SRAN, L-SVM, PCA, VBM 분류기에 의한 알츠하이머 병 분류

Alzheimer disease classification by combination of SRAN, Linear SVM, PCA, and VBM

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요 약

알츠하이머 병과 경도인지장애 같은 전조 증상의 조기 발견은 생명을 좀더 연장한다. 추측하건대 예방법 측정은 알츠하이머의 위험 요소들을 제거하는 치료를 할 수 있다. 바이오마커인 대뇌 수축은 sMRI의 영상에 있어 관찰되어질 수 있다. sMRI는 GM 세션화 후에 형태계측학적 형태를 추출하는 것으로 사용되어진다. 따라서 새로운 접근은 MMSE 스코어에 따라 형태계측학적 형태들을 결합하여 정상적인 제어로부터 알츠하이머 환자의 경도(CDR-1_에서 심한 경도(CDR-0.5)의 진단을 위해 적용되어진다. 최근에 결합된 형태는 PCA를 이용한 차원적 문제를 제거한 후 제안된 SRAN과 Linear SVM으로 제공된다. 제안된 진단 지원 방법의 실험결과는 선형 SVM의 성층화 정밀도가 95.83%이고 높은 민감도와 특이성이 90%의 SRAN 분류기가 83.33%이다.

Abstract

Early accurate detection of Alzheimer disease (AD) and its prognostic stage, i.e., Mild Cognitive Impairment (MCI) is getting more and more vital. The preventive measure could presumably treat to get rid of Alzheimer disease risk factors to generate. The bio-marker, cerebral atrophy could be observed in structural MR imaging (sMRI). Structural MRI imaging is used to extract morphometric features after Grey Matter (GM) segmentation. Finally a novel approach is applied for the diagnosis of very mild (CDR-0.5) to mild (CDR-1) alzheimer disease patients from normal controls combining morphometric features along with MMSE (Mini-Mental State Examination) score. The combined features are fed into recently proposed Self Adaptive Resource Allocation Network (SRAN) and Linear Support Vector Machine (L-SVM) classifier after getting rid of curse of dimensionality using principal component analysis. The experimental result of the proposed diagnosis support methods yield up to 95.83% stratification accuracy with Linear SVM and 83.33% with SRAN classifier along with high sensitivity and specificity above 90%.

1) 교신저자

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키워드: 알츠하이머 병, MMSE 스코어, VBM 형태, PCA, SRAN 분류기, 선형SVM
Keyword: Alzheimer disease, MMSE Score, VBM features, PCA, SRAN classifier, Linear SVM

1. Introduction

AD is a progressive neurodegenerative disorder that causes damage of brain cells, affects cognitive function, behavioral problems, and memory disorder. The senile plaque consists of amyloidal beta-42protein causes cerebral atrophy in cortex and hippocampus, neuro fibrillary tangle consists of tau protein causes in hippocampus. It progressively affects in whole brain. It is the most common type of dementia, and it causes 50 to 80 percent of dementia cases. The statistical report depicts that by 2050 over 135 million people worldwide will have dementia, tripling the amount of people who have it now. The cost of AD patients care is likely to be yielded up to $220 billion per year in the USA and $605 billion globally. Effective early diagnosis of AD and its prodromal stage is always indispensable, can impair and prevents the disease to progress. Several noninvasive and efficient diagnosis techniques are being used like sMRI or fMRI, Position Emission Tomography (PET), and Single Photon Emission Computerized Tomography (SPECT). Many studies are based on automatic or semi-automatic measurement of various a priori brain Region of Interest (ROI) to compare and discriminate between healthy controls (HC), MCI, and AD patients. M. Chupin et al [1] studied that the AD patients suffer significant cerebral atrophy; several brain ROIs, especially the hippocampus and the entorhinal cortex. The researchers unveiled the morphometric difference between subject groups by comparing regional volume of ROIs. P. Padilla et al [2] developed CAD tool for SPECT and PET images using NMF and SVM classifier for the diagnosis of AD patients from healthy controls yielding upto 91% accuracy with high sensitivity and specificity rates(above 90%). M. Lopez [3] developed tool for the diagnosis of AD patients from normal controls using PCA and Bayesian classification rules, and SPECT and PET image dataset classifying 98.3% accurately for SPECT and 88.6% accurately for PET dataset. R. Mahmood et al [4] developed an automatic detection tool using PCA and Artificial Neural Network to identify the CDR scale of entire 457 MR images in the OASIS dataset, and achieved 89.92% accuracy. Daoqiang Zhang et al [5] used multimodal approach of biomarkers, i.e. sMRI, FDG-PET, CSF (cerebro-spinal fluid) for the stratification of AD and MCI patients from healthy controls. The classification accuracy yielded up to 93.2% for AD vs HC and 76.4% for AD vs MCI. When using best individual modality biomarker, they achieved an accuracy of 86.5%, 72% differentiating AD from HC controls and MCI from HC respectively. W. Yanga et al [6] used Independent Component Analysis based stratification of Alzheimer' s disease from HC controls using both whole brain images and gray matter images from the OASIS. They achieved the classification accuracy 73.7% ± 4.5% of gray matter images from the OASIS, and 71.1% ± 4.5% of gray matter images from the ADNI. Shih-Ting Yang [7] discriminated between AD and MCI using SOM and PSO-SVM achieving classification accuracy to 88.89%. A. Savio et al [10] used four different models of Artificial Neural Networks (ANNs) to the same dataset, and reported the result of 83% stratification accuracy.

Several univariate analysis and multivariate

methods are studied where volumes of GM, WM, and CSF regions are being segmented. VBM feature extraction follows Spatial Normalization, Segmentation, Smoothing, and Statistical Parametric Mapping. In this study, PCA based Linear SVM and SRAN classification with train and test strategy is used to diagnose an unknown subject. The dataset used in this approach is same as above [10].

2. Materials and Method

All the structural MR images are spatially normalized into a standard template using SPM8. Then segmentation is done into GM, WM, and CSF. The segmented GM images are smoothed; voxel-wise statistical tests are performed to extract features, and fed into linear SVM and SRAN classifier after applying two-sample t-test and PCA for dimensionality reduction along with MMSE score.

2.1 Overview of the experimental Data

All the sMRI imaging data is being taken from OASIS dataset which is an open access collection of cross sectional sMRI of 416 subjects covering the adult life span aged 18 to 96, right handed including both men and women. Longitudinal data consists of 150 subjects aged 60 to 96, right handed including men and women. The feature extraction technique is illustrated elaborately by Darya Chyzhyk et al [8]. Gender may affect morphometric differences and features. Thus 98 women sMRI data have been selected to extract voxel-based morphometry (VBM) features for training and testing strategy, 49 diagnosed patients with very mild to mild AD, and 49 non demented controls among 98 subjects. The age, education, socioeconomic status, CDR,

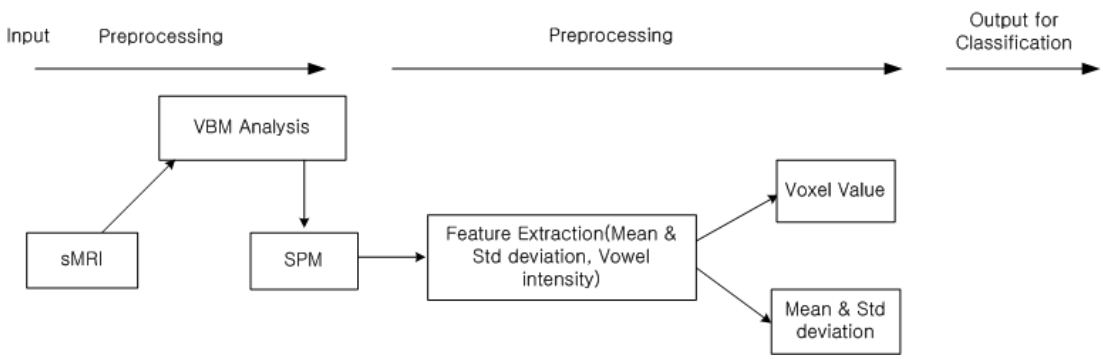

Fig. 1 Block diagram of the feature extraction process from the subject s' GM segmentation volumes

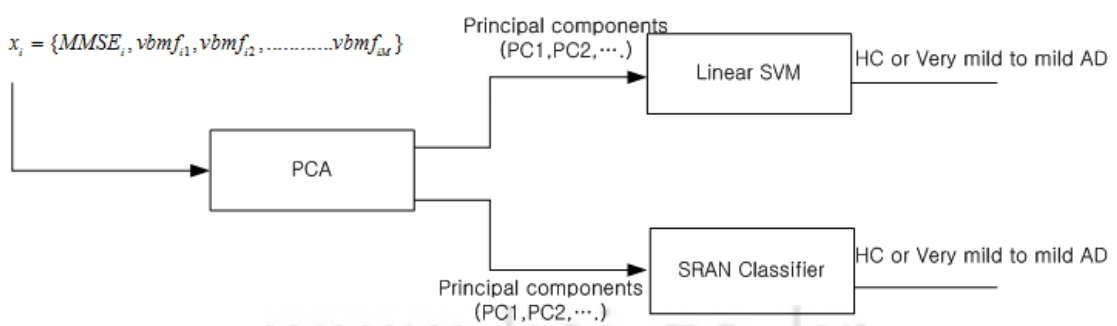

Fig. 2 Schematic diagram proposed approach

and MMSE score details of selected subjects are depicted in Table 1. The CDR is a five point scale, each denoting different stage of dementia as narrated in Table 2.

2.2 Preprocessing and VBM Feature Extraction

The different steps of feature extraction process are depicted in Fig 1. The averaged, registered images resampled with 1-mm isotropic image in atlas space and the bias field corrected [4] are already available in OASIS cross sectional data set. VBM toolbox has been used for preprocessing. The MRI images are manually realigned with template image, spatially normalized, segmented to get GM features. The GM segmented images are spatially smoothed with FWHM of the Gaussian kernel to 10mm isotropic prior to analyze voxel base statistics. A GM mask had been generated from the mean of GM segmentation volumes of the 98 subjects. The binary mask was built from thresholding the average GM segmented volumes consisting of all voxels with probability greater than 0.1. The statistical General Linear Model (GLM) created to analyze using two-sample t-test where the groups mapped to very mild to mild AD patients and Normal controls respectively. In SPM, the several functions have been set as follows: the contrast has been set to [-1 1], a right-tailed (groupN>groupAD), corrected FWE, p-value is 0.05. The feature has extracted from clusters detected by VBM for supervised learning purpose. Statistical significance was regulated using an extent threshold of 0 adjacent voxels for two sample t-test comparisons. The feature consists of the mean and standard deviation of VBM detected clusters, and high dimensional vector of all GM segmentation values of voxel location existing in all cluster.

Table 1. Summary of subject demographics and dementia status.

	Very mild to mild AD	Normal
No. of subjects	49	49
Age	78.08 (66-96)	77.77 (65-94)
Education	2.63 (1-5)	2.87 (1-5)
Socioeconomic status	2.94 (1-5)	2.88 (1-5)
CDR(0.5 / 1 / 2)	31 / 17 / 1	0
MMSE	24(15-30)	28.96(26-30)

Table 2. Summary of a five-point scale, Clinical Dementia Rating (CDR)

CDR	Status
0.5	Very mild dementia
1	Mild
2	Moderate
3	Severe

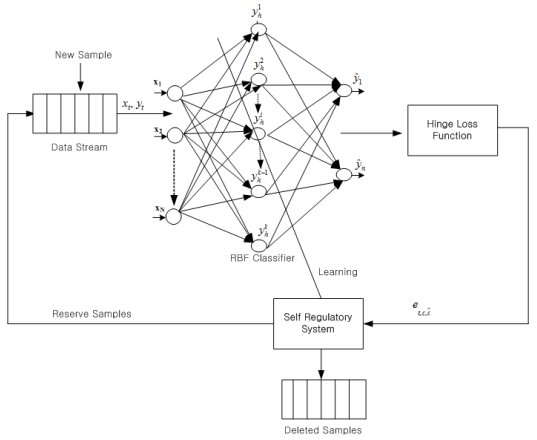

Fig. 3 Bird's eye view of the SRAN algorithm

2.3 PCA-SRAN Classifier

In this paper, a noble approach is applied combining VBM feature along with MMSE score, reducing the curse of dimensionality by using PCA, differentiating very mild AD to mild AD from healthy controls with SRAN classifier and linear SVM as shown in Fig 2.

2.3.1 Principal Component Analysis

To reduce the curse the dimensionality of the extracted features, PCA is applied after performing two sample t-tests. The PCA is

a. Finding mean of the data matrix and zero mean matrix.
b. Constructing covariance matrix.
c. Finding the eigenvalue and the eigenvector.
d. Projecting the data matrix with eigenvectors corresponding to highest to lowest eigenvalues.

2.3.2 Linear SVM

Support Vector Machine, basically a binary classifier is very efficient for classification of both linearly separable and non-separable data. It finds best hyper plane that separates both the classes having optimum margin from support vectors during training phase. While testing with new data point, classifier takes decision on the basis of hyper plane. Spider toolbox is used for linear SVM classification.

2.3.3 SRAN

Self-Adaptive Resource Allocation network classifier proposed by S. Suresh et al [3], recently designed network classifier is also used to differentiate very mild to mild AD from normal controls. The SRAN classifier follows a sequential learning process, a non batch learning approach, training samples arrive one after another, is realized by Radial Basis Function (RBF) framework. The method includes adaptation of network parameters on the basis of distinction of knowledge between the network and the current sample. After considering sample error, new samples arrived for training is used for network training, or pushed into rear stack for later use, or deleted from stack. The method restricts overtraining of the classifier.

2.3.2.1 Problem definition

Suppose we have the samples $(x_1,y_1),(x_2,y_2),(x_t,y_t),...,(x_n,y_n)$ where $x_t \infty R^m$, m dimensional features of sample x_t, and y_t is its coded class level vector. If the feature x belongs to class level c, we can construct coded class level vector as follows:

$$y_i = \begin{cases} 1 & j=c \\ -1 & otherwise \end{cases} j=1,2,3,...,n \quad (1)$$

i.e. $y=[y_1,...,y_{c,...,}y_n]^T=[-1,...,1,...,1]$ and n is the total number of class. The training observation x is used to model probability distribution to predict its corresponding class level with certain probability. For new test sample x_t, to predict its corresponding class level vector, it need to model functional estimated relationship between sequential training data and its corresponding coded class level by using SRAN network algorithm. SRAN classifier uses a radial basis function to build block. The output of the SRAN classifier $y=[\hat{y_1},\hat{y_2},...,\hat{y_n}]$ with k hidden neurons has been expressed as follows:

$$\hat{y_i} = \sum_{j=1}^{k} \alpha_{ij} y_h^j, i=1,2,...,n \quad (2)$$

$$y_h^j = \exp\left(-\frac{||x-\mu_j^l||}{(\sigma_j^l)^2}\right) \quad (3)$$

Where μ_j^l is the mean of j-th neuron corresponding to the l-th class, α_{ij} is the weight with respect to ith output neuron and jth gaussian neuron, σ_j^l is width of the jth neuron. For the new training sample, the corresponding class level can be predicted.

$$\hat{c} = \arg\max(\hat{y_i}), i = 1,2,...,n \quad (4)$$

To calculate error $e = [e_1, e_2, ..., e_n]^T$, hinge loss function is given by

$$e_i = \begin{cases} y - \hat{y_i} & \text{if } y.\hat{y} < 1 \\ 0 & otherwise \end{cases} \quad i = 1,2,3,...,n \quad (5)$$

The predicted posteriori or confidence level of classification modeled by the truncated outputs can be obtained by

$$\hat{p}(c/x) = \frac{T(\hat{y_i}) + 1}{2} \quad (6)$$

where

$T(\hat{y_i}) = \min(\max(\hat{y_i}, -1), 1),\ i = 1,2,...,n$

When new sample x_t fed into the network, based on the sample error (e), the sample is either

a) used for network training (growing/learning) immediately, or;
b) pushed to the rear end of the stack for learning in future, or;
c) deleted from the data set.

Self regularity system is composed of deletion criterions, growing criterion, learning criterion, and sequence altering. The bird view of the SRAN classifier algorithm is depicted in Fig 3. The details of self regulator criteria are narrated in details by S. Suresh et al [9]. It is also efficient because of taking less memory and computational time.

2.3.2.2 Problem definition

SRAN learning begins with zero hidden neuron like other standard online/sequential learning. Addition of new hidden neuron relies on knowledge of current sample.

Suppose we have first sample (x_t, y_t) constitutes first hidden layer with parameters given by

$$\alpha_1 = e, \mu_1^c = x_1, \delta_1^c = k\sqrt{x^t x} \quad (7)$$

Where k is a positive scaling constant for regulating overlap between hidden neurons, c is class level of the sample.

All the samples are learnt one by one in a standard online/sequential learning. Such learning network does not consider a sample sequence. As a result, problem of overtraining of a specific sample occurs. SRAN learning deal with the problem, and sequence of training sample is regulated by self-regulating control parameters. Self-regulatory principle relies on deletion criterion, growing criterion, and sequence altering of samples as explained below.

Suppose the network has *k* hidden neurons from *t-1* training imaging samples.

a) Deletion criterion: The sample is discarded without using it for learning if it meets following condition. The absolute maximum error is $E = \max_{i=1,...,n}|e_i| \leq 0.05$.

The criterion prevents overtraining of a specific sample.

b) Growing criterion: The conditions to add a new hidden neuron for sample x_t is as follows:

$$\hat{c} \neq c \text{ and } E \geq \eta_a \quad (8)$$

where η_a is self-adaptive growing threshold, range is between [0.75 1.5], initialized to 1.5. The

hinge loss is between ± 2 even if the predicted output is not bounded to ± 1. The threshold accommodates the region of misclassified and rightly classified samples with high error. The regulated threshold is being adjusted based on current sample error (E) as

$$\eta_a := \delta \eta_a - (1-\delta)E \quad (9)$$

where δ is a parameter that changes the slope of decaying growth control parameter. It is set close to 1.

If the growing criterion of Eq. (8) is met, new hidden neuron *k+1* is added with setting its parameters as follows:

$$\alpha_{k+1} = e; \mu^c_{k+1} = x_t; \delta^c_{k+1} = k||x_t - \mu^c_{nr}|| \quad (10)$$

where k is positive scalar constant to regulate the overlay between hidden neurons, *nr* is nearest neuron to the current sample to determine width of new neuron, *c* is class label of the sample.

After being added a new hidden neuron, the dimension of error co-variance matrix p_t is changed to

$$p_t = \begin{bmatrix} p_{(t-1)} & 0 \\ 0 & p_0 I \end{bmatrix} \quad (11)$$

where p_0 is an estimate of uncertainty in initial values initialized to the parameters, *I* is the identity matrix having dimension equal to number of newly introduced parameters by the new hidden neuron.

c) Learning criterion: The network learning parameter ($w = [\alpha_0, \alpha_1, \mu^l, \delta^l_1, ..., \alpha_k, \mu^l_k, \delta^l_k]$) are readjusted if following conditions are met.

$$c \equiv \hat{c} \text{ and } E \geq \eta_l \quad (12)$$

where η_l is self-adapted learning regulation is set between [0.05,0.75]. The thresholding parameter is updated with respect to contributed error to learning.

$$\eta_a := \delta \eta_a - (1-\delta)E \quad (13)$$

where δ is a parameter that changes the slope of decaying growth control parameter, usually set close to 1.

The extended kalman filter is used to update network parameter as follows:

$$w_t = w_{(t-1)} + KL_{(t)}e \quad (14)$$

where $KL_{(t)}$ is the kalman gain and e is the hinge loss.

For new training observation, $KL_{(t)}$ is given by

$$KL_{(t)} = p_{(t)}a_{(t)}[R + a^T_{(t)}p_{(t)}a_{(t)}]^{-1} \quad (15)$$

$$a_{(t)} = \triangle(\hat{y})_{(t)} \quad (16)$$

$a_{(t)}$ is partial derivative of predicted output with respect to *w*. $p_{(t)}$ is error covariance matrix.

$p_{(t+1)}$ is being calculated by

$$p_{(t+1)} = [I - KL_{(t)}a^T_{(t)}]p_{(t)} + IP_Q \quad (17)$$

where p_q is artificial process noise to avoid convergence of local minima.

The gradient vector $a_{(t)}$ is given by

$$a_{(t)} = \begin{bmatrix} 1, y_h^1, y_h^1 \frac{2\alpha_1}{(\sigma_1^l)^2}(x_t - \mu_1^l)^T, y_h^1 \frac{2\alpha_1}{(\sigma_1^l)^3}\|x_t - \mu_1^l\|^2 \ldots, \\ y_h^k, y_h^k \frac{2\alpha_k}{(\sigma_1^l)^2}(x_t - \mu_1^l)^T, y_h^k \frac{2\alpha_k}{(\sigma_1^l)^3}\|x_t - \mu_k^l\|^2 \end{bmatrix} \quad (18)$$

d) Sequence altering: If current arriving sample doesn't meet the growing and learning conditions, the sample is moved to rear end for using in future to fine tune network parameters.

The training stops when it satisfies the error criteria.

3. PCA - SRAN Classifier Result

To differentiate very mild to mild AD from normal controls, training and testing samples have been prepared. After applying PCA on extracted features, 50 subjects are selected for training and 48 for testing randomly. The supervised learning of GM segmented image features along with clinical measurement (MMSE score) is used for diagnosis of AD patients. Linear SVM and SRAN classifiers are applied, and the accuracy and efficiency are measured with MMSE score or without the MMSE score. It is obvious that when MMSE score is incorporated with GM segmented image features, the classification accuracy, sensitivity, and specificity gets higher as depicted in Table 3. Although linear SVM performs better, SRAN classifier performs efficiently for higher observations and multi-class classification problem. After integrating MMSE score with the principal components of image features, linear SVM performs 95.83% accuracy with high specificity and sensitivity, increased by 12.5%, and SRAN classifier performs 83.33% accuracy with ample specificity and sensitivity, raised by 4%. The approach performs better than the method used by R. Mahmood et al [4] getting 89.92% accuracy, Savio A et al [10] achieving 83% using same data set, and WenluYanga et al [6] attaining 73.7% ± 4.5%(Mean±Std).

Table 3. Classification result of very mild to mild AD from HC

Classifier	Accuracy	Sensitivity	Specificity
PCA+Linear SVM	83.33%	83.33%	83.33%
PCA+ SRAN	79.17%	79.17%	79.17%
MMSE score+PCA+ Linear SVM	95.83%	100.00 %	91.67 %
PCA+SRAN(With MMSE score)	83.33%	79.17%	87.50%

4. Conclusion

A diagnosis method for the early detection of very mild to mild AD is presented. The system was evolved by performing PCA which drastically reduces the curse of dimensionality of the feature space. The most important components, the three principal components in terms of ability to discriminate are chosen for training and testing of Linear SVM and SRAN classifier for the diagnosis. With the approach, 95.83% and 83.33% classification accuracy values are obtained by linear SVM and SRAN classifier respectively. The accuracy values outperformed the results, classification accuracy of 83% obtained by Savio A et al [10], 73.7% ± 4.5% by Wenlu Yanga et al [6], and 89.92% by R. Mahmood et al [4].

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