Weak Control

a testing procedure controls the FWER weakly if it is controls the FWER under the global null (i.e when all $H_{0,i}$ are true)

Two-step procedure: (Fisher, 1934)

1. Global test for $H_0 = \bigcap_{i=1}^{n} H_{0,i}$
2. Test each hypothesis at level α

Example: 1. Reject H_0 if $\min p_i \le \frac{\alpha}{n}$

2. If H_0 is rejected $\Rightarrow$ reject $H_{0,i}$ if $p_i \le \alpha$

Note: This procedure does not control FWER in a strong sence.

Example: $X_i \sim N(\mu_i, 1)$ independent

$H_{0,i}: \mu_i = 0$

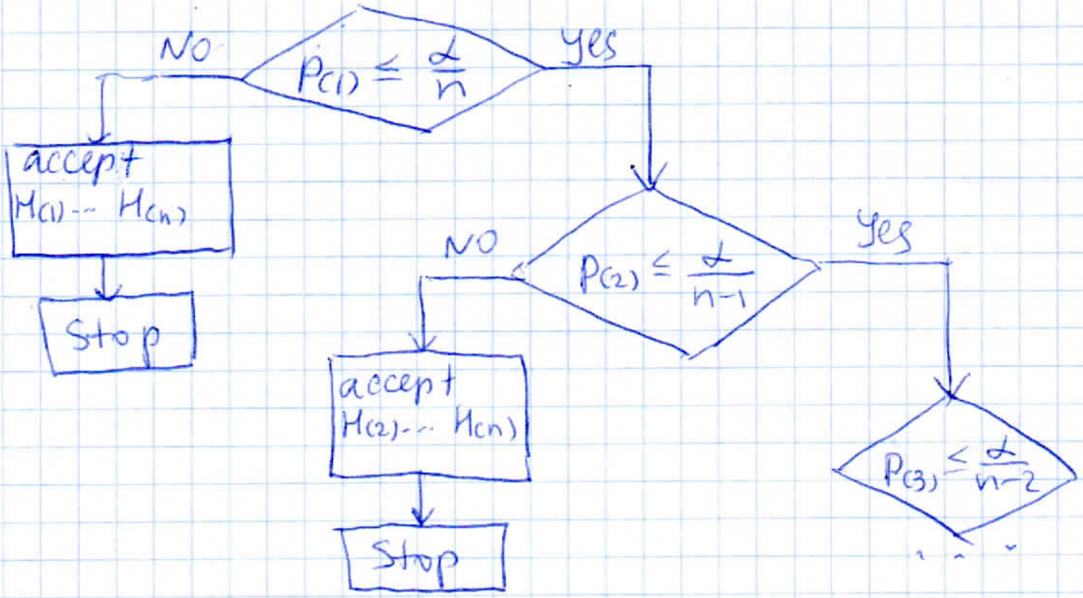
Let μ_1 is very large $\Rightarrow$ reject H_0

$\Rightarrow$ we apply α-level test to all the others

$\Rightarrow$ we maka $\approx \alpha n_0$ false discoveries :(

Holm's procedure (step-down procedure):

$$p_{(1)} \le p_{(2)} \le \dots \le p_{(n)}$$
$$H_{(1)} \quad H_{(2)} \quad \dots \quad H_{(n)}$$



Step i: if $p_{(i)} \le \frac{\alpha}{n-i+1}$ then reject $H_{(i)}$, go to the step $(i+1)$

else accept $H_{(i)} \dots H_{(n)}$ and stop

...

Step n: if $p_{(n)} \le \alpha$ then reject $H_{(n)}$

else accept $H_{(n)}$.

The procedure stops the first time when

$$p_{(i)} \ge \alpha_i = \frac{\alpha}{n-i+1}$$

Note Holm's procedure is less conservative than Bonferroni's procedure (which rejects all $H_{0,i}$: $p_i < \frac{\alpha}{n}$)

Theorem 3. Holm's procedure controls the FWER strongly (without assumption of independence)

⌈ Let $i_0 = \min\{i : H_{0,i} \text{ is true}\}$

$$\underbrace{\begin{matrix} p_{(1)} \le \dots & \le p_{(i_0-1)} \le \\ H_{(1)} & H_{(i_0-1)} \end{matrix}}_{H_{1i} \text{ are true}} \quad \underbrace{\begin{matrix} p_{(i_0)} \le & p_{(i_0+1)} \le & \dots & \le p_{(n)} \\ H_{(i_0)} & H_{(i_0+1)} & \dots & H_{(n)} \end{matrix}}_{H_{0i} \text{ are true and probably a few } H_{1i}}$$

We have n_0 hypotheses when H_{0i} are true.

$\Rightarrow \quad n - i_0 + 1 \ge n_0 \quad \Rightarrow \quad i_0 \le n - n_0 + 1$

Then $\{V \ge 1\} \subset \{p_{(i_0)} \le \underbrace{\frac{\alpha}{n-i_0+1}}_{\le \frac{\alpha}{n_0}}\} \subset \{p_{(i_0)} \le \frac{\alpha}{n_0}\}$

$$\Rightarrow P\{V \ge 1\} \le P(\min_{i \in \mathcal{I}_0} p_i \le \frac{\alpha}{n_0}) \le \sum_{i \in \mathcal{I}_0} P(p_i \le \frac{\alpha}{n_0}) =$$

$$= \sum_{i \in \mathcal{I}_0} \frac{\alpha}{n_0} = n_0 \frac{\alpha}{n_0} = \alpha \quad ⌋$$

Global Testing vs. Multiple Testing

global testing procedures:

- Bonferroni: reject H, if $p_{(1)} \le \frac{\alpha}{n}$
- Simes (independence): reject H if $p_{(1)} \le \frac{\alpha}{n}$ or $p_{(2)} \le \frac{2\alpha}{n} \dots$ or or $p_{(i)} \le \frac{i\alpha}{n}$ or $\dots$ $p_{(n)} \le \alpha$
- Fisher (independence) reject H if $\sum_i 2 \log p_i^{-1} \ge \chi^2_{2n}(1-\alpha)$

Multiple testing

Our goal is to control FWER: we want procedures for which $FWER \le \alpha$.

- Bonferroni: reject H_i if $p_i \le \frac{\alpha}{n}$ controls FWER
- Sims: if $\exists j: p_{(j)} \le \frac{j\alpha}{n} \Rightarrow$ reject $H_{(i)}$ for $i \le j$.
  (independence)
  does not control FWER
  $\Longleftrightarrow$ $i_0 = \max\{i : p_{(i)} \le \frac{i\alpha}{n}\} \Rightarrow$ reject $H_{(i)}$ for $\forall i \le i_0$

Example: $p_{(1)} \le \frac{\alpha}{n}$; $p_{(2)} \le \frac{2\alpha}{n}$, ... Let $n_0 = n-1$
let $p_{(1)}$ is too small $\Rightarrow H_{0(1)}$ is rejected (correct decision)
. Then we have $n-1$ hypotheses $H_{(2)} \dots H_{(n)}$ and the smalest p-value is compared with $\frac{2\alpha}{n}$. But to control FWER $p_{(2)}$ should compare with $\frac{\alpha}{n-1}$
FWER in this case will be $\approx 2\alpha$

Closure Principle

n hypotheses: $\{H_i\}_{i=1}^{n}$

Let us define:

$$H_{ij} = H_i \cap H_j = \{p_i, p_j \sim \mathcal{U}[0,1]\}$$

$$H_I = \bigcap_{i \in I} H_i \quad , \quad I \subset \{1, \dots, n\}$$

Definition: the closure of the famili $\{H_i\}_{i=1}^{n}$ is $\{H_I : \forall I \subset \{1 .. n\}\}$

Example: $n = 4$.

$$H_{1234}$$

$$H_{123} \quad H_{124} \quad H_{134} \quad H_{234}$$

$$H_{12} \quad H_{13} \quad H_{14} \quad H_{23} \quad H_{24} \quad H_{34}$$

$$H_1 \quad H_2 \quad H_3 \quad H_4$$

Let φ is the test that is generated by a global testing procedure (for example, Bonferroni, Fisher, Simes, χ^2 etc.)

We have set of hypotheses $\{H_i : i \in I\}$, we apply φ_I for testing the global null $H_I = \bigcap_{i \in I} H_i$ (assume that φ_I is α-level test for testing H_I, H_I is rejected, if $\varphi_I = 1$.)

$$P(\varphi_I = 1 / H_I) \leq \alpha$$

The Closure procedure:

If H_J is rejected for all $J : I \subseteq J$ (at level α) $\Rightarrow$ H_I is rejected

Example $n = 4$

$$
\begin{array}{cccccc}
 & & H_{1234} & & & \\
H_{123} & H_{124} & H_{134} & H_{234} & & \\
H_{12} & H_{13} & H_{14} & H_{23} & H_{24} & H_{34} \\
 & H_1 & H_2 & H_3 & H_4 &
\end{array}
$$

- H_1 is rejected because $\forall J \subset \{1,2,3,4\}$ s.t. $\{1\} \in J$ H_J is rejected
- H_2 is not rejected, because H_{234}, H_{23}, H_{24} are not rejected.

Theorem 1: The closure principle controls the FWER strongly.

Г $\mathcal{H}_0 = \{ H_i : H_{0i} \text{ is true} \}$ - true nulls

assume that $\mathcal{H}_0 \neq \emptyset$, otherwise we cannot make false discoveries.

$A = \{ V \geq 1 \}$ - we have at least one false discovery

$B = \{ \text{reject } H_{\mathcal{H}_0} \}$ - we reject the set of true nulls

For the closure procedure, $A \cap B = A$
(see example, if we reject H_{04}, for example, then, for the cl. pr. we reject $H_{0,234}$). So

$$P(A) = P(A \cap B) = \underbrace{P(B)}_{= \alpha} \underbrace{P(A/B)}_{\leq 1} \leq \alpha \quad ┘$$

$\Rightarrow$ closure principle provides us with a generic recipe for translating global testing procedures into valid FWER controlling procedures. Only issue is that this is not applicable in practice. For example, let $n = 10\,000 \Rightarrow$ we should test $2^{10.000}$ hypotheses. Not possible at all to test all this products even for the simple tests like Bonferroni.

The question is if we can use the closure procedure to construct some easy test which would be closure of some well-known global procedures.

Closing Bonferroni

We use Bonferroni's procedure to generate φ_I:

$$\varphi_I = 1 \quad \text{iff} \quad \min_{i \in I} p_i \le \frac{\alpha}{|I|}$$

1. $p_{(1)} \le \dots \le p_{(j)} \le \dots \le p_{(n)}$

$H_{(1)} \dots H_{(j)} \dots H_{(n)}$

$\ \ \| \qquad\quad \| \qquad\quad \|$

$H_{i_1} \quad H_{i_j} \quad H_{i_n}$

Consider an index set I:

$p_{(j)} = \min\{p_i : i \in I\}, I \subset \{i_j \dots i_n\}, i_j \in I$

Let $I_{(j)+} = \{i_j \dots i_n\}$ - the index set corresponding to the $n-j+1$ largest p-values: $p_{(j)}, \dots, p_{(n)}$.

Then $\varphi_{I_{(j)}^+} = 1$ implies that $\varphi_I = 1$.

$\ulcorner$ $\varphi_{I_{(j)}^+} = 1 \iff p_{(j)} \le \frac{\alpha}{n-j+1}$

$p_{(j)}$ is the smallest p-value with index in I

$\Rightarrow |I| \le n-j+1$

$\Rightarrow p_{(j)} \le \frac{\alpha}{n-j+1} \le \frac{\alpha}{|I|}$ $\lrcorner$

2. $H_{(j)}$ is rejected $\iff \varphi_{I_{(1)}^+} = 1, \dots, \varphi_{I_{(j)}^+} = 1 \iff$

$\iff p_{(1)} \le \frac{\alpha}{n}, \dots, p_{(j)} \le \frac{\alpha}{n-j+1}$

Γ (⟹) $H_{(j)}$ is rejected $\Rightarrow \bigcap_{i=1}^{n} H_{(i)}, \dots, \bigcap_{i=j}^{n} H_{(i)}$ are rejected $\Rightarrow \varphi_{I^+_{(1)}} = 1, \dots, \varphi_{I^+_{(j)}} = 1$

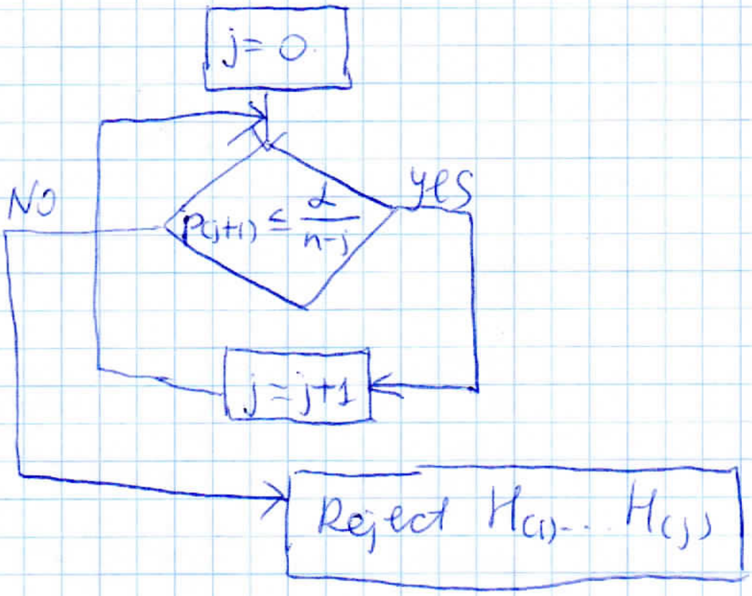
(⟸) $\varphi_{I^+_{(1)}} = 1, \dots, \varphi_{I^+_{(j)}} = 1$.

$\varphi_{I^+_{(j)}} = 1 \Rightarrow \forall I : I \subset \{i_j, \dots, i_n\},\ i_j \in I : \varphi_I = 1$

We can take $I = \{i_j\} \Rightarrow \varphi_{i_j} = 1 \Rightarrow$

$\Rightarrow H_{(j)}$ is rejected ⌋

Procedure Closed Bonferroni:



Closing Simes p-values are independent!

Simes test statistic:

$$\varphi_I = 1 \quad \text{iff} \quad \& \begin{cases} P_{(1,I)} \le \frac{\alpha}{|I|} \\ P_{(2,I)} \le \frac{2\alpha}{|I|} \\ \dots \\ P_{(|I|,I)} \le \frac{|I|\alpha}{|I|} = \alpha \end{cases}$$

Here we derive a simple procedure that is strictly more conservative than the closure of Simes. Our procedure will also control FWER under independence.

Lemma 2.

$$\begin{array}{ccccccccc} p_{(1)} \le & p_{(2)} \le & \dots & \le p_{(j)} \le & \dots & \le p_{(j')} \le & \dots & \le p_{(n)} \\ H_{(1)} & H_{(2)} & & H_{(j)} & & H_{(j')} & & H_{(n)} \\ H_{i_1} & H_{i_2} & & H_{i_j} & & H_{i_{j'}} & & H_{i_n} \end{array}$$

index set I Suppose that:

(a) $i_j \in I$

(b) $\exists j' \ge j$ such that

$$p_{(j')} \le \frac{\alpha}{n-j'+1}$$

Then $\varphi_I = 1$ for the Simes test φ_I.

⌈ Let $k := \max\{\ell : i_\ell \in I,\ \ell \le j'\}$. By (a) k exists and finite. Then

$$p_{(k)} \le p_{(j')} \le \frac{\alpha}{n-j'+1} \le \left| \begin{array}{l} |\{i_{j'+1}, \dots, i_n\}| = n-j' \\ \Rightarrow |\{i_{j'+1}, \dots, i_n\} \cap I| \le n-j' \end{array} \right| \le$$

$$\le \frac{\alpha}{1 + |\{i_{j'+1}, \dots, i_n\} \cap I|} = |\text{by definition of } k| =$$

$$= \frac{\alpha}{|\{i_k, \dots, i_n\} \cap I|} \underset{*}{\le} \frac{|\{i_1, \dots, i_k\} \cap I|}{|I|} \alpha$$

$*$ ⌈ by definition $i_k \in I$.

Let $a = |\{i_1 \dots i_{k-1}\} \cap I|$, $b = |\{i_{k+1} \dots i_n\} \cap I|$

then $a + b + 1 = |I| \Rightarrow |I| \le ab + a + b + 1 =$

$= (a+1)(b+1)$

$$\Rightarrow \frac{1}{b+1} \le \frac{a+1}{|I|} \ \rfloor$$

By definition of Simes procedure $\varphi_I = 1$ ⌋