Functional Connectivity of Resting-State fMRI
A Group Study By Multi-Level Markov Random Field

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Why Resting-State fMRI

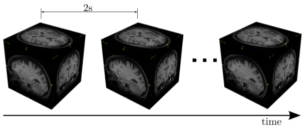
Intrinsic v.s. Reflective

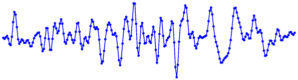
Interpret, respond to, and predict environmental demands.

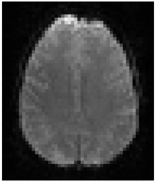
Why Resting-State

- Large energy consumption.
- Matches existing neuro-anatomical systems.
- Reflect increased and decreased activity in task.
- Predict task response as a priori hypothesis.

fMRI Data Acquisition





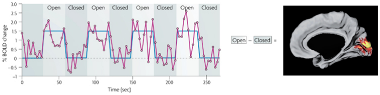


- fMRI is 4D. Many consecutive 3D volumes.
- BOLD signal.
- Spatial dependency.
- Temporal correlation.
- fMRI is noisy.

Task-based v.s. Resting-State fMRI

- Experiment stimulus signal.
- Subjects undertake cognitive tasks.
- General linear model is used for multi-regression analysis between stimulus and BOLD signal of a voxel.

- No experiment paradigm signal.
- Subject stay in scanner. Eyes closed/open to a fixation cross.
- Correlation analysis between two voxels.



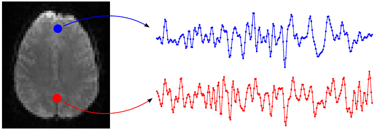


Figure: M. Fox, Nat. Rev., Neuroscience

Issues In Current Group Study

- Arbitrary spatial blurring to enforce spatial dependency.
- Lack of methods for jointly estimate group and subjects.
- Variability analysis.

Thesis Statement

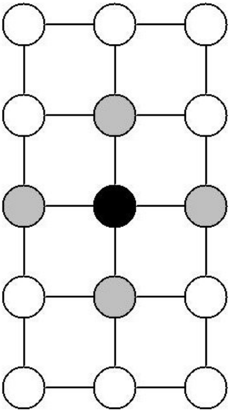
A multilevel Markov Random Field model improves the reliability of the functional network estimation in rs-fMRI group study by taking into account context information as a prior. The data-driven Bayesian model can jointly estimate both population and subjects' connectivity networks, as well as drawing inference on the uncertainty in the estimation, and on the variability across subjects.

Contributions

Thesis Proposal Contributions

- Full pairwise connectivity with spatial coherence.
- Identify consistent, spatially coherent multiple functional networks.
- Hierarchical model for group study. Estimate group and subjects together.
- Uncertainty and variability of resting-state functional network.

Markov Random Field



Definition

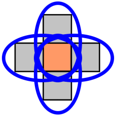
$\mathcal{G} = (\mathcal{V}, \mathcal{E})$: undirected graph.
$s \in \mathcal{V}$: a node/site in $\mathcal{V}$.
$X = \{x_1, \ldots, x_s, \ldots\}$: a collection of random variables defined on graph $\mathcal{G}$.
$\mathcal{N}_s$: the set of sites neighboring s.
$(r, s) \in \mathcal{E} \Leftrightarrow r \in \mathcal{N}_s$.

Definition

A Markov Random Field is a collection of variables X defined on graph $\mathcal{G} = (\mathcal{V}, \mathcal{E})$ if for all $s \in \mathcal{V}$

$$P(X_s | X_{\mathcal{V}-s}) = P(X_s | X_{\mathcal{N}_s})$$

Markov Random Field Cont.



The definition of MRF is a local property.

Theorem (Hammersley-Clifford, 1971)

X is an MRF on $\mathcal{G}$ if and only if X obeys Gibbs distribution in the following form

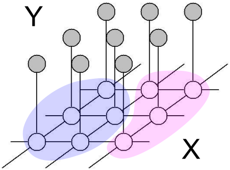
$$P(X) = \frac{1}{Z} \exp\left(-\frac{1}{T} U(X)\right),$$

$$U(X) = \sum_{c \in \mathcal{C}} V_c(X).$$

Gibbs distribution gives a global property that can be used as a prior distribution.

Conditional Random Field: A Generative Model

- The observed time series Y can be seen as *generated* from the hidden variables X.
- X is MRF to guarantee smoothness.
- Inverse problem: Given Y, estimate X.



Full Pairwise Connectivity With Spatial Coherence [Liu10a]

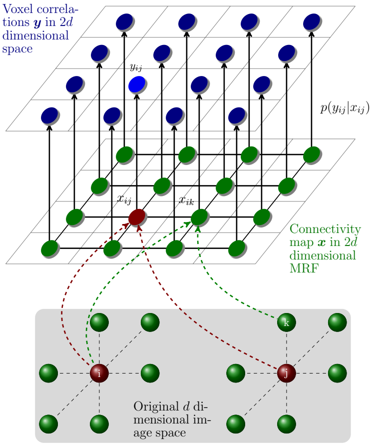
The Goal

- The Connectivity between each pair of voxels.
- No Seed region needed.
- Spatial smoothness as a regularization, without blurring.
- Learn the strength of the smoothness from the data.

Full Pairwise Connectivity With Spatial Coherence [Liu10a] Cont.

Solution

- Define a 6 dimension graph $\mathcal{G}$. Define pairwise connectivity variable on each node. Add an edge (x_{ij}, x_{st}) if any voxels between i, j and s, t are neighbors.
- Likelihood: Gaussian $\mathcal{N}(\mu, \sigma^2)$.
- Two class segmentation: no connectivity and connectivity.
- Gibbs sampling and mean field approximation to compute posterior mean of X.



Experiments on Real data [Liu10a]

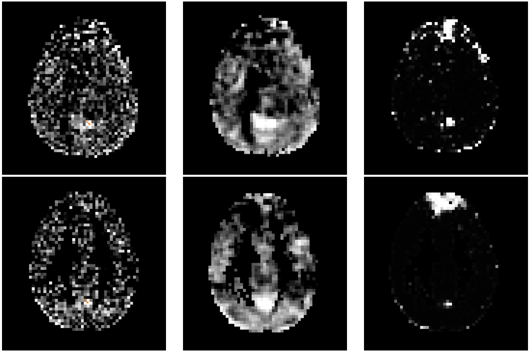


Figure: Correlation map without smoothing; With smoothing; Posterior from MRF

Full Pairwise Connectivity With Spatial Coherence Cont.

Benefits

- Show functional system real-time once given a seed.
- Spatial coherence without over blurring.

Issues

- Can only visualize one functional network.
- Big Computation cost.

Identify Consistent, Spatially Coherent Multiple Functional Networks [Liu11a]

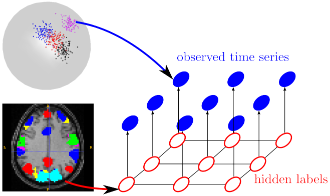
The Goal

- Partition the brain into multiple functional networks.
- Spatial coherence respected.
- Parameter estimation.

Identify Consistent, Spatially Coherent Multiple Functional Networks [Liu11a] Cont.

Solution

- Markov prior $P(X) = \frac{1}{Z} \exp\left(-\beta \sum_{(r,s)\in\mathcal{E}} \psi(x_s, x_r)\right)$.
- Likelihood $P(y_s|X) = C_p(\kappa_l) \exp(\kappa_l \mu_l^\top y_s), y_s \in S^{p-1}$.
- Inference $P(X|Y) \propto P(X) \cdot P(Y|X)$



Identify Consistent, Spatially Coherent Multiple Functional Networks [Liu11a] Cont.

Expectation Maximization

$$Obj = \mathbb{E}_{X|Y}[\log P(X, Y; \theta)]$$

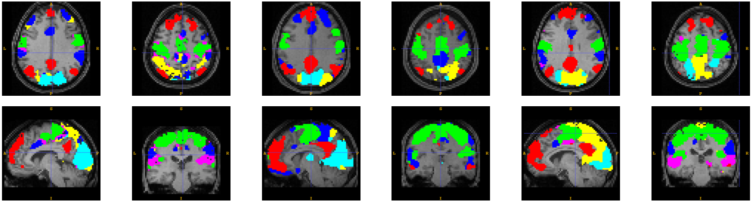
Monte Carlo Expectation Maximization

$$\mathbb{E}_{X|Y}[\log P(X, Y; \theta)] \approx \frac{1}{M} \sum_{m} \log P(X^m; \theta) + \log P(Y|X^m; \theta)$$

Pseudo Likelihood

$$\log P(X^m; \theta) \approx \sum_{s \in \mathcal{V}} \log P(x_s | x_{\mathcal{N}_s}; \theta)$$

Identify Consistent, Spatially Coherent Multiple Functional Networks Cont.



Subject 1 Subject 2 Subject 3

Current Work: Hierarchical Model For Group Study [Liu12a]

Goal

- A Bayesian approach for group analysis.
- Both group and subject functional networks are identified.
- Group and subjects use each other as priors for a joint optimal solution.

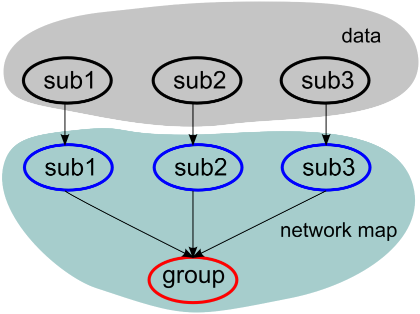
State-of-Art Group Analysis Approach

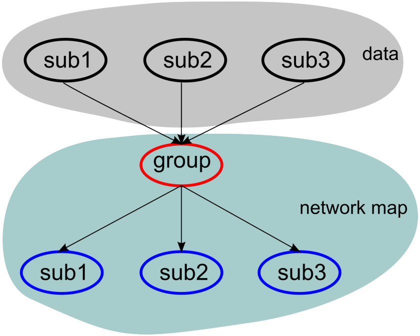
Bottom-up Approach (Heuvel, 2008; Craddock, HBM, 2011)

- Estimate Subject network first.
- Estimate group network from subjects.

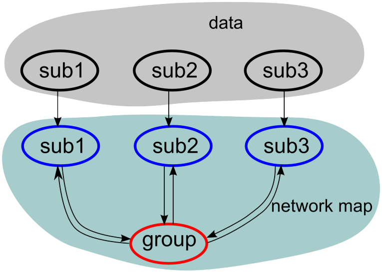
Top-down Approach (Calhoun, HBM, 2001)

- Estimate group network from all subjects.
- Back-reconstruct subject network maps.





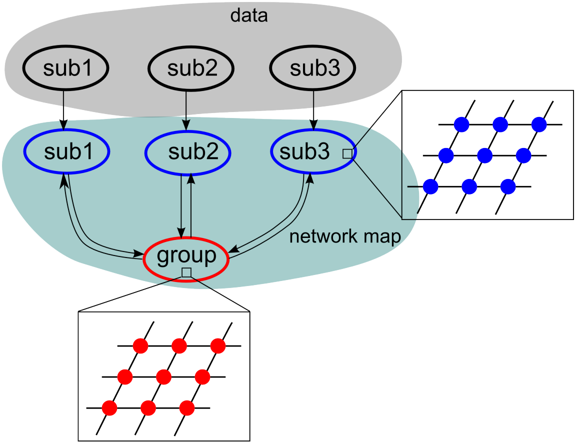
Joint Estimation: a Better Approach [Liu12a]



- Group network map inform subjects as a prior.
- Subject network maps feedback into group estimation.
- Jointly estimate both levels.

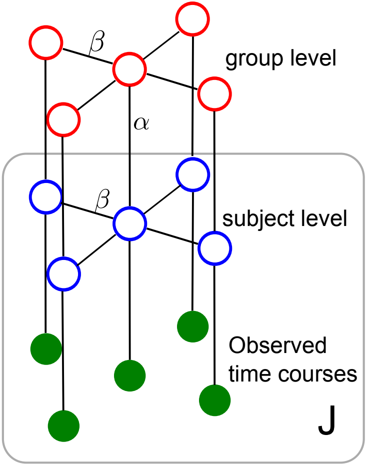
Joint Estimation With MRF

Spatial coherence is again modeled by MRF.



A new MRF including both levels

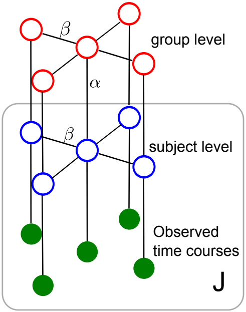
Put group and all subject network label variables in a single graph.



MRF Prior of The New Graph

Definition

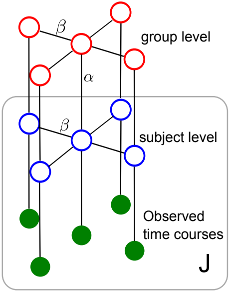
$\mathcal{G}_G = (\mathcal{V}_G, \mathcal{E}_G)$: Graph that represents group map.
$\mathcal{G}_H^j = (\mathcal{V}_H^j, \mathcal{E}_H^j), \forall j = 1, \ldots, J$: subject map.
$\mathcal{G} = (\mathcal{V}, \mathcal{E})$: new graph that includes both group and subject level.
$\mathcal{V} = (\mathcal{V}_H, \mathcal{V}_H^1, \ldots, \mathcal{V}_H^J)$,
$\mathcal{E} = \{(r,s) | (r,s) \in \mathcal{E}_G\} \cup \{(r,s) | r \in \mathcal{V}_G, s \in \mathcal{V}_H^j, r \simeq s\} \cup \{(r,s) | (r,s) \in \mathcal{E}_H^j\}$.



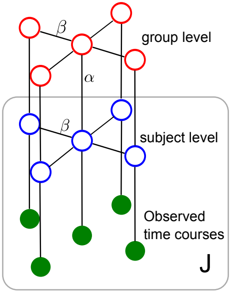
MRF Prior of The New Graph

Energy Function

$$U(X) = \sum_{(s,r)\in\mathcal{E}_H} \beta\psi(x_s, x_r) + \sum_{j=1}^{J}\left(\sum_{s\in\mathcal{V}_G, \tilde{s}\in\mathcal{V}_H^j} \alpha\psi(x_s, x_{\tilde{s}}) + \sum_{(s,r)\in\mathcal{E}_H^j} \beta\psi(x_s, x_r) \right).$$



Likelihood



y_s: normalized time series in p-sphere.

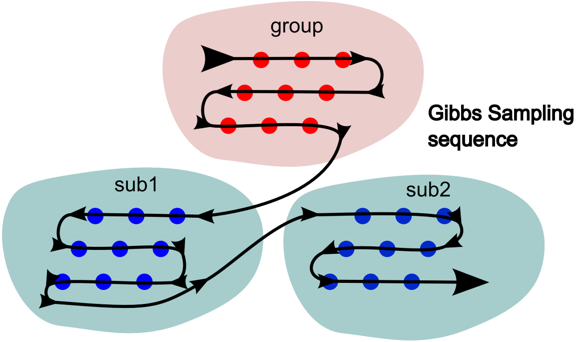
Likelihood

$$P(y_s|X) = C_p(\kappa_l)\exp(\kappa_l \mu_l^\top y_s), y_s \in S^{p-1}.$$

$$\log P(Y|X) = \sum_{s \in H} \log p(y_s|x_s)$$

Bayesian Inference: Gibbs Sampling

- Monte-Carlo Sampling used to approximate $\mathbb{E}_{X|Y}[\log P(X, Y; \theta)]$
- Gibbs sampling also in a multi-level fashion.



The Algorithm

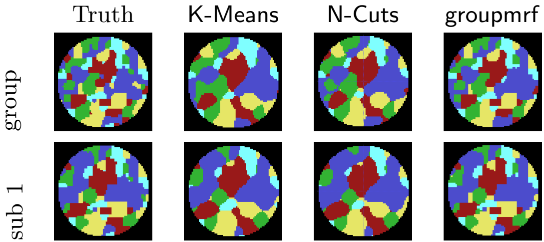
Data: Normalized fMRI, initial group label map
Result: Group and subjects label map X, parameters $\{\alpha, \beta, \mu, \sigma\}$

while $\mathbb{E}[\log p(X, Y)]$ *not converge* **do**
- **repeat**
  - **foreach** $s \in \mathcal{V}_G$ **do** Draw consecutive samples of x_s ;
  - **foreach** $j = 1 \dots J$ **do**
    - **foreach** $s \in \mathcal{V}_H^j$ **do** Draw consecutive samples of x_s ;
  - **end**
  - Save sample Y^m after B burn-ins;
- **until** $B + M$ *times*;
- **foreach** $l = 1 \cdots L$ **do** Estimate $\{\mu_l, \kappa_l\}$ by maximizing $\frac{1}{M} \sum_{m=1}^{M} \log p(Y|X^m)$;
- Estimate $\{\alpha, \beta\}$ by maximizing $\frac{1}{M} \sum_{m=1}^{M} \log p(X^m)$;

end

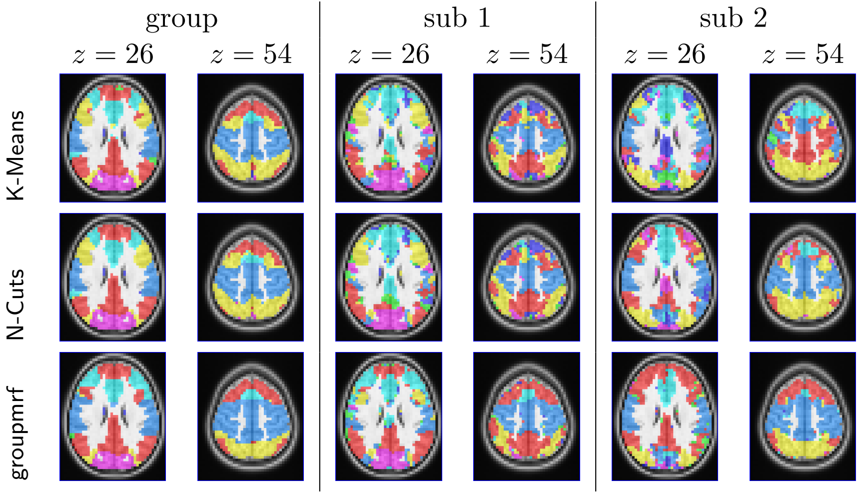
Run ICM on current samples to estimate final label maps.

Synthetic Data Experiment



	group	mean(sub)	var(sub)
K-means	92.9	87.0	0.67
N-Cuts	85.4	87.1	0.58
groupmrf	95.7	97.5	0.59

Real rs-fMRI Data



Variability of Resting-State Functional Network

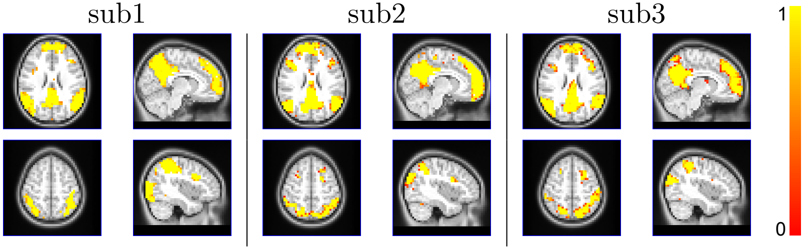
- Uncertainty: Posterior mean and variance.
- Variability: Spatial pattern's shape change.

Posterior mean and variance

posterior variance

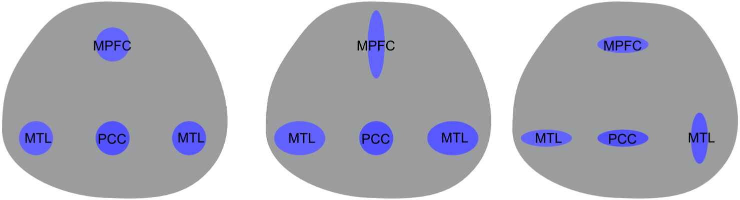
the sample variance of the network label variables inferred from posterior density.

Preliminary results shows the probability of network labels estimated from samples drawn from posterior density.



Variability: Spatial pattern's shape change

- The variability of Multivariate labels across can be represented by shape changes.
- Multivariate pattern analysis method: principal component analysis, etc.



Timeline

- **Fall 2012:** Network variability analysis.
- **Spring 2013**: Submit a journal paper on the hierarchical model. Continue on variability analysis.
- **Summer 2013**: Dissertation writing and Ph.D thesis defense.

Publications

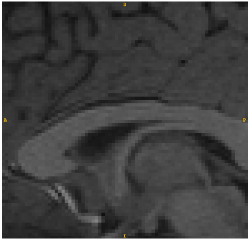
W. Liu, P. Zhu, J. Anderson, D. Yurgelun-Todd, and P.T. Fletcher.
Spatial Regularization of Functional Connectivity Using High-Dimensional Markov Random Fields.
Medical Image Computing and Computer-Assisted Intervention–MICCAI 2010, pages 363–370, 2010.

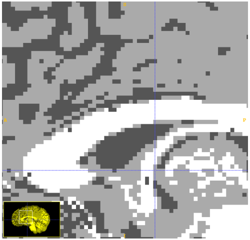
W. Liu, S. Awate, J. Anderson, D. Yurgelun-Todd, and P.T. Fletcher.
Monte Carlo Expectation Maximization with Hidden Markov Models to Detect Functional Networks in Resting-State fMRI.
Machine Learning in Medical Imaging, pages 59–66, 2011.

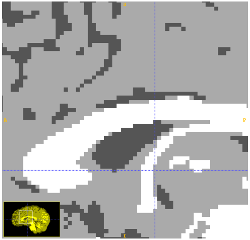
W. Liu, S. Awate, and P.T. Fletcher.
Group analysis of resting-state fMRI by hierarchical Markov Random Fields.
MICCAI 2012, In Press.

Thanks very much!
Questions? Comments?

Backup: Segmentation with MRF

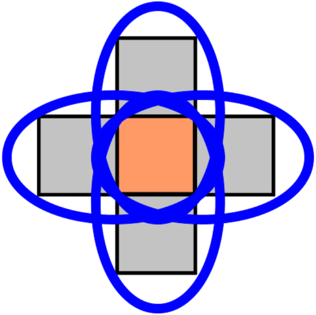






Neighbor System and Cliques

Cliques for a 4-neighbor system.



Bayesian Inference: Gibbs Sampling At Voxel Level

$$p(x_s|x_{-s},Y) \propto \frac{1}{Z_s}\exp\{-U(x_s|x_{-s})\}\cdot p(y_s|x_s)$$

$$= \frac{1}{Z_s}\exp\{-U_p(x_s|x_{\mathcal{N}_s},y_s)\}$$

$$U_p = \alpha\sum_{j=1}^{J}\psi(x_s,x_{\tilde{s}}^{j}) + \beta\sum_{r\in\mathcal{N}_s}\psi(x_s,x_r), \quad \forall s\in\mathcal{V}_G,$$

$$U_p = \alpha\psi(x_s,x_{\tilde{s}}) + \beta\sum_{r\in\mathcal{N}_s}\psi(x_s,x_r) - \kappa_l{\mu_l}^{\top}y_s - \log C_p,\ \forall s\in\mathcal{V}_H^j.$$