4D Reconstruction of Dynamic Studies with the Discovery NM 530c SPECT Camera

by

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Abstract

Single photon emission computed tomography (SPECT) is a nuclear medicine imaging technique. Functional imaging allows doctors to study the physiology and function of living organs. As physiological processes in a human body are dynamic, studying changes of their temporal characteristics and spatial distribution may provide important diagnostic information. This thesis investigates various aspects of dynamic functional SPECT imaging. The algorithms are tailored for a dedicated cardiac camera system, namely the GE Discovery NM530c, a pinhole camera that can acquire views from different angles simultaneously.

A fundamental feature of dynamic reconstruction is that the problem is highly underdetermined. Hence, any given consistent dataset allows infinitely many solutions. The existing dSPECT method “regularizes” the solutions by introducing constraints based on the underlying physics; it reconstructs the dynamic activity by solving one large system, as opposed to the frame-by-frame static reconstruction approach. Therefore, dSPECT reconstruction maintains temporal correlations. In this thesis, the dSPECT method was used to reconstruct images that had been scanned with the Discovery NM530c. The time activity curves of reconstructed images obtained from dSPECT are smoother than those obtained from static reconstructions. A new method, dSPECTpv, was developed to allow for successful reconstruction of dynamic behaviour that had not been observed previously in dynamic SPECT studies. Although the time activity curves of reconstructed images are much smoother, little or no improvement is observed when those reconstructions are used to estimate kinetic parameters.

In this thesis, the Discovery NM530c acquisition process was modeled with the Monte Carlo method, using the simulation software GATE. Hence, computer simulations can be used to investigate the camera geometry. Our software is a useful tool in optimizing camera setup and the acquisition protocol.

Keywords: Single photon emission computed tomography (SPECT); functional imaging; dynamic reconstruction; Monte Carlo Simulation; Discovery NM530c
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In this project, the static reconstruction code with the sensitivity map for the Discovery NM530c was provided by Dr. Glenn Wells at the University of Ottawa Heart Institute. The dSPECT method was provided by MIRG, Medical Imaging Research Group Vancouver. Dynamic pig heart data were provided by University of Ottawa Heart Institute, and the analysis by the kinetic analysis software “FlowQuant” was done at the University of Ottawa Heart Institute.
# Table of Contents

| Approval | ii |
| Abstract  | iii |
| Acknowledgements | iv |
| Table of Contents | v |
| List of Tables | vii |
| List of Figures | viii |

## Chapter 1. Outlines
1. Outline of Thesis ................................................................. 1
2. Thesis Organization ................................................................. 3

## Chapter 2. Introduction
2.1. Medical imaging, nuclear medicine and SPECT. Basic principles and applications ................................................................. 5
2.2. Functional imaging and dynamic information................................................................. 7
2.3. Dynamic SPECT, applications and traditional SPECT camera ......................................... 7
2.4. Short review of dynamic SPECT approaches ................................................................. 9
   2.4.1. Slow camera rotation ........................................................................ 10
   2.4.2. Fast camera rotation ..................................................................... 12
   2.4.3. Combination of dynamic planar acquisitions and a SPECT acquisition ........................................................................ 15
2.5. Dynamic studies of myocardial blood flow and flow reserves ....................................... 15
2.6. Discovery NM530c and why it is good for dynamic studies ........................................... 18

## Chapter 3. Tomographic reconstructions
3.1. Principles of tomographic image reconstruction: FBP, iterative reconstruction methods ................................................................. 20
   3.1.1. Projection Operator: Radon Transform .............................................. 20
   3.1.2. Analytical Reconstruction method: FBP ............................................ 23
   3.1.3. Iterative reconstruction methods ..................................................... 25
3.2. Dynamic reconstructions using dSPECT (dEM, d2EM) ..................................................... 32
   3.2.1. dEM reconstruction (Constraints on the 1st derivative) .................... 32
   3.2.2. d^2EM reconstruction (Constraints on the 2nd derivative) ............... 39
3.3. Introduction of pinhole reconstruction ........................................................................ 41

## Chapter 4. Pinhole SPECT
4.1. New cardiac camera - GE Discovery NM530c ......................................................... 42
4.2. Use of Monte Carlo methods in Nuclear Medicine ..................................................... 43
4.3. GATE simulation of the system geometry ................................................................. 44
   4.3.1. GATE version 6.2 ............................................................................. 44
   4.3.2. Modeling of Camera Geometry ....................................................... 45
   4.3.3. Tests of correctness of the camera model ...................................... 47
4.4. Development of static and dynamic reconstruction algorithms: Original version .................................................................................................................... 48
4.4.1. Original reconstruction methods ............................................................... 48
4.4.2. Simulation of Dynamic Acquisitions ....................................................... 49
4.4.3. Static reconstruction of a point source and line sources ....................... 50
4.4.4. Static reconstruction of the letter “F” shape ........................................ 53
4.4.5. Dynamic reconstruction of a line source ............................................... 55
4.4.6. Discussion ................................................................................................. 57
4.5. New Static and Dynamic Reconstruction methods with Sensitivity Map 58
4.5.1. Modification of Static reconstruction code with sensitivity map to Dynamic reconstruction ............................................................ 58
4.5.2. Reconstructions with the new static and dynamic reconstruction method ...................................................................................................... 59
4.5.3. Results ...................................................................................................... 60

Chapter 5. Dynamic Reconstructions with dSPECT using Analytical Data .... 70
5.1. Creation of analytical dynamic data in Matlab ........................................... 70
5.1.1. Process of creating dynamic data from three sources in Matlab ........... 71
5.2. Experiments and Results ............................................................................. 74
5.2.1. Reconstruction with the dSPECT method ............................................. 74
5.2.2. The dSPECT method with projection data divided into two parts ....... 81

Chapter 6. Modification of dSPECT method: dSPECTpv ............................... 88
6.1. The dSPECTpv algorithm ............................................................................. 88
6.2. Correctness of dSPECTpv method (pattern 1) ............................................. 92
6.2.1. Method: Pattern1 Dynamic activities ..................................................... 92
6.2.2. Results .................................................................................................... 94
6.3. Investigation of Capability of dSPECTpv Method (pattern2) ...................... 104
6.3.1. Method: Pattern2 dynamic activities ..................................................... 104
6.3.2. Results .................................................................................................... 106
6.3.3. Numerical Error Analysis .................................................................... 129

Chapter 7. Dynamic reconstruction with Pig data ........................................ 134
7.1. Experiment with Tc-99m ........................................................................... 134
7.2. Results for the static method and dSPECTpv method ................................ 135
7.3. Analysis with FlowQuant software ............................................................ 142

Chapter 8. Discussion, conclusion and future work ..................................... 151

References ......................................................................................................... 153
List of Tables

Table 2.1 Common radioisotopes used for nuclear medicine imaging ................................. 6
Table 5.1 Locations of three line sources .................................................................................. 71
Table 5.2 Two patterns of activity behaviours for three line sources ......................................... 72
Table 5.3 Separation of three line sources. Three line sources were divided into three regions in order to extract TACs ................................................................. 74
Table 5.4 Labeling of TACs. TACs were extracted from three regions (left, middle, right or top, middle, bottom). To compare shapes of the curves, the sums of counts in each line were normalized (divided by 3) and plotted as a “line”. ................................................................. 75
Table 5.5 Scheme of separating 19 projection data into two parts ........................................... 82
Table 6.1 Level numbers and various peak counts of sources in pattern 1 ......................... 93
Table 6.2 Level numbers and various peak counts of sources in pattern 2 ....................... 105
Table 6.3 Summary of Results with various iteration numbers for NO background
Δ: not enough iterations, Ω: reasonable, - : no further improvement ......................................................... 116
Table 6.4 Summary of Results with various iteration numbers for with background
Δ: not enough iterations, Ω: reasonable, - : no further improvement ......................................................... 128
Table 6.5 Numerical Errors from dSPECT, static and dSPECTpv methods for Pattern 1 dynamic activity ................................................................. 130
Table 6.6 Numerical Errors from the static and the dSPECTpv methods for Pattern 2 dynamic activity without background ........................................... 131
Table 6.7 Numerical Errors from the static and the dSPECTpv methods for Pattern 2 dynamic activity with background ......................................................... 132
Table 7.1 Parameter names and explanations ........................................................................ 149
List of Figures

Figure 2.1 Hawkeye Infinia, GE Healthcare ................................................................. 8
Figure 2.2 Schematic Image of Rotating camera heads of Conventional SPECT ........ 8
Figure 2.3 Two-compartment model used to fit the dynamic data using tetroxime in the heart in [Smith 1994, 1996] .................................................. 13
Figure 2.4 MBF estimation with a one-tissue-compartment model including regional blood spillover and myocardial recovery (partial volume) correction ................................................................. 17
Figure 2.5 Schematic TACs of Figure 2.5 The blue curve shows the activity of increase-decrease-then-increase ................................................................. 18
Figure 3.1 Parametrization of Radon Transform in 2D .................................................. 21
Figure 3.2 Schematic presentation of the discretized detector and the object ............. 22
Figure 3.3 The flowchart of an iterative reconstruction algorithm ............................. 30
Figure 3.4 Time difference matrix for increasing (Top left), decreasing (Top right), and increasing-then-decreasing (Bottom) with 7 time frames (the maximum occurs at time frame 3) respectively. ........................................ 37
Figure 3.5 The schematic diagrams of a peak position for (A) increasing, (B) decreasing, and (C) increasing-then-decreasing cases ............................... 39
Figure 3.6 Examples of increasing activity with concave up (left) and down (right), decreasing activity with concave up (left) and down (right) ............... 40
Figure 4.1 (A) The Discovery NM530c system, (B) schematic view of its 19 camera heads arrangement, and (C) a view of the external shield of the pinhole collimator. (GE Healthcare: www3.gehealthcare.com) ................................................................. 42
Figure 4.2 Detector geometry. The system has 5 triplets (a triplet is a column) and 4 singlets ................................................................. 45
Figure 4.3 GATE simulation of Discovery NM530c Top: The front view; Bottom: The side view; Red, blue and green dots in the images indicate the positive direction of axes ................................................................. 46
Figure 4.4 Schematic representation of the procedure that was used for creating a dynamic dataset. Using a model time activity curve (TAC), 19 equally-spaced points on a time axis were selected. The scale factor for the peak-activity was set to 1. Then, scale factors for the other 18 points were determined using the TAC. 19 new projection datasets (corresponding to 19 time frames) were created by multiplying each projection of the static dataset by the scaling factor corresponding to a particular time frame ........................................ 50
Figure 4.5 Experimental projection data of a point source from Discovery NM530c camera ......................................................................................... 51
Figure 4.6 Simulated projection data of a point source obtained from GATE. .......... 51
Figure 4.7 Profile shapes of a point source acquired by Head 9 from Discovery NM530c (left) and GATE simulation (right). ................................................................. 51
Figure 4.8 Experimental projection data of a line source on the z-axis from Discovery NM530c. ........................................................................................................ 52
Figure 4.9 Simulated projection data of a line source on the z-axis from GATE. ...... 52
Figure 4.10 Profile shapes of a line source acquired by Head 9 from Discovery NM530c (left) and GATE simulation (right). ................................................................. 52
Figure 4.11 Reconstructed point source and line source from Discovery NM530c (top low) and GATE simulation (bottom row). The reconstructions were done with our static reconstruction software. ............................... 53
Figure 4.12 Experimental projection data of “F” shaped source from Discovery NM530c .................................................................................................................. 54
Figure 4.13 Simulated projection data of “F” shaped source from GATE .......... 54
Figure 4.14 Reconstructed images of the source in the shape of letter “F”. Left column: experimental F, Right column: simulated F................................. 55
Figure 4.15 TACs obtained from the data modeling dynamic acquisition of the line source with changing activity. Black: true dynamic behavior of activity in the line source, Blue: TACs from a series of separate static reconstructions, Red: TACs from simultaneous dSPECT dynamic reconstruction.............................................................. 56
Figure 4.16 Experimental projection data of a point source from the Discovery NM530c .................................................................................................................. 61
Figure 4.17 Simulated projection data of a point source obtained from GATE .......... 61
Figure 4.18 Selected detector’s projection image and profiles: Images of projection and profiles of detector 3, 10 and 17. Top: Experimental data, Bottom: GATE simulations. Profiles were plotted by cutting the projection data with a vertical line......................................................... 62
Figure 4.19 Experimental projection data of a line source from the Discovery NM530c .................................................................................................................. 63
Figure 4.20 Simulated projection data of a line source obtained from GATE. .... 63
Figure 4.21 Selected detector’s projection image and profiles: Images of projection and profiles of detector 3, 10 and 17. Top: Experimental data, Bottom: GATE simulations. Profiles were plotted by cutting the projection data with a vertical line......................................................... 64
Figure 4.22 Reconstructed point source and line source from Discovery NM530c (top low) and GATE simulation (bottom row). The reconstructions were done with the static reconstruction software................................. 65
Figure 4.23 Experimental projection data of “F” shaped source from Discovery NM530c .................................................................................................................. 66
Figure 4.24 Simulated projection data of “F” shaped source from GATE ....................... 66
Figure 4.25 Reconstructed images of the source in the shape of letter “F”. Left column: experimental F, Right column: simulated F.................. 67
Figure 4.26 TACs obtained from the data modeling dynamic acquisition of the line source with changing activity. Black: true dynamic behavior of activity in the line source, Blue: TACs from a series of separate static reconstructions, Red: TACs from simultaneous dSPECT dynamic reconstruction.................................................................................. 69
Figure 5.1 Schematic explanation of coordinates of three line sources.......................... 71
Figure 5.2 Dynamic behaviours of sources: Pattern 1 (Left) and Pattern 2 (Right) Curves were plotted per line source. (18 voxels) ........................................ 72
Figure 5.3 Separation of three line sources: The source F are separated in 3 regions accordingly........................................................................................................ 74
Figure 5.4 Pattern 1 with High statistic data: TACs from the static reconstructions (Top) and the dynamic reconstructions (Bottom) .......................................... 76
Figure 5.5 Pattern 1 with Low statistic data: TACs from the static reconstructions (Top) and the dynamic reconstructions (Bottom) ........................................ 77
Figure 5.6 Pattern 2 with High statistic data: TACs from the static reconstructions (Top) and the dynamic reconstructions (Bottom). We notice that the increase-decrease-increase dynamic activity (green lines) was not recovered in the dynamic reconstructions. .................................................. 79
Figure 5.7 Pattern 2 with Low statistic data: TACs from the static reconstructions (Top) and the dynamic reconstructions (Bottom). We notice that the increase-decrease-increase dynamic activity (green lines) was not recovered in the dynamic reconstructions. .................................................. 80
Figure 5.8 Valley point occurs at Time frame 11 in pattern 2: Dynamic data were divided into two parts at TF 11 and 2 parts were reconstructed separately. .................................................................................................................. 81
Figure 5.9 Pattern 1 with High statistic data: TACs from dynamic reconstruction. Top: 30 iterations (left) and 60 iterations (left). Bottom Only time frames 9 to 13 were plotted for 30 iterations (left) and 60 iterations. The values of time frame 11 were plotted twice, i.e. the values from the first half and the second half were plotted. .................. 83
Figure 5.10 Pattern 1 with Low statistic data: TACs from dynamic reconstruction. Top: 30 iterations (left) and 60 iterations (left). Bottom Only time frames 9 to 13 were plotted for 30 iterations (left) and 60 iterations. The values of time frame 11 were plotted twice, i.e. the values from the first half and the second half were plotted. The disjoint parts were slightly more obvious than in High statistic data. .... 84
Figure 5.11 Pattern 2: TACs from dynamic reconstruction with high statistic data.
Top: 30 iterations (left) and 60 iterations (left). Bottom Only time frames 9 to 13 were plotted for 30 iterations (left) and 60 iterations. The values of time frame 11 were plotted twice, i.e. the values from the first half and the second half were plotted. Source 2 (green color lines) can recover the shape of true dynamic activity................................................................. 85

Figure 5.12 Pattern 2: TACs from dynamic reconstruction with low statistic data.
Top: 30 iterations (left) and 60 iterations (left). Bottom Only time frames 9 to 13 were plotted for 30 iterations (left) and 60 iterations. The values of time frame 11 were plotted twice, i.e. the values from the first half and the second half were plotted. Source 2 (green color lines) can recover the shape of true dynamic activity................................................................. 86

Figure 6.1 True dynamic behaviour of 3 sources in pattern 1 ....................... 93

Figure 6.2 True image (TF5, slice 38) and the profile of each line source for Level 0 (Highest counts) in pattern 1. The image and profiles were plotted in [0, 6.5x10^6]. In the left top figure, source1 is the left vertical line (blue), source 2 is the horizontal line, and source 3 is the right vertical line (yellow). ................................................................. 94

Figure 6.3 The bottom images of Figure 5.4 Pattern 1 with High statistic data
Dynamic reconstruction. The count is equivalent to Level 2 in this section. ........................................................................................................ 95

Figure 6.4 The bottom images of Figure 5.5 Pattern 1 with Low statistic data
Dynamic reconstruction. The count is equivalent to Level 3 in this section. ........................................................................................................ 95

Figure 6.5 TACs with counts Level 0, Top: TACs from the static reconstructions with 30 iterations (left) and 90 iterations (right), Bottom: TACs from the dynamic reconstructions with 30 iterations (left) and 90 iterations (right). No improvement was observed with more than 90 iterations for the static reconstruction and the dynamic reconstruction. ................................................................. 96

Figure 6.6 Reconstructed image (TF5, slice 38) and the profile of each line source with Level 0. Static reconstruction with 90 iterations (top) and Dynamic reconstruction with 90 iterations (bottom). The image and profiles were plotted in [0, 6.5x10^6]......................................................... 97

Figure 6.7 TACs with counts Level 1, Top: TACs from the static reconstructions with 30 iterations (left) and 90 iterations (right), Bottom: TACs from the dynamic reconstructions with 30 iterations (left) and 90 iterations (right). No improvement was observed with more than 90 iterations for the static reconstruction and the dynamic reconstruction. ................................................................. 98
Figure 6.8 Reconstructed image (TF5, slice 38) and the profile of each line source with Level 1. Static reconstruction with 90 iterations (top) and Dynamic reconstruction with 90 iterations (bottom). The image and profiles were plotted in $[0, 2 \times 10^5]$.

Figure 6.9 TACs with counts Level 2, Top: TACs from the static reconstructions with 30 iterations (left) and 60 iterations (right), Bottom: TACs from the dynamic reconstructions with 30 iterations (left) and 60 iterations (right). The TACs from the static reconstruction are the same as those in Figure 5.4 Top images.

Figure 6.10 Reconstructed image (TF5, slice 38) and the profile of each line source with count Level 2. Static reconstruction with 60 iterations (top) and Dynamic reconstruction with 60 iterations (bottom). The image and profiles were plotted in $[0, 7 \times 10^5]$.

Figure 6.11 TACs with counts Level 3, Top: TACs from the static reconstructions with 30 iterations (left) and 60 iterations (right), Bottom: TACs from the dynamic reconstructions with 30 iterations (left) and 60 iterations (right). The TACs from the static reconstruction are the same as those in Figure 5.5 Top images.

Figure 6.12 Reconstructed image (TF5, slice 38) and the profile of each line source with count Level 3. Static reconstruction with 60 iterations (top) and Dynamic reconstruction with 60 iterations (bottom). The image and profiles were plotted in $[0, 1.7 \times 10^5]$.

Figure 6.13 True dynamic behaviour of 3 sources in pattern 2.

Figure 6.14 True image (TF5, slice 38) and the profile of each line source. The image and profiles were plotted in $[0, 6.5 \times 10^5]$. In the left top figure, source 1 is the left vertical line (blue), source 2 is the horizontal line, and source 3 is the right vertical line (yellow). In the right top figure, the profile of source 1 is non-uniform. This is because a part of source 2 is included in the left edge.

Figure 6.15 TACs with counts Level 0, Top: TACs from the static reconstructions with 30 iterations (left) and 90 iterations (right), Bottom: TACs from the dynamic reconstructions with 30 iterations (left) and 150 iterations (right). No improvement was observed with more than 90 iterations for the static reconstruction and 150 iterations for the dynamic reconstruction.

Figure 6.16 Reconstructed image (TF5, slice 38) and the profile of each line source for L0. Static reconstruction with 90 iterations (top) and Dynamic reconstruction with 150 iterations (bottom). The image and profiles were plotted in $[0, 6.5 \times 10^5]$.

Figure 6.17 TACs with counts Level 1 Top: TACs from the static reconstructions with 30 iterations (left) and 90 iterations (right), Bottom: TACs from the dynamic reconstructions with 30 iterations (left) and 150 iterations (right).
Figure 6.18 Reconstructed image (TF5, slice 38) and the profile of each line source for L1. Static reconstruction with 90 iterations (top) and Dynamic reconstruction with 150 iterations (bottom) The image and profiles were plotted in $[0, 15\times 10^5]$. .................................................. 111

Figure 6.19 TACs with counts Level 2 Top: TACs from the static reconstructions with 30 and 60 iterations, Bottom: TACs from the dynamic reconstructions with 30 and 60 iterations (right). The TACs from the static reconstruction are the same as those in Figure 5.6 Top images. .................................................................................................. 112

Figure 6.20 The reconstructed image (TF5 slice 38) and the profile of each line source for L2. Static reconstruction with 60 iterations (Top), Dynamic reconstruction with 60 iterations (bottom) scale: $[0, 5.5\times 10^5]$. .................................................................................................. 113

Figure 6.21 TACs with counts Level 3 left: TACs from the static reconstructions with 30 and 60 iterations (top), TACs from the dynamic reconstructions with 30 and 60 iterations. The TACs from the static reconstruction are the same as those in Figure 5.7 Top images. .................................................................................................. 114

Figure 6.22 The reconstructed image (TF5 slice 38) and the profile of each line source for L3. Static reconstruction with 30 iterations (Top), Dynamic reconstruction with 60 iterations (bottom). The image and profiles were plotted in $[0, 1.5\times 10^5]$. ................................................ 115

Figure 6.23 Left: True dynamic activities for Source 1 (red), 2 (green) and 3 (blue). Background (black line) is set such that the count per voxel is 1/10 of the highest count of source 1. The true time activity curves are plotted for 6 voxels, thus the peak counts decrease to 1/3 of the ones mentioned above as well as background. Right: The values of the location of letter F were as 0 in background. ....................................................................................... 117

Figure 6.24 Background. Background was created around the source of letter F. The voxels of the source location were set as the value of 0, and the rest was set as some value. Top left: Box as background, Top Right: the xz-plane view, Bottom Left: the xy-plane view, Bottom Right: the yz-plane view. ....................................................................... 118

Figure 6.25 True image (Time Frame 5, slice 38) and the profile of each line source with background: The image and profiles were plotted in $[0, 6.5\times 10^5]$. .................................................................................................. 119

Figure 6.26 L0 High Counts projection data with Background Top: TACs from the static reconstructions with 30 iterations (left) and 150 iterations (right), Bottom: TACs from the dynamic reconstructions with 30 iterations (left) and 300 iterations (right). .................................................. 120

Figure 6.27 Reconstructed images (Time Frame 5 slice 38) and profiles of each line sources for L0: The static reconstruction with 150 iterations and the dynamic reconstruction (bottom) with 300 iterations. The image and profiles were plotted in $[0, 3\times 10^6]$. .................................................. 121
Figure 6.28 L1 (1/4 of the highest counts) data with Background Top: TACs from the static reconstructions with 30 iterations (left) and 150 iterations (right), Bottom: TACs from the dynamic reconstructions with 30 iterations (left) and 300 iterations (right). ............................................... 122

Figure 6.29 Reconstructed images (Time Frame 5 slice 38) and profiles of each line sources for L1 from the static reconstruction with 150 iterations and the dynamic reconstruction (bottom) with 300 iterations. The image and profiles were plotted in [0, 8x10^5] ................. 123

Figure 6.30 L2 (1/10 of the highest counts) data with Background. Top: TACs from the static reconstructions with 30 iterations (left) and 150 iterations (right), Bottom: TACs from the dynamic reconstructions with 30 iterations (left) and 210 iterations (right). .................................. 124

Figure 6.31 Reconstructed images (Time Frame 5 slice 38) and profiles of each line sources for L2 from the static reconstruction with 150 iterations and the dynamic reconstruction (bottom) with 210 iterations. The image and profiles were plotted in [0, 2.8x10^5] .............. 125

Figure 6.32 L3 (1/40 of the highest counts) data with Background. Top: TACs from the static reconstructions with 30 iterations (left) and 120 iterations (right), Bottom: TACs from the dynamic reconstructions with 30 iterations (left) and 210 iterations (right). .................................. 126

Figure 6.33 Reconstructed images (Time Frame 5 slice 38) and profiles of each line sources for L3 from the static reconstruction with 120 iterations and the dynamic reconstruction (bottom) with 210 iterations. The image and profiles were plotted in [0, 6.5x10^4] .............. 127

Figure 6.34 Error plot of Table 6.5 Left: level 0, Middle: Level 2, Right: Level 3, Red: dSPECT, Blue: Static, Green: dSPECTpv. ................................... 130

Figure 6.35 Error plot for Table 6.6 Left: level 0, Middle: Level 2, Right: Level 3, Blue: Static, Green: dSPECTpv. ............................................................ 131

Figure 6.36 Error plot for Table 6.7 Left: level 0, Middle: Level 2, Right: Level 3, Blue: Static, Green: dSPECTpv. ............................................................. 132

Figure 7.1 The ROI used to extract TACs. The 3-by-3-by-3 voxels [ (x, y, z) = (44:46, 44:46, 29:31) ] was indicated in the red circle. ......................... 135

Figure 7.2 Time Activity curves and Reconstructed images of 75% counts of the original data; Top: TACs from static (blue) and dynamic (red) reconstructions, Bottom: Reconstructed image (Time frame 17, slice 35 to 38) from static (left, scale in [0, 36000]) and dynamic (right, scale in [0, 3000]) reconstructions .................................................. 136

Figure 7.3 Time Activity curves and Reconstructed images of 50% counts of the original data; Top: TACs from static (blue) and dynamic (red) reconstructions, Bottom: Reconstructed image (Time frame 17, slice 35 to 38) from static (left, scale in [0, 36000]) and dynamic (right, scale in [0, 3000]) reconstructions .................................................. 137
Figure 7.4 Time Activity curves and Reconstructed images of 25% counts of the original data, Top: TACs from static (blue) and dynamic (red) reconstructions, Bottom: Reconstructed image (Time frame 17, slice 35 to 38) from static (left, scale in [0, 18000]) and dynamic (right, scale in [0, 1500]) reconstructions............................................... 138

Figure 7.5 Time Activity curves and Reconstructed images of 12.5% counts of the original data, Top: TACs from static (blue) and dynamic (red) reconstructions, Bottom: Reconstructed image (Time frame 17, slice 35 to 38) from static (left, scale in [0, 9600]) and dynamic (right, scale in [0, 800]) reconstructions................................................. 139

Figure 7.6 Time Activity curves and Reconstructed images of 6.25% counts of the original data, Top: TACs from static (blue) and dynamic (red) reconstructions, Bottom: Reconstructed image (Time frame 17, slice 35 to 38) from static (left, scale in [0, 4800]) and dynamic (right, scale in [0, 400]) reconstructions................................................. 140

Figure 7.7 Time Activity curves and Reconstructed images of 3.125% counts of the original data, Top: TACs from static (blue) and dynamic (red) reconstructions, Bottom: Reconstructed image (Time frame 17, slice 35 to 38) from static (left, scale in [0, 2400]) and dynamic (right, scale in [0, 200]) reconstructions................................................. 141

Figure 7.8 MBF estimation with a 1-tissue-compartment model: 75% of the original Top: Static reconstruction, Bottom: Dynamic reconstruction........................................................................................ 143

Figure 7.9 MBF estimation with a 1-tissue-compartment model: 50% of the original Top: Static reconstruction, Bottom: Dynamic reconstruction........................................................................................ 144

Figure 7.10 MBF estimation with a 1-tissue-compartment model: 25% of the original Top: Static reconstruction, Bottom: Dynamic reconstruction........................................................................................ 145

Figure 7.11 MBF estimation with a 1-tissue-compartment model: 12.5% of the original Top: Static reconstruction, Bottom: Dynamic reconstruction........................................................................................ 146

Figure 7.12 MBF estimation with a 1-tissue-compartment model: 6.25% of the original Top: Static reconstruction, Bottom: Dynamic reconstruction........................................................................................ 147

Figure 7.13 MBF estimation with a 1-tissue-compartment model: 3.215% of the original Top: Static reconstruction, Bottom: Dynamic reconstruction........................................................................................ 148

Figure 7.14 Parameters and Error plots........................................................................ 150
Chapter 1.

Outlines

1.1. Outline of Thesis

The goal of this project is to improve the accuracy of dynamic studies of the heart using a new dedicated cardiac camera, namely the GE Discovery NM530c. The camera head of Discovery NM530c does not rotate during the data acquisition, subsequently, data are consistent for each time frame. However with the static reconstruction method, data for each time frame are reconstructed independently, thus, the relationship between time frames may be lost. In contrast, the dSPECT method reconstructs all time frames simultaneously. A focus of our research is to investigate the differences in the reconstructed images when each time frame is reconstructed separately and when all time frames are reconstructed simultaneously.

This thesis contains several components. First, the geometry of the Discovery NM530c system was modelled in Monte Carlo simulation software GATE and the camera geometry and the process of data acquisition were examined. In the meantime, our own static reconstruction method for Discovery NM530c was developed, since the manufacturer’s reconstruction code was proprietary. Then, the static reconstruction method was modified to process multiple time-frames of dynamic acquisitions.

However, our static and dynamic reconstruction methods developed for Discovery NM530c did not include a sensitivity map. Both these static and dynamic methods were able to capture general features of the camera system. To obtain more accurate reconstructed images, however, we decided to modify a “static reconstruction code with sensitivity map” for this camera system to handle dynamic reconstructions by adapting the dSPECT mechanism.
Throughout the thesis except Chapter 4, analytical data from Matlab were used for the experiments instead of projection data from GATE simulations. This was because analytical data in Matlab were faster and easier to create/obtain, and easier to modify than Monte Carlo simulations. For example, with Monte Carlo software, it took 58 hours (2.5 days) to obtain projection data for a line source (radius 0.4mm, length 45mm, and the activity 14.1MBq) for a 5 minutes simulation.

Then, the dynamic reconstruction method, dSPECT was tested using analytical data with various dynamic activities in order to investigate its capability and limitations. At this stage, it was discovered that some voxels in cardiac studies have an activity that increases at first, decreases and then increases again. Because of the constraints used in the dSPECT method, such an activity cannot be reconstructed accurately, and hence modifications of the method were required. At first, we divided the dynamic projection data into two parts and reconstructed them separately. This approach was easy and straightforward as it did not require a modification of the method, and we used a-priori knowledge of the shape of the time-activity curve. For a much more robust approach, a new reconstruction algorithm, dSPECTpv, was developed to handle a special dynamic radiotracer distribution of increasing-decreasing-then-increasing behaviour that was observed in dynamic studies of the heart.

Lastly, the new reconstruction method dSPECTpv was used for dynamic cardiac studies with pig heart data.

My contribution to this project was to model the camera geometry of Discovery NM530c using Monte Carlo simulation. It helped us to understand the geometry and data acquisition process of the camera system. At the same time, our own static and dynamic reconstruction codes for this camera system were developed.

The static reconstruction method with the sensitivity map was modified to a dynamic reconstruction method by adapting the dSPECT mechanism. As well, I developed the new dSPECTpv algorithm, and we used this algorithm in our animal studies.
1.2. Thesis Organization

This thesis is divided into the following chapters:

CHAPTER 2 – INTRODUCTION

In this chapter, the fundamental concept of medical imaging, nuclear medicine, SPECT, its basic principles and applications, as well as functional imaging and current dynamic SPECT applications are discussed. A short review of dynamic SPECT approaches and dynamic studies of myocardial blood flow and flow reserves are presented.

CHAPTER 3 – TOMOGRAPHIC RECONSTRUCTIONS

Principles of tomographic image reconstruction are described. The mathematical models and image reconstruction methods used in SPECT imaging are presented in this section. Dynamic reconstruction with the dSPECT method is discussed in detail, and pinhole camera reconstruction is discussed.

CHAPTER 4 – PINHOLE SPECT

In this chapter, the characteristic of a new dedicated cardiac camera Discovery NM530c are discussed in detail. The use of Monte Carlo method in nuclear medicine is briefly discussed and geometry model of the Discovery NM530c are explained. Using data obtained from the modeled camera geometry in GATE, which is a Monte Carlo software, static reconstructions are performed. As well, dynamic data are created from the simulated data and dynamic reconstructions are performed. Then, a new static reconstruction method with sensitivity map is modified to fit dynamic reconstructions by adapting the dSPECT method. The experimental data and the data from GATE simulation are reconstructed with this new method, and results are compared.

CHAPTER 5 – DYNAMIC RECONSTRUCTIONS WITH DSPECT METHOD USING ANALYTICAL DATA

Capabilities and limitations of the conventional dSPECT method are evaluated. Several experiments are done with the dSPECT method using analytical data that are created in
Matlab. As explained, Monte Carlo simulation is time consuming, thus analytical data created in Matlab are used for experiments except for the experiments in Chapter 4. The results of this chapter motivate us to modify the conventional dSPECT method so it can handle increasing-decreasing-then-increasing activity.

CHAPTER 6– MODIFICATION OF DSPECT METHOD

A modified dSPECT method, called dSPECTpv, is presented. The design and implementation of a modified algorithm are explained. The correctness of the dSPECTpv method is tested and the performance is assessed with analytical source data with and without background. The numerical error analyses for the static, the dSPECT and the dSPECTpv methods are included.

CHAPTER 7– DYNAMIC RECONSTRUCTIONS WITH PIG DATA

In this chapter, the series of static reconstruction method and the modified dSPECT method (dSPECTpv) are used to reconstruct real data (pig heart data) acquired with the Discovery NM530c. The purpose of this investigation is to see the differences in the reconstructed images when each time frame is reconstructed separately and when all time frames are reconstructed simultaneously. The performance of both methods are compared by analyzing TACs and examining the reconstructed images. As well, the FlowQuant software [Klein 2010a] is used to analyze the reconstructed images quantitatively, and the results are examined.

CHAPTER 8 – DISCUSSIONS, CONCLUSIONS AND FUTURE WORK

The findings in this thesis are summarized. As well, future works to be conducted are included.
Chapter 2.

Introduction

2.1. Medical imaging, nuclear medicine and SPECT. Basic principles and applications

Medical imaging is a technique to visualize the interior of a body for research and medical diagnostic purposes. Medical imaging can be broadly classified into two categories: anatomical imaging which tells how something looks, and physiological or functional imaging which tells how something works. Modalities of medical imaging used for anatomical imaging are, for example, X-ray, computed tomography (CT), and magnetic resonance imaging (MRI), and modalities used for functional imaging are, for example, single photon emission computed tomography (SPECT) and positron emission tomography (PET), both are nuclear medicine imaging techniques.

Nuclear medicine uses radioactive substances for the diagnosis and treatment of disease. In nuclear medicine, a radiopharmaceutical is injected, taken orally, or inhaled in the human body. A radiopharmaceutical is a radioactive substance, which contains a small amount of radioactive isotope, but has no pharmacological effect. It is a chemical compound in which one or more atoms are replaced by radioisotope atoms, so that it can be localized in the body by detecting its radioactive emissions. About 95% of nuclear medicine procedures are used for diagnostic purposes, of which medical imaging is about 90% and non-imaging 10%; the remaining 5% are therapeutic uses.

For nuclear medicine imaging, the radiation emitted from the radiopharmaceutical injected into the patient body is detected by a special camera, and the acquired data or reconstructed images are used for diagnostic purposes. For therapeutic use, much larger amounts of radiative materials are injected to kill cancerous cells, reduce the size of a tumour, or reduce pain. Ideally, therapy planning should include dosimetry calculations to
determine optimal radiation doses for each individual patient, as the knowledge of radiation dose received by different organs in each individual body is crucial to evaluate risks and benefits of radionuclide therapy procedures.

When nuclear medicine imaging is used for diagnosis, its objective is to examine functions and structures of organs and tissues in the human body. When the radiotracer is introduced into the body, it is supposed to act like a chemical substance that the human body usually uses. Therefore, the body tissue takes it up or washes it out, during which time the radioactive isotope emits electromagnetic (gamma) radiation which is detected by a camera. The type of radiotracer used for medical imaging depends on the tissues or organs being examined.

<table>
<thead>
<tr>
<th>Isotopes</th>
<th>Symbol</th>
<th>Half-Life</th>
<th>Primary Imaging Gamma energy (keV)</th>
<th>Technique</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbon-11</td>
<td>$^{11}$C</td>
<td>20.3 m</td>
<td>511</td>
<td>PET</td>
</tr>
<tr>
<td>Fluorine-18</td>
<td>$^{18}$F</td>
<td>110 m</td>
<td>511</td>
<td>PET</td>
</tr>
<tr>
<td>Gallium-67</td>
<td>$^{67}$Ga</td>
<td>78.2 h</td>
<td>93, 185</td>
<td>SPECT</td>
</tr>
<tr>
<td>Indium-111</td>
<td>$^{111}$In</td>
<td>67.2 h</td>
<td>171, 245</td>
<td>SPECT</td>
</tr>
<tr>
<td>Iodine-123</td>
<td>$^{123}$I</td>
<td>13.3 h</td>
<td>159</td>
<td>SPECT</td>
</tr>
<tr>
<td>Nitrogen-13</td>
<td>$^{13}$N</td>
<td>9.97 m</td>
<td>511</td>
<td>PET</td>
</tr>
<tr>
<td>Oxygen-15</td>
<td>$^{15}$O</td>
<td>2.0 m</td>
<td>511</td>
<td>PET</td>
</tr>
<tr>
<td>Rubidium-82</td>
<td>$^{82}$Rb</td>
<td>1.27 m</td>
<td>511</td>
<td>PET</td>
</tr>
<tr>
<td>Technetium-99m</td>
<td>$^{99m}$Tc</td>
<td>6.02 h</td>
<td>140</td>
<td>SPECT</td>
</tr>
<tr>
<td>Thallium-201</td>
<td>$^{201}$TI</td>
<td>72.9 h</td>
<td>71, 167</td>
<td>SPECT</td>
</tr>
<tr>
<td>Xenon-133</td>
<td>$^{133}$Xe</td>
<td>125.8 h</td>
<td>81</td>
<td>SPECT</td>
</tr>
</tbody>
</table>

Table 2.1 Common radioisotopes used for nuclear medicine imaging

There are several techniques in nuclear medicine imaging. For instance, scintigraphy forms two-dimensional images (planar); in contrast, single photon emission computed tomography (SPECT) and positron emission tomography (PET) form three-dimensional images. Planar scintigraphy and SPECT use radioisotopes emitting gamma radiation, while PET detects annihilation photons coming from isotopes decaying with
emission of positrons. Radioactive isotopes commonly used for nuclear medicine imaging are listed in Table 2.1, together with their half-life and energies of gamma emissions.

2.2. Functional imaging and dynamic information

Functional imaging is a method which allows doctors to study physiology and functions of a living organism. In particular, it can be used to study metabolism or blood flow by measuring changes of regional distribution of chemical compounds in-vivo. As physiological processes in the human body are dynamic, imaging techniques that can detect temporal changes of distribution of radioactive tracers can provide important functional information and enable health care practitioners to give a more accurate diagnosis than when using only static imaging methods.

2.3. Dynamic SPECT, applications and traditional SPECT camera

As mentioned above, studying changes of tracers’ temporal characteristics may provide important diagnostic information. For example, performing quantitative dynamic imaging of myocardial blood flow (MBF) and myocardial flow reserve (MFR, which is the ratio of the blood flow at stress to the blood flow at rest) can potentially improve the diagnosis of heart disease. [Celler et al 2015]

Dynamic imaging can be performed by using the PET technology. An important advantage of PET imaging over SPECT imaging is its higher sensitivity. As well, due to the structure of the PET equipment, it can acquire projection data of 360-degree view simultaneously around the patient. Dynamic PET imaging is used in studies of reducing respiratory motion artifacts of lung cancer [Sadek 2003], investigating the use of one-compartment model of Rb-82 kinetics for the quantification of myocardial blood flow [Lortie 2007], investigating the use of Carbon-11-acetate as a metabolic tracer for renal disease [Shreve1995] and quantifying β-amyloid plaques in the mouse model of Alzheimer’s disease. [Toyama 2005]. While PET is suited to dynamic studies, there are several challenges in its clinical use. These challenges include the higher cost of the PET
equipment compared to SPECT cameras, and the necessity of a cyclotron to produce radioactive tracers for the PET scan. The most popular radiotracer for cardiac PET is Rubidium-82 which does not require a cyclotron as it is generator produced. However, it is expensive so a high volume of cardiac studies is required to rationalize the costs. As a result, the SPECT system is more widely used in hospitals. Therefore, the possibility of dynamic imaging performed by SPECT equipment is advantageous and profitable.

Figure 2.1 Hawkeye Infinia, GE Healthcare

Figure 2.2 Schematic Image of Rotating camera heads of Conventional SPECT

However, in reality, dynamic SPECT studies are rarely performed in a clinic setting. This is because a conventional SPECT camera has to rotate around a patient to acquire
a complete dataset, unlike a PET system that can acquire projection data from all angles at same time, as mentioned above. A complete dataset provides projection data that cover at least a 180-degree view of the patient and that is what is required for reconstruction of a tomographic image. Thus, if the activity distribution changes in a dynamic object (in this case - in the human body) during the camera rotation, the camera at each position captures a different activity distribution, and this results in what is called an inconsistent dataset. Figure 2.1 shows a conventional dual-head SPECT camera (Hawkeye Infinia, GE healthcare). During data acquisition the camera heads rotate around the patient. Figure 2.2 shows a schematic image of conventional SPECT camera rotation.

The problem of inconsistent projections would not exist if all projections necessary for image reconstruction could be acquired simultaneously. Such a situation occurs in PET and some special-geometry SPECT cameras. In particular, in 2009, GE Healthcare introduced a dedicated cardiac system, the Discovery NM530c. The important feature of this system is that the camera does not rotate during data acquisition. As there is no detector or collimator movement during the scan, the system can simultaneously collect data from about a 180 degree angular range, hence temporal inconsistency due to camera rotation is prevented.

2.4. Short review of dynamic SPECT approaches

There are several approaches to dynamic SPECT studies. Dynamic SPECT methods are mainly classified into two methods: one that employs slow camera rotation and another that requires fast camera rotation. We define slow camera rotation when the time of acquisition of a complete dataset is comparable or longer to the temporal changes of the radioactive tracer distribution. On the other hand, fast camera rotation means that the acquisition is fast relative to the temporal changes of the radioactive tracer distribution. A different approach could be a mixture of these two methods, such as the combination of series of fast dynamic planar acquisitions followed by a static SPECT acquisition method.
2.4.1. Slow camera rotation

In slow camera rotation dynamic SPECT method, the changes of the radioactive tracer distribution in the object are rapid compared to the time required for data acquisition. Therefore, the data acquired with this method have inconsistencies. Thus, when these data are reconstructed using the standard static system matrix, there are more unknowns than equations. The result is an underdetermined system of equations, hence additional information is required to help the user to select one of many possible solutions. That is, constraints are required for the reconstruction process. Mathematically, this is referred to as regularization.

One method [Limber et al 1995] used a dual exponential function to restrict the possible solutions, assuming that the temporal behaviour of the tracer is described by a dual exponential model. In this method, the activity in each pixel is modelled as a parameterized function of time, and the parameters of the time-activity curve in each pixel are recovered directly from the projection data. An explicit exponential functional form for time activity distribution for each pixel is modelled as

\[ x_i(t) = A_i e^{-\lambda_i t} + B_i e^{-\eta_i t} + C_i, \quad (2.1) \]

where \( x_i \) is the number of photons detected from the \( i \)\(^{\text{th}} \) region of the interest at time \( t \) and \( A_i, B_i, C_i, \lambda_i, \text{ and } \eta_i \) are constants to be determined. To see if accurate time activity curves are recovered with this method, analytically generated data were used to simulate spatiotemporal changing activity distributions. The disadvantages of this method are that assuming only two exponential modes may not be realistic to describe complex physiology; and that the method requires finding a solution to a non-linear optimization problem, which is more complicated than linear optimization.

The linearized version of the above method was developed in [Hebber et al 1997]. He assumed \( a(x,y,t) \) to be a time dependent tracer distribution model under reconstruction, and \( d_i(t_j) \) the projection data collected in bin \( i \) at time \( j \). Then, the relationship between the tracer distribution and projection data can be mathematically written as the Radon transform:
where $c_i$ is the $i^{th}$ ray, and $a$ is built from a basis of exponentials as in a Laplace transform:

$$a(x,y,t) = \int_0^\infty m(x,y,\lambda)e^{-\lambda t}d\lambda.$$  

(2.3)

By substituting (2.3) into (2.2), we get:

$$d_i(t_j) = \int_{c_i} \int_0^\infty m(x,y,\lambda)e^{-\lambda t_j}d\lambda dl.$$  

(2.4)

The equation (2.4) is a linear integral equation of the first kind for $m(x,y,\lambda)$ [Hebber et al 1997], and the nonlinearity of finding dynamic parameters $\lambda$ in the previous method is replaced by finding a value of $m(x,y,\lambda)$.

Instead of using a specific model to describe changes of the radiotracer distribution, another approach imposes constraints on the temporal behaviour of this distribution. The dSPECT method [Farncombe 1999] uses temporal constraints on each voxel to link its activity though all time frames assuming that the distribution of the radioactive tracer in each time frame changes smoothly over time. The activity in each voxel may be independently increasing, decreasing or increasing-then-decreasing. This method solves a set of linear equations where the sign of the first derivative of every time activity curve of each voxel is allowed to change at most once. Section 3.2 provides a detailed description of this method.

The modification of dSPECT, namely d2EM, was introduced in [Humphries 2011]. This approach imposes stronger constraints than dSPECT so that the time activity curves (TAC) in each voxel will be smooth.

Yet another approach uses a factor analysis (FA) of the data in which factors and factor coefficients are determined directly from the projection data [Sitek et al 2000, Sitek et al 2001]. This method does not require any kinetic model.
2.4.2. Fast camera rotation

With fast camera rotation methods, the camera rotates fast enough for the distribution of radioactive tracer in the object, so that the distribution of radioactive tracer can be considered constant over the time required for acquisition of each complete dataset. Therefore, projection data may be assumed to be consistent over each camera rotation. In order to obtain the projection data within a very short time, triple-head camera systems have been used as they have higher sensitivity than single-head or double-head systems. In clinics, however, mostly double-head cameras are used.

Dynamic imaging requires obtaining a series of complete datasets, and each dataset corresponds to one time frame. To acquire temporal information, the camera rotates multiple times and projection data acquired during each rotation are reconstructed (by using a static reconstruction algorithm) separately forming a time-series of images. It is important to note that when images are reconstructed time-frame by time-frame with a static reconstruction algorithm, correlations between time frames are ignored during the reconstruction even though these correlations may provide us with meaningful and critical information.

There are several approaches to perform dynamic SPECT studies with data acquired using fast camera rotation. One approach is to extract time activity curves from a series of reconstructed images and use them to obtain kinetic parameters of the compartment model. A compartment model is a description of the processes in the body that uses a collection of compartments, where compartments represent different states of a tracer and its metabolites and reflect biological processes. By using a compartment model, tracer kinetic analysis can be performed using the following series of steps:

1. Select the compartment model for your problem
2. Define physiological parameters to be determined
3. Use tracer which follows physiology but does not alter the system
4. Measure tracer concentrations relevant to the problem
5. Apply mathematics of the appropriate compartmental model
6. Generate kinetic parameters corresponding to the model
7. Compare with normal values and make a diagnosis
Several mathematical compartment models have been proposed and clinically used. The number of compartments used depends on the chemical and biological properties of radioligand [Watabe 2006]. The simplest model involves two parameters, a single-tissue (or two compartments) compartment model. A single-tissue compartment model is in some cases sufficient to describe the kinetics of ligand. But more complex models, such as a two-tissue (or three compartments) model and three-tissue (or four compartments) compartment mode are also used.

Figure 2.3 shows the two-compartment model that was employed in a cardiac perfusion study in [Smith 1994,1996]. Investigation of myocardial perfusion was performed by sampling of time activity curves in the region of interest (ROI), and those curves were fit to a two-compartment model. The parameter B(t) corresponds to tracer concentration in the blood compartment and C(t) in the extravascular space. The model assumes that (1) the TACs of the blood compartment can be measured independently of the extravascular compartment, (2) all tissue has the same TACs, (3) the tracer distribution is uniform throughout the regions, and (4) the tissue region contains only blood and extravascular compartments.

\[ \text{Figure. 2.3 Two-compartment model} \]

used to fit the dynamic data using teboroxime in the heart in [Smith 1994, 1996]

In this model the activity concentration C(t) in the extravascular compartment is given by the first order ordinary differential equation
\[
\frac{d}{dt} C(t) = k_{21} B(t) - k_{12} C(t)
\]  

(2.5)

which describes the kinetic exchange for the compartment model shown in Figure 2.3. The parameters $k_{21}$ and $k_{12}$ are wash-in and wash-out rate constants, respectively, to be estimated in the experiment. In [Smith 1994, 1996], $^{99m}$Tc-labeled teboroxime and a three-detector SPECT camera were used in imaging studies of a canine model. This differential equation can be solved in terms of $C(t)$ as follow:

\[
C(t) = k_{21} e^{-k_{12}t} \otimes B(t)
\]

(2.6)

where $\otimes$ represents the convolution operation.

Likewise, studies of myocardial perfusion was performed in four canines using Thallium-201. The imaging was done on a three-head gamma camera equipped with fan bean collimators, and the dynamic data were fit to a two-compartment model in [Khare 2001]. More recent work of these studies was done in human patients using a dual-head SPECT/CT scanner with $^{99m}$Tc-sestamibi. [Hsu 2014]

Images reconstructed from fast camera rotation acquisitions were used to estimate kinetic parameters using a three-compartment model. $^{123}$I iomazenil was injected into six healthy male volunteers to compute brain ligand transport and receptor binding using triple-head rotating gamma camera. [Onish 1996]

Another approach used in a number of studies is to calculate kinetic parameters directly from projection data without reconstructing images. For example, in order to simultaneously estimate physiological parameters and myocardial boundaries, an “observation model” [Chiao 1994] which relates parameters of interest to the projection data and measured noise was constructed and a maximum likelihood estimator was used to estimate parameters directly from the projection data. In another example four-dimensional spatiotemporal estimation of $^{99m}$Tc teboroxime distribution directly from projections was performed using a spatial segmentation and temporal B-splines [Reutter 2000].
The disadvantage of the fast camera rotation method is that the images reconstructed using this approach suffer from low signal-to-noise ratio due to extremely low counts in the projection data. However, this approach has been used in several clinical studies to investigate not only myocardial perfusion [Smith 1994, 1996] and brain receptors [Onishi 1996], but also myocardial fatty acid metabolism with $^{99m}$Tc tetrofosmin and $^{123}$I-BMIPP [Okizaki 2007], encephalitis (common brain infection) with $^{99m}$Tc methyl cysteinate dimer (Tc-ECD) [Kataoka 2007] as well as pulmonary function using Xenon-133 gas washout [Suga 1996], renal plasma flow in kidney with $^{99m}$Tc MAG3 [Akahira 1999] and renal function in kidney with $^{99m}$Tc DTPA [Miyazaki 2010].

2.4.3. Combination of dynamic planar acquisitions and a SPECT acquisition

An approach that avoids temporal constraints which are necessary with slow camera rotation or the need for higher temporal sampling which is used with fast camera rotation, is to use a combination of dynamic planar acquisitions followed by a static SPECT acquisition. This method is employed when the uptake of a radiotracer in the body is rapid and the washout is slow. In the fast tracer uptake phase, a two-dimensional scan can be used, followed by the three dimensional SPECT acquisition in the phase of the slow tracer washout. In [Sugihara 2001] myocardial blood flow was calculated with this approach using technetium99m tetrofosmin. In [Daniele 2011], the diagnostic value of coronary flow reserve was assessed in 106 patients with this approach using Tc-99m sestamibi. However, one of the disadvantages of this approach is that it is not possible to accurately quantify data from planar acquisition.

2.5. Dynamic studies of myocardial blood flow and flow reserves

The dynamic exchange of activity between atrial blood and myocardial tissue can be described using a compartment model [Klein 2010b]. The activity concentrations for the arterial blood and the myocardial tissue are expressed as a function of time, $C_A(t)$ and $C_M(t)$. 
and $C_i(t)$, respectively, and $k_{21}$ is the uptake rate of the radioactive tracer from blood to
tissue, and $k_{12}$ is the washout rate in the reverse direction. (See Figure 2.3) $C_m(t)$ is the
concentration measured in the myocardium and, due to limited spatial resolution of the
measuring equipment, is assumed to consist of a mixture of both arterial blood and
myocardial tissue activities.

As explained in Equations 2.5 and 2.6 in Section 2.4.2, the tracer kinetics can be
represented mathematically by the differential equation

$$\frac{dC_i(t)}{dt} = k_{21} \cdot C_b(t) - k_{12} C_i(t), \quad (2.7)$$

and $C_i(t)$ can be obtained as

$$C_i(t) = k_{21} e^{-k_{12}t} \otimes C_b(t). \quad (2.8)$$

The TACs of $C_b(t)$ and $C_m(t)$ are commonly measured in a series of dynamic images by
sampling activities in ROIs defined in the left atrium blood cavity and the myocardium. The
assumptions for $C_b(t)$ and $C_m(t)$ are that $C_b(t)$ consists of pure arterial blood activities,
and $C_m(t)$ consists of both arterial blood and myocardial tissue activities. The reasons for
$C_m(t)$ consisting of two components activities are: 1) that there can be spillover from
arterial blood in the ventricles into myocardium tissues; this is because of spill-in from the
right ventricle (RV), however spill-in also occurs more importantly from the left ventricle
(LV), and 2) from the presence of capillaries throughout the myocardial tissues such that
any ROI physically contains vessels filled with blood. Thus $C_m(t)$ can be expressed as

$$C_m(t) = FBV \cdot C_b(t) + RC \cdot C_i(t), \quad (2.9)$$

where FBV is referred to as the fractional blood volume, which includes activities
associated with the spillover from arterial blood and the fractional content of blood vessels
within the myocardium, and RC is referred to as the recovery coefficient. Further details
can be found in [Klein 2010b].
For MBF analysis, using the blood curve $C_b(t)$ estimated from the LV as the arterial input function, the dynamic image data are fed into the kinetic analysis software called “FlowQuant” [Klein 2010a], a clinical research tool for quantifying MBF developed at the University of Ottawa Heart Institute. Figure 2.4 is an example of the output plot from FlowQuant.

**Figure 2.4** MBF estimation with a one-tissue-compartment model including regional blood spillover and myocardial recovery (partial volume) correction

In Figure 2.4, the red solid curve is the blood activity concentration measured in the series of dynamic images, and the red dashed curve is the plasma activity concentration. The blue points are the measured samples of the TAC from a region in the myocardium, the solid blue line is a fit to the blue points. The green points are the residuals of the difference between the measured blue points and the fitted blue curve. The cyan curve is the one-compartment fit for the “pure” myocardium TAC. In Figure 2.4, the shape of TAC of the myocardium (the solid blue curve) is increasing-decreasing-then-increasing due to the contribution from arterial blood to measured concentration $C_m(t)$. In order to view the curves clearly, the schematic TACs in red, blue and cyan colors are drawn in Figure 2.5. More details can be found in [Klein 2010b].
Figure 2.5 Schematic TACs of Figure 2.5 The blue curve shows the activity of increase-decrease-then-increase.

2.6. Discovery NM530c and why it is good for dynamic studies

As mentioned in the previous section, conventional SPECT cameras need to rotate around the patient in order to acquire a complete set of projections. However, standard image reconstruction assumes that the tracer distribution is constant, and thus the projections correspond to different views of the same tracer distribution.

If the distribution of the radiotracer changes in the object during data acquisition time, this generates inconsistency in projection data. Then, when the image is reconstructed with conventional reconstruction algorithms, it suffers from artifacts, which might cause erroneous diagnosis. Artifacts have been observed if the characteristic time of the radiotracer change is one half or less than the data acquisition time. [Celler et al 2015].

The Discovery NM530c is a dedicated cardiac camera introduced by GE Healthcare in 2009. An important feature of this system is that it acquires a complete data
set without any rotation. The camera heads stay in a fixed position relative to the patient body during data acquisition. An array of multiple detectors with pinhole collimators is shaped in such a manner that it allows the system to simultaneously collect data over about 180 degrees; hence temporal inconsistency due to camera rotation is prevented. This is a significant advantage for cardiac studies.

The Discovery NM530c consists of 19 pinhole collimators, and each pinhole collimator is associated with one cadmium zinc telluride (CZT) detector. Each CZT detector has 4 modules and a module is pixelated into 16x16 pixels. Nineteen pinhole-detector pairs are arranged in three rows located in an arc such that the focal lines of pinholes in the middle row are perpendicular to the patient long axis, and the focal lines of pinholes in the top and bottom rows are angulated to point towards the center of the field of view (FOV). Analysis of camera sensitivity using cardiac phantom images shows that, the Discovery NM530c has about 3.5 times better sensitivity than the conventional SPECT camera. The central spatial resolution for the Discovery NM530c is 6.7mm whereas 15.3mm for conventional SPECT camera. [Imbert 2012] Also, the scan time for the conventional dual-head SPECT camera is about 15 minutes for each stress and rest scan, whereas the scan time for the Discovery NM530c is 3 minutes for stress and 2 minutes for rest. [Buechel 2010]

However, for dynamic studies, a series of projection data acquired from the Discovery NM530c are reconstructed time-frame by time-frame with conventional reconstruction methods. Each dataset corresponds to one time frame, therefore when each time frame is reconstructed independently of others, the relationship between time frames is ignored and some time-dependent physiological information is neglected.

The aim of our project is to improve the accuracy of Discovery NM530c dynamic cardiac studies by simultaneously reconstructing all time frames with our dynamic SPECT method, dSPECT [Wells 2014, Timmins 2015].
Chapter 3.

Tomographic reconstructions

3.1. Principles of tomographic image reconstruction: FBP, iterative reconstruction methods

An image of the inside of a human body can be obtained by tomographic image reconstruction from the data acquired at different angular directions around the patient. Tomography is an imaging technique for obtaining cross-sectional images through a human body. The process for SPECT involves gathering projection data from multiple angles and processing these projection data by computer using a tomographic reconstruction algorithm. There are many different reconstruction algorithms which can be used for SPECT. In this section some analytical and iterative reconstruction methods are briefly discussed. More details can be found in [Bruyant 2002, Wernick 2004]

The basic principle of SPECT is that first a gamma emitting radioactive tracer is administered (injected, inhaled or ingested) to the patient. Then these radioisotope’s gamma emissions are measured by a gamma camera. The image obtained at one angle of view corresponds to the projection of a three-dimensional activity distribution onto the two-dimensional detector plane. When parallel collimators are used, the number of counts recorded at any point on the detector plane is proportional to the line integral of the activity distribution in the human body along the normal to this point.

3.1.1. Projection Operator: Radon Transform

The process of obtaining projection data by a gamma camera can be described mathematically by the Radon Transform. The Radon transform is an integral transform of a differentiable function in n-dimensions. The transformed function at a given point is the
integral of the function over a straight line — see (3.1) and Figure 3.1. Consequently, its inverse determines the images from the projection data.

For simplicity, Figure 3.1 shows the Radon transform $p(s, \theta)$ of a function $f(x, y)$ in two dimensions. The Radon transform is the line integral of the values of $f(x, y)$ (corresponding to activity distribution in the patient) along the line perpendicular to the line rotated about the x-axis with an angle $\theta$ at a distance $s$ from the origin.

$$p(s, \theta) = \int_{-\infty}^{\infty} f(s \cos \theta - t \sin \theta, s \sin \theta + t \cos \theta) dt$$  \hspace{1cm} (3.1)

Figure 3.1 Parametrization of Radon Transform in 2D

This is because using trigonometry in Figure 3.1, we get

$$\begin{align*}
x_0 &= s \cos \theta \\
y_0 &= s \sin \theta
\end{align*} \quad \text{and} \quad \begin{align*}
x_0 - x &= t \sin \theta \\
y_0 - y &= t \cos \theta
\end{align*}$$

Solving for $x$ and $y$, we get,
\[ \begin{align*}
  x &= s \cos \theta - t \sin \theta \\
  y &= s \sin \theta + t \cos \theta.
\end{align*} \]

Then, if we solve for \( s \) and \( t \) using the trigonometric identity \( \sin^2 \theta + \cos^2 \theta = 1 \), we get

\[ \begin{align*}
  s &= x \cos \theta + y \sin \theta \\
  t &= -x \sin \theta + y \cos \theta.
\end{align*} \]

Therefore, for each detector position defined by angle \( \theta \), when the point \( P \) on the line \( D_\perp \) is projected on the detector plane \( D \), the direction of each point \( s \) on the detector plane is defined by the line \( D_\perp \) whose equation is:

\[ s = x \cos \theta + y \sin \theta. \tag{3.2} \]

Since the integral can be expressed as the sum of values along the line, \( p(s, \theta) \) is equal to the sum of values along the line \( D_\perp \). In a discrete presentation, the image can be discretized into voxels, which are three-dimensional version of pixels. The activity distribution can be represented by a vector \( f \). Then the activity distribution in each voxel of the object is projected onto the detector. Similarly, the detector plane at each projection angle can be discretized into bins, and the activity in each bin can be represented as a vector \( p \).

**Figure 3.2** Schematic presentation of the discretized detector and the object
Figure 3.2 shows the case of the detector plane being discretized into 4x4 bins and the object to be imaged into 3x3x3 voxels. Since the detector rotates around the object and stops at several angles to obtain projection data, the total number of bins is equal to the number of discretization of the detector plane (in the Figure 3.2, for example 4x4= 16 bins) times the number of angles stopped.

In fact, it is necessary to express \( p(s, \theta) \) in a discrete format since the computer can only deal with discrete functions. Let \( I \) be the total number of image voxels and \( J \) be the total number of the detector bin, where \( J = K \times S \) with \( K \) is the number of bins of one detector plane and \( S \) is the number of the angles stopped, and \( A_{ji} \) is the weighting factor representing the contribution of the \( i^{th} \) object voxel to the counts detected in the detector’s \( j^{th} \) bin. Then, the discrete Radon transform can be also written as:

\[
p_j = A_{j_1}f_1 + A_{j_2}f_2 + \cdots + A_{j_I}f_I = \sum_{i=1}^{I} A_{ji} f_i \quad \text{for} \quad j = 1, \cdots, J.
\]  

(3.3)

This discrete projection operation can be defined as a matrix-vector product as:

\[
p = Af
\]  

(3.4)

The equation above is a system of linear equations where \( p \) is the vector of the discretized detector (bins), \( f \) is the vector of the discretized image to be reconstructed (voxels) and \( A \) is the forward projection operator, which is called system matrix of dimension \( J \times I \). However, in order to obtain a more realistic model, not only the geometric relation between the image voxel and the detector bin, but also other important physical information such as sensitivity map and attenuation correction are included the matrix \( A \). This is because the correct selection of each value of \( A_{ji} \) is crucial for the iterative reconstruction as will be explained later.

### 3.1.2. Analytical Reconstruction method: FBP

There are some analytical reconstruction methods for SPECT. Here, the filtered back projection algorithm, that is most commonly used analytical method, is presented. The backprojection operation is defined as:
Backprojection represents the accumulation of the line integral of all lines passing through any point \( P(x, y) \) in the activity distribution \( f(x, y) \). The backprojection operation maps each bin value to all voxels along the direction of the activity, not only to the originating voxel. The backprojection operation assumes that infinitely many projections are available. When the number of projection is small, streak artifacts (or star artifacts) may be observed in the reconstructed image. The important point is that the backprojection operation is not the inverse of the projection operation.

The central slice theorem is a fundamental theory in analytical reconstruction. The theorem states that the Fourier transform of a one-dimensional projection taken at an angle \( \theta \) is equivalent to a profile at the same angle through the center of the two-dimensional Fourier transform of the object. Thus, if all of the projections of the object are transformed in this manner into a two-dimensional Fourier plane, the full two-dimensional Fourier transform of the object is obtained. The object is then recovered using a two-dimensional inverse Fourier Transform.

With the filtered backprojection algorithm, first the projection data are Fourier transformed into frequency domain. Next, in the frequency domain, Fourier transformed data are filtered with the ramp filter. Then, the filtered Fourier transformed data are inverse Fourier transformed back to projection data. And finally projection data are backprojected by the equation (3.5) to obtain the image. The filtered backprojection (FBP) reconstruction algorithm is given by:

\[
f(x, y) = \int_{0}^{\pi} p^F(s, \theta) d\theta.
\]  

(3.6)

where the filtered projection \( p^F(s, \theta) \) is given by:
and, \( F_1 \) is the one-dimensional Fourier transform, and \( |v| \) is the ramp filter. When the ordering of backprojection and filtering is reversed, the algorithm is called the backprojection filtering (BPF). With the FBP approach, the low-frequency components are reduced by filtering, thus in the reconstructed image the sharp edges are boosted. However, usually the spectrum of the image is dominated by low-frequency components. Thus the ramp filter amplifies the noise-dominant frequencies, hence the noise is also present in the reconstructed image.

### 3.1.3. Iterative reconstruction methods

In contrast to analytical reconstruction methods, iterative reconstruction algorithms try to find a solution of the equation (3.4) by correcting successive estimates. As mentioned in the previous section, when solving equation (3.4) with iterative methods, physical information such as the sensitivity map and/or attenuation can be included the system matrix. This is one of the advantages of iterative methods over analytical ones. In iterative methods, if some of the voxel values of the image \( f(x, y) \) become negative during the iterations and if it is known that the image voxels values are non-negative, those values can be set to a non-negative value for the next iteration.

A common situation in image reconstruction is that the total number of bins in the detector planes for all projection angles is not equal to the total number of voxels in the image to be reconstructed. In this case, the system of linear equations is overdetermined or underdetermined, thus there may be no unique solution.

**Algebraic Reconstruction Technique**

The algebraic reconstruction technique (ART) is one of the iterative reconstruction algorithms. The principle method used in ART was proposed by Stefan Kaczmarz in the 1930s, thus it is also called the Kaczmarz method. The Kaczmarz method is an iterative algorithm for solving a system of linear equations \( \mathbf{p} = \mathbf{A}\mathbf{f} \) as defined in (3.4). The vector equation (3.4) can be written as an expanded form:
where each equation represents a hyper-plane. An image represented by a vector \( \vec{f} = (f_1, f_2, \ldots, f_j) \) can be considered as a point in \( l \)-dimensional space. At first an initial guess denoted by \( \vec{f}^{(0)} = (f_1^{(0)}, f_2^{(0)}, \ldots, f_j^{(0)}) \) is made, then the initial guess is orthogonally projected on the hyper-plane represented by the 1st equation of (3.8) producing \( \vec{f}^{(1)} \). Next, \( \vec{f}^{(1)} \) is projected on the hyper-plane represented by the 2nd equation in (3.8) to yield \( \vec{f}^{(2)} \), and so on. When \( f^{(J)} \) is computed after successive projections, \( f^{(J)} \) is projected back to the first hyper-plane in (3.8) and the process is repeated. Successive projections performed in this manner yield \( \vec{f}^{(2J)}, \vec{f}^{(3J)}, \ldots \). If a unique solution exists, the solutions will converges to that unique solution \( \vec{f} \). [Kak 1987]

The \( i^{\text{th}} \) component of the image to be reconstructed at the \( n^{\text{th}} \) iteration is updated by the formula:

\[
f_{i}^{(n+1)} = f_{i}^{(n)} + \frac{p_{j} - \sum_{k=1}^{l} a_{jk} f_{k}^{(n)}}{\sum_{k=1}^{j} a_{jk}^2} a_{ji}
\]  

(3.9)

where \((n+1) \mod J = j\), where \(J = K \times S\). For the ease of implementation of the ART algorithm, (3.9) is further simplified as:
In (3.10), the denominator of the equation (3.9) is replaced by $N_j$, which is the number of voxels along the $j^{th}$ ray, and the second term in the numerator is replaced by $\sum_{k=1}^{f_{j,n}}$, which is the sum of counts of voxels along the $j^{th}$ ray.

From equations (3.9) and (3.10), we can see that if the current estimate of a projection is close to the measured one, the term to be added is close to zero. Thus the new estimate of the image is very similar to the previous estimate. The disadvantage of the simplified formula of (3.10) is that salt-and-pepper noise appears in the reconstructed image due to the inconsistencies introduced by approximations. More details can be found in [Kak 1987].

**Maximum Likelihood Expectation Maximization Algorithm**

Maximum likelihood expectation maximization (MLEM) algorithm derived by [Shepp 1982] is an iterative reconstruction method that takes into account the fact that the data are noisy. This is a statistical reconstruction method based on the Poisson distribution and, in this context, the expectation function is maximized.

As radioactive decay is modeled with Poisson distribution, if we let the expected value of photons detected in the detector bin $j$ be $\tilde{p}_j$, and let the measured number of photons detected in the same bin be $p_j$, then the probability of detecting $p_j$ photons is given by the Poisson Model as:

$$P(p_j | \tilde{p}_j) = \frac{\tilde{p}_j^{p_j} e^{-\tilde{p}_j}}{p_j!}$$

Since the expected numbers of photons detected in each bin are independent, the likelihood of observing the number of photons which were detected when the activity distribution was in $f(x,y)$ is given by the conditional probability:
\begin{align*}
\mathcal{L}(f) &= P(p \mid f) = P(p_1)P(p_2)\cdots P(p_J) \\
&= \prod_{j=1}^{J} P(p_j) = \prod_{j=1}^{J} \frac{\tilde{p}_j^{p_j}e^{-\tilde{p}_j}}{p_j!}.
\end{align*}

(3.12)

The maximum value for the likelihood \( \mathcal{L}(f) \) can be found by calculating the first derivative of the equation (3.12) and setting it equal to zero. Note that if we take the logarithm of the right-hand side of the equation (3.12) for the index \( j \), we get:

\[ \ln \left( \frac{\tilde{p}_j^{p_j} e^{-p_j}}{p_j!} \right) = \ln(\tilde{p}_j^{p_j} e^{-p_j}) - \ln(p_j!) \]

\[ = p_j \ln(\tilde{p}_j) - p_j \ln(e) - \ln(p_j!) \]

\[ = p_j \ln(\tilde{p}_j) - p_j - \ln(p_j). \]

Here, by first taking the logarithm of both sides of the equation (3.12), we get:

\[ \ln(\mathcal{L}) = \sum_{j=1}^{J}(p_j \ln(\tilde{p}_j) - \tilde{p}_j - \ln(p_j)) \]

(3.13)

As \( \tilde{p}_j \) can be written as \( \tilde{p}_j = \sum_i a_{ji} f_i \), the equation (3.13) is rewritten as:

\[ \ln(\mathcal{L}) = \sum_{j=1}^{J} \left( p_j \ln \left( \sum_{i=1}^{I} a_{ji} f_i \right) - \sum_{i=1}^{I} a_{ji} f_i - \ln(p_j) \right) \]

(3.14)

Now, we take the first derivative of (3.14) with respect to \( f_i \), and set it equal to zero. Then we get:

\[ \frac{\partial}{\partial f_j} \ln(\mathcal{L}) = \sum_{j=1}^{J} \frac{p_j}{\sum_{k=1}^{I} a_{jk} f_k} a_{ji} - \sum_{j=1}^{J} a_{ji} = 0 \]

(3.15)

We multiply (3.15) by \( f_i \):
This equation is equivalent to

\[ f_i = \frac{1}{f_i} \sum_{j=1}^{J} a_{ji} \left( \sum_{j=1}^{J} \frac{p_j}{\sum_{k=1}^{I} a_{jk} f_k} a_{ji} \right), \]  

and by fixed-point iteration, we get the iterative form of MLEM,

\[ f_i^{(n+1)} = f_i^{(n)} \frac{1}{\sum_{i=1}^{I} a_{ji}} \sum_{j=1}^{J} a_{ji} \left( \sum_{j=1}^{J} \frac{p_j}{\sum_{k=1}^{I} a_{jk} f_k^{(n)}} a_{ji} \right). \]  

To show that the likelihood (3.13) attains the maximum value, we take the second derivative of (3.13) (equivalently, the derivative of (3.14)) with respect to \( f_j \):

\[ \frac{\partial^2}{\partial f_j^2} \ln(L) = -\sum_{j=1}^{J} \frac{p_j}{\sum_{k=1}^{I} a_{jk} f_k} a_{ji}^2 < 0. \]  

The second derivative is always negative, thus the likelihood \( L(f) \) attains its maximum at \( f_j \).

The implementation of any iterative algorithm is schematically presented below.
First, the initial estimate of the image (in the absence of additional information, for example, a value of one for all voxels) is forward projected, i.e. the image estimate is multiplied by the system matrix A. The outputs of this operation are the projection data of the initial estimate. Next, these projection data are compared with the measured projections. The MLEM algorithm computes a ratio of measured projection data and estimated projection data. Then, this ratio is backprojected, i.e., the ratio of the projection data is mapped back to the image space. Then, the image is normalized, and is again forward-projected for the next iteration, this is repeated until the convergence criterion is satisfied. As can be seen from the algorithm, if the estimated projection is close to the measured projection, the ratio is close to one, and the updated image will not change much from the previous estimate.

When the image is reconstructed with the MLEM algorithm, as the number of iterations increases, the reconstructed image tends to get noisier. This is because once the main features of the image have been obtained, subsequent iterations start fitting the noise in the image.

The maximum a posteriori (MAP) algorithm is a variation of the MLEM algorithm that penalizes the noise in the image. This method uses a maximum posterior probability estimation that takes into account the smoothness of the distribution of radioactive tracers.
In order to reduce noise in the image, a penalization term for the noisy image is added to the MLEM algorithm.

The iterative formula for MAP is given by:

\[
f_i^{(n+1)} = f_i^{(n)} \frac{1}{\sum_j a_{ji} + \beta \frac{\partial U(f^{(n)})}{\partial f_i}} \sum_j a_{ji} \frac{p_j}{\sum_k a_{jk} f_k^{(n)}}.
\]  

(3.18)

In equation (3.18), \( U \) is a function of \( f \) which describes the prior knowledge. One common approach is to enforce that the image is piecewise smooth. \( \beta \) is a weight factor. Notice that if either \( \beta \) or \( \frac{\partial U(f^{(n)})}{\partial f_i} \) are equal to zero, the formula becomes the MLEM algorithm.

Another variation of MLEM is the ordered-subset expectation maximization (OSEM) algorithm, which was proposed to accelerate the reconstruction process. The set of projections is divided into subsets, and the MLEM is applied to each subset as a sub-iteration. For instance, if there are 64 projection data, they may be divided into 4 subsets in the following manner with each subset containing 16 projections.

| Subset 1:   | 1, 5, 9… 61 |
| Subset 2:  | 2, 6, 10… 62 |
| Subset 3:  | 3, 7, 11… 63 |
| Subset 4:  | 4, 8, 12… 64 |

In this example, one full iteration of the OSEM over 4 subsets requires, in general, the same computation time as one iteration of the MLEM. However, the quality of the reconstructed image with one full iteration of OSEM algorithm is almost the same as the one yielded with four full MLEM iterations. In general, OSEM converges the number of subsets times (in this example, 4 times) faster than MLEM.

In some statistical reconstruction approaches, the Gaussian distribution is used instead of the Poisson distribution to derive an objective function for the least-squares
method. Historically, the least-squares method was used for the PET reconstruction [Kaufman 1993]. The objective function (3.4) to be minimized is:

$$ h(x) = \frac{1}{2} \| p - Af \|_2^2 $$  \hspace{1cm} (3.19)

subject to a non-negativity constraint. As the method does not enforce non-negativity of the solution, non-negativity has to be enforced by including a constraint. In contrast, the MLEM approach ensures non-negativity of the solution as its formula consists of multiplication only.

### 3.2. Dynamic reconstructions using dSPECT (dEM, d2EM)

#### 3.2.1. dEM reconstruction( Constraints on the 1st derivative )

In dynamic SPECT studies, we want to investigate spatial distribution of activities as well as changes of this activity distribution over time. Therefore, for dynamic reconstructions, a series of complete projection data is required. Each complete projection dataset has to cover at least 180 degrees of camera rotation and, when reconstructed, will provide information about activity distribution at the time when it was acquired (i.e. one time frame).

When conventional reconstruction methods are used for the reconstruction, the projection data are assumed to be consistent. However as explained in Chapter 2, in situations when activity distribution changes over time (dynamic study) the projection data obtained by conventional SPECT cameras such as single-, dual- and triple-head systems may not be consistent. Thus if projection data obtained by conventional SPECT camera are reconstructed by conventional reconstruction methods for dynamic SPECT studies, not only are there inconsistencies in the reconstruction, but also important temporal information about functions in the body will be lost. In order to avert this problem, several approaches including a couple of methods discussed in Chapter 2 are used. However, the dSPECT method does not assume that projection data are consistent; it takes a different approach.
The dSPECT method was introduced by MIRG in 1999 [Farncombe 1999]. One important feature of the dSPECT method is that it does not assume that all projection data are acquired at the same time, but allows activity distributions to be different at each camera position. The dSPECT method uses a set of linear inequality constraints for each image voxel over the entire time interval and it generates a series of three-dimensional images. As the physiological processes in the human body are continuous, the distribution of the radiotracer activity should not change suddenly, but rather smoothly over time. Therefore, the dSPECT approach assumes that the radiotracer activity in the investigated organ changes smoothly over time, and it may be “monotonically increasing”, “monotonically decreasing” or “monotonically increasing then monotonically decreasing” over time in each voxel in the investigated field-of-view (FOV).

The case of increasing activity can be thought as the case of uptake of the tracer. When we look at a single voxel of the investigated object, the activity should be monotonically increasing until it reaches a maximum amount. Therefore, the relationship between activities in each voxel can be mathematically written as:

\[
0 \leq x_i(t_1) \leq x_i(t_2) \leq \cdots \leq x_i(t_n) \leq \cdots \leq x_i(t_{N-1}) \leq x_i(t_N) \quad \text{for } t = 1,\ldots,N \tag{3.20}
\]

where, \(x_i(t_n)\) is the value of activity of the \(i^{th}\) voxel at time frame \(n\). The radiotracer activity in the human body can never be negative, thus \(x_i(t_n)\) always has a nonnegative value or otherwise is equal to zero. When we look at the activities in a voxel at two consecutive time frames \(x_i(t_{n-1}) \leq x_i(t_n)\), we also can get the relationship \(x_i(t_n) - x_i(t_{n-1}) \geq 0\). Therefore if we let the difference matrix be \(C\) and the difference of activities between two consecutive time frames be \(\tilde{x}\) this relationship could be written in matrix-vector multiplication format:
The important mechanism of dSPECT is that every element in \( \tilde{x}_i \) is kept positive so that the difference of activities between two consecutive time frames \( x_i(t_n) - x_i(t_{n-1}) \) is also kept positive. Then the inverse mapping from \( \tilde{x}_i \) to \( x_i \) (multiplication by \( C^{-1} \)) forces the temporal behaviour of \( x_i \) to be positive. For example, in row 1 in the linear system (3.21), the first element of \( x_i(t_1) \) is set equal to \( \tilde{x}_{i,1} \). Thus, it guarantees that \( x_i(t_1) > 0 \). Then, in row 2 in (3.21), since the value of \( \tilde{x}_{i,2} \) is positive, the mapping provided by \( C_i \) ensures that \( x_i(t_n) - x_i(t_{n-1}) > 0 \).

The case of decreasing activity can be thought of as the case of washout of the tracer or its physical decay. When we look at a single voxel of the investigated object, the activity should be monotonically decreasing until it reaches a minimum value which is nonnegative as it is impossible to have a negative value of activity. Therefore, in a similar manner to the increasing case with inequalities reversed, the relationship between activities in each voxel can be expressed mathematically as:

\[
x_i(t_1) \geq x_i(t_2) \geq \cdots \geq x_i(t_n) \geq \cdots \geq x_i(t_{N-1}) \geq x_i(t_N) \geq 0 \quad \text{for } t = 1, \ldots, N \tag{3.22}
\]

This relationship can be written in matrix-vector multiplication form.
Again every element of $\vec{x}_i$ is kept positive and the last element of $x_i(t_N)$ is set equal to $\vec{x}_{i,N} \geq 0$. Thus, the inverse mapping from $\vec{x}_i$ to $x_i$ guarantees $x_i(t_{n-1}) - x_i(t_n) \geq 0$.

The case of increasing-then-decreasing activity represents the case of initial uptake followed by washout of activity. The activity in a voxel will increase up to a maximum value at time $t$, followed by a decrease. This can be expressed as follows:

$$0 \leq x_i(t_1) \leq x_i(t_2) \leq \cdots \leq x_i(t_{p-1}) \leq x_i(t_p) \geq x_i(t_{p+1}) \geq \cdots \geq x_i(t_{N-1}) \geq x_i(t_N) \geq 0 \quad (3.24)$$

For this case, the relationship between the peak point time-frame and the one before and the one after the peak point time $x_i(t_{p-1}) \leq x_i(t_p) \geq x_i(t_{p+1})$ can be rewritten as:

$$2x_i(t_p) \geq x_i(t_{p-1}) + x_i(t_{p+1}) \quad (3.25)$$

Therefore, the difference matrix $C$ for increasing-then-decreasing can be written as follows. For simplicity, the number of time frames is set to 7 and the maximum value is achieved at the time frame 4, namely $t_4$. 

\[
\tilde{x}_i = \begin{bmatrix}
    x_i(t_1) - x_i(t_2) \\
    x_i(t_2) - x_i(t_3) \\
    \vdots \\
    x_i(t_{N-1}) - x_i(t_N) \\
    x_i(t_N) - 0
\end{bmatrix}
= \begin{bmatrix}
    1 & -1 & 0 & \cdots & 0 \\
    0 & 1 & -1 & \ddots & \vdots \\
    \vdots & \ddots & \ddots & \ddots & 1 \\
    \vdots & \ddots & \ddots & \ddots & -1 \\
    0 & \cdots & \cdots & 0 & 1
\end{bmatrix}
\begin{bmatrix}
    x_i(t_1) \\
    x_i(t_2) \\
    \vdots \\
    x_i(t_{N-1}) \\
    x_i(t_N)
\end{bmatrix}
= Cx \quad (3.23)
\]
The above inequalities (3.20), (3.22) and (3.24) describe the relationships between activities in each individual voxel for a series of time frames. It relates the amount of activity in the \( i \)th voxel at any given time to the amount of activity in the same voxel at a different time frame. As well, these relationships enforce non-negativity of the solution, i.e. \( Cx \geq 0 \).

It should be emphasised that with the dSPECT method, it is possible for each voxel to behave differently from other voxels. For example, the activity in one voxel may only increase or only decrease, while the activity in its neighbour’s voxel may increase-then-decrease in the same series of time frames.

For the dSPECT method, the expectation maximization (EM) algorithm is effectively applied to \( Cx = \bar{x} \),

\[
\bar{x}^{\text{new}} = \frac{\sum (AC^{-1})^T \rho}{\sum (AC^{-1})^T \bar{x}^{\text{old}}} \bar{x}^{\text{old}}
\]

Here, \( A \) is the system matrix that is the forward projector which transforms the activity distributions in a three-dimensional object into the projections in a two-dimensional detector plane. Since the difference matrix \( C \) is the operator to calculate the difference of activities in two consecutive time frames and \( \bar{x} \) is the vector that contains differences of activities in two consecutive time frames (as shown in above \( Cx = \bar{x} \) ), the activity distribution in the object \( x \) is recovered by \( C^{-1}\bar{x} \). The inverse of \( C \) can be easily obtained.
decreasing case are presented respectively in Figure 3.4. For simplicity, seven timeframes are used and the peak activity is assumed to occur at the time frame 4.

\[
C^{-1} = \begin{bmatrix}
1 & 1 & 1 & 1 & 1 & 1 & 1 \\
1 & 1 & 1 & 1 & 1 & 1 & 1 \\
1 & 1 & 1 & 1 & 1 & 1 & 1 \\
1 & 1 & 1 & 1 & 1 & 1 & 1 \\
1 & 1 & 1 & 1 & 1 & 1 & 1 \\
1 & 1 & 1 & 1 & 1 & 1 & 1 \\
1 & 1 & 1 & 1 & 1 & 1 & 1 \\
\end{bmatrix}, \quad \text{and} \quad
\begin{bmatrix}
1 \\
1 \\
1 \\
1 \\
1 \\
1 \\
1 \\
\end{bmatrix}
\]

\[
\begin{bmatrix}
1/2 & 1/2 & 1/2 & 1/2 & 1/2 & 1/2 \\
1 & 1 & 1 & 1 & 1 & 1 \\
1 & 1 & 1 & 1 & 1 & 1 \\
1 & 1 & 1 & 1 & 1 & 1 \\
1 & 1 & 1 & 1 & 1 & 1 \\
1 & 1 & 1 & 1 & 1 & 1 \\
\end{bmatrix}
\]

**Figure 3.4** Time difference matrix for increasing (Top left), decreasing (Top right), and increasing-then-decreasing (Bottom) with 7 time frames (the maximum occurs at time frame 3) respectively.

In real applications, the time frame where the peak activity occurs is not known ahead of the reconstruction process. Therefore, the dSPECT method has a special mechanism to determine the peak time frame during the reconstruction.

The difference matrix for increasing-then-decreasing case in the system of linear equations (3.26) assumes that the peak activity occurs at \( t_4 \). But in reality, the peak activity may occur in any time frame \( t_p \), where \( p \in (0, N) \) and \( N \) is the total number of time frames. (When the peak activity occurs at the first or the last time frame, then the situation will change to purely decreasing or purely increasing respectively.) The dSPECT method
initially sets the middle-time frame to be the peak activity frame for each voxel, and the method allows the peak time frame to move by one time frame, namely \( t_{p-1}, t_p \) or \( t_{p+1} \), in each iteration. This shift is done by using the inequalities \( 2x_i(t_p) \geq x_i(t_{p-1}) + x_i(t_{p+1}) \) in (3.25). When we solve the linear equation for the row where the peak activity occurs, which is

\[-x_i(t_{p+1}) + 2x_i(t_p) - x_i(t_{p-1}) = \tilde{x}(t_p),\]

for \( x_i(t_p) \), we get

\[x_i(t_p) = \frac{1}{2} \left[ x_i(t_{p-1}) + x_i(t_{p+1}) \right] + \tilde{x}(t_p). \tag{3.28}\]

Also, from equation (3.25), we have

\[x_i(t_p) \geq \frac{1}{2} \left[ x_i(t_{p-1}) + x_i(t_{p+1}) \right]. \tag{3.29}\]

The equations (3.28) and (3.29) say that \( x_i(t_p) \) is the average of the activities in one time frame before and one time frame after the current time frame, plus some value given by \( \tilde{x}(t_p) \). Therefore, the peak activity’s time frame may occur in time frame \( p-1, p \) or \( p+1 \). After each iteration the algorithm checks the values of these consecutive three points and shifts the peak position if necessary.
The solid horizontal line represents $\frac{f(t_{p-1}) + f(t_{p+1})}{2}$.

**3.2.2. d²EM reconstruction (Constraints on the 2nd derivative)**

The constraints exploited in the dSPECT method, namely the activity in each voxel over time must increase, decrease or increase-then-decrease, eliminate some nonphysical solutions and force the change of activities to be fairly smooth over time. However, the current version of the constraints does not force the time activity curves (TAC) in each voxel to be smooth. This is because, for increasing or decreasing, the
concavity could be up or down. The figures below show the increasing and the decreasing case with concavity up and down.

The d²EM method was introduced by Humphries in 2011 [Humphries 2011]. It was intended to impose a stronger constraint than dEM so that the TACs in every voxel will be smooth. With the d²EM method, the concavity of the TAC is allowed to change once. Changing the concavity is equal to changing the sign of the second derivative. However, allowing the second derivative to change the sign once could allow the first derivative to change the sign twice, which violates the dSPECT method's constraint. Therefore, only the cases where the first derivative changes its sign at most once and the second derivative changes the sign once are permitted in the implementation of the d²EM method. The sign of the second derivative can change from negative to positive or positive to negative, unlike the dSPECT method allowing the sign of the first derivative to change only from positive to negative.
For details of the implementation of the d²EM method the reader is referred to [Humphries 2011].

3.3. Introduction of pinhole reconstruction

The standard gamma camera consists of a collimator, detector, array of photomultiplier tube (PMT) and electric components. For the collimator, a parallel-hole collimator is commonly used, and the detector is usually built with a single scintillator crystal such as sodium iodine. In order to acquire data, traditional SPECT camera, composed of 1 to 3 detectors with collimators, have to perform at least $180^\circ$ rotation around the patient. Therefore, conventional reconstruction methods are developed for a gamma camera with parallel-hole collimators imaging stationary activity distributions.

However, as discussed in Chapter 2, the new stationary cardiac camera Discovery NM530c uses multiple pinhole collimators instead of commonly used parallel-hole collimator and multiple solid state CZT detectors. The objective of our research is to improve the accuracy of dynamic studies performed using the Discovery NM530c with the dSPECT method. To this end, a new dynamic reconstruction algorithm for pinhole collimators has to be developed.

The details of the Discovery NM530c geometry will be discussed in the next chapter.
Chapter 4.

Pinhole SPECT

4.1. New cardiac camera - GE Discovery NM530c

In 2009, GE Healthcare introduced a dedicated cardiac camera, the Discovery NM530c [Bocher et al. 2010, Esteves et al. 2009]. The Discovery NM530c has 19 pinhole collimators (Figure 4.1), each with its own Cadmium Zinc Telluride (CZT) detector.

Figure 4.1 (A) The Discovery NM530c system, (B) schematic view of its 19 camera heads arrangement, and (C) a view of the external shield of the pinhole collimator. (GE Healthcare: www3.gehealthcare.com)

As briefly discussed in Chapter 2, the most important feature of this new system is that, unlike conventional SPECT cameras, the camera head does not rotate during the data acquisition. Typically, dynamic studies require the acquisition of a series of complete datasets where each dataset must correspond to one time frame. When the corresponding images are reconstructed, each image represents the distribution of the radiotracer in the body at a specific time frame. With a conventional approach, these images are
reconstructed one-by-one (time-frame by time-frame) using a static reconstruction method. Thus, correlations between consecutive time frames are not taken into account during the reconstruction process. This approach is currently used for dynamic studies with the Discovery NM530c camera [Wells et al 2014]. On the other hand, the dSPECT method reconstructs all time frames at the same time.

For our research, in order to understand the characteristics of the Discovery NM530c camera system and its data acquisition, the system was modelled with Monte Carlo software and data acquisitions were simulated. The results of our simulations are compared with phantom experiments performed using the Discovery NM530c camera located at the University of Ottawa Heart Institute.

### 4.2. Use of Monte Carlo methods in Nuclear Medicine

Monte Carlo methods have been used for many years as a vital tool for investigating complex systems in nuclear medicine. They employ numerical techniques based on random sampling of probability density functions describing physical processes to solve problems that are difficult to solve analytically. Commonly, very large numbers of samples are obtained to simulate the distribution of an unknown probabilistic entity. Results from simulations with Monte Carlo methods do not model all of the complexities of the real world and hence cannot replace clinical experimental measurement. However, when the geometry of imaging systems, activity distribution of radiotracers and patient's geometry are accurately modeled and proper reconstruction methods are used, the results can provide substantial insight into the behavior of the system which can be used to validate and develop new methods to improve medical imaging [Ljungberg et al 2013].

Applications of Monte Carlo methods range from the design of new medical imaging systems that include detector, collimator and shield design, to optimization of acquisition protocols. They also include the development and assessment of image reconstruction algorithms and correction techniques that include corrections for scatter, attenuation, and partial volume effects [Buvat and Castiglioni 2002, Buvat and Lazaro 2006, Jan et al 2004]. Monte Carlo methods are also applied to calculations of internal radiation doses from diagnostic procedures and radionuclide therapies, as well as cyclotron production of medical radioisotopes [Celler 2014].
The use of Monte Carlo simulations in emission tomography, such as SPECT and PET, has been slowly increasing since 1995 [Buvat and Lazaro 2006]. There are various Monte Carlo simulation packages such as EGS4, MCNP, SimSET, SIMIND, GEANT, Penelope and GATE, which have been widely used in nuclear medicine research. The increased use of GEANT and Penelope showed that users were seeking a generic Monte Carlo code that could be used for wide range of applications. This was one of the motivations for the development of GATE which encapsulates GEANT4 inside its architecture. More details about the evolution of Monte Carlo simulations codes are presented in [Buvat and Lazaro 2006].

4.3. GATE simulation of the system geometry

Monte Carlo simulations performed with GATE version 6.2 were used in this research project. The dSPECT method (MIRG 1999) was used for dynamic SPECT reconstructions.

4.3.1. GATE version 6.2

GATE, the Geant4 Application for Tomographic Emission (SPECT and PET), was publicly released in May 2004 by the OpenGATE collaboration [Jan et al 2004]. It was designed so that (1) no knowledge of programming is required (especially C++ as Geant4 was written in C++), (2) it is general enough to fit any context, making its subroutines and simulation results reusable, (3) it is modular and able to evolve in the future, (4) it is able to model time-dependent processes, such as source distribution changes and detector motion [Buvat and Lazaro 2006, Jan et al 2004].

When we started this project in 2011, the only available GATE version was 6.1 which did not allow for simulation of multiple camera heads in one macro file. The issue was resolved with GATE version 6.2, allowing a single simulation to model the whole camera instead of having to patch together the results from 19 separate simulations of individual camera heads.
4.3.2. Modeling of Camera Geometry

First, the camera geometry and configuration of detector-collimator pairs were modeled using GATE 6.2. As mentioned earlier, the Discovery NM530c has 19 pinhole collimators paired with 19 CZT detectors. Each detector is subdivided into 4 modules, where one module is about the size of 4cm x 4cm x 5mm, and each module is pixelated into a 16 x 16 matrix of 2.46 mm x 2.46 mm pixels [Bocher et al 2010, Alcyone 2009].

![Figure 4.2 Detector geometry.](image)

The system has 5 triplets (a triplet is a column) and 4 singlets.

Figure 4.2 shows the schematic representation of the Discovery NM530c detectors’ configuration. The system has 9 columns of detectors of which 5 are triplets having three pinhole-detector pairs and 4 are singlets having only one pinhole-detector pair in the middle row. All pinhole-detector pairs are arranged in an arc such that all pinholes point toward the centre of the field of view (FOV) of the camera.

Because each of the 19 camera heads has a different collimator-detector distance and a different angle between the detector normal and the direction of the pinhole focal axis, it was necessary to model each head individually. Additionally, the axes of the 5 heads in the top row and 5 heads in the bottom row are angled towards the middle of the system. To assure that only photons going through the pinholes were detected, lead shielding with a thickness of 4 mm was modeled around each camera head. In order for the heads not to overlap, they were modeled using trapezoidal prism shapes. The efficiency of the CZT detectors was not modelled in this study.

The front view and the side view of the Discovery NM530c geometry modeled in GATE are shown in Figure 4.3.
Figure 4.3 GATE simulation of Discovery NM530c Top: The front view; Bottom: The side view; Red, blue and green dots in the images indicate the positive direction of axes.
4.3.3. Tests of correctness of the camera model

To verify that our modeled geometry of the Discovery NM530c was correct, first, acquisitions of simple activity configurations, such as point sources and line sources were simulated. In parallel, experimental acquisitions using similar point and line sources were performed.

Our simulation tests began with a point source and three line sources. Both sources were created by using a capillary tube with the inner diameter 1.1mm for the experiment. The point source was positioned at the center of the system at (0,0,0) and for the experiment, it was positioned in the middle of the FOV of the camera. The three line sources were modeled separately. They were simulated at the center of the system along the z-axis, then along the x-axis and along the z-axis but removed by 2.4 cm from the central axis. The length of each line source was 63 mm, and the activities for a point source and a line source were 2.4 MBq and 34.6 MBq, respectively. The scan time for the experiment and the run time for the simulation were both 600 seconds which resulted in a total of $1.44 \times 10^8$ and $2.076 \times 10^8$ photons being simulated for the point and line source, respectively.

However, as the camera geometry is very complex, the position of the origin of its coordinate system and the direction of the axes in the simulated geometry relative to the coordinate system of the clinical camera (“truth”) could not be clearly determined with projection data of these simple sources. In particular, with pinhole geometry, the projection data should show the image having a reversed shape relative to the object (flipped upside-down and left-right). But with simple sources it was impossible to see this effect due to symmetry of the object. Therefore, it was necessary to simulate an asymmetric source to verify that the geometry of the system simulated in GATE agreed with the geometry of the clinical camera. For this purpose, we used a source in the shape of the letter “F” and compared its shape in the simulated and experimental projections.

For the experiment, the phantom in the shape of letter “F” was created manually by combining three capillary tubes filled with radiotracer. The activity of each capillary tube was about 9.4 MBq and the inner diameter was about 1.1mm. The length of activity in each capillary tube was 75mm. The tubes were positioned on the patient bed at the center of the FOV of the camera. The line corresponding to the vertical part of letter “F” was aligned along the z-axis, and the scan time was 300 seconds.
For GATE simulations, the similar phantom configuration was created with three line sources with lengths of 60 mm and 58 mm for the horizontal lines, and 80 mm for the vertical line of “F”. The simulated phantom was positioned the same way as in the experiment. The diameter of each line was equal to 2 mm and the activity of each line was set to be 34.6 MBq. The simulation was run for 600 seconds resulting in \(62280 \times 10^6\) simulated photons.

### 4.4. Development of static and dynamic reconstruction algorithms: Original version

In order to generate 3D images from the acquired data, tomographic reconstruction was needed. However, the manufacturer’s code used for clinical reconstructions was proprietary, and was not available for our project. Therefore, it was necessary to develop our own reconstruction method based on Discovery NM530c.

It turned out that our original static and dynamic reconstruction methods developed in this section were not used in later analyses. However, the development of these methods helped us to understand the geometry of the camera system and the reconstruction algorithm for the pinhole collimators, and the knowledge we gained in this section helped us in subsequent studies.

#### 4.4.1. Original reconstruction methods

The original static reconstruction algorithm developed was based on a maximum likelihood expectation maximization approach (MLEM). To calculate the system matrix for the pinhole geometry, the ray-driven backward and forward projection method was used. As the pinhole's aperture causes blurring in the image, not one, but a total of seven rays were generated to approximate this effect [Andreyev 2006, 2007, Vanhove et al 2007]. As explained, each of detector planes in the Discovery NM530c system was divided into 32x32 pixels. Thus, projection data obtained from the camera system were recorded on the plane of a 32x32 matrix. However, for our original reconstruction method, the detector was further subdivided into a 64x64 in order to get more sample points on the detector plane for the ray-driven method to reconstruct better images. Yet, we were aware that it
was a better idea not to change raw projection data before the reconstruction. And this problem was solved in next section.

To verify the correctness of our static reconstruction code, experimental and simulated projections of the point and line sources and projections of the source in the shape of letter “F” were reconstructed using our original software and the manufacturer’s software, respectively, and the resulting images were compared.

Next, our static reconstruction method was modified to process multiple time-frames of dynamic acquisitions. Our dSPECT reconstruction method [Farncombe 1999] which uses linear inequalities to constrain the solution by restricting the temporal behavior of activity in every voxel was combined with the newly developed static MLEM reconstruction algorithm.

4.4.2. Simulation of Dynamic Acquisitions

As the objective of our project was to develop a dynamic reconstruction methodology for the Discovery NM530c system, data that would represent dynamic acquisition of a time-changing activity distribution in an object were required. To create such dynamic acquisition data, we modified a set of static projection data of the line source obtained from Monte Carlo simulations.

The simulation of data acquisition for the Discovery NM530c resulted in the creation of 1 projection. Using this projection, 18 additional datasets (18 projections) were created in the following way:

(1) 19 datasets corresponding to the activity of the line source at 19 consecutive time points were created by rescaling the static projection by a scale factor. This factor was obtained from the time activity curve (TAC) (Figure 4.4) corresponding to experimentally determined activity changes in pig myocardium [Wells et al 2014].

(2) Poisson noise was added to every pixel in each projection.

From this dynamic dataset two different dynamic datasets were generated: one set corresponding to a high activity acquisition with 200,000 counts in the peak-activity time frame, and the second corresponding to a low activity acquisition with a total of 20,000 counts in the peak-activity time frame.
Figure 4.4 Schematic representation of the procedure that was used for creating a dynamic dataset. Using a model time activity curve (TAC), 19 equally-spaced points on a time axis were selected. The scale factor for the peak-activity was set to 1. Then, scale factors for the other 18 points were determined using the TAC. 19 new projection datasets (corresponding to 19 time frames) were created by multiplying each projection of the static dataset by the scaling factor corresponding to a particular time frame.

The images were reconstructed using the following two methods:

(1) The 19 datasets corresponding to each of the 19 time frames were reconstructed individually with our static reconstruction algorithm,

(2) All 19 time-frames were processed concurrently with our dynamic reconstruction algorithm.

4.4.3. Static reconstruction of a point source and line sources

Projection data of a point source from the experiment and the GATE simulation were shown in Figure 4.5 and Figure 4.6, respectively. The correspondence between experimental and simulated projections was investigated by viewing a horizontal profile through each projection at the center of the image. Figure 4.7 shows a comparison of the profile shapes acquired by head 9 from the Discovery NM530c and the GATE simulation (left and right respectively). The full-width at the half-maximum (FWHM) obtained from these profiles are 2.8 pixels and 2.4 pixels for experimental data and simulated data, respectively.
Figure 4.5 Experimental projection data of a point source from Discovery NM530c camera.

Figure 4.6 Simulated projection data of a point source obtained from GATE.

Figure 4.7 Profile shapes of a point source acquired by Head 9 from Discovery NM530c (left) and GATE simulation (right).

The projection data of a line source positioned on the z-axis from the experiment and the GATE simulation are shown in Figure 4.8 and Figure 4.9 respectively. Again, the horizontal profile shapes viewed through the projection data were investigated. Measured
FWHM values were 2.5 pixels and 2.3 pixels for experimental data and simulated data respectively (Figure 4.10 left and right respectively).

Figure 4.8 Experimental projection data of a line source on the z-axis from Discovery NM530c.

Figure 4.9 Simulated projection data of a line source on the z-axis from GATE.

Figure 4.10 Profile shapes of a line source acquired by Head 9 from Discovery NM530c (left) and GATE simulation (right).
The reconstructed three-dimensional (3D) images of a point source and a line source on the z-axis are shown in Figure 4.11. The reconstructions were done with our static reconstruction software. The top row shows the reconstructed images of experimental data, and the bottom row shows reconstructed images from GATE simulation. These images show that the model of Discovery NM530c used in our simulation reproduces the true geometry of the system well. However, it is also obvious that since these sources are symmetrical, the pinhole effect cannot be observed.

Figure 4.11 Reconstructed point source and line source from Discovery NM530c (top low) and GATE simulation (bottom row). The reconstructions were done with our static reconstruction software.

4.4.4. Static reconstruction of the letter “F” shape

The comparison of simulated and experimental projections corresponding to the “F” shaped source allowed us to identify the position of the origin of the coordinate system and direction of the axes. The experimental projection data from Discovery NM530c and
the projection data from the GATE simulation are shown in Figure 4.12 and Figure 4.13, respectively.

Figure 4.12 Experimental projection data of “F” shaped source from Discovery NM530c

Figure 4.13 Simulated projection data of “F” shaped source from GATE

However, we could not directly compare the experimental and the simulated projection data because the position of the source in the experiment could not be exactly correlated to its simulated counterpart. Nevertheless, we can see the similarity of the projection data, such as the direction of distortion and flip of the letter. Visual comparison confirms that our modeling of the camera is correct.

Next, the projection data from the experiment and from the simulation were reconstructed with our own static reconstruction code and with the manufacturer’s reconstruction software for comparison. The images in the top row in Figure 4.14 were reconstructed with our own software using the experimental projection data (left) and the
simulated projection data in GATE (right), respectively. The images in the bottom row in Figure 4.14 were reconstructed with GE reconstruction software. The shape of the letter “F” and its position in all these images correspond well to each other.

Figure 4.14  Reconstructed images of the source in the shape of letter “F”. Left column: experimental F, Right column: simulated F.

4.4.5.  Dynamic reconstruction of a line source

The TACs obtained from images of the line source reconstructed using two dynamic reconstruction approaches, namely a series of separate static reconstruction of each time frame and simultaneous reconstruction of all time frames using the dSPECT method (as outlined in Section 4.4.2) are presented in Figure 4.15. The left and right images in Figure 4.15 show the TACs for a line source simulated in GATE with high statistics and low statistics, respectively. TACs obtained from simultaneous processing of
dynamic studies (in red) are much smoother than those from individual reconstructions (in blue). The curves are less noisy and very closely follow the theoretical ones.

Quantitative evaluation of the accuracy of dynamic reconstruction was performed by analyzing differences between time frames of the images corresponding to the true activity in the line source and the activity determined from images obtained using the static and dynamic reconstruction methods. The error was calculated as:

$$\text{Error} = \sqrt{\frac{\sum_{i} (E_i - T_i)^2}{\sum_{i} T_i^2}}$$

where $E_i$ is the experimental value of the total counts in the image corresponding to the $i^{th}$ time frame and $T_i$ is the true value of activity in the same frame.

For low statistics data the errors for dynamic dSPECT reconstruction and for separate reconstruction were 3% and 18%, respectively, while for high statistics data the error for dynamic reconstruction and separate reconstruction was 2% and 9% respectively.

**Figure 4.15** TACs obtained from the data modeling dynamic acquisition of the line source with changing activity. Black: true dynamic behavior of activity in the line source, Blue: TACs from a series of separate static reconstructions, Red: TACs from simultaneous dSPECT dynamic reconstruction.
In the left image of Figure 4.15, the peak of TAC from static reconstruction (blue curve) is lower than the truth (black curve). For this experiment, only 10 iterations were used. This discrepancy may decrease if more iterations are performed.

4.4.6. Discussion

Comparing the results from the GATE simulation and the experiment was not an easy task as the positions of the sources in the experiment and the simulation could not be exactly correlated. For the GATE simulation, we exactly knew the origin of the coordinate system and the size of each source. On the other hand, for the experiment, the location of the origin of the coordinate system of the camera was difficult to be exactly determined and the effects related to attenuation, scatter and mispositioning of physical objects on the camera bed were not negligible. As pinhole collimators are very sensitive to the location of the source, a slight difference in the positioning of the source could result in significant difference in the reconstructed images such as spatial resolution.

Simulation experiments allowed us to understand the geometry and data acquisition of the Discovery NM530c. The accuracy of our static and dynamic reconstruction methods were tested and verified by using data acquired from the modeled camera. The results of our simulations allowed for close comparison with experiments performed using the Discovery NM530c camera.

An important advantage of using Monte Carlo simulations in this project was that this approach allowed us to develop and validate a static reconstruction code specifically for the very complex geometry of the Discovery NM530c imaging system as the manufacturer code was not available. Subsequently this code was modified to allow for simultaneous processing of the dynamic datasets, an approach which, as our preliminary tests suggest, will be more accurate than sequential processing of individual time frames.

Reconstructions using our dynamic algorithm took about 14 minutes, while our static algorithm took slightly longer when each time frame was processed one by one. Both reconstructions were performed with 10 iterations on our Linux machine (Intel®Core™i7 CPU870@2.93GHz x 8).

Problems in the experiments in this section were first, our reconstruction method required to modify raw projection data; i.e. subsampling into 64x64 matrix. Second, the
positions of the sources in the simulations and the experiments were not well correlated. These problems were solved in the following section.

4.5. New Static and Dynamic Reconstruction methods with Sensitivity Map

As explained in the previous sections, while the geometry of the Discovery NM530c system was modelled in Monte Carlo simulation software, we developed our own static and dynamic reconstruction methods for Discovery NM530c.

However, for our original reconstruction methods, it was necessary to subsample projection data to obtain more sampling points on the detector plane, and yet we recognized that it was better not to process raw projection data before reconstruction. Also our original static and dynamic reconstruction methods did not include a sensitivity map.

Therefore, we decided to modify a new static reconstruction code with sensitivity map for this camera system to fit dynamic reconstructions.

4.5.1. Modification of Static reconstruction code with sensitivity map to Dynamic reconstruction

The static reconstruction code with sensitivity map was provided by Dr. Glenn Wells of the University of Ottawa Heart Institute. The reconstruction algorithm was based on a maximum likelihood expectation maximization approach (MLEM). To calculate the system matrix for the pinhole geometry, the analytical backward and forward projection method was used. The correctness of the method was confirmed beforehand.

In order to modify this static reconstruction code to fit the dynamic reconstruction, again the dSPECT algorithm was adapted to the static method.

For our dynamic studies, time frames of projection data had variable lengths in order to model dynamic activities which could occur in dynamic heart studies shown in Section 2.5. Since the conventional dSPECT method could not handle variable time frame length for reconstruction, the dSPECT algorithm was adjusted to be able to handle different time frame length in this modification.
In dSPECT method, all time frames had to have the same length due to the mechanism of its simultaneous processing of all time frames. In order to handle variable time-frame lengths, the following process was added in the reconstruction.

1. The length of the first time-frame was set as the base.
2. The scale factor of each time-frame was determined by dividing each time length by the base.
3. The estimated projection data were multiplied by the scale factor before taking the ratio of the estimated projection data and the true projection data in the algorithm in equation (3.27).

4.5.2. Reconstructions with the new static and dynamic reconstruction method

In Section 4.4, one of basic problems in GATE simulation was that projection data of the point source and the line source from the simulations and the experiments did not correlate well as it was a challenge to correlate the position of the sources in the simulation and the experiment. Therefore, in order to better correlate the simulation and the experiment, new experiments were done, and based on these new experiments, the simulations were repeated.

Newly defined Point source and Line sources

As in previous experiments, sources were created by using a capillary tube with the inner diameter 1.1mm for the experiment. The point source was positioned at the center of the system at (0,0,0) and for the experiment, it was positioned in the middle of the FOV of the camera. The three line sources were modeled separately. They were simulated at the center of the system along the z-axis, then along the x-axis and along the z-axis but removed by 5 cm from the z-axis and 5 cm from the x-axis. The length of each line source was 45 mm, and the activities for a point source and a line source were 1.3 MBq and 14.1 MBq, respectively. The scan time for the experiment and the run time for
the simulation were both 300 seconds which resulted in a total of $390 \times 10^6$ and $4230 \times 10^6$ photons being simulated for the point and line source, respectively.

For the experiment of the letter F, the same experimental projection in Section 4.4 was used. However for GATE simulation for the letter F, more careful positioning than in the previous experiment was used in order for the simulation to correlate the experiment. The activity of each line in the letter F was set as 9.4 MBq, the diameter 1 mm, and the length of each line 75mm. The line corresponding to the vertical part of letter “F” was aligned along the z-axis, and the scan time was 300 seconds resulting in $282 \times 10^7$ simulated photons.

4.5.3. Results

**Static reconstruction of the point and line source**

Projection data of a point source from the experiment and the GATE simulation are shown in Figure 4.16 and Figure 4.17, respectively. As well, the selected detectors’ images and profiles are shown in Figure 4.18. The total counts in the projection data of the point source from the GATE simulation and the experimental data were 191,474 and 184,540 respectively. The difference in counts between GATE simulations and the experimental data was approximately 3.5%.

Similarly, the projection data of a line source from the experiment and the GATE simulation are shown in Figure 4.19 and Figure 4.20, respectively as well as the selected detectors’ images and profiles in Figure 4.21. The total counts in the projection data of the line source from the GATE simulation and the experimental data were 1,701,897 and 1,788,000. The difference in counts between GATE simulations and the experimental data was approximately 4.5%.
Figure 4.16 Experimental projection data of a point source from the Discovery NM530c.

Figure 4.17 Simulated projection data of a point source obtained from GATE.
Figure 4.18 Selected detector’s projection image and profiles: Images of projection and profiles of detector 3, 10 and 17. Top: Experimental data, Bottom: GATE simulations. Profiles were plotted by cutting the projection data with a vertical line.
Figure 4.19 Experimental projection data of a line source from the Discovery NM530c

Figure 4.20 Simulated projection data of a line source obtained from GATE.
From the profiles shown in Figures 4.18 and 4.21, we see that the positions of the sources in the experiment and the simulation were not exactly correlated although considerable attention was paid to ensuring the position of the source in GATE simulation to match the position of the source in the experiment. As pinhole collimators are very sensitive to the locations of the source, a slight difference in the positioning of the source could result in significant difference. The projections of experimental point source were
more spread than the one from GATE simulation even though the same diameter and activity were used for the experiment and the simulation. We see a gap in the line source only in the experimental line source (Figure 4.21 (A) image 10). This could be caused by air in the capillary tube.

The reconstructed three-dimensional (3D) images of a point source and a line source on the z-axis are shown in Figure 4.22. The top row shows the reconstructed images of experimental data, and the bottom row shows reconstructed images from GATE simulation.

![Figure 4.22 Reconstructed point source and line source from Discovery NM530c (top row) and GATE simulation (bottom row). The reconstructions were done with the static reconstruction software.](image)

**Static reconstruction of the letter “F” shape**

The experimental projection data from Discovery NM530c and the projection data from the GATE simulation with the adjusted source position and activity are shown in Figure 4.23 and Figure 4.24, respectively.
Figure 4.23 Experimental projection data of “F” shaped source from Discovery NM530c

Figure 4.24 Simulated projection data of “F” shaped source from GATE
For this experiment, as the source F was carefully created and positioned in the GATE simulation, projection data shown in Figure 4.23 and Figure 4.24 were better correlated than Figure 4.12 and Figure 4.13.

Next, the projection data from the experiment and from the simulation were reconstructed. The images in Figure 4.25 were the experimental projection data (left) and the simulated projection data in GATE (right), respectively. The shape of the letter “F” and its position in images correspond very well to each other. The total count in the reconstructed image of the experimental projection is approximately $1.3 \times 10^9$ and the total count in the reconstructed image of the GATE simulation is approximately $1.5 \times 10^9$. The total count of the reconstructed image from GATE simulation is 1.19 times more than for the experimental data.

![Figure 4.25 Reconstructed images of the source in the shape of letter “F”. Left column: experimental F, Right column: simulated F](image)

**Dynamic reconstruction of a line source**

Dynamic projection datasets created in Section 4.4.2 were used for reconstructions with the static reconstruction and the dynamic reconstruction method.
In section 4.4.2, two different dynamic datasets with a high activity acquisition with 200,000 counts in the peak-activity time frame, and a low activity acquisition with a total of 20,000 counts in the peak-activity time frame were created. In this section, additionally to these data sets, a lower activity acquisition with 2,000 counts in the peak-activity was reconstructed. We called the 200,000 counts data high statistics, 20,000 counts data as low statistics to be consistent with the previous experiment. The 2,000 counts data was called as lowest statistics.

Figure 4.26 shows the TACs for high statistics, low statistics and lowest statistics data. TACs obtained from simultaneous processing of dynamic studies (in red) are smoother than those from individual reconstructions (in blue). Quantitative evaluation of the accuracy of dynamic reconstruction was also performed as before.

For high statistics data the error for dynamic reconstruction and separate reconstruction was 2.8% and 3.4%, respectively. For low statistics data the errors were 4% and 3.4%, respectively, and, for the lowest statistics data the errors were 8.6% and 9.4%, respectively.

There was no large difference between TACs from the high statistics and the low statistics data when the reconstruction method with sensitivity map was used, compared to the case of our original dynamic reconstruction method was used. This was because without sensitivity map, the counts in projection data did not change during the reconstruction. However with sensitivity map, the original counts in the object were recovered according to the sensitivity map, thus the number of counts in projection data was boosted. Therefore, the reconstruction method without sensitivity map was more sensitive to the change in the total counts. When we decreased the peak activity count to the lowest statistics, we could observe the same phenomenon as the one we saw in Section 4.4.5.
Figure 4.26 TACs obtained from the data modeling dynamic acquisition of the line source with changing activity. Black: true dynamic behavior of activity in the line source, Blue: TACs from a series of separate static reconstructions, Red: TACs from simultaneous dSPECT dynamic reconstruction.
Chapter 5.

Dynamic Reconstructions with dSPECT using Analytical Data

In this chapter, the static reconstruction method with sensitivity map and the dynamic reconstruction method modified from the static method with sensitivity map in Section 4.5 were used for reconstructions, and the capability and the limitation of the dSPECT method were investigated.

As shown in Section 3.2.1, the dSPECT method works when the activity concentration of an individual voxel is monotonically increasing, monotonically decreasing or monotonically increasing-then-monotonically-decreasing. However, this is not always the case for the time activity curves (TACs) of the arterial blood and myocardial tissue as discussed in Section 2.5.

Our experiments were performed with analytical sources created in Matlab, as this way was more efficient than working with Monte Carlo simulations.

First, the dSPECT method was tested on normal data (which is called pattern 1 that contain the dynamic activity behaviours of increase and increase-decrease) and special data (pattern 2 that contain the dynamic activity behaviours of increase-decrease or increase-decrease-increase). Then, a new method, dividing projection data into two parts was tested.

5.1. Creation of analytical dynamic data in Matlab

The shape of letter F was used as a source to perform the experiments for this purpose. Certainly, a real human heart is a more complex structure and is not easy to create a model analytically in Matlab. However, the letter F is a sufficiently complicated shape as well as being asymmetric, yet easy to create in Matlab. Three different dynamic activities were assigned to each line in the letter F.
Analytically created sources were used to investigate the capability of the dSPECT method: first three line sources were created in Matlab, then dynamic data were generated as described in section 4.4.2. After generating dynamic data, they were (forward-) projected to create projection data. Forward projections were done with the forward projector from our static reconstruction code.

5.1.1. Process of creating dynamic data from three sources in Matlab

Dynamic data were created such that the three line sources had three different behaviours of radiotracer activity over time. The procedure was as follows:

1. Three box-shaped objects of dimension 70x70x50 voxels were created in Matlab.
2. Inside of each box-shaped object created in step 1, a line source of the size of 1x1x18 voxels was placed at three different locations.

<table>
<thead>
<tr>
<th>Location (x,y,z)</th>
<th>Source 1</th>
<th>Source 2</th>
<th>Source 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>(23 to 40, 38, 18)</td>
<td>(22,38, 18 to 35)</td>
<td>(23 to 40, 38, 28).</td>
<td></td>
</tr>
</tbody>
</table>

Table 5.1 Locations of three line sources

Figure 5.1 Schematic explanation of coordinates of three line sources
3. Activity changes in each of the three line sources were modeled according to the shape of time activity curves. The dynamic behaviours of each source were shown in Table 5.2 and Figure 5.2. As explained in section 4.4.2, the scale factor for the peak-activity was set to 1. Then, scale factors for the other 18 time points were determined using the shape of TAC.

<table>
<thead>
<tr>
<th>Activity Behaviour</th>
<th>Source 1</th>
<th>Source 2</th>
<th>Source 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pattern 1</td>
<td>increase-decrease</td>
<td>Increase only</td>
<td>increase-decrease</td>
</tr>
<tr>
<td>Pattern 2</td>
<td>increase-decrease</td>
<td>increase-decrease-increase</td>
<td>increase-decrease</td>
</tr>
</tbody>
</table>

**Table 5.2 Two patterns of activity behaviours for three line sources**

Figure 5.2 Dynamic behaviours of sources: Pattern 1 (Left) and Pattern 2 (Right)
Curves were plotted per line source. (18 voxels)
High statistics

For **pattern 1**, source 1 has a dynamic behaviour of increasing and decreasing with the peak count (maximum count) of 2.7x10^6 (1.5x10^5 per voxel). Source 2 has a dynamic behaviour of monotonically increasing with the maximum count of 5.4x10^6 (3.0x10^5 per voxel). And finally, source 3 has a behaviour of increasing-then-decreasing with the maximum count of 1.08x10^7 (6.0x10^5 per voxel).

For **pattern 2**, source 1 and source 3 have exactly the same dynamic behaviours and the maximum counts of those in **pattern 1**. However, source 2 has a dynamic behaviour of increasing-decreasing-then-increasing with a maximum count of 6.75x10^6 (3.75x10^5 per voxel).

Low statistics

For **pattern 1**, the peak counts are 6.75x10^5, 1.35x10^6 and 2.7x10^6 for source 1, source 2 and source 3, respectively.

For **pattern 2**, the peak counts for source 2 is 1.6875x10^6. Source 1 and source 3 are the same as **pattern 1** low statistics.

For low statistics, the counts are 1/4 of the original counts for each source.

4. For **pattern 1** and **2** (high and low statistics), three line sources were combined to form the shape of letter F. That is, three different dynamic behaviours were represented in the source having the shape of letter F.

5. Then the letter F was forward-projected by using the forward-projector function in the static reconstruction code.

The dSPECT method assumes that the radiotracer activities are monotonically increasing, monotonically decreasing or increasing-then-decreasing. Therefore, the method should be able to handle the three line sources with **pattern 1**. **Pattern 2** has increasing-decreasing-then-increasing activity which can be observed in dynamic studies of myocardial blood flow and flow reserves as explained in Section 2.5. The purpose of the experiments was to investigate the behaviour of the dSPECT method with **pattern 2**.
5.2. Experiments and Results

5.2.1. Reconstruction with the dSPECT method

The letter F was reconstructed with 30 and 60 iterations using both the static reconstruction method and the dSPECT method. TACs were then extracted from ROIs defined in the following way. Each line source was divided into 3 regions, and 54 voxels (6x3x3=54 voxels) were used to extract TACs for each region in each source.

<table>
<thead>
<tr>
<th>Source 1</th>
<th>Source 2</th>
<th>Source 3</th>
</tr>
</thead>
</table>

Table 5.3 Separation of three line sources. Three lines sources were divided into three regions in order to extract TACs.

Figure 5.3 Separation of three line sources: The source F are separated in 3 regions accordingly.
Henceforth, the TACs were plotted using different colors and line styles corresponding to the left, middle or right (or top, middle or bottom) regions of each line. The “line” in Table 5.4 corresponds to the average of the three regions.

<table>
<thead>
<tr>
<th>source 1</th>
<th>source 2</th>
<th>source 3</th>
<th>True</th>
</tr>
</thead>
<tbody>
<tr>
<td>s1 Lft</td>
<td>s2 Top</td>
<td>s3 Lft</td>
<td>s1 true</td>
</tr>
<tr>
<td>s1 Mdl</td>
<td>s2 Mdl</td>
<td>s3 Mdl</td>
<td>s2 true</td>
</tr>
<tr>
<td>s1 Rgt</td>
<td>s2 Btm</td>
<td>s3 Rgt</td>
<td>s3 true</td>
</tr>
<tr>
<td>s1 line</td>
<td>s2 line</td>
<td>s3 line</td>
<td></td>
</tr>
</tbody>
</table>

Table 5.4 Labeling of TACs. TACs were extracted from three regions (left, middle, right or top, middle, bottom). To compare shapes of the curves, the sums of counts in each line were normalized (divided by 3) and plotted as a “line”.

In fact, a TAC is extracted from a ROI (6x3x3 voxels) whereas the true object is 18x1x1 voxels. However, in reality since a reconstructed object is not as sharp as the original object, there is no difference when the ROI contains extra voxels nearby the source unless there is no background. This is not true when background is included, and we will see this in next chapter.

**Reconstruction of Pattern 1 dynamic activities**

Figures 5.4 and 5.5 show the TACs of high statistic data and low statistic data, respectively, from the static reconstruction method and the dSPECT method. The dSPECT method reconstructs the images well when the dynamic activities are increasing-decreasing (source 1), increasing only (source 2) and increasing-decreasing (source 3) regardless of the maximum counts in three sources.

We notice that there are more fluctuations in the TACs of the static reconstructions, whereas the TACs from the dynamic reconstructions are fairly smooth. For both the static reconstruction and the dynamic reconstruction, source 3 did not reach its maximum height with 30 iterations, but it reached the maximum height with 60 iterations.
High counts

Figure 5.4 Pattern 1 with High statistic data: TACs from the static reconstructions (Top) and the dynamic reconstructions (Bottom)
Low counts

Figure 5.5 Pattern 1 with Low statistic data: TACs from the static reconstructions (Top) and the dynamic reconstructions (Bottom)

For the dynamic reconstructions, especially with low statistic data, some oscillations were observed in TACs (for example, the right bottom image in Figure 5.5). This is because when a TAC was extracted from an ROI, values of 54 voxels (6x3x3 voxels) were added. Therefore, even though the individual voxel has one of dynamic
activity behaviour of increasing, decreasing or increasing-decreasing over time, the summed values exhibited fluctuations.

**Reconstruction of Pattern 2 dynamic activities**

Then the three sources of pattern 2 were reconstructed with the static reconstruction method and the dSPECT method. The TACs are shown in Figure 5.6 and 5.7. The same as with pattern 1, the images were reconstructed with 30 and 60 iterations and TACs were extracted in the same ways as in pattern 1.

For the dynamic reconstructions, TACs were fairly smooth with high statistic data. However, the shape of source 2 (green color lines) did not match the shape of the true curve. When low statistic data were reconstructed, more fluctuations were observed in the TACs from the static reconstruction than in the TACs from the dynamic reconstruction. Again, the TACs in green color from the dynamic reconstructions did not match the shape of the true curve.

Therefore, we can conclude that for pattern 2, the conventional dSPECT method cannot recover the dynamic activity of the shape of increasing-decreasing-then-increasing case. This was expected given the design of the dSPECT algorithm.

To handle dynamic activities of pattern 2 with the dSPECT method, the simplest way was to divide projection data into two parts at the valley point. The other option was to modify the dSPECT method to find not only a peak point but also a valley point. The two methods were tested in the following sections.
High counts

Figure 5.6 Pattern 2 with High statistic data: TACs from the static reconstructions (Top) and the dynamic reconstructions (Bottom). We notice that the increase-decrease-increase dynamic activity (green lines) was not recovered in the dynamic reconstructions.
Low counts

**Figure 5.7 Pattern 2 with Low statistic data:** TACs from the static reconstructions (Top) and the dynamic reconstructions (Bottom). We notice that the increase-decrease-increase dynamic activity (green lines) was not recovered in the dynamic reconstructions.
5.2.2. The dSPECT method with projection data divided into two parts

In the previous section, it was shown that the conventional dSPECT method cannot handle the activity changes of increase-decrease-increase. However, as discussed in the previous section, for handling this exceptional dynamic activity of pattern 2 using dSPECT method, the simplest way was to divide the projection data into two parts at the valley point. Then the first half block of data would contain increasing-then-decreasing activity, and the second half block would contain increasing activity. This method did not require modifying the dSPECT reconstruction algorithm itself.

Therefore, in this section pattern 1 and 2 dynamic projection data were divided into two parts and images were reconstruction by the dSPECT method. Since we knew the location of the lowest peak (the valley point) in pattern 2 being at the time frame (TF) 11 in the analytical data, we used this information to divide the projection data into two parts at the valley point.

![Figure 5.8 Valley point occurs at Time frame 11 in pattern 2: Dynamic data were divided into two parts at TF 11 and 2 parts were reconstructed separately.](image)

As the valley point in source 2 occurs at the time frame 11, the 19 time frames were split into the first part and the second part, and then reconstructed.
Nineteen time frames were separated into 2 blocks at Time frame 11 with overlapping 3 time-frames shown in Table 5.5. The same as in Section 5.2.1, the images were reconstructed with 30 and 60 iterations and each source was divided into three regions to plot the TACs. The locations of the selected voxels for each source are the same as the previous experiments.

<table>
<thead>
<tr>
<th>First half block</th>
<th>Second half block</th>
<th>Overlapped time frames</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frame 1-12</td>
<td>Frame 10-19</td>
<td>10,11,12</td>
</tr>
</tbody>
</table>

Table 5.5 Scheme of separating 19 projection data into two parts

Reconstruction of Pattern 1 dynamic activities

In Figure 5.9 and 5.10, TACs from the first half (Time Frame 1 to 11) and the second half (Time Frame 11 to 19) were plotted together for source 1, source 2 and source 3. The value of time frame 11 was twice plotted from the first half and the second half. As we can see in these figures, the pattern 1 sources (cases of increasing-only or increasing-decreasing) were handled as well as before for high statistic data and low statistic data. With 60 iterations, source 3 (blue curve) reached its maximum count. In the bottom images of Figure 5.9 and 5.10, TACs were not completely connected at time frame 11. With low statistic data, disjoint parts of TACs at time frame 11 were more obvious.
High Counts

Figure 5.9 Pattern 1 with High statistic data: TACs from dynamic reconstruction. Top: 30 iterations (left) and 60 iterations (left). Bottom Only time frames 9 to 13 were plotted for 30 iterations (left) and 60 iterations. The values of time frame 11 were plotted twice, i.e. the values from the first half and the second half were plotted.
Low counts

Figure 5.10 Pattern 1 with Low statistic data: TACs from dynamic reconstruction. Top: 30 iterations (left) and 60 iterations (left). Bottom Only time frames 9 to 13 were plotted for 30 iterations (left) and 60 iterations. The values of time frame 11 were plotted twice, i.e. the values from the first half and the second half were plotted. The disjoint parts were slightly more obvious than in High statistic data.

Reconstruction of Pattern 2 dynamic activities

In Figures 5.11 and 5.12, TACs from the first half (Time Frame 1 to 11) and the second half (Time Frame 11 to 19) were plotted in the same way as pattern 1. As we can see in these figures, the pattern 2 sources (case of increasing-only, increasing-decreasing,
or increasing-decreasing-increasing) were handled well for high and low statistic data even though some fluctuations were observed in low statistic data. Again, with 60 iterations, source 3 (blue curve) reached its maximum count.

**High counts**

![Figure 5.11 Pattern 2: TACs from dynamic reconstruction with high statistic data. Top: 30 iterations (left) and 60 iterations (left). Bottom: Only time frames 9 to 13 were plotted for 30 iterations (left) and 60 iterations. The values of time frame 11 were plotted twice, i.e. the values from the first half and the second half were plotted. Source 2 (green color lines) can recover the shape of true dynamic activity.](image-url)
Low counts

\[
\text{LOW: } 30 \text{ iter. 1st half: 1-12 \& 2nd half: 10-19} \\
\text{LOW: } 60 \text{ iter. 1st half: 1-12 \& 2nd half: 10-19}
\]

\[
\text{LOW: } 30 \text{ iter. 1st half: 9-11 \& 2nd half: 11-13} \\
\text{LOW: } 60 \text{ iter. 1st half: 9-11 \& 2nd half: 11-13}
\]

Figure 5.12 Pattern 2: TACs from dynamic reconstruction with low statistic data. Top: 30 iterations (left) and 60 iterations (left). Bottom Only time frames 9 to 13 were plotted for 30 iterations (left) and 60 iterations. The values of time frame 11 were plotted twice, i.e. the values from the first half and the second half were plotted. Source 2 (green color lines) can recover the shape of true dynamic activity.

In pattern 2, the same phenomena were observed at the valley point in time frame 11 as with in pattern 1. Figure 5.11 and 5.12, TACs were not completely connected at
time frame 11, and with low statistic data, disjoint parts of TACs at time frame 11 were more obvious.

From this experiment, we conclude that when the valley point is known a priori, the conventional dSPECT method can be used by splitting dynamic data at the time frame where the valley point occurs.

However, in reality, it is not possible to know the exact location of the valley point a priori. Moreover, there may be multiple time frames where the valley points could occur, as all voxels behave differently. Thus, it may be impossible to divide the projection data into two parts at one time frame. This motivated us to develop a new algorithm to handle an increasing-decreasing-increasing case.
Chapter 6.

Modification of dSPECT method: dSPECTpv

In order to handle the activity behaviour of increasing-decreasing-then-increasing case that may arise in dynamic studies of myocardial blood flow and flow reserves discussed in Section 2.5, it was necessary to develop a new algorithm. We call the new algorithm dSPECTpv, where “pv” stands for peak-valley, indicating that the method can handle increasing-decreasing-then-increasing activity. It automatically locates the peak and the valley in this pattern.

6.1. The dSPECTpv algorithm

The new algorithm is a modification of the dSPECT method which finds the peak and valley activities during the iteration. The activity in a voxel will increase up to the maximum amount at time $p$ (time frame $p$ for peak), then it will decrease until the minimum amount is reached at time $v$ (time frame $v$ for valley), then the activity will increase again. Thus, exploiting the equations (3.20), (3.22) and (3.24), this relationship can be expressed as follow:

$$0 \leq x_i(t_1) \leq x_i(t_2) \leq \cdots \leq x_i(t_{p-1}) \leq x_i(t_p) \geq x_i(t_{p+1}) \geq \cdots \geq x_i(t_{v-1}) \geq x_i(t_v) \leq x_i(t_{v+1}) \leq \cdots \leq x_i(t_{N-1}) \leq x_i(t_N) \quad (6.1)$$

The relationship in (6.1) guarantees the positivity of the first time frame up to the valley point. For the valley point, if the similar manner as the peak point relationship described in Section 3.2.1 is used, the relationship between the valley point time frame and the one before and the one after the valley point time, $x_i(t_{v-1}) \geq x_i(t_v) \leq x_i(t_{v+1})$ can be expressed as:
When we write this relationship in matrix-vector multiplication form similar to (3.26), the linear equation for the row where the valley activity occurs is

\[ x_i(t_{v-1}) - 2x_i(t_v) + x_i(t_{v+1}) = \frac{\ddot{x}}{x_v} . \] (6.3)

If we set the row where the valley occurs as Equation (6.3), and assume that the total number of time frames is 8 and the peak and valley points occur at time frames 3 and 6, respectively, the simplest way to write a difference matrix by adapting the design of the dSPECT method is as follows.

\[
\begin{bmatrix}
1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
-1 & 1 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & -1 & 2 & -1 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 1 & -1 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 1 & -1 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 1 & -2 & 1 \\
0 & 0 & 0 & 0 & 0 & 0 & 1 & -1 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 1
\end{bmatrix} .
\] (6.4)

However, the determinant of the matrix (6.4) is zero, thus the matrix is not invertible. Moreover, with this inequality for the valley point, the value of the valley is allowed to be negative. Yet, it is necessary to keep the positivity of voxel values during the reconstruction process as the count of radioactive tracers must never be negative. To guarantee the positivity of the valley point value, the algorithm was designed such that only the positivity of the valley point was enforced in the difference matrix. That is, the valley point value is enforced to be simply greater or equal to zero in the difference matrix, i.e.

\[ x_i(t_v) \geq 0, \text{  thus  } x_i(t_v) = \frac{\ddot{x}}{x_v} \geq 0 . \] (6.5)

Now the difference matrix C for increasing-decreasing-increasing case is defined in (6.6). The system equation (6.6) shows the relationship between the difference matrix C and the difference of activities between two consecutive time frames \( \ddot{x} \) in the matrix-
vector multiplication form. For the sake of simplicity, setting the total number of time frames be 8 and the maximum value (the peak) is assumed to achieve at time frame 3, namely $t_3$ and the minimum value (the valley) at time frame 6, namely $t_6$.

\[
\tilde{x} = \begin{bmatrix}
    x_i(t_1) \\
x_i(t_2) - x_i(t_1) \\
-x_i(t_2) + 2x_i(t_3) - x_i(t_4) \\
x_i(t_4) - x_i(t_5) \\
x_i(t_5) - x_i(t_6) \\
x_i(t_6) \\
x_i(t_7) - x_i(t_6) \\
x_i(t_8) - x_i(t_7)
\end{bmatrix} = \begin{bmatrix}
    1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
-1 & 1 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & -1 & 2 & -1 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 1 & -1 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 1 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 1 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & -1 & 1 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & -1 & 1
\end{bmatrix} \begin{bmatrix}
x_i(t_1) \\
x_i(t_2) \\
x_i(t_3) \\
x_i(t_4) \\
x_i(t_5) \\
x_i(t_6) \\
x_i(t_7) \\
x_i(t_8)
\end{bmatrix} = Cx. \tag{6.6}
\]

As we can see in the row 6 of the difference matrix $C$ in (6.6), the valley point value is set as $x_i(t_6) = \tilde{x}_i(t_6)$. Thus, as long as $\tilde{x}_i(t_6) \geq 0$, it is guaranteed that $x_i(t_6) \geq 0$.

In the difference matrix $C$, the first entry of $C$, i.e. $C(1,1)$ is set to 1 to guarantee the positivity of $x_i(t_1) = \tilde{x}_i(t_1) > 0$. The activity increases up to time frame 3, and decreases down to time frame 6, at where, the positivity of the activity is guaranteed. Then again the activity increases. The determinant of this matrix is non-zero, thus $C$ is invertible, and the inverse of the difference matrix $C$ can be written as:

\[
C^{-1} = \begin{bmatrix}
1 & 1 & 1 \\
1 & 1 & 1 \\
1 & 1 & 1 \\
1 & 1 & 1 \\
1 & 1 & 1 \\
1 & 1 & 1 \\
1 & 1 & 1 \\
1 & 1 & 1
\end{bmatrix}. \tag{6.7}
\]
The difference matrix $C$ was developed for handling a specific case, an increase-decrease-increase activity that may occur in our dynamic cardiac studies. However, in reality, the activities of radioactive tracer administered in a human will eventually decrease.

One could easily modify the difference matrix $C$, so that it can also handle the case of increase-decrease-increase-then-decrease activity. Again, for the sake of simplicity, we assume that the total number of time frames is 11, and the peak at time frame 3, the valley at time frame 6, then the second peak at time frame 9. Then we can write a modified difference matrix $C'$ as shown in (6.8). The matrix $C'$ is simply the difference matrix $C$ plus additional rows and columns:

\[
C' = \begin{bmatrix}
1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
-1 & 1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & -1 & 2 & -1 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 1 & -1 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 1 & -1 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 1 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & -1 & 1 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & -1 & 1 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & -1 & 2 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1
\end{bmatrix}
= \begin{bmatrix}
C \\
* \\
*
\end{bmatrix}.
\]

Asterisks in (6.8) indicate new entries addition to the difference matrix $C$. With the additional entries of the difference matrix $C'$, the activity increases up to time frame 9 as before, and it reaches to the peak activity count at time frame 9, then subsequently the activity decrease. The determinant of $C'$ is nonzero, therefore, it is invertible. The inverse of $C'$ is given as the form of (6.9).
In this thesis, the capability of the modified difference matrix $C'$ is not investigated. However, as the format of the inverse of $C'$ is very similar to the inverse of $C$, the implementation of $C'$ would not be difficult and will be performed in future work.

6.2. Correctness of dSPECTpv method (pattern 1)

For this experiment in Section 6.2 and next section 6.3, the same source with the shape of letter F was used as the experiments of Chapter 5. Again, the F shape source is not realistic compared to a human heart, yet, it is a fairly complex shape and asymmetric enough to test the correctness of the algorithm.

6.2.1. Method: Pattern1 Dynamic activities

In order to check if the new algorithm dSPECTpv can handle the normal dynamic activities, pattern 1 source activity behaviours used in Chapter 5 were tested. For pattern 1, source 1 had a dynamic behaviour of increasing and decreasing with the peak count (maximum count) of $2.70 \times 10^7$, source 2 had a dynamic behaviour of increasing only with a maximum count of $5.4 \times 10^7$, and source 3 had a behaviour of increasing-then-decreasing with a maximum count of $1.08 \times 10^8$ for Level 0. The maximum values of three sources
which were used in first experiment were 10 times higher of those in the experiments of Chapter 5. Three more count levels were tested as explained in Table 6.1.

<table>
<thead>
<tr>
<th>Source</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Max counts</td>
<td>$2.70 \times 10^7$</td>
<td>$5.4 \times 10^7$</td>
<td>$1.08 \times 10^8$</td>
</tr>
<tr>
<td>Level</td>
<td>Counts</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>1 / 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>1 / 4 of Level 0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>1 / 10 of Level 0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>1 / 40 of Level 0</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 6.1 Level numbers and various peak counts of sources in pattern 1

As explained in Chapter 5, each line source has 18 voxels. But when TACs are plotted, each line source is divided into three regions. Therefore, here, the true time activity curves are plotted for 6 voxels, thus the peak counts are decreased to 1/3 of the values mentioned above.

Figure 6.1 True dynamic behaviour of 3 sources in pattern 1
Figure 6.2 True image (TF5, slice 38) and the profile of each line source for Level 0 (Highest counts) in pattern 1. The image and profiles were plotted in $[0, 6.5 \times 10^6]$. In the left top figure, source1 is the left vertical line (blue), source 2 is the horizontal line, and source 3 is the right vertical line (yellow).

The two dimensional images of time frame 5 slice 38 is shown in the left top in Figure 6.2. In this image, source1 is the left vertical line (blue), source 2 is the horizontal line, and source 3 is the right vertical line (yellow). The profile is shown at $x=18$ for source 1, $x=28$ for source 3, and $y=22$ for source 2, where the x-axis is horizontal and the y-axis is vertical in the theft top image.

### 6.2.2. Results

The TACs and profiles of the reconstructed images of each count level from the static reconstruction and the dynamic reconstruction are shown in this section. TACs from the dSPECTpv are very similar to those from the conventional dSPECT shown in Section 5.2.1. In Section 5.2.1 the number of total counts tested were equivalent to level 2 and 3 in this section. Thus, these reconstructed images from the conventional dSPECT methods were again displayed for comparison in Figure 6.3 and Figure 6.4.
Figure 6.3 The bottom images of Figure 5.4 Pattern 1 with High statistic data Dynamic reconstruction. The count is equivalent to Level 2 in this section.

Figure 6.4 The bottom images of Figure 5.5 Pattern 1 with Low statistic data Dynamic reconstruction. The count is equivalent to Level 3 in this section.
**Level 0 (Highest counts)**

Figure 6.5 TACs with counts Level 0, Top: TACs from the static reconstructions with 30 iterations (left) and 90 iterations (right), Bottom: TACs from the dynamic reconstructions with 30 iterations (left) and 90 iterations (right). No improvement was observed with more than 90 iterations for the static reconstruction and the dynamic reconstruction.
Figure 6.6 Reconstructed image (TF5, slice 38) and the profile of each line source with Level 0. Static reconstruction with 90 iterations (top) and Dynamic reconstruction with 90 iterations (bottom). The image and profiles were plotted in $[0, 6.5 \times 10^6]$.
Figure 6.7 TACs with counts Level 1, Top: TACs from the static reconstructions with 30 iterations (left) and 90 iterations (right). Bottom: TACs from the dynamic reconstructions with 30 iterations (left) and 90 iterations (right). No improvement was observed with more than 90 iterations for the static reconstruction and the dynamic reconstruction.
Figure 6.8 Reconstructed image (TF5, slice 38) and the profile of each line source with Level1. Static reconstruction with 90 iterations (top) and Dynamic reconstruction with 90 iterations (bottom). The image and profiles were plotted in $[0, 2 \times 10^6]$.
Figure 6.9 TACs with counts Level 2, Top: TACs from the static reconstructions with 30 iterations (left) and 60 iterations (right), Bottom: TACs from the dynamic reconstructions with 30 iterations (left) and 60 iterations (right). The TACs from the static reconstruction are the same as those in Figure 5.4 Top images.
Figure 6.10 Reconstructed image (TF5, slice 38) and the profile of each line source with count Level 2. Static reconstruction with 60 iterations (top) and Dynamic reconstruction with 60 iterations (bottom). The image and profiles were plotted in [0, 7x10^5].
Level 3 (1/40 of the highest counts)

Figure 6.11 TACs with counts Level 3, Top: TACs from the static reconstructions with 30 iterations (left) and 60 iterations (right), Bottom: TACs from the dynamic reconstructions with 30 iterations (left) and 60 iterations (right). The TACs from the static reconstruction are the same as those in Figure 5.5 Top images.
Figure 6.12 Reconstructed image (TF5, slice 38) and the profile of each line source with count Level 3. Static reconstruction with 60 iterations (top) and Dynamic reconstruction with 60 iterations (bottom). The image and profiles were plotted in \([0, 1.7\times10^5]\)
The results show that the dSPECTpv method works as well as the conventional dSPECT method when the dynamic activity behaviours are increasing only or increasing and decreasing. The TACs from the dSPECTpv method were less oscillatory than the TACs from the static reconstructions when the numbers of counts were decreased, and the profiles were more uniform.

The profile drawn along the line source 3 (the right vertical line in yellow color in the 2D image) was flat in the true image. However, profiles in the reconstructed images were consistently non-uniform. The activity at the left end of the profile was always lower than that at the right end. This was because the left end of source 3 was close to source 2, thus the left end activity was lowered due to the lower activity of source 2. However, the right end was not close to anything, this side was not affected by other activities. As the joint part of source 2 and 3 forms a T shape, and the line sources are by themselves thin, as a result, it seems that is difficult for the reconstruction algorithm to recover the original shape. This phenomenon was observed when more iterations were performed. The same behaviour was observed in the experiments in Section 6.3.

### 6.3. Investigation of Capability of dSPECTpv Method (pattern2)

After testing the capability of the dSPECTpv to handle **pattern 1** activity (we call it a normal case), **pattern 2** dynamic activities were investigated. Our objective in this section was to see whether dSPECTpv could handle the dynamic activity of increasing-decreasing-increasing case.

#### 6.3.1. Method: Pattern 2 dynamic activities

For **pattern 2**, source 1 and 3 were the same as in Section 6.2, (source 1: a behaviour of increasing-decreasing with the peak count of \(2.70 \times 10^7\), source 3: a behaviour of increasing-decreasing with a maximum count of \(1.08 \times 10^8\)), but source 2 had a dynamic behaviour of increasing-decreasing-then-increasing with a maximum count of \(6.75 \times 10^7\) for Level 0. As the same as in **pattern 1**, the maximum values of three
sources at the beginning were 10 times higher than those in the experiments of Chapter 5, and gradually decreased, as shown in Table 6.2.

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Table 6.2 Level numbers and various peak counts of sources in pattern 2

As explained in Section 6.2.1, the true time activity curves are plotted for 6 voxels, thus the peak counts decrease to 1/3 of the values mentioned above.

![Graph of time activity curves for 3 sources](image)

Figure 6.13 True dynamic behaviour of 3 sources in pattern 2

The two dimensional images of time frame 5 slice 38 is shown in the left top in Figure 6.14. As explained in Section 6.2.1, source 1 is the left vertical line (blue), source
2 is the horizontal line, and source 3 is the right vertical line (yellow). The profile is shown at $x=18$ for source 1, $x=28$ for source 3, and $y=22$ for source 2 where the x-axis is horizontal, and the y-axis is vertical.

Figure 6.14 True image (TF5, slice 38) and the profile of each line source. The image and profiles were plotted in $[0, 6.5 \times 10^6]$. In the left top figure, source 1 is the left vertical line (blue), source 2 is the horizontal line, and source 3 is the right vertical line (yellow). In the right top figure, the profile of source 1 is non-uniform. This is because a part of source 2 is included in the left edge.

For the dSPECTpv reconstructions, it is more difficult than for the static reconstruction to reach a stable condition since all time frames are processed at the same time and it is necessary to determine the locations of all peak and valley points. Thus, more iterations than in the experiment of the previous section were used, typically, 150. This number was determined experimentally.

6.3.2. Results

The image was reconstructed with the dSPECTpv method and the static reconstruction method with and without background. In real life, situations when the radioactive tracer is administered to a patient, not only the targeted organ (in our research,
a heart) will show uptake the radioactive tracers, but also other body parts will do that. Subsequently, when the heart is scanned, the emissions from other tissues or organs near the heart are also detected. Therefore, the effect of background on the reconstructions was investigated. The results with background will be presented after the investigation without background.

**Reconstruction without Background**

TACs from the static reconstruction with 90 iterations are equivalent to the TACs from the dynamic reconstruction with 150 iterations in Figure 6.15. Thirty iterations are not enough for both methods to reach a stable condition as activity reconstructed in source 3 (blue color lines) was lower than the true curve when 30 iterations were used. No improvement was observed for more than 90 iterations for the static reconstruction and 150 iterations for the dynamic reconstruction. When high statistic data were reconstructed, more iteration made the TACs smoother.

In Figure 6.16, the reconstructed images from the static reconstruction with 90 iterations and the dynamic reconstruction with 150 iterations were used to view the two dimensional images of time frame 5 slice 38 and the profiles of vertical line sources, source 1 (x=18), source 2 (y=22) and source 3 (x=28). The values of profiles of source 2 and 3 from the dynamic reconstructions were higher than the ones from the static reconstruction.
Figure 6.15 TACs with counts Level 0, Top: TACs from the static reconstructions with 30 iterations (left) and 90 iterations (right). Bottom: TACs from the dynamic reconstructions with 30 iterations (left) and 150 iterations (right). No improvement was observed with more than 90 iterations for the static reconstruction and 150 iterations for the dynamic reconstruction.
Figure 6.16 Reconstructed image (TF5, slice 38) and the profile of each line source for L0. Static reconstruction with 90 iterations (top) and Dynamic reconstruction with 150 iterations (bottom). The image and profiles were plotted in $[0, 6.5 \times 10^6]$
Level 1 (1/4 of the highest counts)

Figure 6.17 TACs with counts Level 1 Top: TACs from the static reconstructions with 30 iterations (left) and 90 iterations (right), Bottom: TACs from the dynamic reconstructions with 30 iterations (left) and 150 iterations (right)
Figure 6.18 Reconstructed image (TF5, slice 38) and the profile of each line source for L1. Static reconstruction with 90 iterations (top) and Dynamic reconstruction with 150 iterations (bottom). The image and profiles were plotted in [0, 15x10^5].
Figure 6.19 TACs with counts Level 2 Top: TACs from the static reconstructions with 30 and 60 iterations, Bottom: TACs from the dynamic reconstructions with 30 and 60 iterations (right). The TACs from the static reconstruction are the same as those in Figure 5.6 Top images.
Figure 6.20 The reconstructed image (TF5 slice 38) and the profile of each line source for L2. Static reconstruction with 60 iterations (Top), Dynamic reconstruction with 60 iterations (bottom) scale: [0 5.5x10^5]
Level 3 (1/40 of the highest counts)

Figure 6.21 TACs with counts Level 3 Top: TACs from the static reconstructions with 30 and 60 iterations, Bottom: TACs from the dynamic reconstructions with 30 and 60 iterations. The TACs from the static reconstruction are the same as those in Figure 5.7 Top images.
Static: 60 iterations

Dynamic: 60 iterations

Figure 6.22 The reconstructed image (TF5 slice 38) and the profile of each line source for L3. Static reconstruction with 30 iterations (Top), Dynamic reconstruction with 60 iterations (bottom). The image and profiles were plotted in [0, 1.5x10^5].
When higher statistics data were used, there was no significant difference in the results between the static reconstruction and the dynamic reconstruction. However, as the levels of counts were decreased, there were fewer fluctuations in TACs of the images from the dynamic reconstruction than in those from the static reconstruction. In level 2 and 3, the profiles of the line sources from the dynamic reconstruction were slightly smoother than those from the static reconstruction. For fewer counts in the original sources, the dynamic reconstruction did not require many iterations to reach a stable condition.

The summary of results for different iteration numbers were shown in Table 6.3.

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Table 6.3 Summary of Results with various iteration numbers for NO background
Δ: not enough iterations, O: reasonable, - : no further improvement.
The results show that the dSPECTpv method can handle the case of increasing-decreasing-increasing. When high statistic data were used, the dynamic reconstruction requires more iterations to reach a stable condition. With low statistic data, 60 iterations were enough for the dynamic reconstruction. Otherwise, the TACs become more oscillatory as the algorithm tries to fit noise.

**Reconstruction with Background**

Next, background was added to the source of the shape of letter F. The background was created as a box with dimensions of 28x11x28 voxels around the source F, and the values of zero were assigned to the location of the source. The values of the background were assigned such that the counts in the background are uniform throughout the time frames and the activity count per voxel was equal to $1/10$ of the peak counts of source 1 (The peak count of source 1 occurs at time frame 12). The different levels of counts in the source used in the previous section were again tested, and the $1/10$ of the peak count of source 1 was assigned to each voxel in background for each different level.

![Figure 6.23 Left: True dynamic activities for Source 1 (red), 2 (green) and 3 (blue). Background (black line) is set such that the count per voxel is 1/10 of the highest count of source 1. The true time activity curves are plotted for 6 voxels, thus the peak counts decrease to 1/3 of the ones mentioned above as well as background. Right: The values of the location of letter F were as 0 in background.](image)
Figure 6.24 Background. Background was created around the source of letter F. The voxels of the source location were set as the value of 0, and the rest was set as some value. Top left: Box as background, Top Right: the xz-plane view, Bottom Left: the xy-plane view, Bottom Right: the yz-plane view.
In order to plot TACs, the ROIs defined as 6x3x3 voxels (1/3 of the original length and additional 1 voxel for both sides) were used as explained in Section 5.2.1. In Section 5.2.1, there was no background, therefore extra voxels next to a source had no effect on the total count of the ROI. However, since there were background counts in nearby voxels, and we plotted TACs in the same way as before, the total count of the ROI would be boosted due to background counts. Therefore, the counts of background were subtracted from 8 voxels around the line source when TACs were plotted. For plotting TACs, the same colors and line types were used for each line source explained in Section 5.2.1, and additionally background was plotted in cyan color.

The results are shown in Figures 6.26 to Figure 6.33. The number of iterations was determined such that the three line sources roughly recovered the shapes of the true activities. For the static and the dynamic reconstructions, 90 and 150 iterations, respectively, were enough to reach the shapes of the true curves when there was no background and the highest statistic data were reconstructed. However, when the highest statistics data were reconstructed with background, 150 and 300 iterations were required.
to recover the shapes of the truth. We also noticed that the widths of each profile with background became wider than those without background.

**Level 0 (Highest count)**

Figure 6.26 L0 High Counts projection data with Background Top: TACs from the static reconstructions with 30 iterations (left) and 150 iterations (right), Bottom: TACs from the dynamic reconstructions with 30 iterations (left) and 300 iterations (right).
Static: 150 iterations

![Static reconstruction with 150 iterations](image)

Dynamic: 300 iterations

![Dynamic reconstruction with 300 iterations](image)

Figure 6.27 Reconstructed images (Time Frame 5 slice 38) and profiles of each line sources for L0: The static reconstruction with 150 iterations and the dynamic reconstruction (bottom) with 300 iterations. The image and profiles were plotted in $[0, 3 \times 10^6]$.
Level 1 (1/4 of the highest count)

Figure 6.28 L1 (1/4 of the highest counts) data with Background Top: TACs from the static reconstructions with 30 iterations (left) and 150 iterations (right). Bottom: TACs from the dynamic reconstructions with 30 iterations (left) and 300 iterations (right).
Figure 6.29 Reconstructed images (Time Frame 5 slice 38) and profiles of each line sources for L1 from the static reconstruction with 150 iterations and the dynamic reconstruction (bottom) with 300 iterations. The image and profiles were plotted in $[0, 8 \times 10^5]$
Figure 6.30 L2 (1/10 of the highest counts) data with Background. Top: TACs from the static reconstructions with 30 iterations (left) and 150 iterations (right). Bottom: TACs from the dynamic reconstructions with 30 iterations (left) and 210 iterations (right).
Figure 6.31 Reconstructed images (Time Frame 5 slice 38) and profiles of each line sources for L2 from the static reconstruction with 150 iterations and the dynamic reconstruction (bottom) with 210 iterations. The image and profiles were plotted in $[0, 2.8 \times 10^5]$
Level 3 (1/40 of the highest count)

Figure 6.32 L3 (1/40 of the highest counts) data with Background. Top: TACs from the static reconstructions with 30 iterations (left) and 120 iterations (right). Bottom: TACs from the dynamic reconstructions with 30 iterations (left) and 210 iterations (right).
Figure 6.33 Reconstructed images (Time Frame 5 slice 38) and profiles of each line sources for L3 from the static reconstruction with 120 iterations and the dynamic reconstruction (bottom) with 210 iterations. The image and profiles were plotted in $[0, 6.5 \times 10^4]$.
This experiment showed that more iterations were required for both the static and dynamic reconstructions when there was background, compared to the case without background. As well, when the low statistics data were reconstructed, TACs from the dynamic reconstructions were less oscillatory than those from the static reconstructions. The summary of results according to the iteration numbers are shown in Table 6.4.

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Table 6.4 Summary of Results with various iteration numbers for with background
Δ: not enough iterations, O: reasonable, -: no further improvement.

The experiments in this chapter demonstrate that dSPECT pv can handle the situation of increasing-decreasing-increasing time activity. When the high statistics data was used for the reconstruction, there was no significant difference between the results of the static reconstruction and the dynamic reconstruction. However, for low statistics
data or low statistics data with background, the dSPECTpv produced much smoother TACs. Since one of our goals is to reduce the amount of the radioactive tracers administered to a patient, dSPECTpv’s ability to handle low statistics data better is encouraging.

When the source with background was reconstructed using the dSPECTpv method, the valley seemed to be smoothed-out, i.e. the valley did not reach the expected minimum in the green curve. This phenomenon was more noticeable when low statistic data were reconstructed (see Figure 6.30). This is due to the mechanism of the dSPECTpv method that smooths the voxel behaviour over time which prevents the TAC from reaching the expected minimum.

For the reconstruction time, with 30 iterations, the static reconstruction code required 7 minutes 41 seconds to reconstruct 19 time frames separately, whereas the dynamic reconstruction code required 4 minutes 37 seconds to reconstruct all 19 time frames simultaneously. The reconstruction was done with Linux 32bit OS, Ubuntu 14.04.2.

6.3.3. Numerical Error Analysis

The errors were calculated numerically using formula 4.1 for three reconstruction methods, the static, the dSPECT, and the dSPECTpv method for Pattern 1 dynamic activity, and for two methods, the static and the dSPECTpv method for Pattern 2.

The error analysis was done for three level counts, namely Level 0, 2, and 3. As Level 1 has small difference (1/4 of Level 0 counts) in the counts from Level 0, it was not included. For numerical error analysis plots in Figure 6.34, 6.35 and 6.36, the red curves indicate the errors from the dSPECT method, the blue curves from static reconstruction, and the green curves from the dSPECTpv method.

**Pattern 1 Dynamic activity**

**Level 0**

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Table 6.5 Numerical Errors from dSPECT, static and dSPECTpv methods for Pattern 1 dynamic activity

Figure 6.34 Error plot of Table 6.5 Left: level 0, Middle: Level 2, Right: Level 3, Red: dSPECT, Blue: Static, Green: dSPECTpv.
**Pattern 2 Dynamic activity with NO background**

**Level 0**

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**Table 6.6 Numerical Errors** from the static and the dSPECTpv methods for Pattern 2 dynamic activity without background.

**Figure 6.35 Error plot for Table 6.6** Left: level 0, Middle: Level 2, Right: Level 3, Blue: Static, Green: dSPECTpv.
**Pattern 2 Dynamic activity with background**

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**Level 2**

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**Table 6.7 Numerical Errors** from the static and the dSPECTpv methods for Pattern 2 dynamic activity with background

**Figure 6.36 Error plot for Table 6.7** Left: level 0, Middle: Level 2, Right: Level 3, Blue: Static, Green: dSPECTpv
Observations

For Pattern 1 dynamic activity, when the results from the static, dSPECT and dSPECTpv methods were compared, for the highest statistic data (Level 0), the errors from three reconstruction methods were very similar. However, as counts decreased (Level 2 and 3 statistic data), the errors from dSPECT became slightly smaller than those from dSPECTpv. The errors from the static reconstructions were the largest for all count levels.

For Pattern 2 dynamic activity with or without background, when the results from the static and dSPECTpv methods were compared, the static reconstructions had smaller errors when the highest count level source (Level 0) with background was reconstructed. However, for all other cases, even though the dSPECTpv methods required more iterations, the errors from the dSPECTpv method were smaller than those from the static method with and without background for all count levels.

When the number of iteration increased, the error became smaller, but as the number of counts decreased, the errors became larger for all methods. These results were as we expected.

In general, when the count level was high, the static method worked fine. For low count levels, dSPECTpv method worked better, however it required more iterations.
Chapter 7.

Dynamic reconstruction with Pig data

In the previous chapter, we examined the dSPECTpv’s ability to handle the dynamic activity behaviour of increase-decrease-increase. As discussed in previous sections, this dynamic activity could be observed in dynamic studies of myocardium flow reserves. In this chapter, dynamic studies of the pig heart were performed on a pig with occluded heart using the dSPECTpv method developed in Chapter 6.

The pig heart data were reconstructed using the static reconstruction method and the dSPECTpv method. The attenuation and scatter corrections were not included. After reconstructing images with the two methods, images were also analyzed with the kinetic analysis software FlowQuant.[Klein 2010a] (Section 2.5).

7.1. Experiment with Tc-99m

The dynamic projection data that consisted of 19 time frames were obtained by the Discovery NM530c using Tc-99m tetrofosmin as the radioactive tracer in the University of Ottawa Heart Institute. Data were acquired with variable time frames. The length of time frames was 10 seconds for time frames 1 to 9 (9 time frames), 15 seconds for time frames 10 to 15 (6 time frames), and 120 seconds for time frames 16 to 19 (4 time frames).

After obtaining the dynamic projection data (called the original data), six new low counts dynamic projection data sets, corresponding to 75%, 50%, 25%, 12.5%, 6.25% and 3.125% of the counts of the original data were created. To ensure the subsamples have appropriate Poisson noise character, sampling was done based on time intervals.

The dynamic projection data were recorded in the list mode, and an event (or multiple events) was recorded every millisecond within the list mode. In list-mode processing, data was recorded as it arrived, and time stamps were put in the data stream every 1 millisecond. Thus, for example, to obtain 75% of the original counts, the first 3 of
every 4 milliseconds of data were kept to ensure the subsampled data had corresponding Poisson noise.

7.2. Results for the static method and dSPECTpv method

As the pig heart data had variable time frames, for the static reconstruction, the TACs were plotted by normalizing the time-frame duration to 10 seconds. For the dynamic reconstruction, the reconstruction algorithm requires uniform time frame length, normalization of time frame to 10 seconds was performed during the reconstruction. The number of iterations to be used was decided by examining the reconstructed images. For extracting TACs, a 3-by-3-by-3 voxels in Figure 7.1 (approximately the region of the red circle) were used as the ROI to extract TACs for all data.

![Image](image.png)

**Figure 7.1** The ROI used to extract TACs. The 3-by-3-by-3 voxels \((x, y, z) = (44:46, 44:46, 29:31)\) was indicated in the red circle.

The images shown in Figure 7.2 to Figure 7.7 were from time frame 17 slice 35 to 38. Since time frame 17 has time duration of 120 sec, the reconstructed images from the static reconstruction have the counts for 120 seconds, whereas the reconstructed images from the modified dSPECT method have the counts for 10 seconds as the variable time frames were normalized to 10 seconds during the reconstruction.
(1) 75 percent of the original counts: 50 iterations

Figure 7.2 Time Activity curves and Reconstructed images of 75% counts of the original data; Top: TACs from static (blue) and dynamic (red) reconstructions, Bottom: Reconstructed image (Time frame 17, slice 35 to 38) from static (left, scale in [0, 36000]) and dynamic (right, scale in [0, 3000]) reconstructions
(2) 50 percent of the original counts: 50 iterations

Figure 7.3 Time Activity curves and Reconstructed images of 50 % counts of the original data; Top: TACs from static (blue) and dynamic (red) reconstructions, Bottom: Reconstructed image (Time frame 17, slice 35 to 38) from static (left, scale in [0, 36000]) and dynamic (right, scale in [0, 3000]) reconstructions
(3) 25 percent of the original counts: 50 iterations

Figure 7.4 Time Activity curves and Reconstructed images of 25% counts of the original data, Top: TACs from static (blue) and dynamic (red) reconstructions, Bottom: Reconstructed image (Time frame 17, slice 35 to 38) from static (left, scale in [0, 18000]) and dynamic (right, scale in [0, 1500]) reconstructions
(4) 12.5 percent of the original counts: 40 iterations

Figure 7.5 Time Activity curves and Reconstructed images of 12.5% counts of the original data, Top: TACs from static (blue) and dynamic (red) reconstructions, Bottom: Reconstructed image (Time frame 17, slice 35 to 38) from static (left, scale in [0, 9600]) and dynamic (right, scale in [0, 800]) reconstructions
(5) 6.25 percent of the original counts: 30 iterations

Figure 7.6 Time Activity curves and Reconstructed images of 6.25 % counts of the original data , Top: TACs from static (blue) and dynamic (red) reconstructions, Bottom: Reconstructed image (Time frame 17, slice 35 to 38) from static (left, scale in [0, 4800]) and dynamic (right, scale in [0, 400]) reconstructions
Figure 7.7 Time Activity curves and Reconstructed images of 3.125% counts of the original data, Top: TACs from static (blue) and dynamic (red) reconstructions, Bottom: Reconstructed image (Time frame 17, slice 35 to 38) from static (left, scale in [0, 2400]) and dynamic (right, scale in [0, 200]) reconstructions.
From these results, we noticed that the images from dynamic reconstructions were not notably better than those from the static reconstructions. However, the TACs from the dynamic reconstructions were effectively smoother than those from the static reconstructions and showed fewer fluctuations.

The total counts in the reconstructed images for time frames 10 to 19 from the static reconstruction and the dynamic reconstruction are different. The total counts from the dynamic reconstructions were approximately 1.5 times less than the counts in the images from the static reconstructions in time frames 10 to 15, and 12 times less than the counts in time frames 16 to 19. This is because the variable time frames had to be normalized during the reconstruction for dynamic reconstructions. However, the scaling data counts with a constant scaling factor will scale noise as well, thus the relative noise levels remain constant.

### 7.3. Analysis with FlowQuant software

We analyzed the reconstructed images with the FlowQuant software. The software fits the kinetic model to the data. As a result, it effectively smooths noisy data. Therefore, the pre-smoothing with the four dimensional reconstruction by dSPECTpv cannot necessarily be expected to give us an advantage over directly fitting a model to the noisy data. And it may even be detrimental by introducing biases by the pre-smoothing before the analysis.

Figure 7.8 to Figure 7.13 are the output plots from the FlowQuant software. As explained in Section 2.5, the red solid curve is the blood activity concentration measured in the series of dynamic images, and the red dashed curve is the plasma activity concentration. The blue points are the measured samples of the TAC from a region in the myocardium; the solid blue line is a fit to the blue points. The green points are the residuals of the difference between the measured blue points and the fitted blue curve. The cyan curve is the one-compartment fit for the “pure” myocardium TAC.

We can clearly see that the red curves and the values of the residuals in green points are much smoother and smaller, respectively, from the dynamic reconstruction than the red curves from the static reconstruction.
Figure 7.8 MBF estimation with a 1-tissue-compartment model: 75% of the original. Top: Static reconstruction, Bottom: Dynamic reconstruction.
Figure 7.9 MBF estimation with a 1-tissue-compartment model: 50% of the original Top: Static reconstruction, Bottom: Dynamic reconstruction
Figure 7.10 MBF estimation with a 1-tissue-compartment model: 25% of the original. Top: Static reconstruction, Bottom: Dynamic reconstruction.
Figure 7.11 MBF estimation with a 1-tissue-compartment model: 12.5% of the original Top: Static reconstruction, Bottom: Dynamic reconstruction
Figure 7.12 MBF estimation with a 1-tissue-compartment model: 6.25% of the original. Top: Static reconstruction, Bottom: Dynamic reconstruction.
Figure 7.13 MBF estimation with a 1-tissue-compartment model: 3.215% of the original Top: Static reconstruction, Bottom: Dynamic reconstruction
In the analysis of the reconstructed images by the FlowQuant software, the parameter values from two reconstructions were compared and plotted in Figure 7.14. The parameters examined are explained in Table 7.1.

<table>
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<th>Parameter name</th>
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<td>K1</td>
<td>The rate constant for extraction of the tracer from the blood compartment into the tissue compartment</td>
</tr>
<tr>
<td>TBV</td>
<td>Total blood volume = Fraction of volume occupied by blood</td>
</tr>
<tr>
<td>R² (R-squared)</td>
<td>It measures the quality of the fit of the model to the TAC in each voxel.</td>
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Table 7.1 Parameter names and explanations

From the plots in Figure 7.14, we can say that there is not a substantial difference between any of the measures except for $R^2$ values. With $R^2$ values, the static images show a steady decrease with decreasing counts in the data. This is expected as the images and therefore TACs become noisier with decreased counts. The flatter values of $R^2$ for the dSPECTpv reconstructions reflect the reduced noise in the TACs for that reconstruction. The overall similarity of the results suggests that the dSPECTpv reconstruction does not provide a substantial benefit over static reconstructions for the purpose of kinetic model fitting.

As explained at the beginning of this section, the software fits the kinetic model to the data, and it effectively smooths noisy data. The smoother images provided by dSPECTpv apparently do not lead to better parameter estimation.
Figure 7.14 Parameters and Error plots
Chapter 8.

Discussion, conclusion and future work

The objective of this thesis was to improve the accuracy of dynamic cardiac studies for data acquired by Discovery NM530c by using the dSPECT method. The dSPECT method reconstructs all time frames simultaneously, thus the relationship between time frames are taken into account during the reconstruction. As we are interested not only in spatial distribution of radioactive tracers in one time frame, but particularly in the distribution of radioactive tracer over time, the mechanism of the dSPECT method is well suited for dynamic studies.

While analyzing the performance of the conventional dSPECT method we realized that the behaviour of radioactive tracers in some regions of the heart exhibited a time-dependent behaviour that could not be reconstructed by the conventional dSPECT method. The activity level was increasing at first, then decreasing, and then increasing again due to the contribution from arterial blood to measured concentration of myocardial tissue activities.

To reconstruct this kind of activity, we first tried the simplest and most straightforward work-around, namely dividing the projection data into two parts for reconstructions. This approach although successful to some extent, requires a-priori knowledge of the activity to be reconstructed; it is not satisfactory in practice. Hence we developed a new method, a modification of the dSPECT method, called dSPECTpv, which, unlike conventional dSPECT, could handle the dynamic behaviour observed in this experiment.

When dSPECTpv was used for reconstructions, TACs were considerably smoother than those from the static reconstructions. This was particularly true when lower
statistic data with or without background were reconstructed: the resulting TACs had fewer fluctuations and were smoother than those from static reconstruction.

In future work the dSPECT method should be further modified so it is able to handle more dynamic behaviours. Had data been acquired for a longer time interval in our experiment, we would have observed activity ultimately decreasing. In Section 6.1 we briefly outline how such a modification could be implemented. As well, we could investigate the reasons behind the requirement of large numbers of iterations for dSPECTpv method to reach a stable condition.

In this thesis, the geometry of the Discovery NM530c was modeled in Monte Carlo simulation software, GATE. Even though modelling the camera geometry in GATE was very challenging and complex, we gained substantial knowledge about the camera system. Through this process, we were able develop our own static and dynamic reconstruction methods. With our simulation software one could devise algorithms to optimize the acquisition protocol. Another project would be to use the simulation software to tweak the camera geometry to optimize sensitivity.
References


Buvat I, Lazaro D 2006 Monte Carlo simulations in emission tomography and GATE: An overview Nucl. Instr. and Meth. A 569 323–329

Buvat I, Castiglioni I 2002 Monte Carlo simulations in SPECT and PET Q J Nucl. Med. 46 48-61


