

Multi-class Alzheimer Disease Classification using Hybrid Features

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Abstract—Alzheimer disease (AD) is one of the most common form of dementia. Accurate detection of AD and its initial stage i.e., mild cognitive impairment (MCI) is a challenging task. In this study, a computer-aided diagnosis (CAD) system is implemented on clinical and diagnostic imaging data from OASIS database. Amygdala and hippocampus are the regions that are most affected by Alzheimer and are located inside the grey matter region of brain. Features used for classification are calculated using grey level co-occurrence matrix (GLCM) such as entropy, energy, homogeneity, and correlation. The ratios of the grey matter and white matter volume to the cerebrospinal fluid volume are also used. Clinical features are also used improving the classification accuracy achieving 94.6% for binary classification. The proposed algorithm is also used for multi-class classification where three classes, namely, normal (N), Alzheimer disease (AD), and mild cognitive impairment (MCI) are considered. An accuracy of 79.8% on these classes is achieved that is significant since the classes considered are highly similar. We have achieved improved results in comparison to state-of-the-art techniques for binary classification and have also performed multi-class classification.

Keywords—Alzheimer; hybrid features; classification; multi-class

I. INTRODUCTION

Dementia is a general term used to describe progressive degeneration in brain function including memory, concentration, and reasoning. Its most well-known cause is Alzheimer disease (AD) and generally it is found in people of mature age. It is a dynamic, neuro-degenerative disease defined by serious disintegration in cognitive function, particularly memory loss. It is the foremost public health problem where about 44 million individuals around the world are currently suffering from Alzheimer's or associated dementia [1]. These figures are expected to increase exponentially over time [2]. An increasing occurrence of AD requires efficient biomarkers and early detection techniques for proper diagnosis and treatment [2], [3].

For early diagnosis, study of the symptomatic pre-dementia phase of disease, also known as mild cognitive impairment (MCI) is necessary [4]. Episodic and spatial memory resides in hippocampus, which serves as mean of communication between the brain and body. The first area to be effected in brain in response to AD is the hippocampus region. Cerebral imaging techniques, such as magnetic resonance imaging (MRI) is used for detection and diagnosis of AD. Recently, national institute on Aging-Alzheimers Association (NIA-AA) recommended inclusion of some advanced features measured

using neuroimaging techniques for AD detection including: 1) volume of cerebrospinal fluid (CSF); 2) amyloid and tau; 3) neurogenetic- testing measurements; and 4) neuronal injury. In particular, despite being a non-invasive technique, MRI has been able to detect cerebral atrophic regions even before dementia is apparent [4]. However, subjective assessment of AD by observing changes in morphology of MR images is an extremely troublesome and tedious clinical practice. Numerous brain image features e.g., cortical thickness, volume, white matter, cerebrospinal liquid and hippocampus have been utilized for classification of AD in subjects [5].

An automated computer-aided diagnosis (CAD) system extracted features using structural magnetic resonance imaging (sMRI) data [6]. Classification error estimation has been used for feature selection from grey matter (GM) atrophy clusters of volumes of interests (VOIs) that are determined using a voxel-based morphometry (VBM) analysis. Another approach is based on image-derived biomarkers and multiple kernel learning. Visual features are extracted in this method from structural MRI and diffusion tensor imaging (DTI) along with mean diffusivity (MD) maps and combined in multiple kernel learning to discriminate between AD and MCI subjects [7]. Partial least square (PLS) and principle component analysis (PCA) have been combined for feature extraction from brain tissues for AD detection and diagnosis [8]. Two classifiers based on SVM using linear and RBF kernel, have been used to test PLS and PCA. Key slices in 3D volumetric data has been determined by using maximum inter-class variance (ICV) [9]. The most important eigenbrain (MIE) has been obtained from these slices using Welch's t-test (WTT), and classification is performed in final step using SVM [10]. In [11], the work on eigenbrain has been extended to 3D (3D-EB), where classification is performed using deep learning. Three feature selection measures i.e WTT, Students t-test (STT) and Bhattacharyya distance (BD) have been used in [12] to classify AD subjects. AD detection has been done via an automatic 3D caudate nucleus (CN) segmentation by means of combined dictionary learning with a level set design [13].

Various anatomical MRI measures are consolidated to enhance classification and diagnosis of AD subjects, such as 1) cortex density; 2) cortex area; 3) curvature; 4) grey matter volume; 5) sub-cortical volumes; and 6) hippocampal shape using net logistic regression [14]. Despite rich literature, research on classifying Alzheimer's disease is still ongoing and a bright prospect in modern age.

In this study, the proposed methodology classifies AD into

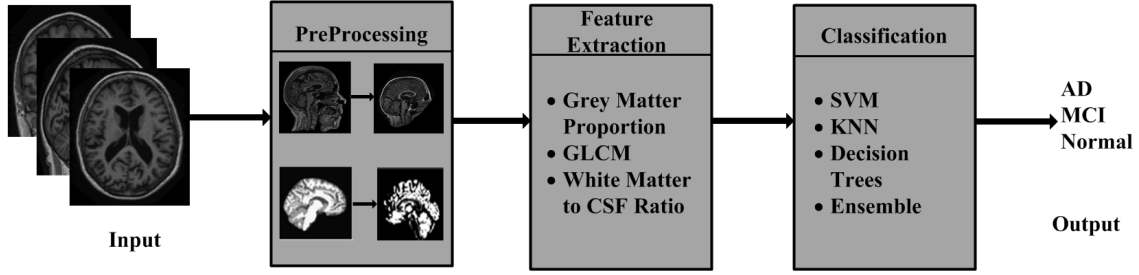


Fig. 1. Block diagram shows different stages in method. The input consists of a 3D NIFTI data which is skull stripped, Atlas registered, motion corrected and thresholded in the pre-processing step. This is followed by feature extraction which is then classified using different classifiers.

binary as well as multiclass classification. MR images are skull stripped, atlas registered and motion corrected. Hybrid feature extraction is performed to get distinguishing features for Alzheimer then these features are given as input to multiple classifiers. Most of the existing techniques have implemented binary classification whereas the proposed methodology has also been validated for multi-class classification with promising results.

II. PROPOSED METHODOLOGY

The proposed system has three main modules namely pre-processing, feature extraction, and disease classification. The input images consist of 3D NIFTI data that is skull stripped, atlas registered, motion corrected and thresholded in the pre-processing step followed by feature extraction and classification using different classifiers. The proposed methodology is shown in Fig. 1 and discussed in the following subsections.

A. Preprocessing

The dataset is minimally preprocessed to make it coherent for feature extraction task. Images in dataset are three-dimensional consisting of sagittal, coronal, and transversal views. The OASIS dataset images are segmented into three classes, namely white matter (WM), grey matter (GM) and cerebrospinal fluid (CSF) by using FAST tool. This step makes it easy to extract volumetric features. Each scanning session for individual patients incorporate 3-4 images averaged together to increase signal to noise ratio (SNR) making images noise free. Images are also motion-corrected and finally brain masked with atlas space of Talairach and Tournoux [15]. The locations of brain structures are mapped using this atlas space regardless of difference from individual in the overall shape and size of brain.

B. Feature Extraction

The pixels labelled as 1, 2 and 3 are extracted from the whole brain to calculate WM, GM and CSF volume ratios that are used as features for selected classifiers. The features computed in this study are discussed in detail in following sections.

1) Grey Level Co-occurrence Matrix (GLCM) Features:

Grey-level co-occurrence matrix (GLCM) is a statistical method [16] used for examining texture while keeping in view the spatial resolution of pixels. GLCM calculates occurrences of pixel pairs with specified values that are in a relationship

with each other to determine texture of image. These occurrences are then used to compute statistical information from GLCM matrix. Co-occurrence matrix has been used to extract contrast, correlation, homogeneity, and entropy. These features have high distinguishing power and are calculated as,

$$Contrast = \sum_{x,y} |x - y|^2 \log P_{r,\theta}(x, y) \quad (1)$$

$$Correlation = \sum_{x,y} \frac{(x - \mu_1)(y - \mu_2)P_{r,\theta}(x, y)}{\sigma_1\sigma_2} \quad (2)$$

$$Homogeneity = \sum_{x,y} \frac{P_{r,\theta}(x, y)}{1 + |x - y|^2} \quad (3)$$

$$Entropy = - \sum_{x,y} P_{r,\theta} \log P_{r,\theta}(x, y) \quad (4)$$

where co-occurrence matrix $P_{r,\theta}$ is a two-dimensional array of size $m \times m$, where, 'm' is the number of grey levels in an image and μ is the mean value. The (x,y) element of $P_{r,\theta}$ is the probability of transition from a pixel with intensity x to a pixel with intensity y lying at distance r with a given orientation θ in the slice.

2) *Grey Matter Proportion*: The size of brain structures like GM and CSF change with the intensity of disease. Hence, grey matter volume (GMV) and the volume of the CSF are used as features. The pixels labeled as 2 are used to obtain GMV from the segmented GM. To remove the anomaly arising due to different brain sizes in different human beings, the GM volume is normalized and used to calculate the ratio by dividing with CSF volume calculated by the following equation:

$$VolumeGM = - \sum_{slice=1}^n \sum_{a=1}^x \sum_{b=1}^y f(a, b) == 2 \quad (5)$$

$$VolumeCSF = - \sum_{slice=1}^n \sum_{a=1}^x \sum_{b=1}^y f(a, b) == 3 \quad (6)$$

where (a,b) represents location of each pixel in the segmented image.

TABLE I. CLASSIFIER ACCURACY WITH IMAGE BASED FEATURES

Classifier	AD vs N	MCI vs N	AD vs MCI	AD vs MCI vs N
SVM	82.1	75	67.9	60
Ensemble	75	71.4	80.4	60.7
KNN	73.2	69.6	67.9	57.1
Decision Tree	78.6	76.8	71.4	60.7

TABLE II. CLASSIFIER ACCURACY WITH HYBRID FEATURES

Classifier	AD vs N	MCI vs N	AD vs MCI	AD vs MCI vs N
SVM	92.9	83.9	87.5	79.8
Ensemble	94.6	85.7	80.4	73.8
KNN	92.9	80.4	80.4	72.6
Decision Tree	91.1	85.7	76.8	77.4

3) *White Matter Volume to Cerebrospinal Volume Ratio:*

The volume of white matter is used as a feature since its size decreases with progression of AD. Label 1 is used for WM in the segmented images. WM volume is divided by the CSF volume which increases as the disease spreads out. The white matter volume to the cerebrospinal volume ratio is calculated as,

$$VolumeWM = - \sum_{slice=1}^n \sum_{a=1}^x \sum_{b=1}^y f(a, b) == 1 \quad (7)$$

C. Classification

The selected classifiers including SVM, ensemble, K nearest neighbor (KNN), and decision tree, are trained to classify data into normal (N), mild cognitive impairment (MCI) and Alzheimer disease (AD) class using supervised learning. The classes are divided into three binary groups, namely, AD/N, AD/MCI, MCI/N, and a multi-class group i.e., AD/MCI/N. The purpose of this categorization of output classes is to obtain binary class classification, because most texture based classifiers provide good results on binary classification e.g., SVM, decision trees, and ensemble etc. The training data is divided into 80:20 training validation ratios. Models are trained using cross validation to get effective classification performance.

III. EXPERIMENTAL SETUP

A. Dataset

The MRI data from database of Open Access Series of Imaging Studies (OASIS) [17] is used. It consists of longitudinal and cross sectional MR images of 416 patients with age ranging between 18 to 90 years.

The T1 weighted images consists of all classes of data, with AD, MCI and cognitive normal (CN) people i.e. people without the disease or any kind of dementia. The dataset also contains information about age, sex, and handedness of patients. Clinical data has also been provided for example mini-mental state examination (MMSE), a brief questionnaire test with 30-point through which cognitive impairment and dementia are screened [18]. Crucial data has also been provided like the estimated total intra-cranial volume (eTIV), clinical dementia ratio, normalized whole brain volume (nWBV) and atlas scaling factor (ASF). The ratings of CDR varies from

0 to 2, where 0 represents normal, 0.5 is for mild cognitive impairment, 1 is for Alzheimer’s disease.

B. Results and Discussion

In training, CDR is used as the output label. CDR is used for evaluating the severity of symptoms of dementia [19]. For subjects whose CDR is 0 are labelled as normal (N), CDR of 0.5 is labelled as MCI and CDR of 1 is labelled as AD. Different cross validation folds are used to assess the performance of selected classifiers. One-fold is used as test and the remaining k-1 folds are used as training data. In particular, 2, 5 and 10-fold cross validation is performed and best results are achieved with 5-fold cross validation. One subset of features extracted from segmented images excluding clinical features, consist of 6-dimensional vector (Grey level co-occurrence matrix, grey matter, and white matter volume to CSF volume ratio). Classification accuracy achieved using these features over binary classification is shown in Table I. The complete feature space is a thirteen-dimensional vector that is a hybrid of volumetric features, extracted from segmented MR images, and clinical features. Clinical features include, total Intra-cranial volume, normalized whole brain volume, atlas scaling factor, and MMSE. Classification accuracy achieved using these hybrid features is shown in Table II.

Classification results for different binary classes show high feature similarity in MCI and normal classes. AD vs. normal category gives the best classification, results portraying high dissimilarity in these classes. Models are trained for 10 iterations and average accuracy is reported in this study. The results show, all classifiers performing equally well for binary categories. Multi-class classification results are also reported where both ensemble and decision trees performed best when only volumetric features were used but SVM outperformed other algorithms when complete feature space is used. Fig. 2 and Fig. 3 show the sensitivity and specificity values achieved using texture features only and complete feature space respectively. A comparison of the proposed method with state-of-the-art techniques is presented in Table III. It can be seen from the table that the proposed methodology achieved better accuracy

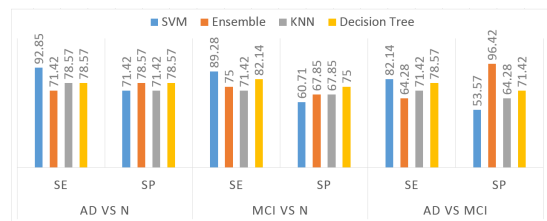


Fig. 2. Sensitivity (SE) and Specificity (SP) of classifiers for image based feature.

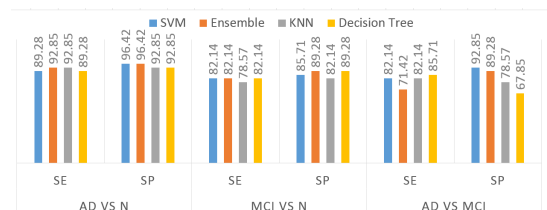


Fig. 3. Sensitivity (SE) and Specificity (SP) of classifiers for hybrid feature.

TABLE III. COMPARISON OF DIFFERENT STATE-OF-THE-ART TECHNIQUES FOR BINARY CLASSIFICATION

Author	Technique	Accuracy
Zhang et.al [10]	Eigen brain + WTT + SVM	93.36%
Yudong Zhang et.al [11]	3D-EB + Pol-SVM	92.81%
Shuihua Wanga et.al [12]	3D-DF+WTT+TSVM	93.05%
Wang et. al. [20]	WE + MLP + BBO	92.4%
	Proposed Methodology	94.6 %

than state-of-the-art techniques, while also being applicable in multi-class classification.

IV. CONCLUSION

A classification algorithm for different Alzheimer's stages using a hybrid of texture and clinical features is presented. In the proposed approach, GLCM, grey matter proportion and white matter volume to cerebrospinal volume ratio along with clinical features are used for classification. The results indicate that using clinical features alongside texture based features can boost classification accuracy significantly. Multiclass classification for AD, N and MCI is also addressed although it is very challenging due to similarity between AD and MCI subjects. The proposed method achieves improved accuracy for binary classes and significant accuracy for multi-class classification.

REFERENCES

- [1] S. B. Shree and H. Sheshadri, "Diagnosis of alzheimer's disease using naive bayesian classifier," *Neural Computing and Applications*, pp. 1–10, 2016.
- [2] E. Moradi, A. Pepe, C. Gaser, H. Huttunen, J. Tohka, A. D. N. Initiative et al., "Machine learning framework for early mri-based alzheimer's conversion prediction in mci subjects," *Neuroimage*, vol. 104, pp. 398–412, 2015.
- [3] O. B. Ahmed, M. Mizotin, J. Benois-Pineau, M. Allard, G. Catheline, C. B. Amar, A. D. N. Initiative et al., "Alzheimer's disease diagnosis on structural mr images using circular harmonic functions descriptors on hippocampus and posterior cingulate cortex," *Computerized Medical Imaging and Graphics*, vol. 44, pp. 13–25, 2015.
- [4] L. Nanni, C. Salvatore, A. Cerasa, I. Castiglioni, A. D. N. Initiative et al., "Combining multiple approaches for the early diagnosis of alzheimer's disease," *Pattern Recognition Letters*, vol. 84, pp. 259–266, 2016.
- [5] C. Jongkreangkrai, Y. Vichianin, C. Tocharoenchai, H. Arimura, A. D. N. Initiative et al., "Computer-aided classification of alzheimer's disease based on support vector machine with combination of cerebral image features in mri," in *Journal of Physics: Conference Series*, vol. 694, no. 1. IOP Publishing, 2016, p. 012036.
- [6] I. Beheshti, H. Demirel, F. Farokhian, C. Yang, H. Matsuda, A. D. N. Initiative et al., "Structural mri-based detection of alzheimer's disease using feature ranking and classification error," *Computer Methods and Programs in Biomedicine*, vol. 137, pp. 177–193, 2016.
- [7] O. B. Ahmed, J. Benois-Pineau, M. Allard, G. Catheline, C. B. Amar, A. D. N. Initiative et al., "Recognition of alzheimer's disease and mild cognitive impairment with multimodal image-derived biomarkers and multiple kernel learning," *Neurocomputing*, vol. 220, pp. 98–110, 2017.
- [8] L. Khedher, J. Ramirez, J. M. Górriz, A. Brahim, F. Segovia, A. s Disease Neuroimaging Initiative et al., "Early diagnosis of alzheimer s disease based on partial least squares, principal component analysis and support vector machine using segmented mri images," *Neurocomputing*, vol. 151, pp. 139–150, 2015.
- [9] S.-H. Wang, Y. Zhang, Y.-J. Li, W.-J. Jia, F.-Y. Liu, M.-M. Yang, and Y.-D. Zhang, "Single slice based detection for alzheimers disease via wavelet entropy and multilayer perceptron trained by biogeography-based optimization," *Multimedia Tools and Applications*, pp. 1–25.
- [10] Y. Zhang, Z. Dong, P. Phillips, S. Wang, G. Ji, J. Yang, and T.-F. Yuan, "Detection of subjects and brain regions related to alzheimer's disease using 3d mri scans based on eigenbrain and machine learning," *Frontiers in Computational Neuroscience*, vol. 9, p. 66, 2015.
- [11] Y. Zhang, S. Wang, P. Phillips, J. Yang, and T.-F. Yuan, "Three-dimensional eigenbrain for the detection of subjects and brain regions related with alzheimers disease," *Journal of Alzheimer's Disease*, vol. 50, no. 4, pp. 1163–1179, 2016.
- [12] S. Wang, Y. Zhang, G. Liu, P. Phillips, and T.-F. Yuan, "Detection of alzheimers disease by three-dimensional displacement field estimation in structural magnetic resonance imaging," *Journal of Alzheimer's Disease*, vol. 50, no. 1, pp. 233–248, 2016.
- [13] S. D. S. Al-shaikhli, M. Y. Yang, and B. Rosenhahn, "Alzheimer's disease detection via automatic 3d caudate nucleus segmentation using coupled dictionary learning with level set formulation," *Computer Methods and Programs in Biomedicine*, vol. 137, pp. 329–339, 2016.
- [14] F. de Vos, T. M. Schouten, A. Hafkemeijer, E. G. Dopper, J. C. van Swieten, M. de Rooij, J. van der Grond, and S. A. Rombouts, "Combining multiple anatomical mri measures improves alzheimer's disease classification," *Human brain mapping*, 2016.
- [15] R. L. Buckner, D. Head, J. Parker, A. F. Fotenos, D. Marcus, J. C. Morris, and A. Z. Snyder, "A unified approach for morphometric and functional data analysis in young, old, and demented adults using automated atlas-based head size normalization: reliability and validation against manual measurement of total intracranial volume," *Neuroimage*, vol. 23, no. 2, pp. 724–738, 2004.
- [16] S. Bhattacharyya, *Handbook of Research on Advanced Hybrid Intelligent Techniques and Applications*. IGI Global, 2015.
- [17] D. S. Marcus, T. H. Wang, J. Parker, J. G. Csernansky, J. C. Morris, and R. L. Buckner, "Open access series of imaging studies (oasis): cross-sectional mri data in young, middle aged, nondemented, and demented older adults," *Journal of cognitive neuroscience*, vol. 19, no. 9, pp. 1498–1507, 2007.
- [18] G. Kuslansky, M. Katz, J. Verghese, C. B. Hall, P. Lapuerta, G. LaRuffa, and R. B. Lipton, "Detecting dementia with the hopkins verbal learning test and the mini-mental state examination," *Archives of Clinical Neuropsychology*, vol. 19, no. 1, pp. 89–104, 2004.
- [19] M. M. Williams, M. Storandt, C. M. Roe, and J. C. Morris, "Progression of alzheimers disease as measured by clinical dementia rating sum of boxes scores," *Alzheimer's & Dementia*, vol. 9, no. 1, pp. S39–S44, 2013.
- [20] S.-H. Wang, Y. Zhang, Y.-J. Li, W.-J. Jia, F.-Y. Liu, M.-M. Yang, and Y.-D. Zhang, "Single slice based detection for alzheimers disease via wavelet entropy and multilayer perceptron trained by biogeography-based optimization," *Multimedia Tools and Applications*, pp. 1–25.