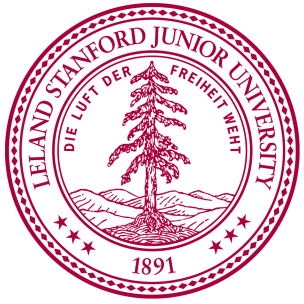
# Statistics for the Big Data Era

Emmanuel Candès




*Leçons Jacques-Louis Lions 2017, Paris, March 2017*

# Goals for these lectures

(1) Emphasize the importance of modern statistical inference problems

(2) Discuss ways in which the statistical community responds to pressing contemporary problems

# Agenda

## Lecture 2: Controlled variable selection via the knockoff filter

- Feature selection
- Model-free knockoffs
- Feature selection via the knockoff filter
- FDR control
- Examples
- Knockoff filter for linear regression with fixed design

# Collaborators

Knockoffs v1.0

- Rina Foygel Barber (Chicago)

Knockoffs v2.0

- Lucas Janson (Stanford)
- Yingying Fan (USC)
- Jinchi Lv (USC)

# Yesterday: big data and a new scientific paradigm

Collect data first $\Longrightarrow$ Ask questions later

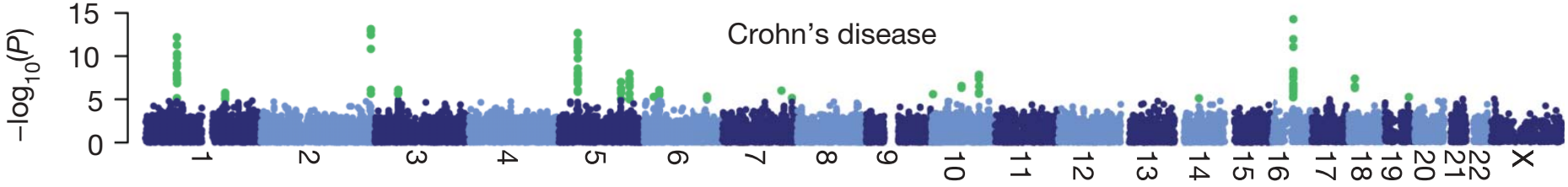
- Large data sets available prior to formulation of hypotheses
- Need to quantify "reliability" of hypotheses generated by data snooping

Very different from hypothesis-driven research

# If ignored... selective reporting/statistical bias

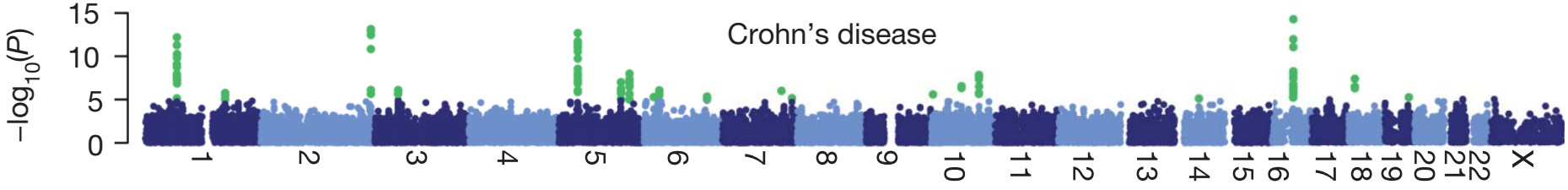
# *The Feature Selection Problem*

# Contemporary problem




- $Y \in \{0, 1\}$: disease status (e.g. Crohn's disease)
- $X_j \in \{0, 1, 2\}$: # of minor alleles at marker $j$ (SNP info)

# Contemporary problem




- $Y \in \{0, 1\}$: disease status (e.g. Crohn's disease)
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Which genetic variations are important for understanding the risk of a disease?

# A master problem of (big) data science

- Which genetic features influence the risk of a disease?
- Which electronic medical record entries influence future medical costs?
- Which demographic or socioeconomic variables influence political opinions?
- Which software characteristics predict user engagement?

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Response $Y$ and thousands/millions of covariates $X$

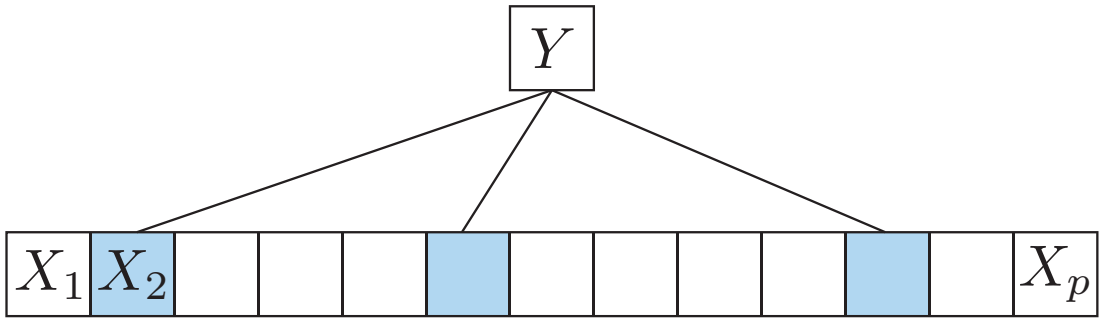
Which ones are important?

Distribution of $Y \mid X$ depends on $X$ through which variables?

# Selection problem

Subset $\mathcal{S}$ of relevant variables

$$Y \mid \{X_j\}_{j \in 1:p} \quad \stackrel{d}{=} \quad Y \mid \{X_j\}_{j \in \mathcal{S}}$$



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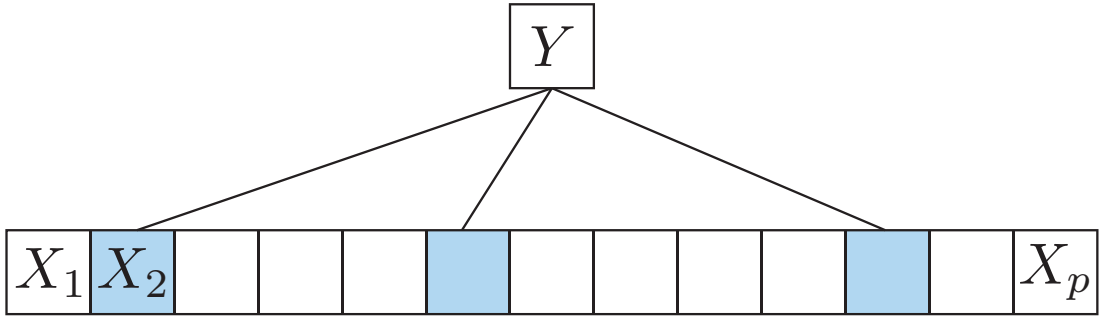


Goal: select set $\hat{\mathcal{S}}$ of features $X_j$ that are likely to be relevant
without too many false positives – do not run into the problem of irreproducibilty

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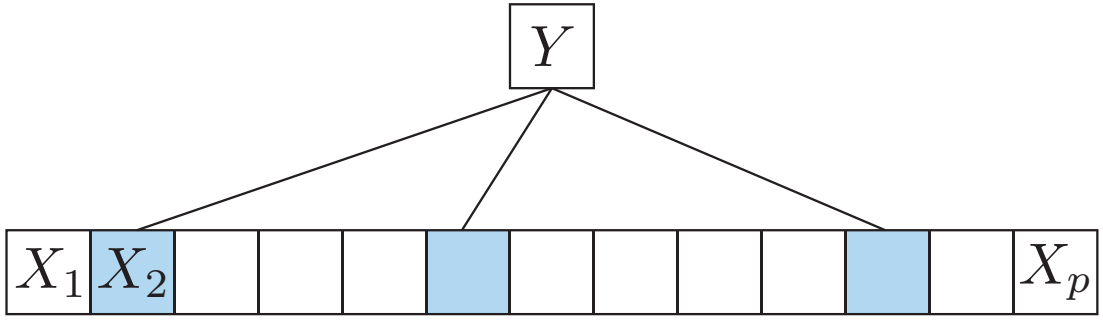


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$$\underbrace{\text{FDR}}_{\text{False discovery rate}} = \mathbb{E} \underbrace{\frac{\#\text{ false positives}}{\#\text{ features selected}}}_{\text{False discovery proportion}} = \mathbb{E}\left[\frac{|\hat{\mathcal{S}} \setminus \mathcal{S}|}{|\hat{\mathcal{S}}|}\right]$$

# Problem statement

## Working definition of null (unimportant) variables

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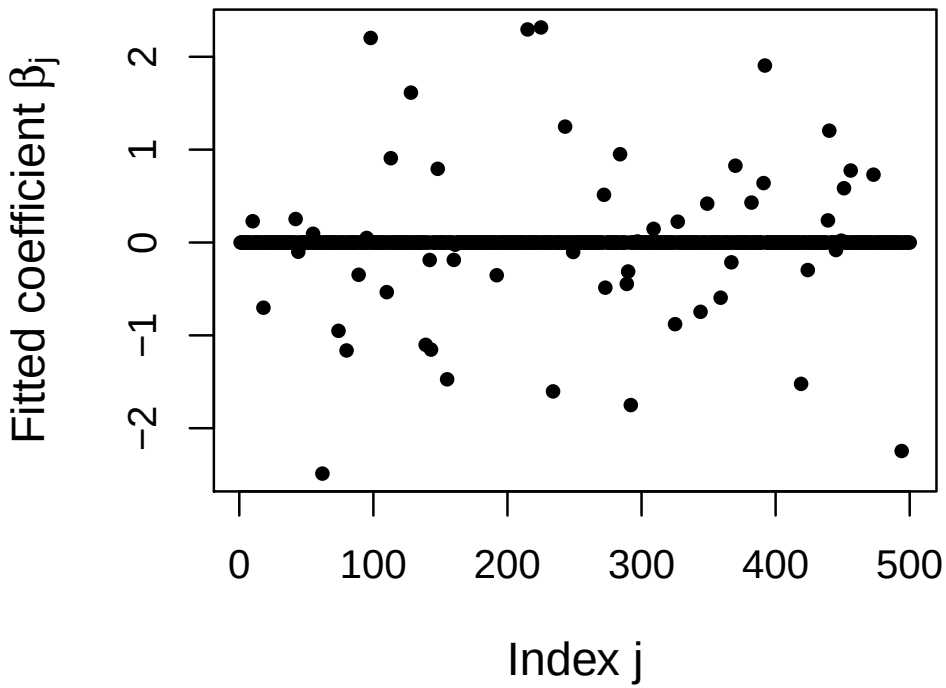
Logistic model: $$\mathbb{P}(Y = 0|X) = \frac{1}{1 + e^{X^\top \beta}}$$

If variables $X_{1:p}$ are not perfectly dependent, then $j \in \mathcal{H}_0 \iff \beta_j = 0$

# Subtlety of the selection problem

(Logistic) LASSO model

$$\min_{\boldsymbol{b}\in\mathbb{R}^p} \quad -\ell(\boldsymbol{y};\, \boldsymbol{X}\boldsymbol{b}) + \lambda\|\boldsymbol{b}\|_1$$



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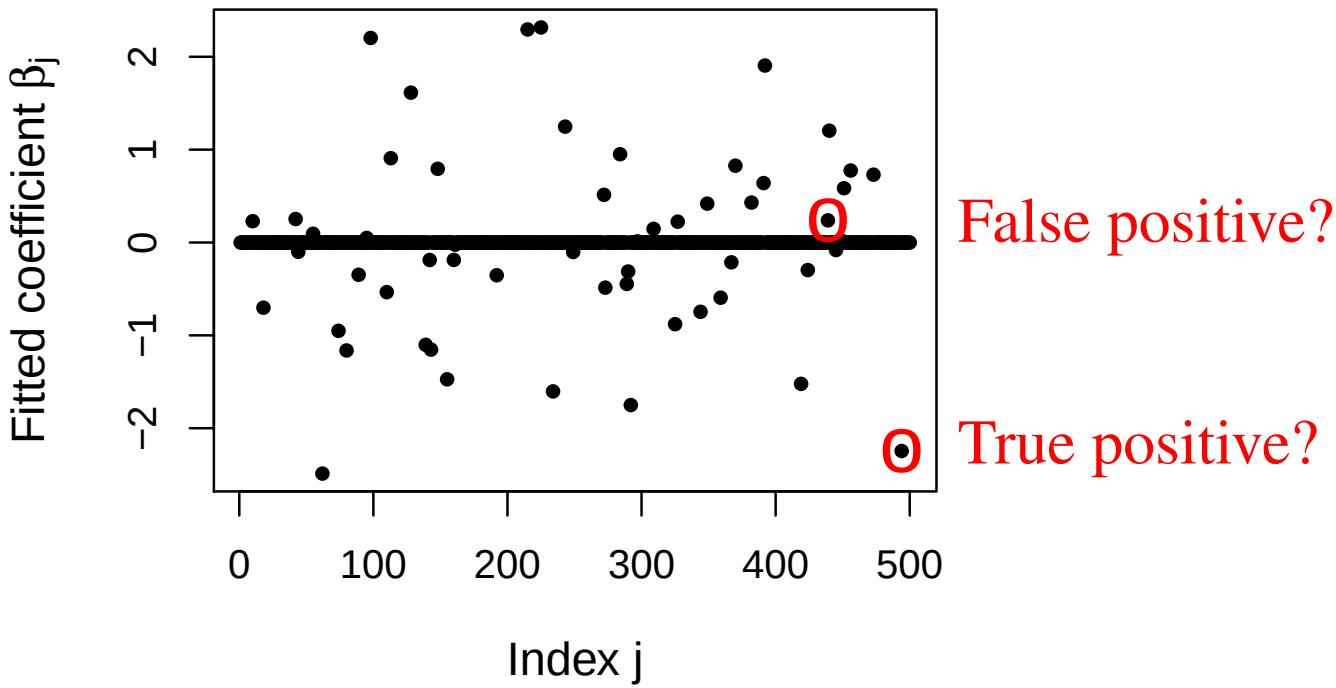

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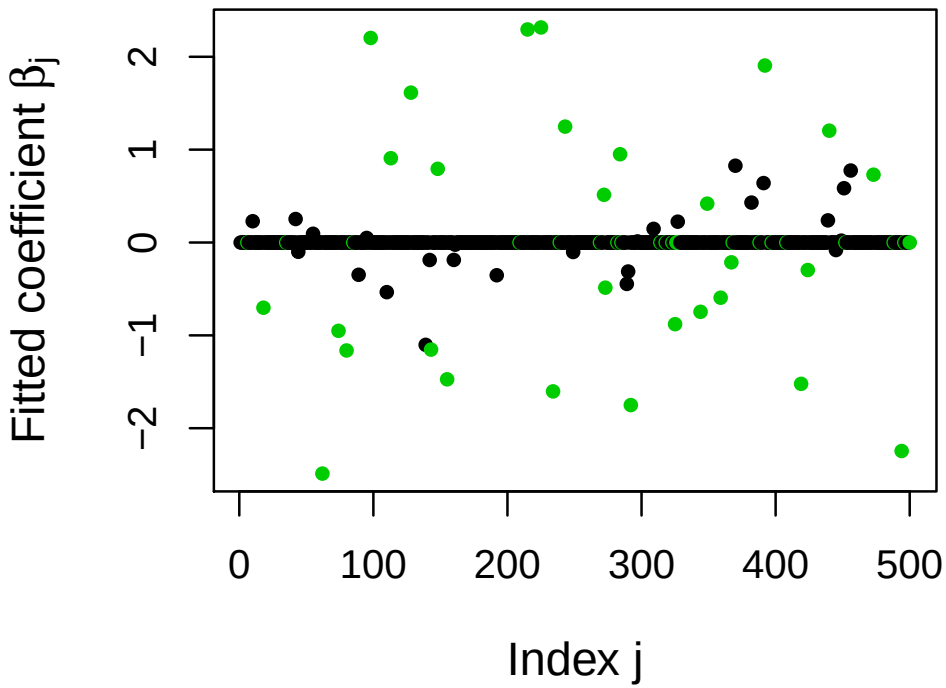


$\text{FDP} = \frac{26}{55} = 47\%$

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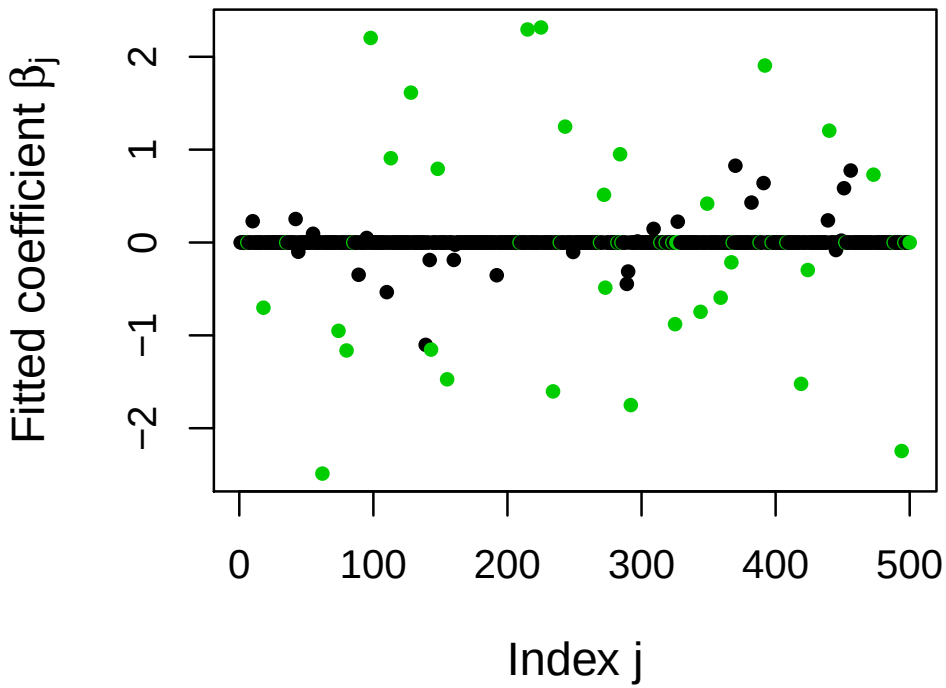


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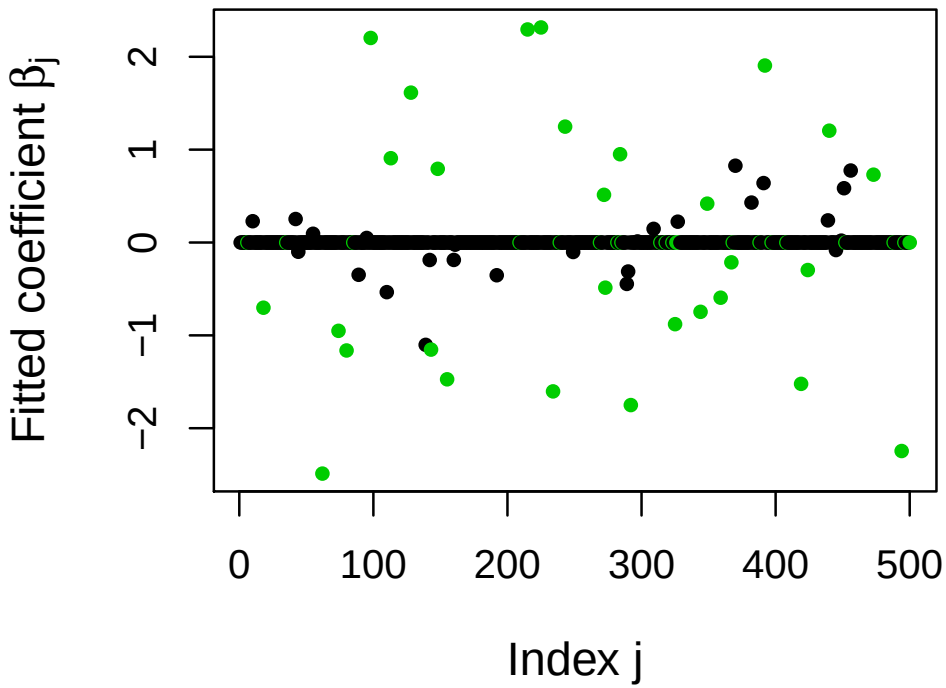


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Estimate FDP? ...

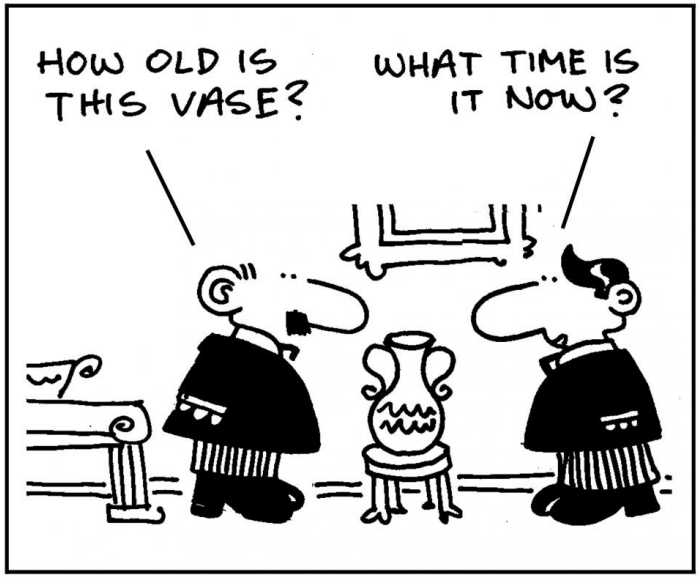
# *Model-Free Knockoffs*

*Joint with Janson, Fan and Lv*

# Knockoffs

*It's not a name brand bag*
*just a cheap knockoff*

Thesaurize.com



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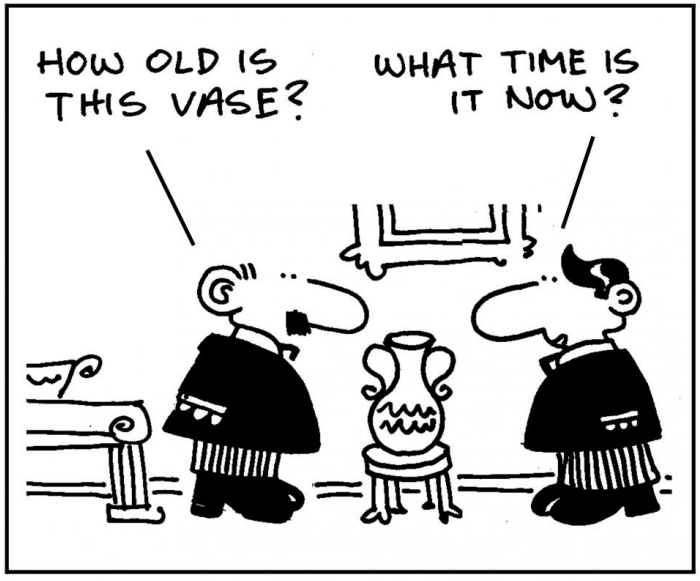


For each feature $X_j$, construct a knockoff version $\tilde{X}_j$
The knockoffs serve as a "control group" $\Rightarrow$ can estimate FDP

# Model-free knockoff variables

i.i.d. samples $(X^{(i)}, Y^{(i)}) \sim F_{XY}$

- Distribution of $X$ known
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(1) Pairwise exchangeability

$$(X, \tilde{X})_{\text{swap}(S)} \stackrel{d}{=} (X, \tilde{X})$$

e.g.

$$(X_1, X_2, X_3, \tilde{X}_1, \tilde{X}_2, \tilde{X}_3)_{\text{swap}(\{2,3\})} \stackrel{d}{=} (X_1, \tilde{X}_2, \tilde{X}_3, \tilde{X}_1, X_2, X_3)$$

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No need for new data or experiment

# Why?

Run same procedure on original and knockoff variables 'serving as controls'

$$\min_{\boldsymbol{b} \in \mathbb{R}^{2p}} \quad -\ell(\boldsymbol{y};\, [\boldsymbol{X}\ \tilde{\boldsymbol{X}}]\, \boldsymbol{b}) + \lambda \|\boldsymbol{b}\|_1$$

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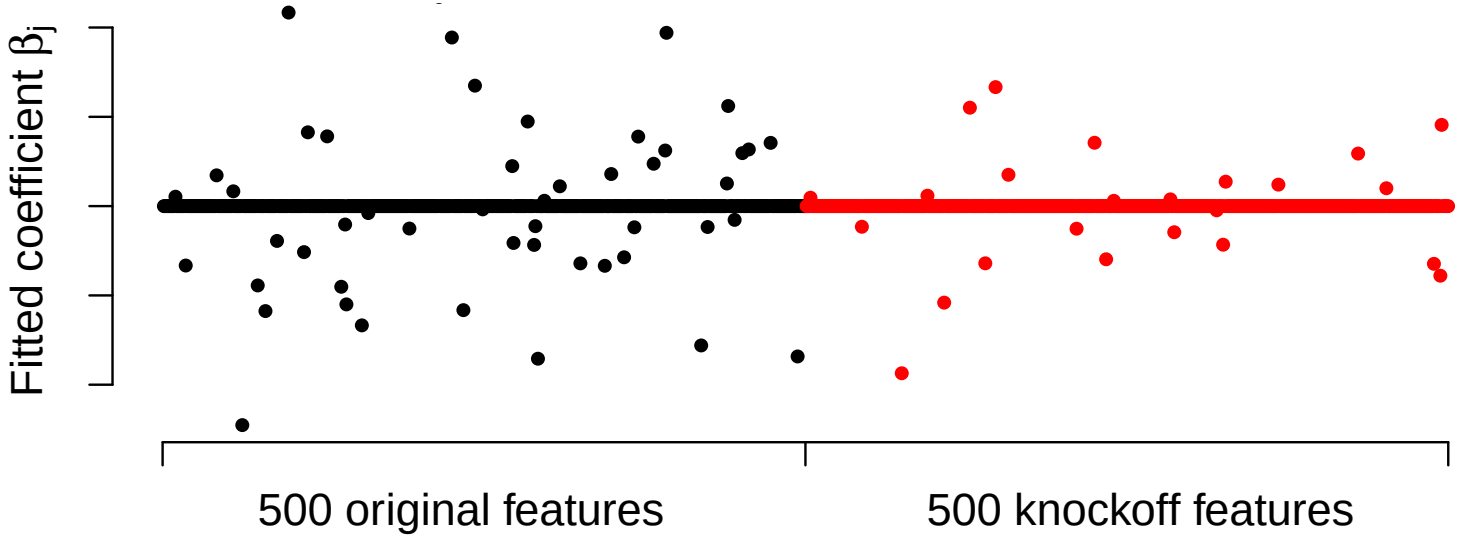


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$\Longrightarrow$ probably $\approx$ 24 false positives among 49 original features

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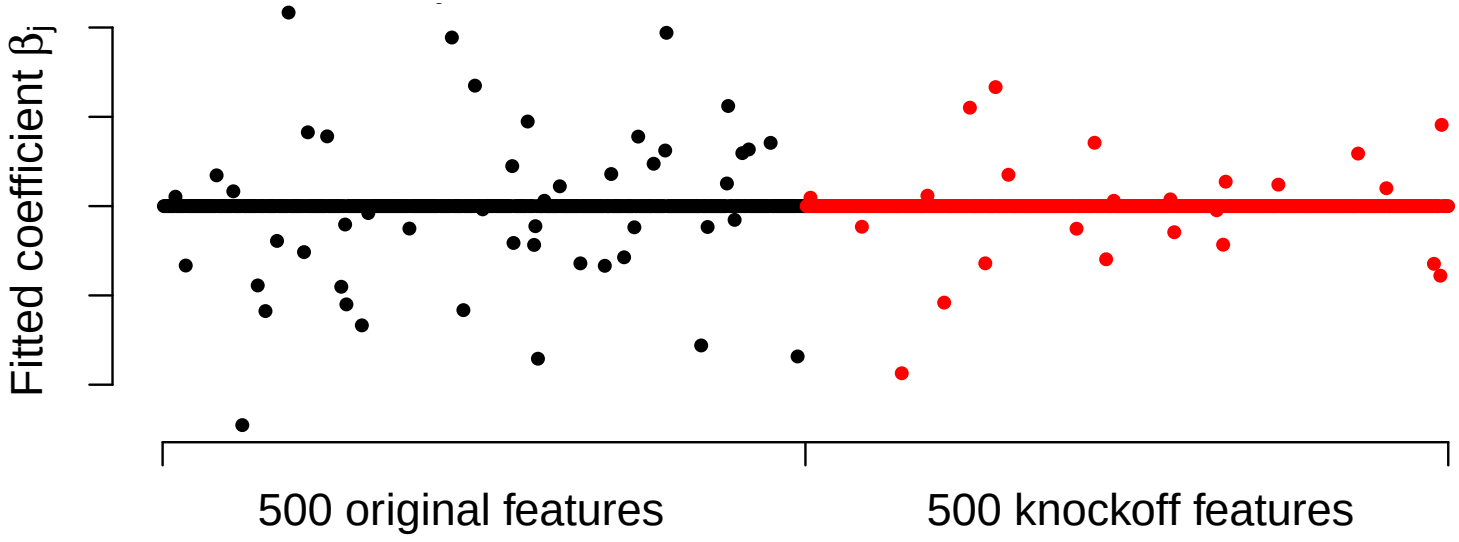


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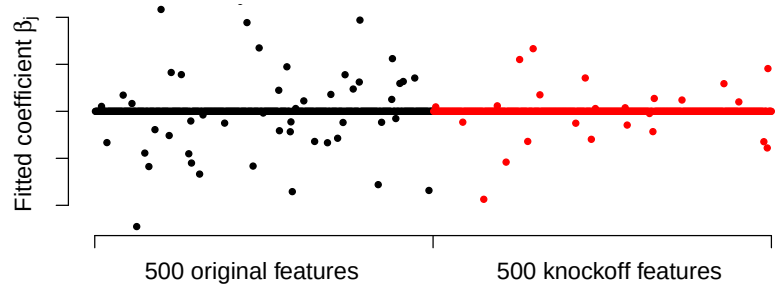

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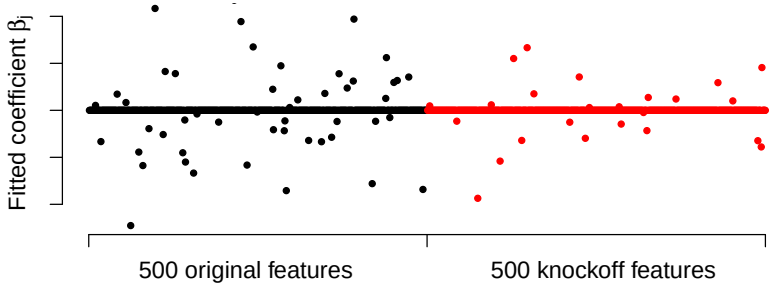
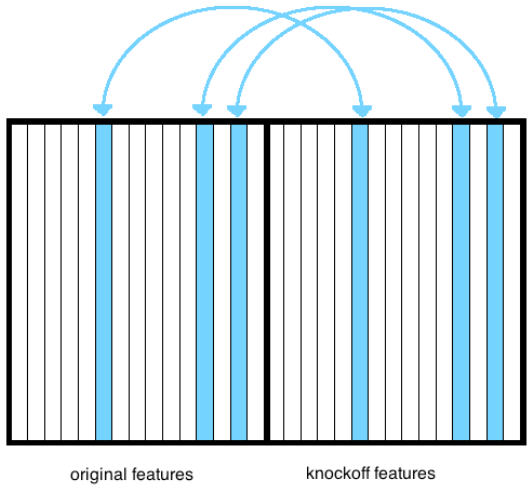



Swapping originals and knockoffs swaps the $Z$'s

$$\overbrace{(Z_1, \tilde{Z}_2, \tilde{Z}_3, \tilde{Z}_1, Z_2, Z_3)}^{(Z, \tilde{Z})_{\text{swap}\{2,3\}}} = z([\boldsymbol{X}, \tilde{\boldsymbol{X}}]_{\text{swap}\{2,3\}}, \boldsymbol{y})$$



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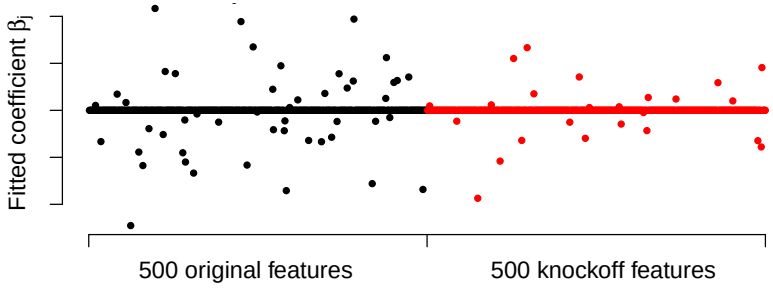


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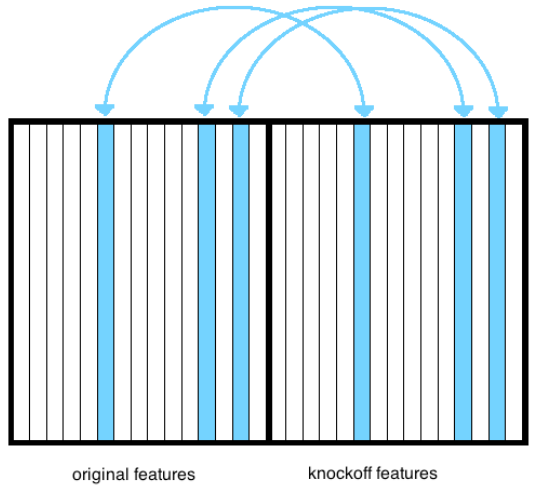


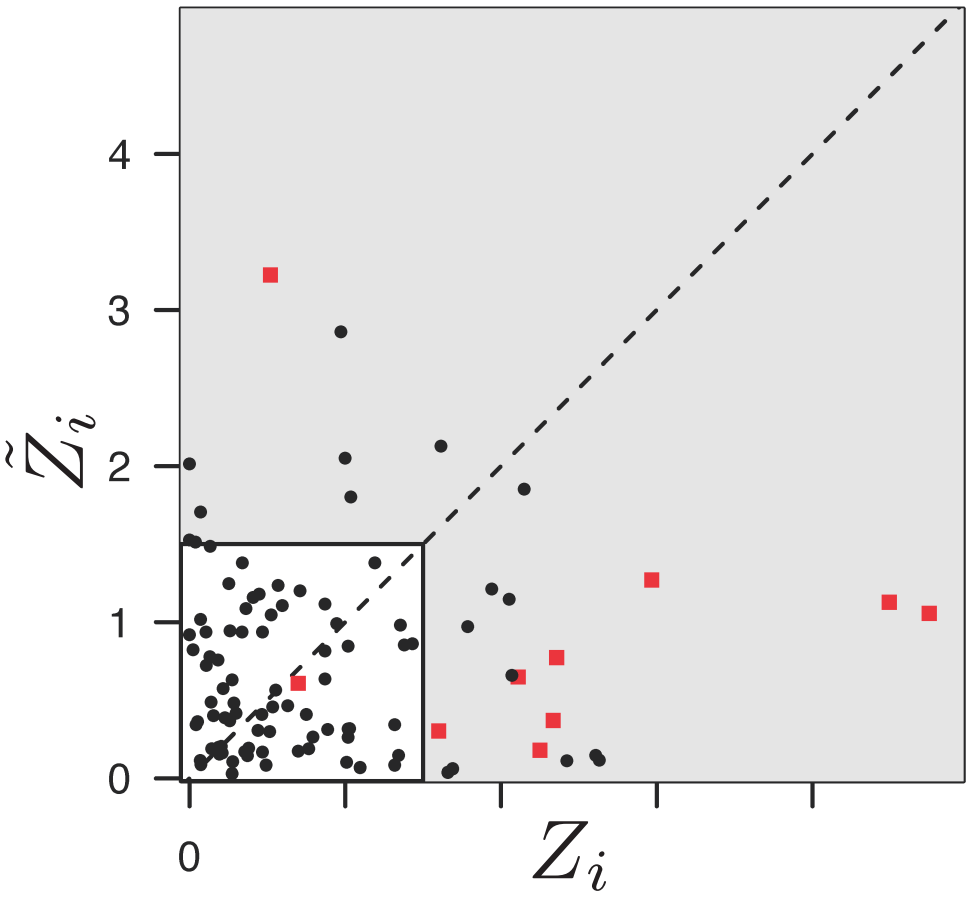

## Theorem (C., Fan, Janson Lv ('16))

*For any subset $\mathcal{T} \subset \mathcal{H}_0$ of nulls ($j \in \mathcal{H}_0$ iff $Y \perp\!\!\!\perp X_j \,|\, X_{-j}$)*

$$(Z, \tilde{Z})_{\text{swap}(\mathcal{T})} \stackrel{d}{=} (Z, \tilde{Z})$$

*This holds no matter the relationship between $Y$ and $X$*

# Exchangeability of the nulls




Signal
Null

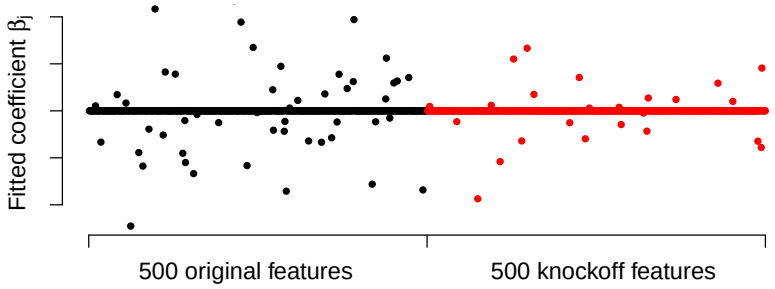
exchangeable

$$(Z_1, Z_2, Z_3, \ldots, Z_p, \tilde{Z}_1, \tilde{Z}_2, \tilde{Z}_3, \ldots, \tilde{Z}_p)$$

exchangeable

# Feature importance statistics

$$(\underbrace{Z_1, \ldots, Z_p}_{\text{originals}}, \underbrace{\tilde{Z}_1, \ldots, \tilde{Z}_p}_{\text{knockoffs}}) = z([\boldsymbol{X}, \tilde{\boldsymbol{X}}], \boldsymbol{y})$$




## Statistics $W_j$ (anti-symmetric)

$$W_j = W_j(Z_j, \tilde{Z}_j) \qquad W_j(\tilde{Z}_j, Z_j) = -W_j(Z_j, \tilde{Z}_j)$$

e.g. $W_j = Z_j - \tilde{Z}_j$

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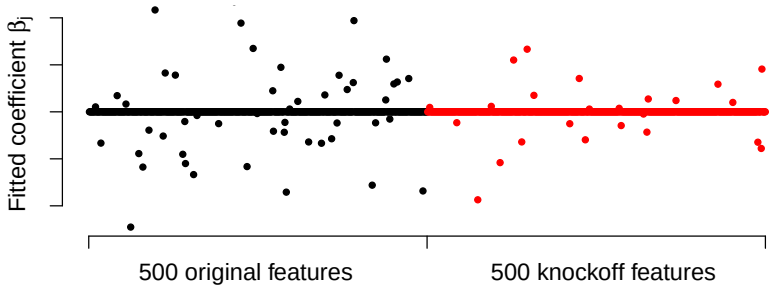


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- The null $W_j$'s are symmetrically distributed
- Conditional on $|W|$, the signs of the null $W_j$'s are i.i.d. coin flips

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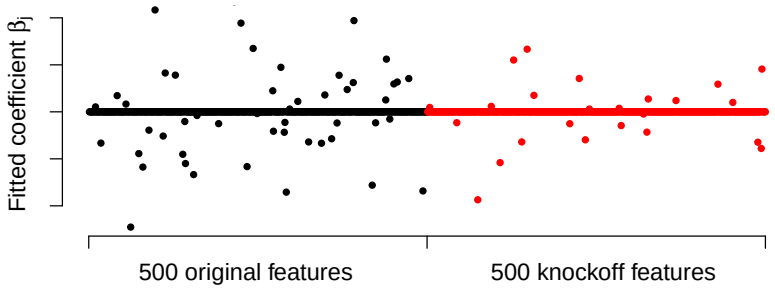


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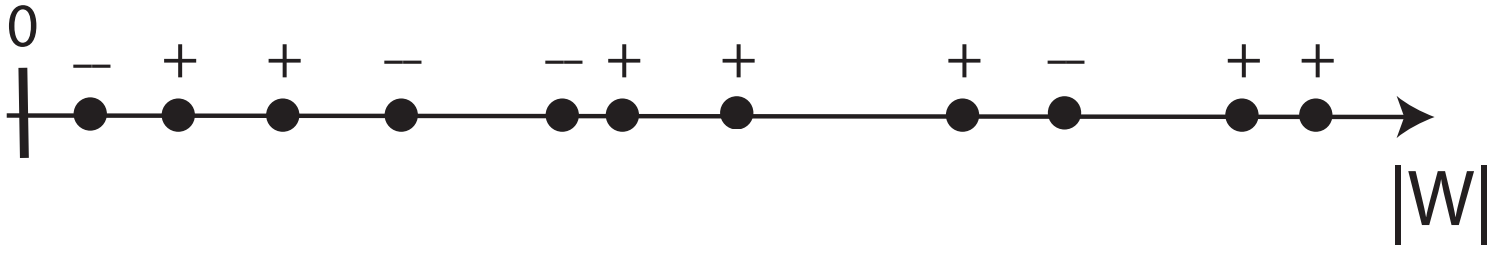
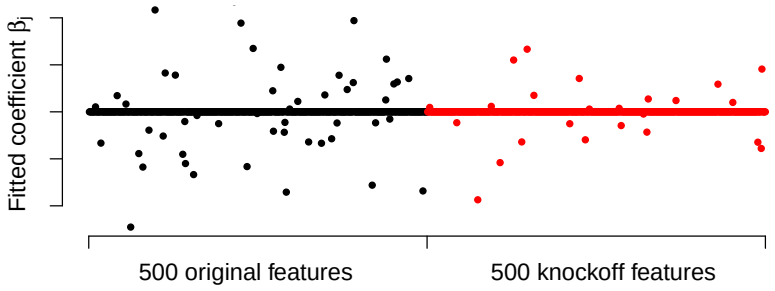


# Feature importance statistics

$$(\underbrace{Z_1, \ldots, Z_p}_{\text{originals}}, \underbrace{\tilde{Z}_1, \ldots, \tilde{Z}_p}_{\text{knockoffs}}) = z([\boldsymbol{X}, \tilde{\boldsymbol{X}}], \boldsymbol{y})$$

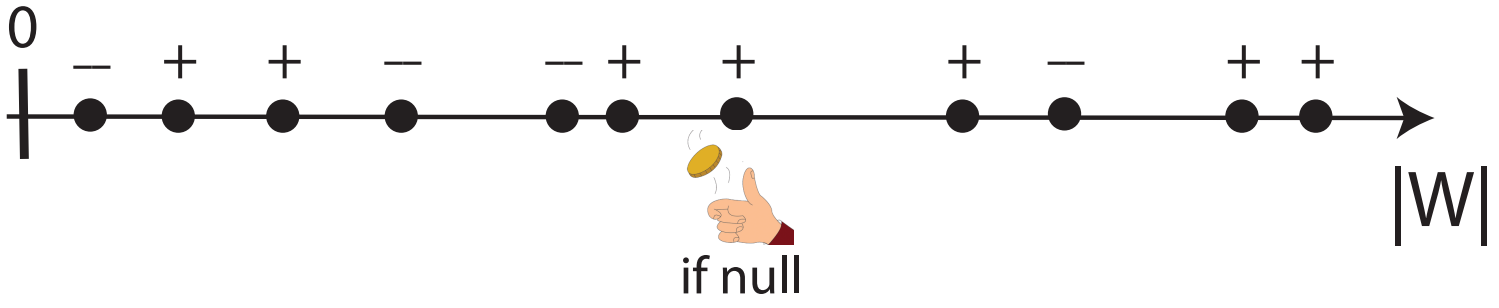



## Statistics $W_j$ (anti-symmetric)

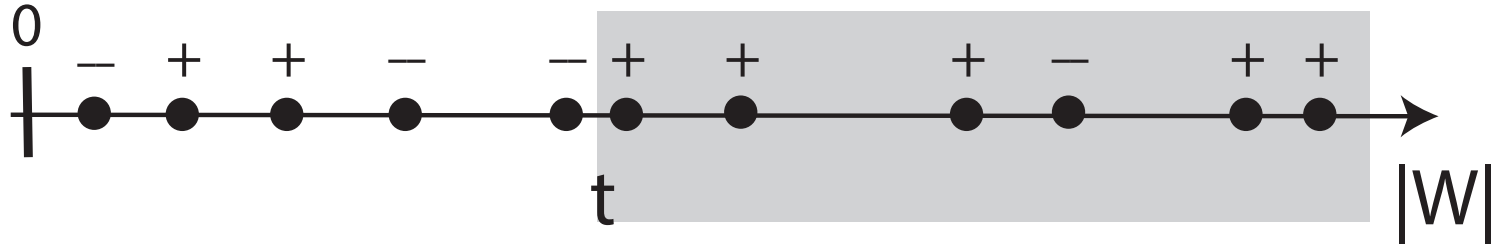
$$W_j = W_j(Z_j, \tilde{Z}_j) \qquad W_j(\tilde{Z}_j, Z_j) = -W_j(Z_j, \tilde{Z}_j)$$

e.g. $W_j = Z_j - \tilde{Z}_j$

- The null $W_j$'s are symmetrically distributed
- Conditional on $|W|$, the signs of the null $W_j$'s are i.i.d. coin flips



# Knockoff estimate of FDR




Interested in selecting $\{j : W_j \geq t\}$

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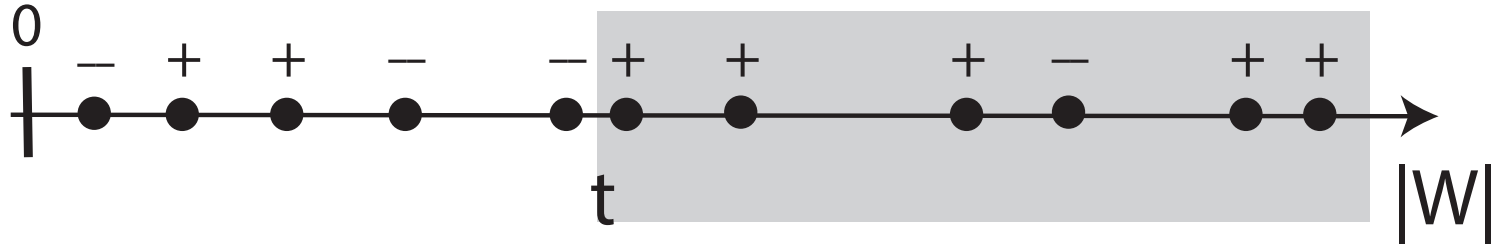


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$$\text{FDP}(t) = \frac{\#\{j \text{ null } : W_j \geq t\}}{\#\{j : W_j \geq t\} \vee 1}$$

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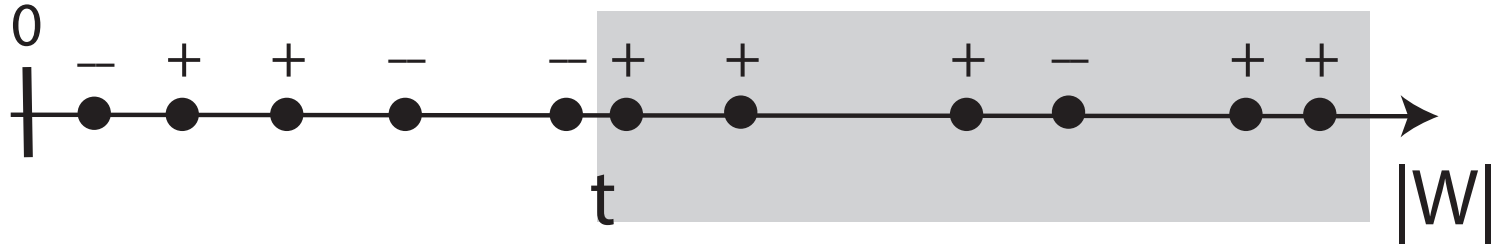


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$$\text{FDP}(t) = \frac{\#\{j \text{ null } : W_j \geq t\}}{\#\{j : W_j \geq t\} \vee 1} \approx \frac{\#\{j \text{ null } : W_j \leq -t\}}{\#\{j : W_j \geq t\} \vee 1}$$

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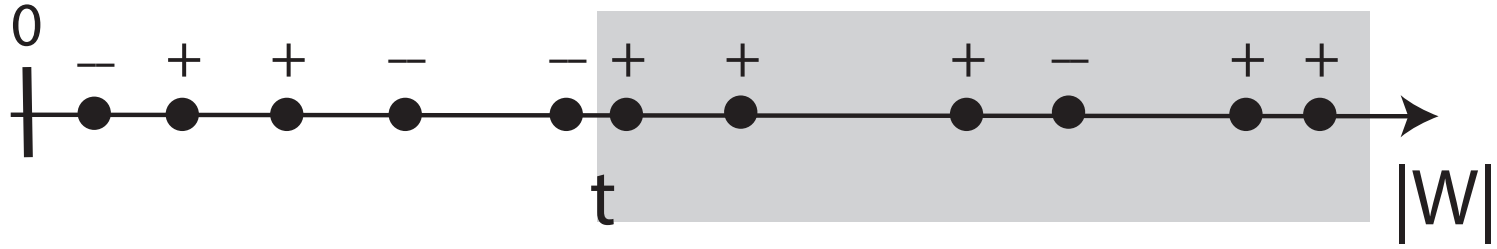


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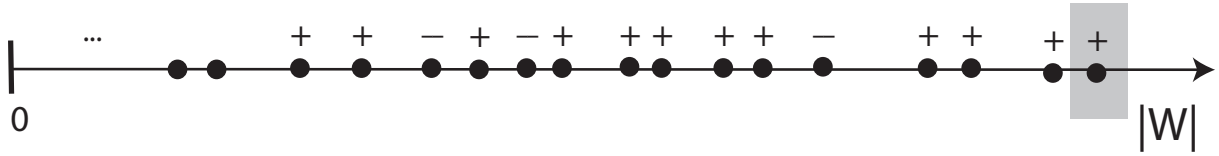
$$\leq \frac{\#\{j : W_j \leq -t\}}{\#\{j : W_j \geq t\} \vee 1} := \widehat{\mathsf{FDP}}(t)$$

# Selection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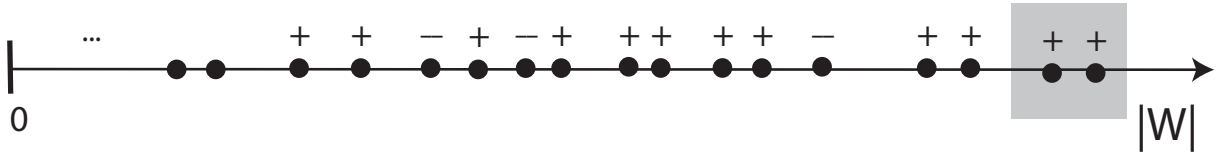
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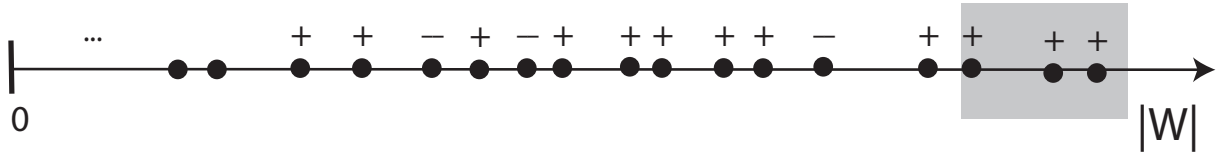
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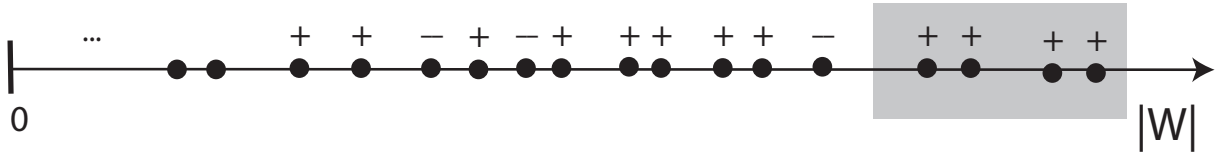
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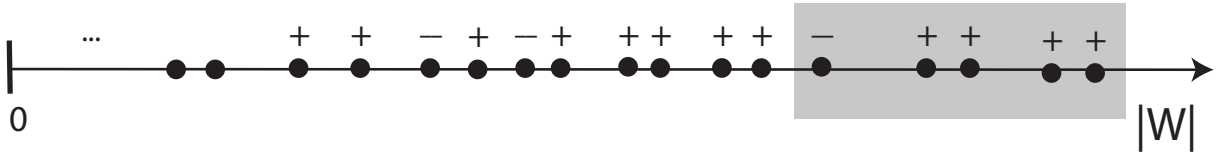
# Selection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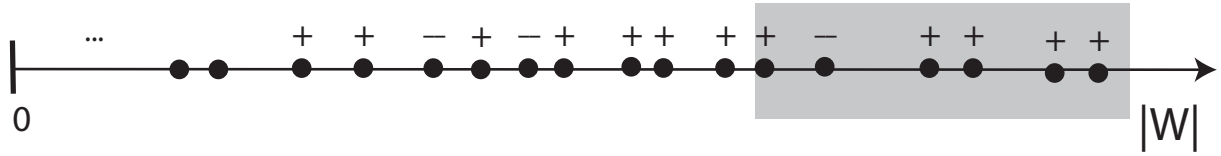
# Selection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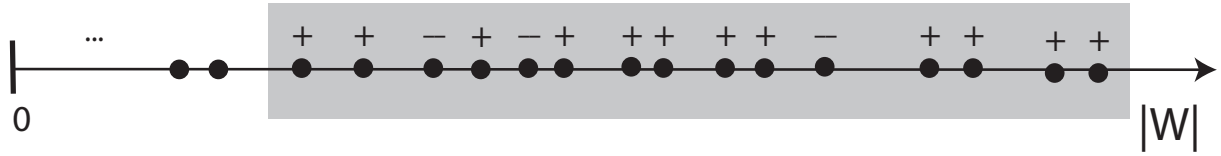
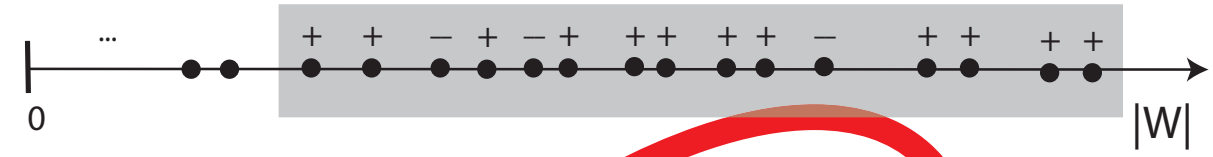
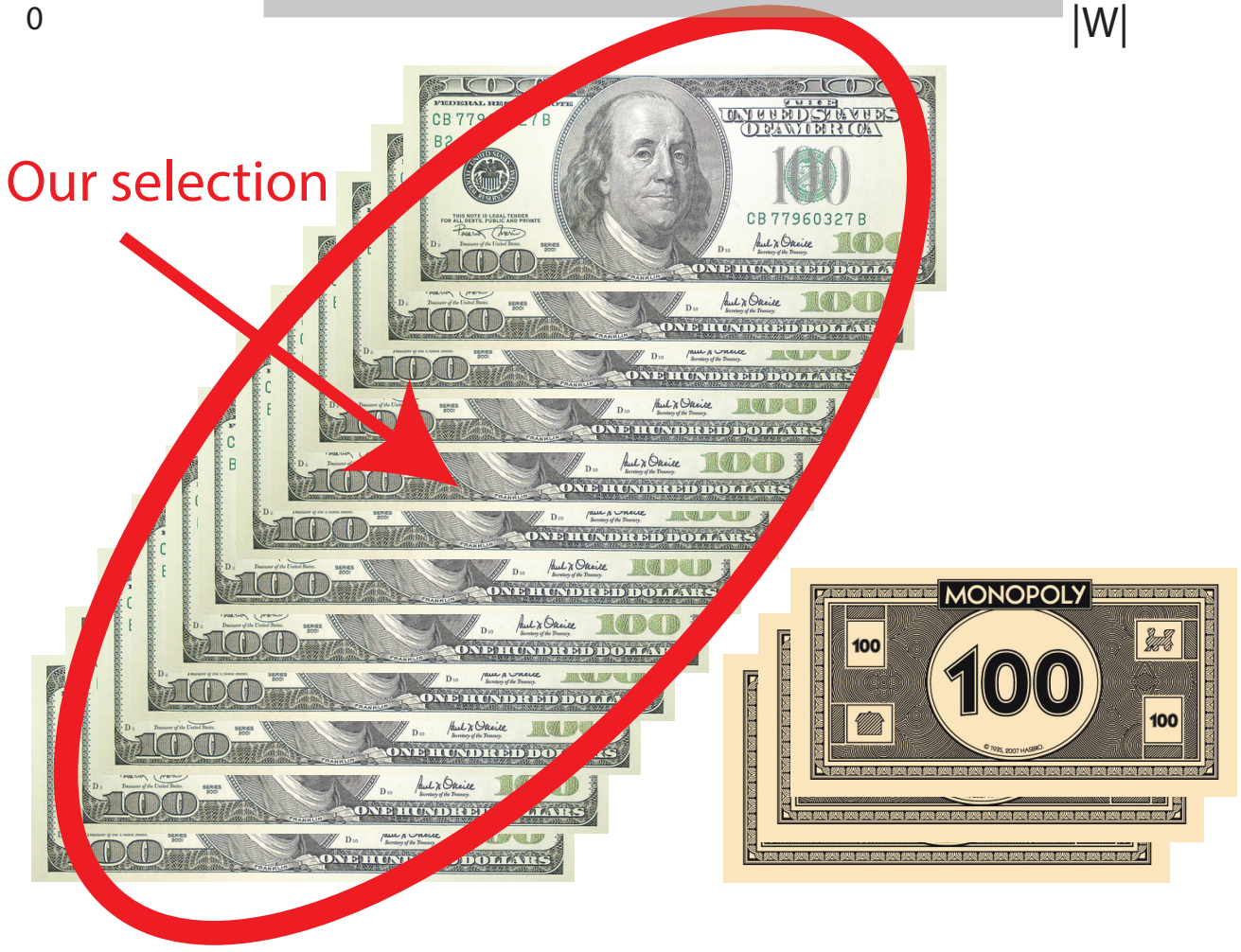




Stop last time ratio between '-' and '+' below target FDR level

# Selection



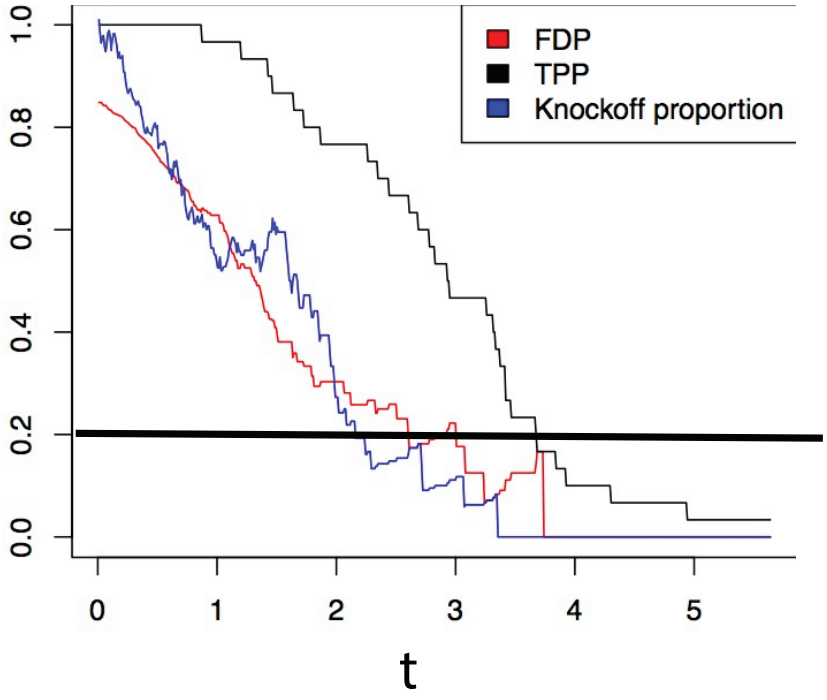

Select '+'s

# FDR control

$$N^{\pm}(t) = \#\{j : |W_j| \geq t \text{ and } \operatorname{sgn}(W_j) = \pm\}$$

$$T = \min\left\{t : \widehat{\mathsf{FDP}}(t) = \frac{1+N^{-}(t)}{1 \vee N^{+}(t)} \leq q\right\}$$

$$\hat{\mathcal{S}} = \{W_j \geq T\}$$



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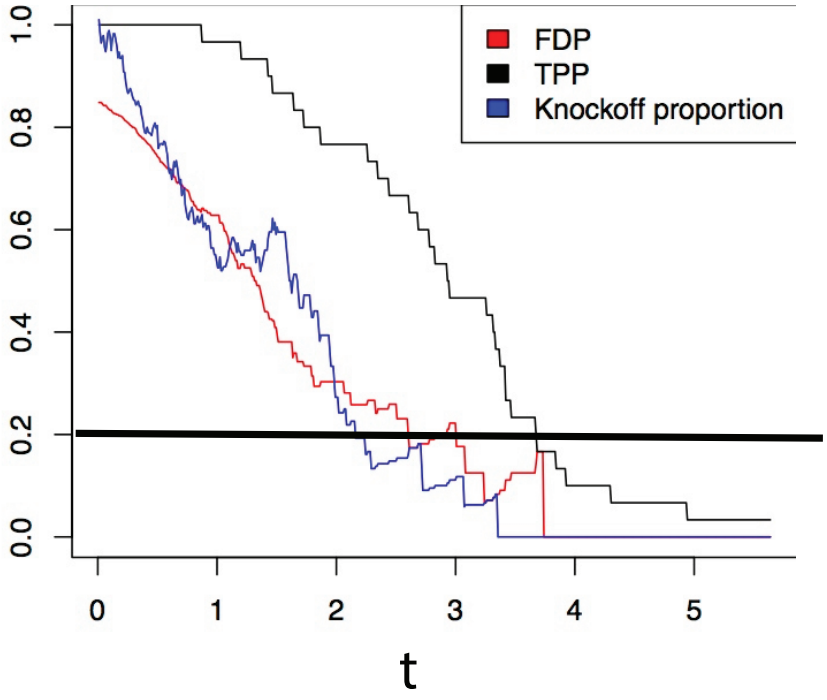


## Theorem

- *Knockoff*

$$\mathbb{E}\left[\frac{V}{R + q^{-1}}\right] \leq q$$

$V$ : # false positives
$R$ : total # of selections

- *Knockoff+*

$$\mathbb{E}\left[\frac{V}{R \vee 1}\right] \leq q$$

# Not just dummy variables

For linear models, A.J. Miller ('84) creates "dummy" variables whose entries are drawn i.i.d. at random

- Forward selection procedure is applied to augmented list of variables
- Stop when selects a dummy variable for the first time

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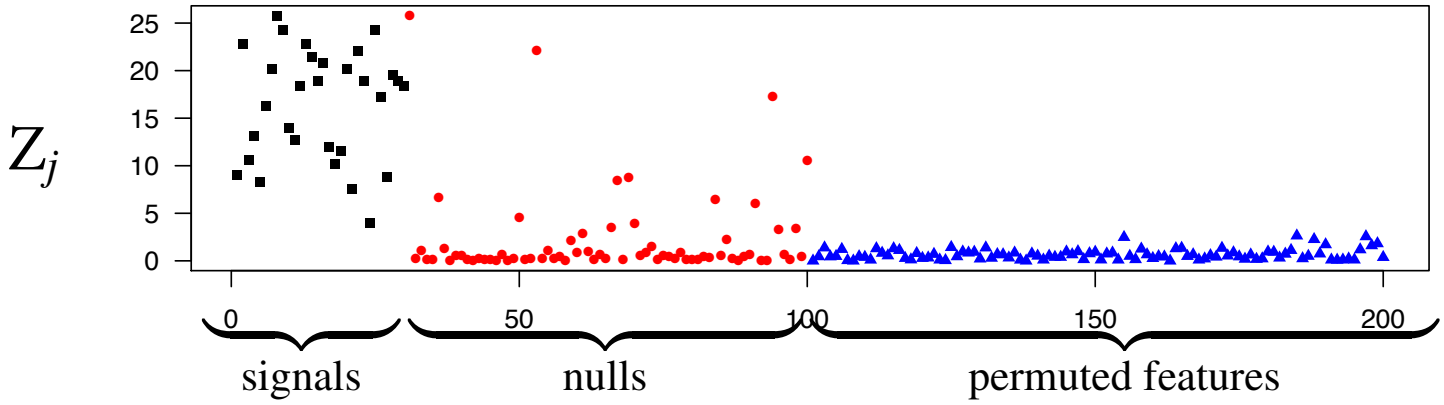
Importance statistics for originals and dummies




Dummies cannot serve as controls

# Towards pairwise exchangeability

To serve as controls, pairwise correlations need to be preserved

$$\mathrm{Cov}(X_i, X_j) = \mathrm{Cov}(\tilde{X}_i, X_j) \quad i \neq j$$

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For non-linear models, want something like

$$X_i \,|\, X_{-i} \quad \stackrel{d}{=} \quad \tilde{X}_i \,|\, X_{-i}$$

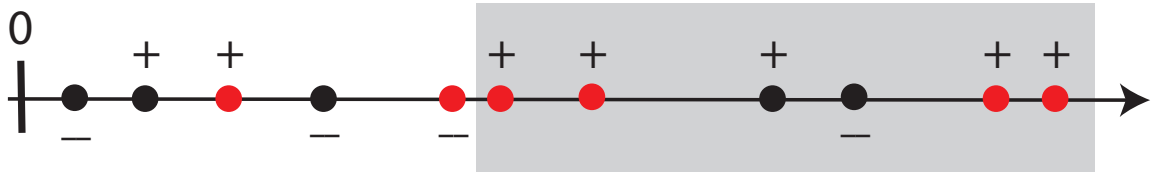
Implied by

$$(X, \tilde{X})_{\mathsf{swap}(S)} \quad \stackrel{d}{=} \quad (X, \tilde{X})$$

*Martingales: for Mathematicians... (Hopefully)*

# Why does all this work?

$$T = \min\left\{t : \frac{1+|\mathcal{S}^-(t)|}{|\mathcal{S}^+(t)| \vee 1} \leq q\right\} \qquad \begin{aligned}\mathcal{S}^+(t) &= \{j : W_j \geq t\} \\ \mathcal{S}^-(t) &= \{j : W_j \leq -t\}\end{aligned}$$



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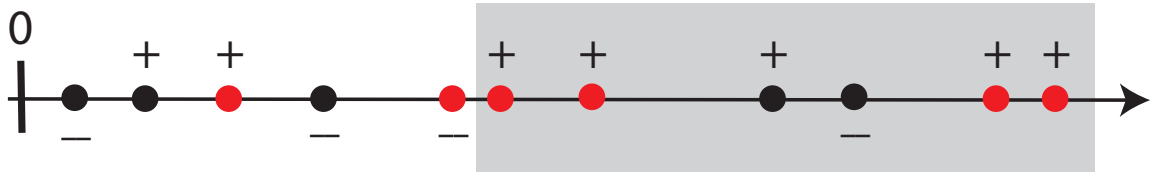


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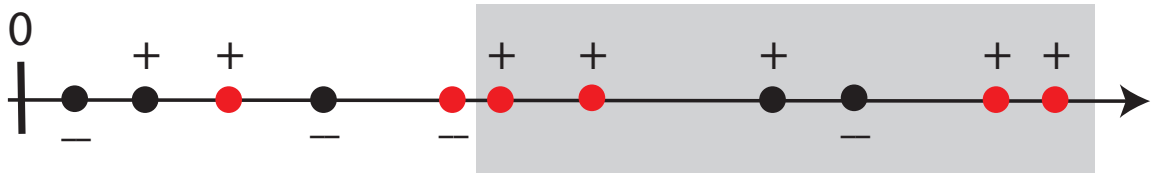


$$\mathsf{FDP}(t) = \frac{\#\{j \text{ null} : j \in \mathcal{S}^+(t))\}}{\#\{j : j \in \mathcal{S}^+(t)\} \vee 1} \cdot \frac{1 + \#\{j \text{ null} : j \in \mathcal{S}^-(t)\}}{1 + \#\{j \text{ null} : j \in \mathcal{S}^-(t)\}}$$

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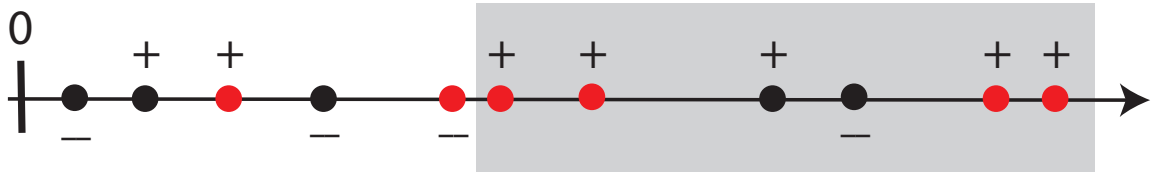


$$\mathsf{FDP}(t) \leq q \cdot \frac{\overbrace{\#\{j \text{ null} : j \in \mathcal{S}^+(t)\}}^{V^+(t)}}{1 + \underbrace{\#\{j \text{ null} : j \in \mathcal{S}^-(t)\}}_{V^-(t)}}$$

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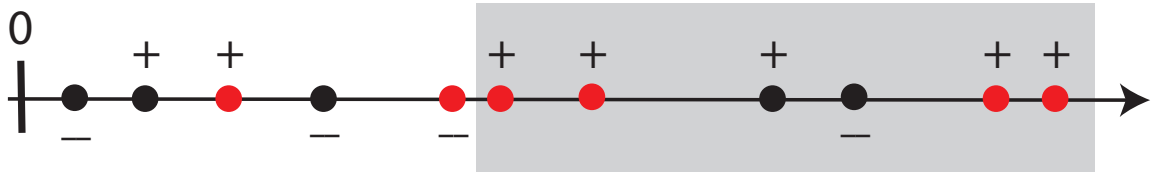


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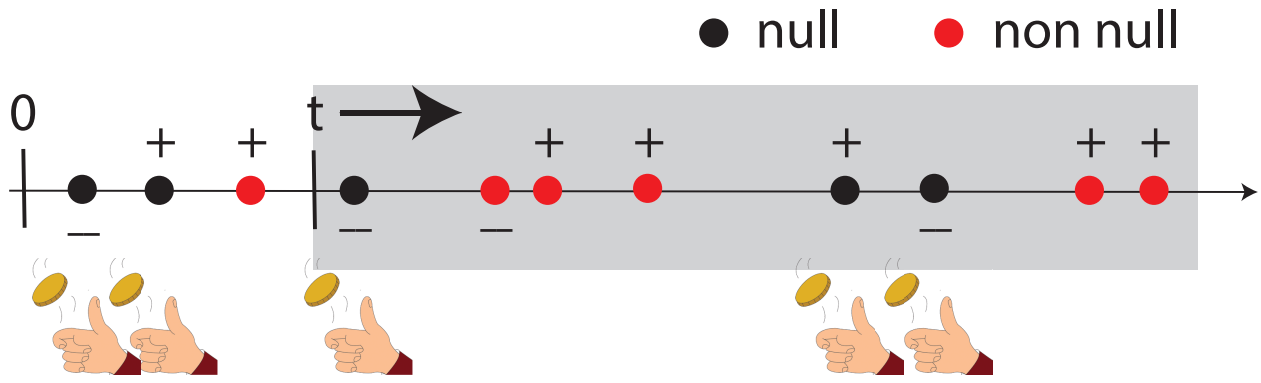
- $V^+(t)/(1+V^-(t))$ is a super-martingale w.r.t. well defined filtration
- $T$ is stopping time

# Optional stopping time theorem




$$\text{FDR} \leq q\, \mathbb{E}\left[\frac{V^+(T)}{1+V^-(T)}\right]$$

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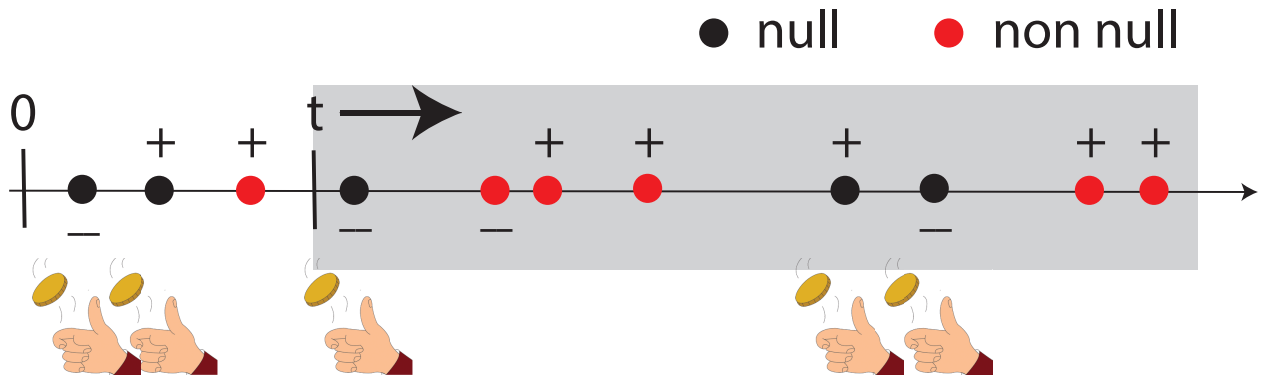


$$\text{FDR} \leq q\ \mathbb{E}\left[\frac{V^+(T)}{1+V^-(T)}\right] \leq q\ \mathbb{E}\left[\frac{V^+(0)}{1+V^-(0)}\right]$$

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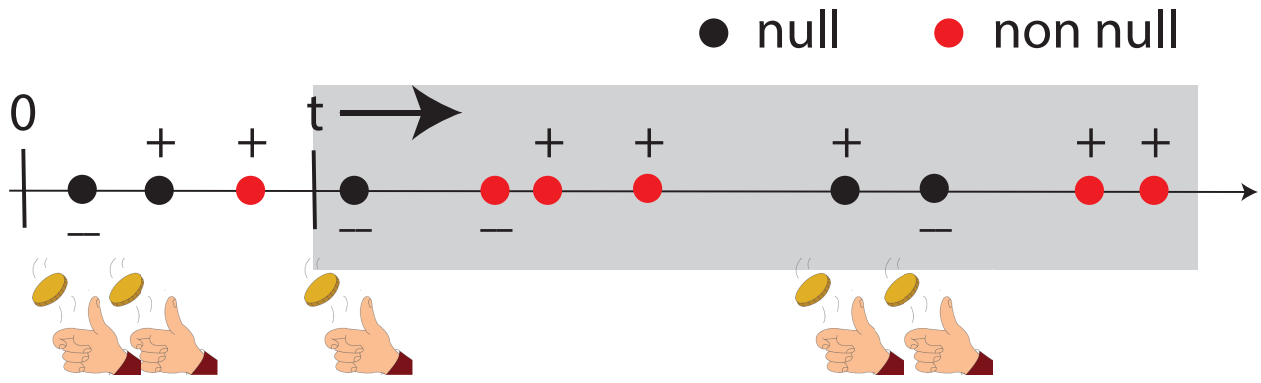


$$\text{FDR} \leq q\ \mathbb{E}\left[\frac{V^+(T)}{1+V^-(T)}\right] \leq q\ \mathbb{E}\left[\frac{V^+(0)}{1+V^-(0)}\right] = q\ \mathbb{E}\left[\frac{\overbrace{V^+(0)}^{\text{Ber}(\#\text{nulls},1/2)}}{1+\#\text{nulls}-V^+(0)}\right]$$

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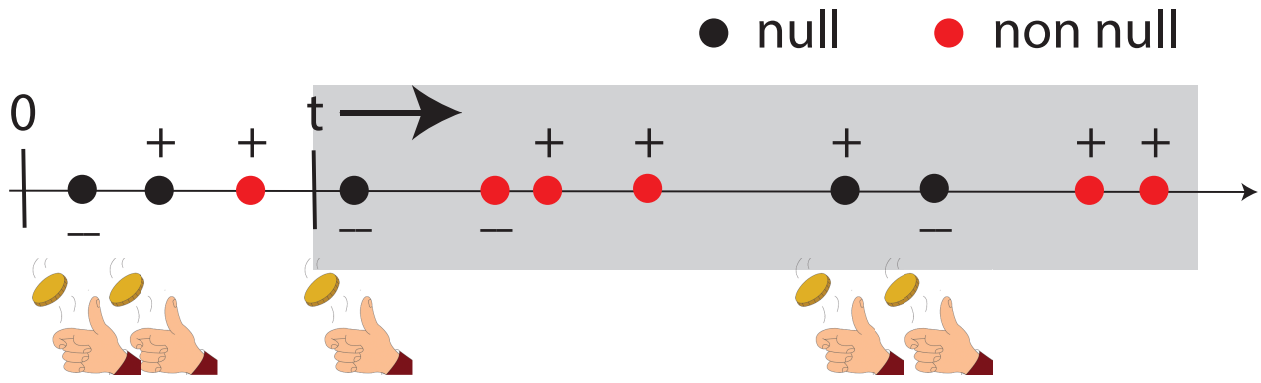


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# *Some Remarks*

# Panning for gold

- Thousands/millions of variables
- No idea how response depends on all of these

Model-free knockoff filters controls FDR

$$\text{FDR} = \mathbb{E}\,\frac{\#\text{ variables falsely selected}}{\text{total }\#\text{ of selections}}$$

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Pros:

- No parameters
- No p-values
- Holds for finite samples
- No matter the dependence between $Y$ and $X$
- No matter the dimensionality

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Pros:

- No parameters
- No p-values
- Holds for finite samples
- No matter the dependence between $Y$ and $X$
- No matter the dimensionality

Cons: Need to know something about the distribution of covariates

# Obstacles to obtaining p-values

$$Y \mid X \sim \text{Bernoulli}(\text{logit}(X^\top \beta))$$

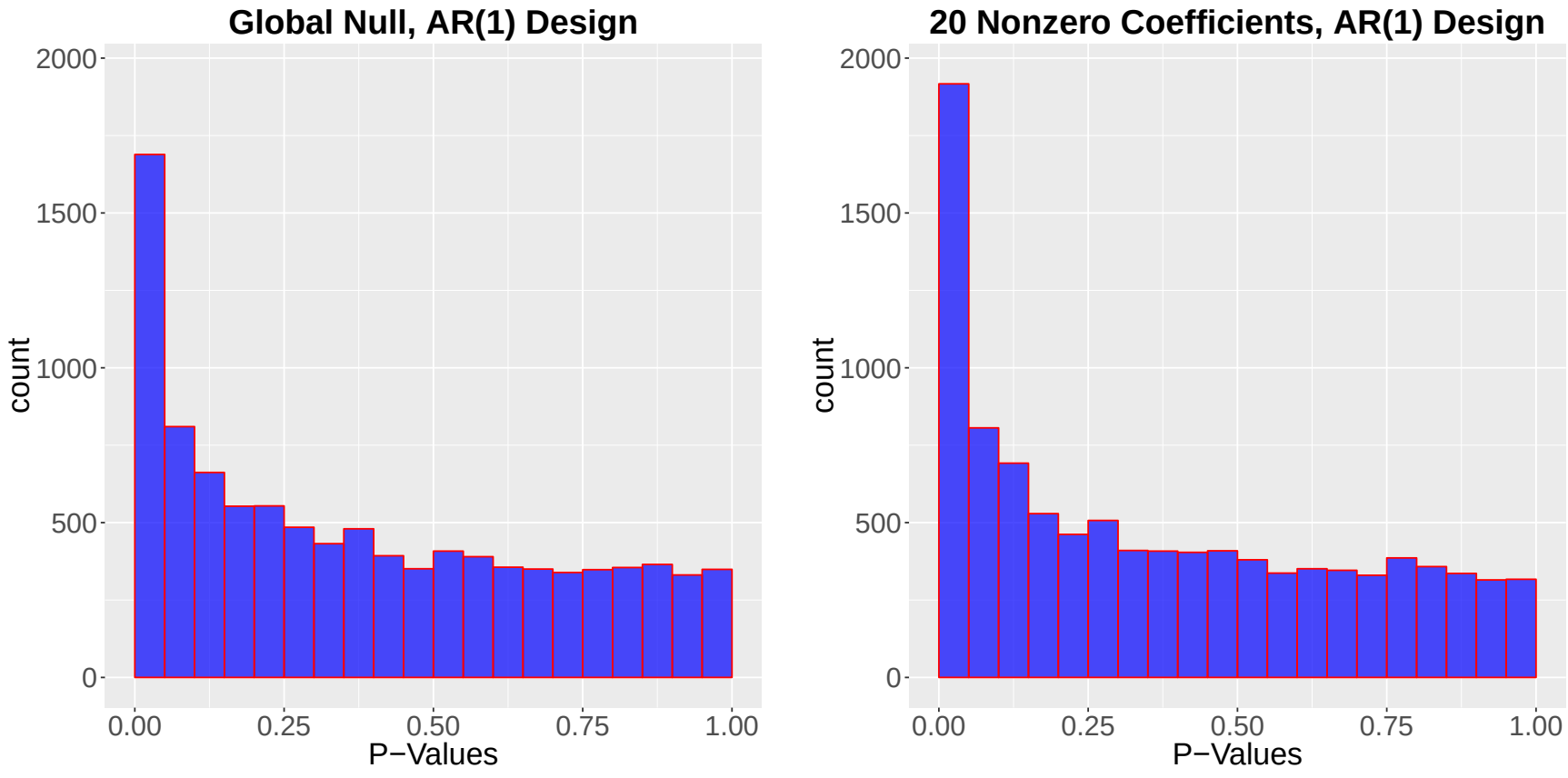


Figure: Distribution of null logistic regression p-values with $n = 500$ and $p = 200$

# Obstacles to obtaining p-values

| $\mathbb{P}\{p\text{-val} \leq \ldots\%\}$ | Sett. (1) | Sett. (2) | Sett. (3) | Sett. (4) |
|---|---|---|---|---|
| 5% | 16.89% (0.37) | 19.17% (0.39) | 16.88% (0.37) | 16.78% (0.37) |
| 1% | 6.78% (0.25) | 8.49% (0.28) | 7.02% (0.26) | 7.03% (0.26) |
| 0.1% | 1.53% (0.12) | 2.27% (0.15) | 1.87% (0.14) | 2.04% (0.14) |

Table: Inflated p-value probabilities with estimated Monte Carlo SEs

# Relationship with classical setup

| Classical | MF Knockoffs |
| --- | --- |

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| Classical | MF Knockoffs |
| --- | --- |
| Observations of $X$ are fixed<br>Inference is conditional on obs. values | Observations of $X$ are random[1] |

1 Often appropriate in 'big' data apps: e.g. SNPs of subjects randomly sampled

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| Classical | MF Knockoffs |
|---|---|
| Observations of $X$ are fixed<br>Inference is conditional on obs. values | Observations of $X$ are random[1] |
| Strong model linking $Y$ and $X$ | Model free[2] |

1. Often appropriate in 'big' data apps: e.g. SNPs of subjects randomly sampled
2. Shifts the 'burden' of knowledge

# Relationship with classical setup

| Classical | MF Knockoffs |
|---|---|
| Observations of $X$ are fixed<br>Inference is conditional on obs. values | Observations of $X$ are random[1] |
| Strong model linking $Y$ and $X$ | Model free[2] |
| Useful inference even if model inexact | Useful inference even if model inexact[3] |

1. Often appropriate in 'big' data apps: e.g. SNPs of subjects randomly sampled
2. Shifts the 'burden' of knowledge
3. More later

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Different from knockoffs of Foygel Barber and C. (2015)

Must always have

$$\mathbb{E}\, X = \mathbb{E}\, \tilde{X} \qquad \mathrm{Cov}(X, \tilde{X}) = **$$

Knockoffs obeying this only $\longrightarrow$ *second-order knockoffs*

# *Some Examples*

# Logistic model with dependent covariates

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$$W_j = Z_j - \tilde{Z}_j$$

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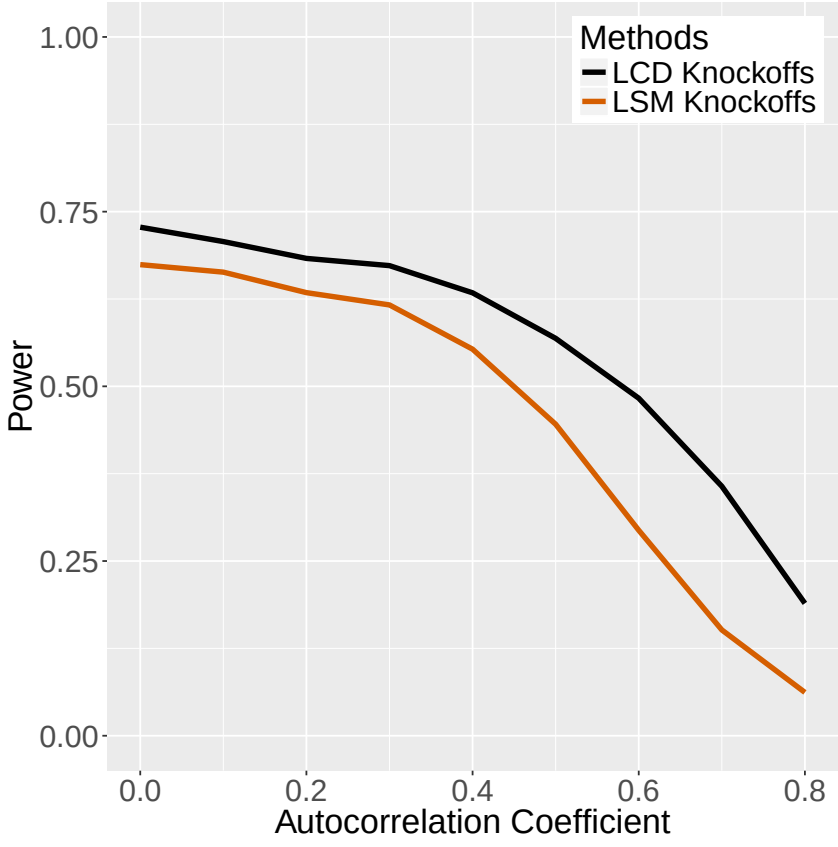


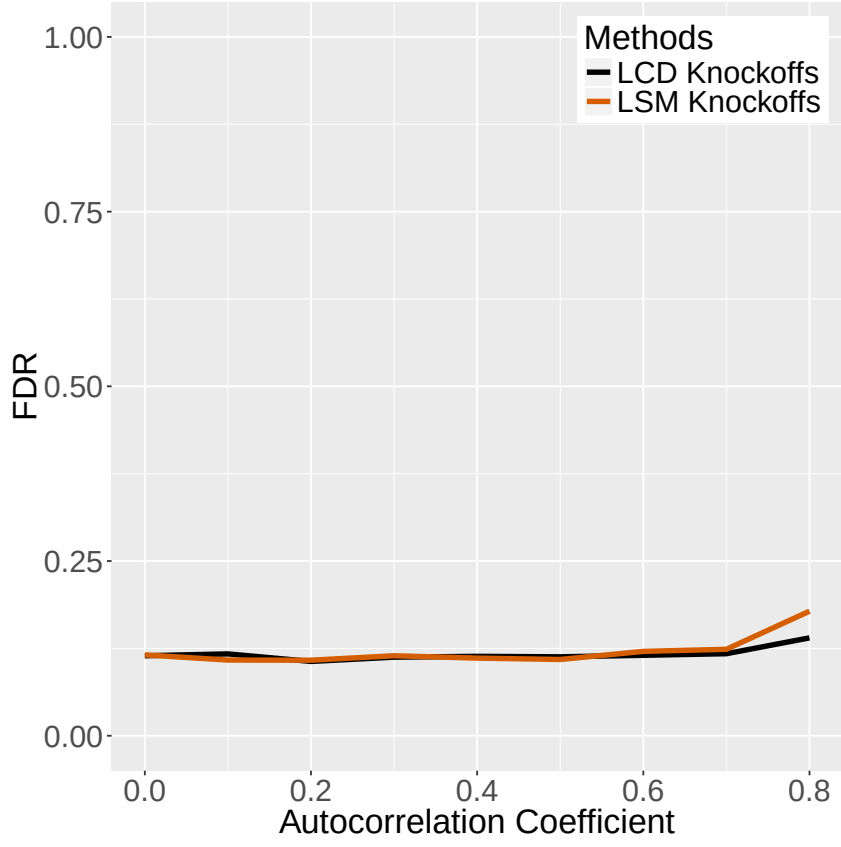


Figure: $n = 3000$, $p = 1000$, 60 regression coeffs. of magnitude 3.5 and random signs

# Bayesian knockoff statistics

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BVS (Bayesian variable selection)

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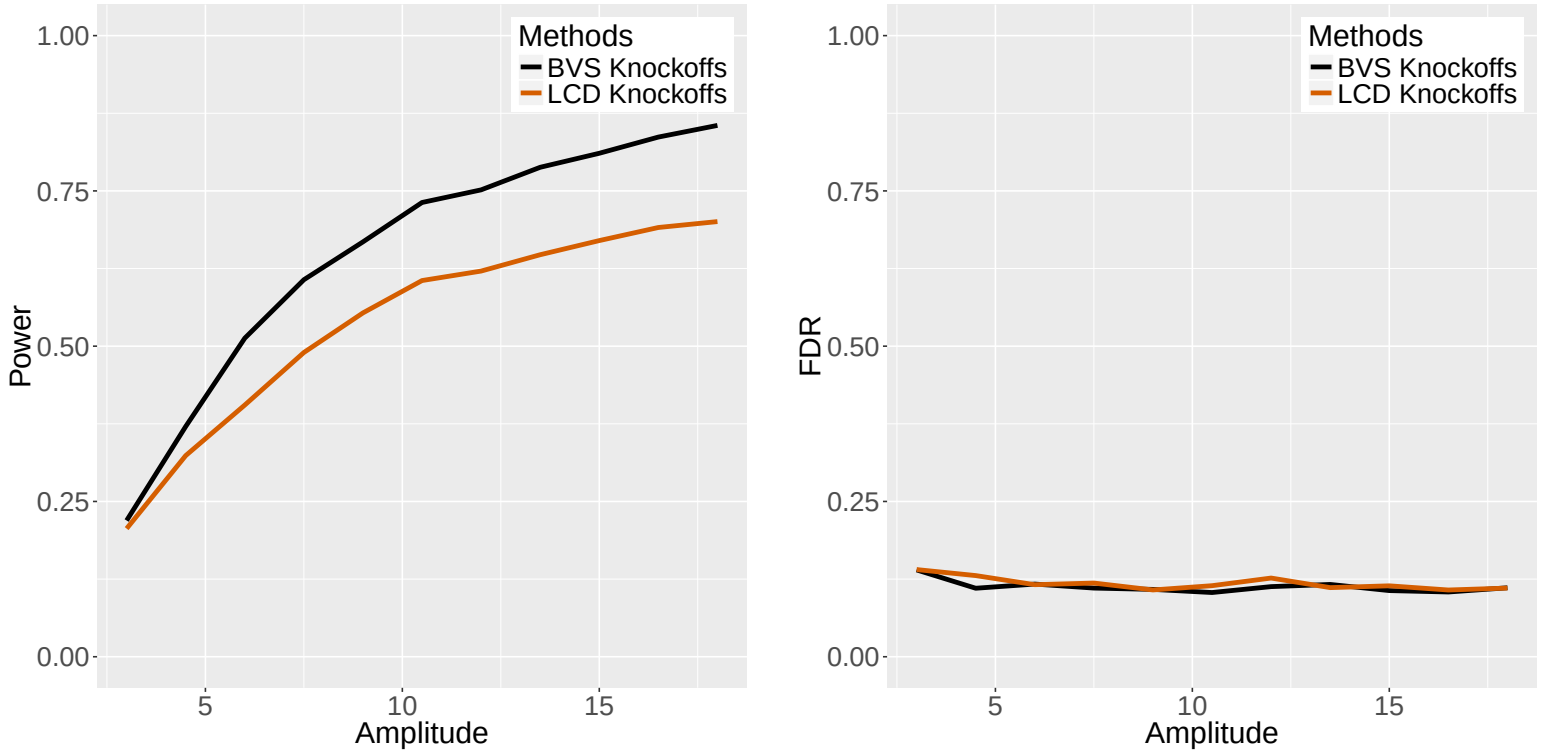


Figure: $n = 300$, $p = 1000$ and Bayesian linear model with 60 expected variables

Inference is correct even if prior is wrong or MCMC has not converged

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e.g. $Z_j$ $=$ absolute value of LASSO coeff.
or
some random forest feature importance
depending on which model has lower CV error

# Power comparisons: linear model with indep. covariates

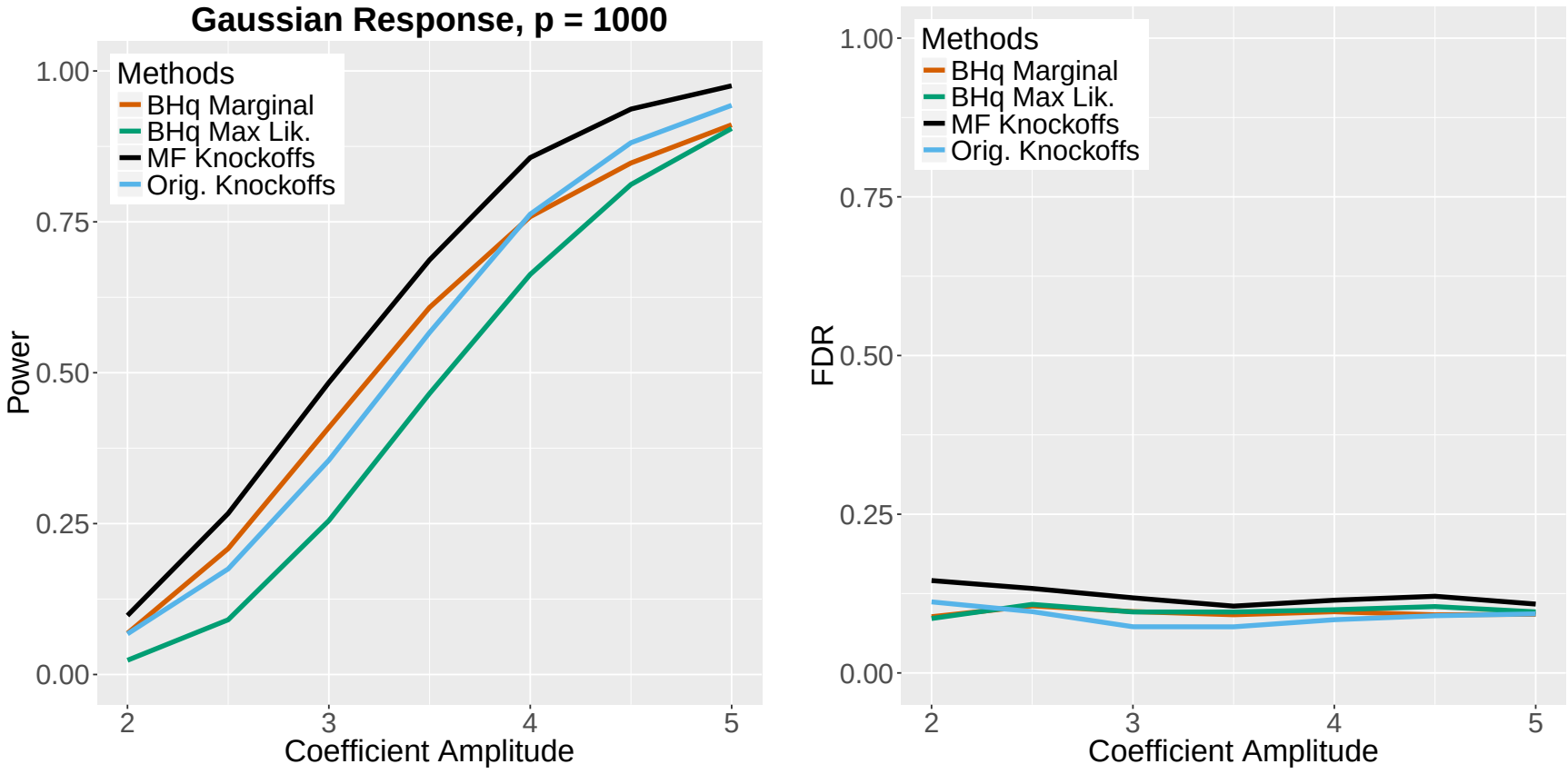


Figure: Low-dimensional setting: $n = 3000$, $p = 1000$

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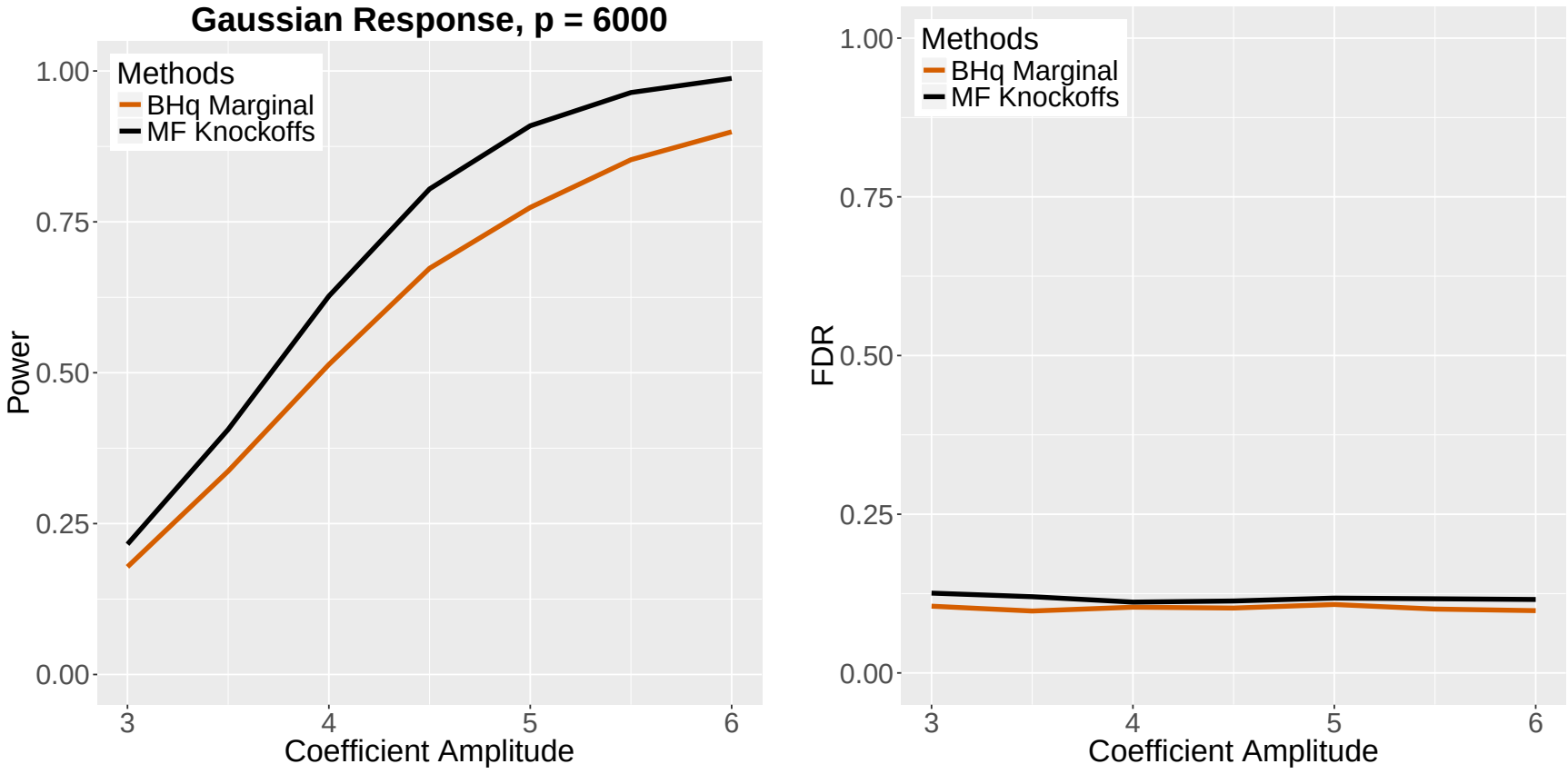


Figure: High-dimensional setting: $n = 3000$, $p = 6000$

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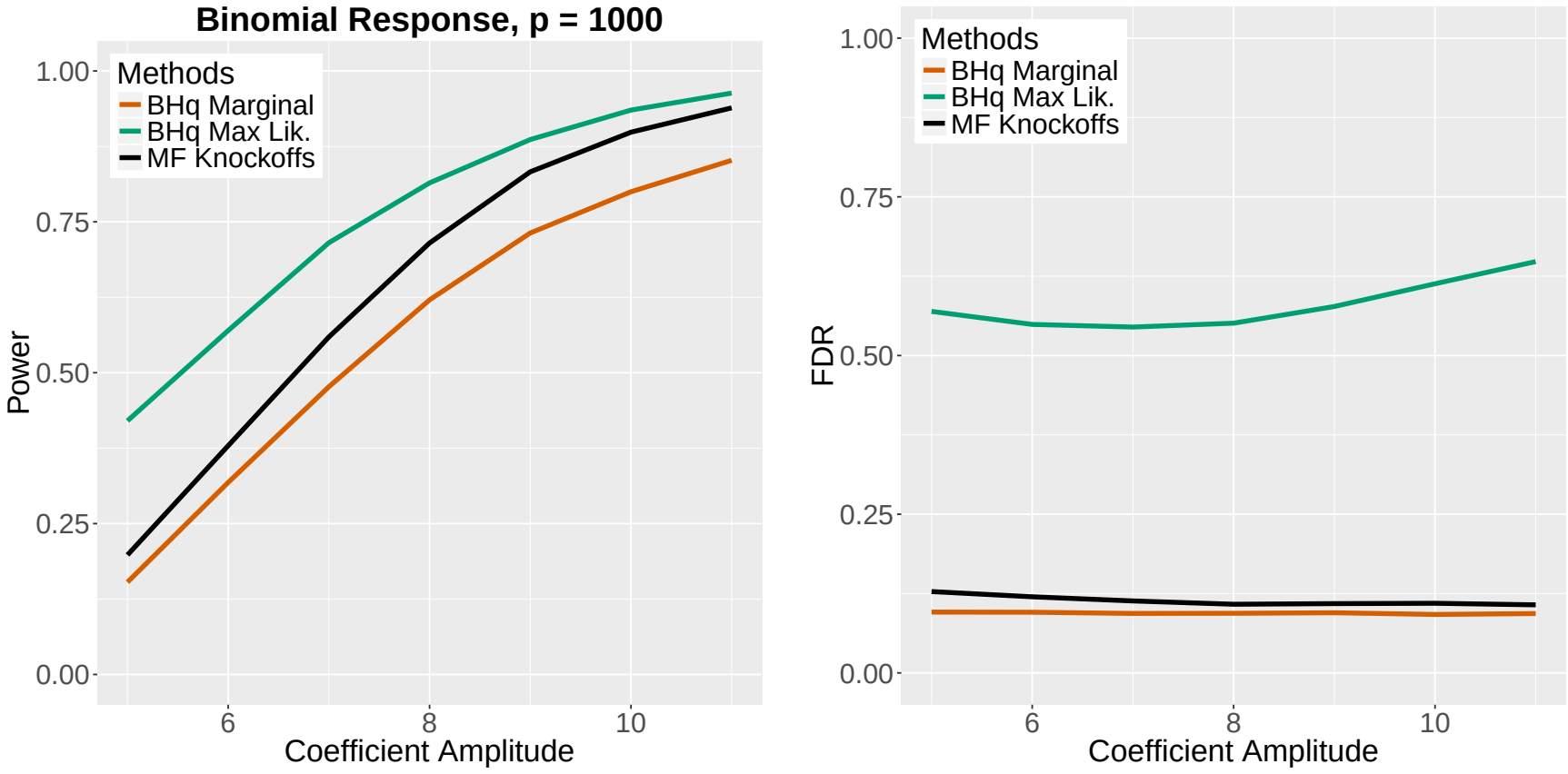


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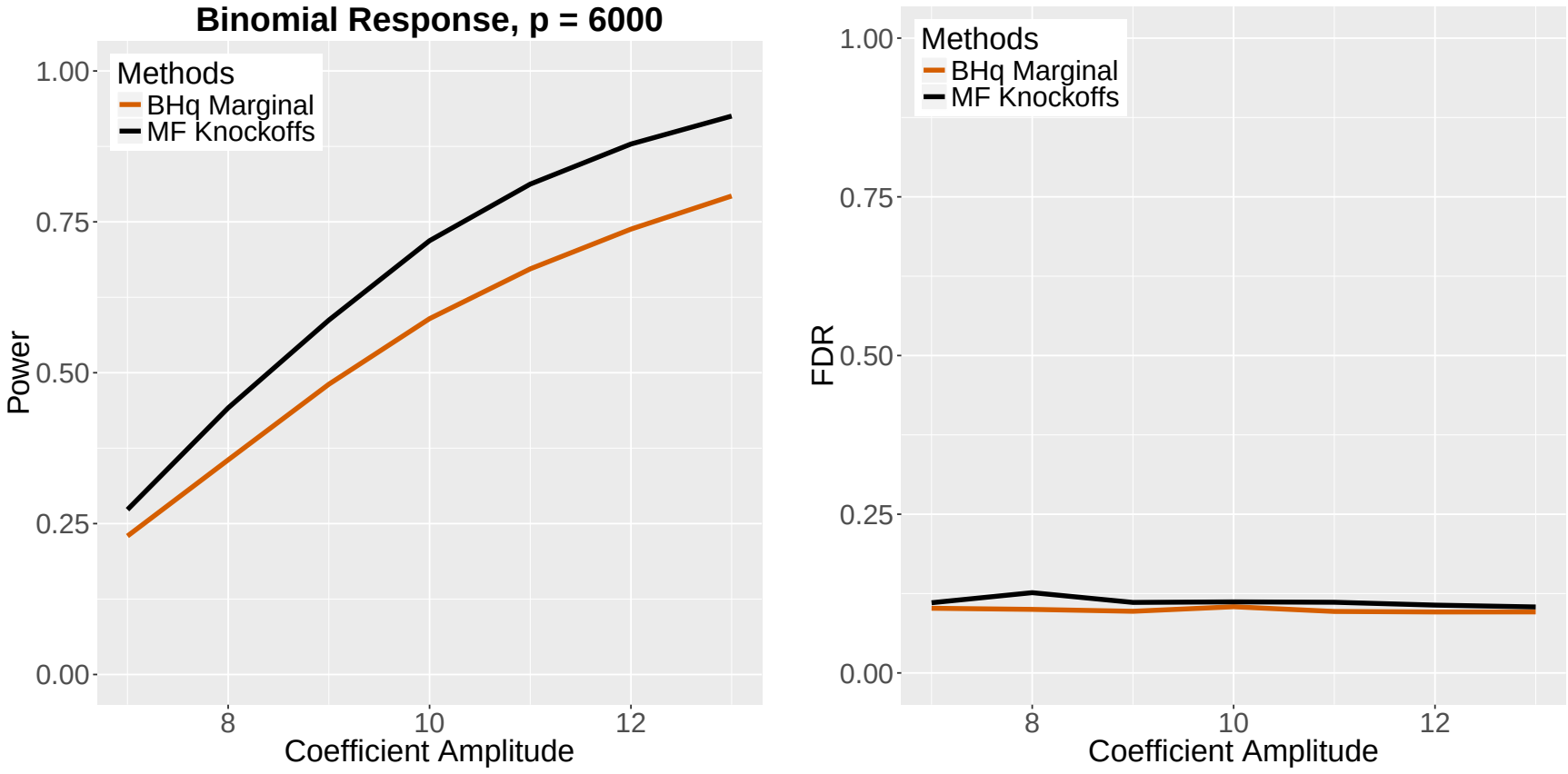


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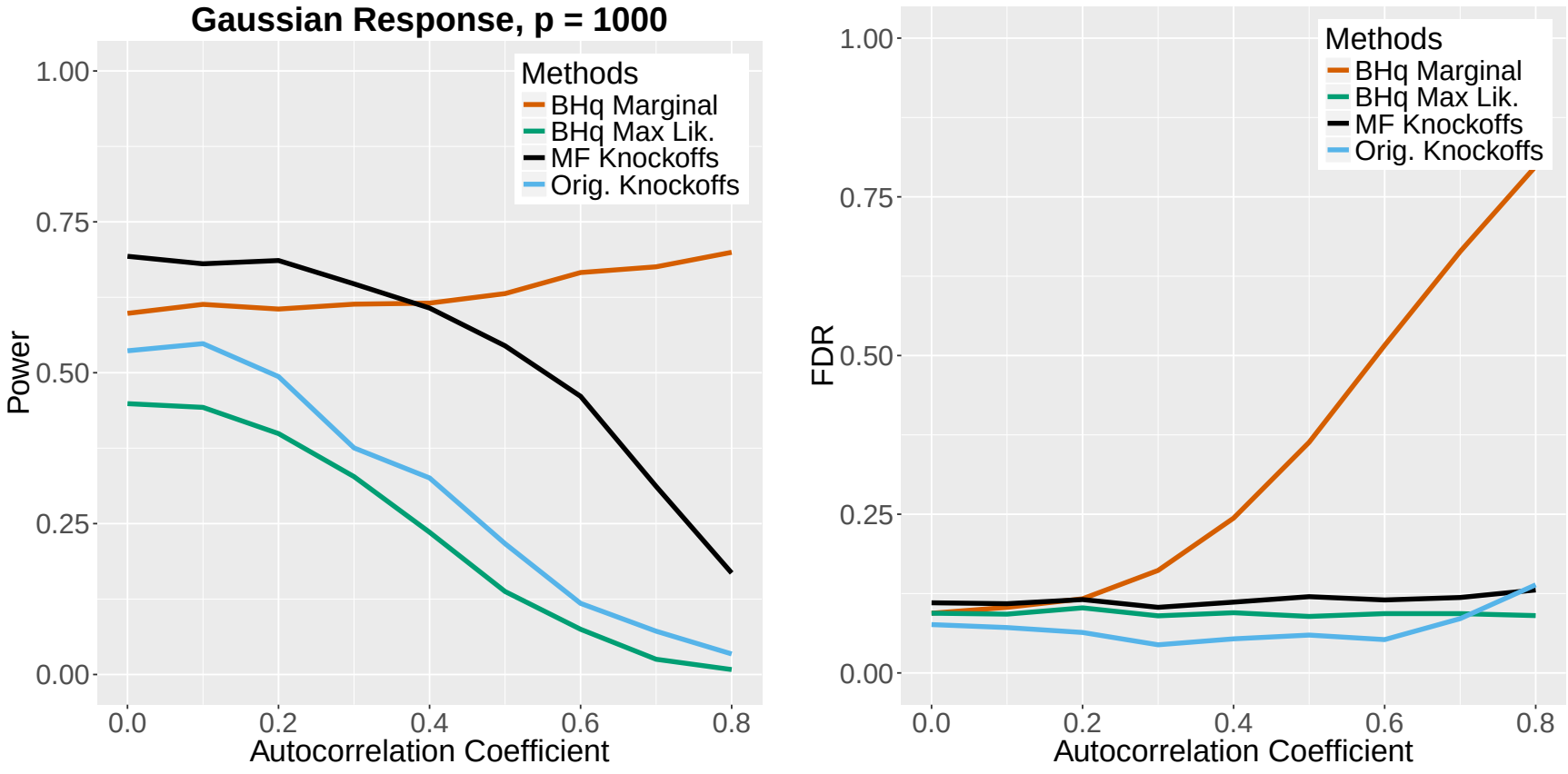


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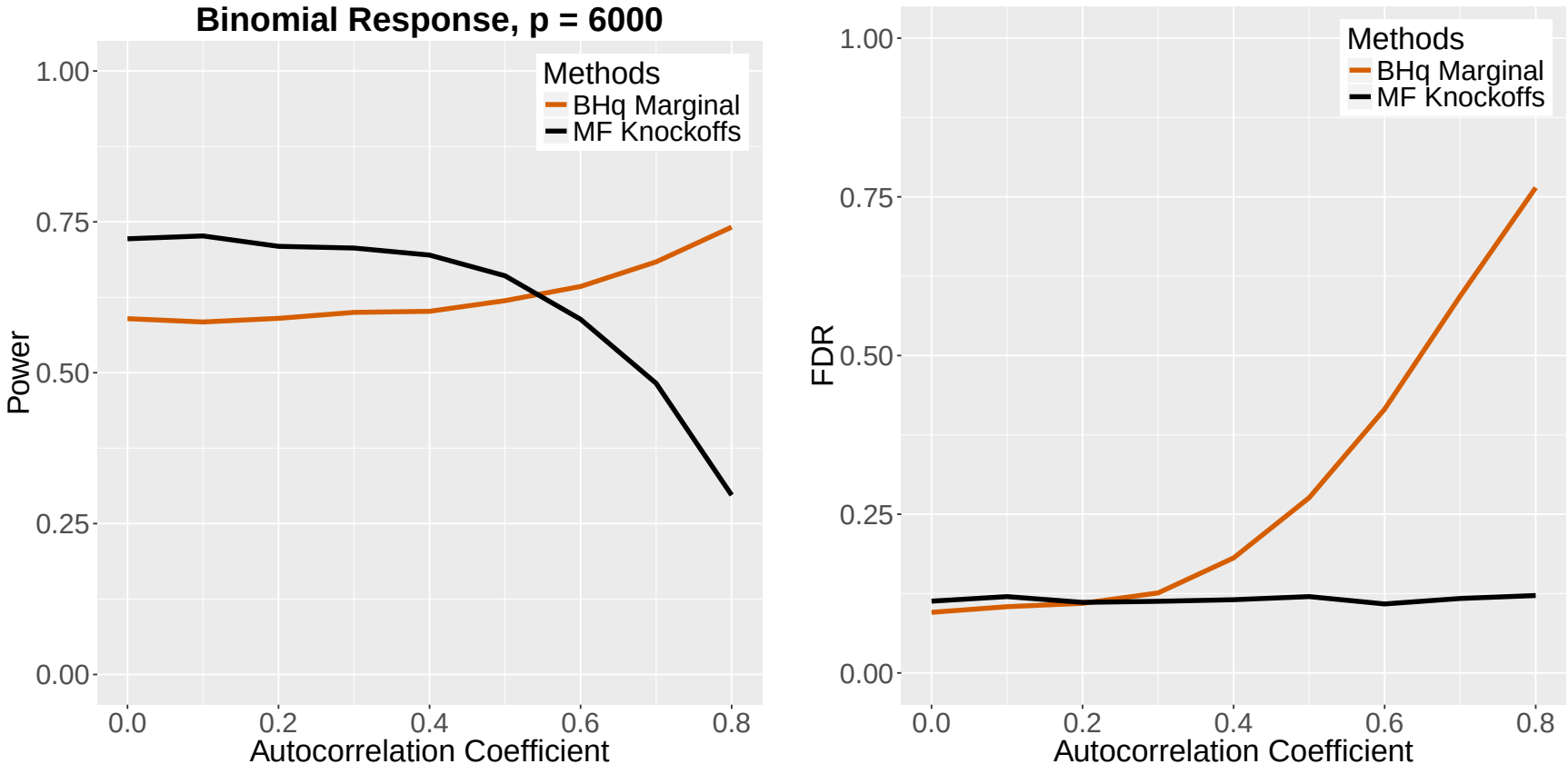


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$X$ is AR(1) and autocorrelation $\rho = 0.3$

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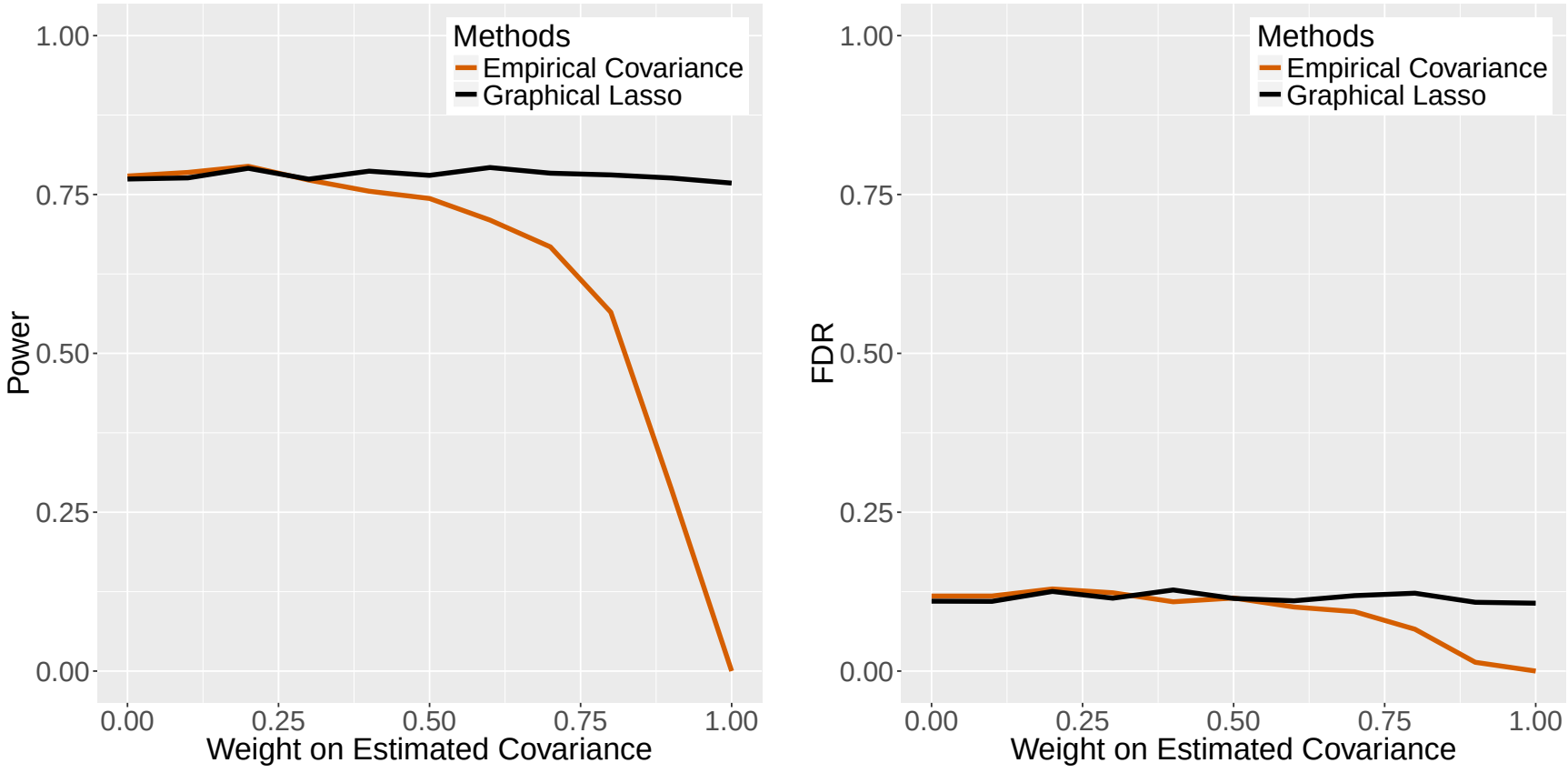


Figure: High-dimensional logistic model with $n = 800$, $p = 1500$

*Real Data Analysis*

# Genetic analysis of Crohn's disease (CD)

Data provided by the Wellcome Trust Case Control Consortium (WTCCC)

- $n \approx 5,000$ subjects
  - $\approx 2,000$ CD patients
  - $\approx 3,000$ healthy controls
- $p \approx 400,000$ SNPs
- Previously analyzed in WTCCC (2007)

# Peek at the results

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  - Evidence from independent studies about adjacent genes shows some of the top unconfirmed hits to be promising candidates

| Selection frequency | SNP (Cluster Size) | Chrom. | Confirmed in Franke et al.'10? | Selected in WTCCC '07? |
|---|---|---|---|---|
| 100% | rs11805303 (16) | 1 | Yes | Yes |
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Table: SNP clusters discovered to be important for CD over 10 repetitions of knockoffs. Clusters not found in Franke et al. ('10) represent promising sites, especially rs6601764 and rs4692386, whose nearest genes have been independendently linked to CD

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**Covariance estimation**

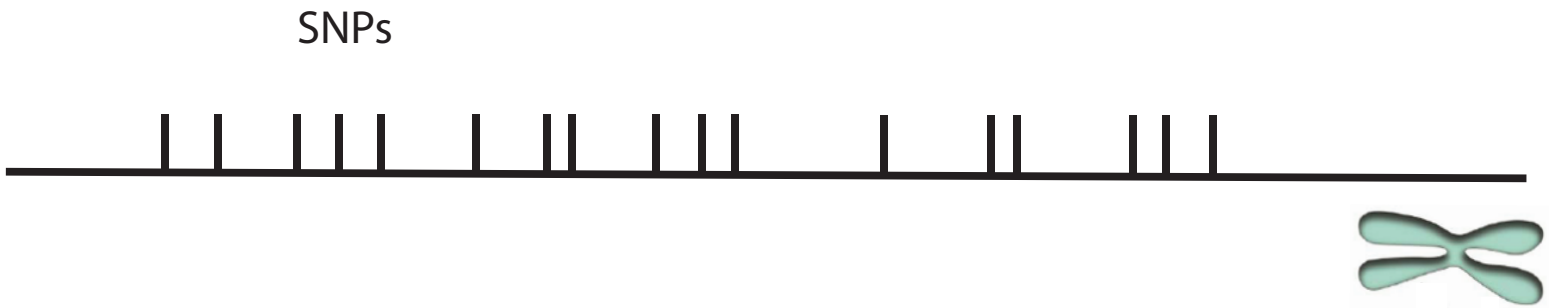
- Methodology of Wen and Stephens (2010)

  Shrink off-diagonal entries of empirical covariance matrix using genetic distance info estimated from the HapMap CEU population

- Second-order knockoffs assuming $\hat{\mathbf{\Sigma}}$ as population covariance

# High correlations

Hard to choose between two or more nearly-identical variables if the data supports at least one of them being selected



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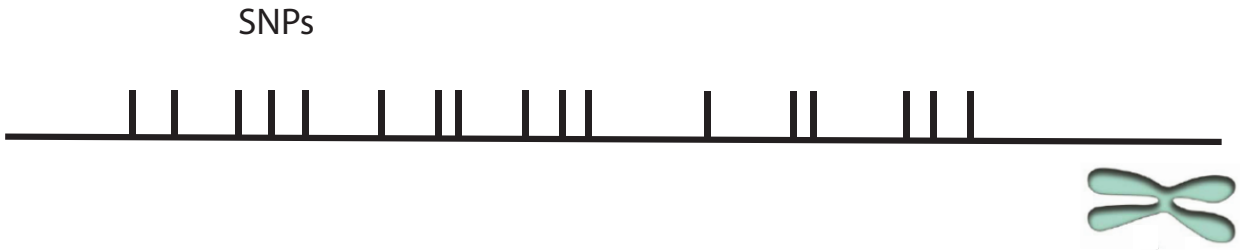

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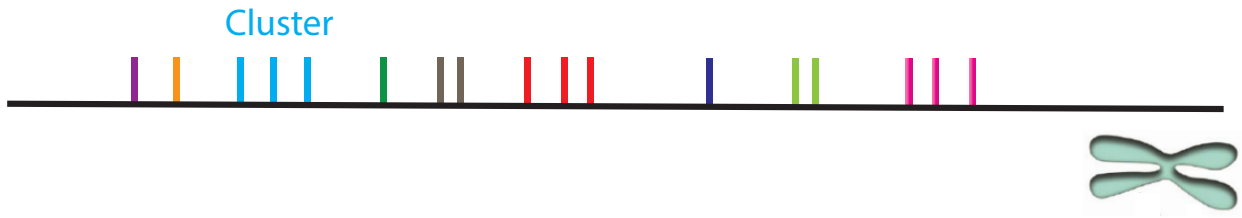


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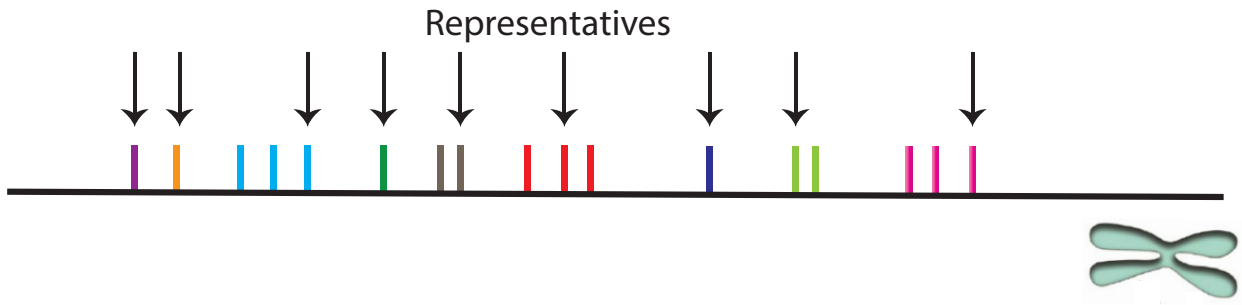


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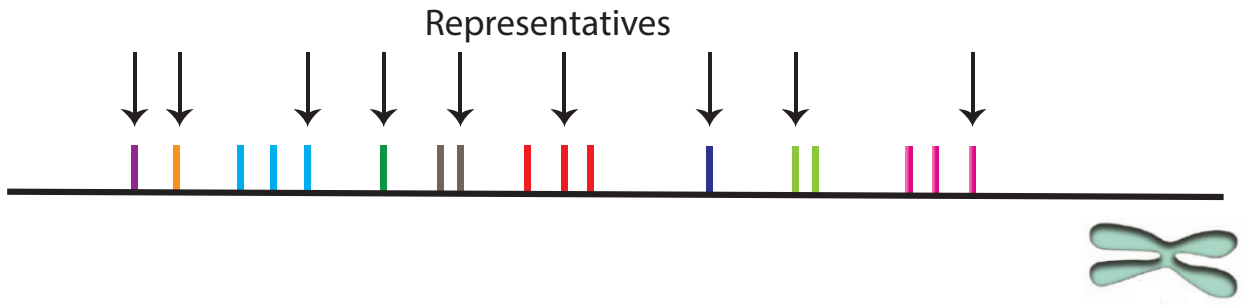


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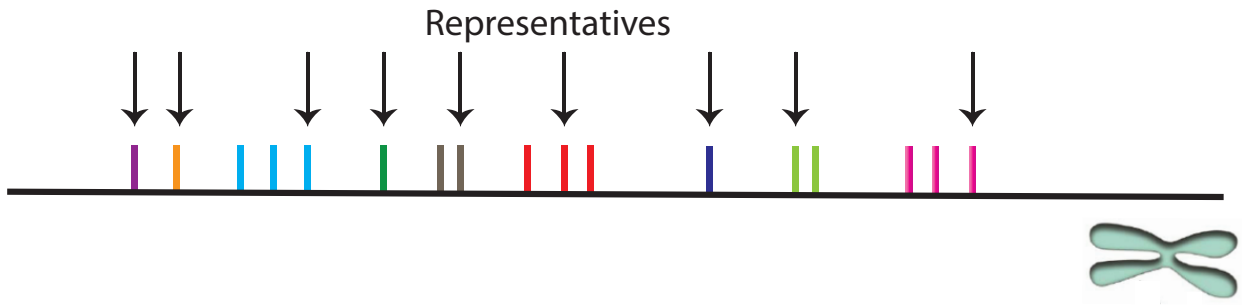


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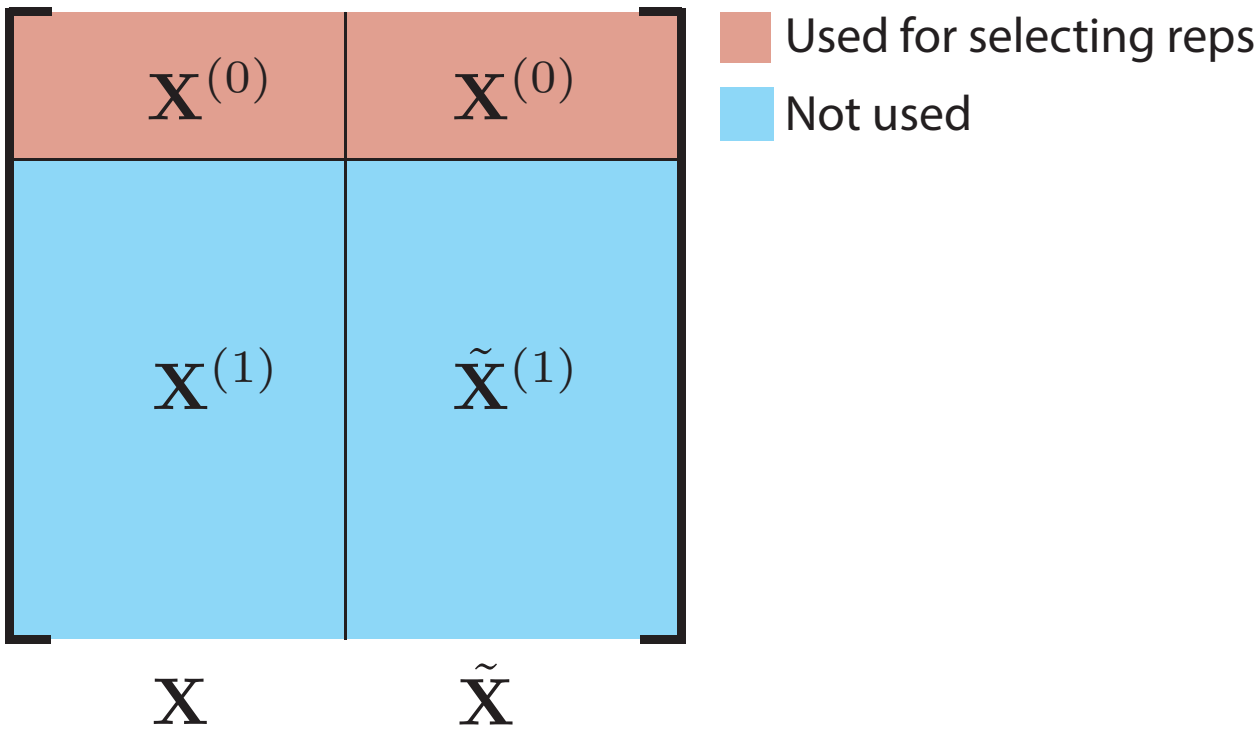
- Safe data re-use (optimize power) as in Foygel Barber and C. (2016)

# Safe data re-use



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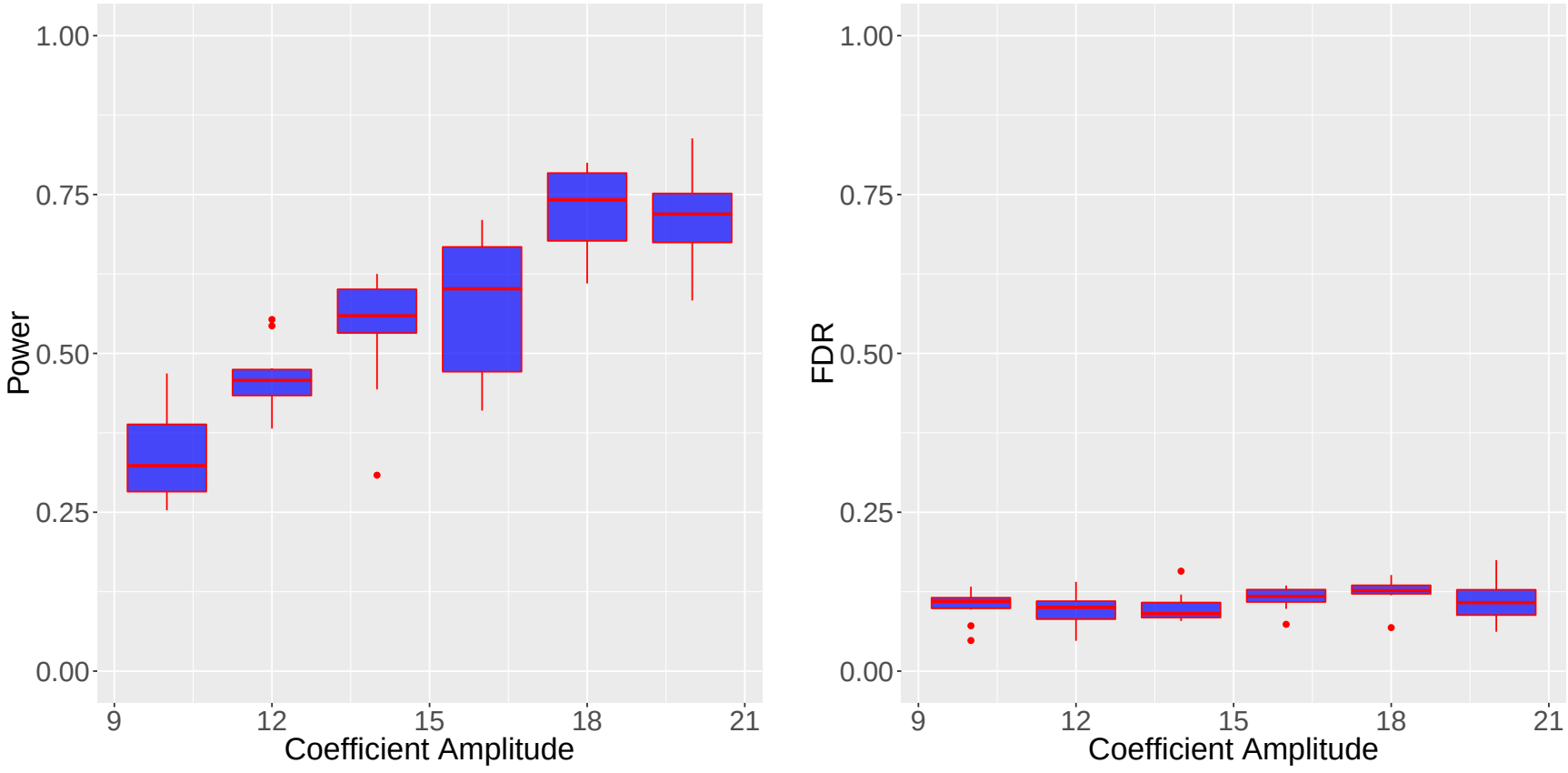


Figure: Power and FDR (target is 10%) for knockoffs with LCD statistic. Each boxplot represents 10 $\neq$ models with $\neq$ $X$'s and $Y$'s

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# *Knockoffs for Fixed Designs*

*Joint with Foygel Barber*

# Fixed designs

- Sometimes we do not know the distribution of $X$
- Sometimes $X$ is not random

Wish that inferential properties hold *conditionally on the value of* $X$

# Controlled variable selection in linear model

$$\underset{n\times 1}{y} = \overbrace{\underset{n\times p}{X}\underset{p\times 1}{\beta}}^{\sum_j \beta_j X_j} + \underset{n\times 1}{z} \qquad y \sim \mathcal{N}(X\beta, \sigma^2 I)$$

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Goal: select set of features $X_j$ that are likely to be relevant without too many false positives

$$\underbrace{\text{FDR}}_{\text{False discovery rate}} = \mathbb{E}\Big[\underbrace{\frac{\#\text{ false positives}}{\#\text{ features selected}}}_{\text{False discovery proportion}}\Big] \qquad \text{`}0/0 = 0\text{'}$$

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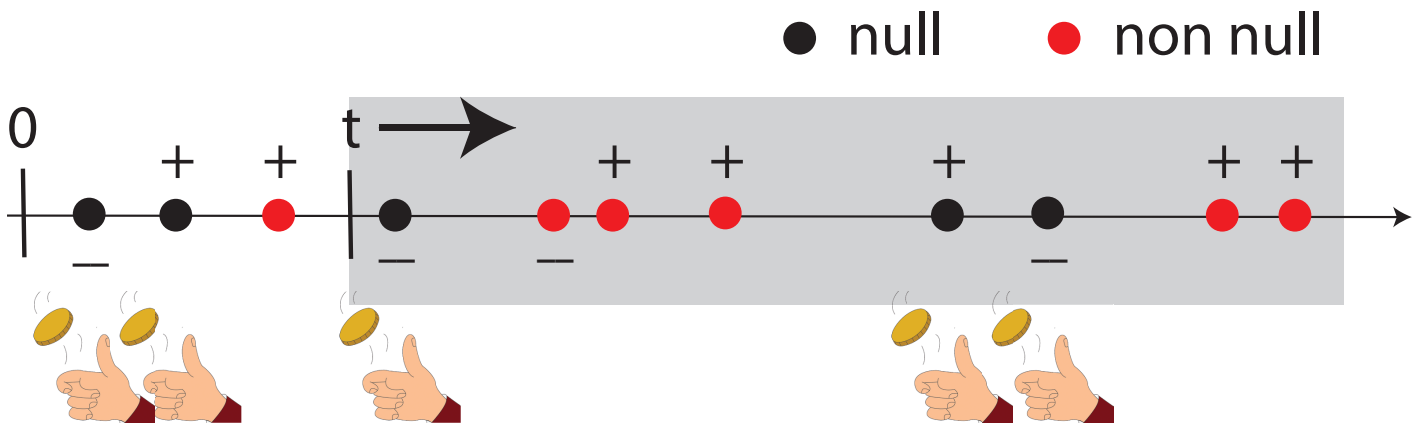
Context of multiple testing (with possibly many irrelevant variables)

$$H_j : \beta_j = 0 \qquad j = 1, \ldots, p$$

# Objective




(1) Signs of null statisitics are iid coin flips

(2) Good ordering

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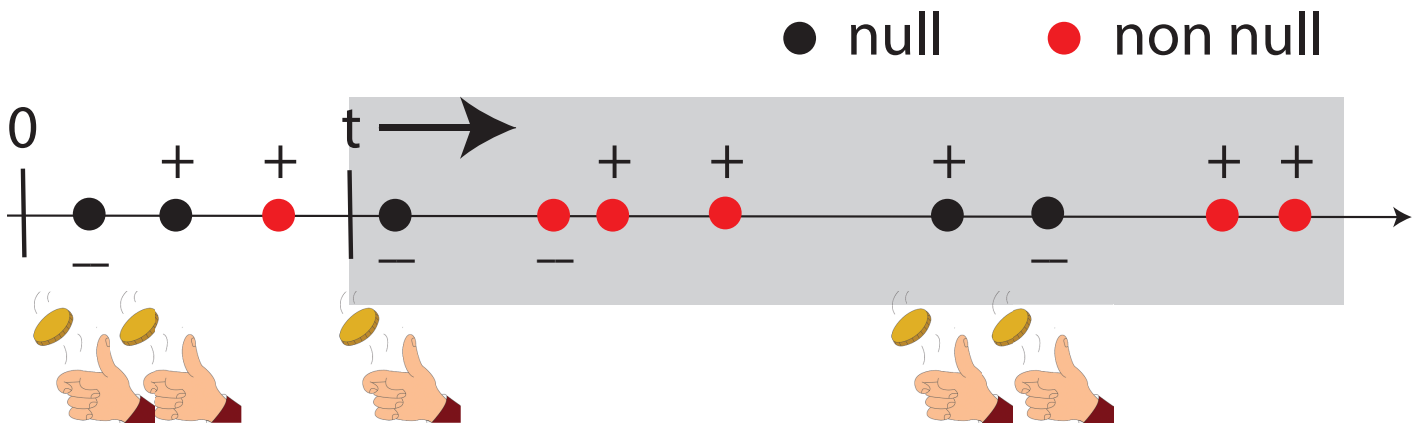


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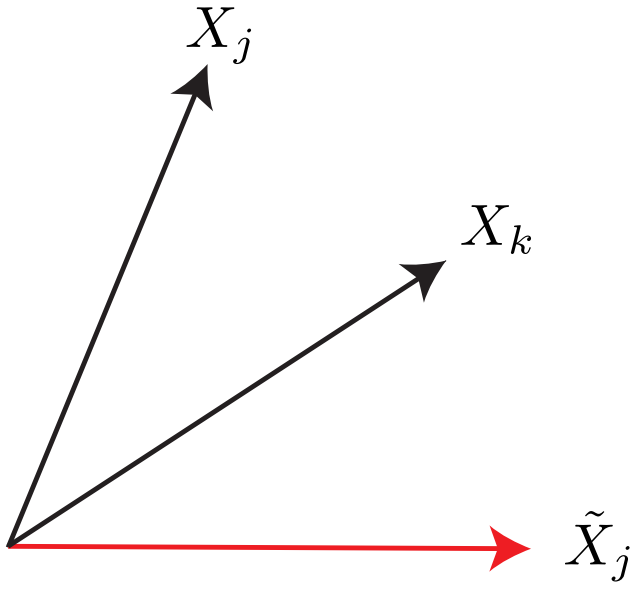
If (1) then machinery applies $\Longrightarrow$ exact FDR control

# Knockoff features for fixed designs

$$\tilde{X}_j' \tilde{X}_k = X_j' X_k \qquad \text{for all } j, k$$
$$\tilde{X}_j' X_k = X_j' X_k \qquad \text{for all } j \neq k$$



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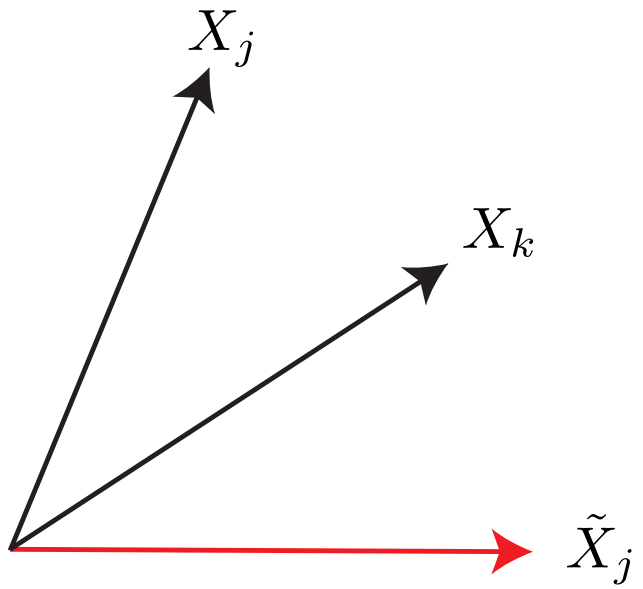


$$[X \;\; \tilde{X}]^\top [X \;\; \tilde{X}] = \begin{bmatrix} \Sigma & \Sigma - \mathrm{diag}\{s\} \\ \Sigma - \mathrm{diag}\{s\} & \Sigma \end{bmatrix} \succeq 0 \qquad s \in \mathbb{R}^p$$

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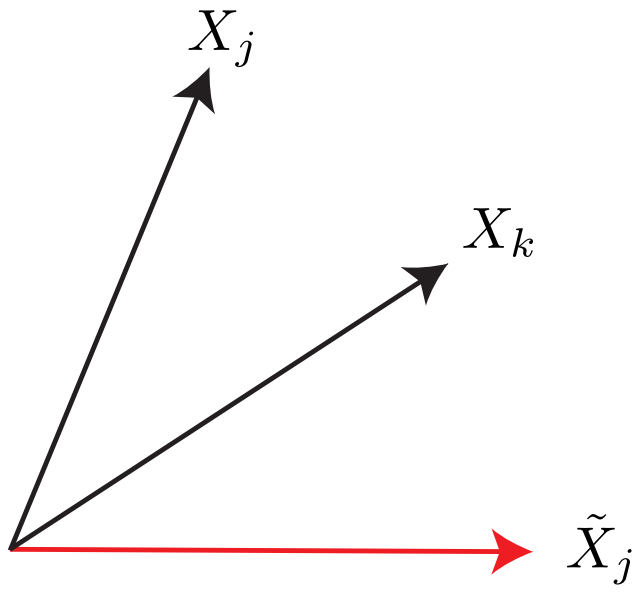


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Construction via matrix computations and/or numerical optimization

- No need for new data or experiment
- No knowledge of response $y$

# Symmetric statistics $\{W_j\}$

(1) *Anti-symmetry property:* swapping changes signs

$$W_j\left([X \;\; \tilde{X}]_{\mathsf{swap}(S)}, y\right) = W_j\left([X \;\; \tilde{X}], y\right) \cdot \begin{cases} +1 & j \notin S \\ -1 & j \in S \end{cases}$$

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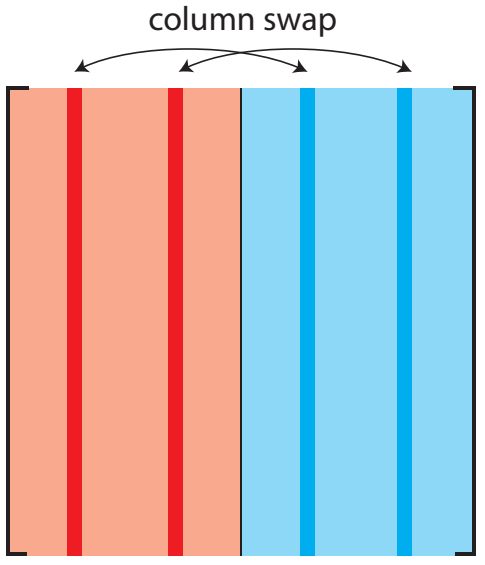


(2) *Sufficiency property:*

$$W = f\left(\left[X \;\; \tilde{X}\right]' \left[X \;\; \tilde{X}\right], \left[X \;\; \tilde{X}\right]' y\right)$$

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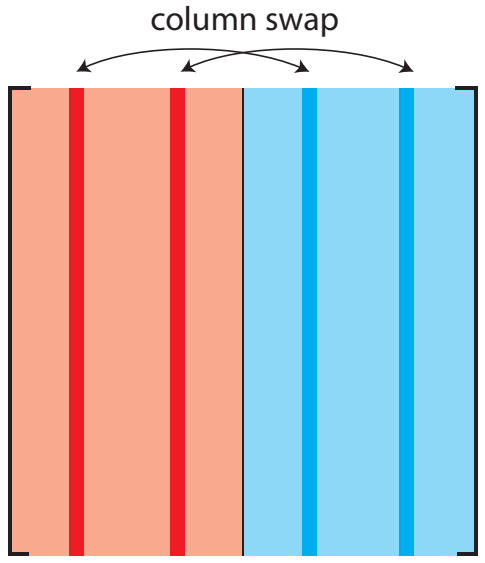


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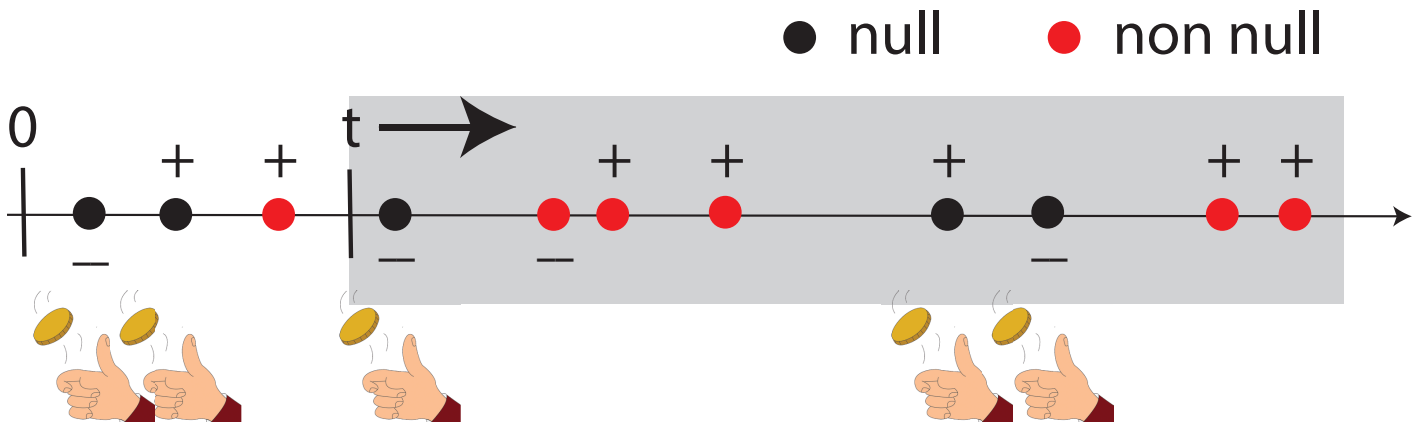
Guarantees iid coin flips for nulls



# Examples of statistics

- $Z_j = \sup\{\lambda : \hat{\beta}_j(\lambda) \neq 0\}$, $j = 1, \ldots, 2p$, and $\hat{\beta}(\lambda)$ sol. to augmented Lasso

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- ... (endless possibilities)

# HIV drug resistance

| Drug type | # drugs | Sample size | # protease or RT positions genotyped | # mutations appearing $\geq 3$ times in sample |
|---|---|---|---|---|
| PI | 6 | 848 | 99 | 209 |
| NRTI | 6 | 639 | 240 | 294 |
| NNRTI | 3 | 747 | 240 | 319 |

- response $y$: log-fold-increase of lab-tested drug resistance
- covariate $X_j$: presence or absence of mutation $\#j$

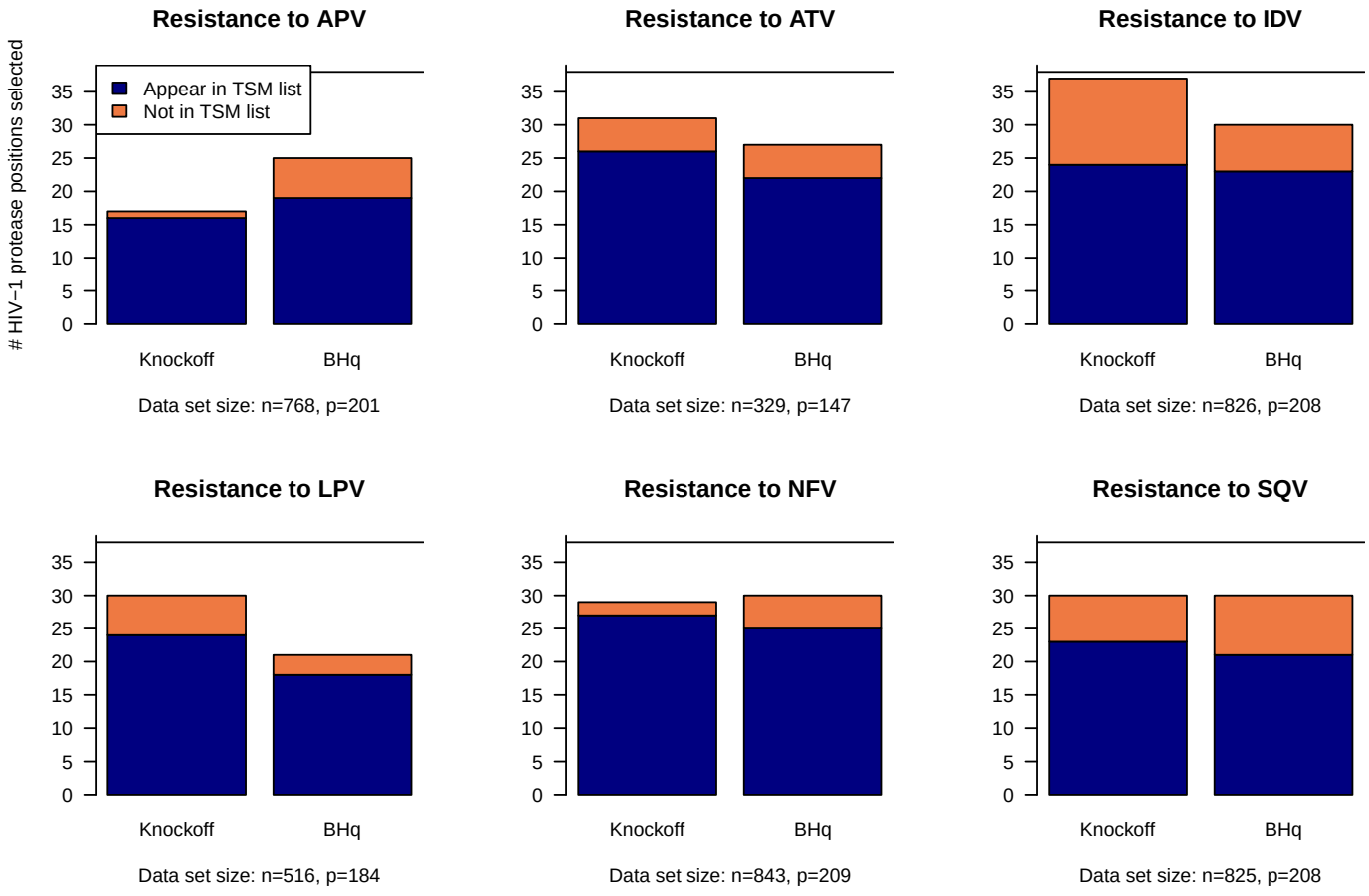
Data from R. Shafer (Stanford) available at:

`http://hivdb.stanford.edu/pages/published_analysis/genophenoPNAS2006/`

# HIV data

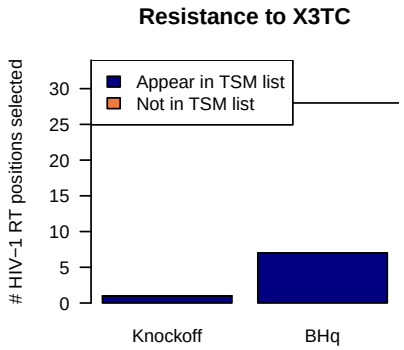
TSM list: mutations associated with the PI class of drugs in general, and is not specialized to the individual drugs in the class

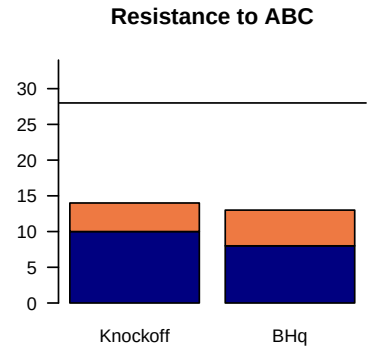
Results for PI type drugs

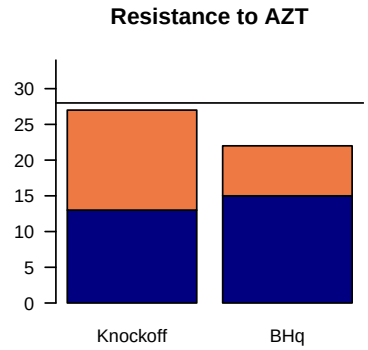


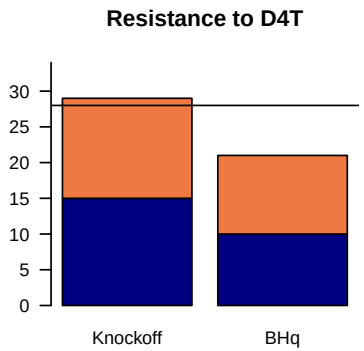
# HIV data

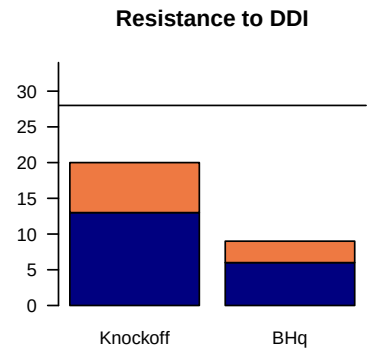
Results for
NRTI type drugs

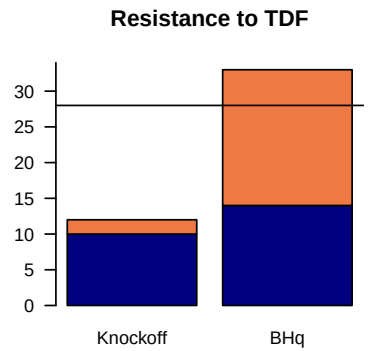



Results for
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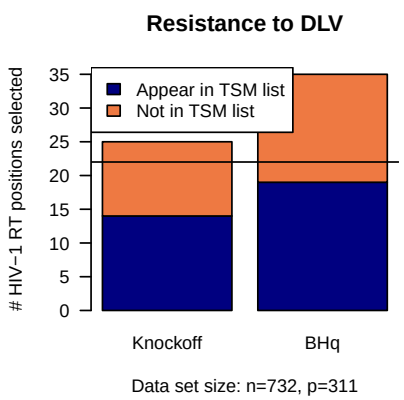


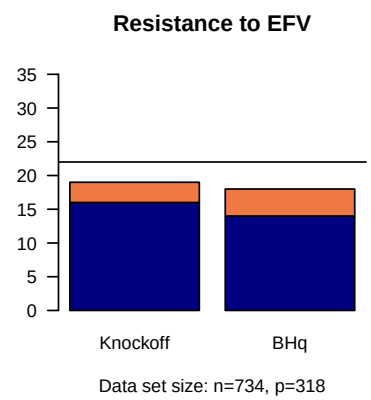


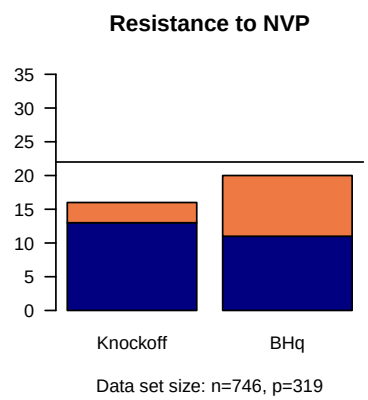

# Summary and open questions

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E. Candès, Y. Fan, L. Janson, and J. Lv. "Panning for gold: model-free knockoffs for high-dimensional controlled variable selection" (2016)

R. Foygel Barber and E. Candès. "Controlling the false discovery rate via knockoffs" *Annals of Statistics* (Oct. 2015)