Principal Component of Explained Variance

High-Dimensional Estimation and Inference

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Introduction

- In modern statistics, we often encounter multivariate data of large dimension ($p > n$).
  - In biomedical sciences (e.g. neuroimaging, genomics), pattern recognition, text recognition, finance, etc.
- We are often faced with the following problem:
  - Given two multivariate datasets $\mathbf{W} = (W_1, \ldots, W_p)$ and $\mathbf{Z} = (Z_1, \ldots, Z_q)$, **how do we test for global association, and how do we identify which variables drive the association?**

Introduction

- Regression: $E(\mathbf{W}|\mathbf{Z}) = B^T\mathbf{Z}$.
  - The matrix B of regression parameters controls the global association **and** the contribution of each components of $\mathbf{Z}$.
- Regularized regression can also be used to detect sparse signals (e.g. Lasso, SCAD).
- However, this framework can be cumbersome when $\mathbf{W}$ has dimension greater than one, especially when we have heterogeneous variable types (e.g. continuous and categorical).

Motivating Examples

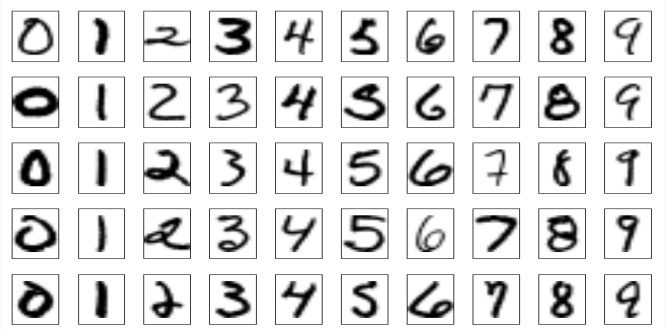
Motivating Examples

The next examples have the following in common:

We have a (possibly high-dimensional) multivariate vector $\mathbf{Y}$ and a set of covariates $\mathbf{X}$.

We are interested in low dimensional representations of $\mathbf{Y}$ that **summarise** the relationship between $\mathbf{Y}$ and $\mathbf{X}$.

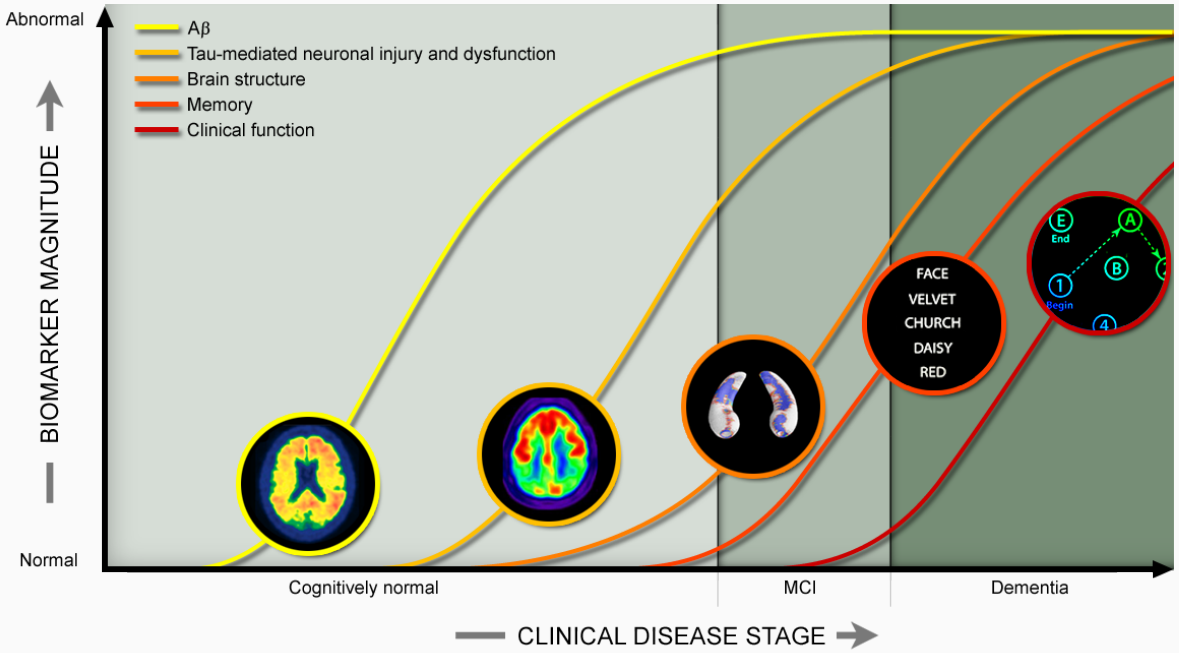
Motivating Example #1



- *Digit recognition*: A famous example in machine learning coming from Le Cun *et al.* (1990).
- Consists of 28×28 gray scale images of digits (i.e. 784 pixels), where the goal is to automatically identify the digit.
- $\mathbf{Y}$ is the set of gray scale values for each pixel, and $\mathbf{X}$ is the digit to which the image corresponds
- We would like to extract lower-dimensional features to use for predicting the digit.

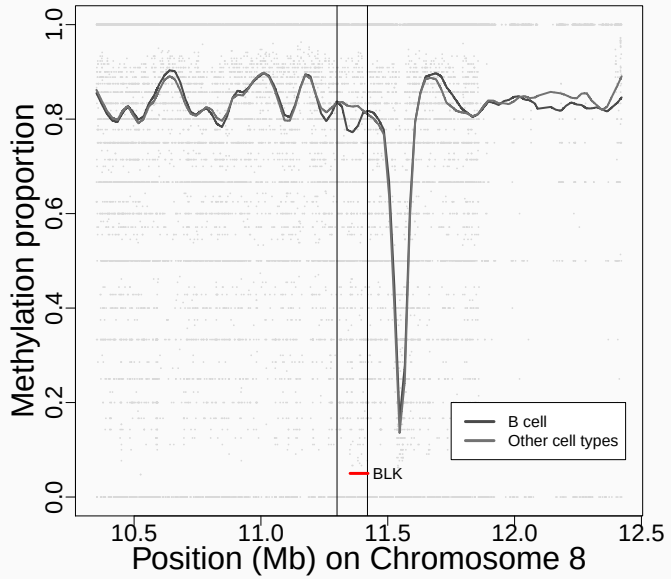
Motivating Example #2

- Data from 340 participants from the Alzheimer's Disease Neuroimaging Initiative (ADNI)
- Brain imaging was employed to assess amyloid-β (Aβ) protein load in 96 brain regions
- **Y** is the set of Aβ load values for each brain region, and **X** is the (binary) disease status.



Motivating Example #3

- The dataset consists of 40 blood samples, separated into different cell types (T cells, B cells, monocytes), and for which methylation levels were measured at 24,000 locations along the genome.
- **Y** is the set of DNA methylation values for all 24,000 locations, and **X** is the cell type.



Principal Component of Explained Variance (PCEV)

- Provides an **optimal** strategy for selecting a low dimensional summary of $\mathbf{Y}$ that can be used to test for association with one or several covariates of interest.
- **Goal**: Find the linear combination (or component) that maximises the *proportion of variance explained by the covariates*

Summary

1. Estimation strategies
2. Analytical framework for hypothesis testing
   - High-dimensional inference
3. An `R` package implementing this method (`pcev` available on CRAN)

Methods

PCEV: Statistical Model

Let $\mathbf{Y}$ be a multivariate outcome of dimension p and $\mathbf{X}$, a vector of covariates.

We assume a linear relationship:

$$\mathbf{Y} = B^T\mathbf{X} + \varepsilon.$$

The total variance of the outcome can then be decomposed as

$$\begin{aligned}\mathrm{Var}(\mathbf{Y}) &= \mathrm{Var}(B^T\mathbf{X}) + \mathrm{Var}(\varepsilon) \\ &= V_M + V_R.\end{aligned}$$

PCEV: Statistical Model

Decompose the total variance of $\mathbf{Y}$ into:

1. Variance explained by the covariates;
2. Residual variance.

PCEV: Statistical Model

The PCEV framework seeks a linear combination $w^T\mathbf{Y}$ such that the proportion of variance explained by $\mathbf{X}$ is maximised; this proportion is defined as the following Rayleigh quotient:

$$R^2(w) = \frac{w^T V_M w}{w^T (V_M + V_R) w}.$$

We can solve this maximisation problem by looking at the largest eigenvalue of $(V_M + V_R)^{-1} V_M$.

Key observation: $R^2(w)$ measures the strength of the association

More Dimension Reduction

- **PCA**: Maximise total variance
- **CCA**: Maximise correlation
- **PLS**: Maximise covariance
- **RDA**: Maximise redundancy index
- **PCEV**: Maximise proportion of variance explained

All these methods (except PCA) have serious limitations with high-dimensional data.

Block-diagonal Estimator

With high-dimensional data, the sample covariance matrix is no longer invertible, and therefore we cannot use it to estimate the largest eigenvalue of $(V_M + V_R)^{-1} V_M$.

We propose a **block approach** to the computation of PCEV in the presence of high-dimensional outcomes.

- Suppose the outcome variables can be divided in blocks of variables in such a way that
  - Variables **within** blocks are correlated
  - Variables **between** blocks are uncorrelated

$$\mathrm{Cov}(\mathbf{Y}) = \begin{pmatrix} * & \mathbf{0} & \mathbf{0} \\ \mathbf{0} & * & \mathbf{0} \\ \mathbf{0} & \mathbf{0} & * \end{pmatrix}$$

Block-diagonal Estimator

- If the blocks are small enough, we can perform PCEV on each of them, resulting in a component for each block.
- Treating all these "partial" PCEVs as a new, multivariate pseudo-outcome, we can perform PCEV again; the result is a linear combination of the original outcome variables.

With the above assumption, I showed that this is **mathematically equivalent** to performing PCEV in a single-step. (*Stat Meth Med Res*, 2018)

Finally, we can compute p-values using a permutation procedure.

Simulations

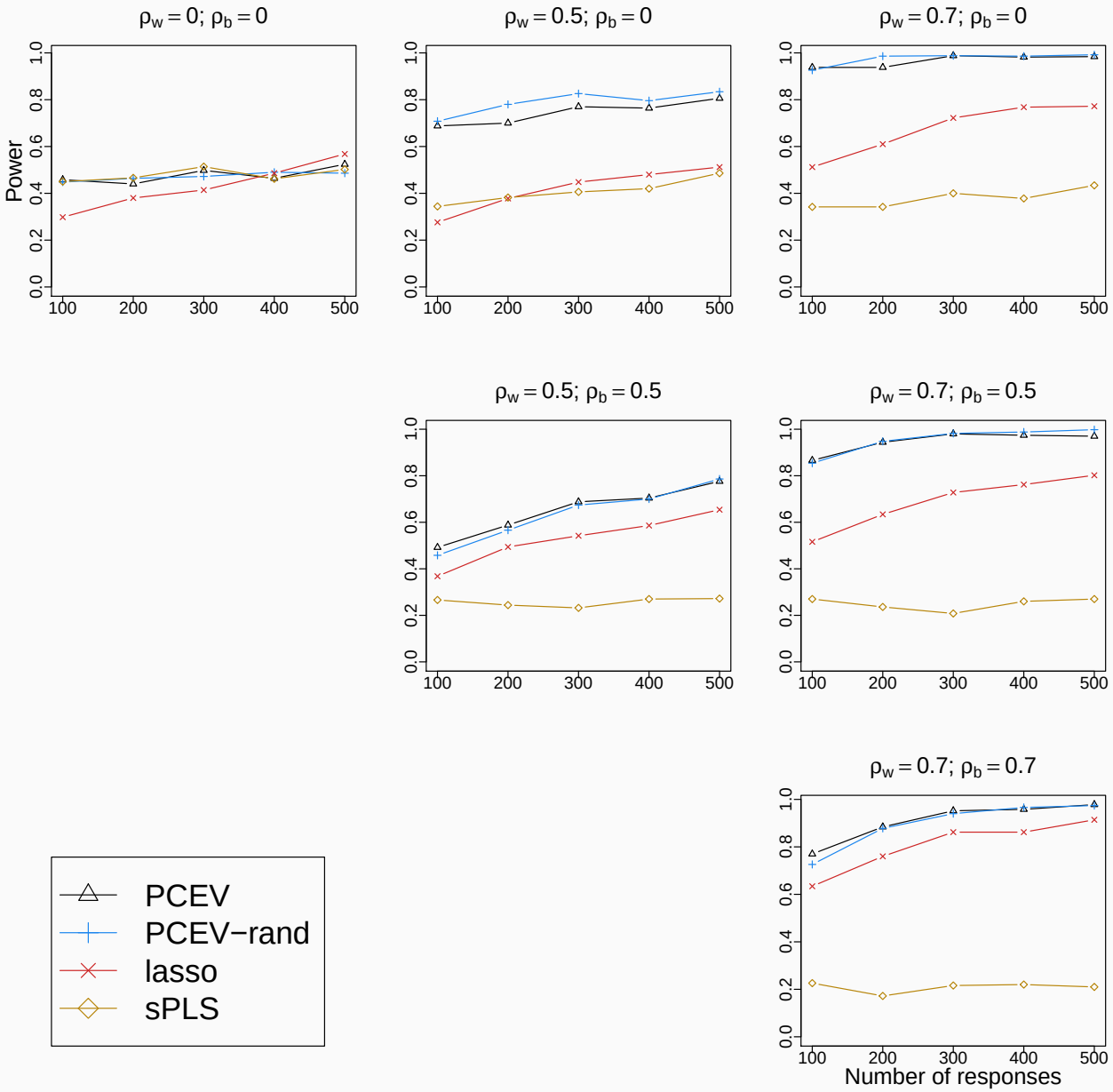
Simulation Setting

- We compared 4 different approaches:
  - PCEV-block, with blocks assumed known a priori
  - PCEV-block, with blocks selected randomly
  - Lasso
  - Sparse Partial Least Squares (sPLS)
- We fixed the sample size at $n = 100$ and simulated $p = 100, 200, 300, 400, 500$ outcomes; we distributed the outcome variables in 10 blocks.
- We also varied the correlation between (ρ_b) and within (ρ_w) blocks (0, 0.5, 0.7).
- We simulated a single continuous covariate from a standard normal distribution. 25% of the outcomes in each block are associated with $\mathbf{X}$.

Simulation Setting

- Whereas PCEV treats the multivariate, p-dimensional $\mathbf{Y}$ as the outcome variable and $\mathbf{X}$ as the covariate, we inverted these roles for both Lasso and sPLS, so that variable selection happens on $\mathbf{Y}$.
- The test statistics for Lasso and sPLS were as follows:
  - **Lasso**: Correlation between $\mathbf{X}$ and $\hat{\beta}_L \mathbf{Y}$
  - **sPLS**: Maximised covariance
- P-values were computed using a permutation procedure.

Simulation Results: Power analysis



Data analysis

Motivating Example #2

- Recall: Data on amyloid-β accumulation in $p = 96$ brain regions, measured on $n = 340$ subjects. We are interested in the association with Alzheimer's disease.
- We used this dataset to compare the block approach to the traditional approach (since $n > p$)
- We defined blocks using hierarchical clustering.

Results

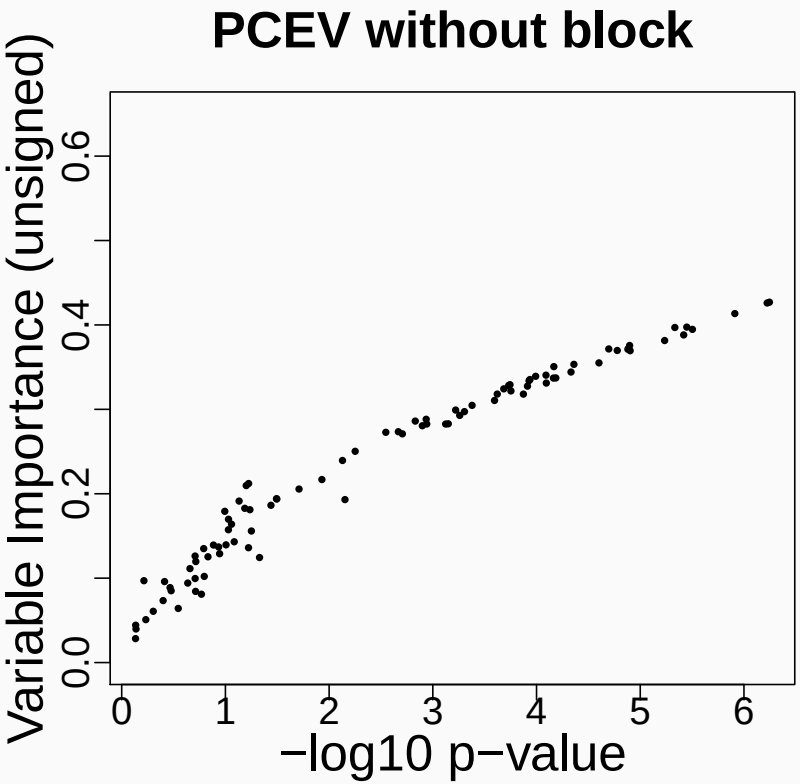
P-values for the joint association between amyloid-β accumulation and disease status. Permutation tests were performed using 100,000 permutations.

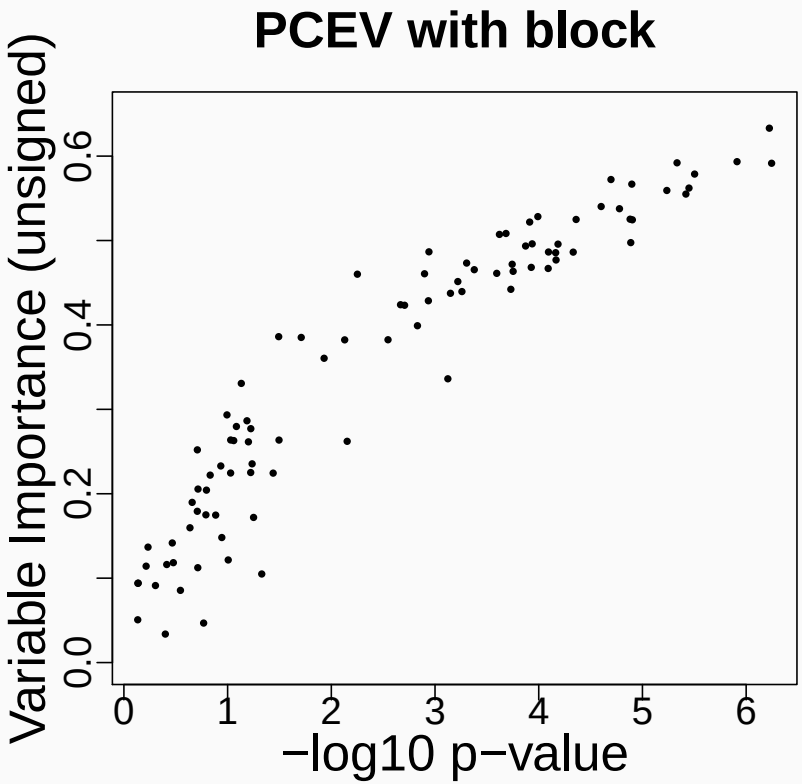
	PCEV	PCEV with blocks
Exact test	8.13×10^{-5}	—
Permutation test	2×10^{-5}	5×10^{-5}

Variable Importance Factor

- **VIF**: Correlation between a single variable Y_j in $\mathbf{Y}$ and the PCEV component (in absolute value).
- VIF allows us to decompose the global association into individual components; the higher the VIF, the stronger the contribution of an individual variable.

Variable Importance Factor



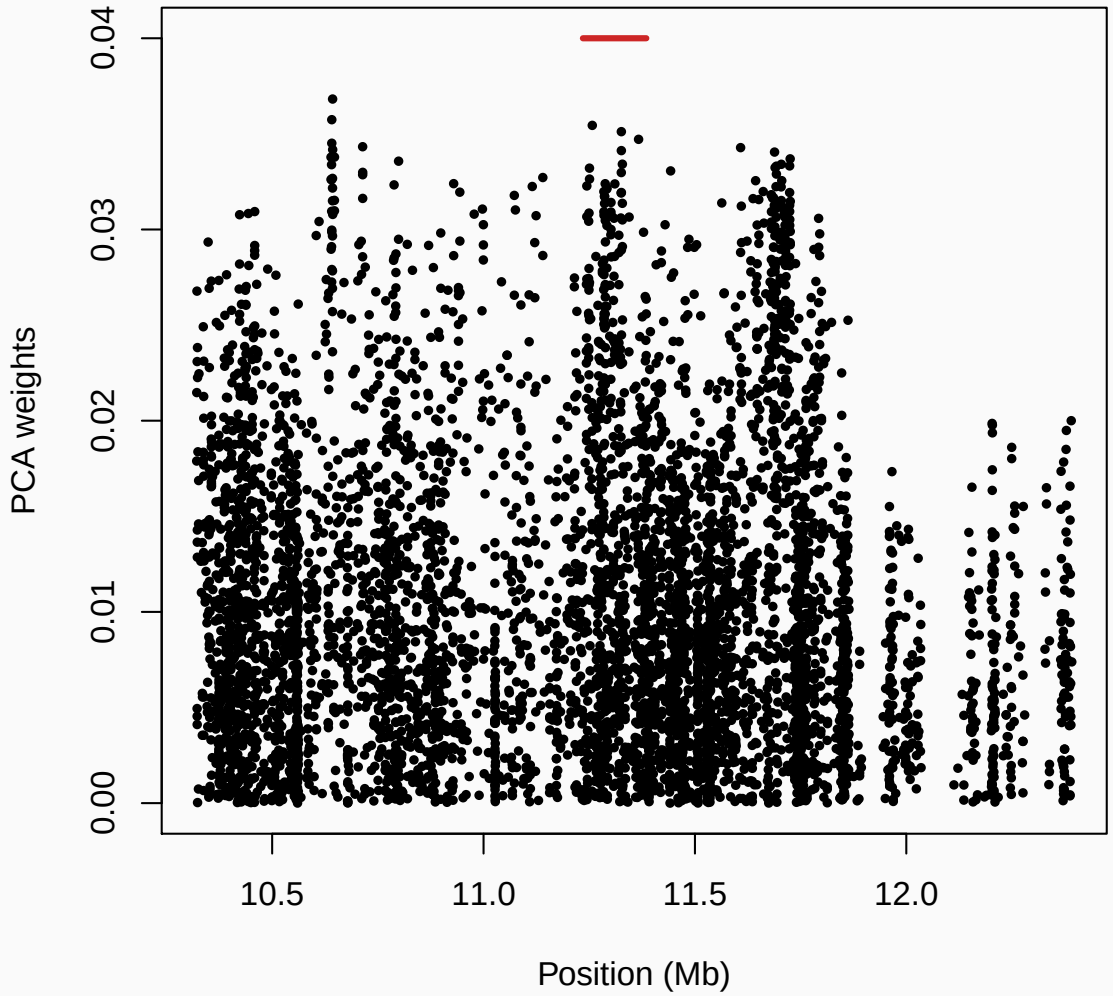


Motivating Example #3

- BLK gene, located on chromosome 8
- Data provided by Tomi Pastinen (McGill)
- $n = 40$ blood samples, from 3 different cell types
  - B cells (n=8)
  - T cells (n=19)
  - Monocytes (n=13)
- $p = 24,068$ locations on the DNA

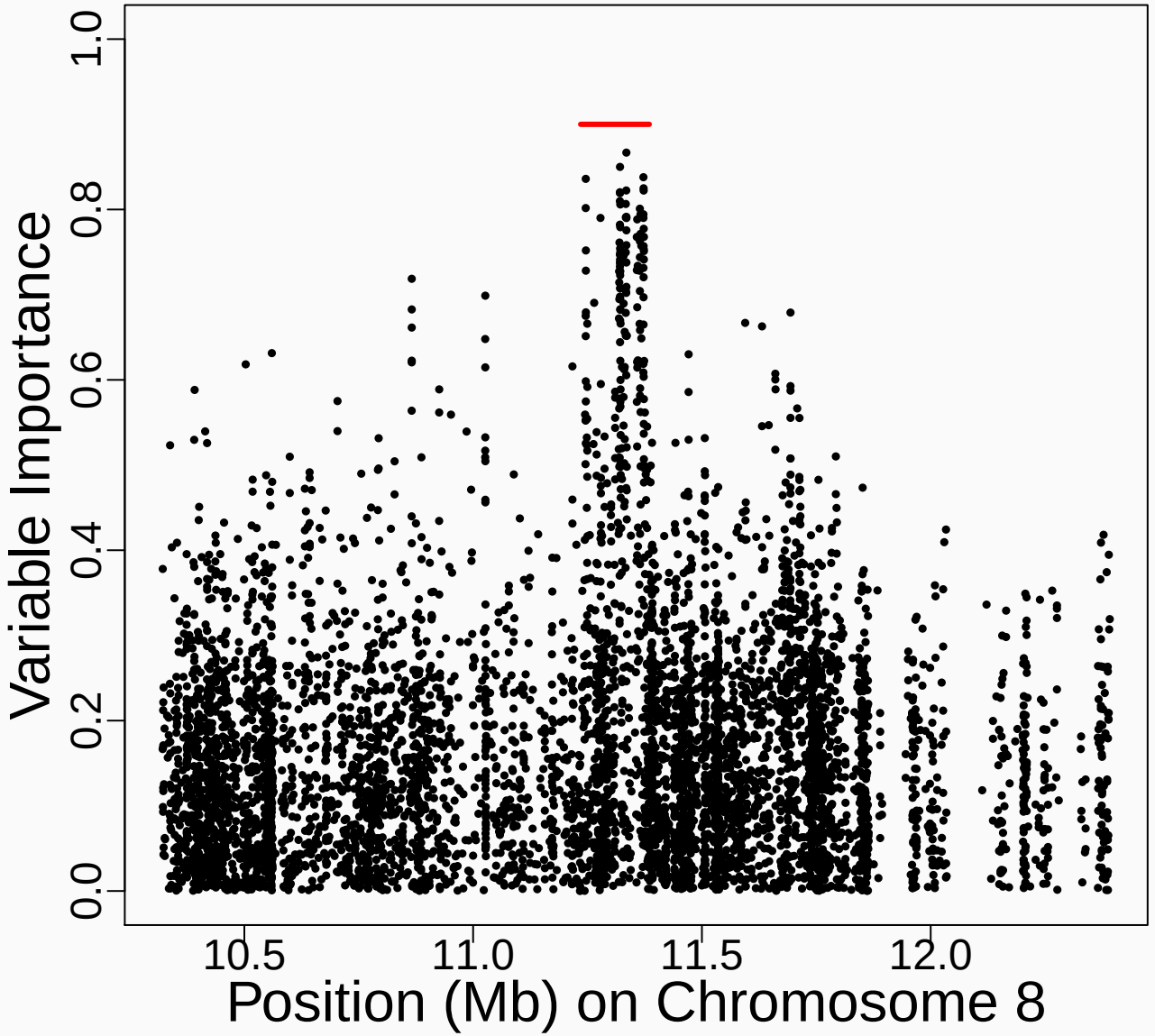
Goal: Investigate the association between methylation levels in the BLK region (outcomes) and cell type (covariate: B cell vs T cell and monocytes)

PCA



Results

- We used the block approach, where blocks were defined using physical distance: CpGs within 500kb are grouped together
  - 951 blocks were analysed
- Using PCEV, we obtained a single p-value, which is less than 6×10^{-5} (using 100,000 permutations)
- Hence, a single test for all variables, and no tuning parameter was required.


Variable Importance
0.0
0.2
0.4
0.6
0.8
1.0
10.5
11.0
11.5
12.0
Position (Mb) on Chromosome 8

Summary

- The block approach has good power compared to common high-dimensional methods
- Results are robust to how blocks are defined
  - P-values are similar
  - Power is similar
  - Variable Importance Factors are also similar

High-dimensional inference

Double Wishart Problem

- Recall that PCEV is maximising a Rayleigh quotient:

$$R^2(w) = \frac{w^T V_M w}{w^T (V_M + V_R) w}.$$

- This approach is equivalent to finding the largest root λ of a *double Wishart problem*:

$$\det\left(\mathbf{A} - \lambda(\mathbf{A} + \mathbf{B})\right) = 0,$$

where $A = V_M, B = V_R$.

Double Wishart Problem

There are many well-known examples of double Wishart problems:

- Multivariate Analysis of Variance (MANOVA);
- Canonical Correlation Analysis (CCA);
- Testing for independence of two multivariate samples;
- Testing for the equality of covariance matrices of two independent samples from multivariate normal distributions;
- **Principal Component of Explained Variance (PCEV)**.

In all the examples above, the largest root λ summarises the strength of the association.

Contributions

The main contribution:

1. I provide an empirical estimate of the distribution of the largest root of the determinantal equation. This estimate can be used to compute valid p-values and perform high-dimensional inference.

I illustrate this approach using PCEV, but it is applicable to **any** double Wishart problem (e.g. CCA and LDA).

Inference

There is evidence in the literature that the null distribution of the largest root λ should be related to the **Tracy-Widom distribution**.

Theorem
(Johnstone 2008) Assume $\mathbf{A} \sim W_p(m, \Sigma)$ *and* $\mathbf{B} \sim W_p(n, \Sigma)$ *are independent, with* Σ *positive-definite and* $\boldsymbol{n \leq p}$*. As* $p, m, n \to \infty$*, we have*

$$\frac{\operatorname{logit} \lambda - \mu}{\sigma} \xrightarrow{\mathcal{D}} TW(1),$$

where $TW(1)$ *is the Tracy-Widom distribution of order 1, and* μ, σ *are explicit functions of* p, m, n*.*

Inference

- However, Johnstone's theorem requires an invertible matrix.
- *More evidence*: The null distribution of λ is asymptotically equal to that of the largest root of a scaled Wishart variate (Srivastava).
  - The null distribution of the largest root of a Wishart is also related to the Tracy-Widom distribution.
- More generally, random matrix theory suggests that the Tracy-widom distribution is key in central-limit-like theorems for random matrices.

Empirical Estimate

We propose to obtain an empirical estimate as follows:

Estimate the null distribution

1. Perform a small number of permutations (~ 50) on the rows of $\mathbf{Y}$;
2. For each permutation, compute the largest root statistic.
3. Fit a location-scale variant of the Tracy-Widom distribution.

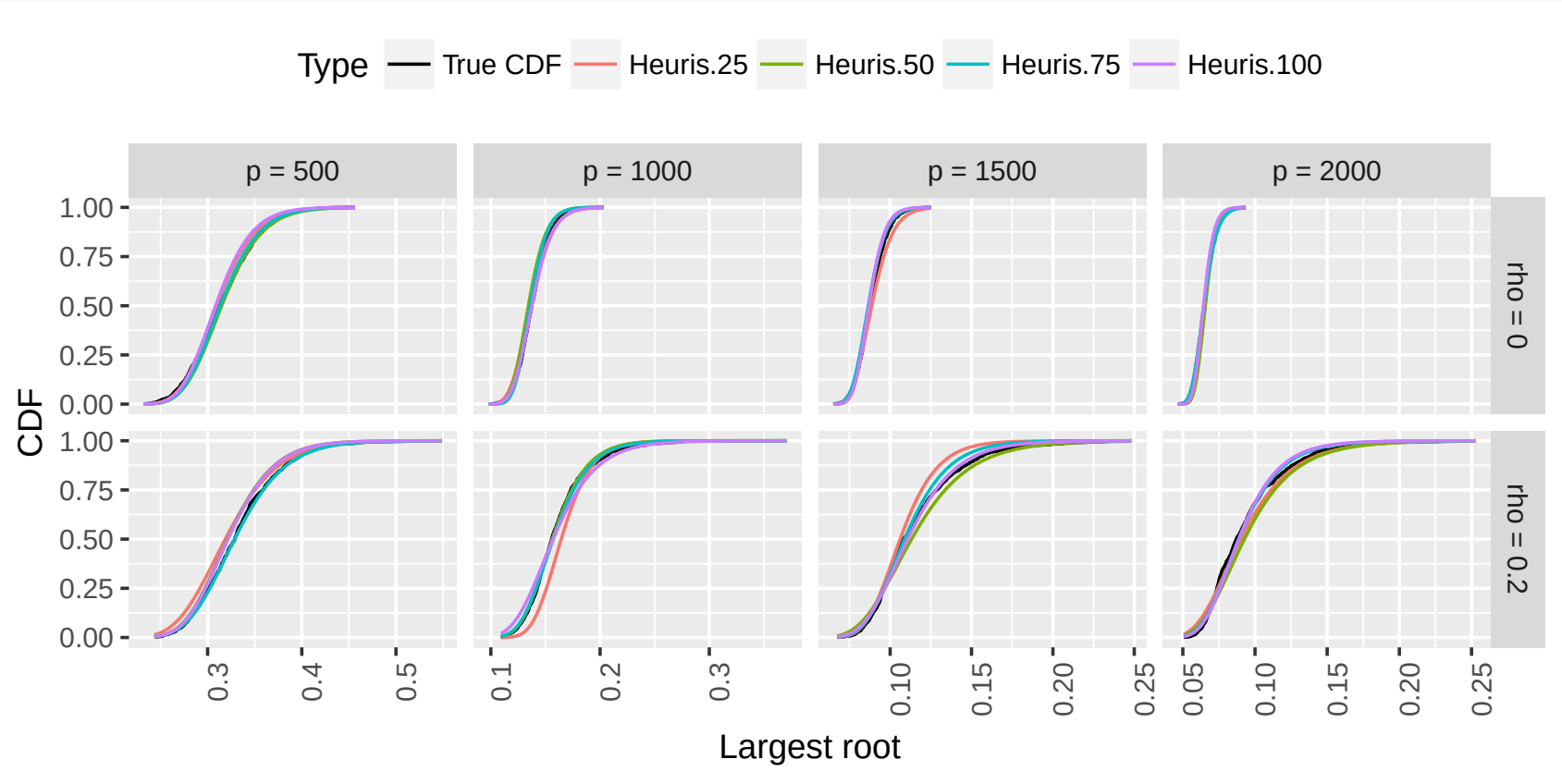
Numerical investigations support this approach for computing p-values. The main advantage over a traditional permutation strategy is the computation time.

Simulations

Distribution Estimation

- We generated 1000 pairs of Wishart variates $\mathbf{A} \sim W_p(m, \Sigma)$, $\mathbf{B} \sim W_p(n, \Sigma)$ with $m = 96$ and $n = 4$ fixed
  - MANOVA: this would correspond to four distinct populations and a total sample size of 100
- We varied $p = 500, 1000, 1500, 2000$
- We looked at two different covariance structures: $\Sigma = I_p$, and an exchangable correlation structure with parameter $\rho = 0.2$.
- We looked at four different numbers of permutations for the empirical estimator: $K = 25, 50, 75, 100$.
- We compared graphically the CDF estimated from the empirical estimate with the true CDF

Distribution Estimation

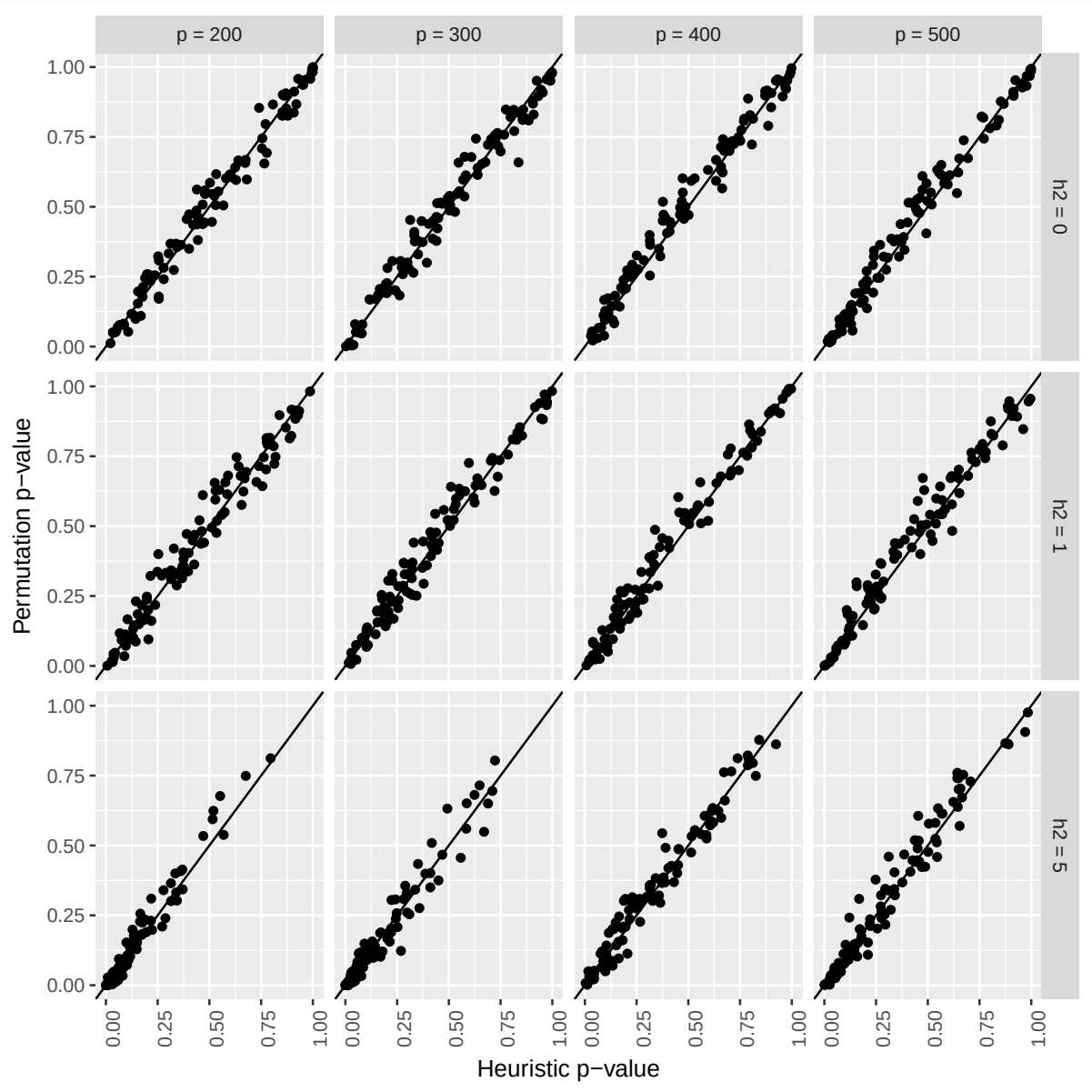


P-value Comparison

We looked at the following high-dimensional simulation scenario:

- We fixed $n = 100$ and a balanced binary covariate $\mathbf{X}$.
- We varied the number of response variables $p = 200$, 300, $400, 500$ and the association between $\mathbf{X}$ and the first 50 response variables in $\mathbf{Y}$.
- We compared the empirical estimate with a permutation procedure (250 permutations).
- Each simulation was repeated 100 times.

P-value Comparison



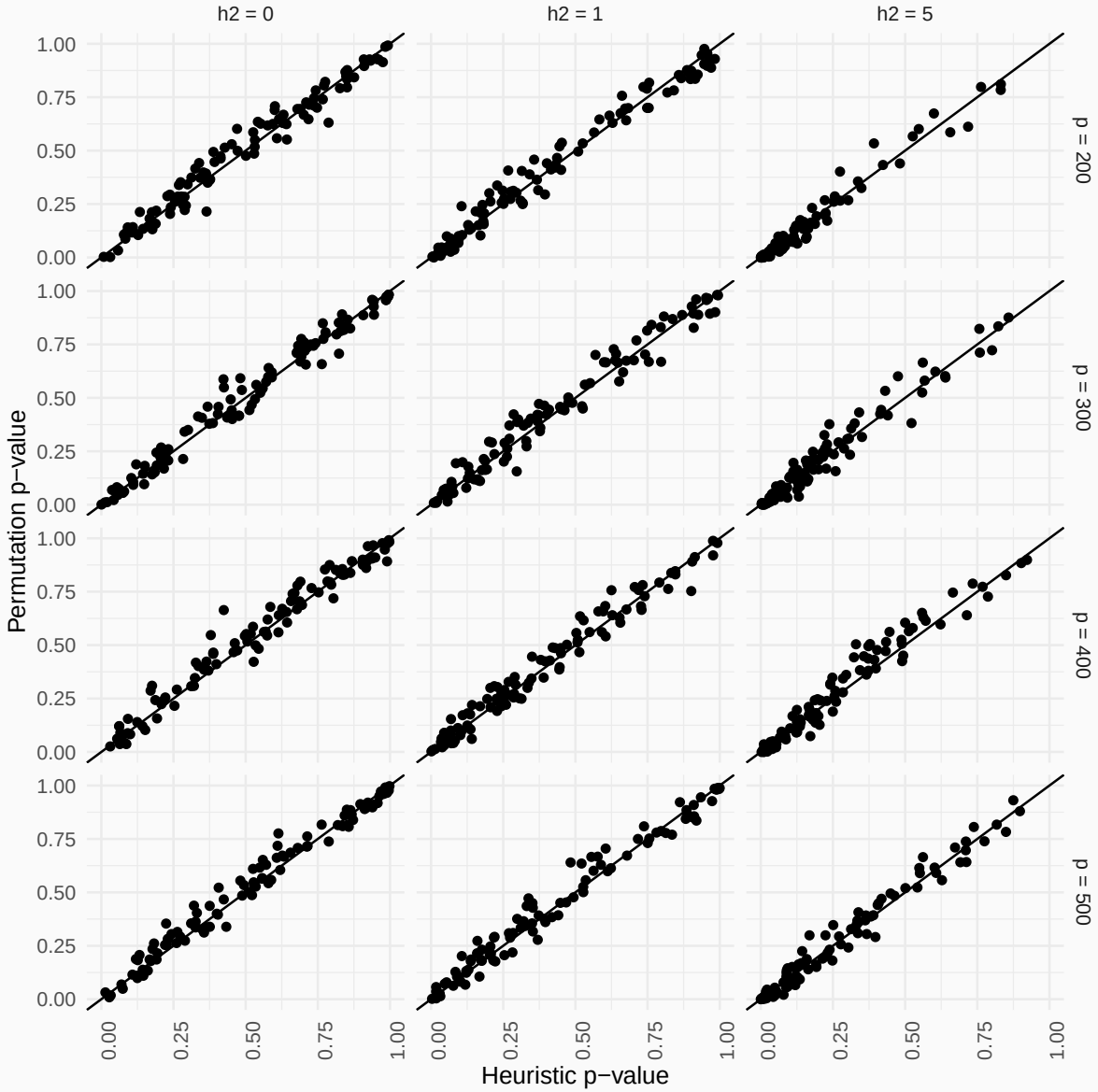
Extension to linear shrinkage covariance estimators

- The setting above follows closely the result of Johnstone (all random matrices are Wishart)
- On the other hand, our empirical estimator also shows good performance when we replace V_R by a *linear shrinkage estimator*.
- Ledoit & Wolf (2004) studied covariance estimators of the form $\Sigma^* = \rho_1 I + \rho_2 S$
- They found explicit expressions for optimal ρ_1, ρ_2 and derived consistent estimators for these quantities.

PCEV with shrinkage

- To assess the performance of our Tracy-Widom empirical estimator under this extended setting, we repeated our p-value comparison from above.
- We replaced the matrix V_R in PCEV by its linearly shrunk version.
- We compared with the p-values obtained from a permutation strategy.

P-value Comparison



Data Analysis

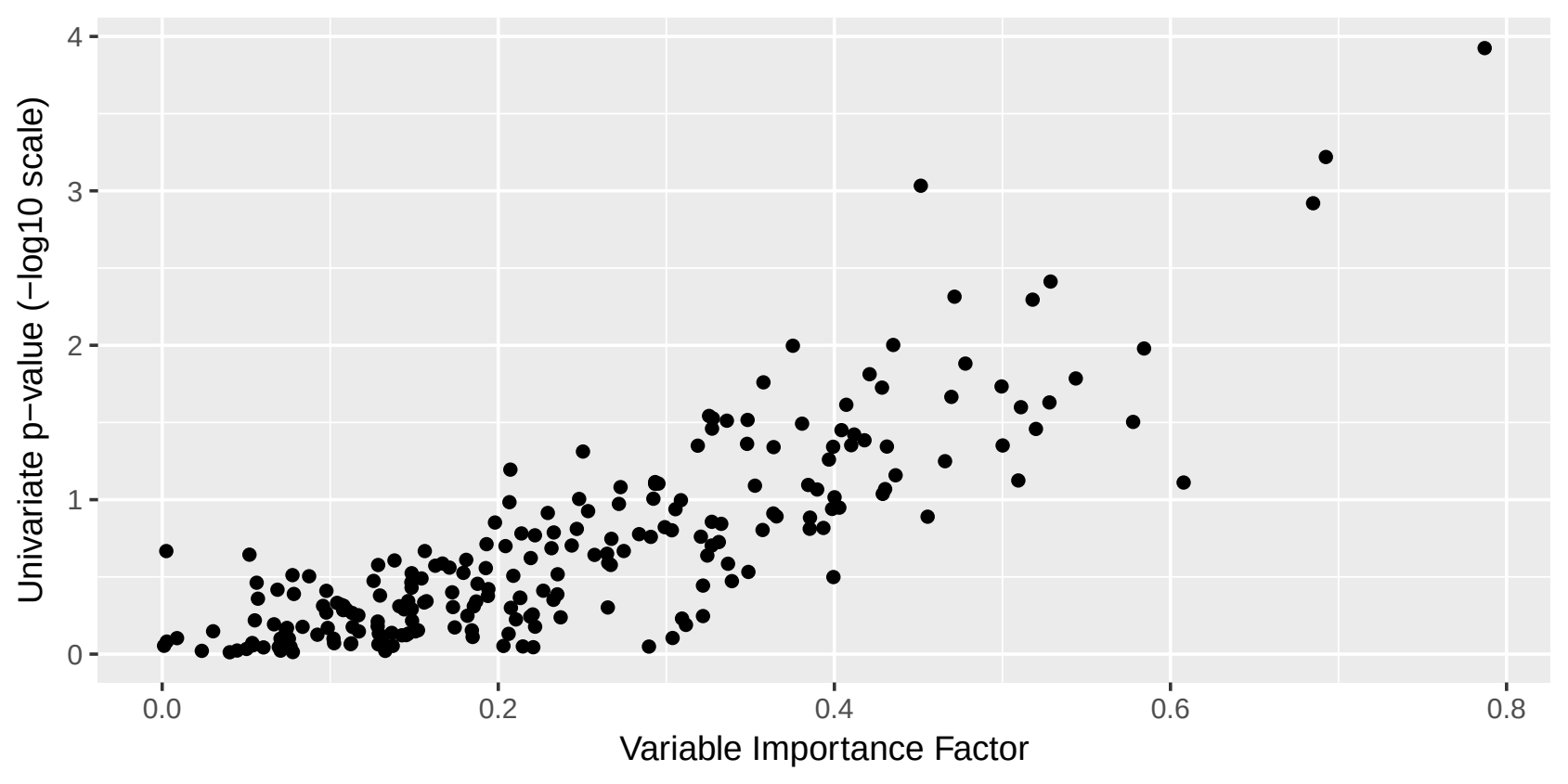
Data

- DNA methylation measured with Illumina 450k on 28 cell-separated samples
- We focus on Monocytes only.
- 18 patients suffering from Rheumatoid arthritis, Lupus, Scleroderma
- We group locations by biological KEGG pathways
  - The number of genomic locations per pathway ranged from 39 to 21,640, with an average around 2000 dinucleotides.
  - 134,941 CpG dinucleotides were successfully matched to one of 320 KEGG pathways
  - On average, each locations appears in 4.5 pathways $\Rightarrow$ effectively 70 independent hypothesis tests

Results

Description	P-value	P-value (permutation)
Glutamatergic synapse	1.91×10^{-4}	7.00×10^{-4}
Ras signaling pathway	1.33×10^{-3}	1.40×10^{-3}
Circadian rhythm	1.52×10^{-3}	1.00×10^{-4}
Histidine metabolism	1.59×10^{-3}	3.00×10^{-4}
Pathogenic E. coli infection	1.65×10^{-3}	5.20×10^{-3}

Results



path:hsa00120—Glutamatergic synapse: Comparison of VIF and univariate p-values for the most significant pathway.

Conclusion

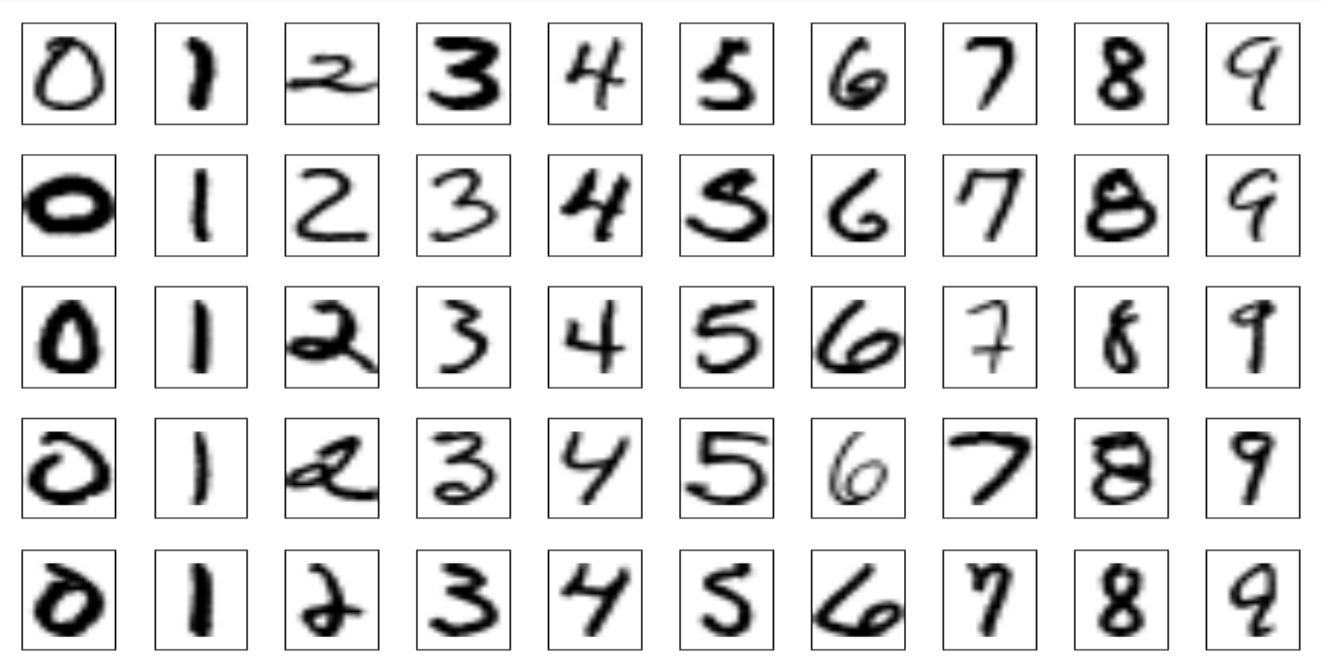
- Dimension reduction techniques aim to summarise high-dimensional vectors with low-dimensional ones *while retaining important features in the data*.
- Principal Component of Explained Variance is an interesting alternative to PCA
  - It is optimal in capturing the association with covariates
- In a high-dimensional setting, **estimation** and **inference** are more challenging
  - Estimation: Truncated SVD, or block-diagonal estimator
  - Inference: Fitted location-scale Tracy-Widom, or permutation strategy.

Conclusion

- Our approach is computationally simple and provides good power.
- Simulations and data analyses confirm its advantage over a more traditional approach using PCA, as well as other high-dimensional approaches such as regularized regression and sparse PLS.
- The empirical estimate of the distribution of λ has already been successfully applied to other double Wishart problems (test of covariance equality and CCA).
- Everything presented today has been implemented in an `R` package called `pcev` (available on CRAN).

Motivating Example #1

- PCEV could be used to extract features from data and possibly increase predictive accuracy.
- However, there is evidence in the literature that linear features have limited predictive power in pattern recognition.
- We would therefore need a *nonlinear* variant of PCEV



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Questions or comments?

For more information and updates, visit

`maxturgeon.ca`.