Bayesian Approaches for Inference on Brain Connectivity Networks

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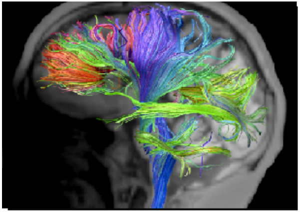
Outline of the Talk

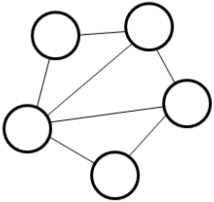
- Brain connectivity
- Bayesian integrative approach
  - Resting-state fMRI data, multiple subjects
  - Vector autoregressive model
  - Spatial priors that also incorporate structural data
  - Group- and subject-level inference
- Dynamic functional connectivity

Brain connectivity

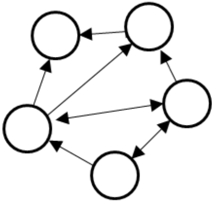
How neurons, neuronal populations, or brain regions interact



Structural Connectivity



Functional Connectivity



Effective Connectivity

- Structural connectivity, as anatomical structure (DTI, MRI)
- Functional connectivity, as undirected association, or temporal correlation (fMRI).
- Effective connectivity, as directed influence of one brain region on other regions (fMRI).

Graphs over multiple groups of subjects, multiple tasks, ...

Graphical Modeling Approaches to Connectivity

Natural setting for graphical models.

- Functional (fMRI): Undirected graphs.

  - Graphical Lasso (Varoquaux et al., 2010; Cribben et al., 2012)
  - Bayesian models (Hinne et al., 2014; Warnick et al. 2018)

- Effective (fMRI): Models for directed graphs estimation

  - VAR and SVAR (Gorrostieta et al. 2013; Ting et al 2017)
  - Bayesian approaches
  (Yu et al. 2016; Chiang et al. 2017; Kook et al. 2021)

Vector autoregressive model formulation

Data

$\mathbf{x}_t^{(s)}$: $(R \times 1)$ vector of fMRI BOLD signal at time t for subject s for the R regions (micro-areas of brain)

η_s: known disease group for subject s, $\eta_s = g$

Model

Multivariate VAR process of order L for each subject s:

$$(\boldsymbol{x}_t^{(s)} | \eta_s = g, \phi_{l,g}^{(s)}, \Xi) = \sum_{l=1}^{L} \phi_{l,g}^{(s)} \boldsymbol{x}_{t-l}^{(s)} + e_t^{(s)}, \quad e_t^{(s)} = e_t \sim \mathsf{N}(0, \Xi)$$

$\phi_{l,g}^{(s)} \rightarrow R \times R$ VAR coefficients capturing lag-specific effective connectivities between regions for subject s

Prior on subject-level effective connectivities

For subject s in group g, we model the subject-level parameters as random deviations from a baseline process

$$p(\underline{\beta}_g^{(s)}|\Omega^{(g)}, \Sigma^{(g)}) \;=\; \mathsf{N}\left(\Omega^{(g)}, \Sigma^{(g)}\right)$$

- $\underline{\beta}_g^{(s)}$ is the vectorized subject-level effective connectivities for subject s in group g
- $\Omega^{(g)}$ is a baseline process that captures the vectorized effective connectivities for group g
- Estimate non-zero connectivities (i.e., edges) at group level via *spike-and-slab* priors. Impose sparsity at group level while allowing subject-specific connectivities to deviate from group mean.

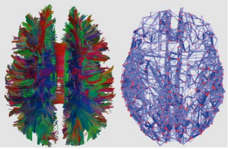
Spatial *Spike-and-Slab* Prior

Introduce binary $\gamma_k^{(g)}$ to indicate whether connectivity k in group g is non-zero

$$\omega_k^{(g)} \sim \gamma_k^{(g)} \mathsf{N}\left(\frac{\sum_{k'=1}^{LR^2} S_{kk'}\omega_{k'}^{(g)}}{\sum_{k'=1}^{LR^2} S_{kk'}}, \frac{q}{\sum_{k'=1}^{LR^2} S_{kk'}}\right) + (1-\gamma_k^{(g)})\delta_0(\omega_k^{(g)})$$

- *Slab* ICAR prior, encouraging smoothness across regions and lags.
- Prior probability of non-zero effective connectivity increases with stronger structural connectivity ($N_k^{(g)}$ strength of structural connectivity)

$$p(\gamma_k^{(g)} = 1) = \Phi\left(\alpha_0^{(g)} + \alpha_1^{(g)} N_k^{(g)}\right)$$



- Normal prior on $\alpha_1^{(g)}$; sparsity parameter $\alpha_0^{(g)}$

Posterior inference

MCMC sampling

- Metropolis-within-Gibbs sampler
- Data augmentation with latent variable $z_k^{(g)}$ to sample parameters of probit prior
- Gibbs step on $(\beta_g^{(s)}, \Omega^{(g)}, \xi_1^{(g)}, \xi_0^{(g)}, z_k^{(g)}, \alpha_1^{(g)}, \zeta_j)$
- Joint Metropolis-Hastings step with between and within-model steps for γ_j and $\Omega^{(g)}$ using SSVS

Effective connectivity inference using VAR coefficients

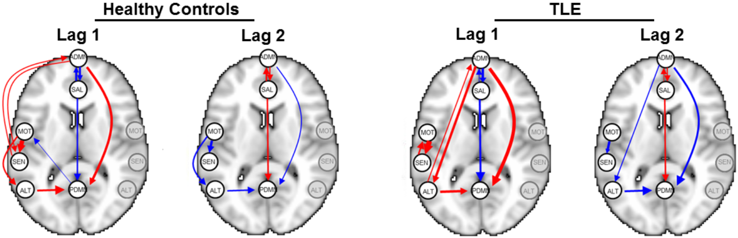
- VAR coefficients measure the magnitude and directionality of effective connectivity (EC) between two regions
- Group-level EC estimated from posterior sample of $\Omega^{(g)}$
- Subject-level EC estimated from posterior sample of $\beta_g^{(s)}$
- Non-zero group ECs estimated from posterior sample of γ

Case Study on Temporal Lobe Epilepsy

- Rs-fMRI + structural T1 data on n_1=23 healthy controls and n_2=25 TLE patients, from UCLA Seizure Disorder Center
- R=6 resting-state networks were extracted from rs-fMRI data using group ICA (Calhoun et al., 2001)
- Mean time-series for each network for each subject
- $N_k^g \rightarrow$ Informed selection using structural T1 data (Pearson correlation coefficients between grey matter volumes of each pair of components)
- $S_{kk'} = 1$ for connectivities at a given lag that initiate from the same node or connectivities between the same nodes at different lags.

Results

- Group-level connectivities ($L = 2$ by BIC)
- Red edges indicate positive VAR coefficient; blue edges indicate negative VAR coefficient



- Known relationships of anterior and posterior DMN
- Epileptic brains engage other parts of the brain to handle alertness tasks.

Chiang *et al.* (2017, *Human Brain Mapping*)

Methods comparison

Two-step approaches

- Two-step estimation using Granger causal inference followed by group-level t-testing (FDR control, 0.05)
- Two-step estimation using Granger-causal inference, followed by generation of subject-level p-value maps and combination for group maps using Fisher's method (FDR control, 0.05)

Simulated data

- $R = 5$ regions, $n = 20$ subjects, $G = 2$, VAR(1), $T = 300$
- Non-zero group connectivities from Unif(0,0.5) with underlying structural connectivity ($\alpha_0^{(g)} = 1.5$, $\alpha_1^{(g)} = 5$)
- Subject-level connectivities generated by adding random matrix with eigenvalues (-0.4, -0.25, -0.1, 0.05, 0.2) to group-specific connectivities

Performance for detection of non-zero effective connectivity at group level

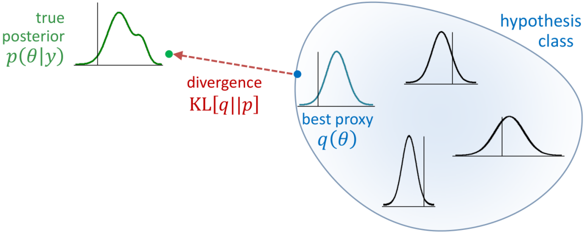
- FPR, FNR, accuracy, *F1*-score

		Proposed	Multi-step methods	
			t-test	Fisher
Group 1	FPR	**0.01**	0.27	0.70
	FNR	**0.18**	0.31	0.16
	Accuracy	**0.91**	0.71	0.56
	F_1-score	**0.89**	0.69	0.64
Group 2	FPR	**0.14**	0.40	0.68
	FNR	**0.09**	0.12	0.24
	Accuracy	**0.88**	0.73	0.52
	F_1-score	**0.87**	0.74	0.58

- t-test approach outperformed Fisher approach
- Proposed approach gives better detection than multi-step approaches
- Confirmed by averaged MSEs of subject-level connectivity ($\beta_g^{(s)}$)

Scaling it up via Variational Inference

- Variational inference turns inference into an optimization problem. Faster and more scalable than MCMC.
- Underlying idea: pick family of distributions $q_\phi(\boldsymbol{\theta}) \in \mathcal{Q}$, with free variational parameters ϕ; use gradient descent to minimize KL divergence between q and posterior $p(\boldsymbol{\theta}|\mathbf{y})$, i.e. maximize ELBO



$$q_{\phi*} = \arg\min_{q_\phi \in Q} KL\left(q_\phi \parallel p\right) = \log p(\mathbf{y}) - \left(\mathbb{E}_{q_\phi(\boldsymbol{\theta})}[\log p(\boldsymbol{\theta}, \mathbf{y})] + \mathbb{H}[q_\phi(\boldsymbol{\theta})]\right)$$

Mean Field VI

- Fully factorized approximation to reduce complexity

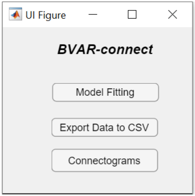
$$\prod_{s=1}^{n} q\left(\underline{\beta}_g^{(s)}\right) \prod_{j=1}^{R} q\left(\zeta_j\right) \prod_{g=1}^{G} q\left(\alpha_1^{(g)}\right) q\left(\xi_1^{(g)}\right) q\left(\xi_0^{(g)}\right) \prod_{k=1}^{LR^2} q\left(\tilde{\omega}_k^{(g)} \mid \gamma_k^{(g)}\right) q\left(\gamma_k^{(g)}\right) q\left(\phi_k^{(g)}\right)$$

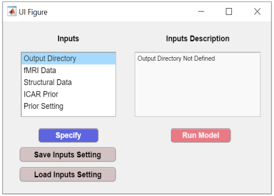
- Choose approximating distributions from same family as prior distributions, to exploit conjugacy.
- Comparable performance, 40h vs 1min (R=10; 30 replicates)

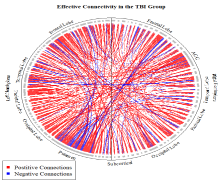
		MCMC	VB
Group 1	FPR	0.0113	0.0196
	FNR	0.2207	0.1527
	Accuracy	0.9024	0.9250
	F_1-score	0.866	0.9032
Group 2	FPR	0.0047	0.0239
	FNR	0.2205	0.1274
	Accuracy	0.8714	0.9343
	F_1-score	0.9087	0.9141

BVAR-connect (https://github.com/marinavannucci/)

MATLAB GUI implementing the Bayesian VAR model with VI







Model fitting interface: Inputs: Output Directory, fMRI Data, Structural Data, ICAR Prior, Prior Setting.

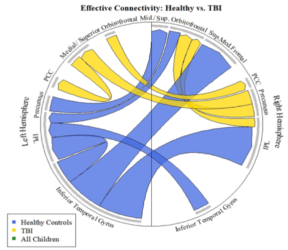
Visualization interface: Connectograms.

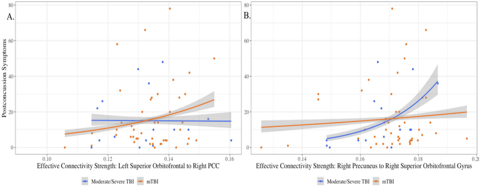
Export connectivities to a CSV file.

Kook *et al.* (2021, *NeuroInformatics*)

Case Study on Traumatic Brain Injury

- DTI and fMRI data on 70 pediatric TBI patients with mild or moderate/severe TBI and 50 healthy controls.
- Goals: examine group-level DMN reorganization and relate individual variability to post-concussion symptoms (PCS).
- Effective connectivity may be a sensitive neuroimaging marker of PCS (for both TBI and mTBI)





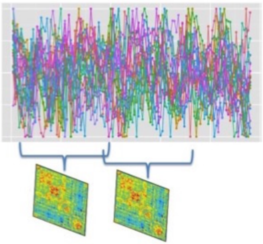
Vaughn *et al.* (2020, *Human Brain Mapping*, revised)

Dynamic Connectivity

- Traditional approaches assume stationarity in time.
- Increased realization that brain connectivity is dynamic.
- Naive approach: Sliding window (Allen et al. 2012; Cribben et al. 2012; Xu and Lindquist 2015)

Many (All?) approaches often require multiple-steps for obtaining the relevant inference, e.g.

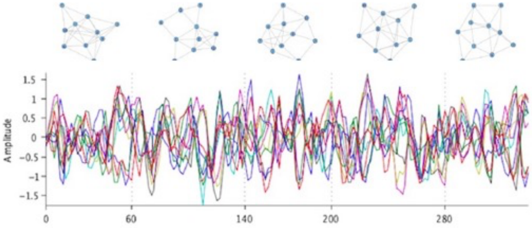
- **select windows**
- **estimate windowed covariance matrices (Glasso?)**
- **Cluster those matrices through k-means**



Many aspects need to be taken into consideration (task vs resting state data, single vs multiple subjects).

Hidden Markov Models

- Incorporate HMM in graphical modeling approaches



- Simultaneous change points detection (via HMMs) and network estimation over *noncontiguous* time points (via graphs).
- Functional connectivity: Undirected GGMs (Warnick et al. 2018)
- Effective connectivity: SVAR (Samdin et al 2017) - single subject

- Bayesian VAR model for multi-subject fMRI data
- Group- and subject-level connectivity networks
- Sparsity priors that also incorporate structural data
- Flexible structure for the incorporation of external information and/or data integration.
- Variational inference approximations for scalability.
- Improved performance over competitive (two-stage) approaches.

Chiang *et al.* (2017, *Human Brain Mapping*) Kook *et al.* (2021, *NeuroInformatics*)

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