

# Research Statement

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The human brain is known to have a complicated structural network which supports and modulates the functional connectivity. Identifying the structural and functional connectivity helps the construction of the brain network and better understanding of the functional integration and segregation. Various non-invasive techniques are used to identify the anatomical and functional connectivity of the *in vivo* human brain. Among them, functional MRI (fMRI) is widely used to identify brain's functional connectivity. The blood oxygenation level-dependent (BOLD) signal of fMRI detects the locations of increased neuro activity by measuring the blood oxygen levels at consecutive time points. The connectivity is usually defined as the temporal correlation between spatially remote regions. Compared to other imaging techniques, fMRI has lower temporal resolution (about 2s) but higher spatial resolution (3mm).

Conventional functional MRI measures the BOLD signal change when subjects are conducting cognitive tasks. It was found [6] that there are consistent patterns of activity at subject's resting state, where subjects do not receive any stimulus during scan. This make it possible to find the functional connectivity without the involvement of any cognitive task.

The goal of my research is to characterize the functional connectivity among the regions (voxels) of the human brain cortex by fMRI. I build models and look for computational methods that can identify consistent connectivity among multiple subjects. Specifically I focus on the hierarchical model with a *group* functional network that has bidirectional interaction with individual's network, and also use Markov Random Field theory to mitigate the ambiguity of conventional spatial smoothing.

**Past work** The highly noisy fMRI need statistical methods like Statistical Parametric Mapping (SPM), where the effects of a stimulus signal is estimated as a linear regression problem, with BOLD signal of stimulus as predictor variable, and BOLD signal of any brain voxel as response variables. Activation or no activation is decided by the significance of the effects (i.e. regression coefficients) under the null hypothesis of no activation. This method is often regarded as mass univariate, in the sense that the effects of the stimulus on voxel  $i$  is independent on the effect of voxel  $j$ , even  $i$  and  $j$  are spatially adjacent. In practice, a spatial smoothing Gaussian filter is always applied as preprocessing step, and introduces dependence between spatially adjacent voxels' intensities (and the effects of SPM).

While regular fMRI experiments are block design or event-related where a stimulus is given to the subject under study, there is increasing interest in resting-state fMRI for functional connectivity study. Because of the lack of stimulus signal, the standard SPM method does not apply and people have new computational methods that fall into a few categories [5] listed as below.

Seed-based methods look for the linear correlation between an *a priori* region-of-interest (ROI) and all other regions (voxels) in the whole brain. This straightforward method has the drawback of the *a priori* manual selection of ROI. Independent Component analysis (ICA) methods look for statistically independent components without the need of selecting ROI. But users need to man-

usually select meaningful component by visual inspection. Clustering-based methods partition the brain voxels into distinct regions (clusters), and voxels in same regions belong to same functional networks. If the goal is to discriminate the patients and healthy control groups, pattern classification method can also be used. There are also graph theory based methods that treats each ROI (or voxel) as a node on the graph, and the connectivity between them as edges, and a rich set of graph algorithms can be used to learn the graph structure (small-worldness, modularity, etc). Last there are local methods which only look at the direct neighborhood of individual voxels.

Our first attempt [3] on detecting functional network aims to explicitly model the spatial smoothness of the network. Instead of applying a Gaussian filter spatially on fMRI data as preprocessing, we use Markov Random Field (MRF) to model the fact that if two voxels are functionally connected, their neighbors are likely connected, too. Because the goal is to find *pairwise* connectivity among gray matter voxels, we build a graph with twice the dimension of the original image space. A node on the graph is defined as a pair of voxels in original image. There are links between two nodes if any voxels in the two pairs are spatial neighbors. A mixture of Gaussian (2-class, connected v.s. not connected) clustering is followed to identify the connectivity variables. To learn the parameter from the data we use *Maximum a Posteriori* and *Expectation-Maximization* to estimate the connectivity as well as estimating the parameters. Because the interactions of the spatially adjacent nodes, exactly solution is computationally intensive, so we use mean field theory to get the approximate solution.

This method is able to detect functional networks like default mode network. The downside is the computation cost mostly due to the high dimensional graph, making it difficult for generalizing to group study. Then we consider clustering the brain voxels into non-overlapped partitions within their original space instead of in a higher dimensional space. We notice the mean intensity and the variance (both over all the time points) of the time course at each voxel is not a indicator whether they belong to same functional network, so each time course are normalized by subtracting its mean and dividing by its standard deviation. This is equivalent to project the time courses to a high dimensional sphere so they can be modeled by mixture of von-Mises Fisher (vMF) distribution (similar to mixture of Gaussian on Euclidean space). The linear correlation between two time series in original image space is equivalent to the inner product of two points on the sphere. MRF is again used as a spatial smoothness prior on the hidden network labels. We estimate the network labels by maximizing its posterior probability in a EM framework, such that voxels with same estimated labels have larger inner product, which amounts to have larger correlation in original space and belong to same functional network. The introduction of MRF again poses the difficulty of computing the expectation directly, We use Monte-Carlo Sampling to approximate the expectation value in EM. By this method [4] we are able to detect most significant brain networks like motor, visual, motion, salience and executive control, and default mode network with precision and consistency competitive to standard ICA method.

**Current work** The high noise level of fMRI data is one main reason of the inconsistency among individual subject's connectivity map. It is a natural assumption that a group of subjects must share similar patterns of functional connectivity. We are constructing a hierarchical MRF model by adding a group network label map on top of subjects' map. It can be seen as a generative model where individual subjects' label maps are generated given the group label map, and time courses are generated on the sphere given the individual subjects' labels. With this three-level model, we can estimate individual subject's label map with group map as a prior, hence use other subjects' information during the inference on current subject, while still allowing some degree of difference among individuals. The group and subjects' label map are estimated iteratively to jointly maximize the likelihood of the fMRI data. A free parameter is used to tune the degree to which the group and individuals shared their networks. Other parameters in MRF and mixture of vMF, can be manually set or estimated in a EM framework. We are doing experiments to know if estimating all parameters is appropriate or feasible.

**Future work** The data clustering and graph method are two branches of methods to represent

the brain connectivity. There is no straightforward mapping between them. I propose that the clusters or partitions of the brain cortex obtained from our methods can be used to define the ROI, or nodes in the functional network's graph. The nodes should be regions with coherent functional properties, and the definition of nodes have large influence on the neurobiological interpretation of network topology [1]. A simple parcellation scheme may group functionally different voxels into single nodes, adding difficulties of finding consistent connections between nodes. Our methods can be used to find a set of representative voxels from each connected component of each functional network. Some critical issues still remain, such as the number of clusters need to be decided.

The linear correlation as a measure of connectivity between two regions is problematic, because it neglects the possible influence from other variables. Two regions might have some connections as shown from their marginal linear correlation, but actually they might be independent if the common cause from a third region is removed. The partial correlation or conditional dependency is better measurement to represent the direct connections. Another issue is when we estimate the brain network, we want a sparse graph as a representation of the sparsity of the network. The sparsity of the graph is consistent with the small-world properties of human brain network: any two regions of the brain can be connected through few intermediate nodes, yet the direct connections should be sparse [7]. In most current methods, an arbitrary thresholding is applied on the correlation matrix to get a sparse binary network. We can instead apply the widely used regularized linear regression technique to get a sparse estimation of the network. There are various methods to estimate the conditional independence in a graph. Among them, group lasso [8] and related methods can estimate the sparse structures of multiple graphical models, hence can be used in group fMRI analysis.

Functional network can also be improved by integrating structural connectivity obtained from Diffusion Tensor Imaging (DTI). It has been shown that wherever there is an anatomical connectivity between two regions, the functional connectivity may happen more likely. However, consistent functional connectivity is also found between regions without direct anatomical link [2]. This is probably because the marginal connectivity includes both direct and indirect links as mentioned above. This suggests that the anatomical connectivity can be used as *a priori* knowledge when estimating the sparseness of the functional network. The conditional independence will happen with larger probability between regions without direct anatomical connections. It will be an interesting and challenging task to build a computational model to add DTI prior in the current multi-subject graph estimation algorithms.

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