False Discovery Rates, A New Deal

Matthew Stephens

2014/5/8

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- No experimental data!
- No fancy heatmaps!
- 100% Money-back guarantee to half the False Discovery Rate (FDR) in your data!

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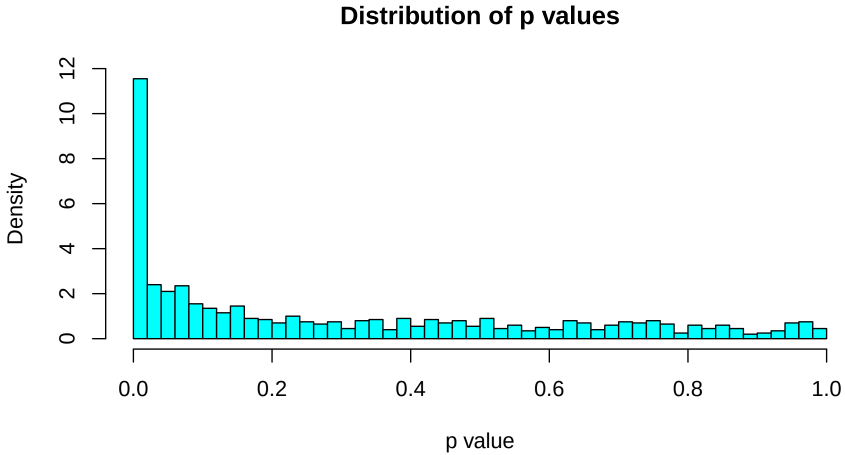
Example: FDR estimation



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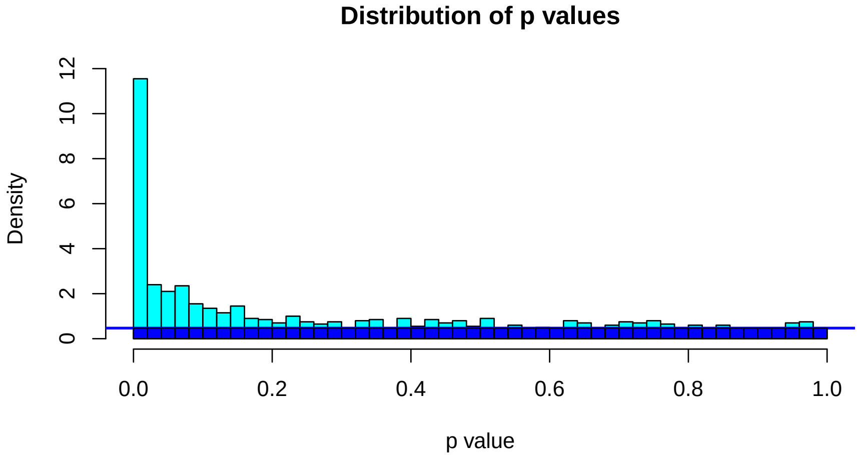

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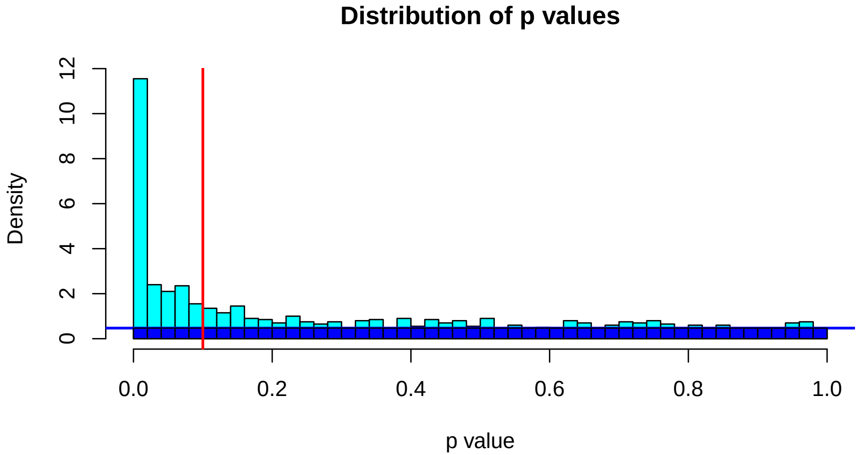

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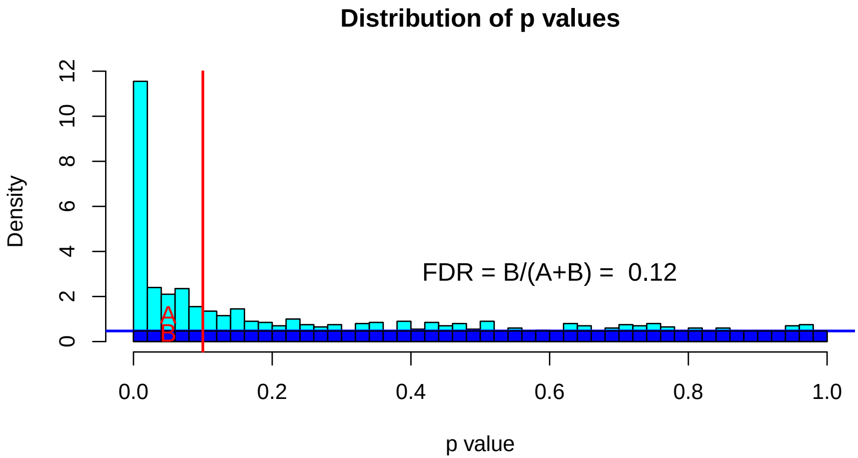

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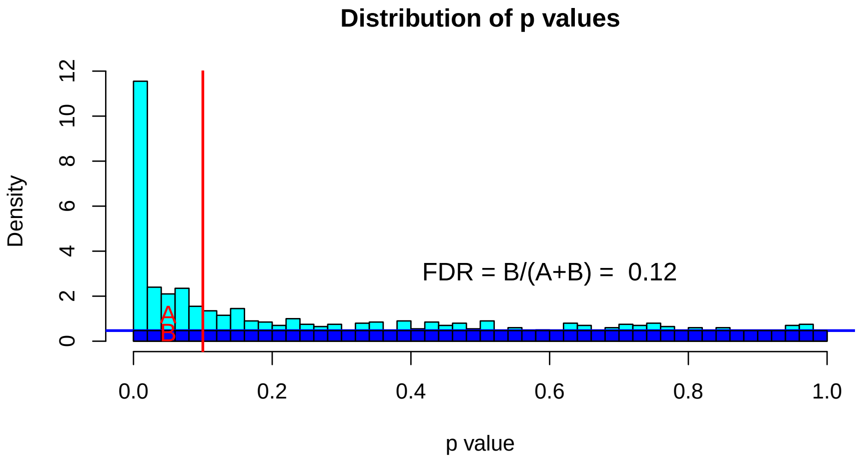
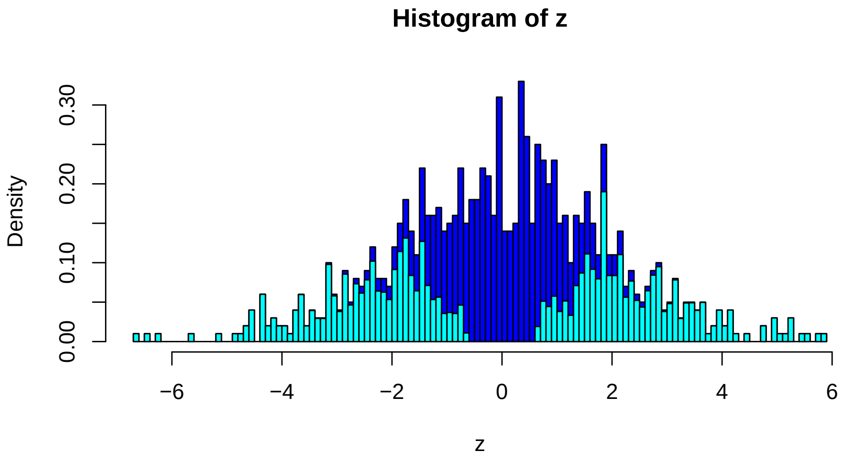
- Analogously, one can assume that all Z scores near 0 are null. Efron refers to this as the "Zero Assumption".
- Seems initially natural.

Implied distribution of p values under H_1



Implied distribution of Z scores under alternative



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- Eg effect sizes of rare SNPs have larger standard error than those of common SNPs
- Eg Expression levels of low-expressed genes have less precision than high-expressed genes
- If some effects are measured less precisely than others, those tests "lack power" and dilute signal, increasing FDR

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- 500 "poor" observations with very high standard error ($s_j = 10$)

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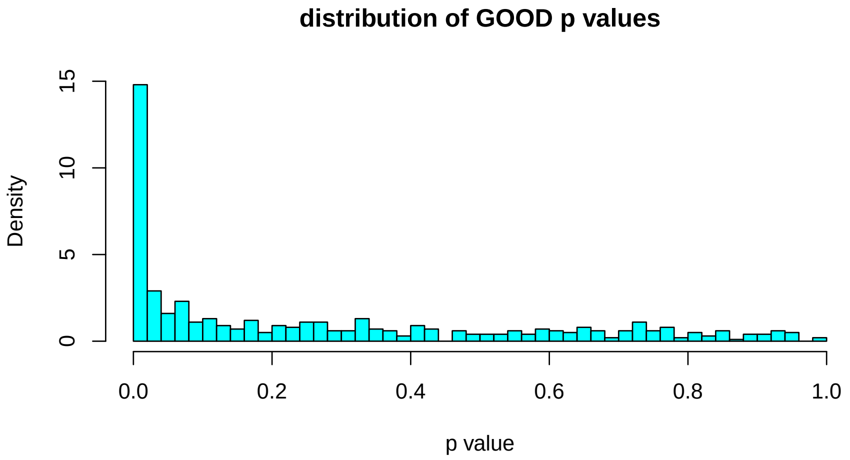

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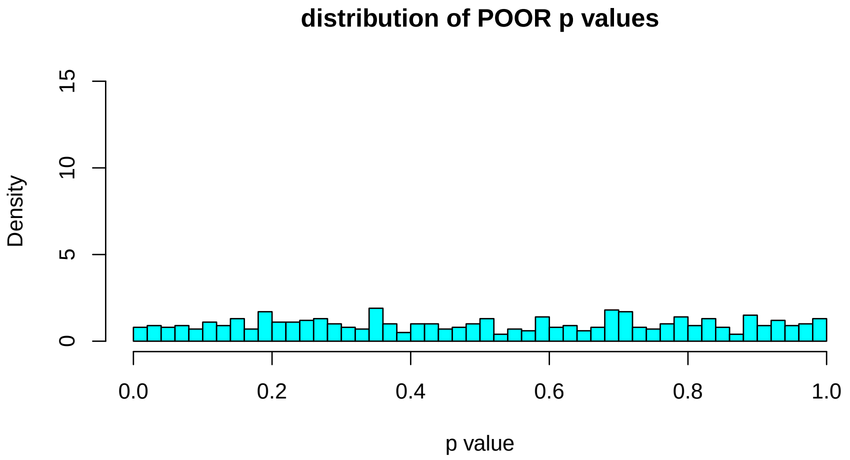

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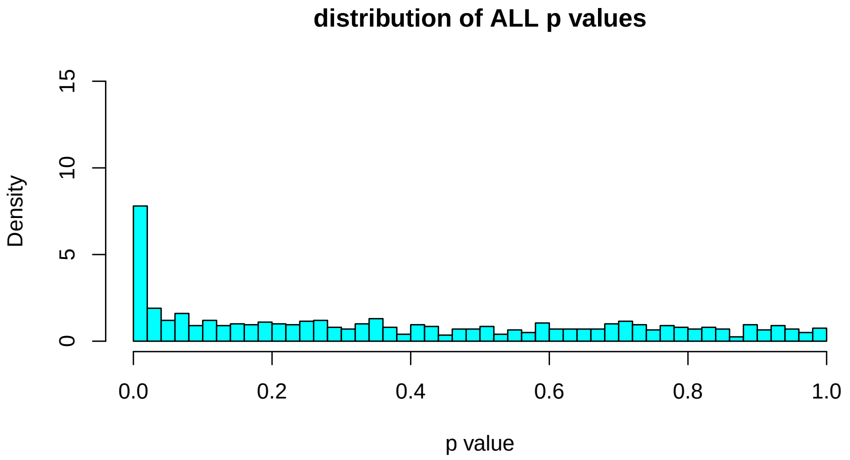

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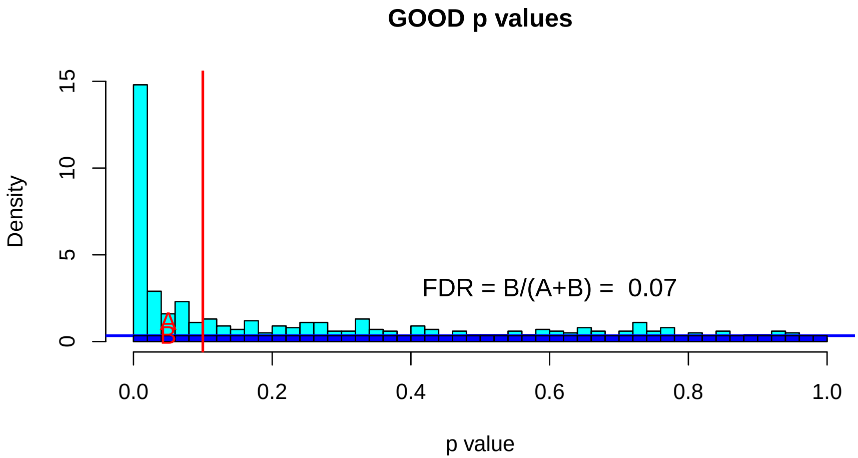

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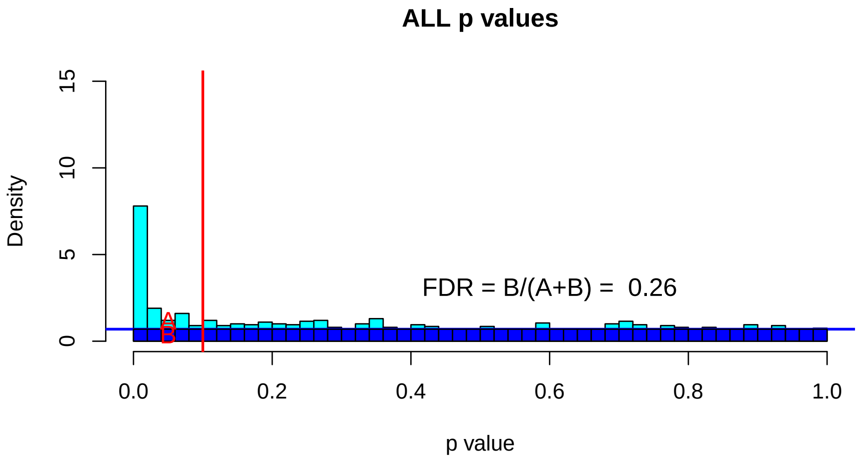

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- By focussing on p values, low-precision measurements can dilute high-precision measurements.

FDR via Empirical Bayes

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  where f_1, π_0 are to be estimated from the data.
- Once f_1 and π_0 estimated, FDR calculations are straightforward.

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- Constrain g to be unimodal about 0; estimate g from data.
- *Incorporate precision* of each observation $\hat{\beta}$ into the likelihood. Specifically, approximate likelihood for β_j by assuming

$$\hat{\beta}_j \sim N(\beta_j, s_j)$$

FDR - A New Deal

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- Estimating g comes down to estimating π. Joint estimation of π_0, π easy by maximum likelihood (EM algorithm).
- By allowing K large, and σ_k to span a dense grid of values, we get a flexible unimodal symmetric distribution.
- Can approximate, arbitrarily closely, any scale mixture of normals. Includes almost all priors used for sparse regression problems (spike-and-slab, double exponential/Laplace/Bayesian Lasso, horseshoe).

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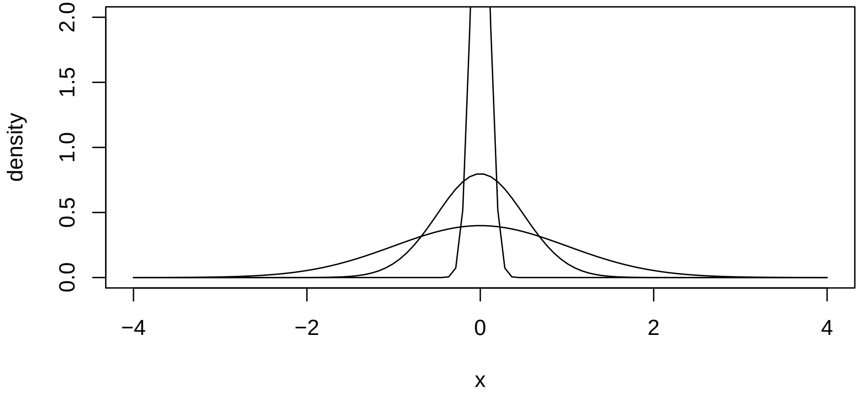
- If allow a very large number of uniforms this provides the non-parametric mle for g; cf Grenander 1953; Cordy + Thomas 1997.

Illustration: g a mixture of 0-centered normals



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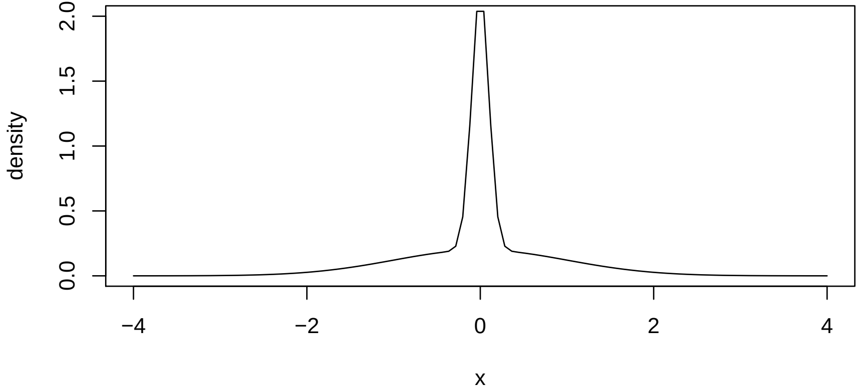

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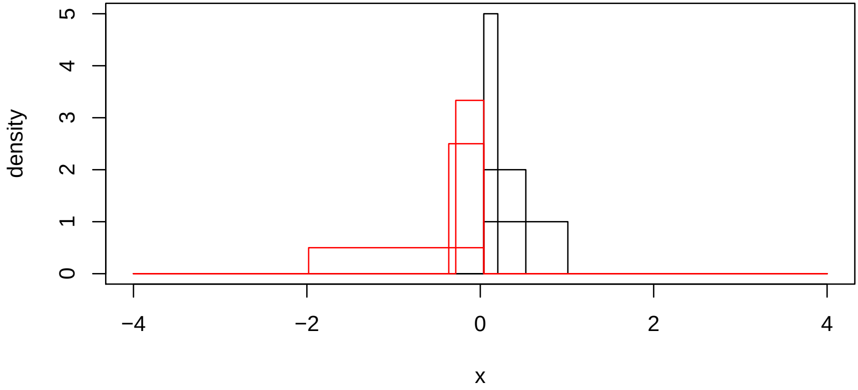

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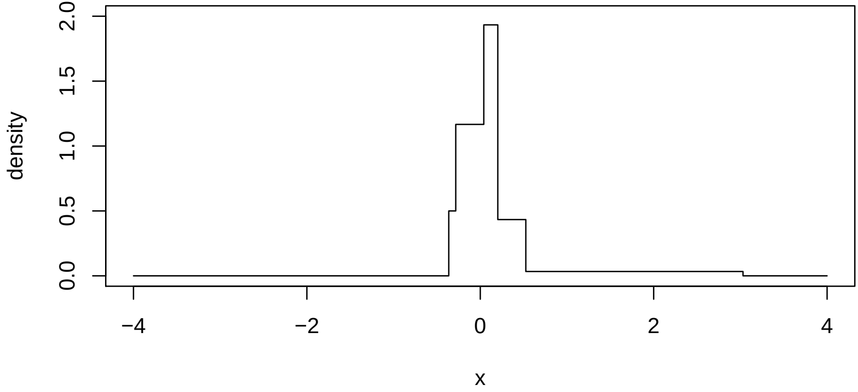
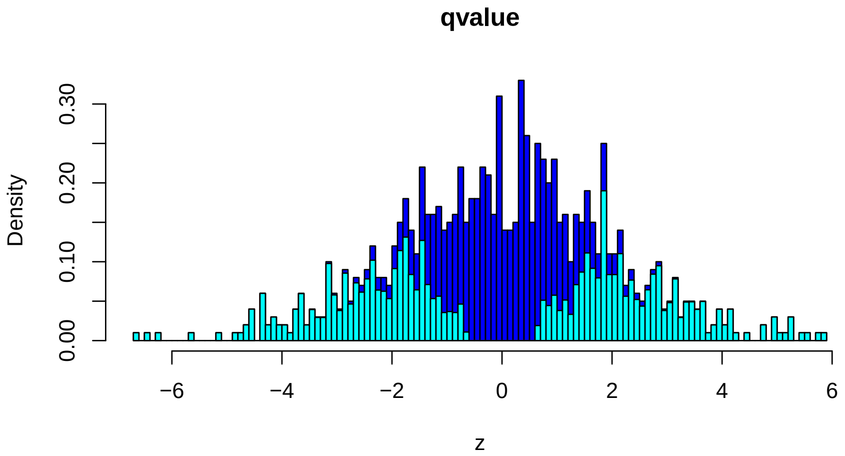


Recall Problem 1: distribution of alternative Z values multimodal



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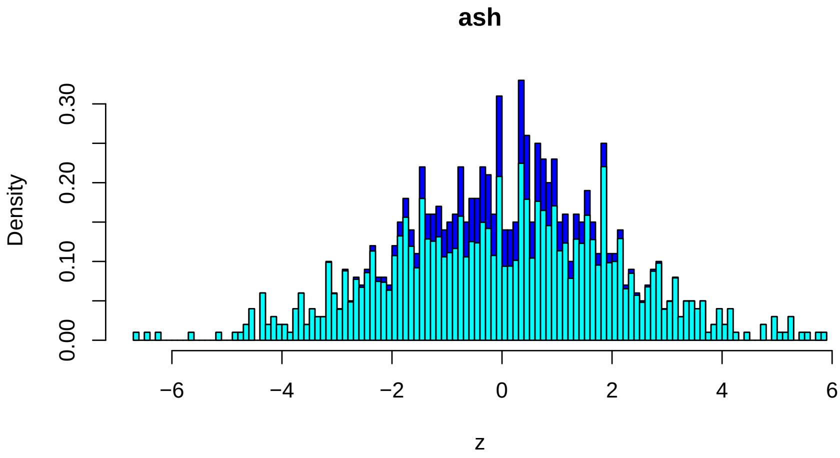

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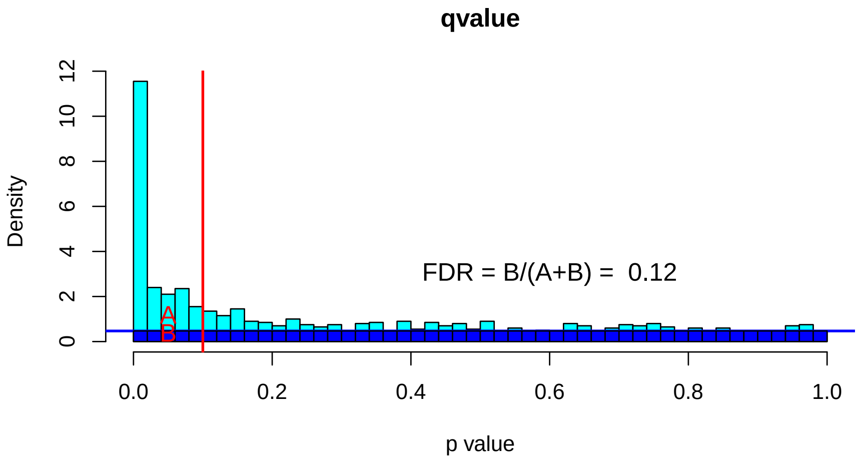

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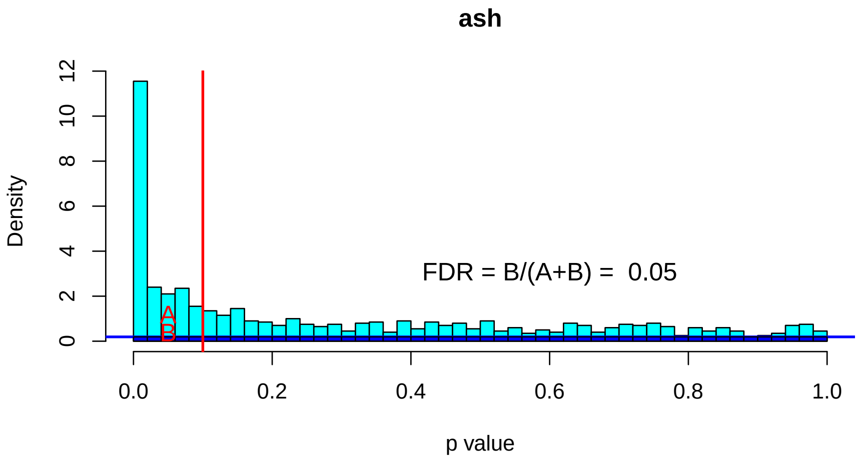

Recall Problem 2: poor measurements dilute good measurments

Number of findings at (estimated) FDR=0.05:

```
## id          qvalue    ash
## ------   ---------   -----
## ALL            114    211
## GOOD           193    209
```

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- In the illustrative example, the maximum q value is 0.18

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- But for some β_j we still may have little information about actual value
- Suggests a change of focus: assume *none* of the β_j are zero ("one group approach"), and ask for which β_j are we confident about the sign (Gelman et al, 2012).

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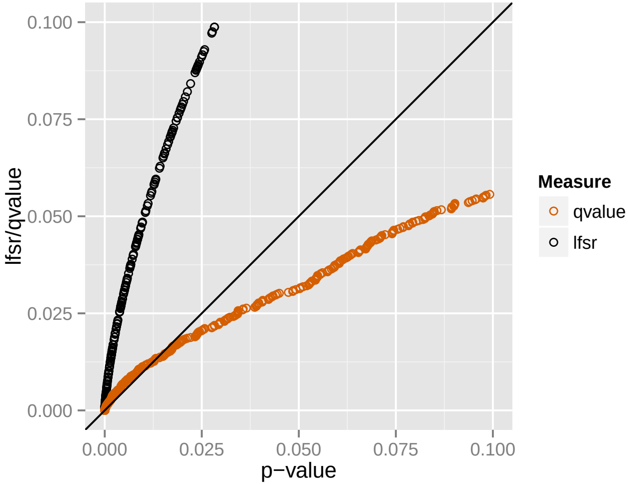
- Example: suppose we estimate that $\Pr(\beta_j < 0) = 0.975$ and $\Pr(\beta_j > 0) = 0.025$. Then we report β_j as a “(negative) discovery“, and estimate its fsr as 0.025.

Even with many signals, large *p* values have high lfsr



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- Unimodal assumption for effects reduces conservatism
- But by using two numbers $(\hat{\beta}, s)$ instead of one (p values or z scores) precision of different measurement is better accounted for.
- In high-signal contexts, False Sign Rate is preferable to False Discovery Rate.

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- "an article about a computational result is advertising, not scholarship. The actual scholarship is the full software environment, code and data, that produced the result." [Claerbout]

This talk is reproducible!

- http://www.github.com/stephens999/ash

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- Helps communications among researchers (eg student + advisor).

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Pandoc Command used

`pandoc -s -S -i --template=my.beamer -t beamer -V theme:CambridgeUS -V colortheme:beaver slides.md -o slides.pdf`

(alternative to produce html slides; but figures would need reworking) `pandoc -s -S -i -t dzslides --mathjax slides.md -o slides.html`

Here is my session info:

```
print(sessionInfo(), locale = FALSE)
```

```
## R version 3.0.2 (2013-09-25)
## Platform: x86_64-apple-darwin10.8.0 (64-bit)
##
## attached base packages:
## [1] splines   stats     graphics  grDevices utils     datas
## [8] base
```

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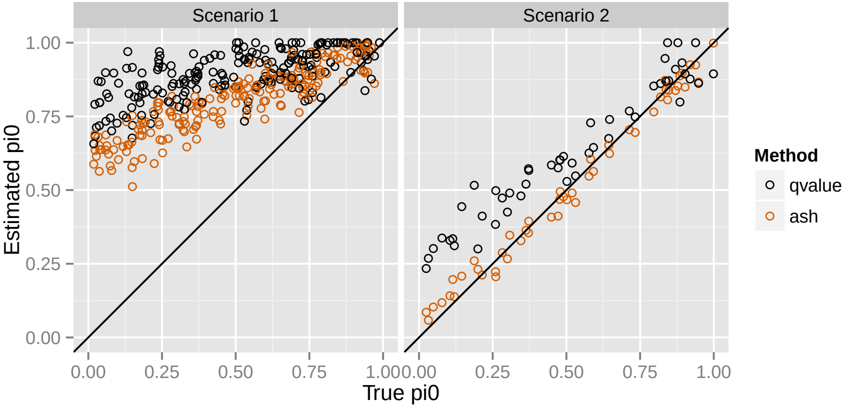
- Use penalized likelihood to make π_0 "as big as possible", subject to the unimodal constraint.

Approach remains conservative (if unimodal assumption holds)



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- That is three times a day for the last 19 years!

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- The q value for observation j is $q_j = \text{FDR}(p_j)$.

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- Because $f(\beta)$ is unimodal, the point estimates will tend to be "shrunk" towards the overall mean (0).
- Because $f(\beta)$ is estimated from the data, the amount of shrinkage is adaptive to the data. And because of the role of s_j, the amount of shrinkage adapts to the information on each gene.
- So we call the approach "Adaptive Shrinkage" (ASH).