

Rank-adaptive covariance changepoint detection for estimating dynamic functional connectivity from fMRI data

David Veitch^{1,2}

Joint work with Yinqui He³ Jun Young Park^{1,2}

¹University of Toronto ²Data Sciences Institute at the University of Toronto ³University of Wisconsin-Madison

ENAR March 11 2024



Agenda

1 Scientific Background

2 Research Question

3 Methodology

4 Theoretical Results

5 Real Data Analysis

6 Discussion

7 Appendix

Functional MRI (fMRI)

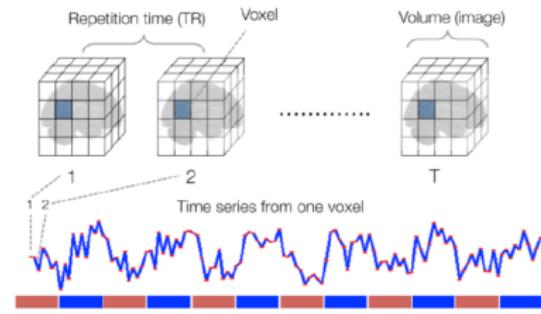
Magnetic resonance imaging (MRI) comes in two types

- **Structural:** anatomy and pathology of brain
- **Functional (fMRI):** brain activity

Brain activity is generally measured via **Blood Oxygen Level Dependent (BOLD)** signals. Safe to collect, 95%+ of fMRI studies use this.



(a) MRI scanner [1]



(b) Illustration of data collected for each voxel over time [2]

Functional Connectivity (FC)

“**Functional connectivity** is defined as the undirected association between two or more fMRI time series” [2].

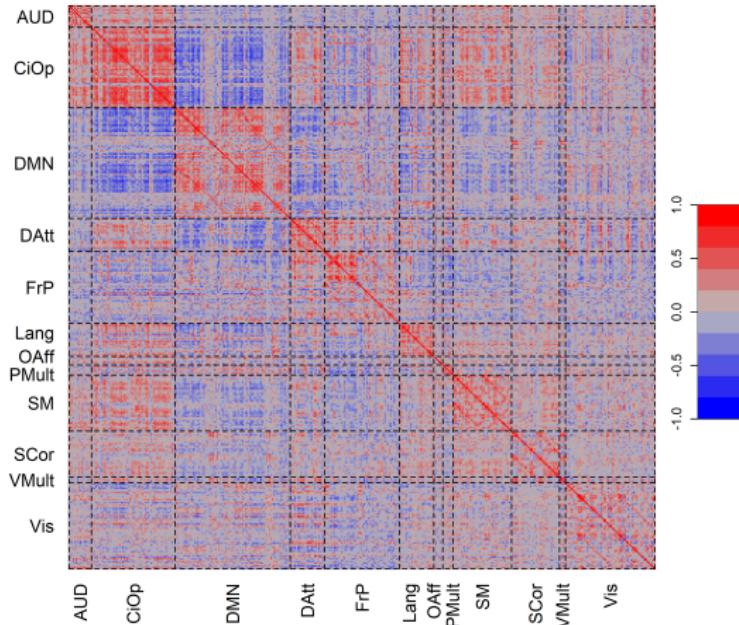


Figure: Functional connectivity matrix (sample correlation) of fMRI time series using all time points. A clear low-rank block structure is present.

Dynamic Functional Connectivity

- **Dynamic functional connectivity (DFC)**: functional connectivity which changes over time.
- Unknown if DFC best characterized as changing in discrete fashion (e.g. ABAABA) or continuously.

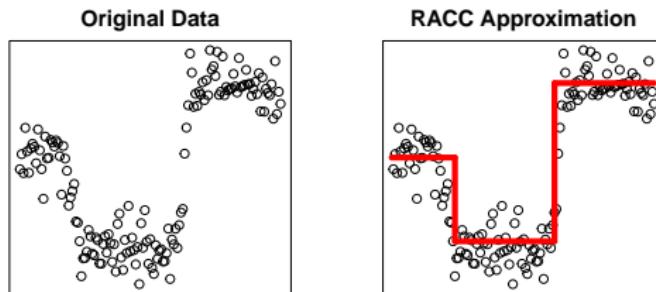


Figure: Illustration of RACC's approximation of FC

Potential biomarkers:

- Number of changes
- Time per state
- High connectivity vs. low connectivity

Time-Varying Sample Covariance Matrix - Windowed

Covariance matrix of rs-fMRI data for an example subject. Window width of 20 observations.

RACC Segmentation of rs-fMRI Data

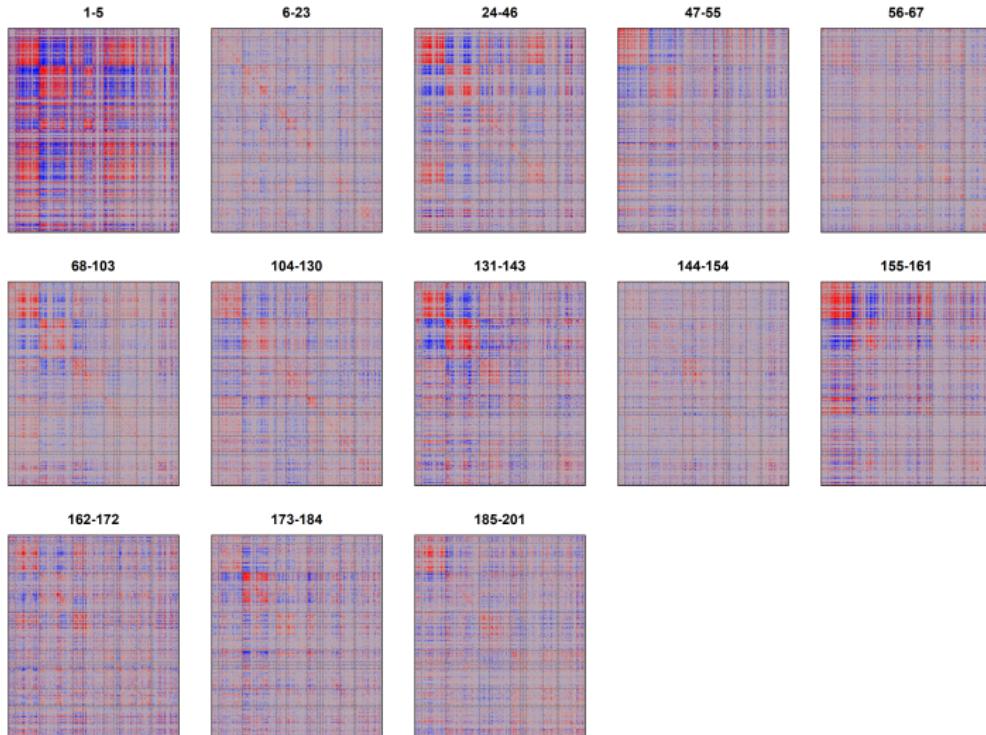


Figure: Empirical covariance matrices for the 13 segments of constant covariance after changepoints were identified by RACC.

Research Question

Our research addresses how to best segment resting state fMRI (rs-fMRI) time series into segments with constant covariance structure. We take a changepoint detection approach and propose RACC: **R**ank **A**daptive **C**ovariance **C**hangepoint detection.

Challenges of rs-fMRI Segmentation

- Type I error control & selective inference
- $p \gg n$

Features of RACC

- Binary Segmentation Algorithm
- Permutation Test (and controlled Type I errors)
- Adaptive test statistic (low-rank covariance structure)

RACC Methodology

To test H_0 of constant covariance structure we use the following test statistic

$$T = \underbrace{\max_{i \in q, \dots, n-q}}_{\text{max over time}} \quad \underbrace{\max_{s \in \mathcal{S}}}_{\text{max over matrix norms}} \frac{||\hat{\Sigma}_i^L - \hat{\Sigma}_i^R||_s - \hat{\mu}_{H_0, i, s}}{\hat{\sigma}_{H_0, i, s}}$$

$$\hat{\mu}_{H_0, i, s} = \hat{E}_{H_0} \left[||\hat{\Sigma}_i^L - \hat{\Sigma}_i^R||_s \right] \quad \text{and} \quad \hat{\sigma}_{H_0, i, s}^2 = \widehat{\text{Var}}_{H_0} \left[||\hat{\Sigma}_i^L - \hat{\Sigma}_i^R||_s \right]$$

Use permutations to find critical values of T , if reject null changepoint identified at $\hat{i} = \operatorname{argmin}_i \max_{s \in \mathcal{S}} \frac{||\hat{\Sigma}_i^L - \hat{\Sigma}_i^R||_s - \hat{\mu}_{H_0, i, s}}{\hat{\sigma}_{H_0, i, s}}$

Adaptive Ky-Fan(k) Statistic

$$T = \max_{i \in q, \dots, n-q} \max_{s \in \mathcal{S}} \frac{||\hat{\Sigma}_i^L - \hat{\Sigma}_i^R||_s - \hat{\mu}_{H_0, i, s}}{\hat{\sigma}_{H_0, i, s}}$$

- Covariance matrix of rs-fMRI characterized by low-rank block structure
- Seek to improve power by looking at largest singular values of $\hat{\Sigma}_i^L - \hat{\Sigma}_i^R$

$$||\hat{\Sigma}_i^L - \hat{\Sigma}_i^R||_{\text{Ky-Fan}(k)} = \sum_{\ell=1}^k \sigma_\ell(\hat{\Sigma}_i^L - \hat{\Sigma}_i^R)$$

- $\mathcal{S} = \{\text{Frobenius}^2, \text{Ky-Fan}(1), \text{Ky-Fan}(2), \dots, \text{Ky-Fan}(K)\}$

Assuming normal data distinct eigenvalues, common eigenvectors

$$\Sigma_1 - \Sigma_2 = \sum_{j=1}^d u_{l_j} (\lambda_{\delta,j}) \tilde{u}_{l_j}^\top, \text{ where } \tilde{u}_{l_j} \text{ and } \lambda_{\delta,j} = |\lambda_{1,l_j} - \lambda_{2,l_j}|$$

Theorem (Limits of Singular Values)

- $\lambda_{\delta,j} \neq 0$: $\sqrt{n}(\hat{\lambda}_{\delta,j} - \lambda_{\delta,j}) \xrightarrow{d} \mathcal{N}(0, 2(\lambda_{1,l_j}^2 + \lambda_{2,l_j}^2))$
- $\lambda_{\delta,j} = 0$: $\sqrt{n}\hat{\lambda}_{\delta,j} \xrightarrow{d} \mathcal{F}(0, 2(\lambda_{1,l_j}^2 + \lambda_{2,l_j}^2))$ where \mathcal{F} a folded normal distribution

Theorem (Limits of Ky-Fan(k)-norm)

Suppose exists $k \in \{1, \dots, p\}$ s.t. $j \leq k_0$ $\lambda_{\delta,j} \neq 0$ and $j > k_0$, $\lambda_j = 0$

- $k \leq k_0$: $\sqrt{n}(\|\hat{\Sigma}_1 - \hat{\Sigma}_2\|_{(k)} - \|\Sigma_1 - \Sigma_2\|_{(k)}) \xrightarrow{d} \mathcal{N}\left(0, \sum_{j=1}^k 2(\lambda_{1,l_j}^2 + \lambda_{2,l_j}^2)\right)$
- $k > k_0$: $\sqrt{n}(\|\hat{\Sigma}_1 - \hat{\Sigma}_2\|_{(k)} - \|\Sigma_1 - \Sigma_2\|_{(k)}) \xrightarrow{d} \mathcal{N}\left(0, \sum_{j=1}^{k_0} 2(\lambda_{1,l_j}^2 + \lambda_{2,l_j}^2)\right) + \sum_{j=k_0+1}^k \mathcal{F}\left(0, 2(\lambda_{1,l_j}^2 + \lambda_{2,l_j}^2)\right)$

Theorem (Proposition 3 - Signal to Noise Ratio)

For two indexes $k_1 < k_2 \in \{1, \dots, p\}$

$$\beta_{k_1, k_2} = \frac{\sum_{j=k_1+1}^{k_2} \lambda_{\delta, j}}{||\Sigma_1 - \Sigma_2||_{(k)}}$$

$$\gamma_{k_1, k_2} = \frac{\sum_{j=k_1+1}^{k_2} \sigma_j^2}{\sigma_{1:k_1}^2}$$

$SNR_{k_1} \geq SNR_{k_2}$ when $\beta_{k_1, k_2} \geq \sqrt{\gamma_{k_1, k_2} + 1} - 1$

Real Data Analysis - Single Subject

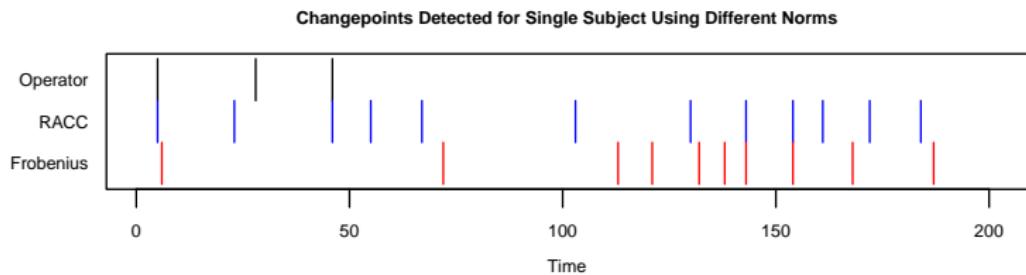


Figure: Final segmentation produced by RACC (utilizing Ky-Fan(k) norms), compared to just using operator or Froebnus norms.

Previous research has investigated number of changes in FC differed in case vs. control

- More changes for subjects with Parkinson's [3]
- No differences for subjects with Mild Cognitive Impairment [4]
- More changes for subjects with moderate to severe non-suicidal self-injury [5]

We examine 135 subjects from the SPINs study (85 with schizophrenia, 45 healthy controls, 5 unknown). Find no statistically significant difference between number of changepoints identified by RACC (10.79, 10.59 average number of changepoints for case and control groups).

- How to choose an optimal K to choose
- Theory around consistency of detected changepoint in multiple changepoint case
- More comprehensive preprocessing to ensure exchangability of data
- Non-linear dimension reduction techniques
- Clustering dFC after segmentation

Thank you!

Preprint available at <https://arxiv.org/abs/2309.10284>

References I

- [1] Mri scan <https://www.nhs.uk/conditions/mri-scan>.
- [2] Tor D Wager and Martin A Lindquist. Principles of fmri. *New York: Leanpub*, 2015.
- [3] Jinhee Kim, Marion Criaud, Sang Soo Cho, María Díez-Cirarda, Alexander Mihaescu, Sarah Coakeley, Christine Ghadery, Mikael Valli, Mark F Jacobs, Sylvain Houle, et al. Abnormal intrinsic brain functional network dynamics in parkinson's disease. *Brain*, 140(11):2955–2967, 2017.
- [4] Núria Mancho-Fora, Marc Montalà-Flaquer, Laia Farràs-Permanyer, Daniel Zarabozo-Hurtado, Geisa Bearitz Gallardo-Moreno, Esteban Gudayol-Farré, Maribel Peró-Cebollero, and Joan Guàrdia-Olmos. Network change point detection in resting-state functional connectivity dynamics of mild cognitive impairment patients. *International Journal of Clinical and Health Psychology*, 20(3):200–212, 2020.
- [5] Mark B Fiecas, Christian Coffman, Meng Xu, Timothy J Hendrickson, Bryon A Mueller, Bonnie Klimes-Dougan, and Kathryn R Cullen. Approximate hidden semi-markov models for dynamic connectivity analysis in resting-state fmri. *bioRxiv*, pages 2021–03, 2021.

- [6] Erich Leo Lehmann, Joseph P Romano, and George Casella. *Testing statistical hypotheses*, volume 3. Springer, 2005.

Identification of a Changepoint via Permutation Test

Distribution of T complex; permutation tests ensure Type I error control under null for *any* test statistic of the data [6]. Use permutations to set critical value of T and estimate $\hat{\mu}_{H_0,i,s}, \hat{\sigma}_{H_0,i,s}^2$.

Under null of equal covariances across time

$$\underbrace{X_1, X_2, X_3, X_4, X_5}_{\Sigma_{1:5}} | \underbrace{X_6, X_7, X_8, X_9, X_{10}}_{\Sigma_{6:10}} \Rightarrow \Sigma_{1:5} - \Sigma_{6:10} = 0$$

$$\underbrace{X_8, X_4, X_1, X_7, X_{10}}_{\Sigma_{1:5}^*} | \underbrace{X_9, X_2, X_3, X_5, X_6}_{\Sigma_{6:10}^*} \Rightarrow \Sigma_{1:5}^* - \Sigma_{6:10}^* = 0$$

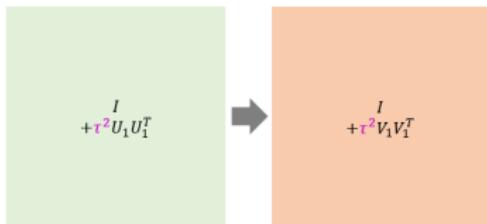
Under alternative of change in covariance at $t = 5$

$$\underbrace{X_1, X_2, X_3, X_4, X_5}_{\Sigma_{1:5}} | \underbrace{X_6, X_7, X_8, X_9, X_{10}}_{\Sigma_{6:10}} \Rightarrow \Sigma_{1:5} - \Sigma_{6:10} \neq 0$$

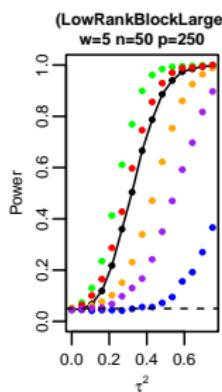
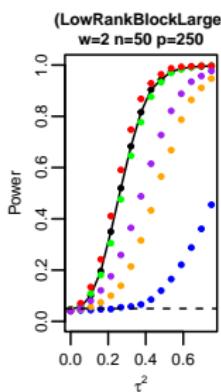
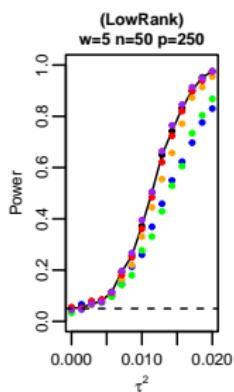
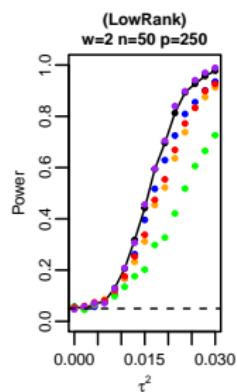
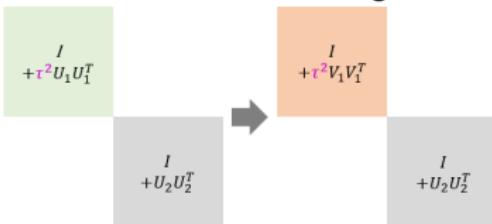
$$\underbrace{X_8, X_4, X_1, X_7, X_{10}}_{\Sigma_{1:5}^*} | \underbrace{X_9, X_2, X_3, X_5, X_6}_{\Sigma_{5:8}^*} \Rightarrow \Sigma_{1:5}^* - \Sigma_{5:8}^* \approx 0$$

Simulation Results - Power

S1. LowRank



S2. LowRankBlockLarge



- Operator
- KF-4
- KF-10
- KF-25
- F
- RACC

Here w represents the rank of the covariance matrix before and after a change-point.

Simulation Results - Two Changepoint Case

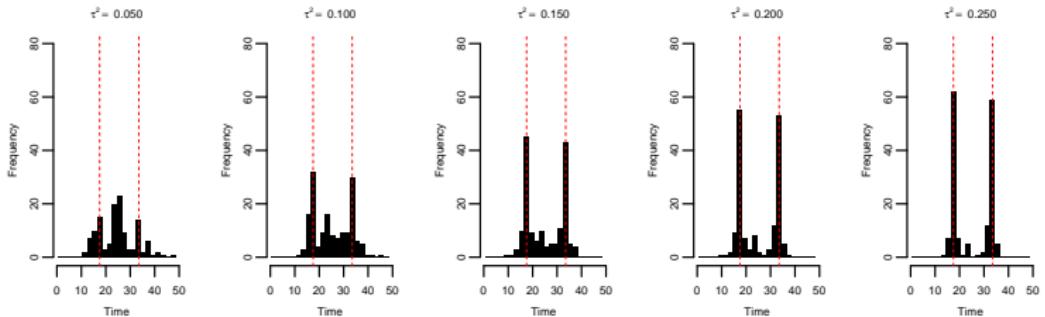


Figure: Power results for two equally spaced changepoints, (LowRank) $w = 5$ setting for increasing magnitude of difference τ^2 .

Real Data Analysis - Single Subject

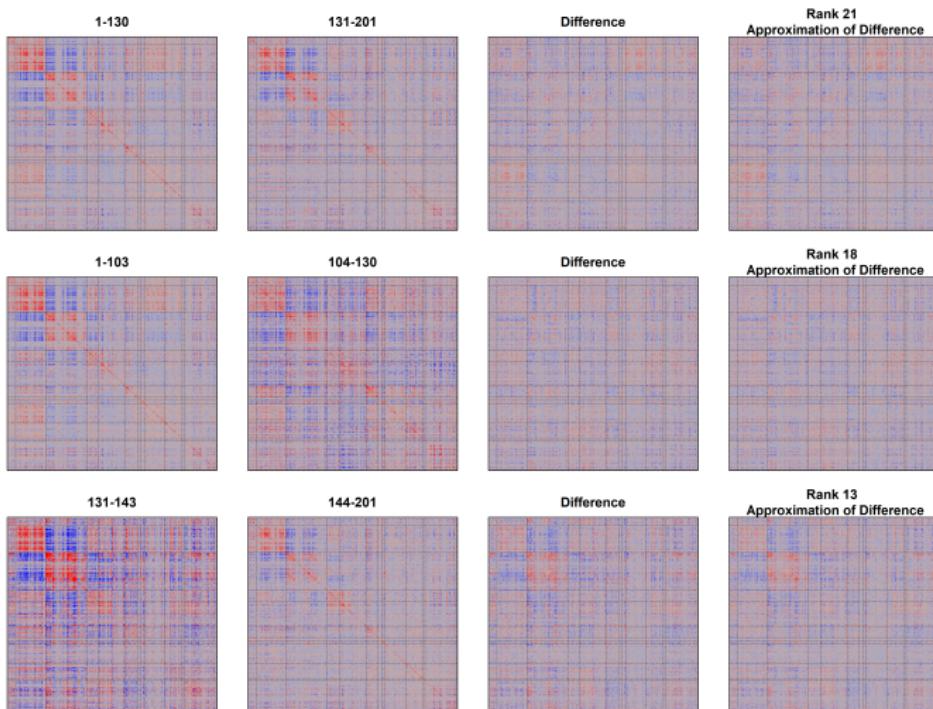


Figure: Visualization of first three steps of binary segmentation algorithm.