# Is *BC* the new *BH*?

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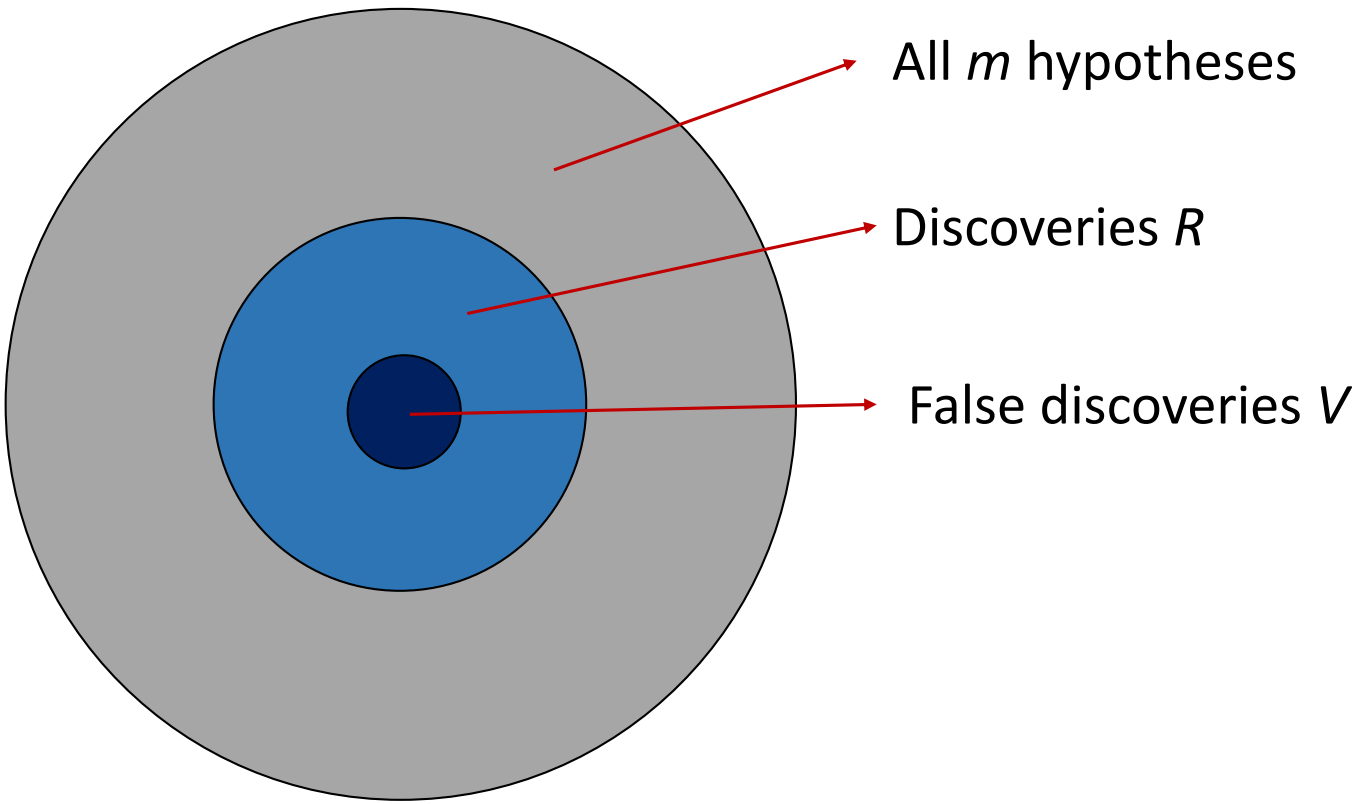
# Shifting my statistical focus...

- **Before**
  - exponential families
  - measurement error models
  - latent variable models
- **Now**
  - multiple testing and false discovery rates
  - conditional independence testing
  - negative control methods
  - robust inference
  - martingale applications

# Multiple testing review

Consider $m$ hypothesis $H_1, \ldots, H_m$. Suppose that we test these hypotheses and make $R$ discoveries. Of these discoveries, suppose that $V$ are *false* discoveries (i.e., true nulls) and that $V - R$ are *true discoveries* (i.e., true alternatives).



# Multiple testing review: FDR and FWER

The family-wise error rate (FWER) is the probability of making even 1 false discovery:

$$FWER = \mathbb{P}(V \geq 1).$$

The false discovery rate (FDR) is the expected fraction of false discoveries:

$$FDR = \mathbb{E}\left(\frac{V}{\max\{R, 1\}}\right) := \mathbb{E}\left(FDP\right).$$

If $R = 0$ (i.e., no discoveries), then

$$FDR = 0.$$

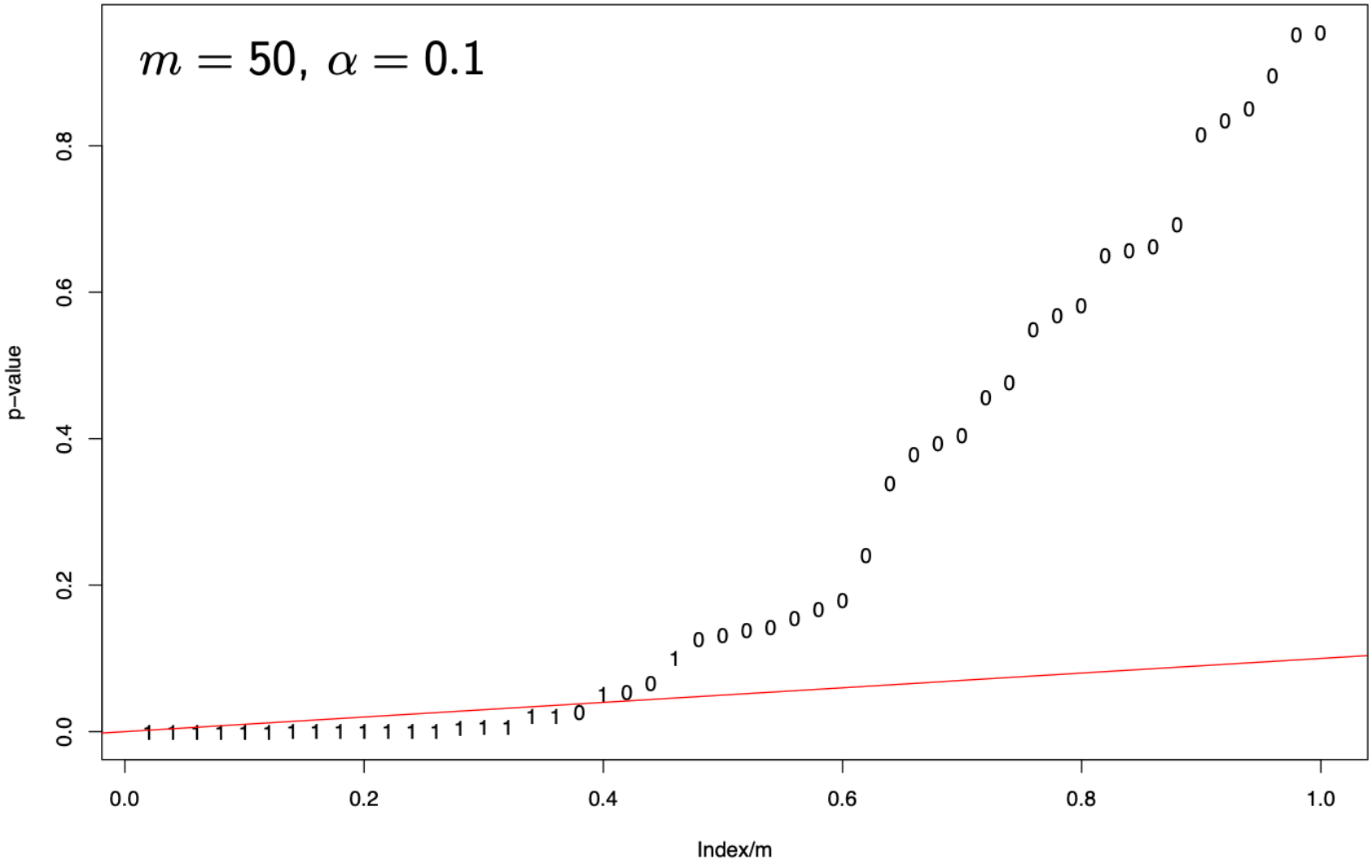
# Benjamini-Hochberg (BH)

**BH Procedure**: Suppose that we calculate $p$-values $p_1, \ldots, p_m$ for the hypotheses $H_1, \ldots, H_m$. Suppose that the $p$-values corresponding to the true null hypotheses are $U(0,1)$, and suppose that the $p_i$s are independent. Let $p_{(1)} \leq \ldots, \leq p_{(m)}$ be the ordered $p$-values and $H_{(1)}, \ldots, H_{(m)}$ the corresponding ordered hypotheses. Let $\alpha \in (0,1)$ be the user-chosen FDR level (typically, $\alpha \in \{0.05, 0.1, 0.2\}$). Define

$$\hat{k} = \text{argmax}_k \{p_{(k)} \leq \alpha k/m\}.$$

Reject $H_{(1)}, \ldots, H_{(\hat{k})}$.
**Theorem**: The BH procedure controls the FDR at level $\alpha$, i.e. $FDR \leq \alpha$.

# Visual interpretation of BH




(source: Chris Genovese)

# The Barber-Candés (BC) procedure

**BC procedure** (**Barber2015**) : Let $X_1, \ldots X_m$ be test statistics corresponding to the hypotheses $H_1, \ldots, H_m$, with large values indicating evidence against the null hypothesis. Assume that the density $\psi$ of the null test statistics is symmetric about 0, i.e. $\psi(x) = \psi(-x)$ for all $x \geq 0$. Also, assume that the $X_i$s are independent. Let $|X| := \{|X_i| : i = 1, \ldots, n\}$ be the set of sample absolute values, and let

$$\widehat{FDP}(t) := \frac{1 + \#\{i : X_i \leq -t\}}{\max\left(1, \#\{i : X_i \geq t\}\right)}$$

be the empirical false discovery proportion for given $t \in |X|$. Finally, let $\alpha \in (0, 1)$ be the FDR target. The BC threshold is $\tau_{\mathrm{BC}} = \min\left\{t \in |X| : \widehat{FDP}(t) \leq \alpha\right\}$. Reject all $X_i \geq \tau_{\mathrm{BC}}$.

**Theorem**: The BC procedure controls FDR at level $\alpha$, i.e. $FDR \leq \alpha$.

# BC procedure note

**Note**: The null $X_i$s are **not** $p$-values. Instead, the null $X_i$s are test statistics with a shared, symmetric density. For example:

- Gaussian
- Double exponential (AKA Laplace)
- Student's $t$
- Rademacher
- Unknown symmetric distribution
- etc.

**Tim's thought**: We can run BC on transformed $p$-values. Let $p_i \sim \mathrm{U}(0,1)$ be a null $p$-value. Let $X_i := -p_i + 1/2$. Then $X_i \sim \mathrm{U}(-1/2, 1/2)$, with large values indicating evidence against the null. **Therefore, BC is more flexible than BH.**

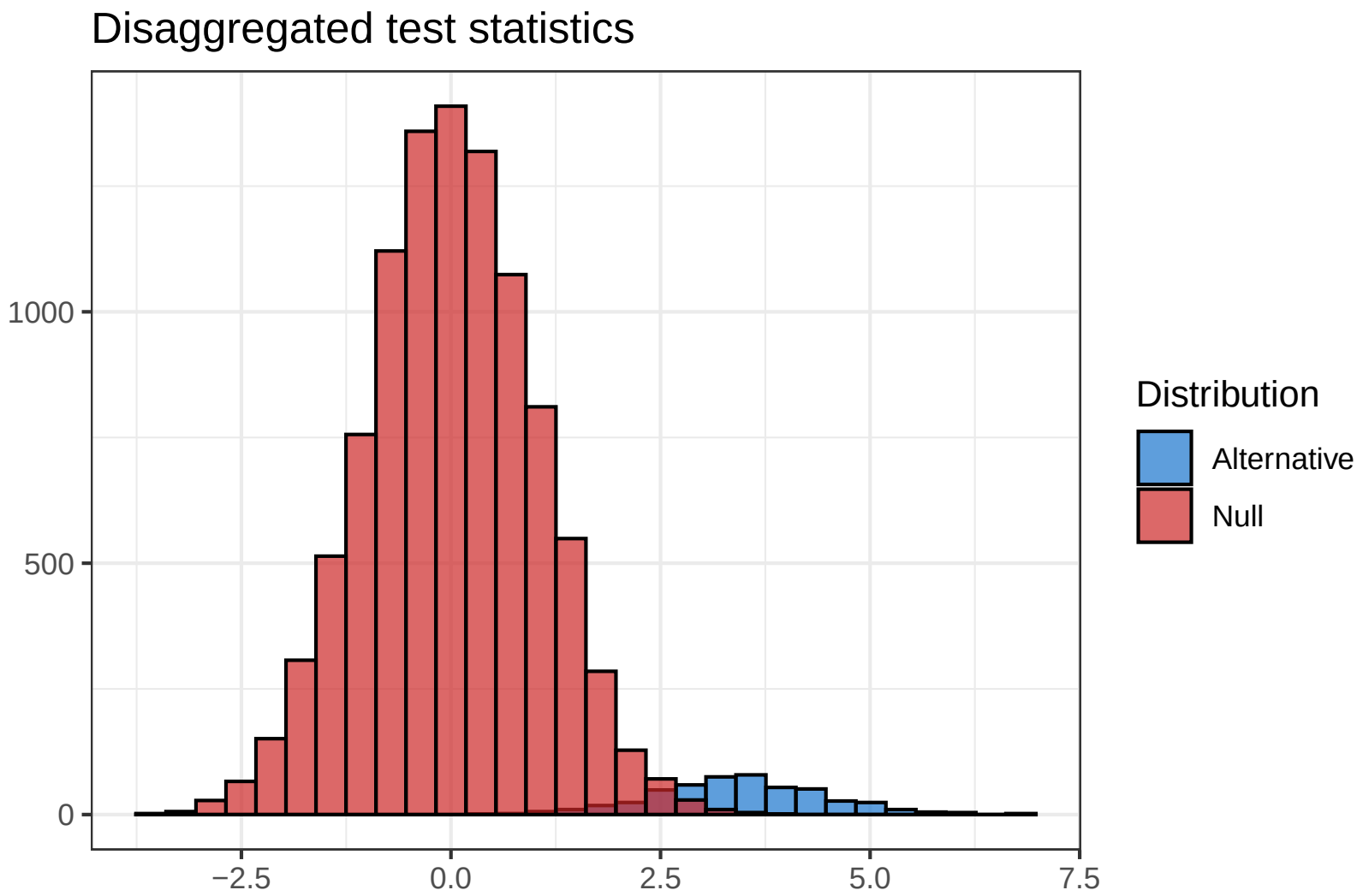
# Visual interpretation of BC

- Let $X_1, \ldots, X_{10,000} \sim N(0,1)$ be the test statistics under the null hypothesis. Let $Y_1, \ldots, Y_{500} \sim N(3.5,1)$ be the test statistics under the alternative hypothesis. Let

$$Z := [X_1, \ldots, X_{10,000}, Y_1, \ldots, Y_{500}]$$

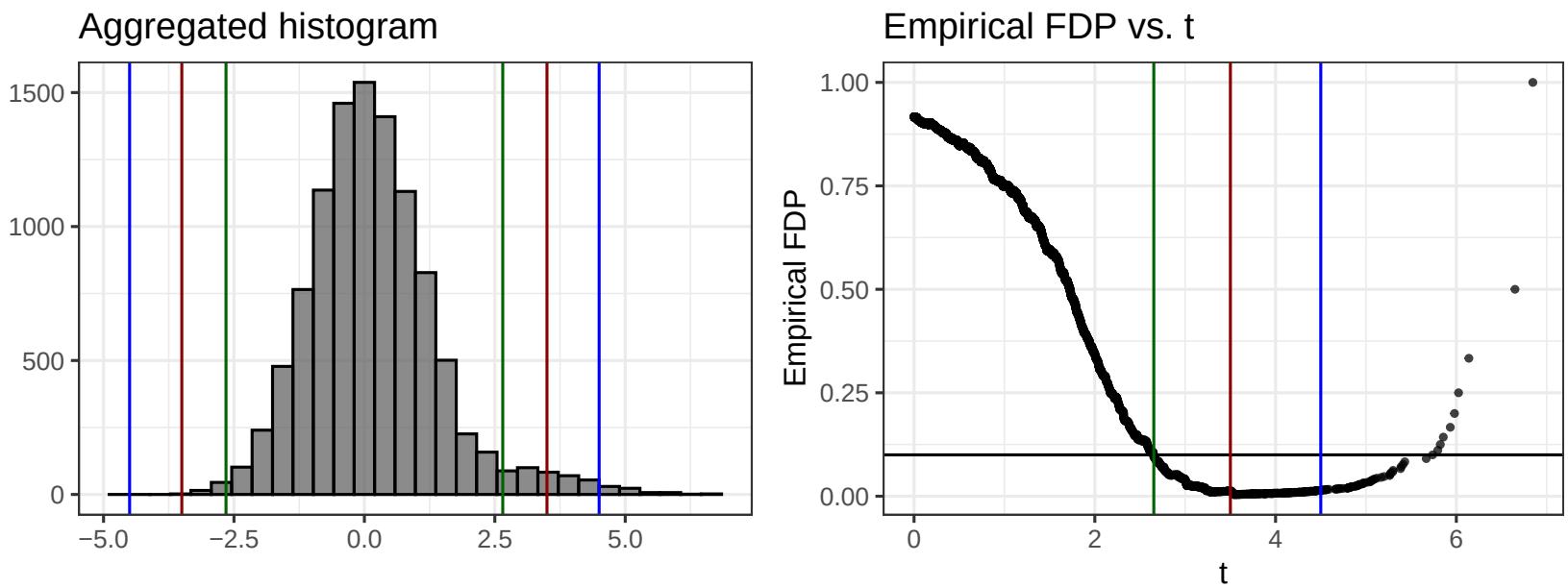
  be the full vector of test statistics.
- We apply BC to $Z$ with the goal of discovering the $Y_i$s with FDR control at level 0.1.

# Visual interpretation of BC



# Visual interpretation of BC

The blue, red, and green vertical lines represent different candidate thresholds (at 4.5, 3.5, and 2.65, respectively).



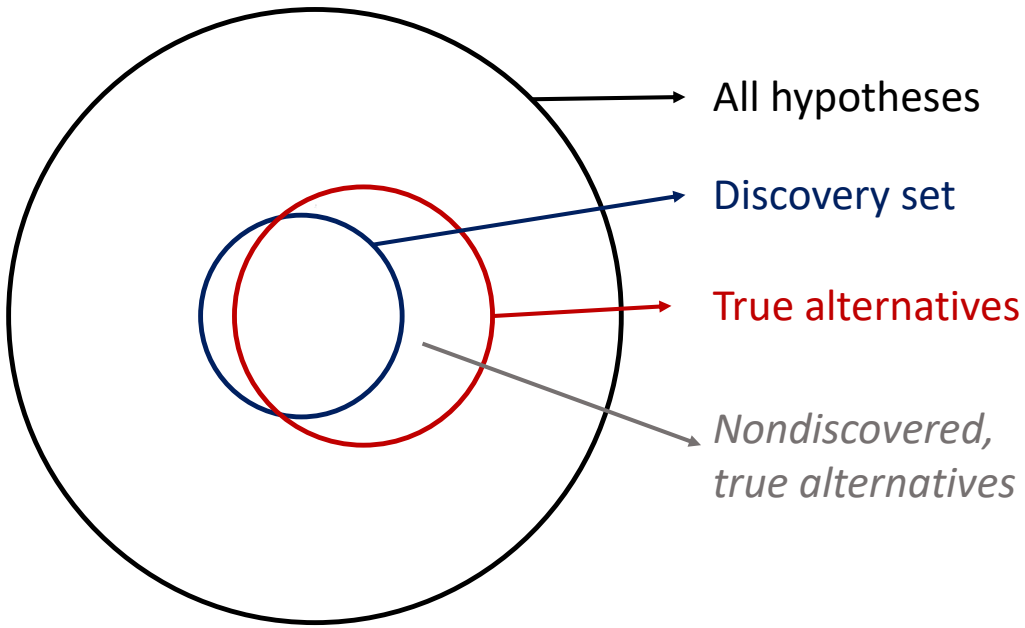

The BC threshold is at 2.65; thus, we reject all test statistics greater than this value.

# Type II error

- Let $S$ be the number of *true alternatives*, and let $Q$ be the number of *non-discovered* true alternatives. The *false non-discovery rate* ($FNR$) is

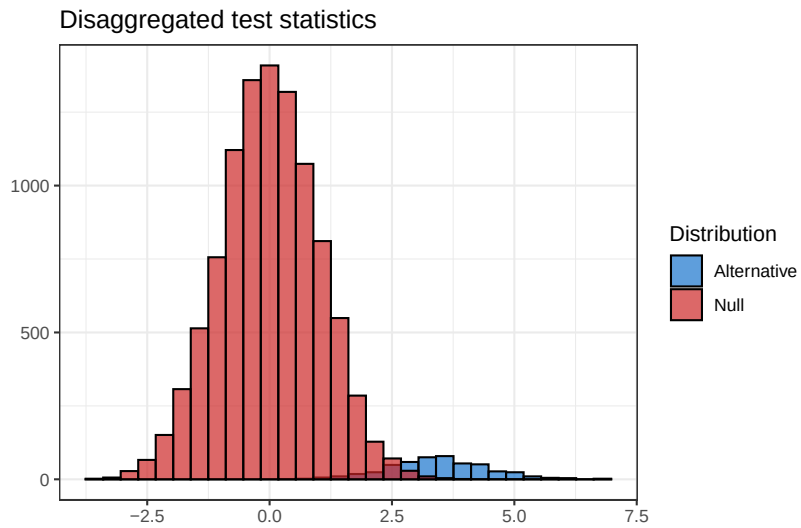
$$FNR := \mathbb{E}\left[\frac{Q}{\max\{S, 1\}}\right].$$

- FDR is analogous to type I error; FNR is analogous to type II error.



# Power: numerical experiment

I ran a small simulation experiment ($B = 50$ replicates) to compare the FDR (target: $\leq 10\%$) and FNR (smaller is better) of BC and BH in the example above. The results were similar across methods.




| | BH | BC |
|---|---|---|
| FDR | 9.7 % | 9.8 % |
| FNR | 19.1 % | 19.2 % |

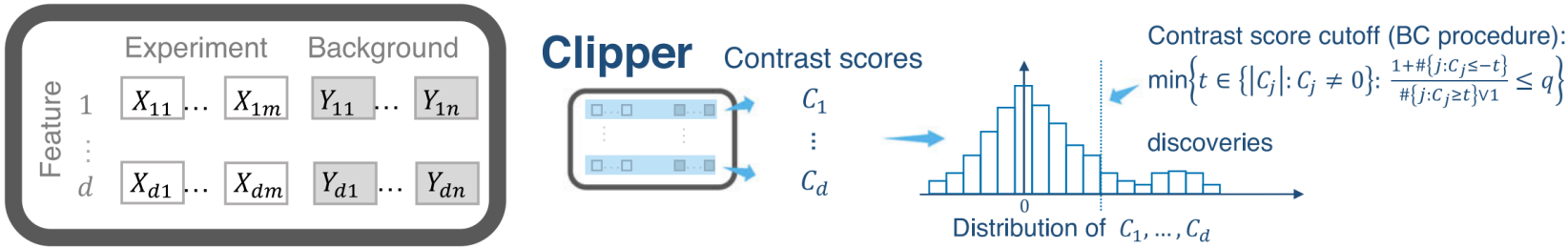
# Power: theoretical result

- **Arias-Castro2017** showed that BC and BH have asymptotically identical power when the test statistics are Gaussian (as above).
- The empirical experiments of **Arias-Castro2017** confirm their theoretical results. However, BC empirically seems lose power in "ultrasparse" (i.e., $< 1/1000$ hypotheses true) settings. More investigation is required.

# BC opens the door to new strategies for high-dimensional, robust, and/or nonparametric FDR control.

1. High-dimensional, nonparametric two-sample testing (**Ge2021**).
2. Signal recovery in the (possibly high-dimensional) linear model (**Barber2015**).
3. Doubly-robust, finite-sample calibration with negative controls (us 2022+?).

# Clipper enables FDR control on high-throughput genomics data.




- Clipper is an ingenious method for nonparametric, high-dimensional, two-sample testing with few samples.
  - Computes a "contrast score" for each of the $d$ features (no $p$-values); runs the BC method on the contrast scores.
  - Contrast scores constructed in such a way that BH holds.
- Overcomes limitations of $p$-value-based approaches.
  - Parametric test: not robust.
  - Rank- or permutation-based test: too few samples.

# Clipper applies to ChIP-seq, bulk RNA-seq, mass spec., and Hi-C data.