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Suresh

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Regularized Spatial Filtering Method (R-SFM) for detection of Attention Deficit Hyperactivity Disorder (ADHD) from resting-state functional Magnetic Resonance Imaging (rs-fMRI)

Abhay M S Aradhya^{1*}, Vigneshwaran Subbaraju^{2**}, Suresh Sundaram^{3*}, Narasimhan Sundararajan^{4*}

Abstract—Attention deficit hyperactivity disorder (ADHD) is a common neurodevelopmental problem in children. Resting state functional magnetic resonance imaging (rs-fMRI) provides an important tool in understanding the aberrant functional mechanisms in ADHD patients and assist in clinical diagnosis. Recently, spatio-temporal decomposition via spatial filtering (Fukunaga-Koontz transform, ICA) have gained attention in the analysis of fMRI time-series data. Their ability to decompose the blood oxygen level dependent (BOLD) rs-fMRI time series data into discriminative spatial and temporal components have resulted in better classification accuracy and the ability to isolate the important brain circuits responsible for the observed differences in brain activity. However, they are prone to errors in the estimation of covariance matrices due to the significant presence of atypical samples in the ADHD dataset. In this paper, we present a regularization framework to obtain a robust estimation of the covariance matrices such that the effect of atypical samples is reduced. The resulting approach called as regularized spatial filtering method (R-SFM) further uses Mahalanobis whitening to lower the effect of two-way correlations while preserving the spatial arrangement of the data in the feature extraction process. R-SFM was evaluated on the benchmark ADHD200 dataset and not only obtained a 6% improvement in classification accuracy, but also a 66.66% decrease in standard deviation over the previously developed SFM approach. Also R-SFM produces higher specificity which results in lower misclassification of ADHD, thereby reducing the risk of misdiagnosis. These results clearly show that R-SFM provides an accurate and reliable tool for detection of ADHD from BOLD rs-fMRI time series data.

I. INTRODUCTION

Attention deficit hyperactivity disorder (ADHD) is a highly prevalent psychiatric disorder, affecting 3-10% of children worldwide. Traditionally ADHD is diagnosed using a battery of standardized cognitive tests and interviews such as [1]. However, such a diagnosis procedure suffers from issues such as inaccuracy/incompleteness of the information provided by the care givers, inter-rater variability and also standardization of the tests over different cultures, backgrounds and language/IQ abilities. To overcome these, objective measurements of the brain effects are sought by researchers via brain imaging, which also paves the way in understanding the etiopathogenesis. Recently, [2] and [3] have used blood oxygen level dependent (BOLD) functional

magnetic resonance imaging (fMRI) time series data with neural networks to diagnose ADHD. To support the research on ADHD International Neuroimaging Data-sharing Initiative (INDI) consolidated the resting state functional magnetic resonance imaging (rs-fMRI) data from 947 subjects under the ADHD200 consortium [9].

Studies using ADHD200 dataset [4] have had limited success mainly due to high variations inherently found in the fMRI data, caused by differences in brain development trajectories in children [5]. As a result, the features generated from the ADHD data are characterized by poor separability between ADHD and Typically Developing Children (TDC) classes. [6] and [7] have used spatial filtering method (SFM) to extract discriminant features by projecting the BOLD fMRI time series data in orthogonal dimensions to increase the separability between the classes in the autism spectrum disorder dataset. However, extracting features of the ADHD dataset using SFM results in high distortions as the mean covariance matrices used in SFM are highly susceptible to inherent variations of the rs-fMRI data.

To overcome these shortcomings, in this paper, we propose a Regularized Spatial Filtering Method (R-SFM) to obtain better classification and improved diagnosis of ADHD using rs-fMRI data. R-SFM uses a regularized covariance matrix estimation and a Mahalanobis whitening transformation in order to extract distinguishable features from the rs-fMRI dataset. First, regularization is used to bias the covariance matrix mean away from the sample mean to obtain a true representation of the class. Second, Mahalanobis whitening is utilized to eliminate the lower order correlations while preserving the spatial arrangement of the data. Finally, SFM is used to project the data orthogonally to extract the highly discriminant features.

These features are used in conjunction with Projection Based Learning - Meta-cognitive Radial Basis Function Network (PBL-McRBFN) [8] classifier to achieve improved classification performance. The performance of R-SFM is presented in terms of accuracy, sensitivity, specificity and F-score. For the ADHD200 dataset, R-SFM not only provides a higher classification accuracy of 70.39% but also reduces the standard deviation by 66.66%. Also, a 15% higher specificity is achieved with R-SFM which is critical to the prevention of misclassification, thereby eliminating the misadministration of medicines. The results indicate that R-SFM provides a reliable and accurate tool for diagnosis of ADHD in comparison with previous studies on this dataset.

*Nanyang Technological University, Singapore

**Singapore Bioimaging Consortium (SBIC), Singapore

1 abhayaradhya@ntu.edu.sg

2 vigneshwaran_subbaraju@sbic.a-star.edu.sg (supported by A*STAR JCO Grant 1335h00098)

3 SSundaram@ntu.edu.sg

4 ENSUNDARA@ntu.edu.sg

This paper is organized as follows: *Section II* describes the regularization, whitening and spatial filtering strategies used to identify the discriminant features. The results of the classification are presented and discussed in *Section III*. Finally, *Section IV* summarizes the observations and conclusions of this study.

II. METHODOLOGY

In this paper, an original feature extraction approach herewith referred to as regularized spatial filtering method (R-SFM) is presented to derive discriminative features from the pre-processed BOLD rs-fMRI data. R-SFM produces highly discriminative features from the time series fMRI signal by projecting the regularized covariance matrices using the 'Fukunaga-Koontz' transform [10]. Spatial filters have been previously used to study the autism spectral disorder using rs-fMRI data [6]. However, they are highly vulnerable to distortion from atypical samples resulting in an untrue modelling of the class. R-SFM extracts robust and reliable features facilitating better separability and classification. In this study, we evaluate the performance of R-SFM using the BOLD rs-fMRI data from the ADHD200 consortium [9].

ADHD200 consortium is a global initiative of International Neuroimaging Data-sharing Initiative (INDI) through which pre-processed rs-fMRIs from 947 subjects from 8 different institutions have been compiled. Of the 947 subjects, 580 were males which reinforces a gender bias among ADHD subjects commonly observed earlier by previous independent studies [11]. A skewed ratio was also observed in the handedness of the subjects in the ADHD200 consortium dataset; 905 right handed subjects, 29 left handed and 2 ambidextrous subjects. Therefore, to obtain a homogeneous dataset in this study, only male right handed subjects were considered. Further, pre-processing was carried out using the ATHENA pipeline as mentioned in [9] and the samples that failed the quality control tests were removed to obtain a dataset of 465 right handed male subjects.

To validate the performance of R-SFM the dataset was divided into a training dataset with 371 subjects and a hold out testing dataset of 94 subjects chosen randomly such that the proportion of ADHD subjects to Typically Developing Children (TDC) remained constant between the training and testing datasets. The training and testing performances of the classifiers are presented to corroborate the improved feature extraction method.

In R-SFM, the normalized covariance matrix S_i is constructed from the individual rs-fMRI samples using *Equation 1*.

$$S_i = \frac{(B_i)(B_i)^T}{\text{trace}(B_i B_i^T)} \quad i = 1, 2, \dots, n \quad (1)$$

where $n \rightarrow$ total number of samples in the dataset, $B_i \rightarrow$ BOLD signals from the i^{th} subject and represents the functional activity of the 90 regions of the brain derived from the automated anatomical labelling (AAL) atlas.

A. Regularized Covariance Matrix Estimation

The discriminative features extracted using traditional SFM algorithm are identified using sample covariance matrix estimation. SFM algorithm is therefore highly prone to distortions when the data is characterized by high variability, leading to both numerical and statistical problems [12]. To overcome this shortcoming we introduce a regularization methodology which biases the estimates of the mean covariance matrices are shifted towards plausible values [13]. Regularization thereby helps in obtaining a true representation of the class mean covariance matrix. This study aims at extending the basic principles of regularization proposed in [13], to obtain the mean covariance matrices of the ADHD and TDC classes from the rs-fMRI data.

The regularized mean covariance matrix for both the classes is calculated using

$$\hat{\Sigma}_c(\beta, \gamma) = (1 - \gamma)\hat{\Sigma}_c(\beta) + \frac{\gamma}{N}\text{trace}[\hat{\Sigma}_c(\beta)] \cdot \mathbf{I}; \quad c = \{1, 2\} \quad (2)$$

where the parameters $0 \leq \beta \leq 1$ and $0 \leq \gamma \leq 1$ are used to moderate the regularization process, c is the class index, N is the number of regions of the brain obtained from the AAL parcellations, where $\mathbf{I}$ represents the identity matrix of dimension $N \times N$ and $\hat{\Sigma}_c(\beta)$ is given by

$$\hat{\Sigma}_c(\beta) = \frac{\sum_{m=1}^M ((1 - \beta) \cdot \hat{S}_c + \beta \cdot S_{(c,m)})}{\hat{M} + M} \quad (3)$$

where $S_{(c,m)}$ represents the covariance matrix derived from the m^{th} sample of the c^{th} class given by *Equation 1*, M denotes the number of training samples in c^{th} class, $\hat{M}$ is the number of generic training trails and $\hat{S}_c$ is the summation of the covariance matrices of $(m-1)$ training samples belonging to class c and is defined as

$$\hat{S}_c = \begin{cases} \sum_{i=1}^{\hat{M}} S_{(c,i)} & m = 1 \\ \sum_{i=1}^{(m-1)} S_{(c,i)} & \text{otherwise} \end{cases} \quad (4)$$

The overall mean connectivity matrix $[\Sigma(\beta, \gamma)]$ is defined as

$$\Sigma(\beta, \gamma) = \hat{\Sigma}_{ADHD}(\beta, \gamma) + \hat{\Sigma}_{TDC}(\beta, \gamma) \quad (5)$$

B. Mahalanobis whitening or zero-phase component analysis (ZCA)

When learning a statistical model, it is beneficial to focus on higher-order correlations rather than get distracted by modelling two way correlations. This will make the model more likely to discover interesting features in the dataset [14], [15].

The whitening removes the second-order structure by multiplying the data matrix by a whitening matrix (W) given by [14]:

$$W = \sqrt{N-1} [\Sigma(\beta, \gamma) \Sigma(\beta, \gamma)^T]^{-\frac{1}{2}} \quad (6)$$

As $[\Sigma(\beta, \gamma) \Sigma(\beta, \gamma)^T]$ is symmetric it can be orthogonally diagonalized as:

$$\Sigma(\beta, \gamma) \Sigma(\beta, \gamma)^T = RDR^T \quad (7)$$

for some orthogonal matrix R and diagonal matrix D . Therefore

$$\begin{aligned} W &= \sqrt{N-1} [RDR^T]^{-\frac{1}{2}} \\ &= \sqrt{N-1} [RD^{-\frac{1}{2}}R^T] \end{aligned} \quad (8)$$

Using the whitening matrix by Equation 8, the whitened mean connectivity matrices of the ADHD class $[\Sigma_{ADHD}(\beta, \gamma)]$ and TDC class $[\Sigma_{TDC}(\beta, \gamma)]$ are given by:

$$\Sigma_{ADHD}(\beta, \gamma) = \hat{\Sigma}_{ADHD}(\beta, \gamma) W \quad (9)$$

$$\Sigma_{TDC}(\beta, \gamma) = \hat{\Sigma}_{TDC}(\beta, \gamma) W \quad (10)$$

C. Spatial Filtering

Spatial Filtering Method (SFM) [6] is then used to extract the most distinguishable features from the time series f-MRI data by orthogonally projecting the mean connectivity matrices Σ_{ADHD} and Σ_{TDC} . Generalized eigenvalue decomposition is used to find the orthogonal projection vector E as:

$$\Sigma_{ADHD} = E \beta_{ADHD} E^T \quad (11)$$

$$\Sigma_{TDC} = E \beta_{TDC} E^T \quad (12)$$

$$\text{where } \beta_{ADHD} + \beta_{TDC} = I \quad (13)$$

The projection matrix P , is used to transform B_i such that the two classes are highly separable. As the matrix P acts as a spatial transformation filter and transforms the data such that the two classes are highly separable, it is referred to as spatial filter matrix.

$$P = E^T \times W \quad (14)$$

$$Y_i = P \times B_i \quad (15)$$

$$f_{(c,i)} = \log(\text{var}(Y_{(c,i)})) \quad i = 1, 2, \dots, n \quad c = \{1, 2\} \quad (16)$$

Finally the training and hold out testing datasets are projected using the projection matrix P and six most discriminant features are extracted using Equation 16, where $f_{(c,i)}$ is the feature derived from the i^{th} projected time-series rs-fMRI sample of the c^{th} class. The obtained features were then used to train the PBL-McRBFN classifier for classification. PBL-McRBFN, with its human like learning ability, is known to provide superior classification performance [17].

III. RESULTS AND DISCUSSION

In this section, the performance of R-SFM in extracting discriminative features from rs-fMRI data between ADHD and TDC is presented. The performance of R-SFM is compared with the earlier SFM approach used in literature.

To obtain the discriminative features, the mean covariance matrix is calculated for each class as per the methodology

Fig. 1: Contour plot of testing accuracy against beta and gamma

given in Section II-A. The regularization parameters $0 \leq \beta \leq 1$ and $0 \leq \gamma \leq 1$ in Equation 5 are chosen to jointly minimize the misclassification rates. Figure 1 presents a contour plot of the variation of ADHD classification accuracy with respect to β and γ . Two sets of values $0.1 \leq \beta \leq 0.4$, $0.6 \leq \gamma \leq 0.7$ and $0.85 \leq \beta \leq 1$, $0 \leq \gamma \leq 0.4$ showed improved classification accuracy. However, on further testing the region with lower γ and higher β values were found to be less consistent, as the regularization procedure acts as a linear discriminant analysis in these limits [13]. Higher classification accuracies were obtained for $\beta = 0.25$ and $\gamma = 0.65$ through cross-validation. Using these values the regularized mean covariance matrices were obtained. To ensure higher separability between the ADHD and TDC samples, the regularized mean covariance matrices were used to orthogonally project the dataset using SFM [6]. The highly discriminative features extracted using R-SFM are used along with PBL-McRBFN classifier and the performance has been evaluated.

TABLE I: PBL-McRBFN classification performance

	Performance measure	SFM		R-SFM	
		Score	S.D	Score	S.D
Training	Accuracy	88.66%	0.20	93.22%	0.03
	Sensitivity	95.61%	0.04	91.62%	0.04
	Specificity	78.50%	0.39	93.58%	0.04
	F-Score	0.8891	0.13	0.9202	0.04
Testing	Accuracy	64.54%	0.06	70.39%	0.02
	Sensitivity	79.32%	0.12	78.09%	0.06
	Specificity	44.58%	0.23	60.00%	0.07
	F-Score	0.7185	0.04	0.7512	0.02

Table I gives the detailed performance results for both the SFM and the newly proposed R-SFM methods. From Table I it can be inferred that R-SFM with PBL-McRBFN [8] provides improved classification performance with both training and test dataset. A mean training accuracy of 93.22%

was achieved using R-SFM, which is 4.5% greater than that obtained using SFM. Moreover, 85% decrease in standard deviation is achieved using R-SFM. Also R-SFM produced 70.39% testing accuracy whereas SFM produced only 64.54%. Similar to the training performance, the standard deviation of the testing data also was reduced by 66.66%. Also, a detailed review of the literature shows that the classification performance of R-SFM is superior to the state of the art works in literature [4]. Therefore, R-SFM provided more reliable and consistent (indicated by lower standard deviation of accuracy) results in comparison to the other methods in the literature.

Apart from accuracy, we also looked at other performance indicators such as sensitivity (ability to recognize an ADHD patient correctly), specificity (ability of the algorithm to identify a subject not having ADHD correctly) and F-score to analyze the efficacy of R-SFM. Using R-SFM, although the sensitivity and the F-score remained relatively unchanged with respect to SFM, a marked improvement in specificity was observed (15% increase in specificity on both the training and testing datasets). This improvement in the ability to identify true negative samples is crucial as misdiagnosis of TDC as ADHD might lead to nonessential and improper medication. Not only [16] has found that pediatric patients are at a higher risk of fatalities in comparison to adults due to the administration of improper medications, but also [9] identified specificity as one of the critical point in the diagnosis of ADHD.

Further, a lower standard deviation in both the training and testing datasets indicate the improved consistency and reliability of R-SFM in diagnosing ADHD. The improvement of the performance gained using R-SFM may be attributed to the two fold approach employed in R-SFM, viz., the regularization described in *Section II-A* and mahalanobis whitening given in *Section II-B*. The Mahalanobis whitening not only reduces the noisy data from the lower order correlations but also preserves the spatial arrangement of the data. Thus a true projection of the data is obtained with the benefits of the whitening process. On the other hand, the regularization lowers the effect of plausible atypical samples of a class on the respective covariance class mean.

IV. CONCLUSIONS

In this paper, a new approach referred to as regularized spatial filtering method (R-SFM) is developed for accurate detection of ADHD from blood oxygen level dependent (BOLD) resting state functional magnetic resonance imaging (rs-fMRI) time series data. R-SFM provides a more accurate and reliable diagnosis using a regularized covariance matrix optimization and Mahalanobis whitening transformation. It overcomes the shortcomings of the class based mean covariance matrix optimization approach used in the earlier developed SFM approach. The ADHD200 dataset is used to corroborate the improved feature extraction methodology using R-SFM. R-SFM with projection based learning - meta-cognitive radial basis function network (PBL-McRBFN) classifier not only provides a higher detection accuracy of

70.39%, but also provides a more consistent result with a low standard deviation of 2%. Moreover R-SFM also provides a 15% increase in the specificity (which is a key performance measure identified by previous studies), thereby reducing misclassification rates and the risk of administration of improper medications. Also as R-SFM uses Spatial Filtering Method (SFM) to project the data orthogonally, further studies using R-SFM analyzing the inverse SFM matrix may help in identifying the bio-markers important brain circuits responsible for ADHD.

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