Addressing Batch Effects in the Covariance Structure of Neuroimaging Data

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1   Introduction

For this project, we evaluate the potential for existing harmonization techniques to address batch effects in covariance structures as well as potentially develop methods better suited to this problem. This investigation stems from the rise of large-scale resting-state fMRI (rsfMRI) studies, which necessitate involvement of multiple sites to obtain an adequate sample. These studies contribute to better understanding of functional connectivity, which is a covariance-based summary metric capturing the functional relationship between brain regions. In this report, we summarize how ComBat can be applied to functional connectivity data as well explain how existing methods could be adapted as alternative harmonization methods.

2   Connectivity Data Structure

Resting-state fMRI data from a single subject is used to generate the functional connectivity matrix via three key steps. First, the rsfMRI data is preprocessed to account for subject head motion, confounding signals, as well as other issues common in fMRI data. Then, a region of interest (ROI) atlas is used at each time point to aggregate voxel intensities into distinct brain regions, enabling easier interpretation as well as a lower dimensional representation. Yu et al. (2018) suggests that the Power atlas is a better choice than the AAL and Gordan atlases for reduced site effects as well as better analyses of biological variability following harmonization. Treating each ROI intensity for each time point as separate observations, functional connectivity between two ROIs is then just the sample Pearson correlation between them.

For this literature review, we focus on the problem of having multiple subjects across different sites, each with their own connectivity matrix. Assume there are N subjects, M sites, and B regions of interest so that the connectivity matrices Σ_{ij}, $i = 1, 2, \ldots, M$, $j = 1, 2, \ldots, N$ are each $B \times B$ symmetric matrices with entries taking values between -1 and 1 inclusive. The goal is to remove site effects from these matrices.

3   ComBat for Functional Connectivity

Fortin et al. (2017) introduced the use of ComBat for harmonization of diffusion tensor

images then shortly after Yu et al. (2018) adapted it for functional connectivity matrices via vectorization of the matrices. This method can be formulated as follows. Let y_{ijv} be the distinct entries in the vectorized Σ_{ij} matrices, such that the index v takes values up through the number of upper triangular elements in the original matrix, $v = 1, 2, \ldots, \frac{B^2 - B}{2}$. Then the ComBat model is formulated as

$$y_{ijv} = \alpha_v + X_{ij}^T \beta_v + \gamma_{iv} + \delta_{iv} \epsilon_{ijv}$$

where α_v is the mean connectivity value for the vth value in the connectivity vector, X_{ij} is the design matrix for subject j in site i, β_v is the vector of regression coefficients for the covariates on the vth connectivity value. We assume that the error terms ϵ_{ijv} are normally distributed with mean 0 and variance σ_v^2. The remaining variables γ_{iv} and δ_{iv} are the additive and multiplicative site effects of the ith site on the vth connectivity value. Fortin et al. (2017) explains that these terms are estimated using an empirical Bayes framework assuming that $\gamma_{iv} \sim N(\gamma_i, \tau_i^2)$ and $\delta_{iv}^2 \sim \text{Inverse Gamma}(\lambda_i, \theta_i)$. The estimates are then the conditional posterior means, γ_{iv}^* and δ_{iv}^*. After obtaining those estimates, the ComBat-harmonized connectivity matrices Σ_{ij} are then just reconstructed from

$$y_{iv}^{ComBat} = \frac{y_{iv} - \hat{\alpha}_v - X_{ij}^T \hat{\beta}_v - \gamma_{iv}^*}{\delta_{iv}^*} + \hat{\alpha}_v + X_{ij}^T \hat{\beta}_v$$

Yu et al. (2018) tested their method on the EMBARC dataset and found that it seemed to remove site effects while preserving correlations between age and functional connectivity metrics. However, the method ignores the connectivity data structure by treating each value as separate from each other, when in reality there are inherent relationships between them since a single ROI has multiple connectivity values with other ROIs. We postulate that there may be other harmonization approaches that take the data structure into account and also can remove site effects from functional connectivity observations.

4 Population Value Decomposition

Proposed by Crainiceanu et al. (2011), population value decomposition presents an intriguing framework that may be adaptable to the setting under investigation. In their original formulation, they assumed that for a sample of $F \times T$ matrices Y_i, $i = 1, 2, \ldots, n$

$$\mathbf{Y}_i = \mathbf{P}\mathbf{V}_i\mathbf{D} + \mathbf{E}_i$$

This resembles a regular singular value decomposition (SVD); however, $\mathbf{P}$ and $\mathbf{D}$ are shared across the population instead of specific to each observation. In the case we consider for this review, the $b \times b$ matrices of interest Σ_{ij} are symmetric so the population value decomposition model is instead

$$\Sigma_{ij} = \mathbf{P}\mathbf{V}_{ij}\mathbf{P}^T + \mathbf{E}_{ij}$$

where $C \times C$ matrices $\mathbf{V}_{ij}$ are subject-specific coefficients, the $B \times C$ matrix $\mathbf{P}$ is the population-specific framing, and $\mathbf{E}_{ij}$ are the $B \times B$ residual matrices. Following the original paper, we can easily obtain the matrices $\mathbf{V}_{ij}i$ once $\mathbf{P}$ is obtained. And we can also adapt

the original paper to obtain $\mathbf{P}$ by first obtaining SVDs for each of the nm observations denoted $\Sigma_{ij} = \mathbf{U}_{ij}\mathbf{A}_{ij}\mathbf{U}_{ij}$ then forming a matrix $\mathbf{U}$ by binding some portion the columns of each individual SVD. The matrix $\mathbf{P}$ is then obtained by finding the main directions of variation among all these column vectors in $\mathbf{U}$, which can be achieved by taking the first C eigenvectors obtained by principal component analysis of $\mathbf{U}\mathbf{U}^T$.

In its original form, this method acts mainly as a tool for dimension reduction by representing a potentially very large connectivity matrices as a smaller matrices $\mathbf{V}_{ij}$ with a population-wide framing defined by $\mathbf{P}$. We hope to explore the possibility that the model can be adapted to account for site effects, say by adding a site-specific framing denoted $\mathbf{D}_i$ incorporated via

$$\Sigma_{ij} = \mathbf{P}\mathbf{V}_{ij}\mathbf{P}^T + \mathbf{D}_i\mathbf{W}_{ij}\mathbf{D}_i^T + \mathbf{E}_{ij}$$

which could then be used to obtain harmonized connectivity matrices as $\Sigma_{ij}^H = \Sigma_{ij} - \mathbf{D}_i\mathbf{W}_{ij}\mathbf{D}_i$. However, further investigation is certainly required before proceeding further with this model.

5   Sparse Connectivity Patterns

Another potential approach would be to adapt the paper by Eavani et al. (2015), which proposes a similar model but incorporating a sparsity constraint when estimating the population framing matrix $\mathbf{B}$. The model can be reformulated in this context as

$$\Sigma_{ij} \approx \mathbf{P}\mathbf{V}_{ij}\mathbf{P}^T$$

where $\mathbf{P} = [\mathbf{p}_1, \mathbf{p}_2, \dots, \mathbf{p}_c]$ is a $B \times C$ matrix with each column being constrained to have L1 norm less than some tuning parameter and also elements constrained to take values between -1 and 1 inclusive to ensure that they generate valid connectivity matrices. The $C \times C$ matrix $\mathbf{V}_{ij} = diag(\mathbf{v}_{ij})$ is just the diagonal matrix of non-negative loadings on each of the sparse connectivity patterns $\mathbf{p}_k\mathbf{p}_k^T$. Estimation proceeds via minimization of the squared Frobenius norm between the observed Σ_{ij} and the estimated $\hat{\Sigma}_{ij} = \mathbf{P}\mathbf{V}_{ij}\mathbf{P}^T$ subject to the aforementioned constraints on the $\mathbf{p}_k$ and $\mathbf{v}_{ij}$. The tuning parameter is selected via a standard cross-validation process, with the objective function to minimize being the sum of squared Frobenius norms between the test set and the estimates $\hat{\Sigma}_{ij}^{test} = \mathbf{P}^{train}\mathbf{V}_{ij}^{test}(\mathbf{P}^{train})^T$ standardized by the variance of the test set.

Similar to the proposition in Section 4, this method could be adapted to include a site-specific set of sparse or non-sparse connectivity patterns. These could be interpretted as site effects on connectivity and represent a flexible model for the kinds of site effects that are possible on connectivity. The harmonized connectivity matrices could again be obtained by removing these estimated site effects.

6   Meta-Analytic Principal Components Analysis

Kim et al. (2018) proposed meta-analytic principal component analysis (MetaPCA) as a method to identify principal components that best capture the variation across multiple sites. One approach called MetaPCA via sum of variance decomposition takes the covariance

matrix generated within each site then calculates a weighted sum. They then perform PCA using that weighted sum of covariance matrices to obtain their MetaPCA estimates. Another approach which performed better in empirical studies is called MetaPCA via sum of squared cosine maximization (SSC). The key idea is that the first principal component is found by choosing a vector then finding the vectors closest in angle to it in each site's eigenspace spanned by some number of the top eigenvectors. The first meta-analytic principal compoent is the vector that has the lowest sum of angles to those vectors in each eigenspace, or essentially the vector that best captures the direction of variation across sites. Subsequent meta-analytic principal components can be identified in a similar manner, but restricted to being orthogonal to the other principal components.

To adapt this method to the current problem requires some extensions, since the original MetaPCA deals with the case that each site has a set of observations that is used to determine the correlation structure. However, in the functional connectivity setting, each subject has a set of observations, covariance matrix, and estimated principal components. If the goal is harmonization, one idea would to try and identify MetaPCs that represent directions of maximal variation across all sites and subjects, then use some subset of those top MetaPCs to best represent each subject's set of observations and thus connectivity matrix. This approach may be sufficient to remove site effects, which are likely captured by MetaPCs that explain less of the variation in the observations.

To implement this under the MetaPCA framework, we could pursue a two-stage approach. First, we apply MetaPCA by SSC using the eigenspaces specific to each subject within that site to obtain a MetaPC estimate for each site. Taking the top l_i eigenvectors from each of the ith site's MetaPCA estimate, we obtain eigenvector matrices $\mathbf{B}_i^{SSC} = [\mathbf{b_{i1}}, \mathbf{b_{i2}}, \ldots, \mathbf{b}_{il_i}]$. These top eigenvectors from each site's MetaPCA can be then used to obtain a MetaPC estimate across all the M sites. We can take the top l eigenvectors from this second MetaPCA and then obtain a single eigenvector matrix $\mathbf{B}^{SSC} = [\mathbf{b}_1, \mathbf{b}_2, \ldots, \mathbf{b}_l]$. The choices of l_i and l can be based on any criteria, but most likely the proportion of variation explained. While this approach may work, there is certainly no guarantee that it is the optimal way to identify PCs across sites across subjects. However, once these population-wide MetaPCs are obtained, it is straightforward to project each subjects' observations into the space spanned by a chosen number of MetaPCs and potentially remove site effects through this procedure.

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