AUTOMATED PET/CT REGISTRATION FOR ACCURATE RECONSTRUCTION OF PET IMAGES

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ABSTRACT

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The use of a CT attenuation correction (CTAC) map for the reconstruction of PET image can introduce attenuation artifacts due to the potential misregistration between the PET and CT data. This misregistration is mainly caused by patient motion and physiological movement of organs during the acquisition of the PET and CT scans. In cardiac exams, the motion of the patient may not be significant but the diaphragm movement during the respiratory cycle can displace the heart by up to 2 cm along the long axis of the body. This shift can project the PET heart onto the lungs in the CT image, thereby producing an underestimated value for the attenuation. In brain studies, patients undergoing a PET scan are often not able to follow instructions to keep their head in a still position, resulting in misregistered PET and CT image datasets. The head movement is guite significant in many cases despite the use of head restraints. This misaligns the PET and CT data, thus creating an erroneous CT attenuation correction map. In such cases, bone or air attenuation coefficients may be projected onto the brain which causes an overestimation or an underestimation of the resulting CTAC values. To avoid misregistration artifacts and potential diagnostic misinterpretation, automated software for PET/CT registration has been developed that works for both cardiac and brain datasets. This software segments the PET and CT data, extracts the brain or the heart surface information from both datasets, and compensates for the translational and rotational misalignment between the two scans. The PET data are reconstructed using the aligned CTAC, and the results are analyzed and compared with the original dataset. This procedure has been evaluated on 100 cardiac and brain PET/CT data sets, and the results show that the artifacts due to the misregistration between the two modalities are eliminated after the PET and CT images are aligned.

Dedicated to my parents

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LIST OF TABLES viii			
LIST OF FIGURES	X		
1 Introduction 1.1 1.1 Motivation 1.2 Background 1.2.1 Positron Emission Tomography 1.2.2 Computed Tomography 1.2.3 Hybrid Single Gantry PET/CT System 1.3 Research Problem 1.4 Approaches to Eliminate PET/CT Artifacts 1.5 Challenges	1 1 1 5 9 1 4 6		
2 Attenuation Correction in PET Brain Data182.1 Introduction182.2 Data Acquisition202.3 Brain Segmentation202.3.1 Segmentation of CT Brain Images272.3.2 Segmentation of PET Brain Images242.4 PET/CT Brain Registration262.4.1 Preprocessing262.4.2 Translational Registration262.4.3 Rotational Registration262.4.4 Image Registration Results262.5 PET Reconstruction32	B B 0 0 1 4 6 6 8 9 2		
3 Attenuation Correction of Cardiac Data423.1 Data Acquisition423.2 Cardiac Image Segmentation423.2.1 Fuzzy Clustering483.2.2 Masking483.2.3 Edge Detection503.3 PET/CT Image Registration583.3.1 Image Registration Results573.3.2 Analysis of PET/CT Image Registration593.4 PET Reconstruction633.5 Polar map Representation of PET Cardiac Data61	2 3388057937		
4 Optimal Respiratory and Cardiac Phases 7' 4.1 Introduction 7' 4.2 Evaluation of Multiple Respiratory Phases 7' 4.2.1 Data Acquisition 7'	1 1 2 2		

4.2.2 PET/CT Image Registration Results	. 73
4.2.3 PET Image Reconstruction Results	. 77
4.3 Validation of the Optimal Cardiac Phase	. 81
4.3.1 Data Acquisition	. 81
4.3.2 Maximizing the PET/CT Cardiac Overlap	. 82
4.3.3 Methodology	. 83
4.3.4 Results	. 86
4.3.5 Analysis of Ungated and End-Diastolic CTACs	. 90
4.3.6 PET Image Reconstruction	. 91
5 Manual vs. Automated Registration	. 93
5.1 Introduction	. 93
5.2 Data Acquisition	. 94
5.3 Manual Registration Process	. 94
5.3.1 Quantitative Analysis of the Shift Values	. 99
5.3.2 User-Dependent Shift Variations	101
5.3.3 Comparison of Unshifted and Shifted Image Reconstructions	102
5.4 Automated vs. Manual Registration	103
6 Discussion	110
6.1 Effects of Overcorrection	112
6.2 Heart and Lung Volume Correlation	116
6.3 Attenuation-Corrected and Non Attenuation-Corrected Data	118
6.4 Hyper-perfusion Artifact	119
7 Summary and Future Work	121
7.1 Summary	121
7.2 Contributions	123
7.3 Future Work	124
7.3.1 Dual Gating for PET Data Acquisition	124
7.3.2 Left Ventricle Deformation Correction	125
7.3.3 Estimation of Myocardial Blood Perfusion	126
7.4 Papers Written	129
BIBLIOGRAPHY	130

LIST OF TABLES

Table 2.1: CT and PET imaging parameters for the brain studies	21	
Table 2.2: Results of the PET and CT image registration		
Table 3.1: Image acquisition parameters for PET/CT imaging system of cardiac patients	44	
Table 3.2: Shifts in the x, y, and z directions required to compensate for the misregistration between the PET and CT images in fifty patients	61	
Table 4.1: Means and standard deviations of the shift values required in the sagittal plane for multiple CTACs acquired at different respiratory phases	74	
Table 4.2: Average shift values required for ungated CTAC and the ECG gated end-diastolic CTAC	91	
Table 5.1: Image acquisition parameters for the PET/CT system	94	
Table 5.2: Average shift values for the manual alignment	100	
Table 5.3: Average shift values required in each plane	100	
Table 5.4: Shift values obtained using our automated software applied to the PET/CT data collected during the rest exam	105	
Table 5.5: Shift values obtained using our automated software applied to the PET/CT data collected during the stress exam	105	
Table 5.6: Average shift values obtained from four users using manual alignment applied to the PET/CT data collected during the rest exam	106	
Table 5.7: Average shift values obtained from four users using manual alignmentapplied to the PET/CT data collected during the stress exam	106	
Table 5.8: Maximum shift values obtained from four users using manual alignment applied to the PET/CT data collected during the rest exam	107	
Table 5.9: Maximum shift values obtained from four users using manual alignment applied to the PET/CT data collected during the stress exam	107	
Table 5.10: Difference in the shift values between the automatically registered and the average manual shifts in the rest exams	108	

Table 5.11: Difference in the shift values between the automatically registered andthe average manual shifts in the stress exams	108
Table 5.12: Difference in the shift values between the automatically registered andthe maximum manual shifts in the rest exams	109
Table 5.13: Difference in the shift values between the automatically registered and the maximum manual shifts in the stress exams	109

LIST OF FIGURES

Figure 1.1: The process of positron emission tomography imaging. (a) The proton- rich radioactive nucleus, (b) decay of the unstable nucleus resulting in the emission of a positron, (c) annihilation of the positron and the electron, and (d) the annihilation resulting in two anti-parallel gamma rays	3
Figure 1.2: The process of detecting true coincidences with pairing signals at opposite detectors within a specified time window	3
Figure 1.3: Selected set of cardiac PET images in the axial plane	4
Figure 1.4: Multiple x-ray projections are collected at different angles to acquire a cross-sectional CT image of the object	6
Figure 1.5: (a) Shows the process of capturing projections of an object from various angles (b) shows the projection profile from position A, (c) shows the projection profile from position B, (d) shows the projection profile from position C, (e) shoes the projection profile from position D, and (f) shows the reconstruction of the object using these four projections	7
Figure 1.6: Helical CT scanning, where z represents the distance covered in millimeters, and t represents the time elapsed in seconds	8
Figure 1.7: Selected set of brain CT images in the axial plane	10
Figure 1.8: Representation of a PET/CT scanner	10
Figure 1.9: Mismatch between the PET and CT images in a cardiac study	13
Figure 1.10: PET reconstruction using (a) misaligned PET and CT images, and (b) reconstruction after the PET and CT datasets are aligned	14
Figure 2.1: The segmentation results for the CT images, where (a) shows a set of unprocessed CT slices in the axial plane, and (b) shows the same CT slices after segmentation	23
Figure 2.2: The segmentation results for the PET images, where (a) shows the unprocessed PET slices in the axial plane, and (b) shows the same PET slices after the images are segmented. The selected axial slices are evenly distributed within the 47 slice dataset. Even with significant differences in the shape of the brain structure among these slices, the segmentation process performs well in each slice	25

Figure 2.3: PET/CT image registration results, where the white lines represent the PET brain contours and the gray scale images show the CT brain. Fig. 3 (a-c) illustrates the original PET and CT data for slice number 33 in the axial plane, slice 64 in the sagittal plane, and slice 64 in the coronal plane, respectively. Fig. 3 (d-f) shows the results of translational registration in the axial, sagittal and coronal planes. Fig. 3 (g-i) demonstrates a significant improvement after translational and rotational registration

Figure 2.4: Reconstructed PET images using misaligned and aligned CTACs. Fig. 2.4 (a-c) shows the reconstructed PET slices in the axial, sagittal, and the coronal planes using the misaligned CTAC. Fig. 2.4 (d-f) shows the same reconstructed PET slices in the axial, sagittal, and coronal planes using the aligned CTAC

32

34

36

39

40

Figure 2.5: PET image reconstruction using misaligned and aligned CTACs for patient number 6. Fig. 2.5 (a) shows sagittal slice number 64 of the misaligned PET and CT images, Fig. 2.5(b) shows the same sagittal slice after the PET and CT images are registered, Fig. 2.5(c) shows the reconstructed PET image using the misaligned CT image, and Fig. 2.5(d) shows the sagittal PET slice reconstructed using the aligned CTAC.

Figure 2.6: Reconstructed PET images using misaligned and aligned CTACs for patient number 8. Fig. 2.6 (a) shows axial slice number 24 of the misaligned PET and CT images, Fig. 2.6(b) shows the same slice after the PET and CT images are registered, Fig. 2.6(c) shows the reconstructed PET image using the misaligned CTAC, and Fig. 2.6(d) shows the axial PET slice reconstructed using the aligned CTAC.

Figure 2.7: Reconstructed PET images using misaligned and aligned CTACs for patient number 8. Fig. 2.7 (a) shows axial slice number 33 of the misaligned PET and CT images, Fig. 2.7(b) shows the same slice after the PET and CT images are registered, Fig. 2.7(c) shows the reconstructed PET image with the misaligned CTAC using the jet colormap in Matlab, and Fig. 2.7(d) shows the axial PET slice reconstructed with the aligned CTAC using the jet colormap in Matlab

Figure 3.2: Averaging in the axial plane indicates which slices to process in the	
sagittal direction	46

Figure 3.3: Averaging results in the coronal plane, where (a) shows the unweighted average and (b) shows the weighted average	47
Figure 3.4: Averaging in the coronal plane indicates which slices to process in the axial direction	47
Figure 3.5: Results of the pre-processing steps in the axial plane, where (a) shows unprocessed axial slice number 23, (b) shows the image after fuzzy clustering is applied, (c) shows the binary mask, and (d) shows the extracted cardiac PET data	49
Figure 3.6: Result obtained after masking in the sagittal plane, where (a) shows the binary mask and (b) shows the extracted cardiac PET data	50
Figure 3.7: Results of the pre-processing steps applied to the PET image, where (a) shows the original axial image, slice number 40 (z-axis coordinate 102.39 mm), (b) shows the fuzzy clustered image containing the cardiac cluster and the unwanted liver cluster, (c) shows the masked image in which the liver cluster is removed, and (d) shows the extracted contour of the cardiac region	53
Figure 3.8: Result of the processed images in the sagittal plane, where (a) shows the original PET image, (b) shows the contour obtained from the processed PET image, (c) shows the original CT image, and (d) shows the contour obtained from the low-pass filtered CT image	54
Figure 3.9: Axial plane slice 24, (a) misregistered image, and (b) after the cardiac geometries are aligned with the automated registration procedure	58
Figure 3.10: Axial Plane slice 33, (a) misregistered image, and (b) after the cardiac geometries are aligned with the automated registration procedure	58
Figure 3.11: PET/CT registration results in the sagittal plane, where the top half portions of (a) and (b) are misaligned, and the lower half portions show the aligned images	59
Figure 3.12: Distribution of the shift values due to the misregistration between PET and CT images (a) in the x direction, (b) in the y direction, and (c) in the z direction	62
Figure 3.13: Axial CT slice 24 of patient 1 from Table 2 with an overlaid PET heart contour, where (a) shows misregistered PET and CT images; (b) shows the result after the cardiac geometries are automatically aligned by the registration software; (c) shows the PET image reconstructed using the misaligned CT image; and (d) shows the same PET image reconstructed using the aligned CT image	64
Figure 3.14: PET images reconstructed with a misaligned CTAC demonstrate artifactual hypoperfusion	66

Figure 3.15: The same PET data used in Fig 3.14, reconstructed using the aligned CTAC, indicate normal perfusion	66
Figure 3.16: A polar map is created from the short axis slices of the heart	69
Figure 3.17: PET images in the axial plane reconstructed using (a) misaligned CT data and (b) aligned CT data. PET images in the coronal plane reconstructed using (c) misaligned CT data and (d) aligned CT data	70
Figure 3.18: Polar maps of reconstructed PET data using (a) misaligned CT data, and (b) aligned CT data	70
Figure 4.1: Contours of PET cardiac images superimposed onto the four CTACs evaluated in the sagittal plane, slice number 78 (y=63.5 mm), before alignment. The results before registration are shown for (a) end normal expiration acquired before the PET stress exam (CTAC1), (b) end normal expiration acquired after the PET stress exam (CTAC2), (c) halfway through normal end expiration (CTAC3), and (d) forced end expiration (CTAC4)	75
Figure 4.2: Contours of PET cardiac images superimposed onto the four CTACs evaluated in the sagittal plane, slice number 78 (y=63.5 mm), after alignment. The results after registration are shown for (e) end normal expiration acquired before the PET stress exam (CTAC1), (f) end normal expiration acquired after the PET stress exam (CTAC2), (g) halfway through normal end expiration (CTAC3), and (h) forced end expiration (CTAC4)	76
Figure 4.3: Sagittal slice 78 (y=63.5 mm) of the PET data reconstructed using unregistered CTACs. Results of PET reconstruction are shown for (a) unregistered CTAC1, (b) unregistered CTAC2, (c) unregistered CTAC3, and (d) unregistered CTAC4	79
Figure 4.4: Sagittal slice 78 (y=63.5 mm) of the PET data reconstructed using registered CTACs. The reconstructed PET results are shown for (a) registered CTAC1, (b) registered CTAC2, (c) registered CTAC3, and (d) registered CTAC4. Fig. 4.4 (a-d) indicates that the perfusion is normal in the entire cardiac region and that the hypoperfusion was an artifact produced by the unregistered CT images	80
Figure 4.5: CT attenuation map generated by averaging all of the CT datasets obtained at different cardiac phases	84
Figure 4.6: CT attenuation map generated by taking the maximum value of each pixel from all of the CT datasets obtained at different cardiac phases	85
Figure 4.7: Contours of the PET image overlaid onto the corresponding CT image at different cardiac phases: (a) the 70% cardiac phase, which corresponds to diastole, and (b) the 30% cardiac phase, which corresponds to systole	88

Figure 4.8: PET cardiac contours in the sagittal plane registered with the corresponding CT images acquired during (a) the diastolic phase and (b) the systolic phase	89
Figure 4.9: Sagittal PET slice reconstructed using (a) a diastolic phase CTAC and (b) a systolic phase CTAC	92
Figure 5.1: Left ventricle activity in the PET image misaligned with the lung in the CT image. Many lines of response (LOR) for the left ventricle activity do not pass through cardiac tissue in the CTAC. PET image reconstruction performs the attenuation correction as if photons originating from left wall of the left ventricle passed through only lung/air	97
Figure 5.2: Reconstructed PET images using a misaligned CTAC, along (a) the long axis, (b) the short axis, and (c) the corresponding polar map	97
Figure 5.3: Left ventricle activity in the PET image that is manually aligned with the cardiac region in the CT image resulting in accurate attenuation correction in the left ventricle. In this image, since the lines of response originating in the cardiac region in the PET data pass through the corresponding cardiac region in the CT data, the correct attenuation parameters are assigned during the reconstruction of the PET data	98
Figure 5.4: Reconstructed PET images using a manually aligned CTAC, along (a) the long axis, (b) the short axis, and (c) the corresponding polar map	98
Figure 5.5: Difference in the shift values in the axial plane for the same patient by two users	102
Figure 5.6: Difference in the shift values in the coronal plane for the same patient by two users	102
Figure 6.1: PET cardiac region overlaid onto (a) the misaligned CTAC in the axial plane, (b) the misaligned CTAC in the coronal plane, (c) the aligned CTAC in the axial plane, and (d) the aligned CTAC in the coronal plane	114
Figure 6.2: Polar plot of the reconstructed PET data generated using the (a) misaligned CTAC and (b) the aligned CTAC. The comparison shows that attenuation artifacts were present in the PET data reconstructed using the misaligned CTAC.	115
Figure 6.3: Polar plot of the difference between the PET data reconstructed using the misaligned CTAC and the aligned CTAC shows that even though there was a	

significant misalignment between the PET and CT data, the error in the

reconstructed PET data is much smaller than the errors caused when the PET heart overlaps with the lung in the CT image	115
Figure 6.4: Normalized volumes of the heart and lung within different cardiac phases using the values calculated from segmented CT data	117
Figure 6.5: Contours of the heart in the 30% cardiac phase, which corresponds to systole, and the 70% cardiac phase, which corresponds to diastole. The systolic cardiac volume shown in blue is significantly smaller than the diastolic cardiac	
volume shown in green	118
Figure 6.6: Calcification in the heart (a) is observed in the CT slice in the axial plane, and (b) causes a hyperperfusion artifact in the reconstructed PET slice	120
Figure 7.1: Transformation of the left ventricle during the cardiac beat cycle where (a) shows two point on the myocardial wall, and (b) shows that the same points do not overlap when the cardiac wall is warped	126
Figure 7.2: Graphical interface for viewing cardiac PET data and for generating and analyzing the polar maps	127
Figure 7.3: Polar maps of the cardiac data acquired at different times	128

1 Introduction

1.1 Motivation

PET/CT is a rapidly growing, non-invasive technology for diagnosing different types of functional abnormalities of various organs. Although PET/CT has shown promising results, the misregistration between PET data and CT attenuation maps often produces artifactual abnormalities in the PET images resulting in false positives [1-8]. A whole-body PET scan takes between 15-30 minutes, and patient movement is inevitable during the PET data acquisition [9]. The patient motions that occur can be classified as voluntary motions or involuntary motions. [9-11]. Voluntary motions are described as the physical movement of the patient during a PET scan, which can be due to discomfort or pain, whereas involuntary movement is due to the transformation of the heart and lungs during cardiac and respiratory cycles [12]. Unlike PET imaging, which acquires data continuously during the scan, CT imaging collects an instantaneous snapshot of the anatomy at a specific point in the respiratory or cardiac cycle. Due to the sequential acquisition of CT and PET data, both voluntary and involuntary movements affect the alignment of the organs in the two modalities. Therefore, CT images are frequently misaligned with the longer duration PET scans [5].

1.2 Background

1.2.1 Positron Emission Tomography

Positron Emission Tomography (PET) shows the functional organ information using radionuclide tracers to track metabolic activity or perfusion rate based on the type of the radiopharmaceutical [13-14]. For PET imaging with fludeoxyglucose (FDG), the PET

image shows the metabolism in terms of the regional glucose uptake [14]. Although FDG is the most common PET tracer, other tracers can also be used in PET imaging [14]. The PET scanning process consists of coincidence detection, attenuation correction, and image reconstruction as described in the following sections.

Radioactive Tracer Injection

As the first step of PET data acquisition, a radionuclide tracer with a relatively short halflife is administered in the body. Once the tracer starts to decay, positively charged particles, namely positrons, are emitted. These positrons collide with electrons in the body, resulting in the annihilation of both particles and producing a pair of 511 keV gamma photons moving in opposite directions. The complete process is depicted in Fig. 1.1, which shows the stages of radioactive decay followed by the positron-electron annihilation, resulting in a pair of anti-parallel gamma rays. These high energy photons are detected by a ring of detectors around the body [15-16].

Coincidence Detection

Once the gamma rays are detected, coincidences are estimated using a short time window. Within this window, if two gamma rays are detected at opposite detectors, then the point of annihilation is calculated on the line of response (LOR) joining the two detectors. The location of the annihilation on the specific line of response is calculated using the time difference in the detection of the pair of gamma rays. Fig. 1.2 shows the process of selecting only coincidence-detected gamma rays within a given time window.



Figure 1.1: The process of positron emission tomography imaging. (a) The proton-rich radioactive nucleus, (b) decay of the unstable nucleus resulting in the emission of a positron, (c) annihilation of the positron and the electron, and (d) the annihilation resulting in two anti-parallel gamma rays.



Figure 1.2: The process of detecting true coincidences with pairing signals at opposite detectors within a specified time window.

Reconstructed PET Images

Using the coincidence-detected data, PET images are reconstructed as shown in Fig. 1.3. The figure shows a set of selected images in the axial plane from a cardiac exam of a patient. These images show the liver as well as the left ventricle of the heart which is due to the high amount of tracer uptake in these organs.



Figure 1.3: Selected set of cardiac PET images in the axial plane.

Attenuation Correction

Depending on the anatomical structures that the gamma rays pass through before hitting the detector, the attenuation of these rays can vary significantly. If the attenuation factor is not taken into account at the time of image reconstruction, then the anatomical structures deep in the body can appear to have much lower tracer uptake [17-19]. To avoid this, PET/CT imaging systems have an integrated CT scanner to acquire the CT data that is used as the anatomical attenuation map for the PET reconstruction [20]. Although CT based attenuation maps generally provide good PET reconstruction, CT based attenuation can sometimes induce significant artifacts due to patient motion [21]. To avoid this problem, the PET and CT datasets are examined for any artifacts prior to the reconstruction process.

1.2.2 Computed Tomography

In CT imaging, multiple X-ray projections are acquired at different angles around the object as shown in Fig. 1.4. These projections, along with the attenuation coefficients of various anatomical structures, are used to reconstruct the cross-sectional image with filtered back-projection [22-30] as shown in Fig. 1.5. Multiple cross-sectional scans are acquired with a slight shift in the axial position of the body in order to create three dimensional volumetric data that describes the anatomical structures.



Figure 1.4: Multiple x-ray projections are collected at different angles to acquire a cross-sectional CT image of the object.



Figure 1.5: (a) Shows the process of capturing projections of an object from various angles (b) shows the projection profile from position A, (c) shows the projection profile from position B, (d) shows the projection profile from position C, (e) shoes the projection profile from position D, and (f) shows the reconstruction of the object using these four projections.

The CT attenuation for homogenous and inhomogeneous (heterogeneous) media is given

by [26]

$$P(\bar{x}) = ln\left[\frac{I_o}{I(\bar{x})}\right] = \mu x \tag{1.1}$$

and

$$P(\bar{x}) = ln\left[\frac{I_0}{I(\bar{x})}\right] = \int_L \mu(\bar{x}) d\bar{x} ,$$
 (1.2)

respectively. In Eqs. 1.1 and 1.2, $P(\bar{x})$ is the projected attenuation, I_0 is the intensity of the incident x-ray, $I(\bar{x})$ is the intensity after attenuation through the object, and $\mu(\bar{x})$ is the attenuation coefficient that varies as a function of space.

The CT data is acquired using axial or helical scanning. In axial scanning, the bed position is adjusted in steps and each slice is acquired. In helical scanning, as shown in Fig. 1.6, the bed slides at a fixed speed while the scanner continuously acquires a series of projections [31]. Relative to axial scanning, helical scanning reduces the time to adjust the bed for each slice. Also, since helical scanning provides continuous projections, the images can be reconstructed using different slice thickness values as desired. Fig. 1.6 shows an example of single detector helical CT scanner. In modern scanners, multiple detector rings are used to scan a wider area in one rotation [32-33].



Figure 1.6: Helical CT scanning, where distance covered is represented in millimeters, and the time elapsed is represented in seconds.

The reconstructed image from a CT scan is a two dimensional array of pixels in which each pixel corresponds to a specific location in the body. The value of each pixel is calculated in terms of Hounsfield units using [26]

$$CT Number (HU) = 1000 \frac{(\mu_{pixel} - \mu_{water})}{\mu_{water}}$$
(1.3)

The CT number is calculated using the attenuation coefficients of different anatomical structures (μ_{pixel}) normalized by the attenuation coefficient of water (μ_{water}). For values of μ_{pixel} that are less than μ_{water} , the resulting CT number is negative, where -1000 corresponds to air. For values of μ_{pixel} greater than μ_{water} , the CT number is positive, which corresponds to other soft tissues and bone. A set of reconstructed CT images from a brain scan of a patient are shown in the axial plane in Fig. 1.7.

1.2.3 Hybrid Single Gantry PET/CT System

Hybrid PET/CT systems [34-35] combine two modalities in a single unit, thus providing functional and anatomical data in a single setup. Fig. 1.8 shows the schematic of the original PET/CT prototype developed by Beyer et al [63]. The other advantage of the hybrid approach is that CT images, which only take a few seconds to acquire, provide excellent resolution for the attenuation map in PET image reconstruction [36].



Figure 1.7: Selected set of brain CT images in the axial plane.



Figure 1.8: Representation of a PET/CT scanner.

At the beginning of a PET scan, the tracer is administered to the patient. After a waiting period of around one hour, the patient is positioned on the bed of the scanner for CT data acquisition. Once the CT scan is completed, the bed position is adjusted to start the PET scanning. The purpose of acquiring the CT images is to perform the attenuation correction of the PET data before the reconstruction process [37].

The main advantage of PET/CT is the shorter overall acquisition time, which results in greater patient throughput. In a traditional standalone PET system, the time required to obtain the transmission map is about 30-40% of the total scan time, which is on the order of several minutes [39-40]. In contrast, CT scans for attenuation correction are acquired in a few seconds. Another advantage of CT based attenuation correction is the lower noise level in CT images compared to traditional transmission scans, resulting in reconstructed PET images with higher signal-to-noise ratios. Also, PET/CT improves the localization of abnormal tracer uptake in small regions which may be difficult to identify in standalone PET scans.

1.3 Research Problem

In hybrid PET-CT imaging, patient motion (voluntary or involuntary) is a major concern in clinical applications, where motion during PET data acquisition results in erroneous positions calculated for the detected photons [41]. The imaging process consists of a CT scan followed by a PET scan, and the patients are instructed to keep still for the entire duration so that the CT and PET images are properly aligned. Alignment is important for both accurate spatial localization of tracer activity and accurate attenuation correction. Certain steps are taken in order to minimize the patient motion, such as: (a) verbal

instructions to the patient to stay still; (b) making sure that the patient is in a comfortable position before the data acquisition starts; (c) having patients empty their bladder before the start of the study; and (d) using head holders and restraining tape for brain imaging [42,56]. Despite these precautionary measures, respiratory and cardiac motion is nevertheless unavoidable. A common problem is demonstrated in Fig. 1.9, which shows the PET cardiac contour overlaid onto the CT image. Because of the misalignment between the CT and PET data, the cardiac region in the PET image is projected onto the lung in the CT image. The white lines represent two different lines of response for the gamma rays generated by positron-electron annihilation events. These lines pass through the soft tissue of the myocardium, but due to the misaligned CT images, they appear to be travelling through the lung. When PET images are reconstructed using this misaligned CT attenuation correction (CTAC) map, erroneous values of the attenuation parameter associated with air (from the lung) are assigned to pixels along these lines, resulting in an under-compensated region showing a significant hypoperfusion artifact.



Figure 1.9: Mismatch between the PET and CT images in a cardiac study.

The PET images for this study are reconstructed first using the misaligned CTAC and then using an aligned CTAC. The results of these two reconstructed PET images are shown in Fig. 1.10. The first image, Fig. 1.10 (a), shows artifactual hypoperfusion in the anterolateral wall, whereas the second image, Fig. 1.10 (b) shows uniform perfusion throughout. Fig. 1.10 (a) depicts the problem caused by a misaligned CTAC in PET/CT imaging, which if uncorrected, may require the patient to go through an unnecessary invasive procedure.



(a)



(b)

Figure 1.10: PET reconstruction using (a) misaligned PET and CT images, and (b) reconstruction after the PET and CT datasets are aligned.

1.4 Approaches to Eliminate PET/CT Artifacts

One approach to address the PET/CT misalignment problem is to obtain multiple CT scans during different respiratory phases in a cardiac exam. The PET images are matched with the CT images, and the CT scan with the smallest registration error is selected for PET attenuation correction [43-44]. This method does not guarantee consistent alignment of PET and CT images because respiratory motion varies between

the PET and the CT exams, particularly when the patient is imaged under a PET stress condition, which can alter the respiratory rate and excursion. In some cases, all of the CT scans are misaligned with the PET data, which introduces hypoperfusion artifacts into all of the reconstructed PET images. The inconsistent alignment between the PET and CT images denies the possibility of using one unregistered respiratory phase for attenuation correction, which reinforces the need for multiple CT scans if no registration software is available. If multiple CT scans are acquired, then the patient is exposed to an unnecessary radiation dose that can be avoided if software-aligned PET and CT images are used. Each CT scan delivers a CT dose index volume (CTDIvol) of 2.35 mGy to the patient, and by acquiring four CT scans, a total CTDIvol of 9.4 mGy is delivered to the patient. The dose length product (DLP) for a single CT scan is 43.10 mGy-cm, and for four CTACs, the total DLP is 172.4 mGy-cm [45-46]. With growing concerns over the radiological risks of CT, radiation dose reduction is very important, and by acquiring only one CTAC for every patient instead of four, a significant reduction in the radiation dose is achieved [47-49]. Also, the multiple CT acquisition approach is also inefficient in terms of the clinical workflow. If multiple CTACs are acquired for every patient, then each CTAC is loaded onto the console and superimposed onto the PET images. If the first CTAC does not align properly with the PET image, then the next CTAC is loaded and compared with the PET image. This process, which is repeated for each CTAC, is potentially timeconsuming and is otherwise inefficient in terms of clinical resources.

Another possible approach reduces the temporal resolution of the CT to match that of the PET examination. This is achieved with an ultraslow CT acquisition or a respirationaveraged CT. These approaches can reduce the breathing-induced misalignment at the

expense of increased radiation dose for the patient or longer acquisition times. However, misalignment resulting from other sources, such as patient motion or changes of the heart location due to pharmacologic stress agents remains uncorrected with this approach.

Manual registration is another option, but this adds the inconvenience of being timeconsuming and observer-dependent. A better solution to this problem is provided by a software program that automatically registers the two modalities and eliminates the attenuation artifacts from the reconstructed PET. The software-based method introduced here aligns the PET and CT data by calculating the distance between the boundaries of the PET and CT brain or heart. An aligned CT attenuation correction (CTAC) map is generated using the shift values obtained from PET/CT image registration. The PET data is then reconstructed using the shifted CT images, which yields a much better result. This approach also eliminates the need for multiple CTACs, thus reducing the radiation dose for the patient. Also, relative to manual registration, automated PET/CT image registration is much more time efficient, which improves the overall clinical workflow. The registration process is also independent of the respiratory phase of CT in cardiac studies, where the new automated approach consistently produces effective registration results for all respiratory phases.

1.5 Challenges

The following challenges need to be addressed to improve PET/CT registration in a clinical environment:

1. The algorithms developed for aligning the CTAC with the PET data need to be efficient in order to improve the clinical workflow relative to manual registration.

The complete process, including reading and generating aligned images, should not take more than a few minutes.

- All of the results obtained from the training datasets need to be validated by an expert through comparisons with manual registration results. This analysis is required to ensure the accuracy of the system.
- 3. The Digital Imaging and Communications in Medicine (DICOM) images generated by the software must be compatible with the GE Discovery STE scanner. New unique identifiers (UIDs) are also required so that no other imaging study has the same UID.

2 Attenuation Correction in PET Brain Data¹

2.1 Introduction

In most neurological applications, the ability of positron emission tomography (PET) to measure metabolic activity has significant implications in diagnosing Alzheimer's disease, frontotemporal dementia, epilepsy, and other neurological conditions because of the relative changes in the glucose metabolism associated with specific disease conditions [50-53]. Such abnormal metabolic activity regions are accurately localized within specific areas of the brain with the help of the anatomical detail provided by the computed tomography (CT) scan [54]. To minimize problems with misregistration artifacts, patients are instructed to remain still during the acquisition process. In most cases, this is a difficult task because a significant percentage of the patients who are required to have a PET/CT exam are demented and cannot follow the verbal instructions given by the technologist. These patients are often imaged using a head-holder device with restraining tape across their foreheads [55-56]. Despite these immobilization techniques, many patients still tend to move throughout the image acquisition process, resulting in highly misaligned PET and CT images. In such cases, the CT scan is repeated in order to obtain a set of images that align with the PET data.

¹Reproduced from K. Khurshid, K. L. Berger, R. J. McGough, Automated PET/CT Brain Registration for Accurate Attenuation Correction, *Engineering in Medicine and Biology Society*, USA, 2009, with the permission of IEEE.

The major drawbacks of this approach are that acquiring multiple CT scans increases the radiation dose for the patient and that there is no guarantee the second CT will be aligned. These problems can be avoided if automated software registration techniques are used.

To improve PET reconstruction using a CT attenuation correction (CTAC) map, automated software has been developed to automatically align the two modalities and generate an attenuation map that is registered with the PET images. has been developed. This software eliminates the need for acquiring multiple CTACs and therefore improves the overall clinical workflow. The software-aligned CTAC is then used for the reconstruction of the PET images. This procedure has been tested on PET/CT data acquired from ten patients. Among the ten patients, four showed significant misregistration errors between the PET and CT brain geometries. The other six datasets were aligned correctly or contained a very small misregistration error that had little or no effect on the reconstruction of the PET images. For all ten patients, the software successfully segmented the brain in the PET and CT images and correctly aligned the segmented brain structures obtained from the two modalities. Based on the translational and rotational motion compensation that is applied to the CT images, an aligned CTAC is generated. The reconstruction of PET data is carried out using the new CTAC, and the results show that the attenuation artifact due to the PET/CT misregistration, when present, is eliminated from the reconstructed PET images. For the datasets with no inherent misregistration error, the PET images were reconstructed with the original CTACs, and the results were the same.

2.2 Data Acquisition

A study was performed with prior consent from ten patients. The imaging procedure included a standard PET and CT scan protocol that was approved by the internal review board (IRB) at Michigan State University. PET/CT scans were acquired for ten consecutive patients, and no prior history was taken into consideration. The scans were acquired using the GE Discovery STE fusion PET/CT scanner, which combines a helical 16 row CT scanner and a full ring PET tomograph with a Bismuth Germanate (BGO) block for detecting high energy photons [57].

Helical CT scans of the head were acquired covering 15.4 cm along the z-axis with a 0.8 sec rotation speed, 11.75 mm per rotation table speed, 140 kVp tube voltage, and 65mA tube current. The CT images were reconstructed in 47 axial slices with 512x512 pixels, 3.75 mm slice thickness, 0.97 mm pixel spacing, and 16 bits per pixel. The PET scan also covered 15.4 cm along the z-axis with a crystal size of 4.7 mm x 6.3mm x 30 mm. The reconstructed PET data consisted of 47 slices with 128x128 pixels, 3.27 mm slice thickness, 2.34 mm pixel spacing, and 16 bits per pixel. The parameters for the CT and PET images are listed in Table 2.1.

2.3 Brain Segmentation

Before the two modalities are aligned, the PET and CT images are segmented in order to extract the brain region. The details of the segmentation process are provided in the following sections.

Table 2.1: CT and PET imaging parameters for the brain studies.

СТ	Width	512 pixels
	Height	512 pixels
	Bit Depth	16 bits
	Color Type	Grayscale
	Slice Thickness	3.75mm
	Field of View	500mm x 500mm
	Pixel Spacing	0.9766mm
	Table Speed	14.0625mm/s
	Revolution Time	0.8s
	Table Feed Per Rotation	11.25mm
	Spiral Pitch Factor	0.5625
PET	Width	128 pixels
	Height	128 pixels
	Bit Depth	16 bits
	Color Type	Grayscale
	Slice Thickness	3.27mm
	Field of View	300mm x 300mm
	Pixel Spacing	2.3438mm
	Radioactive Tracer	Fluorodeoxyglucose (FDG)

2.3.1 Segmentation of CT Brain Images

The CT images are first processed with a low pass filter to smooth the boundary of the brain and to reduce the image noise. To segment the brain from the CT data, a seed based region-growing technique is used [58-59]. The seed point is selected by calculating the mean of the pixel coordinates with Hounsfield units (HU) equal to 40, which
corresponds to brain matter [60]. Selecting a value equal to 40 instead of a range of values reduces the total number of coordinates resulting in faster processing. By averaging these selected coordinates, an approximate center point of the brain is estimated. This seed point or the estimated center of the brain is used as the starting location for the segmentation process. The single-seed region growing technique is fast and easy to implement. First, the seed point is marked as the current pixel and the pixel value is set to 1. Then, all 26 of the connected neighboring pixels are identified from the 3D CT data. The neighboring pixels with Hounsfield units corresponding to the brain are pushed into a processing queue. The remaining neighboring pixels are set to zero, and the first iteration is completed. For the second iteration, the pixel at the top of the queue is popped, and the same process of selecting the neighbors is repeated. In the second iteration, only those neighboring pixels which are not already present in the queue are pushed into the queue. All of the pixels are popped one by one from the top of the queue, and the new selected neighbors are added to the queue. This process is repeated until the queue is empty, which means all of the connected pixels corresponding to the brain matter are marked with 1 and the remaining pixels are set to zero. This process segments the brain in 3D such that all of the anatomical structures that are not connected to the brain are automatically removed. The total number of pixels with a value of 1 gives the total volume of the brain, which is used as an additional boundary condition while segmenting the PET brain. This process, which is similar to watershed segmentation [61], yields the same segmentation results in less time.

Fig. 2.1 (a)-(b) shows the CT segmentation results for a representative patient. Fig. 2.1 (a) shows ten unprocessed CT slices (slice number 6, 10, 14, 18, 22, 26, 30, 34, 38, and

42) in the axial plane out of 47 slices. Fig. 2.1 (b) shows the same axial slices after the segmentation has been performed and all of the unwanted structures are removed. Only the brain remains in Fig. 2.1 (b), and these results are subsequently used for image registration.



(a) Unprocessed CT slice numbers 6, 10, 14, 18, 22, 26, 30, 34, 38, and 42.



(b) Segmented CT slice numbers 6, 10, 14, 18, 22, 26, 30, 34, 38, and 42.

Figure 2.1: The segmentation results for the CT images, where (a) shows a set of unprocessed CT slices in the axial plane, and (b) shows the same CT slices after segmentation.

2.3.2 Segmentation of PET Brain Images

The brain in the PET images is segmented using the same region-growing approach used for the CT images. The seed point is calculated by averaging the coordinates of the segmented CT brain, which gives an estimate for the center of the brain region. Starting from this location, the 26 connected neighboring pixels are set to either 0 or 1 based on the intensity of these pixels. All of the neighboring pixels with intensity values greater than 50 are set to 1, as these pixels represent the presence of metabolic activity. The rest of the neighboring pixels are set to 0. The same process is then repeated for one of the neighboring pixels that was set to 1 in the previous step. The iterations are repeated until all of the connected pixels that show some metabolic activity are set to 1. The rest of the data is assigned a value of 0, and all of the unwanted anatomical structures are removed. Fig. 2.2 (a)-(b) contains the PET segmentation results for the same patient shown in Fig. 2.1. Fig. 1.2 (a) shows unprocessed PET slice numbers 6, 10, 14, 18, 22, 26, 30, 34, 38, and 42 in the axial plane, which correspond to the ten CT slices shown in Fig. 2.1. Fig. 2.2 (b) shows that all of the unwanted structures are removed.



(a) Unprocessed PET slice numbers 6, 10, 14, 18, 22, 26, 30, 34, 38, and 42.



(b) Segmented PET slice numbers 6, 10, 14, 18, 22, 26, 30, 34, 38, and 42.

Figure 2.2: The segmentation results for the PET images, where (a) shows the unprocessed PET slices in the axial plane, and (b) shows the same PET slices after the images are segmented. The selected axial slices are evenly distributed within the 47 slice dataset. Even with significant differences in the shape of the brain structure among these slices, the segmentation process performs well in each slice.

2.4 PET/CT Brain Registration

2.4.1 Preprocessing

Before the PET and CT images are registered, both datasets are resized using the DICOM header information such that, for each pixel in the PET data, there is a corresponding pixel in the CT data. For the CT images, the pixels are expanded from 0.9766mm to 1mm on each side, and for the PET images the pixels are made smaller by 3.27mm to 1mm on each side. Both datasets are cropped to show only the brain region in order to reduce the processing time. Once the images are cropped, the Canny edge detection algorithm [62] is applied to calculate the contours of the PET and CT brains. The registration process is carried out in two steps, where one step accounts for the shifting of the head, and the other step accounts for the rotation of the head during data acquisition.

2.4.2 Translational Registration

To align the CT and PET images, the centroids of the segmented brains from the two modalities are calculated. For this purpose, the centroid is defined as the center point of the brain which lies in the center of the x, y, and z axes with respect to the brain pixels. Once the centroids are aligned, PET and CT image alignment is improved through translational registration. If there is no rotation of the head during the exam, then the datasets will be registered correctly when the centroids of the PET and CT brain are aligned. If the head rotates, translational registration alone is insufficient, and an additional rotation of the CT attenuation correction map is also required, which is explained in the following section.

There are four different cases for the translational registration which are as follows:

- 1. There is no motion between the PET and CT scans.
- There is only a linear shift of the head position along one or more axes between the scans.
- 3. Only rotation of the head occurs between the two scans.
- 4. Both types of misalignments occur.

In the first case, which is the ideal scenario, there is no motion of any kind, and the center of the cropped PET data exactly occupies the same coordinates as the center of the CT data. As a result, the edges of the PET brain coincide with the edges of the CT brain. In this case, the output of the automated registration software yields the original CTAC.

In the second case, only linear motion of the head occurs, which means that the CT data is shifted along one or more axes. The shifts along the x, y and z axes are determined by calculating the distance between the centers of the PET and CT volumes. The CT images are then aligned with the PET images based on the shift values calculated for the x, y, and z directions. Since there is no rotation of the head involved in this case, when the CT images are shifted, the edges of the CT brain will coincide with the edges of the PET brain and the two modalities will be aligned.

In the third case, only rotational motion of the head occurs, so even though the centroids of the PET and the CT data are already aligned, the edges of the PET and CT brains do not overlap. Therefore, rotational registration is required which is explained in the next section.

For the last case, the steps in the previous two cases are combined. First, translational registration aligns the centers of the PET and CT cropped regions, which gives the shifts along the x, y and z axes. This is followed by rotational registration, which completes the alignment of the PET and CT brain structures.

2.4.3 Rotational Registration

During a PET/CT exam, the patients generally have some difficulty staying still throughout the procedure. In most cases, the patients rotate their heads along the x and y axes, corresponding to 'yes' and 'no' motion. To compensate for these motions, additional rotational registration is required. To rotate the CT image in the sagittal plane, an objective function is defined such that the maximum penalty is assigned to the boundary of the brain along the sinus cavity. This section of the PET brain has the highest probability of a metabolic artifact if there is overlap with the sinus cavity of the CT image. The decision regarding the direction of the rotation is made based on the initial projection of the PET brain boundary along the sinus cavity. If the brain region in the PET image is projected onto the sinus cavity in the CT image, then the rotation of the CT image is in the counter-clockwise direction, otherwise the CT image is rotated clockwise until the brain/sinus boundaries in the PET and CT images overlap with each other. This approach has worked well with every dataset tested thus far.

In order to rotate the CT image in the axial plane, the translated PET brain contour is overlaid onto the CT image. The fused axial image is divided into four quadrants, where the origin coincides with the center of the brain. As before, the center of the brain is approximated by averaging the locations of the non-zero pixels which correspond to the brain. In each quadrant, the average distance between the boundary of the PET brain

and the CT brain is calculated. If the PET brain boundary is located to the left of the CT brain boundary in the first and second quadrants and located to the right of the CT brain boundary in the third and fourth quadrants, then the CT image is rotated counterclockwise. Otherwise, if the PET brain boundary is located to the right of the CT brain boundary in the first and second quadrants and located to the left in the third and fourth quadrants, then the CT the third and fourth quadrants, then the CT brain boundary in the first and second quadrants and located to the left in the third and fourth quadrants, then the CT image is rotated clockwise. The rotation in the coronal plane is performed with a similar approach, which divides the image into four quadrants and rotates the CT image based on the distances between the edges of the PET and CT brain images in each quadrant.

2.4.4 Image Registration Results

The automated registration procedure described above is applied to datasets acquired from ten patients. In each dataset, the shift values and the rotation angles required to align the PET and CT images are calculated, and the results are listed in Table 2.2. The results show that the shift along the x and z axes is significant in some of the patients and that the misalignment along the y axis is consistently very small. No y axis shift occurs because, for this kind of misalignment, the patient has to lift his or her head from the table which is the least likely among all of the possible head motions prior to PET image acquisition. The largest rotations were observed in the sagittal plane, where the average of the absolute value of the rotations was 3.5 degrees, followed by the rotations in the axial plane, where the average of the absolute value of the head was observed in the coronal plane for all patients, where the average of the absolute value of the rotations was 0.4 degrees.

	Translational Registration (mm)			Rotational Registration (degrees)		
	x-axis	y-axis	z-axis	Axial Plane	Sagittal Plane	Coronal Plane
Patient 1	9	0	12	5	10	0
Patient 2	-2	0	0	0	0	2
Patient 3	3	0	0	0	-5	0
Patient 4	0	0	0	0	-5	0
Patient 5	5	0	3	5	0	2
Patient 6	0	0	6	0	-15	0
Patient 7	-3	2	0	0	0	0
Patient 8	5	0	3	10	0	0
Patient 9	0	0	3	5	0	0
Patient 10	6	2	6	0	0	0
Average of the absolute value	3.3	0.4	3.3	2.5	3.5	0.4

Table 2.2: Results of the PET and CT image registration.

Fig. 2.3 demonstrates the result of the registration process applied to PET and CT images in the axial, sagittal, and coronal planes. Fig. 2.3 (a) shows CT slice number 33 in the axial plane with the brain contour from the corresponding PET axial slice overlaid onto the CT image. The PET and CT brain structures show significant misalignment near the left boundary of the brain. Fig. 2.3 (b) shows the brain contour from sagittal PET slice number 64 overlaid onto the corresponding CT sagittal slice. Part of the PET brain lies outside of the top boundary of the CT brain, which indicates that patient movement occurred during the exam. Fig. 2.3 (c) shows the PET brain contour overlaid onto the CT image for coronal slice number 64. In this case, the PET brain contour lies outside of the left boundary of the CT brain, which is similar to the misregistration depicted in the axial slice shown in Fig. 2.3 (a).

Fig. 2.3 (d-f) shows the result after translational registration is applied to the PET and CT images. Fig. 2.3 (d) shows the brain contours from the PET image overlaid onto the corresponding CT image in the axial plane after the CT image is shifted to align with the PET image. Fig. 2.3 (e-f) shows the shifted CT image below the PET contour in the sagittal and coronal planes, respectively. After the translational registration step is completed, the brain structures from the two modalities are still misaligned. This is because rotational alignment is also required.

Fig. 2.3 (g-i) shows the results after the PET contours and CT images are rotationally aligned. Fig. 2.3 (g) shows an aligned PET brain contour overlaid onto a CT brain image in axial slice 33. After the images are rotationally aligned, the entire PET brain is located inside the CT brain. Fig. 2.3 (h) shows the result of the rotational registration in the sagittal plane. By rotating the CT image in the sagittal plane, the misalignment near the sinus cavity is eliminated. Fig. 2.3 (i) shows the result of rotational alignment in the coronal plane, which is consistently very small in all patients.

The shift parameters are applied to the CT dataset instead of the PET images because the aligned CT attenuation correction (CTAC) map is required by the system for artifactfree reconstruction of the PET images.



Figure 2.3: PET/CT image registration results, where the white lines represent the PET brain contours and the gray scale images show the CT brain. Fig. 3 (a-c) illustrates the original PET and CT data for slice number 33 in the axial plane, slice 64 in the sagittal plane, and slice 64 in the coronal plane, respectively. Fig. 3 (d-f) shows the results of translational registration in the axial, sagittal and coronal planes. Fig. 3 (g-i) demonstrates a significant improvement after translational and rotational registration.

2.5 PET Reconstruction

To demonstrate the effects of PET/CT misregistration on the attenuation-corrected PET data, PET images were reconstructed with unregistered and the registered CTACs. The reconstructed PET images were compared in the brain region before and after registration. Among the ten patients included in this study, the PET and CT images from six patients had insignificant misregistration errors; therefore, no artifact was observed in

the reconstructed PET data using the unaligned and the aligned CTAC. For the remaining four patients, there was a significant improvement in the reconstructed PET image when the registered CTAC was used.

The results of the PET image reconstruction before and after registration are shown in Fig. 2.4 for patient number 1. Among the 10 patients, this patient contained the largest misregistration error, as shown in Table 2.1, where significant translational and rotational artifacts were observed in the PET brain image. To demonstrate the effect of PET/CT misregistration on the PET reconstruction, selected PET images in the axial, sagittal, and the coronal planes are shown in Fig. 2.4. Fig. 2.4 (a-c) shows the PET slices reconstructed using the misaligned CTAC. The images in this figure show axial slice 33, sagittal slice 64, and coronal slice 64, respectively. In the axial and coronal images, the left half of the PET brain contains a significant artifact due to erroneous attenuation correction with a misaligned CTAC. Similarly, the region of the PET brain image that is projected onto the sinus cavity in the CT image also shows signs of diminished intensity as shown in Fig. 2.4 (b). Once the PET and CT images are aligned and the PET data is reconstructed using the registered CTAC, the image artifacts are eliminated and the result is shown in Fig. 2.4 (d-f). The entire PET brain image obtained after the PET and CT images are aligned shows uniform intensity that corresponds to uniform metabolic activity, indicating a healthy brain.







Figure 2.4: Reconstructed PET images using misaligned and aligned CTACs. Fig. 2.4 (a-c) shows the reconstructed PET slices in the axial, sagittal, and the coronal planes using the misaligned CTAC. Fig. 2.4 (d-f) shows the same reconstructed PET slices in the axial, sagittal, and coronal planes using the aligned CTAC.

The other three patients with noticeable misregistration errors are patients 6, 8, and 10 in Table 2.1. Patient 6 has a z axis shift of 6mm and a rotational misregistration of 15 degrees clockwise. This patient does not demonstrate any x or y axis shift or any rotation in the axial or coronal planes. Since the only misalignment is along the z axis and the only rotation for this patient is in the sagittal plane, a sagittal slice (number 64) is selected to

demonstrate the registration and the reconstruction results. Fig. 2.5 (a) shows the misaligned CT with an overlaid PET brain contour. Due to the rotation of the head in a "yes" motion by the patient, the PET brain overlaps with the sinus cavity in the CT image. Fig. 2.5 (b) shows the same CT sagittal slice after the CT image is aligned with the corresponding PET slice. The reconstruction of the PET data using the misaligned CTAC, as shown in Fig. 2.5 (c), demonstrates diminished metabolic activity in the brain region along the sinus cavity. This artifactual metabolic defect is eliminated in Fig. 2.5 (d) when the PET data is reconstructed using the aligned CTAC.



(a)



(b)



(c)



Figure 2.5: PET image reconstruction using misaligned and aligned CTACs for patient number 6. Fig. 2.5 (a) shows sagittal slice number 64 of the misaligned PET and CT images, Fig. 2.5(b) shows the same sagittal slice after the PET and CT images are registered, Fig. 2.5(c) shows the reconstructed PET image using the misaligned CT image, and Fig. 2.5(d) shows the sagittal PET slice reconstructed using the aligned CTAC.

The PET and CT images for patient number 8 are translationally misaligned by 5 mm along the x axis and by 3 mm along the z axis. These images are rotationally misaligned by ten degrees in the clockwise direction in the axial plane. The improvements in the alignment are especially evident in the axial plane, where axial slice number 24 is selected to show the registration and the reconstruction results. Fig. 2.6 (a) and (b) show the misaligned and aligned PET/CT images, respectively. Before the images are aligned, part of the PET brain in projected outside of the CT brain as shown in Fig. 2.6 (a). This error is corrected after the two modalities are aligned as shown in Fig. 2.6 (b). Fig. 2.6 (c) shows that PET images reconstructed with a misaligned CTAC produces an artifactual metabolic defect near the left boundary of the brain, which is eliminated when the PET images are reconstructed with the aligned CTAC as shown in Fig. 2.6 (d).

For the same patient, the registration and reconstruction results are shown for slice number 33 in Fig. 2.7, where the reconstructed images are shown using a different colormap. Fig. 2.7 (a) and (b) show the misaligned and the aligned PET/CT images, respectively. Fig. 2.7 (c) shows the PET image that is reconstructed using the misaligned CTAC, which suggests that an abnormality is present in the left portion of the brain. Fig. 2.7 (d) shows the reconstructed PET image obtained from the aligned CTAC, which shows no evidence of a brain abnormality.

The fourth patient showing an example of a significant misregistration error is patient number 10 in Table 2.1. The PET and CT images for this patient are translationally misaligned by 6 mm along the x axis, 2 mm along the y axis, and 6 mm along the z axis. There is no rotational misalignment of the PET/CT images for this patient. The primary translational movement is along the x and z axes, where the effects of this motion are

clearly observed in the coronal plane. The registration and reconstruction results are demonstrated in coronal slice 64. Figures 2.8 (a) and (b) show the misaligned and the aligned CTACs with the corresponding PET brain contours. Fig. 2.8 (c) shows coronal PET slice 64 reconstructed using the erroneous CTAC, which demonstrates the effect of PET/CT image misregistration. The misregistration artifact is removed when the software-aligned CTAC is used for the reconstruction of the PET image as shown in Fig. 2.8 (d).



Figure 2.6: Reconstructed PET images using misaligned and aligned CTACs for patient number 8. Fig. 2.6 (a) shows axial slice number 24 of the misaligned PET and CT images, Fig. 2.6(b) shows the same slice after the PET and CT images are registered, Fig. 2.6(c) shows the reconstructed PET image using the misaligned CTAC, and Fig. 2.6(d) shows the axial PET slice reconstructed using the aligned CTAC.



Figure 2.7: Reconstructed PET images using misaligned and aligned CTACs for patient number 8. Fig. 2.7 (a) shows axial slice number 33 of the misaligned PET and CT images, Fig. 2.7(b) shows the same slice after the PET and CT images are registered, Fig. 2.7(c) shows the reconstructed PET image with the misaligned CTAC using the jet colormap in Matlab, and Fig. 2.7(d) shows the axial PET slice reconstructed with the aligned CTAC using the jet colormap in Matlab.



Figure 2.8: Reconstructed PET images using misaligned and aligned CTACs for patient number 10. Fig. 2.8 (a) shows coronal slice number 64 of the misaligned PET and CT images, Fig. 2.8(b) shows the same coronal slice after the PET and CT images are registered, Fig. 2.8(c) shows the reconstructed PET image using the misaligned CTAC, and Fig. 2.8(d) shows the sagittal PET slice reconstructed using the aligned CTAC.

3 Attenuation Correction of Cardiac Data²

Cardiac images acquired with different imaging modalities provide complementary information. Therefore, the fusion of such multimodal datasets can provide important support for a medical diagnosis in cardiology. However, in clinical practice, the use of multimodal imaging techniques is limited due to the misalignment of images acquired from different modalities.

Recently, with the success of hybrid scanners, the clinical need to merge complementary information in cardiac studies has been emphasized. These scanners are able to acquire multimodal data that provides complementary information in a single image session. The most important examples of hybrid imaging systems are PET/CT scanners [63-64], which are widely applied to cardiac imaging studies because of their ability to correlate coronary artery disease (CAD) and myocardial perfusion provided by the CT and PET images, respectively. Although image acquisition in a single session generally minimizes the misalignment between the PET and CT datasets, the spatio-temporal mismatch of cardiac datasets in particular is not completely resolved [65-68]. Thus, manual registration with integrated commercial software is usually performed in clinical practice to align the images [69-70]. For this reason, an automatic alignment method is potentially very useful for cardiac PET/CT image registration [71-73].

²Reproduced from K. Khurshid, K. L. Berger, R. J. McGough, Respiratory Cardiac Motion Compensation in PET/CT for Accurate Reconstruction of PET Myocardial perfusion Images, *Journal of Physics in Medicine and Biology*, 53(20), 5705:5718, 2008 with the permission of Journal of Physics in Medicine and Biology.

3.1 Data Acquisition

The PET/CT image acquisition protocol begins with the intravenous administration of 25-35 mCi of N-13 ammonia at rest or after pharmacologic stress. The patient is positioned in the scanner, and the CT scan is performed with an acquisition field of view (FOV) of 50 cm. The reconstructed FOV for the CT has a default value of 50 cm, which is used for all patients. The patient bed is moved to the starting position, and then the PET scan is initiated. PET images are reconstructed with a field of view of 41.9 cm followed by a left shift of 4.0 cm within a 128 by 128 matrix [74]. The important parameters for PET and CT data acquisition are listed in Table 3.1. The automated processing of the PET and CT cardiac images is explained in the following sections.

3.2 Cardiac Image Segmentation

PET images are averaged separately in the axial and sagittal planes to estimate the location of the heart. Slice averaging in the axial plane is performed by calculating the weighted average of each pixel in the z direction. Although unweighted averaging of each pixel, represented by Eq. 3.1, gives a fair estimate of the extent of the cardiac boundary, applying different weights with Eq. 3.2 to different intensity levels enhances the contrast between the high and low intensity regions to achieve better isolation of the cardiac region [75].

PET	Resolution (pixels)	128 x 128				
	Reconstructed Field of View	419 mm x 419 mm				
	Scan Distance along the z-axis	150 mm				
	Slice Thickness	3.27 mm				
	Bits per Pixel	16				
	Detector Material	BGO				
	Crystal Size	4.7 mm x 6.3mm x 30 mm				
СТ	Resolution (pixels)	512 x 512				
	Reconstructed Field of View	500 mm x 500 mm				
	Scan Distance along the z-axis	150 mm				
	Slice Thickness	3.75 mm				
	Bits per Pixel	16				
	Tube Voltage	140 kVp				
	Tube Current	40 mA				
	Detector Type	LightSpeed16 HiLight Matrix II detector, polycrystalline ceramic				

Table 3.1: Image acquisition parameters for PET/CT imaging system of cardiac patients.

$$g_{x,y} = \frac{1}{N} \sum_{i=1}^{N} f_{x,y}(i)$$
 3.1

$$g_{x,y} = \frac{1}{N} \sum_{i=1}^{N} \omega \times f_{x,y}(i)$$
 3.2

Equations 3.1 and 3.2 contain expressions for computing unweighted and weighted averages at a single image location with coordinates (x,y), where $f_{x,y}$ and $g_{x,y}$ represent the input and the output pixel at the selected image location, respectively, and N represents the total number of slices averaged. In each processed image, if the pixel value is above the threshold, then the selected weight is greater than one, and if the pixel

value is below the threshold, then the weight is set to one. Since most of the slices contain the heart in the PET dataset, the cardiac region is of significantly higher intensity than the liver after weighted averaging, so the heart is easily distinguished from the liver, which facilitates extraction of the heart from the PET data. The weighted averaging in the axial plane indicates the upper and lower bounds of the cardiac region along the x and y axes. Averaging is also performed in the sagittal plane to calculate the z axis bounds for the cardiac region. The z axis bounds define the range of axial PET slices that are used for fuzzy clustering of the heart, as described in section 3.3. The weighted average in the axial plane is also used for masking, as described in section 3.4.

Fig. 3.1 (a) shows the averaged image using equal weights applied to all the intensity levels, whereas Fig. 3.1 (b) demonstrates better isolation of the heart by applying variable weights based on the intensity value of the pixels, which improves the contrast between the low and high intensity values. The weight in Equation 3.2 can be an absolute value or the weight can be defined relative to the normalized intensity of the pixels. In the results above, a subjectively chosen value of five was selected for the weight, and a normalized threshold of 0.45 was selected between the low and high intensities. The objective of this averaging is to select only a few slices in the sagittal plane and to ensure the presence of cardiac region in the selected slices. This technique provides the lower and upper bounds within which the heart is present for the sagittal and the coronal planes.

The same averaging process is applied to the PET slices in the coronal plane. Fig. 3.3 shows the results from unweighted averaging (a) and the results from weighted averaging (b) in the coronal plane. From these results, the lower and upper bounds of the cardiac slices in the axial plane are acquired, as shown in Fig. 3.4.



Figure 3.1: Averaging results in the axial plane, where (a) shows the unweighted average and (b) shows the weighted average.



Figure 3.2: Averaging in the axial plane indicates which slices to process in the sagittal direction.



Figure 3.3: Averaging results in the coronal plane, where (a) shows the unweighted average and (b) shows the weighted average.



Figure 3.4: Averaging in the coronal plane indicates which slices to process in the axial direction.

3.2.1 Fuzzy Clustering

Fuzzy c-mean clustering [76-77] extracts the geometries of the significant clusters from the PET images. Fuzzy clustering is applied only to the selected axial slices, as defined by the extent of the cardiac region determined from weighted averaging. Applying fuzzy clustering only to the slices containing the heart greatly reduces the computation time. The mathematical expressions that are evaluated are given by

$$m_{ik} = \frac{1}{\sum_{j=1}^{c} \left(\frac{d_{ik}}{d_{jk}}\right)^{2/(q-1)}} \text{ and } 3.3$$

$$d_{ik} = \|u_k - c_i\|$$
, 3.4

where, m_{ik} = Point k's membership to cluster i, c = total number of clusters, d_{ik} = distance of point k to the center of cluster i, d_{jk} = distance of point k to the center of cluster j, and q = fuzziness exponent.

Fuzzy clustering obtains the largest clusters from the individual axial PET images that represent the heart and the liver. To separate the cardiac cluster from the other clusters, masking is used as described in the following section.

3.2.2 Masking

Through masking, the cardiac region is isolated and all of the unwanted clusters are removed from the axial slices as shown in Fig. 3.5. The mask is obtained from the weighted average in the axial plane as described in section 3.2, which is converted into binary form. By applying this mask, the boundary of the cardiac region is obtained, and all of the unwanted clusters are removed. After three steps are completed, i.e., estimating the cardiac region, fuzzy clustering, and masking, the remaining PET images contain only the cardiac region.



Figure 3.5: Results of the pre-processing steps in the axial plane, where (a) shows unprocessed axial slice number 23, (b) shows the image after fuzzy clustering is applied, (c) shows the binary mask, and (d) shows the extracted cardiac PET data.

The same process is applied to the sagittal slices to extract the cardiac cluster and the result is shown in Fig. 3.6.



Figure 3.6: Result obtained after masking in the sagittal plane, where (a) shows the binary mask and (b) shows the extracted cardiac PET data.

3.2.3 Edge Detection

The segmented PET images are first processed with a low pass filter that smooths out the boundary of the heart. The Canny edge detection algorithm [62] is then applied to obtain the boundary of the cardiac region. Gradients are calculated for the smoothed image in the x- and y-direction respectively with Eq. 3.5 and Eq. 3.6, which are given by

$$K_{GX} = \begin{pmatrix} -1 & 0 & 1 \\ -2 & 0 & 2 \\ -1 & 0 & 1 \end{pmatrix} \text{ and } 3.5$$

$$K_{GY} = \begin{pmatrix} -1 & -2 & -1 \\ 0 & 0 & 0 \\ 1 & 2 & 1 \end{pmatrix} . 3.6$$

The approximate magnitude of the gradient is calculated using Eq. 3.7, and the direction of the gradients is calculated using Eq. 3.8,

$$|G| = |G_x| + |G_y|$$
 3.7

$$\theta = \tan^{-1} \left(|G_y| / |G_x| \right),$$
 3.8

where G_x and G_y are the derivatives in the x and y directions, respectively. The approximate magnitude of the gradient is represented by |G|, and θ represents the direction of the gradient.

Fig. 3.7 shows the results obtained with these image processing steps evaluated on a representative PET image in the axial plane. Fig. 3.7(a) shows axial slice number 40 from the PET data, which consists of 47 slices. In Fig 3.7(a), the high intensity regions are the heart and the liver. Fig. 3.7(b) shows the result after fuzzy clustering. The heart and liver clusters are clearly shown in this image. The liver region is removed from the image using masking, as shown in Fig. 3.7(c). The result of the edge detection performed on the PET

image is shown in Fig. 3.7(d). This edge information is used for the registration of the PET and CT images.

After the PET contours of the heart are obtained, the corresponding information is extracted from the CT images. First, each CT image is processed with a low pass filter to smooth out the cardiac region. Then, Canny edge detection is applied to the filtered images. The resulting image contains the edges of the heart as well as other structures such as liver and ribs. To extract the cardiac contour from the CT image and eliminate the unwanted contours, the approximate center of the heart is determined by averaging the pixel coordinates of the PET contour of the heart. Starting from this point in the CT image, the nearest edge at all angles is identified as the cardiac contour, and the remaining contours in the CT image are eliminated. Even for the largest misregistration observed between the two modalities, the center point of the PET heart is consistently located within the heart in the CT image, and the contour of CT heart is correctly identified. Once the preprocessing and segmentation is complete, the PET and CT images are registered with a low probability of error because all of the unwanted pixels have been removed from the data as shown in Fig. 3.8.



Figure 3.7: Results of the pre-processing steps applied to the PET image, where (a) shows the original axial image, slice number 40 (z-axis coordinate 102.39 mm), (b) shows the fuzzy clustered image containing the cardiac cluster and the unwanted liver cluster, (c) shows the masked image in which the liver cluster is removed, and (d) shows the extracted contour of the cardiac region.



Figure 3.8: Result of the processed images in the sagittal plane, where (a) shows the original PET image, (b) shows the contour obtained from the processed PET image, (c) shows the original CT image, and (d) shows the contour obtained from the low-pass filtered CT image.

3.3 PET/CT Image Registration

After a PET/CT scan, image registration is necessary to ensure accurate and consistent image reconstruction. Although, the PET images may overlay accurately onto the CT images in some cases; however, in many other cases, the heart geometries extracted from the PET and CT data may not overlap perfectly. In such cases, the reconstruction of PET using the CT can contain areas of false hypoperfusion.

Although voluntary motion can also be important, the main reason for the misalignment of the PET and CT images is the respiratory motion of the patient. Due to the moving diaphragm, the heart is displaced up to 2 centimeters along the long axis of the body during a respiratory cycle [78]. Thus, the alignment of the heart can vary between scans. Since the PET data is averaged over a 15-minute interval, the position of the PET heart is also averaged over the entire respiratory cycle. However, CT images provide the instantaneous location of the heart during the respiratory cycle. Several approaches can be used to eliminate this problem. One method takes multiple CT scans of the patient in different respiratory phases and attempts to find the best match through visual inspection. With this method, the patient goes through additional CT scans, which increases the radiation exposure. Another approach slows the CT scan acquisition and averages over 1-3 respiratory cycles, but this still may not produce enough temporal averaging to match the PET scan. Keeping this in mind, an automated method is developed that can take one CT and one PET scan and align the geometries of the heart using least squares automatic image registration. To ensure alignment for all three degrees of freedom, registration is performed on all three axes. This process is carried out in two steps. In the first step, the PET and CT data is resized so that each pixel from the PET image has a

corresponding CT pixel. After resizing, each pixel in each PET and CT image is 1 mm by 1 mm. This step is necessary because of differences in the resolution and the field of view (FOV) of the PET and CT images. The matrix size of the CT image is 512 by 512 pixels with a field of view of 50 cm by 50 cm, where the FOV is calculated by multiplying the image resolution with the pixel spacing. PET images are 128 by 128 pixels with a field of view of 419 by 419 mm. For the CT images, the pixel size is initially 0.9796 mm by 0.9796 mm, and for the PET images, the pixel size is initially 3.27 mm. Once the images are scaled so that the pixels are the same size for both modalities, the CT and PET contours of the heart are aligned as described in the following section.

Depending upon the phase of respiratory cycle, the amount of mismatch changes. When there is no respiratory motion, the two cardiac geometries are aligned with each other. To compensate for the respiratory motion, least squares minimization is applied to the edges of the PET and CT heart contours, and a motion vector is generated. This motion vector defines the shifts that correct for the displacement.

The edges obtained from the CT correspond to the entire myocardium, whereas the edges obtained from the PET data correspond to the left ventricle. Thus, only the edges corresponding to the anterior and lateral walls are used for image registration. These edges, which share a boundary with the left lung, correspond to the same walls of the left ventricle in both the PET and the CT images. Since the lung attenuation parameters are the main source of the hypoperfusion artifact, aligning the PET and CT cardiac edges along these boundaries eliminates this problem.

The shifts in the x and y directions are determined from the axial plane images, and the z axis shift is determined from the images in the sagittal plane. For the x axis shift, the PET and CT axial images are traversed horizontally from right to left, and the distance between the first CT edge pixel and the first PET edge pixel is calculated. This process is repeated for all of the rows in the PET and CT axial images, and then an average distance between the pixels is calculated using the shift values for each row. This average value provides the shift required to align the PET and CT images along the x axis. The same process is performed for the average y axis shift by traversing the PET and CT axial images vertically from top to bottom for all of the columns. The distance between the first PET and first CT edge pixel for each column is calculated and then the average of these values is computed. To calculate the z axis shift, the PET and CT data is analyzed in the sagittal plane. The sagittal PET and CT images are traversed vertically from top to bottom for all of the columns, and the distance between the first PET edge pixel and first CT edge pixel is calculated for each column and then averaged. The process of calculating the shifts for the x, y, and z axes is then repeated a second time to refine the alignment.

3.3.1 Image Registration Results

In the images below, some of the results generated from selected case studies are shown. In some of these images, the respiratory motion effect is quite significant. The automated registration procedure worked quite well on all of the data sets that demonstrated image misalignment due to respiratory motion.

The first set of images (Fig. 3.9, 3.10) show examples before and after PET/CT image registration in the axial plane, which shows the PET/CT data in the xy plane. The second set of images (Fig. 3.11) show examples before and after PET/CT image registration in
the sagittal plane, which shows the PET/CT data in the yz plane. The grayscale background in these images shows the anatomical information from the CT data, whereas the overlapping white contour represents the boundary of the left ventricle obtained after processing the PET data.



Figure 3.9: Axial plane slice 24, (a) misregistered image, and (b) after the cardiac geometries are aligned with the automated registration procedure.



Figure 3.10: Axial Plane slice 33, (a) misregistered image, and (b) after the cardiac geometries are aligned with the automated registration procedure.



Figure 3.11: PET/CT registration results in the sagittal plane, where the top half portions of (a) and (b) are misaligned, and the lower half portions show the aligned images.

3.3.2 Analysis of PET/CT Image Registration

The misregistration between the PET and CT images was characterized in 50 heart patients using the automatic registration software. Only patients with visual hypoperfusion in the cardiac region of the PET images were selected for this analysis. For each patient, the attenuation corrected (AC) PET images were registered with the CT data, and the shift values in the x, y, and z directions in Table 3.2 were calculated. The shift values in the x direction are significant on both sides of the axis. The largest shift in the x direction

is 12 mm, and the smallest shift value is -6 mm. In the y direction, most of the shift values are zero or close to zero. The shift values in the y direction range from -12 mm to 6 mm. In the z direction, most of the shifts are negative, which indicates that the registration program shifts the CT data upwards along the z axis. The shifts in the z direction range from -26.2 mm to 6.5 mm.

At the end of Table 3.2, the average shifts in the x, y, and z directions are shown. Among x, y, and z, the average shift in the z direction, 8.7 mm, is the largest, followed by the average shift in the x direction, which is 4.1 mm. The smallest average shift is 2.1 mm in the y direction. The large shift along the z axis corresponds to the significant displacement of the heart along the long axis of the body due to the motion of the diaphragm during the respiratory cycle.

Fig. 3.12 displays three histograms that show the distribution of the shift values in the x, y, and z directions. In Fig. 3.12(a), the distribution of shifts in the x direction is centered near 3 mm. Fig. 3.12(b) shows the distribution of shifts in the y direction, which contains a peak at 0 mm, and very few values elsewhere. The distribution of shifts in the z direction in Fig. 3.12(c) contains a peak at -6 mm, where the range of z shifts extends from -26.2 mm to 6.5 mm.

No.	Shift Values (mm)				Shift Values (mm)		
	х	Y	Z	No.	Х	Y	Z
1	9.8	-5.9	6.5	27	4.9	-11.8	-13.1
2	9.8	-3.9	-13.1	28	8.8	0	-16.4
3	3.9	0	-13.1	29	4.9	0	-3.3
4	4.9	-2.9	-16.4	30	6.9	-2	-16.4
5	5.9	3.9	-6.5	31	2	0	0
6	-3.9	0	-6.5	32	3.9	0	-3.3
7	2	0	-6.5	33	4.9	0	-13.1
8	0	0	-13.1	34	0	-2.9	-26.2
9	9.8	2.9	-16.4	35	0	0	-6.5
10	3.9	0	-19.6	36	4.9	0	-3.3
11	2	2.9	-9.8	37	5.9	0	-6.5
12	3.9	2	-9.8	38	7.8	0	-6.5
13	1	2	-6.5	39	3.9	0	-13.1
14	3.9	0	-22.9	40	9.8	5.9	-26.2
15	0	0	0	41	2.9	0	-6.5
16	6.9	-9.8	0	42	11.8	-1	-9.8
17	-5.9	-2.9	-3.3	43	5.9	0	-6.5
18	-2.9	-5.9	-3.3	44	2.9	0	0
19	2	-2	-9.8	45	-2	0	0
20	-2.9	-5.9	-6.5	46	0	0	-3.3
21	-2.9	-6.9	-3.3	47	0	3.9	-6.5
22	0	0	0	48	2	5.9	3.3
23	4.9	0	-13.1	49	5.9	2.9	6.5
24	5.9	-3.9	-13.1	50	3.9	0	3.3
25	0	-3.9	-6.5	Mean	4.1	2.1	8.7
26	0	0	-9.8	Std. Dev.	3.9	3.4	7.5

Table 3.2: Shifts in the x, y, and z directions required to compensate for the misregistration between the PET and CT images in fifty patients.



Figure 3.12: Distribution of the shift values due to the misregistration between PET and CT images (a) in the x direction, (b) in the y direction, and (c) in the z direction.

3.4 PET Reconstruction

The goal of this research is to register PET and CT images to accurately align the heart geometries of both modalities and to generate new shifted CT attenuation correction maps. Once the shifted CT attenuation correction map is created, the PET data is reconstructed using the new shifted CTAC. Since there is no mismatch between the PET data and the new CTAC, the PET images do not contain any examples of artifactual hypoperfusion, so only the actual condition of the heart is depicted in the reconstructed PET image. In the results shown below, the patient had no cardiac abnormality, but the misalignment of PET and CT hearts produced an artifactual perfusion defect. Once the PET images are reconstructed using the new CTAC obtained from the automated alignment software, the results show that the hypoperfusion observed in the anterior and lateral walls of the heart was caused by a misregistered attenuation correction map.

Fig. 3.13 shows an example of unregistered and registered PET and CT images in the axial plane for patient 1 in Table 3.2 along with the corresponding reconstructed PET axial images. Fig. 3.13(a-b) shows the PET cardiac contour from axial slice number 24 in a set of 47 slices overlaid onto the grayscale CT image, where the results are shown before and after registration. Fig. 3.13(c-d) shows the reconstructed PET images obtained from the unregistered and registered CTACs. Fig. 3.13(a) contains an example of an unshifted CT that projects the lateral and anterior region of the PET heart onto the lung and bone of the CT, respectively. In this example, the motion of the patient in the axial plane is most significant in the x direction. When the CTAC in Fig. 3.13(a) is used for PET image reconstruction, the region of the PET heart that is projected outside of the CT heart is incorrectly attenuated, which creates artifactual hypoperfusion in the reconstructed PET

image as shown in Fig. 3.13(c). In Fig. 3.13(b), the registered CT image with an overlaid PET heart contour is shown. After the images are registered, the entire PET heart is projected within the cardiac boundary of the CT image, providing the correct attenuation values for PET image reconstruction and eliminating the hypoperfusion artifacts from the reconstructed PET image as shown in Fig. 3.13(d).



Figure 3.13: Axial CT slice 24 of patient 1 from Table 2 with an overlaid PET heart contour, where (a) shows misregistered PET and CT images; (b) shows the result after the cardiac geometries are automatically aligned by the registration software; (c) shows the PET image reconstructed using the misaligned CT image; and (d) shows the same PET image reconstructed using the aligned CT image.

In the figure above, the hypoperfusion is significant in the anterolateral wall of the heart in the reconstructed PET image in (c), which occurs as a result of the erroneous attenuation correction of the PET cardiac region with the lung parameters of the CT data. The reconstructed PET image in (d) shows uniform perfusion in the entire cardiac region, demonstrating that the artifactual hypoperfusion due to misalignment is eliminated.

Fig. 3.14 shows the reconstructed PET data using the original CT attenuation correction maps. In Fig. 3.14 (e-h), the right half portions of the images were attenuated incorrectly, so artifactual hypoperfusion is observed in these regions. The amount of misregistration error is quite significant in this example, which shows a significant false perfusion defect.

In Fig. 3.15, the reconstructed PET images are shown using the correctly aligned CTAC, which demonstrates normal cardiac perfusion. All of the slices (a)-(h) in Fig. 3.15 contain uniform intensity distributions in the cardiac walls with no sign of a perfusion abnormality.



Figure 3.14: PET images reconstructed with a misaligned CTAC demonstrate artifactual hypoperfusion.



Figure 3.15: The same PET data used in Fig 3.14, reconstructed using the aligned CTAC, indicate normal perfusion.

After the PET and CT images are registered using the automated software, the PET images are reconstructed using the shifted CT attenuation correction map. Among the 50 patients listed in Table 3.2, only two patients (number 15 and number 22) did not require any alignment between the PET and CT data. In these patients, a perfusion defect was diagnosed in the cardiac wall. For 22 out of the 50 patients, the reconstruction of the PET images with the aligned CTAC maps showed uniform perfusion throughout the cardiac region, and the hypoperfusion artifact was eliminated. For the remaining 26 patients, the hypoperfusion was not eliminated despite using the registered CTAC for PET image reconstruction. These patients were diagnosed with a perfusion defect in the cardiac wall. Therefore, for this collection of patients, the hypoperfusion observed in 44% of the unaligned PET images was the result of an artifact caused by the misregistration between the PET and CT data. This artifact, when present, was consistently eliminated with the automated registration software.

3.5 Polar map Representation of PET Cardiac Data

In most cases, instead of displaying all of the slices for the three dimensional cardiac data separately, representing all of the information in a single image with a polar map is preferred. The condition of the heart is quickly analyzed by looking at the polar map so that any abnormality present in the heart is readily localized.

The polar map is generated from short-axis slices of the heart as shown in Fig. 3.16. The slices consist of concentric circles of the cardiac wall with decreasing radius, where the largest circle corresponds to the base of the heart and the smallest circle corresponds to

the apex of the heart. These concentric circles are then merged into a single image with the apex in the center and the base at the outer edge of the circle [79].

Fig. 3.6 (a) shows the selection of the slices along the short axis of the heart. These slices contain the circular myocardial wall with increasing radius from the apex to the base of the heart as shown in Fig. 3.6 (c). These slices are divided into sectors, and the polar map is generated by placing these slices in concentric circles with apex of the heart at the center of the polar map as shown in Fig. 3.16 (c).

An example with substantial misalignment between the PET and CT data is shown in Fig. 3.17. A significant portion of the PET cardiac region is projected onto the lung in the CT image because of patient motion. Figures 3.17 (a) and (c) show the misaligned PET and CT data whereas Figures 3.17 (b) and (d) show the PET overlaid onto correctly aligned CT data. Polar maps are generated for each of the reconstructed PET datasets using the misaligned CTAC as well as the aligned CTAC. These polar maps are shown in Fig. 3.18. The polar map in Fig. 3.18 (a) shows a major hypoperfusion artifact, whereas the polar map in Fig. 3.18 (b) shows normal perfusion throughout the cardiac region.



(a)



(b)



(c)

Figure 3.16: A polar map is created from the short axis slices of the heart.





Figure 3.17: PET images in the axial plane reconstructed using (a) misaligned CT data and (b) aligned CT data. PET images in the coronal plane reconstructed using (c) misaligned CT data and (d) aligned CT data.



Figure 3.18: Polar maps of reconstructed PET data using (a) misaligned CT data, and (b) aligned CT data.

4 Optimal Respiratory and Cardiac Phases³

4.1 Introduction

A significant limitation of CT-based attenuation correction of PET data is the misregistration between the two modalities. The CT attenuation map captures an instantaneous snapshot of the heart at specific respiratory and cardiac phases, whereas the PET images are acquired over multiple respiratory and cardiac cycles, so the PET heart is averaged over a larger region. Differences in the temporal resolution along with patient movement may cause misalignment between the cardiac boundaries of the PET and CT images, drastically reducing the accuracy of the attenuation correction. When PET data is reconstructed using an erroneous attenuation map, this causes misregistration artifacts that create false areas of hypoperfusion in the PET cardiac region, which are in turn projected onto the lung in the CT data. These areas of hypoperfusion can alter interpretation and create false positive diagnosis of ischemia or infarction.

Misregistration between the PET and CT data is a result of involuntary respiratory and cardiac motions. The misregistration due to the respiratory motion is translational and can be corrected using automated registration software [80-81]. The registration software calculates the distance between the edges of the cardiac contours of the PET and CT image to generate a motion vector. The PET and CT data is aligned based on the magnitude and direction of the motion vector.

³Reproduced from K. Khurshid, K. L. Berger, R. J. McGough, Analysis of Multiple Cardiac Phases of CT for Maximal Overlap with PET Images, *International Symposium on Applied Electromagnetics and Mechanics*, USA, 2007, with the permission of IEEE.

However, correcting the misregistration due to the cardiac motion during a heartbeat cycle involves scaling of the heart. During a cardiac cycle, the size of the heart changes significantly from the systolic phase to the diastolic phase. To guarantee that the PET and CT cardiac regions completely overlap, the CT needs to be acquired during the diastolic phase where the heart is the largest. If the CT data is acquired during the systolic phase, the CT heart is the smallest, so the CT heart will not cover the entire cardiac region in the PET dataset. If this is the case, even with proper registration, a substantial portion of the PET cardiac region will be projected onto the CT lung, which will result in erroneous attenuation correction.

4.2 Evaluation of Multiple Respiratory Phases

To demonstrate that the registration results are independent of the respiratory phase of the CT scan, four CT attenuation correction (CTAC) maps were acquired through an institutional review board (IRB) approved procedure and registered with the PET data. The PET images were subsequently evaluated before and after alignment. The CTACs were acquired after the patient was instructed to hold his breath at different stages of respiration [82-83]. For these exams, no additional respiratory monitoring equipment was used. Only verbal instructions were given to the patient, i.e., exhale normally and hold, exhale halfway through and hold, exhale as much as possible and hold. The patient was also told to breathe normally between the different CT scans.

4.2.1 Data Acquisition

Four different CT scans (CTAC1-CTAC4) were acquired for 24 patients at different phases of the respiratory cycle. CTAC1, which was used for the initial attenuation

correction of the PET data, was acquired during normal tidal end expiration before the PET stress exam, where the patient breathes out normally. CTAC2 was obtained at normal tidal end expiration after the PET stress exam, which differs from CTAC1 due to muscle relaxation. CTAC3 was collected halfway through normal tidal end expiration, where the patient breathes out halfway and holds his breath. CTAC4 was obtained during forced end expiration, where the patient was asked to exhale as much as possible and then hold his breath. For all of these CTACs, the PET and CT images were automatically registered with the software described in section 3.3.

4.2.2 PET/CT Image Registration Results

The results obtained without and with the automatic registration software in the sagittal plane for the PET data and four different CTACs are shown in Fig. 4.1. In Fig. 4.1 (a-d), the cardiac contours of the PET image are superimposed onto the unregistered CTACs. Fig. 4.1 (a) shows the PET cardiac contour superimposed onto CTAC1, Fig. 4.1 (b) shows the PET cardiac contour superimposed onto CTAC2, and Figures 4.1 (c) and (d) show the PET cardiac contours on CTAC3 and CTAC4, respectively. In this example, CTAC1 has the smallest misregistration error along the z axis (3 mm) among of all the CTACs, and CTAC4 has the second smallest error of 9 mm, along the z axis. CTAC2 has the second largest misregistration error along z of 12 mm, and CTAC3, shown in Fig. 4.1 (c), has the largest misregistration error of 18 mm along z. The misregistration between the PET data and the four CTACs, which is predominantly along the z axis, differs because of the varying displacement of the heart at different phases of the respiratory cycle due to the motion of the diaphragm. Fig. 4.1 (e-h) shows the results obtained with the automated registration software for the different CT respiratory phases. Fig. 4.1 (e) shows

the registered PET contour and CTAC1, Fig. 4.1 (f) shows the registered PET contour and CTAC2, Fig. 4.1 (g) shows the registered PET contour and CTAC3, and Fig. 4.1 (h) shows the registered PET contour and CTAC4. As shown in these figures, the automated registration process successfully aligns the cardiac geometries in the PET and CT data regardless of the respiratory phase in which the CT scan was acquired. This result, which demonstrates that the software eliminates the misalignment due to respiratory motion, indicates that only one CT scan is required for every patient.

Images are registered for 24 datasets containing one PET scan and four CT scans. The mean and standard deviations of the shift values required for all the CTACs are calculated and are listed in Table 4.1, where the CT images in these datasets are acquired after the patient is instructed to hold his breath at different respiratory phases. CTAC2, which is end normal expiration, was the closest to the average heart location in the PET data.

PET	Respiratory Phase	Mean Shift (mm)	Std. Dev. (mm)
CTAC 1	Normal end expiration before PET stress exam	8.6	6.11
CTAC 2	Normal end expiration after PET stress exam	4.3	3.31
CTAC 3	Halfway through normal end expiration	9.49	7.86
CTAC 4	Forced end expiration	7.10	3.24

Table 4.1: Means and standard deviations of the shift values required in the sagittal plane for multiple CTACs acquired at different respiratory phases.



(a)



(b)



(c)



Figure 4.1: Contours of PET cardiac images superimposed onto the four CTACs evaluated in the sagittal plane, slice number 78 (y=63.5 mm), before alignment. The results before registration are shown for (a) end normal expiration acquired before the PET stress exam (CTAC1), (b) end normal expiration acquired after the PET stress exam (CTAC2), (c) halfway through normal end expiration (CTAC3), and (d) forced end expiration (CTAC4).



(a)



(b)



(c)



(d)

Figure 4.2: Contours of PET cardiac images superimposed onto the four CTACs evaluated in the sagittal plane, slice number 78 (y=63.5 mm), after alignment. The results after registration are shown for (e) end normal expiration acquired before the PET stress exam (CTAC1), (f) end normal expiration acquired after the PET stress exam (CTAC2), (g) halfway through normal end expiration (CTAC3), and (h) forced end expiration (CTAC4).

4.2.3 PET Image Reconstruction Results

To demonstrate the effect of misregistration, PET slices in the sagittal plane are reconstructed using unregistered and registered CTACs are shown in Fig. 4.3 and Fig. 4.4, respectively. These PET images are from the same sagittal plane shown in Fig. 4.1 and Fig. 4.2. A consistent window-level is applied to all of the images to enhance the contrast between the normal and the hypoperfused cardiac regions. The window extends from 120 to 225 in all of the images, where the values in the original images range from 0 to 255.

Fig. 4.3 (a-d) shows the reconstructed PET image using the unregistered CTACs. Fig. 4.3 (a) indicates that unregistered CTAC1 has a small misregistration error with respect to the PET image; therefore, the reconstructed PET image using the unregistered CTAC1 in Fig. 4.3 (a) does not show a significant hypoperfusion artifact. Fig. 4.3 (b) and Fig. 4.3 (c) contain PET images that are reconstructed using unregistered CTAC2 and unregistered CTAC3, respectively. Due to the large misregistration errors between the unregistered PET and CTACs 2 and 3 as shown in Fig. 4.1 (b-c), the reconstructed PET image shows significant false hypoperfusion in the anterior wall, which is caused by the projection of the PET cardiac region onto the lung in the CT attenuation correction map. Fig. 4.3 (d), which shows the reconstructed PET image using unregistered CTAC4, again shows the hypoperfusion artifact in the anterior cardiac wall, but this artifact is not as significant as in Fig. 4.3 (b) and Fig. 4.3 (c).

Fig. 4.4 (a-d) shows the reconstruction of the same PET image in the sagittal plane using the registered CTACs. All four of these reconstructed PET images show a uniform intensity distribution in the cardiac wall with no sign of the hypoperfusion artifact. When

the results from Fig. 4.3 (a-d) and Fig. 4.4 (a-d) are compared, the importance of PET/CT image registration is clearly demonstrated. With a misaligned CT attenuation correction map, the cardiac region of the reconstructed PET image shows a significant hypoperfusion artifact. By aligning the cardiac geometries of the acquired PET and CT data, the hypoperfusion artifact is eliminated from the reconstructed PET images.



(a)



(b)



(c)



(d)

Figure 4.3: Sagittal slice 78 (y=63.5 mm) of the PET data reconstructed using unregistered CTACs. Results of PET reconstruction are shown for (a) unregistered CTAC1, (b) unregistered CTAC2, (c) unregistered CTAC3, and (d) unregistered CTAC4.



(a)



(b)







(d)

Figure 4.4: Sagittal slice 78 (y=63.5 mm) of the PET data reconstructed using registered CTACs. The reconstructed PET results are shown for (a) registered CTAC1, (b) registered CTAC2, (c) registered CTAC3, and (d) registered CTAC4. Fig. 4.4 (a-d) indicates that the perfusion is normal in the entire cardiac region and that the hypoperfusion was an artifact produced by the unregistered CT images.

4.3 Validation of the Optimal Cardiac Phase

PET/CT misalignment due to the incorrect cardiac phase at which the CT data is acquired cannot be corrected using image registration techniques due to significant reduction in the size of the heart in the CT data. To maximize the overlap in the cardiac region for the PET and CT data, the CT images must be acquired at the diastolic phase when the size of the heart is the largest. If the CT data is acquired during the systolic phase when the CT heart is the smallest, the PET and CT cardiac regions will not overlap completely. For CT images acquired during the systolic phase, despite image registration, a major portion of the PET cardiac region is projected onto the lung in the CT data, so the reconstructed PET data will be attenuated incorrectly.

4.3.1 Data Acquisition

Ten consecutive patients (7 men, 3 women) who were referred to our institution for a PET/CT exam were selected for this study. There was no prior knowledge of any hypoperfusion defects in the selected patients. The average age of this group was 61 years with a standard deviation of 7 years. The data from these patients was used to estimate the diastolic cardiac phase for the CT images that achieve maximum overlap with the PET cardiac region.

PET and CT images were acquired with a GE Discovery STE fusion PET/CT imaging system with a helical 16 row CT scanner at one end and a full ring PET tomograph with crystal size of 4.7 mm x 6.3 mm x 30 mm at the other end. The CT scanner uses a tube current of 40 mA and a tube voltage of 140 kVp. The acquired CT data consists of 47 slices with a resolution of 512 by 512. The reconstructed field of view for the CT images is 500 mm by 500 mm. The CT data is cardiac gated using an ECG system [84]. CT data

acquisition is initiated by the QRS peak of the ECG signal, and the data is binned into 10 equally spaced intervals called phases. To minimize the effects of breathing motion, the end expiration respiratory phase is selected for the CT acquisition due to the smaller misregistration error on average with the PET data than any other respiratory phase. The PET data consists of 47 slices with a resolution of 128 mm by 128 mm. The reconstructed field of view for the PET images is 419 mm by 419 mm.

4.3.2 Maximizing the PET/CT Cardiac Overlap

To maximize the overlap in the cardiac region for the PET and the CT data, two different approaches are used. In the first approach, the maximum intensity projection for all of the corresponding coordinates from ten CT volumes is calculated. The noise pixels can play an important role in the resulting CTAC and therefore can introduce attenuation artifacts in the reconstructed PET images. The second approach takes the average of all the corresponding pixels of the CT volumes from ten bins. Averaging the pixels can greatly affect the attenuation parameters, especially along the heart and lung boundary where the average value of the attenuation correction parameter can create artifactual hypoperfusion in the reconstructed cardiac region. Both of these approaches require multiple CT acquisitions over one cardiac cycle, which increases the radiation dose for the patient.

To minimize the attenuation artifacts due to averaging and maximum intensity projection, ten cardiac phases from several patients are analyzed to estimate the diastolic phase in which the heart is at the maximum size. By selecting the diastolic phase, the average intensity projection and the maximum intensity projection techniques are avoided, which reduces attenuation artifacts. The results show that, among the ten equally spaced

CTACs in a cardiac cycle, the 7th bin (i.e., 70% phase) captures the heart at the maximum size, where this phase overlaps the PET cardiac region more than any of the other phases. The 30% phase corresponds to systole, and at this phase, the CT heart is the smallest.

Once the phase corresponding to diastole is calculated, i.e., 70% of the ECG cycle, the CTAC is acquired only at that particular phase, and the CT scanner remains off for the rest of the cardiac cycle. Thus, radiation dose to the patient is significantly reduced without negatively impacting the reconstruction results for the PET data.

4.3.3 Methodology

Average Intensity Calculation

To generate the average intensity CT attenuation correction map, the corresponding pixels for all of the CT datasets, which are acquired at different phases of the cardiac cycle, are averaged together to generate a single CT dataset. The drawback of this approach is that some of the cardiac region in the diastolic phase projects onto the lung in the systolic phase, so some regions in the image are assigned the averaged value of the heart and lung. Therefore, an error is introduced in the value of the attenuation parameter obtained from the CT images, which creates artifacts in the reconstructed PET data. Fig. 4.5 shows a CT attenuation map generated from the average values of all pixels at a given coordinate.



Figure 4.5: CT attenuation map generated by averaging all of the CT datasets obtained at different cardiac phases.

Maximum Intensity Projection

In the approach that uses the maximum intensity projection, the maximum values at all of the corresponding pixels in all of the phases are found, and a new CTAC with these maximum values is generated. This process alters the entire CT dataset, and slight movement of the patient changes the output greatly by assigning high attenuating parameters of bones to other objects like heart, muscle, and fat. Fig. 4.6 shows an example of a CT attenuation map that is generated using the maximum pixel value at each coordinate.



Figure 4.6: CT attenuation map generated by taking the maximum value of each pixel from all of the CT datasets obtained at different cardiac phases.

Diastolic Phase Estimation

To avoid the problems in the two approaches described above, the CT scan in the diastolic phase is used for attenuation correction. Instead of processing the CTACs and generating an altered CT attenuation map, the CT data is acquired during the diastolic phase in which size of the heart is the largest. The resulting CTAC maximally overlaps with the PET heart while providing the smallest error for PET image reconstruction. With this approach, the CT scans are acquired in ten equally spaced cardiac phases that are binned over a cardiac cycle. Since the cardiac gating is triggered by the contraction of the right ventricle, the exact phase of diastole is unknown. This method is used to compare all of the phases acquired over the cardiac cycle, and then the diastolic phase is found, which differs slightly from patient to patient. If the sampling interval between the phases is small, the exact location of the diastolic phase can be found for every dataset. Otherwise, the nearest sampled phase is selected.

To determine which cardiac phase corresponds to diastole, where the heart is the largest, all of the CT datasets are segmented to obtain the cardiac boundary. Once the cardiac region is defined, the volume of the heart is calculated in all of the phases. To calculate the volume of the heart, the pixels in the cardiac region are counted in each of the segmented volumetric datasets. These pixels are then multiplied by the pixel spacing and the slice thickness to estimate the volume of the heart. Once the volumes are calculated for each cardiac phase, the phase with the maximum volume is selected to represent diastole, and the phase with the smallest heart volume is selected to represent systole.

4.3.4 Results

The estimation of the diastolic phase is then validated through image fusion, which combines the PET data with the CT data from different cardiac phases. After image fusion, the pixels in the PET heart that are projected onto the lung in the CT data are calculated for each CT phase. Results show that the estimated diastolic CT phase maximally overlaps with the PET cardiac region, demonstrating the least amount of misalignment error between the two modalities. Thus, the diastolic phase is optimal for the reconstruction of the PET images.

The PET/CT registration results are shown in Fig. 4.7 for two different CT cardiac phases. Fig. 4.7 (a-b) contains the contour of the heart from the PET data superimposed onto the 30% and 70% CT cardiac phases. The degree of misalignment between the CT and PET data depends on the size of the heart, which is based on the cardiac phase in the ECG cycle. The CT data at the diastolic phase overlaps almost the entire PET heart as shown in Fig. 4.7 (a). In the systolic phase, the misalignment error is greater due to the smaller size of the cardiac region in the CT data as shown in Fig. 4.7 (b). The main difference between the two phases is observed near the anterolateral wall of the heart. Some of the PET cardiac contour is projected onto the lung from the systolic CT image, whereas the entire PET cardiac contour is projected onto the CT heart from the diastolic phase. This was demonstrated in experiments performed with several data sets obtained from different patients. The results show that the 70% phase of the cardiac cycle, which corresponds to the diastolic phase in the CT data, is optimal for the attenuation correction of PET data.



(a)



(b)

Figure 4.7: Contours of the PET image overlaid onto the corresponding CT image at different cardiac phases: (a) the 70% cardiac phase, which corresponds to diastole, and (b) the 30% cardiac phase, which corresponds to systole.

The registration of the PET cardiac region with the corresponding CT cardiac region in the sagittal plane is shown in Fig. 4.8. Fig 4.8 (a) shows the CT heart in the diastolic phase, where the entire PET cardiac contour is contained within the heart in the CT image. Fig. 4.8 (b) shows that the size of the CT heart in the systolic phase is much smaller and therefore does not contain the complete PET cardiac contour, which means that false attenuation parameters are assigned for PET image reconstruction. This misalignment cannot be corrected using image registration, so attenuation artifacts are expected in the reconstructed PET data if the CT images acquired during the systolic phase are used for PET image reconstruction.





Figure 4.8: PET cardiac contours in the sagittal plane registered with the corresponding CT images acquired during (a) the diastolic phase and (b) the systolic phase.

4.3.5 Analysis of Ungated and End-Diastolic CTACs

For ten patients, the misalignment between the PET data and two CTACs was determined. The first CTAC was acquired at the end-expiration phase of the respiratory cycle with no cardiac gating. The second CTAC was acquired at the end-expiration and end-diastolic (ED) phase of the cardiac cycle. The total shift values (Euclidian) were calculated manually by four users for the ungated CTAC and the end-diastolic phase CTAC.

For each patient, the shift values were calculated in the axial, coronal, and the sagittal plane by four users. The total Euclidean shifts were calculated by determining the shift distances in all three planes. The value of the Euclidean shift was calculated by averaging the values provided by the four users. Table 4.2 lists the mean and standard deviations of the shift values for the two types of CTACs for each patient.

The mean shift required for the ungated CTAC was 16.8 mm with a standard deviation of 2.4 mm. For the end-diastolic CTAC, the mean shift value was 10.1 mm with a standard deviation of 1.9 mm. On average, the end diastolic CTAC required a smaller shift to align with PET data. The largest shift required for the ungated exam was 29.1 mm, whereas the largest shift for the end-diastolic exam was 23.7 mm. A comparison between the results obtained with the ungated CTAC and the end-diastolic CTAC reveal that, due to the larger size of the heart in the end-diastolic phase, the overall misalignment between the PET data and the CTAC is reduced.

	Ungated	CTAC	End Diastolic CTAC		
Patient	Mean Shift (mm)	Std. Dev. (mm)	Mean Shift (mm)	Std. Dev. (mm)	
1	10.5	1.4	7.1	2.0	
2	8.7	2.6	5.1	3.1	
3	14.8	1.4	7.7	2.7	
4	29.1	3.9	23.7	1.4	
5	9.9	3.6	1.5	1.0	
6	15.1	2.0	12.0	0.9	
7	28.4	3.2	10.7	2.7	
8	15.9	1.9	3.6	2.1	
9	11.8	1.6	11.7	0.7	
10	23.4	2.6	17.7	2.7	
Avg.	16.8	2.4	10.1	1.9	
Max.	29.9	3.9	23.7	3.1	
Min.	8.7	1.4	1.5	0.7	

Table 4.2: Average shift values required for ungated CTAC and the ECG gated end-diastolic CTAC.

4.3.6 PET Image Reconstruction

PET images are reconstructed using both the diastolic and the systolic phase CT attenuation correction maps. The resulting PET images in the sagittal plane are shown in Fig. 4.9. When the PET images are reconstructed using diastolic phase CTACs, the correct attenuation parameters are assigned throughout the PET cardiac region, which shows uniform perfusion throughout the myocardium as demonstrated in Fig. 4.9 (a). In contrast, Fig. 4.9 (b) shows that the PET cardiac region near the anterior wall uses an

incorrect attenuation parameter that produces false regions of hypoperfusion in the reconstructed PET images.



Figure 4.9: Sagittal PET slice reconstructed using (a) a diastolic phase CTAC and (b) a systolic phase CTAC.

5 Manual vs. Automated Registration

5.1 Introduction

In PET/CT imaging, the alignment of the two modalities is important because misalignment can cause hypoperfusion artifacts that can potentially result in a diagnostic misinterpretation. For cardiac applications of PET/CT imaging, this misalignment is caused by patient motion and involuntary physiological movement of the organs.

Certain steps are taken in order to minimize the patient motion, such as, (a) verbal instructions to the patient to stay still; (b) making sure that the atient is in a comfortable position before data acquisition starts; (c) having patients empty their bladder before the study begins; and (d) using head holders and restraining tape for brain imaging [42,56]. However, the misalignment caused by differences in the position and size of the heart between CTAC and PET data acquisitions attributable to the following factors is unavoidable:

- Cardiac displacement during respiration
- Cardiac phase/volume mismatch due to contraction of the heart
- Possible cardiac movement due to pharmacologic stress

- Temporal averaging which occurs over the length of the PET data acquisition Commercially available applications can assess and manually correct the misalignment between the PET and CT data. The goals of this study were to investigate the problem of CTAC misalignment in cardiac PET imaging, validate the effectiveness of automated registration with manual alignment, and calculate the variations in the registration results performed manually by multiple people.
5.2 Data Acquisition

The images were acquired using the Discovery STE PET/CT system (GE Healthcare). Ten patients with a high degree of visual CTAC misalignment in either the rest exam or the stress exam were selected out of 25 total patients. The acquisition parameters for the PET and the CT data are listed in Table 5.1.

PET	Resolution (pixels)	128 x 128
	Reconstructed Field of View	419 mm x 419 mm
	Scan Distance along the z-axis	150 mm
	Slice Thickness	3.27 mm
	Bits per Pixel	16 bits
СТ	Resolution (pixels)	512 x 512
	Reconstructed Field of View	500 mm x 500 mm
	Scan Distance along the z-axis	150 mm
	Slice Thickness	3.75 mm
	Bits per Pixel	16 bits

Table 5.1: Image acquisition parameters for the PET/CT system.

5.3 Manual Registration Process

Using the GE Healthcare PET/CT visual alignment application, the selected exams were manually registered. Four users with varying experience registered the PET and CTAC data from each exam. The PET and CTAC images were loaded into the Attenuation Correction Quality Control application (ACQC, GE Healthcare), and each user performed visual alignment of the left ventricle activity in the PET image with the CTAC. Axial, coronal, and sagittal shift vectors were recorded for the alignment of the CTAC by each user.

The manual alignment procedure is outlined below. The users were asked to ensure that all LV PET activity in the original image reconstructions is contained within the cardiac tissue in the CTAC, but users were not coached during the shifting process. The instructions were as follows:

- Make any necessary adjustments, i.e. contrast adjustment and image scaling, for optimal viewing of the fused images.
- 2) Align the PET and CTAC data sets first in the sagittal plane, then axial, and lastly the coronal plane. Since the primary direction of respiratory motion is along the long axis of the body, the vertical axis in the sagittal plane was the expected direction of largest shift.

We determined that, based on the artifacts observed, overcorrection is better than undercorrection during manual registration of the PET and CTAC data. In particular, making sure that all of the left ventricle (LV) activity is contained within the cardiac tissue is preferred over leaving some PET activity aligned with lung in the CTAC. Also, care should be taken to ensure that operators are well-trained in manual alignment techniques and that they understand the potential pitfalls.

Fig. 5.1 shows the misaligned PET and CT image where some portion of the left ventricle of the PET heart is projected onto the lung in the CT image. The red lines represent the lines of response (LOR) which are greatly affected by the misalignment. These lines of

response for the left ventricle activity do not pass through cardiac tissue in the CTAC. PET image reconstruction performs attenuation correction as if photons originating from the left wall of the left ventricle passed through only lung/air, resulting in underestimated PET values for the region in the left ventricle which contains artifactual hypoperfusion. The thickness of the myocardial wall is most impacted by such lines that run parallel to the wall. Some lines of response, however, remain relatively unchanged by the CTAC shift, as shown by the blue line in the figure.

Fig. 5.2 shows the reconstructed PET images before alignment. Fig 5.2 (a) shows the long axis slice of the reconstructed image. The cardiac wall along the lung shows the most significant artifact. Fig. 5.2 (b) shows the short axis view of the reconstructed image. The polar map image is shown in Fig. 5.2 (c), with hypoperfusion visible in the anterolateral region.

Fig. 5.3 shows the result that is obtained after manual alignment is applied to the axial images. The lines of response which were represented in red in Fig. 5.1 are now represented in green. These lines of response pass through the cardiac region after alignment, therefore the correct attenuation parameters are now assigned to the PET data.

Fig. 5.4 shows the reconstructed PET images after manual alignment. Fig. 5.4 (a) and (b) show the reconstructed PET images along the long axis and the short axis, respectively. The cardiac region shows uniform perfusion throughout the entire myocardial wall. The corresponding polar map for the reconstructed PET data is shown in Fig. 5.4 (c).



Figure 5.1: Left ventricle activity in the PET image misaligned with the lung in the CT image. Many lines of response (LOR) for the left ventricle activity do not pass through cardiac tissue in the CTAC. PET image reconstruction performs the attenuation correction as if photons originating from left wall of the left ventricle passed through only lung/air.



Figure 5.2: Reconstructed PET images using a misaligned CTAC, along (a) the long axis, (b) the short axis, and (c) the corresponding polar map.



Figure 5.3: Left ventricle activity in the PET image that is manually aligned with the cardiac region in the CT image resulting in accurate attenuation correction in the left ventricle. In this image, since the lines of response originating in the cardiac region in the PET data pass through the corresponding cardiac region in the CT data, the correct attenuation parameters are assigned during the reconstruction of the PET data.



Figure 5.4: Reconstructed PET images using a manually aligned CTAC, along (a) the long axis, (b) the short axis, and (c) the corresponding polar map.

5.3.1 Quantitative Analysis of the Shift Values

The mean and the standard deviation of the shift values obtained from the alignment results for the ungated CTACs and the end-diastolic (ED) CTACs were calculated. The shift values are listed in Table 5.2. The mean shift required for the ungated CTACs was 15.7 mm with a standard deviation of 6.9 mm. For the end-diastolic CTACs, the mean shift required was 10.5 mm with a standard deviation of 6.1 mm.

The size of the heart is maximized in the end-diastolic CTAC, so much smaller shifts are required on average to align with the PET data. The magnitude of the largest shift required for any exam was 32.9 mm. The mean shifts in each direction for the ungated CTACs and the end-diastolic CTACs for all users over all exams are listed in Table 5.3. The most prominent shift was in the axial plane. For the gated CTACs, the sagittal plane received the largest shift reduction compared to the standard CTAC shifts.

To assess whether the gated and standard CTACs generated substantially different results after shifting, the polar plots from the largest user shift with the standard CTAC were quantitatively compared to those from the largest user shift with the gated CTAC. In the polar plots, the maximum difference in any region was 9%, and the average difference was 5%. Out of all regions (20 exams x 5 regions), 11% of these had a difference greater than or equal to 5%.

		Standard CTAC/End-		End-diastolic CTAC/End-	
			ation	Expl	ration
Patient	Rest/Stress	Mean(mm)	Std Dev (mm)	Mean (mm)	Std Dev (mm)
1	Rest	11.4	1.5	8.5	2.2
I	Stress	10.5	1.4	7.1	2.0
2	Rest	7.3	1.0	4.2	1.7
Z	Stress	8.7	2.6	5.1	3.1
2	Rest	16.6	3.0	11.2	3.4
3	Stress	14.8	1.4	7.7	2.7
Λ	Rest	29.0	3.0	20.1	2.2
4	Stress	29.1	3.9	23.7	1.4
Б	Rest	10.6	3.1	3.2	2.7
5	Stress	9.9	3.6	1.5	1.0
6	Rest	16.1	2.6	14.2	2.2
0	Stress	15.1	2.0	12.0	0.9
7	Rest	7.2	2.0	19.8	4.2
1	Stress	28.4	3.2	10.7	2.7
8	Rest	14.5	2.2	4.7	2.8
0	Stress	15.9	1.9	3.6	2.1
0	Rest	8.4	3.4	11.3	2.9
9	Stress	11.8	1.6	11.7	0.7
10	Rest	20.4	7.1	16.3	6.5
10	Stress	23.4	2.6	17.7	2.7
Moon	Rest	14.1	2.9	11.3	3.1
IVIEALI	Stress	16.8	2.4	10.1	1.9
Mean	All Exams	15.5	2.7	10.7	2.5

Table 5.2: Average shift values for the manual alignment.

Table 5.3: Average shift values required in each plane.

	Axial Plane	Coronal Plane	Sagittal Plane
Ungated CTAC	9.1 mm	3.1 mm	6.7 mm
End Diastolic CTAC	6.7 mm	1.7 mm	2.6 mm

5.3.2 User-Dependent Shift Variations

To quantitatively assess the impact of the user variation in manual PET/CTAC shifts on the resulting PET images, reconstructions were generated using the smallest and largest manual shift magnitudes for each exam. The goal of this assessment was to capture the extremes in the user variation for the manual CTAC alignment, focusing on cases where the shift difference was significant relative to the resolution of the PET imaging system.

CardIQ Physio (GE Healthcare) was used for visualizing and comparing the images that were obtained from different CTAC shifts. The surface detection algorithm in CardIQ Physio automatically segmented the left ventricle. This segmented volume then provided the input for the polar plots. Polar plots were compared quantitatively after they were divided into 5 sectors. Changes in activity were then detected in the anterior, posterior, septal, and lateral regions of the left ventricle. Percentage scores for each region were computed based on the mean activity in each sector divided by the maximum activity in the left ventricle.

Using the data from ten patients with a total of 20 exams (10 rest, 10 stress), out of which 7 exams (35%) contained more than a 5% difference in at least one of the five regions within the polar plots generated from reconstructions using the largest and smallest user shifts, only 1 exam (5%) contained more than a 10% difference in one region (which had an 11% difference). In this exam, the minimum user shift did not place all of the PET activity within the cardiac tissue in the CTAC, where visual verification demonstrated that this user under-corrected the misregistration as shown in Fig. 5.5 and Fig. 5.6. This is an example of extreme user shift variation, which resulted in the largest regional difference between the manual shifts. The first user recorded a 3.9 mm right shift, a 1.6 mm posterior

shift, and a 2.3 mm inferior shift. The second user recorded an 11 mm right shift, a 1.8 mm anterior shift, and a 3.0 mm inferior shift.









5.3.3 Comparison of Unshifted and Shifted Image Reconstructions

Shifted standard CTAC reconstructions were compared to the original unshifted reconstructions for the ten patients listed in Table 5.2 in order to quantify the impact of the registration. For these misaligned exams, the reconstruction based on the maximum user shift was compared to the original CTAC alignment. The maximum regional difference was 37%, and the maximum regional difference per exam averaged across all

misaligned exams was 20%. The primary region of artifact/polar plot difference was the lateral/anterior boundary of the heart.

5.4 Automated vs. Manual Registration

To compare the manually shifted values, PET data and the standard CTAC data were automatically aligned using our automatic registration algorithm. This algorithm registered the data by first segmenting the heart in the PET data using fuzzy c-mean clustering. The cardiac region in the CT image is then estimated based on the seeded region-growing approach. The edge information from the PET clustered images and the CT cardiac/lung boundary is then used to find the minimum distance between the edges of the two modalities in a least squares sense.

The automated registration process was performed on the datasets of eight patients containing 16 exams (rest and stress). The PET and CT images were aligned using our automated software, and all of the shift values were recorded. The same datasets were aligned manually by four users, and the shift values that were assigned by each user were recorded. A detailed analysis was performed to extract any inconsistences in the shift values due to the subjective assessments of different users.

The shift values obtained from these automated and manual alignments are listed in Table 5.4 through Table 5.13. Tables 5.4 and 5.5 show the shift values in the x, y, and z planes for the rest and stress exams, respectively. Tables 5.6 and 5.7 show the average of the shift values obtained by four different users for the rest and stress exams, respectively. The average magnitude of the shift values obtained with the automatic registration software, including both the rest and the stress exams, was 14.31 mm, which is greater than the average magnitude of the shift values obtained with manual

registration for the rest and stress exams, which was 12.45 mm. Tables 5.8 and 5.9 show the maximum shifts assigned by the users in the x, y, and z planes for the rest and stress exams, respectively. Tables 5.10 and 5.11 show the difference in the shift values obtained using our automated registration software and the shift values obtained by averaging the shift values from the four users. Tables 5.12 and 5.13 show the difference in the shift values obtained using the automatic registration software and the maximum shift values from the four users. The Euclidean shift value given in each table characterizes the overall effect of the three shift values.

Exam	X (mm)	Y (mm)	Z (mm)	Euclidean (mm)
1	-8.0	-2.0	-18.8	20.5
2	7.0	-6.0	11.3	14.5
3	-12.0	-3.0	-15.0	19.4
4	-3.0	0.0	-11.3	11.6
5	-7.0	1.0	-11.3	13.3
6	-11.0	-3.0	-15.0	18.8
7	-7.0	0.0	-7.5	10.3
8	-6.0	-3.0	0.0	6.7
Avg.	-5.88	-2.00	-8.44	14.40

Table 5.4: Shift values obtained using our automated software applied to the PET/CT data collected during the rest exam.

Table 5.5: Shift values obtained using our automated software applied to the PET/CT data collected during the stress exam.

Exam	X (mm)	Y (mm)	Z (mm)	Euclidean (mm)
1	-5.0	4.0	-15.0	16.3
2	25.0	-6.0	22.5	34.2
3	-4.0	0.0	-11.3	11.9
4	-3.0	2.0	-7.5	8.3
5	-6.0	2.0	-7.5	9.8
6	0.0	0.0	-15.0	15.0
7	-4.0	-1.0	-11.3	12.0
8	-5.0	0.0	-3.8	6.3
Avg.	-0.25	0.13	-6.09	14.22

Exam	X (mm)	Y (mm)	Z (mm)	Euclidean (mm)
1	-7.0	-3.2	-11.1	13.5
2	-0.4	-2.4	4.8	5.5
3	-8.8	-5.3	-12.0	15.8
4	-7.2	-1.1	-3.4	8.0
5	-9.4	-1.5	-3.8	10.3
6	-13.6	-6.4	-5.2	15.8
7	-6.6	-0.8	-2.4	7.0
8	-11.0	-1.6	0.6	11.2
Avg.	-8.00	-2.78	-4.04	10.89

Table 5.6: Average shift values obtained from four users using manual alignment applied to the PET/CT data collected during the rest exam.

Table 5.7: Average shift values obtained from four users using manual alignment applied to the PET/CT data collected during the stress exam.

Exam	X (mm)	Y (mm)	Z (mm)	Euclidean (mm)
1	-11.9	-3.4	-9.0	15.3
2	19.9	-1.4	19.9	28.2
3	-10.7	-6.8	-7.2	14.7
4	-10.0	-3.2	-4.8	11.6
5	-9.2	0.1	-3.2	9.7
6	-9.1	-6.7	-7.9	13.8
7	-7.7	0.0	-3.4	8.4
8	-10.5	-0.1	0.1	10.5
Avg.	-6.15	-2.73	-1.92	14.01

Exam	X (mm)	Y (mm)	Z (mm)	Euclidean (mm)
1	-7.3	-7.9	-12.8	16.7
2	-2.4	0	9.1	9.4
3	-11	-8.5	-14	19.7
4	-11.6	0	-2.4	11.8
5	-11.6	-6.1	-6.1	14.5
6	-20.1	-4.9	-0.6	20.7
7	-7.9	0	-3.5	8.6
8	-12.1	-2.3	-3.3	12.8
Avg.	-10.5	-3.7	-4.2	14.3

Table 5.8: Maximum shift values obtained from four users using manual alignment applied to the PET/CT data collected during the rest exam.

Table 5.9: Maximum shift values obtained from four users using manual alignment applied to the PET/CT data collected during the stress exam.

Exam	X (mm)	Y (mm)	Z (mm)	Euclidean (mm)
1	-14	-9.7	-7.3	18.5
2	24.8	-1.9	20	31.9
3	-14.9	-8.6	-3.5	17.6
4	-12.2	-4.3	-5.5	14.1
5	-11	-1.8	-3	11.5
6	-12.1	-7.3	-8.2	16.3
7	-11	0	-1.2	11.1
8	-11.6	0	0	11.6
Avg.	-7.75	-4.20	-1.09	16.58

Exam	X (mm)	Y (mm)	Z (mm)	Euclidean (mm)
1	1.00	1.20	7.65	7.8
2	7.45	3.55	6.40	10.4
3	3.18	2.33	2.98	4.9
4	4.18	1.08	7.90	9.0
5	2.43	2.53	7.45	8.2
6	2.55	3.38	9.85	10.7
7	0.45	0.75	5.10	5.2
8	5.05	1.43	0.63	5.3
Avg.	3.28	2.03	5.99	7.70

Table 5.10: Difference in the shift values between the automatically registered and the average manual shifts in the rest exams.

Table 5.11: Difference in the shift values between the automatically registered and the average manual shifts in the stress exams.

Exam	X (mm)	Y (mm)	Z (mm)	Euclidean (mm)
1	6.88	7.35	6.03	11.7
2	5.10	4.63	2.63	7.4
3	6.73	6.88	4.00	10.4
4	7.03	5.23	2.75	9.2
5	3.20	1.90	4.35	5.7
6	9.13	6.70	7.05	13.3
7	3.68	1.00	7.88	8.8
8	5.50	0.08	3.83	6.7
Avg.	5.90	4.22	4.81	9.15

Exam	X (mm)	Y (mm)	Z (mm)	Abs. Euc (mm)
1	0.7	5.9	5.95	8.4
2	9.4	6	2.15	11.4
3	1.0	5.5	1	5.7
4	8.6	0	8.85	12.3
5	4.6	7.1	5.15	9.9
6	9.1	1.9	14.4	17.1
7	0.9	0	4	4.1
8	6.1	0.7	3.3	7.0
Avg.	5.05	3.39	5.60	9.49

Table 5.12: Difference in the shift values between the automatically registered and the maximum manual shifts in the rest exams.

Table 5.13: Difference in the shift values between the automatically registered and the maximum manual shifts in the stress exams.

Exam	X (mm)	Y (mm)	Z (mm)	Euclidean (mm)
1	9.0	13.7	7.7	18.1
2	0.2	4.1	2.5	4.8
3	10.9	8.6	7.75	15.9
4	9.2	6.3	2	11.3
5	5.0	3.8	4.5	7.7
6	12.1	7.3	6.8	15.7
7	7.0	1	10.05	12.3
8	6.6	0	3.75	7.6
Avg.	7.50	5.60	5.63	11.68

6 Discussion

The ability of positron emission tomography (PET) to depict the metabolic activity variations between healthy and affected areas of the brain has greatly improved the accuracy of detecting and staging different neurological disorders including Parkinson's disease, neurodegenerative disease, epilepsy, etc. [85-86]. However, due to the low resolution of PET scans and the lack of anatomical details, the localization of abnormalities becomes a big challenge. Some of these details can be estimated through the tracer uptake in various anatomical structures, but these are not comparable to the fine details provided by other imaging techniques such as computed tomography (CT) [87-90]. To address this, the fusion of functional and anatomical imaging is used for many clinical applications.

A problem that is inherent to hybrid PET/CT imaging of the brain is patient motion during data acquisition. The patients suffering from neurological disorders are often incapable of following verbal instructions and are more likely to shift the position of their head during the exam. Head restraints are used is some cases, but these are not sufficient to eliminate the head motion completely.

In cardiac studies, even if other physical motion of the patient is constrained, physiological movement of the organs during the respiratory cycle due to the motion of the diaphragm cannot be prevented. A recent study by Gould *et al.* (2007) at the Weatherhead PET center for preventing and reversing atherosclerosis showed that 40% of PET/CT exams contain a hypoperfusion artifact that is caused by misregistration between the two modalities [5]. Misregistration has a greater effect on the anterior and anterolateral

segments of the PET heart, producing a significant reduction in the measured uptake in these areas. This is due to the large difference in the attenuation parameters of cardiac and lung tissue and the fact that the anterior and lateral segments have the largest common surface with the lungs, whereas the septal and inferior walls are in contact with other soft tissue (right ventricle, liver, etc.). Thus, misalignment less frequently produces significant errors in the attenuation factors for these other areas.

One approach to address the PET/CT misalignment problem is to obtain multiple CT scans. The PET images are matched with the CT images, and the CT with the smallest registration error is selected for PET attenuation correction. This method does not guarantee consistent alignment between PET and CT images, and in some cases, none of the CT scans align with the PET data, which introduces metabolic or perfusion artifacts into the reconstructed PET images.

Another possible approach is to reduce the temporal resolution of the CT to match that of the PET examination. This is achieved with an ultraslow CT acquisition or a respiration-averaged CT. These approaches can reduce the breathing-induced misalignment at the expense of increased radiation dose for the patient or longer acquisition times. However, misalignment resulting from other sources, e.g., patient motion or changes in the heart location due to pharmacologic stress agents, remains uncorrected with this approach. The inconsistent alignment between the PET and CT data reinforces the need for image registration software that can automatically align the two modalities and generate a CTAC that completely overlaps with the PET data. In the brain studies, the registration of the PET and CT data is a linear procedure that is limited only to translation and rotation. When linear transformations are applied to the misaligned CT, the size and shape of the

brain remains unchanged, which makes the alignment process much easier. The image registration in cardiac PET/CT exams is more complex, where nonlinear transformations are needed when the heart contracts, expands, and rotates nonlinearly. In such cases, data warping or deformation algorithms can also be required for accurate alignment.

PET/CT brain registration utilizes 6 degree of freedom (DOF) linear transformations, which means that the segmented brain geometry obtained from the CT data is translated and rotated with respect to the x, y, and z axes to correct any misalignment of the head that occurs during the exam. These include shifts and rotations in the sagittal, coronal, and the axial planes, where the rotations are with respect to the x, y, and z axes, respectively. The results from multiple case studies indicate that most of the translational misregistration is along the x and z axes, whereas little or no misalignment occurs along the y axis. The reason that no y-axis misalignment occurs is that, for this type of motion, the patient has to lift his or her head from the bed which, in most cases, is restricted using a restraining band on the forehead. The source of rotational misregistration is that the patient's head is mostly rotated either in a 'yes' motion or a 'no' motion. The third type of rotation, where the head rotates around the y-axis (or towards the shoulders), is rarely observed in any of the patient data.

6.1 Effects of Overcorrection

A large CTAC shift does not always result in a significant difference in the reconstructed images [91]. In the example below, the initial CTAC demonstrated severe misalignment (one of the largest misalignments in any of the studies), which was most likely caused by patient motion. The PET activity was initially aligned right and inferior of the left ventricle

in the CTAC images. Since the PET heart was initially positioned over soft tissue, this provided similar attenuation correction to that of cardiac tissue. Therefore, the artifacts were not as significant as the hypo-perfusion artifacts created when the left ventricle activity is superimposed over the lung in the CTAC. However, in this example, there was still a difference of 7% in the lateral polar plot region. Figures 6.1 (a) and (b) show the misaligned PET and CT images in the axial and coronal planes, and Figures 6.1 (c) and (d) show the same images after alignment. Figures 6.2 (a) and (b) show the polar plots of the PET images generated before and after alignment. Fig. 6.3 shows the difference between the two polar plots. The difference plot shows that, even though the error in the PET data reconstructed with the misaligned CTAC is noticeable, these are much smaller than the errors caused when the PET heart overlaps with the lung in the CT image.



(a)



(b)



(C) R 1 50 % PET (d)

Figure 6.1: PET cardiac region overlaid onto (a) the misaligned CTAC in the axial plane, (b) the misaligned CTAC in the coronal plane, (c) the aligned CTAC in the axial plane, and (d) the aligned CTAC in the coronal plane.



Figure 6.2: Polar plot of the reconstructed PET data generated using the (a) misaligned CTAC and (b) the aligned CTAC. The comparison shows that attenuation artifacts were present in the PET data reconstructed using the misaligned CTAC.



Figure 6.3: Polar plot of the difference between the PET data reconstructed using the misaligned CTAC and the aligned CTAC shows that even though there was a significant misalignment between the PET and CT data, the error in the reconstructed PET data is much smaller than the errors caused when the PET heart overlaps with the lung in the CT image.

6.2 Heart and Lung Volume Correlation

To find the diastolic phase among the ten different phases within which the CT is gated, all of the phases are compared with respect to the number of pixels in the lungs, and the CT dataset with the smallest number of pixels within the lungs is chosen to represent the diastolic phase where the heart is the largest. This is because the CT is acquired in a breath-held state, so the difference in the size of the lung is caused by the change in the size of the heart. PET/CT registration results are generated with all of these phases, and the shift values are calculated for each of the datasets. The shifts required for each of these datasets is then analyzed to find the CT phase that maximally overlaps the PET image in the cardiac region.

After all of the datasets are analyzed, the correlation between the changes in the heart volume and the corresponding changes in the lung volume during the cardiac cycle is determined. Due to the very high contrast between the lung and all of the other organs, automatic and efficient segmentation of the lung is achieved much more easily than automatic segmentation of the heart. Once the lung is segmented, the volume of the lung within each cardiac phase is calculated for every patient and then is compared to the heart volume. Fig. 6.4 shows that the volume of the lung and the heart is consistently correlated within different phases. For most patients, the volume of the heart is maximized at the 70% phase, and the lung volume is minimized at this phase. The opposite holds for the 30% phase. Due to this consistent relationship between the lung volume and the heart volume, the lung segmentation results can be used to efficiently estimate the diastolic phase. Fig. 6.5 shows a scatter plot of the heart contours at the systolic phase and at the diastolic phase. The blue dots represent the contours of the heart at systole,

and the green dots represent the contours of the heart at diastole. As shown in Fig. 6.5, the size of the heart is much larger in the diastolic phase.



Figure 6.4: Normalized volumes of the heart and lung within different cardiac phases using the values calculated from segmented CT data.



Figure 6.5: Contours of the heart in the 30% cardiac phase, which corresponds to systole, and the 70% cardiac phase, which corresponds to diastole. The systolic cardiac volume shown in blue is significantly smaller than the diastolic cardiac volume shown in green.

6.3 Attenuation-Corrected and Non Attenuation-Corrected Data

Automatic segmentation and registration is applied to the attenuation corrected (AC) PET images as opposed to the non-attenuation corrected (NAC) PET images which are less homogeneous due to differential attenuation of the brain region and due to the higher noise factor. The problem, however, with the AC PET data is the inherent hypometabolism artifact that can be present in the attenuation correction with a misregistered CTAC. To ensure the robustness of the brain segmentation results and to uncover any bias present in the segmented brain boundary due to a possible hypo-metabolized brain region, both the AC and the NAC PET data are segmented in all patients with hypo-

metabolic artifacts. The results show that a consistent brain boundary is generated for both the NAC and the AC PET data. The pixel intensities for the hypo-metabolized region, which are lower than those for the normal brain region, still have sufficient contrast with the air and bone intensities to ensure correct boundary detection for the brain. The segmented brain contours using the hypo-metabolized PET images show no bias due to the inherent hypo-metabolic artifact. For all of the patients with misregistered PET/CT images, the reconstructed PET images using the registered CTACs are again processed with the automated registration software, and the two images consistently align correctly.

6.4 Hyper-perfusion Artifact

In one exam, the PET data showed abnormally high blood perfusion in the left ventricle, which was caused by calcification in the heart. The CT attenuation map used for PET image reconstruction also showed calcification in the heart. When this occurs, the attenuation parameter for bone is assigned to this region, resulting in erroneous overcorrection. Fig. 6.6 (a) shows a CT image in the axial plane in which the bright region within the left ventricle represents the calcification. Fig. 6.6 (b) shows the corresponding PET slice with artifactual hyperperfusion after reconstruction.





Figure 6.6: Calcification in the heart (a) is observed in the CT slice in the axial plane, and (b) causes a hyperperfusion artifact in the reconstructed PET slice.

7 Summary and Future Work

The work of this Ph.D. thesis is summarized below along with a list of improvements that are expected to further enhance PET/CT image reconstruction.

7.1 Summary

Single gantry hybrid PET/CT imaging systems provide noninvasive assessment of functional information as well as structural detail. The main advantage of PET/CT imaging over the use of PET transmission attenuation correction maps for image reconstruction is the shorter overall acquisition time resulting in greater patient throughput. In a traditional standalone PET system, the time required to obtain the transmission map is about 30-40% of the total scan time, which is on the order of several minutes. In contrast, CT scans for attenuation correction are acquired in a few seconds. Another advantage of CT based attenuation correction is the lower noise level in CT images than in traditional transmission scans, resulting in reconstructed PET images with higher signal to noise ratios.

A common pitfall of PET/CT imaging is the potential mismatch between the position of the heart in the PET and the CT data. One of the reasons for this mismatch is patient motion. The PET images are acquired several minutes after the CT scan, providing the opportunity for significant patient motion. Even if the patient manages to stay still during the entire image acquisition process, physiologic respiratory motion can cause misregistration between the PET and the CT data. This misregistration can significantly affect the reconstructed PET image by projecting erroneous CT attenuation parameters

onto the PET data, thereby creating false areas of low or high tracer uptake that can increase the chances of diagnostic misinterpretation.

One approach to address the PET/CT image misalignment problem is to obtain multiple CT scans, but this method does not guarantee accurate alignment of PET images with any of the acquired CTACs. Also, multiple CT acquisitions cause unnecessary radiation exposure in the patient. Another approach is to manually align all of the PET/CT exams, which is quite time-consuming and can vary depending on the subjective judgement of the operator.

A better solution to this problem is provided by a software program that automatically registers the two modalities to eliminate the attenuation artifacts from the reconstructed PET data. This software-based method aligns the PET and CT data by calculating the distance between the cardiac boundaries of the PET and CT data. An aligned CT attenuation correction (CTAC) map is generated using the shift values obtained from PET/CT image registration. The PET images are then reconstructed using the shifted CT data. Tests on PET/CT images from several patients were performed to ensure the consistency of the automated registration software in aligning the two modalities and eliminating the attenuation artifacts. Results show that only one CT scan is required for each patient and that the registered CT attenuation map successfully generates artifact-free PET images. By acquiring only one CT scan for PET data reconstruction, the radiation dose delivered to the patient is minimized, and an efficient clinical workflow is achieved.

7.2 Contributions

This thesis makes the following contributions to PET/CT imaging:

- Automated software was created for the registration of volumetric PET/CT data in order to remove artifactual attenuation defects from reconstructed PET images. The software ensures a minimal radiation dose for the patients by eliminating the need for multiple CT acquisitions.
- Multiple respiratory phases were evaluated for the CT images to determine the phase which consistently gives better alignment than the other phases.
- The software was validated for all the respiratory phases with automated respiratory motion compensation of the heart to accurately align the PET and CT cardiac geometries.
- The optimal cardiac phase of the CT images that maximally overlap with the cardiac region in the PET images was estimated. To ensure that the cardiac region in the PET images completely overlaps the cardiac region in the CT images, the CT images must be acquired in the diastolic phase. Analysis shows that the 70% phase corresponds to diastole and is optimal for the reconstruction of PET data.
- GE Discovery STE compatible DICOM images of the aligned CTAC were generated with our registration software to reconstruct PET images for efficient clinical workflow and minimum manual intervention.

- Non-attenuation corrected (NAC) PET data and the pre-attenuation corrected (AC)
 PET data were analyzed to identify any inherent bias in the segmentation process.
- The automated image segmentation/ registration was validated against the manual alignment performed independently by multiple technicians on the same datasets in a comprehensive study.
- A multi-slice to polar map transformation of the left ventricle data was performed to give a better representation of the condition of the heart.

7.3 Future Work

Some of the aspects that can be explored in the future are discussed below.

7.3.1 Dual Gating for PET Data Acquisition

Data acquisition for the PET scans takes several minutes wherein the readings are averaged over multiple cardiac and respiratory cycles, which causes blurring of the image data resulting in reduced spatial resolution. To minimize this problem, simultaneous respiratory and cardiac gating should be performed.

List-mode data should be associated with the triggers from respiratory and cardiac cycles and then reconstructed after compensating for the two types of motions. During a cardiac cycle, there is a significant change in size as the heart goes from systole to diastole, and during the respiratory motion of the patient, the heart can be displaced up to 2 cm due to the movement of the diaphragm. This translation and deformation of the heart results in blurring of the data due to the overlapping of different parts of the heart acquired at different times. The blurring of the data restricts the use of PET/CT images for small defects. If all of the transformations are compensated before averaging the data points, then sharper images can be acquired in which minute defects can also be detected and analyzed.

7.3.2 Left Ventricle Deformation Correction

In addition to the translation of the heart during the respiratory cycle and the change in the size of the heart during the cardiac cycle from systole to diastole, the heart walls also go through a non-linear warping [92], as shown in Fig. 7.1. Due to this warping, corresponding points on the surface of the heart wall appear at significantly different locations in the three dimensional image space. The uncompensated averaging of the PET data produces an erroneous averaged value for each location in the heart. In order to average the exact physical points of the heart over time, compensation for the deformation that the heart undergoes in a cardiac cycle is also needed. Depending on the cardiac region to correlate all of the corresponding points at different acquisition times. After compensating for the deformation, the volumetric data can be averaged together in order to obtain the correct intensity values at all points in the heart. Fig. 7.1 shows the left ventricle at two different phased of the cardiac cycle in which the corresponding points of the heart do not overlap with each other.



Figure 7.1: Transformation of the left ventricle during the cardiac beat cycle where (a) shows two point on the myocardial wall, and (b) shows that the same points do not overlap when the cardiac wall is warped.

7.3.3 Estimation of Myocardial Blood Perfusion

Noninvasive measurements of myocardial blood flow are difficult to accomplish because of the low spatial resolution of currently available systems [93]. The quantification of blood flow is important in estimating the condition of the heart. If the flow to the heart is insufficient, this can result in myocardial ischemia, which in turn can lead to infarction. With a contrast agent, tracer kinetic models can be used to estimate the regional blood flow, but this can only be achieved with high temporal resolution. Due to the low spatial resolution of the PET scanners, the physiological motion of the heart during the cardiac and respiratory cycles significantly degrades the quality of the image which limits the accuracy of the quantitative studies for myocardial blood perfusion. If the deformations of the heart are accurately compensated as mentioned in the previous sections, the kinetic models can be helpful in the estimation of the blood flow. A graphical user interface for viewing and analyzing PET data in different planes and in polar map form is shown in Fig. 7.2.



Figure 7.2: Graphical interface for viewing cardiac PET data and for generating and analyzing the polar maps.

Fig. 7.3 shows the polar maps generated using the PET data acquired at different times during the dynamic study. The intensity values at the corresponding locations in all of the polar maps can be used in a kinetic model to estimate tissue parameters.



Figure 7.3: Polar maps of the cardiac data acquired at different times.

7.4 Papers Written

- 1. K. Khurshid, K. L. Berger, R. J. McGough, "Respiratory Cardiac Motion Compensation in PET/CT for Accurate Reconstruction of PET Myocardial Perfusion Images", Journal of Physics in Medicine and Biology (PMB), 53(20):5705:5718, 2008.
- K. L. Berger, J. L. Seamans, K. Khurshid, E. Philps, R. J. McGough "CTAC Misregistration in PET/CT Cardiac Imaging: Correction with a Dedicated CTAC/PET Alignment Visualization Application, an Automated Registration Algorithm, and ECG-Gated CTAC", American Society of Nuclear Cardiology, Journal of Nuclear Cardiology, 2007, Vol. 14 Issue 4, pS105.
- 3. D. J. VanderLaan, K. Khurshid, J. J. Ireland, F. J. Krassel, R. J. McGough, "Automated follicle segmentation in ultrasound scans of bovine ovaries", Journal of Applied Electromagnetics and Mechanics (AEM), 28(2):49:54, 2008.
- 4. K. Khurshid, W. Liyong, K. L. Berger, R. J. McGough, "PET/CT Misregistration Attenuation Correction Artifact Eliminated by Least Squares Cardiac Alignment" Academy of Molecular Imaging (AMI), USA, March 2006.
- 5. K. Khurshid, K. L. Berger, R. J. McGough, "Automated PET/CT Cardiac Registration for Accurate PET Reconstruction" IEEE Electro Information Technology (EIT), USA, May 2006.
- 6. K. Khurshid, K. L. Berger, R. J. McGough, "Analysis of Multiple Cardiac Phases of CT for Maximal Overlap with PET Images", International Symposium on Applied Electromagnetics and Mechanics (ISEM), USA, Sept. 2007.
- 7. K. Khurshid, K. L. Berger, R. J. McGough, "Automated PET/CT Brain Registration for Accurate Attenuation Correction", Engineering in Medicine and Biology Society (EMBS), USA, 2009.
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