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

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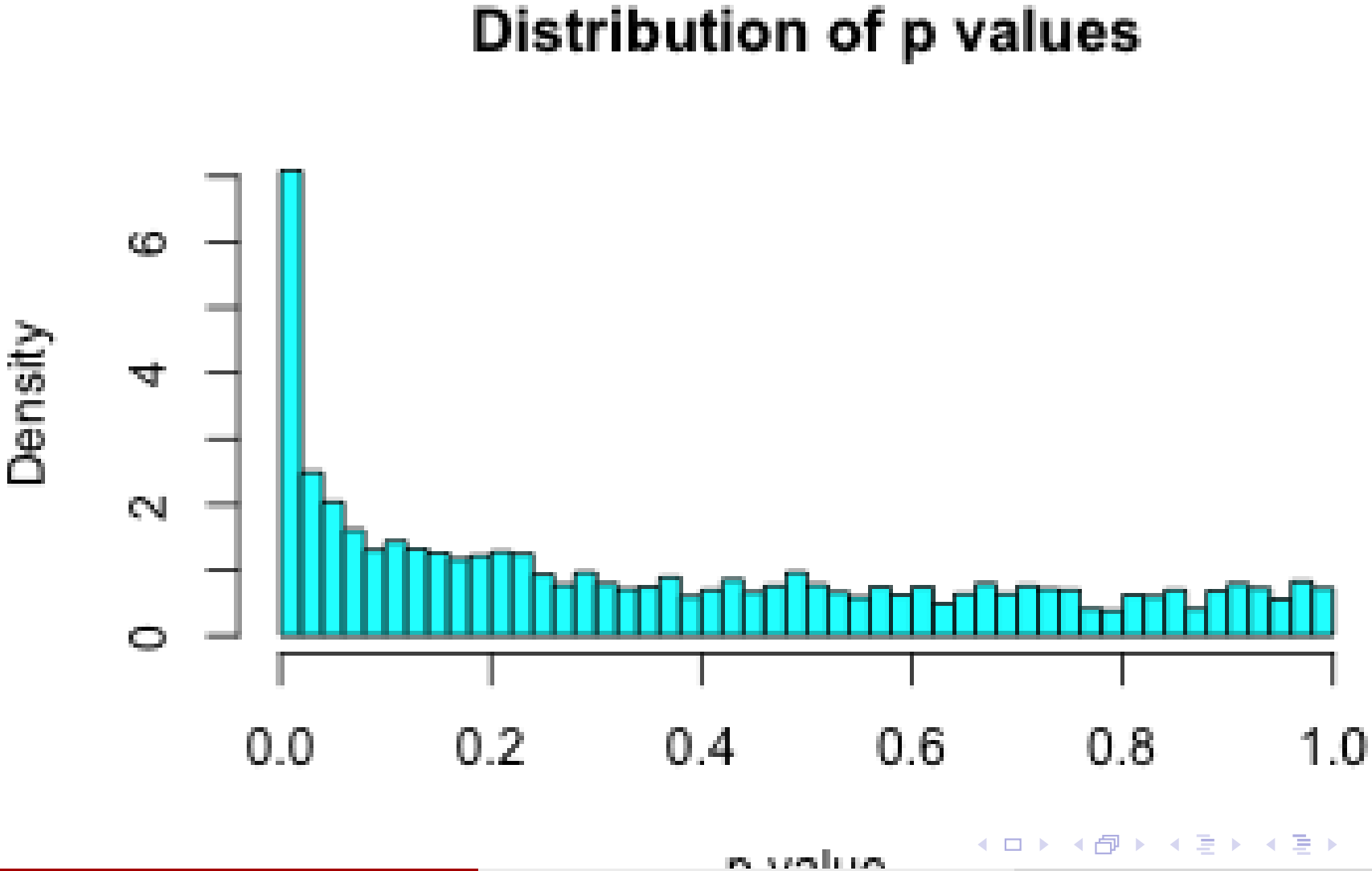
Example: BRCA1 vs BRCA2 expression



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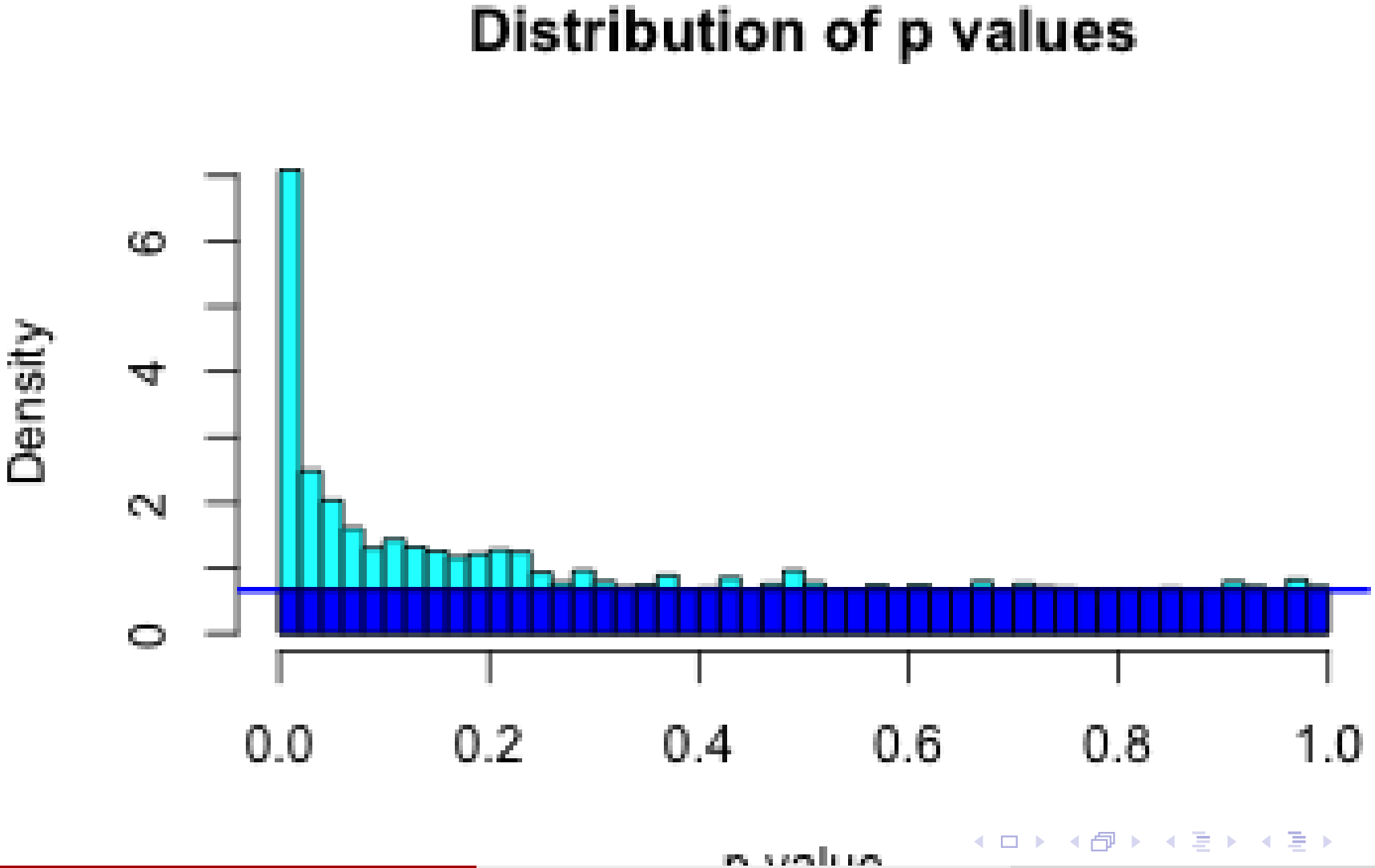

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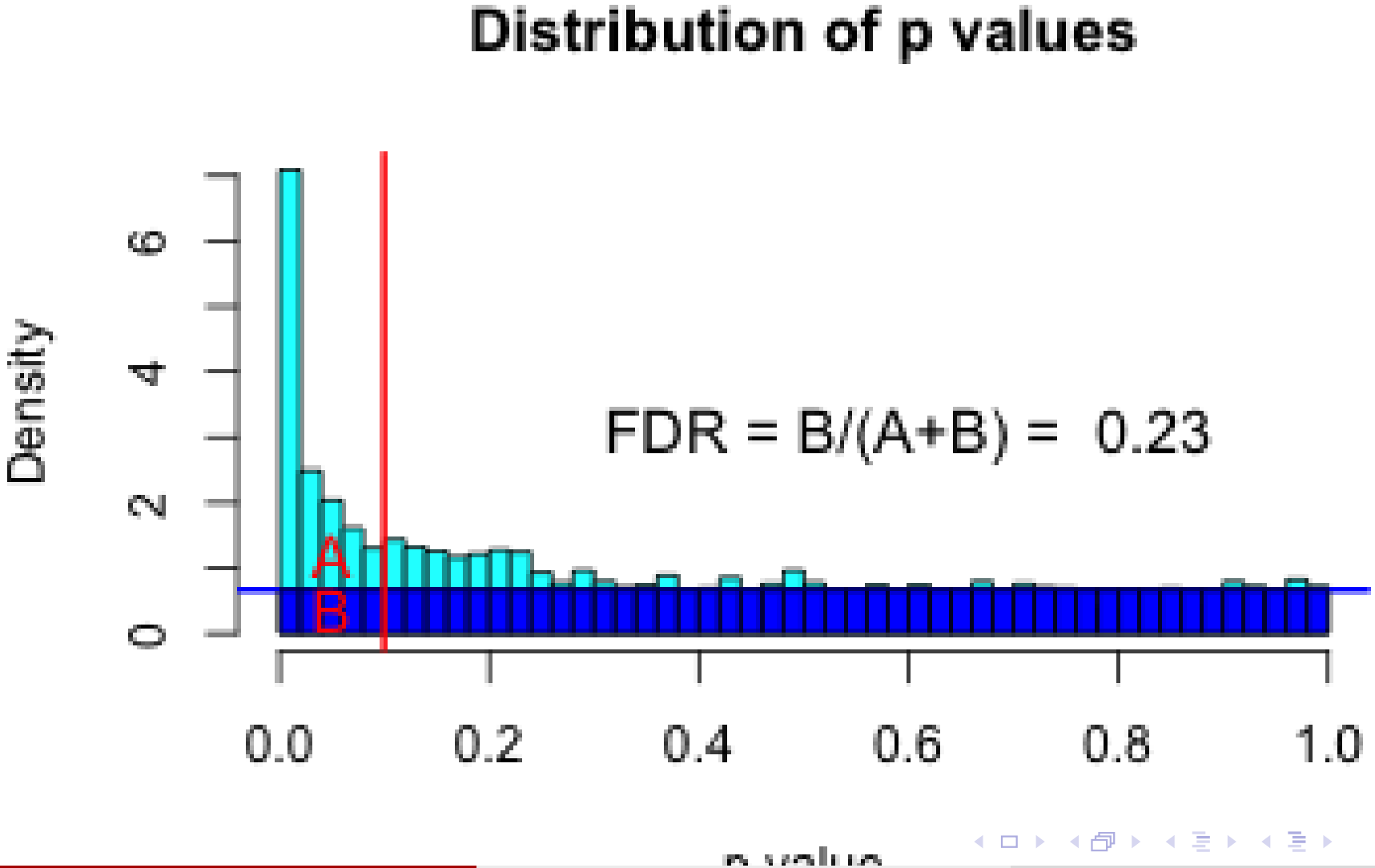

Example 2: Mouse Heart Data

```
##      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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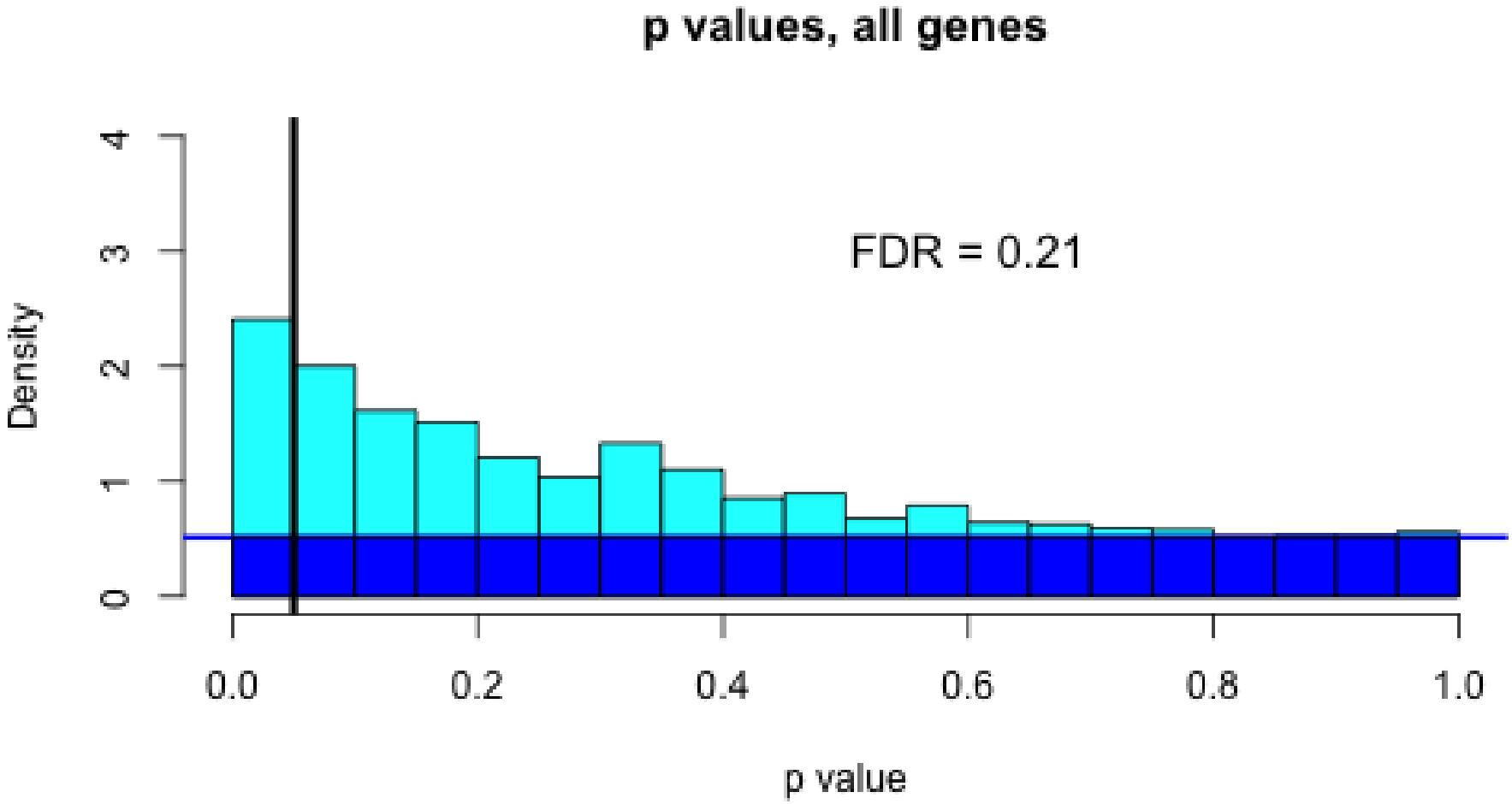
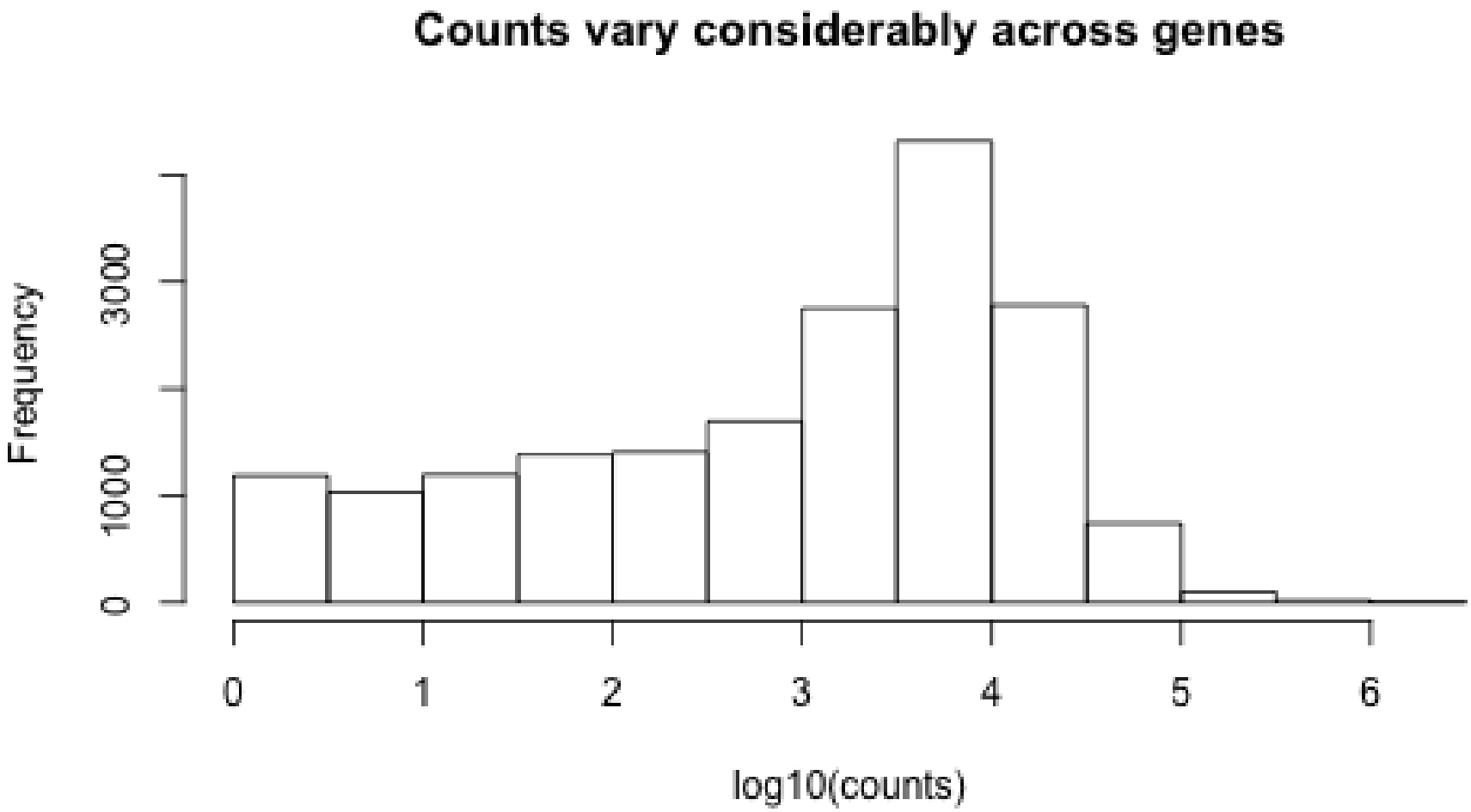
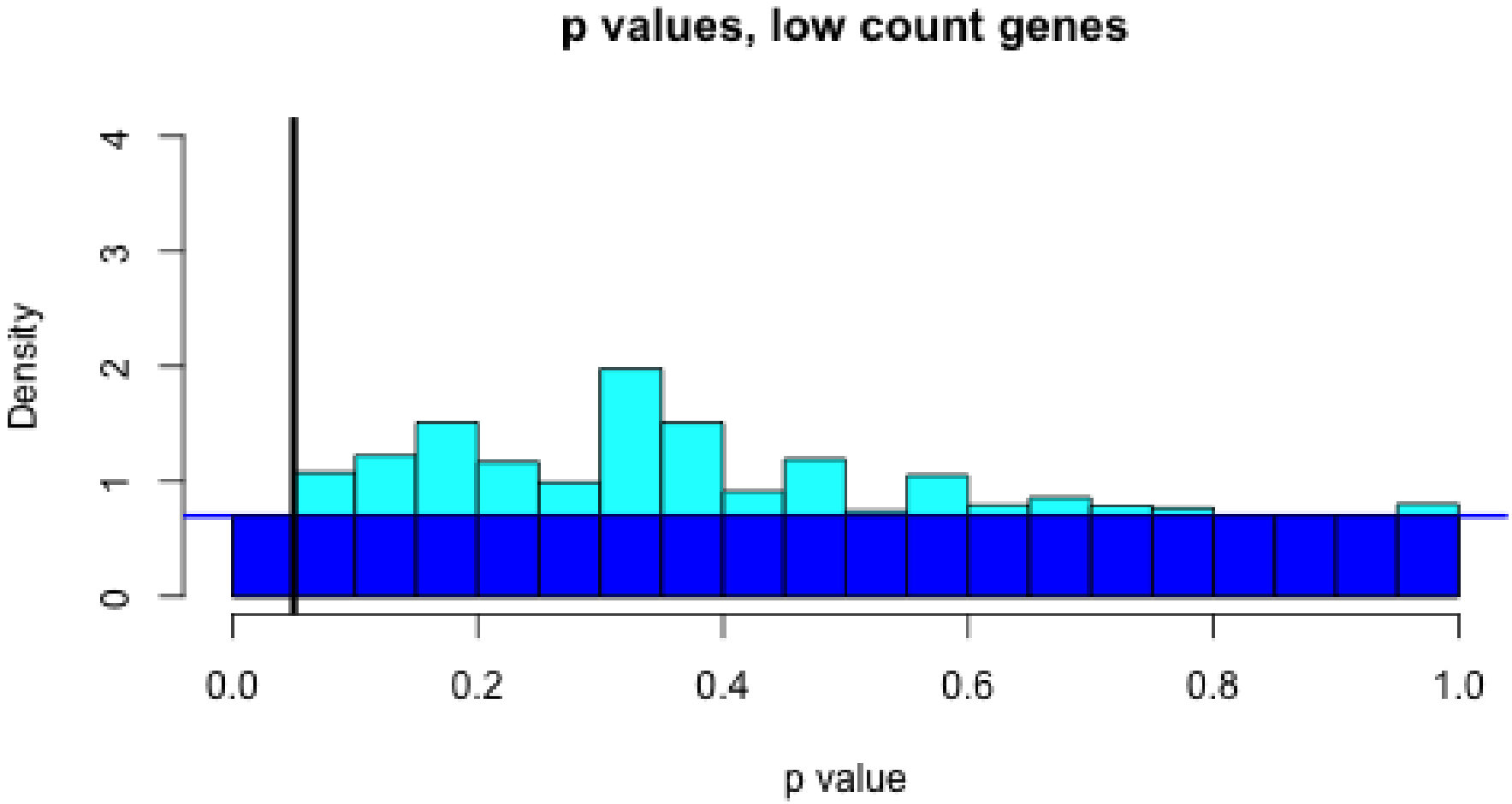


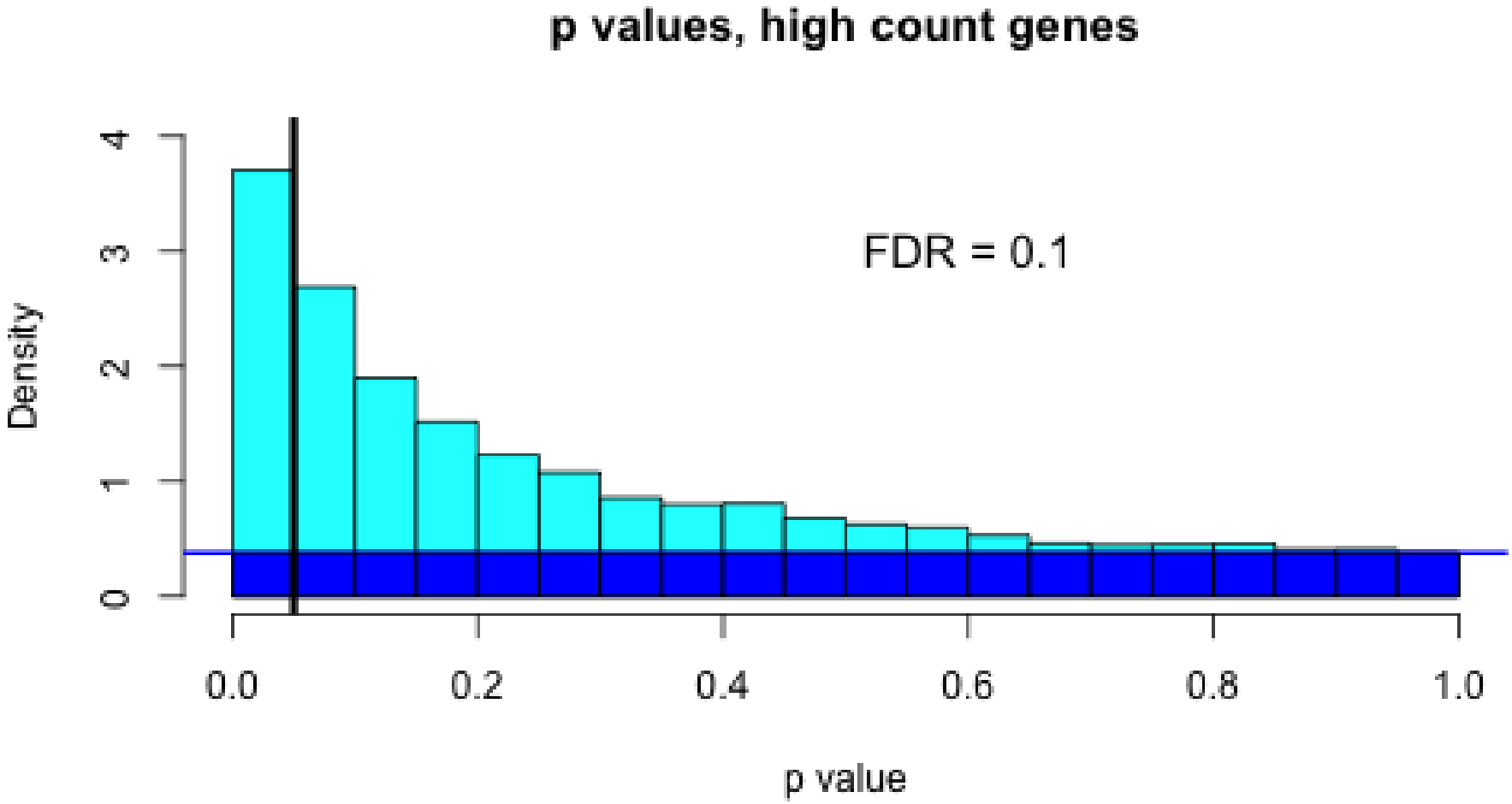
FDR problem 1: different genes have different precision/power



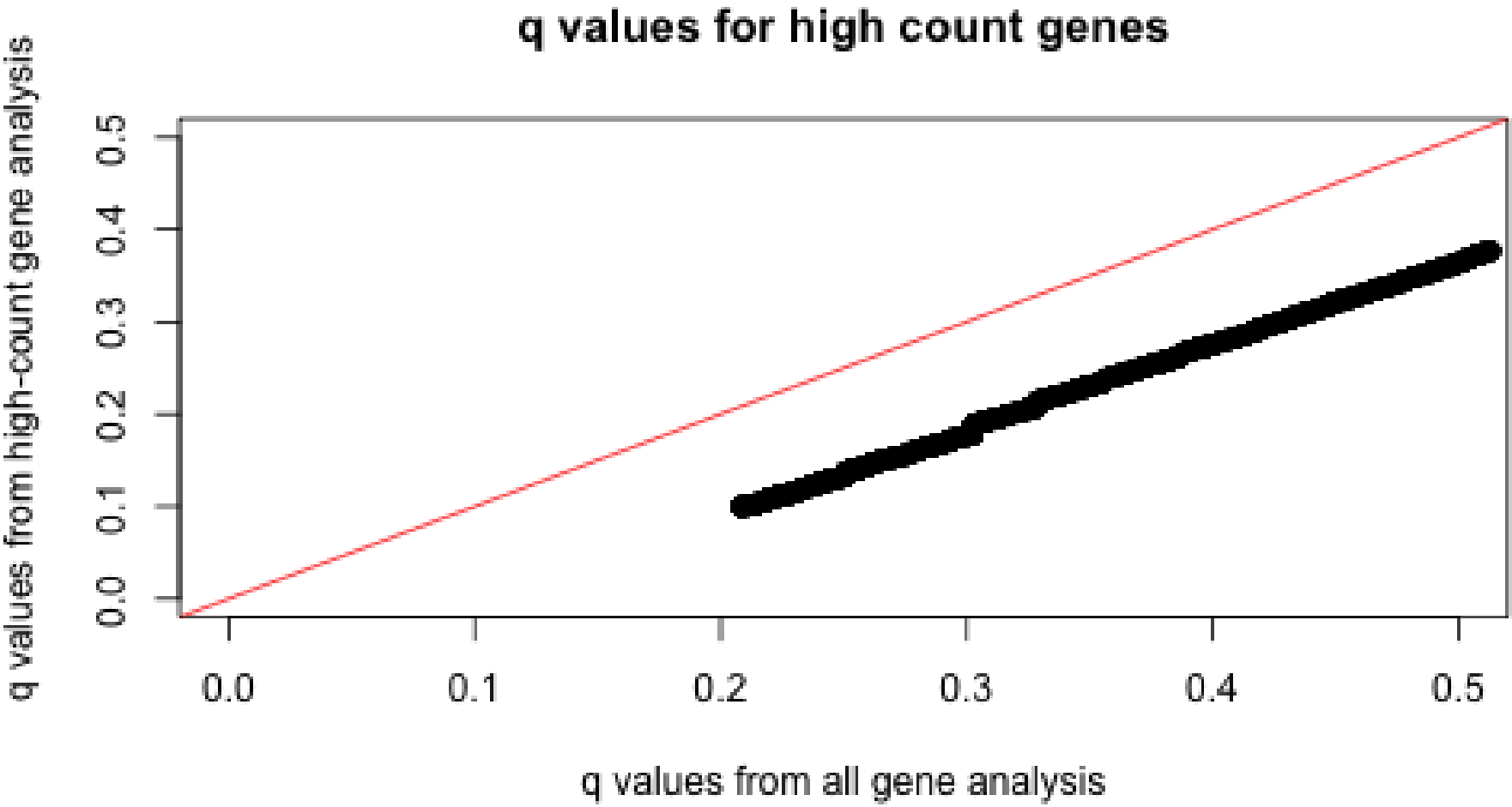
FDR problem 1: lower count genes, less power, add noise



FDR problem 1: higher count genes, more power



FDR problem 1: q values increased by low count genes



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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".
- This allows us to estimate π_0 "conservatively" using the density of p values near 1.

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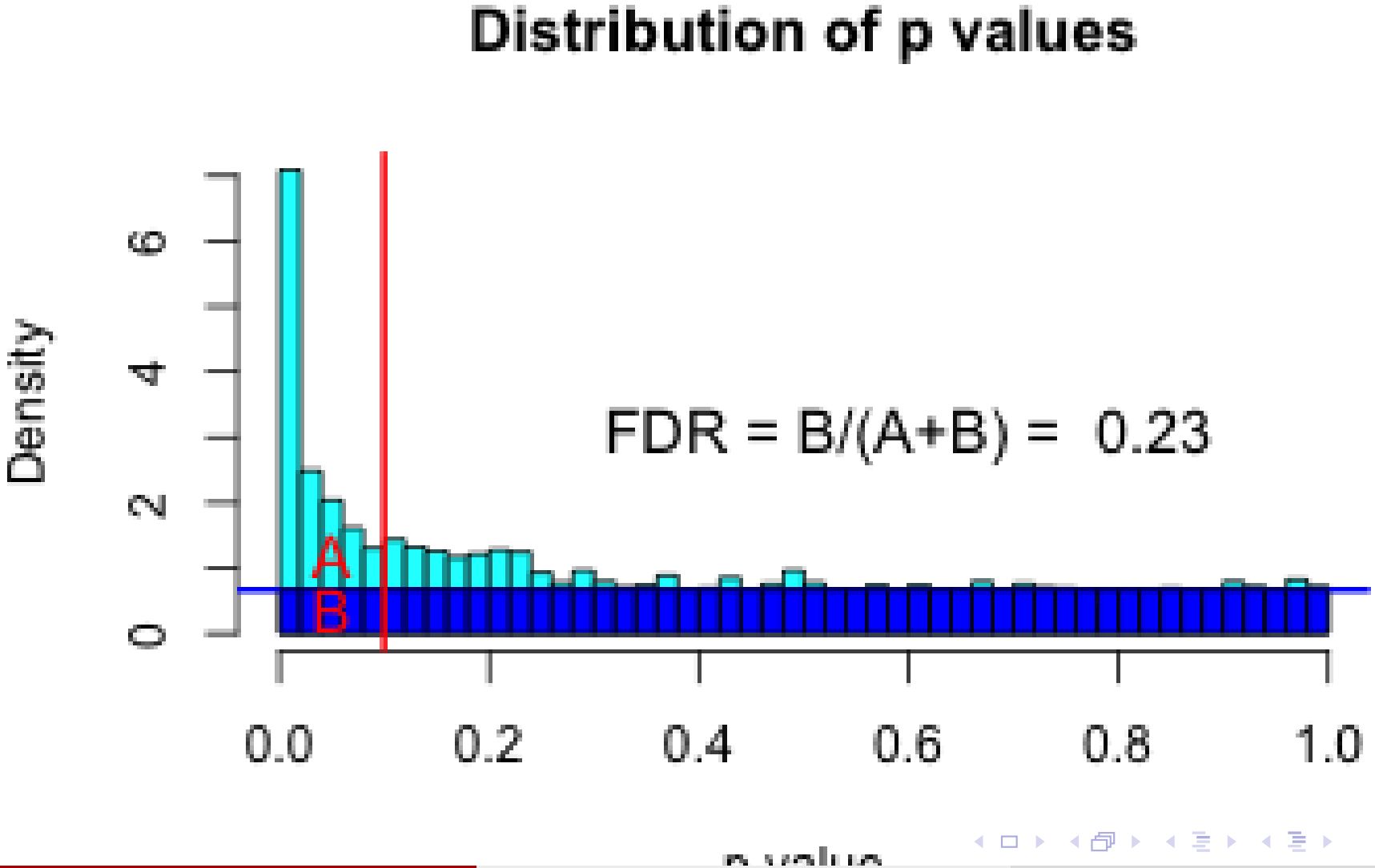
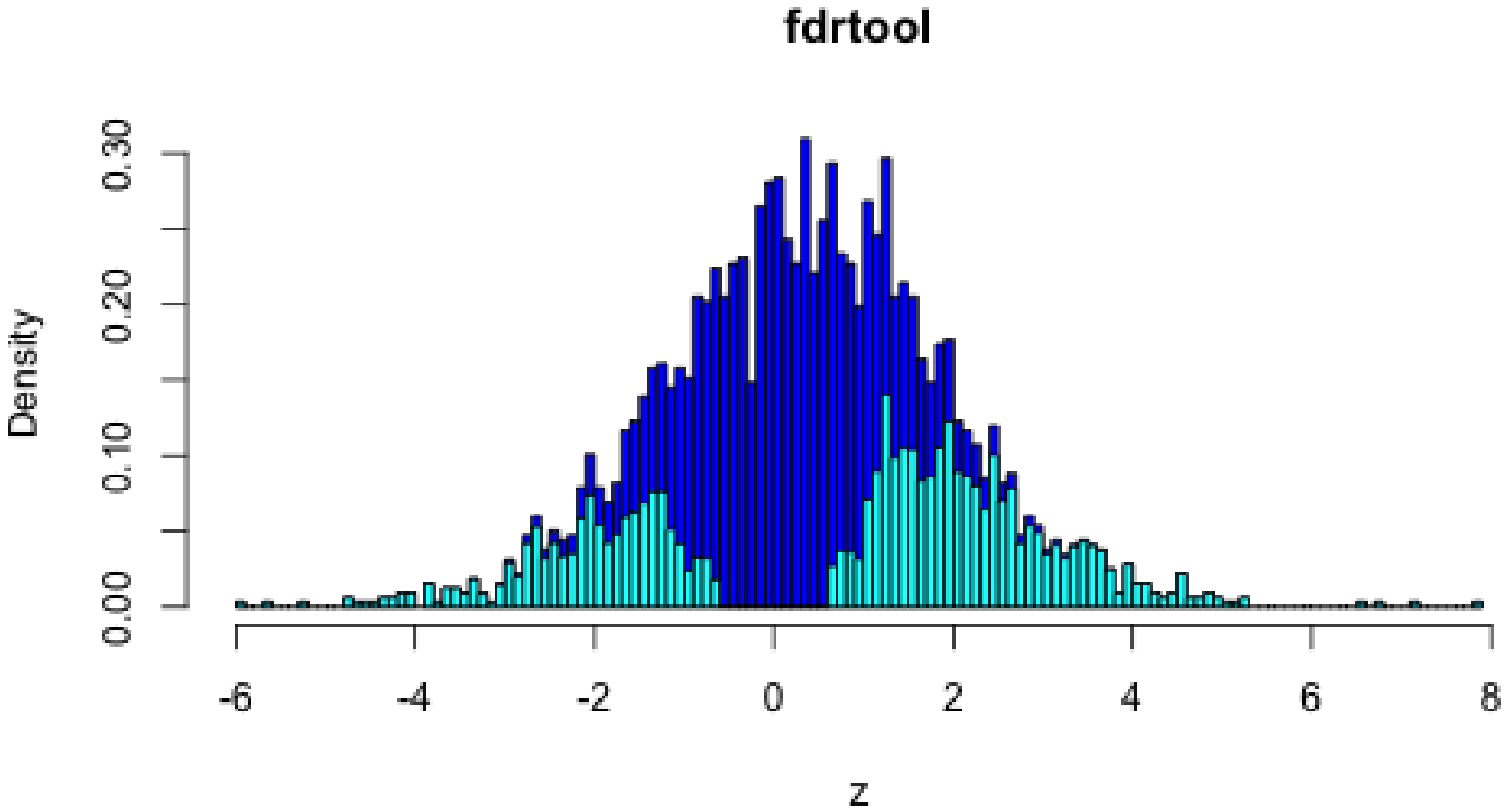
- However, it turns out to imply unrealistic assumptions about the distribution of non-zero effects.

Implied distribution of p values under H_1



Implied distribution of Z scores under alternative (fdrtool)



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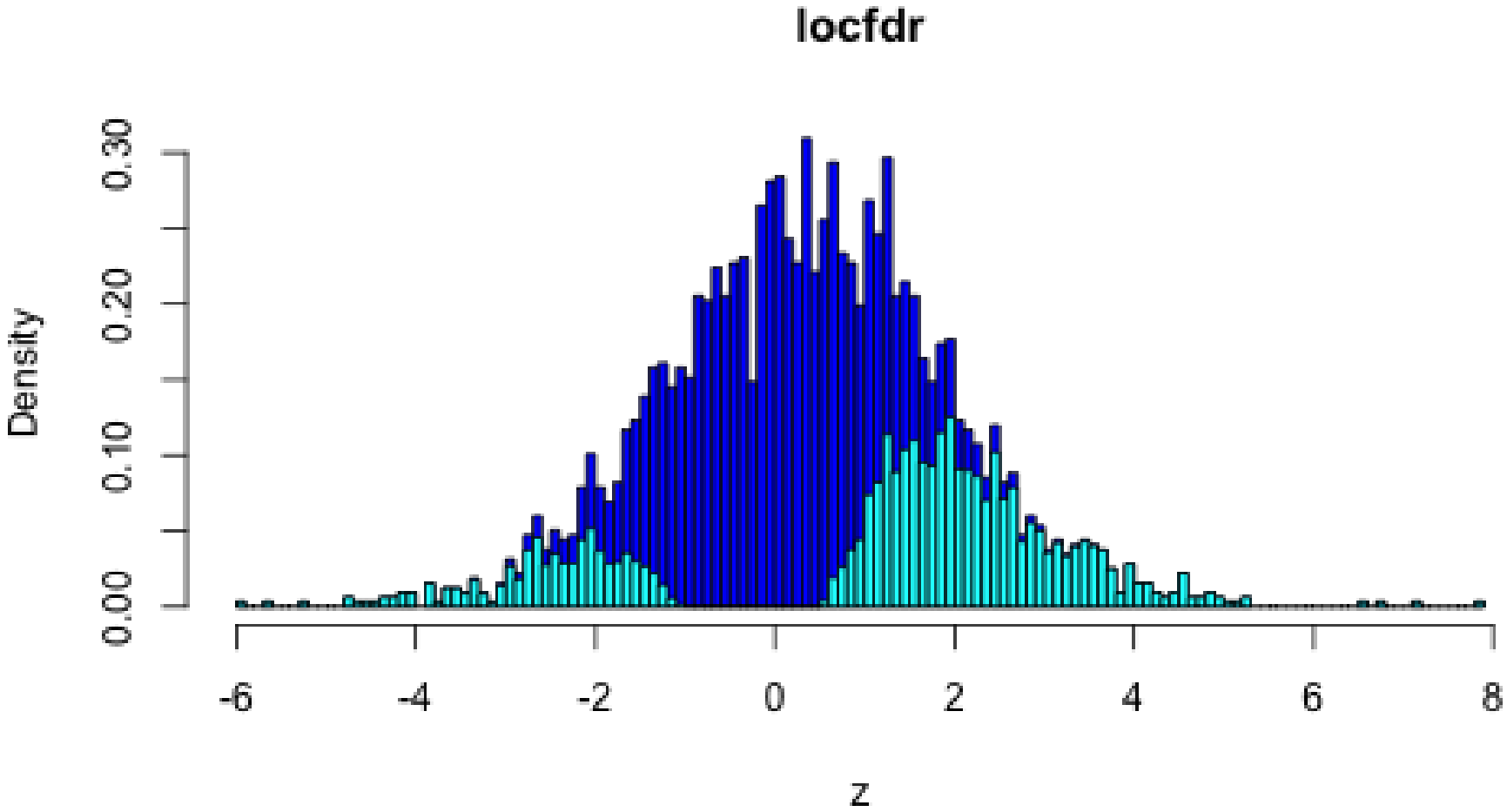
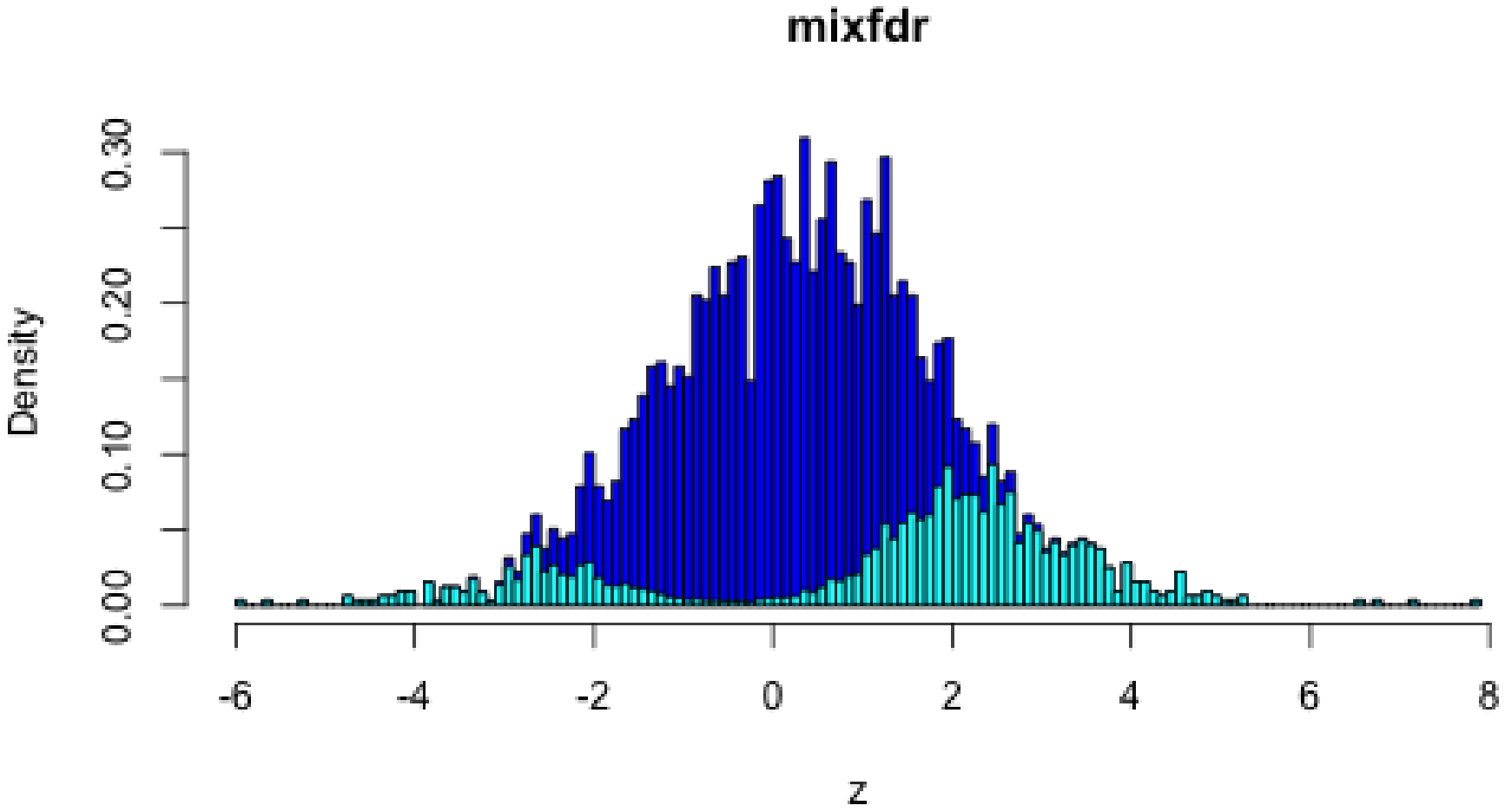


Implied distribution of Z scores under alternative (mixfdr)




```
## 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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- *Incorporate the precision* of the observations $\hat{\beta}$ into the likelihood. Specifically, we approximate likelihood for β_j by a normal ("Laplace") approximation:

$$L(\beta_j) \propto \exp(-0.5(\beta_j - \hat{\beta}_j)^2/s_j^2).$$

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- *Directly model the underlying distribution of* β, using a unimodal family of distributions g; estimate g from the data.

Proposed Alternative: More details

- A convenient way to model g is by a mixture of 0-centered normal distributions:

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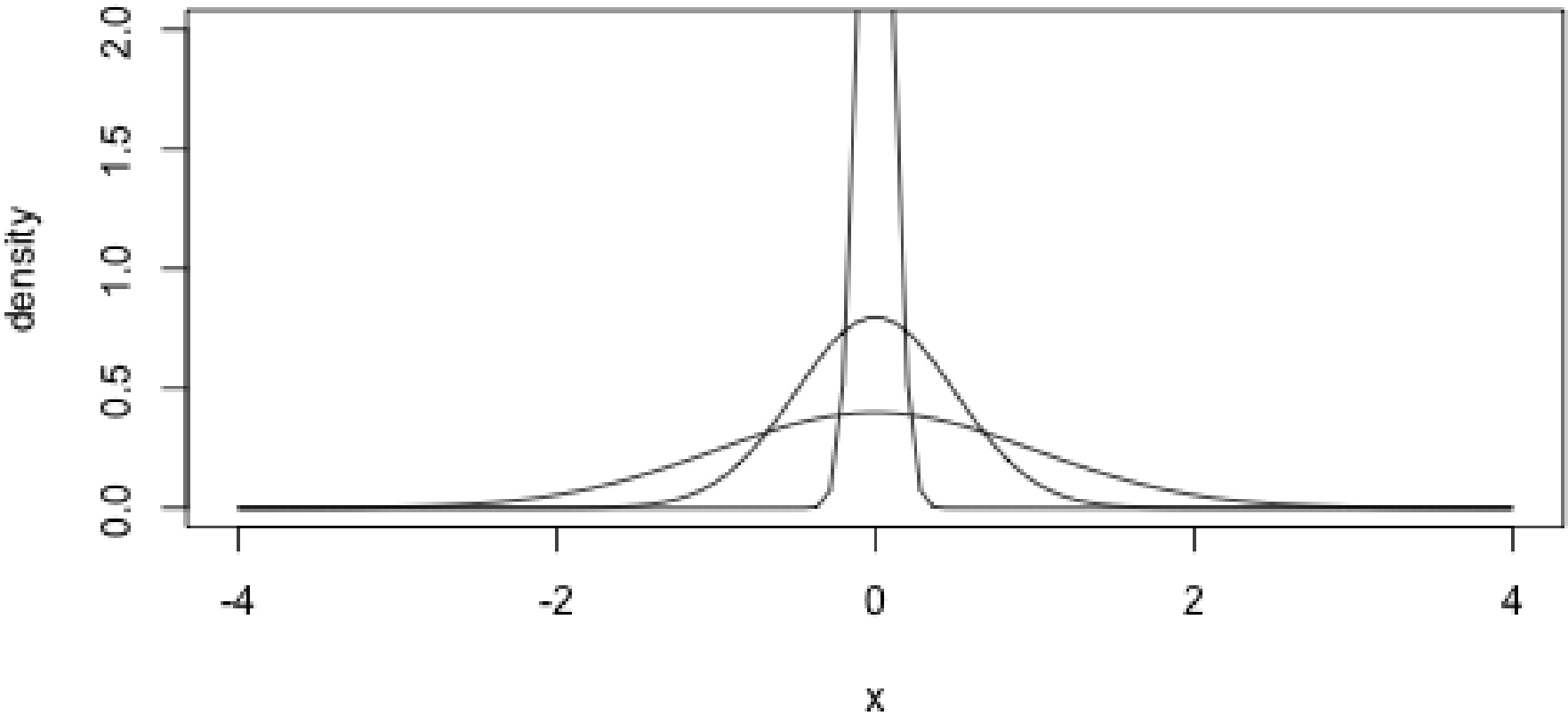
- By allowing K large, and σ_k to span a dense grid of values, we get a fairly flexible unimodal symmetric distribution.
- Alternatively, a mixture of uniforms, with 0 as one end-point of the range, provides still more flexibility, and in particular allows for asymmetry. (Grenander 1953 shows this provides the non-parametric mle in the "no error" case; Campy + Thomas do the equal-errors case)

Illustration: g a mixture of 0-centered normals



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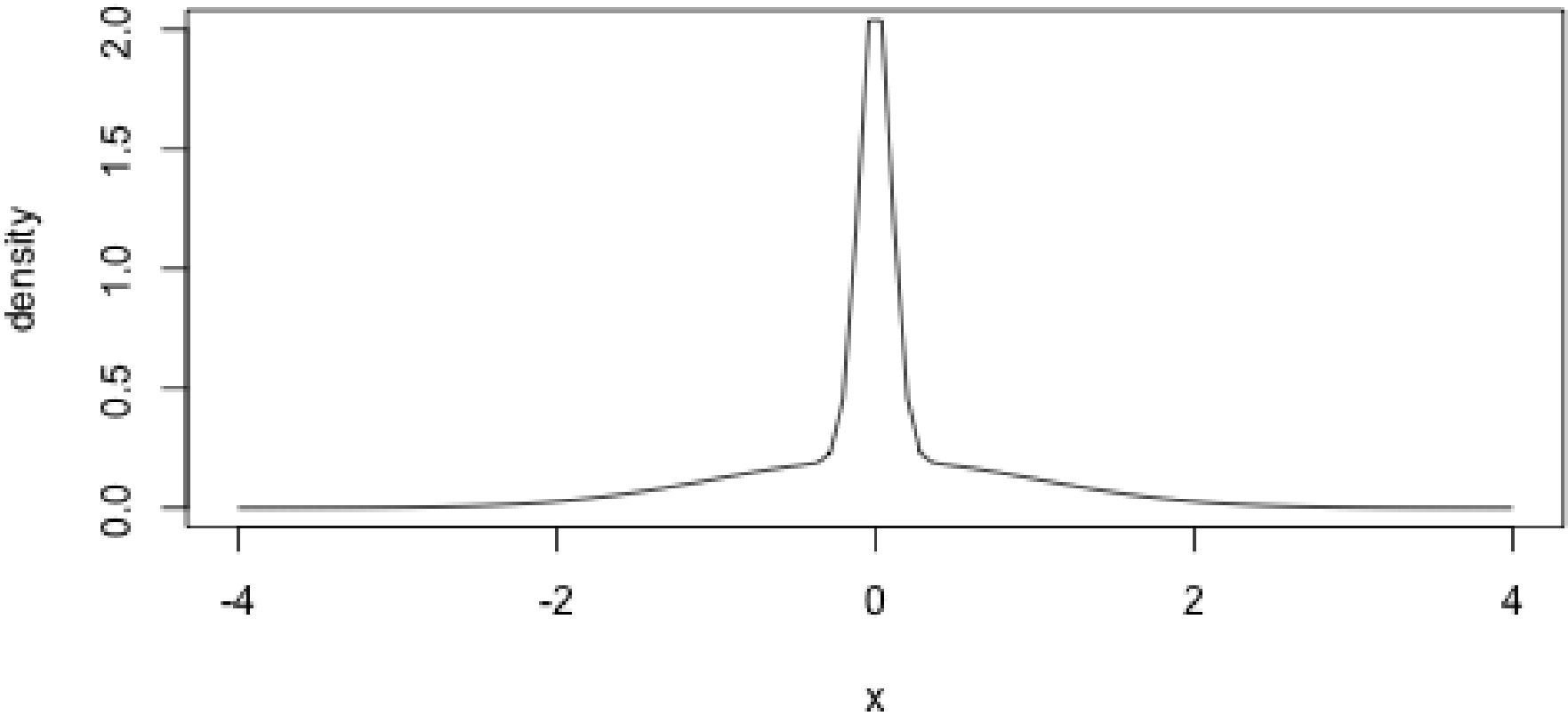

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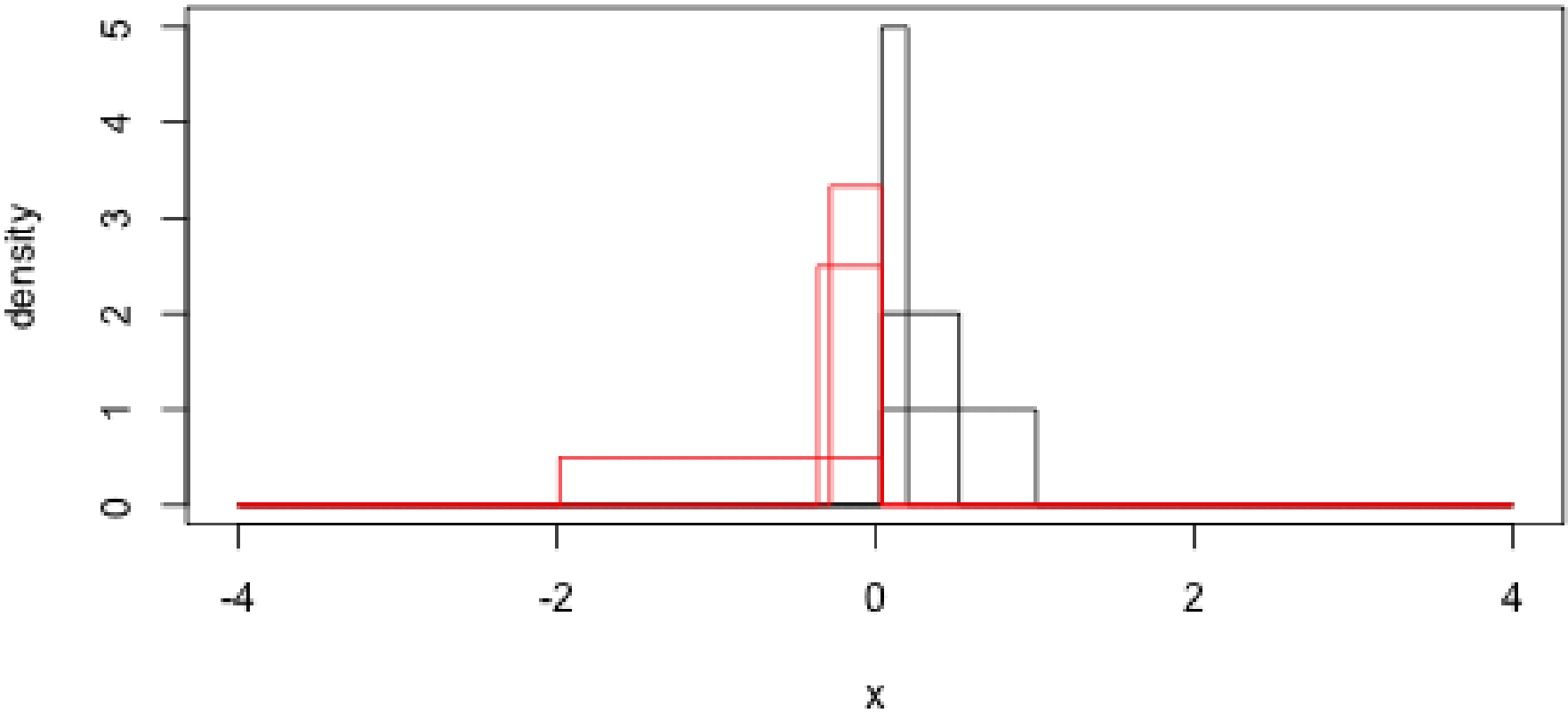

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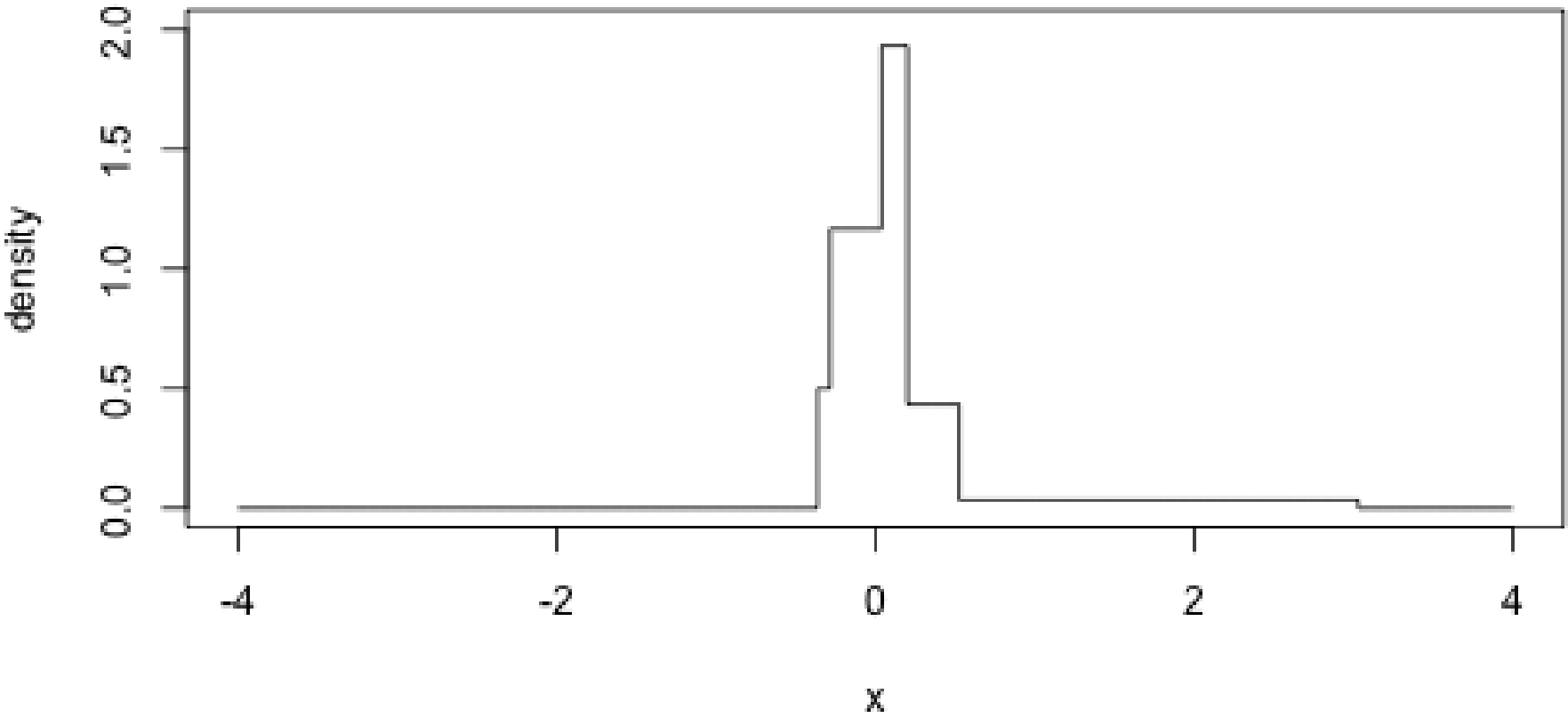
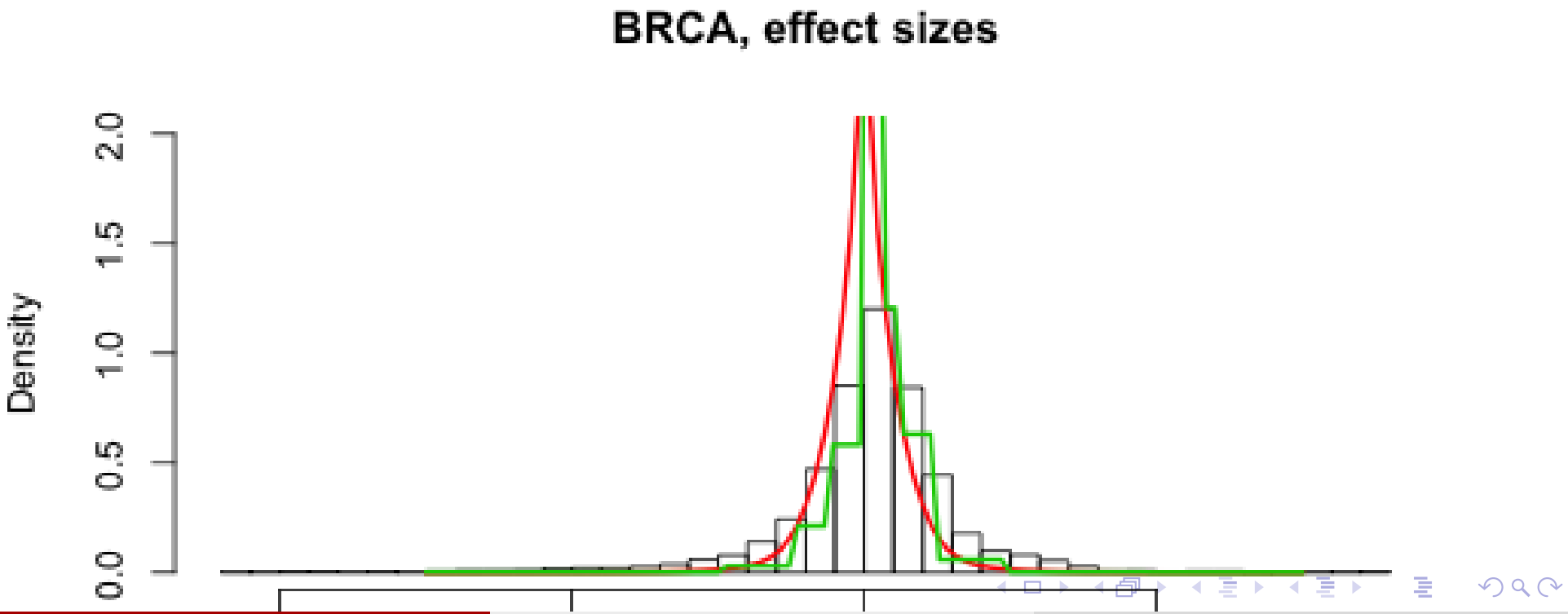


Illustration: BRCA data

```
hh.ash = ash(hh.betahat, hh.sebetahat)
hh.ash.hu = ash(hh.betahat, hh.sebetahat, mixcompdist = "halfu

## [1] "Warning: Posterior SDs not yet implemented for uniform
```



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```
## Error: error in evaluating the argument 'x' in selecting a
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##   object 'hh.ashz' not found
```

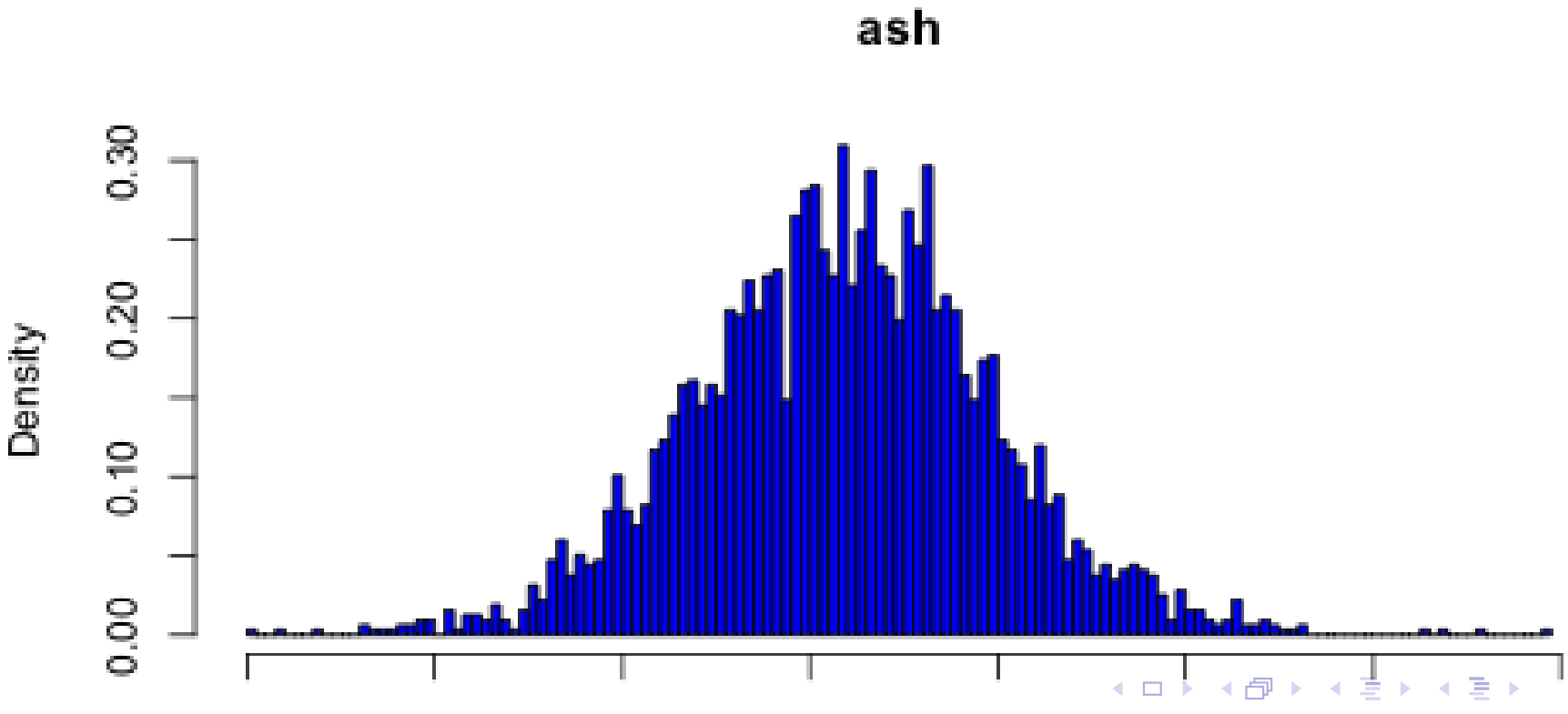

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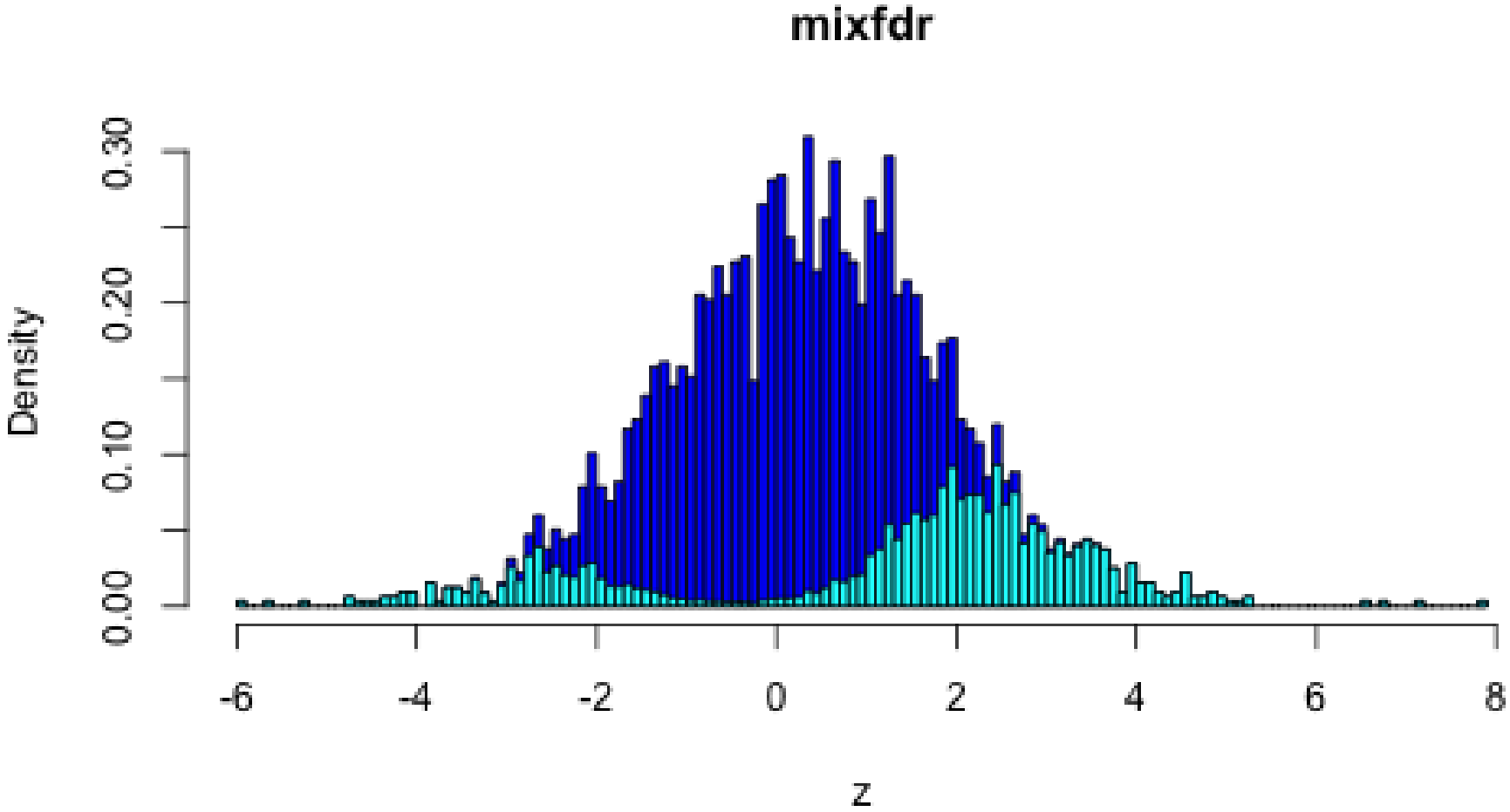

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- Of course this is true regardless of the method used!

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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).

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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.

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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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- 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)

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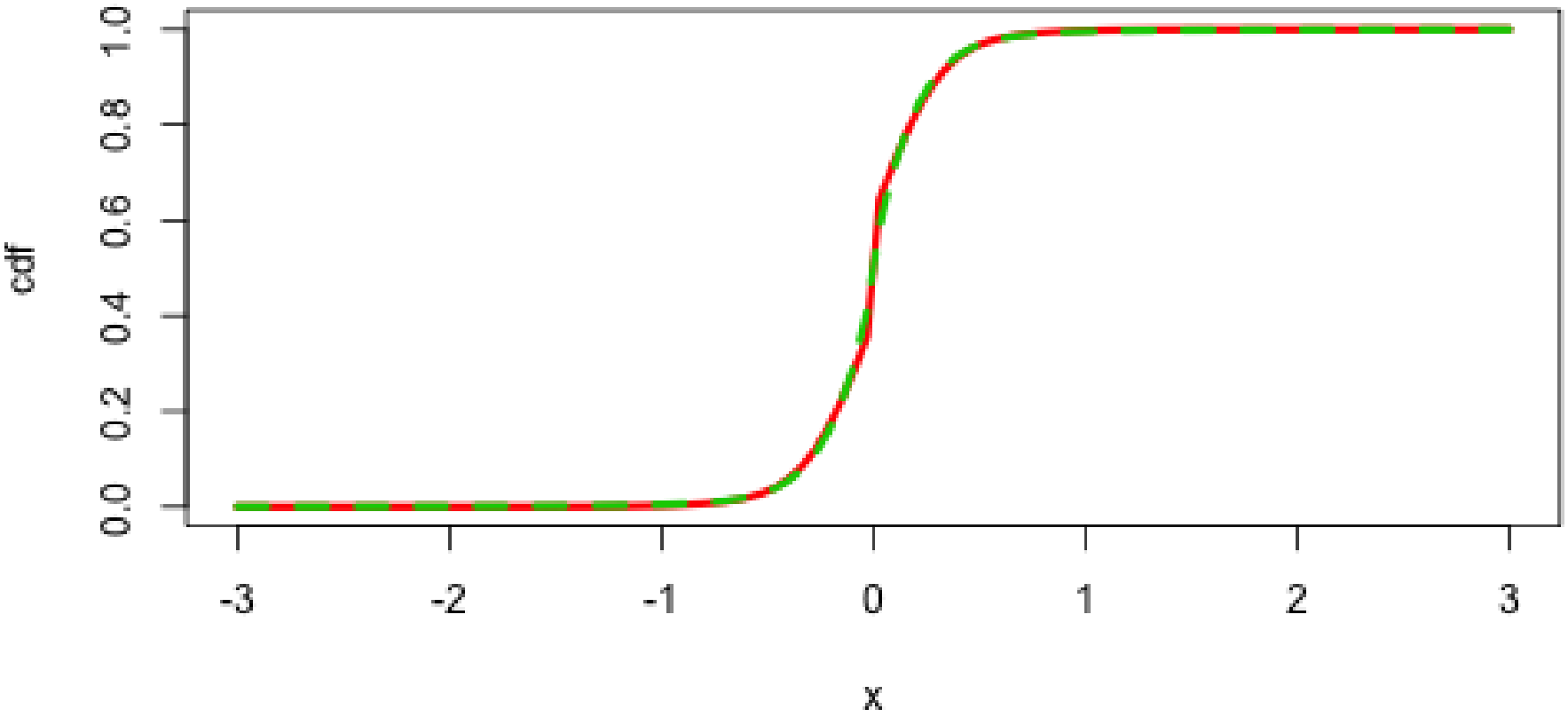
- So for example we can easily compute fdrs for discoveries other than "non-zero" (eg genes with at least 2-fold difference between conditions

Example: BRCA data

Compare fit of g both allowing $\beta_j = 0$ and not allowing it.



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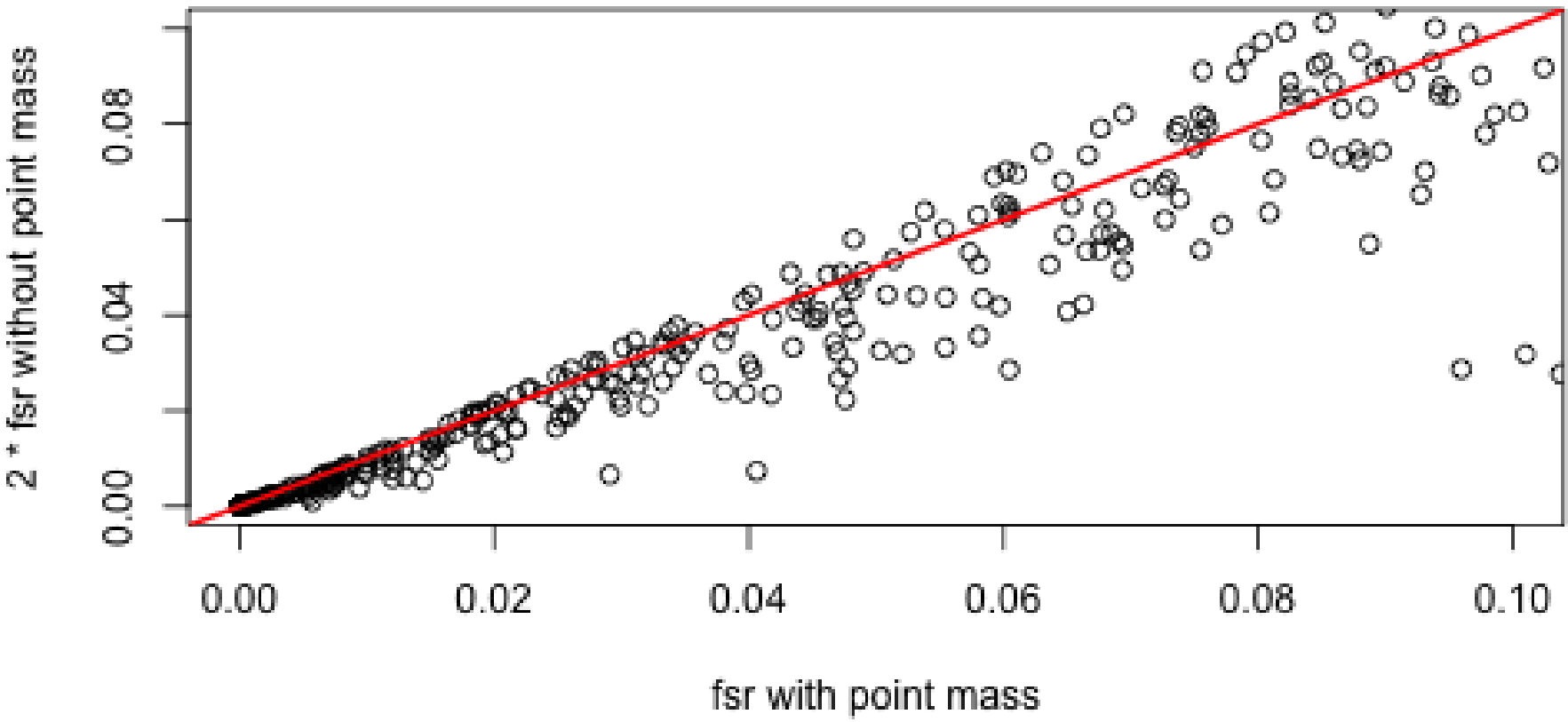

- Because π is estimated from the data, the amount of shrinkage is

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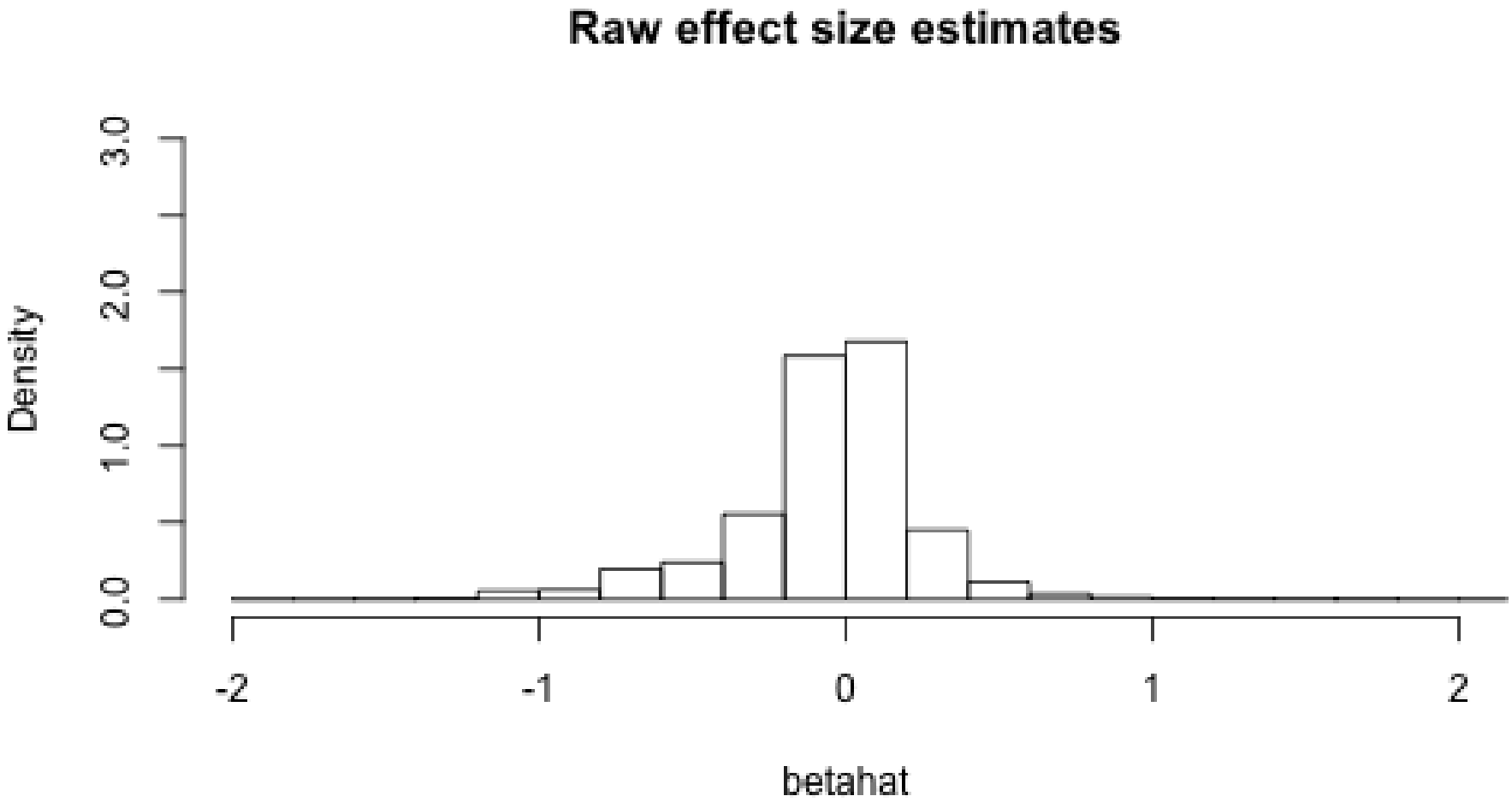

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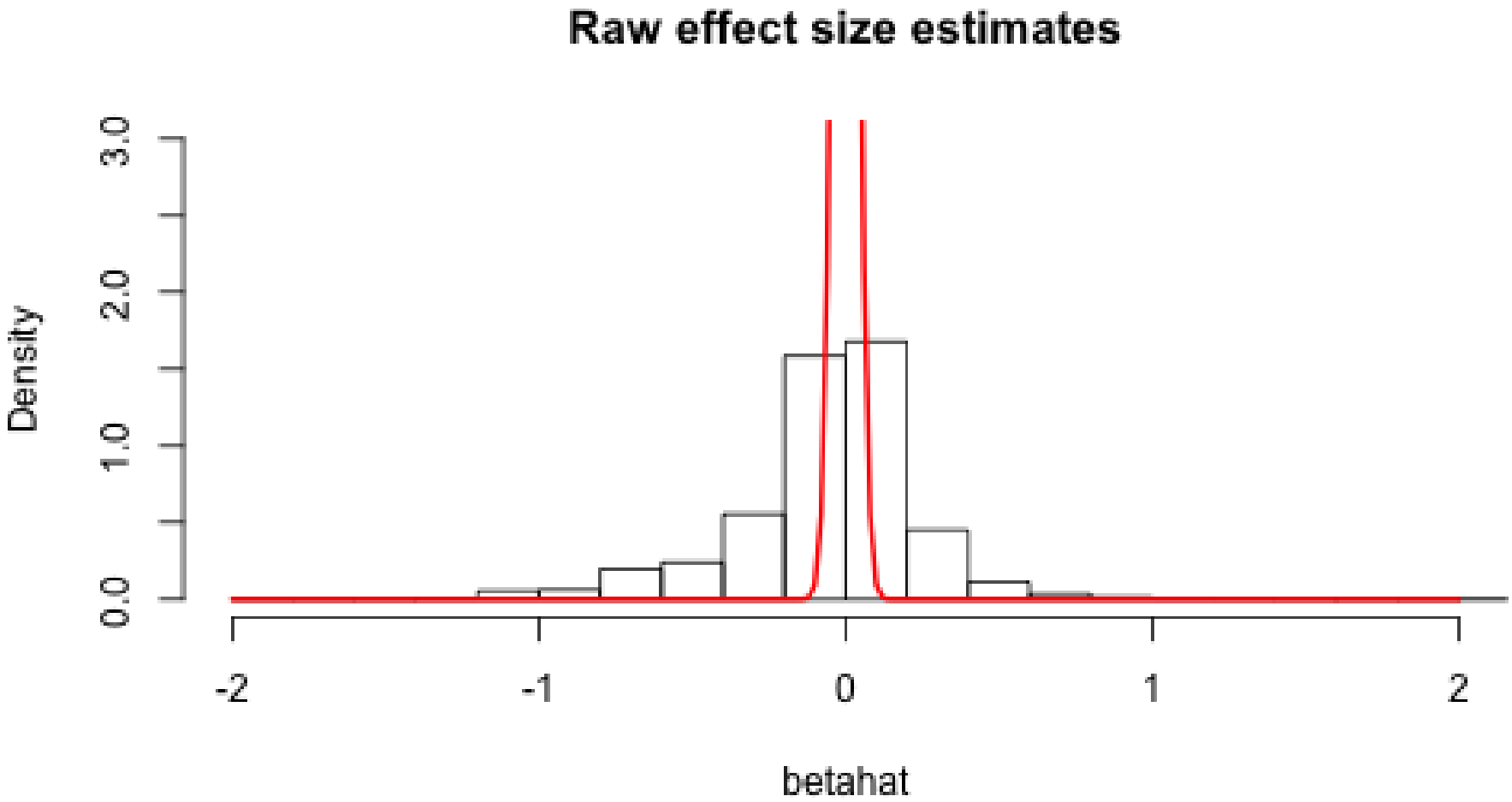

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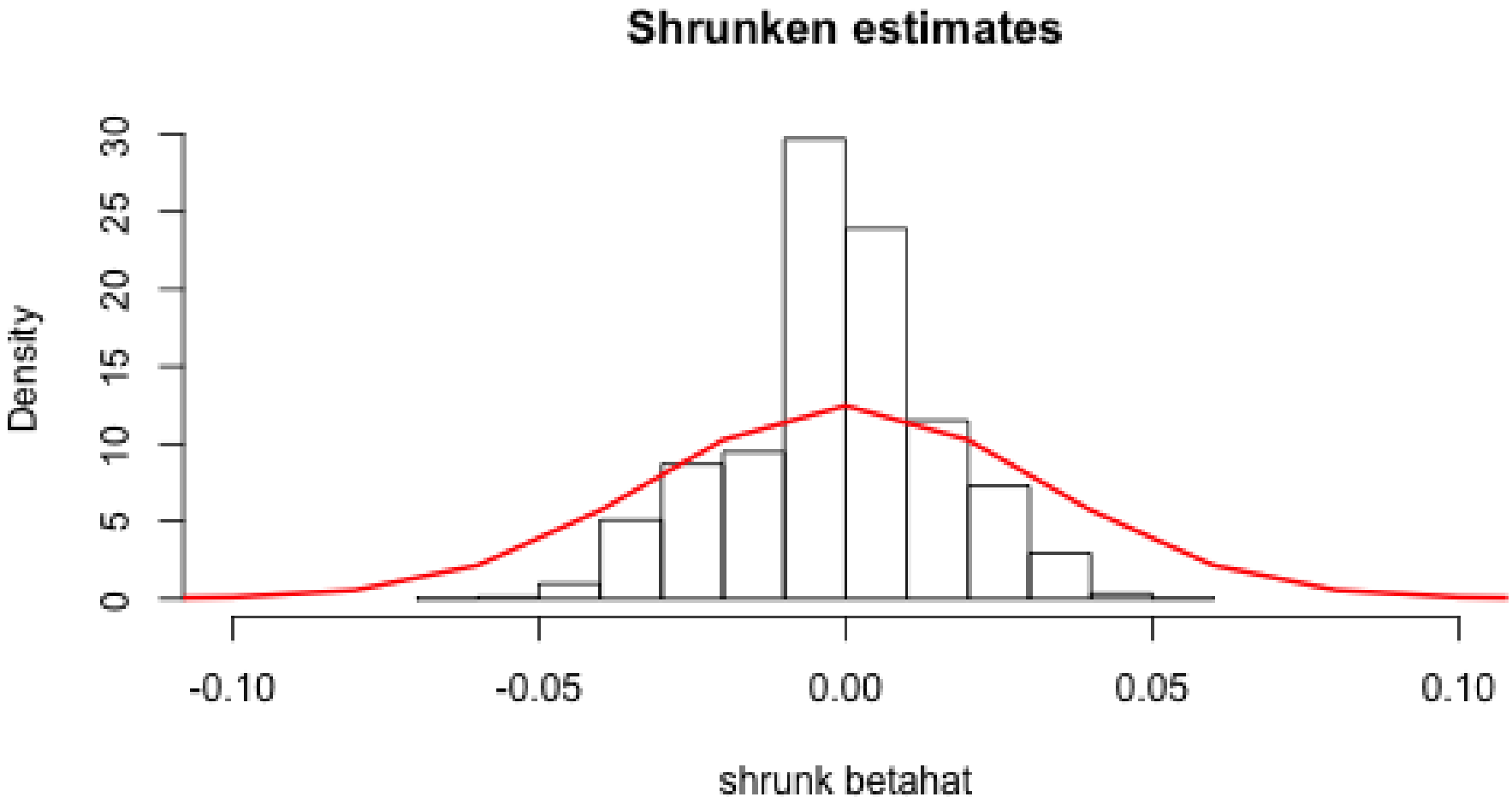
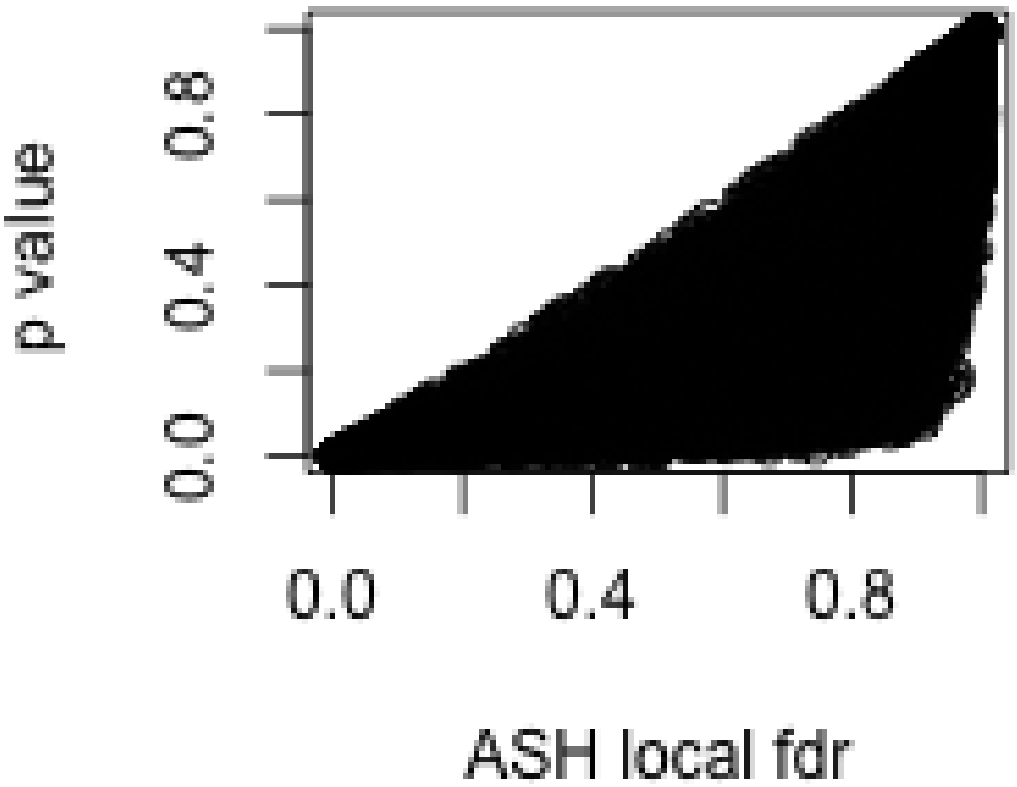


Shrinkage is adaptive to information



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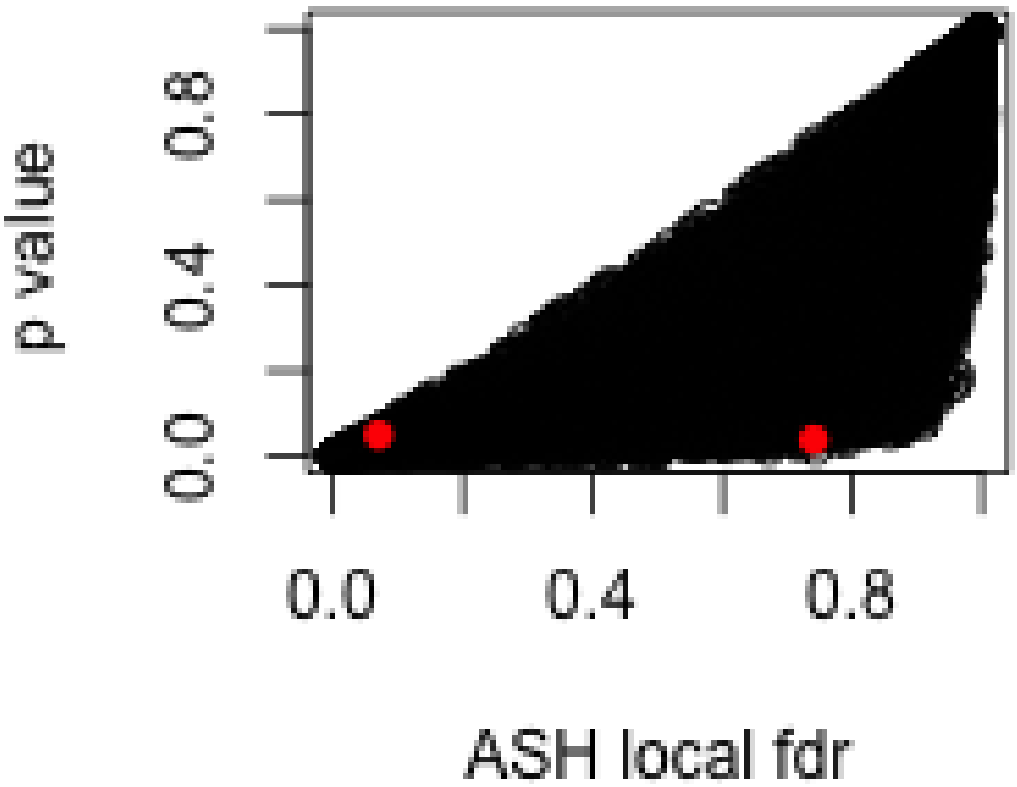

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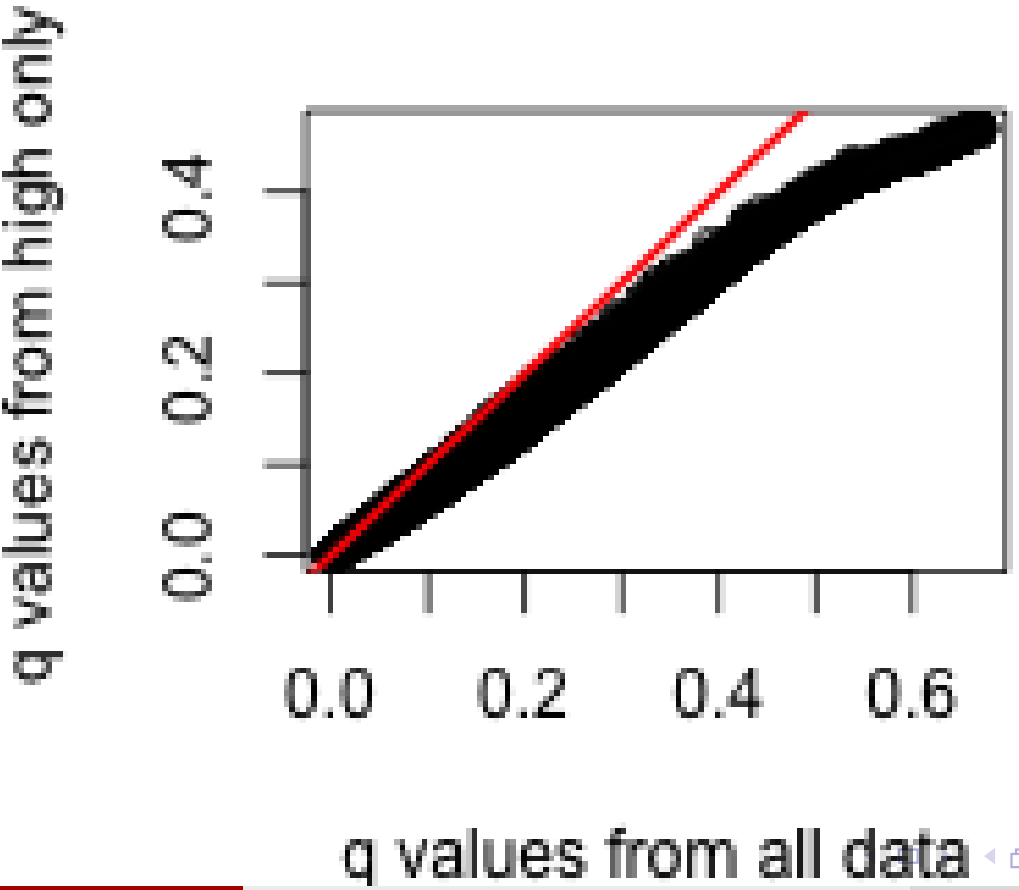
```
## Error: incorrect number of dimensions
```

Compare q values for high count genes, with and without low count genes



BRCA1: Compare π_0 estimates

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

```
## Error: object 'hh.ashz' not found
```

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))
```

```
## Error: object 'hh.ashz' not found
```

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- 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 $\hat{\beta}_j$.

Thanks

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- Especially Mengyin Lu who coded the VB algorithm.

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 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