A Spatial Modeling Framework for Functional Neuroimaging Data

DuBois Bowman

Department of Biostatistics and Bioinformatics
Rollins School of Public Health
Emory University

January 15, 2011

University of Florida Workshop on High Dimensional Inference

EMORY ROLLINS SCHOOL OF PUBLIC HEALTH

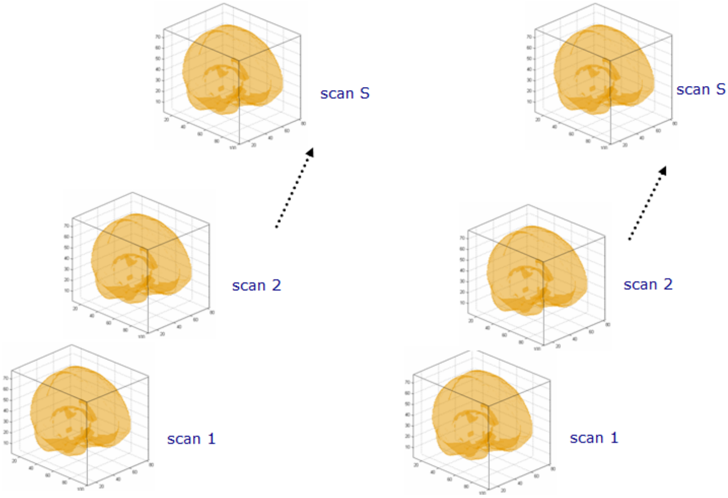
CBIS Center for Biomedical Imaging Statistics

Outline

EMORY ROLLINS SCHOOL OF PUBLIC HEALTH | CBIS Center for Biomedical Imaging Statistics

Data Characteristics

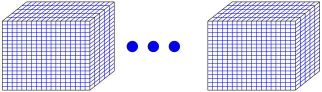
EMORY ROLLINS SCHOOL OF PUBLIC HEALTH | CBIS Center for Biomedical Imaging Statistics



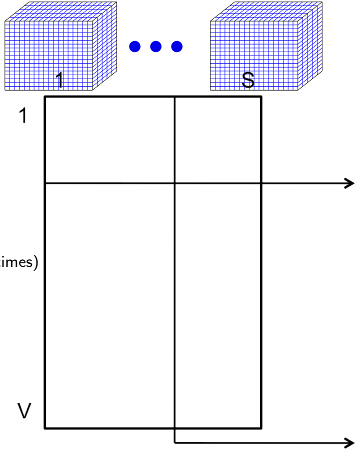
Session 1
(e.g. baseline)

Session 2
(e.g. post-treatment)

Data Characteristics



Data Characteristics

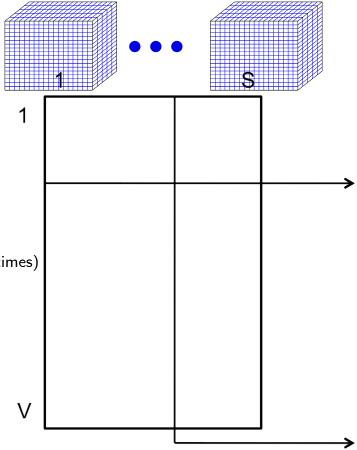


$V \times S$

(#voxels)$\times$(#meas. times)

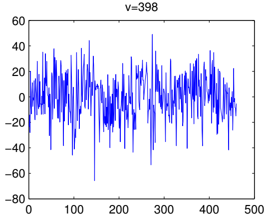
Data Characteristics

EMORY ROLLINS SCHOOL OF PUBLIC HEALTH CBIS Center for Biomedical Imaging Statistics



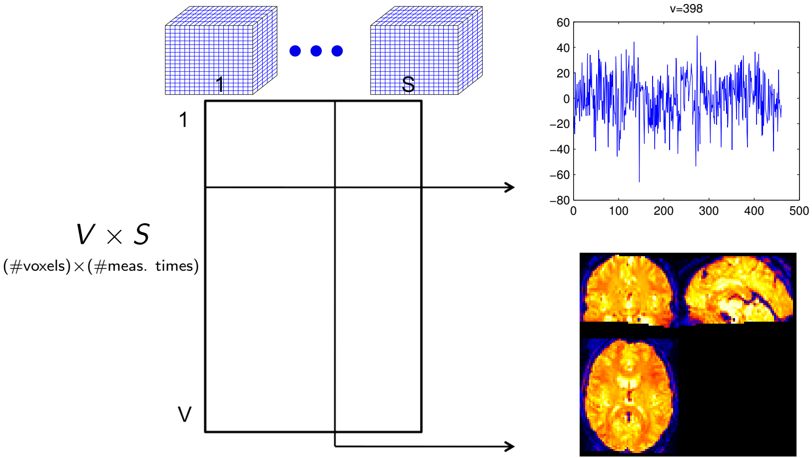
$V \times S$

(#voxels)$\times$(#meas. times)



Data Characteristics

EMORY ROLLINS SCHOOL OF PUBLIC HEALTH | CBIS Center for Biomedical Imaging Statistics



Data Example

EMORY ROLLINS SCHOOL OF PUBLIC HEALTH | CBIS Center for Biomedical Imaging Statistics

Working Memory in Schizophrenia Patients

- N=28 subjects: 15 schizophrenia patients and 13 healthy controls
- fMRI Tasks: Serial Item Recognition Paradigm (SIRP)
  - Encoding set: Subjects asked to memorize 1, 3, or 5 target digits.
  - Probing set: Subjects sequentially shown single digit probes and asked to press a button:
    - with their index finger, if the probe matched
    - with their middle finger, if not.
- 6 runs per subject: (177 scans per run for each subject)
  - 3 runs of working memory tasks on each of 2 days
- Objective: Compare working memory-related brain activity between patients and controls.

Data from the Biomedical Informatics Research Network (BIRN) [1]: Potkin et al. (2002), Proc. 41st Annu. Meeting Am. College Neuropsychopharm.

Data Characteristics

EMORY ROLLINS SCHOOL OF PUBLIC HEALTH | CBIS Center for Biomedical Imaging Statistics

- Massive data sets

  $N = 28$ subjects, $V \approx 900,000$ voxels, $S = 177$ scans per run, 3 runs each day, 2 days (sessions)

- Almost 1 billion spatio-temporal data points per subject! 26 billion for all subjects!!

- Temporal correlations

- Complex spatial correlations

Common Neuroimaging Objectives

1. Activation studies: localize regions of the brain activity when performing an experimental task
2. Connectivity studies: identify what brain areas show similar patterns of activity over time $\Rightarrow$ distributed networks of brain function
3. Prediction studies: use functional brain images to
   - predict neural activity
   - predict experimental conditions, behavior or a subject's group membership (e.g. psychiatric condition, treatment response)

General Analysis Approach

EMORY ROLLINS SCHOOL OF PUBLIC HEALTH | CBIS Center for Biomedical Imaging Statistics

- Fit a linear model separately for each subject (at each voxel)
  - Address correlations between scans using AR models (+ white noise)
    - Pre-coloring/temporal smoothing [Worsley and Friston, 1995]
    - Pre-whitening [Bullmore et al, 1996; Purdon and Weisskoff, 1998]
    - Alternative structures available for PET [Bowman and Kilts, 2003]
- Fit Stage II linear model that combines subject-specific estimates
  - A two-stage (random effects) model
    - Simplifies computations*
    - Sacrifices efficiency
- Compute t-statistics at each voxel and threshold
  - Consider a multiple testing adjustment (Bonferonni-type, FDR, RFT)

Stage II Model Properties

EMORY ROLLINS SCHOOL OF PUBLIC HEALTH | CBIS Center for Biomedical Imaging Statistics

- Voxel-by-voxel analyses
- Assumes independence between brain activity measures at different brain locations
- Targets activation analyses
- Disregards functional connectivity

Spatial Correlations

Distances

- Physical (Geometric)
- Anatomical
- Functional

- The complex neuroanatomy and neurophysiology make basic assumptions of many spatial methods questionable for neuroimaging

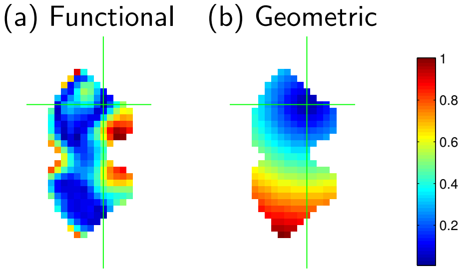
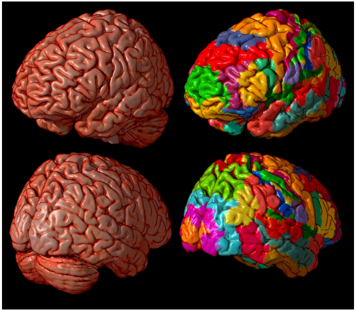


Figure: Selected axial slice of the cerebellum.

Bowman (2007), *JASA*.

Spatial Modeling Framework

- Stage I: perform voxel-level GLM analyses for each individual (AR model for temporal correlations).
- Stage II: we propose models that address spatial correlations
  - Define brain regions using neuroanatomic parcellation (e.g. Brodmann or AAL)
  - Spatial correlations
    - Within regions
    - Between regions
  - Inferences
    - Voxel-level
    - Regional



BSMac

EMORY ROLLINS SCHOOL OF PUBLIC HEALTH | CBIS Center for Biomedical Imaging Statistics

Stage II: Bayesian Spatial Model for Activation and Connectivity (BSMac):

$$\begin{aligned}
\mathbf{Y}_{igj} \mid \boldsymbol{\mu}_{gj}, \alpha_{igj}, \sigma^2_{gj} &\sim \mathrm{Normal}(\boldsymbol{\mu}_{gj} + \mathbf{1}\alpha_{igj}, \sigma^2_{gj}\mathbf{I}) \\
\boldsymbol{\mu}_{gj} \mid \lambda^2_{gj} &\sim \mathrm{Normal}(\mathbf{1}\mu_{0gj}, \lambda^2_{gj}\mathbf{I}) \\
\sigma^{-2}_{gj} &\sim \mathrm{Gamma}(a_0, b_0) \\
\boldsymbol{\alpha}_{ij} \mid \boldsymbol{\Gamma}_j &\sim \mathrm{Normal}(\mathbf{0}, \boldsymbol{\Gamma}_j) \\
\lambda^{-2}_{gj} &\sim \mathrm{Gamma}(c_0, d_0) \\
\boldsymbol{\Gamma}^{-1}_j &\sim \mathrm{Wishart}\left\{(h_0\mathbf{H}_{0j})^{-1}, h_0\right\}
\end{aligned}$$

- $\mathbf{Y}_{igj} = (Y_{igj1}, \ldots, Y_{igjV_g})'$, $\boldsymbol{\mu}_{gj} = (\mu_{gj1}, \ldots, \mu_{gjV_g})'$, and $\boldsymbol{\alpha}_{ij} = (\alpha_{i1j}, \ldots, \alpha_{iGj})'$

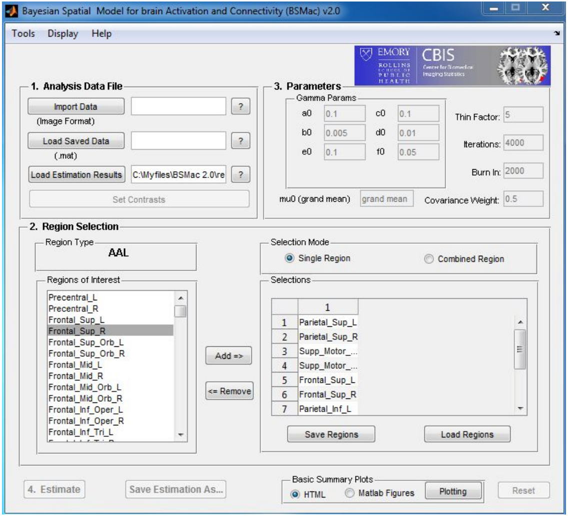
Bowman et al. (2008), *NeuroImage*

BSMac

- MCMC via Gibbs Sampler
- Exchangeable correlation structure between voxels within the same brain region
- $\boldsymbol{\Gamma}_j$ yields (unstructured) correlation model between regions
- Relatively fast estimation
- MATLAB Software available at www.sph.emory.edu/bios/CBIS/
- Related Spatial Models / Extensions: Derado et al. (2010), *Biometrics*
  - Extends model to capture temporal correlations between multiple scanning sessions (e.g. days or treatment periods)
  - BUT, does not capture between region spatial correlations

BSMac MATLAB Toolbox

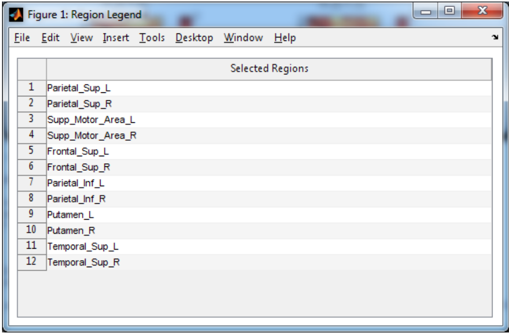
GUI Interface

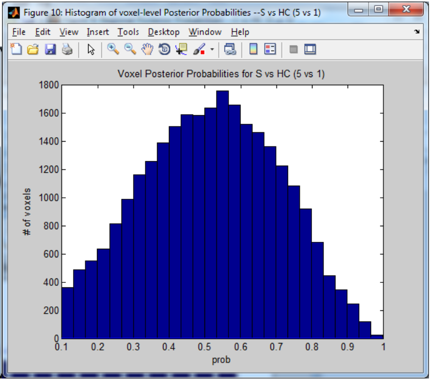


BSMac MATLAB Toolbox

EMORY ROLLINS SCHOOL OF PUBLIC HEALTH CBIS Center for Biomedical Imaging Statistics

Basic Summary Plots

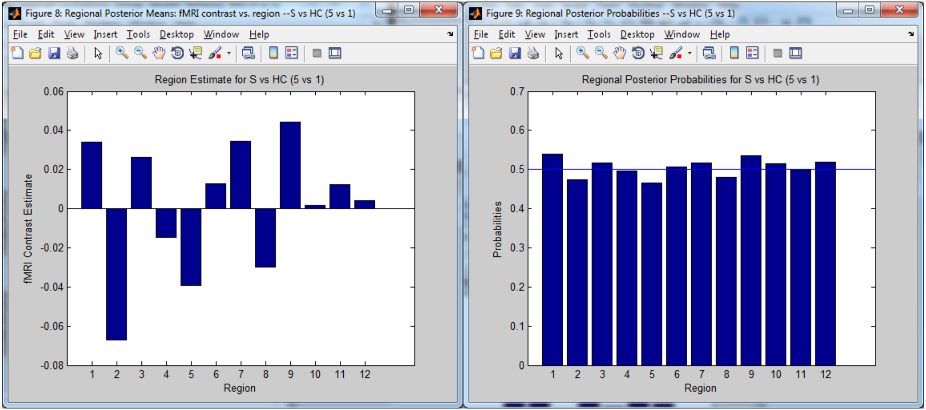




BSMac MATLAB Toolbox

EMORY ROLLINS SCHOOL OF PUBLIC HEALTH CBIS Center for Biomedical Imaging Statistics

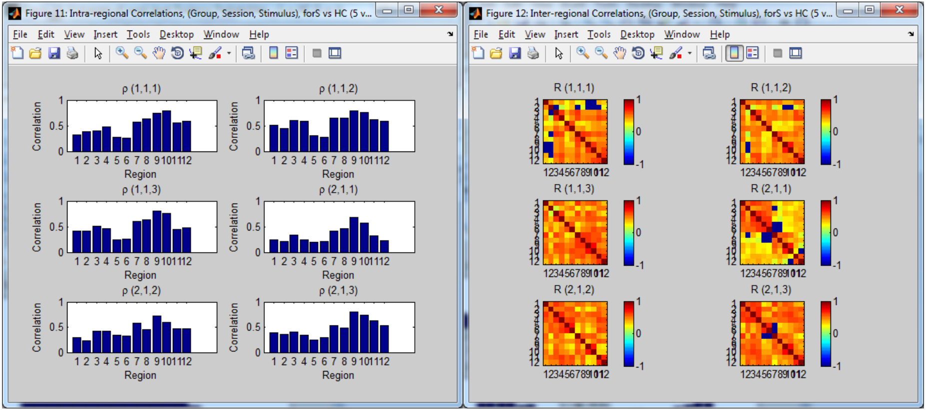
Basic Summary Plots



BSMac MATLAB Toolbox

EMORY ROLLINS SCHOOL OF PUBLIC HEALTH CBIS Center for Biomedical Imaging Statistics

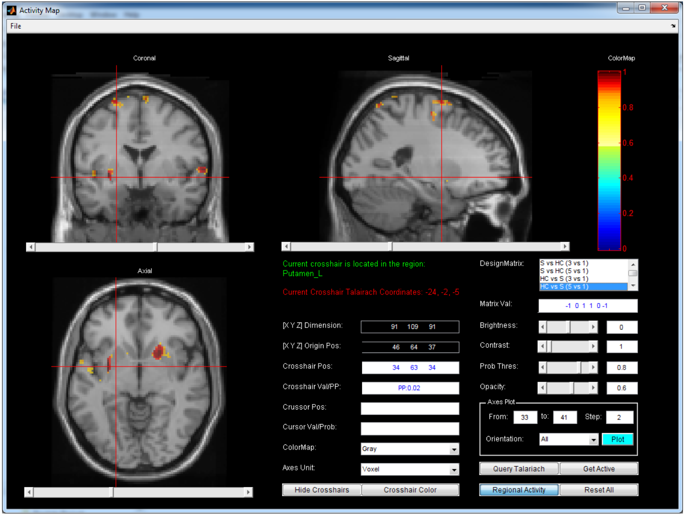
Basic Summary Plots



BSMac MATLAB Toolbox

EMORY ROLLINS SCHOOL OF PUBLIC HEALTH
CBIS Center for Biomedical Imaging Statistics

Interactive Activation Maps

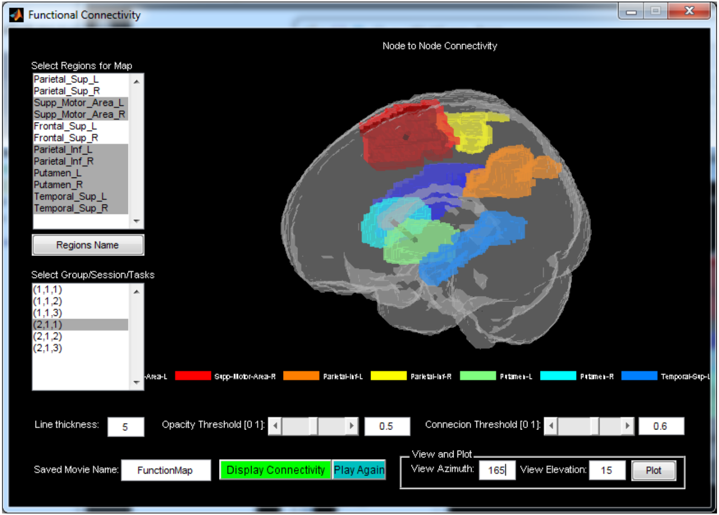


BSMac MATLAB Toolbox

Interactive Activation Maps

BSMac MATLAB Toolbox

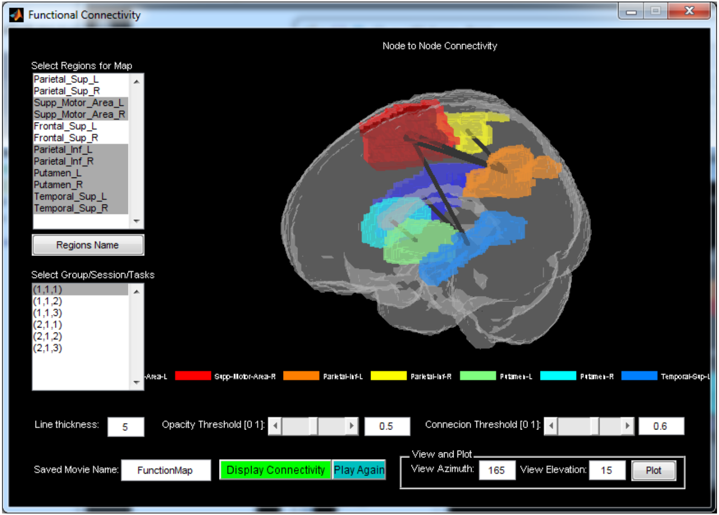
Task-Related Connectivity Maps: Schizophrenia Patients



BSMac MATLAB Toolbox

EMORY ROLLINS SCHOOL OF PUBLIC HEALTH
CBIS Center for Biomedical Imaging Statistics

Task-Related Connectivity Maps: Healthy Controls



Conclusions: BSMac

EMORY ROLLINS SCHOOL OF PUBLIC HEALTH | CBIS Center for Biomedical Imaging Statistics

BSMac framework

- Considers activation objectives and task-related functional connectivity
- Models correlations in brain activity
  - Within defined neuroanatomic regions
  - Between neuroanatomic regions
- Performs global analyses (not voxel-by-voxel)
- Permits voxel-level and region-level inferences

Limitations

- Does not account for temporal dependence between multiple sessions
- Fairly simple intra-regional correlation model

Prediction Studies

EMORY ROLLINS SCHOOL OF PUBLIC HEALTH | CBIS Center for Biomedical Imaging Statistics

- Emerging direction in neuroimaging
- Increase clinical applicability
  - Use imaging data to predict clinical outcomes (e.g. to distinguish treatment responders and non-responders)
  - We address intermediate objective of predicting neural responses
    - Forecast neural representations of disease progression
    - Predict neural responses to various treatments
- We develop a spatial modeling framework within this prediction context

Motivating Data Example

- From the Alzheimer's Disease Neuroimaging Initiative (ADNI) database `http://www.loni.ucla.edu/ADNI/`.
- Goal of ADNI project: to develop biomarkers of Alzheimer's Disease in elderly subjects.
- Study participants receive $[^{18}\mathrm{F}]$-2-fluoro-2-deoxy-2-glucose (FDG) PET scans at: baseline, 6 months, 12 months and 24 months.
- In our analysis, we used the baseline and month 6 scans.
- Participants classified as: mild cognitive impairment (MCI) patients, Alzheimer's disease (AD) patients, or healthy controls (HC).
- Training data set: 40 AD and 40 HC subjects; Testing data set: 33 AD and 33 HC subjects.

Bayesian spatial hierarchical model

EMORY ROLLINS SCHOOL OF PUBLIC HEALTH
CBIS Center for Biomedical Imaging Statistics

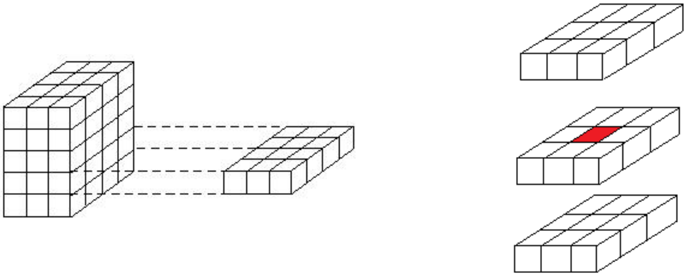
- We propose a novel Bayesian spatial hierarchical model for predicting follow-up neural activity based on baseline functional neuroimaging data and other patient characteristics.
- Model borrows strength from the spatial correlations present in the data.

Notation

- Let $i = 1, \ldots, n$ denote subjects, $v = 1, \ldots, V$ voxels, $g = 1, \ldots, G$ regions.
- Let $Y(v)$ denote the regional cerebral blood flow (rCBF) (a proxy for brain activity) at voxel v.
- Let $\mathbf{Y}_{ig}(v) = \left(Y_{ig}(v)^{(1)}, Y_{ig}(v)^{(2)}\right)^T$, (1)=baseline, (2)=follow-up

Spatial dependence: 3D neighborhood

- For each voxel in the analysis, we define a 3D neighborhood as the 26 immediate neighboring voxels.



- Borrow strength *locally*.
- We consider only within-region neighbors.
- This information is saved in a connectivity matrix W.

Model

$$
\begin{aligned}
\mathbf{Y}_{ig}(v)|\boldsymbol{\beta}_g, \boldsymbol{\phi}_g, \boldsymbol{\alpha}_{ig}, \gamma_{gv}, \mathbf{Z}_g &\sim \mathrm{N}(\boldsymbol{\beta}_g(v) + \boldsymbol{\phi}_g(v) + \boldsymbol{\alpha}_{ig} + \mathbf{X}_{ig}\gamma_g, \mathbf{Z}_g) \\
\phi_v|\phi_{v'}, v \neq v', \Sigma, v = 1\ldots, V &\sim \mathrm{N}(\rho \sum \frac{w_{vv'}}{w_{v+}} \mathbf{I}\, \phi_{v'}, \frac{1}{w_{v+}}\Sigma) \quad (\mathrm{MCAR}(\rho, \Sigma)) \\
\boldsymbol{\beta}_{gj}(v)|\lambda^2_{gj} &\sim \mathrm{N}(\boldsymbol{\beta}_{0gj}, \lambda^2_{gj}) \quad (\lambda_{vgj} = \lambda_{gj}, \forall v \in \text{region } g) \\
\mathbf{Z}_g^{-1} &\sim \text{Wishart}((c_1\boldsymbol{\Omega}_1)^{-1}, c_1) \\
\boldsymbol{\Sigma}^{-1} &\sim \text{Wishart}((c_2\boldsymbol{\Omega}_2)^{-1}, c_2) \\
\boldsymbol{\alpha}_{ij}|\boldsymbol{\Gamma}_j &\sim \mathrm{N}(\mathbf{0}, \boldsymbol{\Gamma}_j) \quad (\boldsymbol{\alpha}_{ij} = \boldsymbol{\alpha}_i^{(j)}) \\
(\boldsymbol{\Gamma}_j)^{-1} &\sim \text{Wishart}\{(h_j H_j)^{-1}, h_j\} \;\; j = 1, 2 \\
\lambda^{-2}_{gj} &\sim \text{Gamma}(a_j, b_j) \\
\gamma_{gjq}|\tau^2_{gjq} &\sim \mathrm{N}(0, \tau^2_{gjq}) \quad q = 1, \ldots, Q \text{ (covariates)} \\
\tau^{-2}_{gjq} &\sim \text{Gamma}(e_0, f_0) \\
\rho &\sim \text{Uniform}(\{0, 0.05, 0.1, ..., 0.9, 0.91, ..., 0.99\})
\end{aligned}
$$

▸ Model Details

Estimation and Prediction

EMORY ROLLINS SCHOOL OF PUBLIC HEALTH | CBIS Center for Biomedical Imaging Statistics

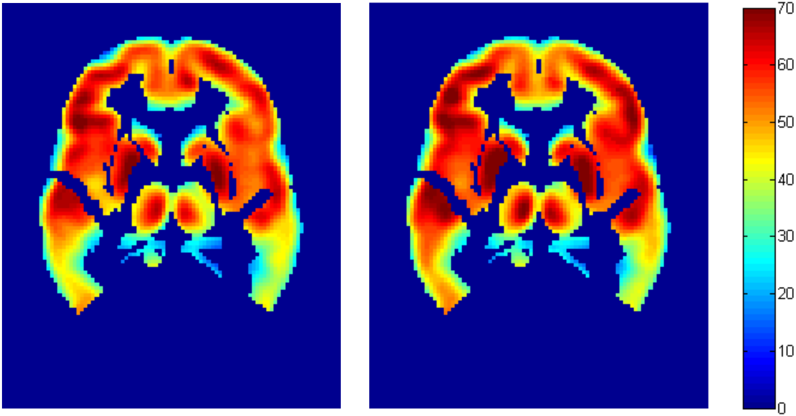
- Estimation is performed using MCMC techniques implemented via Gibbs sampler.
- Prediction:
  - For region g, we can write $\mathbf{Y}_g = (\mathbf{Y}_{g,1}^T, \mathbf{Y}_{g,2}^T)^T \sim \mathrm{N}\big((\boldsymbol{\mu}_{g,1}^T, \boldsymbol{\mu}_{g,2}^T)^T, \boldsymbol{\Sigma}_g\big)$, where $\boldsymbol{\Sigma}_g = \mathbf{Z}_g \otimes \mathbf{I}_{V_g}$.
  - Then $\mathbf{Y}_{i^*g,2}|\mathbf{Y}_{i^*g,1} \sim \mathrm{N}(\mathbf{b}_{i^*g}, \mathbf{A}_{i^*g})$, where

$$\mathbf{b}_{i^*g} = \boldsymbol{\mu}_{i^*g,2} + \boldsymbol{\Sigma}_{12}^T \boldsymbol{\Sigma}_{11}^{-1} (\mathbf{Y}_{i^*g,1} - \boldsymbol{\mu}_{i^*g,1})$$

    and $\boldsymbol{\mu}_{i^*g} = \boldsymbol{\beta}_g + \boldsymbol{\phi}_g + \mathbf{1}_{V_g} \otimes \boldsymbol{\alpha}_{i^*g} + \mathbf{1}_{V_g} \otimes \mathbf{X}_{i^*gv} \gamma_{gv}$.

  - Inputting the posterior mean of the parameters obtained from the MCMC estimation $\Rightarrow$ estimated conditional mean $\hat{\mathbf{b}}_{i^*g}$
  - The follow-up rCBF $\mathbf{Y}_{g,2}$ are predicted using the mean of the estimated conditional distribution , i.e. $\hat{\mathbf{b}}_{i^*g}$.

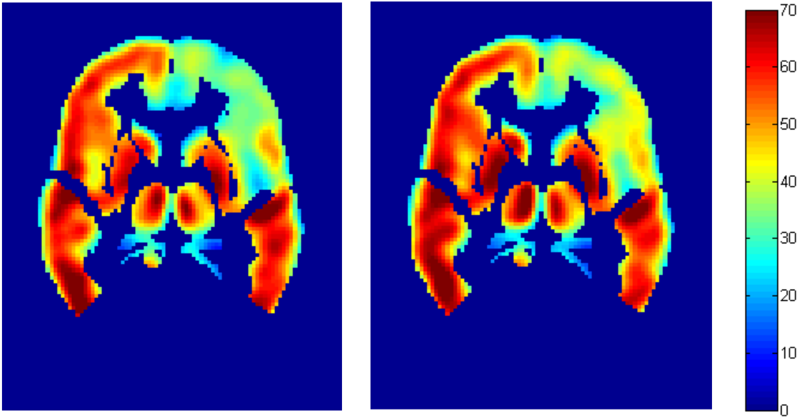
Results: Prediction for PET study of AD



Subject 1: observed $Y^{(2)}$ Subject 1: predicted $Y^{(2)}$

Figure: Individualized observed and predicted 6 month follow-up rCBF measurements for a test subject in the AD group (axial slice 40).

Results cont.



Subject 19: observed $Y^{(2)}$ Subject 19: predicted $Y^{(2)}$

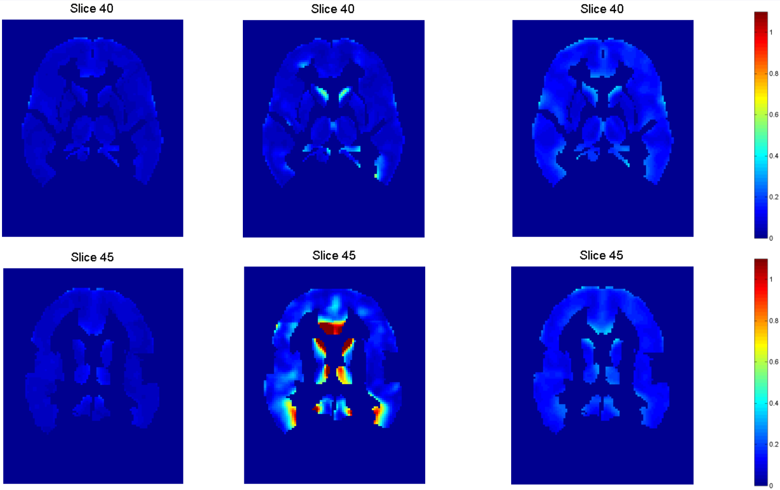
Figure: Individualized observed and predicted 6 month follow-up rCBF measurements for a test subject in the AD group (axial slice 40).

Prediction Error

- We evaluate the prediction error using a scale-free (squared error) loss function, which adjusts for local magnitude of brain activity

$$\text{stPMSE}\left(\{Y_i^{(2)}(v)\},\{\hat{Y}_i^{(2)}(v)\}\right)=\frac{\sqrt{\frac{1}{N}\sum_{i=1}^{N}[\hat{Y}_i^{(2)}(v)-Y_i^{(2)}(v)]^2}}{\frac{1}{N}\sum_{i=1}^{N}Y_i^{(2)}(v)}$$

Comparative Analyses



Model	BSPM	BSMac	GLM
Aver. error	0.083	0.154 (85.5% increase)	0.157 (89.2% increase)

Simulation Study

EMORY ROLLINS SCHOOL OF PUBLIC HEALTH CBIS Center for Biomedical Imaging Statistics

- We simulated 100 data sets for 15 subjects.
- Selected 5 AAL regions with sizes ranging from 234 to 4,655 voxels.
- Specified the *true* values for β_g, ϕ_g, α_i, and γ_g.
- The rest of the (hyper)parameters drawn from their prior distributions.

Param.	Region 1		2		3		4		5	
	True	Est.	True	Est.	True	Est.	True	Est.	True	Est.
Z_g^{11}	323.26	321.09	160.61	159.99	11.46	11.46	3.44	3.44	3.57	3.57
Z_g^{22}	120.75	120.46	45.30	45.11	37.24	37.19	10.45	10.45	3.38	3.38
Z_g^{12}	-41.95	-41.25	-33.70	-33.40	16.32	16.30	4.08	4.08	2.40	2.40

Table: Summary of the simulation results for the parameters in the covariance matrix $\mathbf{Z}_g$.

Conclusions: Prediction Model

EMORY ROLLINS SCHOOL OF PUBLIC HEALTH | CBIS Center for Biomedical Imaging Statistics

Our model

- Incorporates both local within-region spatial correlations and long-range correlations between neuroanatomic regions.
- Accounts for temporal dependence between baseline and follow-up brain activity.
- Yields a method for predicting follow-up brain activity based on the baseline activity and relevant subject characteristics.
- Exhibits increased accuracy relative to GLM and BSMac

Limitations

- Does not account for local spatial correlations across entire brain region
- Current estimation procedure computationally costly

Summary

We propose:

1. BSMac: a spatial modeling framework for combined activation and connectivity analyses of fMRI data
    - Captures *spatial correlations*, both between voxels in the same anatomical region and between regions
    - Yields more informative analyses and more efficient estimates than conventional methods
    - Recommended use for studies in which it is not important to model correlations between multiple scanning sessions

Summary

We propose:

1. BSMac: a spatial modeling framework for combined activation and connectivity analyses of fMRI data
    - Captures *spatial correlations*, both between voxels in the same anatomical region and between regions
    - Yields more informative analyses and more efficient estimates than conventional methods
    - Recommended use for studies in which it is not important to model correlations between multiple scanning sessions
2. A novel prediction framework for functional neuroimaging data
    - Captures *spatial correlations*, both between voxels in the same anatomical region and between regions, as well as *temporal correlations* between multiple scanning sessions
    - May be used for activation and task-related connectivity inferences
    - In context of prediction objectives, yields improved prediction error

Acknowledgements and References

EMORY ROLLINS SCHOOL OF PUBLIC HEALTH | CBIS Center for Biomedical Imaging Statistics

Many thanks to

- Dr. Gordana Derado
- Dr. Ying Guo
- Dr. Lijun Zhang
- Shuo Chen

References

1. Bowman, F. D. (2007). Spatio-Temporal Models for Region of Interest Analyses of Functional Neuroimaging Data. *Journal of the American Statistical Association*, 102(478), 442-453.
2. Bowman, F. D., Caffo, B. A, Bassett, S., and Kilts, C. (2008). Bayesian Hierarchical Framework for Spatial Modeling of fMRI Data. *NeuroImage*, 39, 146156.
3. Derado, G., Bowman, F. D. and Kilts, C. D. (2010). Modeling the spatial and temporal dependence in fMRI data, *Biometrics*, 66, 949-957.
4. Gelfand, A. E. and Vounatsou, P. (2003). Proper multivariate conditional autoregressive models for spatial data analysis. *Biostatistics*, **4** (1), 11–25.
5. Guo, Y., Bowman, F.D., Kilts, C. (2008). Predicting the brain response to treatment using a Bayesian Hierarchical model with application to a study of schizophrenia. *Human Brain Mapping*, **29**, 1092–1109.