

# Support Vector Machine-Based Classification of AD on Bootstrap Method

R. Viswanathan<sup>1</sup>, Dr. K. Perumal<sup>2</sup>

Assistant Professor, Department of Information Technology and Management, Arul Anandar College, Karumathur, Madurai, Tamilnadu, India<sup>1</sup>

Associate Professor, Department of Computer Applications, Madurai Kamaraj University, Madurai, Tamilnadu, India<sup>2</sup>

**ABSTRACT:** To present and evaluate a new automated method based on support vector machine (SVM) classification of whole-brain anatomical magnetic resonance imaging to discriminate between patients with Alzheimer's disease (AD) and elderly control subjects. Here the main approach is based on the use of structural images of magnetic imaging, mild cognitive impairments and AD patients to distinguish the normal controls between their phase images. Independent Component Analysis technique is used for extracting the features from the inputs of support vector machine. Based upon the characteristics of gray matter extracted from each ROI, we used an SVM algorithm to classify the accuracy, effectiveness, subjects and statistical procedures based on bootstrap resampling to ensure the robustness of the results.

**KEYWORDS:** Alzheimer's disease Diagnosis, ICA techniques, Support vector machine, Sensitivity, Specificity.

## I. INTRODUCTION

Alzheimer's disease (AD) is the leading cause of dementia in the elderly accounting for 50–60% of all cases. AD patients benefit from early cholinesterase inhibitors and would consequently gain from early and accurate diagnosis of AD. In recent years, the early clinical signs of AD have been extensively investigated, leading to the concept of amnesic mild cognitive impairment (MCI). Pathological studies have shown that neuro degeneration in AD begins in the medial temporal lobe, successively affecting the entorhinal cortex, the hippocampus, the limbic system, then extending toward neocortical areas. Therefore, there has been considerable effort put on the detection of medial temporal lobe atrophy (MTA), and particularly in the hippocampus, the entorhinal cortex, and the amygdala. MTA has been evaluated using visual rating scales, linear or volumetric measurements, and voxel-based approaches. Overall, the sensitivity and specificity of hippocampus measurements for distinguishing AD patients from healthy aged subjects have been evaluated to range from 80% to 95%. Recent classification methods have been developed that allow an individual class prediction. Among them, machine-learning techniques have been proposed to distinguish magnetic resonance (MR) images from two groups of subjects (e.g., patients vs. healthy subjects). All these techniques require a training population, i.e., well-characterized subjects (for instance healthy subjects and patients with known diagnosis), in order to categorize new subjects, who belong to the so-called test population, into one of the classes the subjects of the training population belong to.

Support Vector Machines (SVM) has recently been used to help distinguish AD subjects from elderly control subjects using anatomical MR imaging (MRI). Classification methods have also been recently applied to the classification of MCI subjects compared to control subjects to help differentiate AD from front temporal lobar degeneration. Even though feature parameters can be determined from the whole brain, these parameters may have no relevant physiological interpretation, or only a selected set of most discriminating voxels or regions are eventually used to classify the subjects.

The purpose is to individually classify AD patients and healthy elderly control subjects by using a whole-brain MR image analysis. We use a histogram analysis of the MR images to extract feature parameters. Thereby, we focus on characteristics of the distribution of the gray matter (GM), white matter (WM), and cerebrospinal fluid (CSF), which intuitively makes sense when dealing with neurodegenerative diseases in general and AD in particular.

A histogram analysis of the distribution of the intensity in the voxels is performed, which identifies the respective contributions of GM, WM, and CSF in the region. From this analysis, a parameter is extracted that characterizes the subject and has a physiological meaning, since it represents the relative weight of GM compared to WM and CSF. Finally, based upon this parameter estimated in all the ROIs of the whole brain, the method classifies the subjects with an SVM algorithm. Most importantly, robust classification results are ensured even for small groups, since we use statistical procedures based on bootstrap resampling.

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## II. PROBLEM DEFINITION

The main approach is based on the use of structural images of magnetic imaging, mild cognitive impairments and AD patients to distinguish the normal controls between their phase images. Independent Component Analysis technique is used for extracting the features from the inputs of support vector machine. Based upon the characteristics of gray matter extracted from each ROI, SVM algorithm is used to classify the accuracy, effectiveness, subjects and statistical procedures based on bootstrap resampling method.

## III. RELATED WORKS

### Materials and methods:

#### Patients and subjects:

More than ten patients with AD and twenty two healthy aged control subjects (CS) were recruited. All patients and control subjects signed an informed consent form after the nature of the procedures.

Inclusion criteria were the following:

1. Fulfillment of the National Institute of Neurological and Communication Disorders and Stroke/ Alzheimer Disease and Related Disorders Association criteria for probable AD.
2. Clinical Dementia Rating scale (CDR)  $\geq 0.5$  (all patients but two had CDR=1, two patients had CDR=0.5).
3. No clinical or neuroimaging evidence of focal lesions including brain tumor, subdural hematoma, and central nervous system infection.
4. No cortical or sub cortical vascular lesions on MRI visible on the structural image.
5. No medical conditions that may interfere with cognitive performance or follow up.

#### SVM classifier algorithm:

The SVM is a learning machine for two-class classification problems. SVM conceptually implements the idea that vectors are nonlinearly mapped to a very high dimension feature space. In this feature space, a linear separation surface is created to separate the training data by minimizing the margin between the vectors of the two classes. The training ends with the definition of a decision surface that divides the space into two subspaces. Each subspace corresponds to one class of the training data. Once the training is completed, the test data are mapped to the feature space.

“Support Vector Machine” (SVM) is a supervised machine learning algorithm which can be used for both classification and regression challenges. However, it is mostly used in classification problems. In this algorithm, the plotting of each data item as a point in n-dimensional space (where n is number of features you have) with the value of each feature being the value of a particular coordinate. Then, perform classification by finding the hyper-plane that differentiates the two classes. Support Vector Machine is a frontier which best segregates the two classes are hyper-plane and line.

## IV. STATISTICAL ANALYSIS

### Discriminate function of feature parameter:

The whole set of 90 ROIs was used to classify the patients. Nevertheless, it was important to evaluate the discriminating power of the feature parameter  $\alpha_2$  and investigate whether and in which brain regions this parameter was indeed able to distinguish AD patients from healthy controls. Group differences in the value of  $\alpha_2$  in each ROI between AD patients and CS were assessed as follows. For each ROI, tests whether the distribution of  $\alpha_2$  in CS significantly differed from that in AD patients, by using a two-sample T test. As the number of subjects examined was relatively limited ( $n_{CS} = 22$  healthy CS and  $n_{AD} = 11$  AD patients), to assume that this test was not robust enough. By using a bootstrap method, work with the null hypothesis  $H_0$  that there was no difference between the two groups. The initial set of subjects S was divided into  $S_1$  of cardinal  $n_{CS}$ , initially containing all the healthy CS, and  $S_2$  of cardinal  $n_{AD}$ , initially containing all the AD patients, and the initial value  $T_0$  of the T test was calculated. Then resample the set S under the hypothesis  $H_0$ , creating resampled sets  $S_1^{i+1}$  and  $S_2^{i+1}$  by drawing with replacement  $n_{CS}$  and  $n_{AD}$  subjects from the whole set S. To perform n resampling and calculate the percentile corresponding to the initial value  $T_0$  of the T test in the set of values  $fT; i; i 2 \frac{1}{2} 1; n \& g$ , i.e.,  $n$  residual  $\delta T; i T_0 P=n$ . According to the bootstrap theory, this percentile is a good estimate of the p value of the T test if n is large enough.

### Testing a data using a bootstrap method:

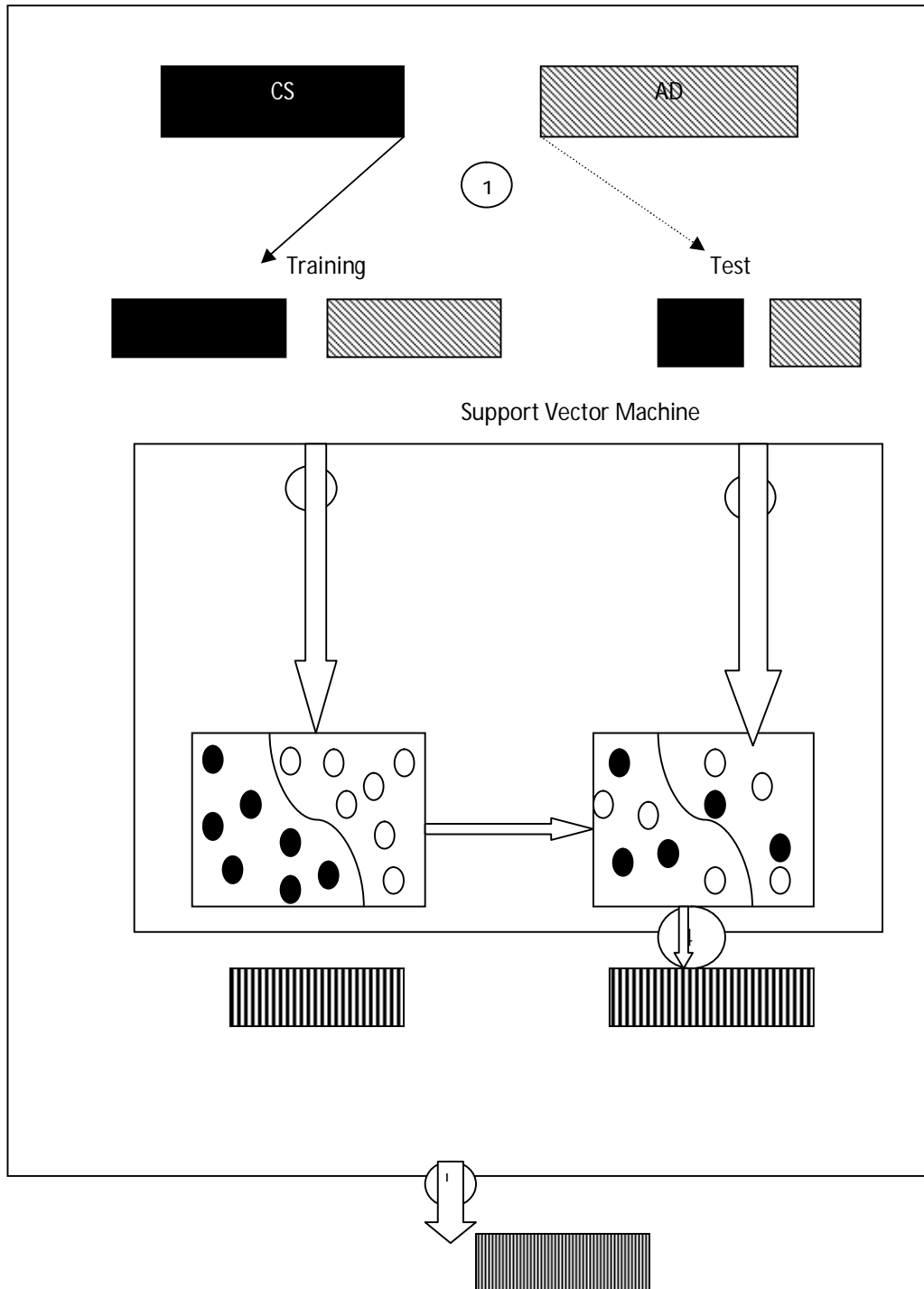
The classification method on a population with a known Alzheimer's disease diagnosis and to draw without replacement one subset of each group for test data. The cardinal of those subsets was approximately 25% of the cardinal of the initial groups. The remaining subjects were used as training data to create a separation surface in order to classify the test data. In the below figure 1 the method for data selection to perform classification on one population of known diagnosis.

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Fig – 1: Method for Data Selection to perform classification



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### Choice of SVM Parameters:

In this method, the two classes were “AD patient” or “CS”; each subject was represented by a vector of the  $\alpha_2$  values in all 90 ROIs. A kernel function needs to be chosen for SVM: It reflects the nonlinear mapping from the input space to the feature space. A commonly used radial basis function of the form  $(x, y) \rightarrow K(x, y) = e^{-\gamma \|x - y\|^2}$ . To determine the optimal values of two constants:  $\gamma$ , width of the radial basis function, and C, an input parameter for the SVM algorithm, which represents the error/trade-off parameter that adjusts the importance of the separation error in the creation of the separation surface.

### Most Significant different ROIs:

In this record of work five ROIs had a p value less than  $10^{-4}$  and 34 ROIs had a p value less than  $10^{-2}$  (Fig.2). These small p values indicate that there was a significant difference between AD patients and CS in the characteristics of gray matter in these ROIs as measured by the parameter  $\alpha_2$ . The most significant ROIs included regions classically affected in AD, such as the hippocampus or the para hippocampal gyrus. Those ROIs are listed in Table 1.

ROI	Bootstrap estimate of the p value
Left parahippocampal gyrus	$<2.5 \times 10^{-6}$
Right parahippocampal gyrus	$<2.5 \times 10^{-6}$
Left hippocampus	$<2.5 \times 10^{-6}$
Right lingual gyrus	$5 \times 10^{-6}$
Left lingual gyrus	$5 \times 10^{-6}$
Right insula	$5 \times 10^{-6}$
Left middle occipital gyrus	$5 \times 10^{-6}$
Left precuneus	$3 \times 10^{-5}$
Left middle temporal gyrus	$3.75 \times 10^{-5}$
Left inferior temporal gyrus	$4.75 \times 10^{-5}$

Table 1: ROIs discriminate patients with Alzheimers Disease and Control Subjects

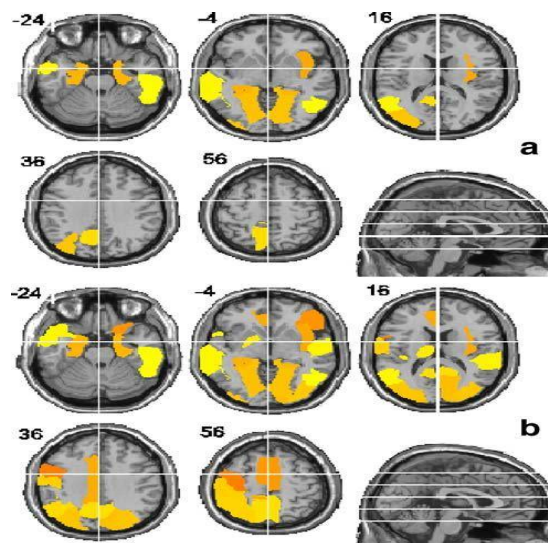


Figure 2: ROIs Discriminate Patients with Alzheimers Disease and Control Subjects

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## Feature parameter:

The design feature parameter that showed a discriminating power between patients with AD and healthy CS, and this feature parameter is to create a classifier that can predict whether a single subject belongs to the AD or the CS group. As gray matter modifications are well known in AD, it makes sense to focus on the distribution of the gray matter for the choice of the feature parameter and, consequently, on the parameters ( $\mu_2$ ,  $\sigma_2$  and  $\alpha_2$ ) estimated by the Gaussian mixture model. All three parameters convey some information that could be used either separately or in combination as representative features for the ROIs in the classification algorithm. There are two main reasons. Firstly,  $\alpha_2$  has a physiological meaning in that it is the relative weight of GM compared to WM and CSF. Therefore, it intuitively reflects the modifications that are well known to be induced by AD, namely, a decrease in GM compared to WM and CSF. Secondly, this parameter is more invariant with respect to the acquisition parameters, as opposed to  $\mu_2$  and  $\alpha_2$ , which are more likely to depend on the contrast in the images.

## Classification method:

The SVM classifier involves a nonlinear mapping from the input parameter space to the feature space. The nonlinear mapping was performed using a radial basis function. Bootstrap resampling methods were used both to select test and training data to evaluate the classification accuracy of our method and to estimate the SVM parameters. For this latter purpose, alternative approaches have been proposed in the literature, for instance, cross-validation methods such as leave-one-out or n-fold cross-validation. For instance, Vemuri et al. used a technique in which patients and controls were first divided in two groups (training and testing sets), the training group being in turn divided into three subgroups used for feature selection and model optimization and one subgroup used for testing. This leads to perform the classification on much smaller groups, and they repeated their method ten times and averaged the results to increase the robustness of their classification.

In our study, since a nonlinear mapping of the parameters is performed, bootstrap is the method of choice, as leave-one-out has been shown to be less robust than bootstrap when applied to nonlinear cases.

## Classification results:

The results with the proposed classifier yielded a sensitivity of 91.5% and a specificity of 96.6%, for a 94.5% mean correct classification rate. The MR images of all subjects were of similar quality. However, the SVM classified four subjects with a correct classification rate less than 90%, as shown in Table 1, which may be explained by clinical considerations. Patient who was never classified correctly, had a very particular clinical evolution. At the time the MRI was performed, the scores for this patient were CDR= 1 and MMSE=19, which happened to be the lowest MMSE of all the subjects. The initial clinical examination was very suggestive of AD: starting with amnesic symptoms and an initially normal neurological examination in particular, no extra pyramidal syndrome.

## SVM-based methods in Alzheimer's disease classification:

Other whole-brain SVM-based classification methods have been proposed recently. Fan et al. used a pattern classification method to obtain a 94.3% correct classification rate between AD patients (mean MMSE, 23.07) and control subjects. Their results were quite comparable to ours; however, a different method was used. In particular, the regions from which the features were extracted were calculated for each training data and therefore varied for each sample, while in the present study, the same regions from a single labeled anatomical template were used for all subjects. The SVM-based classification method proposed by Vemuri et al. is based on MRI features that were different from those used in the present study: The features parameters were initially all the voxels from the segmented MRI and were subsequently reduced to a subset of voxels that best distinguished AD from CS. The studied AD patients were at a more advanced stage than in the present study (the mean MMSE was 20, compared to 23.1 in our group), and the classification was slightly less accurate (the accuracy was 86% when using only MRI data and 89.3% when adding demographic information, compared to 94.5% in our study). Klöppel et al. also proposed a method for classifying AD patients and elderly control subjects using SVM and achieved 95% correct classification on a group of patients with 16.7 mean MMSE. The correct classification rate was up to 89% on a group of patients at an earlier stage of the disease (mean MMSE, 23.5), quite similar to that in the present study; however, their results were slightly less accurate than ours. It should be noted, however, that a thorough comparison between our study and others is not easy since different datasets were used, and the quality of imaging data is obviously an important factor. Nevertheless, on the basis of

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reported correct classification rates and MMSE values, it can be concluded that the method proposed in this paper performs very well compared to existing classification approaches.

## Possible improvements of the proposed method:

The use of bootstrap and resampling methods ensured a statistical robustness to the procedure. This allowed us to obtain significant results on relatively small MRI datasets. Nevertheless, the results of our study require confirmation in much larger groups of participants.

The classifier was developed using a specific procedure to parcellate the brain into ROIs. To perform parameter extraction at a regional scale, thus making the method robust to registration imperfections and anatomical variations across individuals. The current parcellation yielded good classification results, but it can be improved.

Indeed, the proposed method extracted one feature parameter for each ROI. Therefore, it cannot take variations of the feature parameter within the ROI into account. Consequently, using a parcellation into smaller ROIs could be sensitive to variations of the feature parameter at smaller scales and thus better fit the atrophy pattern of the disease and improve the classification results. However, it is expected that the smaller the ROIs, the less robust the estimation of the feature parameter, as possible registration errors would likely introduce larger errors when estimating the proportion of gray matter from the histogram analysis and hence yield a decrease in sensitivity. A parcellation at a finer scale should then take this trade-off issue into consideration. Improvement may also include other routines to denormalize the labeled anatomical template to the individual MRI or the use of a different labeled template.

## V. CONCLUSION

To develop a method that is able to classify automatically patients with early Alzheimer's disease from control subjects. This method has a potential for early diagnosis of Alzheimer's disease. The method will be evaluated in MCI patients and for other neurodegenerative diseases and its robustness will be assessed in patients with images obtained from different MR scanners with various acquisition parameters.

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