High-Dimensional Variable Selection in Nonlinear Models that Controls the False Discovery Rate

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Problem Statement

Controlled Variable Selection

Given:

- Y an outcome of interest (AKA response or dependent variable),
- $X_1, \ldots, X_p$ a set of p potential explanatory variables (AKA covariates, features, or independent variables),

How can we select important explanatory variables with few mistakes?

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To make sure we do not make too many mistakes, we seek to select a set $\hat{S}$ to control the **false discovery rate (FDR)**:

$$\text{FDR}(\hat{S}) = \mathbb{E}\left(\frac{\#\{j \text{ in } \hat{S} \,:\, X_j \text{ unimportant}\}}{\#\{j \text{ in } \hat{S}\}}\right) \leq q \;\; \text{(e.g. 10\%)}$$

"Here is a set of variables $\hat{S}$, 90% of which I expect to be important"

Sneak Peak

New interpretation of knockoffs solves the controlled variable selection problem

- Allows any model for Y and $X_1, \ldots, X_p$
- Allows any dimension (including $p > n$)
- Finite-sample control (non-asymptotic) of FDR
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Model-free knockoffs used the same FDR of 10% and made **18** discoveries, with many of the new discoveries confirmed by a larger meta-analysis

Review of Methods for Controlled Variable Selection

What is required for valid inference?

	Low dimensions	Model for Y	Asymptopic regime	Sparsity	Random design
OLSp+BHq	Yes	Yes	No	No	No

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Orig KnO	Yes	Yes	No	No	No
New KnO	No	No	No	No	Yes*

The Knockoffs Idea

Knockoffs (Barber and Candès, 2015)

$\boldsymbol{y}$ and $\boldsymbol{X}_j$ are $n \times 1$ column vectors of data: n draws from the random variables Y and X_j, respectively; design matrix $\boldsymbol{X} := [\boldsymbol{X}_1 \cdots \boldsymbol{X}_p]$

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- Sufficiency: W_j only a function of $[\boldsymbol{X}\ \tilde{\boldsymbol{X}}]^\top [\boldsymbol{X}\ \tilde{\boldsymbol{X}}]$ and $[\boldsymbol{X}\ \tilde{\boldsymbol{X}}]^\top \boldsymbol{y}$
- Antisymmetry: swapping values of $\boldsymbol{X}_j$ and $\tilde{\boldsymbol{X}}_j$ flips sign of W_j

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Comments:
- Finite-sample FDR control and leverages sparsity for power
- Requires data follow low-dimensional $(n \geq p)$ Gaussian linear model
- Canonical approach: condition on $\boldsymbol{X}$, rely heavily on model for $\boldsymbol{y}$

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Coin-flipping property: The key to knockoffs is that steps (1) and (2) are done specifically to ensure that, conditional on $|W_1|, \ldots, |W_p|$, the signs of the *unimportant/null* W_j are independently ± 1 with probability $1/2$

New Interpretation of Knockoffs

Knockoffs Without a Model for Y (Candès et al., 2016)

Instead of modeling $\boldsymbol{y}$ and conditioning on $\boldsymbol{X}$, condition on $\boldsymbol{y}$ and model $\boldsymbol{X}$
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Explicitly,

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where G can be arbitrary but is assumed known

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- Robust to overfitting $\boldsymbol{X}$'s distribution in preliminary experiments

Robustness

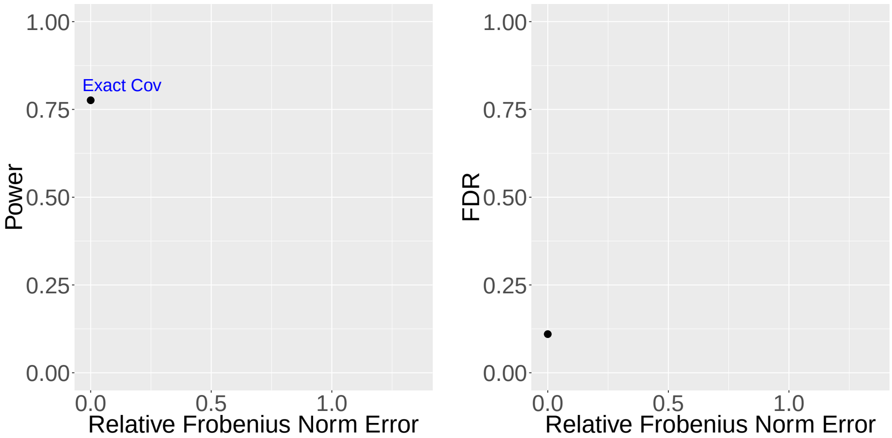

Figure: Covariates are **AR(1) with autocorrelation coefficient 0.3**. $n = 800$, $p = 1500$, and target FDR is 10%. Y comes from a binomial linear model with logit link function with 50 nonzero entries.

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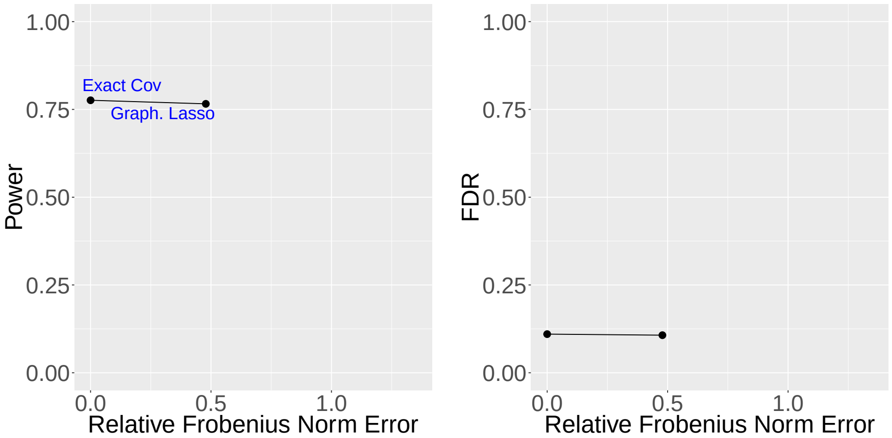

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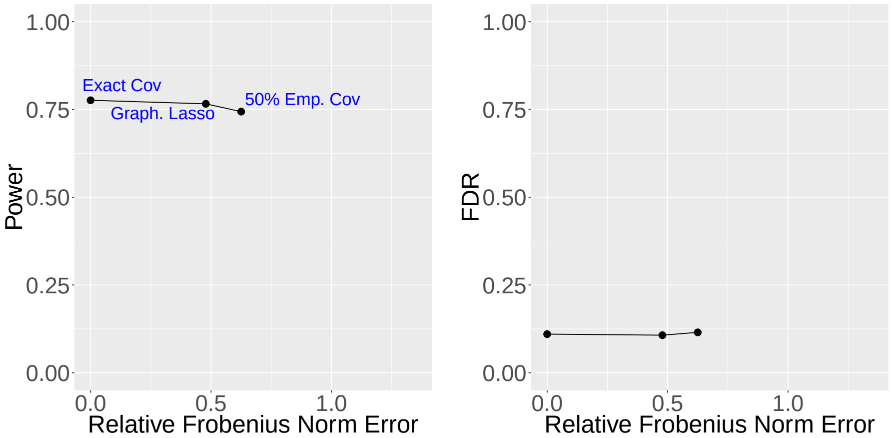

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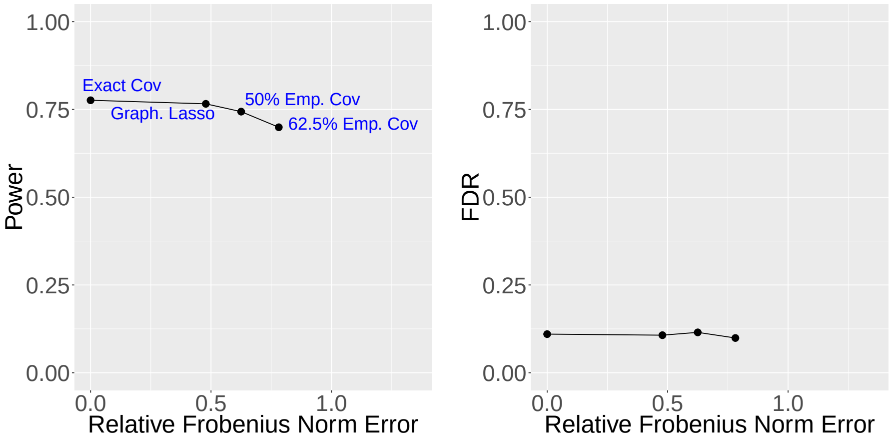

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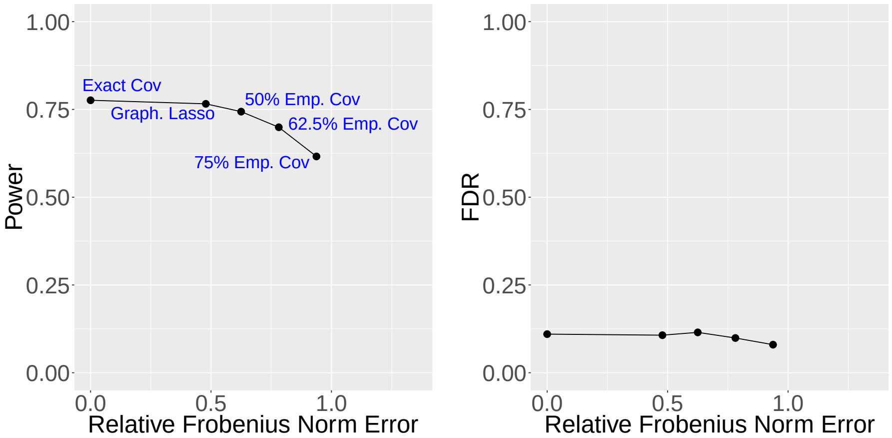

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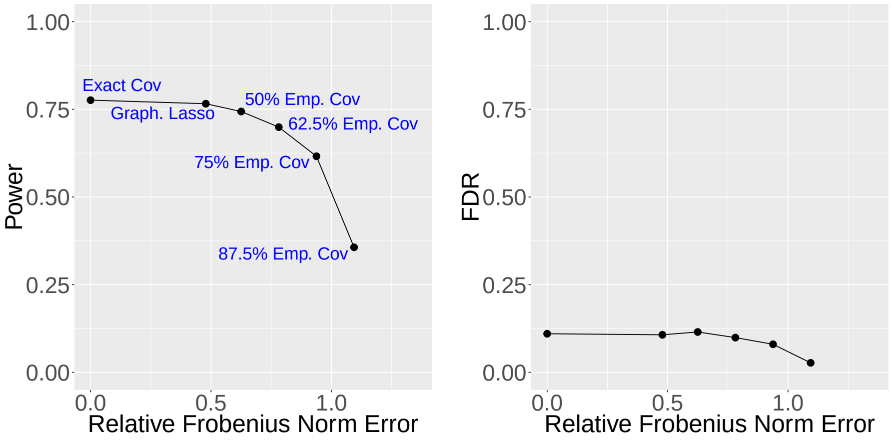

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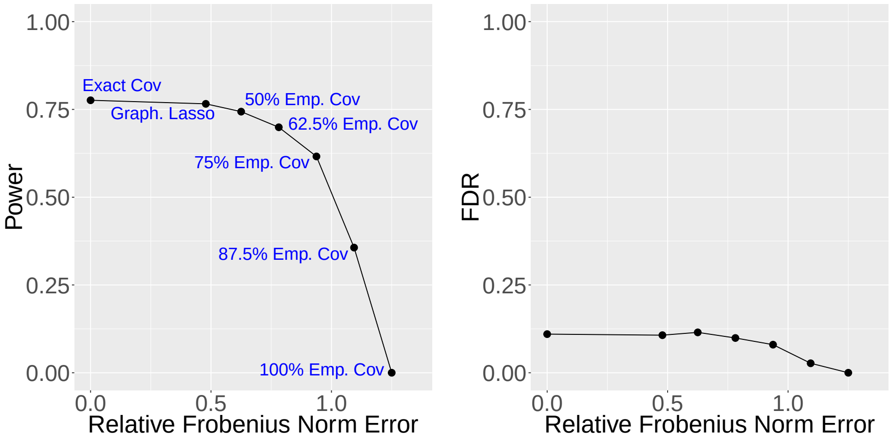

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2b. Other studies have collected same or similar SNP arrays on different subjects

The New Knockoffs Procedure

(1) **Construct knockoffs**: Exchangeability

$$[\boldsymbol{X}_1 \cdots \boldsymbol{X}_j \cdots \boldsymbol{X}_p \, \tilde{\boldsymbol{X}}_1 \cdots \tilde{\boldsymbol{X}}_j \cdots \tilde{\boldsymbol{X}}_p] \overset{\mathcal{D}}{=} [\boldsymbol{X}_1 \cdots \tilde{\boldsymbol{X}}_j \cdots \boldsymbol{X}_p \, \tilde{\boldsymbol{X}}_1 \cdots \boldsymbol{X}_j \cdots \tilde{\boldsymbol{X}}_p]$$

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(2) **Compute knockoff statistics**:

- Variable importance measure Z
- Antisymmetric function $f_j : \mathbb{R}^2 \to \mathbb{R}$, i.e.,

$$f_j(z_1, z_2) = -f_j(z_2, z_1)$$

- $W_j = f_j(Z_j, \widetilde{Z}_j)$, where Z_j and $\widetilde{Z}_j$ are the variable importances of $\boldsymbol{X}_j$ and $\tilde{\boldsymbol{X}}_j$, respectively

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Step (1): Construct Knockoffs

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Proof that valid knockoff variables can be generated for any X distribution

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For $\mathrm{Cov}(X_1, \ldots, X_p) = \boldsymbol{\Sigma}$:

$$\mathrm{Cov}(X_1, \ldots, X_p, \tilde{X}_1, \ldots, \tilde{X}_p) = \begin{bmatrix} \boldsymbol{\Sigma} & \boldsymbol{\Sigma} - \mathrm{diag}\{\boldsymbol{s}\} \\ \boldsymbol{\Sigma} - \mathrm{diag}\{\boldsymbol{s}\} & \boldsymbol{\Sigma} \end{bmatrix}$$

For non-Gaussian X, still second-order-correct approximate knockoffs

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$$\mathrm{Cov}(X_1, \ldots, X_p, \tilde{X}_1, \ldots, \tilde{X}_p) = \begin{bmatrix} \boldsymbol{\Sigma} & \boldsymbol{\Sigma} - \mathrm{diag}\{\boldsymbol{s}\} \\ \boldsymbol{\Sigma} - \mathrm{diag}\{\boldsymbol{s}\} & \boldsymbol{\Sigma} \end{bmatrix}$$

For non-Gaussian X, still second-order-correct approximate knockoffs

- Linear algebra and semidefinite programming to find good $\boldsymbol{s}$
- Recently: construction for Markov chains and HMMs (Sesia et al., 2017)
- Constructions also possible for grouped variables (Dai and Barber, 2016)

Step (2): Compute Knockoff Statistics

Strategy for Choosing Knockoff Statistics

Recall W_j an antisymmetric function f_j of Z_j and $\widetilde{Z}_j$ (the variable importances of $\boldsymbol{X}_j$ and $\tilde{\boldsymbol{X}}_j$, respectively):

$$W_j = f_j(Z_j, \widetilde{Z}_j) = -f_j(\widetilde{Z}_j, Z_j)$$

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Lasso Coefficient Difference (LCD) statistic:

$$W_j = |\beta_j| - |\tilde{\beta}_j|$$

Exchangeability Endows Coin-Flipping

Recall exchangeability property: for any j,

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Adaptivity and Prior Information in W_j

Recall LCD: $W_j = |\beta_j| - |\tilde{\beta}_j|$, where β_j, $\tilde{\beta}_j$ come from ℓ_1-penalized regression

Adaptivity

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Prior information

- **Bayesian approach**: choose prior and model, and Z_j could be the posterior probability that X_j contributes to the model
- Still strict FDR control, **even if wrong prior or MCMC has not converged**

Step (3): Find the Knockoff Threshold

Find the Knockoff Threshold

Example with $p = 10$ and $q = 20\% = 1/5$:

Find the Knockoff Threshold

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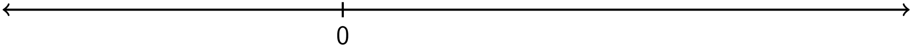

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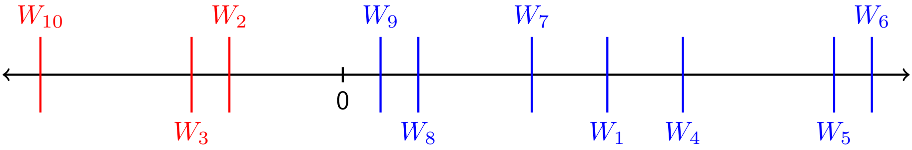

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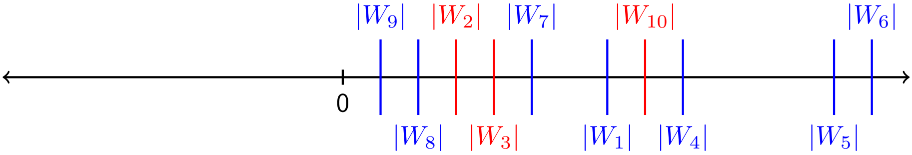

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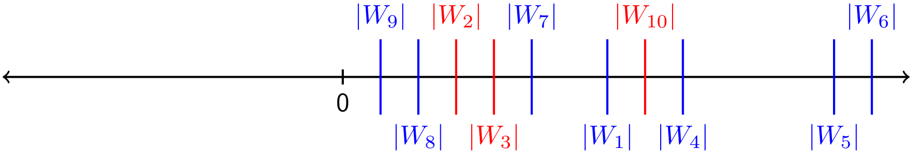

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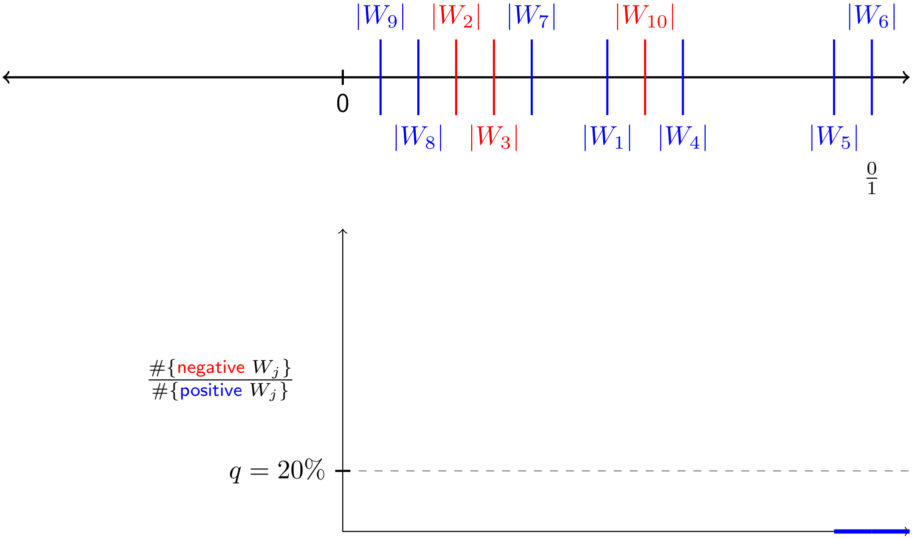

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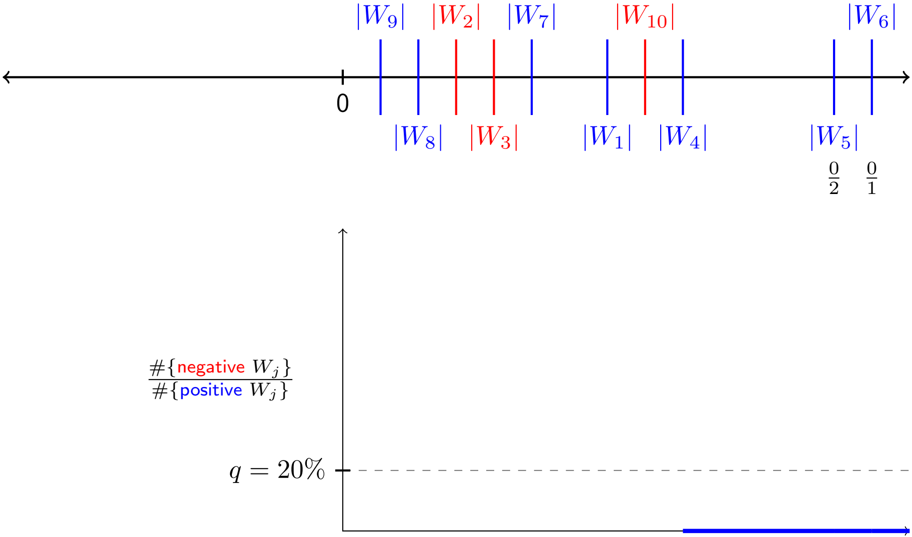

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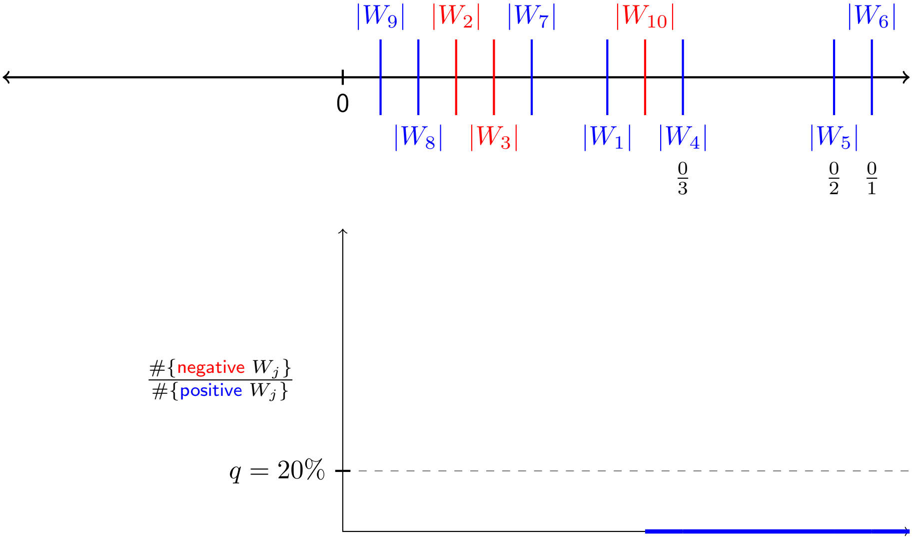

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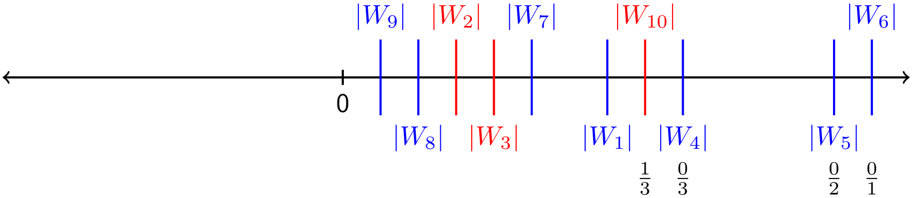

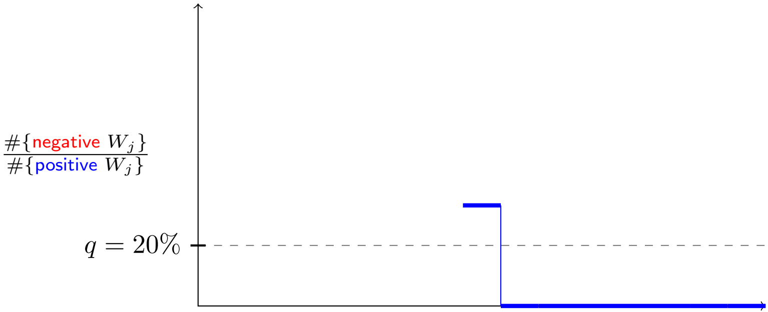

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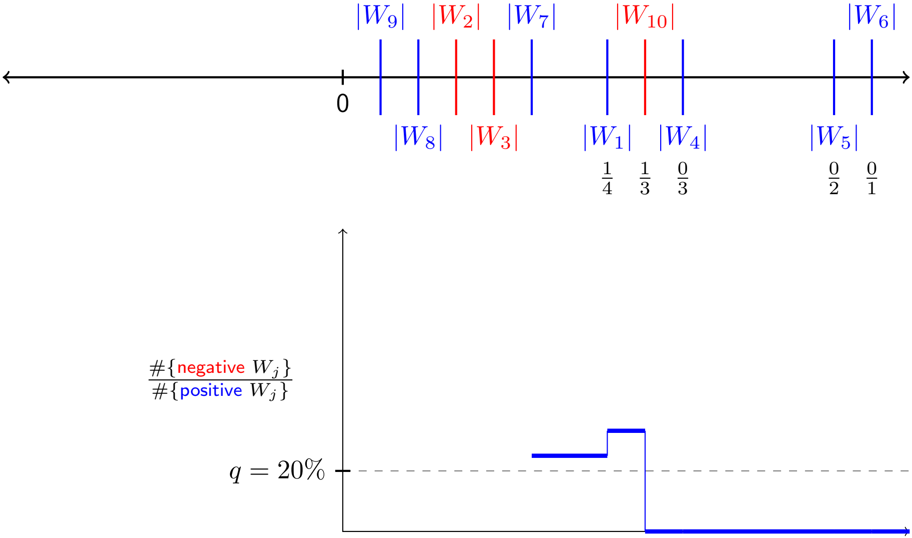

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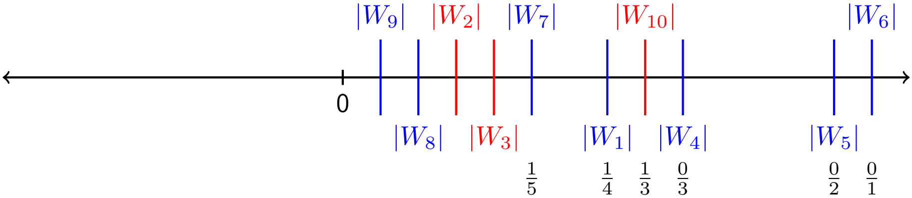

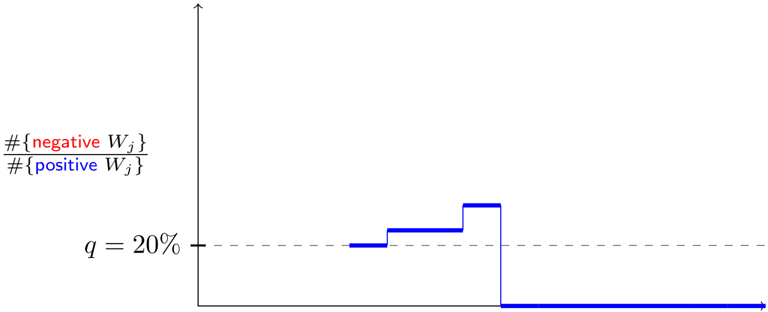

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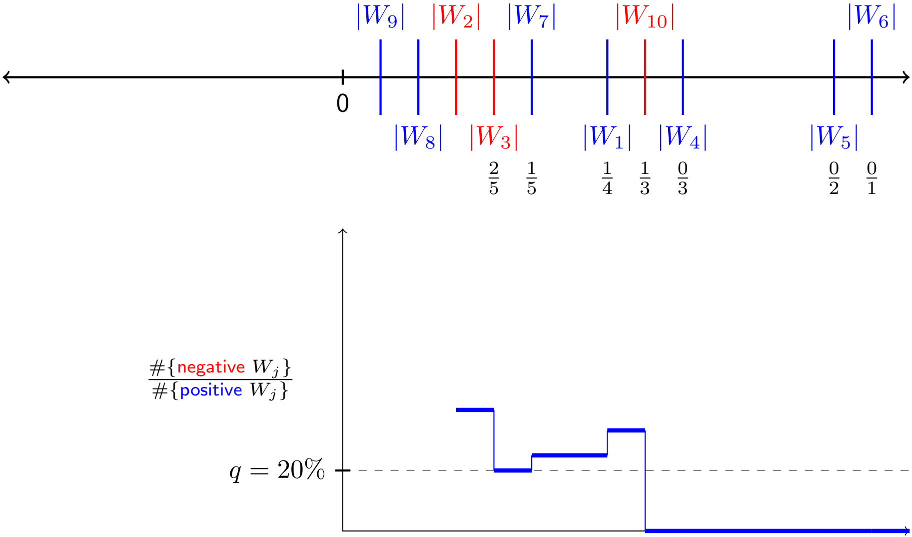

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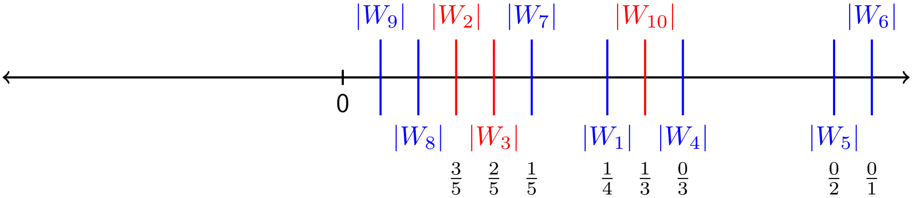

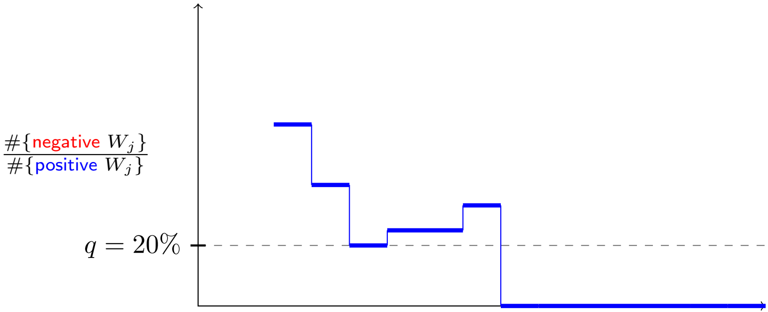

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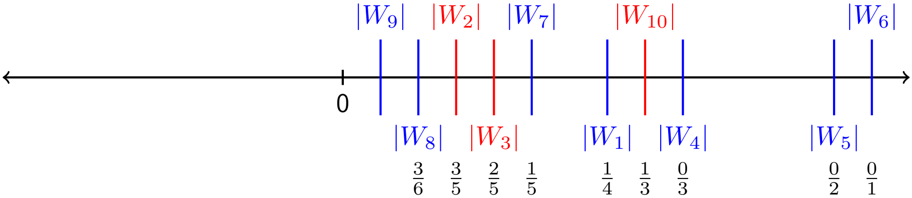

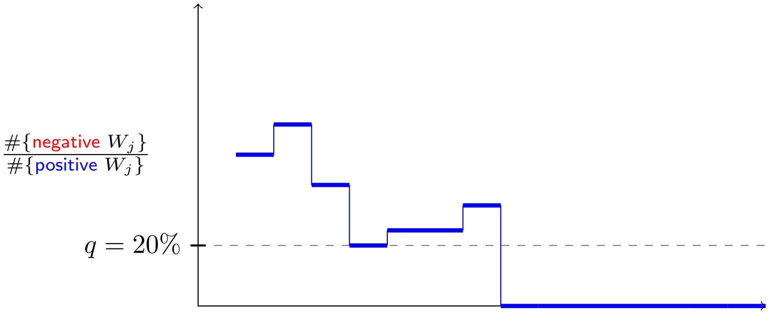

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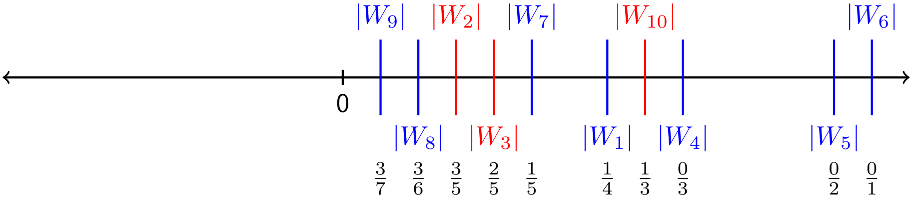

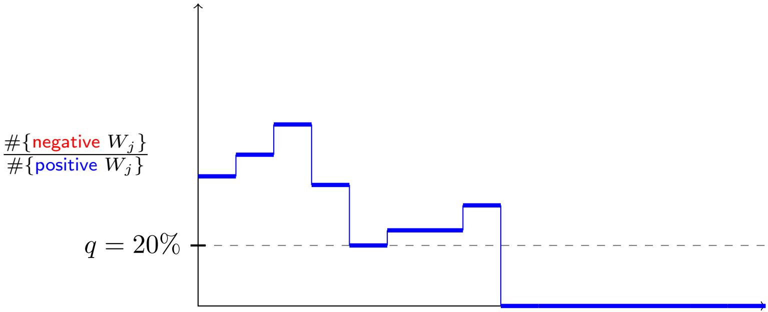

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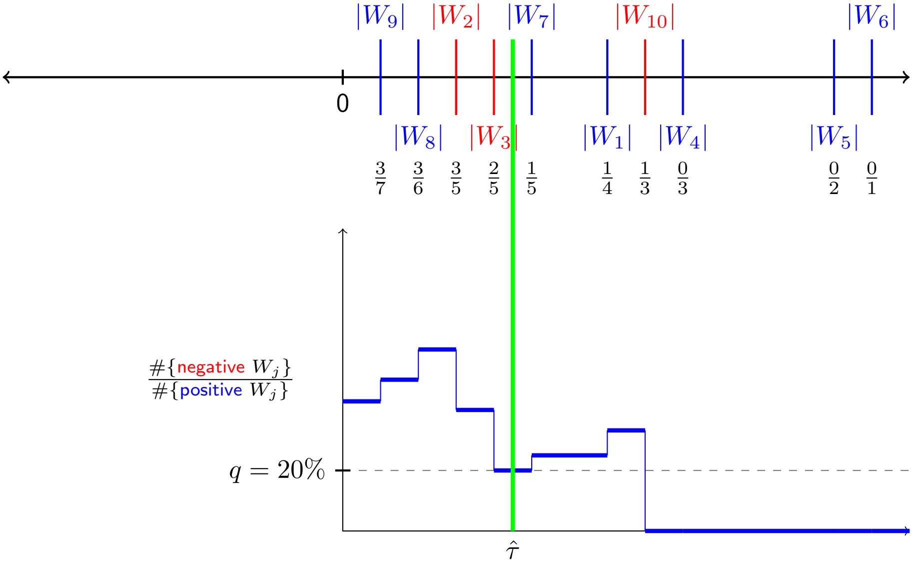

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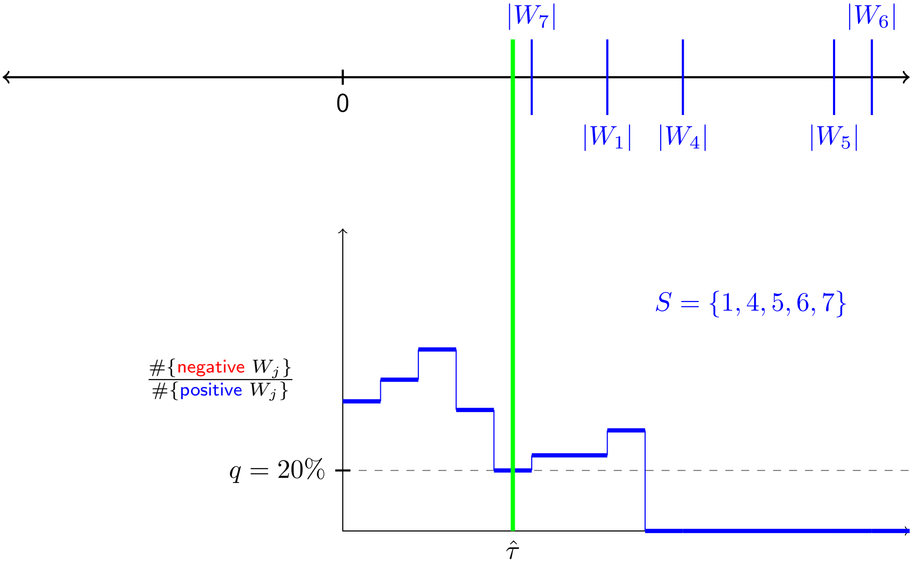

Intuition for FDR Control

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&\approx \mathbb{E}\left(\frac{\#\{\text{null negative } |W_j| > \hat{\tau}\}}{\#\{\text{positive } |W_j| > \hat{\tau}\}}\right)
\end{aligned}$$

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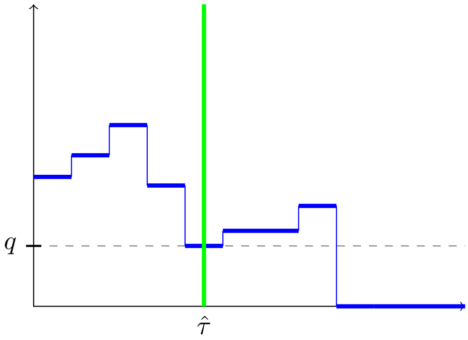

GWAS Application

Genetic Analysis of Crohn's Disease

2007 case-control study by WTCCC

- $n \approx 5,000$, $p \approx 375,000$; preprocessing mirrored original analysis

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  - Similar result when HMM knockoffs applied to same data (Sesia et al., 2017)

Discussion

Summary and Next Steps

By conditioning on Y and modeling X, knockoffs can be applied to high-dimensional and nonlinear problems, where it is powerful, flexible, and appears robust

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Thank you!

Appendix

References

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Simulations in Low-Dimensional Linear Model

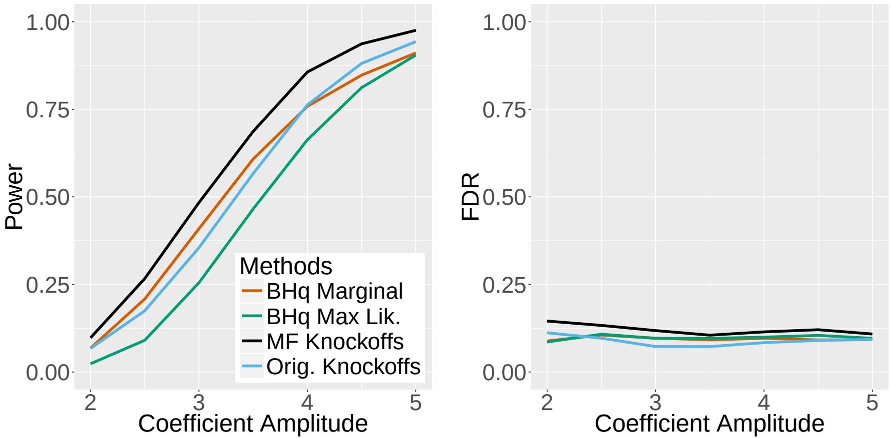

Figure: Power and FDR (target is 10%) for MF knockoffs and alternative procedures. The design matrix is i.i.d. $\mathcal{N}(0, 1/n)$, $n = 3000$, $p = 1000$, and y comes from a Gaussian linear model with 60 nonzero regression coefficients having equal magnitudes and random signs. The noise variance is 1.

Simulations in Low-Dimensional Nonlinear Model

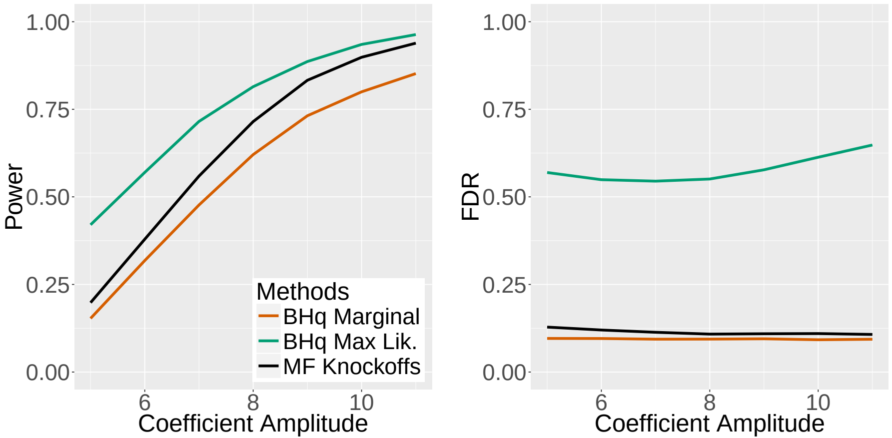

Figure: Power and FDR (target is 10%) for MF knockoffs and alternative procedures. The design matrix is i.i.d. $\mathcal{N}(0, 1/n)$, $n = 3000$, $p = 1000$, and y comes from a binomial linear model with logit link function, and 60 nonzero regression coefficients having equal magnitudes and random signs.

Simulations in High Dimensions

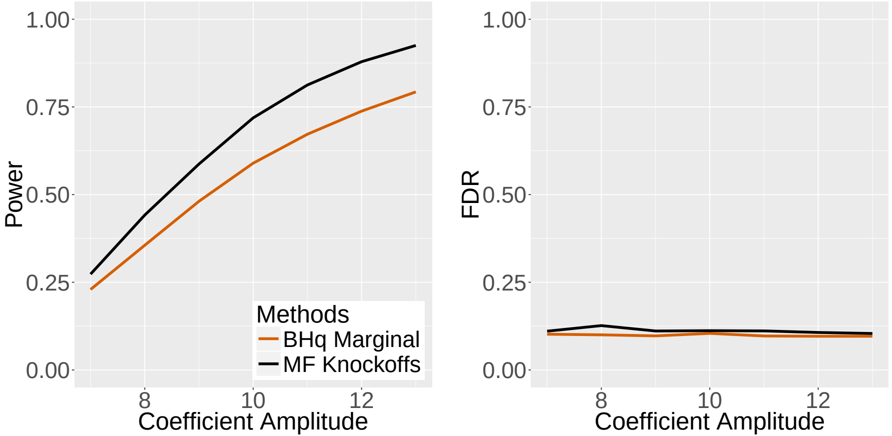

Figure: Power and FDR (target is 10%) for MF knockoffs and alternative procedures. The design matrix is i.i.d. $\mathcal{N}(0, 1/n)$, $n = 3000$, $p = 6000$, and y comes from a binomial linear model with logit link function, and 60 nonzero regression coefficients having equal magnitudes and random signs.

Simulations in High Dimensions with Dependence

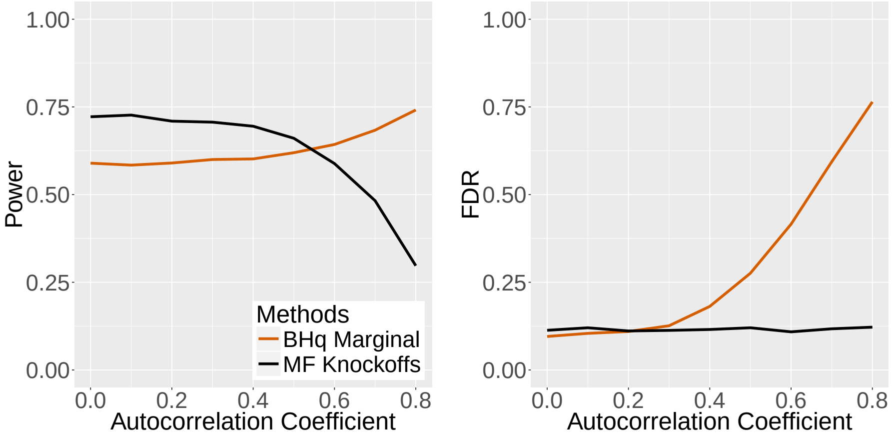

Figure: Power and FDR (target is 10%) for MF knockoffs and alternative procedures. The design matrix has AR(1) columns, and marginally each $X_j \sim \mathcal{N}(0, 1/n)$. $n = 3000$, $p = 6000$, and y follows a binomial linear model with logit link function, and 60 nonzero coefficients with random signs and randomly selected locations.

Checking Sensitivity to Misspecification Error

	Concern about misspecification	
	$Y \mid X$	X
Canonical (model Y, not X)	Yes	No
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Can actually **check sensitivity** to misspecification error!

Robustness on Real Data

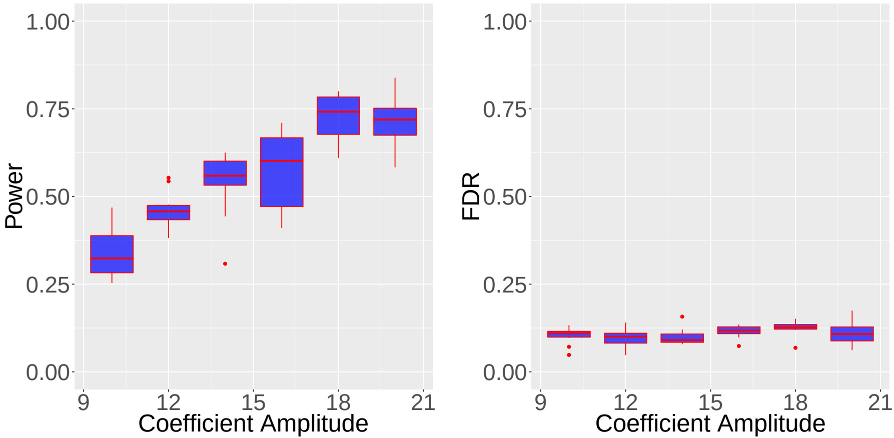

Figure: Power and FDR (target is 10%) for model-free knockoffs applied to subsamples of a chromosome 1 of real genetic design matrix; $n \approx 1,400$.

Computation of Second-Order Knockoffs

$\mathrm{Cov}(X_1, \ldots, X_p) = \boldsymbol{\Sigma}$, need:

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- **(New) Approximate SDP**:
  - Approximate $\mathbf{\Sigma}$ as block diagonal so that SDP separates
  - Bisection search scalar multiplier of solution to account for approximation
  - faster than SDP, more powerful than EQ, and easily parallelizable

Sequential Independent Pairs Generates Valid Knockoffs

Algorithm 1 Sequential Conditional Independent Pairs

for $j = \{1, \ldots, p\}$ **do**
  Sample $\tilde{X}_j$ from $\mathcal{L}(X_j \,|\, X_{\text{-}j}, \tilde{X}_{1:j-1})$ conditionally independently of X_j
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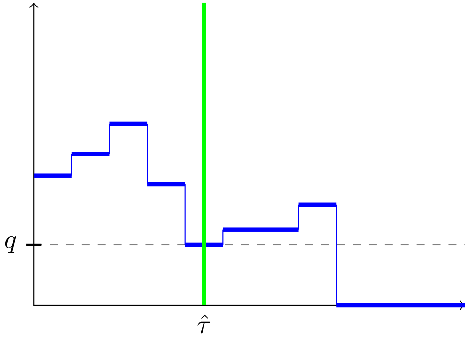

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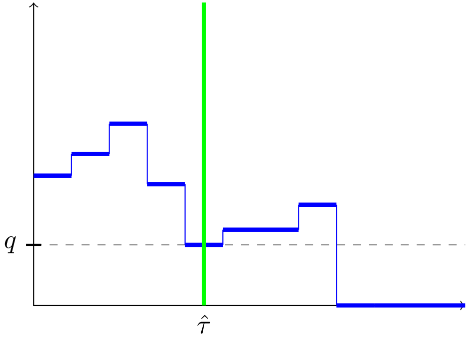

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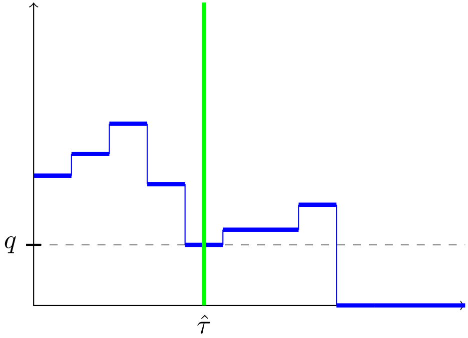

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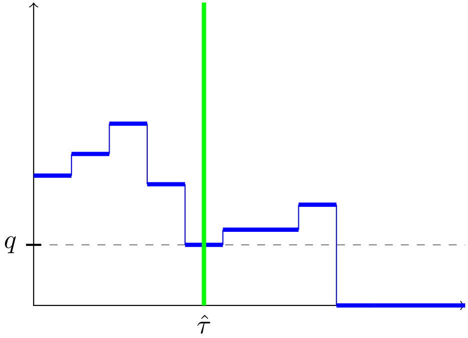

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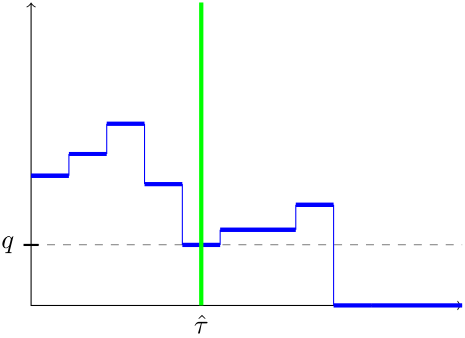

More precisely:

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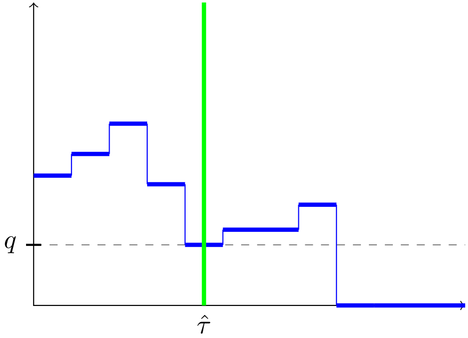

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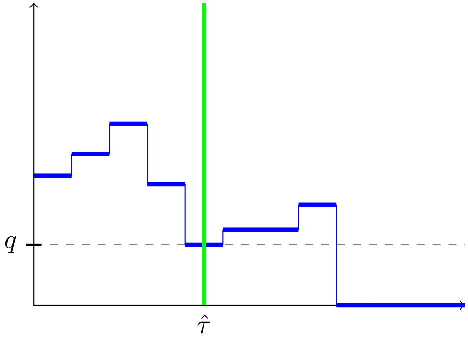


More precisely:

$$\text{mFDR} = \mathbb{E}\left(\frac{\#\{\text{null } \boldsymbol{X}_j \text{ selected}\}}{q^{-1} + \#\{\text{total } \boldsymbol{X}_j \text{ selected}\}}\right) = \mathbb{E}\left(\frac{\#\{\text{null positive } |W_j| > \hat{\tau}\}}{q^{-1} + \#\{\text{positive } |W_j| > \hat{\tau}\}}\right)$$

$$= \mathbb{E}\left(\frac{\#\{\text{null positive } |W_j| > \hat{\tau}\}}{1 + \#\{\text{null negative } |W_j| > \hat{\tau}\}} \cdot \underbrace{\frac{1 + \#\{\text{null negative } |W_j| > \hat{\tau}\}}{q^{-1} + \#\{\text{positive} |W_j| > \hat{\tau}\}}}_{\leq q \text{ by definition of } \hat{\tau}}\right)$$

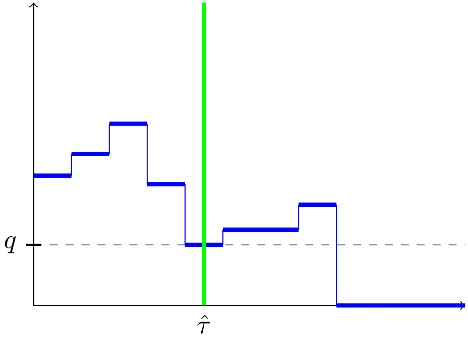
Proof of Control

$$\text{FDR} = \mathbb{E}\left(\frac{\#\{\text{null } \boldsymbol{X}_j \text{ selected}\}}{\#\{\text{total } \boldsymbol{X}_j \text{ selected}\}}\right)$$

$$= \mathbb{E}\left(\frac{\#\{\text{null positive } |W_j| > \hat{\tau}\}}{\#\{\text{positive } |W_j| > \hat{\tau}\}}\right)$$

$$\approx \mathbb{E}\left(\frac{\#\{\text{null negative } |W_j| > \hat{\tau}\}}{\#\{\text{positive } |W_j| > \hat{\tau}\}}\right)$$

$$\leq \mathbb{E}\left(\frac{\#\{\text{negative } |W_j| > \hat{\tau}\}}{\#\{\text{positive } |W_j| > \hat{\tau}\}}\right)$$



More precisely:

$$\text{mFDR} = \mathbb{E}\left(\frac{\#\{\text{null } \boldsymbol{X}_j \text{ selected}\}}{q^{-1} + \#\{\text{total } \boldsymbol{X}_j \text{ selected}\}}\right) = \mathbb{E}\left(\frac{\#\{\text{null positive } |W_j| > \hat{\tau}\}}{q^{-1} + \#\{\text{positive } |W_j| > \hat{\tau}\}}\right)$$

$$= \mathbb{E}\left(\underbrace{\frac{\#\{\text{null positive } |W_j| > \hat{\tau}\}}{1 + \#\{\text{null negative } |W_j| > \hat{\tau}\}}}_{\substack{\text{Supermartingale } \leq 1 \\ \text{with } \hat{\tau} \text{ a stopping time}}} \cdot \underbrace{\frac{1 + \#\{\text{null negative } |W_j| > \hat{\tau}\}}{q^{-1} + \#\{\text{positive} |W_j| > \hat{\tau}\}}}_{\leq q \text{ by definition of } \hat{\tau}}\right)$$