Improving quantification in non-TOF 3D PET/MR by incorporating photon energy information

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I, Ludovica Brusaferri, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the work.
“Sometimes I’ve believed as many as six impossible things before breakfast.”

Lewis Carroll, *Alice in Wonderland*
Abstract

Hybrid PET/MR systems combine functional information obtained from positron emission tomography (PET) and anatomical information from magnetic resonance (MR) imaging. In spite of the advantages that such systems can offer, PET attenuation correction still represents one of the biggest challenges for imaging in the thorax. This is due to the fact that the MR signal is not directly correlated to gamma-photon attenuation. In current practice, pre-defined population-based attenuation values are used. However, this approach is prone to errors in tissues such as the lung where a variability of attenuation values can be found both within and between patients.

A way to overcome this limitation is to exploit the fact that stand-alone PET emission data contain information on both the distribution of the radiotracer and photon attenuation. However, attempts to estimate the attenuation map from emission data only have shown limited success unless time-of-flight PET data is available. Several groups have investigated the possibility of using scattered data as an additional source of information to overcome reconstruction ambiguities. This thesis presents work to extend the previous methods by using PET emission data acquired at multiple energy windows and incorporating prior information derived from MR.

This thesis is organised as follows. We first cover both the literature and mathematical theory relevant to the framework. Then, we present and discuss results on the case of attenuation estimation from scattered data only, when the activity distribution is known. We then give an overview of several candidates for joint reconstruction, which reconstruct both the activity and attenuation from scattered and unscattered data. We present extensive results using simulated data and compare the proposed methods to state-of-the-art MLAA from a single energy window acquisition. We conclude with suggestions for future work to bring the proposed method into clinical practice.
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Impact Statement

One of the main challenges of non-TOF PET/MR thorax imaging is the lack of a reliable attenuation correction method and consequently the possibility of reconstructing quantitative accurate PET images. Accuracy in quantification of activity concentrations is essential for monitoring disease progression and treatment effectiveness.

Methodologies to improve on existing methods have been proposed and implemented throughout this thesis. In particular, the feasibility of exploiting low energy photon information has been explored. Previous to the work of this thesis, this approach was only at its early stage of development; state-of-the-art studies were restricted to simple 2D phantoms and ideal energy resolution values. The Chapters of this thesis have progressed this technique from being a simple idea - only supported by proof-of-concept studies - to having a solid understanding of the method and its limitations. The added value of combining unscattered and scattered data has been demonstrated and the dependency of over-simple assumptions included in other previous work has been eliminated.

New reconstruction algorithms that exploit both scattered and unscattered photon energy information have been developed. The image quality of the reconstructed activity image was also improved by incorporating anatomical information from the MR image. All proposed algorithms have been thoroughly evaluated with simulated data-sets and promising results are obtained. A further validation of the proposed methodology with Monte Carlo generated data was also conducted, leading to a better understanding of the strengths and weaknesses of the method.

With the increased interest in image quantification, these algorithms could be utilised by future researchers for exploring possible clinical applications. The proposed methods could lay the foundation of further research or commercial software at both a national and international level.

The potential for such a method of attenuation correction has wide appeal in PET/MR
imaging given the need to overcome quantitative errors of conventional MR-AC methods, improving the reliability of the quantitative images.
## Contents

1 Introduction 29

1.1 Motivation ................................................. 29

1.1.1 Benefits offered by PET/MR tomographs .......... 29

1.1.2 Challenges in lung PET/MR attenuation correction 29

1.1.3 Challenges in Emission-Based non-TOF PET attenuation correction 30

1.1.4 Objective of this work ................................. 32

1.2 Overview of the thesis ...................................... 32

2 Background 35

2.1 Positron Emission Tomography ................................. 35

2.1.1 The physics of PET ........................................ 35

2.1.1.1 Brief overview of PET ............................... 35

2.1.1.2 Photon interaction with matter ........................ 36

2.1.1.3 Photon attenuation ....................................... 38

2.1.2 Data acquisition in PET ................................... 40

2.1.2.1 Photon detection ........................................ 41

2.1.2.2 Coincidence processing ................................. 45

2.1.2.3 Limits of spatial resolution in PET .................. 46

2.1.2.4 Data organisation ........................................ 46

2.1.3 Image Reconstruction ..................................... 48

2.1.3.1 Introduction to inverse problems ..................... 48

2.1.3.2 Analytic reconstruction methods ...................... 49

2.1.3.3 Iterative reconstruction methods ..................... 51

2.1.4 Data corrections .......................................... 57

2.1.5 Estimation of the scatter component .................... 57
3.2.1 Unscattered Events .............................................. 81
3.2.2 Scattered Events ................................................. 82
   3.2.2.1 Probability of scattering .......................... 83
   3.2.2.2 Effect of reduced energy on attenuation after Compton
         scattering ............................................. 84
3.3 Jacobian of the forward scatter model .......................... 84
   3.3.1 Analytical derivation ...................................... 84
      3.3.1.1 Attenuation ..................................... 85
      3.3.1.2 Activity ......................................... 86
   3.3.2 Discretisation and implementation ..................... 87
      3.3.2.1 Discrete formulation of SSS and SSS-Jacobian .... 87
      3.3.2.2 STIR implementation strategy .................... 88
      3.3.2.3 Numerical validation ............................ 88
      3.3.2.4 Considerations on the scatter Jacobian .......... 88
3.4 Gradient of the log-likelihood ................................ 89
3.5 Detector efficiency model ..................................... 90
   3.5.1 Photopeak window ......................................... 90
      3.5.1.1 Detection efficiency model ....................... 90
   3.5.2 Generic energy window ................................. 91
      3.5.2.1 Detection efficiency model ....................... 91
3.6 Discussion and Conclusion ..................................... 93

4 Attenuation estimation from energy window data below the photopeak window 94
4.1 Introduction ...................................................... 94
4.2 MLTR-EB .......................................................... 95
   4.2.1 Statistical Model .......................................... 95
   4.2.2 Optimisation ................................................ 96
      4.2.2.1 Image updates .................................... 96
      4.2.2.2 Implementation .................................... 97
      4.2.2.3 Penalised MLTR-EB ............................... 97
   4.2.3 Simulation Setup .......................................... 97
      4.2.3.1 Preliminary study: point sources ................ 97
      4.2.3.2 3D XCAT torso phantom ......................... 98
## 4.2.4 Reconstruction Setup

4.2.4.1 MLTR-EB ................................. 99
4.2.4.2 MLTR-EB + PLS ......................... 99

## 4.2.5 Results

4.2.5.1 Initial investigations ...................... 100
4.2.5.2 3D XCAT torso phantom reconstruction .......... 100

## 4.2.6 Discussion

## 4.2.7 Conclusion ............................... 106

## 5 Joint Activity, Attenuation and Scatter estimation: alternating approach 108

5.1 Introduction .................................. 108

5.2 MLAA-EB-P .................................. 109

5.2.1 Statistical model ............................ 109

5.2.2 Optimisation ................................ 110

5.2.2.1 Initialisation via OSEM-SSS ................. 111
5.2.2.2 Image updates .......................... 111
5.2.2.3 Photopeak scatter update ............... 111

5.2.3 Simulation setup ............................ 112

5.2.3.1 Cylindrical simulations .................. 112
5.2.3.2 XCAT simulations ....................... 113

5.2.3.3 Implementation ........................... 114

5.2.3.4 Initial conditions ....................... 114
5.2.3.5 Reconstruction parameters ............... 114
5.2.3.6 Analysis: ............................... 114

5.2.4 Results ................................... 115

5.2.5 Discussion ................................. 115

5.3 Analysis of the nature of the joint problem .......... 117

5.3.1 Log-likelihood contour plot analysis .............. 117

5.3.1.1 Effects of phantom size .................. 118
5.3.1.2 Accounting for the dependency of scatter on the activity and attenuation ........ 119

5.3.2 Results ................................... 119

5.3.2.1 Effects of phantom size .................. 119
5.3.2.2 Accounting for the dependency of scatter on the activity and attenuation ........................................ 121

5.3.3 Discussion ......................................................................................................................... 122

5.4 Conclusion ........................................................................................................................... 123

6 Joint Activity, Attenuation and Scatter estimation: simultaneous approach ................................. 125

6.1 Introduction .......................................................................................................................... 125

6.2 MLAA-EB-S ......................................................................................................................... 126

6.2.1 Optimisation ...................................................................................................................... 126

6.2.2 Initialisation via OSEM/SSS ............................................................................................ 127

6.2.3 Algorithm outline ............................................................................................................. 127

6.2.3.1 Image updates ............................................................................................................... 127

6.2.3.2 Photopeak scatter update ............................................................................................ 128

6.2.3.3 Implementation ............................................................................................................ 128

6.2.3.4 Stopping criteria .......................................................................................................... 128

6.2.4 Evaluation .......................................................................................................................... 128

6.2.4.1 Statistical Model .......................................................................................................... 128

6.2.4.2 3D Phantoms ............................................................................................................... 129

6.2.4.3 Projection data ............................................................................................................. 129

6.2.4.4 MLAA-S ....................................................................................................................... 130

6.2.4.5 MLAA ......................................................................................................................... 131

6.2.4.6 LBFGS-AC ................................................................................................................. 131

6.2.4.7 Reconstruction Parameters .......................................................................................... 131

6.2.4.8 Initial Conditions ........................................................................................................ 131

6.2.4.9 Analysis ....................................................................................................................... 132

6.2.5 Results ................................................................................................................................ 132

6.2.5.1 Cylindrical Phantoms ................................................................................................. 132

6.2.5.2 XCAT Reconstruction - Noise free data .................................................................... 133

6.2.5.3 XCAT Reconstruction - Noisy data ......................................................................... 135

6.2.6 Discussion .......................................................................................................................... 137

6.3 Conclusion ............................................................................................................................. 139
7 Towards realistic data: extension of the forward model and Monte Carlo data reconstructions

7.1 Introduction ................................................. 141
  7.1.1 Statistical model of the data ......................... 142
  7.1.2 STIR simulation of Siemens mMR Biograph ........... 143
  7.1.3 GATE simulation of a Siemens mMR Biograph ........ 143

7.2 Training and testing of the proposed detection efficiency model ............. 144
  7.2.1 Introduction .............................................. 144
  7.2.2 Theory .................................................. 144
  7.2.3 Experiments and results ............................... 144
    7.2.3.1 Detection efficiency fitting ...................... 144
    7.2.3.2 Assessment of STIR and GATE simulated scanner consistency .......... 145
  7.2.4 Discussion .............................................. 147

7.3 Maximum-Likelihood Estimation of Normalisation Factors of GATE data .......... 148
  7.3.1 Introduction .............................................. 148
  7.3.2 Theory .................................................. 149
  7.3.3 Experiments and results ............................... 150
  7.3.4 Discussion .............................................. 150

7.4 XCAT Torso Phantom Simulations. Evaluation in projection space .............. 153
  7.4.1 Projection data .......................................... 153
    7.4.1.1 STIR Projection data .............................. 153
    7.4.1.2 GATE Monte Carlo generated data .................. 153
  7.4.2 Experiments and results ............................... 154
  7.4.3 Discussion .............................................. 155

7.5 Joint estimation of activity and attenuation from Monte Carlo data .......... 158
  7.5.1 Introduction .............................................. 158
  7.5.2 Statistical Model ....................................... 158
  7.5.3 Optimisation ............................................ 158
  7.5.4 Evaluation .............................................. 160
    7.5.4.1 Phantom ............................................. 160
    7.5.4.2 STIR Projection data .............................. 160
### Contents

7.5.4.3 GATE Monte Carlo generated data ........................................ 160
7.5.4.4 MLAA-S-alt ................................................................. 160
7.5.4.5 Reconstruction parameters ............................................. 161
7.5.4.6 Prolongation/Restriction operators: .................................. 161
7.5.4.7 Regularisation parameters ............................................. 161
7.5.4.8 Initial conditions ......................................................... 161
7.5.4.9 Analysis: ................................................................. 162
7.5.5 Results ........................................................................... 162
7.5.6 Discussion ...................................................................... 163
7.6 Conclusion .......................................................................... 169

8 Conclusions ........................................................................... 171

8.1 Summary of main conclusions ............................................. 172
8.2 Summary of original contributions ..................................... 176
  8.2.1 Algorithm development ................................................... 176
  8.2.2 Algorithm implementation ............................................... 177
  8.2.3 Evaluation and analysis .................................................... 178
8.3 Suggestions for future work ................................................ 178
8.4 Publications and presentations .......................................... 182
  8.4.1 Peer-Reviewed Journals ................................................... 182
    8.4.1.1 Published ................................................................. 182
    8.4.1.2 Work in progress ..................................................... 182
  8.4.2 Conference proceedings ................................................. 182
    8.4.2.1 Published ................................................................. 182
    8.4.2.2 Accepted for publication .......................................... 183
  8.4.3 Published conference abstracts ........................................ 183
  8.4.4 Other presentations ....................................................... 183

Appendices .............................................................................. 184

A XCAT 3D phantom ............................................................... 184

B GATE Voxelized source and phantom .................................. 185
Contents

C Implementation of the unlisting procedure for multiple energy window sinograms into the STIR library 186

D Consistency of STIR and GATE coordinate systems 187

Bibliography 188
List of Figures

1.1 Scatter is the enemy ........................................... 34
2.1 Positron-electron annihilation ................................. 37
2.2 Illustration of Compton Scattering ............................. 37
2.3 Detectors A and B record attenuated count rates arising from the source X located a distance \( a \) from detector A and \( b \) from detector B ......................... 40
2.4 From left to right: true (a), scatter (b) and random (c) events ........................................... 41
2.5 Illustration of the detection energy spectrum for an incoming photon of 511 keV. The Compton Edge marking is at value 340.7 keV. ......................... 42
2.6 Conventional PET vs TOF PET ................................ 45
2.7 PET local coordinate system ................................... 47
2.8 Forward and Inverse Problem ................................ 48
2.9 Visual interpretation of the three Hadamard criteria. In this illustration, \( x \) indicates the set of parameter of interest and \( y \) the set of measurements. .. 50
2.10 Single scatter event from an emission in \( E \in [A,S] \) and a scatter location \( S \), detected by a pair of detectors A and B. Detector A detects the unscattered photon with an energy \( E_{\gamma A} = 511 \text{ keV} \) and detector B the scattered photon with an energy \( E_{\gamma B} < 511 \text{ keV} \). ........................................... 61
2.11 Precession of protons in a magnetic field \( B_0 \), one with spin “up” and the other with spin “down”. ........................................... 66
2.12 Brief summary of the attenuation estimation types in PET/MR. Advantages and disavantages for: segmentation, atlas/mappin and emission-based attenuation correction methods. Adapted from (Lillington et al. 2020) ............ 70
2.13 TCA for a pair of detectors AB, a measured energy \( E’ \) in \( B \) and a scatter angle \( \phi \). ............................... 75
List of Figures

3.1 Schematic representation of the forward scatter model. θ: full resolution image space, ˜θ: low resolution image space, ˜y: low resolution projection space, y: full resolution projection space. R: restriction operator mapping from full resolution to low resolution image space, P: prolongation operator mapping from low resolution to full resolution projection space. 83

3.2 Attenuation Gradient Implementation vs Finite Differences: Image Profile 89

3.3 Contribution of each one of the three terms of the Jacobian: negative terms (a,b) and positive term (c), relative to a cylindrical phantom and a detector pair A and B in the bottom-left and right-hand corner. 89

4.1 Illustration of the forward model used in this Chapter. The operator R and P are assumed to be identity matrices. Images and sinograms are therefore in low spatial resolution. 96

4.2 Point source phantom. From left to right: true activity (a) and true attenuation images (b). The activity image is expressed in arbitrary units (a. u.) and the attenuation is in cm$^{-1}$. 98

4.3 XCAT Phantom. From left to right: true activity and true attenuation images. First row: axial view. Second row: coronal view. The activity image is expressed in arbitrary units (a. u.) and the attenuation is in cm$^{-1}$. 98

4.4 Single scatter sinograms from different energy window pairs. $U = 500 – 550$keV and $L = 300 – 350$keV. Note the different maxima used for colour scale. 101

4.5 UL Single scatter sinograms from different energy window thresholds. 101

4.6 MLTR-EB reconstruction of lung values within the lung mask. Graph: MPE error in the lung over iterations. 102

4.7 Estimated attenuation map over iterations without (first row) and with (second row) anatomical information in the initialisation. Low Noise. Number of counts = 1.4 E+09. 102

4.8 ROI analysis (lung, mediastinum and left arm) from two different initialisations: MRAC and UNIF. The table shows the Initial and Final MPE for each ROI. 103
4.9 Uniform initialisation. Estimated attenuation map over iterations without (first row) and with (second row) PLS prior. Low Noise. Number of counts =1.4 E+09. Images have the same grey scale.  

4.10 Bias images. Initial attenuation estimates: first column, axial view; third column, coronal view. Reconstruction attenuation estimates: second column, axial view; fourth column, coronal view.  

4.11 First row, from left to right: true attenuation image, reconstructed images with MLTR+PLS from MRAC, reconstructed images with MLTR+PLS from UNIF. Second row: image profiles at last iteration.  

5.1 Illustration of the forward model used in this Chapter. The operator $R$ and is assumed to be an all-ones matrix. Images are therefore in low spatial resolution. The operator $P$ is used to upsample the photopeak scatter to full resolution.  


5.4 Reconstruction error from the small cylinder (D = 8 cm) simulated data. First and second row: error in the attenuation. Third and fourth row: error in the activity image. First column: initial error (reconstruction input). Second column: reconstruction error. Graph: Mean percentage Error (MPE) in the inner cylinder over iterations for both the estimated attenuation and the activity images.  

5.5 Reconstruction error from the XCAT simulated data. First and second row: error in the attenuation. Third and fourth row: error in the activity image. First column: initial error (reconstruction input). Second column: reconstruction error. Graph: Mean percentage Error (MPE) in the lung over iterations for both the estimated attenuation and the activity images.
List of Figures

5.6 Cylindrical Phantoms of increasing diameters: 8 cm (first column), 16 cm (second column), 24 cm (third column), 32 cm (forth column). First and second rows: attenuation image axial and sagittal view. Third and fourth rows: activity image, axial and sagittal view. The attenuation is expressed in cm$^{-1}$, the activity is in arbitrary units. .................................................. 118

5.7 From left to right: likelihood plots for cylinders of increasing diameters with a two-energy-window acquisition. First row: UL+LU likelihood functions. Second row: UU likelihood function ................................. 120

5.8 First row: Contour plots related to the 8 cm cylinder, w.r.t the lower (a) and upper (b) energy window. Second row: Contour plots related to the 32 cm cylinder, w.r.t the lower (a) and upper (b) energy window. ................. 121

5.9 Log-likelihood plots for cylindrical phantoms. From left to right: the diameter increases. From top to bottom: the energy window varies. $\kappa$ indicates the condition number of each contour plot. .................................................. 122

5.10 Contour plots relative to the small cylindrical phantom (D = 8 cm). Ellipse fitting to the level-sets for a multiple energy window acquisition. From left to right: the diameter increases and so does the condition number $\kappa$. .... 122

6.1 XCAT Phantom. First row: axial view. Second row: sagittal view. From left to right: MRAC used as initialisation $\mu^{\text{init}}$, true attenuation $\mu^{\text{true}}$, true activity $\lambda^{\text{true}}$, lung mask $\mu^{\text{mask}}$. The attenuation is expressed in cm$^{-1}$, the activity in arbitrary units. .................................................. 129

6.2 XCAT Phantom. Simulated data for Energy-Based Simultaneous Maximum Likelihood reconstruction of Activity and Attenuation (MLAA-EB-S). UU data (first column, and UL data (second column). For display purpose: 2D sinograms obtained by summing over the rings (first row) and relative profiles (second row). .................................................. 130

6.3 MPE over outer iterations for the attenuation (left) and activity (right) estimations. First row: MLAA-S. Second row: MLAA-EB-S. ......................... 133

6.4 Comparison between Energy-Based Pseudo Maximum Likelihood reconstruction of Activity and Attenuation (MLAA-EB-P) and MLAA-EB-S. ... 134

6.5 Likelihood and gradient updates .................................................. 134
6.6 MPE over outer iterations for the attenuation (left) and activity (right) estimations. First row: Simultaneous Maximum Likelihood reconstruction of attenuation and activity with photopeak scatter re-estimation (MLAA-S). Second row: MLAA-EB-S. ................................................................. 135

6.7 Error metrics in the XCAT images for different reconstruction algorithms: Maximum Likelihood reconstruction of Activity and Attenuation (MLAA) (UU_{\text{std}}), MLAA-S(UU_{\text{std}}), first column; MLAA-S (WW), second column; MLAA-EB-S, third column; LBFGS emission reconstruction using the true attenuation map (LBFGS-AC), fourth column. From the top to the bottom: MPE images [%] (a-d) and variance (VAR) (j-m) for the attenuation from 100 noise realisations; MPE images [%] (e-i) and variance (VAR) (n-r) for the activity image. Covariance (COV) images (s-v). ................................................................. 136


7.1 Illustration of the forward model used in this Chapter. The operators $R$ and $P$ are used as downsampling and upsampling operators in image and sinogram space, respectively, in all the energy windows. ......................................................... 143

7.2 Proposed detection efficiency model: training-set (511 keV point source emission positioned at the centre of the scanner) and testing-set (370 keV point source emission positioned at the centre of the scanner). .......................... 145

7.3 Energy spectrum obtained from HATE for an incoming photon of 511 keV with indication of energy windows used: upper energy window (pink) and low energy window (light blue). The percentage of true events measured in each energy window is reported. ................................................................. 146

7.4 Point source emitters (a) and attenuation phantom (b) within the GATE simulated mMR scanner (c). ................................................................. 146

7.5 Simulated projection data, axial view. From top to bottom: True counts in UU, scattered counts in UU, scattered counts in LU, scattered counts in UL. First column: GATE simulated data. Second column. Proposed model. Third column: difference error ................................................................. 147
7.6 Simulated projection data, tangential view. From top to bottom: True counts in UU, scattered counts in UU, scattered counts in LU, scattered counts in UL. First column: GATE simulated data. Second column: Proposed model. Third column: difference error 148

7.7 Cylindrical phantom with elliptical section used for computing the normalisation sinograms 151

7.8 Efficiency factors sinograms obtained from the cylindrical phantom (a-b, c-d). Sinograms at different axial positions were summed for display purposes. Sinogram profiles at view = 100, comparing normalised STIR simulated data and GATE Monte Carlo generated data (c, f) for the same phantom 151

7.9 Zoomed-in view of each efficiency factors sinogram (from Fig. 7.8) for different energy windows 152

7.10 3D XCAT Thorso Phantom. From left to right: MRAC, true attenuation image, true activity image, attenuation mask. First row: axial view. Second row: coronal view 154

7.11 Illustration of the GATE XCAT simulation 154

7.12 Comparison in sinogram space between Monte Carlo and analytical 3D XCAT torso simulation. Here the forward model relies on a Gaussian detection efficiency model and one unique normalisation sinogram from the true counts efficiency factors. First row: UU data. Second row: UL data. Third row: LU data. First column: GATE Monte Carlo generated data. Second column: analytical simulation. Third column: sinogram profile (view = 44). Sinograms at different axial positions were summed for display purposes 155

7.13 Comparison in sinogram space between Monte Carlo and analytical 3D XCAT torso simulation. Here the forward model relies on the proposed detection efficiency model and specific normalisation sinogram for each energy window from the cylindrical phantom with a global attenuation value set to the one of the ‘lung’. First row: UU data. Second row: UL data. Third row: LU data. First column: GATE Monte Carlo generated data. Second column: analytical simulation. Third column: sinogram profile (view = 44). Sinograms at different axial positions were summed for display purposes 156
7.14 Reconstruction error from the noise-free STIR simulated data reconstructed with MLAA-EB-A. First and second row: error in the attenuation. Third and fourth row: error in the activity image. First column: initial error (reconstruction input). Second column: reconstruction error. Graph: Mean percentage Error (MPE) within the ROIs over iterations relative to the estimated attenuation and the activity images. 163

7.15 Reconstruction error from the noisy STIR simulated data reconstructed with MLAA-EB-A. Penalty strengths: $\beta_\mu = 80$ and $\beta_\lambda = 1,5$. First and second row: error in the attenuation. Third and fourth row: error in the activity image. First column: initial error (reconstruction input). Second column: reconstruction error from a low penalty ($\beta_\lambda = 1$). Third column: reconstruction error from a higher penalty ($\beta_\lambda = 5$). Graph: Mean percentage Error (MPE) within the ROIs over iterations relative to the estimated attenuation and the activity images. 164

7.16 Reconstruction error from GATE Monte Carlo generated data. First and second row: error in the attenuation. Third and fourth row: error in the activity image. First column: initial error (reconstruction input). Second column: reconstruction error from Energy-Based Alternating Maximum Likelihood reconstruction of Activity and Attenuation (MLAA-EB-A) without heuristic normalisation scaling ($\zeta = 1$) factor in the low energy windows. Penalty strengths: $\beta_\mu = 80$ and $\beta_\lambda = 5$. Third column: reconstruction using from MLAA-EB-A an heuristic normalisation scaling factor for the low energy windows ($\zeta = 0.93$). Fourth column: reconstruction from MLAA-S-alt. Penalty strengths: $\beta_\mu = 60$ and $\beta_\lambda = 3$. Fifth column: emission reconstruction from LBFGS-AC. Penalty strength: $\beta_\lambda = 3$. Sixth column: emission reconstruction from LBFGS-MRAC (using the initial attenuation image). Graph: Mean percentage Error (MPE) within the ROIs over iterations relative to the estimated attenuation and the activity images. ROI means from MLAA-S-alt were also computed as comparison. 165

8.1 Evolution of the forward model throughout the chapters. The prolongation and restriction operators $P$ and $R$ are used as downsampling and upsampling operators in image and sinogram space, respectively. 173
List of Figures

8.2 Scatter is challenging .................................................. 177
## List of Tables

2.1 Physical properties of scintillators commonly used in PET: LYSO, BGO and LSO (Pepin et al. 2004) .............................................................. 43

2.2 Comparison of state-of-the-art methods for Joint Reconstruction of Activity and Attenuation (JRAA) from multiple energy window data for both PET and SPECT applications ............................................. 77

4.1 Total counts in UU, UL, LU and LL energy window pairs, for a point source simulation. ................................................................. 100

5.1 MLAA-EB-P. Reconstruction parameters .................................................. 114

5.2 Energy windows used for the log-likelihood analysis ............................... 119

6.1 Energy Window Thresholds [keV] ............................................................ 130

6.2 MLAA-EB-S. Reconstruction Parameters ............................................... 132

6.3 ROI analysis (in the lung region). Mean values computed for: relative bias (RB), variance (VAR) and covariance (COV). $\hat{\lambda}$\textsuperscript{true} = 0.3260 and $\hat{\mu}$\textsuperscript{true} = 0.2865 ................................................................. 137

7.1 Fitted parameters for the proposed detection efficiency model, obtained from a Monte Carlo simulation of a point source emitter. .................... 145
Acronyms

AC  Attenuation Correction 70
APD  Avalanche Photo-Diode 43
BFGS  Broyden–Fletcher–Goldfarb–Shanno 54
BGO  Bismuth Germanium Oxide 43
CNN  Convolutional Neural Network 63
CT  Computed Tomography 35
DEW  Dual Energy-Window 58
EM  Expectation Maximisation 52
ET  Emission Tomography 52
FBP  Filtered Back Projection 50
fMRI  functional Magnetic Resonance Imaging 29
FORE  Fourier Rebinning 48
FOV  Field Of View 35
FT  Fourier Transform 68
FWHM  Full Width Half Maximum 46
GATE  Gated Application Tomography Emission 142
JRAA  Joint Reconstruction of Activity and Attenuation 25
Acronyms

**JTV**  Joint Total Variation 57

**keV**  kiloelectron Volt 36

**KN**  Klein-Nishina 83

**LAC**  Linear Attenuation Coefficient 73

**LBFGS**  Limited-memory Broyden–Fletcher–Goldfarb–Shanno 55

**LBFGS-AC**  LBFGS emission reconstruction using the true attenuation map 21

**LOR**  Line Of Response 36

**LSO**  Lutetium oxyorthosilicate 43

**LYSO**  lutetium–yttrium oxyorthosilicate 43

**ML**  Maximum Likelihood 52

**MLAA**  Maximum Likelihood reconstruction of Activity and Attenuation 21

**MLAA-EB-A**  Energy-Based Alternating Maximum Likelihood reconstruction of Activity and Attenuation 23

**MLAA-EB-P**  Energy-Based Pseudo Maximum Likelihood reconstruction of Activity and Attenuation 20

**MLAA-EB-S**  Energy-Based Simultaneous Maximum Likelihood reconstruction of Activity and Attenuation 20

**MLAA-S**  Simultaneous Maximum Likelihood reconstruction of attenuation and activity with photopeak scatter re-estimation 21

**MLAA-S-alt**  Alternating Maximum Likelihood reconstruction of attenuation and activity with photopeak scatter re-estimation 160

**MLEM**  Maximum Likelihood Expectation Maximisation 52

**MLTR**  Maximum Likelihood gradient-ascent algorithm for Transmission Tomography 53

**MLTR-EB**  Energy-based Maximum Likelihood for Transmission Tomography 96
Acronyms

MPE  Mean Percentage Error 99
MRAC  MR-based Attenuation Correction image 30
MRI  MR Imaging 30
OSEM  Ordered Subset Expectation Maximisation 53
pCT  pseudo-CT 71
PET  Positron Emission Tomography 30
PET/CT  Positron Emission Tomography/Computed tomography 29
PET/MR  Positron Emission Tomography/Magnetic Resonance 29
PLS  Parallel Level Sets 56
PMT  Photomultiplier tubes 43
QP  Quadratic Prior 55
RDP  Relative Difference Prior 56
SNR  Signal to Noise Ratio 65
SPECT  Single Photon Emission Computed Tomography 31
SSRB  Single Slice Rebinning 48
SSS  Single Scatter Simulation 63
STIR  Software for Tomographic Image Reconstruction 87
TEW  Triple Energy-Window 58
TOF  Time-Of-Flight 31
UTE  Ultrashort Echo Time 30
WCs  Wolfe Conditions 55
ZTE  Zero Echo Time 30
Chapter 1

Introduction

1.1 Motivation

1.1.1 Benefits offered by PET/MR tomographs

Multi-modality scanners have recently made great strides in medical imaging. Positron Emission Tomography/Computed tomography (PET/CT) is generally the modality of choice in many clinical conditions, particularly in oncology (Jadavar et al. 2013). However, the last decade has experienced a rapid growth of combined Positron Emission Tomography/Magnetic Resonance (PET/MR) systems, which are now available for clinical use.

The key strength of PET/MR systems is their capability for simultaneous data acquisition of the two modalities. Furthermore, PET/MR combines the unique features of MR - including excellent soft tissue contrast, diffusion-weighted imaging, functional Magnetic Resonance Imaging (fMRI) and other specialised sequences - with the quantitative functional information that is provided by PET (Jadavar et al. 2013; Jung et al. 2016).

For some specific clinical applications, PET/MR may be preferred over PET/CT. For instance, PET/MR is best suited for those patients undergoing repeated imaging for whom the need of keeping the radiation dose as low as possible is essential. Other benefits include the possibility of acquiring temporally and spatially matched anatomical MR images with PET metabolic data and the availability of noninvasive MR-based tools for improving PET quantification (Lillington et al. 2020). However, the exact role and potential clinical utility of PET/MR will need to be better defined in the coming future.

1.1.2 Challenges in lung PET/MR attenuation correction

A well-known challenge in PET/MR is the need to find an accurate and reliable method for estimating PET attenuation maps. This is due to the fact that PET attenuation coefficients
1.1. Motivation

depend on the electron density of the tissues, whilst the MR signal is related to both proton density and longitudinal (T1) and transverse (T2 and T2*) magnetisation relaxation times. At present, there is no straightforward transformation able to map MR intensities into PET attenuation values (Mehranian et al. 2017).

Particularly challenging is lung attenuation estimation. Firstly, the MR signal originating from the lung is weak and decays rapidly following radio-frequency excitation. This is due to the following reasons: (i) the lung proton density is significantly lower than other tissues (Lillington et al. 2020); (ii) the presence of lung-air interfaces creates magnetic susceptibility differences that lead to an ultra-short T2* (0.5-3 ms at 3T). Secondly, MR Imaging (MRI) commonly suffers from image artefacts in lung studies. These include blood flow (a result of the lung’s high vascularity) and blurring artefacts from cardiac or respiratory motion. As a result, obtaining high-quality lung MRI is very challenging.

Recently, MR imaging has advanced to address the aforementioned challenges. In particular, MR sequences with near-zero echo times (such as Ultrashort Echo Time (UTE) and Zero Echo Time (ZTE)) give the potential for detecting lung signal despite the rapid signal decay (Johnson et al. 2013). Furthermore, such sequences may offer improved lung contrast, potentially allowing for better lung (and bone) segmentation. However, these advantages come at the cost of long acquisition times compared to standard MR sequences (Dournes et al. 2015; Lillington et al. 2020).

In addition to the aforementioned limitations, standard MR-based attenuation correction is prone to errors in the lung: current practice is to assign population-based attenuation coefficients to different tissue classes obtained by segmenting the MR image. However, lung tissue exhibits a high variability of attenuation values both on a regional basis and from person to person (Holman et al. 2016; Berker et al. 2012b).

1.1.3 Challenges in Emission-Based non-TOF PET attenuation correction

Positron Emission Tomography (PET) emission-based schemes attempt to estimate the attenuation image (together with the activity image) directly from PET measured data. This approach seems to be particularly useful in PET/MR, as it gives the possibility to overcome quantification errors induced by conventional MR-based Attenuation Correction image (MRAC).

One advantage of emission-based attenuation schemes is the possibility of avoiding motion artefacts due to misalignment between PET and MR (or CT) mismatch (Rezaei
1.1. Motivation

This class of methods provide a useful alternative to standard attenuation correction methods, most commonly with a joint MLAA. However, a stable solution for the joint problem only exists for the case of Time-Of-Flight (TOF)-PET and the attenuation and activity can be only determined up to a constant (Defrise et al. 2012). The latter can be potentially overcome by imposing the correct attenuation value in regions such as soft tissues (Rezaei et al. 2019). Recently, TOF-MLAA was proven to be as reliable as a CT-based attenuation correction for brain TOF-PET imaging (Rezaei et al. 2019).

If TOF information is not available, the estimated activity and attenuation maps suffer from cross-talk artefacts (Berker et al. 2016), where the features of the activity map propagate into the attenuation map and vice versa. Therefore, further solutions need to be found for reconstructing accurate PET images from non-TOF MLAA.

An additional source of error in the final images estimate is due to the presence of scattered events, that can represent up to 40% of the total recorded coincidences in a thorax acquisition (Sulka et al. 2006). Scattered events are normally estimated by a 3D model-based simulation (C. C Watson et al. 1996; Ollinger 1996) and are generally considered as a source of degradation of contrast and quantification errors. As an example, ‘Scatter is the enemy’ is a quotation attributed to the late Ed Hoffman in the context of PET (Fig. 1.1). Quantitative errors in the attenuation image propagate in the scatter estimation, and therefore in the reconstructed activity distribution.

However, attenuation and scatter are intrinsically linked both on a physical level and when deriving the scatter and attenuation estimates. This linking has led several authors to attempt to use information contained in the scattered counts to estimate attenuation. As Compton scattering decreases the energy of the scattered photon, this could be achieved by using data acquired in several energy windows.

Energy-based methods for attenuation estimation have first been investigated in Single Photon Emission Computed Tomography (SPECT) (Cade et al. 2013; Bousse et al. 2016) and then extended to the case of PET (Berker et al. 2014; Berker et al. 2017b). The majority of the studies present in literature have been conducted with simple 2-D phantoms and ideal energy resolution measurements. However, scatter is inherently 3D. At present, emission-based attenuation correction methods that incorporate scatter information represent a field of active research.
1.1.4 Objective of this work

The aim of this work is to assess the feasibility of joint reconstruction of the activity and attenuation distribution from multiple energy window measurements by using a maximum likelihood framework.

The idea is to extend and improve on recent techniques by investigating both algorithms and more accurate modelling of the physical processes. Experiments will be conducted on simulations of 3D phantoms.

A core part of this research will be related to the design of a reconstruction algorithm able to output an accurate activity, attenuation and scatter estimate. Improvements on the existing scatter forward model will also have to be addressed, including modelling the detection efficiency of PET detectors for incoming low-energy photons and accounting for such effects as detector scatter.

1.2 Overview of the thesis

In Chapter 2 a general overview to the Physics of PET and the theory of image reconstruction is given. Scatter estimation techniques are also explained. The basic principles for other imaging modalities (MR and CT) are briefly described. The problem of PET/MR attenuation correction is outlined and an overview of existing attenuation correction methods is provided. Then, emission based attenuation correction methods are presented, and the problem of joint reconstruction of PET activity and attenuation is described in detail.

In Chapter 3 the forward model at the core of this thesis is presented. An overview of the statistical model of the measured data and its gradient is also given. Implementation strategies are discussed. Finally, a detection efficiency model for a generic energy window is proposed.

In Chapter 4 the research undertaken to understand the amount of information contained in the standalone scatter events is presented. A preliminary investigation on point sources is conducted. Subsequently, benefits of using different energy windows for each individual annihilation photon to perform attenuation estimation with known activity distribution are discussed. The reconstruction algorithm MLTR-EB for transmission tomography is presented. Benefits of incorporating an anatomical prior into the reconstruction algorithm are also explained. Finally, results on 3D XCAT torso phantom simulations using the geometry of the Siemens mMR scanner are shown.

In Chapter 5 the possibility of incorporating a 3D probabilistic scatter model into a
1.2. Overview of the thesis

joint reconstruction scheme from both photopeak and low energy window data is investigated. We name the algorithm MLAA-EB-P. We provide a preliminary evaluation of the performance of the method on simulated data. Cases when the algorithm was shown to fail are also discussed. A simplistic toy-problem is used to investigate the cases where divergence was observed. Contour plots of the objective function are visualised and the ill-posedness of the joint problem is discussed.

In Chapter 6 the MLAA-EB-S algorithm is presented to overcome the challenges faced in previous chapters. An initial investigation is conducted with similar simplistic assumption as for MLAA-EB, i.e. absence of true counts in the low energy windows and Gaussian efficiency model. The main difference between MLAA-EB-P and MLAA-EB-S lies in the optimisation framework. Results from MLAA-EB-P and MLAA-EB-S are compared. Then, the proposed method MLAA-EB-S is evaluated against: (i) a simultaneous estimation from a single energy window (MLAA-S), (ii) an LBFGS implementation of MLAA and (iii) an emission estimation from the correct photopeak scatter and correct attenuation image (LBFGS-AC).

In Chapter 7 the forward model is extended to overcome some of the assumptions of previous chapters, including detector scatter and the presence of unscattered events in the low energy window. A new normalisation technique for low energy window data is discussed. Then, the proposed forward model is evaluated on Monte Carlo simulated data using GATE, open-source software dedicated to numerical simulations in medical imaging and radiotherapy. Sinogram data from phantom of increasing complexity are compared. Eventually, a new reconstruction algorithm capable of handling high resolution images from realistic projection data is proposed: MLAA-EB-S-A. The algorithm is tested on both simulated data from our software and Monte Carlo generated data.

Finally, in Chapter 8 the main results and findings of the research presented in this thesis are summarised and suggestions for future work are discussed.
Scatter is the enemy

[E.J. Hoffman]

Figure 1.1: Scatter is the enemy
Chapter 2

Background

2.1 Positron Emission Tomography

This chapter gives an overview of the principles of PET imaging. Firstly, we address the physics at its foundation, secondly we cover image reconstruction theory and related algorithms. Additionally, the basics of Computed Tomography (CT) and MRI - often used in conjunction with PET - are presented. Lastly, challenges related to PET/MR attenuation correction are discussed and attenuation estimation methods are introduced.

2.1.1 The physics of PET

2.1.1.1 Brief overview of PET

PET is a functional imaging technique that allows for the investigation of metabolic processes in the body. After the administration of a radiotracer - a molecule labelled with a positron-emitting radionuclide - usually into the bloodstream, the patient is placed within the Field Of View (FOV) of the scanner so that the distribution of the radiotracer inside the patient’s body can be determined. The tracer moves through the body with a preferential uptake in certain types of cells - depending on the specificity of the tracer itself.

Examples of radionuclides used in PET are: carbon-11 ($\approx$ 20 min), nitrogen-13 ($\approx$ 10 min), oxygen-15 ($\approx$ 2 min), fluorine-18 ($\approx$ 110 min), gallium-68 ($\approx$ 67 min), and rubidium-82 ($\approx$ 1.2 min) - where times indicate the radionuclide half life. The choice of the radionuclide depends on the specific application. For instance, rubidium-82 undergoes rapid uptake by myocardiocytes, which makes it a reliable tool for identifying myocardial perfusion and determine the extent of myocardial ischemia (Selwyn et al. 1982).

The most commonly used radiotracer is $^{18}$F-FDG (fluorodeoxyglucose), a glucose analogue, with $^{18}$F substituted for the normal hydroxyl group (-OH) at the C-2 position in the
Positron Emission Tomography

2.1. Positron Emission Tomography

When $^{18}$F-FDG enters the cell, it is enzymatically phosphorylated to FDG-6-phosphate. Since the missing hydroxyl group (-OH) is needed for the next step of glycolysis, the tracer cannot be further metabolised and remains trapped intra-cellularly during its radioactive decay. As a result, the distribution of the radiotracer in the body is a good reflection of glucose uptake (Weiss 2016).

Characteristic patterns of altered metabolism can help to investigate some pathological conditions and to improve the clinical diagnosis of certain diseases. As an example, PET is often used in oncology to stage some types of cancer (A. Zhu et al. 2011).

The radionuclide decays via a process known as $\beta^-$ decay (Conti et al. 2016), which consists of the conversion of a proton within the radionuclide nucleus into a neutron. This process releases a positron and a neutrino:

$$A^ZX \rightarrow A^{Z-1}Y + 0^+\beta^+ + \nu$$ (2.1)

The emitted positron eventually collides with its respective antiparticle (electron), with a process known as annihilation (Fig. 2.1). Electron-positron annihilation results in the emission of two 511 kiloelectron Volt (keV) photons in opposite directions - according to conservation of energy and momentum (Shukla et al. 2006). However, if the input momentum is non-zero when the annihilation occurs the two photons are not emitted strictly at 180°.

The finite distance that a positron travels between its emission and annihilation position is known as positron range.

PET scanners are designed to detect the pairs of gamma rays emitted from the body of the patient: when a pair of photons is picked up by two opposing detectors of the scanner, two almost simultaneous electric pulses are generated. If these occur within a certain timing window, a coincidence is recorded. The path between two opposing detectors is named Line Of Response (LOR) and is used to localise the annihilation position. Further details on data acquisition are given in Sec. 2.1.2.

2.1.1.2 Photon interaction with matter

While travelling through the body of the patient, high energy photons can interact with the surrounding matter via three main mechanisms (Khalil 2011): (i) the Photoelectric Effect, (ii) Compton Scattering, and (iii) Pair Production.

**Photoelectric Effect:** The Photoelectric Effect is a type of photon interaction with orbital electrons in an atom. It occurs when the photon transfers all of its energy to the orbital
A portion of the photon energy is used to overcome the binding energy of the electron, the remaining part is transferred to the electron in the form of kinetic energy. As a result, the orbital electron is ejected from the atom (photo-electron) and an outer orbital electron drops down to occupy the vacancy. This process causes the emission of X-rays with an energy equal to the binding energy difference of the two levels (Fig. 2.2).

In human tissue, the Photoelectric Effect dominates at photon energies lower than approximately 100 keV. As photons in PET are emitted with an energy of 511 keV, the
2.1. Positron Emission Tomography

probability of a photon undergoing Photoelectric Effect is only marginal (Bailey et al. 2006).

**Compton Scattering:** Compton scattering occurs when a photon and a loosely bound orbital electron interact. As a consequence of their interaction, the electron is ejected from the atom and the photon undergoes a change in direction, imparting part of its energy to the electron. The new energy of the photon depends only on the scatter angle and is given by (Bailey et al. 2006):

\[
E'_{\gamma} = E_{\gamma} \left(1 + \frac{E_{\gamma}}{m_{e}c^2} (1 - \cos(\phi_{S}))\right)
\]

with \(E_{\gamma}\) being the energy of the photon before scattering. For positron annihilation radiation \(E_{\gamma} = 511\ \text{keV}\), Eq. 2.2 results in:

\[
E'_{\gamma} = \frac{511\text{keV}}{2 - \cos(\phi_{S})}
\]

The probability of scattering at a certain angle is non uniform, and it is given by the Klein-Nishina equation (Klein et al. 1929):

\[
\frac{d\sigma}{d\Omega} = Zr_0^2 \left(\frac{1}{1+\Lambda(1-\cos(\phi_{S}))}\right)^2 \left(\frac{1 + \cos^2(\phi_{S})}{2}\right) \left(1 + \frac{\Lambda^2(1 - \cos(\phi_{S}))^2}{(1+\cos^2(\phi_{S}))(1+\Lambda(1-\cos(\phi_{S})))}\right)
\]

where \(\frac{d\sigma}{d\Omega}\) represents the differential cross section of photons scattered from a single electron, \(Z\) is the atomic number of the medium, \(r_0\) is the classical electron radius and \(\Lambda = E_{\gamma}/m_{e}c^2\).

**Pair Production:** Pair Production is the creation of a subatomic particle and its antiparticle from a fundamental particle (such as a photon). It often refers specifically to a photon creating an electron–positron pair usually in the vicinity of an atomic nucleus. This event occurs when a photon with an energy greater than 1.022 MeV (at least twice the total rest mass energy of an electron) spontaneously convert a photon to a positron and electron.

The probability of pair production increases with photon energy and with the square of atomic number of the nearby atom. The probability of pair production in PET is negligible given the range of PET photon energies.

2.1.1.3 Photon attenuation

The main consequence of photon interaction with matter is the loss of flux intensity through a medium, due to either absorption or scattering. This process is known as photon attenuation,
or simply attenuation (Bailey et al. 2006). At PET photon energies, photon attenuation is primarily a result of Compton scattering and leads to a loss of counts ranging from 50% to 95% (Mettler 2012).

Given \( I_0 \) incident photons travelling across a path of length \( D \), the number of non-attenuated photons follows the Beer-Lambert exponential law:

\[
I(D) = I_0 \cdot \exp \left( \int_0^D -\mu_E(r)dr \right)
\] (2.5)

where \( \mu_E(r) \) is the attenuation coefficient of the media crossed by the photons. Note that Eq. 2.5 implies that the attenuation coefficient \( \mu \) has dimension of an inverse length (in PET, it is typically given in units of cm\(^{-1}\)), but can also be expressed in terms of mass attenuation coefficient \( \mu/\rho \) [cm\(^2\)/g], where \( \rho \) is the density of the material. Note that the total mass attenuation coefficient is linked to the total cross section \( \sigma \) for photons by the rule given in Hubbell 2006:

\[
\frac{\mu}{\rho} = \frac{\sigma}{m_0A}
\] (2.6)

where \( m_0 \) is the atomic mass unit and \( A \) is the relative atomic mass of the material. In PET, the total cross section \( \sigma \) is is mostly due to Compton scattering and can be obtained from Eq. 2.4 by integrating over all scattering angles.

If we now consider a pair of detectors \( A, B \), an emitting source of radioactivity \( X \) located at distance \( a \) from detector \( A \) and \( b \) from detector \( B \), along an LOR of total length \( D = a + b \) (Fig. 2.3), the probability \( P \) of detecting an annihilation event occurring in \( X \) is given by the combined probability of detecting both coincidence photons (Fig. 2.3):

\[
P = \exp \left( \int_a^D -\mu_E(r)dr \right) \cdot \exp \left( \int_{D-a}^D -\mu_E(r)dr \right) = \exp \left( \int_D -\mu_E(r)dr \right)
\] (2.7)

Eq. 2.7 shows that the probability of measuring a pair of photons along a certain LOR is unrelated to the position of the annihilation event within the LOR itself.
2.1. Positron Emission Tomography

2.1.2 Data acquisition in PET

PET scanners consist of several rings of detector elements that may or may not be separated by thin annular rings (septa) of photon-absorptive material, typically tungsten, that provide collimation. With collimation, all data is acquired in 2-dimensional slices between the septa. This type of acquisition is therefore called 2D, even though the reconstructed stack of images gives 3-dimensional information about the tracer uptake throughout the patient. Without a septa, coincidences from oblique axial angles in the FOV will be accepted, making this a fully-3D acquisition (Schmitz et al. 2013). Recent PET scanners do not have septa and therefore measure in 3D only.

The number of coincidence events is measured by a pair of detectors in a given detector ring and it is related to the amount of radioactivity on the LOR associated to that pair of detectors.

A coincidence event is recorded when: (i) two photons hit two opposing detectors within a chosen coincidence time window - depending on the timing resolution of the detectors, (ii) the detected photon energies are within a chosen energy window, and (iii) the corresponding LOR is within a valid acceptance angle for the tomograph.

Despite these selection criteria, some undesired events are usually also recorded. Therefore, the collected events $g$ are composed of the sum of true, scatter, and random events:

$$g = g^{\text{true}} + g^{\text{scatter}} + g^{\text{random}}$$ (2.8)
2.1. Positron Emission Tomography

Figure 2.4: From left to right: true (a), scatter (b) and random (c) events

defined as follows:

- **True event**: detection of two unscattered photons coming from the same annihilation event (Fig. 2.4a).

- **Scatter event**: one or both photons produced by an annihilation event underwent Compton scattering prior to detection, but they are still detected as a coincidence event (Fig. 2.4b). If the energy loss caused by the change of direction - while scattering - is large enough, the scattered photons can be rejected with a sufficiently narrow energy window (see below). If not, the detection of a scatter event will lead to the recording of a (false) annihilation event in the LOR between the two opposing detectors. The energy window (Sec. 2.1.2.1) plays a key role in rejecting as many scatter events as possible, ideally without affecting the detection of true events.

- **Random event**: two photons produced by two unrelated annihilation are measured by a detector pair within the coincidence timing window (Fig. 2.4c). Analogously to the energy window used to discriminate between scattered and unscattered photons, the timing window has to be set large enough to allow true events to be accepted, but small enough to exclude as many random events as possible.

2.1.2.1 Photon detection

In current PET scanners, the detection of the gamma photons is achieved via the use of scintillation crystals coupled to a photo-detector.

**Scintillation process and crystals used in PET**: A scintillator is a material that exhibits scintillation when excited by ionising radiation. It absorbs the incoming energy which is then re-emitted in the form of visible light.
2.1. Positron Emission Tomography

Figure 2.5: Illustration of the detection energy spectrum for an incoming photon of 511 keV. The Compton Edge marking is at value 340.7 keV.

When an incident photon hits the crystal, different scenarios could manifest: (i) the gamma photon undergoes Photoelectric effects within the crystal and loses all its energy; (ii) the gamma particle scatters off an electron in the crystal.

Providing situation (ii), the scattered photon could: (ii.a) leave the crystal depositing only part of its energy, or (ii.b) be absorbed.

The fraction of the incoming photon energy deposited in the crystal depends on the scattering angle of the incoming photon, leading to a spectrum of energies each corresponding to a different scattering angle. The highest energy that can be deposited corresponds to full back-scatter ($\phi_S = \pi$) and is called the “Compton edge”. For 511 keV incident photons it is placed at 340.7 keV (Eq. 2.3). The relatively flat region extending from the Compton edge to lower energies is called “Compton Plateau” (Fig. 2.5).

The desirable properties for scintillators in PET imaging are (i) high stopping power for 511 keV photons, (ii) low decay time, (iii) high light output.

The stopping power of a scintillator is characterised by the mean distance (attenuation length) the photon travels before it deposits all its energy. Scintillators with a short attenuation length will provide maximum efficiency in stopping the incident photons. Their attenuation length depends upon its density, thickness and the effective atomic number (Z). The decay time determines the time necessary to process each pulse individually. A low decay time is desired at high counting rates, as well as to reduce the number of random coincidence events. It also enables TOF (Sec. 2.1.2.2). The light output quantifies the number of scintillation photons produced per keV of deposited energy.
The most common crystal materials used in PET detectors are: Bismuth Germanium Oxide (BGO), Lutetium oxyorthosilicate (LSO) and lutetium–yttrium oxyorthosilicate (LYSO). Table 2.1 reports some of their characteristics.

<table>
<thead>
<tr>
<th></th>
<th>LYSO</th>
<th>BGO</th>
<th>LSO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Density [g/cm³]</td>
<td>5.37</td>
<td>7.13</td>
<td>7.35</td>
</tr>
<tr>
<td>Effective Z</td>
<td>54</td>
<td>58</td>
<td>65</td>
</tr>
<tr>
<td>Attenuation length for 511 keV [mm]</td>
<td>20</td>
<td>11.6</td>
<td>12.3</td>
</tr>
<tr>
<td>Decay time [ns]</td>
<td>53</td>
<td>300</td>
<td>40</td>
</tr>
<tr>
<td>Light Output (photons/keV)</td>
<td>75</td>
<td>15</td>
<td>75</td>
</tr>
</tbody>
</table>

Table 2.1: Physical properties of scintillators commonly used in PET: LYSO, BGO and LSO (Pepin et al. 2004).

No one material exists which fits all of the desired properties mentioned above. Therefore some properties, and therefore materials, are favoured depending on the specific purpose. While BGO was once the material of choice, now LSO and LYSO are preferred due to their increased performance in light output and decay time (Brunner et al. 2017).

**Photo-detector:** The light output generated by the scintillator is converted to an electrical signal by a photo-detector.

Until recently, one of the most used photo-detectors in PET was the Photomultiplier tubes (PMT). It consists of a number of electrodes called dynodes placed within a vacuum tube. Each dynode is held at a greater positive potential than the preceding. A primary electron leaves the photocathode (a negative charged electrode) with the energy of the incoming photon and moves toward the first dynode and is accelerated by the electric field. When striking each dynode, more electrons are emitted, and these are in turn accelerated toward the next dynode. The geometry of the dynode chain is such that a cascade occurs with an exponentially-increasing number of electrons being produced at each stage. At the last stage, called the anode, the large number of electrons results in a sharp current pulse signalling that a photon arrived at the photocathode approximately 50 nanoseconds earlier (Bailey et al. 2006).

PMT technology is incompatible within the presence of a magnetic field, such as found in hybrid PET/MR systems. The solution adopted by Siemens for the Biograph mMR (Karlberg et al. 2016) was to replace PMTs with Avalanche Photo-Diode (APD)s, solid-state photon detectors. A drawback of APDs is a relatively low timing resolution. As a result, Siemens mMR detectors do not support TOF - available in GE PET/MR scanners (Grant
et al. 2016) which use silicon-photomultiplier detector technology. This technology is also
the one of choice for the majority of PET/CTs scanners (D. et al. 2019).

**Energy Window:** When a photon hits the crystal, the incoming energy is measured with a
certain accuracy depending on the detector characteristics (Sec. 2.1.2.1). In case of perfect
energy resolution, the “measured energy” will match exactly the incoming energy. However,
in reality there is always a certain degree of uncertainty in measurements.

PET detectors use energy windows to accept (or reject) detected energies when they
fall inside (or outside) a lower and upper discriminator. The measured energy information
will be available in terms of *energy bin*. Typically, the higher and the lower energy window
thresholds are set to around 350 keV and 650 keV (Phelps 2006), respectively, in order
to maximise the detection of 511 keV photons and to reject undesired low energy photons
(scattered photons). The better the energy resolution the narrower the energy window chosen.

In many systems, such as the Siemens mMR, only a single energy window can be used,
while some tomographs, such as the GE SIGNA PET/MR, can use multiple energy windows,
resulting in an energy window pair for each coincidence. Benefits of using multiple energy
windows will be discussed in Chapter 3.

**Detector Efficiency:** The detector efficiency of current PET detectors depends on both non-
geometric and geometric effects (Ollinger 1995). Non-geometric effects include optical
coupling between the scintillator and the photo-detector, and electronics. Geometric effects
are related to the direction and energy of the incoming photon and include those that vary
with the inclination of the LOR respect to the normal to the detector surface and solid angle
subtended by the detector.

The sensitivity matrix $A_{\text{sens}}$ can be therefore expressed as (Casey et al. 1995; Hogg et al.
2001):

$$
[A_{\text{sens}}]_{i,j}(E_i, E_j) = \varepsilon_i(E_i)\varepsilon_w(E_j)[G_{s,w}]_{i,j}
$$

(2.9)

where $G_{s,w}$ accounts for the change in sensitivity due to the radial position of each detector
pair and their relative position within a block; it depends on the incoming energy of both
photons hitting a pair of detector $i,j$ and the energy window pair $w,v$ used for acquiring
the data. The diagonal matrix $G_{s,w}$ can be estimated from phantom acquisitions of known
geometry (Sec. 7.3). The crystal efficiency $\varepsilon_s(E)$ is also a function of the incoming photon
energy and the energy window. The response function of photo-detectors over the range of
incident photon energies is an important factor in this work, and it will be therefore explained
2.1.1. Positron Emission Tomography

2.1.2. Coincidence processing

A coincidence is recorded when two timing pulses are generated in two different channels in a time range \([t + \tau; t - \tau]\) - where \(2\tau\) equals the timing window (Sec. 2.1.2) of the detection system. For sufficiently small values of \(\tau\), TOF effects become important.

**Time-of-flight** A TOF-PET system can measure the difference in arrival times between the two coincident photons for each annihilation event with a time resolution in the range of 500–600 ps. Hypothetically, with perfect TOF information the location of each annihilation event could be identified based only on coincidence pairs and time difference information. However, there is uncertainty on the detected arrival times determined by the timing resolution. Given the difference in arrival times \(\Delta t\) then, the annihilation position \(\Delta x\) can be computed as (Ullah et al. 2016):

\[
\Delta x = c \frac{\Delta t}{2}
\]

The uncertainty in the TOF measurement is typically modelled as a Gaussian distribution, centred on the annihilation position. The availability of TOF offers an improvement over conventional PET, where a uniform probability is assigned to the whole LOR (Fig. 2.6).

The idea of using TOF information in PET image reconstruction was proposed in the 1960’s at a very early stage (Karp 2006). However, the detection systems at that time were not stable enough (temperature dependence, electronic drift) to support TOF. These problems
have been resolved in recent detectors, such as the ones used in the GE SIGNA PET/MR.

2.1.2.3 Limits of spatial resolution in PET

The fundamental limits of spatial resolution in PET are mostly due to:

- Detector size: the response function for each LOR is approximately a triangle whose Full Width Half Maximum (FWHM) is half of the detector width.

- Positron range: the positron emitted with $\beta$-decay can travel some distance before annihilating.

- Acollinearity: if the positron has a non-zero kinetic energy at the moment of annihilation the pair of photons are not emitted strictly back-to-back. This angular uncertainty causes approximately Gaussian blurring.

- Crystal penetration: when the photon hits the scintillator, it usually travels some distance before interacting with the detector itself. In some extreme cases the photon might interact with a different crystal other than the one that it originally impinged upon. As a result, the photon might be measured by an adjacent crystal.

- Block effect: most current PET scanners use block detectors, composed of multiple scintillation crystals coupled to a series of photomultiplier tubes. Some of the loss of spatial resolution in PET is attributed to the use of block detectors, because a photon that interacts with one crystal in the block may be incorrectly positioned, resulting in blurring of the reconstructed image.

Overall, PET resolution for current clinical systems ranges around 5 mm, roughly equal to the crystal size (Nieman et al. 2015).

2.1.2.4 Data organisation

Output data are organised in two different ways: (i) a list of all detected events (list-mode), or (ii) histogrammed data (“sinograms”).

**List-mode:** A listmode file is a series of “records” which sequentially list information ( crystals, arrival time, energies, etc.) for each detected event. Once acquired, the listmode data can be converted into sinograms with a process named unlisting.

**PET Sinograms:** LORs between two detectors in the same plane orthogonal to the scanner axis can be characterised by: (i) their orientation angle, (ii) an average axial location $\bar{z}$, and
Figure 2.7: PET local coordinate system

(iii) their distance from the centre of the gantry. By integrating along all adjacent parallel LORs for a specific time frame at an angle $\phi$, a projection $p(s, \phi)$ is formed. The projections are organised into a matrix (**sinogram**) such that each row of the matrix represents the projection acquired at angle $\phi$. The name sinogram relates to the fact that a sinusoid can be observed when imaging a point source at a location $(x_1, x_2)$.

For a 2D acquisition, a local coordinate system stationary with respect to the detectors can be introduced to express the relationship between the matrix element $p(s, \phi)$ and the tracer distribution at a location $(x_1, x_2)$ (Fig. 2.7).

A point on a line $L(s, \phi)$ making an angle $\phi$ with the $x_1$-axis can be identified by three parameters $(s, l, \phi)$, where $l$ is a parameter along $L(s, \phi)$ and $s$ is the distance from the origin to the line $L(s, \phi)$. The Cartesian Coordinate System $(x_1, x_2)$ can be expressed in terms of cylindrical Coordinates $(s, l, \phi)$ by equations:

\[
x_1 = s \cos(\phi) - l \sin(\phi) \\
x_2 = s \sin(\phi) + l \cos(\phi)
\]  

(2.11)

In the following, we refer to **bin** to indicate a single element in a sinogram, specified by its axial position, orientation $\phi$ with respect to the reference system and distance from the origin $s$. 
Data acquired in 3-D mode can also be described by a stack of sinograms related to a particular slice \( z \), with an additional dimension given by the ring difference \( \vartheta \). Those sinograms can be converted to 2-D mode sinograms by using a rebinning algorithm, such as Fourier Rebinning (FORE) (Defrise et al. 1998) and Single Slice Rebinning (SSRB) (Daube-Witherspoon et al. 1987).

2.1.3 Image Reconstruction

PET image reconstruction is an example of an inverse problem: the radiotracer distribution of an object is estimated from the coincidence events detected by the PET scanner. The next sections are organised as follows. First, a brief introduction to inverse problems is given. Then, image reconstruction methods are discussed.

2.1.3.1 Introduction to inverse problems

In an inverse problem we try to estimate the causal factors that produced a set of observations (Fig. 2.8). An example is the reconstruction of the tracer distribution from its measured projection data.

The prediction of the outcome of a set of measurements requires: (i) a forward model that computes the mean measurement for a given parameter of interest; and (ii) a noise model. Given a set of observable \( \mathbf{y} \) and a parameter of interest \( \mathbf{x} \), then the forward problem is formulated as \( \mathbf{y} = \mathbf{A}(\mathbf{x}) \). In the case of a linear forward mapping, this relationship simply becomes \( \mathbf{y} = \mathbf{A} \mathbf{x} \). To solve for the parameters that fit the data, one may want to invert the matrix \( \mathbf{A} \), so that \( \mathbf{x} = \mathbf{A}^{-1} \mathbf{y} \).

However, \( \mathbf{A} \) may have no inverse. In fact, it is often the case that the numbers of unknowns may differ from the number of measurements so that matrix \( \mathbf{A} \) is not square and therefore not invertible. Furthermore, noise may be such that the measured data is not nec-
essarily an output of the forward problem. Consequently, only an optimal set of parameters that best match the data can be found. This can be achieved through the maximisation of a function that maps a certain event or value of one or more variables onto a real number representing some “cost” associated with the event. This function is named “cost function”.

Cost function: One example of cost function is the squared norm of the residuals:

\[
Q(x) = |y - Ax|^2
\]

The least squares solution to a system of linear equations minimises the error in the predicted estimates from the observed data, and is also known as pseudo-inverse solution \(x^+ = A^+ y\), where \(A^+\) is the pseudo-inverse of \(A\).

Other costs function can be also used. One example is the likelihood \(L(y|x)\) of measuring \(y\) given the model parameters \(x\).

Ill-posedness and ill-conditioning: Inverse problems are often ill-posed. An ill-posed problem is one which does not meet at least one of the Hadamard criteria (Hadamard 1902), defining well-posed problems (see Fig. 2.9): (i) existence, (ii) uniqueness and (iii) stability of the solution. The stability of the solution is defined as its sensitivity to changes in the input data.

If the forward model is expressed in matrix form, the concept of ill-conditioning can also be introduced. A matrix \(A\) is said to be ill-conditioned if small errors in the entries lead to large errors in the output. An ill-conditioned problem is indicated by a large condition number \(\kappa\). The condition number of a matrix \(A\) is defined as its largest singular value divided by its smallest nonzero singular value:

\[
\kappa(A) = \frac{\sigma_{\text{max}}(A)}{\sigma_{\text{min}}(A)}
\]

where \(\sigma_{\text{max}}(A)\) and \(\sigma_{\text{min}}(A)\) are maximal and minimal singular values of \(A\). The greater \(\kappa\), the greater the aspect ratio, the more ill-conditioned the problem. An example of computation for \(\kappa\) is given in Sec. 5.3.1.2. For a squared matrix, \(\kappa\) is given by the ratio of the largest and smallest eigenvalues.

2.1.3.2 Analytic reconstruction methods

An analytic model for the measurement process offers a direct mathematical solution for estimating the tracer distribution from the known projections \(p(s, \phi)\). In the absence of noise,
2.1. Positron Emission Tomography

Figure 2.9: Visual interpretation of the three Hadamard criteria. In this illustration, \( \mathbf{x} \) indicates the set of parameter of interest and \( \mathbf{y} \) the set of measurements.

Attenuation and scattering, a projection can be approximated as the line integrals of the tracer distribution:

\[
p(s, \phi) = \int_{-\infty}^{+\infty} \lambda(x_1 = s \cos(\phi) - l \sin(\phi), x_2 = s \sin(\phi) + l \cos(\phi)) dl
\]

where \( l \) is defined in Sec. 2.1.2.4.

The line-integral transform of \( \lambda(x_1, x_2) \to p(s, \phi) \) is called the X-ray transform, which in 2-D corresponds to the Radon transform (Alessio et al. 2006).

The most basic approach for analytic image reconstruction is by back-projecting the acquired projection data. The back-projection is defined as the adjoint of the forward projection operator that formed the projections of the acquired object. For definition of the adjoint see Eq. 3.31.

The image obtained by backprojecting the measured data is blurred. This problem can be overcome with the so-called Filtered Back Projection (FBP) algorithm, which filters the projections accentuating values at higher frequencies of the Fourier space.

For decades, FBP represented the gold standard for PET image reconstruction, given its high computational speed and its quantitative reliability. However it has several limitations including: (i) artefacts caused by incomplete data acquisition, (ii) streak artefacts if few events are acquired, (iii) assumption of a deterministic nature of the data.

At present, FBP has been almost completely replaced by the iterative approach.
2.1.3.3 Iterative reconstruction methods

Iterative reconstruction provides an alternative to filtered back-projection. The unknown image is estimated through successive iterations of the algorithm. Requirements for iterative image reconstruction (further discussed below) are: (i) a system model that relates the unknown image to the expected measurements, (ii) a similarity measure that assesses the match between the measured and the estimated data, (iii) an algorithm for maximising the objective function, (iv) an initial estimate and (v) a stopping criteria.

The major advantage offered by this approach compared to the analytical method is the possibility of incorporating a noise model in the reconstruction process. This is generally done by considering the observed data as Poisson distributed. The iterative approach however does lead to a higher complexity and greater computational demand.

As the iterative approach is the one of choice for this thesis, it will be discussed in further details in the following sections.

**Imaging Model:** A common way to represent the imaging system is by using the following affine relationship:

\[
\tilde{g}(\mu, \lambda) = A(\mu)\lambda + \tilde{g}^{sc} + \tilde{g}^r
\]

where \(\mu \in \mathbb{R}^{n_v}\) and \(\lambda \in \mathbb{R}^{n_v}\) denote respectively the attenuation and the activity images, \(n_v\) is the number of voxels in the image, \(\tilde{g}(\mu, \lambda) \in \mathbb{R}^{n_b}\) refers to the expected counts, \(A(\mu) \in \mathbb{R}^{n_b \times n_v}\) is the system matrix that defines the mapping from image-space to data-space, \(n_b\) is the number of bins, \(\tilde{g}^{sc} \in \mathbb{R}^{n_b}\) and \(\tilde{g}^r \in \mathbb{R}^{n_b}\) are the expected scatter and random events, respectively.

The system matrix \(A(\mu)\) is defined as the matrix of \(a_{i,j}\), denoting the probability of detecting a coincidence event originating from voxel \(i\) at detector pair \(j\) with ideal detection of unscattered photon pairs from annihilations. It can be expressed as the product of several matrices:

\[
A = A^{\text{sens}} A^{\text{atten}}(\mu) A^{\text{FP}} A^{\text{positron}}
\]

The geometrical projection matrix is indicated with \(A^{\text{FP}}\). The diagonal matrices \(A^{\text{sens}}\) (Sec. 2.1.2.1) and \(A^{\text{atten}}\) contain, respectively, detector normalisation factors and attenuation factors (Sec. 3.2.1). The positron range factor \(A^{\text{positron}}\) is usually disregarded for \(^{18}\text{F}\) (Moses...
2.1. Positron Emission Tomography

Although the scatter component is commonly considered as a fixed background vector, in this thesis we will account for its dependency on the activity and attenuation distribution. This results in $\bar{g}^{sc}$ being replaced by $\bar{g}^{sc}(\lambda, \mu)$. In this work, the dead-time effects are not included in the model.

**Statistical model of the data:** A reasonable statistical model for PET measurements is to assume that the measured data $g \in \mathbb{R}_{+}^{n_b}$ is Poisson distributed (Bailey et al. 2006).

For $\theta = [\lambda, \mu]'$, the likelihood $L(g|g(\theta))$ (Sec. 2.1.3.1) of measuring $g$, given the mean values $\bar{g}_i(\theta)$ for every sinogram element $i$ can be expressed as:

$$L(g|g(\theta)) = \prod_{i=1}^{n_b} \exp(-\bar{g}_i(\theta)) \left(\frac{\bar{g}_i(\theta)}{g_i}\right)^{g_i}$$  \hspace{1cm} (2.17)

where $i$ is the index for sinogram elements.

Taking the logarithm of Eq. 2.17 and omitting terms independent of $\theta$, the objective function based on the log-likelihood estimation is obtained:

$$\mathcal{L}(g|\bar{g}(\theta)) = \sum_{i=1}^{n_b} \left(g_i \log(\bar{g}_i(\theta) - \bar{g}_i(\theta))\right)$$  \hspace{1cm} (2.18)

The log-likelihood is convenient for maximum likelihood estimation.

**Maximum likelihood:** A method of estimating the parameters of a given statistical model is to maximise the likelihood function in Eq. 2.17. Please note that maximising the likelihood is equivalent to maximising the log-likelihood (Eq. 2.18). The Maximum Likelihood (ML) estimate of the parameter values is given by:

$$\hat{\theta} = \arg\max_{\theta \geq 0} \mathcal{L}(g|\bar{g}(\theta))$$  \hspace{1cm} (2.19)

**Optimisation via EM:** One way to find to find ML estimates for model parameters is via the Expectation Maximisation (EM) algorithm. An EM method for Emission Tomography (ET), known as Maximum Likelihood Expectation Maximisation (MLEM), was proposed by (Shepp et al. 1982). Here the goal is to reconstruct the emission distribution $\lambda$, i.e. $\theta = \lambda$.

The image estimate is updated as follows:

$$\lambda_{j+1} = \frac{\lambda_j}{\sum_i c_{ij} \lambda_j} \sum_i c_{ij} g_i b_i$$  \hspace{1cm} (2.20)

where $t$ is the iteration number, $b_i = \sum_k c_{ik} \lambda_k$ is the total activity along the $i$-th LOR, $c_{ij}$ is
the detector sensitivity and \( a_i = \exp(-\sum_k l_{ik}\mu_k) \).

One of the major limitations of MLEM is that it converges very slowly. Although it is not necessary to converge to the ML-solution due to the ill-conditioned property of the problem (Sec. 2.1.3.1), the algorithm requires a large number of iterations to obtain a visually appealing image.

**Optimisation via OSEM:** In order to overcome the slow convergence rate of MLEM, the Ordered Subset Expectation Maximisation (OSEM) algorithm was proposed (Hudson et al. 1994). The basic idea of the method is to divide the entire set of data in subsets and perform each image update only on a subset of the data, speeding up the computation time by a factor proportional to the number of subsets. In fact, one iteration of OSEM with \( S \) subsets provides an image roughly similar to that from \( S \) iterations of MLEM. However, a trade-off between number of subsets and image quality exists: for large subset numbers, enhanced noise structures appear in the final image estimate. Furthermore, OSEM was found to converge to a limit cycle (converge to a closed orbit) (Browne et al. 1996) rather than to a unique solution (Mettivier et al. 2011).

Relaxed Ordered Subsets algorithms (Browne et al. 1996; Ahn et al. 2003) were subsequently proposed to guarantee convergence. However, practical question of whether it is preferable to achieve convergence by using relaxation or by reducing the number of subsets with iteration remains open.

**Optimisation via gradient ascent/descent:** An optimisation problem can be also solved via gradient ascent, which aims to find the local maximum of a function \( \mathcal{L} \) along a search direction given by the gradient \( \nabla \mathcal{L} \). The corresponding update is given by:

\[
\theta^{t+1} = \theta^t + \xi \nabla \mathcal{L}(\theta^t)
\]

with \( \xi \) being the step-size.

Convergence rate of ascent/descent methods can be modified using preconditioning matrices which transforms the problem into a new coordinate system where it is easier to solve Eq. 2.19. Ideally, the preconditioner would be the inverse of the Hessian (Qi et al. 2006) (Sec 2.1.3.3).

With regard to transmission tomography, a preconditioned gradient ascent algorithm, called Maximum Likelihood gradient-ascent algorithm for Transmission Tomography (MLTR), was proposed in (Nuyts et al. 1999). Here the goal is to estimate the attenua-
tion coefficients $\mu_j$ for each pixel $j$ in the object of interest, when the emission source is known ($\theta = \mu$). The MLTR update is given by:

$$
\mu_j^{t+1} = \mu_j^t + \xi \left( 1 - \frac{\sum c_{ij} g_i}{\sum c_{ij} a_i b_i} \right)
$$

(2.22)

where $c_{ij}, b_i$ and $a_i$ have been defined in Sec. 2.1.3.3.

**Second-order Optimisation Methods**: Second order optimisation methods aim to find a solution of the inverse problem by fitting of a paraboloid to the surface of the objective function at an estimate $\theta^t$ at iteration $t$, and then proceeding to the maximum (or minimum) of that paraboloid:

$$
\mathcal{L}(\theta) \approx \mathcal{L}(\theta^t) + (d')^T \nabla \mathcal{L}(\theta^t) + \frac{1}{2} (d')^T H(\mathcal{L}(\theta^t)) d'
$$

(2.23)

where $d' = (\theta - \theta^t)$ is the search direction, $\nabla \mathcal{L}(\theta^t)$ and $H(\theta^t)$ are respectively the gradient and the Hessian of the objective function computed at $\theta^t$.

To find $\theta$ so that $\theta^t + d'$ is a stationary point, one can solve:

$$
0 = \frac{\partial}{\partial d} \left( \mathcal{L}(\theta^t) + (d')^T \nabla \mathcal{L}(\theta^t) + \frac{1}{2} (d')^T H(\mathcal{L}(\theta^t)) d' \right)
$$

(2.24)

from which results:

$$
d' = - \left[ H^{-1}(\mathcal{L}(\theta^t)) \right] \nabla \mathcal{L}(\theta^t)
$$

(2.25)

where $H^{-1}(\mathcal{L}(\theta^t)) \in \mathbb{R}^{n_t}$ is the inverse of the Hessian $H$.

The image update is then given as follows:

$$
\theta^{t+1} = \theta^t + \xi \left[ H^{-1}(\mathcal{L}(\theta^t)) \right] \nabla \mathcal{L}(\theta^t)
$$

(2.26)

The Newton method is an example of second order optimisation algorithms that brings the advantage of faster convergence compared to first-order algorithms.

In large scale problems, it is unfeasible to calculate, store in memory or invert $H$. A solution to this problem is to replace $H^{-1}$ with an approximation $B$. This class of algorithms bears the name of quasi-Newton methods.

**Limited-memory Broyden-Fletcher-Goldfarb-Shanno**: An example of quasi-Newton methods is the so-called Broyden–Fletcher–Goldfarb–Shanno (BFGS) (Byrd et al. 1995). An
2.1. Positron Emission Tomography

ulterior sub-set method is given by Limited-memory Broyden–Fletcher–Goldfarb–Shanno (LBFGS), which only stores a few vectors that represent the approximation $B$ of the Hessian $H$. In order to initialise the construction of $B$, the LBFGS implementation performs gradient descent at the first iteration.

To ensure convergence and sufficient fast progress, the step length is obtained using a “backtracking” algorithm, which gradually decreases the step size from an initial value $\xi^{\text{init}} \leq 1$ (Tsai et al. 2017). The value is decreased until the Wolfe Conditions (WCs) are satisfied (More et al. 1994). Previous studies (Byrd et al. 1994) have demonstrated that a reliable approximation of the Hessian can be obtained from few previous gradient calculations. Therefore, $B_{\mu}$ is generally constructed with a history length $m = 5$.

As a second-order optimisation method, LBFGS is expected to have a fast convergence rate. However, its performance was found to be dependent on image and data scale (C. Zhu et al. 1995). This problem has been addressed for ET in (Tsai et al. 2017) by introducing better initialisation and an additional diagonal preconditioning.

**Penalised-likelihood (PL) image reconstruction:** Image reconstruction using ML estimation is often an ill-posed (See Sec. 2.1.3.1) problem and the ML solution is usually very noisy. As a result, in practice most algorithms are often stopped at early iterations, before convergence is reached. Alternatively, including regularisation into the reconstruction algorithm can allow to control the noise level in the estimated image (Alessio et al. 2006). Instead of maximising the log-likelihood $\mathcal{L}(g | \theta) = \sum_i g_i \log \bar{g}_i(\theta) - \bar{g}_i(\theta)$, penalised maximum likelihood image reconstruction optimises an objective function $\phi$ defined as follow:

$$\phi(g | \mathbf{g}(\theta)) = \mathcal{L}(g | \mathbf{g}(\theta)) - \beta U(\theta)$$  \hspace{1cm} (2.27)

where $U$ represents the penalty function and $\beta$ is a parameter controlling its strength. The optimisation problem then becomes:

$$\hat{\theta} = \arg\max_{\theta \geq 0} \phi(g | \mathbf{g}(\theta))$$  \hspace{1cm} (2.28)

Several penalty functions have been proposed for PET imaging. One example is the Quadratic Prior (QP) (Geman et al. 1984):

$$U(\theta) = \sum_{j=1}^{n_c} \sum_{k \in N_j} w_{jk} (\theta_j - \theta_k)^2.$$  \hspace{1cm} (2.29)
where \( w_{jk} \) weights the distance between the two voxels \( j \) and \( k \), \( N_j \) is the neighbourhood of a voxel \( j \).

An extension of QP is the Relative Difference Prior (RDP) (Nuyts et al. 2002), defined as:

\[
U(\theta) = \sum_{j=1}^{n} \sum_{k \in N_j} w_{jk} \frac{(\theta_j - \theta_k)^2}{(\theta_j + \theta_k) + \gamma |\theta_j - \theta_k|}
\]

(2.30)

where \( \gamma \) is a hyper-parameter which controls edge preservation. The penalty is designed such that edges are preserved while background noise is suppressed. This prior is used in the Q. Clear reconstruction algorithm (Ross 2014).

One of the advantages of having a PET/CT or PET/MR scanner is that anatomical information (either from the CT or the MR) can be included into the reconstruction algorithm to enhance/preserve the edges of PET features.

One example is the prior proposed by Ehrhardt et al, designed for synergistic PET/MR reconstruction (Ehrhardt et al. 2015). For two distributions \( x(r) \) and \( y(r) \), \( r \in \Omega \subset \mathbb{R}^N \), and \( N \in \{2, 3\} \), the synergistic Parallel Level Sets (PLS) encourages the alignment of the gradients \( \nabla x \) and \( \nabla y \):

\[
\text{PLS}_{\text{syn}}(x, y) := \int_\Omega \left( \alpha^2 + |\nabla x(r)|^2 |\nabla y(r)|^2 - \langle \nabla x(r), \nabla y(r) \rangle^2 \right)^{1/2} dr
\]

(2.31)

where \( \langle .. \rangle \) is the Euclidean scalar product, and \(|..|\) denotes the L_2-norm. This prior was then extended to its asymmetric version, when the MR image \( (w) \) is known (Ehrhardt et al. 2016):

\[
\text{PLS}_{\text{anat}}(x, y) := \int_\Omega \left( \alpha^2 + |\nabla x(r)|^2 - \langle \nabla x(r), h(r) \rangle^2 \right)^{1/2} dr
\]

(2.32)

with

\[
h(r) := \frac{\nabla y(r)}{|y(r)|_\eta}
\]

(2.33)

and \( \alpha \) and \( \eta \) are smoothing parameters. Please note that \(|..|_\eta\) indicates the smoothed norm.

A major drawback of the synergistic PLS is that this prior is not able to remove noise when the side information is flat; this issue is potentially overcome by the asymmetrical version of the prior thanks to the presence of smoothing parameters \( \alpha \) and \( \eta \). Indeed, when there is no information in the anatomical image, the anatomical PLS reduces to the (smooth)
total variation penalty of the PET image.

Other methods to incorporate anatomical information include the Bowsher’s prior and Joint Total Variation (JTV). The Bowsher prior (Bowsher et al. 2004) weights the local differences between voxels using weighting factors $w_{j,k}$, encouraging smoothing within regions defined by the anatomical images and avoiding too smooth boundaries. Similarly to PLS, the Bowsher prior operates voxel-by-voxel, eliminating the necessity of segmenting the anatomical image. However, as any anatomical prior, it is vulnerable to the case of mismatches between the MR/CT and the PET image. A study from (Schramm et al. 2018) reported that the PLS was found to have superior bias-noise characteristics compared to the symmetric Bowsher prior.

The joint total variation prior follows this expression:

$$JTV(x,y) := \int_{\Omega} \left( \alpha^2 + |\nabla x(r)|^2 + |\nabla y(r)|^2 \right)^{1/2} dr$$  (2.34)

As the total variation normally encourages images with sparse gradients, the joint total variation favours sparsity in both gradient domains and therefore encourages common edges between the two distributions.

### 2.1.4 Data corrections

In order to obtain quantitatively accurate measures of the tracer concentration from PET data, corrections need to be applied. These corrections are mostly related to the effect of attenuation of the annihilation photons in the body and the presence of scattered and random photons. The first lowers the resulting number of detected events whilst the latter identify inaccurate LORs. Attenuation estimation will be discussed in more detail in Sec. 2.3.

### 2.1.5 Estimation of the scatter component

The presence of scatter in the measured data translates as a loss of contrast and quantitative accuracy of the reconstructed activity distribution due to a mispositioning of the reconstructed annihilation events (Werling et al. 2002). As the amount of scatter in 3D PET can reach 40% of the total detected events (Cherry et al. 1991; Badawi et al. 1996), an accurate scatter estimate is mandatory. The next sections cover scatter estimation methods in the context of activity image reconstruction. As some of the following methods are not suitable for the objective work of this thesis, they will only be briefly described.
2.1. Dual and Triple energy-window approaches

Dual Energy-Window (DEW) methods were first proposed in SPECT in the late 80’s (Jaszczak et al. 1984). This represents one of the earliest scatter correction methods introduced for SPECT imaging and involved the use of a lower energy window to measure the scatter component (Hutton et al. 2011). The underlying assumption of this method was that the scatter distribution in the low energy window can be scaled by an appropriate factor, in order to provide an estimate of the scatter contribution in the photopeak window. This implies that the spatial distribution of the scattered events in both lower-energy and photopeak windows are assumed to be very similar.

This idea was followed by the Triple Energy-Window (TEW) approach (Ogawa et al. 1992) which relies on relatively narrower energy windows, respectively lower and higher than the photopeak window. The photopeak scatter distribution is obtained by a weighted average of the scatter in the upper and lower energy window. The TEW method is nowadays the standard approach for SPECT scatter correction, largely due to its simplicity and reliability in quite complex scatter situations.

The idea of using multiple energy window to estimate the scatter component was also applied to PET in the following years. One attempt was to consider two adjacent windows, with a lower-energy window placed just below the photopeak (Grootoonk et al. 1992) where a majority of scatter events is expected to be found. A scaled subtraction of the two energy windows produces an estimate of the distribution of scatter in the photopeak window.

An alternative dual-energy window approach (Bendriem et al. 1993) uses one broad energy window, collecting both true and scattered events. A very narrow window (around the photopeak) is then used to collect (mostly) true events. With this setting, scaling the true counts from the photopeak window and subtracting it from the total number of counts detected in the total broad window leads to a more accurate estimate of the scatter. A drawback of this approach is that very few counts are collected in the narrow photopeak window.

An important limitation of the multiple energy window scatter estimation approach lies in the fact that the scatter distributions in the two (or three) energy windows are in reality quite different in PET, as the multiple scatter fraction is higher in the lower window compared to the photopeak window. As the effect of multiple-scatter interactions is generally considered to broaden the single scatter distribution, this approach is prone to errors in the case where the multiple scatter component is considerably large.
2.1.5.2 Energy spectrum analysis approach

The interest in energy-based scatter correction methods had a sharp increase with the advent of list-mode data storage, which holds the energy information for each detected photon. (Levkovitz et al. 2001) proposed to assign a different weight to each detected event depending on whether photon energies are above (or below) a certain threshold. The weights and the threshold were empirically determined. This method was then extended (H.-T. Chen et al. 2003; H.-T. Chen et al. 2005); weights were computed by averaging Monte Carlo simulation results for different activity and attenuation configurations.

Inspired by this, (Popescu et al. 2006) proposed to use the list-mode data energy information to estimate the scattered events distributions. The central idea of their approach is the two-dimensional detector energy response model, which is a linear combination of four components: (i) both photons unscattered; (ii) one is scattered and the other is not and (iii) vice versa; (iv) both photons scattered. The energy model was incorporated into the image reconstruction algorithm with the major approximation that the scatter contribution does not depend on the activity image, and it is therefore treated as a background event.

The main novelty of this approach is represented by the energy-dependent scatter correction, through the use of four independent scatter coefficients. These coefficients are obtained empirically from Monte Carlo simulation.

In the subsequent years, this idea was extended by Guerin et al. 2011 where an object-specific estimation of the primary and scattered coincidences energy probability density functions was used.

2.1.5.3 Monte Carlo simulations

Monte Carlo methods are a broad class of computational algorithms that rely on repeated random sampling to make numerical estimations of unknown parameters. The uses of Monte Carlo simulations are incredibly wide-ranging, and find application in many different fields spanning from game theory to physics and finance. Despite the variety of applications they all share the commonality of using random number generation to solve problems ruled by stochastic processes.

The relative number of annihilation in each voxel is determined from the input emission image, read by the Monte Carlo simulator. If the photon escapes the attenuating medium and hits a detector in the gantry, the event is recorded with details as to the photon’s energy and timing (Sec. 7.1).
The scatter distribution is estimated from the reconstructed 3-D volume and its attenuation medium, and requires an appropriate model of the scanner geometry and the physics of photon interactions (Levin et al. 1995; Holdsworth et al. 2001; Barret et al. 2015; K. et al. 2006). The initial estimate of the activity distribution is obtained from the measured emission data, scatter corrected with the default method from the manufacture. For instance, the TEW scatter estimate (Sec. 2.1.5.1) in (K. et al. 2006) and SSS (Sec. 2.1.5.4) in (Holdsworth et al. 2001).

The expected scatter component can then be obtained by subtracting the number of (Monte Carlo) simulated unscattered photons from the total number of simulated events. As the Monte Carlo simulation could output in a different scale to the measured data (depending on the total number of simulated counts), the sinograms may require re-scaling. The global scaling factor is obtained by fitting the total simulated data to the measured data.

This approach is mostly limited by the high computational burden, and requires the use of fast hardware and parallel computing. This challenges the possibility of using this method in routine clinical application.

2.1.5.4 Analytical - Single scatter approximation

The single scatter distribution in a 3D PET acquisition can be described analytically (C. C Watson et al. 1996; Ollinger 1996). This approach is based on the assumption that only one of the two photons resulting from an annihilation undergoes a single Compton interaction (when scatter occurs). The concept of the single scatter analytical model is the estimation of the number of scattered coincidences along LORs; given two detectors \( i \) and \( j \) and a scatter point \( S \), two different contributions must be considered when evaluating the expected number of scattered counts, depending on which side of the scatter point the emission point lies (C. C Watson et al. 1996):

\[
\hat{g}^{sc}_{i,j,s} = A^{sens}(E,511)
\left(I_{i,s,j} + I_{j,s,i}\right)
\]  

(2.35)

with \( E \) indicating the photon energy after (single) Compton scattering (in keV) and \( A^{sens}(E,511) \) denoting the sensitivity matrix (Eq. 2.9). Please note that in the case of a single energy window acquisition \( A^{sens}(E,511) = A^{sens}(511,E) \). Furthermore, consider that the \( i, j \) indices in \( I_{i,s,j} \) and \( I_{j,s,i} \) have been intentionally swapped: the first indicates an emission placed on the \( i \)-side of the scatter point, and vice versa. An expression for \( I_{i,s,j} \) is given in Chapter 3, Eq. 3.9; a schematic visualisation is given in Fig. 2.10.
2.1. Positron Emission Tomography

Figure 2.10: Single scatter event from an emission in \( E \in [A, S] \) and a scatter location \( S \), detected by a pair of detectors A and B. Detector A detects the unscattered photon with an energy \( E_{\gamma A} = 511 \text{ keV} \) and detector B the scattered photon with an energy \( E_{\gamma B} < 511 \text{ keV} \).

The discretisation strategy of Eq. 2.35 approximates the line integrals in the forward model by line ray tracing between the centre of a given detector and a scatter point location. The set of scatter points is uniformly distributed on a rectilinear mesh with specified grid spacing in the volume of the object determined by the attenuation image. To avoid numerical artefacts, each scatter point is then randomly displaced within the mesh. Then, each scatter point is assigned an attenuation coefficient according to the \( \mu \)-map values. This set of scatter points is used to evaluate the scatter for every sampled LOR.

This model has been recently extended to TOF-SSS where the non-uniform distribution of scatter events over the TOF bins is taken into account (C. C. Watson 2007). The TOF effect has been incorporated into the SSS model by introducing a detection efficiency function \( \varepsilon_t(\Delta r) \), where \( \Delta r \) denotes spatial offset of the emission point from the midpoint of the path, \( \Delta r = \frac{r_{BS} - r_{AS}}{2} \pm r \).

**Adjustments to the estimated single scatter component** In 2D PET (Sec. 2.1.2), the septa prevent most of the photons originating from outside the field-of-view to reach the detectors. In contrast, due to septa removal, 3D PET suffers from a high probability of detection of scattered events that originate from radioactivity outside the FOV (Sossi et al. 1995). Furthermore, the presence of multiple scatters makes the single scatter approximation inaccurate. To accommodate for errors due to the inaccuracy of the single scatter approximation, some
adjustments are needed. Several methods have been proposed over the years to account for the factors disregarded from the single scatter model, all of which involving some degree of approximation.

- **Convolution methods:** Ollinger et al. (Ollinger 1996) proposed to adjust the single scatter simulation by modelling the contribution from multiple-scatter as the convolution of the single-scatters with a one-dimensional Gaussian kernel. Scatter from outside the field of view is estimated by assuming prior knowledge of the emission and transmission images for all regions contributing scattered events to the data. This method starts to fail for large objects relative to the scanner diameter. The convolution method can be improved (Qian et al. 2010) by considering both the amplitude and standard deviation of the Gaussian kernel as a function of the path length (computed from the attenuation map).

- **Fitting Techniques:** Another way to correct the single scatter estimate is to fit the single scatter component to the measured data in a sinogram region corresponding to LORs outside of the body of the patient (assumed to measure scatter events only). This approach is named “tail-fitting” (C. C. Watson et al. 1996). This idea was extended to a "total-fitting" method (Thielemans et al. 2007; Defrise et al. 2014), in order to avoid using only the tails of the data. The sum of an estimate of the unscattered data and scaled single scatters is fit to the measured data. The motivation for this approach is the possibility of having a noisy tail-fitting in case of large patients and a high amount of multiple scatter in the tails.

- **Analytical - Double Scatter Approximation:** the possibility of modelling the double scatter is an alternative to finding a scale factor for the single scatter distribution. A double scatter model was first proposed in (Tsoumpas et al. 2005) and then further investigated in (Markiewicz et al. 2007; C. C Watson et al. 2018; C. C. Watson 2019). It was also recently shown in (Tsoumpas et al. 2005) that the biggest contribution to multiple scatters (in modern scanners with sufficiently good energy resolution) is given by double scatter. The increase of computation time when modelling multiple scatters (with respect to single scatter only) remains clinically viable (C. C Watson et al. 2018; C. C. Watson 2019).

- **Exponential Model:** An approximate exponential relation between Single and Multi-
Provided that a method for correcting the single scatter estimate is chosen, the Single Scatter Simulation (SSS) algorithm iteratively estimates the scatter component as follows: (i) initialise the scatter estimate (generally zero); (ii) reconstruct the activity image from the current scatter estimate and measured data; (iii) estimate a preliminary single scatter sinogram using the previous activity image and the known attenuation map; (iv) correct the single scatter estimate (i.e. using tail-fitting); (v) Restart from point 2 (until a given maximum number of iterations).

2.1.5.5 Deep Learning methods

The analytical methods have the potential drawback of being impeded by a high computational cost. A deep scatter estimation (DSE) method was proposed to reproduce single scatter distributions from known input data, opening the door to faster and more accurate scatter correction in clinical PET (Berker et al. 2018). This approach was trained and tested on Siemens mMR data and was found to be around 7 times faster than the SSS (according to the log files of Siemens Siemens-provided offline tools on the same workstation). Input for the network are photo-peak measurements (prompts) and attenuation correction factors (ACF). The target/ground truth scatter was assumed to be the result of SSS. Results showed promise; however, data sets substantially different from the training data led to high errors in the scatter estimate.

In the same year, (Yang et al. 2019) proposed to optimise a Convolutional Neural Network (CNN) for joint attenuation and scatter correction (ASC) in PET image space without additional anatomical imaging or the need of relying on iterative scatter simulation. The method was evaluated against an emission reconstruction from CT-based scatter and attenuation estimated estimates; both showed comparable results. However, the method was tested on brain images only. According to the authors, this approach has the potential of clinical application in brain-dedicated PET/MR systems where it could provide a practical and robust way for attenuation and scatter correction.

Recently Qian and Rui (Qian et al. 2017) proposed to use deep learning for PET multiple scatter estimation, claiming that scatter correction methods have a trade-off between accuracy and computational cost, and that deep learning has a potential to achieve both accuracy and computational efficiency. Their method replaces the Gaussian kernels with a neural network, in order to predict multiple scatter profiles from the single scatter ones. The
2.2. Other imaging modalities

PET images are usually combined with either MR or CT, providing a complementary anatomical information (in high resolution). A brief overview of the two modalities can be found in the following sections.

2.2.1 Computed Tomography

X-ray Computed Tomography (CT) is an imaging modality that allows for the computation of cross-sectional images by taking multiple X-rays at different angles around the body. X-rays are produced by an X-ray tube and directed towards the patient. A proportion of photons are absorbed by each tissue the X-ray beam passes through and a different number of X-ray photons exit the body (Eq. 2.5). The out-coming radiation intensity is measured by scintillating detectors coupled with photo-diodes. CT scanners usually have a rigid assembly X-ray source/detector that rotates around the patient as the data is gathered.

2.2.1.1 Physics of CT

The physical principles of CT share similarities with the one of PET, with the main difference being that: (i) photons are emitted from an external (and known) source; (ii) CT only measures single incident photons; (iii) the energy of the CT photons is much lower than the PET ones, typically with energy levels between 20 and 150 keV.

The latter statement implies that the types of photon interactions with matter differ between PET and CT.

Attenuation values are usually expressed in Hounsfield Units (HU), defined as:

\[
HU_j = 1000 \frac{\mu_j - \mu_{\text{water}}}{\mu_{\text{water}}} \tag{2.36}
\]

where \( \mu_{\text{water}} \) is the linear attenuation of water and \( \mu_j \) is the attenuation of the object at voxel \( j \).
2.2 Other imaging modalities

2.2.1.2 Image reconstruction

CT image reconstruction models the photon attenuation with the exponential attenuation law (Eq. 2.5), which relates the intensity of incoming radiation $I_0$ to the intensity of radiation exiting an attenuating medium ($I$). CT imaging aims to map the internal attenuation distribution of the object $\mu_E(r)$ with measurements of $I$ from different angles. Contrary to PET, $I_0$ is known in CT.

Analogously to PET, two major categories of reconstruction methods exist for CT: analytical and iterative reconstruction. The most commonly used analytical reconstruction methods on CT scanners are in the form of FBP. Iterative methods share common roots with algorithms used for PET attenuation reconstruction from known emission (Sec. 2.1.3.3).

2.2.1.3 Limits of spatial resolution in CT

CT detectors are much smaller than the ones in PET, leading to a significantly higher spatial resolution and Signal to Noise Ratio (SNR), which is the primary strength of this modality. CT spatial resolution values are in the order of half millimetre in all directions (x y and z). The resolution of CT is generally superior to the one of MR (Lin et al. 2009).

2.2.1.4 CT for PET attenuation correction

Bi-linear scaling methods can be applied to obtain the $\mu$-map at 511 keV from the CT Hounsfield Units, so that it can be used for PET-AC (Carney et al. 2006).

Potential problems of CT-based AC are: (i) bi-linear scaling approximation approximates the different tissue classes with air, soft tissue and one type of bone; (ii) propagation of CT artefacts into PET images; (iii) presence of motion and/or difference in PET/CT respiratory patterns; (iv) truncation of CT images.

As in hybrid PET/CT the two tomographs are combined in a single gantry, and the two modalities are acquired sequentially (non simultaneously), the problem of attenuation mismatch between the PET and the attenuation map obtained from the CT is reduced - but not removed.

In spite of these limitations, CT is currently the gold-standard technique for PET attenuation correction.

2.2.2 Magnetic Resonance Imaging

MRI is a non-invasive and technique that is used to image the anatomy of the body by exploiting the magnetic quantum mechanical properties of nuclei, commonly hydrogen. Nuclei can be excited into high energy states using radio waves; they subsequently emit a
2.2. Other imaging modalities

Figure 2.11: Precession of protons in a magnetic field $B_0$, one with spin “up” and the other with spin “down”.

radio signal while returning to equilibrium. This radio signal is measured using receiving coils that can be used for making detailed images of body tissues. MR is classified as a non-ionising technique, carrying the main advantage of not being harmful for the patient.

2.2.2.1 Physics of MR

The physical basis of MR centres around the concept of magnetic moment exhibited by certain particles when placed in a magnetic field. More specifically, this is related to a property known as spin. For protons the spin $s$ can only assume two values: $s = \pm \frac{1}{2}$.

Particles with spin possess a magnetic dipole moment, just like a rotating electrically charged body in classical electrodynamics (see Fig. 2.11). In a state of equilibrium, the magnetic fields relative to each proton are randomly oriented within the water nuclei of the tissue, leading to a null net magnetisation. However, under the application of an external magnetic field, protons can: (i) become aligned with the external magnetic field direction (“spin up”) or (ii) against it (“spin down”). The spin-up state (in alignment) is slightly preferred, and thus has a lower energy level. In contrast, the spin-down state corresponds to
a higher energy state. A nucleus can change its energy state configuration by either giving up or absorbing energy. The energy difference between these states is determined by the strength of the applied magnetic field:

$$\Delta E = 2\omega_0 h = 2\gamma B_0 h$$  \hspace{1cm} (2.37)

with $h = 6.62607004 \cdot 10^{-34}$ [J · s] being the Planck constant, $\hbar = h/2\pi$ and $\omega_0$ is the Larmor Frequency (Larmor 1897). The latter refers to the rate of precession of the magnetic moment of the proton around the external magnetic field, where $\gamma$ is a proportionality constant known as the gyromagnetic ratio (equal to 42.58 MHz/T for the hydrogen).

**Origin of the MR signal:** When an external magnetic field $B_0$ is applied, the number of protons orienting in the low-energy state is superior to the case of high-energy. This results in a non-zero total magnetisation. The ratio between the two populations $N_+$ and $N_-$ (parallel and anti-parallel) can be computed as:

$$\frac{N_+}{N_-} = \exp\left(-\frac{\Delta E}{k_B T}\right)$$  \hspace{1cm} (2.38)

with $k_B = 1.38064852 \cdot 10^{-23}$ [J/K] being the Boltzmann constant and $T$ the absolute temperature (Das 2011). For $T = 310K$ and $B_0 = 1T$, $\frac{N_+}{N_-} \approx 7e - 6$. That is, for every million nuclei in the spin-down state, there are about 1 million plus 7 extra nuclei in the spin-up state.

**Excitation with an RF pulse:** After the application of the static magnetic field $B_0$, the system is perturbed by an oscillating magnetic field $B_1$, usually referred to as a radio-frequency (RF) pulse:

$$B_1(t) = \begin{bmatrix} B_1 \cos(\omega_0 t) \\ -B_1 \sin(\omega_0 t) \\ 0 \end{bmatrix}$$  \hspace{1cm} (2.39)

The two magnetic fields ($B_0$ and $B_1$) are usually chosen to be perpendicular to each other as this maximises the MR signal strength. The RF pulse $B_1$ oscillates at the Larmor frequency $\omega_0$ and the system is therefore put into a resonant state (Das 2011).

**Relaxation times $T_1$ and $T_2$:** After the application of the RF pulse, each tissue returns to its equilibrium state by two independent relaxation processes known as $T_1$ and $T_2$. Both recovery events can be described with an exponential decay.

$T_1$ is defined as the time necessary to recover 63% of the magnetisation in the direction
of the external static field $B_0$, whilst $T_2$ denotes the time necessary to lose 37% of the transverse magnetisation (Das 2011). The evolution of the magnetisation over time is described by Bloch equations (Bloch 1946).

Given inhomogeneities of the field $B_0 (B_0 \pm \Delta B)$, the time-constant for the transverse relaxation is actually given by $T_2^*$:

$$\frac{1}{T_2^*} = \gamma \Delta B + \frac{1}{T_2} \quad (2.40)$$

The loss of transverse magnetisation after the application of a RF pulse is named free induction decay (FID), and two successive RF pulses produce a spin echo (SE). The time elapsed between the first RF pulse and the appearance of the echo takes the name of echo time (TE). The echo generates the measurable signal in MR.

The RF pulses are repeated with a certain repetition time (TR). TE and TR can be varied for enhancing different tissue properties. For instance, long(TR)&long(TE) give $T_2$-weighted images, whilst short(TR)&short(TE) result in the so-called $T_1$-weighted images, long(TR)&short(TE) is known as ‘proton-density’-weighting. According to MR-imaging grey scale conventions, tissues with long $T_2$s appear white in $T_2$-weighted images; in contrast, bright regions of $T_1$-weighted image correspond to tissues with short $T_1$s.

2.2.2.2 Image generation

To be able to encode the information contained in the MR signal, three different magnetic field gradients are utilised: the slice selection gradient (Z); the phase encoding gradient (X); the frequency encoding gradient (Y).

Given the gradient $G(r)$, which might serve as either a slice- frequency- or phase-encoding gradient, $k(t)$ can be defined as:

$$k(t) = \int_0^t G(t', r) dt' \quad (2.41)$$

Then, the total signal received by the coil is given by (Das 2011):

$$s(t) = e^{-\frac{t}{T_2}} \int_V q(r) \exp \left[ -i2\pi k(t) \cdot r \right] dr \quad (2.42)$$

This expression can be interpreted as the Fourier Transform (FT) of the proton density of the object $q(r)$. The MR image can be reconstructed through inverse Fourier transforma-
2.2. Other imaging modalities

2.2.2.3 k-space sampling

The MR data is stored in the so called k-space matrix and it approximately corresponds to the FT of the unknown object distribution.

The dominant method for filling k-space over the last decade has been the Cartesian method (sampling line-by-line). At present, spiral and radially oriented trajectories are becoming more popular. The Cartesian method fills each row of the k-space with the echo data obtained from a single application of the phase-encoding gradient.

Spiral acquisition uses spiral trajectories to collect data in k-space, significantly reducing the total acquisition time due to reduced number of repetition times. Radial methods fill the k-space through radial trajectories, bringing the advantage of a lower sensitivity to motion artefacts as they are ‘spread’ across the entire image.

2.2.2.4 Limits of spatial resolution in MR

The spatial resolution of MR images mostly depends on: k-space size, FOV, and on the slice thickness.

The size of the k-space is related to the maximum number of frequency and phase encoding steps. The higher the number of steps the better the resolution. However, a higher number of phase steps come at the cost of a longer acquisition time.

The FOV is also related to the spatial resolution: a bigger FOV increases the size of the voxel - and therefore decreases the resolution (assuming everything else constant).

Finally, the slice thickness - which determines the z-resolution - depends on the maximum strength of the z-gradient coils.

At present, most MRI scanners have a static magnetic field intensity ranging between 1.5 and 3 T with a resolution of 1–2 mm for most sequences (Lin et al. 2009).

2.2.2.5 MR and PET interaction in PET/MR

As MR and PET scanners coexist in hybrid PET/MR tomographs there is reason to question whether PET suffers from the presence of the MR. The static magnetic field of the MR device does affect the trajectory of the positrons emitted after the $\beta$-decay. This translates into an elongation of the positron range distribution along the direction of the magnetic field (z-direction), leading to a worse axial resolution. The effect is more marked for tracer with bigger positron range (such as $^{68}$Ga). In some cases this can lead to misinterpretation of the PET images (Kolb et al. 2015). This is currently an area of active research.
2.3. PET/MR attenuation correction

One of the biggest challenges in PET/MR is the need for a reliable (and accurate) method of performing Attenuation Correction (AC). Unlike with PET/CT, there is no existing method to directly map MR image intensities to a 511 keV photon attenuation map (Wagenknecht et al. 2013).

The magnitude of MR signals depends on proton density and longitudinal (T1) and transverse (T2) magnetisation relaxation properties of the tissues and does not relate to tissue attenuation. This effect becomes obvious with respect to bones and cavities, which corresponds the highest and the lowest attenuation value in PET, but have similar signal intensities in images obtained from many MR sequences. Therefore, PET/MR attenuation estimation is still a topic of active research (Wagenknecht et al. 2013; Lillington et al. 2020).

Attenuation estimation methods for PET/MR are briefly summarised in Fig. 2.12 and this section. See (Lillington et al. 2020) for a recent review related to the thorax.

### 2.3.1 MR-based Attenuation Correction (MR-AC)

Current PET/MR scanners rely on MR-based attenuation correction methods, which consist in generating a pseudo-CT (pCT) from the MR image (Y. Chen et al. 2017). Depending on the specific technique applied to obtain the pseudo-CT, MR-AC can be classified as:
2.3. PET/MR attenuation correction

Template-based approaches: Template-based methods construct an attenuation map template by averaging a number of previously acquired CT scans of the patient. Together with the attenuation map template, a co-registered MR template is also generated. Thereafter, the MR template is alligned to the patient MR image with a non linear registration, and the same transformation is applied to the attenuation map template (Wagenknecht et al. 2013).

Atlas-based approaches: Atlas-based methods aim to predict a patient-specific attenuation map (using a continuous scale) by deforming one representative CT data set to match the patient MR image of the patient. The synthetic pseudo-CT (pCT) is then used for PET AC.

This method was successively extended by Burgos et al. for head and neck to a multi-atlas approach (Burgos et al. 2014), where the pCT is obtained as a composition of locally optimised image patches, computed by weighted averaging of a larger atlas database. This idea was introduced to reduce registration errors and patient variability. The resulting pseudo-CT is then converted into PET attenuation values and used for PET AC.

Segmentation-based approaches: Segmentation-based methods make use of predefined linear attenuation coefficients that are assigned to discrete anatomical regions. The number of anatomical regions strongly depends on the segmentation procedure as well as the MR sequence that is used. Segmentation methods can be further divided into different classes, depending on whether the segmentation includes bones. Current clinical practice relies on either Dixon (Dixon et al. 1984) or UTE sequences (Aitken et al. 2014). This class of method is generally the most used in clinical practice (Wagenknecht et al. 2013).

MR-CT learning: Machine learning is making rapid advances in many different areas. In the case of medical imaging, it could offer the possibility of learning the unknown relation between the MR and CT images.

As MR-CT learning approaches have shown success for the brain (Liu et al. 2019), there might be a value for a lung application. However, this approach has to face some challenges in the lung that are not present in other regions of the body and in particular the brain: the accuracy of MR-CT learning is related to the quality of the training dataset. Challenges may therefore arise in the case of misalignment between MR-CT pairs, mostly due to the high presence of motion in the thorax region. Furthermore, the low MR-signal in the lung region may be challenging for the network. Here the use of sequences such as ZTE
or UTE could be beneficial.

2.3.2 Emission-based Attenuation Correction

Emission-based attenuation estimation strategies seem to be particularly promising for overcoming the quantification errors induced by conventional MR-AC methods.

Emission-based AC methods can be divided into two classes: analytic and iterative. The analytic algorithms rely on the consistency conditions of the attenuated Radon transform (Welch et al. 1998; Bronnikov 2016; Kacperski 2011) and estimate the attenuation coefficients without the need of estimating the activity map. The iterative algorithms instead aim to find both the activity and the attenuation distributions of the object via successive estimates.

As this thesis focuses on works intended to jointly reconstruct both activity and attenuation from PET data, the iterative approach will be widely discussed in the following section.

2.4 Joint reconstruction of PET activity and attenuation

The joint reconstruction of PET activity and attenuation aims to estimate both the activity and the attenuation distributions \( \theta = [\lambda, \mu] \) by maximising a cost function defined as in Eq. 2.18 (or Eq. 2.28 for penalised reconstruction). For a known activity distribution, the problem can be reduced to the case of transmission tomography (Sec. 2.1.3.3).

2.4.1 Maximum likelihood reconstruction of activity and attenuation (MLAA)

The most common approach for iterative joint reconstruction is known as MLAA.

2.4.1.1 Optimisation algorithm

The MLAA algorithm consists in solving Eq. 2.19 by updating \( \lambda \) and \( \mu \) alternatively:

\[
\begin{align*}
\lambda^{k+1} &= \arg \max_{\lambda \geq 0} L(g | \hat{g}(\lambda, \mu^k)) \\
\mu^{k+1} &= \arg \max_{\mu \geq 0} L(g | \hat{g}(\mu, \lambda^{k+1}))
\end{align*}
\]  

(2.43)

At each step, the problem can be reduced to either emission or transmission tomography. This implies that two inner sub-algorithms are required to estimate \( \lambda \) and \( \mu \) separately.

Alternatively, one could choose to update \( \theta \) all at once (Fuin et al. 2017; Brusaferri et al. 2019b).

In absence of TOF information, the JRAA suffers from cross-talk artefacts: errors in
the activity estimate that propagate in the attenuation map and vice versa (Salomon et al. 2011; Defrise et al. 2012). Therefore, without TOF, this approach does not lead to a stable and unique solution unless some prior assumptions on either the attenuation or the activity image are incorporated.

2.4.1.2 TOF-MLAA

The advent of TOF-PET has opened new horizons for the joint reconstruction problem. As TOF furnishes additional information on the position of the source within each line of response, the ill-conditioning of the problem is reduced; the non-uniqueness of the solution in the case of TOF-MLAA is reduced to a global attenuation sinogram offset (Defrise et al. 2012).

Salomon et al proposed the incorporation of additional MR information into the reconstruction algorithm (Salomon et al. 2011). Their approach aims to simultaneously estimate the activity and the density distribution using the segmented MR image as anatomical reference. This method constrains the update of the attenuation coefficients estimates within different regions that correspond to the segments of the MR image. The attenuation coefficient of each region is initialised with the attenuation of water at 511 keV. The method showed promise under the assumption of high quality level MR data, to enable an accurate segmentation of different tissue regions.

Recently, research studies (Rezaei et al. 2019) were conducted to evaluate the performance of TOF-MLAA in PET/MR brain imaging against the gold-standard PET/CT. They show that TOF-MLAA can provide an accurate and effective solution to the attenuation correction problem of PET/MR for brain studies, with regional errors in the range of a few percent.

There are limited studies that focus on MLAA with respect to lung imaging; the following section will focus on this topic. A constrained TOF-MLAA algorithm (Berker et al. 2012b) was proposed to estimate the mean lung Linear Attenuation Coefficient (LAC) by using a whole-body MRAC divided in five tissue classes. The mean lung attenuation value was initially assigned a homogeneous value of either 0 or 0.05 cm$^{-1}$ and was subsequently updated while maintaining the $\mu$ values of the rest of the body at a predetermined values. Their results showed that the algorithm was unable to solve the scaling problem of TOF-MLAA. Furthermore, a high bias was found in the reconstructed PET images, possibly due to out-of-FOV scatter.
More recent studies (Mehranian et al. 2015) proposed to use TOF-MLAA to derive continuous (and patient-specific) lung attenuation coefficients. This approach showed a notable improvement over previous methods, only able to predict mean lung attenuation values. Similarly to (Berker et al. 2012b), only the lung attenuation coefficients of a four-tissue-classes MRAC are assumed to be unknown. A Gaussian tissue-preference prior was also incorporated in this study, consisting in a Gaussian function centred at the expected value of lung attenuation coefficients based from population values. This prior will therefore penalise the large variation of the estimated lung attenuation values from their expected value. PET quantification accuracy of both MLAA and MRAC methods (with air, lung, soft tissue and fat as tissue classes) were evaluated against the reference CT-based AC method. In this study, the proposed algorithm was able to estimate lung and bones with an error of -2.9% ± 7.1 % and -15.3% ± 2.3%, respectively.

The aforementioned approaches assume that the MRAC information is sufficiently reliable in certain regions, e.g. outside the lung, and therefore can be kept fixed. However this is not necessarily the case since potential segmentation and classification errors in addition to uncertainties in tissue attenuation values could potentially arise. Furthermore, incorporating a Gaussian tissue-preference prior on lung values might add bias in the reconstruction if the patient lung attenuation values significantly differ from the population ones.

### 2.4.2 Beyond true coincidences

In the absence of TOF information, further efforts need to be made in order to provide a stable solution of the joint reconstruction problem.

As attenuation and scatter are intrinsically linked on a physical level, this has led several authors to attempt to use information contained in the scattered counts to estimate the attenuation distribution of the object.

#### 2.4.2.1 Attenuation estimation from scattered data

The first study on attenuation estimation from scatter in PET dates back to 2014 (Berker et al. 2014). This work extends from early suggestions of use of individual photon energy information in image reconstruction (Sec. 2.1.5.2). It relies on the idea that in PET, given detector locations and the corresponding measured energies for a coincidence, the set of possible scattering locations can be described geometrically.

A surface of revolution, named TCA (Two Circular Arcs), describes the location of the scatter points for a certain scatter angle. This surface (Fig. 2.13) can have different shapes
Figure 2.13: TCA for a pair of detectors AB, a measured energy $E'$ in B and a scatter angle $\varphi$.

depending on the scatter angle $\varphi$. For $0 < \varphi < \frac{\pi}{2}$ the shape is comparable to that of an American-football.

Tracing back to the scatter point locations given the measured energy is only straightforward if the energy measurements of the scattered photons are perfect, which is assumed in (Berker et al. 2014). The reconstruction algorithm relies on a “scatter-to-attenuation” (S2A) back-projection approach, which consists of backprojecting detected scatter coincidences onto “broken-paths” defined by the TCA curve. Corrections for such effects as detector geometry and scatter probabilities, are applied as multiplicative constants. This work provided a proof-of-concept for the reconstruction of an attenuation image from the scattered energy window only (assuming a known emission image).

In following years, the group moved from a heuristic back-projection method to a gradient-ascent optimisation algorithm (Berker et al. 2017b). However, this method has several limitations: (i) a 2-D scatter model, (ii) both the forward scatter model and its gradient do not account for the energy dependency of the attenuation distribution, (iii) no mismatch between simulation and reconstruction model, (iv) noise-free simulated data, (v) absence of energy and resolution modelling.

This approach will be extended throughout this thesis.

2.4.2.2 Activity estimation from scattered data

Alongside attenuation estimation, other groups have also observed that the scatter information can benefit emission reconstruction (Manavaki et al. 2003). In particular, the incorporation of the scatter model into the EM algorithm leads to significantly higher levels of contrast in the resulting images. However, this is only achieved with a significant increase in computation time, a large limitation of this method.

Following this, Conti et al. demonstrated that scatter data can provide independent spa-
2.4. Joint reconstruction of PET activity and attenuation

Information on the position of the source and is particularly useful in the reconstructions of low-count data-sets (Conti et al. 2012). Furthermore, they also observed that decreasing the lower energy threshold leads to include more scatter data and increased sensitivity.

A few years later, a study on the effect of the limited energy resolution of PET detectors when estimating the activity from both scattered events was conducted by (Zhang et al. 2014). A Gaussian distribution, centred around the photon energy, was used to model the detector energy response. While the local contrast almost disappears when the energy resolution is greater than 8%, the average activity distribution was found to be consistent with the ground truth distribution.

2.4.2.3 Joint reconstruction from scattered and unscattered data

The idea of joint reconstruction of activity and attenuation from scattered and unscattered data was first considered in SPECT (Sitek et al. 2007; Cade et al. 2013; Bousse et al. 2016) and then extended to PET (Berker et al. 2017a); some of the work of (Berker et al. 2017a) was performed in parallel with this thesis. A comparison of state-of-the-art methods is given in Table 2.2 and further discussed in the next sections. As it can be noticed from Table 2.2), PET research studies were only at their early stage of development until late 2016. Some of the state-of-the-art approaches will be discussed in the next section.

**SPECT application:** A maximum likelihood gradient ascent method was developed in (Cade et al. 2013) to estimate an attenuation map from measured scattered data. In order to estimate both the attenuation map and activity distribution, iterations of the proposed attenuation estimation methods alternate with a maximum likelihood expectation maximisation algorithm from photopeak data. This method relies on the assumption that the LACs along the scatter path - before and after the scatter point - is considered as constant for a given iteration. This assumption will be discussed in Chapter 3. An approximate model of the energy resolution of the gamma camera is included in the model. The method was shown to reduce the typical cross-talk between activity and attenuation that normally occurs in MLAA alone, but it was unable to eliminate it entirely. This method was tested on 2D phantoms and noise-free simulated data. Preliminary results were shown for a phantom acquisition; an empirically derived scaling factor was used to normalise the scatter distribution, in order to compensate for the sensitivity of the gamma camera and the inaccuracy of the scatter model. The effect of noise was not explicitly considered and assessing the effect of clinically realistic noise levels was mentioned in the suggested future work.
Table 2.2: Comparison of state-of-the-art methods for JRAA from multiple energy window data for both PET and SPECT applications

<table>
<thead>
<tr>
<th>Literature</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>One objective function</td>
<td>×</td>
<td>×</td>
<td>×</td>
</tr>
<tr>
<td>Second-order optimisation method</td>
<td>×</td>
<td>×</td>
<td>✓</td>
</tr>
<tr>
<td>3D input/output</td>
<td>×</td>
<td>×</td>
<td>✓</td>
</tr>
<tr>
<td>Noise in the data</td>
<td>×</td>
<td>×</td>
<td>✓</td>
</tr>
<tr>
<td>Energy resolution modelling</td>
<td>×</td>
<td>✓</td>
<td>×</td>
</tr>
<tr>
<td>Attenuation estimation</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Activity estimation</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Photopeak scatter</td>
<td>×</td>
<td>×</td>
<td>×</td>
</tr>
<tr>
<td>Full resolution photopeak data</td>
<td>×</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Full resolution low energy window data</td>
<td>×</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>True events in all windows</td>
<td>×</td>
<td>×</td>
<td>×</td>
</tr>
<tr>
<td>Full resolution output images</td>
<td>×</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Detector sensitivity normalisation</td>
<td>×</td>
<td>✓</td>
<td>×</td>
</tr>
<tr>
<td>Detector scatter model</td>
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<td>×</td>
<td>×</td>
</tr>
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<td>×</td>
<td>×</td>
<td>×</td>
</tr>
<tr>
<td>Out-of-field scatter</td>
<td>×</td>
<td>×</td>
<td>×</td>
</tr>
</tbody>
</table>

1 PET methods: Berker et al. 2017a and Berker et al. 2019.
2 SPECT method: Cade et al. 2013

This approach was then extended by (Bousse et al. 2016) to overcome some of the aforementioned limitations. They proposed a reconstruction scheme based on the ‘pseudo-maximisation’ of the joint likelihood \( \phi(\lambda, \mu) \) of scatter and non-scatter data. At each iteration, the activity image is updated with a standard EM update using the photopeak (true) counts only. The attenuation update relies on LBFGS and is obtained from both true events in the photopeak and low energy scatter events. Because only the ‘true-counts-likelihood’ is maximised in \( \lambda \), the overall algorithm is considered to be a ‘pseudo-maximisation’.

As shown in Table 2.2, the major improvement over (Cade et al. 2013) approach are: (i) account for the presence of noise in the data, (ii) 3D input/output and (iii) more sophisticated optimisation strategy. Results from both simulations and phantom data acquisition show that using scatter in addition to photo-peak information in the JRAA problem does reduce the cross-talk in the estimated distributions but it is not able to remove it completely. This study does not explicitly mention either energy resolution modelling or normalisation factors.
The aforementioned approaches were mostly limited by the assumption that the two data-sets of scattered and unscattered events could be measured separately: the photopeak was assumed to contain true events only (potentially after an initial scatter correction), and the low energy window contains only single scattered events. Furthermore, neither multiple scatter or out-of-field scatter events were taken into account.

The problem of simultaneous source and attenuation reconstruction in SPECT by using lower energy scattering data was also addressed analytically (Courdurier et al. 2015). This work relies on several assumptions, including: (i) isotropic scattering kernel, (ii) separation of the variables for the scattering kernel, (iii) the scattering kernel is independent on the scattering angle. The last hypothesis represents a poor approximation, because the scattering kernel does depend on the scatter angle and the probability of scattering is not uniform for all the angles, accordingly to Klein-Nishina formula (Sec. 2.1.1.2). Therefore, this work would need further refinement. By differentiating the non-linear operator that links unscattered and scattered measurements with the activity and attenuation distributions, they obtained a linearised inverse problem. Therefore, they were able to give an explicit formulation of the inverse of this linear operator.

PET application: Based upon the evidence that scatter information had the potential to bring extra information to the JRAA problem, Berker et al. proposed the first joint reconstruction algorithm from PET scatter and unscattered data (Berker et al. 2017a). The algorithm consists in an iterative approach in which the activity image is estimated using MLEM (Sec. 2.1.3.3) from the true counts data whilst the attenuation image update relies on a gradient-ascent-like algorithm (MLGA) from the scattered events. This approach was shown to be sufficient for small rat scanner reconstructions but was unable to converge for patient-scale objects. This problem will be also discussed in Sec. 5.3. A four-step alternating approach was used to estimate the activity and the attenuation for large objects (Berker et al. 2019). Further details will be given in Chapter 6. Berker et al. method had several limitations, including the restriction to simple 2D phantoms: (i) 18x18 voxels with size 0.5x0.5 cm$^2$ in a 2-D PET scanner of 8cm radius and (ii) 18x18 voxels with size 2.5x2.5 cm$^2$ in a 2-D PET scanner of 40cm radius (Berker et al. 2019). The presence of scatter in the photopeak window was not taken into account and the energy resolution was assumed to be perfect. Furthermore, PET scatter is inherently 3D; therefore, 2D phantoms are insufficient to accurately assess this methodology. This study was conducted in parallel with the research presented in this
thesis and it represents the closest approach to our method amongst all the existing studies that investigate benefits of using scatter information.

The further development of the joint reconstruction of activity and attenuation from scattered and unscattered data in non-TOF PET constitutes the object of this thesis.
Chapter 3

Model and approximations for a multiple energy window acquisition

This chapter presents the forward model that is the basis of this Thesis (Sec. 3.2-3.4) and a model for the detection efficiency for a generic energy window is also introduced in Sec. 3.5.

3.1 Introduction

The objective of this work is to jointly reconstruct the activity and the attenuation distributions from PET projection data with a Maximum Likelihood approach (see Sec. 2.4). As explained in Chapter 2, MLAA is an ill-posed inverse problem with infinitely many solutions. Therefore, further solutions need to be found to accurately estimate the activity distribution from standalone non-TOF PET data. In fact, any offset $X$ in the projections of the attenuation, can be compensated by a multiplicative factor $e^X$ in the activity image when the two distributions are estimated from one measurement. Referring to the Hadamard criteria (Sec. 2.1.3.1), the solution of MLAA is neither unique nor stable (Defrise et al. 2012).

The rationale behind this work is to reduce the ill-posedness of the joint problem by incorporating additional information into both the activity and attenuation distributions from multiple energy window measurements. As discussed in Sec. 2.4.2.3, the possibility of deriving additional information from low energy photons has been first explored in SPECT and only recently in PET. State-of-the-art methods rely on several simplistic assumptions that prevent a possible application of this approach in practice. Therefore, several adjustments are needed to be made to progress this technique.

In this Chapter, adjustments to the forward model are presented so that the additional information from low energy window data can be incorporated in the reconstruction process.
These modifications include:

- Incorporation of the scatter model into the forward model and its Jacobian
- Accounting for the dependency of the attenuation on the energy of the photon
- Accounting for the presence of both scattered and unscattered events in all the measured data
- Accounting for detector scatter

### 3.2 Statistical model of the measured data

The primary assumption of this work is that the observed counts $g_{vw}$ in each energy window pair $(v, w)$ can be described as a sum of independent Poisson processes with expected value $\bar{g}_{vw}$:

$$
\bar{g}_{vw}(\lambda, \mu) = \bar{g}_{vw}^{\text{unsc}}(\lambda, \mu) + \bar{g}_{vw}^{\text{sc}}(\lambda, \mu) + \bar{g}_{vw}^{r}
$$

(3.1)

where $\bar{g}_{vw}^{\text{unsc}}$ denotes the expected unscattered events, $\bar{g}_{vw}^{r}$ is a background term incorporating randoms and $\bar{g}_{vw}^{\text{sc}}$ indicates the expected single scatter events; the background term could incorporate multiple scatters (see Sec. 7.6 for further details).

#### 3.2.1 Unscattered Events

The expected unscattered events $\bar{g}_{vw}^{\text{unsc}}(\lambda, \mu)$ are modelled as follows:

$$
\bar{g}_{vw}^{\text{unsc}}(\lambda, \mu) = A(\mu)\lambda
$$

(3.2)

where $A(\mu) \in \mathbb{R}_{+}^{nD \times n_v}$ is a linear transformation mapping from image space to data space, describing the probability that an emission occurring in voxel $u \in \{1, \ldots, n_v\}$ is detected by a pair of detectors $(h, k) \in \{1, \ldots, n_D\}^2$. As shown in Eq. 2.16, $A$ is given by the product of several matrices, including the one containing the attenuation factors $A^{\text{atten}}$, defined as:

$$
A^{\text{atten}}(\mu)_{h,k} = \exp\left(-K_{h,k} \mu\right)
$$

(3.3)

where $K$ is the operator that computes the line integral along the line $h, k$.

By referring to Eq. 2.9, $A$ also includes the sensitivity matrix; for the unscattered events, this is defined as:

$$
A^{\text{sens}}_{vw}(511,511) = \epsilon_v(511)\epsilon_w(511)G_{vw}
$$

(3.4)
3.2. Statistical model of the measured data

3.2.2 Scattered Events

We introduce here the variable \( \theta = [\lambda, \mu] \). A detailed formulation for the expected scatter events \( \bar{g}_{vw}^{sc}(\theta) \) now follows.

Let \( P \in \mathbb{R}^{n_D \times n_D'} \) and \( R \in \mathbb{R}^{n_v' \times n_v} \) be prolongation and restriction operators, respectively. Both operators are linear. The first maps a sinogram from low resolution (\( n_D \) total detector pairs) to high resolution (\( n_D' \) total detector pairs). The latter maps an image from high resolution (\( n_v \) voxels) to low resolution (\( n_v' \) voxels). Let also be \( n_D' = \gamma n_D \) and \( n_v = \eta n_v' \), with \( \gamma \) and \( \eta \) defining the downsampling and upsampling factors in image and sinogram space, respectively. Then, the scatter component \( \bar{g}_{vw}^{sc}(\theta) \) is given by the following relationship (see Fig. 3.1):

\[
\bar{g}_{vw}^{sc}(\theta) = PS_{vw}R(\theta) = PS_{vw}(\tilde{\theta})
\]  

where:

\[
\tilde{\theta} = R \theta
\]

\( S_{vw}(\tilde{\theta}) \in \mathbb{R}^{n_D' \times n_v'} \) is the forward operator computing the expected scatter at each energy window pair \((v, w)\) for every pair of detectors \((i, j) \in \{1, \ldots, n_D'\} \):

\[
[S_{vw}(\tilde{\theta})]_{i,j} = \sum_{s=1}^{n_s} g_{vw,i,j,s}^{sc}(\tilde{\theta})
\]  

where \( n_s \) is the total number of scatter points. The scatter forward model \( \bar{g} \) is given by:

\[
g_{vw,i,j,s}^{sc}(\tilde{\theta}) = \frac{1}{\eta} \left( A_{vw}^{sens}(E, 511)I_{i,s,j}(\tilde{\theta}) + A_{vw}^{sens}(511, E)I_{j,s,i}(\tilde{\theta}) \right)
\]  

where \( E \) is the photon energy after (single) Compton scattering (in keV) as a function of the scatter angle \( \phi \) for a scatter point at voxel \( s \), \( \eta = \frac{3}{4 \pi} \frac{\sigma_i \sigma_j}{2 \pi r_{ij}^2} \) approximates the solid angle of each detector \( i, j \) with respect to the centre of the scanner, \( \sigma_i \) is the cross section of detector \( i \) presented normally to the \( \gamma \)-rays incident along the line \( ij \) (C. C. Watson et al. 1996), and:

\[
I_{i,s,j}(\tilde{\theta}) = \frac{\sigma_i \sigma_j}{4 \pi r_{ij}^2} \frac{d \sigma}{d \Omega}(\phi) \mu_{511,s}(\tilde{\lambda}) e^{-K_{i,s} \mu_{511} e^{-K_{j,s} \mu_E}}
\]  

where \( \frac{d \sigma}{d \Omega}(\phi) \) is the differential cross section given by the Klein-Nishina equation (Klein et al. 1929), \( \mu_E \) is the distribution of attenuation coefficients at photon energy \( E \), \( r_{i,s} \) is the distance between the scatter point \( s \) and detector \( i \), \( \sigma_{i,s} \) denotes the detector cross-section
3.2. Statistical model of the measured data

Figure 3.1: Schematic representation of the forward scatter model. \( \theta \): full resolution image space. \( \tilde{\theta} \): low resolution image space. \( \tilde{y} \): low resolution projection space. \( y \): full resolution projection space. \( R \): restriction operator mapping from full resolution to low resolution image space. \( P \): prolongation operator mapping from low resolution to full resolution projection space.

presented to the ray \( i, s \), and \( K_{i,s} \) indicates the line integral operator along the line \( i, s \).

Analogously to Eq. 3.4, the sensitivity matrix \( A_{vw}^{\text{sens}}(E, 511) \) is given by:

\[
A_{vw}^{\text{sens}}(511, E) = \epsilon_v(511)\epsilon_w(E)G_{vw}
\]  

(3.10)

Please note that:

\[
A_{vw}^{\text{sens}}(511, E) \neq A_{vw}^{\text{sens}}(E, 511), \quad \forall (v \neq w)
\]  

(3.11)

In this chapter, we refer as ‘broken-path’ as the triangular path defined by a pair of detector \( i, j \) and a scatter point \( s \). Eq. 3.9 can be interpreted as the contribution of an emission placed between a detector \( i = A \) and a scatter point location \( s = S \), with a detector \( j = B \) measuring the scattered photon at an energy \( E \) (Fig. 2.10).

3.2.2.1 Probability of scattering

The Klein-Nishina (KN) formula (Eq. 2.4) predicts the number of photons that will scatter with a certain angle \( \phi \), which can be also related to the change in photon energy via the Compton equation (Sec 2.1.1.2). According to KN equation, the final energy of the scattered photon only depends on the scattering angle and on the original photon energy.
3.2.2.2  Effect of reduced energy on attenuation after Compton scattering

The Compton scattering process results in the reduction of the photon energy as well as change in direction (Sec. 2.1.1.2). As a result, the attenuation experienced by photons after the point of scatter is increased. This effect can be included in the scatter model by applying a scaling factor to the attenuation at each voxel along the ‘broken-path’ following the scatter point (Cade et al. 2013).

Here we address the dependency of the attenuation on the energy in the scatter model by assuming that the attenuation is only due to Compton scatter and is therefore proportional to the total Compton scatter cross-section $\sigma_{\text{tot}}$ at a particular energy $E$:

$$\mu_E = \frac{\sigma_{\text{tot}}(\Lambda)}{\sigma_{\text{tot}}(1)} \mu_{511} = f^* \mu_{511} \tag{3.12}$$

$\sigma_{\text{tot}}$ can be obtained by integrating the Klein-Nishina equation (Eq. 2.4) over all solid angles. The scaling factor $f^*(E)$ is then given by:

$$f^* = -18\Lambda(2 + \Lambda(1 + \Lambda)(8 + \Lambda))$$

$$-9(1 + 2\Lambda)^2(-2 + (-2 + \Lambda)\Lambda)\log(1 + 2\Lambda))/((\Lambda^3(1 + 2\Lambda)^2(-40 + 27\log(3))) \tag{3.13}$$

where $\Lambda = \frac{E}{511}$. The forward model can therefore be re-written with respect to the attenuation coefficient at reference energy (511 keV).

3.3  Jacobian of the forward scatter model

One of the most important factors to consider for the algorithms presented in this Thesis is the Jacobian of the forward scatter model (Eq. 3.8) with respect to both the attenuation and activity images. Here we give an overview of its analytical derivation and its discretisation.

3.3.1  Analytical derivation

The Jacobian $J^{sc}$ of the forward scatter model with respect to the input distributions $\lambda$ and $\mu$ is defined as follows:

$$J^{sc} = \begin{bmatrix} J^{sc}_{\lambda} & J^{sc}_{\mu} \end{bmatrix} \tag{3.14}$$

In the following, we replaced the vectors $\lambda$ and $\mu$ by two functions $\lambda : \mathbb{R}^3 \to \mathbb{R}^+$ and $\mu : \mathbb{R}^3 \to \mathbb{R}^+$ for variational formulation. For simplicity the same notation for the line integral operator $K$ and the scatter point $s$ is used.
3.3. Jacobian of the forward scatter model

3.3.1.1 Attenuation

Here we compute the (variational) Jacobian of the scatter model with respect to the attenuation image $\mu$. To remove the dependency on the energy of the attenuation, the Jacobian is computed with respect to $\mu_{511}$, which is considered the parameter of reference for all the photon energies (see Eq. 3.12):

$$J^{sc}_{\mu_{511}} = \frac{\delta \tilde{g}^{sc}(\lambda, \mu_{511})}{\delta \mu_{511}}$$ (3.15)

We report the relevant calculations for a pair of detectors $(i, j)$, an energy window pair $(v, w)$, and a scatter point location $s$.

To compute $J^{sc}_{\mu_{511}}$, we rely on the definition of variational derivative (Giaquinta et al. 1996):

$$\int \frac{\delta \tilde{g}^{sc}_{vw,i,j,s}(\mu_{511} + \epsilon \phi)}{\delta \mu_{511}(r)} \phi(r) dr = \lim_{\epsilon \to 0} \tilde{g}^{sc}_{vw,i,j,s}(\mu_{511} + \epsilon \phi) - \tilde{g}^{sc}_{vw,i,j,s}(\mu_{511})$$ (3.16)

where $\phi : \mathbb{R}^3 \to \mathbb{R}$ is an arbitrary function. For simplicity of notation, in the following equations we omit the dependency of $\tilde{g}^{sc}_{vw,i,j,s}$ on $(\lambda, \mu)$. In addition, we group in a constant $C_{i,s,j}$ all the terms that are independent of $\mu$:

$$C_{i,s,j} = A_{vw}^{sens}(511, E) \frac{\sigma_i \sigma_j}{r_i r_j^2} \frac{d\sigma}{d\Omega}(\phi) K_{i,s}$$ (3.17)

Therefore, the equation for the forward scatter model (Eq. 3.9) becomes:

$$\tilde{g}^{sc}_{vw,i,j,s}(\lambda, \mu) =$$

$$C_{i,s,j} \mu_{511}(s) e^{-f^* K_{i,s} \mu_{511}} e^{-f^* K_{j,s} \mu_{511}} +$$

$$C_{j,s,i} \mu_{511}(s) e^{-f^* K_{i,s} \mu_{511}} e^{-f^* K_{j,s} \mu_{511}}$$ (3.18)

where $f^*$ replaces $\frac{\sigma_{ad}(E)}{\sigma_{tot}(511)}$ (Eq. 3.12). In the following, we omit the dependency of $C_{j,s,i}$ on $E$ and $\phi$. By taking the limit of Eq. 3.16, we obtain:

$$\tilde{C}_{i,s,j} \left[ \phi(s) - \mu_{511}(s) \left( K_{i,s} \phi + f^* K_{j,s} \phi \right) \right] +$$

$$\tilde{C}_{j,s,i} \left[ \phi(s) - \mu_{511}(s) \left( f^* K_{i,s} \phi + K_{j,s} \phi \right) \right]$$ (3.19)

where:
3.3. Jacobian of the forward scatter model

\[ \tilde{C}_{i,s,j} = C_{i,s,j} \left[ e^{-K_{i,s} \mu_{511}} e^{-f^* K_{j,s} \mu_{511}} \right] \]  

(3.20)

In order to obtain \( \frac{\delta g_{vw,i,j,s}}{\delta \mu_{511}} \) from Eq. 3.16, an integral expression for Eq. 3.19 is needed. This can be computed by considering the following integral:

\[ \phi(s) = \int \phi(r) \delta_s(r) dr \]  

(3.21)

where \( \delta_s \) is a Dirac function centred on the scatter point \( s \) and

\[ K_{i,s} \phi = \int_{L_{i,s}} \phi(r) dr = \int \phi(r) \delta_{L_{i,s}}(r) dr \]  

(3.22)

where \( \delta_{L_{i,s}} \) can be interpreted as a measure of integration along the line segment \( L_{i,s} \) between detector \( i \) and the scatter point location \( s \). Using this notation, the first line of Eq. 3.19 can be re-written as:

\[ \tilde{C}_{i,s,j} \left[ \phi(r) \delta_s(r) - \mu_{511}(s) \left( \phi(r) \delta_{L_{i,s}}(r) + f^* \phi(r) \delta_{L_{i,s}}(r) \right) \right] dr \]

and it follows that:

\[ \frac{\delta g_{vw,i,j,s}}{\delta \mu_{511}(r)} = \]  

(3.23)

\[ \tilde{C}_{i,s,j} \left[ \delta_s(r) - \mu_{511}(s) \left( \delta_{L_{i,s}}(r) + f^* \delta_{L_{i,s}}(r) \right) \right] + \tilde{C}_{j,s,i} \left[ \delta_s(r) - \mu_{511}(s) \left( f^* \delta_{L_{i,s}}(r) + \delta_{L_{j,s}}(r) \right) \right] \]

3.3.1.2 Activity

The Jacobian \( J^c_\lambda \) with respect to the activity can be obtained using a similar derivation to the one of the attenuation. We group all terms of the scatter forward model (Eq. 3.9) which are independent of \( \lambda \):

\[ F_{i,s,j} = A^{\text{det}}_{vw} (511, \mathcal{E}) \frac{\sigma_{i,s} \sigma_{j,s}}{r^{L_{i,s}} f^{j,s} d\Omega} \frac{d\sigma}{d\Omega} (\phi) \mu_{511}(s) e^{-K_{i,s} \mu_{511}} e^{-f^* K_{j,s} \mu_{511}} \]  

(3.24)

This results in:

\[ \tilde{g}_{vw,i,j,s} = F_{i,s,j} K_{i,s} + F_{j,s,i} K_{j,s} \]  

(3.25)
and obtain:

\[
\frac{\delta \tilde{g}^{\text{sc}}_{\text{vw},i,j,s}}{\delta \lambda(r)} = F_{i,x,j} \delta_{i,j}(r) + F_{f,s,i} \delta_{i,s}(r) \tag{3.26}
\]

### 3.3.2 Discretisation and implementation

In order to be suitable for numerical computing, the variational derivatives shown in 3.3.1 need to be transformed to (ordinary) derivatives with respect to the discretised images \( \mu \) and \( \lambda \).

#### 3.3.2.1 Discrete formulation of SSS and SSS-Jacobian

The Software for Tomographic Image Reconstruction (STIR) (Tsoumpas et al. 2004) SSS implementation approximates the line integrals in the forward model by line ray tracing between the centre of a detector and a scatter point. The ray sums are obtained by computing the length of intersection \( V_{i,s,n} \) of a line from a scatter point in voxel \( s \) at \( s \) to detector \( i \) with the voxel \( n \) at location \( r_n \):

\[
K_{i,s} \lambda \approx \sum_{n=1}^{N} V_{i,s,n} \lambda_n \tag{3.27}
\]

where \( \lambda_n \) is the activity value at voxel \( n \) of the discretised image \( \lambda \). Please note that the same applies to the attenuation image. Both attenuation and the activity image discretisation schemes are described in (Tsoumpas et al. 2004).

After discretisation, Eq. 3.23 becomes:

\[
\frac{\partial \tilde{g}^{\text{sc}}_{\text{vw},i,j,s}}{\partial \mu_{511,n}} =
\]

\[
\mathcal{C}_{i,s,j} \left[ \delta_{i,n} - \mu_{511,n} \left( V_{i,s,n} + f^s V_{j,s,n} \right) \right] + \mathcal{C}_{j,s,i} \left[ \delta_{j,n} - \mu_{511,n} \left( f^s V_{i,s,n} + V_{j,s,n} \right) \right]
\]

where \( \delta_{i,n} \) is the Kronecker delta. Similarly, Eq. 3.26 can be discretised as:

\[
\frac{\partial \tilde{g}^{\text{sc}}_{\text{vw},i,j,s}}{\partial \lambda_n} = F_{i,x,j} V_{i,s,n} + F_{f,s,i} V_{j,s,n} \tag{3.29}
\]

Finally, the Jacobian \( J^{\text{sc}}_{\mu} \) and \( J^{\text{sc}}_{\lambda} \) are obtained as:
3.3. Jacobian of the forward scatter model

\[ J^\text{sc}_\mu = P \frac{\partial S}{\partial \mu} R = P J^\text{sc}_\mu R \]
\[ J^\text{sc}_\lambda = P \frac{\partial S}{\partial \lambda} R = P J^\text{sc}_\lambda R \]  

(3.30)

with \( \tilde{\mu} = R \mu \) and \( \tilde{\lambda} = R \lambda \).

3.3.2.2 STIR implementation strategy

The implementation of the Jacobian matrix into the STIR libraries is constructed in terms of its adjoint operator \( J^* \), where \( J \) denote either \( J^\lambda \) or \( J^\mu \). From Eq. 3.30 follows that:

\[ J^* = R^* \left( \frac{\delta S}{\delta \alpha} \right)^* P^* \]  

(3.31)

where:

\[ < R^* y, x > = < y, Rx > \]  

(3.32)

for every \( x : \mathbb{R}^{n_v} \) and \( y : \mathbb{R}^{n'_v} \), with \( n_v \) and \( n'_v \) being high and low resolution number of voxels, respectively. Eq. 3.32 also applies to \( P \) and \( S \).

The following strategy was adopted for the implementation of \( J^* \) into the STIR libraries:

(i) select a scatter point \( s \) from the set of sample scatter points and a pair of detectors \( (i, j) \);  
(ii) compute the scatter angle \( \phi_{i,s,j} \); (iii) compute the corresponding scattered energy \( E(\phi_{i,s,j}) \) and all terms related to it (differential cross section, detection probabilities, etc.); and (iv) compute the discretised adjoint-Jacobian.

3.3.2.3 Numerical validation

The implementation of \( J^* \) was tested by comparing it against a finite-difference approximation to the Jacobian of \( \mu_n \) using a small perturbation in the \( n \)-th voxel on a 3D XCAT (Segars et al. 2010) torso phantom (Fig. 5.3). The accuracy of the implementation was evaluated in terms of absolute error between the gradient and the finite differences, normalised with respect to the maximum absolute value of the Jacobian. For \( \varepsilon = 0.0005 \), the order of magnitude of the mean and maximum relative error were found to be \( 10^{-4} \) and \( 10^{-3} \), respectively. Fig. 3.2 shows a visual assessment of the goodness of the implementation, by comparing a profile along the y-axis of the gradient and finite difference images.

3.3.2.4 Considerations on the scatter Jacobian

One of the biggest challenges in attenuation (and activity) estimation from low energy data is the complexity of the system matrix and the consequent computational cost for the Jacobian...
3.4. Gradient of the log-likelihood

Let \( \mathcal{L} \in \mathbb{R} \) be the objective function defined as:

\[
\mathcal{L}(g|\tilde{g}(\lambda, \mu)) = \sum_{(v,w)=1}^{n_v} \sum_{(h,k)=1}^{n_D} \left( g_{vw,h,k} \log(\tilde{g}_{vw,h,k}(\lambda, \mu)) - \tilde{g}_{vw,h,k}(\lambda, \mu) \right)
\]  

(3.33)
3.5 Detector efficiency model

The performance of an iterative reconstruction method is strongly related to the accuracy of the forward model of the data. For the work presented in this Thesis, a key role is played by the detector energy response model $\varepsilon_w$. The efficiency of PET detectors depends on several effects that need to be included in the forward model, either through normalisation or by direct analytical calculation (see 2.1.2.1). In the following, we refer to detection efficiency ($\varepsilon_w(E)$) as the probability to detect an incoming photon of a given energy $E$.

A model describing the detector efficiency of PET detectors for incident Gamma-rays with energies close to 511 keV has been well established since the past decade. However, detector efficiency modelling for low energy photons is still an open field of research.

3.5.1 Photopeak window

Here we present the standard approach to model the detector energy spectrum in the photopeak window. An overview of geometric effects and normalisation is also given.

This detection efficiency model will be used in Chapters 4-6.

3.5.1.1 Detection efficiency model

The detection of optical photons in the photo-detector is subject to Poisson statistics. A fairly realistic method to model the energy response of PET detector in the photopeak window is to use an energy-dependent Gaussian broadening. The probability of detection $\varepsilon(E, r_{\text{ref}}, t_L, t_H)$ is then obtained by integrating the Gaussian function between the boundary of the energy window (C. C. Watson 2007; Tsoumpas et al. 2005). The resulting detection efficiency depends on the incident photon energy $E$, the energy resolution of the detector $r_{\text{ref}}$ at a...
3.5. Detector efficiency model

reference energy of 511 keV (expressed as FWHM), the higher \( t_H \) and the lower \( t_L \) threshold of the energy window (Tsoumpas et al. 2005):

\[
\varepsilon(E, r_{ref}, t_L, t_H) = 0.5 \left( \text{erf} \left( \frac{t_H - E}{\sqrt{2} \sigma_p} \right) - \text{erf} \left( \frac{t_L - E}{\sqrt{2} \sigma_p} \right) \right)
\]

with

\[
\sigma_p = \sqrt{E \cdot E_{ref}} \cdot \frac{r_{ref}}{2.35482}
\]

where \( E_{ref} \) is normally equal to 511 keV, and \( r_{ref} \) is the energy resolution of the detector for the reference energy given as FWHM, \( \sigma_p \) being the standard deviation in the photopeak window and \( \text{erf} \) is an error function.

3.5.2 Generic energy window

The Gaussian model, presented in the previous section, is a very good approximation for the photopeak window, usually chosen with \( t_L = 430 \) keV and \( t_H = 610 \) keV (Karlberg et al. 2016). However, for either wider energy windows or for the case of multiple energy windows placed below the photopeak, this approximation is prone to errors. Consequently, the use of multiple energy windows introduces new problems for the determination of the normalisation factors and detection efficiency model. The following sections discuss the strategies adopted in this Thesis to address this problem.

3.5.2.1 Detection efficiency model

Detector response varies as a function of the energy of the incoming photon. A semi-empirical response function for photon energies between 0.5 and 1.5 MeV was recently proposed (Li et al. 2014). This model was adapted in this Thesis to the case of LSO detectors (the detector type used in the Siemens mMR) and to PET energy ranges. The proposed model is described in the following.

Similarly to the case of the photopeak window, the detection probability is obtained by integrating the probability of detecting the energy response function \( f(E, E_m) \) between the boundaries of the energy window \( t_L \) and \( t_H \):

\[
\varepsilon(E, t_L, t_H) = \int_{t_L}^{t_H} f(E, E_m)dE
\]

Please note that \( E \) and \( E_m \) indicate respectively the incoming and measured photon en-
energy. The detection efficiency model \( f(E, E_m, r_{ref}) \) is given by the sum of four contributions, of which the following paragraphs give an overview:

\[
f(E, E_m) = f_1(E, E_m) + f_2(E, E_m) + f_2(E, E_m) + f_3(E, E_m)
\]  

(3.39)

**Photoelectric effect:** A Gaussian distribution function is adopted to describe the photo peak:

\[
f_1(E, E_m) = \frac{\sigma_f}{\sqrt{2\pi}\sigma_p} \exp\left(-\frac{(E_m - E)^2}{2\sigma_p^2}\right)
\]  

(3.40)

\( \sigma_p \) is the standard deviation of the photopeak. The amplitude of the peak is proportional to the total photoelectric cross section \( \sigma_f \), given by:

\[
\sigma_f = \frac{Z_{eff}^5}{E}
\]  

(3.41)

For lower energy photons, the photoelectric cross section increases, and the amplitude of the photopeak is therefore expected to be higher. The expression \( Z_{eff} \) indicates the atomic number of hypothetical single element that would attenuate photons at the same rate as the composite material in question (Birgani et al. 2012). The (effective) atomic number \( Z_{eff} \) was set to 66, corresponding to that of LSO crystal. The standard deviation of the photopeak was expressed in terms of FWHM for 511 keV (see 3.37).

**Compton Scattering:** To model detector scatter the function proposed by (Li et al. 2014) was modified hereby incorporating the dependency on the total Compton cross section \( \sigma_C \) and the effective atomic number \( Z_{eff} \). The resulting function becomes:

\[
f_2(E, E_m) = H_1 Z_{eff} \sigma_C \left[ \left( \frac{E'}{E} \right) + \left( \frac{E'}{E} - 2 \right) \right] \left[ \exp\left(-\frac{(E_m - E \cdot p_1)^2}{4p_2\sigma_p}\right) \right]
\]  

(3.42)

where \( E' \) is the energy after Compton scatter with \( \phi = \pi \) (the scatter angle was fixed for reducing the complexity of the model), \( H_1, p_1 \) and \( p_2 \) are parameters to scale the amplitude, determine the centre of the Compton plateau and its standard deviation, respectively. The \( Z_{eff} \) could have be incorporated in \( H_1 \) but was intentionally left out to make this model plausible for different materials.

**Flat continuum:** An ‘almost’ flat continuum from zero to the photo peak energy found to exist in the spectrum (Li et al. 2014), possibly resulting from the presence of electronic noise.
3.6 Discussion and Conclusion

It is modelled as:

\[ f_3(E, E_m) = H_2 \left[ \text{erfc} \left( \frac{E_m - E}{\sqrt{2} \sigma_P} \right) \right] \]  

(3.43)

where \( H_2 \), is a parameter to scale the amplitude of the flat continuum. For \( E > E_m \), \( f_3(E, E_m) = 0 \) and \( \text{erfc} = 1 - \text{erf} \).

**Exponential tail:** This last function relates to the presence of an exponential tail in the region of low energy side of the spectrum. The representative function is given by:

\[ f_4(E, E_m) = H_3 \left[ \exp \left( \frac{E_m - E}{\sqrt{2} \pi P_3 \sigma_P} \right) \right] \left[ \text{erfc} \left( \frac{E_m - E}{\sqrt{2} \sigma_P} + \frac{1}{2 P_3} \right) \right] \]  

(3.44)

where \( H_3 \) and \( P_3 \) are parameters that scale the amplitude the standard deviation and the slope of the exponential tail, respectively. Pair production was not included in the model given the zero probability of this effect occurring for incoming photon energies of 511 keV (or lower).

A validation of the proposed model is given in Chapter 7.

3.6 Discussion and Conclusion

In this Chapter, the forward model at the core of this Thesis was presented. An overview of the statistical model of the measured data and its gradient was also given.

As one of the biggest challenges in the incorporation of scatter information in PET image reconstruction lies in the complexity of the system matrix, particular focus on implementation strategies was given.

Whilst many authors were limited to use 2D phantoms for computational reasons, the proposed implementation strategy enabled us to incorporate the full gradient formula into the reconstruction method. The dependency of the attenuation on the energy was incorporated into the forward model. Furthermore, a new model for the detection efficiency accounting for detector scatter was presented.

The forward model is given here in its general formulation. Some simplified assumptions on the forward model will be made in the next chapter and then gradually removed throughout the Thesis.
Chapter 4

Attenuation estimation from energy window data below the photopeak window

In Chapter 2 the concept of Maximum Likelihood Estimation of Activity and Attenuation (MLAA) was introduced. The ill-posed nature of the inverse problem was further discussed in Chapter 3. The possibility of improving upon the original non-TOF MLAA by incorporating energy information was also presented.

This chapter takes a step back from the main topic of this thesis - joint reconstruction of the activity and attenuation - to focus entirely on attenuation reconstruction from PET data with a known emission distribution. This is motivated by the necessity to understand if some additional (and useful) information was present in the low energy window data in the perspective of the grander scheme.

4.1 Introduction

As presented in Chapter 2, a theoretical obstacle with non-TOF MLAA (Sec. 2.4) lies in the non-uniqueness of the estimated attenuation sinogram when estimated from standalone unscattered coincidences.

Recent studies have investigated the possibility to use scattered data to reconstruct attenuation maps in SPECT (see Sec. 2.4.2). This idea has been translated to PET imaging but it is still at an early stage of development (Sec. Sec. 2.4.2). In particular, PET attenuation distribution of point-sources and simple 2D phantoms have been estimated from scatter events. State-of-the-art methods have been discussed in Sec. 2.4.2.3.

For the purposes of clarity, this thesis will discuss detected events in terms of energy information, rather than scattered and unscattered events. In this regard, rather than referring to a scatter likelihood, (Bousse et al. 2016) the optimisation problem is formulated in terms
of likelihood of the data at a certain energy window. This will reduce to the case of scatter likelihood in the case when that particular energy window only measures scatter events.

In contrast to SPECT, PET scanners detect coincidence events; furthermore, one or more energy window can be used during the acquisition (Sec. 2.1.2.1). Benefits of using a different energy window for each individual annihilation photon to perform attenuation estimation are presented in this chapter. This study is intended to be a first preliminary investigation to set up the basis for the joint reconstruction algorithm (Chapter 5). Part of this Chapter was presented in (Brusaferri et al. 2017).

Many of the initial simplified assumptions presented throughout this Chapters are removed in the following ones.

4.2 MLTR-EB: Energy-Based Maximum Likelihood for TRansmission tomography

4.2.1 Statistical Model

It is assumed that each photon, of a coincidence pair, can be assigned to either the photopeak window (U) or to a lower energy window (L). As a result, four different 3D sinogram data sets are measured, one corresponding to each energy-binning combination ($g_{UU}$, $g_{UL}$, $g_{LU}$, $g_{LL}$). For this initial study, the observed counts $g_{vw}$ in any energy window pair $(v, w) \in \{U, L\}^2$ are assumed to be described as a Poisson process centred in $\bar{g}_{vw}$ given by (single) scatter events only. This assumption was made to investigate the amount of information contained in standalone single scatter events. An overview of the forward scatter model was given in Sec. 3.2. All the results presented in this chapter are in low resolution; the attenuation and activity images are indicated with $\tilde{\mu}$ and $\tilde{\lambda}$, respectively. For $\tilde{\theta} = [\tilde{\lambda}, \tilde{\mu}]$, the forward model for each energy window pair is therefore given by:

$$\bar{g}_{vw}(\tilde{\theta}) = \bar{g}^{sc}_{vw}(\tilde{\theta})$$

(4.1)

where $\bar{g}^{sc}_{vw}$ is given by Eq. 3.5. For computation reason, low energy windows UL and LU input data are downsampled in low resolution: $g' = P^*(Pg)$. Furthermore, the operator $R$ (Sec. 3.2.2) is assumed to be an all-ones matrix; therefore, all the experiments presented in this chapter are conducted in low spatial resolution. A visual interpretation of the forward model used in this chapter is given in Fig. 5.1. The probability of detecting incoming photons with a certain energy $E$ was modelled as Gaussian function (Sec. 3.5.1.1).
4.2. MLTR-EB

4.2.2 Optimisation

We propose an Energy-based Maximum Likelihood for Transmission Tomography (MLTR-EB) for attenuation estimation (Brusaferri et al. 2017) to address the problem stated in Sec. 4.1.

It consists of a maximum likelihood estimation of the attenuation image $\hat{\mu}$ from the PET data with a known emission, obtained by maximising the log-likelihood $\mathcal{L}$ such that the image estimate fits the data in the low energy windows pairs UL and LU:

$$\hat{\mu} = \arg \max_{\mu \geq 0} \left( \mathcal{L}_{UL}(g'_UL | \gamma S_{UL}(\mu)) + \mathcal{L}_{LU}(g'_LU | \gamma S_{LU}(\mu)) \right) \quad (4.2)$$

with $g'_vw$ indicating downsampled sinogram and $\gamma = n_D/n'_D$ the down-sampling factor (Sec. 3.2.2). Please note that $\sum_{D} g \sum_{D'} g' = \gamma$.

4.2.2.1 Image updates

The image updates rely on a line-search step in a quasi Newton direction (Sec. 2.1.3.3):

$$\hat{\mu}^{i+1} = \hat{\mu}^i + \xi B_{\hat{\mu}} \left[ \nabla \mathcal{L}_{UL}(\hat{\mu}^i) + \nabla \mathcal{L}_{LU}(\hat{\mu}^i) \right] \quad (4.3)$$

where $\nabla \mathcal{L}$ is the gradient of the objective function, $B_{\hat{\mu}}$ is a LBFGS approximation of the inverse Hessian matrix computed following the implementation from (Byrd et al. 1995) and $\xi$ is the step-size. A history length $m = 5$ was maintained for constructing $B_{\hat{\mu}}$.

Algorithm 1 shows pseudo-code for MLTR-EB.
Algorithm 1: Pseudo-code for MLTR-EB.

Input: $\mathbf{g}_{UL}$, $\mathbf{g}_{LU}$, $\lambda_{true}$, $\mu_{init}$

Output: Estimated attenuation image $\mu_{est}$

$\mu^0 \leftarrow \mu_{init}$

for $k = 0, \ldots, \text{MaxIter} - 1$ do

$\mu^{k+1} \leftarrow \text{LBFGS-B}(\mathbf{g}_{UL}, \mathbf{g}_{LU}, \mu^k)$

end

$\mu_{est} \leftarrow \mu^{\text{MaxIter} - 1}$

4.2.2.2 Implementation

The MLTR-EB algorithm framework was written in MATLAB (MATLAB, MathWorks, Natick, MA; version R2018a) and the implementation of L-BFGS-B employed in this study is summarised in (Byrd et al. 1995). The objective and gradient functions for the unscattered model were implemented in MATLAB, whilst those related to the scatter model were written in C++ and implemented in a private fork of STIR (Thielemans et al. 2012). The Simplified Wrapper and Interface Generator (Beazley 1996) was used to call the STIR functions from MATLAB.

4.2.2.3 Penalised MLTR-EB

Regularisation methods can help in guiding reconstruction algorithms towards a more stable solution (Sec. 2.1.3.3).

The benefits of incorporating an anatomical MR prior, in particular PLS (Ehrhardt et al. 2016), into our reconstruction algorithm MLTR-EB is investigated here. This prior utilises directional information of edges in the MR image to encourage edges in the reconstructed image (see Sec. 2.1.3.3).

4.2.3 Simulation Setup

This section covers the simulation setup used for the results reported in Sec. 4.2.5. All simulation inputs, outputs, and scatter model are in 3D.

4.2.3.1 Preliminary study: point sources

Initial investigations were conducted on a simulation of a simple phantom, made of two identical point source emitters and symmetric with respect to the attenuation medium (Fig. 4.2).
4.2. MLTR-EB

Simulated Data: Experiments were conducted with volumes of dimension 155x155x15 with voxel size 0.3129x0.3129x0.675 cm$^3$.

Scatter sinograms were simulated as a down-sampled Siemens mMR (Karlberg et al. 2016) scanner (31 tangential positions, 21 views and 8 rings) for computational reasons. Direct sinograms only were used. The upper energy window $U$ was set to 500–550keV and the lower energy threshold was varied amongst experiments, ranging from 200 to 450keV. Energy resolution was set to 16%, in the range of the mMR energy resolution (Karlberg et al. 2016).

4.2.3.2 3D XCAT torso phantom

A 3D volume from the XCAT (Segars et al. 2010) torso phantom was used to investigate the performance of the MLTR-EB algorithm in a more realistic scenario. More details on the
XCAT phantom are given in Appendix A.

**Simulated Data:** The 3D XCAT volume was cropped into a 77x77x15 matrix with voxel sizes of 0.6258x0.6258x0.675 cm$^3$. A single slice of the phantom and the corresponding attenuation map are shown in Fig. 4.3. Scatter sinograms were generated in the same manner as in Sec. 4.2.3.1.

A lower energy window $L = 350 – 460$ keV and an upper energy window $U = 460 – 570$ keV was used. Energy resolution was set to 16%. Poisson noise was added to simulated data.

### 4.2.4 Reconstruction Setup

#### 4.2.4.1 MLTR-EB

**Initialisation:** An initial investigation was conducted with the attenuation map containing an initial error of 20% in the lung and with the constraint that only lung values within a lung mask would be updated (Fig. 4.6). The incorporation of the mask aims to reduce the complexity of the problem (similar to (Mehranian et al. 2015)).

In subsequent experiments the lung mask was removed. Two different $\mu$-map initialisations were investigated: (i) a uniform image of value $\hat{\mu}_{\text{init}} = 0.03$ cm$^{-1}$ inside the edges of the phantom, and 0 outside (Fig. 4.7a), and (ii) MRAC: no arms, 20% error in the lung (Fig. 4.7c). A non-zero background ($\hat{\mu} = 0.025$ cm$^{-1}$) was added in the region outside the phantom in the MRAC.

**Stopping criteria:** The MLTR-EB algorithm has three separate stopping criteria: (i) the normalised difference between two consecutive image estimates; (ii) the norm of the projected gradient and; (iii) the maximum number of outer iterations (MaxOuterIter). Default values for L-BFGSB (Byrd et al. 1995) were used, the maximum number of outer iterations was set to 200.

**Analysis** An initial assessment for MLTR-EB was conducted in terms of voxel-wise relative percentage error with respect to the ground truth in the estimated image at last iteration. Further analyses were conducted in terms of Mean Percentage Error (MPE) in a region of interest (ROI) of the estimated images with respect to the ground truth.

#### 4.2.4.2 MLTR-EB + PLS

**Initialisation:** This experiment relies on the same initialisation used in Sec. 4.2.4.1. In addition, we also investigated a third case where no lung structures are present in the initial
4.2. MLTR-EB

MRAC (Fig. 4.10e). As in Sec. 4.2.4.1, the lung mask was not used during MLTR-EB updates.

**Stopping Criteria:** MLTR+EB + PLS uses stopping criteria described in (Sec. 4.2.4.1).

**Anatomical Prior:** Experiments were conducted by using an “MRAC” image containing lung structures as anatomical prior (Fig. 4.7c). Note, the anatomical prior has missing information in the arm region.

The PLS (Eq. 2.32) smoothing factor parameters $\alpha$ and $\eta$ were set to 0.01, approximately the lowest attenuation value in the MRAC. The global strength $\beta$ was deliberately chosen to be quite high to emphasise the effects of the prior. Fine tuning of the prior was not the objective of this work.

**Analysis:** A visual assessment for MLTR-EB + PLS was conducted in terms of voxel-wise relative percentage error in the estimated image at the last iteration.

### 4.2.5 Results

**4.2.5.1 Initial investigations**

Fig. 4.4 shows sinograms relative to point source emitters (Sec. 4.2.3.1) when a low energy threshold is set to $L = 300 - 350$keV.

If the same energy window is used for both detectors (and a Gaussian model for the detection efficiency), only a small number of counts are detected in LL (Table 4.1, Fig. 4.4d), while UU measures a higher amount of scatter events with angles close to zero (Table 4.1, Fig. 4.4c). On the other hand, UL (Fig. 4.4a) and LU (Fig. 4.4b) sinograms exhibit two key characteristics: (i) the number of scatter counts is comparable to UU (Table 4.1), and (ii) the two energy windows provide complementary information regarding each of the emission point sources (Fig. 4.4a,b).

<table>
<thead>
<tr>
<th></th>
<th>UU</th>
<th>UL</th>
<th>LU</th>
<th>LL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Counts</td>
<td>$1.44\times10^2$</td>
<td>$0.872\times10^2$</td>
<td>$0.872\times10^2$</td>
<td>$6.24\times10^{-4}$</td>
</tr>
</tbody>
</table>

**Table 4.1:** Total counts in UU, UL, LU and LL energy window pairs, for a point source simulation.

Another experiment (Fig. 4.5a-c) reveals that when the limits of the lower energy window are decreased, counts from different scattering angles may be detected.

**4.2.5.2 3D XCAT torso phantom reconstruction**

**MLTR-EB:** Figure 4.6 shows a first attempt to recover patient-specific lung attenuation coefficients from known activity, where the image update is constrained to voxel values
4.2. MLTR-EB

Figure 4.4: Single scatter sinograms from different energy window pairs. $U = 500 - 550$ keV and $L = 300 - 350$ keV. Note the different maxima used for colour scale.

Figure 4.5: UL Single scatter sinograms from different energy window thresholds.

within a lung mask. Here the MLTR-EB algorithm is able to compensate for the initial error in the attenuation value (-20%) and converges to a final MPE of -0.225 % in the lung region.

Subsequent experiments conducted by allowing the updates of the entire phantom (removing the lung mask) show that MLTR-EB is able to estimate an attenuation map from the low energy window data (Fig. 4.7 b), even if with low spatial resolution. However, when the MRAC is used as initialisation for the algorithm (Fig. 4.7 c) the reconstruction output improves. Here MLTR-EB is able to compensate for errors due to the wrong assignment of population based density values in the lung without degrading the initial spatial resolution of the image. In both cases, the reconstruction method is able to recover the arms (Fig. 4.7b,d).

ROI analysis was also performed to investigate the attenuation recovery in three different regions of interest: 3x3x3 voxels ROIs were placed respectively in the lung, mediastinum and arms (Fig. 4.8). The error in the image estimate at the last iteration was assessed in terms of MPE. The initialisation from MRAC leads to a lower MPE in the three ROIs of choice. The error in the lung is reduced from -20% to 2.29%; the mediastinum region (where the initial attenuation value was correct), remains quite close to its original value in the recon-
4.2. MLTR-EB

**Figure 4.6:** MLTR-EB reconstruction of lung values within the lung mask. Graph: MPE error in the lung over iterations.

**Figure 4.7:** Estimated attenuation map over iterations without (first row) and with (second row) anatomical information in the initialisation. Low Noise. Number of counts =1.4 E+09.

constructed attenuation map (final error 2.23 %). Finally, the arms are recovered with a final MPE of -4.11 %.

**MLTR-EB + PLS:** Figure 4.9 compares the reconstructed attenuation image at different iteration numbers (0, 25, 35, 60, 130) with and without anatomical prior from a uniform initialisation. Results demonstrate that the incorporation of the anatomical prior enables noise suppression and improves the resolution in the final $\mu$-map estimate. However, some
4.2. MLTR-EB

Figure 4.8: ROI analysis (lung, mediastinum and left arm) from two different initialisations: MRAC and UNIF. The table shows the Initial and Final MPE for each ROI.

<table>
<thead>
<tr>
<th></th>
<th>Lung ROI</th>
<th>Mediastinum ROI</th>
<th>Arm ROI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Initialisation:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MRAC</td>
<td>-20%</td>
<td>2.29%</td>
<td>0%</td>
</tr>
<tr>
<td>UNIF</td>
<td>-24.4%</td>
<td>42.3%</td>
<td>-78.6%</td>
</tr>
</tbody>
</table>

Figure 4.9: Uniform initialisation. Estimated attenuation map over iterations without (first row) and with (second row) PLS prior. Low Noise. Number of counts =1.4 E+09. Images have the same grey scale.

features absent in the anatomical image - such as the arms - are over-smoothed as the reconstruction progresses.

A quantitative assessment was subsequently conducted and the bias in the estimated images from different initialisations was compared. Fig. 4.10 a-d shows that the incorporation of the anatomical prior helps in recovering high resolution features when a uniform initialisation is used. Further improvements can be visualised when an MRAC is used as initialisation (Fig. 4.10 e-h) and if the lung structures are already present in the initial attenuation estimate 4.10 i-l). Overall, a positive bias is observed in the lung region, probably due to an excessive global strength of the prior.
4.2. MLTR-EB

Figure 4.10: Bias images. Initial attenuation estimates: first column, axial view; third column, coronal view. Reconstruction attenuation estimates: second column, axial view; fourth column, coronal view.

Figure 4.11: First row, from left to right: true attenuation image, reconstructed images with MLTR+PLS from MRAC, reconstructed images with MLTR+PLS from UNIF. Second row: image profiles at last iteration.

Finally, a comparison of image profiles from two different initialisations is shown in Fig. 4.11, evidencing that MLTR + PLS is able to accurately estimate the attenuation image when some anatomical information are provided in the initialisation.
4.2.6 Discussion

This chapter has investigated the potential benefits of incorporating low energy window information when reconstructing the attenuation image from standalone PET data. To assess the amount of information contained in scattered events, all the energy windows were assumed to detect only (single) scatter events, i.e. unscattered events were excluded. This approximation will be restricted to this Chapter only.

A preliminary study was conducted on simple point sources to visualise the information measured by different energy window pairs (Fig. 4.4). Results show that UL and LU provide complementary information to the other energy window pairs. Furthermore, by varying the energy window limits (Fig. 4.5) different single scatter sinograms can be obtained. These different sinograms correspond to the measurement of higher scattering angles at lower energy windows.

The proposed MLTR-EB algorithm was capable of reconstructing the PET attenuation maps from low energy window data (UL and LU) and a known activity distribution even when the energy resolution is set to a realistic value (16 %), demonstrating that scatter coincidences, contained in the low energy window, yield information regarding the attenuation distribution in 3D objects. All the experiments were conducted at low spatial resolution.

Firstly, MLTR-EB was tested in a simplistic scenario where an initial error in the $\tilde{\mu}$-map is located exclusively in the lung region, and the algorithm was constrained to update the attenuation values within a lung mask (Fig. 4.6). Results show that MLTR-EB is able to correct for the initial error in the lung attenuation values (-20 %) and achieve a final MPE of -0.225 % within the 3D lung mask region.

Secondly, the lung-mask constraint was removed and consequences of various initialisations were investigated. In particular, a uniform image and an MRAC with (i) 20 % error in the lung region and (ii) truncated arms were used (Fig. 4.7).

Results from the uniform initialisation evidences that it is possible to obtain an attenuation map from scattered PET data only, albeit with a low spatial resolution (Fig. 4.7b). The initialisation from the MRAC facilitates MLTR-EB, and the final $\tilde{\mu}$-map estimate approaches the ground truth. The presence of anatomical features in the initial image does not appear to be deteriorated during reconstruction (Fig. 4.7d). The ROI analysis provided insight into the effectiveness of the proposed MLTR-EB, showing that the error in the lung ROI is reduced from -20% to 2.29%. In both cases, the reconstruction method was shown to
be able to recover the arms (Fig. 4.7b, d) with a final error of approximately 4% (within a 3D ROI placed in the arm region). Fig. 4.7c) shows that a small background was added in the region outside the edges of the phantom; this was done to compensate for an observed behaviour of LBFGS-B, which was not able to recover missing features (arms) when the initial value was set to 0.

As the outcome of MLTR-EB is sensitive to the initialisation, it is likely that the objective function is quite flat in the region close to the solution. Therefore, benefits of regularisation were investigated. In particular, benefits of incorporating an MR-derived anatomical prior into the iterative reconstruction algorithm were assessed. An edge-preserving regularisation method (the PLS prior from (Ehrhardt et al. 2016)) was incorporated. A deliberately large penalisation factor was used to clearly show the effect of the prior.

According to results shown in Fig. 4.10, the incorporation of a penalty term into the proposed MLTR-EB algorithm helps in suppressing the noise, enhancing the edges and improving the final image estimate. Overall, all the three initialisations converge to a similar solution (Fig. 4.10). However, a higher bias in the lung region is found for the uniform initialisation. This could be due to an excessive weight of the prior, that could be needed to be adjusted for each individual experiment. Potentially, the slow convergence could also have affected this result. An interesting decrease of the estimated attenuation value in correspondence of some lung structures for the case of uniform initialisation was observed (Fig. 4.11, image profiles), very likely due to a bad tuning of the hyperparameters of the PLS.

This preliminary study indicates that using an anatomical prior for attenuation estimation is beneficial for the proposed MLTR-EB algorithm, although parameter tuning is non-trivial. Compensating for potential misalignment between the attenuation map and the MR image, as well as fine-tuning of the prior parameters, constitutes objects of future work.

4.2.7 Conclusion

This study was intended to be a preliminary investigation to understand the amount of information contained in low energy window data placed below the photopeak. It showed that this kind of measurement does furnish information on the attenuation distribution of 3D objects - although with low spatial resolution.

Here we proposed a reconstruction algorithm MLTR-EB which aims to estimate the $\tilde{\mu}$-map when the activity image is known. Input data for MLTR-EB are low energy window measurements and an initial estimate of the attenuation map, usually furnished by the
Results have shown that MLTR-EB is able to compensate for errors due to the assignment of wrong population values to the MRAC. Constraining the update to the lung region significantly helped (similarly to (Berker et al. 2012b; Mehranian et al. 2015)) and convergence was reached in a few iterations.

Without any prior information on the attenuation image, the reconstruction algorithm seems to be sensitive to initialisation, meaning that the objective function is likely to be quite flat in the region close to the solution. However, MLTR-EB was able to reduce the error in the initial attenuation estimate. A very interesting result is related to the fact that the algorithm was able to recover the arms of the patient, absent in the initialisation.

An anatomical prior was then incorporated to guide MLTR-EB towards the solution. The presence of the PLS in the reconstruction was found to be beneficial for recovering some high resolution features and to suppress noise whilst enhancing phantom edges. Furthermore, a more stable solution was reached from all the initialisations.

The next Chapter will investigate the incorporation of MLTR-EB into a joint reconstruction scheme, where the activity distribution is unknown.
Chapter 5

Joint Activity, Attenuation and Scatter estimation: alternating approach

Chapter 3 showed that the PET detector energy response can be efficiently modelled in both photopeak and low energy window acquisitions. Furthermore, it was demonstrated in Chapter 4 that it is possible to estimate the attenuation distribution of the object from energy window data, below the photopeak, for a known emission image.

This Chapter explores the benefits of incorporating a 3D probabilistic scatter model into a joint reconstruction scheme. In contrast to previous work, we do not assume that scatter is absent from higher energy, photopeak, window. This is demonstrated with a preliminary evaluation using simulated data.

5.1 Introduction

Emission-based attenuation correction methods aim to simultaneously reconstruct the activity and the attenuation from one set of PET measurements (Sec. 2.3.2). For non-TOF PET, this approach suffers from cross-talk in the estimated activity and attenuation distributions. TOF PET emission data instead, can determine the attenuation sinogram $K\hat{\mu}$, but only up to an unknown offset (Defrise et al. 2012). This limitation translates into an unknown scaling factor in the reconstructed activity image $\hat{A}$. Another type of additional available information is given by low energy window data, which may be used to overcome the aforementioned limitations. Initial studies focused on either attenuation estimation with known emission (Berker et al. 2012a; Brusaferri et al. 2017) or vice versa (Conti et al. 2012; Zhang et al. 2014).

This idea was extended to a joint reconstruction scheme in the last decade. The concept of incorporating the scatter information into a MLAA-like reconstruction algorithm was
first proposed in SPECT (Cade et al. 2013; Bousse et al. 2016) and subsequently in PET (Berker et al. 2017a; Berker et al. 2019). These studies paved the way to a novel joint reconstruction methodology, which exploits the information contained in low energy photons. Whilst promising, these works do present some limitations (listed in Sec. 2.4.2). Furthermore, the performance of the algorithm proposed in Berker et al. 2017a was found to depend on the spatial scale of the phantom.

This Chapter aims to extend on existing literature by investigating the feasibility of this approach using realistic energy measurement scenarios. The spatial scale issue, as discussed in Berker et al. 2017a, will be also investigated in Sec. 5.3.

As MLTR-EB showed its best performance when the update was constrained to the lung region (Chapter 4), this strategy will also be adopted for the joint reconstruction problem presented in this Chapter. This restriction will be only applied to the attenuation estimate.

Part of this Chapter was presented in (Brusaferri et al. 2018) and (Brusaferri et al. 2019a).

5.2  MLAA-EB-P: Energy-Based Pseudo Maximum Likelihood reconstruction of Activity and Attenuation

5.2.1  Statistical model

Similarly to Sec. 4.2.1, it is assumed that each photon of a coincidence pair may be assigned to either the photopeak window (U) or to a lower energy window (L). This results in the possibility to measure four different sinograms: $g_{UU}$, $g_{UL}$, $g_{LU}$, $g_{LL}$.

In this study, the assumption introduced in Chapter 4, regarding absence of unscattered counts in the upper window (U), is removed. However, the expectation of finding only single scatter events in the lower window (L) is maintained.

Both scattered and unscattered events are modelled as Poisson process centred in $g_{sc}^{UU}$ and $g_{sc}^{UL}$, respectively. For $\theta = [\lambda, \mu]$, the expected sinogram data are defined as:

$$g_{UU}(\theta) = g_{sc}^{UU}(\theta) + \bar{g}_{UU},$$
$$g_{UL}(\theta) = g_{sc}^{UL}(\theta) + \bar{g}_{UL},$$
$$g_{LU}(\theta) = g_{sc}^{LU}(\theta) + \bar{g}_{LU}$$

(5.1)

where $g_{sc}^{UU}(\theta)$, $g_{sc}^{UL}(\theta)$ and $g_{sc}^{LU}(\theta)$ are given by Eq. 3.5 and $\bar{g}_{vw}$ denotes a background of random events.
5.2. MLAA-EB-P

For computation reason, low energy windows UL and LU input data are downsampled in low resolution: \( g' = P^*(Pg) \), with \( P^* \) being the adjoint of \( P \) and \( P^*P = \gamma P \). A visual interpretation of the forward model used in this chapter is given in Fig. 5.1.

Analogously to Sec. 4.2.1, the restriction operator \( R \) (defined in Sec. 3.2.2) is assumed to be an all-ones matrix; therefore, all the experiments presented in this chapter are conducted in low spatial resolution. The probability of detecting incoming photons with a certain energy \( E \) was modelled as a Gaussian function (Sec. 3.5.1.1). The photopeak scatter \( UU \) is up-sampled to full resolution via linear interpolation using the operator \( P \).

5.2.2 Optimisation

MLAA-EB-P consists of an alternating maximisation in \( \hat{\lambda} \) and \( \hat{\mu} \). The emission image \( \hat{\lambda} \) is reconstructed with a Maximum Likelihood (ML) estimator from UU data, whilst the attenuation image \( \hat{\mu} \) is estimated with the MLTR-EB algorithm (Sec. 4.2.1) using the other energy window pairs (UL and LU):

\[
\hat{\lambda} = \operatorname{argmax}_{\lambda \geq 0} \left( L_{UU}(g_{UU} | \tilde{g}_{UU}^{unc}(\tilde{\lambda}) + g_{UU}^{sc}) \right)
\]

\[
\hat{\mu} = \operatorname{argmax}_{\mu \geq 0} \left( L_{UL}(g'_{UL} | \gamma S_{UL}(\tilde{\mu})) + L_{LU}(g'_{LU} | \gamma S_{LU}(\tilde{\mu})) \right)
\]

(5.2)

with \( g'_{vw} \) indicating downsampled sinogram and \( \gamma = n_D/n'_D \) the down-sampling factor (Sec. 3.2.2). Please note that \( \frac{\sum v \cdot g}{\sum v' \cdot g} = \gamma \) and that the attenuation update is the same as for Eq. 4.2.
5.2. MLAA-EB-P

5.2.2.1 Initialisation via OSEM-SSS

Initial activity $\lambda_{\text{init}}$ and photopeak scatter estimates $\hat{g}_{\text{UU}}^{\text{sc,init}} \approx \hat{g}_{\text{UU}}^{\text{sc,init}}(\tilde{\theta})$ are obtained from the photopeak data as follows: (i) set initial scatter estimate to zero, (ii) reconstruct the activity image with OSEM (7 subsets, 70 sub-iterations), (iii) estimate photopeak scatter with SSS. The algorithm is initialised with a uniform image of ones. This process is repeated iteratively (Sec. 2.1.5.4). Pseudo-code for OSEM-SSS is given in Algorithm 2.

Algorithm 2: Pseudo-code for OSEM/SSS.

| Input: | $g_{\text{UU}}$, $\mu_{\text{init}}$, $\hat{g}_{\text{UU}}^{\text{sc,init}} = 0$; |
| Output: | Initial activity estimate $\lambda_{\text{init}}$; |
| $\hat{g}_{\text{UU}}^{\text{sc,0}} \leftarrow \hat{g}_{\text{UU}}^{\text{sc,init}}$; |
| for $i = 0, \ldots, \text{MaxOSEMandSSSIter} - 1$ do |
| $\lambda^{i} \leftarrow \text{OSEM}(g_{\text{UU}}, \mu_{\text{init}}, \hat{g}_{\text{UU}}^{\text{sc,i}})$; |
| $\hat{g}_{\text{UU}}^{\text{sc,i+1}} \leftarrow \text{SSS}(\lambda^{i}, \mu_{\text{init}})$; |
| end |
| $\lambda_{\text{init}} \leftarrow \lambda^{{\text{MaxOSEMandSSSIter}-1}}$; |

Algorithm 3 shows pseudo-code for MLAA-EB-P.

5.2.2.2 Image updates

Both image updates rely on a line-search step in a quasi Newton direction (Sec. 4.2.2):

$$
\lambda^{i+1} = \lambda^{i} + \xi_{\lambda} B_{\lambda} \nabla L_{\text{UU}}(\lambda^{i})
$$

$$
\mu^{i+1} = \mu^{i} + \xi_{\mu} B_{\mu} \left[ \nabla L_{\text{UL}}(\mu^{i}) + \nabla L_{\text{LU}}(\mu^{i}) \right]
$$

(5.3)

where $\nabla L_{\text{UU}}$ is the gradient of the objective function in UU (and similarly for the other energy windows), $\xi$ is the step-size, $B_{\lambda}$ and $B_{\mu}$ are a LBFGS approximation of the inverse Hessian matrix, computed using the implementation found in (Byrd et al. 1995).

5.2.2.3 Photopeak scatter update

The scatter component in the photopeak UU is updated one-step-late and computed with SSS (Sec. 3.2.2) from the current estimate of the attenuation and emission images.

For computational reasons, this current estimate of the photopeak scatter is computed first in down-sampled sinograms and then up-sampled via linear interpolation with the operator $P$ (Sec. 3.2.2). As the photopeak scatter is computed one-step-late, the scatter gradient in UU is 0. Algorithm 3 shows pseudo-code for MLAA-EB-P.
Algorithm 3: Pseudo-code for MLAA-EB-P.

Input: $g_{U,U}$, $g_{UL}$, $g_{LU}$, $\lambda_{init}$, $\mu_{init}$, $\hat{\delta}_{U,U}^{sc,init}$.
Output: Estimated activity and attenuation images $\lambda^{est}$, $\mu^{est}$;

\[ \lambda^0_{0} \leftarrow \lambda_{init}; \]
\[ \mu^0_{0} \leftarrow \mu_{init}; \]
\[ \hat{\delta}_{U,U}^{sc,0} \leftarrow \hat{\delta}_{U,U}^{sc,init}; \]

for $t = 0, \ldots, \text{MaxOuterIter} - 1$ do
  for $k = 0, \ldots, \text{MaxInnerIterMu} - 1$ do
    $\mu^t_k \leftarrow \text{LBFGS-B}(g_{UL}, g_{LU}, \lambda^t_0, \mu^t_k)$
  end
  $\mu^{t+1}_0 \leftarrow \mu_{\text{MaxInnerIterMu} - 1}^{t+1}$;
  $\hat{\delta}_{U,U}^{sc,t+1} \leftarrow \text{SSS}(\lambda^t_0, \mu^{t+1}_0)$;
  for $k = 0, \ldots, \text{MaxInnerIterLambda} - 1$ do
    $\lambda^t_k \leftarrow \text{LBFGS-B}(g_{U,U}, \lambda^t_k, \mu^{t+1}_0)$;
  end
  $\lambda^{t+1}_0 \leftarrow \lambda_{\text{MaxInnerIterLambda} - 1}^{t+1}$;
end
\[ \lambda^{est} \leftarrow \lambda_{\text{MaxOuterIter} - 1}; \]
\[ \mu^{est} \leftarrow \mu_{\text{MaxOuterIter} - 1}; \]

5.2.3 Simulation setup

This section covers the simulation setup used for the results reported in Sec. 5.2.4. Simulation inputs, outputs and scatter model are 3-D.

5.2.3.1 Cylindrical simulations

Preliminary experiments were conducted on a small cylinder with an insert. Inner and outer ring diameters are respectively 6 and 8 cm (Fig. 5.2).

Simulated data: Experiments were conducted with images of dimension 25x25x8 with voxel size 1.2x1.2x3.25 cm$^3$. Projection data acquisition was simulated with a model of a Siemens mMR (Karlberg et al. 2016) scanner: 344 tangential positions and 252 views. Only direct sinograms were used. The scanner was simulated with 8 rings 3.25 cm apart to match the z-voxel size and number of slices of the phantom image.

Scatter sinograms rely on a 'down-sampled' version of the Siemens mMR (Karlberg et al. 2016): 31 tangential positions, 21 views and 8 rings. The lower energy window range was set to $L=350-460$ keV and the upper one to $U=460-570$ keV, with an energy resolution of 16% (similar to the one of the mMR).

The random background was set to 0 for the results presented in this chapter.
Phantom mask: A mask was used to constrain the attenuation estimation in the inner cylinder with the attenuation value outside the mask is assumed to be known. This constraint is not used for the emission update, for which we only assumed the absence of activity outside the phantom (Fig. 5.2).

5.2.3.2 XCAT simulations

A 3D volume from the XCAT (Segars et al. 2010) torso phantom was used to test MLAA-EB-P in a more realistic and complex scenario.

Simulated data: The 3D XCAT volume was cropped to a 50x50x8 matrix with voxel size 1.095x1.095x3.25 cm$^3$. Fig. 5.3 shows axial and coronal view of the phantom and the corresponding attenuation map. Input data was simulated similarly to that of the Cylindrical simulations (Sec. 5.2.3.1).
Phantom mask: A lung mask was used to constrain the attenuation estimation. The attenuation values outside the lung are assumed to be known. This constraint is not used for the emission update, for which the absence of activity outside the phantom is assumed (Fig. 5.3).

5.2.3.3 Implementation

The algorithm framework was written in MATLAB (MATLAB, MathWorks, Natick, MA; version R2018a). The implementation of LBFGS employed in this study is summarised in (Byrd et al. 1995). $B_\theta$ is constructed with a history length of 5 (inner) iterations. The objective and gradient functions for the unscattered model were implemented in MATLAB, whilst those related to the scatter model were written in C++ and implemented in STIR (Thielemans et al. 2012). The Simplified Wrapper and Interface Generator (SWIG (Beazley 1996)) was used to call the STIR functions from MATLAB.

5.2.3.4 Initial conditions

For both phantoms, an initial attenuation image was generated by decreasing the lung (and inner cylinder) attenuation values by 20% with respect to the ground truth. All the reconstructions were initialised with the same activity estimate, obtained by iterating between OSEM (3 subsets 100 sub-iterations) and SSS (Sec. 5.2.2.1) with MaxOSEMIter = 3.

5.2.3.5 Reconstruction parameters

The activity and the attenuation updates of MLAA-EB-P relies on LBFGS-B (Sec. 2.1.3.3). Stopping criteria were set to default values for L-BFGSB implementation (Byrd et al. 1995; Tsai et al. 2017). Table 5.1 reports reconstruction parameters used in the reconstruction of both phantoms.

<table>
<thead>
<tr>
<th>MaxOsemIter</th>
<th>MaxInnerIterMu</th>
<th>MaxInnerIterLambda</th>
<th>MaxOuterIter</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>1</td>
<td>8</td>
<td>35</td>
</tr>
</tbody>
</table>

Table 5.1: MLAA-EB-P. Reconstruction parameters

5.2.3.6 Analysis:

To assess the performance of the MLAA-EB-P algorithm, voxel-wise relative percentage error in the estimated image at final iteration and a quantitative analysis was conducted in terms of MPE in a region of interest (lung) of the estimated images with respect to the ground truth. The MPE was computed at each outer iteration.
5.2. Results

Results for a small cylindrical phantom show that the algorithm compensates for errors in the initial attenuation estimate. Figure 5.4 visualises the relative percentage error in the initial estimates of the activity and the attenuation, and the final relative percentage error in the estimated images with MLAA-EB-P. The figure reports both axial and coronal view, showing that the relative error uniformly converges to zero. The MPE in the insert over iteration is also reported; this graph evidences that MLAA-EB-P converges to the ground truth in a few outer iterations.

Figure 5.5 shows the MLAA-EB-P fails to jointly reconstruct the 3D XCAT volumes and the error present in the lung region increases over iterations of the algorithm.

5.2.5 Discussion

Results from simulations demonstrated that the proposed MLAA-EB-P algorithm is capable of correctly reconstructing both the activity and the attenuation distributions for a small cylindrical phantom (Fig. 5.4). The results of the incorporation of low energy window data into an MLAA-like reconstruction algorithm proved that this approach is beneficial (and fast) for small objects (Fig. 5.4). After a few outer iterations, MLAA-EB-P converges to the
5.2. MLAA-EB-P

Figure 5.5: Reconstruction error from the XCAT simulated data. First and second row: error in the attenuation. Third and fourth row: error in the activity image. First column: initial error (reconstruction input). Second column: reconstruction error. Graph: Mean percentage Error (MPE) in the lung over iterations for both the estimated attenuation and the activity images.

However, the subsequent study, conducted on a 3D XCAT volume (Fig. 5.5), showed the MLAA-EB-P diverged for human-size objects. (Berker et al. 2017a) found a problematic behaviour of their own reconstruction algorithm for large phantom scales. Therefore, this could explain our XCAT reconstruction results. However, many other aspects could come into play to cause divergence for an XCAT phantom. Therefore, understanding such behaviour needs a detailed analysis that will be undertaken in the rest of this Chapter.

A first additional explanation of MLAA-EB-P performance in the case of large objects could be attributed to the facts that the algorithm effectively “pseudo maximise” the joint log-likelihood in \( \tilde{\lambda} \) and \( \tilde{\mu} \): the activity and the attenuation update relies on the maximisation of two different objective functions (Eq. 5.2). This strategy could be sub-optimal for some objective function shapes.

Overall, improvements have been made with respect to previous literature. These include: (i) the use of 3D phantoms, (ii) accounting for the presence of photopeak scatter and (iii) finite energy resolution of PET detectors. Furthermore, it should be noted that due to computational demand in the scatter gradient calculation, low resolution considerations
are not uncommon in recent studies regarding image reconstruction from scattered photons (Berker et al. 2019).

This study has several limitations, including: (i) neglecting multiple scatter and detector scatter, (ii) using the same forward model for simulating and reconstructing the data, (iii) using low-dimensional objects and data, (iv) results depend on the spatial scale of the object.

5.3 Analysis of the nature of the joint problem

In previous sections we have shown that it is possible to integrate the scatter information into an alternating reconstruction framework, where the activity and the attenuation distribution are estimated from different energy window measurements. This approach has shown promise for small objects, but we observed divergence as the phantom size increased. A similar problematic behaviour was observed in (Berker et al. 2017a).

Therefore, we decided to investigate in detail the nature of the joint problem (Brusaferri et al. 2018; Brusaferri et al. 2019a) to understand this problem such that it can be resolved by designing a different algo. Subsequently, similar analyses on the nature of the joint problem were conducted in (Berker et al. 2019).

Here we present an exemplar two-variable problem, used to investigate the aforementioned challenges. Experiments were conducted on cylindrical phantoms of increasing diameters with a conical insert; the algorithm is constrained to estimate two single values: the activity and the attenuation in the insert. This enabled us to draw the contour plots of the log-likelihood function in $\tilde{\lambda}$ and $\tilde{\mu}$ and to outline the reasons why MLAA-EB-P was shown to fail.

Overall, two main questions needed to be addressed: (i) does the ill-posedness of the joint problem vary for big and small objects? (ii) can the availability of scatter information guide an MLAA-like algorithm towards a more stable solution?

The following sections will be dedicated to answer these questions.

5.3.1 Log-likelihood contour plot analysis

Expected scatter and true counts were computed according to Eq. 3.2 and Eq. 3.8, respectively. The forward model refers to the one used in Sec. 5.2.1; the presence of photopeak scatter is therefore taken into account.

Data were simulated in agreement to the geometry of the Siemens mMR scanner. To exclude problems due to ill-conditioning due to low energy resolution, the energy resolution
5.3. Analysis of the nature of the joint problem

Figure 5.6: Cylindrical Phantoms of increasing diameters: 8 cm (first column), 16 cm (second column), 24 cm (third column), 32 cm (forth column). First and second rows: attenuation image axial and sagittal view. Third and fourth rows: activity image, axial and sagittal view. The attenuation is expressed in cm$^{-1}$, the activity is in arbitrary units.

was set to 1% for the following experiments.

5.3.1.1 Effects of phantom size

Four cylinders of increasing diameters (respectively 8, 16, 24 and 32 cm) with a conical insert were chosen for this experiment (Fig. 5.6). The conical shape was chosen to simulate the lung. The image size was 30x30x8 and the voxel dimensions were equal to 1.2x1.2x3.25 cm$^3$.

The log-likelihood function was computed by varying the value in the insert with $\delta\tilde{\mu} = \{-0.03, 0.03\}$ and $\delta\tilde{\lambda} = \{-0.2, 0.2\}$. An expression for the log-likelihood as a function of $\tilde{\mu}$ and $\tilde{\lambda}$ is given by Eq. 3.33.

We also conducted an MLAA-EB-P reconstruction for the extreme cases of 8 cm and 32 cm diameters. The constraint of having a unique value in the insert was used during the reconstruction (similarly to how the contour plots were computed) for both the activity and the attenuation updates. The region outside the insert was considered as known. The photopeak scatter was also assumed as known. This enabled us to visualise the behaviour of each image update together with the objective function contours.
5.3.1.2 Accounting for the dependency of scatter on the activity and attenuation

In addition to the phantom size, we also investigated benefits of accounting for the dependency of the scatter on the activity and attenuation. We conducted the analysis for the case of one and two energy windows: a single energy window $UU$, a single (but wider) energy window $WW$ and two energy windows $UU + LU + UL + LL$. For these experiments $g_{LL} = 0$.

Table 5.2 reports the energy window values considered for this experiment. Please note that we refer to $WW$ as one wide energy window defined as $W = U + L$ and, therefore, $g_{WW} = g_{UU} + g_{UL} + g_{LU} + g_{LL}$.

**Condition number analysis:** For a quantitative assessment, each contour plot was used to compute the condition number $\kappa$.

For this purpose, two main considerations have been made:

- Given an objective function $\mathcal{L}$ and its Hessian $H$, an ellipse can be drawn in the region close to the maximum. The singular values of $H$ can be interpreted as the magnitude of the semi-axes of the ellipse in 2D.

- The condition number $\kappa$ can be obtained by dividing the maximum and the minimum of the singular values $\sigma_{\text{min}}$ and $\sigma_{\text{max}}$.

Therefore, the condition number $\kappa$ was obtained by fitting an ellipse to the contours in the region close to the maximum and computing its aspect ratio. For each energy window pair, the contour plots were computed: (i) with a constant and correct scatter estimate, (ii) when the scatter component is treated as a function of $\tilde{\lambda}$ and $\tilde{\mu}$.

<table>
<thead>
<tr>
<th>Energy Window</th>
<th>[keV]</th>
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<tbody>
<tr>
<td>$W$</td>
<td>350 - 570</td>
</tr>
<tr>
<td>$U$</td>
<td>460 - 570</td>
</tr>
<tr>
<td>$L$</td>
<td>350 - 460</td>
</tr>
</tbody>
</table>

**Table 5.2:** Energy windows used for the log-likelihood analysis

### 5.3.2 Results

#### 5.3.2.1 Effects of phantom size

Fig. 5.7 shows the contour plots for the simulations of the cylinders of increasing diameters (8, 16, 24 and 32 cm) both for $UL + LU$ and $UU$ data. With increasing size, the different orientation between the $UL + LU$ and $UU$ valley decreases, becoming almost null for the case
Figure 5.7: From left to right: likelihood plots for cylinders of increasing diameters with a two-energy-window acquisition. First row: UL+LU likelihood functions. Second row: UU likelihood function of a 32 cm cylinder. This will influence the convergence rate in any optimisation algorithm that alternates between UL + LU and UU log-likelihoods.

In particular, Fig. 5.8 (first row) shows MLAA-EB-P updates superimposed on the contour plots for the case of a small object (8 cm cylinder). The algorithm starts from an attenuation ($\tilde{\mu}$) update (blue line) in UL + LU space; the update follows the direction of the gradient of this objective function. Then, the activity image ($\tilde{\lambda}$) is updated (red line) following the gradient direction in UU. Here the mutual orientation of the valleys is in favour of the joint optimisation, and MLAA-EB-P converges to the Maximum Likelihood solution in a few steps.

Fig. 5.8 (second row) instead, visualises MLAA-EB-P updates superimposed on the contour plots for the case of a big object (32 cm cylinder). Here the mutual orientation between the valleys is a fundamental challenge for the optimisation algorithm. In fact, the attenuation updates happened to be always in the region above the diagonal of the UL + LU objective function (where the gradient is negative) bringing the following activity updates in the region below the diagonal of the UU objective function (where the gradient is positive).
5.3. Analysis of the nature of the joint problem

5.3.2.2 Accounting for the dependency of scatter on the activity and attenuation

Fig. 5.9 shows the log-likelihood contour plots for different energy windows for a set of cylinders of diameters ranging between 8 and 32 cm. The first row shows the objective function contour plots for a single-energy window acquisition UU when the scatter component is considered as a known (and correct) background. In the second, third and fourth row instead, the dependency of scatter on the activity and attenuation was taken into account in the forward model (Eq. 3.1). The increased curvature and a lower condition number $\kappa$ demonstrate that incorporation of the scatter information can reduce the ill-posedness of the joint problem, with larger benefit for lower energy thresholds (third row) and multiple energy windows (fourth row).

An insight to the ellipse-fitting to the contour plot (relative to the 8cm cylinder for a...
5.3. Analysis of the nature of the joint problem

Figure 5.9: Log-likelihood plots for cylindrical phantoms. From left to right: the diameter increases. From top to bottom: the energy window varies. $\kappa$ indicates the condition number of each contour plot.

Figure 5.10: Contour plots relative to the small cylindrical phantom ($D = 8\ cm$). Ellipse fitting to the level-sets for a multiple energy window acquisition. From left to right: the diameter increases and so does the condition number $\kappa$.

5.3.3 Discussion

The aim of this study was to investigate the effects of the size of the phantom and detected photon energy information on the conditioning of the joint problem. We conducted experiments on cylindrical phantoms of increasing diameters by constraining the image update...
5.4. Conclusion

In this Chapter one new method is presented, MLAA-EB-P, for the JRAA with a Maximum Likelihood estimation approach. It makes use of both photopeak and lower energy window data to estimate the activity and the attenuation distribution of the object. In particular, MLAA-EB-P alternates between an activity estimate from the photopeak data and an attenuation estimation from low energy window data. This approach was found to be efficient and fast for small objects, but insufficient for patient-scale phantoms.

A detailed analysis of the objective function values in an exemplar two-variable problem enabled us to investigate and understand the reason for such behaviour. This study brought us to the conclusion of abandoning the idea of a ‘pseudo-maximisation’ of the joint likelihood and led us to the development of a new algorithm: MLAA-EB-S. This approach will be
discussed in next Chapter.
Chapter 6

Joint Activity, Attenuation and Scatter estimation: simultaneous approach

In previous chapters the joint estimation of the activity, attenuation and photopeak scatter was introduced. A reconstruction algorithm named MLAA-EB-P was proposed, which alternates between emission reconstruction from the photopeak UU data and attenuation estimation from the lower energy window photon pairs (UL and LU).

In Chapter 5, MLAA-EB-P was found to diverge for large objects. A detailed analysis was therefore conducted to attempt to understand the reason behind MLAA-EB-P behaviour. This investigation led to the conclusion that optimising one unique objective function, in \( \tilde{\mu} \) and \( \tilde{\lambda} \), would be the right path to follow for our approach. The objective function in question can be obtained by summing the likelihood function for each energy window. This chapter presents a reconstruction algorithm based on this idea: MLAA-EB-S. This new algorithm will be tested where MLAA-EB-P failed and further evaluated against state-of-the-art methods on analytically simulated data.

6.1 Introduction

The idea of jointly reconstruct PET activity and the attenuation distributions from both scattered and unscattered events was recently proposed (Berker et al. 2017a) and then extended in (Brusaferri et al. 2018). Although the two approaches differ in many aspects (such as the energy resolution modelling), a common feature lies in the fact that both methods estimate the activity distribution from photopeak data and the attenuation from low energy measured photons. This strategy was found to be: (i) sufficient and fast for estimating low attenuation values (Berker et al. 2017a) and small objects (Brusaferri et al. 2018), (ii) insufficient for reconstructing high attenuation objects (Berker et al. 2017a) and large objects (Brusaferri et al. 2018).
Given the non-linearity of the scatter model, the two aspects are strongly linked. An explanation for this behaviour is given in Sec. 5.3 and (Brusaferri et al. 2019a); subsequently also explored in (Berker et al. 2019).

One possible solution to (ii) was proposed in (Berker et al. 2019): extend the “two-step algorithm” (Berker et al. 2017a) to a “four-step algorithm”. The idea is to alternate between four different sub-algorithms: (i) attenuation estimation from true counts, (ii) attenuation estimation from scattered counts, (iii) activity estimation from true counts, (iv) activity estimation from scattered counts. Further details are given in Sec. 2.4.2.3. However, neither the presence of scatter in the photopeak, nor the presence of true counts in the low energy window was taken into account in Berker et al. 2019.

Another possible solution to (ii) is presented in this Chapter. Here we investigate the feasibility of a joint reconstruction of activity and attenuation distributions from multiple energy window measurements by using a maximum likelihood framework in a realistic setting.

This Chapter is organised as follows. We first give an overview of the proposed algorithm. Then, we present results for the same forward model used in Chapter 5, from the new reconstruction algorithm MLAA-EB-S. Please note that a more advanced model is discussed in Chapter 7.

Part of this Chapter was presented in (Brusaferri et al. 2020).

6.2 MLAA-EB-S: Energy-Based Simultaneous Maximum-Likelihood reconstruction of Activity and Attenuation

This section presents MLAA-EB-S, an evolution of MLAA-EB-P improved by two main aspects: (i) the optimisation relies on one single objective function, (ii) the alternating approach is replaced by simultaneous optimisation of the two unknown distributions \( \mu \) and \( \lambda \).

6.2.1 Optimisation

The optimisation algorithm finds an estimate of \( \hat{\theta} = [\hat{\lambda}, \hat{\mu}] \) effectively trying to fit the data in all the \( n_P \) energy window pairs. The objective function is given by the sum of the log-likelihood at every energy window pair:
\[
\mathcal{L}^{\text{tot}}(\tilde{\theta}) \triangleq \mathcal{L}_{UU}(g_{UU} \mid \tilde{g}^{\text{inc}}_{UU}(\tilde{\theta}) + \bar{g}^{\text{sc}}_{UU}) + \mathcal{L}_{UL}(g'_{UL} \mid \gamma S_{UL}(\tilde{\theta})) + \mathcal{L}_{LU}(g'_{LU} \mid \gamma S_{LU}(\tilde{\theta}))
\] (6.1)

with \(g'_{vw}\) the downsampled sinogram and \(\gamma = n_D/n'_D\) the down-sampling factor (Sec. 3.2.2). Please note that \(\gamma = \frac{\sum g}{\sum g'}\).

In this chapter, we chose to update both \(\tilde{\lambda}\) and \(\tilde{\mu}\) all at once – similar to (Fuin et al. 2017) – mainly to avoid complications related to the settings of inner loop parameters:

\[
\hat{\theta} = \arg\max_{\tilde{\theta} \geq 0} \mathcal{L}^{\text{tot}}(\tilde{\theta})
\] (6.2)

In the following sections we describe the algorithm framework used for the joint reconstruction of the activity and the attenuation images. Inputs for the reconstruction are the measured data \(g\) and an estimate of the \(\mu\)-map, for instance on a PET-MR scanner obtained via MRAC.

### 6.2.2 Initialisation via OSEM/SSS

Initial activity \(\tilde{\lambda}^{\text{init}}\) and photopeak scatter estimates \(\bar{g}^{\text{sc,init}}_{UU}\) are obtained as in Sec. 5.2.2.1.

### 6.2.3 Algorithm outline

The reconstruction algorithm, MLAA-EB-S is summarised in **Algorithm 4**. Both unknown distributions \(\tilde{\lambda}\) and \(\tilde{\mu}\) are reconstructed from all the available data: \(g_{UU}, g_{UL}\) and \(g_{LU}\).

The scatter gradient is computed during the reconstruction only for the UL and LU windows for computational reasons.

#### 6.2.3.1 Image updates

The activity and the attenuation estimates are updated with LBFGS (Byrd et al. 1995). Every update consists of a line-search step in a quasi-Newton direction:

\[
\theta^k = \theta^{k+1} - \alpha B_\theta \nabla_{\theta} \mathcal{L}^{\text{tot}}
\] (6.3)

where \(\nabla_{\theta} \mathcal{L}^{\text{tot}}\) is the gradient of the objective function, \(B_\theta\) is an approximation of the inverse Hessian matrix of \(\mathcal{L}\) at \(\hat{\theta}\) and \(\alpha\) is the step-size found by a line-search. Compared to MLAA-EB-P (Sec. 6.2.3), where the attenuation image was estimated from the low energy window data and the activity image from the photopeak data, here true and scattered events contribute to the estimation of both unknown distributions.
6.2.3.2 Photopeak scatter update

The photopeak scatter estimate $\bar{g}_{UU}^{sc}$ is iteratively updated via a one-step-late approach. This current estimate of the photopeak scatter is obtained first in downsampled sinograms and then upscaled via prolongation operator $P$ with a cubic B-spline interpolation (Sec. 3.2.2).

Algorithm 4: Pseudo-code for MLAA-EB-S.

- **Input:** $g_{UU}$, $g_{UL}$, $g_{LU}$, $\lambda^{\text{init}}$, $\mu^{\text{init}}$, $\bar{g}^{sc,\text{init}}_{UU}$
- **Output:** Estimated activity and attenuation images vector $\theta^{\text{est}}$;

\[
\begin{align*}
\theta^0_0 & \leftarrow [\lambda^{\text{init}}, \mu^{\text{init}}]; \\
\bar{g}^{sc,\text{init}}_{UU} & \leftarrow \bar{g}^{sc,\text{init}}_{UU}; \\
\text{for } t = 0, \ldots, \text{MaxOuterIter} - 1 \text{ do} \\
\quad & \text{for } k = 0, \ldots, \text{MaxInnerIter} - 1 \text{ do} \\
\quad & \quad \theta^{t+1}_k \leftarrow \text{LBFGS-B}(g_{UU}, g_{UL}, g_{LU}, \theta^t_k, \bar{g}^{sc,t}_{UU}); \\
\quad & \text{end} \\
\quad & \theta^{t+1}_0 \leftarrow \theta^{\text{MaxInnerIter}-1}_{t+1}; \\
\quad & \bar{g}^{sc,t+1}_{UU} \leftarrow P \cdot S_{UU}(\theta^{t}_t); \\
\text{end} \\
\theta^{\text{est}} & \leftarrow \theta^{\text{MaxOuterIter}-1}_{\text{MaxInnerIter}-1};
\end{align*}
\]

6.2.3.3 Implementation

The algorithm framework follows the implementation strategy described in Sec. 5.2.3.3.

6.2.3.4 Stopping criteria

The reconstruction algorithms rely on three main stopping criteria: normalised difference between two consecutive image estimates and norm of the projected gradient. Default values for LBFGS implementation were used. Furthermore, a maximum number of inner (MaxInnerIter) and outer iterations (MaxOuterIter) were set. The photopeak scatter is re-estimated every MaxInnerIter iterations. See Sec. 6.2.4.7 for details.

6.2.4 Evaluation

The performance of MLAA-EB-S was evaluated with digital phantoms of differing complexity. Simulations input and output are 3D.

6.2.4.1 Statistical Model

In this Chapter, experiments were conducted under the same acquisition model used for testing MLAA-EB-P (Chapter 5). Such assumptions are summarised here: (i) absence of true counts in UL and LU windows, (ii) the operator $R$ (Sec. 3.2.2) is an all-ones matrix, (iii) the input data in UL and LU are downsampled to low resolution via the operator $P*$ (Sec.
6.2. MLAA-EB-S

Figure 6.1: XCAT Phantom. First row: axial view. Second row: sagittal view. From left to right: MRAC used as initialisation $\mu_{\text{init}}$, true attenuation $\mu_{\text{true}}$, true activity $\lambda_{\text{true}}$, lung mask $\mu_{\text{mask}}$. The attenuation is expressed in cm$^{-1}$, the activity in arbitrary units.

3.2.2) for computational reasons, and (v) the probability of detecting incoming photons with a certain energy $E$ is modelled as a Gaussian function (Sec. 3.5.1.1).

6.2.4.2 3D Phantoms

A first investigation was conducted on a cylindrical phantom with a conical insert (Sec. 5.2.3.1, Fig. 5.2). The conical shape was chosen to simulate the lung. The image size was 30x30x8 and the voxel dimensions were equal to 1.2x1.2x3.25 cm$^3$.

The algorithm was also tested in more realistic scenarios. A 3D volume from the XCAT torso phantom (Segars et al. 2010) was generated, cropped to a 60x60x8 matrix with voxel size of 0.8x0.8x3.25 cm$^3$. Axial and sagittal views of the phantom are shown in Fig. 6.1. Please note that both cylindrical and XCAT phantoms have the same length in z-direction, covering the length of the scanner (26 cm) and the activity distribution is expressed in arbitrary units.

6.2.4.3 Projection data

Unscattered data were simulated by forward projecting the ground truth activity image (taking attenuation into account) into sinograms, using the Siemens mMR geometry and specifications (Karlberg et al. 2016): 242 views and 344 tangential positions. The number of rings was downsampled to 8 to match the image voxel size.

The scatter component is computed in low resolution with 21 views, 31 tangential positions and 8 rings. Simulations use in-plane detector pairs only. The energy resolution was set to 16%. Experiments were conducted with both one and two energy windows. For the single window acquisition, we investigated the case of a standard window, as well as the case of a wide energy window WW, where $g_{WW} = g_{UU} + g_{UL} + g_{LU} + g_{LL}$. Energy thresholds are shown in Table 6.1. Please note that the energy window $U_{\text{std}}$ was introduced...
6.2. MLAA-EB-S

![XCAT Phantom](image)

Figure 6.2: XCAT Phantom. Simulated data for MLAA-EB-S. UU data (first column, and UL data (second column). For display purpose: 2D sinograms obtained by summing over the rings (first row) and relative profiles (second row).

To have a fair comparison with the standard energy window used in mMR,

<table>
<thead>
<tr>
<th>Table 6.1: Energy Window Thresholds [keV]</th>
</tr>
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<tbody>
<tr>
<td>L</td>
</tr>
<tr>
<td>350 -- 460</td>
</tr>
</tbody>
</table>

For noisy data, a uniform background was added to simulate “random” coincidences equal to 39% of the total number of counts of the noise-free prompt data. The level of Poisson noise was chosen accordingly to the one of a 240-second PET/MR FDG thorax scan acquired in our institution.

6.2.4.4 MLAA-S

To fairly compare our approach with a single energy window acquisition, we implemented a MLAA-S. The algorithm relies on the following strategy: (i) simultaneous optimisation of both activity and attenuation maps with LBFGS (as for MLAA-EB-S), (ii) photopeak scatter re-estimation (as for MLAA-EB-S), (iii) single energy window input data. The main difference between MLAA-S and MLAA-EB-S lies in the input data (one vs multiple energy window). This implies that no scatter gradient is computed during MLAA-S iterations, as the only scatter information comes from the photopeak window where the scatter is updated with a one-step-late approach (and therefore the gradient is null). Algorithm 5 gives pseudo-code...
for MLAA-S.

**Algorithm 5:** Pseudo-code for MLAA-S.

**Input:** $g_w$, $\lambda$,$\mu$,$\tilde{g}_{sc}$,$\hat{g}_{w}$ init;

**Output:** Estimated activity and attenuation images vector $\theta$;

\[
\begin{align*}
\theta^0_0 &\leftarrow \lambda_{\text{init}}, \mu_{\text{init}}; \\
\hat{g}_{sc}^0 &\leftarrow \hat{g}_{w}^{\text{init}};
\end{align*}
\]

for $t = 0,\ldots,\text{MaxOuterIter} - 1$ do

for $k = 0,\ldots,\text{MaxInnerIter} - 1$ do

$\theta^{t+1}_{k+1} \leftarrow \text{LBFGS-B}(g_w, \theta^t_k, \hat{g}_{sc})$;

end

$\theta^{\text{MaxInnerIter}}_t \leftarrow \theta^t_{\text{MaxInnerIter}}$;

$\hat{g}_{sc}^{t+1} \leftarrow P S_U(\theta^{t+1}_{\text{MaxInnerIter}})$;

end

$\theta^{\text{est}} \leftarrow \theta^{\text{MaxOuterIter}}_{\text{MaxInnerIter}}$.

---

6.2.4.5 MLAA

In this study, an implementation of “MLAA” was also used: the framework is identical to MLAA-S, without the photo peak scatter re-estimation. This method was first proposed in (Fuin et al. 2017).

6.2.4.6 LBFGS-AC

An LBFGS-AC was also used as further comparison. The algorithm outputs an estimate of the activity image based on the following inputs: (i) ground truth attenuation image $\hat{\mu}_{\text{true}}$, (ii) ground truth photopeak scatter $\hat{g}_{sc}^{\text{true}}$, (iii) photopeak window projection data $g_{UU}$.

6.2.4.7 Reconstruction Parameters

Both activity and attenuation updates within MLAA-EB-S, MLAA-S and MLAA use LBFGS. In the current results, lung segmentation was incorporated in the algorithm by only updating the attenuation values within the inner cylinder/lung mask during iterations. This constraint is not used for the emission update, for which we only assumed the absence of activity outside the phantom (Fig. 6.1). Reconstruction parameters are shown in Table 6.2. No regularisation was added at this stage, as it was not the object of this study.

6.2.4.8 Initial Conditions

An MRAC was generated by decreasing the lung attenuation values by 20% with respect to the ground truth. In order to avoid dependency on initialisation for the different algorithms, all the reconstructions were initialised with the same activity estimate, obtained by iterating
6.2. MLAA-EB-S

<table>
<thead>
<tr>
<th>Phantom</th>
<th>MaxOSEMandSSSIter</th>
<th>MaxInnerIter</th>
<th>MaxOuterIter</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cylinder</td>
<td>3</td>
<td>40, 100</td>
<td>30</td>
</tr>
<tr>
<td>XCAT (noise free)</td>
<td>3</td>
<td>40, 100</td>
<td>30</td>
</tr>
<tr>
<td>XCAT (noisy)</td>
<td>3</td>
<td>100</td>
<td>15</td>
</tr>
</tbody>
</table>

Table 6.2: MLAA-EB-S. Reconstruction Parameters

between OSEM (3 subsets, 70 sub-iterations) and SSS (C. C Watson et al. 1996) with MaxOSEMIter = 3.

6.2.4.9 Analysis

**Cylindrical Phantom:** The performance evaluations of MLAA-EB-S and MLAA-S were assessed for different iteration schemes (Table 6.2). Analyses were conducted in terms of MPE in the inner cylinder of the estimated images over iterations.

**XCAT Torso Volumes:** As for the cylindrical phantom, the performance evaluations of MLAA-EB-S and MLAA-S were assessed for different iteration schemes (Table 6.2). Analysis were conducted in terms of MPE in the lung of the estimated images over iterations.

For noisy simulated data, 100 noise realisations were used to compute the (voxel-wise) mean reconstructed images ($\bar{\lambda}$ and $\bar{\mu}$), the variance and covariance images, denoted $\text{VAR}(\bar{\lambda})$, $\text{VAR}(\bar{\mu})$, $\text{COV}(\bar{\lambda}, \bar{\mu})$. The covariance image can be used to assess the cross-talk previously observed in the joint estimation task.

6.2.5 Results

6.2.5.1 Cylindrical Phantoms

Fig. 6.3 shows the MPE in the volume of interest, the inner cylinder (lung), for every outer iteration of both MLAA-S and MLAA-EB-S. We only report curves pertaining to the 8 and 32 cm cylinders, since the intermediate diameters follow a similar trend.

According to the toy-problem analysis conducted in Chapter 5, reconstructing the big cylinder is a harder problem. Nevertheless, MLAA-EB-S manages to find the correct and stable solution for different iteration schemes and for all the phantom sizes. By contrast, MLAA-S was not able to converge to the true solution, with results dependent on the exact iteration scheme.

At the last iteration (N=30), MLAA-EB-S achieved a maximum MPE in the attenuation image of 1.259% and 1.44% in the activity image for the 32cm diameter. For the same phantom, MLAA-S showed a maximum MPE of 9.418% and 12.42% in the estimated attenuation and activity images, respectively (Fig. 6.3, purple curve).
6.2. MLAA-EB-S

We also show the profiles for the reconstructed activity and attenuation images in Fig. 6.3. The displayed profiles are for the 24 cm cylinder, for \( z = 4 \) (central slice) and \( x = 15 \), reconstructed with different algorithms. MLAA-S used a single wide window \( WW \). Starting from the initial condition (red curve), both MLAA and MLAA-S (yellow and purple curves) show the typical cross-talk in the reconstructed images, whilst MLAA-EB-S (green curve) converges to the ground truth solution (blue curve).

6.2.5.2 XCAT Reconstruction - Noise free data

We tested MLAA-EB-S on the same data-sets were MLAA-EB-P was shown to fail (Sec. 5.2.4). Fig. 6.4 shows that MLAA-EB-S is able to converge to the ground truth solution, and to overcome the object-size dependency of the algorithm performance. This result demon-
strates that the intuition of attributing the divergent behaviour to the ‘pseudo-maximisation’ of the joint likelihood (Eq. 5.2) is correct.

The convergence rate of MLAA-EB-S is shown in Fig. 6.5; here the MPE in the lung region is plotted against the total number of likelihood and gradient updates. Overall, MLAA-EB-S approaches the region of 5% error in both the activity and the attenuation images after approximately 100 gradient and likelihood updates. Please note that the ‘spikes’ in the graph are attributed to the restarting of the LBFGS algorithm with the new scatter estimate.

Finally, we compare MLAA-S and MLAA-EB-S for different iteration schemes (varying the number of inner iterations before recomputing the photopeak scatter) in Fig. 6.6. Results confirm findings from the cylindrical phantoms discussed in Sec. 6.2.5.1: MLAA-
Figure 6.6: MPE over outer iterations for the attenuation (left) and activity (right) estimations. First row: MLAA-S. Second row: MLAA-EB-S.

EB-S converges to a stable solution, whilst MLAA-S results depend on the exact iteration scheme. Furthermore, only few photopeak scatter estimations were needed so that MLAA-EB-S could reach convergence.

6.2.5.3 XCAT Reconstruction - Noisy data

Axial views of the mean error images from all the noise realisations for MLAA (from a standard energy window), MLAA-S (from both standard and wide energy windows) and MLAA-EB-S at the last iteration – where convergence is reached – are shown in Fig. 6.7. Table 6.3 also reports the ROI mean values in the lung region for relative bias, variance, and covariance.

Results showed that MLAA and LBFGS-AC achieved the worst and best results, respectively, amongst all the four reconstruction methods. MLAA-S outperforms MLAA, thanks to the photopeak scatter re-estimation over iterations, with better results from wider energy window (WW). MLAA-S further improves on MLAA-S in terms of stability of the solution. In particular, both MLAA-EB-S and MLAA-S converge in mean to a similar solution (Fig. 6.7 b-d, Fig. 6.7f-h), with a higher noise level in the lung region compared to the one.
6.2. MLAA-EB-S

Figure 6.7: Error metrics in the XCAT images for different reconstruction algorithms: MLAA (UUstd), MLAA-S(UUstd), first column; MLAA-S (WW), second column; MLAA-EB-S, third column; LBFGS-AC, fourth column. From the top to the bottom: MPE images [%] (a-d) and variance (VAR) (j-m) for the attenuation from 100 noise realisations; MPE images [%] (e-i) and variance (VAR) (n-r) for the activity image. Covariance (COV) images (s-v).

from an LBFGS-AC (Fig.6.7i). However, MLAA-EB-S shows a lower variance with respect to both MLAA-S (WW) and MLAA-S (UUstd) for both the attenuation (Fig.6.7 k-m) and activity distributions (Fig.6.7 o-r). Furthermore, MLAA-EB-S was found to have the lowest covariance (Fig.6.7 t-v) between the four algorithms, demonstrating that the joint variability of the two unknown images is reduced. Results from Table 6.3 show that MLAA-EB-S converged in mean to a solution with mean relative bias and standard deviation comparable to the one obtained with an LBFGS-AC reconstruction.

Finally, we compared the error in the photopeak scatter estimate for MLAA-S (WW), MLAA-S (UUstd) and MLAA-EB-S (Fig. 6.8). MLAA-EB-S shows the lowest error in the photopeak scatter estimate.
6.2. MLAA-EB-S

Table 6.3: ROI analysis (in the lung region). Mean values computed for: relative bias (RB), variance (VAR) and covariance (COV). \( \lambda_{true} = 0.3260 \) and \( \mu_{true} = 0.2865 \)

<table>
<thead>
<tr>
<th></th>
<th>MLAA (Ustd)</th>
<th>MLAA-S (Ustd)</th>
<th>MLAA-S (WW)</th>
<th>MLAA-EB-S</th>
<th>LBFGS-AC</th>
</tr>
</thead>
<tbody>
<tr>
<td>RB((\bar{\mu}))</td>
<td>4.02 e-04</td>
<td>-9.83 e-04</td>
<td>-9.52 e-04</td>
<td>-1.56 e-04</td>
<td>0.343 e-04</td>
</tr>
<tr>
<td>VAR((\bar{\mu}))</td>
<td>2.39 e-04</td>
<td>1.15 e-04</td>
<td>0.77 e-04</td>
<td>0.343 e-04</td>
<td>1.05 e-03</td>
</tr>
<tr>
<td>RB((\bar{\lambda}))</td>
<td>59.2 e-03</td>
<td>2.40 e-03</td>
<td>-2.81 e-03</td>
<td>1.1 e-03</td>
<td>2.50 e-03</td>
</tr>
<tr>
<td>VAR((\bar{\lambda}))</td>
<td>44.6 e-03</td>
<td>19.0 e-03</td>
<td>10.5 e-03</td>
<td>2.50 e-03</td>
<td>2.40 e-03</td>
</tr>
<tr>
<td>COV((\bar{\lambda}, \bar{\mu}))</td>
<td>33.7 e-04</td>
<td>7.67 e-04</td>
<td>5.83 e-04</td>
<td>2.21 e-04</td>
<td>1.05 e-03</td>
</tr>
</tbody>
</table>


6.2.6 Discussion

We have proposed a new method for the joint reconstruction of PET activity and attenuation, named MLAA-EB-S. The algorithm takes into account the mutual dependence of scatter, activity and attenuation. The activity and attenuation distributions are updated simultaneously, whilst the photopeak scatter estimate uses a one-step-late approach.

MLAA-EB-S was proposed to overcome the limitation of the previous algorithm MLAA-EB-P (Sec. 5.2), found to diverge for large-scale objects. This new algorithm was tested on the same data-sets where MLAA-EB-P showed a problematic behaviour. Furthermore, it was evaluated against MLAA-S: a reconstruction algorithm that follows the same framework of MLAA-EB-S, that relies however on a single energy window set of data. Further evaluations were conducted against an LBFGS-AC reconstruction (from the correct attenuation and correct photopeak scatter estimates).

Results from cylindrical phantom simulations of increasing diameters showed that
MLAA-EB-S was able to converge in mean to the ground truth solution. Furthermore, it was found to be stable for different iteration schemes, outperforming the single energy window optimisation MLAA-S (see Fig. 6.3). Overall both MLAA-EB-S and MLAA-S benefit from the re-estimation of the photopeak scatter, as from the first outer iteration the output error was further reduced. Please note that the first outer iteration would correspond to our LBFGS-B implementation of MLAA as for (Fuin et al. 2017).

Simulations on noise-free simulated 3D XCAT data showed that MLAA-EB-S improved on a standard MLAA reconstruction and converged in mean to the ground truth solution in the case where MLAA-EB failed (Fig. 6.4). MLAA-EB-S was able to enter the ±5% error zone after approximately 100 total number of iterations (Fig. 6.5). A further analysis on different iteration schemes showed that MLAA-EB-S outperformed MLAA-S in terms of stability of the solution (Fig. 6.6).

Simulations on 3D XCAT volumes with different noise realisations confirm previous results on noise-free data with regard to the stability of the ML solution. The ROI analysis in Table 6.3 shows that MLAA-EB-S converges in mean to the ground truth solution, with a variance only slightly higher than the one of LBFGS-AC. Reconstructions from MLAA-S exhibited a higher variance and covariance, with increasingly worse results for narrow windows (WW, and UU_{std}), confirming the previous observations on the level-set plots (Fig. 5.9) and noise-free XCAT reconstructions (Fig. 6.4). As the co-variance can be interpreted as a measure of cross-talk, this result illustrates the ill-conditioning of non-TOF MLAA. Overall, MLAA-EB-S outperformed MLAA-S in terms of stability of the ML solution. We noted that images from MLAA-EB-S and MLAA-S appear noisier than the one from LBFGS-AC in the lung region (see Fig. 6.7:a-c and 6.7:g-j); we believe this is because of additional uncertainty brought by the unknown attenuation values in the lung region.

The current study has however several limitations. In the current evaluation, the same forward model is used for the simulation of the projection data as for the reconstruction. While this allowed us to assess the accuracy of the reconstruction and the stability of the solution in absence of model mismatch, the effects of errors in the forward model will need to be investigated. An additional limitation is the reconstruction of low resolution object. Possibly, multi-resolution methods (Raheja et al. 2000) could be explored. However, the possibility of recovering high frequency features will need further investigation.

An additional limitation is related to the absence of multiple scatter events. This aspect
will be further discussed in Sec. 7.5.6.

Our current model neglects detector scatter. In practice, the probability of scatter within the crystal itself will result in partial energy deposition of photopeak events. Consequently, these photons can be wrongly assigned to the low energy windows. This effect could be taken into account via modification of the detection efficiency model (see next Chapter).

The large voxel size in the simulation/reconstruction leads to a relatively low amount of noise in the reconstructed images. When using realistic voxel sizes, noise-suppressing penalties may be required (see Chapter 7).

In addition to the aforementioned limitations, assuming the knowledge of attenuation values outside the lung region represents a further restriction of our method. Nevertheless, among the different tissue classes defined in standard MRAC methods, the lungs have the largest inter-patient attenuation values variability (Mehranian et al. 2015). Therefore, this assumption is fairly common in PET/MR studies (Mehranian et al. 2015; Berker et al. 2012b).

Furthermore, the activity and attenuation images used in this study were in similar intensity scale. However, since the scale of the activity can vary with applications, a preconditioner could be introduced into the reconstruction (Tsai et al. 2017).

### 6.3 Conclusion

A new reconstruction algorithm, MLAA-EB-S was proposed in order to overcome the problematic behaviour of MLAA-EB observed in Chapter 5: MLAA-EB was unable to satisfactorily reconstruct patient-scale objects. Initially, MLAA-EB-S was tested where the previous algorithm MLAA-EB was shown to fail, demonstrating that this new approach overcame the scaling problem of MLAA-EB.

Then, the method was tested on digital 3D cylindrical phantoms and XCAT volumes and compared against: (i) a simultaneous estimation from a single energy window (MLAA-S), (ii) an LBFGS implementation of MLAA and (iii) an emission estimation from the correct photopeak scatter and correct attenuation image (LBFGS-AC). Both MLAA-EB-S and MLAA-S re-estimate the photopeak scatter during the reconstruction. Quantitative results demonstrate that taking scatter into account reduces the cross-talk between the activity and attenuation images (as MLAA-S outperforms MLAA) and that by using multiple energy windows, MLAA-EB-S outperforms MLAA-S.

This study provides the first evidence that the incorporation of scatter information is
beneficial for joint activity and attenuation reconstruction in non-TOF 3D PET, even with finite energy resolution.
Chapter 7

Towards realistic data: extension of the forward model and Monte Carlo data reconstructions

This chapter further extends the methods presented in this thesis to be able to handle realistic data obtained with Monte Carlo simulations, albeit while still excluding multiple scatter data. A subsequent validation study assesses two main concerns: (i) accuracy of the forward model and (ii) feasibility of the proposed joint reconstruction algorithm for realistic data-sets, where a mismatch exists between simulation and reconstruction models.

7.1 Introduction

In previous chapters, we have demonstrated the benefits of incorporating a probabilistic 3D scatter model into the system model in an iterative image reconstruction framework. Several improvements were made with respect to other methods present in literature, including: (i) using a realistic model of PET detectors energy response, (ii) accounting for uncertainty in the measurement of photon energies, (iii) high resolution 3D input and output, (iv) accounting for the presence of noise in the data, (v) input projection data that simulate geometry of existing clinical scanners.

These improvements on the state-of-the-art are however not yet sufficient to make this approach applicable to real data acquisitions. In fact, some important questions remain to be answered: (i) how accurate is the proposed forward model for real measurements? and (ii) what is the impact of input/model mismatch on the output of the reconstruction algorithm?

In order to answer these questions, this chapter uses Monte Carlo generated data, based on an accurate and independent model. Monte Carlo methods were introduced in Sec. 2.1.5.3.
In this Chapter we use Gated Application Tomography Emission (GATE) (Jan et al. 2004), an open software for emission tomography that allows the modelling of complex physics phenomena including detector energy response.

One important aspect that needs to be taken into account when dealing with low-energy photon measurements is the detection efficiency. In previous chapters, we have used a previously proposed Gaussian model, see Sec. 3.5.1.1. In fact, the detector response can significantly vary for scattered and unscattered incoming photons for two main reasons: (i) the scattered photons arrive at the detector at lower energies and (ii) over a different distribution of angles of incidence. The first factor influences the detector energy response, the latter changes the geometric effects (Sec. 2.1.2.1). These aspects will be further investigated in this Chapter.

The Chapter is organised as follows. First, an overview of the statistical model of the data used in this study is given, as well as an outline of STIR and GATE simulations of the mMR scanner. Subsequently, the detection efficiency model from Sec. 3.5 is trained and tested on Monte Carlo data and comparison of the forward model and GATE generated data is provided in projection space from point source emitters. Then, normalisation techniques for data with different energy windows are discussed. Projection data from an XCAT simulation of both STIR and GATE generated data are compared. Finally, Monte Carlo generated data are reconstructed with a new reconstruction algorithm, MLAA-EB-A.

### 7.1.1 Statistical model of the data

Here we give a brief outline of the statistical model used in this Chapter. Similarly to Chapter 4 and 5, we assume that each photon of a coincidence pair can be assigned to either the photopeak window (U) or to a lower energy window (L), resulting in four different 3D sinograms, one for each energy window combination ($g_{UU}$, $g_{UL}$, $g_{LU}$, $g_{LL}$). However, here we assume that for all energy window pairs $(v, w) \in \{U, L\}^2$, the observed counts $g_{vw}$ can be described as a Poisson process centred on $\bar{g}_{vw}$, given by the sum of expected scattered $\bar{g}_{vw}^{sc}$, unscattered events $\bar{g}_{vw}^{unsc}$ and a background of random events $\bar{g}_{vw}^r$. For $\theta = [\lambda, \mu]$, the expected data are therefore given by:

\[
\begin{align*}
\bar{g}_{UU}(\theta) &= \bar{g}_{UU}^{unsc}(\theta) + \bar{g}_{UU}^{sc}(\theta) + \bar{g}_{UU}^r \\
\bar{g}_{UL}(\theta) &= \bar{g}_{UL}^{unsc}(\theta) + \bar{g}_{UL}^{sc}(\theta) + \bar{g}_{UL}^r \\
\bar{g}_{LU}(\theta) &= \bar{g}_{LU}^{unsc}(\theta) + \bar{g}_{LU}^{sc}(\theta) + \bar{g}_{LU}^r \\
\bar{g}_{LL}(\theta) &= \bar{g}_{LL}^{unsc}(\theta) + \bar{g}_{LL}^{sc}(\theta) + \bar{g}_{LL}^r
\end{align*}
\]
7.1. Introduction

The operators $R$ and $P$ are used as downsampling and upsampling operators in image and sinogram space, respectively, in all the energy windows. 

where $\bar{g}_{UU}^{sc}(\theta)$, $\bar{g}_{UL}^{sc}(\theta)$ and $\bar{g}_{LU}^{sc}(\theta)$ are given in Eq. 3.5. A visual interpretation of the forward model used in this Chapter is given in Fig. 7.1.

7.1.2 STIR simulation of Siemens mMR Biograph

The input activity and attenuation images are forward projected (taking attenuation into account) into sinograms, using geometry and specifications similar to the Siemens mMR and specifications as in Sec. 7.4: 344 tangential positions, 252 views, 64 rings and 504 detector per ring. Rings are 0.40624 cm apart.

The scatter component is computed in low resolution with 21 views, 31 tangential positions and 8 rings and then up-sampled to full resolutions. Simulations use in-plane detector pairs only. The energy resolution was set to 14%.

Here all the energy windows measures both scattered and unscattered events (Sec. 7.1.1).

7.1.3 GATE simulation of a Siemens mMR Biograph

Simulations of a Siemens mMR Biograph (Karlberg et al. 2016) acquisition presented in this Chapter are based on a GATE Monte Carlo simulation (Jan et al. 2004). The PET system includes 64 rings, with each containing 56 blocks. Each block consists of 1x8x9 Lutetium Oxyorthosilicate (LSO) crystals. Please note that the real mMR uses a 1x8x8 block; therefore, the gaps between the detector blocks are reduced in our simulations. Eight blocks are placed in axial direction, resulting in a total of 64 rings and 504 detector per ring. The inner ring diameter is 65.6 cm. The energy resolution was set to 14 %, according to the
7.2 Training and testing of the proposed detection efficiency model

7.2.1 Introduction

This section covers two main aspects. First, the detection efficiency model presented in Sec. 3.5.2.1 is trained and tested on GATE Monte Carlo data. Then, the forward model (Sec. 7.1.1) with the so-obtained detection efficiency model is compared against GATE Monte Carlo data. In particular, the following specifics are addressed: (i) accounting for a possible translation between the origins of GATE and STIR Cartesian coordinate systems; (ii) accounting for a possible tilt between STIR and GATE Cartesian coordinate systems; (iii) agreement in the sinogram shape and orientation.

7.2.2 Theory

In Chapter 3 an improved detection efficiency model was proposed, able to account for detector scatter (Sec. 3.5.2.1). Here, it is incorporated in the forward model presented in Sec. 7.1.1.

7.2.3 Experiments and results

7.2.3.1 Detection efficiency fitting

A point source of 511 keV located at the centre of the scanner was used to generate the training-set data. The SciPy (Virtanen et al. 2019) library was used to fit the proposed model.
7.2. Training and testing of the proposed detection efficiency model

Figure 7.2: Proposed detection efficiency model: training-set (511 keV point source emission positioned at the centre of the scanner) and testing-set (370 keV point source emission positioned at the centre of the scanner).

The detection efficiency model (Sec. 3.5.2.1) was trained to a GATE mMR simulation. Once the model was trained, it was tested with a GATE data-set from a point source emitting 370 keV photons. Table 7.1 reports the values of the fitting output parameters.

Fig. 7.2 shows the model versus the training and test data. According to GATE simulations, Fig. 7.3 illustrates that 83.5% of 511 keV photon will be detected in the photopoint window $U = 460 - 570$ keV and 16.4% will be measured in a low energy window $L = 250 - 660$ keV.

<table>
<thead>
<tr>
<th>Fitting Output Parameters</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>$Z$</td>
<td>66</td>
</tr>
<tr>
<td>FWHM (511 keV)</td>
<td>0.14</td>
</tr>
<tr>
<td>$H_1$</td>
<td>0.940 $10^{26}$</td>
</tr>
<tr>
<td>$H_2$</td>
<td>0.7 $10^1$</td>
</tr>
<tr>
<td>$H_3$</td>
<td>0.260 $10^2$</td>
</tr>
<tr>
<td>$p_1$</td>
<td>0.598 $10^{-2}$</td>
</tr>
<tr>
<td>$p_2$</td>
<td>0.296 $10^2$</td>
</tr>
<tr>
<td>$p_3$</td>
<td>-0.817 $10^{-2}$</td>
</tr>
</tbody>
</table>

Table 7.1: Fitted parameters for the proposed detection efficiency model, obtained from a Monte Carlo simulation of a point source emitter.

7.2.3.2 Assessment of STIR and GATE simulated scanner consistency

Four point sources were placed in (asymmetric) positions within the field of view. Input images are shown in Fig. 7.4. The attenuation medium consisted in a cylindrical phantom of radius $r = 1.8$ cm and height $h = 0.4$ cm; it was placed in the centre of the scanner in $x - y$
7.2. Training and testing of the proposed detection efficiency model

Figure 7.3: Energy spectrum obtained from HATE for an incoming photon of 511 keV with indication of energy windows used: upper energy window (pink) and low energy window (light blue). The percentage of true events measured in each energy window is reported.

Figure 7.4: Point source emitters (a) and attenuation phantom (b) within the GATE simulated mMR scanner (c).

direction, at an axial position $z = 45$ and simulated as water. STIR and GATE projection data were obtained as in Sec. 7.1.2 and in Sec. 7.1.3, respectively. The scattered and unscattered expected events (from STIR) were scaled according to the acquisition time. Further details on this validation study are given in Appendix D.

Fig. 7.5 and Fig. 7.6 compares the sinograms obtained from GATE and the proposed
7.2. Training and testing of the proposed detection efficiency model

The detection efficiency model proposed in Chapter 3 was trained and tested on point sources emitting photons with energies of 511 keV and 370 keV, respectively. This choice was made to simulate ‘true’ and ‘scattered’ events without the need to rely on an attenuation medium. Results showed that the proposed model was able to fit GATE simulated data for both training and testing incoming energies (Fig. 7.2). In particular, the relative amplitude of the photopeak and Compton plateau varied consistently between our model and GATE simulated data for different incoming energies.

Subsequently, an evaluation of STIR simulations (Sec. 7.1.2) from point source emitters was provided. Sinogram data were compared against GATE Monte Carlo generated data from the same input images (Sec. 7.1.3).

Scattered and unscattered sinograms showed good agreement and seemed well aligned. Corrections for block efficiency and other geometric effects were not included in this initial assessment. The comparison in projection space showed good agreement between GATE and STIR simulations. However, the difference images show some remaining issue with

Figure 7.5: Simulated projection data, axial view. From top to bottom: True counts in UU, scattered counts in UU, scattered counts in LU, scattered counts in UL. First column: GATE simulated data. Second column: Proposed model. Third column: difference error.
7.3 Maximum-Likelihood Estimation of Normalisation Factors of GATE data

In this section, we describe a methodology for estimating normalisation factors for multiple energy window measurements obtained with GATE Monte Carlo generated data.

7.3.1 Introduction

An accurate estimation of the tracer distribution from PET data requires accounting for the changes in sensitivity of the emission data due to changes in the response of the detector pairs (Defrise et al. 1991). In addition, any analytical model of the acquisition will disregard some effects, for instance factors related to the geometric effects (Sec. 2.1.2.1). Therefore, normalisation factors are introduced to account for discrepancies between the model and the actual measurement.

The calculation of the correction factors in PET involves the comparison of the emission data to an expectation of the source activity distribution for large sources, i.e. overall modelling detection efficiency, implying that the normalisation technique is inevitably projector scaling. This will be addressed in the next section.

Figure 7.6: Simulated projection data, tangential view. From top to bottom: True counts in UU, scattered counts in UU, scattered counts in LU, scattered counts in UL. First column: GATE simulated data. Second column: Proposed model. Third column: difference error scaling. This will be addressed in the next section.
7.3. Maximum-Likelihood Estimation of Normalisation Factors of GATE data

The appropriate correction coefficients are generally obtained with two sets of measurements: geometric factors can be determined from low-scatter planar source (Oakes et al. 1998); crystal efficiencies can be measured by measuring the response of all LORs to a calibrated source of activity of known geometry (often a cylindrical phantom) (Ollinger 1995). The same normalisation sinogram is then often used to correct both scattered and unscattered estimates (Rezaei et al. 2019). However, low energy windows see a higher number of low energy photons, for which geometric factors might differ markedly from those corresponding to the photopeak window (where the 511 keV photons prevail). In other words, scatter events show a considerable high heterogeneity of the probability of angles of incidence and points of origination (Ollinger 1995). This is likely to be important for low energy window measurements and will be discussed in this Chapter.

7.3.2 Theory

Here we want to investigate whether there is a necessity for new model-based corrections for the normalisation of PET emission data from multiple-energy windows. Therefore, we differentiate for variation in sensitivity of both scattered and unscattered events, leading to the following:

\[
\bar{g}_{vw} = G_{vw}^{\text{unsc}} \bar{g}_{vw}^{\text{unsc}} + G_{vw}^{\text{sc}} \bar{g}_{vw}^{\text{sc}}
\]  

(7.2)

where \( \bar{g}_{vw} \) includes the energy-dependent detection efficiency model \( \epsilon(E) \) (Sec. 3.5). The efficiency factors \( G_{vw}^{\text{unsc}} \) and \( G_{vw}^{\text{sc}} \) have been introduced in Eq. 3.4 and Eq. 3.10, respectively, and are defined as:

\[
G_{ij}^{\text{unsc}} = \epsilon_i \epsilon_j g_{ij}^{\text{unsc}}
\]

\[
G_{ij}^{\text{sc}} = \epsilon_i \epsilon_j g_{ij}^{\text{sc}}
\]

(7.3)

where \((i, j)\) is a detector pair in the scanner, \( \epsilon_i \epsilon_j \) indicates crystal efficiency factors (not included in the energy-dependent model \( \epsilon(E) \)) and \( g_{ij} \) is a geometric factor accounting for the change in efficiency due to the radial position of the detector pair and relative position of each detector pair within a block; it also depends on the angle of incidence of the incoming photon, reason why we differentiate between \( g_{ij}^{\text{unsc}} \) and \( g_{ij}^{\text{sc}} \).

In the following, we will refer to \( \frac{1}{g} \) as normalisation factors and \( G \) as efficiency factors. Let now \( \bar{g}_{vw}^{\text{unsc}} \) and \( \bar{g}_{vw}^{\text{sc}} \) be respectively the measured unscattered and scatter events from a GATE Monte Carlo simulation. Then, a log-likelihood function \( \mathcal{L} \) can be defined, denoting the probability that measured data \( \bar{g} \) are observed, given a known object and the (unknown)
efficiency factors $G$. Then, the efficiency factors can be estimated for each energy window pair $(v, w)$ with a ML estimation:

$$\hat{G}_{vw}^{\text{unsc}} = \arg\max \left( \mathcal{L}_{vw}(g_{vw}^{\text{unsc}} | \bar{g}_{vw}^{\text{unsc}}(G_{vw}^{\text{unsc}})) \right)$$

(7.4)

$$\hat{G}_{vw}^{\text{sc}} = \arg\max \left( \mathcal{L}_{vw}(g_{vw}^{\text{sc}} | \bar{g}_{vw}^{\text{sc}}(G_{vw}^{\text{sc}})) \right)$$

(7.5)

Please note that in a GATE simulation, the efficiencies $\varepsilon_i\varepsilon_j$ of all the crystals are identical in the simulation. Therefore, the optimisation problem reduces to the estimation of the geometric factors.

### 7.3.3 Experiments and results

A maximum-likelihood estimation of normalisation factors for PET detectors (Hogg et al. 2001) was conducted to estimate efficiency factors specific for scattered and unscattered events ($G_{vw}^{\text{unsc}}$ and $G_{vw}^{\text{sc}}$). In particular, they were obtained by comparing GATE simulated data (Sec. 7.1.3) to an estimate of the projection data obtained with STIR (Sec. 7.1.2) from the forward model in Sec. 7.1.1. The efficiency factors of the true counts in the region outside the support of the activity image are undefined and were therefore set to 0. According to (Hogg et al. 2001) we imposed symmetry between blocks, allowing us to reduce noise in the estimated efficiency factors.

Fig. 7.7 shows the cylindrical phantom with elliptical section (covering the region occupied by the XCAT 3D volume) used for the calculation of the detector sensitivity. The attenuation value was set to the value of the lung material defined in default GATE database ($\mu = 0.0247$). Normalisation sinograms relative to both scattered and unscattered events are shown in Fig. 7.8.

### 7.3.4 Discussion

Variations in detector sensitivity must be taken into account when reconstructing PET images. For a single window acquisition, the appropriate correction coefficients can be obtained by measuring the response of all coincidence lines to a calibrated source of activity where scatter events are assumed to be absent. The detector sensitivity obtained from the true events can be then used to correct both expected unscattered and scattered events. However, in the case of multiple-energy window data, the accuracy of this approach is yet unknown. As scattered events dominate the low-energy windows, using one unique sensitivity normalisation
Figure 7.7: Cylindrical phantom with elliptical section used for computing the normalisation sinograms.

Figure 7.8: Efficiency factors sinograms obtained from the cylindrical phantom (a-b, c-d). Sinograms at different axial positions were summed for display purposes. Sinogram profiles at view = 100, comparing normalised STIR simulated data and GATE Monte Carlo generated data (c, f) for the same phantom.
Figure 7.9: Zoomed-in view of each efficiency factors sinogram (from Fig. 7.8) for different energy windows.

In order to assess the aforementioned hypothesis, we have generated a set of multiple-energy window GATE measurements from a cylindrical source phantom of known attenuation. For each energy window, data were unlisted into two separate sinograms: (i) measured unscattered events; (ii) measured unscattered events. Then, the normalisation sinograms were obtained by comparing: (i) measured unscattered and expected unscattered events; (ii) measured scattered and expected scattered events. Both sensitivities were obtained via a maximum likelihood estimation.

We show the normalisation sinograms in Fig. 7.8. Results demonstrate that the geometric effects vary significantly between the photopeak and the lower window. Furthermore, a global scale factor between the upper and lower energy window was found. The photopeak scatter normalisation sinogram (UU) differs to the one for the UL and LU windows. The latter look more homogeneous and flat and with a less marked ‘end block efficiency-drop’ effect (stripes on the sinogram). A ‘zoomed version’ is given in Fig. 7.9. Furthermore, the UL and LU normalisation sinograms show a mirror symmetry; this corresponds to the fact that only one of the photons is scattered, and therefore the geometric effect appears more ‘blurred’ in correspondence of the scattered photon only. Concerns arose in regards to the dependency of the scatter normalisation sinograms to the attenuation of the phantom used for computing the normalisation. For this reason, the cylinder was filled with 'lung attenuation
values’ so that a reasonable scatter distribution could be obtained. This particular topic will be further investigated in the future.

This study investigated the problem of low-energy window normalisation and differences between unscattered and unscattered efficiency factors. These normalisation factors also compensate for errors in the analytical model presented in Chapter 3, including global scale factors.

The normalisation method used in this section relies on the possibility of differentiating between scattered and unscattered events, which is possible in Monte Carlo simulations, but not in real measured data. One possible solution for measured data could be the following. First, the unscattered count efficiency factors could be obtained from a thin moving line source as in (Badawi et al. 1996). Once obtained, the true count sensitivity could be incorporated in the forward model so that the only unknown sensitivity is the one related to the scatter events. Then, the scatter sensitivity $C_{\text{unsc}}^{\text{wv}}$ could be estimated from the total measured events.

The incident angles of the incoming scattered photons depend on the actual scatter distribution. This indicates that in practice, the normalisation factors for the scattered data are likely to be object dependent. Therefore, future study will be directed towards the investigation of the effects of phantom geometry on the normalisation sinograms.

7.4 XCAT Torso Phantom Simulations. Evaluation in projection space

In this section, we compare projection data of XCAT 3D volumes obtained with both GATE and our software.

7.4.1 Projection data

7.4.1.1 STIR Projection data

STIR projection data were obtained as described in Sec. 7.1.2. The efficiency factors obtained with the cylindrical phantom acquisition (Fig. 7.8) were incorporated in the simulated data.

7.4.1.2 GATE Monte Carlo generated data

GATE simulations of a Siemens mMR Biograph (Fig. 7.11) were obtained as illustrated in Sec. 7.1.3. The global activity concentration results in the acquisition of 333M counts (as for Chapter 6). Randoms and multiple scatter were excluded in the set of measurements.
7.4. XCAT Torso Phantom Simulations. Evaluation in projection space

Figure 7.10: 3D XCAT Thorso Phantom. From left to right: MRAC, true attenuation image, true activity image, attenuation mask. First row: axial view. Second row: coronal view.

Figure 7.11: Illustration of the GATE XCAT simulation

7.4.2 Experiments and results

A 3D volume from the XCAT torso phantom (Segars et al. 2010) was generated, cropped to a 120x120x64 matrix with voxel size of 0.4x0.4x0.40625 cm³. Both axial and coronal views of the phantom are shown in Fig. 7.10. The distribution represents the normalised radioactivity distribution corresponding a static FDG acquisition. As in all the experiments presented so far, the attenuation map was assumed to be perfectly aligned with the activity image.

Sinograms for UU, UL and LU windows were obtained as illustrated in Sec. 7.4.1.1 from: (i) Gaussian efficiency model (Sec. 3.5.1.1) with one efficiency factors computed from true events in UU (Fig. 7.8 a) and (ii) the proposed efficiency model (Sec. 3.5.2.1) and normalisation sinograms computed for both scattered and unscattered events (Fig. 7.8...
7.4. XCAT Torso Phantom Simulations. Evaluation in projection space

Figure 7.12: Comparison in sinogram space between Monte Carlo and analytical 3D XCAT torso simulation. Here the forward model relies on a Gaussian detection efficiency model and one unique normalisation sinogram from the true counts efficiency factors. First row: UU data. Second row: UL data. Third row: LU data. First column: GATE Monte Carlo generated data. Second column: analytical simulation. Third column: sinogram profile (view = 44). Sinograms at different axial positions were summed for display purposes.

a-d). Projection data were compared to those from GATE (Sec. 7.4.1.2) for the same digital phantom.

Fig. 7.12 shows result from (i) and Fig. 7.13 shows results from (ii). In both figures, GATE generated data are added as comparison. Results show that (i) and (ii) lead to very similar results in the photopeak window, both matching closely GATE data. However, results from (i) and (ii) significantly differ in the low energy window, with better results from (i).

7.4.3 Discussion

Benefits of incorporating low-energy photons information in PET image reconstruction have been discussed in (Conti et al. 2012; Brusaferri et al. 2018; Berker et al. 2019). However, to accurately predict the expected measurements, an appropriate model for the detector energy response is mandatory.

A common method to model the energy response of PET detector in the photopeak window is to use an energy-dependent Gaussian broadening (Chapter 3). However, this
7.4. XCAT Torso Phantom Simulations. Evaluation in projection space

Figure 7.13: Comparison in sinogram space between Monte Carlo and analytical 3D XCAT torso simulation. Here the forward model relies on the proposed detection efficiency model and specific normalisation sinogram for each energy window from the cylindrical phantom with a global attenuation value set to the one of the ‘lung’. First row: UU data. Second row: UL data. Third row: LU data. First column: GATE Monte Carlo generated data. Second column: analytical simulation. Third column: sinogram profile (view = 44). Sinograms at different axial positions were summed for display purposes.

model is expected to be only accurate enough for UU, but it is inappropriate for UL and LU because of detector scatter.

As discussed in Sec. 6.2.6, scatter within the crystal itself will result in the incomplete deposit of the energy of the impinging photon to the scintillation crystal. Consequently, these photons will be wrongly assigned to a measured lower energy value. A detection efficiency model suitable for a generic energy window was proposed in Sec. 3.5.2.1. Furthermore, the results obtained for the normalisation sinograms (Fig. 7.8) show that variation in sensitivity in the different energy windows arise due to the radial position of each detector pair and their relative position within a block (Fig. 7.8).

In this Chapter, the accuracy of both the efficiency (energy-dependent) model and the normalisation factors was tested on GATE simulations.

Simulated projection data for the same input images were computed for the case of: (i)
Gaussian efficiency model and one normalisation sinogram (Fig. 7.12); (ii) proposed model and specific normalisation sinogram for scattered and unscattered events in each energy window (Fig. 7.13). Simulated projection data were compared to the ones obtained with GATE.

Results show that both the energy-dependent efficiency model and the normalisation technique play a key role in the accuracy of the forward model. The Gaussian model is accurate enough for the photopeak window but results in the under-estimation of the true events in the low energy window (mostly because of neglecting detector scatter). The proposed energy-dependent model matches GATE data closely, compensating for the underestimation of true events in UL and LU from the Gaussian model. However, a small error is still present in the low-energy window (Fig. 7.13), where the analytical simulation overestimates GATE data. This is potentially due to the fact that the efficiency model (Sec. 3.5.2.1) is not accurate enough and cannot accommodate for different shapes/distribution on the phantom. Furthermore, additional parameters could be introduced to obtain better fits of the heuristic model at different energies. It could be possible that using an object that matches the actual patient as close as possible to determine the normalisation factors would give the best results. However, this hypothesis will need to be confirmed in the future.

Another consideration with respect to the normalisation sinogram relates to the fact that end-block effects in the STIR simulation appeared more marked in the low energy window when only one normalisation sinogram is used (Fig. 7.12 vs 7.13); the introduction of a specific normalisation sinogram for scattered events reduces this effect, and the STIR simulations match closer GATE data (Fig. 7.13).

A brief discussion on related research work now follows. In (Conti et al. 2012), the size of the detector block in the GATE simulations was increased so that a very high fraction of the 511 keV photons would be eventually absorbed in the crystal and the amount of detector scatter would be minimal. For this reason, the choice of a Gaussian efficiency model was found to be appropriate. In (Berker et al. 2019), the assumption of perfect energy resolution was made, avoiding the need to accurately model the detection efficiency for low-energy photons. A similar hypothesis was made in (Zhang et al. 2014), where the reconstruction method was evaluated using a simulated PET scanner (with GATE) with an ideal energy resolution of 0.1% FWHM.

This section has developed a methodology to model the energy dependent detection
efficiency including geometric and block effects. The results show that when using these detection efficiencies, our analytic simulations correspond in good approximation to the Monte Carlo simulations, albeit with some small deviations. In the next section, we will incorporate the complete model into a joint reconstruction method to investigate joint reconstruction on realistic input data. The effect of those ‘small deviations’ on the joint reconstruction estimation of the activity and the attenuation will be therefore investigated.

7.5 Joint estimation of activity and attenuation from Monte Carlo data

7.5.1 Introduction

In previous chapters, several assumptions on the data were made, such as the absence of true events in the low-energy windows (UL, LU and LL). However, as shown in the previous section, some of these assumptions do not apply to Monte Carlo data with realistic detection modelling. Because of these simplifying assumptions, it would not be possible to use MLAA-EB-S for reconstructing input data as the one presented in Sec. 7.4. In Sec. 7.1.1 we have proposed several modifications to the forward model removing the need for those assumptions. Here a new reconstruction algorithm, MLAA-EB-A, is introduced.

7.5.2 Statistical Model

An overview of the statistical model used in this Chapter was given in Sec. 7.1.1.

7.5.3 Optimisation

Here we describe the main algorithm MLAA-EB-A. The cost function is obtained by summing the log-likelihoods of each energy window pair (excluding LL as in previous Chapters):

\[
\mathcal{L}^{\text{tot}}(\theta) \triangleq \mathcal{L}(g_{UU} \mid \hat{g}_{UU}^{\text{unc}}(\theta) + \hat{g}_{UU}^{\text{rec}}) + \mathcal{L}(g_{UL} \mid \hat{g}_{UL}(\theta)) + \mathcal{L}(g_{LU} \mid \hat{g}_{LU}(\theta))
\]  

(7.6)

Please note that the total log-likelihood (Eq. 7.6) is different from the one used in MLAA-EB-S (Eq. 6.1) as all data are now in full resolution.

In previous chapter, we used an optimisation algorithm that simultaneously updates \( \lambda \) and \( \mu \). However, such an approach is feasible if both gradients are in the same scale and/or both scales are known. However, if the two variables are in different scales, this approach may lead to slow convergence. As we want to get closer to clinical data application (where
the two distributions do have different scales which moreover depend on the patient), an alternating approach is chosen to optimise the objective function (Eq. 7.6). Please note that this idea is different from MLAA-EB (5) as we are now in the case of one unique objective function maximisation. The activity and the attenuation estimates are updated using an alternating scheme with L-BFGS-B (Byrd et al. 1995):

\[
\mu^{k+1} = \mu^k - \xi \mu B \mu \nabla \mu \left[ L^{tot}(\lambda^k, \mu^k) - \beta \mu U_\mu (\mu^k) \right]
\]
\[
\lambda^{k+1} = \lambda^k - \xi \lambda B \lambda \nabla \lambda \left[ L^{tot}(\lambda^k, \mu^{k+1}) - \beta \lambda U_\lambda (\lambda^k) \right]
\]

(7.7)

where \(\nabla \lambda L^{tot}\) and \(\nabla \mu L^{tot}\) are the gradients of the objective function with respect to the current estimate of the activity and attenuation image, respectively, \(B_\lambda\) and \(B_\mu\) approximate the inverse Hessian matrix of \(L\), in \(\lambda, \mu\) respectively and \(\xi\) is the step-size, and \(U(\mu)\) are penalty functions weighted by global strength parameters \(\beta_\lambda\) and \(\beta_\mu\), respectively. For the results presented in this paper, the PLS penalty (Eq. 2.32) was chosen as penalty term.

Pseudo code for MLAA-EB-A is shown in Algorithm 6.

Algorithm 6: Pseudo-code for MLAA-EB-A.

Input: \(g_{LU}, g_{UL}, g_{LU}, \lambda_{init}, \mu_{init}, g_{LU}^{init}\);
Output: Estimated activity and attenuation images \(\lambda^{est}, \mu^{est}\);

\[\lambda_{0}^{0} \leftarrow \lambda_{init};\]
\[\mu_{0}^{0} \leftarrow \mu_{init};\]
\[\hat{g}_{LU}^{0} \leftarrow \hat{g}_{LU}^{init};\]

for \(t = 0, \ldots, \text{MaxOuterIter} - 1\) do

\[\text{for } k = 0, \ldots, \text{MaxInnerIterMu} - 1 \text{ do}
\]

\[\mu_{k}^{t} \leftarrow \text{LBFGS-B}(g_{LU}, g_{UL}, g_{LU}, \lambda_{0}^{t}, \mu_{0}^{t});\]

end

\[\mu_{0}^{t+1} \leftarrow \mu_{\text{MaxInnerIterMu} - 1};\]
\[\hat{g}_{LU}^{t+1} \leftarrow \text{SSS}(\lambda_{0}^{t}, \mu_{0}^{t+1});\]

\[\text{for } k = 0, \ldots, \text{MaxInnerIterLambda} - 1 \text{ do}
\]

\[\lambda_{k}^{t} \leftarrow \text{LBFGS-B}(g_{LU}, g_{UL}, g_{LU}, \lambda_{0}^{t+1}, \mu_{0}^{t});\]

end

\[\lambda_{0}^{t+1} \leftarrow \lambda_{\text{MaxInnerIterLambda} - 1};\]

end

\[\lambda^{est} \leftarrow \lambda_{\text{MaxOuterIter} - 1};\]
\[\mu^{est} \leftarrow \mu_{\text{MaxOuterIter} - 1};\]
7.5.4 Evaluation

The proposed method was initially evaluated against: (i) similar conditions as in previous chapters, i.e. using the correct forward model for simulating the input data; (ii) Monte Carlo generated data.

7.5.4.1 Phantom

A 3D volume from the XCAT torso phantom was used to investigate the performance of the proposed reconstruction method (Fig. 7.10).

7.5.4.2 STIR Projection data

STIR projection data were computed as illustrated in Sec. 7.1.2. The forward model (Sec. 7.1.1) uses the proposed efficiency model (Sec. 3.5.2.1) and the efficiency factors specific for scattered and unscattered events (Fig. 7.8). Experiments were conducted with and without a background of random events. Poisson noise was added to STIR simulated data so that STIR and GATE projection data had a similar noise level. The restriction operator $R$ (Sec. 3.2.2) was used to down-sample the images during the scatter simulation from the ground truth images with a factor 2 in x-y plane and of a factor 8 in z direction for the computation of the scatter forward model and gradient. The prolongation operator $P$ (Sec. 3.2.2) up-samples the estimated scatter in all the energy window of a factor 12 both in views and tangential position and of a factor 8 in axial direction.

Projection data are shown in Fig 7.13 (red curve).

7.5.4.3 GATE Monte Carlo generated data

Gate data were generated as explained in 7.1.3. Projection data are shown in Fig 7.13 (blue curve).

7.5.4.4 MLAA-S-alt

GATE Monte Carlo data reconstructions from MLAA-EB-A were compared against a reconstruction from a single energy window acquisition (UU) with scatter re-estimation: we implemented a Alternating Maximum Likelihood reconstruction of attenuation and activity with photpeak scatter re-estimation (MLAA-S-alt), which is a variation of MLAA-S (Sec. 6.2.4.4). Here the activity and attenuation images are updated in an alternating manner, to be consistent with the optimisation scheme of MLAA-EB-A. The rationale behind using an alternating scheme is the same as for MLAA-EB-A and is discussed in Sec. 7.5.3.
7.5. Joint estimation of activity and attenuation from Monte Carlo data

7.5.4.5 Reconstruction parameters

The activity and the attenuation updates of MLAA-EB-A use LBFGS (Sec. 2.1.3.3). Stopping criteria were set to the default values for LBFGS implementation (Byrd et al. 1995) (Tsai et al. 2017). The maximum number of inner iterations for the attenuation update (MaxInnerIterMu) was set to 5, whilst the one for the activity (MaxInnerIterLambda) was set to 12. The maximum number of outer iterations was set to 65.

In the current results, lung segmentation was incorporated in the algorithm by only updating the attenuation values within the inner cylinder/lung mask during iterations. The mask extends beyond the exact lung edges (Fig. 7.10). This constraint is not used for the emission update, for which we only assumed to know the support of the activity image (as in previous Chapters).

As the forward model slightly over-estimates the expected counts in the low-energy window (Fig 7.13, red curve) a heuristic global scaling factor $\zeta = 0.93$ was incorporated in the low-energy window normalisation so that the expected total counts from the analytical simulation matched the Monte Carlo simulation. The reconstruction was performed both with and without scaling factor to assess the effect of model mismatch.

7.5.4.6 Prolongation/Restriction operators:

Prolongation and restriction operators ($P$ and $R$) were used during the computation of the scatter gradient. Further details are given in Sec. 7.5.4.2.

7.5.4.7 Regularisation parameters

The MRAC (Fig. 7.10) image was used as anatomical image for the PLS prior. For MLAA-EB-A reconstructions, the penalty strength $\beta_\mu$ of the PLS prior on the attenuation image (Eq. 7.7) was set to 80; the penalty strength $\beta_\lambda$ of the PLS prior on the activity image (Eq. 7.7) was assigned to either the value of 1 or 5. Smoothing parameters (Eq. 2.32) were set to 0.03.

For reconstructions from UU windows only (MLAA-S-alt and LBFGS-AC), the penalty strength was reduced of a factor $f = \frac{Z_{UU}}{Z_{UU} + Z_{UL} + Z_{LU}}$. The log-likelihood values were computed from the ground truth images.

7.5.4.8 Initial conditions

The initial attenuation image (MRAC) was generated by decreasing the lung attenuation values by 15% with respect to the ground truth. The reconstruction was initialised with an activity estimate obtained by iterating between OSEM (3 subsets 100 sub-iterations) and SSS (Sec. 5.2.2.1) for one outer iteration. In the case of noisy simulations, the activity image
thus obtained was postfiltered with a Gaussian filter with a FWHM of 5mm.

7.5.4.9 Analysis:
The performance evaluation of MLAA-EB-A was conducted in terms of relative percentage error with respect to the ground truth. A visualisation of the bias in the reconstructed image was used as initial assessment. Further investigations were conducted in terms of MPE of the estimated images over iterations in different ROIs: (i) 10x10x5 ROI placed within the right lung, (ii) the whole image.

7.5.5 Results
Fig. 7.14 visualises the relative percentage error in the reconstructed activity and attenuation distributions from MLAA-EB-A from noise-free STIR simulated data. The initial error in the attenuation map is significantly reduced; the error in the activity image due to a wrong initial scatter estimate (in the region outside the lung) are visibly diminished. Overall, a slight amount of bias is still present in the estimated activity and attenuation images; however, both images converge in mean to the ground truth solution.

For this experiment, the lung mask was removed in the attenuation update after 20 iterations; the reconstruction remains stable to a mean percentage error lower than 2% in both $\mu$ and $\lambda$.

Fig. 7.15 shows the relative percentage error in the reconstructed activity and attenuation images using MLAA-EB-A from noisy STIR simulated data. Two different global penalty weights (Eq. 7.7) on the activity images were investigated: $\beta_{\lambda} = 1$ or $\beta_{\lambda} = 5$. The initial error in both the attenuation and activity images is significantly reduced. A higher bias seems to be present near the edge of the phantom, probably due to an excessive global weight of the prior on the attenuation image. However, the inner part of the lungs (excluding the edges) converges to the ground truth solution. This is confirmed by the ROI analysis in Fig. 7.15.

Fig. 7.16 shows the reconstruction error in the activity and attenuation images from GATE Monte Carlo generated data. The reconstruction was computed with and without scaling factor (Sec. 7.5.4.5), used to match the expected total number of counts from the ground truth images in all the energy windows with GATE data. Fig. 7.16 also compares the reconstruction to the one from both LBFGS-AC (Sec. 6.2.4.6), MLAA-S-alt from UU data (Sec. 7.5.4.4) and LBFGS-MRAC (activity reconstruction from the MRAC attenuation map); the unknown photopeak scatter is estimated iteratively. Overall, errors in the forward
7.5. Joint estimation of activity and attenuation from Monte Carlo data

Figure 7.14: Reconstruction error from the noise-free STIR simulated data reconstructed with MLAA-EB-A. First and second row: error in the attenuation. Third and fourth row: error in the activity image. First column: initial error (reconstruction input). Second column: reconstruction error. Graph: Mean percentage Error (MPE) within the ROIs over iterations relative to the estimated attenuation and the activity images.

Model propagate in the estimated activity and attenuation maps. In particular, effects of remaining model mismatch on the final estimates seem to arise in the region outside the lung - consistent in all the three reconstructions. With regards to the lung region, a better solution (closer to the one from LBFGS-AC) is achieved when a scaling factor is incorporated in the normalisation. Overall, ROI means from MLAA-EB-A (with $\zeta = 0.93$) and MLAA-S-alt appear similar.

7.5.6 Discussion

A new algorithm for the joint reconstruction of PET activity and attenuation in full resolution - including an accurate detection efficiency model - was proposed, named MLAA-EB-A. Prolongations and restriction operators (Sec. 3.2.2) were incorporated in order to input full resolution projection data and output full resolution images. Both operators were incorporated in the gradient of the scatter forward model. Please note that the incorporation of the prolongation operator $P$ in the scatter gradient implies that the photopeak scatter update could be computed during the reconstruction (potentially outperforming the one-step-late approach). However, computing the gradient for $\mathbf{b}^{\text{LU}}_{\text{ac}}$ would be more computationally expensive and it is unlikely to bring any benefit. However, this possibility will need to be investigated in the future.
Figure 7.15: Reconstruction error from the noisy STIR simulated data reconstructed with MLAA-EB-A. Penalty strengths: $\beta_\mu = 80$ and $\beta_\lambda = 1.5$. First and second row: error in the attenuation. Third and fourth row: error in the activity image. First column: initial error (reconstruction input). Second column: reconstruction error from a low penalty ($\beta_\lambda = 1$). Third column: reconstruction error from a higher penalty ($\beta_\lambda = 5$). Graph: Mean percentage Error (MPE) within the ROIs over iterations relative to the estimated attenuation and the activity images.
7.5. Joint estimation of activity and attenuation from Monte Carlo data

Figure 7.16: Reconstruction error from GATE Monte Carlo generated data. First and second row: error in the attenuation. Third and fourth row: error in the activity image. First column: initial error (reconstruction input). Second column: reconstruction error from MLAA-EB-A without heuristic normalisation scaling ($\zeta = 1$) factor in the low energy windows. Penalty strengths: $\beta_\mu = 80$ and $\beta_\lambda = 5$. Third column: reconstruction using from MLAA-EB-A an heuristic normalisation scaling factor for the low energy windows ($\zeta = 0.93$). Fourth column: reconstruction from MLAA-S-alt. Penalty strengths: $\beta_\mu = 60$ and $\beta_\lambda = 3$. Fifth column: emission reconstruction from LBFGS-AC. Penalty strength: $\beta_\lambda = 3$. Sixth column: emission reconstruction from LBFGS-MRAC (using the initial attenuation image). Graph: Mean percentage Error (MPE) within the ROIs over iterations relative to the estimated attenuation and the activity images. ROI means from MLAA-S-alt were also computed as comparison.
7.5. Joint estimation of activity and attenuation from Monte Carlo data

Results from the ‘full model’ noise-free simulations (Fig. 7.13, red curve) showed that MLAA-EB-A was able to satisfyingly reconstruct full resolution activity and attenuation images (Fig. 7.14). The outputs converge in mean to the ground truth solution (Fig. 7.14). However, a slight amount of bias is still present in the estimated activity and attenuation distributions, analogously to results from Chapter 6.

A further assessment was conducted from noisy data simulated using our software, from an activity distribution corresponding to a standard FDG acquisition. Here the incorporation of a penalty term was necessary to handle noise in the reconstructed images. A fine tuning of the penalty was not the objective of this study; however, some considerations can be made on this matter. First of all, the attenuation and activity updates required two different penalty strengths; in addition to this, even when the penalty on the attenuation image update was considerably high compared to the penalty on the activity image $\beta_\mu \approx 20 \beta_\lambda$, the estimated attenuation image still looks quite noisy. The penalty strength was not further increased as a positive bias was observed for higher $\beta_\mu$ values. Nevertheless, the activity update does not seem to significantly suffer from the presence of high noise in the attenuation map.

For both experiments, ROI mean values were computed in two different regions: (i) 10x10x5 ROI placed in the right lung, (ii) the whole image. The ROI analysis shows that the algorithm is able to reduce the initial error in both activity and attenuation images (from 15 % to less than 2 %). With regards to the activity image, the region outside the lung also shows a final error lower than 2 % for both noisy and noise-free simulations, meaning that the error in the photopeak scatter estimate is also reduced.

It is worth mentioning that results from STIR noise-free and noisy simulations were found in good agreement with results from previous Chapters. In particular, in spite of the smaller voxel size and the more complex acquisition model, the final error in the activity and attenuation estimate was comparable with XCAT results from Chapter 6.

A final assessment was conducted on GATE Monte Carlo generated data, in order to establish the effects of model mismatch on the estimated activity and attenuation maps. With appropriate adjustment of the model, results show that MLAA-EB-A is able to reduce the error due to the wrong assignment of population based attenuation values to the lung region on Monte Carlo simulated data (Fig. 7.16).

The output of MLAA-EB-A from GATE Monte Carlo simulated data was compared against an LBFGS-AC reconstruction from the correct attenuation image (Sec. 6.2.4.6) and
MLAA-S-alt (Sec. 7.5.4.4) from UU data. Results from MLAA-EB-A were obtained with and without a heuristic scaling factor ($\zeta = 1$ and, $\zeta = 0.93$) in the normalisation sinogram (Sec. 7.5.4.5), so that the number of total counts in the lower window matched the one from GATE for the ground truth images. From the relative percentage error (Fig. 7.16) shows that the incorporation of the scaling factor ($\zeta = 0.93$) leads to a final error in the activity estimate comparable to the one from an LBFGS-AC reconstruction. On the other hand, the MLAA-EB-A reconstruction with $\zeta = 1$ shows a final negative bias. A reconstruction from MLAA-S-alt (Sec. 7.5.4.4) was also added as further comparison. Results show that MLAA-EB-A and MLAA-S-alt converged in mean to a similar solution (according to results showed in Chapter 6). With regard to MLAA-S-alt reconstruction, the penalty strength in both attenuation and activity update was reduced according to the global scale of the likelihood ($\mathcal{L}_{UU} \text{ vs } \mathcal{L}_{UU} + \mathcal{L}_{UL} + \mathcal{L}_{LU}$) computed from the ground truth distributions. However, comparing reconstructions from different cost functions and penalty strength is challenging. Further assessments are required in this regard, such as varying the penalty strengths and investigating multiple noise realisations.

Some artefacts are present in all the reconstructed images, such as an asymmetric bias in the region outside the lung. This error is consistent in all the three reconstructions and is very likely due to inconsistency between model and the GATE data. Some experiments conducted on a cylindrical phantoms confirmed this hypothesis, but further investigations will be needed to correct for this effect.

According to the results presented in this Chapter, some aspects would favour MLAA-S-alt to MLAA-EB-A: (i) lower computational burden, (ii) no real need to accurately model detector scatter - for a standard single energy window acquisition -, (iii) no need to acquire data in multiple energy windows. However, MLAA-EB-A brings additional benefits due to the higher stability of the solution (shown in Chapter 6), as long as the forward model is sufficiently accurate. Furthermore, using multiple energy windows could allow the possibility of accounting for higher scattering angles, potentially avoiding the need of performing tail-fitting. One option could be to use MLAA-S-alt for the initial iterations and then switch to MLAA-EB-A. This hypothesis should be investigated in the future.

Overall, the following improvements on previous chapters were achieved: (i) possibility to account for the presence of unscattered counts in UL and LU windows, (ii) accounting for detector scatter, (iii) high resolution input and output, (iv) investigation of the input/model
mismatch on the estimated images. However, this study still has some limitations.

Although the expected events from the ground truth images (with the normalisation from the cylindrical phantom) were in good agreement with GATE generated data, the low-energy windows seemed to slightly overestimate the total number of counts (Fig. 7.13). Therefore, a scaling factor ($\zeta = 0.93$) was introduced so that analytical and Monte Carlo simulation could match in the total number of counts in all the energy windows. As both detection efficiency modelling and sensitivity calculations play a key role in the accuracy of the forward model (Sec. 7.4), this approach strongly depends on the accuracy of both corrections. The heuristic scaling would not be applicable to reconstruct real data acquisitions, but could be potentially overcome via improvement of the normalisation technique or the analytical model.

It is a possibility that the accuracy of the reconstruction could also vary with the incorporation of a different penalty term. Furthermore, the accuracy of the PLS depends on the reliability of the MR information. One option could be to use an image-based penalty (such as TV - Sec. 2.1.3.3). Alternatively, one could think to use the joint prior proposed in (Brusaferri et al. 2019b) which couples the activity and attenuation images. It relies on the expectation that the reconstructed attenuation and activity images are likely to share image structures and was found to be beneficial for MLAA-EB-S on simple phantoms. Further investigations will be needed to assess the behaviour of the penalty on more realistic data-sets.

Comparing the accuracy of the reconstruction with respect to different down-sampling factors for the scatter gradient calculation also remains to be addressed in the future. It is possible that reducing the down-sampling factor might lead to a better image estimate (however increasing linearly the computation time). The possibility of multiple-resolution reconstruction represents a topic of future research. For instance, one could think of varying the resolution of the estimated images during reconstruction.

The initial activity image and scatter estimates were deliberately chosen ‘wrong enough’ to assess the outcome of the algorithm in a sufficiently unfavourable initial condition. However, it is possible that different initialisation might lead to instability. Nevertheless, results from MLAA-EB-A (Chapter 6) suggest that the proposed method would still be more stable than a joint reconstruction from a single energy window.

One other aspect to consider is that MLAA-EB-A and MLAA-S-alt rely on an alternat-
ing approach, meaning that settings of inner loops are needed to be established. Although a few different iteration schemes were tested on some preliminary experiments, showing consistent results, it is possible that an optimal iteration scheme setting could lead to fast convergence; this is however beyond the scope of this thesis. The alternating approach was preferred given the different intensity scale of the activity and attenuation gradient. One possible solution could be to use the simultaneous approach (as in MLAA-EB-S) and to include pre-conditioning, similar to (Tsai et al. 2017).

In addition to the aforementioned limitations, assessing the accuracy of the reconstruction in the case of non-uniform lung values and in presence of lung lesions will be subject of future work. The cross-talk is expected to be higher for smaller structures. However, further studies will need to confirm this hypothesis.

Finally, future work could be directed towards exploring the benefits of using more than two windows, as well as the possibility of extending our approach to TOF-PET.

7.6 Conclusion

In this Chapter, the forward model was extended to overcome some of the assumptions of previous chapters, including detector scatter and the presence of unscattered events in the low energy window. Prolongation and restriction operators were also incorporated in the forward scatter model and its gradient in order to be able to handle high resolution input data. The forward model was compared with Monte Carlo generated data of a Siemens mMR acquisition, giving an insight of the realistic potential of this approach. The evaluation was conducted on phantoms of increasing complexity.

A new normalisation technique for multiple-energy window GATE data was also proposed. Results have shown that the detection sensitivity of the low energy window is significantly different from the one of the photopeak window.

The proposed reconstruction algorithm MLAA-EB-A was tested on both STIR and GATE simulated data. Results from STIR noise-free and noisy simulations were found in good agreement with results from previous Chapters. The algorithm was able to compensate for the assignment of wrong initial population values. A noise-suppressing penalty was incorporated for the case of noisy data. The fine tuning of the noise-suppressing term was found to be challenging.

GATE generated data were used to investigate the effects of input/model mismatch on the proposed reconstruction method. Results showed that for a sufficiently accurate forward
model, the output of the MLAA-EB-A reconstruction of GATE data matches closely an LBFGS-AC reconstruction which used the correct attenuation map. A further comparison with MLAA-S-alt evidenced that reconstructing GATE data from one energy window only (and re-estimating the scatter) could be sufficient to achieve a good quantification. However, comparing different objective functions and penalty strengths is challenging. One option for a practical algorithm implementation could be to start with MLAA-S-alt for the initial iterations and then further refine the reconstruction with MLAA-EB-A.

Multiple scatter events are not included in the model. Potentially, multiple scatter estimation (Tsoumpas et al. 2005; C. C Watson et al. 2018) could be incorporated into our algorithm using the same strategy as for the single scatter estimation in the photopeak window (one-step-late approach). However, accurate estimation of multiple scatter is likely to be more difficult and computationally expensive for the low energy windows. This could impact the performance of the proposed algorithms. The fraction of multiple scatters will be larger in LL in the case of a multiple energy window acquisition. It might therefore be beneficial to ignore this data, indicating another potential advantage of MLAA-EB-S compared to using a single wide energy window WW (as in Chapter 6). However, further studies will be needed to confirm this hypothesis.
Chapter 8

Conclusions

The problem of AC of PET images can be regarded as solved, to a large extent, for hybrid PET/CT scanners. However, it still represents a challenge for PET/MR systems where no existing relationship exists to map MR image intensities value to PET 511 keV attenuation coefficients (Wagenknecht et al. 2013).

Attenuation estimation strategies from PET data seem particularly promising for overcoming the quantification errors induced by conventional MR-based approaches (Berker et al. 2016). For thorax acquisitions, the MR-AC approach is prone to errors for two main reasons: (i) inaccuracy of population-based lung attenuation values, (ii) misalignment problems can arise due to patient motion between acquisition of MR and PET data.

One of the most popular method amongst the emission-based attenuation estimation methods is MLAA introduced in (Nuyts et al. 1999), a (penalised) maximum likelihood-based iterative algorithm that alternates between activity and attenuation estimation. This approach allows for the misalignment to be intrinsically accounted for during the acquisition of the image as both the activity and the attenuation distributions are reconstructed from the same data-set. Furthermore, it does not rely on a data-set of population attenuation values. However, in the absence of TOF, the joint estimation problem is strongly ill-posed (Defrise et al. 2012) and the activity and attenuation images estimated from non-TOF-MLAA suffer from cross-talk artefacts: the features of the activity map propagate into the attenuation map and vice versa.

Several groups (Berker et al. 2014; Conti et al. 2012; Manavaki et al. 2003) have considered the option of using scattered emission data to improve activity reconstruction accuracy. In fact, attenuation and scatter are intrinsically linked both on a physical level and when deriving the scatter and attenuation estimates. This idea has been explored in
both SPECT and PET to estimate both attenuation and activity. With regard to PET, state-of-the-art studies have been restricted to simple 2D phantoms and ideal energy resolution values.

The aim of this work was to assess the feasibility of joint reconstruction of the activity and attenuation distribution of 3D objects from multiple energy window measurements by using a maximum likelihood framework in a realistic setting.

In this chapter, the main conclusions of each of the previous Chapters are summarised. Then, an outline of the novel contributions follows. Subsequently, an overview of the possible topics of future work is given. Finally, a list of the publications that have arisen from the work presented in this thesis is presented; the list includes collaborations with other research projects, not mentioned in this thesis.

8.1 Summary of main conclusions

In Chapter 3, both the forward and the inverse problem at the core of this thesis were presented. The single scatter forward model was extended to the case of multiple energy window measurements. A formulation of the Jacobian of the multiple energy-window scatter forward model was given. Finally, implementation strategies were discussed. The forward model is given in its general formulation. However, early investigations used simplified assumptions. Throughout the thesis, many of the assumptions were gradually removed. Figure 8.1 shows the evolution of the forward model over the course of Chapter 4, 5, 6 and 7.

In Chapter 4, benefits of using different energy windows for each annihilation photon to perform attenuation estimation were discussed. A reconstruction algorithm MLTR-EB for transmission tomography is presented.

The potential advantages of incorporating an anatomical prior into the reconstruction algorithm were also explained. Results showed that without any prior information on the attenuation image, MLTR-EB is able to recover an attenuation map from scatter data only; albeit with low spatial resolution. Without any prior information, high resolution features could not be recovered. However, the presence of the PLS anatomical prior in the reconstruction was found to be beneficial for recovering some high resolution features and to suppress noise whilst enhancing phantom edges. Constraining the update to the lung region significantly helped MLTR-EB (similarly to (Berker et al. 2012b; Mehranian et al. 2015)) and convergence was reached in a few iterations.

In Chapter 5, a new method was presented, MLAA-EB-P, for the joint reconstruction
8.1. Summary of main conclusions

Figure 8.1: Evolution of the forward model throughout the chapters. The prolongation and restriction operators $P$ and $R$ are used as downsampling and upsampling operators in image and sinogram space, respectively.

of the activity and attenuation with a Maximum Likelihood estimation approach. MLAA-EB-P exploits both photopeak and lower energy window data to estimate the activity and the attenuation distribution of the object. It alternates between an activity estimate from the photopeak data and an attenuation estimation from low energy window data. This approach was found to be efficient and fast for small objects, but insufficient for patient-scale phantoms. A detailed analysis of the objective function values in an exemplar two-variable problem enabled us to investigate and understand the reason for such behaviour.

This study led to the conclusion that the idea of a ‘pseudo-maximisation’ of two different objective functions was to be abandoned; it also lay the foundation for the development of a new algorithm: MLAA-EB-S.

In Chapter 6, the MLAA-EB-S algorithm was presented to overcome the main chal-
8.1. Summary of main conclusions

The challenge of MLAA-EB-P: reconstructing patient-scale objects. An initial investigation is conducted with similar simplified assumptions as for MLAA-EB-P, i.e. absence of true counts in the low energy windows and a Gaussian efficiency model. The main difference between MLAA-EB-P and MLAA-EB-S lies in the fact that all energy window pairs are used for the estimation of both activity and attenuation, and the optimisation framework. The method was tested on digital 3D cylindrical phantoms and XCAT volumes.

Initial investigations demonstrated that MLAA-EB-S overcame the size-dependency problem of MLAA-EB-P. Then, MLAA-EB-S was compared against: (i) a simultaneous estimation from a single energy window (MLAA-S), (ii) an LBFGS implementation of MLAA and (iii) an emission estimation from the correct photopeak scatter and correct attenuation image (LBFGS-AC). Both MLAA-EB-S and MLAA-S re-estimate the photopeak scatter during the reconstruction. Quantitative results demonstrated that taking scatter into account reduces the cross-talk between the activity and attenuation images (as MLAA-S outperforms MLAA) and that by using multiple energy windows, MLAA-EB-S outperforms MLAA-S in terms of cross-talk reduction.

This study provides valuable evidence that the incorporation of scatter information is beneficial for joint activity and attenuation reconstruction in 3D non-TOF PET. Moreover, the results were obtained with simulations of a PET system with an energy resolution of 16%, similar to currently commercially available systems.

In Chapter 7, the forward model was extended to overcome some of the assumptions of previous chapters, including detector scatter and the presence of unscattered events in the low energy window. Prolongation and restriction operators were also incorporated in the forward scatter model and in the scatter gradient in order to be able to handle high resolution input data. The forward model was compared against Monte Carlo generated data of a Siemens mMR acquisition. The evaluation was conducted on point sources and 3D cylindrical phantoms. A new normalisation technique for multiple-energy window GATE data was also proposed. Results have shown that the detection sensitivity of the low energy window is significantly different from the one of the photopeak window, and that a specific normalisation technique for the case of multiple energy windows is to be considered. Subsequently, the proposed reconstruction algorithm MLAA-EB-A was tested on both STIR and GATE simulated data. Results from STIR noise-free and noisy simulations were found in good agreement with results from previous chapters, even with the more realistic modelling and
8.1. Summary of main conclusions

Clinically relevant voxel sizes. The algorithm was able to compensate for the assignment of wrong initial population values. A noise-suppressing penalty was incorporated for the case of noisy data. The fine tuning of the noise-suppressing term was found to be challenging. GATE generated data were used to investigate the effects of input/model mismatch on the proposed reconstruction method. Results showed that for a sufficiently accurate forward model, the output of the MLAA-EB-A reconstruction of GATE data matches closely an LBFGS-AC reconstruction that used the correct attenuation map. A further comparison with MLAA-S-alt (reconstruction algorithm from a single energy window with scatter re-estimation) showed that reconstructing data from only the “traditional” photopeak window could be sufficient to achieve a good estimate of the attenuation map, as long as re-estimating the scatter is incorporated during the iterative estimation. Together with the fact that MLAA-EB-A was shown to be sensitive to errors in the forward modelling of the data in the lower energy windows, this raises the question if the use of multiple energy windows will be beneficial in practice. This is discussed in the future work section.

Improvements of MLAA-EB-A over the previous reconstruction methods presented in this thesis as well as other state-of-the-art methods are summarised in Table ?? These improvements include: (i) accounting for the presence of detector scatter, (ii) accounting for the presence of true events in all the energy windows, (iii) being able to input/output full resolution data/images.

In summary, the incorporation of the low energy photon information in PET image reconstruction has been investigated throughout this thesis. Methodologies to improve on existing methods, and to exploit the energy information available in non-TOF-PET have been proposed and implemented. The advantages of incorporating the MR information were also discussed. The potential for such a method of attenuation correction has wide appeal in PET/MR imaging because of the requirement to overcome quantitative errors of conventional MR-AC methods.

Overall, the added value of combining unscattered and scattered data has been demonstrated in this thesis. This work eliminates the dependency of over-simple assumptions that have been included in other previous work, such as: taking into account the finite energy resolution of PET detectors, reconstructing 3D volumes with data simulated for a clinical PET/MR system in the presence of noise and considering the presence of detector scatter. The Chapters of this thesis have progressed this technique from being a simple idea - only
supported by proof-of-concept studies - to having a solid understanding of the method and its limitations. Multiple energy window reconstruction was here explored in all its facets. One crucial finding is related to the importance of an accurate detection efficiency model and normalisation technique. Furthermore, the evaluation of the proposed algorithm on Monte Carlo generated data constitutes a significant step towards real data application in PET imaging of this type of methodology. Investigating the possibility of translating this approach in clinical practice remains the objective of future work.

8.2 Summary of original contributions

The main contributions provided by the author among the research presented in this thesis are summarised below.

8.2.1 Algorithm development

- Derivation and evaluation of the single scatter gradient from the forward model proposed in (C. C Watson et al. 1996) and extended in (Brusaferri et al. 2017).

- Development of MLTR-EB, a reconstruction algorithm for transmission tomography.

<table>
<thead>
<tr>
<th>Table 8.1: Comparison of reconstruction methods presented in this thesis with other state-of-the-art methods for JRAA from multiple energy window data</th>
<th>MLTR-EB</th>
<th>MLAA-EB-P</th>
<th>MLAA-EB-S</th>
<th>MLAA-EB-A</th>
<th>Literature 1</th>
<th>2</th>
<th>3</th>
</tr>
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<tr>
<td>One objective function</td>
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<td>x</td>
<td>✓</td>
<td>✓</td>
<td>x</td>
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<tr>
<td>Second-order optimisation method</td>
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<td>✓</td>
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<td>x</td>
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<tr>
<td>3D input/output</td>
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<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
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<td>x</td>
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<tr>
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<td>✓</td>
<td>✓</td>
<td>✓</td>
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<td>x</td>
</tr>
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<tr>
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<td>✓</td>
<td>✓</td>
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<tr>
<td>Activity est</td>
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<td>✓</td>
<td>✓</td>
<td>x</td>
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<td>Full res photopeak data</td>
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<tr>
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<tr>
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<td>✓</td>
<td>✓</td>
<td>x</td>
<td>x</td>
</tr>
</tbody>
</table>

1 PET methods: Berker et al. 2017a and Berker et al. 2019.
2 SPECT method: Cade et al. 2013
8.2. Summary of original contributions

Figure 8.2: Scatter is the enemy

from low energy data.

- Development of MLAA-EB-P, a reconstruction algorithm for alternating estimation of attenuation, activity and photopeak scatter via ‘pseudo-maximisation’ of the likelihood functions from multiple energy window input data; suitable for low resolution images and low resolution input data.

- Development of MLAA-EB-S, a reconstruction algorithm for the simultaneous estimation of attenuation, activity and photopeak scatter from multiple energy window input data; suitable for low resolution images and low resolution input data.

- Development of MLAA-S, a reconstruction algorithm for the simultaneous estimation of attenuation, activity and photopeak scatter from a single energy window input data; suitable for full resolution images and full resolution input data. Computationally feasible due to one-step-late photopeak scatter re-estimation.

- Development of MLAA-EB-A, reconstruction algorithm for the simultaneous estimation of attenuation, activity and photopeak scatter; suitable for full (spatial) resolution images and full (spatial) resolution input data.

- Development of a normalisation technique suitable for low energy window data.

8.2.2 Algorithm implementation

- Implementation of the single scatter Gradient in C++ within the STIR code for the Single Scatter Simulation. (source code implemented on a private fork of STIR, copyrighted by UCL).
8.3 Suggestions for future work

Several aspect of the research presented in this thesis would benefit from further investigation.

In most of the thesis, evaluations were performed restricting the attenuation update to the lung region (Chapter 5, 6, 7). Among the different tissue classes defined in standard MRAC methods, the lungs have the largest variability of inter-patient attenuation values (Mehranian et al. 2015). Therefore, this assumption is fairly common in PET/MR studies (Mehranian et al. 2015; Berker et al. 2012b). However, the methods developed in this thesis do not depend on the mask and preliminary results in Chapter 4 indicate that this assumption could be relaxed, potentially with the help of the incorporation of prior information. This hypothesis was tested in (Brusaferri et al. 2019b) on simple phantoms. Therefore, assessing
the feasibility of the incorporation of a synergistic prior on XCAT phantom reconstructions could be an interesting research study.

The possibility of handling high resolution input images was addressed via the introduction of prolongation and restriction operators into our reconstruction method (Chapter 7). However, the ability to estimate high frequency features in the attenuation map still needs further investigation. For example, a study involving the reconstruction of images with lung lesions of different diameters should be considered. We expect that cross-talk effects to be higher in correspondence of high resolution features in the activity (potentially versus low resolution features for the attenuation) as the scatter information is unlikely to be able to recover these features (as observed in Chapter 4). However, this hypothesis will be needed to be confirmed.

In all the experiments conducted in this thesis, the lung attenuation value was constant. However, lung attenuation values vary both within the lung region itself and during respiration (Holman et al. 2016). As no mathematical constraint was applied to the lung values, the method should be able to recover such variations. Nevertheless, further studies are required to confirm this hypothesis.

In order to be able to apply the proposed methodology to real data measurements, several things still remain to be investigated. First, assessing the feasibility of this method on patient data would bring additional value to this proposed method. However, to make this approach applicable in clinics, further efforts would be required. These include the need of accounting for multiple scatters and out-of-fov scatters, and to improve on the normalisation method. Second, there is a need to validate the proposed detection efficiency model on real measurements from clinical scanners.

According to the results presented in Chapter 7, some aspects would favour a practical application of MLAA-S-alt compared to MLAA-EB-A: (i) lower computational burden, (ii) no real need to accurately model detector scatter - for a standard single energy window acquisition -, (iii) no need to acquire data in multiple energy windows. However, MLAA-EB-A brings additional benefits due to the higher stability of the solution (shown in Chapter 6), providing that the forward model is sufficiently accurate. Furthermore, using multiple energy windows could allow the possibility of accounting for higher scattering angles in the model, potentially avoiding the need of performing tail-fitting. Given the lower computational cost, one practical option could be to use MLAA-S-alt for the initial iterations and then use
8.3. Suggestions for future work

MLAA-EB-A to further refine the solution. This hypothesis should be investigated in the future.

The incorporation of the prolongation operator $P$ (Sec. 3.2.2) in the scatter gradient implies that the photopeak scatter update could be computed during the reconstruction in both MLAA-S-alt and MLAA-EB-A (potentially outperforming the one-step-late approach). However, computing the gradient for $\tilde{g}_{sc}$ (Sec. 7.1.1) would be more computationally expensive and it is unlikely to bring any benefit. However, this possibility could represent an interesting future study.

Multiple scatter estimation (Tsoumpas et al. 2005; C. C Watson et al. 2018) could be incorporated into our algorithm using the same strategy as for the single scatter estimation in the photopeak window (one-step-late approach). However, this will need adapting existing multiple scatter estimation code to using multiple energy windows, and establishing the accuracy of the existing multiple scatter models for low energy windows. For a multiple energy window acquisition the prevalence of multiple scatters is expected to be predominantly restricted to LL. A study could therefore be performed to establish the percentage of multiple scatter events in each energy window pair. This would then form the basis for deciding optimal energy window pairs for the optimisation.

The normalisation method proposed in Chapter 7 relies on the possibility of differentiating between scattered and unscattered events, which is possible in Monte Carlo simulations, but not in real measured data. One possible solution for measured data could be the following. First, the unscattered counts efficiency factors could be obtained from a thin moving line source as in (Badawi et al. 1996). Once obtained, the true counts efficiency factors could be incorporated in the forward model so that the only unknown sensitivity is the one related to the scatter events. Then, the scatter sensitivity could be estimated from the total measured events on other phantom data where scatter is present.

The incident angles of the incoming scattered photons depend on the actual scatter distribution. This indicates that in practice, the normalisation factors for the scattered data are likely to be object dependent. Therefore, future studies should investigate the effects of phantom geometry on the normalisation sinograms.

One other aspect to mention is that MLAA-EB-A and MLAA-S-alt Chapter 7 rely on an alternating approach, meaning that settings of inner loops are needed to be established. The alternating approach was preferred given the different intensity scales of the activity and
8.3. Suggestions for future work

One possible way to avoid the alternating scheme could be to use the simultaneous approach (as in MLAA-EB-S and MLAA-S) and to include pre-conditioning, similar to (Tsai et al. 2017).

Having a scanner with better energy resolution is also likely to further improve on the proposed methodology. A better energy resolution reduces the uncertainty in the scatter point location; encouraging results in TOF-PET imaging come from the work of (Conti et al. 2012), showing that the spatial information carried by the scatter (in the case of excellent energy and time resolutions) was found to be almost as good as the spatial information carried by the trues in absence of TOF information.

The possibility of extending our method to TOF-PET would therefore represent an interesting direction of future research. The TOF information could improve on the poor conditioning of the problem, but comes with the main limitation of a global scaling factor in the estimated activity distribution (Defrise et al. 2012). Exploring whether the scatter information could solve the scaling issues of TOF-MLAA could be an interesting direction for future research studies. Furthermore, MLAA-type algorithms are known to be limited by the possibility of estimating attenuation values in LORs within the support of the activity distribution (Mehranian et al. 2015). However, by using additional information from scatter events it is possible that both MLAA-S and MLAA-EB-S could recover more of the attenuation image. This hypothesis was also suggested in Berker et al. 2014 and will be investigated in future studies.

Out-of-fov scatters could be also accounted for by our method as the only constraint on the scatter locations is given by the boundaries of the attenuation map. The template image given to the algorithm could be extended beyond the FOV to place scatter locations outside the edge of the scanner. Similarly to how the arm regions were recovered in Chapter 4, the methods proposed in this thesis that take scatter into account for the joint reconstruction might allow estimating activity and attenuation elsewhere, albeit mostly likely at low spatial resolution.

Finally, the possibility of improving on the reconstruction methods discussed in this thesis by using more than two energy windows should be investigated. Both the theoretical framework of the proposed methods and their implementations are suitable for this extension. However, the computational complexity of the algorithm scales exponentially with the number of energy windows. Therefore, an optimal value for the energy window should be
found where the computational cost in the algorithm is offset by the quantitative accuracy of the result.

8.4 Publications and presentations

8.4.1 Peer-Reviewed Journals

8.4.1.1 Published


8.4.1.2 Work in progress

- E. C. Emond, A. Bousse, **L. Brusaferri**, A.M. Groves, B.F. Hutton, K. Thielemans, “Improved PET/CT Respiratory Motion Compensation by Incorporating Changes in Lung Density.”

8.4.2 Conference proceedings

8.4.2.1 Published


8.4.2.2 Accepted for publication


8.4.3 Published conference abstracts

• L. Brusaferri, A. Bousse, Y.-J. Tsai, D. Atkinson, S. Ourselin, B. F. Hutton, S. Arridge and K. Thielemans. “Attenuation estimation using non-TOF PET scattered photon energy information and an anatomical MRI prior”. [oral presentation] In 7th Conference on PET-MRI and SPECT-MRI (PSMR), Isola d’Elba, Italy, 2018

• L. Brusaferri, A. Bousse, D. Atkinson, S. Ourselin, C. C. Watson, B. F. Hutton, S. Arridge and K. Thielemans. “Effects of detected photon energies and phantom size on MLAA from scattered and unscattered data”. [oral presentation] In 9th Conference on PET-MRI and SPECT-MRI (PSMR), Munich, Germany, 2019

8.4.4 Other presentations


• L. Brusaferri and K. Thielemans. “Scattered data to improve quantification in non-TOF MLAA”. [oral presentation] In CDT Summer School, Edinburgh, UK, 2019
Appendix A

**XCAT 3D phantom**

Recent advances in computerised digital phantoms have resulted in the development of phantoms able to provide an accurate (virtual) model of the patient’s anatomy and physiology and represent a useful tool to evaluate new imaging techniques. The main advantage in using digital phantoms is that the exact anatomy of the phantom is known, thus furnishing a “ground truth” from which to evaluate and improve imaging devices and techniques. The XCAT phantom (Segars et al. 2010), for example, provides a realistic and flexible model of the entire human body for the study of medical imaging techniques such as CT, PET, and SPECT.
Appendix B

GATE Voxelized source and phantom

To import digital phantoms or patient data as a voxelised geometry, GATE uses a special “navigator” algorithm that allow to track particles from voxel to voxel. The default navigation algorithm performs fast direct neighbouring voxel identification without a large memory overhead. Recently, some GATE developers have proposed a new method for efficient particle transportation in voxelised geometry for Monte Carlo simulations, named Regionalised parametrisation method. It was shown to significantly reduce computational time compared to other methods. This approach was therefore chosen for the simulations presented in this Chapter, mainly for computational reasons.

In this work, the voxelised input phantom was converted to an interfile format for use in the GATE toolkit. The input volume was assigned to five different tissue classes: lung, body, adipose, muscle and spine bone. The administered doses to various organs such as the skin, cord, brain, eye, lung, heart was estimated from patient measurements conducted in our departments.
Appendix C

Implementation of the unlisting procedure for multiple energy window sinograms into the STIR library

List-mode files (Sec. 2.1.2) outputted by PET scanners store the energy of the detected gamma photons into a given number of energy bins. In the vast majority of commercial PET scanners, a single energy bin is used. Therefore, the only available energy information is related to whether the measured energy falls within a certain energy acceptance window.

In the original STIR code, the energy bin information is not used during the unlisting process, and only one sinogram is outputted in the case of non-TOF PET. The unlisting code was extended to properly handle the energy information in the list-mode file similarly to (Efthumiou et al. 2019) for the case of TOF bin information.

These extensions include the following. A class `CListEnergy` was created, for storing and using an energy record from a listmode file. Furthermore, the function `get_bin_for_det_pair` in `ProjDataInfoCylindricalNoArcCorr` was modified so that the energy information could be correctly handled during the unlisting process.

The aforementioned modifications made to the unlisting framework are generic and are therefore not restricted to GATE input data only.
Appendix D

Consistency of STIR and GATE coordinate systems

For an odd x-y number of voxels, the 0 coordinate is placed consistently in the centre of the image for both STIR and GATE. However, for an even x-y number of voxels, the 0 coordinate is half a pixel off between STIR and GATE. Therefore, the source image need to be shifted accordingly in the GATE simulations for an input image with an even x-y number of voxels. Furthermore, x-y GATE and STIR axes were found to be tilted by $2.896\degree$ (corresponding to an offset of 4 detectors). The unlisting framework was modified to correct for these factors.
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