ENHANCED ALZHEIMER'S DISEASE CLASSIFICATION SCHEME USING 3D FEATURES

AOW YONG LI YEW

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DEDICATION

I dedicated this thesis to God my strength, my hope, wisdom and understanding. I also dedicated this work to my parents for their love and support throughout my life.

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ABSTRACT

Alzheimer's disease (AD) is a neurodegenerative brain illness that leads to death due to complications. Many studies on AD classification with Magnetic Resonance Imaging (MRI) images were conducted to act as a computer-aided diagnosis. Feature extraction and feature selection were performed to reduce the number of features and extract significant features concurrently. However, the classification of stable mild cognitive impairment (SMCI) and progressive mild cognitive impairment (PMCI) is far from satisfactory due to the high similarity between the groups. Therefore, this research aimed to enhance the AD classification scheme to solve the problem. The proposed method has included shape enhancement before feature extraction to maximize the difference between healthy patients (normal control (NC)+SMCI) and sick patients (PMCI+AD). The sick patient has a thinner brain boundary compared to a healthy patient. Therefore, a 3D opening morphological operation was proposed to eliminate the thinner boundary and restore the thicker boundary. After that, the proposed 3-level 3D Discrete Wavelet Transform (DWT) and Principal Component Analysis (PCA) were combined for feature extraction. Using the Haar filter, 3-level 3D-DWT extracted 3D significant features to improve the classification result. PCA further reduced the number of features by projecting the training set and test set to lower-dimensional space. The number of features was greatly reduced from 2,122,945 to 159. Feature selection was removed from the proposed scheme after realizing the process would eliminate important features to segregate the classification groups. Linear Support Vector Machine (SVM) was employed to perform binary classification. The proposed scheme achieved higher mean accuracy compared to the previous method, which was from 79% to 80%, from 81% to 84%, from 80% to 84 % on the datasets collected at time points of 24 months, 18 months before stable diagnosis and at the stable diagnosis time point, respectively.

ABSTRAK

Penyakit Alzheimer (AD) adalah penyakit neurodegeneratif yang menyebabkan kematian akibat komplikasi. Banyak kajian mengenai klasifikasi AD menggunakan Pengimejan Resonans Magnetik (MRI) telah dijalankan untuk bertindak sebagai alat sokongan dalam diagnosis berbantukan komputer. Pengekstrakan ciri dan pemilihan ciri telah dilakukan untuk mengurangkan bilangan ciri dan mengekstrak ciri penting secara serentak. Walau bagaimanapun, klasifikasi kemerosotan kognitif ringan stabil (SMCI) dan kemerosotan kognitif ringan progresif (PMCI) adalah jauh dari memuaskan kerana persamaan yang tinggi antara kumpulan. Oleh itu, kajian ini bertujuan untuk mempertingkatkan skim klasifikasi AD bagi menyelesaikan masalah tersebut. Skim yang dicadangkan telah merangkumi penambahbaikan bentuk sebelum pengekstrakan ciri untuk memaksimumkan perbezaan antara pesakit yang sihat (kawalan normal (NC)+SMCI) dan pesakit yang sakit (PMCI+AD). Pesakit yang sakit mempunyai sempadan otak yang lebih nipis berbanding pesakit yang sihat. Oleh itu, operasi morfologi pembukaan 3D telah dicadangkan untuk menghapuskan sempadan yang lebih nipis dan memulihkan sempadan yang lebih tebal. Selepas itu, gabungan Transformasi Gelombang Diskrit 3D (3D-DWT) 3-peringkat dan Analisis Komponen Utama (PCA) telah digunakan untuk pengekstrakan ciri. Menggunakan penapis Haar, 3D-DWT 3-peringkat berjaya mengekstrak ciri penting 3D untuk meningkatkan keputusan klasifikasi. PCA mengurangkan lagi bilangan ciri dengan mengunjurkan set latihan dan set ujian ke ruang berdimensi lebih rendah. Bilangan ciri telah dikurangkan dengan banyak daripada 2,122,945 kepada 159. Pemilihan ciri telah dialih keluar dari skim yang dicadangkan setelah menyedari proses tersebut akan menghapuskan ciri penting yang memisahkan kumpulan klasifikasi. Mesin Penyokong Vektor (SVM) linear telah digunakan untuk melaksanakan klasifikasi binari. Skim yang dicadangkan mencapai ketepatan purata yang lebih tinggi berbanding kaedah sebelumnya, iaitu dari 79% kepada 80%, dari 81% kepada 84%, dari 80% kepada 84% pada data set yang dikumpulkan pada masa 24 bulan, 18 bulan sebelum diagnosis stabil dan pada titik masa diagnosis yang stabil masing-masing.

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LIST OF ABBREVIATIONS

ACC	-	Accuracy
AD	-	Alzheimer's Disease
ADNI	-	Alzheimer's Disease Neuroimaging Initiative
ALBSPM-TOP	-	Advanced Local Binary Pattern Sign Magnitude from Three Orthogonal Planes
aMCI	-	Amnestic MCI
ANN	-	Artificial neural networks
AUROC	-	Area under receiver operating characteristic
CAD	-	Computer aided diagnosis
CAT12	-	Computational Anatomy Toolbox
CCA	-	Cross-sectional area
CF	-	Choroid fissure
CIR	-	Circularity
CNN	-	Convolutional neural network
CT	-	Computerized Tomography
CVP	-	Cross-validation partition
DARTEL	-	Diffeomorphic Anatomical Registration through Exponentiated Lie algebra algorithm
Db	-	Daubechies wavelet
DWT	-	Discrete wavelet transform
ECOC	-	Error correcting output codes
EN	-	Elastic net
EO-AD	-	Early-onset Alzheimer's Disease
ERC	-	Entorhinal cortex
FDG-PET	-	Fluorodeoxyglucose Positron Emission Tomography
FDR	-	Fisher's discriminant ratio
FE	-	AD classification scheme which involves pre-processing, feature extraction and classification
FE + FS	-	AD classification scheme which involves pre-processing, feature extraction, feature selection and classification

FN	-	False negative
FP	-	False positive
GM	-	Grey matter
HarP	-	Harmonized segmentation protocol
HB	-	Hippocampal body
HH	-	Hippocampal head
HT	-	Hippocampal tail
ICA	-	Independent component analysis
Isomap	-	Isometric feature mapping
KNN	-	K-nearest neighbour
kSVM-DT	-	Kernel support vector machine decision tree
L1	-	Lasso regularization
LBP	-	Local binary pattern
LDA	-	Linear discriminant analysis
LLE	-	Local linear embedding
LR	-	Logistic regression
Mb	-	Mammillary bodies
MCI	-	Mild cognitive impairment
mMCI	-	Multidomain mild cognitive impairment
MMSE	-	Mini Mental State Examination
MRI	-	Magnetic Resonance Imaging
MR	-	Magnetic Resonance
MTA	-	Medial temporal lobe atrophy
MTL	-	Medial temporal lobe
NC	-	Normal control
(NC+SMCI)	-	Healthy patients
NIPALS	-	Non-linear iterative partial least square
NN	-	Neural network
OASIS	-	Open Access Series of Imaging Studies database
OPLS	-	Orthogonal partial least squares to latent structures
PC	-	Principal component
PCA	-	Principal component analysis
PET	-	Positron Emission Tomography

PKPCA	-	Polynomial kernel PCA
PLS	-	Partial least square
PMCI	-	Progressive mild cognitive impairment
(PMCI+AD)	-	Sick patients
PSO	-	Particle swarm optimization
Pwm	-	White matter of parahippocampal
PZM	-	Pseudo Zernike moments
QP	-	Quadratic programming
RBF	-	Radial basis function
RFE	-	Recursively feature elimination
ROI	-	Region of interest
Rs	-	Rhinal sulcus
SBS	-	Sequential backward selection
SDM	-	Soft discriminant maps
SEN	-	Sensitivity
SFS	-	Sequential forward selection
SMCI	-	Stable mild cognitive impairment
SMO	-	Sequential minimal optimization
SPE	-	Specificity
SPM	-	Statistical Parametric Mapping
SVD	-	Singular value decomposition
SVM	-	Support vector machine
Sym	-	Symlet wavelet
TN	-	True negative
TP	-	True positive
Trees	-	Decision trees
UMCI	-	Unknown MCI
VBM	-	Voxel-based morphometry
VBM8	-	Voxel-based Morphology software
VT	-	Variance threshold
WM	-	White matter

LIST OF SYMBOLS

A, B, C	-	Example of 3D images
(a x b x c)	-	Size of structuring element
β	-	Regularization value
C	-	The number of classification groups
Cov	-	Covariance
d	-	Bias
e, s	-	Residuals in PLS
f	-	Structuring element
g	-	Neighbour pixels
h	-	High pass filter
i, j	-	Indices of 1D image
$K(z_i, z_j)$	-	Kernel function
k	-	Classification group
l	-	Low pass filter
M	-	Mixing matrix of ICA
m	-	Total number of samples
μ	-	Mean
n	-	Total number of features of the image
P	-	Scaling
(p, q, r)	-	Indices of the 3D image
Q	-	Translation parameters
S	-	Source matrix of ICA
$[S_1]$, $[S_2]$, $[S_3]$	-	Different AD schemes
S_B	-	Between-class scatter matrix
Σ	-	Singular values
S_W	-	Within-class scatter matrix
T	-	Transpose matrix
t_i	-	The *i* component from the projection of *X* in PLS
U	-	Left singular vector

u_i	-	The *i* component from the projection of *y* in PLS
V	-	Right singular vector or principal components
σ^2	-	Variance
v_i	-	The weight of u_i component
w	-	Weight
w_i	-	The weight of t_i component in PLS
X	-	Training set
x	-	Each sample
ξ	-	Distance of the outliers in SVM
X_t	-	Test set
X_{test}	-	Projected test set obtained from PCA
X_{train}	-	Projected training set obtained from PCA
y	-	Label
$\ominus$	-	Erosion
$\oplus$	-	Dilation

CHAPTER 1

INTRODUCTION

1.1 Background

Alzheimer's Disease (AD) is the degenerative brain disease which even leads to death due to complications (Alzheimer's Association, 2020). It is the most common cause of dementia, which is estimated around 60% to 80% of cases. The person suffers AD involves brain changes. It leads to several symptoms, such as memory deficit, communication impairment and disorientation. World Alzheimer Report 2015 estimated that there are 46.8 million people suffer for dementia in year of 2015 and number will increase almost double every 20 years in the worldwide (Prince *et al.*, 2015). It is a large number of people will be affected but the disease has no cure. Therefore, the early detection of AD is to help in improving the life quality of the patient.

In clinical diagnosis, Magnetic Resonance Imaging (MRI) is the commonly used brain imaging technique to assess the cognitive impairment level of a patient due to it is free from ionizing radiation (Soucy *et al.*, 2013). MRI displays the soft tissues of the brain in three dimensional. Therefore, structural MRI provides the information about shape, size, and integrity of grey matter and white matter. A repeat MRI scans will be required to observe the biomarkers. Biomarkers are the measurements that show the biological and pathological processes of normal and abnormal brain in AD diagnosis. In AD diagnosis, atrophy of the brain is one of the supportive neurodegeneration biomarkers. The assessment can be done through visual scoring or volumetry (Dubois *et al.*, 2007).

The existing computer aided diagnostics (CAD) for AD detection or AD classification can be divided to four categories, which are voxel-based, sliced-based, patched-based and region of interest (ROI) based methods (Ebrahimighahnavieh *et al.*,

2020). Voxel-based involves whole brain measurement which provides 3-dimensional (3D) information of the brain. But it is high computational due to high dimensional data, and it neglects the local information since each voxel is treated independently. Sliced-based approach or 2D based approach simplifies the classification model, but it loses the information about the relationship between the slices. Patched-based approach is sensitive to the small changes, but it is hard to select the most significant patches. ROI-based concentrates on the significant brain region for AD diagnosis. This avoids the high dimensional data, but it loses the information on other parts of the brain.

In AD classification, the research was conducted to compare different stages of AD. The normal control (NC) is the healthy subject who is free from the disease. AD refers to the patient suffers the disease while mild cognitive impairment (MCI) refers to the patient suffers symptoms of AD. However, MCI can be categorized to stable MCI (SMCI) or progressive MCI (PMCI). SMCI refers to the patient remains in MCI after the follow up, while PMCI refers to the patient converts to AD after a certain of period. Currently, the AD classification achieved good result in the discrimination of AD patient from NC, even in distinguishing MCI patient. However, there is room to improve when involving SMCI and PMCI in the classification (Cuingnet *et al.*, 2011; Liu *et al.*, 2015; Ledig *et al.*, 2018). In order to achieve early detection of the disease, the discrimination of SMCI and PMCI play an important role. Therefore, more research focused on these stages in predicting the conversion to AD.

1.2 Problem Background

Structural MRI is treated as supportive feature for AD diagnosis and follow-up (Pais *et al.*, 2020). The brain's atrophy is believed spread from medial temporal lobe (MTL) to other areas of the brain. The atrophy of the brain involves both white matters and grey matters. In order to conduct whole brain analysis, it requires high computational resources to process the data due to high dimensionality. The 3D image contains millions of features, which causes overfitting due to excessive information.

Therefore, feature extraction and feature selection are the essential processes to lower the number of features from extracting or selecting the important features. The extracted or selected features shall increase the distinguishing power of the image especially in segregating SMCI patients and PMCI patients. Nevertheless, it can be a trade-off between dimensionality reduction and extracting significant features due to the image details might be washed out when there is too few number of features to be retained (Cangelosi and Goriely, 2007; Zhang *et al.*, 2015).

The unsupervised and supervised machine learning approaches were adopted to transform the data in feature extraction. The deep learning approach is normally used as a supervised learning, which can extract the features and classify the groups as one stop solution (Islam and Zhang, 2018). However, the methods also can be implemented after feature extraction to classify the data (Dolph *et al.*, 2017; Baskar *et al.*, 2019). The concerns on applying deep learning approach are hyperparameter tuning, training size and high computational resources. There are multiple possible combinations to determine the hyperparameters in the network (Islam and Zhang, 2017). It is time consuming to find the stable hyperparameters to build a good network. It will require high computational resources to build a deep network. Convolutional neural network is commonly used to deal with the image data. However, there is no guidance on the number of hidden layers, the number of neurons in each layer, and the combination of different types of layers. The formation of the network is done through trial-and-error or the prior experience (Ebrahimighahnavieh *et al.*, 2020).

On the other hand, the other machine learning approaches such as principal component analysis (PCA), fuzzy clustering, discrete wavelet transform (DWT), partial least square (PLS) can be done with less intervention or without involving the hyperparameters (Chaddad *et al.*, 2016; Salvatore *et al.*, 2018; Li *et al.*, 2019). However, the performance of some techniques are not consistent. Herrera *et al.* (2013) claimed that the combination of DWT and PCA decreased the classification result compared to use DWT alone. On the other hand, there are many other researchers used PCA to reduce the number of features and it had achieved higher classification result (Zhang *et al.*, 2015; Lama *et al.*, 2017; Ejaz *et al.*, 2018). This situation is possible due to different types of features were used in the research. The examples of geometric

measures were volume, shape, texture and cortical thickness (Sørensen *et al.*, 2017). The researchers also can choose to focus on 1-dimensional (1D), 2D or 3D feature extraction. Currently, most of the feature extraction approaches are based on 1D or 2D approaches. It requires to concatenate the features into a long feature vector or focuses on the slices of the MR images. The 1D or 2D feature extraction is much easier to implement but it loses the connection between the slices compared to 3D feature extraction. The different combination of features and techniques contribute to the different classification result.

Instead of transforming the data, feature selection chooses the useful features from the existing features. However, the needs of using feature selection remains a controversial issue. Feature selection tends to increase the sensitivity to the training set and eventually causes overfitting (Cuingnet *et al.*, 2011). Furthermore, the selection of different subsets of features is also proved that it has high impact on the classification results (Prasad *et al.*, 2015). Nevertheless, many researchers also adopted feature selection in their research and achieved a good classification result. The sequential forward selection (SFS) and multiple criterion feature selection were considered newer approaches. Sørensen *et al.* (2017) adopted SFS to select the significant texture, volume and thickness features from the regions of interest. Baskar *et al.* (2019) implemented multiple criterion feature selection to select the significant texture and shape features. The SFS and multiple criterion feature selection techniques were adopted to deal with the high dimensionality when different types of features were extracted from the data.

In the classification process, most of the researchers focused on differentiating NC, MCI and AD patients. They have succeeded in classifying AD from NC, even MCI stage (Sarwinda and Bustamam, 2016; Liu *et al.*, 2020). Few researchers focused on the transition from SMCI to PMCI. By classifying a patient as SMCI or PMCI, a doctor can predict the disease progression earlier and give a better treatment to the patient. However, the classification results for SMCI and PMCI is far from satisfactory compared to AD and NC, especially when using imagery data alone (Islam and Zhang, 2018; Ledig *et al.*, 2018; Salvatore *et al.*, 2018; Li *et al.*, 2019; Zhang *et al.*, 2021). The accuracy obtained from the previous studies mostly below 80%.

Besides that, the major concern on AD classification is the benchmarking with previous works. Alzheimer's Disease Neuroimaging Initiative (ADNI) is the well-known database, and it was used by many researchers. But, the population studies were different due to most of the researchers did not provide the subject identification number (Demirhan *et al.*, 2015; Beheshti and Demirel, 2016). The classification results can have a big difference by using different datasets which consists of different populations. Therefore, it is a challenge to conduct benchmarking. To the best of our knowledge, Cuingnet *et al.* (2011) was the only research which applied and compared the existing techniques by using same dataset throughout the years. Moreover, the size of the dataset also will influence the classification result. Small sample size may not able to reflect the classification result accurately (Westman *et al.*, 2011). In view of the limitation and challenges of existing AD classification, there are still rooms to improve the AD classification scheme. Apart from the techniques, the development of the AD classification needs to consider the data collection, features, and the necessity of the processes.

1.3 Problem Statement

Based on the problem background, several issues are identified and need to be solved to improve the accuracy of AD classification scheme. The first issue is related to the feature extraction. By using 1D or 2D feature extraction methods, it leads to the loss of spatial information of 3D images. As a result, it might eliminate the significant features to differentiate the classification groups. Besides, the performances of previous works are inconsistent even in the situation that same techniques were implemented in the studies. This might because of using different features to conduct the studies. Furthermore, the methods which require hyperparameters tuning will cause the difficulty in achieving consistent results due to the hyperparameters tuning is fully affected by training set or validation set.

The second issue is the low accuracy in differentiating the SMCI and PMCI groups. The problem occurs because of the high similarity between the groups. SMCI is a heterogenous group which might convert to PMCI after a short period of time

(Cuingnet *et al.*, 2011). This situation indicates that the brain structure of SMCI and PMCI might be very close to each another. The third issue is the processes involved in AD classification. Based on Cuingnet *et al.* (2011), feature selection might increase the model sensitivity towards the training set, and it did not improve much on the classification result. Therefore, it is necessary to reconsider of including it in the AD classification scheme.

1.4 Research Goal and Objectives

This study aims to enhance AD classification scheme for improving the accuracy through evaluating the processes involve in the conventional scheme, which are pre-processing, feature extraction, feature selection and classification. In order to achieve this goal, three research objectives are formulated as follows:

i. To identify suitable morphological operation with optimal parameter for reducing similarity on the thickness of brain boundary between SMCI and PMCI.
ii. To enhance the feature extraction techniques by selecting optimal parameters to achieve dimensionality reduction and extracting significant features.
iii. To enhance AD classification scheme by identifying suitable combination from the existing state-of-art methods with proposed 3D shape enhancement and feature extraction.

1.5 Research Scope

The research scope is defined based on the reference paper to allow benchmarking (Salvatore *et al.*, 2018). The population study and the feature used in the research are consistent to the reference paper. On the other hand, the collection of the data was limited based on the availability of the data. The research scopes are described in following:

i. Evaluations on ADNI database comprising four groups, which are NC, SMCI, PMCI and AD. The NC and SMCI patients are grouped together as healthy patient (NC+SMCI) and PMCI and AD patients are grouped together as sick patient (PMCI+AD). Hence, a binary classification is performed in this research, which is to differentiate between (NC+SMCI) and (PMCI+AD).
ii. The feature used in this research is volumetry feature. The other features such as texture, cortical thickness and shape are beyond the scope.
iii. Use of MR images only instead of including neuropsychological data.
iv. Performance measurement is accuracy.

1.6 Significance of the Study

AD is an irreversible disease which is not only affect the patients but also the people surround them. Special care for daily routine and financial support are going to be the big challenges for them. Therefore, early diagnosis of AD is always desirable to provide a better treatment to the patient (Alzheimer's Association, 2017). This study conducts the cross-sectional analysis across different time points, which can serve as a supportive tool for doctor to evaluate the condition of the outpatient. The dataset collected at time point of 24 months before stable diagnosis allows the examination on early diagnosis. Besides, the research outcome is also expected to contribute on the prediction of conversion to AD. The subjects are grouped into two classes, which are NC+SMCI and PMCI+AD. Hence, this research does not only contribute to early diagnosis of AD, but it is also able to predict the development of AD. In terms of CAD, this research plans to deal with the high similarity of SMCI and PMCI. It is expected to develop a new AD classification scheme from the state-of-art.

1.7 Organization of the Thesis

This thesis is organized in seven chapters to explain the research has been conducted thoroughly. Chapter 1 determines the goal, objectives and scope through the problem background and problem statement. The significant of this study is also presented in this chapter. Chapter 2 provides the knowledge on the cause of AD and the progression of AD. The clinical diagnosis and existing AD classification methods are presented. Chapter 3 describes the research framework. It explains the situational analysis and the design of the research. It also provides the information on the data collection and testing analysis.

Chapter 1 to chapter 3 provide an overview on the research planning. The remaining chapters show the processes involved in developing the AD classification scheme. Chapter 4 discusses about the formation of brain's boundary shape enhancement technique to maximize the difference of SMCI and PMCI. Chapter 5 presents the feature extraction with DWT and PCA. Chapter 6 reveals the development of AD classification scheme and the experiments involved in the development process. This chapter also presents the benchmarking result. At last, Chapter 7 concludes the results and contributions of this thesis. The future works also are suggested in this chapter.

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