UNIVERSITI PUTRA MALAYSIA

PREDICTION OF ALZHEIMER DISEASES USING IMPROVED MMSE ENSEMBLE REGRESSOR BASED ON MAGNETIC RESONANCE IMAGES

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By

ALI FARZAN

Thesis Submitted to the School of Graduate Studies, Universiti Putra Malaysia, in Fulfilment of the Requirements for the degree of Doctor of Philosophy

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PREDICTION OF ALZHEIMER DISEASES USING IMPROVED MMSE ENSEMBLE REGRESSOR BASED ON MAGNETIC RESONANCE IMAGES

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February 2015

Chair: Syamsiah Binti Mashohor, PhD

Faculty:Engineering

Cognitive scores are the most common measures in diagnosing Alzheimer's disease which are measured clinically. These scores are mostly useful in late and severe stages of disease which symptoms of the disease are appeared. Nowadays, it is obvious that onset of the disease can be even decades before manifestation of the symptoms and it can be revealed by investigating the brain structures. Early prognosing of Alzheimer's disease by analyzing brain MR images and inspecting effect of it on brain structures is a hard task. Moreover, predicting severity of disease based on the cognitive scores is a more challenging process especially for future prediction by using the anatomical parameters in the past. One of major problems is high dimensionality of anatomical feature space which must be reduced to a small feature set of discriminative ones and another issue is to relate them to the cognitive scores in the future. This thesis addresses these problems and investigates in the relationships between AD progression and brain degenerations. Brain MR Images of Alzheimer's Disease NeuroImaging (ADNI) dataset are used in the thesis. A total of 108 subjects who pass the imaging process at four successive time scans of screening, 12^{th} month, 24^{th} month and 36^{th} month are selected. 30 subjects from Normal Controls (NC), 30 from Alzheimer's disease (AD) holders, 30 subject with Mild Cognitive Impairments (MCI) and 18 converters, all convert at 36^{th} month, from MCI to AD are included in the dataset. Brain MR Images are analysed by the established Freesurfer algorithms to extract the volumetric and thickness features of brain structures in all four time scans. These features are used as raw data in the rest of the thesis. The thesis has four major objectives. First, discriminative features which vary significantly during the disease monitoring period are identified according to the cognitive scores. Next, regarding to the ordered nature of cognitive scores it aims to find those features that impose smaller error to the cognitive scores as predicted output values. These two objectives are going to solve high dimensionality issue. To tackle on relationship between cognitive scores in future and anatomical features, third objective is proposed to find a relationship between the selected anatomical features throughout the monitoring period and MMSE scores at the end of period or 36^{th} month. It is obvious that using anatomical feature values at 36^{th}

month to predict the MMSE scores at the same time is clinically unworthy. Fourth objective is to overcome this shortcoming and relate the anatomical feature values at the 36^{th} month to those of the screening, 12^{th} month and 24^{th} month. To achieve the first objective, an evolutionary hypothesis test is proposed to reduce the feature size and chose those ones that their variation during the 36 months of screening is significant and was not stable in the duration. Additionally, they must differ significantly according to the cognitive scores. A minimal set of feature who passed the above criteria and can differentiate all of cognitive score pairs is selected by using a genetic search algorithm. Chernoff bound as upper bound of Bayes error for class separability is computed for evaluating the feature selection method. A reduction from 69.1 to 50.2 is achieved for the proposed evolutionary hypothesis test. In the proposed feature selection algorithm, the ordered nature of cognitive scores or ranks and the amount of error value that can be imposed by any feature over any rank are never considered. So, a rank based feature selection algorithm is proposed to address these issues. It assigns three measures to any pair of feature and rank. These three measures are sorted in each rank and truncated based on a threshold of their derivatives. Those features that are kept in all three truncated feature sets are chosen as final selected features which are 10 features. Chernoff bound decreases again from 50.2 to 46.3 by using the rank based feature selection algorithm. As noted in the third objective, these selected features are used to predict the MMSE scores at the 36^{th} month of screening. Four various core regressors are used including multilayer perceptron regressor, general regression neural network, support vector regressor and relevant vector regressor. Each of the core regressors participate in a boosting algorithm and then, a bulk of 40 regressors participate in designing final ensemble regressor. To this end, the feature space must be clustered into some small perfect hyperspaces. Each hyperspace is assumed as perfect hyperspace if at least three of the regressors can predict perfectly all data pattern in it. Averaging method is adopted for predicting MMSE scores in any cluster. Mean square error value of 0.0112 and correlation coefficient of 0.9556 reveal competence of the proposed method. Predicting MMSE scores of 36^{th} month by using the anatomical features of the same time is not clinically beneficial. To address it and accomplish the fourth objective, some ensemble regressors are proposed to predict anatomical features of 36^{th} month or long term features by using their short term counterparts from start of screening up to the 24^{th} month. The same proposed ensemble regression method is used in designing these regressors. Mean square errors range between 0.0064 and 0.0111 and correlation coefficients range between 0.8393 and 0.09355 indicate suitability of proposed algorithm even in predicting other type of features. The really measured long term features in the designed ensemble regressor are replaced by the predicted counterparts to achieve a feasible MMSE ensemble regressor. A mean square error of 0.0213 and correlation coefficient of 0.9350 indicates that the feasible ensemble regressor is a good representative of the one which is designed by the real long term features.

Abstrak tesis yang dikemukakan kepada Senat Universiti Putra Malaysia sebagai memenuhi keperluan untuk ijazah Doktor Falsafah

RAMALAN PENYAKIT ALZHEIMER MENGGUNAKAN PENGUNDUR KELOMPOK MMSE YANG DITAMBAHBAIK BERDASARKAN IMEJ-IMEJ RESONANS MAGNET

Oleh

ALI FARZAN

Februari 2015

Pengerusi: **Syamsiah Binti Mashohor, PhD**

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Skor kognitif merupakan ukuran yang biasa dalam mendiagnosis penyakit Alzheimer yang mana ianya diukur secara klinikal. Skor ini selalunya berguna bagi mengukur tahap penyakit yang kritikal dimana simptom penyakit tersebut dapat dilihat. Pada masa kini, ianya jelas bahawa permulaan penyakit boleh timbul berdekat sebelum manifestasi symptom dan ianya dapat dilihat dengan mengkaji struktur otak. Prognosis awal penyakit Alzheimer dengan menganalisis imej MR otak dan memeriksa kesan tersebut kepada struktur otak merupakan tugas yang sukar. Tambahan lagi, meramal keterukan penyakit berdasarkan skor kognitif merupakan proses yang lebih mencabar terutama sekali bagi ramalan akan datang dengan menggunakan parameter anatomi pada masa lalu. Salah satu masalah utama ialah dimensi tinggi ruang ciri anatomi dimana perlu dikurangkan kepada set ciri diskriminasi yang lebih kecil dan isu lain berkaitan terhadap skor kognitif pada masa hadapan. Tesis ini mengutarakan masalah-masalah tersebut dan mengkaji hubungan antara perkembangan AD dan kemerosotan otak. Imej MR otak bagi data set Pengimejan Neuro Penyakit Alzheimer (ADNI) digunakan di dalam tesis ini. Sejumlah 108 subjek yang lulus proses pengeimejan pada empat kali penyaringan imbasan berturutan, iaitu bulan ke-12, bulan ke-24 dan bulan ke-36 telah dipilih. 30 subjek daripada Kawalan Normal (NC), 30 pengidap penyakit Alzheimer (AD), 30 subjek mengidap Kecacatan Kognitif Ringan (MCI) dan 18 pengubah, iaitu semua berubah pada bulan ke-36, daripada MCI ke AD dimasukkan ke data set. Imej MR otak dianalisis menggunakan algoritma *Freesurfer* bertapak untuk mengekstrak ciri volumetri dan ketebalan struktur otak bagi empat kali imbasan. Ciri ini digunakan sebagai data mentah sepanjang tesis ini. Tesis ini mempunyai empat objektif utama. Pertama, ciri diskriminatif yang berbeza secara signifikan sepanjang tempoh pemantauan penyakit dikenal pasti mengikut skor kognitif. Seterusnya, berhubung sifat berturut skor kognitif ia bertujuan untuk mencari ciri yang mengenakan ralat yang lebih kecil bagi skor kognitif seperti ramalan nilai output. Kedua-dua objektif ini akan menyelesaikan isu kedimensian tinggi. Untuk menangani perhubungan antara skor kognitif dalam ciri masa hadapan dan anatomi, objektif ketiga dicadangkan untuk mencari perhubungan antara ciri anatomi terpilih sepanjang tempoh pemantauan dan skor MMSE pada akhir bulan ke-36. Adalah jelas dengan menggunakan nilai ciri

anatomi pada bulan ke-36 bagi meramal skor MMSE pada masa yang sama adalah tidak boleh dipercayai dari sudut klinikal. Objektif keempat ialah untuk menangani kelemahan ini dan mengaitkan nilai ciri anatomi pada bulan ke-36 pada mereka yang disaring pada bulan ke-12 dan bulan ke-24. Bagi mencapai objektif pertama, satu ujian hipotesis evolusi dicadangkan untuk mengurangkan saiz ciri dan memilih yang mana variasi mereka sepanjang penyaringan bulan ke-36 adalah signifikan dan tidak stabil pada jangka masa tersebut. Tambahan lagi, ia mestilah berbeza secara signifikan mengikut skor kognitif. satu set minimum bagi ciri yang lulus bagi kriteria diatas dan boleh membezakan semua pasangan skor kognitif dipilih dengan menggunakan algoritma carian genetik. Batas *Chernoff* sebagai batas atas bagi ralat *Bayes* bagi kebolehpisahan kelas dikira bagi menilah kaedah pemilihan ciri. Penurunan daripada 69.1 to 50.2 dicapai bagi cadangan ujian hipotesis evolusi. Di dalam cadangan pemilihan ciri algoritma, sifat berturut skor atau peringkat kognitif dan jumlah nilai ralat yang boleh dikenakan oleh mana-mana ciri lebih dari peringkat tidak pernah dipertimbangkan. Oleh itu, pemilihan ciri algoritma bersifat peringkat dicadangkan bagi mengutarakan isu tersebut. Ia menetapkan tiga ukuran pada mana-mana pasangan ciri atau peringkat. Ketiga-tiga ukuran ini disusun pada setiap peringkat dan dipangkas berdasarkan ambang penurunannya. Ciri tersebut yang disimpan pada ketiga-tiga set ciri pangkasan dipilih sebagai ciri pilihan akhir iaitu 10 ciri. Batas *Chernoff* menurun lagi dari 50.2 kepada 46.3 dengan mengunakan pemilihan ciri algoritma bersifat peringkat. Seperti yang nyatakan dalam objektif ketiga, ciri-ciri terpilih ini digunakan untuk meramal skor MMSE pada penyaringan bulan ke-36. Kami menggunakan 4 peregresi teras termasuk peregresi perseptron berbilang lapis, peregresi rangkaian neural umum, peregresi vektor sokongan dan peregresi vektor relevan. Setiap satu peregresi teras menyertai dalam meningkatkan algoritma dan sebahagian besar daripada 40 peregresi menyertai dalam mereka bentuk peregresi ensembel akhir. untuk tujuan ini, ruang ciri tersebut mestilah berkelompok kepada hiper ruang sempurna yang kecil. Setiap hiper ruang dianggap sebagai hiper ruang sempurna jika sekurang-kurangnya tiga peregresi dapat meramal dengan sempurna semua pola data di dalamnya. Kaedah pemurataan digunakan dalam meramal skor MMSE dalam mana-mana kluster. Nilai ralat min kuasa dua bernilai 0.0112 dan pekali korelasi sebanyak 0.9556 menunjukkan kecekapan kaedah yang dicadangkan. Meramal skor MMSE pada bulan ke-36 menggunakan ciri anatomi pada masa yang sama adalah tidak berfaedah dari segi klinikal. Bagi mengutarakan dan mencapai objektif keempat, beberapa peregresi ensembel dicadangkan untuk meramal ciri anatomi bulan ke-36 atau ciri jangka panjang dengan menggunakan kaunterpart jangka pendek daripada mulanya penyaringan sehingga bulan ke-24. Cadangan kaedah peregresi ensembel yang sama digunakan dalam mereka bentuk peregresi tersebut. Ralat min kuasa dua dalam lingkungan 0.0064 dan 0.0111 serta pekali korelasi dalam lingkungan 0.8393 dan 0.09355 menunjukkan kesesuaian algoritma yang dicadangkan walaupun dalam meramal jenis ciri yang lain. Peregresi yang benar-benar mengukur ciri jangka panjang di dalam reka bentuk peregresi ensembel diganti dengan kaunterpart yang diramal bagi mencapai peregresi ensembel MMSE yang tersaur. Ralat min kuasa dua bernilai 0.0213 dan pekali korelasi dengan nilai 0.9350 menunjukkan bahawa peregresi ensembel tersaur merupakan wakil yang baik bagi satu yang direka dengan ciri jangka panjang yang sebenar.

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This thesis was submitted to the Senate of Universiti Putra Malaysia and has been accepted as fulfillment of the requirement for the degree of Doctor of Philosophy. The members of the Supervisory Committee were as follows:

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LIST OF ABBREVIATIONS

AD	Alzheimer's Disease
ADNI	Alzheimer's Disease Neuroimaging Initiative
CAUC	Complement of Area Under Curve
CSF	CerebroSpinal Fluid
GA	Genetic Algorithm
GM	Gray Matter
GRNN	Generalized Regression Neural Network
MCI	Mild Cognitive Impairment
MLPR	Multi Layer Perceptron Regression
MRI	Magnetic Resonance Imaging
NC	Normal Control
NRCM	Normal Reverse Contribution Measure
PET	Positron Emission Tomography
RPM	Reverse Pertinence Measure
RVM	Relevance Vector Machine
RVR	Relevance Vector Regression
SVM	Support Vector Machine
SVR	Support Vector Regression
WM	White Matter

CHAPTER 1

INTRODUCTION

1.1 Overview

Alzheimer's disease (AD) is the late-life ailment that starts cunningly and gradually redounds to cognitive impairment. AD is known as the major cause of more than half of the dementias. It is estimated that more than 10 million people living worldwide with AD and until 2025 this population will be nearly double [1-2]. AD and related dementias cost about $600 billion annually [3]. Nowadays, there is no effective clinical treatment for AD but some neuro-protective agents designed to stabilize the disease and decelerate its progress.

Pathogenesis of AD starts with establishing an abnormal τ protein in some impressionable neurons which disrupts microtubules amenable for transporting substances between cellular compartments, preventing axonal transport and altering the cytoskeleton. This process eventually lead to the formation of neuropil threads and neurofibrillary tangles (NFTs). Independent of the abovementioned intraneural alterations, deposition of beta-amyloid (Aβ) is another degradation which occurs as an onset of AD. This is an extracellular phenomenon and may lead to the development of senile plaques [4].

Definite diagnosis of AD is based on the post mortem examination and approved if a certain density and distribution of these two parameters (NFTs and senile plaques) revealed [5]. But, they appear in majority of elderly people regardless of that they eventually fall in AD or not [6]. Some argue that occurrence of these two parameters are normal effects of aging in healthy elderly [7], whereas some others assert that it cannot be a normal consequence of aging [8].

As the age proceeds, agglomeration of NFT comply consistent spatial and temporal patterns but it is not the case with the amyloid plaques [4]. Meanwhile, that cognitive and behavioural decline in AD course has correlated with the accumulation of NFT in the brain. It appears first at the Entorhinal cortex and by the progression of disease, densifies and spreads into the hippocampus and other limbic and paralimbic cortices, eventually intruding upon the neocortical areas and the striatum [5]. After these degenerations of brain structures, memory lapses appear followed by functional and lingual decline. Memory impairments specially in learning abilities and retention of new information are the first clinically manifested symptoms in subjects influenced by AD. Other problems such as lingual and spatial disorders in finding words to express sentences and finding the ways in familiar places are the next signs of AD [9-10].

These changes always appear in the same order, but they may overlap each other in various disease stages [11]. These orders and overlaps are revealed in Figure1-1.

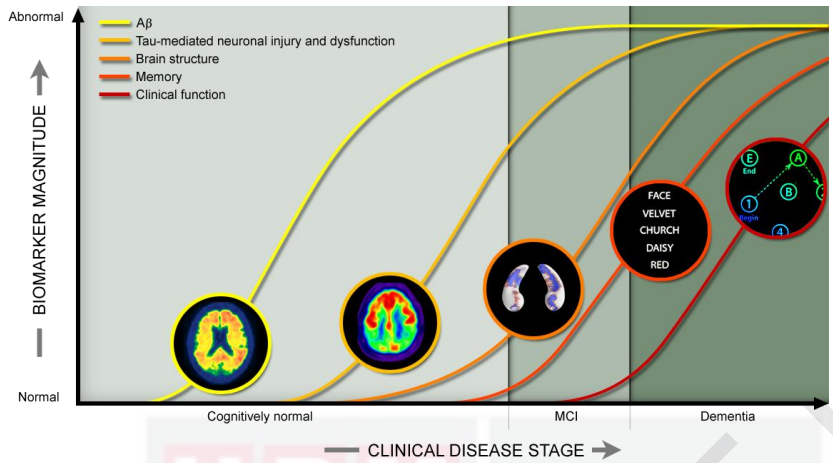

Figure 1-1 Various biomarkers of AD and the stage of disease they are affective [11]

The first three biomarkers can be used to prognosis of AD prior to dementia diagnosis (Adapted from http://adni.loni.ucla.edu/about/biomarkers (Accessed 5/2/2012)).

As shown in the Fig. 1, disease evolution has been divided into three phases based on the severity of disease. The first phase is normal controls (NC) including peoples without any clinical disease symptoms. The second phase is Mild Cognitive Impairments (MCI). Subjects in this category complain against some memory lapses but not in a stage that influence their normal daily activities. That is, MCI is an intermediate state between normal control and AD. Subjects, who fall in MCI may or may not convert to AD in the next future years. Last phase, the AD phase, includes those people whose disease has clinically approved. According to the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's disease and Related Disorders Association (NINCDS-ADRDA) criteria, a clinical test for diagnosing the AD must clarify the existence of dementia, deficits in two or more cognitive abilities, progressive impairment of memory in spite of no other systemic brain disorder capable of producing dementia. Mini Mental Score Exam (MMSE), Clinical Dementia Rating (CDR), Functional Assessment Staging Scale (FAST), Global Deterioration Scale (GDS) and Alzheimer's disease Assessment Scale (ADAS) are some popular clinical tests which are used to diagnose people with AD clinically. Moreover, definite diagnosis of AD requires histopathological confirmation based on biopsy or autopsy [12].

1.2 Problem Statement

It is obvious that clinical measures are useful only in the third stage of disease and cannot be used in the first and second stages due to no manifest behavioural or memory impairment [13-14]. Furthermore, diagnosing based on singly clinical scores are not accurate enough and biopsy or autopsy based identification of density and location of amyloid plaques as well as the existence of neurobiology tangles are required. Autopsy derived information in post mortem studies are useful in investigating the location and

nature of pathology but cannot be used in tracking the progression of disease in living individuals. Furthermore, biopsy is an invasive process and cannot be considered as a common diagnostic for AD. These limitations motivate researchers to look for some complementary biomarkers for exact diagnosis of AD [15].

Referring Figure 1-1, analyzing brain structures and their characteristics can be a good complementary biomarker in diagnosing AD even in early stages of it. Various modalities of brain imaging such as Positron Emission Topography (PET), Computer Tomography (CT), Functional Magnetic Resonance Imaging (fMRI) and Magnetic Resonance Imaging (MRI) are used in designing complementary biomarkers of AD. Among them, brain MR Images because of their high resolution and non-invasive nature seem to be plausible candidates for realizing microscopic degenerations in brain structures. MRI based neuroimaging methods, offer promise in being able to analyze AD in vivo. Characteristics of the degenerations may be explored to get strong relationships between them and disease progression [16-22]. Different anatomical structures of the brain such as Entorhinal Cortex, Hippocampus and Cerebral Cortex have been influenced of AD, and their morphometric characteristics such as volume and thickness can be used as biomarkers of neurodegenerative diseases such as AD [16, 23-26].

Major reason in designing new powerful markers of AD is the need for monitoring in vivo disease progression in designing new therapeutic trials and also early prognosis to stabilize cognition or at least to decelerate its decline [27-28]. Most of the neuroimaging methods focus on analyzing morphological features and statistically evaluate their discrimination power in classifying subjects into their well known appropriate groups such as NC, Non-Converter MCI, Converter-MCI and AD [11, 29-32]. These methods never explored on ways that one can use to categorize individuals into the groups based on these features. Some others go further and propose classification methods as well as feature extraction methods to assign each subject into its appropriate class of disease [29, 33-34]. It is known that classification is a dichotomous process and classifies each subject into the one of two or more groups whereas, some pathology such as AD follow a continuous trajectory of structural and functional changes. It starts even decades before its final clinical stage and progress gradually. So estimating the clinical disease scores seems imperative for evaluating severity of disease and analyzing its progress. This can help in managing patients and also is very helpful to monitor brain effect of drugs in developing new pharmacotherapeutic trials. Nowadays, just a few neuroimaging methods focus on the AD analysis based on the continuous disease related grades [35-37]. Nevertheless, they suffer from some shortcomings and improvements can be made on them.

1.3 Motivations

The onset of the AD starts even decades before appearing its clinical symptoms. Brain structures have been influenced in early stages of disease and degeneration of these structures and their characteristics can be used as biomarkers of AD. Due to the non-invasive nature of medical imaging and higher resolution of MR images, they seem as a convenient modality for analyzing brain structures and their characteristics in response to the disease effects.

Regarding the nature of AD, its pathogenesis is a gradual phenomenon and for definite analysis of AD the severity of disease must be evaluate by a continuous quantitative mark. These continuous marks help scientists to track the disease as it progresses even in the early stages of the disease. This ability helps in analyzing effects of newly developed drugs whether they are controlling disease to stabilize or even amend it. Furthermore, realizing the onset of disease in its early stages before manifestation of clinical symptoms can lead to a better and more efficient therapy.

1.4 Objectives

In this thesis, main aim is to investigate the relationships between AD progression and brain degenerations which reveal and parameterize by analyzing MR images. There are four major objectives must be achieved.

1- To analyze brain MR extracted features statistically and selecting most discriminative ones in a meta-heuristic manner.
2- To design a rank based feature selection method in order to evaluate each feature's contribution in misclassifying the data patterns, and also their pertinence in imposing the error to the output values.
3- To implement an ensemble regressor for estimating long term morphological features based on short term morphological features.
4- To implement an ensemble regressor for estimating clinical scores based on real short term and estimated long term morphological features.

To achieve the first objective, it is needed to find those features which vary significantly during the monitoring period and also their variations significantly correlated with the changes in MMSE scores. Selecting minimum set of features by which all MMSE score pairs can be discriminated is desired.

Second objective is to involve the ordinal nature of MMSE scores in selecting those features, which impose minimum error in predicting the MMSE scores. Two newly proposed measures along with the area under curve of receiver operating characteristic curve are used in a pseudo-voting manner to select such valuable features.

According to the third objective, an ensemble regressor is proposed by which the morphological features at the 36^{th} month (long term) can be predicted by the MMSE scores and morphological features of previous scans, screening and 12^{th} and 24^{th} month, (short term) which are extracted from corresponding MR images.

Designing and developing a new ensemble regressor for predicting MMSE scores of 36^{th} month by using the extracted short term atrophic features and MMSE scores along with the predicted atrophic features of 36^{th} month is the fourth objective of the thesis.

1.5 Aim and Scope

The Alzheimer's Disease Neuroimaging Initiative (ADNI) [38-39] is a large study of MRI and FDG-PET (Fluorodeoxyglucose Positron Emission Tomography) over 800 individuals in a period of 5 years. 50 different imaging centers and hospitals from the United States and Canada have participated in this study. Participants are between 55 and 90 years old and 200 of them were normal controls, 400 subjects had MCI and the remained 200 are identified as AD. The ADNI was launched in 2003 by the National Institute on Aging (NIA), the National Institute of Biomedical Imaging and Bioengineering (NIBIB), the Food and Drug Administration (FDA), private pharmaceutical companies and non-profit organizations, as a $60 million, 5-year public–private partnership [40].

The major goals of the ADNI are to develop improved methods which will lead to uniform standards for acquiring longitudinal, multi-site MRI and PET data on patients with AD, MCI and elderly NCs. Furthermore, developing methods with maximum power in determining treatment effects and collecting a generally accessible data repository which describes longitudinal changes in brain structure and metabolism are other main objectives of ADNI.

Among 800 subjects of ADNI, a total of 131 subjects with complete longitudinal scans are selected for this study. It includes 30 normal controls, 30 MCIs, 30 patients with AD and 41 of them are Converters from which 23 are Converter-MCIs, 16 are Converter-NCs and 2 of them are normal controls who converted directly to AD without any match to intermediate MCI state. Converter-MCIs are subjects currently diagnosed as MCI but convert after a while to the AD. On the other hand, Converter-NCs are subjects currently detected as normal controls but convert to the MCI in a period of time. T1-weighted modality of MR images are used for analysis. The major reason for choosing MR images is their higher resolution which makes them suitable for investigating fine details of brain degeneration. Images in the database have been analyzed and their qualities have been approved by some radiology experts.

This thesis focuse on those subjects with complete T1 weighted MRI scans in 4 desired timelines of screening, 12^{th} month, 24^{th} month and 36^{th} months. A total of 131 subjects including 30 normal controls, 30 subjects with mild cognitive impairments, 30 Alzheimer's disease holders and 41 Converters from which 23 are Converter-MCIs (convert from MCI to AD), 16 are Converter-NCs (convert from NC to MCI) and 2 of them are normal controls who converted directly to AD without any match to intermediate MCI state.

Major aim of the thesis is to feasibly predict the MMSE scores at 36^{th} months. That is, to predict the MMSE scores of 36^{th} month without using any of the features at that time, but just by using the information from previous timelines. To this aim, extracted information from short term scans, including atrophic features and MMSE scores along with the predicted atrophic features of 36^{th} month (based on the short term features) are used to predict the 36^{th} month MMSE scores.

1.6 Limitations

Subjects who have been incorporated in this study are limited to those in the ADNI dataset who passed all monitoring requirements and have MRI scans in time slices of screening, 12^{th} month, 24^{th} month and 36^{th} month of scanning.

Proposed algorithms aim to predict the MMSE as a major clinical score in the 36^{th} month by using the anatomical structures in the past three time slices.

1.7 Thesis Outline

The rest of this thesis is organized as follows:

Chapter 2 will give a brief overview of the Alzheimer's disease severity prediction methods. There are a huge number of researches on diagnosing the Alzheimer's disease, but only a few of them focus on predicting the disease related cognitive scores. This chapter will cover all the major works have been done in predicting or even calculating the cognitive scores.

Chapter 3 will present the proposed methodology of the thesis. Detail of the algorithms, experimental design, performance metrics and evaluation methods of this work will be explained clearly.

Chapter 4 is dedicated to experimental results of the proposed systems. Results of feature selection algorithms as well as the regression methods will be presented in this chapter.

Chapter 5 provides a summary of the work presented in this study and outlines the conclusions that can be drawn. It will also include the suggestion for future works.

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