Closed testing

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XXXVII cycle

Outline

Comparing three groups

Simultaneous control of false discovery proportions

Main references

- Goeman, J.J. and Solari, A. (2022) Comparing three groups. The American Statistician, 76, 168-176.
- Goeman, J.J. and Solari, A. (2011) Multiple Testing for Exploratory Research. Statistical Science, 26, 584–597.
- Goeman, J.J., Meijer, R.J., Krebs, J.T.P. and Solari, A. (2019) Simultaneous Control of All False Discovery Proportions in Large-Scale Multiple Hypothesis Testing. Biometrika, 106, 841–856.

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Suppose that genetically similar seeds are randomly assigned to be raised either under standard conditions (control) or in two different nutritionally enriched environments (treatments I and II).

After a predetermined period all plants are harvested, dried and weighed. The results, expressed as dried weight in grams, for samples of $n = 10$ plants from each group are given in the following Table (data from Dobson, 1983, Table 7.1):

Control	4.17	5.58	5.18	6.11	4.50	4.61	5.17	4.53	5.33	5.14
Treatment I	4.81	4.17	4.41	3.59	5.87	3.83	6.03	4.89	4.32	4.69
Treatment II	6.31	5.12	5.54	5.50	5.37	5.29	4.92	6.15	5.80	5.26

Four hypotheses

We may formulate four null hypotheses to compare the group means μ_1, μ_2, and μ_3.

First, the so-called ‘global’ null hypotheses that all three group means are equal:

$$H_{123} \colon \mu_1 = \mu_2 = \mu_3.$$

Next, there are the three pairwise comparisons between groups:

$$H_{12} \colon \mu_1 = \mu_2; \qquad H_{13} \colon \mu_1 = \mu_3; \qquad H_{23} \colon \mu_2 = \mu_3.$$

Four scenarios

For the three-group comparison case we distinguish four scenarios for the choice of primary and secondary hypotheses.

1. *The global hypothesis H_{123} is primary*: This is natural when the presence of any difference between the means can directly be meaningfully interpreted, regardless of the location of such difference.
2. *All three pairwise hypotheses, H_{12}, H_{13} and H_{23}, are primary*: This is natural when the three groups represent categories of a nominal variable, and all three groups are equally important.
3. *Two of the pairwise hypotheses, say H_{12} and H_{13}, are primary*: This is natural when Group 1 represents a reference against which both other groups are compared.
4. *One of the pairwise hypotheses, say H_{12}, is primary*: This is natural when one of the groups (Group 3) is of secondary interest.

Scenario A is appropriate if we would first and foremost want to show that there is some effect of different growing conditions, regardless of which.

Scenario B would be chosen if we would be equally interested in showing a difference between any of the groups, but if only rejecting the global hypothesis would be unsatisfactory.

Scenario C would be appropriate if we would be primarily interested in finding at least one of the treatments is different from the control.

Scenario D prioritizing H_{12} would be most appropriate if demonstrating the effectiveness of treatment I with respect to the control would be of primary interest.

F tests

The standard tests for H_{123}, H_{12}, H_{13} and H_{23} in the one-way ANOVA model (with equal-size groups) are the (partial) *F*-tests based on the estimates $\hat{\mu}_1$, $\hat{\mu}_2$, $\hat{\mu}_3$, and pooled variance estimate $\hat{\sigma}^2$.

The partial *F*-test statistic for H_{12} is proportional to the standardized squared group difference

$$S_{12} = \frac{(\hat{\mu}_2 - \hat{\mu}_1)^2}{\hat{\sigma}^2}$$

analogous for H_{13} and H_{23}. The distributions of S_{12}, S_{13}, S_{23} are identical under the null hypotheses; let c_α be the $1 - \alpha$-quantile of that distribution.

For H_{123} the *F* test is proportional to the test statistic

$$S_{123} = S_{12} + S_{13} + S_{23}$$

Tukey HSD and Dunnett methods

Tukey's Honest Significant Difference (HSD) method rejects when $S_{ij} \geq \tilde{c}_\alpha$, where $\tilde{c}_\alpha$ is the $(1-\alpha)$-quantile of the distribution of

$$\tilde{S}_{123} = \max(S_{12}, S_{13}, S_{23}),$$

which is proportional to a studentized range distribution

Dunnett's procedure rejects H_{12} and/or H_{13} when the corresponding test statistics exceed $\tilde{c}_\alpha^1$, where $\tilde{c}_\alpha^1$ is the $(1-\alpha)$-quantile of the distribution of

$$\tilde{S}_1 = \max(S_{12}, S_{13}).$$

Note that Dunnett's critical value is less stringent than Tukey's one, i.e. $c_\alpha < \tilde{c}_\alpha^1 < \tilde{c}_\alpha$.

Restricted combinations

The four hypotheses H_{123}, H_{12}, H_{13}, and H_{23} are logically related to each other: if any two are true, then all must be true.

For example, if H_{12} and H_{13} are true, then $\mu_1 = \mu_2$ and $\mu_1 = \mu_3$, so that we have $\mu_1 = \mu_2 = \mu_3$, which implies that H_{123} and H_{23} are also true.

The number of true hypotheses among H_{123}, H_{12}, H_{13}, and H_{23} can therefore be either 0, 1, or 4, but never 2 or 3.

Additionally, if only one hypothesis is true, this cannot be H_{123}.

These logical implications between hypotheses are also known as restricted combinations

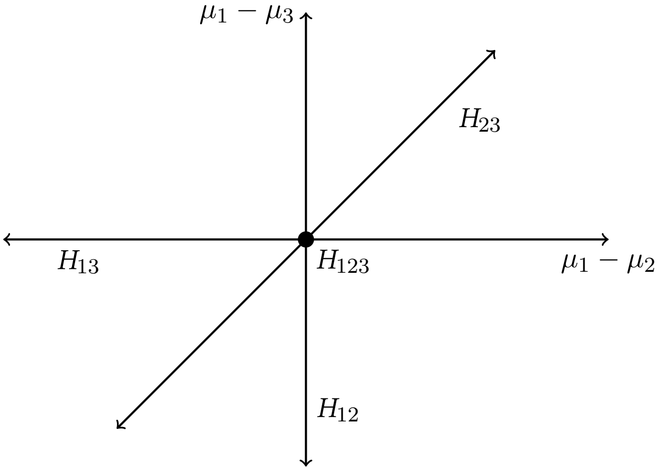


Figure: Visualization of the four hypotheses H_{12}, H_{13}, H_{23} and H_{123} in a parameter space with axes $\mu_1 - \mu_2$ and $\mu_1 - \mu_3$. Note that H_{23} is the diagonal line for which $\mu_1 - \mu_2 = \mu_1 - \mu_3$. In the origin all four hypotheses are true; elsewhere at most one.

A closed testing procedures in the three-group design take this general form:

1. Test H_{123} with a valid α-level test
2. If H_{123} was not rejected, stop; otherwise, test each of H_{12}, H_{13}, and H_{23} with a valid α-level test.

The four procedures have the following Step 1, with test statistics chosen so as to maximize power of the primary hypotheses:

1. *Classic closed testing*: H_{123} is tested with test statistic S_{123};
2. *Closed Tukey*: H_{123} is tested with test statistic $\tilde{S}_{123} = \max(S_{12}, S_{13}, S_{23})$;
3. *Closed Dunnett*: H_{123} is tested with test statistic $\tilde{S}_1 = \max(S_{12}, S_{13})$;
4. *Gatekeeping*: H_{123} is tested with test statistic S_{12}.

For H_{12}, H_{13}, and H_{23} we will always simply use the test that rejects when $S_{ij} \geq c_\alpha$

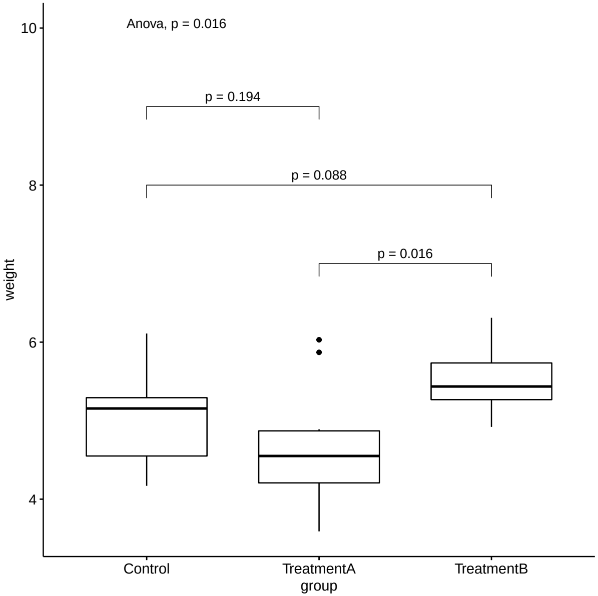
The adjusted p-value of H_{ij} in a closed testing procedure is therefore

$$\tilde{p}_{ij} = \max(p_{ij}, \tilde{p}_{123}),$$

where $\tilde{p}_{123}$ is the p-value for H_{123} in the procedure. These we can calculate for each of the four procedures as follows:

$$\begin{array}{rcl} \tilde{p}^{A}_{123} & = & p_{123}; \\ \tilde{p}^{B}_{123} & = & \min(\tilde{p}^{Tuk}_{12}, \tilde{p}^{Tuk}_{13}, \tilde{p}^{Tuk}_{23}); \\ \tilde{p}^{C}_{123} & = & \min(\tilde{p}^{Dun}_{12}, \tilde{p}^{Dun}_{13}); \\ \tilde{p}^{D}_{123} & = & p_{12}. \end{array}$$

Method	H_{12}	H_{13}	H_{23}	H_{123}
(A) Classic closed testing	0.194	0.088	0.016	0.016
(B) Closed Tukey	0.194	0.088	0.012	0.012
(C) Closed Dunnett	0.194	0.153	0.153	0.153
(D) Gatekeeping	0.194	0.194	0.194	0.194


Anova, p = 0.016
p = 0.194
p = 0.088
p = 0.016
weight
10
8
6
4
Control
TreatmentA
TreatmentB
group

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fMRI experiment

Subjects perform mental tasks in MRI scanner
MRI measures oxygenated blood flow in brain (brain activity)

Brain activity map

Significance (*p*-value) for brain activity at each location (*voxel*)

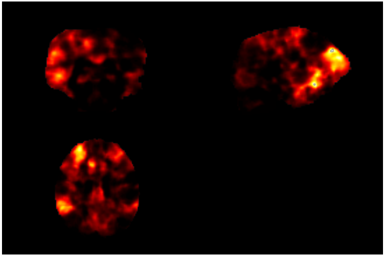
Goal

Identify emphregions of brain activity

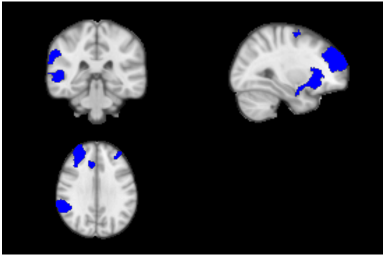
Aggregation

Micro-inferences (voxels) $\rightarrow$ larger-scale inferences (regions)

fMRI data



Brain activity map



Selection

The problem of post-selection inference

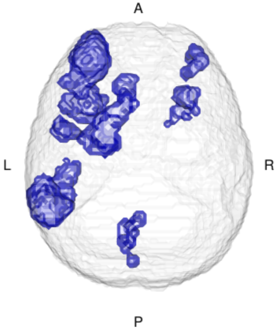
Examining the data to *select* interesting patterns,
then carrying out *inference* about the selection with the same data

Question

How to correct for overoptimism in inference due to data-driven selection?

Selected clusters

cluster ≡ contiguous voxels with $p < t = 0.0007$



9 clusters of size 2191, 1835, 1400, 698, 421, 304, 245, 232, 187

Simultaneous inference

For every selected region, return

$$\text{estimate} \quad \underbrace{[(1-\alpha)\ \text{confidence lower bound}, 100\%]}_{\text{one}-\text{sided confidence interval}}$$

for the *true discovery proportion* in the selection

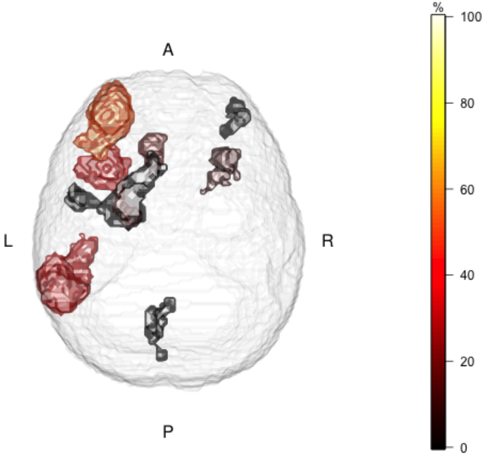
All lower bounds are *simultaneously* correct with probability $\geq 1-\alpha$

True discovery proportion

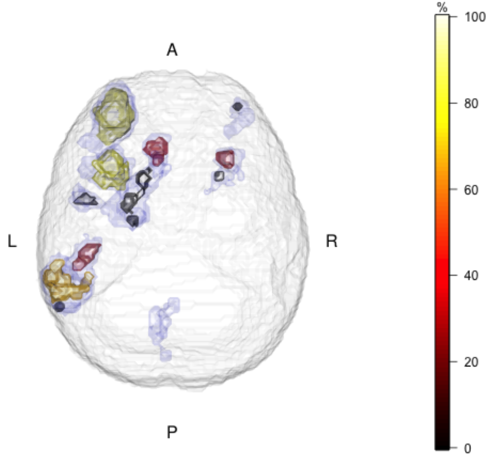
selection	*size*	$\widehat{\mathrm{TDP}}$	$[\,\underline{\mathrm{TDP}}\,,\ 100\%\,]$
S_1	2191	88%	[29% , 100%]
S_2	1835	86%	[46% , 100%]
S_3	1400	81%	[32% , 100%]
S_4	698	62%	[0% , 100%]
S_5	421	42%	[6% , 100%]
S_6	304	49%	[11% , 100%]
S_7	245	0%	[0% , 100%]
S_8	232	20%	[0% , 100%]
S_9	187	1%	[0% , 100%]

All lower bounds are correct with probability $\geq 95\%$

True discovery proportion



Zoom in



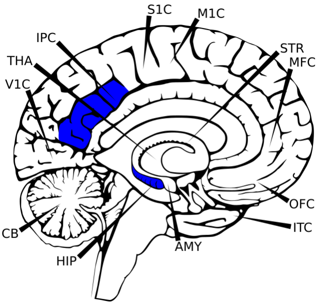
Sub-clusters

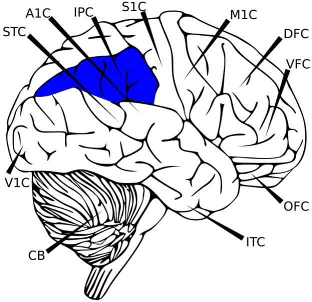
sub-cluster ≡ contiguous voxels with $p < t' = 0.00003$

selection	*threshold*	*size*	TDP
S_1	$p < t$	2191	29 %
S_1'	$p < t'$	405	66 %
S_1''	$p < t'$	133	23 %
S_1'''	$p < t'$	6	0 %
S_2	$p < t$	1835	46 %
S_2'	$p < t'$	963	86 %

$\vdots$

Domain-knowledge regions





$M = \{1, \ldots, m\}$	collection of $m = \|M\|$ voxels
$M_0 \subseteq M$	null voxels with $m_0 = \|M_0\|$ and $\pi_0 = m_0 / m$
$M_1 = M \setminus M_0$	non-null voxels with $m_1 = m - m_0$ and $\pi_1 = 1 - \pi_0$
$H_i : i \in M_0$	voxel null hypothesis with p-value $p_i, \quad i \in M$

Selection

$S \subseteq M$	selected voxels
$m_1(S) = \|M_1 \cap S\|$	number of true discoveries in the selection
$m_0(S) = \|S\| - m_1(S)$	number of false discoveries in S
$\pi_0(S) = m_0(S)/\|S\|$	false discovery proportion in S
$\pi_1(S) = 1 - \pi_0(S)$	true discovery proportion in S

Simultaneous confidence bound

$$\mathrm{P}\Big(\forall\, S \subseteq M :\ \underset{\text{lower bound}}{\underline{m}_1(S)} \ \le \underset{\text{parameter}}{m_1(S)}\Big) \ge 1-\alpha$$

Closed testing

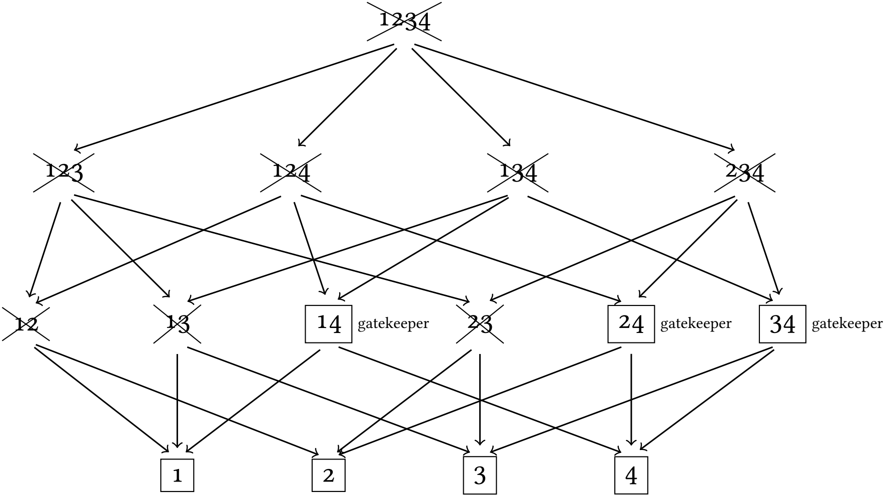
$H_1, \ldots, H_m$	elementary hypotheses
$H_S = \bigcap_{i \in S} H_i \qquad \forall\ S \subseteq M$	intersection hypotheses
$\phi_S = \mathbb{1}\{H_S \text{ rejected at level } \alpha\}$	local tests
$\tilde{\phi}_S = \min \left\{ \phi_K : S \subseteq K \subseteq M \right\}$	closed testing adjusted tests

Closed testing guarantees familywise error rate control at α over all intersection hypotheses

Four-pixel brain

1	2
3	4

Closed testing rejections



Confidence bound

$$\underline{m}_1(S) = |S| - \max_{K \subseteq S} \left\{ |K| : \tilde{\phi}_K = 0 \right\}$$

The size of S minus the size of the largest subset of S for which the corresponding intersection hypothesis is not rejected by closed testing

S	$\underline{m}_1(S)$	$\underline{\pi}_1(S)$
$\{1\}$	0	0%
$\{2\}$	0	0%
$\{3\}$	0	0%
$\{4\}$	0	0%
$\{1, 2\}$	1	50%
$\{1, 3\}$	1	50%
$\{1, 4\}$	0	0%
$\{2, 3\}$	1	50%
$\{2, 4\}$	0	0%
$\{3, 4\}$	0	0%
$\{1, 2, 3\}$	2	66.6%
$\{1, 2, 4\}$	1	33.3%
$\{1, 3, 4\}$	1	33.3%
$\{2, 3, 4\}$	1	33.3%
$\{1, 2, 3, 4\}$	2	50%

Closed testing bottleneck

The required number of tests is 2^m

Shortcut

Computation time can be reduced to polynomial time by specific choice of local tests

Simes test

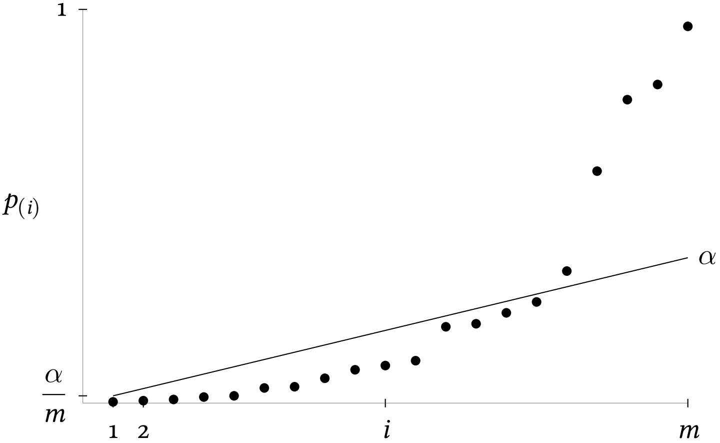
Simes test for H_S

$$\phi_S = \mathbb{1}\Big\{ \bigcup_{i \in S} \{ p_{(i\,:\,S)} \leq \frac{i\alpha}{|S|} \} \Big\}$$

where $p_{(i\,:\,S)}$ is the ith smallest p-value in $\{p_i : i \in S\}$

Assumption
Simes inequality holds for null p-values

$$\mathrm{P}\left(\bigcap_{i=1}^{m_0} \left\{ p_{(i\,:\,M_0)} > \frac{i\alpha}{m_0} \right\} \right) \geq 1 - \alpha$$



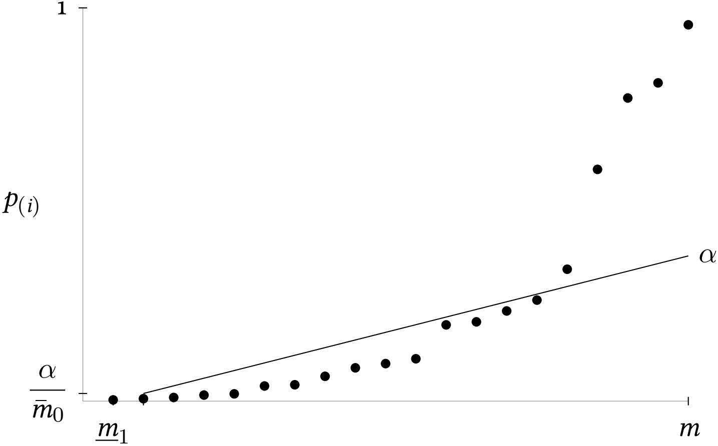
$m_0 = m$? No. Then $m_0 \leq \bar{m}_0 = m - 1$

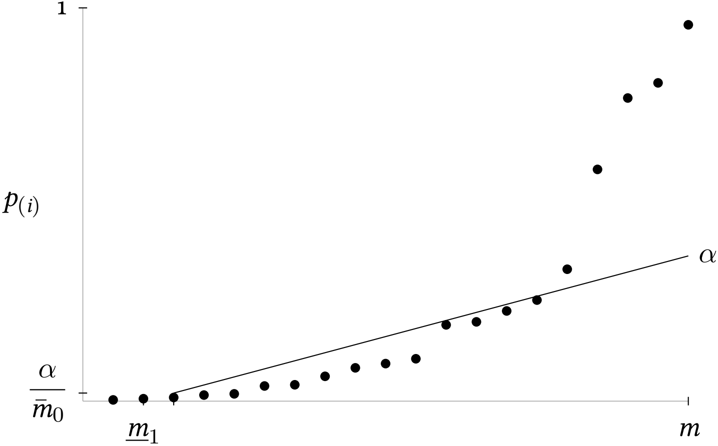
Upper bound for m_0

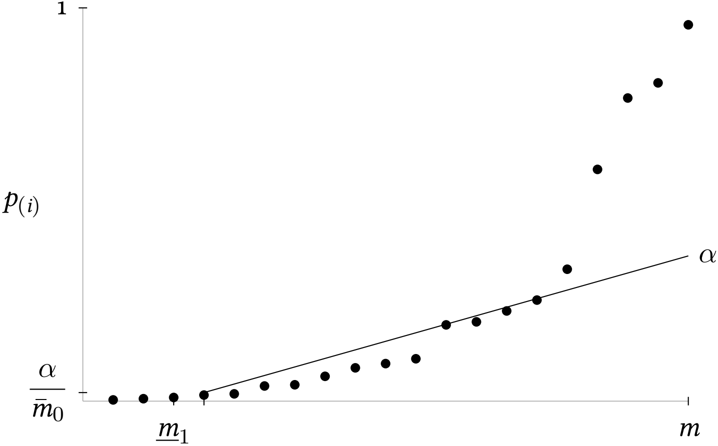
$$\bar{m}_0 = \max\left\{0 \leq k \leq m : \bigcap_{i=1}^{k} \left\{p_{(m-k+i)} > \frac{i\alpha}{k}\right\}\right\}$$

so the lower bound for the overall number of true discoveries is

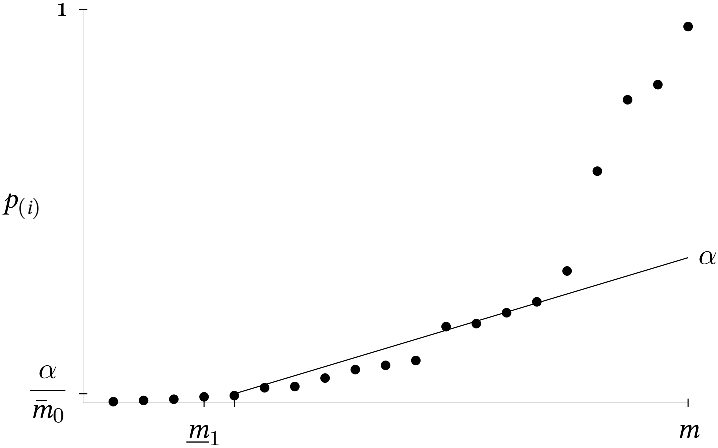
$$\underline{m}_1 = m - \bar{m}_0$$

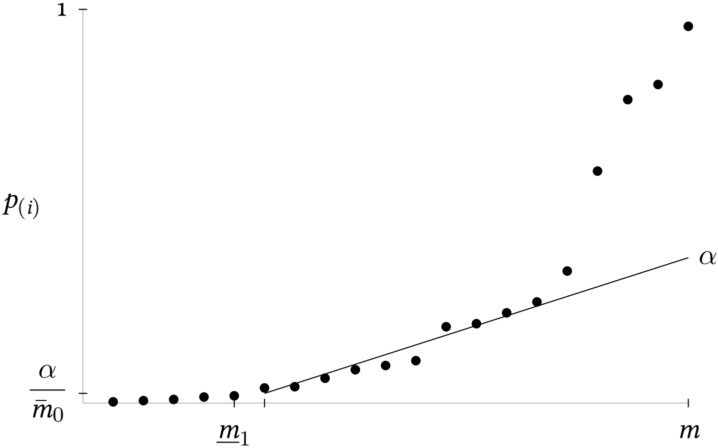

1
$p_{(i)}$
α
$\frac{\alpha}{\bar{m}_0}$
$\underline{m}_1$
m

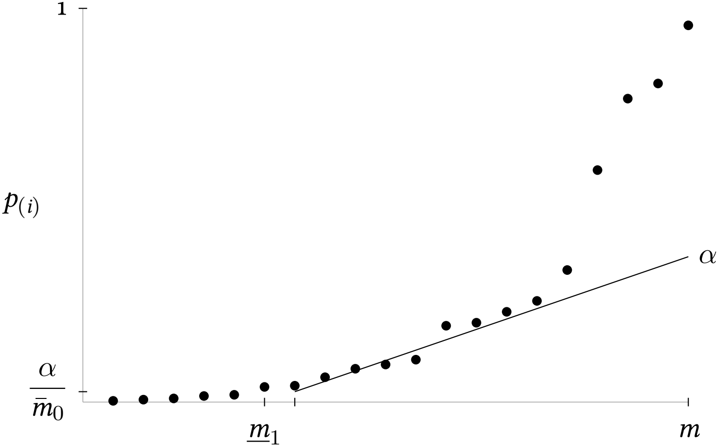

1
$p_{(i)}$
α
$\frac{\alpha}{\bar{m}_0}$
$\underline{m}_1$
m



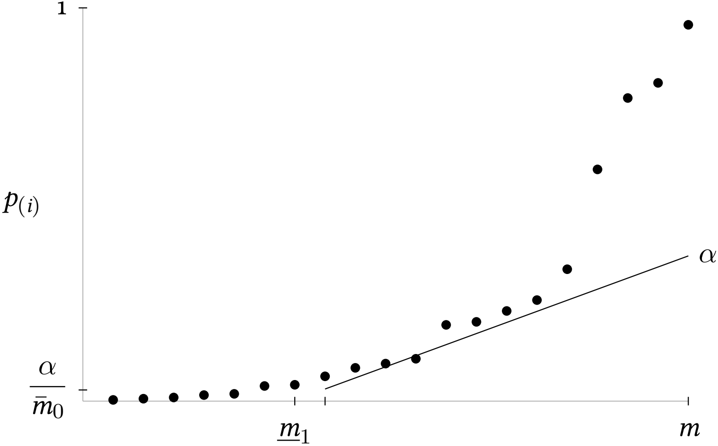
1
$p_{(i)}$
α
$\frac{\alpha}{\bar{m}_0}$
$\underline{m}_1$
m

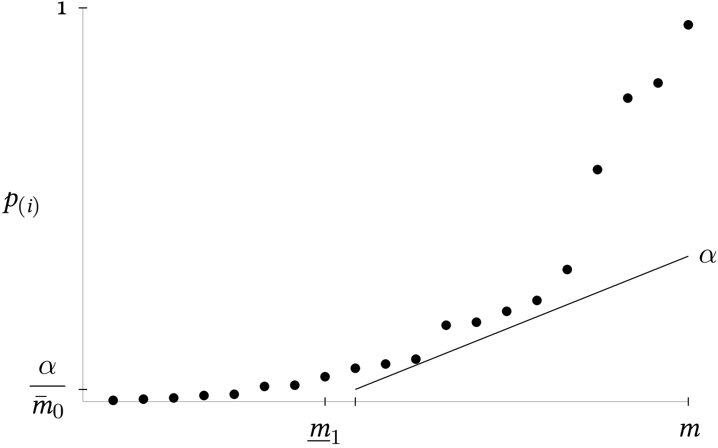

1
$p_{(i)}$
α
$\frac{\alpha}{\bar{m}_0}$
$\underline{m}_1$
m


1
$p_{(i)}$
α
$\frac{\alpha}{\bar{m}_0}$
$\underline{m}_1$
m

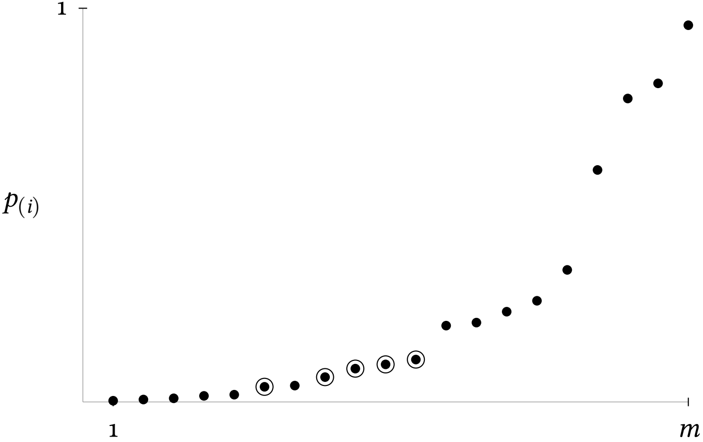


1
$p_{(i)}$
$\frac{\alpha}{\bar{m}_0}$
α
$\underline{m}_1$
m


1
$p_{(i)}$
$\frac{\alpha}{\bar{m}_0}$
$\underline{m}_1$
m
α


1
$p_{(i)}$
α
$\frac{\alpha}{\bar{m}_0}$
$\underline{m}_1$
m

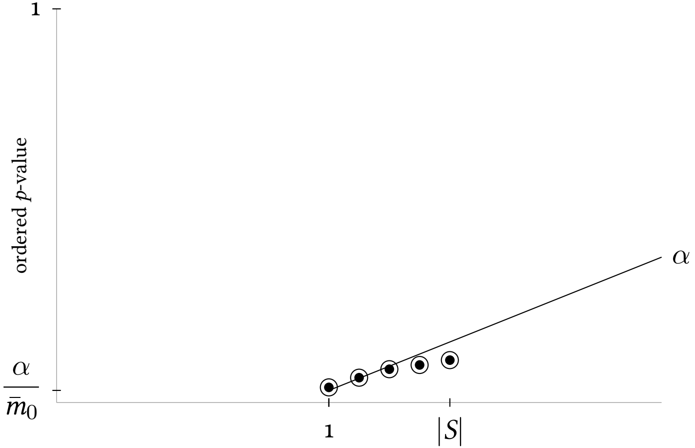
Arbitrary selection

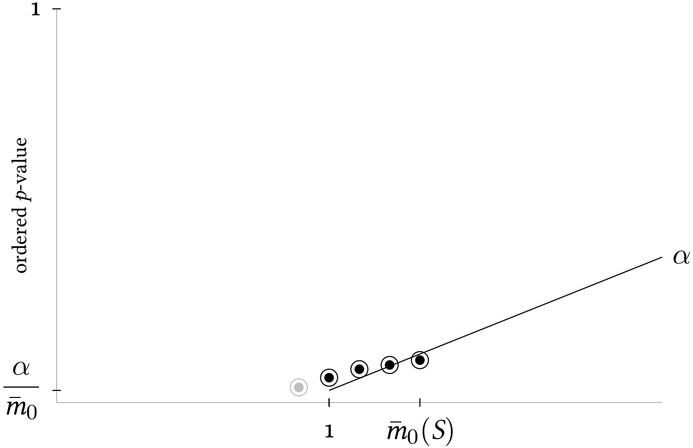


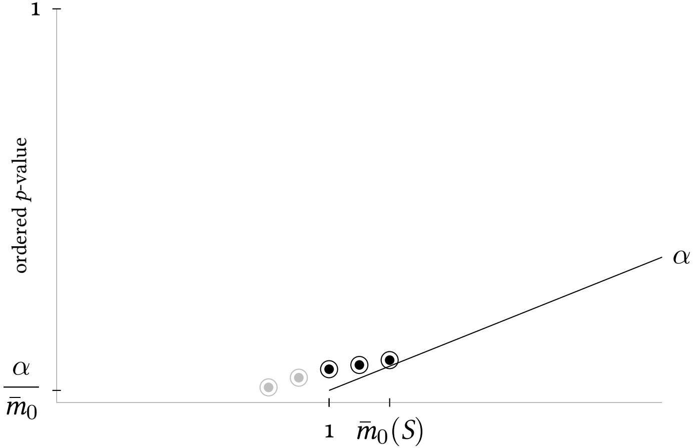
$S \subseteq M$

Confidence bound

$$\underline{m}_1(S) = \min\left\{0 \le k \le |S| : \bigcap_{i=1}^{|S|-k} \left\{p_{(k+i\,:\,S)} > \frac{i\alpha}{\bar{m}_0}\right\}\right\}$$


1
ordered p-value
$\frac{\alpha}{\bar{m}_0}$
α
1
$|S|$


1
ordered p-value
α
$\frac{\alpha}{\bar{m}_0}$
1
$\bar{m}_0(S)$


1
ordered p-value
$\frac{\alpha}{\bar{m}_0}$
α
1
$\bar{m}_0(S)$

Algorithm

	Operation	*Complexity*
1	Sort the p-values	$O(m \log m)$
2	Compute $\bar{m}_0$	$O(m)$
3	Compute $\underline{m}_1(S)$	$O(\|S\|)$

- $\bar{m}_0$ in linear time

  Meijer, Krebs, Goeman (2019)

- Implemented in the R package `hommel`

Relationship to Hommel (FWER)

- Reject the hypotheses with indexes in

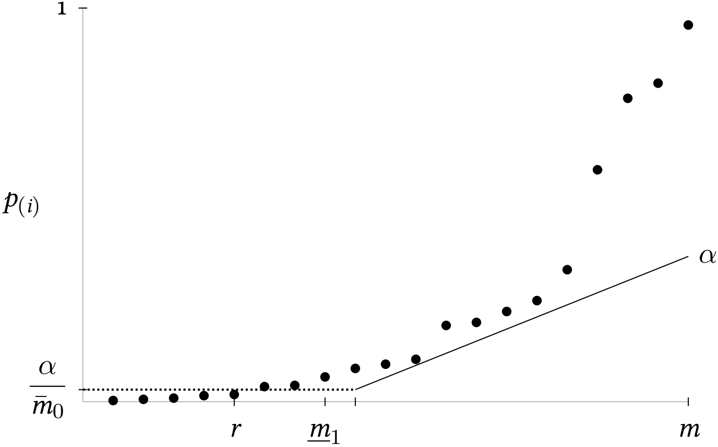
$$R = \left\{ i \in M : p_i \leq \frac{\alpha}{\bar{m}_0} \right\}$$

  with familywise error rate control at α

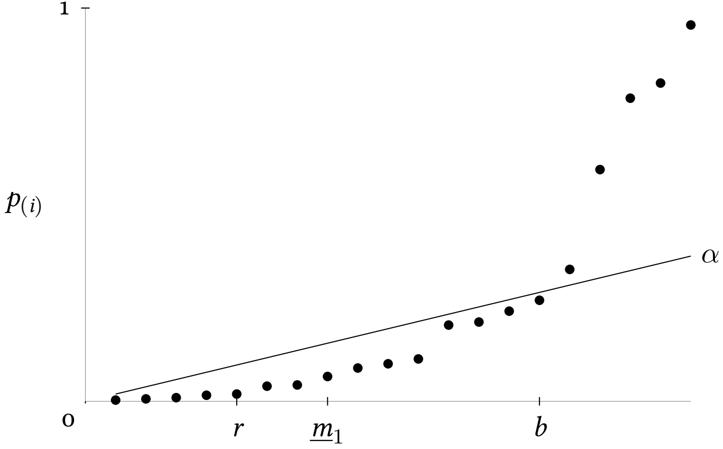
- Voxels in R represent *localized true discoveries*

$$\underline{m}_1(R) = |R| = r$$

Hommel rejections



Relationship to Benjamini-Hochberg (FDR)



Large-scale testing

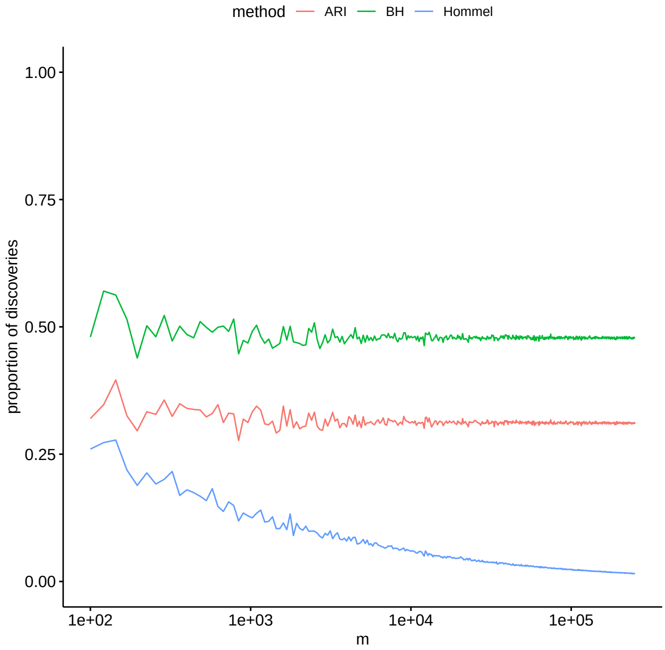
Assume $p_1, \ldots, p_m \overset{i.i.d.}{\sim} F$
with a mixture distribution $F(u) = \pi_0 u + \pi_1 F_1(u)$

Fix $\alpha \in (0,1)$. As the number of hypotheses $m \to \infty$

$$\operatorname*{plim}_{m\to\infty} \frac{r}{m} = 0 \qquad \operatorname*{plim}_{m\to\infty} \frac{m_1}{m} = k > 0 \qquad \operatorname*{plim}_{m\to\infty} \frac{b}{m} = k' > 0$$

if a minimal level of signal is present[1]

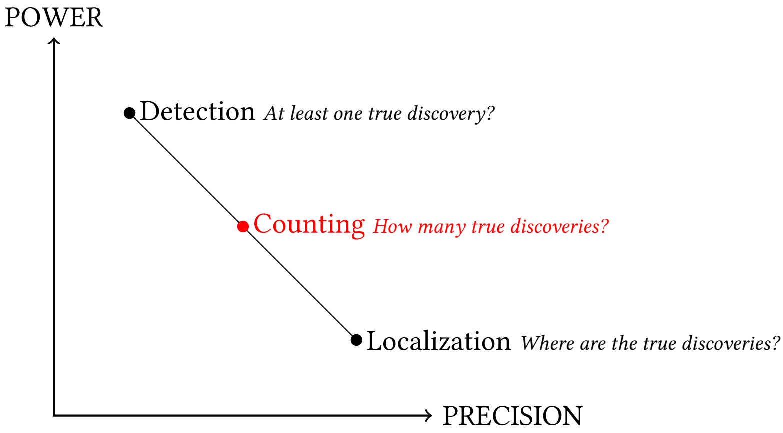
[1] "criticality" of Chi (2007), i.e. if $F(u\alpha) > u$ for at least one $0 \leq u < 1$


method
ARI
BH
Hommel
1.00
0.75
0.50
0.25
0.00
proportion of discoveries
1e+02
1e+03
1e+04
1e+05
m

Localized true discoveries

S	$\lvert S\rvert$	$\underline{\pi_1}(S)$	$\lvert S \cap R\rvert / \lvert S\rvert$
S_1	2191	29%	0.3%
S_2	1835	46%	4%
S_3	1400	32%	6%
S_4	698	0%	0%
S_5	421	6%	0%
S_6	304	11%	0%
S_7	245	0%	0%
S_8	232	0%	0%
S_9	187	0%	0%

Trade-off


POWER
Detection *At least one true discovery?*
Counting *How many true discoveries?*
Localization *Where are the true discoveries?*
PRECISION

The less specific the question is, the more power to answer it