WHITE-MATTER LESION SEGMENTATION IN BRAIN MRI USING ADAPTIVE TRIMMED MEAN APPROACH

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WHITE-MATTER LESION SEGMENTATION IN BRAIN MRI USING ADAPTIVE TRIMMED MEAN APPROACH

by

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LIST OF ABBREVIATIONS

Adaboost Adaptive Boosting

AIR Automated Image Registration

AMDI Advanced Medicine and Dentistry Institute

APICTA The Asia Pacific ICT Awards

BET Brain Extraction Tool

CSF Cerebrospinal Fluid

CT Computed Tomography

CAT Computerized Axial Tomography

CAD Computer-Aided Diagnosis

CHB Children's Hospital Boston

DICOM The Digital Imaging and Communications in Medicine

EM Expectation-Maximization

FCM Fuzzy C-Mean

FLAIR Fluid Attenuated Inversion Recovery

FWHM Full Width at Half Maximum

FPF False Positive Fraction

GBD Global Burden of Disease

GM Gray Matter

IC Intra-Cranial

ITK Insight Toolkit

kNN k-Nearest Neighbour

MRI Magnetic Resonance Imaging

MIPAV Medical Image Processing, Analysis, and Visualization

MICCAI Medical Image Computing and Computer Assisted Intervention

MNI Montreal Neurological Institute

MS Multiple Sclerosis

NABT Robust Estimation of Normal Appearing Brain Tissues

NMRI Nuclear Magnetic Resonance Imaging

PD Proton Density

PDF Probability Density Function

UNC University of North Carolina

RF Radio Frequency

T1-W T1-Weighted

T2-W T2-Weighted

TE Echo Time

SOM Self-Organizing Maps

SVM Support Vector Machine

TR Reception Time

TPF True Positive Fraction

WHO World Health Organization

WM White Matter

SEGMENTASI LESI JIRIM PUTIH PADA IMEJ MRI OTAK MENGGUNAKAN PENDEKATAN MIN TERPAPAS SECARA ADAPTIF

ABSTRAK

Lesi jirim putih merupakan ketaknormalan jirim putih bauran yang sering kelihatan sebagai kawasan keamatan yang tinggi (cerah) dalam Pengimejan Resonans Magnetik kranial. Lesi jirim putih biasanya diperhatikan pada golongan yang lebih tua dan merupakan petanda penting bagi strok, sklerosis berganda, dementia dan kecelaruan lain yang berkaitan dengan otak. Pengesanan lesi jirim putih secara manual amat menjerihkan dan pendekatan penskoran secara penglihatan yang diguna pakai pada masa kini untuk penggredan lesi adalah sangat subjektif. Dalam tesis ini, satu pendekatan baru bagi segmentasi lesi jirim putih secara adaptif dicadangkan. Dalam pendekatan yang dicadangkan ini, kewujudan lesi jirim putih dikesan sebagai unsur luaran dalam taburan keamatan bagi Pengimejan Resonans Magnetik *Fluid Attenuated Inversion Recovery* (FLAIR) menggunakan teknik Pengesanan Unsur Luaran Adaptif. Unsur luaran dikesan menggunakan gabungan yang terdiri daripada kaedah Min Terpapas dan analisis Plot Kotak Statistik. Selain itu, pendekatan ini juga mengandungi langkah pra-pemprosesan untuk mengurangkan kesalahan klasifikasi bagi lesi jirim putih dan pasca-pemprosesan yang disebabkan oleh artefak Pengimejan Resonans Magnetik yang lazimnya diperhatikan dalam jujukan FLAIR. Pendekatan ini ditentusahkan dengan menggunakan jujukan Pengimejan Resonans Magnetik kranial bagi 38 subjek. Korelasi yang signifikan ($R = 0.8506, P = 3.94x10^{-6}$) diperhatikan di antara pendekatan automatik dan keputusan kuantifikasi lesi berdasarkan penglihatan secara manual yang kenali sebagai Skala Perubahan Jirim

Putih Berkaitan Umur. Ketepatan pendekatan yang dicadangkan telah ditentusahkan seterusnya dengan membandingkan kepadatan lesi yang dihitung antara pendekatan automatik dan segmentasi lesi secara manual oleh seorang pakar radiologi. Pendekatan ini juga ditentusahkan dengan menggunakan set data penanda aras.

WHITE-MATTER LESION SEGMENTATION IN BRAIN MRI USING ADAPTIVE TRIMMED MEAN APPROACH

ABSTRACT

White Matter (WM) lesions are diffuse white matter abnormalities, that appear as hyper-intense (bright) regions in cranial Magnetic Resonance Imaging (MRI). WM lesions are often observed in older population and are important indicators of stroke, multiple sclerosis, dementia and other brain-related disorders. Manual detection of WM lesions is laborious and the currently adopted visual scoring approaches for lesion grading is very subjective. In this thesis, a new approach for automated WM Lesions Segmentation is presented. In the proposed approach, the presence of WM lesions is detected as outliers in the intensity distribution of the Fluid Attenuated Inversion Recovery (FLAIR) MR images using an Adaptive Outlier Detection technique. Outliers are detected using a novel adaptive Trimmed Mean and Box-Whisker Plots. In addition, the approach includes pre and post-processing steps to reduce False Positives attributed to MRI artefacts commonly observed in FLAIR sequences. The proposed approach is validated using the cranial MRI sequences of 38 subjects. A significant correlation ($R = 0.8506, P = 3.94x10^{-6}$) is observed between automated approach and manual visual scoring (Age-related White Matter Changes Scale). The accuracy of the proposed approach was further validated by comparing the lesion volumes computes using the automated approach and lesions manually segmented by an expert radiologist. The proposed approach is also compared against leading lesion segmentation algorithms using a benchmark dataset.

CHAPTER 1

INTRODUCTION

1.1 Introduction

White matter lesions (WM Lesions) are areas of dead tissue in the white matter region of the brain. WM lesions are also known as WM Hyperintensities or *Leukariosis*. These lesions are commonly found in the brains of individuals who are over 65 years old. In clinical practice, computed tomography and magnetic resonance scans are widely used to detect WM lesions. In Magnetic Resonance Imaging, WM lesions are observed as hyper-intense (bright) regions as compared to the surrounding white matter tissue. WM lesions have been shown to be predictors of several neurological disorders such as vascular dementia (Peters and Dichgans, 2010; Debette and Markus, 2010; Cavalieri et al., 2010), stroke (Yamauchi et al., 2002; Debette and Markus, 2010) and Alzheimer's disease (Cavalieri et al., 2010; Park et al., 2010). In addition, WM lesions are also associated with functional impediments to older populations, such as depression, gait disorders and cognitive decline (Launer, 2004; O'Sullivan, 2008; Silbert et al., 2008).

According to the World Health Organization (WHO) (WHO, 2000), it is estimated that 16.4% of the projected current 6.9% of global population will be older than 65 years by 2050. One of the major causes of disability in later life is Dementia, which affects up to 66% of the 24 million elderly people who live in undeveloped and developing countries (WHO, 2006). The increasing size of the ageing population worldwide naturally leads to greater occurrences of neurological disorders in the foreseeable future.

There is no simple test to predict neurological disorders effectively. However, WM lesions, being early indicators of neurological disorders, are routinely observed through diagnostic imaging and could be used as an immediate and effective diagnosis strategy in order to detect the onset of neurological disorders. In screening patients for WM lesions, a radiologist often needs to examine between twenty and hundreds of individual MRI slices. The T2-Weighted (T2-W) and T1-Weighted (T1-W) sequences, and more significantly, the FLAIR (Fluid Attenuated Inversion Recovery) sequences are examined manually by radiologists and neurologists (Appenzeller et al., 2008).

1.2 White Matter Lesions

White matter (WM) lesions occur when the brain tissue called myelin in the white matter region is destroyed (demyelination), thus prohibiting nerve signals to be transmitted effectively in the white matter. Consequently, WM lesions result in the impairment of hearing ability, memory acquisition, movement and etc. WM lesions can be visually identified in T2-weighted MRI sequences and in FLAIR (Fluid-Attenuated Inversion Recovery) sequences, in which they show up as hyper-intensities in the white matter region as shown in Fig. 1.1. WM lesions vary in their shape, distribution and size from one individual to another.

1.3 Assessment of White Matter Lesions

Assessment of White Matter Lesions refers to the medical image examination by clinical experts, usually radiologists, who would identify or locate the presence of WM lesions and rate their severity. There are two common approaches that are currently being used in assessment; (a) visual assessment, or simply referred as visual scoring and (b) quantitative measurements.

Visual assessment refers to a manual procedure to assess the severity of white matter le-

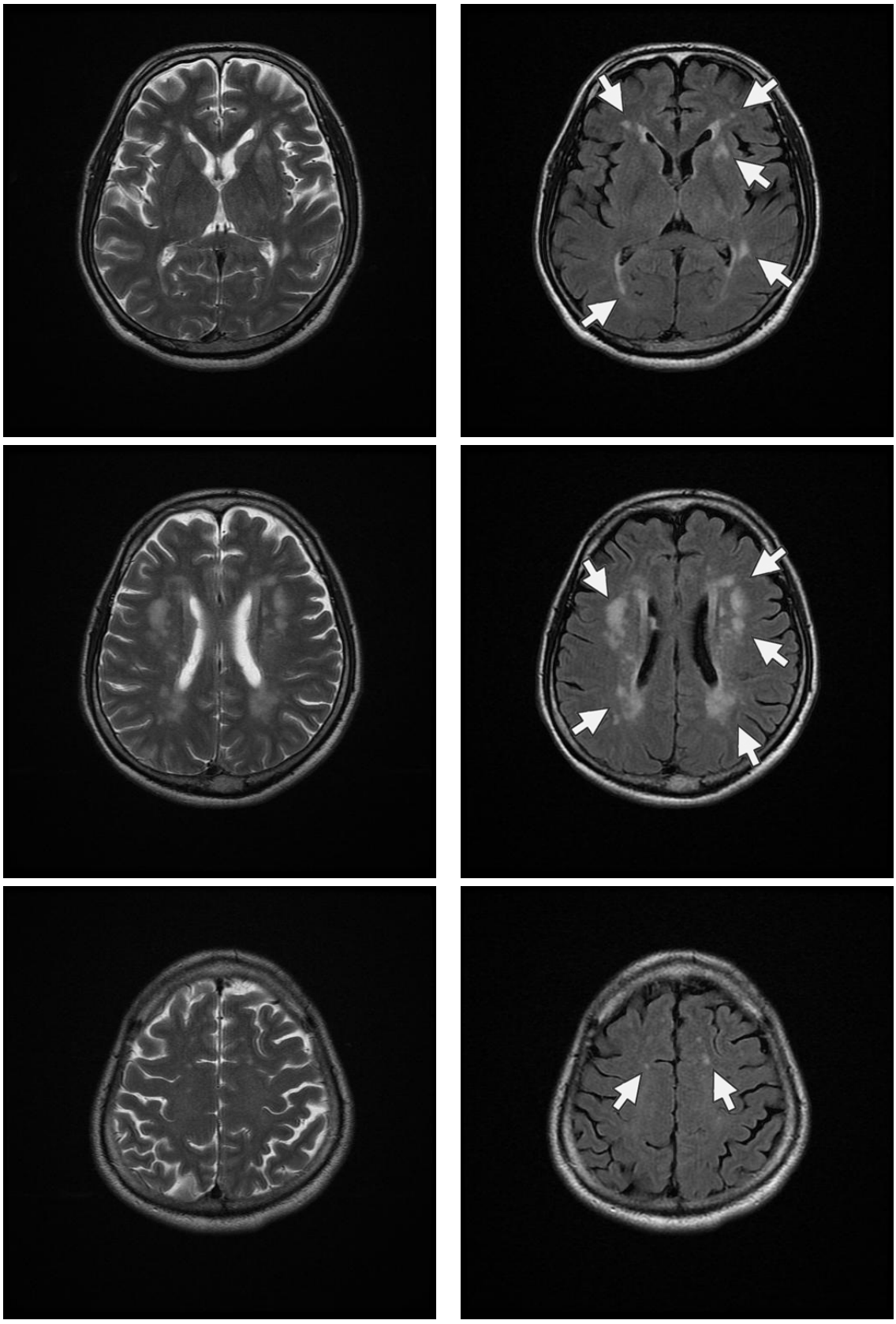

Figure 1.1: Multi-spectral MR Images (axial view) on 1.5T MRI scans. T1-weighted images (first column), FLAIR images (second column). Arrows indicate the presence of lesions.

sions which are present in medical images. The visual assessment is important in studies on the progression of white matter lesions. There are a variety of rating system that have been proposed by researchers, which includes the Fazekas scale (Fazekas et al., 1987), the Scheltens scale (Scheltens et al., 1993) and the Age-Related White Matter Changes (ARWMC) scale (Wahlund et al., 2001). In visual scoring of white matter lesions, a radiologist will assign a severity score for each image slice based on the visual similarity to a set of reference images. The rating results will be used as as the base line to compare against follow up rating results typically after a year or after a few years; depending upon the objective of the clinical study. The advantage of using visual rating scales is that they are simple and easy to be used in practice, requiring no computer-aided analysis in the process. Since visual scoring approaches are subjective in nature, it is difficult, not only to determine which is the best visual scoring approach to use, but also to apply them in large-scale WM lesions progression studies. Enzinger et al. (2007) highlights several factors which makes manual visual scoring challenging:

1 Scoring reproducibility, sensitivity and specificity is highly dependent on the selection of visual scoring scale.

2 Large scale progression studies usually involves more than one medical or research institutions. This implies subjectivity in scoring between one radiologist to another from different institutions.

3 Manual visual scoring need experienced radiologists and is often a very laborious process.

Accurate quantification is important in the analysis of white matter lesion progression. In volumetric medical images, such as Computed Tomography or Magnetic Resonance Imaging, quantification refers to the determination of the number of voxels that represents the WM lesions. There are varying levels of computer automation to lesion quantification, from man-

ual segmentation of lesions from each image slice to fully automated lesion segmentation and quantification. The quantification process typically involves a radiologist who uses the region of interest (ROI) tool provided in image analysis applications to outline each lesion for a given slice. The sum of voxels of the outlined regions for the entire image series is computed and the lesion load (volume) can then be determined.

1.3.1 Typical Computer Aided Detection and Diagnosis System

In recent years, as medical image analysis research became more mature in terms of technique and imaging technology, computer-aided WM lesion segmentation approaches have been investigated. Traditionally, it was necessary for the radiologist to manually outline each and every lesion for every single image for quantification and analysis purposes. This obviously was very impractical in large scale studies as hundreds or thousands of images may need to be manually examined. Hence, it fueled the research into computer-aided detection and quantification approaches, with the aim of not only speeding up the process, but also to have an objective means of quantification. Semi-automated quantitative measurement and automated quantitative measurement are two different approaches that are often used to segment WM lesions. Semi-automated quantitative measurement typically requires the intervention of a radiologist to segment WM lesions. Radiologists are required to identify “seed-points" of suspected WM lesions, before computer algorithms “grow" regions originating from these seed points, to cover all lesions in an image. Techniques that are based on this approach include Level Set algorithm, Fuzzy Connectedness and region-growing techniques(Herman and Carvalho, 2001; Udupa et al., 2002; Gibou and Fedkiw, 2005; Zhuang et al., 2006; Liu et al., 2008). However, these methods remain labour intensive and tedious for trials on large numbers of clinical cases as the determination of seed points remain challenging. On the other hand, automatic quantitative measurement which require no manual intervention during the detection process, uses computer algorithms to replace or mimic the manual intervention process. According to liter-

ature, there is a growing interest in automatic approaches to segment the WM lesions (Anbeek et al., 2004; Admiraal-Behloul et al., 2005; Wu et al., 2006; Zacharaki et al., 2008; De Boer et al., 2009). Ultimately, fully automatic quantitative measurement is perhaps the best choice in large-scale clinical studies of WM lesions.

1.4 Motivation

As mentioned earlier, the examination of MRI images to detect and quantify WM lesions still remains a tedious job for the radiologists. The manual visual scoring approach, while simple in implementation, is very subjective. Since the presentation of WM lesions vary both in severity, as well in distribution and appearance, from one patient to the other, it may be difficult and time consuming to perform accurate segmentation of these lesions. Not withstanding, there can be considerable variability between different radiologists in terms of the score given. In mass screening or large scale clinical studies, it may be impractical for radiologists to perform manual segmentation of WM lesions, therefore the need for an automated approach, which is not only fast, but also sensitive and accurate. Current computer-aided approaches to WM lesion detection and quantification also suffer from several drawbacks. While a more elaborate discussion of these drawbacks will be presented in the Chapter 2, it suffices to mention here that these existing approaches either require prior training, need minimal post-processing to effectively remove False Positives or vary in the amount of human intervention necessary during the analysis.

1.5 Research Problem

Generally there are several challenges in computer-aided WM lesion segmentation as listed in following:

1. The occurrence of WM lesions in the brain varies in shape, size and location,

2. MRI is the primary imaging modality used to visualise WM lesions. However, MRI technology has several drawbacks which includes intensity non-uniformities, image noise, low contrast, the lack of standardization of MRI signals intensities.

3. It is very difficult to determine the range of intensities which constitute WM lesions and healthy brain tissue , therefore it is a challenge for automated approaches to differentiate between healthy tissues and abnormal tissues (WM lesions, in this case).

1.6 Research Objectives

As the need for automatic WM lesion detection and quantification has been clearly established, this work proposes a fully automated system to do the same. In line with that, the objectives of the research can be stated as follows:

1. To investigate a WM lesion segmentation approach which:

    i. Can adaptively handle variations in size, location, shape of the lesions.

    ii. Robust to characteristics of MRI in terms of intensity non-uniformities, image noise, low contrast, the lack of standardization of MRI signals intensities.

    iii. Able to reliably differentiate healthy brain tissues and lesions.

    iv. Is fully automated.

    v. Does not require any prior training data or training phase.

    vi. Is fast and accurate with high specificity and sensitivity.

2. To validate the proposed framework using benchmark data and gold standards (radiologist segmentation).

1.7 Research Scope

The proposed work will focus on the detection and segmentation of WM lesions from cranial MR images, specifically the T1-W and FLAIR sequence. The thesis shall consider only 16-bit DICOM image format of size 512x512 voxels.

1.8 Overview of the Approach

This study proposes a new fully automated and adaptive technique to detect WM lesions in cranial MR images. There are three main stages of proposed algorithm: the preprocessing stage which includes

a. skull stripping, inhomogeneity correction and normal brain tissue classification,

b. the WM lesions segmentation stage,

c. and the postprocessing stage to reduce False Positives.

The overall scheme of the automated approach is shown in Fig. 1.2 The process is described in the following.

There are two sequence of images used as inputs for WM lesion segmentation, T1-weighted and Fluid Attenuated Inversion Recovery(FLAIR) images. Although FLAIR is the preferred sequence to visualize WM lesions due to their excellent tissue contrast, intensity-based WM lesions segmentation approaches could fail as non-brain voxels such as the skull and the optic nerve also appear hyper-intense in the FLAIR modality. Thus, there is a need to perform *skull stripping* which essentially means that the voxels belonging to the skull are removed from the image sequence, preserving only the tissues that belong to the brain structures. The removal of the skull tissue facilitates the further processing of the FLAIR images to detect the WM

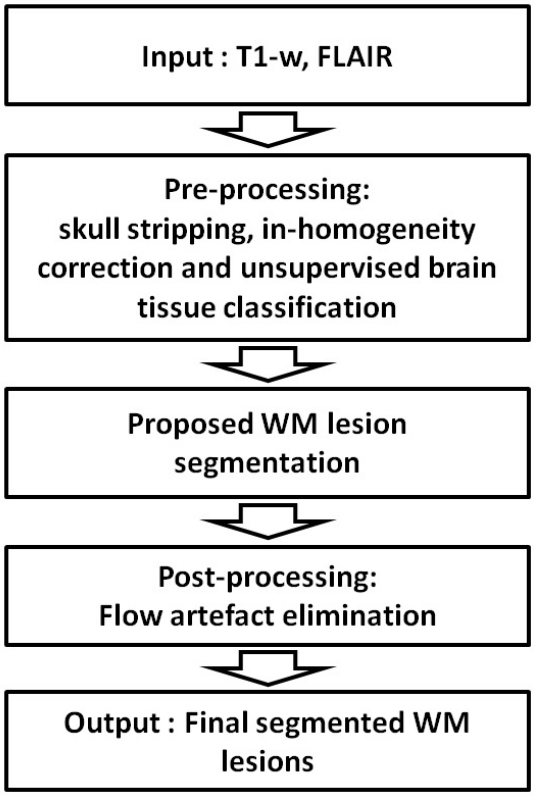

Figure 1.2: An overview of proposed automatic WM lesions segmentation protocol.

lesions.

The inputs to the proposed WM lesions segmentation algorithm are the skull-stripped FLAIR sequence. The CSF, normal brain tissue (GM and WM) and WM lesions could be identified based on the voxel intensity distribution (histogram) of the skull-stripped FLAIR image sequence. In order to determine WM lesions (abnormal brain tissue), it is first necessary to identify the voxels belonging to the normal brain tissue. In this work, the abnormal WM lesions are modeled as outliers in the probability distribution of voxels in the FLAIR sequence. To detect the presence of outliers, an adaptive outlier detection approach is proposed in this thesis. The proposed adaptive outlier detection approach is based on a statistical measure called Box-Whisker plots (Tukey, 1977; Schwertman et al., 2004) and will be discussed in detail in Chapter 4.

After the detection of WM lesions is completed, it is still necessary to remove voxels which are known as False Positives (FP). False Positives are voxels which share similar intensity levels as true WM lesions, but are in fact not WM lesions, and are the consequence of MR imaging artefacts. Hence, the post processing always is needed to minimize and reduce these false positives. Specifically, the voxels classified as CSF and WM in the T1-weighted sequences are used in conjunction with morphological processing to reduce False Positives. The morphological processes include a combination of Dilate, Erode and Fill holes operations. This post processing effectively removes hyper-intense voxels in the peri-ventricular region which are due to an imaging artefact, known as the *peri-ventricular flow artefact*. These artefacts are predominantly present adjacent to the frontal horns of the lateral ventricles of the brain (Bailey, 2007). After post-processing is complete, voxels which are highly probable to be WM lesions could be effectively determined.

After the segmentation of WM lesion is completed, the lesion load (volume) is then calculated and reported. The proposed method is then validated with the several datasets obtained from Universiti Sains Malaysia's hospital and from a publicly available benchmark dataset.

1.9 Contributions of the Research

There are two significant contributions of this research:

1 An automated WM lesions segmentation algorithm that does not require training data or training phase and is fast due to its computationally efficient algorithm.

2 Delivering a fully automatic WM lesions segmentation algorithm and complete software diagnosis application that will assist radiologist in screening of patient data in their large scare of clinical trials. Specifically, this thesis presents a novel adaptive trimmed-mean approach to reliably detect outliers using the intensity distribution of FLAIR image. This

adaptive trimmed mean approach is then used in conjunction with the Box-Whisker plot analysis to automatically detect the presence of outliers (WM lesions) without the need for any prior modeling.

1.10 Thesis organization

This thesis is structured according to the tasks involved in the proposed automated WM lesions segmentation approach.

Chapter 2 presents a concise review of the pertinent literature in the area of WM lesions segmentation. A critical discussion on the advantages and disadvantages of various WM lesions segmentation approaches is presented.

Chapter 3 presents the theoretical description behind each component in the proposed WM lesions segmentation framework. Specifically, the skull stripping, brain tissue classification, inhomogeneity correction, morphological operations and the statistical outlier detection approach will be discussed in depth.

Chapter 4 presents the proposed WM lesions segmentation framework. In addition, the approach for performance evaluation will also be described in Chapter 5.

The conclusion of the research in terms of advantages of the proposed scheme, practical achievements and recommendations for future work is presented in Chapter 6.

CHAPTER 2

LITERATURE REVIEW

2.1 Introduction

In recent years, a number of computer-aided WM lesion segmentation approaches have been reported in the literature. This chapter presents a critical review of the pertinent literature related to the segmentation and analysis of WM lesions. Generally, these computer-aided approaches can be classified as either semi-automatic approaches or fully automatic approaches. The former requires some form of human intervention in the analysis process, while the latter requires little or no human intervention in the analysis of WM lesions. Judging from the recent work in this area (Anbeek et al., 2004; Admiraal-Behloul et al., 2005; Quddus et al., 2005; Lao et al., 2006; Wu et al., 2006; De Boer et al., 2007; Zacharaki et al., 2008; Anbeek et al., 2008; Beare et al., 2009; De Boer et al., 2009), it is evident that fully automated WM lesions segmentation approaches have received more attention than semi-automated approaches. This is understood since semi-automated WM lesion segmentation is still tedious when dealing with large number of images.

Apart from WM lesion segmentation, related research on Multiple Sclerosis (MS) lesions is also included in this review. This is because MS lesions have similar characteristics as WM lesions in MRI and therefore need similar techniques for analysis. The main difference between MS lesions and WM lesions are that MS lesions are brain lesions that are found on patients who are confirmed to suffer from the MS disorder, while WM lesions, refers to similar lesions found on a wider range of patient profiles who may not exhibit specific symptoms of a

particular neurological disorder.

2.2 Semi-automatic WM lesion segmentation

As mentioned earlier, semi-automatic approaches refer to lesion segmentation techniques that require human intervention during the analysis process. The degree of human intervention varies from one technique to another. Semi-automatic approaches typically result in reduced variability in the detected lesion volume loads as compared to manual segmentation approaches.

An early method to semi-automatically segment and quantify Multiple Sclerosis (MS) lesions in MRI was proposed by Udupa (1997) using the principles of fuzzy-connectedness. The principle of fuzzy-connectedness uses of two important elements, fuzzy adjacency(μ_α) and fuzzy affinity(μ_k) for each pair of voxels (a,b), to describe how strong two voxels "hang together" in terms of space and intensity. A detailed of mathematical description of the fuzzy connectedness theory is given in (Udupa, 1997; Udupa et al., 2002). The framework used in the study consists of three major steps in segmenting MS lesions (Udupa, 1997). The reliable detection of MS lesions requires first the accurate segmentation of CSF, WM, and GM. The first step requires the radiologist to identify the WM, GM and CSF by specifying a few *spels* (points). This is achieved by pointing to locations of various brain tissues types on the image. Using these seed points, the fuzzy connectedness algorithm “grows” the voxels in 3-dimensional space to produce a 3-D fuzzy object. The union of 3-D fuzzy objects(CSF, WM and GM) will form the whole brain. Potential lesions will appear as “holes” in these 3-D fuzzy objects. The location of these “holes” are subsequently used as initial seed points to detect and segment potential lesions as a 3-D fuzzy object. Finally, the decision to accept or reject the identified potential lesions will be made by a radiologist.

Interestingly, this semi-automatic technique does not require the radiologist to manually

identify the seed points for every single slice in the dataset; rather fuzzy-connectedness algorithm grows the seed voxels in 3-dimensional space. Therefore, it is simpler and less time consuming compared to the manual lesions segmentation methods currently used in clinical trials. The only disadvantage of this method is the inconsistency in the reproducibility that has been reported (Payne et al., 2002; Kikinis et al., 1992; Udupa, 1997; Admiraal-Behloul et al., 2005). This is mainly due to the variability in interpretation of radiologist in the verification phase. More recently, fuzzy connectedness has been successfully applied by Wu et al. (2006) to segment WM lesions while Liu et al. (2008) used it for brain segmentation.

Payne et al. (2002) proposed an early approach to the quantitative assessment of MS lesions using a supervised semi-automatic segmentation based on the k-Nearest Neighbour (k-NN) Classification algorithm. In their approach, a modified version of the **MrX software**, created by GE Corporate Research and Development was used (Kikinis et al., 1992). The k-NN training step requires a set of images containing predefined lesions to be made available. As such, a detailed procedure for providing seed points different types of lesions, such as peri-ventricular lesions, deep white matter lesions and sub-cortical gray matter lesions are presented and this requires considerable attention by the radiologist during the training phase. This detailed approach was also limited by technology. The MRI protocol in their study was first utilized in 1994 and, due to the longitudinal nature of this project, this lesion method was constrained by the technology available at that time. Although moderate correlation was reported against qualitative scoring measures, namely the Coffey and Boyko scales, the time taken to analyze a scan varied between 25-45 mins (Payne et al., 2002).

In (Grimaud et al., 1996), a comparison of the three computer-assisted techniques, i.e. full manual outlining, semi-automated lesion contouring and intensity based thresholding techniques for quantitative analysis of MS lesions load was conducted. The experiments were conducted after all the images were corrected for inhomogeneity. The details of each technique

are described in the following:

I. **Full manual outlining technique** is a manual approach where a radiologist uses the computer mouse to control the cursor to trace the outline of the lesions. The lesions size is then computed.

II. **Semi-automatic lesion segmentation using contouring technique**. This technique requires a radiologist to allocate seed points near the boundary of the lesions. Subsequently, the lesions will be outlined automatically. The algorithm utilises the edge information which starts from the stronger edge in the neighbourhood of a user-selected point. The seed point is then searched over a 5x5 pixels squared area from the center towards 4 directions (north, east, south, and west). The next contour point has to be above the threshold of the starting point. A contour is then completed from the set of points in an iterative manner.

III. **Intensity based thresholding technique**. A threshold value is chosen by the radiologist to perform a global thresholding. The threshold value is selected such that the hyper-intense white matter lesions are distinguished from the surrounding normal brain tissues. In order to perform the thresholding, the brain tissue is first extracted from the skull first. The pixel below the threshold value will be discarded and the pixel above the threshold value will be grouped as the region of interest. All image slices on a particular scan will be thresholded based on a single threshold value. Finally, this technique requires human intervention to manually delete hyper-intense regions that do not correspond to MS pathology.

It was concluded in this paper that the evaluated techniques were not only time consuming but also depended very much on human intervention during the segmentation process. In fact, the semi-automated method actually took a longer time than the fully manual segmentation

method. However, one advantage of the semi-automated lesions segmentation using the contouring technique is that it was more consistent in reproducibility. As a whole, the process of MS lesions analysis is generally speeded up for a large scale clinical trial due to the reduction in inter- and intra-variability between radiologists.

As can be noted from the reviewed work in this section, the major limitation of semi-automated approaches are the time required to complete the analysis of each scan as well as the need for radiologists. The next section in this literature review will focus on the more attractive but challenging fully automated approaches for lesion segmentation.

2.3 Automatic WM lesion segmentation

Automatic approaches for quantification of WM lesions have recently gained significance. These approaches can be generally categorized into voxel classification approaches, region growing approaches, and approaches that perform a threshold-based segmentation using the intensity histogram. Various approaches that are reviewed in this thesis have been categorized as shown in Table. 2.1.

Table 2.1: Summary of reported automatic WM lesions segmentation approaches.

Voxel classification	**Threshold-based**	**Region growing**
Anbeek et al. (2004)	Hirono et al. (2000)	Wu et al. (2006)
Admiraal-Behloul et al. (2005)	Jack et al. (2001)	
Quddus et al. (2005)	Wen and Sachdev (2004)	
Lao et al. (2006)	De Boer et al. (2007)	
Zacharaki et al. (2008)	Bricq et al. (2008)	
Anbeek et al. (2008)	Souplet et al. (2008)	
Garcia-Lorenzo et al. (2008)	De Boer et al. (2009)	
Morra et al. (2008)		
Prastawa M. (2008)		
Souplet et al. (2008)		
Shiee and Bazin (2008)		
Kroon D. (2008)		
Beare et al. (2009)		

Typically, in order to achieve the goal of fully automatic WM lesions segmentation, a series of image pre-processing steps are necessary. While the actual image pre-processing steps vary from one approach to another, common steps include one or more of the following:

1 **Skull stripping** is used to remove the skull from the brain tissue (Smith, 2002; Zhuang et al., 2006). Skull tissue is removed because its intensity range is similar to that of the lesions and may result in false positives during the segmentation process. In MRI, the T1-Weighted sequence is the best modality to be used to remove the skull voxels effectively. Generally, skull stripping techniques can be categorised into morphology-based (Dogdas et al., 2005) and deformable model-based methods (Smith, 2002).

Morphology-based methods normally require combination morphological operations and thresholding (Dogdas et al., 2005) or edge detection (Shattuck et al., 2001) to remove skull and scalp voxels. Morphological operations use a structuring element as input to perform intersection, union, inclusion, or complement on a binary image. Dilation and erosion are the basic operations that are often used to construct more complex operation namely opening and closing. The combination of these four operations can be devised to tackle more complex problems. A sequence of morphological operations and thresholding was used by Dogdas et al. (2005) to perform skull and scalp segmentation. Cube, 3-D Cross, 3-D Octagon, and their corresponding 2-D structuring elements: square, cross, and octagon have been applied in their study. The T1-W images were used as input for the brain extraction tool. Further, the scalp and skull were segmented using morphological operations and thresholding method. The details of the combination several morphological operations and thresholding can be obtained in Dogdas et al. (2005). Although their method required no user intervention for majority of cases, however, in their experiments manual tuning of the skull threshold parameter was still required for some cases, notably in cases the skull model where contained holes near the eye sockets.

The brain surface extraction was the morphology-based method combination between morphological operations and edge detection developed by Shattuck et al. (2001). The boundaries of the brain anatomic region are first identified using the Marr Hildreth edge detector (Marr and Hildreth, 1980). Next, the tissues were segmented used morphological operators. As the method consisted of the anisotropic diffusion filter and Bias Field Corrector for preprocessing. The main potential disadvantage of the method is that there were too many parameters to be adjusted and the parameters were empirically generated.

In deformable approaches to skull stripping, a brain extraction tool has been developed by (Smith, 2002). A sphere's surface initial inside the brain and using a forces that keep surface deform slowly move to brain's edge. Active contours are deformed and propagated to latch on the boundary of brain. The brain is then segmented from the entire image and non-brain voxels are discarded. In Zhuang et al. (2006), a level-set approach (Osher and Sethian, 1988) has been applied to automate the skull stripping for each slice of MRI image.

2 **Intensity normalization** is used to standardize image intensity scales in MRI for each scan (Nyul and Udupa, 1999; Nyul et al., 2000). Intensity normalization is required because the intensities value on MRI cannot be associated to specific tissue types, unlike CT images where the Houndsfield unit (HU#) can be used to differentiate between various tissue densities. MRI only shows relative intensity differences between various tissues. Therefore, segmentation algorithms, which rely on voxel intensity levels need to be standardized from one image to another for a given scan. (Anbeek et al., 2004; Lao et al., 2006; Zacharaki et al., 2008; Souplet et al., 2008; Bricq et al., 2008; Scully et al., 2008; De Boer et al., 2007, 2009).

3 **Brain tissue segmentation** is used to classify brain tissue voxels into white matter tissue, grey matter tissue and the cerebrospinal fluid. When the voxels belonging to normal WM

tissue are identified, false positive can be reduced by discarding hyper-intense voxels that do not occur within the WM region of the brain. (Admiraal-Behloul et al., 2005; De Boer et al., 2007; Shiee and Bazin, 2008; Bricq et al., 2008; Prastawa M., 2008; De Boer et al., 2009; Beare et al., 2009).

4 **Bias field correction** is used to compensate for the shading effect caused by the MR Scanner receiver coil sensitivity variations (Jack et al., 2001; Zacharaki et al., 2008; Morra et al., 2008; Prastawa M., 2008; Garcia-Lorenzo et al., 2008; Scully et al., 2008; De Boer et al., 2007, 2009; Beare et al., 2009).

5 **Rigid registration** is used correct and re-align the position as well as orientation of particular sequences to reference sequences of MRI (Anbeek et al., 2004; Wen and Sachdev, 2004; Quddus et al., 2005; Lao et al., 2006; Admiraal-Behloul et al., 2005; Wu et al., 2006; Zacharaki et al., 2008; Kroon D., 2008; De Boer et al., 2007, 2009; Beare et al., 2009).

Preprocessing steps are crucial for fully automated methods to ensure accurate segmentation of lesions in each slice. In the proposed work, similar steps of pre-processing are performed and will be further explained in Section 4.3.

2.3.1 Voxel classification approaches

In voxel classification approaches, artificial intelligence-based methods such as k-NN, Fuzzy Inference and Neural Networks have been used for lesion segmentation.

Anbeek et al. (2004, 2008) used k-Nearest neighbours (k-NN) classification method to determine the lesion probability of each voxel. Pre-processing steps which include intensity normalization, rigid registration and skull stripping are applied prior to classification of voxels. In their study, a total of five different sets of features as listed in Table 2.2 are defined. The

Table 2.2: List of features for k-NN classifier.

F	only voxel intensities
F_{xy}	voxel intensities and spatial features x and y
F_{xyz}	voxel intensities and spatial features x, y and z
$F_{\rho\varphi}$	voxel intensities and ρ and φ
$F_{\rho\varphi}$	voxel intensities and ρ, φ and z

coordinate ρ represents the Euclidean distance(x and y) from the center of gravity and φ the angle with the horizontal axis. The voxels in the image are visualized as a probability map where every voxel was determined by k-nearest neighbours and the voxel was examined in the feature space. The lesion probability of every voxel is defined as the fraction of lesion voxels among those K neighbours. The advantage of using probabilities for lesion segmentation is that it provides a way to obtain different binary segmentations. Therefore, segmentations with better agreement to the golden standard that is constructed by a consensus of several radiologists can be produced.

A Fuzzy Inference System (FIS) that uses linguistic variables was investigated by Admiraal-Behloul et al. (2005). This approach included two stages, which are the adaptive stage and reasoning stage. Adaptive stage is used to distinguish image intensity ranges and image contrasts. On the other hand, reasoning stage uses linguistic variables in the FIS to mimic radiologist reasoning. Their framework consists of six main processes which are listed below:

I. Image registration is used to correct possible patient movement. In order to speed up this process the author cropped the images before applying the automatic registration provided by the AIR(Automated image registration) library.

II. Template mapping in Talairach space (Talairach and Tournoux, 1988) was used to classify the brain tissue into intra-cranial (IC), white matter (WM), gray matter (GM) and cerebrospinal fluid (CSF). The atlas used in this classification process is provided by the Montreal Neurological Institute (MNI) (Talairach and Tournoux, 1988). In addition,

authors mention that the success of the whole segmentation is highly dependent on the outcome of this registration.

III. Fuzzification is the process of mapping intensity to linguistic values. It is applied on every sequence of MR image (proton density (PD), T2-W and FLAIR). Authors cluster those images using Fuzzy C-Mean into 3 clusters and every cluster is associated with their label.

IV. Brain stripping is applied to extract the intra-cranial tissue on the proton density(PD) image using the regions obtained through fuzzy clustering. Subsequently, a morphology operation applied on the skull-stripped image to reduce the intracranial/skin "connections" as much as possible. In addition, a region-growing algorithm is applied to segment the Intra-cranial tissue in PD image.

V. CSF and lesion detection are detected using fuzzy membership functions and fuzzy inference rules.

VI. User preference is the step that allows user to specifically identify any brain region on the template image in Talairach space (Talairach and Tournoux, 1988). It is only applicable when running the algorithm for the first time.

The accuracy of this WM Lesion detection approach is highly dependent on accurate registration between the 3-D brain tissue probability model (template or atlas) and spatial information on brain structures. Furthermore, the complete brain data-set is needed to run the process. In addition, inhomogeneity bias correction is not considered in their study. Consequently, severe in-plane inhomogeneity may affect the accuracy of lesion segmentation.

Several other approaches such as support vector machine (SVM) and AdaBoost have also been used as the classification model. These approaches require a training phase prior to WM

lesion segmentation (Quddus et al., 2005; Lao et al., 2006; Zacharaki et al., 2008).

In Lao et al. (2006), SVM was used as a classifier and AdaBoost to reduce training errors. Prior to running the classifier, the following pre-processing steps were performed:

I. Mutual-information-based image registration, to co-register the FLAIR image as the reference to T1-W, T2-W and PD images.

II. Skull-stripping using the Brain Extraction Tool (BET) is then performed. BET is a popular technique for skull stripping and is based on deformable models (Smith, 2002).

III. Intensities normalization is used to correct inhomogeneity across different subjects.

The features used for training are the voxels of each modality(FLAIR, T1-W, T2-W and PD). Each feature vector includes local intensities of corresponding voxels and the intensities of neighbouring voxels from the 4 modalities. Each image modality is smoothed using a Gaussian filter in order to make feature vectors robust to noise. The SVM is then used to classify the WM lesions. Adaboost (Adaptive Boosting) algorithm is a popular iterative procedure (Schapire and Robert, 1997) to adaptively improve the performance of classifiers. The algorithm essentially takes the linear combination of a number of "weak classifiers" to build a "strong" classifier. 45 test subjects were used in the experiment. The method was compared with two manual segmentation results from an experienced rater. Their evaluation methods consists of the Pearson correlation, (PC), Spearman correlation (SC), coefficient of variation (CV) and reliability coefficient (RC). The results obtained show that there is good correlation to manual segmentation performed by the raters. The approach was proven to be consistent and reliable relative to the inter-rater agreement. False positive in this study mainly occur due to the mis-registration in the cortex area and orbital hyperintense regions such as eye and fat. To compensate for the false positives, morphological operation combined with adaptive thresh-

olding were used. In conclusion, SVM and AdaBoost were successfully used to segment WM lesions. This approach can also be adopted to other tissue segmentation and segmentation of atrophy.

SVM and AdaBoost ware also used by Zacharaki et al. (2008) for WM lesion segmentation. 42 participants with diabetes were examined for approximately a 3 year inter-scan period. In their framework, the preprocessing steps included co-registration of multi spectral(sequences) images of the same patient, skull-stripping (Smith, 2002), intensity normalization, and inhomogeneity correction (Sied et al., 1998). The FLAIR image used as the reference to co-register the T1-W, T2-W and PD images. The classification model is built based on a set of training samples which was manually segmented by a radiologist. A binary SVM was used to find an optimal separating hyperplane between the lesion and non-lesion tissue. Finally, the trained model is then used to segment WM lesions. Their experimental results indicated that tiny lesions could be accurately segmented using their approach. Similar to the work by Lao et al. (2006), two types of false positives occured in this study, (i) due to incomplete skull stripping and (ii) due to hyper-intense voxels in the orbital regions attributed to the eye tissue. Therefore, morphological operation is combined with adaptive thresholding to remove the false positive caused by incomplete skull stripping, while the remaining false positives are further compensated by applying unsupervised clustering to detect hyper-intense voxels and then masking out voxels that do not belong to the white matter region. While this supervised classification technique was able to segment WM lesions accurately, however this technique was restricted to a particular training data-set and was dependent on the radiologist's interpretation of WM lesions for its segmentation.

An interesting work proposed by Beare et al. (2009) uses morphological technique to detect potential WM lesions and subsequently use an adaptive boosting classifier to segment WM lesions. In the preprocessing stage, the authors first performed image registration between

the T1 and FLAIR sequences and subsequently classified the WM, GM and CSF in brain images using probability maps obtained from an atlas [1]. Inhomogeneity correction was then performed. The outcome of this preprocessing stage is the WM mask that is used for the lesion segmentation. The extracted WM region is then used as a morphological watershed to produce consistent boundaries to detect potential WM lesions. Several statistical classifiers were used to differentiate true and false WM lesions from the potential WM lesions. These statistical classifiers include recursive partitioning trees, linear and quadratic discriminant classifiers (LDC and QDC respectively), k-nearest neighbours (KNN) and adaptive boosting (ADAb). In summary, authors successfully applied advanced morphology to automate WM lesion segmentation and it is considered a pioneering concept in the WM lesion segmentation problem. The main aim of this work is to detect small and peripheral lesions. However, due to the sensitivity issues in detecting tiny lesions, there is a higher probability of false positives occurring as well. Therefore, careful manual post-processing is still required to remove these false positive.

Dyrby et al. (2008) used an artificial neural network to perform WM lesion segmentation. In this study, 8th degree polynomial was fitted to the mean intensity of each slice to correct for imperfect slice profiles and registration is performed using the SPM2 [2] software. Probability maps provided in SPM2 was used to segment the brain tissues into GM, WM and CSF. N3 correction (Sied et al., 1998) was applied to reduce the shading effect caused by Radio Frequency (RF) inhomogeneity while an intensity standardization algorithm called the *standard z-score* was used to suppress center-specific intensity variations. In their study, artificial neural network was implemented as a fully connected 2-layer feed-forward network. The input feature consists of various voxel intensities such as preprocessed T1W (T1), FLAIR (F), T2W (T2) and 3 x 3 neighbouring voxels (N3x 3) and relative positions in 3-D (Sxyz). Surprisingly, the data-set collected from multiple centers were found to be segmented consistently using the

[1] Montreal Neurological Institute (MNI)

[2] Department of Imaging Neuroscience, www.fil.ion.ucl.ac.uk/spm

proposed neural network segmentation despite using only five subjects as training samples.

Expectation Maximization which is often used for data classification in machine learning was adopted by Garcia-Lorenzo et al. (2008). The modalities used were T1-W, T2-W and FLAIR sequences. In their framework, the intensity in-homogeneity correction was performed on the T1-W and FLAIR sequences. This is then followed by skull stripping using BET. The lesion segmentation framework consists of three important components. These are (1) robust estimation of Normal Appearing Brain Tissues (NABT) parameters, (2) refinement of outliers detection and (3) Application of lesion rules.

In the NABT, image intensities were constructed using a 3-class finite multivariate Gaussian mixture. Each class is associated to a specific brain tissue such as WM, GM and CSF. In order to calculate the optimum parameters to be used in NABT, a modified Expectation Maximization algorithm, called mEM, based on the Trimmed Likelihood (TL) Estimator is employed. The detailed mathematical equations can be found (Garcia-Lorenzo et al., 2008). In the subsequent refinement of outlier detection stage, the Mahalanobis distance between each voxels in the image and each model of the NABT was computed. Thus, the voxels in each image will be defined as outlier when the distance between each class is greater than the threshold value the X^2 law, for a given p-value. To ensure all the potential outliers are detected, p-value was set to 0.4. Therefore, many potential lesion and false positive will be detected in the image. In the next stage, authors applied the lesion rules to distinguish lesions and false positives by defining a heuristic rule: $3.0 \times \sigma_{WM} \pm \mu_{WM}$, where σ_{WM} and μ_{WM} are the standard deviation and the mean of the voxels white matter on T2-W respectively. To further reduce more false positives, Garcia-Lorenzo et al. (2008) discard lesions smaller than 3 mm^3.

In summary, notable drawbacks of voxel classification-based approaches are that (i) there is a requirement for a representative sample of radiologist segmentations to be made available