Shrinkage, False Discovery Rates, and an Alternative to the Zero Assumption

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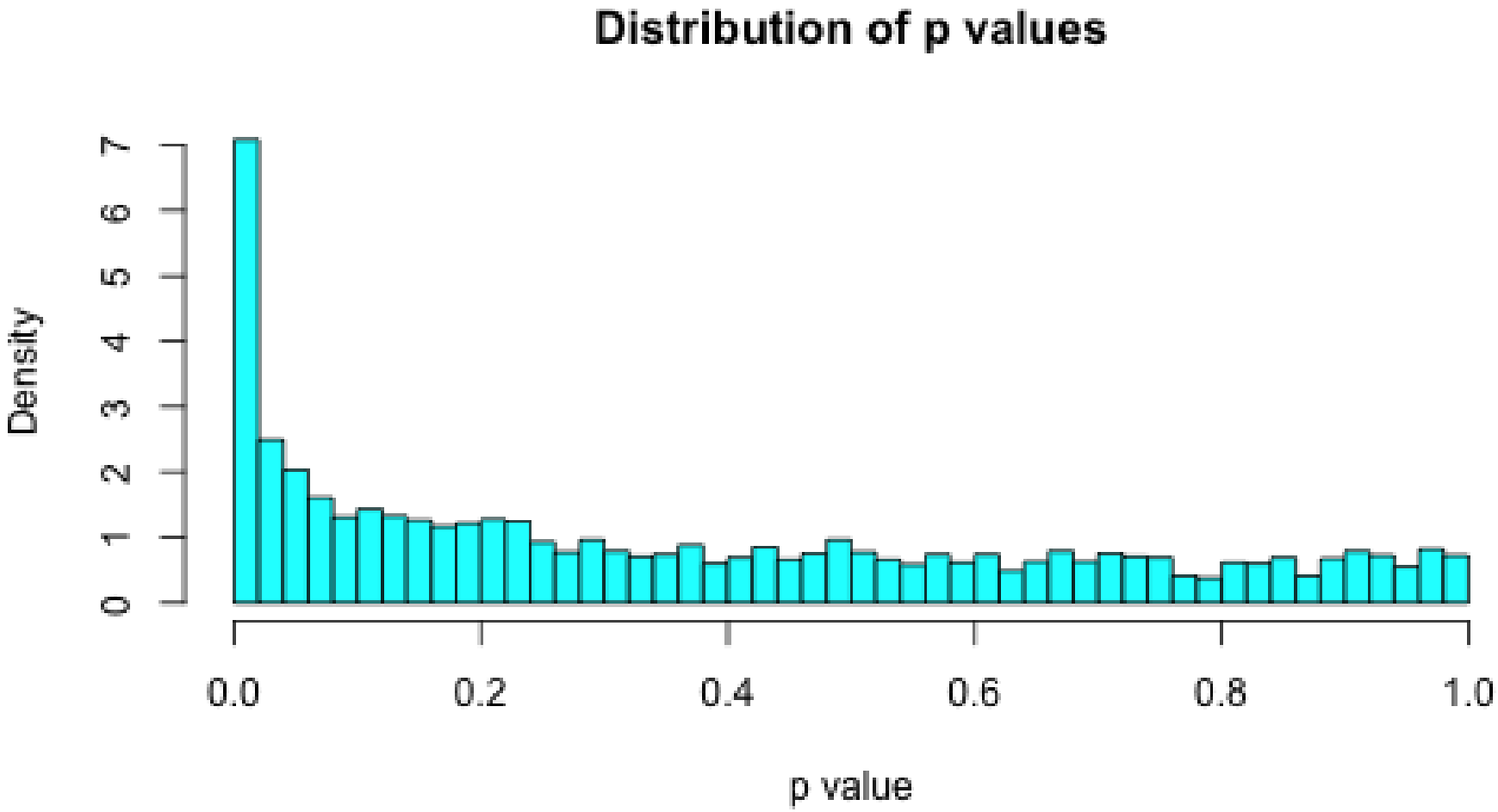
- The fdr is more relevant, but slightly harder to estimate than FDR because it involves density estimation rather than tail-area estimation.

Example: FDR estimation



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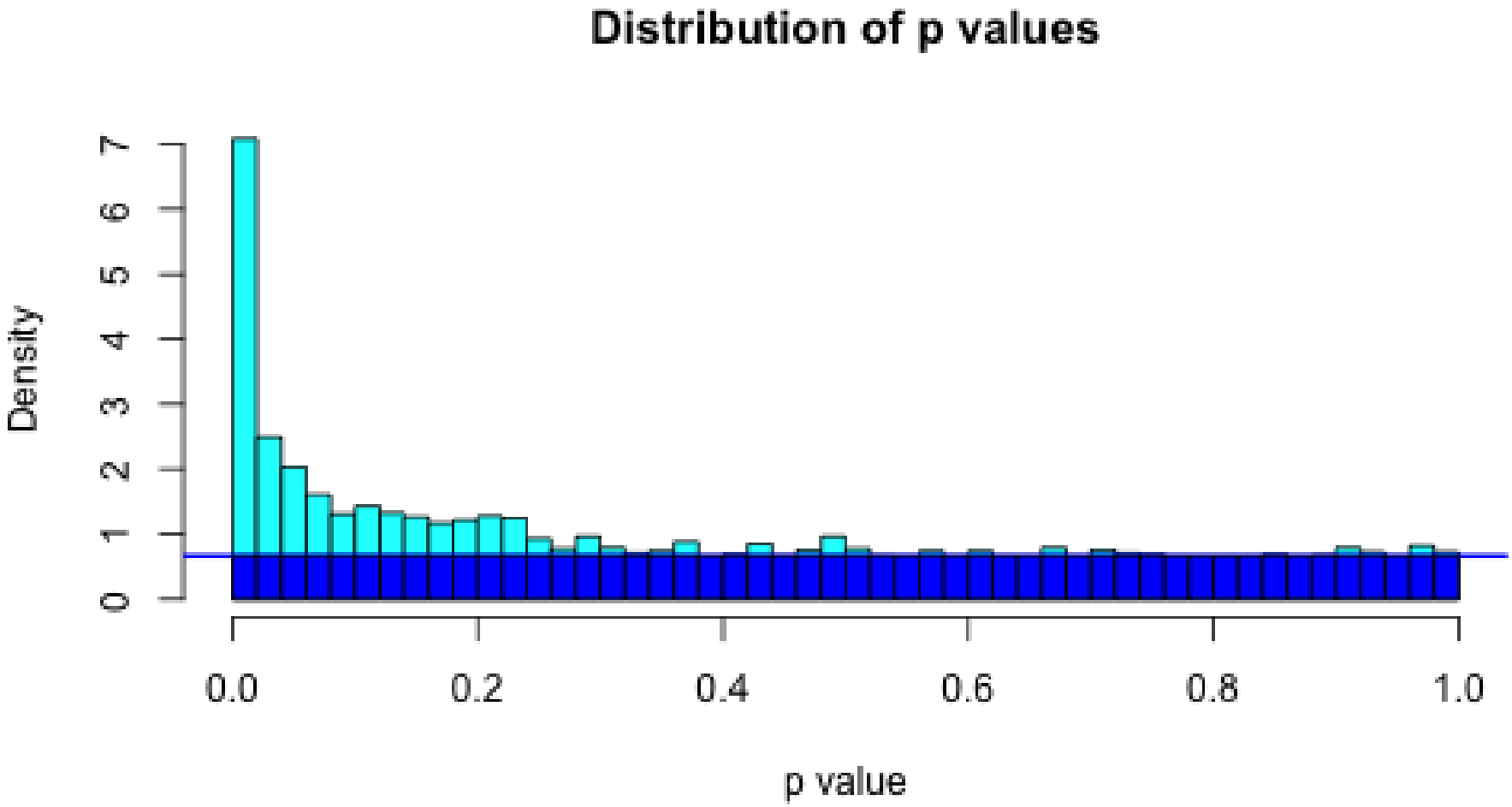

Data from Hedenfalk et al. comparing BRCA1 vs BRCA2 expression

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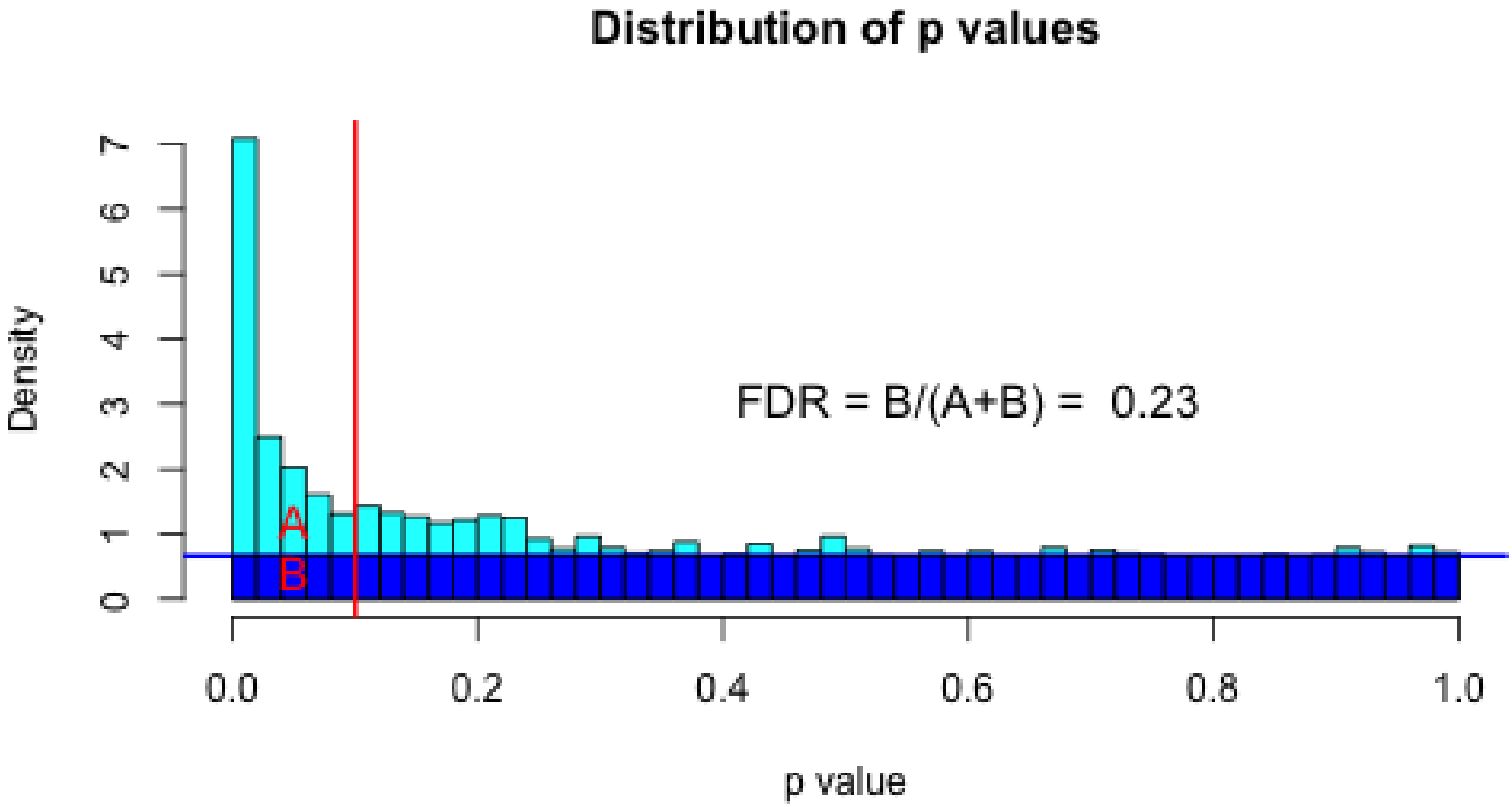
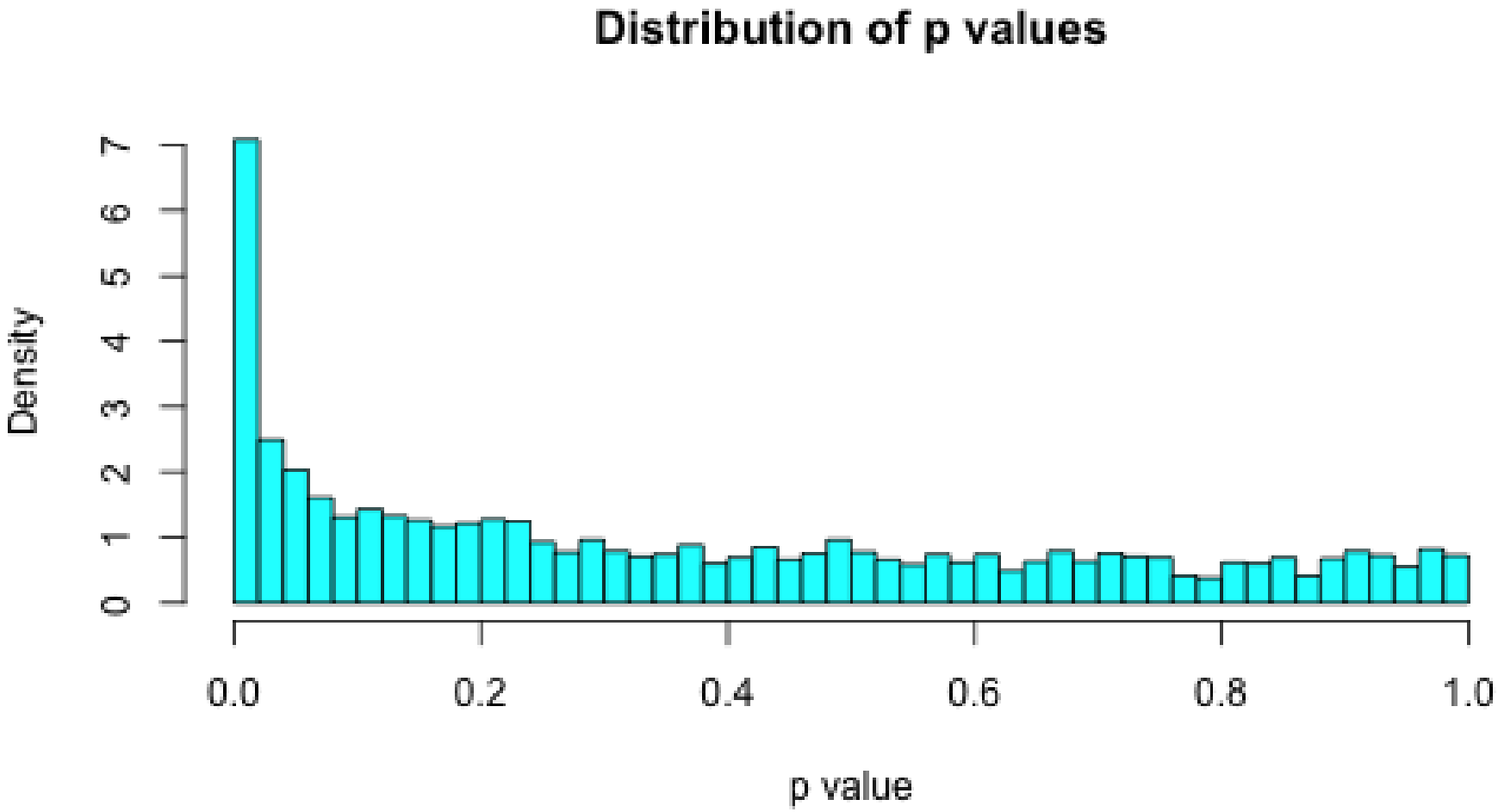


Example: fdr estimation



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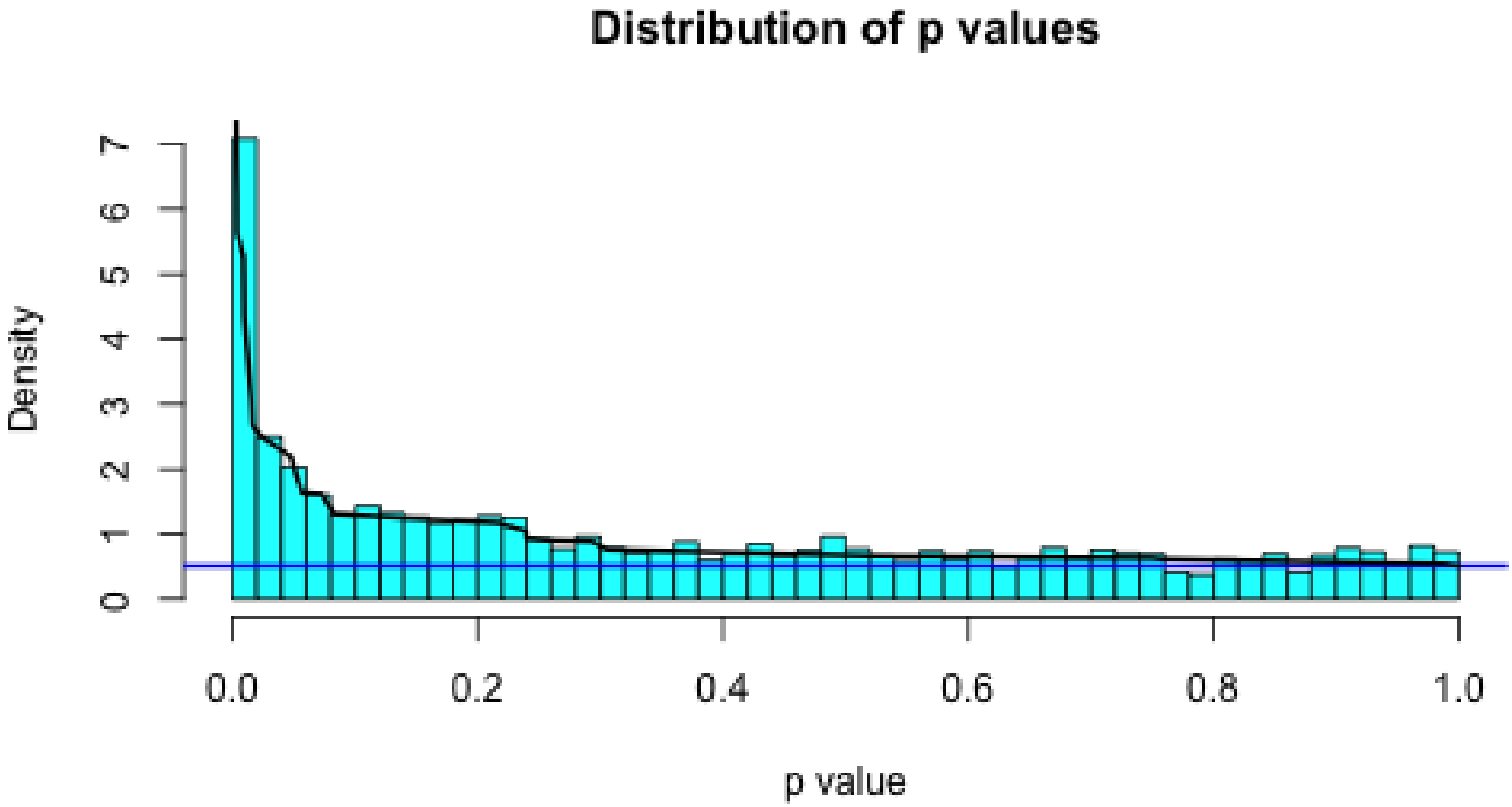

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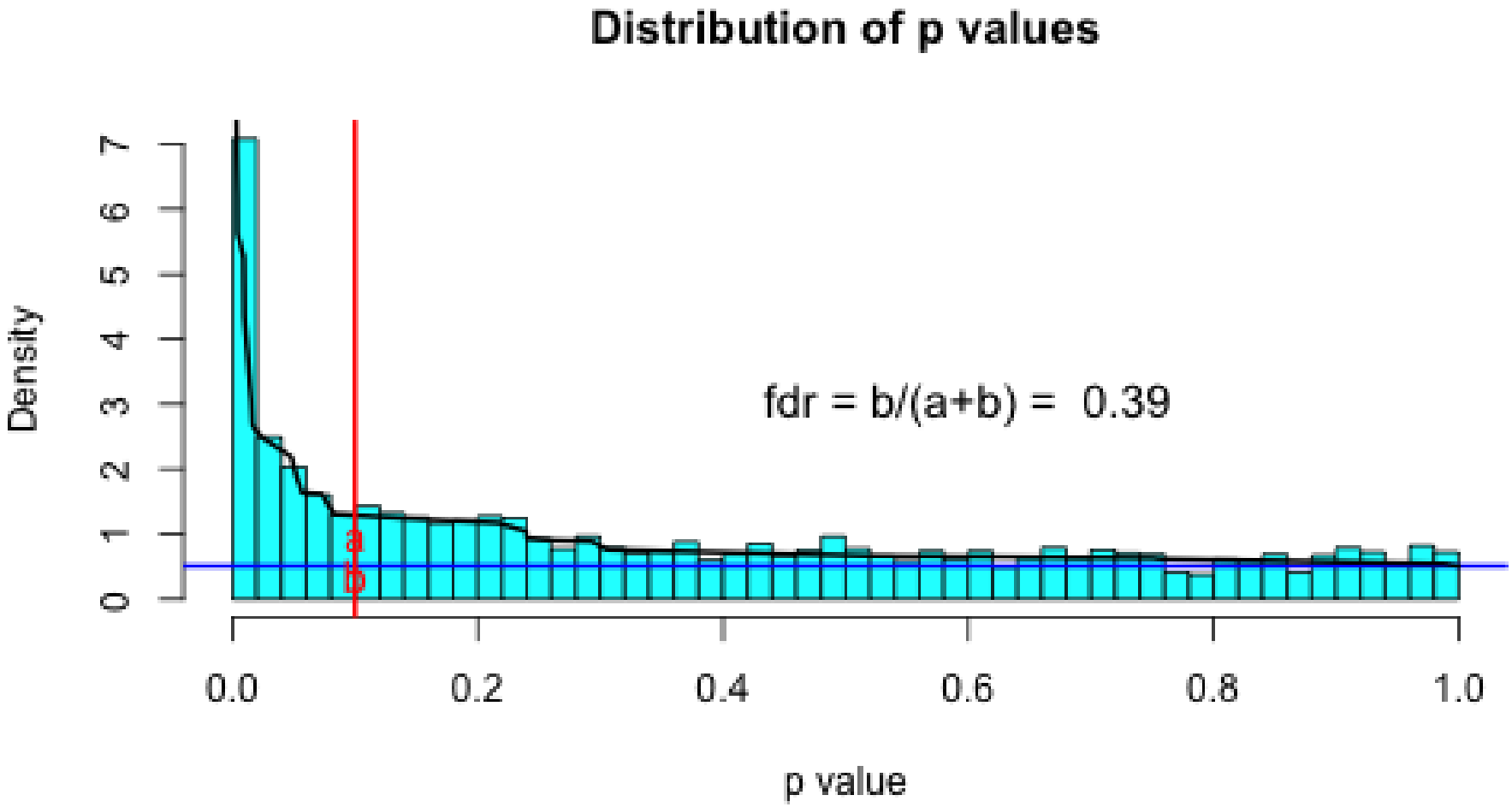

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- If some effects are measured very imprecisely, those tests "lack power" and simply add noise
- In particular, such tests increase the estimated number of nulls, and increase the FDR for other tests
- It would seem preferable to simply ignore the 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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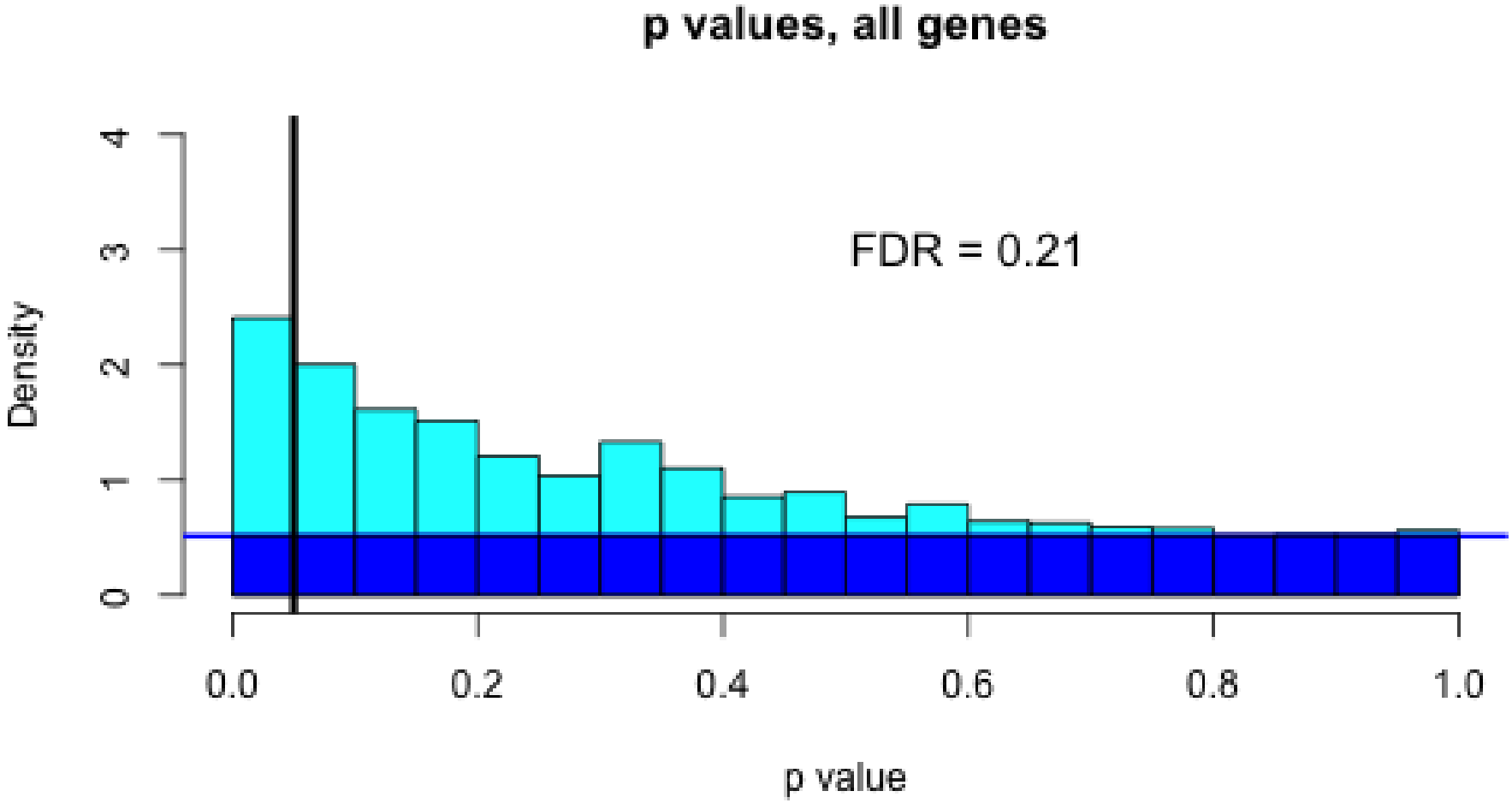
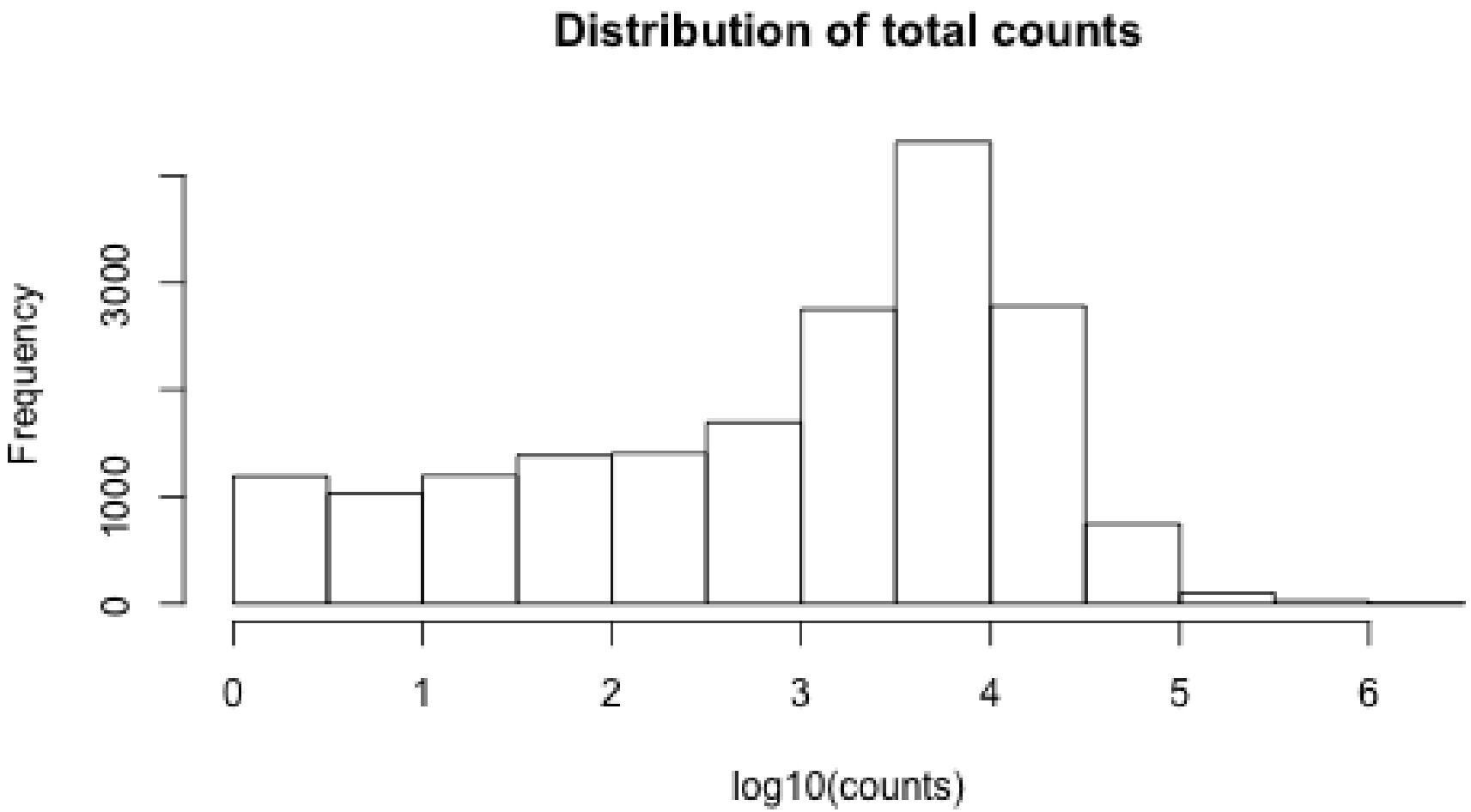
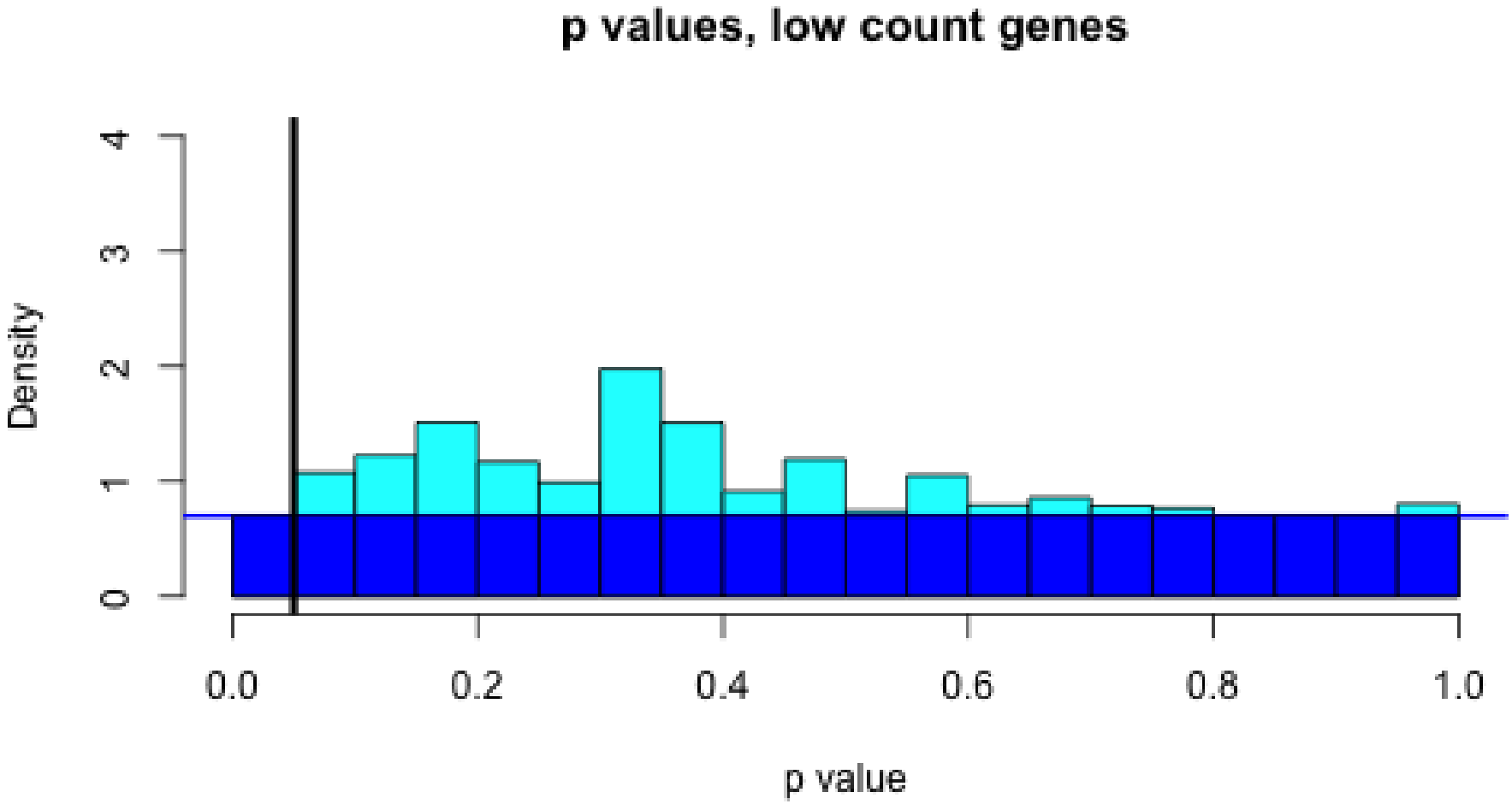


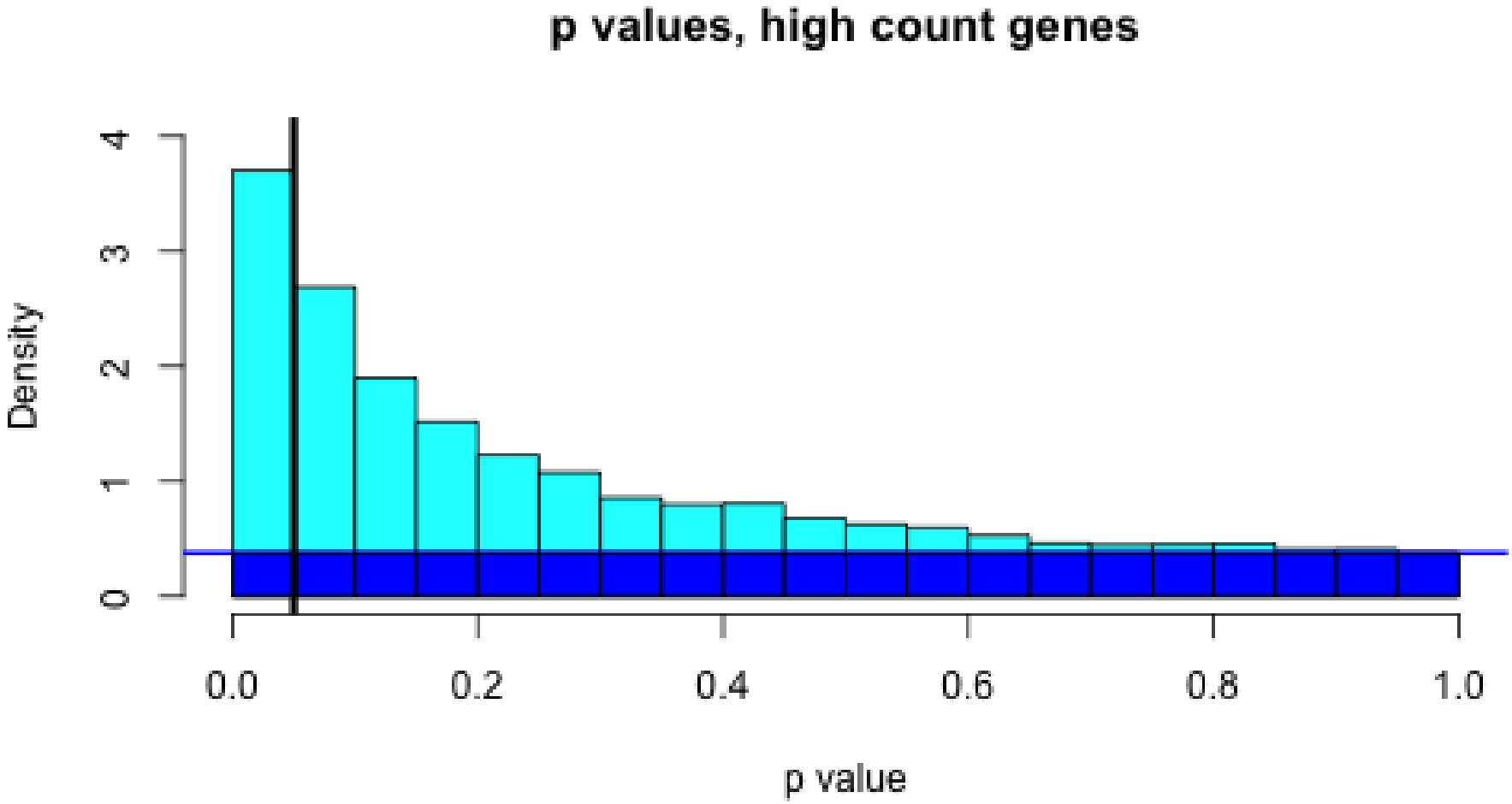
Mouse Data: Counts vary considerably across genes



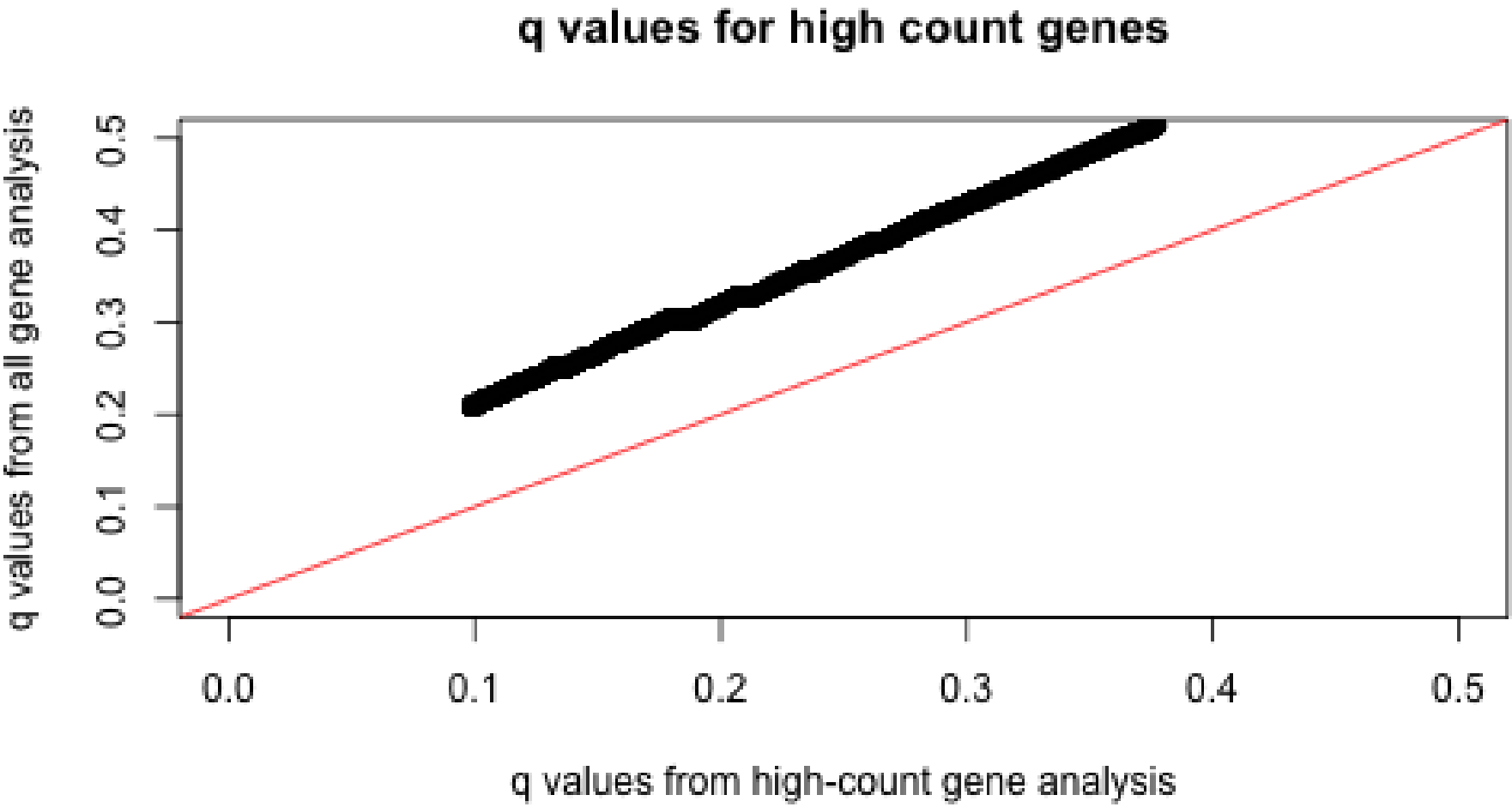
Lower count genes, less power



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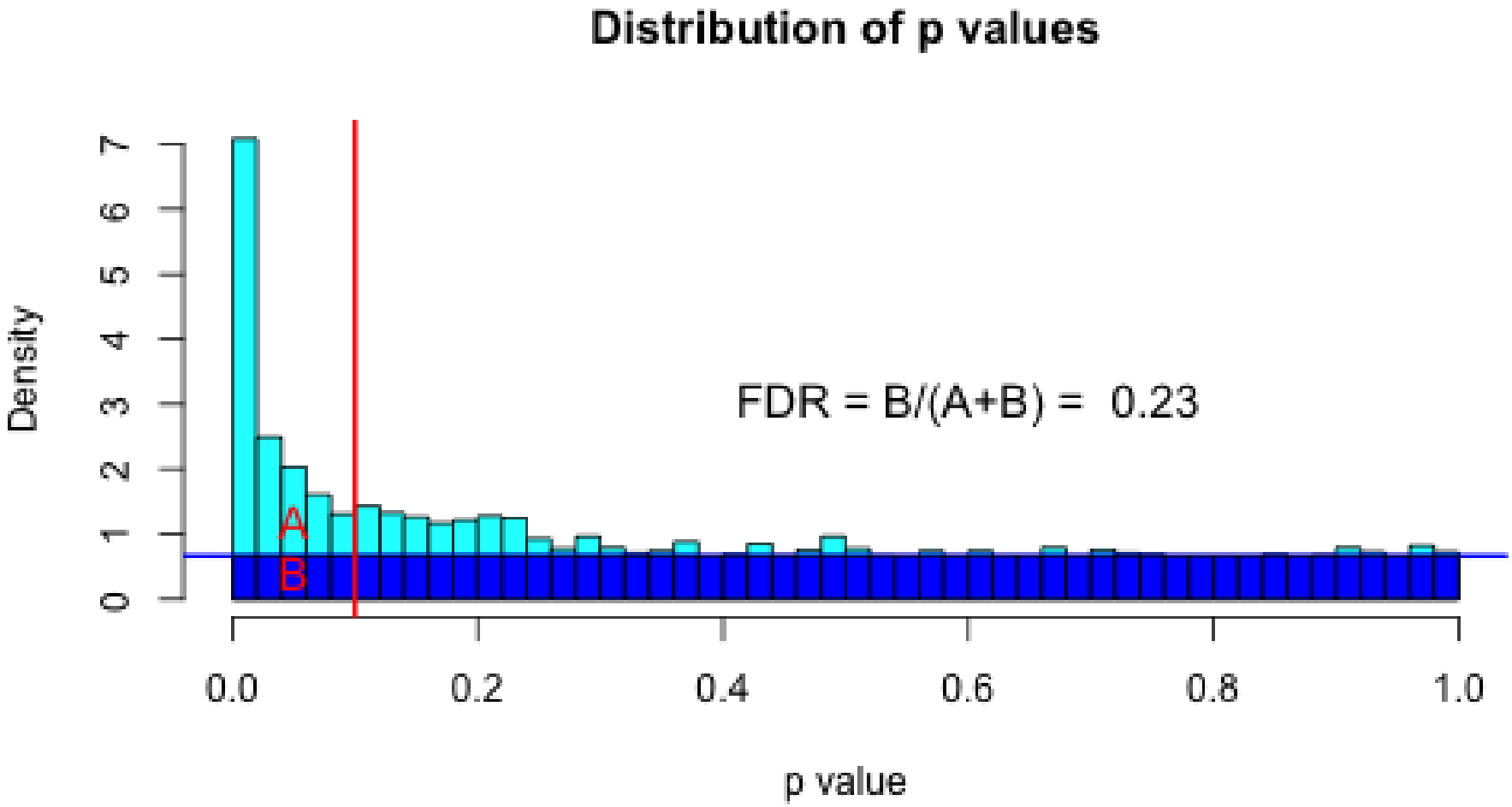
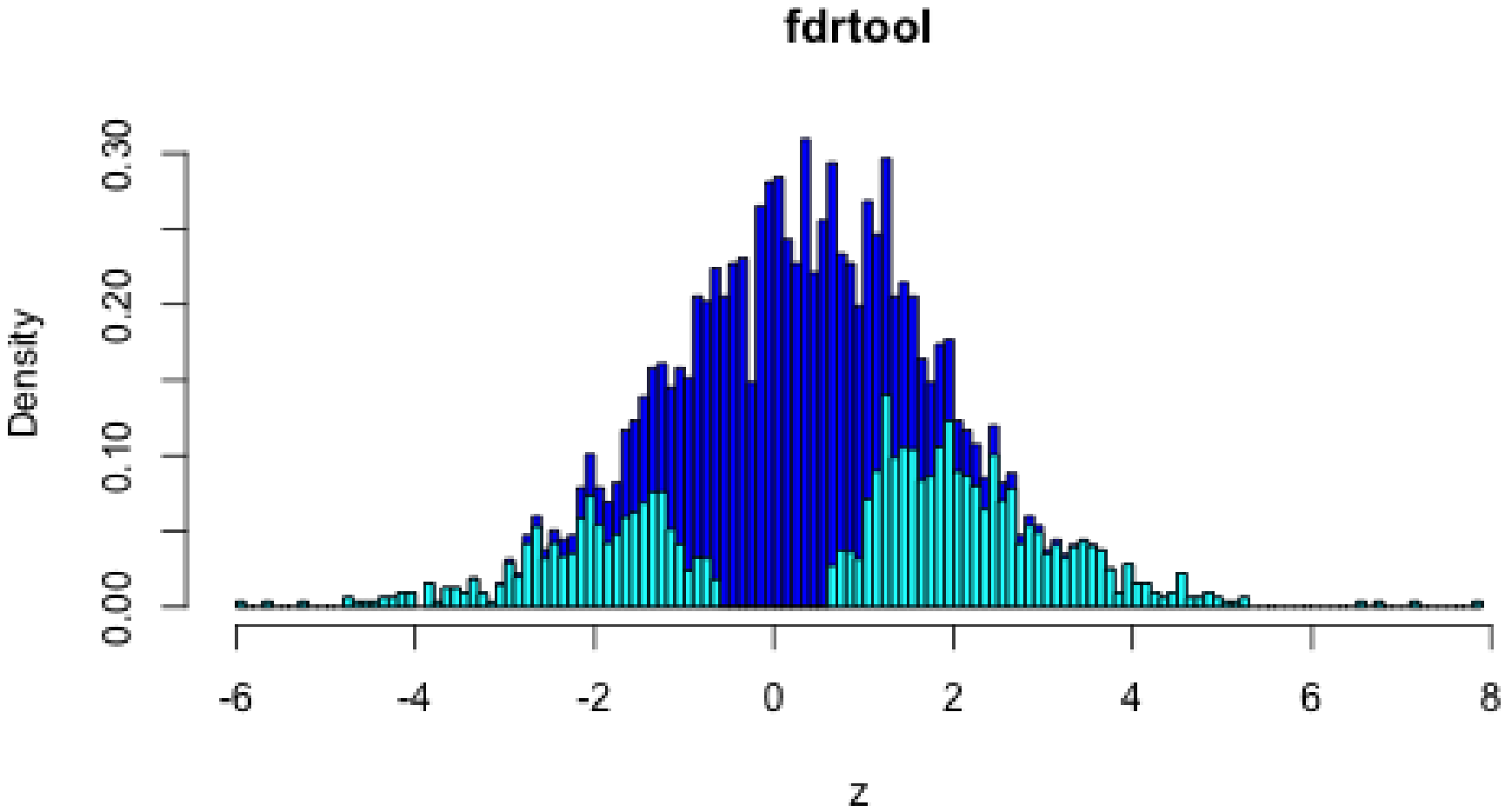
- However, it turns out to imply unrealistic assumptions about the distribution of non-zero effects.

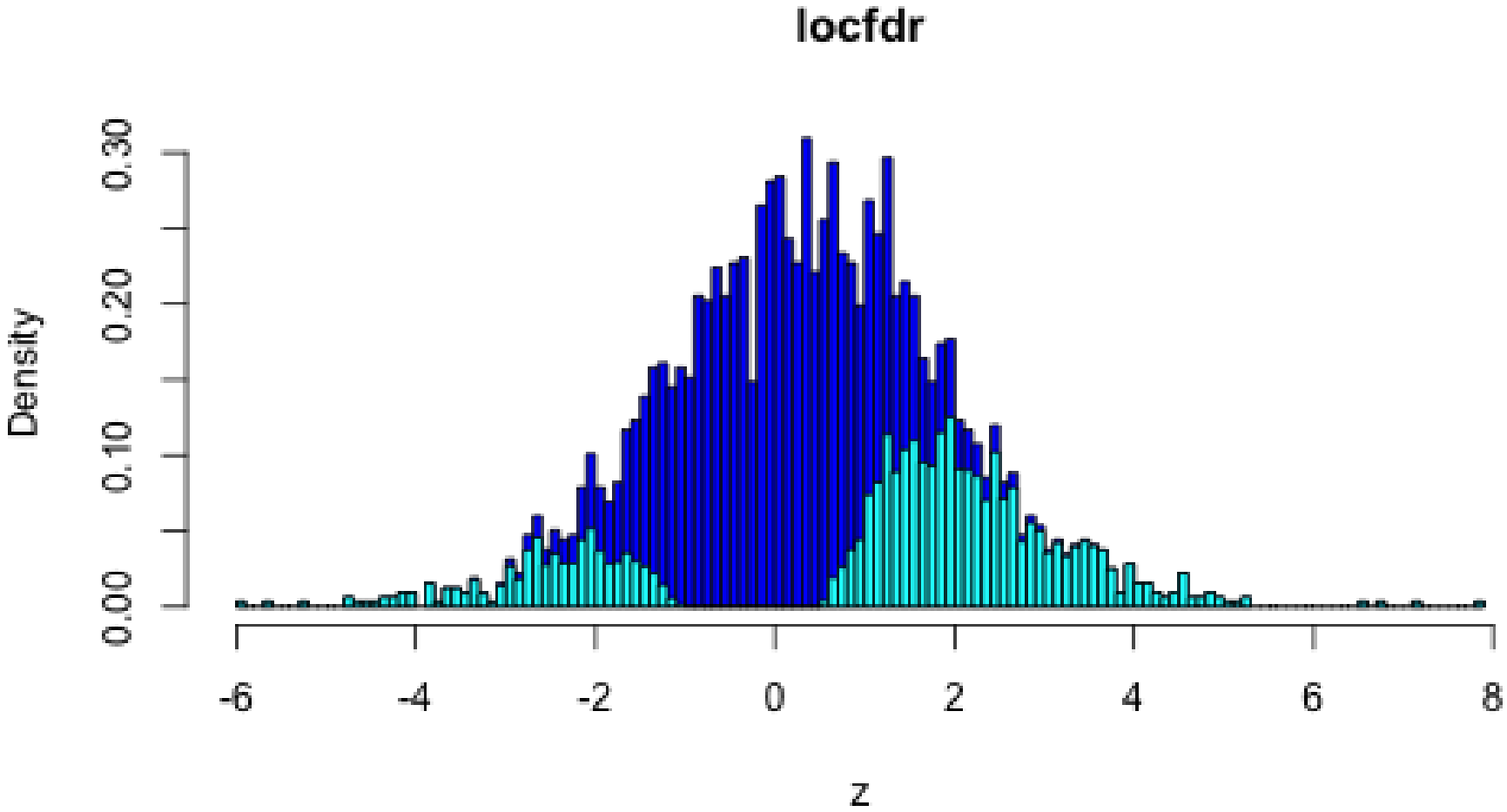
Implied distribution of p values under H_1



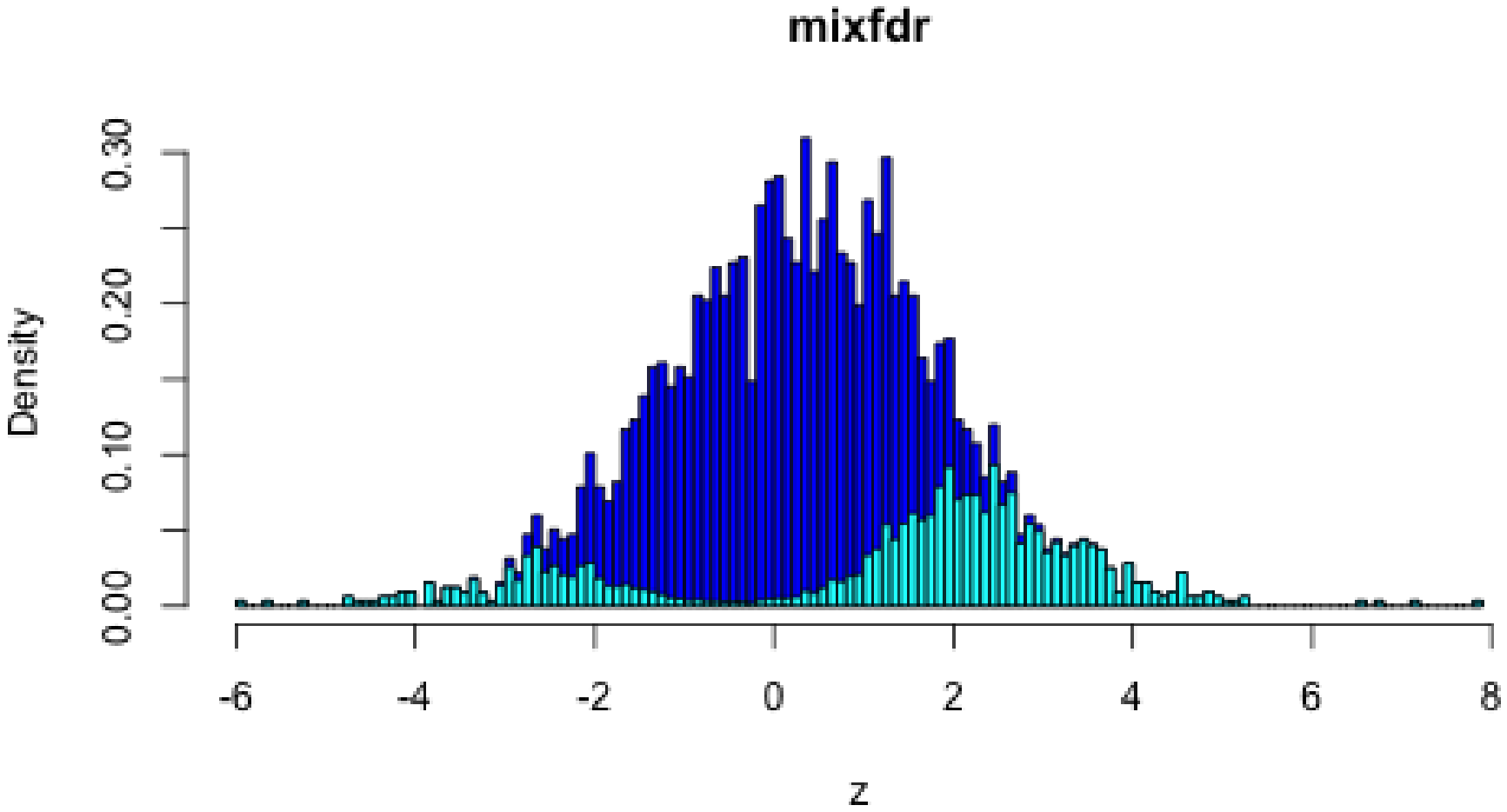
Implied distribution of Z scores under alternative (fdrtool)



Implied distribution of Z scores under alternative (locfdr)



Implied distribution of Z scores under alternative (mixfdr)




```
## null device
```

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

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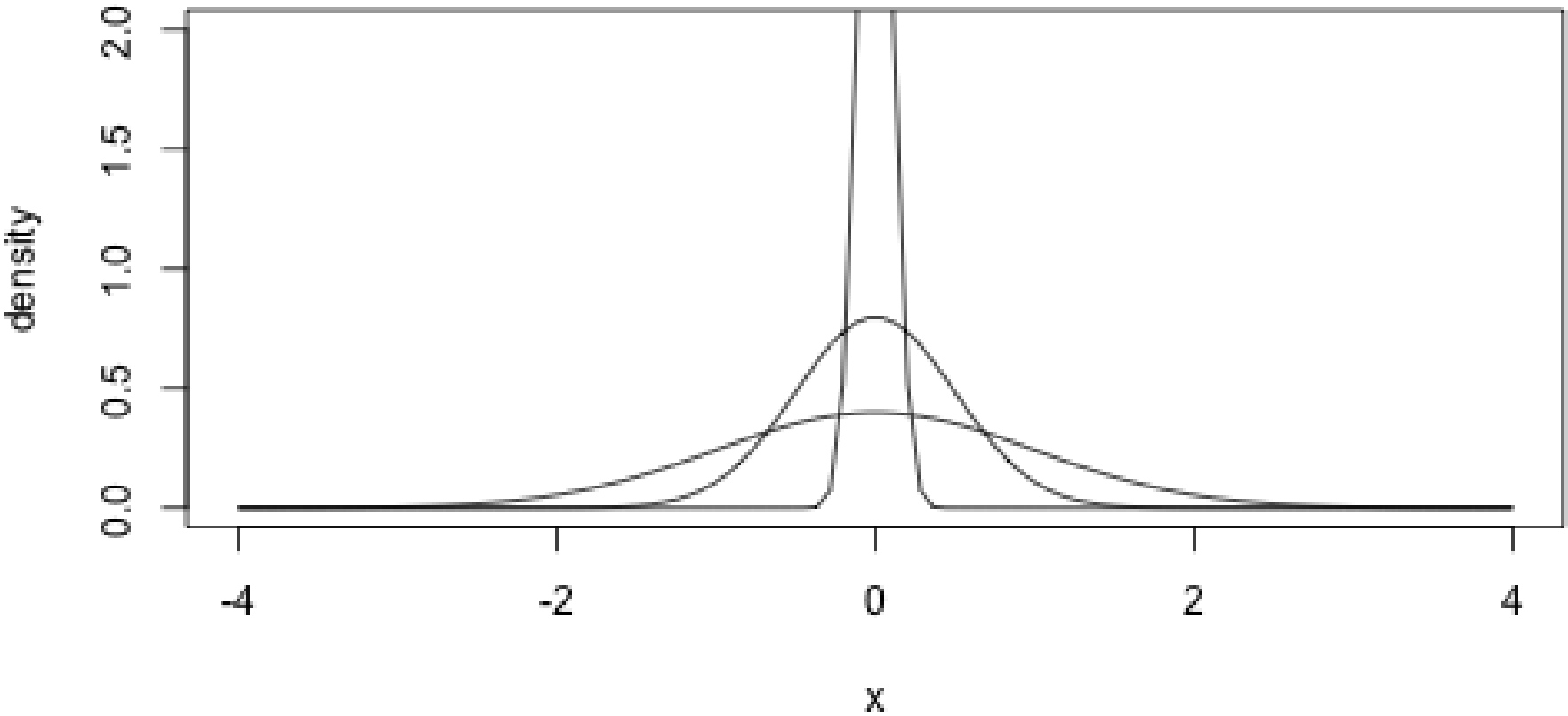
- If allow a very large number of uniforms this provides the non-parametric mle for g; cf Grenander 1953; Campy + Thomas.

Illustration: g a mixture of 0-centered normals



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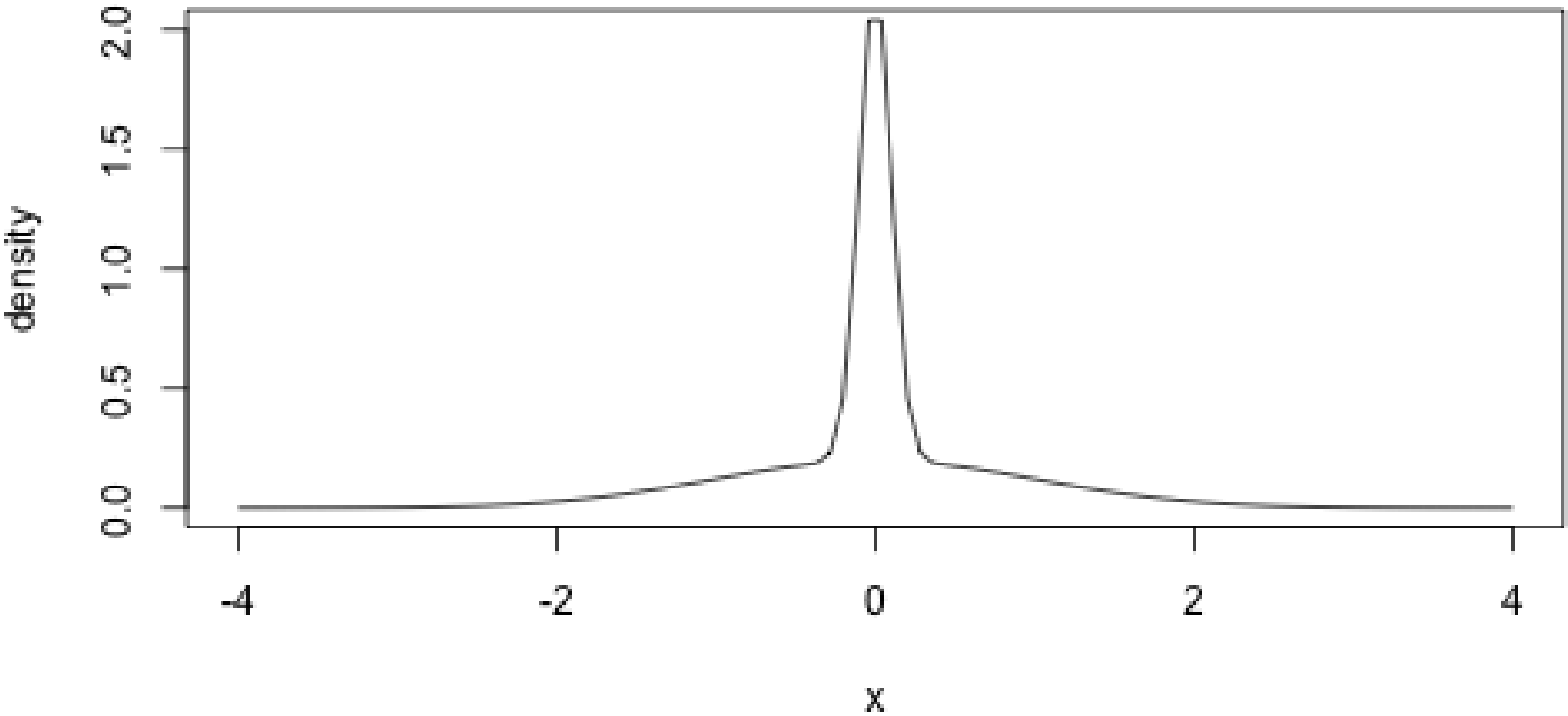

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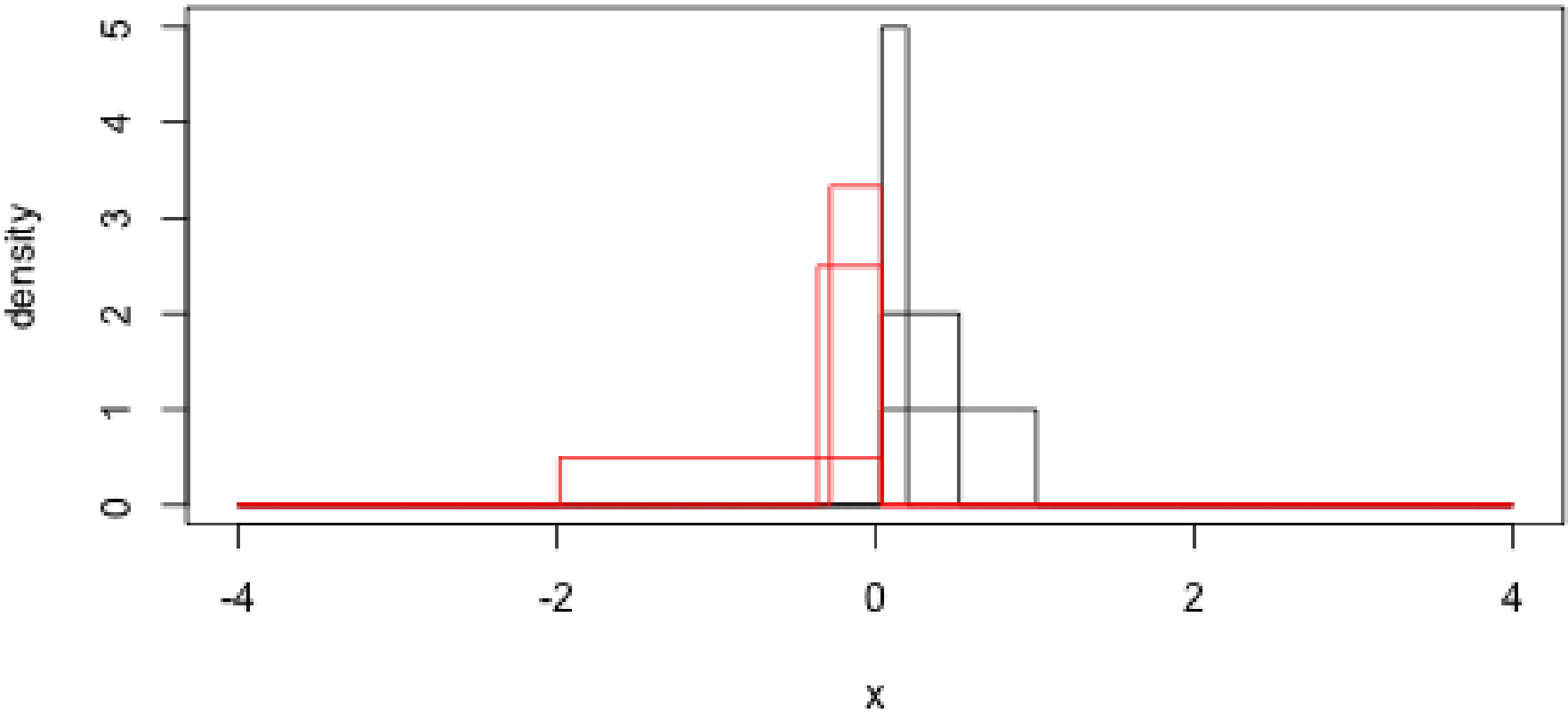

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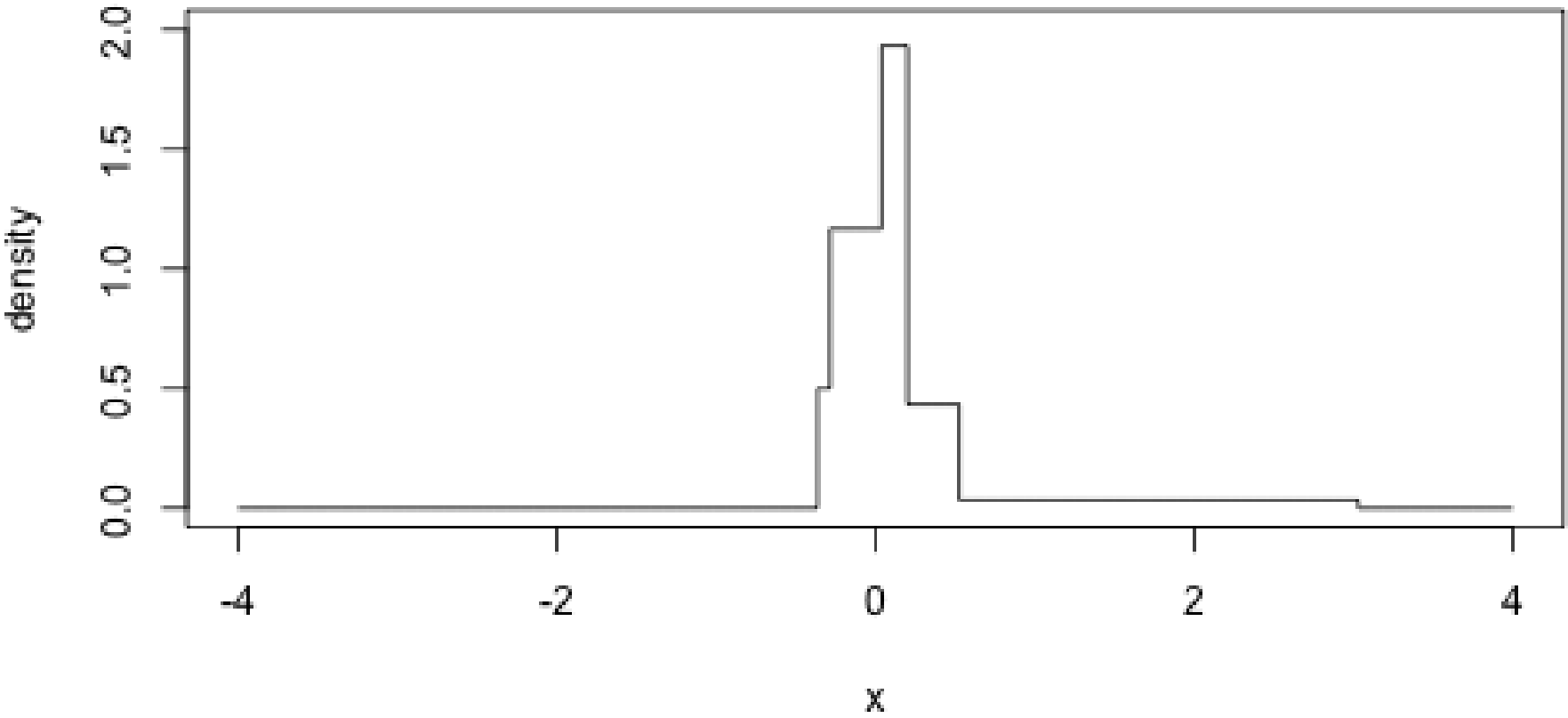

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- However, the data cannot distinguish between $\beta_j = 0$ and β_j "very small"
- As a result π_0 is formally unidentifiable. Eg data can never rule out $\pi_0 = 0$.

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- That is it provides an "upper bound" on π_0

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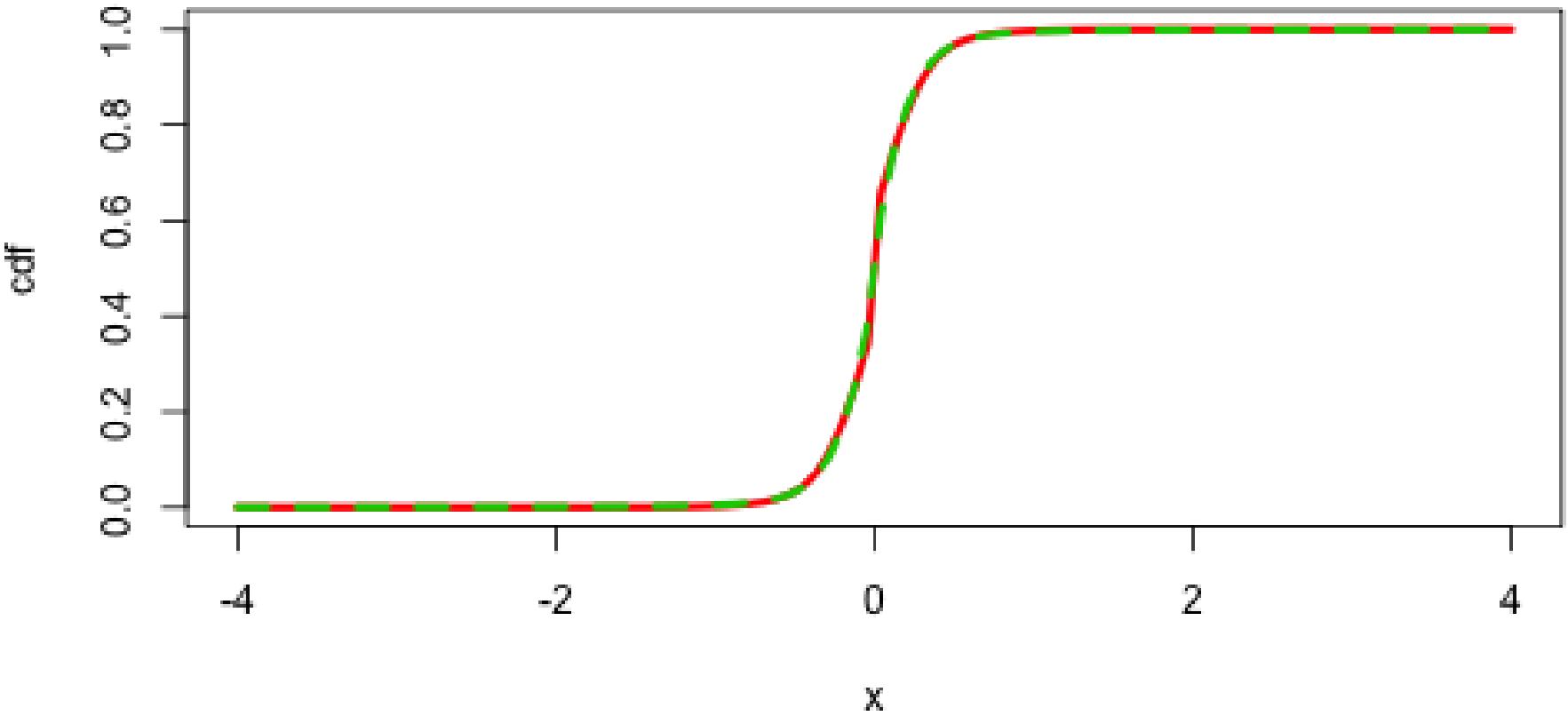
- In practice, implement upper bound by putting prior on π_0 that encourages it to be big, then estimate π by posterior mean (VB).

Illustration: BRCA data

Example: BRCA data

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



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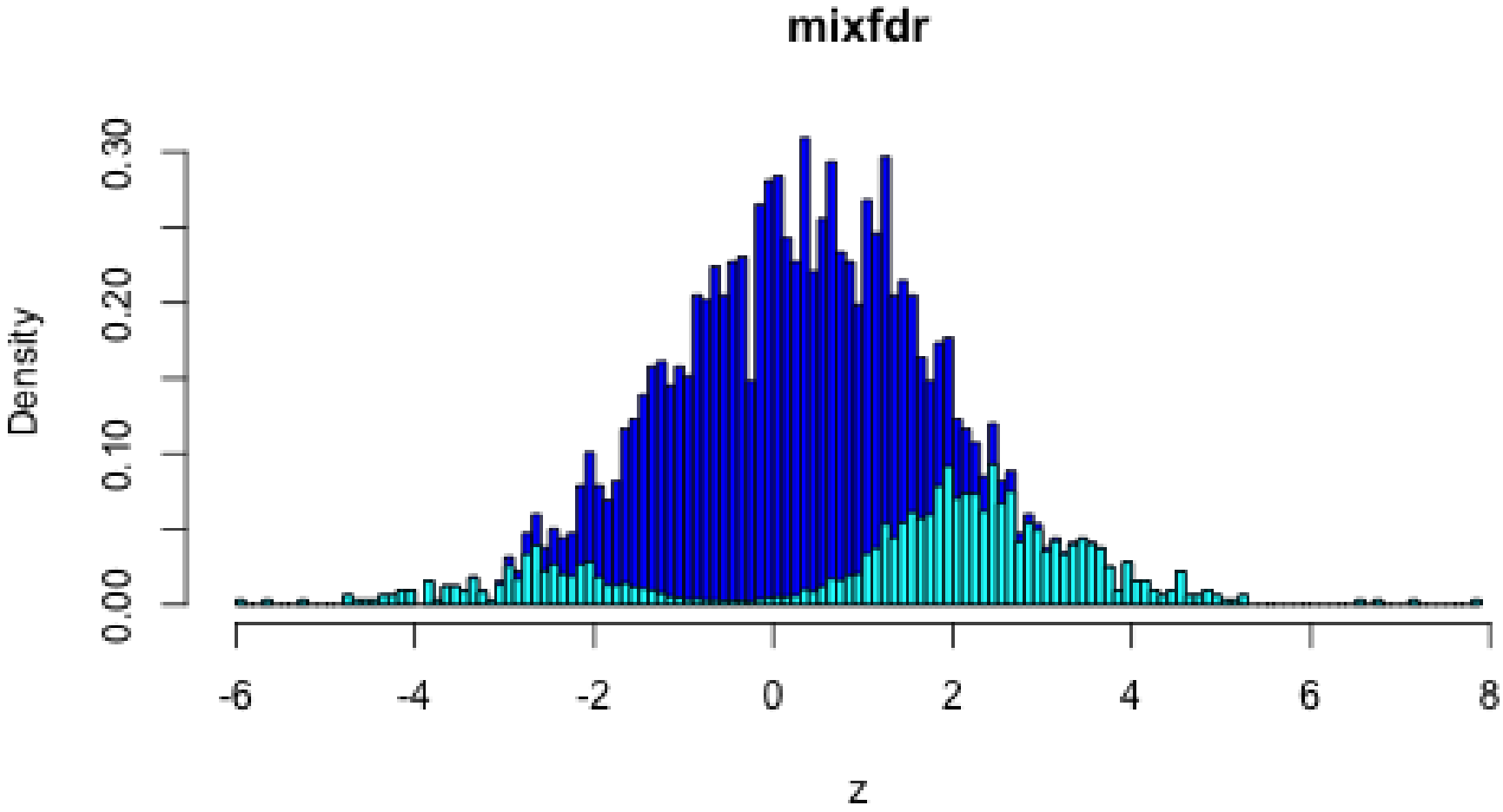

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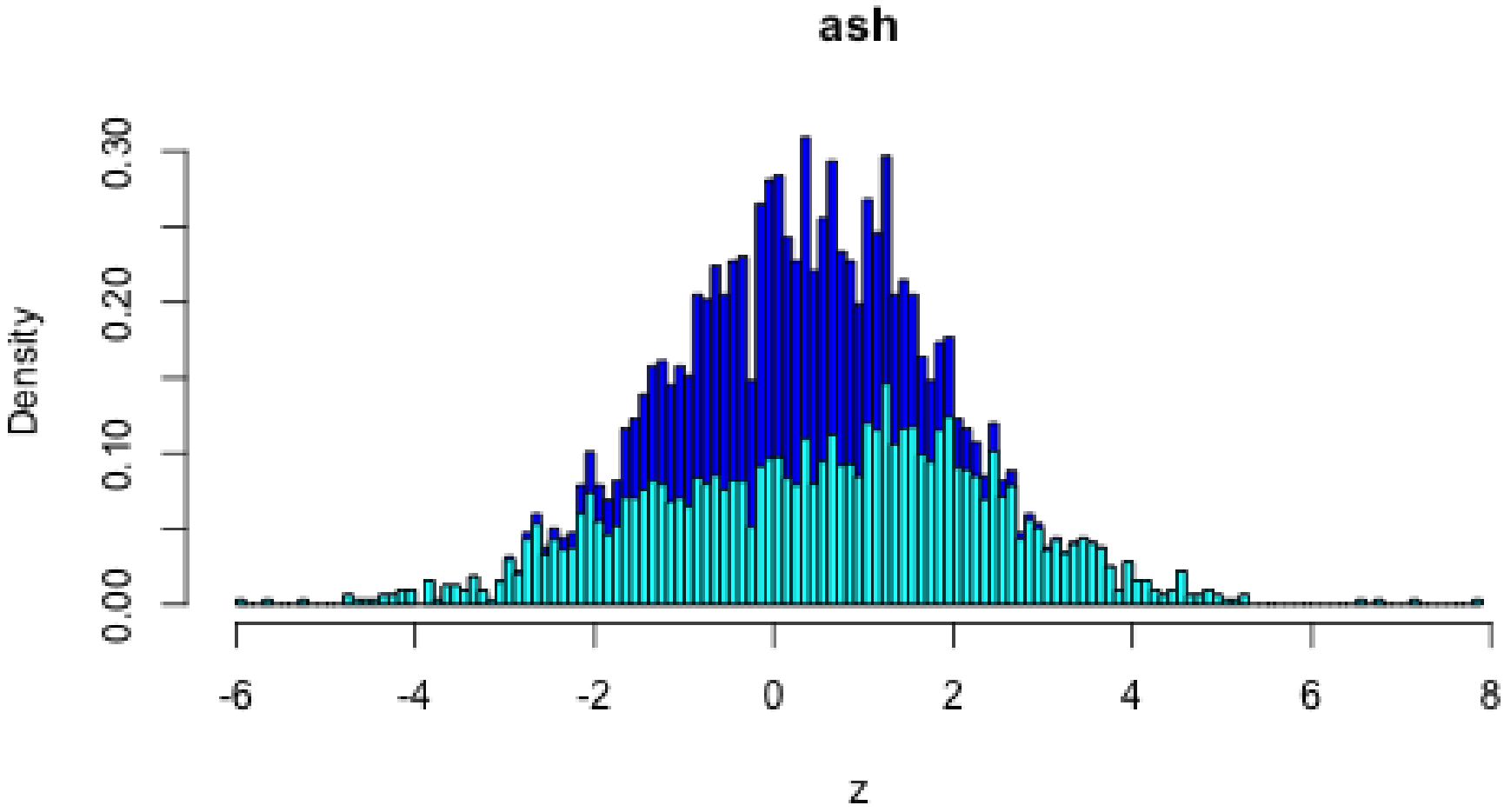

BRCA1: Compare π_0 estimates

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

```
## [1] 0.64 0.74 0.80 0.47
```

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] 154 171 162 197
```

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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.

Identifiability of π_0: Solution 2

- Identifiability of π_0 is primarily an issue if we insist on asking question is $\beta_j = 0$?
- How about we change 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).
- Positive and negative effects are often treated differently in practice anyway.
- 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.

A technicality

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- Suppose you estimate $\Pr(\beta_j < 0) = 0.98$, $\Pr(\beta_j > 0) = 0.01$, $\Pr(\beta_j = 0) = 0.01$.
- Should you declare an fdr of 0.01 or 0.02?
- Maybe fsr makes more sense anyway?

Unification of one-group and two-group solutions

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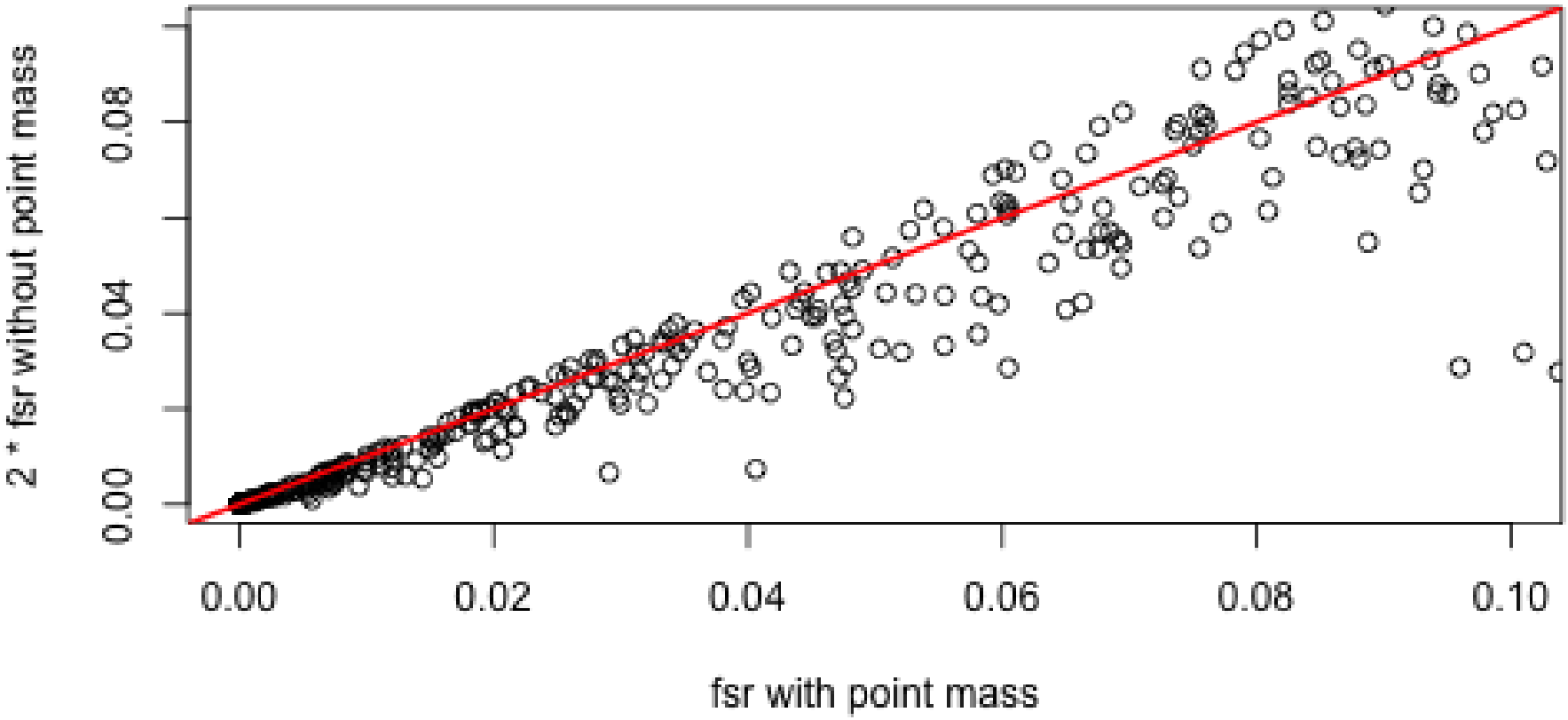
- Consider our example, with $\Pr(\beta_j > 0) = 0.025$. If we actually allowed $\beta_j = 0$ then possibly all of this probability might actually land at $\beta_j = 0$.
- I argue that, assuming symmetry of g near 0, this also provides an upper bound of how much of the $\Pr(\beta_j < 0) = 0.975$ might also move to 0.
- Therefore a more conservative estimate of the fsr might be 0.05 (or, more generally, double what you get allowing for point mass)

Example: BRCA data



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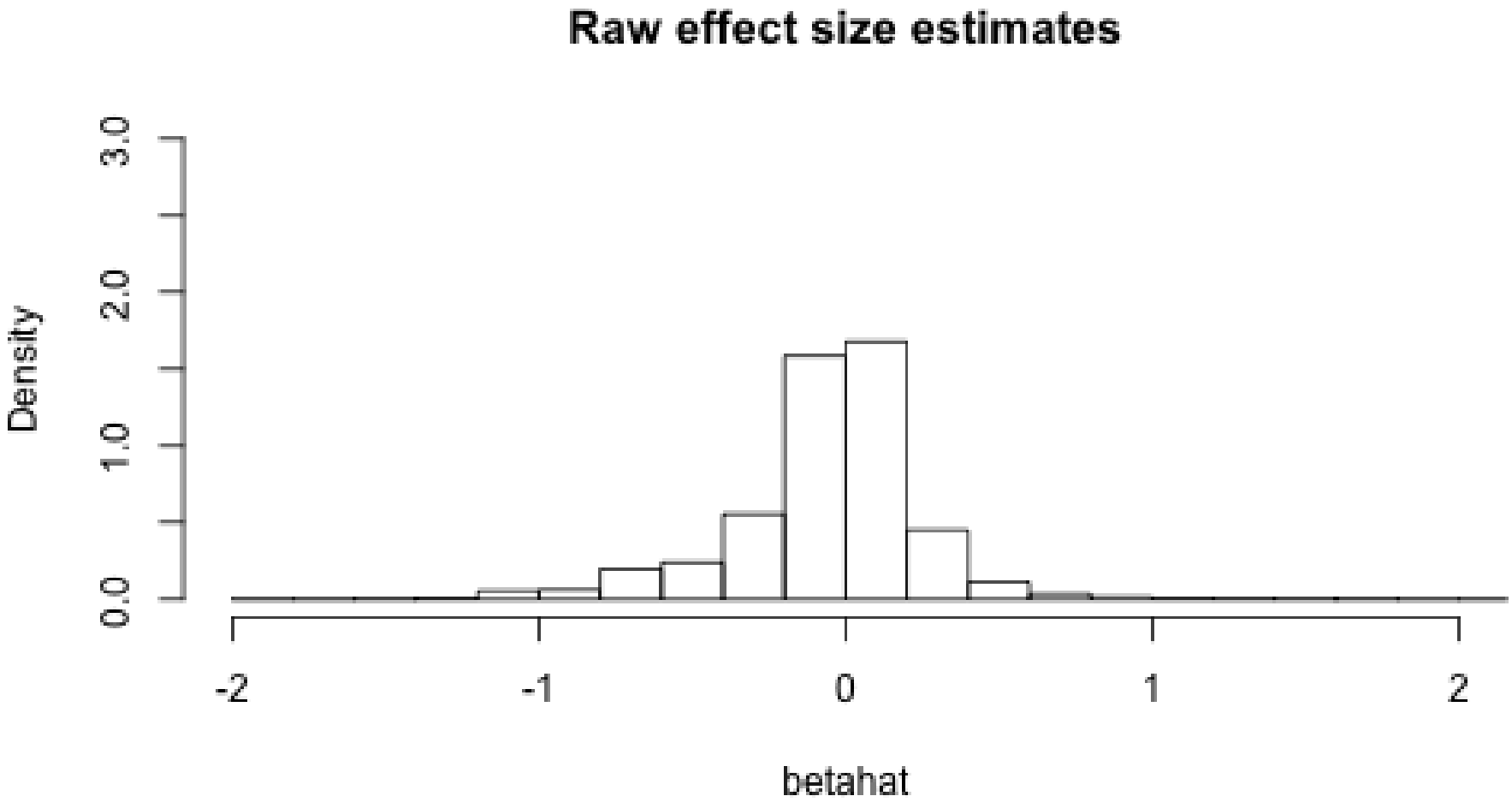
- So we call the approach "Adaptive Shrinkage" (ASH).

Example: ASH applied to mouse data



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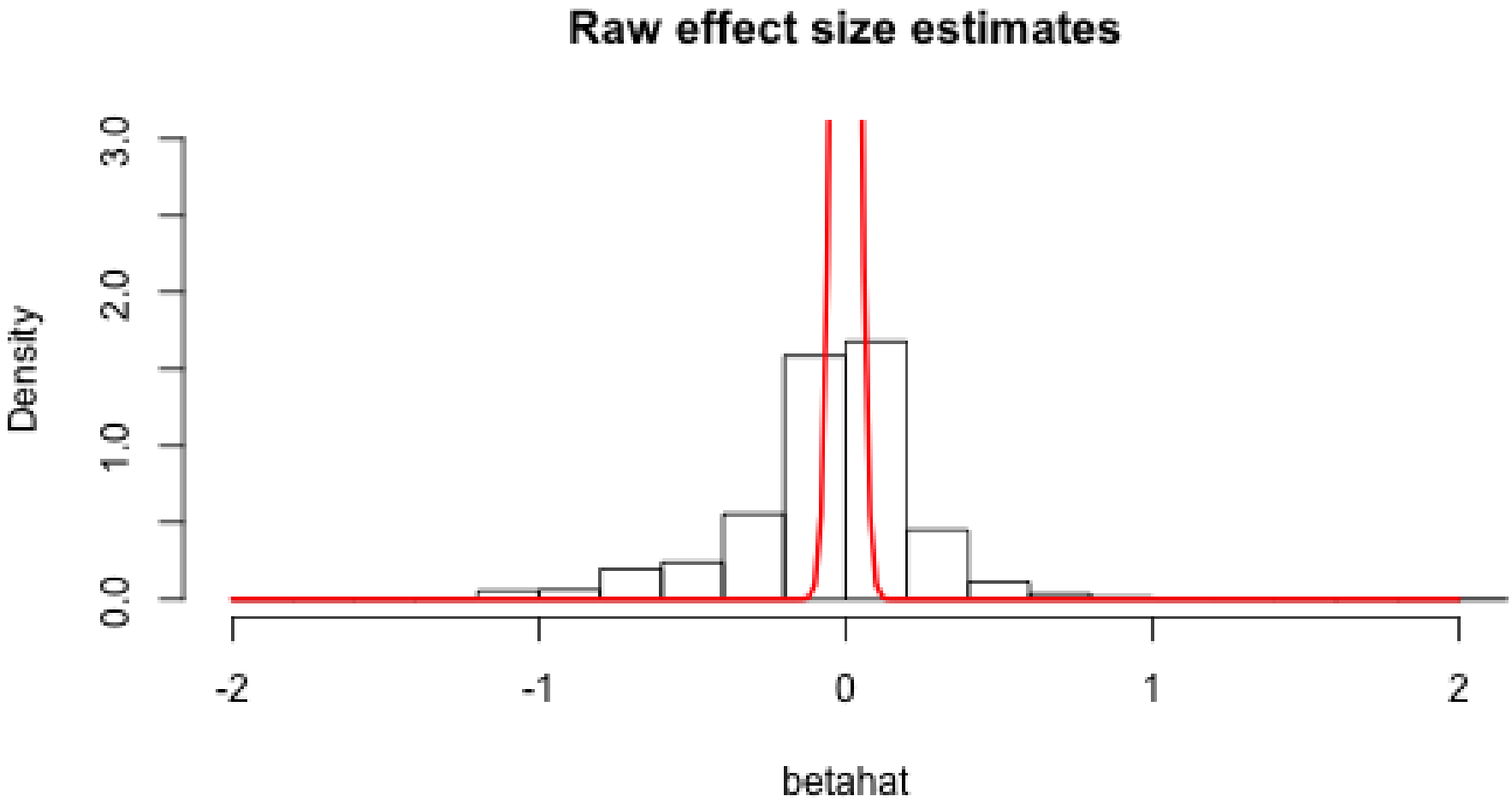

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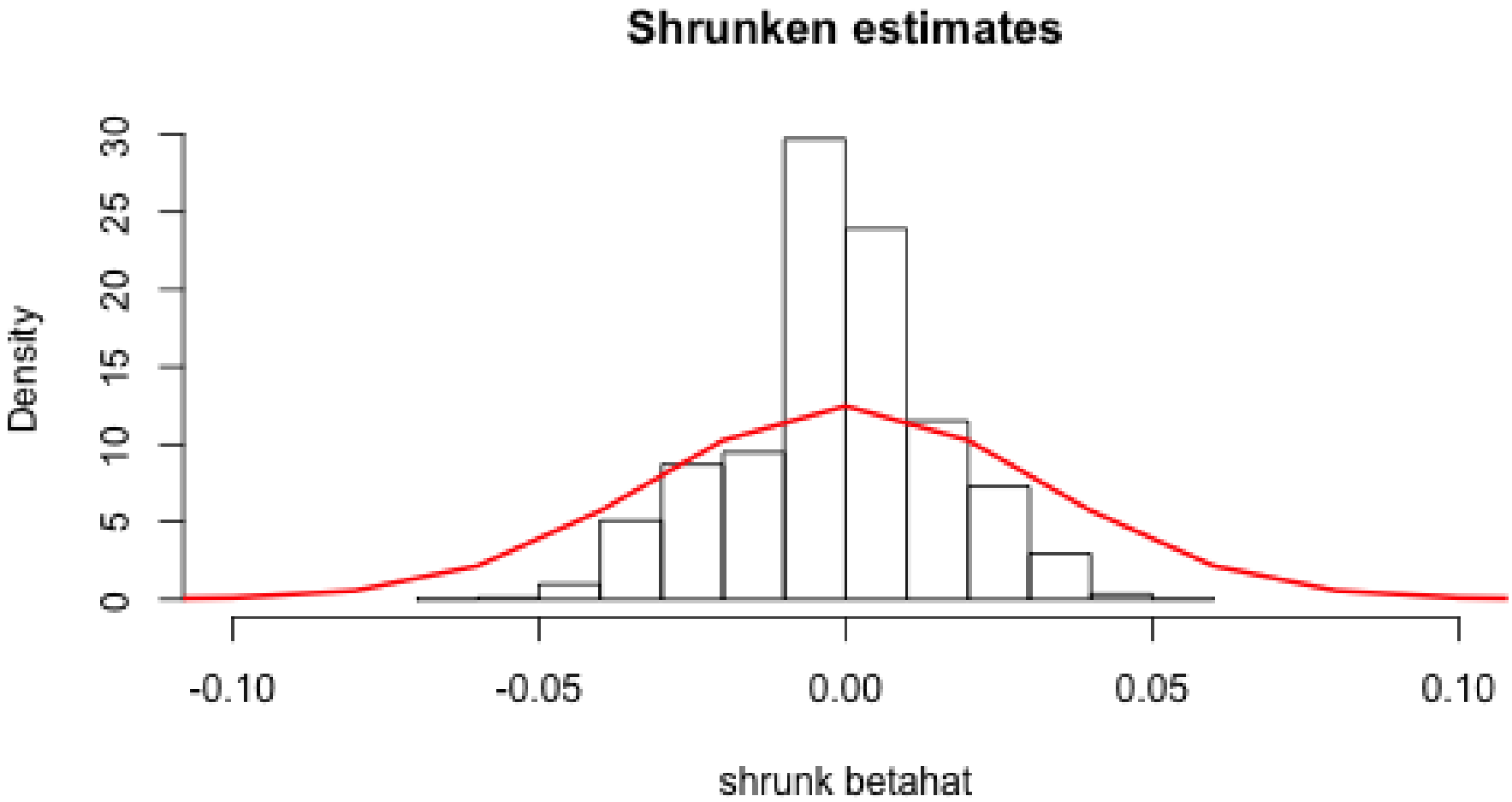
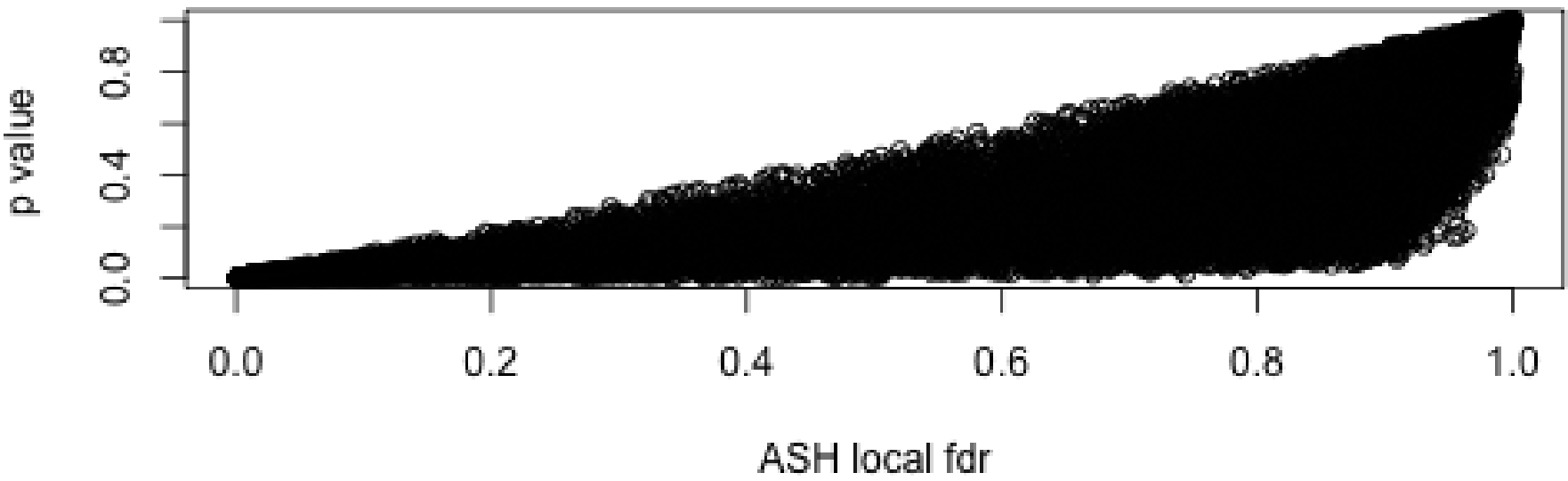


Shrinkage is adaptive to information



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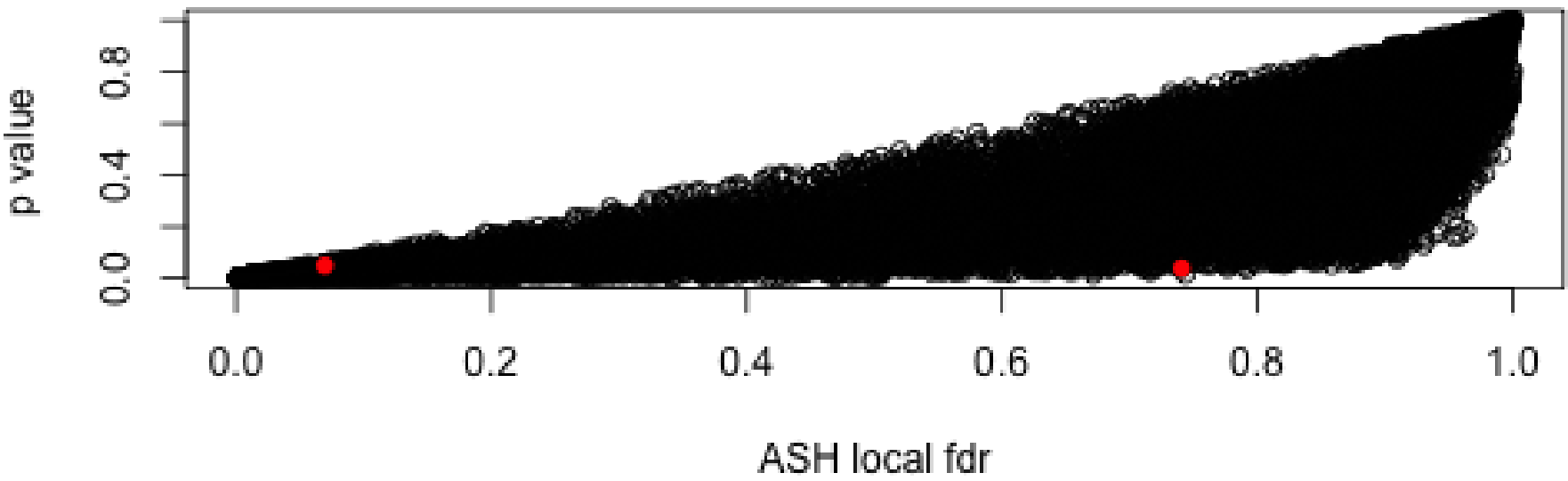
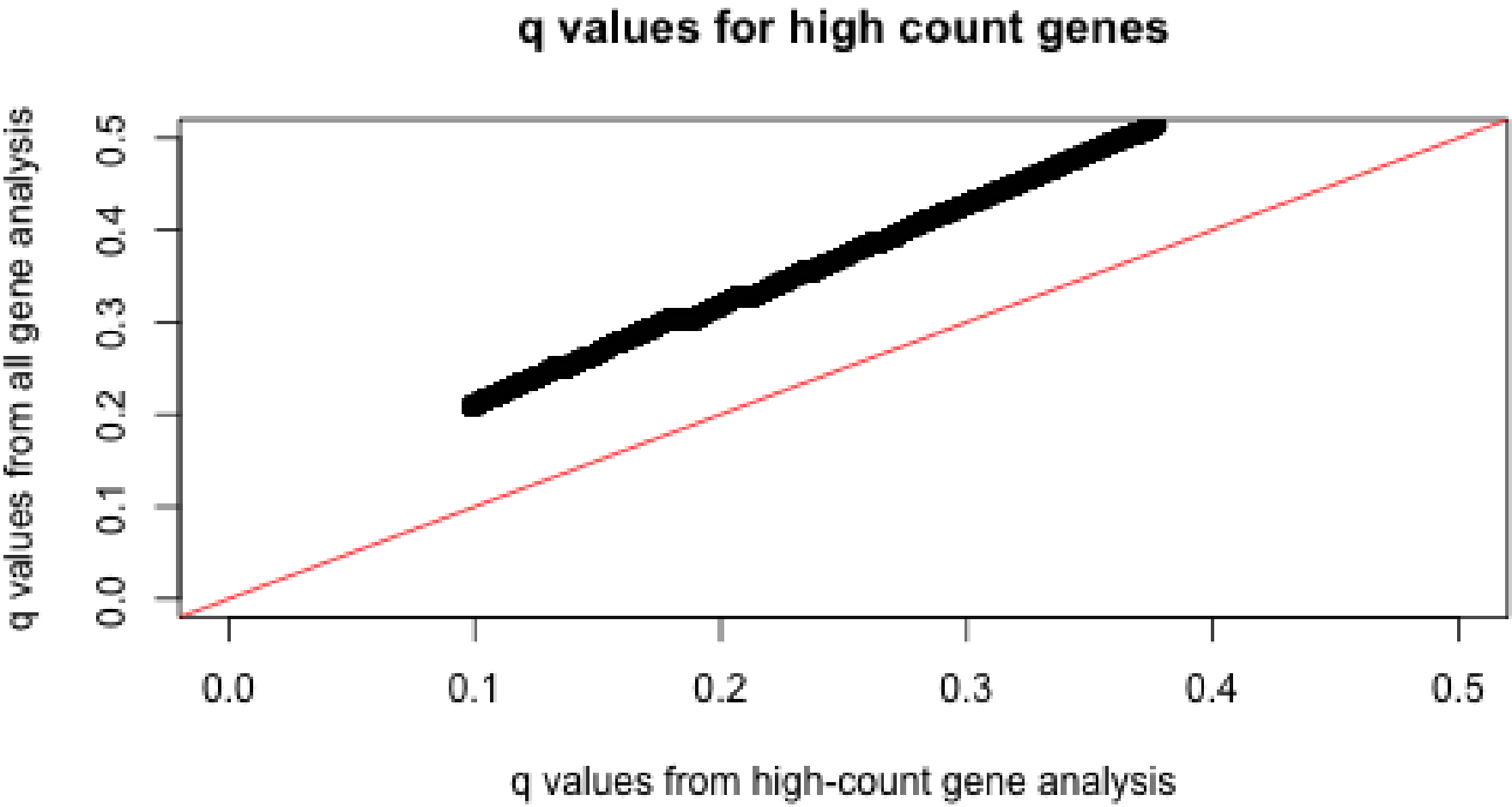


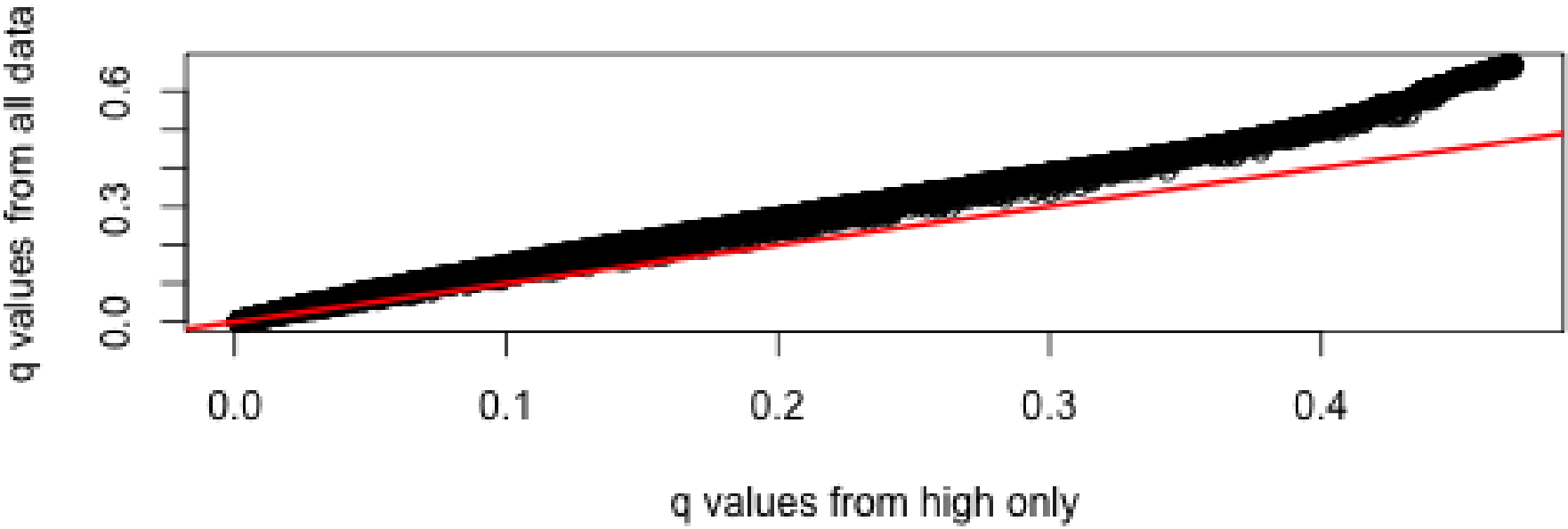
Shrinkage is adaptive to information

```
##          gene  lv1  lv2  rv1  rv2    pval zdat.ash$localfdr
## 19422 Mgat5b    7   10  320  452 0.03795           0.74069
## 20432  Sec63 1042 1034 5496 6649 0.04908           0.06952
```

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



ASH q values more robust to inclusion of low count genes



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Summary: FDR via Adapative Shrinkage

- Both provide a rational approach to identifying "significant" findings.
- Both are generic and modular: once you have the summary data, you can forget where they came from.
- But by using two numbers $(\hat{\beta}, s)$ instead of one (p values) precision of different measurementscan be better accounted for.
- ASH borrows information for estimation, as well as testing.

Other Applications

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- Could also use effect size estimate and p value for each variable, by converting to effect size estimate and (pseudo-) standard error.
- Currently applying it to wavelet shrinkage applications.

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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- Especially Mengyin Lu who coded the VB algorithm.

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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 ilike-slides.md -o
ilike-slides.pdf
```

(alternative to produce html slides; but figures would need reworking)

```
pandoc -s -S -i -t dzslides --mathjax NSmeet2013.md -o
NSmeet2013.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

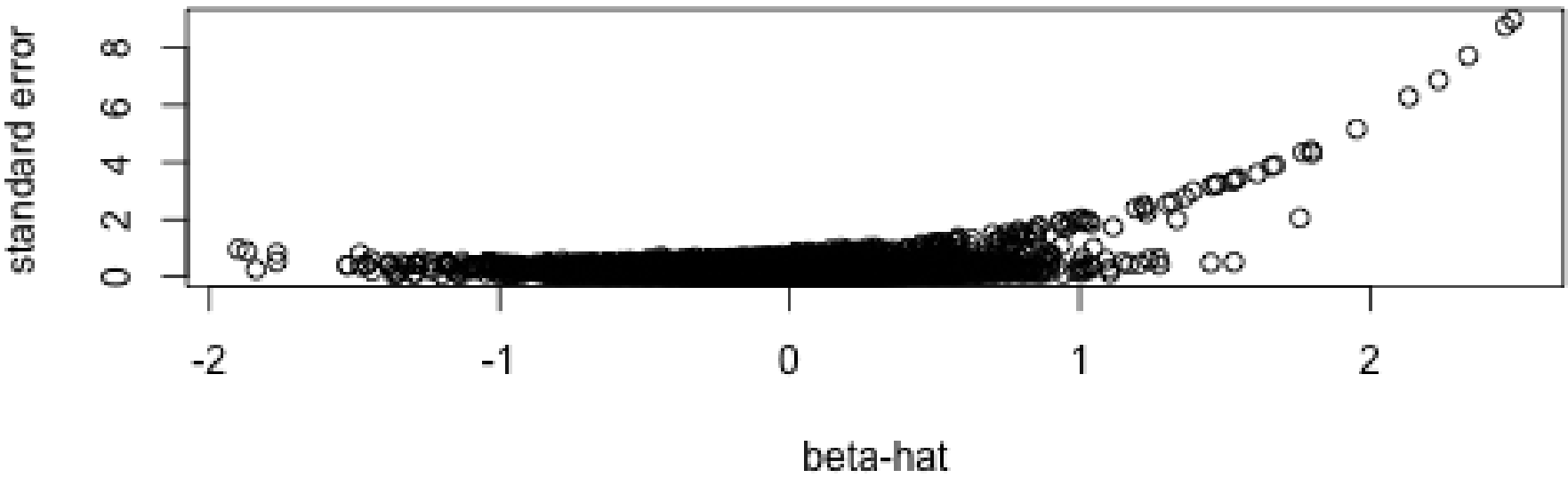

Figure : plot of chunk unnamed-chunk-43

```
##          gene lv1 lv2 rv1   rv2 genelength
## 17711   Napsa   0   1   7   779       1470
```