Adaptive Mantel Test for High-dimensional Inference

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Overview of Talk

1. **Scientific motivation** from imaging genetics.
2. **Kernel 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 Motivation

What is the heritability of brain connectivity features (measured from fMRI or EEG)?

Data Description

- **350 students** from the Beijing Normal University
- ~10 minute 64 channel **EEG** recording during **Visual Working Memory task**
- **13 SNPs** selected for analysis, previously identified as potential factors for **Alzheimer's disease risk**.

Scientific Motivation

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

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

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).

Kernel Mantel Test

- Given **similarity functions** $\mathcal{K}_X : \mathrm{R}^p \times \mathrm{R}^p \to \mathrm{R}$ and $\mathcal{K}_Y : \mathrm{R} \times \mathrm{R} \to \mathrm{R}$, 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 matrices is

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

Kernel 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.

Kernel Mantel Test

Similarity with Weighted Inner Products

For two vectors $u, v \in \mathrm{R}^{\mathrm{p}}$, 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

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

Kernel 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

$$K_E = XX^T,$$

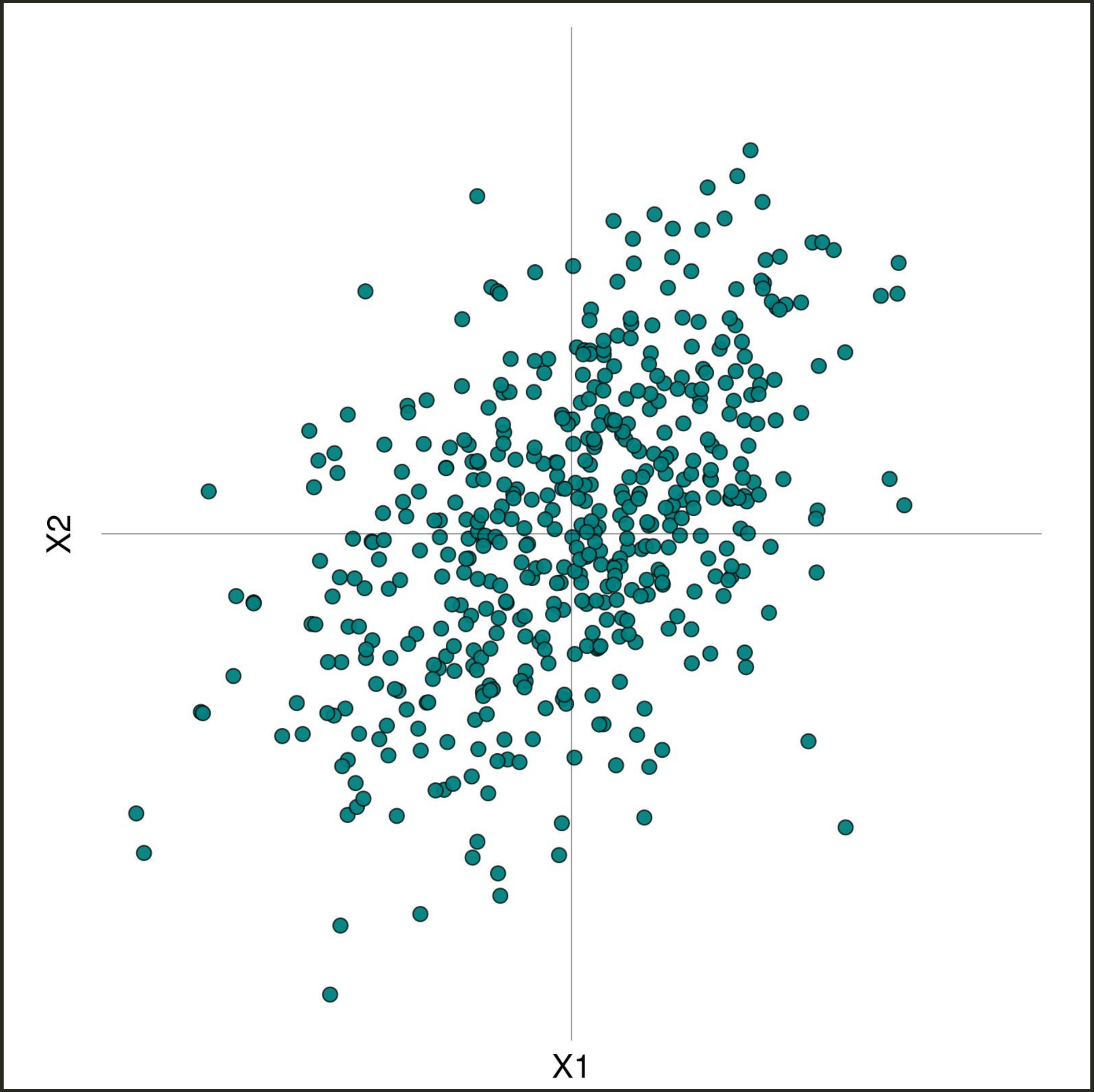
which is the Gram matrix for the standard Euclidean inner product.

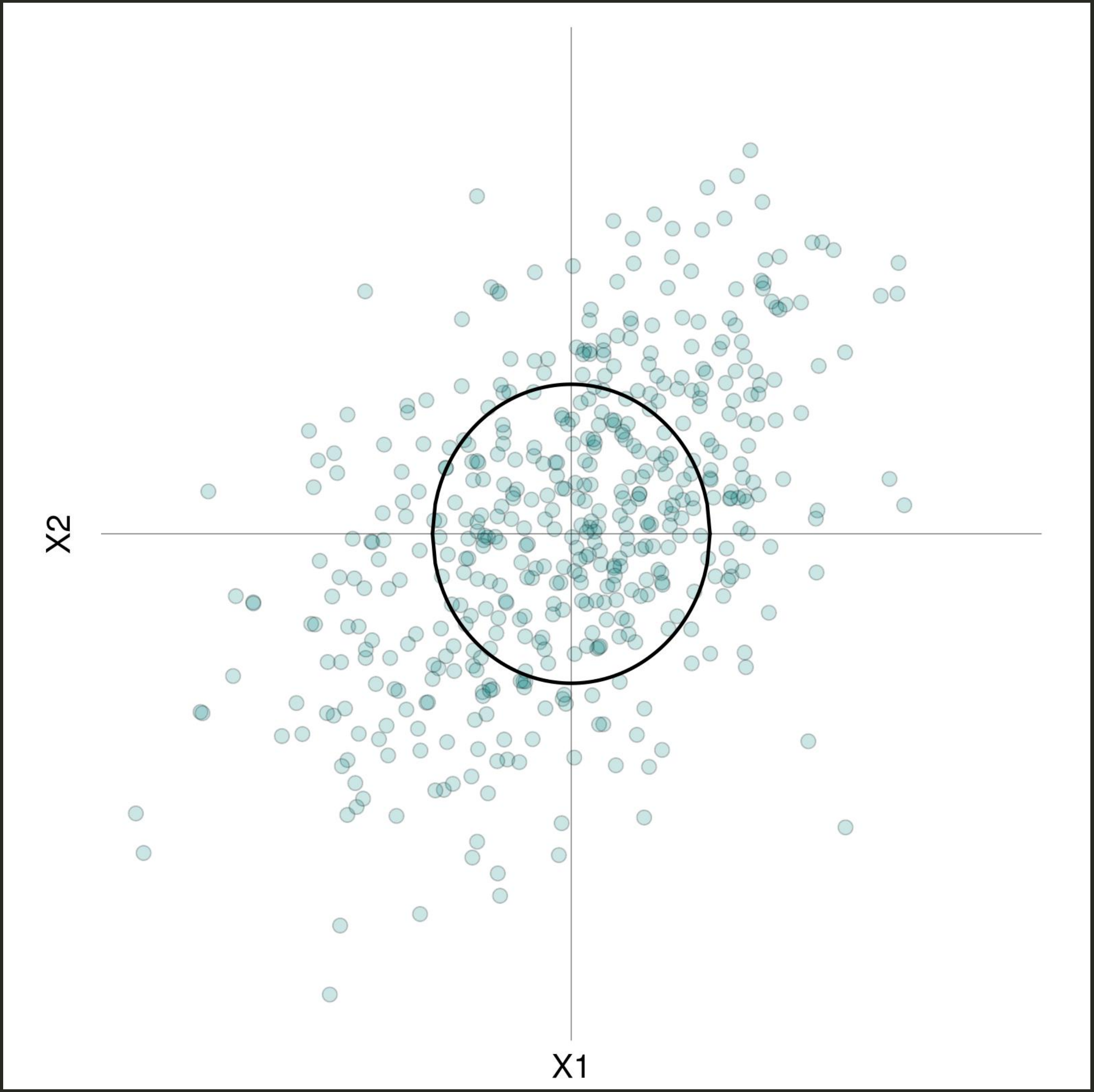
Mahalanobis Similarity

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

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

which is a similarity matrix related to the Mahalanobis distance, and is the projection matrix for the column space of X.


X2
X1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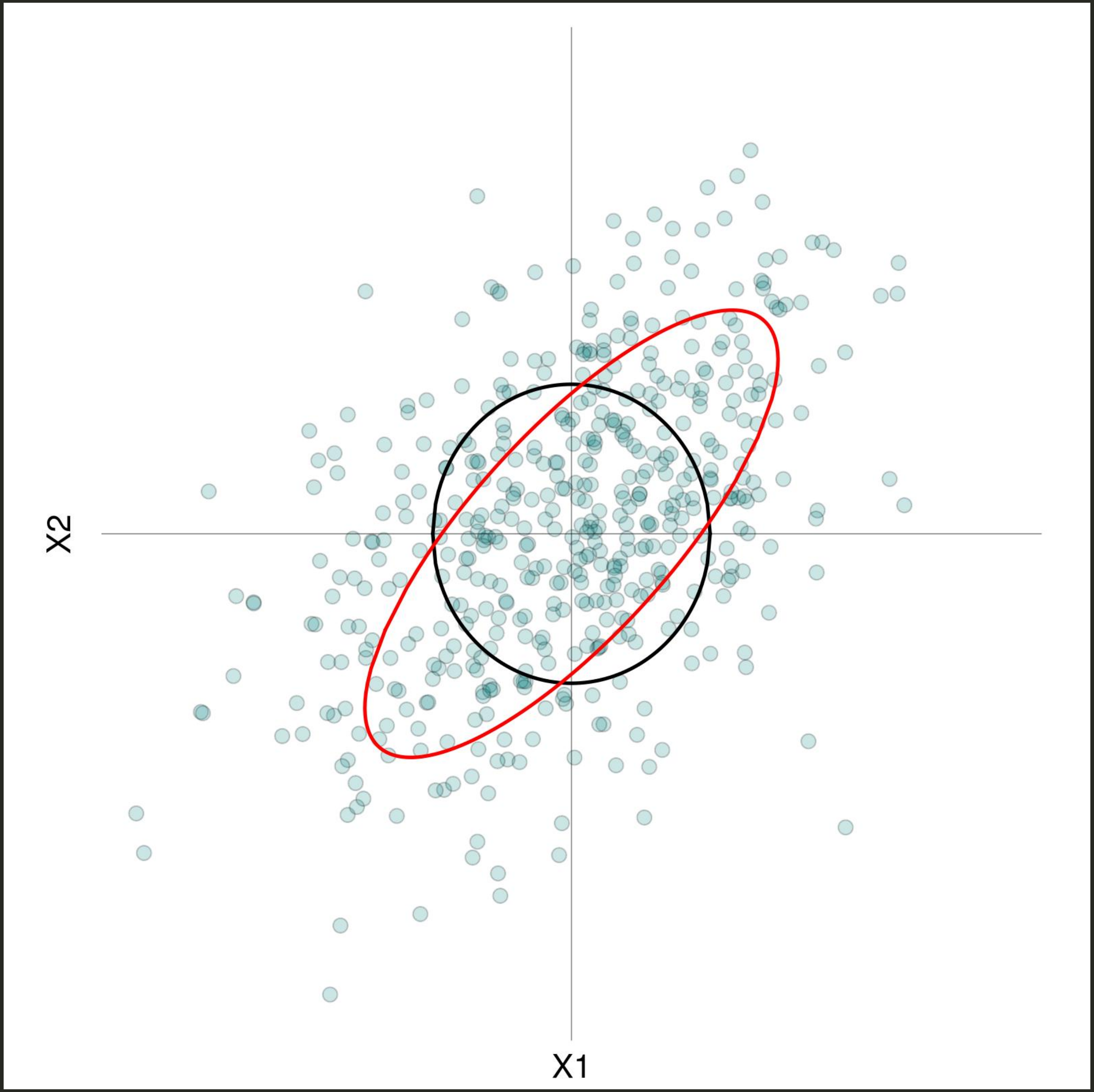
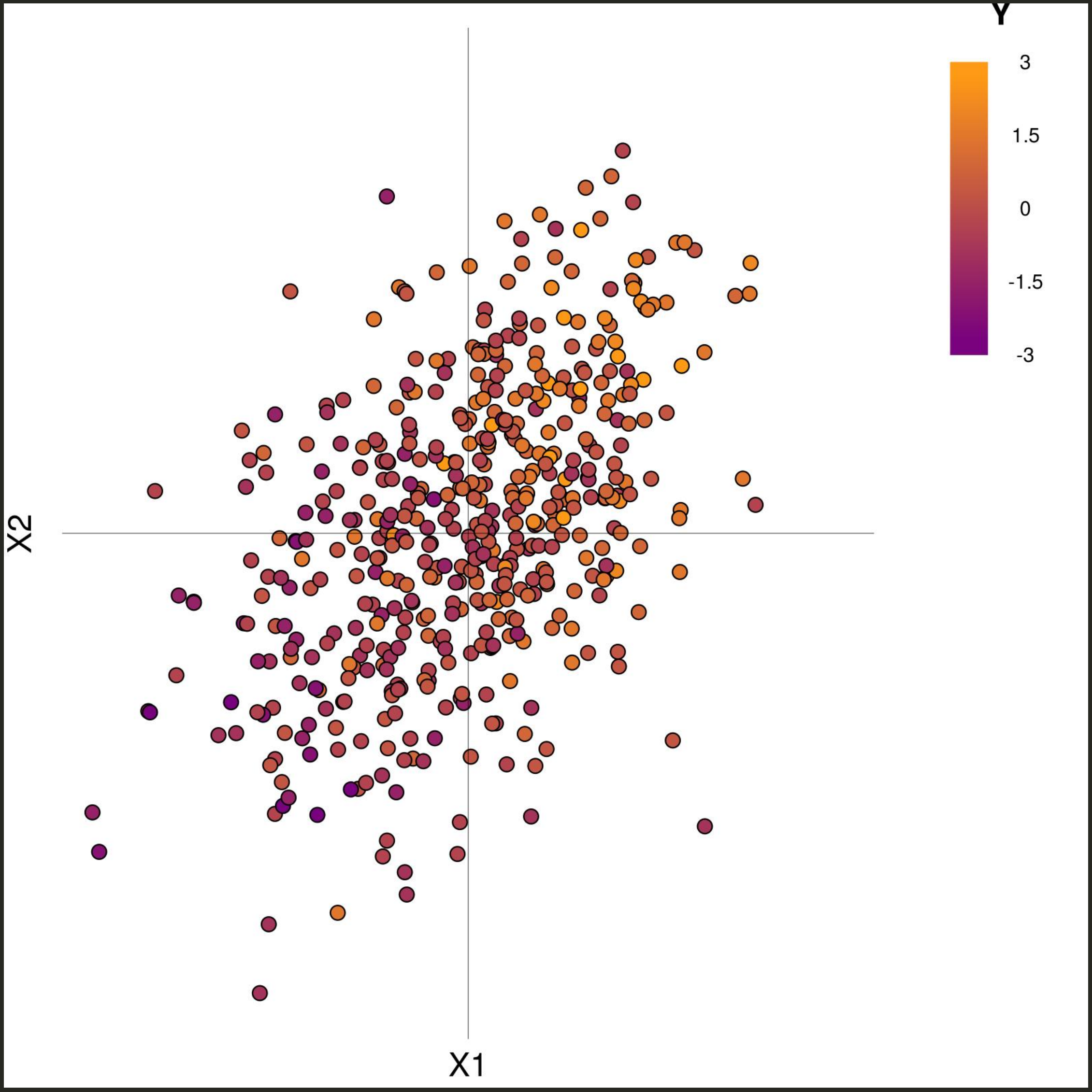
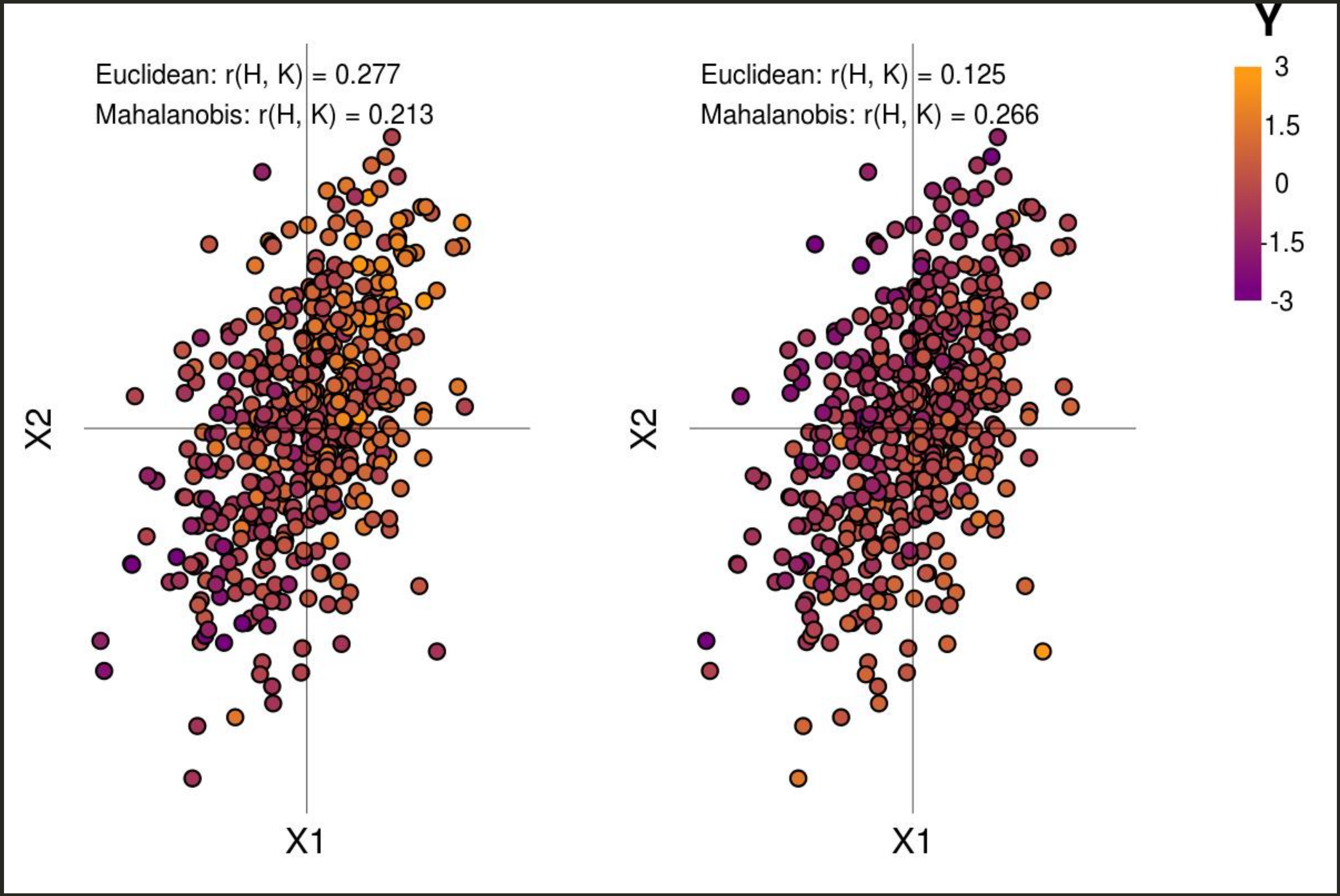

X2
X1

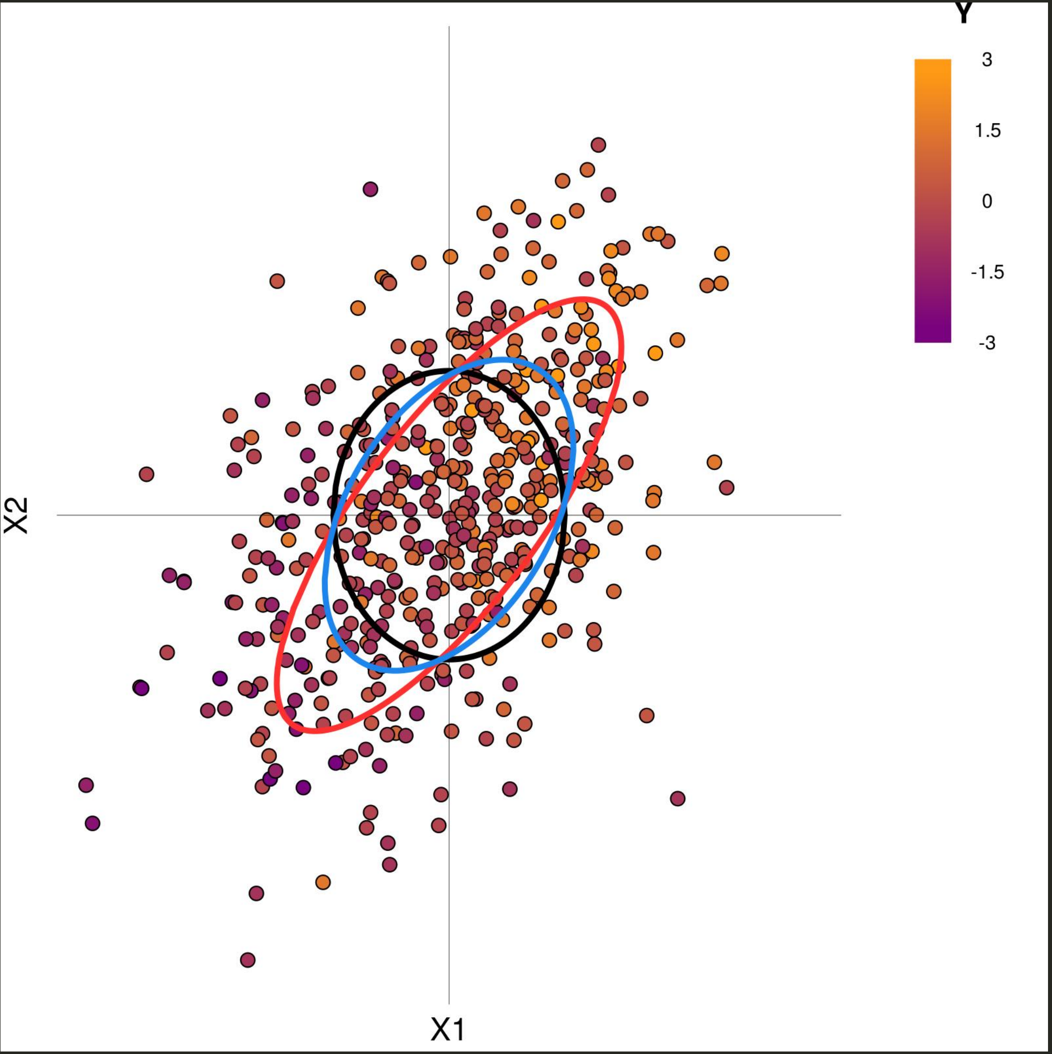
Data generated from variance components model with $\sigma_b^2 = 1$





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**.

Kernel Mantel Test

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
Mahalanobis	$K_M = X(X^T X)^{-1} X^T$
Euclidean	$K_E = XX^T$
Ridge Kernel	$K_\lambda = X(X^T X + \lambda I)^{-1} X^T$

Kernel Mantel Test

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

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

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

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

This implies limit relationships between the three measures of correlation:

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

Kernel Mantel Test

Linear Model Definitions

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

Linear Model Score Tests

Model	Score Stat.	Equivalent Stat.	Null Distribution
Fixed	$S = Z^T D(D^T D)^{-1} D^T Z$	$T_M = \mathrm{tr}(K_M H)$	$c_1 \chi_p^2$
Random	$S = Z^T D D^T Z$	$T_E = \mathrm{tr}(K_E H)$	$c_2 \sum_{j=1}^{r} \eta_j \chi_1^2$
Ridge	$S = Z^T D(D^T D + \lambda I_p)^{-1} D^T Z$	$T_\lambda = \mathrm{tr}(K_\lambda H)$	$c_3 \sum_{j=1}^{r} \frac{\eta_j}{\lambda + \eta_j} \chi_1^2$

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

Problem

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

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.

Adaptive Mantel Test

Algorithm 1: Adaptive Mantel Algorithm

Input: $X, Y, \Lambda = \{\lambda_j\}_{j=1}^{m}$.

Output: Adaptive Mantel P-value.

$H^{(0)} \leftarrow YY^T$

for $j = 1, \ldots, m$ **do**

$\quad K_{\lambda_j} \leftarrow X(X^T X + \lambda I_p)^{-1} X^T$

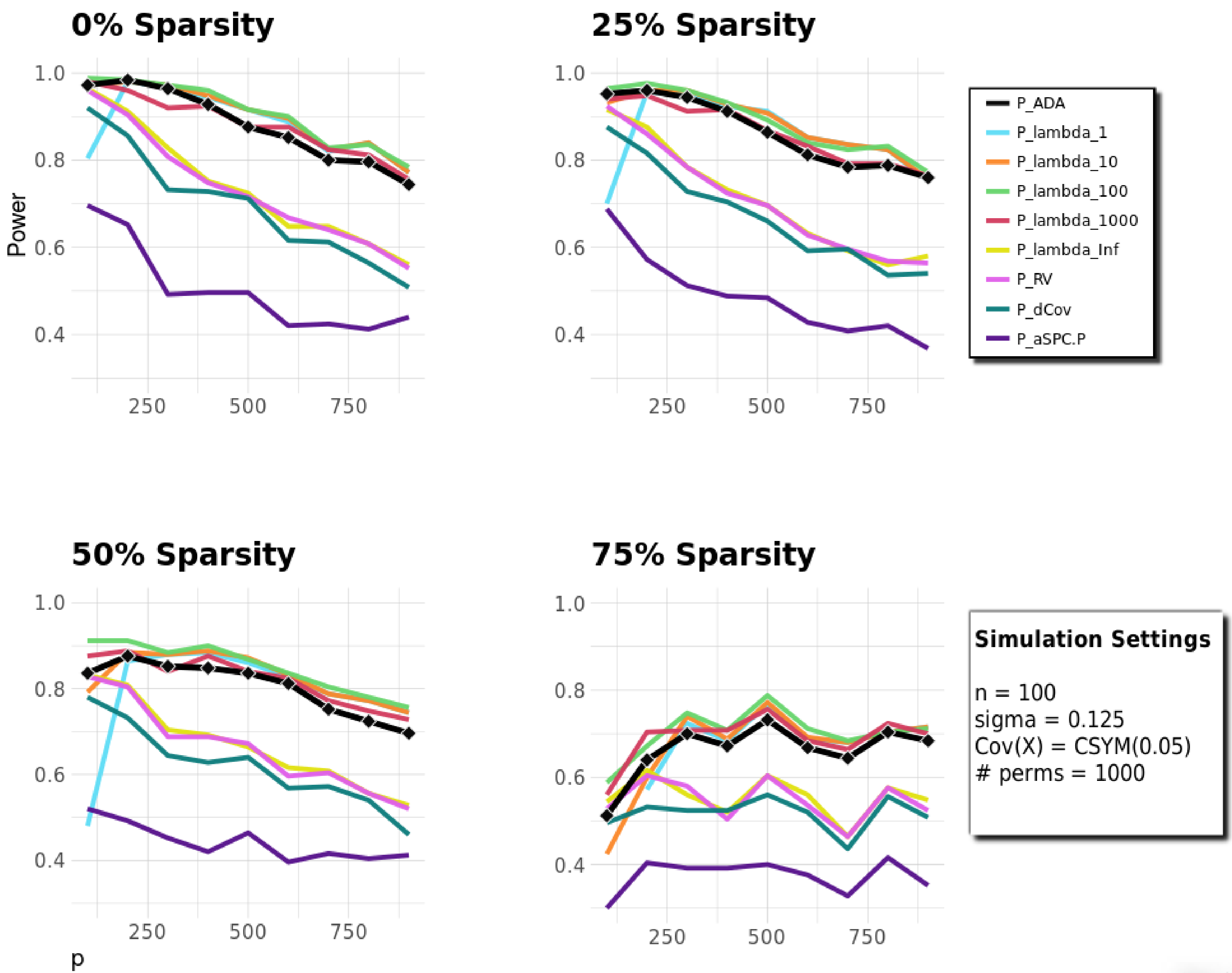
Generate B permutations of $H^{(0)}$, labeled $H^{(b)}, b = 1, \ldots, B$

$T_j^{(b)} \leftarrow \mathtt{tr}(H^{(b)} K_{\lambda_j}), \quad \forall b = 0, \ldots, B; j = 1, \ldots, m$

$P_j^{(b)} \leftarrow \frac{1}{B+1} \sum_{b'=0}^{B} \mathbb{1}(T_j^{(b)} \geq T_j^{(b')}), \quad \forall b = 0, \ldots, B; j = 1, \ldots, m$

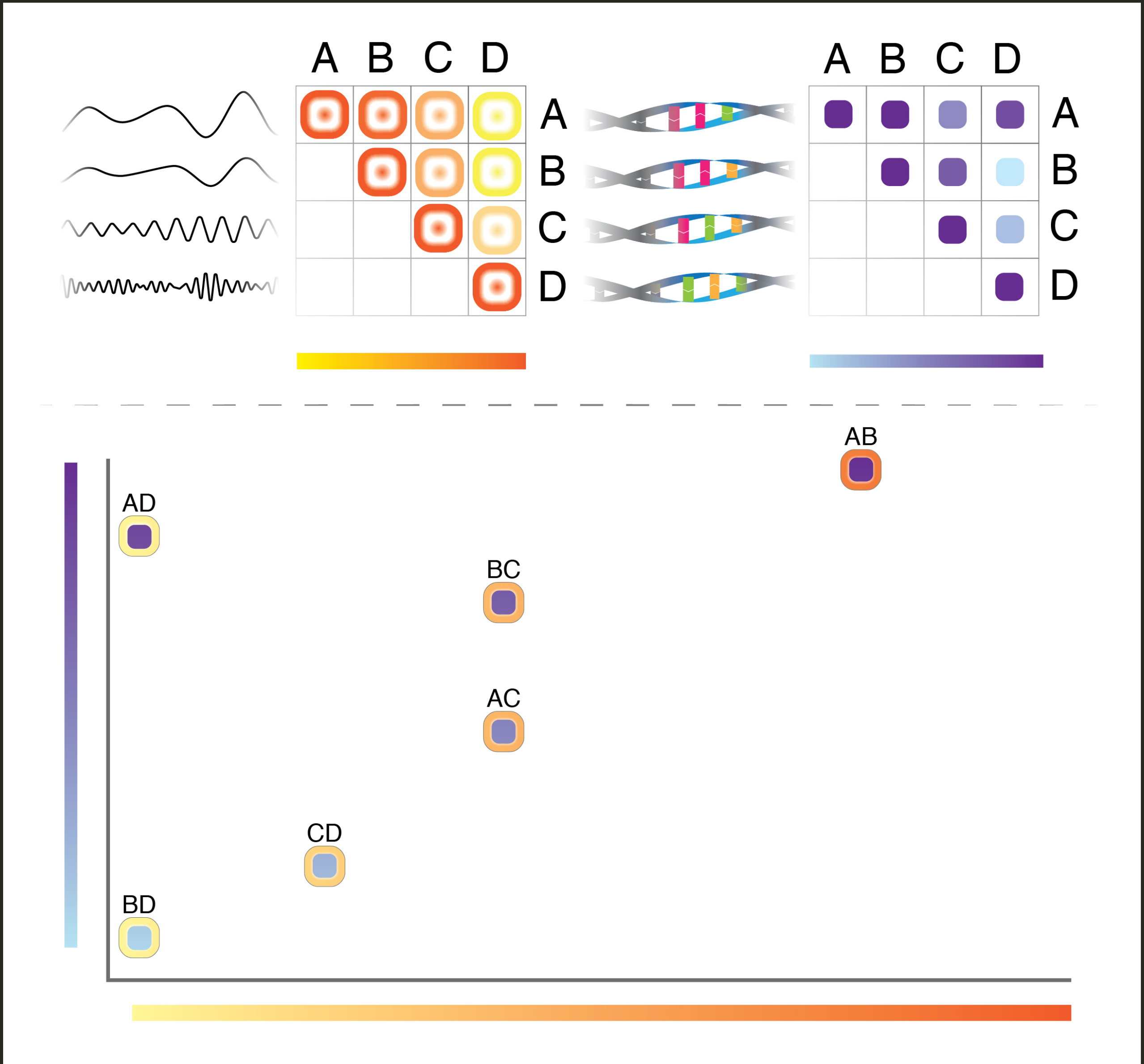
$P^{(b)} \leftarrow \min_j P_j^{(b)}, \quad \forall b = 0, \ldots, B$

$P_{ADA} \leftarrow \frac{1}{B+1} \sum_{b=0}^{B} \mathbb{1}(P^{(0)} \leq P^{(b)})$


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

Application Example

- 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 quality control checks


A B C D
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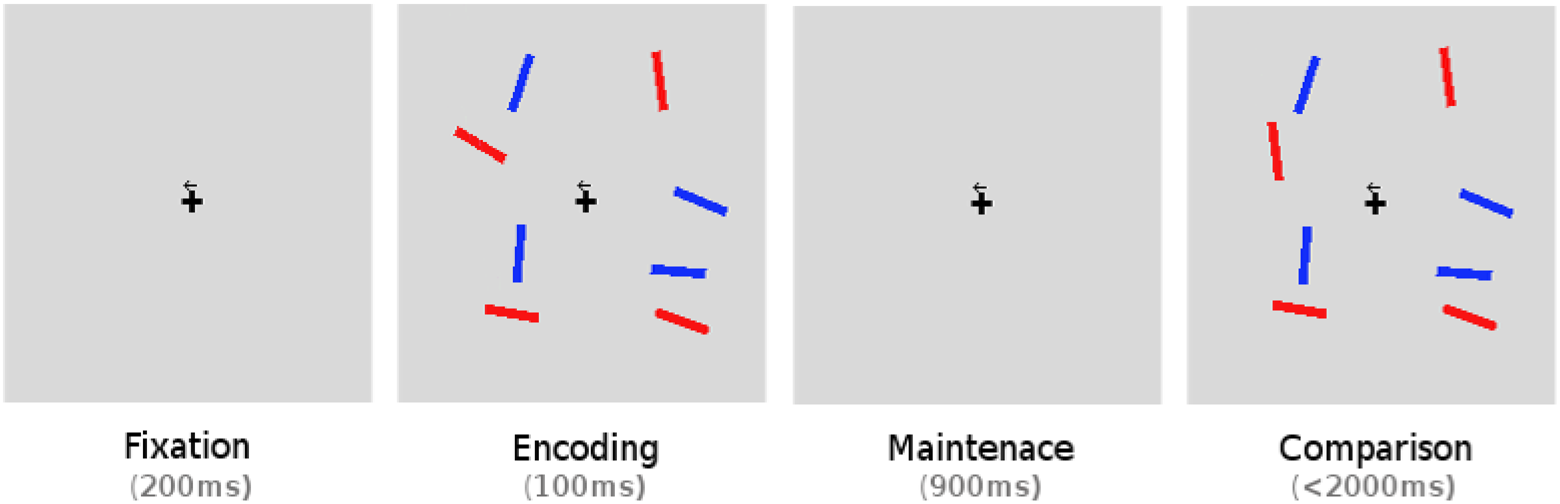
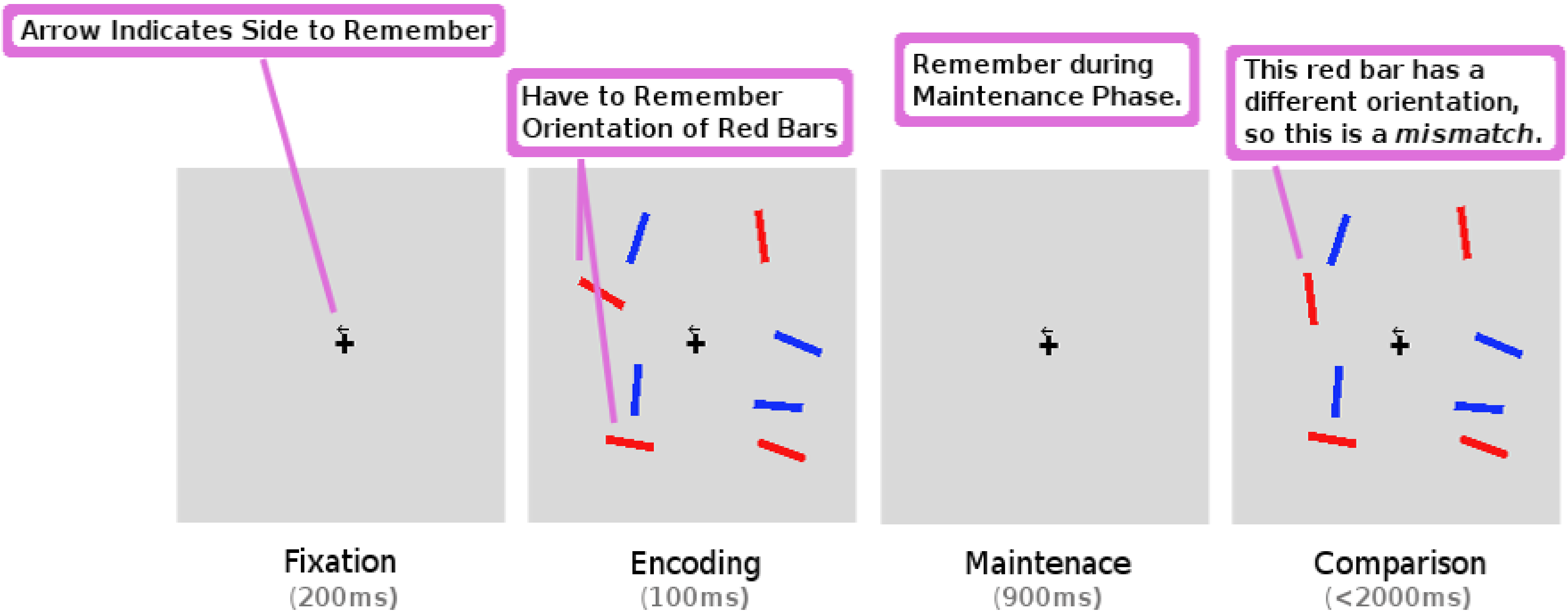
Visual Working Memory Experiment



Visual Working Memory Experiment



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.