June 2012

MRI-Based Attenuation Correction in Emission Computed Tomography

Harry R. Marshall
*The University of Western Ontario*

Supervisor
Robert Z Stodilka
*The University of Western Ontario*

Graduate Program in Medical Biophysics

A thesis submitted in partial fulfillment of the requirements for the degree in Doctor of Philosophy

© Harry R. Marshall 2012

Follow this and additional works at: [https://ir.lib.uwo.ca/etd](https://ir.lib.uwo.ca/etd)

Part of the *Biomedical Devices and Instrumentation Commons, Medical Biophysics Commons, Nuclear Commons*, and the *Radiology Commons*

**Recommended Citation**


[https://ir.lib.uwo.ca/etd/559](https://ir.lib.uwo.ca/etd/559)

This Dissertation/Thesis is brought to you for free and open access by Scholarship@Western. It has been accepted for inclusion in Electronic Thesis and Dissertation Repository by an authorized administrator of Scholarship@Western. For more information, please contact tadam@uwo.ca.
MRI-BASED ATTENUATION CORRECTION IN EMISSION COMPUTED TOMOGRAPHY

by

Harry R. Marshall

Graduate Program in Medical Biophysics

A thesis submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy

The School of Graduate and Postdoctoral Studies
The University of Western Ontario
London, Ontario, Canada

© Harry R. Marshall 2012
The thesis by

Harry Robert Marshall

entitled:

MRI-Based Attenuation Correction in Emission Computed Tomography

is accepted in partial fulfillment of the requirements for the degree of Doctor of Philosophy

Date

Chair of Examining Board
Abstract

The hybridization of magnetic resonance imaging (MRI) with positron emission tomography (PET) or single photon emission computed tomography (SPECT) enables the collection of an assortment of biological data in spatial and temporal register. However, both PET and SPECT are subject to photon attenuation, a process that degrades image quality and precludes quantification. To correct for the effects of attenuation, the spatial distribution of linear attenuation coefficients (\(\mu\)-coefficients) within and about the patient must be available. Unfortunately, extracting \(\mu\)-coefficients from MRI is non-trivial. In this thesis, I explore the problem of MRI-based attenuation correction (AC) in emission tomography.

In particular, I began by asking whether MRI-based AC would be more reliable in PET or in SPECT. To this end, I implemented an MRI-based AC algorithm relying on image segmentation and applied it to phantom and canine emission data. The subsequent analysis revealed that MRI-based AC performed better in SPECT than PET, which is interesting since AC is more challenging in SPECT than PET.

Given this result, I endeavoured to improve MRI-based AC in PET. One problem that required addressing was that the lungs yield very little signal in MRI, making it difficult to infer their \(\mu\)-coefficients. By using a pulse sequence capable of visualizing lung parenchyma, I established a linear relationship between MRI signal and the lungs’ \(\mu\)-coefficients. I showed that applying this mapping on a voxel-by-voxel basis
improved quantification in PET reconstructions compared to conventional MRI-based AC techniques.

Finally, I envisaged that a framework for MRI-based AC methods would potentiate further improvements. Accordingly, I identified three ways an MRI can be converted to $\mu$-coefficients: 1) segmentation, wherein the MRI is divided into tissue types and each is assigned an $\mu$-coefficient, 2) registration, wherein a template of $\mu$-coefficients is aligned with the MRI, and 3) mapping, wherein a function maps MRI voxels to $\mu$-coefficients. I constructed an algorithm for each method and catalogued their strengths and weaknesses. I concluded that a combination of approaches is desirable for MRI-based AC. Specifically, segmentation is appropriate for air, fat, and water, mapping is appropriate for lung, and registration is appropriate for bone.

Keywords: PET/MRI, SPECT/MRI, hybrid imaging, attenuation correction, lung density, segmentation, registration, mapping
Co-Authorship

None of the research chapters contained herein were produced alone. The following credits all co-authors and details their contributions, followed by my contributions.

Chapter 2 was co-authored by Dr. Robert Z. Stodilka, Dr. Jean Théberge, Dr. Eric Sabondjian, Dr. Alexandre Legros, Ms. Lela Deans, Ms. Jane M Sykes, Dr. R. Terry Thompson, and Dr. Frank S. Prato. Drs. Stodilka, Théberge, Legros, Thompson, and Prato helped conceive, formalize, and develop the idea, Drs. Stodilka, Théberge, and Sabondjian, Ms. Deans, and Ms. Sykes assisted with the experimental design, Drs. Théberge and Sabondjian, Ms. Deans, and Ms. Sykes partook in data collection, Drs. Stodilka and Sabondjian contributed to the data analysis, and Drs. Stodilka, Théberge, Thompson, and Prato critically reviewed the manuscript. I collected the data, coded the attenuation correction algorithm, designed and conducted the analysis, and wrote the manuscript.

Chapter 3 was co-authored by Dr. Frank S. Prato, Ms. Lela Deans, Dr. Jean Théberge, Dr. R. Terry Thompson, and Dr. Robert Z. Stodilka. Drs. Prato and Stodilka helped conceive, formalize, and develop the idea, Drs. Prato, Stodilka, and Théberge, and Ms. Deans assisted with the experimental design, Ms. Deans partook in data collection, and Drs. Prato, Théberge, Thompson, and Stodilka contributed to the data analysis in addition to critically reviewing the manuscript. I conceived the idea, designed the experiment, collected the data, coded the attenuation correction
algorithms, designed and conducted the analysis, and wrote the manuscript.

Chapter 4 was co-authored by Dr. Frank S. Prato, Mr. John Patrick, Dr. David Laidley, Mr. John Butler, Dr. Jean Théberge, Dr. R. Terry Thompson, and Dr. Robert Z. Stodilka. Dr. Stodilka and Mr. Patrick helped conceive, formalize, and develop the idea, as well as assisting with the experimental design, Mr. Patrick and Mr. Butler partook in data collection, Dr. Laidley contributed to the data analysis, and Drs. Stodilka, Théberge, Thompson, and Prato, and Mr. Patrick critically reviewed the manuscript. I conceived the idea, designed the experiment, collected the data, coded the attenuation correction algorithms, designed and conducted the analysis, and wrote the manuscript.
To Laura,

for filling my life

with love and laughter.
Acknowledgments

No man is an island, and a veritable archipelago of individuals have helped make this thesis a reality. First and foremost, I would like to thank my supervisor, Dr. Rob Stodilka. Whenever I ran into a problem, big or small, he was always there to guide me through it. Moreover, despite remaining mindful of the challenges imposed by my tight timeline, Rob still granted me a great deal of independence, encouraging me to pursue the problems that interested me. This not only made my entire Ph.D. lots of fun, but was indispensable in building my confidence as a young scientist. So thank you Rob for all you’ve done; you are ever an inspiration to me.

Next, I would like to thank my advisory committee members, Dr. Frank Prato, Dr. Terry Thompson, and Dr. Ian Cunningham. At our first meeting, you were all very kind and encouraging, which was exactly what I needed as a nervous student just starting his project. By the time our second meeting came about, I thought I knew much more than I had before, and entered with a swagger. Within ten minutes, my cocksure attitude has dissipated, and by the time I departed I was an empty, broken shell of a man. There’s nothing like an advisory committee to teach humility, and I got that lesson in spades. But, as before, it was exactly what I needed. It taught me to be cautious in my assertions, prudent in my claims, and wary of my assumptions, qualities that have served me well ever since (especially in subsequent committee meetings). In all seriousness though, thank you for your insightful comments and
critiques, they have been of tremendous value. It is also to you that I attribute my understanding of what a thesis should be.

Additionally, though he did not sit on my advisory committee, Jean Théberge played just as important a role in my work. Whether he was revising manuscripts, helping plan experiments, or conveying some aspect of his vast knowledge of MRI, Jean has been helping me since the beginning, and for that I am very grateful.

And speaking of MRI, I would not have been able to conduct any of my experiments without John Butler. Not only did he teach me how to use the Verio, he spent countless hours helping me fiddle with pulse sequences to get them working properly. Further, he was kind enough to run the scanner whenever I required patient data. His professional demeanour clearly put them at ease, and made collecting data for Chapter 4 a pleasure.

The other key piece of imaging equipment I required was, of course, the PET/CT. I owe a great debt to Jenn Hadway, Dr. Aaron So, and Dr. Steve Ross, all of whom altruistically imparted their expertise regarding the operation of the Discovery VCT. A special thank you to Jenn for tolerating my many, many emails to the effect of “Can I use the PET/CT tonight?”. 

With respect to PET/CT skills, however, I did not hold a candle to the nuclear medicine techs, Don Kuhl, Ben Reyes, Gina Iacobelli, Karen Keys, Peter Masters, Paul Sery, and Jessica Wall. Not only did they patiently endure my frequent questions and missteps, they were responsible for all the patient PET/CT data in Chapter 4. Incidentally, I would not have been able to recruit any patients for my study if not for Lindsay Douglas and Tracy Zurbrigg, the masters of the nuclear medicine front desk. Lindsay, thank you for organizing and mailing that endless stream of letters of intent, and Tracy, thank you for allowing me to sit next to you as I lay in wait for my next unsuspecting victim.
Assuredly, many of my experiments relied on dogs, not patients. It is the expertise Lela Deans, Jane Sykes, and Terrie Ann Campbell that these experiments were made possible. They deftly navigated the complex, obtuse world of animal use protocols, and were nothing short of exceptional when handling the canines, which in one case involved the swift administration of propofol to a dog who was awaking in the PET/CT, followed by cardiopulmonary resuscitation when that same dog crashed in the MRI. Thanks to the vet techs’ unmatched talent, the dog was just fine.

I would also like to thank my lab for their support. Eric Sabondjian, Omar El-Sherif, and John Patrick have been outstanding colleagues and collaborators. It was Eric who taught me the ins and outs of working with $\gamma$-ray emitters, as well as how to operate the SPECT/CT. I always felt I could turn to him when I was stuck, a bit like an older brother. If Eric was like an older brother, then Omar was more like a twin sibling. Our similar ages, academic stages, and interests made him an ideal person to commiserate with over the trials and tribulations of graduate school, though I’m glad we got to celebrate its benefits on the tropical sands of Hawai’i and in the frigid air of Sweden. Finally, despite his seniority in a strict chronological sense, I believe that initially I was to John as Eric was to me. Now, having passed on all the information I have, it remains an absolute pleasure to speak with John about MRI-based attenuation correction, amongst life’s other points of interest.

Numerous others have helped shape this project, be it through discussion, planning, revision, or otherwise. In particular, I would be remiss not to acknowledge Dr. William Pavlosky, Dr. Gerry Wisenberg, Dr. David Laidley, Dr. Irina Rachinsky, Dr. Jean-Luc Urbain, Dr. James White, Dr. Donna Goldhawk, Dr. Kim Blackwood, and Dr. Jodi Miller. Additionally, thank you to Brenda Dubois, Michele Avon, and Shelagh Ross for assisting me with all things administrative.

Also, I cannot in good faith fail to state my appreciation for my peers (and former
peers) in the M.D./Ph.D. program. Notably, Dr. Derek Cool, Dr. Tom Appleton, Dr. Michael Berger, Dr. Matt Lanktree, and Dr. Piya Lahiry have all served as mentors, helping guide me through the program. I am equally grateful for my other brothers- and sisters-in-arms, perhaps especially Pencilla Lang, one of the few M.D./Ph.D. students who shares the frustrations of working in medical imaging. Finally, without the outstanding (former) leadership of Dr. Jim Lewis and administrative gifts of the seemingly omniscient Vicki Vanstrien, our program would not exist at all, and Western would be worse for it.

But for all the aptitude, intelligence, emotional support, and goodwill on Earth, no research would ever get done without money. For their generous financial contributions, I would like to thank my sources of funding, including the Natural Sciences and Engineering Research Council of Canada, the Canada Foundation for Innovation, the Canadian Institutes of Health Research, the Ontario Research Fund, and Multi-Magnetics Incorporated.

In closing, I wish to thank those closest to me, for without them I surely would have gone mad a few months in. Nate and Kate Denig, Chris Rennick, and Sandra Rohfrietsch, thank you for being the best friends I could have asked for. I hope that in the years and decades to come, that never changes. Mom, thank you for supporting me not just through my Ph.D., but through my whole life prior. You and Dad have been tremendous parents to me since the very beginning. And last but certainly not least, to my wife Laura, thank you for everything: for your love, devotion, patience, and kindness. Thank you for helping me rise early and get to bed at a reasonable hour, thank you for interrupting my work with your hugs and lovely smile, and thank you for rescuing me from my dearth of common sense. But most of all, thank you for giving a simple nerd a beautiful life.
# Contents

Certificate of Examination .................................. ii

Abstract .................................................................... iii

Co-Authorship ............................................................. v

Dedication .................................................................. vii

Acknowledgments ....................................................... viii

Contents .................................................................... xii

List of Tables ................................................................ xvi

List of Figures ........................................................... xvii

List of Appendices ..................................................... xix

Nomenclature ............................................................ xx

## 1 A Bird’s Eye Perspective of Attenuation Correction in PET/MRI  1

1.1 Introduction ....................................................... 1

1.2 The Value of Quantitative PET/MRI ....................... 4

1.2.1 Oncology ...................................................... 4

1.2.2 Neurology ..................................................... 7

1.2.3 Cardiology ..................................................... 10

1.3 Factors Influencing Quantification ......................... 14

1.3.1 PET Physics Primer ....................................... 14

1.3.2 Physical Factors .......................................... 20

1.3.2.1 Photon Statistics ..................................... 20

1.3.2.2 Spatial Resolution and the Partial Volume Effect 23

1.3.2.3 Observed Radiopharmaceutical Distribution 27

1.3.3 Biological Factors .......................................... 28

1.3.4 Technical Factors .......................................... 31

1.3.4.1 Image Reconstruction ............................... 31
3 Variable Lung Density Consideration in Attenuation Correction of Whole-Body PET/MRI 124
3.1 Introduction ........................................ 124
3.2 Materials and Methods ............................ 125
  3.2.1 Experimental Protocol .......................... 125
  3.2.2 Subjects .......................................... 127
  3.2.3 Imaging ......................................... 127
  3.2.4 Image Registration ............................... 129
  3.2.5 Image Segmentation ............................. 129
  3.2.6 Quantitative Analysis ......................... 130
3.3 Results ............................................. 132
3.4 Discussion ......................................... 141
3.5 Conclusion .......................................... 145
References ........................................... 146

4 To Segment, Register, or Map? A Comparison of Three MRI-Based Attenuation Correction Methods for Whole-Body PET 150
4.1 Introduction ........................................ 150
4.2 Materials and Methods ............................ 151
  4.2.1 Data Acquisition ................................ 151
  4.2.2 MRI-Based $\mu$-Maps from Segmentation .... 153
  4.2.3 MRI-Based $\mu$-Maps from Registration ..... 155
  4.2.4 MRI-Based $\mu$-Maps from Mapping ...... 155
  4.2.5 Processing the MRI-Based $\mu$-Maps ....... 156
  4.2.6 Data Analysis .................................. 157
4.3 Results ............................................. 158
  4.3.1 Overview ....................................... 158
  4.3.2 Global .......................................... 158
  4.3.3 Local ........................................... 164
4.4 Discussion ......................................... 166
  4.4.1 Overview ....................................... 166
  4.4.2 Lungs .......................................... 166
  4.4.3 Fat .............................................. 167
  4.4.4 Water .......................................... 167
  4.4.5 Bone ........................................... 168
  4.4.6 Lesions ........................................ 169
  4.4.7 Hybrid Approaches ............................. 169
  4.4.8 Errors from Image Registration ............ 170
4.5 Conclusion .......................................... 171
References ........................................... 172
5 Expanding Horizons

5.1 MRI-Based AC in SPECT
   5.1.1 Where We Stand
   5.1.2 Where To Go

5.2 MRI-Based AC in the Lungs
   5.2.1 Where We Stand
   5.2.2 Where To Go

5.3 MRI-Based AC Algorithms
   5.3.1 Where We Stand
   5.3.2 Where To Go

5.4 Conclusion

References

A Ethics Approvals

B Copyright Releases

C Curriculum Vitae
List of Tables

1.1 Physical factors that impact quantification ......................... 21
1.2 Biological factors that impact quantification ........................ 29
1.3 Technical factors that impact quantification ........................ 32
1.4 Human factors that impact quantification ........................... 40
1.5 Obtaining a $\mu$-map without a transmission scan ................. 49
1.6 Transmission scan geometries ................................. 51
1.7 Transmission scan energies ..................................... 55
1.8 Future work ...................................................... 69
2.1 $\mu$-coefficients assigned to materials ................................. 101
2.2 Results of global error analysis on canines ......................... 110
2.3 Results of global error analysis on phantom ........................ 110
2.4 Results of local error analysis on canines ........................... 111
2.5 Results of local error analysis on phantom ......................... 112
3.1 ANOVA results ....................................................... 134
3.2 Results of local error analysis ..................................... 140
4.1 Global error analysis two-way ANOVA results ....................... 163
4.2 Global error analysis one-way ANOVA results ....................... 164
4.3 Local error analysis one-way ANOVA results ....................... 165
# List of Figures

1.1 PET/CT and PET/MRI .................................................. 3  
1.2 Lines of response ..................................................... 16  
1.3 Dominant photon/matter interactions ............................... 19  
1.4 Realistic line of response ............................................. 25  
1.5 Impact of detector size on LOR localization ...................... 26  
1.6 Ill-conditioned PET .................................................... 35  
1.7 Attenuation measurement .............................................. 41  
1.8 Components of $\mu_m$ over a range of energies .................... 44  
1.9 Transmission scan geometries ....................................... 53  
1.10 Segmented MRI-based $\mu$-map ................................... 62  
1.11 Registered MRI-based $\mu$-map .................................... 65  
1.12 Mapped MRI-based $\mu$-map ....................................... 67  

2.1 VOI placement ......................................................... 105  
2.2 Example of an MRI-based $\mu$-map ................................ 106  
2.3 Comparison of canine SPECT and PET reconstructions ........... 108  
2.4 Comparison of phantom SPECT and PET reconstructions ........ 109  
2.5 Comparison of SPECT and PET scatter plots ...................... 109  
2.6 Example of PET sensitivity to MRI-based $\mu$-map ................. 113  
2.7 Example of SPECT sensitivity to MRI-based $\mu$-map .............. 114
2.8 Results of sensitivity analysis ........................................ 114
3.1 VOI placement ............................................................ 131
3.2 $T_2^*$ and proton density versus CT signal ......................... 133
3.3 Spatial correlation of lung signal in CT versus MRI ............... 134
3.4 MRI to CT lung mappings .............................................. 135
3.5 Pre-$\mu$-maps of the lungs ............................................ 136
3.6 Results of global error analysis ..................................... 137
3.7 Profiles through sample PET reconstructions ...................... 138
4.1 Sample $\mu$-maps and associated errors ............................. 159
4.2 Results of global error analysis ..................................... 160
4.3 Results of local error analysis ....................................... 161
4.4 Joint histogram of lung signal in CT versus MRI .................. 162
List of Appendices

Ethics Approvals 189
Copyright Releases 192
Curriculum Vitae 195
<table>
<thead>
<tr>
<th>Symbol</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>$a$</td>
<td>Mean activity per unit time</td>
</tr>
<tr>
<td>$\tilde{a}$</td>
<td>Actual activity at each voxel of PET image</td>
</tr>
<tr>
<td>$\bar{a}_e$</td>
<td>Mean estimated activity</td>
</tr>
<tr>
<td>$\bar{a}_t$</td>
<td>Mean true activity</td>
</tr>
<tr>
<td>AC</td>
<td>Attenuation correction</td>
</tr>
<tr>
<td>$b$</td>
<td>Y-intercept of LOBF</td>
</tr>
<tr>
<td>$c$</td>
<td>Speed of light</td>
</tr>
<tr>
<td>CT</td>
<td>Computed tomography</td>
</tr>
<tr>
<td>$\text{CT}_{\text{clin}}$</td>
<td>Clinical quality CT</td>
</tr>
<tr>
<td>$\text{CT}_{\text{pre-} \mu}$</td>
<td>CT precursor to $\mu$-map</td>
</tr>
<tr>
<td>$D$</td>
<td>Training data for SVM</td>
</tr>
<tr>
<td>df</td>
<td>Degrees of freedom</td>
</tr>
<tr>
<td>$E$</td>
<td>Energy or error, depending on context</td>
</tr>
<tr>
<td>$F$</td>
<td>$F$-statistic</td>
</tr>
<tr>
<td>FDG</td>
<td>$^{18}$F-fluorodeoxyglucose</td>
</tr>
<tr>
<td>FRC</td>
<td>Functional residual capacity</td>
</tr>
<tr>
<td>$I$</td>
<td>Photon beam intensity after attenuation</td>
</tr>
<tr>
<td>$I_0$</td>
<td>Initial photon beam intensity</td>
</tr>
<tr>
<td>ITK</td>
<td>Insight Segmentation and Registration Toolkit</td>
</tr>
<tr>
<td>$k(x_i, x_j)$</td>
<td>Kernel function</td>
</tr>
<tr>
<td>$L$</td>
<td>Length of material attenuating photon beam</td>
</tr>
<tr>
<td>LOBF</td>
<td>Line of best fit</td>
</tr>
<tr>
<td>LOR</td>
<td>Line of response</td>
</tr>
<tr>
<td>$m$</td>
<td>Slope of LOBF or mass, depending on context</td>
</tr>
<tr>
<td>MIBI</td>
<td>$^{99m}$Tc-sestamibi</td>
</tr>
<tr>
<td>MRI</td>
<td>Magnetic resonance imaging</td>
</tr>
<tr>
<td>$\text{MRI}_{\text{lung}}$</td>
<td>MRI of the lungs</td>
</tr>
<tr>
<td>$\text{MRI}_{\text{lungPD}}$</td>
<td>Proton density map of the lungs</td>
</tr>
<tr>
<td>$\text{MRI}_{\text{lungSTE}}$</td>
<td>Short echo time MRI of the lungs</td>
</tr>
<tr>
<td>$\text{MRI}_{\text{lungT}_2}$</td>
<td>$T_2^*$ map of the lungs</td>
</tr>
<tr>
<td>MRIWB</td>
<td>MRI of whole body</td>
</tr>
<tr>
<td>$N$</td>
<td>Number of photons detected per unit time</td>
</tr>
</tbody>
</table>
TR  Repetition time
T₁  Spin-lattice relaxation time
T₂  Spin-spin relaxation time
T₂* Spin-spin relaxation time with local magnetic field inhomogeneities
uᵢ  Class membership in SVM
UTE Ultrashort TE
VOI Volume of interest
xᵢ  True normalized PET activity
xᵢ  Feature vector for SVM
yᵢ  Estimated normalized PET activity
Z   Atomic number
z   Longitudinal cylindrical coordinate
α   Maximal acceptable probability of type-1 error
β   Standard deviation of Gaussian radial basis function
ΔI  Change in photon beam intensity
ε   Degree of sphericity
η   Part of mass attenuation coefficient due to coherent scattering
θ   Azimuthal cylindrical coordinate
κ   Part of mass attenuation coefficient due to pair production
μ   Linear attenuation coefficient
μₘ  Mass attenuation coefficient
μ-coefficient Attenuation coefficient
μ-map Attenuation map
ρ   Density
σ   Part of mass attenuation coefficient due to Compton scattering
τ   Part of mass attenuation coefficient due to photoelectric effect
ϕ(xᵢ) Mapping implicitly applied by k
2D  Two-dimensional
3D  Three-dimensional
Chapter 1

A Bird’s Eye Perspective of Attenuation Correction in PET/MRI

1.1 Introduction

One of the most intriguing aspects of positron emission tomography (PET) is its fundamentally quantitative nature. That is to say, given a patient with a radiopharmaceutical on board, the activity distribution can be expressed in absolute terms, e.g. MBq/mL. This capability, considering PET’s capacity to image a variety of molecular biological processes, makes PET an extraordinarily powerful tool.

However, creating quantitatively accurate PET images is not trivial. Several factors can adversely impact quantification and years of research have been devoted to addressing them. The most important cause of quantification error is photon attenuation, a phenomenon wherein \( \gamma \)-rays emitted from the radiopharmaceutical interact with the patient’s body and thus remain undetected. One can compensate for attenuation provided an attenuation map (\( \mu \)-map) is available. A \( \mu \)-map is an image of the patient that is composed of attenuation coefficients (\( \mu \)-coefficients), values that indicate how likely a photon/matter interaction is to occur at a specified position. For example, air has a low \( \mu \)-coefficient as most photons pass through it undeterred.
Conversely, cortical bone has a high $\mu$-coefficient as it impedes many photons incident upon it. The most straightforward way of obtaining a $\mu$-map is to transmit photons through the patient and record the fraction that makes it through to the other side. By repeating this from different angles around the patient, a tomographic reconstruction of the $\mu$-map is generated. There are many variations on the theme, but the general principle remains the same. For this reason, virtually every PET scanner has some form of transmission imaging system built in, the most common today being X-ray computed tomography (CT), i.e. PET/CT.

While combining PET and CT is useful from the point of view of attenuation correction (AC), another major motivating factor is that the modalities yield complementary information: CT provides an anatomical context for the functional PET images. A similar line of reasoning led to the conception of another hybrid modality combining PET with magnetic resonance imaging (MRI), i.e. PET/MRI. Like CT, MRI can produce anatomical images, but with improved soft tissue contrast (albeit with poor delineation of bones). In addition, image contrast in MRI can be altered, highlighting different structures and pathologies. MRI also boasts multiple functional imaging options including blood oxygen level dependent effects, blood flow, perfusion, diffusion, and chemical shift imaging [140]. What’s more, this is done without exposing the patient to ionizing radiation. Researchers have been aware of these advantages for some time, and accordingly, work began on PET/MRI in the late 1990s [162, 188] preceding the completion of PET/CT [19]. That said, the first human simultaneous PET/MRI images were not published until much later [182]. The delay was caused in part by a temporary shift in interest away from PET/MRI owing to the remarkable success of PET/CT, but also because of the technical difficulties associated with placing PET and MRI systems in close proximity without compromising the performance of either modality. Several groups’ approaches to solving these problems are reviewed
by Pichler et al [163]. It is thanks to their combined efforts that PET/MRI is now a reality. Both a PET/CT and PET/MRI image are presented in Figure 1.1

Figure 1.1: (A) Whole-body PET scan displayed as a maximum intensity projection, (B) PET/CT overlay (PET is in orange), and (C) PET/MRI overlay (PET is in orange). All images are of the same patient and were acquired on the same day. Oncologic lesions suspected of being malignant are visible in the PET scan in the neck, chest, and lungs. Adapted from Drzezga et al [54].

There remains an unresolved issue, however: it is difficult to obtain a $\mu$-map. In simultaneous PET/MRI scanners physical space is limited and costs are high, so including an integrated or attached transmission imaging system is not feasible [221]. Further, obtaining a transmission scan from a separate machine (e.g. a detached CT) is not viable because the patient would have to move from the PET/MRI to the transmission system, resulting in differences in positioning that may produce severe AC errors [69, 90, 153]. How then is AC to be performed? The obvious recourse is to
derive the $\mu$-map from MRI images. But in MRI, signal is dictated primarily by proton density and magnetic relaxation times, i.e. $T_1$, $T_2$, and $T_2^*$ [140]. Unfortunately, these parameters are not easily relatable to $\mu$-coefficients. Thus, MRI-based AC of PET images is an open and challenging problem that must be solved if PET/MRI is ever to be a quantitative imaging modality.

In this chapter, I examine the issue of MRI-based AC in detail. First, I discuss the value of quantitative PET with respect to PET/MRI. Next, I catalogue and explain the major factors that impact quantification in PET images to provide a broader context for the role that photon attenuation plays. I subsequently focus on AC and how it has been conducted historically, complete with the advantages and disadvantages of each method. I then explain how MRI-based AC is conducted, describing three general approaches to the problem. Finally, I identify unresolved problems and suggest avenues for further research.

1.2 The Value of Quantitative PET/MRI

1.2.1 Oncology

By far, the most common clinical application of PET is imaging cancers, altering management in 36.5% of cases overall [84]. PET’s adoption in this arena owes to one radiopharmaceutical, 2-deoxy-2-(18F)fluoro-D-glucose, commonly referred to as $^{18}$F-fluorodeoxyglucose or FDG. A glucose analog, FDG enters the glycolysis chemical pathway as would regular glucose, but stalls after phosphorylation to FDG-6-phosphate due to its absent 2’ hydroxyl group. Consequently, FDG preferentially accumulates in cells exhibiting high metabolic activity. As glycolysis is upregulated in most cancers [63], FDG PET may be used to visualize malignancies. An immediate application of this capacity is staging, where PET has proved useful in several
cancers [57, 97, 174, 213]. Indeed, staging is likely to play a part in the clinical role of PET/MRI [5].

However, accurate quantification is generally not essential for staging; the appearance of cancerous hot spots is sufficient to localize the disease. In fact, there is some evidence that, with respect to lesion detection in FDG PET, there is no benefit to performing AC at all [104]. In other words, AC is not always necessary for qualitative aspects of PET image interpretation. However, oftentimes it is valuable to quantify a tumour’s FDG uptake, an impossibility without AC. For example, the lesion’s degree of FDG uptake has been associated with the cancer’s aggressiveness and the patient’s prognosis [12, 15, 155]. Perhaps even more interesting, multiple studies indicate that after the initiation of a chemotherapeutic regimen, declining levels of FDG uptake from baseline correlate with the treatment’s efficacy [2, 175, 179]. This may have tremendous implications for drug development, i.e. in deciding which candidate therapies should be advanced to large-scale, phase III clinical trials [211]. Further, the ability to predict an anti-cancer drug’s efficacy on a patient-by-patient basis yields exciting possibilities for personalized medicine.

The rationale for accurate quantification in oncological PET imaging is well established, but how does PET/MRI fit in? In particular, when is quantitative PET/MRI more appropriate than quantitative PET/CT? One likely scenario is for brain tumours. MRI is widely accepted as the modality of choice in neuro-oncology. This is because of MRI’s excellent anatomical delineation of intracranial masses—often correlating with histological features and clinical behaviour [81]—and its functional imaging options. For instance, magnetic resonance spectroscopy (MRS) has demonstrated utility in several applications such as grading [164], biopsy site selection [44], and differentiating progressive disease from radiation necrosis [173] while both diffusion tensor imaging and functional MRI (known as fMRI) can aid in neurosurgical
planning [147, 185]. Like MRI, PET provides a wealth of information about brain tumours. Interestingly, in neuro-oncology, FDG is not the radiopharmaceutical of choice due to an inherently low contrast to noise ratio caused by strong uptake in healthy gray matter [216]. But using alternate radiopharmaceuticals such as O-(2-[\textsuperscript{18}F]fluoroethyl)-L-tyrosine, the addition of PET to MRI has demonstrated potential, including the determination of tumour extent [158] and in radiation treatment planning [148] amongst other applications [21]. With special pertinence to quantitative PET, PET/MRI may prove a powerful tool for assessing treatment response [50, 94]. Although the field is young and there is still much speculation, the first clinical studies evaluating the use of simultaneous PET/MRI in neuro-oncology are beginning to emerge, and the initial results are encouraging [26].

PET/MRI’s role in clinical oncology will not likely be confined to the brain, however. For example, CT does not play a major role in breast cancer imaging whereas there is extensive interest in MRI as it is the most sensitive modality for identifying local extent of the disease, although it suffers from low specificity [14]. Thus, PET/MRI is a more natural fit for breast cancer than PET/CT, assuming of course that PET adds value to the study. Indeed, PET has been shown to be useful for predicting response to neoadjuvant chemotherapy [179, 187], which may be synergistic to treatment response information provided by MRI [35, 100, 156, 165] and MRS [137].

Another area that quantitative PET/MRI may find application outside the brain is in imaging neoplasms that occur primarily during childhood. CT is a significant source of radiation (about 15 mSv for an adult, whole-body, diagnostic quality scan), often more so than the radiopharmaceutical itself (about 7 mSv) [28]. Further, radiation exposure can be increased as CT scanners are pushed to image faster and yield images of higher quality [146]. This is highly undesirable in the paediatric pop-
ulation [101]. If PET is indicated in a child with cancer, it would be better if both the anatomical localization and AC was performed with MRI, provided of course the CT is not serving an important clinical function. A good example would be in the initial evaluation of soft tissue sarcomas, where MRI is often the modality of choice for visualizing the primary lesion [48] and quantitative PET may be useful for grading and predicting malignancy [12].

The preceding discussion is by no means comprehensive; many possible oncological applications of quantitative PET/MRI have been omitted. Rather, the select examples above should serve as an indication that PET/MRI may have an important role to play in evaluating a significant subset of cancers.

1.2.2 Neurology

As mentioned earlier in the context of brain tumours, PET/MRI can generate a wealth of information, both anatomical and functional, regarding the central nervous system. Of course, diseases of the brain are not limited to neoplasms; in this section, the prospect of using quantitative PET/MRI to improve the management of some additional cerebral pathologies is explored. In particular, I touch on Alzheimer’s disease, ischemic stroke, and epilepsy.

Alzheimer’s disease is an excellent example of a pathology that is well suited to imaging with PET/MRI. In routine medical practice the diagnosis of Alzheimer’s is essentially a clinical one, though anatomic MRI is often indicated as well, largely to exclude other pathologies [116]. This is problematic in that a diagnosis cannot be made until relatively severe and likely irreversible cortical damage has accrued. However, significant advances in the understanding of Alzheimer’s pathogenesis indicate that a sequence of measurable changes begin well before dementia occurs. Further, these changes follow a general temporal ordering: according to a recent hypothesis,
the order is given by 1) β-amyloid accumulation in the cortex, 2) tau mediated neuronal injury, 3) brain atrophy, 4) memory loss, and finally 5) impaired clinical function [99]. Many of these biomarkers can be detected via imaging, which is important as they follow characteristic spatial patterns. For instance, it is well established that PET can be used to detect β-amyloid burden [96], while both PET and MRI can indirectly measure neuronal damage via reduced metabolism [102, 172] and cerebral atrophy [22], respectively. Making use of these techniques has the potential to permit early diagnosis and accurate staging of Alzheimer’s [99], and there are ongoing efforts to incorporate them into diagnostic criteria [55]. Indeed, PET and MRI provide complimentary information in Alzheimer’s [98, 192], while their hybridization bears technical benefits such as MRI-guided partial volume effect correction of the PET images [202].

However, without quantification, PET’s ability to characterize Alzheimer’s disease is limited to observing the presence or absence of biomarkers. With quantification, PET can determine how much biomarker is present, compare concentrations between different regions of the brain, and track changes over time, all of which are likely clinically relevant [99, 192]. Furthermore, PET has shown promise for therapeutic monitoring in Alzheimer’s [170], another application that demands proper quantification.

In ischemic stroke, the concept of the penumbra is of great interest. Simply put, the penumbra comprises a region of brain tissue surrounding the necrotic core that exhibits impaired function owing to hypoxia induced by hypoperfusion, but remains salvageable provided perfusion is restored quickly [7]. From a clinical standpoint, “quickly” has been found to be within 4.5 hours of the ischemic insult, meaning that thrombolytic therapy with tissue plasminogen activator is generally indicated prior to the 4.5 hour mark [74]. But not all penumbras convert to infarcted tissue at the same
rate; penumbral tissue has been documented even 16 hours post-insult in humans, suggesting that in some cases the therapeutic window should be extended [11].

The penumbra can be visualized with MRI by collecting both diffusion weighted and perfusion weighted images, the former identifying the necrotic core and the latter localizing perfusion deficits [10]. The penumbra is seen as the mismatch between the perfusion and diffusion lesions. Accordingly, several clinical trials have evaluated the use of MRI in selecting patients eligible for tissue plasminogen activator administration beyond the traditional therapeutic window, but results have been disappointing [53, 139]. One of the potential problems is that MRI exhibits inaccuracies identifying the true penumbra and necrotic core [80]. PET, conversely, is recognized as the gold standard for the detecting the penumbra and infarcted tissue [11], but is not used in clinical practice because the exam is logistically complex. The immediate role for PET/MRI in stroke is likely not in the management of individual patients, but in the validation of improved MRI protocols to better delineate the penumbra [215]. This is a situation wherein the simultaneity of data collection is pivotal considering the relatively fast dynamics involved. Additionally, the PET images should be quantitative, as they must enumerate the degree of hypoperfusion in the penumbra for the MRI to be checked against.

In the future, PET/MRI may prove more directly useful in stroke, such as for localizing thrombi with dual probes [207]. Also, given the potential neuroprotective strategies [135] that have been proposed on the basis of the evolving concept of multiple “molecular” penumbras [189], PET/MRI may play a major role in the evaluation of novel stroke therapeutics.

Finally, PET/MRI might prove helpful in a subset of focal epilepsy cases that remain uncontrolled despite the administration of antiepileptic drugs. Under these circumstances, neurosurgical intervention often induces remission via resection of the
epileptogenic focus [195]. Said focus is generally identified as a lesion on anatomical MRI, the modality of choice for surgical planning in epilepsy [56]. However, a lesion is not always apparent on MRI, and in such cases additional imaging with PET (which visualizes the epileptic focus as an area of reduced cerebral metabolism using FDG) is both helpful [125, 176, 214] and cost-effective [151]. Generally, one identifies an area of reduced cerebral uptake by comparison to the contralateral side of the brain. If the PET images are not quantitative, there is no guarantee of symmetry, especially if the patient’s head is tilted with respect to the scanner. What’s more, without quantification, the decreased uptake might itself be obscured.

PET appears especially useful for surgical planning if coregistered with MRI [125, 176], a task for which simultaneous PET/MRI is the gold standard. Beyond this clinical application, sophisticated PET radiopharmaceuticals and MRI protocols make PET/MRI well suited for exploring epilepsy’s pathophysiology [56, 121, 169].

There are numerous applications of PET/MRI to neurology and neuroscience that are not mentioned above, several of which are reviewed elsewhere [21, 79, 83, 141].

1.2.3 Cardiology

There are already several modalities and protocols available to the clinician to evaluate cardiac function, so the addition of PET/MRI to the list of options may seem superfluous. However, this hybrid platform has the potential to have a significant clinical impact, as evidenced by the following example.

Coronary heart disease is responsible for approximately 1 of every 6 deaths in the United States [127]. In coronary heart disease, plaques in the coronary arteries restrict blood flow to regions of the heart, which, if severe enough, will lead to cardiac dysfunction. One of the important clinical issues is to determine if dysfunctional myocardium is irreversibly injured or dead, or if it remains viable but its function is
compromised because of reduced blood flow. Myocardial cells can exhibit reduced or absent contractility but remain viable; such cells are known as either “hibernating” [167] or “stunned” [111] depending on the length of the ischemic insult, but appear similarly dysfunctional. There is evidence from several retrospective studies that patients with dysfunctional yet viable myocardium are more likely to benefit from revascularization procedures such as percutaneous transluminal coronary angioplasty or coronary artery bypass grafting than patients without salvageable myocardial tissue [34, 181]. This observation motivated three prospective randomized controlled trials assessing whether cardiac viability imaging for treatment selection improves patient outcomes [13, 25, 38]. The results of all three trials were negative, but with some major caveats. The outcome of a clinical trial studying a test for guiding therapy depends not only on the accuracy of the test itself, but also upon clinicians’ adherence to the test result and the efficacy of the treatments. Indeed, in the PET and Recovery Following Revascularization-2 (PARR-2) trial, adherence to viability test-based recommendations was only 75.4% [13]. It was found that in the subgroup of patients where revascularization decisions were based on PET viability testing, imaging was associated with improved outcomes (death, myocardial infarction, and heart failure). Further, in some patients, medical management may provide comparable outcomes as would be achieved with surgical intervention [160]. There is evidence that viability imaging may be useful in optimizing treatment within the subpopulation of sickest patients where surgical risk is highest [13]. So, despite the apparent negative outcomes of the trials, there may be a place for viability assessment for treatment selection in some patient groups. Further randomized trials are currently underway that will adopt a more rigorous, test-guided approach to revascularization decisions to try and confirm the results seen in the PARR-2 adherence patients. Regardless of whether viability imaging is useful in therapeutic guidance, there is little doubt that
it is an excellent prognostic indicator [25].

For the reasons discussed above, determining cardiac viability remains a key issue in patients with coronary heart disease. Viability can be assessed with several imaging modalities including single photon emission computed tomography (SPECT), dobutamine echocardiography, PET, and MRI [203]. However, no single modality has emerged as the most accurate test [181]. Since the tests assess viability through differing mechanisms, it may be that they are complimentary rather than competitive. For instance, in PET, both cardiac perfusion and glucose metabolism scans are assessed; areas of reduced perfusion and increased glycolysis are predictive of viable tissue at risk of death [204] since the myocardium switches from primarily fatty acid to glucose metabolism when ischemic [144]. Areas of altered perfusion and glycolysis cannot be reliably identified unless the PET images are quantitative, nor can the degree of aberration be assessed. MRI, in comparison to PET, can provide information about viability in alternate ways [177]. For instance, several minutes after injection with a contrast agent called Gadolinium diethylene triamine pentaacetic acid (usually referred to as Gd-DTPA), infarcted tissue can be reliably identified as it enhances (sequesters the tracer) more than viable tissue due to altered cellularity and clearance kinetics [105, 203]. Therefore, MRI is assessing the extent of irreversibly injured scar, with the inference that dysfunctional myocardium that is not scar is viable. Another approach is to acquire MRI images of the beating heart at baseline and after the administration of dobutamine, a sympathomimetic drug, to identify wall motion abnormalities; this test is similar to dobutamine echocardiography but provides a high-resolution volume dataset and can incorporate myocardial tagging to improve wall motion assessment [120]. Viable myocardium will respond to the inotropic stimulus of dobutamine with improved contractility whereas dead tissue will remain dysfunctional. By combining the information obtained from PET and
MRI, an unprecedentedly comprehensive picture of myocardial status should be attainable. Further, a detailed anatomical context provided by MRI will be available to facilitate the interpretation of PET. In fact, the resolution and signal-to-noise ratio (SNR) of the PET images themselves can be improved by virtue of MRI’s ability to correct for cardiac and respiratory motion [52, 72]. Considering all these advantages, PET/MRI may well provide the most accurate means available to noninvasively assess myocardial viability. However, it will need to be demonstrated that enhanced diagnostic accuracy translates into improved patient outcomes assessed in well designed randomized clinical trials.

Beyond myocardial viability assessment, PET/MRI bears some exciting prospects for cardiovascular imaging. Briefly, one of the most intriguing is the localization and characterization of atherosclerotic plaques. Magnetic resonance angiography is a popular method to identify luminal stenoses throughout the body (e.g. carotid arteries, peripheral vasculature, and even coronary arteries), but it provides limited information about the plaque itself. A means to examine the plaque could enable the clinician to estimate the risk of rupture if it can identify an inflammatory component which often precedes acute events such as myocardial infarction. Both MRI [205] and PET [152] have demonstrated potential on this front, with numerous applications such as stroke prevention [206], therapeutic monitoring and drug development [152], and the early diagnosis of atherosclerosis [178]. There is a multitude of other possibilities for PET/MRI in cardiovascular imaging, and the reader is referred elsewhere for further discussion [118, 145].
1.3 Factors Influencing Quantification

1.3.1 PET Physics Primer

The basic premise underlying PET image formation is relatively simple, but as with most things, the devil is in the details. I will begin with a simplified explanation of how PET works and subsequently catalogue the physical (§1.3.2), biological (§1.3.3), technical (§1.3.4), and human (§1.3.5) factors that limit the system’s performance, elaborating on salient details as required.

Essentially, PET’s purpose is to determine the location and magnitude of physiological processes in the body. Given a process of interest (e.g. glucose metabolism or perfusion), a chemical probe that targets said process is introduced into the body. After a period known as the uptake time, the probe will have distributed itself within the body in approximate proportion to the physiological process. PET is merely a clever means of inferring where the probe went. The trick is that the probe is bound to a radioactive element; PET uses the radiation to determine where the nucleus that released it must have been. It is for this reason that the probe is generally referred to as a radiopharmaceutical or radiotracer.

For PET to work, the radioactive nucleus must decay by a process known as positron emission, wherein one of the radionuclide’s protons is converted to a neutron via the expulsion of a positron and a neutrino. The neutrino is unimportant in PET, but the positron is critical. Once released, it will collide with its antiparticle (the electron) and annihilate, generating a pair of photons in the process. In order to conserve a net zero momentum, the photons travel in opposite directions, tracing out a straight line. In a PET system, the subject is surrounded by a cylindrical array of detectors tuned to identify these photons.

Since photons travel at the speed of light, no matter where a photon pair originates
the photons will strike the detectors within a few nanoseconds of each other. So if a pair of detectors is activated nanoseconds apart, the PET system assumes that the photons that struck them must have originated from the same positron annihilation. This is known as a “coincidence”. Moreover, since the photons travel along a straight line, the positron annihilation must have occurred somewhere in between the two activated detectors. The imaginary line connecting a pair of activated detectors is called the line of response, or LOR for short (Figure 1.2). Once many LORs have been collected, they are input into a reconstruction algorithm, a mathematical model that converts the raw data collected by the PET scanner into an image (details in §1.3.4).

In theory, by computing the difference between the arrival times of the two photons involved in a coincidence, one can determine where along the LOR the positron annihilation occurred, improving the quality of data collected by the PET scanner. This is termed time-of-flight, referring to the amount of time the photons travel for prior to detection. In practice, time-of-flight requires that the PET system make very accurate measurements of time, an ability characterized by a parameter called timing resolution. No current PET system can localize annihilation events to a single point (which requires a timing resolution of about 3 ps), but it is possible to localize annihilations to a particular region along the LOR.

Unfortunately, whether using time-of-flight or not, sometimes the PET system can detect false LORs, thereby deteriorating image quality. This can happen two ways. First, suppose two positron annihilations occur within nanoseconds of each other. Suppose further that one member of the photon pair from each annihilation is lost somehow, for instance via attenuation (see §1.4.1) or passing through the detector without stopping. If the two remaining photons are detected, a false LOR is formed between them (Figure 1.2). Such LORs are termed “randoms”, since they
Figure 1.2: Real and false LORs. The outer ring is a cylindrical array of PET detectors. The light grey ellipse in the centre represents a patient’s body. Black circles are positron annihilations and the solid black lines emanating from them are photon trajectories. Trajectories terminating with an arrow denote photon detection, while those terminating with an ‘X’ indicate that the photon was lost. The dashed lines represent false LORs. There are three types of LOR: (A) true, (B) random, and (C) scatter.
arise from the chance detection of two unrelated photons. Second, suppose that one (or both) of the photons emitted from an annihilation is deflected prior to detection. The resulting LOR will be deflected as well (Figure 1.2). LORs formed in this way are known as “scatter”, its name derived from Compton scattering, the physical process that deflects photons. Incidentally, all true LORs (i.e. created by an actual, undeflected photon pair) are unsurprisingly called “trues”.

There is an additional feature of photon pairs arising from positron annihilation that warrants explanation. Recall that mass and energy are equivalent according to Einstein’s famous equation, $E = mc^2$, where $E$ is energy, $m$ is mass, and $c$ is the speed of light. Using this equation, one can show that the energy contained in the mass of a positron is 511 keV. Similarly, as electrons have the same mass as positrons, they also bear 511 keV of energy. Accordingly, when a positron and electron collide and annihilate, the total energy released is 1022 keV. This is divided equally between the photon pair, giving each 511 keV. Photons are the particles that mediate electromagnetic radiation, and electromagnetic radiation with 511 keV of energy falls into the $\gamma$-ray region. Hence, PET operates by detecting 511 keV $\gamma$-rays.

PET systems take advantage of the fact that photons derived from positron annihilations have an initial energy of 511 keV. Recall that photons can be deflected prior to detection giving rise to false LORs called scatter. The primary mechanism that deflects photons at 511 keV is called Compton scattering, wherein the photon collides with a bound electron and changes course. In the process, the photon transfers some of its energy to the electron; the larger the angle of deflection, the more energy it transfers. In short, deflected photons have energies below 511 keV. PET systems capitalize on this phenomenon by measuring the energy of every photon they detect. In principle, by rejecting coincidences wherein one or both photons have less than 511 keV of energy, scatter would be completely eliminated. However, PET systems
cannot measure photon energy perfectly. Every measurement of energy is associated with an error characterized by a parameter called energy resolution. Therefore, in practice, PET systems will accept photons with energies in a predefined region around 511 keV, and reject those that fall outside this region. Said region is called the acceptance window. For reference, the acceptance window of most clinical PET scanners is about 350 keV to 650 keV [92]. Thus, some scatter can be rejected, but a significant proportion still falls within the acceptance window.

Finally, a word about photon attenuation. Attenuation and its correction are discussed in detail in §1.4, but it for now, it will suffice to know how it arises. Attenuation describes the phenomenon that some photons are “lost” prior to detection, and therefore fail to generate a LOR at all. Photons can be lost three ways: 1) by being absorbed by a bound electron via a mechanism called the photoelectric effect, 2) by undergoing Compton scattering to such a degree that the photon’s energy loss excludes it from the acceptance window, and 3) by colliding with a nucleus and transforming into a positron and electron, a process called pair production. At PET’s energy, 511 keV, the photoelectric effect is negligible and pair production impossible (the photon would require at least 1022 keV of energy to generate the mass contained in a positron and electron). Hence, attenuation in PET is due almost exclusively to Compton scattering (Figure 1.3), creating an interesting relationship between attenuation and scatter. Specifically, all scattered photons should be deemed attenuated, and thereby handled by attenuation correction algorithms. Unfortunately, due to PET’s limited energy resolution, some scattered photons are able to generate false LORs and must be accounted for by scatter correction algorithms.
Figure 1.3: Dominant photon/matter interactions according to atomic number (Z) and photon energy. Adapted from Yip [219].
1.3.2 Physical Factors

As described in §1.3.1, the goal in PET is to infer the underlying spatial distribution of a positron emitting substance that gives rise to measured electromagnetic radiation. In broad terms, there are three mechanisms that deteriorate the ideal distribution: the statistical nature of radioactive decay, positional uncertainty concerning the site of positron emission, and biases in the detected radiation. Each will be discussed in turn and the associated impact on quantification will be assessed. A summary of these factors is presented in Table 1.1

1.3.2.1 Photon Statistics

The inherently statistical nature of radioactive decay dictates that it is impossible to recover the true underlying radiopharmaceutical distribution. Conceptually, the problem can be illustrated with the following example. Imagine that there are two identical radioactive sources resting inside two identical radiation detectors. The detectors are both turned on for the same amount of time, and each records how many photons are released from its radioactive source. Since radioactive decay is a random process, the numbers will not be the same. There is therefore an inherent uncertainty when attempting to determine “how radioactive” a source is.

This uncertainty can be described mathematically. Given a radioactive source with mean activity per unit time $a$, the probability of recording $N$ events (with a perfect detector) in a unit time follows a Poisson distribution, $P(N; a) = (e^{-a}a^N)/N!$. The associated uncertainty of the measurement is $100%/\sqrt{N}$. Thus, the fewer photons one detects, i.e. the lower $N$, the more uncertain your estimate of the source’s activity. In PET, there are numerous factors that limit $N$. Some obvious ones include finite time available for the scan and the radiation safety limits dictating the maximum allowable patient dose.
Table 1.1: Physical factors that impact quantification.

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Factor</th>
<th>Explanation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Statistical uncertainty of measurements</td>
<td>Scan time</td>
<td>More time allows for more counts to be recorded</td>
</tr>
<tr>
<td>Administered activity</td>
<td>More activity leads to more counts per unit time</td>
<td></td>
</tr>
<tr>
<td>Geometric efficiency</td>
<td>Extent of detectors’ spatial coverage, proportional to counts</td>
<td></td>
</tr>
<tr>
<td>Intrinsic efficiency</td>
<td>Proportion of photons that interact with the detectors</td>
<td></td>
</tr>
<tr>
<td>Photofraction</td>
<td>Proportion of detected trues that are accepted</td>
<td></td>
</tr>
<tr>
<td>Attenuation</td>
<td>Lost photons reduce trues</td>
<td></td>
</tr>
<tr>
<td>Deadtime losses</td>
<td>High count rates cause pileup and reduce recorded counts</td>
<td></td>
</tr>
<tr>
<td>Time-of-flight capability</td>
<td>Improves “utility” of counts</td>
<td></td>
</tr>
<tr>
<td>Partial volume effect by impacting spatial resolution</td>
<td>Positron emission and annihilation sites different</td>
<td></td>
</tr>
<tr>
<td>Photon pair noncolinearity</td>
<td>Actual LOR is “bent”, shifting observed LOR</td>
<td></td>
</tr>
<tr>
<td>Detector size</td>
<td>Cannot localize interaction site</td>
<td></td>
</tr>
<tr>
<td>Radiation not representative of underlying distribution</td>
<td>Attenuation</td>
<td>Photons passing through much matter preferentially lost</td>
</tr>
<tr>
<td>Randoms</td>
<td>False counts throughout image</td>
<td></td>
</tr>
<tr>
<td>Scatter</td>
<td>Severely mislocalized LORs</td>
<td></td>
</tr>
<tr>
<td>Detector imperfections</td>
<td>Generates image distortions (nonlinearities, nonuniformities)</td>
<td></td>
</tr>
</tbody>
</table>
There are four additional factors that reduce $N$: these are geometric efficiency, intrinsic efficiency, photofraction, and attenuation, and will be described in turn. As the detectors do not completely surround the patient, only a fraction of total positron annihilations will produce radiation incident on the detectors. This fraction is the geometric efficiency. Further, the detectors themselves are imperfect and only interact with a fraction of the photons incident upon them, i.e. the intrinsic efficiency. Unfortunately, even if a photon/detector interaction does occur, sometimes it still does not register. This occurs if the photon does not deposit sufficient energy in the detector to land in the acceptance window. Such events are indistinguishable from scatter and are erroneously rejected. The proportion of trues interacting with the detectors that do fall in the acceptance window is the photofraction. Finally, attenuated γ-rays either never make it to the detectors or fall beneath the acceptance window, further decreasing the number of available trues. Ultimately, the net sensitivity of the system for trues can be expressed as the product of geometric efficiency, intrinsic efficiency, photofraction, and a factor accounting for losses due to attenuation.

But beyond the PET system’s net sensitivity, an even greater proportion of trues are lost when there is a high rate of coincidences (also called a high count rate). These are called dead time losses, stemming from limitations in the PET photon counting system. Specifically, every time a photon interacts with a detector, a pulse is created in the associated electronics. If two photons interact with the same detector one immediately after the other, the electronic pulses will overlap, summing to one big pulse. This is aptly named pulse pileup, and will result in the loss of at least one of the two photons since the PET system only “sees” one pulse. Worse, the height of the pulse is used to infer the incident photon’s energy; the bigger the pulse, the higher the energy. If the summed pulse borne of the two photons is large enough, it will fall outside the acceptance window, resulting in the rejection of both photons.
The shortest time between two pulses wherein the PET scanner can still resolve both pulses is known as the dead time. A shorter deadtime results in less pileup and fewer deadtime losses.

In short, considering all the factors that reduce $N$, only a relatively small, finite number of positron decays are ever detected, fundamentally limiting the reliability of quantification. Interestingly, typical PET scans generally have less than one coincidence event per LOR in a three-dimensional (3D) acquisition. Incidentally, a 3D acquisition is one where all possible LORs are recorded, compared to a two-dimensional (2D) acquisition where only LORs parallel to the axial plane are recorded.

### 1.3.2.2 Spatial Resolution and the Partial Volume Effect

Positional uncertainty regarding the site of positron emission degrades spatial resolution, which in turn can cause severe quantification errors (i.e. $> 50\%$) through a mechanism called the partial volume effect [194]. The partial volume effect impacts small objects, in particular those more than two or three times smaller than the PET system’s resolution. Essentially, since small objects cannot be properly resolved, their activity is diffused over a larger area. Consequently, though the sum total activity remains constant, the maximal activity is greatly reduced.

The ensuing commentary discusses the reasons that PET cannot perfectly localize positron emissions, thereby limiting resolution and giving rise to quantification errors via the partial volume effect. For simplicity, it is also assumed that only trues are detected, ignoring false LORs (i.e. scatter and randoms).

Numerous issues prevent the precise localization of positron emissions. For one, PET systems do not detect positron emission; they detect positron annihilation, which occurs some distance away from the site of emission. This is because at emission, positrons have some kinetic energy as dictated by the nuclear energy levels and
the proportion of kinetic energy given to the neutrino that is also produced in the reaction. Since positron annihilation is more probable when the positron is moving slowly (and hence has more time to interact with the electron), the positron generally dissipates some of its initial kinetic energy in the form of a series of collisions prior to annihilation. Thus, the positron effectively follows a random walk from the site of emission prior to emitting the photon pair. The typical distance a positron travels before it annihilates is called the positron range, and varies from one radionuclide to another [37].

Further, the assumption that the coincident photons are emitted at 180° to one another is false. The positron typically has a non-zero momentum at annihilation. Therefore, according to the conservation of linear momentum, the two photons produced from the annihilation must have the same net momentum as the positron. As velocity and momentum vectors are parallel, this implies the vector sum of the photon velocities is nonzero. Of importance to PET imaging, this induces a slight noncolinearity of 180° ± 0.25° thereby mislocalizing the LOR. The effects of positron range and photon pair noncolinearity are illustrated in Figure 1.4.

More important than positron physics is the finite size of each detector, making it impossible to know exactly where a given photon struck the device. There is uncertainty with respect to LOR localization both in two directions parallel and the one direction perpendicular the the detector face (Figure 1.5. The latter case is known as the depth-of interaction effect [92], referring to at what depth the photon interacts with the detector.

Finally, a few words about time-of-flight information are warranted as it behaves differently than the other factors that degrade resolution. Time-of-flight is not necessary to reconstruct PET images, nor does it improve spatial resolution. Rather, by providing an estimate of the photon’s origin along the LOR, each photon becomes
Figure 1.4: Realistic LOR affected by positron range and photon pair noncolinearity. The outer ring is a cylindrical array of PET detectors. The light grey ellipse in the centre represents a patient’s body. The star is the site of positron emission. The thin, irregular line emanating from the site of positron emission represents the positron’s path prior to annihilation at the black circle. The thick black lines originating from the annihilation site are the photon trajectories. Note that they are at an (exaggerated) angle to one another, preserving the initial momentum of the positron. The dashed line is the observed LOR, which does not cross the positron emission site.
Figure 1.5: Impact of detector size on LOR localization. The outer ring is a cylindrical array of PET detectors. The light grey ellipse in the centre represents a patient’s body. Activated detectors are marked with a white circle. (A) If there is a photon pair strikes two detectors directly opposite one another, the uncertainty of the positron annihilation site is only as large as the detector face, as indicated by the translucent grey rectangle. (B) If the photon pair strikes a pair of detectors that are not directly opposite, there is additional uncertainty as to the positron annihilation site as indicated by the larger translucent grey rectangle. This occurs because the depth within the detector at which the interaction occurred is unknown, i.e. the depth-of-interaction effect.
more “useful” in determining the underlying distribution. Thus, a reconstruction making use of time-of-flight can achieve the same image quality as one that does not, but with fewer recorded counts [199]. In other words, time-of-flight boosts the statistical power of a PET scan.

1.3.2.3 Observed Radiopharmaceutical Distribution

The last physical mechanism that undermines PET’s quantitative fidelity is that detected radiation is not representative of the underlying radiopharmaceutical distribution. Attenuation [113], randoms [27], and scatter [223] are responsible for this disconnect. Attenuation reduces the number of trues coming from the patient by well over an order of magnitude, especially in regions where the photons must travel through large amounts of matter to escape [113]. The result is a grossly inaccurate image including, but not limited to, disproportionately low counts towards the patient’s centre and seemingly “hot” lungs (since the lungs are mostly air and do not interact with many photons). Randoms, in contrast, are detected by chance essentially approximately uniformly over the entire field of view, posing as trues. In whole-body imaging, randoms often exceed trues, resulting in substantial overestimates of activity over the whole image in addition to deteriorating SNR with the excess artifactual activity [27]. Finally, scatter neither removes trues nor adds fallacious ones, but rather shifts the apparent LOR of a true to an incorrect location. Typically, the result is a specious migration of activity from the edge of the patient towards the centre. As with randoms, the amount of scatter can easily exceed the number of trues in whole-body imaging with serious consequences for quantification [223].

In addition to attenuation, randoms, and scatter, imperfections and geometrical variation in the detectors can also alter the perceived radiopharmaceutical distribu-
tion potentially causing image distortions. There are two characteristic distortions: nonlinearity, wherein linear objects appear curved, and nonuniformities, wherein objects with uniform activity appear to have variable activity. These problems are often detected via routine quality control and are rectified using normalization procedures.

In sum, a great number of physical factors preclude perfect quantification in PET imaging. Each limitation can be categorized according to whether it adversely impacts count statistics, degrades resolution, or alters the appearance of the radiopharmaceutical distribution.

1.3.3 Biological Factors

When a radiopharmaceutical is administered, its distribution and behaviour is dictated by the organism’s physiology. Consequently, multiple biological factors influence quantification (Table 1.2).

In the most general terms, uptake is a function of how much radiotracer reaches and attaches to a given tissue. This in turn is impacted by the route of tracer administration, the blood perfusion of the tissue of interest, the rate and strength of binding, and the availability of binding sites. A thorough discussion of these factors is beyond the scope of this article, but there are reviews that delve into some of these issues more deeply [154, 159]. Furthermore, radiotracer uptake is a dynamic process, so quantification becomes a function of time. The allowed uptake period not only impacts clinical interpretation of PET images [128], but is also a critical consideration when comparing PET scans to one another [23].

Additionally, there are innumerable processes that can modify one or more of the factors that directly determine a radiopharmaceutical’s biodistribution. For example, a well-known confounder that impacts FDG uptake is blood glucose level [126]. In tumours, glucose competes with FDG for uptake resulting in an inverse relationship
Table 1.2: Biological factors that impact quantification.

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Factor</th>
<th>Explanation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Directly impacts biodistribution</td>
<td>Route of radiotracer administration</td>
<td>May alter capacity to reach different parts of the body</td>
</tr>
<tr>
<td></td>
<td>Perfusion</td>
<td>Often mechanism by which radiotracer is transported</td>
</tr>
<tr>
<td></td>
<td>Binding affinity</td>
<td>Faster and stronger binding increase uptake</td>
</tr>
<tr>
<td></td>
<td>Binding sites</td>
<td>More sites implies more uptake</td>
</tr>
<tr>
<td></td>
<td>Uptake time</td>
<td>Radiotracer uptake is dynamic</td>
</tr>
<tr>
<td>Modifies factors that impact biodistribution</td>
<td>Blood glucose</td>
<td>Competitive binding with FDG in certain tissues</td>
</tr>
<tr>
<td></td>
<td>Physical activity / patient discomfort</td>
<td>Stimulates FDG uptake in muscles</td>
</tr>
<tr>
<td></td>
<td>Hypoxia</td>
<td>Affects cell membrane transporters that import FDG</td>
</tr>
<tr>
<td></td>
<td>Medications</td>
<td>Huge range of effects</td>
</tr>
<tr>
<td>Alters perceived biodistribution</td>
<td>Patient motion</td>
<td>Blurs image and causes emission / transmission mismatch</td>
</tr>
<tr>
<td></td>
<td>Superposition of activity</td>
<td>Multiple sources of uptake may occur within one voxel</td>
</tr>
</tbody>
</table>
between glucose level and activity, whereas in muscles the association is reversed with glucose stimulating additional FDG uptake. (Incidentally, FDG uptake in muscles is also stimulated by physical activity and patient discomfort [60].) Correction algorithms have been proposed to account for blood glucose, but their benefit is not clear [142] and they remain a matter of debate [23]. Another example is hypoxia, which impacts cell membrane transporters that handle FDG [159]. A third is medication status, and depending on what medication is being taken and what radiopharmaceutical is being used, the potential effects are practically infinite. This list is by no means comprehensive, as essentially anything that alters the body’s chemical environment could influence radiotracer uptake.

Quantification errors also arise if a biological process alters the perceived biodistribution. One example is patient motion. The motion can be physiological (e.g. respiration, cardiac activity, peristalsis, etc.) or gross (e.g. shifting weight). Part of motion-induced error stems from a blurring of the emission data, creating a pseudo-partial volume effect. A more subtle aspect of the error, with particular relevance to CT-based attenuation correction, is that motion creates a fundamental mismatch between emission and transmission data. Emission data is collected over a relatively long period of time, during which the patient moves. In contrast, the CT scan is acquired quickly, representing the patient at an instant in time. The mismatch can lead to substantial quantification and lesion localization errors [61, 69]. Correction of motion artifact is an arena in which PET/MRI is likely to excel because MRI can be used to collect movies (or more properly, “cines”) of patient motion without exposing them to any ionizing radiation. The cines can then be used to guide PET image reconstruction [52, 72]. In contrast, motion correction via CT is usually not practical because of the associated radiation burden.

Another factor that alters perceived radiotracer uptake is the complexity of biolog-
ical systems. Many physiological processes alter the pattern of radiopharmaceutical distribution, potentially misleading the observer. For instance, if multiple sources of radiotracer uptake are superimposed in the same spatial location, separating them becomes challenging if not impossible. Inflammation surrounding a tumour in FDG PET is a good example. In this case, uptake in the tumour is likely the property of interest, but its quantification is confounded by uptake owing to the inflammatory response. A number of additional examples are reviewed by Gorospe *et al* [68]. A familiarity with typical patterns of tracer uptake is helpful in identifying this type of mistake [60].

### 1.3.4 Technical Factors

The operator has many options in PET imaging. There are multiple ways to reconstruct the images, multiple approaches to extract quantitative data, and multiple image acquisition protocols. The choices the operator makes on each of these fronts influences quantification; I refer to this type of quantitative variation as technical error, the sources of which are summarized in Table 1.3.

#### 1.3.4.1 Image Reconstruction

Before delving into how image reconstruction algorithms impact quantification, some background is necessary. PET systems do not collect images. Rather, they collect LORs (and sometimes time-of-flight information) that serve as inputs for a reconstruction algorithm that creates the image. To do so, every reconstruction algorithm models the photon detection process and the associated noise; the better the model, the better the output image.

Reconstruction methods can be classified as either analytic or iterative. Roughly speaking, analytic methods generate an image by solving a mathematical equation.
Table 1.3: Technical factors that impact quantification. (SUV = standardized uptake value.)

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Factor</th>
<th>Explanation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alters raw data to image conversion</td>
<td>Reconstruction algorithm</td>
<td>Huge selection, each with different assumptions</td>
</tr>
<tr>
<td></td>
<td>Free parameters</td>
<td>Reconstruction algorithms can usually be tuned</td>
</tr>
<tr>
<td>Alters the information extracted from the image</td>
<td>Model</td>
<td>Many kinetic models and simple measures like SUV</td>
</tr>
<tr>
<td></td>
<td>Free parameters</td>
<td>Tune kinetic models, variable SUV interpretation</td>
</tr>
<tr>
<td>Alters raw data</td>
<td>2D v.s. 3D acquisition</td>
<td>3D mode increases trues, randoms, and scatter</td>
</tr>
<tr>
<td></td>
<td>Transmission scan</td>
<td>Choice dictates attenuation map’s form</td>
</tr>
<tr>
<td></td>
<td>Contrast agents</td>
<td>Creates artifacts in CT-based attenuation maps</td>
</tr>
</tbody>
</table>
This is called a closed-form solution. In contrast, iterative methods start with a crude guess of the image, compare it to the data collected by the scanner, and update the guess in such a way that it better matches the observed data. This process is repeated (i.e. the algorithm iterates) until some stopping criterion is reached. For instance, the algorithm might continue until the guess stops changing or until a predefined number of iterations is reached.

All iterative algorithms possess an “objective function”. This is an equation that compares the current guess to the observed data. For the purposes of this discussion, the better the guess, the bigger the number the objective function calculates. (In actuality, in some objective functions smaller numbers equate with better guesses, but this is a triviality that is easily reversed by introducing a negative sign.) Thus, the objective function is what guides the guessing: the iterative algorithm seeks the guess that maximizes the objective function. In many ways, the shape of the objective function dictates how well the iterative algorithm will work. For example, if the function looks like a hill, with only one maximum surrounded by a smooth descent, finding the peak is relatively easy. However, if the function looks more like the sea during a storm, there are multiple peaks, and it becomes very difficult to find the largest. This type of function is undesirable because it becomes possible for the guess to converge on the wrong peak.

Let us now return to how reconstruction methods influence quantification, starting with analytic methods. Analytic reconstruction methods—the most common one known as filtered backprojection—were borne of the notion that the number of true for any detector pair is directly proportional to the activity between them. The 3D closed-form solutions of this model have long been known [40] and modified to accommodate the practical reality of truncated datasets [114], that is, situations where the patient is not completely surrounded by detectors. (Recall the discussion
of geometric efficiency in §1.3.2.)

Analytic methods are fast and relatively easy to implement, so they unsurprisingly served as the workhorse of PET reconstruction for many years. However, the model upon which analytic methods are based is flawed, failing to account for physical phenomena such as positron range and photon pair noncollinearity. It also does not account for the fact that detector sensitivity changes depending on where the annihilation event happened. Further, the statistical nature of radioactive decay is not considered. Ergo, images reconstructed with analytic techniques do not make optimal use of the acquired data and suffer from degraded resolution and noise characteristics. For these reasons, analytic reconstruction methods are increasingly falling out of favour and are certainly not ideal for accurate quantification.

Iterative reconstruction algorithms, which are reviewed by Qi and Leahy [166], are an excellent alternative. Popularized in the 1980s [122, 190] iterative algorithms can elegantly incorporate the physics of the photon detection process and radioactive decay statistics into a probabilistic model. However, depending on the specific algorithmic choice, four main problems may become manifest: i) it can take a long time, ii) it can produce the wrong answer, iii) it may never reach an answer, and iv) the problem may be ill-conditioned, i.e. the answer may be sensitive to small changes in the acquired data. For instance, the first iterative algorithm (i.e. the maximum likelihood expectation maximization algorithm) [190] converges to a definitive answer, but is slow and ill-conditioned. In practice, it has been supplanted by the ordered subset expectation maximization algorithm [91], which is much faster but may not in fact converge on a single answer.

Ill-conditioning is a very common problem for reconstruction algorithms. In practice, its effect is to create a checkerboard pattern on the image after many iterations. Thus, ill-conditioning is often approached by either terminating the iterations early
or filtering the images [191] to get rid of the checkerboard effect. Alternatively, ill-conditioning can be abetted by modifying the objective function such that it promotes image smoothness (i.e. penalizes sharp changes in intensity) [62]. This can be accomplished equivalently by incorporating into the algorithm a prior notion of what the reconstructed image should look like; this is the so-called Bayesian approach [70] (Figure 1.6). Unfortunately, both these workarounds complicate the objective function by introducing multiple peaks [166]. They also make implementation more difficult and can increase computational burden.

Figure 1.6: Two reconstructions of simulated data from the Shepp-Logan phantom. (A) No compensation for ill-conditioning. (B) Bayesian approach. Note the former appears noisy compared to the latter. Adapted from Teng et al [201].

In short, there is no perfect reconstruction algorithm; quantification is a function of not only which algorithm is chosen, but also the values assigned to the chosen algorithm’s free parameters [1].
1.3.4.2 Quantitative Model

Once a PET image is reconstructed, the quantitative information of interest must be extracted. If precise physiologic measurements in absolute terms are required, such as the rate of glucose uptake from the blood into cells, a kinetic model will likely be needed. These are techniques that model the radiotracer concentration in various body compartments (e.g. blood and intracellular) and its transfer between them. However, multiple kinetic models are available [93, 95, 157, 193], and as with image reconstruction, the results one gets depend on model selection and the choice of free parameters.

Though kinetic modeling techniques provide detailed quantitative information, they are often laborious and impractical, requiring, for example, arterial blood sampling and a constant patient bed position in the PET scanner. For this reason, the most popular approach to extract numeric data from PET images is via the standardized uptake value (SUV). This semi-quantitative parameter is free from many of the restrictions imposed by kinetic models but nonetheless correlates well with gold standard measures [58, 88]. The idea is to measure the radioactivity within a user defined region called a volume of interest (VOI), and to somehow normalize this measurement across patients. Thus, the SUV is defined as:

\[
SUV = \frac{(\text{measure of activity in a volume of interest}) \times (\text{normalization factor})}{\text{administered dose corrected for decay}}
\]

The preceding definition is left intentionally broad because variations in its interpretation lead to technical errors. Let us first focus on what is meant by a “measure of activity”. The most common method to measure activity in the SUV is to use the maximal activity in the VOI [211]. Since the maximal activity is solely determined by
a single voxel, this method is resistant to the partial volume effect and VOI selection. By the same token, it is highly susceptible to image noise [24]. Alternatively, one can compute the mean activity in the VOI, an approach that is less susceptible to noise but sensitive to the partial volume effect and VOI structure [24]. Thus, VOI selection can dramatically affect the SUV, and the choices abound with respect to both shape and placement.

Clearly, much variation can be introduced in the “measure of activity in a VOI” term of SUV’s definition. Let us now turn to the “normalization factor” term. Traditionally, this is the subject’s body weight. However, as FDG exhibits low uptake in white fat, normalizing by body weight in obese patients results in overestimations [198]. Therefore, alternate normalization factors including lean body mass and body surface area have been developed that largely eliminate the SUV’s dependence on body weight [198]. Of course, the SUV will vary depending upon which normalization factor is selected.

Regarding the “administered dose corrected for decay” term, the errors impacting it are human in nature and are covered in §1.3.5. The variation in SUV measurements induced by alternate formulations points to an urgent need for standardization [23, 211], without which comparisons of SUVs across sites and PET systems become meaningless [180].

1.3.4.3 Data Acquisition

A final mechanism giving rise to technical error is via the image acquisition protocol. For instance, many PET systems have the option of acquiring in 2D or 3D mode. Recall that this amounts to whether only LORs parallel to the axial plane are recorded or whether all LORs are recorded, respectively. The characteristics of the acquired data vary significantly based on this choice; in particular, though sensitivity
to trues is vastly greater in 3D mode than in 2D mode, the proportion of coincidence events attributable to scatter and randoms increases markedly as does deadtime [92]. This in turn impacts quantification [124, 208]. Issues also arise with respect to the transmission scan for attenuation correction. The PET reconstruction is strongly dependent on the transmission method be it a positron source, gamma ray source, or x-ray source (see §1.4.3) [113]. Further, if x-ray CT is used, oftentimes intravenous and/or oral contrast is administered for diagnostic purposes [6], a practice that will bias the attenuation map and hence, the PET image. That said, this phenomenon may not be clinically significant [71, 218].

It should now be clear that quantification in PET is not only impacted by physics and biology, but by the operator’s choices with respect to image reconstruction, methods of analysis, and image acquisition protocol.

1.3.5 Human Factors

Human errors can compromise the quantitative fidelity of PET acquisitions (Table 1.4). Errors of this sort generally have to do with incorrectly measuring the amount of radioactivity in the patient’s body at a given time. With respect to the SUV, the “administered dose calibrated for decay” term is affected. For instance, this term will be overestimated if the residual radiation left in the syringe after an injection is not subtracted from the injected dose, producing an underestimated SUV. This also occurs in the event of a paravenous injection, wherein much of the radiopharmaceutical never actually makes it into the blood stream. Additionally, as the administered dose must be corrected for radioactive decay, the operator must accurately record when the dose was drawn up, injected, and assessed for residual activity. This information is typically entered into the PET system, which automatically applies the appropriate corrections using predicted exponential decay based on the radionuclide’s
half life. However, the reliability of these corrections hinges on the synchronization of the operator’s and PET system’s clocks. Finally, the PET system must be properly calibrated; that is to say, the relationship between count rate per unit volume and true activity concentration must be established. Further, the PET system must be cross-calibrated with the well counter (measures the radioactivity of samples, like urine or blood) and dose calibrator (measures the radioactivity administered to the patient). Incorrect calibrations are a real-world problem, posing particular difficulties for multi-centre studies [64].

1.4 Attenuation Correction

1.4.1 Definition of Attenuation

Attenuation is defined as the reduction in intensity of electromagnetic radiation as it travels through a medium and interacts with matter. To better understand attenuation, let us consider an experiment. Imagine there is a beam of photons. Each photon has the same energy, $E$. In other words, the beam is monoenergetic. The intensity of the beam, that is the number of photons passing through a unit area per unit time, is $I_0$. This beam is directed through a homogenous element of thickness $L$, atomic number $Z$, and density $\rho$. An ideal detector is positioned directly opposite the incident beam, only identifying photons with unaltered trajectories and energies, i.e. those that did not interact with the material. The intensity of the recorded beam is denoted $I$. The experimental setup is shown in Figure 1.7.

Let us define the change in beam intensity, i.e. $I_0 - I$, as $\Delta I$. Note that $I_0 \geq I$, since as the beam passes through the homogenous element, it can lose photons but not gain them. Therefore, $\Delta I \geq 0$. The fraction of photons that interacted with the element is given by the change in beam intensity divided by the initial intensity, i.e.
Table 1.4: Human factors that impact quantification.

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Factor</th>
<th>Explanation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alters perceived radiation in patient’s body</td>
<td>Not accounting for residual activity in syringe</td>
<td>Overestimates activity in body</td>
</tr>
<tr>
<td>Paravenous injection</td>
<td>Radiopharmaceutical not distributed throughout body, so activity effectively overestimated</td>
<td></td>
</tr>
<tr>
<td>Not accounting for radioactive decay</td>
<td>Overestimates activity in body</td>
<td></td>
</tr>
<tr>
<td>Inaccurate recording of important times</td>
<td>Time dose drawn up, injected, and checked for residual activity needed for radioactive decay correction</td>
<td></td>
</tr>
<tr>
<td>Operator and PET clock not synchronized</td>
<td>Biases time measurements, as PET system applies corrections</td>
<td></td>
</tr>
<tr>
<td>PET calibration to real activity</td>
<td>Without calibration, PET measurements are not quantitatively accurate</td>
<td></td>
</tr>
<tr>
<td>PET cross-calibration with other instruments</td>
<td>Well counter, dose calibrator, and PET must give the same readings or quantification will be biased</td>
<td></td>
</tr>
</tbody>
</table>
Figure 1.7: Experiment to measure attenuation. A radioactive source is positioned at the far left, with photon trajectories indicated by the lines emanating from it. Since it emits radiation in all directions, a source collimator is needed to create the photon beam. As the beam passes through a homogenous element, some photons reach the detector undeterred, while others interact with matter and are scattered. A detector collimator prevents scattered radiation from reaching the detector.
\[ \frac{\Delta I}{I_0} = -\mu L \]  

(1.1)

The negative sign simply indicates that the beam intensity has decreased. \( \mu \) has units of inverse length, typically \( \text{cm}^{-1} \).

Let us examine \( \mu \) in more detail. It essentially characterizes how effectively the element in our experiment interacted with the photon beam. The bigger it is, the more photons interact. But clearly different elements will have different propensities to interact with photons, so \( \mu \) must depend on the atomic number, \( Z \). Furthermore, it serves to reason that the denser the material, the more photons it will affect. This intuition is true, and it turns out \( \mu \) and density, \( \rho \), are directly proportional. Oftentimes it is desirable to remove this density dependence, and to do so one must simply divide \( \mu \) by \( \rho \), leading to the definition of the “mass attenuation coefficient”:

\[ \mu_m \equiv \frac{\mu}{\rho}. \]  

(The three horizontal lines simply mean “defined as”.) Finally, the energy of the photon beam influences the probability of photon/matter interactions, so \( \mu \) depends on \( E \) as well. In summary, for the mathematically inclined, \( \mu \) and \( \mu_m \) are both multivariate functions, related as follows:

\[ \frac{\mu(Z, \rho, E)}{\rho} = \mu_m(Z, E) \]  

(1.2)

Incidentally, \( \mu_m \) of composite materials (i.e. made of multiple elements) is easily calculated as the weighted average of its constituents’ \( \mu_m \)s.

But recall from §1.3.1 that there are multiple ways photons and matter can interact. In particular, the photoelectric effect, Compton scattering, and pair production
were described. There is also an additional interaction called coherent (Rayleigh) scattering that is similar to Compton scattering but is not associated with a loss of photon energy. So which of these interactions does $\mu$ characterize? All of them; $\mu$ accounts for photons that interact with matter via any mechanism. In fact, $\mu$ can be decomposed into the individual mechanisms of photon interaction. This is generally expressed in terms of the mass attenuation coefficient: $\mu_m = \eta + \tau + \sigma + \kappa$, where $\eta$ is the part of $\mu_m$ due to coherent scattering, $\tau$ is the part due to the photoelectric effect, $\sigma$ is the part due to Compton scattering, and $\kappa$ is the part due to pair production. Figure 1.8 illustrates the relationship between $\mu_m$, $\eta$, $\tau$, $\sigma$, and $\kappa$ over a range of photon energies in water, a good approximation for much of the human body. Note that at PET’s energy of 511 keV, $\mu_m$ is composed virtually entirely of Compton scattering, in agreement with our earlier discussion (Figure 1.3).

Now, let us return to the photon beam experiment outlined above but use a new material where $\mu$ varies along its length. We will reference what position we are at in the element with a new variable, $s$. Since $\mu$ depends on $s$, we can write it as a function, $\mu(s)$. Such a material can be thought of as several homogenous materials, each with its own $\mu$, glued end to end. Suppose that each of these segments is very thin (infinitesimally so, actually), and has a length $ds$. Each segment will cause the beam intensity to change (infinitesimally) by $dI$. Thus, for any arbitrary segment, we can use Equation (1.1) to relate the fraction of photons that make it through, $dI/I_0$, to its particular linear $\mu$-coefficient, $\mu(s)$, and its length, $ds$:

$$\frac{dI}{I_0} = -\mu(s)ds \quad (1.3)$$

By summing up the contributions from each segment, one can determine the total amount of attenuation that occurs. When summing infinitesimal quantities in
Figure 1.8: Component photon/matter interactions that sum to $\mu_m$ over a range of energies. These include coherent scattering ($\eta$), the photoelectric effect ($\tau$), Compton scattering ($\sigma$), and pair production ($\kappa$). Adapted from Yip [219].
mathematics, the operation is called integration, denoted by $\int$. When both sides of Equation (1.3) integrated and rearranged, we find that:

$$\frac{I}{I_0} = e^{-\int_{\text{photon beam path}} \mu(s) \, ds} \quad (1.4)$$

The summation is carried out over the entire path of the beam, through all objects that it might interact with.

Equation (1.4) is important; given any material with arbitrarily varying (and known) $\mu$-coefficients along its length, we are able to compute the proportion of photons that will make it through. Importantly, the expression on the right side of the equation can be interpreted as the probability that a given photon will pass through the material unimpeded.

This result can be adapted to PET by applying Equation (1.4) to both photons that make up a photon pair released from a positron annihilation. In particular, the probability that each photon will reach the ring of detectors is $\exp \left( -\int_{\text{half of LOR}} \mu(\vec{r}) \, ds \right)$. The summation runs over the half of the LOR that one of the two photons traverses. The term $\vec{r}$ is simply shorthand for the three coordinates that describe the photon’s position in 3D space. In order to generate a coincidence event, both photons must be detected. These events are independent: one photon’s fate does not influence the other’s. Thus, the probability of a coincidence is simply the product of the probabilities that each photon will be detected. When computed, the following result emerges:

$$p(\text{coincidence}) = e^{-\int_{\text{LOR}} \mu(\vec{r}) \, ds} \quad (1.5)$$

This is a remarkably simple result. It says that if one knows the spatial distribution of attenuation coefficients, i.e. $\mu(\vec{r})$, or in other words the attenuation map ($\mu$-map), one can calculate the probability that a photon pair will reach the detector along any
LOR. Moreover, the answer only depends on the $\mu$-coefficients along the LOR under consideration.

1.4.2 How Attenuation Is Corrected

Assuming the $\mu$-map, i.e. $\mu(\vec{r})$, is available (the acquisition of which is the subject of §1.4.3), attenuation correction (AC) is quite straightforward. Generally speaking, there are two ways to carry out AC.

One approach is to pre-correct the PET data prior to reconstruction. Suppose that a dataset of coincidence events has been acquired and that all corrections aside from attenuation have already been applied. (AC is often last to be completed in clinical PET systems.) The acquired coincidences can be binned according to which detector pair recorded them, or in other words, which LOR they came from. Suppose that $n$ trues were recorded along a particular LOR. The actual number of positron decays along the LOR, $n_0$, is easily calculated by appealing to (1.5). One must simply divide the number of observed trues by the probability that any given photon pair emitted along the LOR would be detected. Put another way, to figure out how many trues along a given LOR would have been recorded if there was no attenuation, one must multiply the observed number of trues by the following “attenuation correction factor”:

$$\text{attenuation correction factor} = e^{\int_{\text{LOR}} \mu(\vec{r}) \, ds}$$  (1.6)

This simple modification of the observed data effectively erases the effects of attenuation.

Alternatively, AC can be carried out during the reconstruction process. Iterative reconstruction methods depend on an object known as the system matrix, $P$. A given element, $P_{ij}$, represents the probability that a photon pair emitted from the $j$th pixel
will be detected by the $i$th detector pair. Each detector pair has an associated LOR. Using $\mathbf{P}$, one can state the PET reconstruction problem quite elegantly. To do so, let us define two vectors. Let $\vec{a}$ be the actual radioactivity in each image voxel, which is what we wish to find. Let $\vec{n}$ be observed counts along each LOR, which is what the PET scanner measures. The relationship between $\mathbf{P}$, $\vec{a}$, and $\vec{n}$ is simply:

$$\vec{n} = \mathbf{P}\vec{a}$$  \hspace{1cm} (1.7)

All the physics of how $\vec{a}$ gives rise to $\vec{n}$ is modelled in $\mathbf{P}$. Accordingly, the effect of attenuation can be directly incorporated into $\mathbf{P}$. This is done by dividing each row by the $i$th attenuation correction factor [78]. In this way, reconstruction is carried out without modifying the acquired data itself. This technique has some advantages in terms of preserving the Poisson nature of the data when rebinning a 3D acquisition to 2D slices [41].

1.4.3 How the $\mu$-Map Is Obtained

1.4.3.1 Transmission Scan Primer

The crux of AC is in finding $\mu(\vec{r})$, and doing so is the subject of multiple reviews [8, 113, 222, 224]. Finding $\mu(\vec{r})$ is greatly simplified by a process known as transmission scanning. Up to this point, we have been focusing on PET which is an emission scan, i.e. image formation relies on detecting radiation emitted from within the patient. In contrast, in transmission scanning, radiation is produced by a source external to the patient and transmitted through the patient’s body. The fraction of photons that make it through the patient are recorded, much like the experiment described in §1.4.1. This is repeated from several different angles around the patient; the data collected at each angle is referred to as a “projection”. Each projection can be loosely
thought of as a planar image like that produced via standard x-ray radiography. Image reconstruction algorithms are able to convert the planar projections into a 3D volume of $\mu$-coefficients, i.e. $\mu(\vec{r})$!

Transmission scans can take many forms. The most widely known is x-ray CT, but it is by no means the only example. One can categorize transmission scans according to two parameters: 1) the shape of the radioactive source and 2) the energy of the transmitted radiation. These are discussed in detail in §1.4.3.3 and §1.4.3.4, respectively. First, however, I will explain how $\mu(\vec{r})$ can be formed without a transmission scan at all.

### 1.4.3.2 Without a Transmission Scan

There are ways to acquire $\mu(\vec{r})$ without a transmission scan, summarized in Table 1.5. This is appealing as transmission scans can take several minutes to acquire, require additional instrumentation and maintenance, and deliver an additional radioactive dose to the patient, though the dose can vary widely depending on the type of transmission scan acquired. Unfortunately, as will become evident, obtaining a reliable $\mu$-map is challenging if depending only on emission data.

The simplest approach for generating $\mu(\vec{r})$ is to draw it manually based on a reconstruction of the uncorrected emission data [123]. Although this method is easy to implement, it induces a dramatic tradeoff between $\mu(\vec{r})$’s accuracy and the time spent creating it. Further, it is subject to inter-operator variability. A more sophisticated approach is to automate the $\mu$-map drawing process. For example, an early algorithm developed by Bergström et al [16] used the derivatives of the emission projections to infer the boundary of the patient’s head, assigning a constant linear $\mu$-coefficient therein. Techniques like this eliminate human labour and inter-operator variability, but are inherently limited in their capacity to generate detailed $\mu$-maps.
Table 1.5: Benefits and drawbacks of the approaches to obtain $\mu(\vec{r})$ without a transmission scan.

<table>
<thead>
<tr>
<th>Method</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Manual drawing</td>
<td>Easy implementation</td>
<td>Accuracy/effort tradeoff</td>
</tr>
<tr>
<td>Automated drawing</td>
<td>Little or no human effort, repeatable</td>
<td>Limited accuracy</td>
</tr>
<tr>
<td>Image registration</td>
<td>Arbitrary accuracy</td>
<td>Template $\mu$-map may not reflect patient, registration nontrivial</td>
</tr>
<tr>
<td>Reconstruct</td>
<td>Arbitrary accuracy</td>
<td>Image/$\mu$-map crosstalk, complicated objective function</td>
</tr>
<tr>
<td>Consistency conditions</td>
<td>No image/$\mu$-map crosstalk</td>
<td>Limited accuracy</td>
</tr>
</tbody>
</table>

One tactic to add detail to the $\mu$-map is to make use of an atlas consisting of both a nuclear medicine scan and a paired $\mu$-map. First, the former is aligned to the uncorrected reconstructed emission data. The transform used to achieve the alignment is applied to the $\mu$-map, which then serves as $\mu(\vec{r})$. This idea was initially applied in SPECT [197]. Though this approach allows for an arbitrarily detailed $\mu$-map, its reliability depends on how well $\mu(\vec{r})$ represents the patient, a function of both the alignment accuracy and morphological discrepancies between the atlas and patient.

An alternate scheme is to treat $\mu(\vec{r})$ as an unknown and incorporate its discovery into the reconstruction algorithm. This notion was conceived by Censor et al [33], and has since been incorporated into modern iterative reconstruction algorithms [149]. This provides more flexibility in $\mu(\vec{r})$’s construction than do automated drawing procedures, but framing the reconstruction in this manner results in a complicated
objective function with many peaks. Thus, convergence to the correct \( \mu \)-map is in no way guaranteed. This is because the reconstructed PET image and \( \mu(\vec{r}) \) affect one another, a phenomenon called cross-talk. However, by modifying the reconstruction algorithm such that image smoothness is encouraged, the amount of cross-talk can be reduced [149]. (Recall that ill-conditioning is also rectified in such a manner.)

Another interesting means to estimate \( \mu(\vec{r}) \) during image reconstruction is via the use of “consistency conditions”, or more formally, the Helgason-Ludwig conditions. Described in the context of emission tomography by Natterer [143], the premise hinges on the fact that an ideal set of emission data demonstrates internal consistency. In particular, the zeroth condition stipulates that the activity recorded in each projection is equal while the first condition states that the first moments of the projections should trace out a sine wave. This is because the first moment is a stationary point in image space and therefore manifests as a sine wave in the sinogram. Higher order conditions involve the characteristic tracings (sums of sines with different periods) of higher order moments. The \( \mu \)-map that best satisfies these constraints when applied to the emission data is chosen. The problem is that the Helgason-Ludwig conditions alone are not sufficient to compute an arbitrary \( \mu(\vec{r}) \). However, if a template \( \mu \)-map is parameterized, the consistency conditions may be used to find the optimal parameters. For example, an early application to PET used a generic 2D torso phantom parameterized by an affine transformation [212] (i.e. it could be rotated, translated, scaled, and sheared). Unfortunately, though this methodology eliminates the cross-talk between the emission image and \( \mu \)-map, it comes at the cost of greatly limiting \( \mu(\vec{r}) \)'s form since the template \( \mu \)-map can only be transformed certain ways.
Table 1.6: Benefits and drawbacks of various transmission scan geometries.

<table>
<thead>
<tr>
<th>Radioactive source geometry</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ring source</td>
<td>Collect all projection angles simultaneously</td>
<td>Cannot separate transmission from emission data, must use coincidence detection</td>
</tr>
<tr>
<td>Line source</td>
<td>Can separate transmission from emission data, can use coincidence or singles detection</td>
<td>Only one projection angle at a time, deadtime losses with coincidence detection</td>
</tr>
<tr>
<td>Point source</td>
<td>Same as rotating line source, but can also be used in 3D mode</td>
<td>Same as line source, but also not a standard implementation</td>
</tr>
</tbody>
</table>

1.4.3.3 Geometric Considerations for Transmission Scans

Calculating $\mu(\vec{r})$ is simplified via transmission scanning. The first examples of images formed by $\gamma$-ray transmission were described in 1952 by Mayneord [134]. These were planar projection images, similar in appearance to those obtained via conventional radiography. Fourteen years later, the first transmission images acquired in conjunction with emission images were collected for the purposes of anatomic localization [119]. This preceded the development of PET and SPECT, and again, the images were simply projections. Nineteen seventy-five marked the birth of transmission scanning for AC in PET [49, 161].

Transmission scans can take multiple forms. A key defining characteristic of a transmission scan is its acquisition geometry. Geometry refers both to the shape of the photon source and whether the radioactive source is a single photon emitter or photon pair (i.e. positron) emitter. Important geometric features are summarized in Table 1.6.
The most common photon source shapes are a ring, a rotating rod, or a rotating point (Figure 1.9). For transmission scanning to work, one must know where each detected photon originated, otherwise there is no way of knowing what part of body it passed through. With this in mind, consider the ring source. If the radioactive material in the ring was a single photon emitter, that is each radioactive decay released one photon rather than a photon pair, there would be no way to tell which part of the ring any detected photons came from. However, if the radioactive material was a positron emitter, thereby releasing a photon pair with each decay, each coincidence defines a LOR, and its intersection with the ring is where the transmitted photon originated. A problem with this geometry is that there is no reliable method to exclude scatter and randoms. More importantly, the transmission scan cannot be conducted during the emission scan as there is no way to distinguish between emitted and transmitted coincidences; therefore, the transmission scan must be carried out prior to radiopharmaceutical administration, significantly lengthening the patient’s exam.

These problems are addressed by the rotating rod source with a positron emitter. By only accepting LORs collinear with the rod (a process called windowing), scatter and randoms are greatly reduced and the transmitted photons can be separated from emitted ones. Accordingly, transmission scanning can be accomplished during the radiotracer uptake period [30] or even during emission data collection [136]. Unfortunately, a great deal of radiation strikes the detectors adjacent to the rod, leading to significant deadtime effects that compromise the count rate.

Herein lies the value of using a single photon emitter (or singles triggering of a positron emitter) with a line source. Since the concept of coincidence detection is meaningless for single photon emitters, the detectors nearby the rod source can be shielded, mitigating the deadtime problem and substantially increasing count rate.
Figure 1.9: Various transmission scan geometries. The radioactive source is shown in red. (A) Ring photon pair source. Positron annihilations are represented by the black circles. Note that the origin of the transmitted photon can be inferred via coincidence detection; the LOR crosses the ring at two points and either can be selected as the origin. This would not be possible with a single photon emitter as they do not generate a LOR. (B) Rotating line (or point) photon pair source. In this circumstance, scatter and randoms can be largely eliminated by only accepting LORs collinear with the source. However, there are large deadtime losses adjacent to the source. (C) Rotating line (or point) single photon source. Though windowing is no longer possible, the deadtime losses adjacent to the source are eliminated by shielding.
However, windowing becomes impossible as it depended on coincidence detection. Also, as with the ring, the origin of any detected photons is unknown; it could be anywhere along the rod. To circumvent this problem, this approach must be combined with shields called inter-slice septa that block any photons that are not perpendicular to the rod. If this is done, the photon’s path may be computed using the rod’s position and the point of detection within any given axial slice.

The first description of a single photon emitting line source actually used singles triggering of a positron emitter and reported greatly improved statistics compared to a line source with coincidence counting, but deteriorated axial resolution due to the need for inter-slice collimation, eliminating cross plane acquisitions [45]. Later incarnations used $^{137}\text{Cs}$ as the emitter, an isotope that releases 662 keV photons [108, 220]. Not only does $^{137}\text{Cs}$ cost less and have a much longer half-life than $^{68}\text{Ga}/^{68}\text{Ge}$ generator systems (the positron emitters of choice for transmission scanning), its altered photon energy enables transmitted photons to be distinguished from emission data given sufficient energy resolution [108]. However, for many systems (e.g. with bismuth germinate scintillator crystal detectors) this is not feasible [220].

Finally, if one wishes to conduct a fully 3D transmission scan with a single photon emitter, one must use a rotating point source since the photon origin is always known in that case [9, 108].

### 1.4.3.4 Energy Considerations for Transmission Scans

A second key feature of transmission scans is what photon energy is selected. Recall that $\mu$-coefficients are dependent on photon energy (§1.4.1). Thus, only 511 keV will provide the correct values for $\mu(\vec{r})$ since that is the energy of the radiopharmaceutical. If any transmission photon energy is used, the measured $\mu$-coefficients will be biased. (Incidentally, the presence of scatter and randoms has a similar effect.)
Table 1.7: Benefits and drawbacks of various transmission scan energies.

<table>
<thead>
<tr>
<th>Radioactive source type</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positron emitter (511 keV)</td>
<td>(\mu)-coefficients unbiased</td>
<td>Severe transmission time/statistics tradeoff</td>
</tr>
<tr>
<td>Single photon emitter (monochromatic energy, 100s of keV)</td>
<td>Relatively fast scans with good statistics</td>
<td>(\mu)-coefficients slightly biased (depending on energy), requiring mapping or segmentation</td>
</tr>
<tr>
<td>X-ray CT (polychromatic energy, 40–140 keV)</td>
<td>Very fast scans with excellent statistics, doubles as anatomical localization with diagnostic quality</td>
<td>(\mu)-coefficients highly biased, requiring mapping or segmentation, high radiation dose</td>
</tr>
</tbody>
</table>

However, as alluded to in §1.4.3.3, oftentimes using energies aside from 511 keV can accelerate the transmission scan, and/or improve its signal to-noise-ratio. This was the impetus for using single photon emitters. Even greater accelerations can be obtained by using an x-ray source, i.e. PET/CT [115]. The photon flux attainable in CT scans is much greater than that of \(\gamma\)-ray sources, yielding high SNR transmission scans in a matter of seconds. If acquired after radiotracer administration, the CT scan remains uncontaminated by 511 keV emission photons due to their relatively minuscule number in comparison to the x-ray photons.

If the transmission scan is obtained at an energy other than 511 keV, \(\mu(\vec{r})\) must be mapped to the correct 511 keV, linear \(\mu\)-coefficients. One method of accomplishing said mapping is via a mathematical function. When compensating for photon energy differences, the function becomes more complicated the further from 511 keV the transmission photon energy is. For example, as Compton scatter is the dominant
interaction in human tissue for both 511 keV and 662 keV photons (Figure 1.8), attenuation correction factors derived from $^{137}$Cs imaging can be scaled to the appropriate values using a simple exponential relation [220]. However, at x-ray energies, both the photoelectric effect and Compton scatter contribute to attenuation, and furthermore, they contribute to different extents in soft tissue versus bone; this necessitates a bilinear mapping function, often with the lines meeting at 0 HU [29, 115].

More generally, the mapping is a function of both atomic number and density. A means to identify the correct mapping for any materials is by dual-energy CT, which allows the relative contributions of the photoelectric effect and Compton scatter to be inferred over a wide range of energies [4]. This principle has been applied for AC in PET [73, 112], but as it complicates the transmission scanning protocol and can expose the patient to additional ionizing radiation, it is not used routinely.

With respect to CT specifically, there is an additional complication concerning photon energy. The x-rays are not monoenergetic, but rather range from about 40 keV to around 140 keV, depending on the acquisition protocol. The lower energy photons are preferentially attenuated, shifting mean photon energy upwards, a phenomenon known as beam-hardening. The degree of beam-hardening is a function of the patient’s geometry, composition, and photon path, resulting in local intensity variations in the reconstructed image that are not representative of the actual CT number. The problem is exacerbated when highly attenuating materials such as dental implants [107], pacemakers or defibrillator leads [51], and joint replacements [65] are present. (These high atomic number materials also reduce image quality by virtue of increased noise, partial voluming, scatter, and exceeding the image’s dynamic range, i.e. clipping.) All CT scanners apply routine beam-hardening corrections, but they are imperfect and research in the field remains active [209].

A convenient method of correcting biases in $\mu(\vec{r}, t)$, be they from photon energies
other than 511 keV, scatter, or beam hardening, is via image segmentation. In particular, if one can divide $\mu(\vec{r})$ into its component tissues, the appropriate $\mu$-coefficient can simply be assigned to each region. Segmentation also has the advantage of eliminating noise from the transmission scan. First proposed in 1981 by Huang et al [89], a rich body of research has emerged on the subject [17, 115, 138, 217].

Segmenting the $\mu$-map does bear some disadvantages, though. The segmentation can be quite challenging, and the quality of the AC is only as good as the robustness of the segmentation algorithm. Further, by its very nature, segmentation compresses a continuum of values (or, more correctly, a large number of discrete values) to a few numbers, one per tissue type. This is acceptable for relatively uniform tissues, but not for ones with variable $\mu$-coefficients like the lungs [82, 106] and bones [129]. Similarly, if the $\mu$-coefficient distribution in a given tissue varies between individuals, as is the case in the lungs [82] and bones [129], it is invalid to assign the same $\mu$-coefficient to that tissue type in every patient. Additionally, segmentation may impose practical limitations such as the computational time required to post-process the transmission image.

1.4.3.5 Problems Specific to X-ray CT Transmission Scans

Aside from beam hardening (§1.4.3.4), there are other issues that arise only in PET/CT [224]. For example, in many PET/CT systems, the PET field of view is often larger than that of the CT. If the object of interest extends beyond the CT field of view, the CT projections are truncated and the resulting $\mu$-map will not only be missing parts, but display characteristic artifacts near the periphery. Without correction algorithms, the impact on the PET images can be severe [18, 133].

Additionally, patient motion can induce misalignments between the CT-derived $\mu$-map and the emission data as they are collected over different temporal scales.
In essence, the PET scan is collected over several minutes and blurs patient motion together, whereas a CT scan is captured in seconds and is akin to a snapshot in time. The best solution is to acquire a dynamic $\mu$-map, making it a function of time ($t$), i.e. $\mu(\vec{r}, t)$. The emission data can be binned according to $t$ and corrected using the corresponding $\mu(\vec{r}, t)$. In principle, such an approach could account for arbitrary motion induced transmission/emission mismatch, but in practice radiation constraints limit the approach to cyclical motions such as respiration or the cardiac cycle. In this case, $\mu(\vec{r}, t)$ need only be computed for one cycle, rather than necessitate continuous acquisition during the entire emission scan. Many authors have implemented cine-CT acquisitions for AC and have characterized the errors induced by using various time-independent $\mu$-maps [3, 36, 42].

1.5 MRI-Based Attenuation Correction

1.5.1 Relation to Transmission Scans

In many ways, anatomic MRI is disparate from transmission scanning. In particular, the mechanism of signal acquisition is completely different. Simplistically, the former measures voltages induced by precessing magnetization whereas the latter measures the flux of a photon beam passing through the object. Unsurprisingly, the resulting images have dissimilar contrasts. Beyond this, depending on the pulse sequence and characteristic timing parameters such as the repetition time (TR) and echo time (TE), the contrast of MRI images can be drastically altered. Conversely, the contrast of transmission images cannot be changed very much: the more attenuating the material, the brighter it will appear.

In other respects, however, anatomic MRI and transmission scans are not so different. Specifically, they can both generate anatomical images of the body. Yes, the
images do not look the same, but the major components of the body can be visual-
ized in either case. The beauty of this observation is that it suggests, with respect to
μ-map generation, that the approaches historically employed on transmission scans
might be applicable to MRI as well. This intuition is, in fact, correct.

Clearly, an MRI requires post-processing to yield a valid μ-map. We have seen
this concept applied to transmission scans to correct their deficiencies. For instance,
recall that image segmentation can be used to eliminate noise and map the component
tissues to the appropriate 511 keV μ-coefficients [17, 89, 115, 138, 217]. The same
principle can be used to convert MRIs to segmented μ-maps. Also, remember that one
approach of inferring the μ-map from emission data is to align a generic transmission
scan with the uncorrected reconstruction [197]. Again, this methodology is trans-
ferrable to MRI-based AC by using the MRI as the registration target as opposed to
a preliminary emission tomography image. Finally, mathematical functions played a
major role in mapping μ-coefficients acquired at photon energies other than 511 keV
to the correct values [29, 115, 220]. Generally, these were single variable, one-to-one
functions. Though such relations are too simple to model the mapping between MRIs
and μ-maps, more sophisticated functions—especially those originating from the field
of machine learning [85, 87, 103]—have achieved impressive results on this front.

All things considered, there is nothing fundamentally new about MRI-based AC:
the three principle approaches for inferring an μ-map from MRI, namely segmenta-
tion, registration, and mapping, have been present in the AC literature for decades.
In §1.5.2, I describe their application with respect to PET/MRI, building on the
previous review by Hofmann et al [86].
1.5.2 MRI to $\mu$-Map Conversion

1.5.2.1 By Segmentation

The first MRI-based AC algorithm was proposed—rather ahead of its time—in 1994 by Le Goff et al [67]. It was designed for cranial PET and generated the $\mu$-map via segmentation into three tissue classes, namely air, soft tissue, and bone. The segmentation algorithm was based on thresholding and mathematical morphology (i.e. geometric manipulations applied to sets of voxels). It neglected the sinuses and, according to the authors, did not perform well in the slices containing the eyes. Despite this, initial results were encouraging: the relative error in several expertly placed VOIs did not exceed 12% (avoiding slices where the algorithm failed). No global error analysis was reported. Zaidi et al [225] improved upon this approach by using a more robust fuzzy clustering segmentation algorithm that could identify the sinuses. Although it had a tendency to overestimate activity, its performance was good compared to multiple other AC algorithms [226]. In particular, statistical testing showed that absolute quantification in most regions of the brain was not significantly different from AC based on $^{137}$Cs transmission scanning. Globally, the correlation between the MRI-corrected and transmission-corrected volume of interest (VOI) activities was high, with a squared Pearson correlation coefficient ($R^2$) of 0.91.

A problem with both Le Goff’s and Zaidi’s approaches is that they may not be robust to abnormal anatomy. After all, both air and bone appear dark in MRI, so both AC methods implicitly utilize normal anatomy to differentiate between the two. This motivated both Keereman et al [109] and Catana et al [32] to design an alternate segmentation scheme based on ultrashort TE (UTE) pulse sequences [171]. Unlike standard pulse sequences, UTE sequences yield signal from bone, theoretically enabling it to be discriminated from air based solely on voxel intensity. In practice, the
problem is complicated and involves several post-processing steps, but both groups overcame these issues and demonstrated its promise. That said, both studies were proofs-of-principle focussing on developing the algorithm rather than assessing the errors in the resulting PET images. Notably, no statistical analyses were conducted. This is a necessary step to compare it to other AC methods and to ascertain where improvement is needed. It would also be interesting to see whether the UTE AC algorithms do indeed produce better results than alternate approaches when imaging patients with abnormal anatomy.

Segmentation has also been used in whole-body MRI-based AC. Two groups have reported algorithms identifying air, lung, and soft tissue in MRI images [186, 196]. One study was conducted using humans [186] (Figure 1.11) whereas the other used dogs [196], but the algorithms were similar, both involving thresholding and other simple image processing techniques guided by assumptions about normal anatomy. Different means of local error analysis were employed in the studies: SUVs of lesions [186] versus VOIs spanning entire organs [196]. A common observation was that, within bony structures, the activity was systematically underestimated as bone was not included in the segmentation. Conversely, the human study described a systematic overestimate of activity in the abdomen owing to the absence of a tissue class for fat [186]. This was not apparent in the canine study, likely because canines tend to be lean, reducing the importance of fat segmentation. Despite neglecting fat in humans, the global voxel-by-voxel correlation was excellent \( (R^2 = 0.985) \) [186].

Martinez-Möller et al [132] proposed that fat could be included in an AC segmentation model with the aid of the 2-point Dixon pulse sequence [43]. This sequence can partially distinguish between fat and water based on phase differences between their respective nuclei. Though they used 35 patient PET/CT scans to demonstrate the potential merit of a segmented CT-derived \( \mu \)-map comprised of air, lung, fat,
and muscle, they did not consider a segmented CT-derived $\mu$-map without fat, making comparison impossible. Further, their method was only used to generate two MRI-based $\mu$-maps as a proof-of-principle, precluding a meaningful error analysis. Fortunately, a followup study evaluating the methodology in 35 patients was conducted by Eiber et al [59], demonstrating an exceptional correlation between lesion SUVs in MRI-based AC versus CT-based AC PET images ($R^2 = 0.995$).

Ideally, one might think that bones would also be included in the segmentation model. Unfortunately, they are very challenging to identify on whole-body MRI, and though effective in the head, UTE methods are ill-suited for large field of view acquisitions. Thus, bone segmentation remains an open problem in MRI-based AC. However, Schlyer et al [183] used PET/CT scans to demonstrate some pitfalls that arise when using bone segmentation. The dilemma is twofold: 1) can the bones be
segmented accurately and 2) what $\mu$-coefficient should be assigned to them? Regarding the second point, it was found that the best result was produced when patient specific, mean bone $\mu$-coefficients were employed. This information, of course, is not necessarily going to be available for patients receiving a PET/MRI, so it is likely that a fixed $\mu$-coefficient will be required. Interestingly, Schyler et al found that concerning quantification in the chest, a bone $\mu$-coefficient (0.13 cm$^{-1}$) yielded worse results than the $\mu$-coefficient of soft tissue (0.95 cm$^{-1}$), a problem that worsened when the bones were oversegmented. That is not to say bone segmentation is futile. Perhaps the most appropriate $\mu$-coefficient in this region is somewhere between 0.95 cm$^{-1}$ and 0.13 cm$^{-1}$. Admittedly, the optimal $\mu$-coefficient is likely different in other parts of the body, such as the skull or pelvis. Ultimately, the problem is that segmentation collapses the $\mu$-coefficient distribution to a single value that is bound to be suboptimal in some areas. Though very effective for relatively uniform materials such as air, fat, and muscle, segmentation is simply not the best choice for tissues that can assume a wide range of $\mu$-coefficients.

A possible means to improve bone segmentation is to divide it into two classes: cortical and cancellous, thereby quantizing the continuum of $\mu$-coefficients to two values rather than one. Using a digital whole-body phantom, Keereman et al \[110\] found that doing so reduced the relative error in spine lesions from over 10% to under 5%. Interestingly, they also found that quantification in these lesions was relatively insensitive to the $\mu$-coefficient assigned to cortical bone. In lungs, however, another tissue with highly variable $\mu$-coefficients \[82, 106\], this was not the case. Though shedding some light on the effects of segmentation error, Keereman’s findings must be verified in patients. Further, this study used CT to determine the segmentations, yielding near perfect results. This will be much more challenging using MRI. For example, differentiating cortical from cancellous bone may prove difficult since they
are in close proximity and tend not to be easily visualized in MRI.

1.5.2.2 By Registration

An alternate MRI-based AC method relies on image registration, that is, aligning medical images to one another. In particular, one can infer \( \mu(\vec{r}) \) by taking a generic \( \mu \)-map and forcing it into alignment with the patient’s MRI, thereby simulating the true \( \mu \)-map. Unlike segmentation, AC techniques based on image registration do not need to collapse \( \mu \)-coefficient distributions down to single numbers. The generic \( \mu \)-map can be arbitrarily detailed. The problem is that the \( \mu \)-coefficients in the generic \( \mu \)-map may not correspond to the patient’s. Further, the registration itself can be exceptionally challenging, especially in whole-body applications. In fact, the registration may not even be sensible if there are anatomic differences between the generic \( \mu \)-map and the patient. Many of these issues are assuaged if only the head is considered as it exhibits less variance than the rest of the body; accordingly, the application of MRI-based AC exclusively via registration has only been reported in cranial PET. The first study of its kind was too small to make definitive conclusions (\( n = 4 \)), but a VOI analysis suggested its performance was similar to a segmentation-based approach [117].

Another group proposed a deformable registration algorithm and quantified its ability to approximate the true \( \mu \)-map, but only presented PET data for one patient [184]. Despite promising surrogate measures of their approach’s quality, its actual performance in terms of reconstructing PET data remains to be seen.

In an interesting study by Malone et al [130], two generic \( \mu \)-maps were registered to the patient MRI: one was a segmented \( \mu \)-map based on the BrainWeb phantom [39] while the other was an atlas derived from 10 \( ^{68} \text{Ge} \) transmission scans. In both global and local analyses, the latter approach demonstrated less error, a conclusion
that remained valid irrespective of what \( \mu \)-coefficient was assigned to bone in the segmented \( \mu \)-map. A possible confounder, however, is that the registration error was likely different between the two approaches; the moving image used to derive the transform was a segmented pseudo-MRI for the segmented \( \mu \)-map and a real atlas MRI for the atlas transmission scan. The latter may have resulted in more realistic transforms than the former. Nonetheless, the results suggest that generic \( \mu \)-maps based on transmission scans are superior to those based on phantoms.

### 1.5.2.3 By Mapping

The final MRI-based AC method is mapping the MRI directly to a \( \mu \)-map. This generally involves constructing some mathematical function that analyzes the MRI one voxel at a time, converting each one into an estimated \( \mu \)-coefficient. In some ways, mapping combines the strengths of segmentation and registration; like segmentation, mapping can theoretically cope with anatomical anomalies, but like registration, distributions of \( \mu \)-coefficients need not be collapsed to a single value. Beyer et al [20]
were the first to describe a map between MRI and \( \mu \)-maps. Specifically, using aligned MRI / CT pairs, they applied histogram matching to the MRI to scale its values to CT numbers. The function produced by histogram matching is necessarily monotonically increasing, and therefore one-to-one. Hence, for histogram matching to be a truly effective approach, increasing MRI signal intensity would have to correspond to increasing \( \mu \)-coefficients. This is obviously not so (e.g. air versus bone), and therefore histogram matching is fundamentally limited as a mapping technique for MRI-based AC. Beyer et al [20] characterize the method as a toolbox to study pitfalls in MRI to CT mapping rather than as a solution to the problem.

It was Hofmann et al [85, 87] who proposed the first realistic MRI to CT mapping, both in the head [87] (Figure 1.12) and in the whole-body [85]. Their mapping function is called a Gaussian process, which is used in the field of machine learning. For each voxel in the MRI, the Gaussian process accepts a number of inputs and calculates a CT number. A large contributor to the function’s success lies in choosing appropriate inputs, a process known as feature selection. Hoffman et al use two types of features: one type consisted of the voxel intensities in a patch centred upon voxel of interest, while the other type constituted the voxel’s coordinates. Intuitively, the concept is that by examining the MRI voxel’s intensity, its surroundings, and its location, one should be able to do a relatively good job of predicting the CT number. In Hofmann et al’s implementation, the Gaussian process inferred the relationship between the inputs and outputs by exposure to labeled examples drawn from seventeen aligned MRI/CT pairs. This training paradigm is known as supervised learning. In the head, Hoffman et al’s [87] approach generated stunningly detailed pseudo-CT images from MRI images. A global analysis revealed an \( R^2 \) of 0.968 between the voxel-wise estimated and true PET activities. In the whole-body, the quantitative analysis was based on SUVs both in standard anatomic positions and over lesions
Compared to a segmentation-based approach that, importantly, did not include bone, the Gaussian process method provided superior quantification primarily within or nearby bony structures.

Figure 1.12: Example of a cranial μ-map generated via mapping from an MRI. From left to right are the MRI, mapped pseudo-CT, and real CT. Adapted from Hofmann et al [87].

Of the inputs used in Hoffman et al’s implementation of the Gaussian process, the most troublesome are the coordinates. To be meaningful, they must somehow be normalized across the training MRI/CT pairs and the patient under consideration. To accomplish this, Hoffman et al registered each MRI/CT pair to the patient in question, and carried out patient specific supervised learning using standard Cartesian coordinates. That means every time a new patient MRI needs to be converted to a μ-map, not only must a new model be built, but also multiple registrations need to be executed. A more efficient method may involve utilizing a coordinate system that can naturally represent positions in the human body without requiring every subject to be in an identical reference frame. Another option is to avoid using coordinates altogether. This premise is consistent with an approach for cranial PET proposed by Johansson et al [103] wherein voxel intensities from both anatomic and UTE MRI
sequences serve as inputs to a Gaussian mixture model (another machine-learning technique). Similarly to some segmentation schemes \cite{32, 109}, the incorporation of UTE sequences permit discrimination between bone and air independent of position. Additionally, it may provide information about bone density \cite{168}. Unfortunately, though their pseudo-CTs look excellent and the predicted CT numbers correlated well with truth, Johansson et al \cite{103} did not provide any PET data to evaluate their methodology.

### 1.5.3 Ongoing Problems and Future Work

MRI-based AC is still a young field, and hence, there remain multiple un- or partially resolved issues. In the following section, I outline some ongoing problems and propose directions for future research, including those that are explored in the coming chapters of this thesis (Table 1.8).

Recall that in CT-based AC, truncation artifacts were problematic due to CT’s reduced field of view compared to PET. Regrettably, MRI’s field of view is even smaller, often cropping substantial parts of the patient’s body (especially the arms and shoulders), leading to average and maximum biases of about 15% and 50% in the PET images, respectively \cite{47}. Delso et al \cite{47} proposed a method based on active contours to infer the missing portions of the \( \mu \)-map; their method reduced the average bias to well under 10%, but the maximum bias still exceeded 20% in areas where their algorithm erroneously induced attenuating material. Another approach involving the reconstruction of truncated regions based on the emission data has been proposed by Nuyts et al \cite{150}; the initial results are promising, but the algorithm requires more extensive testing. Truncation of MRI-based \( \mu \)-maps remains an open problem ripe for further research.

A problem specific to MRI-based AC is that, unlike CT, many attenuating objects
Table 1.8: Future work in MRI-based AC.

<table>
<thead>
<tr>
<th>Problem Addressed in thesis?</th>
<th>Explanation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Truncation of MRI</td>
<td>No</td>
</tr>
<tr>
<td>MRI invisible objects</td>
<td>No</td>
</tr>
<tr>
<td>Metal artifacts</td>
<td>No</td>
</tr>
<tr>
<td>MRI-based AC in SPECT</td>
<td>Chapter 2</td>
</tr>
<tr>
<td>Lung ( \mu )-coefficients</td>
<td>Chapter 3</td>
</tr>
<tr>
<td>Algorithmic framework</td>
<td>Chapter 4</td>
</tr>
</tbody>
</table>
such as RF coils [46, 200], patient positioning aids [131], and medical probes [46], do not appear in standard MRI images. Under some circumstances, this may not be of much importance. For example, foam positioning aids induced relatively little error (≈ 5%) when imaging the extremities [131], as did surface coils in a phantom study of thoracic imaging [200], while medical probes only caused local artifacts in the PET image [46]. However, more substantial hardware such as head and neck RF coils have been found to induce errors of up to 20% [46, 200]. Further, patient positioning aids contributed to errors over 10% in cranial PET [131]. Only one study proposed a means of correcting some of these problems [46], and much more work is required both to characterize and correct errors induced by MRI invisible objects. Some possible directions include the use of UTE sequences to produce signal from otherwise MRI invisible materials and the emission based inference of missing parts of the μ-map as described in the paragraph on truncation [150].

A related problem occurs when the patient has metal in their body. Metal induces a blooming artifact in MRI which can appear as a signal void, depending on the pulse sequence. This artifact has been shown to seriously disrupt otherwise effective MRI-based AC schemes [85]. As of yet, no studies have been published systematically evaluating the resulting AC errors, nor have any solutions been proposed.

Though truncation, MRI invisible objects, and metal artifacts are important considerations in MRI-based AC, these topics are not explored further in this thesis. The following paragraphs outline the problems that are addressed in the following chapters.

Thus far, I have discussed MRI-based AC in the context of PET, exclusively. However, efforts are already underway to develop SPECT/MRI systems [66, 75]. SPECT/MRI, like PET/MRI, requires MRI-based AC, but virtually no present literature examines the application of MRI-derived μ-maps to SPECT data. However,
as detailed in §1.5.2, numerous MRI-based AC algorithms have been validated using PET. One therefore might ask whether existing MRI-based AC algorithms that have been validated in the context of PET can be expected to perform similarly well when applied to SPECT. The problem is interesting in that SPECT requires “less” attenuation correction than PET (i.e. has smaller attenuation correction factors), but is much more challenging to implement, making it hard to know in which modality (if any) MRI-based AC would be better suited. In Chapter 2, I examine this problem by implementing a simple MRI-based AC algorithm (in particular, a 3 tissue class segmentation model) and apply it to both PET and SPECT canine data. The analysis is focused on identifying differences in the quantitative fidelity between these two modalities.

After exploring the application of MRI-based AC in PET versus SPECT, I elected to attempt to improve existing MRI-based AC algorithms. The problem I chose to investigate is that there is currently no means to accurately predict the $\mu$-coefficients in the lungs, which as mentioned earlier, are highly variable [82, 106]. This, unsurprisingly, adversely impacts quantification in the lungs [85, 110], and quite likely, in surrounding structures as well. The problem is not trivial as the lungs tend to appear black on MRI regardless of their $\mu$-coefficient distribution. This is in part because lung parenchyma has about a third the proton density as soft tissues [77], but more importantly because of its very short $T_2^*$ caused by susceptibility effects from the numerous air/tissue interfaces [31, 76]. Additionally, motion and flow artifacts are abundant and further compromise image quality [77]. In Chapter 3, using a pulse sequence capable of yielding signal from the lungs, I propose a means to map MRI lung signal to CT numbers, which in turn can be converted to $\mu$-coefficients. The approach is tested in healthy canines using PET data.

Finally, after having been exposed to a great variety of MRI-based AC algorithms,
it occurred to me that there was no unified framework for classifying the multitude of techniques. In particular, as explained in §1.5.2, every approach relied on either segmentation, registration, mapping, or some combination thereof, but nowhere were these categories explicitly stated, precluding their direct comparison. Therefore, for my final research project (Chapter 4), I chose to implement a version of each algorithmic class and compare them head-to-head-to-head, seeking to formally identify their strengths and weaknesses. I am of the opinion that without an understanding of the capabilities and limitations of segmentation, registration, and mapping, the development of novel MRI-based AC algorithms will be impeded.

Incidentally, an additional novelty arose from the work in Chapter 4. Bones present a challenge in MRI-based AC. They are not easy to identify using standard pulse sequences, and UTE sequences can become unreliable if the FOV is large, as is the case for whole-body imaging. To date, only one whole-body MRI-based AC method incorporates bones [85]. The authors concluded that their methodology (which uses mapping) is superior to a segmentation approach, but the latter did not include a bone category, making the comparison somewhat unfair. This is addressed in Chapter 4, as the segmentation model includes a bone category, which to the best of my knowledge has not been published.

1.6 Conclusions

PET and MRI are exceptionally powerful technologies. By combining these modalities together in a PET/MRI system, we now have the capability to examine a wide range of physiological and pathological processes with both modalities in spatial and temporal register. But without reliable MRI-based AC, the vast potential of PET/MRI is unattainable.
In this chapter, I have attempted to put MRI-based AC in a broader context. I began by exemplifying the importance of quantitative PET/MRI in three medical fields, namely oncology, neurology, and cardiology. Next, a relatively comprehensive picture of the factors that influence quantification in PET was provided, helping the reader to understand how attenuation fits in. I subsequently focused specifically on attenuation: what it is, how it is corrected, and how to obtain the \( \mu \)-map from emission or transmission data. Ultimately, I discussed MRI-based AC, emphasizing its relationship to existing AC techniques. I went on to discuss some directions for future research, highlighting research covered in the subsequent chapters of this thesis.

In particular, the overarching objective of my thesis is to improve quantification in PET and SPECT images that are attenuation corrected with an MRI-based \( \mu \)-map. I begin by comparing MRI-based AC in PET versus SPECT to see which modality is more quantitatively accurate. I subsequently focus on a particular issue in MRI-based AC: i.e. assigning reliable \( \mu \)-coefficients to the lungs. I finish by comparing the three approaches to making an MRI-based \( \mu \)-map, namely segmentation, registration, and mapping, to establish the circumstances that dictate good versus poor performance.
References


[219] S Yip. 22.101 Applied Nuclear Physics, Fall 2006. Massachusetts Institute of Technology: MIT OpenCourseWare (http://ocw.mit.edu). License: Creative Commons BY-NC-SA.


Chapter 2

A Comparison of MRI-Based Attenuation Correction in PET Versus SPECT*

2.1 Introduction

The idea of combining positron emission tomography (PET) and magnetic resonance imaging (MRI) systems is not a new one. In fact, early work on hybrid PET/MRI [18, 24] preceded the completion of PET/CT [1]. Although it took several years to overcome the technical challenges that constrained PET/MRI to the pre-clinical arena [28], the combined efforts of several groups have made human PET/MRI a reality. Several commercial vendors have recently unveiled whole-body platforms. PET/MRI’s unprecedented capacity to combine anatomical, functional, and molecular information has implications across multiple fields including neurology [9], oncology [21], and cardiology [17].

Like PET, single photon emission computed tomography (SPECT) has been combined with MRI [7, 8]. Research on SPECT/MRI has lagged behind PET/MRI, pos-

sibly due to challenges associated with moving parts and MRI-compatible collimator design [5]. Nevertheless, the potential applications of SPECT/MRI are exciting, especially given SPECT’s ability to simultaneously image multiple radiopharmaceuticals. Accordingly, it is probable that human SPECT/MRI systems will come to fruition within the foreseeable future.

Of the multiple corrections that must be applied to reliably reconstruct PET and SPECT images, attenuation correction (AC) is among the most important. Without AC, gross deviations from the true radiopharmaceutical distribution are observed and accurate quantification is impossible. Traditional methods of obtaining attenuation maps (µ-maps) such as radionuclide transmission imaging or x-ray computed tomography (CT) are generally not possible in PET/MRI or SPECT/MRI due to space and cost restrictions. The obvious alternative is to use MRI images for AC, but this is non-trivial since the signal in MRI arises from proton density, whereas photon attenuation is dictated by electron density. In spite of this, multiple innovative MRI-based AC algorithms have been proposed for application in the brain [4, 10, 13, 22] and body [6, 15, 23, 25]. Although the details of the approaches differ, they share a common feature: they were all validated for PET reconstructions. This is unsurprising given the relatively advanced state of PET/MRI compared to SPECT/MRI, but it does give rise to a natural question. Can an MRI-based AC algorithm that has been designed for PET/MRI be successfully applied to SPECT/MRI as well? The answer depends on several fundamental differences between PET and SPECT, including the amount of attenuation that takes place and the complexity of applying a correction.

In the present work, this question is investigated in detail. A whole-body, MRI-based AC algorithm representative of trends in the literature is described and used to reconstruct both phantom and in vivo canine PET and SPECT images. The deviation of these reconstructions from the truth (obtained via “silver standard” CT-based AC)
is compared between PET and SPECT. The comparisons are done both globally and locally to capture differences in the PET and SPECT reconstruction quality over a wide range of physical scales. Finally, a sensitivity analysis is conducted to assess the impact of variations in the μ-map on the reconstructions’ fidelity.

2.2 Imaging Protocol

2.2.1 Animals

Eight adult female mongrel canines (mass 22 – 24 kg) were included in this study using a protocol approved by The University of Western Ontario animal care committee. Each canine received either PET/CT and MRI imaging \( (n = 4) \) or SPECT/CT and MRI imaging \( (n = 4) \). Particular members of the former experimental group will be referred to as canines P1 through P4, and the latter as canines S1 through S4. The canines in both groups were essentially identical in terms of body size and weight. No canines exhibited any indication of lung pathology which, if present, could compromise the MRI-based AC as discussed in §2.6.

Anesthesia was initiated with propofol and maintained with 2.0%-2.5% isofluorane. After anesthesia and subsequent intubation, artificial ventilation was conducted with a Veterinary ADS 1000 system (Engler Engineering Co., Florida, USA).

To facilitate registration of the MRI to PET/CT or SPECT/CT images, the canines were immobilized on a rigid board for the duration of the experiment. The field of view was from the neck to the lower abdomen for all modalities.
2.2.2 Phantom

In addition to the animal data, imaging of an anthropomorphic torso phantom (model ECT/TOR/P) with a cardiac insert (model ECT/CAR/I) produced by Data Spectrum Co. (North Carolina, USA) was carried out. This phantom simulates several anatomical structures including the lungs, heart, liver, and spine. Further, it accurately simulates the attenuating properties of the human body. When imaged with MRI, the phantom approximates the signals generated by tissues \textit{in vivo}, but certain effects are not reproduced (e.g. very short T$_2^*$ in the lungs owing to magnetic susceptibility).

Imaging was done with PET/CT, SPECT/CT, and MRI using the same protocol as the canine experiments, although the radioisotopes were not bound to biologically active molecules. The concentration of radioactivity was varied according to anatomical compartment in a ratio of 1:3:12:12 for the lungs, soft tissue, heart, and liver respectively. A total of 400 MBq $^{99m}$Tc was used for the SPECT/CT and 800 MBq $^{18}$F for the PET/CT.

2.2.3 PET/CT

The PET/CT imaging was conducted on a Discovery VCT system (GE Healthcare). For the canine studies, $^{18}$F-fluorodeoxyglucose (FDG) was selected as the radiotracer. Following an eight hour fast and an interavenous (IV) glucose infusion to promote cardiac uptake, approximately 250 MBq of FDG was administered. One hour was allotted for uptake to occur. During the 3D PET acquisition, coincidence rates were generally around 400 kcps prior to applying any corrections. Each table position was maintained for 5 minutes. The PET reconstruction was performed using ordered subset expectation maximization (OSEM) with 3 iterations and 8 groups. The re-
constructed volumes’ in-plane resolution was 5.47 mm × 5.47 mm (matrix size 128 × 128) with a slice thickness of 3.27 mm.

The CT acquisition was collected on exhalation with 140 kVp and 30 mAs. The in-plane resolution was 1.37 mm × 1.37 mm (matrix size 512 × 512) with a slice thickness of 3.75 mm.

### 2.2.4 SPECT/CT

The SPECT/CT imaging was conducted on a Symbia T6 system (Siemens Medical). For the canine studies, $^{99m}$Tc-sestamibi (MIBI) was selected as the radiotracer. Following an eight hour fast, approximately 300 MBq of MIBI was administered. Three hours were allotted for uptake to occur. The time per SPECT projection was 30 s and a total of 180 projections were collected. The SPECT reconstruction was performed in the same manner as the PET reconstruction, i.e., OSEM with 3 iterations and 8 groups. The reconstructed volume had an isotropic resolution of 4.8 mm (in-plane matrix size 128 × 128).

The CT acquisition was collected on exhalation with 130 kVp and 20 mAs. The in-plane resolution was 0.98 mm × 0.98 mm with a slice thickness of 5 mm.

### 2.2.5 MRI

The MRI was conducted on a Verio 3 Tesla system (Siemens Medical). Data collection was carried out using a rapid acquisition with refocused echoes (RARE) pulse sequence (TE = 13 ms, TR = 1910 ms) with end-expiration respiratory gating for the canine experiments via a respiratory bellows. RF transmission was through the whole-body coil while both the spine array and body matrix coils were used for reception. The MRI images had an in-plane resolution of 3.13 mm × 3.13 mm with a slice
thickness of 5 mm. The FoV was 400 mm in each dimension (matrix size $128 \times 128 \times 80$). The flip angle was $150^\circ$, the bandwidth per pixel was 130 Hz, the echo train length was 9, and averages = 1. Total imaging time was approximately 5 minutes.

2.3 Image Processing

2.3.1 µ-Map Generation

2.3.1.1 CT-Based

The CT images from both the PET/CT and SPECT/CT were resampled to match the voxel size of the PET and SPECT reconstructions, respectively. The voxel intensities were subsequently converted from Hounsfield units to attenuation coefficients ($\mu$-coefficients) via a bilinear scaling approach \[2, 3\]. The CT associated with the SPECT scan was mapped to $\mu$-coefficients at 140 keV, while the CT associated with the PET scan was mapped to $\mu$-coefficients at 511 keV. The slopes and y-intercept used in the mappings were calibrated specifically for each scanner.

2.3.1.2 MRI-Based

A simple MRI-based AC method designed to produce similar $\mu$-maps as multiple approaches described in the literature \[15, 23, 25\] was developed and implemented in Matlab v7.4.0 (The MathWorks, Massachusetts, USA). This algorithm was used for both the phantom and animal experiments, which was only possible because the phantom was anthropomorphic. The algorithm was based on image segmentation, and in particular, classified each voxel in the MRI image as either air, lung, or soft tissue. Subsequently, each material was assigned a constant $\mu$-coefficient (Table 2.1).

Image segmentation commenced by separating foreground from background air
Table 2.1: μ-coefficients assigned to materials by MRI-based AC algorithm.

<table>
<thead>
<tr>
<th>Energy (keV)</th>
<th>Attenuation coefficient (cm⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Air</td>
</tr>
<tr>
<td>140</td>
<td>0</td>
</tr>
<tr>
<td>511</td>
<td>0</td>
</tr>
</tbody>
</table>

using a single, empirically derived threshold of 25% the mean slice intensity, excluding the darkest 5% of pixels. “Holes” in the foreground mask (e.g. from air in the lungs falling below the threshold) were automatically filled in. All voxels outside the foreground mask were classified as air. The MRI image then was normalized by setting the mean foreground signal intensity of each axial slice to 1.

The lungs were identified using a level set algorithm implemented in ITK-SNAP [30], a free open-source segmentation software. The seed voxels used to initiate the level set were automatically extracted in Matlab. In particular, regions of low signal intensity within the subject were identified by applying a second empirically derived threshold to MRI voxels within the foreground mask. Low signal regions residing outside the lungs were excluded using connected-component analysis. Specifically, only the largest 3D, 26-connected region was retained for use as seed voxels for the level set.

To complete the lung segmentation, the MRI image and lung seed voxels were exported to ITK-SNAP. The MRI image was preprocessed using an intensity region filter that mapped low-signal regions to a value of 1 and high-signal regions to a value of 0 with a sigmoidal transition centred at 0.6. Following pre-processing, the sparse field level set algorithm was initiated. The propagation and curvature terms were set to 1 and 0.2, respectively. The level set was run until convergence was achieved, and the resulting lung segmentation was imported back into Matlab.
The last step in the segmentation was soft tissue identification. All voxels contained in the foreground mask that had not been designated as lung were deemed to be soft tissue.

Finally, the MRI-based $\mu$-map (MRI $\mu$-map) was registered to the CT-based $\mu$-map (CT $\mu$-map). The registration procedure is described in §2.3.2. Once the $\mu$-maps were aligned, the patient bed present in the CT $\mu$-map was added to the MRI $\mu$-map.

### 2.3.2 Registration

Although the purpose of the image registration was to align the MRI $\mu$-map with the CT $\mu$-map, the spatial transform relating the two was obtained by registering the original MRI image to the CT $\mu$-map. This prevented the registration algorithm from inadvertently “correcting” segmentation errors in the MRI $\mu$-map by forcing poorly segmented regions into alignment with the silver standard.

The registration algorithm was implemented using the Insight Segmentation and Registration Toolkit (ITK) [12], an open source software available at www.itk.org. Since the registration was intermodality in nature, Mattes mutual information [16] (a quantity measuring the mutual dependence of two random variables) was selected as the similarity measure. For the phantom, a rigid transformation model was used. However, for the canine studies the transformation model was hierarchical, evolving sequentially from rigid to affine to non-rigid. The non-rigid transformation model was originally described by Rueckert et al [20]. Each transform model was iteratively optimized using a gradient descent scheme prior to evolution to the next model. The final deformation field was applied to the MRI $\mu$-map, and the registration’s fidelity was assessed visually.
2.4 Assessment of MRI-Based AC Quality

2.4.1 Error Analysis

2.4.1.1 Global

The SPECT and PET projections were reconstructed twice, once with the CT \( \mu \)-map, and once with the derived MRI \( \mu \)-map. These nuclear medicine images will be denoted \( \text{SPECT}_{\text{CT}} \), \( \text{SPECT}_{\text{MRI}} \), \( \text{PET}_{\text{CT}} \), and \( \text{PET}_{\text{MRI}} \). This notation is extended in §2.4.2. For reference, reconstructions without any AC were also created and will be denoted \( \text{SPECT}_{\text{none}} \) and \( \text{PET}_{\text{none}} \).

Global errors in the \( \text{SPECT}_{\text{MRI}} \) and \( \text{PET}_{\text{MRI}} \) images were assessed in a tissue specific fashion. By manually thresholding the CT \( \mu \)-maps, lung, soft tissue, and bone voxels were extracted. For the phantom and each subject, three voxel-by-voxel scatter plots of approximate versus true activities were created, one per tissue type. The activities were normalized by expressing them as a fraction of the maximal tissue and subject specific true activity (after AC as per the CT-based \( \mu \)-map). Linear regression was performed on each scatter plot to obtain a line of best fit (LOBF). Systematic bias of the \( \text{SPECT}_{\text{MRI}} \) and \( \text{PET}_{\text{MRI}} \) images was reflected in the LOBF’s slope \( (m) \) and y-intercept \( (b) \), while precision was reflected in the correlation coefficient \( (R^2) \).

In the animal experiments, \( m \), \( b \), and \( R^2 \) were compared statistically between the SPECT and PET scatter plots. In total, 9 comparisons were conducted (3 tissue types × 3 LOBF parameters). The comparisons were conducted using two-tailed, two sample \( t \)-tests. The variances of the samples being compared were not assumed to be equal. The level of statistical significance was set at \( \alpha = 0.05 \), which was adjusted to \( \alpha = 0.0055 \) by the Bonferroni correction for multiple comparisons.
2.4.1.2 Local

An approach based on volumes of interest (VOIs) was used to analyze errors localized to particular spatial positions. Five 3D VOIs (3 voxels × 3 voxels × 3 voxels) were defined for the phantom and fourteen VOIs were defined for each canine using the CT μ-map to determine position (Figure 2.1). A complete list of the VOIs can be found in Tables 2.4 and 2.5. The mean activity in each VOI was calculated for each nuclear medicine reconstruction. The error in each SPECT\textsubscript{MRI} or PET\textsubscript{MRI} VOI was calculated and expressed as a percentage of the true activity in the corresponding SPECT\textsubscript{CT} or PET\textsubscript{CT} VOI. These percent errors were compared, one VOI at a time, between the SPECT\textsubscript{MRI} and PET\textsubscript{MRI} images using the same statistical technique described in §2.4.1.1. Since 14 comparisons were made, \( \alpha = 0.0035 \) with the Bonferroni correction.

2.4.2 Sensitivity Analysis

Since multiple MRI-based AC methods are available, each one yielding different MRI μ-maps, it is valuable to ascertain the sensitivity of SPECT\textsubscript{MRI} and PET\textsubscript{MRI} reconstructions to slight variations in the MRI μ-maps used to create them. To this end, four variants of the original canine MRI μ-maps were created (the phantom was not included in this portion of the analysis). This was done by enlarging (dilating) or shrinking (eroding) the lungs or outer body surface via morphological operations. The erosion/dilation structuring element was composed of a centre voxel with a single voxel extending from each face. Five SPECT\textsubscript{MRI} or PET\textsubscript{MRI} images were generated per subject, one for the original MRI μ-map and one for each of the four derivative MRI μ-maps. To refer to reconstructions made by particular variants of the MRI μ-map, the SPECT\textsubscript{MRI}/PET\textsubscript{MRI} notation is extended by allowing the MRI subscript to have the following secondary subscripts: MRI\textsubscript{0}, MRI\textsubscript{dl}, MRI\textsubscript{el}, MRI\textsubscript{db}, and MRI\textsubscript{eb}. 
Figure 2.1: Sample placement of several VOIs superimposed on CT μ-map (canine S2). Only 11 of the 14 VOIs are shown. (a) Lungs, humeri, and adjacent to humeri. (b) Thoracic spine and adjacent soft tissue. (c) Myocardium. (d) Liver.
representing the original, dilated lung, eroded lung, dilated body, and eroded body MRI $\mu$-maps, respectively.

Error images expressed as a percentage of true activity were derived from each reconstruction. The standard deviation of the errors was computed voxel-by-voxel as a metric of sensitivity to variations in the MRI $\mu$-map. This metric was averaged over three tissue types (lung, soft tissue, and bone) for each subject. The tissue specific mean standard deviations of the error were compared between the SPECT$_{MRI}$ and PET$_{MRI}$ reconstructions using the statistical technique described in §2.4.1.1. One comparison was made for each tissue type, so $\alpha = 0.016$ with the Bonferroni correction.

2.5 Results

Visual inspection of each registered MRI $\mu$-map confirmed the absence of major segmentation or registration errors that could interfere with subsequent analysis. A typical canine MRI image, MRI $\mu$-map, and CT $\mu$-map are shown in Figure 2.2.

![Figure 2.2: Example of an MRI $\mu$-map after image registration. The images are derived from canine S1. (a) Coronal slice through MRI image. (b) Corresponding slice through the MRI $\mu$-map. (c) Corresponding slice through the silver standard CT $\mu$-map. (d) MRI prior to registration for reference.](image)

Each $\mu$-map was applied to projection data which was then processed by the OSEM reconstruction algorithm to yield a nuclear medicine image. Examples (drawn
from the canine experiments) of each class of reconstruction (SPECT\textsubscript{CT}, SPECT\textsubscript{MRI}, PET\textsubscript{CT}, and PET\textsubscript{MRI}) are presented in Figure 2.3, as are reconstructions without AC for comparison (SPECT\textsubscript{none} and PET\textsubscript{none}). For a more quantitative perspective, profiles through the images are also provided. SPECT\textsubscript{CT} and PET\textsubscript{CT} reconstructions of the phantom are provided in Figure 2.4.

The global error analysis was based on scatter plots and properties of their LOBFs. Representative scatter plots are displayed in Figure 2.5, one for SPECT and one for PET. Both are specific to voxels in soft tissue.

The results of the global analysis are tabulated in Tables 2.2 and 2.3 for the animal and phantom experiments, respectively. In the animal experiments, $R^2$ was significantly higher for SPECT than PET in both lung and soft tissue. The trend was similar in bone, but did not reach statistical significance ($p = 0.03$). For both modalities, $m$ tended to be less than its ideal value of 1, excepting soft tissue in SPECT. However, there was a trend for $m$ to be closer to 1 in SPECT than PET for each tissue type, with $p < 0.025$ in all cases. Finally, $b$ was generally very close to 0, except for lung tissue in PET. The results in the phantom were similar, with the exception that PET demonstrated a notably higher $R^2$ in bone than did SPECT.

To inspect errors on a smaller scale and within particular structures, a local error analysis based on VOIs was conducted. The results are presented in Tables 2.4 and 2.5 for the canines and phantom, respectively. In the animal experiments, only one comparison reached statistical significance. However, the mean magnitude of the error was less for SPECT than PET in twelve of the fourteen VOIs. The errors were generally acceptable in soft tissue structures, sometimes even if the VOI was adjacent to bone. Large errors were observed in VOIs within bony anatomy and the lungs, especially in PET. Similarly, the errors in the phantom were smallest in the soft tissue, larger in the lungs, and largest in bone. The absolute value of the errors in SPECT
Figure 2.3: Comparison of SPECT and PET reconstructions. The data presented are typical. The top row corresponds to SPECT (canine S4) and the middle row to PET (canine P1). The slices are axial and pass through the heart, which is the source of the high activity regions. Profiles through the reconstructions are presented in the bottom row. (a) CT $\mu$-map corresponding to slices in the top row. The red line indicates the position of the profiles in (i). (b) SPECT$_{\text{none}}$. (c) SPECT$_{\text{CT}}$. (d) SPECT$_{\text{MRI}}$. (e) CT $\mu$-map corresponding to the slices in the middle row. The red line indicates the position of the profiles in (j). (f) PET$_{\text{none}}$. (g) PET$_{\text{CT}}$. (h) PET$_{\text{MRI}}$. (i) Profiles through the SPECT reconstructions. (j) Profiles through the PET reconstructions. For both (i) and (j), the solid line is through the reconstruction with CT-based AC, the dashed line is through the reconstruction with MRI-based AC, and the dotted line is through the reconstruction without AC.
Figure 2.4: Coronal slices of (a) SPECT\textsubscript{CT} and (b) PET\textsubscript{CT} phantom reconstructions. The lungs, liver, and heart are all visible amongst the background soft tissue.

Figure 2.5: Scatter plots comparing the “true” activities in soft tissue voxels to those obtained with MRI-based AC. Each scatter plot comes from a single canine. All the activities have been normalized by expressing them as a fraction of the maximal tissue and subject specific true activity. Note that although the normalized activities can assume any value between 0 and 1, the plots focus on regions where most of the data resides, although insets showing the complete datasets are provided in the top left corner of each plot. In particular, the axes of the SPECT plot run from 0 to 0.05, while the axes of the PET plot run from 0 to 0.3, the discrepancy owing to the different uptake characteristics of MIBI and FDG. The LOBF is superimposed on each scatter plot. (a) Soft tissue scatter plot for a SPECT reconstruction (canine S3). The equation of the LOBF (calculated using all the data, not just that in the truncated plots) is \( y = 1.02x - 1 \times 10^{-4} \) with \( R^2 = 0.998 \). (b) Soft tissue scatter plot for a PET reconstruction (canine P2). The equation of the LOBF is \( y = 0.92x + 5 \times 10^{-3} \) with \( R^2 = 0.985 \).
Table 2.2: Results from global error analysis. The (dimensionless) LOBF metrics averaged across all canines are displayed for both SPECT \((n = 4)\) and PET \((n = 4)\) for three tissue types. Mean values are presented ± standard deviation. Statistically significant differences between SPECT and PET are bolded. \(p\)-values are provided.

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Metric</th>
<th>SPECT</th>
<th>PET</th>
<th>(p)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung</td>
<td>(R^2)</td>
<td>0.90 ± 0.10</td>
<td>0.21 ± 0.19</td>
<td>0.0019</td>
</tr>
<tr>
<td>Lung</td>
<td>(m)</td>
<td>0.90 ± 0.09</td>
<td>0.30 ± 0.23</td>
<td>0.0094</td>
</tr>
<tr>
<td>Lung</td>
<td>(b)</td>
<td>0.01 ± 0.01</td>
<td>0.15 ± 0.09</td>
<td>0.0577</td>
</tr>
<tr>
<td>Soft tissue</td>
<td>(R^2)</td>
<td>0.998 ± 0.001</td>
<td>0.979 ± 0.005</td>
<td>0.0043</td>
</tr>
<tr>
<td>Soft tissue</td>
<td>(m)</td>
<td>1.01 ± 0.04</td>
<td>0.93 ± 0.03</td>
<td>0.025</td>
</tr>
<tr>
<td>Soft tissue</td>
<td>(b)</td>
<td>(-5 \times 10^{-5} \pm 8 \times 10^{-5})</td>
<td>0.008 ± 0.004</td>
<td>0.032</td>
</tr>
<tr>
<td>Bone</td>
<td>(R^2)</td>
<td>0.96 ± 0.02</td>
<td>0.87 ± 0.05</td>
<td>0.030</td>
</tr>
<tr>
<td>Bone</td>
<td>(m)</td>
<td>0.91 ± 0.01</td>
<td>0.83 ± 0.04</td>
<td>0.021</td>
</tr>
<tr>
<td>Bone</td>
<td>(b)</td>
<td>(-0.004 \pm 0.002)</td>
<td>(-0.03 \pm 0.03)</td>
<td>0.17</td>
</tr>
</tbody>
</table>

Table 2.3: Results from global error analysis on phantom. The (dimensionless) LOBF metrics are displayed for both SPECT and PET for three tissue types.

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Metric</th>
<th>SPECT</th>
<th>PET</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung</td>
<td>(R^2)</td>
<td>0.917</td>
<td>0.840</td>
</tr>
<tr>
<td>Lung</td>
<td>(m)</td>
<td>1.114</td>
<td>1.027</td>
</tr>
<tr>
<td>Lung</td>
<td>(b)</td>
<td>(-0.027)</td>
<td>0.032</td>
</tr>
<tr>
<td>Soft tissue</td>
<td>(R^2)</td>
<td>0.999</td>
<td>0.995</td>
</tr>
<tr>
<td>Soft tissue</td>
<td>(m)</td>
<td>0.998</td>
<td>0.959</td>
</tr>
<tr>
<td>Soft tissue</td>
<td>(b)</td>
<td>(-0.001)</td>
<td>0.003</td>
</tr>
<tr>
<td>Bone</td>
<td>(R^2)</td>
<td>0.751</td>
<td>0.915</td>
</tr>
<tr>
<td>Bone</td>
<td>(m)</td>
<td>0.751</td>
<td>0.726</td>
</tr>
<tr>
<td>Bone</td>
<td>(b)</td>
<td>(-0.122)</td>
<td>(-0.068)</td>
</tr>
</tbody>
</table>
Table 2.4: Results from local error analysis. The mean percent errors in fourteen VOIs are presented ± standard deviation for both SPECT and PET images. Statistically significant differences between SPECT and PET are bolded. *p*-values are provided.

<table>
<thead>
<tr>
<th>VOI</th>
<th>Mean error ± SD (%)</th>
<th>SPECT</th>
<th>PET</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left lung</td>
<td>−5.1 ± 17.5</td>
<td>−25.7 ± 11.6</td>
<td>0.10</td>
<td></td>
</tr>
<tr>
<td>Right lung</td>
<td>−8.9 ± 14.3</td>
<td>−45.2 ± 25.7</td>
<td>0.060</td>
<td></td>
</tr>
<tr>
<td>Rostral liver</td>
<td>0.1 ± 9.6</td>
<td>−6.8 ± 1.5</td>
<td>0.25</td>
<td></td>
</tr>
<tr>
<td>Caudal liver</td>
<td>−3.2 ± 2.6</td>
<td>−5.6 ± 0.9</td>
<td>0.17</td>
<td></td>
</tr>
<tr>
<td>Medial left ventricle</td>
<td>−3.6 ± 5.3</td>
<td>−4.1 ± 1.4</td>
<td>0.88</td>
<td></td>
</tr>
<tr>
<td>Lateral left ventricle</td>
<td>2.6 ± 4.2</td>
<td>−10.6 ± 11.4</td>
<td>0.099</td>
<td></td>
</tr>
<tr>
<td>Thoracic vertebra</td>
<td>−8.9 ± 2.6</td>
<td>−16.9 ± 6.0</td>
<td>0.069</td>
<td></td>
</tr>
<tr>
<td>Lumbar vertebra</td>
<td>−28.3 ± 7.6</td>
<td>−23.4 ± 5.8</td>
<td>0.35</td>
<td></td>
</tr>
<tr>
<td>Left humerus</td>
<td>−9.2 ± 1.9</td>
<td>−14.5 ± 5.8</td>
<td>0.17</td>
<td></td>
</tr>
<tr>
<td>Right humerus</td>
<td>−13.4 ± 1.6</td>
<td>−19.6 ± 6.0</td>
<td>0.13</td>
<td></td>
</tr>
<tr>
<td>Near thoracic vertebra</td>
<td>−5.7 ± 1.5</td>
<td>−10.7 ± 1.1</td>
<td>0.0022</td>
<td></td>
</tr>
<tr>
<td>Near lumbar vertebra</td>
<td>−21.8 ± 7.0</td>
<td>−13.8 ± 7.3</td>
<td>0.16</td>
<td></td>
</tr>
<tr>
<td>Near left humerus</td>
<td>−4.3 ± 5.4</td>
<td>−8.0 ± 2.5</td>
<td>0.28</td>
<td></td>
</tr>
<tr>
<td>Near right humerus</td>
<td>−4.3 ± 0.9</td>
<td>−5.0 ± 2.4</td>
<td>0.063</td>
<td></td>
</tr>
</tbody>
</table>

were smaller than those in PET in three VOIs, approximately the same in one (the myocardium), and larger in the remaining VOI (the spine).

To assess the sensitivity of reconstructions to variations in the MRI µ-map, multiple reconstructions were generated using the original canine MRI µ-map and four derivatives. Referring to Figure 2.6, one can see both how the MRI µ-map was modified and how the PET reconstructions were influenced as a result. Figure 2.7 is analogous, but presents data from a SPECT scan. The reconstructed activity at a voxel is linearly related to its error, and thus Figure 2.6 parts (d) and (e) provide some insight into the origin of the metric used in the sensitivity analysis. In particular, a pronounced dependence of activity on the MRI µ-map implies the same of the error, and consequently a high standard deviation of the error taken across all five
Table 2.5: Results from local error analysis on phantom. The percent errors in five VOIs are presented for both SPECT and PET images.

<table>
<thead>
<tr>
<th>VOI</th>
<th>SPECT</th>
<th>PET</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left lung</td>
<td>12.8</td>
<td>17.0</td>
</tr>
<tr>
<td>Right lung</td>
<td>5.3</td>
<td>10.4</td>
</tr>
<tr>
<td>Liver</td>
<td>−0.1</td>
<td>−3.6</td>
</tr>
<tr>
<td>Myocardium</td>
<td>1.7</td>
<td>−1.4</td>
</tr>
<tr>
<td>Spine</td>
<td>−51.8</td>
<td>−44.4</td>
</tr>
</tbody>
</table>

The results of the sensitivity analysis, broken down by tissue type, are presented in Figure 2.8. In both lung and soft tissue, PET was more sensitive to changes in the MRI $\mu$-map than was SPECT. For both modalities, the lung was the most sensitive tissue while bone was the least.

2.6 Discussion

The goal of the present study was to compare the fidelity of MRI-based AC in SPECT versus PET. The issue was investigated using a three part analysis identifying global quality, local quality, and a sensitivity to MRI $\mu$-map variations. Each component of the analysis points towards the same conclusion: SPECT$_{MRI}$ approximates SPECT$_{CT}$ better than PET$_{MRI}$ approximates PET$_{CT}$.

A suggestion of SPECT$_{MRI}$’s superiority over PET$_{MRI}$ can be readily observed in Figure 2.3. Visually, it is difficult to identify any differences between the SPECT$_{MRI_0}$ and SPECT$_{CT}$ images. In contrast, although the PET$_{MRI_0}$ image does closely resemble its PET$_{CT}$ counterpart, some discrepancies are obvious. Notably, PET$_{MRI_0}$ exhibits reduced activity in parts of the lungs and both humeri. Further, deviations
Figure 2.6: Example of the variations induced in a PET reconstruction (canine P3) by alterations in the MRI μ-map. (a) and (b) are visual depictions of how the MRI μ-map was modified. Either the lung (a) or the body contour (b) segmentation was altered. The colours indicate the border of the structure when it was eroded (yellow), left unchanged (green), or dilated (blue). The PET reconstruction corresponding to the unchanged MRI μ-map is presented in (c). Profiles were taken through the blue line. (d) Profiles from reconstructions produced by altering the lungs (i.e. PET_{MRI_{el}} and PET_{MRI_{dl}}, with PET_{MRI_{0}} for reference). (e) Profiles from reconstructions produced by altering the body contour (i.e. PET_{MRI_{eb}} and PET_{MRI_{db}}, with PET_{MRI_{0}} for reference).
Figure 2.7: Example of the variations induced in a SPECT reconstruction (canine S1) by alterations in the MRI $\mu$-map. The SPECT reconstruction corresponding to the unchanged MRI $\mu$-map is presented in (a). Profiles were taken through the blue line. (b) Profiles from reconstructions produced by altering the lungs (i.e. SPECT$_{MRI_0}$ and SPECT$_{MRI_{di}}$, with SPECT$_{MRI_0}$ for reference). (c) Profiles from reconstructions produced by altering the body contour (i.e. SPECT$_{MRI_{eb}}$ and SPECT$_{MRI_{db}}$, with SPECT$_{MRI_0}$ for reference).

Figure 2.8: Results of the sensitivity analysis broken down by tissue type. The dark bars correspond to SPECT and the white bars to PET. Asterisks denote statistically significant differences. Error bars represent the standard deviation of the sample.
are present in soft tissue. These are made most apparent by examining the profiles through the PET reconstructions from $-120 \text{ mm}$ to $-40 \text{ mm}$ and from $60 \text{ mm}$ to $75 \text{ mm}$. In both regions, $\text{PET}_{\text{MRI}}$ overestimates the true activity. In comparison, the profile through the $\text{SPECT}_{\text{MRI}}$ image is a near perfect match with $\text{SPECT}_{\text{CT}}$.

Another comparison of $\text{SPECT}_{\text{MRI}}$ and $\text{PET}_{\text{MRI}}$’s performance in soft tissue is presented in Figure 2.5. These are scatter plots of estimated versus true activity in every soft tissue voxel, a more comprehensive point of view than profiles, but still limited to individual canines. The main point to note is that the spread of points about the LOBF in PET is much wider than in SPECT. This implies that given a particular true activity at a voxel, $\text{PET}_{\text{MRI}}$ is less able to make a consistent estimate (good or bad) of the truth than $\text{SPECT}_{\text{MRI}}$. In other words, $\text{SPECT}_{\text{MRI}}$ has greater precision than $\text{PET}_{\text{MRI}}$. This trait was quantified by computing $R^2$ of the LOBF.

Tables 2.2 and 2.3 summarize the findings of the global analysis. With respect to $R^2$, it was confirmed that $\text{SPECT}_{\text{MRI}}$ is more precise than $\text{PET}_{\text{MRI}}$ within lung and soft tissue. The same trend appeared within bone in the animal experiments but was reversed in the phantom. In the canine studies, the correlation coefficient computed for soft tissue in PET ($R^2 = 0.979 \pm 0.005$) agrees closely with values reported by other groups that validated MRI-based AC algorithms for PET images of the whole body ($R^2 = 0.985 \pm 0.006$) [23] and brain ($R^2 = 0.968 \pm 0.011$) [10]. However, the results reported here are the first time that $R^2$ has been computed within different tissue types as opposed to over the entire image.

In both the animal and phantom experiments, precision is better in soft tissue than in bone or lung. One aspect of the explanation relates to the variation of $\mu$-coefficients within each tissue type. Although soft tissue does exhibit some variability, it is not as pronounced as the other two tissues. For instance, not only do the attenuating properties of bone depend on whether the bone is cortical or cancellous,
but on the subject as there are large differences in bone density between individuals [14]. The situation is equally complicated in the lungs because in addition to wide inter-subject variability, the observed μ-coefficient is a function of inflation and gravitational dependency [27]. Further, the presence of pathology affecting the bones or lungs can cause each tissue’s μ-coefficient distribution to deviate significantly from healthy population norms. MRI-based AC would benefit greatly from a means to measure patient specific μ-coefficients. A potential approach to this end is to utilize ultrashort echo time (UTE) pulse sequences. UTE sequences have already been used to aid in bone segmentation for MRI-based AC [4, 13], and have shown promise inferring the density of both bone [19, 29] and lung [26] tissue. However, if UTE (which can take well over ten minutes) is to be used in addition to conventional sequences, imaging time for attenuation correction is lengthened which is undesirable from a clinical standpoint.

Admittedly, physiological variation within the μ-coefficient distribution cannot adequately explain why $R^2$ was reduced in the phantom’s simulated bone, which is a homogenous material. Of importance, there was no true activity in the simulated bone, so activity localized to this region was due to scatter and the partial volume effect. It is therefore likely that the reduced $R^2$ is related to these phenomena rather than AC. Indeed, the simulated spine having a relatively small diameter is susceptible to partial voluming and presents challenges for scatter correction which struggles at high spatial frequencies.

The other two metrics in the global analysis, $m$ and $b$, measured systematic bias of the MRI-based reconstructions. Generally, $b$ was approximately nil, indicating that the activity in $\text{SPECT}_{\text{MRI}}/\text{PET}_{\text{MRI}}$ reconstructions was not over- or underestimated by an additive constant. With regards to $m$, the ideal value is 1, and deviations from this value imply a consistent over- or underestimation of true activity by a constant
multiplicative factor. In all cases save one, \( m \) was closer to 1 in SPECT\(_{\text{MRI}}\) than PET\(_{\text{MRI}}\), indicating SPECT\(_{\text{MRI}}\) has less systematic error. Although the results were not statistically significant, the trend was strong with \( p < 0.025 \) for each comparison. Generally \( m < 1 \), suggesting activity was systematically underestimated. One contributor to this bias is that bone was neglected in the MRI \( \mu \)-maps, leading to underestimated activity both within and in proximity to bony anatomy (Table 2.4). Similar findings have been reported by several groups [15, 23, 25].

Another factor leading to systematic underestimates of activity was a mismatch between the predefined \( \mu \)-coefficient assigned to lung parenchyma (Table 2.1) and the actual mean lung \( \mu \)-coefficient of the canines in the experiment. The numbers used in this work were were taken from published values [2, 11], but as previously mentioned, there is a great deal of variation of \( \mu \)-coefficients in lungs. The 511 keV \( \mu \)-coefficients assigned to lung tissue in other MRI-based AC algorithms are diverse, including 0.018 cm\(^{-1}\) [15], 0.024 cm\(^{-1}\) [23], and 0.03 cm\(^{-1}\) [25]. The choice of optimal \( \mu \)-coefficients for segmented MRI \( \mu \)-maps is non-trivial, depending on the population under investigation and the efficacy of scatter correction (narrow-beam versus broad-beam geometry). This will remain an important issue in MRI-based AC and warrants further study.

The primary result from the local analysis was that the magnitude of the observed errors were smaller in SPECT\(_{\text{MRI}}\) than PET\(_{\text{MRI}}\) for twelve of the fourteen canine VOIs and three of the five phantom VOIs. Admittedly, only one comparison between the canine groups reached statistical significance. This is best understood by recognizing that distribution of errors at a single VOI across several canines can be quite wide, owing to differences in local MRI \( \mu \)-map quality. Likely, the statistical power required to reach significance when comparing these broad distributions was not met with four canines in each group. Nevertheless, the pattern remains clear.
The final component of the analysis was the assessment of the sensitivity of SPECT\textsubscript{MRI}/PET\textsubscript{MRI} reconstructions to variations in the MRI $\mu$-map. As exhibited in Figure 2.8, PET\textsubscript{MRI} was more sensitive than was SPECT\textsubscript{MRI} within lung and soft tissue, although no difference was seen in bone. When combined with the findings of the global and local analyses, this result indicates that not only is SPECT\textsubscript{MRI} more quantitatively accurate than PET\textsubscript{MRI}, the accuracy is less dependent on the characteristics of the MRI $\mu$-map itself.

The sensitivity metric (plotted on the y-axis of Figure 2.8) has an interesting interpretation: increasing or decreasing the segmented size of the lungs or body by one voxel will change the estimated activity, on average, by the value of the sensitivity metric. With this in mind, the results of the sensitivity analysis signify the importance of accurate segmentation in this class of MRI $\mu$-map. Further, they provide some insight into the magnitude of quantification errors due to misregistration of the CT $\mu$-map and MRI $\mu$-map since misregistration makes it appear that the MRI $\mu$-map was segmented erroneously.

With all three components of the analysis indicating that MRI-based AC is more reliable in SPECT than PET, it is natural to seek an explanation. Indeed, the result is counterintuitive in that the mechanics of attenuation correction in SPECT are more complicated than in PET; the former generally relies on iterative algorithms with embedded attenuation correction while the latter reduces to pixel-by-pixel multiplication of two sinograms prior to reconstruction. That said, AC relies on entities called AC factors derived from line integrals through the $\mu$-map. In SPECT, since one photon is emitted per radioactive decay, the line integrals traverse from the decay site to the site of detection. In PET, each decay produces a positron which subsequently annihilates, generating a pair of photons emitted at 180$^\circ$ to one another. As both photons must be detected to register the decay event, the line integrals pass between
the two detectors involved. In short, the line integrals in SPECT are shorter than those in PET, and thus tend to generate smaller AC factors. However, SPECT is typically done at lower photon energies than PET and therefore its µ-maps are comprised of higher µ-coefficients, tending to generate larger AC factors. Of these two phenomena, the line integral length generally has more influence, and consequently SPECT has lower AC factors than PET. (As an illustration, in the profiles presented in Figure 2.3, notice that there is a larger difference between PETnone and PETCT than SPECTnone and SPECTCT.) Consequently, differences between the MRI µ-map and CT µ-map are not magnified in SPECT to the extent that they are in PET. Thus, MRI-based AC is more forgiving in SPECT than in PET.

The present study contains some inherent limitations. For instance, there are several varieties of MRI-based AC algorithms, of which only one is investigated. Although it is plausible that the results of this experiment hold for related algorithms, this may not be so for other techniques. Further, the segmentation used to generate MRI-based µ-maps was rather simple, only comprising three tissue types; notably, bone was excluded. However, to the best of our knowledge no group has successfully implemented a whole-body MRI-based AC algorithm accounting for bone, and such an endeavour is beyond the scope of this paper.

Another limitation is that, due to practical considerations (excessive length of anaesthesia and concurrent use of two radiotracers thereby interfering with photon detection), different cohorts of canines were used for SPECT and PET imaging. Imagining the same animals with both modalities would remove a source of variation in the data and potentially improve the statistical power of the study. Such an experimental design would be useful to pursue in future work.

Finally, due to cardiac and respiratory motion, there was a fundamental mismatch between both the CT- and MRI-based µ-maps and the emission data. The µ-maps
were acquired at expiration whereas the emission data was ungated. The emission data and corresponding reconstructions were therefore blurred over the respiratory cycle, a phenomenon that was not reflected in the \( \mu \)-maps which are more akin to snapshots in time. However, as this effect was present for both nuclear imaging modalities, it is unlikely that it would significantly alter the conclusions described in this work.

In summary, we have demonstrated that MRI-based AC in SPECT performs better than PET. Specifically, it is more precise, more accurate, and less sensitive to the particulars of the MRI \( \mu \)-map. The implication is that if an MRI-based AC algorithm has been adequately validated for application to PET, it can be appropriately applied to SPECT as well.
References


Chapter 3

Variable Lung Density Consideration in Attenuation Correction of Whole-Body PET/MRI

3.1 Introduction

After a decade and a half of development, human whole-body PET/MRI systems are now a reality [12]. It has been widely speculated that PET/MRI will prove useful in several clinical disciplines [10, 23, 26], a prediction that is in the nascent stages of realization [1, 34]. However, without a means of attenuation correction (AC), accurate quantification in PET is not possible.

Multiple approaches have been proposed to create MRI-based attenuation maps (µ-maps) [3, 13, 14, 18, 22, 25, 29, 31, 32]. However, none measure the attenuation coefficients (µ-coefficients) of the lungs, which vary both between individuals [11] and within a given individual [6, 17] and are influenced by inflation [11, 17, 35], gravitational dependency [6, 35], and pathology [7, 17, 19].

Visualizing lung parenchyma with MRI is challenging. The lungs have a low proton density [9] and short transverse relaxation time ($T_2^*$) [2, 8], compromising available MRI signal. Also, the lungs are mobile and highly vascular, generating motion and flow artifacts, respectively [9].

In this work, an MRI-based AC method that incorporates patient specific measures of lung $\mu$-coefficients is developed. First, a standard MRI pulse sequence capable of visualizing lung tissue is described. Next, the relationship between MRI signal and CT signal in the lungs is evaluated. Said relationship was used to create $\mu$-maps with patient specific $\mu$-coefficients. The quantitative fidelity of PET reconstructions produced using these $\mu$-maps was compared to reconstructions done with $\mu$-maps that assumed a constant $\mu$-coefficient in the lungs across all subjects.

### 3.2 Materials and Methods

#### 3.2.1 Experimental Protocol

Five canines were imaged with PET/CT and MRI. One set of PET emission data was collected per canine, but CT scans were acquired at three respiratory states (via a ventilator) to simulate different lung densities. The CT scans yielded a clinical quality CT (CT$_{\text{clin}}$) and a pre-$\mu$-map for AC (CT$_{\text{pre-$\mu$}}$). Two types of MR image were acquired: one of the whole body (MRI$_{\text{WB}}$) and one of the lungs (MRI$_{\text{lung}}$). As with CT, MRI was acquired at three respiratory states. Further, MRI$_{\text{lung}}$ was acquired at four TEs enabling the computation of a lung $T_2^*$ map (MRI$_{\text{lung$T_2^*$}}$) and extrapolated proton density map (MRI$_{\text{lungPD}}$). The MRI$_{\text{lung}}$ image with the shortest TE was given the name MRI$_{\text{lungSTE}}$, where STE stands for short TE.

The MRI signal was related to CT$_{\text{clin}}$ signal in the lungs rather than 511 keV $\mu$-maps because the latter exhibited severe partial volume effects. First, MRI$_{\text{lungSTE}}$
was registered to $CT_{\text{clin}}$. Three scatter plots of $CT_{\text{clin}}$ lung signal versus $MRI_{\text{lungSTE}}$ signal were produced: one relating signal intensities at individual voxels, one relating mean signal intensities of coronal slices—coronal slices were chosen to preserve the dorsal/ventral lung density gradient that arises in supine subjects [6, 17], and the last relating mean signal intensities of the lungs in their entirety. Linear regression was carried out on each scatter plot, and the resulting mappings were termed voxel-by-voxel, slice-by-slice, and global, respectively. The process was repeated for $MRI_{\text{lungT}_2}$ and $MRI_{\text{lungPD}}$, but for reasons discussed in the results, only $MRI_{\text{lungSTE}}$ was used to create $\mu$-maps.

Next, multiple MRI-derived pre-$\mu$-maps (CT-like objects that the PET/CT scanner converts to $\mu$-maps) were formed. First, $MRI_{\text{WB}}$ was segmented into air, lung, and soft tissue. Air and soft tissue were assigned values of $-1000$ HU and $0$ HU, respectively. Three pre-$\mu$-maps were formed by registering $MRI_{\text{lungSTE}}$ to $MRI_{\text{WB}}$, and applying either the voxel-by-voxel, slice-by-slice, or global mappings to the lungs. PET reconstructions using these pre-$\mu$-maps are denoted PET$_{\text{voxels}}$, PET$_{\text{slices}}$, and PET$_{\text{global}}$, respectively. Eleven pre-$\mu$-maps were formed by assigning the lungs a constant CT number ranging from $-900$ HU to $-400$ HU in 50 HU increments. PET reconstructions using these pre-$\mu$-maps are referred to by subscripting the CT number assigned to the lungs, e.g. PET$_{-650}$. Reconstruction using any MRI- or CT-based $\mu$-map, are termed PET$_{\text{MRI}}$ and PET$_{\text{CT}}$, respectively.

The quality of the PET$_{\text{MRI}}$ reconstructions was assessed by comparison to PET$_{\text{CT}}$. The analysis included both global and local components. Statistical testing was done with ANOVAs and Tukey’s tests.
3.2.2 Subjects

This work was conducted on five female beagles (mass 8-12 kg). The protocol was approved by The University of Western Ontario’s animal care committee.

Anesthesia was initiated with propofol and maintained with 2.0-2.5% isofluorane. After intubation, artificial ventilation was conducted with a Veterinary ADS 1000 system (Engler Engineering Co., FL, USA). To facilitate coregistration of the PET/CT and MRI images, the canines were immobilized on a rigid board during the experiment.

3.2.3 Imaging

Imaging consisted of an 18F-FDG PET/CT on a Discovery VCT (GE Healthcare) and an MRI on a Verio 3 T (Siemens Medical). Following an overnight fast (mimicking the clinical protocol for whole-body PET/CT), the 18F-FDG was administered intravenously one hour prior to the PET/CT. The injected activity was approximately 10 MBq/kg. The acquisition was 3D with 5 minutes/table stop. Reconstructions were done with ordered subset expectation maximization (2 iterations, 28 subsets). The PET images had in-plane pixel size of 5.47 mm × 5.47 mm (128 × 128 matrix size) with 3.27 mm slice thickness. The acquisition was ungated.

CTs were acquired at three respiratory states: functional residual capacity (FRC) was attained by halting ventilation and two levels of inspiration were achieved by applying a positive inspiratory pressure (PIP) of 8 cm H2O and 16 cm H2O.

All CT scans had a kVp of 140, a mAs of 110, and were reconstructed with filtered back projection. CT_{clin} had an in-plane pixel size of 0.98 mm × 0.98 mm, a matrix size of 512 × 512, and slice thickness of 3.27 mm. CT_{pre-µ} had a larger in-plane pixel size (1.37 mm × 1.37 mm). The scanner converted CT_{pre-µ} into a µ-map by
downsampling via voxel averaging to a $128 \times 128$ matrix size, smoothing with a Gaussian filter (full-width half-maximum 10 mm), and then applying a lookup table.

The MRI protocol was repeated for each respiratory state. MRI$_{WB}$ was a 2D Turbo-FLASH with a TR of 392 ms, TE of 1.3 ms, 1 signal average, in-plane pixel size of $1.95 \text{ mm} \times 1.95 \text{ mm}$, matrix size of $128 \times 128$, axial slice thickness of 5 mm without gaps, flip angle of $10^\circ$, pixel bandwidth of 630 Hz/pixel, and anterior/posterior phase encode direction. The acquisition was spread over four table positions aligned with the isocentre, each consisting of 36 slices acquired in 15 s. MRI$_{lung}$ was also acquired with Turbo-FLASH, but with some altered parameters: a TR of 121 ms, TE of 0.75 ms (shortest allowable TE given the other parameters), in-plane pixel size of $1.87 \text{ mm} \times 1.87 \text{ mm}$, coronal slice thickness of 10 mm without gaps, pixel bandwidth of 1532 Hz/pixel, and right/left phase encode direction. The acquisition was acquired in one table position and consisted of 18 slices. MRI$_{lung}$ was cardiac gated in diastole via three lead ECG. Imaging time was approximately 10 s. MRI$_{lung}$ was repeated three more times with three different TEs of 0.85 ms, 0.95 ms, and 1.03 ms (longest allowable TE given the other parameters) to compute MRI$_{lungT_2}$ via a voxel-by-voxel exponential fit as a function of TE.

MRI$_{lungSTE}$ was normalized to the signal from a reference vial of saline placed next to the canine’s neck. MRI$_{lungPD}$ was computed by voxel-by-voxel extrapolation of MRI$_{lungSTE}$ to TE = 0 ms via MRI$_{lungT_2}$.

Radio frequency (RF) transmission was via the body coil and signal reception was through elements of the spine array, body matrix, and large flex RF coils adjacent to the field of view. The body matrix was secured loosely to avoid obstructing chest wall expansion. Prescan normalization was carried out prior to each acquisition to reduce RF shading.
3.2.4 Image Registration

MRI_{\text{lung}^{\text{STE}}}, MRI_{\text{lung}^{\text{T}2}}, \text{ and } MRI_{\text{lung}^{\text{PD}}} \text{ were registered to } CT_{\text{clin}} \text{ in order to generate the mappings. Resolution was matched by voxel averaging. Registration was carried out using the Insight Segmentation and Registration Toolkit (ITK) [16]. Mattes mutual information was chosen as the similarity measure since it is suitable for inter-modality registrations. At FRC, there was excellent anatomical agreement between } CT_{\text{clin}} \text{ and } MRI_{\text{lung}} \text{ so a rigid transform was used. For the other two respiratory states, the diaphragm’s position oscillated slightly. To accommodate the minor discrepancies in lung inflation, a hierarchical transform model was chosen, evolving sequentially from rigid to affine to non-rigid [24]. Evolution of the transform type was initiated when the previous transform converged on a solution.}

Similarly, MRI_{\text{lung}^{\text{STE}}} \text{ was registered to } MRI_{\text{WB}} \text{ and completed MRI-based pre-}\mu\text{-maps were rigidly registered to the CT-based pre-}\mu\text{-maps. Once aligned, the background of the CT-based pre-}\mu\text{-map (patient bed, rigid board securing the canines’ positioning, etc.) was added to the MRI-based pre-}\mu\text{-map.}

3.2.5 Image Segmentation

MRI_{\text{WB}} \text{ was segmented into air, lung, and soft tissue using a semi-automated algorithm developed in-house and implemented on Matlab v7.9.0.529 (The MathWorks, MA, USA). The details of the segmentation algorithm have been described previously [21]. Briefly, the subject’s body was identified using an empirical threshold. Voxels outside the body were deemed air. The lungs were segmented by applying a level set algorithm implemented in ITK-SNAP [36] to seed voxels identified with a second empirical threshold. The air in the trachea was segmented by hand, and segmentation errors were corrected manually. All remaining voxels were classified as soft tissue.}
3.2.6 Quantitative Analysis

The global quality of PET\textsubscript{MRI} images was assessed in lung, soft tissue, and bone. Masks of these tissues were generated by thresholding the CT-based pre-\(\mu\)-map (\(-950\) HU < lung \(-150\) HU < soft tissue \(100\) HU < bone). Only axial slices containing lung were included in the analysis. For each PET\textsubscript{MRI} reconstruction, a voxel-by-voxel scatter plot of PET\textsubscript{MRI} activity versus PET\textsubscript{CT} activity was created in lung, soft tissue, and bone. The scatter plots were normalized to the maximum PET\textsubscript{CT} activity. Three metrics were computed on each scatter plot: (1) the integral from 0 to 1 of the squared difference between the line of best fit (LOBF) computed via linear regression and the line of identity, \(D_{y=x}^2\), (2) the squared Pearson product-moment correlation coefficient, \(R^2\), and (3) the root mean squared error, \(E\), defined as \(\sqrt{\frac{\sum_{i=1}^{n} (y_i - x_i)^2}{n}}\) where \(y_i\) and \(x_i\) are the (normalized) estimated and true activities, respectively, at voxel \(i\), and \(n\) is the number of voxels. \(D_{y=x}^2\) measures the proximity of the LOBF to the line of identity, i.e. accuracy. \(R^2\) measures the spread of points about the LOBF, i.e. precision. \(E\) is impacted by both accuracy and precision; in particular, \(E\) approaches zero if and only if \(D_{y=x}^2\) approaches zero and \(R^2\) approaches one.

Each metric was analyzed statistically using a three-way AVOVA (\(\alpha = 0.05\)) with respiratory state, tissue type, and \(\mu\)-map as factors. Significant results were followed by Tukey’s test.

Local magnitude of relative error (\%) was assessed in eight \(1.094\) cm \(\times\) \(1.094\) cm \(\times\) \(0.981\) cm rectangular volumes of interest (VOIs) (Figure 3.1). Statistical analysis was the same as above, except the tissue type factor was changed to VOI in the ANOVA.

Steps were also taken to identify experimental errors. Lung segmentation error in MRI\textsubscript{WB} was computed as the percent difference in lung volume at FRC as compared to CT\textsubscript{clin}. To see whether these errors were dependent on lung inflation, this was repeated for the other respiratory states and the means and standard deviations were
Figure 3.1: VOI placement on canine 1 at PIP = 16 cm H₂O for local analysis. (A) Axial CT<sub>clin</sub> slice with VOIs superimposed. Red = right lung, green = left lung, blue = peripheral left ventricle, yellow = central left ventricle, purple = vertebral body, orange = chest wall. (B) The same VOIs superimposed on PET<sub>CT</sub>. (C) Coronal CT<sub>clin</sub> slice with the remaining VOIs. Cyan = vena cava, beige = dome of liver. (D) These two VOIs superimposed on PET<sub>CT</sub>.
compared statistically with a one-way ANOVA and Bartlett’s test for equal variances, respectively.

The effect of misregistration between MRI\textsubscript{lung} and CT\textsubscript{clin} on the voxel-by-voxel mapping (most sensitive to registration error) was inferred by shifting the registered MRI\textsubscript{lung} by \(-1\) cm to \(+1\) cm in 0.5 mm increments along each of the X, Y, and Z axes, and recalculating $R^2$ as a function of the shift.

### 3.3 Results

Of MRI\textsubscript{lungSTE}, MRI\textsubscript{lung$T_2$}, and MRI\textsubscript{lungPD}, only MRI\textsubscript{lungSTE} could be used to predict CT signal; thus neither MRI\textsubscript{lung$T_2$} nor MRI\textsubscript{lungPD} were included in the subsequent analysis (Figure 3.2). Good agreement between the spatial distribution of lung signal in CT and MRI\textsubscript{lungSTE} can be observed in Figure 3.3. The mappings from MRI\textsubscript{lungSTE} to CT number are presented in Figure 3.4. A linear relationship was demonstrated between the modalities.

The MRI-based pre-$\mu$-maps that incorporate lung information are contrasted with a CT-based pre-$\mu$-map in Figure 3.5. The global mapping retains the least spatial information, whereas the voxel-by-voxel mapping retains the most.

The results of the tissue-specific analysis are presented in Figure 3.6 and the ANOVAs are found in Table 3.1. The results of the post hoc test are best visualized in Figure 3.6; points without overlapping error bars are significantly different. The $\mu$-map class had little influence on the metrics in soft tissue and bone, but a marked impact in the lungs. Within the lungs, PET\textsubscript{voxels} exhibited the best accuracy, as reflected by $D^2_{y=x}$. PET\textsubscript{slices} and PET\textsubscript{voxels} were the most precise, as reflected by $R^2$. The lowest $E$ was achieved by PET\textsubscript{voxels}, followed by PET\textsubscript{slices}.

The VOI analysis (Table 3.2) revealed that the minimum error in the lungs, heart,
Figure 3.2: Voxel-by-voxel relationship between (A) MRI\textsubscript{lungT$^*$} and CT number and (B) MRI\textsubscript{lungPD} and CT number. The data from all five canines is plotted on each scatter plot. Each point’s colour represents the canine’s respiratory state, where dark blue is FRC, red is PIP = 8 cm H$_2$O, and light blue is PIP = 16 cm H$_2$O. The T$_2^*$ estimates were too noisy to make either of these correlations useful.
Figure 3.3: Spatial correlation between lung signal in CT (left) and MRI$_{\text{lungSTE}}$ (right). A coronal slice from canine 1 at FRC is shown. The MRI is registered to the CT. The CT image display ranges from $-1000$ to $-700$ HU, and the MRI from 0 to 180 arbitrary units.

Table 3.1: Results of ANOVAs on canine PET$_{\text{MRI}}$ metrics of overall quantitative fidelity and quantification error in the myocardium.

<table>
<thead>
<tr>
<th>Metric</th>
<th>Factor</th>
<th>$F$</th>
<th>$p$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$D_{y=x}^2$</td>
<td>Respiratory state</td>
<td>4.45</td>
<td>0.01</td>
</tr>
<tr>
<td></td>
<td>Tissue</td>
<td>271.41</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td></td>
<td>µ-map class</td>
<td>11.45</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>$R^2$</td>
<td>Respiratory state</td>
<td>13.72</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td></td>
<td>Tissue</td>
<td>899.97</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td></td>
<td>µ-map class</td>
<td>3.10</td>
<td>0.0001</td>
</tr>
<tr>
<td>$E$</td>
<td>Respiratory state</td>
<td>0.13</td>
<td>0.88</td>
</tr>
<tr>
<td></td>
<td>Tissue</td>
<td>570.71</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td></td>
<td>µ-map class</td>
<td>9.35</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Magnitude of relative</td>
<td>Respiratory state</td>
<td>44.65</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>error in VOIs</td>
<td>VOI</td>
<td>109.21</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td></td>
<td>µ-map class</td>
<td>25.63</td>
<td>&lt; 0.0001</td>
</tr>
</tbody>
</table>
Figure 3.4: Relationship between MRI\textsubscript{\text{lungSTE}} signal and CT number. Points on the scatter plots represent (A) voxels, (B) coronal slices, and (C) all lung tissue. The LOBF equations are $y = 1116x - 916$, $y = 1223x - 932$, and $y = 1251x - 937$, respectively. The data from all five canines is plotted on each scatter plot. Each point’s colour represents the canine’s respiratory state, where dark blue is FRC, red is PIP = 8 cm H\textsubscript{2}O, and light blue is PIP = 16 cm H\textsubscript{2}O. As expected, an increased volume of air in the lungs reduces both the MRI and CT signals.
Figure 3.5: Axial slice through four pre-µ-maps obtained from canine 5 at PIP = 16 cm H₂O. (A) CT-based. The others are MRI based and incorporate information from MRI_lungSTE via the (B) global, (C) slice-by-slice, and (D) voxel-by-voxel mappings. The window and level are identical for all images and set to emphasize the lungs.

and liver was achieved by PET_voxels, PET_global, and PET_slices, respectively. Error was minimized in the chest wall, vena cava, and vertebral bodies by PET_{−900}, PET_{−700}, and PET_{−400}, respectively. However, in many VOIs the differences were not statistically significant.

Representative profiles through the PET images are presented in Figure 3.7. The effect of altering the lungs’ µ-coefficients is propagated into nearby soft tissues, including the myocardium, diminishing as the distance from the lungs increases. In this example PET_voxels is the most representative of the profile through PET_CT.

The lungs were undersegmented at FRC by 16% ± 8%, at PIP = 8 cm H₂O by 14% ± 12%, and at PIP = 16 cm H₂O by 18% ± 11%. Neither the means (p = 0.82) nor the standard deviations (p = 0.81) were significantly different between the respiratory states.

Regarding the effect of misregistration on the voxel-by-voxel mapping, $R^2$ was found to be an approximately Gaussian function of shift, peaking at 0.8 when no shift was applied. To maintain $R^2$ within 10% of its optimum, the maximum allowable shift was ±1.25 mm left/right and ±2.75 mm anteriorly/posteriorly or superi-
Figure 3.6: Three metrics of PETMRI's quantitative fidelity broken down by tissue type and $\mu$-map class. The metrics include (A) $D^2_{y=x}$, (B) $R^2$, and (C) $E$. The leftmost blocks of data are from within the lungs, the middle blocks from soft tissue, and the rightmost blocks from bone. Each point within a given block corresponds to a different PETMRI reconstruction. Error bars indicate 95% confidence intervals.
Figure 3.7: Sample profiles through PET reconstructions of a canine at FRC. (A) Transaxial slice through CT-based $\mu$-map for anatomical reference. Profiles were taken through the cyan line that can be seen to pass through the humeri, lungs, and heart. (B) Corresponding slice through the PET$\text{CT}$ image. (C) Profiles through PET$-900$ and PET$-400$. Profiles through all other PETMRI images are bounded by these curves. The solid line represents the truth as obtained via PET$\text{CT}$. (D) Profiles through PET$\text{global}$, PET$\text{slices}$, and PET$\text{voxels}$. Again, the black line represents the truth.
orly/inferiorly.
Table 3.2: Average magnitude of relative error in VOIs as a function of $\mu$-map. The mean error is recorded as a percentage of the true activity with the standard deviation in brackets. The best result in each VOI is bolded, while results that are not statistically different from the best result according to Tukeys test are italicized. LV = left ventricle.

<table>
<thead>
<tr>
<th>VOI</th>
<th>$-900$</th>
<th>$-850$</th>
<th>$-800$</th>
<th>$-750$</th>
<th>$-700$</th>
<th>$-650$</th>
<th>$-600$</th>
<th>$-550$</th>
<th>$-500$</th>
<th>$-450$</th>
<th>$-400$</th>
<th>global</th>
<th>slices</th>
<th>voxels</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right lung</td>
<td>30 (10)</td>
<td>23 (11)</td>
<td>17 (11)</td>
<td>13 (9)</td>
<td>12 (7)</td>
<td>13 (9)</td>
<td>17 (13)</td>
<td>23 (17)</td>
<td>31 (19)</td>
<td>40 (21)</td>
<td>50 (22)</td>
<td>13 (11)</td>
<td>10 (8)</td>
<td>5 (3)</td>
</tr>
<tr>
<td>Left lung</td>
<td>34 (13)</td>
<td>28 (14)</td>
<td>22 (14)</td>
<td>18 (12)</td>
<td>15 (10)</td>
<td>14 (10)</td>
<td>16 (12)</td>
<td>20 (14)</td>
<td>26 (18)</td>
<td>33 (22)</td>
<td>41 (24)</td>
<td>8 (5)</td>
<td>8 (5)</td>
<td>4 (4)</td>
</tr>
<tr>
<td>Outer LV</td>
<td>17 (7)</td>
<td>14 (7)</td>
<td>11 (6)</td>
<td>9 (6)</td>
<td>6 (5)</td>
<td>5 (4)</td>
<td>4 (3)</td>
<td>5 (4)</td>
<td>7 (6)</td>
<td>9 (7)</td>
<td>12 (8)</td>
<td>4 (3)</td>
<td>4 (4)</td>
<td>5 (4)</td>
</tr>
<tr>
<td>Central LV</td>
<td>7 (2)</td>
<td>6 (2)</td>
<td>5 (2)</td>
<td>4 (2)</td>
<td>3 (2)</td>
<td>2 (1)</td>
<td>2 (2)</td>
<td>2 (2)</td>
<td>3 (3)</td>
<td>4 (3)</td>
<td>1 (1)</td>
<td>2 (1)</td>
<td>2 (1)</td>
<td></td>
</tr>
<tr>
<td>Vena cava</td>
<td>18 (11)</td>
<td>15 (8)</td>
<td>12 (7)</td>
<td>9 (8)</td>
<td>9 (9)</td>
<td>12 (9)</td>
<td>17 (11)</td>
<td>22 (13)</td>
<td>28 (14)</td>
<td>35 (15)</td>
<td>42 (16)</td>
<td>15 (9)</td>
<td>14 (8)</td>
<td>23 (6)</td>
</tr>
<tr>
<td>Vertebrae</td>
<td>16 (3)</td>
<td>15 (3)</td>
<td>15 (3)</td>
<td>14 (3)</td>
<td>13 (3)</td>
<td>13 (3)</td>
<td>12 (3)</td>
<td>11 (4)</td>
<td>11 (4)</td>
<td>10 (4)</td>
<td>10 (5)</td>
<td>12 (3)</td>
<td>12 (4)</td>
<td>11 (4)</td>
</tr>
<tr>
<td>Liver</td>
<td>6 (5)</td>
<td>6 (4)</td>
<td>6 (4)</td>
<td>5 (4)</td>
<td>5 (4)</td>
<td>5 (5)</td>
<td>5 (5)</td>
<td>6 (6)</td>
<td>6 (6)</td>
<td>7 (7)</td>
<td>8 (7)</td>
<td>5 (5)</td>
<td>4 (5)</td>
<td>5 (5)</td>
</tr>
<tr>
<td>Chest wall</td>
<td>5 (4)</td>
<td>5 (4)</td>
<td>6 (4)</td>
<td>7 (4)</td>
<td>7 (5)</td>
<td>8 (6)</td>
<td>9 (7)</td>
<td>10 (8)</td>
<td>11 (9)</td>
<td>12 (10)</td>
<td>14 (10)</td>
<td>9 (6)</td>
<td>9 (6)</td>
<td>7 (5)</td>
</tr>
</tbody>
</table>
3.4 Discussion

In this work, a means of using MRI to infer the spatial µ-coefficient distribution in the lungs was developed and tested on five canines. The evidence suggests doing so improves quantification in PET images.

In Figure 3.6, observe that in lung tissue the µ-map class influences each of the three metrics of quantitative fidelity; this was statistically significant in all cases (Table 3.1). Moreover, PET\textsubscript{voxels} performed the best according to all three metrics. Additionally, PET\textsubscript{voxels} had the least error in the lung VOIs (Table 3.2). These results suggest that PET\textsubscript{voxels} is the best choice for quantification in the lung.

Though µ-map choice did not influence quantification in soft tissue or bone when averaged over the whole thorax (Figure 3.6), it did affect structures near the lungs (Figure 3.7), notably the vena cava and peripheral left ventricle (Table 3.2). In the latter, there was a benefit to estimating the lung’s µ-coefficients, which is potentially of clinical significance as even subtle alterations in viability or perfusion PET imaging can impact clinical impression [27]. However, in the vena cava (which crudely simulated a pulmonary lesion), PET\textsubscript{−700} performed the best. This may have been due to limitation of MRI-based AC algorithms relying on segmentation. Notice in Figure 3.5A that in the CT-based µ-map the vena cava was subject to the partial volume effect. Segmentation cannot reproduce this phenomenon as each voxel must be classified as air, lung, or soft tissue. In the MRI-based µ-maps (Figure 3.5B-D), the voxels about the vena cava were preferentially deemed soft tissue. The MRI-based estimates of activity were therefore inflated relative to PET\textsubscript{CT}. One means of compensating is to underestimate the lung’s µ-coefficients. As the mean lung CT number across all subjects and respiratory states was −600 HU, PET\textsubscript{−700}’s apparent success was probably attributable to undervaluing the true mean by 100 HU. Further, notice
that $\text{PET}_{\text{voxels}}$ achieved the lowest standard deviation in the vena cava, suggesting that albeit biased, it is the most precise, and therefore amenable to correction with a scaling factor. In sum, accurate quantification of lung lesions in PET/MRI may prove challenging even with patient specific estimates of the lungs’ $\mu$-coefficients.

As the amount of adjacent lung tissue near the VOI decreases, so does the lung’s impact on quantification. For instance, in the central left ventricle, vertebral body, liver’s dome, and chest wall, the error was never changed by more than 9% based on $\mu$-map selection, and no statistically significant differences emerged. In these regions, what $\mu$-coefficients are assigned to the lungs is therefore less important.

The importance of reliable quantification in the heart and lung lesions is clear, but several potential applications of PET/MRI depend on accurate PET images of the lung parenchyma itself. For instance, while PET has demonstrated utility in identifying lung inflammation and infection in cystic fibrosis [20], CT-based AC is undesirable considering the predominantly paediatric patient population and ionizing radiation that accompanies CT scans; MRI-based AC could provide a convenient alternative, consistent with the “image gently” campaign. PET/MRI may also prove useful in understanding the inflammatory response in acute lung injury; pulmonary models of $^{18}$F-FDG kinetics [30] might be complemented by functional measures such as perfusion via MRI [15]. There are several other instances where PET/MRI may be useful for lung imaging [4], all of which will require accurate MRI-based AC of the lungs.

To the authors’ knowledge, no other approach has been able to measure the lungs’ $\mu$-coefficients. Some assign a constant $\mu$-coefficient to the lungs [21, 22, 31, 32] while others permit $\mu$-coefficient distributions [13], but none are patient specific. One method allows patient specific $\mu$-coefficients to be estimated by an iterative reconstruction algorithm [25], but correct convergence is not guaranteed. Ours is the first
approach to directly link MRI to CT signal in the lungs, but is subject to several limitations.

First, there remains a great deal of variance in Figure 3.4A unexplained by the regression. One source is that the MRI signal is dependent on magnetic timing parameters (notably $T_2^*$), which are location and subject specific [8]. Pure proton density images would avoid this problem, but our measures of $T_2^*$ proved too noisy to reliably extrapolate the signal at $TE = 0 \mu s$. Eliminating $T_2^*$ dependence may prove even more important if pathology is present, but in this work the impact of disease on the relationship between MRI and CT lung signal was not assessed. Exploring how disease affects the connection between MRI and CT signal in the lungs should be a priority for future work in this area, since ultimately, the method is intended for patients with pathologies.

Another contributor to the unexplained variance in the scatterplots in Figure 3.4 is registration error. By exploring the impact of misregistration via translation on $R^2$, it was found that there exists a 1.25 mm to 2.75 buffer (depending on direction) before the correlation deteriorates beyond 10%. It is difficult to quantify registration error, especially for non-rigid transformations; however, given the precautions taken to immobilize the dogs, the visual agreement between the registered images, and the misregistration buffer, registration error likely had a limited impact on the results.

$B_1$ inhomogeneity also adds to the scatterplots’ variance by making lung MRI signal a function of spatial position. However, prescan normalization reduced this problem. Retrospectively, it was found that the prescan normalization was also sufficient to standardize the MRI signal across subjects, rendering the additional step of normalizing to the signal from a saline vial unnecessary. This, however, may depend on the manufacturer.

Apart from the assignment of erroneous $\mu$-coefficients in the lungs, a major con-
troublier to the observed errors in the PET\textsubscript{MRI} images was missegmentation. The improper classification of air, lung, and soft tissue can alter quantification, even in remote regions [21]. Indeed, our analysis found that the lungs were systematically undersegmented by about 15% in all respiratory states. This problem might be assuaged with higher resolution MRI images to better delineate the lung boundaries. Also, bone was ignored, explaining bone’s higher $D_{y=x}^2$ and $E$ than soft tissue’s (Figure 3.6A,C). Neglecting bone propagates underestimates of activity into adjacent tissues, but this effect is localized and relatively small [28]. Accounting for bone remains a challenge in MRI-based AC, with only one group doing so for whole-body PET [13].

Another complication is that respiration occurs throughout the PET acquisition while a single phase of respiration was used to create the $\mu$-maps in this experiment, a problem referred to as transmission/emission mismatch. Thus, the PET\textsubscript{CT} image is not a true gold standard; it may contain errors of considerable magnitude [5]. Nevertheless, these errors are separate from those induced by assigning erroneous $\mu$-coefficients to the lungs and do not alter the conclusions of this study. On the contrary, without a means to account for the changing lung $\mu$-coefficients with respiration [11, 17, 35], optimal correction of the transmission/emission mismatch (via a time-varying $\mu$-map) would be flawed.

The principle reason that this study was carried out using a large animal model was that it allowed for precise control of their ventilation; the lungs could be held at the same respiratory state during the CT and MRI. A means of controlling respiratory state in humans would be helpful to extend MRI-based estimates of lung $\mu$-coefficients to patients. An impediment to translating the methodology described here to humans is that people necessitate a larger field of view. Accordingly, if resolution were to be maintained, scan time and consequently breath hold duration may increase. One solution is to eliminate cardiac gating, accelerating the acquisition.
Gating was employed in this study to facilitate image registration, but was likely over-conservative. However, eliminating cardiac gating is not a panacea. Additional problems will inevitably arise when modifying the pulse sequence for humans (e.g. altered signal-to-noise ratio, unanticipated artifacts, etc.), for which different solutions will be necessary. It should also be noted that this method is not fully automated; if this approach is to be used clinically, automation is pivotal.

Most of the challenges associated with AC of the lungs in PET/MRI result from MRI’s difficulty in reliably acquiring signal from lung parenchyma. An exciting prospect is to use ultrashort TE pulse sequences to overcome lung tissue’s short $T_2^*$. This method has been used to successfully demonstrate a correlation between signal intensity and lung inflation in mice [33]. However, ultrashort TE pulse sequences are harder to implement for large fields of view and the acquisition generally takes several minutes. In the immediate future, standard gradient echo and turbo spin sequences with relatively short TEs are more tenable [8, 9].

\subsection{3.5 Conclusion}

Until now, MRI-based AC algorithms have treated the $\mu$-coefficients of the lungs as unknown, undermining quantification in PET images. We have demonstrated that MRI can be used to infer $\mu$-coefficients and applied this principle to MRI-based AC. As a result, quantification is clearly improved in the lungs, and is likely improved in the surrounding tissues.
References


Chapter 4

To Segment, Register, or Map? A Comparison of Three MRI-Based Attenuation Correction Methods for Whole-Body PET

4.1 Introduction

There are several avenues through which PET/MRI technology can be advanced [26]. One of the most important is the development of robust MRI-based attenuation correction (AC) strategies [7]. Though the particulars of converting MRI images into attenuation maps (µ-maps) can vary immensely [1, 3, 6, 8, 12, 14, 15, 16, 17, 21, 22, 24, 27], the majority of approaches can be classified according to three categories: segmentation, registration, and mapping.

MRI-based AC methods relying on segmentation [3, 12, 15, 16, 17, 22, 24, 27] divide an MRI image into regions according to composition. Each region is assigned a representative attenuation coefficient (µ-coefficient). Problems arise in tissues that are not adequately characterized by a single µ-coefficient, such as the lungs [13, 15].
Errors also arise from erroneous segmentation [13, 16, 20].

An alternate approach is to align a template $\mu$-map with the patient’s MRI via image registration [14, 21]. The template may be arbitrarily spatially complex and offer a continuum of $\mu$-coefficients. However, as the template $\mu$-map is generic, its $\mu$-coefficients may not accurately reflect the patient’s. Moreover, finding the transform relating the template $\mu$-map with the patient’s MRI can be challenging. In fact, if there are anatomical differences between the two, a sensible transform may not even exist.

Finally, in techniques relying on mapping, one constructs a function that maps MRI image voxels to $\mu$-coefficients [1, 6, 8, 15]. It places no restrictions on $\mu$-map complexity and the $\mu$-map is derived directly from the patient. The challenge lies in finding an appropriate mapping function and input data.

In this work, we implemented three MRI-based AC algorithms employing segmentation, registration, and mapping. We compared their performances quantitatively on whole-body PET scans of cancer patients. PET scans reconstructed with CT-based $\mu$-maps were used as the silver-standard. Our aim was to identify some strengths and weaknesses of each method and, in so doing, determine how they might be combined synergistically.

4.2 Materials and Methods

4.2.1 Data Acquisition

Twelve oncologic patients (10 male, 2 female, mean age ± SD of 60 ± 10 y) were imaged from head to pelvis with FDG PET/CT (Discovery VCT, GE Healthcare) and MRI (Verio, Siemens Medical). The experiment was approved by The University of Western Ontario’s human research ethics board.
Following an overnight fast, 5 MBq/kg of FDG was administered intravenously one hour prior to the PET/CT. During uptake, the patients rested supine in a dark room. The acquisition was 3D with 210 s/table stop. Reconstructions were done with ordered subset expectation maximization (2 iterations, 28 subsets). The PET images had an in-plane pixel size of 5.47 mm × 5.47 mm (128 × 128 matrix size) with 3.27 mm slice thickness. The acquisition was ungated.

The CT scan, acquired during free but shallow breathing, had kVp of 140, mAs of 110, and was reconstructed via filtered back projection with in-plane pixel size of 1.37 mm × 1.37 mm, matrix size of 512 × 512, and slice thickness of 3.27 mm. The scanner converted the CT into a µ-map by downsampling, smoothing, and applying a lookup table.

Following the PET/CT, the patient received an MRI within twenty minutes. The whole-body MRI (MRI$_{WB}$) was acquired at functional residual capacity (breath-hold) with a 2D Turbo-FLASH sequence. The sequence parameters included TR of 786 ms, TE of 1.32 ms, in-plane pixel size of 1.95 mm × 1.95 mm, matrix size of 256 × 256, axial slice thickness of 5 mm without gaps, flip angle of 10°, pixel bandwidth of 630 Hz/pixel, and anterior/posterior phase encode direction. Five table positions, each with 36 slices and lasting 15 s, were acquired to form the whole-body image. A separate 2D Turbo-FLASH sequence was also acquired to infer lung density (MRI$_{lung}$) [15]. It had TR of 121 ms, TE of 0.75 ms, in-plane pixel size of 3.125 mm × 3.125 mm, matrix size of 128 × 128, coronal slices with thickness of 10 mm (no gaps), flip angle of 10°, pixel bandwidth of 1532 Hz/pixel, and right/left phase encoding.

RF transmission was via the body coil and signal reception was through elements of the spine array, body matrix, and large flex RF coils adjacent to the field of view. Prescan normalization was carried out prior to each acquisition to reduce RF shading. The algorithm is proprietary, but achieves similar ends as the N3 correction [23] (a
well known post processing method to remove low frequency intensity variation).

4.2.2 MRI-Based $\mu$-Maps from Segmentation

$\text{MRI}_{\text{WB}}$ was segmented into air, lung, soft tissue, and bone using a semi-automated algorithm developed in-house and implemented on Matlab v7.9.0.529 (The MathWorks, MA, USA). The details of the air, lung, and soft tissue identification have been described previously [16], involving empirical thresholding, mathematical morphology, and level set techniques [25]. However, the addition of a bone class is new, and relied on a support vector machine (SVM) implemented in the open source software SVM$^{\text{light}}$ [10].

SVMs are supervised learning methods often used for classification or regression problems, image segmentation being of the former type. The SVM is trained with a set of data, $\mathcal{D} = \{(x_i, u_i) \mid x_i \in \mathbb{R}^q, u_i \in \{-1, +1\}\}_{i=1}^n$, where each $x_i$ is a vector of $q$ inputs called features, and $u_i$ is a binary variable indicating class membership. If the $x_i$ are plotted in $q$-dimensional space, two point clouds are defined by the two values of $y_i$. Provided the point clouds are separated, a “decision boundary” can be constructed between them and the membership of unseen examples is dictated according to which side of the boundary they reside. Ideally, the point clouds are linearly separable; that is, the decision boundary is a hyperplane. In the native $q$-dimensional space, this is often not so. Thus, the SVM maps $\mathcal{D}$ to a higher (or even infinite) dimensional space such that the modified $\mathcal{D}$ is linearly separable. Subsequently, the SVM computes the hyperplane that “maximally” separates the point clouds in the high dimensional space.

Conveniently, the high dimensional mapping is not computed explicitly. The SVM only relies on inner products of vectors in the high dimensional space, which are computed by the “kernel function”, $k(x_i, x_j) = \phi(x_i) \cdot \phi(x_j)$, where $\phi$ is the mapping.
Therefore, \( \phi \) is implicitly defined by the choice of kernel.

We used a leave-one-out cross-validation approach to train our SVM. That is, for each patient, \( D \) was drawn from all the other patients. For training purposes, rather than manually segment the bone in MRIWB, we registered each patient’s CT to their MRIWB and deemed voxels with a CT number greater than 300 HU cortical bone. Voxels used for training were randomly selected and approximately equally distributed between “bone” and “not bone” classes.

Each \( x_i \) comprised 79 features. Three features were cylindrical coordinates \((r, \theta, z)\) normalized in a patient specific fashion. In particular, the \( z \) axis ran in the superior/inferior direction and passed through the patient’s centre of mass as computed on a binary, thresholded image. The \( r \) coordinate was divided by the lungs’ maximal left/right width, \( \theta \) was arbitrarily defined to be zero when pointing anteriorly, and \( z \) was set to 0 at the most superior slice and 1 at the most inferior slice, varying linearly in between. One feature was a measure of body size, computed as the fraction of the field of view occupied by the patient. Finally, the remaining 75 features were the intensities of a \( 5 \times 5 \times 3 \) voxel patch surrounding the voxel of interest.

Our kernel was the Gaussian radial basis function defined as:

\[
k(x_i, x_j) = \exp \left[ \frac{||x_i - x_j||^2}{2\beta^2} \right]
\]

with free parameter \( \beta \) chosen by cross-validation. The induced mapping is to an infinite dimensional Hilbert space.

Once the four tissue classes were identified, they were each assigned CT numbers: air was set to \(-1000 \) HU, lung to \(-750 \) HU, and soft tissue to 0 HU. To further examine the impact of including bone in the segmentation, bone was set to either 0, 300, 600, or 900 HU; one \( \mu \)-map was made for each of these values. The segmentation
of air, lung, and soft tissue took a few minutes, but the bone segmentation lasted several hours.

4.2.3 MRI-Based $\mu$-Maps from Registration

For a given target MRI$_{WB}$, the template to be registered was the CT scan of another patient included in this study. Specifically, the gender-matched individual with the closest body volume as a fraction of the field of view was designated the template. This was a crude way to ensure the template and target had similar physiques.

Rather than register the template CT directly to the target MRI$_{WB}$, a potentially challenging inter-patient, inter-modality registration, we started by registering the template patient’s MRI$_{WB}$ to their CT (inter-modality but intra-patient), yielding an MRI/CT pair. We then registered the MRI component of this pair to the target MRI$_{WB}$ (inter-patient but intra-modality), carrying the CT along by applying the same transform.

These registrations, as well as all the others reported in this manuscript, were accomplished using the BRAINSFit module of 3D Slicer [18]. Briefly, the registration utilized a hierarchical transform model, evolving sequentially from rigid to affine to non-rigid [19], with a mutual information similarity metric. The registrations generally took a few minutes.

4.2.4 MRI-Based $\mu$-Maps from Mapping

To define a mapping between MRI and CT signal, we used a simple modification of the SVM approach described above. The sampling procedure, features, and kernel were identical, however the SVM was instructed that it was to solve a regression problem rather than a classification one. Thus, the labels $u_i$ on the training examples were
actual CT numbers rather than merely +1 or −1. In this case, the SVM was charged with the task of finding the hyperplane that optimally fit the data, as opposed to the hyperplane that best divided the data into two clusters. Predictions were made by computing the value of the hyperplane for the given $x_i$.

There is one caveat, however. The lungs exhibit virtually no signal in most MRI images, including MRI_{WB}, making it difficult to predict CT number. This is why MRI_{lung} was collected. In dogs, we have demonstrated that not only does MRI_{lung} show signal from lung parenchyma, but this signal can be linearly mapped voxel-by-voxel to CT numbers [15]. Accordingly, we determined a linear mapping between MRI_{lung} and Hounsfield units in humans; this relationship was used to map the lungs to CT numbers. The rest of the body was mapped using the regression SVM, which, like the bone segmentation, took several hours.

4.2.5 Processing the MRI-Based $\mu$-Maps

Each MRI-based $\mu$-map precursor had to be aligned with the PET projection data. This was done by registering them to the patient’s CT scan. The MRI-based $\mu$-map precursor derived from segmentation was registered first, and the resulting transform was applied to the other $\mu$-map precursors, thereby eliminating registration differences between them.

Once aligned, the background of the CT (patient bed, positioning aids, etc.) was added to the MRI-based $\mu$-map precursors. They were then imported into the PET/CT system, and were converted to 511 keV $\mu$-maps using the native software.

To refer to PET images reconstructed using a particular $\mu$-map, a subscript notation is used. PET\textsubscript{CT} denotes the image created with the CT-based $\mu$-map (the silver standard). As for the images created by the MRI-based $\mu$-maps, PET\textsubscript{seg0}, PET\textsubscript{seg300}, PET\textsubscript{seg600}, and PET\textsubscript{seg900} denote those derived from segmentation (the number indi-
cating the CT number assigned to bone), PET\textsubscript{reg} that derived from registration, and PET\textsubscript{map} that derived from mapping.

### 4.2.6 Data Analysis

The data were analyzed two ways: globally in specific tissues and locally in volumes of interest (VOIs).

The global analysis was conducted in lung, fat, “water” (e.g. muscles and organs), and bone. Masks of these tissues were generated by thresholding the CT scan ($-990$ HU $<$ lung $\leq -600$ HU, $-150$ HU $<$ fat $\leq -25$ HU $<$ water $\leq 100$ HU $<$ bone). Within each tissue, a voxel-by-voxel scatter plot of estimated activity versus true activity was created, normalized to the maximum PET\textsubscript{CT} activity. Three metrics were computed: 1) $D_{y=x}^2$ equal to the integral from 0 to 1 of the squared difference between the line of best fit (LOBF) computed via linear regression and the line of identity, 2) $R^2$ which is the squared Pearson product-moment correlation coefficient, and 3) $E = 100(\bar{a}_e - \bar{a}_t)/\bar{a}_t$ where $\bar{a}_e$ is the mean estimated activity and $\bar{a}_t$ is the mean true activity. $D_{y=x}^2$ measures the proximity of the LOBF to the line of identity, i.e. accuracy. $R^2$ measures the spread of points about the LOBF, i.e. precision. $E$ is the relative error expressed as a percent.

The statistics on the global analysis commenced with a 4 (tissue) $\times$ 6 ($\mu$-map) repeated measures MANOVA (dependent variables = $D_{y=x}^2$, $R^2$, $E$). Significant effects were followed up with 4 $\times$ 6 repeated measures ANOVAs applied to each dependent variable in isolation. When the interaction term was significant, one-way (factor = $\mu$-map) repeated measures ANOVAs were carried out. Post-hoc testing was via paired t-tests corrected for multiple comparisons via the Holm procedure [9]. The significance level was set to 0.05 for all statistical testing. Further, the Greenhouse-Geisser correction for violated sphericity was applied for all ANOVAs used in this
For the local analysis, spherical VOIs with a radius of 1 cm were placed in fourteen standard positions and about pathological lesions in the thorax (n = 13), abdomen (n = 4), and pelvis (n = 5). Wherever there were two symmetric structures for the VOI to be placed in (e.g. caudate nucleus), the one on the patient’s right was selected. The relative error, $E$, was computed in each VOI. The statistical procedure for this component of the analysis was the same as that described above, except since there was only one dependent variable, the initial MANOVA was not necessary. Rather, the initial test was a 14 (VOI excluding lesions) $\times$ 6 (µ-map) repeated measures ANOVA. The lesions were analyzed separately, commencing with one-way ANOVAs.

4.3 Results

4.3.1 Overview

An example of the three classes of MRI-based µ-map, i.e. derived from mapping, registration, or segmentation, is shown with the associated CT-based µ-map in Figure 4.1. The results of the global and local analyses are presented in Figure 4.2 and Figure 4.3, respectively. The data used to derive the linear relationship between MRI and CT lung signal that was used in the mapping technique are presented in Figure 4.4. The equation we calculated was $CT = 3.28 \times MRI - 864$.

4.3.2 Global

The statistical results of the global analysis are as follows. The 4 (tissue) $\times$ 6 (µ-map) repeated measures MANOVA revealed a significant multivariate within-subjects effect for tissues (Wilks’ $\lambda = 0.01, F(9,75.596) = 47.032, p < 0.0005$), for µ-maps (Wilks’
Figure 4.1: Coronal slice through μ-maps from subject one. Superimposed in colour are the relative errors in the corresponding PET reconstructions. Blue represents underestimated activity and red overestimated activity, from -50% to +50% error. (A) CT-based μ-map. (B) MRI-based μ-map obtained via mapping. A large portion of the skull is missing (white arrow), resulting in underestimated activity in the head. Also, parts of the vertebrae are filled with air (black arrow). (C) MRI-based μ-map obtained via registration. The skull is present (white arrow), and error in the head is low. However, the patient’s hilar mass is not reproduced (black arrow), invoking underestimated activity. Further, large errors are present throughout the lung parenchyma (green arrow) from mismatches in vasculature between the patient and template. (D) MRI-based μ-map obtained via segmentation. The skull is segmented (white arrow), but cranial activity is underestimated because the assigned bone μ-coefficient is too low. Mis-segmentations are also visible: bone is oversegmented in the hilar mass (black arrow), and undersegmented in the scapula (green arrow), with associated errors in activity. Additionally, the impact of classifying fat as water is an overestimate of activity (pink arrow).
Figure 4.2: Results of the global analysis, broken down by tissue type. All values are mean ± SD. (A) Accuracy, i.e. $D^2_{y=x}$. (B) Precision, i.e. $R^2$. (C) Relative error, i.e. $E$. The results of statistical testing are indicated by the sets of parallel horizontal lines commencing with a green dot. The comparisons were made between all six µ-maps for a given tissue and metric. Along a particular line, the green dot represents the µ-map being compared to the others, and red dots indicate significant differences. Each dot is vertically aligned with the µ-map it refers to.
Figure 4.3: Results of the local analysis. All values are mean ± SD. (A) Coronal and (B) sagittal slices though subject five’s PET/CT depicting VOI placement. Relative error in VOIs placed in (C) lung, (D) soft tissue, (E) bone, and (F) lesions. The results of statistical testing are indicated by the sets of parallel vertical lines commencing with a green dot. The comparisons were made between all six £-maps for a given VOI. Along a particular line, the green dot represents the £-map being compared to the others, and red dots indicate significant differences. Each dot is horizontally aligned with the £-map it refers to.
Figure 4.4: Joint histogram of CT versus MRI lung signal. The mapping derived from this data was CT = 3.28 × MRI − 864.
Table 4.1: Results of 4 (tissue) × 6 (\(\mu\)-map) repeated measures ANOVAs for the global analysis. The \(p\) values are reported before correction for multiple comparisons.

<table>
<thead>
<tr>
<th>Factor</th>
<th>Measure</th>
<th>Hypothesis df</th>
<th>Error df</th>
<th>(\epsilon)</th>
<th>(F)</th>
<th>(p)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tissue</td>
<td>(D_{y=x}^2)</td>
<td>2.063</td>
<td>22.695</td>
<td>0.688</td>
<td>16.665</td>
<td>&lt; 0.0005</td>
</tr>
<tr>
<td>Tissue</td>
<td>(R^2)</td>
<td>1.180</td>
<td>12.980</td>
<td>0.393</td>
<td>201.591</td>
<td>&lt; 0.0005</td>
</tr>
<tr>
<td>Tissue</td>
<td>(E)</td>
<td>1.068</td>
<td>11.753</td>
<td>0.356</td>
<td>15.777</td>
<td>0.001</td>
</tr>
<tr>
<td>(\mu)-map</td>
<td>(D_{y=x}^2)</td>
<td>1.996</td>
<td>21.960</td>
<td>0.399</td>
<td>4.198</td>
<td>0.029</td>
</tr>
<tr>
<td>(\mu)-map</td>
<td>(R^2)</td>
<td>1.045</td>
<td>11.469</td>
<td>0.209</td>
<td>5.352</td>
<td>0.039</td>
</tr>
<tr>
<td>(\mu)-map</td>
<td>(E)</td>
<td>1.237</td>
<td>13.608</td>
<td>0.247</td>
<td>31.270</td>
<td>&lt; 0.0005</td>
</tr>
<tr>
<td>Tissue*(\mu)-map</td>
<td>(D_{y=x}^2)</td>
<td>3.639</td>
<td>40.032</td>
<td>0.243</td>
<td>8.640</td>
<td>&lt; 0.0005</td>
</tr>
<tr>
<td>Tissue*(\mu)-map</td>
<td>(R^2)</td>
<td>1.112</td>
<td>12.227</td>
<td>0.074</td>
<td>6.307</td>
<td>0.025</td>
</tr>
<tr>
<td>Tissue*(\mu)-map</td>
<td>(E)</td>
<td>1.226</td>
<td>13.491</td>
<td>0.082</td>
<td>13.009</td>
<td>0.002</td>
</tr>
</tbody>
</table>

\(\lambda = 0.12, F(15,146.711) = 11.287, p < 0.0005\), and their interaction (Wilks’ \(\lambda = 0.181, F(45,485.012) = 8.387, p < 0.0005\)). Every follow up 4 × 6 repeated measures ANOVA was also significant for tissues, \(\mu\)-maps, and their interactions (Table 4.1). Given the significant interaction terms, one-way (factor = \(\mu\)-map) repeated measures ANOVAs were carried out for each metric and tissue (Table 4.2). Concerning both \(D_{y=x}^2\) and \(E\), the only tissue in which there were no significant differences between the \(\mu\)-maps was lung. For \(R^2\), however, it was only water that had no significant differences. The results of the post-hoc paired-sample t-tests are presented visually in Figure 4.2.

The statistical testing revealed that in lung, there was no difference between the \(\mu\)-maps in terms of accuracy or relative error, though PET\(_{\text{map}}\) was more precise than the rest.

Conversely, in fat, precision was essentially constant amongst the \(\mu\)-maps, but there were significant effects in accuracy and relative error. In particular, PET\(_{\text{reg}}\) outperformed the other \(\mu\)-maps, while assigning larger \(\mu\)-coefficients to bone deteriorated PET\(_{\text{seg}}\)’s quality.
Table 4.2: Results of the one-way (factor = µ-map) repeated measures ANOVAs for the global analysis. The $p$ values are reported before correction for multiple comparisons.

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Measure</th>
<th>Hypothesis df</th>
<th>Error df</th>
<th>$\epsilon$</th>
<th>$F$</th>
<th>$p$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung</td>
<td>$D^n_{y=x}$</td>
<td>2.020</td>
<td>22.222</td>
<td>0.404</td>
<td>1.950</td>
<td>0.166</td>
</tr>
<tr>
<td>Lung</td>
<td>$R^2$</td>
<td>1.041</td>
<td>11.449</td>
<td>0.208</td>
<td>5.137</td>
<td>0.043</td>
</tr>
<tr>
<td>Lung</td>
<td>$E$</td>
<td>1.079</td>
<td>11.866</td>
<td>0.216</td>
<td>1.597</td>
<td>0.233</td>
</tr>
<tr>
<td>Fat</td>
<td>$D^n_{y=x}$</td>
<td>1.273</td>
<td>14.001</td>
<td>0.255</td>
<td>33.504</td>
<td>$&lt; 0.0005$</td>
</tr>
<tr>
<td>Fat</td>
<td>$R^2$</td>
<td>1.464</td>
<td>16.101</td>
<td>0.293</td>
<td>4.737</td>
<td>0.033</td>
</tr>
<tr>
<td>Fat</td>
<td>$E$</td>
<td>1.259</td>
<td>13.847</td>
<td>0.252</td>
<td>53.105</td>
<td>$&lt; 0.0005$</td>
</tr>
<tr>
<td>Water</td>
<td>$D^n_{y=x}$</td>
<td>1.488</td>
<td>16.369</td>
<td>0.298</td>
<td>4.0009</td>
<td>0.049</td>
</tr>
<tr>
<td>Water</td>
<td>$R^2$</td>
<td>1.110</td>
<td>12.212</td>
<td>0.222</td>
<td>1.545</td>
<td>0.241</td>
</tr>
<tr>
<td>Water</td>
<td>$E$</td>
<td>1.283</td>
<td>14.109</td>
<td>0.257</td>
<td>42.862</td>
<td>$&lt; 0.0005$</td>
</tr>
<tr>
<td>Bone</td>
<td>$D^n_{y=x}$</td>
<td>1.153</td>
<td>12.686</td>
<td>0.231</td>
<td>4.854</td>
<td>0.043</td>
</tr>
<tr>
<td>Bone</td>
<td>$R^2$</td>
<td>1.205</td>
<td>13.254</td>
<td>0.241</td>
<td>60.360</td>
<td>$&lt; 0.0005$</td>
</tr>
<tr>
<td>Bone</td>
<td>$E$</td>
<td>1.905</td>
<td>20.958</td>
<td>0.381</td>
<td>219.133</td>
<td>$&lt; 0.0005$</td>
</tr>
</tbody>
</table>

In water, neither accuracy nor precision displayed any significant effects, but both PET$_{reg}$ and PET$_{seg0}$ achieved significantly less error than the others. As with fat, the higher the µ-coefficient assigned to bone, the worse PET$_{seg}$’s quality.

Finally, in bone, accuracy was significantly deteriorated in PET$_{seg0}$, while precision was sequentially deteriorated further and further in PET$_{seg300}$, PET$_{seg600}$, and PET$_{seg900}$. PET$_{reg}$ achieved the lowest relative error in bone, while the PET$_{seg}$ series went from negative to positive error as a function of the bone µ-coefficient assignment.

### 4.3.3 Local

For the local analysis, the initial 14 (VOI excluding lesions) $\times$ 6 (µ-map) repeated measures ANOVA revealed a significant effect of VOIs ($\epsilon = 0.278$, $F(3.620, 39.816) = 11.167$, $p < 0.0005$), of µ-maps ($\epsilon = 0.328$, $F(1.638, 18.019) = 125.084$, $p < 0.0005$), and their interaction ($\epsilon = 0.075$, $F(4.845, 53.296) = 16.167$, $p < 0.0005$). Of the
Table 4.3: Results of one-way (factor = $\mu$-map) repeated measures ANOVAs for local analysis. The $p$ values are reported before correction for multiple comparisons.

<table>
<thead>
<tr>
<th>VOI</th>
<th>Hypothesis df</th>
<th>Error df</th>
<th>$\epsilon$</th>
<th>$F$</th>
<th>$p$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Upper lung</td>
<td>1.371</td>
<td>15.080</td>
<td>0.274</td>
<td>2.830</td>
<td>0.104</td>
</tr>
<tr>
<td>Lower lung</td>
<td>1.253</td>
<td>13.786</td>
<td>0.251</td>
<td>1.548</td>
<td>0.241</td>
</tr>
<tr>
<td>Caudate nucleus</td>
<td>1.987</td>
<td>21.852</td>
<td>0.397</td>
<td>104.049</td>
<td>&lt; 0.0005</td>
</tr>
<tr>
<td>Cerebellum</td>
<td>1.455</td>
<td>16.008</td>
<td>0.291</td>
<td>23.051</td>
<td>&lt; 0.0005</td>
</tr>
<tr>
<td>Aortic arch</td>
<td>1.283</td>
<td>14.116</td>
<td>0.257</td>
<td>10.592</td>
<td>0.004</td>
</tr>
<tr>
<td>Cardiac septum</td>
<td>1.059</td>
<td>11.651</td>
<td>0.212</td>
<td>1.253</td>
<td>0.289</td>
</tr>
<tr>
<td>Liver</td>
<td>1.488</td>
<td>16.369</td>
<td>0.298</td>
<td>8.237</td>
<td>0.006</td>
</tr>
<tr>
<td>Spleen</td>
<td>1.321</td>
<td>14.535</td>
<td>0.264</td>
<td>5.041</td>
<td>0.033</td>
</tr>
<tr>
<td>Iliacus</td>
<td>1.496</td>
<td>16.460</td>
<td>0.299</td>
<td>3.840</td>
<td>0.053</td>
</tr>
<tr>
<td>Sigmoid colon</td>
<td>1.469</td>
<td>16.154</td>
<td>0.294</td>
<td>20.654</td>
<td>&lt; 0.0005</td>
</tr>
<tr>
<td>Occipital protuberance</td>
<td>1.876</td>
<td>20.638</td>
<td>0.375</td>
<td>14.875</td>
<td>&lt; 0.0005</td>
</tr>
<tr>
<td>Vertebral body of T8</td>
<td>1.404</td>
<td>15.443</td>
<td>0.281</td>
<td>46.602</td>
<td>&lt; 0.0005</td>
</tr>
<tr>
<td>Spinal process of L2</td>
<td>1.480</td>
<td>16.277</td>
<td>0.296</td>
<td>86.380</td>
<td>&lt; 0.0005</td>
</tr>
<tr>
<td>Iliac crest</td>
<td>1.841</td>
<td>20.256</td>
<td>0.368</td>
<td>26.532</td>
<td>&lt; 0.0005</td>
</tr>
<tr>
<td>Thoracic lesions</td>
<td>1.801</td>
<td>21.610</td>
<td>0.360</td>
<td>91.509</td>
<td>&lt; 0.0005</td>
</tr>
<tr>
<td>Abdominal lesions</td>
<td>1.261</td>
<td>3.784</td>
<td>0.252</td>
<td>9</td>
<td>0.041</td>
</tr>
<tr>
<td>Pelvic lesions</td>
<td>1.584</td>
<td>6.337</td>
<td>0.317</td>
<td>24.324</td>
<td>0.001</td>
</tr>
</tbody>
</table>

one-way ANOVAs in each VOI (including lesions) with $\mu$-map as the factor (Table 4.3), those in the lower and upper lung, cardiac septum, and iliacus did not show a significant effect. The results of the post-hoc testing are shown in Figure 4.3.

The VOIs in the lung tended to have means close to zero, but exhibited large standard deviations. Notably, PET$_{map}$ had about half the standard deviation of the others in both the upper and lower lung.

In soft tissue, again most of the errors were relatively small, with the exception of sigmoid colon. Though often small, many VOIs showed a significant effect of what $\mu$-coefficient was assigned to bone in PET$_{seg}$. PET$_{reg}$ had a mean error most consistently close to zero, but oftentimes the highest standard deviation.

The VOIs in bone exhibited the largest errors, generally with a pronounced impact
of the $\mu$-map. Again, $\text{PET}_{\text{reg}}$ was typically closest to zero, followed by $\text{PET}_{\text{map}}$. Which $\text{PET}_{\text{seg}}$ scan performed the best was a function of the VOI (i.e. $\text{PET}_{\text{seg}900}$ in the external occipital protuberance, $\text{PET}_{\text{seg}300}$ in T8 and L2, and $\text{PET}_{\text{seg}0}$ at the iliac crest).

In lesions, activity tended to be overestimated in all reconstructions, save $\text{PET}_{\text{reg}}$.

4.4 Discussion

4.4.1 Overview

In this work, we illuminate some strengths and weaknesses of three approaches to MRI-based AC: segmentation, registration, and mapping. Our analysis comprised global and local components to assess performance in healthy tissue and pathological lesions. We discuss our results in tissues and lesions, comment on hybridizing the approaches, and conclude with limitations stemming from image registration.

4.4.2 Lungs

The lungs are a challenge for MRI-based AC as their $\mu$-coefficients vary widely both between [5] and within [11] patients, while conventional pulse sequences yield little signal. Previously [15] we established a linear mapping between MRI and CT in dogs and now extend it to humans (Figure 4.4). Thus, our mapping-based $\mu$-maps captured relative $\mu$-coefficient variation in the lungs, so $\text{PET}_{\text{map}}$ exhibited the highest precision (Figure 4.2). However, no benefit in accuracy was observed, likely because the patients were not at identical states of respiration during the CT and MRI. Accordingly, overall lung density varied between the CT and MRI, leading to erroneous mean $\mu$-coefficient assignments. Unfortunately, strict respiratory control was not possible as several
patients were unable to hold their breath for the duration of the CT scan, (thirty seconds). Nonetheless, in the lung VOIs (Figure 4.3C), the relative error in PET$_{map}$ was more tightly clustered about zero than the other approaches, as indicated by the reduced standard deviation.

4.4.3 Fat

In fat the differences between the $\mu$-maps were in accuracy and relative error (Figure 4.2). Unsurprisingly, accuracy was poor for the PET$_{seg}$ series as fat was not included as a tissue class, so activity was universally overestimated (Figures 4.1D and 4.2C). Interestingly, accuracy deteriorated in proportion to the $\mu$-coefficient assigned to bone, mainly due to fat being misclassified as bone; the degree of overestimation is determined by bone’s $\mu$-coefficient. This was a recurring theme in the data and can be seen in the (global) relative error in fat and water, as well as in the sigmoid colon VOI, an area susceptible to mis-segmentation. It also featured in the lesion VOIs, though only significantly in the thorax.

PET$_{reg}$, in contrast to the PET$_{seg}$ series, included fat in the template $\mu$-maps and had a much improved accuracy and relative error. The mapping approach incorporated fat to some degree (Figure 4.1B), but the SVM lacked sufficient information to do it properly. A useful addition would be a pulse sequence capable of fat/water separation, as has been proposed by Martinez-Möller et al [17] and validated by Eiber et al [4].

4.4.4 Water

Of all the tissues, water had the best precision and accuracy, with no significant differences in either (Figure 4.2). Though there were some significant differences in
relative error, the magnitude of the errors was small, under 10% for all μ-maps. This agrees with the VOI data, which demonstrated small errors in all cases except the sigmoid colon, wherein bowel gas created problems. Oftentimes, bowel gas present in the sigmoid colon during the CT had migrated elsewhere during the MRI, and as a result was erroneously deemed soft tissue. This is unavoidable in experiments comparing MRI-based to CT-based AC algorithms, but not a problem in true simultaneous PET/MRI systems. That said, MRI-based AC algorithms must account for bowel gas. Not doing so leads to apparently increased activity in the colon wall, an artifact that may be confused with colon cancer in suspect patients.

4.4.5 Bone

Predictably, in bone, accuracy is worst when bone is ignored, as it was in PET_{seg0} (Figure 4.2). Additionally, if the mean μ-coefficient of bone is overestimated, as in PET_{seg900}, accuracy also suffers. Precision also deteriorates because properly segmented bone voxels receive a larger magnitude of AC than mis-segmented ones. The estimated activity in these groups of voxels diverges as a function of bone’s μ-coefficient, decreasing precision. Regarding relative error, PET_{reg} was closest to 0%, perhaps because it not only included the entire skeleton in the μ-map template, but it effectively accounted for the intrinsic variability of bone density within a given individual.

Segmentation is incapable of doing the latter. This is best illustrated by the VOI analysis: in bones with low density, such as the vertebral body of T8, μ-maps with lower bone μ-coefficients (e.g. PET_{seg300}) had less error than those with high bone μ-coefficients (e.g. PET_{seg900}). Conversely, in dense bone, like the external occipital protuberance, the pattern is reversed. Simply put, tuning the μ-coefficient of bone to work well in one area will inevitably lead to failures in other areas with
different bone density. Segmentation is therefore ill suited to MRI-based AC in bone. Incidentally, like registration, mapping can theoretically model bone well, but in our implementation, it did not perform as well as registration (Figure 4.1B versus Figure 4.1C).

4.4.6 Lesions

The local analysis included VOIs over lesions of a pathological nature. Unlike the VOIs in normal soft tissue (Figure 4.3D), the activity in lesions was generally over-estimated (Figure 4.3F). In retrospect, most of the normal soft tissue VOIs, save the sigmoid colon, were in structures predominantly composed of water. In contrast, many of the lesions were surrounded by fat, and as described above, \( \text{PET}_{\text{reg}} \) proved the best at incorporating fat into its \( \mu \)-map. It is therefore unsurprising that \( \text{PET}_{\text{reg}} \) exhibited the lowest errors in lesions, especially in the abdomen and pelvis where fat is abundant.

4.4.7 Hybrid Approaches

If one was forced to choose a “victor” of the three MRI-based AC approaches, registration was arguably the most effective overall, though its capacity to handle fat gave it an edge. However, a more instructive conclusion is that each approach has advantages and disadvantages. Segmentation was generally excellent in water, and likely would have been so in all soft tissue had fat been included as a tissue class. Registration had low mean errors in general, but it has the capacity to introduce large errors as evidenced by its large standard deviations. This is especially true when patient and template anatomy differ, as is the case in the lung. Mapping was best in the lungs and reasonable in bone, but requires some improvements to make it
more robust. Likely, the key to effective MRI-based AC is the hybridization of these approaches.

There are many ways segmentation, registration, and mapping can be combined; one example is Hofmann et al’s “atlas registration and pattern recognition” approach [6, 8] which makes use of all three with excellent results. Briefly, the approach is based on mapping via supervised learning, but registration is used to put the MRI/CT pairs used for training into a common coordinate system with the patient, while some features are drawn from a segmented version of the patient MRI. Segmentation is also used in a post-processing step to override the mapping in certain cases for fat, water, and bowel gas.

We propose some suggestions for future research in hybridized approaches. First, air, water, and fat are all amenable to segmentation as their $\mu$-coefficient is essentially constant and they are easily identifiable using the appropriate pulse sequences. Lungs and bones, however, have broad $\mu$-coefficient distributions, and are ill suited to segmentation. Lungs are easy to locate, and likely a preliminary segmentation followed by mapping is the most straightforward path [15]. The complex anatomy of the skeleton, however, is not easy to determine on MRI, and registration likely has a role to play in locating it. Unfortunately, a template $\mu$-map can only capture general trends of $\mu$-coefficient variation in space; ultimately, some patient-specific measures will be required in bone to generate realistic $\mu$-maps. Perhaps ultrashort echo time sequences have a role to play in determining the $\mu$-coefficient distribution on a patient-by-patient basis [2].

4.4.8 Errors from Image Registration

A limitation of this work not mentioned heretofore is that the registration of MRI-based $\mu$-maps to CT-based $\mu$-maps is imperfect. Therefore, the observed error is
a function not only of actual differences between the \( \mu \)-maps, but of any misalignments as well. As these were non-rigid registrations, quantifying the error is difficult. However, the global analysis spanned entire tissues, likely suppressing the impact of localized registration error. As for the local analysis, we looked for registration error about each VOI, but found none so large that we thought our results would be compromised.

4.5 Conclusion

The performance of each MRI-based AC approach was tissue and location dependent. Segmentation is appropriate for tissues with a constant \( \mu \)-coefficient, but mapping and/or registration are more suitable otherwise. The most effective MRI-based AC algorithms will hybridize these approaches in such a way that each method’s strengths are exploited.
References


Chapter 5

Expanding Horizons

5.1 MRI-Based AC in SPECT

5.1.1 Where We Stand

In Chapter 2, I explored the relationship between MRI-based attenuation correction of PET versus SPECT. I found that when a three tissue segmentation algorithm was used to convert the MRI images to $\mu$-maps, MRI-based AC produced superior quantitative results in SPECT compared to PET. This was true both globally across specific tissues including lung, soft tissue, and bone, as well as locally in VOIs placed in standard anatomic positions. The result held for both animal and phantom studies. Further, SPECT proved more resistant to small changes to the MRI-based $\mu$-maps than did PET. I hypothesized that the findings were due to PET’s tendency to have larger attenuation correction factors than are generally found in SPECT.

5.1.2 Where To Go

Though my study suggests that SPECT may be more quantitatively accurate when using MRI-based AC MRI-based AC than PET, much work remains to be done. Of particular importance, there are potentially circumstances under which my conclu-
sions will prove false. For instance, I only tested one MRI-based AC algorithm, which
in turn approximates the true $\mu$-map in a particular way. As we have seen, there are
innumerable other algorithms to choose from. Some, like the one I used, employ seg-
mentation [9, 31, 39, 49, 52, 57], but not all use the same tissue classes [9, 31, 39, 57].
Others, rely primarily on registration [38, 48] or mapping [3, 27, 28], which estimate
the true $\mu$-map by different means than segmentation. Perhaps the discrepancy be-
tween MRI-based AC’s efficacy in SPECT and PET is a function of the algorithm
itself. If that’s the case, there may be ramifications for which class or implementa-
tion of an algorithm is the best choice for SPECT/MRI systems [19, 22]. Additional
studies are needed to address this issue. It would also be of benefit to increase the
sample size. This pilot study provides the data necessary to make informed power
calculations.

Furthermore, though PET is always conducted at 511 keV, SPECT is capable of
imaging tracers with a range of energies [43]. My SPECT imaging used $^{99m}$Tc as the
radioisotope, which releases photons at 140 keV, but there are other choices, some
with higher energies and some with lower energies. As attenuation correction factors
are energy dependent, it is likely that MRI-based AC’s quality in SPECT is as well.
Studies with tracers aside from $^{99m}$Tc would help characterize this relationship.

Another major factor that was not examined in my study were the reconstruction
algorithms. SPECT and PET data may be reconstructed via multiple approaches,
and most approaches have free parameters [45]. It is entirely possible that my findings
would change were a different reconstruction algorithm chosen, or even if the param-
eters I chose (i.e. number of iterations and subsets) were altered. This brings up the
interesting question of which class of reconstruction algorithm is most likely to gener-
ate quantitatively accurate SPECT or PET images when applying MRI-based AC, a
critical practical consideration. In other words, some reconstruction algorithms may
be more robust to approximate $\mu$-maps. The same may be true of how AC is implemented in SPECT, which unlike PET, is nontrivial [1]. To the best of my knowledge, these issues have not as of yet received any attention.

As a final note, it may be of value to frame the problem of using approximate $\mu$-maps in SPECT versus PET in a formal mathematical framework. Specifically, it would be interesting to understand how different types of errors in the $\mu$-map are reflected in the emission images, both in terms of appearance and magnitude. Such studies might help us predict the maximum expected errors given a particular MRI-based AC algorithm and emission image reconstruction algorithm. Though there is extensive literature concerning the mathematics of emission tomography and its reconstruction [41], comparison between the two major nuclear medicine imaging modalities is generally not emphasized.

5.2 MRI-Based AC in the Lungs

5.2.1 Where We Stand

In Chapter 3, I devised and tested a method of determining the lungs’ $\mu$-coefficients with MRI. Though the pulse sequence I selected was not able to provide reliable $T_2^*$ (and hence extrapolated proton density) images, I nonetheless demonstrated an approximately linear correlation MRI and CT signal in the lungs. Though spatial averaging reduced the variance of said correlation, it came at the expense of reduced spatial information. When using the correlations to map MRI into pseudo-CTs which were subsequently used to perform AC on PET images, it was found that maintaining spatial information was more valuable than reducing noise by voxel averaging. In fact, the voxel-by-voxel mapping (as opposed to slice-by-slice or whole-lung mapping) yielded the best quantitative results in the lungs with respect to accuracy, precision,
and root mean squared error. Moreover, quantitative benefits extended to structures adjacent to the lungs, including the heart. However, these benefits quickly diminished as the distance from the lungs increased.

Also, though Chapter 4 did not focus on lung imaging, I nonetheless adapted the method described in Chapter 3 to humans. Some benefits in the quantification of PET images was observed, but the approach’s full potential was not realized owing to a lack of respiratory matching between the patients’ CT and MRI scans.

5.2.2 Where To Go

The most challenging aspect of MRI-based AC in the lungs is finding a pulse sequence that yields signal from lung tissue that is consistently relatable to $\mu$-coefficients. It is difficult to do so with even a moderate signal-to-noise ratio (SNR) given lung’s low proton density and short $T_2^*$, especially at high main magnetic field strengths [8, 24, 25]. I elected to use a single-shot gradient echo sequence which have been used extensively for lung imaging [5, 17, 24], but turbo spin echo sequences are another viable option [25, 34, 37], and perhaps even ultrashort TE sequences [53, 55]. An alternate (or better optimized) sequence may provide more useful images than the one I chose. In particular, a sequence capable of reliably estimating $T_2$ or $T_2^*$ is able to generate pure proton density images, free from the effects of magnetic relaxation times that add undesirable variability to the MRI signal [24].

Additional complications arise when adapting pulse sequences from (smaller) animals to humans. For example, I found that when the sequence I used was used on humans, the SNR decreased, and Gibbs ringing appeared at the lungs’ edges. Thus, for any sequences that have not been validated in humans, some work will be required to make the leap. This will prove especially challenging for ultrashort TE sequences [53, 55] which struggle with large fields of view. Once the leap is made, however, the
human study must be done with appropriate respiratory matching between MRI and CT, lest the correlation between the signals be masked.

An important extension of the work presented in Chapter 3 is to validate that the relationship between MRI and CT signal in the lungs is maintained in disease states. It is well documented that lung density is a function of pathology [23, 30, 33], and therefore it is essential that the correct $\mu$-coefficients can be estimated if lung disease is present (which it is in many, many patients). Perhaps a formal model of how MRI signal and CT signal in the lungs are related would shed some light on this issue.

Finally, a critical consideration when imaging the lungs with PET is that they are not stationary. The PET scan usually takes several minutes, and the patient breathes throughout. Therefore, the application of a static $\mu$-map is fundamentally flawed, and leads to localization and quantification errors [16, 20]. The so-called emission/transmission mismatch is best addressed by using a dynamic $\mu$-map. MRI is well suited to capture the motion of the lungs [14, 21], but not for capturing the associated variations in lung density, which is exactly what my method is designed to do. A fascinating contribution to the field of MRI-based AC would be to combine the method described in Chapter 3 with lung motion estimates to eliminate the emission/transmission mismatch.

### 5.3 MRI-Based AC Algorithms

#### 5.3.1 Where We Stand

In Chapter 4, I examined the performance of three classes of MRI-based AC algorithm, namely those relying on segmentation, registration, or mapping. I found that the best approach depended on the tissue under consideration. Specifically, mapping yielded the best results in lung tissue, registration was best in fat (though segmentation
likely would have performed as well or better if a fat category had been included), segmentation was best in water, and registration was best in bones.

Also, the MRI-based AC algorithm using segmentation was the first of its kind to include a bone class. Therefore, I tested the effects of assigning different $\mu$-coefficients to bone. Though globally, quantification in bone was optimized using the $\mu$-coefficient corresponding to a CT number of 600 HU, it was evident that no single $\mu$-coefficient could yield low errors in all bones. This is unsurprising since bones have variable $\mu$-coefficients within and between subjects [35]. Further, including bone as a tissue class actually deteriorated quantitative fidelity in other tissues including fat and water due to oversegmentation (i.e. bone segmented where it is not actually present). In brief, segmentation is not well suited for bones.

The conclusions of this study can be summarized as follows: segmentation is useful for tissues with relatively constant $\mu$-coefficients, mapping using patient specific measurements is ideal in the lungs, and registration will play a key role in the treatment of bone. Thus, hybrid approaches are critical to the success of MRI-based AC algorithms.

### 5.3.2 Where To Go

Arguably the most important recommendation stemming from the work in Chapter 4 is that hybrid MRI-based AC algorithms should be pursued. The question is how go about hybridizing segmentation, registration, and mapping. One group has proposed an algorithm that uses segmentation and registration implicitly as inputs to a mapping function, and then uses segmentation again in a post-processing step [27]. There are other possibilities though. For instance, each approach could be implemented as a separate step; e.g. one could start with segmentation of air, fat, and water, then apply mapping to the lungs, and then registration for the bones. Alternatively, mapping
could be carried out first, and segmentation and registration used to modify voxels that the mapping was “uncertain” of. There are many combinations and permutations that could be explored, begetting possibilities for new research.

Another area that will surely receive attention is in the improvement of individual algorithmic classes. There are multiple ways to accomplish segmentation [4, 42, 51], registration [13, 26, 44, 58], and mapping [2, 10, 15, 29, 40, 50, 54], and only a few of these have yet been explored in the context of MRI-based AC. It is essential to determine which algorithms are the most effective for the task at hand so that when they’re combined, the best possible results are realized.

Moreover, each individual algorithmic class has general unanswered questions associated with it. For example, if using segmentation, which tissue classes should be included [32]? For registration, what should the template $\mu$-map be [38]? For mapping, what features are the most informative? At present our answers to these questions are incomplete at best.

Also, no current MRI-based AC algorithm is able to make patient specific measures of bone density, which as I have repeatedly indicated, is highly variable [35]. At present, since bones have such a short T$_2$, the only feasible way of extracting bone density information via MRI is with ultrashort TE sequences [7, 46]. However, at present these sequences are not fit for whole-body imaging. Perhaps as a first step a small proportion of the patients’ bones could be imaged, and based on said images, average bone density could be extrapolated. In the future, with the aid of improvements in imaging speed via techniques such as parallel imaging [6] and compressed sensing [36], ultrashort TE sequences may be adapted to larger fields of view.

Finally, when attempting to validate any whole-body MRI-based AC algorithm, there is a confounder that always taints the results. In order to conduct such an experiment, three sets of images are required: PET, MRI, and some gold standard
µ-map, usually derived from CT. Since there is no imaging system that incorporates all of PET, MRI, and CT, generally the patient is imaged using PET/CT and then MRI or PET/MRI. This gives rise to the inevitable confounder: the MRI-based µ-map must be registered to the CT-based µ-map, an imperfect process that propagates errors into the PET reconstructions that are not due to imperfections of the MRI-based µ-map. Separating registration errors from true errors is extremely challenging. In fact, characterizing the errors present in registrations is a field of study unto itself [11, 12, 18, 47, 56]. Nonetheless, an exposition on how registration error impacts the validation of MRI-based AC algorithms would be a welcome contribution to the field.

5.4 Conclusion

PET/MRI and SPECT/MRI are exciting technologies, ushering in a new set of possibilities for data collection in medical imaging. However, without proper attenuation correction, the emission images lose much of their value. Though turning MRI images into µ-maps is no easy task, MRI-based AC has come a long way in just a few years. Nonetheless, much remains to be done, and I suspect that research concerning MRI-based AC will remain captivating for many years to come.

The overarching objective of this thesis was to improve MRI-based AC. I have done so by identifying that SPECT is more robust to MRI-based AC than PET, devising a procedure for estimating µ-coefficients in the lungs, and exploring the strengths and limitations of three methods for converting MRIs into µ-maps.
References


# Ethics Approvals

<table>
<thead>
<tr>
<th>PRINC_INVESTIGATOR</th>
<th>AUP_NUMBER</th>
<th>AUP TITLE</th>
<th>AUP APPROVAL DATE</th>
<th>AUP EXPIRY DATE</th>
<th>AUP RENEWAL DATE</th>
<th>PAU PRIMARY</th>
<th>2nd PAU</th>
<th>BREEDING</th>
<th>DRUGS/AGENTS</th>
<th>SURGERY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stadnik, Rob</td>
<td>2009-059</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>No</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Correcting for Attenuation Using Slow and Fast CT Design in SPECT/CT</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Purpose: General Electric SPECT/CT utilizes slow-rotation CT, Siemens SPECT/CT utilizes fast-rotation CT. Studies need to be performed to see if these designs are best for heart imaging. Hospitals in the area will review this study to assist them in future purchases.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Procedure Description: Animals are placed under general anesthesia and injected with Technetium-99m. SPECT/CT is performed on equipment manufactured by Siemens and General Electric. Attenuation correction is being studied as there is debate on the method of CT acquisition between the two systems.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stadnik, Rob</td>
<td>2010-385</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Imaging for Cardiovascular Therapeutics: PET/CT and MRI Fused Imaging Development</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Use of Human Subjects - Ethics Approval Notice

Principal Investigator: Dr. R.Z. Stodlka
Review Number: 17253
Review Date: July 06, 2010
Protocol Title: Determination of human whole-body PET/MRI attenuation correction factors: a pilot study
Department and Institution: Nuclear Medicine, St. Joseph’s Health Care London
Sponsor: ONT RESEARCH / CARDIOVASCULAR THERAPEUTICS
Ethics Approval Date: August 26, 2010
Documents Reviewed and Approved: UWO Protocol (including instruments listed in Section 6.1) and Letter of Information and Consent Form dated 2010 and Release of Information Form.

Documents Received for Information:

This is to notify you that the University of Western Ontario Research Ethics Board for Health Sciences Research Involving Human Subjects (HSREB) which is organized and operates according to the Tri-Council Policy Statement: Ethical Conduct of Research Involving Humans and the Health Canada/ICH Good Clinical Practice Practices Consolidated Guidelines; and the applicable laws and regulations of Ontario has reviewed and granted approval to the above referenced study on the approval date noted above. The membership of this REB also complies with the membership requirements for REBs as defined in Division 5 of the Food and Drug Regulations.

The ethics approval for this study shall remain valid until the expiry date noted above assuming timely and acceptable responses to the HSREB’s periodic requests for surveillance and monitoring information. If you require an updated approval notice prior to that time you must request it using the UWO Updated Approval Request Form.

During the course of the research, no deviations from, or changes to, the protocol or consent form may be initiated without prior written approval from the HSREB except when necessary to eliminate immediate hazards to the subject or when the change(s) involve only logistical or administrative aspects of the study (e.g., change of monitor, telephone number). Expedited review of minor changes in ongoing studies will be considered. Subjects must receive a copy of the signed information/consent documentation.

Investigators must promptly report to the HSREB:

a) changes increasing the risk to the participant(s) and/or affecting significantly the conduct of the study;

b) all adverse and unexpected experiences or events that are both serious and unexpected;

c) new information that may adversely affect the safety of the subjects or the conduct of the study.

If these changes/adverse events require a change to the information/consent documentation, and/or recruitment advertisement, the newly revised information/consent documentation, and/or advertisement, must be submitted to this office for approval.

Members of the HSREB who are named as investigators in research studies, or declare a conflict of interest, do not participate in discussion related to, nor vote on, such studies when they are presented to the HSREB.

Chair of HSREB: Dr. Joseph Gilbert
FDA Ref. #: IRB 00000940

Ethics Officer to Contact for Further Information

☐ Janice Sutherland (jsutherl@uwo.ca)
☐ Elizabeth Wambolt (ewambolt@uwo.ca)
☐ Grace Kelly (grace.kelly@uwo.ca)
☐ Denise Grafton (dgrafton@uwo.ca)

This is an official document. Please retain the original in your files.
LAWSON HEALTH RESEARCH INSTITUTE

FINAL APPROVAL NOTICE

RESEARCH OFFICE REVIEW NO.: R-10-422

PROJECT TITLE: Determination of human whole-body PET/MRI attenuation correction factors: a pilot study.

PRINCIPAL INVESTIGATOR: Dr. Rob Stodilka

DATE OF REVIEW BY CRIC: September 3, 2010

Health Sciences REB#: 17253

Please be advised that the above project was reviewed by the Clinical Research Impact Committee and the project:

Was Approved

PLEASE INFORM THE APPROPRIATE NURSING UNITS, LABORATORIES, ETC. BEFORE STARTING THIS PROTOCOL. THE RESEARCH OFFICE NUMBER MUST BE USED WHEN COMMUNICATING WITH THESE AREAS.

Dr. David Hill
V.P. Research
Lawson Health Research Institute

All future correspondence concerning this study should include the Research Office Review Number and should be directed to Sherry Paiva, CRIC Liaison, LHSC, Rm. C210, Nurses Residence, South Street Hospital.

cc: Administration
APPENDIX B

Copyright Releases

Assignment of copyright - Institute of Physics and Engineering in Medicine

1. IOP Publishing Limited ("IOP") agrees, on behalf of the Institute of Physics and Engineering in Medicine ("IPEM"), to publish:

Manuscript Title: A comparison of MR-based attenuation correction in PET versus SPECT ("the Article") written by

Names of all Authors: Harry Marshall, Robert Z Stodilka, Jean Theberge, Eric Sabondjian, Alexandre Legros, Lela Deans, Jane Sykes, Terry Thompson, Frank S Prato ("the Named Authors") in the following journal Physics in Medicine and Biology ("the Journal")

2. Transfer of Copyright Agreement

2.1 On acceptance for publication the undersigned author(s) ("Author") of the Article assigns exclusively to IPEM the entire worldwide copyright in the Article (whether vested, contingent or future) for the full term and for all media and formats in all material published as part of the Article, which expression includes but is not limited to the text, abstract, tables, figures and graphs, but excludes any supplementary material.

2.2 If any of the Named Authors are Government employees, on acceptance for publication the Author shall grant IPEM a royalty free exclusive licence for the full term of copyright for all media and formats to do in relation to the Article all acts restricted by copyright worldwide.

2.3 On acceptance for publication the Author shall grant IPEM a royalty free non-exclusive licence for the full term of copyright for all media and formats to do in relation to any supplementary material deemed to be part of the Article all acts restricted by copyright worldwide.

3. Author Rights

3.1 IPEM grants the Named Authors the rights specified in 3.2 and 3.3. All such rights must be exercised for non-commercial purposes, if possible should display citation information and IPEM's copyright notice, and for electronic use best efforts must be made to include a link to the on-line abstract in the Journal. Exercise of the rights in 3.3 additionally must not use the final published IOP format but the Named Author's own format (which may include amendments made following peer review).

3.2 The rights are:
3.2.1 To make copies of the Article (all or part) for teaching purposes;

3.2.2 To include the Article (all or part) in a research thesis or dissertation;

3.2.3 To make oral presentation of the Article (all or part) and to include a summary and/or highlights of it in papers distributed at such presentations or in conference proceedings; and

3.2.4 All proprietary rights other than copyright.

3.3 The additional rights are to:

3.3.1 Use the Article (all or part) without modification in personal compilations or publications of a Named Author's own works (provided not created by third party publisher);

3.3.2 Include the Article (all or part) on a Named Author's own personal web site;

3.3.3 Include the Article (all or part) on web sites of the institution (including its repository) where a Named Author worked when research for the Article was carried out; and

3.3.4 No sooner than 12 months after publication to include the Article (all or part) on third party web sites including e-print servers, but not on other publisher's web sites.
The Journal of Nuclear Medicine (JNM) is pleased to publish your article:

**Manuscript Title:** Variable lung density consideration in attenuation correction of whole-body PET/MRI

**MS Number:** JNUMED/2011/098350  **Date:** Feb 21, 2012

**Section A—to be completed by non-U.S. government employees.** (If the article has multiple authors, each author must individually transfer his or her copyright in the work by signing this section. If the article is not published in JNM, the following copyright transfer agreement will not take effect.)

Upon acceptance by *The Journal of Nuclear Medicine*, all copyright ownership for the article named above is transferred to the Society of Nuclear Medicine. We, the undersigned coauthors of this article, have contributed to (1) data design, analysis, or interpretation; (2) writing or critiquing drafts of the manuscript; and (3) approval of the final manuscript before publication. We share in the responsibility for the release of any part or all of the material contained within the manuscript. We also affirm that the manuscript has been seen and approved by all authors. The undersigned warrant that the manuscript (or its essential substance) is new and original, has not been published other than as an abstract in any language or format, and has not been submitted elsewhere for print or electronic publication consideration.

We warrant that the manuscript does not contain any material the publication of which would violate any copyright or other personal or proprietary right of any person or entity. We will obtain and include with the manuscript written permission from any respective copyright owners for the use of any textuel, illustrative, or tabular materials that have been previously published or are otherwise copyrighted and owned by third parties. We agree that it is our responsibility to pay any fees charged for permissions.

We also warrant that any human and/or animal studies undertaken as part of the research from which this manuscript was derived are in compliance with regulations of our institution(s) and with generally accepted guidelines governing such work.

We further warrant that we have herein disclosed any and all financial or other relationships that could be construed as a conflict of interest and that all sources of financial support for the study have been disclosed and are indicated in the acknowledgments.

1. Copyright transfer: The authors hereby transfer all copyrights in and to the manuscript titled above in all forms and media, now or hereafter known, to the Society of Nuclear Medicine effective if and when the article is accepted for publication in *JNM*.

2. Permission to reprint: The authors retain the following nonexclusive copyrights, to be exercised only after the article has been published in final format in the print version of *JNM*.
   (a) Reprint the article in print collections of the author's own writing.
   (b) Present the article orally in its entirety.
   (c) Use the article in theses and/or dissertations.
   (d) Reproduce the article for use in courses the author is teaching. (If the author is employed by an academic institution, that institution may also reproduce the article for course teaching.)
   (e) Distribute photocopies of the article to colleagues, but only for noncommercial purposes.
   (f) Reuse original figures and tables in future works created by the author.
   (g) Post a copy of the article on the author's personal website, departmental website, and/or the university's intranet, provided a hyperlink to the article on the *JNM* website is included.
   (h) In all the instances under clauses 2a through 2g above, the author will give proper credit to the original publication in *JNM* as follows:
      This research was originally published in *JNM*. Author(s). Title. *JNM*. Year;vol:pp-pp. © by the Society of Nuclear Medicine, Inc.

3. Publish Ahead of Print policy: The authors understand that if and when the manuscript is accepted for publication in *JNM*, it will be prepublished online as a Publish Ahead of Print paper. The authors acknowledge that *JNM*’s Publish Ahead of Print papers undergo full peer review and editorial preparation, such as copyediting, typesetting, and proofreading.
APPENDIX C

Curriculum Vitae

Education

M.D./Ph.D. Candidate, 2007 – present
The University of Western Ontario, London, ON
Department of Medical Biophysics
Thesis: MRI-based attenuation correction in emission computed tomography
Supervisor: Dr. Robert Stodilka
Anticipated completion dates: PhD – 6/2012, MD – 5/2014

Bachelor of Medical Sciences, 2004 – 2007
The University of Western Ontario, London, ON
Honors Specialization in Medical Biophysics
Thesis: Estimation of the Young’s modulus of the intact rat eardrum
Supervisors: Drs. Abbas Samani and Hanif Ladak

First Year of Undergraduate Degree, 2003 – 2004
The University of Toronto, Toronto, ON

Honors

First prize for best Biomedical Imaging & Engineering poster at London Health Research Day – $500, 2012

Second prize for best poster in the Ontario Preclinical Imaging Consortium at the 9th imaging symposium of Imaging Network Ontario – $300, 2011

Nominated for Graduate Student Teaching Award (UWO), 2010
Natural Sciences and Engineering Research Council (NSERC) Alexander Graham Bell Canada Graduate Scholarship Doctoral Level (CGS D) – $35000 per annum renewable for three years, 2009

Ontario Graduate Scholarship (OGS) – Declined in favour of the NSERC CGS D, 2009

Nominated for Graduate Student Teaching Award (UWO), 2009

Nominated by The University of Western Ontario for an NSERC Vanier CGS D – four Ph.D. students were nominated for this award valued at $50000 per annum renewable for three years, 2008

Nominated for Graduate Student Teaching Award (UWO), 2008

NSERC CGS Masters level – Declined as I was accepted into medical school, 2007

OGS – Declined as I was accepted into medical school, 2007

The University of Western Ontario Gold Medal for Honors Specialization in Medical Biophysics – awarded to student with highest aggregate marks in the honors specialization medical biophysics program, 2007

Dean’s Honor List (UWO), 2007

Graduated from undergraduate program with distinction (UWO), 2007

Scored in the 99.6th percentile of the Medical College Admission Test, 2006

NSERC Undergraduate Student Research Award (USRA) – $4500, supervisor: Dr. Abbas Samani, 2006

Dr. G. E. Hall Scholarship in Medical Biophysics – awarded to the biophysics student with the highest average in third year (UWO), 2006

Richard Konrad Scholarship in Science – awarded to a third or fourth year undergraduate student in the faculty of science based on academic excellence (UWO), 2006

Dean’s Honor List (UWO), 2006

Scored 1510/1600 and 6/6 on the Graduate Record Exam, 2005

NSERC USRA – $4500, supervisor: Dr. Frank Prato, 2005
In-course scholarship (UWO), 2005

University of Toronto Scholar – one of one hundred first year scholarships awarded based on academic merit – $1500, 2004

Dr. James A. & Connie P. Dickson Scholarship in the Sciences & Mathematics – awarded based on academic excellence (U of T), 2004

University of Toronto Golden Key Chapter invitation, 2004

Dean’s Honor List (U of T), 2004

Howard Ferguson Provincial Scholarship – Highest academic award presented by University College at The University of Toronto, $2500 per annum renewable for four years, 2003

Governor General’s Academic Medal (Bronze), 2003

High school Valedictorian (student elect), 2003

Publications

Refereed Journals


Provisional Patents


Refereed Conference Proceedings


PET/MRI attenuation correction. Canadian Society for Clinical Investigation / Clinician Investigator Trainee Association of Canada Young Investigator’s Forum, Sept 12 – 14, 2011, Ottawa, ON, Canada. (Poster)


Reports


Invited Presentations

How should attenuation correction in PET/MRI be performed? Alan C. Burton Day, Dept. of Medical Biophysics, UWO. April 12, 2012, London, ON, Canada.


Contributions to Grant Applications


Prato et al. Physiological simulation of pericardial disease (PhySiOCard). Application to the 7th European Framework small or medium-scale focused research project (STREP). The Lawson Health Research Institute, June 2009.

Professional Experience

Graduate Research Assistant, 2007 – 2009
Lawson Health Research Institute, London, ON
Department of Medical Imaging
Supervisor: Dr. Robert Stodilka
Preliminary work on PhD thesis
Research Assistant, 2006 – 2008
The University of Western Ontario, London, ON
Department of Medical Biophysics
Supervisors: Dr. Abbas Samani and Dr. Hanif Ladak
Validation of micro-indentation technique for stiffness measurements
Determination of Young’s modulus of rat tympanic membrane

Research Assistant, Lawson Health Research Institute, 2005 – 2006
Department of Medical Imaging
Co-supervisors: Dr. Alex Thomas, Dr. Frank Prato
Exploration of therapeutic potential of weak magnetic fields

Teaching Experience

Teaching Assistant, 2007 – 2012
The University of Western Ontario, London, ON
Class: MBP 3330F, 3rd year undergraduate biomechanics
Tutorial leader and principal marker

Science Tutor, 2005 – 2007
Western Young Tutor’s Club
Taught grade 8 through 1st year undergraduate students

Professional Service

Referee for the Journal of Medical Imaging and Radiation Science, 2010 – present

Junior Editor, 2009 – present
Clinical and Investigative Medicine Trainee Section Editorial Committee
Clinical Investigator Trainee Association of Canada
Review submissions and relay comments to senior editors
Write interest pieces (e.g. scientific overviews, etc.)

Professional Associations

Canadian Medical Association, 2007 – present

Ontario Medical Association, 2007 – present

Clinical Investigator Trainee Association of Canada, 2007 – present
Canadian Federation of Medical Students, 2007 – present