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Clustering-Based Detection of Alzheimer's Disease Using Brain MR Images

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***Abstract*—**This paper presents a comprehensive survey of recent research studies to segment and classify brain MR (magnetic resonance) images in order to detect significant changes to brain ventricles. The paper also presents a general framework for detecting regions that atrophy, which can help neurologists in detecting and staging Alzheimer. Furthermore, a prototype was implemented to segment brain MR images in order to extract the region of interest (ROI) and then, a classifier was employed to differentiate between normal and abnormal brain tissues. Experimental results show that the proposed scheme can provide a reliable second opinion that neurologists can benefit from.

***Keywords*—**Alzheimer, brain images, classification techniques, Magnetic Resonance Images, MRI.

I. Introduction

ALZHEIMER'S disease (AD) is the most common form of dementia affecting seniors age 65 and over. *AD* causes nerve cell death and tissue loss throughout the brain, resulting to brain tissue shrinking and larger ventricles (chambers within the brain that contain cerebrospinal fluid). When AD is suspected, the diagnosis is first confirmed with behavioral assessments and cognitive tests and often followed by a brain scan [1].

Early detection of Alzheimer is an active research area that aims to generate future treatments that could target the disease in its earliest stages, before causing irreversible brain damage or mental decline. Different diagnosis techniques have been developed such as brain imaging/neuroimaging, cerebrospinal fluid (CSF) proteins, proteins in blood, genetic risk profiling and mild cognitive impairment [2].

Magnetic resonance imaging (MRI) is a radiation free medical imaging technique that uses a magnetic field and radio waves to visualize detailed images of the internal structures (soft tissue) of the body, producing cross-sectional gray level images of the body [3]. These images can be reconstructed into three-dimensional (3D) images and processed using image processing techniques to de-noise the images and to extract meaningful information that might help the clinical diagnostic.

One of the first brain tissue segmentations studies was conducted by Kapur et al. [4], in the mid-nineties, which presented a method for segmentation from magnetic resonance images using a parallel implementation of three existing computer vision techniques: Expectation/maximization segmentation, binary mathematical morphology, and active contour models. In the same way, a more accurate technique was developed by Wells et al. [5] based on adaptive segmentation of MRI data in contrast to the intensity based techniques. This method used knowledge of tissue intensity properties and intensity inhomogeneity in addition to the expectation-maximization (EM) algorithm and carried the results of more than 1000 brain scans.

Held et al. [6] developed 3D segmentation technique that classifies brain MR images into gray and white matters, CSF, scalp-bone and background. They used Markov random fields (MRFs) by extracting three features related to the MR images, i.e., nonparametric distributions of tissue intensities, neighbourhood correlations, and signal inhomogeneity.

Various segmentation methods were applied in MR images afterwards. In 2000, Pham et al. [7] presented an extensive survey of those methods, which include:

- Thresholding or multithresholding (based on the intensity values and the image histograms),
- Region growing (based on intensity values and the image contours),
- Region classification methods (supervised methods based on pattern recognition techniques such as the k-nearest neighbours, maximum-likelihood or Bayes classifier that use training data),
- Clustering (similar to the classification techniques without the training data, including K-means, ISODATA algorithm, Fuzzy C-Mean algorithm, and the EM algorithm),
- MRF Models (which is a statistical model that shows the spatial correlations between close pixels. MRF is combined with clustering algorithms to provide proper segmentation),
- Artificial Neural Networks (or *ANN*s which are parallel networks of nodes that simulate biological learning)
- Other approaches including; model-fitting, watershed algorithms, atlas guided approaches and deformable models.

Zhang et al. [8] suggested an HMRF-EM framework segmentation of brain MR images using a Hidden Markov Random Field (HMRF) model and the EM algorithm. The HMRF model is a random process produced by an MRF, which can be modeled by estimating the observations. They chose the EM algorithm to match the HMRF model.

In 2002, Fischl et al. [9] developed an Automated Labeling

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technique, in addition to a registration procedure, that appoints a label value, from a 37 labels' training dataset, to each voxel of the neuroanatomical structures in the human brain. The labels include left and right caudate, putamen, pallidum, thalamus, lateral ventricles, hippocampus, and amygdala. According to the authors, the results were accurate when they applied their procedure to detect volumetric changes in mild AD.

Van Leemput et al. [10] demonstrated an enhanced statistical framework for partial volume segmentation (PV) using parametric statistical image model as a spatial prior knowledge and an EM algorithm that estimates the model's parameters and performs a PV classification at the same time.

To overcome the disadvantages of using the watershed transform when segmenting MR images into gray matter/white matter, Grau et al. [11] used an enhanced version of the transform, by adding prior information and atlas registration.

Other researchers tried to automatically segment the brain MR images into more specific regions, e.g., CSF, gray matter (GM), white matter (WM) and white matter lesions (WMAL). De Boer et al. [12], [13] used a trained k-nearest neighbour classifier with an extra step for the segmentation of WMAL. In the same manner, Tu et al. [14] created a hybrid discriminative/generative classifier model. The learning process of their classifier used probabilistic boosting tree (PBT) framework and a high dimensional vector of attributes with different scales in order to extract different anatomical structures of 3D MRI volumes. The resulting information is introduced within a hybrid model and an energy function is minimized in order to perform the final segmentation process.

For the purpose of assisting the diagnosis of AD, Colliot et al. [15] used NINCDS-ADRDA criteria [16] for patients with AD and Petersen et al.'s criteria [17] for patients with mild cognitive impairment (MCI). Their purpose was to extract the hippocampus and the amygdale structures using competitive region-growing. Their algorithm started from known landmarks (positions) as a prior knowledge.

Zhang et al. [18] developed a new hybrid active contour model using level-set method whose energy function is not sensitive to image derivatives since it relied on both the object's contour and region information.

Concerning the work of Morra et al. [19], an auto context model (ACM) was created; to segment the hippocampus automatically in 3D T1-weighted MRI scans of subjects from the ADNI database. Their algorithm used 21 hand-labeled segmentations to learn a classification rule that classifies a hippocampus region from a non-hippocampus one using an AdaBoost method and a large vector of attributes (image intensity, position, image curvatures, image gradients, tissue classification maps of gray/white matter and CSF, and mean, standard deviation, and Haar filters of size $1 \times 1 \times 1$ to $7 \times 7 \times 7$). They employed the Bayesian posterior distribution of the labeling to recalculate the new system's attributes. Finally, they validated their algorithm by comparing their results with hand-labeled segmentations.

Following Adaboost algorithm, another popular classifier was applied to segment T1-weighted brain MRIs in order to extract the hippocampus region, i.e. the Support Vector Machine (SVM) as in Morra et al.'s work [19], [20]. The authors compared the hierarchical AdaBoost, SVM with manual feature selection and hierarchical SVM with automated feature selection (Ada-SVM). They validated their results with the FreeSurfer brain segmentation package [21]. In the same manner, Shattuck et al. [22] validated their brain segmentation methods by implementing a web-based test environment [23] using many datasets and a number of metrics to evaluate the segmentation's accuracy and the performance of skull-stripping (removal of extra-meningeal tissues from the MRI volume) in T1-weighted MRI. According to the authors, their web-test framework had been satisfactory on 3 popular algorithms named: The Brain Extraction Tool [24], the Hybrid Watershed Algorithm [25], and the Brain Surface Extractor [26].

The segmentation based on edge detection was also used, e.g. Huang et al. [27] applied a geodesic active contour using the image edge geometry and the voxel statistical homogeneity in the purpose of extracting complex anatomical structures.

Since the subcortical grey matter structures (located in the deep brain region) are low in contrast, which delimitates the segmentation results, Helms et al. [28] proposed a semi-quantitative magnetization transfer (MT) imaging protocol that overcomes limitations in T1-weighted (T1w) magnetic resonance images.

Other authors were more inclined in using 3D segmentation in spite of the long computation problem. AlZu'bi et al. [29] suggested Multiresolution analysis segmentation using Hidden Markov Models (HMMs) and extracted the vector of attributes with the assistance of 3D wavelet and ridgelet.

To optimize the accuracy and speed of segmentation, Lötjönen et al. [30] created an optimised pipeline for multi-atlas brain *MRI* segmentation using different similarity measures. Additionally, they combined multi-atlas segmentation and intensity modelling through expectation maximisation (EM) and optimisation via graph cuts.

Even though the segmentation of *MR* human brain images with multiple atlases was more successful, the method was less effective when it comes to the ventricular enlargement that is not caught by the atlas database. Heckemann et al. [31] added tissue classification information into the image registration and resumed their work into MAPER, multi-atlas propagation with enhanced registration [32].

As the MRIs of the brain present an intensity non-uniformity (INU) phenomenon, which affects the segmentation results, Rivest-Hénault et al. [33] presented a new method that uses local linear region representative and embedded region models.

Magnin et al. [34] developed a classification method based on SVM. They first segmented the image into ROIs, using anatomically labelled template of the brain developed by Tzourio-Mazoyer et al. [35] to obtain probability masks for GM, WM, and CSF. Indeed, the histogram of each ROI showed 3 modes corresponding to the 3 probability masks.

The segmented ROI was modelled with a linear combination of three Gaussians. They use the SVM algorithm to classify the subjects and statistical procedures, based on bootstrap resampling, into AD subjects and elderly control subjects (CS). Likewise, Robinson et al. [36] developed a machine learning approach that determines population differences in whole-brain structural networks from brain atlases. The authors aimed to classify subjects based on their patterns and identify the best features which distinguish between groups, i.e. ROIs are automatically generated by label propagation and followed by classifier fusion, connections are built between ROIs using probabilistic tracking, a vector of attributes is determined using mean anisotropy measurements along those connections and finally combined with the principal component analysis (PCA) and maximum uncertainty linear discriminant analysis. Moreover, Zhang et al. [37] combined different modality of biomarkers to get complementary information for the diagnosis of AD and MCI. According to the authors, previous studies showed that structural MRI is suitable for brain atrophy measurement, functional imaging like FDG-PET is used for hypometabolism quantification, and CSF is best used for quantification of specific proteins. Henceforth, they propose to combine three modalities of biomarkers, i.e., ADNI baseline MRI, FDG-PET, and CSF biomarkers, to accurately distinguish between AD or MCI and healthy subject controls, using a kernel combination method. They extracted and labeled volumetric features from *ROI*s of each MR or FDG-PET image using atlas warping algorithm and used the original values of CSF biomarkers as direct additional features. They performed feature selection method to select the most discriminative MR and FDG-PET features and finally, they apply SVM method to evaluate the classification accuracy, using a 10-fold cross-validation.

Cuingnet et al. [38] performed an automatic classification between patients with AD or MCI and elderly controls (CN) from structural T1w MRI and compared 10 methods based on ADNI database: five voxel-based methods, three methods based on cortical thickness and two methods based on the hippocampus. In another hand, the authors performed their classification methods on three groups: CN vs. patients with probable AD, CN vs. prodromal AD or MCI converters (MCIc) and MCI non-converters (MCInc) vs. MCIc.

The smallest part of data was used for the training process and the optimization of the parameters of the chosen mathematical model and the rest was used to obtain an unbiased estimate of the performance of the methods. They finally compared DARTEL [39] registration versus SPM5 unified segmentation results [40].

A recent review regarding the brain *MRI* image segmentation methods was presented in 2010 by Balafar et al. [41]. This review summarizes the major directions in segmenting MRI brain images including fuzzy clustering algorithm (FCM), Gauss mixture vector, learning vector quantization (LVQ) that is a supervised competitive learning, self-organizing maps (SOM) which is an unsupervised clustering network, watersheds (gradient-based segmentation technique), region growing, active control model, double region based active control, multi region based active control, atlas-based segmentation and MRF.

The rest of this paper is organized as follows. Section II describes the proposed framework. Section III and Section IV present the experimental setup and the obtained results, respectively. Then, Section V offers the conclusions of this paper. Finally, Section VI highlights the major directions to extend this research in future.

II. Methodology

We propose a general framework for detecting Alzheimer from brain MRI images. The proposed framework consists of four major stages. These stages are pre-processing, segmentation, feature extraction and finally a classification stage. Fig. 1 shows the block diagram of the proposed framework. In the following subsections, a description of each stage is introduced.

A. Pre-Processing

The objective of this stage is to improve the quality of the image to achieve better segmentation results. This stage employs both intensity transformations and spatial domain enhancement filters, based on the quality of the original image. It is worth mentioning that this pre-processing stage is completely isolated from the rest of the system. Thus, it can be replaced by any image enhancement stage without affecting the overall system flow.

B. Segmentation

In the proposed prototype, an active contour model was employed to extract the contour of the brain ventricles. The user has to provide an initial contour and then it evolves till reaching the equilibrium state. Fig. 2 shows a sample output from this stage, where the ventricles boundary is highlighted.

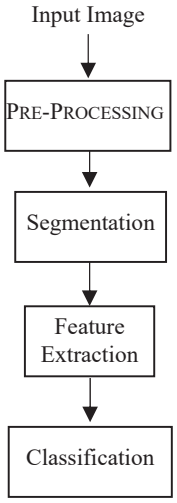

Fig. 1 The block diagram of the proposed framework

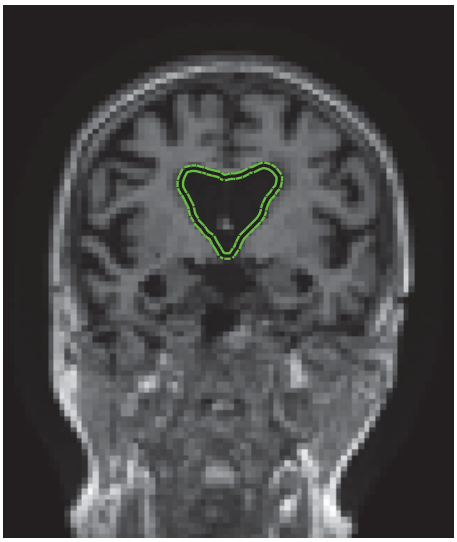

Fig. 2 The output from the segmentation stage. The ventricle contour is highlighted

C. Feature Extraction

Brain ventricles can be characterized based on their morphology using both statistical and geometrical attributes. In the proposed prototype, 35 shape and statistical attributes were utilized. These attributes include, surface area, perimeter, center of gravity, intensity mean and standard deviation, and various horizontal and vertical distance measures. However, it is believed that more analysis is still needed to extract a smaller set of strong features (ones with the highest discriminating power) and neglect weaker ones.

D. Classification

The K-Nearest Neighbors (*KNN*) clustering technique was employed to cluster brain ventricles into two classes: normal and abnormal. More advanced classification techniques (e.g. neural network, AdaBoost and SVM) are expected produce better output.

III. Experimental Setup

We used the MRI data sets from the Alzheimer's disease Neuroimaging Initiative (ADNI) database [42]. ADNI database includes patients with AD, MCI, and elderly controls. ADNI database aims to assist the researchers in the progression of AD by collecting, validating and using predictors for the disease such as MRI and PET images, cognitive tests and CSF.

IV. Results/Discussion

Clinical tests were used to assess the performance of the proposed scheme. The performance of the proposed method was reported based on the following parameters [43]:

- The sensitivity (*SN*) refers to the ability of identifying the *AD* patients.

$$SN = \frac{TP}{(TP + FN)} \times 100$$

- The specificity (*SP*) refers to the ability of identifying the normal or healthy people.

$$SP = \frac{TN}{(TN + FP)} \times 100$$

- The positive predictive value (*PPV*), also called precision or probability of correct positive prediction.

$$PPV = \frac{TP}{(TP + FP)} \times 100$$

- The Negative predictive value (*NPV*), which is the probability of correct negative prediction.

$$NPV = \frac{TN}{(TN + FN)} \times 100$$

- The accuracy (*ACC*), which is the probability of both correct positive and negative predictions.

$$ACC = \frac{TP + TN}{(TP + FP + TN + FN)} \times 100$$

where the parameters TP, FP, TN and FN are defined as:

- True positive (TP): the patient has the AD and the classification result is positive (AD).
- False positive (FP): the patient is normal. However, the classification result is positive.
- True negative (TN): the patient is normal and the classification result is negative (Normal).
- False negative (FN): the patient has the AD but the test is negative.

We tested our system using a set of 120 test cases. 35 different shape and statistical attributes were used to differentiate normal and abnormal cases. The *k*-nearest neighbor (KNN) classifier was used during the last stage of our proposed scheme. The preliminary results are promising. We are currently conducting more experiments to identify the dominant attributes and to ignore weak and/or contradicting ones.

V. Conclusion

In this paper, we proposed a general framework for segmenting and classifying brain ventricles from Magnetic resonance imaging (MRI). A prototype was implemented to demonstrate the feasibility of the proposed framework. The prototype employed both the active contour model and the k-nearest neighbor (KNN) classifier. Both shape and statistical features were utilized. Experimental results over a set of sample images are promising. The proposed framework can be followed toward the implementation of an integrated solution capable of providing a second opinion to help clinician detecting and staging Alzheimer.

VI. Future Work

In future, we plan to focus on the feature extraction and

analysis stage to identify the strong features and neglect the weak ones. Principle component analysis (*PCA*) is a valuable tool toward this goal. Moreover, advanced classification techniques (e.g. neural network, AdaBoost and SVM) have the potential to greatly improve the final results. Upon successful completion, the developed system can be commercialized.

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