Automatic Detection and Segmentation of Brain Lesions from 3D MR and CT Images

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A Dissertation submitted to the Faculty of Engineering
in fulfillment of the requirement for the degree
of Master of Science
at the
University of Cape Town

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May 26, 2014

Declaration

I declare that this dissertation is my own work. All the resources that I have used have been referenced and listed in the Bibliography. It is being submitted for the degree of Master of Science in Engineering at the University of Cape Town and has not been submitted before for any degree or examination at any other university.

I know the meaning of plagiarism and declare that all the work in the document, save for that which is properly acknowledged, is my own.

Signed:_____

Date:_____

Molise Mokhomo

Acknowledgments

I would like to thank the following people

- My supervisor at UCT, Dr. F. Nicolls, for his guidance and motivating me to do this work. Without him this work could have taken months off my life.

- My UCT Co-supervisor, Prof. G. de Jager, for his support and encouragement.

- My supervisor at iThemba LABS, Dr. N. Muller, for his help and encouragement.

- iThemba LABS for the financial support.

- My family for their love and support.

Abstract

The detection and segmentation of brain pathologies in medical images is a vital step which helps radiologists to diagnose a variety of brain abnormalities and set up a suitable treatment. A number of institutes such as iThemba LABS still rely on a manual identification of abnormalities. A manual identification is labour intensive and tedious due to the large amount of medical data to be processed and the presence of small lesions. This thesis discusses the possible methods that can be used to address the problem of brain abnormality segmentation in MR and CT images. The methods are general enough to segment different types of abnormalities. The first method is based on the symmetry of the brain while the second method is based on a brain atlas.

The symmetry-based method assumes that healthy brain tissues are symmetrical in nature while abnormal tissues are asymmetric with respect to the symmetry plane dividing the brain into similar hemispheres. The three major steps involved in this approach are the symmetry detection, tilt correction and asymmetry quantification. The method used to determine the brain symmetry automatically is discussed and its accuracy has been validated against the ground-truth using mean angular error (MAE) and distance error (DE). Two asymmetric quantification methods are studied and validated on real and simulated patient's T1- and T2-weighted MR images with low and high-grade gliomas using true positive volume fraction (TPVF), false positive volume fraction (FPVF) and false negative volume fraction (FNVF).

The atlas-based method is also presented and relies on the assumption that abnormal brain tissues appear with intensity values different from those of the surrounding healthy tissues. To detect and segment brain lesions the test image is aligned onto the atlas space and voxel by voxel analysis is performed between the atlas and the registered image. This methods is also evaluated on the simulated T1-weighted patient dataset with simulated low and high grade gliomas. The atlas, containing prior knowledge of normal brain tissues, is built from a set of healthy subjects.

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Abbreviations

CAD	Computer Aided Diagnosis
CT	Computed Tomography
DE	Distance Error
FLAIR	Fluid-Attenuated Inversion Recovery
FNVF	False Negative Volume Fraction
FPVF	False Positive Volume Fraction
GPA	Generalized Procrustes Analysis
LM	Levenberg-Marquardt
MAE	Mean Angular Error
MI	Mutual Information
MRI	Magnetic Resonance Imaging
MSER	Maximally Stable Extrema Region
MSP	Mid-Sagittal Plane
NMI	Normalized Mutual Information
RECIST	Response Evaluation Criteria in Solid Tumors
SSD	Sum of Square Difference
TPVF	Truth Positive Volume Fraction

Symbols and Notations

R   Reference image

F   Floating image

$\mathbf{T}_i$ 3D affine transformation

$\mathbf{T}_{RF}$ 3D reflection matrix

$\mathbf{M}_I$ Mean intensity volume of the atlas

$\mathbf{M}_V$ Mean displacement field norm

$\mathbf{V}_I$ Intensity variations for each voxel

$\mathbf{V}_V$ Displacement field variations for each voxel

p   Vector point in 3D

u   Optimization parameter

μ Damping factor

λ Maximum intensity difference ratio

ζ Threshold

Chapter 1

Introduction

Medical imaging is a routine and essential part of medicine where computerized applications are used to assist clinicians and radiologists to carry out daily activities within healthcare. A number of applications include computer aided pathology diagnosis, computer aided image registration, planning and guiding treatment, and monitoring disease progression based on the information extracted from medical images. The major advantage of this field is that health problems can be observed directly rather than derived from the symptoms. Health problems can, for example, be broken bones, brain abnormalities, breast, and prostate cancer. In this work much attention is put on computer aided brain lesions diagnosis.

A brain lesion is a localized abnormal structural change of the brain tissues. Various factors that lead to brain lesion development include brain injuries, vascular disorders and brain tumors. Brain lesions are often a threat to life hence their diagnosis and treatment is of great importance to patients suffering from them. Nowadays, different imaging modalities are used to acquire medical images for visualization of internal human body structures such as tissues of the brain and neck. The most common imaging technologies used are computed tomography (CT) and magnetic resonance imaging (MRI). The advantage that MRI has over CT is that it is harmless, since it does not use ionization radiation, and produces high quality images with soft tissue contrast that is much better than that with CT [4]. Moreover, MRI can distinguish tissues that have similar intensities and are hard to distinguish using CT scans.

Automatic detection and segmentation of brain abnormalities from CT or MR images is a challenging task since lesions can appear at any location and have different intensity distributions. However, having prior knowledge about healthy tissues of the brain can simplify this task. The prior knowledge about the symmetry of healthy brain tissues can be used to detect a number of brain pathologies. Additionally it can also be the grey level distribution of healthy tissues which can be presented in the form of the brain atlas. The brain atlas is built from single image or a set of specific population images aligned onto a common coordinate frame through image registration.

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Image registration is the process of bringing two images of the same or different patients taken at the different times into a common coordinate frame such that the images can be compared, combined or analyzed voxel by voxel. The registration technique can either be global or local. Global registration methods apply a single transformation to the entire image to correct rotation, translation, scaling and shearing between the two images. Local registration techniques apply different transformations on each voxel to correct shape differences.

The accurate delineation of brain abnormalities is of great importance for setting a suitable treatment for a patient diagnosed with brain tumors. In this thesis, symmetry and atlas-based methods for automated brain anomaly segmentation are developed and applied to a large dataset of brain T1- and T2-weighted MR images.

1.1 Problem Statement

Hand labeling of brain pathologies in medical images is often regarded as the gold-standard technique to segment brain abnormalities. This method is currently used at iThemba LABS by a radiologist to monitor the response of the brain tumors before and after the treatment. However, this approach becomes tedious in the presence of small sized brain lesions and time consuming due to the large amount of data to be analyzed or the presence of multiple tumors having different sizes. Moreover, the results are usually operator-dependent. Therefore developing an automated computer aided brain pathology diagnostic application can save radiologists time in setting up a suitable treatment for a patient diagnosed with brain tumors.

Numerous automated methods for segmenting brain pathologies have been developed. These methods vary depending on the characteristics of the tumors to be segmented and the type of image modality used [5]. The lesion attributes which have made automated segmentation a challenging task include the variety of shapes and sizes the lesions may possess. Additionally they have a likelihood of appearing at any location and with different intensity distributions. Because of these factors, there is no general brain lesions segmentation method which can be adopted widely in every application.

1.2 Objectives of the Study

Implementing a fast and efficient computer aided diagnosis (CAD) technique for brain pathologies is quite useful. Hence this work seeks to solve the mentioned challenges by developing a model of healthy brain tissues. The model will be used to assist radiologists at iThemba LABS to identify the presence of brain lesions in medical images and to monitor the deviation of the lesions from previous and future CT and MR images before and after the patient is treated. The other objective is to evaluate the accuracy of the implemented methods against the ground truth. This will determine

how well the methods perform under varying condition.

1.3   Contributions

Two knowledge-driven methods have been developed to detect and segment a large number of low and high-grade brain tumors in 3D MR images. They utilize prior knowledge of healthy brain tissues to address a variety of brain pathologies. The prior information used include the symmetry of the brain and expected grey level distribution of healthy brain tissues.

Firstly using the knowledge about the symmetry of a healthy brain, two novel methods have been developed for the quantification of brain asymmetry level to determine brain pathologies. One of the techniques analyzes the intensity difference between the left and right hemispheres to estimate the location of brain pathologies in the two hemispheres. Given the suspected tumor regions, the method further analyzes the intensities of the voxels surrounding these regions to find the ill hemisphere. The other approach uses a region of interest detection method to determine hemispheres with asymmetric tissues which often represent brain tumors. An algorithm that detects the symmetry plane in healthy and abnormal 3D brain scans was also implemented.

Secondly an atlas-based method, which uses prior information about healthy anatomical structures of the brain, is developed to address the mentioned problems. This algorithm is automatic and segments different brain anomalies in test images having a modality similar to those of the images used to build the atlas. An improved atlas construction method is also proposed. The atlas consists of the information similar to the work presented in [6].

1.4   Organization of this Document

The remaining parts of this document are organized as follows. Chapter 2 presents the background knowledge of the brain tumor characteristics and covers the literature of the different computer aided diagnostic methods used to detect and segment brain lesions. Chapter 3 describes global medical image registration with much attention paid to 3D image datasets. In Chapter 4, the proposed two methods used to detect and segment brain anomalies are presented. The first approach is based on the symmetry of a healthy human brain while the second technique is founded on a model of healthy brain tissues. The implementation and testing of brain symmetry detection and analysis methods are given in Chapter 5. Chapter 6 describes the implementation and results of the atlas-based method. Finally, Chapter 7 concludes the thesis and gives suggestions for future work and for some improvements.

Chapter 2

Brain tumor and Computer Aided Diagnosis Methods

A solid background knowledge about the characteristics of brain tumors is useful for researchers to implement computerized applications used to detect and segment tumors in medical images. This chapter discusses different criteria and characteristics used to classify some of the commonly known brain tumors and their appearance in medical images in Section 2.1. It further gives an overview of some of the techniques proposed in the literature used to assist radiologists to estimate the location of brain pathologies in medical images in Section 2.2. The conclusion is provided in Section 2.3.

2.1 Brain tumors

This thesis focuses on methods used to detect and segment brain tumors. A brain tumor is an abnormal new mass of tissue arising from brain cells and brain structures. It can be classified as either a primary or a secondary brain tumor [7, 8]. A tumor is said to be primary if it is the major cause of the cancer in the brain and secondary if it is caused by the spread of cancer from other body organs, for example breast or lung cancer spreading to the brain.

Primary brain tumors containing no cancer cells are called benign while those that contains cancer cells are called malignant. The cells of the benign tumor rarely invade healthy tissues around them. Malignant brain tumors are likely to grow rapidly and invade neighboring brain tissues hence are often a threat to life [7]. The malignancy of the tumor is determined based on its location, growth rate and historical features.

Primary brain tumors are normally classified based on the tissue of origin. The most common type of tumors are called gliomas which originate from glial cells. They can be described as low-grade (slow growing) or high-grade (very aggressive) [7]. Different types of gliomas include:

(1) astrocytoma which originate from astrocytes and glioblastoma multiforme which is a form of high-grade astrocytoma, (2) oligodendroglioma which develops from oligodendrocytes. Another common type of brain tumors is called meningioma and arises from meninges surrounding the brain and spinal cord.

The cause of brain tumors is still an unanswered question and studies have been made to find out whether people with certain risk factors are likely to develop a brain tumor. The results found a major environmental risk factor is exposure to ionizing radiation [7]. Moreover there are major concerns that heredity could be one of the causes of brain cancer. Figure 2.1 shows the appearance of a number of brain tumors in T2-weighted MR images for patients diagnosed with a low-grade glioma, meningioma and astrocytoma. The tumors differ in shape, location and have different appearances. In the first and the third image, the tumors appear having lower intensity values than those of the surrounding healthy tissues. The middle image shows a meningioma located on the left frontal lobe having intensity values larger than those of the white matter surrounding it.
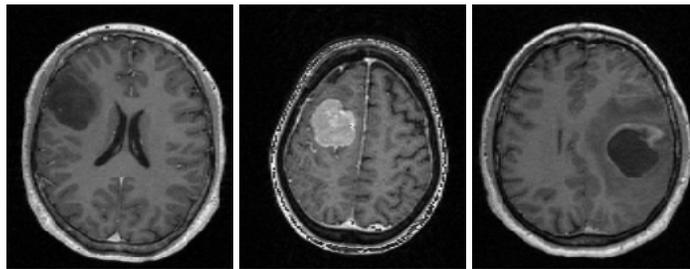
Figure 2.1: Illustration of the appearance of brain tumors on MRI. From left to right: axial slice of patient diagnosed with low-grade glioma, patient diagnosed with meningiomas, patient diagnosed with astrocytoma. Dataset is from [1].

2.1.1   Diagnosis and Treatment of Brain Tumors

Imaging modalities are used to diagnose different brain tumors and then treatment follows. The two common imaging techniques used are MRI and CT. MRI uses magnetic fields, electromagnetic radiation and a computer to reconstruct images of the brain while CT uses X-rays and a computer to reconstruct brain images [4]. MRI gives good contrast between different soft tissues while CT provides a better contrast between bone and soft tissues. In addition, MRI is said to be harmless to patients compared to CT as it does not use ionizing radiation as the external source of energy. When a patient is diagnosed with a brain tumor a specific treatment is suggested based on a number of factors such as the type, size and location of the tumor, age and general health of the patient. The treatment options for people with brain tumors are surgery, radiation therapy, and chemotherapy. A combination of treatments can also be suggested. Figure 2.2 shows the appearance of the healthy brain from two different patients on CT and MR images.
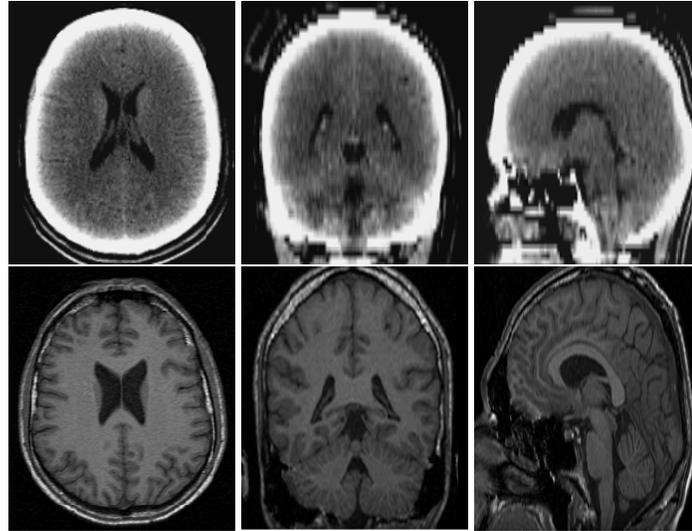
Figure 2.2: The appearance of healthy brain tissues on CT and MR images: (first row) axial, coronal and sagittal slice CT scan, (second row) axial, coronal and sagittal slices from MR scan. The CT data is from iThemba LABS and MR is taken from [2].

2.2 Computer Aided Diagnosis (CAD) in Brain Pathologies

Computer aided diagnosis is the concept of using a computerized application to process and manipulate multidimensional medical images of anatomical structures of patients to visualize the diagnostic features [9]. It is used in applications such as detection and segmentation of brain anatomical structures, breast and brain cancers tissues and other body organs in MR and CT images. Additionally it is used to register images of the same or different patients acquired at different times. The major role that CAD has brought to the field of medicine is the increase of the diagnostic accuracy as the radiologist uses results from the application as a second opinion to make final decisions [9]. It also reduces the processing time hence giving the doctors a chance to decide the best treatment for the diagnosed disease on time. However, automatic identification and segmentation of diagnosed brain structures is still a challenging problem due to the variability of protocols used during scanning and orientation from patient to patient.

This section discusses different methods proposed in the literature used to detect and segment brain pathologies in medical images. It also discusses the techniques used to detect the symmetry plane and atlas construction of the brain.

2.2.1 Knowledge-Based Brain Tumor Detection Techniques

Knowledge-based brain tumor methods use the information extracted from a knowledge source to detect brain tumors from medical images. The knowledge base is built using anatomical features of the tumor of interest such as expected size, grey level pixel color, shape and neighborhood relation-

ships with other brain tissues. The knowledge is then encoded into rules which can be inferred or is transformed into a geographical template with tissue labels assigned [10]. The advantage these methods have is that less training data is required. Their major drawback is that they are static in nature and hence are likely to fail to model a variety of brain tumors since tumor's anatomical properties vary from patient to patient [10, 11].

2.2.2 Supervised Brain Tumor Detection Methods

Supervised brain tumor detection methods rely on the use of manually annotated training data. These methods develop the model from the training data set and uses the same model to recognize new test data at a later stage. The major disadvantage of these methods is that they are labour intensive and time consuming. Also they are likely to fail to perform well if there is an overlap of intensity distributions between healthy and abnormal brain tissues.

A number of supervised methods have been proposed and used to detect and segment brain tumors from CT and MR images. In [12] Patil and Udupi propose a probabilistic neural network to classify brain tumors. Their technique consists of four main stages which include preprocessing, segmentation, feature extraction and classification. Cherifi et al. [13] implemented a classification method based on expectation maximization segmentation. Their method is automatic and works for both tissue recognition and tumor extraction. Jafari and Kasaei in [14] present a neural network-based method for automatic classification of brain MR images. Their method classifies tissues into three categories: normal, tumor benign and malignant. They use the discrete wavelet transform (DWT) to obtain features related to each MRI and applied principal component analysis to reduce feature dimensions to obtain more meaningful features. After the essential features have been extracted, a supervised feed-forward back-propagation neural network technique is used to classify the subjects. Khalid et al. [15] use k-nearest neighbor to segment abnormalities from brain MR images. They perform preliminary data analysis to extract feature vectors of the brain structures and use minimum, maximum and mean grey level pixel values as their feature vectors components. In other research Abdullah [5] introduces a new method used to segment multiple sclerosis (MS) lesions from brain MRI data. The technique uses textural features to detect MS lesions in a fully automatic approach. A trained support vector machine (SVM) is used to classify regions of MS lesions and non-MS lesions.

2.2.3 Unsupervised Brain Tumor Detection Methods

Unsupervised methods also need training data but the data need not to be annotated. Instead the training data is annotated using clustering algorithms which make unsupervised method less labor intensive when compared to supervised methods [16, 17]. The elements in each cluster are related to each other in some way. For example, they may be closer, in terms of distance, to a particular point than to other elements in a different cluster. Like supervised methods they also fail to perform

well if there is an overlap of intensity distributions between healthy and abnormal brain tissues. This normally occurs if they rely on bad features such as intensity alone. Hence the appropriate choice of the features has to be taken into consideration.

In [13] Cherifi et al provide a comparison between two image segmentation methods. One of the methods is based on segmentation using thresholding techniques and the other method is based on expectation maximization (EM) segmentation. They use these techniques to detect, segment, classify and measure properties of normal and abnormal brain tissues. From their analysis they find that EM gives better results when compared to thresholding especially when detecting small regions. Anitha et al. in [18] design a method used to automatically identify the white matter lesions found in the brains of elderly people. The method starts by preprocessing input images and then follows by clustering using fuzzy c-means (FCM), geostatistical possibilistic clustering (GPC) and lastly geostatistical fuzzy clustering (GFCM). They conclude that GFCM detects the large region of lesions and gives a smaller false positive rate when compared to FCM and GPC.

2.2.4 Atlas Based Methods

A brain atlas is the average brain image of an individual or multiple individuals in a specific age or race group [9]. It contains the knowledge base of brain structures in the form of intensity or probability distribution and is used to register different images onto the same coordinate space to allow subsequent comparison of brain structures and functions across individuals [19]. To construct an atlas from a group of individual images, one of the images is selected as the reference image. The remaining images are registered to the reference image and then an average image is computed from the aligned images. The difficulty faced by atlas-based methods is variability of brain size and shape across groups of people [9, 19]. Hence researchers often prefer to build a population based brain atlas.

2.2.4.1 Research in Brain Atlas Construction

Various algorithms have been developed to construct brain atlases. An atlas is constructed over a defined coordinated space onto which all images must be aligned. One of the most used coordinate spaces is the Talairach atlas [20]. It applies a piecewise affine transform to 12 rectangular regions of the brain to register new images in defined spaces [19]. It became a gold-standard used to align images for functional activation sites in positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) studies [19, 21, 22]. Though it was adopted as the gold-standard the Talairach atlas still has a number of limitations. Firstly the brain used by Talairach and Tournoux was smaller in size compared to average brain size [21, 22, 23]. Secondly the atlas was created based on single subject (postmortem brain) of a 60-year old French woman hence it does not provide anatomy of all living subjects. Lastly the slice gap and thickness, and the inconsistency of the orthogonal plane sections, have presumably limited the use of their work in

recent studies [21, 22, 23].

Ortega et al. [24] construct a deformable brain atlas and used it to identify subthalamic nucleus in T1-weighted MRI. Firstly an MRI dataset is transformed into the Talairach coordinate system manually. Secondly segmentation of homologous structures both in the atlas and MRI image of the patient's brain follows, and lastly non-rigid registration is applied between the segmented structures.

In order to address limitations of the Talairach atlas, the Montreal Neurological Institute (MNI) created a population-specific brain atlas, MNI-305 [21, 22]. This template was generated by manually registering 250 images of 305 brain MRI right-handed images onto the Talairach brain atlas and the aligned images were averaged to construct the MNI-250 brain atlas. The remaining 55 images were automatically registered onto MNI-250 using a linear transform. The manually registered 250 images and the 55 linearly registered images were averaged to form the MNI-305 brain atlas. Specific medical groups around the world adopted MNI templates as their standard [21]. They build brain atlases after aligning their data set onto MNI space. Despite the dominant use of MNI space and the fact that it is population specific some researchers have proposed novel techniques, though still population dependent, to construct their atlases. For example, a Korean brain template and a French brain template were constructed and used to represent the brain characteristics of Asian and French populations respectively [22, 23, 25, 26]. Tang et al. [22] develop a new brain atlas to facilitate computational brain studies in Chinese populations using MRI. Their template is also population specific for Chinese people. They use 3.0 Tesla MRI scans of 56 right-handed Chinese males. In [21] Mandal et al. summarize the history, construction and application of brain atlases. Their study focuses on brain atlases starting from the Talairach atlas to a Chinese brain atlas. They also provide a new automated work-flow protocol they use to design a population-specific brain atlas from MRI data.

2.2.4.2 Delineating Brain Tumors Using a Brain Atlas

Several methods have been proposed to encode the knowledge base of healthy brain tissue in the form of a brain atlas. These methods have given radiologists across the globe a chance to understand functional activities of the brain. They are also helpful to diagnose and detect different pathologies arising from brain tissues [6, 27, 28, 29]. Prastawa et al. [29] describe an automated brain tumor segmentation framework from MR images; both T1-weighted and T2-weighted images are used. Their proposed method detects abnormal tissues using a registered brain atlas as a model of a healthy brain. They use T2 image densities to determine whether there is an edema in the abnormal region, and then apply geometric and spatial constraints to separate the edema and the tumor. In another research report, Bourouis and Hamrouni [27] present a novel deformable model for 3D tumor segmentation based on a level-set concept. They use both boundary and regional information to define the speed function. Their method is automatic and applicable to T1-weighted pre-contrast and post contrast 3D images.

Cuadra et al. [28] discuss a method that transforms a deformable brain atlas and a tumorous subject into the same coordinate space, based on a priori knowledge of lesion growth. They use an affine registration to align the atlas and patient images onto the same coordinate space. Laliberte et al. [6] present an automated method for screening single photon emission computed tomographic (SPECT) studies to detect diffuse disseminated abnormalities based on the atlas of normal regional cerebral blood flow. They generate the atlas from a set of normal brain SPECT images aligned together. The atlas contains average intensity, and the nonlinear displacement mean and variance of the activity patterns.

2.2.5 Symmetry Quantification Methods

The brain symmetry plane, also called mid-sagittal plane (MSP), is defined as the plane that travels vertically and divides the head into two similar halves. A slight difference is expected to remain because of different function and morphological difference between the two hemispheres [10]. This section provides a review of the techniques used to estimate the MSP and those that analyse the symmetry of the brain to detect brain pathologies from medical images.

2.2.5.1 Research in Brain Symmetry Plane Estimation

A variety of methods have been proposed to estimate the brain symmetry plane from medical images. Some of these methods were found to be sensitive to the initial position of the head or size of brain tumor if present or the type of image modality used.

Ruppert et al. [30] introduce a novel algorithm for extracting the MSP from brain images of different modalities with isotropic pixels. Their method is based on edge features extracted from the image using a 3D Sobel operator. A linear search is performed to find three optimal non-collinear points lying in a candidate plane that maximize the correlation between the original image and its reflected copy. They also use a multi-scale search to reduce the search space and speed up convergence to the optimal solution. Their study indicates that it is possible to estimate such a plane. However, their technique uses enhanced images.

In [31] Fu et al. present a new method to extract the MSP from 3D MR images, which uses the symmetry principal axis, a local search method and the local symmetry coefficient. Their algorithm works on a selected set of 2D axial slices to estimate the orientation of principal axis from the gradient orientation of the image. The position of the principal axis is computed from the mass center of the object. A local linear search is then performed to extract the final position of a fissure line with the minimum local symmetry coefficient in the search region using the principal axis as the reference axis of the slice of interest. A least square error fit is applied to all inliers, remaining fissure line segments, to determine the equation of the MSP. This method can estimate the MSP even for large angular deviations of the head. However, in cases when the head is strongly tilted

it cannot estimate the MSP as it will be difficult to estimate the symmetry principal axis of axial slices [32]. Also it works only in MRI images as fissure lines are only visible in this modality.

Ekin [33] introduces a feature-based MSP estimation technique that uses RANSAC to estimate the inter-hemispheric fissure in the stack of 2D slice images. Each slice is analyzed independently to detect the feature points corresponding to the inter-hemispheric fissure. The slice with the largest percentage of inliers is selected, and its fissure line is used to compute inliers in the remaining slices. The symmetry line is then re-computed using new feature points in the least square sense. The algorithm is fast as it uses only relevant feature points. Moreover, it is insensitive to abnormalities. However, it requires the availability of proton density contrast to detect the MSP.

2.2.5.2 Delineation of Brain Tumors Using Asymmetry Analysis

Asymmetry analysis of the brain has played a significant role in detecting pathologies in the brain. With the assumption that abnormal tissues in the brain appear asymmetrical along the MSP a variety of studies have been done proposing techniques that take into account the brain symmetry to detect brain pathologies. Some of these methods make use of image registration techniques to align left and right hemispheres, reflected over the candidate plane, and perform asymmetry analysis using threshold and statistical features to detect abnormal mass. Other techniques divide the left and right hemisphere into small squares of the same size to detect asymmetrical regions using first and/or second order statistics features.

Pedoia et al. [34] design a fully automatic technique to detect brain tumors using symmetry analysis and graph-cut clustering methods. Their approach reflects the right hemisphere across the MSP and computes voxel by voxel differences from the left hemisphere and the mirrored right hemisphere to derive a volume that highlights the regions with greater intensity difference with respect to the background as asymmetric components. Graph-cut is then used to extract this area and the resulting region is mirrored across the MSP. The normalized histograms of the left and right hemisphere are computed and histogram analysis is performed to recognize the ill hemisphere. The limitation of their method is that it only recognizes hyperintense tumors.

Khotanlou et al. [35] use a combination of fuzzy classification and symmetry analysis to detect different types of tumors from T1-weighted MR images. A fuzzy classification method detects abnormalities based on the assumption that the tumor appears in the image with specific grey-level values; hence it does not generalize for other types of tumors. An asymmetry analysis method computes histogram differences between the left and right hemispheres, with manual selection of tumor grey level range to detect the pathological hemisphere. Their method is able to detect both enhancing and non-enhancing tumors although it still requires manual selection of the intensity range. By combining both fuzzy classification and symmetry analysis methods they were able to detect a wide range of tumors.

In other research Roy and Bandyopadhyay [36] use thresholding technique to convert the left and right hemispheres into binary images. A watershed method is used to segment the tumor region. They use Otsu's method to choose the threshold that minimizes the inter-class variance of the black and white pixels. Although their method is automatic, it only works for hyperintense tumors. Moreover, it is not applicable to 3D data.

Kropatsch et al. [37] use active contours or snakes [38] to remove the skull and set the symmetry to the center of the remaining part of the image. Their method divides the resultant image into square blocks of the same size for both left and right hemispheres. The blocks from one hemisphere are compared with those in the opposite hemisphere using the Bhattacharya coefficient. The blocks which are highly asymmetric give the highest value of Bhattacharya coefficient and the brightest block is used to detect the ill hemisphere.

Yu et al. [39] present a novel method to detect asymmetrical blobby tumors within a brain image. They use center-surround distribution distance (CSDD) [40] to detect blobby regions from the 2D brain axial slice. Feature vectors of each blob are extracted and compared with the feature vectors of corresponding reflected regions using the earth mover distance (EMD) [41]. Regions which give a high asymmetric score are retained. K-means clustering with $k = 2$ is then used to cluster this blob into two groups: normal or abnormal regions. Maximum likelihood estimation is used to retain expected tumor blobs. Their approach is very fast as no registration is required and is fully automatic. Ray [42] proposed a very fast real-time algorithm which requires no registration. This method locates the brain abnormality by putting a bounding box around the tumor. The bounding box provides a rough estimate of the abnormal region and it sometimes covers the healthy regions around the tumor.

2.3 Conclusion

This chapter reviews characteristics of brain tumors and different research methods proposed to perform the task of detecting and segmenting brain tumors. Despite the enormous amount of work that has been done there is no widely accepted method to do this task. Based on these facts, finding an automated and accurate brain lesion detection and segmentation method is useful and gives researchers an opportunity to come up with new ideas in trying to solve the same problem.

Any comparison of the test images and the atlas or extraction of the brain symmetry would require registration of the images, and this is discussed in the next chapter.

Chapter 3

Medical Image Registration

Medical images provide vital information used by clinicians to diagnosis and monitor the progress of brain pathologies. Multiple images of organs of interest are taken at different times and compared to quantify the amount of abnormal growth. However, because of the variation of acquisitions protocols or orientation of patient, images always have different contrast and alignment. Hence in order to compare one image with another, image registration has to take place. Image registration is the technique used to bring two or more images onto the same coordinate frame so that the aligned images can be compared, combined or analyzed. Given a floating image ($\mathbf{F}$) and the reference image ($\mathbf{R}$) having the same dimensions and do not differ in intensity, the main objective of registration process is to find transformation, $\mathbf{T_u}$ of parameter $\mathbf{u}$, such that

$$\mathbf{R}(x,y,z) = \mathbf{F}(\mathbf{T_u}(x,y,z)). \tag{3.1}$$

In this chapter the general theoretical concepts of 3D medical image registration is given with much attention paid to global or rigid registration. This process can better be addressed by separating it into four major components: (1) feature space, (2) similarity measure, (3) transformation model, (4) optimization method. The features space defines attributes of the two images to be compared and the similarity measure computes how close the floating image is to the reference image by comparing the features between the two images. The transformation model defines a mapping function which aligns coordinates of one image to another while the optimization method searches for the transformation parameters that optimize the similarity measure. The same concepts presented here can also be applied on 2D images by omitting the z-axis.

3.1 Feature Spaces

The first step in image registration is to define the feature space that will be used when aligning two images. The feature space defines image attributes that will be compared when computing the similarity measure. The two most common approaches are feature-based and intensity-based methods. The feature-based methods use extracted features to estimate the transformation parameters by mapping features from one image to their counterpart in another image. The features are either extracted automatically or manually from medical images. They include corners, landmarks, edges for 2D, and surfaces for 3D. Intensity-based methods use raw image pixel intensity values to perform registration. The major advantage that feature-based methods have over intensity-based methods is the reduction in computational cost since they do not use the entire image information. However, they rely heavily on robust feature extraction and matching methods [43].

3.2 Transformation model

When aligning two images a transformation $\mathbf{T}_u$ such that Equation 3.1 holds for all (x, y, z) has to be found. The better choice of the transformation model often results with perfect alignment between the two images. The transformation model can be rigid, affine or nonrigid. A rigid transformation involves rotation and translation while an affine transformation consists of rotation, translation, scale and shear. Both affine and rigid are categorized as global transformations since the single transformation is applied on the entire image domain. A homogeneous coordinates is used in this case and the transformations are represented by a 4×4 matrices while a 3×1 vector point, $\mathbf{x} = [x, y, z]^T$, is represented by a 4×1 vector point, $\mathbf{x} = [x, y, z, 1]^T$ [44]. A nonrigid transformation maps different parts of the image with different transformations, hence is a local transformation.

3.2.1 Rigid Transformation

A rigid transformation in 3D is made up of six parameters: three rotational angles θ, β, ϕ and the translation parameters T_x, T_y, T_z along x- , y- and z-axes. It is mostly used when aligning rigid body structures such as head or legs of the same patient. Given the vector parameter $\mathbf{u} = [\theta, \beta, \phi, T_x, T_y, T_z]$ the rigid transformation $\mathbf{T}_u$ is given as

$$\mathbf{T}_u = \mathbf{T}_l \mathbf{R}_x \mathbf{R}_y \mathbf{R}_z, \tag{3.2}$$

where $\mathbf{T}_l$ is the translation matrix describing the displacement while $\mathbf{R}_x$, $\mathbf{R}_y$ and $\mathbf{R}_z$ describe rotation matrices about x-, y- and z-axes respectively are given as

$$
\mathbf{T}_l =
\begin{bmatrix}
1 & 0 & 0 & T_x \\
0 & 1 & 0 & T_y \\
0 & 0 & 1 & T_z \\
0 & 0 & 0 & 1
\end{bmatrix}, \qquad
\mathbf{R}_x =
\begin{bmatrix}
1 & 0 & 0 & 0 \\
0 & cos\theta & -sin\theta & 0 \\
0 & sin\theta & cos\theta & 0 \\
0 & 0 & 0 & 1
\end{bmatrix},
$$

$$
\mathbf{R}_y =
\begin{bmatrix}
cos\beta & 0 & sin\beta & 0 \\
0 & 1 & 0 & 0 \\
-sin\beta & 0 & cos\beta & 0 \\
0 & 0 & 0 & 1
\end{bmatrix}, \qquad
\mathbf{R}_z =
\begin{bmatrix}
cos\phi & -sin\phi & 0 & 0 \\
sin\phi & cos\phi & 0 & 0 \\
0 & 0 & 1 & 0 \\
0 & 0 & 0 & 1
\end{bmatrix}.
\tag{3.3}
$$

3.2.2 Affine Transformation

An affine transformation is applied when aligning the same subjects but with different sizes and orientation. It models a combination of four simple transformations (translation, rotation, scaling and shearing) to correct global distortions in the images to be registered. It is used when aligning rigid body structures such as head or legs of different patients. An affine transformation consists of 12-parameters $\mathbf{u} = [u_1, u_2, ..., u_{12}]^T$. Like in 2D case [45] this transformation can be decomposed into a product of translation, rotation, scale and shear using a 15-parameter vector $\mathbf{w} = [\theta, \beta, \phi, T_x, T_x, T_y, T_z, S_x, S_y, S_z, S_{xy}, S_{xz}, S_{yx}, S_{yz}, S_{zx}, S_{zy}]^T$ which describes the mentioned four transformation. A 12-parameter affine transformation is written as

$$
\mathbf{T}_u =
\begin{bmatrix}
u_1 & u_2 & u_3 & u_{10} \\
u_4 & u_5 & u_6 & u_{11} \\
u_7 & u_8 & u_9 & u_{12} \\
0 & 0 & 0 & 1
\end{bmatrix}.
\tag{3.4}
$$

This tranformation can be broken down into a product of translation, rotation, scale and shear in x-, y- and z-axis as

$$
\mathbf{T}_w = \mathbf{T}_l \mathbf{R}_x \mathbf{R}_y \mathbf{R}_z \mathbf{S} \mathbf{S}_h,
\tag{3.5}
$$

where $\mathbf{S}$ and $\mathbf{S}_h$ describe scale and shear matrices as

$$
\mathbf{S} =
\begin{bmatrix}
S_x & 0 & 0 & 0 \\
0 & S_y & 0 & 0 \\
0 & 0 & S_z & 0 \\
0 & 0 & 0 & 1
\end{bmatrix}, \qquad
\mathbf{S}_h =
\begin{bmatrix}
1 & S_{xy} & S_{xz} & 0 \\
S_{yx} & 1 & S_{yz} & 0 \\
S_{zx} & S_{zy} & 1 & 0 \\
0 & 0 & 0 & 1
\end{bmatrix},
\tag{3.6}
$$

where S_x, S_y, S_z are the scaling parameters in the x, y and z-axes. The shear factors along the

x-, y- and z-directions are described by (S_{yx}, S_{zx}), (S_{xy}, S_{zy}) and (S_{xz}, S_{yz}) respectively and are not all non-zero. The shear transformation leaves at least one of the three coordinate axes of the object fixed while the remaining coordinates are changed by the amount proportional to the fixed coordinate. For an example, shearing a point $\mathbf{x}=[x, y, z, 1]^T$ along z-axis leaves the z-coordinate remains unchanged while x- and y-coordinate are altered and $(S_{yx} = S_{zx} = S_{xy} = S_{zy} = 0)$. This can be represented mathematically as

$$x_1 = x + zS_{xz}, \qquad y_1 = y + zS_{yz}, \qquad z_1 = z \ . \tag{3.7}$$

3.2.3 Nonrigid Transformation

A nonrigid transformation defines the displacement or deformation vector which aligns each point in one image with its corresponding point in another image. Compared to a global transformation such as an affine transformation, which applies the same transformation to the entire image domain, a nonrigid transformation can account for more general transformations since it allows each voxel to be displaced independently from its neighboring voxel [43, 46]. Hence it is often used to remove small tissue variation arising from different images. The transformation is usually defined as $\mathbf{T}_v(\mathbf{v} : \mathbf{x}) = \mathbf{x} + \mathbf{v}(\mathbf{x})$ such that $\mathbf{R}(\mathbf{x}) = \mathbf{F}(\mathbf{T_v}(\mathbf{v} : \mathbf{x}))$, where $\mathbf{v}(\mathbf{x})$ is the displacement field of the voxel at location $\mathbf{x}$. Finding an optimal displacement field that minimizes the similarity between the two images is an ill-posed problem hence arbitrary displacement such as oscillation or folding can occur. To make sure that the displacement is smooth, a regularization term that penalizes some undesirable transformation is often added to the similarity measure [43, 46]. A review of different regularization terms and their applications in image registration is given in [43].

3.3 Similarity Measure

A similarity measure compares how close the floating image matches the reference image. It is defined based on the transformation parameters. The similarity measures used in image registration include but are not limited to the following: sum of square difference (SSD), absolute difference (AD), mutual information (MI), normalized mutual information (NMI) and cross correlation (CC). For intensity-based registration models, the images to be aligned must have the same dimension.

3.3.1 Sum of Square Difference (SSD)

SSD evaluates the closeness of $\mathbf{R}$ and $\mathbf{F}$ of dimensions $N_x \times N_y \times N_z$ by computing voxel by voxel difference between images and then summing the square of the results [47, 45]. It is one of the simplest similarity measures that is minimized during registration [47]. This measure is only applicable when registering images of the same modality such as MR to MR or CT to CT. Another

drawback of this measure is that it is very sensitive to the voxels that have large intensity differences between **R** and **F** [47]. The equation for computing SSD is defined as

$$SSD(\mathbf{u}) = \frac{1}{2} \sum_{x=0}^{N_x-1} \sum_{y=0}^{N_y-1} \sum_{z=0}^{N_z-1} [\mathbf{R}(x,y,z) - \mathbf{F}(\mathbf{T}(\mathbf{u}:x,y,z))]^2 = \frac{1}{2} ||\mathbf{R}(\mathbf{x}) - \mathbf{F}(\mathbf{T}(\mathbf{u}:\mathbf{x}))||_{L_2}^2, \quad (3.8)$$

where $\mathbf{R}(x,y,z)$ and $\mathbf{F}(\mathbf{T}(\mathbf{u}:x,y,z))$ are corresponding voxels in volume **R**, and **F** and $|| \cdot ||_{L_2}$ denotes the L_2 norm.

3.3.2 Absolute Difference (AD)

AD measures the quality of registration by computing sum of absolute voxel by voxel difference of the two images. It is calculated as

$$AD(\mathbf{u}) = \frac{1}{2} \sum_{x=0}^{N_x-1} \sum_{y=0}^{N_y-1} \sum_{z=0}^{N_z-1} |\mathbf{R}(x,y,z) - \mathbf{F}(\mathbf{T}(\mathbf{u}:x,y,z))|. \quad (3.9)$$

AD is easy to compute, but it is only used when registering images of the same modality [3]. It is minimized when the correct alignment is reached.

3.3.3 Correlation Coefficient (CC)

This method evaluates the dependency between two image variables. It is applicable for multi-modal image registration [3, 46, 47]. However, it suffers from expensive computations [3]. The correlation coefficient was applied for mid-sagittal plane detection in neuroimages [10, 30]. Given two images, **R** and **F**, CC is calculated as

$$CC(\mathbf{u}) = \frac{\sum_{x=0}^{N_x-1} \sum_{y=0}^{N_y-1} \sum_{z=0}^{N_z-1} (\mathbf{R}(x,y,z) - r) (\mathbf{F}(\mathbf{T}(\mathbf{u}:x,y,z)) - f)}{\sqrt{\sum_{x=0}^{N_x-1} \sum_{y=0}^{N_y-1} \sum_{z=0}^{N_z-1} (\mathbf{R}(x,y,z) - r)^2 \sum_{x=0}^{N_x-1} \sum_{y=0}^{N_y-1} \sum_{z=0}^{N_z-1} (\mathbf{F}(\mathbf{T}(\mathbf{u}:x,y,z)) - f)^2}}, \quad (3.10)$$

where r and f are the mean intensity values of **R** and **F** respectively. It is maximized when the images are correctly aligned [47].

3.3.4 Mutual Information (MI)

Mutual information (MI) measures the amount of information one variable is dependent on another variable. It measures how well one image explains the other [46, 47]. MI is maximized when the

value of a voxel in the first image is a good predictor of the corresponding voxel in the second image [46], and it can be used to align images of different modalities [46, 48]. The drawback of this measure is that it is sensitive to the amount of overlap between the images [3]. MI between image **R** and **F** is expressed as

$$MI(\mathbf{F}, \mathbf{R}) = H(\mathbf{R}) + H(\mathbf{F}) - H(\mathbf{F}, \mathbf{R}), \tag{3.11}$$

where $H(\mathbf{F})$ and $H(\mathbf{R})$ are the entropies of **F** and **R**, and $H(\mathbf{F}, \mathbf{R})$ is the joint entropy. These quantities are defined by

$$H(\mathbf{F}) = -\sum_f P_F(f) \quad \log_2(P_F(f)),$$

$$H(\mathbf{R}) = -\sum_r P_R(r) \quad \log_2(P_R(r)), \tag{3.12}$$

$$H(\mathbf{F}, \mathbf{R}) = -\sum_f \sum_r P_{FR}(f, r) \quad \log_2(P_{FR}(f, r)),$$

where $P_F(f)$ and $P_R(r)$ denote the marginal distributions of the image intensities of **F** and **R** respectively, and $P_{FR}(f, r)$ is their joint probability [3]. To compute MI, the intensity histogram of each image has to be calculated. The histogram consists of histogram bins or clusters which contain voxels having the intensity value that falls within the defined range. The number of voxels in each histogram bin is then divided by the total number voxels in each image to determine the probability distribution for each cluster. Mathematically, the histogram function $\mathbf{G}_F$ and the probability distribution P_F of voxels in $i-th$ cluster of **F** are calculated as follows

$$\mathbf{G}_F(i, w) = \cup_{k=1}^{N} \delta\left(\mathbf{F}(k), i, w\right), \qquad \delta\left(j, i, w\right) = \begin{cases} \mathbf{F}(k), & (i-1) * w \le j < (i * w) \\ & \text{otherwise continue} \end{cases}, \tag{3.13}$$

$$P_F(i) = \frac{|\mathbf{G}_F(i, w)|}{N}, \tag{3.14}$$

where N is the total number of voxels in **F** and w is the width of histogram bins. Also for **R**, this is given as

$$\mathbf{G}_R(i, w) = \cup_{k=1}^{N} \delta\left(\mathbf{R}(k), i, w\right), \qquad \delta\left(j, i, w\right) = \begin{cases} \mathbf{R}(k), & (i-1) * w \le j < (i * w) \\ & \text{otherwise continue} \end{cases}, \tag{3.15}$$

$$P_R(i) = \frac{|\mathbf{G}_R(i, w)|}{N}. \tag{3.16}$$

The joint probability $P_{FR}(f,r)$ of $r-th$ and $f-th$ clusters in $\mathbf{R}$ and $\mathbf{F}$ respectively is given as

$$P_{FR}(f,r) = \frac{|\mathbf{G}_R(f,w) \bigcap \mathbf{G}_F(f,w)|}{N}. \tag{3.17}$$

3.4 Optimization Methods

The main objective of the optimization method is to find a set of transformation parameters for which the similarity measure, a function of these parameters, is minimized. These methods generally formulate the registration model in a mathematical equation that incorporates the transformation parameters. This can be represented mathematically as $\mathbf{u}^* = \arg\min\{C(\mathbf{u}:\mathbf{F}, \quad \mathbf{R})\}$ where the function C represents the similarity measure, which can either be SSD, AD or negated MI, between $\mathbf{R}$ and $\mathbf{F}$, and $\mathbf{u}$ represents the parameter vector containing variables of the transformation function. For example, in affine registration $\mathbf{u}$ is made up of 12 parameters.

Usually an iterative approach is followed to determine optimal values of set of parameters in $\mathbf{u}$. Firstly an initial estimate of the parameters is given. At each iteration the registration model evaluates the similarity measure using the current parameter estimates. If the stopping criterion is not met, parameters are updated and the process continues to the next iteration. Otherwise the process terminates. The parameters are updated as

$$\mathbf{u}_{k+1} = \mathbf{u}_k + \alpha_k \mathbf{d}_k \tag{3.18}$$

for $k = 0, 1, 2, ..., k_{max}$ where $\mathbf{d}_k$ and α_k represent the search direction and the scalar gain factor respectively. At each iteration k the search direction and gain factor are modified such that $C(\mathbf{u}_{k+1} : \mathbf{F}, \mathbf{R}) < C(\mathbf{u}_k : \mathbf{F}, \mathbf{R})$. Several optimization methods exist in the literature which differ in the way to compute the search direction and gain factor. These include gradient descent, Gauss-Newton, Levenberg-Marquardt and Quasi-Newton [49, 45, 44, 46, 50, 51, 52]. A brief review of some of the optimization methods used in image registration is given below where the objective function is given as

$$C(\mathbf{u} : \mathbf{F}, \mathbf{R}) = \frac{1}{2}||\mathbf{F}(\mathbf{T}(\mathbf{u} : \mathbf{x})) - \mathbf{R}(\mathbf{x})||_{L_2}^2, \tag{3.19}$$

for voxels in $\mathbf{R}$ and $\mathbf{F}$ represented in lexicographical order and $\mathbf{u} \in R^n$. The stopping criterion is met when $||\mathbf{d}_k|| < \varepsilon_1$, where ε_1 is a small positive number defined by the user. If ε_1 is very small and the updated value of the search direction does not reduce the value of the cost function then another stopping criteria, $k > k_{max}$, has to be defined to safeguard against an infinite loop. The optimization methods are likely to be trapped in a local minima hence initialization of these methods has to be taken into consideration.

3.4.1 Gradient Descent (GD) Method

The GD method is a general minimization technique which updates parameter values in the direction opposite to the gradient of the cost function. The gradient is computed by taking the derivative of the objective function as

$$\mathbf{g}(\mathbf{u}) = \nabla_{\mathbf{u}} C(\mathbf{u} : \mathbf{F}, \mathbf{R}) = \mathbf{J}^T(\mathbf{u})(\mathbf{F}_u(\mathbf{x}) - \mathbf{R}(\mathbf{x})), \tag{3.20}$$

where $\mathbf{F}_u$ is the transformed $\mathbf{F}$, $\mathbf{J}$ is $N_u \times N$ Jacobian matrix representing the local sensitivity of the function to the variation in the parameters $\mathbf{u}$, N_u is the total number of parameters in $\mathbf{u}$ and N is the total number of voxels in $\mathbf{R}$. The Jacobian matrix is given by

$$\mathbf{J}(\mathbf{u}) = \nabla \mathbf{F}_u(\mathbf{x}) \frac{\partial \mathbf{T}_u(\mathbf{x})}{\partial \mathbf{u}}. \tag{3.21}$$

The search direction at the kth iteration is calculated as $\mathbf{d}_k = -\mathbf{g}(\mathbf{u}_k)$ and the gain factor α_k may be chosen as a decaying function of k: $\quad \alpha_k = a/(k+A)^\alpha$ where $a > 0$, $A \geq 1$ and $0 \leq \alpha \leq 1$ are user defined. Another approach used to determine α_k is by using a line search method [49, 51, 52].

3.4.2 Newton's Method

This method makes use of a second order Taylor series expansion to estimate the search direction. The Taylor expansion of Equation 3.20 at the next iteration is calculated as

$$C(\mathbf{u}_k + \mathbf{d}_k : \mathbf{F}, \mathbf{R}) = C(\mathbf{u}_k : \mathbf{F}, \mathbf{R}) + \nabla_{\mathbf{u}_k} C(\mathbf{u}_k : \mathbf{F}, \mathbf{R})\mathbf{d}_k + O(||\mathbf{d}_k||^2)$$
$$\tag{3.22}$$
$$\cong C(\mathbf{u}_k : \mathbf{F}, \mathbf{R}) + \nabla_{\mathbf{u}_k} C(\mathbf{u}_k : \mathbf{F}, \mathbf{R})\mathbf{d}_k,$$

and its derivative with respect to $\mathbf{u}$ is computed as

$$\nabla_{\mathbf{u}_k} C(\mathbf{u}_k + \mathbf{d}_k : \mathbf{F}, \mathbf{R}) = \nabla_{\mathbf{u}_k} C(\mathbf{u}_k : \mathbf{F}, \mathbf{R}) + \nabla_{\mathbf{u}_k \mathbf{u}_k} C(\mathbf{u}_k : \mathbf{F}, \mathbf{R})\mathbf{d}_k. \tag{3.23}$$

Setting Equating 3.23 to zero, the search direction is calculated as $\mathbf{d}_k = -\left[\nabla_{\mathbf{u}_k \mathbf{u}_k} C(\mathbf{u}_k : \mathbf{F}, \mathbf{R})\right]^{-1} \nabla_{\mathbf{u}_k} C(\mathbf{u}_k : \mathbf{F}, \mathbf{R})$, where $\nabla_{\mathbf{u}_k \mathbf{u}_k} C(\mathbf{u}_k : \mathbf{F}, \mathbf{R})$ is the second derivative (Hessian matrix of size $N_u \times N_u$) of the objective function evaluated at $\mathbf{u}_k$. The (i, j) entry of the Hessian matrix is given by $\partial C(\mathbf{u}_k : \mathbf{F}, \mathbf{R})/\partial u_i \partial u_j$. This method requires the Hessian to be calculated at each iteration. Hence it may not be suitable in registering two images for practical applications because computing higher order derivatives is time consuming and numerically unstable [45].

3.4.3 Quasi-Newton (QN) Method

The quasi-Newton method is a gradient-based multi-dimensional optimization method inspired by the well known Newton-Rapson algorithm [49, 52]. It constructs and updates an approximation of the inverse of the Hessian matrix numerically as $\mathbf{L}_k \approx [\mathbf{H}(\mathbf{u}_k)]^{-1}$. A direct approximation of the inverse avoids the need for matrix inversion. The general equation for QN methods is given as

$$\mathbf{u}_{k+1} = \mathbf{u}_k - \alpha_k \mathbf{L}_k \mathbf{g}(\mathbf{u}_k), \tag{3.24}$$

where $\mathbf{d}_k = \mathbf{L}_k \mathbf{g}(\mathbf{u}_k)$ and α_k is determined using a line search routine to ensure that the progress is towards the solution. Numerous methods have been proposed to estimate $\mathbf{L}_k$. They include symmetric-rank-1 (SR1), Davidon-Fletcher-Powell (DFP) and Broyden-Fletcher-Goldfarb-Shanno (BFGS) [49, 46, 51, 52]. From the literature it is found that BFGS out performs other methods in various applications. It updates L_k using the following rule

$$\mathbf{L}_{k+1} = \left(\mathbf{I} - \frac{\mathbf{sy}^{\mathbf{T}}}{\mathbf{s}^{\mathbf{T}}\mathbf{y}} \right) \mathbf{L}_k \left(\mathbf{I} - \frac{\mathbf{ys}^{\mathbf{T}}}{\mathbf{s}^{\mathbf{T}}\mathbf{y}} \right) + \frac{\mathbf{ss}^{\mathbf{T}}}{\mathbf{s}^{\mathbf{T}}\mathbf{y}}, \tag{3.25}$$

where $\mathbf{I}$ is the identity matrix, $\mathbf{s} = \mathbf{u}_{k+1} - \mathbf{u}_k$ and $\mathbf{y} = \mathbf{g}(\mathbf{u}_{k+1}) - \mathbf{g}(\mathbf{u}_k)$.

3.4.4 Gauss-Newton (GN) Method

The Gauss-Newton method minimizes the objective function based on the calculated first derivatives of the components of the vector function. Like QN it is also inspired by the Newton-Rapson algorithm [44]. At each iteration the Hessian matrix $\mathbf{H}(\mathbf{u}_k)$ is estimated directly from the first derivatives of the cost function as

$$\mathbf{H}(\mathbf{u}_k) \cong \mathbf{J}^T(\mathbf{u}_k)\mathbf{J}(\mathbf{u}_k). \tag{3.26}$$

The Hessian estimate is used to compute the search direction by solving $\mathbf{H}(\mathbf{u}_k)\mathbf{d}_k = -\mathbf{g}(\mathbf{u}_k)$. The gain factor, α_k, ensures that GN reduces the cost function and is determined by solving a line search problem with a backtracking algorithm which is based on the Armijo-Goldstein condition [45, 51, 49]. Given the current parameter estimates $\mathbf{u}_k$, the search direction $\mathbf{d}_k$ and the initial guess $\alpha_k = 1$ the algorithm produces a series of gain factors, $\alpha_1, \alpha_2, ...,$ to find the minimizer of

$$\alpha_k^* = \arg\min\{C(\mathbf{u}_k + \alpha_k \mathbf{d}_k : \mathbf{F}, \quad \mathbf{R})\}, \tag{3.27}$$

where both $\mathbf{u}_k$ and $\mathbf{d}_k$ are fixed and $\alpha_k > 0$.

3.4.5 Levenberg-Marquardt Method (LM)

The Levenberg-Marquardt method is a hybrid of both GD and GN. It augments the Hessian esti-
mate in Gauss-Newton with a diagonal damping parameter. It also adaptively switches the parame-
ter updates between GD and GN. When it is far from the optimum it behaves like the GD, and thus
always travels in a direction to decrease the objective function. When it approaches the optimum
it behaves like GN in order to converge quickly [44, 53, 51]. LM computes the search direction by
solving

$$\left[\mathbf{J}^T(\mathbf{u}_k)\mathbf{J}(\mathbf{u}_k) + \mu\mathbf{I}\right]\mathbf{d}_k = -\mathbf{g}(\mathbf{u}_k), \tag{3.28}$$

where μ is a damping parameter that has several effects on the rule. For all $\mu \gg 0$ the resulting
matrix is positive definite hence ensures that $\mathbf{d}_k$ is the descent direction. When μ is very small the
resulting equation is similar to Equation 3.24 which estimates the Hessian matrix from the Jacobian
matrix. Hence μ influences both the search direction and the gain parameter. Its initial value is
set based on the size of the elements in the Hessian matrix as $\mu = \max(\mathbf{H}_{ii}(\mathbf{u_k}))\,\tau$, where τ is a
scalar defined by the user [44, 51, 53]. At the next iteration the damping factor is decreased if the
updated search direction computed from Equation 3.18 leads to a reduction in the cost function.
Otherwise the damping factor is increased and the augmented Equation 3.28 is solved repeatedly
until a value of $\mathbf{g}(\mathbf{u}_k)$ that reduces the cost function is found. The updating process is controlled by
the gain ratio

$$\rho = (C(\mathbf{u}_k) - C(\mathbf{u}_k + \mathbf{d}_k)) / (L(0) - L(\mathbf{d}_k)), \tag{3.29}$$

where the denominator is defined as

$$L(0) - L(\mathbf{d}_k) = \frac{1}{2}\mathbf{d}_k^T(\mu\mathbf{d}_k - \mathbf{g}(\mathbf{u}_k)) \tag{3.30}$$

and is guaranteed to be positive. A large value of the gain ratio indicates that $L(\mathbf{d}_k)$ is a good
approximation of $C(\mathbf{u}_k + \mathbf{d}_k)$. Hence μ can be decreased and the algorithm continues to the next
iteration. If the gain ratio is small or even negative, then $L(\mathbf{d}_k)$ gives a poor approximation of
$C(\mathbf{u}_k + \mathbf{d}_k)$. Therefore μ is increased. The Jacobian matrix in Equation 3.28 is sometimes approx-
imated numerically using either a backward or forward difference method [44, 53].

3.5   Techniques to Improve Optimization Methods

The optimization methods discussed in Section 3.4 are sensitive to the initial guesses of the transformation parameter. The methods are likely to be trapped in a local minimum if the initial guess is far from the optimal solution. They also require a high computational costs for large sized images. This section discusses some of the methods used to provide a good initial guess.

3.5.1   Multi-Resolution Approach

During registration, the function to be minimized might have multiple local optimum points which are likely to trap most of the optimization methods. Also if the images are severely misaligned the registration computation time becomes the problem. To overcome these challenges a multi-resolution approach is adopted in the registration process [10, 30, 45, 53, 54]. The idea of a multi-resolution approach is to divide the registration process into different levels to reduce the number of local optimum and speed up the registration process. Figure 3.1 illustrates this approach.

As shown the images to be registered are down-sampled to different scales and then registration is computed based on resulting images. It begins at the coarsest level and progresses to a higher level after convergence is reached. The process continues until the final registration at the highest level is completed. The parameters at each level are set based on the results obtained on the previous level and the same optimization method is used at the different levels.

3.5.2   Sampling Strategies

The most common approach to register two images is to use all voxels in the images. For images having large sizes this procedure is time consuming. The common approach used to speed up intensity-based methods is to use a subset of voxels sampled on a uniform grid. With this approach the voxels separated by a uniform distance are used to evaluate the cost function [49]. Another alternative is to use a defined mask image specifying a region of interest supplied by the user [49]. The region of interest can be a bounding volume in 3D or a bounding box in 2D around the object.

3.6   Conclusion

In this chapter the general framework of 3D image registration is presented. The main components of global image registration have been discussed and an overview of local registration is also given. The most used similarity measures and some of the nonlinear optimization methods used to find the optimal parameter values of the cost function were discussed. Additionally different techniques used to speed up this process such as the use of a defined mask, a uniformly sampled grid or adoption of multi-resolution have been described as well.
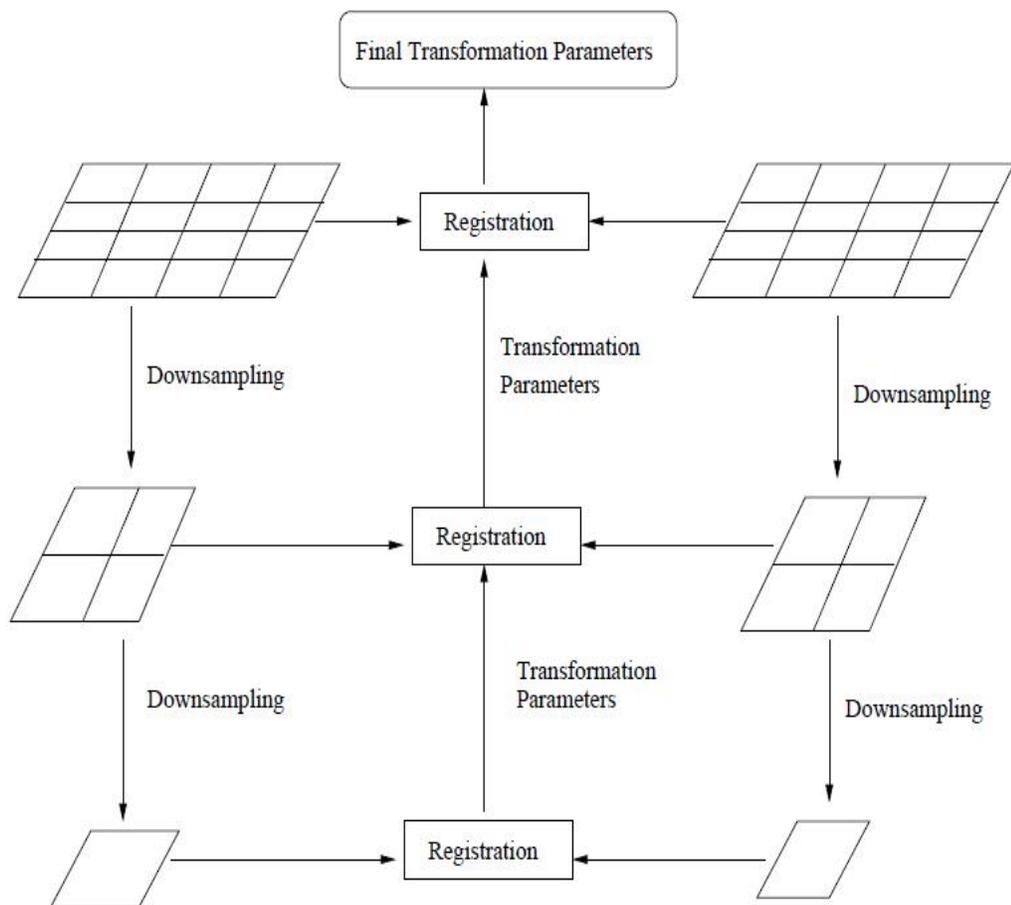
Figure 3.1: Image registration using multi-resolution. Adapted from [3].

Chapter 4

Overview of the Symmetry and Atlas-Based Methods

Chapter 2 and 3 discuss different techniques proposed in the literature employed for the task of segmenting brain lesions and registration of medical images respectively. Despite the existence of numerous methods which give promising results to detect and segment brain abnormalities there has not been a gold-standard technique developed to perform this task because of varying acquisition protocols, varying brain lesions attributes such as grey level intensity or location, and different image modalities and brain sizes between different age groups. The lack of an accurate method which segments brain lesions under varying conditions gives researchers an opportunity to propose new methods which try to solve the problem. The majority of the approaches proposed in the literature make use of information used by radiologists to perform this task. Information used includes but is not limited to the following: expected grey level values of brain lesions, brain lesions appearing asymmetric along the plane, appearance, and location of normal brain tissues.

In this chapter, two different methods which make use of some of the ideas presented in the literature to detect and segment brain lesions are proposed. One of the methods uses the knowledge about the symmetry of a healthy brains while the other method is based on prior knowledge of the expected grey level values of healthy brain tissues to characterize a variety of brain lesions. The symmetry based method is applied to CT and T1-, and T2-weighted brain MR images. The second method relies on the prior knowledge about grey level values of healthy brain tissues. The knowledge is presented in the form of a brain atlases. This method is applied on T1-weighted MR images with hyperintense and hypointense lesions. The proposed method is automatic and general enough to be applied to other image modalities by creating different brain atlases for different image modality.

The outline of this chapter is as follows. The reasons for choosing the symmetry and atlas-based methods are given in Section 4.1. Section 4.2 describes the assumptions made in each method while Section 4.3 gives a workflow of each approach and discusses their different components.

Section 4.4 concludes the chapter.

4.1 Motivation for Choosing Knowledge-Driven Methods

Anomaly detection and segmentation methods can be categorized under two umbrella terms, namely knowledge-driven and data-driven methods. Knowledge-driven methods utilize prior anatomical knowledge about the properties of healthy brain structures to guide segmentation, while data-driven methods are supervised or unsupervised and statistical in nature. The symmetry-based and atlas-based methods are classified as knowledge-driven methods. Figures 4.1 and 4.2 show a graphical illustration under which knowledge and data-driven methods are likely to succeed or fail using prototype axial slices with a simulated brain tumors at different locations.

Data-driven methods (supervised and unsupervised) are limited to the problem they are designed to solve and often fail to give correct results in cases where there is an overlapping intensity distribution between healthy tissue and abnormal tissue, as shown in Figure 4.2. Additionally, when they are used on a different image modality they need to be re-engineered since they misclassify normal and tumorous tissues. The cross variability of intensity distribution between healthy and abnormal tissues still remains a challenge within the supervised methods, and some of the unsupervised methods have adopted the selection of seed points for initialization though it limits such methods not to be fully automatic.

The symmetry method works well when the lesion is localized in one hemisphere as shown in the first image of Figures 4.1 and 4.2. In cases where the lesions are symmetrically placed on both hemispheres as illustrated in the second image of Figures 4.1 and 4.2, this method is likely to fail. Moreover if the lesion is large enough to cross the symmetry axis, as depicted in the last image of Figures 4.1 and 4.2, it becomes difficult to use the symmetry alone to detect abnormal tissues. This method is applicable to different image modalities and need not be redesigned or retrained when it is subjected to such variations. The same set of rules can be employed to detect and segment asymmetric brain tissues without human input.

An atlas-based method works correctly only when it is applied to images of modality similar to those it was constructed with. It is expected to mark the location of the brain lesion, regardless of whether the lesion is symmetric or not, or if there is an overlapping intensity distribution between the lesion and healthy tissue. However, when it is employed on subjects of a different modality it can misclassify healthy and abnormal tissues. This problem can be solved by constructing a multi-modality brain atlas without a need to re-engineer or redesign. Given the sample atlas depicted in Figure 4.3, this method is likely to delineate the abnormalities illustrated in Figure 4.1 and 4.2 by analyzing either the intensity difference between the test image and the atlas or the displacement field after applying the registration.
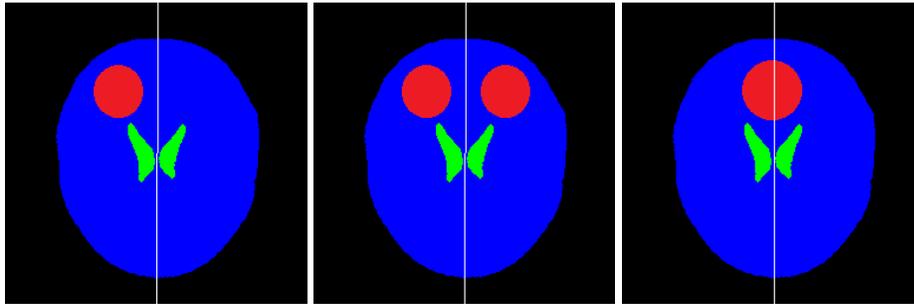
Figure 4.1: Simulated axial slices showing symmetric and asymmetric brain abnormalities (red) with the symmetry axis (white line) superimposed on each slice. From left to right: asymmetric lesion (red) lying on the left hemisphere, two symmetric lesions (red) placed on both hemispheres and a large lesion crossing the symmetry axis.
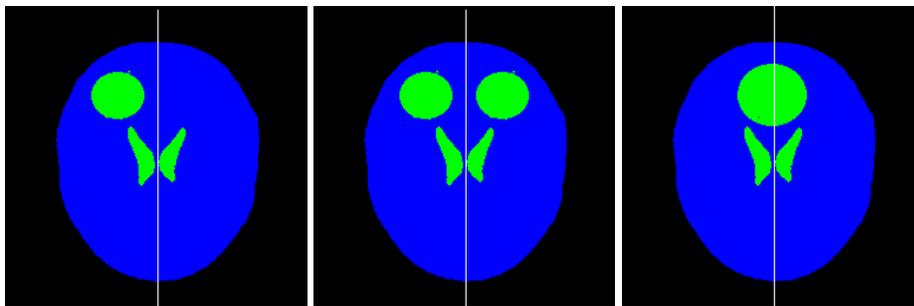
Figure 4.2: Simulated axial slices showing symmetric and asymmetric brain abnormalities (green) having overlapping intensity with healthy tissues. The symmetry axis (white line) is superimposed on each slice. From left to right: asymmetric lesion (green) lying on the left hemisphere, two symmetric lesions placed on both hemispheres and a large lesion crossing the symmetry axis.
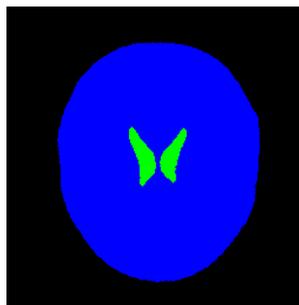
Figure 4.3: Illustration of the atlas sample.

4.2   Assumptions

There are three fundamental assumptions in the asymmetry quantification method.

1. The healthy brain tissue is symmetric in both hemispheres with minimal shifting expected due to the swelling of the brain lesions such as meningiomas.

2. The lesions do not cross the symmetry axis and are localized in one of the hemispheres.

3. Also they have intensity values different from their surrounding healthy brain tissues.

For analysis in atlas-based methods the following assumptions are made for normalization of different subjects.

1. Because of the different shapes and sizes of patient's brains across age or race groups, a population specific brain atlas is constructed under the prime assumption that the topological structures of the brain remain invariant among normal subjects.

2. The affine registration is capable of resolving global misalignment and size between different subjects.

3. A nonrigid registration resolves local shape difference between internal structures of the subjects. The registration algorithms assume the same intensity for corresponding brain structures in the two images to be aligned.

4.3   Outline of the Proposed Methods

In this section a detailed workflow of each method is presented, so that subsequent chapters discussing the implementations can be easily understood. The atlas is constructed from the set of healthy brain images which have been aligned onto one coordinate space.

4.3.1   Anomaly Detection Using Symmetry Analysis Method

The symmetry analysis method is based on the assumption that the brain appears symmetrical and the symmetry is breached in cases where various conditions of brain pathologies occur. The conditions include brain lesions appearing only on one side of the brain hemisphere or appearing on both hemispheres but at different locations. Figure 4.4 illustrates a series of steps associated with the symmetry-based method. The major components involved in this approach include: (1) detection of the symmetry plane, (2) tilt correction and (3) asymmetry quantification.

Detection of the Symmetry Plane: the mid-sagittal plane (MSP) is the plane dividing the brain into similar hemispheres. This is the main building block for asymmetry analysis since all the
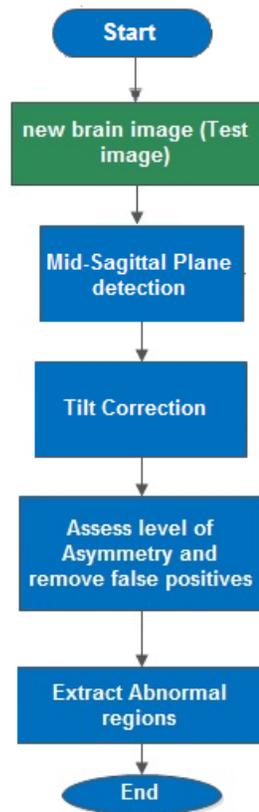
Figure 4.4: General workflow of the symmetry analysis method.

operations, such as reflection of the head and comparison of regions found on both left-hand and right-hand brain hemispheres are performed over this plane. The extracted plane is also used to remove head scan rotation and tilting. If this step fails then so do the succeeding steps.

Tilt Correction: given the MSP an affine tranformation is formulated which is employed to correct rotation and tilting of the head such that it is correctly centered around the center of the grid volume and each axial slice represents the brain at the same axial level. This transformation consists of both translation and rotation. The main advantage of applying the transformation is that it makes it easier to perform the symmetry analysis on slice bases. It also helps to enforce the constraint of the minimum number of slices the lesion is expected to appear in.

Asymmetry Quantification: this step involves the evaluation of the brain tissue similarity appearing on the two hemispheres. At first the right hemisphere is reflected over the MSP such that healthy brain tissues from the reflected right hemisphere and left hemisphere map exactly to one another. Numerous approaches have been employed in the literature, of which some rely on the registration of these hemispheres and others make use of interest region detection methods. In this thesis a registration-based method which assesses the similarity of suspicious regions and their surrounding region is proposed. The accuracy of the proposed technique is compared with that of a region detection method against the ground-truth. The implementations of the two methods are given in Section 5.4 and 5.5.

4.3.2   Anomaly Detection Using an Atlas

Two main operations are needed to detect abnormal tissues whose grey level intensity values deviate from the expected values. The first operation is the construction of the model of healthy brain tissues, and the second operation is the application of the heuristics to determine whether new brain scans consist of pathologies by assessing their similarity to the model. A number of methods have been proposed in the literature, including eigenbrains [55] and the use of a brain atlas [6, 21, 28, 29]. The strategy adopted in this thesis is somewhat related to the work presented in [6] where the model is represented in the form of brain atlas. The atlas consists of the average and variance of the intensity for each voxel. Also it comprises the average and variance of the displacement field for each voxel.

4.3.2.1   Atlas Construction

The atlas is constructed from a set of healthy brain scans which have been aligned onto one coordinate space. At first all brain scans are mapped onto a Euclidian space where each voxel represents a cubic millimeter, to remove anisotropic scaling. Images are then mapped by a 9-parameter affine transformation to a reference image selected from the set of healthy scans. The estimated parameters are 3-rotation angles, 3-scaling factors and 3-translations along x-, y- and z-axes. After

employing the affine transformation a nonrigid registration is also applied to correct any slight deformation that may result between the reference image and other images. After aligning the entire dataset onto the same coordinate frame, the atlas is developed.

4.3.2.2   Detecting Anomalies

Evaluating the similarity between a new brain scan (taken in axial format) and the atlas requires the scan to be aligned onto the atlas space. Two different approaches are followed to estimate the affine transformation between the new scan and the atlas. One approach is based on registering full scans and the other is based on registering partial scans. Aligning partial data to atlas space is a challenging task due to a lot of missing data between the subject and the atlas. The procedure to estimate the transformation using a 2D affine transformation between midsagittal and coronal slices is discussed below.

The affine transformation between partial scan and the atlas is computed from a set of 2D affine transformations estimated by aligning mid-sagittal and coronal slices of the scan and atlas. At first a mid-sagittal slice from two volumes is used to find the transformation that scales, positions and rotates sagittal slices of the subject to match sagittal slices of the atlas. The same principle is applied to coronal slices to find the transformation which scales coronal slices of these volumes to the same size. The two transformations are then combined and the final transformation is applied to the data. Registering a full scan onto the atlas space requires the estimation of a 3D affine transformation which is determined in a similar fashion to that employed when constructing the atlas. After applying the affine transformation a nonrigid registration is performed to remove local displacement of brain tissues. A drawback of nonrigid registration is that it introduces artifacts in cases where brain structures between two images do not match correctly. This often occurs in the presence of abnormal tissues in the subject which are not present in the brain atlas.

After mapping the test image into the atlas space, the corresponding voxels between the registered scan and atlas are compared to determine voxels with intensity values deviating from the expected values. These voxels are classified as abnormal and mark the proposed location of the brain tumor.

4.4   Conclusion

This chapter reviewed different components associated with the symmetry-based and atlas-based methods. It also provided reasons for choosing these two approaches. The assumptions have been stated for each method. The implementation and evaluation of the symmetry-based methods on T1- and T2-weighted MR images are given in Chapter 5. Chapter 6 describes the implementation and evaluation of the atlas-based method on T1-weighted MR images.

Chapter 5

Symmetry Plane Detection and Asymmetry Quantification in CT and MR Images

This chapter gives a detailed description of the method used for extraction of the mid-sagittal plane (MSP) and detection of brain lesions using asymmetry. A 2D or 3D object is said to have a bilateral symmetry if there exists a line or plane respectively that separates the object into two identical parts. The asymmetry quantification method used addresses a variety of brain pathologies in CT and MR images which appear asymmetric along the inter-hemispheric (longitudinal) fissure bisecting the brain, the MSP in this case, into similar hemispheres. The following three steps are performed to detect and segment brain lesions: (1) detection of the MSP, (2) tilt correction and (3) asymmetry quantification.

The detection of the MSP is modeled as an optimization problem which minimizes the similarity measure to find the optimal values of the symmetry plane parameters. It is based on the assumption that the scan has a single region of interest which is ellipsoidal in shape. To detect and segment asymmetric brain lesions from 3D MR and CT images, two asymmetry quantification methods have been implemented. They are based on the assumption that healthy human brain tissues appear symmetrical with respect to the MSP and the symmetry is violated by the presence of lesions. The first technique is a registration-based method which aligns healthy brain tissues from the two hemispheres while the second one is based on 2D region detection.

The outline of this chapter is as follows. Section 5.1 describes the symmetry axis in 2D images. Section 5.2 discusses the MSP detection algorithm in detail while Section 5.3 gives a description of the procedure followed to transform a tilted head scan so that each axial slice represents the brain at the same axial level. Sections 5.4 and 5.5 describe asymmetry analysis methods based on registration and region of interest detection respectively. Section 5.6 concludes with results and

discussion.

5.1 Symmetry Axis in 2D Images

Symmetry plays an important role in describing the geometry and the appearance of an object [56]. It is widely used in the field of computer vision and computer graphics, or machine intelligence because of its capability to minimize redundancy and reduce computation time [10, 56]. Despite significant use in these fields it is still confronted by a number of challenges such as computational cost, presence of noise and distortion of the digitized real world data. Numerous methods have been proposed in the literature for detecting and quantifying symmetry in 2D images [57, 58]. In this section a method which detects the symmetry axis in 2D images is presented. The symmetry axis is represented by the angle (between the symmetry line and positive x-axis) and the y-intercept parameters.

5.1.1 Symmetry Detection

In general a straight reflection line in the Cartesian coordinate system is defined as $y = mx + c$, where m and c represent the slope and y-intercept parameters. The optimal values of these parameters form a symmetry axis which divides the object in a 2D image into two similar parts such that there is no significant difference between the object and its reflected copy about this axis. The reflection matrix [59] about this line can be shown to be

$$\mathbf{T}_{RF} = \frac{1}{m^2 + 1} \begin{bmatrix} 1 - m^2 & 2m & -2mc \\ 2m & m^2 - 1 & 2c \\ 0 & 0 & m^2 + 1 \end{bmatrix}. \tag{5.1}$$

However, vertical lines of the form $x = b$ pose a problem to Equation 5.1 as they give rise to unbounded values of the gradient parameter m. To address this challenge a limit as $m \to \infty$ is taken by substituting $m = \tan\theta$ into this equation and then simplifying to give the following

$$\mathbf{T}_{RF} = \frac{1}{\tan^2\theta + 1} \begin{bmatrix} 1 - \tan^2\theta & 2\tan\theta & -2\tan\theta c \\ 2\tan\theta & \tan^2\theta - 1 & 2c \\ 0 & 0 & m^2 + 1 \end{bmatrix} = \begin{bmatrix} \cos 2\theta & \sin 2\theta & -c\sin 2\theta \\ \sin 2\theta & -\cos 2\theta & 2c\cos^2\theta \\ 0 & 0 & 1 \end{bmatrix}, \tag{5.2}$$

where θ is the angle between the line of symmetry and the positive x-axis. Given a 2D image $\mathbf{R}$ the sum of square difference (SSD)

$$SSD(\mathbf{u}) = \frac{1}{2}||\mathbf{R} - \mathbf{F}(\mathbf{u})||^2_{L_2}, \qquad (5.3)$$

is used as the symmetry measure to determine the closeness of $\mathbf{R}$ to its reflected copy $\mathbf{F}(\mathbf{u}) = \mathbf{R}(\mathbf{T}_{RF}(\mathbf{x}, \mathbf{u}))$ where $\mathbf{u} = [\theta, c]^T$ and $\mathbf{x} = [x, y]^T$. The optimal values of θ and c are found by omitting the z-axis and employing the Levenberg-Marquardt optimization and multiresolution method as described in Section 5.2.6.

5.1.2 Symmetry Detection Results

The method was tested on randomly selected axial slices of MR and CT scans. It was also tested on simulated binary images. A total of nine test images were used: three images from MR, CT and binary images. In some datasets bright and dark asymmetric rectangular regions, of dimensions 40×20 pixels, are created and overlaid on the test images to determine if the presence of asymmetry lesions could affect the accuracy of the method. Figure 5.1 illustrates the results for the best symmetry axis found in these images. From these results the conclusion that can be drawn is that the tested method can estimate a line of symmetry regardless of the presence of asymmetric regions. However, the algorithm sometimes is trapped if the global minimum is far from the initial guess or one of the object's symmetrical halves is more sheared than the other. This can be seen in the right-bottom binary image of Figure 5.1. The method is extended to 3D in the next section to detect the MSP in 3D brain CT and MR images.

5.2 Mid-Sagittal Plane Detection

The extraction of the MSP is formulated as an optimized registration problem in a manner similar to the 2D case just described. Given the brain MR or CT scan $\mathbf{R}$ and initial values of the candidate plane parameter a transformation is formed which is used to reflect $\mathbf{R}$ over the plane to create a new scan $\mathbf{F}$. The method searches for the optimal plane parameter values that minimizes the sum of square difference (SSD) between $\mathbf{R}$ and $\mathbf{F}$.

5.2.1 Geometry of the MSP

There are various ways to represent a plane in 3D Cartesian coordinates. The equation of the plane can be deduced from three non-collinear points $(\mathbf{p}_1, \mathbf{p}_2, \mathbf{p}_3)$ lying on the plane [30]. It can also be deduced from the given point $\mathbf{p}_0 = [x_0, y_0, z_0]^T$ that lies on the plane and a perpendicular vector, $\mathbf{n}$, to the plane [10]. A general equation of the plane is given as

$$Ax + By + Cz + D = 0, \qquad (5.4)$$
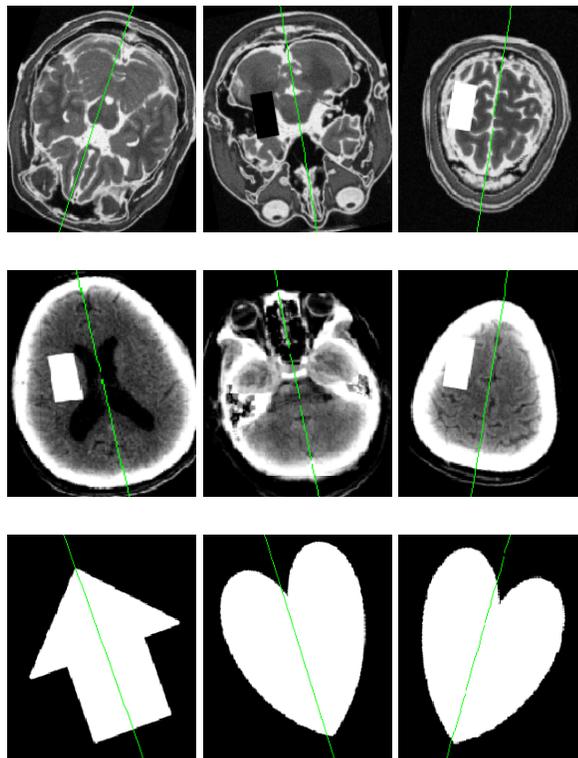
Figure 5.1: Symmetry detection results on 2D images. The symmetry line (green) is overlaid on MR (first row), CT (second row) and simulated binary images (third row). In the right-bottom image, the algorithm converged to the global minimum of the cost function and there is no clear symmetry in this image due to the shearing of the left half of the object.

where A, B, C are real numbers and are not all zero, $\mathbf{n} = [A, B, C]^T$ is the normal vector perpendicular to the plane and $L = D/\sqrt{A^2 + B^2 + C^2}$ is the distance of the plane away from the origin with $D = -(Ax_i + By_i + Cz_i)$ for an arbitrary point, $[x_i, y_i, z_i]^T$, lying on the plane. The parameters to be optimized are A, B, C and D. Figure 5.2 demonstrates the 3D view of a full scan head with the MSP passing through the volume.
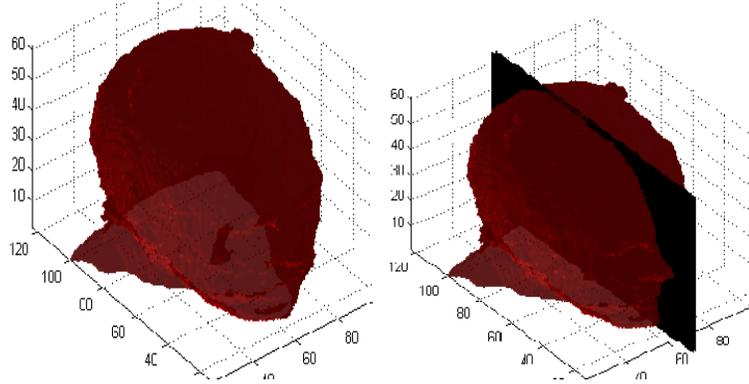
Figure 5.2: From left to right: 3D view of a full scan head, illustration of the MSP (black) passing through the head.

5.2.2 Isotropic Resampling

The medical images used in this work possess different voxel dimensions. The work discussed in [60] investigates the impact of the voxel dimensions on image quality. The results showed that it easy to delineate body structures using decreased voxel size. However, this comes at cost of large signal losses due the reduced voxel size. In another research Caivano et al. [61] showed that the slice thickness of scanned images has be taken into consideration to accurately determine the lesion volume. They found that a more accurate lesion volume is achieved if the slice thickness is 1 or 2 mm in lesions with small volumes while slice thickness >2 mm is suitable for large volume lesions.

Given the fact that the slice thickness affects the volume determination of small abnormal brain tissues it is also expected that healthy tissues with small volume are affected as well. Hence to minimize the defects that may hinder the accuracy of estimating the MSP, the brain volumes are resampled such that each voxel represents 1 cubic millimeter. For image of dimensions $N_x \times N_y \times N_z$ voxels and each voxel having dimensions $d_x \times d_y \times d_z$ mm the transformation matrix $\mathbf{S}$ used to resample the image is formulated as

$$\mathbf{S} = \begin{bmatrix} d_x & 0 & 0 & -N_x d_x/2 \\ 0 & d_y & 0 & -N_y d_y/2 \\ 0 & 0 & d_z & -N_z d_z/2 \\ 0 & 0 & 0 & 1 \end{bmatrix}. \tag{5.5}$$

The new dimensions of the transformed image is $N'_x \times N'_y \times N'_z$ where $N'_x = N_x d_x$, $N'_y = N_y d_y$ and $N'_z = N_z d_z$. Backward Cubic interpolation is employed remove the holes that arises between the voxels of the resampled image.

5.2.3 Feature Space

The registration between the original brain image and its reflected copy uses an intensity-based approach. The images are aligned using their raw voxel intensity values, hence preprocessing steps for feature extraction are not required. The drawback of this approach is the high computational cost since the entire set of image information is used. A common approach used to speed up intensity-based methods is to use a subset of voxels sampled on a uniform grid or a defined mask image locating the region of interest supplied by the user [49]. In this work a subset of voxels sampled on a uniform 3D grid is adopted since it limits human interaction.

5.2.4 3D Reflection Transformation Matrix

The registration process requires a transformation matrix to align one image onto another. In the MSP detection problem a 4D reflection matrix $\mathbf{T}_{RF}$ is used to reflect the 3D medical image over the candidate symmetry plane. The general equation of $\mathbf{T}_{RF}$ is deduced from Equation (5.4) as follows. Given a point $\mathbf{p}_0 = [x_0, y_0, z_0]^T$, to be reflected over the plane, a line that passes through $\mathbf{p}_0$ and perpendicular to plane is defined as

$$\mathbf{r} = \mathbf{p}_0 + \alpha \mathbf{n} = [x_0, y_0, z_0]^T + \alpha [A, B, C]^T = [x_0 + \alpha A, y_0 + \alpha B, z_0 + \alpha C]^T, \tag{5.6}$$

where α is distance in the direction of the normal to the plane. Equation (5.6) is substituted into Equation (5.4) to solve for α which is substituted back into Equation (5.6) to find the intersection point $\mathbf{p}_1 = [x_0 + \alpha A x_0, y_0 + \alpha B y_0, z_0 + \alpha C z_0]^T$ of the line and the plane. The intersection point acts as an intermediate point between the original point $\mathbf{p}_0$ and its reflected copy $\mathbf{p}_2$. The value for α is calculated as

$$\alpha = -(\frac{A x_0 + B y_0 + C z_0 + D}{A^2 + B^2 + C^2}), \tag{5.7}$$

where A, B, C are not all zero. Hence, knowing the coordinates of $\mathbf{p}_1$, the coordinates of $\mathbf{p}_2$ are obtained as $\mathbf{p}_2 = 2\mathbf{p}_1 - \mathbf{p}_0$ [62]. Using homogeneous coordinates [44] $\mathbf{p}_2$ can be represented by a 4×4 matrix and 4×1 vector point as follows

$$\mathbf{p}_2 = \mathbf{T}_{RF}\mathbf{p}_0 = \frac{1}{\Lambda}\begin{bmatrix} \Lambda - 2A^2 & -2AB & -2AC & -2AD \\ -2AB & \Lambda - 2B^2 & -2BC & -2BD \\ -2AC & -2BC & \Lambda - 2C^2 & -2CD \\ 0 & 0 & 0 & \Lambda \end{bmatrix}\begin{bmatrix} x_0 \\ y_0 \\ z_0 \\ 1 \end{bmatrix}, \tag{5.8}$$

where $\Lambda = A^2 + B^2 + C^2$ and $\mathbf{p}_0 = [x_0, y_0, z_0, 1]^T$.

5.2.5 Similarity Measure

The original MR or CT image $\mathbf{R}$ and its reflected copy $\mathbf{F} = \mathbf{R}(\mathbf{T}_{RF}(\mathbf{x}, \mathbf{u}))$ represent images of the same modality for $\mathbf{u} = [A, B, C, D]^T$. The sum of square difference (SSD) is used as the similarity criterion to measure how well the two images match one another. SSD is chosen since it is simple to compute and uses the whole image information [47]. This measure is minimized to find the optimal values of plane parameters. SSD between the $\mathbf{R}$ and $\mathbf{F}$ is given as

$$SSD(\mathbf{u}) = \frac{1}{2}||\mathbf{R} - \mathbf{F}(\mathbf{u})||_{L_2}^2 = \frac{1}{2}\mathbf{f}(\mathbf{u})^T\mathbf{f}(\mathbf{u}), \tag{5.9}$$

where $\mathbf{f}(\mathbf{u}) = \mathbf{R}(\mathbf{x}) - \mathbf{R}(\mathbf{T}_{RF}(\mathbf{x}, \mathbf{u}))$, $\mathbf{T}_{RF}$ is the reflection matrix, and $\mathbf{x} = [x, y, z]^T$ is an abitrary 3D point.

5.2.6 Optimization Using Levenberg-Marquardt (LM) Method

The Levenberg-Marquardt method is utilized to minimize the SSD between the MR or CT image $\mathbf{R}$ and its reflected copy $\mathbf{F}$. This is a nonlinear least square problem in which the function to be minimized is represented as the sum of square difference of the corresponding voxels in the two images [51]. LM is adopted in this work as an optimization method due to the fact that it inherits the speed of Gauss-Newton algorithm and the stability of Steepest Descent to find the minimum of the similarity measure SSD [44, 45, 53].

The vector parameter used to formulate the reflection transformation is described by $\mathbf{u} = [A, B, C, D]^T = [u^1, u^2, u^3, u^4]^T$. This vector is updated at each iteration after computing the derivative of the SSD with respect to $\mathbf{u}$. As it can be seen from Equation 5.9 $\mathbf{F}(\mathbf{u}) = \mathbf{R}(\mathbf{T}_{RF}(\mathbf{x}, \mathbf{u}))$ is a function of $\mathbf{u}$. This means if $\mathbf{u}$ is perturbed by a tiny amount, $\mathbf{F}$ is also expected to change. Hence the derivative of $\mathbf{F}$ with respect to $\mathbf{u}$ is used to estimate the Jacobian matrix $\mathbf{J}(\mathbf{u})$ [44]. Given the initial parameter value $\mathbf{u}_0 = [u_0^1, u_0^2, u_0^3, u_0^4]^T$ the derivative of $\mathbf{F}$ is carried out numerically to compute the Jacobian matrix $\mathbf{J}(\mathbf{u})$ as described in [44]:

$$\mathbf{J}^{ij}(\mathbf{u}) = \partial\mathbf{F}^j/\partial u^i. \tag{5.10}$$

Numerical differentiation of Equation (5.10) computed using the forward difference method is as

follows

$$\mathbf{J}^{ij}(\mathbf{u}) = \left(\mathbf{F}(\mathbf{u} + \delta\vec{u^i}) - \mathbf{F}(\mathbf{u})\right)/\delta, \tag{5.11}$$

for $1 \leq i \leq 4$, $1 \leq j \leq N_x N_y N_z$, and where $\vec{u^i}$ is the unit direction vector along the u^i-axis. A routine is developed in which $\mathbf{R}$ is reflected over the candidate plane to generate a new image $\mathbf{F}^{u^i}$ every time after each independent variable u^i is modified by δ. The value for δ is set to the maximum of $|10^{-4}u^i|$ and 10^{-6} as described in [44]. The same routine is used to compute $\mathbf{J}(\mathbf{u})$ to improve convergence and computation speed slightly [44]. The Hessian matrix is constructed directly from the first derivatives, and its diagonal elements are augmented as described in Section 3.4.5. The search direction $\mathbf{d}_k$ is also computed as described in Section 3.4.5. If the newly computed value of the vector parameter $\mathbf{u}_{k+1} = \mathbf{u}_k + \mathbf{d}_k$ reduces the error function, then the new parameter is accepted, the damping factor μ is reduced by a factor of 10, and the algorithm continues to the next iteration if convergence is not reached. Otherwise μ is increased by a factor of 10 if $\mathbf{u}_{k+1}$ leads to an increased error and equations are solved again with the new value of μ. The damping factor μ is updated based on the value of the gain ratio as described in Section 3.4.5. The summary of the algorithm consists of the following steps.

Input: (MR or CT scan in axial format $\mathbf{R}$, initial parameter $[\mathbf{u}_0, \mu]$, stopping criterion $[k_{max}, \varepsilon_1]$)

Output: ($\mathbf{u}_k^* = [A, B, C, D]^T$)

Algorithm

Begin

Step 0: Load input variables into memory.

Step 1: while $k < k_{max}$, do

    Step 2: Compute $\mathbf{J}$ using forward difference.

    Step 3: Augment diagonal elements of the Hessian estimate by μ.

    Step 4: Solve for the search direction, $\mathbf{d}_k$, from augmented equations.

    Step 5: if $||\mathbf{d}_k|| < \varepsilon_1$, Goto **Step 9**.

    Step 6: Update plane parameter temporarily, $\mathbf{v} = \mathbf{u}_k + \mathbf{d}_k$, and compute gain ratio ρ .

    Step 7: If $\rho > 0$, increase iterations by 1 ($k = k+1$), decrease damping factor by 10

    ($\mu = \mu/10$), permanently update plane parameters ($\mathbf{u}_k = \mathbf{v}$). Goto **Step 1**.

    Step 8: Increase damping factor by 10 ($\mu = 10\mu$). Goto **Step 3**.

Step 9: Return final results after convergence is reached.

End

The algorithm is slow for large image sizes and is often trapped in the local minima if the initial guess of the plane parameter value is far from the optimal value. Therefore, to provide a good initial guess of plane parameter value a multi-resolution is applied.

5.2.7 Multi-Resolution

Multi-resolution is adopted to speed up the registration problem and to provide a reliable guess of the plane parameter vector $\mathbf{u}$ [10, 30, 45]. The image of interest $\mathbf{R}$ is downsampled to low resolution images which are used to estimate the plane parameters with reduced computational load [30, 49, 45]. Given that the dimensions of $\mathbf{R}$ at the highest level L are $N_x \times N_y \times N_z$, the size of the image at the coarser level l is obtained by down scaling the image at the finest level by a scale factor of 2^{L-l}, followed by the interpolation. In this work the total number of levels is set to four. At each level l, the Levenberg-Marquardt method described in Section 5.2.6 is used to compute the reflection transformation while estimating the optimal parameters of the plane up to some defined tolerance or number of iterations.

The initial guess of plane parameters is used at the coarsest level and the parameters are updated after each iteration. In this thesis three initial guesses, $(\mathbf{u}_{01}, \mathbf{u}_{02}, \mathbf{u}_{03})$ of plane parameter are used at the coarsest level to reduce the problem of the algorithm being trapped in a local minimum. The initial guess that leads to convergence with the minimum error between the three is considered as the best guess and is used in succeeding levels. With the assumption that the brain scan is in axial format $\mathbf{u}_{01} = [0, 1, 0, N_y/2]^T$ is the sagittal plane that divides the volume lattice into two halves with equal size. The guesses $\mathbf{u}_{02}$ and $\mathbf{u}_{03}$ are derived by rotating $\mathbf{u}_{01}$ with the rotational angle $\theta = 25°$ and $\theta = -25°$ respectively about the z-axis. The value of the rotational angle is set empirically based on the observation that LM gets trapped in a local minimum if the head is severely tilted. When convergence is reached the optimum results obtained are modified and used as the initial guess at the next level. In this problem only the last parameter D is modified while others remain unchanged. Since the size of the image at the next level is twice larger than the size at the coarser level so does the distance of the plane away from the origin. This can be written mathematically as

$$\left[A^{(L-l-1)}, B^{(L-l-1)}, C^{(L-l-1)}, D^{(L-l-1)} \right]^T = \left[A^{(L-l)}, B^{(L-l)}, C^{(L-l)}, 2 * D^{(L-l)} \right]^T, \qquad (5.12)$$

for $1 \leq l < L$. The whole process continues until the highest level is reached, and the optimal results found at this level are used as the final estimate of the MSP.

Input: (CT or MR scan in axial format $\mathbf{R}$, initial parameter $[\mathbf{u}_{01}, \mathbf{u}_{02}, \mathbf{u}_{03}, \mu]$, stopping criterion $[k_{max}, \varepsilon_1, \varepsilon_2]$, number of levels L_{max})

Output: ($\mathbf{u}_k^* = [A, B, C, D]^T$)

Algorithm

Begin

Step 0: Load input variables into memory.

Step 1: downsample $\mathbf{R}$ by $2^{L_{max}}$ to get new volume $\mathbf{R}_1$.

Step 2: Evaluate the LM method given in 5.2.6 at ($\mathbf{R}_1$, $[\mathbf{u}_{01}, \mu]$, stopping criterion $[k_{max}, \varepsilon_1]$).

Step 3: Evaluate the LM method given in 5.2.6 at ($\mathbf{R}_1$, $[\mathbf{u}_{02}, \mu]$, stopping criterion $[k_{max}, \varepsilon_1]$).

Step 4: Evaluate the LM method given in 5.2.6 at ($\mathbf{R}_1$, $[\mathbf{u}_{03}, , \mu]$, stopping criterion $[k_{max}, \varepsilon_1]$).

Step 5: Set $l = 1$ and $\mathbf{u}_l$ to optimal parameter (in step 3,4 and 5) that converged with the minimum error.

Step 6: if ($l < L_{max}$), then update $\mathbf{u}_l$ using equation 5.12.

Step 7: while $l \leq L_{max}$, do

    Step 8: down sample $\mathbf{R}$ by $2^{L_{max}-l}$ to get new volume $\mathbf{R}_1$.

    Step 9: Evaluate the LM method given in Section 5.2.6 at ($\mathbf{R}_1$, $[\mathbf{u}_1, \mu]$, Stopping criterion $[k_{max}, \varepsilon_1]$).

    Step 10: if ($l < L_{max}$), then update $\mathbf{u}_l$ using Equation 5.12.

    Step 11:$l = l + 1$, update the level. Goto **Step 7**.

Step 12: Return final results after convergence is reached at level $l = L_{max}$.

End

5.3   Tilt Correction

The orientation of the patient sometimes leads the scanned head appearing tilted about y-axis or rotated about z-axis. The rotations about x-axis has no impact on repositioning tissues that are on the same axial level. The tilted and rotated image makes it difficult, even for a radiologist, to perform asymmetry analysis as corresponding regions might be at different axial levels. Hence the MSP is used to align the head with the volume lattice and center it within the volume. Given the candidate plane Equation (5.4) the rotation matrices $\mathbf{R}_z$, $\mathbf{R}_y$ and the translation matrix $\mathbf{T}_l$ can easily be determined. The rotation transformations $\mathbf{R}_z$ and $\mathbf{R}_y$ correct the rotations of the head about the z-axis and the y-axis respectively while the translation transformation $\mathbf{T}_l$ defines the center of rotation. The rotational angles β and ϕ are obtained by taking a dot product between the plane normal vector and unit vectors $XY = [0,0,1]^T$ and $XZ = [0,1,0]^T$ respectively. The unit vectors, $[0,0,1]^T$ and $[0,1,0]^T$, are the normal vectors of the XY and XZ planes respectively. The final rotation $\mathbf{M}_R$ is given as follows:

$$\mathbf{M}_R = \mathbf{R}_z\mathbf{R}_y = \begin{bmatrix} cos\phi & -sin\phi & 0 & 0 \\ sin\phi & cos\phi & 0 & 0 \\ 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 1 \end{bmatrix} \begin{bmatrix} cos\beta & 0 & sin\beta & 0 \\ 0 & 1 & 0 & 0 \\ -sin\beta & 0 & cos\beta & 0 \\ 0 & 0 & 0 & 1 \end{bmatrix}. \tag{5.13}$$

The translation matrix $\mathbf{T}_l$ is given as shown below:

$$\mathbf{T}_{l1} = \begin{bmatrix} 1 & 0 & 0 & T_x \\ 0 & 1 & 0 & T_y \\ 0 & 0 & 1 & T_z \\ 0 & 0 & 0 & 1 \end{bmatrix}, \tag{5.14}$$

where (T_x, T_y, T_z) is the center of rotation. Given the center of the image grid $C = (x, y, z)$, the center of the rotation is calculated as the midway point between C and the reflected copy of C over the plane. The final rigid transformation matrix is given as $\mathbf{M}_A = \mathbf{T}_l\mathbf{M}_R\mathbf{T}_l^{-1}$. Cubic interpolation is used to get rid of holes and produce an acceptable images. Figure 5.3 illustrates results after tilt corrections are performed on a MR and a CT dataset.
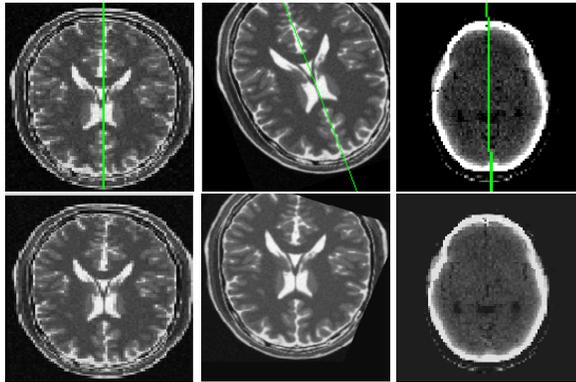
Figure 5.3: Results for CT and MRI scan after tilt correction: (first row) misaligned scans with the MSP overlaid on each slice; (second row) corresponding slices after tilt correction.

5.4 Asymmetry Quantification Using Registration

A fully automatic method to detect and segment brain tumors in 3D CT and MR scans using symmetry analysis is proposed. The technique presented here follows the same principle as the work described in [34] with the assumption that tumorous tissues are not symmetrically placed in both hemispheres. A nonrigid registration is used to correct slight displacement of corresponding voxels of the left hemisphere and a reflected copy of the right hemisphere. Analysis of intensity differences followed by a thresholding technique is employed to determine the presence of asymmetric tissues. Constraints are then applied to remove false positive regions. For illustration purpose in

each step a 3D CT data from iThemba LABS is used.

5.4.1 Nonrigid Registration

An aligned MR or CT image **I** is divided into two hemispheres: the left hemisphere **R** and the reflected copy of the right hemisphere **F** . Though the brain might appear largely symmetrical there is a tendency of the right frontal lobe to be larger than the left one and the left occipital lobe to be larger than the right one [63]. Hence nonrigid registration is applied to correct these differences.

The Medical Image Registration Toolbox (MIRT) implemented in MATLAB is used [43]. It is made freely available for research purposes. The toolbox implements both 2D and 3D nonrigid image registration. It also has multiple similarity measures such as SSD, MI, normalized mutual information (NMI), residual complexity (RC) and many others already implemented. More information about MIRT can be found in [43]. The following settings have been used based on the results presented in [43]. The choice of similarity measure used is SSD since the hemispheres to be registered are of the same modality and it is fast to compute. A three-level multi-resolution pyramid is also adopted to speed up the registration and increase accuracy. The maximum number of iterations is set to 100 to avoid the infinite loop while the tolerance between the previous error measure and the current is set to 6^{-8} as the stopping criteria. Figure 5.4 depicts the image difference between left and right hemispheres before and after registration:
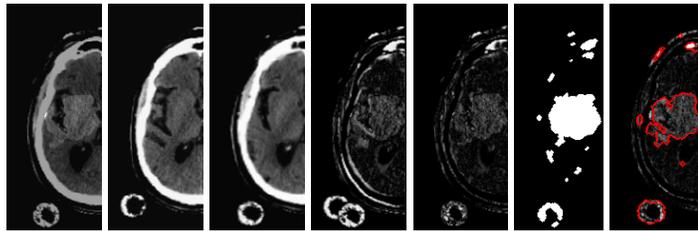
Figure 5.4: Results for image difference before and after applying nonrigid registration. From left to right: (1) axial slice from left hemisphere, (2) right hemisphere before registration, (3) registered right hemisphere, (4) intensity difference before registration, (5) intensity difference after registration, (6) suspected lesions regions for $\lambda = .8$ and $\zeta = .001$, (7) lesion regions overlaid on intensity difference. The parameters λ and ζ define the maximum intensity difference ratio and threshold between feature vectors respectively and are discussed later in Section 5.6.3.

5.4.2 Detection of Abnormal Region by Thresholding Image Difference

Since images are already aligned through rigid transformation after tilt correction, large intensity differences are expected to occur around the regions which are not symmetric. These regions mark the suspected tumor location in both hemispheres. An intensity difference volume **V** is used to describe the absolute intensity difference between the left and the registered right hemisphere. A

threshold $T = \lambda \max(\mathbf{V})$, where $\max(\mathbf{V})$ returns the largest value in $\mathbf{V}$, is applied to $\mathbf{V}$ followed by morphology operations [64], to produce a binary image volume $\mathbf{L}$ that estimates the location of the asymmetric regions. After enforcing the constraints discussed in Section 5.4.3 to removed false positives, a connected component labeling algorithm based on 3D region growing is used to extract the remaining regions. The seed point for the region growing method is selected automatically from the domain of remaining regions.

5.4.3 Removing False Positives

A number of constraints are enforced to penalize unlikely lesion regions and favor the likely ones. The constraints are set based on the response evaluation criteria in solid tumors (RECIST) standard published in [65, 66]. RECIST is a diameter-based approach which measures a single-axial slice containing the largest diameter of the lesion. Though this standard has not been widely adopted for clinical trials of neck and brain lesions, it is employed in this work to get rid of unmeasurable lesions. According to RECIST a lesion is declared unmeasurable on CT or MR scans if none of its axial slice has the longest diameter ≥ 10 mm while a measurable lesion at least has a single axial slice with the mentioned measurement. Therefore the default minimal false positive lesion diameter is set to 10 mm to penalize regions with smaller diameters. This number can be changed manually if lesions of interest have diameters $\gg 10$ mm or slice thickness is > 5 mm [65, 66].

The second constraint is based on inter-slice operations. It enforces tumorous region to appear in at least two successive slices. This means spurious regions that only appear in a single slice are discarded. Figure 5.5 illustrates left and right hemispheres attached together after nonrigid registration is applied and the longest diameter (LD) passing across each asymmetric regions.
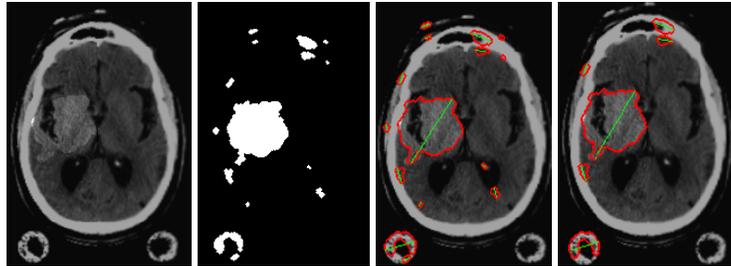
Figure 5.5: Estimated artificial lesion's longest diameter (LD): (a) Welded left-hand and right-hand hemispheres after performing nonrigid registration, (b) Highly asymmetric regions for $\lambda = .8$ and $\zeta = .001$, (c) Asymmetric regions (red contour) and LD (green line) for each region superimposed on axial slice, (d) Asymmetric regions with LD≥ 10 mm.

5.4.4 Detect the Ill Hemisphere Using Feature Factors

The analysis so far has been based on the binary volume $\mathbf{L}$ which was created by thresholding the intensity difference volume $\mathbf{V}$. There are still two possibilities that the tumor might be located

either on the left or right hemisphere. Hence two approaches are used to determine the exact location of the tumor between the two hemispheres. The first technique is based on the prior knowledge of the physical properties of brain tissues and tumor appearance. The second is based on the extraction of first order feature vectors of the region of interest and its surrounding region. Features are then compared to find which region deviates significantly from its surrounding.

5.4.4.1 Uncover Ill Hemisphere Using Prior Knowledge

With this approach a simple technique that compares mean intensities of the corresponding region is applied. The idea behind this approach is that a tumorous region always has an intensity that is different from the surrounding region. Hence given the prior information that lesions appear hyperintense or hypointense, a region with the highest or lowest intensity mean can be detected. The results are then used to determine the ill hemisphere.

5.4.4.2 Uncover Ill Hemisphere Without a Priori Knowledge

First-order statistic features describe the information concerning the frequency of the appearance of grey level in the examined image region [5, 67]. In most cases the grey level values of a lesion region are often different from those of healthy tissues surrounding it. This means that comparison of a lesion region's feature vectors and those of its surrounding area could reveal crucial information. The information is used to specify the proposed location of the lesion between the two hemispheres.

Given a region function $\mathbf{G}(k)$ of single variable $k = 1, 2, ..., N$, which can take on discrete values $i = 0, 1, ..., M - 1$, the intensity histogram function $\mathbf{H}(i)$ representing, for each intensity i, the total number of pixels in the whole region having this intensity is given as

$$\mathbf{H}(i) = \sum_{k=1}^{N} \delta\left(\mathbf{G}(k), i\right), \qquad \delta\left(j, i\right) = \begin{cases} 1, & j = i \\ 0, & j \neq i \end{cases} \tag{5.15}$$

Dividing the histogram $\mathbf{H}(i)$ by a total number of pixel N in a region estimates the probability of occurrence of the voxels with intensity $i = 0, 1, ..., M - 1$ as $\mathbf{P}(i) = \mathbf{H}(i)/N$. Hence the first-order features that can be extracted are defined as:

$$\text{mean: m} = \sum_{i=0}^{M-1} i\mathbf{P}(i), \qquad \text{Skewness: } m_3 = \frac{1}{\sigma^3} \sum_{i=0}^{M-1} (i - m)^3 \mathbf{P}(i),$$

$$\text{Variance: } \sigma^2 = \sum_{i=0}^{M-1} (i - m)^2 \mathbf{P}(i), \qquad \text{Kurtosis:} m_4 = \frac{1}{\sigma^4} \sum_{i=0}^{M-1} (i - m)^4 \mathbf{P}(i), \tag{5.16}$$

$$\text{Entropy: H} = -\sum_{i=0}^{M-1} \mathbf{P}(i) \log_2(\mathbf{P}(i)), \qquad \text{Energy:} E = \sum_{i=0}^{M-1} \mathbf{P}(i)^2.$$

Put in vector format the feature vectors for the left hand hemisphere region, its surrounding region, and those that are extracted from the right hand hemisphere are given as $\mathbf{v}_L = \left[m, \sigma^2, m_3, m_4, H, E\right]^T$, $\mathbf{v}_{SL} = \left[m, \sigma^2, m_3, m_4, H, E\right]^T$, $\mathbf{v}_R = \left[m, \sigma^2, m_3, m_4, H, E\right]^T$, and $\mathbf{v}_{SR} = \left[m, \sigma^2, m_3, m_4, H, E\right]^T$. Therefore given these feature vectors the correct lesion location is determine by evaluating the following indicator function

$$f\left(\mathbf{v}_L, \mathbf{v}_{SL}, \mathbf{v}_R, \mathbf{v}_{SR}\right) = \begin{cases} 2, & ||\mathbf{v}_L - \mathbf{v}_{SL}|| + \zeta < ||\mathbf{v}_R - \mathbf{v}_{SR}|| \\ 1, & ||\mathbf{v}_L - \mathbf{v}_{SL}|| > \zeta + ||\mathbf{v}_R - \mathbf{v}_{SR}|| \\ 5, & \text{otherwise,} \end{cases} \tag{5.17}$$

where ζ is a predefined threshold, set empirically, determining how well the magnitude of the difference of the left hemisphere region and its surrounding region feature vectors should differ from those of the right hand hemisphere. The returned values 2 and 1 show that lesion is precisely located on the right and left hemispheres respectively. In cases where the difference falls within the predefined threshold, the value 5 is emitted signaling that the model is unable to determine the exact pathological hemisphere. Hence the result remains unchanged and is left for the radiologist to make the final decision. Figure 5.6 shows the suspected location of lesions on the two hemispheres and the regions surrounding each lesion.
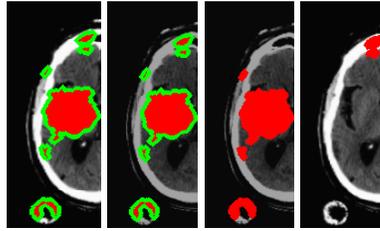
Figure 5.6: Suspected lesions locations on both hemispheres. From left to right: the regions (green) surrounding lesion regions (red) superimposed on the left hemisphere, the regions (green) surrounding lesion regions (red) superimposed on the right hemispheres, most asymmetric regions (red) on the left hemisphere, most asymmetric regions (red) on the right hemisphere.

5.5 Asymmetry Quantification Using Maximally Stable Extrema Region Detection

The approach presented in Section 5.4 depends largely on a nonrigid registration method which adds more computation time to the process. It is also sensitive to very large intensity differences. Although this technique might give correct results at the cost of computation, an alternative approach which does not rely on nonrigid registration is proposed. The new method is based on detection and comparison of prominent regions between the two hemispheres. Given the left hemisphere $\mathbf{R}$ and a reflected copy $\mathbf{F}$ of the right hemisphere interest regions are extracted and compared

to determine those that are not symmetric over the candidate plane.

5.5.1   Literature on Region Detection

Many of algorithms have been proposed in the literature to detect salient regions and generate features that are invariant to image transformation [68, 69, 70]. One of the recent affine region detection methods uses the center-surround distribution distance presented (CSDD) in [40]. This method is based on comparing features between a central foreground region and a surrounding ring of background pixels. Hence it detects dark and light blobs surrounded by light and dark background respectively. Martin et al. [68] describe a new approach for affine invariant region detection and description. They select high contrast regions as salient regions using a hierarchical clustering mechanism which is based on the bounded irregular pyramid (BIP). Itti et al. [71] present a visual attention system. They extract image features using Gaussian pyramids and combine them into a single topographical saliency map. A single feed-forward neural network is used to select the most salient region. This method works on RGB images.

Mikolajczyk et al. in [69] provide a review of affine covariant region detectors and compare their performance on a set of test images under varying imaging conditions. The six investigated detectors include the following: Hessian- and Harris-affine detectors, maximally stable extrema region (MSER), intensity extrema-based region detector (IBR), edge-based region detector (EBR) and salient regions. The performances of these detectors are evaluated based on two criteria, namely repeatability and accuracy. They conclude that the MSER detector, followed by Hessian-Affine detector, outperform the other detectors in various tests. MSER performs well on images containing homogeneous regions with distinctive boundaries. A detailed description of MSER can be found in [70] and an open source package [72] which implements MSER is used.

5.5.2   Detection of Interest Region

Healthy and pathological brain tissues usually appear as a connected regions in medical images unless the image was subjected to noise. Clear boundaries between different tissues can often be identified especially in MR images, whereas in CT images visible boundaries appear mostly between healthy and pathological tissues. Therefore given **R** and **F**, interest region are extracted on each slice of the two volumes, using the MSER detection method. The extracted regions are then compared with their reflected copies to remove false positives and determine those that are asymmetric. MSER is chosen based on its performance when compared to other interest region detectors [69]. Figure 5.7 illustrates the most asymmetric regions on axial slices of CT scans.
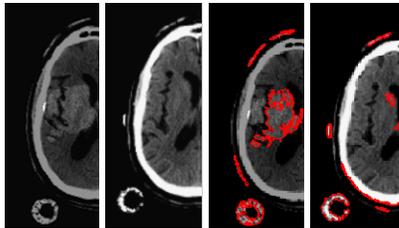
Figure 5.7: Results for MSRE region detection. From left to right: input axial slice from the left hemisphere, input axial slice from the right hemisphere, highly asymmetric stable regions detected on the left hemisphere, highly asymmetric stable regions detected on the right hemisphere for $\zeta = 0.001$.

5.5.3 Removing False Positives

Given a 2D region $\mathbf{G}_1$ and its reflected copy $\mathbf{G}_2$ the feature vectors given in Section 5.4.4.2 are extracted and stored in vector $\mathbf{v}_1$ and $\mathbf{v}_2$. The region $\mathbf{G}_1$ is considered to be a true positive if the Euclidian distance between the two feature vectors is greater than some predefined threshold ζ and a false negative otherwise. The Euclidian distance is computed by the function f which takes $\mathbf{v}_1$ and $\mathbf{v}_2$ as its input arguments and outputs either 1 or 0:

$$f(\mathbf{v}_1, \mathbf{v}_2) = \begin{cases} 1, & ||\mathbf{v}_1 - \mathbf{v}_2|| > \zeta \\ 0, & \text{otherwise.} \end{cases} \tag{5.18}$$

The constraints discussed in Section 5.4.3 are further applied to remove the remaining false positives.

5.6 Results and Discussion

This section describes the experiments performed to detect and segment brain tumors using registration-based and region detection-based asymmetry analysis methods. The two techniques are tested on real and simulated brain lesions. Simulated brain lesions are created by modifying voxel intensity values of one of the two hemispheres such that it appears asymmetric over the MSP. The most important aspect in using artificial lesions is that anomalies of varying intensity values can be created hence it often makes it easier to test different conditions under which the proposed methods are likely to succeed or fail.

5.6.1 Dataset Used

Real CT, and both simulated and real MR images scanned in axial format are used in this experiment. CT images are provided by iThemba LABS while MR images are downloaded from the Internet [1, 2]. Out of seventeen CT scans available only six are full scans and the rest are partial

scans. Among the six full scans, only one image shows a patient with brain lesions. Pixel dimensions and slice thicknesses of this dataset vary from one image to another with pixel dimension ranging from 0.5 mm to 2 mm and slice thickness ranging from 0.5 mm to 4 mm.

The cubic millimeter dataset from [2] consists of multi-contrast MR scans of 30 glioma patients (both low-grade and high-grade). For each patient, T1, T2, FLAIR, and post-Gadolinium T1 MR images are available. Simulated MR images for 25 high-grade and 25 low-grade glioma subjects are also available in this dataset. MR images from [1] comprise of images from 10 patients with meningiomas, gliomas and astrocytoma. Figure 5.8 depicts some of the the images used in this experiment.
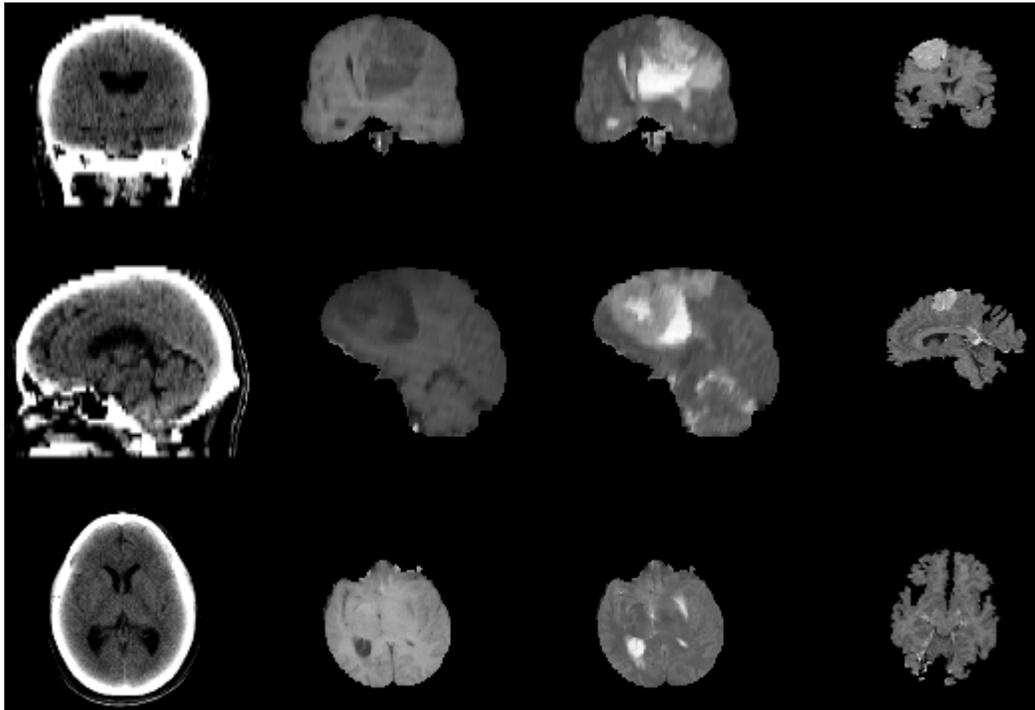
Figure 5.8: Dataset used to validate lesion asymmetry analysis method. First column shows a healthy CT scan. Second and third columns depict T1- and T2-weighted MR scans respectively of a single patient with high-grade gliomas. The last column shows the MR image of a patient with high-grade meningiomas.

5.6.2 Determining Accuracy Measure

The performance of the algorithm is measured based on the quantitative analysis of the method accuracy using three metrics: (1) truth positive volume fraction (TPVF), (2) false positive volume fraction (FPVF) and (3) false negative volume fraction (FNVF) [10]. These measures require ground-truth regions to be defined. TPVF describes the fraction of the overlap of the segmented brain lesion between the ground-truth and the method being evaluated. FPVF indicates the fraction of the healthy brain tissues falsely identified as brain lesions, and FNVF denotes the fraction of abnormal tissue that was missed during segmentation. Given two sets of voxels $\mathbf{S}_T$ and $\mathbf{S}$ which

represent segmented regions by the ground-truth and the proposed method respectively, accuracy measures can be defined as

$$\text{TPVF}(\mathbf{S},\mathbf{S}_T) = \frac{|\mathbf{S} \cap \mathbf{S}_T|}{|\mathbf{S}_T|}, \quad \text{FPVF}(\mathbf{S},\mathbf{S}_T) = \frac{|\mathbf{S} - \mathbf{S}_T|}{|\mathbf{S}_T|}, \quad \text{FNVF}(\mathbf{S},\mathbf{S}_T) = \frac{|\mathbf{S}_T - \mathbf{S}|}{|\mathbf{S}_T|}. \quad (5.19)$$

Since asymmetry analysis methods rely heavily on the MSP detection method, a series of experiments are performed to evaluate the algorithm accuracy by subjecting test images to different conditions such as rotations and artificial asymmetric tumors [10, 73]. The mean angular error (MAE) and distance error (DE) have been used as the performance measure to quantify the accuracy of the extracted MSP [10]. MAE is computed as the average of the two rotational angle differences the ground-truth and extracted MSP's make with the axial and sagittal slices. This measure evaluates the magnitude of angle deviation, in degrees, that the extracted MSP is from the ground-truth. DE denotes the distance error between the ground-truth and extracted MSP from the origin of the image. Given two vectors $\mathbf{v}_T = [\phi_T, \beta_T, d_T]^T$ and $\mathbf{v} = [\phi, \beta, d]^T$ which represent the orientation angles and distance from the origin of the target and extracted MSP, these accuracy measures are determined as

$$\text{MAE} = (|\phi_T - \phi| + |\beta_T - \beta|)/2, \quad \text{DE} = |d_T - d|. \quad (5.20)$$

5.6.3   Determining Parameter Values

In this section experiments are conducted to determine optimal values of the parameters that have a major influence on the performance of the segmentation. Throughout the implementation it has been observed that maximum intensity difference ratio (λ) and threshold (ζ) are involved in the asymmetry analysis method which employs registration and region detection. The parameter λ defines the relative ratio of the maximum intensity difference between hemispheres and is used to determine the threshold T (Section 5.4.2). A high value of λ implies that only small intensity differences exist, hence the brain is likely to be symmetric, while the lower value means large intensity differences exist hence the brain is likely to be asymmetric. The parameter ζ is used to describe how well a segmented region from one hemisphere should correspond to its reflected copy on the other hemisphere.

These parameters are adjusted in a controlled manner until the optimal values are found using healthy subjects. The optimum values are chosen such that the algorithm tolerates moderate false positives. The purpose of allowing false positives is to increase the likelihood of the algorithm detecting low-grade brain lesions whose grey level value is almost identical to the surrounding healthy brain tissues. Figure 5.9 shows the results of an experiment in which the parameter values are changed until the desired values are obtained. The second row of this figure shows detected

regions which fall within the range of maximum intensity difference for $\lambda = 0.5$ and $\lambda = 0.7$. When λ is close to 0 the algorithm is likely to fail to detect an asymmetric region whose appearance does not deviate substantially from its reflected copy. On the other hand, a large value of λ, close to 1, degrades the performance and accuracy of the method due to a large number of false positives being detected. That being said, the default value of λ is set to 0.5 on CT images.

Given the estimated location of asymmetric tissues, the parameter $\zeta = 0.1$ is used. Through the experiment it was observed that values of ζ larger than 0.1 tolerates few false positives, as depicted in the third column. Hence this could even lead to failure of the algorithm to detect low-grade brain lesions. The default value of ζ is set to 0.1 on the CT dataset. However, the optimal values of both λ and ζ could be different if a different modality is used.
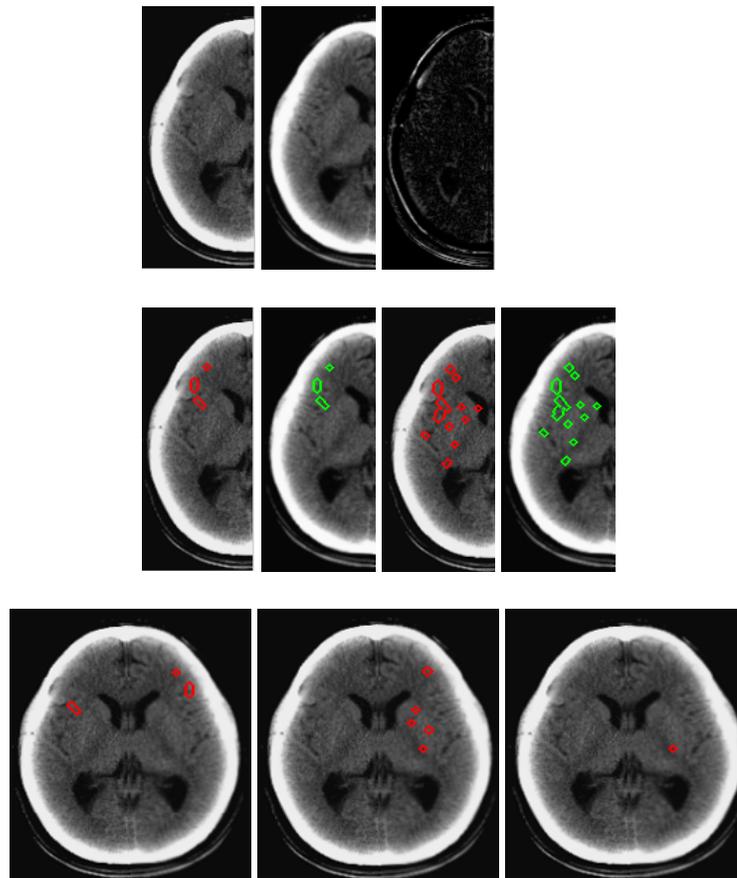
Figure 5.9: The effect of varying parameters on a healthy subject. First row: Left, and reflected right hemisphere and the absolute difference between the hemispheres. Second row: Detected false positives superimposed on left and right hemisphere as parameter λ is varied. λ is set to 0.5 in the first two columns and to 0.7 in the last two columns. Third row: welded left, and right hemispheres after an ill hemisphere is determined for $\zeta = 0.1$ and $\lambda = 0.5$. In the second and third image $\zeta = 0.1$ and $\zeta = 0.2$ respectively for $\lambda = 0.7$. It is noticed that increasing the value of ζ reduces the number of false positives.

5.6.4   Results

The discussion in this section is based on a series of tests performed to evaluate the accuracy of the MSP estimation method and asymmetric brain lesion segmentation methods. In the first experiment healthy CT and simulated MR scans are subjected to different conditions and in each case the closeness of the extracted MSP to the ground-truth is evaluated using performance measures MAE and DE. In the second experiment both registration and region detection-based asymmetry analysis method performance are quantified using TPVF, FNVF and FPVF. The two approaches are further compared to determine the method which is more accurate.

5.6.4.1   Evaluation of the MSP

An experiment procedure similar to the one described in [10, 73] is followed whereby the system's tolerance to varying conditions such as pathology asymmetries, rotations and noise is evaluated. In all cases the target MSP is determined from three non-collinear inter-hemispheric points which have been selected manually from the volume.

A. **Tolerance to asymmetry**

To study tolerance to the pathological asymmetries large artificial asymmetric lesions of radius 20 to 60 mm and 10 mm thickness are created and overlaid upon data from healthy subjects. As depicted in Table 5.1 the algorithm gives average MAE and stdAE (standard deviation error) of 2.76^o and 1.51^o. The DE also remains almost constant with a mean value of 10.52 mm irrespective of the radius of the introduced lesion. However these values are expected to change if a different test subject is used. Although the value of DE is bit large, it remains around 10.5 mm throughout the experiment, it is likely that some of the internal structures brain in the test image are not symmetric and the algorithm converged to the global minima.

Figure 5.10 shows the extracted MSP projected on axial and coronal slices. It also depicts a 3D view of the plane cutting through the subject. The extracted MSP is further used to correct tilting and rotation, also depicted in a figure. These results justify the fact that the evaluated method could correctly estimate MSP regardless of the presence of asymmetric pathologies.

Table 5.1: Tolerance to pathological asymmetries.

Radius (*mm*)	MAE (^{o})	stdAE(^{o})	DE (*mm*)
20	2.78	1.51	10.67
30	2.78	1.50	10.73
40	2.76	1.50	10.65
50	2.75	1.52	10.49
60	2.74	1.54	10.37
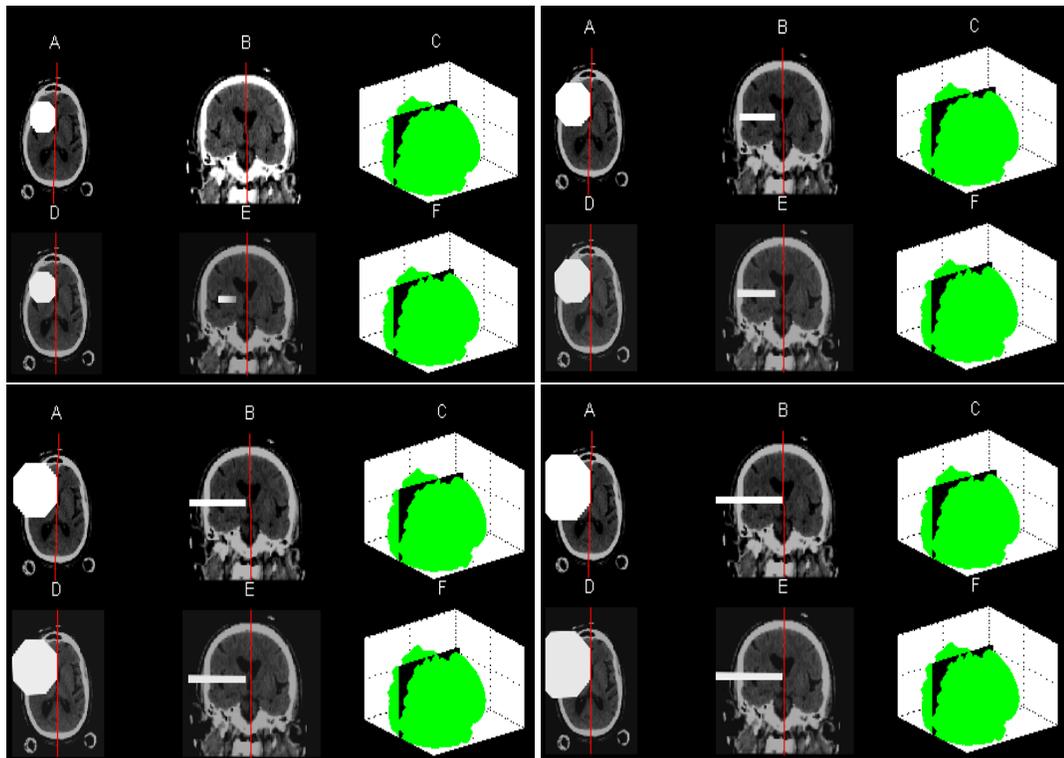
Figure 5.10: Top left, top right, bottom left and bottom right quadrants show the subject with artificial lesion of radius 30, 40, 50 and 60 mm respectively. In each quadrant first and second column (first row before tilt correction, second row after tilt correction) show the MSP projected and overlaid on the axial and coronal slices. The third column depicts a 3D view of the MSP cutting through the head.

B. **Tolerance to Rotation**

Tolerance to rotation is depicted in Figure 5.11 and Table 5.2. Healthy subjects are rotated from 0° to 25° in 5° intervals about each axis and around all three axes simultaneously [73]. From the table it can be seen that the algorithm is robust to rotation about either of the three axes. Even rotation of 25° the MSP is well estimated. The average MAE is found to be 2.66^o with average standard deviation of $1.30^o$and a slight improvement of the mean DE, which is 6.24 mm when rotation is performed about the x-axis. The rotations about the y-axis give average MAE and stdAE of 2.93^o and 1.33^o respectively. Mean DE is a bit higher and has the value of 12.61 mm.

On the other hand, rotations about the z-axis cause the MSP estimate to deviate from the ground-truth by 7.05^o when the rotation angle exceeds 25°. The other failure of the algorithm occurs when the rotation angle about all axes reaches 15°. It is likely that the failure results because some of the subject's data is lost during transformation. The bottom right quadrant in Figure 5.11 depicts an incorrect MSP estimate superimposed on axial and coronal slices.

Table 5.2: Tolerance to rotation.

Rotation about x-axis				Rotation about y-axis			
Angle (^{o})	MAE (^{o})	stdAE (^{o})	DE (*mm*)	Angle (^{o})	MAE (^{o})	stdAE (^{o})	DE (*mm*)
0	2.79	1.51	10.72	0	2.79	1.51	10.72
5	2.43	0.65	9.95	5	3.12	1.41	11.72
10	2.77	0.91	9.27	10	3.39	1.27	12.74
15	3.14	1.73	2.27	15	3.13	1.40	13.09
20	2.42	1.70	1.24	20	2.85	1.57	13.97
25	2.41	1.30	3.97	25	2.14	1.02	13.42
Rotation about z-axis				Rotation about xyz-axis			
Angle (^{o})	MAE (^{o})	stdAE (^{o})	DE (*mm*)	Angle (^{o})	MAE (^{o})	stdAE (^{o})	DE (*mm*)
0	2.79	1.51	10.72	0	2.79	1.51	10.72
5	2.93	1.14	10.90	5	2.95	2.01	11.10
10	2.88	1.48	11.10	10	6.47	2.01	11.22
15	2.92	1.13	11.21	15	8.36	4.22	11.21
20	2.92	1.14	11.32	20	12.07	0.60	11.33
25	7.05	1.68	32.79	25	14.54	1.65	36.79

5.6.4.2 Evaluation of Registration and Region Detection Asymmetry Analysis Method

The two approaches are validated against the ground-truth using the T1- and T2-weighted datasets described in Section 5.6.1. The metrics measures TPVF, FPVF and FNVF are used to evaluate the accuracy of these methods. The experiment is performed using patient images with low- and high-grade brain tumor.

A. **High-Grade Tumors**

The quantitative results obtained on high-grade tumors are presented in Table 5.3. The mean
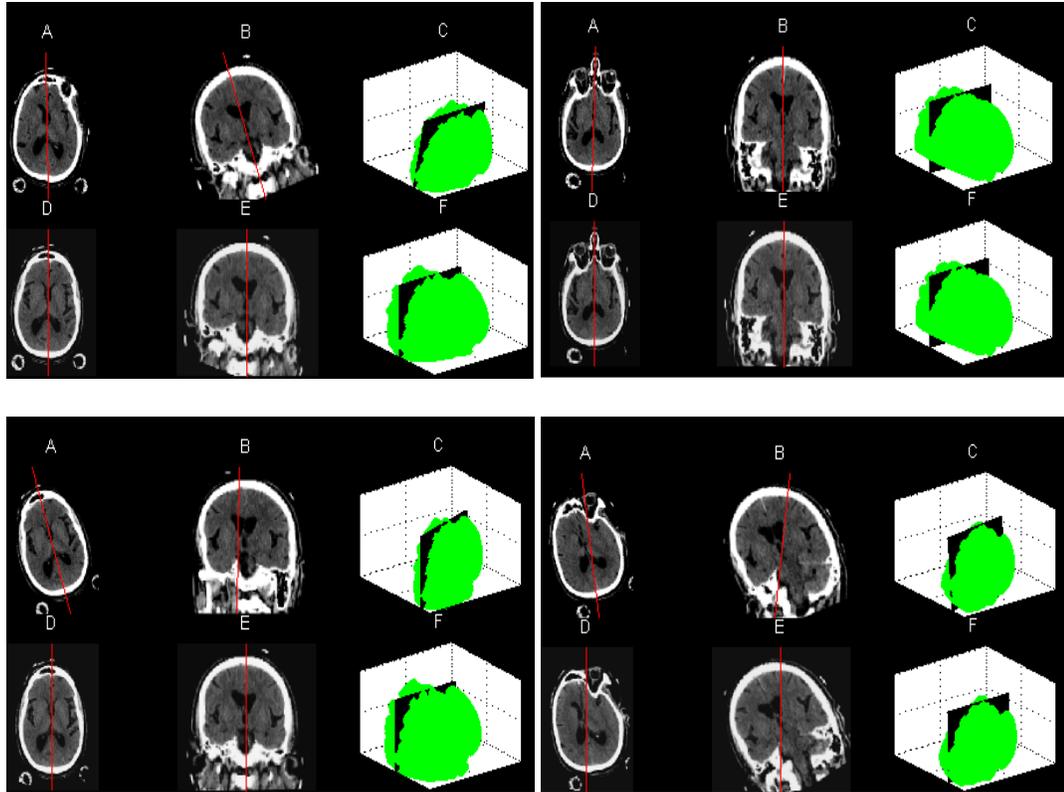
Figure 5.11: Results for a volume subjected to rotation transformation. Top left, top right, bottom left and bottom right quadrants shows the subject rotated by 20⁰ about x-, y-, z- and xyz-axes respectively. In each quadrant first column shows the MSP projected on the axial slice before and after tilt correction. The second column shows the MSP projected and overlaid on the coronal slices. The third column depicts 3D view of the MSP cutting through the head.

TPVF, FPVF and FNVF of the registration method is 0.6793, 0.8607 and 0.3207 respectively for parameter $\lambda = 0.7$, and $\zeta = 0.01$ on T2 subjects and $\zeta = 0.005$ on T1 subjects. On the other hand the mean TPVF, FPVF and FNVF for the region detection method is found to be 0.6583, 0.6773 and 0.3417 in the order given.

In both methods the value of FPVF appears to be large. This implies that there are a large number of voxels of healthy brain tissues classified as brain lesions. It is likely that one of the major factors that lead to an increase of this error measure is the swelling of the tumor which often shifts some of the healthy internal structures of the brain. FNVF also seems to be large in both methods and this results in cases whereby the voxels from healthy hemisphere have overlapping intensity values with those at the corresponding location in the ill hemisphere.

Figure 5.12 presents the results found on three T2-weighted MR patient data, and two T1- and T2-weighted MR on simulated data. The segmented asymmetric regions are superimposed on each image.
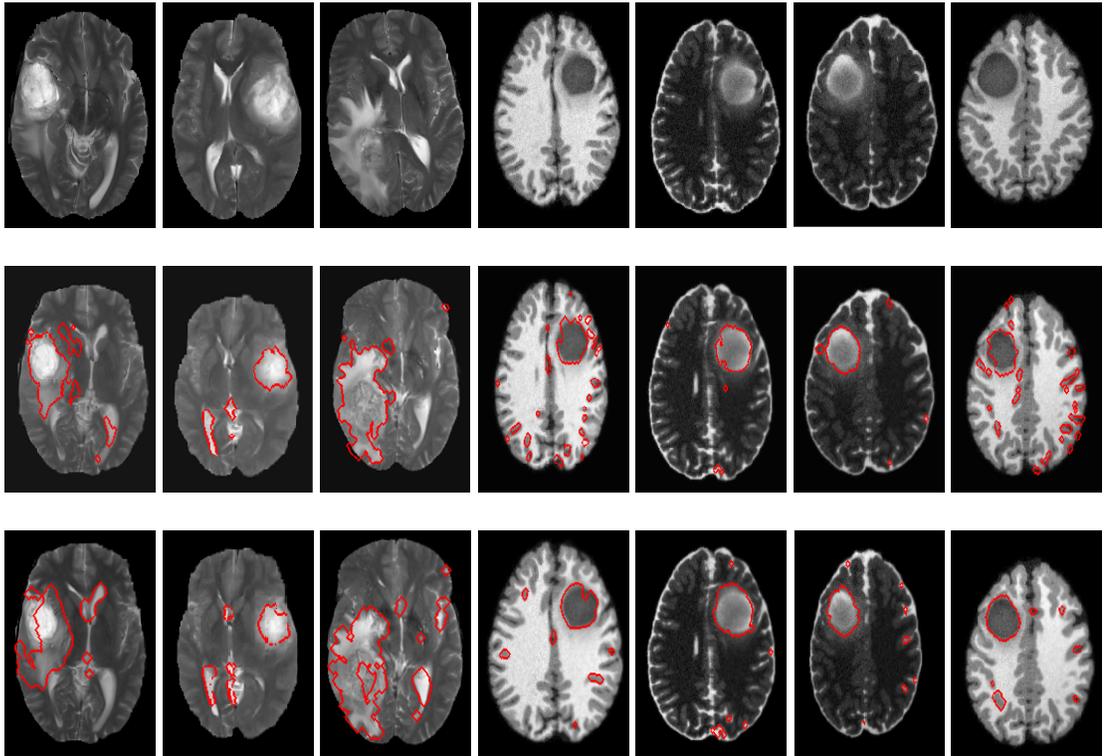
Figure 5.12: Results shown on axial slices for patients (first column to third column) and simulated dataset (fourth to seventh column) with high-grade gliomas. First row shows the raw input data while the second and the third row depicts the results obtained using the registration and region detection methods respectively.

B. Low-Grade Tumors

All the results of quantitative evaluation of the two methods on low-grade tumors are detailed in Table 5.4. There is significant improvement in FNVF while FPVF is increased compared to values obtained in high-grade tumors. The parameters are set to $\lambda = 0.8$, and $\zeta = 0.01$ on T2-weighted

Table 5.3: Accuracy results for patient and simulated dataset with high-grade gliomas.

Method	Metric	Real Data				Simulated Data			
		hg01T2	hg04T2	hg07T2	hg08T2	hg01T1	hg01T2	hg02T1	hg02T2
	TPVF	0.7259	0.7332	0.6110	0.6822	0.5908	0.7003	0.6949	0.6962
Reg	FPVF	0.5780	0.1385	0.1214	0.2282	2.3449	0.8658	1.8313	0.7776
	FNVF	0.2741	0.2668	0.3890	0.3178	0.4092	0.2997	0.3051	0.3038
	TPVF	0.6195	0.6401	0.5248	0.6392	0.5119	0.7650	0.7590	0.8070
MSRE	FPVF	1.0662	0.3864	0.1661	0.3636	0.4846	1.1817	0.5991	1.1707
	FNVF	0.3805	0.3599	0.4752	0.3608	0.4881	0.2350	0.2410	0.1930

and $\zeta = 0.005$ on T1-weighted dataset. The mean TPVF, FPVF and FNVF for registration method are found to be 0.8337, 2.2282 and 0.1663 while those that are obtained when region detection method is employed are 0.7658, 1.6123 and 0.2342 respectively. In this experiment a high false alarm rate is again observed due to low grey level values of tumorous regions, which are very similar to grey level values of healthy tissues. Other factors that might have lead to an increased over segmentation and how it should be improved are described in Section 5.6.4.2.

Figure 5.13 depicts segmented regions obtained when the registration and region detection methods are used. The results of each method are overlaid over the subject to mark the suspected location of asymmetric regions.

Table 5.4: Quantitative results for patient and simulated dataset with low-grade gliomas.

Method	Metric	Real Data				Simulated Data			
		lg08T2	lg11T1	lg11T2	lg12T2	lg03T1	lg03T2	lg02T1	lg02T2
	TPVF	0.8428	0.8345	0.9176	0.5309	0.9137	0.9856	0.7415	0.9034
Reg	FPVF	2.0893	1.7115	0.9532	2.8786	2.7896	2.4607	2.7722	2.1703
	FNVF	0.1572	0.1655	0.0824	0.4691	0.0863	0.0144	0.2585	0.0966
	TPVF	0.8757	0.7908	0.7884	0.8173	0.6150	0.9399	0.5085	0.7905
MSRE	FPVF	1.8413	0.2102	1.6083	3.4689	0.7494	1.6367	2.2607	1.1232
	FNVF	0.1243	0.2092	0.2116	0.1827	0.3850	0.0601	0.4915	0.2095

5.6.4.3 Summary

The asymmetric analysis techniques have been evaluated on real patient and simulated T1- and T2-weighted MR images with gliomas. Overall there is a high segmentation quality in the simulated dataset compared to the real patient dataset. This bias might have resulted due to fact that most of the simulated tumors are localized hence they were easy to be segmented. In each dataset better results are found on T2-weighted images as compared to T1-weighted images. The success on T2 data is due to the fact that intensity of tumorous tissue appears more prominent than that of healthy tissues hence it is often easy to separate them.

Based on the experiment conducted, the majority of low-grade gliomas were correctly segmented as opposed to high-grade gliomas, even though high segmentation quality was expected to occur
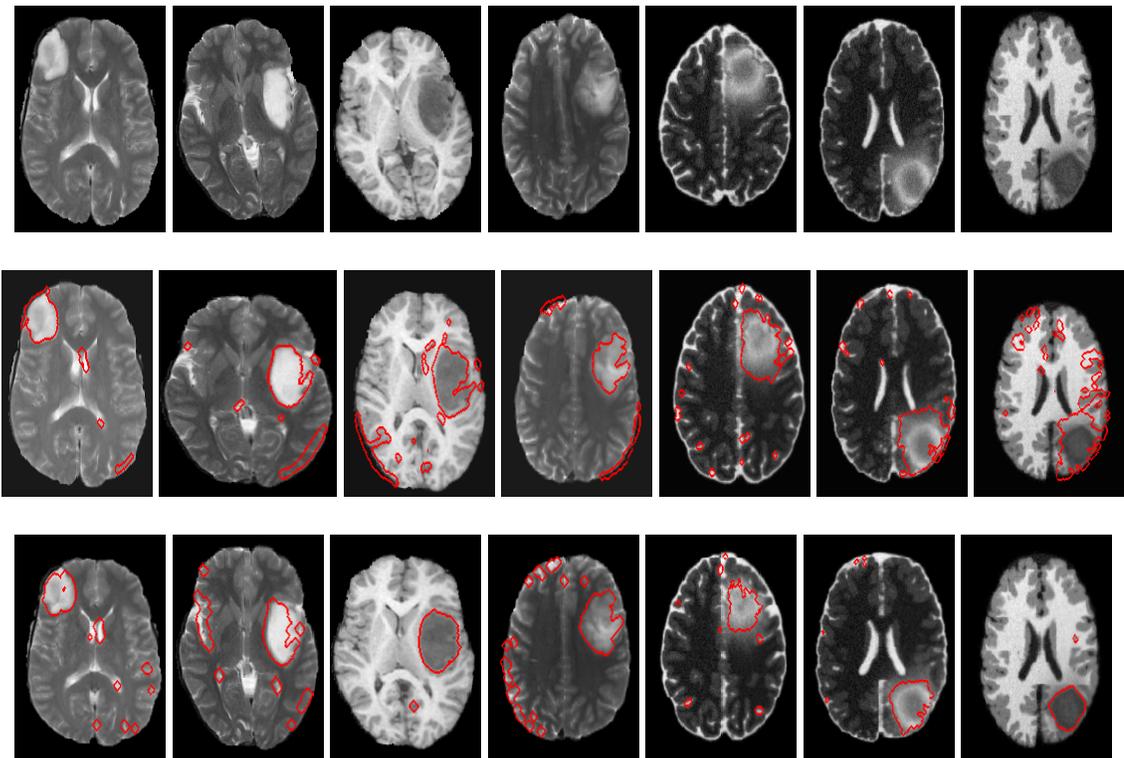
Figure 5.13: Results depicted on axial slices for patients (first column to fourth column) and simulated dataset (fifth to seventh column) with low-grade gliomas. First row shows the raw input data while the second and the third row depicts the results obtained using the registration and region detection methods respectively.

on high-grade gliomas. The major contributing factor to this bias could be the difference in patient dataset used as most of high-grade gliomas are large in size and often have overlapping intensity distribution with brain ventricles. In some datasets the symmetry plane passes through the tumor and this makes small portions of the tumor on the other hemisphere to appear symmetric over the plane.

For most of the experiments done, the registration-based method achieved a higher TPVF than the region detection-based method. This simply means that a large number of tumor voxels are correctly classified with the registration-based method. However, the value of FPVF is also large which signals that this technique is likely to classify healthy brain tissues as brain tumors.

The parameter values for λ and ζ are systematically changed to obtain a good tumor segmentation based on the image modality and the type of tumors to be segmented. For both high-grade and low-grade gliomas, when the value of λ is increased the number of false tumor voxels increases faster than the number of correct ones. Hence the fraction of false detection increases notably on high-grade tumors. On the other hand, reducing the value of λ drops the percentage of correct classification as many of the lesion's voxels are missed, especially on low-grade gliomas. For this reason the value of λ is set a bit larger on low-grade gliomas than on high-grade lesions. The parameter ζ is set to a small value on patient images with low-grade gliomas since lesions of this type appear with low grey level voxel values which sometimes overlap with other healthy brain structures. On patient datasets with high-grade gliomas ζ is set to a larger value to reduce the error of classifying healthy brain tissues.

Chapter 6

Atlas-Based Pathology Detection

This chapter presents a knowledge-based method used to develop a model of healthy brain tissues. This model is further used to detect abnormal tissues in future medical scans. The knowledge is represented in the form of brain atlas constructed from a set of healthy medical images. The same principles applied in [6] are adopted with some improvements on the procedure used for atlas construction. Functionality for incorporating partial datasets into the atlas space has been added.

The outline of this chapter is as follows. Section 6.1 describes the approach followed in constructing the atlas. In Section 6.2 a detailed description to detect pathological tissues is given while Section 6.3 describes methods used to remove false positives. The chapter concludes with results and discussion in Section 6.4.

6.1   Building Atlas

The method presented in [6] follows a single pass approach to construct the atlas. The drawback of this approach is that it does not necessarily minimize the error between the atlas and the remaining set of images. Hence it does not perform some optimizations needed to generate a high quality atlas. To address this weakness the atlas construction method is formulated as an optimization problem which minimizes the sum of square difference between the current atlas estimate and a reference image. This technique is inspired by the popular shape alignment approach, generalized Procrustes analysis (GPA), which aligns shapes with corresponding numbers of points so that the sum of the distance of each shape to the mean is minimized [74].

6.1.1   Generalized Procrustes Analysis (GPA)

This is an iterative technique used to align shapes onto the same shape-coordinate space such that the square error distance between each shape to the mean shape is minimized [74]. In this work the

same method is adopted with the objects of interest to be aligned being brain scans having different sizes and orientations. The algorithm converges if the SSD between the reference image and mean image is less than some predefined threshold.

6.1.1.1 Choosing Initial Reference

The initial reference image is chosen manually from the existing set of images through inspection that it best represents the average population [75]. The arbitrarily chosen reference image is likely to bias the atlas to a specific patient especially if the patient scan is not within the average population the atlas is was constructed for [75]. This image defines the estimate of the coordinate space onto which the entire set of images will be mapped. All the images have the same dimensions with voxels of cubic millimeter in size. After aligning these images the atlas is constructed, which consists of mean and maximum variance of the intensity and displacement field for each voxel [6]. Maximum variance of the intensity and displacement fields define the grey level and deformation field thresholds on every voxel.

6.1.1.2 Image Alignment

Given a reference image $\mathbf{R}$ a group-wise image registration is applied to map each image $(\mathbf{F}_1, ..., \mathbf{F}_N)$ to a single coordinate frame defined by $\mathbf{R}$. The registration process is performed in two steps. At first affine transformations are applied to the rest of the images to globally match the reference image. For each image $\mathbf{F}_i$ a transformation $\mathbf{T}_i$, which minimizes the similarity measure between $\mathbf{F}_i$ and $\mathbf{R}$, has to be found to map $\mathbf{F}_i$ onto $\mathbf{R}$. After performing a global alignment between the two images, a nonrigid registration [43] is applied to remove local deformations which might have occurred because of differences in shape of internal brain structures. A multiresolution technique is adopted during registration to improve the performance.

When performing affine registration SSD is used as the similarity measure to be minimized between the two images. SSD is used since the images to be aligned are of the same modality and it is easy to compute. Also it can be optimized easily using the LM method. The mathematical formulation of this similarity measure is defined as

$$SSD(\mathbf{u}) = \frac{1}{2} \sum_{x=1}^{N_x} \sum_{y=1}^{N_y} \sum_{z=1}^{N_z} [\mathbf{F}_i(\mathbf{T}_i(\mathbf{x} : \mathbf{u})) - \mathbf{R}(\mathbf{x})]^2, \tag{6.1}$$

where $\mathbf{x} = (x, y, z)$, $\mathbf{T}_i(\mathbf{x} : \mathbf{u})$ represents a 9-parameter affine transformation and $\mathbf{u} = [\theta, \beta, \phi, T_x, T_y, T_z, S_x, S_y, S_z]^T$ is the parameter vector used to define the transformation. A literature on medical image registration is discussed in Chapter 3. A homogeneous coordinates is used in this case and the affine transformation is represented by a 4×4 matrix [44]. The transformation consists of three rotational angles, translation and scale parameters along the three axes and can be written as

$$\mathbf{T}_i(\mathbf{u}) = \mathbf{T}_l \mathbf{R}_x \mathbf{R}_y \mathbf{R}_z \mathbf{S}, \tag{6.2}$$

where

$$\mathbf{T}_l = \begin{bmatrix} 1 & 0 & 0 & T_x \\ 0 & 1 & 0 & T_y \\ 0 & 0 & 1 & T_z \\ 0 & 0 & 0 & 1 \end{bmatrix}, \qquad \mathbf{S} = \begin{bmatrix} S_x & 0 & 0 & 0 \\ 0 & S_y & 0 & 0 \\ 0 & 0 & S_z & 0 \\ 0 & 0 & 0 & 1 \end{bmatrix},$$

$$\mathbf{R}_y = \begin{bmatrix} \cos\beta & 0 & \sin\beta & 0 \\ 0 & 1 & 0 & 0 \\ -\sin\beta & 0 & \cos\beta & 0 \\ 0 & 0 & 0 & 1 \end{bmatrix}, \quad \mathbf{R}_z = \begin{bmatrix} \cos\phi & -\sin\phi & 0 & 0 \\ \sin\phi & \cos\phi & 0 & 0 \\ 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 1 \end{bmatrix}, \tag{6.3}$$

$$\mathbf{R}_x = \begin{bmatrix} 1 & 0 & 0 & 0 \\ 0 & \cos\theta & -\sin\theta & 0 \\ 0 & \sin\theta & \cos\theta & 0 \\ 0 & 0 & 0 & 1 \end{bmatrix}.$$

The optimal value of $\mathbf{u}$ is determined by an iterative optimization method. The LM method is used in this work because of its mechanism of switching back and forth between GD and GN, hence acquiring the capabilities of the two methods such as stability and convergence speed [44, 51, 53].

In summary the general flow for finding $\mathbf{u}$ follows the same principles applied in Section 5.2.6 when searching for the optimal value of the plane parameter vector. The changes that have been made are the use of $\mathbf{T}_i$ instead of the reflection transformation $\mathbf{T}_{RF}$ and an increase of the number of optimization parameters in $\mathbf{u}$ from four to nine. This transformation is applied on $\mathbf{F}_i$ to generate a new image $\mathbf{F}_i^u$. Numerical differentiation of $\mathbf{F}_i^u$ is computed to estimate the Jacobian Matrix $\mathbf{J}(\mathbf{u})$ of size $9 \times N_x N_y N_z$. The search direction $\mathbf{d}_k$ is calculated after diagonal elements of the Hessian matrix estimate $(\mathbf{J}^T(\mathbf{u})\mathbf{J}(\mathbf{u}))$ are augmented with a damping factor μ. Values of both μ and δ are set and updated as detailed in Section 5.2.6. Multi-resolution is also adopted in this case and only the translation parameters are modified after the convergence is reached at the coarser level.

Even though $\mathbf{F}_i$ globally maps to $\mathbf{R}$ after the affine transformation is applied, this does not necessarily mean that the internal structures of the brain scans match one another. Hence local registration has to be applied to remove these local differences. The nonrigid registration toolbox MIRT, presented in [43] is employed at this stage.

6.1.1.3 Procrustes Distance (PD)

The Procrustes distance is a measure of the sum of the distances between corresponding points of two shapes. It evaluates how close one shape is to another. Hence the lower the value is the closer the two shapes are. In this thesis PD is computed as the sum of squared intensity difference between corresponding voxels of two volumes. Given a reference volume $\mathbf{R}$ and the mean intensity volume $\mathbf{M}_I$, the PD is computed as shown below:

$$PD = \frac{1}{2} \sum_{x=1}^{N_x} \sum_{y=1}^{N_y} \sum_{z=1}^{N_z} [\mathbf{R}(x,y,z) - \mathbf{M}_I(x,y,z)]^2, \tag{6.4}$$

where $N_x \times N_y \times N_z$ is the size of each volume.

6.1.2 Atlas Construction

Given a set of normal brain images that have been correctly mapped onto one coordinate space, the mean and maximum variance volumes are computed to represent the brain atlas. The mean intensity ($\mathbf{M}_I$) and mean displacement ($\mathbf{M}_V$) volume define the expected grey level and displacement fields of each voxel respectively. They are calculated by averaging the intensity and deformation field norm of the aligned images as

$$\mathbf{M}_I = \frac{1}{N} \sum_{i=1}^{N} \overline{\mathbf{F}_i}, \qquad \mathbf{M}_V = \frac{1}{N} \sum_{i=1}^{N} \mathbf{V}_i, \tag{6.5}$$

where N is the total number of aligned volumes, $\overline{\mathbf{F}_i} = \mathbf{F}_i(\mathbf{T}_i(\mathbf{x}:\mathbf{u}))$ is the registered image, $\mathbf{V}_i$ is the magnitude of the displacement field, while subscripts I and V represent intensity and displacement field respectively. Maximum variance intensity ($\mathbf{V}_I$) and maximum variance displacement field ($\mathbf{V}_V$) volume define for each voxel a threshold value for which the voxel intensity and displacement is expected to deviate from $\mathbf{M}_I$ and $\mathbf{M}_V$ respectively for it to be considered normal. Maximum variance intensity is computed by calculating the variance of each aligned volume and retaining the voxels with a high confidence grey level difference. Also maximum variance displacement field defines voxels with a high confidence shift difference from $\mathbf{M}_V$. These can be represented mathematically as

$$\mathbf{V}_I(x,y,z) = \underset{1 \leq i \leq N}{\arg\max} \left\{ [\mathbf{F}_i(x,y,z) - \mathbf{M}_I(x,y,z)]^2 \right\},$$

$$\tag{6.6}$$

$$\mathbf{V}_V(x,y,z) = \underset{1 \leq i \leq N}{\arg\max} \left\{ [\mathbf{V}_i(x,y,z) - \mathbf{M}_V(x,y,z)]^2 \right\},$$

where $1 \leq x \leq N_x$, $1 \leq y \leq N_y$ and $1 \leq z \leq N_z$. In summary the algorithm involves the following steps to create a brain atlas from the set of healthy brain images.

Input: (set of brain scans in axial format $(\mathbf{F}_1, \mathbf{F}_2, \mathbf{F}_3, ..., \mathbf{F}_N)$, stopping criterion $[\varepsilon_0]$)

Output: (mean and maximum variance of intensity and displacement volume $(\mathbf{M}_I, \mathbf{V}_I, \mathbf{M}_V, \mathbf{V}_V)$)

Algorithm

Begin

        Step 0: Manually select the reference volume $\mathbf{R}$.

        Step 1: Perform rigid and nonrigid registration to align each image $\mathbf{F}_i$ onto $\mathbf{R}$.

        Step 2: Compute mean volume $\mathbf{M}_I$ from aligned images.

        Step 3: Calculate SSD between $\mathbf{M}_I$ and $\mathbf{R}$. if SSD $< \varepsilon_0$ goto **Step 5.**

        Step 4: Update reference volume with mean volume, $\mathbf{R} = \mathbf{M}_I$, goto **Step 1**.

        Step 5: Compute maximum variance intensity volume $\mathbf{V}_I$, $\mathbf{M}_V$ and $\mathbf{V}_V$.

End

Figure 6.1 shows the axial, sagittal and coronal view slices of the constructed atlas. The atlas is built using healthy simulated T1-weighted brain MR images. The bright regions in intensity and deformation field variance mark voxels expected to have large intensity and displacement field variations respectively.

6.2 Abnormal Tissue Detection

In this section details of two different approaches followed to detect abnormal tissues are given. They follow the same principles used when constructing the brain atlas. The differences between these methods are a consequence of differences in the dataset to be handled. The first technique detects abnormalities on a full scanned volume while the second method detects abnormal masses on partial scans. A dataset is declared partial if the volume does not contain the entire brain. For example the volume may only cover the information from the brain-stem to the corpus callosum or from the corpus callosum to the scalp.

6.2.1 Abnormality Detection on Full Scans

The main objective of an abnormal tissue detection algorithm is to produce a binary volume $\mathbf{L}$ that estimates the proposed location of tumorous tissues in the brain. These tissues have intensity values that deviate from the expected values $\mathbf{M}_I$ of a healthy brain. To detect these tissues a two stage technique which follows the same principles used to construct the atlas is proposed.

The initial step is to align patient volume $\mathbf{F}$ with the atlas template $\mathbf{M}_I$. The alignment is achieved by dividing the registration process into two steps. Firstly, a global registration is performed using
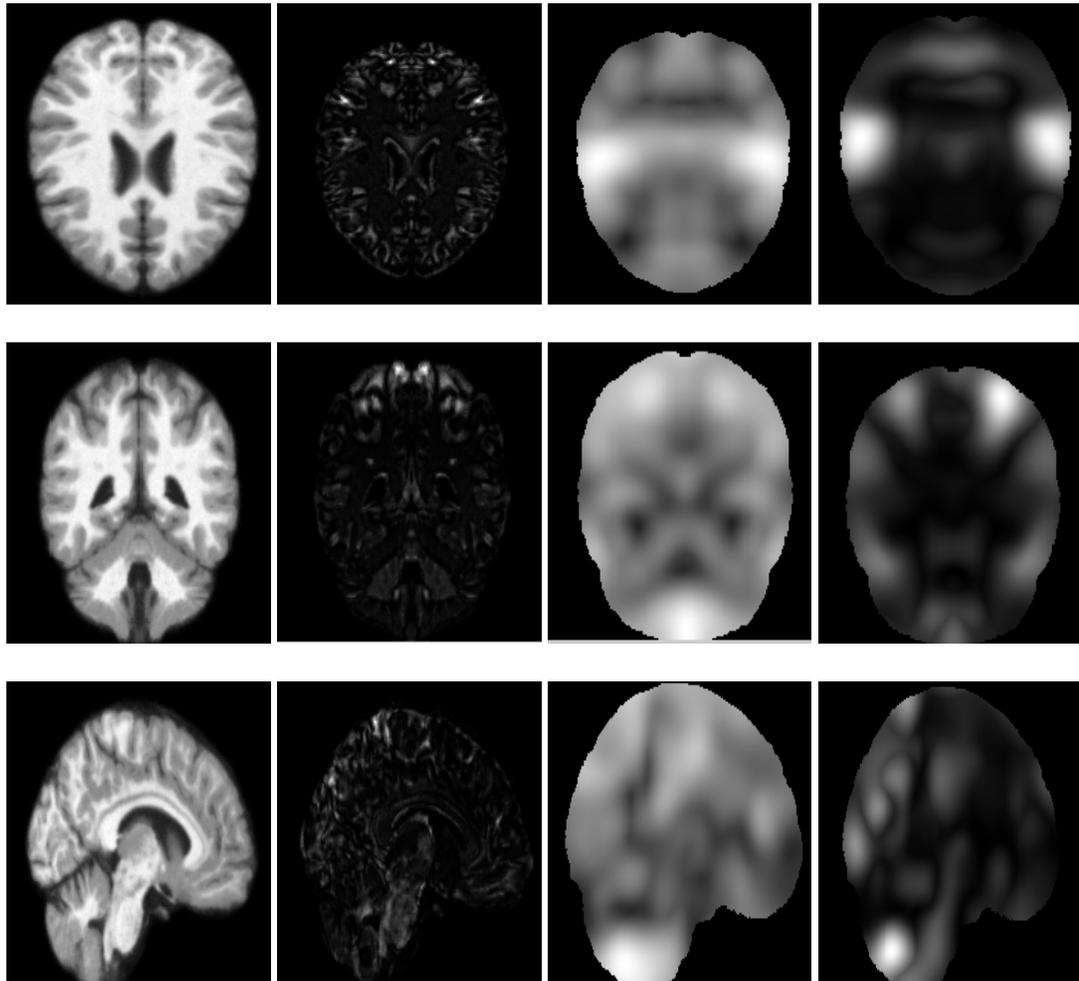
Figure 6.1: Brain atlas in T1-weighted MR images acts as the model of healthy brain tissues. From top to bottom: axial, coronal and sagittal view of the atlas. From left to right: expected grey level, maximum intensity variance, expected norm of the displacement field, and maximum variance norm of the displacement field for each voxel.

a 9-parameter affine transformation with SSD as the similarity measure to bring the two volumes into global correspondence. Secondly, a nonrigid registration is applied to compensate for the morphological differences between internal structures of the brain, with large deformation expected to arise on the regions that have been deformed by the tumor. The deformation magnitude of each voxel is defined in a volume $\mathbf{U}$.

After the alignment, the intensity square difference between the atlas and the registered patient volume is calculated for each voxel. This value defines the amount by which a voxel deviates from its expected grey level value. Also, the deformation field difference between the atlas mean and test image displacement field is computed to determine the displacement variance of each voxel. A voxel is declared abnormal if its intensity square difference is greater than its maximum variance intensity or its displacement square difference is greater than its maximum variance deformation norm. Mathematically this is represented by the following function:

$$\mathbf{L}(x,y,z) = \begin{cases} 1 & , \mathbf{M}_V(x,y,z) < \mathbf{D}_I(x,y,z) \text{ or } \mathbf{V}_V(x,y,z) < \mathbf{D}_V(x,y,z) \\ 0 & , \text{Otherwise}, \end{cases} \tag{6.7}$$

where $\mathbf{D}_I(x,y,z) = \left[\mathbf{M}_I(x,y,z) - \bar{\mathbf{F}}(x,y,z)\right]^2$ is the square difference between atlas mean the $\mathbf{M}_I$ and a registered patient volume $\bar{\mathbf{F}}$, and $\mathbf{D}_V(x,y,z) = \left[\mathbf{M}_V(x,y,z) - \mathbf{U}(x,y,z)\right]^2$. Figure 6.2 shows intermediate results for detecting voxels having intensity values and deformation field larger or smaller than expected.

6.2.2 Abnormality Detection on Partial Scans

Given a partial scan $\mathbf{P}$ the main idea is to align $\mathbf{P}$ onto the the atlas space so that analysis can be performed to determine anomalies. Aligning partial scans becomes a challenging task since there are data missing from $\mathbf{P}$. Hence in order to bring $\mathbf{P}$ into global correspondence with the atlas, a tranformation $\mathbf{T}$ is estimated from 2D transformations using mid-sagittal and coronal slices of both $\mathbf{P}$ and $\mathbf{M}_I$. This is done firstly by defining a new volume $\mathbf{Q}$ which has the same dimensions as $\mathbf{M}_I$. $\mathbf{P}$ is then embedded into $\mathbf{Q}$ such that the center of grid volume of $\mathbf{P}$ maps exactly with the center of grid volume of $\mathbf{Q}$. The MSP in $\mathbf{Q}$ is extracted using the method described in Section 5.2, which is then used to remove tilting and rotation such that mid-sagittal slice passes through the center of the grid volume.

Normally MSP is used to determine the rotation transformations about the y-axis and z-axis but it is still a challenging problem to estimate the rotation transformation about x-axis. To determine the transformation automatically, one of the options is to find two of the eight Talairach point landmarks: the anterior commissure (AC) and the posterior commissure (PC) located on the mid-sagittal slice [76, 20]. AC and AP are then joined by a straight line and the angle which this line makes with the XY plane marks the rotation angle about x-axis. A drawback of this approach is
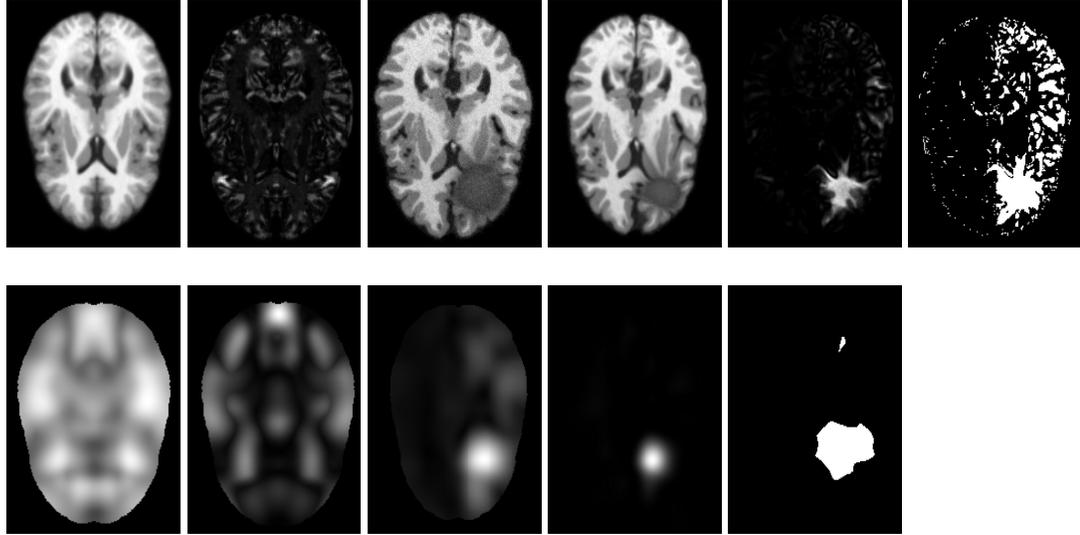
Figure 6.2: Intermediate results for atlas-based tumor detection method. Top row from left to right: mean intensity ($\mathbf{M}_I$), maximum intensity variance ($\mathbf{M}_V$), test image before registration ($\mathbf{F}$), deformed test image after registration ($\bar{\mathbf{F}}$), the intensity square difference ($\mathbf{D}_I$) between ($\mathbf{V}_I$) and ($\bar{\mathbf{F}}$), binary image where ($\mathbf{D}_I > \mathbf{V}_I$). Bottom row from left to right: mean displacement field ($\mathbf{M}_V$), maximum variance of the displacement field ($\mathbf{V}_V$), the deformation field norm ($\mathbf{U}$) of the registered test image, displacement field square difference ($\mathbf{D}_V$) between ($\mathbf{M}_V$) and ($\mathbf{U}$), binary image where ($\mathbf{D}_V > \mathbf{V}_V$). The binary images mark the suspected location of the anomalies.

that AC and AP are visible only in MR images and are manually annotated.

A general method to estimate the transformation about x-axis is based on the assumption that both $\mathbf{M}_I$ and $\mathbf{Q}$ are of the same modality. Firstly, 2D mid-sagittal slices $\mathbf{S}_M$ and $\mathbf{S}_Q$ are extracted from $\mathbf{M}_I$ and $\mathbf{Q}$ respectively. A 2D affine transformation about the x-axis ($\mathbf{T}_{2x}$) which maps $\mathbf{S}_Q$ onto $\mathbf{S}_M$ is then obtained by minimizing the SSD between the two slices. The transformation is formulated into a 4×4 affine transformation $\mathbf{T}_{3x}$, since homogeneous coordinates are used, and applied to $\mathbf{Q}$ to generate a new volume $\mathbf{Q}_x$ which has the same number of coronal slices with those of $\mathbf{M}_I$. Secondly, two arbitrary coronal slices, $\mathbf{C}_M$ and $\mathbf{C}_Q$ at the same level are chosen from $\mathbf{M}_I$ and $\mathbf{Q}_x$ in the order given. These slices are used to obtain a 2D affine transformation $\mathbf{T}_{2y}$ which aligns $\mathbf{C}_Q$ onto $\mathbf{C}_M$ which is also formulated into a 4×4 matrix $\mathbf{T}_{3y}$. In reality if $\mathbf{Q}_x$ was to be transformed using $\mathbf{T}_{3y}$ that would have subjected $\mathbf{Q}$ to large degradation due to multiple interpolation. Hence, instead of applying $\mathbf{T}_{3y}$ to $\mathbf{Q}_x$, a better solution is to combine $\mathbf{T}_{3x}$ and $\mathbf{T}_{3y}$ to form a single transformation $\mathbf{T} = \mathbf{T}_{3y}\mathbf{T}_{3x}$ which globally aligns $\mathbf{Q}$ onto $\mathbf{M}_I$.

A nonrigid registration stage is performed to compensate for local displacement, with large deformation expected to occur in regions which have been severely damaged by brain tumors. The registration is applied on the volume containing the partial data by omitting some slices in $\mathbf{M}_I$ which correspond to empty slices in $\mathbf{Q}$. After the alignment is achieved the square difference between the two partial volumes is computed and abnormal voxels are declared as described in Section 6.2.1.

6.3 Removing False Positives

The same constraints described in Section 5.4.3 are applied here to reduce falsely classified healthy brain tissues. The constraints include the inter-slice operation which is based on the assumption that the lesion must appear in at least two succeeding slices and adoption of the RECIST standard which forces the suspected lesions regions to have a longest diameter of 10 mm.

The last constraint applied forces any voxel to be considered abnormal to have a displacement field and intensity difference larger, or smaller, than expected. Figure 6.3 shows the axial slice of the registered test image and binary images depicting voxels with unexpected deformation field and intensity distribution.
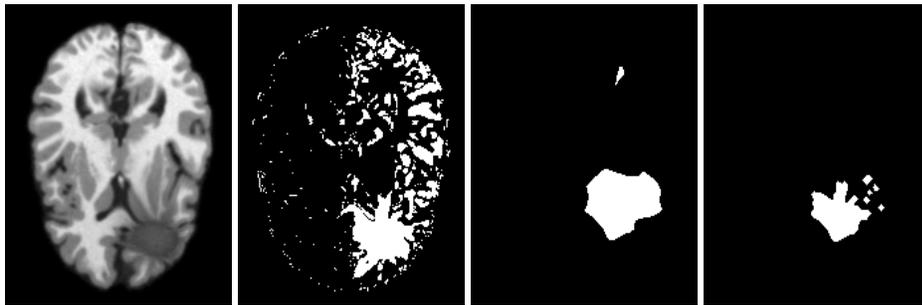
Figure 6.3: Illustration of removing false positives using binary images where voxels (with white intensity color) have unexpected intensity distribution or deformation field. From left to right: (a) deformed input image, and voxels with: (b) unexpected grey level values, (c) large deformation field, (d) unexpected grey level values and large deformation field. The rightmost binary image marks the final suspected location of the lesions.

6.4 Results and Discussion

This section discusses the experiments performed to validate the atlas-based method. The dataset used in this work is the simulated brain MR images with high and low-grade gliomas from [2]. Each image in the dataset consists of different tumor shape, size and location. The three metrics: (1) truth positive volume fraction (TPVF), (2) false positive volume fraction (FPVF) and (3) false negative volume fraction (FNVF), described in Section 5.6.2, are used as the accuracy measures to determine the performance of the method.

6.4.1   Evaluation on Full Scan

A. High-Grade Tumor

Figure 6.4 illustrates the suspected locations of the lesions in each test image. These regions mark voxels with intensity and deformation field norm larger or smaller than the expected values. In some images, such as the third image in the bottom row of Figure 6.4, the suspected abnormal region covers the healthy regions surrounding them.

The quantitative results of the method on high-grade gliomas are shown in Table 6.1. The average TPVF, FPVF and FNVF are found to be 0.6501, 0.8971 and 0.3499 respectively. Though the bottom row of Figure 6.4 shows axials with tumors entirely covered, the algorithm did not detect abnormal voxels in other axial slices hence the reason why FNVF is high. The value of FPVF are found to be large and this indicates that the method misclassifies a large number of healthy tissue subjects. It is likely that the major contributing factor is the large deformation occurring around lesions because of the minimization of the cost function by the nonrigid registration process.
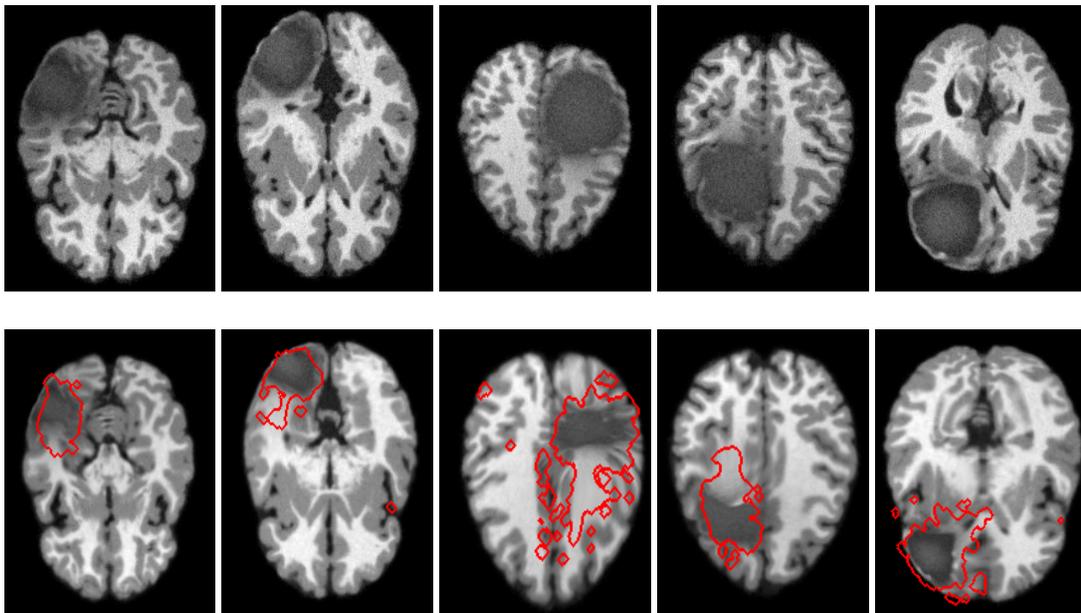
Figure 6.4: The results for atlas-based method depicted on axial slice for simulated dataset with high-grade gliomas. First row: raw input data, second row: deformed test image with suspected location (red contour) overlaid on each image.

B. Low-Grade Tumor

The performance of the method is also evaluated on low-grade gliomas. Figure 6.5 illustrates visual results for six T1-weighted MR images. In each dataset the visual results are shown in axial view by selecting an abitrary axial slice containing the tumor. Table 6.2 shows quantitative results on these dataset. The mean TPVF, FPVF and FNVF of the proposed method on low-grade gliomas are 0.7132, 1.9565 and 0.2868 in the order given. The value of FPVF being larger than 1 implies

Table 6.1: Accuracy results for atlas-based method applied on simulated T1-weighted dataset with high-grade gliomas.

Metric	Simulated Subjects				
	hg11T1	hg12T1	hg16T1	hg18T1	hg19T1
TPVF	0.6450	0.6010	0.6924	0.6323	0.6797
FPVF	0.2215	0.3926	2.211	0.1697	1.4909
FNVF	0.3550	0.3990	0.3076	0.3677	0.3203

the majority of the segmented voxels come from the healthy brain tissues. It is anticipated that the healthy tissues can be the regions around the abnormal area or those that have different shapes from the atlas. This number can be reduced by introducing some other constraints methods.
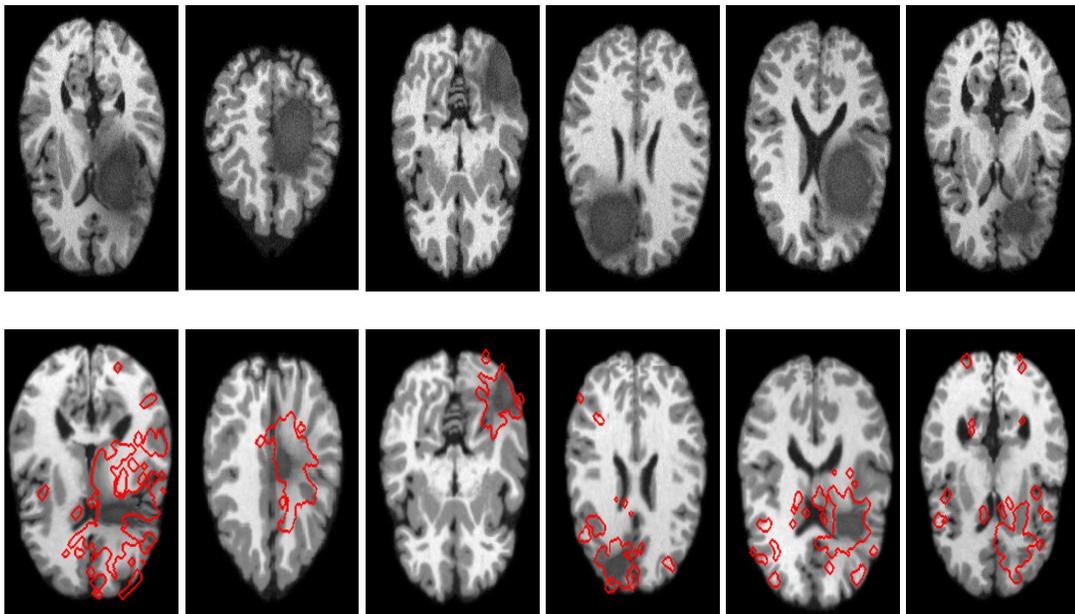
Figure 6.5: The results for atlas-based method depicted on axial slice for simulated dataset with low-grade gliomas. First row: raw input data, second row: deformed test image with the estimated location (red contour) of the lesions superimposed on each image.

Table 6.2: Quantitative results for atlas-based method applied on simulated T1-weighted dataset with low-grade gliomas.

Metric	Simulated Subjects					
	lg01T1	lg05T1	lg07T1	lg09T1	lg10T1	lg11T1
TPVF	0.7537	0.6704	0.6798	0.6899	0.7495	0.7356
FPVF	1.8992	0.6881	0.9503	2.5261	2.9608	2.7146
FNVF	0.2463	0.3296	0.3202	0.3101	0.2505	0.2644

6.4.2   Summary

The work presented here showed that a brain atlas can be used to estimate a model of healthy brain tissues and can further be utilized to accurately detect and segment brain lesions in future images. The atlas was constructed from scratch using a set of healthy T1-weighted MR images and the proposed method, which is fully automated, was evaluated on high-grade and low-grade gliomas. To determine the performance of the method its accuracy is compared to that of the gold-standard technique, manual segmentation, and it gives reasonable results. A detailed description of the approaches employed to remove non-tumorous voxels was also given.

In summary TPVF and FPVF are found to be 0.6501 and 0.8971 on high-grade gliomas and 0.7132, and 1.9565 on low-grade gliomas. A large value of FPVF means most of the voxels classified as brain lesions come from the healthy brain tissues. Hence over segmentation is performed. This is caused by large displacement of healthy brain tissues surrounding the lesions which are left out during manual segmentation. Since this is an error, a constraint which takes into consideration the intensity distribution and displacement field of the surrounding tissues was applied to reduce it.

Chapter 7

Conclusion

The main objective of this thesis was to develop an automatic CAD method which is able to detect and segment brain abnormalities in 3D MR and CT data accurately. Two automatic methods have been developed. The first method is based on the analysis of the symmetry of the brain, and has been tested and evaluated on T1- and T2-weighted MR datasets. The second method, based on the expected intensity values of healthy brain tissues, has been evaluated on T1-weighted MR dataset. In this chapter the discussed techniques are reviewed and the limitations, and possible future improvements, on each method are suggested.

7.1   Summary of this Thesis

The proposed symmetry-based method consists of three steps: detection of the symmetry, tilt correction and asymmetry quantification. The symmetry detection method starts first by isotropically resampling the MR dataset to cubic voxels to avoid the influence of the slice thickness on the volume of small-sized tissues. It then estimates the parameters of the symmetry plane by formulating the task as a registration problem and adopts Levenberg-Marquardt as the optimization algorithm. The obtained optimal parameter values are then compared to ground-truth using two accuracy measures: MAE and DE. The plane is further used to correct tilting of the head such that it becomes upright.

Having found the symmetry plane the algorithm continues to analyze the symmetry of the brain to segment out asymmetric regions, suspected to be brain abnormalities. Two automatic approaches have been developed to quantify asymmetric regions. They are based on the assumption that the brain shows a bilateral symmetry and this symmetry is only violated if the patient is suffering from brain lesions. The first method analyzes the voxel intensity difference between brain hemispheres, with large absolute difference expected to appear in regions which are asymmetric. The second approach is based on a 2D region detector. They are further compared to the ground-truth using TPVF, FPVF and FNVF as accuracy measures and the results obtained show that it is possible to

estimate the location of brain tumors using asymmetry.

The experiments showed that the registration method was more accurate than the region detector based method though at the cost of a high false negative rate and computational costs. Both experiments were performed on a personal computer. The total run time, per $256 \times 256 \times 181$ cubic voxel volume, for the registration-based method is 26.17 ± 2.34 minutes and 9.616 ± 1.30 minutes for the region detection-based method. A good estimate of the symmetry plane is achieved with a run time of 4.81 ± 1.50 minutes.

An atlas-based brain tumor segmentation method was also studied in this work, using voxel intensities and displacement fields as the prior knowledge of healthy brain tissues. The atlas was constructed from a set of healthy simulated T1-weighted MR images adopting GPA to align different subjects onto the same coordinate space. The atlas consists of the expected intensity value and displacement field for each voxel. It also has threshold values (intensity and displacement field) for each voxel which are set automatically from the healthy subjects.

The experiments were performed using simulated subjects with artificial abnormalities and the segmented regions were compared with the ground-truth using TPVF, FPVF and FNVF as accuracy measures. Promising results were obtained though at the cost of higher false positive rates. Different subjects having different types of tumors were tested and the results on each type were discussed. The overall computational time was 31.42 ± 4.3 minutes per $256 \times 256 \times 181$ cubic voxel volume, and is affected by the nonrigid registration process and the presence of a large number of false positives to be removed.

7.2 Limitations and Future Work

The major limitation of the symmetry-based method is inability to handle large symmetric lesions which crosses the symmetry line, or a pair of symmetric lesions. These challenges still remains as obstacles in the work in the literature. For the case where the pair of lesions have different sizes or lesions crossing the symmetry line do not occur symmetrically on both hemispheres [10] have added the functionality of the region growing techniques to address this issues. The seed points are selected automatically from the remaining asymmetric fractions after computing the intensity difference between the hemispheres to cancel out symmetrical portions.

The other remaining challenge is the issue of a large number of false positives, in both methods, despite the number of constraints which were enforced. Future work will be to investigate other possible methods to reduce the falsely-classified healthy tissues.

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