Respiratory Motion Correction in Positron Emission Tomography

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Trinity Term 2010
This thesis is submitted to Department of Engineering Science, University of Oxford, in partial fulfilment of the requirements for the degree of Doctor of Philosophy. The thesis is entirely my own work, and except where otherwise stated, describes my own research.

Wenjia Bai, Wolfson College, Oxford

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Abstract

In this thesis, we develop a motion correction method to overcome the degradation of image quality introduced by respiratory motion in positron emission tomography (PET), so that diagnostic performance for lung cancer can be improved. Lung cancer is currently the most common cause of cancer death both in the UK and in the world. PET/CT, which is a combination of PET and CT, providing clinicians with both functional and anatomical information, is routinely used as a non-invasive imaging technique to diagnose and stage lung cancer. However, since a PET scan normally takes 15-30 minutes, respiration is inevitable in data acquisition. As a result, thoracic PET images are substantially degraded by respiratory motion, not only by being blurred, but also by being inaccurately attenuation corrected due to the mismatch between PET and CT. If these challenges are not addressed, the diagnosis of lung cancer may be misled.

The main contribution of this thesis is to propose a novel process for respiratory motion correction, in which non-attenuation corrected PET images (PET-NAC) are registered to a reference position for motion correction and then multiplied by a voxel-wise attenuation correction factor (ACF) image for attenuation correction. The ACF image is derived from a CT image which matches the reference position, so that no attenuation correction artefacts would occur. In experiments, the motion corrected PET images show significant improvements over the uncorrected images, which represent the acquisitions typical of current clinical practice. The enhanced image quality means that our method has the potential to improve diagnostic performance for lung cancer.

We also develop an automatic lesion detection method based on motion corrected images. A small lung lesion is only 2 or 3 voxels in diameter and of marginal contrast. It could easily be missed by human observers. Our method aims to provide radiologists with a map of potential lesions for decision so that diagnostic efficiency can be improved. It utilises both PET and CT images. The CT image provides a lung mask, to which lesion detection is confined, whereas the PET image provides distribution of glucose metabolism, according to which lung lesions are detected. Experimental results show that respiratory motion correction significantly increases the success of lesion detection, especially for small lesions, and most of the lung lesions can be detected by our method. The method can serve as a useful computer-aided image analysing tool to help radiologists read images and find malignant lung lesions.

Finally, we explore the possibility of incorporating temporal information into respiratory motion correction. Conventionally, respiratory gated PET images are individually registered to the reference position. Temporal continuity across the respiratory period is not considered. We propose a spatio-temporal registration algorithm, which models temporally smooth deformation in order to improve the registration performance. However, we discover that the improvement introduced by temporal information is relatively small at the cost of a much longer computation time. Spatial registration with regularisation yields similar results but is superior in speed. Therefore, it is preferable for respiratory motion correction.
Acknowledgements

Firstly, I am very grateful to my supervisor Professor Sir Michael Brady, for his support and guidance over the course of my D.Phil. He is always full of energy, very happy to share his academic and life experiences, and super fast to read manuscripts and reply to emails and questions. He has given me not only a cutting-edge research topic, but also the freedom to do what I like to do. When I come across difficulties, he is always there to help. I would like to thank UK-China Scholarships for Excellence, Siemens Molecular Imaging Oxford, and Henry Lester Trust for funding me.

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Finally, I am extremely grateful to my family, my mother Chunmei Zhang, my father Shuangbao Bai, and my beloved wife Yingsong Zhang, for their endless support over all these years!
Related Publications

Journal Papers

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Conferences Papers

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2. Bai W. and Brady M., Motion correction and attenuation correction for respiratory gated PET images, Medical Imaging Understanding and Analysis 2010, Warwick, UK, pp:253-257.


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ITK     Insight Segmentation and Registration Toolkit
MAP     maximum a posteriori
MBF     myocardial blood flow
ML-EM   maximum likelihood expectation-maximisation
MRD     maximum ring difference
MRF     Markov random field
MRI     magnetic resonance imaging
NCAT    NURBS-based cardiac torso phantom
NMR     nuclear magnetic resonance
NSCLC   non-small cell lung cancer
NURBS   non-uniform rational basis spline
OS-EM   ordered subset expectation-maximisation
PA      posteroanterior
PD      proton density
PET     positron emission tomography
PET-AC  attenuation corrected PET
PET-NAC non-attenuation corrected PET
PET-SORTEO the name of a PET simulator developed by Anthonin Reilhac et al.
PMT     photomultiplier tube
PSF     point spread function
PTV     planning target volume
PVE     partial volume effect
RF      radio frequency
ROC     receiver operating characteristic
ROI     region-of-interest
RPM     real-time position management
RT      radiation therapy
SCLC    small cell lung cancer
SNR     signal-to-noise ratio
STIR    Software for Tomographic Image Reconstruction
SUV     standardised uptake value
Sv      sievert
TAC     time-activity curve
TNM     tumour, node and metastasis staging system
TP      true positive
WMVL    Wolfson Medical Vision Laboratory
XCAT    extended cardiac torso phantom
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Chapter 1

Introduction

1.1 Positron Emission Tomography (PET)

Positron emission tomography (PET) is a molecular imaging technique which provides in vivo images of biological processes in the human body. It is now widely established as a powerful tool for diagnosing, staging, and restaging a variety of cancers [109, 164]. It is also widely used to diagnose and evaluate neurological disorders [32, 190] and cardiovascular diseases [109], to monitor therapeutic responses [130, 177], and to guide treatment planning in radiation therapy [54, 116].

PET involves intravenous injection of a radioactive tracer into the human body. The radioactive tracer is essentially a compound of interest that is labelled with a positron emitting isotope, such as $^{18}$F, $^{15}$O, $^{11}$C, or $^{64}$Cu. A number of radiotracers have been developed to reveal different aspects of the biological processes of interest. Some commonly used radiotracers are listed in Table 1.1.

Among all these radiotracers, $^{18}$F-fluorodeoxyglucose ($^{18}$FDG) is the one that is most commonly used in clinical PET imaging. $^{18}$FDG is an analogue of glucose. Just like glucose, it is transported into cells by glucose transport proteins (GLUT) and then phosphorylated by hexokinase. Normally, phosphorylated glucose continues along the pathway of glycolysis for energy production. However, phosphorylated FDG can not undergo glycolytic breakdown and becomes trapped in cells. As a result, $^{18}$FDG can be used as a marker to show the distribution of glucose metabolic activity in PET imaging.
Table 1.1: Some commonly used PET radiotracers. This table is adapted from [159, 190].

<table>
<thead>
<tr>
<th>Tracer</th>
<th>Biological process</th>
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<tr>
<td>$^{18}$FDG</td>
<td>Glucose metabolism</td>
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<tr>
<td>$^{18}$FMISO</td>
<td>Hypoxia</td>
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<tr>
<td>$^{64}$Cu-ATSM</td>
<td>Hypoxia</td>
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<tr>
<td>$^2$H$^{15}$O</td>
<td>Blood flow</td>
</tr>
<tr>
<td>$^{18}$F-dopa</td>
<td>Dopamine storage</td>
</tr>
<tr>
<td>$^{11}$C-methionine</td>
<td>Cellular amino acid uptake</td>
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Because cancer cells grow and divide more rapidly than normal cells, they metabolise more glucose for energy. The increased glucose uptake of these cancer cells can then be identified and localised in $^{18}$FDG-PET images.

A metric commonly used to interpret a PET image is the standardised uptake value (SUV) [77]. It is intended to represent the radiotracer uptake corrected for other factors such as the injected dose and body weight, and it is formulated as follows:

$$SUV = \frac{\text{radiotracer concentration}}{\text{injected dose/body weight}}$$  \hspace{1cm} (1.1)

For lung lesions, an empirical SUV threshold of 2.5 has been suggested to differentiate malignant and benign lesions [139, 164]. This threshold should be used with caution, especially for small lesions. Due to the partial volume effect (PVE), the intensity of a small lesion tends to be underestimated [187], which means a small lesion with a SUV less than 2.5 is very likely to be malignant. Besides, the image reconstruction method and the SUV measurement method also have a great impact on the measured SUV.

Although PET reveals valuable functional information in the human body such as the distribution of glucose metabolism, the information it provides is currently limited, not least by its poor spatial resolution. Most PET scanners available in medical centres have a spatial resolution of approximately 5 mm full width at half maximum (FWHM), though the recently launched state-of-the-art high definition (HD) PET achieves a reso-
olution of 2 mm FWHM. Because of its relatively poor spatial resolution, PET is normally combined with computed tomography (CT), which provides detailed anatomical information in an excellent spatial resolution of less than 1 mm FWHM. Another benefit of PET combined with CT is that the CT can be used for attenuation correction of the PET data, which makes PET and CT usefully complementary. In thoracic imaging, however, due to respiratory motion, the CT scan does not align with the PET data and thus poses a challenge for accurate attenuation correction. This challenge will be further discussed in Section 1.4 of this chapter.

Figure 1.1 and 1.2 respectively show a Siemens Biograph PET/CT scanner and some images acquired using the scanner. Currently, PET/CT is routinely used in clinical diagnosis to provide both functional and anatomical information, significantly increasing diagnostic accuracy compared to using PET or CT alone [5, 35].

1.2 Lung Cancer

Lung cancer is currently the most common cause of cancer deaths both in the UK and in the world [132, 200]. Every year in the UK, around 34,500 people die from lung
Figure 1.2: PET and CT images acquired from a Siemens Biograph PET/CT scanner. The coronal view (X-Z plane) is shown. A lung tumour is indicated by the arrow. The tumour is highlighted in the PET image as a result of the accumulated FDG concentration, whereas the anatomy of the lungs is clearly shown in the CT image. Image courtesy of Maastro Clinic, Netherlands.

cancer, that is around 95 per day. Worldwide, lung cancer accounts for around 1.3 million deaths each year. Tobacco use is the single most important risk factor for lung cancer.

Lung cancer is mainly divided into two types: small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC) [202]. Both are thought to be carcinoma, i.e. solid tumours that are derived from epithelial cells. Small cell lung cancer is so called because the cancer cells are very small under a microscope, mostly filled with the nucleus. On the contrary, for non-small cell lung cancer, the cancer cells are not so small. Figure 1.3 compares the microscopic images of the two types of lung cancers. Non-small cell lung cancer is the more common form, accounting for about 80% of lung cancers. It is further divided into three subtypes: squamous cell carcinoma, adenocarcinoma, and large cell carcinoma. These are grouped together as NSCLC because they have a similar prognosis and treatment management. Common symptoms of lung cancer include chronic coughing or change in regular coughing pattern, coughing up blood, chest pain, fatigue, loss of appetite, losing weight, etc.

Some cancers in the lungs are metastases from other parts of the body. Cancer cells
Figure 1.3: Comparison of the microscopic images of small cell lung cancer and non-small cell lung cancer. (a) Small cell carcinoma, showing cells with high nuclear-cytoplasmic ratios; (b) Squamous cell carcinoma, showing nests and cords of neoplastic cells. Squamous cell carcinoma is a type of non-small cell lung cancer. The figures are taken from [15].

Figure 1.4: The venous systems of most tissues drain to the right side of the heart and thereafter into the capillary bed of the lungs. The veins draining the spleen and gut first empty into the liver via the portal circulation and then goes to the heart. The figure is reproduced from [211].
Table 1.2: Lung cancer survival rates (unit: %). This table is taken from [125].

<table>
<thead>
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<th>Clinical stage (number of cases)</th>
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<td>IA (n=687)</td>
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<td>IIIB (n=1,030)</td>
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<td>IV (n=1,427)</td>
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are spread through the bloodstream or lymphatic system from a primary tumour to other sites of the body. As Figure 1.4 shows, the venous systems of most tissues drain to the right side of the heart and thereafter into the capillary bed of the lungs [211]. As a result, the lungs become a common site for metastasis. Common cancers that spread to the lungs include bladder cancer, breast cancer, colon cancer, neuroblastoma, prostate cancer, sarcoma, and Wilm’s tumour [147]. However, almost any cancer has the ability to spread to the lungs. These secondary cancers are classified according to the site of origin. For example, breast cancer that has spread to the lungs remains breast cancer and responds to breast cancer treatment.

Lung cancer staging is an assessment of the extent of the cancer. The stage is usually defined using the tumour, node and metastasis (TNM) system [125]. It accounts for the degree of spread of the primary tumour (T), the extent of regional lymph node involvement (N), and the presence or absence of distant metastasis (M). For example, a T1N1M0 cancer means the patient has a T1 tumour (i.e. tumour ≤ 3 cm), N1 lymph node involvement, and no distant metastasis. According to the TNM descriptor, lung cancer is classified into stages from 0 to IV. The larger the number, the more advanced the stage is. Details of the TNM staging system are given in Appendix A.

The prognosis for patients with lung cancer is strongly correlated to the stage of the disease at the time of diagnosis. Whereas patients with clinical Stage IA lung cancer
have a 5-year survival rate of 61%, those with clinical Stage IIIB lung cancer only have a 5-year survival rate of 5%. Table 1.2 lists the survival rates against the stages. It shows that the survival rate is higher when the cancer is diagnosed earlier. However, unfortunately, over two-thirds of lung cancer cases are diagnosed at an advanced stage when curative treatment is not possible. Overall, less than 10% of lung cancer patients survive the disease after 5 years of treatment. Therefore, early detection of lung cancer is critical for improving the survival rate.

1.3 PET in Lung Cancer Studies

A CT scan or a radiograph of the chest is the first step for lung cancer diagnosis when patients report symptoms. A common finding is lesions, i.e. abnormalities, in the lungs. A lesion is often called a nodule if it is smaller than 3 cm. Otherwise, it is called a mass. The lesion can be caused either by lung cancer, or by some non-malignant diseases, such as tuberculosis, pneumonia, or inflammation. For example, studies show that many of the pulmonary nodules are benign and only around 20% are malignant, i.e. cancerous. Whether a lesion is benign or malignant must be addressed before any subsequent treatment is planned.

The malignancy of some lesions may be assessed by their morphological features. But in many cases shape and intensity information are insufficient to distinguish benign and malignant lesions. Needle biopsy or thoracoscopic surgery can be used to directly evaluate the malignancy of a lesion. However, either the patient or the referring clinician is hesitant about such invasive procedures and the associated risks and potential complications. As a result, traditionally, diagnosis of a lung lesion is established through radiological evaluation of follow-up CT scans or radiographs. It takes at least 3-6 months after the initial detection of a pulmonary node to demonstrate the potential malignancy through its growth.

Because FDG-PET is non-invasive and is able to identify malignant lesions which are associated with increased glucose metabolism, it has been shown to be a very useful addition to CT in evaluation of lung lesions. Most non-small cell lung cancers
accumulate FDG, therefore appear bright on PET images. The functional information provided by PET can be well combined with the accurate anatomical information provided by CT, leading to more accurate diagnosis [22]. It has already been shown that combined PET/CT significantly increases diagnostic accuracy compared to PET or CT alone [5, 35, 205, 212]. Besides the improved accuracy, due to the incorporation of PET, a lung lesion can be non-invasively diagnosed without waiting for 3-6 months until it has grown larger. The benefit of earlier diagnosis is that the patient can also be treated earlier, which leads to more treatment options, less invasive surgery and a higher survival rate [28].

Apart from lung cancer diagnosis, the application of PET in radiation therapy (RT) planning for lung cancer has also been extensively studied and evaluated [41, 47, 48, 50, 54, 116, 159]. Computer-assisted 3D planning, such as 3D conformal radiotherapy (3DRT), intensity-modulated radiation therapy (IMRT) and image-guided radiation therapy (IGRT), facilitates delivery of high radiation dose to the tumour and decreases damage to normal tissue [116]. To do so, it is essential to accurately delineate the target. Traditionally, prior to radiation therapy, CT is used to delineate the anatomical boundary of a tumour. The introduction of PET provides an approach to delineate the functional boundary of the tumour, which augments the information available to radiation therapy planning. Studies have shown that the incorporation of PET more accurately defines tumours, assesses treatment responses, and predicts survivals [41, 47, 50, 116]. Although patient outcomes as a result of using PET in radiation therapy planning remain to be examined, PET/CT has been proved to provide the best available information for lung cancer and is recommended for use in clinical practice by the IAEA expert group [116].

1.4 Challenges

A typical whole-body PET scan takes about 15-30 minutes and represents the sum of information over the whole period of acquisition. Movement of the subject is inevitable during this period. Motions can be grouped into two categories, voluntary and invol-
Voluntary motions include unpredictable movements of the subject during data acquisition. For example, a subject lying on the couch in the PET scanner may reposition his/her body or move his/her head in order to relieve pain or pressure points. Involuntary motions include periodic movements of the organs, such as respiratory and cardiac motions. These motions substantially degrade PET images, because the information in the PET images will be dispersed over an area proportional to the magnitude of motion, resulting in motion blur.

In the context of lung PET imaging, a major challenge is respiratory motion. There are several impacts of respiration on lung PET imaging.

First of all, images are blurred and the spatial resolution is degraded. The effective spatial resolution of a PET scanner can be approximated using the following formula:

$$d_e = (d_s^2 + d_m^2)^{1/2},$$

where $d_e$ is the effective spatial resolution measured using the FWHM, $d_s$ is the spatial resolution of the scanner, and $d_m$ is the FWHM of the position distribution of the object moving around a mean position. Regarding the magnitude of motion, the diaphragm moves about 15-20 mm due to respiration; since many of the conventional PET scanners currently deployed in hospitals have a spatial resolution of approximately 5 mm FWHM, respiration substantially reduces the effective spatial resolution. Figure illustrates the effects of respiratory motion on simulated PET images. As we can see, the lung lesion is blurred in the image with motion and might be missed in diagnosis. Also, the boundary of the heart is not so clear due to blurring. For state-of-the-art HD-PET scanners which have a resolution of 2 mm FWHM, the negative impact of respiratory motion is even greater. The advantage of high definition (HD) is completely lost due to motion blur.

Second, respiration causes a problem in attenuation correction of PET. For PET/CT,
Figure 1.5: Effects of respiratory motion on simulated PET images. (a) An ideal image without any motion; (b) An image with respiratory motion. A lesion at the bottom of the right lung is indicated by the red arrow. The images were simulated using PET-SORTEO.

Figure 1.6: Artefacts in PET attenuation correction due to respiratory motion. (a) An artefact in the CT image, in which the dome of the liver is displaced into the base of the right lung; (b) An artefact in the PET image, introduced by attenuation correction using the CT image. This figure is taken from [195].
Figure 1.7: The reconstructions of the same PET data, attenuation corrected using CT images at different time points. (a) CT acquired at end-expiration; (b) PET attenuation corrected using the end-expiration CT; (c) CT acquired at end-inspiration; (d) PET attenuation corrected using the end-inspiration CT. The bottoms of the two lungs are marked by red lines. The CT images were generated using the NCAT phantom, whereas the PET images were simulated using PET-SORTEO.

Attenuation correction of PET data is performed using a CT scan acquired prior to PET acquisition [195]. If the patient is instructed to breathe normally during the CT scan, it incurs artefacts in the CT image, especially near the bottom of the lungs and the dome of the liver [21, 137, 195]. The artefacts are then introduced into the PET image, as shown in Figure 1.6. In this figure, the dome of the liver is displaced into the base of the right lung in the CT image. This artefact is further propagated into the PET image because of attenuation correction using the corrupted CT image. Therefore, it is recommended to use a breath-hold protocol in CT acquisition [21].

The CT scan is completed in just a few seconds, which makes breath hold possible. However, because PET data contain information over the whole process during which motion occurs while a breath-hold CT scan corresponds to a time point, only a proportion of the PET data can be accurately attenuation corrected using this single CT scan. The PET image reconstruction is largely affected by the time point that the CT
scan is acquired, as demonstrated in Figure 1.7. As we can see from this figure, the boundaries of both the right and the left lungs in the PET image are dependent on the time point of the attenuation CT scan.

Third, degradation of PET images has an adverse impact on subsequent clinical diagnosis. Studies have shown that the intensity of a lesion is reduced and its size is overestimated due to motion [43, 46, 59, 128]. Also, serious lesion mislocalisation may occur, especially for lesions near the boundary between the lung and the liver [43, 59, 133]. These effects lead to inaccurate lung cancer diagnosis and staging, which are dependent on the intensity, size, and location of a lesion. Radiation therapy planning is also affected since the lesion size tends to be overestimated, which results in an enlarged planning target volume (PTV).

For all the above reasons, respiratory motion in PET data must be corrected for in order to yield clear and accurate images for lung cancer diagnosis. Otherwise, diagnosis will be misled.

### 1.5 Contributions

This thesis describes methods to estimate respiratory motion in PET data and correct for such motions. In order to avoid incorrect attenuation correction, we use non-attenuation corrected PET (PET-NAC) images for motion estimation. These images are aligned to the same position using a B-spline registration algorithm. As a result, motion is corrected for. Then we use a voxel-wise attenuation correction factor (ACF) image to perform attenuation correction on the motion corrected image, resulting in an attenuation corrected PET (PET-AC) image.

Chapter 2 briefly reviews common image modalities for lung cancer diagnosis, including radiography, CT, MRI and PET. The focus of the chapter is on PET, introducing the basic principles, data correction and reconstruction techniques of PET, as well as multi-modality imaging techniques such as PET/CT and PET/MRI.

A major challenge in evaluating medical image analysis algorithms is to compare results to “ground truth”. However, it is both money and time consuming to build a
Figure 1.8: Images before and after motion correction. A 10 mm lesion at the bottom of the right lung is indicated by the red arrow.

Figure 1.9: Lesion profiles before and after motion correction. The profiles are plotted along the dashed red lines in Figure 1.8.

substantial clinical PET data base for study. Also, it is hard to assess performance on real data only due to the lack of ground truth. An alternative strategy is to use simulated data to develop algorithms and validate them. Chapter 3 describes the protocol to simulate not real but very realistic PET data affected by respiratory motion. The human anatomy and respiratory motion are accurately modelled by the NCAT phantom. The emission and attenuation images given by the NCAT phantom are then passed to a Monte-Carlo based simulator PET-SORTEO for simulation of a PET scan. Finally, simulated PET data are reconstructed using an iterative reconstruction algorithm OS-EM.

Chapter 4 presents the main contribution of this thesis, describing our motion correction and attenuation correction method in detail. Gated PET images are registered
Figure 1.10: The lesion detection results for a 8 mm lesion at different locations. The arrow indicates a detected lesion, whereas the cross indicates a miss.

to a reference position, so that respiratory motion is compensated for, and a CT image matching the reference position is used for attenuation correction. Simulated PET data validate the method. Figure 1.8 demonstrates the improvement of image quality introduced by motion correction. A 10 mm lesion is situated at the bottom of the right lung. Figure 1.9 shows the corresponding lesion profiles. As the figures clearly show, after motion correction, the lung lesion can be better identified and its size can be better characterised.

Chapter 5 describes an automatic lung lesion detection algorithm for motion corrected PET images. It first detects a number of lesion candidates and then screens the candidates according to contrast and size criteria. Experimental results show that our method can successfully detect most of the lung lesions in both simulated and real
Figure 1.11: The lesion trajectories estimated by spatial registration and spatio-temporal registration respectively, as well as ground truth. The displacements along the X, Y, and Z directions are shown in different colours.
images. In addition, motion correction can greatly improve the performance of lesion detection. Figure 1.10 shows the lesion detection results for an 8 mm lesion at different locations. Although the 8 mm lesion has a marginal contrast and is barely seen by human eyes, all the lesions are successfully detected by our method, except the one at the bottom of the left lung.

Chapter 6 explores a spatio-temporal image registration algorithm which utilises temporal continuity in respiratory gated PET data. The additional temporal information aids in improving the registration performance, yielding more accurate estimates of respiratory motion. Figure 1.11 demonstrates the improvement introduced by temporal information in estimating the lesion trajectory. As is clear, the trajectory estimated by spatio-temporal registration is smoother across the gates than that by spatial registration and it looks closer to ground truth. However, a disadvantage of the proposed algorithm is that it significantly increases the computational cost. So its clinical deployment would require implementation on a GPU or parallel computer for speedup. We did not have time to pursue this option during the course of the thesis.

Finally, Chapter 7 summarises the work and indicates areas for future work.
Chapter 2

Imaging Modalities

In this chapter, we introduce several common imaging modalities used in lung cancer diagnosis and staging, namely radiography, computed tomography (CT), magnetic resonance imaging (MRI), and position emission tomography (PET). We first briefly describe radiography, CT and MRI. Then we focus on PET. We also introduce the multi-modality imaging techniques: PET/CT and PET/MRI.

2.1 Radiography

Radiography depends on the fact that X-rays are attenuated to a certain extent as they pass through the body \cite{9}. In radiography, the intensities of the X-rays after attenuation are recorded by a 2D film or digital detector. The extent of attenuation depends on the tissue type, such as gas, fat, soft tissues or calcified structures. Gas is the least X-ray absorptive and therefore causes the most darkening on the radiograph. On the contrary, calcified structures are the most absorptive and appear white. Soft tissues, with the exception of fat, appear gray, while fat appears a little darker than the other soft tissues.

A radiograph represents the X-ray attenuation through the body along a certain projection angle. In a chest scan, a posteroanterior (PA) or anteroposterior (AP) projection is routinely performed. Sometimes, an additional lateral scan is performed to gain information about the third dimension.
Chest radiography is the most common X-ray examination and often serves as an initial scan for clinical diagnosis. It is easy to perform and low cost. However, since all the 3D information is superimposed on a 2D plane, it is very difficult to interpret [9]. When a condition is suspected on a radiograph, additional imaging of the chest using other modalities is often required for accurate diagnosis.

An X-ray is a form of electromagnetic radiation. It is sufficiently energetic that when interacting with atoms, it has the potential to liberate electrons from the atoms that bind them [20]. It is therefore a form of ionising radiation, which is harmful to dividing cells and contributes a genetic risk. The radiation dose of a typical chest radiography is 0.1 mSv [156].

### 2.2 Computed Tomography (CT)

Like radiography, CT also relies on X-rays but it provides a 3D image of tissue attenuation properties. The first clinically useful CT scanner was invented by Sir Godfrey Hounsfield at Electrical and Musical Industries (EMI), England [20]. The scanner was installed at Atkinson Morley Hospital in Wimbledon, London, where the first patient was scanned in 1971 [16]. In 1979, Hounsfield shared the Nobel Prize in Physiology or Medicine with Alan Cormack, who made fundamental contributions to reconstruction algorithms for CT.

During a CT scan, X-rays, which are emitted by the X-ray tube, pass through the subject being imaged and are then collected by the detectors, as shown in Figure 2.1. The intensities of the X-rays received by the detectors depend on the attenuation that the X-rays have encountered in the medium at this angle. The X-ray tube and detectors rotate around the object, so that attenuation information at different angles is recorded. Finally, an image of the subject is reconstructed from the data.

Each pixel or voxel of the image represents the local attenuation coefficient, ex-

---

1The sievert (Sv) is the unit of dose equivalent, which attempts to reflect the biological effects of radiation. It is defined by multiplying the absorbed dose, the unit of which is gray (Gy), by a Q factor, depending on the radiation type, and by another N factor, depending on all the other pertinent factors such as the organ or tissue types. The millisievert (mSv) is commonly used to measure the effective dose in diagnostic medical imaging.
pressed in Hounsfield units (HU). The Hounsfield unit is a linear transformation of the original attenuation coefficient, which maps the value of water to 0, air to -1000, and bone to approximately 1000. It is formulated as

$$HU = \frac{\mu - \mu_{\text{water}}}{\mu_{\text{water}} - \mu_{\text{air}}} \times 1000,$$

(2.1)

where $\mu$ denotes the attenuation coefficient. The value range to be displayed on the computer screen is known as the “window”, and can be selected by controls in order to emphasise different tissue types.

Conventionally, a CT scan is performed in a step-and-shoot manner. The scanner rotates the tube for scanning of a slice, then moves the patient table, and stops for scanning of the next slice. The modern helical (also known as spiral) scanner rotates the tube and moves the table simultaneously, so that the effective path of the X-ray beam is helical, as shown in Figure 2.2. Compared to the conventional scanner, helical CT offers a greater volume of coverage for a given scan time. As a result, the scan time and the radiation dose build-up can be reduced. However, it broadens the slice sensitivity profile due to the motion of the table. The slice sensitivity profile for spiral

$^{2}$The slice sensitivity profile is the longitudinal profile of the point spread function (PSF) of a CT
Figure 2.2: Helical scanning. The table moves continuously while the X-ray tube is rotating.

geometry with linear interpolation is determined by the original profile convolved with the motion function [87].

The introduction of multislice helical CT allows multiple slices, which means more data, to be acquired in a single rotation. Compared to single-slice CT, it uses the tube output more efficiently, reduces the scan time significantly and improves longitudinal spatial resolution [20][168]. When multislice scanners were first introduced, there were only 4 slices. Nowadays, some manufacturers produce scanners of up to 256 slices. The modern multislice CT scanners can finish a scan in seconds and provide an isotropic spatial resolution that is sub-millimetre. For example, the latest Siemens SOMATOM Definition Flash scanner has a maximum scan speed of 45.8 cm/s and the rotation time is 0.28 s. It can provide an isotropic spatial resolution of 0.33 mm.

CT scans are routinely performed for lung cancer diagnosis and staging [3]. It is often performed for more accurate diagnosis when a suspected condition is found on the radiograph. Compared to radiography, CT displays a 3D volume and provides more information for diagnosis. It is more sensitive than radiography in differentiating tissue types. Since CT collects data from all the projection angles, it utilises more X-rays than radiography. The radiation dose is 7 mSv for a typical chest CT scan, and 19 mSv for a whole-body scan [156][195]. For comparison, the worldwide average annual dose due to natural radioactive background is 2.4 mSv [195].
2.3 Magnetic Resonance Imaging (MRI)

Due to their discoveries concerning MRI, Paul Lauterbur and Sir Peter Mansfield were jointly awarded the Nobel Prize in Physiology or Medicine for 2003. In 1973, Paul Lauterbur introduced gradients in the magnetic field so that a 2D image could possibly be reconstructed. Sir Peter Mansfield further developed the utilisation of gradients. He showed how signals could be mathematically analysed and how fast imaging could be achievable.

MRI is developed based on the phenomenon of nuclear magnetic resonance (NMR). In a magnetic field, hydrogen protons align with the direction of the field and precess around the axis at a rate given by the Larmor equation [68]:

$$\omega = \gamma B_0 \ ,$$  \hspace{1cm} (2.2)

where $\omega$ denotes the angular precessional frequency of a proton, $\gamma$ denotes the gyromagnetic ratio, and $B_0$ denotes the strength of the external magnetic field. If a radio frequency (RF) pulse is applied and its frequency matches the Larmor frequency $\omega$, “resonance” occurs. Resonance results in the RF pulse adding energy to the protons and boosting some protons from the lower energy state to the higher energy state. The precession of the protons flips by a certain angle, and they become in phase with each other. When the RF pulse is switched off, the protons return to their lower energy state and release the energy as RF signal, which is received by coils.

The RF signals can be spatially encoded using three orthogonal gradient coils. The slice-select gradient applies a linear gradient in the magnetic field along the Z axis, so that an RF pulse can only activate the slice whose Larmor frequency matches the RF pulse frequency. In addition, the frequency-encoding gradient and the phase-encoding gradient respectively encode the X and Y coordinates by frequency and phase. The received RF signals, which encode the three coordinates, are then reconstructed to form a 3D image.

The intensity of a voxel in the image depends not only on proton density, but also
on two relaxation times, T1 and T2 [9]. T1 depends on the time the protons take to return to their original axis of precession, which is the direction of the magnetic field, whereas T2 depends on the time the protons take to dephase. T1 and T2 are inherent properties of tissues and are thus fixed for a specific tissue at a given magnetic field strength. Using different RF pulse sequences, we can obtain T1-weighted, T2-weighted, or proton density (PD) weighted images. Most pathological processes show increased T1 and T2 times and these processes appear darker on a T1-weighted image and brighter on a T2-weighted image [9]. MRI can also achieve sub-mm spatial resolution. But it takes a longer scan time than CT. Depending on the type of examination, an entire MRI scan usually takes 15 to 45 minutes [155].

MRI has excellent contrast in soft tissues and involves no ionising radiation. It is often used for imaging and study of the brain. In lung cancer diagnosis, however, MRI only plays a small role [9]. For example, chest MRI is not recommended to be routinely performed for staging the mediastinum [3]. But for patients with clinical IIIA and IIIB disease, head MRI is often used for imaging extra-thoracic metastases.

It has to be noted, that the magnitude of MRI signal depends on the number of proton spins aligning with the direction of the magnetic field. Actually, only a tiny little more than 50% of the spins align with the direction of the magnetic field, while the others align with the inverse direction. It is the excess spins which affect the MRI signal intensity. The ratio between the number of parallel spins and that of anti-parallel spins at equilibrium is determined by the Boltzmann distribution [181]:

$$\frac{N^+}{N^-} = e^{\frac{\gamma h B_0}{2kT}} ,$$

(2.3)

where $N^+$ and $N^-$ respectively denote the number of parallel spins and anti-parallel spins, $h$ denotes the Planck constant, $k$ denotes the Boltzmann constant and $T$ denotes the absolute temperature in Kelvin. It follows that

$$\frac{N^+ - N^-}{N^+ + N^-} \approx \frac{\gamma h B_0}{2kT} .$$

(2.4)
In a typical 1.5 Tesla magnetic field and at body temperature, the spin excess is only five in a million. Equation (2.4) shows that the spin excess is linearly proportional to the strength of the magnetic field. Therefore, a lot of efforts have been made to apply progressively higher fields to MRI. 7 Tesla MRI scanners have already been produced, though currently FDA only approves 3 Tesla MRI for clinical use.

An alternative solution to increase signal intensity is to use contrast agents in MRI. A very promising contrast agent is xenon (Xe-129) gas. The xenon gas is hyperpolarised by optical pumping techniques so that the Boltzmann equilibrium is exceeded and there are a lot more excess spins, resulting in a very strong signal. It is harmless and inhaled by the patient prior to the scan. Hyperpolarised xenon MRI can be used to measure the gas diffusivity in lung spaces and quantify changes in regional lung microstructures [146]. It is a rapidly evolving MRI imaging modality especially for the chest. A xenon MRI scanner is due to be installed at Churchill Hospital, Oxford, this October.

2.4 Positron Emission Tomography (PET)

2.4.1 Principles

The physics underlying PET is that a positron emitted by a certain kind of radionuclide annihilates with an electron nearby to produce a pair of high energy photons (also known as gamma rays), which are then recorded by detectors. Figure 2.3 shows the process of positron emission and subsequent positron-electron annihilation. The radionuclide is attached to a chemical compound to form a biological radiotracer, which is injected into the subject under study and accumulates in regions of interest. From the annihilation photon pairs recorded by detectors, an image of the radiotracer distribution in the subject can be reconstructed.

There are many radionuclides which decay by positron emission. Table 2.1 presents a selection of the radionuclides commonly used in PET imaging and the corresponding half-lives [164]. Among these radionuclides, $^{18}$F is by far the most widely used. The
decay of $^{18}\text{F}$ is as follows:

$$^{18}\text{F} \rightarrow ^{18}\text{O} + e^+ + \nu , \quad (2.5)$$

where $e^+$ denotes a positron and $\nu$ denotes a neutrino. Once produced, the positron leaves the decay site and rapidly loses its kinetic energy in interactions with atomic electrons in the surrounding tissue [142]. After most of its energy is lost, the positron eventually annihilates with an electron:

$$e^+ + e^- \rightarrow \gamma + \gamma , \quad (2.6)$$

where $\gamma$ denotes a photon. The mass of the positron and electron is converted into energy. In order to preserve the energy and near-zero momentum, both photons have an energy of 511 keV, which falls in the energy range of gamma rays, and leave the annihilation site in nearly opposite directions.

By tagging different chemical compounds with radionuclides, various radiotracers can be formed, which provide a wide range of biochemical probes. In Chapter 1, we have already introduced some radiotracers and the corresponding biological processes which they reveal. Among them, $^{18}\text{F}$-FDG is the one most commonly used in clinical PET
Table 2.1: A selection of radionuclides commonly used in PET imaging and the corresponding half-lives. This table is adapted from [164].

<table>
<thead>
<tr>
<th>Radionuclide</th>
<th>Half-life</th>
</tr>
</thead>
<tbody>
<tr>
<td>$^{18}$F</td>
<td>110 min</td>
</tr>
<tr>
<td>$^{11}$C</td>
<td>20 min</td>
</tr>
<tr>
<td>$^{13}$N</td>
<td>10 min</td>
</tr>
<tr>
<td>$^{15}$O</td>
<td>122 sec</td>
</tr>
</tbody>
</table>

FDG-PET imaging shows the distribution of glucose metabolism. Cancer cells consume more glucose than normal cells and therefore are highlighted in the image, which provides important evidence for diagnosis.

The annihilation photon pair travels through the subject and is recorded as a coincidence event by a pair of detectors coupled to a timing circuit. Figure 2.4 shows the process of coincidence detection. The position of annihilation is located along the line between the pair of detectors. This line is called the line of response (LOR). The number of coincidence events recorded by the detector pair is proportional to the total number of positron emissions along the LOR. Detectors are coupled with each other to form a detector ring and a number of detector rings form a PET scanner. After measuring the coincidence events along the LORs at different angles through the subject, an image of the radiotracer distribution can be reconstructed by one of several mathematical algorithms, such as FBP, ML-EM and OS-EM. While a detailed account is not necessary for this thesis, we provide a brief overview of the reconstruction algorithms in Subsection 2.4.3.

There are two ways to record coincidence events in a data file, respectively in a sinogram and in list-mode. A sinogram is a histogram, in which the number of events detected by each detector pair is recorded, whereas list-mode data records each coincidence event individually, along with its LOR and the time of occurrence. Sinogram data is more efficient in terms of memory, except when the number of LORs is extremely large and thus the average number of events per LOR is less than 1. List-mode data occupies more memory but provides the additional information of time. It can be
Figure 2.4: The annihilation photon pair are recorded as a coincidence event by a pair of detectors coupled to a timing circuit.

![Annihilation Photon Pair Diagram](image)

Figure 2.5: Axial section of the PET scanner in 2D and 3D acquisition modes. histogrammed to form sinogram data.

According to whether or not the detector rings are separated by septa (lead or tungsten shields) between adjacent rings, a PET scanner can work either in 2D or 3D acquisition mode. In 2D mode, photons travelling between rings are stopped by the septa, whereas in 3D mode such photons are detected. A schematic view of the two modes is shown in Figure 2.5. The 3D acquisition mode collects far more coincidence events than the 2D mode in a given scan time and results in better image quality with less noise. Studies have already shown that 3D PET significant reduces image noise relative to 2D PET for similar scan times [91, 114], or 3D PET performs diagnostically
Figure 2.6: The differences between static and dynamic PET. The static PET scan acquires a static frame over a fixed length of time, whereas the dynamic scan collects a sequence of dynamic time frames. Image courtesy of Andrew McLennan [121].

Similar to 2D PET but taking only half the scan time [189]. Therefore, it is preferable in diagnosis, though reconstruction is more complicated and computationally demanding.

According to the data acquisition protocol, the PET scanner can perform either static or dynamic acquisition. Figure 2.6 illustrates the differences between static and dynamic PET. Static PET scan is performed when radioactivity concentration has become relatively static and a single frame over a fixed length of time is acquired. It is the typical acquisition mode used in lung cancer diagnosis. This thesis mainly deals with static PET images. However, its extension to work with dynamic PET would be a very interesting avenue for future research.

Dynamic PET collects a sequence of dynamic time frames following intravenous injection of the radiotracer. It is used to follow the temporal evolution of radioactivity concentration and extract parameters of interest from the time-activity curve (TAC). Since each frame is quite short and only contains a limited amount of coincidence events, the reconstruction is normally very noisy. Many studies have been devoted to improve image quality by incorporating underlying temporal information across the frames [121, 207, 213]. An important application of dynamic PET is to quantify neuroreceptors, transporters and enzymes in the living human brain for investigating neuropsychiatric
Like X-rays, gamma rays used in PET are also ionising radiation. The average whole-body dose for a typical 370 MBq \(^3\) injection of FDG is about 7 mSv \(^4\). A whole-body PET scan normally takes 15-30 minutes.

### 2.4.2 Data Corrections

In order to produce an image which represents the true radioactivity concentration, a number of corrections need to be applied to PET data, including attenuation correction, scatter and random correction, dead time correction and normalisation.

**Attenuation Correction**

Attenuation refers to the loss of photons due to interactions in the subject being imaged. Attenuation leads to the radiotracer concentration inside the subject being underestimated, because the photons inside have to pass through more material in order to reach the detectors than the photons outside. This effect needs to be corrected for.

Consider a photon pair along a LOR. Attenuation along the LOR, i.e. the survival probability that the photon pair can pass the subject and reach both detectors, is formulated as

\[
P_l = e^{-\int_{l_1} - \mu(x) \, dx} \cdot e^{-\int_{l_2} - \mu(x) \, dx}
= e^{-\int_{l_1+l_2} \mu(x) \, dx}
= e^{-\int_{l} \mu(x) \, dx},
\]

where \(l\) denotes the LOR, \(l_1\) and \(l_2\) denote respectively the paths of the two photons, and \(\mu(x)\) denotes the attenuation coefficient at \(x\). As Equation (2.7) shows, attenuation is independent of the location along the LOR where annihilation occurs. This equation forms the basis for attenuation correction. There are two major methods, namely measured attenuation correction and calculated attenuation correction.

\(^3\)The becquerel (Bq) is the unit of radioactivity. One Bq is defined as the activity of a quantity of radioactive material in which one nucleus decays per second.
Measured attenuation correction determines the attenuation map through direct measurement \[134\]. Because attenuation is independent of the annihilation location, a radiotracer source outside the subject will result in the same amount of attenuation as a source in the subject. This method places a source outside the subject, then performs a blank scan (without the subject) and a transmission scan (with the subject). Attenuation for each LOR is determined from the ratio of the count rate of the transmission scan to that of the blank scan. The attenuation correction factors (ACFs) are the reciprocals of the attenuation. The difficulty with this method is to collect enough counts per LOR in order to reduce statistical noise, especially for the whole-body scan where the majority of the photons are attenuated through the body. In addition, it takes additional time to perform a transmission scan.

Calculated attenuation correction assumes that the shape and structure of the subject and the attenuation coefficients are already known. The attenuation map is calculated from Equation (2.7) and used to correct PET data. Conventionally, the shape and structure of the subject are either already known, e.g. for the phantom, or segmented from the emission or transmission scan \[179, 217\]. This method is free of statistical noise, but is limited by the accuracy of image segmentation and attenuation coefficient assumption. Fortunately, with the introduction of PET/CT scanners, these questions have been addressed. CT provides excellent spatial resolution so that accurate anatomy of the subject can be obtained. Also, attenuation coefficients can be directly determined from the CT image, which presents the distribution of the attenuation coefficients at a different energy level (40-140 keV) but can be transformed to fit the energy level of PET (511 keV) \[25, 88, 94, 195, 210\]. As a result, the ACFs can be calculated more accurately. CT-based attenuation correction is currently the standard method for correction.

**Scatter Correction**

The coincidence events collected by detectors can be categorised into four types, namely true, scattered, random and multiple events \[142\]. The first three types are illustrated in Figure \[2.7\]. A true coincidence is an event in which the two detected annihilation
photons originate from the same radioactive decay and have not changed direction before being detected. A scattered coincidence is an event where one or both of the two photons interacts in the subject and changes direction prior to detection, mainly through Compton scattering interactions [142]. This results in both a loss of the energy and mis-positioning of the event. A random coincidence is generated by two photons originating from two separate annihilations. It contributes no spatial information to reconstruction and results in background noise. A multiple coincidence is the event where three or more photons are detected simultaneously. It is normally rejected. The total number of events collected by a PET scanner are called prompt coincidences, which consist of true, scattered, and random coincidences. The latter two have to be corrected for.

A scattered event is indistinguishable from a true event except for its energy. There are two difficulties associated with energy discrimination. One is the limited energy resolution of detectors. The other is that some true events only deposit a proportion of their energy in detectors, so they fall in the same energy range as scattered events. Therefore we need other methods to correct for scattered events. There are three main approaches to do this, respectively analytic, dual energy and simulation methods.

The analytic method assumes that the scatter distribution varies slowly across the field of view. The distribution is approximated using Gaussian fitting of the scattered
counts outside the subject, i.e. the tails of projections [33]. This method is fast and estimates a smooth scatter distribution. However, it fails in whole-body scans, where the scatter tails available are very short because the body occupies a large proportion of the field of view (FOV). In addition, it is also not suitable for PET scans where the radioactivity concentration is highly localised so the scatter distribution contains more structures.

The dual energy method uses dual energy windows for coincidence collection, e.g., 380-850 keV and 200-380 keV. The idea is that the high energy window contains both scattered and unscattered events and the low energy window mainly contains scattered events. A scaled subtraction of the two windows can correct for the scattered events [63]. The scale for subtraction is normally determined from phantom studies. This method is typically only used in studies where the geometry is well-defined and remains fairly constant between studies, such as brain scans [142].

The simulation method first reconstructs the image and determines the attenuation map, and then simulates scattering based on the reconstruction, either using a simple single scatter model [1, 131, 209], or using a Monte Carlo simulation [13, 29, 105]. This method accounts for the distribution of radioactivity and attenuation and thus is very accurate. It is used in commercial PET scanners, such as Siemens Biograph systems.

Random Correction

The two photons in a random coincidence come from different radioactive decays and contribute no spatial information to reconstruction. There are two main approaches to correct for random coincidences.

One way is to individually measure the singles count rate for each detector and estimate the random count rate for a given detector pair using the following equation:

\[ N_r = 2\tau N_1 N_2, \]  

\(^{(2.8)}\)

\(^{4}\)Single scatter means that only one of the pair of annihilation photons undergoes Compton scattering interaction and it only undergoes a single interaction. Single scatters account for about 80% of scattered events [131].
where $N_r$ denotes the random count rate, $2\tau$ denotes the coincidence time window, $N_1$ and $N_2$ denote the singles count rates of two detectors. This method has the advantage that since the singles count rates are much higher than the random count rates for the detectors, the statistical quality of the estimate $N_r$ is good. The disadvantage is that the coincidence time window needs to be known accurately for each detector pair, otherwise systematic bias is introduced.

An alternative is to directly measure random coincidences using a delayed coincidence window. The signal from a detector is delayed so that the coincidence events in the detector pair contain only random coincidences, without any true coincidences. The random coincidences in a delayed coincidence window have the same probability distribution as those in the prompt coincidence window. The measured random coincidences are then subtracted from PET data. This method is free of systematic bias. However, the statistical quality is poorer than the singles estimation method, because the random count rates are lower than the singles count rates. This method is implemented and available in most PET scanners. The measurement for random coincidences can be saved in sinograms [83]. However, many conventional scanners only output the randoms-precorrected data in order to save storage [2, 218].

**Dead Time Correction**

Dead time correction aims to correct for the loss of coincidence events due to detector and system dead time. The main source of dead time in most PET systems comes from processing of each event in the detector front-end electronics [132]. Usually the measured and true count rates are modelled using a dead time model, the parameters of which are determined by experiments involving repeated measurements of a decaying source. The model is then used to restore the true count rates from the measured rates in PET data. State-of-the-art scanners use much faster electronics for front-end signal processing, e.g. digital time resolution of Siemens Pico-3D Electronics is as low as 500 picoseconds, therefore significantly reduce the dead time effect.
Normalisation

The non-uniformities in individual detector efficiencies, geometrical variations, and detector electronics result in variations in coincidence detection efficiencies for different LORs. The process to correct for such non-uniformities is referred to as normalisation. A straightforward correction method is to measure the efficiency of each LOR through a PET scan using a source of uniform radioactivity. The reciprocal of the efficiency is the normalisation correction factor. The difficulty with this method is to collect enough counts per LOR to reduce statistical variance.

An alternative is the component-based method, which factorises the normalisation correction factor for each LOR into components of single detector efficiencies and geometrical variations [10, 73, 142]. The number of detectors is much smaller than the number of LORs. It follows that the counts per detector is much more than that per LOR. Statistical noise is largely reduced and this method is used in modern PET scanners. The normalisation factors are typically determined once for a particular scanner using a very high count acquisition at the factory and assumed to be constant.

2.4.3 Reconstruction

The goal of image reconstruction is to provide an image of radiotracer distribution in the subject from the detected coincidence events. There are two main approaches for image reconstruction, namely analytic and iterative.

Analytic Reconstruction

Analytic reconstruction is based on the mathematics of computed tomography. In the absence of an attenuating medium, the projection along a LOR is approximately the line integral of the radiotracer concentration through the subject, as Figure 2.8 shows. The set of the line integrals at different angles forms a Radon transform. It is formulated as

\[ P_\theta(u) = \int_{-\infty}^{\infty} \int_{-\infty}^{\infty} f(x,y) \delta(x \cos \theta + y \sin \theta - u) dx dy , \]  

(2.9)
where $f(x, y)$ denotes the subject, $\theta$ denotes the angle of the radial line, $u$ denotes the coordinate along the radial line, and $P_\theta(u)$ denotes the projection. The image $f(x, y)$ can be reconstructed from the inverse Radon transform of $P_\theta(u)$, which is usually performed using the filtered backprojection (FBP) algorithm \[86, 93\].

The advantage of analytic reconstruction is that it is very fast. However, it does not take into account the statistical variance inherent in the process of data collection, i.e. the count of coincidence events collected by each detector bin is not exactly equal to the integral. The resulting noise is normally suppressed using a filter with a cut-off frequency, at the expense of spatial resolution.

**Iterative Reconstruction**

Iterative reconstruction aims to model the data collection process, including statistical variance as well as other factors such as scattered and random coincidence events. As a result, it can provide more accurate reconstruction, but at the expense of computation. It is usually formulated as an optimisation problem and iteratively looks for a solution image that is most consistent with the measured PET data \[103\].

Let $f = \{f_j, \; j = 1, \ldots, N\}$ be the distribution of radiotracer concentration in the
subject, which is a 3D volume represented as a 1D vector by concatenating all the voxels. The voxel value denotes the number of decays, and $N$ denotes the number of voxels. Let $y = \{y_i, i = 1, \ldots, M\}$ be the projection data, which record the number of coincidence events in each detector bin. $y$ and $f$ are related through a projection matrix, also known as the system matrix, $P = \{p_{ij}\}_{M \times N}$, where $p_{ij}$ represents the probability that a photon pair emitted from the $j$th voxel is detected at the $i$th bin.

The mean of $y$ is formulated as

$$\bar{y} = E[y] = Pf.$$  \hfill (2.10)

The emission of positrons from a large number of radionuclides is known to follow a Poisson distribution. The sum of independent Poisson random variables is still a Poisson random variable. The projection data $y_i$ in the $i$th bin collects the emission of annihilation photon pairs from all the pixels along the LOR, therefore it follows a Poisson distribution. The probability distribution of $y$ conditioned on $f$ is given by

$$P(y|f) = \prod_{i=1}^{M} \frac{\bar{y}_i^{y_i} e^{-\bar{y}_i}}{y_i!}. \hfill (2.11)$$

This is known as the likelihood function. The corresponding log-likelihood function, after dropping the constants, is

$$\log P(y|f) = \sum_{i=1}^{M} \left[ y_i \log \bar{y}_i - \bar{y}_i \right]. \hfill (2.12)$$

Reconstruction is an optimisation problem which aims to maximise the log-likelihood function $\log P(y|f)$, i.e. looking for an image $f$ most consistent with the observation $y$. The log-likelihood has been proved to be concave so that a global maximum exists \[178\]. The optimisation problem can be solved effectively under an expectation-maximisation (EM) framework \[42, 103, 178\]. The solution is an elegant closed-form update equation:

$$f^{(k+1)}_j = \frac{\sum_i p_{ij} y_i}{\sum_i \sum_l p_{il} f^{(k)}_l}. \hfill (2.13)$$
Note that Equation 2.13 naturally preserves the non-negativity of the estimate if $y \geq 0$. This algorithm is called the maximum likelihood EM (ML-EM) reconstruction algorithm.

Data corrections, such as attenuation correction, scatter and random correction, can be performed prior to image reconstruction. An alternative is to incorporate all these effects into the data model, in which the mean of $y$ is formulated as

$$\overline{y} = E[y] = P f + r + s, \tag{2.14}$$

where $r$ and $s$ respectively denote the estimates of random and scattered coincidence events. Note that in this case, the system matrix $P$ not only represents the probability of event detection due to scanner geometry, but also due to attenuation, detector efficiency, positron range etc [103, 149, 153]. A closed-form update equation can be derived similarly:

$$f_j^{(k+1)} = \frac{f_j^{(k)} \sum_i p_{ij} \sum_i p_{il} f_l^{(k)} + r_i + s_i}{\sum_i p_{ij} y_i}. \tag{2.15}$$

Iterative reconstruction models the detection process more accurately and handles the statistical variance in photon detection as well. In practice, it shows considerable improvement of image quality over analytic reconstruction. As a result, it is preferable in reconstruction.

However, there are two problems with the ML-EM iterative reconstruction [69],

1. Convergence is very slow.

2. Due to the ill-conditioned nature of the reconstruction problem, the reconstruction tends to have a high variance as the ML solution is approached.

The two problems will be addressed in the following subsections.

**Acceleration**

Convergence can be accelerated using the ordered subset EM algorithm (OS-EM) [78]. The projection data is grouped into an ordered sequence of subsets. The standard EM algorithm is applied to each of the subsets in turn, using the rows of the system matrix.
corresponding to these projections. The resulting reconstruction becomes the initial value for the next subset. An iteration of OS-EM is defined as a single pass through all the subsets.

Let $\{S_m\}_{m=1}^{Ns}$ be a disjoint partition of the projection index set $\{1, \ldots, M\}$, where $Ns$ denotes the number of subsets and $M$ denotes the number of projections. Let $k$ denote the index for an OS-EM iteration and $m$ denote the index for a sub-iteration. Define $f^{(k-1)} \equiv f^{(k,0)}$ and $f^{(k)} \equiv f^{(k,Ns)}$. Then the update equation for OS-EM is given by

$$f^{(k,m)}_j = \frac{f^{(k,m-1)}_j \sum_{i \in S_m} p_{ij} y_i}{\sum_{i \in S_m} \sum_l p_{il} f^{(k,m-1)}_l}.$$  \hspace{1cm} (2.16)

It has been recommended that balanced subsets should be chosen, which means that the voxel radioactivity contributes equally to each subset. With regard to the order of the subsets, it is encouraged that substantial new information is introduced as quickly as possible [78]. For example, the subsets can be chosen to have maximum separation in angle between successive subsets.

Because the computational cost of the EM reconstruction algorithm is proportional to the number of projections, an OS-EM iteration will have a similar computation time to that of a standard ML-EM iteration. However, an OS-EM iteration consists of a number of sub-iterations, each of which converges similar to an ML-EM iteration. Therefore the OS-EM algorithm accelerates convergence by a factor proportional to the number of subsets [78].

**Regularisation**

The high variance problem in the ML-EM algorithm can be addressed by terminating the algorithm before convergence [206], post-smoothing the reconstruction using a Gaussian kernel [113], or introducing a prior distribution into the likelihood function as a smoothness constraint, which forms the maximum a posteriori (MAP) algorithm [51, 69, 152]. OS-EM suffers a similar problem as ML-EM, which can be addressed similarly. In practice, OS-EM with Gaussian post-filtering is most often used for reconstruction, which is fast and produces images of good quality.
2.4.4 Multi-modality

Current clinical practice often requires a combination of two or more modalities, which provide clinicians with multiple views of a disease and may facilitate the final diagnosis. PET provides functional information, such as the distribution of glucose metabolism. However, additional anatomical detail is often needed for the localisation of increased radiotracer uptake and interpretation of the PET images. Therefore, numerous efforts have been made to combine PET with other modalities.

Software image fusion is one solution to the problem [26, 92, 117, 183, 216]. It usually involves registration of images of different modalities, which are acquired for the same patient but at different times, different places, and using separate scanners. Patient repositioning and movement is inevitable across the acquisitions. The choice of the registration algorithm depends on the type of movement, which may be either rigid or non-rigid. For brain imaging, movement is often regarded as rigid (3D rotation + 3D translation) and registration accuracy can be less than 1 mm (subvoxel) [117]. However, for other parts of the body, such as the chest or the abdomen, movement needs to be regarded as non-rigid due to respiration and heart beating. Registration accuracy can be 1 cm or more [92, 183].

An alternative solution is hardware fusion, which means integration of two modalities within a single device, so that images are intrinsically coregistered and can be interpreted with greater accuracy and confidence [67, 145, 195]. Also, since image acquisitions are performed in the same scanner, it saves time and greatly enhances the convenience to both the patient and the operation of the imaging centre. In the following, we will introduce two kinds of multi-modality scanners, namely PET/CT and PET/MRI.

**PET/CT**

Current commercial PET/CT scanner designs consist of a multislice spiral CT scanner in tandem with a PET scanner [195, 196]. Figure 2.39 shows a schematic diagram of a typical PET/CT scanner. Separate CT and PET scanners are fit within a single gantry
and shares the same bed. The patient can go through the CT and PET scanners successively while the bed moves, without repositioning. The separation of the FOV of the two scanners is compensated by the movement of the bed, so that the acquired images are intrinsically coregistered, which is an advantage over software image fusion.

Traditional PET scanners usually rely on a lengthy transmission scan for attenuation correction. With the introduction of PET/CT, CT provides not only accurate anatomical detail, but also an attenuation map with good image quality, thus eliminating the need for the transmission scan and substantially reducing the scan time. For a whole-body scan, it can reduce the scan time by at least 40% [195].

The first commercial PET/CT scanner came onto the market in 2001. Since then it has been rapidly adopted by nuclear medicine and radiology departments. As a result, the sales of PET/CT scanners have drastically increased and in 2006 it completely replaced the sales of PET-only scanners [195].

The combination of PET and CT provides more information for clinicians and leads to more accurate diagnosis. It has been shown that PET/CT significantly improves

Figure 2.9: A schematic diagram of a typical PET/CT scanner, where a CT scanner is in tandem with a PET scanner.
diagnostic accuracy for a variety of cancers compared to PET or CT alone and sometimes can even lead to a treatment change [33]. PET/CT is now routinely used in diagnosing and staging lung cancer.

However, PET images are substantially degraded due to respiratory motion. The motion not only results in image blurring, but also introduces mismatch between PET and CT images and causes attenuation correction artefacts, misleading the diagnosis. The impacts of respiratory motion have been discussed in detail in Chapter II. The aim of this thesis is to correct for respiratory motion in PET images and recover image quality.

**PET/MRI**

Along with the combination of PET and CT, concepts for PET integrated into MRI have also emerged [119, 144, 145, 180]. MRI offers excellent soft-tissue contrast and has no ionising radiation. It is good at detection of brain, bone and liver metastases. Therefore, a combination of PET and MRI has the potential to improve diagnostic accuracy of these diseases.

There are two fundamentally different PET/MRI designs. One design closely fits a PET scanner into a MRI scanner, such as the Siemens prototype and Paul Marsden’s small animal prototype [119, 144]. This design simultaneously acquires PET and MRI images, which are both spatially and temporally matched. Temporal matching of PET and MRI images may allow correlation of radiotracer uptake and brain perfusion in neurological studies in the future [145]. In the other design, the two scanners are separated by a few metres but share the same patient bed; this is the approach taken in the Philips prototype. This design reduces interference of the two modalities and technical difficulties in combination. However, it lacks temporal matching between PET and MRI images.

There are a few technical challenges to meet in order to successfully combine PET and MRI, especially for the integrated design. First, MRI should not interfere with PET. The challenge is that the photomultiplier tubes (PMT), which are one of the main components of a PET scanner, are distorted by a magnetic field. The Siemens
prototype replaces conventional PMTs with avalanche photodiodes (APD), which are magnetic field insensitive. Paul Marsden’s prototype separates PMTs from scintillators and connects them by long optical fibres, so that the PMTs can be situated in a low magnetic field region several metres away from the magnet. The Philips prototype physically separates the two scanners to avoid interference and individually shields all the PMTs for further protection.

The second challenge is that PET should not interfere with MRI. In the Siemens prototype, radiofrequency coils in MRI are rebuilt so that interference with the PET electronics is minimised.

The third challenge is attenuation correction. The MRI image is determined by the proton densities and relaxation time properties of tissues, instead of the photon attenuation properties. New algorithms for attenuation correction are being developed, which normally derive an attenuation map from MRI segmentation or local pattern recognition [74, 90].

Currently, PET/MRI is still in the stage of research and pre-clinical studies. As technology matures, however, it is very likely to change the way of clinical diagnosis, especially of the brain, just as PET/CT has done in the past decade.

2.5 Summary

In this chapter, we introduced several common imaging modalities used for lung cancer diagnosis. Among them, both radiography and CT utilise X-rays for imaging and therefore involve ionising radiation. Radiography compresses all the information on a 2D image and it is difficult to interpret. It has a relatively small radiation dose. CT provides a 3D image of better spatial resolution and it is much easier to interpret. However, its radiation dose is also much higher. Clinicians usually use radiography for initial examination of the lungs and run CT scans afterwards for further, more accurate diagnosis. MRI has the advantage in differentiating soft tissues. It is routinely used in brain studies. Regarding lung cancer, MRI is often used for examining extrathoracic metastases for late-stage cancer patients. PET is different from either CT
or MRI, because it provides functional information (for example, glucose metabolic information) instead of anatomical information (accurate delineation of the anatomy). Currently, PET/CT is routinely used for lung cancer diagnosis. It combines functional and anatomical information and significantly improves diagnostic accuracy than PET or CT alone.
Chapter 3

Data Simulation

Clinical PET data sets are expensive to acquire (currently between £750 and £1000 per clinical FDG scan and considerably more than this for other research radiopharmaceuticals) and only a few hospitals in the UK have deployed PET scanners [201]. As a result, it is both money and time consuming to build a substantial clinical PET data base for study. Due to the limitation of available clinical PET data, an alternative strategy is to use simulated but realistic PET data to develop algorithms and validate them. We adopt this strategy for most of the experiments reported in this thesis. With simulated data, it is convenient to design experiments, adjust parameters, and validate new ideas. A human anatomical phantom, NCAT, is combined with a Monte-Carlo based PET simulator, PET-SORTEO, to generate data which are highly realistic though not real, but for which ground truth exists.

3.1 Human Anatomical Phantom

Human anatomy during respiration is modelled using the NURBS-based cardiac torso (NCAT) phantom [173, 174, 175, 199]. With its basis in human data, the 4D NCAT phantom realistically simulates human anatomy and motions such as respiratory and cardiac motions. Therefore it provides an excellent tool to study the effects of respiratory motion on PET images.

The most important muscle of respiration during quiet breathing is the diaphragm.
On inspiration, the diaphragm contracts, forcing the abdominal organs downwards and outwards \[214\]. In the meantime, the rib cage moves upwards and outwards. Both of these motions increase the volume of the thorax, causing the lungs to inflate. On expiration, the diaphragm relaxes, allowing the abdominal organs to move upwards and inwards, and the rib cage moves downwards and inwards. The volume of the thorax is decreased, causing the lungs to deflate. The respiratory model of the NCAT phantom is built from 4D respiratory gated CT data and it accurately describes the motions of these organs \[175\]. The organ shapes are modelled with non-uniform rational B-spline (NURBS) surfaces. Furthermore, the NCAT phantom also incorporates a cardiac model based on 4D MRI data. Figure 3.1 illustrates the NCAT phantom and the motion models.

Given a parameter file, the NCAT program produces a series of emission and attenuation images across a respiratory cycle. An emission image is a 3D volume, where each voxel represents the label or the intensity of an organ. An attenuation image is
a volume, where each voxel represents the local attenuation coefficient for gamma rays at 511 keV. The attenuation image is equivalent to an CT image. They both represent the distribution of attenuation coefficients for gamma rays and only differ in the energy level (511 keV for an NCAT attenuation image and 40-140 keV for CT). They can be converted into each other using a scaling function [25, 195].

The magnitude and period of respiratory motion, the labels of organs, and the dimension of the volume are all defined in a parameter file. It is also possible to insert a lesion into the lung or the liver, so that motion effects on a lesion can be studied. However, a current limitation of the NCAT program is that it does not provide the deformation fields between successive frames, which substantially restricts its use on validation of image registration algorithms.

3.2 PET Simulator

Monte-Carlo methods have been widely used in simulating a wide range of physical and mathematical processes, particularly for those in which there is substantial uncertainty or non-determinism. In the domain of PET, it is well accepted that Monte-Carlo based simulation is the most reliable way to generate data in accordance with the properties of the detection system, the emission phantom, and the processes inherent in coincidence detection, such as attenuation, scatter and random events etc. [112, 162]. Simulated data are especially useful for designing and validating correction and reconstruction algorithms [158, 204], for subsequent image processing and analysis [11], and for performance prediction of PET prototypes [102].

PET-SORTEO is a Monte Carlo-based simulation tool that can be used to generate realistic PET projection data [161, 162]. It accurately models the scanner geometry and takes into account most of the phenomena that affect the final image quality, including attenuation and interaction in the human tissues and detector materials, scatter and random events, and system dead-time. It has been thoroughly validated for the ECAT Exact 962 scanner (also known as ECAT Exact HR+) against experimental measurements in both 2D and 3D modes [162]. The simulated scanner is made of
32 detector rings with 576 detection units each, allowing simultaneous acquisition of 63 transverse planes. The field of view (FOV) dimensions are 15.28 cm and 56.2 cm respectively along the axial and transverse directions.

PET-SORTEO is installed on the PC cluster in the Wolfson Medical Vision Laboratory (WMVL), University of Oxford. It is used in my work, in combination with the NCAT phantom, in order to generate realistic PET data for study of respiratory motion correction. Three major steps are involved in data simulation using PET-SORTEO. First, a text protocol file is created, describing the acquisition mode, the scan duration, the emission and attenuation volumes of the phantom. Second, the command ‘CompileProtocol’ processes the text protocol file and generates a binary protocol file. Finally, the command ‘sorteo’ takes the protocol file as input and generates PET projection data either as sinograms or as list-mode data. The format of the phantom file and the output data file is ECAT7. Appendix B shows an example of the PET-SORTEO protocol file.

PET-SORTEO is a multi-process program, which means that simulation can be launched on multiple processors in order to increase the speed. There are 40 nodes on the WMVL cluster so that the maximum process number can be set to 40 if all the nodes are available. A high process number increases the speed of simulation. However, it also occupies more computational resources of the cluster.

### 3.3 Simulation Protocol

In the NCAT phantom, the maximum magnitude of the diaphragm motion is set to 20 mm, which models normal breathing. Eight emission images are produced throughout a normal respiratory cycle of 5 s, so that each image corresponds to 0.625 s in a cycle. Meanwhile, eight attenuation images are also produced. The emission and attenuation images are shown in Figure 3.2.

The NCAT phantom is built from a normal male person 192 cm tall. My focus is on the thorax and abdomen. Therefore, only the volume containing the lungs, the liver, and the heart is needed. The volume is further scaled down by a factor of 1.2 so that
Figure 3.2: The NCAT phantom and the reconstructed PET image from simulated data. (a) NCAT emission image, where each voxel represents the label of an organ; (b) NCAT attenuation image, where each voxel represents the attenuation coefficient (unit: cm\(^{-1}\)); (c) the reconstruction of simulated PET data, where each voxel represents the SUV (unit: g/mL).

it does not exceed the axial FOV of the simulated scanner, which is 15.28 cm. The resulting volume represents the thorax of a 160 cm tall man with normal breathing. The dimension of the volume is 320×320×153, spacing 1×1×1 mm\(^3\).

In order to study the effects of motion correction on lung lesions, a spherical lesion is added to the lung region using the NCAT program. The lesion is placed in one of six different locations, respectively the top, middle, and bottom of the left and right lungs. Also, different lesion sizes are tested: namely 8, 10, 12 mm in diameter. Due to the poor spatial resolution of conventional PET scanners and the respiratory motion blurring, small lung lesions can be missed in diagnosis. As a result, radiologists are recommended to use PET to characterise only lesions at least 10 mm in diameter [3, 163]. We are testing the 8, 10, and 12 mm lesions in our experiments in order to show that the visibility can be improved by motion correction even for such small lesions, not to mention larger ones.

The NCAT volume is passed to PET-SORTEO for simulation. Normal organ FDG
Table 3.1: Radioactivity concentrations of organs, calculated from SUV measurements in [160].

<table>
<thead>
<tr>
<th>Site</th>
<th>Concentration (Bq/cc)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Background</td>
<td>0</td>
</tr>
<tr>
<td>Myocardium</td>
<td>24950</td>
</tr>
<tr>
<td>Blood pool</td>
<td>8150</td>
</tr>
<tr>
<td>Body</td>
<td>5100</td>
</tr>
<tr>
<td>Liver</td>
<td>10850</td>
</tr>
<tr>
<td>Lung</td>
<td>2400</td>
</tr>
<tr>
<td>Stomach</td>
<td>7200</td>
</tr>
<tr>
<td>Kidney</td>
<td>83900</td>
</tr>
<tr>
<td>Spleen</td>
<td>8250</td>
</tr>
<tr>
<td>Rib</td>
<td>5100</td>
</tr>
<tr>
<td>Spine head</td>
<td>5100</td>
</tr>
<tr>
<td>Spine process</td>
<td>5100</td>
</tr>
<tr>
<td>Pelvis</td>
<td>5100</td>
</tr>
<tr>
<td>Bone cartilage</td>
<td>5100</td>
</tr>
<tr>
<td>Artery</td>
<td>8350</td>
</tr>
<tr>
<td>Vein</td>
<td>8350</td>
</tr>
<tr>
<td>Intestine</td>
<td>8200</td>
</tr>
<tr>
<td>Rectum</td>
<td>7700</td>
</tr>
<tr>
<td>Airway tree</td>
<td>0</td>
</tr>
<tr>
<td>Lung lesion</td>
<td>19200</td>
</tr>
</tbody>
</table>
activity concentrations are assumed during simulation. The concentrations are calculated from SUV measurements in the literature [160] and listed in Table 3.1. The lesion intensity is set to 8 times the lung intensity. This lesion-to-lung contrast of 8:1 has also been used by other groups in simulation [99, 127].

The simulated scan duration is set to 10 min, which is the normal duration per bed position. Three types of acquisitions are simulated, namely a scan with time-based gating, an ungated scan, and an ideal scan.

1. To simulate a scan with time-based gating, each of the eight frames is simulated for a scan lasting 1.25 min. Thus eight sinograms are generated in total.

2. To simulate an ungated PET scan, the eight sinograms are summed.

3. An ideal scan means a scan without any motion. To simulate such a scan, a single frame is simulated for 10 min.

The sinograms are then reconstructed by 3D OS-EM with 10 iterations and 12 subsets with 4 mm (about 2 voxels) Gaussian post-filtering. The NCAT attenuation images can be used for attenuation correction. Image reconstruction and attenuation correction are performed using the STIR package [19, 80, 193]. The reconstructed images are volumes of size 160×160×61, spacing 2×2×2.425 mm³. The reconstructions are calibrated so that the intensity of each voxel denotes the local radioactivity concentration. The calibration factor is calculated by dividing the ground truth concentration distribution by a test reconstruction. In practice, the ground truth concentration distribution is measured by a dosimeter. Finally, the distribution of the standardised uptake value (SUV) is calculated using Equation (1.1), with the injected FDG dose of 350 MBq and the body weight of 70 kg as in the literature [160]. It takes approximately 2 minutes for reconstruction of each gate on a personal computer with a 3.19 GHz CPU and 2 GB memory. Since PET data are recorded in sinograms, the reconstruction time is independent of the scan duration. Figure 3.2 (c) shows an example of the reconstruction.

1http://stir.sourceforge.net/
3.4 Conclusions

In this chapter, we described the data simulation tools as well as the simulation and reconstruction protocols. The NCAT phantom, which models respiratory and cardiac motions, provides input to the PET-SORTEO simulator. The FDG radioactivity distribution is configured to accord with clinical measurements. The PET-SORTEO simulator, which is Monte-Carlo based and has been thoroughly validated against experimental measurements, is used to generate realistic PET data. The PET data are then reconstructed by the 3D OS-EM algorithm, which is routinely used in commercial reconstruction software. The simulated PET data sets will be used for most of the experiments reported in this thesis.
Chapter 4

Respiratory Motion Correction and Attenuation Correction

4.1 Introduction

As we discussed in Section 1.4, respiratory motion results in blurring and artefacts in PET images, adversely affecting clinical diagnosis. Such motion must be estimated and corrected for in order to yield clear and accurate images for diagnosis.

A common method to overcome respiratory motion effects is respiratory data gating. Typically, a respiratory cycle is divided into a number of time slots called “gates”, during each of which the imaged object is assumed to be static. Coincidence events for each gate are collected separately, as illustrated in Figure 4.1. As a result, a motion-free image can be reconstructed for each gate [128]. A fundamental problem with single-gate reconstruction is that it only makes use of a proportion of coincidence events, resulting in noisy images. In order to maintain the image quality of the reconstruction, either the acquisition time is prolonged or the radiotracer dose is increased, neither of which is satisfactory. To avoid this, a number of motion correction methods have been proposed to estimate motion between the gates and, as a result, to make use of all the coincidence events. Such methods can be grouped mainly into four categories.

First, summation of aligned images. In this method, each gate is reconstructed independently. The reconstructed PET images are aligned to the reference position by
Figure 4.1: Illustration of respiratory data gating. Coincidence events for each respiratory phase are collected separately, so that PET data are divided into a number of gates.

image registration algorithms and then summed \[11, 37, 40\]. In this way, any motion is corrected for and satisfactory reconstruction can be obtained. Dawood et al. used the optic flow method to align non-attenuation corrected PET (PET-NAC) images \[40\]. Attenuation correction of the motion corrected image was mentioned in the Discussion Section of Dawood’s paper, however, it does not seem to have been explored \[37\]. Since attenuation correction is crucial for quantitatively analysing a PET image, it is necessary to further explore the attenuation correction method for the motion corrected image, which is one of the main topics of this chapter.

Second, event rebinning. Motion between gates is estimated. PET data are rebinned by aligning the line-of-response (LOR) of each event to the reference position using the motion estimates \[22\]. A disadvantage with event rebinning is that the mapping of a LOR is independent of the event location, which means that the method is only applicable to rigid motion. For this reason, the method is most commonly used in motion correction for brain imaging where the motion can often be regarded as rigid and can be tracked by an optical tracking device \[23, 57, 84, 157\]. Since respiration consists of alternate expansion and contraction of the lungs and the thoracic and abdominal organs undergo motions in different directions with different magnitudes, rigid motion is not an appropriate approximation in our case. That is, respiration must be regarded as inducing a non-rigid motion and so this method is not applicable.
Third, reconstruction using a time-varying system matrix. Motion is estimated and a time-varying system matrix which accounts for motion is used for image reconstruction \cite{53, 100, 106, 151, 154}. This method can be applied to non-rigid motion. It has been shown to provide better correction performance than summation of aligned images; but it is more complex to implement \cite{100}. In order to obtain accurate motion estimates, Lamare et al. used gated CT images for image registration, which significantly increases the radiation burden to the patient. The average whole-body dose of a typical 370 MBq injection of FDG is 7 mSv, whereas the radiation dose of a typical whole-body CT scan is 19 mSv (or 3 mSv for low-dose CT) \cite{195}. Evidently, a number of gated CT scans result in a significant increase of the radiation burden. Because radiation is particularly harmful to dividing cells and may result in genetically adverse mutations, its use should follow the ALARA principle: “as low as reasonably achievable” \cite{9}. Therefore, it would be preferable to estimate motion just from PET images.

Fourth, simultaneous motion estimation and image reconstruction. This method embeds motion parameters into the likelihood function of image reconstruction, so that motion parameters and the image can be jointly estimated \cite{81}. This method solves the problems of motion correction and image reconstruction in one go. However, it is computationally expensive. Jacobson et al. only tested the method on a small 2D phantom. More evaluations on 3D images are required.

In this thesis, we propose a novel method to correct for respiratory motion in PET data and to perform attenuation correction after motion correction. Our method belongs to the first category, i.e. summation of aligned images. It differs from previous ones in two aspects. First, motion correction is performed using a regularised registration algorithm. The deformation fields between gates are modelled using B-splines. Therefore, non-rigid motion can be handled. The deformation fields are assumed to be a Markov random field (MRF) for regularisation \cite{11}. Second, attenuation correction of the motion corrected image is performed. To this end, a voxel-wise attenuation correction factor (ACF) image is calculated and applied to the PET-NAC image. It is straightforward to implement and computationally fast. We require only a single CT scan, so the radiation dose is controlled, which reduces hazard risks. Simulated but
highly realistic PET data are used to validate the proposed method. Experimental results show that this method can effectively correct for respiratory motion and improve PET image quality.

4.2 Methods

4.2.1 Scenario

We assume that the PET data have already been divided into a number of gates, each corresponding to a particular phase of the respiratory cycle. In this way, the data for each gate contain only slight motion and can be regarded as static. The breathing cycle is normally monitored either using a video camera or by a chest belt. Commercial video camera solutions include the Varian real-time position management (RPM) system (Varian Medical Systems Inc., Palo Alto, California) and the Polaris optical tracking system (Northern Digital Inc., Ontario, Canada). Both attach a few infrared-reflective or infrared-emitting markers to the chest of the patient and then monitor the motion of the chest using an infrared camera. Commercial chest belt solutions include the AZ-733V respiratory gating system (Anzai Medical Co., Tokyo, Japan) and the RespiTrace R250 inductive respiration monitor (Studley Data Systems, Oxford, UK). A belt is placed around the chest of the patient and respiration is monitored by a pressure sensor.

The breathing signal from the respiratory monitor is used to trigger the PET scanner to perform data gating. Two gating strategies can be used, namely time-based and amplitude-based. In time-based gating, also called phase gating, the data are sorted according to the time in each respiratory cycle. In amplitude-based gating, the data are sorted according to the amplitude of the breathing signal. It has been shown in a study that the amplitude-based method captures motion better than the time-based method especially when patients have irregular breathing patterns [38]. However, current commercial PET scanners only provide the option of time-based gating [30]. In this work, time-based gated PET data are used for experiments, but the proposed motion correction method is also applicable to amplitude-based gated data.
Figure 4.2: The flowchart for motion correction and attenuation correction.
Prior to the PET scan with respiratory gating, a breath-hold CT scan is acquired to provide both anatomical information and attenuation correction. Because respiration can be monitored during both PET and CT acquisitions, the CT scan can be matched to a gate of the PET scan. This single CT scan matches only one gate and does not align with the other gates. It cannot be used for attenuation correction of the other gates. Otherwise, artefacts are introduced in reconstruction, as shown in Section 1.4.

In order to avoid the artefacts, we reconstruct each gate without attenuation correction and use these PET-NAC images for motion correction. Although these images are not attenuation corrected, they also contain respiratory motion information. The PET gate coincident with the CT scan is regarded as the “reference” image, whereas all the other gates are regarded as “test” images (“reference” and “test” follow the nomenclature now widely established in the literature on image registration). Deformation fields between the reference and test images are estimated using B-spline registration. All the gated PET-NAC images are aligned to the same position and then summed to form a motion corrected image. We assume that the CT scan is acquired at mid-expiration so that the average motion between the reference image and the test images is minimal. Dawood et al. have shown that this tends to benefit the registration performance [40].

Finally, because the motion corrected image aligns with the CT scan, it can be attenuation corrected accurately. A voxel-wise ACF image is calculated for the reference gate. It is applied to the motion corrected image, resulting in an attenuation corrected PET (PET-AC) image, which is the final result.

The whole framework is illustrated in Figure 4.2.

4.2.2 Regularised B-spline Registration

B-spline Registration

The test images are aligned to the reference image using B-spline registration [98, 166, 169, 170, 192]. The goal of registration is to find a transformation $g : x \rightarrow g(x|\theta)$

\footnote{A breath-hold CT scan is a CT scan in which patients are instructed to hold their breath during the scan time. It is feasible to instruct the patients to hold their breath at a specific respiratory phase, such as mid-expiration, full-expiration, or full-inspiration, as shown in the studies [62, 156].}
which maps the reference image $f_r(x)$ to a test image $f_t(x)$ so that $f_r(x)$ corresponds to $f_t(g(x|\theta))$ at each location, $x \in \Omega$ denotes a pixel in a 3D PET image, and $\theta$ denotes a number of B-spline control points located on a 3D lattice, which parameterises the transformation $^2$.

The transformation is modelled by B-spline interpolation $^9$. The local deformation $g(x|\theta)$ at $x$ is determined by the weighted sum of its neighbouring B-spline control points:

$$
g(x|\theta) = x + d(x|\theta) = x + \sum_{u \in S(x)} w(x,u) \theta(u), \tag{4.1}
$$

where $d(x|\theta)$ denotes the displacement, $S(x)$ denotes the spatial support region of $x$, $w(x,u)$ denotes the weight, and $\theta(u)$ denotes the deformation vector at a control point $u$. By “support region”, we mean the region within which the weight function is non-zero. Figure 4.2.2 illustrates the arrangement of the control points and the spatial support region for a pixel $x$.

The weight function is defined by cubic B-splines, which have the advantage of being smooth functions with explicit derivatives and finite support $^19$:

$$
w(x,u) = \prod_{m=1}^{3} b^{(3)}(x^m \frac{x}{h_m} - u_m), \tag{4.2}
$$

where the weight is the product of B-spline functions along three dimensions, $m$ denotes one of the three dimensions, $b^{(3)}$ denotes the cubic B-spline function, and $h_m$ denotes the spacing of the control points. Because the cubic B-spline function has a finite support, spanning 4 control points, $w(x,u)$ also has a finite support. It is non-zero only on $4 \times 4 \times 4$ control points around $x$. Meanwhile, its derivative is also only related to these control points. The property of finite support enables efficient implementation and computation.

Registration is formulated as an optimisation problem, where a cost function consists of a data term which measures the discrepancy between the reference image $f_r(x)$ and the transformed test image $f_t(g(x|\theta))$, and a regularisation term which imposes a

$^2$If this transformation $g(x)$ is deformable, i.e. spatially-varying, we also call it a deformation field.
Figure 4.3: Illustration of the arrangement of control points and the spatial support region. The control points are located on the blue lattice, which covers the 3D image. In order to evaluate the deformation at pixel $x$, only its neighbouring control points are needed, which are marked as red points. For the cubic B-spline function, the support region consists of $4 \times 4 \times 4$ control points around $x$.

smoothness constraint on the control point lattice $\theta$. The cost function is minimised with respect to $\theta$, which has to be estimated.

The negative correlation coefficient (CC) is used to measure the discrepancy between the two images, since it has the twin merits of mathematical simplicity and computational efficiency [71]. CC is formulated as

$$
CC = \frac{\sum_{x \in \Omega} [f_r(x) - \bar{f}_r(x)] \cdot [f_t(g(x|\theta)) - \bar{f}_t(g(x|\theta))]}{\sqrt{\sum_{x \in \Omega} [f_r(x) - \bar{f}_r(x)]^2 \cdot \sum_{x \in \Omega} [f_t(g(x|\theta)) - \bar{f}_t(g(x|\theta))]^2}},
$$

(4.3)

where $\bar{f}_r(x)$ and $\bar{f}_t(g(x|\theta))$ respectively denote the mean of the reference image and the transformed test image. It is able to compare two gated images even if they have different durations of acquisition, which means that their intensities do not coincide but are linearly related\(^3\). It follows that the method is applicable both to time-based and

\(^3\)Since we are processing static PET images instead of dynamic PET images and the gated PET images represent the distribution of the radioactivity concentration averaged across a long period for
Regularisation

The regularisation term is derived assuming that the control point lattice is a Markov random field (MRF) [11], which imposes a local smoothness constraint on the deformation field and has been widely used in image processing [69 118 124 165 197].

This term is expressed as a Gibbs energy function [18], which is a sum of potentials defined on the lattice $\theta$:

$$U(\theta) = \sum_{j \in J} \sum_{k \in N(j)} V(\theta_j, \theta_k), \quad (4.4)$$

where $N(j)$ denotes the neighbourhood of $j$, and $V(\theta_j, \theta_k)$ denotes the potential function. Of the several potential functions that have been proposed in the literature [69], in this work, the Geman-McClure potential function is used. It is formulated as

$$V(\theta_j, \theta_k) = \frac{||\theta_j - \theta_k||^2}{\delta^2 + ||\theta_j - \theta_k||^2}. \quad (4.5)$$

This function acts like a quadratic penalty when $||\theta_j - \theta_k|| \ll \delta$ but is bounded above by 1. It follows that, if we choose a suitable value for $\delta$, the potential function is able to progressively penalise small differences within uniform regions, without over-penalising large differences, which usually correspond to region boundaries.

Finally, the cost function for image registration is formulated as

$$E(\theta) = -CC(f_r(x), f_t(g(x|\theta))) + \frac{\beta}{\text{card}(J)}U(\theta), \quad (4.6)$$

where $CC$ denotes the correlation coefficient between two images, $\beta$ denotes the hyperparameter, and $\text{card}(J)$ denotes the number of control points. To gain a more intuitive understanding of the relative weighting between the image discrepancy term and the regularisation term, we define $k_\beta$ as

$$k_\beta = \frac{\beta}{\text{card}(J)} \frac{U(\theta)}{CC(f_r(x), f_t(g(x|\theta)))}. \quad (4.7)$$

each respiratory phase, we assume that the gated PET images are linearly correlated.
In registration, we set the parameter $k_\beta$ and calculate the value of $\beta$ correspondingly.

Gradient descent is used to minimise the cost function. The gradient is straightforward to derive from the cost function. The step size is estimated adaptively at each iteration \[98\]. For more detail, the reader is referred to Appendix C. The algorithm is terminated either after a minimal incremental improvement to the cost function or after a pre-set maximum number of iterations.

### 4.2.3 Voxel-wise Attenuation Correction

After the gated PET-NAC images are aligned to the reference position, they are summed, resulting in a motion corrected PET-NAC image. Attenuation correction is required in order to obtain an accurate distribution of the radioactivity concentration. To this end, a voxel-wise attenuation correction factor (ACF) image is calculated, which is used to attenuation correct the PET-NAC image in a voxel-wise manner. This differs from conventional attenuation correction, which corrects PET data bin-wise, i.e. for each projection bin.

Figure 4.4 shows a diagrammatic model of the chest, which consists mainly of two tissue types with different attenuation coefficients $\mu_1$ and $\mu_2$, representing the lung and the body respectively. $l$ denotes the intersection between a gamma ray and the medium. Due to respiratory motion, the lung deforms (from the solid curve to the dashed curve). As a result, the voxel $x$ moves to $x'$, and the intersection $l$ moves to $l'$.
the body respectively. According to Chang’s paper \cite{31}, the attenuation factor at a voxel $x$ can be estimated as

$$A(x) = \frac{1}{M} \sum_{i=1}^{M} e^{-\mu_{1}l_{i,1} - \mu_{2}l_{i,2}}, \quad (4.8)$$

where $M$ denotes the total number of projections, $i$ denotes the index of a projection, $l_{i,1}$ and $l_{i,2}$ respectively denote the intersections of projection $i$ with two tissue types. $A(x)$ is actually the average attenuation over all the projections and is named the attenuation image in this work.\footnote{The attenuation image $A(x)$ is different from a CT attenuation image. Each voxel of $A(x)$ represents an attenuation factor (unit: $1$), which accounts for the difference between the reconstructions with and without attenuation correction. On the contrary, each voxel of a CT image represents the attenuation coefficient of the local medium (unit: $\text{cm}^{-1}$), i.e. the remaining proportion of a gamma ray after travelling across $1$ cm of such medium.} As a result, the reciprocal of $A(x)$ can be used for attenuation correction of the intensity of each voxel, and is named the attenuation correction factor (ACF) image.

As shown in the figure, if the shape of the model deforms a little, the voxel $x$ moves to $x' = g(x|\theta)$, and the intersection $l$ moves to $l'$. The change of $A(x)$ can be approximated by the first-order term:

$$\Delta A = A_t(g(x|\theta)) - A_r(x) \approx \frac{1}{M} \sum_{i=1}^{M} e^{-\mu_{1}l_{i,1} - \mu_{2}l_{i,2}} \cdot (-\mu_{1}\Delta l_{i,1} - \mu_{2}\Delta l_{i,2}), \quad (4.9)$$

where $A_r(x)$ and $A_t(g(x|\theta))$ denote the attenuation factor of a voxel in the reference image and the test image respectively.

In normal respiration, the diaphragm moves a maximum distance of $2$ cm. If we select the mid-expiration gate as the reference image, the largest movement between two gates is about $1$ cm. The anterior-posterior dimension of the chest is about $20$ cm, whereas the left-right dimension is over $30$ cm. Considering the dimension of the chest, the magnitude of the movement is relatively small. Therefore, the approximation in Equation (4.9) is reasonable.
It follows that

$$|\Delta A| \leq \frac{1}{M} \sum_{i=1}^{M} e^{-\mu l_{i,1} - \mu l_{i,2}} \cdot |\mu_1 \Delta l_{i,1} + \mu_2 \Delta l_{i,2}|$$

$$\leq \frac{1}{M} \sum_{i=1}^{M} e^{-\mu l_{i,1} - \mu l_{i,2}} \cdot \mu_m |\Delta l_{i,m}|$$

$$\leq A \cdot \mu_m |\Delta l_{m}| , \quad (4.10)$$

where $\mu_m = \max(\mu_1, \mu_2)$, $|\Delta l_{i,m}| = \max(|\Delta l_{i,1}|, |\Delta l_{i,2}|, |\Delta l_{i,1} + \Delta l_{i,2}|)$, $|\Delta l_{m}| = \max_i |\Delta l_{i,m}|$.

The two tissue types represent the lung and the body respectively. We have $\mu_1 = 0.032 cm^{-1}$ (lung) and $\mu_2 = 0.096 cm^{-1}$ (body). Therefore,

$$|\Delta A| \leq A \cdot \mu_m |\Delta l_{m}| = 0.096 A \cdot (4.11)$$

Evidently, $|\Delta A|$ is relatively small and can be neglected. As a result, $A_r(x) \approx A_t(g(x|\theta))$, and $ACF_r(x) \approx ACF_t(g(x|\theta))$, which means that we can use the ACF image for the reference gate to attenuation correct all the other gates.

Figure 4.4 is only a diagrammatic model. In the chest, there are actually more than two tissue types. A generalisation of Equation (4.8) is

$$A(x) = \frac{1}{M} \sum_{i=1}^{M} e^{-\int_{l_i} \mu ds} , \quad (4.12)$$

where the integral replaces the summation. We can similarly derive

$$|\Delta A| \leq A \cdot \mu_m |\Delta l_{m}| . \quad (4.13)$$

Bone has the highest attenuation coefficient in the chest, $\mu_{\text{bone}} = 0.13 cm^{-1}$. However, even if we take the bone into account, $|\Delta A|$ is still only $0.13 A$. It has also to be noted that in the derivation of Equation (4.10), three inequalities have been used. The actual value of $|\Delta A|$ may be much lower than its upper bound $A \cdot \mu_m |\Delta l_{m}|$.

Chang’s attenuation factor in Equation (4.12) was derived based on FBP reconstruction [31]. It has been used for attenuation correction of FBP reconstruction in the
literature \cite{198}. However, for iterative reconstruction, there is no such formula for direct calculation of the attenuation factor of each voxel. PET data are normally attenuation corrected for each projection bin, multiplied by a factor of $e^{\int \mu ds}$. Nevertheless, the property that the change of attenuation $|\Delta A|$ is small should also be valid for iterative reconstruction. The reason is that the medium that a gamma ray emitted from a voxel has to pass does not change much, regardless of the reconstruction algorithm. We will calculate the voxel-wise attenuation factor by other means and observe the change of its value through experiments.

The attenuation factor for each voxel is calculated by reconstructing the PET image twice, namely with and without bin-wise attenuation correction using the CT scan. We then divide the two reconstructions:

$$A(x) = \frac{f_{NAC}(x)}{f_{AC}(x)}, \quad (4.14)$$

where $f_{NAC}(x)$ and $f_{AC}(x)$ denote the reconstructed PET-NAC and PET-AC images respectively, and $A(x)$ denotes the attenuation image.

In a simulation study, we use the NCAT phantom with normal respiration. Eight gated images are reconstructed by the OS-EM iterative reconstruction algorithm, with and without attenuation correction using the known CT images for each gate. Voxel-wise attenuation images for each gate are then calculated from eight PET-NAC images and eight PET-AC images. To observe the change of attenuation, we select a number of sample points near the boundary of the right lung and the liver, where the change of attenuation is most drastic during respiration. Figure 4.5 (a) displays the sample points. Because the NCAT phantom provides the ground truth trajectories of these sample points, we can track their attenuation value changes during the process of respiration.

The attenuation factors of the sample points are plotted against gates in Figure 4.5 (b). As we can see from the figure, even at boundary positions, the change of attenuation is small. Table 4.1 lists the attenuation factors of the sample points and the corresponding changes. Note that the maximal change of the attenuation factor $|\Delta A|$ is 0.104 $A$, which is less than the theoretical upper bound. Nine of the ten sample
Figure 4.5: Observation of the changes of voxel-wise attenuation factors for the sample points. The sample points in the right lung are shown in red, whereas those in the liver are shown in green. For the subfigures in (b), the abscissa represents the gate index (from 1 to 8), whereas the ordinate represents the attenuation factor.
Table 4.1: The attenuation factors of the sample points and the changes. $A_i$ denotes the attenuation factor for Gate $i$, and $S_j$ denotes the $j$th sample point. The change $|\Delta A|$ is calculated as the difference between $A_i$ and $A_1$, where Gate 1 is regarded as the reference gate.

<table>
<thead>
<tr>
<th></th>
<th>$S_1$</th>
<th>$S_2$</th>
<th>$S_3$</th>
<th>$S_4$</th>
<th>$S_5$</th>
<th>$S_6$</th>
<th>$S_7$</th>
<th>$S_8$</th>
<th>$S_9$</th>
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<tbody>
<tr>
<td>$A_1$</td>
<td>0.212</td>
<td>0.247</td>
<td>0.297</td>
<td>0.216</td>
<td>0.196</td>
<td>0.229</td>
<td>0.173</td>
<td>0.089</td>
<td>0.123</td>
<td>0.080</td>
</tr>
<tr>
<td>$A_2$</td>
<td>0.200</td>
<td>0.246</td>
<td>0.296</td>
<td>0.216</td>
<td>0.191</td>
<td>0.207</td>
<td>0.179</td>
<td>0.090</td>
<td>0.126</td>
<td>0.082</td>
</tr>
<tr>
<td>$A_3$</td>
<td>0.199</td>
<td>0.243</td>
<td>0.297</td>
<td>0.213</td>
<td>0.187</td>
<td>0.213</td>
<td>0.181</td>
<td>0.091</td>
<td>0.126</td>
<td>0.085</td>
</tr>
<tr>
<td>$A_4$</td>
<td>0.192</td>
<td>0.246</td>
<td>0.297</td>
<td>0.214</td>
<td>0.201</td>
<td>0.206</td>
<td>0.177</td>
<td>0.090</td>
<td>0.121</td>
<td>0.082</td>
</tr>
<tr>
<td>$A_5$</td>
<td>0.216</td>
<td>0.249</td>
<td>0.297</td>
<td>0.221</td>
<td>0.196</td>
<td>0.221</td>
<td>0.172</td>
<td>0.095</td>
<td>0.120</td>
<td>0.081</td>
</tr>
<tr>
<td>$A_6$</td>
<td>0.218</td>
<td>0.250</td>
<td>0.300</td>
<td>0.220</td>
<td>0.216</td>
<td>0.213</td>
<td>0.183</td>
<td>0.098</td>
<td>0.121</td>
<td>0.083</td>
</tr>
<tr>
<td>$A_7$</td>
<td>0.211</td>
<td>0.254</td>
<td>0.298</td>
<td>0.220</td>
<td>0.215</td>
<td>0.217</td>
<td>0.184</td>
<td>0.090</td>
<td>0.129</td>
<td>0.082</td>
</tr>
<tr>
<td>$A_8$</td>
<td>0.208</td>
<td>0.249</td>
<td>0.298</td>
<td>0.222</td>
<td>0.206</td>
<td>0.214</td>
<td>0.182</td>
<td>0.093</td>
<td>0.119</td>
<td>0.082</td>
</tr>
</tbody>
</table>

Max($|\Delta A|/A_1$) | 0.093 | 0.031 | 0.009 | 0.025 | 0.100 | 0.098 | 0.063 | 0.104 | 0.045 | 0.055    |
Min($|\Delta A|/A_1$) | 0.003 | 0.001 | 0.001 | 0.004 | 0.001 | 0.032 | 0.006 | 0.011 | 0.015 | 0.007    |
Mean($|\Delta A|/A_1$) | 0.039 | 0.012 | 0.003 | 0.016 | 0.049 | 0.068 | 0.038 | 0.042 | 0.025 | 0.024    |

points have a average change of less than 0.05$A$, and three sample points have a average change of less than 0.02$A$. As we can see, for iterative reconstruction, $|\Delta A|$ is also relatively small and so we contend that the approximation $A_r(x) \approx A_t(g(x|\theta))$ and $ACF_r(x) \approx ACF_t(g(x|\theta))$ is justified.

The ACF image is the reciprocal of the attenuation image $A_r(x)$:

$$ACF_r(x) = \frac{1}{A_r(x)} = \frac{f_{r,AC}(x)}{f_{r,NAC}(x)}.$$  

(4.15)

In order to avoid dividing by zero, a very small number $\epsilon = 1^{-10}$ is added to the denominator. Figure 4.6 shows the reference ACF image.

As we discussed above, the ACF image for the reference gate can be used to attenuation correct all the other gates, resulting in a number of PET-AC images. The sum
Figure 4.6: The ACF image for the reference gate. It is the reciprocal of the attenuation image in Figure 4.5 (a).

Of the PET-AC images are

\[
fs,AC(x) = fr,AC(x) + \sum_i fi,AC(g(x|\theta_i))
\]

\[
= fr,NAC(x) \cdot ACF_r(x) + \sum_i fi,NAC(g(x|\theta_i)) \cdot ACF_i(g(x|\theta_i))
\]

\[
\approx fr,NAC(x) \cdot ACF_r(x) + \sum_i fi,NAC(g(x|\theta_i)) \cdot ACF_r(x)
\]

\[
= [fr,NAC(x) + \sum_i fi,NAC(g(x|\theta_i))] \cdot ACF_r(x)
\]

\[
= fs,NAC(x) \cdot ACF_r(x) ,
\]

(4.16)

where \(fr\) denotes the reference image, \(fi\) denotes one of the test images, \(fs\) denotes the sum of all the images, the subscript \(AC\) and \(NAC\) respectively denote the PET-AC and PET-NAC images.

As Equation (4.16) shows, we do not need perform attenuation correction for each gate separately. In our method, after all the PET-NAC images are aligned to the reference gate, they are summed to form a motion-corrected PET-NAC image \(fs,NAC\). We only need to perform attenuation correction for this image:

\[
fs,AC(x) = fs,NAC(x) \cdot ACF_r(x) .
\]

(4.17)

Appendix D briefly discusses noise propagation in the process of voxel-wise attenuation
correction.

The whole process requires just one CT image, namely for the reference gate. The calculation of the ACF image can be achieved by running the reconstruction program twice, namely with and without attenuation correction. The only additional work is to multiply the motion corrected PET-NAC image by the reference ACF image. The method is straightforward to implement.

4.3 Results

Experiments are carried out on simulated PET data. First, the results of registration are shown and evaluated quantitatively. Then, the effects of motion correction and attenuation correction are illustrated and the improvement of image quality is evaluated. In the experiments, the performance of the proposed method based on PET-NAC images is compared to an alternative method, in which each gate is reconstructed with attenuation correction using a single CT scan, the resulting PET-AC images are aligned to the reference position and then summed. The methods represent two strategies for motion correction when only a single CT scan is available.

4.3.1 Parameter Selection

There are several major parameters whose values need to be set in image registration, including: the size of the control point lattice, and the regularisation parameters $\delta$ and $k_\beta$.

We assume that the deformation field varies smoothly, so that it can be modelled using a lattice which is coarser than the image lattice. The control point lattice was set to $20 \times 20 \times 20$. Since the size of a PET image is $160 \times 160 \times 61$, with spacing $2 \times 2 \times 2.425$ mm$^3$, a control point covers 8 voxels (16 mm) along the X and Y axes, and about 3 voxels (7.4 mm) along the Z-axis. This resolution is sufficiently accurate to model the smoothly varying deformation field.

The value of $\delta$ controls the behaviour of difference penalisation. We have found that between the reference and the test images, some part of the body does not move much,
while the bottom of the lungs might move by as much as 10 mm. In order to penalise small differences within uniform regions, but without over-penalising large differences across boundaries, we chose $\delta = 5$ mm as half the deformation difference between the body and the lungs. We note that Mumcuoglu et al. used a similar strategy in their selection of a value for $\delta$ [126].

The value of $k_\beta$ was set empirically to 0.0001, which performed well in experiments. It should be noted, however, as mentioned by Rueckert [166], that the intrinsic smoothness property of the B-spline function means that the choice of $k_\beta$ is not critical if the control points are sparsely located, as in this case. The regularisation term will become more important if the control points are densely located or the deformation field is highly localised.

The algorithm was implemented in C++, using the ITK library [79]. It took approximately 44 minutes to register one image on a cluster node with a 1.79 GHz CPU and 1GB memory, and about 2 seconds to perform image summation and attenuation correction. Because the registrations of all the gated images were carried out in parallel on the cluster, the total computation time was about 44 minutes. Of course, this time could be reduced by a range of methods, not least implementation on GPUs. However, even in its relatively preliminary state, this is already acceptable for practical PET imaging, considering the post-injection waiting time of 1 hour and the acquisition time of 15-30 minutes.

4.3.2 Registration Accuracy

First, we show the results of PET-NAC image registration. Figure 4.7 shows the registration results of Gate 3 (end-expiration) to Gate 1 (mid-expiration, the reference gate). A 10 mm lesion is located at the bottom of the right lung. The figure shows that the lesion is almost aligned to the reference position after image registration, even though the images are so noisy. The corresponding deformation field shows the upward movement of the lesion from Gate 1 to Gate 3. Figure 4.8 displays the registration results of Gate 7 (end-inspiration) to Gate 1. It shows that the lesion is well aligned
Figure 4.7: The PET-NAC image registration results of Gate 3 (end-expiration) to Gate 1 (mid-expiration, the reference gate) and the corresponding deformation field from Gate 1 to Gate 3. The reference position of the lesion is marked with the red rectangle. Local deformation is marked with the red ellipse.

Figure 4.8: The PET-NAC registration results of Gate 7 (end-inspiration) to Gate 1 (mid-expiration, the reference gate) and the corresponding deformation field from Gate 1 to Gate 7. The reference position of the lesion is marked with the red rectangle. Local deformation is marked with the red ellipse.
Figure 4.9: The PET-AC registration results of Gate 3 (end-expiration) to Gate 1 (mid-expiration, the reference gate) and the corresponding deformation field from Gate 1 to Gate 3. The reference position of the lesion is marked with the red rectangle. Local deformation is marked with the red ellipse.

Figure 4.10: The PET-AC registration results of Gate 7 (end-inspiration) to Gate 1 (mid-expiration, the reference gate) and the corresponding deformation field from Gate 1 to Gate 7. The reference position of the lesion is marked with the red rectangle. Local deformation is marked with the red ellipse.
to the reference position. The corresponding deformation field shows the downward movement of the lesion from Gate 1 to Gate 7.

Then, we show the results of PET-AC image registration. Figure 4.9 shows the registration results of Gate 3 to Gate 1. It is clear that the lesion has not been aligned to the reference position. Also, the deformation field shows little movement near the lesion, which means that the registration algorithm failed in this region. Figure 4.10 shows the registration results of Gate 7 to Gate 1. Again, the lesion has not been aligned. The reason for misalignment of the lesion is that the gated images are attenuation corrected using the same CT scan. As a result, the boundaries of the lungs appear very similar in all the gated PET-AC images, though in practice they should be moving and represent different respiratory phases. The attenuation correction artefacts force the registration algorithm to produce a nearly zero-valued deformation field in the lung region. Therefore, the movement of a lesion, particularly a small lesion, could not be captured.

To quantitatively evaluate registration accuracy, noise-free NCAT phantom images were registered. The resulting deformation fields are regarded as ground truth. The registration error is then defined as

$$e(x) = ||d(x) - d_t(x)||,$$  \hspace{1cm} (4.18)

where $d(x)$ denotes the displacement of a voxel $x$ estimated by either PET-NAC or PET-AC image registrations and $d_t(x)$ denotes ground truth. Figure 4.11 shows the
registration errors for the deformation fields in Figure 4.7(d) and Figure 4.9(d) respectively. It shows that for PET-AC image registration, there are significant registration errors near the bottoms of the lungs, whereas the corresponding errors for PET-NAC image registration are much lower.

The average registration error for an organ or for the whole volume is calculated as

$$e_P = \frac{1}{n_g - 1} \sum_{k=2}^{n_g} \frac{1}{\text{card}(P)} \sum_{x \in P} e_k(x),$$

where $P$ denotes a part of the body, $\text{card}(P)$ denotes the number of voxels in $P$, $k$ denotes the index of the test image, and $n_g$ denotes the number of gates. Table 4.2 lists the average registration errors of the lungs, the lung lesion, the liver, the other organs and the whole volume for PET-NAC and PET-AC image registrations respectively. Figure 4.12 compares the average registration errors in a bar chart. As the table shows, the average overall registration error for PET-NAC image registration is 1.74 mm, which is lower than that for PET-AC image registration, 1.87 mm. In particular, the average registration error of the lesion for PET-NAC image registration is 2.24 mm, which is much lower than that for PET-AC image registration, 3.56 mm. The difference is more significant for lesions at the bottom of the lungs than those at the top. For example, the registration error of the 10 mm lesion at the bottom of the right lung is 1.78 mm for PET-NAC registration, but is as high as 5.03 mm for PET-AC registration.

As we have discussed before, the higher error for PET-AC image registration is caused by attenuation correction using a single CT scan.

### 4.3.3 Attenuation Correction and Motion Correction Results

Figure 4.13 illustrates the effects of attenuation correction. It shows the motion corrected PET-NAC image (the sum of the registered PET-NAC images), the ACF image, and the PET-AC image after attenuation correction. The PET-AC image is obtained by multiplying the PET-NAC image by the ACF image. As can be seen, after attenuation correction, the anatomical structures such as the lungs, the heart, and the liver are better displayed. Figure 4.14 displays horizontal profiles across the three images.
Table 4.2: The average registration errors of the lungs, the lung lesion, the liver, the other organs and the whole volume for PET-NAC and PET-AC image registrations respectively (unit: mm). The errors for a number of simulated images, with lesions at different locations and of different diameters are shown, as well as the mean errors for all the simulated images.

<table>
<thead>
<tr>
<th>Location</th>
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<th>PET-AC</th>
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<tr>
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<td>Left bottom</td>
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Figure 4.12: The average registration errors of the lungs, the lung lesion, the liver, the other organs and the whole volume for PET-NAC and PET-AC image registrations respectively (unit: mm).

Figure 4.13: The motion corrected PET-NAC images, the ACF image, and the PET-AC image after attenuation correction.
Figure 4.14: Horizontal profiles across the PET-NAC image, the ACF image, and the PET-AC image. The profiles are plotted along the dashed red lines in Figure 4.13.
Figure 4.15: Comparison of the image of Gate 1, the uncorrected image, the ideal image and the motion corrected images using different strategies. The ideal image is the reconstruction of ideal PET data without any motion. A 10 mm lesion at the bottom of the right lung is indicated by the red arrow.
Figure 4.16: Vertical profiles across the image of Gate 1, the uncorrected image, the ideal image and the motion corrected images using different strategies. The profiles are plotted along the dashed red lines in Figure 4.15.
From the profile of the ACF image, we can see that in the middle of the image, attenuation correction compensates for the intensities as gamma rays emitted from here need to cross more material than elsewhere. In the lungs, attenuation correction tends to suppress the intensities as gamma rays emitted from here can cross the material more easily than elsewhere due to the low attenuation coefficient of the lungs. In this way, attenuation correction accounts for the non-uniform attenuation across the body and yields an accurate distribution of the radioactivity concentration in the PET-AC image.

Figure 4.15 compares the image of Gate 1, the uncorrected image, the ideal image and the motion corrected images using different strategies, namely PET-NAC registration and PET-AC registration. The ideal image is the reconstruction of ideal PET data without any motion, which represents the upper bound of image quality, given the current PET scanner and the reconstruction algorithm used. Although the image of Gate 1 can be regarded as motion-free and provides a snapshot of the body, it is reconstructed from only a proportion of the PET data and inevitably suffers from poor image quality. In the uncorrected image, it is difficult to see the 10 mm lesion and it is very likely to be missed by a human observer. Motion correction based on PET-AC images fails to recover the lesion. However, the PET-NAC based method successfully recovers the lesion. The lesion can be seen clearly in the motion corrected image and its appearance is similar to that in the ideal image. We can also see that the boundary of the heart appears sharper in the motion corrected image than in the uncorrected one.

Figure 4.16 shows vertical profiles across the lesion. In the profile of Gate 1, the lesion has a good contrast against the background. However, the background has many ripples compared to the profile of the ideal image. In particular, two bumps appear in the first few slices (Z from 1 to 10) due to reconstruction noise. The intensities in the end slices (Z near 60) are also overestimated. In the uncorrected image, the intensities of the lesion are dispersed along the Z direction, that is, the superior-inferior direction, which is the principal direction of respiratory motion. After PET-AC based motion correction, the lesion profile is only slightly improved. However, after motion correction using our method, the profile of the lesion is recovered so that the lesion has a higher contrast with respect to the background.
4.3.4 Quantitative Evaluation

As we have placed a lesion at different locations in the lungs and of different diameters, we can quantitatively compare the motion corrected and uncorrected images by the measurements of the lesion size and the lesion-to-lung contrast. The size of a lesion is measured using a 3D Gaussian fit to the intensities and determined by the FWHM of the Gaussian fit. The lesion-to-lung contrast is measured by region-of-interest (ROI) analysis. The lesion intensity is determined by the maximum intensity inside a spherical ROI around the lesion with a diameter equal to the lesion size, whereas the lung intensity is determined by the mean intensity inside the lungs. Measurements in the ideal image are regarded as ground truth and the estimation error of the lesion size is computed.

Table 4.3 lists the lesion size estimation errors for lesions at different locations and of different diameters. Figure 4.17 shows the average estimation errors in a bar chart. It shows that motion correction substantially reduces lesion size estimation errors, especially along the Z direction (superior-inferior). For the uncorrected image, lesion size estimation errors are consistently very large for lesions at the bottom of either the right lung or the left lung, because respiratory motion is most prominent at the bottom of the lungs. The improvement due to motion correction is also most obvious at these positions. It is seen that the smaller the lesion, the larger the estimation error. This indicates, as expected, that smaller lesions are more susceptible to motion. The Z-axis estimation errors for the 8 mm lesion are still large even after motion correction. Of the two motion correction methods, the PET-NAC based method performs better. On average, the size estimation error along the Z direction is 69.81% for the PET-AC based method, but is only 21.32% for the PET-NAC based method.

Table 4.4 lists the lesion-to-lung contrasts. Figure 4.18 shows the bar chart for the average lesion-to-lung contrasts. It shows clearly that the motion corrected image using the PET-NAC based method significantly increases the contrast compared to the uncorrected one, although the contrast is still lower than the ideal image on average. The PET-AC based method also increases the lesion contrast, but the improvement is less. Because the visibility of a lesion mainly depends on its contrast, the improvement
Table 4.3: The lesion size estimation errors for lesions at different locations and of different diameters (unit: %).

<table>
<thead>
<tr>
<th>Location</th>
<th>Diameter</th>
<th>Uncorrected</th>
<th>Corrected&lt;sub&gt;AC&lt;/sub&gt;</th>
<th>Corrected&lt;sub&gt;NAC&lt;/sub&gt;</th>
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</thead>
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<td>Y</td>
<td>Z</td>
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</tr>
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</tr>
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<td></td>
<td>10 mm</td>
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</tr>
<tr>
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Figure 4.17: The average lesion size estimation errors for uncorrected and motion corrected images (unit: %).

Figure 4.18: The average lesion-to-lung contrasts for uncorrected, motion corrected and ideal images.
Table 4.4: The lesion-to-lung contrasts for lesions at different locations and of different diameters.

<table>
<thead>
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<th>12 mm</th>
<th>8 mm</th>
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<th>8 mm</th>
<th>10 mm</th>
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<td>1.16</td>
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Table 4.5: The signal-to-noise ratios (SNRs) for a number of simulated images, with lesions at different locations and of different diameters (unit: dB).

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<th>Cor\textsubscript{NAC}</th>
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<td>33.11</td>
<td>32.76</td>
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of the lesion contrast implies that it is more likely to detect the lesion after motion correction. It is also seen that the smaller the lesion, the lower the contrast. The explanation for this phenomenon is the partial volume effect (PVE), which underestimates the intensity of a small lesion \[187\]. The spatial resolution of the simulated PET scanner is approximately 5 mm. Therefore, the lesion size we are testing is only about 2 times the spatial resolution, resulting in a remarkable PVE. The smaller the lesion, the greater the intensity underestimation and thus the lower the lesion contrast. Another consequence of the PVE is that the contrast improvement for smaller lesions after motion correction is smaller than the improvement for larger lesions, which is clear in the table. For example, the contrast the 12 mm lesion at the bottom of the left lung is increased from 1.33 to 1.78 after PET-NAC based motion correction, that is, by 0.45, whereas the 8 mm lesion at the same location is only increased by 0.07. This is because the low contrasts of small lesions in gated images could not provide enough force to drive the registration process in order to align the lesions and recover the intensities, considering the low signal-to-noise ratios (SNRs) of the gated PET images.

Table 4.5 lists the SNRs of the images. Figure 4.19 shows the bar chart for the average SNRs. The SNR of an image is measured by the logarithm of the ratio of
mean to standard deviation in a 10 mm spherical ROI placed in the lung region. As the table shows, the average SNR gain by motion correcting and summing all the registered images is nearly 8 dB. The two motion correction methods achieve similar SNRs, because essentially they utilise the same amount of coincidence events. The SNR after motion correction is close to that of the ideal image.

In summary, the lesion size estimate and the lesion contrast are substantially improved after motion correction, compared to uncorrected images. Of the two methods in comparison, the proposed method, i.e. the PET-NAC based method, performs better. The improvements make detection of a small lung lesion possible in clinical diagnosis. It also means the lesion characteristics can be more accurately measured in thoracic PET imaging, which provides more reliable information for radiologists. Image quality, in terms of the SNR, is also improved after motion correction, compared to a single gate image.

4.4 Discussion and Conclusions

The method we have proposed is essentially summation of the aligned PET-NAC images with subsequent attenuation correction. As mentioned in the Introduction Section, another strategy capable of handling non-rigid respiratory motion is to perform motion correction using a time-varying system matrix. This method has been shown to provide better correction performance than summation of aligned images. In Lamare’s study [100], regarding the lesion measurement in Gate 1 as ground truth, the time-varying system matrix method had a lesion contrast estimation error of 0.13-5.28%, whereas summation of aligned images had an estimation error of 0.69-10.83%. In this study, the time-varying system matrix was derived from gated CT images, which substantially increased the radiation burden. A possible alternative is to use motion information from gated PET-NAC images instead. A disadvantage of this method is that the system matrix is normally very large, with its dimension being determined by the number of voxels and the number of projection bins, and is in the order $10^{13}$ [103]. Calculating a time-varying system matrix poses a major challenge for computational resources. In
Lamare’s study, the normal reconstruction time for a list-mode data set of 10 million coincidence events was less than 4 minutes per iteration and 7 iterations were found to be optimum. Incorporating a time-varying system matrix into the reconstruction and attenuation correction process increased the time by over a factor of 10. Although an accelerated version of the method based on tri-linear interpolation had also been implemented, this version introduced inaccuracies in regions with large deformations and sacrificed motion correction performance by about 10-20% in terms of the accuracy of lesion measurement. On the contrary, our method only needs to sum the registered PET-NAC images and apply a voxel-wise ACF image. The latter is essentially voxel-wise multiplication of two images, and overall the summation and multiplication together take a few seconds. Therefore, it is straightforward to implement and computationally fast.

An alternative method for attenuation correction is to deform the CT image from the reference gate to the other gates using the deformation fields obtained from PET-NAC image registration, resulting in a number of CT images for each gate. The gated PET data can then be attenuation corrected by the CT images and reconstructed to form gated PET-AC images. However, a disadvantage with this method is that the resulting gated PET-AC images represent each phase of the respiratory cycle and still require registration to the reference position. Since CT image deformation (reference to other gates) and PET-AC image alignment (other gates to reference) use the deformation fields in both directions (direct and inverse) and the B-spline deformation field is non-invertible or computationally expensive to be inverted [7, 34], image registration needs to be performed twice in both directions. As mentioned in the Results Section, the computational cost mainly depends on image registration. As a result, the alternative method will double the computational cost and is less preferable.

This study mainly aims to address the problem of respiratory motion in thoracic PET imaging and to recover image quality especially for the lungs. Cardiac motion is another major physiological motion in the thorax, which affects image quality. Since the cardiac period (about 1 second) is different from the respiratory period (about 5 seconds), respiratory gating could not provide enough information about cardiac
motion. Therefore, for cardiac studies, cardiac gating has to be used. In addition, dual cardiac-respiratory gating is being explored by some research groups [95, 97, 120], where PET data are divided into a number of gates according to both the cardiac phase and the respiratory phase. The proposed method has the potential to be extended to motion correction in cardiac imaging.

As mentioned in the Results Section, smaller lesions are more susceptible to respiratory motion. Their contrasts are also lower than larger lesions due to the PVE, even after motion correction or in the ideal image. This is a problem caused by the limited spatial resolution of the PET scanner. Reliable detection of small lesions, for example 8 mm lesions, depends on the combination of both respiratory motion correction and improved spatial resolution, as provided by the latest HD-PET scanners. In addition, partial volume correction is also an important aspect in order to improve the accuracy of quantitative measurements.

In this study, both the NCAT phantom used for data simulation and the image registration algorithm are based on B-splines, but in different ways. The NCAT phantom models the organ shapes with non-uniform rational B-spline (NURBS) surfaces. Respiratory motion is implemented by transforming the control points of the NURBS surfaces according to the motion model of each organ [174]. In B-spline registration, uniform B-splines are used to model the deformation field. B-splines are essentially basis functions for describing a 3D vector field. They are more suitable in describing the field than some other basis functions such as the radial or Fourier basis functions, because B-splines have the properties of compact support, good approximation, and fast evaluation [98]. Since the deformation field is normally a continuous function without singularities, it can be well approximated by a number of B-splines using a suitable knot spacing. Therefore, B-spline registration has found its use for image alignment and motion estimation in many applications of various imaging modalities [72, 98, 104, 166]. Regarding the application of respiratory motion correction, B-spline registration should also work for clinical patient data.

We acquired three real data sets from Siemens Molecular Imaging, Oxford. The data sets were originally scanned at the Maastro Clinic, Maastricht, Netherlands. All
Figure 4.20: The gated PET-AC images at end-expiration and at end-inspiration, as well as the CT image used for attenuation correction. The red lines represent the reference positions of the bottoms of the two lungs, marked based on the CT image.

The data were respiratory gated in acquisition using eight gates. However, unfortunately, the data had already been attenuation corrected using the same CT scan at the mid-expiration phase and then reconstructed, resulting in a number of gated PET-AC images. Raw PET data or gated PET-NAC images were not available. As a result, all the gated PET-AC images mimic the CT scan. Figure 4.20 shows the gated PET-AC images at end-expiration and at end-inspiration, as well as the CT image used for attenuation correction. As is clear, the two PET images look similar and the bottoms of the lungs seem to be at the same position as in the CT image. Such images provide little information about motion and are not suitable for motion correction purposes. Registration of the images yielded almost uniform deformation fields. Therefore, our method was only evaluated on simulated PET data.

It would be interesting to acquire raw clinical PET data in the future, so that gated PET-NAC images can be reconstructed for evaluating the method. A common roadblock in translating the motion correction method from simulated data to real clinical data is that real data often have a different spatial resolution and noise level from
simulated data, which would affect the performance of image registration. Despite the inconsistency in data properties, Dawood et al. successfully translated their method from phantom data to clinical patient data [37, 40]. Their study showed that the noise level has a significant impact on registration accuracy. However, under normal acquisition conditions (20 minute acquisition), their motion correction method performed well.

In conclusion, the proposed method compensates for respiratory motion, which is inevitable in thoracic imaging, without increasing the acquisition time or the radiation burden. Motion is estimated and corrected for by registering the gated PET-NAC images to the reference position. Attenuation correction is performed using a voxel-wise ACF image generated from a single CT scan, which aligns with the phase of the motion corrected PET image. As experimental results show, the motion corrected image improves image quality in terms of the visibility of possible lesions, the lesion size and contrast. The resulting image is able to provide improved information for radiologists in lung cancer diagnosis and staging.
Chapter 5

Detection of Lung Lesions in Thoracic PET/CT Images

5.1 Introduction

Lung lesion detection in thoracic PET/CT images plays an important role in the diagnosis of lung cancer. PET/CT combines functional and anatomical information and is currently the best imaging modality for lung lesion detection. However, the detection of lung lesions, especially small lung lesions (≤ 12 mm), is a difficult task for the following reasons. First, many of the conventional PET scanners have relatively poor spatial resolution (about 5 mm FWHM). Although CT has high spatial resolution, often it alone cannot determine whether or not a lesion is malignant and PET has to be used. In a PET image, a small lesion is only 2 or 3 voxels in diameter and so is easily missed by human observers. The partial volume effect (PVE) for a small lesion further leads to underestimation of the lesion contrast and aggravates this problem. Second, respiratory motion substantially degrades image quality, blurring small lesions and reducing their visibility. Motion correction has to be performed in order to recover image quality. Third, visual inspection of a large number of 3D images is both time-consuming and tedious. Also, it can be error-prone. For these reasons, a computer aided method for processing and analysing thoracic PET/CT images is required, which can automatically detect lung lesions and which can provide the radiologist with a map of potential lesions.
for decision. In this way, diagnostic efficiency can be improved.

In the literature, the performance of lesion detection has been used by many researchers as a figure of merit to evaluate and compare different image acquisition, attenuation correction and image reconstruction protocols [44, 49, 85, 101, 129, 150]. A model observer, such as the Hotelling observer or the channelised Hotelling observer, is often used to evaluate the lesion detection performance. In these applications, however, lesion detection is only used as a tool to study image quality. Automatic lesion detection is not the focus of the research. The mean and covariance images with respectively lesion presence and lesion absence have to be used by the model observer, which means that the location and the intensity of a possible lesion is assumed to be known in these applications.

In previous efforts to address the problem of lesion detection, Huang et al. proposed statistical hypothesis testing on a suspected region of interest (ROI), where the null hypothesis and the alternative hypothesis are namely uniform distribution (lesion absence) and inhomogeneous distribution (lesion presence) [76]. The mean and covariance in the ROI are estimated in the reconstruction using the hypothesised models as priors. However, the suspected ROI needs to be selected by a clinician, which means that human interaction is required and so the method is only semi-automatic. Ballangan et al. detected lesions based on the difference between the CT lung segmentation and a lung atlas, and then confirmed the detected lesions by checking the intensities in the PET image [12]. The method combines well the high resolution of CT and the malignancy sensitivity of PET, but it might miss some lesions if they are seen only on PET and not seen on CT, or at least if they are not so obvious on CT. Ying and Jafar proposed to segment the lungs in either the PET transmission image or the CT image, then to detect lesions in the lungs by multiple thresholding [82, 219]. As multiple thresholding results in a large number of lesion candidates, many of which are false positives, these candidates are then selected and ranked according to some empirical rules formulated by radiologists. Saradhi et al. applied the framework of pattern classification and trained a classifier for lesion detection using texture-based features [167]. Tomei et al. compared two classifiers, namely the Hotelling classifier and the support vector
machine, using wavelet coefficients as features \cite{194}. The classifiers go through all the voxels, classifying each voxel as either lesion or background. A well-designed classifier can have an excellent performance on a specific task, but many samples are required for training the classifier.

In this work, an automatic method is proposed for lung lesion detection. It differs from previous work in two respects. First, lesion detection is performed from the perspective of interest point detection, that is, the detection of bright blobs on a dark background. A scale-invariant blob detection algorithm is applied to the image for lesion detection. No training set is required in the method. Second, lung lesion detection is performed on images which have been corrected for respiratory motion, so that the lesion contrast is recovered and lesion mis-localisation can be avoided. As a result, the detectability of a small lesion is increased. The proposed method is evaluated using both simulated data and real clinical patient data. Experimental results show that most of the lung lesions can be successfully detected by the method, and respiratory motion correction significantly increases the success of lesion detection, especially for small lesions.

5.2 Methods

5.2.1 Scenario

In this method, we assume that respiratory gated PET scans and a single CT scan are acquired. The PET data are corrected for respiratory motion using the method proposed in Chapter 4. The resulting motion corrected PET-AC image aligns with the CT image in the respiratory phase. The PET and CT images are to be processed and analysed by this method.

The lungs can be automatically segmented on the CT image either by intensity thresholding combined with morphological operations \cite{75} or by atlas registration \cite{184}. We adopt the former approach. The lungs are segmented by Otsu thresholding \cite{135} because they exhibit completely different intensities from the other organs and the
Figure 5.1: The flowchart for lung lesion detection.
body. Then the airways are removed from the lungs also by Otsu thresholding. Finally, morphological closing is applied to the lungs in order to smooth the segmentation and fill in the holes caused by pathologies. Lung segmentation is not the focus of our work and has been developed by many other researchers [8, 24, 75, 184, 185]. Therefore, we do not elaborate this process in this thesis.

Since the motion corrected PET image aligns with the CT image, we can apply the lung mask segmented from the CT image to the PET image. As a result, lesion detection can be confined to the lungs. The lesion detection method consists of two stages. In the first stage, a scale-invariant blob detector is used with a low threshold, resulting in many lesion candidates. In the second stage, these lesion candidates are further screened by the contrast and size criteria. The threshold for lesion detection is determined using the noise characteristics of the reconstruction.

The whole framework is illustrated in Figure 5.1.

5.2.2 Scale-invariant Lesion Candidate Detection

In the area of computer vision, a blob refers to a region in an image which is either brighter or darker than its surroundings. Blob detection [110], together with edge detection [27], corner detection [66, 186], and ridge detection [188], are referred to as feature detection or interest point detection [122], which is an important low-level operation in image processing. Because a malignant lung lesion accumulates FDG and appears brighter than the surrounding normal tissue in the PET image, we consider it as a blob and apply a scale-invariant blob detector to the PET image for lesion detection.

The scale-invariant blob detector consists of a bank of Laplacian-of-Gaussian (LoG) filters, each of which has a different scale and which is best suited to detecting blobs at this scale [110, 111]. Given a 3D PET image \( f(x, y, z) \), the image is convolved with a Gaussian kernel \( h(x, y, z; \sigma) \):

\[
L(x, y, z; \sigma) = f(x, y, z) \ast h(x, y, z; \sigma),
\]

\[
h(x, y, z; \sigma) = \frac{1}{(\sqrt{2\pi\sigma})^3} e^{-\frac{x^2+y^2+z^2}{2\sigma^2}},
\]

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where \((x, y, z)\) denotes the coordinates in 3D, \(*\) denotes the convolution operator, \(L(x, y, z; \sigma)\) denotes the scale-space representation of the image, \(\sigma\) denotes the variance of the Gaussian kernel and represents the scale. The local Hessian matrix for \(L(x, y, z; \sigma)\) is calculated:

\[
H = \begin{pmatrix}
L_{xx} & L_{xy} & L_{xz} \\
L_{xy} & L_{yy} & L_{yz} \\
L_{xz} & L_{yz} & L_{zz}
\end{pmatrix}.
\]  

(5.3)

Let \((p, q, r)^T\) be a local coordinate system so that \((x, y, z)^T = A \cdot (p, q, r)^T\). The Hessian matrix with respect to \((p, q, r)^T\) is related to the original Hessian matrix:

\[
\begin{pmatrix}
L_{pp} & L_{pq} & L_{pr} \\
L_{pq} & L_{qq} & L_{qr} \\
L_{pr} & L_{qr} & L_{rr}
\end{pmatrix} = A^T \begin{pmatrix}
L_{xx} & L_{xy} & L_{xz} \\
L_{xy} & L_{yy} & L_{yz} \\
L_{xz} & L_{yz} & L_{zz}
\end{pmatrix} A.
\]  

(5.4)

If we construct the local coordinate system using the eigenvectors of \(H\), i.e. the columns of \(A\) comprise the eigenvectors, then the Hessian matrix with respect to the new coordinate system becomes diagonalised:

\[
\begin{pmatrix}
L_{pp} & L_{pq} & L_{pr} \\
L_{pq} & L_{qq} & L_{qr} \\
L_{pr} & L_{qr} & L_{rr}
\end{pmatrix} = \begin{pmatrix}
\lambda_1 \\
\lambda_2 \\
\lambda_3
\end{pmatrix}.
\]  

(5.5)

As a result, the local second order structure is decomposed in the new coordinate system and is characterised by the eigenvalues \(\lambda_1\), \(\lambda_2\), and \(\lambda_3\). Since we are looking for bright blobs on a dark background, for which all of the three eigenvalues should be negative and of a large magnitude \[55\], we define the blob-like feature as

\[
L_b(x, y, z; \sigma) = \begin{cases} 
-\sigma^2 \cdot (\lambda_1 + \lambda_2 + \lambda_3) & \text{if } \lambda_i < 0, \ i = 1, 2, 3 \\
0 & \text{otherwise}
\end{cases}
\]  

(5.6)
where multiplying by $\sigma^2$ ensures the scale-invariance of the detector. Otherwise, the magnitude of the detector response decreases with the scale $\sigma$, i.e. larger blobs tend to produce smaller responses [111]. A negative symbol is also added to the equation so that a bright blob has a positive response. The sum of the eigenvalues is actually equal to the Laplacian of Gaussian. Therefore, this detector is essentially a normalised Laplacian-of-Gaussian filter.

The maximum of the detector response across all the scales is a measurement of the saliency of the blob-like feature at the most suitable scale:

$$L_{b,m}(x, y, z) = \max_{\sigma} L_b(x, y, z; \sigma),$$  \hspace{1cm} (5.7)

$$\sigma^* = \arg \max_{\sigma} L_b(x, y, z; \sigma),$$  \hspace{1cm} (5.8)

where $L_{b,m}(x, y, z)$ measures how much the local signal at $(x, y, z)$ looks like a blob, and $\sigma^*$ denotes the optimal scale, at which a Gaussian kernel matches the local signal.

The maximum of the detector response in space localises a blob:

$$(x^*, y^*, z^*) = \arg \max_{x,y,z} L_{b,m}(x, y, z) = \arg \max_{x,y,z} L_b(x, y, z; \sigma^*),$$  \hspace{1cm} (5.9)

where $(x^*, y^*, z^*)$ denotes the location of the blob. We define a lesion candidate as a blob, whose maximum response is larger than or equal to a threshold: $L_b(x^*, y^*, z^*; \sigma^*) \geq t_b$.

At this stage, we apply a relatively low threshold, in order to detect a large number of lesion candidates, including both true positives and false positives.

### 5.2.3 Lesion Candidate Screening

In the second stage, we measure the size and the contrast of each lesion candidate and screen the lesion candidates according to empirical criteria. The size and the contrast are measured by 3D weighted Gaussian fitting. Since the majority of the small lesions are approximately spherical or ovoid in shape [70], and the point spread function (PSF) of a PET imaging system can be approximately modelled as a Gaussian distribution
especially when a Gaussian post-filter is used in reconstruction, it is reasonable to assume that the intensity distribution of a small lesion also follows Gaussian. The lesion model is formulated as

$$g(x, y, z) = k \cdot e^{-\frac{(x-\mu_x)^2}{2\sigma_x^2}} - \frac{(y-\mu_y)^2}{2\sigma_y^2} - \frac{(z-\mu_z)^2}{2\sigma_z^2} + b,$$

where $\mu$ and $\sigma$ denote the position and the size of the Gaussian kernel, $k$ denotes the intensity difference between the lesion and the background, and $b$ denotes the intensity of the background.

The cost function for weighted Gaussian fitting is

$$\min E(\mu, \sigma, k, b) = \sum_{(x,y,z) \in S} [w(x, y, z) \cdot (f(x, y, z) - g(x, y, z))]^2,$$

where $f(x, y, z)$ denotes the observation, $g(x, y, z)$ denotes the Gaussian model, $w(x, y, z)$ denotes the weight, and $S$ denotes the set of voxels used for Gaussian fitting. The cost function is minimised with regard to $\mu$, $\sigma$, $k$ and $b$ using the Levenberg-Marquardt algorithm [148].

The weight $w(x, y, z)$ represents the confidence in the observation $f(x, y, z)$. We have less confidence in those voxels near the boundary of the lungs for two reasons. First, the boundary is affected by possible segmentation errors. Second, the high intensities of the heart and the liver have a spill-in effect on the voxels near the boundary, resulting in overestimation of the voxel intensities [187]. As a result, the voxels near the boundary of the lungs are given lower weights than interior voxels. The weight is formulated as

$$w(x, y, z) = \begin{cases} 
  d/a & \text{if } d < a \\
  1 & \text{if } d \geq a 
\end{cases},$$

where $d$ denotes the distance from the voxel $(x, y, z)$ to the boundary, and $a$ denotes the bandwidth for low-confidence voxels. The distance to the boundary of the lungs is calculated using the Euclidean distance transform [36].

The lesion-to-background contrast $c$ and the size $s$ (FWHM) of the lesion candidate
is given by the Gaussian fit:

\[ c = 1 + \frac{k}{b}, \quad (5.13) \]

\[ s_i = 2\sqrt{2 \ln 2} \cdot \sigma_i, \quad i = x, y, z. \quad (5.14) \]

The lesion candidates from the first stage are screened using the following criteria:

1. The lesion-to-background contrast is larger than or equal to a threshold: \( c \geq t_c \). The contrast threshold \( t_c \) is determined by the PET scanner, the scanning protocol, and the reconstruction algorithm.

2. The size of the Gaussian kernel is larger than or equal to the spatial resolution of the PET scanner and the voxel spacing of the reconstruction: \( s_i \geq \max\{r_i, v_i\}, \quad i = x, y, z \), where \( r \) denotes the spatial resolution, and \( v \) denotes the voxel spacing. Otherwise, it is considered as a noise spike, which also results in a large blob detector response in the first stage.

3. The centre of the Gaussian kernel may be slightly different from the initial position estimate in the first stage. We require the blob detector response of the kernel centre still be positive: \( L_{b,m}(\mu_x, \mu_y, \mu_z) > 0 \).

4. The kernel centre is inside the lungs. This is because we confine lesion detection to the lung region.

### 5.2.4 Determination of Thresholds

Assume that the image in the lung region consists of a background signal \( b \) and Gaussian noise \( n \), i.e. \( f = b + n \), where \( n \sim N(0, \sigma_n) \). The ratio between the noise level \( \sigma_n \) and the background level \( b \) determines the lowest lesion-to-background contrast that we can reliably detect. Figure 5.2 shows a constant background added with Gaussian noise. If we select the contrast threshold as

\[ t_c = 1 + k_c \cdot \frac{\sigma_n}{b}, \quad (5.15) \]
Figure 5.2: The background $b$ added with Gaussian noise $n$. The red dashed line shows $b + k_c \sigma_n$, where $\sigma_n$ denotes the standard deviation of the Gaussian noise.

where $k_c$ is a coefficient to determine the threshold. The probability that the contrast of a random noise spike exceeds the threshold $t_c$, being detected as a false positive, is formulated as

$$P(c > t_c) = P\left((1 + \frac{n}{b}) > (1 + k_c \frac{\sigma_n}{b})\right)$$

$$= \int_{k_c \sigma_n}^{\infty} \frac{1}{\sqrt{2\pi} \sigma_n} e^{-\frac{x^2}{2\sigma_n^2}} dx$$

$$= \frac{1}{2} \cdot \text{erfc} \left( \frac{k_c}{\sqrt{2}} \right), \quad (5.16)$$

where $\text{erfc}(x)$ denotes the complementary error function, $\text{erfc}(x) = \frac{2}{\sqrt{\pi}} \int_{x}^{\infty} e^{-t^2} dt$. The larger the coefficient $k_c$, the less the probability of a false positive being detected. For example, if $k_c = 5$, $P(c > t_c) \approx 2.87 \times 10^{-7}$, that is about 3 false positives for $10^7$ voxels.

Apart from $k_c$, the threshold $t_c$ is also determined by the ratio $\sigma_n/b$. The noise property of PET reconstruction has been studied by many researchers \[14, 52, 152, 208, 215\]. As a result, theoretically, $\sigma_n$ can be estimated. In addition, since we confine lesion detection in the lung region, the background $b$ represent the distribution of radioactivity...
in a single organ and without any lesion. It can be regarded as a smoothly-varying signal. As a result, \( b \) can be estimated either using surface fitting or using smooth-filtering of the PET image. It follows that the ratio \( \sigma_n/b \) can be estimated and the threshold \( t_c \) can be set for each voxel adaptively.

However, theoretical noise estimation of PET reconstruction is not the focus of this thesis and we did not have an available algorithm to estimate it. In order to study the noise property, we estimate noise by calculating the standard deviation of a number of reconstructions of PET data, which are simulated from the same phantom but with different realisations of noise, i.e. using Monte-Carlo estimation. Figure 5.3 shows the mean \( b \), the standard deviation \( \sigma_n \), and the ratio \( \sigma_n/b \), estimated from 18 reconstructions of lesion-free PET data\(^1\). As we can see from the figure, the noise image appears to have the same structure as the mean image, i.e. the higher the mean value, the higher the noise. The ratio \( \sigma_n/b \) is uniform across the image, except for the extreme slices (the uppermost and lowermost slices). This phenomenon has been demonstrated by Barrett et al: for ML-EM reconstruction, they have found that the standard deviation is proportional to the mean value, though not strictly \([14, 215]\). It follows that the ratio \( \sigma_n/b \) is uniform across most of the image. However, for the extreme slices, because many oblique events are lost in 3D PET acquisition and there are fewer coincidence events than the inner slices, reconstruction noise is increased and the ratio \( \sigma_n/b \) becomes larger. Figure 5.4 shows the average profile of \( \sigma_n/b \) along the Z axis of the 3D image. It is clearly seen that the ratio \( \sigma_n/b \) is relatively flat for the inner slices, and increases gradually for the end slices. The above observation suggests that we had better set the contrast threshold \( t_c \) adaptively according to the ratio \( \sigma_n/b \).

In this work, we consider two strategies for selection of the threshold \( t_c \), namely adaptive thresholding and global thresholding. In adaptive thresholding, we assume that \( \sigma_n/b \) is already known, either using theoretical computation or using simulation studies, and is a function dependent on the slice index \( z \). The threshold \( t_c \) is adaptively set for each slice, according to Equation (5.15). This means that higher thresholds are

\(^1\)Of course, more reconstructions result in more accurate Monte-Carlo estimates. Since it took over 32 hours for PET-SORTEO to simulate just one PET data on the cluster, we only simulated 18 PET data.
Figure 5.3: The mean $b$, the standard deviation $\sigma_n$, and the ratio $\sigma_n/b$, estimated from 18 reconstructions of lesion-free PET data. The coronal view (X-Z plane) of the 3D image is shown.

Figure 5.4: The average profile of $\sigma_n/b$ along the Z axis (from the first slice to the 61st slice).
used for the end slices due to higher noise, whereas lower thresholds are used for the inner slices. In global thresholding, we simply apply a fixed threshold to all the slices.

The contrast threshold $t_c$ is an essential parameter in the second stage, whereas in the first stage, the threshold for the blob detector response $t_b$ is relatively flexible, as long as it detects as many true positive lesion candidates as possible. However, we would not like to use a extremely low threshold, which results in too many lesion candidates, significantly increasing the computational cost for the second stage. Therefore, we estimate a reasonable value for the threshold $t_b$. It is empirically set to half the blob detector response of an isotropic lesion of the contrast $t_c$, which is the contrast threshold.

The image region around the isotropic lesion is formulated as

$$
\begin{align}
    f(x, y, z) &= b(t_c - 1) \cdot e^{-\frac{x^2+y^2+z^2}{2\sigma_0^2}} + b,
\end{align}
$$

where $\sigma_0$ denotes the size of an isotropic Gaussian kernel. The diameter of the lesion $s_0$ is measured as the FWHM of the Gaussian distribution, $s_0 = 2\sqrt{2 \ln 2} \sigma_0$. Since the convolution of two Gaussian distributions still follows the Gaussian distribution, the scale-space representation of the image is

$$
L(x, y, z; \sigma) = f(x, y, z) * h(x, y, z; \sigma)
= \frac{b(t_c - 1)\sigma_0^2}{(\sigma_0^2 + \sigma^2)^{3/2}} \cdot e^{-\frac{x^2+y^2+z^2}{2(\sigma_0^2 + \sigma^2)}} + b.
$$

(5.18)

We can then calculate its second derivatives and derive the blob detector response at the centre of the lesion:

$$
L_b(0, 0, 0; \sigma) = \frac{3b(t_c - 1)\sigma_0^2}{(\sigma_0^2 + \sigma^2)^{5/2}}.
$$

(5.19)

The blob detector response achieves its maximum when $\sigma = \sqrt{\frac{2}{3}} \sigma_0 = \frac{1}{2\sqrt{3\ln 2}} s_0$:

$$
L_{b,m} = L_b(0, 0, 0; \sqrt{\frac{2}{3}} \sigma_0) = \frac{18\sqrt{15}}{125} b(t_c - 1).
$$

(5.20)
The threshold $t_b$ is empirically selected as half the blob detector response:

$$t_b = \frac{9\sqrt{15}}{125}b(t_c - 1) ,$$

(5.21)

where $t_c$ denotes the contrast threshold. We use the contrast threshold for the innermost slice to calculate a fixed value for $t_b$, so it is low enough for lesion candidate selection in both the end slices and the inner slices.

Note, an isotropic Gaussian model is used in Equation (5.17) so that the maximum of the blob detector response can be expressed analytically. The maximum response of an elliptical lesion can not be analytically expressed, however, numerical computation shows that the value is close to Equation (5.20). As a result, the threshold $t_b$ is suitable to detect not only an isotropic lesion, but also an elliptical lesion, which has the lesion-to-background contrast $t_c$. Details are shown in Appendix E.

5.3 Results

Experiments are carried out on both simulated PET data and real clinical data. The performance of the lung lesion detector is shown, in terms of the number of true positives and the number of false positives. In addition, the performance of the detector on respectively motion corrected and uncorrected images are compared.

5.3.1 Experiments on Simulated Data

Parameter Selection

The thresholds $t_b$ and $t_c$ for the two stages are determined by the ratio $\sigma_n/b$ and the coefficient $k_c$, where $\sigma_n/b$ is assumed to be known and $k_c$ scales the thresholds. In the following experiments, we plot the receiver operating characteristics (ROC) curves by varying the coefficient $k_c$.

Apart from the thresholds $t_b$ and $t_c$, there are two other parameters whose values need to be set, including: the scale series $\sigma$ and the width $a$.

The parameter $\sigma$ represents a series of scales, at which blobs in an image are observed
and detected. As shown above, an isotropic lesion of FWHM $s_0$ is detected by the blob detector at scale $\sigma = \frac{1}{2\sqrt{3\ln 2}} s_0$. Therefore we set $\sigma = [3, 4, 5, 6, 7]$ mm, which corresponds to lesion diameters ranging from about 8 mm to 20 mm.

The parameter $a$ represents the width of the band along the boundary of the lungs, in which the voxel intensities are given less confidence than the other voxels. Because the high intensities of the liver and the heart cause a spill-in effect on the voxels as far as 15 mm away from the boundary, we empirically set $a = 15$ mm. However, we have found that $a \in [10, 20]$ mm achieves similar performance.

The algorithm was implemented in C++, using the ITK library [79]. It took about 90 seconds to carry out the blob detection algorithm for a PET image of size $160 \times 160 \times 61$, of which 70 seconds were required for Stage 1 and 20 seconds for Stage 2.

**Comparison of Adaptive and Global Thresholding**

First, we compare the strategies of adaptive thresholding and global thresholding. Adaptive thresholding utilises an adaptive ratio $\sigma_n/b$ which is dependent on the slice index, whereas global thresholding fixes the ratio. We vary the coefficient $k_c$, which controls the threshold in Equation (6.15), and test the detector on 18 simulated images. A lesion of different diameters (8, 10, 12 mm) is placed at six different locations in the lung region. The receiver operating characteristic (ROC) curve is plotted, which is a plot of the number of true positives (TP) against the number of false positives (FP) as the threshold varies. It is commonly used to compare the performance of model observers or imaging systems.

Figure 5.5 compares the ROC curves namely for adaptive thresholding and global thresholding on motion corrected images. It shows that at the same level of false positives, adaptive thresholding detects more true positives than global thresholding. However, when $k_c$ tends to 0, both thresholding strategies detect almost all the true positives (17 out of the 18 lesions), at the cost of more false positives. Only the 8 mm lesion at the bottom of the left lung is not detected, because its profile is unclear even after respiratory motion correction, as shown in Figure 5.7 (f).
Figure 5.5: Comparison of the ROC curves namely for adaptive thresholding and global thresholding on motion corrected images as \( k_c \) is varied from 1 to 50. The value of \( k_c \) is marked on the curves.

Figure 5.6: Comparison of the ROC curves namely for motion corrected image and uncorrected image as \( k_c \) is varied from 1 to 50, both using adaptive thresholding for lesion detection. The value of \( k_c \) is marked on the curves.
Comparison of Motion Corrected and Uncorrected Images

The ROC curve evaluates the combined performance of respiratory motion correction and subsequent lesion detection. Therefore, the results of motion correction also affects the ROC curve. Figure 5.6 compares the ROC curves namely for motion corrected images and uncorrected images, both using adaptive thresholding for lesion detection. It illustrates that respiratory motion correction substantially improves the performance of lung lesion detection. At the same level of false positives, the method detects more true positives on the motion corrected images than on the uncorrected images, because the degraded lesion contrasts are restored after respiratory motion correction. We have also noticed that all the missed lesions for the uncorrected images are located at the bottom of the lungs. This is not surprising, since the bottom of the lungs is where the most prominent motion occurs.

Lesion Detection Results

The ROC curve shows that the optimal performance for adaptive thresholding on the motion corrected images is to detect 17 true positives with 0 false positive. Figure 5.7 shows the lesion detection results for a 8 mm lesion at different locations. The arrow indicates a detected lesion, whereas the cross indicates a miss. As the figure shows, although the 8 mm lesion has a marginal contrast and is barely seen by human eyes, all the lesions are successfully detected by the method, except again for the one at the bottom of the left lung. The detection method can serve as a very useful tool to assist radiologists in reading images and finding malignant lung lesions.

5.3.2 Experiments on Real Data

Limitation of the Available Real Data

As mentioned in Chapter 4 the real data we acquired had already been attenuation corrected using a single CT scan. All the gated PET-AC images mimic the CT scan and provide little information about motion. Therefore, they were not used to evaluate the motion correction method. However, the images can still be used for evaluating
Figure 5.7: The lesion detection results for an 8 mm lesion at different locations. The arrow indicates a detected lesion, whereas the cross indicates a miss.

the lesion detection method. We sum the gated PET-AC images and apply the lesion detection method to the summed image.

Parameter Selection

We measured the noise $\sigma_n$ using the standard deviation in a small ROI and estimated the average value of $\sigma_n/b$. The coefficient $k_c$ was set empirically to 10. The thresholds $t_b$ and $t_c$ were then determined. We set $\sigma = 3 \sim 11$ mm, which corresponds to lesion diameters ranging from about 8 mm to 30 mm, and set $a = 15$ mm.

The PET images are of size $128 \times 128 \times 55$, with spacing $5.346 \times 5.346 \times 3$ mm$^3$. Since the body only occupies the central region of the volume and there is almost nothing in the remaining region, we cropped the volume to size $64 \times 64 \times 55$ in order to save
Lesion Detection Results

We invited an experienced chest radiologist to read the PET/CT images in his preferred manner (going through the transaxial slices both forwards and backwards a few times, inspecting both the PET and CT images simultaneously) and, based on this, to mark the malignant lesions and lymph node metastases. The automatic detection results were not shown to the radiologist, in order to avoid interfering with his judgement. We then compared the automatic detection results to those of the expert.

Of the three patient data sets, the radiologist marked 2 lung tumours, 2 left hilar lymph node metastases, and 3 right hilar lymph node metastases. All of these were successfully detected by our method, as shown in Figure 5.8. The left and hilar lymph nodes were detected by our method because they were just on the boundary of the lung mask. As well, the radiologist also marked 6 malignancies outside the lung mask:
1 aortopulmonary lymph node, 1 right paratracheal lymph node, 2 subcarinal lymph nodes, 1 malignancy at the left great vessel, 1 malignancy at the oesophagus. Figure 5.9 shows two examples of the missed metastases. Since our detection method only focuses on the lungs, these malignancies were not considered by our method. Regarding the expert results as ground truth, our method also detected 9 false positives, most of which were of marginal contrasts. Examples of the false positives are shown in Figure 5.10. We also tested the lesion detection performance for $k_c = 8$ and 12. Both thresholds successfully detected all of the lung lesions and hilar lymph node metastases, respectively with 16 and 7 false positives.

In general, our method has demonstrated good performance on real patient data. However, unfortunately, these data only contain medium or large size lesions of high contrasts, and so to date we have not been able to test the performance of our method on small lesions.
5.4 Discussion and Conclusions

The method requires estimation of noise in order to adaptively set the contrast threshold. Theoretically, the noise property of PET reconstruction can be estimated [14, 52, 152, 208, 215]. It follows that the noise property of a motion corrected image can be studied and thus the contrast threshold can be set. However, we use a Monte-Carlo estimate of noise for the simulated images instead, due to lack of an off-the-shelf noise estimation program. Noise estimation of a motion corrected image would be a component of our future work. It not only provides an adaptive threshold, but can also replace the weight in Gaussian fitting since the reciprocal of noise can serve as a measure of confidence in the voxel intensity.

The method confines lesion detection in the lungs so that the increased radioactivity only comes from a malignancy, not from transition from one organ to another. In order to detect lesions in other organs, we can segment each specific organ and apply the detection method to that organ. An alternative is to develop a whole-body lesion detection method, which is also an interesting direction for exploration. However, in a recent study, Tomei et al. showed that, a predictive model fitted to a specific organ performs better than a model trained for the whole body [194].

In the simulated images, we have found that the SUV of a small lung lesion may be as low as 0.5. As a result, the conventionally recommended threshold of 2.5 [139, 164] is not able to differentiate such a small lesion from background. However, our method can accurately detect such a small lesion in the simulated images. Unfortunately, as we have noted above, the available real data sets that we used in this study only contain medium or large lesions, and so we cannot, at this time, extend the claim for our method to small lesions in real clinical data. In order to further test the performance of our method on small lesions, we need to acquire more real data sets, which contain small lesions, whose malignancy can be confirmed by other means, such as needle biopsy.

A promising direction of PET lesion detection is to detect lesions based on dynamic PET images [107, 108]. Dynamic PET imaging differentiates malignant lesions from background based on the fact that lesions and normal tissues present completely dif-
fferent time-activity curves (TACs). As a result, it may be more sensitive to lesions than static PET imaging, which only relies on intensities. However, in order to make full use of the power of dynamic PET on lung lesion detection, respiratory motion correction of the dynamic PET images has to be addressed first. Otherwise, accurate characterisation of the TACs is impossible.

In conclusion, the proposed method can automatically detect lung lesions based on PET and CT images, the results of which can provide radiologists with a map of potential lesions so that diagnostic efficiency can be improved. The CT image provides anatomical information, i.e. the region of the lungs, whereas the PET image is used for lesion detection. The method detects lesions as bright blobs on a dark background and applies an adaptive threshold for the lesion-to-background contrast according to the noise level. Lesion detection is carried out on motion corrected images in order to increase the detectability of lesions. The proposed method is evaluated using both simulated data and real patient data. Experimental results show that respiratory motion correction significantly increases the success of lesion detection, especially for small lesions, and most of the lung lesions can be detected by our method. Therefore, the method can serve as a useful computer-aided image analysing tool to help radiologists read images and find malignant lung lesions.
Chapter 6

Spatio-temporal Image Registration

6.1 Introduction

In Chapter 4, the B-spline registration algorithm was used to align each gated image to the reference gate. That is to say, registration for each gate was performed separately, resulting in a spatial deformation field for each gate. However, since respiration is a temporally smooth process, the deformation fields, considered across all the gates, should also form a continuous and smooth change. Based on this observation, in this chapter we incorporate temporal information into the B-spline registration algorithm in order to improve registration accuracy.

The spatio-temporal registration algorithm was originally proposed by Ledesma-Carbayo et al. to register 2D ultrasound images\[104\]. In this work, we extend the algorithm to a new application, namely 3D PET image registration. The performance of spatial registration and spatio-temporal registration is compared in the context of respiratory motion correction. Simulated PET data are used for validation. Experimental results show that spatio-temporal registration improves registration accuracy, but the improvement is very limited, at the cost of increased computation time. In terms of the motion correction effects, spatio-temporal registration and spatial registration with regularisation achieve very similar performance.

\[1\] Perperidis et al. also proposed a spatial-temporal registration algorithm [140, 141], which has a different meaning. In their work, temporal registration means temporal alignment of two cardiac MR image sequences, instead of temporal smoothness of all the deformation fields.
6.2 Methods

We first revisit the registration algorithm used in Chapter 4 for respiratory motion correction, then introduce the spatio-temporal registration algorithm.

6.2.1 Spatial Registration

In Chapter 4, we used the B-spline registration algorithm to align the test image \( f_t(x) \) to the reference image \( f_r(x) \). It amounts to a minimisation problem of the following cost function:

\[
\min_{\theta} E(\theta) = -CC(f_r(x), f_t(g(x|\theta))) ,
\]

(6.1)

where \( CC \) denotes the normalised correlation coefficient between the reference image \( f_r(x) \) and the deformed test image \( f_t(g(x|\theta)) \), and \( \theta \) denotes the deformation parameter located on a 3D lattice. The deformation field \( g(x|\theta) \) is determined by \( \theta \):

\[
g(x|\theta) = x + d(x|\theta) = x + \sum_{u \in S(x)} w(x, u) \theta(u) ,
\]

(6.2)

where \( d(x|\theta) \) denotes the displacement, \( S(x) \) denotes the spatial support region of \( x \), \( w(x, u) \) denotes the weight, and \( \theta(u) \) denotes the deformation vector at a control point \( u \).

Further, a regularisation term based on the MRF assumption is derived and added to the cost function:

\[
\min_{\theta} E(\theta) = -CC(f_r(x), f_t(g(x|\theta))) + \frac{\beta}{\text{card}(J)} U(\theta) ,
\]

(6.3)

where the first term denotes the data term and the second term denotes the regularisation term, which imposes a local smoothness constraint on the deformation parameter \( \theta \).

Denote the reference gated image by \( f_1(x) \), and the other gated images by \( f_i(x) \), \( i = 2, 3, ..., N \), where \( N \) denotes the number of gates. In order to correct for respiratory motion, the registration algorithm aligns each \( f_i(x) \) to \( f_1(x) \) separately, resulting in a
separate deformation parameter $\theta_i$ for each pair of images:

$$\min_{\theta_i} E(\theta_i) = -CC(f_1(x), f_i(g(x|\theta_i))) + \frac{\beta}{\text{card}(J)} U(\theta_i), \ i = 2, 3, ..., N . \quad (6.4)$$

Since this registration algorithm determines the deformation field using only spatial information, by matching the spatial intensity distribution of a pair of images, we call it “spatial registration” from now on.

### 6.2.2 Spatio-temporal Registration

In spatio-temporal B-spline registration, the deformation fields across all the gated images are considered together, as defined by a 4-D spatio-temporal deformation parameter $\theta$. The registration takes into account the reference image $f_1(x)$ and all the test images $f_i(x)$ in a single cost function:

$$\min_{\theta} E(\theta) = \sum_{i=2}^{N} \left[-CC(f_1(x), f_i(g(x, i|\theta)))\right] , \quad (6.5)$$

where $g(x, i|\theta)$ denotes the deformation field from the reference image $f_1(x)$ to the test image $f_i(x)$. It is determined by

$$g(x, i|\theta) = x + d(x, i|\theta) = x + \sum_{v \in T(i)} \sum_{u \in S(x)} w(i, v)w(x, u)\theta(u, v) , \quad (6.6)$$

where $T(i)$ denotes the temporal support region of gate $i$, $S(x)$ denotes the spatial support region of pixel $x$, $w(i, v)$ and $w(x, u)$ denote the corresponding weights, and $\theta(u, v)$ denotes the deformation vector at a control point $(u, v)$. In this way, the deformation fields across all the gates achieve not only spatial smoothness, but also temporal continuity.
The weights are defined by cubic B-splines:

\[ w(i, v) = b^{(3)} \left( \frac{i}{h_t} - v \right) , \quad (6.7) \]
\[ w(x, u) = \prod_{m=1}^{3} b^{(3)} \left( \frac{x_m}{h_{s,m}} - u_m \right) , \quad (6.8) \]

where \( b^{(3)} \) denotes the cubic B-spline function, \( h_t \) and \( h_s \) denote respectively the temporal and spatial spacing of the lattice, and \( m \) denotes one of the three dimensions in space.

Due to the periodicity of the respiratory motion, the deformation parameter \( \theta \) is also periodic along the temporal direction:

\[ \theta(u, v) = \theta(u, v + \frac{N}{h_t}) . \quad (6.9) \]

In addition, since \( f_i \) is the reference image, we have the constraint that the displacement \( d(x, i|\theta) \) is zero for \( i = 1 \)

\[ d(x, 1|\theta) = \sum_{u \in S(x)} w(x, u) \sum_{v \in T(1)} w(1, v)\theta(u, v) = \vec{0}, \quad \forall x \in R^3 , \quad (6.10) \]

where \( \vec{0} \) denotes a zero-valued displacement vector. Let \( y(u) \equiv \sum_{v \in T(1)} w(1, v)\theta(u, v) \), we have

\[ \sum_{u \in S(x)} w(x, u)y(u) = \vec{0}, \quad \forall x \in R^3 , \quad (6.11) \]

where \( y(u) \) is actually the B-spline coefficient for interpolating a zero-valued image. Since the B-spline coefficients are determined simply by convolution of the image with the direct B-spline filter \([191, 203]\), it leads to \( y(u) = \vec{0} \), i.e.

\[ \sum_{v \in T(1)} w(1, v)\theta(u, v) = \vec{0} . \quad (6.12) \]

The above two constraints, Equations \((6.10)\) and \((6.12)\), comprise additional prior information and help improve the registration performance. Gradient descent is used to
minimise the cost function. The step size is estimated adaptively at each iteration as in Chapter 4. The algorithm is terminated either after a minimal incremental improvement to the cost function or after a pre-set maximum number of iterations.

6.3 Results

In the experiments based on simulated PET images, we compare the performance of spatial registration namely with and without regularisation, as well as spatio-temporal registration. The comparisons are made in terms of computation time, registration accuracy, and motion correction effects.

6.3.1 Parameter Selection

For spatial registration, the parameters were set as in Chapter 4: the control point lattice was set to $20 \times 20 \times 20$, $k_\beta$ was set to 0 or 0.0001, namely representing without or with regularisation. For spatio-temporal registration, the control point lattice was set to $20 \times 20 \times 20 \times 8$, that is one control point per gate along the temporal direction. Regarding optimisation, the minimum incremental improvement to the cost function was set to $10^{-8}$ and the maximum number of iterations was set to 50.

6.3.2 Computation Time

The algorithms were implemented in C++, using the ITK library [79]. For spatial registration without regularisation, it took approximately 42.8 minutes to register one image on a cluster node with a 1.79 GHz CPU and 1GB memory. When regularisation is applied, it took approximately 43.7 minutes, which was only slightly longer than that without regularisation. Since the registration of the seven gated images were carried out in parallel on the cluster, the computation time was still around 43 minutes and the total computational cost amounted to 301 CPU minutes.\footnote{CPU minute is a measurement of computational resource consumption in parallel computing. The number is the sum of the computation time on all of the nodes used for computing. It provides an indication of how much time it would take if a single processor were used.} For spatio-temporal regis-
Figure 6.1: The lesion trajectories estimated by spatial registration without and with regularisation, by spatio-temporal registration, and ground truth. The displacements along the X, Y, and Z directions are shown in different colours.

6.3.3 Registration Accuracy

A lesion of different diameters (8, 10, 12 mm) is placed at six different locations in each of the simulated image. The ground truth lesion trajectory across the gates is given by the NCAT phantom. In order to evaluate the registration accuracy, we compare the lesion trajectory estimated by the registration algorithms to ground truth.
Figure 6.2: The average registration errors of the lungs, the lung lesion and the whole volume using different registration algorithms (unit: mm).

compares the trajectories for a 10 mm lesion located at the bottom of the right lung. As is clear, the trajectory given by spatio-temporal registration is smoother across the gates than by spatial registration and it looks closer to ground truth.

The registration error is defined in the same way as in Chapter 4, regarding the deformation field from noise-free phantom image registration as ground truth. Table 6.1 lists the registration errors of the lungs, the lung lesion and the whole volume for spatial registration without and with regularisation, as well as spatio-temporal registration. Figure 6.2 shows the bar chart for the average registration errors. At it shows, spatial registration without regularisation has the highest registration error. Both spatial registration with regularisation and spatio-temporal registration reduce the error. For example, the average registration error for the lesion using spatial registration without regularisation is 2.35 mm, whereas that for spatio-temporal registration is 2.24 mm. However, the improvement is not striking though noticeable, considering the voxel spacing of $2 \times 2 \times 2.425$ mm$^3$. On average, spatio-temporal registration has the lowest error.
Table 6.1: The registration errors of the lungs, the lung lesion and the whole volume for spatial registration without and with regularisation, as well as spatio-temporal registration (unit:mm). The errors for a number of simulated images, with lesions at different locations and of different diameters are shown, as well as the mean errors for all the simulated images.

<table>
<thead>
<tr>
<th></th>
<th>Spatial w.o. Lungs</th>
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<th>Spatio-temporal Lungs</th>
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Figure 6.3: Comparison of the uncorrected image and the motion corrected images using different registration algorithms. A 10 mm lesion at the bottom of the right lung is indicated by the red arrow.

6.3.4 Motion Correction Effects

The registration algorithms are used for respiratory motion correction using the flowchart proposed in Chapter 4. Figure 6.3 compares the uncorrected image and the motion corrected images using different registration algorithms. A 10 mm lesion is located at the bottom of the right lung. As the figure shows, all the three registration algorithms improve image quality, recovering the lesion contrast. However, the difference between the three motion corrected images is negligible.

In order to quantitatively compare the motion correction effects by different registration algorithms, we list the lesion-to-lung contrasts for the uncorrected images and the motion corrected images in Table 6.2. Figure 6.4 shows the bar chart for the average contrasts. All of the three registration algorithms substantially increase the lesion-to-lung contrasts compared to the uncorrected images. Among the three algorithms, spatial registration without regularisation performs slightly worse than the other two. Spatial registration with regularisation and spatio-temporal registration achieve very similar performance.
Table 6.2: The lesion-to-lung contrasts for the uncorrected images and the motion corrected images using different registration algorithms, namely spatial registration without and with regularisation, as well as spatio-temporal registration.

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To summarise, spatio-temporal registration produces temporally smooth trajectories. The average registration error is smaller than that of spatial registration. However, the improvement is relatively small, especially when regularisation is used for spatial registration. Regarding respiratory motion correction, spatio-temporal registration achieves similar performance as spatial registration with regularisation.

6.4 Discussion and Conclusions

In this exploration, the improvement of displacement trajectory estimation introduced by temporal information is relatively small, probably due to the limited number of gates per period. There are only eight gates and so each gate covers one-eighth of a period. Estimation of the deformation field at a gate gains limited information from its neighbouring gates. For example, motion estimation at the end-expiration gate (Gate 3) is not helped much by the 75% expiration gate (Gate 2) and the 25% inspiration gate (Gate 4). On the contrary, in Ledesma-Carbayo’s application of ultrasound cardiac motion estimation [104], there are 25 frames per period. As a result, each frame resembles its neighbouring frames and so motion estimation gains a lot from the intro-
duction of temporal information. More gates could be used in respiratory gated PET imaging so that motion can be captured more accurately and spatio-temporal registration may demonstrate its benefit more obviously. However, it would reduce the number of coincidence events per gate and results in noisier reconstructed images, which would negatively affect the registration performance. So normally less than 10 gates are used for respiratory gating in current research [39, 100, 138].

Spatio-temporal registration takes much longer computation time than spatial registration because of the additional temporal dimension in the deformation parameter. In order to evaluate the deformation of a voxel, which is the major computational cost of a registration program, more control points have to be evaluated for spatio-temporal registration than for spatial registration. As a result, computation time is substantially increased. However, GPU implementation or parallel implementation of the spatio-temporal algorithm on the cluster may reduce computation time to an acceptable level. Currently, we can only run the spatial registration algorithm parallel on the cluster for each image pair.

We have not introduced regularisation into the spatio-temporal registration algorithm so that any change of performance is completely caused by introduction of temporal information. In addition, the deformation parameter now becomes 4D. Regularisation for a parameter on the 4D lattice requires further exploration.

As a conclusion, in the application of respiratory motion correction, spatio-temporal registration improves the performance slightly at the cost of longer computation time. We would prefer to use spatial registration with regularisation because it is superior in speed and does not sacrifice the motion correction effects, in terms of the recovered lesion contrast.
Chapter 7

Conclusions and Future Work

In this chapter, we summarise the main conclusions and contributions of this thesis and present possible directions for future work.

7.1 Conclusions

This thesis addresses the challenge of respiratory motion in PET imaging, which has a negative impact on image quality and lung cancer diagnosis. In Chapter 1 we briefly introduced the lung cancer, which is the most common cause of cancer death. PET/CT combines both functional and anatomical information and provides a powerful tool for lung cancer diagnosis and staging. However, thoracic PET images are substantially degraded due to respiratory motion, not only by being blurred, but also by being inaccurately attenuation corrected due to the mismatch between PET and CT. If these challenges are not addressed, the diagnosis of lung cancer may be misled. In Chapter 2 we reviewed common image modalities concerned with lung cancer diagnosis, including radiography, CT, MRI and PET. The focus of the chapter is on PET, introducing the basic principles, data correction and reconstruction techniques of PET, as well as multi-modality PET/CT and PET/MRI. In Chapter 3 we described the simulated PET data set used for this work, the simulation tools and protocols.

Chapter 4 presents the main contribution of this thesis. A novel process for respiratory motion correction is proposed, in which non-attenuation corrected PET images
PET-NAC are registered to a reference position for motion correction and then multiplied by a voxel-wise ACF image for attenuation correction. The ACF image is derived from a CT image which matches the reference position in respiratory phase, so that no attenuation correction artefacts would occur. The motion corrected images show significant improvements over the uncorrected images, which represent the acquisitions typical of current clinical practice. The improvements include better characterisation of lesion size and increased lesion-to-lung contrast. However, the method was only validated on simulated data set, due to the limitation of available real data. The enhanced image quality of simulated images shows that our method has the potential to improve diagnostic performance on thoracic PET images.

Chapter 5 explores the technique of automatic lesion detection on motion corrected PET images. A small lung lesion is only 2 or 3 voxels in diameter and of marginal contrast. It could easily be missed by human observers. In this chapter, we proposed an automatic lesion detection method, which can provide radiologists with a map of potential lesions for decision. It consists of two stages. First, a scale-invariant blob detection algorithm finds a number of lesion candidates. Then, the lesion candidates are screened mainly based on the lesion-to-background contrast, the threshold of which is adaptively determined by local noise level. In the experiments with simulated images, our method successfully detected almost all the lung lesions, even for lesions as small as 8 mm. It also shows that respiratory motion correction and adaptive thresholding are beneficial for small lesion detection. In the experiments with a few clinical patient images, all of the lung lesions and hilar lymph node metastases were successfully detected.

In Chapter 6 we explored the possibility of incorporating temporal information into respiratory gated PET image registration. Conventionally, gated PET images are individually registered to the reference position. Temporal continuity across the gates is not considered. In this chapter, a spatio-temporal registration algorithm was proposed, which models temporally smooth deformation in order to improve registration accuracy. We discovered that the improvement of registration accuracy is relatively small at the cost of a much longer computation time. Spatial registration with regularisation yields similar motion correction results but is superior in speed. Therefore, it is preferable for
respiratory motion correction.

7.2 Future Work

Extensions to current work and directions for future exploration are listed below.

7.2.1 Simulated and Real PET Data

In this thesis, we validated our motion correction method mainly based on simulated PET data. The data was simulated by combining the NCAT phantom and the PET-SORTEO simulator. As the thesis was in its final draft, we learnt that a new version of the phantom, the extended cardiac torso (XCAT) phantom, has been released [176]. The new version includes highly detailed whole-body anatomies (more than 9000 anatomical objects) for both the male and the female based on high resolution CT images (0.33 mm resolution), whereas the older version was developed on relatively low resolution images (0.898×0.898×1 mm³) and only for the male. It also includes more accurate respiratory and cardiac motion models. Therefore, the new phantom allows simulation of more realistic data. In addition, the new phantom includes vector programs to output motion vectors from the phantom, which enables validation of the registration results. However, the developers of the phantom have started to charge a license fee for both the NCAT and the XCAT phantoms from this year. Originally, it was free of charge.

Validation of the motion correction method is limited by the availability of real PET data. The real data that we acquired has already been attenuation corrected using the CT scan at the mid-expiration phase and then reconstructed. As a result, only gated PET-AC images are available. All these images mimic the CT scan and provide little information about motion. In order to validate our method, raw PET data, which has not been attenuation corrected, is required, so that PET-NAC images can be reconstructed for registration.
7.2.2 Image Registration

In our experiments, it took over 40 minutes to register a PET image using the B-spline registration algorithm. Speedup of the algorithm would allow faster access for clinicians to the motion corrected image after a PET scan. The computation time of B-spline image registration mainly depends on the number of voxels, the maximum number of iterations, choice of similarity metric, image interpolation algorithm, optimisation algorithm and source code implementation.

Reduction of the number of voxels can be realised via a multi-resolution framework, which registers a pyramid of images from coarse-to-fine levels. We intend to test an ordered subset framework, which is a modification of multi-resolution. Order subsets are commonly used in image reconstruction, but have never been applied to image registration. In ordered subset registration, a high-resolution image \( f(x, y), 0 \leq x, y \leq N \) is downsampled to form a subset of low-resolution images \( \{f(2x, 2y), f(2x + 1, 2y), f(2x, 2y + 1), f(2x + 1, 2y + 1)\}, 0 \leq x, y \leq N/2 \). Registration successively goes through the images, searching for optimal transformation parameters. The conventional multi-resolution framework only registers the image \( f(2x, 2y) \) at the low-resolution level. As a result, it loses 75% information at this level. The ordered subset framework is able to utilise all the information at any level of the pyramid. It might improve the registration performance, but still needs testing.

It is a popular trend to accelerate an algorithm using GPU or parallel implementation. Since the computation in image registration is voxel-wise and can be easily divided to a number of independent tasks, it may be possible to use GPU or parallel programming to speed up the registration algorithm. This task requires learning new programming skills and may be challenging. At the time when I was revising the thesis, I found that GPU-based B-spline registration has just been implemented by Marc Modat et al. at UCL and released as an open source software package named NiftiReg\[1\]. It has been shown to increase the speed by over 10-fold than CPU-based implementation.

\[1\]http://sourceforge.net/projects/niftyreg/
Another registration algorithm which has been used in motion correction of PET images is the optic flow method [40, 96]. The optic flow method assumes that the intensity of a moving point keeps constant and the movement between frames is sufficiently small. It is not good at registering images with varying intensities or handling large deformations. However, it does not involve image interpolation in motion estimation. As a result, it may be faster than the B-spline registration algorithm we use, which performs image interpolation in each iteration for calculating the similarity metric. It is interesting to compare the optic flow method with the B-spline registration algorithm, in terms of speed and registration accuracy.

7.2.3 Correction for Cardiac PET

Cardiac PET has been used increasingly by clinicians over the past decade, as a powerful and non-invasive imaging technique to provide both diagnostic and prognostic evidences for coronary artery disease (CAD) [17, 143]. However, like thoracic PET imaging, cardiac PET imaging is also negatively affected by motions, not only by cardiac motion but also by respiratory motion. For example, a study shows that mis-registration of PET and attenuation CT images results in severe artefacts, leading to frequent diagnostic errors [60]. In order to correct for the motions, dual cardiac-respiratory gating is being explored by some research groups [95, 97, 120], where PET data are divided into a number of gates according to both the cardiac phase and the respiratory phase. The motion correction method that we have developed in this thesis has the potential to be applied to cardiac PET.

However, there is a roadblock in translating the method from thoracic PET to cardiac PET. Thoracic PET usually acquires data in the static acquisition mode, resulting in a single PET image for diagnosis. On the contrary, cardiac PET often acquires dynamic data, that is a number of dynamic frames across time. Parameters of importance for diagnosis, such as myocardial blood flow (MBF) or coronary flow reserve (CFR), are then derived from time-activity curves (TACs) [6, 89, 115, 143]. All of the dynamic frames are contaminated by motion and requires motion correction individually.
Because the starting frames are very short (5 to 10 seconds), gated images for these frames are very noisy, which affects registration accuracy. Motion correction for the short frames may not be successful. A possible solution is to estimate a global motion pattern from gated images for the whole duration of dynamic PET. The global motion pattern is relatively accurate and can be applied to each individual frame for motion correction.

7.2.4 Noise Estimation

In Chapter 5, we discovered that noise estimate is useful for lesion detection. A lesion candidate in a low noise region is probably a lesion, whereas a candidate in a high noise region is very likely to be a noise spike. However, we only estimated a coarse noise distribution from relatively few Monte-Carlo realisations (only 18). As we have mentioned, the noise property of PET reconstruction has already been studied by many researchers [14, 52, 152, 208, 215]. It would be an extension to current work that the noise property of a motion corrected image is at least approximately derived, based on the noise property of each gated PET image, and then applied to adaptive lesion detection.
Appendix A

TNM Staging System

Table A.1: Stage Grouping - TNM Subsets*. Taken from [125].

<table>
<thead>
<tr>
<th>Stage</th>
<th>TNM Subset</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Carcinoma <em>in situ</em></td>
</tr>
<tr>
<td>IA</td>
<td>T1N0M0</td>
</tr>
<tr>
<td>IB</td>
<td>T2N0M0</td>
</tr>
<tr>
<td>IIA</td>
<td>T1N1M0</td>
</tr>
<tr>
<td>IIB</td>
<td>T2N1M0</td>
</tr>
<tr>
<td></td>
<td>T3N0M0</td>
</tr>
<tr>
<td>IIIA</td>
<td>T3N1M0</td>
</tr>
<tr>
<td></td>
<td>T1N2M0</td>
</tr>
<tr>
<td></td>
<td>T2N2M0</td>
</tr>
<tr>
<td></td>
<td>T3N2M0</td>
</tr>
<tr>
<td>IIIB</td>
<td>T4N0M0</td>
</tr>
<tr>
<td></td>
<td>T4N1M0</td>
</tr>
<tr>
<td></td>
<td>T4N2M0</td>
</tr>
<tr>
<td></td>
<td>T1N3M0</td>
</tr>
<tr>
<td></td>
<td>T2N3M0</td>
</tr>
<tr>
<td></td>
<td>T3N3M0</td>
</tr>
<tr>
<td></td>
<td>T4N3M0</td>
</tr>
<tr>
<td>IV</td>
<td>Any T Any N M1</td>
</tr>
</tbody>
</table>

*Staging is not relevant for occult carcinoma, designated TXN0M0.
### Table A.2: TNM Descriptors. Taken from [125].

<table>
<thead>
<tr>
<th><strong>Primary tumour (T)</strong></th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>TX</td>
<td>Primary tumour cannot be assessed, or tumour proven by the presence of malignant cells in sputum or bronchial washings but not visualised by imaging or bronchoscopy</td>
</tr>
<tr>
<td>T0</td>
<td>No evidence of primary tumour</td>
</tr>
<tr>
<td>Tis</td>
<td>Carcinoma in situ</td>
</tr>
<tr>
<td>T1</td>
<td>Tumour ≤ 3 cm in greatest dimension, surrounded by lung or visceral pleura, without bronchoscopic evidence of invasion more proximal than the lobar bronchus* (ie, not in the main bronchus)</td>
</tr>
</tbody>
</table>
| T2                     | Tumour with any of the following features of size or extent:  
                           - > 3 cm in greatest dimension  
                           - Involves main bronchus, ≥ 2 cm distal to the carina  
                           - Invades the visceral pleura  
                           - Associated with atelectasis or obstructive pneumonitis that extends to the hilar region but does not involve the entire lung |
| T3                     | Tumour of any size that directly invades any of the following: chest wall (including superior sulcus tumours), diaphragm, mediastinal pleura, parietal pericardium; or tumour in the main bronchus ≤ 2 cm distal to the carina, but without involvement of the carina; or associated atelectasis or obstructive pneumonitis of the entire lung |
| T4                     | Tumour of any size that invades any of the following: mediastinum, heart, great vessels, trachea, esophagus, vertebral body, carina; or tumour with a malignant pleural or pericardial effusion,† or with satellite tumour nodule(s) within the ipsilateral primary-tumour lobe of the lung |

<table>
<thead>
<tr>
<th><strong>Regional lymph nodes (N)</strong></th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>NX</td>
<td>Regional lymph nodes cannot be assessed</td>
</tr>
<tr>
<td>N0</td>
<td>No regional lymph node metastasis</td>
</tr>
<tr>
<td>N1</td>
<td>Metastasis to ipsilateral peribronchial and/or ipsilateral hilar lymph nodes, and intrapulmonary nodes involved by direct extension of the primary tumour</td>
</tr>
<tr>
<td>N2</td>
<td>Metastasis to ipsilateral mediastinal and/or subcarinal lymph node(s)</td>
</tr>
<tr>
<td>N3</td>
<td>Metastasis to contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular lymph node(s)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Distant metastasis (M)</strong></th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>MX</td>
<td>Presence of distant metastasis cannot be assessed</td>
</tr>
<tr>
<td>M0</td>
<td>No distant metastasis</td>
</tr>
<tr>
<td>M1</td>
<td>Distant metastasis present‡</td>
</tr>
</tbody>
</table>

*The uncommon superficial tumour of any size with its invasive component limited to the bronchial wall, which may extend proximal to the main bronchus, is also classified T1.

†Most pleural effusions associated with lung cancer are due to tumour. However, there are a few patients in whom multiple cytopathologic examinations of pleural fluid show no tumour. In these cases, the fluid is nonbloody and is not an exudate. When these elements and clinical judgement dictate that the effusion is not related to the tumour, the effusion should be excluded as a staging element and the patients disease should be staged T1, T2, or T3. Pericardial effusion is classified according to the same rules.

‡Separate metastatic tumour nodule(s) in the ipsilateral nonprimary-tumour lobe(s) of the lung also are classified M1.
Appendix B

PET-SORTEO Protocol File

This is an example of the PET-SORTEO protocol file, which defines the radioactivity concentration and the attenuation medium type for each organ in the NCAT volume “ncat_lesion_right_bottom_d10_1.v”. It tells PET-SORTEO to simulate a 75 second 3D PET scan for the NCAT volume, which is the duration for one gate. The sinogram is saved in the file “ncat_lesion_right_bottom_d10_em1.S”. 16 nodes are used for parallel simulation.

```plaintext
protocol_begin
configuration emission default3d
frame 75
volume emission ncat_lesion_right_bottom_d10_1.v
eregion 1 myocardium 2 F-18 Bq/cc
tac 0 24950
tac 75 24950
eregion 2 bloodpool 2 F-18 Bq/cc
tac 0 8150
tac 75 8150
eregion 3 body 2 F-18 Bq/cc
tac 0 5100
  tac 75 5100
eregion 4 liver 2 F-18 Bq/cc
tac 0 10850
  tac 75 10850
eregion 6 lung 2 F-18 Bq/cc
tac 0 2400
  tac 75 2400
eregion 7 stomach_wall 2 F-18 Bq/cc
tac 0 7200
  tac 75 7200
```
eregion 9 kidney 2 F-18 Bq/cc
tac 0 83900
tac 75 83900
eregion 10 spleen 2 F-18 Bq/cc
tac 0 8250
tac 75 8250
eregion 11 rib 2 F-18 Bq/cc
tac 0 5100
tac 75 5100
eregion 12 spine_head 2 F-18 Bq/cc
tac 0 5100
tac 75 5100
eregion 13 spine_process 2 F-18 Bq/cc
tac 0 5100
tac 75 5100
eregion 14 pelvis 2 F-18 Bq/cc
tac 0 5100
tac 75 5100
eregion 15 bone_cartilage 2 F-18 Bq/cc
tac 0 5100
tac 75 5100
eregion 16 artery 2 F-18 Bq/cc
tac 0 8350
tac 75 8350
eregion 17 vein 2 F-18 Bq/cc
tac 0 8350
tac 75 8350
eregion 20 intestine 2 F-18 Bq/cc
tac 0 8200
tac 75 8200
eregion 21 rectum 2 F-18 Bq/cc
tac 0 7700
tac 75 7700
eregion 30 airway_tree 2 F-18 Bq/cc
tac 0 0
tac 75 0
eregion 31 lesion 2 F-18 Bq/cc
tac 0 19200
tac 75 19200
volume attenuation ncat_lesion_right_bottom_d10_1.v
aregion 0 background air
aregion 1 myocardium water
aregion 2 bloodpool water
aregion 3 body water
aregion 4 liver water
aregion 5 gall_bladder water
aregion 6 lung lung
aregion 7 stomach_wall water
aregion 8 stomach_contents air
aregion 9 kidney water
aregion 10 spleen water
aregion 11 rib bone
aregion 12 spine_head bone
aregion 13 spine_process bone
aregion 14 pelvis bone
aregion 15 bone_cartilage bone
aregion 16 artery water
aregion 17 vein water
aregion 18 bladder water
aregion 19 prostate water
aregion 20 intestine water
aregion 21 rectum water
aregion 22 seminal_vesicle water
aregion 23 vas_deferens water
aregion 24 testicular water
aregion 25 intest_rectum_air air
aregion 26 ureter water
aregion 27 urethra water
aregion 28 lymph_normal water
aregion 29 lymph_abnormal water
aregion 30 airway_tree air
aregion 31 lesion lung
sinogram emission ncat_lesion_right_bottom_d10_em1.S
process_number 16
protocol_end
Appendix C

Gradient Descent with Adaptive Step Size Estimation

Let the update function of optimisation be $\theta_{n+1} = \theta_n + \Delta \theta$. The cost function $E(\theta_{n+1})$ can be approximated by its Taylor expansion to the second order:

\[
E(\theta_n + \Delta \theta) \approx E(\theta_n) + \Delta \theta^T \cdot \nabla E(\theta_n) + \frac{\Delta \theta^T}{2} \cdot H(\theta_n) \cdot \Delta \theta .
\] (C.1)

In order to avoid computation of the Hessian matrix, which is time consuming due to the high dimension of the variable $\theta$, we assume that $H(\theta_n) = \alpha I$ [98], so that

\[
E(\theta_n + \Delta \theta) = E(\theta_n) + \Delta \theta^T \cdot \nabla E(\theta_n) + \alpha \cdot ||\Delta \theta||^2 .
\] (C.2)

To achieve the local minimum, let

\[
\frac{dE(\theta_n + \Delta \theta)}{d\Delta \theta} = \nabla E(\theta_n) + 2\alpha \cdot \Delta \theta = 0 .
\] (C.3)

It follows that

\[
\Delta \theta = -\frac{1}{2\alpha} \nabla E(\theta_n) .
\] (C.4)

The parameter $\alpha$ can be determined using the previous value of the function $E(\theta_{n-1})$. 

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We have

$$E(\theta_{n-1}) = E(\theta_n) + (\theta_{n-1} - \theta_n)^T \cdot \nabla E(\theta_n) + \alpha \cdot ||\theta_{n-1} - \theta_n||^2.$$  \hspace{1cm} (C.5)

As a result,

$$\alpha = \frac{E(\theta_{n-1}) - E(\theta_n) - (\theta_{n-1} - \theta_n)^T \cdot \nabla E(\theta_n)}{||\theta_{n-1} - \theta_n||^2}.$$  \hspace{1cm} (C.6)

So the update equation is

$$\theta_{n+1} = \theta_n - s \cdot \nabla E(\theta_n),$$

$$s = \frac{||\theta_{n-1} - \theta_n||^2}{2[E(\theta_{n-1}) - E(\theta_n) - (\theta_{n-1} - \theta_n)^T \cdot \nabla E(\theta_n)]},$$ \hspace{1cm} (C.7)

where \(s\) denotes the step size for gradient descent, which is adaptively estimated in each iteration. If the step size does not reduce the value of the cost function, it is set to half of the previous step size as a fallback strategy.
Appendix D

Noise Propagation in Attenuation Correction

For voxel-wise attenuation correction, the final image is determined by multiplying the motion corrected PET-NAC image with the ACF image. The ACF image comes from dividing two PET images and thus suffers from noise. Here we discuss the propagation of noise from the ACF image into the final image.

We adopt the notation of element-wise vector operation in the literature \[14\]. If \(a\) and \(b\) are \(N\times1\) vectors, we have \(ab\) and \(a/b\) defined by

\[
[ab]_i \equiv a_i b_i ,
\]

\[
[a/b]_i \equiv a_i / b_i .
\]

(D.1)

It is the same as the element-wise operators “.*” and “./” in Matlab. This notation is a complement for the conventional notation of vector operation. Note that the expression \(a \cdot b^T\) still follows the conventional notation and represents matrix multiplication, where \(T\) denotes transpose.

For conciseness, we abbreviate Equation (4.17) as follows:

\[
f_{sa} = f_{sn} c ,
\]

(D.2)
where \( f_{sa} \) denotes the final PET-AC image, \( f_{sn} \) denotes the summed PET-NAC image, and \( c \) denotes the ACF image. \( f_{sa}, f_{sn}, \) and \( c \) are \( N \times 1 \) column vectors, where \( N \) denotes the number of voxels.

The first derivative of \( f_{sa} \) with respect to \((c, f_{sn})\) is

\[
\nabla f_{sa} = \begin{pmatrix} f_{sn} \\ c \end{pmatrix} .
\]

(D.3)

Taylor expansion of \( f_{sa} \) to the first order about \((\bar{c}, \bar{f}_{sn})\) is

\[
f_{sa} \approx \bar{f}_{sn}\bar{c} + \bar{f}_{sn}(c - \bar{c}) + \bar{c}(f_{sn} - \bar{f}_{sn}) ,
\]

(D.4)

where the bar denotes the expectation or the mean of a variable. As a result, the expectation of \( f_{sa} \) is

\[
E[f_{sa}] = \bar{f}_{sn}\bar{c} ,
\]

(D.5)

which means the mean of the final image is simply the product of the mean PET-NAC image and the mean ACF image.

Denote the covariance matrix as \( K_{sa} \). It can be calculated as

\[
K_{sa} = E[(f_{sa} - \bar{f}_{sa}) \cdot (f_{sa} - \bar{f}_{sa})^T] .
\]

(D.6)

The element \( K_{sa|ij} \), where \( i \) and \( j \) denote the subscripts of the matrix, is

\[
K_{sa|ij} = \bar{f}_{sn|i}\bar{f}_{sn|j}E[(c_i - \bar{c}_i)(c_j - \bar{c}_j)] + \bar{f}_{sn|i}\bar{c}_jE[(c_i - \bar{c}_i)(f_{sn|j} - \bar{f}_{sn|j})] + \bar{c}_i\bar{f}_{sn|j}E[(f_{sn|i} - \bar{f}_{sn|i})(c_j - \bar{c}_j)] + \bar{c}_i\bar{c}_jE[(f_{sn|i} - \bar{f}_{sn|i})(f_{sn|j} - \bar{f}_{sn|j})] .
\]

(D.7)

A special and important case is the diagonal elements, which give the variance of
each voxel:

\[
K_{sn|ii} = f_{sn|ii}^2 E[(c_i - \bar{c}_i)^2] + \bar{c}_i^2 E[(f_{sn|ii} - \bar{f}_{sn|ii})^2]
+ 2f_{sn|ii}\bar{c}_i E[(c_i - \bar{c}_i)(f_{sn|ii} - \bar{f}_{sn|ii})]
= f_{sn|ii}^2 \text{var}(c_i) + \bar{c}_i^2 \text{var}(f_{sn|ii}) ,
\]

where the first term represents the variance of the ACF image multiplied by the square of the mean PET-NAC image, and the second term represents the variance of the PET-NAC image multiplied by the square of the mean ACF image. This equation describes how noise propagates from the ACF image and the PET-NAC image into the final image.

Since the motion corrected PET-NAC image \( f_{sn} \) is the sum of gated PET-NAC images reconstructed from independent PET data, noise in \( f_{sn} \) can be determined by the reconstruction noises of the gated images. However, the ACF image \( c \) is determined by dividing two PET images reconstructed from the same PET data, whose noises are correlated in a complicated way. Noise in \( c \) is more difficult to be derived. But it could be studied using the Monte-Carlo method. Finally, noises in \( f_{sn} \) and \( c \) can be related to noise in \( f_{sa} \) through Equation (D.8).
Appendix E

Maximum Blob Detector Response of the Lesion Model

Given an anisotropic Gaussian lesion model

\[
  f(x, y, z) = b(t_c - 1) \cdot e^{-\frac{x^2}{2\sigma_x^2} - \frac{y^2}{2\sigma_y^2} - \frac{z^2}{2\sigma_z^2}} + b, \tag{E.1}
\]

where \(\sigma\) denotes the size of the Gaussian kernel, \(b\) denotes the background level, \(t_c\) denotes the lesion-to-background contrast. The scale-space representation of the lesion model is

\[
  L(x, y, z; \sigma) = f(x, y, z) * h(x, y, z; \sigma) = \frac{b(t_c - 1)\sigma_x\sigma_y\sigma_z}{\sigma_u\sigma_v\sigma_w} \cdot e^{-\frac{x^2}{2\sigma_x^2} - \frac{y^2}{2\sigma_y^2} - \frac{z^2}{2\sigma_z^2}} + b, \tag{E.2}
\]

where \(\sigma_u = (\sigma_x^2 + \sigma_y^2)^{1/2}\), \(\sigma_v = (\sigma_y^2 + \sigma_z^2)^{1/2}\), and \(\sigma_w = (\sigma_z^2 + \sigma_u^2)^{1/2}\).

The blob-like feature at the centre of the lesion is

\[
  L_b(0, 0, 0; \sigma) = -\sigma^2 \cdot (\lambda_1 + \lambda_2 + \lambda_3) \\
  = -\sigma^2 \cdot (L_{xx} + L_{yy} + L_{zz}) \\
  = b(t_c - 1)\sigma_x\sigma_y\sigma_z\sigma^2 \cdot \left(\frac{1}{\sigma_u^3\sigma_v\sigma_w} + \frac{1}{\sigma_u\sigma_v^3\sigma_w} + \frac{1}{\sigma_u\sigma_v\sigma_w^3}\right). \tag{E.3}
\]
For the optimal scale $\sigma^*$, we have $\frac{dL_b(0,0,0;\sigma)}{d\sigma}|_{\sigma=\sigma^*} = 0$. It leads to the following polynomial equation:

\[
9 \cdot \sigma^{10} + 10 \cdot (\sigma_x^2 + \sigma_y^2 + \sigma_z^2) \cdot \sigma^8 + 2 \cdot (2\sigma_x^4 + 2\sigma_y^4 + 2\sigma_z^4 + 3\sigma_x^2\sigma_y^2 + 3\sigma_x^2\sigma_z^2 + 3\sigma_y^2\sigma_z^2) \cdot \sigma^6 \\
+ 2 \cdot (\sigma_x^4\sigma_y^2 + \sigma_x^2\sigma_z^4 + \sigma_y^4\sigma_z^2 + \sigma_x^2\sigma_y^2 + \sigma_y^2\sigma_z^4 - 6\sigma_x^2\sigma_y^2\sigma_z^2) \cdot \sigma^4 + (\sigma_x^4\sigma_y^4 + \sigma_x^4\sigma_z^4 + \sigma_y^4\sigma_z^4 - 6\sigma_x^2\sigma_y^2\sigma_z^2 - 6\sigma_x^2\sigma_y^4\sigma_z^2 - 6\sigma_x^2\sigma_y^2\sigma_z^4) \cdot \sigma^2 - 2 \cdot (\sigma_x^4\sigma_y^2\sigma_z^2 + \sigma_x^2\sigma_y^4\sigma_z^2 + \sigma_x^2\sigma_y^2\sigma_z^4) = 0.
\]

(E.4)

There is no analytical expression for the solution of $\sigma^*$. However, for a given ratio of $\sigma_x : \sigma_b : \sigma_z$, we can numerically calculate the value of $\sigma^*$ and the corresponding maximum blob detector response. Table E.1 lists the numerical results for different ratios of $\sigma_x : \sigma_b : \sigma_z$, which represent different shapes of the lesion model. As the table shows, the maximum blob detector response $L_b(0,0,0;\sigma^*)$ for an elliptical lesion is about 5-10% less than that for an isotropic lesion. We set the threshold $t_b$ to half the blob detector response of an isotropic lesion, which is suitable to detect not only an isotropic lesion, but also an elliptical lesion, which has the lesion-to-background contrast $t_c$.

Table E.1: The optimal scale $\sigma^*$ and the maximum blob detector response $L_b(0,0,0;\sigma^*)$ for different ratios of $\sigma_x : \sigma_b : \sigma_z$, which represent different shapes of the lesion model.

<table>
<thead>
<tr>
<th>$\sigma_x : \sigma_b : \sigma_z$</th>
<th>$\sigma^* : \sigma_x$</th>
<th>$L_b(0,0,0;\sigma^*)$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 : 1 : 1</td>
<td>0.8165</td>
<td>0.5577 $\cdot b(t_c - 1)$</td>
</tr>
<tr>
<td>1 : 1 : 2</td>
<td>0.9556</td>
<td>0.5379 $\cdot b(t_c - 1)$</td>
</tr>
<tr>
<td>1 : 1 : 3</td>
<td>0.9869</td>
<td>0.5219 $\cdot b(t_c - 1)$</td>
</tr>
<tr>
<td>1 : 2 : 2</td>
<td>1.2047</td>
<td>0.5270 $\cdot b(t_c - 1)$</td>
</tr>
<tr>
<td>1 : 2 : 3</td>
<td>1.2853</td>
<td>0.5082 $\cdot b(t_c - 1)$</td>
</tr>
<tr>
<td>1 : 3 : 3</td>
<td>1.3955</td>
<td>0.4868 $\cdot b(t_c - 1)$</td>
</tr>
</tbody>
</table>
References


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