Multiple testing

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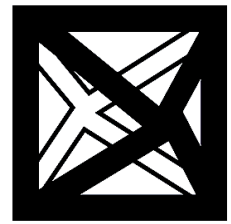


XXXVII cycle

Outline

Global testing

Error rates

Methods for familywise error rate control

Main references

- Candés (2022) Stats 300C - Theory of Statistics. Lectures 1-7 https://candes.su.domains/teaching/stats300c/index.html
- Goeman and Solari (2014) Multiple Hypothesis Testing in Genomics. Statistics in Medicine, 33, 1946–78.

$$Y = \begin{pmatrix} Y_1 \\ \vdots \\ Y_m \end{pmatrix} \sim N_m \left(\begin{pmatrix} \mu_1 \\ \vdots \\ \mu_m \end{pmatrix}, \begin{bmatrix} \sigma_1^2 & \sigma_{12} & \cdot & \sigma_{1m} \\ \sigma_{21} & \sigma_2^2 & \cdot & \sigma_{2m} \\ \cdot & \cdot & \cdot & \cdot \\ \sigma_{m1} & \cdot & \cdot & \sigma_m^2 \end{bmatrix} \right)$$

The parameter of interest is $\mathrm{E}(Y) = \mu$, where $\mu_j = 0$ means "no effect" and $\mu_j \neq 0$ means "effect" in the jth component

The nuisance parameter is the variance/covariance matrix $\mathrm{Var}(Y) = \Sigma$

Three questions

1. *Detecting effects*: There is at least one μ_j different from 0?
2. *Counting effects*: How many μ_j are different from 0?
3. *Identifying effects*: Which μ_j are different from 0?

Table of Contents

Global null hypothesis

$$H_0 : \mu = 0, \text{ i.e. } \bigcap_{j=1}^{m} \{\mu_j = 0\} \text{ vs } H_1 : \mu \neq 0, \text{ i.e. } \bigcup_{j=1}^{m} \{\mu_j \neq 0\}$$

For simplicity, consider $\Sigma = I_m$ and the one-sided alternative

$$H_0 : \bigcap_{j=1}^{m} \{\mu_j = 0\} \text{ vs } H_1 : \bigcup_{j=1}^{m} \{\mu_j > 0\}$$

MaxT test

$(Y_1, \ldots, Y_m)^t \overset{H_0}{\sim} N_m(0, I_m)$

$T_{\max} = \max(Y_1, \ldots, Y_m)$

The critical value $t_{1-\alpha}$ of $T_{\max}$ is

$$\mathrm{pr}_0(T_{\max} \geq t_{1-\alpha}) = \alpha$$

where $t_{1-\alpha}$ is the $1-\alpha$ quantile of the distribution of the maximum of m independent standard normal variables

$$\int_{t_{1-\alpha}}^{\infty} m\phi(y)\Phi(y)^{m-1} dy = \alpha$$

where ϕ and Φ are the density and cdf of $N(0,1)$

Bonferroni approximation

We can replace $t_{1-\alpha}$ by $z_{1-\frac{\alpha}{m}}$

$$\begin{aligned}
\mathrm{pr}_0(T_{\max} \geq z_{1-\frac{\alpha}{m}}) &= \mathrm{pr}_0\Big(\bigcup_{j=1}^{m}\{Y_j \geq z_{1-\frac{\alpha}{m}}\}\Big) \\
&\leq \sum_{j=1}^{m}\mathrm{pr}_0(Y_j \geq z_{1-\frac{\alpha}{m}}) = m\frac{\alpha}{m} = \alpha
\end{aligned}$$

The union bound might seem crude, but with independent Y_js the size of the test is very near α

$$\begin{aligned}
\mathrm{pr}_0(T_{\max} \geq z_{1-\frac{\alpha}{m}}) &= 1 - \prod_{j=1}^{m}\mathrm{pr}_0(Y_j < z_{1-\frac{\alpha}{m}}) \\
&= 1 - \left(1 - \frac{\alpha}{m}\right)^m \overset{m\to\infty}{\to} 1 - e^{-\alpha}
\end{aligned}$$

For $\alpha = 0.05$, $1 - e^{-\alpha} = 0.0487$

Magnitude of Bonferroni critical value

How large is the threshold $z_{1-\frac{\alpha}{m}}$? For large m

$$\begin{aligned} z_{1-\frac{\alpha}{m}} &\approx \sqrt{2\log m} - \frac{\log(2\log m) + \log 2\pi}{2\sqrt{2\log m}} \\ &\approx \sqrt{2\log m} \end{aligned}$$

with no dependence on α

$$\frac{\phi(t)}{t}(\frac{t^2}{t^2+1}) \leq \text{pr}(N(0,1) > t) \leq \frac{\phi(t)}{t}$$

where $\phi(t)$ is the probability density function of $N(0,1)$. This result implies that for large t, $\frac{\phi(t)}{t}$ is a good approximation to the normal tail probability. Let $z^* = z_{1-\frac{\alpha}{m}}$. We have
$\frac{\alpha}{m} = \text{pr}(N(0,1) > z_{1-\frac{\alpha}{m}}) \approx \frac{\phi(z^*)}{z^*}$, which implies
$\alpha/m \approx \frac{1}{z^*\sqrt{2\pi}} e^{-\frac{(z^*)^2}{2}}$. Taking the logarithm

$$\log m \approx \frac{1}{2}\log(2\pi) + \frac{1}{2}(z^*)^2 + \log(z^*) + \log(\alpha)$$

Note that z^* is increasing in m, i.e. $m \to \infty$ induces $z^* \to \infty$. As $\frac{1}{2}\log(2\pi) + \log(z^*) + \log(\alpha)$ is negligible compared to $(z^*)^2$ when m goes to ∞, it gives

$$z_{1-\frac{\alpha}{m}} \approx \sqrt{2\log m}$$

Needle in a haystack problem

$$H_0 : \mu_j = 0 \text{ for all } j = 1, \ldots, m$$
$$H_1 : \mu_j = c_m > 0, \mu_k = 0 \text{ for } k \neq j$$

What is the limiting power of Bonferroni test?

$$\lim_{m \to \infty} \text{pr}_1\left(T_{\max} > z_{1-\frac{\alpha}{m}}\right)$$

Assume without loss of generality that $\mu_1 = c_m$ and let $\epsilon > 0$ small.

Suppose $c_m > (1+\epsilon)\sqrt{2\log m}$. Then, for $m \to \infty$

$$\mathrm{pr}_1(T_{\max} > z_{1-\frac{\alpha}{m}}) \geq \mathrm{pr}_1(Y_1 > z_{1-\frac{\alpha}{m}}) = \mathrm{pr}(N(0,1) > z_{1-\frac{\alpha}{m}} - c_m) \to 1$$

Suppose $c_m < (1-\epsilon)\sqrt{2\log m}$. Then for $m \to \infty$

$$\begin{aligned}
\mathrm{pr}_1(T_{\max} > z_{1-\frac{\alpha}{m}}) &\leq \mathrm{pr}(Y_1 > z_{1-\frac{\alpha}{m}}) + \mathrm{pr}(\max_{j>1} Y_j > z_{1-\frac{\alpha}{m}}) \\
&= \mathrm{pr}(N(0,1) > z_{1-\frac{\alpha}{m}} - c_m) + \mathrm{pr}(\max_{j>1} Y_j > z_{1-\frac{\alpha}{m}}) \\
&\to 0 + (1 - e^{-\alpha})
\end{aligned}$$

and Bonferroni test has no power

Can we do better than this test? The optimal test given by Neyman-Pearson lemma for the simple hypotheses

$$H_0 : \mu_j = 0 \text{ for all } j$$
$$H_1 : \{\mu_j\} \sim \pi$$

where π selects a coordinate $\mathcal{J}$ uniformly and sets $\mu_{\mathcal{J}} = c_m$ with all other $\mu_j = 0$.

However, even the optimal likelihood ratio test fails when $c_m = (1 - \epsilon)\sqrt{2 \log m}$:

$$\text{pr}_1(\text{type II error}) \to 1 - \alpha$$

In summary, there is no test that is asymptotically able to distinguish between the null and alternative hypotheses when the mean of the needle in the haystack, c_m, is smaller than the $\sqrt{2 \log m}$ threshold

MinP test

Let $p_j = 1 - \Phi(Y_j)$ be the jth p-value, $j = 1, \ldots m$

Assume $p_1, \ldots, p_m$ i.i.d. Uniform$(0, 1)$ under H_0

The MinP test is based on the minimum p-value

$$p_{\min} = \min(p_1, \ldots, p_m) \overset{H_0}{\sim} \text{Beta}(1, m)$$

The MinP test rejects H_0 if $p_{\min} \leq 1 - (1 - \alpha)^{\frac{1}{m}}$ and has size α:

$$\begin{aligned} \text{pr}_0(p_{\min} \leq 1 - (1 - \alpha)^{\frac{1}{m}}) &= 1 - \text{pr}_0\left(\bigcap_{j=1}^{m} \{p_j > 1 - (1 - \alpha)^{\frac{1}{m}}\} \right) \\ &= 1 - [(1 - \alpha)^{\frac{1}{m}}]^m = \alpha \end{aligned}$$

Bonferroni method

Assume that p_j is a valid p-value under H_0, i.e.

$\text{pr}(P_j \leq u; H_0) \leq u$ for all $u \in (0, 1)$

The Bonferroni method (Bonferroni, 1936) rejects H_0 if $p_{\min} \leq \alpha/m$:

$$\begin{aligned} \text{pr}_0(p_{\min} \leq \alpha/m) &= \text{pr}_0\Big(\bigcup_{j=1}^{m}\{p_j \leq \alpha/m\}\Big) \\ &\leq \sum_{j=1}^{m}\text{pr}_0\Big(p_j \leq \alpha/m\Big) \\ &= m\frac{\alpha}{m} = \alpha \end{aligned}$$

An appealing property of Bonferroni's method is that it controls the Type I error rate even when the p-values $p_1, \ldots, p_m$ are arbitrarily dependent.

Kolmogorov-Smirnov test

Empirical cdf $\hat{F}_m(t) = \dfrac{\sum_{j=1}^{m} \mathbb{1}\{p_j \leq t\}}{m}$ for $t \in [0,1]$.

Assume $p_1, \ldots, p_m$ i.i.d. Uniform$(0,1)$ under H_0. Then

$$m\hat{F}_m(t) \overset{H_0}{\sim} \text{Binomial}(m, t)$$

Kolmogorov (one-sided) test statistic (Kolmogorov, 1933) is

$$T_{\text{KS}} = \sup_{t \in (0,1)} \{\hat{F}_m(t) - t\}$$

A useful inequality developed by Massart (1990) shows that

$$\text{pr}_0(T_{\text{KS}} \geq u) \leq e^{-2mu^2}$$

for $u \geq \sqrt{\log 2/2m}$

Tukey's higher criticism

Number of significant tests at level α

$$\frac{\text{observed} - \text{expected}}{\text{standard deviation}} = \frac{m\hat{F}_m(\alpha) - m\alpha}{\sqrt{m\alpha(1-\alpha)}}$$

Tukey's higher criticism statistic (Tukey, 1976; Donoho and Jin, 2004) is

$$T_{\text{hc}} = \max_{\alpha \leq \alpha_0} \frac{\hat{F}_m(\alpha) - \alpha}{\sqrt{\alpha(1-\alpha)/m}}$$

Sparse mixture

Assume that

$$\begin{aligned} H_0 &: Y_j \overset{i.i.d}{\sim} N(0,1) \\ H_1 &: Y_j \overset{i.i.d}{\sim} \pi_0 N(0,1) + \pi_1 N(\mu,1) \end{aligned}$$

where $\pi_0 + \pi_1 = 1$

Asymptotic analysis with

$$\begin{aligned} \pi_1(m) &= m^{-\beta} & \frac{1}{2} < \beta < 1 \\ \mu(m) &= \sqrt{2r \log m} & 0 < r < 1 \end{aligned}$$

Needle in a haystack problem: $\beta = 1$ and $r = 1$

If π_1 and μ were known, then the optimal test would be the likelihood ratio test

Detection boundary

$$\rho(\beta) = \begin{cases} \beta - \frac{1}{2} & \text{if } \frac{1}{2} < \beta \leq \frac{3}{4} \\ (1 - \sqrt{1-\beta})^2 & \text{if } \frac{3}{4} \leq \beta < 1 \end{cases}$$

If $r > \rho(\beta)$, then the Neyman-Pearson optimal test has full power. Higher criticism also has full power, i.e.

$$\text{pr}_1(\text{reject } H_0) \to 1 \quad m \to \infty$$

without knowledge of π_1 and/or μ

If $r < \rho(\beta)$, then the Neyman-Pearson optimal test has no power.

Bonferroni method has suboptimal threshold if $\beta \in (1/2, 3/4)$

$$\rho_{\text{Bonferroni}}(\beta) = \quad (1 - \sqrt{1-\beta})^2 \quad \text{if } \frac{1}{2} < \beta < 1$$

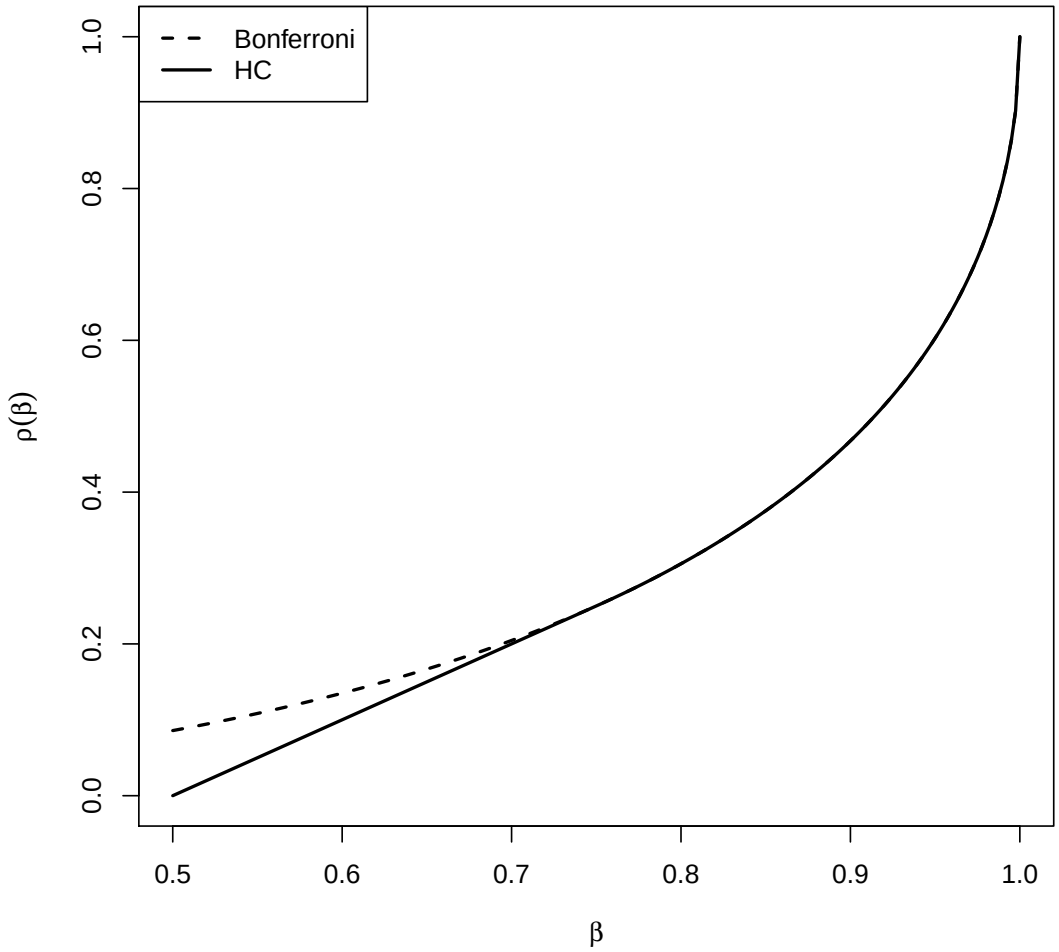

Bonferroni
HC
ρ(β)
β
0.0
0.2
0.4
0.6
0.8
1.0
0.5
0.6
0.7
0.8
0.9
1.0

Table of Contents

In a single test, the probability of making a type I error is bounded by α, conventionally set at 0.05

Problems arise, however, when researchers do not perform a single hypothesis test but many of them

There are many ways of dealing with type I errors. We will focus on three types of multiple testing methods:

1. those that control the *FamilyWise Error Rate*
2. those that control the *False Discovery Rate*
3. those that estimate the *False Discovery Proportion* or make confidence intervals for it

Rejections

Suppose we have a collection $\mathcal{H} = \{H_1, \ldots, H_m\}$ of m null hypotheses.

An unknown number m_0 of these hypotheses is true, whereas the other $m_1 = m - m_0$ is false. The proportion of true hypotheses is $\pi_0 = m_0/m$

The collection of true hypotheses is $\mathcal{T} \subseteq \mathcal{H}$ and of false hypotheses is $\mathcal{F} = \mathcal{H} \setminus \mathcal{T}$

The goal of a multiple testing procedure is to choose a collection $\mathcal{R} \subseteq \{H_1, \ldots, H_m\}$ of hypotheses to reject. If we have p-values $p_1, \ldots, p_m$ for $H_1, \ldots, H_m$, a natural choice is

$$\mathcal{R} = \{H_i : p_i \leq c\}$$

rejecting all hypotheses with a p-value below a critical value c

Errors

Ideally, the set of rejected hypotheses $\mathcal{R}$ should coincide with the set $\mathcal{F}$ of false hypotheses as much as possible. However, two types of error can be made:

Type I errors: true hypotheses that we rejected, i.e. $\mathcal{R} \cap \mathcal{T}$

Type II errors: false hypotheses that we failed to reject, i.e. $\mathcal{F} \setminus \mathcal{R}$

Rejected hypotheses are sometimes called *discoveries*, hence the terms *true discovery* and *false discovery* are sometimes used for correct and incorrect rejections

Type I errors

Type I errors are traditionally considered more problematic than type II errors

If a rejected hypothesis allows publication of a scientific finding, a type I error brings a false discovery, and the risk of publication of a potentially misleading scientific result

Type II errors, on the other hand, mean missing out on a scientific result. Although unfortunate for the individual researcher, the latter is, in comparison, less harmful to scientific research as a whole

2×2 table

We can summarize the numbers of errors in a contingency table:

	true	false	total
rejected	V	U	R
not rejected	$m_0 - V$	$m_1 - U$	$m - R$
total	m_0	m_1	m

We can observe m and $R = |\mathcal{R}|$, but all quantities in the first two columns of the table are unobservable

False Discovery Proportion

The False Discovery Proportion (FDP) Q is defined as

$$Q = \frac{V}{\max(R, 1)} = \begin{cases} V/R & \text{if } R > 0 \\ 0 & \text{otherwise,} \end{cases}$$

the proportion of false rejections among all rejections, defined as o if no rejections are made

FamilyWise Error Rate and False Discovery Rate

$$\text{FWER} = \text{pr}(V > 0) = \text{pr}(Q > 0)$$

the probability that the rejections contains any Type I error

$$\text{FDR} = \text{E}(Q)$$

the expected proportion of Type I errors among the rejections

We say that FWER or FDR is *controlled* at level α when the set $\mathcal{R}$ is chosen in such a way that the corresponding aspect of the distribution of Q is guaranteed to be at most α, i.e.

$$\text{FWER} \leq \alpha \quad \text{or} \quad \text{FDR} \leq \alpha$$

FWER $\geq$ FDR

The two error rates FDR and FWER are related. Because $0 \leq Q \leq 1$, we have $Q \leq \mathbb{1}\{Q > 0\}$ and

$$\mathrm{E}(Q) \leq \mathrm{P}(Q > 0)$$

which means that FWER control implies FDR control

If all hypotheses are true, FDR and FWER are identical; because $R = V$ in this case, Q is a Bernoulli variable, and

$$\mathrm{E}(Q) = \mathrm{P}(Q > 0)$$

Both FDR and FWER are proper generalizations of the concept of Type I error to multiple hypotheses: if $m = 1$, the two error rates are identical and equal to the Type I error rate

$m = 100$, $m_0 = 80$, $Y_i \sim N(\mu_i, 1)$, $\mu_i = 0$ if H_i true, $\mu_i = 2$ otherwise

	1	2	3	4	5	6	7	8	9	10
R	20	17	23	16	20	16	15	17	20	17
V	4	5	6	5	5	3	3	5	7	4
$\mathbb{1}\{V > 0\}$	1	1	1	1	1	1	1	1	1	1
V/R	0.20	0.29	0.26	0.31	0.25	0.19	0.20	0.29	0.35	0.24

Reject H_i if $p_i \leq 0.05$ gives FWER = 0.984 and FDR = 0.232

Null p-values

All methods we will consider start from a collection of p-values $p_1, \ldots, p_m$, one for each hypothesis tested.

We call these p-values *raw* as they have not been corrected for multiple testing yet

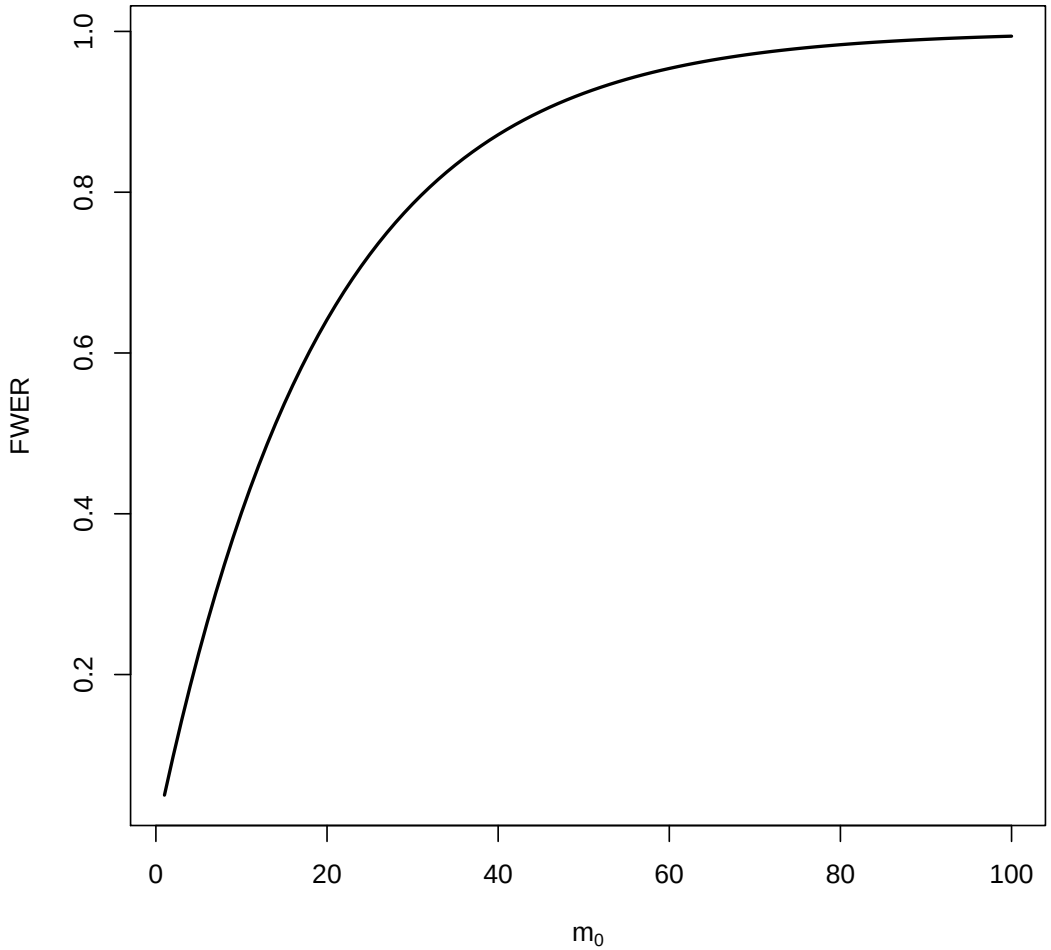
Assumptions on the p-values often involve only the p-values of true hypotheses. We denote these *null* p-values by

$$q_1, \ldots, q_{m_0}$$

Null p-values are assumed to be *valid* in the sense

$$\mathrm{P}(q_i \leq u) \leq u$$

with equality when $q_i \sim \mathrm{Uniform}(0, 1)$



Assume $q_1, \ldots, q_{m_0}$ i.i.d. Uniform$(0, 1)$.

Then $\mathcal{R} = \{H_i : p_i \leq 0.05\}$ has FWER $= 1 - (1 - 0.05)^{m_0}$

Expected number of Type I errors

Consider the expected number of type I errors $\mathrm{E}(V)$ (also called Per Family Error Rate, PFER). By Markov's inequality

$$\mathrm{pr}(V > 0) \leq \mathrm{E}(V)$$

we obtain

$$\mathrm{FDR} \leq \mathrm{FWER} \leq \mathrm{PFER}$$

If we consider

$$\mathcal{R} = \{H_i : p_i \leq c\}$$

then

$$V = \sum_{i=1}^{m_0} \mathbb{1}\{q_i \leq c\}$$

Assume $q_i \sim \text{Uniform}(0,1)$ for $i = 1, \ldots, m_0$. Then

$$\begin{aligned}
\text{E}(V) &= \sum_{i=1}^{m_0} \mathbb{E}(\mathbb{1}\{q_i \leq c\}) = m_0 c \\
\text{Var}(V) &= \sum_{i=1}^{m_0} \sum_{j=1}^{m_0} \text{Cov}(\mathbb{1}\{q_i \leq c\}\mathbb{1}\{q_j \leq c\}) = m_0 c(1-c) + \\
&+2 \sum_{i<j} \left[\text{pr}(\mathbb{1}\{q_i \leq c, q_j \leq c\}) - \text{pr}(\mathbb{1}\{q_i \leq c\})\text{pr}(\mathbb{1}\{q_j \leq c\}) \right] \\
&= m_0 c(1-c) + 2 \sum_{i<j} \left[\text{pr}(\mathbb{1}\{q_i \leq c, q_j \leq c\}) - c^2 \right]
\end{aligned}$$

where the first term represents the independence structure and last term the *overdispersion*

Table of Contents

Bonferroni method

$$\mathcal{R}_{\text{Bonferroni}} = \left\{ H_i : p_i \leq \frac{\alpha}{m} \right\}$$

Assume that null p-values are valid. Bonferroni method controls the PFER at level α:

$$\mathrm{E}(V) = \sum_{i=1}^{m_0} \mathrm{pr}\left(q_i \leq \frac{\alpha}{m} \right) \leq m_0 \frac{\alpha}{m}$$

Bonferroni conservativeness

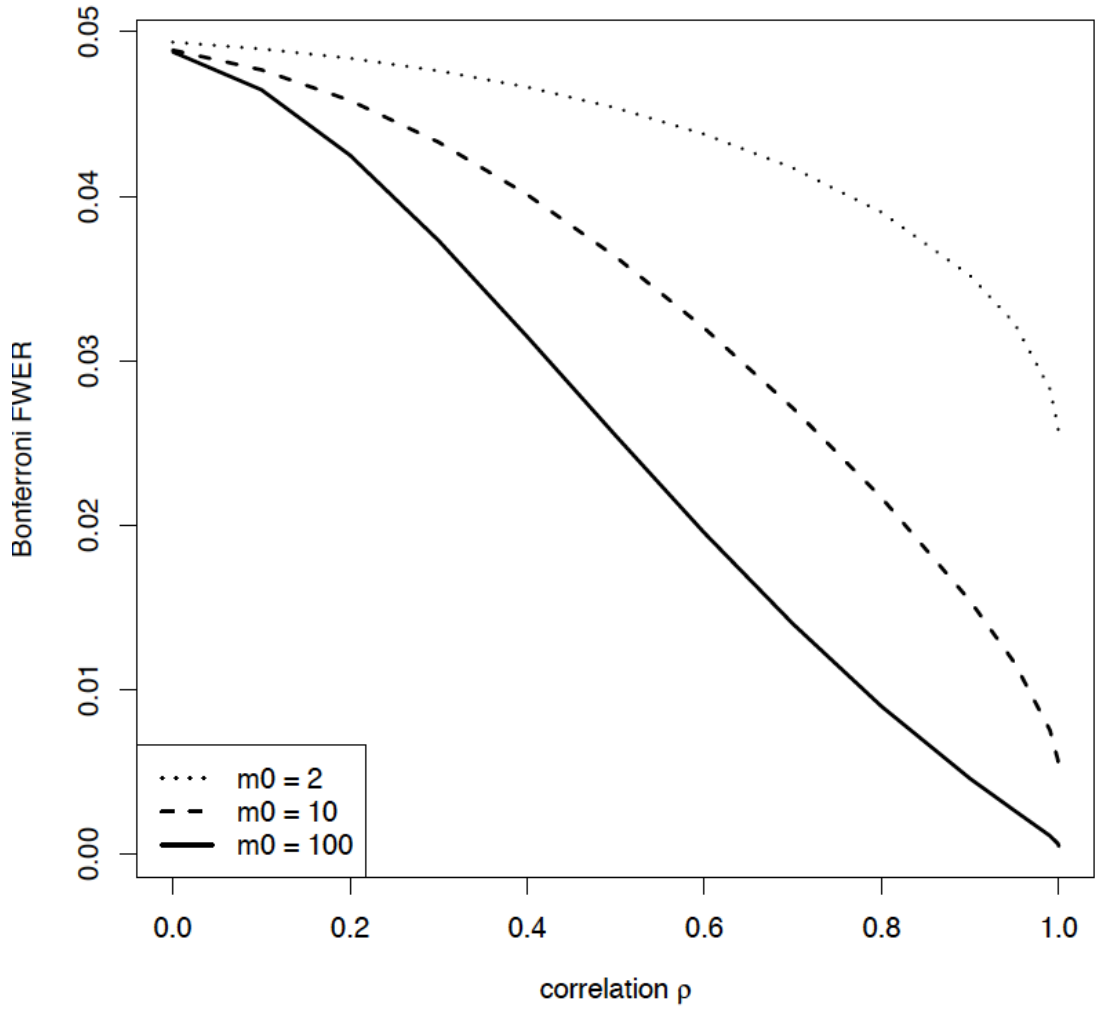
$$\mathrm{pr}\Big(\bigcup_{i=1}^{m_0}\{q_i \leq \frac{\alpha}{m}\}\Big) \leq \sum_{i=1}^{m_0}\mathrm{pr}\Big(q_i \leq \frac{\alpha}{m}\Big) \leq m_0\frac{\alpha}{m}$$

The two inequalities indicate in which cases the Bonferroni method can be *conservative*, i.e. FWER $< \alpha$

The right-hand one shows that Bonferroni controls the FWER at level $\pi_0\alpha$, where $\pi_0 = m_0/m$. If there are many false null hypotheses, Bonferroni will be conservative

The left-hand inequality is due to Boole's inequality, i.e. for any collection of events $E_1, \ldots, E_k$, we have $\mathrm{P}\big(\bigcup_{i=1}^{k} E_i\big) \leq \sum_{i=1}^{k}\mathrm{P}(E_i)$. This inequality is a strict one in all situations except the one in which all events $\{q_i \leq \alpha/m\}$ are disjoint. With independent p-values, the conservativeness is present but very minor

Much more serious conservativeness can occur if p-values are positively correlated. Suppose that the correlation matrix is such that $\{\Sigma\}_{ij} = \rho$ for $i \neq j$



Adjusted p-values

When testing a single hypothesis, we often do not only report whether a hypothesis was rejected, but also the corresponding p-value

By definition, the p-value is the smallest chosen α-level of the test at which the hypothesis would have been rejected

The direct analogue of this in the context of multiple testing is the *adjusted* p-value, defined as the smallest α level at which the multiple testing method would reject the hypothesis.

For the Bonferroni method, this adjusted p-value is given by

$$\tilde{p}_i = \min(mp_i, 1)$$

where p_i is the raw p-value

Sidak method

$$\mathcal{R}_{\text{Sidak}} = \{H_i \in \mathcal{H} : p_i \leq 1 - (1-\alpha)^{1/m}\}$$

Assume that null p-values are i.i.d. Uniform$(0, 1)$. Sidak method controls the FWER at level α.

$\text{pr}\Big(\bigcup_{i=1}^{m_0}\big\{q_i \leq c\big\}\Big) = 1 - \prod_{i=1}^{m_0}\text{P}\Big(q_i > c\Big) = 1 - (1-c)^{m_0}$ which equals α for $c = 1 - (1-\alpha)^{1/m_0}$. Since we don't know m_0, we can use

$$1 - (1-\alpha)^{1/m} \leq 1 - (1-\alpha)^{1/m_0}$$

The ratio between the Bonferroni and Sidak critical values

$$\frac{\alpha/m}{1-(1-\alpha)^{1/m}} \overset{m\to\infty}{\to} \frac{-\log(1-\alpha)}{\alpha}$$

which evaluates to only 1.026 for $\alpha = 0.05$

Holm method

Holm's method is a sequential variant of the Bonferroni method that always rejects at least as much as Bonferroni's method, and often a bit more, but still has valid FWER control under the same assumptions

In the first step, all hypotheses with p-values at most α/h_0 are rejected, with $h_0 = m$ just like in the Bonferroni method. Suppose this leaves h_1 hypotheses unrejected. Then, in the next step, all hypotheses with p-values at most α/h_1 are rejected, which leaves h_2 hypotheses unrejected, which are subsequently tested at level α/h_2. This process is repeated until either all hypotheses are rejected, or until a step fails to result in any additional rejections

Holm algorithm

Step 0 Begin by ordering the p-values in ascending order

$$p_{(1)} \leq p_{(2)} \leq \cdots \leq p_{(m)}$$

and let $H_{(1)}, H_{(2)}, \ldots, H_{(m)}$ be the corresponding hypotheses

Step 1 : If $p_{(1)} \leq \alpha/m$ reject $H_{(1)}$ and go to Step 2. Stop otherwise

Step 2 : If $p_{(2)} \leq \alpha/(m-1)$ reject $H_{(2)}$ and go to Step 3. Stop otherwise

...

Step j : If $p_{(j)} \leq \alpha/(m-j+1)$ reject $H_{(j)}$ and go to Step $j+1$. Stop otherwise

...

Step m : If $p_{(m)} \leq \alpha$ reject $H_{(m)}$