Early Detection of Alzheimer's Disease using Graph Signal Processing on Neuroimaging Data

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***Abstract*—Brain imaging signals obtained using different imaging modalities mostly reside on irregular structures. While most of the classical signal processing methods are designed for signals having a regular structure, a new field of signal processing called Graph Signal Processing (GSP) is growing rapidly which deals with the irregularly structured data. So, GSP has become a natural choice for many brain image analysis applications. In this paper, we consider the problem of detection of Alzheimer's Disease (AD) in the early stages using fMRI data obtained from ADNI dataset. Firstly, we extract efficient discriminating features from resting state fMRI data using our novel hypothesis which is based on the outcomes of two neurological experiments carried out independently. Then we classify these graph signals by designing a classifier based on recently proposed graph convolutional neural network (GCNN). GCNN is the generalization of convolutional neural network (CNN) to the irregular domain using the concepts of GSP. We constructed brain graphs using different connectivity measures and compared the performance obtained using these graphs to find the best suitable connectivity measure for our application. Our proposed model outperforms state-of-the-art AD detection methods with a classification accuracy of 92.44%. This improvement can be associated with the fact that we first extracted highly discriminating features using graph frequency analysis performed with suitably constructed graphs and then applied properly designed GCNN classifier to classify the input graph signals.**

***Index Terms*—Alzheimer's Disease, Graph Signal Processing, Graph Fourier Transform, Graph Convolutional Neural Network**

I. Introduction

There are nearly 50 million patients who are suffering from Alzheimer's disease (AD) or some related form of dementia, worldwide, and the number is increasing every year. This number is likely to grow to 130 million by the year 2050 [1]. AD is broadly categorized into two stages. The initial stage is called Mild Cognitive Impairment (MCI) while the next stage is characterized by dementia due to AD. Presently available medical treatments are unable to stop or slow down the progression of AD reliably, though some may temporarily improve the symptoms. But researchers working in this domain believe that future treatments to cure AD will be most effective when administered early in the disease. So, detection of AD in the early stages is important so that an affected individual could receive proper treatments when become available [2].

In this paper, we consider the problem of early detection of AD which is one of the most critical challenges before the scientific community to control this neurodegenerative disease. Many efforts are made to solve this detection problem using different modalities like graph theory [3],[4], network diffusion models [5], machine learning [6],[7] etc. Recently, methods based on an evolving signal processing field called Graph Signal Processing (GSP) are also being used to diagnose MCI in early stages [8]. In the present work, we first related outcomes of two neurological experiments involving graph frequency analysis of brain signals and then exploited recent advancements in GSP to design a novel method to detect AD at early stages.

Traditionally, signal processing theory and techniques have been developed mainly for the signals residing on regular structures. But, in the current era of data explosion, the structural regularity constraint assumed in the classical signal processing is barely satisfied in many domains, e.g., sensor networks, biological networks, etc. So, to overcome this limitation, there is growing interest in the field of GSP which deals with the irregularly structured data. Serious efforts are being made to extend the classical DSP concepts like shifting, filtering, convolution, Fourier transform, etc. from regular domain to the graph domain [9],[10]. Besides these fundamental operations, researchers are also working on generalizing more involved signal processing tasks like classification in graph domain. For regularly structured data, CNN performs exceptionally well in classification task in many applications e.g. image, video, audio data classification [11]. This motivated generalization of CNN to the non-Euclidean domain for graph signal classification purpose. Many architectures of this graph-CNN (GCNN) have been proposed, which usually involves a specific localized graph filtering operator for the convolution operation and a graph coarsening algorithm for pooling purpose [12],[13],[14].

Compared to traditional signal processing approaches, GSP has an advantage of exploiting the additional relational information between the data points. As a result, GSP has found applications in various domains including sensor networks [15], image processing [16] and machine learning [13],[14]. In biological networks, hitherto, the primary focus of the research has been on the study of properties of underlying graphs rather than on the signal residing on graph. But recently, researchers have started using GSP methods in various biomedical domains spanning from brain networks, protein interaction networks to gene regulatory networks [8],[17].

In this paper, we proposed a method to improve the detection of AD in the early stages by using graph frequency

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analysis of brain signals along with the properly designed GCNN classifier. Our hypothesis to detect AD using graph frequency analysis is based on the findings of two neurological experiments conducted separately. First experiment talks about the correlation between high graph frequency content of the signal and the switch cost of an individual [18]. The other experiment is related to the task switching capacities in persons with AD and MCI [19]. The proposed hypothesis relating findings of these two experiments will be presented in section III.

Brain connectivity graph used for the graph frequency analysis can be constructed using different connectivity measures like functional connectivity, structural connectivity etc. which can have a significant impact on the models performance [20],[21]. So, we conducted accuracy analysis of our proposed model by using the commonly used brain connectivity graphs to find the best suited connectivity measure for our model. For performing graph frequency analysis, we need to evaluate Fourier transform of graph signals which is not defined uniquely unlike its regular domain counterpart [9],[10],[22]. So, we also need to select a particular definition of Graph Fourier Transform (GFT) depending on our application. Details about the Fourier basis selection criterion will be discussed in the subsequent sections.

Rest of the paper is organized as follows: In section II, we first review some basic concepts of graph signal processing including GFT. Then we discuss about different brain connectivity measures along with a brief overview of graph CNN architectures. Section III is devoted to our proposed hypothesis for efficient feature extraction using graph frequency analysis and the design of graph signal classifier using GCNN. In section IV, we illustrate the performance of our AD detection model using different brain connectivity graphs and GFT methods and compare it with state-of-the-art methods. We conclude our work in section V along with the future scope.

II. BASIC PRELIMINARIES AND RELATED WORK

A. Graph Signal Processing Overview:

Graph Signal Processing (GSP) deals with the analysis of datasets wherein the data samples are related to each other according to some connectivity measure. Consider a dataset with N elements, for which some connectivity information between its data elements is known e.g. brain imaging signals in which different nodes are connected by functional or effective connectivity. This information can be expressed by a graph $G = (\mathcal{V}, \mathbf{W})$, where $\mathcal{V} = \{v_0, \ldots, v_{N-1}\}$ denotes the set of nodes and $\mathbf{W}$ corresponds to graph adjacency matrix. Each data element is associated with a node v_n and edge weight $\mathbf{W}_{n,m}$ from v_m to v_n quantifies the extent of similarity between n^{th} data element to the m^{th} one. A graph signal is then defined as a map

$$\begin{aligned} \mathbf{s} : \mathcal{V} &\longrightarrow \mathbb{C} \\ v_n &\longmapsto s_n \end{aligned}$$

Now, since the space of graph signal $\mathcal{S}$ is isomorphic to $\mathbb{C}^N$, the graph signal $\mathbf{s}$ can be represented by N-dimensional vector $(s_0, s_1, \ldots, s_{N-1})^T$.

After introducing the concept of graph and signal defined over it, we will now discuss in detail about Fourier decomposition of graph signals as it plays an important role in our graph frequency analysis application. As stated earlier, there exist various state-of-the-art approaches to define GFT which can be broadly categorized as follows:

1) Graph Laplacian-based Approach: The basic building block of this approach is a graph Laplacian which is defined as $\mathbf{L} = \mathbf{D} - \mathbf{W}$ where $\mathbf{D}$ is a diagonal matrix with diagonal elements $\mathbf{D}_{n,n} = \sum_{m=0}^{N-1} \mathbf{W}_{n,m}$. In the classical Fourier transform, the signal is expressed in terms of complex exponentials which are nothing but the eigenfunctions of the 1-D Laplacian operator as,

$$\Delta(e^{jwt}) = -w^2 e^{jwt} \quad (1)$$

Extending the same analogy in the graph domain, the Fourier modes for GFT are defined as the eigenvectors of the graph Laplacian matrix $\mathbf{L} = \mathbf{D} - \mathbf{W}$ [9]. Graph Laplacian used here is one of the many possible graph Laplacians which includes normalized Laplacian, random walk Laplacian etc.

2) Approach based on Jordan Decomposition of Adjacency Matrix: This approach is rooted on Algebraic Signal Processing (ASP) theory where the adjacency matrix $\mathbf{W}$ is adopted as a shift operator for graph signal $\mathbf{s}$ [23]. In classical Fourier transform, a signal is expanded in terms of basis signals which are invariant to filtering. But, authors in [10] showed that all LSI graph filters are polynomials in adjacency matrix $\mathbf{W}$ which implies that GFT can be defined as decomposition of signal space into $\mathbf{W}$-invariant subspaces. These invariant subspaces can be obtained using Jordan decomposition of adjacency matrix $\mathbf{W}$, thus making the generalized eigenvectors of $\mathbf{W}$, the basis of this GFT [10].

3) Graph Clustering-based Approach: Recently, a new approach to obtain Fourier basis has been proposed which is based on the minimization of some particular objective function [22]. This approach is motivated for applying GFT on the signals having clustering property which is characterized by a smooth variation of signals within the region of highly interconnected nodes called clusters, while arbitrary variation between different clusters e.g. brain imaging signals. In this method, we look for a set of orthonormal basis vectors which minimizes the graph cut size as its minimization helps in finding clusters in data. Continuous extension of graph cut size can be represented by function

$$h(\mathbf{x}) = \sum_{i,j=1}^{N} \mathbf{W}_{j,i}[x_i - x_j]_+ := GDV(\mathbf{x}) \quad (2)$$

Thus, the Fourier basis search problem can be mathematically formulated as,

$$\min_{\mathbf{X} \in \mathbb{R}^{N \times N}} GDV(\mathbf{X}) := \sum_{k=1}^{N} GDV(\mathbf{x}) \quad \text{s.t.} \quad \mathbf{X}^T\mathbf{X} = \mathbf{I} \quad (3)$$

where the matrix $\mathbf{X} := (\mathbf{x}_1, \ldots, \mathbf{x}_N) \in \mathbb{R}^{N\times N}$ is the matrix containing all the basis vectors. The above problem can be solved using standard optimization methods.

B. Brain Connectivity Graphs:

Graphs can be constructed from a given brain imaging data using different brain connectivities like functional connectivity, structural connectivity, and effective connectivity. Functional connectivity provides a measure of statistical dependency or association between different brain regions which are represented by nodes of the graph. Structural connectivity quantifies anatomical connections between these different brain regions. Effective connectivity indicates a causal relationship between different brain regions which can also be interpreted as the directed influence of different brain regions on each other [20].

In this paper, we used two functional connectivity measures and one effective connectivity measure for brain graph construction. Given a resting state fMRI (rs-fMRI) time series vectors $\mathbf{x_i}$ and $\mathbf{x_j}$ of two different brain regions denoted by i and j respectively, the weight matrix $\mathbf{W}$ using different connectivities is obtained as follows:

1) Correlation Connectivity: In this functional connectivity graph, edge weight $\mathbf{W_{i,j}} = corr(\mathbf{x_i}, \mathbf{x_j})$ [21].

2) Coherence Connectivity: In this functional connectivity measure, $\mathbf{W_{i,j}} = coh(\mathbf{x_i}, \mathbf{x_j})$ [21].

3) Granger Causality (GC) Connectivity: To evaluate this effective connectivity, first, a signal $\mathbf{x}$ is predicted using univariate and multivariate AR models [21]. Denoting variance of error in prediction of $\mathbf{x_i}$ given past samples of $\mathbf{x_i}$ by $e(\mathbf{x_i}|\mathbf{x_i^-})$, variance of error in prediction of $\mathbf{x_i}$ given past samples of both $\mathbf{x_i}$ and $\mathbf{x_j}$ by $e(\mathbf{x_i}|\mathbf{x_i^-}, \mathbf{x_j^-})$ and similarly defining $e(\mathbf{x_j}|\mathbf{x_j^-})$, $e(\mathbf{x_j}|\mathbf{x_j^-}, \mathbf{x_i^-})$, the Granger causality is defined as $GC_{\mathbf{x_i}\to\mathbf{x_j}} = \ln \frac{e(\mathbf{x_i}|\mathbf{x_i^-})}{e(\mathbf{x_i}|\mathbf{x_i^-}, \mathbf{x_j^-})}$ and $GC_{\mathbf{x_j}\to\mathbf{x_i}} = \ln \frac{e(\mathbf{x_j}|\mathbf{x_j^-})}{e(\mathbf{x_j}|\mathbf{x_j^-}, \mathbf{x_i^-})}$ [21].

C. Graph Convolutional Neural Networks:

In the last few years, CNN has been used extensively in signal processing applications, thanks to its ability to extract the high level nonlinear features automatically and exploit the local stationarity of input data [11]. But, CNN architectures were originally designed for data residing on regular grid, limiting its application in graph domain. So, various approaches have been proposed to extend it to graph domain. CNN architecture is built using three basic principles: local receptive fields of filters, sharing of filter weights and pooling operation. First two principles are incorporated by using convolutional layer and the third using pooling layer. So, any generalization of CNN to graph need to define: 1. a localized convolutional filter on graph and 2. a graph coarsening method for grouping the similar nodes together for pooling operation [14]. Graph convolution has been defined in both spectral and spatial domain giving rise to two different approaches of GCNN implementations [12]. In this paper, we used the spectral convolution based ChebNet model proposed in [14] which is discussed in brief below.
ChebNet model has two important steps:

1) Localized Spectral Filtering: For a graph signal $\mathbf{x}$ defined on a graph with graph Laplacian $\mathbf{L}$, output signal $\mathbf{y}$ after applying a filter g_Λ is defined as

$$\mathbf{y} = g_\Lambda(\mathbf{L})\mathbf{x} \tag{4}$$

where $g_\Lambda(\mathbf{L}) = \sum_{m=1}^{M} \lambda^m \mathbf{L}^m$
Authors in [14] showed that filters obtained using M^{th} order polynomial are M-localized. Thus, by learning the parameter g_Λ, localized spectral filter can be designed.

2) Graph Coarsening and Pooling: In CNN, pooling operator takes feature map (output from convolutional layer) as an input and produces the condensed feature map at the output by summarizing small image region using some predefined criterion. So, equivalent operation in graph domain should cluster similar nodes of graph and summarize them using a single node. Graph clustering exactly performs the above operation and for multiple layers, this can be achieved using multi-level graph clustering algorithms. There exist many graph clustering algorithms out of which the authors have used Graclus [24] in the ChebNet architecture. In Graclus, two nodes i and j of a given graph are combined on the basis of their local normalized cut $\mathbf{W_{i,j}}(1/d_i + 1/d_j)$ where d_i and d_j denote the degree of nodes i and j respectively. Node i is combined with its neighbour j which has maximum local normalized cut value. Edge weight in the coarsened graph is set as the sum of their edge weights.

III. Proposed Model for AD Detection

A. AD Detection Hypothesis:

Our hypothesis that the AD can be detected using the graph frequency characteristics of the brain signal has been motivated by the results of two separately conducted neurological experiments which are discussed in brief below:

In the first experiment [18], the volunteers were asked to perform a particular switching task and their corresponding brain signals were recorded. Then these signals were analysed using the GSP approach. Connectivity graph was constructed using this acquired brain data and GFT was applied to the signals. The signal was then decomposed into aligned (low frequency), medium frequency and liberal (high frequency) components. It was found that switch cost of an individual is highly correlated with the corresponding liberality concentration and it increases almost linearly with the increase in liberality concentration.

The second experiment [19] was related to task switching capacities in persons with AD and MCI. In this work, authors conducted task switching experiments on persons with AD, MCI and the healthy control using switching task blocks and non-switching blocks. It was found that persons with AD and MCI showed a larger switch cost than healthy controls.

Now, the switch cost increases with the liberality (graph high frequency content) and the switch cost is also high in the persons with AD or MCI. So, it can be concluded that a person with AD or MCI should have a larger high frequency content than the healthy counterpart. Therefore, our hypothesis is that the high frequency content of brain signal can act as a discriminating feature for the detection of AD. Block diagram indicating the major steps of our proposed AD detection model is shown in Fig. 1

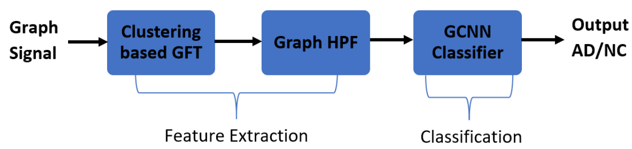

Fig. 1. Block diagram of the proposed AD detection model

Connectivity measure of brain graph and GFT method are two important parameters to be selected in the feature extraction process. To select an optimum connectivity measure for our AD detection purpose, we implemented our model using three different connectivity measures described in last section and selected the one giving highest classification accuracy. Details about this will be presented in the next section.

As far as selection of GFT method is concerned, we exploit the characteristics of brain signals to select the optimum method. Brain graph signal exhibit the natural property of clustering as the brain signal within different lobes e.g. frontal, temporal, parietal, occipital etc. is generally smooth and can vary significantly between different lobes. So, clustering-based GFT approach is a natural choice for our application as it is better able to capture the clustering behaviour of the brain graph signals. For experimental validation purpose, we also performed the analysis using two other GFT approaches. Performance of the model using different GFT approaches are compared in section IV.

B. Classifier Design using ChebNet:

Consider rs-fMRI data of a given subject in ADNI dataset [25] be denoted by a matrix $\mathbf{X} \in \mathbb{R}^{N \times T}$ where N = 90 is the number of brain regions obtained using AAL template [26] and T = 130 is the number of time points. Now, each column in data matrix $\mathbf{X}$ which represents rs-fMRI data at different time step t = 1,2,...,T, can be considered as an individual N dimensional graph signal.

In this work, we use ChebNet architecture to design our classifier to classify MCI and normal control (NC) subjects. To train our GCNN model, we first consider a training data from ADNI dataset which consists of data matrix X for each subject along its label i.e. MCI or NC. We label each individual column vector from this matrix $\mathbf{X}$ with the label of $\mathbf{X}$ itself. Now, these column vectors which are nothing but the graph signals at different time instants are passed through the graph-HPF to extract most discriminating features from them. These filtered graph signals along with their labels are then used to train the GCNN classifier.

Once the classifier has been trained in this way, we can use it to detect whether a given subject is MCI or NC. Given a test subject with data matrix $\mathbf{Y} \in \mathbb{R}^{N \times T}$, we can again consider it as a set of T individual graph signals, corresponding to T different time steps. For the detection purpose, we classify each of these signals using the already trained GCNN classifier and label the subject with a class having larger number of signals associated with it.

IV. Experiments and Results

In this section, we will illustrate the results obtained using our proposed AD detection model and compare it with state-of-the-art methods. In the present work, we considered 100 MCI and 100 NC subjects from ADNI dataset. 70% of this data was used for training the model and remaining 30% for testing purposes.

As discussed in the last section, in order to optimize the model performance, we have to select the best suited connectivity measure to construct brain graph and then use an appropriate GFT method to extract most discriminating feature. So, we conducted our experiments using two functional connectivities: correlation connectivity and coherence connectivity and one effective connectivity: Granger causality connectivity. To experimentally validate the optimum GFT method for our AD detection application, we also carried the analysis using three commonly used GFT methods: Laplacian based method, adjacency matrix based method and clustering based method which were explained in section II-A. Classification accuracy of proposed AD detection model obtained using these graph connectivities and GFT methods are presented in table I.

TABLE I
Classification accuracy using different connectivities and GFT

Connectivity\GFT	Laplacian [9]	Jordan [10]	Clustering [22]
Correlation	0.898	0.889	0.910
Coherence	0.884	0.877	0.893
Granger Causality	0.915	0.898	0.924

From table I, it can be observed that brain connectivity graph constructed using GC measure generally leads to higher accuracy in our classification task which also agrees with observations made in another recent brain signal classification study [21]. Table I also shows that the highest classification accuracy is obtained using the clustering based GFT method which experimentally validates the optimality of the clustering based GFT method in brain signal analysis applications.

After discussing about the optimum graph connectivity and GFT method, we will compare the performance of our proposed AD detection model with that of other state-of-the-art methods. Table II shows the comparison of different AD detection methods in terms of classification accuracy.

TABLE II
Classification accuracy comparison with state-of-the-art methods.

	Classification Accuracy (%)
MSD-G [8]	88.62
RsBN-DL [27]	86.47
Sparse-Cov [28]	85.28
EN-LogReg [29]	79.00
Proposed Model	**92.44**

Classification accuracy values in table II shows that our proposed AD detection model performs better than the existing AD detection methods. Improvement in performance can be associated with the fact that, in the proposed method, we first extracted the highly discriminating features from original fMRI input signal which is then applied to the graph signal classifier unlike the methods in [8],[27] where frequency analysis of the input graph signal was not performed explicitly to extract meaningful information. Apart from that, most of the existing methods [28],[29] used conventional machine learning tools like SVM, logistic regression or recently some authors [27] also used standard neural networks for classification purpose which are not optimized for irregularly structured data like brain imaging data. As opposed to this, we designed our classifier using recently developed ChebNet architecture which is tailored for the graph signal classification purpose which might be another factor behind the increase in the classification accuracy.

V. Conclusion and Future Scope

In this paper, we proposed a model to detect AD at early stages by using graph frequency analysis to extract features and then applying them to a graph signal classifier designed using ChebNet architecture. Experiments were conducted to determine the best suited brain connectivity and GFT method for feature extraction purpose. Granger causality connectivity along with clustering-based GFT resulted in highest classification accuracy. Proposed model classified the subjects in ADNI dataset with the accuracy of 92.44%, corresponding to an increase of almost 4% with respect to state-of-the-art methods which might be attributed to our efficient feature extraction scheme and the use explicitly designed GCNN classifier.

Our present model which is limited by the use of brain imaging data only can be further improved by exploiting other phenotypic information as well. In this work, we used the ChebNet architecture to design the graph signal classifier. Other geometric deep learning methods [12] can also be applied to design the graph signal classifier which may improve the overall model performance.

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