

A practical evaluation of recent methods in high-dimensional inference

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Problem and motivation

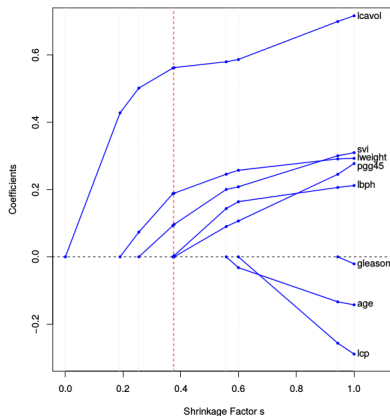
- $x \in \mathbb{R}^p, y \in \mathbb{R}$ have a joint distribution P where $y|x \sim N(x^T \beta, \sigma^2)$
- Observe $X = (x_1, \dots, x_n)^T, Y = (y_1, \dots, y_n)$ iid
- Problem: test $H_i : \beta_i = 0$ for $i = 1, \dots, p$
- Motivation: x are SNPs (mutations), y is phenotype

| | Control | $p > n$ |
|--|----------|---------|
| Classical inference (Pearson 1930) | Marginal | No |
| Debiased lasso (Javanmard et al. 2014) | Marginal | Yes |
| Knockoffs (Barber et al. 2014) | FDR | ? |
| Covariance test (Lockhart et al. 2014) | ?? | Yes |
| ... + FDR control (G'Sell et al. 2013) | FDR | Yes |
| | | |

The LASSO path

All three methods share an association with LASSO:

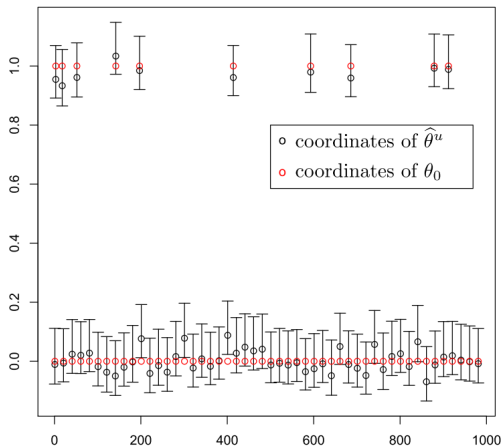
$$\hat{\beta}_{\lambda} = \operatorname{argmin}_{\beta} \frac{1}{2} \|X\beta - Y\|^2 + \lambda \|\beta\|_1$$



(Image credit: ??)

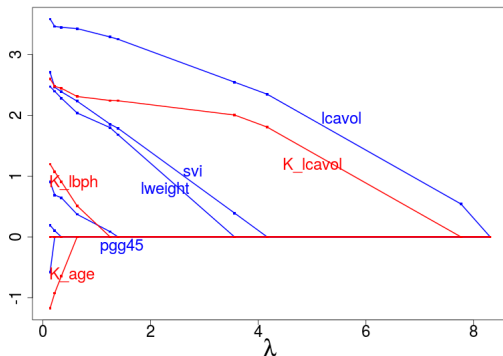
Debiased regularized M-estimators

- (2014) Javanmard and Montanari
- Standard assumptions + sparsity condition on β + large n and p asymptotics



Knockoff filter

- (2014) Barber and Candés
- *Finite sample* $Y \sim N(X\beta, \sigma^2 I)$, $n \leq p$, control FDR
- Extension to $p > n$, FWER control, etc. forthcoming...



| | |
|---------|---------|
| lweight | 22.5652 |
| lcavol | 20.5199 |
| svi | 4.4871 |
| lbph | 1.1865 |
| age | 0.0829 |
| gleason | 0.0387 |
| lcp | -0.2359 |
| pgg45 | -3.3742 |

Covariance test

- (2014) Lockhart, Taylor, Tibshirani ($\times 2$)
- Standard assumptions $Y \sim N(X\beta, \sigma^2 I) + \text{large } p \text{ asymptotics}$
- See *also* non-asymptotic exact test (Lee, Sun $\times 2$, Taylor 2015)
- FDR control: G'Sell, Wager, Chouldechova, Tibshirani (2013)
- What is the meaning of these p -values?

| Step | Predictor entered | Forward stepwise | Lasso |
|------|-------------------|------------------|-------|
| 1 | lcavol | 0.000 | 0.000 |
| 2 | lweight | 0.000 | 0.052 |
| 3 | svi | 0.041 | 0.174 |
| 4 | lbph | 0.045 | 0.929 |
| 5 | pgg45 | 0.226 | 0.353 |
| 6 | age | 0.191 | 0.650 |
| 7 | lcp | 0.065 | 0.051 |
| 8 | gleason | 0.883 | 0.978 |

Formulations for hypothesis testing

- For a subset E of the variables, define $\beta^E = (X_E^T X_E)^{-1} X_E^T X \beta$

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- **The full model null.** Test multiple hypotheses $H_i : \beta_i = 0$
- **Selective inference.** Condition on a randomly selected subset E , test hypotheses $H_i : \beta_i^E = 0$ for all $i \in E$

Formulations for hypothesis testing

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- **The full model null.** Test multiple hypotheses $H_i : \beta_i = 0$
- **Incremental null.** (Informal explanation).
 - Test variables as they are added to the model
 - I make a mistake whenever I add a variable which *doesn't* improve the fit of the model
 - If a variable I added previously *becomes* redundant later, it doesn't count against me

Formulations for hypothesis testing

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- **The full model null.** Test multiple hypotheses $H_i : \beta_i = 0$
- In this talk, we define type I errors according to *full model null*...

There is yet another method which is commonly used for variable selection...!

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| ... + FDR control (G'Sell et al. 2013) | FDR | Yes |
| Marginal screening | ??? | Yes |

Statistical Validation

- These procedures are derived under strong assumptions (linearity, gaussianity, homoscedasticity)
- How well do they work in real data where these assumptions are violated?
- We could validate inference procedures in real data if only we knew the 'true' β , (re)defined as

$$\beta = \mathbf{E}[\mathbf{x}\mathbf{x}^T]^{-1}\mathbf{E}[\mathbf{y}\mathbf{x}]$$

Statistical Validation

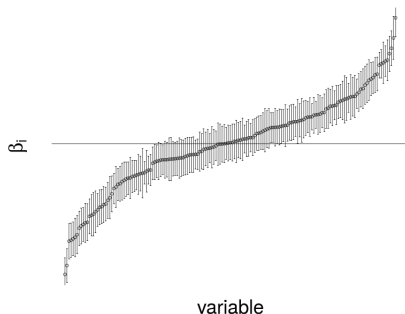
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- Possibility: take a dataset with large p and *humongous* n , so we can get an extremely precise estimate of β using OLS. Then test the high-dimensional inference procedures on subsamples of size $n_0 \leq p < n$ of the data

Example: personality data

Data with $p = 163$ survey questions from an online personality test,
 $n = 49086$ (after processing)



These coefficient estimates are still too uncertain!

- It is surely not *impossible* to get large enough data to estimate high-dimensional β , with say, $p > 100$
- But if were *easy* to get such large n data... we wouldn't need these new inference techniques in the first place!

Why not use simulations?

- Simulations can be used to test robustness of the procedure
- In simulations, we can add all the nonlinearities, nongaussianity, etc. that we want

Why not use simulations?

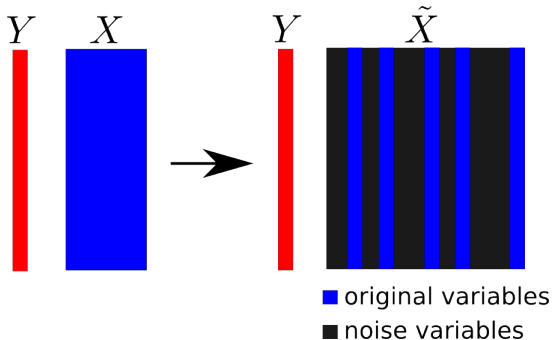
- Advantage: In simulations, we not only know β , but exactly how the data is generated
- Advantage: We can vary simulation parameters and get a lot of insight about the procedure being tested

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- Advantage: In simulations, we not only know β , but exactly how the data is generated
- Advantage: We can vary simulation parameters and get a lot of insight about the procedure being tested
- **Disadvantage:** Are these simulations relevant? How can we tell the simulated models are realistic?

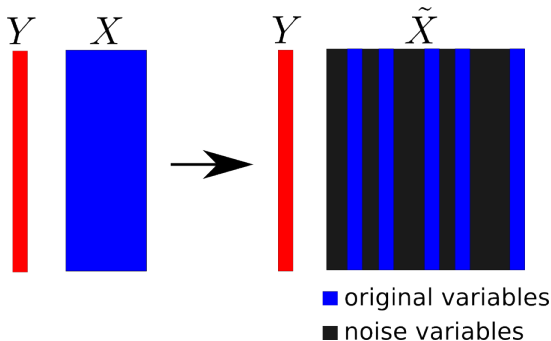
Idea

I give you real data *mixed in* with noise variables



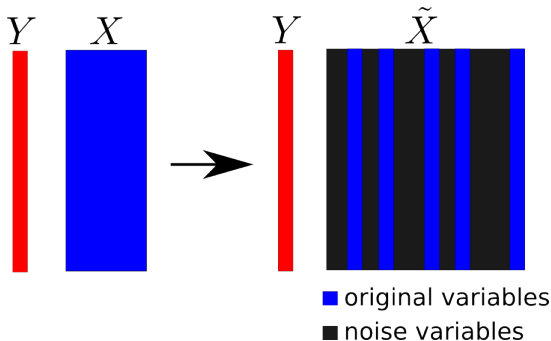
- Can you identify the original columns from the noise columns?

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- Can you identify the original columns from the noise columns?
- I can test your procedure this way, because I know the ground truth!

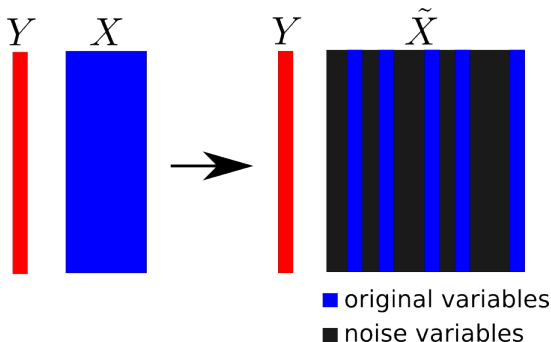
I give you real data *mixed in* with noise variables



- Can you identify the original columns from the noise columns?
- I can test your procedure this way, because I know the ground truth!
- **Caveat:** this test is unrealistically 'easy' (due to lack of correlations)

Synthetic Negative Controls

- Synthetic negative controls (SNCs) are artificial columns *which are correlated to X* , yet still have zero (population) regression coefficients
- Suppose I give you real data + SNCs, then you apply high-dimensional inference. If you reject any SNCs, we know these are errors!
- **The hope:** this will give us an idea of how well these procedures would work in real, high-dimensional data



Synthetic Negative Controls

- Given random vector $x \in \mathbb{R}^p$, let e be noise in \mathbb{R}^p independent of x .
- Let Γ be a fixed $p \times q$ matrix. *Define* synthetic negative controls $z \in \mathbb{R}^q$ by

$$z = x'\Gamma + e$$

and let $\tilde{x} = (x, z)$, so that

$$\tilde{x}_1 = x_1, \dots, \tilde{x}_p = x_p$$

$$\tilde{x}_{p+1} = z_1, \dots, \tilde{x}_{p+q} = z_q$$

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- Let

$$\beta = \mathbf{E}[xx^T]^{-1}\mathbf{E}[yx], \quad \tilde{\beta} = \mathbf{E}[\tilde{x}\tilde{x}^T]^{-1}\mathbf{E}[y\tilde{x}]$$

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- Let

$$\beta = \mathbf{E}[xx^T]^{-1}\mathbf{E}[yx], \quad \tilde{\beta} = \mathbf{E}[\tilde{x}\tilde{x}^T]^{-1}\mathbf{E}[y\tilde{x}]$$

- Then

$$\forall i \in \{1, \dots, p\} : \beta_i = \tilde{\beta}_i$$

$$\forall i \in \{p+1, \dots, p+q\} : \tilde{\beta}_i = 0$$

Why is this...?

- Recall that $\hat{\beta}_i$ is the *univariate regression* coefficient of Y on $X_{i|-i}$, where $X_{i|-i}$ is the *residual* of X_i after X_i is regressed on the other columns..
- Population version: $\beta_i = 0$ if the projection of X_i on the null space of the other covariates is uncorrelated with Y

Why is this...?

- Population version: $\beta_i = 0$ if the projection of X_i on the null space of the other covariates is uncorrelated with Y
- For $i = 1, \dots, q$, we have

$$\tilde{X}_{p+i} = x' \Gamma_i + E_i$$

where here \tilde{X}_{p+1} denotes the random variable (not the column of the design matrix)

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- The orthogonal projection P_X^\perp of \tilde{X}_{p+1} is

$$P_X^\perp \tilde{X} = P_X^\perp X \Gamma_i + P_X^\perp E_i = 0 + E_i$$

since $P_X^\perp X = 0$; meanwhile since $E_i \perp X$, $P_X^\perp E_i = E_i$.

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since $P_X^\perp X = 0$; meanwhile since $E_i \perp X$, $P_X^\perp E_i = E_i$.

- Since $E_i \perp y$, we have $\text{Cor}(P_X^\perp \tilde{X}_{p+i}, y) = 0$, hence $\tilde{\beta}_{p+i} = 0$

Why is this...?

- Population version: $\beta_i = 0$ if the projection of X_i on the null space of the other covariates is uncorrelated with Y
- Since $E_i \perp y$, we have $\text{Cor}(P_X^\perp \tilde{X}_{p+i}, y) = 0$, hence $\tilde{\beta}_{p+i} = 0$
- And since $\tilde{\beta}_j = 0$ for all the added variables $j = p+1, \dots, p+q$, it follows that $\tilde{\beta}_i$ is unchanged for $i = 1, \dots, p$.

Using SNCs to evaluate procedures

- Take low-dimensional real data mixed with SNCs (synthetic negative controls), apply inference procedure
- *Proxy for Type I error*: Rejected SNCs
- *Proxy for Power*: Rejected original variables

A step-by-step tutorial (in R)

1. Take the prostate data

```
> data(prostate)
> x <- prostate[, 1:8]
> y <- prostate[, 9]
> colnames(x)
[1] "lcavol"  "lweight" "age"      "lbph"     "svi"
     "lcp"    "gleason" "pgg45"
```

```
> dim(x)
[1] 97 8
```

A step-by-step tutorial

2. Construct 20 synthetic negative controls

```
> GAMMA <- matrix(rnorm(8 * 20), 8, 20)
> E <- matrix(rnorm(97 * 20), 97, 20)
> sncs <- as.matrix(x) %*% GAMMA + 2 * E
> sncs <- data.frame(sncs)
> colnames(sncs)
[1] "X1"  "X2"  "X3"  "X4"  "X5"  "X6"  ...
[19] "X19" "X20"
```

3. Create combined design matrix

```
> x2 <- cbind(x, sncs)
```

A step-by-step tutorial

4. Try marginal screening

```
> cors <- cor(x2, y)
> cors[order(-abs(cors)), , drop = F]
      [,1]
lcavol  0.7344603
svi      0.5662182
lcp      0.5488132
X6       -0.4591506
X16      0.4482263
lweight  0.4333194
X4       -0.4326898
```

A step-by-step tutorial

5. Try covariance test

```
> library(covTest)
> covTest(lars(as.matrix(x2), y), as.matrix(x2), y)
$results
```

| Predictor_Number | Drop_in_covariance | P-value |
|------------------|--------------------|---------|
| 1 | 69.0292 | 0.0000 |
| 5 | 1.5390 | 0.2219 |
| 2 | 6.8094 | 0.0020 |
| 11 | 0.8559 | 0.4294 |

(Numbers 1, 5, 2 are original, 11 is a SNC)

A step-by-step tutorial

6. Try debiased lasso (code at <http://web.stanford.edu/~montanar/sslasso/>)

```
> res <- SSLasso(as.matrix(x2), y)
[1] "10% done"
...
[1] "90% done"
> rej <- (res$up < 0) | (res$low > 0)
> names(x2)[rej]
[1] "lcavol" "lweight" "svi"
```

A step-by-step tutorial

7. Try knockoffs

```
> library(knockoff)
```

```
> knockoff.filter(x2, y)
```

Call:

```
knockoff.filter(X = x2, y = y)
```

Selected variables:

| | |
|---------|----|
| lweight | X7 |
| 2 | 15 |

Disclaimer!

- I am *not* proposing SNCs as a methodology for *inference*
- There is a danger of inferring *that Type I error has been controlled* from lack of rejection of SNCs. There are no formal guarantees of this!
- One should interpret results from experiments with SNCs in the same way one interprets simulation results with purely synthetic data

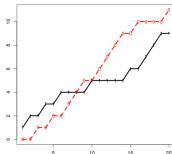
More Experiments!

| Data | n | p_1 | Linear? | Gaussian? | Constant σ^2 ? |
|-------------|------|-------|---------|-----------|-----------------------|
| Personality | 3000 | 163 | No | No | No |
| fMRI | 1750 | 53 | No | OK | No |
| HIV | 842 | 207 | No | Yes? | OK? |
| Galaxy | 323 | 4 | No | OK | No |

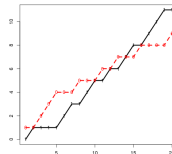
- We add $n/2 - p_1$ synthetic negative controls
- X is scaled, Γ is a gaussian matrix, $\text{Var}(E)$ is chosen to yield 'interesting' results
- Personality data is subsampled
- The 53 variables for fMRI were *selected* from a larger set of 10,000 variables (Gabor filters)... *should we be concerned?*

Marginal Screening

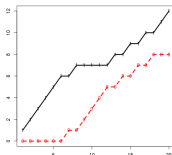
Personality



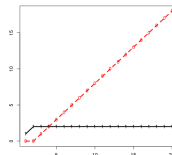
fMRI



HIV



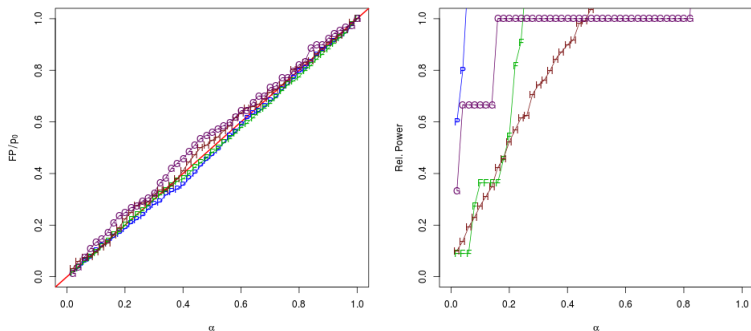
Galaxy



Legend: 0 = False positives, 1 = True positives

Ordinary Least Squares

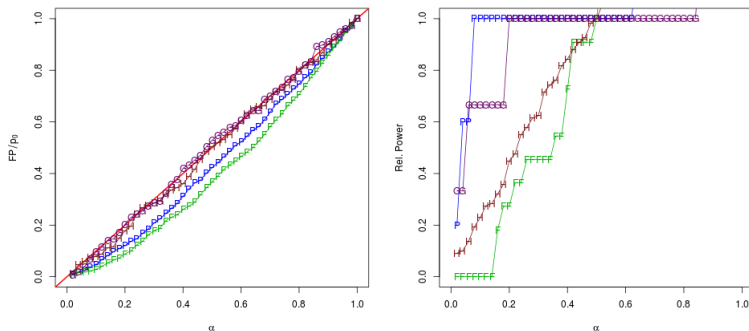
“Rel. power” = $TP / (\text{max number of TPs at } \alpha = 0.5 \text{ for any method})$



Legend: **P** = Personality, **F** = fMRI, **H** = HIV, **G** = Galaxy

Debiased Lasso

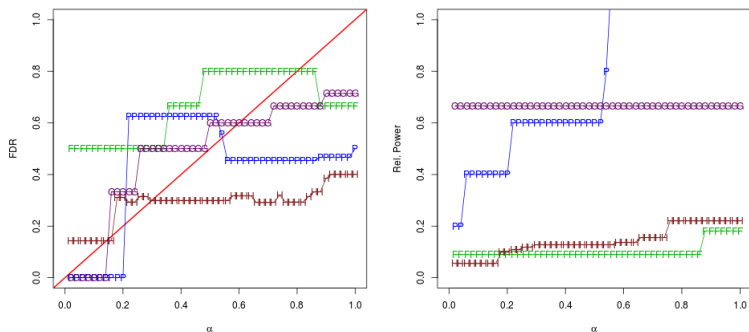
Can you spot the difference from the previous slide?



Legend: **P** = Personality, **F** = fMRI, **H** = HIV, **G** = Galaxy

Covariance Test

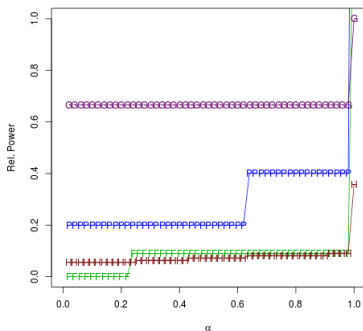
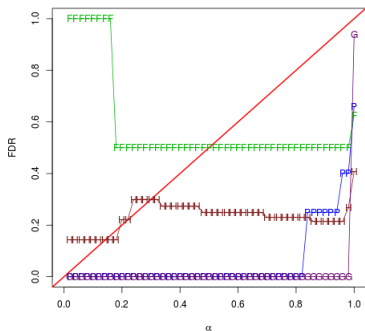
Forward Stop: reject first \hat{k} , where $-\frac{1}{\hat{k}} \sum_{i=1}^{\hat{k}} \log(1 - p_i) \leq \alpha$



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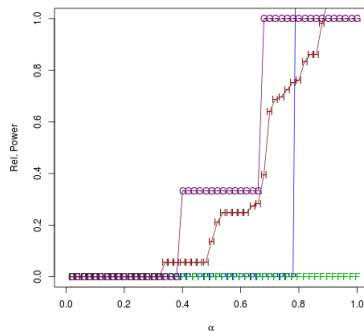
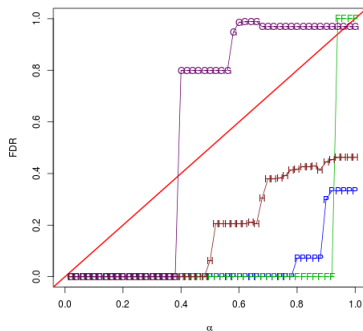
Strong Stop: reject first \hat{k} , where $\frac{m}{\hat{k}} e^{\sum_{j=\hat{k}}^p \log(p_j)/j} \leq \alpha$



Legend: **P** = Personality, **F** = fMRI, **H** = HIV, **G** = Galaxy

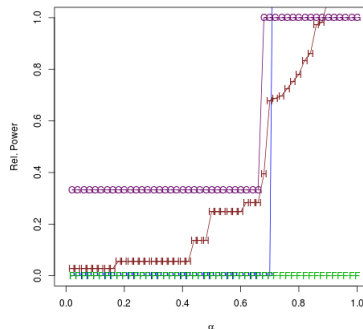
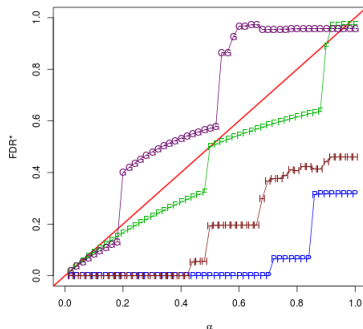
Knockoffs

Using Knockoff+ threshold



Legend: **P** = Personality, **F** = fMRI, **H** = HIV, **G** = Galaxy

Note: $FDR^* = \mathbf{E}[FP/(FP + TP + 1/\alpha)]$

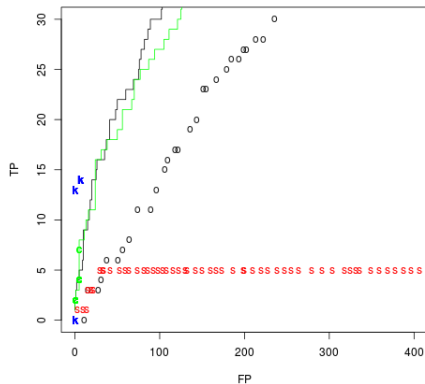


Legend: **P** = Personality, **F** = fMRI, **H** = HIV, **G** = Galaxy

Variable Ranking Criteria

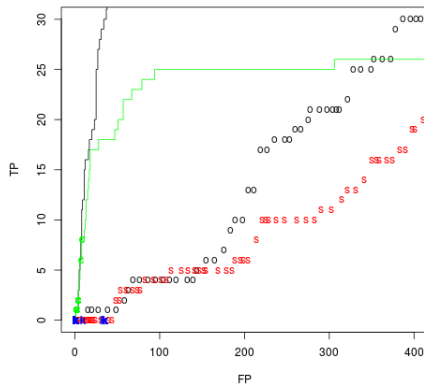
- Forget about Type I error for a second...
- Use procedures to *rank* variables by p-value
- Easy to compare procedures with different Type I criteria and also non-inference variable selection
- (Optional) score by Area Under Curve (AUC), etc.

Variable Ranking: Personality



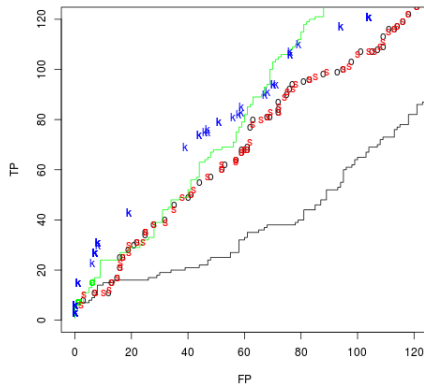
Legend: o = OLS, c = covariance test, k = knockoff, s = debiased lasso, (line) = marginal screening, (line) = lasso path

Variable Ranking: fMRI



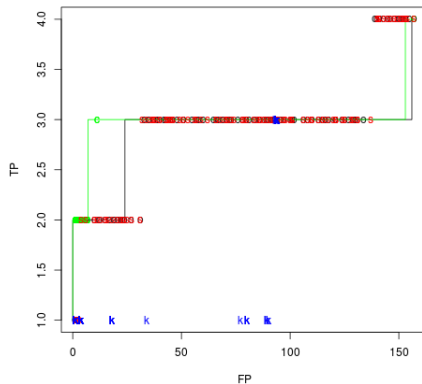
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Variable Ranking: HIV



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Variable Ranking: Galaxy



Legend: o = OLS, c = covariance test, k = knockoff, s = debiased lasso, (line) = marginal screening, (line) = lasso path

Initial reaction...

- Debiased lasso similar to OLS but more conservative, less powerful
- Knockoffs vs covariance test:
 - Knockoffs may control FDR more robustly than Covariance test (especially at small α)
 - Knockoffs and covariance are similar in power overall but have different case-by-case behavior
- Variable ranking:
 - Marginal screening does very well in "fMRI" even though it is not designed for regression, why is this?
 - In HIV data, knockoffs and regression do much better than marginal screening

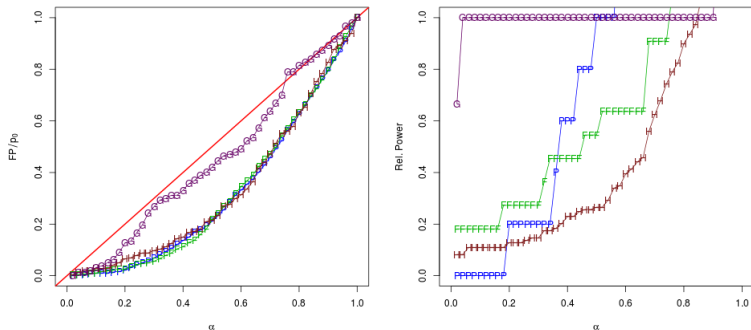
There are good explanations for some of these phenomena!

Low sample size

| Data | n | p | p_1 | Linear? | Gaussian? | Constant σ^2 ? |
|-------------|-----|------|-------|---------|-----------|-----------------------|
| Personality | 100 | 1500 | 163 | No | No | No |
| fMRI | 100 | 875 | 53 | No | OK | No |
| HIV | 100 | 421 | 207 | No | Yes? | OK? |
| Galaxy | 100 | 161 | 4 | No | OK | No |

- Reduce the sample size to 100, so that $p \gg n$
- Same number of negative controls, but larger added noise (easier)
- Covariance test requires estimate $\hat{\sigma}$: “cheat” by using OLS estimate from *original* data

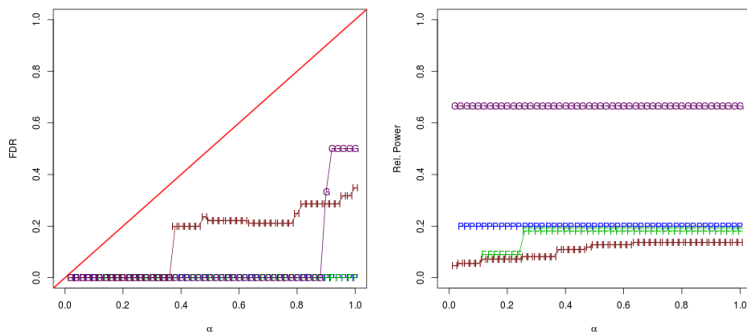
Debiased Lasso



Legend: **P** = Personality, **F** = fMRI, **H** = HIV, **G** = Galaxy

Covariance Test

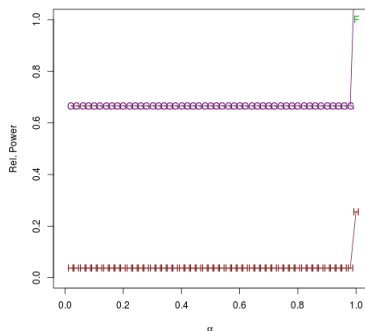
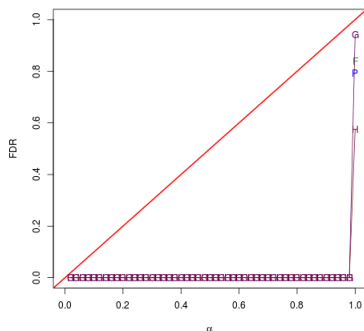
Forward Stop: reject first \hat{k} , where $-\frac{1}{\hat{k}} \sum_{i=1}^{\hat{k}} \log(1 - p_i) \leq \alpha$



Legend: **P** = Personality, **F** = fMRI, **H** = HIV, **G** = Galaxy

Covariance Test

Strong Stop: reject first \hat{k} , where $\frac{m}{\hat{k}} e^{\sum_{j=\hat{k}}^p \log(p_j)/j} \leq \alpha$



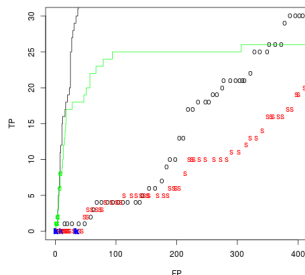
Legend: **P** = Personality, **F** = fMRI, **H** = HIV, **G** = Galaxy

- Debiased lasso and Covariance test + forward stop continue to control Type I error while finding true positives
- Covariance test + strong stop appears too conservative
- *Next:* explanations for the results in the first set of experiments..

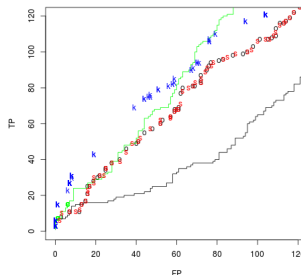
When can we beat marginal screening?

Legend: **k** = knockoff, (line) = marginal screening, (line) = lasso path

fMRI



HIV

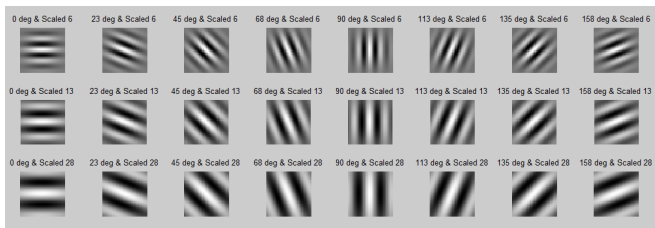


- Marginal screening does well in fMRI data, but badly in HIV data.
- Explanation is due to the dimensionality and *nature of the signal* in the original data!

When can we beat marginal screening?

fMRI data

- It is theorized that neurons in V1 can be described as *Gabor filters* which respond to a single image feature
- The response y is the activity in a voxel from the V1 visual system, the variables in the fMRI are *candidate* Gabor filters
- The 53 predictors were selected (using LASSO) from a larger set of 10000 such filters



When can we beat marginal screening?

fMRI data

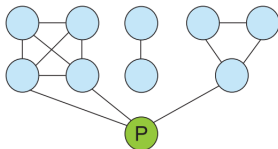
- The theorized “Gabor filter” for y does not exactly match any of the 10,000 candidate filters, but is best described as a *mixture* of some of those filters.
- Result: the 53 predictors selected were all heavily correlated to each other as well as the response. The optimal prediction is an weighted average of those predictors.
- Result: it is easy for marginal screening to find the original variables based on correlation!

$$\begin{array}{c} Y \\ \boxed{\bullet} \end{array} \approx 0.25 \begin{array}{c} X_1 \\ \boxed{\bullet} \end{array} + 0.25 \begin{array}{c} X_2 \\ \boxed{\bullet} \end{array} + 0.25 \begin{array}{c} X_3 \\ \boxed{\bullet} \end{array} + 0.25 \begin{array}{c} X_4 \\ \boxed{\bullet} \end{array}$$

When can we beat marginal screening?

HIV data

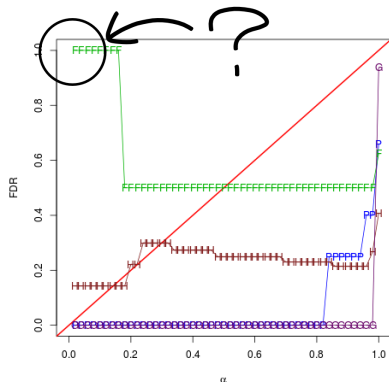
- Drug resistance of various HIV strains
- y = drug resistance, X = genotypes of the strains (various mutations)
- Predictors were selected based on unsupervised criterion (minimum number of occurrences)
- Most of the active features are only weakly correlated with the response, but combined they have much more predictive power than any one feature



Marginal screening cannot detect this kind of “hidden” structure!

Another look at covTest

Strong stop type I error

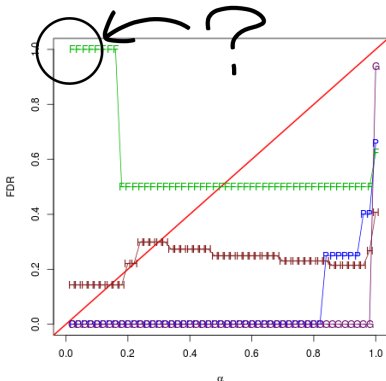


- Why did this negative control get rejected in the fMRI data at such a low α ?
- The particular negative control happened to have *mostly positive* coefficients...

(thanks to Stefan!)

Another look at covTest

Strong stop type I error

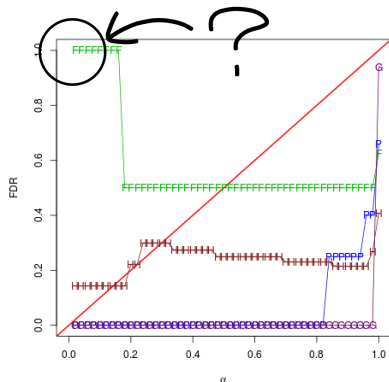


- According to the *incremental null*, the negative control was not a mistake... it is the best single predictor by far!

(thanks to Stefan!)

Another look at covTest

Strong stop type I error



- It is true that $\beta_i = 0$ for the rejected variable... but should we really disregard such strong "proxy" variables?

(thanks to Stefan!)

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- Is it really fair to only consider one definition of error (the full model null)? How can we decide which definition of Type I error is most appropriate?
- The difficulties we encounter in interpreting the results of these experiments remind us how *feedback from the practitioner* remains indispensable for evaluating procedures.

“ Both the client and the statistician... must base their thinking on a recognition that their assumptions will always require review and reappraisal... ”

– John Tukey

Acknowledgements

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