Preliminary Results on Using Clustering of Functional Data to Identify Patients with Alzheimer's Disease by Analyzing Brain MRI Scans

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Abstract: This study delves into the effectiveness of funWeightClust, a sophisticated model-based clustering technique that leverages functional linear regression models to pinpoint patients diagnosed with Alzheimer's Disease. Our research entailed a thorough analysis of voxelwise fractional anisotropy data derived from the Alzheimer's Disease Neuroimaging Initiative (ADNI) dataset, with a particular emphasis on the Cingulum and Corpus Callosum, which are critical regions of interest in understanding the disease's impact on brain structure. Through a series of experiments, we established that funWeightClust is efficient at distinguishing between patients with Alzheimer's Disease and healthy control subjects. Notably, the clustering model yielded even more pronounced and accurate results when we focused our analysis on specific brain regions, such as the Left Hippocampus and the Splenium. We postulate that integrating additional biomarkers could significantly enhance the accuracy and reliability of funWeightClust in identifying patients who exhibit signs of Alzheimer's Disease.

1 INTRODUCTION

Alzheimer's Disease (AD) is a complex and chronic neurodegenerative disorder that primarily impacts the brain, leading to a progressive decline in cognitive functions such as memory, reasoning, and overall behavior. Unlike the natural aging process, Alzheimer's is not a typical consequence of aging and is characterized by its irreversible nature, meaning that once the disease sets in, it cannot be reversed or cured.

This condition is the most common form of dementia, accounting for an estimated 60% to 80% of all dementia cases worldwide. The disease is marked by the accumulation of amyloid plaques and tau tangles in the brain, which ultimately disrupt communication between neurons and result in cell death.

According to a comprehensive report by the Alzheimer Society of Canada (Armstrong et al., 2022), the prevalence of dementia within the Canadian population is anticipated to escalate significantly in the coming years. It is projected that nearly 1 million individuals in Canada could be living with dementia by the year 2030, leading to an alarming increase of approximately 187,000 new cases annually. Furthermore, by the year 2050, estimates suggest that this number could rise to more than 1.7 million Canadians affected by dementia, highlighting the urgent need for enhanced awareness, research, and resources to address this growing health crisis.

Grasping the progression of Alzheimer's disease is essential for facilitating early detection, implementing effective treatment strategies, and ultimately enhancing the quality of life for those impacted by the condition, as well as their families. The diagnosis of AD involves a comprehensive approach that includes detailed clinical evaluations, the identification of specific biomarkers, advanced brain imaging techniques, and thorough neuropsychological assessments. Significant advancements in any of these domains can greatly improve the efficiency and accuracy of early AD detection, paving the way for timely interventions that can make a substantial difference in patient outcomes.

Numerous papers have explored the use of machine learning and deep learning techniques for diagnosing Alzheimer's Disease (Dara et al., 2023). These studies cover a range of topics, including comparisons between cognitively normal (CN) individuals and those diagnosed with AD, as well as comparisons between CN subjects and those with mild cognitive impairment (MCI). As a result, the accuracy of findings across these studies varies significantly, ranging

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from as low as 30% to as high as 90%.

The survey by Kaur et al (Kaur et al., 2024) investigates various techniques for detecting Alzheimer's disease, focusing on datasets, input modalities, algorithms, libraries, and performance metrics to identify the most effective strategies. The study analyzed 100 research articles published between 2019 and 2022. It found that most studies used deep learning strategies, with datasets primarily from the Alzheimer's Disease Neuroimaging Initiative (ADNI). Convolutional Neural Networks achieved the highest accuracy (100%) in classifying AD vs. CN subjects, while Support Vector Machines were the most frequently used machine learning algorithm, with a maximum accuracy of 99.82%.

Diffusion Tensor Imaging (DTI) is regarded as one of the most effective methods for detecting AD in patients (Oishi et al., 2011). A study examining DTI indicators of white matter impairment associated with AD was conducted in (Nir et al., 2013). The study concluded that AD patients exhibited clear disruptions in anisotropy and diffusivity, particularly in the cingulum and corpus callosum.

The study conducted in (Schouten et al., 2017) explored the use of fractional anisotropy (FA) independent components analysis (ICA) as a potential protocol for classifying Alzheimer's disease. In this research, FA, mean diffusivity, axial diffusivity, and radial diffusivity were independently utilized for clustering through independent components, aiming to extract the mixing weights. The classification method presented achieved an accuracy of 85%. The authors also noted that determining the required weightings for ICA can be challenging, particularly in extended studies.

In (Ma et al., 2019), researchers investigate the relationship between Mini-Mental State Examination (MMSE) scores and brain imaging data from various regions of interest (ROIs), along with multiple single nucleotide polymorphisms across different quantiles. The findings indicate that the left thalamus, left hippocampus, and right lateral ventricle are the most significant ROIs. Additionally, the study highlights that education level and age are the key factors influencing MMSE scores.

Clusterwise functional linear regression models are employed in (Li et al., 2021) to explore the relationship between fractional anisotropy curves along the cingulum and the body of corpus callosum skeletons with Mini-Mental State Examination scores in Alzheimer's disease and cognitively normal patients from the ADNI (adni.loni.usc.edu) dataset. The most effective methods achieve a Rand index of 0.9 and an adjusted Rand index of 0.8.

In this paper, we explore the effectiveness of funWeightClust. This innovative model-based clustering technique leverages a mixture of functional linear regression models specifically designed for identifying subjects with Alzheimer's disease. One of the key strengths of funWeightClust is its capability to manage complex functional multivariate responses and predictors, making it well-suited for the nuanced nature of medical data. To evaluate the performance of funWeightClust, we utilize a comprehensive dataset obtained from ADNI. Our preliminary findings suggest that this novel method significantly enhances the ability to differentiate between individuals diagnosed with AD and those in the control group, indicating its potential as a valuable tool in clinical diagnostics.

2 METHODS

2.1 Data Collection and Processing

We conducted a detailed analysis of the functional data derived from pre-processed Diffusion Tensor Imaging scans from the Alzheimer's Disease Neuroimaging Initiative data set. Our research focused on two distinct groups: individuals diagnosed with Alzheimer's disease and cognitively normal participants. The AD group comprised 75 participants whose ages ranged from 62 to 92 years. Within this group, there were 50 males and 25 females.

In contrast, the CN group included 137 participants, with ages spanning from 60 to 93 years. This group contained 74 males and 63 females, providing a balanced representation of both genders.

This comprehensive data collection allows for a nuanced exploration of the differences in brain structure and function between individuals with Alzheimer's disease and cognitively healthy individuals.

Data imbalance can adversely impact the performance of functional clustering algorithms. To address the class imbalance, we use the adjusted Rand index (ARI) as a measure of clustering accuracy. This ensures that our clustering results are reliable despite the inherent data imbalances.

We selected the corrected FA images for each subject and applied skeletonization using the TBSS-ENIGMA pipeline. The TBSS-ENIGMA function is part of the ENIGMA (Enhancing NeuroImaging Genetics through Meta-Analysis) DTI project, which aims to standardize and improve the analysis of diffusion tensor imaging data across multiple sites (Jahanshad et al., 2013). TBSS (Tract-Based Spatial Statistics) (Smith et al., 2006) is a method used to an-

alyze DTI data, focusing on the white matter tracts in the brain. The TBSS-ENIGMA function specifically involves registering and skeletonizing fractional anisotropy images to a common DTI atlas, allowing for consistent and comparable analysis across different datasets.

We carefully selected the corrected fractional anisotropy images for each participant in our study. These images were processed using the Tract-Based Spatial Statistics (TBSS) pipeline developed by the ENIGMA consortium, which encompasses several critical preprocessing steps. Specifically, the pipeline includes procedures for eddy current correction to minimize distortions in the diffusion-weighted images, masking to isolate brain structures of interest, tensor calculation for encoding the diffusion properties of the tissue, creation of the FA images that quantify the directional coherence of water diffusion, and a series of quality control checks to ensure the integrity of the data. As part of the standardization process, we projected the ENIGMA template onto the selected images (Smith et al., 2006), ensuring a consistent spatial resolution of 1x1x1 mm. This high-resolution projection is crucial for accurate and reliable extraction of imaging features.(Smith et al., 2006)

This process allowed us to gather data from the regions of interest in the corpus callosum and cingulum. We utilized a Python script to extract fractional anisotropy values from the masked images for each voxel, filtering out zero values. As a result, we obtained 1,118 FA values for the cingulum and 7,318 for the corpus callosum.

We subsequently gathered the latest Mini-Mental State Examination scores for each individual associated with the corresponding images. In our analysis, we found that the average MMSE score for the cognitively normal group was 28.78, showing a relatively small variation with a standard deviation of 1.50. In contrast, the average MMSE score for the Alzheimer's disease group was significantly lower, at 22.4, accompanied by a standard deviation of 3.9, indicating greater variability among the scores in this group. To facilitate further analysis, we carefully compiled all relevant data - voxelwise measurements, MMSE scores, and demographic information such as age and sex, along with unique subject identifiers - into two distinct .csv files. These files were specifically organized to correspond to the corpus callosum and cingulum regions of the brain, ensuring clear and structured data for subsequent evaluation.

2.2 Clustering Data with funWeightClust

We utilize funWeightClust (Anton and Smith, 2024b), an advanced model-based clustering approach that leverages a mixture of functional linear regression models. This innovative method is particularly beneficial as it accommodates functional multivariate responses and predictors, allowing for a more nuanced analysis of complex data structures. By incorporating functional data analysis techniques, funWeightClust enables us to capture the inherent variability and relationships within multivariate datasets more effectively. This capability is crucial for accurately identifying clusters in situations where traditional methods may struggle to account for the multidimensional nature of the data.

The voxelwise data and MMSE scores are represented as functions, making model-based clustering methods challenging to apply; this is because the notion of a probability density function generally does not exist for functional data (Delaigle and Hall, 2010). FunWeightClust employs a two-step approach: first, the functional data is decomposed into a basis of functions, and then a probabilistic model is constructed for the coefficients of these basis functions. B-spline functions are mainly used for smooth curves, but Fourier bases are preferred for data that exhibit a repetitive pattern. (Schmutz et al., 2020).

We aim to cluster the n observed response and predictor curves $\{(\boldsymbol{y}_1,\boldsymbol{x}_1),\ldots,(\boldsymbol{y}_n,\boldsymbol{x}_n)\}$ into K homogeneous groups. In this context, the response curves $\boldsymbol{y}_i$ represent the MMSE scores, while the predictor curves $\boldsymbol{x}_i$ are derived from the voxelwise data. For each pair of curves $(\boldsymbol{Y}_i,\boldsymbol{X}_i)$, we assume that these curves belong to a finite-dimensional space, and we have:

$$Y_i(t)=\sum_{r=1}^{R^Y} c_{Y,ir}\xi_{Y,r}(t), \quad X_i(t)=\sum_{r=1}^{R^X} c_{X,ir}\xi_{X,r}(t). \quad (1)$$

Here $\{\xi_{Y,r}\}_{1\le r\le R^Y}$ and $\{\xi_{X,r}\}_{1\le r\le R^X}$ are the bases, R^Y and R^X are the number of basis functions, and $c_{Y,ir}$, $c_{X,ir}$ are the coefficients for the curves $\{\boldsymbol{Y}_1,\ldots,\boldsymbol{Y}_n\}$ and the curves $\{\boldsymbol{X}_1,\ldots,\boldsymbol{X}_n\}$, respectively.

We assume that for each cluster $k\in\{1,\ldots,K\}$, the observations come from the following functional regression model:

$$\boldsymbol{Y}_i(t)=\beta_0^k(t)+\int_{\mathcal{T}_X}\beta^k(t,s)\boldsymbol{X}_i(s)ds+\boldsymbol{E}^k(t), \quad t\in\mathcal{T}_Y, \quad (2)$$

where $i=1,\ldots,n$, $\beta_0^k(t)$, $\beta^k(t,s)$ are the regression coefficients, and $\boldsymbol{E}^k(t)$ is the random error process

which is uncorrelated with $\boldsymbol{X}_i(s)$ for any $(s,t) \in \mathcal{T}_X \times \mathcal{T}_Y$.

The method funWeightClust builds upon the approach used in funHDDC (Schmutz et al., 2020). It is based on multivariate functional principal component analysis (MFPCA) (Jacques and Preda, 2014), assuming that the scores follow multivariate normal distributions. To address regression relationships, funWeightClust also incorporates extensions of cluster-weighted models used for multivariate data (Dang et al., 2017). Additionally, funWeightClust offers several parsimonious models.

The Expectation-Maximization (EM) algorithm estimates the model's parameters. The number of clusters is denoted as K, and the parsimonious model is selected by maximizing the Bayesian Information Criterion (BIC) (Schwarz, 1978). As in the case of funHDDC, the group-specific dimension d_k is determined using the Cattell scree test, which compares the differences between eigenvalues against a specified threshold ε (Bouveyron and Jacques, 2011).

When the true classifications are known, the Correct Classification Rate (CCR) and the Adjusted Rand Index (ARI) are used to measure the accuracy of the classification. The CCR represents the ratio of correctly classified observations to the total number of observations. The ARI adjusts for variations in cluster sizes, resulting in an expected value of 0 and a perfect classification value of 1.

3 PRELIMINARY RESULTS

We conducted a series of experiments using the R programming language implementation of the funWeightClust method. In our experiments, we applied the functional clustering method with the number of cluster parameters set to two. This configuration allowed us to partition the data effectively into two distinct groups: corresponding to the AD and CN subjects. We focused on exploring Fourier bases of varying sizes - specifically, 20, 30, and 50 - due to the repetitive patterns observed in our data. We selected a Fourier basis size of 50 because it provided the best approximation of all initial curves. For the parameter ε, we experimented with values of 0.4, 0.2, 0.1, 0.05, 0.01, 0.005, and 0.001. Using the Bayesian Information Criterion, which is a criterion for model selection among a finite set of models, we determined that $\varepsilon = 0.001$ was the most appropriate value. The BIC helps in selecting the model that best balances complexity and goodness of fit.

Our analysis included several datasets, specifically targeting the corpus callosum data, the cingulum data, and the results from a combined dataset comprised of both ROI's data sets. Through this approach, we aimed to uncover meaningful insights from the underlying structures in the data.

We conducted two sets of experiments: Experiment A, which included only the voxelwise data, and Experiment B, which incorporated the voxelwise data along with age as input variables. In Experiment A, the results of funWeightClust for the cingulum and corpus callosum data varied based on the values of ε. The most favorable outcomes were achieved using a Fourier base of size 50 with $\varepsilon = 0.001$, as shown in tables 1, 2 and 3. For the combined data in Experiment A, the results remained consistent across all ε values.

Experiment B yielded similar results. Including age data resulted in a slight improvement in the adjusted Rand index while causing a marginal decrease in the correct classification rate. For instance, using a Fourier base of size 50 with $\varepsilon = 0.001$ for the combined cingulum and corpus callosum datasets, Experiment B produced an ARI of 0.6132 and a CCR of 0.7954. In this preliminary investigation, we prioritized Experiment A because the improvements in Experiment B were too small.

For comparison purposes, we also performed similar experiments using funHDDC (Schmutz et al., 2020) and tFunHDDC (Anton and Smith, 2024a). funHDDC (Functional High-Dimensional Data Clustering) is a method designed to cluster high-dimensional functional data, while tFunHDDC is an extension that uses t-distribution instead of a normal distribution. Both funHDDC and tfunHDDC do not include a linear regression relationship, so we ran these methods only on the predictor curves derived from the voxelwise data. We used the same setup for the dataset and parameters, specifically the size of the Fourier basis and the value of ε.

The results of Experiment A, funHDDC and tfunHDDC for the cingulum, the corpus callosum and the combination of the two ROIs are presented in tables 1, 2 and 3, respectively.

Taking into account the conclusions of (Ma et al., 2019), we performed a variation of Experiment A, where we filtered the cingulum data to contain only the Left Hippocampus and the corpus callosum data to contain only the Splenium. The best results were obtained with a Fourier base of size 30 and are presented in Table 4. The ε values did not influence the results.

Our proposed approach successfully identifies patients with Alzheimer's disease. We believe that incorporating additional biomarkers could further enhance these results.

Table 1: Results for the Cingulum ROI dataset for Fourier base of size 50 and $\varepsilon = 0.001$.

Method	ARI	CCR
funWeightClust	0.5737	0.8820
funHDDC	0.1299	0.6839
tfunHDDC	0.1163	0.6745

Table 2: Results for the Corpus Callosum ROI dataset for Fourier base of size 50 and $\varepsilon = 0.001$.

Method	ARI	CCR
funWeightClust	0.5737	0.8820
funHDDC	0.0978	0.6603
tfunHDDC	0.1163	0.6745

Table 3: Results for the combination of the Cingulum and the Corpus Callosum ROI datasets for Fourier base of size 50 and $\varepsilon = 0.001$.

Method	ARI	CCR
funWeightClust	0.5452	0.8726
funHDDC	0.1159	0.6698
tfunHDDC	0.1163	0.6745

Table 4: Experiment A results for selected regions. Fourier base of size 30 and $\varepsilon = 0.001$.

Region	ARI	CCR
Left Hippocampus	0.7014	0.9198
Splenium	0.5606	0.8773

4 CONCLUSIONS

This initial study highlights the potential of funWeightClust, a model-based clustering method that employs functional linear regression models for identifying patients with Alzheimer's disease. By analyzing voxelwise fractional anisotropy data from the ADNI dataset, we successfully distinguished between the Alzheimer's disease and cognitively normal groups.

The inclusion of age data slightly improved the adjusted Rand index while causing a marginal decrease in the correct classification rate. This suggests that demographic factors can enhance clustering accuracy. Further analysis of specific brain regions, such as the left hippocampus and the splenium, yielded better results. Our preliminary findings indicate that funWeightClust is a promising tool for the early detection of Alzheimer's disease. The proposed new functional clustering method demonstrates better clustering results than other existing similar methods. A key strength of funWeightClust lies in its flexibility with response variables. Unlike our preliminary study, where we used only MMSE as the response variable, this new approach allows for the extension to functional values. This means that the response can be a vector of multiple scores, such as a combination of MMSE, Montreal Cognitive Assessment (MoCA), and auditory verbal learning test (AVLT), thus providing a more comprehensive and nuanced analysis. This capability enhances the method's applicability and effectiveness, making it a significant advancement. Future research should focus on expanding the dataset and incorporating additional biomarkers to further enhance the method's effectiveness, thereby improving early detection techniques for AD.

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