A Hierarchical Graphical Model for Big Inverse Covariance Estimation with an Application to fMRI

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Abstract. Brain networks has attracted the interests of many neuroscientists. Statistical tools have been developed to infer brain networks, especially from functional MRI data. However, the scale of whole-brain fMRI, usually in tens of thousands variables, challenges the applicability of these methods. We develop a hierarchical graphical model (HGM) to remediate this difficulty. This model introduces a hidden layer of networks based on sparse Gaussian graphical models, and the observed data are sampled from individual network nodes. In fMRI, the network layer models the underlying signals of different brain functional units, and how these units directly interact with each other. The introduction of this hierarchical structure not only provides a formal and interpretable approach, but also enables efficient computation for inferring big networks with hundreds of thousands of nodes. Based on the partially conditional convexity of our formation, we develop an alternating update algorithm to compute all the HGM model parameters simultaneously. The effectiveness of this approach is demonstrated on simulated data and a real dataset from a stop/go fMRI experiment.

Keywords: Convex optimization; Graphical models; fMRI; K-means; Lasso.

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XL would like to acknowledge partial support from National Institutes of Health grants P01AA019072, P20GM103645, P30AI042853, R01NS052470, and S10OD016366, a Brown University Research Seed award, a Brown Institute for Brain Science Pilot award, and a Brown University faculty start-up fund.

This paper has been presented orally at Yale University on February 18, 2014, and at the Eastern North American Region Meeting of the International Biometric Society on March 18, 2014.

An R package of the proposed method will be publicly available on CRAN.
1 Introduction

Graphical models is a statistical tool to describe the relationships between multiple variables. In functional MRI or fMRI, the variables are the brain activities at different regions (also known as voxels) of the human brain. One important scientific question is how these brain regions are connected, which is called brain connectivity. However, the dimensionality of original fMRI data is usually in hundreds of thousands, and this scale of such data challenges direct application of existing graphical model methods. In this paper, we propose a novel approach to provide interpretable and direct inference for big fMRI data, and this general approach may have applications for other big data problems as well.

The fMRI dataset in this paper comes from one subject performing a cognitive experiment–stop/go trials, which is made public available by its investigators (Xue et al., 2008). After preprocessing the data (see details in Section 4), it consists of the bold measures from 230,590 voxels in 180 time points. Due to the dimensionality of such data, previous research on stop/go fMRI has been mostly focusing on individual voxel activations, and their implications for phenotypes and behavior outcomes. For instance, stop/go voxel activations have been studied using meta-analysis (Simmonds et al., 2008) and causal inference (Luo et al., 2010; Luo et al., 2013). The problem of studying the whole brain connections is an emerging and important direction, but is also challenging methodologically.

There are two major types of connectivity analysis: functional connectivity and effective connectivity, see Friston (2011); Smith et al. (2013); Bowman (2014) for review. The simplest measure for inferring functional connectivity is probably pair-wise correlations. This is computationally inexpensive but is less biologically meaningful (Buckner, 2010; Smith et al., 2013). For example, it does not differentiate direct and indirect connection. Alternative approaches include clustering (Goutte et al., 1999; Bowman and Patel, 2004), and independent component analysis or ICA (Calhoun et al., 2001; Beckmann and Smith, 2004; Guo, 2011; Eloyan et al., 2013). However, they again lack identification of direct and indirect connectivity. Effective connectivity, on the other hand, seeks to infer directional relationships between directly connected brain regions. The popular approaches for effective connectivity include dynamic causal modeling (Friston et al., 2003), structural equation models, and Granger causality. These tools enable identification of direct influence of one region on another, but, due to the complexity of computation and modeling, they are applied for a small number of preselected voxels or regions, usually based particular hypotheses. For example, they can be picked based on either prior knowledge (e.g. anatomical and functioning annotations), or activation studies (Duann et al., 2009). Recently, voxel correlations are used provide more accurate selection of voxels for a certain region of the brain (Zhang and Li, 2013). Despite these attempts, the result, however, may be sensitive to the selection of regions (Bowman, 2014). The results are valid if the influence from the omitted brain regions is small, which is usually hard to check in practice.

To infer large-scale connectivity, we will further develop a popular type of graphical models, called sparse Gaussian graphical models (Yuan and Lin, 2007; Banerjee et al., 2008), hereafter sGGM. This type of models has a solid probabilistic foundation for differ-
entiating direct and indirect connections \cite{Dempster1972, Lauritzen1996}. Suppose we observe a multivariate observation \( X_{n \times p} \), with \( n \) iid observations from a \( p \)-variate normal distribution \( N(\mu, \Sigma) \). This approach represents the relationships between \( p \) variates by a network of \( p \) nodes, where each node represents a variable and there are a few connections between nodes. Methodologically, inference of connections between \( p \) nodes is reduced to estimate a sparse inverse covariance \( \Omega = \Sigma^{-1} \), where a nonzero off-diagonal entry in \( \Omega \) means that the corresponding row and column variables/nodes are directly connected and a zero entry means no connections, see \cite{Lauritzen1996}. In fMRI applications, direct connectivity is more biologically interpretable than indirect functional connectivity \cite{Friston2011}. The sGGM approach also performs reasonably well on a simulation study using a small number of regions \cite{Smith2011}.

Recently, several estimators for sGGM have been proposed based on the \( \ell_1 \) heuristic \cite{Chen1994, Tibshirani1996}. These approaches can be divided according to three major estimation principals: penalized conditional likelihood or neighborhood selection \cite{Meinshausen2006, Yuan2010}, penalized full likelihood or Graphical lasso \cite{Yuan2007, Banerjee2008, Friedman2008}, and algebraic properties \cite{Cai2011, Liu2012}. The last type of sGGM estimators, especially, has faster statistical convergence rates for a general class of distributions with polynomial tails \cite{Cai2011}, and is statistically adaptive and computationally efficient \cite{Liu2012}. However, all these approaches usually don’t scale up to hundreds of thousands of voxels, though some algorithmic improvements have been made recently for large scale sGGM using penalized likelihood \cite{Hsieh2013}.

Leveraging these scientific findings and methodological advances, we propose a unified statistical model for big data generated from networks in a complex way. A conceptual sketch of this model is plotted in Figure 1. We employ a hidden layer of variables to model the network, and the observations are multiple samples from each node. This model is motivated by the biological process of brain networks along with indirect sampling from this network (e.g. fMRI), see Section 2 for this connection. Under this framework, we describe three goals: signal extraction, voxel clustering, and network estimation. These three goals are interwoven with each other. We thus develop a generic alternating updating algorithm for carrying out them simultaneously, see Section 3. The advantages of our method are demonstrated on the fMRI data in Section 4 and on simulated data in Section 5. We will conclude with discussion in Section 6. The technical details are postponed to Section 7.

2 A Hierarchical Graphical Model

We first collect the notations used in this paper. Let \( M = (M_{ij}) \) be any matrix. \( M_j \) stands for the \( j \)th column of \( M \), and \( M_i \) for the \( i \)th row. The following matrix norms on \( M \) will be used: \( \|M\|_2 = \sqrt{\sum_{i} \sum_{j} M_{ij}^2} \) for the Frobenius norm; \( \|M\|_1 = \sum_{i,j} |M_{ij}| \) for the \( \ell_1 \) norm. The trace and determinant of \( M \) are denoted by \( \text{tr}(M) \) and \( \text{det}(M) \) respectively. A diagonal matrix is denoted by \( \text{diag}(M_1, \ldots, M_p) \) where the diagonal entries...
Figure 1: A conceptual sketch of the HGM model with a hidden network of 3 nodes $Z_i$, $i = 1, 2, 3$. The observed data $X_{i,j}$, $j = 1, \ldots, k_i$, are the corresponding $Z_i$ plus independent noises. A similar topology of network models has been proposed in the science literature (Guimerà and Amaral, 2005; Power et al., 2013), but they assume $Z$ are observed.

$M_i$ are shortened notations for $M_{ii}$ for any $i$. The cardinality of a set $S$ is given by $|S|$.

We now introduce the formulation of our hierarchical graphical model. Without loss of generality, we assume all variables in our model are mean centered. This could be achieved by subtracting the mean for each variable first. In fMRI, the overall means across time are usually arbitrary, and such a mean centering approach is usually employed in the preprocessing pipeline.

Suppose that all the $p$ variables/columns of the observed data matrix $X$ are separated into one and only one of the $K$ disjoint group sets $G_k \subset \{1, \ldots, p\}$, $k = 1, \ldots, K$. We introduce a hierarchical variable denoted by $Z$, where each column $Z_k$ represents the hidden signal for group $G_k$. The hierarchical variable $Z$ relates to the observed variable $X$ as

$$X_{ij} = Z_{ik} + \epsilon_{ijk} \quad \text{for } j \in G_k, \ i = 1, \ldots, n, \ k = 1, \ldots, K,$$

where the noise variables $\epsilon_{ijk} \sim N(0, \phi_k)$ for each group $k$ are independent of each other and independent of all $Z$. Denote the overall error variance matrix $\Phi = \text{diag}(\phi_1, \ldots, \phi_K)$.

As discussed in the introduction, we assume that the hierarchical variable is generated from a Gaussian graphical model, with iid observations from

$$Z \sim N(0, \Sigma)$$

where the inverse covariance (or precision) matrix $\Omega = \Sigma^{-1}$. A graphical representation of this hierarchical graphical model is shown in Figure 1. An alternative interpretation is to regard hierarchical variables as “hubs” in a network (Guimerà and Amaral, 2005; Power et al., 2013), though they are not measured directly in contrast to the standard definition of hubs.

The observed $X$ under Model (1) and (2) is multivariate normal and thus can be represented by a Gaussian graphical model. It is possible to directly estimate a $p \times p$ precision matrix $\Omega_X$ of $X$ for moderate size $p$, using various methods for graphical models (Friedman et al., 2008; Cai et al., 2011; Liu and Luo, 2012). This task, however, becomes
very challenging in computation and storage at least, when \( p \) is in the size of tens of thousands. We will instead estimate a smaller precision matrix \( \Omega \) of size \( K \times K \) based on the hierarchical variable \( Z \), where \( K \) could be much smaller than \( p \). The resulting precision matrix also has an interpretation of graphical models \cite{Lauritzen1996}. The introduction of the hierarchical variable \( Z \) and the group assignment \( G \) provides additional advantages in modeling and interpretation as we will outline below.

The group assignment \( G \) allows dimension reduction of the original observed variables, from \( p \) to \( K \). This also makes the resulting network model interpretable because each node can be interpreted as a functional unit that consists of several variables. In fMRI, \( X \) is the original data where each column is a voxel, and the voxels in each \( G_k \) forms a unit commonly known as region of interest (ROI) to neuroscientists. Our approach allows \( G \) be estimated based on prior knowledge or estimated from the data by an iterative algorithm in Section 3.

The hierarchical variable \( Z \) models the underlying signal within each group \( G_k \). Given the group assignment \( G \), an popular estimate for \( Z \) is given by, for each observation \( i \),

\[
\bar{Z}_{ik} = \sum_{j \in G_k} X_{ij}, \quad \text{for } k = 1, \ldots, K. \tag{3}
\]

This is a commonly used method for extracting signals from ROIs in fMRI analysis. As we will show momentarily, our estimator of \( Z \) is different from \( \bar{Z} \) due to the underlying network structure \( \Omega \).

3 Method

3.1 Likelihood Formulation and Convexity

We introduce the approach to estimate the parameters \((Z, G, \Omega, \Phi)\) in Model (1) and (2). We consider two approaches of introducing sparsity in \( \Omega \), either via penalized likelihood \cite{Friedman2008} or sparse covariance inversion \cite{Liu2012}. Because the latter is also motivated by the penalized likelihood framework, we will focus on describing the penalized likelihood approach first, while the difference will be pointed out later. The negative log-likelihood function under our hierarchical model is, ignoring constants and scaling factors,

\[
L(Z, G, \Omega, \Phi) = \sum_{k=1}^{K} \left[ \sum_{j \in G_k} \frac{\|X_{j} - Z_{.k}\|^2_2}{(n \phi_k)} + |G_k| \log \phi_k \right] + \frac{1}{n} \text{tr} (Z \Omega Z^T) - \log \det (\Omega) + K \log (2\pi). \tag{4}
\]

To introduce sparsity on \( \Omega \), we adopt a LASSO penalty (i.e. the \( \ell_1 \) norm) approach via minimizing the following objective

\[
L(Z, G, \Omega, \Phi) + \lambda \|\Omega\|_1 \tag{5}
\]
where $\lambda > 0$ is a penalization parameter. The objective function (5) is unfortunately not jointly convex for $(Z, G, \Omega, \Phi)$, and thus it is in general a combinatorial optimization problem, partly due to the group assignment $G$. However, it is straightforward to see that, conditional on all the remaining parameters, (5) is conditionally convex for each parameter except the group assignment $G$. It is expected that the group assignment is an NP-hard problem.

**Proposition 1.** The objective function (5) is conditionally convex in $Z$, $\Omega$ and $\Phi^{-1}$ respectively, conditional on all the remaining parameters.

### 3.2 An Alternating Update Algorithm

Due to the conditional convexity in Proposition 1, we propose to solve the problem via alternating iterative updates of each parameter, where the updating step minimizes the conditional objective function. Though even the conditional minimization problem is not convex in the group assignment $G$, similar alternating procedures has been effective in practice ([Lloyd, 1982], [Forgy, 1963], [MacQueen et al., 1967], [Hartigan and Wong, 1979]). The alternating algorithm also works for updating $G$ as well.

The conditional minimization for $Z$ and $\Phi^{-1}$ are given in explicit forms in the following proposition. Though the minimization is over $\Phi^{-1}$, the solution is conveniently given in terms of $\Phi$. This is the reason that we decide to keep parameter formulation $\Phi$ instead of $\Phi^{-1}$ in this paper. The conditional minimization over $\Omega$ is equivalent to the Glasso minimization problem.

**Proposition 2.** The conditional minimizer for $Z$ is

$$Z^* = \bar{Z}D_G [D_G + \Omega \Phi]^{-1}$$

where $D_G = \text{diag} (|G_1|, \ldots, |G_K|)$. That is, $Z^*$ minimizes the following conditional minimization objective, while $(G, \Omega, \Phi)$ are fixed,

$$L_Z = \frac{1}{n} \sum_{k=1}^{K} \sum_{j \in G_k} \|X_{i,j} - Z_{.k}\|_2^2 / (n \phi_k) + \frac{1}{n} \text{tr} (Z\Omega Z^T).$$

The conditional minimizer for $\Phi$ is

$$\phi^*_k = \frac{1}{n |G_k|} \sum_{j \in G_k} \|Z_{.j} - X_{i,j}\|_2^2, \quad \text{for } k = 1, \ldots, K,$$

where the conditional objective is

$$L_{\Phi^{-1}} = \frac{1}{n} \sum_{k=1}^{K} \left[\phi^{-1}_k \sum_{j \in G_k} \|X_{i,j} - Z_{.k}\|_2^2 - |G_k| \log \phi^{-1}_k\right].$$

The conditional minimization problem of $\Omega$ is equivalent to the Glasso objective

$$L_\Omega = \frac{1}{n} \text{tr} (Z\Omega Z^T) - \log \det (\Omega) + \lambda \|\Omega\|_1.$$
We use the conditional minimizers for $Z$ and $\Phi$ as our iterative updates respectively. Because the purpose of the conditional objective $L_\Omega$ is to produce a sparse precision matrix $\Omega$, we consider two estimation approaches, Glasso, and SCIO. Glasso minimizes $L_\Omega$ exactly, and SCIO is based on the algebraic properties derived from $L_\Omega$ (Cai et al., 2011; Liu and Luo, 2012), which may have advantages especially when the distribution assumption in $L_\Omega$ is moderately satisfied (e.g. heavier tails).

The update rule for $Z$ is scaled from the classical choice $\bar{Z}$ by multiplying a matrix factor depends on all other parameters. This is due to the shrinkage effect introduced by the hierarchical variable (Lehmann and Casella, 1998), and the amount of shrinkage also depends on the covariance of $Z$ as captured by $\Omega$ and its ratio with the error variance $\Phi$. Therefore, the shrinkage theory implies that our approach is expected to yield estimates with smaller MSEs than $\bar{Z}$.

There are many ways to update $G$, see for example Lloyd (1982); Forgy (1965); MacQueen et al. (1967); Hartigan and Wong (1979). For simplicity, we use a hybrid rule for finding the group assignment $G$. In the first stage, we initialize $(Z, G)$ from Hartigan’s k-means (Hartigan and Wong, 1979) because it usually provides good clustering in practice. For the sequential alternating updates, we use a simple assignment rule suggested by Lloyd (1982); Forgy (1965); MacQueen et al. (1967), where each point is reassigned to the closest cluster center $Z_k$. Because k-means suffers from the issue of converging to a local optima, our alternating algorithm may also suffer from this issue. Thus, we consider multiple runs of our algorithm and select the one with the smallest likelihood.

The algorithm for solving our hierarchical graphical model problem is summarized in Algorithm 1. The convergence criterion for stopping the iterative updates is

$$\frac{\|Z^{(t-1)} - Z^{(t)}\|_2}{\max (1, \|Z^{(t-1)}\|_2)} < e_{tol} \quad \text{and} \quad G^{(t)} = G^{(t-1)}$$

where $e_{tol}$ is a tolerance level (e.g. $10^{-4}$), $Z^{(t)}$ is the update at iteration $t$, and similar definition for $G^{(t)}$.

### 3.3 Choice of the Tuning Parameters

Our model contains two tuning parameters, $K$ and $\lambda$. These can be chosen using either existing scientific knowledge or model selection methods. We employ the scientific choice in Section 4 and here we describe a model selection approach when such scientific knowledge is not available. The model selection approach is based on Bayesian Information Criterion (BIC), because our model yields a unified criterion

$$L_{K,\lambda} + \frac{\log p}{n} (s/2 + p + K (n + 2) - 1)$$

where $L_{K,\lambda}$ is the likelihood evaluated at the solutions produced by Algorithm 1 with the choice of $K$ and $\lambda$, and $s$ is the number of nonzeros in the off-diagonals of the solution $\Omega$. This comes from the fact that there are $K - 1$ class probabilities from $G$, $K$ variance
Algorithm 1 An alternating update algorithm for estimating hierarchical graphical models.

Initialize: \((Z^{(0)}, G^{(0)}, \Omega^{(0)}, \Phi^{(0)})\), \(t = 0\).
Repeat until the convergence criterion is met:

1. Given \((Z^{(t)}, G^{(t)}, \Omega^{(t)}, \Phi^{(t)})\), update \(Z^{(t+1)} = \overline{ZD_{G^{(t)}}[D_{G^{(t)}} + \Omega^{(t)}\Phi^{(t)}]}^{-1}\).

2. Given \((Z^{(t+1)}, G^{(t)}, \Omega^{(t)}, \Phi^{(t)})\), update \(\phi_k = \frac{1}{n_{|G_k|}} \sum_{j \in G_k} \|Z_k - X_{j}\|_2^2\) for \(k = 1, \ldots, K\).

3. Given \((Z^{(t+1)}, G^{(t)}, \Omega^{(t+1)}, \Phi^{(t+1)})\), update \(\Omega^{(t+1)}\) by a precision matrix estimation method (either Glasso or SCIO).

4. Given \((Z^{(t+1)}, G^{(t)}, \Omega^{(t+1)}, \Phi^{(t+1)})\), update \(G^{(t+1)}\) such that it minimizes (5).

5. Update \(t = t + 1\).

Estimates from \(\Phi\), \(K\) estimates from \(Z\), \(s/2 + p\) nonzeros from \(\Omega\). The tuning parameter \(\lambda\) controls the number of nonzeros in \(\Omega\), and one can perform a grid search on \(\lambda\) first to pick the optimal value. The tuning parameter \(K\) controls the number of clusters. One then compare the optimal BIC values from the previous step with different choices of \(K\), and choose the \(K\) that produces the smallest BIC overall.

4 A fMRI Study on Motor Prohibition

We use an fMRI dataset (Xue et al., 2008) to illustrate the effectiveness of HGM. This dataset is publicly available from Open fMRI (https://openfmri.org/data-sets) under the accession number ds000007. This whole dataset consists of 20 subjects scanned under several sessions, with different kinds of stop/go event tasks. For the illustration purpose, we analyze the session 1 data of subject 1.

We employ the same preprocessing procedure using the FMRIB software library (FSL, available from http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/), as suggested by the authors (Xue et al., 2008). Briefly, this procedure includes slice timing correction, alignment, registration, normalization to the average 152 T1 MNI template, and smoothed with a 5mm full-width-half-maximum Gaussian kernel. The data are denoised using FSL MELODIC and a high pass filter with a 66s cut-off. After preprocessing, general linear models (GLM) for each voxel (Friston et al., 1994) are used to remove the non-stationary components, including motion correction and event-related activation. The standardized GLM residuals are retained for our HGM analysis, because they are stationary, similar to resting-state fMRI (Fair et al., 2007).

The resulting dataset consists of the residual bold activity from 230,590 voxels in 180 time points, or equivalently an input matrix \(X\) with \(n = 180\) and \(p = 230,590\). To make
each variable in $X$ comparable, we standardize each one to have mean zero and unit variance. To illustrate the complex networks that can be recovered by HGM, we fix $K = 200$ and $\lambda = 0.5$, because these choices roughly matches the number of brain parcellations usually used in neuroscience, and the resulting network has interesting scientific interpretations. Other choices can be taken depending on the scientific goals. For example, larger $K$ will give finer parcellations of the brain, smaller $\lambda$ usually yields densely connected networks, and vice versa.

To avoid local minima due to group assignments, our HGM algorithm (Algorithm 1) is repeated 10 times with random starts. More number of repeats are allowed if more computing resources are available, but we find that 10 repeats are sufficient and the parcellations are stable across runs, see Section 5 for a simulation evaluation as well. The repeat with the smallest negative loglikelihood is reported in Figure 2. The voxel groups shows some symmetry between left and right hemispheres, though this is not imposed in HGM. This approximate bilateral symmetry coincides with classic theory of (approximately) mirrored functions of the two hemispheres. We thus are inclined to postulate that the HGM grouping recovers different sources of brain functions. It is challenging to visualize all the resulting voxel groups and their connections in (B), and we thus examine one group in detail.

The region preSMA (anterior part of supplementary motor area) has been shown to play an important role during stop/go trials [Duann et al., 2009], and it is tagged as group 1 by HGM. Note that the group index numbers are arbitrary. We examine the overlays of big voxel clusters ($\geq 100$ voxels) in group 1 and three other directly or indirectly connected groups, see Figure 3. The detailed coordinates and cluster sizes are included in the supplemental information of this paper. Each group may contain multiple regions clustered together, and most of them are closely located in the brain and mirrored on both left

Figure 2: Recovered voxel groups (A) and network edges (B) by HGM. (A) voxel groups are indexed by color, overlaid on the average 152 T1 MNI template. (B) Connections between two groups are shown in black entries in the matrix, where the two groups are given by the row and column index colors respectively; no connections are shown in white.
and right hemispheres. Some of these clusters have been indicated in correlation analysis (Zhang et al., 2012), but HGM is able to differentiate direct and indirect connections. For instance, the connection between preSMA and rIFC have been studied before using only a small number of brain regions (Duann et al., 2009), and here the whole brain HGM confirms such connection is direct. Insula activation has been implicated in a previous study (Luo et al., 2013), and it was found to correlate with preSMA (Zhang et al., 2012). The HGM result, however, recovers a group of anterior insula and rIFC. This yields an interesting question of whether the insula correlation is a consequence or cause of the direct connectivity between rIFC and preSMA. Our HGM result also suggests that the insula grouping depends on the anterior and posterior positions, consistent with the findings of another study (Jakab et al., 2012). Finally, the HGM group 1 contains two far regions, preSMA and superior part of cuneus (or Brodmann area 19, superior), which is believed to be related to motion-related visual processes. Their possible connection has also been indicated by an ICA study (Sauvage et al., 2011), and these findings invite further investigation of this region.

5 Simulations

We assess the performance of HGM using the following simulation model. The hierarchical variable $Z$ are 180 iid samples from mean zero multivariate normal with a $200 \times 200$ precision matrix $\Omega^*$. The precision matrix is block diagonal with block size 5 where each block has off-diagonal entries equal to 0.8 and diagonal 1. The order of nodes are then randomly permuted. A similar precision matrix has been used before (Liu and Luo, 2012).

In each run, each column of $Z$ is added by 50 noise vectors respectively to generate 50 columns of $X$ within the same group, and this yields the observed matrix $X$ of dimension $180 \times 10,000$. The simulation parameters ($n = 180$, $p = 10,000$, $K = 200$) are similar to the scale of the fMRI data. All simulations are repeated 50 times.

5.1 Network Estimation

It is difficult compare results with different group assignments $G$. We first consider the true $G$ is given to our HGM algorithm, and we don’t perform the group update step in Algorithm 1. We compare two methods to estimate the precision matrix $\Omega$, SCIO and Glasso. Both methods contain a tuning parameter controlling the sparsity of the matrix, and thus we compare the receiver operating characteristics (ROC) curves on identifying the network edges. Overall, our HGM algorithm with both methods (HGM-SCIO, HGM-Glasso) has good performance, and HGM-SCIO clearly outperforms HGM-Glasso, see Figure 4. When the tuning parameter $\lambda$ is chosen by BIC for both methods, HGM-SCIO also has higher sensitivity than HGM-Glasso, while maintaining high specificity.
Figure 3: The overlays of voxel groups on the average 152 T1 MNI template, for the preSMA group (group 1) recovered by HGM, two directly connected groups (134, 200), and one group (group 66) connected to the previous two groups. The group index numbers are arbitrary. preSMA: anterior part of supplementary motor area; rMTG: right middle temporal gyrus, or Brodmann area 22; insula-a: anterior insula; insula-p: posterior insula; rIFC: right inferior frontal cortex; sC: superior cuneus, or Brodmann area 19; STG: superior temporal gyrus; TT-p: posterior transverse temporal, or Brodmann area 42; L: left; R: right.
Figure 4: Average receiver operating characteristics on estimating the network edges by embedding SCIO (red solid line) and Glasso (blue dash line) estimators in the HGM algorithm, averaged across 50 runs. The sensitivity and specificity values in the first 15 runs with BIC tuned $\lambda$ are overlaid by red circles (HGM-SCIO) and blue triangles (HGM-Glasso). HGM-SCIO: HGM with SCIO embedded; HGM-Glasso: HGM with Glasso embedded.
5.2 Group Estimation

To assess the group assignment accuracy, we use the following simple measure, coherence rate, for comparing each estimated $\hat{G}$ and the true group $G$,

$$r_k = \max_i \frac{\left| \hat{G}_i \cap G_k \right|}{|G_k|}, \quad k = 1, \ldots, K. \quad (6)$$

For each run, we initialize with 10 different initial group assignments, and retain the $\hat{G}$ from the model with the maximum likelihood. Due to the symmetry of our simulated groups, we pool the coherence measures from different $k$ across 50 runs. By this measure, the HGM is stable with varying choices of $\lambda$, and 89% of the coherence rates equal to 1 exactly, showing the high accuracy of group estimation in HGM.

6 Discussion

The interpretation of connectivity in HGM should be treated with caution. It has been well known that fMRI bold signals are confounded by varying hemodynamic processes across the brain, and thus the connectivity should be interpreted on the bold level. Moreover, the spatial resolution of fMRI is insufficient for inferring neuronal connections. Thus direct connections in HGM should not be regarded as direct neuronal connections.

There are several possible hypotheses for the voxel grouping. One may conjecture that smoothness may play a part, and thus nearby voxels will be grouped together. However, this is not completely the case as we observe long-range connections in HGM. We are inclined to hypothesize that the grouping is mostly due to close brain functions. Certainly nearby voxels may share similar brain functions. By grouping, HGM also provides two levels of interpretation: one on how one group is connected to another, and the other on how brain regions are grouped. It is interesting to investigate the biological and graph theoretical foundations of these two levels.

The theoretical aspects of HGM are not developed here. Though there is finite sample theory concerning the precision matrix estimation (Cai et al., 2011; Liu and Luo, 2012), the assumptions are difficult to test in fMRI. We provide the HGM model only as an interpretable approximation to the underlying processes in the brain, and it does not necessarily truly models the neuronal processes as discussed before. Therefore, it makes even harder to study the theory of HGM under testable assumptions for fMRI.

The distribution assumptions can be relaxed. Even if the distribution of $Z$ has heavier tails, the resulting convergence rates on estimating $\Omega$ does not change much based on modified Gaussian graphical model methods (Cai et al., 2011; Liu and Luo, 2012). More general distributions by using nonparametric covariance estimates (Lafferty et al., 2012). It will be interesting to explore these nonparametric approaches.

The independent assumption in $Z$ can also be replaced with a matrix normal distribution (Leng and Tang, 2012) to describe temporal dependence. In our application example, the
Figure 5: Boxplots of the coherence rates with varying $\lambda$ over 50 runs for all groups. Over 89% of the coherence rates equal to 1 exactly across all choices of $\lambda$. 
whitening step in preprocessing may reduce such dependence. It is also interesting to
develop spatio-temporal models to validate this assumption, such as Kang et al. (2012).

Several extensions of HGM are possible. For instance, one may consider modeling the
probability of group assignments for each voxel. One may consider studying the group-level
HGM from multiple subjects and sessions, either by embedding HGM in mixed models or
by the group Lasso penalty (Yuan and Lin, 2006). One may also consider incorporating
the distance between voxels to help group assignments, but it should be pointed out that
the choice of metric may be challenging. For example, Euclidean distance is usually not a
good choice of metric for voxels (Bowman, 2014). We will leave these directions to future
research.

7 Proofs

The proof of Proposition 2 implies the proof of Proposition 1, and thus the latter is omitted.

The terms in $L$ that are relevant to $Z$ are, ignoring other factors irrelevant of $Z$,

$$
L_Z = \sum_{k=1}^{K} \sum_{j \in G_k} \| X_j - Z_k \|^2_2 / (n \phi_k) + \frac{1}{n} \text{tr} \left( Z \Omega Z^T \right).
$$

The derivative of $L_Z$ with respect to $Z_k$ is proportional to

$$
Z D_G \Phi^{-1} + Z \Omega - Z D_G \Phi^{-1}.
$$

Multiplying the derivative by nonsingular $\Phi$, solve $Z$ that sets the product zero to yield
the minimizer

$$
Z = Z D_G \left[ D_G + \Omega \phi \right]^{-1}.
$$

Similar to the derivation of the minimizer for $Z$, the conditional objective function is

$$
L_{\phi^{-1}} = \frac{1}{n} \sum_{k=1}^{K} \left[ \phi_k^{-1} \sum_{j \in G_k} \| X_j - Z_k \|^2_2 - |G_k| \log \phi_k \right].
$$

(7)

the derivative with respect to $\phi_k^{-1}$ equals to, for every $k$,

$$
\frac{1}{n} \sum_{j \in G_k} \| X_j - Z_k \|^2_2 - |G_k| \phi_k.
$$

The solution that sets the derivatives to zero is, for every $k$,

$$
\phi_k = \frac{1}{n |G_k|} \sum_{j \in G_k} \| Z_k - X_j \|^2_2.
$$

(8)

Finally, the terms relevant to $\Omega$ in $L$ are

$$
L_\Omega = \frac{1}{n} \text{tr} \left( Z \Omega Z^T \right) - \log \det (\Omega) + \lambda \| \Omega \|_1,
$$

(9)

and the minimization is thus equivalent to a Glasso problem.
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