Research Article
Alzheimer's Disease Classification Using Hybrid Neuro Fuzzy Runge-Kutta (HNFRK) Classifier

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Abstract: Alzheimer's Disease (AD) exists more prior to the over appearance of clinical symptoms and is characterized by brain changes. In this study, Functional Magnetic Resonance Imaging (FMRI) offers considerable promise as a tool for detecting brain changes in Alzheimer disease pretentious patients. Therefore, FMRI may offer the unique ability to detention of the dynamic state of change in the collapsing brain. Improve the accuracy of brain FMRI image segmentation, a robust Spatial Fuzzy C-Means (SFCM) is utilized and a combination of Adaptive Neuro Fuzzy Inference System and Runge-Kutta Learning Algorithm called Hybrid Neuro Fuzzy Runge-Kutta (HNFRK) classifier is used for prediction of Alzheimer's Disease (AD). The performance of the proposed classifier is compared with SVM and ANFIS classifier. The results show that the sensitivity and specificity of HNFRK classifier is more compared to the SVM and ANFIS. The sensitivity and specificity of HNFRK is above 90% which is below 90% in case of SVM and ANFIS classifier. Thus it can be shown that HNFRK performs accurate classification than SVM and ANFIS.

Keywords: Alzheimer's Disease (AD), ANFIS (Adaptive Neuro Fuzzy Inference System), FMRI images, Runge-Kutta Learning algorithm (RKLM), Spatial Fuzzy C-Means (SFCM)

INTRODUCTION

Alzheimer's Disease (AD) remains the most widely known type of dementia in all age groups. AD is a dynamic neurodegenerative disorder related with an interruption of neuronal function and a progressive disintegration in function, behavior and cognition. AD is pathologically described by the existence of amyloid and neurofibrillary tangles together with the loss of synapses and cortical neurons (Matsuda, 2007). At present there is no cure for AD. Diagnosing AD at an early stage is of great significance.

Pharmacotherapy medicines for anticipating disease progression or decelerating it must be begun as early as possible before extensive infestation of the brain. Moreover, developments of new pharmacotherapy medicines need to screen the impact of medications in distinctive parts of brain (Liu *et al*., 2009). Some general clinical tests, for example, Clinical Dementia Rating (CDR) and Mini-Mental State Examination (MMSE) have been utilized for diagnosing Alzheimer's disease.

Diagnostics focused around clinical symptoms is susceptible to error and their test-retest accuracy is generally low (Hua *et al*., 2009). The reason for this untrustworthiness could be diverse instructive level of subjects and their cognitive abilities with the goal that some individuals can adapt to prodromal cognitive disabilities. This makes the diagnostic results unclear. Moreover, the clinical indications of disease are covered up by the late period of disease and appear only when the brain structures have been pervaded by the disease. The necessity for discovering some new systems for early diagnose of disease prompted the introduction of Neuro imaging technique.

Neuro imaging techniques are utilized for assessing anatomical degenerations brought about via disease. Diverse imaging modalities, for example, Positron Emission Tomography (PET) (Beckett *et al*., 2010; Shin *et al*., 2010), structural Magnetic Resonance Imaging (MRI) and Functional Magnetic Resonance Imaging (FMRI) (Tripoliti *et al*., 2010, 2008; McGeown *et al*., 2009) have been utilized in previous works.

FMRI provides several advantages over other imaging techniques including higher temporal and spatial resolution, repeatability and non-invasion because of the absence of radiation. Likewise FMRI analyzes the brain connectivity amid performance of

sensory and cognitive tasks and, hence, gives powerful intends to distinguish disturbed neural circuits that cause disorders, for example, AD (Evathia *et al*., 2008). FMRI studies have showed an assortment of contrasts between healthy volunteers and AD patients (Bassett *et al*., 2006).

This stored information is regularly hard to translate visually and, after the initial reading, does not give added clinical quality other than as a retroactive reference for clinicians and patients. In any case, from the point of view of machine learning, it could be the cornerstone for accelerating the identification of disease. In addition, machine learning strategies can be used to create precise anticipation, provided that a prior classification stage is refined with meticulousness.

The objective of this study is to classify between the healthy controls and AD patients from the whole brain FMRI images. The proposed approach comprises of the following steps:

- First, the acquired FMRI images are preprocessed to remove noise and the images are normalized using SPM2.
- The whole brain FMRI images are then parcellated into 8 Regions of Interest (ROI) using spatial fuzzy c means algorithm and discriminative features are extracted from the ROIs.
- Finally, the discriminative features are then fed into the Hybrid Neuro Fuzzy Runge Kutta (HNFRK) classifier to distinguish between healthy controls and AD patients.

LITERATURE REVIEW

Classification of Alzheimer's disease plays a vital role for early diagnosis of the disease. Several attempts have been made for the classification of AD. In Liu *et al*. (2012) a local patch-based subspace ensemble method has been proposed to classify Alzheimer's disease by constructing multiple individual classifiers based on various subsets of local patches. Particularly, to capture local spatial consistency, the brain is divided into a number of local patches and a subset of the patches is chose randomly in order to construct a weak classifier. The approach considers 652 subjects from ADNI database and achieves 90.9% accuracy for AD classification and 87.85% accuracy for MCI classification.

Dinesh *et al*. (2013) utilized Nonnegative Matrix Factorization (NMF) and Support Vector Machines (SVM) for the diagnosis of Alzheimer's disease. This approach used for Functional Magnetic Resonance Image (FMRI), Positron Emission Tomography (PET) and Single Photon Emission Computed Tomography (SPECT) images for diagnosis purpose. The features are selected using Fisher Discriminant Ratio (FDR) and Nonnegative Matrix Factorization (NMF) is employed for extracting the selected features. The resulting features are then fed SVM based classifier for classifying AD patients.

Zhang *et al*. (2014) used a hybrid classifier for distinguishing between MCI, NC and AD control from structural MRI images. This system uses clinical examination, demographics, derived anatomic volume and MRI data as training data set and Clinical Dementia Rating (CDR) is used as the target data. Moreover, Principal Component Analysis (PCA) (Ramesh Kumar and Anbumani, 2014) is utilized to reduce the feature vector dimensionality. The features are applied to the kSVM-DT classifier to classify between NC, MCI and AD control. The classification accuracy of the proposed classifier is about 80%.

Belmokhtar and Benamrane (2012) an automatic approach for classifying between MCI, control subjects and AD from 3D structural MRI images. A binary support vector machine based classifier has been developed by combining Voxel-Based Morphometry (VBM) and neuropsychological tests to distinguish between the three groups of subjects.

Dyrba *et al*. (2013) used Diffusion Tensor Imaging (DTI) as a biomarker, for diagnosis of alzheimer's disease. Here, Support Vector Machine (SVM) and a Naïve Bayes (NB) (Ramakrishnan and Nalini, 2014) classifier are used for classification of AD using DTI indices Fractional Anisotropy (FA) and Mean Diffusivity (MD).

Joshi *et al*. (2010) alzheimer's disease and Parkinson's disease were classified employing neural networks and machine learning techniques. Here, the most prompting risk factors has been selected using rank search method and it has been observed that age, genetic factors and smoking are the vital risk factors for Alzheimer's disease and age, genes, diabetes and stroke are the influencing risk factors for Parkinson's disease.

MATERIALS AND METHODS

Materials: The subjects utilized in this study were obtained from Alzheimer's disease Neuroimaging Initiative (http://www.loni.ucla.edu/ADNI) database (www.loni.ucla.edu). The study has been made for AD patients. One hundred and fifty brain scan images were downloaded from the ADNI database including the scans of AD patients (95) and healthy controls (55). The imaging parameters are as follows: repetition time-2000 msec, epcho time-10 msec, flip angle 10°, slice thickness-1 mm.

Methods: The framework of the proposed approach is shown in Fig. 1. The individual FMRI images are first preprocessed to remove noise and then parcellated into 8 Regions of Interest (ROI) using Spatial Fuzzy C-Means algorithm. Features are then extracted from these regions of interest. Finally the individual subjects are classified using HNFRK classifier.

Preprocessing-noise removal and normalization: The FMRI images should be preprocessed in order to remove noise before applying the segmentation operation. The noise removal is done by using
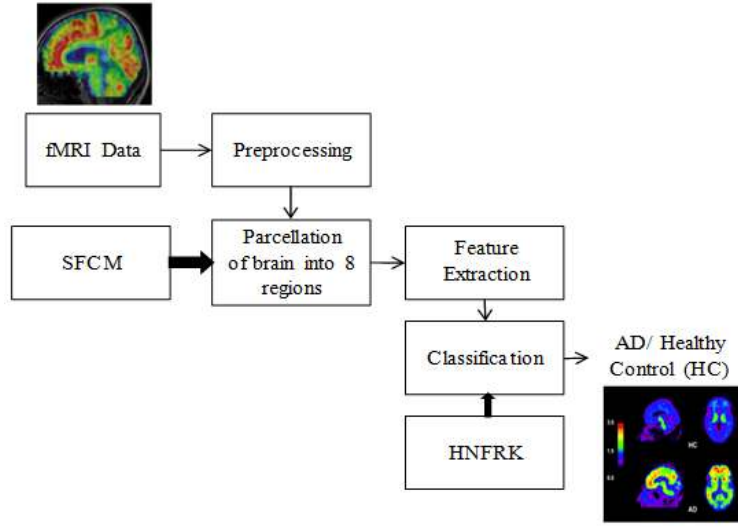
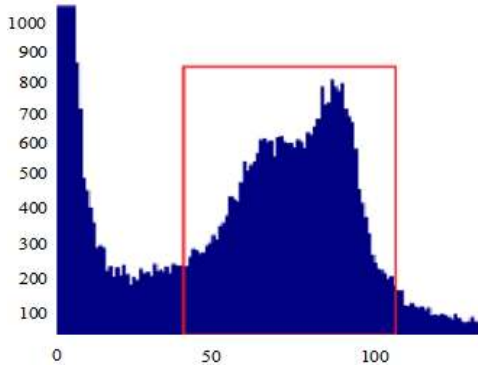Fig. 1: Framework for the classification of AD

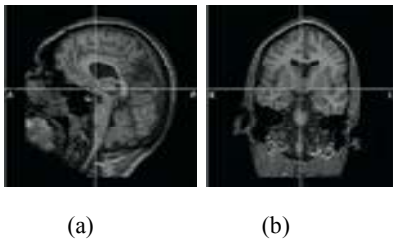Fig. 2: Histogram of the FMRI image

(a)   (b)

Fig. 3: (a) Pre-central, frontal superior and frontal superior middle and 3, (b) superior motor area

histogram based thresholding approach and only the soft tissues of the brain is obtained. Figure 2 shows histogram of the brain image, representing pixel count along the y-axis and intensity along the x-axis, the pixels surrounded by the rectangular box corresponds to the soft brain tissues while the remaining pixels are considered as noise and are removed employing thresholding technique.

Let t_1 and t_2 be the two predefined threshold values. Let P be the pixel whose value ranges from 0 to 255. If the value of the pixel is less than the t_1 and greater than t_2 are considered to be noise.

As the brain scan may vary in shape and size for individual subjects, wrapping these to a standard template will aid in the identification of the anatomical structure. In this study the FMRI images are normalized to Montreal Neurological Institute (MNI) standard space using SPM2.

To further analyze the FMRI images, the whole brain is parcellated into 8 Regions of Interest (ROI): Precentral_L (Precentral Left Region), Precentral_R (Precentral Right Region), Frontal_Sup_L (Frontal Superior Left Region), Frontal_Sup_R (Frontal Superior Right Region), Frontal_Mid_L (Frontal Superior Middle Left Region), Frontal_Mid_R (Frontal Superior Middle Right Region), Supp_Motor_Area_L (Superior Motor Area Left), Supp_Motor_Area_R (Superior Motor Area Right).

Parcellation of brain into 8 regions using spatial fuzzy C-means: The segmentation of the brain into 8 Region of Interest (ROI) is based on the Spatial fuzzy C-Means (SPCM). Figure 3 shows the regions considered in this study. Spatial information are included into the traditional FCM algorithm to improve the segmentation result in the medical images (Meena and Raja, 2013). To utilize the spatial information, a spatial function is described as:

$$S_{ij} = \sum_{c \in B(x_i)} U_{jc} \qquad (1)$$

where, $S_{i,j}$ represents the probability that the pixel x_i belongs to the jth cluster.

The spatial function is integrated into the membership function as:

$$U_{ij}^* = \frac{U_{ij}^a * S_{ij}^b}{\sum_{c=1}^n U_{ci}^a * S_{ci}^b}, \; i = 1.2, \ldots.n$$
$$\text{and } j = 1, 2, \ldots\ldots m \qquad (2)$$

where, a and b are the controlling parameters. There are two steps in each clustering iteration. First, the membership function is calculated in the spatial domain and then the membership function of every pixel is mapped to the spatial domain.

Feature extraction: Neuro-imaging aids in the early detection of AD as they contain vital information necessary to discriminate between AD patients and healthy controls. However, the major issue here is the large size of the neuro images which takes more time to classify these images. Furthermore, all information in the image is not required for the classification purpose since most of the information is inappropriate. Thus, feature extraction is performed in order to find the discriminative feature (Nixon and Aguado, 2012; Padmanabhan and Prabakaran, 2014). The features utilized in the proposed approach are as follows.

The mean Apparent Diffusion Coefficient (ADC) is calculated for each of the 8 ROIs. Then, a multimodal feature is calculated which is the ratio between concentration of GM and ADC in each voxel. The feature vector for each subject consists of mean ADC, the mean of the multimodal parameter and mean DTI which is the ratio of ADC and Fractional Anisotrophy (FA) for each of the 8 regions of interest. These feature vectors are utilized as input to the classifier.

Classification using HNFRK: Subjects are classified into healthy control and AD using Hybrid Neuro Fuzzy Runge-Kutta (HNFRK) classifier. The ANFIS is a fuzzy sugenomodel placed in the adaptive system framework in order to facilitate adaptation and learning (Boyacioglu and Avci, 2010). The ANFIS learns the feature vectors from the data set and the system parameters are adjusted according to a given error condition and the classifier is trained with Runge Kutta learning algorithm.

Given the training vectors the classifier classifies into two classes AD and healthy controls and assigns labels ($y \in R^n$) for every observation such that AD is considered as a positive class and Healthy controls are considered as negative class. Given the unlabeled data classes, the output of the classifier is as given as:

$$y = \sum_{i=1}^{n} x_i \tag{3}$$

where, n is the number of observations. The output of the classifier is the linear function of the defuzzifier parameters. The parameters are adjusted using the fourth order Runge Kutta learning algorithm (Musa *et al*., 2010). The update mechanism relies on error back propagation. The neural networks based classification approach can be determined by the following equations:

$$\hat{x} = f(x, \tau) \tag{4}$$

$$x(t+1) = x(i) + \frac{h}{6}(p_0 + 2p_1 + 2p_2 + p_3) \tag{5}$$

$$p_0 = N(x; \alpha) = N(x_0; \propto) \tag{6}$$

$$p_1 = N\left(x + \frac{1}{2}hp_0; \propto\right) = N(x_1; \propto) \tag{7}$$

$$p_2 = N(x + hp_1; \propto) = N(x_2; \propto) \tag{8}$$

$$p_3 = N(x + hp_2; \propto) = N(x_3; \propto) \tag{9}$$

where, α is the generic parameter. Two paths are considered in this propagation. First the direct connection to the output summation and second via the neural network stages. Hence, each derivation, except the first derivation contains two terms. The fourth order Runge-Kutta approximation is summarized as follows:

$$\frac{\partial p_1}{\partial \propto} = \frac{\partial p_1}{\partial x_1}\frac{\partial x_1}{\partial p_0}\frac{\partial p_0}{\partial \propto} + \frac{\partial p_1}{\partial \propto} \tag{10}$$

$$\frac{\partial p_2}{\partial \propto} = \frac{\partial p_2}{\partial x_2}\frac{\partial x_2}{\partial p_1}\frac{\partial p_1}{\partial \propto} + \frac{\partial p_2}{\partial \propto} \tag{11}$$

$$\frac{\partial p_3}{\partial \propto} = \frac{\partial p_3}{\partial x_3}\frac{\partial x_3}{\partial p_2}\frac{\partial p_2}{\partial \propto} + \frac{\partial p_3}{\partial \propto} \tag{12}$$

$$\Delta_{\propto(i)} = \frac{rh}{6}\left(v^T(i) - x^T(i)\right)$$
$$(\partial p_0 + \frac{2\partial p_1}{\partial \propto} + \frac{2\partial p_2}{\partial \propto} + \frac{2\partial p_3}{\partial \propto}) \tag{13}$$

where,
r : The learning rate
$v^T(i)$: The measured state vector at the time t

RESULTS AND DISCUSSION

Results: The performance of the proposed approach is measured using two different types of classifiers (SVM, ANFIS). A Ten-fold cross validation approach is utilized to evaluate the proposed scheme. The metrics employed to evaluate the performance of the classifier is given below:

$$Sensitivity = \frac{True\ Positive}{\sum(True\ Positive\ and\ False\ Negative)} \tag{14}$$

$$Specificity = \frac{True\ Negative}{\sum(True\ Negative\ and\ False\ Positive)} \tag{15}$$

Here, True Positive indicates AD patients who are correctly identified as AD, True Negative indicates healthy controls who are correctly classified as healthy, False Negative indicates AD patients who are incorrectly classified as healthy and False positive represents healthy controls who are incorrectly classified as AD. Table 1 show the classification accuracy of the proposed classifier with different features and Table 2 shows confusion matrix that is obtained after prediction.

Table 1: Classification results with different features

Features	Sensitivity	Specificity
ADC	72.50	70.80
GM	85.54	82.65
ADC+FA	75.86	73.48
ADC+GM	92.45	91.68

Table 2: Confusion matrix

	Predicted class	
Actual class	AD	Healthy controls
AD	55	13
Healthy controls	10	40

Table 3: Statistical results of extracted features

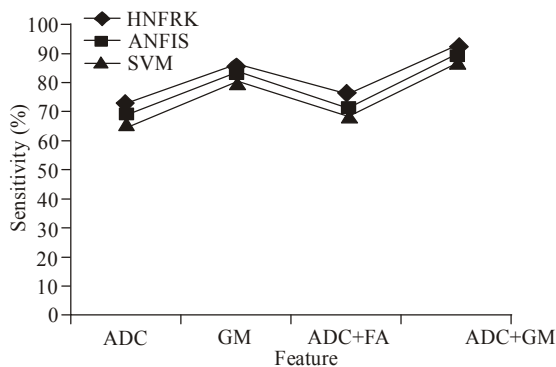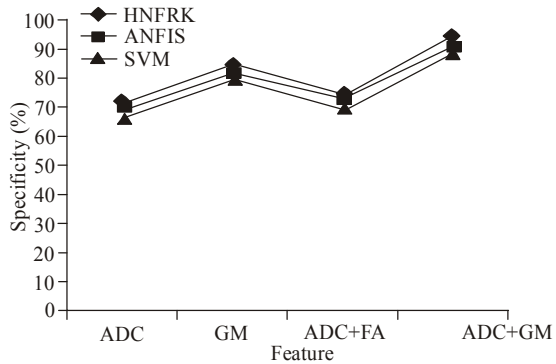| Features	AD	Healthy control
ADC (10^{-3} mm^2/sec)	1.97±0.82	0.69±0.25
FA	0.53±0.05	0.89±0.35
GM	48.67±2.50	43.45±50.23

Fig. 4: Sensitivity percentage of three classifiers

Fig. 5: Specificity percentage of three classifiers

In the above confusion matrix, rows corresponds to the actual class and columns corresponds to the predicted class. In above matrix, 55 patients are correctly classified as AD while 10 patients are incorrectly classified as healthy controls and 40 patients are correctly classified as healthy controls while 13 patients are incorrectly classified as AD. Table 3 shows the statistical results of extracted features.

Discussion: The HNFRK classifier performs better than the Support Vector Machine (SVM) and Adaptive Neuro Fuzzy Inference System (ANFIS). It can be seen that GM as individual feature provides better results

when compared to the ADC. Similarly the combination of GM and ADC provides better results compared to ADC and FA. Comparing GM, ADC and FA, it is obvious that GM outperforms ADC and FA. Figure 4 and 5 shows the sensitivity and specificity rates of three classifiers (SVM, ANFIS and HNFRK).

From the above results, it is evident that the proposed HNFRK provides good sensitivity and specificity rates as compared to that of the SVM and ANFIS classifier. Thus, it can be concluded that the HNFRK classifier provides better classification between healthy controls and AD patients.

CONCLUSION

Alzheimer's Disease is a dynamic neurodegenerative disorder related with an interruption of neuronal function and a progressive disintegration in function, behavior and cognition. Diagnosing AD at an early stage is of great significance. In this study, a Hybrid Neuro Fuzzy Runge Kutte (HNFRK) classifier has been proposed for the classification of Alzheimer's disease from FMRI images. The dataset employed in this study are obtained from ADNI database. The proposed approach is based on the extraction of three types of features after preprocessing and segmentation. The extracted features are fed into the classifier for improving the classification accuracy. The proposed approach is evaluated using two classification models based on the individual and the combination of features. The comparison results show that the proposed HNFRK provides better classification results compared to SVM and ANFIS.

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