Using Knockoffs to Find Important Variables with Statistical Guarantees

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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)**:

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

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

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Everything in this talk works for this setting! (Dai and Barber, 2016)

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Model-X knockoffs uses knowledge of X's distribution to solve the controlled variable selection problem with

- Any model for Y and $X_1, \ldots, X_p$
- Any dimension (including $p > n$)
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Knockoffs used the same FDR of 10% and made **18** discoveries, with many of the new discoveries confirmed by a larger meta-analysis

Existing Methods for Controlled Variable Selection

- Marginal p-values
  - Excellent exploratory tool
  - Answer wrong question $Y \perp\!\!\!\perp X_j$ instead of $Y \perp\!\!\!\perp X_j \mid X_{\text{-}j}$
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- Machine learning
  - Excellent for prediction
  - Cross-validation comes with no statistical guarantees
  - Statistical analysis exists only for simplest methods (lasso) and makes unrealistic assumptions

Knockoffs

View from 10,000 feet

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- n data samples of Y and X stacked into $\boldsymbol{y} \in \mathbb{R}^n$ and $\boldsymbol{X} \in \mathbb{R}^{n \times p}$

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  - This need not be based on any statistical model, or have any statistical properties at all
  - For instance, you could fit any machine learning method and use the drop in prediction accuracy when $\boldsymbol{X}_j$ is removed from the data

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Overview of the Knockoffs Procedure

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- Artificial versions ("knockoffs") of each variable
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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 $1/2$

A Picture for Intuition

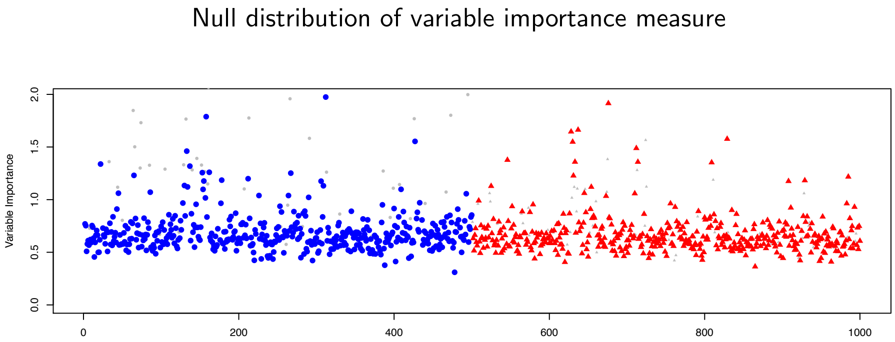

Figure: Variable importances for 500 variables and their knockoffs. Colored points are nulls, grey are non-nulls.

Step (1): Construct Knockoffs

Knockoff Construction

Valid knockoffs are defined by

(1) Swap exchangeability:

$$
\begin{aligned}
&[\boldsymbol{X}_1, \cdots, \boldsymbol{X}_j, \cdots, \boldsymbol{X}_p, \widetilde{\boldsymbol{X}}_1, \cdots, \widetilde{\boldsymbol{X}}_j, \cdots, \widetilde{\boldsymbol{X}}_p] \\
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Example: $(X_1, \ldots, X_p) \sim \mathcal{N}(\mathbf{0}, \boldsymbol{\Sigma})$, need

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

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Semidefinite program construction for $\boldsymbol{s}$:

$$\begin{array}{rl} \text{minimize} & \sum_j |\Sigma_{jj} - s_j| \\ \text{subject to} & s_j \geq 0 \\ & \text{diag}\{\boldsymbol{s}\} \preceq 2\boldsymbol{\Sigma}, \end{array}$$

Other Knockoff Constructions

Valid knockoff variables can always be generated:

Algorithm 1 Sequential Conditional Independent Pairs

for $j = \{1, \ldots, p\}$ **do**

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- Multivariate Gaussian (Candès et al., 2018)
- Discrete Markov chains (Sesia et al., 2018)
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Approximate knockoff constructions (no theoretical guarantees):

- Second-order knockoffs (tend to work well with regression-based statistics) (Candès et al., 2018)
- Deep learning, including GANs (empirically valid in low-dimensions $n > p$) (Romano et al., 2018; Liu and Zheng, 2018; Anonymous, 2018)

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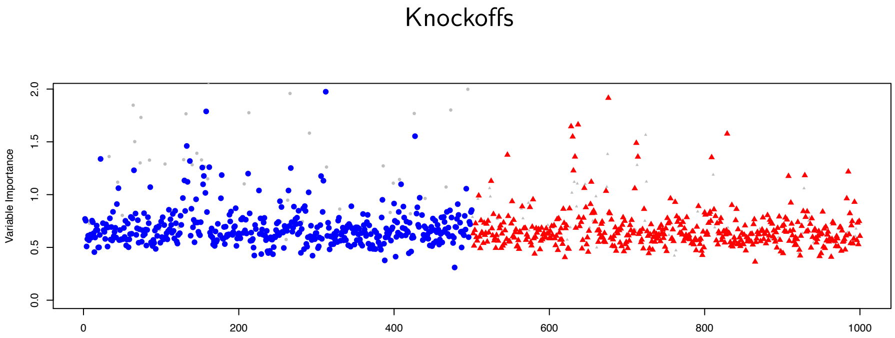

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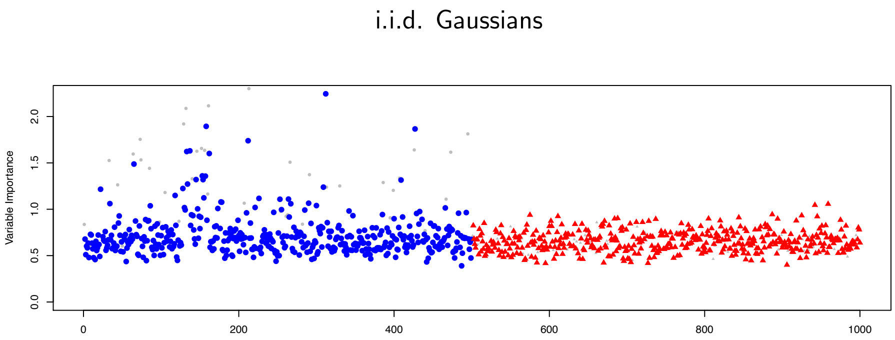

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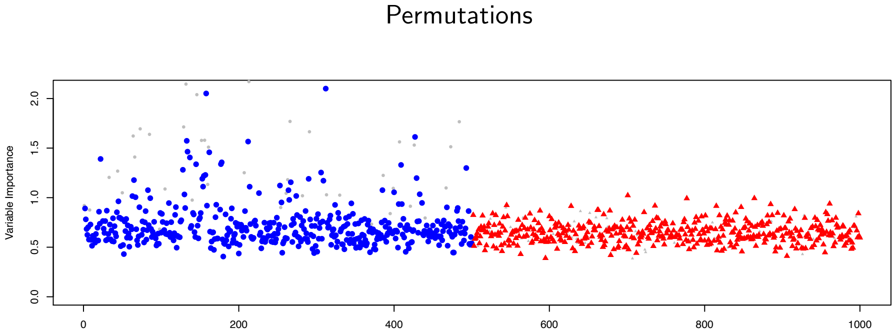

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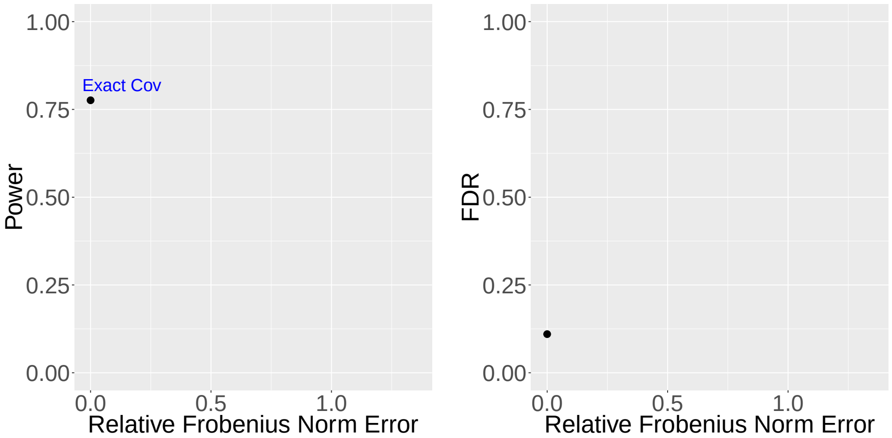

Figure: Covariates are **AR(1) with autocorrelation coefficient 0.3**. $n = 800$, $p = 1500$, and target FDR is 10%. Y comes from a binomial linear model with logit link function with 50 nonzero entries.

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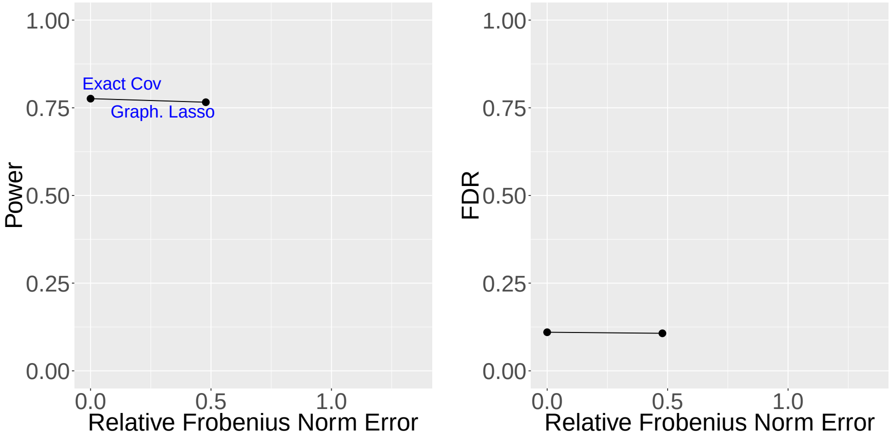

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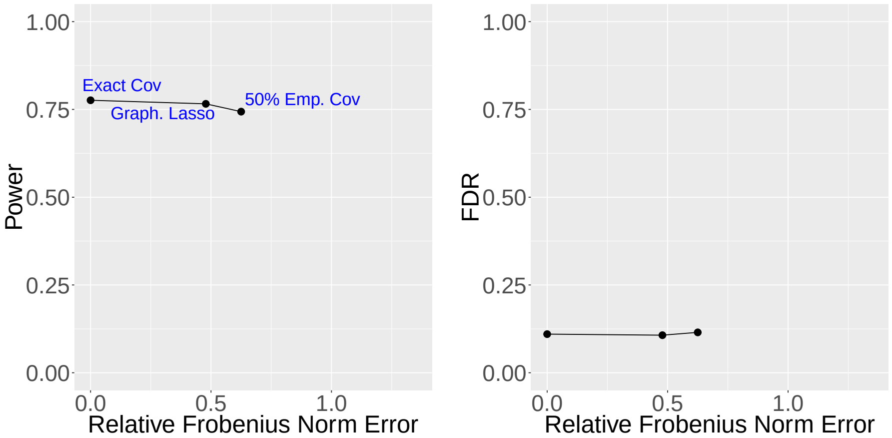

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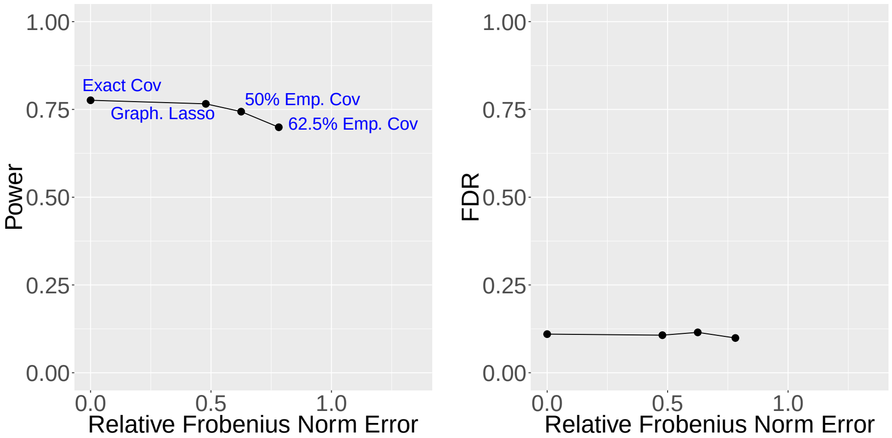

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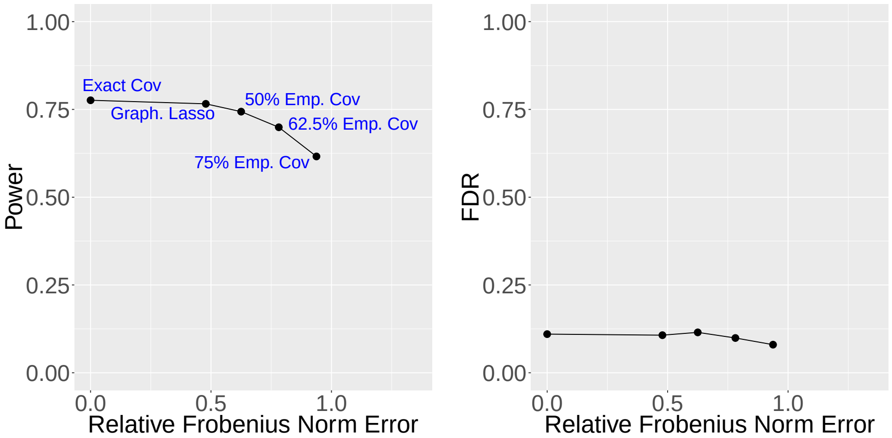

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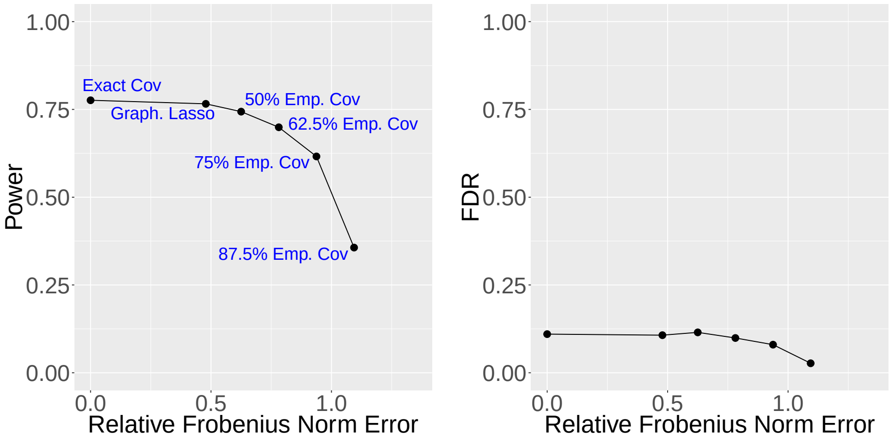

Figure: Covariates are **AR(1) with autocorrelation coefficient 0.3**. $n = 800$, $p = 1500$, and target FDR is 10%. Y comes from a binomial linear model with logit link function with 50 nonzero entries.

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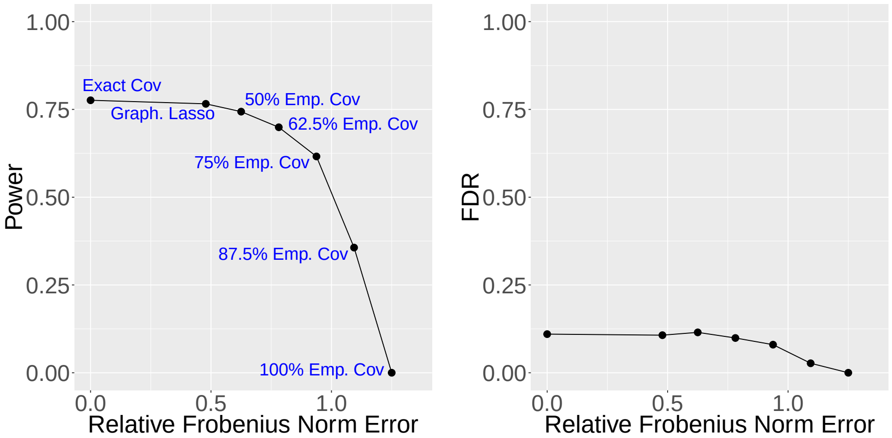

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Step (2): Compute Knockoff Statistics

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- Variable importance measures for all original and knockoff variables

$$Z_1, \ldots, Z_p, \widetilde{Z}_1, \ldots, \widetilde{Z}_p$$

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Example 2:

- Fit machine learning method (e.g., deep learning) to $\boldsymbol{y}$ with features $[\boldsymbol{X}\, \widetilde{\boldsymbol{X}}]$
- Z is increase in cross-validation error when variable is dropped; same f_j

$$(\mathsf{CV}_{\text{-}j} - \mathsf{CV}) - \left(\widetilde{\mathsf{CV}}_{\text{-}j} - \mathsf{CV}\right) = \mathsf{CV}_{\text{-}j} - \widetilde{\mathsf{CV}}_{\text{-}j}$$

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- **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**

Why Does it Work?

Recall swap exchangeability property: for any j,

$$\begin{aligned}&[\boldsymbol{X}_1, \cdots, \boldsymbol{X}_j, \cdots, \boldsymbol{X}_p, \widetilde{\boldsymbol{X}}_1, \cdots, \widetilde{\boldsymbol{X}}_j, \cdots, \widetilde{\boldsymbol{X}}_p] \\ \overset{\mathcal{D}}{=} &[\boldsymbol{X}_1, \cdots, \widetilde{\boldsymbol{X}}_j, \cdots, \boldsymbol{X}_p, \widetilde{\boldsymbol{X}}_1, \cdots, \boldsymbol{X}_j, \cdots, \widetilde{\boldsymbol{X}}_p]\end{aligned}$$

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Step (3): Find the Knockoff Threshold

Simple Example

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

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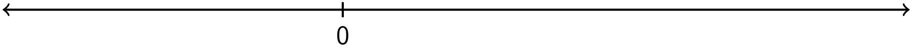

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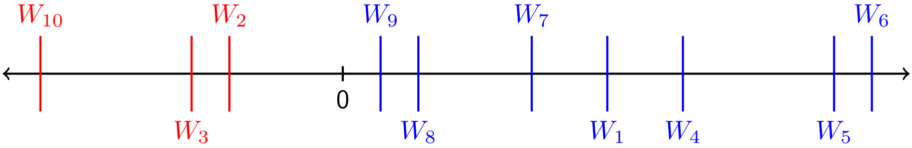

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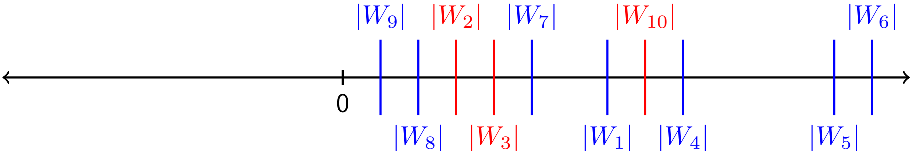

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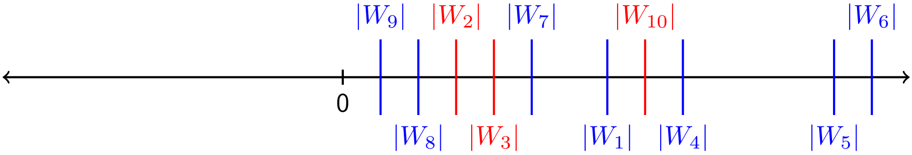

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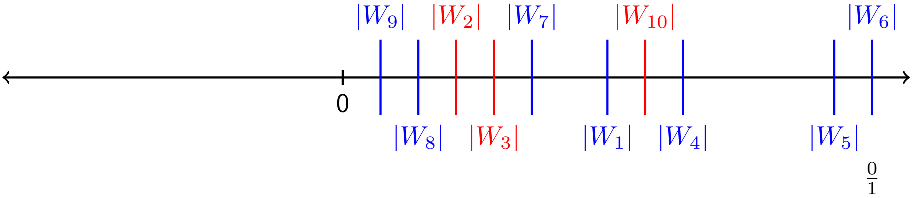

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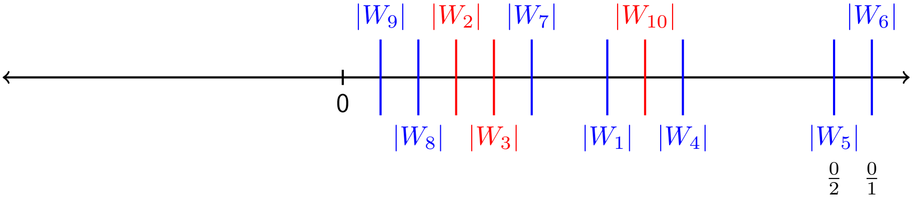

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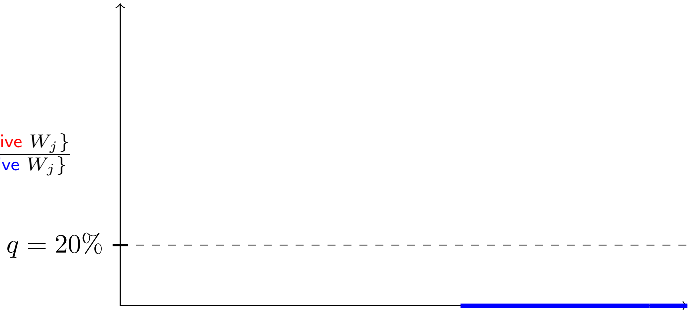

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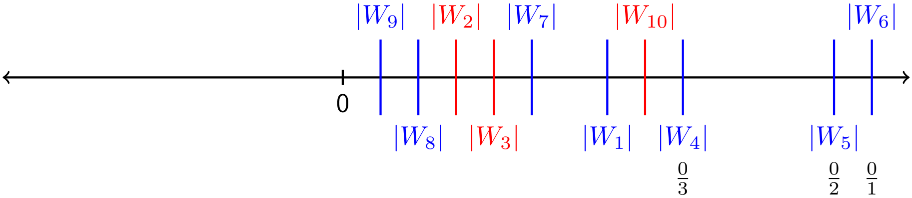

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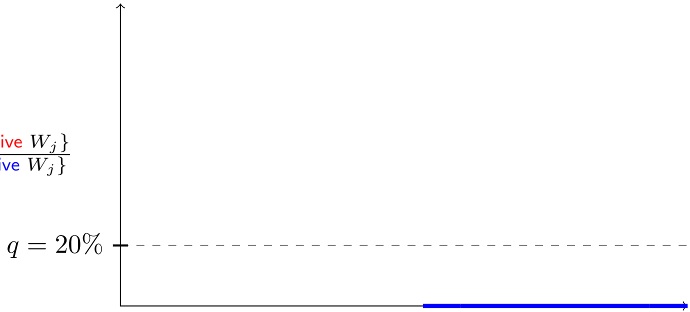

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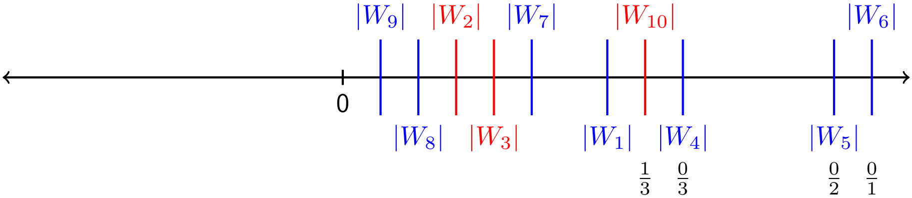

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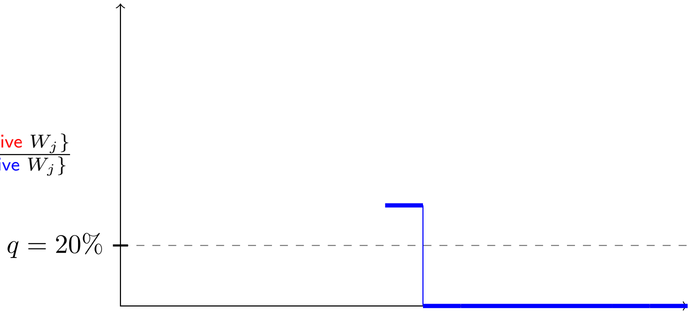

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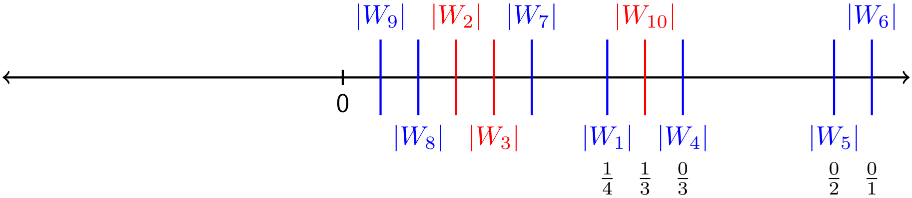

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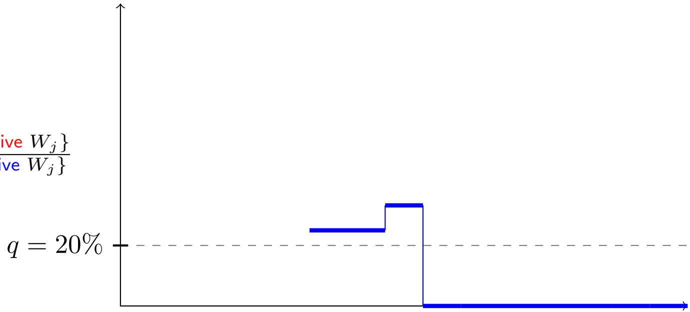

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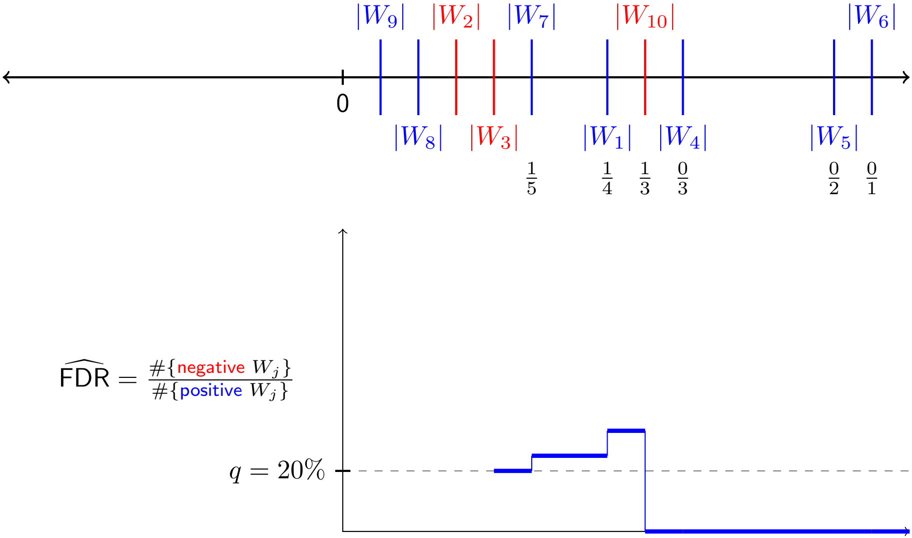

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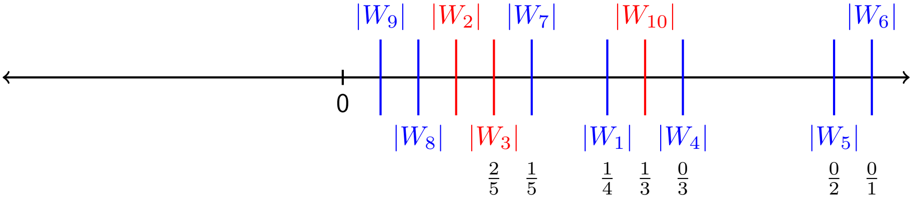

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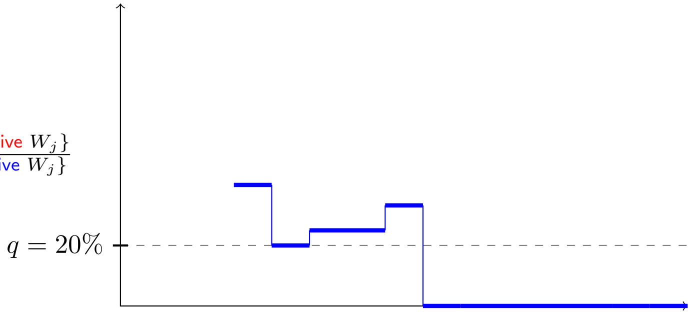

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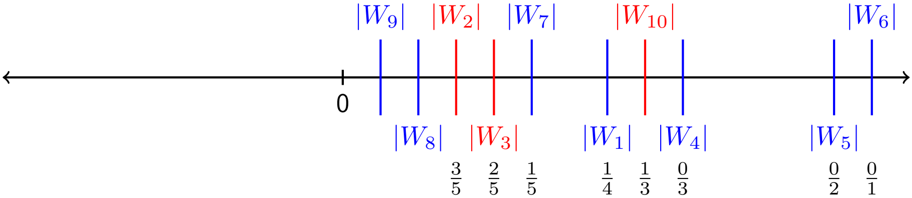

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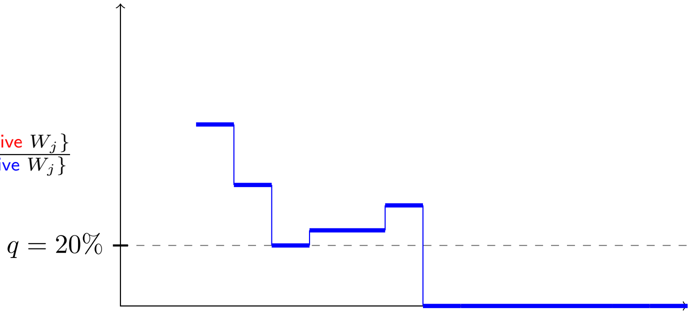

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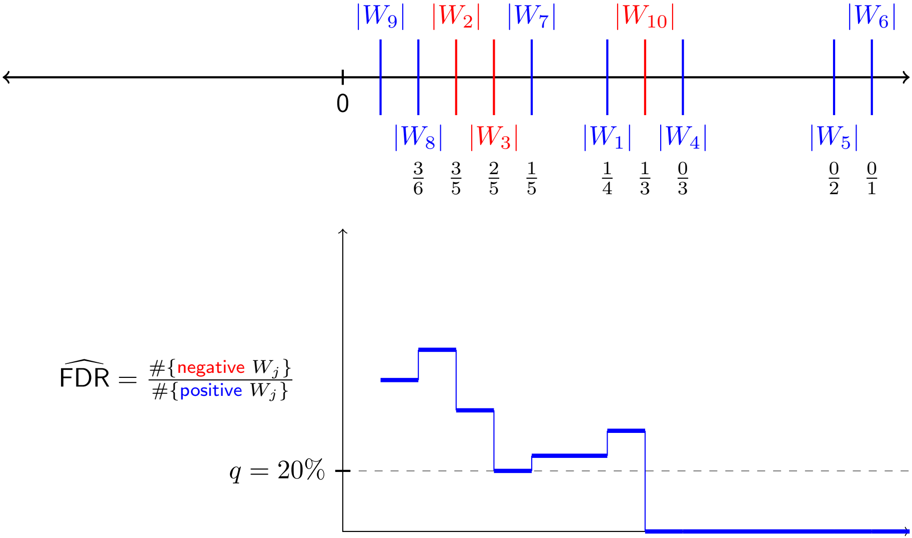

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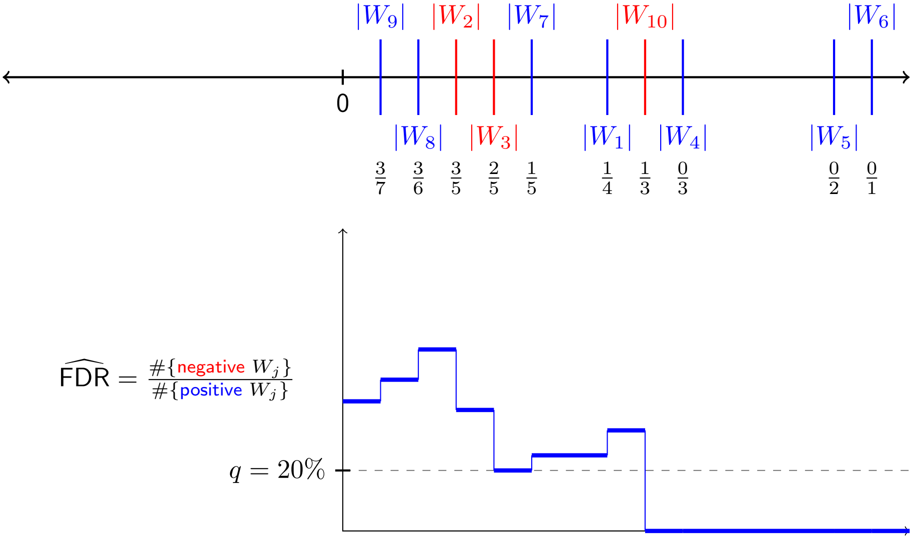

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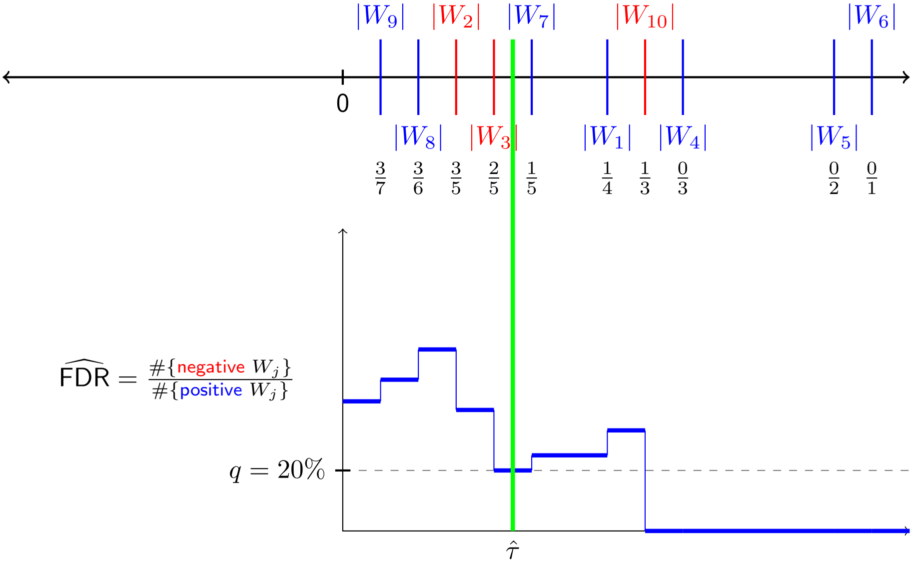

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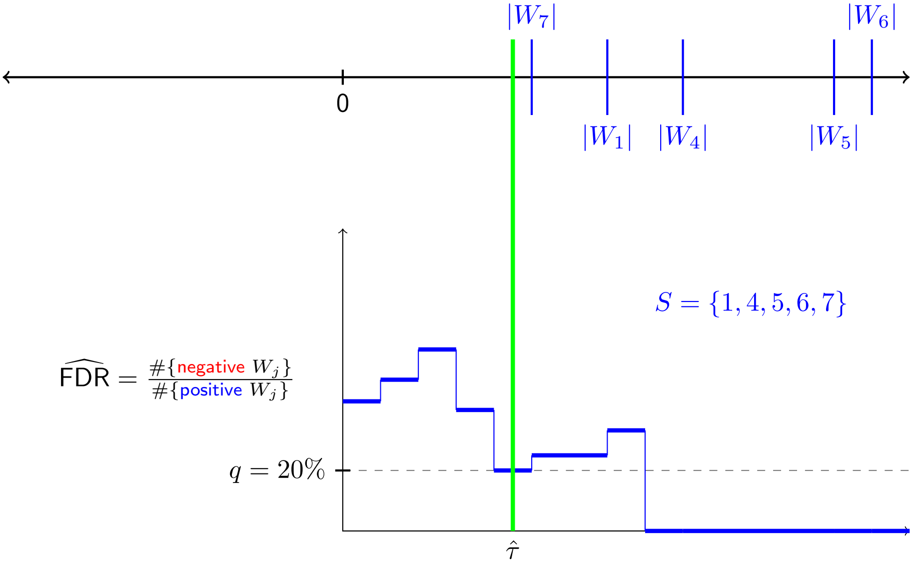

Tracking the FDR

$$\text{FDR} \;= \mathbb{E}\left[\frac{\#\{\text{null } \boldsymbol{X}_j \text{ selected}\}}{\#\{\text{total } \boldsymbol{X}_j \text{ selected}\}}\right]$$

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\end{aligned}
$$

Numerical Results

Simulations in Low-Dimensional Linear Model

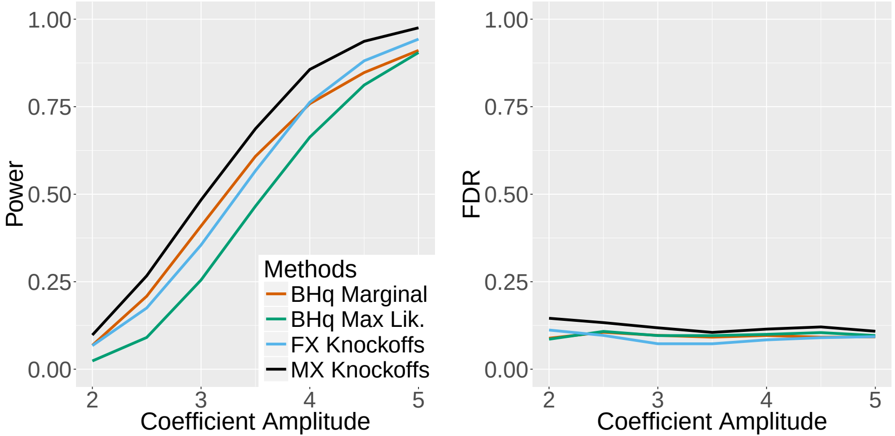

Figure: Power and FDR (target is 10%) for knockoffs and alternative procedures. The design matrix is i.i.d. $\mathcal{N}(0, 1/n)$, $n = 3000$, $p = 1000$, and y comes from a Gaussian linear model with 60 nonzero regression coefficients having equal magnitudes and random signs. The noise variance is 1.

Simulations in Low-Dimensional Nonlinear Model

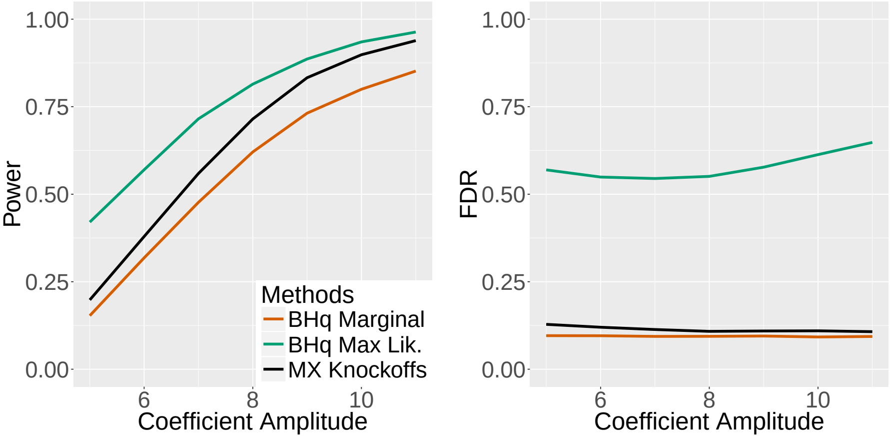

Figure: Power and FDR (target is 10%) for knockoffs and alternative procedures. The design matrix is i.i.d. $\mathcal{N}(0, 1/n)$, $n = 3000$, $p = 1000$, and y comes from a binomial linear model with logit link function, and 60 nonzero regression coefficients having equal magnitudes and random signs.

Simulations in High Dimensions

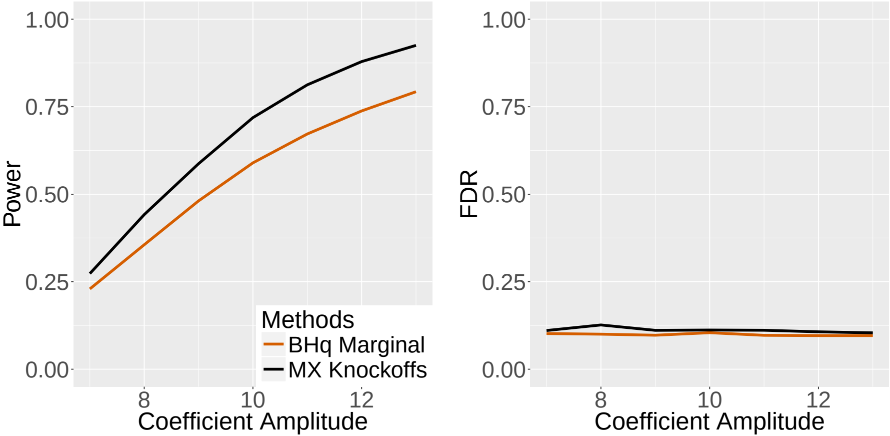

Figure: Power and FDR (target is 10%) for knockoffs and alternative procedures. The design matrix is i.i.d. $\mathcal{N}(0, 1/n)$, $n = 3000$, $p = 6000$, and y comes from a binomial linear model with logit link function, and 60 nonzero regression coefficients having equal magnitudes and random signs.

Simulations in High Dimensions with Dependence

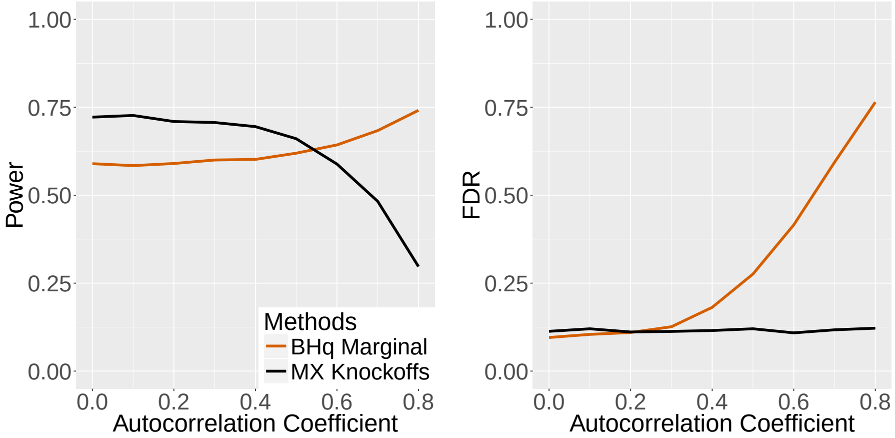

Figure: Power and FDR (target is 10%) for knockoffs and alternative procedures. The design matrix has AR(1) columns, and marginally each $X_j \sim \mathcal{N}(0, 1/n)$. $n = 3000$, $p = 6000$, and y follows a binomial linear model with logit link function, and 60 nonzero coefficients with random signs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

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 obtained with X model taken from **existing genomic imputation software** (Sesia et al., 2018)

Computation and Software

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- Need to compute $Z_1, \ldots, Z_p, \widetilde{Z}_1, \ldots, \widetilde{Z}_p$
    - Just compute variable importances for twice as many variables
    - Generally only constant slower than computing variable importances without knockoffs

Checking Sensitivity to Misspecification Error

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	$Y \mid X$	X
Canonical (fixed-X)	Yes	No
Model-X	No	Yes

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Model-X: can actually **check sensitivity** to misspecification error!

Robustness on Real Data

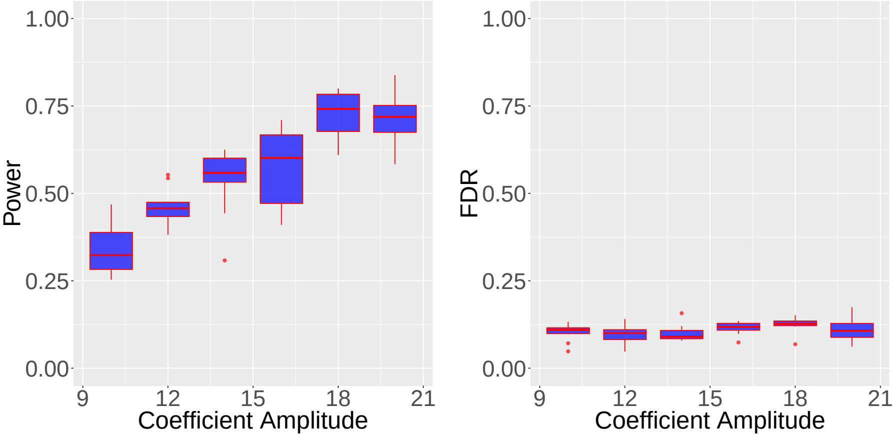

Figure: Power and FDR (target is 10%) for knockoffs applied to subsamples of a chromosome 1 of real genetic design matrix; $n \approx 1,400$.

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The controlled variable selection problem is ubiquitous in modern science, and knockoffs is a powerful, flexible, and robust solution

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Thank you!

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ljanson@fas.harvard.edu

Appendix

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Existing Methods: Low-Dimensional Linear Model

Suppose we assume that our data:

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$$Y = X_1\beta_1 + \cdots + X_p\beta_p + \varepsilon, \qquad \varepsilon \sim \mathcal{N}(0, \sigma^2),$$

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Minor caveats:

- FDR control not exact (but good enough in practice)
- Sparsity not used (reduces power to find important variables)

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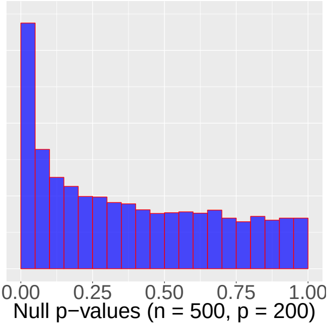

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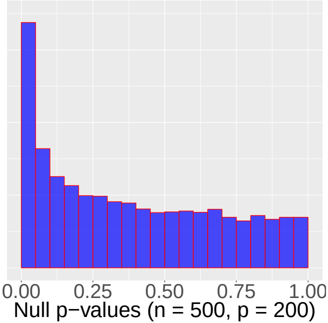

High-dimensional ($n < p$) generalized linear models

- Apply BHq to p-values from
  - Debiased lasso, e.g., Zhang and Zhang (2014), Javanmard and Montanari (2014), van de Geer et al. (2014), Cai and Guo (2015)
  - Causal inference, e.g., Belloni et al. (2014), Athey et al. (2016), Farrell (2015)
  - Inference after selection, e.g., Berk et al. (2013), Lee et al. (2016), Fithian et al. (2014)
- Asymptotic, require sparsity and random design assumptions

Sequential Independent Pairs Generates Valid Knockoffs

Algorithm 2 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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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

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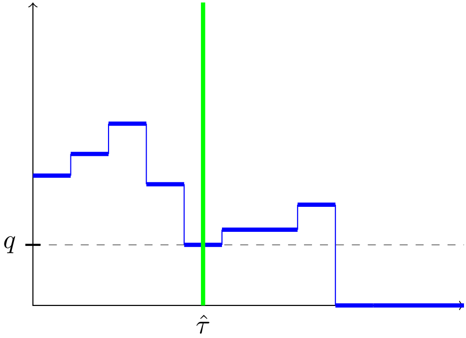

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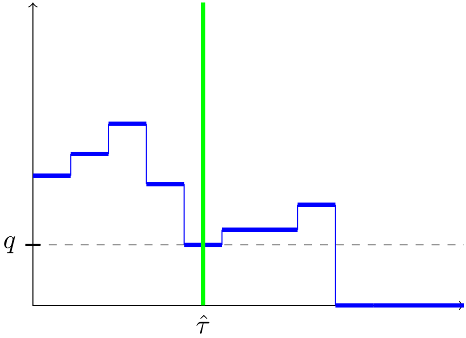
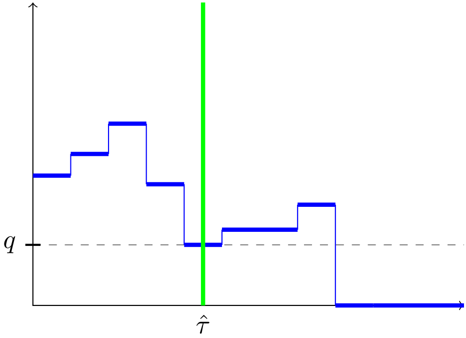
$$= \mathbb{E}\left[\frac{\#\{\text{null positive } |W_j| > \hat{\tau}\}}{\#\{\text{positive } |W_j| > \hat{\tau}\}}\right]$$



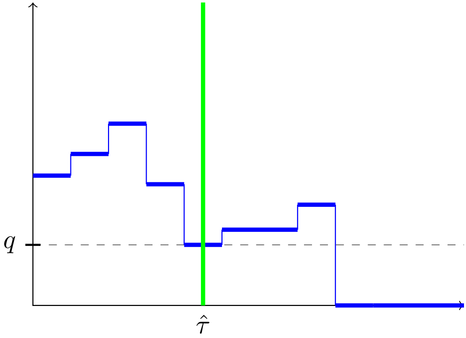
Proof of Control

$$\begin{aligned}\text{FDR} &= \mathbb{E}\left[\frac{\#\{\text{null } \boldsymbol{X}_j \text{ selected}\}}{\#\{\text{total } \boldsymbol{X}_j \text{ selected}\}}\right] \\ &= \mathbb{E}\left[\frac{\#\{\text{null positive } |W_j| > \hat{\tau}\}}{\#\{\text{positive } |W_j| > \hat{\tau}\}}\right] \\ &\approx \mathbb{E}\left[\frac{\#\{\text{null negative } |W_j| > \hat{\tau}\}}{\#\{\text{positive } |W_j| > \hat{\tau}\}}\right]\end{aligned}$$



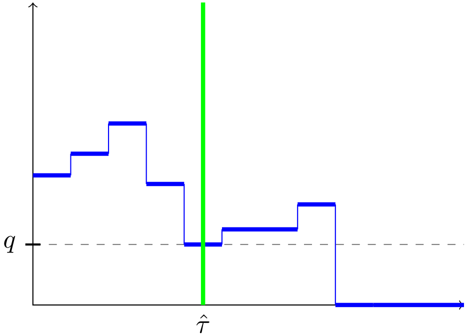
Proof of Control

$$\begin{aligned}
\text{FDR} &= \mathbb{E}\left[\frac{\#\{\text{null } \boldsymbol{X}_j \text{ selected}\}}{\#\{\text{total } \boldsymbol{X}_j \text{ selected}\}}\right] \\
&= \mathbb{E}\left[\frac{\#\{\text{null positive } |W_j| > \hat{\tau}\}}{\#\{\text{positive } |W_j| > \hat{\tau}\}}\right] \\
&\approx \mathbb{E}\left[\frac{\#\{\text{null negative } |W_j| > \hat{\tau}\}}{\#\{\text{positive } |W_j| > \hat{\tau}\}}\right] \\
&\leq \mathbb{E}\left[\frac{\#\{\text{negative } |W_j| > \hat{\tau}\}}{\#\{\text{positive } |W_j| > \hat{\tau}\}}\right]
\end{aligned}$$



Proof of Control

$$
\begin{aligned}
\text{FDR} &= \mathbb{E}\left[\frac{\#\{\text{null } \boldsymbol{X}_j \text{ selected}\}}{\#\{\text{total } \boldsymbol{X}_j \text{ selected}\}}\right] \\
&= \mathbb{E}\left[\frac{\#\{\text{null positive } |W_j| > \hat{\tau}\}}{\#\{\text{positive } |W_j| > \hat{\tau}\}}\right] \\
&\approx \mathbb{E}\left[\frac{\#\{\text{null negative } |W_j| > \hat{\tau}\}}{\#\{\text{positive } |W_j| > \hat{\tau}\}}\right] \\
&\leq \mathbb{E}\left[\frac{\#\{\text{negative } |W_j| > \hat{\tau}\}}{\#\{\text{positive } |W_j| > \hat{\tau}\}}\right]
\end{aligned}
$$

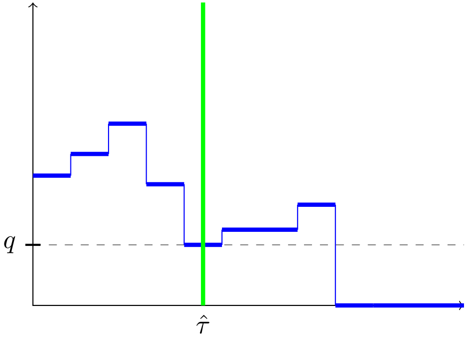


More precisely:

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

Proof of Control

$$\begin{aligned}
\text{FDR} &= \mathbb{E}\left[\frac{\#\{\text{null } \boldsymbol{X}_j \text{ selected}\}}{\#\{\text{total } \boldsymbol{X}_j \text{ selected}\}}\right] \\
&= \mathbb{E}\left[\frac{\#\{\text{null positive } |W_j| > \hat{\tau}\}}{\#\{\text{positive } |W_j| > \hat{\tau}\}}\right] \\
&\approx \mathbb{E}\left[\frac{\#\{\text{null negative } |W_j| > \hat{\tau}\}}{\#\{\text{positive } |W_j| > \hat{\tau}\}}\right] \\
&\leq \mathbb{E}\left[\frac{\#\{\text{negative } |W_j| > \hat{\tau}\}}{\#\{\text{positive } |W_j| > \hat{\tau}\}}\right]
\end{aligned}$$



More precisely:

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

Proof of Control

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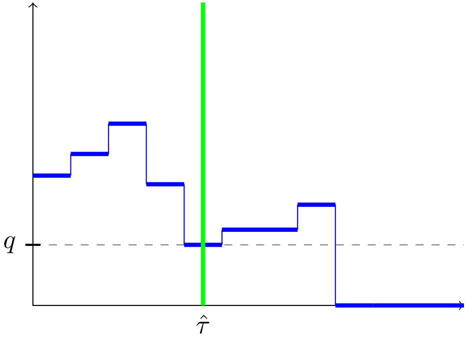
\text{FDR} &= \mathbb{E}\left[\frac{\#\{\text{null } \boldsymbol{X}_j \text{ selected}\}}{\#\{\text{total } \boldsymbol{X}_j \text{ selected}\}}\right] \\
&= \mathbb{E}\left[\frac{\#\{\text{null positive } |W_j| > \hat{\tau}\}}{\#\{\text{positive } |W_j| > \hat{\tau}\}}\right] \\
&\approx \mathbb{E}\left[\frac{\#\{\text{null 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]
\end{aligned}$$

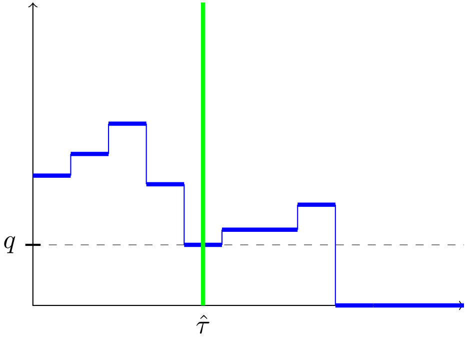


More precisely:

$$\begin{aligned}
\text{mFDR} &= \mathbb{E}\left[\frac{\#\{\text{null } \boldsymbol{X}_j \text{ selected}\}}{q^{-1} + \#\{\text{total } \boldsymbol{X}_j \text{ selected}\}}\right] = \mathbb{E}\left[\frac{\#\{\text{null positive } |W_j| > \hat{\tau}\}}{q^{-1} + \#\{\text{positive } |W_j| > \hat{\tau}\}}\right] \\
&= \mathbb{E}\left(\frac{\#\{\text{null positive } |W_j| > \hat{\tau}\}}{1 + \#\{\text{null negative } |W_j| > \hat{\tau}\}} \cdot \underbrace{\frac{1 + \#\{\text{null negative } |W_j| > \hat{\tau}\}}{q^{-1} + \#\{\text{positive} |W_j| > \hat{\tau}\}}}_{\leq q \text{ by definition of } \hat{\tau}}\right)
\end{aligned}$$

Proof of Control

$$\begin{aligned}
\text{FDR} &= \mathbb{E}\left[\frac{\#\{\text{null } \boldsymbol{X}_j \text{ selected}\}}{\#\{\text{total } \boldsymbol{X}_j \text{ selected}\}}\right] \\
&= \mathbb{E}\left[\frac{\#\{\text{null } {\color{blue}\text{positive}}\ |W_j| > \hat{\tau}\}}{\#\{{\color{blue}\text{positive}}\ |W_j| > \hat{\tau}\}}\right] \\
&\approx \mathbb{E}\left[\frac{\#\{\text{null } {\color{red}\text{negative}}\ |W_j| > \hat{\tau}\}}{\#\{{\color{blue}\text{positive}}\ |W_j| > \hat{\tau}\}}\right] \\
&\leq \mathbb{E}\left[\frac{\#\{{\color{red}\text{negative}}\ |W_j| > \hat{\tau}\}}{\#\{{\color{blue}\text{positive}}\ |W_j| > \hat{\tau}\}}\right]
\end{aligned}$$



More precisely:

$$\begin{aligned}
\text{mFDR} &= \mathbb{E}\left[\frac{\#\{\text{null } \boldsymbol{X}_j \text{ selected}\}}{q^{-1} + \#\{\text{total } \boldsymbol{X}_j \text{ selected}\}}\right] = \mathbb{E}\left[\frac{\#\{\text{null } {\color{blue}\text{positive}}\ |W_j| > \hat{\tau}\}}{q^{-1} + \#\{{\color{blue}\text{positive}}\ |W_j| > \hat{\tau}\}}\right] \\
&= \mathbb{E}\left(\underbrace{\frac{\#\{\text{null } {\color{blue}\text{positive}}\ |W_j| > \hat{\tau}\}}{1 + \#\{\text{null } {\color{red}\text{negative}}\ |W_j| > \hat{\tau}\}}}_{\substack{\text{Supermartingale } \leq 1 \\ \text{with } \hat{\tau} \text{ a stopping time}}} \cdot \underbrace{\frac{1 + \#\{\text{null } {\color{red}\text{negative}}\ |W_j| > \hat{\tau}\}}{q^{-1} + \#\{{\color{blue}\text{positive}}|W_j| > \hat{\tau}\}}}_{\leq q \text{ by definition of } \hat{\tau}}\right)
\end{aligned}$$