

Thesis Proposal

Wei Liu

(advisor: Tom Fletcher)

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Committee:

Jeff Anderson

Suyash Awate

Tom Fletcher

Guido Gerig

Tolga Tasdizen

Abstract

Resting-state fMRI is widely used to study the mapping of brain's functional network. Such study typically starts by defining a set of nodes and then estimate the functional connections between them. For group study, a summary network map is usually estimated from individual's map. In this proposal, I aim to estimate the functional connectivity with clustering based methods with each voxel defined as a variable. We also take context information into account. *Context* here means 1) the spatial neighbors of variables at each voxel in order to get spatially coherence network maps, and 2) the variables at same spatial location of other subjects and population network map, in order to build a multi-level network map including group and subject levels. The group functional map estimated from such model respects the variability among subjects, as well as collecting all shared information of them.

1 Problem Statement

The goal of my research is to identify the functional connectivity of the human brain cortex by using resting-state fMRI. I build hierarchical models for consistent estimation of both population and individual subject's functional network map, and use Markov Random Field to represent the context information within and across subjects.

The phrase *Context* have two meanings: 1) The functional patterns of human brain is spatially coherent. Neighboring voxels have more probability of being in the same functional network. 2) functional network that a voxel belongs to in one subjects is dependant on the networks of the voxels in other subjects at same location. The patterns of functional networks from rs-fMRI study are shared by multiple subjects, while the variability across subjects must be taken into account.

2 Contributions

- **Pairwise Connectivity With Spatial Coherence**

A method that can estimate pairwise functional connectivity of single subject, without *a priori* knowledge of the seed region, and also take into account the spatial context information.

- **Identify Consistent, Spatially Coherent Multiple Functional Networks**

A parametric model that can cluster the gray matter of single subject's brain into functional networks, while respecting the spatial coherence of the voxels.

- **Hierarchical Model For Group Study**

A hierarchical model that can estimate functional networks from a group of subjects. The model will estimate population's functional network map as well as individual subjects at the same time. When Clustering the voxel into different networks, both spatial neighbors within subjects and cross subjects will be used as complementary information.

3 Introduction

The human brain consists of a complicated structural network which supports and modulates the functional connectivity. There are two fundamental principles in probing brain's functional organization: *functional integration* and *functional specialization*. Functional specialization means an anatomically segregated cortex region is specialized for some aspects of a mental process. A cortical infrastructure that support such process may involve many specialized areas. Functional integration says these areas do not exist in isolation, but are mediated by the information flows via the action potentials carried by axons, which are bundled into large fiber tracts.

Identifying the structural and functional connectivity helps the construction of the brain network and better understanding of the functional integration and specialization. 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 distant regions. Compared to other imaging techniques, fMRI has lower temporal resolution (about 2s) but higher spatial resolution (3mm).

fMRI is originally used for detect the neuro activity in experiments with task paradigm. It was found [19] that there are consistent patterns of activity even at subject's resting state, when subjects do not receive any external stimulus during scan. In recent years the emphasis of neuroimaging is shifting from blobology (functional specialization/segregation) towards connectology (functional integration)[20], such spontaneous activity estimated from resting-state fMRI (rs-fMRI) have provide insight into the intrinsic architecture of the human brain.

It should be noted the brain is not really at *resting-state* during a rs-fMRI acquisition period due to the visual attention from the fixed cross or auditory attention from

the scanner noise. And the individual’s random thoughts is one source of the variability across subjects, which pose a challenge to be addressed in section 5.3.

[what is functional network??]

[Compare task experiment and resting-state.]

[shortly mention structural network vs functional network.]

[directed connectivity. And why fMRI is not good for that purpose. need to say my work does not address this.]

[Functional localization discounts the interactions. Localizationism is not a complete or sufficient explanation of cortical organization.] – don’t say this.

[network vs system] – don’t say this.

[resting-state vs intrinsic vs spontaneous]

[Need revise to prove this is an important problem and I have promising method to solve it]

4 Literature Review

The Majority of functional neuroscience studies has a task or stimulus for the subject to conduct, and the resulting changes in neuro activity are measured. For data obtained in such experiments, the core methods such as Statistical Parametric Mapping (SPM) use General Linear Model [25] to test a null hypothesis, hence a hypothesis driven method. The effects of a stimulus signal is estimated as a multiple 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 one voxel is independent on the effect of others, even they are spatially adjacent. In practice, a Gaussian filter is always applied for spatial smoothing in preprocessing step, and introduces dependence between spatially adjacent voxels’ intensities (and also the effects of SPM).

In rs-fMRI study, the aim is to look for spontaneous neuro activity when there is no external input. Because of the lack of stimulus signal, the standard SPM method does not apply to the rs-fMRI data. New computational methods, sometimes called data-driven analysis, borrow technical concepts from many fields including machine learning and computer vision. These methods fall into a few categories [14] listed as below.

Seed-based methods look for the linear correlation between an *a priori* region-of-interest (ROI) and all other regions or voxels in the whole brain [8]. This approach is inherent simple, sensible, and easy to interpret. However, a *a priori* manual selection of ROI is required, and only one functional system can be detected at a time.

Independent Component analysis (ICA) methods look for statistically independent components without the need of selecting ROI [3]. But users need to manually 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

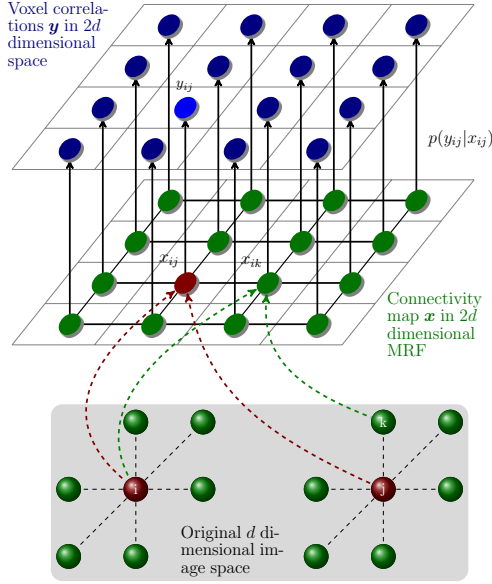


Figure 1: A MRF defined on high dimensional graph that model the pairwise connections of gray matter voxels. A node in the high dimension graph is defined as a pair of voxels in original image. an edge are added when any voxels in the two pair of voxels are spatially neighbors. This MRF is embedded into a generative model as a prior distribution, i.e. we suppose , a sample correlation is *generated* from the given random variable of connectivity or no connectivity. For inference of the connectivity given the observed sample correlation data, *Maximum a Posteriori* is used, together with the Gibbs Sampling and mean field theory approximation.

algorithms can be used to learn the graph structure (small-worldness, modularity, etc).

5 Methodology and Preliminary work

5.1 High Dimensional MRF for Full connectivity without ROI

Our first attempt [11] on detecting functional network aims to explicitly model the spatial smoothness of the network. In both task-based and resting-state fMRI the impact of imaging noise can be reduced by taking advantage of the spatial correlations between neighboring voxels in the image. A common approach used for instance in Statistical Parametric Mapping (SPM)[25] is to apply a spatial Gaussian filter to smooth the signal prior to statistical analysis. However, this can lead to overly blurred results, where effects with small spatial extent can be lost and detected regions may extend beyond their actual boundaries. An alternative approach to spatial regularization that has been proposed for task activation paradigms is to use a Markov Random Field (MRF) prior [17, 6, 7, 24, 4], which models the conditional dependence of the signals in neighboring voxels.

We propose [11] to use MRF models in resting-state fMRI to leverage spatial correlations in functional connectivity maps. Unlike previous MRF-based approaches, which use the neighborhood structure defined by the original image voxel grid, the neighborhoods in functional connectivity must take into account the possible relationships between spatially distant voxels. Therefore, we define the neighborhood graph on the set of all voxel pairs. This results in a Markov structure on a grid with twice the dimensions of the original image data, i.e., the pairwise connectivities for three-dimensional images results in a six-dimensional MRF. The neighborhood structure is defined so that two voxels are more likely to be connected if they are connected to each other's spatial neighbors. See figure 1 for a illustrative view.

We combine the Markov prior on functional connectivity maps with a likelihood model of the time series correlations in a posterior estimation problem. Furthermore, we model solve for the unknown parameters of the MRF and likelihood using an Expectation Maximization (EM) algorithm. In the estimation step the posterior random field is sampled using Gibbs Sampling and estimated using Mean Field theory.

Fig. 2 compares the real data results using no spatial regularization, Gaussian smoothing, and the proposed MRF model. Though the posterior connectivity of the MRF is computed between every pair of voxels within a slice, for visualization purposes, only the posterior of the connectivity between one voxel and the slice is shown. We chose to visualize the connectivity to a voxel in the posterior cingulate cortex (PCC) because this is known to be involved in the Default Mode Network [19], with connections to the medial prefrontal cortex (MPFC). The results show that Gaussian smoothing is able to remove noise, but is unable to find a clear connection between the PCC and the MPFC. Our proposed MRF model (rightmost plot) is able to remove spurious connections, and also clearly shows a connection to the MPFC.

It is noted that this approach does not need *a priori* knowledge of the ROI. Once the algorithm finishes, it outputs all the pairwise connectivity for all gray matter voxels. Putting this large connectivity matrix into a visualization tool, users can explore the functional networks with various seed regions and see the real-time results.

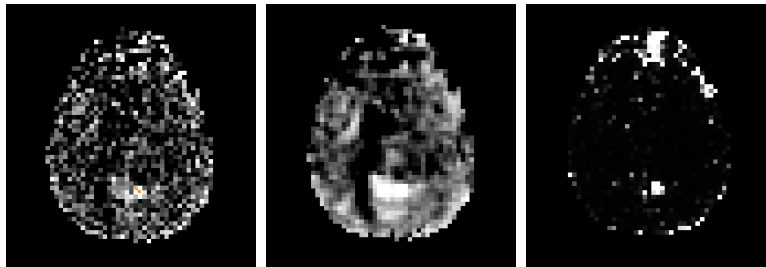


Figure 2: Correlation map and Posterior Connectivity map between seed voxel and slice containing the seed. From left to right: the correlation map computed from data without spatial smoothing; correlation map of data after smoothing; Posterior probability computed from MRF.

5.2 A Parametric Model of rs-fMRI Clustering With Spatial Coherence

The above method in section 5.1 is able to detect functional networks such as default mode network, there are two issues that have to be addressed. 1) With one seed region at a time, only one functional system can be shown. The functional architecture would be better understood if multiple systems are shown together in the same image. 2) The computation cost is huge, mostly due to the high dimensional graph and the optimization problem. This is partly mitigated by a GPU implementation in current single subject analysis, but would be difficult for generalizing to group study.

One possible solution is to employ clustering techniques to automatically partition the brain into functional networks. In such methods, a similarity metric is defined

first, e.g., correlation [9] or frequency coherence [21], and then a clustering method such as k -means or spectral clustering is used to group voxels with similar time series. A drawback of these approaches is that they disregard the spatial position of voxels, and thus ignore the fact that functional networks are organized into sets of spatially coherent regions.

We introduce a new data-driven method [12] to partition the brain into spatial coherent, non-overlapping networks of functionally-related regions from rs-fMRI. The proposed algorithm does not require specification of a seed, and there is no ad hoc thresholding or parameter selection. We make a natural assumption that functionally homogeneous regions should be spatially coherent. Our method incorporates spatial information through a Markov random field (MRF) prior on voxel labels, which models the tendency of spatially-nearby voxels to be within the same functional network.

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 series is first normalized to zero mean and unit norm, which results in data lying on a high-dimensional unit sphere. We then model the normalized time-series data as a mixture of von Mises-Fisher (vMF) distributions [1]. Each component of the mixture model corresponds to the distribution of time series from one functional network.

Solving for the parameters in this combinatorial model is intractable, and we therefore use a stochastic method called Monte Carlo Expectation Maximization (MCEM), which approximates the expectation step using Monte Carlo integration. The stochastic property of MCEM makes it possible to explore a large solution space, and it performs better than a standard mode approximation method using iterated conditional modes (ICM).

The proposed method is related to previous approaches using MRFs to model spatial relationships in fMRI data. Descombes et al. [6] use a spatio-temporal MRF to analyze task-activation fMRI data. Our previous methods [11] use an MRF model of rs-fMRI to estimate pairwise voxel connections. However, neither of these approaches tackle the problem of clustering resting-state fMRI into functional networks.

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 [12] 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, as can be found in figure 3.

5.3 Current work: Hierarchical MRF of Group Analysis

The availability of large rs-fMRI databases opens the door for systematic group studies of functional connectivity. It is a natural assumption that a group of subjects must share similar patterns of functional connectivity, while keeping individual subject’s variability. Such variability may come from subject random thoughts, despite that

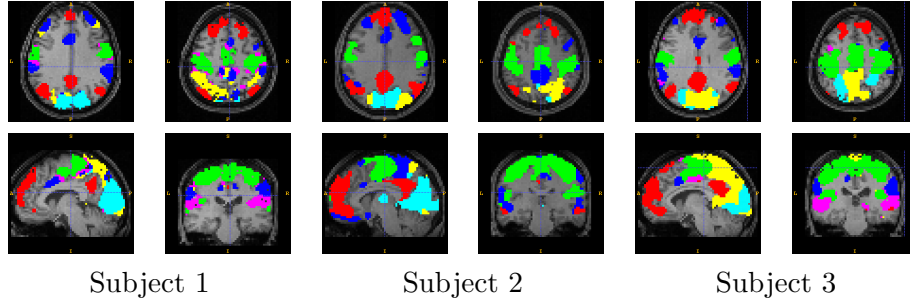


Figure 3: Functional networks detected by the proposed method for 3 subjects overlaid on their T1 images. The clusters are the visual (cyan), motor (green), executive control (blue), salience (magenta), dorsal attention (yellow), and default mode (red) networks.

they are instructed not to think anything specifically. While the inherently high level of noise in fMRI makes functional network estimation difficult at the individual level, combining many subjects’ data together and jointly estimating the common functional networks is more robust. However, this approach does not produce estimates of individual functional connectivity. Such individual estimates are an important step in understanding functional networks not just on average, but also how these networks vary across individuals.

The method we propose in above section [12] works specifically on single subject analysis, and my next aim is to build a model that estimate functional networks among a group of subjects. Most current studies estimate the networks in a sequential approach, i.e., they identify each individual subject’s network independently to other subjects, and then estimate the group network from the subjects networks. This one-way flow of information prevents one subject’s network estimation benefiting from other subjects.

Group ICA [3] is a generalization of ICA to multiple subjects, in which all subjects are assumed to share a common spatial component map but have distinct time courses. The time courses from all subjects are concatenated temporally, followed by a single ICA. Although the subject component maps are obtained by a back-reconstruction procedure, there is no explicit statistical modeling of the variability between the group and subject component maps. Ng et. al [16] use group replicator dynamics (RD) to detect subject’s sparse component maps, with group information integrated into each subject’s RD process. In clustering-based methods, the subjects clusterings are usually averaged to obtain a group affinity matrix and are followed by a second level clustering on the group similarity matrix [2, 22]. Because the group level clustering is conducted after subject level clustering, the clustering of one subject is unaware of the information from other subjects, as well as the group clustering.

We propose a Bayesian hierarchical model [13] to identify the functional networks from rs-fMRI that includes both subject and population levels. We assume a group network label map that acts as a prior to the label maps for all subjects in the population. This Bayesian perspective provides a natural regularization of the estimation problem of a single subject using information from the entire population. The variability between the subjects and group are taken into account through the conditional

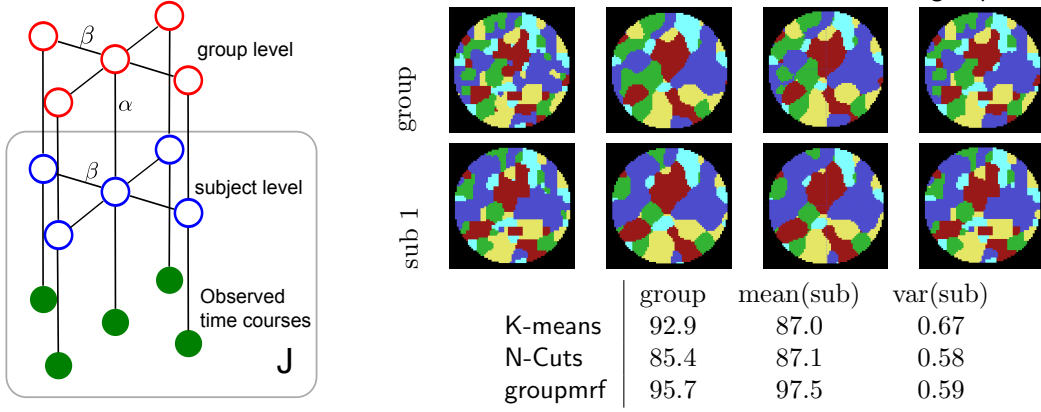


Figure 4: Left: Hierarchical MRF depicted by undirected graph. The J subjects are compactly represented by a box with label J . Right: clustering of K-means and N-Cuts on synthetic time series with spatial smoothing, and **groupmrf** without smoothing. Top is group label map and bottom is one of subjects label map. The table gives the rand index accuracy between estimated label map and ground truth image. The rand index of all subjects are summarized by a mean and variance value.

distributions between group and subjects. The within-subject spatial coherence is again modeled by a MRF. The group and all subjects network map are connected into a larger graph, with edges between corresponding voxels between group and subjects, and between adjacent voxels within single subjects.

The concept of this hierarchical model is similar to the multi-level modeling of linear regression. Estimation the functional network on single on single subject correspond to no pooling since it fit a model for each subject separately. A sequential approach to estimate group network after subjects networks is like complete pooling, since it ignores the group information when estimating subjects network. And the hierarchical model corresponds to the partial pooling, i.e., the multi-level model where a tradeoff defined by a pooling factor, or a shrinkage factor. Compared to the *pooled* averaging method, our hierarchical model respect the individual variability, hence also better estimate the group’s functional network.

Both the group clustering and subject clusterings are estimated simultaneously with a Monte Carlo Expectation Maximization (MCEM) algorithm. The model is data-driven in that all parameters, regularized by two given hyper-parameters, are estimated from the data, and the only parameter that must be specified is the number of networks.

[Context: means both spatial neighbors or the same voxels in other subjects....]

ours is the first hierarchical MRF applied to fMRI for modeling both group and individual networks. The model of Ng et al. [15] combines all subjects into a single MRF and bypasses the need for one-to-one voxel correspondence across subjects, but the edges are added directly between subjects without a group layer. In our model, a group layer network map is explicitly defined, and the consistency between subjects is encoded through adding edges between group and subjects labels. Our method differs from other clustering methods [2, 22] in that their methods identify the subject’s

functional network patterns independently, without any knowledge of other subjects or group population. Instead, our method estimates both levels of network patterns simultaneously. The proposed approach can be seen as a counterpart on the clustering branch of the multi-subject dictionary learning algorithm [23], which also has a hierarchical model and a spatially smoothed sparsity prior on the group component map.

[Add a little more details of the hierarchical method here]

6 Future work and Timeline

In the following year I will continue to polish the hierarchical model that we proposed in section 5.3.

- **Fall 2012:** Submit a journal paper on the hierarchical model in section 5.3. This includes the following works:

1. Currently our model has a parameter that controls how much the subject function network maps should *shrink* towards the group network map. I aim to find some guidance of how to set the parameter value based on either the data itself or some physiology knowledge.
2. Convergence test. The inference of posterior from the hierarchical model that we proposed in [13] pose a difficult optimization problem, and a Markov Chain Monte Carlo (MCMC) method is used to obtain approximate solution. In general Markov Chain sampling, some convergence tests are available [5] as guidance of when to stop the chain. However, since MCMC on MRF is a multivariate problem, it is difficult to have a stopping rule to guarantee that the number of iterations is sufficient.

My aim is to find a method that can give a bound of the required iterations before the samples are from the stationary distribution. One method is the coupling technique [10, 18], where two or more parallel chains are sampled based on same sequence of random number. The sampling procedure converges when all the parallel chains coupled, i.e. reach to same state.

- **Spring 2013:** Dissertation writing.
- **Summer 2013:** Ph.D thesis defense.

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List of Publications

- [1] Wei Liu, Peihong Zhu, Jeffrey S. Anderson, Deborah Yurgelun-Todd, and P. Thomas Fletcher. Spatial Regularization of Functional Connectivity Using High-Dimensional Markov Random Fields. In Tianzi Jiang, Nassir Navab, Josien P.W. Pluim, and Max A. Viergever, editors, *Medical Image Computing and Computer-Assisted Intervention MICCAI 2010*, volume 6362 of *Lecture Notes in Computer*

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