False Discovery Rates, A New Deal

Matthew Stephens

2014/2/24

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- Organized researchers get more done (and better!).
- Many of them are more organized than I am!
- Thought: I should get organized; I should help others get organized.

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- Use version control git and internet repositories (bitbucket, github) to organize notes, code, etc.
- Use knitr to help make your research reproducible.

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- An amateur example: `http://github.com/stephens999/ash`

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- This talk was written with knitr (with RStudio)!

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- "publishing figures or results without the complete software environment could be compared to a mathematician publishing an announcement of a mathematical theorem without giving the proof" (Buckheit and Donohoe)
- "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]

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- If you do not publish code implementing your methods, your methods will likely go unused.

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- Google "donohoe buckheit" for "Wavelab and reproducible research"

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FDR, local fdr, and q values

Although precise definitions vary depending on whether one takes a Bayesian or Frequentist approach to the problem, roughly

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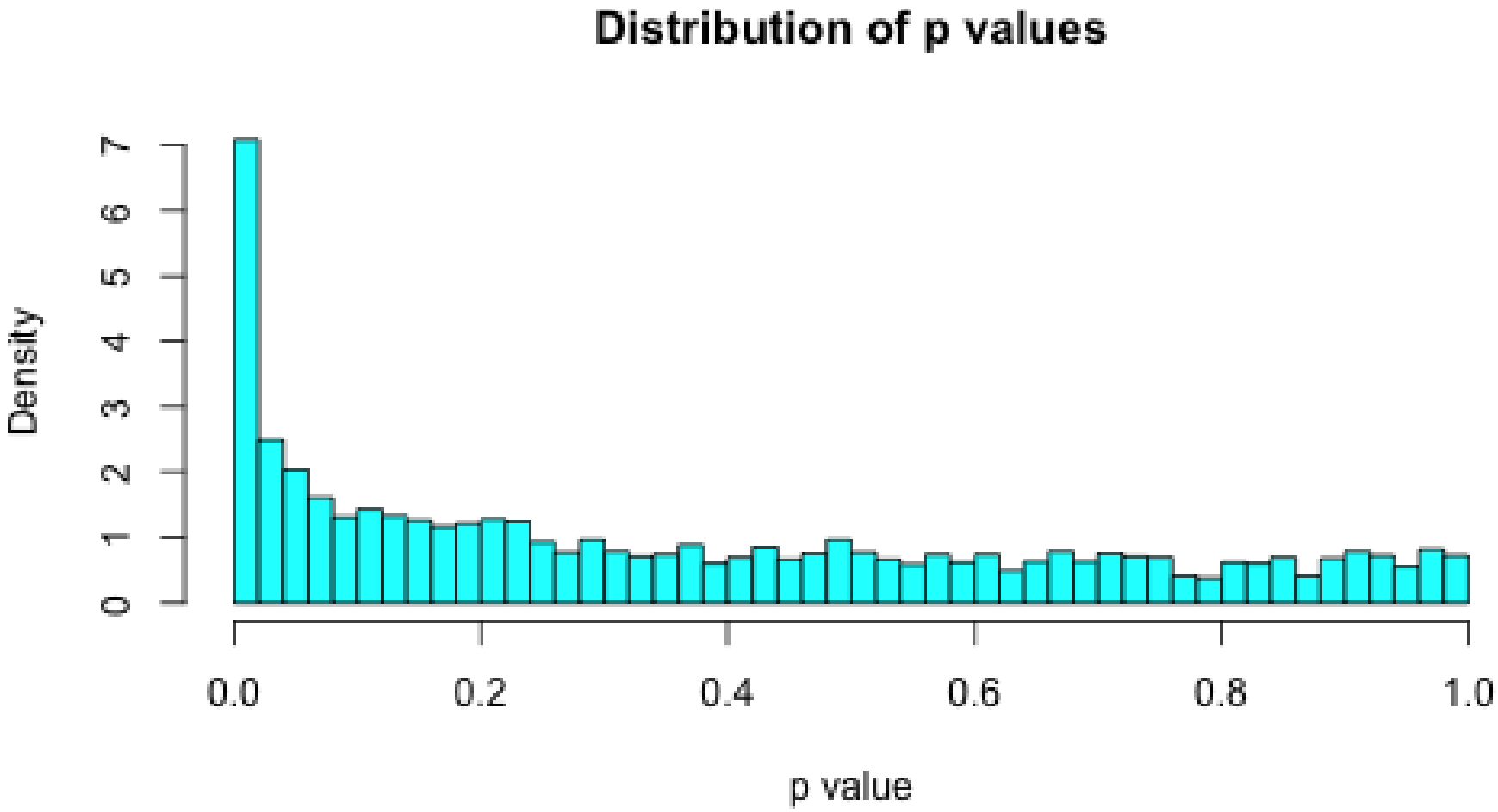
- The fdr is more relevant, but slightly harder to estimate than FDR because it involves density estimation rather than tail-area estimation.

Example: FDR estimation



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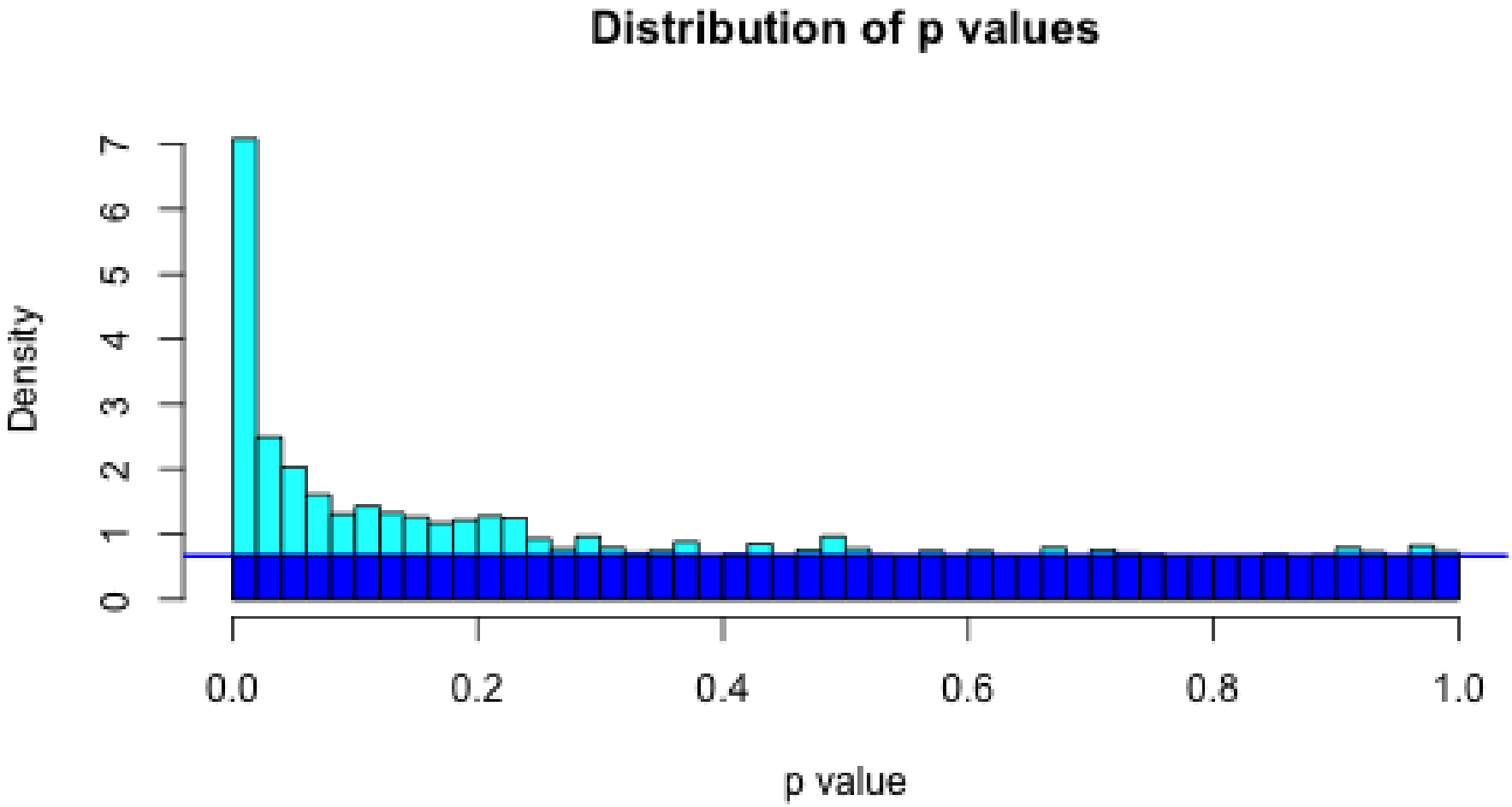

Data from Hedenfalk et al. comparing BRCA1 vs BRCA2 expression

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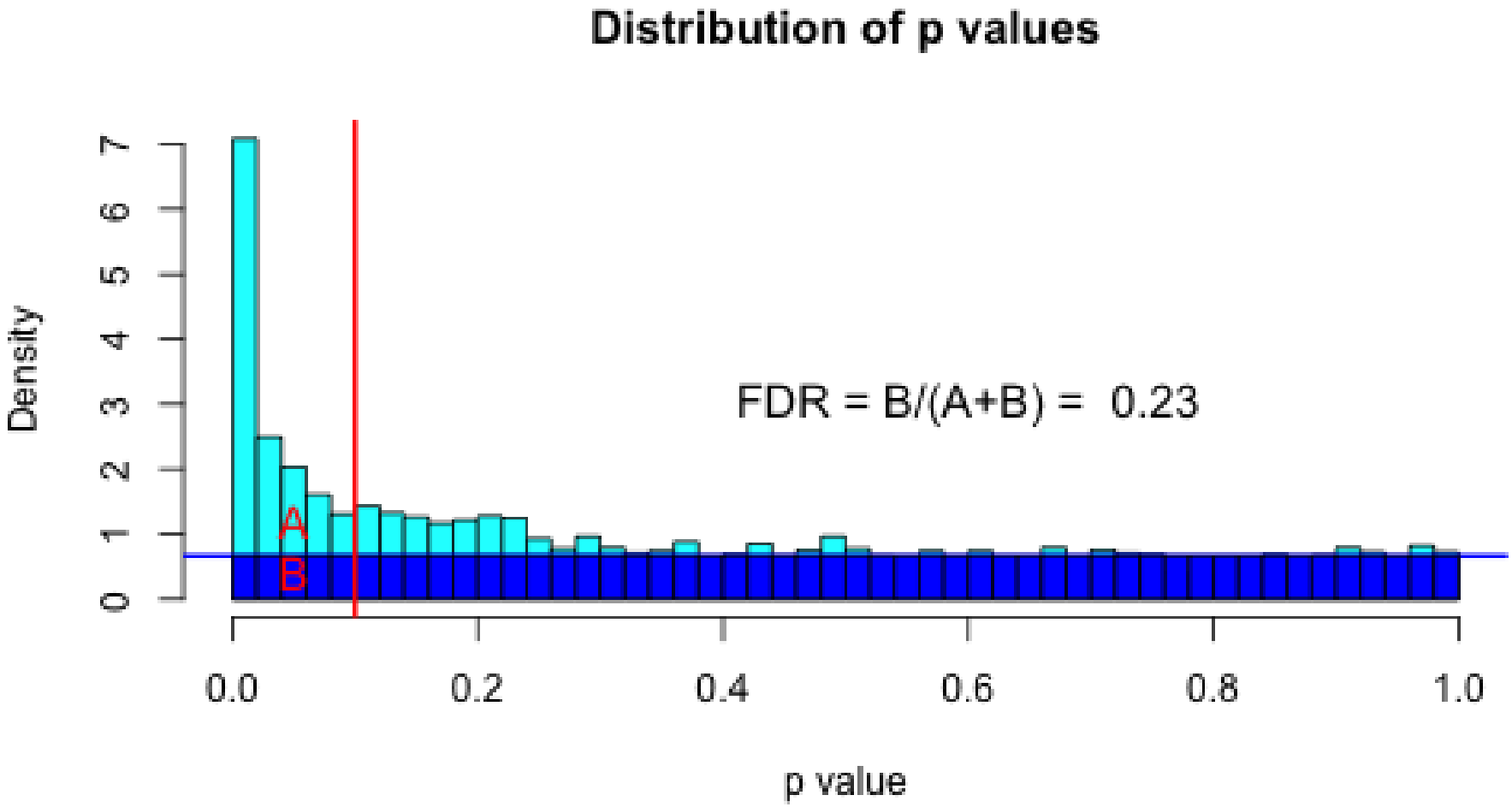

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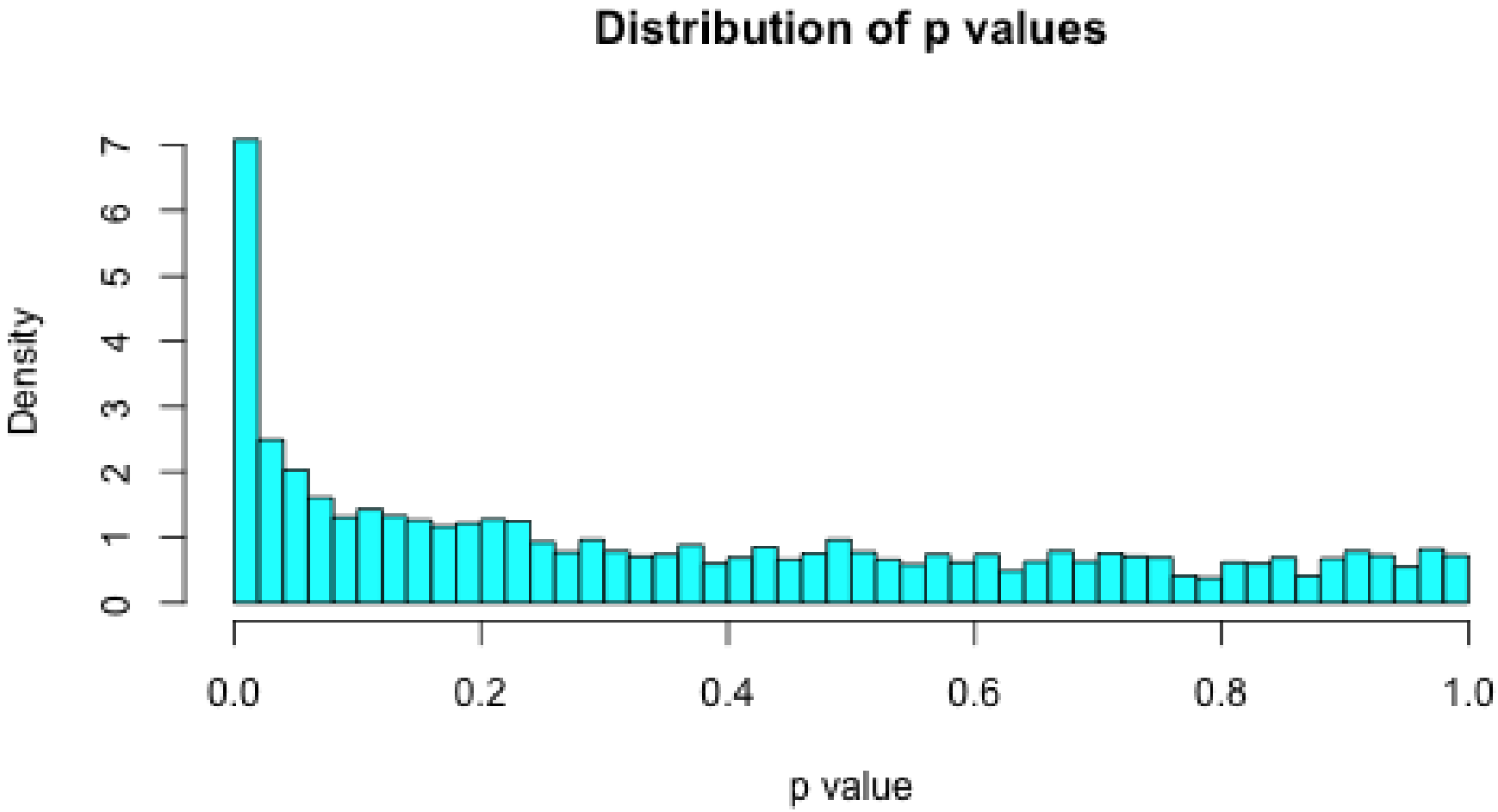

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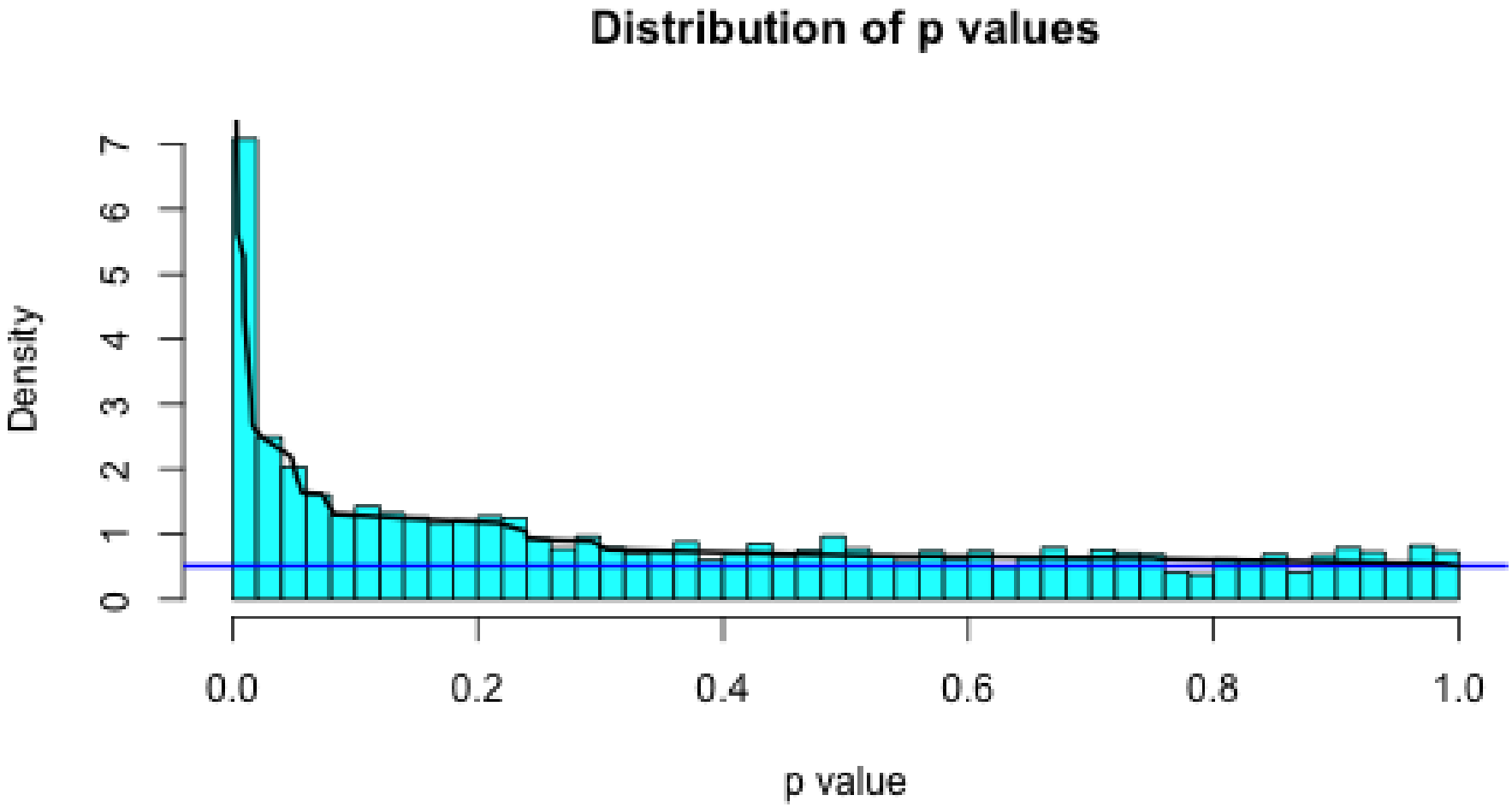

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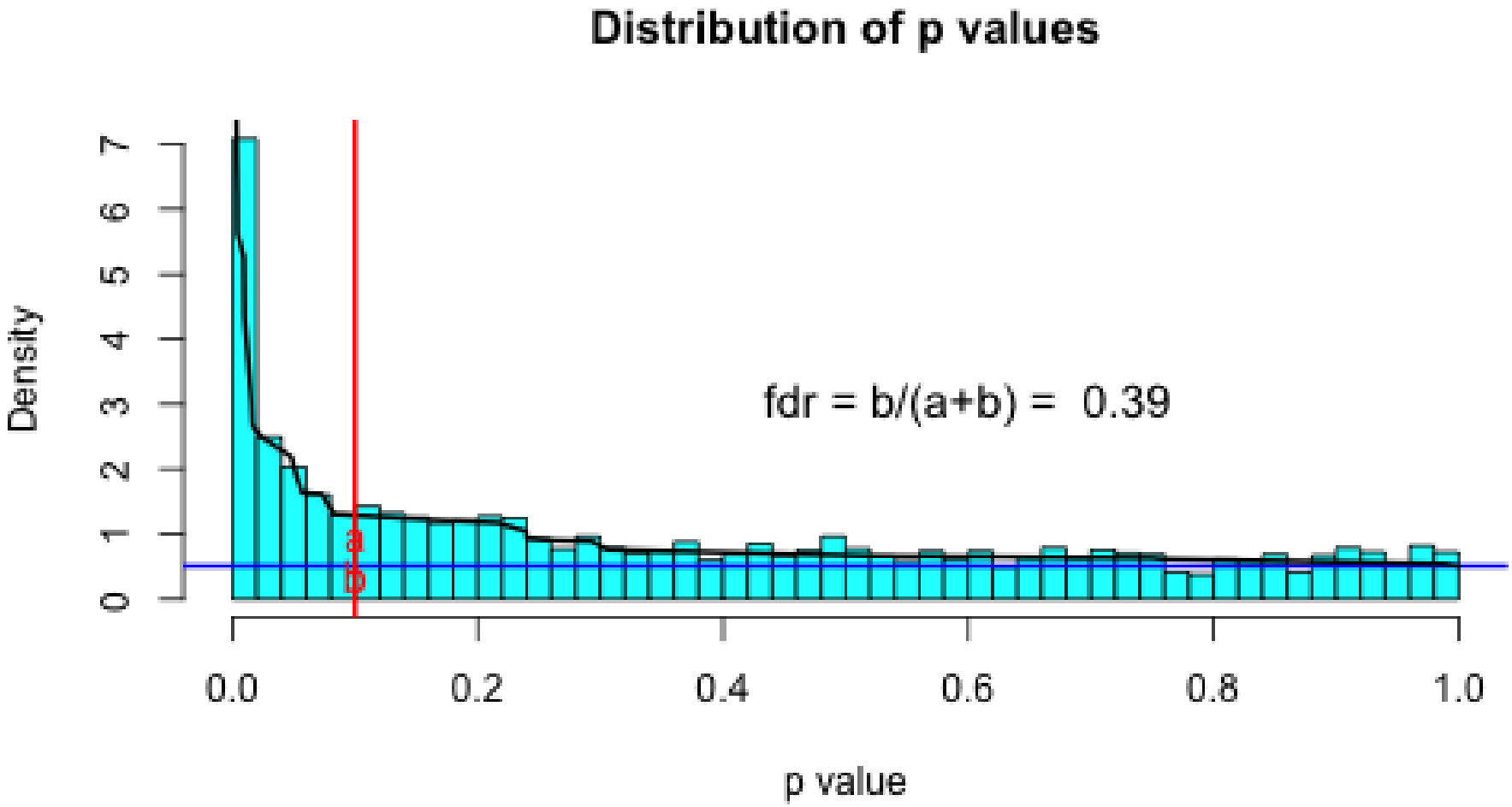

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- If some effects are measured very imprecisely, those tests "lack power" and simply add noise
- In particular, such tests increase the estimated number of nulls, and increase the FDR for other tests
- It would seem preferable to simply ignore the tests with very low precision. Summarizing each test by a p value (or Z score) loses the information about precision.

Example: Mouse Heart Data

```
##       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
```

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

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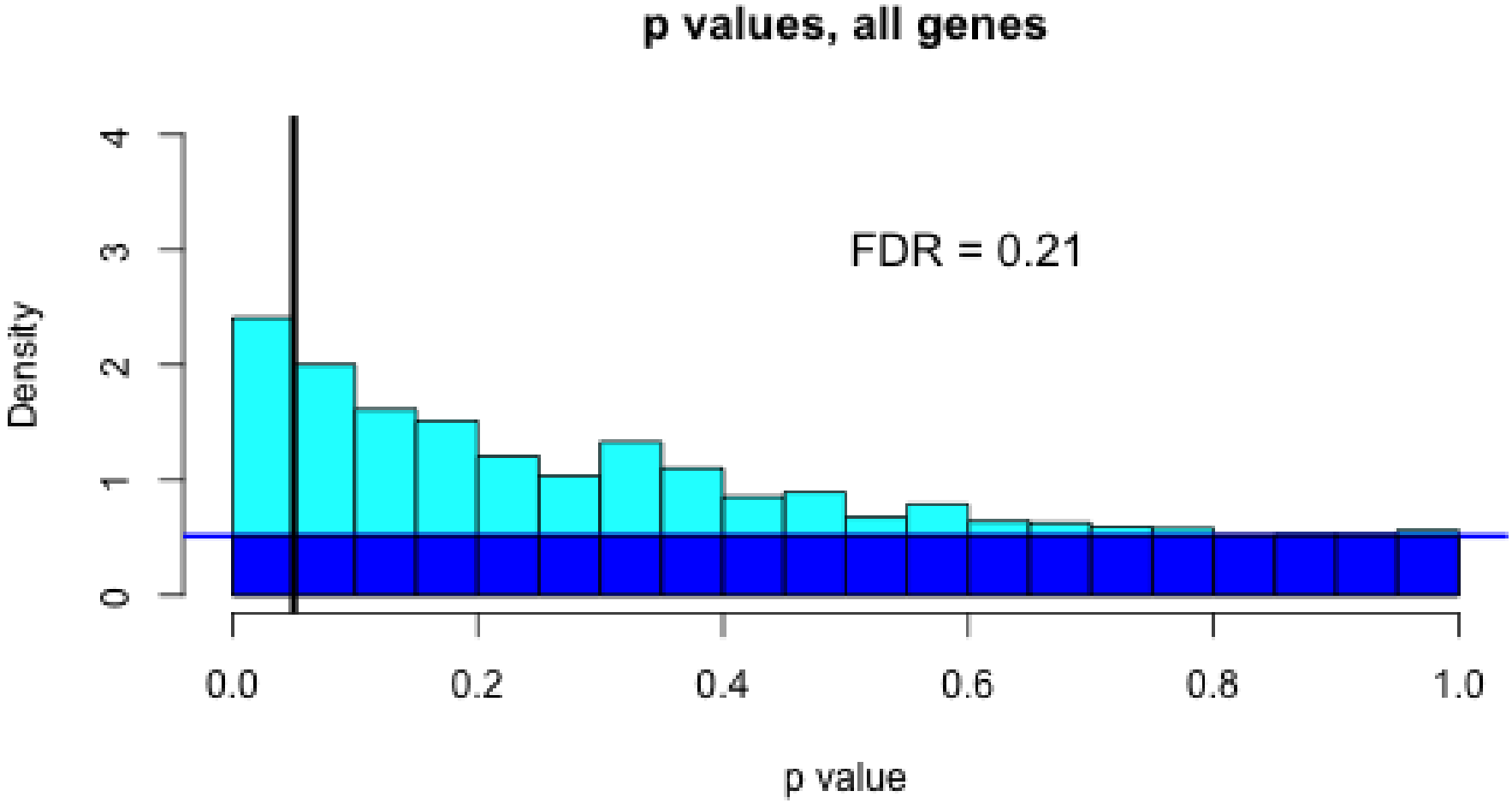
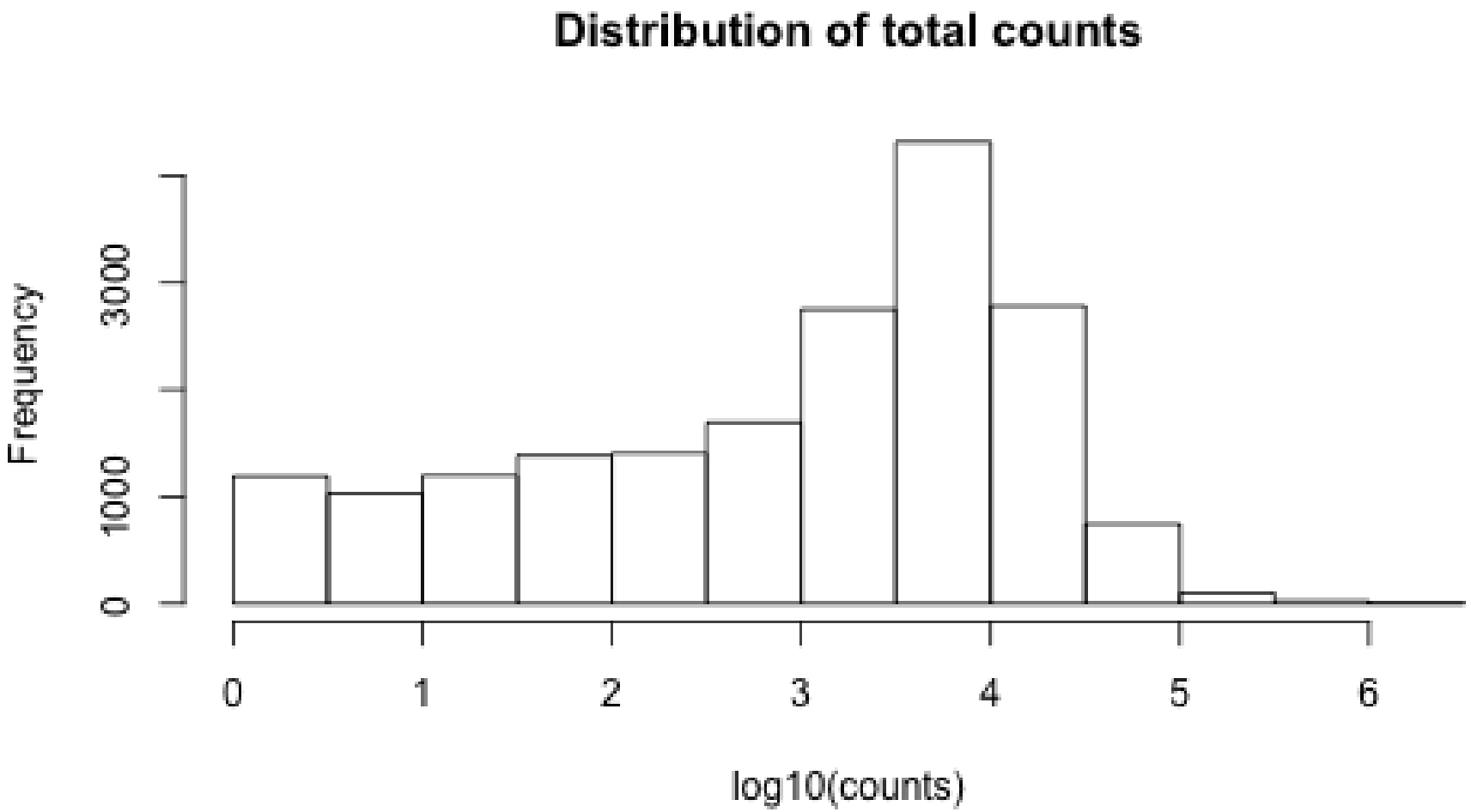
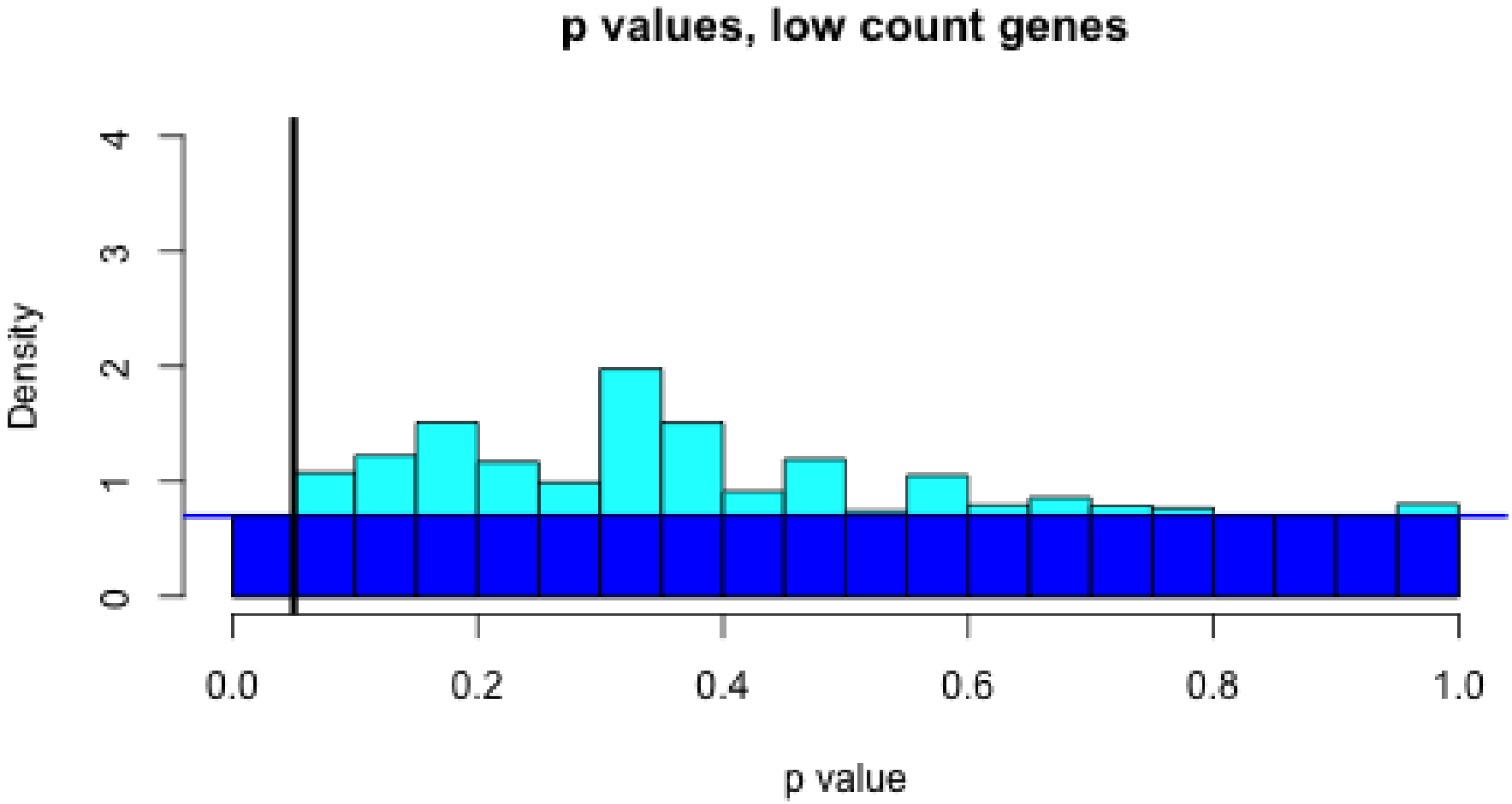


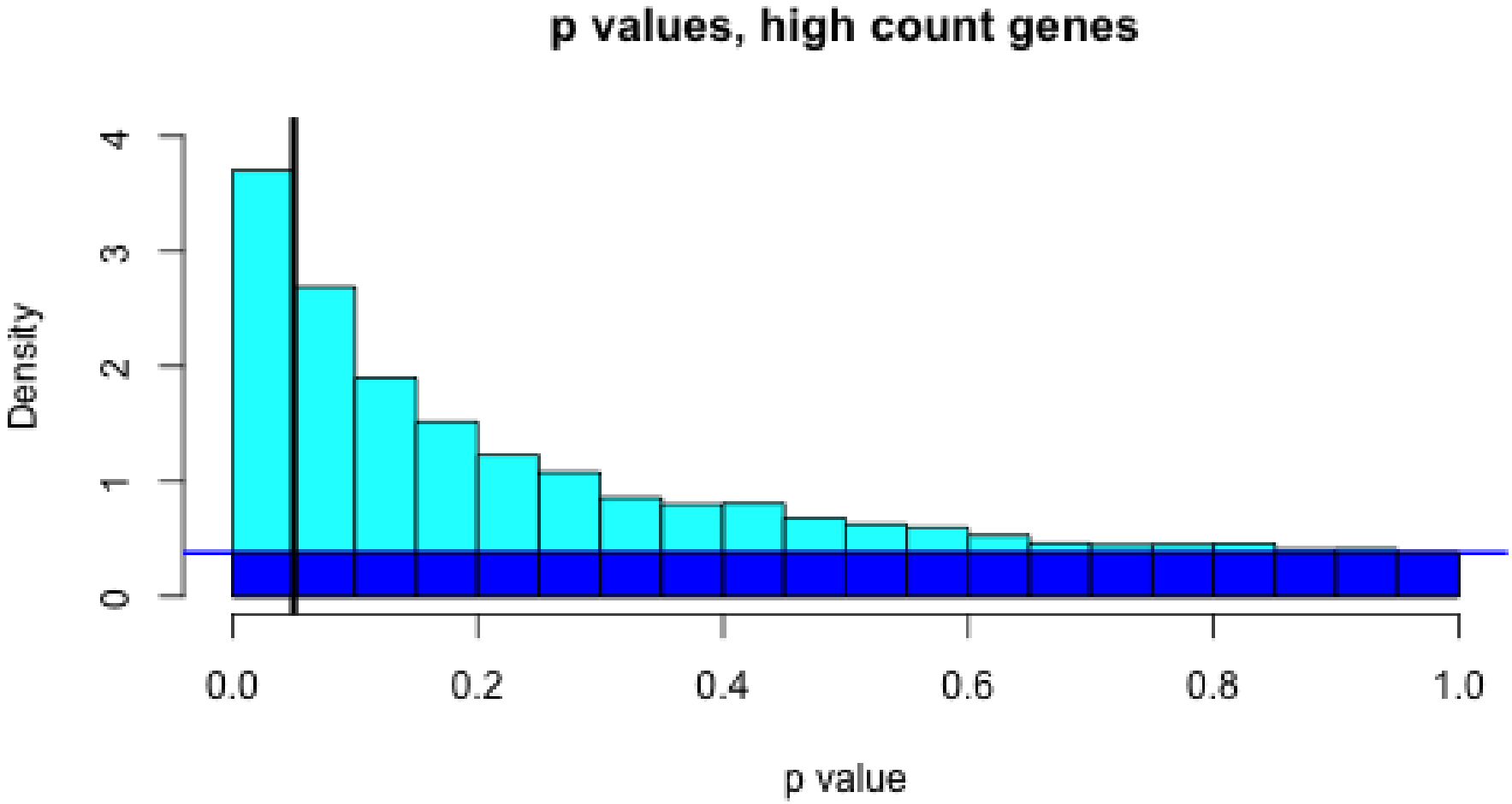
Mouse Data: Counts vary considerably across genes



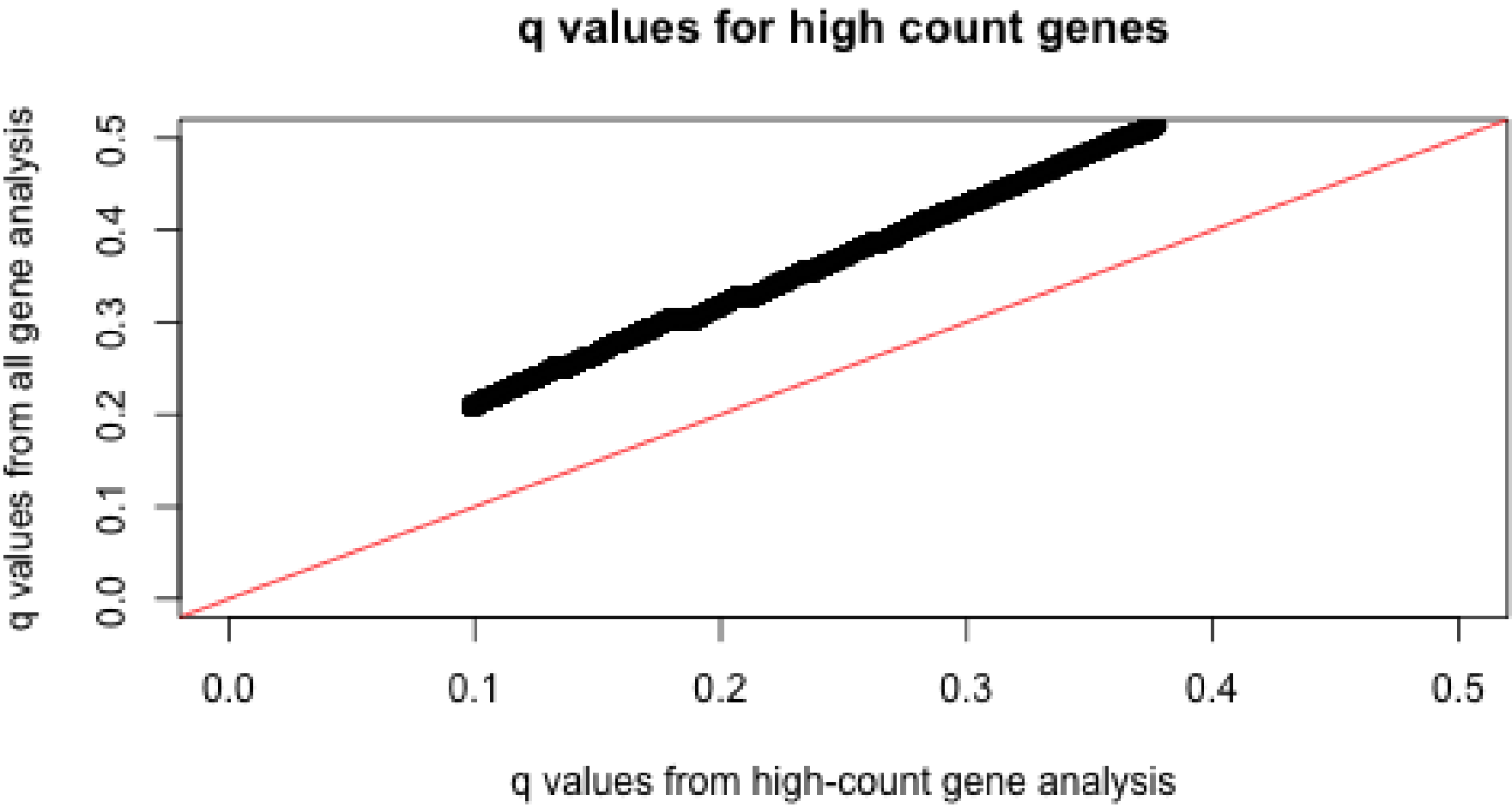
Lower count genes, less power



Higher count genes, more power



FDR problem 1: low count genes add noise, increase q values



FDR problem 1: Summary

- Analyzing p values or Z scores doesn't fully account for measurement precision.

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- The standard `qvalue` approach assumes that all the p values near 1 are null.
- Analogously, one can assume that all Z scores near 0 are null. Efron refers to this as the "Zero Assumption".
- The ZA allows us to estimate the null proportion, π_0, using the density of p values near 1 (or Z scores near 0).

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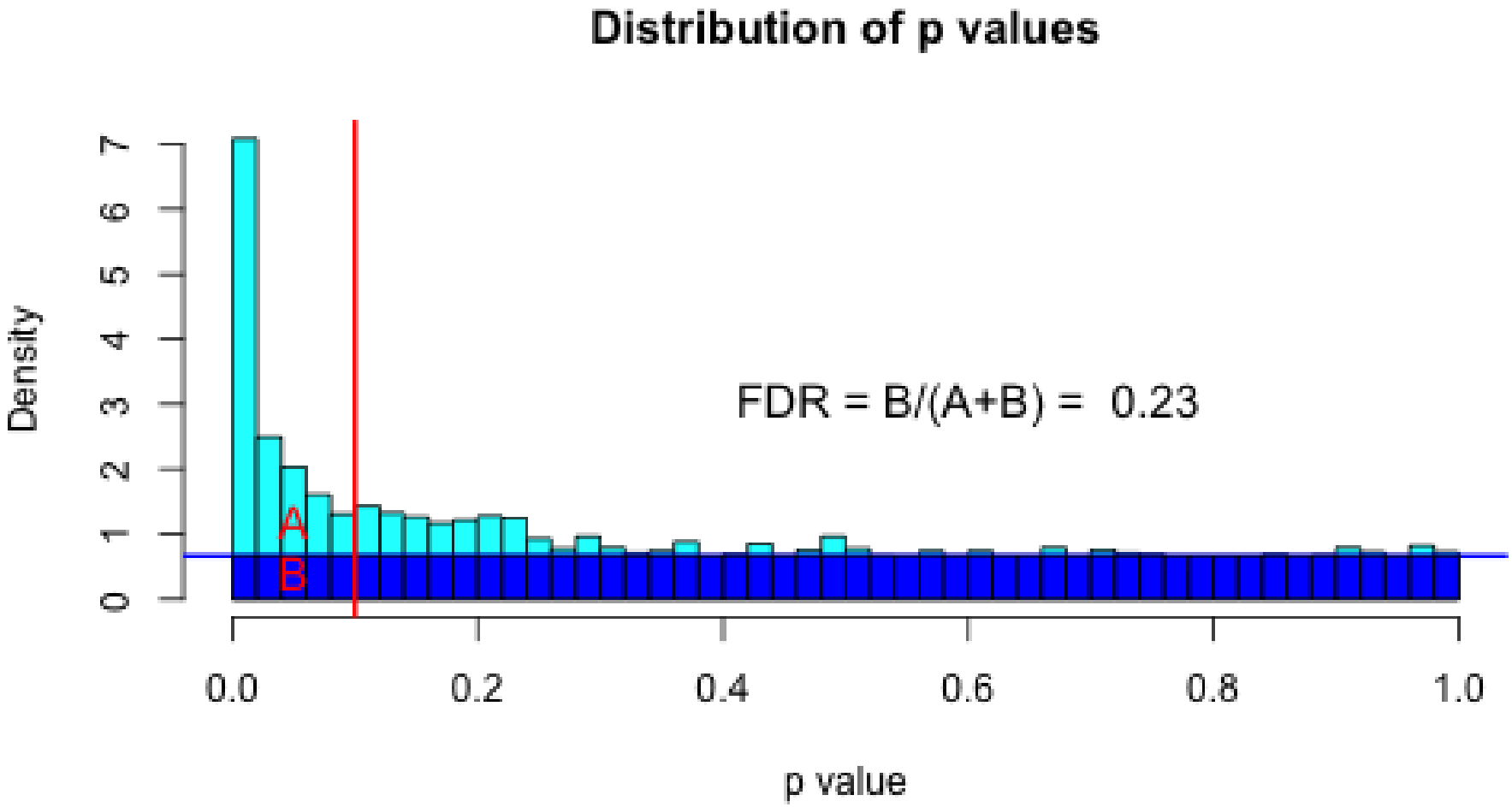
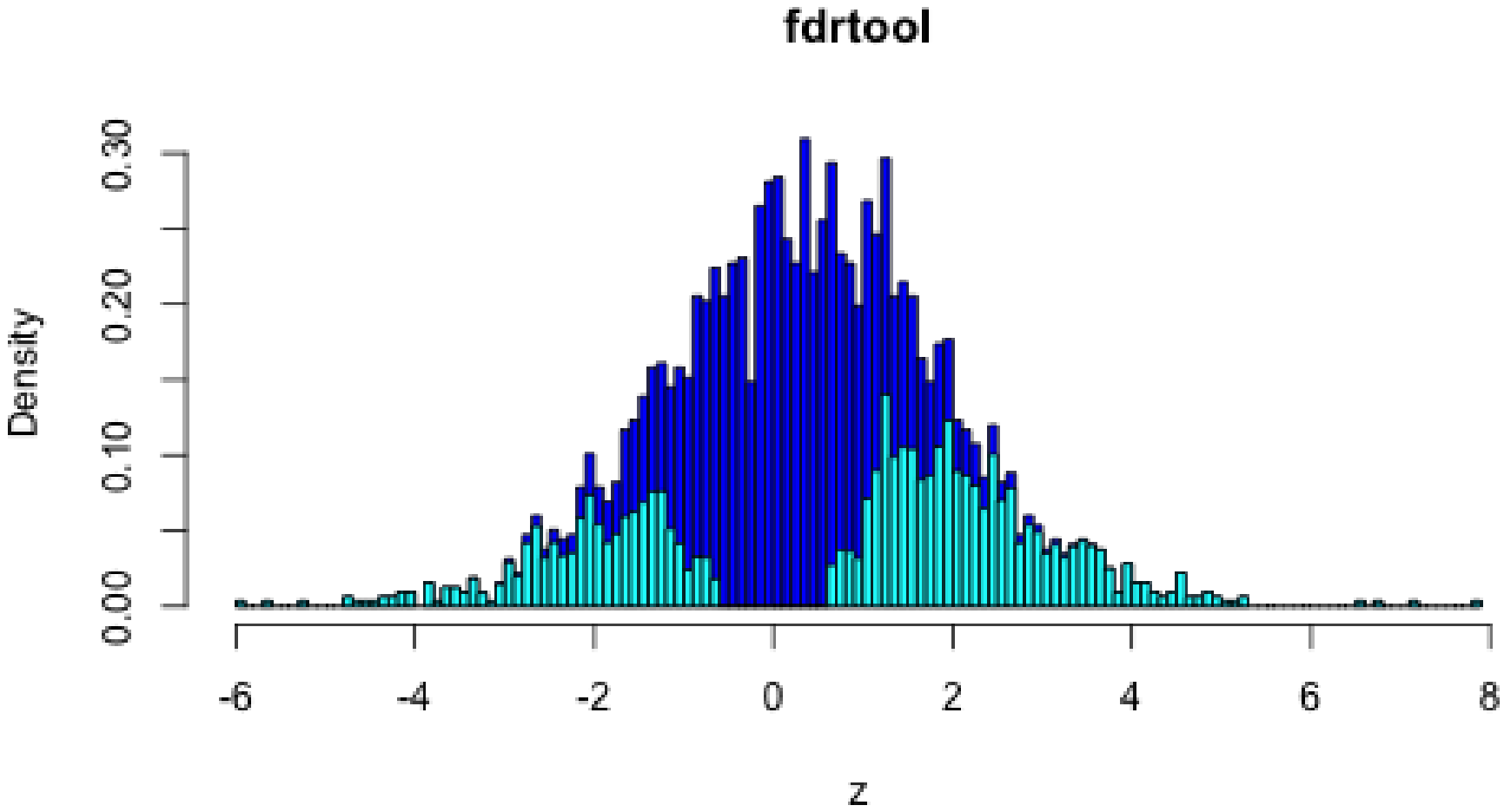
- However, it turns out to imply unrealistic assumptions about the distribution of non-zero effects.

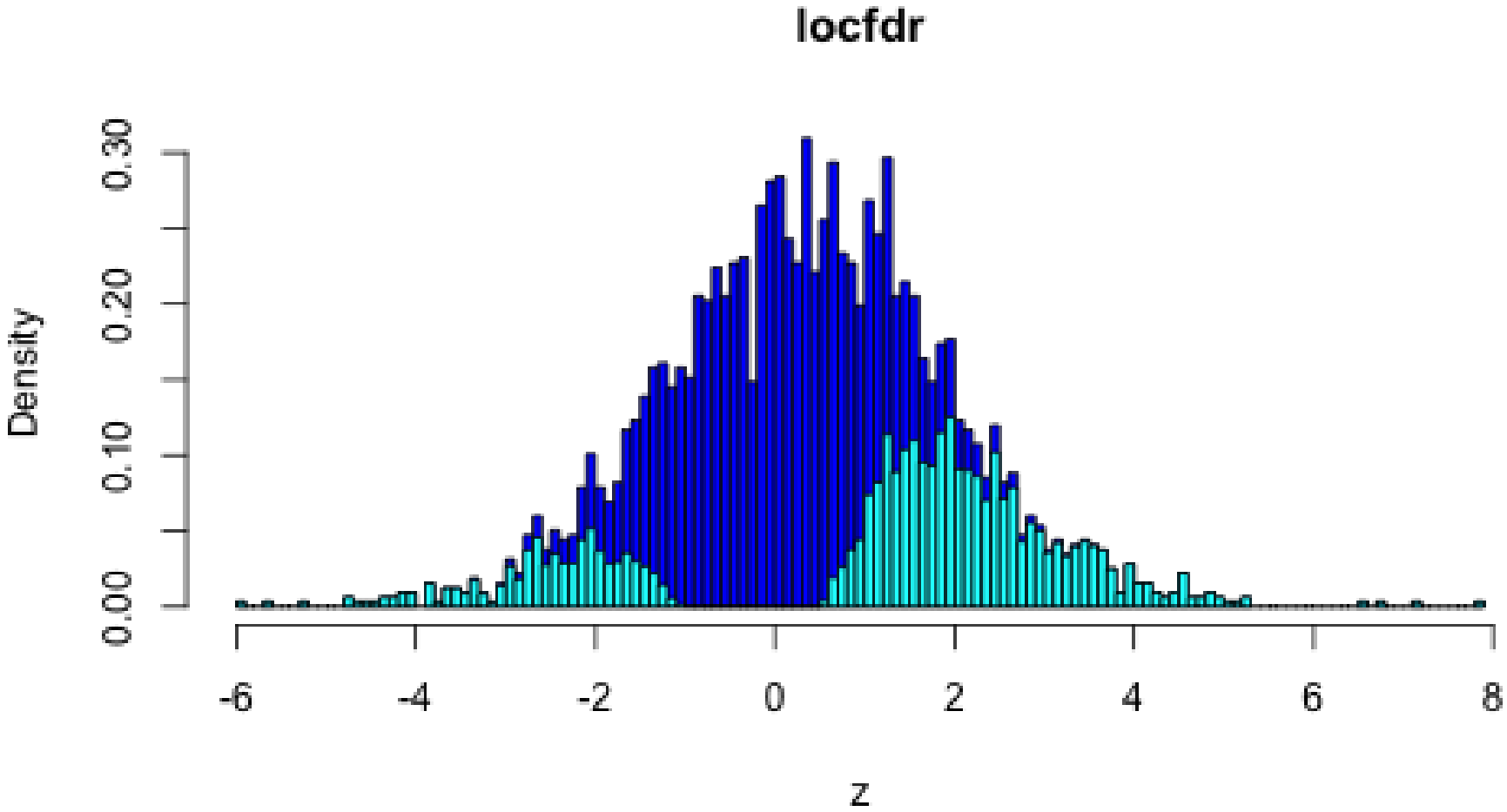
Implied distribution of p values under H_1



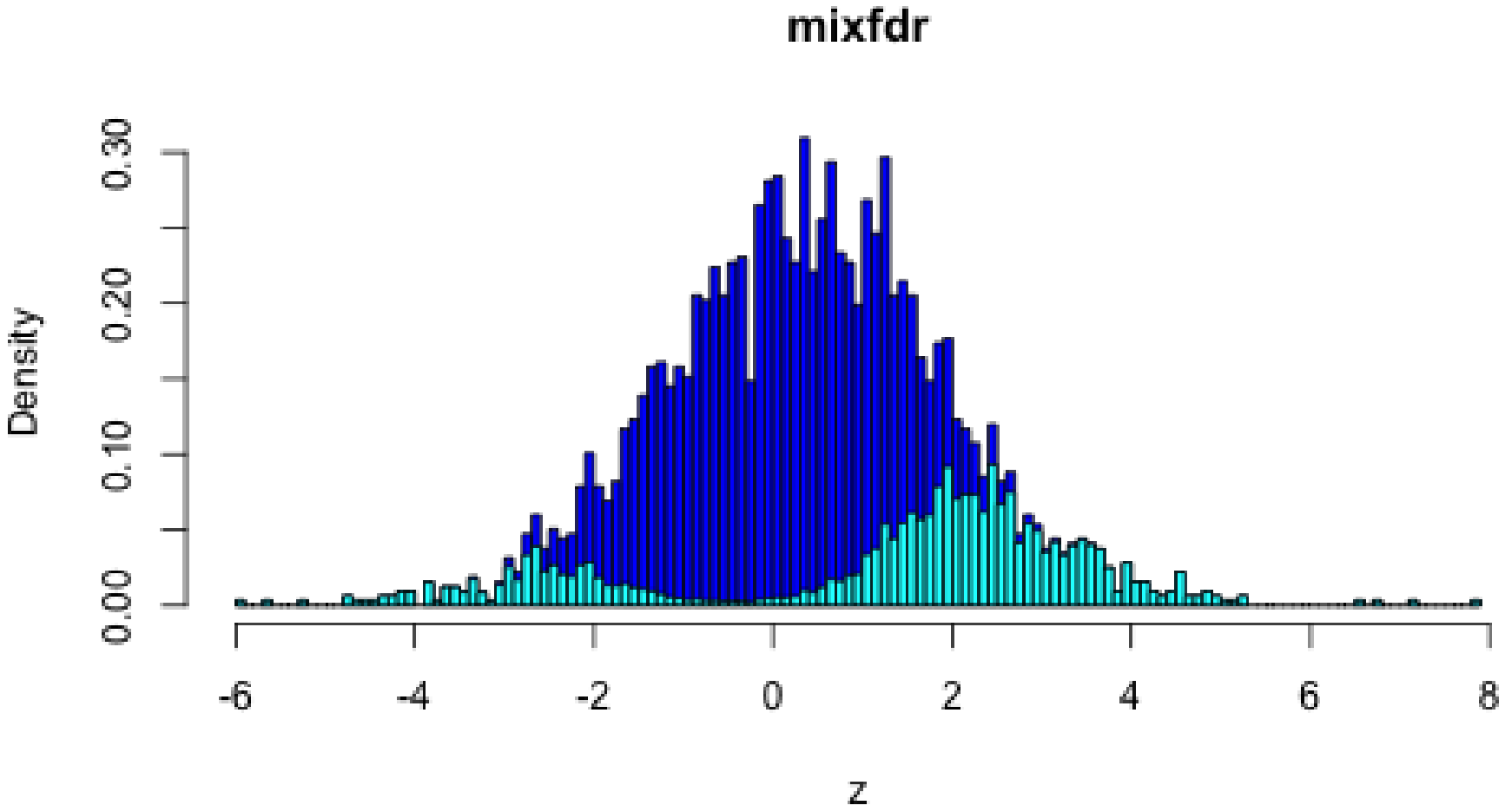
Implied distribution of Z scores under alternative (fdrtool)



Implied distribution of Z scores under alternative (locfdr)



Implied distribution of Z scores under alternative (mixfdr)




```
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```

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- By summarizing each observation by a Z score or p value, standard fdr tools ignore precision of different measurements
- Standard tools make the ZA, which implies actual effects have a (probably unrealistic) bimodal distribution. [and tends to overestimate π_0, losing power]
- Also standard tools focus only on zero vs non-zero effects. (eg what if we would like to identify genes that have at least a 2-fold change?)

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- Various semi-parametric approaches taken to estimating f_1. For example, Efron uses Poisson regression; Muralidharan uses mixture of normal distributions.
- $\text{fdr}(Z) \approx \pi_0 N(Z; 0, 1)/f_Z(Z)$

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- fdr given by

$$p(\beta_j = 0 | \hat{\beta}_j) = \pi_0 p(\hat{\beta}_j | \beta_j = 0) / p(\hat{\beta}_j)$$

FDR - A New Deal

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- By allowing K large, and σ_k to span a dense grid of values, we get a fairly 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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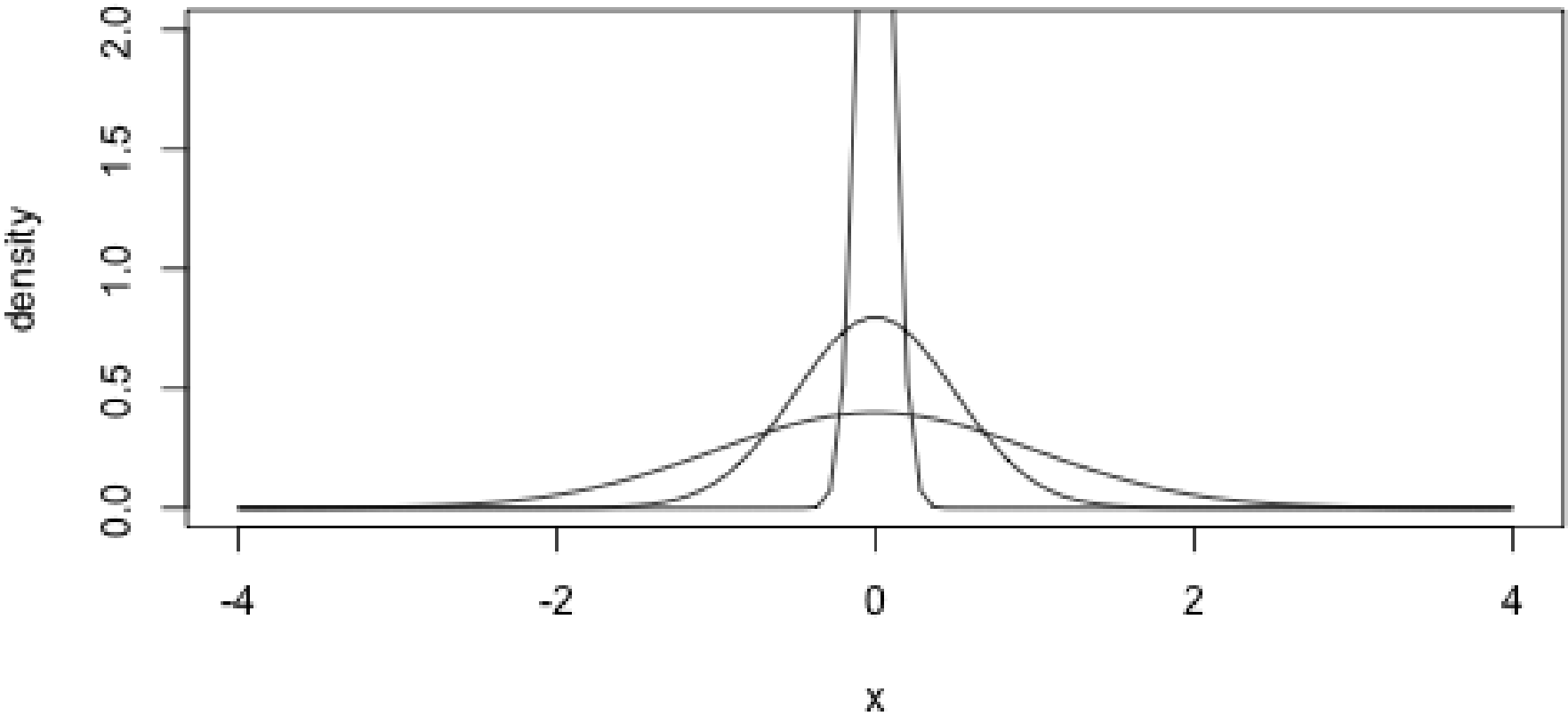
- If allow a very large number of uniforms this provides the non-parametric mle for g; cf Grenander 1953; Campy + Thomas.

Illustration: g a mixture of 0-centered normals



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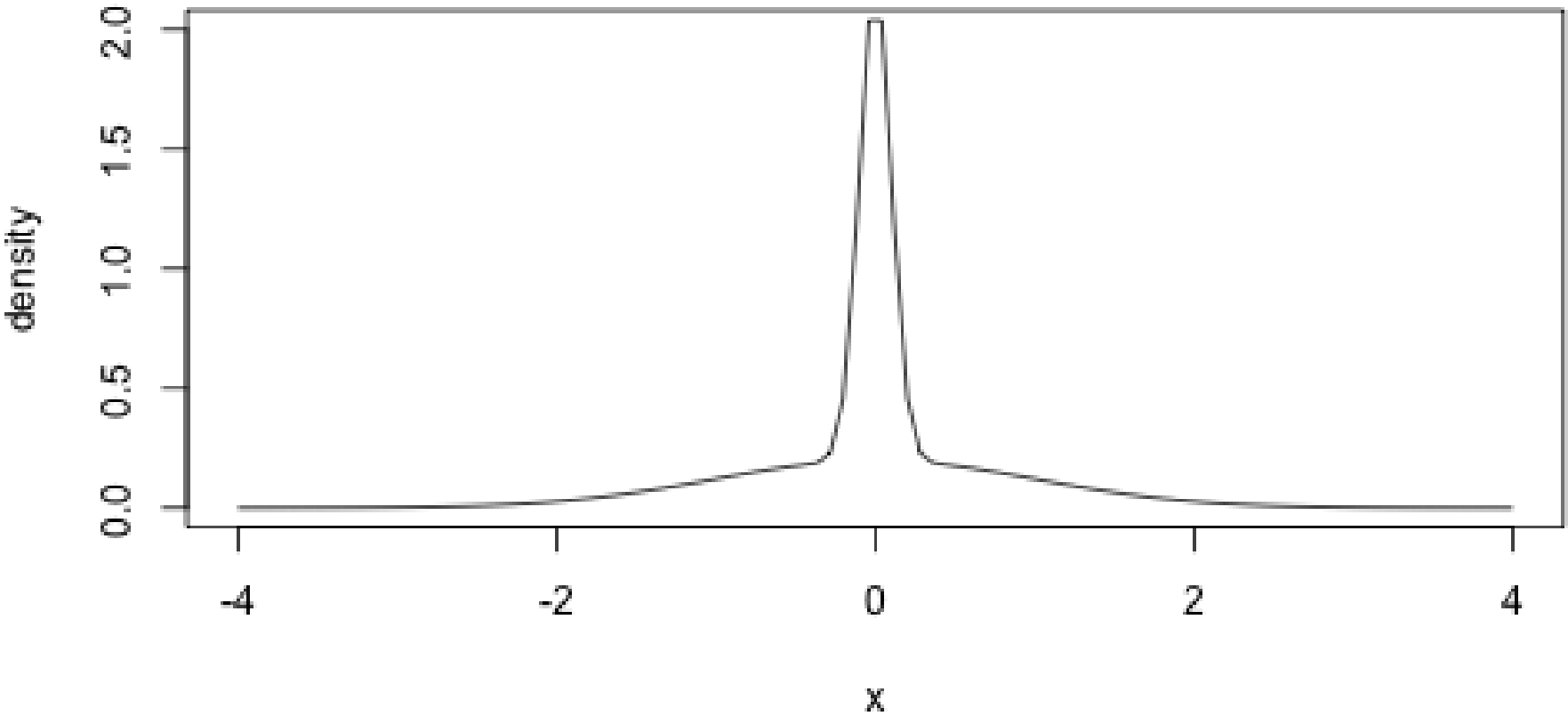

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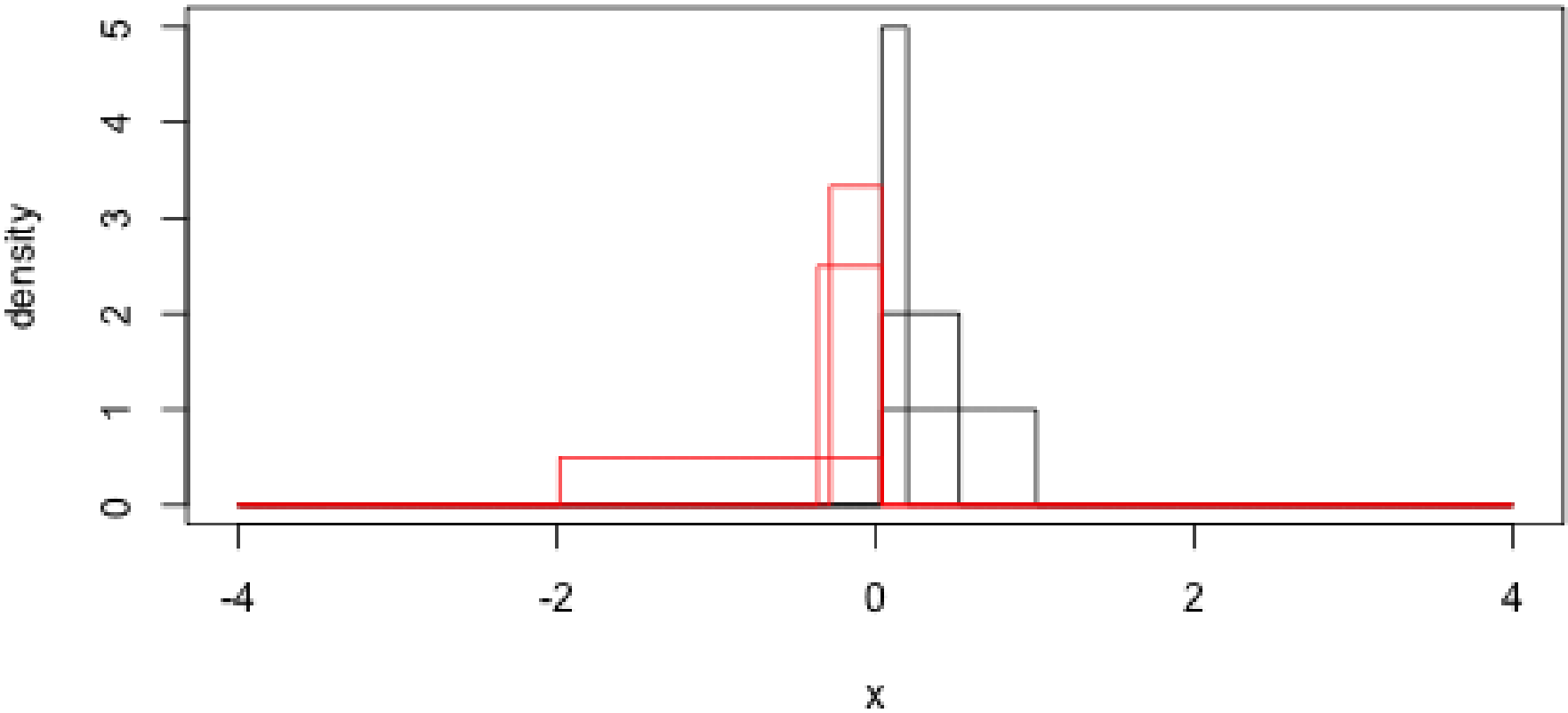

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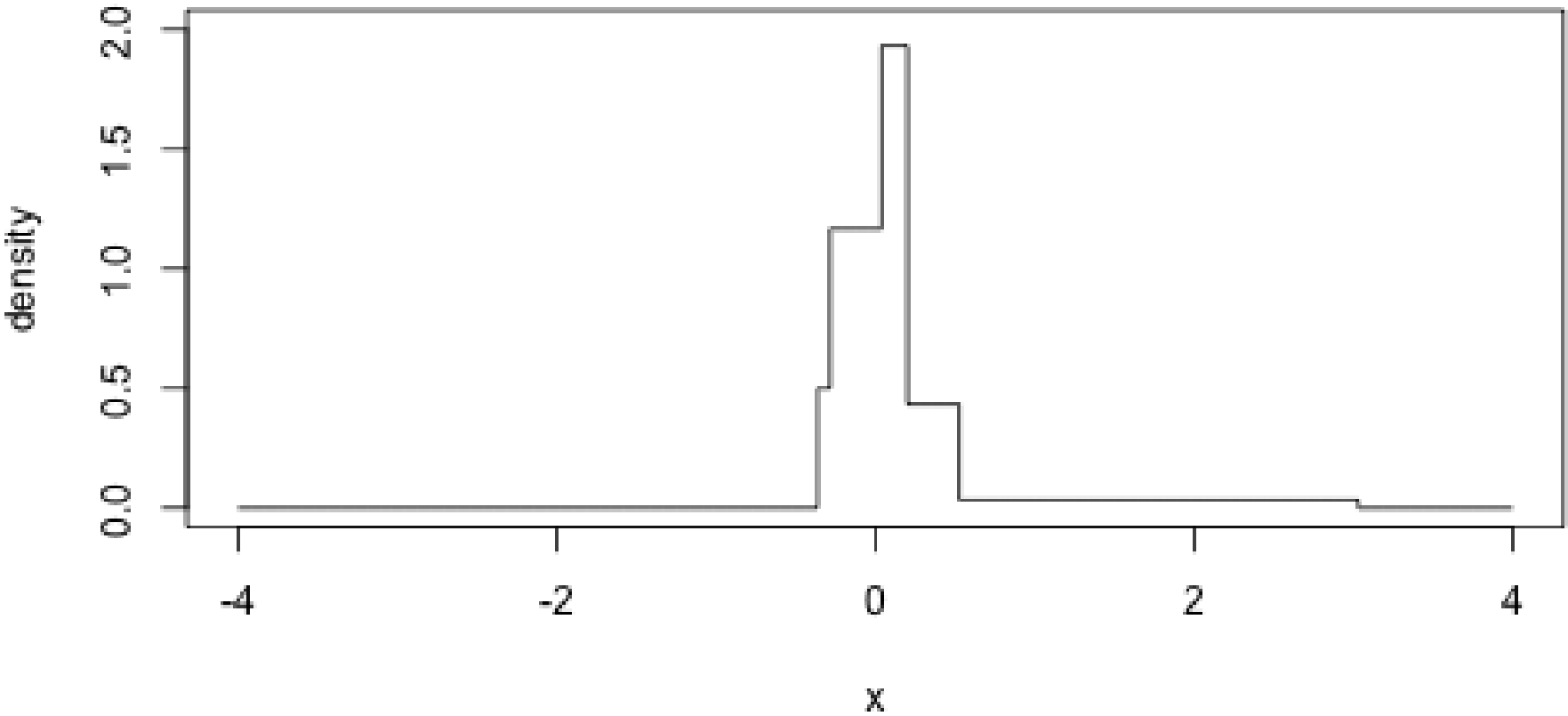

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- For estimating False Discoveries, we are asking whether $\beta_j = 0$.
- However, the data cannot distinguish between $\beta_j = 0$ and β_j "very small"
- As a result π_0 is formally unidentifiable. Eg data can never rule out $\pi_0 = 0$.

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- The ZA makes π_0 identifiable.
- Another view is that the estimate of π_0 under ZA will systematically tend to overestimate π_0, and so is "conservative".
- That is it provides an "upper bound" on π_0

Identifiability of π_0: Solution 1

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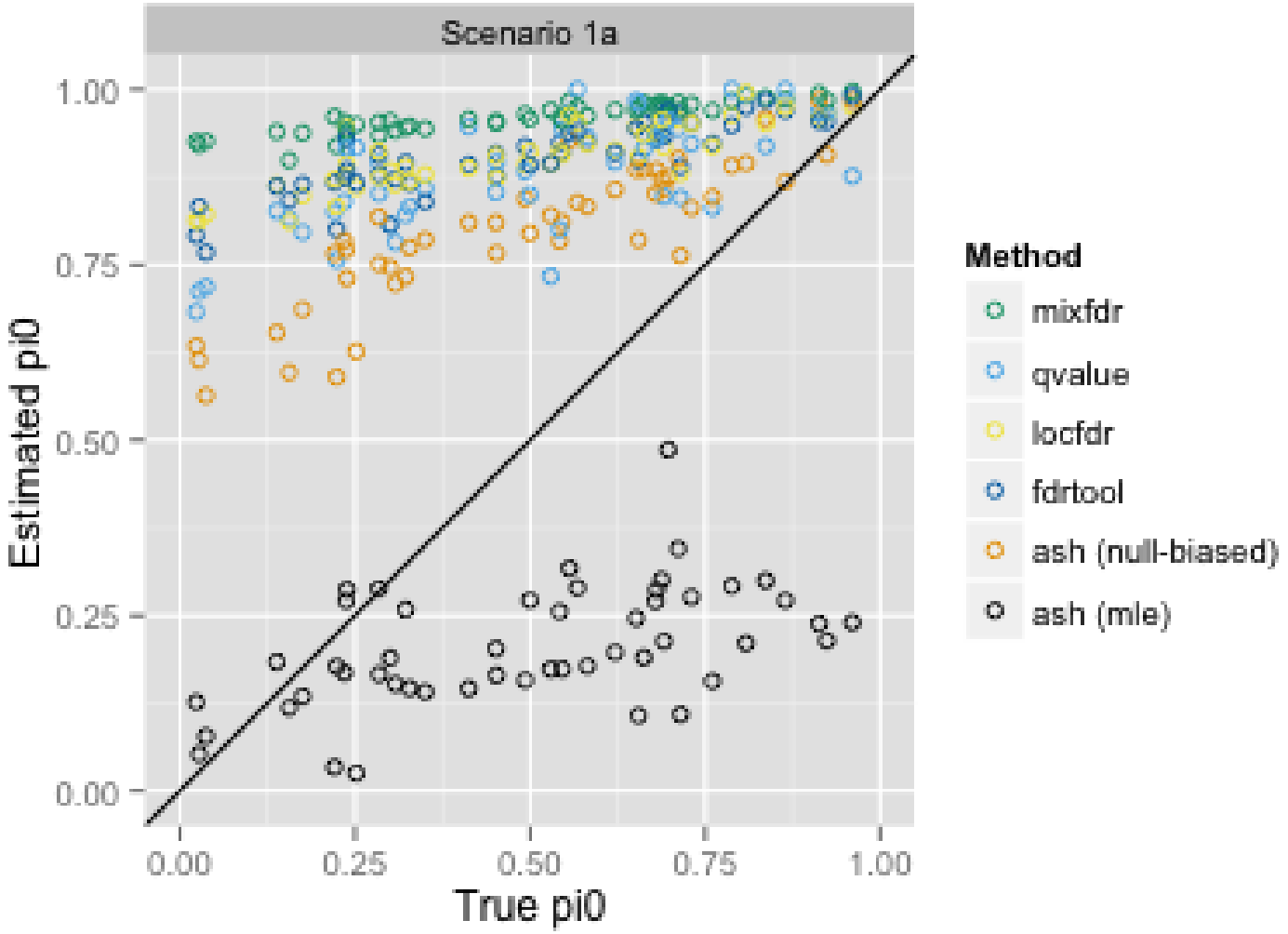
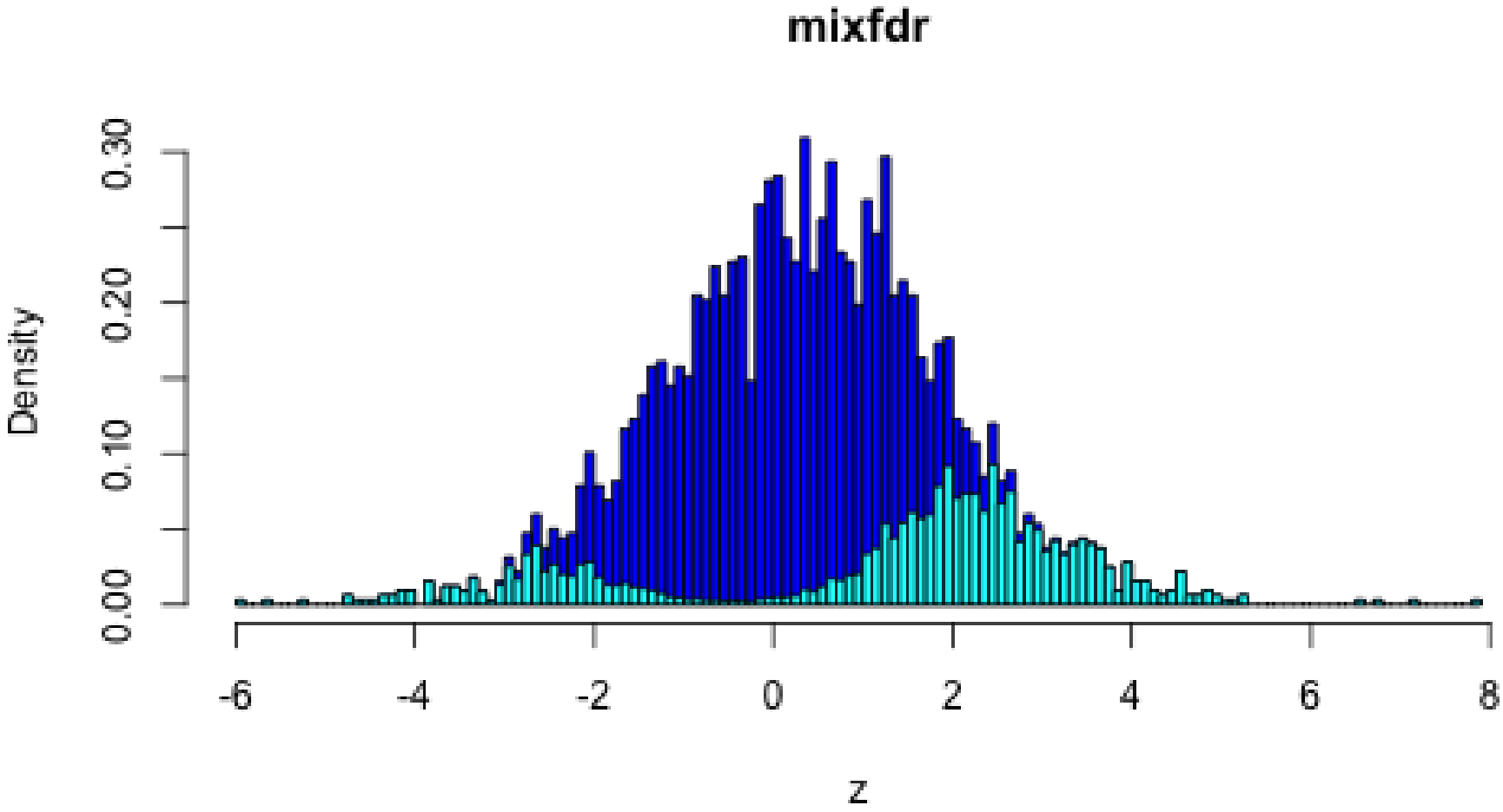
- In practice, implement upper bound by using penalized likelihood that encourages π_0 to be as big as possible.

Illustration: Simulated Example

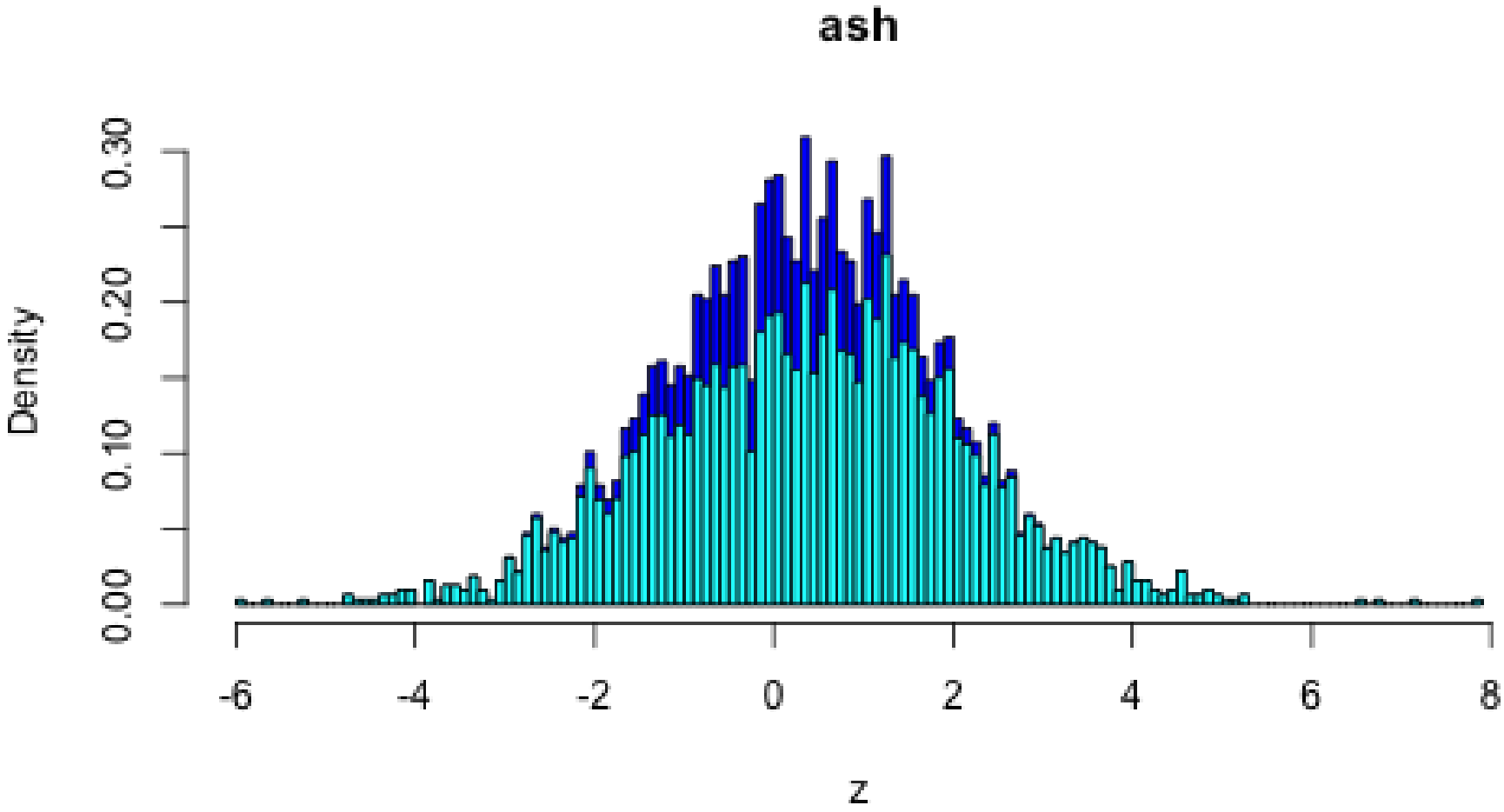


Example: BRCA data

Recall Problem: distribution of alternative Z values multimodal



Problem Fixed: distribution of alternative Z values unimodal



BRCA1: Compare π_0 estimates

```
round(c(hh.fdrtool$param[3], hh.locfdr$fp0[1, 3], hh.mixfdr$pi
    2)
```

```
## [1] 0.64 0.74 0.80 0.21
```

BRCA1: Compare number significant at fdr<0.05

```
c(sum(hh.fdrtool$lfdr < 0.05), sum(hh.locfdr$fdr < 0.05), sum(
    0.05), sum(hh.ashz$ZeroProb < 0.05))
```

```
## [1] 154 171 162 341
```

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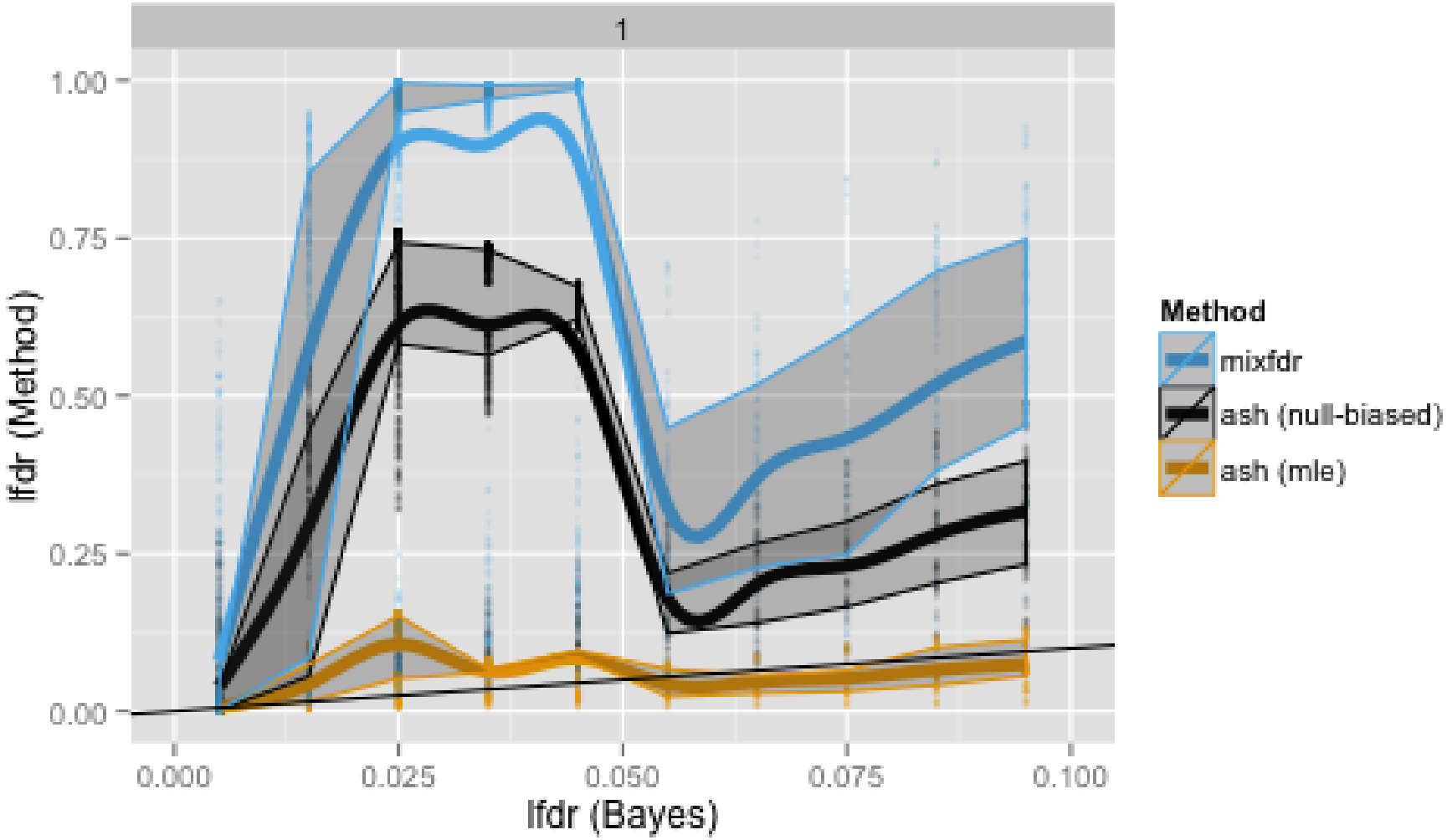
- That is we replace fdr with False Sign Rate (fsr), the probability that if we say an effect is positive (negative), it is not.
- Example: suppose we estimate that $\Pr(\beta_j < 0) = 0.975$ and $\Pr(\beta_j > 0) = 0.025$. Then we report β_j as a "(negative) discovery", and estimate its fsr as 0.025.

The fsr is more robust than fdr



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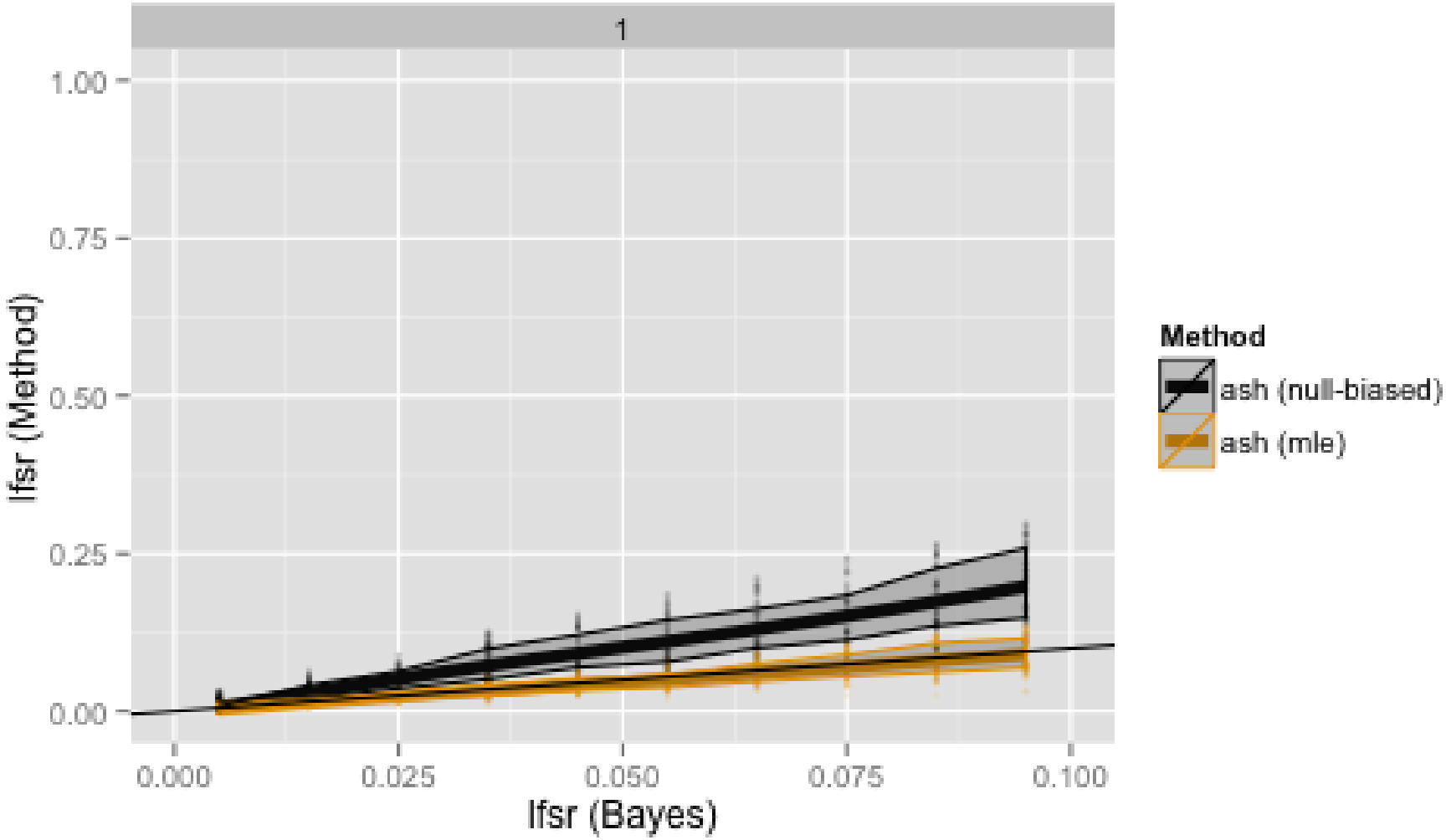

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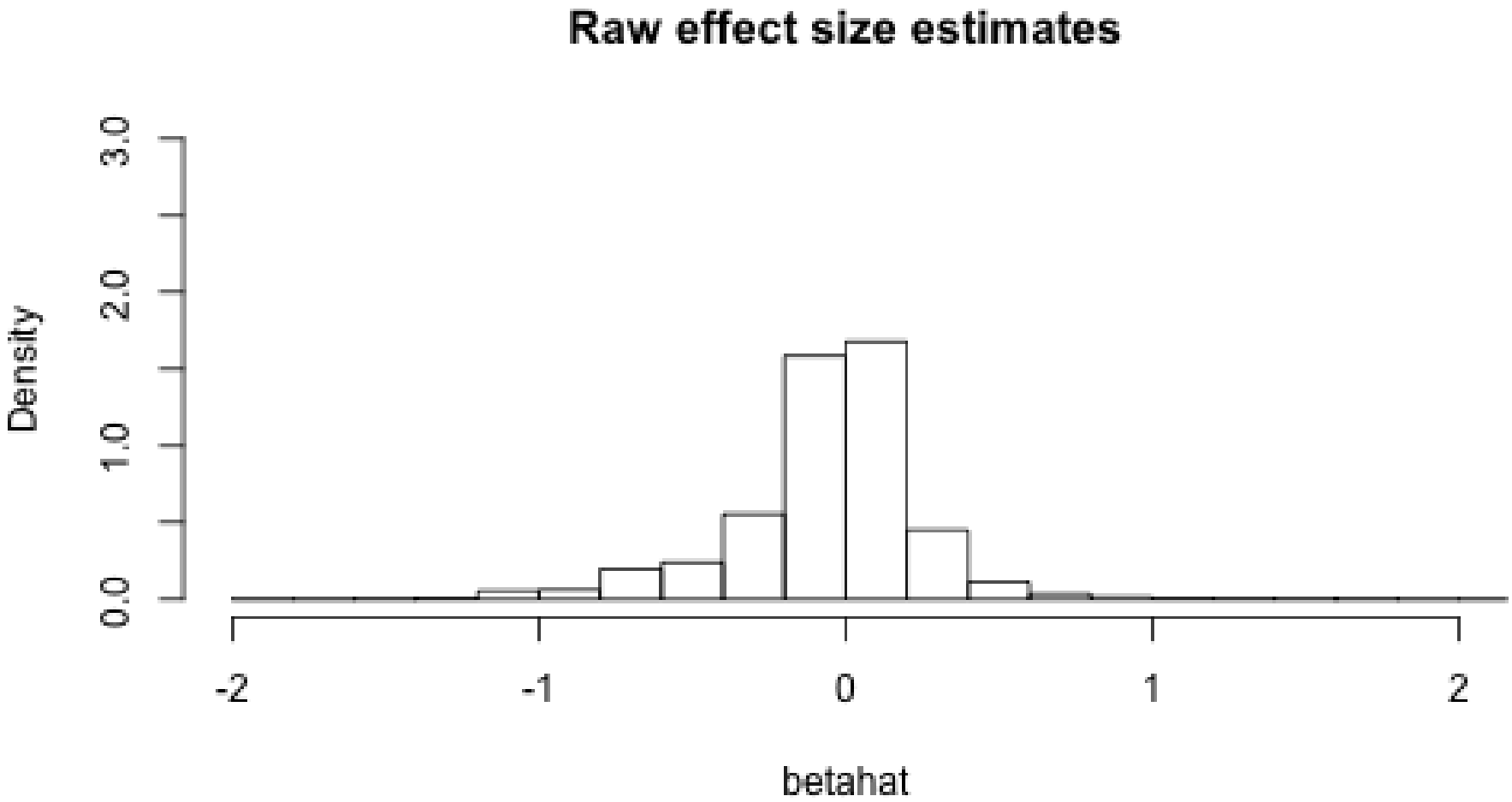
- So we call the approach "Adaptive Shrinkage" (ASH).

Example: ASH applied to mouse data



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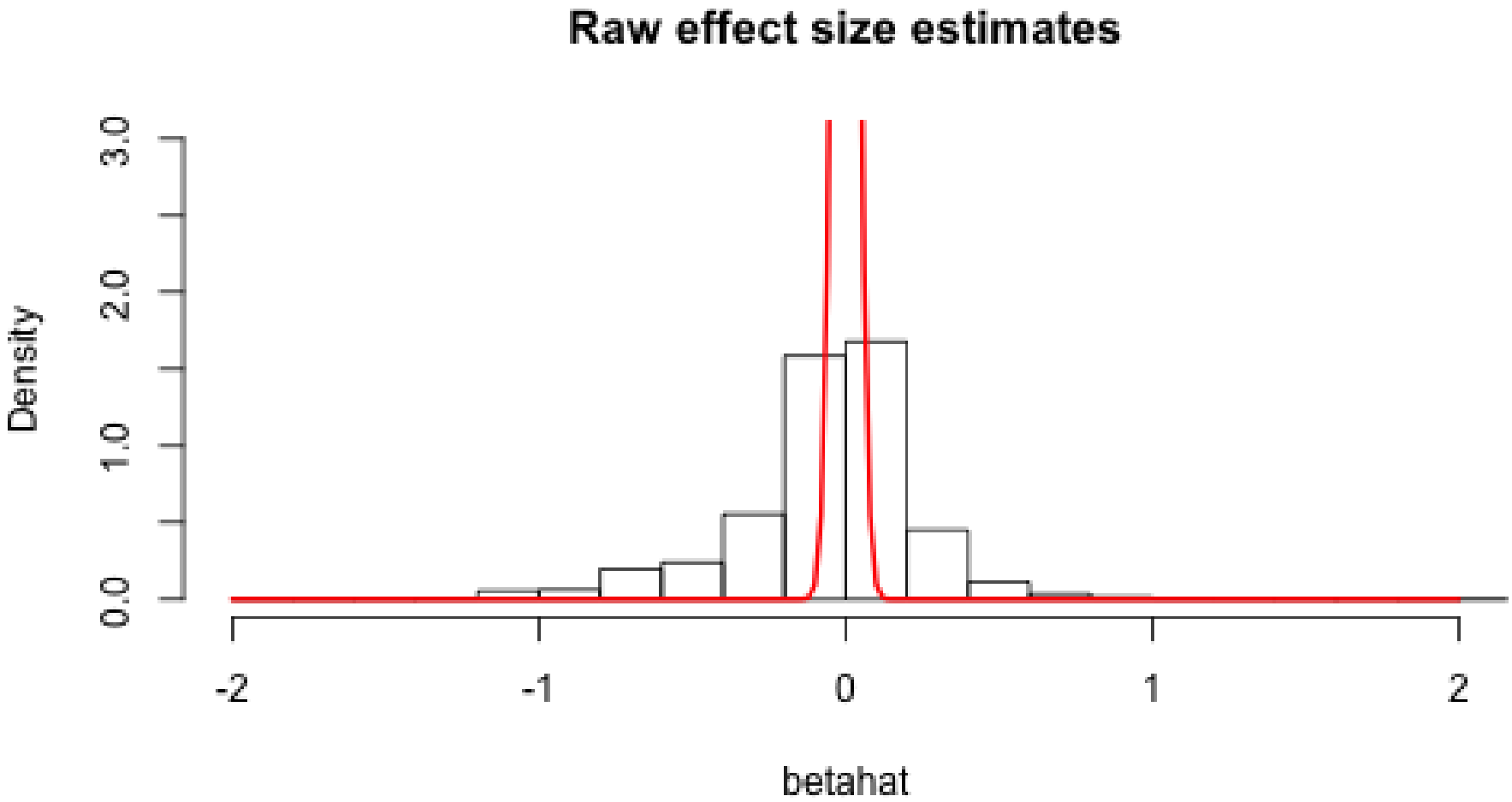

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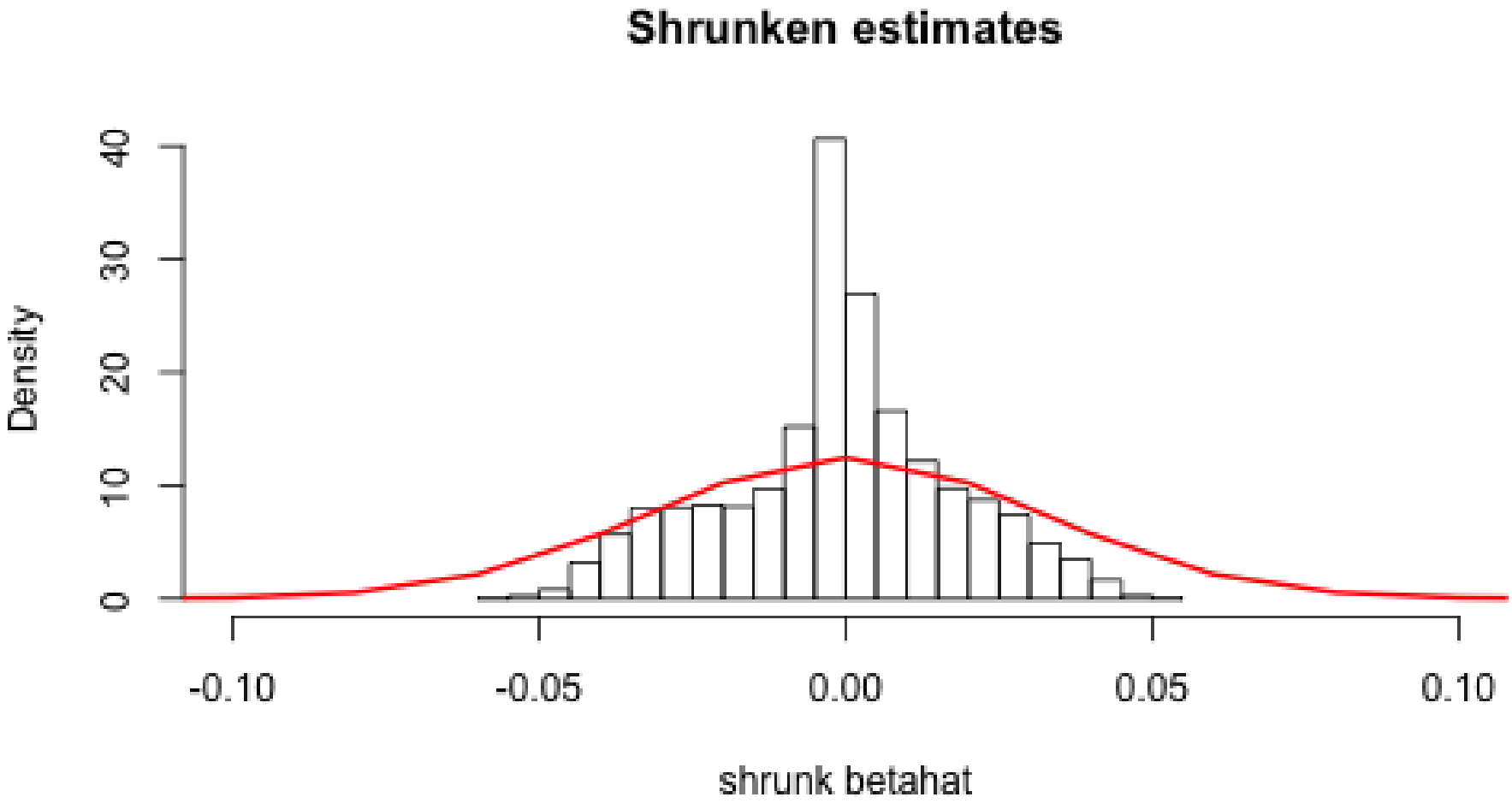

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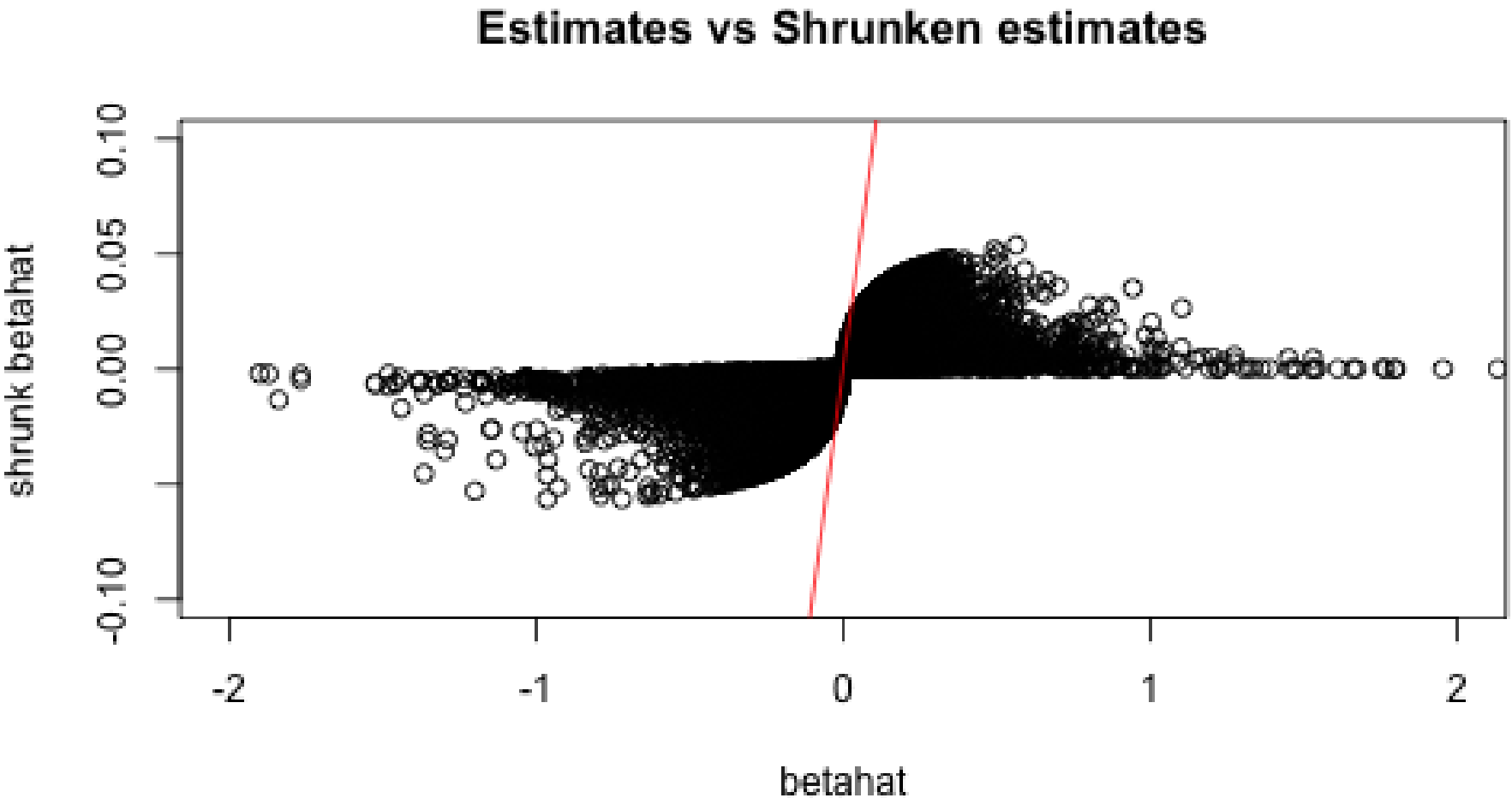

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- But by using two numbers $(\hat{\beta}, s)$ instead of one (p values or z scores) precision of different measurementscan be better accounted for.
- Unimodal assumption for effects reduces conservatism
- False Sign Rate is more robust to assumptions, and perhaps therefore preferable, than False Discovery Rate.

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- Currently applying it to wavelet shrinkage applications.

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- Including Scott Powers, Mengyin Lu, Tian Sen, Wei Wang, Zhengrong Xing.

Reproducible research

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- Website: `http://stephenslab.uchicago.edu`

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   parallel  stats     graphics  grDevices utils
## [8] methods   base
```

Some odd things in the data

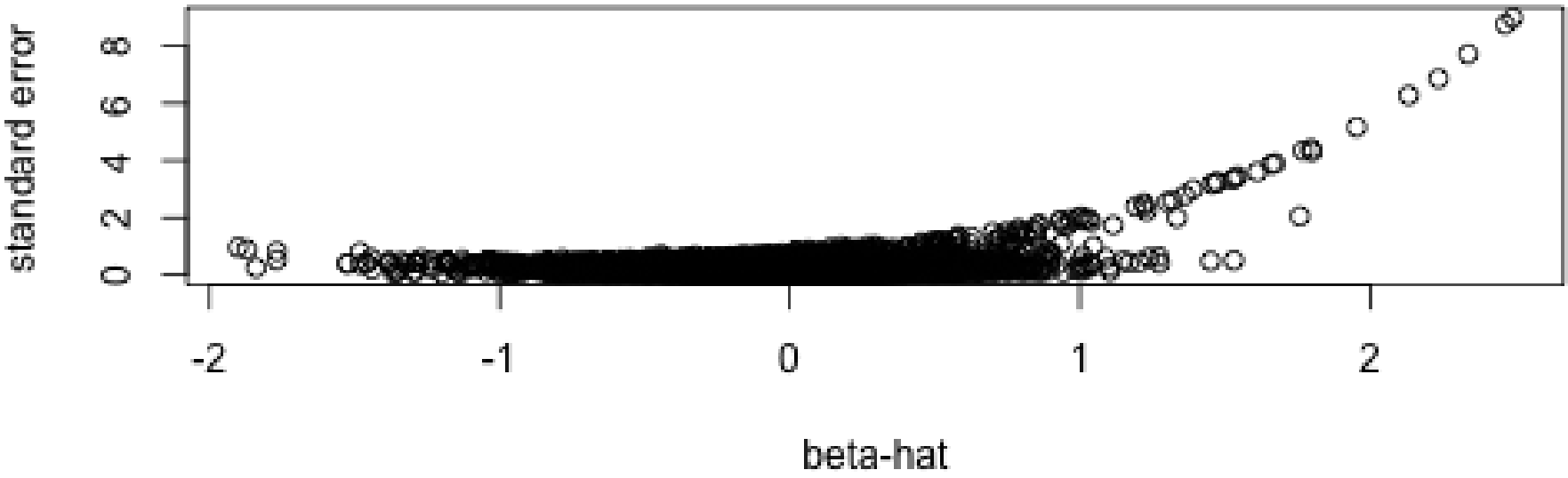

Figure : plot of chunk unnamed-chunk-40

```
## Error: incorrect number of dimensions
```

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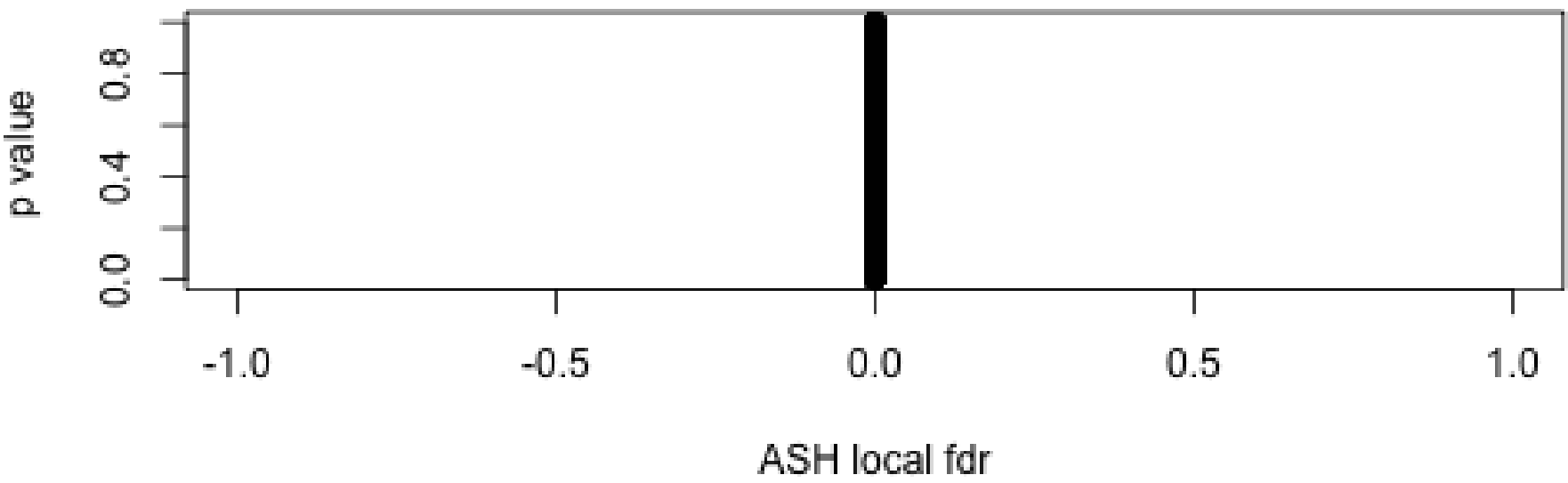
- Maybe fsr makes more sense anyway?

Shrinkage is adaptive to information

Need to fix counts.associate to use fdr method in ash



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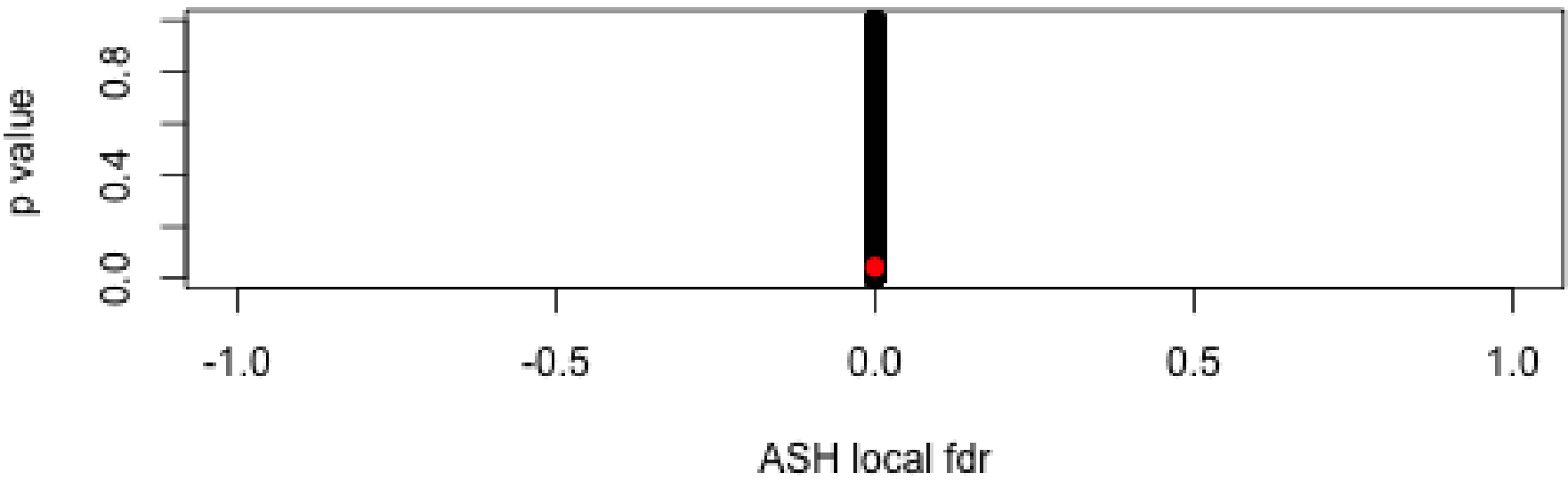
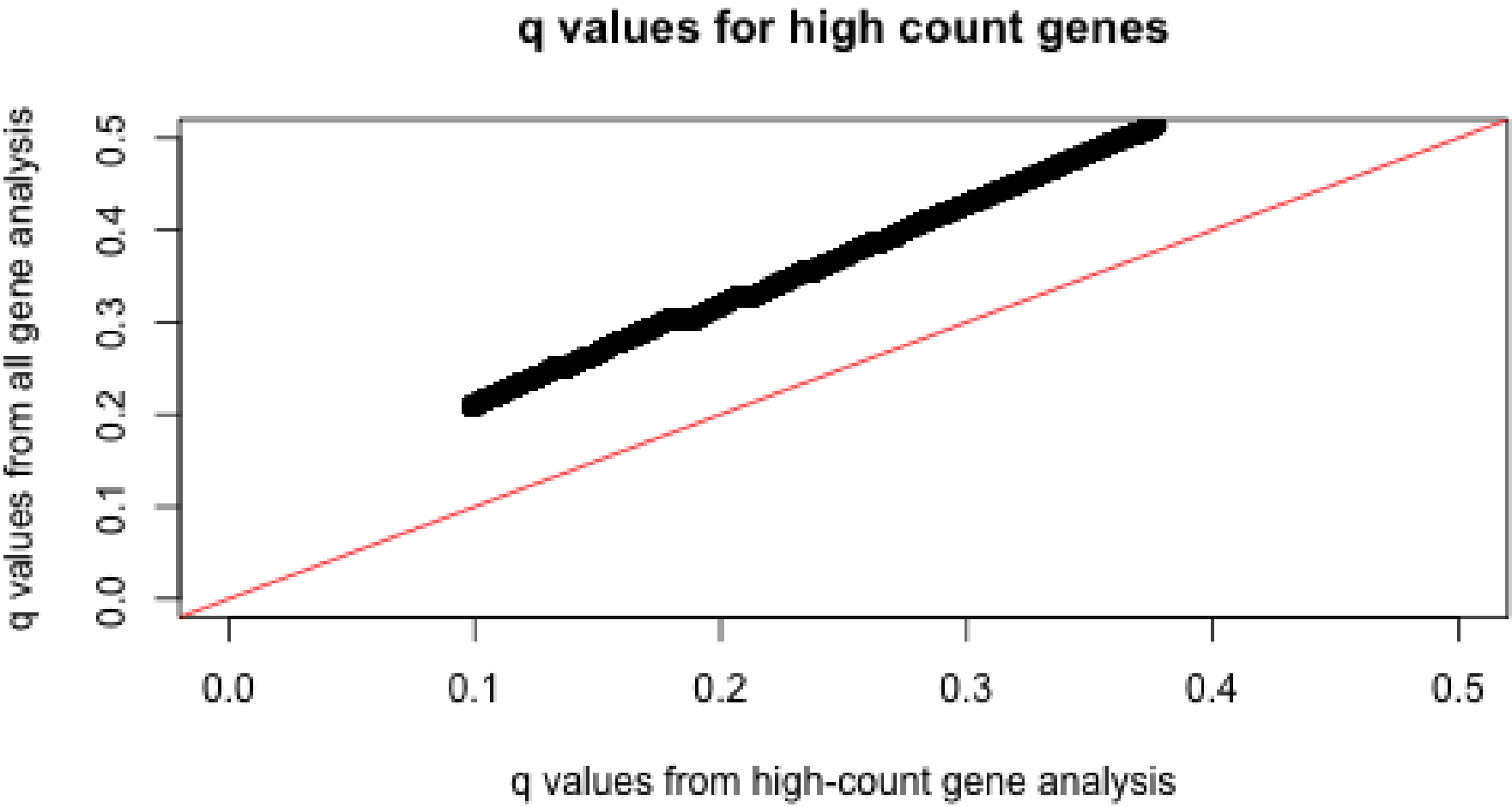


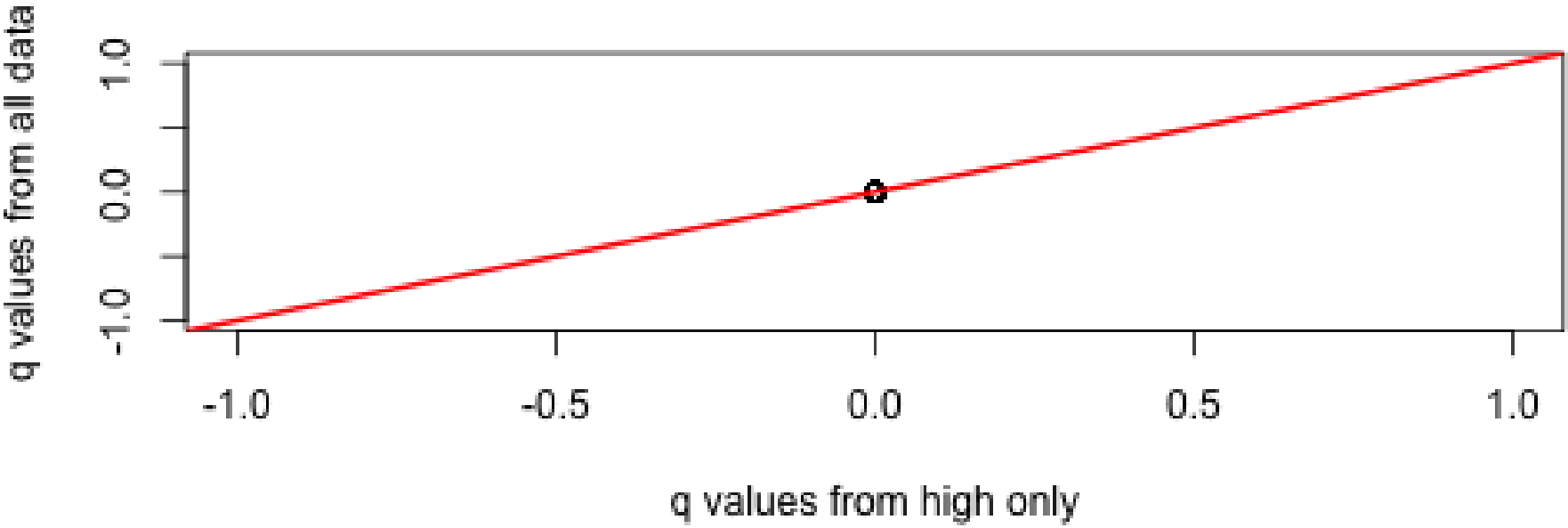
Shrinkage is adaptive to information

```
##          gene  lv1  lv2  rv1  rv2    pval zdat.ash$lfdr
## 19422 Mgat5b    7   10  320  452 0.03795             0
## 20432  Sec63 1042 1034 5496 6649 0.04908             0
```

Recall FDR problem 1: q values increased by low count genes



ASH q values more robust to inclusion of low count genes



Compare fitted $f(\beta)$, both estimating π_0 and fixing $\pi_0 = 0$.