Adaptive Shrinkage and False Discovery Rates by Laplace Approximation

Matthew Stephens

2013/5/13

Outline

- Prelude

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- Allegro (ma non troppo)

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- Coda

Prelude

- Consider testing the null hypothesis $H_0 : \beta = 0$, vs the alternative $H_1 : \beta \neq 0$ in the logistic regression model:

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- In genome-wide association studies, we may wish to do this for millions of different genetic variants (X).

Prelude

$$BF = \frac{\int p(Y|\mu, \beta, X) p_1(\mu, \beta|X)\, d\mu d\beta}{\int p(Y|\mu, \beta = 0, X) p_0(\mu|X)\, d\mu},$$

where p_0 and p_1 denote priors under H_0 and H_1.

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- These integrals generally don't have closed forms, but being low-dimensional they are simple to approximate.
- For $p_1 : \beta \sim N(0, \phi^2)$, Wakefield, 2009 (see also Johnson, 2008) suggested a particularly simple *Approximate Bayes Factor* (ABF) based on the maximum likelihood estimate, $\hat{\beta}$, and its (estimated) standard error s.

Prelude

$$ABF = \sqrt{1-k}\exp(0.5kT^2)$$

where $k := \phi^2/(s^2+\phi^2)$ and $T := \hat{\beta}/s$.

- ABF arises if we assume $\hat{\beta}|s,\beta \sim N(\beta, s^2)$ and treat $\hat{\beta}$ as the observed "data".

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- ABF arises if we assume $\hat{\beta}|s,\beta \sim N(\beta, s^2)$ and treat $\hat{\beta}$ as the observed "data".
- Equivalently ABF can be derived as a "Laplace approximation", approximating the likelihood $L(\beta)$ as Normal, centered on $\hat{\beta}$, with variance s^2:

$$L(\beta) \propto \exp[-0.5(\beta-\hat{\beta})^2/s^2].$$

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  - Applicable to any regression where $\hat{\beta}$ and s are available.
  - Easily computed using results of standard software or published analyses (e.g. CI).
- A simple transformation of T can improve accuracy for small samples (analagous to t test vs Z test); Wen and Stephens, Arxiv.

Extensions of ABF

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- Eg In Wen and Stephens, we consider S subgroups, and approximate the BF for $H_0 : \beta_s = 0$ for all s, vs a general alternative $H_0 : \beta_s \neq 0$.

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- The problem: you have imperfect measurements of many "similar" things, and wish to estimate their values.
- Particularly common in genomics. For example, a very common goal is to compare the mean expression (activity) level of many genes in two conditions.

Example: Mouse Heart Data

- Data on 150 mouse hearts, dissected into left and right ventricle (courtesy Scott Schmemo, Marcelo Nobrega)

```
##       gene  lv1  lv2   rv1   rv2 genelength
## 1    Itm2a 2236 2174  9484 10883       1626
## 2   Sergef   97   90   341   408       1449
## 3 Fam109a  383  314  1864  2384       2331
## 4     Dhx9 2688 2631 18501 20879       4585
## 5    Ssu72  762  674  2806  3435       1446
## 8   Eif2b2  736  762  3081  3601       1565
```

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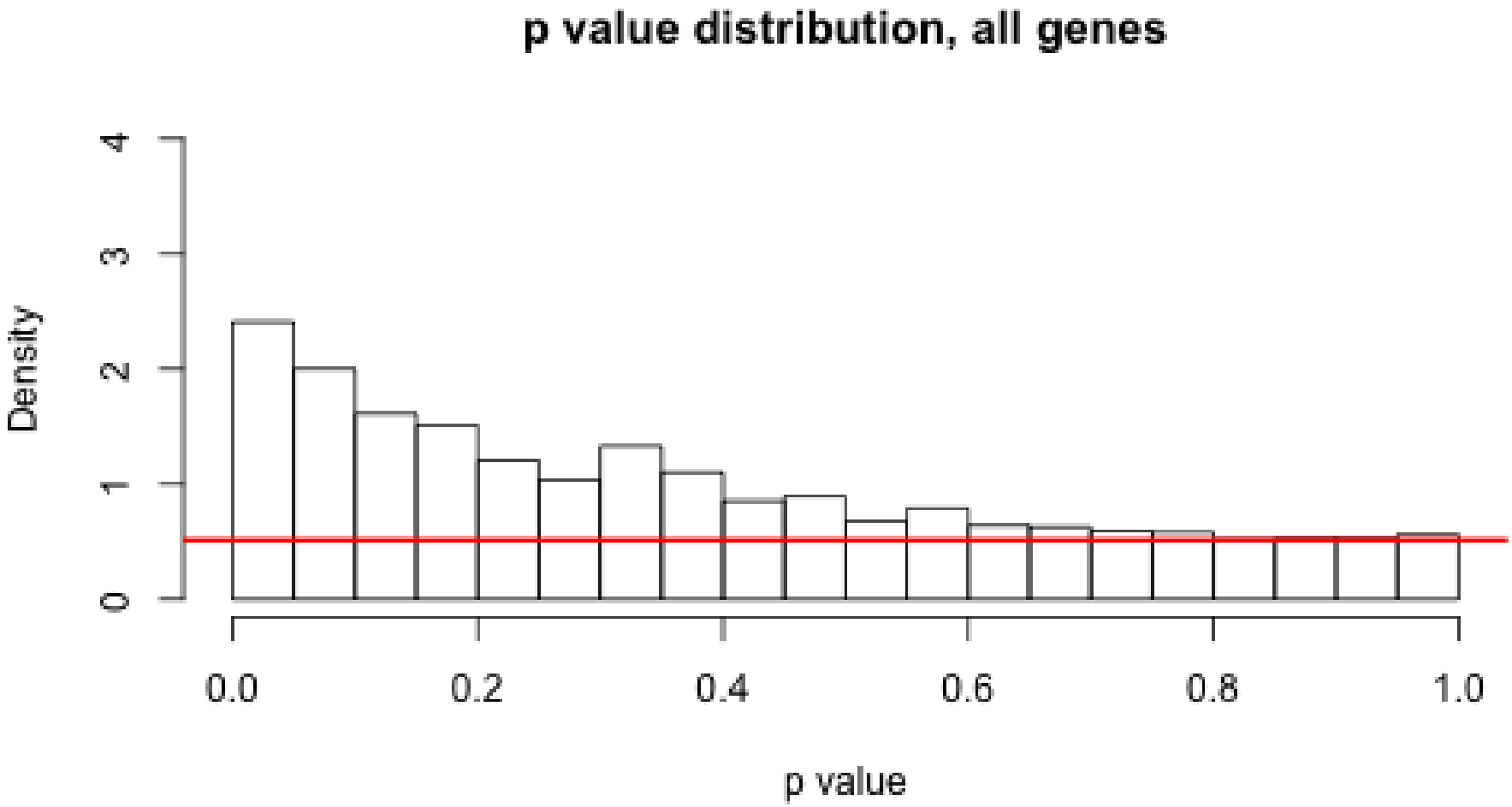
  - Convert this to a p value for each gene, e.g. by a t test on β_j/s_j.
  - Use the distribution of p values to estimate the false discovery rate (FDR) at a given threshold.

False Discovery Rates



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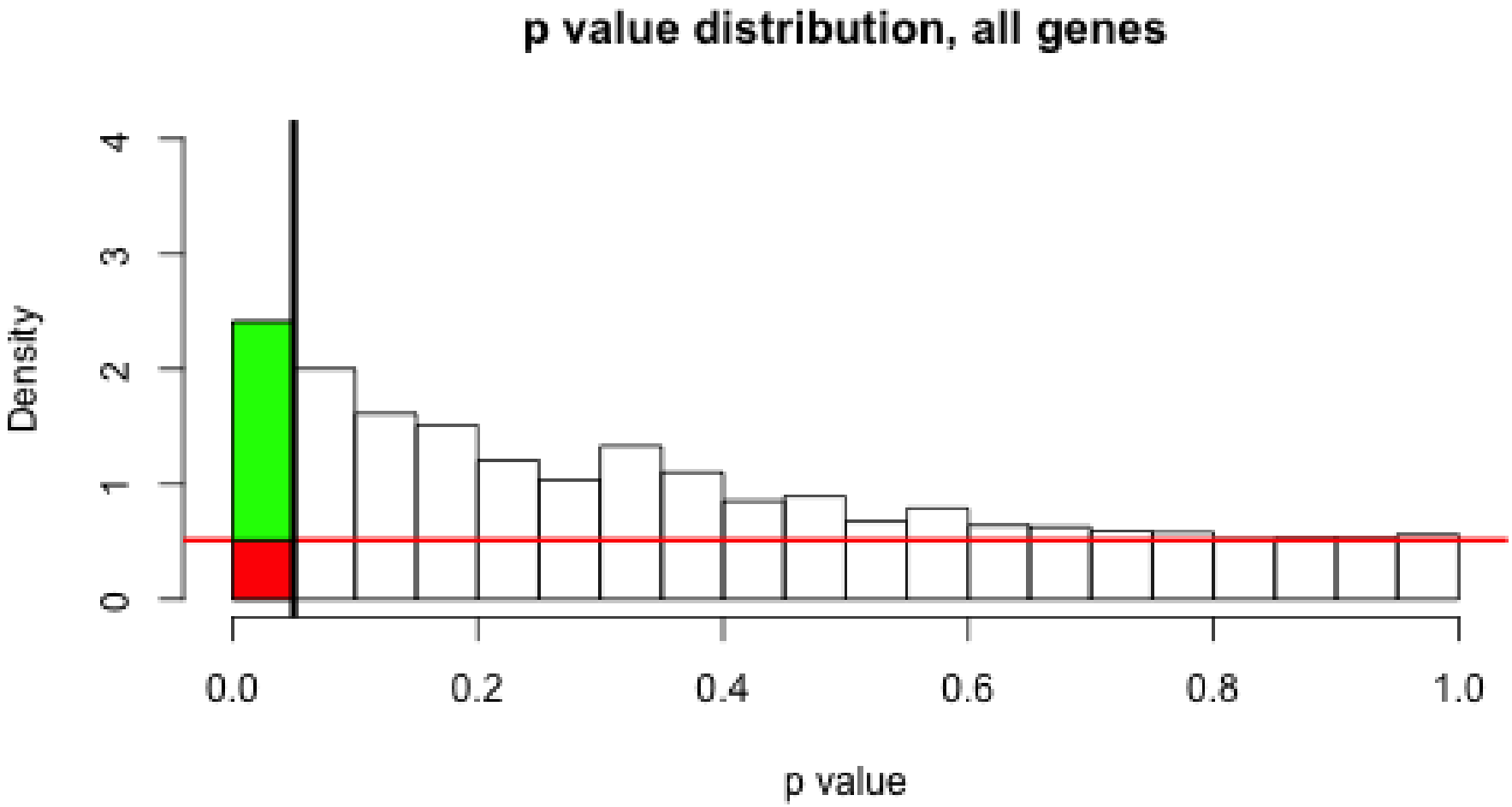
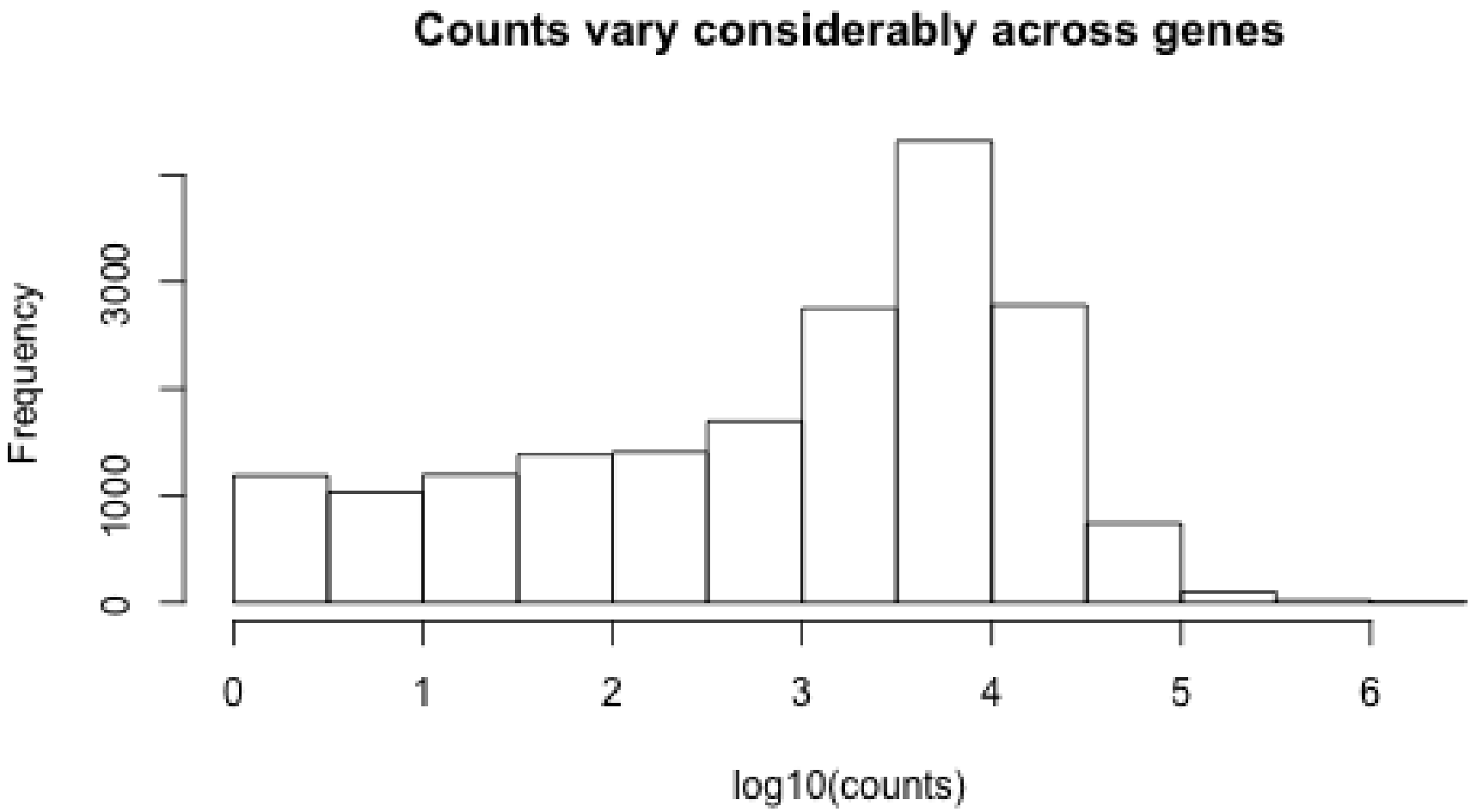
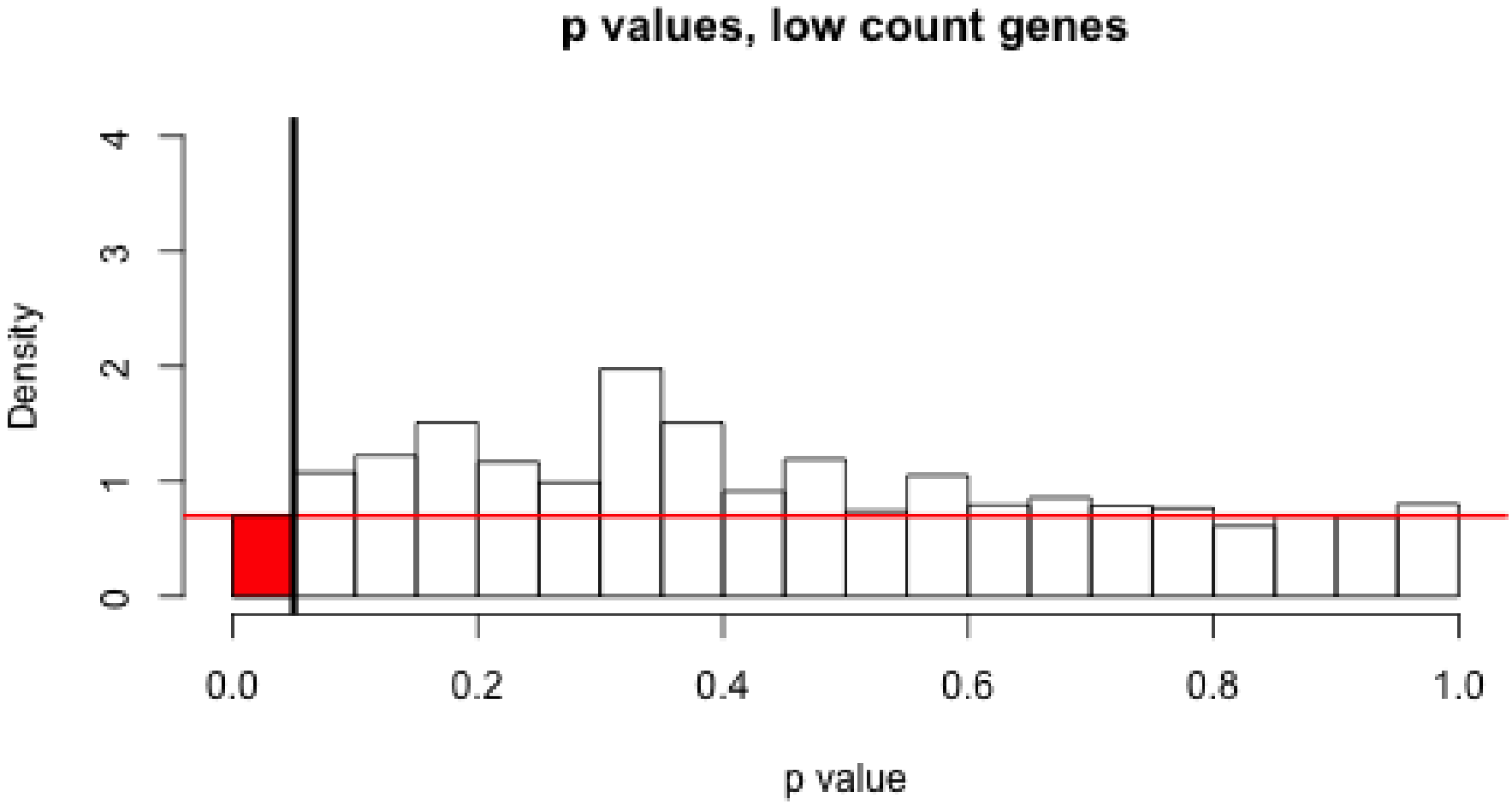


Figure : FDR=0.21

FDR problem: different genes have different precision/power



FDR problem: lower count genes, less power, add noise



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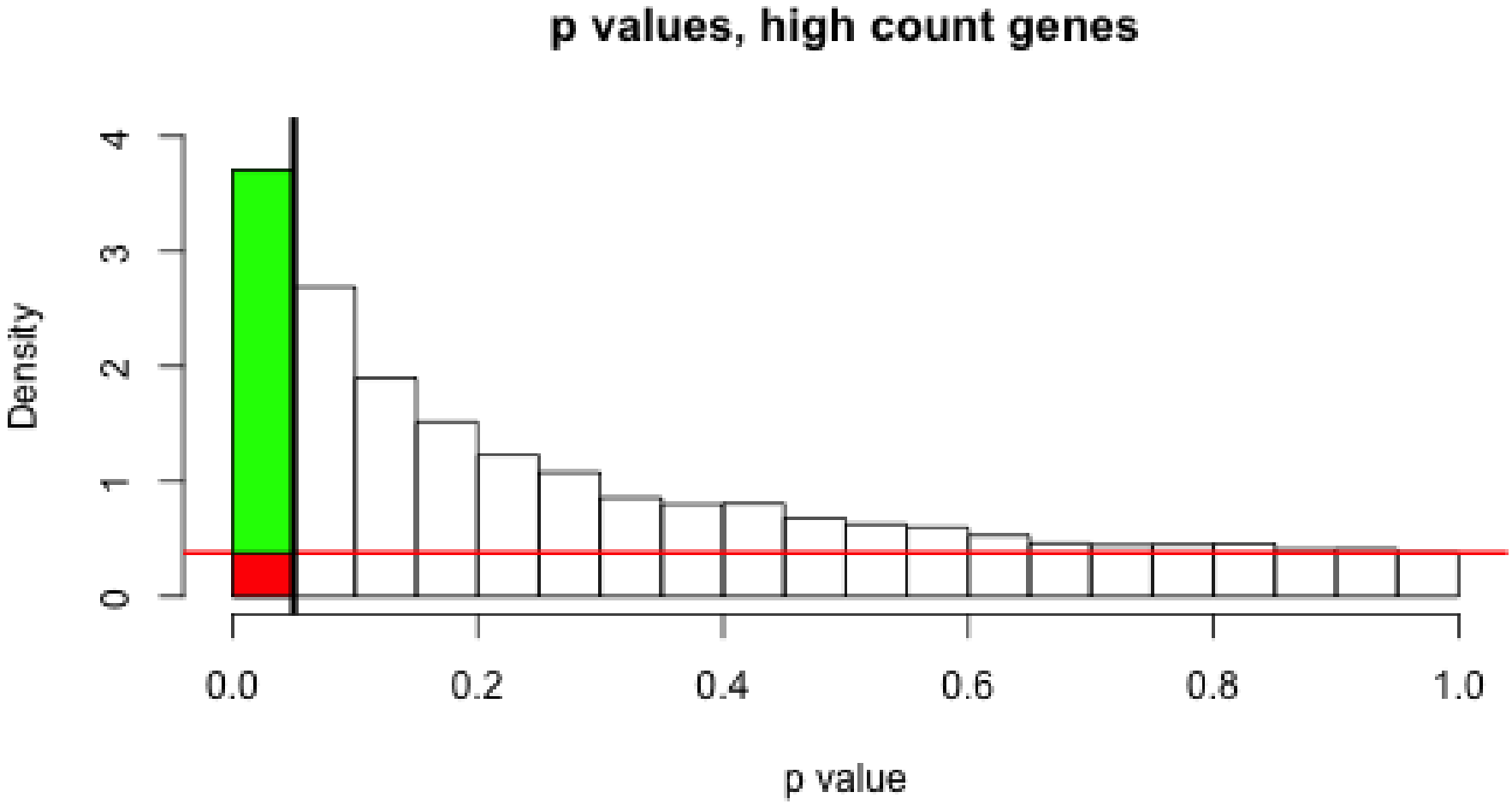

Figure : FDR=0.10

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- Despite a long-standing literature on these types of methods - e.g. Greenland and Robins 1991, Efron and Tibshirani 2002, Gelman et al 2012 - they are much less widely used (in genomics at least).
- Possibly this is due, in part, to the lack of a simple, flexible, and generic implementation?

Generic adaptive shrinkage via Laplace approximation

- Summarize data on each gene by two numbers, $\hat{\beta}_j$ and its standard error s_j. (a la Wakefield; Greenland and Robins 1991)

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- Letting $g(\cdot;\pi)$ be a mixture of normal distributions provides both flexibility, and analytic calculations.
  - very small variances can capture effects that are "effectively" zero.

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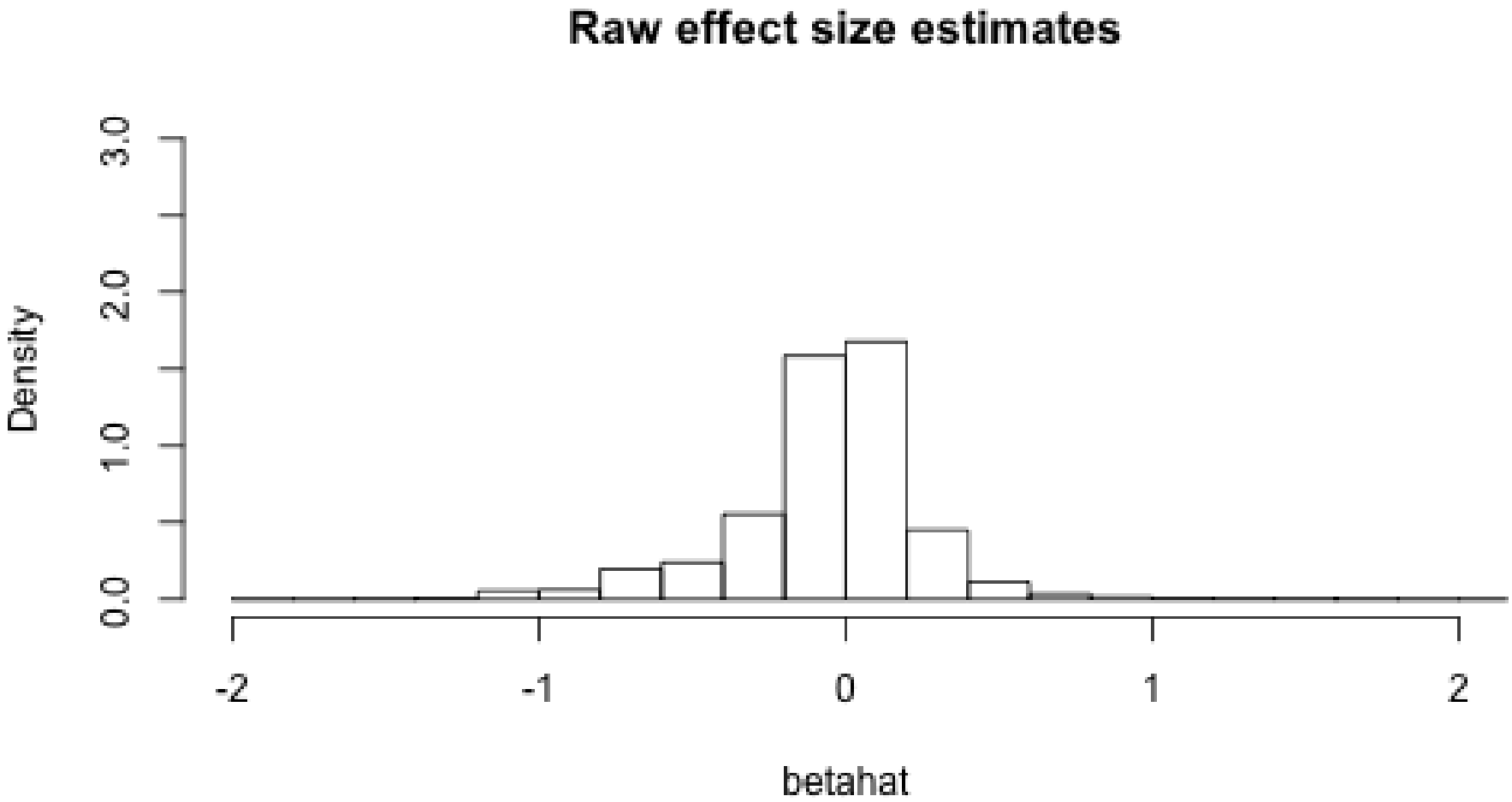
- Because π is estimated from the data, the amount of shrinkage is adaptive to the data. And because of the role of s_j, the amount of shrinkage adapts to the information on each gene.

Example: ASH applied to mouse data



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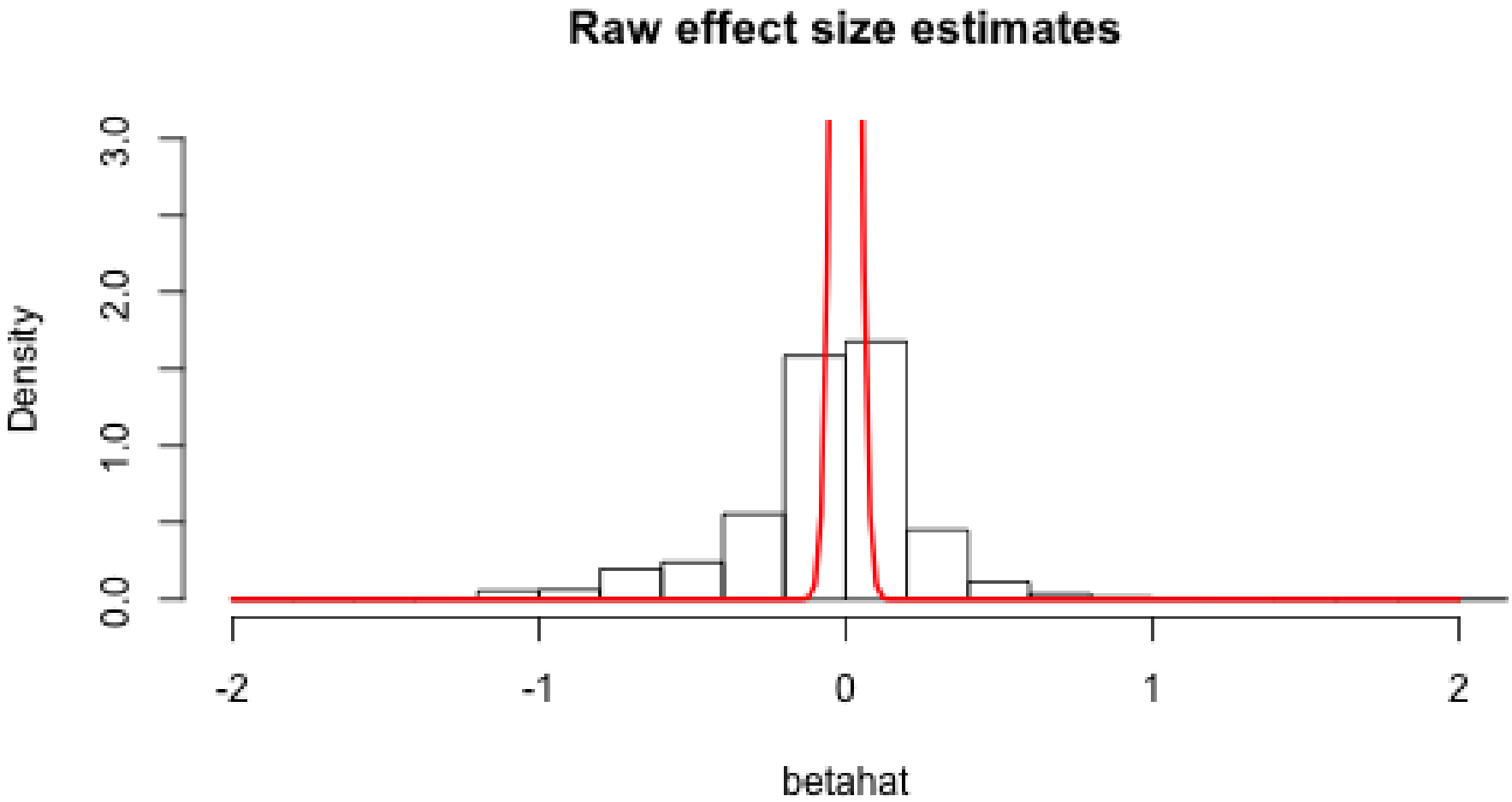

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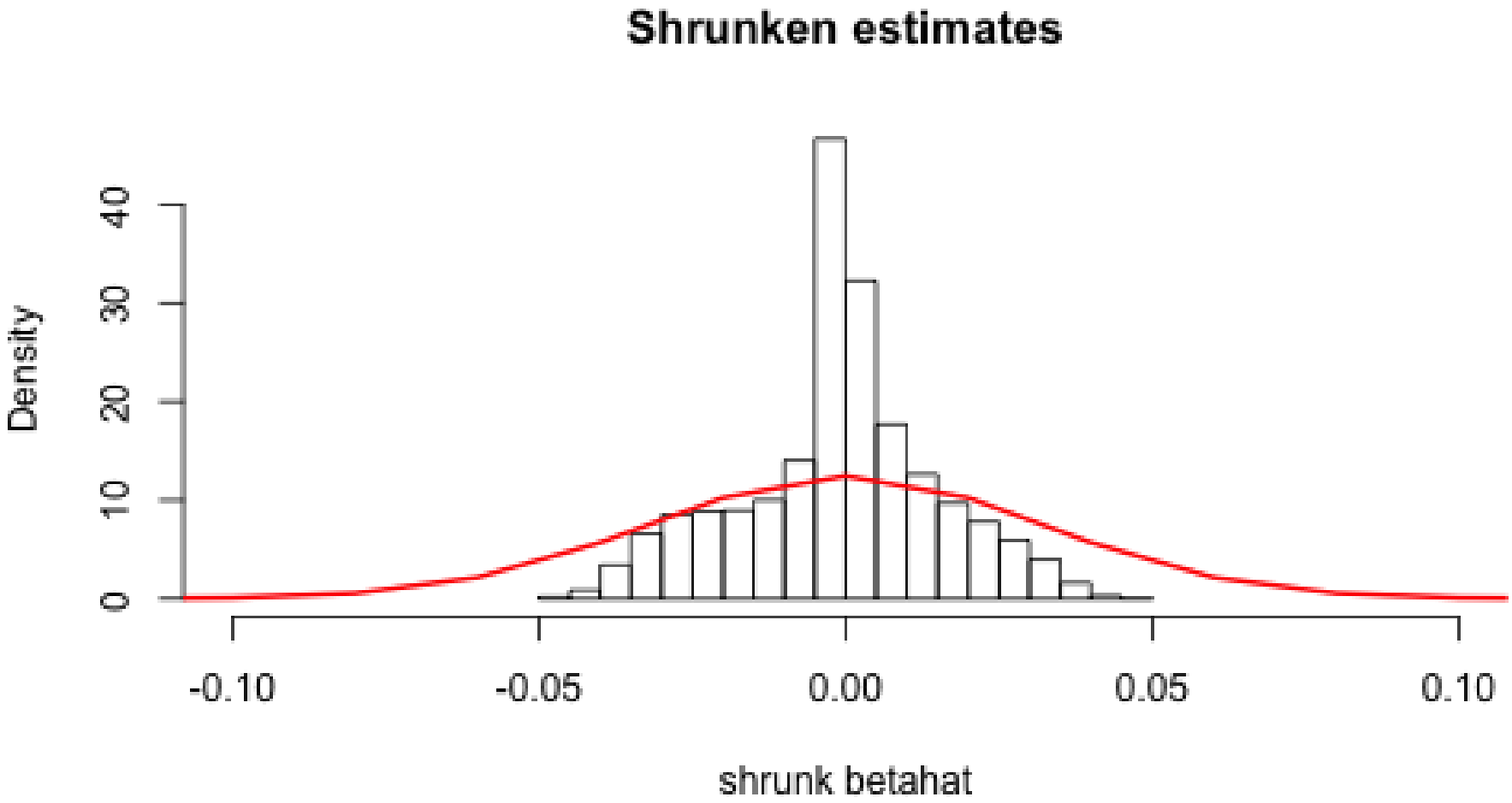
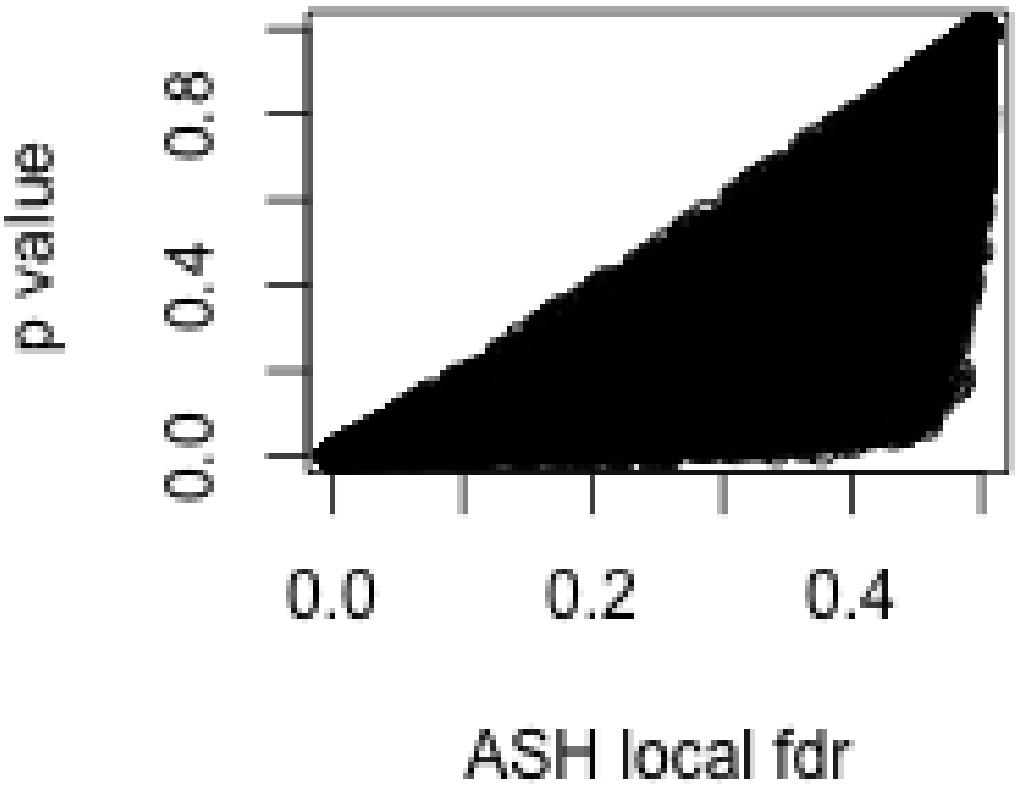


Shrinkage is adaptive to information



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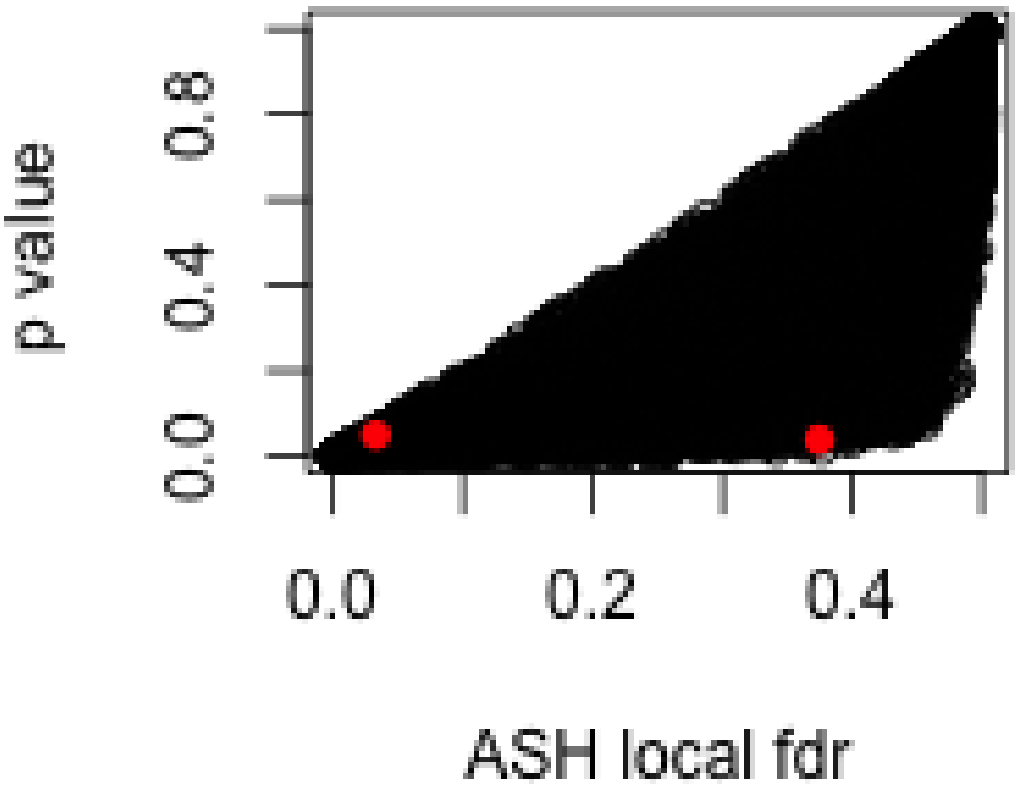

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```
##          gene  lv1  lv2  rv1  rv2    pval zdat.ash$localfdr
## 19422 Mgat5b    7   10  320  452 0.03795           0.37448
## 20432  Sec63 1042 1034 5496 6649 0.04908           0.03251
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- But by using two numbers $(\hat{\beta}, s)$ instead of one (p values) precision of different measurements can be better accounted for.
- ASH borrows information for estimation, as well as testing.

Guarantees?

- "I think you have some nice ideas. How will you convince people to use them?" (C Morris)

Next steps?

- Extend to allow $g(\cdot; \pi)$ to depend on covariates X.

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- Extend to allow for correlations in the measured $\hat{\beta}_j$.

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- BSLMM software, runs with thousands of individuals, hundreds of thousands of variables. (Zhou et al, 2013)
- Also variational approximations (Carbonetto and Stephens, Bayesian Analysis)

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- And to the NIH for funding, and i-like for inviting me.

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Pandoc Command used

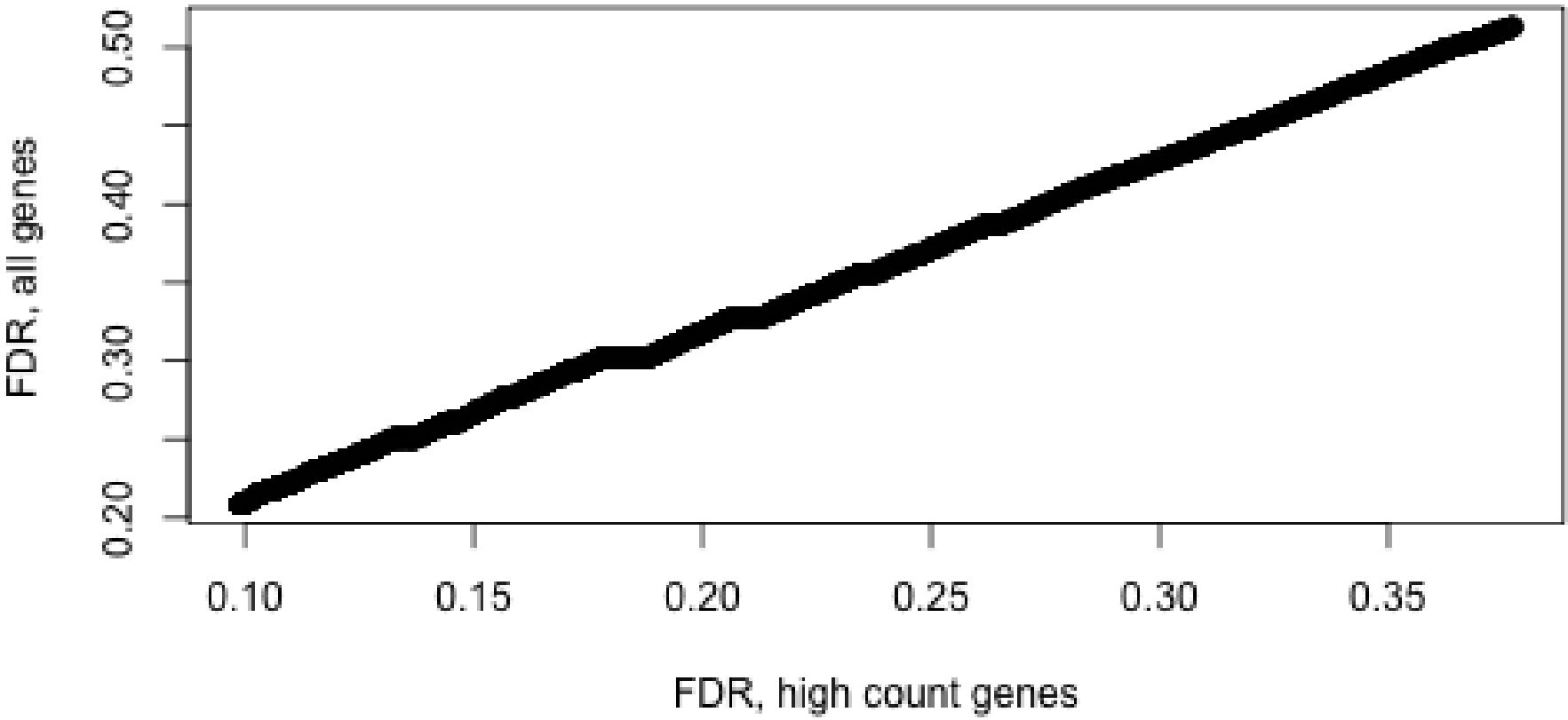
pandoc -s -S -i –template=my.beamer -t beamer -V theme:CambridgeUS -V colortheme:beaver ilike-slides.md -o ilike-slides.pdf

Here is my session info:

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

```
## R version 2.15.1 (2012-06-22)
## Platform: x86_64-apple-darwin9.8.0/x86_64 (64-bit)
##
## attached base packages:
## [1] stats     graphics  grDevices utils     datasets  metho
##
## other attached packages:
## [1] qvalue_1.30.0 knitr_1.1
##
## loaded via a namespace (and not attached):
## [1] codetools_0.2-8 digest_0.6.3    evaluate_0.4.3  formatR
```

FDRs for higher count genes affected by lower count genes



Some odd things in the data