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Evaluating a fractal features method for automatic detection of Alzheimer's Disease in brain MRI scans

A QUANTITATIVE STUDY BASED ON THE METHOD DEVELOPED BY LAHMIRI AND BOUKADOUM IN 2013

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Abstract

The field of computer-aided diagnosis has recently made progress in the diagnosing of Alzheimer's disease (AD) from magnetic resonance images (MRI) of the brain. Lahmiri and Boukadoum (2013) have research this topic since 2011, and in 2013 they presented a system for automatic detection of AD based on machine learning classification. Their proposed system achieved a classification accuracy of 100% (2013, p. 1507) using support vector machines with quadratic kernel classifiers. The MRI scans were first translated to 1-dimensional signals, from which three features were extracted to measure the signals self-affinity. These three features were Hurst's exponent, the total fluctuation energy of a detrended fluctuational analysis and the same analysis' scaling exponent. The results of their study were validated using a dataset of 23 MRI scans from brains with AD and normal brains.

This report makes an attempt at implementing the method proposed by Lahmiri and Boukadoum in 2013 and evaluating its accuracy on a dataset of 120 cases, out of which 60 are cases of AD and 60 are normal cases. The results were validated using both leave-one-out cross-validation and 3-fold cross-validation. A dataset of 23 cases consistent with Lahmiri and Boukadoum's in size was considered and the larger dataset of 120 cases. The best classification accuracy for the small and large were obtained from the 3-fold cross-validation was 78,26% respectively 65,00%.

The results of this study are to some extent similar to those of Lahmiri and Boukadoum's, however this study fails to verify how their method performs on a larger dataset, as their results for a small dataset could not be reproduced in this implementation. Thus the results of this report are inconclusive in verifying the accuracy of the implemented method for a larger dataset. However this implementation of the method shows promise as the accuracy for the large dataset was fairly good when comparing to other research done in the field.

Referat

Området datorstödd diagnos har nyligen gjort framsteg när det gäller diagnostik av Alzheimers sjukdom (AD) från magnetresonansbilder (MRI) i hjärnan. Lahmiri och Boukadoum (2013) har forskat i ämnet sedan 2011, och 2013 presenterade de ett system för automatisk detektering av AD, som bygger på maskininlärningsklassificering. Deras föreslagna system uppnådde en klassificeringsnoggrannhet på 100 % (2013, s. 1507) med hjälp av stödvektormaskiner med kvadratiska kärnor. MRI:er blev först översatta till endimensionella signaler, från vilken tre utmärkande faktorer som mäter signalens själv samhörighet extraherades. De tre faktorerna var Hurst exponent, den totala fluktuationsenergin hos en detrenderad fluktuationsanalys och skalningsexponenten gavs av samma analys. Resultaten av deras studie validerades med en datamängd bestående av 23 MRI från hjärnor med AD och normala hjärnor.

Denna rapport gör ett försök till att implementera metoden utvecklad av Lahmiri och Boukadoum under 2013, och utvärdera dess riktighet på en datamängd av 120 fall, varav 60 är fall av AD och 60 är normalfall. Resultaten validerades med både lämna-ett-ute korsvalidering och 3-faldig korsvalidering. En datamängd av 23 fall, som är förenlig med Lahmiri och Boukadoums storlek, och en större datamängd av 120 fall prövades. De bästa korrekthetsvärdena för den mindre och större datamängderna som erhölls från 3-faldig korsvalidering var 78,26% respektive 65,00%.

Resultaten av denna studie är i viss mån förenliga med Lahmiri och Boukadoums resultat, men denna studie lyckades inte bekräfta att deras metod fungerar på en större datamängd, eftersom deras resultat för en liten datamängd inte kunde återskapas i denna implementering. Således är resultaten av denna rapport inte övertygande i att kontrollera riktigheten i den implementerade metoden för en större datamängd. Men denna implementering av metoden visar potential, eftersom noggrannheten för den stora datamängden var relativt bra när vid jämförelse med annan forskning som gjorts inom området.

Contents

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Data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report. A complete listing of ADNI investigators can be found at: <http://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf>

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Chapter 1

Introduction

The idea of using computers for diagnosing diseases emerged during the 20th century, and since then the field of computer-aided diagnosis (CAD) has emerged and facilitated the diagnosing of many medical conditions and diseases. Specifically, a subfield of how to correctly diagnose Alzheimer's disease (AD) has been vastly researched the last decade. AD is a chronic neurodegenerative disease and a form of dementia. The disease is caused by the gradual death of cells in the brain, giving symptoms that gradually get worse. Symptoms are bad short-term-memory, problems understanding language, and difficulty in achieving everyday tasks (Aquilonius). Since the symptoms are not very distinguished, and it still is debatable which symptoms are to be counted to AD, the disease can be difficult to discover, especially in its early stages. About 100'000 people in Sweden have AD and the cost of care for them is approximated to 63 billion SEK (Aquilonius). Moreover, diagnosing the disease can be both expensive for society and uphold the quality of life for patients and their friends and family.

During the last years many articles have been published on the field of application for using CAD to diagnosing AD. To apply the resources of computers to analyzing data collected in the diagnosing process, such as magnetic resonance imaging (MRI) scans, opens up for new possibilities and challenges. The fact that a computer effectively can analyze data, in ways that humans cannot, has made it possible to investigate relationships between different components in the collected data. Correlations between components can be investigated, and since a computer can process images as well as applying algorithms to the result these possibilities have been thoroughly investigated the last years. Many of these attempts to find methods for diagnosing AD with CAD have resulted in complex algorithms that rely on great computer resources. However Lahmiri and Boukadoum (2013) have developed a simpler approach to the problem than those previously presented. Their research applies a new method (Lahmiri and Boukadoum, 2013.) to a dataset consisting of 23 MRI scans and obtains 100% classification accuracy. Their CAD system is notably less complex than many others proposed, and proved to be efficient in processing time as well. However, their method was never tested on a

larger dataset, hence their study has paved a path for future experiments. Since most other CAD systems are complex to implement and leave room for error along the processing chain, the method developed by Lahmiri and Boukadoum has an advantage in being relatively simple. Their impressive accuracy obtained in the study from 2013 (p. 1507) adds promise to the CAD system developed. Since the dataset was very small the system needs to be tested on a larger dataset to see how well the performance, in terms of accuracy of diagnosis, scales in a larger study. This report aims to implement the method developed by Lahmiri and Boukadoum in 2013, and test the approach on a dataset consisting of 127 MRI scans.

1.1 Problem definition

This study will investigate how well the system for diagnosing AD developed by Lahmiri and Boukadoum in 2013 scales to a larger problem domain. In other words this report will aim to evaluate whether the accuracy of their method of classification can be established for a larger dataset, as it was only validated by using a total of 23 brain MRI scans.

1.2 Scope and constraints

The focus of this report is to implement a method as consistent as possible towards that developed by Lahmiri and Boukadoum in 2013. Thus, the correlation between the method and the level of accuracy obtained in the results of this study will be evaluated, in an attempt to verify the performance of the method on a large dataset.

Finally, the purpose of the whole field of CAD for AD is to achieve a way of accurately diagnosing AD. Owing to the methods accuracy in diagnosing AD, can we know whether the method is a suitable one to distinguish normal brain MRI scans from MRI scans of brains with AD? In this study a binary classification will be performed on the MRI scans used, meaning that either the cases are classified as normal or they are classified as cases of AD. The proposed system of diagnosis will not be able to determine how early the algorithm can discover AD. Consequently, mild cognitive impairment (MCI) – although relevant to the research of AD – is considered to be outside of the scope of this study and will thus not be considered in the classification step. MCI is however relevant to the research of AD and will therefore be mentioned in this report.

1.3 Outline

This thesis introduces the research previously presented by Salim Lahmiri and Mounir Boukadoum with the purpose to copy their method developed in 2013. In the background AD and MCI is presented together with the state-of-the-art in CAD for AD. Furthermore, a background about the Machine Learning methods used is given. The previous work by Lahmiri and Boukadoum is also accounted

for along with their original data. In methods the data used in this study is accounted for, and then the implementation is described in depth. The results are divided into the graphic representations of the 1-dimensional signals, computation time and classification accuracy obtained by the system developed. The part about classification accuracy is divided by the result of the leave-one-out cross validation and 3-fold cross validation. In the discussion general points about the study is first raised, then there is a part with a deeper discussion about the data used, followed by a deeper discussion on the implementation. Finally the conclusion of the study is presented.

Chapter 2

Background

The aim of this background is to introduce the notions, concepts and techniques which are used in this study. In 2.1 dementia and AD are described. The points of interest are how the disease progresses and what the symptoms are. In 2.2 MCI is shortly explained. In 2.3 state-of-the-art in CAD for dementia and AD is presented. The main source is the paper by Bron E.E et al. summarizing the CAD dementia grand challenge. In 2.4 we introduce the technical concepts needed for our study. First of all what a MRI is and how it can be used in CAD. Then an introduction to the extraction of fractal features is given. That includes what Detrended fluctuation analysis (DFA) is and what Hurst's exponent is. The last part in the technical background is about classification with a Support Vector Machine (SVM). Lastly in 2.5 a recap on Lahmiri and Boukadoum's most recent work is given, with focus on their study in 2013.

2.1 Alzheimer's Disease

Dementia is a term that describes a range of symptoms indicating a loss of functionality in the brain (Nationalencyklopedin, 2009). It is often associated with a decline in memory skills, and there are many different forms of dementia. Dementia can be caused by damage to the brain or caused by a disease, and to what extent the diseases are genetically inherited can also vary. However, the symptoms of dementia diseases are often similar, as they often cause reduced memory loss, problems communicating through language and problems achieving everyday tasks.

AD is a form of dementia (Nationalecyklopedin, 2009) that today is considered to be a collection of very similar conditions and diseases. AD also deteriorates causing new and more severe symptoms over time. That is why an early diagnosis improves the possibilities of a good care for the patient (alz.org, n.d). Overall the affected person can appear to be very confused, and in the early stages of the disease people close to the affected often mistake the symptoms for normal aging (Medicinenet, 2015). However, AD is not a normal part of aging but a medical condition.

AD is caused by nerve cells losing their ability to function and eventually, during

the decline of the disease, the nerve cells die. The presence of AD starts in the frontal lobe and then spreads to other parts of the brain. The frontal lobes are the memory centers of the brain, which is why bad short-term memory is such a common symptom that presents early.

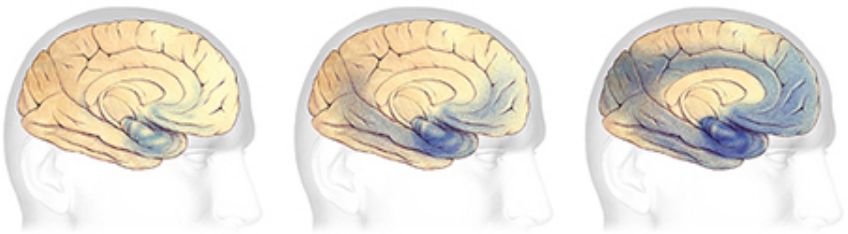

Figure 2.1. AD progressing in a human brain (alz.org, n.d).

The exact reason for why AD breaks out is not yet identified. However, it is known that in brains affected by AD there are proteins that create neurofibrillary tangles in, and between, nerve cells and amyloid plaques (Nationalencyklopedin, 2009). That is how nerve cells are disturbed to lose function and eventually die. The plaque has a core of the protein beta-amyloid and is surrounded by damaged or dead nerve cells. Even though it is not certain these plaques and tangles are believed to be the cause of AD.

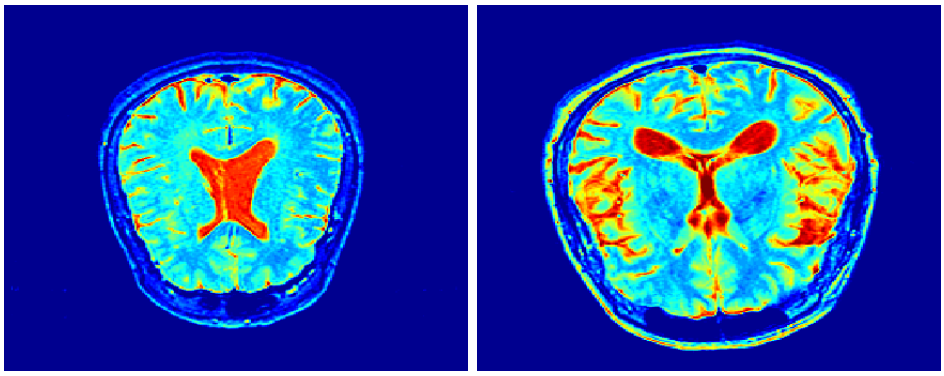

Figure 2.2. Normal brain to the left, AD brain to the right, displayed in double color format to enhance the difference between normal brain MRIs and AD brain MRIs (Harvard Medical School webpage, n.d cited in Lahmiri and Boukadoum, 2013, p. 1508).

2.1.1 Mild cognitive impairment

Mild cognitive impairment (MCI) is a reduction of a person's cognitive abilities that is more prominent than the effect of normal aging, however not as severe as to

classified as dementia. It does not affect the ability of performing everyday tasks, and at present day MCI is not formally considered a medical diagnosis. It has similar symptoms to dementia but does not cause as severe impairments, however it is a common yet unconfirmed hypothesis that MCI often evolves into dementia (Nationalecyklopedin, n.d).

2.2 State-of-the-art analysis for CAD for AD

CAD is and has been a subject of research since the 1950s. Applying it for diagnosing AD has for the last few years been a growing subfield. In 2015 Bron E.E et al published a paper (Bron E.E et al, 2015) summarizing the first results of the CAD dementia grand challenge. The challenge was announced in 2014 and contains 29 algorithms from 15 international research teams. The challenge was specified to develop algorithms for diagnosing AD using MRIs as data. In the conclusions of the report they claim "The framework defines evaluation criteria and provides a previously unseen multi-center data set with the diagnoses blinded to the authors of algorithms" (Bron E.E et al, 2015). Bron E.E et al. (2015, p.15) state that whether they have collected the best algorithms in the field is unsure. To participate in the challenge was very demanding, on top on the task of developing an algorithm for CAD Dementia, therefore some teams with good solutions may have chosen not to participate. However the paper provides the first tests where the algorithms do not execute on data very similar to the data it has been trained with. This gives a first insight to what the algorithms would be like in actual clinical situations. The best algorithm had a 63% accuracy. 19 out of 29 algorithms had an accuracy between 45% and 55%, out of which three algorithms performed worse, and seven performed better. The Sørensen-equal algorithm was the best algorithm in the CAD dementia challenge and the only one with a resulting accuracy of over 60%. Since there are not many other comparative studies in the field it is not sure if there are better algorithms than those submitted in the competition or not. There was no trend found in what classifiers make the best algorithms, so there is no standardization in this area yet. Although all the algorithms in the CAD-Dementia challenge use MRIs as data, they use different features that can be extracted from the MRIs. Some algorithms combined features and other used only one, but it was concluded that the best performing algorithms combined different features. The most commonly used features extracted from the MRIs were volume, thickness and shape of the brain. Intensities of the images was a common feature, although less common than the previously mentioned ones. The databases used in the measuring and testing were ADNI and AIBL (AIBL, cited in Bron E.E et al, 2015, p.6). Even though most of the recent algorithms discovered in the field involve distinguishing and diagnosing MCI in patients, the CAD dementia challenge did not address that issue (Bron E.E et al, 2015). Therefore the algorithms were only tested on their abilities to diagnose dementia.

Lahmiri and Boukadoum have since 2011 published different papers on how

to diagnose AD by classifying brain MRIs using machine-learning techniques. In 2011 they published the paper "Brain MRI classification using an ensemble system and LH and HL wavelet sub-bands features", where they presented an entirely new method to classify healthy brain MRIs and those with abnormalities (Lahmiri and Boukadoum, 2011). The features they used to analyze the MRI were LH and HL sub-bands and first order statistics. The classification was done with a combination of k-nearest neighbor, learning vector quantization, probabilistic neural networks and support vector machines. As their work has progressed it has become more specialized. In the paper "Automatic brain MR images diagnosis based on edge fractal dimension and spectral energy signature" (Lahmiri and Boukadoum, 2012) they tried to adjust the algorithms to find different pathologies in brain MRI, among them Alzheimer's Disease. In 2013 they published the paper "Automatic Detection of AD in Brain Magnetic Resonance Images Using Fractal Features" (Lahmiri and Boukadoum, 2013) in which a simpler approach was presented when comparing with other available algorithms. During the development they have become more specialized towards diagnosing AD. To make sophisticated algorithms for that aim they have changed some of their mathematical methods. In 2013 other features were extracted from the MRIs than in 2011. A few features and functionality were kept, for example MRI images were still analyzed and SVMs are still used for classification.

2.3 Technical background

This section provides the background for the technical aspects of the report and study.

2.3.1 Magnetic resonance imaging and computer-aided diagnosis

Magnetic resonance imaging (MRI) is a noninvasive medical test that aids physicians to diagnose and treat medical conditions. When performing an MRI scan on the brain powerful magnetic pulses and radio wave energy are used to create an image of the brain and the surrounding nerve tissue is created (WebMD, 2012). In the diagnosing of AD an MRI is often used to rule out other diseases that may cause symptoms similar to those of AD, since an MRI can reveal tumors, strokes, build-up of fluid, damage and indications of severe trauma on the head (alz.org, n.d). As AD is characterized by gradual loss of neurons and synapses this can cause a change in the brain's tissue and geometrical features (Wenk G.L, 2003 cited in Lahmiri and Boukadoum, 2013, p.1506).

Since the brain's tissue and geometrical features change during the progression of AD it is possible to investigate how different features can be used for CAD of AD. In simple terms the differences created by AD have a visual component in the scans, and therefore different features present in these scans can be used in the CAD. As explained in the state-of-the-art analysis, a wide range of features have been researched and tested against each other. Once a feature or a group of features

that have significance for the diagnosing of AD have been identified, these features from the basis for the computer classification of the original MRI scan. The features can be combined in a feature vector, and by using machine learning techniques this feature vector can be used to detect patterns and correlations between the features and how the differences correspond to different diagnoses. The aim for the machine learning system used is to learn to classify the data originating from healthy brains, as well as those of patients with AD, and correctly diagnosing a patient based on this data.

2.3.2 Extraction of fractal features

A fractal is a geometric shape that is self-similar and has fractional dimensions (Kale and Butar Butar, 2015). Fractal features can be used to measure both self-similarity and local, global and long-range power-law correlations in signals. When examining a MRI scan fractal features are present, but difficult to analyze. However, by transforming the MRI scan to a 1-dimensional signal, it is possible to extract fractal features by the means of signal analysis. The geometrical features of the original scan are represented by deviations in the resulting signal. Thus, if the differences of AD brains and normal brains are present in the MRI scans these differences could translate to the 1-dimensional signal.

The Hurst exponent is a fractal feature, and can be extracted from a 1-D signal as described in the previous paragraph. Hurst exponent describes the scaling behavior of a signal, namely the range of cumulative deviations from the signals mean (Kale and Butar Butar, 2015). It is directly related to the fractal dimension, which measures the smoothness of a surface or a time series (Lahmiri and Boukadoum, 2013, p. 1506).

DFA is a method developed by a C.-K Peng et al. (1994). Today it is know as a method for determining the statistical self-affinity of a signal, and has proven useful in revealing the extent of long-range correlations in time series (Physionet.org). It is similar to Hurst's exponent, however DFA can also be applied to signals whose underlying statistics, such as mean and variance, or dynamics are non-stationary. DFA can also serve as a complement to Hurst's exponent, as it evaluates an image's roughness. When applying DFA on the 1-D signal explored in the previous section the fractal stability of the MRI with regard to scale changes is evaluated, and thus it can be considered to analyzing the image roughness according to the original hypothesis proposed by Lahmiri and Boukadoum. The result of the DFA on the 1-D signal is a scaling exponent and the energy of the detrended fluctuations of the signal. Lahmiri and Boukadoum hypothesize that AD reduces the spread of pixel intensity in the MR image sufficiently to decrease its self- similarity in comparison to white noise or a normal MR image (Lahmiri and Boukadoum, 2013). Thus, they also conclude that the scaling exponent should be different from the obtained Hurst's exponent, and that this method should be able to distinguish an healthy brain from one with AD using the appropriate classifiers.

2.3.3 Support vector machines and classification

Support vector machines (SVMs) are supervised learning models within the field of machine learning. SVMs apply learning algorithms to analyze data and learn to recognize patterns in the dataset. The theory behind SVMs was developed in the 1960s and was first introduced by Vapnik and Chervonenkis (columbia.edu), and is based on statistical learning theory. SVMs are commonly used, and known for their good performance, in bioinformatics (Byvatov and Schneider, 2003), text and image processing among other fields of application. SVMs are trained to identify patterns by feeding them with test data, in which the input data to be processed is correlated to the expected outcome. Based on this training SVMs can be used to classify new data, and has thus been thoroughly used in a lot of research focusing on the uses of CAD for diagnosing AD with a high level of accuracy. A SVM is well suited for solving two-class classification problems, and does this by constructing optimal separating hyper-planes so as to maximize the distance between the two nearest data points in the two classes.

2.3.4 Lahmiri & Boukadoun's methodology

In Lahmiri and Boukadoun's recent work they have started by transforming the MRI image into a 1-dimensional (1-D) signal, on which they can perform a signal analysis and investigate different features in the signal. In their paper from 2014 they make the hypothesis that a healthy brain MRI would present with more regularity, in this context less rough or jagged edges, than that of a brain with AD or MCI (Lahmiri and Boukadoum, 2014. page 34). The method that we are implementing is from their paper on "Automatic Detection of Alzheimer Disease in Brain Magnetic Resonance Images Using Fractal Features", published in 2013. In this paper they propose a simpler approach, that leads to a faster running algorithm than many others that we have come across in the state-of-the-art analysis (Bron E.E et al, 2015). In short their method can be described as transforming the brain MRI scan to a 1-D signal without doing any image preprocessing. Then they extract two features from the obtained signal by using detrended fluctuation analysis, and together with Hurst's exponent for the 1-D signal a three-component vector is formed. This vector consisting of three fractal features is feed to the SVM with quadratic kernels – which perform the classification. In this paper they conclude that the proposed methodology using SVMs with quadratic kernels had 100% detection accuracy, however the dataset only consisted of a small sample of MRI scans (twenty-three).

Data used in the original study

The original study performed by Lahmiri and Boukadoum was validated using a dataset of 23 T2 weighted brain MRIs that were collected from the Harvard Medical School database (2013, p. 1507). The images were all in gray scale and the image size was 256x256. Out of the 23 brain MRIs 10 were of normal brains and 13 were

of brains with AD. In their paper from 2013 they make no statement of whether the full set of scans for all patients were considered, or if only one scan per patient was used in the analysis. Since their paper only mention 1-D signals of a MRI scan, it is assumed that only individual scans are analyzed when performing the diagnosis.

Chapter 3

Metod

This section describes the method of the report and the technical implementation of the techniques previously explained.

3.1 Data and datasets

The data used was collected from the ADNI database, consisting of more than 2000 scans of patients with AD, MCI and healthy brains in total. All images are in gray scale format with 256x256 pixels, the scans are T2-weighted and each slice has a thickness of 3.00 mm. The original images are in DICOM file-format, in other words the images follow the standard known as Digital Imaging and Communications in Medicine. All scans are taken in the axial plane following the same procedure, as all MRI scans used in this project originated from the "ADNI1 – GO month 6" sub study of the ADNI project. For each individual patient a set of 48-52 MRI scans were collected, the number depending on how the data had originally been collected. Each MRI scan for a patient can be analyzed to perform a diagnosis, normal or AD.

A dataset of 23 full brain MRIs was collected from the ADNI database, consisting of 10 normal brain MRI scans and 13 from patients diagnosed with AD. This dataset, hereby referred to as the small dataset, was used in the early stages of the project to validate the approach and system under development. The smaller dataset was chosen to be able to compare the results for a small dataset using our version of Lahmiri and Boukadoum's method with their results directly.

A larger dataset consisting of 120 cases was collected from the ADNI database on the same prerequisites as for the small dataset, this extended dataset is hereby referred to as the large dataset. The purpose of the large dataset was to analyze the performance of the proposed method with a large set of data, and evaluate how well the solution scales with a bigger amount of data to handle. This dataset consists of 60 cases with AD, as well as 60 normal cases.

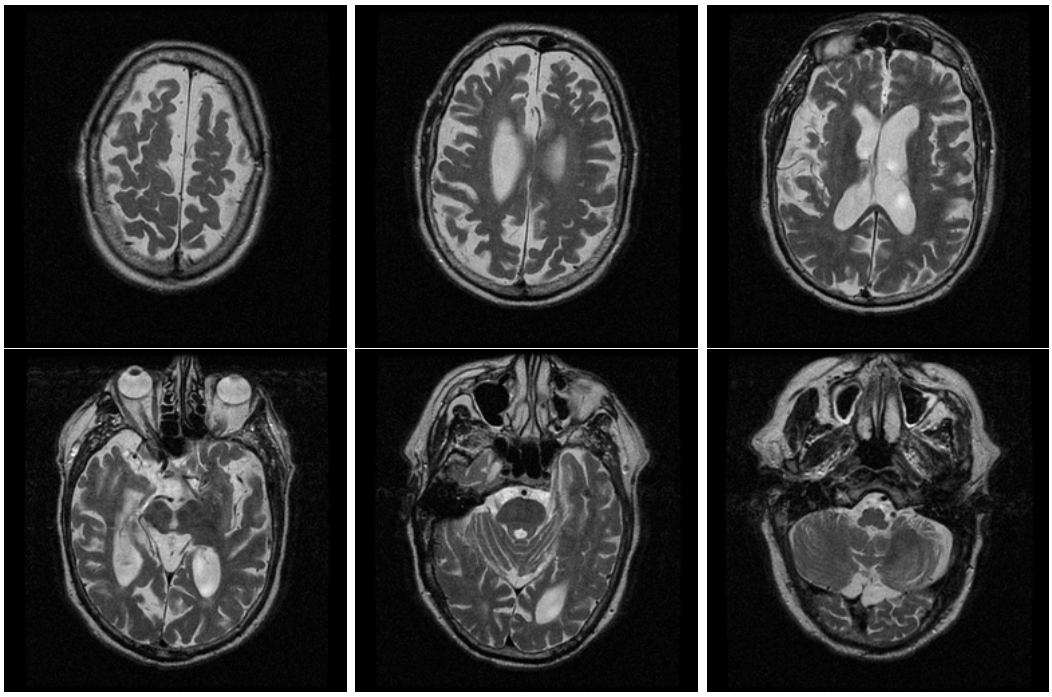

Figure 3.1. Five images from a sequence of 48 illustrating the layers in which the scans are taken. The scan is of a patient with AD (ADNI-database, 2006).

3.1.1 Acknowledgement

Data used in the preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). The ADNI was launched in 2003 as a public-private partnership, led by Principal Investigator Michael W. Weiner, MD. 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). For up-to-date information, see www.adni-info.org.

3.2 Technical approach

The system analyzes one MRI scan in order to perform a diagnosis on the patient using SVM classifiers. Since there is a collection of scans for each patient 5 different layers of the brain will be analyzed and the results evaluated. The scan being analyzed is first transformed into a 1-D signal and thus represented by a row vector in the technical implementation. From this signal the three fractal features are extracted and together they form the three-component feature vector needed for the SVM classifier.

The three features extracted are Hurst's exponent, the total fluctuation energy of a performed DFA and the scaling exponent of the same analysis. The three features are collected in a feature vector, in which each row vector represents a case. A SVM implementation is used from MATLAB's library and used to classify the data. The SVMs were set up with quadratic kernel classifiers and validated by both leave-one-out cross-validation and 3-fold cross-validation.

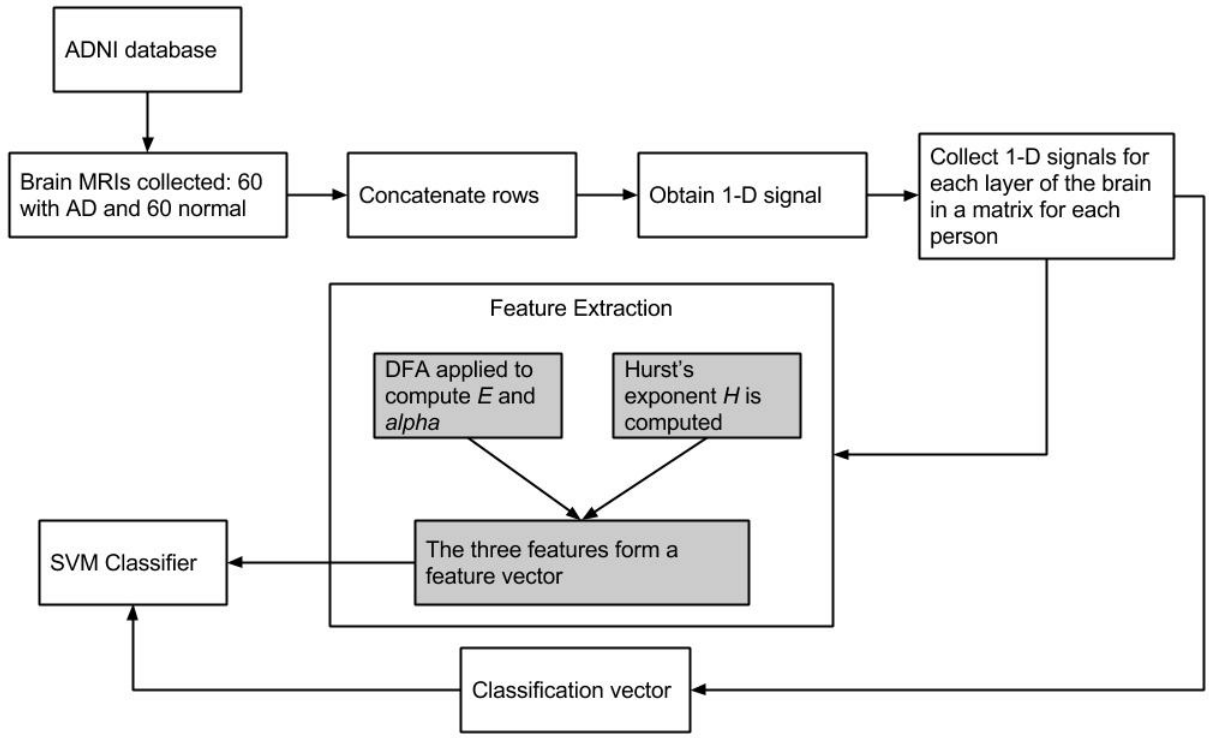

Figure 3.2. An overview of the method applied.

3.2.1 Transforming the MRI to a 1-dimensional signal

The method explored by Lahmiri and Boukadoum is based on signal analysis. The MRI scans used are transformed into 1-D signals, from which the features used in classification are extracted. Their dataset consisted of 23 images in gray scale, and

these images were transformed into a 1-D signal by applying row concatenation (Lahmiri and Boukadoum, 2013. p. 1507). No image preprocessing is needed prior to transforming the image to a signal. In gray scale the image can be interpreted as values representing the intensity in each of the positions in the image. When the image is transformed into a signal this can be done with different results in the resulting signal, in other words the level of how accurate the signal is towards the original image can vary. This level of accuracy depends on how the many positions in the image that are collected into a data point in the resulting matrix representation of the image. In Lahmiri and Boukadoum's study the highest level of accuracy was obtained as each pixel in the MRI scans were represented as data points in the matrix representation. Lahmiri and Boukadoun also concluded that the result of their study persisted even when the 1-D signal was obtained by column concatenation, however this is not validated in this study.

In this study all MRI scans were transformed to 1-D signals using a MATLAB script that was implemented according to Lahmiri and Boukadoum's methodology. Since each person has a collection of brain MRI scans the signals for each scan together form a matrix that is subject to the feature extraction in the next step of the implementation. The collection of scans for each person is first ordered in accordance to the level in which the scans were taken, i.e. from the neck up to the top of the head. This was done prior to forming the matrix to ensure that the different cases were treated consequently in this study.

3.2.2 Feature extraction

Since Lahmiri and Boukadoum (2013, p. 1607) hypothesize that AD reduces the spread of pixel intensity sufficiently to decrease its self similarity, features measuring the self-similarity of the signal are chosen in the applied method. Therefore Hurst's exponent and two features from a DFA are extracted, as they provide a measure of both the self-affinity as well as local, global and long-range deviations of the signals analyzed.

Hurst's exponent

In Lahmiri and Boukadoum's from paper of 2013 (p. 1506) section 2a they describe how they implemented Hurst's exponent. However in this study the generalized Hurst's exponent (Matteo, 2007), implemented in MATLAB, was used instead (Aste, 2013). The generalized Hurst's exponent was extracted from the 1-D-signals representing a MRI by treating the signal as a time series.

Alpha component and total fluctuation energy

DFA is performed on the matrix containing the 1-D signals for each case used in the study. The analysis detects long-range power-law correlations in the fluctuations of a signal treated as a time series. The alpha component computed by DFA is the scaling component and can be regarded as a measure that is similar to Hurst's

exponent. In this study an alpha value equal to or below 0.5 indicates that the original, accumulated signal is white noise, and a value greater than 0.5 and up to 1 indicates the existence of persistent long-range power-law correlations in the signal (Lahmiri and Boukadoum, 2013. p. 1507). The total fluctuation energy of the time series is also computed, and this is done by examining the fluctuations of the vector representing the fluctuations of the matrix. The alpha component is hypothesized to be different in MRIs of brains with AD when comparing to MRIs of normal brains, since AD should decrease the self-similarity. The difference between the two classes of brain cases should also be present in the fluctuation energy since the detrended fluctuations within each sequence of the time data analyzed.

The implementation of the DFA is done in MATLAB and is based on a program developed by Guan Wenye in 2008. His program refers to C-K. Pengs method for performing DFA and appears to be similar to the method applied by Lahmiri and Boukadoum.

3.2.3 Feature classification

The three features extracted, namely Hurst's exponent, the alpha value and the fractal dimension from the performed DFA form the three-component feature vector used for classification of the different cases. A SVM implemented in MATLAB performs the feature classification. The SVM has a quadratic kernel classifier that classifies each case into two classes, namely AD or Normal based on the three features previously explained. The SVM takes both a feature vector and the corresponding classification vector as input. Thus the SVM can be trained with a set of data and the training data's corresponding classes known from the classification vector. When the SVM has been trained with the training set it is tested with a test set of data. The data is divided into train and test datasets according to the validation models explained in the next paragraph.

3.3 Validation of results

In Lahmiri and Boukadoum's study form 2013 they used leave-one-out cross-validation when performing the classification in the SVM implementation in order to evaluate the prediction model that the SVM constitute. Thus, to enable for a comparison to be made between the results of this study and those of Lahmiri and Boukadoum the results will be validated using leave-one-out cross-validation (LOOCV). However, since the dataset is significantly larger than the original study 3-fold cross-validation will also be used in the classification performed by the SVM.

3.3.1 Leave-one-out cross-validation

Leave-one-out cross-validation (LOOCV) is a commonly used validation method. In this method one of the data points in the dataset is chosen for testing the classifier. The rest of the data points are used for training, in this case training the SVM.

The trained SVM is then tested with the one chosen data point. The procedure is repeated until all the data points have been used for testing the classifier, thus the method assures that all data points are used for testing and the training set is as large as possible in each iteration (Schneider, 1997). Because of the exhaustive nature of this method in assuring the largest possible test set, this method of validation is often applied for small datasets.

3.3.2 3-fold cross-validation

3-fold-cross-validation is very closely related to LOOCV. The data points are not chosen one by one, but divided into three sets. Then the same procedure as in LOOCV is repeated, but instead of a single element one of the three sets is chosen and used for testing. The procedure is repeated until all three sets have been used for testing (Schneider, 1997).

Chapter 4

Results

The following sections present the results of this study, gathered according to the previously described method.

4.1 1-dimensional signals of MRI scans

By first inspecting the 1-D signals created by row concatenation of MRI scans there is a clear distinction between the signals of a healthy brain and that of a brain with AD. Consistent with the results of Lahmiri and Boukadoum the healthy brain has a more irregular signal with a broader spread of pixel intensity. This can be illustrated by the images below, where the pixel intensity for the signal is plotted in MATLAB.

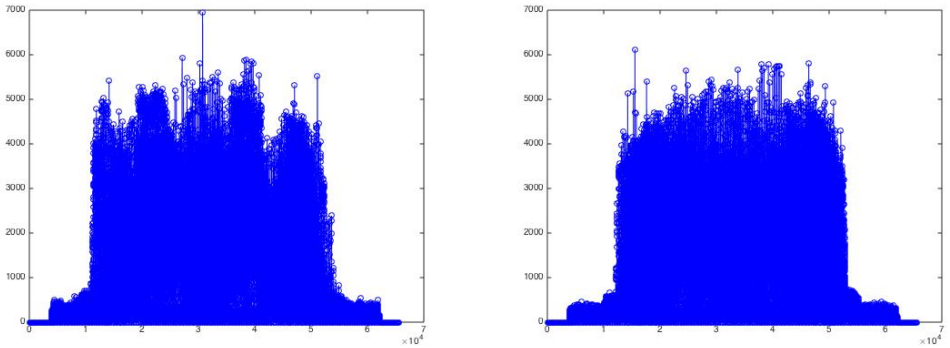

Figure 4.1. Displaying a normal brain MRI 1-D signal to the left and a 1-D signal from an MRI with AD to the right. The MRI scans are taken from the same layer in the brain.

4.2 Computation time

The feature extraction processing time was approximately 106 seconds per case using MATLAB_R2014b© on a 2.6 GHz Intel Core i7 processor on Mac OS X 10.9.4. Performing the DFA is the most time consuming process during the feature extraction, and takes approximately 102 seconds per case.

4.3 Classification accuracy

The below sections present the accuracy of the classification performed by the SVM using the two different validation methods. For both the leave-one-out cross-validation and the 3-fold cross-validation the numbers and measures presented here are extracted using the classperf function in MATLAB, which evaluates the performance of the SVM classifier.

4.3.1 Leave-one-out cross-validation

The correct rate is calculated over the whole set of iterations, therefore the correct rate and error rate presented below are the mean values. Both the small dataset and the larger one are validated using this method.

Results from LOOCV

Scan number	No. AD cases	No. Normal cases	Correct Rate	AEAD	AENO
20	13	10	26,09%	21	13
20	20	20	42,50%	20	26
20	30	30	51,67%	25	33
20	60	60	42,92%	52	85
25	13	10	45,65%	14	11
25	20	20	45,00%	20	24
25	30	30	34,17%	42	37
25	60	60	40,83%	94	48
30	13	10	53,35%	7	14
30	20	20	63,75%	11	18
30	30	30	45,83%	33	32
30	60	60	55,00%	30	78
35	13	10	39,13%	15	13
35	20	20	55,00%	11	25
35	30	30	35,00%	47	31
35	60	60	45,83%	39	91

- Scan number: the number of the scan, referring to its place in the sequence of scans taken.
- No. AD cases: Number of AD cases analyzed.
- No. Normal cases: Number of Normal cases analyzed.
- Correct rate: The average correct rate after running the validation 1 time.
- AEAD: The accumulated error of classification for AD cases when run 1 time. In other words the accumulated number of misclassified AD cases.
- AENO: The accumulated error of classification for Normal cases when run 1 time. In other words the accumulated number of misclassified Normal cases.

Error distribution for the most successful scan

Results were collected to evaluate the error distribution of misclassified cases for the most successful scan, namely scan number 30. These results are also based on the LOOCV.

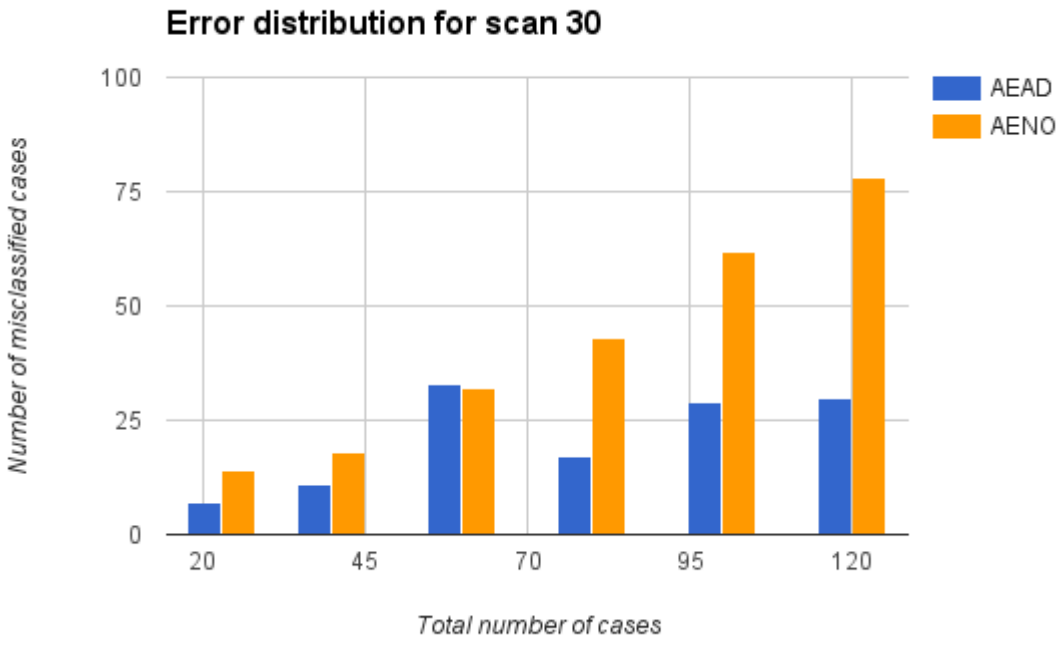

Figure 4.2. Error distribution between AD and normal cases for scan number 30.

4.3.2 3-fold cross-validation

The 3-fold cross-validation ensures that each datapoint is eventually used for both training and testing of the classifier. For this validation the error distribution by class is presented, as well as a table displaying the true and false positives/negatives.

Results from 3-fold cross-validtion

Scan number	No. AD cases	No. Normal cases	Correct Rate	AEAD	AENO	Best correct rate	Worst correct rate
20	13	10	36,95%	718	732	52,17%	21,74%
20	20	20	45,60%	1014	1162	57,50%	25,00%
20	30	30	48,23%	1447	1659	58,33%	35,00%
20	60	60	49,47%	2143	3921	55,83%	40,00%
25	13	10	45,95%	584	659	65,22%	21,74%
25	20	20	44,98%	1100	1101	60,00%	32,50%
25	30	30	38,43%	2015	1679	48,33%	25,00%
25	60	60	43,50%	3529	3251	50,83%	32,50%
30	13	10	59,69%	379	548	78,26%	43,48%
30	20	20	61,15%	607	947	72,50%	45,00%
30	30	30	51,28%	1416	1507	63,33%	38,33%
30	60	60	54,56%	1986	3561	65,00%	42,50%
35	13	10	41,26%	524	827	60,87%	8,70%
35	20	20	51,72%	736	1195	65,00%	35,00%
35	30	30	40,56%	1877	1689	50,00%	26,67%
35	60	60	45,55%	2432	4102	54,17%	34,17%

- Scan number: the number of the scan, referring to its place in the sequence of scans taken.
- No. AD cases: Number of AD cases analyzed.
- No. Normal cases: Number of Normal cases analyzed.
- Correct rate: The average correct rate after running the validation 100 times.
- AEAD: The accumulated error of classification for AD cases when run 100 times. In other words the accumulated number of misclassified AD cases.
- AENO: The accumulated error of classification for Normal cases when run 100 times. In other words the accumulated number of misclassified Normal cases.
- Best correct rate: The best correct rate found when running the validation 100 times
- Worst correct rate: The worst correct rate found when running the validation 100 times

Error distribution for the most successful scan

Results were collected to evaluate the error distribution of misclassified cases for the most successful scan, namely scan number 30. These results are also based on the 3-fold cross-validation.

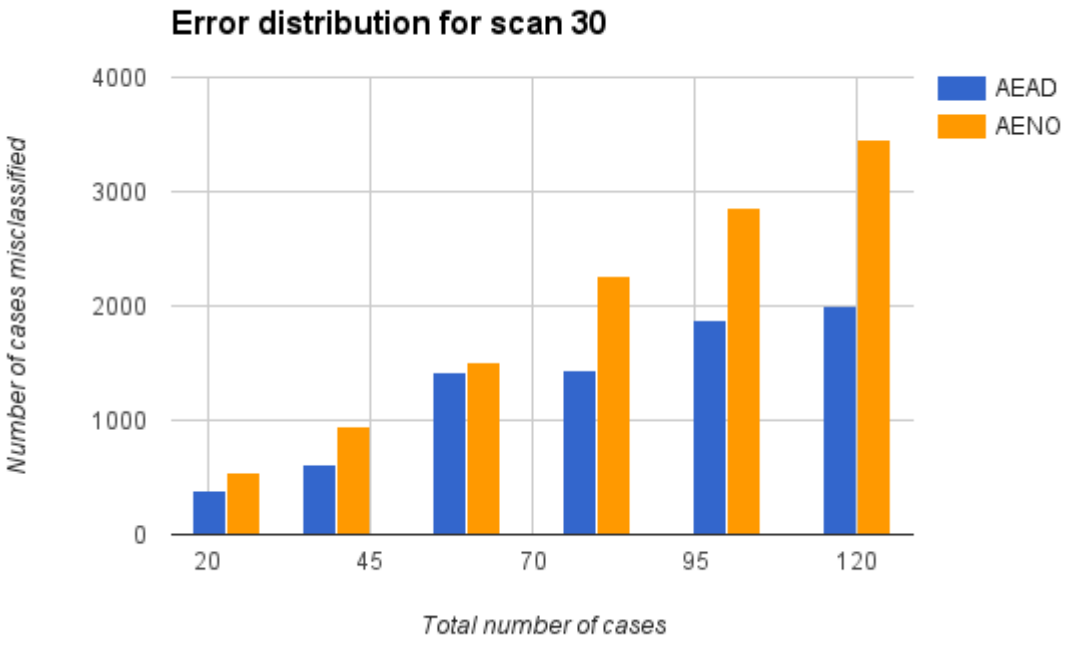

Figure 4.3. Error distribution between AD and normal cases for scan number 30.

Chapter 5

Discussion

The results of this study are to some extent consistent with those of Lahmiri and Boukadoum. Since the aim of the report is to apply the method developed by them in 2013 it is vital that the implementation is as consistent towards theirs as possible for an accurate comparison to be possible. Starting by examining the signals created in our implementation we conclude that the signals are very similar to those presented by Lahmiri and Boukadoum (2013, p. 1508). Therefore this adds credibility to further results of this study, as the consistency between this implementation and the one presented by Lahmiri and Boukadoum is essential. This study concludes that the 30th scan in the sequence had the best classification accuracy when used to perform a diagnosis. In the best case the from the 3-fold cross-validation the accuracy was as high as 65%, which is quite good when comparing to the results of the CAD Dementia challenge. This scan is close to the frontal lobe, and is thus consistent with the theory of AD originating from this area of the brain. When examining the results for the large dataset it becomes apparent that no other layer of the brain can obtain this level of accuracy. The mean accuracy for scan number 30 is 54,56%, comparing to 45,55% for scan number 35, which is the second best scan according to this study. These results are consistent when looking at the results from the LOOCV also. It is also noteworthy that the best accuracy obtained for the smallest dataset with 23 cases is 78,26% from the 3-fold cross-validation, which is a very good result, even if the mean is 59,69%. This result adds promise to the implementation, as it is a good result, even if it cannot compare to the 100% accuracy obtained by Lahmiri and Boukadoum for a dataset of the same size. However, if we only compare with the LOOCV results, as this is the same validation method as used by Lahmiri and Boukadoum, the result is fairly poor as mean accuracy for scan number 30 is 55,0%. However, it is not clear if the 100% accuracy from Lahmiri and Boukadoum was the mean accuracy, although we assume it is the mean value as stating the best accuracy obtained from a LOOCV validation would be trivial.

By regarding the error distribution by class for scan number 30 it appears as if the difficulty of distinguishing AD from normal cases becomes more prominent in the large dataset for both validation methods. In figure 4.2 and 4.3 we observe

that the number of misclassified cases of normal brains increases with the size of the dataset, and that this increase is consistently greater when comparing to the number of misclassified AD cases. For the purpose of the diagnosis it is preferred that the number of misclassified cases is greater for the normal cases than for the AD cases. As the system can be considered more reliable if it is more common to accidently classify a normal case as AD, than actually classifying an AD case as a normal case. Since the purpose of the system is to detect a disease that can be difficult to diagnose by other measures, it is better to send false alarms than to let the disease pass the system unnoticed. Future studies could address the error distribution for a corresponding scan on a larger dataset and investigate if the number of misclassified AD cases decreases at some point.

For both methods of validation the accuracy of the classification declined when attempting to scale the proposed solution to a larger dataset. However, as this study was unable to obtain the excellent level of accuracy even for the small dataset it is plausible that the implementation differs from that of Lahmiri and Boukadoum. Since this study failed to reproduce their results for the small dataset the results presented here cannot be seen as conclusive. It is possible that a small difference in the feature extraction of this study make these results inconclusive when attempting to verifying how well the solution scales to a larger dataset. When considering other factors than the technical implementation itself this study also used another resource for the original data than Lahmiri and Boukadoum did. The ADNI database contains detailed information of each person who participated in the study and by which protocol the MRI scans was collected. It is possible that missing details in the description of the data used in Lahmiri and Boukadoum study led to a difference in the data that could account for some of the differences in the result. Although, the difficulty for the classifier of this study to distinguish between AD and normal cases suggests that the features extracted were too similar between the two classes examined.

5.1 Discussion on the data used

In the paper produced by Lahmiri and Boukadoum in 2013 details about the data used was to some extent left out. Since the idea of diagnosing AD based on geometrical changes in the brain is based on a hypothesis about the sharpness of the edges the level of contrast could change the outcome. In the original paper there is no mentioning of the contrast in the intensity values of the gray scale images, and this could potentially change the accuracy of the classification model. By examining the database they refer to, namely the Harvard Medical School webpage, it is unclear from what study their data was collected. Moreover, if the data was collected from one of the public studies it appears that there in fact is a difference in contrast between the scans used in Lahmiri and Boukadoum's study and ours. Thus, it is possible that the outcome of this study could be different if a pre-processing of the image would take place to slightly increase the contrast. However, this would need

to be evaluated in future studies before drawing any conclusions.

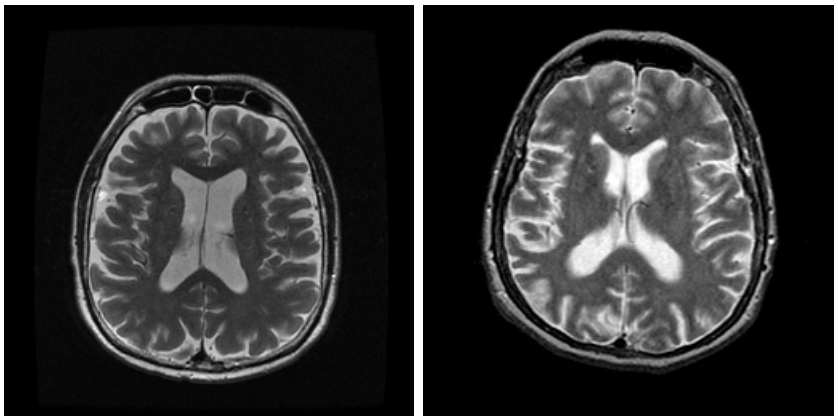

Figure 5.1. To the left you see scan number 30 from an AD case collected from the ADNI database (ADNI-database, 2006), and to the right is the approximate corresponding scan from the Harvard Medical School database (n.d.). These images illustrate the difference in contrast between the two scans..

The dataset used here is considerably larger than that of Lahmiri and Boukadoum (2013, p. 1507), since this dataset consisted of 120 different cases in total, comparing to the 23 cases used in 2013. The ADNI database is remarkable in its size, and the reason that this dataset was limited to 120 cases was that we wanted to ensure the consistency between the different cases. All the cases used in this study were collected using the same scanning protocol, however it is possible that the dataset could be extended in future studies. Moreover, owing to the long calculation time of the DFA it was outside the scope of this study to consider a dataset larger than 200 cases. Thus, it was not considered feasible to extend the dataset during this study.

5.2 Discussion on the method implemented

As the implementation of the SVMs were done using MATLAB's standard library it is assumed that this part of the implementation is reliable. Also, when comparing our 1-D-signals with the ones obtained by Lahmiri and Boukadoum (2013, p.1508) they seem consistent. Thus, when considering the method one other area of uncertainty is whether our feature extraction was consistent with the one performed by Lahmiri and Boukadoum. When implementing Hurst's exponent we found it difficult to find a reliable implementation consistent with the original Hurst exponent as used by Lahmiri and Boukadoum. Therefore we instead extracted the generalized Hurst exponent, treating the data as a time series of first-order moments, since this study does not consider multi-scaling properties of the data analyzed. As stated by Di Metteo, when extracting the generalized Hurst exponent for q = 1, "the value of this exponent is expected to be closely related to the original Hurst exponent, H,

which is indeed associated with the scaling of the absolute spread in the increments" (2007, p. 25). Hence, this study relies on the similarity between the generalized Hurst and the original Hurst during the circumstances stated above.

When thoroughly examining the method as it is presented by Lahmiri and Boukadoum (2013) it becomes apparent that there are two ways of interpreting how the MRI scans were analyzed in their study. Each case consists of a collection of MRI scans, so the diagnosing of AD can either be done considering a whole set or just a chosen scan. Which one of the Lahmiri and Boukadoum (2013) have chosen is not clear. In their methods they only address the question of individual 1-D signals, and do not account for how the collected data for a brain is treated in detail. Their paper only shows two MRI scans of two different brains, one normal and one with AD. However, the images seem to be from slightly different layers, which gave rise to even more uncertainty for the implementation of this study. Yet, their method of performing the signal analysis is highly unlikely to have been performed on a whole brain, but can only have been performed on one 1-D signal representing one layer of a brain. Furthermore, if one contemplates the idea of actually performing the signal analysis on each layer of the brain to then send the resulting feature vectors to a classifier, one quickly discovers that the results of the classification would be inconclusive. As there are many structural differences between layers of the brain we believe that it would be very difficult to train a classifier to perform a diagnosis on such inconsistent data. Moreover, this would imply a massive amount of data for the system to process, considering that for a set of 120 patients, the feature extraction would be performed 6000 times. Taking into account that the DFA takes approximately 102 seconds to perform, computing the features for all layers of 120 brains would take seven days on a 2.6 GHz Intel Core i7 processor on Mac OS X 10.9.4. The time of computation is substantial and constitutes a limit on future investigations.

If each layer of the brain was to be considered separately a future improvement could be to train an ensemble of SVMs, so that there is a SVM specialized for each layer of the brain. Owing to the time constraint of the feature extraction a future investigation could focus on a smaller region of the brain, for example by analyzing scans close to the frontal lobe. In such an approach the number of scans considered per case could be limited to 6 or 8, and a more sophisticated system could be developed to have one SVM specialized for each of the considered layers. Thereby a two step classification could take place, first the individual scans are classified, and then the result for all scans belonging to a case form the basis for classification of the case itself. This is approach would add complexity to the system, but could provide valuable insights to the patterns of AD in a selected region of the brain.

Chapter 6

Conclusion

This study fails to verify how Lahmiri and Boukadoum's method from 2013 performs on a larger dataset, as their results for a small dataset could not be reproduced in this implementation. However, this implementation of the method shows some promise, as the best result for the large dataset was as high as 65% using the 3-fold cross-validation. Since the proposed system does not reach a satisfactory level of accuracy for distinguishing between cases of AD and normal cases no attempt was made at also diagnosing MCI. However, as introduced in the discussion, future research could investigate how well an ensemble of SVMs could be trained to specialize in diagnosing different layers of the brain. By then adding a second classification the collected diagnoses of the layers could form the basis for diagnosing the case as a whole. Future implementations could also consider if small enhancements of contrast in the original MRI scans can improve the classification accuracy by slightly increasing the geometrical differences of the original images prior to the feature extraction.

Chapter 7

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