Inference for Transposable Data: Modeling the Effects of Row and Column Correlations

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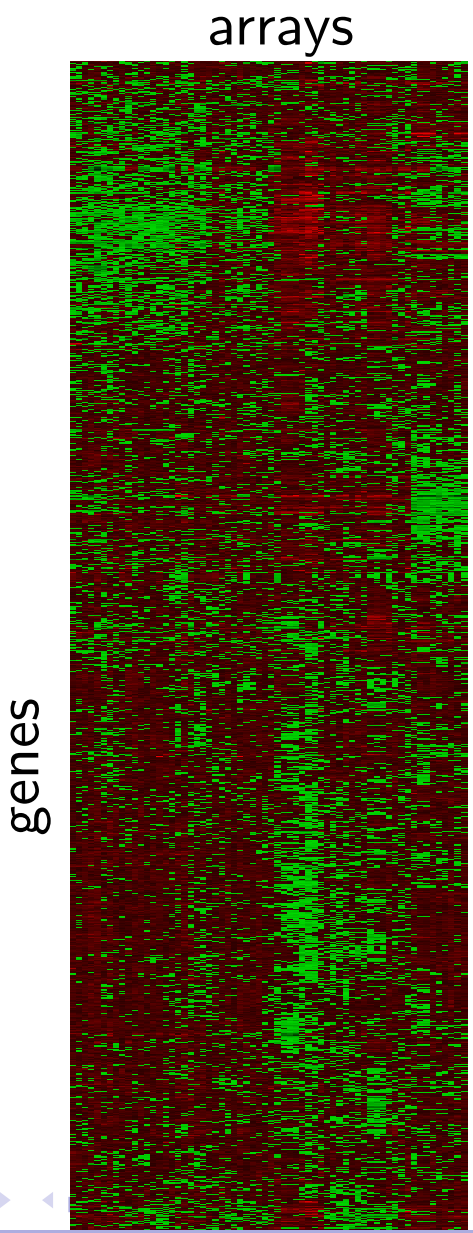
Large-Scale Inference and Genetic Data

Testing the significance of . . .

- Genes in microarrays.
- Isoforms in next-generation sequencing data.
- Biomarkers in protein arrays.

All of these can be arranged in the form of a matrix.

- Question: Is genetic data *transposable*?
  - Rows and/or Columns are features of interest.



In this Talk . . .

1. Introduction: Are our statistical assumptions for large-scale inference correct?

2. What happens when our assumptions are incorrect?
   - Array correlations:

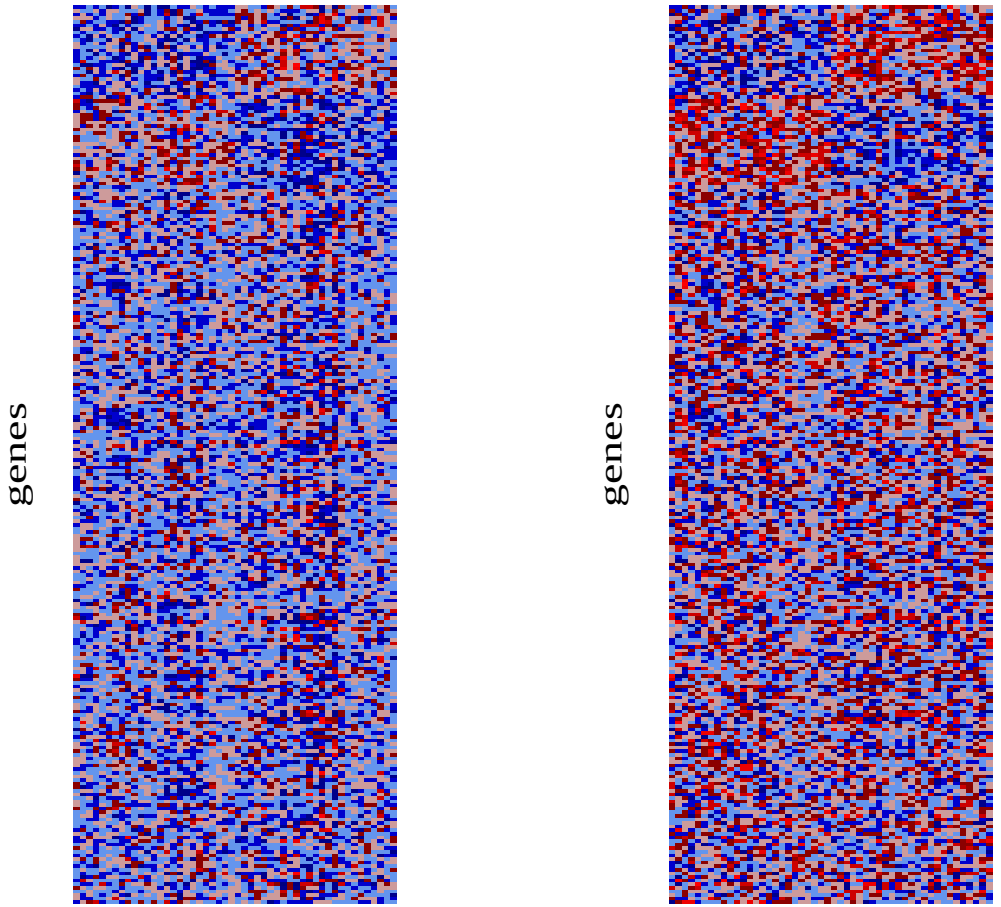
     How does this affect the behavior of our test statistics?
   - Gene and Array correlations:

     How does this affect multiple testing procedures?

3. How do we fix these problems?
   1. Directly model gene and array correlations with *Transposable Regularized Covariance Models*.
   2. De-Correlate or *sphere* the data.

Preview: De-Correlating Microarray Data

Data $\xrightarrow{\text{Sphering}}$ De-Correlated Data



1. Re-orders the ranking of the genes.
2. Allows one to reject more truly significant genes.
3. Obtain better estimates of the False Discovery Rate.

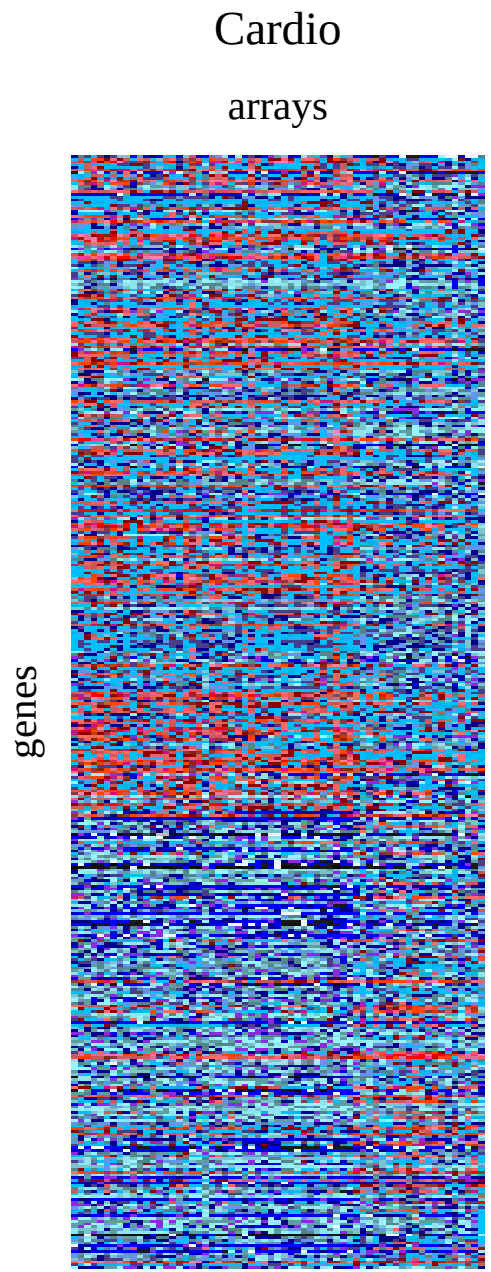
Two-Class Microarray

Goal: Find differentially expressed genes.

Example: "Cardio" data

- Study of cardiovascular disease.
- 20,426 genes and 63 arrays.
- 44 controls and 19 diseased subjects.

(Efron, B., 2009)



Statistical Assumptions

Method

1. For each gene:

   Calculate the two-sample t-test.

Assumptions

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1. Independent Arrays.

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2. Correct for multiple testing:
   - FDR (False Discovery Rate).
   - Examples: Step-up method (Benjamini & Hochberg, 1995), Permutation methods (SAM, Storey, 2002).

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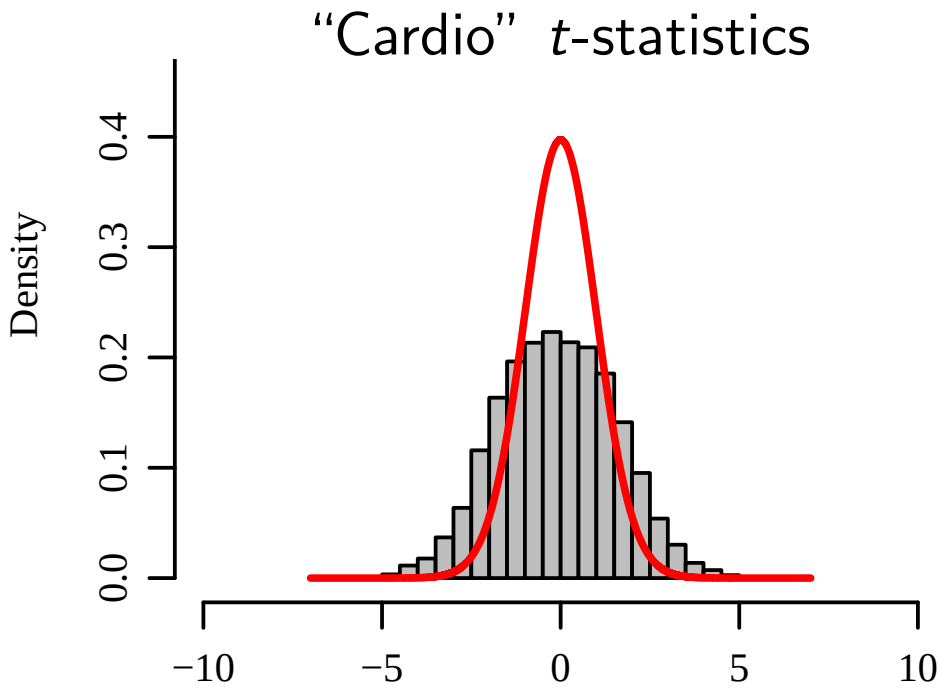
Assumptions

1. Independent Arrays.

2. Limited Gene Dependence (positive regression dependence, weak dependence, local dependence).

Are these Realistic?

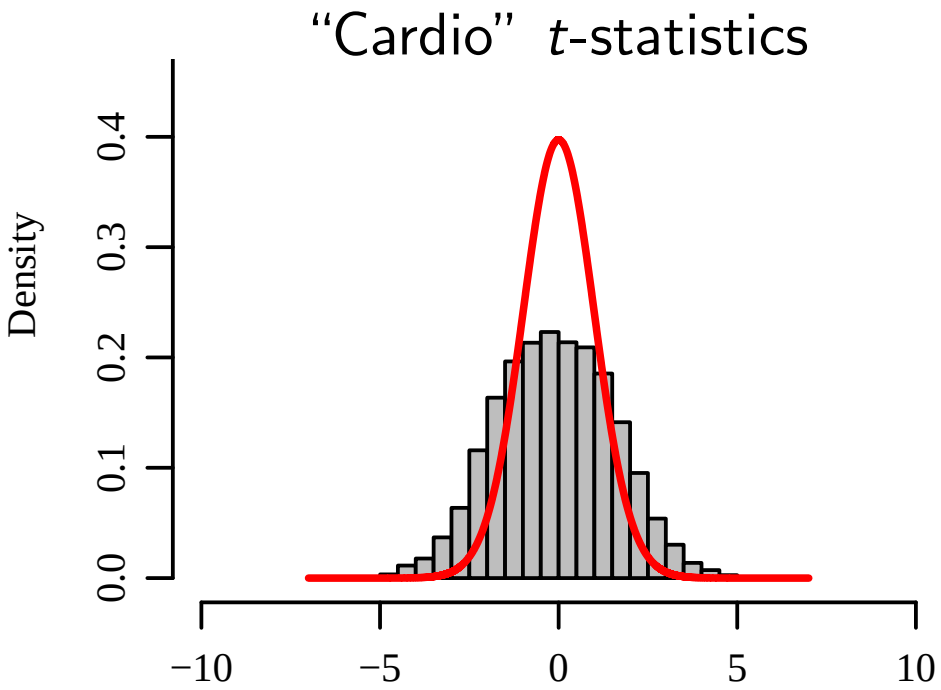


Could this be due to correlations among genes?

Over-dispersion:

- Red: Theoretical Null Distribution: $t_{(61)}$.

Are these Realistic?



Could this be due to correlations among the arrays?

- Measurement process:
  - Instrument drift, batch-effects, time of samples in storage, ...
- Correlated samples:
  - Latent variables such as age, gender or family history ...

Over-dispersion:

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Microarray Matrix Model

$$\mathbf{X}_{m\times n} = \mathbf{M} + \mathbf{S} + \mathbf{N}.$$
$$\text{Data} = \text{Mean} + \text{Signal} + \text{Noise}.$$

where $\mathbf{M}_{m\times n} = \nu \mathbf{1}_{(n)}^T + \mathbf{1}_{(m)}\mu^T$ (mean matrix),

$\mathbf{S}_{m\times n}$ is problem specific (signal matrix),

$\mathbf{N}_{m\times n} \sim N_{m,n}(\mathbf{0}, \mathbf{0}, \mathbf{\Sigma}, \mathbf{\Delta})$ (noise matrix).

- Two-class microarray: $\mathbf{S} = \left[\psi_1 \mathbf{1}_{(n_1)}^T \;\; \psi_2 \mathbf{1}_{(n_2)}^T\right]$, where $\psi_1, \psi_2 \in \Re^m$ are the class signals.
- $\mathbf{X} - \mathbf{S} \sim N_{m,n}(\nu, \mu, \mathbf{\Sigma}, \mathbf{\Delta})$. (*mean-restricted matrix-variate normal*)

Review: Mean-Restricted Matrix-Variate Normal

Matrix extension of the multivariate normal:

$$\mathbf{X}_{m \times n} \sim N_{m,n}(\nu, \mu, \mathbf{\Sigma}, \mathbf{\Delta})$$

- Row means: $\nu \in \Re^m$.
- Column means: $\mu \in \Re^n$.
- Row covariance: $\mathbf{\Sigma} \in \Re^{m \times m}$
- Column covariance: $\mathbf{\Delta} \in \Re^{n \times n}$.

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$$\mathrm{vec}(\mathbf{X}) \sim N\left(\mathrm{vec}(\mathbf{M}), \mathbf{\Omega}\right)$$

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$$\mathrm{vec}(\mathbf{X}) \sim N\left(\mathrm{vec}(\mathbf{M}), \mathbf{\Omega}\right)$$

- $\mathbf{M} = \nu \mathbf{1}_{(n)}^T + \mathbf{1}_{(m)} \mu^T$.

$$\mathbf{M}_{m\times n} =$$

$$\begin{pmatrix} \nu_1 + \mu_1 & \nu_1 + \mu_2 & \cdots & \nu_1 + \mu_n \\ \nu_2 + \mu_1 & \nu_2 + \mu_2 & & \\ \vdots & & \ddots & \vdots \\ \nu_m + \mu_1 & & \cdots & \nu_m + \mu_n \end{pmatrix}$$

Review: Mean-Restricted Matrix-Variate Normal

Matrix extension of the multivariate normal:

$$\mathbf{X}_{m\times n} \sim N_{m,n}(\nu, \mu, \mathbf{\Sigma}, \mathbf{\Delta})$$

- Row means: $\nu \in \Re^m$.
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$$\mathbf{\Omega}_{mn\times mn} = \begin{pmatrix} \Delta_{11}\mathbf{\Sigma} & \Delta_{12}\mathbf{\Sigma} & \dots & \Delta_{1n}\mathbf{\Sigma} \\ \Delta_{21}\mathbf{\Sigma} & \Delta_{22}\mathbf{\Sigma} & & \\ \vdots & & \ddots & \vdots \\ \Delta_{n1}\mathbf{\Sigma} & & \dots & \Delta_{nn}\mathbf{\Sigma} \end{pmatrix}$$

$$\mathrm{vec}(\mathbf{X}) \sim N\left(\mathrm{vec}(\mathbf{M}), \mathbf{\Omega}\right)$$

- $\mathbf{M} = \nu \mathbf{1}_{(n)}^T + \mathbf{1}_{(m)}\mu^T$.
- $\mathbf{\Omega} = \mathbf{\Delta} \otimes \mathbf{\Sigma}$.

(Gupta & Nagar, 1999; G. I. Allen & R. Tibshirani, 2010)

Test Statistic Null Distributions

Question: How do test statistics behave when arrays are correlated?

Two-sample Z-test:

- Independent arrays:

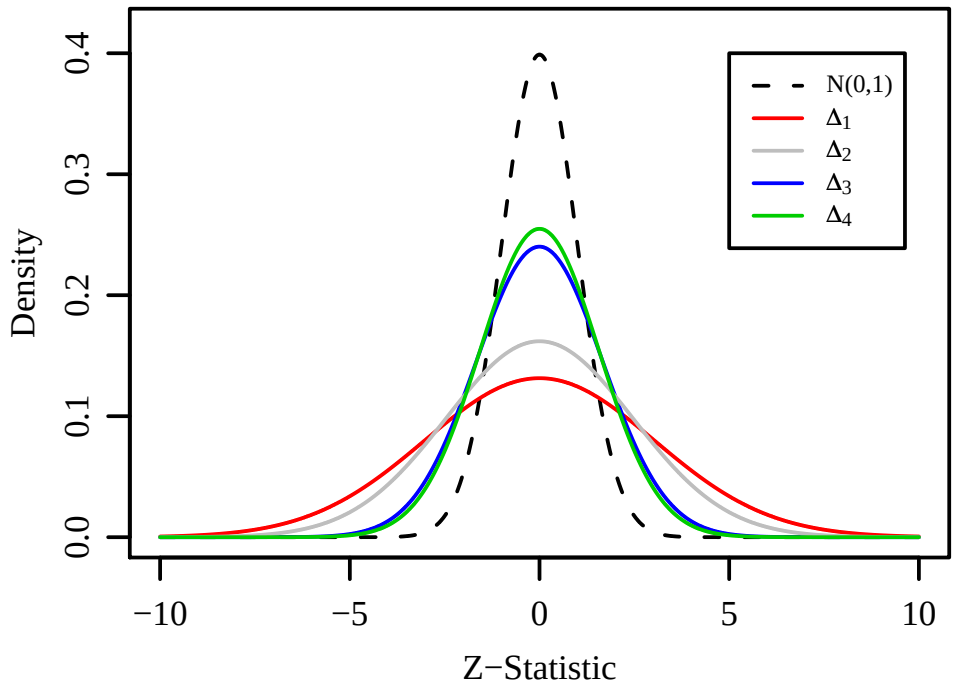
$$Z \sim N(0, 1).$$

- Theorem: Under matrix-variate normal,

$$Z \sim N(0, \eta / c_n),$$

where $c_n = \frac{1}{n_1} + \frac{1}{n_2}$,

η is a function of $\mathbf{\Delta}$.

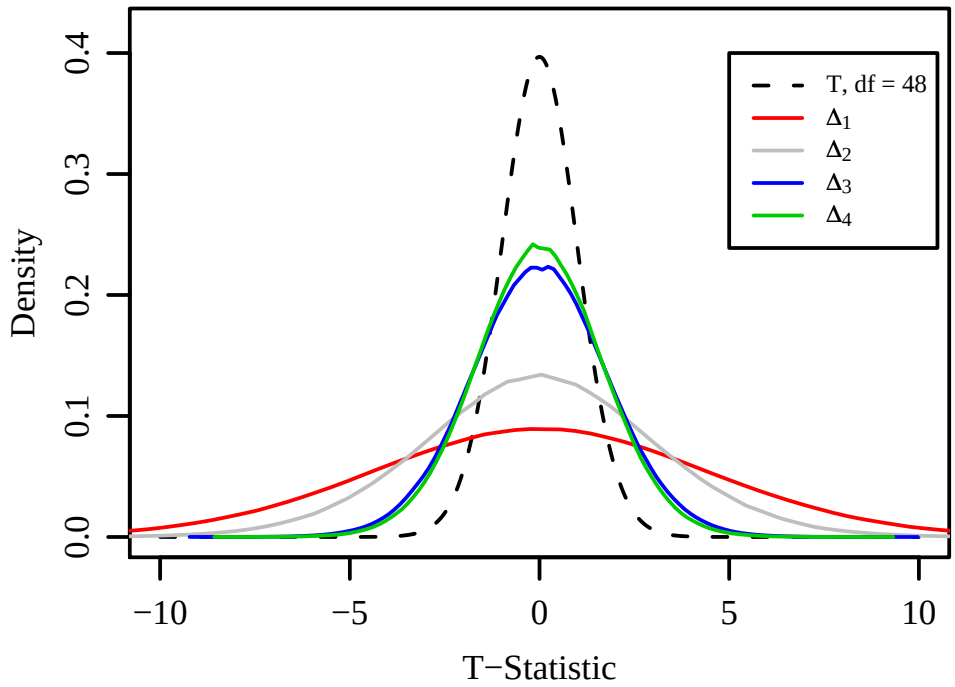


Test Statistic Null Distributions

Question: How do test statistics behave when arrays are correlated?

Two sample T-test:

- Independent Arrays: $T \sim t_{(n-2)}$.
- Correlated Arrays (matrix-variate normal): No closed form distribution.
- Variances estimated by Monte Carlo.



Study: Multiple Testing and Dependence

Simulation Study:

- Data from matrix-variate normal model.
- Used two-sample t-statistics.
- Applied various FDR-controlling procedures.

Conclusions:

1. Good News: FDR controlled under many types of gene dependence.
2. Bad News: FDR NOT controlled under gene AND array dependence.

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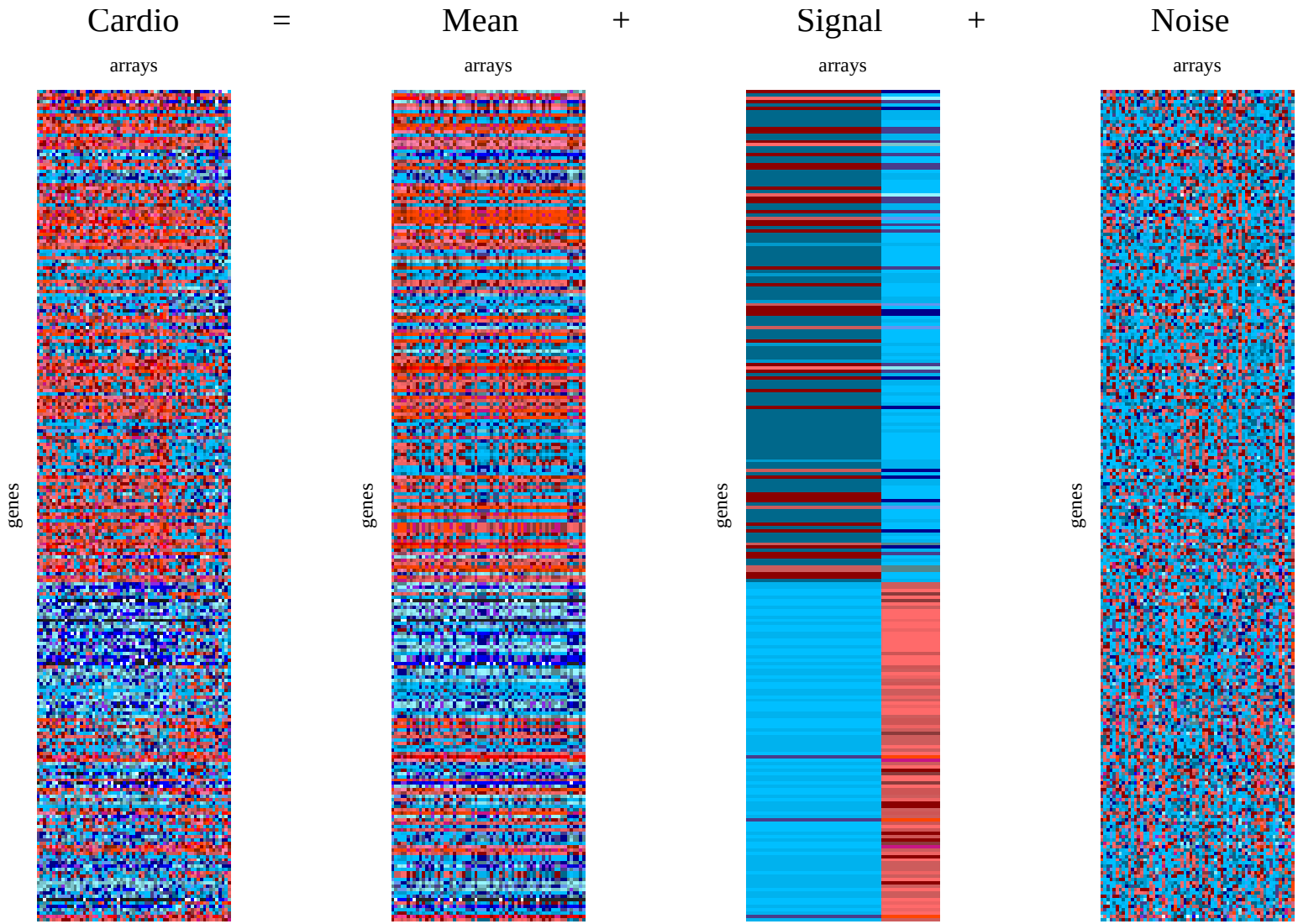
De-Correlating the Data

Step 1: Decompose data into Mean + Signal + Noise.

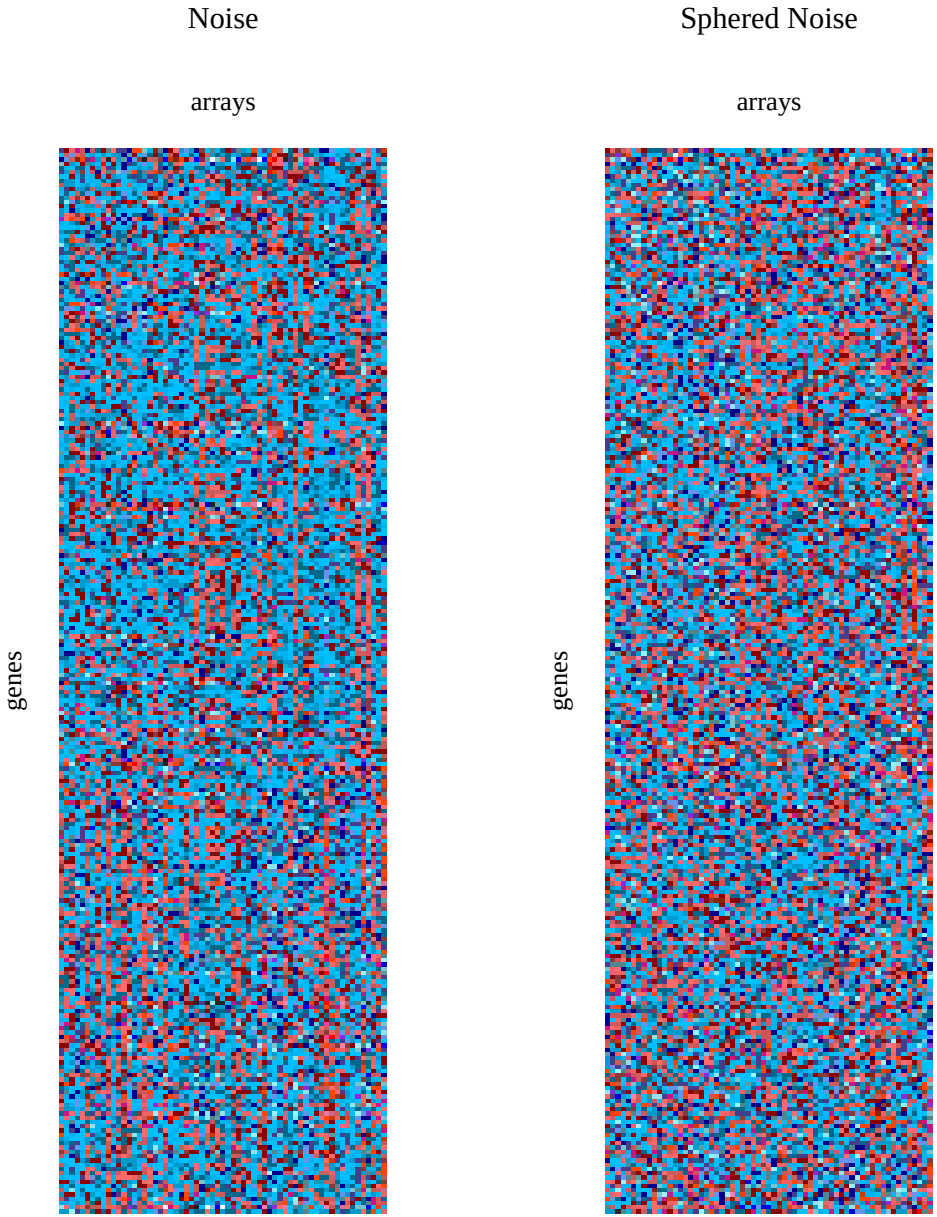


De-Correlating the Data

Step 2: Estimate the Gene and Array Covariances of the Noise. *Sphere* the Noise.

- $\tilde{\mathbf{N}} = \hat{\mathbf{\Sigma}}^{-1/2} \hat{\mathbf{N}} \hat{\mathbf{\Delta}}^{-1/2}$.
- $\hat{\mathbf{\Sigma}}$ & $\hat{\mathbf{\Delta}}$ estimated via *Transposable Regularized Covariance Models*.

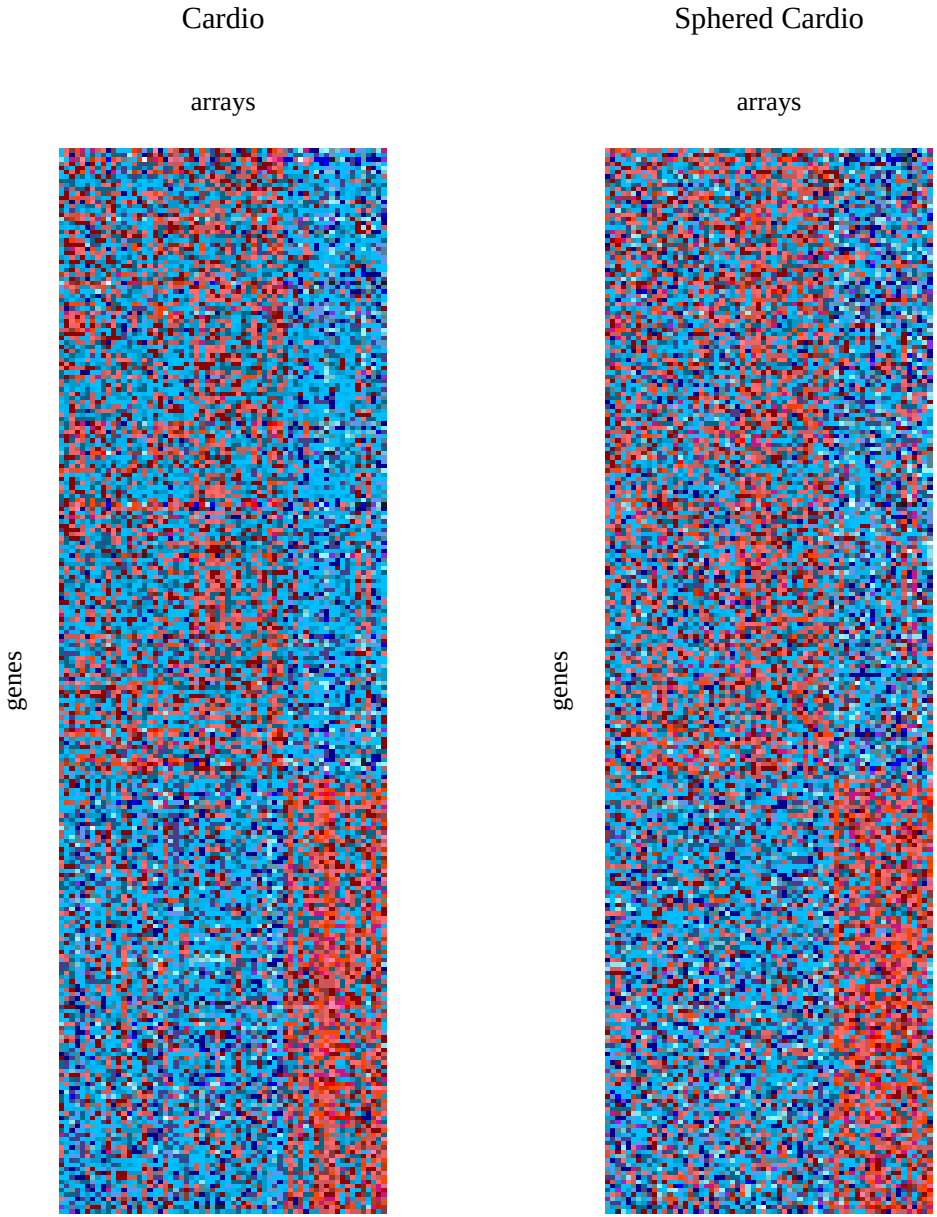
(G. I. Allen & R. Tibshirani, 2010)



De-Correlating the Data

Step 3: De-Correlated Data.

- $\tilde{\mathbf{X}} = \hat{\mathbf{S}} + \tilde{\mathbf{N}}$.
- Approximately independent genes AND arrays.
- T-statistics distributed approximately $t_{(n-2)}$.

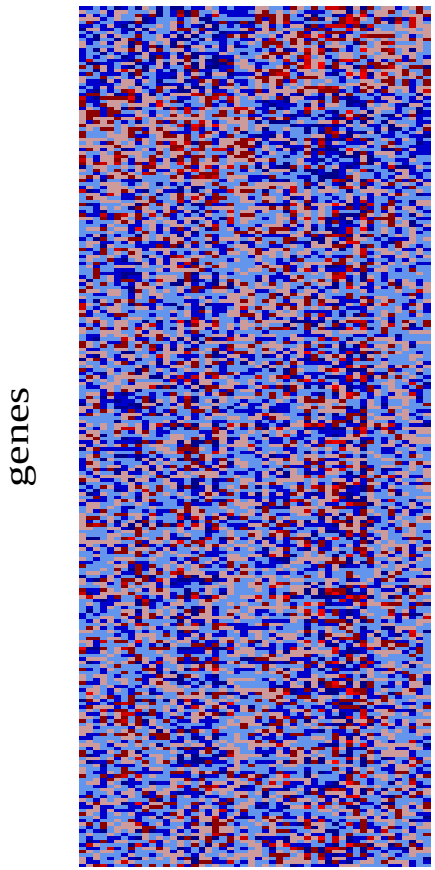


Cardio Results: Data Images

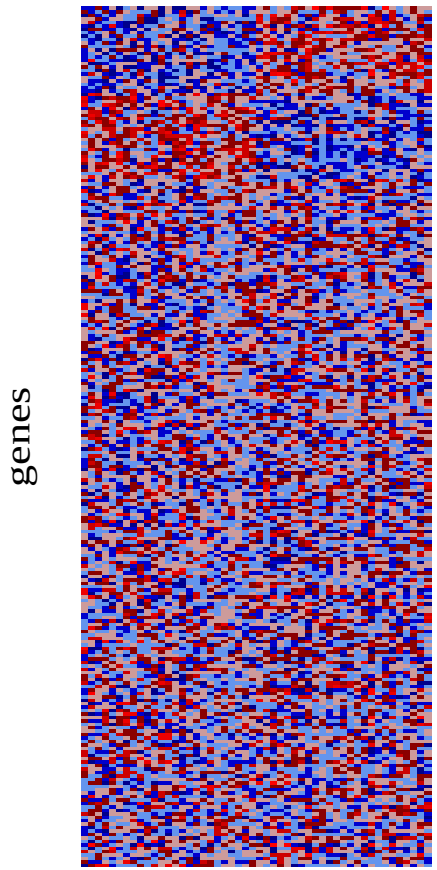
"Cardio"-Inspired Simulation:

- 250 genes, 50 differentially expressed.
- Gene & Array correlations: randomly selected Cardio genes & arrays.

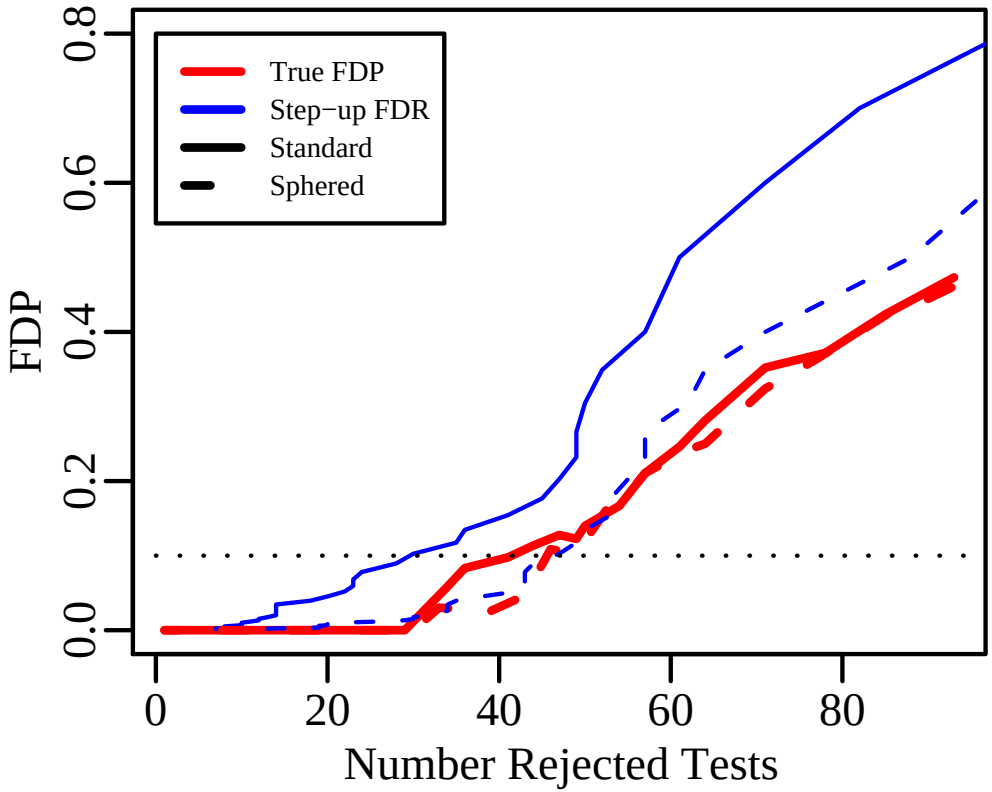
Signal + Cardio Noise



Signal + Sphered Noise



Cardio Results: FDR Curves



Benefits of Sphering:

1. Increased statistical power. (Gene rank is re-ordered.)
   - Standard Method: 38 genes rejected.
   - Sphering: 43 genes rejected

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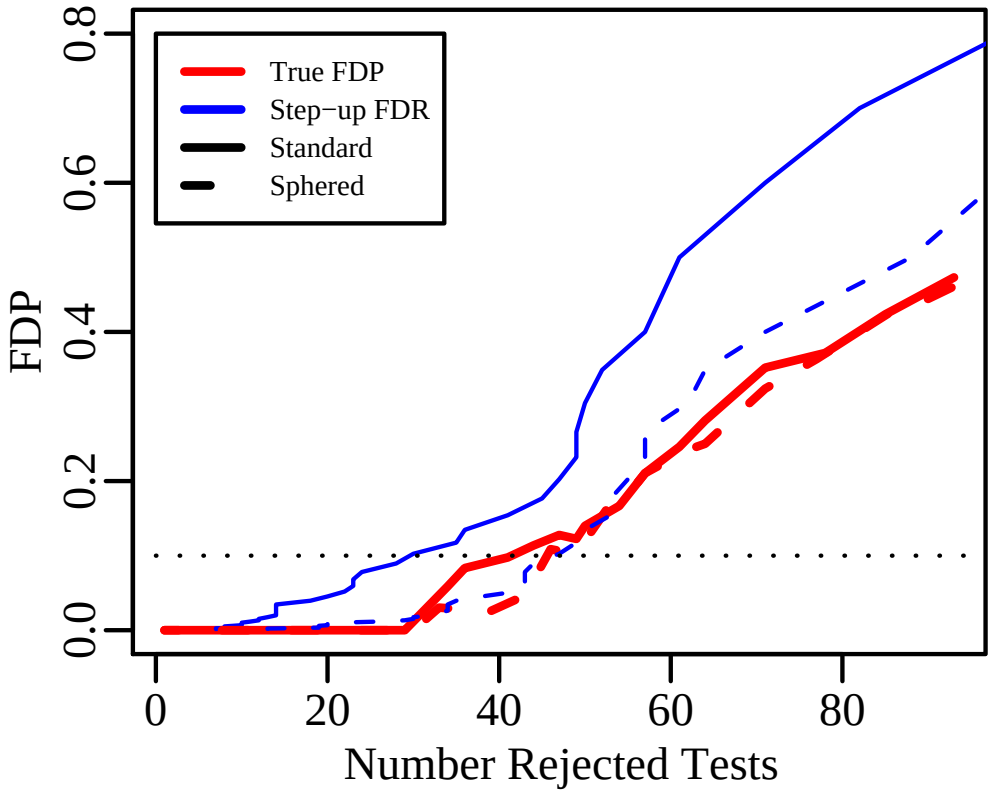

Benefits of Sphering:

1. Increased statistical power. (Gene rank is re-ordered.)
   - Standard Method: 38 genes rejected.
   - Sphering: 43 genes rejected
2. Correct estimation of FDR.
   - Standard Method: 30 genes rejected.
   - Sphering: 43 genes rejected

Results: Other Models

	Standard		Sphered	
	FDP	$\widehat{\text{FDR}}$	FDP	$\widehat{\text{FDR}}$
Latent Variable Model*	0.189	0.383	0.167	0.166
Random Effects Model	0.52	0.0229	0.154	0.207
Gene Correlations	0.169	0.19	0.141	0.185
Gene & Array Correlations	0.111	0.426	0.105	0.124

True FDP and FDR estimated by the step-up method for 55/250 rejected tests averaged over 10 simulations.

*(J. Leek & J. Storey, 2008)

Conclusions & Future Work

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1. Gene and especially Array correlations pose a major problem for large-scale inference.
2. *Sphering* the data can correct these problems.

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Future Work:

- Extensions to categorical data.
  - Application: Next-generation sequencing data.
- Approximations for high-dimensional data.
  - Application: Functional MRIs.

Acknowledgments & References

Acknowledgments:

SF Bay Area Chapter of the American Statistical Association Student Travel Award

References:

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