

False Discovery Rates, A New Deal

Matthew Stephens

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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.

So what can you do?

- Buy a notebook; bring it to meetings; make notes!

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- While doing research, record what you did and what the outcome was.
- 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- If you do not publish code implementing your methods, your methods will likely go unused.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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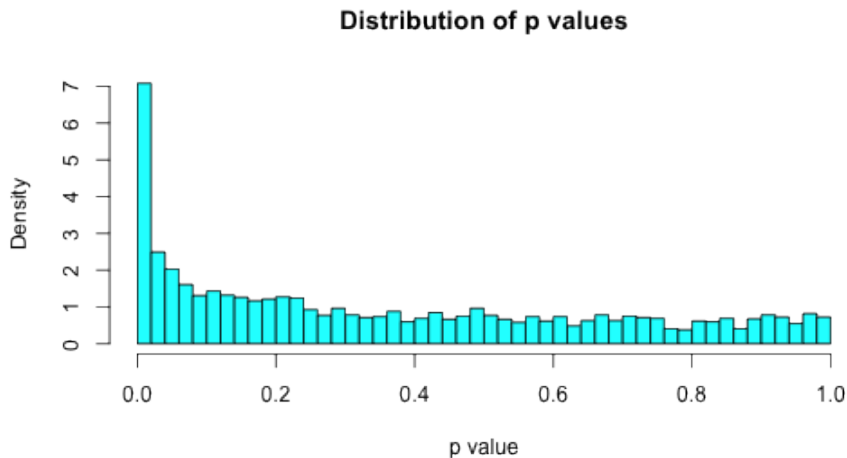
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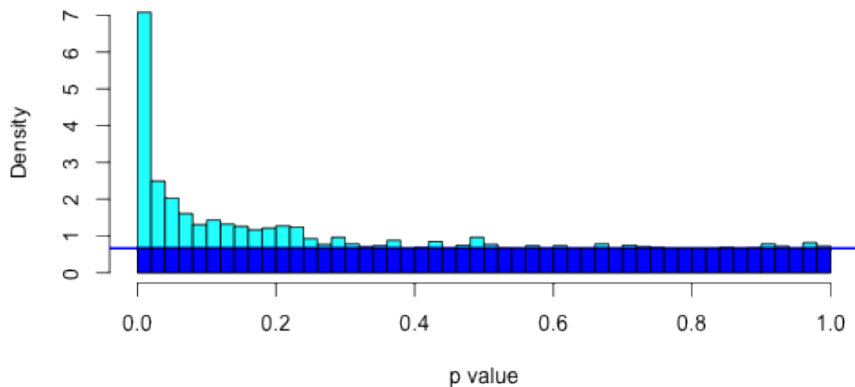
- The fdr is more relevant, but slightly harder to estimate than FDR because it involves density estimation rather than tail-area estimation.

Example: FDR estimation



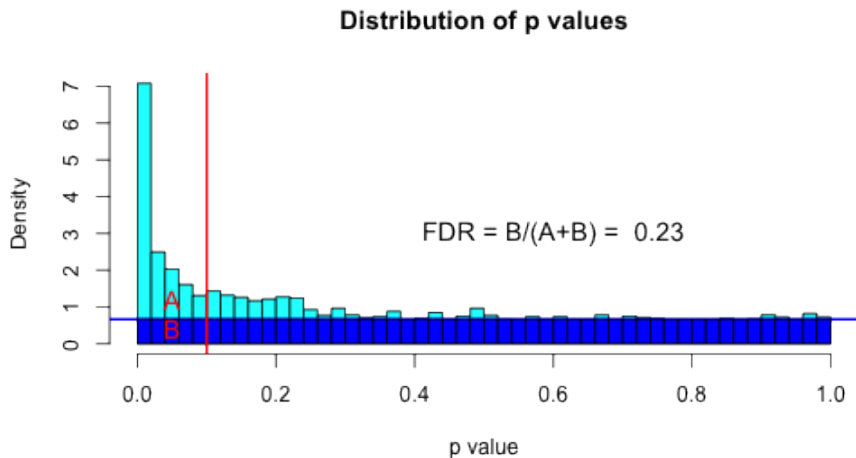
Example: FDR estimation

Distribution of p values

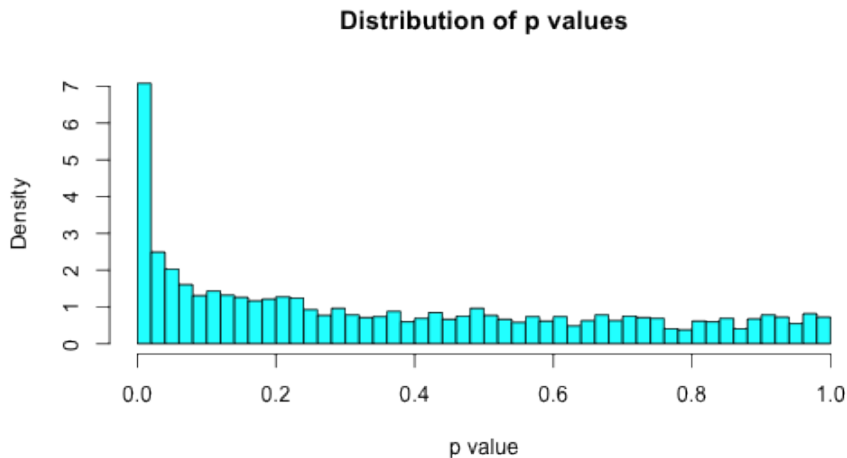


Data from Hedenfalk et al. comparing BRCA1 vs BRCA2 expression

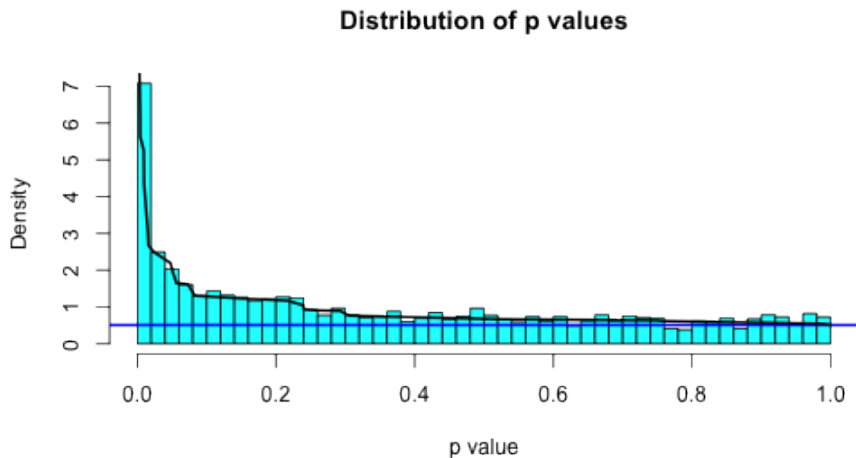
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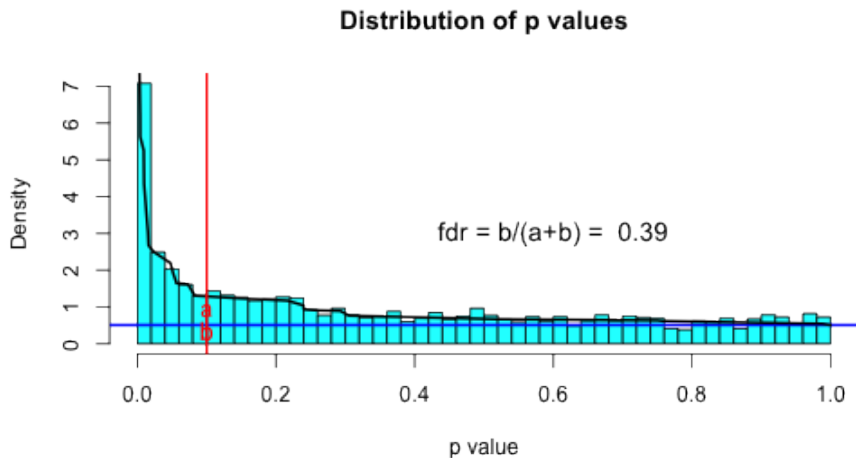
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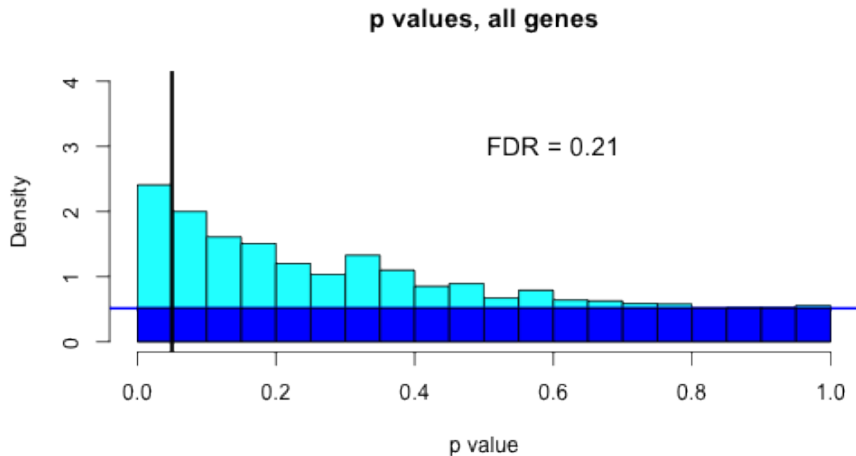
- If some effects are measured very imprecisely, those tests “lack power” and simply add noise
- In particular, such tests increase the estimated number of nulls, and increase the FDR for other tests
- It would seem preferable to simply ignore the tests with very low precision. Summarizing each test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

Example: Mouse Heart Data

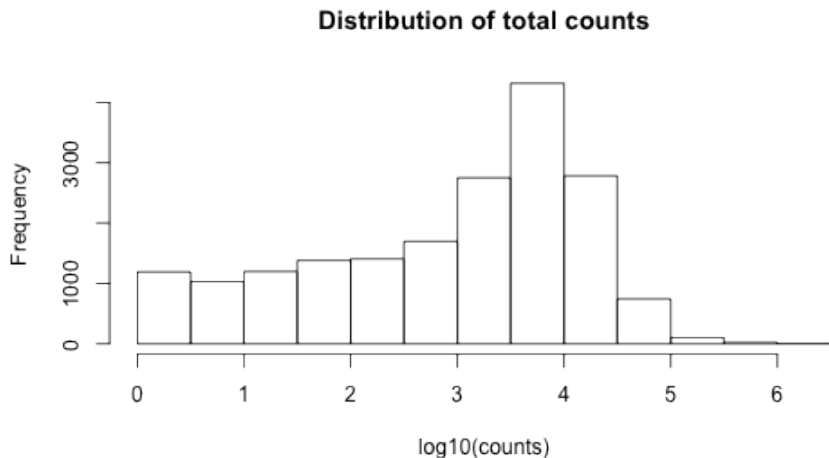
| ## | gene | lv1 | lv2 | rv1 | rv2 | genelength |
|------|---------|------|------|-------|-------|------------|
| ## 1 | Itm2a | 2236 | 2174 | 9484 | 10883 | 1626 |
| ## 2 | Sergef | 97 | 90 | 341 | 408 | 1449 |
| ## 3 | Fam109a | 383 | 314 | 1864 | 2384 | 2331 |
| ## 4 | Dhx9 | 2688 | 2631 | 18501 | 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 Schmemmo, Marcelo Nobrega)

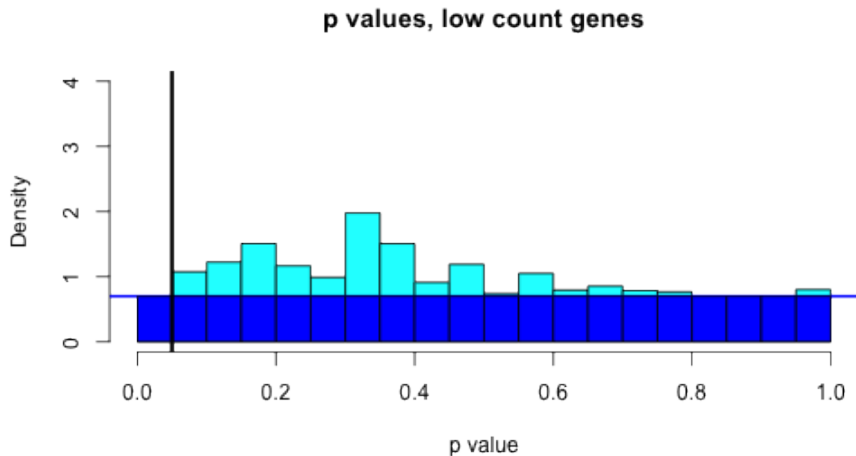
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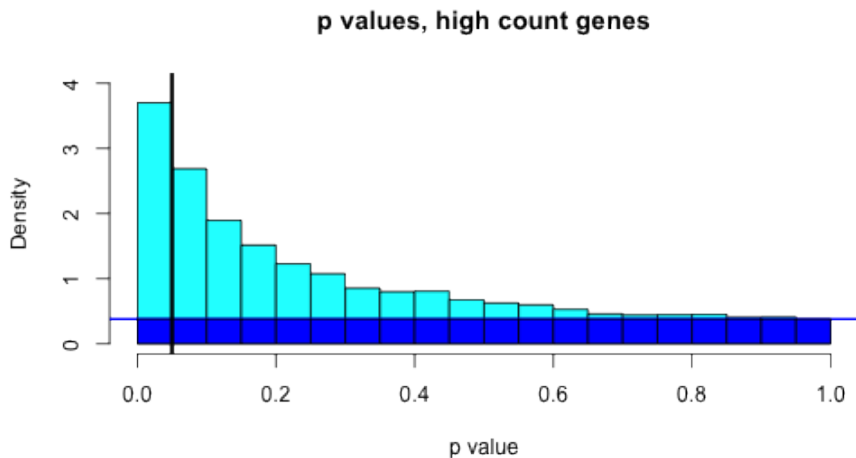
Mouse Data: Counts vary considerably across genes



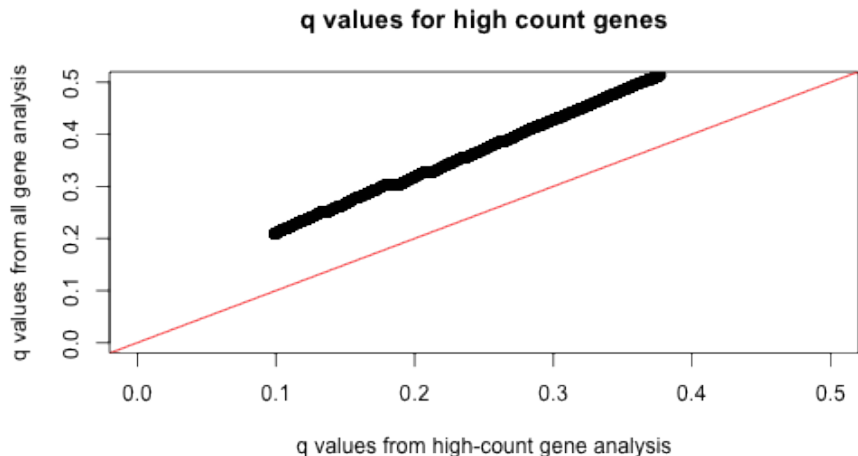
Lower count genes, less power



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).

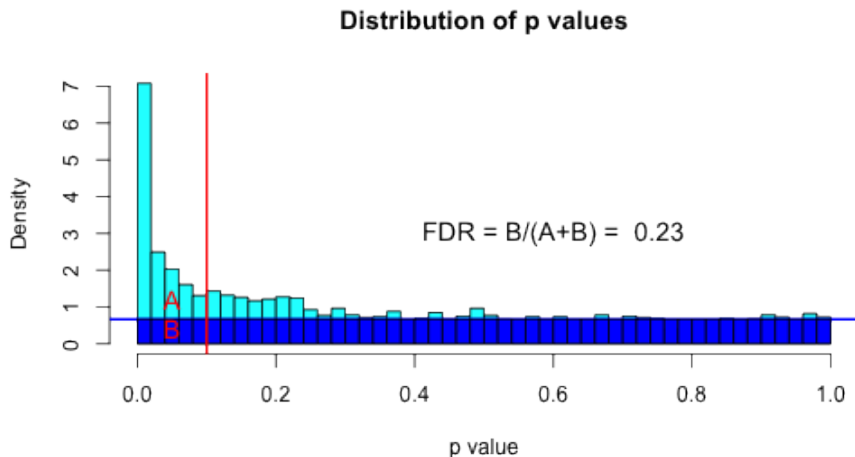
Problem 2: The ZA

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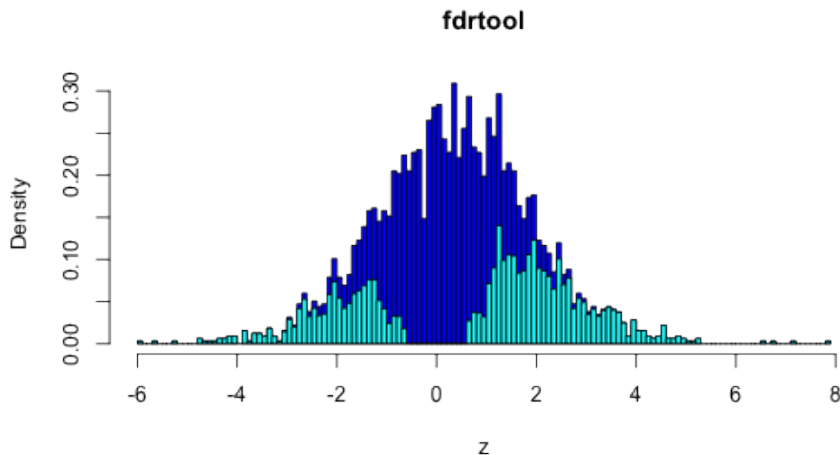
Problem 2: The ZA

- The ZA seems initially natural.
- However, it turns out to imply unrealistic assumptions about the distribution of non-zero effects.

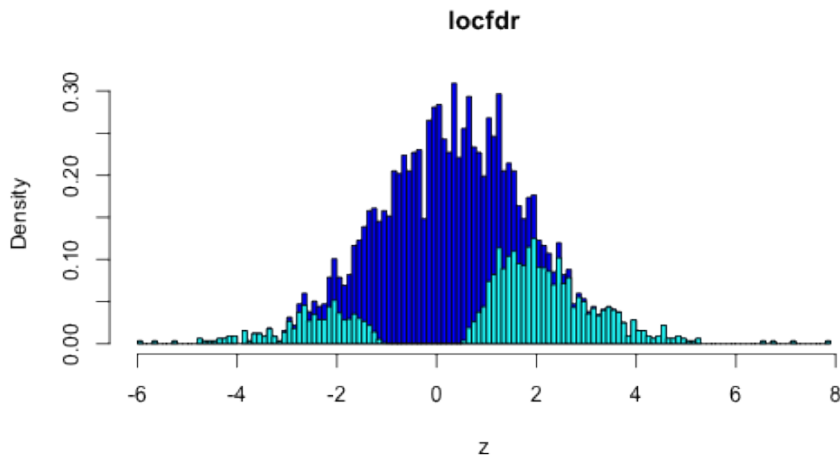
Implied distribution of p values under H_1



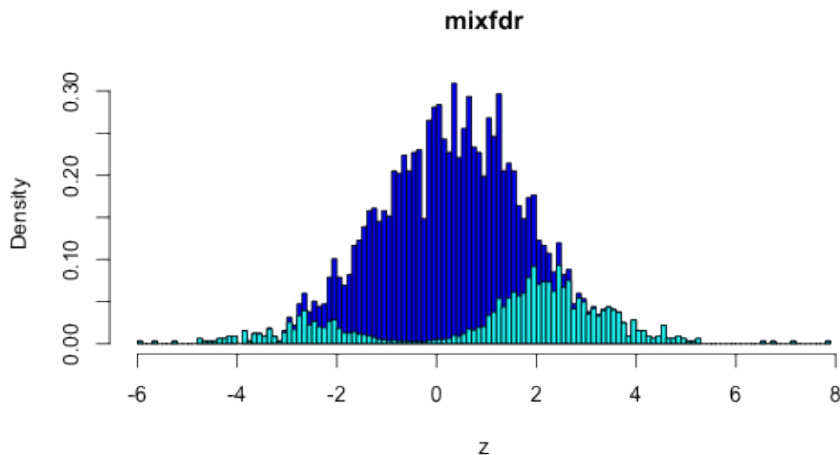
Implied distribution of Z scores under alternative (fdrtool)



Implied distribution of Z scores under alternative (locfdr)



Implied distribution of Z scores under alternative (mixfdr)



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- 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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- $\text{fdr}(Z) \approx \pi_0 N(Z; 0, 1) / f_Z(Z)$

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- fdr given by

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

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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

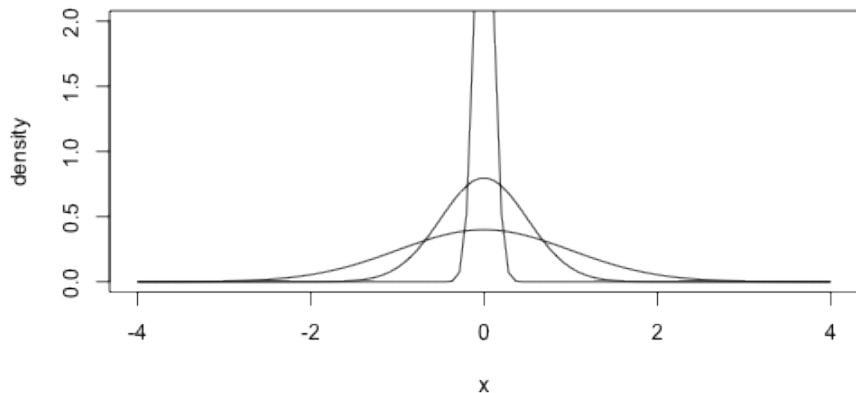


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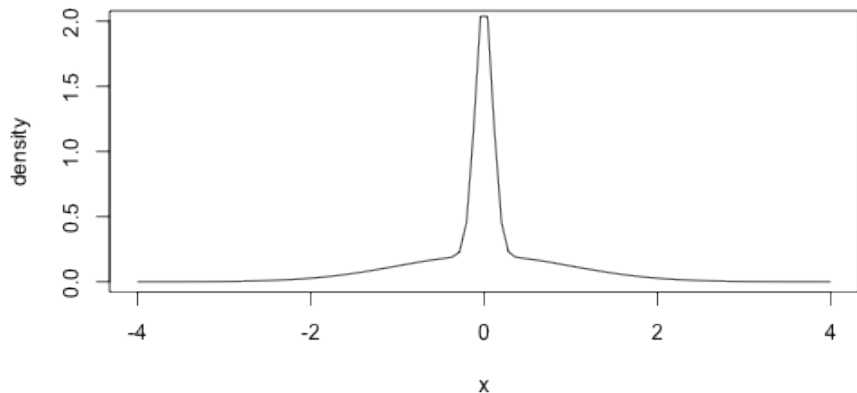


Illustration: g a mixture of 0-anchored uniforms

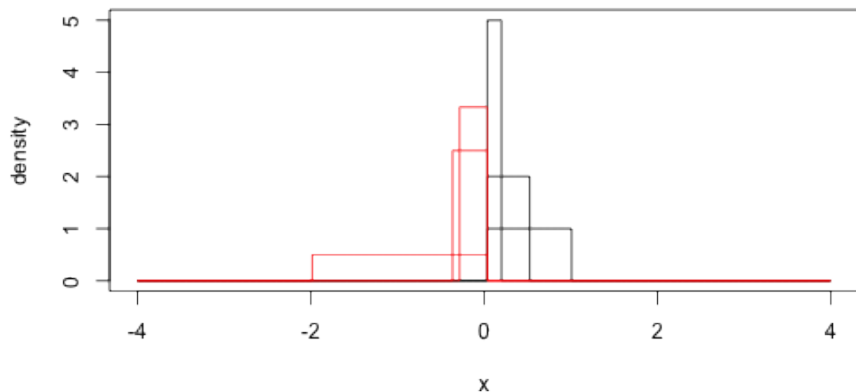
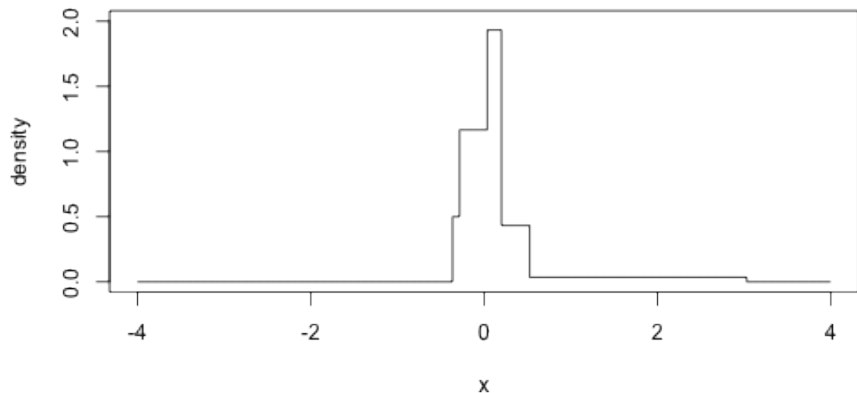


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- For estimating False Discoveries, we are asking whether $\beta_j = 0$.
- However, the data cannot distinguish between $\beta_j = 0$ and β_j “very small”
- As a result π_0 is formally unidentifiable. Eg data can never rule out $\pi_0 = 0$.

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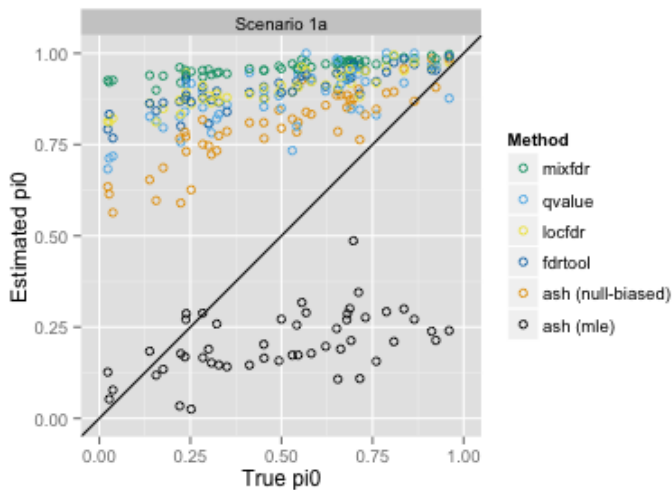
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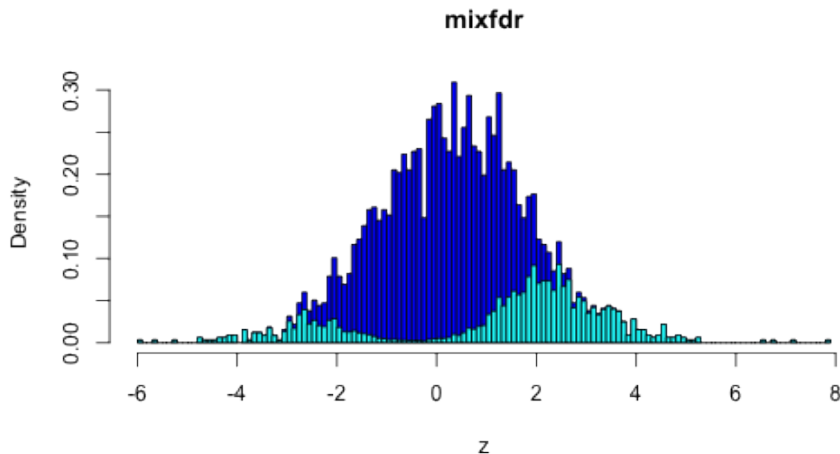
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- Indeed, we saw that when we estimated π_0 under the ZA the data then contradicted the unimodal assumption on g . Thus the upper bound is more conservative than under ZA.
- In practice, implement upper bound by using penalized likelihood that encourages π_0 to be as big as possible.

Illustration: Simulated Example

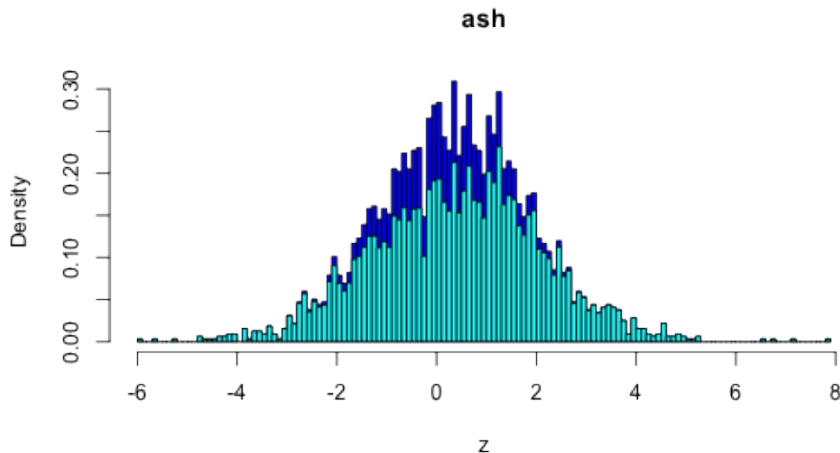


Example: BRCA data

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$pi0[1, 2])
```

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

BRCA1: Compare number significant at $\text{fdr} < 0.05$

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

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

Identifiability of π_0 and the False Sign Rate

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- Positive and negative effects are often treated differently in practice anyway.

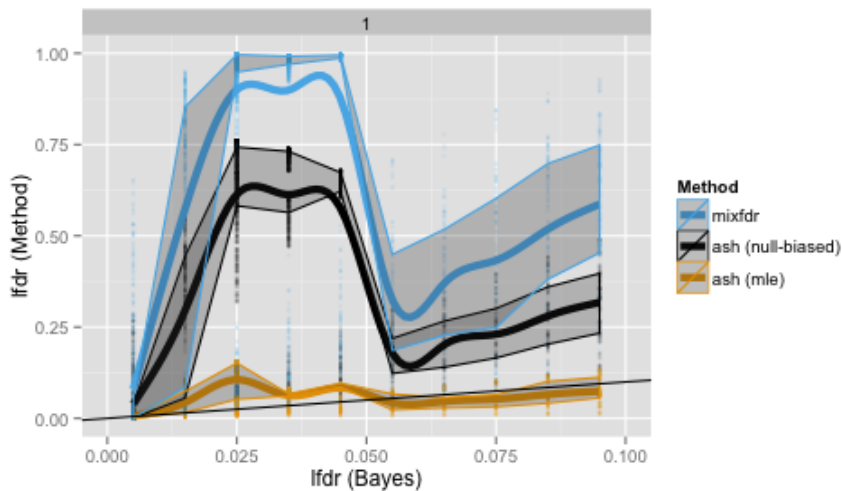
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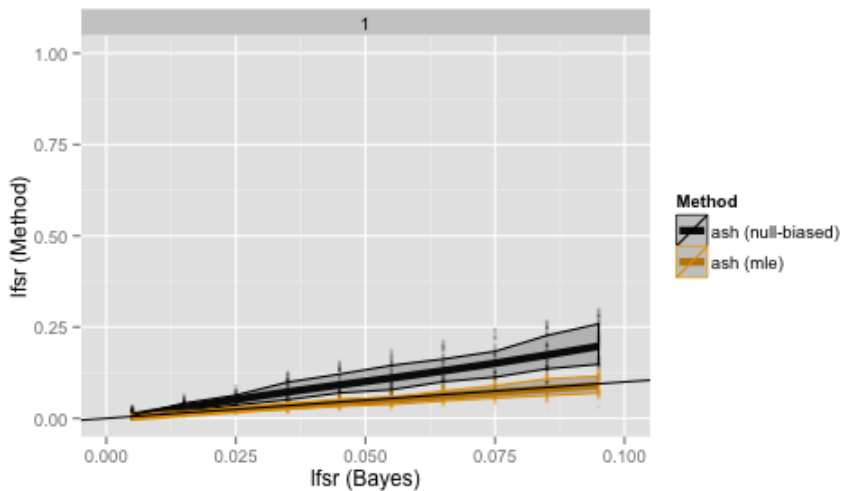
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- Example: suppose we estimate that $\Pr(\beta_j < 0) = 0.975$ and $\Pr(\beta_j > 0) = 0.025$. Then we report β_j as a “(negative) discovery“, and estimate its fsr as 0.025.

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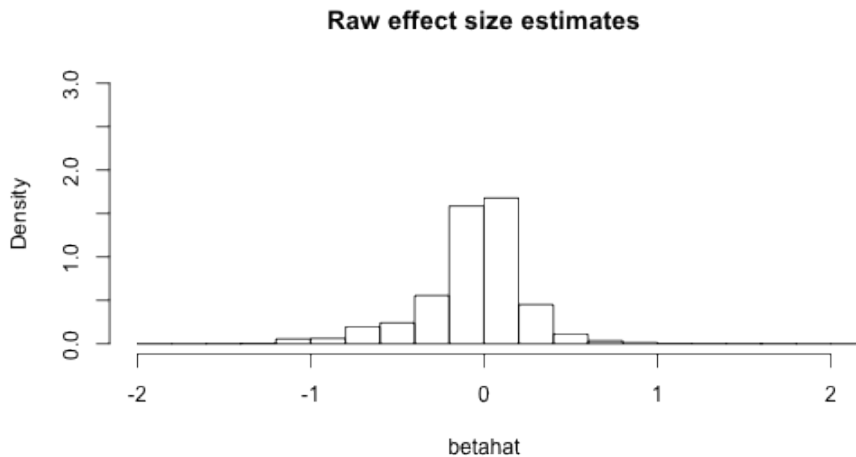
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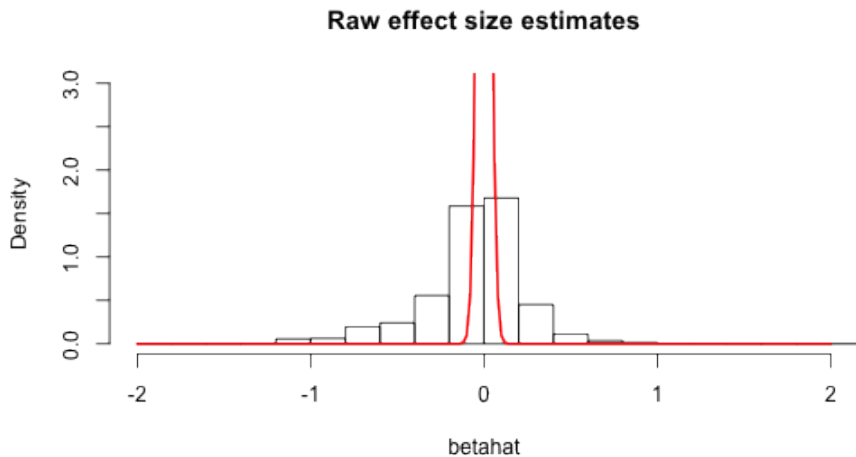
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- So we call the approach “Adaptive Shrinkage” (ASH).

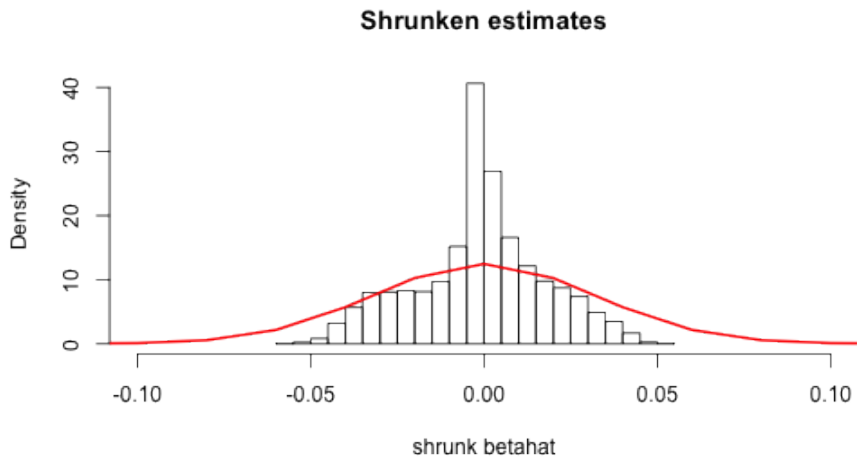
Example: ASH applied to mouse data



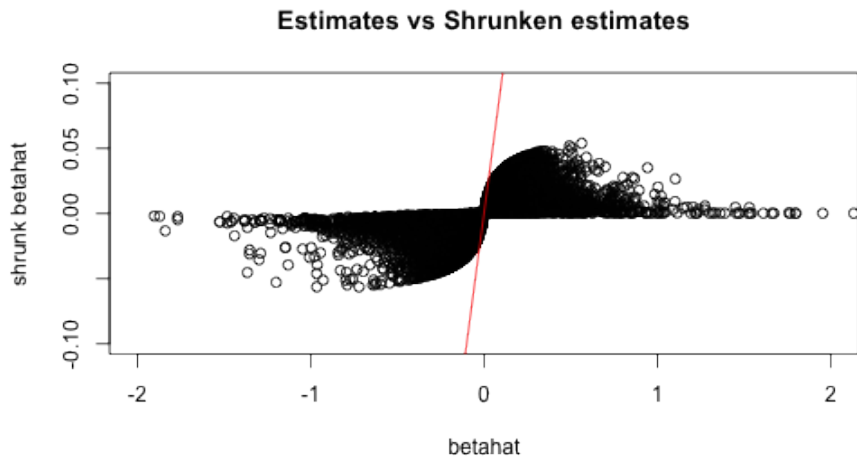
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Summary

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- But by using two numbers ($\hat{\beta}$, s) instead of one (p values or z scores) precision of different measurements can 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.

Other Applications

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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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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

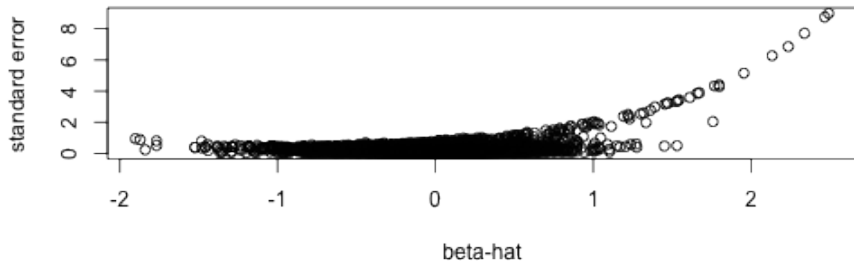


Figure : plot of chunk unnamed-chunk-40

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

A technicality

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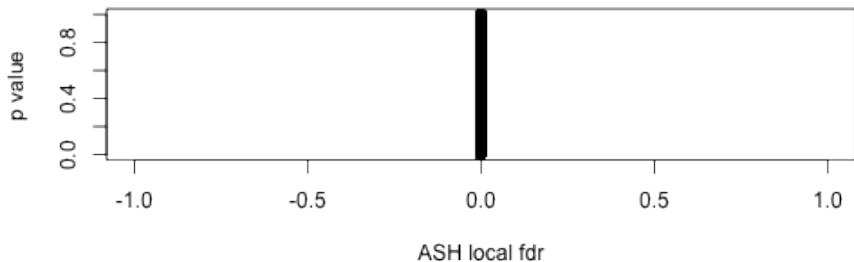
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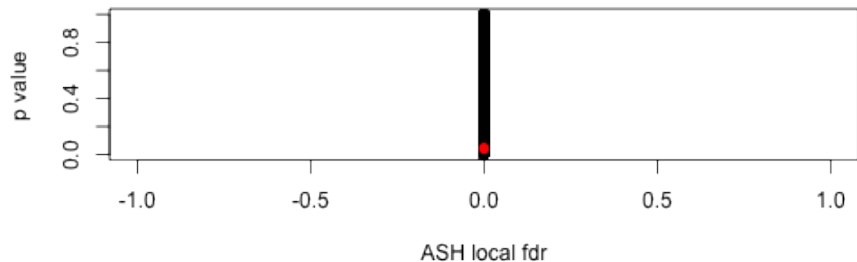
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- Should you declare an fdr of 0.01 or 0.02?
- Maybe fsr makes more sense anyway?

Shrinkage is adaptive to information

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



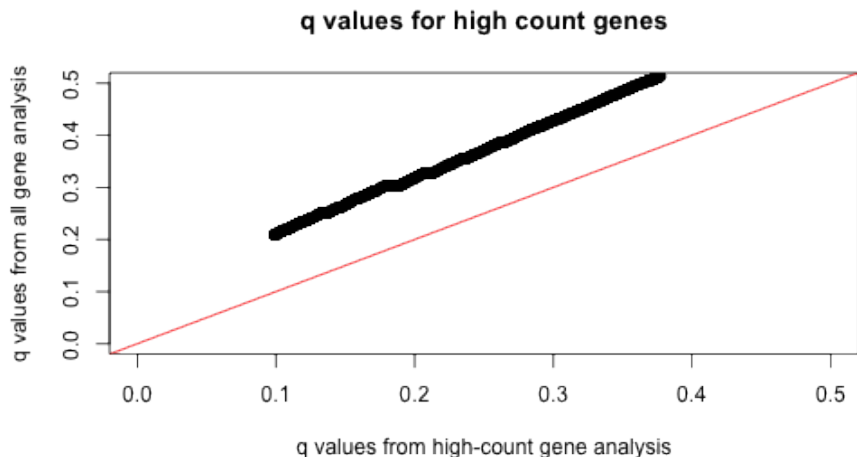
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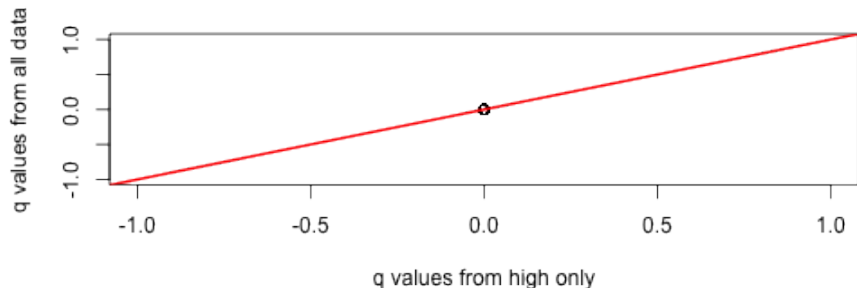
Shrinkage is adaptive to information

| ## | gene | lv1 | lv2 | rv1 | rv2 | pval | zdat.ash\$lfr |
|----------|--------|------|------|------|------|---------|---------------|
| ## 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 $\pi_0 = 0$.