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# ESTIMATING BRAIN CONNECTIVITY USING COPULA GAUSSIAN GRAPHICAL MODELS

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## ABSTRACT

Electroencephalogram (EEG) has been widely used to study cortical connectivity during acquisition of motor skills. Previous studies using graphical models to estimate sparse brain networks focused on time-domain dependency. This paper introduces graphical models in the spectral domain to characterize dependence in oscillatory activity between EEG channels. We first apply a transformation based on a copula Gaussian graphical model to deal with non-Gaussianity in the data. To obtain a simple and robust representation of brain connectivity that explains most variation in the data, we propose a framework based on maximizing penalized likelihood with Lasso regularization utilizing the cross-spectral density matrix to search for a sparse precision matrix. To solve the optimization problem, we developed modified versions of graphical Lasso, Ledoit-Wolf (LW) and the majorize-minimize sparse covariance estimation (SPCOV) algorithms. Simulations show benefits of the proposed algorithms in terms of robustness and accurate estimation under non-Gaussianity and different structures of high-dimensional sparse networks. On EEG data of a motor skill task, the modified graphical Lasso and LW algorithms reveal sparse connectivity pattern among cortices in consistency with previous findings. In addition, our results suggest regions over different frequency bands yield distinct impacts on motor skill learning.

***Index Terms—*** Brain connectivity, EEG, high-dimensional covariance, graphical models, copulas

## 1. INTRODUCTION

A graph is a model representation of a complex system determined by a set of nodes (vertices) and edges connecting them [1]. On the foundation of graph and probability theory, graphical models (probabilistic graphical model) have been widely used in Bayesian statistics, statistical learning and machine learning. In the framework of graphical models, each node represents a random variable and edges denote the probabilistic relationship between nodes. The graph depicts the structure where the joint distribution of random variables can be decomposed into a product of factors depending only on subsets of variables [2].

Graphs have been introduced to modeling brain connectivity where nodes represent cortical and subcortical regions while edges characterize functional and structural connections between cortical nodes [3]. In the literature of brain graph modeling, much work has been done for all major modalities such as the functional magnetic resonance imaging (fMRI) and the electrophysiological data. To name a few, functional brain graphs and their relevant works have been constructed from fMRI [4], electroencephalography (EEG) signals [5, 6], magnetoencephalography (MEG) data [7] and local field potentials (LFPs) signals [8, 9]. From diffusion tensor imaging (DTI) and diffusion spectrum imaging (DSI), structural brain graphs have been studied by [10]. Among them, sparse graphical models, which are widely discussed in [11], are highly efficient in inferring dependence between multielectrode brain recordings. The sparsity of graph provides a robust approach that highlights the most significant interactions between brain cortices and helps to interpret the data [12]. However, most previous works on graphical modeling of brain networks focused on time-domain dependence and assumed Gaussianity in the data.

To address these limitations, we introduce a novel framework based on sparse graphical models in the spectral domain for estimating brain connectivity from EEG data. The main contributions of this paper are as follows: (1.) We introduce copula Gaussian graphical models to account for the non-Gaussianity of signals on frequency domain, inspired by the work of [13]; (2.) We develop a framework to capture the between-channel dependence in the oscillatory activity; (3.) By including a regularization term, we are able to obtain a simple and robust representation that captures the most critical interactions between brain cortices; (4.) Compared to the traditional graphical models, we replace the sample covariance in the penalized likelihood with a spectral matrix to induce a sparse graph in the spectral domain. The pro-

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posed method can be seen as a generalized version of time-domain Gaussian graphical models. Specifically, our method produces sparse estimates of covariance matrices. We regularize the log likelihood with a lasso penalty on the entries of covariance matrix. The penalty is used to reduce the effective number of brain connectivity and thus produces sparse and robust estimates [14]. Many algorithms have been introduced to solve this optimization problem. For example, [15] introduced a novel algorithm with the assumption of ordering to the variables. Another study used relevance networks with an optimization such that pairwise correlation beyond a threshold are linked by an edge [16]. [17] proposed an algorithm by introducing shrinkage operators. [18] utilized lasso-regression based method to solve the optimization problem. In this paper, we develop modified algorithms based on the works of graphical lasso [11], sparse estimation of covariance proposed by [14] and Ledoit-Wolf algorithm [19]. The robustness and performance of the proposed algorithms were evaluated via simulations and applied to estimating brain connectivity network on a motor-task EEG data.

## 2. GRAPHICAL MODELS FOR BRAIN NETWORKS

In this section, we first discuss preliminaries on graphical models and its application to modeling brain connectivity from EEG data. We then formulate the optimization problem in estimating sparse connectivity networks in the spectral domain and propose three algorithms in solving the problem.

### 2.1. Copula Gaussian Graphical Model

Suppose we have non-Gaussian random variables $Y_1, Y_2, \cdots, Y_n$. We define hidden Gaussian random variables $X_1, X_2, \cdots, X_n$ through the relationship that [12]

$$X_k \sim \mathcal{N}(0, \Sigma_k^{-1}), \quad (1)$$

$$Y_k = F_k^{-1}(\Phi(X_k)), \quad (2)$$

where $\Sigma_k$ is the precision matrix, $\Phi$ is the cumulative distribution function of a standard Gaussian random variable and $F_k$ is the empirical cumulative distribution function of $Y_k$. In practice, $F_k^{-1}$ can be estimated by

$$\hat{F}_k^{-1}(y) = \inf\{z, F_k(z) \geq y\}.$$

### 2.2. Modeling EEG Connectivity

In practice, EEGs recorded from different electrodes are highly non-Gaussian multivariate time series. By implementing copula Gaussian graphical models, the original time series is transformed into Gaussian data where conventional Gaussian graphical models can be applied.

Suppose a graphical model $G = (V, E)$ uniquely defines the conditional independence on Gaussian process $X(t) = (X_1(t), \cdots, X_p(t))$. In graph $G$, each node $V_i$ denotes a single time series $X_i(t)$. The absence of edge between $V_i$ and $V_j$ denotes the conditional independence between time series $X_i(t)$ and $X_j(t)$ given the rest of nodes. Under the assumption that the cross-variance function of $X(t)$ is summable,

$$\sum_{\tau=-\infty}^{\infty} |cov\{X_i(t), X_j(t+\tau)\}| < \infty, \forall i, j,$$

we define the cross-spectral density matrix of $X$ as

$$S_{i,j}(\omega) = \mathcal{F}\{cov(X_i, X_j)\},$$

where $\mathcal{F}$ denotes the Fourier transform. The (squared) coherence is defined as $C_{i,j}(\omega) = \frac{|S_{i,j}(\omega)|^2}{S_{i,i}(\omega)S_{j,j}(\omega)}$. As a result of [20], the Gaussian process $X_i$ and $X_j$ are conditional independence if and only if

$$\{S(\omega)^{-1}\}_{ij} = 0, \quad \forall \omega.$$

In practice, we substitute an estimator for $S(\omega)$ using the empirical variance-covariance matrix of the time series $X(t)$.

### 2.3. Proposed Estimation Algorithms

We have transformed the EEG data into quasi-Gaussian time series with empirical variance-covariance matrix $S(\omega)$. In sparse graphical models, true brain connectivity involving the strongest and the most relevant connections is uniquely determined by the sparse precision matrix (the inverse of the covariance matrix). The objective function, defined as the regularized negative log-likelihood function is given by

$$\begin{aligned} \underset{\Sigma}{\text{minimize}} \quad & -\log\det(\Sigma(\omega)) + \text{tr}(S(\omega) * \Sigma(\omega)) + \lambda * ||\Sigma(\omega)||_1 \\ \text{subject to} \quad & \Sigma(\omega) \succeq 0, \end{aligned} \quad (3)$$

where $S(\omega)$ is the empirical spectral density matrix defined above, $||\Sigma(\omega)||_1$ is the $l_1$-norm of $\Sigma(\omega)$ as the sum over the absolute values of entries in matrix $\Sigma(\omega)$, and $\lambda$ is a tuning parameter controlling the amount of $l_1$ shrinkage. We apply three algorithms to solve the optimization problem (3).

*SPCOV (Majorize-Minimize) algorithm.* In the objective function (3), $\text{tr}(S(\omega) * \Sigma(\omega)) + \lambda * ||\Sigma(\omega)||_1$ is convex while $\log\det(\Sigma(\omega))$ is concave, thus a majorize-minimize scheme could be used [11]. In summary, this algorithm consists of two loops, the outer loop approximates the non-convex problem and the inner loop solves each convex relaxation.

*Graphical lasso algorithm.* We also propose a graphical lasso algorithm. The rationale is that suppose $\hat{\Sigma}(\omega)$ is the estimate of $\Sigma(\omega)$, then one can solve the problem by optimizing over each row and corresponding column of $\hat{\Sigma}(\omega)$ in a block coordinate descent fashion.

*Modified Ledoit-Wolf algorithm.* Inspired by the works of [19], [21] and [22], we also implement a modified Ledoit-Wolf algorithm to address the optimization problem (3). Specifically, we utilize the sample covariance $S(\omega)$ and the maximum likelihood estimator $S^{\text{ML}}(\omega)$ to obtain a shrinkage estimator which compromises between variance and bias. The estimator is then denoted as $\hat{\Sigma}(\omega) = \pi * S(\omega) + (1 - \pi) * S^{\mathrm{ML}}(\omega)$ The shrinkage intensity can be estimated by by minimizing a risk function based on mean square errors between the true and estimated precision matrix

$$\hat{\pi} = \operatorname{argmin} \mathbb{E}(||\hat{\Sigma}(\omega) - \Sigma(\omega)||_2)$$

## 3. SIMULATIONS

In this section, various simulation scenarios were considered to evaluate the performance of the proposed algorithms. In each scenario, we created different types of sparse symmetric positive definite matrices to be the true covariance structure. We randomly generated 200 samples from the true covariance structure and then used the data as the input of the proposed algorithms. Each scenario was repeated 1000 times. We evaluated the performance of our method in terms of correctly identifying the zero elements of $\Sigma$ and the discrepancy with the true precision matrix by mean-square error, $||\hat{\Sigma} - \Sigma||_F/p$ and entropy loss, $-\log\det(\hat{\Sigma}\Sigma^{-1}) + tr(\hat{\Sigma}\Sigma^{-1}) - p$ respectively, where $p$ is the number of parameters.

The first scenario used the *cliques model* where we set the precision matrix of the form $\Sigma = \mathrm{diag}(\Sigma_1, \Sigma_2, \Sigma_3)$. Each $\Sigma_i$ in the diagonal represented a $6 * 6$ dense matrix. Other parts of the matrix were zero. The second scenario was random model. The sparse graph was created by assigning $\Sigma_{ij} = \Sigma_{ji}$ to be non-zero with probability 0.02, independently of other elements. The third scenario was based on more realistic connectivity pattern estimated from the real EEG data. The precision matrix was calculated from the real data and used to generate simulated signals based on a *non-Gaussian* distribution (log normal) to evaluate the robustness of our method to possible violation of the Gaussian assumption.

From the Tables 1 and 2, we can see that both graphical Lasso and Ledoit-Wolf methods give smaller mean square error and entropy loss compared to SPCOV in both scenarios. In addition, all the three algorithms were more accurate and robust in random model. In Fig. 1, the different shades of color in the connectivity matrix indicated the correlation between each nodes and darker colors demonstrated stronger correlations. It can be seen that the estimated connectivity matrix obtained from graphical Lasso and Ledoit-Wolf algorithms were in high accordance with the true covariance structure. In summary, simulations suggest that both graphical Lasso and Ledoit-Wolf methods are competitive for identifying the sparsity structure of the simulated data.

Table 3 summarizes the results on the non-Gaussian data simulated based on connectivity network of real EEG. It can be shown that for all estimation algorithms, the proposed copula graphical model clearly outperforms traditional Gaussian graphical models, producing lower errors with relatively small standard errors. This result confirms the robustness of our method when the normality assumption is violated.

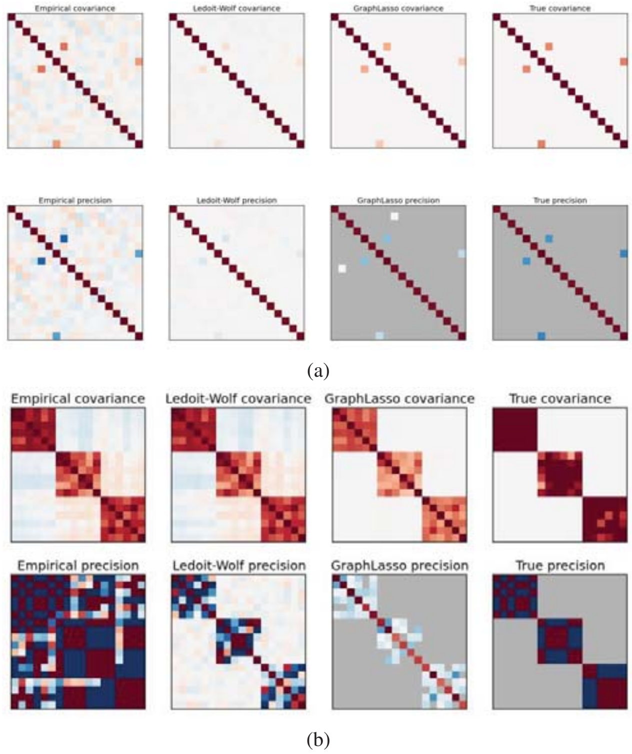


**Fig. 1**: True connectivity matrices simulated using (a) random model and (b) cliques model, and their estimates by different methods.

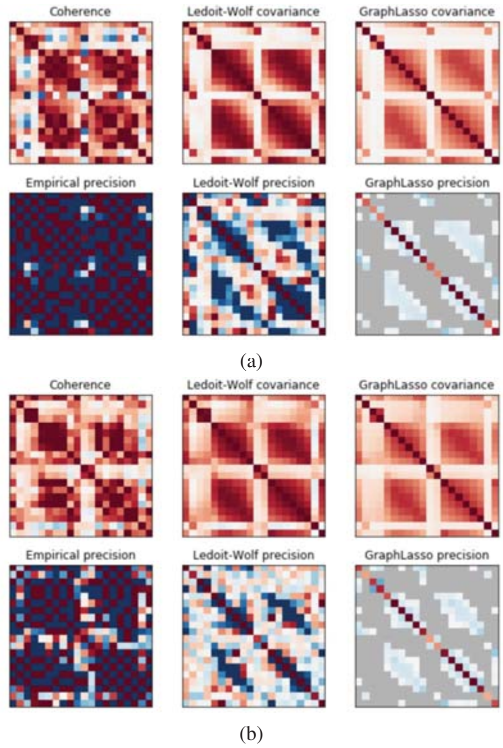


**Fig. 2**: Estimated connectivity matrices from EEGs during motor skill learning for (a) $\beta$ and (b) $\gamma$ frequency band.

**Table 1**: Averages and standard errors of mean-square error and entropy Loss for estimated covariance matrices obtained by different methods, over 1000 replications of simulated data under random model and cliques model.

| Method | Random Model | | Cliques Model | |
|---|---|---|---|---|
| | Mean-Square Error | Entropy Loss | Mean-Square Error | Entropy Loss |
| Graphical Lasso | $2.723 * 10^{-5} \pm 1.020 * 10^{-6}$ | $0.232 \pm 0.003$ | $2.730 * 10^{-5} \pm 1.060 * 10^{-6}$ | $0.230 \pm 0.003$ |
| Ledoit-Wolf | $5.170 * 10^{-5} \pm 6.300 * 10^{-6}$ | $0.180 \pm 0.001$ | $5.270 * 10^{-5} \pm 6.300 * 10^{-6}$ | $0.180 \pm 0.001$ |
| SPCOV | $7.423 * 10^{-5} \pm 9.100 * 10^{-6}$ | $0.732 \pm 0.089$ | $8.200 * 10^{-5} \pm 1.370 * 10^{-6}$ | $0.700 \pm 0.092$ |

**Table 2**: Averages and standard errors of the execution time for covariance estimation by different methods over 1000 replications of simulated data under random model and cliques model.

| Method | Random Model | Cliques Model |
|---|---|---|
| | Execution Time | Execution Time |
| Graphical Lasso | $0.400 \pm 6.012 * 10^{-3}$ | $0.330 \pm 4.023 * 10^{-3}$ |
| Ledoit-Wolf | $0.007 \pm 5.230 * 10^{-5}$ | $0.001 \pm 1.920 * 10^{-5}$ |
| SPCOV | $0.152 \pm 3.323 * 10^{-2}$ | $0.630 \pm 2.272 * 10^{-1}$ |

**Table 3**: Averages and standard errors of the mean-square errors of covariance matrices obtained by the traditional Gaussian and the proposed graphical models, over 1000 replications of simulated data generated by the estimates of EEG data.

| Algorithm | Method | Mean-Square-Error |
|---|---|---|
| Graphical Lasso | Gaussian | $4.234 * 10^{-3} \pm 4.304 * 10^{-4}$ |
| | Proposed Approach | $2.103 * 10^{-3} \pm 3.103 * 10^{-4}$ |
| Ledoit-Wolf | Gaussian | $6.020 * 10^{-3} \pm 5.120 * 10^{-4}$ |
| | Proposed Approach | $5.004 * 10^{-3} \pm 3.290 * 10^{-4}$ |
| SPCOV | Gaussian | $8.239 * 10^{-3} \pm 6.302 * 10^{-4}$ |
| | Proposed Approach | $6.034 * 10^{-3} \pm 5.020 * 10^{-4}$ |

## 4. APPLICATION TO BRAIN CONNECTIVITY FOR STROKE REHABILITATION

We illustrate an application of our method to a EEG dataset from a multi-subject stroke experiment conducted at the University of California Irvine Neurorehabilitation Lab (PI: Cramer). During the experiment, participants sat in a chair facing a monitor in a single session. Their task was to make movements across centers of each circle on the screen. To minimize the variability among individuals, the researchers measured the awake resting-state EEG for 3 minutes (EEG-Rest) at 1000 Hz prior to the motion task. Then, the measurement of each participant's maximum arm movement speed was obtained, and a baseline assessment of motor skill task was recorded. During this procedure, EEG was measured (EEG-Test1). Later on, the participant was required to receive a practice block, followed by another test block. Finally, after three tests and two practice blocks were done, the EEG was obtained, which comprised of four scenarios – EEG-Test(1-3) and EEG-Rest. The dataset consists of 16 subjects. EEG data of 160 trials (epochs), 1000 time points and 256 channels from different cortical regions were recorded for each subject and each condition. In this paper, we chose subject named "YUGR" for analysis and considered 160 epochs from EEG-Rest, 73, 74 and 63 trials from EEG-Test 1-3 respectively.

To study the brain connectivity during the motion experiment, we applied the proposed method to the EEG data. It has been shown that the oscillatory activities of lower $\beta$ and $\gamma$ bands play a critical role in motor learning [23] and thus we mainly focus on these two bands in this paper. One of the interesting scientific questions is to uncover the latent cortical structure that highly correlates to patient motor skill development. Motivated by the results from simulations, we applied our approach to search for the solution. Fig. 2 shows the connectivity matrix across different brain cortices from two algorithms over lower $\beta$ and $\gamma$ bands. It can be found that the two algorithms result in a similar pattern in regrading to the correlation between cortices. In particular, over lower $\beta$ bands, the total cortices can be classified as four regions in which high association can be realized. After compared with the topographic representation, we find that one of the critical regions is associated with the left primary motor area. It has been shown that the coherence from this region is a strong predictor of motor skill acquisition [23]. The other highly associated areas are pre-frontal region, right lateral parietal region and left medial parietal region. For $\gamma$ band, similar patterns can be observed although the sparsity is less obvious. The benefits of using the proposed approach can be easily established when comparing with the original coherence matrix. Our method is able to capture the most critical association patterns that conveys scientific insights. The results of our proposed framework serve as further evidence and also provides alternative directions in understanding how oscillatory activities are associated with motor skill learning.

## 5. CONCLUSION

We have developed a method to model brain connectivity on frequency domain through graphical models based on the framework of copula Gaussian model. We modified the graphical Lasso, Ledoit-Wolf and SPCOV algorithms to solve the optimization problem (3) to estimate a sparse connectivity matrix in the spectral domain. Simulations results show the advantages of the proposed method in handing non-Gaussian data and in recovering different sparsity structures in the connectivity matrix. The proposed algorithms were applied to real EEG data from the motion experiment. Results show the sparsity of the brain connectivity between cortices, which not only agrees with the results from previous studies, but also provides new insights that EEG cortical connectivity at different frequency bands may predict motor skill acquisition. Future work will extend the proposed framework to multi-subject analysis and the time-varying or dynamic effective connectivity based on recent work [24, 25].

## 6. REFERENCES


[1] R. J. Trudeau, *Introduction to graph theory*, Courier Corporation, 2013.

[2] C.M. Bishop, *Pattern Recognition and Machine Learning*, Springer-Verlag, 2006.

[3] E. T. Bullmore and D. S. Bassett, "Brain graphs: Graphical models of the human brain connectome," *Annual Review of Clinical Psychology*, vol. 7, pp. 113–140, 2011.

[4] Y. Wang and Y. Guo, "A hierarchical independent component analysis model for longitudinal neuroimaging studies," *arXiv preprint arXiv:1808.01557*, 2018.

[5] S. Micheloyannis, E. Pachou, C. J. Stam, M. Breakspear, P. Bitsios, M. Vourkas, S. Erimaki, and M. Zervakis, "Small-world networks and disturbed functional connectivity in schizophrenia," *Schizophrenia Research*, vol. 87, no. 1-3, pp. 60–66, 2006.

[6] P. B. Kemmer, Y. Guo, Y. Wang, and G. Pagnoni, "Network-based characterization of brain functional connectivity in zen practitioners," *Frontiers in Psychology*, vol. 6, pp. 603, 2015.

[7] C. J. Stam, "Functional connectivity patterns of human magnetoencephalographic recordings: a small-worldnetwork?," *Neurosci. Lett.*, vol. 355, no. 1-2, pp. 25–28, 2004.

[8] X. Gao, B. Shahbaba, N. Fortin, and H. Ombao, "Evolutionary state-space model and its application to time-frequency analysis of local field potentials," *arXiv preprint arXiv:1610.07271*, 2016.

[9] X. Gao, W. Shen, and H. Ombao, "Regularized matrix data clustering and its application to image analysis," *arXiv preprint arXiv:1808.01749*, 2018.

[10] G. Gong, Y. He, L. Concha, C. Lebel, D. W. Gross, A. C. Evans, and C. Beaulieu, "Mapping anatomical connectivity patterns of human cerebral cortex using in vivo diffusion tensor imaging tractography," *Cerebral Cortex*, vol. 19, no. 3, pp. 524–536, 2008.

[11] J. Friedman, T. Hastie, and R. Tibshirani, "Sparse inverse covariance estimation with the graphical lasso," *Biostatistics*, vol. 9, no. 3, pp. 432–441, 2008.

[12] J. Dauwels, H. Yu, X. Wang, F. Vialatte, C. Latchoumane, J. Jeong, and A. Cichocki, "Inferring brain networks through graphical models with hidden variables," in *Machine Learning and Interpretation in Neuroimaging*, pp. 194–201. Springer, 2012.

[13] H. Yu, J. Dauwels, and X. Wang, "Copula gaussian graphical models with hidden variables.," in *IEEE Int. Conf. Acoustics, Speech, and Signal Process.* Citeseer, 2012, pp. 2177–2180.

[14] J. Bien and R. J. Tibshirani, "Sparse estimation of a covariance matrix," *Biometrika*, vol. 98, no. 4, pp. 807–820, 2011.

[15] A. J. Rothman, P. J. Bickel, E. Levina, J. Zhu, et al., "Sparse permutation invariant covariance estimation," *Electronic J. Statist.*, vol. 2, pp. 494–515, 2008.

[16] A. J. Butte, P. Tamayo, D. Slonim, T. R. Golub, and I. S. Kohane, "Discovering functional relationships between RNA expression and chemotherapeutic susceptibility using relevance networks," *Proc. Natl. Acad. Sci. U.S.A*, vol. 97, no. 22, pp. 12182–12186, 2000.

[17] A. J. Rothman, E. Levina, and J. Zhu, "Generalized thresholding of large covariance matrices," *J. Amer. Statist. Assoc*, vol. 104, no. 485, pp. 177–186, 2009.

[18] A. J. Rothman, E. Levina, and J. Zhu, "A new approach to cholesky-based covariance regularization in high dimensions," *Biometrika*, vol. 97, no. 3, pp. 539–550, 2010.

[19] O. Ledoit, M. Wolf, et al., "Nonlinear shrinkage estimation of large-dimensional covariance matrices," *Annal. Statist.*, vol. 40, no. 2, pp. 1024–1060, 2012.

[20] R. Dahlhaus, "Graphical interaction models for multivariate time series," *Metrika*, vol. 51, no. 2, pp. 157–172, 2000.

[21] M. Fiecas, H. Ombao, C. Linkletter, W. Thompson, and J. Sanes, "Functional connectivity: Shrinkage estimation and randomization test," *NeuroImage*, vol. 49, no. 4, pp. 3005–3014, 2010.

[22] M. Fiecas, H. Ombao, et al., "The generalized shrinkage estimator for the analysis of functional connectivity of brain signals," *Ann. Appl. Statist.*, vol. 5, no. 2A, pp. 1102–1125, 2011.

[23] J. Wu, R. Srinivasan, A. Kaur, and S. C. Cramer, "Resting-state cortical connectivity predicts motor skill acquisition," *NeuroImage*, vol. 91, pp. 84–90, 2014.

[24] H. Ombao, M. Fiecas, C.-M. Ting, and Y. F. Low, "Statistical models for brain signals with properties that evolve across trials," *NeuroImage*, vol. 180, pp. 609–618, 2018.

[25] C.-M. Ting, H. Ombao, S. B. Samdin, and Sh-H. Salleh, "Estimating dynamic connectivity states in fMRI using regime-switching factor models," *IEEE Trans. Med. Imag.*, vol. 37, no. 4, pp. 1011–1023, 2018.