RELIABILITY IMPROVEMENT OF COMPUTER AIDED DIAGNOSTIC SYSTEM USING MUTUAL INFORMATION

by

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B.S., Physics, Boğaziçi University, 2012

Submitted to the Institute of Biomedical Engineering
in partial fulfillment of the requirements
for the degree of
Master of Science
in
Biomedical Engineering

Boğaziçi University
2016

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DATE OF APPROVAL: 29.02.2016

ACKNOWLEDGMENTS

I would like to express my deepest gratitude to Assoc. Prof. Dr. Albert GÜVENİŞ for his guidance, support,patience and kindness. With his supervision and encouragement, i was able to complete this study.

I thank Assist. Prof. Bora Garipcan and Assoc. Prof. Burçin Ünlü for participating in my thesis committee and for their valuable comments on the thesis.

I thank my closest friends Esra Altınışık, Ayşenur Çor , Şeyma Çetinkaya, Zeynep Dagınık, Beyza Karakaya and Betül Özateş who always be my side.

Finally, i express my endless gratitude to my dearest family. I would like to thank my father Bilal Çankaya for his encouragement. I am grateful to my father also for his endless financial and moral support. I would like to thank my dearest mother Işıl Çankaya who never let me feel alone during whole my life and i thank for her endless motivation during my academic life. I am grateful to my dearest brother Yunus Emre Çankaya for his motivation, help and support.

Above all, i would like to thank my husband Yasin Polat for his endless trust, motivation and support. I also want to thank my little daughter Müberra Polat to make me mother and i would like to express my endless love to her via this study.

I acknowledge to ADNI for allowing me to use PET image database.

ABSTRACT

RELIABILITY IMPROVEMENT OF COMPUTER AIDED DIAGNOSTIC SYSTEM USING MUTUAL INFORMATION

Computer aided diagnosis (CAD) is one of the most important topic in recent years since the systems are able to provide a second reliable opinion to physicians and early diagnosis with these systems are possible. In this study we aim to construct a system for the detection of Alzheimer's disease (AD) using PET images from a database.

The CAD system includes a database consisting of a 3D PET image for every query. Via using a similarity metric namely mutual information(MI), every query compares to all other query in database. According to their similarity results, a decision index is calculated. The decision index demonstrate presence or absence of AD. The system was developed and evaluated using two different databases extracted from Alzheimer's disease Neuroimaging Initiative (ADNI) database. All normal and Alzheimer's images are stored and ordered in database. First database consists of 259 normal and 138 AD patient whereas second database consists of 102 normal and 95 AD patient. Main difference of two database is registration. Images in second database are warped with talairach atlas.

CAD performance was evaluated using Receiver Operating Characteristic analysis. For every query, a decision index was calculated. According to our results we observed that accuracy and speed of the CAD system is affected by certain parameters. The method proposed in the article is adequate to distinguish the disease. The mutual information method is very simple, applicable and fast enough to use in clinic area.

Keywords: Computer Aided Diagnosis, Mutual Information, Alzheimer Disease

ÖZET

KARŞILIKLI BİLGİ MİKTARI KULLANILARAK BİLGİSAYAR DESTEKLİ TEŞHİS SİSTEMİNİN GÜVENİLİRLİĞİNİN GELİŞTİRİLMESİ

Bilgisayar destekli teşhis sistemleri son yıllarda üzerinde sıklıkla çalışılan bir konu olmuştur. Bu sistemler doktorlara teşhis koyma esnasında yardımcı olmayı amaçlar. Özellikle erken teşhisin önemli olduğu hastalıklarda bu sistemlerin kullanımı erken teşhis olasılığını artırır. Bu tezin amacı PET görüntülerinden oluşan bir data set kullanarak Alzheimer hastalığını teşhis edecek güvenilir bir sistem kurmaktır.

Önerilen bu sistemde her bir girdi için üç boyutlu PET görüntülerinin oluştuğu bir data set kullanılmaktadır. Karşılıklı bilgi miktarı kullanılarak bu girdilerin birbirlerine benzerlik miktarları ölçülür. Her bir girdi data setteki diğer bütün girdilerle karşılaştırılır ve bir karar indexi hesaplanır. Bu indexe göre bu girdinin hastalığa sahip olup olmadığına karar verilir. Görüntüler Alzheimer's disease Neuroimaging Initiative (ADNI) data setlerinden alınmıştır. İki farklı data set kullanılmıştır. İlk data sette 259 normal ve 128 hasta görüntü vardır. İkinci data sette ise 102 normal ve 95 hasta görüntü bulunmaktadır. İki data set arasındaki en önemli fark ise görüntüleri işleme esnasında talaraih atlas kullanıp kullanılmadığıdır.

Sistemin performanısı hesaplandığı zaman kurulan sistemin, görüntülerin hasta veya normal olduklarını ayırt edebildiği gözlemlenmiştir. Kurulan sistem ve kullanılan metot gayet basit, kolaylıkla uygulanabilir ve klinik alanda kullanılabilecek kadar hızlıdır.

Anahtar Sözcükler: Bilgisayar Destekli Teşhis, Karşılıklı Bilgi Miktarı,Alzheimer Hastalığı

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LIST OF SYMBOLS

D	Desicion index, d value
$D(Q_i)$	D value for query Q
MI	Mutual information
M_j	Image from an Alzheimer's Disease patient
N_j	Image from a Normal participant
P_x	Probability density function of image x
P_y	Probability density function of image y
P_xy	Joint probability of images x and y
Q_i	A query taken from image database

LIST OF ABBREVIATIONS

AD	Alzheimer's Disease
ADNI	Alzheimer's Disease Neuroimaging Initiative
CAD	Computer Aided Diagnosis
CT	Computed Tomography
EEG	Electroencephalography
FDA	Food and Drug Administration
FDG	Fluoro-Deoxy Glucose
MI	Mutual Information
MMSE	Mini Mental State Exam
MRI	Magnetic Resonance Imaging
NIA	National Institute on Aging
NIBIB	National Institute of Biomedical Imaging and Bioengineering
PET	Positron Emission Tomography
SPECT	Single Positron Emission Tomography
SPM	Statistical Parametric Mapping
SVM	Support Vector Machine

1. INTRODUCTION

Since there is no cure for Alzheimer's disease, early diagnosis of the disease is a very important issue. Even though there is no permanent cure, with early diagnosis physicians are able to slow down to progression of the disease. There have been built some computer aided diagnosis programs to help early diagnosis and to give physicians a second opinion, but their reliabilities are very low to use these systems in medical care area. By using mutual information concept, computer aided diagnostic systems aim to be able to have higher reliabilities to be used in medical area.

1.1 Computer Aided Diagnosis

Recently, computer aided diagnosis has become one of the most important topic in medical imaging and medical informatics area. The basic concept of CAD is to provide a computer output as a second opinion to assist radiologists' image interpretation by improving the accuracy and consistency of radiological diagnosis and also by reducing the image reading time. The proposed CAD system is designed for detection of Alzheimer's disease from Positron Emission Tomography (PET) images. PET images represent consumption of glucose level of the brain as well as PET is being actively used in clinical area to support diagnosis of AD [1]. Since Alzheimer's disease is a neurodegenarative disease, neurons of particular regions begin to die. With death of the neurons glucose consumption starts to decrease. In other words, there appear a decrease in glucose consumption in that areas. With PET imaging technique, this metabolic decrease can be detected. These reductions may come from normal aging or AD. Not to misdiagnose, there needs a second opinion to physicians. In addition, early diagnosis of Alzheimer's offers more chance to slow down or for treatment of the disease. Since it is difficult to diagnose Alzheimer's in early stages, there are many works done for the diagnosis of Alzheimer's disease using different kinds of methods and materials in computer aided diagnosis area. On the one hand statistical parametric mapping software is commonly used. A study done by James C Patterson II. represented that evaluation with SPM software are more successful than evaluation with standard clinical processes [2]. And a newly proposed method is that diagnosis of the disease is done by using 3D local binary patterns, and texture analysis. In the study, Pedro M. Morgado, Margarida Silveira and Jorge S. Marques proposed a new method. They retrieved a texture from 3D images. By using the information gotten by textures they build CAD system. Additionally using Local Binary Patterns texture descriptor, they have been successful to diagnose to AD and MCI [3].

On the other hand, in machine learning areas, a common approach used for CAD is support vector machine(SVM). I.A. Illan and his colleagues made a study that uses feature extraction and SVM to reach a final decision. They got a maximum of 88.24 percentage accuracy however their method to make feature extraction is not practical [4]. Another study was published by P. Padilla again using SVM classifiers. They used SVM for classification of certain features getting from 3D PET and SPECT images. They used non negative matrix factorization and Fisher discriminant ratio to select and extract features from images [5]. They got high accuracy results but as above study, there need feature extraction. There needs an extra effort to take some features from images. The third example of SVM classifier is written by M. Lopez and his colleagues. They proposed a CAD system, same as above studies, after extracting features from SPECT and PET images, they used a kernel-based SVM classifiers. They got high results, but they used kernel principal component analysis and linear discriminant analysis for feature extractions [6]. Addition to these, there are other studies using SVM classification methods, but all of them used feature extractions [7, 8].

In addition to SVM classification, artificial neural networks are commonly used while constructing CAD system. As an example, a study is published by Alexhandre Savio and his colleagues. After feature extractions form MRI images, they used four different models for construction of artificial neural network classifiers [9]. There are also other commonly used methods [10-12]. However, reliabilities of the systems are not high enough to use in clinical area as a decision model.

1.2 Mutual Information

Mutual information concept is begun to used in computer aided diagnostic area recently. The main idea of this concept is to calculate similarity between two subject. The more the subjects are similar, the higher mutual information is gotten.

Mutual information theory is used to diagnose various diseases with various diagnostic methods in CAD area. As an example MI is used to diagnose prostate cancer. With using ultrasound images, they built a feature selection algorithm based on mutual information [10]. Another application area of mutual information is to detect mammographic lesions. One study is done by Zheng et al [11]. They use a database having huge number of region of interests images. Then they choose some of similar images using k nearest neighbor strategy. By using mutual information score, they reduce the number of similar cases. One different study is done by Tourassi et al. They also used a database containing region of interests taken form mammograms. Every query in database is compared other queries and using mutual information theory a decision index is calculated [12]. Another study using mutual information is also about to breast cancer. They add machine learning applications to their computer aided diagnostic system. Firstly they construct ensemble classifiers. With different random methods, they divide database into changing number of subclassifiers. A query is compared every member in those subclassifiers and a decision index for whole subclassifiers are calculated. By a combining mechanism, they reach a final decision [13].

Mutual information concept is also used in registration area. A study done by Maes [14] represented that when mutual information of two images are maximum, they are geometrically aligned. In other words, they used mutual information while registration to make sure images are maximally aligned.

Finally, there are lots of other studies using mutual information theory. The theory gives information about how similar two objects. The objects can be a PET image, ultrasound image, mammogram or EEG signal. As an addition, mutual information can be used in feature selection algorithms.

1.3 Motivation

The aim of the study is to build a knowledge based CAD system for Alzheimer's detection in FDG-PET images. Knowledge based (KB) systems provide a decision using a knowledge database by comparing a new case with all cases and relating new case to similar cases in its database. According to similar cases the system makes a final decision about new case whether he is patient or not. The proposed CAD system uses mutual information (MI) concept to reach final decision. MI is calculated for two images and measures how much two objects look like each other. The basic idea of MI is if two objects are very similar to each other their MI is maximal. The study aims to calculate MI of the all images and to see whether MI is useful for 3D PET images and to get high reliability.

The most important advantage and difference from other methods of the proposed method is its being very simple to apply. There is no feature selection and extraction or segmentation process. All images are used in their original 3D form. Algorithm of the CAD system is very basic for physicians and radiologist to apply and understand what they apply. In addition, there is no need to train system,it is very easy to integrate new 3D images. So system can easily use big databases. by the invention of global image search machine, system will be more functional.

1.4 Thesis Organization

Thesis organization is as follows. In chapter 2, we give information about the background of the disease and its diagnostic techniques. In chapter 3, we describe the database and ADNI. We describe data sets and theories used in this study in Chapter 4. In chapter 5, we reported the results of the experiments and discussed important parameters affected the results. Finally, conclusions of the presented study are presented and possible future works are discussed in chapter 6.

2. BACKGROUND

2.1 Introduction

In this chapter, we give information about Alzheimer's Disease and its diagnosis techniques. Also, we mention importance of early diagnosis of the disease.

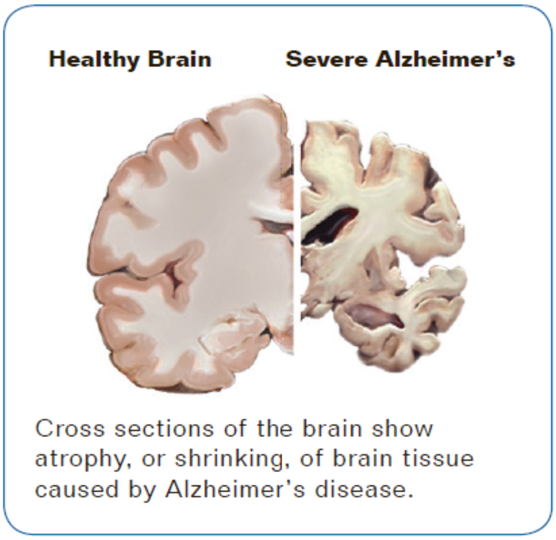
2.2 Alzheimer's Disease

Alzheimer's Disease is the most common cause of dementia where dementia caused by the death of nerve cells in the brain or malfunctioning of nerve cells. As a result of dementia, people lose their cognitive abilities, they suffer to do daily life activities. By death of nerve cell, patients have difficulty to remember. They also lose the ability of reasoning and thinking. There are other cause of dementia such as vascular dementia, Lewy body dementia. And some type of dementias are reversible namely depression, delirium, certain vitamin deficiencies. To differentiate all types of dementia from the dementia caused by AD, certain techniques are applied to patients which will be mentioned in next section.

Alzheimer's disease is an irreversible neuro-degenerative disease. The progression of the disease cannot be stopped. Before appearance of dementia or other symptoms of the disease, the change in brain structure and death of the nerve cells are started.

During very early stage of Alzheimer's, even if any symptoms are occurred, brain change was started. There appear amyloid plaques caused by abnormal deposits of proteins and tau tangles. In addition, nerve cells stop working, lose connections with other neurons and die.The change is started around hippocampus which is responsible for memory. As death of neurons increases, additional parts of the brain are affected.

In final stage of AD, damage spreads all parts of the brain and volume of the brain has decreased significantly [15].



[1]

Figure 2.1 Difference between normal brain and a brain having severe Alzheimer's Disease

There are pharmacological treatments for stopping or treatment of symptoms. However, there are no treatment to stop or slow the progression of disease. When the diagnosis of Alzheimer's Disease can be done at early stage, treatments may help to maintain daily functioning for some time. With early diagnosis, patients will be informed the progression of disease and they are able to learn living with the disease and take precautions about their financial and legal issues. Another advantage of early diagnosis is that, patients will take part in clinical trials such as trials for possible treatments or trials that will be made earlier diagnosis possible.

2.3 Alzheimer's Detection Techniques

There are some tests that diagnose AD done by physicians. First of all doctors ask family history, medical history and they take information about if there is any change in cognitive functions, behaviors and personality of the patient. After taking history, they carry out some tests about patients' memory and cognitive abilities. They also conduct standard blood and urine tests to make sure there are not any other problems that makes same symptoms. Finally they perform brain scans. Common tests are computed tomography(CT), magnetic resonance imaging(MRI), positron emission tomography(PET) and single positron emission tomography(SPECT). By performing these tests, physicians take information about brain structure and functioning of brain.

Additional to above techniques, there are new methods to have an idea about presence of AD in future. A gene called APOE provides a protein carrying cholesterol presents all humans bloodstream. There are some forms of that gene. Having one form of it decreases risk of having AD whereas having one other form of it increase the risk. By searching form of the gene, physicians have an idea of possibility of developing the disease. By knowing that risk, patients can built their life accordingly.

2.3.1 PET and SPECT

Positron emission tomography (PET) and single positron emission tomography (SPECT) give information about the brain metabolic rate of glucose consumption. A radio-tracer is given to patient. Flouro-deoxy-glucose is commonly used radio-tracer and we used PET images taking with this radio-tracer [16].

As mentioned above, as a result of the disease, great number of nerve cells died or lost their normal functions. Since PET and SPECT give functional information, these death regions or not functioning regions are easily seen.

We know that brain cells consume greater amount of glucose while they are functioning. So by using these kind of imaging techniques, doctors are able to see regional glucose consumption. In AD patient, there is a great decrease in hippocampus and decrease will be spread around the cortex with progression of the disease.

2.3.2 CT and MRI

Computed Tomography and Magnetic Resonance Imaging are also used while diagnosis of Alzheimer's Disease. They are used to eliminate other possible cause of symptoms of the disease. There may be same symptoms but different diseases, MRI and CT makes these classifications. For example they eliminate stroke or tumors or trauma that makes same complaints with AD.

These imaging techniques give structural information. Tau tangles and amyloid plaques can be seen by using these imaging modalities.

2.3.3 Other Clinical Techniques

There are also other techniques that physicians used to diagnose AD. By using these techniques, physicians are able to eliminate risk of other disease namely stroke, Parkinson's disease, brain tumors and so on.

Firstly, physicians take medical history. Then they take information about patients' diet, usage of alcohol, check blood pressure, make laboratory testing of urine and blood.

Neurological exam is one of them. These exam includes reflexes, eye movement, speech, sensation and coordination of muscle.

Mental Status tests are also included in these techniques. They evaluate memory, cognitive skills, thinking ability. A commonly used mental status test is called mini-mental state exam (MMSE). 30 questions are asked to patients during the exam about everyday mental skills. According to the number of correct answers, they make a decision about is there a dementia or the status of dementia severe or moderate. Other tests are also applied namely mini-cog and mood assessment.

All these tests help to make sure there is not any other possible causes of symptoms of AD.

3. DATABASE

We used PET images in this thesis. Images were taken from Alzheimer's Disease Neuroimaging Initiative (ADNI).

3.1 Alzheimer's Disease Neuroimaging Initiative

Data used in the preparation of this thesis were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). 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 dolar, 5-year public-private partnership. The primary goal of ADNI has been to test whether serial magnetic resonance imaging (MRI), positron emission tomography (PET), other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of mild cognitive impairment(MCI) and early Alzheimer's disease (AD). Determination of sensitive and specific markers of very early AD progression is intended to aid researchers and clinicians to develop new treatments and monitor their effectiveness, as well as lessen the time and cost of clinical trials.

The Principal Investigator of this initiative is Michael W. Weiner, MD, VA Medical Center and University of California-San Francisco. ADNI is the result of efforts of many co-investigators from a broad range of academic institutions and private corporations, and subjects have been recruited from over 50 sites across the U.S. and Canada. The initial goal of ADNI was to recruit 800 subjects but ADNI has been followed by ADNI-GO and ADNI-2. To date these three protocols have recruited over 1500 adults, ages 55 to 90, to participate in the research, consisting of cognitively normal older individuals, people with early or late MCI, and people with early AD. The follow up duration of each group is specified in the protocols for ADNI-1, ADNI-2 and ADNI-GO. Subjects originally recruited for ADNI-1 and ADNI-GO had the option to be followed in ADNI-2. For up-to-date information, see www.adni-info.org.

3.2 Image Features and Image Processing

Images form ADNI-1 study are taken. Since the most common radio-tracer used in clinic area is flouro-deoxy-glucose (FDG), we chose FDG PET images. Images were taken from particular sites and collected in a center located at University of Michigan. In that center, all images went under some processing process to become same quality level. All images are 3D images and in DICOM format.

We used two database in this first part of the thesis. In second part we used only one database.

First database have only images that went under only pre-processing procedure. All of images are co-registered, averaged, standardized image, in same voxel size and have uniform resolution.

The size of the images is 160 x 160 x 96 and their maximum grey level is 32767. There are 397 PET images including 259 normal and 138 AD patients.

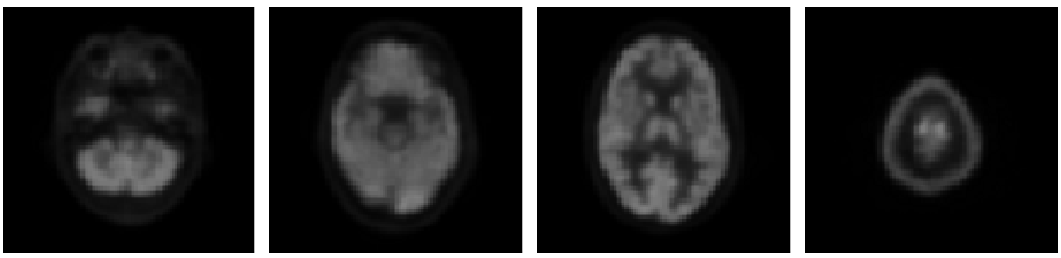


Figure 3.1 PET slices from a normal participant of ADNI Database

Figure 3.1 and 3. 2 are taken from ADNI pre-processed database. There are 96 slices available for one patient's PET image. The above ones are 15th, 29th, 48th and 93th slices respectively. From those slices, differences between AD and normal are

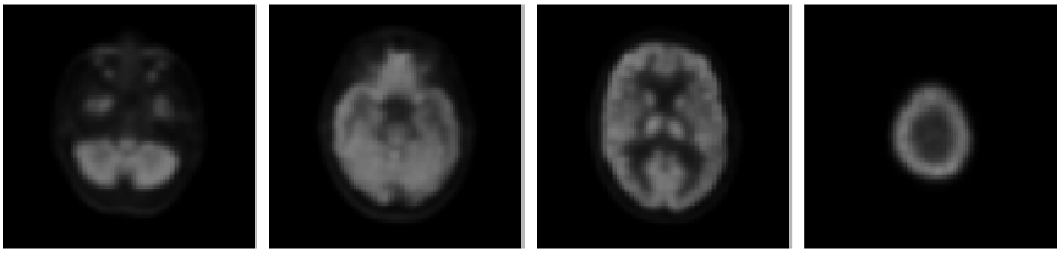


Figure 3.2 PET slices from a participant having AD of ADNI Database

obvious.

3D PET images used as intensity matrices. These 3D matrices store in a 4D matrices. In three dimensions, there is intensity values, in the fourth dimension, there are image indexes.

The second image dataset used in this work contains post-processed images. All of images are co-registered, averaged, standardized image, in same voxel size and have uniform resolution. After the pre-pre-processing, images went under different steps.

The size of the images is 128 x 128 x 60 and their maximum grey level is 32700. There are 197 PET images including 102 normal and 95 AD patients.

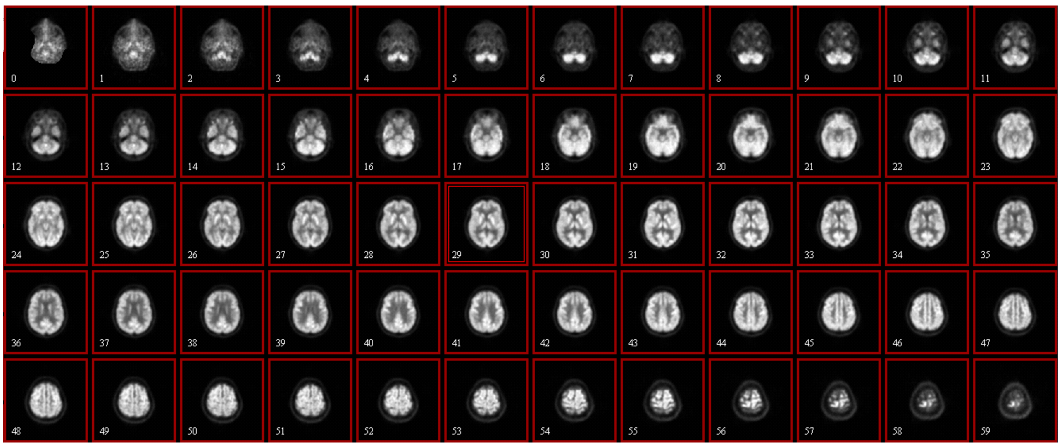


Figure 3.3 PET slices from a Normal participant in ADNI post-processed images' database

Figure 3.3 and 3.4 are examples of normal and AD participant's PET images from the post-processed image database. All of 60 slices are available in images.

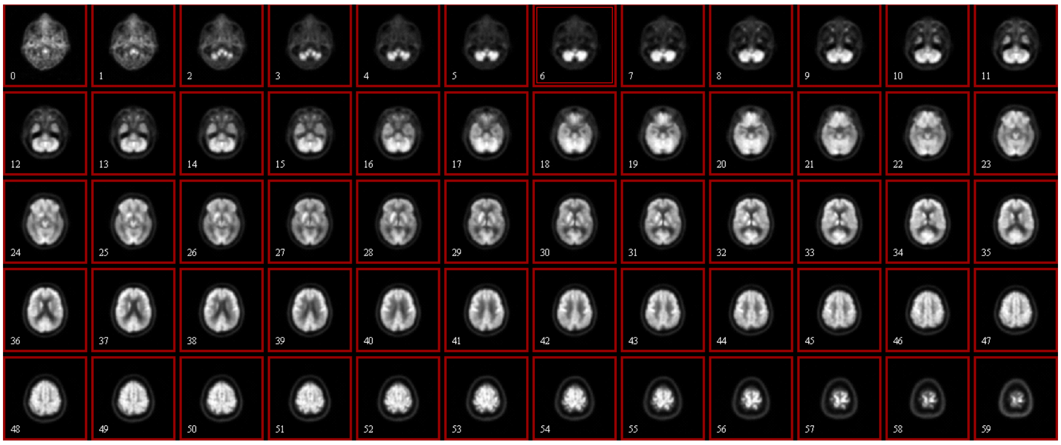


Figure 3.4 PET slices from a AD participant in ADNI post-processed images' database

3.2.1 Pre-Processing

All raw images are collected for quality control at University of Michigan. All pre-processed steps are done there. First step is registration. To register, separate frames are extracted from each image file. Each of these frames is co-registered to the first extracted frame. And the base image and all the co-registered frames are recombined as a co-registered dynamic image set and uploaded as in DICOM format.

By averaging the frames of the co-registered dynamic set, co-registered, averaged image set is constructed. End of this step, a single PET image set is saved. In third step, each participant's PET image is reoriented into a standard voxel grid having same cubic voxels. In this step, spatial re-orientation and intensity normalization has happened.

As fourth and last step, a scanner-specific filter function is used for smoothing to the image sets. Every image set went under a filtration process and images have a uniform isotropic resolution of 8 FWHM, the resolution is the lowest resolution scanners used in ADNI. Images from high resolution scanners are smoothed more then images from lower ones. At the end of all these processes, the images are saved in co-registered, averaged, standardized image and voxel size, uniform resolution dataset.[2]

[2]http://adni.loni.usc.edu/methods/pet-analysis/pre-processing/

3.2.2 Post-Processing

This type of processing is done in Utah by Foster Group. Firstly, every image sets are undergone pre-processing procedure and taken from co-registered, averaged, standardized image and voxel size, uniform resolution dataset. Additionally, some other processes are applied.

Using NeuroStat package, all images went under the process named standardize to baseline FDG. With same package, all images are warped into Talairach space. And finally intensity of the images is again normalized.

4. METHODS AND MATERIALS

4.1 Database

Two database from ADNI were used in this study. As mentioned in sec 3.2 database 1 consists of pre-processed images and there are 397 participants. 259 normal and 138 AD images were used.

In database 2, images were both pre-processed and post-processed. There are 197 images, 102 of them are normal and 95 of them are AD.

4.2 Overview of CAD System

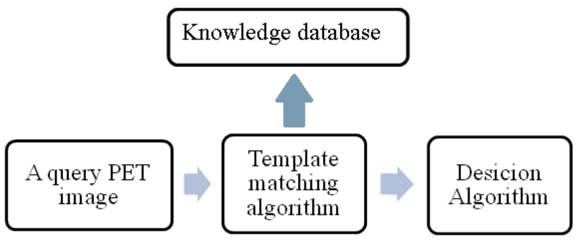


Figure 4.1 Overview of CAD System

There are three critical components of the computer aided diagnostic system namely knowledge database, template matching algorithm and decision algorithm. In first section of the materials and methods chapter, there is given information about the knowledge database. When an unknown image called query image come to the system, it goes firstly template matching algorithm part and in that part the query image compared to all other images in the knowledge database. The outputs from template matching algorithm which is explained in the mutual information section go to the decision algorithm. As a result there is reached a final decision for that query. The decision algorithm is explained in the distance metric section of this paper.

Before system start to work, the images should have to go under some pre and post processes. When the raw PET images are obtained, radiologists should make some adjustments. Firstly, radiologist should follow the ADNI pre-process steps. And secondly, radiologist should follow the ADNI post-process steps as both mentioned in data part of the article.

4.3 Mutual Information

The basic idea of this paper depends on the mutual information theory. The main question is how much similar a given image to the other images in the database. The more the two images are similar, the more information is provided between two images. To calculate mutual information, histogram approach, was used. Mutual Information between two random variables X and Y, in the study X and Y are two images in the database, was calculated by the following formula;

$$MI(X,Y) = \sum_{x}\sum_{y} P_{XY}(X,Y) \log_2 \frac{P_{XY}(X,Y)}{P_X(X)\ P_Y(Y)}. \tag{4.1}$$

Where $P_X(X)$ and $P_Y(Y)$ are the marginal probability density functions of the two images x and y based on their pixel values and their distributions were found from intensity histograms of images x and y. $P_{XY}(X,Y)$ the joint probability density function of the two images depended on their analogous pixel values. The joint pdf was found from a joint 2 dimensional histogram of two images.

Main idea is that if two images are similar, they have similar intensity values in similar pixel area. In other words, two images have similar intensity histograms as well as they have similar intensity distributions if two images are close to each other. The value of mutual information is always equal or greater than zero. In the case of full independence of two images, as example full black and full white images, mutual information is zero.

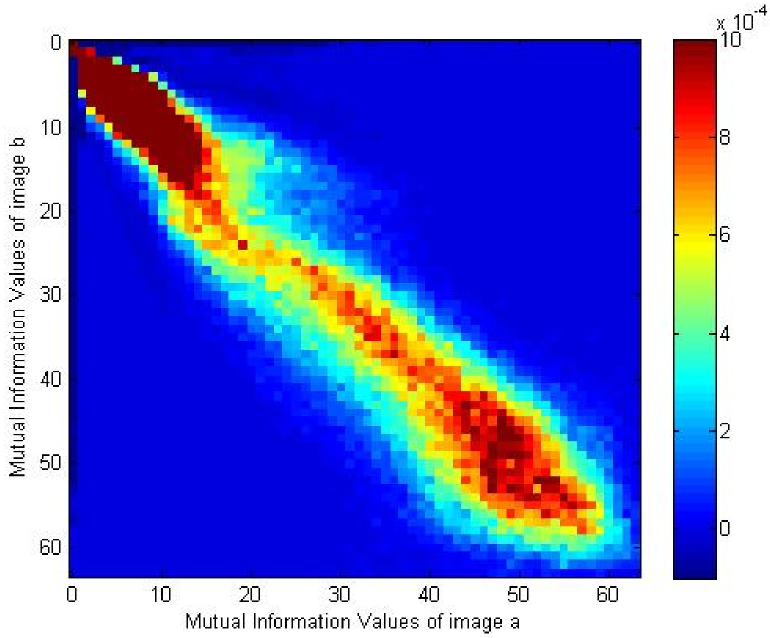


Figure 4.2 2D Histogram of mutual information for two images with AD

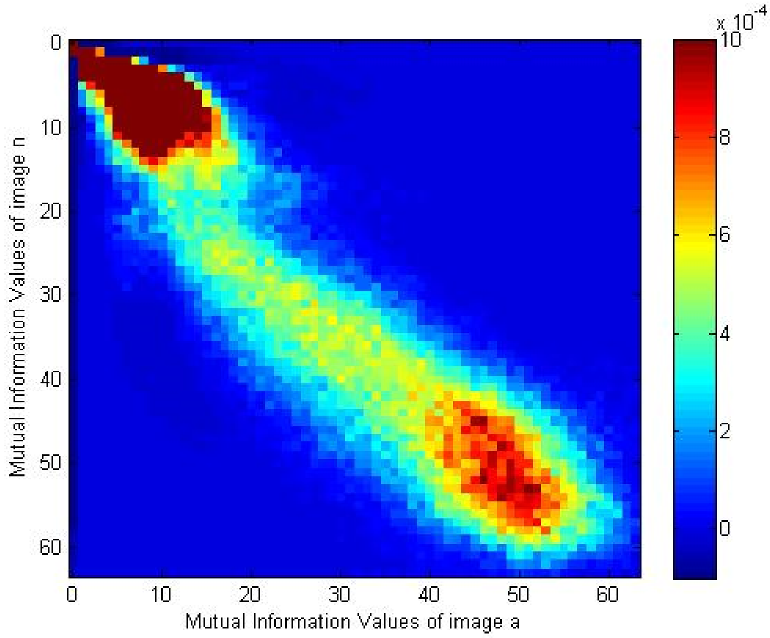


Figure 4.3 2D Histogram of mutual information for one normal image and one image with AD

In first figure, two images are selected from Alzheimer's database ,image a and image b, and mutual information of two images are estimated. Same as first figure, one image are from Alzheimer's database ,image a, and second image is taken from Normal participant's database,image n. As shown in figures, diagonal areas of first figure is more crowded than second. In other words, diagonal of first image has more red points meaning that they have higher values. This represents that images in first figure are similar than images in second figure as expected. If two images were same, the histogram will be purely diagonal with all red points on it.

Based on the histogram method, probability density functions are estimated using intensity histograms of the images. Each histogram bin corresponds to a grey level value. After counting the number of grey levels that fall into its particular bin, every histogram bin is divided into the total number of pixels. Then, mutual information is calculated. The important part is the number of histogram bin or grey levels. If all grey level values, maximum grey level is 32700, are used, histograms will be very detailed and there can happen noise. By decreasing grey level to 256, 128 and so on, we increase our chance of catching similarity at the same time we decreased the noise and some estimation errors.

4.4 Distance Metric

Since this is a computer aided detection system, there need a decision algorithm. After computation of mutual information, a decision index was calculated.

$$D(\ Q_i) = \frac{1}{k}\sum_{j=1}^{k} MI(\ Q_i,\ M_j) - \frac{1}{k}\sum_{j=1}^{k} MI(\ Q_i,\ N_j) \qquad (4.2)$$

Where M_j are images from AD database, N_j are images from normal database, k is the selected number of AD patient and normal in the databases. For first database one leave one out method was used. One image was selected and compared all other images in the database and according to above the formula d value was calculated for the selected image Q. For every image in the database, this procedure was applied. For second database, also leave one out method was used. And for all images a d value is calculated using all the other images in database.

Additionally for different k value, d values were calculated for all images. For first term, the highest mutual information values are selected in with Q, in other words, the best matches are selected in Alzheimer's patient. For second term, the best matches are selected in normal patients. It is important to have high reliabilities since the proposed CAD system will be used in clinical area.

Besides high reliability, speed of the system is important also. In clinical area there is time limit for every patient. The system should give its opinion between the time limit. It should not work for days or hours. In above paragraph k values are altered, to have less images in database to avoid storage problems and also to get faster responses. In addition to k values, there are other impacts on speed of the system. One of them is the computer used in calculation. The more CPU computers have, the faster the results are get. The computer used in this paper will be reported with results. The other important factor that affects the speed of the CAD system is the program used when calculating the results. And the program used while building algorithms is Matlab R2015a.

5. RESULTS

Results of the experiments are given in two sections. In first section, there are area under curve values of two databases, while in section two, the effect of registration and computational time calculations are presented.

5.1 ROC Performance

Receiver Operator Characteristic analysis and area under ROC curve were used to evaluate the systems performance. To make AUC calculation a web-based calculator constructed by John Hopkins Medicine was used[3] . To make system faster, the grey level was decreased and decision indices were calculated with decreased grey level.

5.1.1 AUC Performance for Database 1

The best experimental result was get when the system compares one image to all image except itself with grey level 64, in other words leave one out sampling scheme was used. To avoid biased data, one image compared to all other image except itself.

Table 5.1
AUC results of database1

Grey Level/Resolution	Full	80x80x48	40x40x24
256	0.732±0.026	0.730±0.026	0.616±0.029
128	0.738±0.025	0.737±0.025	0.703±0.027
64	0.744±0.025	0.743±0.025	0.741±0.025

The maximum area under curve had a tolerable value. However it is too low to use the system in medical care area. In this experiment, we used Acer Aspire S3 with

[3]http://www.rad.jhmi.edu/jeng/javarad/roc/JROCFITi.html

1.6 GHz CPU as our computer. And the program used while building algorithms is Matlab R2009a.

5.1.2 AUC Performance for Database 2

5.1.2.1 Step 1. In step one, the ROC performance was calculated as database 1 using the regular distance metric. An image was compared to all other images of entire database. Leave one out sampling scheme was used. Addition to above grey levels, images with 32, 16,8 and 2 grey levels were also calculated and AUC results were obtained.

Table 5.2
AUC results of database2

Grey Level/ Resolution	Full Resolution 128x128x60	Half Resolution 64x64x30	Quarter Resolution 32x32x15
256	0.8404±0.0276	0.6031±0.0393	0.6210±0.0388
128	0.830±0.0265	0.6122±0.0391	0.6277±0.0387
64	0.857±0.0261	0.6298±0.0387	0.6503±0.0381
32	0.8547±0.0263	0.6406±0.0385	0.6761±0.0373
16	0.8586±0.0259	0.6497±0.0382	0.6656±0.0377
8	0.8438±0.0273	0.6392±0.0385	0.6569±0.0379
2	0.8475±0.0273	0.5777±0.0398	0.5533±0.0402

The area under curve had an important value. Most of the images can be categorized correctly according to the AUC value. The maximum value was obtained when resolution is full and grey level is 16.

5.1.2.2 Step 2. In this step, the distance metric was changed a little. Instead of using all images in database, number of images used was changed in every time. K value was changed from one to all. In this part, the most similar cases are chosen. In

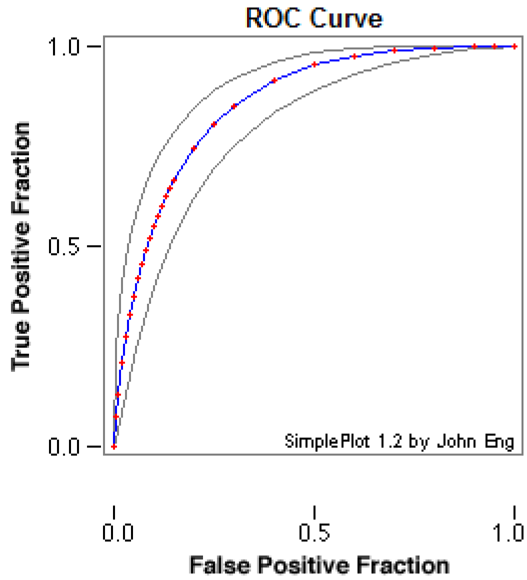


Figure 5.1 ROC Curve for grey level 64 with full resolution

first term, a query and its best match from images of Alzheimer's disease were chosen. In second term, a query and its best match from images of normals were chosen. For this step, full resolution and 64 grey level images are used. In table 4.3, area under curve results are given.

Table 5.3
AUC results for database 2 in second type of distance metric

K Value	K = 1	K = 10	K = 20	K = 50	K =ALL
AUC	0.6398 ± 0.0383	0.8094±0.0301	0.8190 ±0.0293	0.8361±0.0279	0.8573±0.261

According to the results, the more images were used, better results could be obtained.

In this experiment, we used HP Pavilion g6 Notebook PC with 2.50 GHz CPU as our computer. And the program used while building algorithms is Matlab R2015a.

5.2 Computational Time and Effect of Registration

Since the CAD system will be planned to use in the clinical area, response time of the system is important. For a new query if computational time is too high, it will be not useful since there won't be any time to wait both patient and physicians while they are in a doctor's room.

To reach a final decision of a new query, in other words for a new query, time needed of this query to compare and contrast all images in database and to reach a final decision is 934 sec. This time is for first database with full resolution with 64 grey levels. For second database a table 4.4 was constructed.

Table 5.4
Computational time of second database

Computation Time	Full resolution 128x128x60	Half Resolution 64x64x30	Quarter Resolution 32x32x15
Grey Level 256	93 sec	15 sec	5 sec
Grey Level 128	87 sec	12 sec	2 sec
Grey Level 64	84 sec	11 sec	2 sec
Grey Level 32	82 sec	10 sec	1 sec
Grey Level 16	81 sec	10 sec	1 sec
Grey Level 8	80 sec	10 sec	1 sec
Grey Level 2	78 sec	9 sec	1 sec

As seen in the tables, the result with second database with full resolution and 64 grey level is only 84 sec. And time needed for a query to reach its final decision is less than 2 min. Time need for a query is less than 3 min. The system compares a query to around 200 images. As a result, with a faster computer or a super computer computational time will be less and a response can be gotten faster.

There is another issue that affects the overall results of the study. It is registration. The study based on similarity among the correspondence pixels also correspondence regions of the brain. The more the brain structures are similar, the more the value of mutual information is gotten. However, there are structural changes in brain. Even though two people have same diagnosis rather have Alzheimer's or not, they can have very different brain structures for example one of them can have smaller brain. To decrease this kind of variability, spatial normalization is made. In other words, to reduce anatomical differences among patients, a brain atlas is used and called Talairach Atlas.

In this study, two different databases are used. Their main difference is their spatial normalizations. First database contains around 400 images but their brain anatomies differ from one to another. Their brain sizes are different and as a result of this, areas under curve values of first database are low. In second database, spatial normalization is applied. Every image is standardized to a reference brain. For every image, every region locates in the same area of the images. Hence in mutual information calculation, higher results are gained. Even though the database has lower number of images, they have much better results.

6. CONCLUSION and FUTURE WORKS

6.1 Conclusion

Since Alzheimer's disease is an irreversible neurodegenerative brain disease and there is no exact cure for the disease, early diagnosis of the disease is important. In addition with early diagnosis, the progression of the disease will be slowed down.

There are lots of work done to reach early diagnosis with a computer system. Computer aided diagnostic systems will become very famous in medical care areas when they are capable of having high reliability. As an example, a study used statistical parametric mapping software to diagnose Alzheimer's Disease [2]. Another common approach being used is support vector machine. Two studies are used this approach to diagnose the disease. They both extracted features from images using different kinds of methods [4, 5]. There are also other methods used to built CAD systems namely artificial neural network, local binary patterns, fisher discriminant analysis and so on [5,6,9].

In this study, we presented a computer aided detection system for Alzheimer's detection. The CAD system is designed to give a final decision rather the person has disease or not by comparing one new image to all images in the database. With a maximum area under curve value of 0.86, the current CAD system can able to help diagnosis of Alzheimer's disease. Two image databases from ADNI web site are used. Performance of proposed CAD algorithm is evaluated using these databases containing of large number of examples of normal and Alzheimer patients.

To our knowledge for an Alzheimer's disease CAD system, mutual information concept is very new. MI concept can be thought as an innovation in the AD area. MI is an indicator for one image being a patient or a normal by comparing their similarities. Besides that, all studies done to diagnose AD use feature selection and feature extraction processes. They need other algorithms for images in database so that makes their system more complex. With template matching algorithm, there is no need to select or extract features from images. Images can be added to the system with their original format.

The system works well while all images are used but the computation time is too long. The main burden of the system is its computational time. To use CAD in clinic area, the system must finish its computation in minutes. To make system faster, more powerful computers can be used or faster programs may be used instead of Matlab.

In addition the parameters used have an impact on computation time. To make calculations faster, we decreased the grey level values. In the paper, 256 grey levels were used to construct histograms. As a further study, grey levels may be decreased to 128, 64 or even 32.

The other parameter is the k value. If k value is too poor, system won't have enough images to compare, so the results won't separate patient or normal. If k value is high, computation time will rise correspondingly. With a chosen k value, system must give a decision in a short time and correctly.

The most important topics in the proposed work are the registration of images. With no registration the system has lower performance according to the differences in the anatomies of the brain among people. With Talairach space, the brain pictures of the participants are registered a common atlas. By reducing differences among participants' images, the proposed CAD system has a better performance.

To conclude, even if there is a time burden, mutual information metric works properly and the results are above expectation. The algorithm is very basic and there are no complexities Therefore, MI is a promising concept and can be used other areas.

6.2 Future Works

As a future work, we used whole 3D images with all features of the images. If some features of brain are selected before mutual information calculation, there will be less intensity values. In other words, we know that Alzheimer's disease affects initially certain parts of brain. If we can be able to extract those parts and make calculations with these parts, we can reduce noise and probably get higher reliability results. In addition, with small number of intensity values, calculation time will be decrease so as to computation time. In addition to feature selection, we can enhance the system by including machine learning methods. As we mentioned in section 1.2, a study [13] is used ensemble classifiers. Like the study, we can also use ensemble classifiers. By dividing database randomly into certain number of subclassifiers, we calculate certain number of decision indexes. Using a combiner, we can obtain a final decision index. Applying multiclassifier systems, data can be used more efficiently so performance of the system will be improved.

APPENDIX A. ALGORITHM USED WHILE DECREASING RESOLUTION

Algorithm 1 Resolution Decrease

```
for f = 1:197 do
    for i = 1:2:127 do
        for j = 1:2:127 do
            for k = 1:2:127 do
                a((i+1)/2,(j+1)/2, (k+1)/2,f) = ( A(i,j,k,f)+ A(i,j+1,k,f)+ A(i+1,j,k,f)+ A(i+1,j+1,k,f)+ A(i,j,k+1,f)+ A(i,j+1,k+1,f)+A(i+1,j,k+1,f)+ A(i+1,j+1,k+1,f))/8
            end for
        end for
    end for
end for
```

Where a is the image intensity matrix with half resolution and A is the image intensity matrix with full resolution. Averaging method is used to decrease resolution. Since the matrices are 3D, taking 8 neighbor pixels and dividing them to 8, resolution is decreased.

In addition this algorithm is written to decrease resolution from full resolution to half resolution. In other words, the size of images were decreased from 128x128x60 to 64x64x30.

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