Data generation on the scanners

After list-mode acquisition, different files containing raw data are accessible in the scanners. These include the original binary list-mode dataset, the raw CT data, the reconstructed CT image volume (AC-CT) to be used for attenuation correction, the normalization components file, the topogram acquired before the CT acquisition as well as some other patient specific information. Each of these files can be exported to offline in DICOM format, to be used for further processing. Additionally, the PET (list-mode) and CT raw data, can be exported in a Siemens specific format (.PTD, .CTD), while the PET raw data can also be exported in interfile format by accessing the ACS computer. As mentioned before, the image reconstruction process starts immediately after the list-mode histogramming, with no intermediate step and with the correction sinogram generation taking place between these 2 processes in the background. As a consequence, no option exists to obtain the scatter, attenuation and normalization sinograms from the
scanners directly. For that reason, existing software, identical to the one the scanner is using to generate the correction sinograms, was modified and used to obtain the scatter, attenuation and normalization sinograms, as well as to provide other scanner specific corrections.

4.5.2 Data preparation

The sinogram generation and correction software requires the following data inputs:

- The 3-D emission prompts and randoms sinograms as a single 4-D matrix (336×336×313×2 for the HiRez and 336×336×559×2 for the TrueV PET/CT), along with the accompanying headers in interfile format.
- The Normalization components with the accompanying header in interfile format.
- The 2-D attenuation correction factors derived from the CT data, along with the accompanying header in interfile format.

The 3-D emission prompts and random sinograms are generated, as described above, by the in-house list-mode histogrammer, completely bypassing the LMReplay histogrammer in the scanner. Because of the requirement for the 2 emission sinograms to be imported as a single 4-D matrix, the in-house histogrammer also generates this combined sinogram (as such the histogrammer generates 4 different sinograms: prompts (.pr), randoms (.ra), net-trues (.s) and the combined prompts-randoms (.ne) along with the headers (.hdr)).

The normalization components as mentioned in the previous section can be exported from the scanner in DICOM format. As a different file format is needed, the normalization is loaded in Matlab and using a software utility is converted from DICOM to interfile format (.n).

Finally for the attenuation correction, the AC-CT data needs to be converted into attenuation correction factors (ACF). Again Siemens provided software was used for that purpose. For the conversion to take, place apart from the AC-CT file, an emission sinogram is also needed in DICOM format, as header metadata are needed during the conversion process. First information regarding the gantry position are derived from the
DICOM header part of the emission sinogram, such as the horizontal and vertical bed position, but most importantly the x, y, z offsets between the PET and the CT space. Then based on the scanner model, sinogram and geometry specific information is obtained from LUTs before loading the CT data. The CT images are aligned and resampled to the PET bed positions and the CT volume matching the PET bed positions, dimensions and resolution is extracted. The CT volume is converted from CT Hounsfield units (HU) to PET µ-map using hybrid segmentation and scaling. First the CT volume is segmented to classify CT voxels into 2 classes - bone and soft-tissues (non-bone) using a predefined threshold (~300 HU) that differentiates the 2 voxel classes. The software then uses an empirical pre-calibrated LUT composed of 2 straight lines in a coordinate system with the x-axis in CT HU & the y-axis in PET linear attenuation coefficients. This LUT is based on converting the CT volume from Hounsfield units into tissue attenuation coefficients at the effective CT energy and applying 2 scaling factors, one for soft tissue and one for bone, to scale the attenuation coefficients from the CT photon energy to the PET photon energy. The µ-map is finally forward projected to get the ACFs using either direct Fourier transform (DFT) or the classical line integral forward projection with bilinear interpolation. The ACFs are saved in interfile format with their associated header. Alternatively the ACFs could be obtained from the scanner, by replaying the list-mode data and performing a quick reconstruction, saving the intermediate data. The ACFs then can be exported in DICOM format and similar to the normalization components, converted to interfile (.a) via a Matlab utility.

4.5.3 Sinogram generation

To start the process of generating the sinograms, apart from the sinogram data inputs described above, the following numeric inputs are required:

- Number of radial elements in the sinogram (the sinograms are rebinned to this number of radial bins in order to reduce the sinogram size and improve statistics but with a resolution loss )
- Number of angular elements in the sinogram (the sinograms are rebinned to this number of angular bins for the same reason)
- Trim factor (this is a factor to reduce the sinogram size by trimming it)

To maintain the maximum possible resolution, no sinogram rebinning or trimming should be used, with the sinogram size always set to its native 336×336 size. The process begins by checking the input data and associated headers and based on the scanner model (1080 for the HiRez and 1094 for the TrueV), geometric and data acquisition information are obtained through LUTs. Prior to reading the emission data, header information from the emission file, such as span, ring difference, segment table and sinogram dimensions are then passed to data structures for later use. The 4-D emission sinogram is read and split, while random smoothing can be performed if required. A pre-corrected net-trues sinogram is generated by direct subtraction between prompts and randoms.

Normalization in the scanner is indirect component based. There are 7 components which are taken into account:

- Geometric effects
- Crystal interference
- Crystal efficiencies
- Axial effects
- Paralyzing detector ring dead-time parameters
- Non-paralyzing detector ring dead-time parameters
- Transaxial crystal dead-time parameters

To estimate the dead-time parameters, the average singles count rate is measured for groups of 4 blocks (36 for the HiRez and 48 for the TrueV) and used within a count-rate model including paralysing and non-paralysing components. Inclusion of dead time in the normalization based on the singles means that the normalization sinogram is unique to each frame. After the normalization generation and prior to correcting the emission sinogram by direct point-by-point multiplication, the larger of the 2 sinograms is rebinned and/or mashed to accommodate the smaller in the case their dimensions do not match. This can be true if at the beginning of the process a radial and angular rebinning (for example from 336 elements to 168) is selected.
A gap filling operation is then applied to the normalized net-trues sinogram using linear interpolation. If attenuation correction is selected, the ACFs are loaded, checked and rebinned to match the emission sinogram dimensions. If trimming is selected, both emission and ACF sinograms are trimmed.

Following sinogram trimming, the emission sinogram is corrected for geometric effects. As mentioned before, the sinograms generated by the PDR card, are intermediate sinograms in the native LOR space and due to the circular geometry of the scanners, are non-uniformly sampled in the radial coordinate. On top of that, due to the spherical geometry of the HiRez scanner in the axial direction as well, the sinograms are also non-uniformly sampled in the axial coordinate. In order to generate uniformly sampled sinograms then, a geometric correction is needed both in the radial and axial (only in the HiRez) direction to transform the sinograms from arc sampled coordinates to uniformly sampled coordinates. First a set of so called ‘axial zoom factors’ is generated, which are used to correct for the axial effects due to the barrel geometry. The axial zoom factors for the three segments (0, ±1, ±2) in the HiRez scanner are shown in Figure 4.11. These zoom factors are unique for each one of the 313 sinograms and are used to take into account the differential transaxial FOV in every plane. In segment 0 they increase almost linearly towards the centre of the FOV, following the increase in the crystal radius, while in the central part (central block), are equal to unity since there is no curvature. Similar patterns are seen in the other 2 segments. The zoom factors are
defined as the ratio of the plane’s effective radius to the scanner’s effective radius (considered as a sphere), and as such they are also dependent on the axial compression scheme. This dependence is through the effective radius in a specific plane, as this is taken to be the average radii of the planes participating in that plane based on span 11. However, this process is not applicable on the TrueV as it has a cylindrical design and as a consequence the sinogram is uniformly sampled in the axial direction. Radial arc correction though is still necessary to geometrical transform the sinogram from arc-sampled coordinates to uniformly sampled ones. Having the axial zoom factors, arc correction is performed on the emission sinogram. To demonstrate the effect of arc correction in Figure 4.12 a sinogram before and after arc correction along with their difference is shown. Looking at the difference, it is evident that the correction is more pronounced at the edge of the FOV. This is caused by the reduced sampling distance at the edge of the FOV in the arc-sampled sinogram and as such is likely to have more than one LOR per bin in the uniformly sampled sinogram. As a result the sinogram extends further that the transaxial FOV if the original number of bins is preserved in the arc corrected sinogram (a closer look at the edges of the arc corrected sinogram justifies the above). For CT based ACFs which is the case in both scanners, no arc correction is need as the ACFs are already uniformly sampled. After correcting the emission sinogram for geometric effects, scatter estimation can begin, which is based on the single scatter simulation (SSS) algorithm (Watson et al 1996, 2004). First the emission and transmission images are reconstructed at reduced dimension after sinogram rebinning.

![Figure 4.12](image)

**Figure 4.12** The native LOR space sinogram (i), the arc corrected sinogram (ii) and their difference (iii). Towards the edge of the radial FOV the difference is more pronounced as the radial sampling progressively decreases.
The ACFs are rebinned in the radial and angular direction and reconstructed with DIFT to get the \( \mu \)-map image. Then scatter iterations begin. The emission image is reconstructed with DIFT or AW-OSEM in 2-D after rebinning the 3-D sinogram using single slice rebinning (SSRB) and the image is smoothed with a Gaussian filter. The scatter simulation begins with the emission image and the \( \mu \)-map and the scatter sinogram is calculated using the SSS algorithm in 2-D (segment 0) and subtracted from the emission sinogram. First the entire scatter sinogram is subtracted directly from segment 0, while in the other segments subtraction is done by using the centrally located \( X \) planes from the 2-D scatter sinogram, where \( X \) is the number of oblique planes in each segments. Finally the 2-D ACFs are expanded to 3-D, by estimating the ACFs in the oblique planes using inverse Fourier rebinning (I-FORE). The emission sinogram is then corrected for attenuation through point-by-point multiplication. Representative sinograms from a study are shown in Figure 4.13.

**Figure 4.13** Representative prompts (i), randoms (ii), normalization correction sinogram (iii), scatter (iv), attenuation correction sinogram (v) and the fully corrected sinogram from a patient study as generated by the software.
This whole process described above produces a fully corrected sinogram to be used either within an FBP or UW-OSEM reconstruction algorithm. For other reconstruction schemes where corrections are modelled within a factorized system matrix, the correction sinograms are generated and saved individually. One complication with schemes including normalization as a weight in the system matrix, is that the normalization sinogram needs to be arc corrected with the potential to generate artefacts in the reconstructed image. Nevertheless in the algorithms implemented in this project no obvious artefacts were observed. At the end, 6 sinograms are generated (prompts, randoms, scatter, attenuation, normalization correction sinogram and a fully corrected sinogram) which are saved in binary format.

4.6 Deriving the geometric system matrix

One of the key components in an image reconstruction algorithm, as mentioned before, is the system matrix. This matrix provides the linear mapping from the image domain to the projection domain during forward projection. The main component which is of interest here is the one that includes the geometric probabilities ($H^{Ge} \in R^{J \times J}$) (chapter 2.3.2). This matrix is very sparse and is the one that most of the commercial scanners are using due to its simplicity. There are different ways of calculating the geometric probability with varying levels of complexity. Two main categories of methods exist: the pixel driven methods and the ray driven methods.

Ray driven methods

The ray driven methods can be further sub-categorized into the intersection method and the interpolation method

Intersection methods

In this method, the underlying hypothesis is that the image can be discretized into a $J \times J$ matrix, with the intensity being constant within the spatial basis functions (voxels). The method proceeds by calculating the length each LOR (in a projection at a specific azimuthal and polar angle) intersects with each voxel. The line integral is then estimated using the intersected length to weight the contribution of each voxel along the LOR.
(Siddon 1985, Jacobs et al 1998). One drawback of this method is the discontinuity of the spatial basis function model used. A more realistic, but also more time consuming extension is to consider tube of response of finite width.

**Interpolation method**

In this method the hypothesis is that the underlying image is a smooth function. The method, which is widely known as ‘Joseph’s’ method, proceeds by estimating a set of interpolation coefficients. Every LOR traversing a specific row or column in the image grid receives contributions from the neighboring voxels. If we consider the 2-D case for simplicity, then the distance between the center of 2 adjacent voxels and the point where the LOR is traversing the horizontal/vertical line connecting the voxel centers, define a set of interpolation coefficients. Based on these coefficients, the weighted sum is calculated by estimating the intensity at regular intervals along each LOR (in a projection at a specific azimuthal and polar angle) using linear interpolation (Joseph 1982). Based on the above, the interpolation methods, in the absent of a blurring component in the system matrix, are expected to deliver less noisy images of higher resolution, compared to the intersection methods. This is due to the fact that part of the blurring component is inheritably modeled by the geometric component in the interpolation methods, resulting in a smoother system matrix.

**Pixel driven methods**

Another category of methods which are referred to as voxel-driven, are based on calculating a set of interpolation coefficients for a specific voxel at a specific azimuthal angle (Herman 1980). Instead of projecting the voxel intensities along specific LORs, each individual voxels is projected along a specific view with the projection line passing through the voxel centre. The distance between the projection line and the LORs corresponding to the centers of the 2 adjacent projection bins, defines a set of interpolation coefficient. The integral in each projection bin is then formed by multiplication of the respective interpolation coefficients with the voxel intensities. Figure 4.14 shows a schematic representation of the 3 main methods to perform forward and back-projection.
An efficient technique applicable to forward/back-projection methods is the rotation projection technique. Instead of rotating the projection space to estimate the line integral along specific LORs or specific azimuthal angle, the projection space remains fixed and the image space rotates using interpolation methods (Di bella et al 1996, Kadrmas 2008). Different variations of the aforementioned methods exist in the literature, with each one having a different tradeoff between accuracy, complexity and efficiency.

All these methods can be implemented either using projectors corresponding to the native scanner geometry or using projectors corresponding to the arc corrected geometry. In the first case the projection is done along the non-uniformly sampled LORs, while in the second case the projection is taking place along uniformly sampled LORs. Which of the 2 projectors should be used, depends on the geometry of the sinograms Using native scanner geometry projectors, leaves the data ‘clean’ while maintaining Poisson statistics as no interpolation operations are used to resample the data to the parallel beam, arc corrected geometry (Kadrmas 2004). On the other hand, calculating the geometric probabilities for uniformly sampled LORs requires no knowledge of the scanner geometry, opting for the use of symmetries.

Another important consideration regarding the forward and backward projectors is whether to pre-calculate and store the geometric components of the system matrix, so they can be easily loaded and accessed during the projection operations or to compute them on-the-fly (Panin et al 2007). The first approach requires large amounts of memory if the complete system matrix is stored and loaded. With the modern scanners having

![Figure 4.14](image)  
**Figure 4.14** Schematic representation of the ray-driven (intersection method (i) and interpolation method (ii)) and the voxel-driven (iii) methods.
many million projections (35,336,448 million LORs on the HiRez and 63,108,864 million LORs on the TrueV), even taking into account rotational and translational symmetries, still results in a non-feasible matrix to load. Alternatively one can save the system matrix on disk and sequentially loading it during forward and backward operations. On the other hand calculating the system matrix on-the-fly can be very time consuming if complex methods are considered. As such, using a hybrid approach maybe a more feasible choice.

4.6.1 Methods

As the geometric system matrix was not available for the 2 PET/CT scanners, a software package was developed to generate and store the system matrix. The software was developed in a way so as to allow maximum flexibility in terms of the geometries that could be accommodated, enabling derivation of the system matrix for different scanner designs. The whole process is split into 2 different parts.

The first part takes into account the data acquisition scheme that the specific scanner is using to acquire the data and calculates the geometric end coordinates for all the LORs corresponding to arc corrected data using a Cartesian (x,y,z) coordinate system. At the beginning the user specifies scanner specific information such as:

- Number of radial and angular bins per sinogram
- Number of planes per segment
- Axial compression scheme per plane
- Number rings
- Number of crystals per ring
- Scanner radius
- Crystal width.

First, the axial (z) coordinate for each ring-ring combination is calculated (using the geometry of a virtual scanner in which the sinogram data correspond to after the arc correction) and based on the axial compression scheme, the final LOR axial coordinates for each plane in the 3-D sinogram space are generated. For each plane and using the radial geometry of the arc corrected sinogram (2 mm / bin), the radial (x) and tangential
LOR end coordinates are generated for a projection at a specific azimuthal angle. Finally looping through the projection views and based on the angular geometry of the sinogram (0.5357°/bin) and simple geometric transformations, the radial and tangential LOR coordinates are generated for all projection views within every sinogram plane. The x, y, z LOR end coordinates were calculated for both scanners and were saved for further processing.

The second part of the process takes the LOR coordinates and after parameterizing them, uses a ray-driven approach to calculate the length each LOR is intersecting in each voxel. First the user specifies the image space discretization scheme to be used (number of voxels in the x, y and z direction), along with the voxel dimensions. Then the 3-D image space is registered in the LOR coordinate system and ray tracing is performed by looping through the LORs for each axial plane, angular view and projection bin, using an faster 3-D implementation of the ‘Siddon algorithm’ (Jacobs et al. 1998). This is in contrast to the ‘Joseph algorithm’ which is used in the derivation of the geometric system matrix in the HiRez and TrueV scanners. At the end of the process, for each LOR a list of the voxel indexes is generated in the x, y, and z direction along with the intersected length. Performing ray-tracing and saving the geometric probabilities for all 313 or 559 axial planes in the HiRez and TrueV scanners respectively, would require a huge amount of memory and as such a hybrid approach was used. Using translation and mirror symmetries within and across segments, results in having to store the system matrix for only a few planes per segment. Then using the stored (unique) components of the system matrix as a LUT and on-the fly geometric transformations based on these symmetries, geometric probabilities are mapped to each LOR during the forward and back-projection steps.

4.6.2 Results

Figure 4.15 shows the axial profile for LORs for all the planes and for segments $0, \pm 1, \pm 2, \pm 3$ on the TrueV (Figure 4.15 (A)) and segments $0, \pm 1, \pm 2$ on the HiRez PET/CT (Figure 4.15 (B)). The plots show axial profiles for LORs corresponding to the centre of the radial FOV and averaged in the axial direction after taking the span into account (averaging 5 or 6 LORs in the axial direction), for each of the 559 and 313 planes.
Figure 4.15 LOR axial profiles for the 4 segments (i-iv) on the TrueV (A) and the 3 segments (i-iii) on the HiRez (B).
respectively, which was used during the system matrix generation. The symmetric properties that the planes have within a segment, but also across the positive and negative parts of the segment, are apparent. To better visualize the axial profiles in Figure 4.16 a 3-D model of the HiRez scanner is shown in which all the axial plane are overlaid in the axial direction. The scanner model has the exact geometric coordinates in space as the real scanner. In Figure 4.17 the 336 LORs at varying radial positions, corresponding to a projection along a fixed projection view, are plotted for a fixed segment +2 oblique plane on the HiRez. The LORs are now connecting the detector elements belonging to a ‘virtual’ scanner. The same procedure was followed for all projection view, segments and planes to calculate the 3-D LOR end coordinates.

![Figure 4.16](image1.png)

**Figure 4.16** 3-D representation of the HiRez scanner model overlaid with the LOR axial profiles from the 313 planes for LORs corresponding at the centre of the radial FOV.

![Figure 4.17](image2.png)

**Figure 4.17** LORs at varying radial distance from a single projection view within a plane from segment 2 on the HiRez.
Having the 3-D coordinates for all the LOR in the scanner, the geometric probability matrix was calculated. Siddon’s algorithm was implemented in both 2-D and 3-D for pixel and voxel elements. Figure 4.18 shows a schematic representation of the system matrix for a single LOR in the HiRez and for a 336x336 image grid. The intensity in each pixel in Figure 4.18 (ii) is proportional to the geometric probability of an event emitted from that pixel being detected in the bin corresponding to the LOR. As it can be seen, the matrix is very sparse with the non-zero values covering only 1.5% of the matrix. The sparseness of the matrix is even larger in the 3-D case.

4.6.3 Discussion

A software package was developed to generate and store the unique non-symmetric and non-zero elements of the geometric system matrix for the HiRez and TrueV PET/CT scanners. The software makes use of a faster version of Siddon’s algorithm to trace each LOR through the 3-D image domain. Other scanner geometries can also be accommodated with relative ease. As mentioned before, this is in contrast to the Siemens algorithm for generating the system matrix on the scanners, which calculates interpolation coefficients as opposed to intersecting lengths, using ‘Joseph’s method’. Based on the theory section, interpolation methods produce image of superior quality compared to intersection method. As such it is expected images generated using the

Figure 4.18 For simplicity a single LOR passing through a 336x336 image space in 2-D is seen (i) along with the corresponding probability matrix (ii).
factory supplied image reconstruction software on the scanners (including only geometric probabilities and without any measured blurring components) to be of higher resolution and less noisy compared to images generated using image reconstruction software which makes use of the system matrix as described in this section.

4.7 Image reconstruction

The HiRez PET/CT is equipped with fully approved factory supplied image reconstruction software, capable of analytic, as well as iterative reconstruction algorithms. Although the scanner is acquiring data in fully 3-D mode without any septa and uses high resolution detector block to enhance spatial resolution, the 3-D sinogram space is spatially rebinned in the axial direction to a 2-D sinogram space. Rebinning is performed using an implementation of the Fourier rebinning algorithm (FORE) (Defrise et al 1997, 1999, Liu et al 2001). Analytic reconstruction is provided by 2-D discrete inverse Fourier transform (DIFT) which is similar to FBP (Cheung and Lewitt 1991). Iterative reconstruction is provided by 2-D AW-OSEM. Here the fully corrected sinogram is un-corrected for attenuation effects and the attenuation is used as a weight in the system matrix to better preserve the Poisson statistics in the data. On the TrueV PET/CT scanner, 3 improvements on the reconstruction software are included. First the system is supplied with a fully 3-D reconstruction algorithm, avoiding the axial rebinning and preserving the axial resolution. Second an OP-OSEM algorithm is available, which provides superior statistical handling of the data compared to the weighted OSEM flavours. In the OP-OSEM algorithm, to fully preserve Poisson statistics, data are not arc-corrected and reconstruction is performed using projectors corresponding to the native arc-sampled LORs. As the attenuation and scatter sinograms are already arc-corrected, an additional step to undo this correction is required. Finally, the scanner is equipped with the option of using an OP-OSEM algorithm which takes into account the scanner’s blurring component in the system matrix (PSF), derived from point source measurements (TrueX or HD option) (Panin et al 2006, 2007).

4.7.1 Methods

As mentioned in the introduction, no low level access to the image reconstruction software is provided on the scanners and as such new image reconstruction software
was required, to undertake algorithm development. A software package was developed to perform 2-D, 3-D as well as spatiotemporal 4-D image reconstruction on datasets acquired on the 2 PET/CT scanners, making use of the sinograms generated as described in section 4.4 and a pre-calculated system matrix based on the Siddon

Figure 4.19 Schematic diagram showing image reconstruction data flow using an UW-OSEM algorithm to perform 2-D, 3-D and 4-D reconstruction. Black boxes signify processes using existing Siemens software, while red boxes signify processes using in-house software that was developed in this project and described in the previous sections.
algorithm (section 4.6). The image reconstruction platform was developed exclusively in Matlab to facilitate easy debugging during the development process and make use of its visualization and data manipulation features. For that reason, prior to execution the sinograms obtained from the sinogram generation software (section 4.4.3), are converted from binary format to Matlab variables (.mat).

Initially the user is prompted to supply the following parameter inputs.

- Scanner model [options : 0 = HiRez and 1 = TrueV]
- Reconstruction dimensionality [ options : ‘2D’ and ‘3D’]
- Parametric method [ options : ‘post-reconstruction’ and ‘direct’]
- Flavour [options : 0 = OP-OSEM, 1 = ANW-OSEM, 2 = SP-OSEM, 3 = AW-OSEM]
- PSF [options: 0 = no PSF, 1 = PSF from point source measurements using in house linear blurring operations and its adjoint, 2 = spatially invariant PSF using 1-D convolutions Matlab built-in convolution operator
- PSF method* [ options : 0 = spatially variant PSF, 1 = spatially invariant PSF *used only if PSF = 1 ]
- Iterations [ options : numeric value]
- Subsets [ options : 1, 2, 3, 4, 6, 7, 8, 12, 14, 16, 21, 24, 28, 42, 48, 56, 84, 122, 168, 336]
- Scan mode [ options : ‘dynamic’ and ‘static’]
- Mask [ options : 0 = no mask during parameter estimation, 1 = a patient specific pre-calculated mask is used ]
- Number of frames [ option : numeric value]

Depending on whether parameter estimation is performed (direct or post-reconstruction), the user is also prompted to supply an appropriate input function and a patient specific mask if this option is selected. The sensitivity image is calculated and saved at the beginning. When performing 3-D reconstruction, it is loaded once at the beginning of the frame being reconstructed, while in 4-D mode, sensitivity images for each frame are repeatedly loaded, as the reconstruction loops through all temporal frames in every image update. This is due to the sensitivity image being frame dependent when normalization is used as a weight in the system matrix, as frame
dependent dead time effects are incorporated in the normalization. As an example Figure 4.19 shows a schematic representation of the different steps that take place during the reconstruction process for an UW-OSEM algorithm, while in Figure 4.20 representative planes from the sensitivity images for 3 different OSEM flavours, are displayed. At the end of the process, the reconstructed image volume is saved, along with the kinetic parameters in the case of a spatiotemporal 4D reconstruction.

To qualitatively evaluate the new image reconstruction software package and provide an initial comparison against the factory supplied image reconstruction software on the scanner, the NEMA IEC image quality phantom was scanned and reconstructed as defined in the NU 2-2001 PET performance measurements (Daube-Witherspoon et al 2002). The background in the phantom and the six spheres (10, 13, 17, 22, 28 and 37 mm in diameter) were filled with 50 MBq of $[^{18}\text{F}]$ with a 4:1 sphere-to-background activity concentration, and list-mode data were acquired on the HiRez PET/CT for 60 minutes (~350 million prompts). Data were histogrammed into a static sinogram using the in-house developed list-mode histogrammer and after generating the sinograms, the in-house Matlab based image reconstruction software was used to reconstruct the data. The same list-mode dataset was also histogrammed and reconstructed in the scanner, using the factory supplied software for comparison. In both reconstructions, a 2-D AW-OSEM algorithm was used with 4 iterations and 16 subsets.

The Cologne resolution phantom (Max-Planck Institute, Cologne, Germany) was also scanned on the TrueV PET/CT. The phantom has drilled holes in groups of 5×5, with a hole diameter of 5, 4, 3 and 2 mm (325 holes in total) and centre to centre spacing equal to double the hole diameter, in a 28.6 mm thick plexi-glass slice. The insert is stacked between additional plexi-glass slices. On one side, a containment disk squeezes the
solution in the holes, while on the other side a semi-permeable membrane holds the water within the holes letting the air escape. The phantom was filled with 75 MBq of $^{18}$F and a 60-minute scan was acquired in list-mode (~140 million prompts). Similar to the IQ phantom, the raw data were histogrammed and reconstructed both with the in-house software as well as with the factory supplied software. In both reconstructions a 3-D AW-OSEM algorithm was used with 4 iterations and 21 subsets.

4.7.2 Results

Following the methodology as described throughout this chapter, from list-mode histogramming to image reconstruction, the Matlab based reconstruction successfully managed to reconstruct the data in both scanners. From the qualitatively analysis on the IQ phantom reconstructed images both with the in-house and scanner’s software (Figure 4.21), the images are very closely matched. Nevertheless the reconstructed image on the scanner looks slightly less noisy compared to the in-house reconstructed image. This can also be confirmed from a radial profile across the larger hot sphere in Figure 4.22. In terms of quantification, the reconstructions appear to give very similar results, but a more in depth quantitative analysis is presented in the next chapter. Similar to the HiRez reconstructed images, the comparison between the images reconstructed with the 2 image reconstruction packages on the TrueV scanner, appears to follow the same trend. In Figure 4.23 a 2-D plane through the 3-D image space traversing the cologne phantom is shown. The Matlab based reconstruction (Figure 4.23 (i)) is looking noisier and of reduced spatial resolution compared to the images from the scanner (Figure 4.23 (ii)).

Figure 4.21 Representative planes from the IQ phantom (scanned on the HiRez) reconstructed with the in-house Matlab based reconstruction (i) and the factory supplied reconstruction on the scanner (ii).
Figure 4.22 1-D radial profiles through the IQ phantom reconstructed with the in-house Matlab based reconstruction (black line) and the factory supplied reconstruction on the scanner (red line).

On the Matlab based image, the 4 mm and 5 mm tubes can easily be resolved, while the 3 mm and 2 mm tubes are almost indistinguishable. On the other hand, using the factory based reconstruction the 3 mm tubes can just be resolved with only the 2 mm tubes indistinguishable.

Figure 4.23 Representative planes from the Cologne resolution phantom (scanned on the TrueV) reconstructed with the in-house Matlab based reconstruction (i) and the factory supplied reconstruction on the scanner (ii).

4.7.3 Discussion

An independent image reconstruction software package for both the HiRez and TrueV scanners was developed in Matlab, to perform 2-D, 3-D as well as 4-D image reconstruction. The software attempts to produce images of similar image quality to the images reconstructed using the official factory supplied software available on the scanners and example images were shown and qualitatively compared for both scanners. From this initial comparison a common trend was seen in both the IQ and Cologne
phantoms, with the in-house reconstructed images appearing noisier and in the case of the Cologne phantom, of slightly reduced spatial resolution compared to reconstructed images using factory supplied software. This reduced image quality though is expected, as the reconstruction software in the scanners is making use of an interpolation based geometric system matrix, compared to the in-house reconstruction, using an intersection based geometric system matrix (both though being ray-driven algorithms). This reduced image quality though is expected, as the reconstruction software in the scanners is making use of an interpolation based geometric system matrix, compared to the in-house reconstruction, using an intersection based geometric system matrix (both though being ray-driven algorithms). This is due to the fact that the interpolation method produces a smoother system matrix and is similar to what would be seen with a small blurring. Hence the use of Joseph’s method results in similar (but reduced) effect to that seen with RM. As such even though the 2 reconstructions appear slightly different when only a geometric component is used in the system matrix, they are expected to be closely matched when a fully modelled system matrix, incorporating blurring components, is used as it will be shown in the next chapter.

4.8 Conclusion

In this chapter, technical details for the HiRez and TruePoint TrueV PET/CT, along with practical considerations from data acquisition to image reconstruction on the scanners, were described. A software package was developed and successfully tested, to histogram the list-mode data and perform 2-D, 3-D as well as 4-D image reconstruction for both PET/CT scanners. Existing software was also used to derive the correction sinograms. Representative reconstructed images using the developed software were shown and compared against images reconstructed with the factory supplied software in the scanner. Small differences were seen due to the line integral projectors used, but as it was mentioned and will be described in the next chapter, where a more comprehensive performance evaluation is performed, modelling the blurring component of the system matrix based on the specific geometric projectors can compensate for these differences. Most importantly though, the comparison demonstrates that images can be successfully reconstructed with the developed reconstruction platform, which provides the basis upon which further algorithmic development, can be performed. This chapter along with the previous 2 chapters form the basis for chapters 5, 6 and 7 which describe the main research work undertaken during this project.
CHAPTER 5

Space-variant image based PSF parameterization and resolution recovery image reconstruction


5.1 Introduction

In the last few years, tremendous effort has been put into developing image reconstruction algorithms for positron emission tomography (PET). Statistical methods can often provide images of better signal-to-noise ratio (SNR) and resolution compared to conventional analytic algorithms, by accounting for differences in measurement precision and allowing extensive modelling of the emission and detection processes occurring during data acquisition, as described in chapter 2. This can be realized through the use of a system matrix, but in common practice an over-simplified forward and back-projector is used or a line integral model which approximates only the geometric detection probabilities (Joseph 1982, Siddon 1985). This model, although computationally simple, fails to take into account more complex physical phenomena taking place during data acquisition. In reality emission effects like positron range and photon non-collinearity, as well as detection effects like multiple photon interactions within the crystal block, light transport within the crystal array, errors in the crystal identification matrix and errors between the effective and the physical crystal location (Qi et al 1998, Tomic et al 2005), will result in a blurred measurement of the sinogram and subsequently the image.

To correct for these emission/detection blurring effects and accurately model the relationship between image and projection space, these effects can be taken into account during the reconstruction process either in projection space or image space. The measurement of image space point spread function (PSF) kernels, and their use in resolution modelling, has the potential advantage of being able to capture and correct for both emission and detection resolution degrading effects.

The drive behind this chapter as such is five-fold. First deriving the PSF from real point source measurements constitutes one of the most accurate, but also the most challenging approaches. Using a point source to measure the data blurring is time consuming, requiring complex and expensive equipment. Usually sophisticated robots are employed to accurately position and move a single point source throughout the field of view (FOV). Panin et al (2006) was the first to use a 3-D positioning robot with a single $^{68}$Ge source at 1599 positions in his seminal work, while Wiant et al (2009) using a similar design, scanned a single $^{68}$Ge source at 6336 points. Tohme et al (2009) used a robot and a single $^{22}$Na source to sample the PSF at 3064 transaxial positions, but
restricted the measurements in a single axial plane. Finally Cloquet et al (2010) used a single $^{22}$Na source and a grid to guide the source at the measured positions. Limited measurements of a $^{22}$Na point source were also used by Alessio et al (2010) and Rapisarda et al (2010). All these devices can only position one point source at a time and with the need for high count statistics, there is a compromise between the number of sampled points and the acquisition duration. As such there is a need for fast and efficient methodologies to measure the space-variant PSF.

Secondly, the HiRez and TrueV PET/CT, as well as the high resolution research tomograph (HRRT), are high resolution whole body and brain scanners respectively, but their spatial variant resolution characteristics haven’t been studied in detail using image based techniques. Panin et al (2006) measured the space-variant PSF of the B-HiRez PET/CT and extended his work on the TruePoint TrueV PET/CT (Panin et al 2007), but his work was restricted to projection space parameterization. On the other hand the space-variant characteristics of the PSF on the HRRT have been the subject of many investigations, but a comprehensive and detailed evaluation is yet to been done. Jan et al (2004) measured the in-plane resolution at 6 radial positions, while Blinder et al (2005) used 15 point sources at 5 radial and 3 axial positions. Olesen et al (2009) measured the spatial resolution at 36 different radial and angular positions, but restricted the measurements in the central plane. Finally Jian et al (2010) used a line source to measure the spatial variation of the PSF, limiting the area covered within the FOV and the estimation of the full width at half maximum (FWHM) to the 2 axes perpendicular to the line source.

Another effect which has been found to affect the characteristics of the PSF, apart from the parallax error, is the count rate due to pulse pile-up. Germano et al (1990) first came to the conclusion that in detector blocks and at higher singles count rates, coincidence events begin to pile-up, displacing their location towards the centre of the block and consequently degrading the scanner’s resolution. Thon et al (2004) obtained similar findings using an LYSO block detector, while Surti et al (2005) developed a high count rate simulation to investigate the resolution degradation on pixellated anger-logic detectors. On the HRRT scanner the PSF dependency on the count rate is further accentuated due to the dual-layer detector design, resulting in inter-layer pile-up (Rodriguez et al 2007). Jian et al (2010) observed the count rate dependent resolution degradation on the HRRT, but again their measurements were based on line sources,
limiting the resolution degradation measurements to the 2 axes perpendicular to the line source. A detailed evaluation of the PSF count rate dependency would be beneficial especially in dynamic studies, in order to quantify potential changes in the spatial resolution between different time frames having different singles count rates.

Having measured the spatially variant PSF in image space, another objective was the implementation of a spatially variant image based resolution recovery image reconstruction. Image based resolution modelling for PET was first proposed by Reader et al (2001, 2002, 2003), who used a simple Gaussian PSF model to demonstrate enhanced resolution and noise reduction on clinical images. The work continued in Sureau et al (2008), using a similar model on the HRRT, which assessed the impact of such a model on phantom studies and kinetic parameters. Although spatially invariant kernels provide improvements in SNR and resolution, for most scanners which lack depth-of-interaction (DOI) capabilities, use of a spatially variant kernel may be more appropriate. Rahmim et al (2003) used a transaxially variant and anisotropic non-Gaussian model over stationary and isotropic kernels, while in a much later study (Rahmim et al 2008a) proposed an image space technique that incorporates the spatially-variant, medium-dependent nature of positron range. Recently and while this research was in progress, Rapisarda et al (2010) incorporated spatially variant kernels within an image based resolution modelling reconstruction on the GE Discovery STE while Cloquet et al (2010) explored non-Gaussian variant and anisotropic models within a list-mode reconstruction algorithm on the Philips Gemini.

Finally, although image based techniques have been explored by many researchers showing promising results, nevertheless it remains to be demonstrated whether the image based approach is a valid alternative to the projection based approach. As such there is the need for a direct comparison between image based and projection based resolution recovery image reconstruction.

This chapter attempts to address the above scientific questions by means of experimental measurements and algorithmic development. As such a new method was proposed and assessed, based on a printed array of fluorine-18 point sources, in order to rapidly derive the spatially-variant image based blurring component of the system matrix. The method of producing radioactive point sources using a standard inkjet printer has become increasingly popular. Printed point sources have been previously used in SPECT (Van Staden et al 2007) to produce quality assurance phantoms and also
in PET (Sossi et al 2003) for resolution measurements. The method was used to obtain the space-variant PSF on 2 whole-body PET/CT scanners (Biograph 6 B-HiRez PET/CT and Biograph 6 TruePoint TrueV PET/CT) and on a high resolution brain scanner (HRRT). Furthermore the count rate dependency of the PSF was also characterized on the HRRT, by designing a count-rate experiment in conjunction with the point source array. The impact of the DOI capability on the scanner’s spatial resolution was also assessed. Based on the measured kernels from the 2 PET/CT scanners, an image based spatially variant resolution recovery image reconstruction algorithm was implemented and assessed for both scanners.

Finally we conducted a direct comparison between image based and projection based resolution recovery techniques on the same datasets. Specifically we compared three different fully 3-D ordinary Poisson OSEM (OP-OSEM) resolution modelling algorithms: 1) an in house implementation (OP-OSEM) using the measured image based spatially variant PSF (varIMPSF OP-OSEM); 2) an in house OP-OSEM implementation using the spatially invariant measured image based PSF at the centre of the field of view (invIMPSF OP-OSEM); 3) the commercial PSF reconstruction implementation using projection space modelling (varPRPSF OP-OSEM). As a reference we also used an in-house implementation of the standard reconstruction without any resolution modelling (noPSF OP-OSEM). The assessment was carried out using a range of phantom and clinical datasets: point source data; the image quality NEMA phantom data; Cologne resolution phantom data, and clinical data from a [11C]-Antisense oligonucleotide (ASO) and an [18F]- Fluoro-L-thymidine (FLT) scan.

5.2 Materials and methods

5.2.1 Space-variant and count rate dependent PSF parameterization in image space via a printed array

5.2.1.1 Point source production and optimization

An HP 5440 printer was used in order to print radioactive point sources at predefined positions on a sheet of A4 paper. Standard black ink was mixed with small quantities of fluorine-18 saline solution (0.1-0.2 ml), which was injected into an ink cartridge (Figure 5.1). Prior to injection, the ink cartridge was modified by removing the sponge and the
membrane which controls the ink delivery inside the cartridge, in order to apply ink directly to the reservoir for maximum efficiency. In order to optimally space the sources and choose the best source dimensions, point sources with various diameters and distances between sources were scanned on the HiRez PET/CT and on the HRRT, at various locations in the FOV. The same optimized source size and spacing was used for the TrueV as for the HiRez, as both make use of the same block detector design and have similar transaxial FOV and as such is expected to have similar resolution properties (Jakoby et al 2009). For this optimization, the raw point source data were reconstructed using an OP-OSEM algorithm, with fine image voxel sampling (PET/CT: 10 iterations, 21 subsets, 0.66 mm × 0.66 mm × 2 mm voxels – HRRT: 10 iterations, 16 subsets, 1.2 mm × 1.2 mm × 1.2 mm voxels) and the resulting images were qualitatively analyzed using line profiles along the radial and axial directions to determine the degree of overlapping of adjacent PSF profiles. This point source spacing optimization has a direct effect on the number of point sources per array. Maximization of the activity per point source minimizes acquisition time or maximizes the counting statistics and hence is desirable. Increasing the size of the round dot sources and reprinting of the sources using the same paper were investigated as approaches in order to boost the activity per point source. Larger sources will decrease the accuracy of the PSF measurements, with such degradation assessed qualitatively. Reprinting the point source multiple times will potentially degrade the point source resolution if reprinting does not occur in exactly the same location. The latter was checked through examination of microscope-enhanced images. As a compromise between resolution and activity, on the 2 PET/CT scanners a source diameter of 2 mm was chosen matching the dimensions of the reconstructed voxels typically used. On the HRRT a point source diameter of 1 mm was chosen due to the higher spatial resolution of this scanner. Based on this optimization, the dimensions of the sources and their spacing were used to design the array in Microsoft publisher.

5.2.1.2 Positioning and aligning the point source array

5.2.1.2.1 PET/CT

To position the point sources within the FOV and allow them to move in all 3 dimensions, a phantom was designed for the PET/CT (Figure 5.2). The phantom was made out of an aluminium bar, located outside the FOV, in which holes were drilled
Figure 5.1  Picture (a) shows pots with standard black ink (0.3 ml) which was mixed with fluorine-18 (1.2GBq/1.5 ml) and small quantities (~0.3ml) were injected into an ink cartridge via a syringe, while picture (b) shows the point sources as they were being printed in an A4 sheet of paper.

every 2 cm. Attached to the bar were 2 sheets, 3mm width each, made out of a tissue equivalent material (Perspex). The use of a transparent material made positioning and alignment of an A4 sheet of paper easier. The width of 3mm was chosen as a compromise between ensuring positron annihilation occurs within the Perspex and the minimization of attenuation. To move the phantom within the FOV, the aluminium bar was attached to the quality control (QC) phantom holder that was supplied with the scanner and which was subsequently attached to the scanner’s bed. The phantom holder as well as the holes in the metal bar allowed movement in the radial and tangential directions while the movement of the bed through the scanner’s patient handling system (PHS) was used to cover the axial direction.

The point source alignment was done in 2 steps. First the scanner’s laser system was used to align the outermost rows and columns of the array of point sources to the axial and the radial lasers (Figure 5.2), which correspond to the central axis and the edge of the CT FOV. With the sources positioned, a quick CT scout scan was taken to position the phantom axially. Following a short PET emission scan, the within plane segment zero sinograms were examined to observe the axial deviation of a single radial line of point sources and if necessary correct the array position. When the point sources were perfectly aligned with respect to the radial scanner axis, they should appear within the same projection plane. Note that only a single alignment is required and that it is quicker and easier than previous methods, requiring the alignment of a moving robotically positioned point source (Panin et al 2006). Following alignment using the QC phantom holder, the positioning holes within the aluminium bar and the couch, the array could be moved to the desired location.
Figure 5.2 A Perspex phantom was designed (left) to hold the array and provide material for the positron to annihilate. An aluminum bar was used to attach the array to the QC phantom holder. The array after being aligned with lasers, was scanned at different positions (right). The axial movement was done by changing the PET/CT FOV with respect to the topogram FOV, as the array had always a fixed position with respect to the topogram. In the radial direction, movement was provided by moving the Perspex sheets to different holes (discrete movement - 2 cm hole-to hole spacing) or by manually shifting the phantom holder radially for finer sampling (continuous movement with sub-millimetre accuracy).

5.2.1.2.2 HRRT

On the HRRT an already existing phantom was used to position the array in the FOV (Markiewicz et al 2011). The phantom consists of 2 Perspex endplates of a diameter equal to the diameter of the HRRT bore, held together by 4 Perspex rods. A tight fit is always ensured once it is placed inside the scanner, with the axial extent of the phantom being equal to the axial extent of the HRRT bore. Two Perspex sheets, 2 mm in thickness, are placed horizontally and traversing the centre of the transaxial FOV, which were used to sandwich the point source array.

As mentioned in the introduction, apart from the spatial variant dependency of the PSF, the count rate dependency was also investigated on the HRRT. To provide the high singles count rate needed, the phantom was modified. Holes were drilled in both phantom endplates to fit a 70 cm long and 2 mm thick Perspex tube encapsulating a 90cm PVC extension line (Figure 5.3 (c)).

Compared to the PET/CT, the HRRT has no capability to acquire a topogram due to the lack of a CT and that meant that a different approach was needed for the alignment of the phantom. Since the phantom tightly fits inside the bore, its position is highly reproducible between scans. For that reason, test scans were taken with the point source array positioned in the phantom, in order to locate the centre of the FOV axially and radially, by shifting the array at small increments with respect to the phantom and looking at the reconstructed images (Figure 5.3 (a-b)). The laser system was used to provide an initial estimate of the FOV, while the reconstructed images provided further
Figure 5.3 Test scans were acquired to locate the centre of the FOV and to align the axis of the array with the axis of the reconstructed FOV (a-b). After aligning the array, the axes were drawn on the phantom (c) and every subsequent alignment was done with respect to these axes as the phantom’s positioning inside the bore was highly reproducible in every scan and as such was considered as a fix point of reference.

adjustments in the positioning. With the array axial and radially centred, lines were drawn on the phantom to mark the scanner’s axis. Any subsequent alignment of the array was then done with respect to these lines. Azimuthal alignment was provided by means of a small spirit level, attached on the outer endplate. Finally the array was always tangentially centred at a specific azimuthal angle, as the Perspex sheet was designed to be tangentially centred. The latter was also confirmed through evaluation of reconstructed point sources from the test scans.

5.2.1.3 Scanning protocol

5.2.1.3.1 HiRez scanner

On the HiRez, a rectangular grid of 8 (axially) × 15 (radially) point sources, evenly spaced at 20 mm was scanned 120 times, in order to measure the PSF with a fine spatial sampling over a FOV segment assuming radial and rotational PSF symmetries. In the radial direction, the array was scanned at 4 radial positions with a 5 mm step size moving from the centre towards the edge of the FOV. In the axial direction, the array sampled 10 axial positions with a 2 mm step size. This axial sampling was chosen to coincide with the plane width. In the vertical (approximately tangential) direction the sources were scanned at 3 positions 5mm apart. As a result of these scans the PSF is measured for a grid of 60 (radial) × 80(axial) × 3(tangential) points (14400 in total), spaced 5 mm radially and tangentially and 2mm axially (Figure 5.4). Due to the short half-life (109.8 minutes), it was not possible to perform all 120 scans using the same printed sheet. In practice 6 scanning sessions were performed, each of 4 hours duration.
(1 array/session). To account for decay within each scanning session and ensure comparable statistics, progressively longer acquisition periods were used (5-20 min).

5.2.1.3.2 TrueV TruePoint scanner.

On the TruePoint TrueV PET/CT we used a different sampling scheme, in order to assess whether the spatially dependent characteristics of the PSF could be measured using a single scan, and to assess the reproducibility using different scans and positioning. The array was made out of a rectangular grid of 9 (axially) × 14 (radially) point sources, with a 20 mm spacing both in the axial and radial directions. For evaluation and assessment purposes it was scanned at 3 different positions.

In the first scan, which we consider to be the reference scan, the axial centre of the array (middle radial line of point sources) was positioned in the centre of the axial FOV (z = 0 cm) covering almost the entire axial FOV (z = −8 cm…+8 cm). Transaxially the edge of the array was positioned 1 cm from the centre of the transaxial FOV (r = 1 cm…27 cm) having a zero azimuthal angle (φ = 0°) from the horizontal scanner axis. To examine whether the axial sampling using a single array is sufficient, we acquired a second scan at the same radial and azimuthal position but shifting the array in the axial direction by 1 cm. Finally in order to determine if the PSF model is rotationally symmetric, the array was scanned with the same axial and radial position of the reference scan, but at a different randomly chosen azimuthal angle (φ = 37°) to the

![Figure 5.4](image_url) Sampling scheme for the HiRez. The axial extent of the array covered the entire axial FOV and half the transaxial FOV. The green mesh represents the block layout of the scanner.
horizontal. A better approach would be to point the array at the centre and edge of the block to see any differences, something which was difficult to achieve on the PET/CT.

5.2.1.3.3 HRRT scanner

On the HRRT again a different scanning protocol was used due to the geometry of the scanner, with the data acquisition split between 2 scanning sessions. The smaller bore diameter (31.2 cm) compared to the PET/CT (70 cm), allowed the radial FOV to be sampled from one side to the other as opposed to measuring the PSF from the centre to the edge of the radial FOV and assuming radial symmetry based on the geometry of the scanner. The array was made out of a rectangular grid of 11 (axially) × 15 (radially) point sources (165 sources in total), with 18.5 mm and 19.5 mm spacing in the radial and axial directions respectively. In the first scanning session, 2 scans were acquired, with the array placed horizontally within the HRRT and centred transaxially, covering almost the entire radial (-13…+13 cm) and axial (-9.8…+9.8 cm) FOV. First a 10 minute scan of the array was acquired, to measure the spatially variant (axial and radial) characteristics of the PSF. Secondly, to measure the PSF count rate dependency, carbon-11 was used to provide singles count rate levels typically obtained in clinical scans. Without moving the array of fluorine-18 point sources, a second scan was acquired for 150 minutes after injecting 294 MBq of carbon-11 (0.9 ml) into the PVC extension line. The half-life of carbon-11 allows continuous PSF measurements at decreasing count-rate levels, but importantly with minimal decay in the fluorine-18 point sources. In the second scanning session, the array was scanned (without the extension line) at different angular positions,

![Figure 5.5](image-url)

**Figure 5.5** To measure the rotational symmetry of the PSF the array was scanned at 0°, 9°, 18°, 22.5°, 27°, 36°, 45° from the horizontal, with the array pointing towards the centre of a detector head at 0° (a) and 45° (c) and to the gap between the heads at 22.5° (b).
in order to measure the rotational symmetry of the PSF. Compared to the PET/CT though, the HRRT has 8 detector heads with interleaving gaps between them and with a 22.5º angular symmetry dictated by the octagonal geometry of the scanner. As such any assumption for rotational symmetry should be justified.

To test that assumption and whether the rotational symmetry follows the geometry of the scanner, 7 scans of the array were acquired at 0 º, 9 º, 18 º, 22.5 º, 27 º, 36 º, 45 º from the horizontal, with the array pointing towards the centre of a detector head at 0 º and 45 º and to the gap between the heads at 22.5 º (Figure 5.5).

5.2.1.4 Reconstruction of point source data for PSF determination.

5.2.1.4.1 PET/CT

PET data were collected in 32-bit list mode for both PET/CT scanners and organized into prompt and random events using an in-house list-mode histogrammer, which had previously been validated against sinograms produced using the manufacturer’s software as shown in chapter 4, with illustrative sinograms shown in Figure 5.6 for both scanners. Standard HiRez and TrueV software was used for calculating the correction sinograms prior to reconstruction as follows. Prompt data were corrected for geometric effects (axial and radial arc correction for the HiRez and only radial arc correction for the TrueV). Scatter calculation is based on a 2-D implementation of the single scatter simulation method (Watson et al 2004) and then expanded to 3-D as explained in chapter 4. Normalization is indirect component based (geometric effects, crystal interference, crystal efficiencies, axial effects, paralyzing and non-paralyzing ring dead-time parameters), with the dead-time correction being included in the normalization sinogram after taking into account the average singles rate at the detector block level. Finally the standard scanner software uses the CT data to generate the 2-D attenuation correction sinogram. The 3-D attenuation sinogram is then calculated by inverse Fourier rebinning the 2-D sinogram. Images were reconstructed using an in-house 3-D OP-OSEM reconstruction algorithm (10 iterations and 21 subsets), accounting for scatter and randoms. Normalization and attenuation effects were included within a factorized system matrix. Our 3D OP-OSEM algorithm made use of a pre-calculated geometric system matrix, based on a 3-D implementation of the Siddon algorithm (Siddon 1985).
Figure 5.6 Horizontal (left) and transaxial (right) sections through the 3-D sinogram space from segment 0. Moving away from the centre of the FOV the radial elongation is obvious. The spherical design of the HiRez compared to the cylindrical geometry of the TrueV elongates the PSFs also in the axial direction with a correlation between the radial and axial blurring components. The gaps between the crystals are seen as black strips along the axial direction especially when an LOR corresponding to a gap passes through a point source.

For all the reconstructions a fine pixel grid was used (1008 × 1008 × 81) to ensure adequate PSF sampling, having image voxel dimensions of 0.66 mm × 0.66 mm × 2 mm.

5.2.1.4.2 HRRT

PET data were collected in 64-bit list mode and organised into prompt and random events using the standard HRRT list-mode histogrammer. The list mode data from the first 10-minute scan (1st scanning session), which were used to measure the axial and radial variation of the PSF were used to evaluate the effect of the DOI on the scanner’s PSF. This was done by assigning all the back-back, front-back and back-front layer coincidences to front-front coincidences during list mode histogramming, effectively turning off the DOI capability and assuming all the back layer events to originate from the front layer.

To quantify changes in the PSF at different count levels, the list mode dataset from the second scan (1st session) were the carbon-11 was in the extension line, was split into 15 10-minute frames with the singles rate ranging from 33 kcps (1st frame) down to 1.2 kcps (15th frame).
All the datasets on the HRRT were reconstructed using the standard HRRT reconstruction software (Hong et al 2007). Data were reconstructed with OP-OSEM (10 iterations and 16 subsets) on a 256 × 256 × 207 image grid with a 1.2 mm × 1.2 mm × 1.2 mm voxels. To evaluate also the effect on the PSF reconstruction capability that the HRRT software has on the PSF measurements, data were also reconstructed using the spatially invariant PSF OP-OSEM on the standard HRRT reconstruction software (12 iteration and 16 subsets) (Sureau et al 2008).

5.2.1.5. Point spread function parameterization

The PSF data can be used directly if sampled for every voxel in the FOV. Since in practice one can only sample the PSF at a limited number of positions, a PSF model was used in order to fit a number of parameters to the measured data. Each reconstructed PSF was modelled in image space as a mixture of two 3-D Gaussian distributions (with radial, axial and tangential components). The mean for the two Gaussian functions was left unconstrained in order to also take into account the asymmetry in the PSF distributions as a consequence of the parallax error. The use of two Gaussian distributions, potentially with quite different kernel widths enables non-Gaussian distributions to be modelled. Specifically, each PSF was modelled as:

\[
PSF(x',x) = \sum_{i=1}^{2} w_i G_i(x',\mu(x),\Sigma(x)), \quad \sum_{i=1}^{2} w_i = 1 \quad (5.1)
\]

\[
G_i(x',\mu(x),\Sigma(x)) = \frac{1}{(2\pi)^{3/2} |\Sigma(x)|^{1/2}} \exp \left( -\frac{1}{2} (x'-\mu(x))^T \Sigma(x)^{-1}(x'-\mu(x)) \right) \quad (5.2)
\]

\[
\mu = \begin{pmatrix} \mu_r(x) \\ \mu_a(x) \\ \mu_t(x) \end{pmatrix}, \quad \Sigma = \begin{pmatrix} \sigma_r^2(x) & 0 & 0 \\ 0 & \sigma_a^2(x) & 0 \\ 0 & 0 & \sigma_t^2(x) \end{pmatrix} \quad (5.3)
\]

where \( x \) and \( x' \) are position vectors relating to the image space and PSF kernel respectively, \( G_i \) is the function describing a 3 dimensional Gaussian distribution and \( w_i \) is a mixing term. The matrices \( \mu \) and \( \Sigma \) hold the first and second order moments of the probability density function (mean and covariance matrix) for the radial, axial and tangential responses. \( \Sigma^{-1} \) is the inverse of the matrix \( \Sigma \) and superscript T denotes the transpose. The constants in front of the exponential are normalization constants, such
that the integral of equation (5.2) is equal to 1. The covariance matrix was constrained to non-zero diagonal elements based on the data and to reduce the fitted parameters. A total of 13 parameters (6 parameters for each of the two Gaussian distributions \((\mu, \mu, \sigma_t, \sigma_t, \sigma_t, \sigma_t)\) and one mixing coefficient \((w_j)\)) were estimated for each measured PSF. The Expectation Maximization (EM) algorithm was used to construct an object of the gmdistribution class in Matlab (The Mathworks, R2009a), containing maximum likelihood estimates of the parameters using the above Gaussian mixture model.

Figure 5.7 2-D sections through the 3-D fitted PSFs at 2cm (left) and 22cm (right) from the centre of the FOV. Close to the centre of the FOV the PSF is almost symmetric while at the edge of the FOV the radial elongation results in an asymmetric and noisier distribution due to counts spreading in more voxels.

For the point source data acquired at different angles both in the TrueV PET/CT and HRRT scanners and in order to avoid using the non diagonal elements of the covariance matrix, which would increase the number of parameters, the reconstructed images were rotated around the scanner axis at 0° from the horizontal based on knowledge of the angle at which they were acquired. Although in reality such an operation is non ideal, no significant effects from the rotation operation on the PSF data were observed.

5.2.2 Resolution recovery based image reconstruction on the HiRez and TruePoint TrueV PET/CT

5.2.2.1 Space-variant image-based resolution modelling implementation

The derived model parameters were then fitted to 2\(^{nd}\) order polynomial functions dependent on the radial \((r)\) and axial \((z)\) position of the point source. This enables determination of the model parameters for every position in the FOV. Based on the data analysis from the 2 scanners though, only a very small axial dependency of the axial blurring was seen, with the radial and tangential blurring being practically axially
independent. For that reason and to minimize the storage requirements of the overall PSF, each parameter was radially dependent, but invariant to axial and rotational transformations.

Each image voxel within an axial plane was then assigned with a set of model parameters based on its radial distance. Then based on the angle from the horizontal the kernels were rotated for each voxel and were stored in a $K^2 \times \Theta^3$ matrix, where $K$ is the number of pixel in the plane and $\Theta^3$ is the size of the 3-dimensional kernel. Figure 5.7 shows fitted PSFs with a nearly symmetric distribution at the centre and a radially skewed distribution at the edge of the FOV.

To implement a spatially-variant image based resolution modelling algorithm we used an ordinary Poisson ordered subsets expectation maximization (OP-OSEM) algorithm and applied the pre-calculated spatially-variant blurring matrix using linear blurring operations during the forward-projection and back-projection steps (equation 5.4). 

$$
\lambda_{i+1} = \frac{\lambda_i}{\sum_k \theta_k \eta_k} \sum_j \sum_k p_{jk} \sum_{m_j} m_j \theta_{k,j} \lambda_{i+1} + \eta_j, \quad \sigma_k = \sum_j p_{jk} n_j a_j, \quad \eta_j = \frac{r_j}{a_j n_j} + s_j \tag{5.4}
$$

where $\sigma_k$ is the sensitivity image, $\lambda_i$ is the mean number of photon emissions occurring in the $i^{th}$ pixel at the $k^{th}$ iteration, $m_j$ is the measured events in the $j^{th}$ sinogram bin, $p_{jk}$ is the geometric probability matrix of events being detected at $j^{th}$ sinogram bin given emitted from $k^{th}$ image pixel (and determined using Siddon’s algorithm), $a_j$ is the probability of an event not being attenuated, $n_j$ is the photon detection probability in the detectors, $r_j$ are the number of detected randoms at $j^{th}$ sinogram bin, $s_j$ are the scatter events arriving at $j^{th}$ sinogram bin and $\theta_{k,j}$ is the PSF kernel representing the blurring of an event emitted from the $i^{th}$ voxel to the $k^{th}$ voxel. During the back-projection process, the transpose of the blurring kernel is used for the blurring operation. In addition to the spatially-variant PSF reconstruction, the symmetric kernel corresponding to the one obtained at the centre of the FOV was used for all image voxels to produce a spatially-invariant PSF reconstruction.
5.2.2.2 Evaluation of spatially variant and invariant PSF reconstructions

The accuracy and utility of the proposed methodology to determine and correct for image blurring was evaluated by comparing three in house implementations of OP-OSEM (no resolution modelling (noPSF OP-OSEM); image based space invariant RM (invIMPSF OP-OSEM); image based space-variant RM (varIMPSF OP-OSEM)), with the manufacturer’s projection based reconstruction (varPRPSF OP-OSEM). As the varPRPSF is not yet commercially available on the HiRez (at the time of this work), we were only able to compared the image based and projection based resolution modelling reconstruction implementations on the TrueV datasets. For all the datasets, the same pre-processing methods were used as in the reconstruction of the PSF data (section 5.2.1.4.1). On the HiRez and TrueV for all resolution recovery reconstructions we used 8 iterations and 21 subsets to match the maximum number of iterations in the manufacturer’s implementations. For the non-PSF reconstructions we used 5 iterations and 21 subsets to match the statistical background noise in the PSF reconstructions (Sureau et al 2008). For the point source data we also used 15 iterations and 21 subsets. On the NEMA phantom, we reconstructed the data with an attenuation and normalization weighted OSEM (ANW-OSEM) algorithm as well for comparison purposes (invIMPSF ANW-OSEM and varIMPSF ANW-OSEM) and evaluated the different reconstructions using up to 15 iterations and 21 subsets for both scanners. All the reconstructions used a 336×336×109 image grid, with 2 mm voxel side length.

5.2.2.2.1 Point source array

Acquired data from a single point source array with 15×8 (HiRez, ~29 MBq, 13 min acquisition, ~90 million prompts) and 14×9 (TrueV, ~10 MBq, 1h acquisition, ~137 million prompts) fluorine-18 printed sources (2 mm point sources with 200 mm spacing), were used to assess the potential resolution improvements of the different resolution modelling methods (see sections 5.2.1.3.1 and 5.2.1.3.2 for other details). Resolution recovery was assessed qualitatively by looking at point source profiles, as well as quantitatively by calculating the FWHM for the different methods.
To evaluate the bias-variance characteristics of the different algorithms, the NEMA IEC image quality phantom set was used as defined in the NU 2-2001 PET performance measurements (Daube-Witherspoon et al 2002). The background in the phantom and the six spheres (10, 13, 17, 22, 28 and 37 mm in diameter) were filled with 50 MBq of fluorine-18 with a 4:1 sphere-to-background activity concentration. On the HiRez the phantom was scanned without the lung insert (350 Mcounts, 60-minute list-mode acquisition). On the TrueV the largest 2 spheres were filled with non-radioactive solution (water) to simulate cold spot regions in the body (140 Mcounts, 9 min acquisition). Samples were taken from the spheres and the background, measured in a well counter and decay, dead time, background and volume corrected. Data were analyzed qualitatively as well as quantitatively. Six circular regions of interest (ROIs) of similar diameter to the spheres were drawn on the transaxial CT image. For each of the 6 spheres, 12 ROIs in total of the same diameter were drawn on the background in the plane that was used for the sphere analysis as well as in planes ±1 cm and ±2 cm from that one (60 ROIs /per sphere size over the 5 planes). For the bias and the variance assessment, 2 figures of merit where calculated and referred to as the contrast recovery coefficient (CRC) and image roughness (IR) (Equation 5.5 and 5.6 respectively) (Tong et al 2010a).

\[
\text{CRC}_{b,j} = \left( \frac{C_{h,j}}{C_{bg,j}} - 1 \right) \left( \frac{a_h}{a_{bg}} - 1 \right) \times 100\% \tag{5.5}
\]

\[
IR_{j,k} = \frac{\sum_{p=1}^{P_{bg,j}} (C_{bg,j,k,p} - C_{bg,j,k})^2}{\left( P_{bg,j} - 1 \right)} \times \frac{\sum_{k=1}^{N_{bg}} IR_{j,k}}{N_{bg}} \tag{5.6}
\]

Where \( N_{bg} = 60 \) the number of background ROIs, \( C_{h,j} \) is the mean reconstructed activity concentration for the \( j \)th hot sphere, \( C_{bg,j} \) is the mean reconstructed activity concentration for the \( j \)th hot sphere, \( a_{h,j} \) and \( a_{bg,j} \) are the measured activity concentration in the hot spheres and the
background, $C_{bg,j,k}$ is the mean AC for the $j^{th}$ background sphere size and the $k^{th}$ ROI, 
$C_{bg,j,k,p}$ is the reconstructed AC for the $p^{th}$ image voxel within the $k^{th}$ ROI for $j^{th}$ 
background sphere and $P_{bg,j}$ is the number of pixels in the $j^{th}$ background sphere.

5.2.2.2.3 Cologne resolution phantom

The Cologne resolution phantom (Max-Planck Institute, Cologne, Germany) was 
scanned on the TrueV PET/CT to assess the resolution improvements by visual 
evaluation of the images and profiles. The phantom was filled with 75 MBq of fluorine-18 and positioned in the scanner with the centre of the phantom coinciding with the 
centre of the FOV and the tubes parallel to the scanner axis. A 60-minute scan was 
acquired in list-mode and ~140 million counts were collected.

5.2.2.2.4 $[^{11}\text{C}]$ASO abdominal PET/CT study

A single scan from a study examining the bio-distribution of a carbon-11 labelled 
antisense oligonucleotide was used to compare observed resolution improvements with 
the different reconstruction methods on the HiRez (Saleem et al 2009, 2011). With this 
tracer high uptake is observed within the kidney cortex. The patient was administered 
with 441 MBq of $[^{11}\text{C}]$ASO and list-mode data were acquired over a 95 minute period 
using the HiRez PET/CT. Almost 60 million prompts were collected and histogrammed 
into a static sinogram.

5.2.2.2.5 $[^{18}\text{F}]$FLT abdominal PET/CT study

A single oncology $[^{18}\text{F}]$FLT (fluoro-3'-deoxy-3'-L-fluorothymidine) dataset was used 
to assess the different methods on the TrueV PET/CT. The patient was administered 
with 332 MBq of $[^{18}\text{F}]$FLT and list mode data (~2.3 billion prompts ) were acquired 
over a 62 min period on the TrueV PET/CT. The list mode data were histogrammed in a 
static sinogram, with transverse, coronal and sagittal displays of the images from all the 
methods qualitatively assessed.
Figure 5.8 Reconstructed images from the HRRT (a) and the HiRez PET/CT (b) showing examples of different arrays that were used for optimising the sampling distance and the point source diameter as well as example radial profiles through a reconstructed volume from the HiRez PET/CT, with the point sources spaced at decreasing distances toward the edge of the FOV. As the distance between the sources decreases the PSF tails start to overlap. Spacing the sources evenly at intervals of 1.5cm was found to be sufficient to differentiate adjacent PSFs. Microscope enlarged images showed ink droplets being printed outside the point source boundaries for sources smaller than 2mm and after re-printing the array 7 times (Figure 5.8 (c)). Consequently a conservative approach of using 2 cm isotropic spacing of 2mm diameter sources was employed for all subsequent scans. This optimization was done on the HiRez but the same array configuration was also applied on the TrueV. On the HRRT, in order to be able to print

5.3 Results

5.3.1 Space-variant and count rate dependent PSF parameterization in image space via a printed array

5.3.1.1 Optimization of the point source array

Figure 5.8 (a-b,d) shows reconstructed images from the HRRT and the HiRez PET/CT with examples of different arrays that were used for optimising the sampling distance and the point source diameter, as well as example radial profiles through a reconstructed volume from the HiRez PET/CT, with the point sources spaced at decreasing distances toward the edge of the FOV. As the distance between the sources decreases the PSF tails start to overlap. Spacing the sources evenly at intervals of 1.5cm was found to be sufficient to differentiate adjacent PSFs. Microscope enlarged images showed ink droplets being printed outside the point source boundaries for sources smaller than 2mm and after re-printing the array 7 times (Figure 5.8 (c)). Consequently a conservative approach of using 2 cm isotropic spacing of 2mm diameter sources was employed for all subsequent scans. This optimization was done on the HiRez but the same array configuration was also applied on the TrueV. On the HRRT, in order to be able to print
smaller point source without significant ink spilling out, 4 reprints were used which enable 1mm source to be used.

5.3.1.2 PSF parameter estimation

5.3.1.2.1 PET/CT

5.3.1.2.1.1 Radial dependency and symmetric properties of the PSF

In Figure 5.9, the fitted parameters for one row of point sources (14 sources) axially centred in the scanner, are shown both for the HiRez and the TrueV. The 1st Gaussian distribution accounts for the main PSF, while the 2nd one with wider distribution account for the tails in the distribution. The axial component of the 1st Gaussian appears to introduce the highest blurring, followed by the radial and the tangential components (Figure 5.9 top left). At increasing radial distance and in both scanners, there is a synergistic effect between the axial under-sampling induced blurring and the parallax error, resulting in the increased resolution degradation in the axial direction compared to the radial and tangential one. Looking at the relative mean for the 2 Gaussian distributions, we can see that axially and tangentially there is no relative shift between them for all radial positions meaning that the overall distribution is symmetric along these 2 directions. In contrast, the means are displaced radially, with the sum of two Gaussian distributions resulting to a skewed asymmetric distribution. This is possibly as a consequence of parallax errors, with a degree of asymmetry increasing with radial position (Figure 5.9 bottom left). As the radial position increases, the 2nd Gaussian distribution accounts for an increasing proportion over the 1st Gaussian distribution in the overall PSF function (Figure 5.9 bottom right), resulting in PSFs with larger tails and asymmetric in the radial direction. The trend is similar both for the HiRez and the TrueV. Figure 5.10 (top left and right) shows the FWHM of the radial and tangential PSF components on the TrueV as a function of the radial distance from the centre of the FOV at 2 different axial positions (z=0cm, z=-8cm) and at 2 different azimuthal angles (φ=0°, φ=37°). The 2 different positions were taken from the same array position as it covers the entire axial FOV, while for the 2 azimuthal positions the whole array was moved. As in Figure 5.9, the angle-dependent crystal penetration as a function of the radial distance, results in an increasing blurring both in radial and tangential directions.
Looking at the system response at the centre and at the edge of the axial FOV, the radial and the tangential components of the PSF are practically axially symmetric. The same also applies for the system response at the 2 different azimuthal angles effectively making the radial and tangential components rotationally symmetric. Similar results were obtained on the HiRez with minimal axial dependency mainly due to the axially dependent transaxial FOV. For the axial component (Figure 5.10 bottom left) when looking at the FWHM at the centre and the edge of the transaxial FOV \((r = 1 \text{ cm}, r = 27 \text{ cm})\) it also varies as a function of the radial distance.

5.3.1.2.1.2 Axial dependency and symmetric properties of the PSF

In addition to the radial dependency, the axial blurring is also variant in the axial direction (Figure 5.10 bottom left), but rotationally symmetric when compared to the axial response from a different azimuthal angle \((\phi = 37^\circ)\). The axial blurring reduces
slightly towards the edge of the axial FOV, but this axial dependency is very small compared to the radial one. As this axial dependency of the axial blurring is very subtle and in order to reduce the storage of the PSF, it can be approximated by an axially invariant axial blurring component with minimal impact on the model accuracy. Also as said in the previous section, the radially dependent radial and the tangential components of the PSF are almost axially independent.

### 5.3.1.2.1.3 Parameter reproducibility from a single scan

From the above it can be seen that the axial, radial and tangential PSF components are rotationally symmetric and as such only a single 2-dimensional surface through the 3-D image space needs to be sampled, omitting the need for additional acquisitions at different azimuthal angles. As all the PSF components vary slowly within this surface, without any sudden discontinuities, the coarse sampling using a single point source array can capture the smoothly varying blurring properties of the scanner.

**Figure 5.10** Top: Radial (left) and tangential (right) FWHM (TrueV) for different axial, radial and angular positions in the FOV as a function of radial distance. Bottom: Axial FWHM at different radial positions and azimuthal angles as a function of axial distance (left) and axial FWHM versus axial distance for 2 different axial positions of the array and the polynomial fit using data from each position individually or from their respective combination (right). Data were reconstructed using the in-house image reconstruction with no resolution modelling.
This is demonstrated in the bottom right graph from Figure 5.10 where the axial FWHM taken from 2 different axial positions of the array (9 + 9 point sources) shifted by 1cm with respect to each other, is plotted as a function of axial distance. The polynomial fit using only the 9 point sources from each individual scan as well as using 18 point sources from both scans effectively doubling the sampling is also shown. Although it is expected that in each plane the axial FWHM depends on the span and the number of segments contributing to that plane, the fit obtained from a single scan (9 point sources) is very similar to the one using a finer sampling by combining the 2 scans.

5.3.1.2.2 HRRT

5.3.1.2.2.1 Axial, radial and angular PSF dependency – Effect of DOI on PSF

Parametric images of FWHM were generated consisting of one pixel per point source and with the pixel size to be equal to the sampling distance in the array. The axial and radial PSF dependency from the 1st 10-minute scan (1st session) at low count rate (<3kcps – no carbon-11 in the extension line) is shown in Figure 5.11 (i). The spatial resolution (FWHM) degrades, as expected, as a function of the radial distance with the axial FWHM being the worst (2.7 mm-4.12 mm) followed by the radial (2.7mm - 3.96mm) and tangential (2.35 mm - 3.38 mm). The maps appear to be highly symmetric radially, as dictated by the geometry of the scanner. On the other hand, a small non-symmetric gradient is seen mainly in the axial and radial FWHM as a function of axial distance (axial FWHM = 2.7 mm [r = 0 cm, z = 9.8 cm] compared to axial FWHM = 3 mm [r = 0 cm, z = -9.8 cm] and radial FWHM = 2.7 mm [r = 0 cm, z = 9.8 cm] compared to radial FWHM = 2.95 mm [r = 0 cm, z = -9.8 cm]), probably due to the behaviour of the detector elements in that part of the scanner. A closer investigation in the scanner’s normalization revealed a similar axially dependent detector sensitivity pattern. As such, detectors with affected sensitivity may indicate reduced performance, which may also explain the slightly increased spatial resolution. The PSF OP-OSEM (Figure 5.11 (iv)) has substantially improved the FWHM (axially 1.25 mm - 2.92 mm, radially 1.22 mm - 2.61 mm and tangentially 1.18 mm – 2 mm) with a smaller axially dependent gradient in the FWHM. In Figure 5.12 the axial, radial and tangential FWHM is plotted as a function of the radial distance and for all axial positions (error bars). The error bars at small radial distances are larger due to the higher FWHM gradient at
different axial positions as mentioned above. Using PSF OP-OSEM, smaller error bars are seen confirming the smaller axial variation of the PSF, seen in the parametric images, which is not dictated by the geometry of the scanner, but probably is a detector performance related effect as mentioned above.

Figure 5.11 HRRT parametric maps of the axial, radial and tangential FWHM at low count rate (no carbon-11 in line) with (i, iv) and without (ii, v) DOI and at high count rate (after injecting the carbon-11 -1st frame) with DOI (iii, vi) with OP-OSEM (i-iii) and with invariant PSF-OP-OSEM (iv-vi) (Users community software). Each voxel in the maps corresponds to each printed point source in the array.
The same dataset was also analyzed after turning off the DOI capability in the scanner (Figure 5.11 (ii)). The effect of assigning all the LORs in the front crystal layer is immediately apparent, with the radial FWHM considerably increasing especially at the edge of the FOV where the parallax error is larger and the loss in spatial resolution is greater. Less obvious resolution degradation is seen in the tangential and almost no degradation in the axial FWHM. Using the spatially invariant PSF-OSEM (Figure 5.11 (v)) as expected an overall improvement is seen in FWHM (axial, radial and tangential), but most importantly the resolution deterioration from not using DOI is reduced. This can be confirmed looking at Figure 5.13 which shows the FWHM difference between having DOI on and off both with and without PSF. The effect of not using DOI in the axial FWHM is apparent even at small radial distance (Figure 5.13 (i)), while when PSF is used in the reconstruction (Figure 5.13 (ii)) the penalty from not using DOI is minimal and limited at extreme radial positions. In Figure 5.14 the axial, radial and tangential asymmetry is shown as a parametric image with the asymmetry quantified as the difference between the mean positions of the 2 Gaussian distributions. Similar to the spatial resolution, the asymmetry is only present in the radial direction and increases progressively from 0 to 2.2 pixels going from the centre to the edge of the radial FOV when no DOI is used (Figure 5.14 (i)). Using DOI, the radial asymmetry is almost halved to 1.3 pixels at the edge (Figure 5.14 (ii)). Using PSF-OSEM the asymmetry remains largely unchanged (Figure 5.14 (iii-iv)), with only small differences, as the PSF
Figure 5.13 Parametric maps showing the difference between having the DOI on and off in the axial, radial and tangential FWHM with OP-OSEM (i) and PSF OP-OSEM (ii). A degradation up to 0.7mm is seen (OP-OSEM) in the radial FWHM and at extreme radial distances when DOI is off. When using PSF OP-OSEM the FWHM difference is substantially reduced meaning that the resolution modelling has more effect on the data without DOI compared to the data with DOI even though the PSF in the PSF OP-OSEM is symmetric and spatially invariant, corresponding to the PSF in the centre of the FOV.

that is used in the reconstruction is invariant and symmetric. As such although it improves the resolution and noise characteristics of the PSF, it has almost no effect on the radial elongation.

Looking at the angular dependency of the PSF in Figure 5.15 (i-vii) a clear deterioration is seen in the axial and radial FWHM when the array is pointing towards the gap between the detector heads (angle = 22.5°), compared to when the array is pointing in the centre of the detector heads (angle = 0° and 45° degrees). On the other hand the tangential FWHM appears to be improving as opposed to the axial and radial. In Figure 5.16 the axial, radial and tangential FWHM is plotted for point sources at different radial distances (z = 0 cm) as a function of the azimuthal angle of the point source array with respect to the horizontal axis. The variation in the spatial resolution
Figure 5.14  Parametric maps showing the axial, radial and tangential asymmetry (difference between the means of the 2 Gaussians) of the PSF with DOI off (i) and DOI on (ii) using OP-OSEM as well as with DOI off (iii) and DOI on (iv) using PSF OP-OSEM. Reductions in PSF asymmetry are apparent when DOI is on. As expected the asymmetry is meanly in the radial direction of the PSF with almost no asymmetry in the axial and tangential direction.

with the angle of the array, is immediately evident and there is an apparent dependency on these variations with the radial and the azimuthal position on the point source. The PSF at the edge of the radial FOV is more affected under angular transformations while at the centre of FOV the PSF remains unaffected. At 12.95 cm radially (z = 0 cm) going from 0° to 22.5°, the axial FWHM increases by 0.33 mm (9.2 %), the radial by 0.22mm (6 %) while the tangential improves by 0.73 mm (23 %). On the other hand at 0 cm radially (z = 0 cm) no apparent deterioration is seen in the axial and radial FWHM with only a small difference in the tangential by 0.09 mm (4 %).
Figure 5.15 Parametric images of axial, radial and tangential FWHM (OP-OSEM) with the source array pointing radially at 0°, 9°, 18°, 22.5°, 27°, 36°, 45° degrees (i-vii) from the horizontal scanner axis.
Figure 5.16 Graphs showing the axial (i), radial (ii) and tangential (iii) FWHM variation as a function of the point source array angle from the horizontal for point sources at different radial locations. Larger variations in the PSF are observed at point source located at extreme radial positions ($r = 12.95$ cm) with the PSF being almost rotationally symmetric for point sources at the centre of the FOV ($r = 0$ cm). The axial and radial FWHM degrades as the array moves towards the gap ($22.5^\circ$ degrees) while on the other hand the tangential FWHM improves.

5.3.1.2.2 Count rate PSF dependency

Looking at the parametric images of FWHM from the count rate experiment at the highest count rate (Figure 5.11 (iii,vi)), the resolution degradation is evident when compared to the images before injecting the carbon-11 in the line ($1^{\text{st}}$ scan – $1^{\text{st}}$ session) (Figure 5.11 (i,iv)). The degradation pattern appears to follow the axially dependent spatial resolution gradient that was seen at the low count rate scan, possibly signifying that the detector elements with the worst resolution characteristics are the ones which are more affected under high count rate conditions. In Figure 5.17 the axial, radial and tangential FWHM for a point source close to the centre ($r = 1.85$ cm, $z = 0$ cm) and to the edge ($r = 11.1$ cm, $z = 0$ cm) of the radial FOV is plotted as a function of the average block singles count rates and elapsed scan time. Starting from the low count rate, the spatial resolution remains relatively constant up to around 5kcps. As the count rate is increasing, the spatial resolution is starting to deteriorate, with the transition point between 5-8 kcps for both radial locations. Close to the edge of the FOV a maximum degradation of 0.36 mm (10.5%) axially, 0.22 mm (4.7%) radially and 0.29 mm (6.9%) tangentially is seen, while close to the centre of the FOV the maximum degradation is
0.38 mm (12.8%) axially, 0.39 mm (12.9%) radially and 0.19 mm (6%) tangentially at 28-33 kcps. The PSF degradation boundaries in terms of count rate (~5 kcps-33 kcps) compares to an average maximum count rate of 26, 19, 16 and 12 kcps observed during typical $[^{11}C]PK11195$, $[^{11}C]Verapamil$, $[^{15}O]H_2O$ and $[^{11}C]DASB$ clinical scans respectively acquired at the WMIC. The addition of the spatially invariant PSF not only improves the resolution as mentioned before but based on the results it also reduces the count rate dependent degradation with the FWHM degrading by 0.21 mm axially, 0.17 mm radially and 0.26 mm tangentially at the edge and by 0.24 mm axially, 0.28 mm radially and 0.17 mm tangentially at the centre. Furthermore for both radial positions it appears to have slightly shifted the degradation threshold to singles count rate values between 10 and 13 kcps but it difficult to draw into such a conclusion.

**Figure 5.17** Axial radial and tangential FWHM with and without resolution modelling (OP-OSEM and PSF OP-OSEM) as a function of singles count rate (elapsed scan time) for a point source close to the centre (a) of the FOV ($z=0$ cm, $r=1.85$ cm) and close to the edge (b) of the radial FOV ($z=0$ cm, $r=11.05$ cm). As the singles count rate increases above ~10 kcps the degradation in the FWHM is apparent, with minimal degradation below 10 kcps.

### 5.3.2 Resolution recovery based image reconstruction on the HiRez and TruePoint TrueV PET/CT

#### 5.3.2.1 Point source data

When no resolution modelling is used (Figure 5.18), the counts spread out in all directions with increasing blurring towards the edge of the FOV. This results in
asymmetric distributions with decreasing amplitude as quantified by line profiles through the point sources (Figure 5.19). The use of the invIMPSF method results in a dramatic increase in the recovered activity, particularly close to the centre of the FOV (Figure 5.18) as the used kernel matches the scanner’s blurring in this region (4.3 mm FWHM). Away from the centre, there is still clear blurring of the point sources due to the discrepancy between the invariant kernel and the true kernel. With the spatially variant image based and projection based PSF reconstructions, resolution improvements are observed both towards the edge of the FOV as well as close to the centre. Comparing these two algorithms (varIMPSF OP-PSEM and varPRPSF OP-OSEM) at the same iterations and subsets on the TrueV, we get almost identical recovered profiles at the 2 extreme positions in the FOV (Figure 5.19 bottom right), which reflects the very similar performance of these algorithms and that the resolution in now limited by the image voxel sizes. This limited sampling of the image results in observed periodic variability in the maximum point source intensity, with both scanners and both algorithms. Figure 5.20 quantifies the resolution improvements obtained by including resolution modelling within the reconstruction. Using OP-OSEM with no resolution model the axial resolution is the worst, followed by the radial and tangential. Using invIMPSF OP-OSEM the resolution is improved in all directions by almost 2 mm in the centre of the FOV while at the edge the improvement is slightly less pronounced. When the varIMPSF model is used, an almost uniform resolution of 2 mm is achieved in the radial, axial and tangential directions. Comparing the varIMPSF against the varPRPSF at the same number of iterations (8 iterations 21 subsets) we see very similar resolution improvements with the varPRPSF achieving slightly better axial resolution towards the edge of the FOV while the varIMPSF achieves marginally better radial resolution towards the edge of the radial FOV. Finally the resolution (axial, radial and tangential) after 8 iterations is lower than that achieved after 15 iteration, as 8 iterations are insufficient for convergence to be reached and with the effect being greater for points towards the edge of the FOV.
Figure 5.18 Transaxial (z=0) and horizontal sections through the 3-D image space for point source data reconstructed with OP-OSEM, with: no resolution modelling (column a: OP-OSEM); a spatially invariant image based kernel (column b: invIMPSF OP-OSEM); with the measured space-variant image based PSF model (column c: varIMPSF OP-OSEM) and with the measured space-variant projection based PSF model (column d: var PRPSF OP-OSEM).

Figure 5.19 (top row) radial profiles through point source images (z=0) reconstructed using OP-OSEM, invIMPSF OP-OSEM, varIMPSF OP-OSEM and var PRPSF OP-OSEM for HiRez (left) and TrueV (right). 2 point source at the centre and the edge of the FOV are zoomed in the bottom 2 graphs. Nearly identical profiles are seen both for the variant image based and projection spaced PSF reconstructions.
5.3.2.2 NEMA IEC image quality phantom

Figure 5.21 shows reconstructed images from the NEMA image quality phantom, both for the HiRez (high statistics scan) and the TrueV (low statistics scan). Qualitatively the PSF reconstructions can handle the noise better when looking at the uniform background regions, with larger improvements when using the variant PSF model. Improvements are also apparent in the sphere-to-background contrast especially in the smallest sphere (10mm). Looking at the varIMPSF reconstruction from either scanner, as well as the varPRPSF reconstruction, ringing (or Gibbs) artefacts start to appear at the boundaries of the phantom with the Gibbs artefacts slightly more intense in the varPRPSF reconstruction. Figure 5.22 shows the quantitative analysis on the phantom data where the CRC for the 10 mm and 22 mm spheres is plotted against the IR for increasing number of iterations. For the smallest sphere (10 mm) the addition of a resolution model in the reconstruction improves the hot sphere CR as well as the IR in both scanners while for the 22mm sphere the contrast improvements are more subtle. The inclusion of the PSF model in the reconstruction on the other hand changes the convergence characteristics of the algorithms. In particular the value of CR obtained...
Figure 5.21 Reconstructed images using the NEMA phantom on the HiRez (top) and the TrueV (bottom) compared at the same noise level across reconstruction methods. The images with the variant PSF appear to have the best contrast with the penalty of Gibbs artifacts.

Figure 5.22 Contrast recovery coefficient and image roughness trade-off as a function of iteration as calculated using the NEMA IEC phantom scanned on the HiRez (top row) and the TrueV (bottom row) for a 10 mm (left column) and a 22 mm (right column) spheres.

with the non-PSF reconstruction stabilises to a constant value after 4-5 iterations for the high statistic HiRez dataset while for both PSF reconstructions the CR value for the 10 mm sphere increases even after 15 iterations. On the TrueV, the OP-OSEM based reconstructions outperform the ANW-OSEM based ones with lower IR at the same CR level, as the data on the TrueV are noisier (~140 million counts) than that on the HiRez
(~350 million counts) and OP-OSEM can provide a better handling of statistical noise due to preservation of the Poisson distribution in the data and the fact that no sinogram truncation occurs (as randoms and scatter events are no longer subtracted from the prompts leading to negative values). Comparing the image based method against the projection based method for the 10 mm and the 22 mm spheres, the varIMPSF and the varPRPSF algorithms achieved similar CRC at the same IR level with the varIMPSF reconstruction giving slightly better results.

5.3.2.3 Cologne resolution phantom

As shown in Figure 5.23 using no resolution modelling the 4 mm and 5 mm tubes can easily be distinguished from each other but appear noisy while the 2 mm tubes are practically inseparable. Inclusion of a resolution model improves the resolution in the 4 mm and 5 mm tubes. Conversely the separation of tubes for the 2 mm and 3 mm tubes has deteriorated in the invIMPSF, varIMPSF and the varPRPSF reconstructions. One explanation is that the resolution recovery reconstructions will most likely require more iterations due to slower convergence and as the number of iterations in the PRPSF reconstruction in the scanner is limited to 8 our inv IMPSF and var IMPSF reconstructions were also limited to the same number of iterations making it difficult to resolve the smaller 2 mm and 3 mm tubes. In addition at the edge of the block of tubes, particularly for the outer blocks artefacts are seen which are similar to the Gibbs artefacts seen in the NEMA phantom. Looking at the differences between the variant and the invariant PSF based reconstructions these are very subtle and are mainly located

![Figure 5.23](image)

Figure 5.23 Reconstructed images from the Cologne phantom using OP-OSEM (a), invIMPSF OP-OSEM (b) varIMPSF OP-OSEM (c) and var PRPSF OP-OSEM, The PSF methods show improved resolution especially on the 4mm and 5mm spheres with a marginally better resolution for the variant PSF algorithms.
in the 4 mm and 5 mm spheres with the largest radial displacement from the centre of the phantom. Comparing the image based and projection based PSF reconstructions qualitatively no significant difference is seen, with similar resolution performance in the 4 mm and 5 mm spheres.

5.3.2.4 $[^{11}C]$-ASO abdominal PET/CT study

Transverse, coronal and sagittal images from an abdominal study with $[^{11}C]$ASO on the HiRez are shown in Figure 5.24. Visual inspection shows significant variance reduction using the variant PSF reconstruction, especially in the liver region in the transverse images, with potential Gibbs artefacts at the edge of the liver. Looking at a high activity concentration located close to the aorta in the coronal images (urine within the ureter), increased contrast is also seen with the improvements of the variant PSF methods over the invariant method. These differences are more pronounced close to the edge of the FOV, as observed within hand veins close to the injection site. In terms of resolution, a much better delineation of the kidney cortex is seen in the transverse and coronal images, with an improved resolution recovery of the variant PSF over the invariant. This improved delineation is not necessarily accompanied by improved quantitation due to the potential overshoot from the Gibbs artefacts. Apart from this potential artefact common to all PSF based methods, the qualitative assessment
confirms the quantitative improvements obtained in the phantom data. These findings are also confirmed by looking at profiles along the transverse images (Figure 5.26 (a)).

5.3.2.5 \[^{18}\text{F}]\text{FLT abdominal PET/CT study.}\)

On the TrueV, data from an \[^{18}\text{F}]\text{FLT scan were used to qualitatively assess the different reconstruction methods. Figure 5.25 shows the transverse, coronal and sagittal maximum intensity projection images from such a dataset. The resolution modelling methods show a significant variance reduction, especially at the edge of the axial FOV as the reduced sensitivity causes an increase in statistical noise. The spatially variant resolution modelling methods (varIMPSF and varPRPSF) perform better compared to the invIMPSF method, with better delineation of activity within the ribs and within the tubing associated with the injection site. This is consistent with the phantom data with these regions located away from the centre of the FOV. Increased contrast is also seen with background noise suppression and better organ delineation. Comparing the varIMPSF against the varPRPSF again no significant difference can be seen with both methods reconstructing images of high resolution. This is also confirmed looking at profiles along the transverse images (Figure 5.26 (b)).

Figure 5.25 Transverse (I), coronal (II) and sagittal (III) maximum intensity projection images from a \[^{18}\text{F}]\text{FLT study reconstructed with no resolution modelling (a), with an invIMPSF resolution model (b), with a varIMPSF model (c) and with a var PRPSF model (d).}
Figure 5.26 Profiles through the transverse \(^{11}\text{C}\)-ASO (left) and \(^{18}\text{F}\)-FLT (right) patient images for the different image reconstruction algorithms

5.4 Discussion

Recent developments in PET imaging both in terms of software and hardware have enabled the acquisition and reconstruction of quantitative and high resolution clinical images. With most of the new generation clinical scanners taking into account the system’s response during the image reconstruction process, there is a need for developing practical as well as cost and time efficient methodologies for evaluating the scanner’s blurring properties. In this chapter we proposed, and optimised a novel methodology to characterize the image based spatially variant PSF, and implemented this methodology on the Biograph 6 B-HiRez and TruePoint TrueV PET/CT scanners. Furthermore we evaluated the impact of resolution modelling using these measurements on a number of phantom and clinical studies. Of note, for the first time, we present a direct comparison between image based and projection based PSF resolution modelling reconstructions using the same datasets in order to quantify any loss of performance with the image based approach. Based on our findings, not only can the image based resolution modelling method accurately approximate the projection space resolution modelling method, but at the same time scanning a single point source array is sufficient to capture the spatially variant system response in the form of image based kernels. Using a single scan also to derive the blurring kernels greatly facilitates measuring count-rate dependent and isotope specific kernels especially from short-lived isotopes like carbon-11 and even oxygen-15, not previously possible using a single point source.
5.4.1 Experimental design and methodology

From a methodology point of view using a printed point source array enabled us to simultaneously scan 126 and 165 point sources on the PET/CT and the HRRT and measure the changing shape of the PSF kernel. By printing the array multiple times we acquired data with high statistics providing good quality fits during parameterization of the PSFs. For all scanners, the parameters describing the PSF kernels varied sufficiently slowly across the FOV that the chosen spacing was adequate to characterise these variations. This is likely to be the case for other cameras, however if not then finer sampling can be obtained by moving the array in the axial and radial directions as was done with the HiRez data or by shifting the array with respect to the phantom on the HRRT, as the phantom is fixed inside the bore.

Using Perspex phantoms for positioning the point sources provided an excellent alternative to previously used robotic systems, obviating the need for accurate alignment of each source independently, once a single line of sources in the array was aligned. On the HiRez multiple acquisitions were performed to finely sample spatial variations in the PSF kernels which provided us with knowledge regarding sudden discontinuities in the system’s response along the radial and axial directions.

On the TrueV PET/CT, the symmetric properties of the PSF were systematically exploited in image space to optimize the PSF model and reduce its dimensionality. This allowed estimation of the PSF model parameters from a single array scan. As the PSF was modelled in image space where there were no sudden changes in the system’s response from the block edge effect (as opposed to projection space modelling), the 14 radial points in the array provided sufficient sampling to characterize the radial component. In the axial direction the axial compression scheme used in projection space (5 or 6 LORs combined per plane) and the ring gaps destroy the axial translation symmetry in image space as well but the 9 axial point sources per radial position in the array are sufficient to approximate the variation in the axial response (Figure 5.10) as it varies more slowly than the radial response. To further reduce statistical noise the array can be scanned for longer periods as there is no need for acquiring data at multiple positions.

Similarly on the HRRT the sampling was sufficient to capture the spatial variation of the PSF. Furthermore due to the smaller FOV the A4 point source array was able to probe the entire radial and axial FOV enabling systematic evaluation of the symmetric
properties of the scanner. The circular design of the phantom also allowed the rotational characteristics of the PSF to easily be measured, as opposed to the TrueV PET/CT where the angular positioning of the phantom was more susceptible to alignment errors due to the phantom having more degrees of freedom to move inside the FOV. Moving to the count rate dependency of the PSF although injecting the carbon-11 inside the extension line provided the necessary singles count rate typically obtained during clinical scans it restricted the singles distribution to a single line source. Other more realistic activity distributions could be implemented, increasing though the complexity of the dual isotope scanning protocol. Given also the fact that any activity distribution inside the FOV has to be integrated with the point source array phantom, it becomes even more challenging to simulate clinically obtained activity distributions. One alternative would be to position the extension line at different locations in the FOV instead of positioning it centrally in the transaxial FOV, with the detectors being bombarded with differential singles count-rates.

It was not necessary to apply filtering to the data prior to parameterization as done by Rapisarda et al (2010) due to acquiring high counting statistics data, resulting in reduced noise in the reconstructed PSFs. This also preserved the high frequency components of the measured response. Furthermore the polynomial fitting that was applied to the PSF parameters to estimate them at the remaining unmeasured positions in the FOV, provided a natural regularization to the measured response. For the model fitting we chose to parameterize the data as a weighted sum of 3-dimensional Gaussian distributions as opposed to using one Gaussian distribution combined from 2 half Gaussian functions (Panin et al 2006, Rapisarda et al 2010). This allowed us to model the long tails observed on the PSF data which can’t be accounted for when only one Gaussian is used (Sureau et al 2008 , Cloquet et al 2010). Other models could also be considered like the asymmetric modified Pearson model (Cloquet et al 2010). One important aspect of the PSF parameterization on the PET/CT is that the fitted parameters and their positional variation are unique to our forward and back projectors which were based on an implementation of the Siddon algorithm (Siddon 1985). Using other methods which more accurately model the geometric component of the system matrix, will result in a different set of parameters, with less resolution blurring effects left to be modelled by the blurring components of the system matrix.
Looking at the PSF parameterization across the 2 PET/CT scanners, the radial and tangential FWHM appears to be very similar. This is expected mainly due to the almost identical crystal ring diameter and crystal dimensions as well as due to the fact that the response in image space is an average of any detector specific blurring and as such any difference in projection space are averaged in image space. On the other hand the axial resolution was found to be slightly higher on the TrueV looking at the FWHM of the 2nd Gaussian (Figure 5.9) (Jakoby et al 2006, 2009). This could possibly be attributed to the addition of a 4th block ring and an extra segment on the TrueV, allowing LORs with higher co-polar angles to be detected thus creating longer tails in the axial direction of the PSF. Also the barrel shape of the HiRez probably accentuates this difference as it reduces the parallax error in the centre of the axial FOV due to the smaller co-polar angles of the oblique segments.

Based on the results from the HRRT the PSF was found to be radially dependent in all directions but importantly radially symmetric and almost axially independent. From the investigation regarding the angular dependency of the PSF it was found to have a 45 ° rotational symmetry following the octagonal geometry of the scanner, with a 22.5 ° reflection (mirror) symmetry and with the line of symmetry being the axis passing through the centre of the detector head and the gap between detector heads respectively. Using the PSF-OP-OSEM the FWHM improves by almost 1.3mm in all directions but is still radially variable with almost 1 mm degradation within the boundaries within which the brain is typically located. A spatially variant PSF reconstruction using the measured kernels, similar to the one that was implemented on the PET/CT, could potentially provide better resolution recovery especially in brain structures further away from the centre (cerebellum, frontal and occipital lobe). Removing the DOI a clear degradation in the radial FWHM was also observed. Using the scanner’s standard PSF-OP-OSEM though little resolution degradation was seen between having DOI ON and OFF (even though the PSF used in the standard HRRT software is spatially invariant) mainly in the radial FWHM and at extreme radial positions (>10cm) which may not be of interest in clinical scans due to the limited radial extent of the brain. This means that having a scanner with DOI is of little used if PSF reconstruction methods are used and even a spatially invariant kernel can provide significant improvements. Looking at the PSF count rate dependency there is a clear degradation at increasing rates with the transition well within the clinically obtained count rate limits. As such the spatial
resolution is expected to temporally vary during the course of a scan with the degree of degradation spatially dependent.

### 5.4.2 Reconstruction performance evaluation and image versus projection based resolution modelling comparison

We evaluated the impact of the proposed methodology with resolution modelling reconstruction on both the HiRez and the TrueV PET/CT scanners using phantom datasets (point sources, NEMA phantom, Cologne phantoms) to quantify the improvements as well as clinical datasets ([11C]ASO and [18F]FLT) to verify that similar qualitative improvements were observed with real data.

Looking at the reconstructed point sources (Figure 5.18) as well as the 1-D radial profiles (Figure 5.19) we saw similar performance and little difference between the image based and the projection based PSF reconstructions as evaluated for the TrueV scanner. The similarity in these profiles (Figure 5.19 bottom right) demonstrates that the degree of radial asymmetry has been captured by both methods to an almost equal degree of accuracy.

From the analysis of the point sources we measured an almost uniform resolution of 2 mm throughout the FOV using varIMPSF OP-OSEM with the proposed methodology after 15 iterations. We weren’t able to achieve similar resolution improvements (uniform 2mm resolution) with the varPRPSF reconstruction as reported by Panin et al (2006, 2007) due to the scanner’s restriction of a maximum of 8 iterations (although even with 8 iterations resolution was found to be <3mm). To accurately compare the methods though, we reconstructed the data using our in house implementation for 8 iterations in order to match the number of iterations used in the scanner’s varPRPSF reconstruction. In our hands the varIMPSF reconstruction achieved marginally better radial resolution compared to the varPRPSF one probably due to the 2nd Gaussian distribution providing improved tail fitting. On the other hand superior axial resolution was achieved by the varPRPSF method compared to varIMPSF, which can possibly be attributed to the very accurate modelling of the axial blurring in the manufacturer’s implementation. Indeed on the TrueV scanner the modelling and application of the axial blurring is done before the axial compression step for each individual LOR, as opposed to modelling the superimposed axial blurring in a span (Panin et al 2006), which facilitates the use of a depth independent axial blurring (Panin et al 2007). The modelled
forward projected data are then axially compressed to match the axial sampling of the measured sinograms which have been axially compressed by the online rebinner. As such it is difficult for the average axial blurring measured by the varIMPSF method to match this exact LOR-by-LOR axial PSF modelling.

Similar resolution improvements, consistent with the point source data, were observed in the Cologne phantom. Using smaller voxels during reconstruction can potentially reduce these sampling effects. Gibbs artefacts were also seen on the NEMA phantom reconstructed both with the varIMPSF and the var PRPSF method (Reader et al 2003, Wiant et al 2009, Jakoby et al 2009, Tong et al 2010a, Rapisarda et al 2010). One way to minimize the Gibbs would be to use an underestimated kernel compared to the measured one (Snyder et al 1987). Such an approach however would compromise the resolution and SNR improvements, yet could potential minimize the Gibbs artefacts as also suggested by Sureau et al (2008).

On the clinical datasets using the variant PSF reconstructions, results in small improvements compared to the invariant case, but this is sometimes difficult to assess qualitatively. Nevertheless looking at the resolution graphs (Figure 5.20) we can see improvements in the radial and axial resolution of 1 mm and 1.6 mm FWHM respectively at 10 cm away from the centre where many organs and pathologies of interest can be located. Although an almost uniform 2 mm resolution was measured using point sources, this resolution is difficult to achieve in the clinical images. This could be attributed to the presence of statistical noise compared to the high statistics point source data as well as to the non linear nature of the reconstruction algorithm with an activity distribution-resolution correlation (Mustafovic and Thielemans 2004). Furthermore the use of progressively larger kernels moving towards the edge of the FOV creates spatially variant resolution convergence. This is probably due to the reconstruction problem becoming more ill-posed at the edge of the FOV compared to the centre (Alessio et al 2010). Premature reconstruction termination will result in a non uniform resolution in addition to the activity distribution dependent resolution in the image.

To qualitatively compare all the methods we chose to use 5 iterations for the non-PSF reconstruction and 8 iterations for the PSF reconstructions which, according to Sureau et al (2008), equates in terms of statistical noise (background ROI CoV). Equating variance though through choice of iterations is a non-trivial task as in the resolution
recovery reconstructions the covariance structure is different compared to the non resolution recovery reconstruction and this choice may not well represent the current reconstruction method.

Looking at the overall performance of the image based and projection based PSF reconstructions, very little difference were seen between the methods, which were demonstrated not to be relevant in the clinical situation. As our IMPSF and the manufacturer’s PRPSF reconstructions are based on different projectors with distinct implementations, it is difficult to conclude whether any of the very slight performance differences observed are due to the image based versus projection based strategies or implementation characteristics of the reconstructions. Indeed the agreement of the two algorithms is remarkable considering the potential implementation differences. With the majority of blurring effects within the detection of events, and with an image based approach only approximating these effects, it could be expected that projection based approaches outperform image based approaches. Nevertheless we observed that the image based approach managed to match if not surpass in some cases the projection based approach. There are three possible reasons for this. First as both methods use a response parameterization, any benefits from a better modelling of the detector blurring using the projection based approach over the image based approach, would be diluted by the fact that the PSF parameters are further interpolated and extrapolated to calculate the response in every position in the FOV. Secondly the manufacturer’s implementation avoided measuring the response near the detector gaps (block edge effect) (Panin et al 2006) which is a very laborious task and that probably resulted in modelling an average detector response even in projection space, minimizing the potential benefits of better detector modelling compared to the image based approach. Third, the resolution in these 2 methods might converge at a different rate due to using different kernels, with broader kernels resulting in a slower convergence.

5.5. Conclusion

In this chapter a fast and efficient way of measuring the space-variant image based blurring component of the system matrix was proposed by optimizing the PSF model and exploiting image space symmetries. Specific benefits of the proposed approach include:
i) Simultaneous acquisition of multiple point sources (obviating the need for accurate alignment of each source independently, once the reference point in the array is aligned),

ii) Rapid acquisition and characterization of the space-variant PSF. This allows easy measurement of the PSF on a scanner-by-scanner basis or even on a repeated basis to regularly check for any drift in the resolution properties.

The data suggest that scanning a single array of point sources on the PET/CT is sufficient to fully characterize the spatially-variant blurring component of the system matrix without significantly compromising the accuracy of the model. On the HRRT due to the octagonal design of the scanner further scans of the array are needed as the PSF was found not to be invariant to rotational transformations.

Furthermore the PSF was found to depend on the count-rate with the degradation being spatially varying. From our measurements this variation can be parameterized by fitting appropriate functions to the measured data and can be taken into account during image reconstruction to mitigate the space-variant nature of the count rate dependent resolution degradation. Further work is required to evaluate the benefits of such an approach.

The resolution and SNR benefits of characterizing the spatial variant PSF using the proposed methodology were demonstrated by implementing an image based spatial variant resolution modelling image reconstruction algorithm for 2 new generation PET/CT systems: the Biograph 6 HiRez and the Biograph 6 TruePoint TrueV. Finally for the first time a direct comparison between image based and projection based resolution modelling revealed similar resolution and SNR improvements in a variety of phantom and clinical datasets demonstrating that image based methods are valid alternative to projection based techniques.
CHAPTER 6

Implementation and evaluation of direct 4-D parametric image reconstruction in perfusion $[^{15}\text{O}]\text{H}_2\text{O}$ PET/CT imaging
6.1 Introduction

In this chapter, the attention is shifted from static imaging to dynamic data acquisition and from 3-D image reconstruction to spatiotemporal 4-D image reconstruction. As mentioned in the early chapters, PET has the inherent ability to detect and quantify changes in the bio-distribution of an intravenously administered radio-labelled tracer, through dynamic image acquisition of the system under study. By modelling the temporal distribution of the tracer, parameters of interest regarding specific biological processes can be derived. Traditionally parameter estimation is done by first reconstructing a set of dynamic images independently. Then using the emission PET image or if available structural information taken either from CT or MRI, post-reconstruction kinetic analysis is performed usually on a regional level. This approach suffers from reduced SNR due to the reasons explained in chapter 1 of this thesis and results in parameter estimates with increased variance. To maintain the spatial information obtained in the emission images, the kinetic modelling can be performed at the voxel level, reducing the SNR ever further and resulting in noisy parameter estimates. Increasing the counts in the image is therefore of high importance in order to derive accurate model parameters and there is a trade-off between increased temporal resolution and the counting statistics per temporal frame.

Different algorithms have been proposed for direct parameter estimation during image reconstruction in an attempt to improve SNR. These algorithms, similar to the post-reconstruction analysis, make use of common image reconstruction algorithms which have been extended to accommodate either linear or non-linear kinetic models. Linear parametric image reconstruction can be based either on non-negative matrix factorization, to describe the temporal distribution of the radioactivity concentration using a spectrum of exponentially spaced temporal basis functions, such as spectral analysis (Matthews et al 1997, Reader et al 2006, Reader et al 2007c), or make use of graphical analysis techniques such as the Patlak and Logan plots, to derive macro-parameters of interest (Wang et al 2008a, Tsoumpas et al 2008, Rahmim et al 2009, Angelis et al 2011). On the other hand, direct 4-D image reconstruction based on non-linear models can deliver micro-parameters of interest, such as rate constants between blood and tissue (Yan et al 2008, Wang et al 2008b, Kamasak et al 2005), but are usually complex due to the non-linear estimation of parameters. One complication
common in both linear and non-linear parametric image reconstruction algorithms is that due to the respective coupling between the spatial model and the temporal model, these algorithms can suffer from slow convergence. These algorithms are also restricted to a specific combination of spatial and temporal model. To overcome these difficulties, Wang and Qi (2009b) used an optimization transfer approach to decouple the tomographic from the kinetic parameter estimation problem in every iteration, using an algorithm which resembles the post-reconstruction parameter estimation approach, but converges to the solution of the 4-D spatiotemporal problem. By using the optimization transfer approach based on surrogate functions, the maximum likelihood problem is converted into a non-linear least squares problem. The benefit of such an approach is that well established non-linear kinetic modelling algorithms can be used to solve the parameter estimation problem. One drawback of this algorithm though is that the weights during kinetic modelling are very complex and not easily derived. Moreover, even though non-linear optimization using non-linear least squares is extensively used for post-reconstruction kinetic modelling, it is impractical within a 4-D framework, as it is computationally intensive and requires good initial estimates. If voxel-by-voxel parameter estimation is to be considered, an efficient parameter estimation algorithm is needed. With the image volume in state of the art high resolution scanners having more than ~10 million voxels and with the kinetic parameters being estimated in every image update, a fast fitting routine is of paramount importance to achieve reasonable reconstruction times and allow 4-D methods to be routinely used. On the other hand, there are a number of practical post-reconstruction kinetic analysis algorithms, such as linear least squares (LLS) and generalized linear least squares (GLLS) which were shown to efficiently generate parametric images with good accuracy and precision in chapter 3 (Feng and Ho 1993a). These methods use a weighted least squares objective function to solve the constrained or unconstrained optimization problem and can be relatively easily incorporated within a direct parametric reconstruction, provided the weights are appropriately accounted for.

The drive behind this chapter as such is 3 fold. Firstly, to implement a direct spatiotemporal parametric image reconstruction algorithm, for the first time on a PET/CT system, based on a newly proposed 4-D reconstruction scheme (Matthews et al 2010). Although direct spatiotemporal image reconstruction algorithms have existed for more than a decade, these methods have been primarily focused in dynamic neuro-

173
receptor imaging studies (Kamasak et al 2005, Reader et al 2006, Reader et al 2007c, Tsoumpas et al 2008, Yan et al 2008). With an increasing interest in dynamic abdominal studies in oncology, there is the potential that such PET/CT studies can significantly benefit from similar direct parameter estimation schemes. Potential SNR improvements previously seen in brain imaging, can help in improved treatment response monitoring, making parametric imaging in oncology a valuable tool.

Secondly, to apply the implemented algorithm on a dynamic perfusion $[^{15}\text{O}]\text{H}_2\text{O}$ study and compare parametric images, against images obtained using the post-reconstruction kinetic modelling approach using different linearization methods and different models. In oncology, $[^{15}\text{O}]\text{H}_2\text{O}$ parametric imaging specifically is of particular interest, as it can be used to measure perfusion as a biological end point in response to current and future vascular and angiogenic targeting agents (Koetz et al 2009). Cancerous tumours have a highly irregular and non-uniform vasculature including arterio-venous shunts, and in order to capture the macroscopic tumour heterogeneity, voxel-by-voxel parameter estimation is needed, which as mentioned before results in noisy parameter estimates. Moreover in perfusion PET studies, in order to capture the temporal distribution of the rapidly decaying $[^{15}\text{O}]\text{H}_2\text{O}$, extremely short frames are reconstructed, as short as 5 seconds, further degrading counting statistics and SNR and making parametric images of perfusion amongst the noisiest. As such, $[^{15}\text{O}]\text{H}_2\text{O}$ perfusion studies can potentially benefit significantly from the proposed methodology.

Finally, the last research objective of this chapter is to assess the impact of 4-D image reconstruction on the accuracy and precision-reproducibility of parametric image estimation applied to $[^{15}\text{O}]\text{H}_2\text{O}$ PET/CT abdominal imaging and evaluate potential improvements at different noise levels. Due to the short half-life of $[^{15}\text{O}]\text{H}_2\text{O}$ and low radiation dose, repeated scans can take place before and after intervention, allowing rapid treatment response monitoring. Evaluating the significance of changes in surrogate markers such as perfusion, depends on the reproducibility of the method (de Langen et al 2008, Lodge et al 2008) and with increased noise in parametric images contributing to reduced reproducibility, methods for reducing statistical variance in parameter estimates are needed.

The chapter proceeds as follows. First the theory behind a newly proposed spatiotemporal 4-D parametric image reconstruction scheme (Matthews et al 2010) is presented. The algorithm was then applied on abdominal $[^{15}\text{O}]\text{H}_2\text{O}$ PET/CT data to
derive direct parametric images of perfusion ($K_t$), efflux rate ($k_2$), blood volume ($V_a$) and volume of distribution ($V_d$), using the direct 4-D reconstruction. Comparisons were then made against images derived using traditional post-reconstruction kinetic analysis, in order to evaluate the benefits of direct parametric reconstruction in dynamic oncologic studies. An optimization was carried out by comparing 2 linearization methods for the image based problem, previously described in the 3rd chapter, namely the linear least squares (LLS) and the generalised linear least squares (GLLS). Furthermore we also optimized the kinetic model, by comparing 2 model formulations. Based on the outcome of the optimization and to evaluate the accuracy and precision of parametric images obtained with the direct and the post-reconstruction algorithms, a multi-dose study involving six bolus injections of $[^{15}\text{O}]\text{H}_2\text{O}$ administered in a patient diagnosed with hepatocellular carcinoma (HCC) was used for the performance evaluation of the methods. For the highest and the lowest dose scans, bootstrap resampling was used to generate a further 6 datasets for each scan. In addition, 100 noisy simulated datasets were generated using a digital body phantom to represent $[^{15}\text{O}]\text{H}_2\text{O}$ kinetics. For all simulated and patient datasets, parametric maps were generated using independent frame OSEM reconstruction followed by conventional post-reconstruction kinetic analysis and using the direct parametric reconstruction. Coefficient of variation (CoV) images across: repeated patient scans, bootstrap realisations, and noisy simulated realisations were then created.

6.2 Theory

This chapter, as mentioned briefly in the introduction, is based on the implementation as well as application of a direct 4-D spatiotemporal image reconstruction algorithm on PET/CT data and more specifically in perfusion $[^{15}\text{O}]\text{H}_2\text{O}$ imaging with the HiRez PET/CT. The algorithm follows the same principle as the one proposed by Wang and Qi (2009b), but instead of using the more general framework of optimization transfer, as it will be shown, the spatiotemporal 4-D maximum likelihood problem can be transferred into an image based maximum likelihood problem using an expectation maximization framework. The image based ML problem can be compared to a weighted least squares fitting using appropriate weights and a one-step late approximation of these weights. As the algorithm is based on EM it can maintain its properties, like monotonically
increasing likelihood and is applicable to any spatiotemporal model. Finally the weights used in the kinetic model fitting, have a much simpler formulation compared to previous algorithms proposing a decoupling between the tomographic and the image based problem (Wang and Qi 2009b). In this section the most pertinent details of the theory behind this algorithm are summarized.

6.2.1 3-D maximum likelihood problem

Starting from the more trivial 3D maximum likelihood problem, let \( X_j \) be a random variable of events emitted in the \( j \)th voxel, \( \lambda_{X_j} \) the mean number of emissions from the \( j \)th voxel, \( Y_i \) be a random variable of events detected in the \( i \)th bin, \( n_{Y_i} \) the number of events in the \( i \)th bin with \( p_{ij} \) the probability of detection in the \( i \)th projection bin given emission from the \( j \)th voxel, including geometric effects as well as attenuation and detector sensitivity. The construction of the EM algorithm is based on the assumption that we know some complete data which represents the data from which the measured data can be derived (many to one mapping between complete data and measured data). In the context of the image reconstruction problem one option is to define the complete data as the number of events which originated from the \( j \)th voxel and which are detected in the \( i \)th bin defined as \( n_{X_j,Y_i} \).

In the case where the complete data as defined before were known, then the likelihood of the complete data given \( \lambda_{X_j} \) is

\[
P(\mathbf{n}_{X_j,Y_i} \mid \lambda_{X_j}) = \sum_{i,j} n_{X_j,Y_i} \log p_{ij} \lambda_{X_j} - p_{ij} \lambda_{X_j} \quad (6.1)
\]

But as the complete data are not known, the likelihood function cannot be evaluated and consequently with the EM algorithm we first evaluate the expected likelihood function given the measured data \( n_{Y_i} \) and a current estimate of the parameters. The parameters are needed in order to derive the probability density functions needed in the evaluation of the expectation.
Maximizing the expected log-likelihood

\[
\lambda_{X_j}^{(k+1)} = \arg \max_{\lambda_{X_j}} \sum_{i,j} E[n_{X_i,y_i} \mid n_{Y_i}, \lambda_{X_j}^{(k)}] \log \left( \frac{p_y \lambda_{X_j}^{(k)}}{p_{YY, X_j}} \right) - p_y \lambda_{X_j}^{(k)}
\]  

which is done by differentiating with respect to $\lambda_{X_j}$ and setting to zero, gives

\[
\sum_{i,j} \left( E[n_{X_i,y_i} \mid n_{Y_i}, \lambda_{X_j}^{(k)}] - p_y \right) = 0 \Rightarrow \lambda_{X_j} = \frac{\sum_{i,j} E[n_{X_i,y_i} \mid n_{Y_i}, \lambda_{X_j}^{(k)}] p_y}{\sum_{i,j} p_y}
\]  

where the complete data given the measured data is distributed as a multinomial distribution and hence its expected value is

\[
E[n_{X_i,y_i} \mid n_{Y_i}, \lambda_{X_j}^{(k)}] = \frac{p_y \lambda_{X_j}^{(k)}}{\eta_i + \sum_j p_y \lambda_{X_j}^{(k)} n_{Y_i}}
\]  

where $\eta_i$ refers to erroneous events (scatter and randoms). Substituting and rearranging we end up the well known following equation

\[
\lambda_{X_j}^{(k+1)} = \frac{1}{\sum_i p_y} \sum_i \frac{p_y \lambda_{X_j}^{(k)}}{\sum_j p_y \lambda_{X_j}^{(k)} n_{Y_i}} n_{Y_i} = \frac{\lambda_{X_j}^{(k)}}{\sum_i p_y} \sum_j p_y n_{Y_i}
\]  

6.2.2 4-D maximum likelihood problem

Following exactly the same theory, the above framework can be directly applied to the spatiotemporal 4-D problem. Let now the parameter $\alpha$ we want to estimate be related through a spatiotemporal model, with the mean number of emissions from the $j^{th}$ voxel and the $l^{th}$ frame $\lambda_{X_{jl}}$

\[
\lambda_{X_{jl}} = f_{jl}(\alpha)
\]
Directly equivalent to the 3D problem let \( n_{X_j,X_l} \) be the complete data, as the counts detected in the \( i \)th projection bin being emitted from the \( j \)th voxel, during the \( l \)th frame. If the expected log-likelihood is given by

\[
E[\lambda(n_{X_j,X_l} | n_{Y_j} ; \alpha^{(k)})] = \sum_{i,j,l} E[n_{X_j,X_l} | n_{Y_j} ; \lambda^{(k)}_{X_l}] \log_e \left( p_{Y_l} \lambda^{(k)}_{X_l} \right) - p_{Y_l} \lambda^{(k)}_{X_l}
\]  

(6.8)

assuming statistical independence between frames, which means the total log likelihood is the sum over frames of the log likelihood in each frame, with \( \lambda^{(k)}_{X_l} = f_{jl}(\alpha^{(k)}) \), then

\[
\alpha^{(k+1)} = \arg \max_{\alpha} \sum_{i,j,l} E[n_{X_j,X_l} | n_{Y_j} ; \lambda^{(k)}_{X_l}] \log_e \left( f_{jl}(\alpha) \right) - p_{Y_l} f_{jl}(\alpha)
\]  

(6.9)

where because \( \log_e \left( p_{Y_l} f_{jl}(\alpha) \right) = \log_e \left( f_{jl}(\alpha) \right) + \log_e \left( p_{Y_l} \right) \), the \( \log_e \left( p_{Y_l} \right) \) has been dropped being independent of \( \alpha \).

Equivalent to the 3-D problem, based on multinomial distributed complete data, the expectation of the complete data equal to

\[
E[n_{X_j,X_l} | n_{Y_j} ; \lambda^{(k)}_{X_l}] = \frac{p_{Y_l} \lambda^{(k)}_{X_l} n_{Y_j}}{n_d + \sum_j p_{Y_l} \lambda^{(k)}_{X_l}}
\]  

(6.10)

After substituting and rearranging we end up with

\[
\alpha^{(k+1)} = \arg \max_{\alpha} \sum_j \left( \sum_l p_{Y_l} \right) \left( \sum_l E[n_{X_j,X_l} | n_{Y_j} ; \lambda^{(k)}_{X_l}] \right) \frac{\log_e \left( f_{jl}(\alpha) \right) - f_{jl}(\alpha)}{\sum_l p_{Y_l} \lambda^{(k)}_{X_l}}
\]  

(6.11)

As it can be seen

\[
\lambda^{(k+1)}_{X_l} = \frac{\sum_i E[n_{X_j,X_l} | n_{Y_j} ; \alpha^{(k)}]}{\sum_i p_{Y_l}}
\]  

(6.12)

is normal MLEM for each temporal frame, similar to the 3D derivation (Equation 6.4 – 6.5 – 6.6) with \( \sum_i p_{Y_l} \) being the sensitivity image.
6.2.3 Using weighted least squares to solve the ML image based problem

To maximize Equation (6.11) we differentiate with respect to the parameters and set it to zero

$$
\sum_j \left( \sum_i p_{ij} \right) \frac{d f_{jl}}{d \alpha} \left( \frac{\lambda_{X_{jl}}^{(k+1)}}{f_{jl}(\alpha)} - 1 \right) = 0 \quad (6.13)
$$

Considering now the equivalent least square problem and minimizing with respect to the parameters we have

$$
\alpha_{\text{opt}} = \arg \min_{\alpha} \frac{1}{2} \sum_{jl} w_{jl} \left( \lambda_{X_{jl}}^{(k+1)} - f_{jl}(\alpha) \right)^2 \Rightarrow \sum_{jl} \frac{d f_{jl}}{d \alpha}(\alpha) w_{jl} \left( \lambda_{X_{jl}}^{(k+1)} - f_{jl}(\alpha) \right) = 0 \quad (6.14)
$$

where \( w_{jl} \) are weights.

Now comparing Equation (6.13) with Equation (6.14), what is seen is that they are equivalent under the condition of

$$
w_{jl}(\alpha) = \frac{\sum_i p_{ij}}{f_{jl}(\alpha)} \quad (6.15)
$$

This formulation though dictates the weights to depend upon the parameters which we are trying to estimate. As the tomographic problem is interleaved with the kinetic parameter estimation problem iteratively, a good approximation would be to calculate the weights based on previous estimate of the parameters. As such, the algorithm proceeds by executing the following two equations in an interleaving fashion.

$$
\lambda_{X_{jl}}^{(k+1)} = \frac{f_{jl}(\alpha^{(k)})}{\sum_i p_{i,j} \sum_i p_{i,j} n_{i,j}} \sum_i p_{i,j} n_{i,j} \left( \frac{\lambda_{X_{jl}}^{(k)}}{f_{jl}(\alpha^{(k)})} \right) \quad (6.16)
$$

$$
\alpha^{(k+1)} = \arg \min_{\alpha} \frac{1}{2} \sum_{jl} w_{jl}(\alpha^{(k)}) \left( \lambda_{X_{jl}}^{(k+1)} - f_{jl}(\alpha^{(k)}) \right)^2
$$

By transforming the image based ML problem into a WLS problem, opens the road for a number of fast and efficient algorithms to be used, such as LLS and GLLS.
6.3 Materials and methods

6.3.1 Implementation and optimization of direct and post-reconstruction kinetic analysis algorithms

6.3.1.1 Data acquisition and generation

A single $[^{15}O]H_2O$ dataset from a patient was used to assess the different methods. The patient was administered, while in the scanner’s bed, with a bolus of 2.5 mL $[^{15}O]H_2O$ (552 MBq) over the course of 15 seconds using an automated injection system (Hidex Radiowater Generator), followed by a 12.5 mL saline flush. Continuous arterial sampling was carried out during data acquisition by pumping it through a radiation detection system and cross-calibrated against discrete arterial samples. List-mode data were acquired over a 6 minute period ($\sim 210 \times 10^6$ prompts and $\sim 111 \times 10^6$ randoms) using the Biograph 6 HiRez PET/CT and histogrammed into 29 time frames ($1x130$ sec, $14x5$ sec, $5x10$ sec, $3x20$ sec, $6x30$ sec) using an in-house list-mode histogrammer, with the first frame used as a background frame. Figure 6.1 shows a graph of the distribution of the prompts and the randoms during the scan for the 29 frames. As it is seen from the sinograms taken from the 13th frame (5 sec), the data look extremely noisy ($\sim 5.5 \times 10^6$ prompts and $\sim 3.3 \times 10^6$ randoms).

![Figure 6.1](image)

Figure 6.1 Graph showing the prompts and delayed events per frame (pattern for frames of similar duration is visible as the graphs show the total counts in the frame) from a typical 6-minute $[^{15}O]$-H$_2$O scan, along with representative sinograms from a mid-scan frame. Sinograms look extremely noisy due to the small duration of the frames (5 seconds) and the rapid decay of $[^{15}O]$ (Half-life = $\sim 122$ seconds).
6.3.1.2 Kinetic modelling implementation and optimization

Since the time course of the blood activity concentration was sampled at a peripheral artery, corrections for delay and dispersion were applied to the measured arterial data in order to estimate the input function. Delay and dispersion correction are critical in dynamic $^{[15}\text{O}]\text{H}_2\text{O}$ due to the fast kinetics and in order not to increase the number of free parameters in our perfusion model, the input function was pre-corrected with global values for these effects rather than fitting them at a voxel-by-voxel level. To derive an accurate estimate of the relative delay between the sampling site and the part of the body in the FOV, an image derived input function (IDIF) was calculated by drawing a region of interest (ROI) in the aorta using the FBP reconstructed image and in the plane centrally located in the axial FOV. A global delay was then estimated by comparing the measured and the imaged derived IF to calculate their relative delay, assuming no physiological delay between the different regions in the FOV. Even though it is expected regions at the edge of the FOV will have a different delay compared to regions in the centre, the regions of interest (main organs) were centrally positioned in the FOV, minimizing any potential errors from using a global IF taken from the centre of the FOV. The measured IF was then deconvolved with an exponential blurring function using an expectation-maximization algorithm (50 iterations), with a monoexponential dispersion model and with a dispersion decay constant equal to $\tau = 0.1 \text{ sec}^{-1}$, in order to

![Graph showing the measured input function from the blood trolley, the image derived input function (IDIF) by drawing an ROI in the aorta on the CT image and the de-convolved input function used the delay between the measured IF and the IDIF.](image)

**Figure 6.2** Graph showing the measured input function from the blood trolley, the image derived input function (IDIF) by drawing an ROI in the aorta on the CT image and the de-convolved input function used the delay between the measured IF and the IDIF.
calculate an appropriate input function to be used in the model. In Figure 6.2 the measured, the de-convolved and the image-derived input functions are plotted. Based on the difference in the arrival time between the IDIF and the measured IF, a 12 second global delay was used in the de-convolution process.

$[^{15}O]$H$_2$O is a freely diffusible tracer and its temporal distribution can be described using a single tissue compartment model (Kety 1951)

$$\frac{dC_T}{dt} = fC_A(t) - (k_2 + \lambda)C_T(t) \tag{6.17}$$

where $k_2 = \frac{f}{V_d}$, $C_T(t)$ and $C_A(t)$ are the tissue and arterial activity concentration over the time respectively, $f$ is the perfusion ($f = K_1$), $V_d$ is the volume of distribution, $k_2$ is the efflux rate, and $\lambda$ is the decay constant of $[^{15}O]$ ($\lambda = 0.00567$ sec$^{-1}$). Each voxel in the image can sample both tissue and vasculature with a high fraction of arterial blood volume in specific areas such as the heart and the aorta, if these are positioned in the FOV. Having a 3-parameter model with the inclusion of the blood volume, as opposed to not including the blood volume term, can affect the statistical accuracy of the derived parameters. On the other hand in regions with increased arterial vasculature, not including a blood volume would result in biased parameters. For that reason 2 different model formulations were implemented and evaluated, one without blood volume (Equation 6.18) and one including a blood volume term in the operational equation (Equation 6.19).

$$C_T(t) = C'_T(t) \tag{6.18}$$

$$C_T(t) = C'_T(t) - V_a C_A(t) \tag{6.19}$$

where $C'_T(t)$ is the measured PET data and $V_a$ is the fractional blood volume.

One of the benefits of the proposed direct 4-D algorithm is the ability to linearize the non-linear image based problem. As analyzed in the 3rd chapter, popular and fast linearization methods are the LLS and the GLLS (Feng and Ho 1993a). Although both have been used extensively in post-reconstruction kinetic modelling, their behaviour within a 4-D image reconstruction should be evaluated. For that reason both methods were implemented and compared, to evaluate their performance and optimize the parameter estimation step of the direct and post-reconstruction algorithms. Model parameters were fitted to the measured data by minimizing a non-negative weighted
least square objective function (NNWLS). In the LLS method, no initial values for the parameters are needed. On the other hand, in the GLLS as an initial estimate is needed, the same methodology was used as for the 1-D simulations shown in the chapter 3 and performed one LLS fit to provide the initial estimate for the GLLS. 2 internal iterations were used in the GLLS, as the LLS fit ensured good initial estimates. Parameter estimation was performed at the voxel level to capture the heterogeneity while maintaining the spatial resolution of the scanner. In the direct method, the LLS is only executed once after the first image update when using the GLLS, as for subsequent updates-iterations the previous estimate is used as an initial estimate, using a one step late approach. Similarly for the internal iterations within GLLS, the estimate from the 1st iteration is used as an initial estimate in the 2nd iteration.

Based on this fitting scheme, LLS takes ~900 seconds to fit the entire FOV while the GLLS including 2 internal iterations takes ~3200 seconds plus ~900sec for the LLS initial estimate. Even with the linearization of the non-linear model though, these execution times are lengthy. In order to reduce the computation load during the kinetic modelling step, a body mask was used to restrict parameter estimation. To create the mask CT data were threshold using Analyze (Mayo Clinic). This masking resulted in almost 85% reduction in the execution time (1113728 out of 9144576 voxels were being fitted). This reduction, although of minimal importance in the post-reconstruction method, it is of high importance in the direct reconstruction, as the kinetic modelling step takes place after every image update. For a reconstruction with 10 iterations and 21 subsets the kinetic modelling is 210 times more time consuming and as such any strategies to reduce execution time are massively important.

6.3.1.3 Image reconstruction and analysis

For the 3-D independent reconstructions, as well as for the tomographic part of the direct reconstruction, the dynamic data were reconstructed using an in-house ordinary Poisson ordered subsets expectation maximization algorithm (10 iterations, 21 subsets) (Michel et al 1999) including resolution modelling (PSF-OP-OSEM) (Kotasidis et al 2011). Sinogram corrections for scatter, attenuation and normalization were estimated using the standard HiRez software (Panin et al 2006). The images were reconstructed on a 336 × 336 × 81 grid with a 2mm voxel. The direct as well as the post-reconstruction
algorithms execute as follows:

- Post-reconstruction algorithm:

  i) Start with initial image estimate $\lambda_{X,j}^{(k)}$ (uniform image estimate)

  ii) Perform image updates over all temporal frames with conventional OSEM to calculate $\lambda_{X,j}^{(k+1)}$

  iii) Repeat from ii) until maximum number of iterations reached

  iv) Fit kinetic model to the image data

  v) A) If LLS is used, fit the kinetic model in image space using the LLS method to estimate model parameters $\alpha^{(k)}$

  vi) B) If GLLS is used, fit the kinetic model in image space with LLS to estimate initial model parameters $\alpha^{(k)}$. Then

  vii) Fit the kinetic model in image space with GLLS (1 or 2 internal iterations) using $\alpha^{(k)}$ from LLS as initial estimate to calculate parameters $\alpha^{(k+1)}$ as well as to derive the weight from the fitted LLS image.

- Direct 4-D reconstruction algorithm:

  i) Start with initial image estimate $\lambda_{X,j}^{(k)}$ as in post reconstruction method (uniform image estimate)

  ii) Perform one image update over all temporal frames with conventional OSEM to calculate $\lambda_{X,j}^{(k+1)}$

  iii) For the first iteration, fit the kinetic model in image space with LLS to estimate initial model parameters $\alpha^{(k)}$. Otherwise use the value determined from previous step iv.

  iv) Fit the kinetic model in image space with GLLS (1 or 2 internal iterations) using $\alpha^{(k)}$ from LLS as initial estimate to calculate parameters $\alpha^{(k+1)}$ as well as to derive the weight from the fitted LLS image (Equation 6.15).
v) Evaluate the model to calculate the fitted image \( \lambda^{(k+1)}_{X_{ji}} = f_{jl}(\alpha^{(k+1)}) \)

vi) Repeat from ii)

Parametric images of perfusion \( (k_1) \), efflux rate \( (k_2) \), fractional blood volume \( (V_a) \) and volume of distribution \( (V_d) \) were derived using the traditional independent frame reconstruction followed by post-reconstruction kinetic analysis as well as using the direct parametric reconstruction. To quantitatively evaluate the methods, since the true perfusion is not known, we plotted the mean ROI perfusion versus variance performance of the algorithms for different ROIs in the FOV, providing only insights into the relative performance of the methods.

6.3.2 Evaluating parameter estimation precision and accuracy in abdominal \( [^{15}\text{O}]\text{H}_2\text{O} \) PET imaging with direct 4-D image reconstruction

6.3.2.1 Data acquisition and generation

6.3.2.1.1 Patient data

To investigate the effect of 4-D image reconstruction on parameter estimation reproducibility, data from a patient with HCC were used, participating in a multi-dose study (Walker et al 2009). Six bolus injections of \( [^{15}\text{O}]\text{H}_2\text{O} \) at 552, 504, 267, 237, 382 and 172 MBq were administered to the patient within the same scanning session and without moving the scanner’s bed position. An automated injection system (Hidex Radiowater Generator) was used to provide accurate intravenous bolus injections, with a 13 min delay between injections to allow residual activity to decay to background levels. Figure 6.3 (a-b) shows the six measured arterial input functions at the different injected doses, as well as the normalized input functions to the injected activity. The reproducibility between the 6 input functions is remarkable, with almost identical shape and no relative delay. In Figure 6.3 (c) the net-trues events are plotted for the six scans as a function of time. Again the curves are very similar in shape, scaled due to the injected activity. The activity in the external radiation detector that measures the arterial blood arrives \(~37 \text{ seconds}\) later than the initial rise in the events curve. It takes
approximately ~15 seconds for the bolus to pass through the injection line and reach the body through the venous blood supply. From there after reaching the heart it takes another ~10 seconds to be pumped in the abdominal area and reach the organs of interest. At the same time it takes ~22 seconds for the bolus to arrive in the external radiation detector from the heart through the radial artery and the external tubing. As such the relative delay between the measured and the real input function in the abdominal area is ~12 seconds as mentioned in section (6.3.1.2).

**6.3.2.1.2 Bootstrap realizations**

Having 6 consecutive scans within the same session and without moving the patient from the scanner’s bed, provides a unique opportunity to evaluate parameter estimation variability through interscan comparison. Such estimates include variability due to changes in physiology between the scans, variability due to the differential injected dose resulting in parametric images with different statistical properties, as well as intrinsic statistical variability at a specific injected dose. To evaluate the statistical variability of the parametric images generated from the patient data at a specific injected dose and without other confounding factors, using 4-D image reconstruction, non-parametric
bootstrap re-sampling was used to generate a set of statistically equivalent datasets by choosing random samples from the original list-mode dataset. The bootstrap realizations (list-mode realizations) generated from the original list-mode dataset, are assumed to be statistically equivalent to multiple image acquisitions of the system under study. To assess also the 4-D parametric reconstruction at 2 different noise levels, bootstrap re-sampling was used at the 2 statistically extreme datasets. Overall six bootstrap realizations were generated for each of the lowest (172 MBq) and highest (552 MBq) injected activity datasets. The original list-mode dataset was bootstrapped separately for each frame, meaning that to create a specific bootstrap frame, only events from the part

Figure 6.4 Schematic diagram of the non-parametric bootstrap re-sampling scheme that was used to create 6 bootstrapped statistically equivalent realizations for each of the 552MBq and 172MBq injected dose datasets. Random sampling with replacement was applied to each frame individually.
of the list-mode contributing to that frame could be re-sampled. As the list-mode file includes both prompts and delayed events, bootstrap re-sampling was applied to the combined sequence of events, as opposed to bootstrapping separately the prompts and the delayed events (Figure 6.4). This means that the total number of prompts and delayed events vary (similar to what would happen if a second dataset would be acquired).

6.3.2.1.3 4-D Simulation data

Both the sequential scans as well as the bootstrap realizations, provide insights into the variance characteristics of the methods, but since the ground truth in terms of absolute quantification of the kinetic parameters is not known, simulation data can offer additional information and provide a more comprehensive evaluation. For that reason fully 4-D simulations (3 spatial + 1 temporal dimensions) were conducted using a digital 3-D body phantom. The phantom consisted of 9 axial planes (to reduce computations) with a 168 × 168 image grid. To create the phantom, CT data from a patient were used to draw regions of interest representing major organs (kidneys, spleen, liver, lungs, pancreas, heart muscle) and blood volume (aorta). Any structure not categorized as organ or blood volume was considered to represent soft tissue. To these regions, kinetic parameters simulating $[{\text{15}}]\text{O}\text{H}_2\text{O}$ kinetics from a 6-minute scan were assigned. Table 6.1 summarizes the perfusion ($K_1$), efflux rate ($k_2$), fractional blood volume ($V_a$) and volume of distribution ($V_d$) values that were used in the simulation. The counts within image voxels were proportional to

$$fC_A(t) \otimes e^{-(k_2 + l)t} + V_a \cdot C_A(t) \tag{6.20}$$

Only true events were considered, with no attenuation, scatter and normalization effects included in the simulation. Figure 6.5 shows representative simulated parametric images from 2 different planes, while in Figure 6.6 the simulated time-activity curves for the different structures are plotted along with representative emission images from a plane. The dynamic 3-D image (9 planes) was positioned axially at the centre of the axial FOV corresponding to the HiRez PET/CT and then forward projected to a virtual scanner corresponding to the geometry of the HiRez. Due to the image being 9 planes, only 137
direct and oblique sinograms out of 313 3-D sinograms receive contributions and as such only these were used. This also resulted in a considerable speed up during reconstruction with considerable fewer forward and back-projections to perform, enabling an increased number of realizations to be used. Finally Poisson noise was introduced in the projection data. As in the bootstrap data and in order to evaluate the algorithms under different statistics, 2 different noise levels were considered. As only true events were considered in the simulation, to achieve comparable noise levels to the 2 extreme cases considered in the bootstrap realizations (172 MBq and 552 MBq), the counts in the simulated sinograms were matched to the noise-equivalent counts (NEC) from these 2 scans before introducing Poisson noise. Finally for each of the 2 noise levels 100 noisy realizations were generated.

<table>
<thead>
<tr>
<th></th>
<th>$K_1$(ml/sec/ml)</th>
<th>$K_2$(ml/sec/ml)</th>
<th>$V_a$ (ml/ml)</th>
<th>$V_d$ (ml/ml)</th>
<th>Voxel</th>
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<td>0.0309</td>
<td>0.15</td>
<td>0.81</td>
<td>812</td>
</tr>
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<td>0.0319</td>
<td>0.55</td>
<td>0.94</td>
<td>811</td>
</tr>
<tr>
<td>Liver</td>
<td>0.0117</td>
<td>0.0119</td>
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Table 6.1 Table summarizing the kinetic parameters that were used to create the dynamic 4-D digital phantom, along with the size of the different ROI –organ structures that were used in the phantom.

Figure 6.5 Simulated parametric images of perfusion ($K_1$) (a), efflux rate ($K_2$)(b), blood volume ($V_a$) (c) and volume of distribution ($V_d$)(d) for 2 out of the 9 plane of the digital 4-D phantom (i-ii).
Figure 6.6 Graph showing the simulated time-activity curves (TACs) prior to introducing noise, for all the regions in the digital phantom, along with representative images from a single plane at 3 time frames. Frame durations typically used in real patient scans were used in the simulation.

6.3.2.2 Kinetic modelling

For both patient and simulated data, based on the optimization section, the data were modelled using a single compartment model, including a blood volume component.

\[
C_T(t) = fC_A(t)e^{-k_2t} + V_a C_A(t) \quad \text{and} \quad k_2 = \frac{f}{V_d} \quad (6.21)
\]

On the patient data, a 12 second delay was used for all the scans as the timing differences between the six successive scans were found to be minimal. For both patient and simulated data, the GLLS method was used to linearize the operational equation with 2 internal iterations. To provide an initial estimate for the kinetic parameters, the LLS method was used. Similar to the section 6.3.1.2 to reduce computations, a body mask was drawn from CT data and used to mask voxels outside the body in the patient data. On the phantom simulations, only these voxels contributing to different organ structures and blood volumes were taken into account during the kinetic modelling.

6.3.2.3 Image reconstruction and analysis

For the tomographic steps of the direct and post-reconstruction algorithms parameters and data similar to section 6.3.1.3 were used. On the patient data, 10 iterations and 21 subsets were used, while on the simulation data we used up to 15 iterations and 21
subsets. In the simulations no physics effects were simulated during data generation and as such no resolution modelling was used in the reconstruction. Again parametric images were derived using the traditional independent frame reconstruction followed by post-reconstruction kinetic analysis, as well as using the direct parametric reconstruction. Parameter variability was estimated by calculating the coefficient-of-variation (CoV) parametric maps at the voxel level across the 6 successive scans, across the 6 bootstrap realizations for each of the 2 noise levels, as well as across the 100 noisy realizations in the simulated data again for both noise levels. Variance differences between the direct and the post-reconstruction methods were also quantified as a function of noise level for all the parameters. On the simulation data, to assess the accuracy of the 2 reconstruction methods, bias parametric images were estimated for all the parameters for the 2 noise levels since the true kinetic parameter are known. Bias-variance graphs were also plotted for the 2 noise levels and for up to 15 iterations. In addition, graphs of bias and variance as a function of the simulated parameters were plotted to assess any dependency of these metrics on the kinetic parameters.

6.4 Results

6.4.1 Implementation and optimization of direct and post-reconstruction kinetic analysis algorithms

In Figure 6.7 parametric images are shown derived both with LLS and GLLS. The 4 kinetic parameter estimation methods gave noticeably different results, with the 2 direct methods qualitatively outperforming the 2 post reconstruction methods, with apparent less variance within homogeneous organs. Little difference can be seen between the 2 post-reconstruction methods, with the perfusion \((K_1)\) looking slightly less noisy in the GLLS compared to the LLS. Visual analysis of the 2 direct methods suggests that GLLS performs better than the LLS. When compared with the post reconstruction methods, an apparent notable improvement in variance is seen in the perfusion image, with differences being more pronounced in areas of high perfusion. Improved contrast is also seen, with a better delineation of the spleen and the kidney cortex. Larger improvements are observed when looking at the \((k_2)\) images representing the efflux rate. Similar findings can be reported for the \((Vd)\) image, showing an almost uniform distribution with the exception of high perfusion areas and with values within the correct scale.
The tumour rim can easily be seen in the parametric images, with the central part of the tumour giving no signal, reflecting the lack of viable tissue and blood supply due to necrosis. Figure 6.8 (c) shows a profile through the \( K_1 \) parametric image which verifies the qualitative analysis.

To assess the relative quantitative performance of the methods, the image roughness was plotted versus the mean perfusion \( K_1 \) for 2 ROIs in the liver and the spleen (Figure 6.8 (i,ii)). As the true perfusion is not available though, only relative performance differences can be assessed. In both ROIs the direct GLLS achieves the highest perfusion for the same level of variance. In the liver after the 3rd iteration no increase in perfusion is seen as the ROI was large enough, with the variance rapidly increasing after that point. In the spleen again the direct GLLS outperforms all the other methods, achieving significant variance reduction at the same mean perfusion level.
Figure 6.8 Mean perfusion values vs image roughness as a function of iterations (1-10) for a region of interest (ROI) in the spleen (a) (~300 voxels) and the liver (b) (~60 voxels). In the liver, with increasing iteration the estimated perfusion values plateau even after 3 iterations as the ROI is relatively large. In the spleen the direct GLLS methods achieved significant improvements in image roughness at the same perfusion level with the direct GLLS giving the best results. (c) Profile through the perfusion parametric images traversing the liver (while line in Figure 6.7). The direct GLLS method appears to be the least noisy. Negative values appear in the direct LLS as the macro-parameters and not the constant rates are non-negatively constrained.

As mentioned in the theory section, the activity concentration at the voxel level has a vascular component. Although in brain studies it can sometimes be omitted due to the relatively small arterial blood volume, in the body there are a number of large vessels in the FOV. Excluding such a blood component in the model, could lead to an overestimation of the kinetic parameters. As the venous activity concentration reaches equilibrium with the tissue concentration in freely diffusible tracers such as water, the only contribution of the vascular component comes from the arterial blood. Figure 6.9 shows the kinetic parameters for a plane traversing the heart for 2 model formulations, with and without the blood volume component, both for the post-reconstruction and the direct parametric reconstruction. When no blood volume is modelled in the post-reconstruction modelling, perfusion is overestimated within the heart ventricles and
Figure 6.9  Parametric images of perfusion \(K_1\) (a), efflux rate \(k_2\) (b), fractional blood volume \(V_a\) (c) and volume of distribution \(V_d\) (d) along with the weighted residual sum of squares (e) for 2 different model formulations. The residuals in the direct method are the ones calculated from fitting the model after the last image update to match the post reconstruction case. In the direct method the image has only been updated once since the previous model fit compared to the post reconstruction method and a direct comparison is not easy to make but nevertheless it provides a useful error checking mechanism. Removing the blood volume term (i) causes an overestimation in \(K_1\) but at the same time slightly reduces the variance in \(k_2\) (ii) looking at the post-reconstruction method. The direct method on the other hand (iii,iv) has a stronger dependency on the model formulation as the use of an inappropriate model seems to affect the derived parameters more than in the post-reconstruction method. Significantly qualitatively improvements are obtained with the direct method when the blood volume is included in the model as this ensures a good fit in every image update.

attributed to compensate due to incorrect modelling. Due to the fact also that the model does not fit the data, the residuals contain significant structural information instead of random noise had the data been appropriately modelled. Inclusion of a fractional blood volume term results in a separation between the heart muscle and the left ventricle and right atrium. The aorta is also correctly seen in the blood volume image and not in the perfusion image. As a result also less structure appears in the residual image due to fact that the model can more accurately represent the measured data and the residuals are less in magnitude. Looking at the direct methods, a clear improvement is seen in all the
parameters compared to the post-reconstruction methods. Comparing the 3 parameter direct GLLS against the post-reconstruction one, a variance reduction in \((k_2)\) is seen, with a better delineation of the cardiac muscle in the perfusion image. Although this is true for the 3 parameter model, the omission of the blood volume term in the direct reconstruction results in the opposite effect compared to the post-reconstruction method, with voxels in the \((K_1)\) and \((k_2)\) images shooting off to extreme values. Looking at the residuals, the structure pattern in the heart also appears more intense compared to the post-reconstruction 2 parameter GLLS method. In addition, the aorta also appears in the residuals not previously visible, verifying the added penalty in the direct methods due to a poor fit. This could be due to the fact that the data in the post reconstruction GLLS are fitted to the wrong model only once, while in the direct GLLS the data are constantly constrained in every update and fitting errors propagate during the tomographic step.

6.4.2 Evaluating parameter estimation reproducibility and accuracy in abdominal \([^{15}\text{O}]\text{H}_2\text{O}\) PET imaging with direct 4-D image reconstruction

6.4.2.1 Patient data

Parametric images of perfusion \((K_1)\), efflux rate \((k_2)\), fractional blood volume \((V_o)\) and volume of distribution \((V_d)\) using the traditional independent frame reconstruction followed by post-reconstruction kinetic analysis, as well as using the direct parametric reconstruction for the highest (552 MBq) and the lowest injected doses (172 MBq) are shown in Figure 6.10 (i-iv) for a plane traversing the hepatocellular carcinoma (10 iteration – 21 subsets). Variance improvements in the direct method (Figure 6.10 (ii, iv)) are immediately apparent especially in the \((k_2)\) image. This improvement also is partially reflected on the \((V_d)\) parametric image with voxel values within the physiologically expected range, as opposed to the extreme and very noisy data obtained with the traditional post-reconstruction approach. Similar improvements are seen in parametric images obtained for the remaining scans, with the 2 extreme injected doses shown being representative of the overall trend. Looking at the lowest dose (172 MBq) (Figure 6.10 (iii)) the qualitative improvements obtained with the direct method (Figure 6.10 (iv)) are greater than those obtained by tripling the injected dose (552 MBq) (Figure 6.10 (i)), especially in the perfusion \((K_1)\) image.
Figure 6.10 Parametric maps from the same patient for the highest (552MBq) (A) and the lowest (172MBq) (B) dose scans generated with the post-reconstruction kinetic analysis (i,iii) and the direct 4-D reconstruction (ii,iv). Clear qualitative improvements can be seen in all parameters with the direct method especially in $k_2$ and $V_d$. Similar improvements were found in the other 4 scans acquired during this scanning session at the intermediate injected doses. Coefficient of variation (CoV) maps (C) across the six scans, were generated with the direct 4-D reconstruction and the post-reconstruction kinetic analysis. Reduction in parameter variability is observed using direct 4-D reconstruction, particularly in high uptake regions.

To assess the parameter variability, the CoV parametric images across the six scans for all the parameters are shown in Figure 6.10 (v-vi). The greater improvements with the direct method (Figure 6.10 (v)) are seen in the $(k_2)$ and $(V_d)$ images with less significant but still noteworthy benefits in the perfusion image. On the other hand, in the blood volume images no considerable difference in seen between the methods. In Figure 6.11 the mean estimated kinetic parameters across the six scans are plotted against the CoV across the scans for drawn ROIS and for 1-10 iterations. Two volumetric ROI were considered with one located in the spleen (2002 voxels) (Figure 6.11 (A)) and one
in the hepatocellular carcinoma, avoiding the necrotic centre (5538 voxels) (Figure 6.11 (B)), in order to cover regions with varied perfusion values. In both regions, as the iterations increase, the CoV rapidly deteriorates, especially in the post-reconstruction method. As mentioned before, in both regions no significant difference is seen in the blood volume image, with dramatic reductions in the $(k_2)$ CoV when using the direct method.

Apart from the variance differences though, the 2 reconstruction methods produce quantitatively different parameter estimates, with the relative difference being greater in the spleen (high perfusion region), compared to the tumour ROI (low perfusion region). As the true parameters are not known, is not possible to say which of the 2 methods delivers the least biased parameters. However from the graphs it is seen that the parameters in the direct method converge fairly rapidly with minimal change in the parameter estimates after 2-3 iterations, whereas the parameters in the post-reconstruction method have not reached convergence even after 10 iterations. The mean and standard deviation values within the ROIs from the mean and CoV images are summarized in Table 6.2 at the 10th iteration.

As the regions in the spleen and the tumour (HCC) are relatively big and in order to evaluate the spatial heterogeneity at the voxel level, scatter plots of mean parameter estimate versus CoV were plotted (Figure 6.12) for the voxels within the above ROIs from the mean and CoV parametric images, for both methods (parameters estimated at 10th iteration – 21 subset). Comparing the distributions between the direct and the post-reconstruction methods in both ROIs (Figure 6.12 (A)(a) compared to Figure 6.12 (A)(b) for the spleen and Figure 6.12 (B)(a) compared to Figure 6.12 (B)(b) for the HCC), a clear improvement is seen in the direct method with voxels within the ROI being significantly less dispersed and with fewer outliers. Again improvements are more pronounced in the $(k_2)$ and $(Vd)$ scatter plots, with voxels being significantly less scattered around the mean ROI value in the mean and CoV images. As such the direct approach not only manages to improve inter-scan voxel test-retest variability by reducing the statistical variance across successive scans, but also improves voxel covariance within the ROI both in the mean and CoV images. From a clinical point of view one can see the physiological variability in the parameter estimates by comparing the plots not across the 2 methods but across the 2 ROIs within each method individually. Looking at the voxel-wise parameter estimates across the 2 ROIs in the
Figure 6.11 Mean parameter estimates vs CoV across the 6 repeated scans generated by drawing 2 ROIs in the spleen (A) and the hepatocellular carcinoma (B). Mean values within ROIs for all parameters and both post reconstruction and direct GLLS kinetic modelling. $K_1$, $k_2$ and $V_d$ kinetic parameters seem to vary significantly more in the post reconstruction method with $V_a$ showing similar variance performance between the methods. Even though the true parameters are not known the same trend is seen in both ROIs with perfusion ($K_1$) and $k_2$ in the post-reconstruction method lower than the direct while ($V_a$) and ($V_d$) are higher.
Figure 6.12 Scatter plots of mean kinetic parameters versus CoV across the 6 scans for the voxels with an ROI in the spleen (A) and the HCC (B). Scatter plots with the direct method (A)(b) and (B)(b) appear less disperse around the mean value within the ROI both in the mean as well as the CoV parametric images and with reduced CoV.

direct method, where such comparison is easier due to the parameters being less dispersed, it is seen that ($Vd$) varies considerably less in the spleen with values between 0.5 (ml/ml) and 1 (ml/ml) (Figure 6.12 (A)(b)(iv)) compared to the tumour (HCC) (Figure 6.12 (B)(b)(iv)) with values between 0.2 (ml/ml) and 1 (ml/ml). This is probably due to biological differences with different areas having different kinetics, emphasizing the spatial heterogeneity within the tumoral area. In addition in the ($K_1$) and ($k_2$)
tumour scatter plots (Figure 6.12 (B)(b)(i-ii)) the voxels vary more around the mean CoV compared to the spleen (Figure 6.12 (A)(b)(i-ii)) as regions within the tumour vary differently between the 6 scans. As the CoV is normalized by the mean, any change in the CoV cannot be attributed to a change in the mean parameter estimate. This increase could then be due to a differential degree of physiological variation within regions of the tumour, compared to normal tissue (spleen), where the parameter variation is more uniform and possibly signifying that temporal heterogeneity between the 6 successive scans in the tumour parameter estimates is more pronounced (Mollica et al 2002).

### 6.4.2.2 Bootstrap data

Figure 6.13 shows the CoV parametric images (10 iterations – 21 subsets) derived from the bootstrap re-sampling in the high statistics dataset (552 MBq) (Figure 6.13 (A)) and the low statistics dataset (172 MBq) (Figure 6.13 (B)). Similar to the CoV images from the 6 consecutive scans, the direct method achieves significant reduction in the statistical noise between the bootstrap samples. The reduction appears to be higher within the main organs with high perfusion, with fewer differences in the surrounding structures, which are mainly soft tissue (relatively lower perfusion). Although variance improvements are seen in the \( K_1 \), \( K_2 \) and \( V_d \), similar or slightly higher variance for blood volume \( V_a \) is observed for the direct method compared to the post-reconstruction method (Figure 6.13 (A)(c)(i-ii)) looking at the 552MBq scan. The same trend remains at the 172 MBq scan. Compared to the CoV from the repeated scans (Figure 6.10 (v-iv)), the bootstrap derived CoV appears to be less. It is expected that the bootstrap realizations in the absence of repeated scans, are able to provide an accurate estimate of the variance in the reconstructed emission and kinetic parameter images. In reality though the statistical variance in the inter-scan CoV images is only a fraction of the overall kinetic parameter variability, with variability from the physiological differences between the repeated scans and the differential statistical properties of the parameter estimates due to the varying injected doses, contributing to the overall variability. As such the difference between the inter-scan and bootstrap derived CoV are completely justified. It is this relatively high contribution of the statistical noise on the overall variability that allows direct 4-D reconstruction methods to reduce test-retest variability. Results from the tumour ROI analysis are summarized in Table 6.3 for both
bootstrap data sets. Again to assess the within tumour spatial heterogeneity and evaluate the statistical properties of the methods at the voxel level, scatter plots of CoV versus mean estimated kinetic parameter were plotted for the voxels within a tumour ROI (the same that was used in the inter-scan analysis) for both bootstrap datasets (Figure 6.14 (A-B)). The scatter plots again emphasize the previously mentioned improvements of the direct approach, with reduced CoV and less variable mean (across repetitions). Comparing the plots representing the 2 bootstrap datasets, as expected the ones corresponding to the 172 MBq injected dose ((Figure 6.14 (B)) appear more scattered compared to the ones corresponding to the 552 MBq injected dose ((Figure 6.14 (A)) in both kinetic analysis method. Similar though to the qualitative assessment on the parametric images (Figure 6.10), in the post-reconstruction method the improvements in the voxel-wise kinetic parameter CoV going from the 172 MBq ((Figure 6.14 (B)(a)) to

Figure 6.13 CoV maps for the different parameters across the six bootstrap realizations at the highest (A) and lowest (B) dose with post-reconstruction (i, iii) and direct (ii, iv) analysis. Looking within each scan the 4-D improvements are similar to the ones seen in (Figure 6.10 (C)).
Figure 6.14 Scatter plots of mean kinetic parameters versus CoV calculated across the 6 bootstrap realizations for each voxel with an ROI in the HCC at highest (A) and lowest (B) injected dose with post-reconstruction (a) and direct (b) analysis. Scatter plots with the direct methods appear less disperse around the mean value both in the mean as well as in the CoV parametric images and with reduced CoV. The 552 MBq (Figure 6.14 (A)(a)) (so effectively improving the precision of the kinetic parameters by tripling the injected dose) are substantially less than keeping the same injected dose and using the direct reconstruction. Looking at the relative CoV improvements on the parameter estimates derived with the direct method for the 2 bootstrap dataset, no significant qualitative difference with the injected dose can be seen. In other words it is difficult to conclude if there is a dependency in the variance improvements seen in the direct reconstruction with the noise level.
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**Table 6.2** Table summarizing the voxel mean and standard deviation values within the tumour and spleen ROI from the inter-scan mean and CoV parametric images

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**Table 6.3** Table summarizing the voxel mean and standard deviation values within the tumour ROI from the bootstrap mean and CoV parametric images
6.4.2.3 Simulation data

In Figure 6.15 CoV parametric images of perfusion (a), efflux rate (b), blood volume (c) and volume of distribution (d) are shown across the 100 noisy realizations for both the post-reconstruction and direct methods (15 iterations – 21 subsets). The evaluation was performed at 2 different noise levels, which as analysed in the methods section (section 6.3.2.1.3) correspond to the datasets from the 552MBq (Figure 6.15 (A)) and 172MBq (Figure 6.15 (B)) injected doses. Similar to the findings in the patient data, large improvements with the direct method are seen in the \( K_1 \) and \( V_d \) CoV images with improvements in \( K_1 \) being less prominent and within high uptake organs, but still noteworthy and of comparable magnitude to the ones seen in patient data. On the other hand in the \( V_A \) image, the direct method delivers slightly more variable parameters which linking it again with the real data, corresponds well with the CoV analysis in the

(A)

(B)

Figure 6.15 Coefficient of variation maps for the different parameters across the 100 noisy realizations at the highest (A) and lowest (B) NEC both for the post-reconstruction (i,iii) and the direct method (ii,iv) for a plane through the phantom (15 iterations – 21 subsets). As CT data were used to draw all the regions the parametric images are very similar to the ones from the patient data.
Figure 6.16 Parametric images after subtracting the CoV images between the 2 methods (post reconstruction CoV – direct CoV), at the highest (i) and lowest (ii) NEC. At low NEC the improvements with direct 4-D reconstruction are greater compared to high NEC mainly in $k_2$ and $V_d$.

Looking across the 2 statistically different datasets, although the CoV increases considerably in the post-reconstruction analysis when going from the low noise (Figure 6.15 (i)) to the high noise levels (Figure 6.15 (iii)), in the direct analysis only a small degradation in the CoV is seen (Figure 6.15 (ii,iv)). This is particularly true for the $k_2$ and $V_d$ CoV images. As a consequence this translates to the direct 4-D reconstruction achieving greater variance improvements as the data becomes noisier. To qualitatively assess the effect, the relative difference in the CoV between the direct and post-reconstruction methods is shown for the high NEC (Figure 6.16 (i)) and the low NEC data (Figure 6.16 (ii)). The CoV difference between the methods (reduced CoV in the direct method) in the low NEC, are higher compare to the higher NEC. To quantitatively evaluate the variance properties of the methods at different regions in Figure 6.17 the CoV is plotted for 6 ROIs, with each ROI representing the entire region within an organ (kidney, spleen, liver, pancreas, heart, lungs), as a function of true kinetic parameters within the ROI (Table 6.1). The graph provides a plethora of information with respect to the variance characteristics of the algorithms. First as seen from the CoV parametric images, the direct method reduces the CoV mainly in the $k_2$ and $V_d$ with smaller improvements in the $K_1$. In $V_a$ the post-reconstruction method produces marginally lower CoV in some organs. Looking at the CoV as a function of the kinetic parameters, it can be seen that CoV increases with $K_1$ in the post-reconstruction method, with similar trend in the direct method despite the reduction in the CoV overall. On the other hand the CoV in $V_a$ increases as $V_a$ decreases in both algorithms. Finally the graphs show again, similar to the patient
data, that the CoV improvements from collecting higher statistics data by increasing the injected dose, are minimal compared to the CoV reduction by keeping the same dose and using the proposed direct 4-D reconstruction, especially in the $(k_2)$ and $(V_d)$.

In Figure 6.17 graphs showing the mean ROI perfusion (i), efflux rate (ii), blood volume (ii) and volume of distribution (iv) CoV, for 6 ROIs on the CoV parametric image representing 6 organs with different kinetics, as a function of the (true) kinetic parameters at the highest and lowest NEC (15th iteration – 21 subsets). Impressive improvements in CoV are seen in $k_2$ and $V_d$ with the direct method with almost stable variance characteristics across a range of $K_1$ and $k_2$ values. Furthermore CoV reduction appears to be more significant at the low NEC dataset compared to the high NEC. Smaller reduction in CoV is seen in $K_1$ with slightly increased CoV in $V_a$ with the direct method in some organs.

In Figure 6.18 parametric images of percentage bias for all parameter, for both reconstruction methods and for 2 noise levels are shown for a plane through the 3-D phantom (15 iterations – 21 subsets). What is immediately apparent is that parametric images derived with the post-reconstruction methods suffers from considerable negative bias both in $(K_1)$ and $(k_2)$ and $(V_d)$ with a significant positive bias in the blood volume parametric image. Looking at the different organs, the bias appears to depend on the kinetic parameters with regions of high $(K_1)$ and $(k_2)$ like the spleen and the pancreas,
suffering from high negative bias and with regions having increased contribution of blood volume suffering from increased positive bias. This dependency is similar to the dependency seen in the CoV image. On the other hand, the direct method exhibits significantly reduced bias within the main organ regions in both noise levels. The qualitative assessment is verified by plotting the percentage bias as a function of the true kinetic parameters for the different organs in Figure 6.19. As opposed to the CoV were the improvements of the direct method were dependent on the noise level and the kinetic parameter values, in terms of bias, the improvements of the direct method are almost independent of the noise level. Nevertheless the absolute bias is still dependent on the noise level as can clearly be seen in Figure 6.19 (i) with the high NEC dataset showing reduced bias compared to low NEC dataset, both in the direct and post reconstruction methods. This is in agreement with the 1-D simulations from chapter 3 as looking at Figure 3.7 increased negative bias is observed when going from high to low

**Figure 6.18** Percentage bias parametric maps for the different parameters, across the 100 noisy realizations at the highest (A) and lowest (B) NEC for a plane through the phantom (15 iterations – 21 subsets).
Figure 6.19 Graphs showing the mean ROI perfusion (i), efflux rate (ii), blood volume (ii) and volume of distribution (iv) bias, for 6 ROIs on the mean parametric image representing 6 organs with different kinetics, as a function of the (true) kinetic parameters at the highest and lowest NEC (15th iteration – 21 subsets). Considerable bias reduction is seen in K1, k2 and Va with the direct method with the bias increasing as a function of K1 and k2 values for both methods. Furthermore bias reduction appears to be almost independent of the noise level with similar improvements in both NEC datasets. Less dramatic reduction in bias is seen in Vd.

Count levels similar to what is seen in Figure 6.19. In addition the bias improvements are stable as a function of the parameters as both the post-reconstruction and the direct method show increasing bias at increasing \( (K_1) \) and \( (k_2) \) values with the degree of bias degradation being the same in both methods. Linking the bias evaluation of the 2 kinetic analysis methods from the simulation data, to the analysis on the real data (Figure 6.11) a very good agreement is seen in all parameters. On the patient data, the mean ROI \( (K_1) \) and \( (k_2) \) estimates in the post reconstruction method were negatively biased relative to the direct method with the \( (Vd) \) and \( (V_a) \) showing relative positive bias. As mentioned above, identical relative biases were observed between the methods in the simulated data, with the direct method however performing better in terms of absolute bias in all parameters. As such, it can be reasonably hypothesized that in the real data, even though the absolute bias is not known, the parameters derived with the
The direct method are more quantitatively accurate and less biased in absolute terms compared to the traditional post-reconstruction analysis.

To complement the above findings the percentage bias versus CoV is plotted in figure 6.20 for the ROI representing the spleen (up to 15 iterations – 21 subsets) for both methods and noise levels. As it can be seen, the direct method offers dramatic improvements both the bias and variance in ($V_d$) and ($k_2$), which are less impressive but still substantial in ($K_1$). In terms of the blood volume, the direct method achieves significant reduction in bias, but at the cost of slight increase in CoV. Both methods converge relatively fast with no significant change in bias after few iterations. This can be attributed to the spleen ROI being relatively large (811 voxels) and the fact that in the simulation only true events were used, without the addition of any erroneous events (scatter, randoms), thus speeding up the convergence.

Figure 6.20 $K_1$ (i), $k_2$ (ii), $V_a$ (iii) and $V_d$ (iv) percentage bias against CoV for up to 15 iterations for an ROI in the spleen. Comparison is done for both methods and noise levels. The graphs summarize results seen in previous graphs with the direct method providing better bias and variance performance in all parameters with the exception of $V_a$ which shows marginally increased CoV.
6.5 Discussion

With the increasing number of clinical trials on hemodynamic effects of new vascular and angiogenic targeting agents, there is a need for robust and reliable end point parameters, which can provide information about the system under study without compromising the temporal and spatial information. Traditionally parameter estimation is performed first by reconstructing a set of independent dynamic images followed by kinetic modelling. As such noisy parameters are obtained if modelling is performed at the voxel level. Several sophisticated algorithms have been proposed to improve precision and accuracy in the parameters, but are complex in their implementation and their application has only been demonstrated in neuroreceptor brain imaging studies. In this chapter, a novel 4-D direct spatiotemporal image reconstruction algorithm was implemented, based on a recently proposed EM framework (Matthews et al 2010), which separates the tomographic from the image based parameter estimation problem. The algorithm was applied for the first time on an $^{15}$O]H$_2$O oncology PET/CT dataset to estimate direct parametric images of perfusion, efflux rate and fractional blood volume and evaluate the potential improvements in the parameter estimates from such a methodology.

6.5.1 Implementation and optimization of direct and post-reconstruction kinetic analysis algorithms

We used 2 kinetic modelling methods and 2 model formulations to compare parametric images using the direct approach and the more conventional post-reconstruction parameter estimation approach. Based on the results presented, the LLS method performed surprisingly well compared to the GLLS, but gave slightly noisier parameters, with the GLLS performing better both in the direct and the post-reconstruction methods. Inclusion of the blood volume in the model was proven to be the correct choice, as a significant part of the measured tissue activity originates from arterial blood. Furthermore as the data suggest, the direct reconstruction is more heavily affected by the choice of an inappropriate model.

Despite the fact that in the 3 parameter model both in direct and post-reconstruction GLLS methods, the activity concentration in the blood is explicitly accounted for by the blood volume term, there are still areas in the body where the temporal distribution of
the tracer cannot be described by the model. This is specifically true for regions in the body which are located within the scanner FOV and for which the radioactivity arrives substantially earlier than the rest of the body.

6.5.2 Evaluating parameter estimation reproducibility and accuracy in abdominal $^{15}$O$\text{H}_2\text{O}$ PET imaging with direct 4-D image reconstruction

In this section an evaluation of the application of direct 4-D image reconstruction in abdominal $^{15}$O$\text{H}_2\text{O}$ PET/CT imaging was conducted. Contrary to the usual approach where the evaluation of a method is based on simulation data followed in the end by evaluation on patient data, the opposite approach was used in this chapter to emphasize the clinical application and benefits of direct 4-D reconstruction (limited evaluation of 4-D reconstruction strategies on real data to date), with the bootstrap realizations and the simulations in the end used as a way of interpreting the results from the real data. From a methodological point of view, the 6 repeated scans provided a unique opportunity to evaluate the test-retest variability of the kinetic parameters. The differential injected dose protocol used in that study, resulted in an extra degree of variation when estimating parameter reproducibility between the scans, with parametric images at the lower doses being nosier compared to higher injected doses. Nevertheless, as the purpose of our evaluation was not the absolute test-retest reproducibility in $^{15}$O$\text{H}_2\text{O}$ imaging, but the relative performance between the kinetic analysis methods, useful insights were derived from the analysis. To evaluate the methods at a specific injected dose, we used bootstrap realizations which allowed estimation of the statistical variance for the 2 kinetic analysis methods without the physiology induced variance between the repeated scans. Bootstrap has been successfully used in the past to estimate parameter variance. Haynor and Woods (1989) using parametric re-sampling in list mode PET datasets showed that the variance from bootstrap accurately approximates variance in the reconstructed images. Dahlbom (2002) generated replicate list-mode dataset using parametric bootstrap re-sampling and showed that the bootstrap derived standard deviation images resemble inter-scan standard deviation images from replicate acquisitions. Finally the simulations allowed quantitative assessment of the algorithms in terms of absolute bias and variance, in a way complementing the analysis and allowing interpretation of the results seen on the real patient data.
Regarding the performance of the direct and post-reconstruction algorithms the analysis showed that there are significant benefits to be gained from the application of the proposed 4-D parametric reconstruction in $[^{15}\text{O}]{\text{H}}_{2}\text{O}$ perfusion imaging. More specifically in terms of variance the direct method provided significant improvements in $(K_1)$ but more specifically in $(k_2)$ and $(Vd)$. In the $(V_a)$ parametric image both methods demonstrated similar variance characteristics on the real data, which was confirmed in the simulations. Variance reduction achieved by the direct 4-D reconstruction was found to be dependent on the noise level, with slightly larger variance reduction at increasing noise levels. Although in the bootstrap data such a differential improvement was not clearly seen, in the simulation data a larger variance reduction was seen in the dataset corresponding to noise levels from a 172MBq injected dose compared to the 552MBq injected dose. Finally and most importantly the direct reconstruction achieved substantially lower variance in magnitude in $(Vd)$, $(k_2)$ and less in $(K_1)$, than what would have been achieved through tripling of injected dose when using the conventional analysis. In fact looking at Figure 6.17 at the higher $(K_1)$, $(k_2)$ and $(Vd)$ values, a substantial increase at injected dose would be needed with the post-reconstruction method, in order to reach the CoV levels achieved by the 4-D reconstruction, based on the improvements seen going from 172MBq to 552MBq in the post-reconstruction CoV and extrapolating down to the CoV levels of the direct approach. However as the NEC is not increasing linearly with injected activity it would be difficult to improve the statistics in the post-reconstruction method just by injecting more dose. Alternatively one can choose to keep the same CoV levels of the post-reconstruction method by reconstructing the data with the 4-D algorithm but significantly reducing the injected dose below the 172 MBq.

One aspect of the direct 4-D reconstruction, which is often overlooked, is bias performance. Previous methods have largely emphasized on the variance reduction and SNR improvements. Based on the results presented, equally important reduction in bias was seen with the proposed 4-D reconstruction in all 4 parameters with up 50% reduced bias in the $(K_1)$, $(k_2)$ and $(V_a)$ and up to 25% in $(Vd)$. Bias in $(K_1)$ and $(k_2)$ was found to be proportional to the kinetic parameters which corresponds well with the 1-D simulation from chapter 3. Overall a very good agreement was found between the patient and the simulation data.
6.6 Conclusion

In this chapter we implemented a 4-D reconstruction algorithm for the first time on PET/CT data and evaluated the application of a direct spatiotemporal 4-D image reconstruction framework proposed by Matthews et al (2010) on perfusion $[^{15}\text{O}]\text{H}_2\text{O}$ datasets. Based on a comprehensive evaluation on patient, bootstrap and simulation data, it can be concluded that there are significant benefits to be gained from the application of 4-D methods in oncology $[^{15}\text{O}]\text{H}_2\text{O}$ PET/CT data, compared to the conventional methodology of post-reconstruction kinetic analysis, both in terms of variance, with reduced variability in parametric maps, as well as bias. Consequently, direct 4-D reconstruction may be valuable for clinical trials of new treatments which modify tumour vasculature, enabling improved sensitivity in assessing drug effectiveness and increasing statistical power. Direct methods could be beneficial to other oncology imaging protocols utilizing other tracers, but an independent evaluation is needed in each case, as improvements may vary between different tracers. Nevertheless and contrary to neuroreceptor brain imaging studies, in PET/CT abdominal studies a single model is unable to fully describe the kinetics in the entire FOV. As such in the direct 4-D reconstruction there is the potential that any errors (bias) from the discrepancy between the model and the observed kinetics could propagate spatially from unimportant areas to areas of interest and the next chapter focuses exactly on investigating such an effect.
CHAPTER 7

Impact of erroneous kinetic model formulation in direct 4-D image reconstruction
7.1 Introduction

As mentioned in the previous chapter, although many of the sophisticated 4-D image reconstruction algorithms have demonstrated substantial improvements when applied in dynamic neuro-receptor studies (Kamasak et al 2005, Yan et al 2008, Wang et al 2008a, Wang et al 2008b, Tsoumpas et al 2008), little or no evaluation has been done in PET/CT body studies (Kotasidis et al 2010, Rahmim et al 2010, Tang et al 2011). In the previous chapter it was demonstrated that direct 4-D parametric image reconstruction algorithms (Matthews et al 2010) can improve both the accuracy and precision in parameter estimates when applied to dynamic perfusion PET/CT data. In this chapter the attention is shifted from the implementation and evaluation of 4D parameter estimation on PET/CT body data, to the complications encountered during the kinetic modelling step when attempting to directly implement a 4-D algorithm in the body, as opposed to the brain.

In neuroreceptor imaging studies, due to the relatively similar physiological behaviour of the different brain structures (common delivery of activity through the common carotid artery and no organs of excretion where radioactivity enters the FOV from a source other than blood), a single model may be sufficient to describe the time course of the radio-activity concentration throughout the FOV. Outside the brain though, the differential physiological and biochemical behaviour that is seen in the variety of organs that are typically within the FOV, results in a single model not being sufficient to describe the observed kinetics. Movement of the subject or organs (cardiac motion, respiratory motion, movement from bladder filling), differential delay and dispersion of the input function for different areas in the FOV (injection site, thoracic versus abdominal organs), delivery of the activity to a region via a route other than blood such as activity in bile and urine, as well as disparity between the underlying kinetics and the model used (organs with dual arterial and venous blood supply like the liver), can result in non-physiological kinetic parameters in some regions if a single model is used, due to these regions in the image not being represented by the kinetic model (Kotasidis et al 2010). As such, in the conventional post reconstruction kinetic analysis, regions of interest for which the model represents the underlying kinetics, will be accurately modelled, while for region not being of primary interest, a positive or negative bias in the kinetic parameters could be seen as the model doesn’t fit the
measured data. Contrary to the post reconstruction analysis though, in the direct 4-D reconstruction, any errors from inconsistencies between the measured and modelled (reconstructed) data (due to the aforementioned reasons), can potentially propagate to other regions, which are of interest and for which the model accurately describes the underlying kinetics. This propagation can take place during the forward and back-projection operations of the tomographic step in the 4-D algorithm.

In this chapter we conducted a fully 4-D simulation study based on a digital body phantom to investigate this effect and evaluated its impact on the accuracy of the direct reconstruction. Different realistic datasets were simulated, to represent complications typically encountered in body studies, including differential input functions in the FOV and organs with different kinetics and dual blood supply. Parameters of interest ($K_1$, $k_2$, $V_d$, $V_a$) where estimated using the spatiotemporal 4D image reconstruction algorithm described in the previous chapter (Matthews et al 2010) as well as using post-reconstruction kinetic analysis on noiseless and noisy datasets simulating $[^{15}\text{O}]\text{H}_2\text{O}$ kinetics in the body. Bias analysis was conducted to evaluate potential bias propagation in well modelled region from region for which the model doesn’t fit the simulated data.

The chapter proceeds as follows. First a description of the different methods implemented, is presented. The various realistic datasets are analysed, along with the details of the 4D simulation. Then bias and variance analysis is presented at the voxel and region levels, in noiseless as well as noisy datasets. Finally we discuss the findings and assess their effect on parameter estimation in dynamic oncology PET/CT imaging, using direct 4-D image reconstruction algorithms.

### 7.2 Theory

Dynamic perfusion studies in PET usually involve a bolus injection, which after passing through the injection line and entering the venous supply, it reaches the heart from were it is pumped in the rest of the body. As such, there are a number of regions in the body for which the tracer arrival times vary significantly. Two such cases are the activity near the injection site, as it travels through the venous blood, as well as the activity as it enters the heart blood pools. As such, the input function in the main regions of interest located usually in the centre of the axial FOV and supplied with activity through arterial blood, is significantly delayed and dispersed compared to the input function in the heart and the injection site, with all these regions ‘seen’ at the same time.
Figure 7.1 Horizontal sections through the 3-D static emission image (activity concentration) from a dynamic [\textsuperscript{15}O]-H\textsubscript{2}O perfusion scan traversing the injection site (a) and the heart (b) along with the weighted residual sum of squares after fitting a 1-tissue model in the dynamic sequence, summed across all horizontal sections (c). The arterial line and the heart receive the activity earlier than the rest of the body and as a consequence the model cannot describe the data due to the relative delay being different than the one that is globally used.

by the scanner’s FOV. Figure 7.1 shows two such areas, as the activity near the injection site and the heart, arrives earlier compared to the central part of the body, which was used to calculate the global delay. In the first few frames the activity concentration in these areas cannot be accurately modelled, thus appearing as structured residuals as opposed to random residuals in the rest of the body. Many approaches exist in the literature to correct for delay but they are either designed for neuroreceptor imaging studies or result in having too many parameters to fit and are not applicable in [\textsuperscript{15}O]-H\textsubscript{2}O PET/CT perfusion parametric imaging, due to the poor statistical quality of the data (Iida et al 1988a, Meyer 1989, Van de Hoff 1993, Hinz et al 2006).

Figure 7.2 Schematic diagram showing the dual input model with both the hepatic artery and portal vein supplying blood to the liver. The venous blood in the portal vein is drained from the gastro-intestine organs with the blue arrows represent equilibration between tissue and venous concentrations.
Another complication which is encountered in whole body studies, but not in neuro-receptor imaging studies, is regarding the model that is used to describe the delivering of tracer to the target region. Most of the organs comply to the same model, with the delivery of the input function through arterial blood. A notable exception of this model though is the liver, were the delivery of the tracer is described by a dual input system, both from the hepatic artery and the postal vein (McCuskey 1994). Attempting to describe the delivery in the liver with a single input model will result in an underestimation in perfusion. Figure 7.2 shows a schematic representation of the dual input model in the liver.

Despite the above observations, in parametric imaging commonly a global delay is used in the kinetic model, with the delay being correct for the regions which are of interest and usually located in the centre of the axial FOV, but incorrect for the rest of the regions. Along similar lines a common single input model is used to describe the delivery of the tracer, which will be correct for most of the regions in the FOV but not for the liver. In the post-reconstruction method these simplifications will result in deriving correct parameters estimates for the regions which are of interest, by modifying the model to accommodate the delay and input model that is expected in these regions, but non-physiologic parameters for the regions which are not of importance for which the delay and input model are not appropriate. As such, any fitting error in badly modelled regions only occurs locally. Moving to the direct 4-D reconstruction, the previous step occurs in every image update and as such there is the potential that during the forward and back-projection steps along these badly modelled regions, the kinetic modelling induced error (bias) could spatially propagate to other regions for which the model in correct.

7.3 Materials and methods

7.3.1 Data generation

In order to investigate the potential parameter estimation error propagation in direct 4-D image reconstruction due to erroneous model formulation, a number of realistic scenarios were implemented within a fully 4-D simulation. The simulations were based on a digital phantom, similar to the one described in chapter 6. The phantom again was made of 9 axial planes with a 168 ×168 image grid. In the previous chapter a simplified underlying model was used for the kinetics present in the FOV. In this chapter the
Figure 7.3 Simulated parametric images of perfusion ($K_1$) (a), efflux rate ($k_2$) (b), blood volume ($V_a$) (c) and volume of distribution ($V_d$) (d) for 1 out of the 9 plane of the digital 4-D phantom.

evaluation is based on a more detailed and realistic representation of the structures and kinetics typical encountered in dynamic $[^{15}\text{O}]\text{H}_2\text{O}$ scans. Apart from the structures that the phantom had in the previous chapter (kidneys, spleen, liver, pancreas, heart muscle, soft tissue and aorta), 3 more blood volumes were included, to simulate the injection site, as well as the left and right heart ventricles. To these regions, kinetic parameters simulating $[^{15}\text{O}]\text{H}_2\text{O}$ kinetics from a 6-minute scan were assigned. Table 7.1 summarizes the simulated parameters. Representative parametric images are shown in Figure 7.3 for a plane traversing the heart. In the blood volume image (Figure 7.3 (c)) the injection site and the right and left heart ventricles are visible on top of the other structure previously seen in parametric images from chapter 6. Frame definition typical of a clinical scan was used (14x5sec, 5x10sec, 3x20sec, 6x30sec) to split the data in 28 time frames.

Two separate datasets were generated to investigate the different effects. In the first dataset, which is considered to be the reference one, no relative delay was considered between the input functions from the aorta, the injection site and the heart ventricles, with all 3 blood volumes even though located at different positions in the FOV, sharing the same TAC. Furthermore, for all organ structures a single input model was used, assuming tracer delivery from arterial blood (represented by the TAC assigned in the aorta, injection site and ventricles). As such, the counts within image voxels throughout the FOV were proportional to

$$fC_A(t) \otimes e^{-(k_2+\lambda)t} + V_a \cdot C_A(t) \quad (7.1)$$

$C_A(t)$ is the arterial input function activity concentration over time (aorta, injection site and ventricles), $f$ is perfusion ($f = K_1$), $k_2$ is the efflux rate, $V_a$ is the fractional blood volume, $\lambda$ is the decay constant of $[^{15}\text{O}]$ ($\lambda = 0.00567 \text{ sec}^{-1}$), $\tau$ is the dispersion.
Table 7.1 Table summarizing the kinetic parameters that were used to create the dynamic 4-D digital phantom, along with the size of the different ROI–organ structures that were used in the phantom.

<table>
<thead>
<tr>
<th>ROI</th>
<th>$K_1$(ml/sec/ml)</th>
<th>$k_2$(ml/sec/ml)</th>
<th>Va(ml/ml)</th>
<th>Vd(ml/ml)</th>
<th>Voxels</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kidneys</td>
<td>0.0250</td>
<td>0.0309</td>
<td>0.15</td>
<td>0.81</td>
<td>812</td>
</tr>
<tr>
<td>Spleen</td>
<td>0.0300</td>
<td>0.0319</td>
<td>0.55</td>
<td>0.94</td>
<td>811</td>
</tr>
<tr>
<td>Liver</td>
<td>0.0117</td>
<td>0.0119</td>
<td>0.05</td>
<td>0.98</td>
<td>2462</td>
</tr>
<tr>
<td>Pancreas</td>
<td>0.0417</td>
<td>0.0484</td>
<td>0.10</td>
<td>0.86</td>
<td>284</td>
</tr>
<tr>
<td>Heart</td>
<td>0.0167</td>
<td>0.0183</td>
<td>0.15</td>
<td>0.91</td>
<td>208</td>
</tr>
<tr>
<td>Lungs</td>
<td>0.0008</td>
<td>0.0014</td>
<td>0.06</td>
<td>0.60</td>
<td>699</td>
</tr>
<tr>
<td>Soft tissue</td>
<td>0.0005</td>
<td>0.0042</td>
<td>0</td>
<td>0.12</td>
<td>18455</td>
</tr>
<tr>
<td>Aorta</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>199</td>
</tr>
<tr>
<td>Injection site</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>18</td>
</tr>
<tr>
<td>Heart</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>640</td>
</tr>
</tbody>
</table>

constant and $\Delta t$ is the time delay. Figure 7.4 (i) shows the simulated TACs for the first dataset with the TAC in all 3 blood volumes coinciding with no relative delay.

In the second dataset a more realistic scenario was simulated, with differential delay and dispersion in the blood volumes (aorta, injection site and ventricles). Assuming the reference zero time point ($T_{aorta} = T_0 = 0$ seconds) to be the arrival time of the input function in the aorta, then the TAC in the right and left heart ventricles was simulated to arrive earlier and less dispersed compared to the aorta ($T_{ventricles} = T_{aorta} – 8$ seconds, $\tau =0.09$ sec$^{-1}$ ) with the TAC in the injection site arriving earlier and less dispersed compared to the ventricles ($T_{injection} = T_{ventricles} – 6$ seconds = $T_{aorta} – 14$ seconds, $\tau =0.08$ sec$^{-1}$ ). For all the organs apart from the liver, the activity delivery was based on a single input model from the aorta (arterial blood), with identical model and parameters to first dataset. For the liver, the delivery of the input function was based on a dual input model to simulate delivery both from the hepatic artery as well as the portal vein (Kudomi et al 2008). To simulate the portal vein, the gastrointestinal compartment was introduced in the simulation according to Figure 7.2 which is a single compartment model between arterial blood and the gut compartment. No delay between the arterial and portal input function was assumed. Figure 7.4 (ii) shows the simulated TACs for the second dataset with a relative delay between the TAC in the 3 blood volumes (Figure 7.4 (i)) after adding a blood delivery term from the portal vein. Based on the above, the following kinetics were simulated for each region:

In the aorta, the heart ventricles and the injection site the counts were proportional to
\[ V_a \cdot C_A'(t) \] (7.2)

with

\[ C_A'(t) = C_A(t) \] (7.3)

for the aorta where \( C_A(t) \) is the arterial input function activity concentration used in the 1st dataset and with

\[ C_A'(t) = C_A(t - \Delta t) + \tau \frac{dC_A(t - \Delta t)}{dt} \] (7.4)

for the ventricles (\( \Delta t = 8 \) seconds and \( \tau = 0.09 \) sec\(^{-1} \)) and the injection site (\( \Delta t = 14 \) seconds and \( \tau = 0.08 \) sec\(^{-1} \)).

**Figure 7.4** Graphs showing the simulated time-activity curves (TACs) in the digital phantom in both simulated datasets. In the 1st dataset (i) a single model was used to create the TACs while in the 2nd dataset (ii) different models were used in the liver, ventricles and injection site to simulate the differential delay in the input function and the dual input model in the liver.
In the kidneys, spleen, pancreas, lungs, heart muscle and soft tissue the counts we proportional to

\[ fC_A(t) \otimes e^{-(k_2+\lambda)t} + V_a \cdot C_A(t) \] (7.5)

with kinetic parameters according to Table 7.1. Finally in the liver the counts were proportional to

\[ \left( f_A C_A(t) + f_C C_C(t) \right) \otimes e^{-(k_2+\lambda)t} + V_a \cdot C_A(t) \] (7.6)

with

\[ C_C(t) = k_g C_A(t) \otimes e^{-k_g t} \] (7.7)

being the gut compartment with diffusion rate \( k_g = 0.5 \text{ min}^{-1} \) and

\[ k_2 = \left( \frac{f_a + f_p}{V_d} \right), \quad C_A(t) = r_a C_A(t) + r_p C_p(t) \] (7.8)

\[ r_a = \left( \frac{f_a}{f_a + f_p} \right), \quad r_p = \left( \frac{f_p}{f_a + f_p} \right) \] (7.9)

where \( f_a \) and \( f_p \) are the arterial and portal vein blood flows while \( r_a \) and \( r_p \) are the arterial and portal vein blood flow to total hepatic flow ratios respectively. Figure 7.5 shows emission images from representative frames (9th, 14th, 19th, 24th) taken from the 2 simulated datasets and for 2 planes. As it can be seen from the plane traversing the heart, in the earliest frame (9th) from 2nd dataset (Figure 7.5 (A)(ii)(a)), the activity in the injection site has arrived earlier compared to the ventricles (thus having higher activity in that frame), while the activity in the aorta is yet to arrive. This is in contrast to the 14th frame (Figure 7.5 (A)(ii)(b)), where the activity in the aorta is higher as the TACs from the injection site and the ventricle have already began to drop. In (Figure 7.5 (B)(i-ii)) the difference in the liver TAC is seen between the single and dual input model datasets. The dynamic 3-D image for both datasets was forward projected to a virtual scanner corresponding to the geometry of the HiRez, similar to the methodology in the previous chapter, and 100 noisy realizations were generated after introducing Poisson noise in the projection data corresponding to clinical obtained noise levels.
7.3.2 Kinetic modelling

To model the simulated kinetics in both datasets a single tissue model including a blood volume term was used with a single input blood delivery from the aorta.

\[
C_T(t) = fC_A(t) \otimes e^{-(k_2+\lambda)t} + V_d \cdot C_A(t) \quad (7.10)
\]

where \( k_2 = \frac{f}{V_d} \). The models were linearized with the GLLS method with LLS used to provide an initial estimate of the parameters. Similar to the previous chapter the body mask was used to restrict parameter estimation to the regions within the body torso.

7.3.3 Image reconstruction and analysis

Based on the 2 simulated datasets 2 different cases were evaluated both with the post-reconstruction kinetic analysis and the direct 4-D image reconstruction.

In the 1st simple case which it is considered to be the reference, the 1st simulated dataset was analyzed by both the post-reconstruction GLLS and direct GLLS with the temporal distribution modelled by the kinetic model described above. As the kinetic model used
for parameter estimation, was also used to simulate the kinetics in the 1st dataset, then there is a good match between the ‘observed’ kinetics and the kinetic model in all regions.

In the 2nd more complex case, the 2nd dataset was analyzed by both the post-reconstruction GLLS and direct GLLS methods with the temporal distribution modelled by the same kinetic model as in the 1st dataset. In this case the model is representative of the kidneys, spleen, pancreas, lungs, heart muscle and soft tissue, but not in the liver due to the kinetic model having a single input model, as opposed to the simulated dual input in the liver. In addition the kinetic model is not representative in the injection site and ventricles, due to a common delay in the kinetic model, as opposed to a simulated differential delay in these regions. The different datasets are summarized in Table 7.2.

<table>
<thead>
<tr>
<th>1st Dataset</th>
<th>Simulated Kinetics</th>
<th>Kinetic model</th>
<th>Match</th>
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<td>Liver</td>
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<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Pancreas</td>
<td>Single</td>
<td>No</td>
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</tr>
<tr>
<td>Heart</td>
<td>Single</td>
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</tr>
<tr>
<td>Lungs</td>
<td>Single</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Soft tissue</td>
<td>Single</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Aorta</td>
<td>Single</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Injection site</td>
<td>Single</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Heart ventricles</td>
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<table>
<thead>
<tr>
<th>2nd Dataset</th>
<th>Simulated Kinetics</th>
<th>Kinetic model</th>
<th>Match</th>
</tr>
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<td>Input</td>
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<tr>
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</tr>
<tr>
<td>Lungs</td>
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</tr>
<tr>
<td>Soft tissue</td>
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<td>Injection site</td>
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<tr>
<td>Heart ventricles</td>
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</tbody>
</table>

Table 7.2 Tables showing analytically the simulated model during data generation and the kinetic model used for parameter estimation. In the 1st dataset (A) were there was a good match in all regions and in the 2nd dataset (B) were the kinetic model was not representative in the liver, ventricles and injection site but was in all the other regions. In both datasets parameter estimation was performed both with post-reconstruction GLLS and direct GLLS (1st simple dataset + post GLLS, 2nd complex dataset + post GLLS, 1st simple dataset + direct GLLS, 2nd complex dataset + direct GLLS)
In total 4 combinations were considered: 1st simple dataset + post GLLS, 2nd complex dataset + post GLLS, 1st simple dataset + direct GLLS, 2nd complex dataset + direct GLLS. Bias and variance performance in parameter estimates was evaluated for all the combinations, both under noiseless and noisy conditions. Data were reconstructed for up to 15 iterations with 21 subsets while 2 internal iterations were used during parameter estimation with the GLLS. Similar to chapter 6 no physics effects were simulated and as such no resolution modelling was used in the reconstruction.

7.4 Results

As both direct and post-reconstruction methods behaved differently under noiseless and noisy conditions, the results are presented separately for each dataset. In each section, analysis was conducted having in mind two distinct categories of regions within the body phantom, one for which the model matches the observed kinetics and one for which it doesn’t, and graphs are shown for organs belonging in either category.

7.4.1 Noiseless data

Under noiseless conditions the post GLLS and direct GLLS methods were evaluated in both the simple and complex datasets by assessing the bias performance. In Figure 7.6 and Figure 7.7 percentage bias parametric images of perfusion \((k_1)\), clearance rate \((k_2)\), fractional blood volume \((V_a)\) and volume of distribution \((V_d)\) are presented from 2 different planes after 15 iterations (21 subsets). In Figure 7.6 the plane traverses the kidneys, spleen, aorta and liver while in Figure 7.7 the lung, the myocardium along with the ventricles and the aorta is shown. Considering first the 1st simple dataset (where in all regions throughout the phantom, the model represents the simulated kinetics), both the post-reconstruction and the direct method deliver almost identical bias maps. In all regions looking in both figures, bias is practically zero within the main organs with only minimal biases in the organ boundaries due to incomplete convergence. This also establishes a reference point for the rest of the evaluation, as both kinetic analysis methods behave very similar in terms of accuracy when no noise is present in the data and when the model fits the simulated data. Moving to the 2nd more complex dataset (where the model fits the data in all regions apart from the heart ventricle, the injection site and the liver), in the post reconstruction method and in the regions where the model
Figure 7.6 Percentage bias parametric maps for the different parameters (a-d), under noiseless conditions, for the 1st dataset (post-reconstruction (i) – direct (ii)) and 2nd dataset (post-reconstruction (iii) – direct (iv)) for a plane through the liver, spleen kidneys and aorta (15 iterations – 21 subsets).

Figure 7.7 Percentage bias parametric maps for the different parameters (a-d), under noiseless conditions, for the 1st dataset (post-reconstruction GLLS (i) – direct GLLS (ii)) and 2nd dataset (post-reconstruction (iii) – direct (iv)) for a plane through the ventricles, injection site, lungs, aorta and myocardium (15 iterations – 21 subsets). Bias propagation is obvious in the direct method (iv) (2nd dataset) arising from the badly modelled liver, ventricles and injection site.
fits the data (kidneys, spleen, aorta, heart, soft tissue, lungs, pancreas), the bias maps are almost identical with the 1st dataset with practically zero bias. Minute differences though are present compared to the 1st dataset in those regions (up to 0.2%), and are explained as the two datasets in both datasets are slightly different (due to the different kinetics used in the liver, ventricles and injection site). If the 3D images in both datasets had reached convergence, the kinetic modelling would have resulted in completely identical biases (close to zero) in those regions. Due to incomplete convergence of the 3D image (after 15 iterations) and the tomographic nature of the reconstruction, the kinetic modelling results in minimally different parameters, even though in both simulated datasets in those regions the kinetics simulated and the model used for kinetic modelling, are the same. This can also be confirmed from Table 7.3 which shows the mean ROI bias, by looking the mean bias for the above organs for which the model fits the data in the 2nd dataset and comparing them with the same organs from the 1st dataset (so comparing the 1st and 3rd column for each parameter for these organs). Nevertheless these differences are negligible and due to convergence, but it was found important to explain their origin. Staying in the post-reconstruction method and moving to the structures in which the model doesn’t fit the data, as expected positive and negative biases are seen in different parameters. In the liver (Figure 7.6 (iii)) significant underestimation is seen in the ($K_1$, $k_2$) and ($Va$) with 60%, 45% and 49% negative biases respectively while in the ($Vd$) a 70% positive bias is seen (Table 7.3). Also looking at Figure 7.7 (iii)(c) a ~11.7% positive bias is seen in both heart ventricles with a ~9.6% positive bias as well in the injection site. As in the blood volumes the tissue contribution was simulated to be zero, all the activity originates from the blood component and since there is a positive bias in these regions that translates to estimating ($Va$) above the unity. Contrary to the above observations, a different behaviour is seen when looking at the direct method. At the structures for which the model represents the data, and for which the simulated kinetics and the kinetic model are the same with the 1st dataset, non-zero biases are seen, as opposed to the 1st dataset where zero biases were seen. This can lead to the conclusion that biases from the badly modelled regions in the 2nd dataset (liver, ventricles and injection site), spatially propagate to neighbouring regions (spilling in).
Figure 7.8 Graphs of percentage bias versus iterations for all 4 kinetic parameters for the spleen, representing a well modelled region in both simulated datasets. The direct method in the 2nd dataset is biased due to bias propagating (spilling in) from badly model regions which are present in the 2nd dataset.

Figure 7.9 Graphs of percentage bias versus iterations for all 4 kinetic parameters for the liver, representing a badly modelled region in the 2nd dataset. In the 1st dataset both algorithms are unbiased due to the liver being well-modelled. In the 2nd dataset both algorithms are almost equally biased due to the model not being representative of the data.
Figure 7.10 Graphs of percentage bias versus iterations for the blood volume \( \frac{V}{a} \) in the injection site and the heart ventricles, representing badly modelled regions in the 2\textsuperscript{nd} dataset. Similar to the liver in the 1\textsuperscript{st} dataset both algorithms are unbiased due to the liver being well-modelled. In the 2\textsuperscript{nd} dataset both algorithms are almost equally biased due to the model not being representative of the data.

This effect can be seen in both the planes shown in Figures 7.6-7.7 (iv) in all kinetic parameters. Larger biases are seen in the heart with \(~50\%\) and \(~38\%\) negative bias in \( K_1 \) and \( k_2 \) respectively and \(~92\%\) positive bias in \( \frac{V}{a} \). Regarding the spatial nature of the error (bias) propagation, it is can seen from the parametric maps that the errors are larger in the regions which are in close vicinity to the badly modelled regions. This is more clearly seen in Figure 7.7 where due to the discrepancy between the kinetic model and the simulated kinetics in the heart ventricle, the propagated bias is higher in the regions surrounding the ventricles, like the soft tissue, the myocardium and part of the upper lungs.

Looking at the badly modelled regions the biases that are seen, are almost identical to the ones in the post reconstruction method (Figure 7.6 -7.7(iii)). To assess that this bias propagation is not a convergence issue in Figures 7.8-7.10 the mean ROI bias for all parameters within the spleen (Figures 7.8) (representing an accurately modelled region), the liver (Figures 7.9) as well as for \( \frac{V}{a} \) for the ventricles and the injection site (Figures 7.10) (representing badly modelled regions) is plotted as a function of iterations. In the spleen, the bias in direct method in the 2\textsuperscript{nd} dataset is obvious in all parameters, with parameters in all the other method-dataset combinations converging to practically zero biases. In the liver, ventricles and injection site (2\textsuperscript{nd} dataset) both the direct and the post-reconstruction methods showed identical biases compared to the 1\textsuperscript{st} dataset.
Table 7.4 Table of mean ROI percentage bias for the noisy data (15th iteration), for all kinetic parameters estimated with both algorithms in both simulated datasets.

<table>
<thead>
<tr>
<th></th>
<th>1st dataset</th>
<th>2nd dataset</th>
<th>1st dataset</th>
<th>2nd dataset</th>
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<th>2nd dataset</th>
</tr>
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<td>Post</td>
<td>Direct</td>
<td>Post</td>
<td>Direct</td>
<td>Post</td>
<td>Direct</td>
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<td>0.1467</td>
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<td>0</td>
<td>0</td>
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<td>11.6996</td>
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</tbody>
</table>

Table 7.4 Table of mean ROI percentage bias for the noisy data (15th iteration), for all kinetic parameters estimated with both algorithms in both simulated datasets.
7.4.2 Noisy data

Even though the noiseless simulations were useful to evaluate the effect of bias propagation without any other confounding factors, it is not really representative of the situation encountered during typical $[^{15}\text{O}]\text{H}_2\text{O}$ scans. For that reason, the same datasets and methods were evaluated under noisy conditions. Mean parametric images of bias across 100 noisy realizations for all 4 parameters after introducing noise to the datasets, are shown in Figures 7.11-7.12, directly equivalent to the ones in Figures 7.6-7.7. In the 1st dataset and contrary to the noiseless data, even though the kinetic model matches the underlying kinetics the post-reconstruction method is significantly biased, with the direct method (Figures 7.11-7.12 (ii)) exhibiting minimal bias, mainly in the organs with high perfusion ($K_1$). In Figures 7.13-7.14 CoV parametric map across the noisy realization are shown, with the direct method delivering reductions in ($K_1$), ($k_2$) and ($Vd$) CoV and minimal changes in ($Va$) compared to the post reconstruction method. Similar findings were shown in chapter 6 using a slightly more simplistic phantom design. Mean ROI biases for all the phantom regions derived from the mean bias parametric images can be seen in table 7.4. Moving in the 2nd dataset, again a different behaviour is seen compared to the noiseless evaluation.

![Figure 7.11](image)

**Figure 7.11** Percentage bias parametric maps for the different parameters (a-d), across the 100 noisy realizations for the 1st dataset (post-reconstruction (i) – direct (ii)) and 2nd dataset (post-reconstruction (iii) – direct (iv)) for a plane through the liver, spleen kidneys and aorta (15 iterations – 21 subsets).
Figure 7.12 Percentage bias parametric maps for the different parameters (a-d), across the 100 noisy realizations, for the 1\textsuperscript{st} dataset (post-reconstruction (i) – direct (ii)) and 2\textsuperscript{nd} dataset (post-reconstruction (iii) – direct (iv)) for a plane through the ventricles, injection site, lungs, aorta and myocardium (15 iterations – 21 subsets).

In the post-reconstruction method, the organs for which the model fit the data parameters are under/overestimated due to the noise induced bias, similarly to the 1\textsuperscript{st} dataset. In the organs for which the model doesn’t fit the data (liver, ventricles, injection site) the overall bias seen, is a combination of the noise induced bias and the bias due to erroneous fitting. Comparing though the biases between the well-modelled and the badly modelled regions, it appears that the biases due to noise in some well modelled regions are comparable to the bias in the badly modelled regions, giving the impression that the kinetic model induced error in the liver is not significant compared to the noise induced error. For example in the spleen (well-modelled region) \((K_1)\) and \((k_2)\) bias are \(-60\%\) and \(-56\%\) while in the liver (badly modelled region) the respective biases are \(-62\%\) and \(-57\%\). This is true for our specific example because as shown in the previous chapter, in the liver, due to the small perfusion value, the noise induced bias is relatively small compared to the spleen, where due to the high perfusion, the bias is substantially higher. This effect can be seen in a less perfused region like the myocardium in which \((K_1)\) and \((k_2)\) bias is \(-37\%\) and \(-34\%\) substantially lower compared to the liver. Similar though to the noiseless data, the kinetic model induced errors were confined to the regions for which the model didn’t fit the data, with the bias...
in the well-modelled regions occurring due to the behaviour of the post-reconstruction method on noisy data. Finally looking at the direct 4-D reconstruction it appears that in all parameters, bias is significantly reduced compared to the post-reconstruction

\[ \begin{array}{cccc}
K_1 \text{ CoV} & K_2 \text{ CoV} & V_0 \text{ CoV} & V_d \text{ CoV} \\
100 & 200 & 300 & 400 & 100 & 200 & 300 & 400 & 100 & 200 & 300 & 400 & 100 & 200 & 300 & 400 & \% & \% & \% & \% \\
\end{array} \]

Figure 7.13 CoV parametric maps for the different parameters (a-d), across the 100 noisy realizations for the 1st dataset (post-reconstruction (i) – direct (ii)) and 2nd dataset (post-reconstruction (iii) – direct (iv)) for a plane through the liver, spleen kidneys and aorta (15 iterations – 21 subsets).

Figure 7.14 CoV parametric maps for the different parameters (a-d), across the 100 noisy realizations, for the 1st dataset (post-reconstruction (i) – direct (ii)) and 2nd dataset (post-reconstruction (iii) – direct (iv)) for a plane through the ventricles, injection site, lungs, aorta and myocardium (15 iterations – 21 subsets).
method, which is in contrast to what was seen in the noiseless data. In the well-modelled regions it can be seen that even though in both 1st and 2nd dataset (Figure 7.11-7.12 (ii,iv)), the bias is reduced compared to the post reconstruction method (Figure 7.11-7.12 (i,iii)), in the 2nd dataset, bias is higher compared to the 1st dataset. This is due to the fact that under noisy conditions although the overall bias in the direct method has been reduced due the improvements that the 4-D methods offers, bias from badly modelled regions still propagates in the well-modelled regions. As the improvements though that the direct method offers in the noise induced bias over the post-reconstruction method, are much larger than the kinetic model induced bias propagation, the overall bias in the well modelled regions is going to be smaller. However this is true for regions for which the error propagation is minimal. For example in the spleen ($K_1$) bias has improved from $\sim$-60% in the post reconstruction methods (Figure 7.11(i,iii)), to $\sim$-22% in the direct method in the 2nd dataset (Figure 7.11(iv)) which is marginally worst that the $\sim$-15% bias achieved in the 1st dataset (Figure 7.11(ii)) were there was no error propagation. That translates to a $\sim$38% overall reduction in bias despite a 7% bias seen in the direct method due to error propagation. In the absence of error propagation the overall improvement would have been even higher to $\sim$45%, which is the improvement seen in the 1st dataset. Similar is the trend for all the parameters as can be seen in Figure 7.15 (A). For regions though which are in close vicinity to badly modelled regions and which are the most affected from the bias propagation, even the benefit of the 4-D method in terms of noise induced bias improvements, is not sufficient for the direct method to achieve better results compared to the post-reconstruction method. For example in the heart (which was heavily affected from error propagation in the noiseless data), which is close to the ventricles (badly modelled region) ($K_1$) bias deteriorated from $\sim$-37% in the post reconstruction methods (Figure 7.12(i,iii)) to $\sim$56% in the direct method in the 2nd dataset (Figure 7.12(iv)), while in the 1st dataset with no bias propagation (Figure 7.12(ii)), the direct method was only $\sim$9% biased. This again translates to an overall bias deterioration in the direct method compared to the post-reconstruction method, by $\sim$19%. This is due to the fact that even though the direct method reduced the noise induced bias by 28% the kinetic model induced bias propagation was almost $\sim$47% and as such the overall bias in the direct method was worse. Again the same trend is seen in all 4 parameters in Figures 7.15 (B) were parameter bias is plotted for the heart ROI as a function of iterations.
Figure 7.15 Graphs of percentage bias across 100 noisy realizations versus iterations for all 4 kinetic parameters for the spleen (A) and the heart (B), representing well modelled regions in both simulated datasets. In the spleen although the direct method in the 2nd dataset is still more biased compared to the 1st dataset due to bias propagating from the badly modelled regions, the overall bias is better compared to the post reconstruction kinetic analysis due to the direct method significantly reducing the noise induced bias. In the heart (myocardium) due to the fact that the error propagation is quite severe as it is located directly adjacent to the ventricles which are badly modelled, even the reduction in the noise induced bias is not sufficient to improve the overall bias compared to the post-reconstruction method.
Figure 7.16 Graphs of percentage bias across 100 noisy realizations versus CoV for all 4 kinetic parameters ($K_1$ (i), $k_2$ (ii), $V_a$ (iii) and $V_d$ (iv)) for the spleen (A) and the heart (B), representing well modelled regions in both simulated datasets.

Similar results are seen from the bias-variance graphs both for the spleen (Figure 7.16 (A)) and the heart (Figure 7.16 (B)). In the spleen the post-reconstruction method
behaved very similar in both simulated datasets but has worse bias and variance in $(K_1)$, $(k_2)$ and $(V_d)$ with marginally better variance in $(V_a)$ compared to the direct method, despite the bias deterioration in the 2nd dataset due to propagation. In the heart, the direct method in the 2nd dataset due to the bias propagation being severe, it delivers more biased parameters compared to the post-reconstruction method and in the case of $(K_1)$ and $(k_2)$ worse CoV.

7.5 Discussion

Linear and non-linear direct parametric 4-D image reconstruction algorithms have been extensively used the last few years in order to improve parameter estimation accuracy and precision in dynamic PET studies. Although their implementation in neuro-receptor imaging studies has been successfully demonstrated, their applicability in oncology body studies is more challenging and mainly underexplored. Differential delays of the input function at different parts of the body, organ movement, as well as regions with a dual input model, are some of the complications which pose an extra degree of difficulty when using 4-D algorithms in PET/CT body imaging. In the previous chapter, a new direct 4-D algorithm was applied in perfusion $[^{15}\text{O}]{\text{H}_2}\text{O}$ data but despite the impressive improvements in bias and variance, when a suboptimal model was used (no blood volume component) it appeared as if the direct method is paying an extra penalty compared to the post-reconstruction.

In this chapter the impact of erroneous kinetic model formulation, within direct 4-D image reconstruction, on the kinetic parameter estimates, was more extensively investigated. A comparative assessment between different realistic simulated dynamic datasets was conducted under noiseless and noisy conditions. Two combinations of simulated kinetics and kinetic models were evaluated, both within a direct 4-D and a post-reconstruction kinetic analysis framework. In the 1st dataset, representing the reference dataset, the kinetic model matches the simulated kinetics throughout the FOV, while in the 2nd dataset, the model was not representative of all the regions. This gave the opportunity to study any potential propagation from badly modelled regions, to well modelled regions and compared the result with the reference dataset where all regions are well modelled.

From a methodology point of view although organ motion was not simulated, the differential delay and the addition of a dual input were sufficient to demonstrate the
effect of error propagation in direct 4-D reconstruction. The addition of noiseless data to study the 2 simulated datasets and both reconstruction methods provided an excellent opportunity to evaluate the bias propagation effect. Most importantly though it enabled visualization of the spatial variation of the error propagation on the bias parametric images, without any confounding effects from noise. This is true as in the noisy datasets the noise induced bias masked the kinetic model induced bias to a big degree.

In the 2nd simulated dataset, both the effects of having differential delays in the input function, as well as a dual supply in the liver, were simulated within the same dataset. Although this provided a more realistic scenario as these effects occur at the same time within a scan, an extension from a methodology perspective would be to simulate these effects separately and evaluate the importance of each one of these on the bias propagation.

Regarding the results from the data analysis, both in the noiseless and noisy datasets it was shown that the direct reconstruction suffered from bias propagating from badly modelled regions to well modelled regions. On the other hand, this was not an issue in the post reconstruction analysis, as although bias was still present in the badly modelled regions, it was restricted within the region boundaries. In the noiseless data, due to the kinetic model induced bias being the only one contributing in the overall bias, the post-reconstruction analysis produced better bias parametric maps compared to the direct approach. On the noisy datasets, a more complicated situation was encountered with the overall bias in the direct and post-reconstruction methods being a combination of noise induced, organ specific bias and kinetic model induced bias. In the post-reconstruction, as seen in the previous chapter, organs with different perfusion values suffer from noise induced bias to a different degree. Even though the direct reconstruction substantially reduced the noise induced bias, it is still organ dependent. At the same time in the direct reconstruction the kinetic model induced bias propagation was also found to be organ specific, with the organs in the vicinity of badly modelled regions suffering the most. As such the overall bias in the direct method is a combination of 2 different effects and in these regions that suffer the most from the bias propagation, even the reduction in the noise induced bias from the 4-D methodology is not sufficient to improve the overall bias compared to the post-reconstruction method.

The bias propagation effect is something not previously seen before, as in neuro-receptor studies a single model is usually adequate to cover the expected kinetic in the
brain, but is not sufficient when trying to describe the kinetics present in the body. It is expected that the severity of the bias propagation to be highly dependant on the tracer used in the dynamic study, as well as the kinetic model used to describe the kinetics. The main objective then should be that observed kinetics in all regions throughout the FOV (including regions not of primary interest) are adequately described by the kinetic model. In the extreme dataset, a set of top hat temporal basis functions can be used to reconstruct the dynamic dataset. This scheme though is equivalent to and independent 3-D image reconstruction followed by kinetic modelling if applied in the entire FOV and as such the advantages of the 4-D reconstruction would be lost. Another approach would be to mask the regions which are expected not to be accurately described by the model and which are not of interest, using top hats during parameter estimation. This scheme though is based on the assumption that the regions for which the model is badly determined are well known. Moreover delay is constantly changing and as such only a small region in the body would have a relatively constant delay so as to benefit from this scheme.

These complications emphasize the need to develop a new scheme in which the kinetic modelling is performed based on a weighting between the desired compartmental model (a single tissue model in this case) and a more general kinetic model. In that way and based on a criterion, regions for which the primary model is not adequate to describe the kinetics, would not be wrongly constrained by the choice of an inappropriate model (which may be suitable for the primary regions of interest) but would be allowed to be described by a secondary more general model.

7.6 Conclusion

In this chapter using a digital body phantom and simulating different realistic cases of the expected kinetics during a perfusion \(^{15}\text{O}\)-H\(_2\text{O}\) PET/CT scan it was demonstrated that direct 4-D reconstruction methods suffer from bias propagating from badly modelled regions to regions of interest for which the model is well defined. This means that a different approach during the kinetic modelling process is needed if 4-D methods are to be considered as an alternative to post-reconstruction kinetic analysis in body PET/CT studies with approaches such as data-driven adaptive kinetic modelling worth exploring.
CHAPTER 8

Research outcome and future prospects
8.1 Thesis summary

In this thesis, novel as well as recently proposed 3-D and 4-D iterative image reconstruction algorithms were implemented and evaluated using a combination of simulations, phantom experiments as well as patient data from $[^{11}C]ASO, [^{18}F]FLT$ and $[^{15}O]H_2O$ static and dynamic studies that took place at the WMIC. In the previous 7 chapters, a summary of the most pertinent aspects of the research undertaken during the last 3 years was presented, along with a review of the methods used throughout this thesis.

More specifically, in chapter 1, an introduction into dynamic imaging using PET and PET/CT tomographs was presented, along with the limitations of the current methodology in parameter estimation using dynamic studies. These limitations were the drive behind this project, but as the project progressed new findings led to further investigations and opened the road for further research.

In chapter 2, a short review of the current status in iterative image reconstruction was presented. The first part described the key and common components of iterative image reconstruction algorithms. The rest of the chapter then focused in improved model-based approaches within iterative methods, such as resolution modelling and spatiotemporal 4-D image reconstruction algorithms.

In the 1st half of chapter 3, we reviewed the kinetic modelling theory and past as well as present parameter estimation schemes in perfusion imaging. In the rest of the chapter, 3 fast parameter estimation schemes were evaluated using 1-D simulations, to compare their accuracy and precision in generating parametric images of perfusion, but also to assess their ability to be incorporated within a spatiotemporal 4-D algorithm. Despite the fact that the GLLS method is heavily affected under high perfusion conditions, in the perfusion levels most likely to be encountered in $[^{15}O]H_2O$ perfusion scans, it demonstrated reduced MSE amongst the methods under study. Moreover, due to the rapid parameter estimation and the internal iterative scheme which is intrinsic characteristic of the method, the GLLS was found to be suitable to be used within a 4-D parameter estimation framework taking advantage iterative model based algorithms.

The 2 state-of-the-art PET/CT scanners, used in this thesis were introduced in chapter 4, along with the most pertinent details regarding the development an independent image reconstruction platform capable of reconstructing images for both scanners, using a variety of algorithms. The reconstruction platform uses in-house software to histogram
the list-mode data, while it takes advantage existing software to generate a number of
correction sinograms such as the scatter, attenuation and normalization. To generate the
system matrix for both scanners, software based on an improved 3-D version of the
Siddon algorithm was used to calculate the geometric probabilities and store the non
zero elements of the system matrix. Phantom datasets were used to provide an initial
comparison between the in-house and the factory supplied software. Despite some
differences in the noise properties from the 2 software platforms due to distinct
implementation based on projectors with different noise characteristics, the results were
mainly positive and helped to establish a base upon which further algorithmic
development could be undertaken. These chapters laid the foundations for the
subsequent 3 chapters, which portray the main research undertaken during this project.

Chapter 5 described the implementation and validation of a new method to measure
the spatially variant PSF on both PET/CT scanners, as well as on the HRRT. In the
latter, the PSF dependency on count rate was also investigated. Using the new
methodology based on an A4 paper of printed pointed sources, a single scan was found
to be sufficient to characterize the scanner’s blurring properties, with the ability to
acquire further scans in minimal time if a finer sampling is needed. Apart from the
dependency on the position in the FOV, the PSF was also found to be count rate
dependent within the count rate limits obtained in typical dynamic scans. The measured
PSF from both scanners was incorporated in a resolution modelling image
reconstruction algorithm using image based methods and the algorithm was evaluated
using phantom and real patient data. Finally a comparison was made between image
based and projection based resolution modelling image reconstruction algorithms, to
establish if image based techniques can equal if not better projection based techniques.
Evaluation of the method revealed that both techniques achieve similar levels of
resolution, contrast recovery and coefficient of variation, with small differences due to
the implementation of the algorithm used and the methods themselves.

In chapter 6 attention was shifted to dynamic imaging, the implementation of a direct
4-D spatiotemporal image reconstruction algorithm on the B-HiRez PET/CT and the
application of such methodology in perfusion [15O]H2O imaging for direct estimation of
perfusion (K1), volume of distribution (Vd) and fraction blood volume (Va) parameters.
The direct 4-D methodology was compared with the traditional post-reconstruction one,
with 6 consecutive scans at increasing injected doses used to provide mean and COV
parametric images for both methods. Furthermore the list-mode data from the extreme injected doses were bootstrapped to produce further 6 datasets at each injected dose, in order to study the statistical properties of the parametric images without any variance from the differential injected dose scheme or other methodological and physiological variations. Results revealed noticeable improvements in variance characteristics of the parameter estimates using the direct method, mainly on Vd and k2 and less on K1. Differences were also observed in the mean parameter estimates, although bias could not be evaluated as the true values were not available. For that purpose, fully 4-D simulations based on a 4-D digital phantom were used to validate the results from the patient datasets. In terms of the variance, the results confirmed the findings seen in the patient data. In addition, bias improvements were also observed with the direct approach, with such improvements variable for different kinetic parameters and values of those parameters. This agrees well with the 1-D simulation from chapter 3, as the GLLS MSE was found to be a function of perfusion. In the evaluation of the methods, a single model was used to represent the entire FOV, but as opposed to brain studies, this is unlikely to be the case in body studies, mainly due to differential delay and dispersion in the input function, non-rigid motion of organ structures and organs with dual supply, to name a few reason.

To evaluate the effect of erroneous model formulation in direct and post reconstruction methods, 4-D simulations were conducted with the results presented in chapter 7. As opposed to post-reconstruction methods where errors from badly modelled regions is a local effect, in direct 4-D methods such errors spatially propagate from regions potentially not of primary interest into regions which are of interest and for which the model is well defined. Bias propagation was found to be greater in the regions of interest which were in close vicinity to the badly modelled regions.

8.2 Research outcome and future work

In this thesis new and existing techniques were implemented and evaluated not just to add them to an ever increasing list of reconstruction algorithms, but to help understand their significance in improving the quality of the reconstructed images both in static and dynamic imaging application. Despite the fact that in this project we opted to explore in depth as many aspects of the methods as possible, there is always room for
further improvements on the methodology. Moreover, apart from the application of newly proposed algorithms, the new techniques developed in this thesis could also be applied in other modalities opening the road for new investigations.

In chapter 5 a new technique was developed based on printed point sources. Such a method on its own is not new, but the application of such methodology to measure the scanner’s PSF is of interest to investigators and PET centres around the world, as it open the road for comprehensive, fast and efficient measurements of the scanner’s resolution properties. Scanning a single paper of point sources could also be used as a QA test every 6 months for example, in a similar way to the NEMA testing. For scanners with PSF reconstruction capabilities, such a scan could also be used to calculated a new set of PSF kernels, depending on the spatial resolution performance of the scanner. Such a methodology could also be backed by the fact that although image based techniques introduce simplifications, they deliver similar results compared to projection based methods, based on the current approach of a response parameterization as opposed to voxel-by-voxel measurements. Another outcome from this work, which is of importance in dynamic studies, is the count rate dependency of the PSF. To maximize the statistical quality of the data SNR, many studies inject activity levels corresponding to the peak NEC, but increased count rate has a negative effect on the spatial resolution due to increased pile up and in dynamic studies the early frames are expected to suffer from reduced resolution compared to later frames. As such, kinetic parameters depending on the influx part of the TAC are expected to be more affected. Moreover, low count bias (still though within the spatial resolution degradation count rate limits) in iterative reconstruction, which was found to be reduced when using resolution modelling (Walker et al 2011), could be further reduced as in the early frames the PSF would be underestimated. Despite these findings, further work could be done. On the 2 PET/CT scanners we measured the spatially variant PSF and incorporated it on an iterative reconstruction algorithm. Such an image reconstruction implementation is yet to be done on the HRRT, with work already under way by another colleague (Giorgos Angelis) working on the specific scanner. Studies at WMIC are expected to benefit substantially upon completion of the algorithm implementation and evaluation. Another area for future investigations, which resulted from the increased interest and use in resolution modelling image reconstruction algorithms, is the need to eliminate the ringing or else Gibbs artefact in the reconstructed images (Snyder et al...
With many institutions currently recommending not using resolution modelling based image reconstruction algorithms in clinical trials, it has become increasingly important to find a way to avoid these artefacts without sacrificing spatial resolution and SNR improvements (Thielemans et al 2010, Tong et al 2010b). In our opinion, such an optimization is extremely challenging and if possible it would result in an even more complex algorithm, with more parameters to evaluate. One easy way of minimising the problem would be to reduce the kernel by 10-20% to the point where few artefacts are visible. This would result only in a small resolution deterioration compared to the full benefit of the PSF, while having artefact free images of improved resolution and SNR compared to non-PSF reconstructed ones. Finally the proposed methodology could easily be adopted and used in other modalities such as SPECT were possibly the benefits from such an approach could be greater.

In chapter 6 for the first time we implemented a 4-D algorithm on a PET/CT scanner and evaluated the benefits of such methodology in perfusion data. The work presented in this chapter clearly demonstrates that direct parameter estimation in the body has certain advantages, with improved accuracy in parameter estimates compared to the established methodology. Furthermore the reduction in variance achieved in Vd and K1 is of significant importance to studies using them as biomarkers to assess new cancer treatments based on drugs that target the tumour vasculature, enabling improved parameter reproducibility and as an effect improved sensitivity in assessing treatment efficacy. In this thesis, a newly proposed 4-D algorithm was implemented for perfusion studies with [15O]H2O and using a 1-tissue compartment model, but similar dynamic studies with other tracers are expected to also benefit from such methodology. Nevertheless, the application of spatiotemporal algorithms in other tracers in the body should be individually evaluated, with improvements in parameter expected to be tracer, kinetic model and reconstruction algorithm specific. Apart from using the proposed methodology in other application, further improvement in the methodology could also be investigated based on the findings from chapter 7. Despite the improvements that can be achieved using 4-D methods, there are a number of complications when these methods are applied in the body and further work is needed for these methods to be routinely used for parameter estimation. As parameter estimation using a single model for the entire FOV leads to bias propagation in regions of interest, new modelling strategies should be developed. These should allow model fitting in an adaptive way.
where the data should drive the choice of the appropriate model, avoiding the data to be constrained by an inappropriate model. Another effect that also needs further investigation is the impact of movement and its effect on parameter estimates using 4-D methods. This is of particular importance in body studies, due to the complex nature of non-rigid motion. The advent of PET/MRI, currently under clinical evaluation is expected to considerably boost investigations towards motion correction and 4-D image reconstruction strategies are expected to significantly benefit from those.

In this project, a numbers of new and existing image reconstruction methods were implemented in an attempt to improve precision and accuracy in the final parameters of interests, whether these are voxel intensities or physiological variables and deliver images of superior spatial resolution. But more than anything else, this thesis demonstrates the potentials of statistical image reconstruction methods in their ability to model the different spatiotemporal processes that take place during data acquisition in PET, with ever increasing quantitative and qualitative corrections being incorporated within a unified image reconstruction framework.
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List of Publications


List of abstracts


- Fotis A. Kotasidis, Julian C. Matthews, Georgios I. Angelis, William R. Lionheart Andrew, J. Reader Space variant PSF parameterization in image space using printed point source arrays on the HiRez PET/CT (Oral presentation at the IEEE/IST 2010, Thessaloniki, Greece)

- Fotis A. Kotasidis, Julian C. Matthews, Georgios I. Angelis, Bill WR. Lionheart, Andrew J. Reader Space-variant image-based resolution modeling kernels for enhanced whole-body oncology imaging with the HiRez PET/CT scanner (Oral presentation at the SNM 2010, Salt lake city, UT, USA)
- Fotis A Kotasidis, Julian C Matthews, Georgios I Angelis, Pawel J Markiewicz, Azeem Saleem, Patricia Price, William R Lionheart, Andrew J Reader Direct 4D parametric image reconstruction for improved tumour reproducibility in abdominal $[^{15}O]$ water PET-CT scans (Poster presentation at the Turku XII PET conference 2011, Turku, Finland)

- Fotis A Kotasidis, Julian C Matthews, Georgios I Angelis, Pawel J Markiewicz, William R Lionheart, Andrew J Reader Impact of erroneous kinetic parameter model formulation on direct 4D parametric image reconstruction (Oral presentation at the IEEE/MIC 2011, Valencia, Spain)

- Fotis A Kotasidis, Georgios I Angelis, Jack Henderson, Anna Buckley, Pawel J Markiewicz, Michael Green, William R Lionheart, Andrew J Reader and Julian C Matthews Evaluation of image based spatially variant and count rate dependant point spread functions on the HRRT PET scanner (Oral presentation at the IEEE/MIC 2011, Valencia, Spain)

- Georgios Angelis, Andrew Reader, Fotis Kotasidis, William Lionheart and Julian Matthews Performance of fast monotonic and new non-monotonic reconstruction algorithms for high resolution neuroreceptor PET imaging (Oral presentation at the SNM 2010, Salt lake city, UT, USA)


- Pawel J. Markiewicz, Andrew J. Reader, Georgios I. Angelis, Fotis A. Kotasidis, William R. Lionheart and Julian C. Matthews Assessment of Bootstrap Resampling Accuracy for PET Data (Poster presentation at the IEEE/MIC 2011, Valencia, Spain)
Photos

The photos at the beginning of each chapter were taken from various places I visited during this project.

Chapter 1: Highway on the way to Uppsala
Chapter 2: Isolated beach near my hometown in Greece
Chapter 3: Sunset in Copenhagen
Chapter 4: Small bay close to Seattle
Chapter 5: Blue lagoon in Reykjavik
Chapter 6: Manhattan - New York from Rockefeller building
Chapter 7: Sunset close to Eyjafjallajökull volcano
Chapter 8: Lake in the Austrian Alps