FMRI GROUP STUDIES OF BRAIN CONNECTIVITY VIA A GROUP ROBUST LASSO

Xiaohui Chen¹, Z.Jane Wang¹, Martin J. McKeown²

1. Department of Electrical and Computer Engineering, 2. Department of Medicine (Neurology), University of British Columbia, Canada.
Email: xiaohuic,zjanew@ece.ubc.ca, mmckeown@interchange.ubc.ca

ABSTRACT

Inferring effective brain connectivity from neuroimaging data such as functional Magnetic Resonance Imaging (fMRI) has been attracting increasing interest due to its critical role in understanding brain functioning. Incorporating sparsity into connectivity modeling to make models more biologically realistic and performing group analysis to deal with inter-subject variability are still challenges associated with fMRI brain connectivity modeling. To address the above two crucial challenges, the attractive computational and theoretical properties of the least absolute shrinkage and selection operator (LASSO) in sparse linear regression provide a suitable starting point. We propose a group robust LASSO (grpLASSO) model by combining advantages of the popular group-LASSO and our recently developed robust-LASSO. Here group analysis is formulated as a grouped variable selection procedure. Superior performance of the proposed grpLASSO in terms of group selection and robustness is demonstrated by simulations with large noise variance. The grpLASSO is also applied to a real fMRI data set for brain connectivity study in Parkinson’s disease, resulting in biologically plausible networks.

Index Terms— Sparse linear regression, group LASSO, robustness, fMRI, brain connectivity, group analysis.

1. INTRODUCTION

Studying brain connectivity is crucial in understanding brain functioning and can provide significant insight into the pathophysiology of a number of neurological disorders. Increasingly, inferring brain connectivity using functional Magnetic Resonance Imaging (fMRI) is being explored, and many mathematical formalisms, such as structural equation modeling (SEM) [1], multivariate autoregressive models (mAR) [2], dynamic causal modeling (DCM) and dynamic Bayesian networks (DBNs) [3] have been proposed. Despite significant progress during the last decade, there are still a number of challenges associated with inferring brain connectivity from fMRI.

One is the curse of complexity with the above SEM and/or mAR approaches when dealing with practical fMRI data sets where the number of brain regions-of-interest (ROIs) is relatively large and the number of time points is limited. Based on a number of neuroscience studies, the connections between brain regions generally can be considered a priori to form a sparse network, suggesting that sparsity should be incorporated into brain connectivity modeling. For instance, sparse mAR models were studied in [4] where the parameters are estimated using penalized regression. Group analysis of effective brain connectivity has long been another challenging topic, since biomedical research is usually conducted at a group level to extract the population features. Efficient group analysis requires appropriate handling of expected inter-subject variability without destroying inter-group differences. To address the above two crucial challenges, this paper aims at developing a novel, computationally-efficient brain connectivity model that incorporates both sparsity and suitable group analysis.

Several methods for meaningfully extracting group information from fMRI data have been proposed. The common structure (CS) model in the DBNs context [3] enforces the same graphical structure for all subjects within a given group, but the connection coefficients are allowed to vary on a subject-by-subject basis. However, CS inference based on DBNs inevitably requires computationally-intensive algorithms such as the Markov Chain Monte Carlo (MCMC). Another proposed method is that of Bayesian group analysis [5] where several possible model structures are considered and the posterior evidence of models for each subject is estimated. Here we present a different group linear regression model to perform group analysis while incorporating the sparsity principle. More specifically, we adopt the modeling concept on the CS level – whereby brain connections generating the fMRI observations are assumed to be structurally identical among subjects within the same group, but individual connection parameters are allowed to vary between subjects – and propose a group robust LASSO framework to perform group analysis. There are several advantages associated with the proposed novel framework:

1. The proposed model is based on the optimization of a convex objective function and thus is computationally more efficient than graphical modeling approaches such as DBNs.
2. The proposed model represents a unified framework whereby group analysis is based on networks learned directly from the time courses in fMRI data.
3. The proposed model is robust against large variance noise and outliers.

Remark 1. We note that the proposed group robust LASSO approach to infer brain connectivity networks is not based on inverse covariance selection. Nonetheless, this marginal neighborhood selection procedure has been shown to be a consistent variable selection method for constructing a Gaussian graphical model under certain regularity conditions [6].

2. METHODS

2.1. A Group Robust LASSO Model

We propose inferring brain connectivity through a linear regression approach. The Blood Oxygen Level Contrast (BOLD) signal inten-
subjected to the corruption by certain noise: 
\[ y = X\beta + e. \] (1)

Here \( y \) is a response vector, \( X \) is a design matrix with columns representing predictors, \( \beta \) is a coefficient vector, and \( e \) is a zero-mean random error vector which is assumed to have independent and identically distributed (i.i.d.) elements with a common finite variance, \( \sigma^2 \). We consider the situation where the number of potential predictors is large while the number of \textit{bona fide} predictors with non-zero coefficients are only a small fraction of the total. Thus, the goal is to determine the correct underlying sub-model. The LASSO [7] is a popular linear model selection tool that continuously shrinks coefficients to zeros. The LASSO is a regularized linear model and minimization of its penalized squared \( \ell_2 \) loss is known to promote sparsity on the coefficient vector. Nevertheless, the LASSO solution can be unsatisfactory for group analysis because its selection of a predictor is relatively independent of each other and therefore the LASSO estimator in unable to incorporate the potential similarity of structures across subjects. Yet for group analysis, we have certain structural grouping information that is available to us as \textit{a priori}, e.g. the subjects within the same group are assumed to share the same connectivity structure. Therefore, \( \beta \) is composed of \( G \) groups each of which contains \( p_g \) individual coefficients for \( g \in \{1, \cdots, G\} \). In matrix notation, \( \beta = (\beta_1^T, \cdots, \beta_G^T)^T \), and \( X = (X_1, \cdots, X_G) \) is a block design matrix of dimension \( n \times \sum p_g \). With this notation, we can refer to \textit{grouping selection} to mean that the sparsity is promoted at the group level, i.e. corresponding subject-specific coefficients within one group are either all non-zeros or all zeros. Thus the LASSO is a special case of the group version when \( p_g = 1 \) for all \( g \).

To promote sparsity at the group level, we choose to minimize the following objective function:
\[
 f(\beta) = L(\beta; y, X) + \lambda_n \sum_{g=1}^G \| \beta_g \|_{\ell_2} \] (2)

where \( L(\cdot) \) can be any cost function. Unlike the \( \ell_1 \) penalty in the LASSO, summation of block Euclidean norms (a.k.a. blocked \( \ell_1 \) norm) in the penalty term encourages grouping selection [8]. The group LASSO is a the special case where \( L \) is the standard squared \( \ell_2 \) loss [9]. More generally, we can adopt robust losses that are less sensitive to noise that includes large variability or even outliers. For instance, the convex combination of \( \ell_1 \) and squared \( \ell_2 \) losses [10] or the Huber loss [11] coupled with the block \( \ell_1 \) regularization yields a group robust LASSO. In this paper, we propose a group robust LASSO by using the convex combined loss with a robustness tuning parameter \( \delta \in [0, 1] \)
\[
 L(\beta; y, X) = (1 - \delta) \| y - X\beta \|_{\ell_1} + \delta \| y - X\beta \|_{\ell_2}^2 . \] (3)

The group LASSO is thus a reduced case when \( \delta = 1 \). In general, a smaller \( \delta \) gives more robustness. In the case of robust LASSO \((p_g = 1, \forall g)\), the asymptotic behavior of its estimator has been studied in [10] where it is shown therein that the asymptotic variance is stabilized. Furthermore, the robustness tuning parameter can be chosen by the minimal asymptotic variance criterion when the error distribution is known. The proposed group robust LASSO estimator is defined to be any minimizer of (2), i.e. \( \arg \min_{\beta} f(\beta) \). Note that there is a corresponding model for each \( \lambda_n \), so determining a proper shrinkage amount is important to make the subsequent inference. The optimal shrinkage parameter \( \lambda_n \) is determined by the BIC which is computed as follows: we first solve for the group robust LASSO for a fixed \( \lambda_n \). Once the model is determined, we fit the corresponding subset of data to the selected model by unregularized least squares. We then obtain an estimator of \( \beta \) with the shrinkage effect removed. An estimator of \( \sigma^2 \) is given by the maximum likelihood 
\[
 \sigma^2 = \frac{L(\hat{\beta}; y, X)}{(2 - \delta)n} . \]

The estimator \((\hat{\beta}, \hat{\sigma}^2)\) is called the Gauss group robust LASSO estimator which corrects for the bias of underestimating non-zero coefficients and thus is more suitable for accurate estimation. Note that the likelihood under which \( \beta \) is computed is assumed to be Gaussian (equivalent to the least squares estimator) while the likelihood to estimate the variance, \( \sigma^2 \), is a blend of Gaussian(\( (0, \sigma^2) \) and Laplace(\( 2\sigma^2 \)) distributions.

Now the BIC can be calculated from the Gauss group robust LASSO estimate
\[
\text{BIC} = -2 \log\text{-likelihood}(\hat{\beta}, \hat{\sigma}^2) + k \log(n) = \frac{1 - \delta}{\sigma^2} \| y - X\hat{\beta} \|_{\ell_1} + \delta \| y - X\hat{\beta} \|_{\ell_2}^2 + 2(1 - \delta)n \log(4\hat{\sigma}^2) + 2\delta n \log(\hat{\sigma}^2) + k \log(n) \] (4)

where \( k \) is the number of predictors in the selected model. Finally, the optimal model is chosen by the minimal BIC value among the set of different shrinkages.

To summarize, proposed procedure contains the following steps:
1. Choose a set of shrinkage parameters \( \lambda_n \). Run the group robust LASSO for each shrinkage.
2. For each shrinkage, identify the non-zero coefficients and use this submodel to compute \((\hat{\beta}, \hat{\sigma}^2)\).
3. Compute BICs using estimates from step 2 and choose the model corresponding to the minimal BIC value as the optimal model.

We use the group robust LASSO as a model selection tool and estimate parameters based on the selected model. We refer this (variant) Gauss group robust LASSO as the \textit{grpRLASSO} in this paper unless otherwise indicated.

2.2. A group sparse SEM+mAR(1) model

The brain connectivity model we assume has a \textit{unified} SEM framework that captures both spatial and temporal brain connections, where we combine the standard SEM model [1] (to represent the relations considered instantaneous at the temporal resolution of fMRI) and the 1\textsuperscript{st}-order mAR model [2] (to represent longitudinal temporal relations). Suppose there are \( p \) ROIs and the brain is MRI scanned at time \( 1, \cdots, T \). We also assume that there are \( S \) subjects belonging to \( G \) groups. Denote by \( y_{s,j} \) the fMRI measurement vector of the \( j \)-th ROI of subject \( s \), for \( j \in \{1, \cdots, p\} \) and \( s \in \{1, \cdots, S\} \), as the response variable.

Before introducing the group SEM+mAR(1) model, we introduce a few useful notations first. For the \( s \)-th subject, let \( Y_{s}^{(0)} \) be the \((T - 1) \times p \) matrix with the \( j \)-th column containing the fMRI measurements of the \( j \)-th ROI from time 2 to \( T \), and let the \((T - 1) \times p \) matrix \( Y_{s}^{(1)} \) be the time-shifted version of \( Y_{s}^{(0)} \) with lag 1. \( Y_{s,j}^{(1)} \)
RLASSO
grpRLASSO
Oracle

<table>
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<th>LASSO</th>
<th>RLASSO</th>
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<td>(1.63)</td>
<td>(5.33)</td>
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Table 1. MSEs for the estimated coefficients with their standard deviations shown in brackets. grpLASSO abbreviates for the group LASSO, RLASSO for the robust LASSO with the convex combined loss, and grpRLASSO for the group robust LASSO. Oracle is the maximum likelihood estimate (for the Gaussian likelihood) obtained from the model with knowing the true non-zero locations.

denotes the $(T - 1) \times (p - 1)$ matrix with the $j$th column $y_s,j$ being removed. With these notations, for each subject $s \in \{1, \cdots, S\}$, we have the following SEM+mAR(1) model:

$$
y_{s,j} = \sum_{t \in \{0, 1\}} Y_t^{(0)} S_{s,j}^{(t)} + e_s
$$

where $e_s$ means the error vector for each subject $s$, and $\beta_{s,j}^{(0)}$ and $\beta_{s,j}^{(1)}$ represent respectively the SEM and mAR connection strength coefficients to be estimated.

Putting all subjects together and rewriting in matrix form, we can reach the ambient linear regression model (6) with a block diagonal design matrix $X$ and a coefficient vector $\beta$ with a group structure.

$$
\begin{pmatrix}
  y_{1,j} \\
  y_{2,j} \\
  \vdots \\
  y_{S,j}
\end{pmatrix} = \text{diag} \begin{pmatrix}
  (Y_1^{(0)}, Y_2^{(1)})_{s=1}^S
\end{pmatrix} \beta + e
$$

where

$$
\text{diag} \begin{pmatrix}
  (Y_1^{(0)}, Y_2^{(1)})_{s=1}^S
\end{pmatrix} =
\begin{pmatrix}
  Y_{1,-j}^{(0)} & Y_1^{(1)} \\
  Y_{2,-j}^{(0)} & Y_2^{(1)} \\
  \vdots & \vdots \\
  Y_{S,-j}^{(0)} & Y_S^{(1)}
\end{pmatrix}
$$

Now for each target ROI $j$, the proposed grpRLASSO can be applied to (6) to learn a sparse coefficient vector with grouping structures. Brain connectivity networks are constructed by enumerating all the ROIs and our network analysis is based on the learned grpRLASSO coefficient matrices.

3. A SIMULATION EXAMPLE

A synthetic example is used to demonstrate empirical evidence for the improved detection and estimation performance of the proposed grpRLASSO over the group LASSO, LASSO, and robust LASSO. A design matrix containing 400 observations and 200 predictors is realized from a Gaussian Ensemble in each synthetic data set. The true sparse coefficient vector $\beta^0$ is set to have a block structure. That is, $\beta^0$ contains three blocks of non-zero coefficients of different magnitudes ($1.5$, $-3$, and $2$, respectively) distributed in intervals located in $[20, 30]$, $[90, 95]$, and $[180, 188]$, respectively. The shrinkage amount is set on an evenly spaced grid over $[0, 2000]$. BIC (4) is used to choose the optimal model. The error $e$ is simulated from a Student-t distribution with parameters $\nu = 3$ and $\sigma^2 = 9$ so that it has a variance 27.

The mean squared errors (MSEs) computed from 100 simulations are shown in Table 1. We note that the grpRLASSO achieves the same performance as when the non-zero locations are known in advance (the “oracle property”). Hence, this implies that the proposed grpRLASSO is very accurate and robust in terms of both model selection and parameter estimation. In contrast, the group LASSO model has a very large MSE, even worse than the LASSO. This is not surprising after a careful investigation on the nature of a grouping variable selection tool. Suppose that if the group LASSO falsely identifies a non-zero coefficient, then the rest elements in the group are all non-zeros which render a high estimation error. In contrast, since selection procedure of the LASSO is independent among predictors, incorrect selection of one variable has little influence on others.

4. FMRI GROUP ANALYSIS IN PARKINSON’S DISEASE

In this section, we apply the grpRLASSO to a fMRI data collected from subjects with and without Parkinson’s disease (PD) and report the group analysis results of the learned brain connectivity networks.

4.1. Data description

fMRI scans for ten normal people and eight subjects with PD were collected in the study. Subjects were asked to continually squeeze a bulb in their right hand to control an inflatable ring so that the ring moved through an undulating tunnel without touching the sides. PD subjects performed the same task after been withdrawn from their L-dopa medication for 12hrs. Images were acquired at a sampling rate of 0.5Hz and a trial lasted for five minutes so that 150 data points were obtained for each subject.
SMA) and SMA)). Second, there appeared to be a left GLP). This GLP), R PUT) → THA. Presumably the connections between regions SMA and right thalamus (R PUT) may reflect that these regions become entrained in oscillations which were connections between the right prefrontal cortex (R PFC) and frontal regions on the opposite side of the brain. Third, there connections between homologous (Fig.1) provide a mechanism through which PD subjects in both networks with significantly different means (t-test with size 0.05).

4.2. Learned brain connections

The robustness tuning parameter δ is fixed to 0.5. It is worth noting that this parameter can be further optimized if required [10]. For each target ROI, there are 35 possible directed edges pointing to it, 17 from SEM and 18 from mAR(1). Since we have the normal (10 subjects) and PD off-medication (8 subjects), a linear regression model for each target node has $2 \times 35 = 70$ groups partitioning the total 630 coefficients.

Generally speaking, the (robust) LASSO networks yielded many more connections that are inconsistent among subjects within a group. Hence they are less useful for group studies and not reported further. The network learned from grpRLASSO for the normal group is shown in Fig.1 and the difference between the normal and PD group networks is shown in Fig.2. Edges shown in Fig.1 have significant non-zero coefficients with a t-test (against zero mean) of size 0.05. There are four main findings of biological significance. First, as seen in Fig.1, there were many reciprocal connections between homologous regions in both groups (e.g. left supplementary motor area (L_SMA) ↔ right supplementary motor area (R_SMA)). Second, there appeared to be a left ↔ right shift in the regions active when comparing normal subjects to PD subjects, despite the fact that all subjects were using their right hand during the motor task. For example, while normal subjects recruited the R_SMA and right thalamus (R_THA), PD subjects recruited the L_SMA and L_THA. Presumably the connections between regions homologous (Fig.1) provide a mechanism through which PD subjects can recruit regions on the opposite side of the brain. Third, there were connections between the right prefrontal cortex (R_PFC) and right caudate (R_CAU) in normal subjects that were missing in PD subjects. This likely reflects alterations in the secondary dopaminergic pathway to medial prefrontal regions known to be affected in PD [12]. Fourth, there was enhanced connectivity within basal ganglia regions (e.g. right putamen (R_PUT) → right globus pallidus (R_GLP), R_THA → L_PUT, right caudate (R_CAU) → R_GLP). This may reflect that these regions become entrained in oscillations which might enhance the functional connectivity observed with fMRI [13].

5. CONCLUSIONS AND DISCUSSIONS

We presented in this paper a group robust LASSO (grpRLASSO) framework for inferring group-level, sparse brain connectivity networks. A simulation example suggested that the proposed grpRLASSO can accurately and robustly estimate a grouped coefficient vector. The proposed grpRLASSO was applied to fMRI obtained from subjects with and without PD, and found significant group differences in biologically plausible regions. We suggest that the proposed method provides a computationally-efficient means to infer group brain connectivity from fMRI data.

References