

PROPOSAL OF A NEW TRACTOGRAPHIC FEATURE FOR ANALYSIS OF WHITE MATTER IN ALZHEIMER DIFFUSION MR IMAGES

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ABSTRACT

Alzheimer's disease (AD) is a leading cause of dementia in elderly adults. In this, the white matter (WM) tracts in brain are disintegrated leading to loss of important cognitive functionality. Recent analysis have shown that early diagnosis of AD is still a challenging task. Although several reports are available, tractography remains the most promising and clinically relevant method for in-vivo study of WM tracts. In tractography, continuous WM pathways are reconstructed from voxel based models of discrete fiber orientation generated using diffusion tensor images. In this work an attempt has been made to classify AD using average length of tracts, a significant feature extracted from tractographic brain maps. The diffusion weighted images for AD and matched controls were obtained from ADNI, an international open access repository for Alzheimer's study. Data from equal number of AD and controls were used for this study. Fiber tracking was performed for the whole brain using tract based spatial statistics algorithm. *ICBM Mori Labels 1* atlas provided in the *Network Analysis* option of *ExploreDTI* was used to divide the WM into 48 anatomical regions. Classification was performed using random forest, random tree and decision stumps, and their performance indices were compared. The results show that all the classifiers are able to classify AD and controls using the extracted feature. An accuracy of 78.4% is obtained using decision stumps. Random forest and random tree provide an increased accuracy of 96% and 97% respectively. The precision and recall is also found to be higher for random forest and random tree as compared to decision stumps. These results suggest that random forest and random tree are suitable for classification of AD and controls using average tract length as a feature. In this paper, the introduction, objectives, materials and methods, results and discussions and conclusions are presented in detail.

Keywords: Classifier, tractography, tract based spatial statistics, diffusion tensor images.

INTRODUCTION

Alzheimer's disease (AD) is one of the leading causes of deaths in elderly adults [1]. This has led to extensive research focus on AD in present times [2]. The pattern of neuronal degradation in normal aging and AD is a crucial factor for diagnosis and is still under investigation. Early diagnosis of AD is an essential condition for the few available treatment options to be effective. Also the challenges involved in determining the effectiveness of non-invasive methods in diagnosing AD have been studied for almost two decades [3]. Histological studies have demonstrated loss of white matter (tracts) as one of the leading causes of AD. Chemical biomarkers such as amyloid- β and tau proteins have been associated with the degradation of WM tracts. These proteins damage the structural aspects of WM tracts leading to functional impairment [4].

Diffusion tensor imaging (DTI) is an in-vivo method to study the white matter (WM) tracts in human brain. The governing principles here are Fick's law of diffusion and Einstein's predictive model for

movement of a particle under diffusion. Stejskal - Tanner equation describes the parameters of diffusion weighting that need to be monitored during image acquisition. A varying magnetic gradient is applied along different axes (6 or more) in space to record the proton dephasing induced by it. The numbers of axes (also referred as directions) influence the accuracy of reconstructed WM tracts. This technique has been used for extensive investigation of AD in the recent years. Studies have aimed at finding features that can aid in the classification of AD from normal controls (NC). Diffusion indices, obtained using various combinations of eigen values of image, have been used to study the biological developments to the image parameters [5]. The atlas based diffusion features provide an average estimate of the anisotropy and diffusivity of a given anatomical region. Tractography is a method to reconstruct the WM fiber bundles of the brain. This provides precise information about the pathological condition as the WM tracts, which are primarily affected in AD, are mapped.

The precedence of machine learning methods for AD diagnosis has increased in recent times [6,7]. A number of classifiers are available with different principles of class identification and data separation. A few of these have been used in the current study to separate pathological from normal data. In AD pathology, the degree of degradation varies for regions of WM. In such cases region specific features give better performance for classifiers. In this work, a new feature - average length of tracts, is proposed for classification of NC from AD. Tree based algorithms, random tree, decision stump and random tree, are used for classification using the proposed feature. The performance of classifiers is evaluated based on quantitative scores.

METHODOLOGY

Data and Preprocessing

The data used in present study was obtained from Alzheimer Disease Neuroscience Initiative (ADNI), a repository of real subjects. This database comprises of images from different modalities along with corresponding clinical evaluation scores for both AD and age matched control subjects [8]. ADNI has different protocols for image acquisition and the data used for this study was obtained using ADNIGO and ADNI2 protocols. The level of dementia for each patient was predefined based on clinical evaluations using a scoring system. Mini-mental state examination (MMSE) is the most widely used test scheme developed to quantify the memory loss by asking patients to answer simple questions regarding daily activities. The datasets were divided into NC and AD based on this score, where a score of 28 and above was considered normal and anything below that was AD. A total of 34 subject data was used for this study, 19 NC and 15 AD subjects (<http://adni.loni.ucla.edu>).

The time of acquisition is high due to the large number of orientations to be imaged for each slice. Under this situation, the patient may undergo a series of movements. To correct for these the eddy correct tool [9] from FSL is used. This aligns all the slices to average b0 image (image without any sensitizing gradient). The cranial part of image can lead to errors in further analysis. These are thus removed using the brain extraction tool (BET) [10] provided by FSL.

Feature Extraction

Regions of WM are extracted from the skull stripped diffusion tensor images (DTI) using brain atlas. A number of atlases have been developed for studying different anatomical regions of brain. In this work, the *ICBM Mori Labels 1* atlas [11] is used to divide the entire WM into 48 segments. Nearest neighbor interpolation algorithm is used to avoid the mixing of labels. The atlas is matched to co-ordinate space of each DTI map and then the regions are extracted.

Tract based spatial statistics (TBSS) [12] algorithm is used to generate the fiber bundles in each region of WM. The length of each tract bundle is calculated using a voxel based approach. Seed and target points are marked for each tract bundle. Threshold values for minimum FA and maximum angle of curvature (for a given fiber bundle) was initialized as 0.2 and 35° respectively. A midline is marked along the fiber bundle, by estimating its center, using the width information. Length of tracts is given by the number of voxels along the midline of fiber bundle. The average length of tract for each anatomical region of WM is used as a feature for this study. The feature values from all 48 regions are used for further analysis.

Classification

The dataset obtained for the average length of tracts is used for classifying between AD and NC subjects. Three classifiers were used for the present study are random forest, random tree and decision stump. All these classifiers work on binary decision making strategy.

Decision stumps are used as an integral component of bagging and boosting algorithms used predominantly in machine learning applications [13]. This is a single level decision tree. A single internal and single terminal node is used in this work. The feature in this work has discrete values for each subject but it lies in a range of values for normal and pathological cases. Resulting classifier is a simple threshold on a single feature

- Outputs is +1 if the attribute is above a certain threshold
- Outputs is -1 if the attribute is below the threshold

Random forest is based on the combination of a number decision trees used for training. The final output class is decided based on a voting rule using weights obtained from each tree. This algorithm combines two machine learning approaches, bagging and random feature selection [14]. The algorithm of random forest proceeds as follows:

- Sample with replacement to form N bootstrap samples $\{B_1, \dots, B_N\}$
- Use each sample B_k to construct a tree classifier T_k
- When constructing T_k , at each node splitting one first randomly select m variables, then one chooses the best split from these m variables and
- Final prediction is the average or majority votes of T_k .

The number of trees in each forest was considered to be 10.

Random tree is a single tree of multiple decision nodes. This can be referred as a combination of multiple decision stumps. Increased numbers of decisions enhance the performance of classifier. Number of nodes used for the tree in this work was 19.

The performance of classifiers were assessed using parameters such as accuracy, precision and recall which are calculated as described by eq. (1), (2) and (3) respectively.

$$Accuracy = \frac{TP + TN}{TP + TN + FP + FN} \quad (1)$$

$$Precision = \frac{TP}{TP + FP} \quad (2)$$

$$Recall = \frac{TP}{TP + FN} \quad (3)$$

RESULTS

The data for 34 subjects obtained from ADNI repository was used for this study. Demography of subjects involved is presented in table 1. A considerable variation in the age of studied subjects is evident from table 1. The data comprised of equal number of males and females. The mini mental state examination (MMSE) score was used as an initial identifier to categorize the obtained data. This test tends to quantify the cognitive and memory loss based on simple questions related to everyday life or recent tasks given to the subjects. The categorization is done by experts since some overlap always exist between NC and AD groups.

Table 1: Demographic distribution of subjects studied.

| Groups | Number | Age ± SD | MMSE ± SD |
|--------|--------|----------|-----------|
| NC | 19 | 74 ± 14 | 28 ± 1.0 |
| M | 10 | 75 ± 7 | 29 ± 0.9 |
| F | 9 | 74 ± 14 | 29 ± 1.1 |
| AD | 15 | 72 ± 17 | 22 ± 5.7 |
| M | 7 | 71 ± 10 | 22 ± 6.0 |
| F | 8 | 73 ± 16 | 23 ± 5.1 |

The tracts for WM of whole brain were constructed using TBSS algorithm. The length of tracts was calculated using voxel counting approach. Tree based algorithms were used for classification of NC and AD data based on extracted feature. The average length of tract acts as a useful feature to aid in the classification of NC and AD data. Figure 1 shows the comparison of length values of Superior Corona Radiata (both left and right) region for NC and AD subjects. A significant difference in magnitude is observed between the two groups. The average length of tracts is always lower for AD subjects in

comparison to NC subjects. This reduction may be due to the loss of neuronal pathways. Hence, this tractographic feature aids in quantifying the neural degradation.

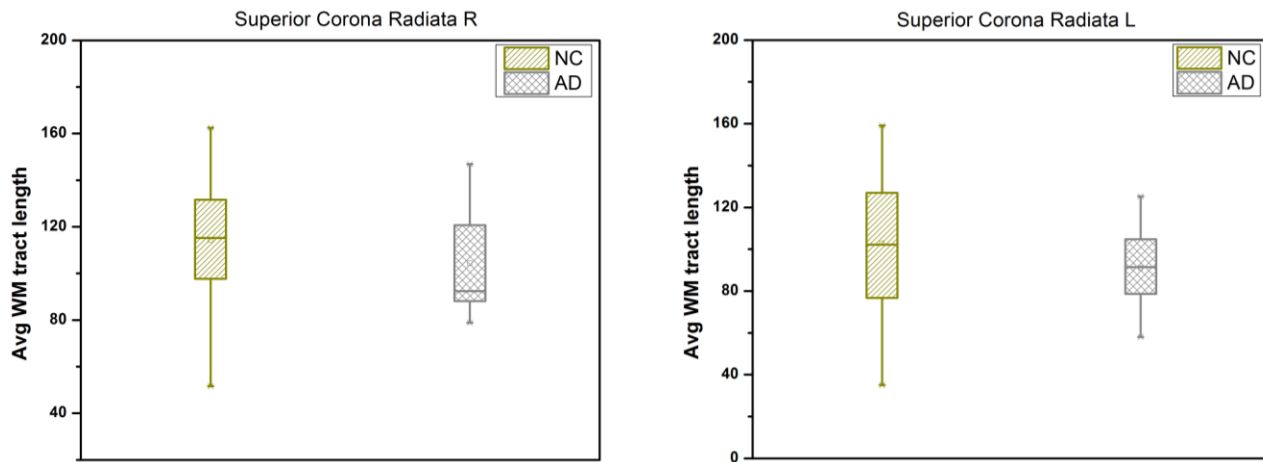


Figure 1. Feature value distribution for Superior Corona Radiata of WM.

The data from all 48 regions of WM was used for classification. Results show that all the classifiers are able to categorize NC and AD subjects. The performances of classifiers were assessed by indices like accuracy, precision and recall. Table 2 shows the numerical values of these performance indices. Higher order tree algorithms like random tree and random forest were found to have enhanced accuracy as compared to a single node decision stump. Similar trends were shown by precision and recall values for all the classifiers used. The near equal values of metrics for random tree and random forest indicate that a single tree with optimum number of nodes will provide considerably better performance. Increasing the number of trees only provides a marginal enhancement in performance.

Table 2. Comparison of classifier performance.

| Classifier | Accuracy (%) | Precision (%) | Recall (%) |
|-----------------------|---------------------|----------------------|-------------------|
| Decision Stump | 76.4 | 79.5 | 76.5 |
| Random Tree | 96.2 | 96.1 | 96.2 |
| Random Forest | 97.1 | 97.2 | 97.1 |

CONCLUSIONS

In this work a new tractographic feature is introduced for identification of AD using tree based classifiers. Average length of WM tracts provide an indication of the level of neuronal degradation in that particular region. Tree based classifiers were able to render a high value of classification accuracy (96%) which ascertains the effectiveness of proposed feature in pathology identification. The results for present feature are comparable to those obtained using diffusion indices and structural features.

This study can be further improved by including region selection to enhance feature relevance. Specific regions can be targeted for identifying regions with significant degradation. The single tree approach

will help in mass screening to enhance identification of AD in addition to existing scores. Further, different classifiers can be tested to verify the diagnostic potential of proposed method. Also other similar approaches can be developed to enhance the diagnostic relevance of proposed feature.

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