Chapter

# An Ensemble of Classifiers for the Early Diagnosis of Alzheimer’s Disease

Loris Nanni1, Nicolò Zaffonato1, Christian Salvatore2, Isabella Castiglioni2,[[1]](#footnote-1)\* and the Alzheimer’s Disease Neuroimaging Initiative

1Department of Information Engineering, University of Padua,   
Padua, Italy

2Institute of Molecular Bioimaging and Physiology, National Research Council (IBFM-CNR), Segrate, Milano, Italy

## Abstract

In this chapter, a method for performing an early diagnosis of AD is proposed, and it combines different feature selection approaches on brain MRI studies. Each selected set is used to train a separate Support Vector Machine (SVM); the results of the ensemble are then combined by a weighted sum rule. Moreover, a novel approach for considering the feature vector as an image is proposed that allows different state-of-the-art texture descriptors to be extracted. We report the performance obtained by a histogram of the gradient descriptor.

The superior performance of the proposed system is obtained without any ad hoc parameter optimization; in other words, the same ensemble of classifiers and the same parameter settings are used for all datasets.

The code to reproduce the experiments will be available at https://www.dropbox.com/s/bguw035yrqz0pwp/ElencoCode.docx?dl=0.

**Keywords:** Alzheimer’s Disease, ensemble of classifiers, pattern recognition, feature selection

## 1. Introduction

Alzheimer’s disease (AD) is a neurological pathology that affects more than 47 million people worldwide, being the first cause of neurodegenerative dementia. For effective treatments to be administered that are capable to slow down the progression of the disease, an early and definite diagnosis of AD is necessary. However, the goal of reaching an early and accurate diagnosis requires an investigation of the symptomatic pre-dementia stage of the disease, called Mild Cognitive Impairment (MCI). This stage involves the challenging question of predicting whether MCI will (MCIc) or will not (MCInc) convert to AD.

Clinical individual diagnosis of AD is still primarily based on the neuropsychological assessment and examinations that are administered to the patients. A definite diagnosis, however, is only possible through post-mortem analyses.

The clinical diagnostic criteria for AD, which were developed in the 1980s by the National Institute of Neurologic and Communicative Disorders and Stroke and the Alzheimer’s Disease and Related Disorders Association (NINCDS-ADRDA), are still in progress and have seen a progressive evolution. The diagnostic process were first mainly based on the presence of a cognitive impairment [1]. Neuropathological information was then introduced, based on the presence of senile plaques and neurofibrillary tangles [2]. These criteria were recently revised by the National Institute on Aging-Alzheimer’s Association (NIA-AA) workgroup, which introduced additional supportive features for the diagnosis of AD, such as: 1) neurogenetic testing, 2) measurement of cerebrospinal fluid (CSF), 3) amyloid and tau, and 4) neuronal injury biomarkers as measured through neuroimaging techniques, i.e., Magnetic Resonance Imaging (MRI) and Positron Emission Tomography (PET).

The introduction of imaging techniques in the diagnostic criteria of AD, and in particular of MRI and PET, was due to their ability to provide measurements of atrophy and of metabolism/amyloid markers, respectively. Changes in these features can be detected even before dementia is apparent [3],[4] thus representing a strong support for the diagnosis of AD. Besides this aspect, MRI shows the further advantage of being a non-invasive technique.

Because of these reasons, in the last few years a considerable research effort has been focused on implementing and developing advanced MRI processing techniques that utilize machine learning (ML) systems for improving the diagnostic accuracy of AD. Automatic systems capable of distinguishing pathological subjects from normal subjects based on their MRI brain studies (without requiring a priori hypotheses regarding where information relevant to diagnosis is located in the images) would make significant strides towards the goal of early AD detection. One problem with automatic classification of AD, however, is that the usual dimension of the MRI feature vectors is extremely high and most datasets contain few training patterns. This confluence of factors leads to the curse-of-dimensionality problem. To develop powerful automatic classification systems for AD, it is essential to find approaches for selecting a subset from the original set of features for which the classification performance is still high.

In this work, we propose a new classification system based on a ML approach. The idea is to create an ensemble of Support Vector Machines (SVMs) that is built training each SVM with a different set of features. Different feature selection approaches are compared, in order to select a subset of the whole set of original features for training SVMs. Moreover, we run several experiments for comparing a set of approaches for representing a feature vector as an image. We extracted a texture descriptor (Histogram of gradients [11]) from the images to train a SVM which is combined (by sum rule) with SVM trained using the original feature vector. The system has been tested using two different brain MRI studies.

## 2. Proposed System

In this section, we briefly explain some feature selection methods and texture descriptor approaches. As reported above, we have used the well-known SVM [5] as classifier (LibSVM implementation https://www. csie.ntu.edu.tw/~cjlin/libsvm/).

### 2.1. Feature Selection

In this experimental section, we have tested the following feature selection (FS) approaches:

* Fisher score (Fi) [5]: this is an approach based on discriminative methods;
* Kernel PS (KPS) [15]: this method is a feature selection technique that discovers non-linear correlation among the features. This method tries to find an approximation between a given matrix and a given vector of labels;
* Lagrange Multipliers (LM) [16]: this is a method that processes the feature selection according to a rank corresponding to the values of the Lagrange multipliers;
* F2graph (F2G) [17]: this is an unsupervised feature selection method that considers both sample-level and feature-level relations in the data by integrating a subspace learning method into a sparse feature-level self-representation technique;
* Aggregate selection (AS) [18], it is a feature selection approach that combines the feature ranking obtained by the following three approaches: Fisher score [5]; T-test [5]; Sparse Multinomial Logistic Regression via Bayesian L1 Regularization [22].

To reduce the computation time the different FS are run on a subset of 10000 features selected by Fisher score, not on the original feature vector.

### 2.2. 2D Representation

To represent the patterns it is normally adopted the one-dimensional representation, but this is not the only way. It is possible to represent the patterns through a matrix in order to capture correlations among features. For example, in [6], [7] classifiers developed for handling 2-D patterns are proposed. In [8] is shown that continuous wavelet can be used to transform a vector into a matrix in order to represent it through textural descriptors.

The idea to represent a vector as an image is normally used in CNN, in some topic, as audio classification, speech and natural language processing.

In this paper, we tested three methods for reshaping a vector in a matrix:

* Continuous wavelet (CW) [8]: we apply Meyer wavelets to the original d-dimensional feature vector. We built a 100×d image considering the wavelet power spectrum of 100 different decomposition scales.
* Random Reshaping (RS): In this approach we create a random matrix of size d0.5×d0.5 where d is the original vector length. Each entry of matrix is randomly filled using a value of the original input vector.
* Sum (Sum): In this approach we create a random matrix of size d×d where d is the original vector length. Each entry of matrix is filled with the average of a random number, between 2 and 6, of randomly extracted original features.

We improve the performance using a random sorting reshape N (N = 50) of the original feature vector. For each reshape we extracted a different descriptor, each used to feed a different SVM, then we combined the 50 SVMs by sum rule.

Fisher feature selection is used to select the best 10000 features then a subset of 4000 features is retained using other feature selection approaches (see the experimental section). To avoid to build large images we divide the 4000-dimensional feature vector in 25 subsets, each subset is represented as a matrix and then described by a texture descriptor. Twenty-five different SVMs are trained and combined by sum rule.

Each 2D representation is described by the Histogram of Gradient feature [11]. The Histogram of Gradient (HOG) is a widely used feature descriptor in image processing. The idea is to divide the image in sub windows and to represent the image by a set of histograms that count occurrences of gradient orientations in each local sub window of the image. In this work, the input matrix is divided into 5×6 non-overlapping sub windows, the different histograms are concatenated to represent the original matrix.

## 3. Experimental Results

Different datasets have been used to test the performance of our methods and of the ensemble of SVM. The benchmarks belong to two different brain MRI studies:

* ADNIset This dataset is composed of 509 subjects collected from 41 radiology centers, and it consists of 137 AD, 76 MCIc, 134 MCInc and 162 CN. The follow-up period to observe the conversion to AD was 18 months. This dataset was already used in [12] and [20] for the automatic classification and prediction of conversion to AD. All data included in this set were obtained from the database of the Alzheimer’s Disease Neuroimaging Initiative (ADNI, 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, 5-year public private partnership. The primary goal of ADNI has been to test whether serial MR, PET, other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of MCI and early AD.

The dataset is made up of T1-weighted structural MR images of the patients acquired at 1.5 T (according to the standard ADNI acquisition protocol [13]). For each patient, data from the screening or the baseline were considered. Preprocessed images (3D-gradwarp geometry correction for gradient nonlinearity and B1 intensity correction for non-uniformity) were downloaded from the ADNI data repository. A further preprocessing (see [12] for details) was applied to downloaded images, including: 1) image re-orientation; 2) cropping; 3) skull-stripping; 4) image normalization to MNI standard space (MNI152 T1 1mm brain template); 5) tissue segmentation into Gray and White Matter tissue probability maps. The final size of MRI volumes was 121x145x121 voxels. These volumes were given as input to the ML system in order to perform the following classification tasks: AD vs. CN, MCIc vs. CN, MCIc vs. MCInc. The performance of the classifier when using Gray-Matter tissue probability maps was compared to those obtained using White Matter (WHITE) and Whole-Brain (WHOLE, i.e., without tissue segmentation) volumes. The validation of the classifier was performed through a nested 20-fold Cross Validation (CV) process.

* MRI This dataset is composed of 260 patients collected from the ADNI data repository, and it consists of 130 AD and 130 CN. This dataset was already used in [14] for the automatic diagnosis of AD, and it is made up of T1-weighted structural MR images. The same features extracted in [14] were used in the present work, these being voxel clusters detected through voxel-based morphometry on MRI images and voxel values as volume of interest. Moreover, the validation of the classifier was performed through a 10-fold CV (as in the original work).

The performances of our classification system when different feature-selection techniques were used are reported in Table 1. Specifically, we first reduced the number of original features to 104 using Fisher score, with the aim of reducing the computational cost. Then, the different feature-selection techniques were applied to the reduced set of features. The classification system was based on SVM with Intersection kernel, and the Area Under the ROC Curve (AUC) [5] was used to evaluate the classification performance.

In each cell of Table 1 there are three performance values:

1. Performance obtained selecting 2000 features;
2. Performance obtained selecting 4000 features;
3. Performance obtained selecting 6000 features.

On average the best performance is obtained retaining 4000 features. Notice that, to reduce the computation time the different FS are run on a subset of 10000 features selected by Fi, not on the original feature vector.

Table 1. Performance obtained by different feature selection approaches

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | AD vs. CN | MCIc vs. CN | MCIc vs. MCInc | MRI |
| KPS | 92.1 93.3 92.9 | 91.2 90.8 91.2 | 62.5 63.5 64.7 | 95.2 96.5 96.9 |
| F2G | 91.7 92.2 92.4 | 86.5 88.0 88.2 | 69.6 71.9 70.1 | 96.3 97.2 97.5 |
| LM | 92.2 93.0 93.1 | 90.0 90.6 90.7 | 67.1 68.2 67.5 | 95.9 96.6 97.1 |
| AS | 92.2 93.0 93.0 | 89.3 89.6 90.1 | 61.3 64.6 66.6 | 96.9 97.2 97.2 |

In the following table 2 we report the performance obtained by:

* Fi(2000), performance obtained retaining the first 2000 features selected by Fi. It the best stand-alone method in [20];
* FUS, fusion by sum rule among Fi(2000) and the four feature selection methods (retaining 4000 features) reported in Table 1.
* RS10000, random subspace [5] of 50 SVMs each trained with a subspace built using 5000 features randomly extracted from the set of 10000 features selected by Fi.

Table 2. Proposed method vs literature

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | AD vs. CN | MCIc vs. CN | MCIc vs. MCInc | MRI |
| Fi(2000) | 92.4 | 85.5 | 67.5 | 96.8 |
| FUS | 93.7 | 90.5 | 68.1 | 97.3 |
| RS10000 | 92.8 | 90.7 | 66.0 | 97.3 |
| [20] | 93.3 | 88.9 | 68.6 | 96.9 |
| [14] | --- | --- | --- | 95.3 |

The new method obtains performance slightly better than [20] using a simpler approach, in [20] we have shown that the proposed approach compares favorably respect different state of the art methods, applied to the same dataset used in our study (ADNIset), reported in the paper by Cuingnet et al [19].

We try to improve the performance using WHITE and WHOLE matter, WHOLE is always useless with low performance, WHITE obtains interesting performance only in the AD vs CN problem. In table 3 we report the performance obtained using Fi feature selection coupled with WHITE matter. Same performance is obtained retaining 2000 or 4000 features.

Table 3. White matter

|  |  |  |  |
| --- | --- | --- | --- |
|  | AD vs. CN | MCIc vs. CN | MCIc vs. MCInc |
| Fi(2000) | 91.5 | 79.0 | 55.8 |
| Fi(4000) | 91.5 | 79.0 | 55.8 |

We have added Fi(2000) coupled with WHITE in the previous ensemble named FUS, in AD vs CN the new ensemble obtains the interesting AUC of 94.3% outperforming FUS, instead in the other two problems adding Fi(2000) coupled with WHITE in FUS deteriorates its performance.

In the following table 4 we report the performance of the different 2D representation approaches (RS, CW, Sum). Moreover, we report the results obtained by:

* FS, performance obtained by SVM trained with the feature vector selected by the feature selection approaches (KPS, F2G, AS) applied to the original features. I.e., the methods reported in table 1, when 4000 features are retained.
* 2×FS+RS fusion by weighted sum rule between RS (2D representation approach) and FS.

Notice that Fisher feature selection is used to select the best 10000 features then a subset of 4000 features is retained using other feature selection approaches (KPS, F2G, AS). The 2D representation approaches are run on the 4000 features. See section 2.2 for details.

We have not run the tests using LM as feature selector due to the large computation time of that approach.

Table 4. Performance of the 2D representation approaches

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| KPS | AD vs. CN | MCIc vs. CN | MCIc vs. MCInc | MRI |
| RS | 92.3 | 88.6 | 66.0 | 96.1 |
| CW | 92.2 | 88.0 | 66.3 | 95.6 |
| Sum | 91.8 | 86.8 | 65.7 | 94.7 |
| FS | 93.3 | 90.8 | 63.5 | 96.5 |
| 2×FS+RS | 93.3 | 90.6 | 64.7 | 96.6 |

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| F2G | AD vs. CN | MCIc vs. CN | MCIc vs. MCInc | MRI |
| RS | 91.7 | 87.4 | 68.8 | 97.1 |
| CW | 91.3 | 86.8 | 68.2 | 96.6 |
| Sum | 90.5 | 85.0 | 68.1 | 96.3 |
| FS | 92.2 | 88.0 | 71.9 | 97.2 |
| 2×FS+RS | 92.6 | 88.4 | 71.1 | 97.4 |

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| AS | AD vs. CN | MCIc vs. CN | MCIc vs. MCInc | MRI |
| RS | 91.9 | 87.4 | 66.2 | 96.9 |
| CW | 91.8 | 87.1 | 65.9 | 96.6 |
| Sum | 90.4 | 84.8 | 66.9 | 95.9 |
| FS | 93.0 | 89.6 | 64.6 | 97.2 |
| 2×FS+RS | 93.3 | 89.6 | 65.5 | 97.5 |

The 2D representation approach allows to outperform the standard FS method. From the comparison of FS and 2×FS+RS, it was shown that 2×FS+RS outperforms FS with a p-value of 0.1 (Wilcoxon signed rank test [21]). We further tried to improve FUS using the 2×FS+RS approach instead of FS. Unfortunately, in this last case the improvement is negligible. However, from these results it can be derived that reshaping the feature vector as a matrix is useful. In order to further improve the classification performance, new and more texture descriptors should be tested in future.

## Conclusion

In this chapter, we have proposed to combine a set of SVMs, trained using a different feature set for performing an early diagnosis of AD. The original features are extracted from the brain MRI, the different sets are extracted using different feature selection approaches. For each selected set of features a different SVM is trained, this set of SVMs is then combined by weighted sum rule.

Because further improvements for the performance of different methods for considering the feature vector as an image are tested, the best performance is obtained using the Histogram of Gradient descriptor for describing the images.

To validate our approach, the system has been tested using two different brain MRI studies (a total of 4 datasets). Avoiding the overfitting of the proposed system is achieved without any ad hoc parameter optimization; in other words, the same ensemble of classifiers and the same parameter settings are used for all 4 datasets.

To reproduce our experiments our code will be available at https://www.dropbox.com/s/bguw035yrqz0pwp/ElencoCode.docx?dl=0.

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1. \* Corresponding author. Tel.: +39-02-21717552; fax: +39-02-21717558; e-mail: isabella. castiglioni@ibfm.cnr.it. 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. [↑](#footnote-ref-1)