Testing for group differences in brain functional connectivity

Junghi Kim, Wei Pan, for ADNI

Division of Biostatistics, School of Public Health, University of Minnesota,
Minneapolis, MN 55455

Banff

Feb 4, 2016

Outline

- Introduction: problem.
- Methods: aSPU and aNBS tests.
- ADNI data example.
- Simulations
- Discussion
- Refs: Pan et al (2014, *Genetics*); Kim et al (2014, *NeuroImage*); Kim et al (2015a, *Brain Connectivity*); Kim et al (2015b, *NeuroImage: Clinical*).

Introduction

- Functional connectivity (FC): statistical correlations of brain activities.
- Increasing evidence of altered brain FC networks associated with neurological diseases like AD.
- Given rs-fMRI data: BOLD time series at N brain ROIs for n subjects;
  $\implies$ a connectivity measure for each pair of the ROIs for each subject, i.e. Pearson's correlation or partial correlation, then Fisher transformed
  $\implies X_i = (X_{i1}, X_{i2}, ..., X_{ik})'$, $k = N(N-1)/2$.
- Each subject i is in one of two groups: $Y_i = 0$ or 1; possible covariates Z_i.
- Q: any association between Y_i and X_i (after ajusting for Z_i)? a high-dim two-sample problem: n in 10s-100s; k in 1000s.

Introduction

- Standard approaches:
  1. Mass-univariate: t-tets on (Y_i, X_{ij})'s for each j; low powered for multiple weak signals;
  2. Derive some network summary statistics, e.g. clustering coefficient, then t-test; not easy, over-simplified?
- Ours: a global test; why?
  can rank the changes.

Methods: SPU tests

- Logistic regression model:

$$\text{Logit}\left[Pr(Y_i = 1)\right] = \beta_0 + \sum_{j=1}^{k} X_{ij} \cdot \beta_j + \sum_{m=1}^{l} Z_{im}\delta_m. \quad (1)$$

- H_0: $\beta = (\beta_1, ..., \beta_k)' = 0$.
- Score vector: $U = \sum_{i=1}^{n}(Y_i - \hat{Y}_i^0)X_i$
  $\hat{Y}_i^0$: fitted value from the null model (under H_0);
  $U \propto \hat{\beta}$; $U \propto \bar{X}^{(1)} - \bar{X}^{(2)}$ if no Z_i's.
  Usual asymptotics: $U \sim N(0, V)$; not used for large k.
- SPU tests: for a $\gamma > 0$,

$$SPU(\gamma) = \sum_{j=1}^{k} U_j^{\gamma} \propto ||U||_\gamma,$$

$$SPU(\infty) = ||U||_\infty = \max_j |U_j|.$$

Methods: SPU tests

-
$$SPU(\gamma) = \sum_{j=1}^{k} U_j^{\gamma} = \sum_j U_j^{\gamma-1} \cdot U_j,$$

- Remarks:
  1) Challenge: many U_j's non-informative (i.e.aedge j not changed); noise accumulation!
  2) Var selection: too difficult with weak signals;
  3) Weighting: weighted score with $w_j = U_j^{\gamma-1}$;
  4) Use an odd vs even integer for γ ...

Methods: aSPU test

- SPU tests: $SPU(\gamma) = \sum_{j=1}^{k} U_j^{\gamma}$, $SPU(\infty) = \max_j |U_j|$.
- GEE-SPU(1) = Sum/burden test;
  under assumtipn $\beta_1 = ... = \beta_k$; huge dim reduction.
- SPU(2) = distance-based reg/nonprametric MANOVA = KMR (or SKAT) if ...;
  McArdle & Anderson (2001, *Ecology*); Wessel & Schork (2006, *AJHG*); Liu, Lin & Ghosh (2007, *Biometrics*), Lee et al, Wu et al (*AJHG*); Pan (2011, *Genet Epi*).
- $SPU(\infty) \approx$ mass-univariate t-test;
- Optimal γ unknow, data-dependent.
- aSPU:
$$T_{aSPU} = \min_{\gamma \in \Gamma} P_{SPU(\gamma)}.$$

  $\Gamma = \{1, 2, 3, ..., 8, \infty\}$; use permutations (or simulations) to calculate the p-value.

Methods: Extensions

- Connectivity X_i: use (regularized) cov or precision matrix? how much regularization?
  Use Glasso: $\Omega = R^{-1}(\lambda)$ or $R(\lambda)$;
  Use the density c (i.e. prop of non-zeros), instead of λ in $R^{-1}(\lambda)$.

- Use $X_i(c, \Omega)$, define $U(c, \Omega))$ and $SPU(\gamma, c, \Omega)$,

$$T_{aSPU(\gamma,\Omega)} = \min_{c \in C} P_{SPU(\gamma,c,\Omega)}.$$

$$T_{daSPU(\Omega)} = \min_{\gamma \in \Gamma} P_{aSPU(\gamma,\Omega)}.$$

$$T_{taSPU} = \min_{\Omega \in \{\widehat{\Theta}, \widehat{\Sigma}\}} P_{daSPU(\Omega)}.$$

- Permuting residuals to calculate p-values.

- NBS(t): the size of the largest subnetwork with significant edges (their t-stat $> t$);
  similarly define aNBS, daNBS, taNBS.

Example: ADNI-2 data

- 30 AD patients, 38 cognitively normal (CN) controls;
- 116 AAL ROIs; $N = 116$
- Covariates: age ($p = 0.09$), gender (NS), education in years (NS).
- $k = 116 \times (116 - 1)/2 = 6670$ edges;
- taSPU: $p = 0.02$; taNBS: $p = 0.06$.
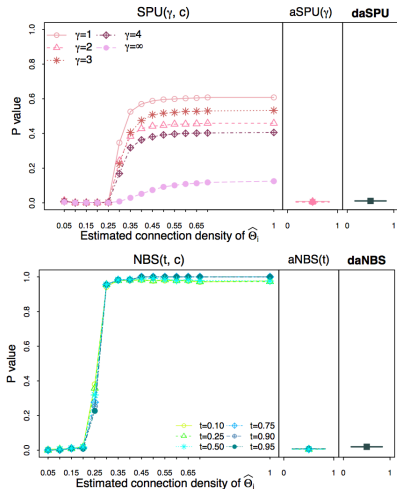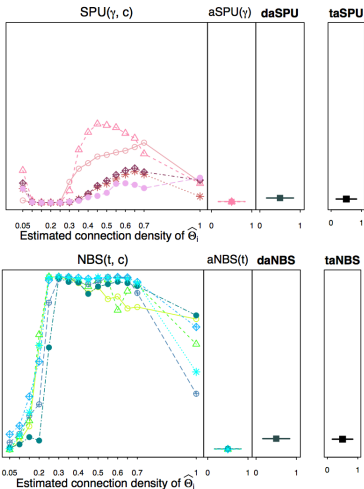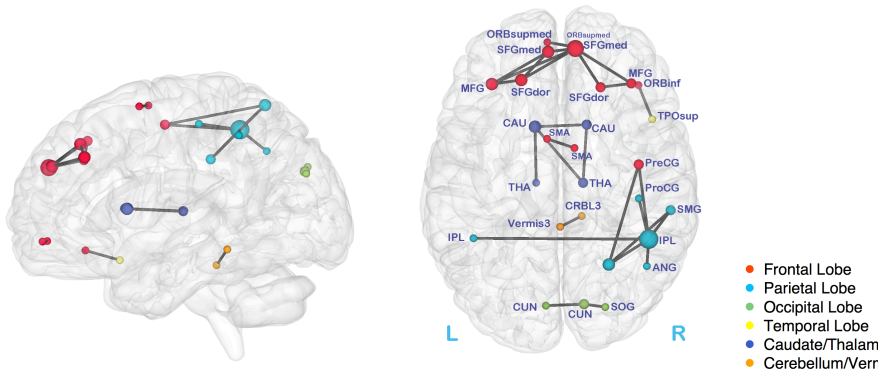
Figure: P-values for the ADNI data.
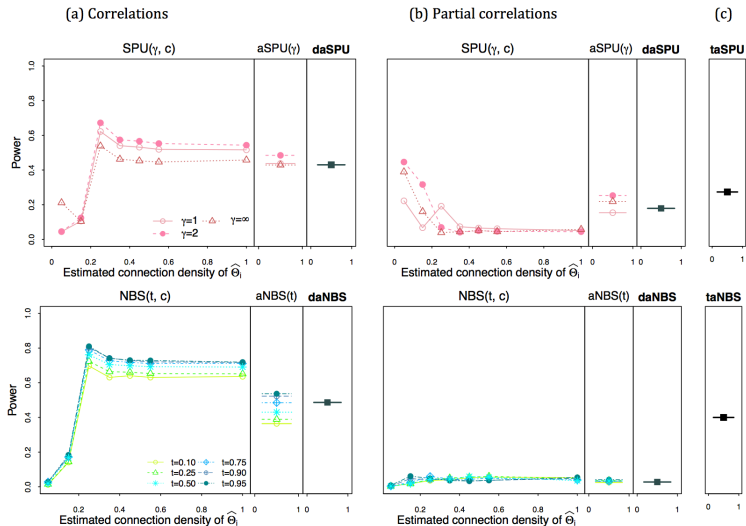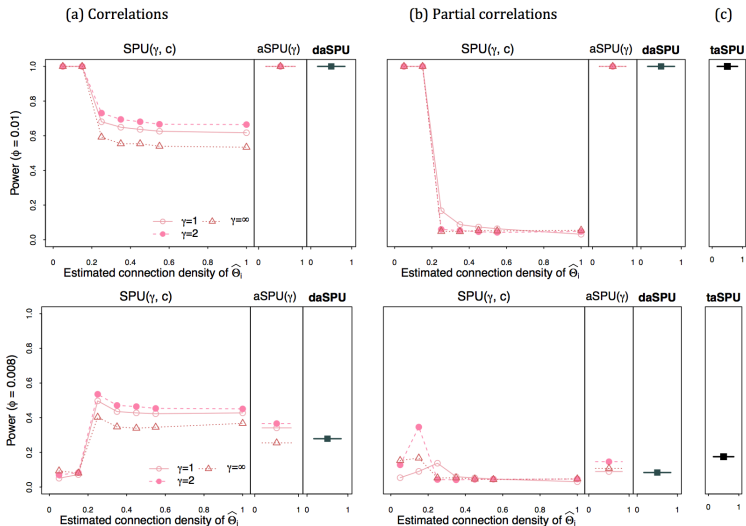
Figure: Altered brain connectivity for AD.

Figure: Simulation: power with sparse precision matrices.

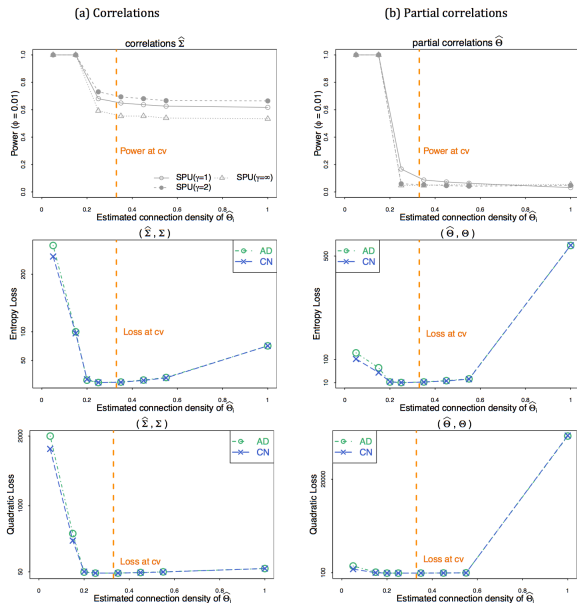Figure: Simulation: power with sparse precision matrices.

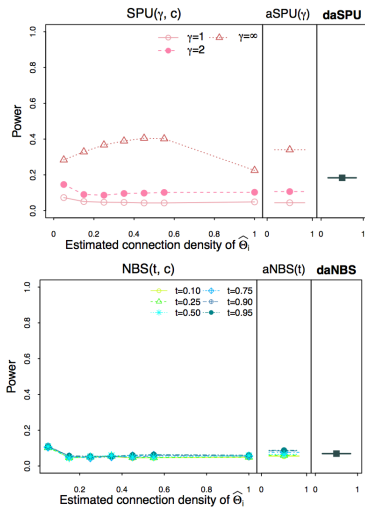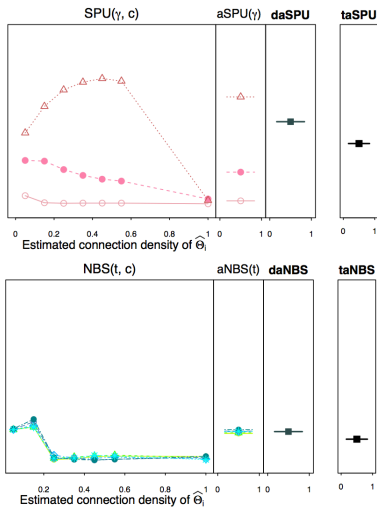Figure: Simulation: power with sparse precision matrices and CV-selected tuning parameters.

Figure: Simulation: power with sparse cov matrices.

Discussion

- ▶ Being adaptive is good!
- ▶ Easy to use: rigorous control of type I errors.
  In practice, noisy data, small n, ...
- ▶ Connection with testing on high-dim cov matrices:
  Li & Chen (2012, *AoS*): $\approx SPU(2)$;
  Cai et al (2013, *JASA*): $\approx SPU(\infty)$;
  but theirs: no regularization, no S vs S^{-1}.
- ▶ When using the sample cov or Glasso, ignored temporal
  correlations; OK?
  A working independence model!
  Theory (Shu & Nan 2014; Zhou 2014, *AoS*).
- ▶ Current work: neuroimaging genetics ...
- ▶ Others: theory, other applications (ordinal or multivariate
  Y)...

Acknowledgement

- http://www.biostat.umn.edu/~weip
  R packages aSPU and highmean on CRAN.
- This research was supported by NIH and Minnesota Supercomputing Institute at U of MN.
- **Thank you!**