A practical evaluation of recent methods in high-dimensional inference

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Problem and motivation

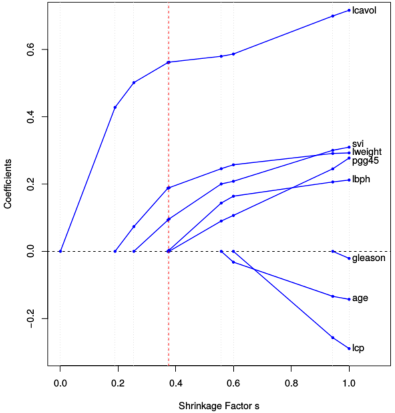
- $x \in \mathbb{R}^p, y \in \mathbb{R}$ have a joint distribution P where $y|x \sim N(x^T\beta, \sigma^2)$
- Observe $X = (x_1, \dots, x_n)^T$, $Y = (y_1, \dots, y_n)$ iid
- Problem: test $H_i : \beta_0 = i$ for $i = 1, \dots, p$
- Motivation: x are SNPs (mutations), y is phenotype

Methods

	Control	$p > n$
Classical inference (Pearson 1930)	Marginal	No
Covariance test (Lockhart et al. 2014)	FWER?	Yes
Debiased lasso (Javanmard et al. 2014)	Marginal	Yes
Knockoffs (Barber et al. 2014)	FDR	?

The LASSO path

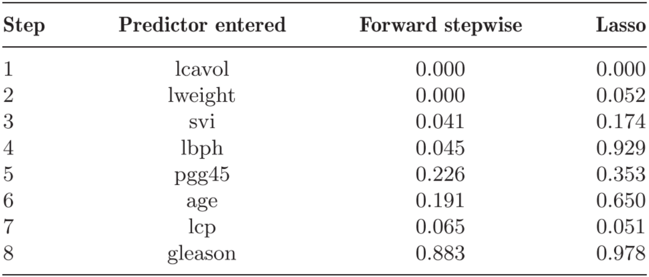
$$\hat{\beta}_\lambda = \text{argmin}_\beta \frac{1}{2}||X\beta - Y||^2 + \lambda||\beta||_1$$



(Image credit: ??)

Covariance test

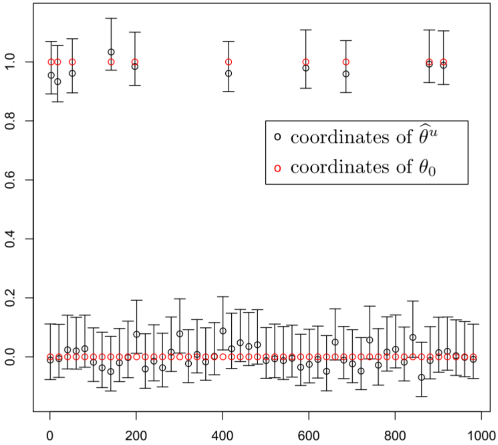
- (2014) Lockhart, Taylor, Tibshirani (x 2)
- Standard assumptions $Y \sim N(X\beta, \sigma^2 I)$ + large p asymptotics
- *See also* non-asymptotic exact test (Lee, Sun x 2, Taylor 2015)



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

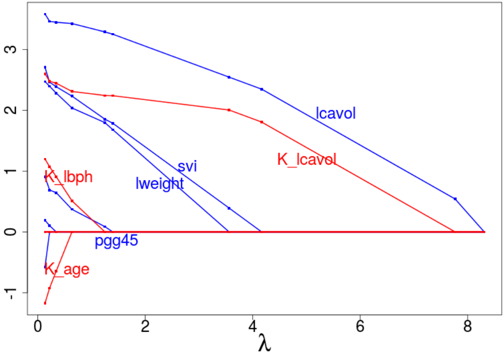
Debiased regularized M-estimators

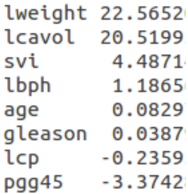
- (2014) Javanmard and Montanari
- Standard assumptions + sparsity condition on β + large *n* and *p* asymptotics



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
```

Methods

But what's actually used in practice?

	Control	$p > n$
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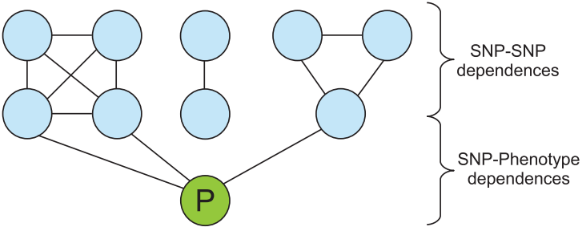
Marginal screening	???	Yes

Regression vs Marginal Screening

Testing $H_i : \beta_i = 0$ is better than testing $H_i : \text{Cov}(X_i, Y) = 0$ when you are looking for X_i *directly* linked to Y



SNP-SNP dependences $\beta_i = 0$

SNP-Phenotype dependences $\beta_i \neq 0$

(Adapted from *Mourad 2012*)

Statistical Validation

- These procedures are derived under strong assumptions (lienarity, gasusianity, homoscedasticty)
- 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, defined as

$$\beta = \mathbf{E}[xx^T]^{-1}\mathbf{E}[yx]$$

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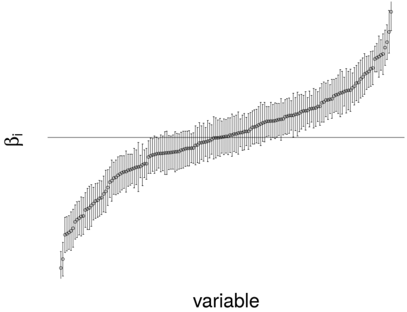
- Possibility: take a dataset with large p and *humongous* n, so we can get an extremely precise estimate of β using OLS. Then test the high-dimensional inference procedures on subsamples of size $n_0 \leq p < n$ of the data

Example: personality data

- Data with $p = 163$ survey questions from an online personality test, $n = 49086$ (after processing)
- Predict self-reported age of respondent, y, from their responses
- Is n large enough for us to confidently say which $\beta_i = 0$ (for use as ground truth?)

Example: personality data

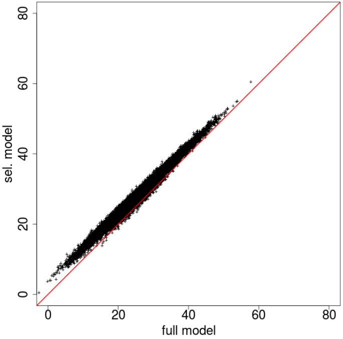
Coefficient estimates ± 3 sd



Consider declaring all variables whose intervals cross 0 to be null. Then $p_1 = 105$ (out of 163)

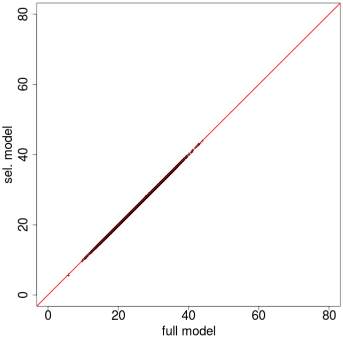
Example: personality data

- If n were large enough, then for the selected model S we should have $\hat{y} = \sum_{i=1}^{p} X\hat{\beta}_i$ close to $\hat{y}_S = \sum_{i \in S} X_i \hat{\beta}_i$
- But...



Example: personality data

- Here n is not large enough for $p = 163$
- If we reduce the dimensionality to 15 by subsampling columns, it looks more convincing that we selected the correct 10 variables



Dillemma

- It is by no means *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

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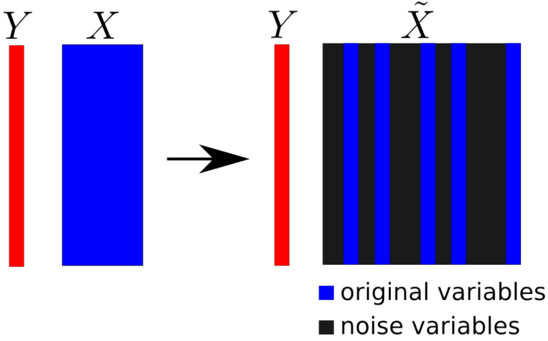
- **Disadvantage:** Are these simulations relevant? How can we tell the simulated models are realistic?

Idea

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



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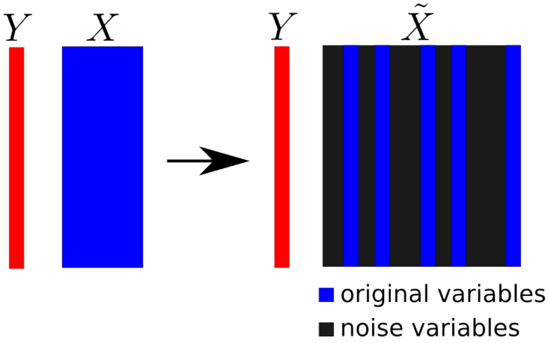

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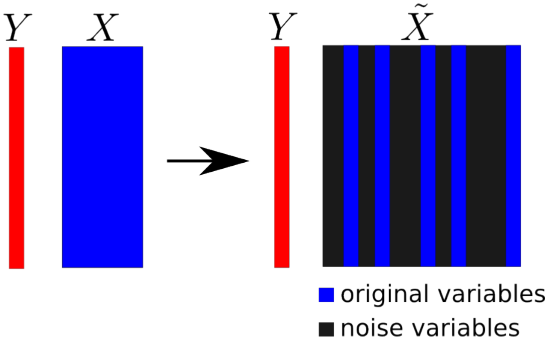
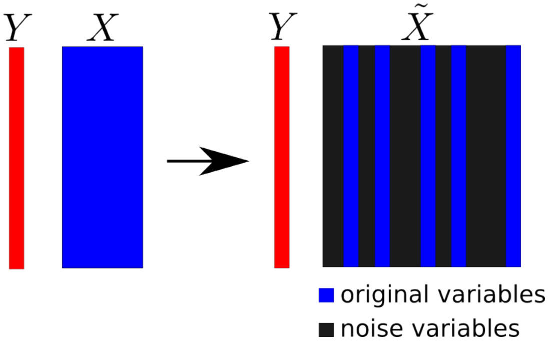


- Can you identify the original columns from the noise columns?
- I can test your procedure this way, because I know the ground truth!
- **Caveat**: this test is unrealistically 'easy' (due to lack of correlations)

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!
- This gives us some measure of performance on "real" data (maybe?)

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 by

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

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

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

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

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- Let

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

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

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

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where here $\tilde{X}_{p+1}$ denotes the random variable (not the column of the design matrix)
- 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 $\tilde{\beta}_{p+i} = 0$

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- 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 $\mathrm{Cor}(P_X^{\perp}\tilde{X}_{p+i}, y) = 0$, hence $\tilde{\beta}_{p+i} = 0$
- And since $\tilde{\beta}_j = 0$ for all the added variables $j = p + 1, \ldots p + q$, it follows that $\tilde{\beta}_i$ is unchanged for $i = 1, \ldots, p$.

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!

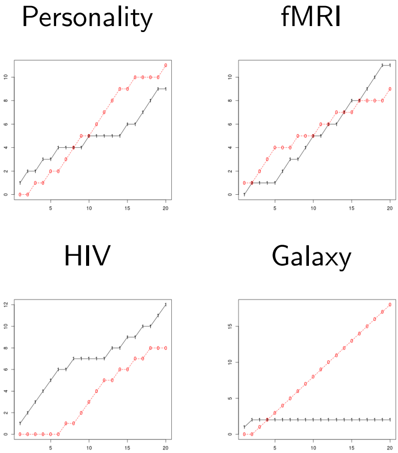
- I am *not* proposing SNCs as a methodology for *inference*
- There is a danger of inferring *that Type I error has been controlled* from lack of rejection of SNCs. There are no formal guarantees of this!
- One should interpret results from experiments with SNCs in the same way one interprets simulation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

More Experiments!

Data	n	p_1	Linear?	Gaussian?	Constant σ^2?
Personality	49k	163	No	No	No
fMRI	1750	44	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, $Var(E)$ is chosen to yield 'interesting' results
- Multiple trials averaging over the randomness of generating SNCs

Marginal Screening


Personality

fMRI

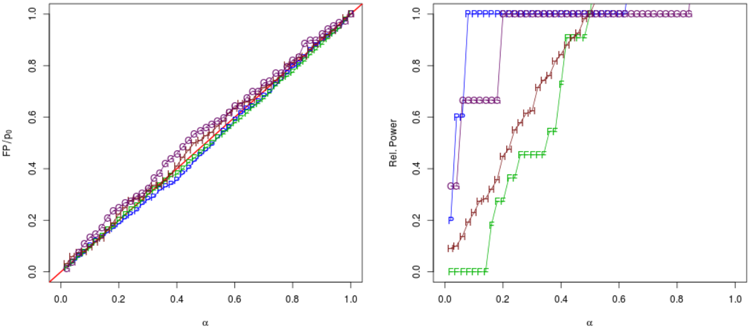
HIV

Galaxy

Legend: 0 = False positives, 1 = True positives

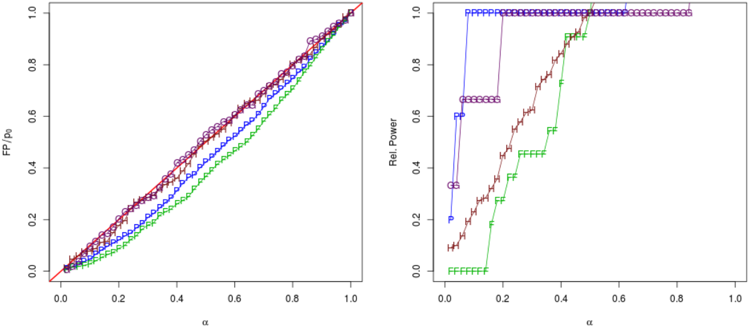
Ordinary Least Squares

"Rel. power" $=$ TP/(max number of TPs at $\alpha = 0.5$ for any method)



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

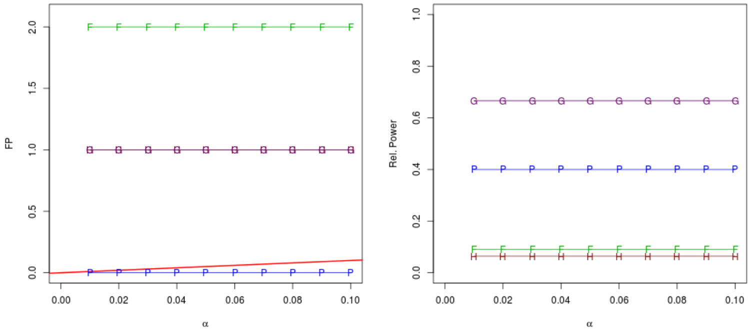
Debiased Lasso



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

Covariance Test

Procedure: continue rejecting until $p > \alpha$, then accept all other variables



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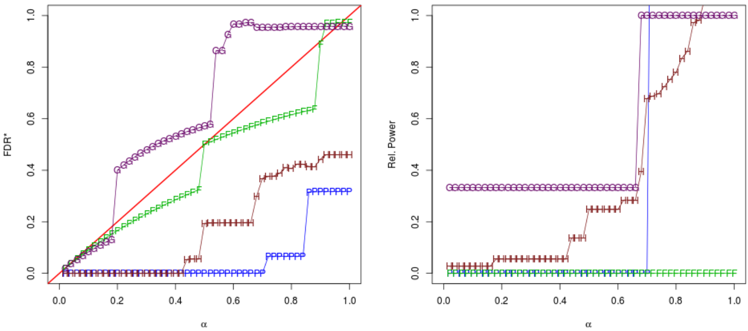
Knockoffs

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



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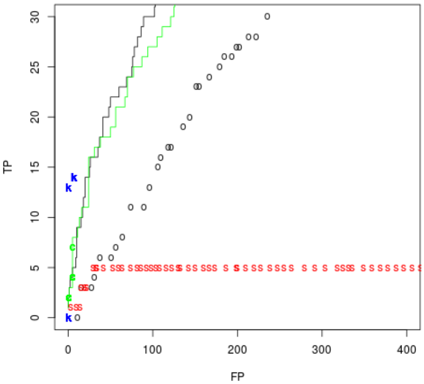
Variable Ranking Criteria

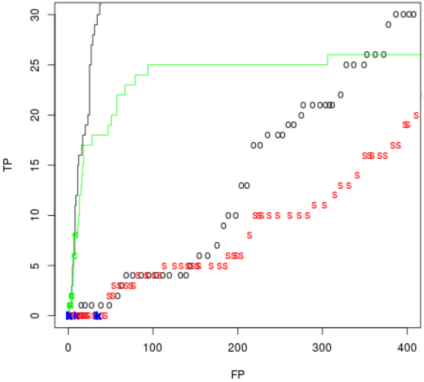
- Forget about Type I error for a second...
- Use procedures to *rank* variables by p-value
- Easy to compare procedures with different Type I criteria and also non-inference variable selection
- (Optional) score by Area Under Curve (AUC), etc.

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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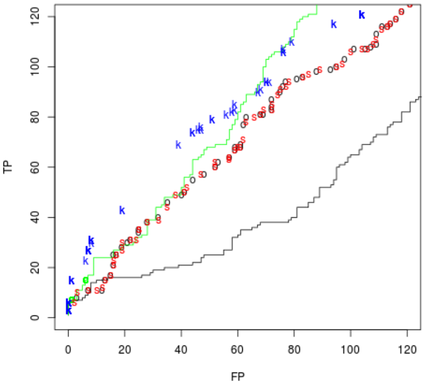
Variable Ranking: HIV



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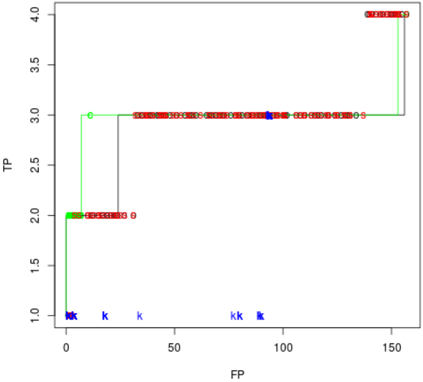

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- Example (GWAS): There is a new disease (say, liver cancer) where we have little prior info. I have data for a 'similar' disease, (say, stomach cancer) for which I have *partial information* about the relevant causes. In particular, I know *the most important* the genes involved stomach cancer
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- Testing your procedure directly on the stomach cancer data is uninformative: if you reject a gene which is not *a priori* known to cause stomach cancer... it could still be a new discovery!
- Rather than test your inference procedure on the full stomach cancer data, test it on the subset of the *known genes* plus SNCs
- Tricky part: choosing the size of the noise for the SNCs. To be safe, try several noise levels.

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- Possible to run a Kaggle-style competition for *inference* rather than prediction
- Recognizing that different procedures can have differing strengths creates room for a diversity of approaches

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- The answer is no: scientific validation is as important as ever.
- SNCs can be used to get an idea of our performance on the *regression hypothesis testing problem* in realistic settings
- However, how can we tell if the *regression hypothesis testing problem* is right framework for the real-world problem we are trying to solve? There may be better statistical frameworks, like graphical models, which are a better fit to the problem.

Do SNCs reduce the need for scientific validation?

- The gold standard of validation: obtaining *scientific confirmation* of the *scientific hypotheses* suggested by the inference procedure
- The answer is no: scientific validation is as important as ever.
- SNCs can be used to get an idea of our performance on the *regression hypothesis testing problem* in realistic settings
- However, how can we tell if the *regression hypothesis testing problem* is right framework for the real-world problem we are trying to solve? There may be better statistical frameworks, like graphical models, which are a better fit to the problem.
- Ultimately, we need the practitioner to measure the value of the results we obtain from the inference procedure.

Closing thoughts

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

– John Tukey

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