AUTOMATIC WHITE MATTER LESIONS DETECTION AND SEGMENTATION OF BRAIN MAGNETIC RESONANCE IMAGES

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To my family, especially my wife for the nice cuppas of coffee every night. Thanks for her encouragement and support. Her constant love have sustained and motivate me throughout my life.

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ABSTRACT

White matter lesions (WML) are frequently associated with neuronal degeneration in ageing and can be an important indicator of stroke, multiple sclerosis, dementia and other brain-related disorders. WML can be readily detected on Magnetic Resonance Imaging (MRI), but manual delineation of lesions by neuroradiologists is a time consuming and laborious task. Furthermore, MRI intensity scales are not standardised and do not have tissue-specific interpretation, leading to WML quantification inaccuracies and difficulties in interpreting their pathological relevance. Numerous studies have shown tremendous advances in WML segmentation, but flow artefact, image noise, incomplete skull stripping and inaccurate WML classification continue to yield False Positives (FP) that have limited the reliability and clinical utility of these approaches. The present study proposed a new MRI intensity standardisation and clustered texture feature method based on the K-means clustering algorithm. Enhanced clustered texture features and histogram features were constructed based on the proposed standardisation method to significantly reduce FP through a Random Forest algorithm. Subsequently, a local outlier identification method further refined the boundary of WML for the final segmentation. The method was validated with a test set of 32 scans (279 images), with a significant correlation coefficient (R=0.99574, p-value $<$ 0.001) between the proposed method and manual delineation by a neuroradiologist. Furthermore, comparison against three state-of-the-art methods for the 32 scans demonstrated that the proposed method outperformed five of seven well-known evaluation metrics. This improved specificity in WML segmentation may thus improve the quantification of clinical WML burden to assess for correlations between WML load and distribution with neurodenegerative disease.

ABSTRAK

Lesi Jirim Putih (WML) sering dikaitkan dengan degenerasi neuron dalam penuaan dan boleh menjadi petunjuk penting bagi strok, sklerosis berganda, demensia dan kecelaruan lain yang berkaitan dengan otak. WML boleh dikesan dengan mudah dengan Pengimejan Resonans Magnetik (MRI), tetapi penentuan lesi secara manual oleh ahli neuroradiologi adalah tugas yang sukar dan memakan masa. Selain itu, skala intensiti MRI yang tidak diseragamkan dan tidak mempunyai tisu tafsiran yang khusus akan membawa kepada ketidaktepatan kuantifikasi WML dan kesulitan dalam menafsirkan patologi berkaitannya. Banyak kajian telah menunjukkan kemajuan yang besar dalam segmentasi WML, tetapi artifak aliran, hingar imej, pengasingan tengkorak yang tidak lengkap dan klasifikasi WML yang tidak tepat terus menghasilkan Positif-Palsu (FP) yang membatasi kebolehpercayaan dan utiliti klinikal pendekatan-pendekatan tersebut. Kajian ini mengusulkan kaedah penstabilan intensiti MRI baru dan kaedah ciri tekstur berkumpulan berdasarkan algoritma pengumpulan K-purata. Ciri-ciri tekstur yang dipertingkatkan dan ciri histogram yang dibina berdasarkan kaedah penstabilan telah dicadangkan untuk mengurangkan FP secara signifikan melalui algoritma *Random Forest*. Seterusnya, kaedah pengenalpastian luar tempatan menapis sempadan WML untuk memperoleh segmentasi akhir. Kaedah ini telah disahkan dengan set ujian 32 imbasan (279 imej), dengan pekali korelasi yang signifikan (R = 0.99574, nilai-p < 0.001) antara kaedah yang dicadangkan dengan manual yang digariskan oleh ahli neuroradiologi. Tambahan pula, perbandingan terhadap tiga kaedah yang terkini untuk 32 imbasan menunjukkan bahawa kaedah yang dicadangkan mengatasi lima daripada tujuh metrik penilaian terkenal. Ini meningkatkan kekhususan segmentasi WML, justeru akan menyenangkan kuantifikasi WML klinikal untuk menilai hubungkait di antara jumlah WML dan pengedaran dengan penyakit neurodenegeratif.

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LIST OF ABBREVIATIONS

Acc	–	Accuracy
AD	–	Average Distance
ASD	–	Average Symmetric Surface Distance
BET	–	Brain Extraction Tool
BSE	–	Brain Surface Extractor
CAVASS	–	Computer Aided Visualization and Analysis Software System
CT	–	Computed Tomography
CV	–	Coefficient of Variation
DICOM	–	Digital Imaging and Communication in Medicine
DI	–	Dice Index
DSI	–	Dice Similarity Index
EF	–	Extra Fraction
EM	–	Expectation Maximization
FCM	–	Fuzzy C-Mean
FLAIR	–	Fluid Attenuated Inversion Recovery
FN	–	False Negative
FNR	–	False Negative Rate
FP	–	False Positive
FPR	–	False Positive Rate
FWHM	–	Full Width at Half Maximum
GLCM	–	Gray Level Co-occurrence Matrix
GPGPU	–	General Purpose Computing on Graphics Processing Units
HU	–	Houndsfield Unit
HMC	–	Hidden Markov Chain
ICBM	–	International Consortium for Brain Mapping

ICC	–	Intraclass Correlation Coefficient
IOI	–	Intensity of Interest
IQR	–	Inter Quartile Range
JI	–	Jacard Index
KL	–	Kullback-Leibler
kNN	–	k-Nearest Neighbor
Lin	–	Corresponding Linear Coefficient
LOF	–	Local Outlier Factor
LPA	–	Lesion Prediction Algorithm
NAWM	–	Normal Appearing White Matter
MAE	–	Mean Absolute Error
MICCAI	–	Medical Image Computing and Computer Assisted Intervention
MRI	–	Magnetic Resonance Imaging
MRF	–	Markov Random Field
MS	–	Multiple Sclerosis
OF	–	Overlap Fraction
OSR	–	Over Segment Rate
PD	–	Proton Density
PPV	–	Positive Predictive Value
R	–	Correlation Coefficient
RF	–	Random Forest
SLS	–	SALEM-LS
SPM	–	Statistical Parametric Mapping
SVM	–	Support Vector Machine
TL	–	Trimmed Likelihood
TMOD	–	Trimmed Mean Outlier Detection

TN	–	True Negative
TNR	–	True Negative Rate
TP	–	True Positive
TPR	–	True Positive Rate
TTPs	–	Tissue Type Priors
T1-W	–	T1-Weighted
T2-W	–	T2-Weighted
USR	–	Under Segment Rate
VD	–	Volume Different
WML	–	White Matter Lesion

LIST OF SYMBOLS

$\emptyset$	–	Zero level set
$\emptyset(x, y)$	–	Level set
F_{curv}	–	Morphological smoothing force
F_{img}	–	Brain surface attraction force
I_{max}	–	Local maximum of intensity
MAX	–	Maximum elements of an array
MIN	–	Minimum elements of an array
v	–	Measured signal
u	–	True signal reflex from tissue
f	–	Function of the unknown shading signal
n	–	Gaussian noise
$\hat{u}$	–	Independent variable of U distribution
$\hat{v}$	–	Independent variable of V distribution
$\hat{f}$	–	Independent variable of F distribution
U	–	Probability densities of $\hat{u}$
V	–	Probability densities of $\hat{v}$
F	–	Probability densities of $\hat{f}$
ω	–	Smoothing parameter
$\hat{F}*$	–	Complex conjugate of the Fourier transform of F
$\mu_{i,j}^{k}$	–	Fuzzy membership function of a voxel in coordinate i, j with k constant value of fuzziness
C_i	–	Number of cluster centroids
f_3	–	Outlier
F_3	–	Extreme outlier
Q_1	–	25 percentile of the voxel distribution

Q_3	–	75 percentile of the voxel distribution
σ	–	Standard deviation
μ	–	Mean
T	–	Threshold parameter
Θ_k	–	A set of random features vector of k
n	–	Number of elements
P_{cl}	–	Local minimum point at the left side of distribution
P_{cr}	–	Local minimum point at the right side of distribution
P_{1i}	–	Left landmark constructed from a histogram based on the outlier detection approach
P_{2i}	–	Right landmark constructed from a histogram based on the outlier detection approach
V_{FLAIR}	–	Volume image of the FLAIR MR sequence
$g_i(x;y)$	–	Intensity function in two dimensions
$L1$	–	Landmark 1 (left) of a standard intensity scale
$L2$	–	Landmark 2 (right) of a standard intensity scale
H_i	–	Histogram of i preprocessed brain image slice
P_{before}	–	The probability intensity distribution before image standardisation
P_{after}	–	The probability intensity distribution after image standardisation
Img_{before}	–	The image slice before standardisation process
Img_{after}	–	The image slice distribution after standardisation process
F_{before}	–	The feature extracted before standardisation process
F_{after}	–	The feature extracted slice distribution after standardisation process
$P(g)$	–	Discrete probabilities of gray levels image intensity
$Prob(i,j)$	–	Discrete probabilities of gray level co-occurrence matrix

α	–	Training data
β	–	Testing data
$d(o_\alpha, p_\alpha)$	–	Nearest distances in between o_α voxel intensity to p_α voxel intensity
$MinPts_\alpha$	–	Minimum number of voxel intensity under training dataset
lrd	–	Local reachability distances
R	–	Pearson correlation
$*$	–	A statistical significance level of 0.05, where p-value < 0.05
$**$	–	A statistical significance level of 0.01, where p-value < 0.01
$***$	–	A statistical significance level of 0.001, where p-value < 0.001
$Vol(S_{auto})$	–	Volume of WML segmented by automated method
$Vol(GT)$	–	Volume of WML delineated by neurologist
$BP(S_{auto})$	–	Boundary point of WML extracted by automated method
$BP(GT)$	–	Boundary point of WML identified by neurologist
$\pm$	–	Plus or minus indicates a choice of two possible number

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CHAPTER 1

INTRODUCTION

1.1 Overview

White Matter Lesion (WML) are the region of the dead cell in the white matter tissue areas of the brain. WML are commonly known as white matter change, white matter hyperintensity or *Leukoaraiosis*. They are generally developed and found in the brain of elderly people. The ageing population is growing rapidly worldwide and the number of people over 65 years old or older is expected to triple to nearly 1.5 billion by 2050. This figure is about 16% of the population worldwide (WHO, 2011).

Many clinical research studies have shown that WML are predictors of several brain diseases. They included Multiple Sclerosis (MS) (Bagley *et al.*, 1999; He *et al.*, 2009; Werring *et al.*, 2000), Vascular dementia (Cavalieri *et al.*, 2010; Debette and Markus, 2010; Diniz *et al.*, 2013; Mortamais *et al.*, 2014; Peters and Dichgans, 2010), Ischemic strokes (Debette and Markus, 2010; Yamauchi *et al.*, 2002), and Alzheimer's disease (Cavalieri *et al.*, 2010; Diniz *et al.*, 2013; McAleese *et al.*, 2017; Park *et al.*, 2010). These research studies have also shown that WML are one of the leading cause of later-life depression, gait disorders, cognitive decline and mild cognitive impairment which often happen in the elderly population (Diniz *et al.*, 2013; Launer, 2004; Mortamais *et al.*, 2014; O'Sullivan, 2008; Silbert *et al.*, 2008; Veselý and Rektor, 2016). Coincidentally, mobility impairment and hypertension are the most common compared to other chronic diseases; and disability have been reported in WHO (2011).

In a recent analysis, it has been estimated that about 27 to 36 million older population worldwide are suffering from Dementia and Alzheimer disease (WHO, 2011). Until today, no robust test has been able to predict these chronic diseases on elderly people. Therefore, assessment of WML load could be a fast and effective channel used to detect neurological disorders in the early stage. These lesions can be detected and diagnosed by noninvasive imaging techniques such as magnetic resonance imaging in several pulse sequences. They are T1-Weighted (T1-W), T2-Weighted (T2-W), Fluid Attenuated Inversion Recovery (FLAIR) and Proton Density (PD). Specifically, FLAIR sequence shows that WML are hyperintensed (bright) voxels that are different in appearance from the adjacent cerebrospinal fluid. Due to the prominence and easy visibility of the WML (Appenzeller *et al.*, 2008), FLAIR sequence is a prominent sequence preferred by neuro-radiologists to detect WML. However, manual assessment or visual score assessment of WML could be a painful and tedious process for a neuro-radiologist. This is mainly because it requires evaluation of twenty to hundreds of image slices of cranial images from a particular sequence per subject. Hence, WML assessment using automatic computation to quantify white matter lesion load is the preferred choice of a neuro-radiologist.

1.2 Research background

White matter lesions are abnormal tissues which occur in white matter. They indicate the damage of the myelin sheath that surrounds the axon of a neurone. When signals transited by axon is interrupted, the process is named as neurodegeneration and also known as demyelination. This results in several brain disorders such as Vascular dementia, multiple sclerosis, ischemic strokes and Alzheimer's disease. The characteristics of white matter lesions vary in shape, size and distribution. They are usually detected and visualised as a brighter (hyperintensity) region in white matter region on FLAIR images as shown in Figure 1.1

The visual assessment of white matter lesions is usually performed by experienced neuroradiologists to identify and locate the WML; and subsequently, rate their severity or measure lesion load. To date, there are two common approaches that have been used in assessments by current clinical practice; (a) visual scoring assessment and (b) quantitative measurements.

Visual scoring assessment rates the severity of white matter lesions on the MRI with bare eyes. Many visual scoring methods have been proposed in the literature. It is found that the most well-known visual scoring methods are the Scheltens scale (Scheltens *et al.*, 1993), the Fazekas scale (Fazekas *et al.*, 1987) and the age-related white matter changes (ARWMC) scale (Wahlund *et al.*, 2001). The advantage of using

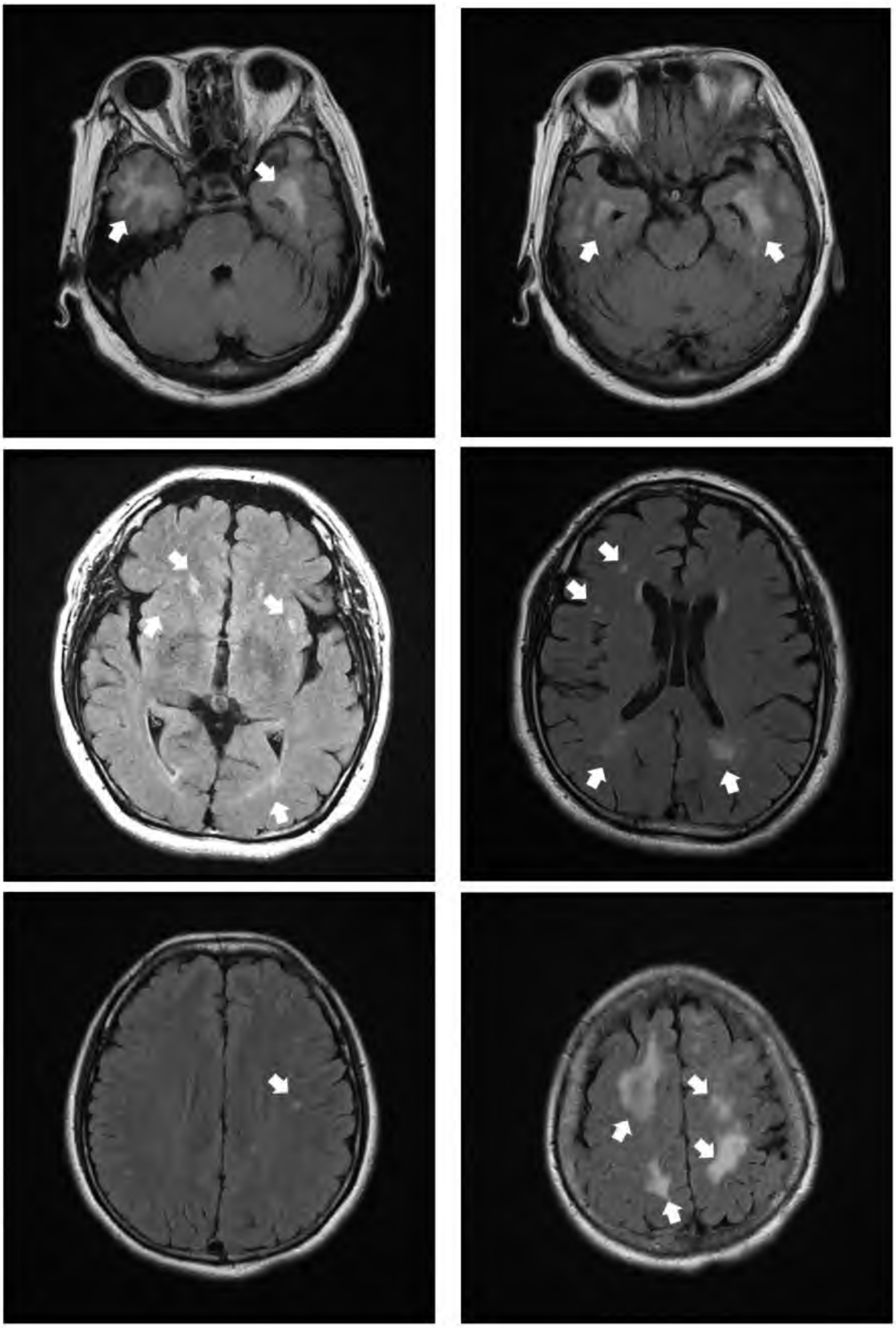

Figure 1.1 FLAIR MR Images (axial view) on 1.5T MRI scans. Arrows indicate the presence of lesions.

visual scoring method is it is easy to be implemented and the approaches do not require high computational performance computer-aided analysis in the assessment process. In a recent study, the assessment of WML can be evaluated by Fazekas visual rating scale without influent by stroke lesions in the subjects at risk of developing stroke during follow-up as reported by Hernández *et al.* (2013). However, visual assessment often shows a high variation of intra- and inter-reader agreement. It becomes challenging when it is applied on a longitudinal cohort study of elderly people. Several difficulties of visual scoring methods have been reported by Enzinger *et al.* (2007):

1. The result of visual scoring such as reproducibility, sensitivity and specificity are highly dependent on the specific visual scoring scale.
2. The scoring exercised by the neuroradiologist is different from that in various medical institutions. Hence, result used for comparison is very subjective for large scale WML progression studies.
3. A trained neuroradiologist is required to perform visual scoring manual with bare eyes, which is a laborious, painful and tedious process.

Besides the visual scoring assessment, WML load quantification is the approach preferred by clinicians. Quantification refers to the sum of the voxel that is indicated in WML region and associated with image calibration value to determine the WML load (mL). In fact, the automation of the lesion quantification process consists of varying levels, from fully manual segmentation, to semi-automated and fully automatic WML detection and segmentation. The fully manual segmentation typically requires an observer to outline the WML region manually by using the annotation tool provided in the image analysis software package. Semi-automated WML detection refers to the manual detection involving artificial intelligent techniques to segment the WML region, where they often require a “seed” of WML location that is detected by an observer and let the algorithm to segment WML region. The fully automated WML segmentation often does not require human intervention; their implementation is much complicated and requires advance artificial intelligent techniques such as machine learning.

White matter lesions assessment such as visual scoring approach remains a labour intensive and tedious work for radiologists. The visual assessment is the most common method of approach that is often applied in clinical practice due to the simple implementation. However, interpretation of visual scoring is very subjective since the judgement of the lesion shape, size and its distribution varies from one radiologist to another. Therefore, the scores given by different radiologists are considered as variables. This becomes an important question to perform large scale clinical studies, and it may not be practical to perform visual scoring assessment. Therefore, automatic examination of white matter lesions using computation is the preferred choice of a radiologist. The automated solution can fast detect and quantify the white matter lesions accurately. Up to now, the automatic lesion segmentation and quantification using computation approach suffers from several drawbacks. Details of the elaboration of these drawbacks using existing methods will be discussed in Chapter 2. It is pertinent to mention here that many exisitng approaches either need minimal human intervention to eliminate false positive, or they are not effective in reducing the false positive lesion because simple morphology operations are performed.

1.3 Research statement

Several challenges have been identified and addressed to improve white matter lesion segmentation results. First, it is difficult to determine tissue intensity range between white matter lesions and healthy brain due to the lack of standardisation of MRI intensities. Second, MR image artefact and inaccurate white matter lesion segmentation produce many false positive lesions. Third, the edge of white matter lesions is fuzzy and diffused. It makes it complicated to differentiate between voxels of white matter and white matter lesions. Therefore, a challenge for automated approaches to a segment between the voxels of healthy tissues and white matter lesion, furthermore to reduce false positive.

Based on the statement above, the research questions that need to be addressed are:

1. What is the suitable method to accurate and sensitive to WML segmentation on MRI that has been evaluated with the dataset from multicentre?
2. It is difficult to determine tissue intensity range between white matter lesions and healthy brain due to the lack of standardisation of MRI intensities. How

to standardise the image intensity range on MRI to improve the classification results that caused by the intra-scan and inter-scan image intensity variations due to the MRI instrumentation?

3. Image artefact and inaccurate white matter lesion segmentation by TMOD method produce many false positive lesions. Hence, how can the proposed cluster-based texture feature and histogram intensity feature to classify them into (False Positive) FP and WML?

4. The edge of white matter lesions is fuzzy and diffused. It makes it difficult to differentiate between voxels of white matter and white matter lesions. Can the proposed LOF scheme able to address this problem?

5. How can the performance of proposed WML segmentation be evaluated by the quantitative and qualitative method?

1.4 Research objectives

Quantification of white matter lesions loaded by manual delineation is time-consuming and labour intensive to neuro-radiologists. In addition, bare eyes and delineation by hand on fuzzy and diffused white matter lesion is challenging and tedious. This study proposes an automatic white matter lesion segmentation and quantification system. Therefore, the objectives of the study are listed as follows:

1. To propose an image intensity standardisation method to improve the accuracy of WML detection.

2. To propose a new cluster-based grey-level co-occurrence matrix (GLCM) texture feature to identify true positive (white matter lesions) and eliminate false positive (incomplete skull stripping region, FLAIR artefact, and image noise).

3. To propose an accurate white matter lesion boundary delineation by using Local Outlier Factor (LOF) scheme.

4. To validate the proposed method using benchmark method and evaluation metrics compare to gold standards (neuroradiologist delineation).

1.5 Contributions of the study

Three significant expected contributions can be concluded in this research study:

1. Delivering an automatic intensity standardisation algorithm to standardise MRI intensity scale adaptively for different subjects and its different time points especially for large scale WML analysis study.
2. Developing cluster-based texture feature and standardising image intensity feature to identify tiny lesions (true positive) and MRI artefact (false positive) accurately.
3. Implementing an automated white matter lesion segmentation using voxels based on local outlier detection technique.

1.6 Research overview

The research methodology of this research study focuses on the proposed WML detection and segmentation method. The method is implemented based on new enhanced standardisation intensity features and clustered texture features to identified as WML. The boundary of WML is further determined based on LOF scheme. Figure 1.2 present the overview of the conducted research.

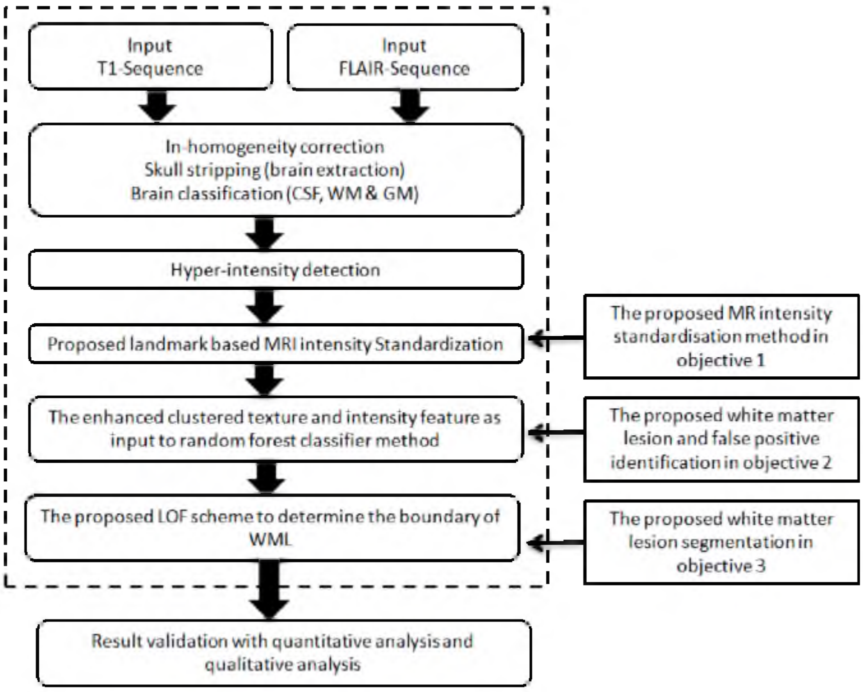

Figure 1.2 The overview of proposed research flow.

T1-w sequence and FLAIR sequence of MRI are used as inputs for the proposed method. They are obtained from the clinical study of the protective effects of palm vitamin E tocotrienols on brain white matter (Gopalan *et al.*, 2014). Both of the sequences are first pre-processed with the in-homogeneity correction to reduce Field inhomogeneity artifact (Sled *et al.*, 1998). FLAIR sequence is the preferred imaging sequence used to detect and visualise the white matter lesions by radiologists. This is mainly because voxel of white matter lesion appearances are the brightest and also known as hyper-intensity compared to voxels of healthy brain tissue (grey matter and white matter). However, the additional voxels such as skull and optic nerves also appear in hyper-intensity voxels. Hence, skull stripping process is required to obtain brain voxels. T1-w is the suitable sequences used to prepare skull stripping image data proposed by Zhuang *et al.* (2006) since it provides promising contrast between hard and soft tissues. Thus, T1-w is used as input for skull stripping process. Extracted brain voxel and its regions are then used as a mask to FLAIR sequence to obtain brain only voxels. They are further used to detect and segment white matter lesions.

Additionally, the lack of intensity standardisation on MRI has often caused difficulty when operating with the supervised learning approach to detect and segment white matter lesions. Hence, a new intensity standardisation on MRI is proposed. Details of the proposed method is described in Chapter 3. In general, the approach applies the WML detection method proposed by Ong *et al.* (2012) to detect the potential white matter lesions (hyperintensity region). The detected hyperintensity region is used as an input to compute the cluster-based texture feature and standardise image intensity feature. These proposed features are used to further classify the true positive lesion and false positive lesion using random forest algorithm. Random forest is preferred in the study because it has been validated and reliable performance compared with ten different classification method in segmenting WML as reported by (Dadar *et al.*, 2017) recently. The details of the proposed algorithm will be further discussed in Chapter 4. The proposed method is robust and efficient to WML segmentation and identify false positive that consists of incomplete skull stripped data, noise artefact of MRI and imaging artefact (Bailey, 2007) such as *peri-ventricular flow artefact.* Subsequently, the region boundary of all true positive of the lesion will be redefined with Local outlier factor scheme. Thus, the output of this step is the final segmented WML. The proposed methods are validated with MR image datasets obtained from Tocotrienols and Neuroprotection study (Gopalan *et al.*, 2014).

Lastly, qualitative and quantitative analysis is performed in image detection and segmentation evaluation. It is crucial to review the quality output as the outcome images will explain the illustration of experimental results. Moreover, a quantitative analysis of the various evaluation metrics is proposed to evaluate the dissimilarity and accuracy of ground truth and segmented WML. For the qualitative analysis, the binary output of segmented WML by proposed methods was superimposed on top of an original 2D image for visual agreement purpose. Also, three dimensional WML and brain were reconstructed to understand the overview of segmentation and false positive reduction performance.

1.7 Research scope and limitation

The proposed method is aimed to reduce white matter lesion segmentation and false positive from brain MR images. The sequence of the MR modality used in this study is limited to 2-Dimensional axial resolution T1-W and FLAIR sequence. 16-bit DICOM image with matrix 512x512 voxels will be only used in this study. Besides, the use of longitudinal WML dataset not taken into consideration in the current study although WML is a progressive brain disorder. The JAVA programming language and Matlab scripting language have been chosen used to develop the proposed method to speed up the implementation of the research work. The limitation of the study is the proposed MR intensity standardisation method was only employed on brain extracted dataset. Also, the proposed cluster-based texture features using random forest algorithm successfully addressed the differentiation of voxels between the FP and white matter lesions, it has not addressed the challenges faced when differentiating white matter lesions from the cortical grey matter on FLAIR, due to low contrast between normal grey matter and white matter hyperintensities on FLAIR. This becomes particularly important when segmenting white matter hyperintensities that are located in subcortical and juxtacortical white matter as opposed to the hyperintensities in the areas further away from the cortical grey matter such as periventricular and deep white matter.

1.8 Thesis organisation

This thesis is organised according to the work involved in the proposed automated WML segmentation and false positive elimination method.

Chapter 1 presents the objective of the studies by reviewing the research area and the research background. The scope, limitation, contribution of research and research overview are also highlighted.

Chapter 2 presents an intensive review of the literature in the field of white matter lesion segmentation and their false positive elimination approach. A critical discussion on the advantages and disadvantages of different types of automated WML segmentation approaches is put forward.

Chapter 3 explains the research methodology that consist of data preparation, research framework, research operational procedure, principal and theoretical background of the proposed algorithms applied in this WML segmentation study.

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