Methods for High-dimensional Inference, with Applications to Imaging Genetics

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Overview of Talk

1. Scientific background of **connectome genetics**.
2. **Mantel test** and metric-based association testing.
3. The **adaptive Mantel test** for penalized inference.
4. Application to test heritability of EEG coherence during a working memory task.

Scientific Background

Estimating Heritability with Variance Components Model

- Let X be an $n \times p$ matrix of single nucleotide polymorphism (SNP) data, and Y be an observed scalar phenotype.

$$Y = g + \varepsilon,$$

where $g \sim N(0, \sigma_g^2 G)$, for $G = XX^T/p$, and $\varepsilon \sim N(0, \sigma_\varepsilon^2 I_n)$.

Narrow-sense heritability of the phenotype measured by Y can then be estimated as

$$\hat{h}^2 = \frac{\hat{\sigma}_g^2}{\hat{\sigma}_g^2 + \hat{\sigma}_\varepsilon^2}.$$

$$\hat{h}^2 = \frac{\operatorname{tr}\left(\hat{\Sigma}_g\right)}{\operatorname{tr}\left(\hat{\Sigma}_g\right) + \operatorname{tr}\left(\hat{\Sigma}_\varepsilon\right)},$$

where $\hat{\Sigma}_g = \hat{\sigma}_g^2 G, \hat{\Sigma}_\varepsilon = \hat{\sigma}_\varepsilon^2 I_n$.

Metric-based Association Testing

The Inference Goal

Given observations of n subjects across two data modalities $\mathbf{X}$ and $\mathbf{Y}$, is similarity in $\mathbf{X}$ significantly associated with similarity in $\mathbf{Y}$?

Setup

- In our application, $X \in \mathrm{X}^n$ is an $n \times p$ matrix of SNP measurements, and $Y \in \mathrm{Y}$ is an $n \times 1$ vector of scalar phenotype measurements.
- Assume X and Y have been column centered and scaled.
- A bounded, symmetric, positive semi-definite similarity function $\mathcal{K}$, e.g. $\mathcal{K}(u, v) = u^T v$.

Association Testing Methods

- **Mantel's test** (Mantel 1967) uses the inner product of the pairwise distance/similarity matrices from X and Y.
- The **RV coefficient** (Escoufier 1976) uses a test statistic based on the multivariate correlation between X and Y.
- The **distance covariance** (dCov) test (Szekely, Rizzo, Bakirov, 2007) is defined as the covariance of distances between X and Y.
- **Adaptive sum of powered score test** (Xu et. al 2017).

Mantel Test

- Given **similarity functions** $\mathcal{K}_X : \mathbb{R}^P \times \mathbb{R}^P \to \mathbb{R}$ and $\mathcal{K}_Y : \mathbb{R} \times \mathbb{R} \to \mathbb{R}$, we can form two $n \times n$ **Gram matrices** K and H, where

$$K_{ij} = \mathcal{K}_X(X_i, X_j)$$

$$H_{ij} = \mathcal{K}_Y(Y_i, Y_j).$$

- The **correlation** of these distance matrices is

$$r(H, K) := \frac{\langle K, H \rangle}{\|K\| \cdot \|H\|},$$

Mantel Test

How should we test the significance of the correlation?

Mantel's original approach (1967) is to **permute** rows and columns of one of the pairwise distance matrices to generate the reference distribution.

That is, for test statistic

$$T = \langle K, H \rangle = \sum_{i=1}^{n} \sum_{j=1}^{n} K_{ij} H_{ij} = \mathrm{tr}(KH),$$

we compute the **permutation** P**-value** by permuting H to approximate the reference distribution.

Mantel Test

Similarity with Weighted Inner Products

For two vectors $u, v \in \mathbb{R}^p$, the **weighted inner product** $\langle \cdot, \cdot \rangle_{\mathcal{W}}$ for some positive semi-definite matrix $\mathcal{W}$, is defined as

$$\langle u, v \rangle_{\mathcal{W}} = u^T \mathcal{W} v.$$

The **Mantel Test Statistic** for similarity $\langle \cdot, \cdot \rangle_{\mathcal{W}}$ is

$$T_{\mathcal{W}} = \mathrm{tr}(X \mathcal{W} X^T Y Y^T) = Y^T X \mathcal{W} X^T Y.$$

Mantel Test

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Question

How does the choice of weight matrix affect the test characteristics?

How should the weight matrix be chosen?

Weight Matrices

Euclidean Inner Product

- Choosing $\mathcal{W} = I_p$ gives

$$K = XX^T,$$

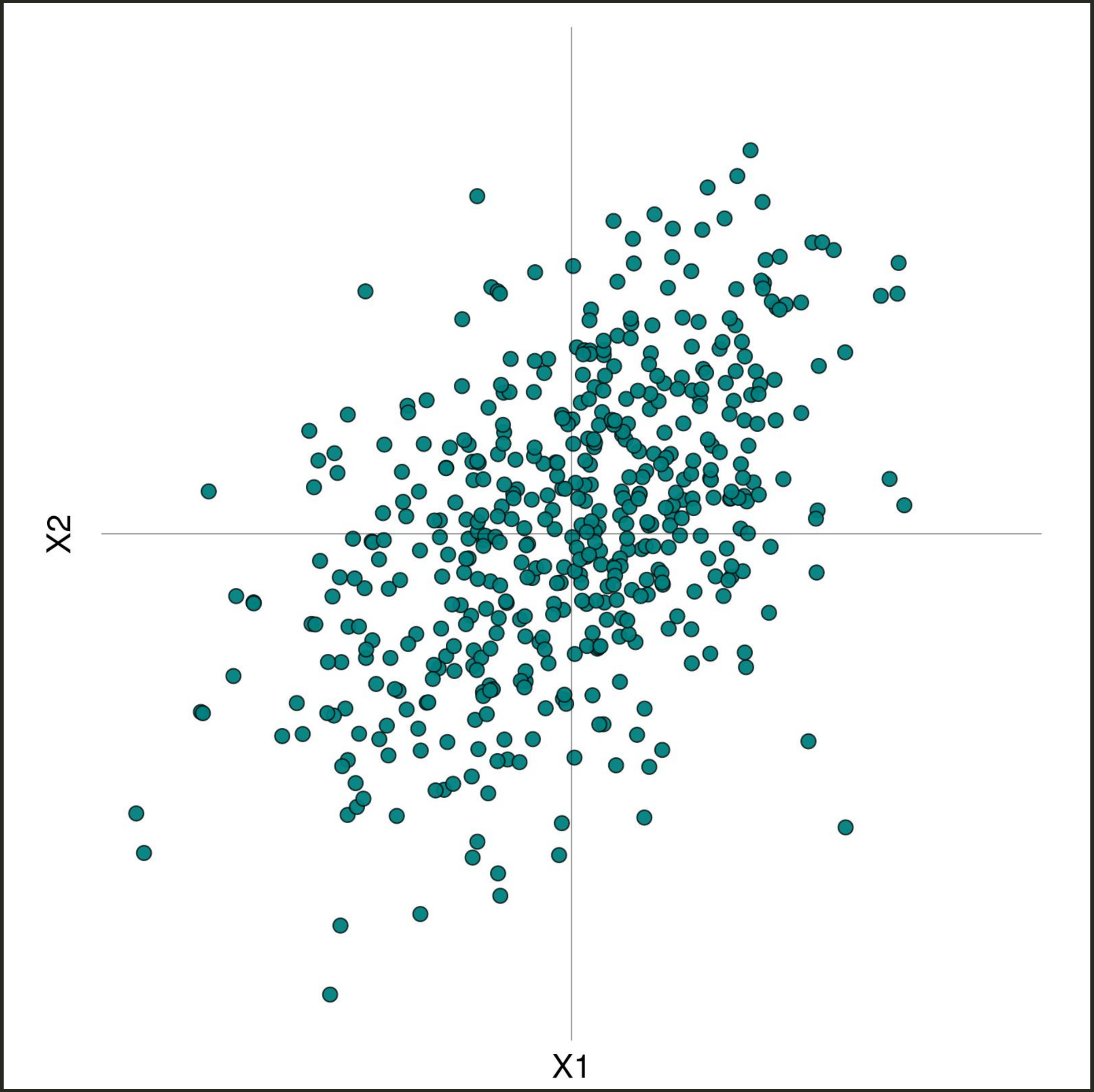
which is the Gram matrix for the standard Euclidean inner product.

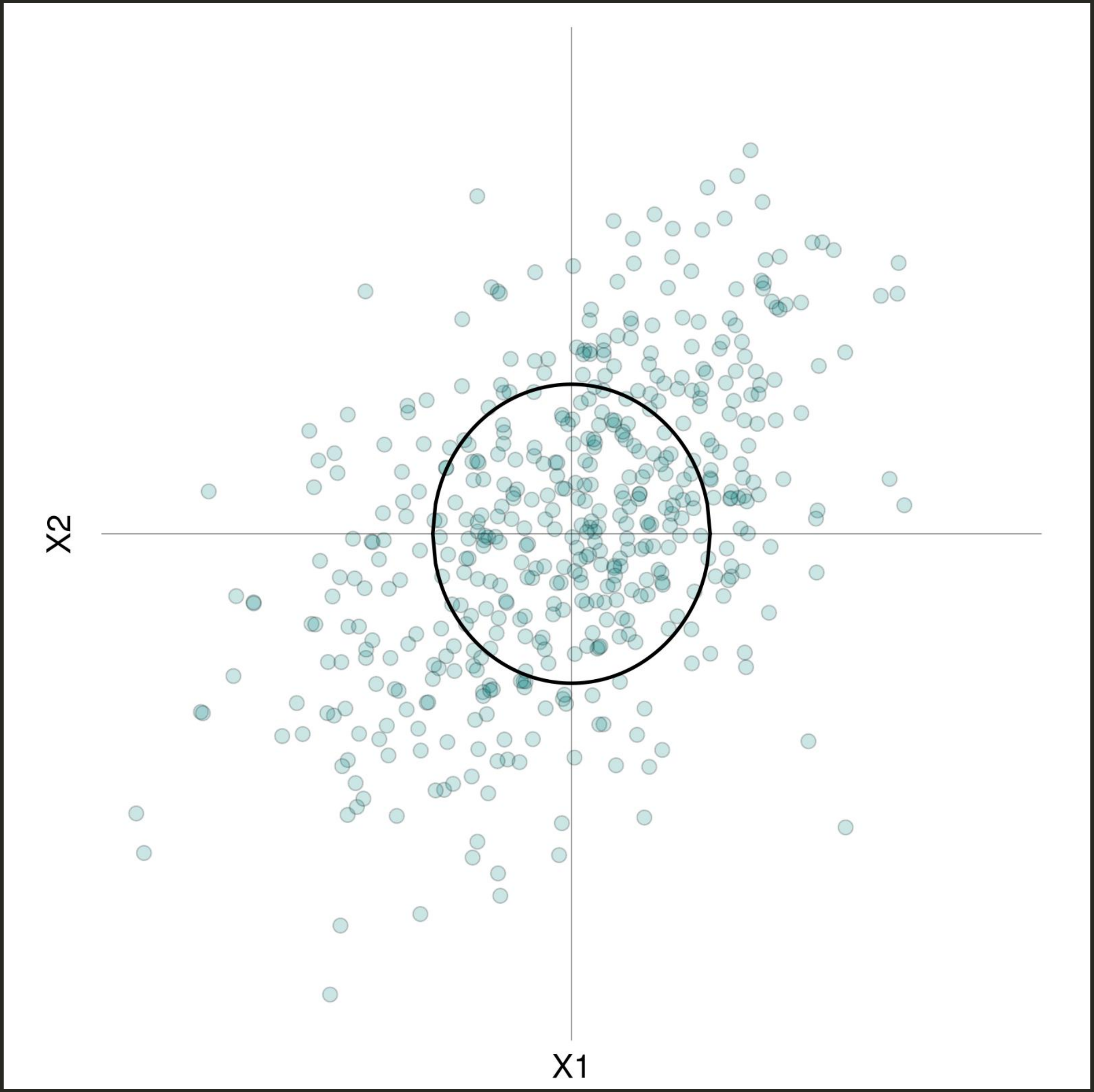
Mahalanobis Similarity

- Choosing $\mathcal{W} = (X^T X)^{-1}$ gives

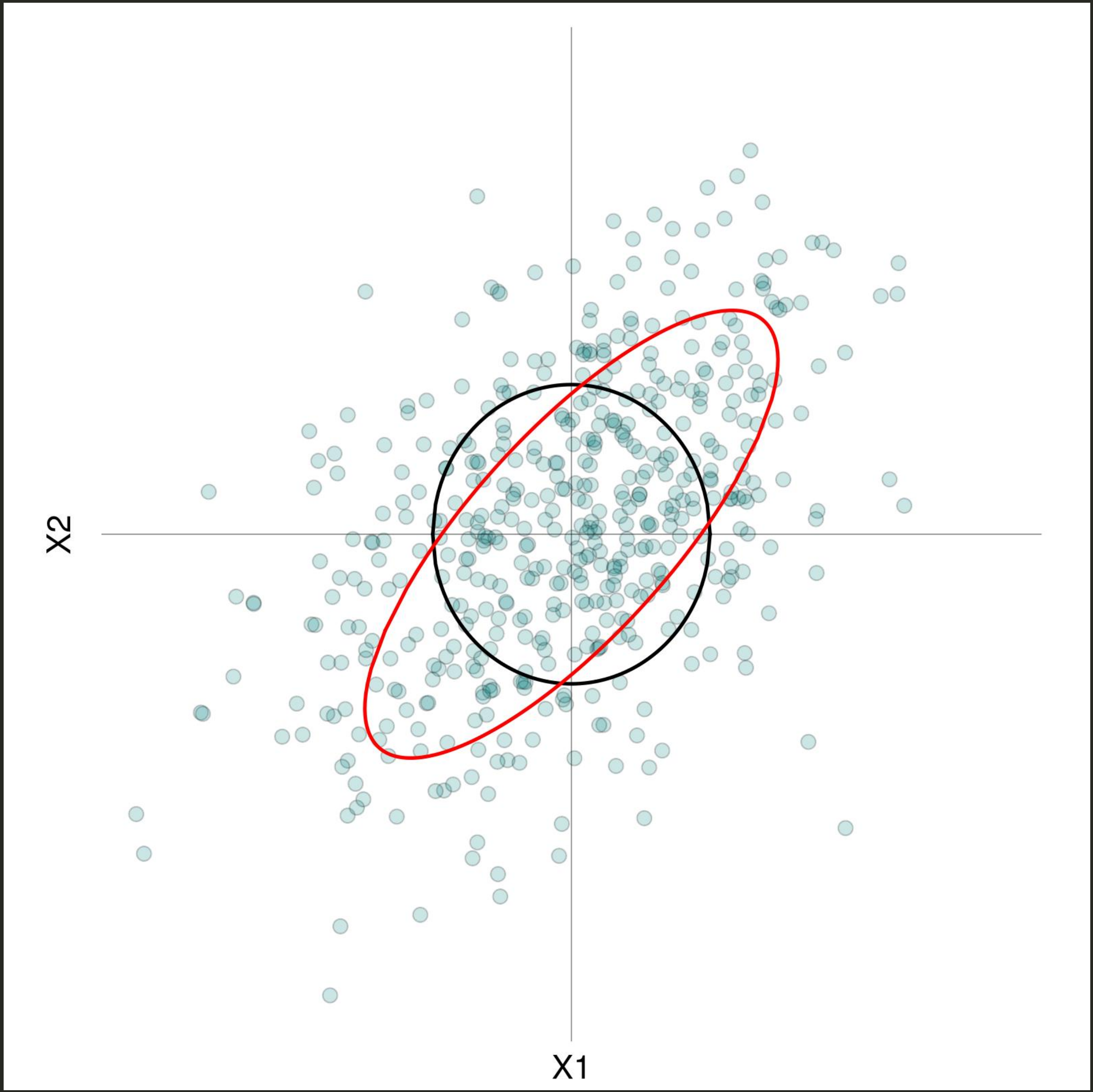
$$K = X(X^T X)^{-1} X^T,$$

which is a similarity matrix related to the Mahalanobis distance.

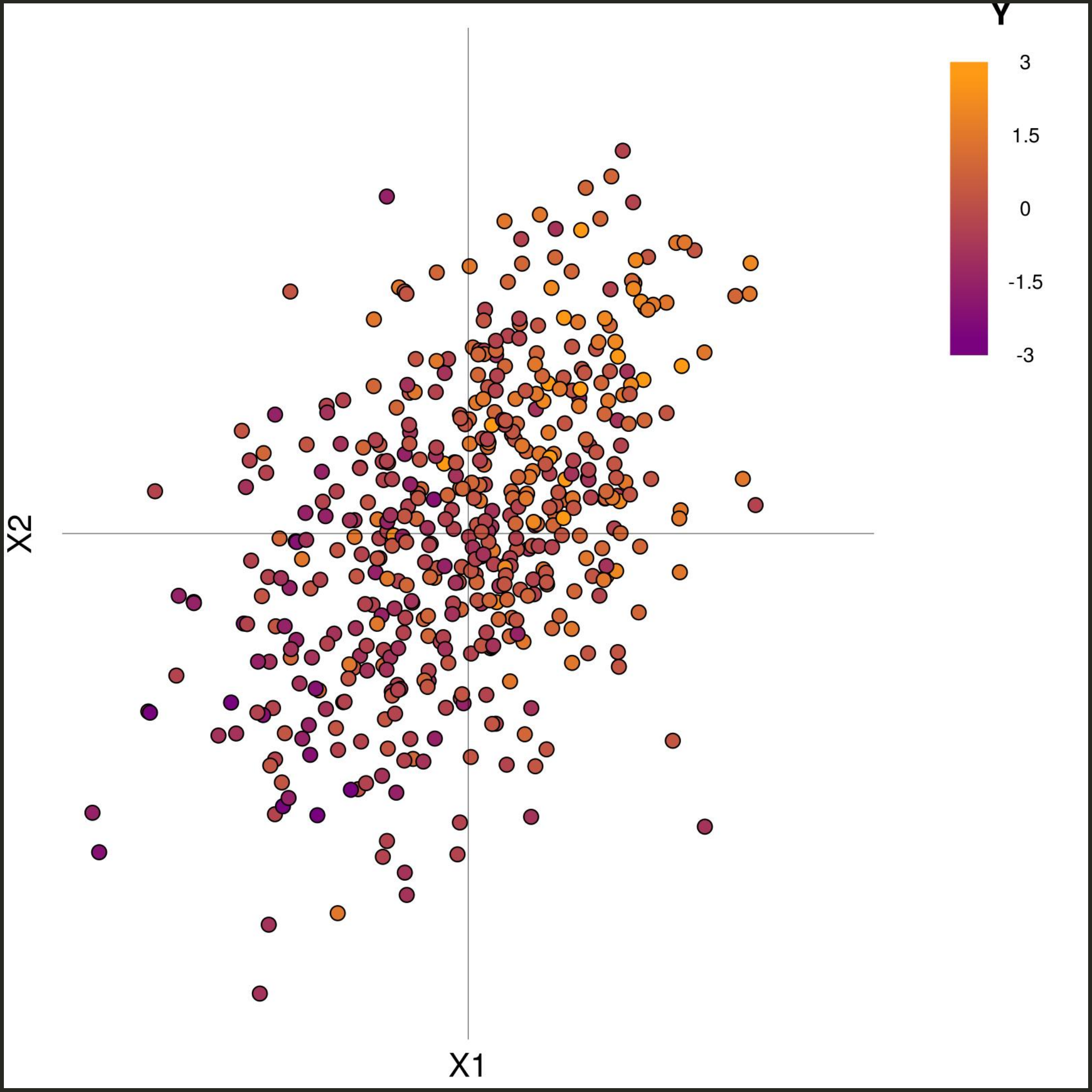

X2
X1



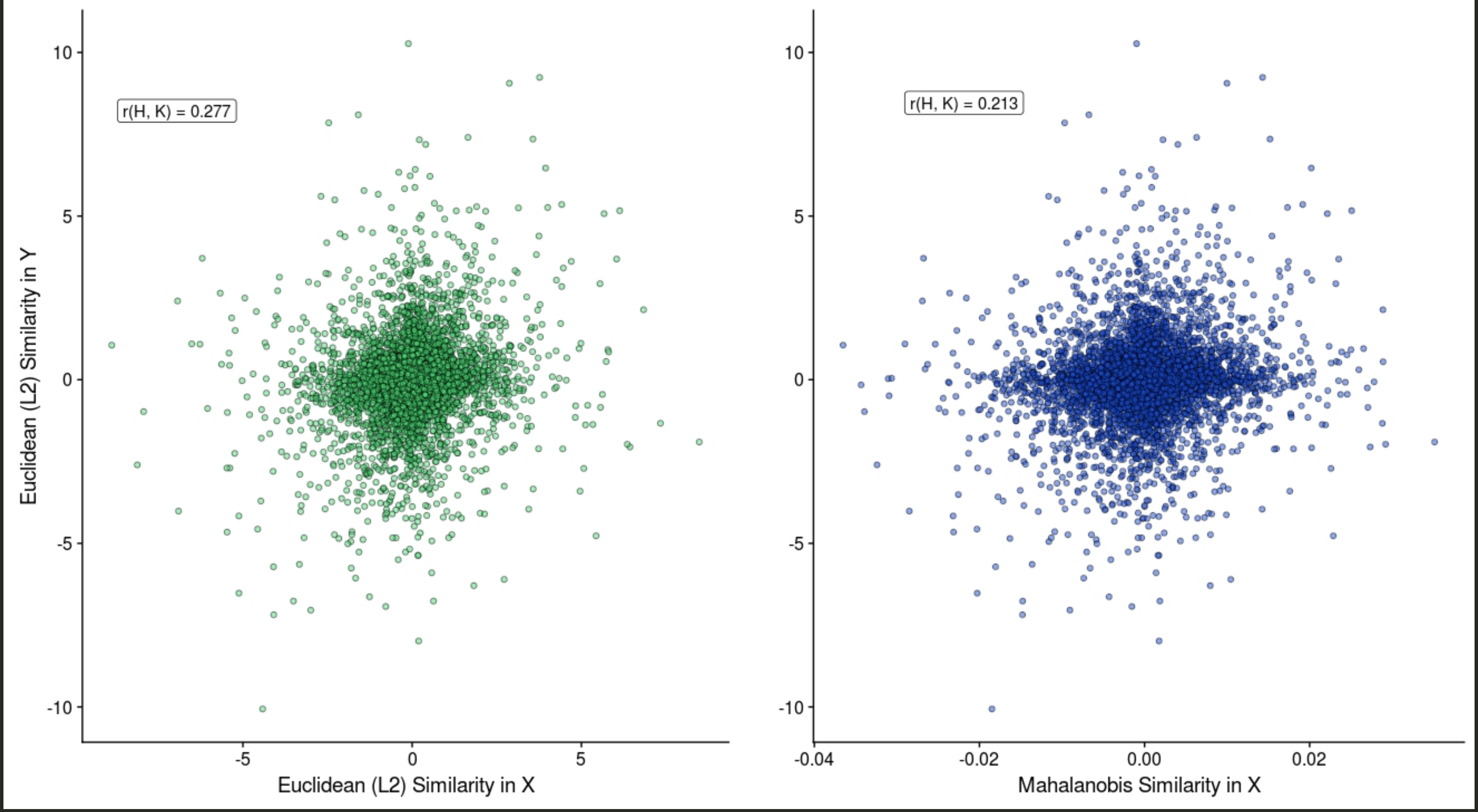
X2
X1

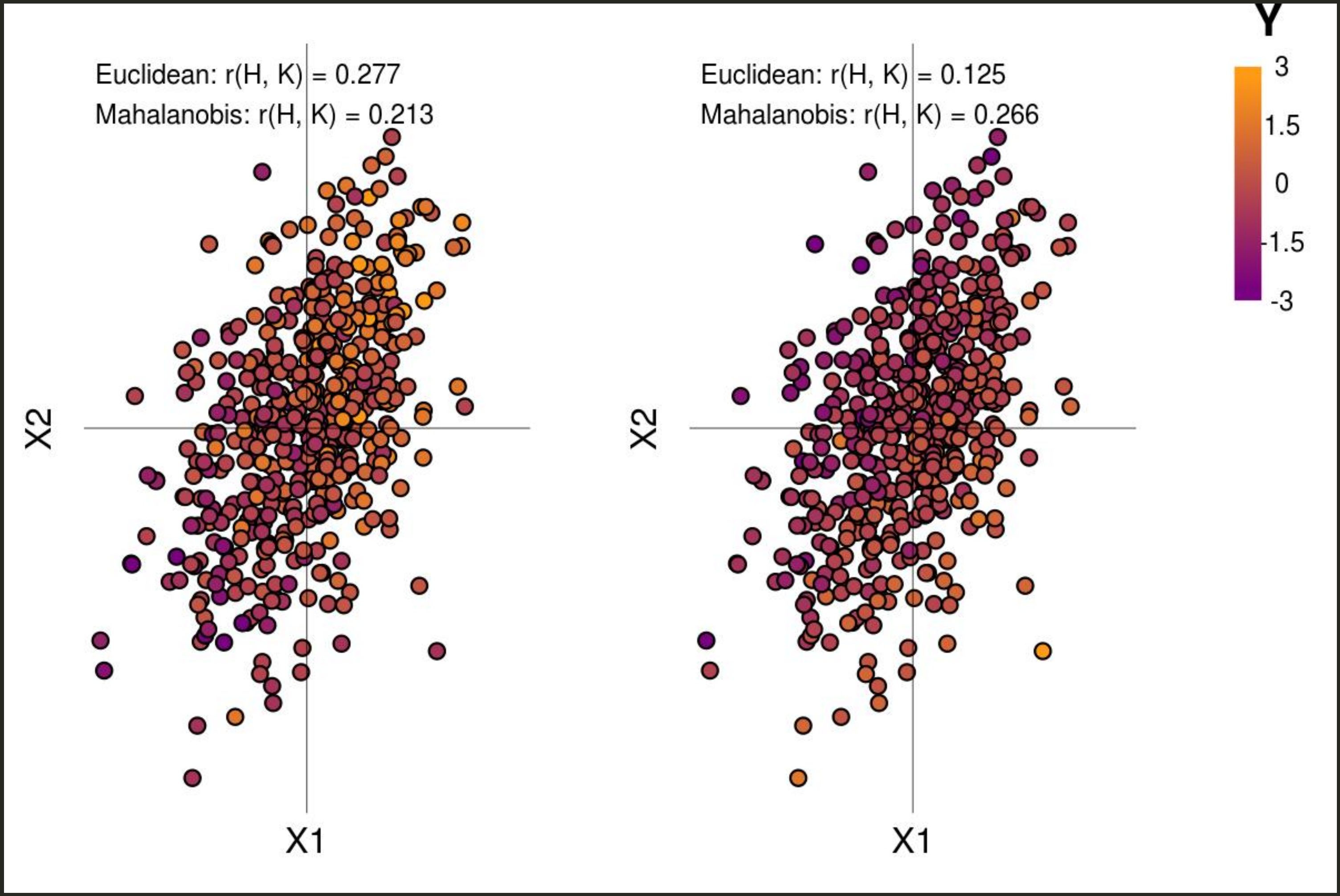

X2
X1

Data generated from variance components model with $\sigma_b^2 = 1$



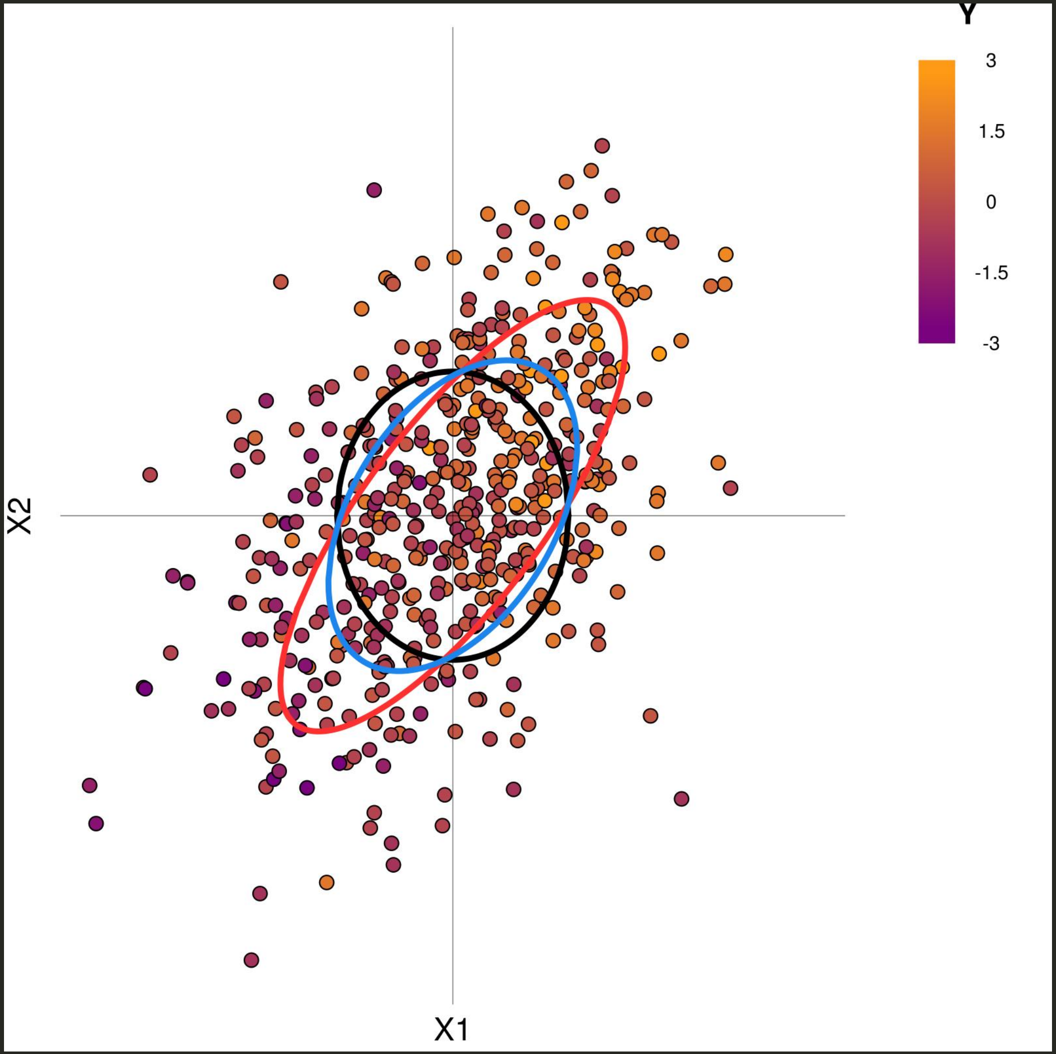
Comparing Similarity-Similarity Plots





Left Data generated from variance components model with $\sigma_b^2 = 1$. **Right** Data generated from fixed effects model with $\beta = (0.75, -0.75)$.

Can we compromise between the Mahalanobis and Euclidean metrics?



Weight Matrices

Goal

We want a weight matrix that adjusts for the correlation structure in the data like the Mahalanobis metric, but which is closer to the Euclidean metric.

Weight Matrices

Goal

We want a weight matrix that adjusts for the correlation structure in the data like the Mahalanobis metric, but which is closer to the Euclidean metric.

Solution: Penalize the Mahalanobis weight matrix.

- Let $\lambda \geq 0$. Consider the penalized weight matrix:

$$\mathcal{W}_\lambda = (X^T X + \lambda I_p)^{-1}.$$

- As $\lambda \to \infty$, the penalty term λI_p dominates $X^T X$, and so W_λ tends to a constant diagonal matrix.
- We call $\mathcal{K}(u, v) = u^T \mathcal{W}_\lambda v$ the **ridge kernel**.

Weight Matrices

- **Summarizing**, the Euclidean and Mahalanobis inner products are linked by the ridge kernel, where $W_{\lambda=0}$ gives the Mahalanobis metric, and $\lambda \to \infty$ gives the Euclidean metric.

Metric	Gram Matrix	Mantel Stat.
Mahalanobis	$K_F = X(X^TX)^{-1}X^T$	$T_F = \mathrm{tr}(K_F H)$
Euclidean	$K_R = XX^T$	$T_R = \mathrm{tr}(K_R H)$
Ridge Kernel	$K_\lambda = X(X^TX + \lambda I)^{-1}X^T$	$T_\lambda = \mathrm{tr}(K_\lambda H)$

Mantel Test

Correlation of Similarities

Assume $\mathrm{rank}(X) = r$ with singular value decomposition $X = U_{n\times r} D_{r\times r} V_{p\times r}^T$, where $\eta_j, j = 1, \cdots, r$ are the squared singular values. Let $H = YY^T$ and $Z = U^T Y$.

Mahalanobis Metric $$r(H, K_F) = \frac{\sum_{j=1}^r z_j^2}{\sqrt{p}\sum_{i=1}^n y_i^2},$$

Euclidean Metric $$r(H, K_R) = \frac{\sum_{j=1}^r \eta_j z_j^2}{\sqrt{\sum_{j=1}^r \eta_j^2 \sum_{i=1}^n y_i^2}},$$

Ridge Similarity $$r(H, K_\lambda) = \frac{\sum_{j=1}^r \frac{\eta_j}{\lambda+\eta_j} z_j^2}{\sqrt{\sum_{j=1}^r \left(\frac{\eta_j}{\eta_j+\lambda}\right)^2 \sum_{i=1}^n y_i^2}}.$$

Mantel Test

Correlation of Similarities

Assume $\mathrm{rank}(X) = r$ with singular value decomposition $X = U_{n\times r} D_{r\times r} V_{p\times r}^T$, where $\eta_j, j = 1, \cdots, r$ are the squared singular values. Let $H = YY^T$ and $Z = U^T Y$.

Mahalanobis Metric $\quad r(H, K_F) \asymp \sum_{j=1}^r z_j^2 \quad = \mathrm{tr}(HK_F) = T_F,$

Euclidean Metric $\quad r(H, K_R) \asymp \sum_{j=1}^r \eta_j z_j^2 \quad = \mathrm{tr}(HK_R) = T_R,$

Ridge Similarity $\quad r(H, K_\lambda) \asymp \sum_{j=1}^r \frac{\eta_j}{\lambda+\eta_j} z_j^2 = \mathrm{tr}(HK_\lambda) = T_\lambda.$

Mantel Test

Linear Model Definitions

Model Name	Definition	
Fixed	$Y \sim N(X\beta, \sigma_\varepsilon^2 I_N)$	
Random	$Y \sim N(0, \sigma_b^2 G + \sigma_\varepsilon^2 I_N),$	$G = XX^T/p$
Ridge	$Y \sim N(X\beta, \sigma_\varepsilon^2 I_N),$	$\lVert\beta\rVert_2^2 < c(\lambda)$

Linear Model Score Tests

Model	Score Stat.	Equivalent Stat.	Null Distribution
Fixed	$S_F = Z^T D(D^T D)^{-1} D^T Z$	$T_F = \mathrm{tr}(K_F H)$	$c_1 \chi_p^2$
Random	$S_R = Z^T D D^T Z$	$T_R = \mathrm{tr}(K_R H)$	$c_2 \sum_{j=1}^{r} \eta_j \chi_1^2$
Ridge	$S_\lambda = Z^T D(D^T D + \lambda I_p)^{-1} D^T Z$	$T_\lambda = \mathrm{tr}(K_\lambda H)$	$c_3 \sum_{j=1}^{r} \frac{\eta_j}{\lambda + \eta_j} \chi_1^2$

Mantel Test

Limiting Relationship

From the previous results, we get the following limiting relationships between the ridge test, and tests for the fixed effects and random effects models.

$$T_{\lambda=0} = T_F$$

$$T_\lambda \asymp \left\{ \lambda \sum_{j=1}^{r} \frac{\eta_j}{\lambda + \eta_j} z_j^2 \right\} \quad \overset{\lambda \to \infty}{\to} \quad T_R$$

Similarly, for the matrix correlations

$$r(H, K_{\lambda=0}) = r(H, K_F)$$

$$\lim_{\lambda \to \infty} r(H, K_\lambda) = r(H, K_R)$$

Linear Model Score Tests

Geometric Interpretation

Consider $Z = U^T Y$, as the projection of Y into the column space of X.

1. The *Random Effects* model tests the **weighted Euclidean norm** of Z, where the jth component is weighted by the jth eigenvalue η_j.

2. The *Fixed Effects* model tests the **Euclidean norm** of Z

3. The *Ridge Penalization* **weights the Euclidean norm of Z proportional to the eigenvalues**, but these weights are now **flattened** by a factor of $(\lambda + \eta_j)^{-1}$.

Adaptive Mantel Test

Choosing a good penalty term for inference can be difficult, since we must control the type I error.

Interpretation of λ

- The best linear unbiased predictors for the regression coefficients in the random effects model result from $\lambda = \frac{\sigma_\varepsilon^2}{\sigma_b^2}$ as a ridge penalty term.
- Since the noise to signal ratio can be calculated from h^2, a "reasonable" range for λ can be determined from a range for h^2

$$\lambda = \frac{p(1-h^2)}{h^2}.$$

Adaptive Mantel Test

Idea

To simultaneously test a set of tuning parameters, use the **minimum** *P*-**value** across all parameters as the test statistic, and approximate the reference distribution using permutations.

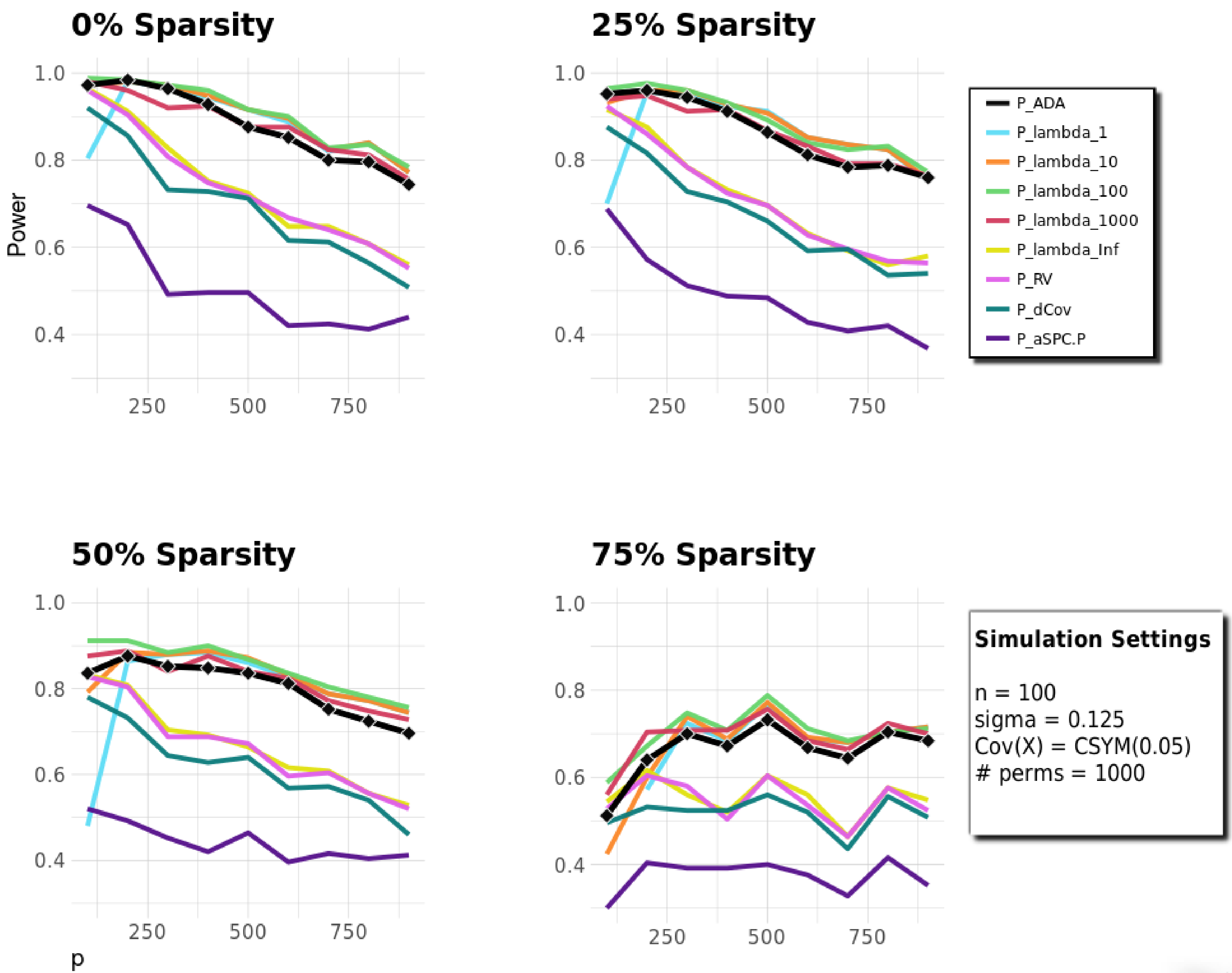
Algorithm

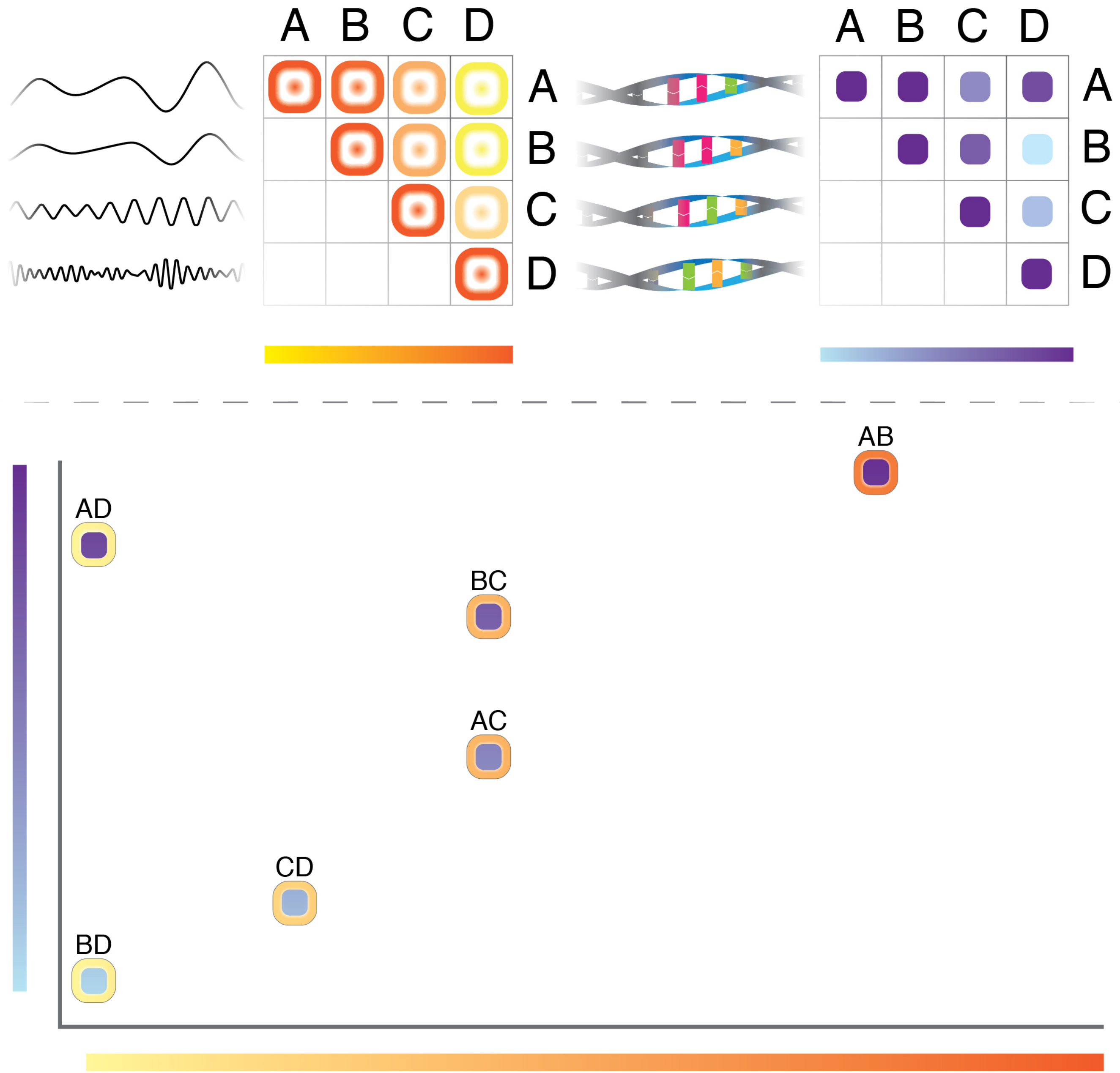
- **Input:**
    - $X, n \times p$ covariates, column centered and scaled
    - $Y, n \times 1$ response, centered and scaled
    - $\left\{\left(\mathcal{K}_m^{\mathrm{X}}, \mathcal{K}_m^{\mathrm{Y}}\right)\right\}, m = 1, \cdots, M$
- **Output:** P_{ADA} = adaptive Mantel *P*-value for global test of significant association

Adaptive Mantel Test

Algorithm

for $m = 1, \ldots, M$ **do**
    $K_m \leftarrow \delta_m^{\mathbf{X}}(X)$
    $H_m \leftarrow \delta_m^{\mathbf{Y}}(Y)$
    Calculate $Z_m^{(0)} \leftarrow Z_m := \mathrm{tr}(K_m H_m)$
end for
Generate B permutations of H_m, labeled $H_m^{(b)}\ \ \forall\, m = 1, \ldots, M; b = 1, \ldots, B$.
$Z_m^{(b)} \leftarrow \mathrm{tr}(K_m H_m^{(b)})\ \ \forall\, m = 1, \ldots, M; b = 1, \ldots, B$
$P_m^{(b)} \leftarrow \frac{1}{B+1} \sum_{b=0}^{B} I\left(Z_m^{(b)} \leq Z_m^{(b')}\right)\ \ \forall\, m = 1, \ldots, M; b = 1, \ldots, B$
$P^{(b)} \leftarrow \min_{m=1,\cdots,M} P_m^{(b)}\ \ \forall\, b = 1, \ldots, B$
$P_{AMT} \leftarrow \frac{1}{B+1} \sum_{b=0}^{B} I\left(P^{(0)} \leq P^{(b)}\right)$


0% Sparsity
25% Sparsity
50% Sparsity
75% Sparsity
Power
p
1.0
0.8
0.6
0.4
250
500
750
P_ADA
P_lambda_1
P_lambda_10
P_lambda_100
P_lambda_1000
P_lambda_Inf
P_RV
P_dCov
P_aSPC.P
Simulation Settings
n = 100
sigma = 0.125
Cov(X) = CSYM(0.05)
# perms = 1000


A B C D
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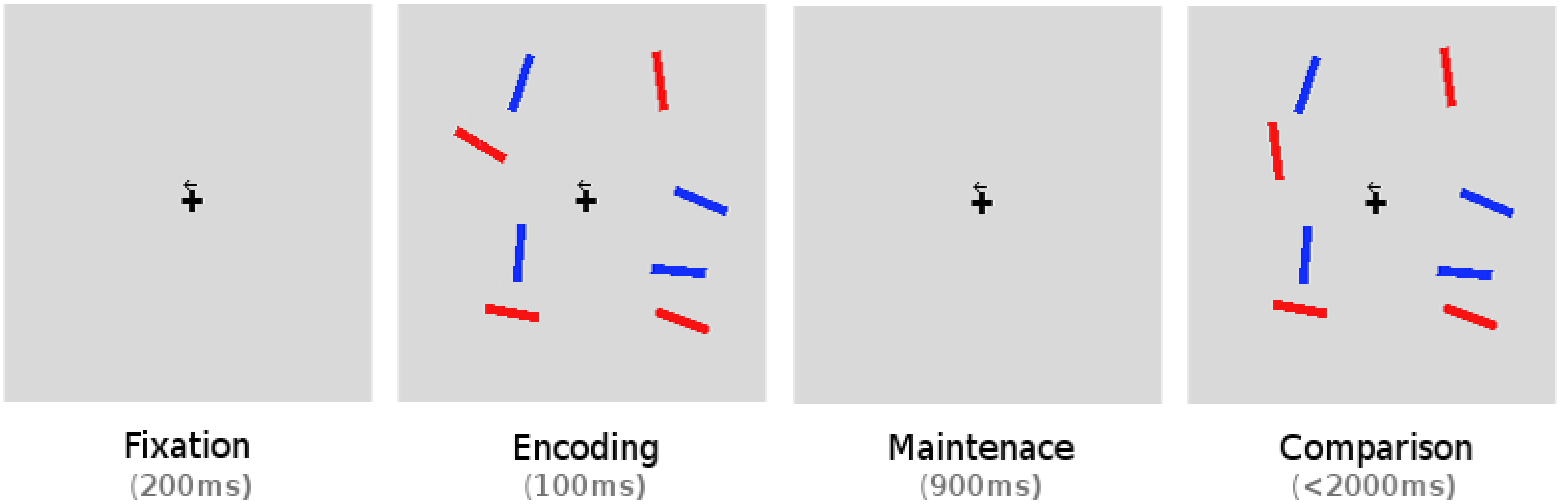
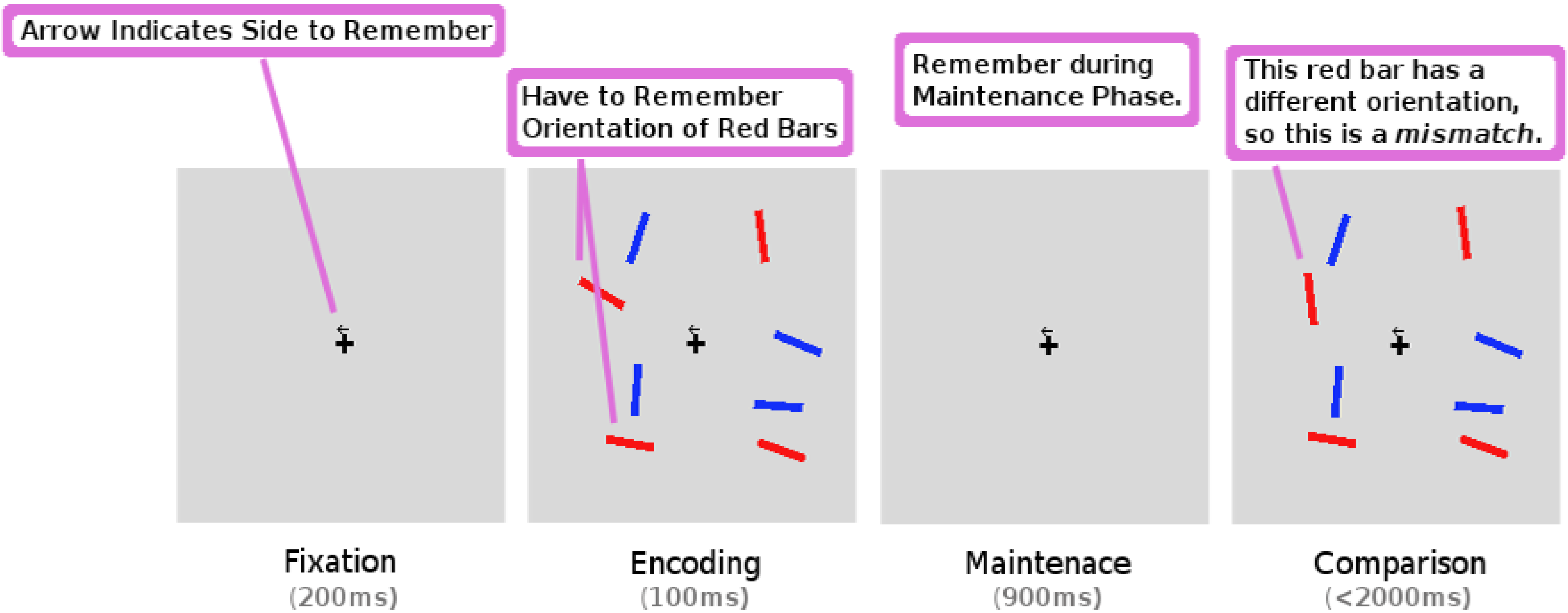
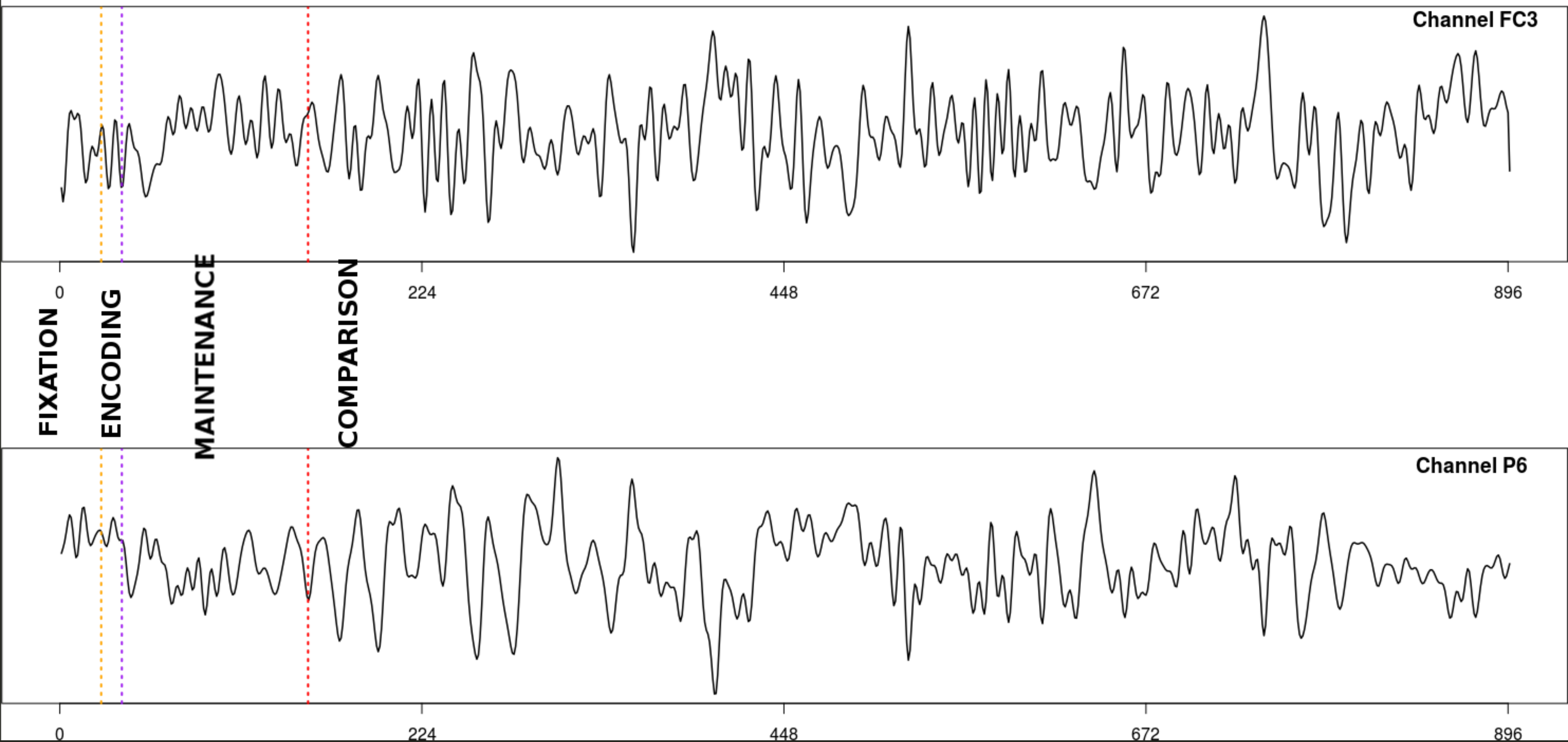
Visual Working Memory Experiment



Visual Working Memory Experiment



Visual Working Memory Experiment



Data Description

- 350 Subjects from the BNU data set
- ~10 minute 64 channel EEG recording during VWM task
  - Preprocessed according to standard pipeline
  - Coherence measures for each channel pair was calculated by the FFT, and grouped into five frequency bands (in Hz): $\delta\ (1-4), \theta\ (4-8), \alpha\ (8-16), \beta\ (16-32), \gamma\ (32+)$
- 13 SNPs selected for analysis, previously identified as potential factors for Alzheimer's disease risk
  - All 13 SNPs passed standard MAF and HWE quality control checks

Adaptive Mantel Test Results

- Results of adaptive Mantel test for association of AD SNPs and EEG Coherence at particular frequency bands
- Used L_2 similarity for SNPs, and ridge kernel similarity for coherence, with penalty terms $\Lambda = \{0.5, 1, 5, 10, 100, 1000, \infty\}$

Band	Channels	$P -$ value
β	All	0.619
β	Frontal	0.517
α	All	0.075
α	Frontal	0.381
θ	All	0.416
θ	Frontal	0.081
δ	All	0.015
δ	Frontal	0.088

Links

- **Adaptive Mantel Test Paper:** arxiv.org/pdf/1712.07270.pdf
- **Slides available:** github.com/dspluta/Presentations/
- **Adaptive Mantel R Package:** github.com/dspluta/adamant

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Appendix

Adaptive Mantel Test

Computing the adaptive Mantel test can be done efficiently using either the SVD or a linear algebra trick, depending on the relative sizes of n and p.

SVD

- Computing the SVD $X = UDV^T$ can be completed in $O(np^2)$.
- When $rank(X) = r \leq n$, the Mantel statistic can be then be computed in $O(n^2)$:

$$T = \sum_{i=1}^{r} \eta_i z_i^2$$

- Using B permutations gives a total complexity of $O(np^2 + Bn^2)$.

Adaptive Mantel Test

Linear Algebra Trick

When $p \gg n$, it is better to instead use the following reformulation for K:

$$K_\lambda = X(X^T X + \lambda I_p)^{1} = (XX^T + \lambda I_n)^{-1} XX^T.$$

Calculating K_λ with this alternative form can be done in $O(n^2 p)$, giving a total computational cost of $O\left(n^2(p + B)\right)$.

- The computation for the adaptive test scales this cost linear relative the number of tuning parameters included.
- The computations can be easily parallelized.

EEG Pre-processing

- **EEG pre-processing:**

  1. Downsample from 1024 Hz to 128 Hz
  2. Remove bad channels
  3. Band-pass filter from 1 Hz to 45 Hz
  4. Interpolate/re-reference bad channels
  5. ICA to remove eyeblinks and motion artifacts
  6. Remove remaining bad trials. Exclude subjects if > 5% of trials removed.

- **Calculate coherence** for all subjects and all channels using the FFT, and compute mean coherence by frequency band.