

Lecture 2: Advanced multiplicity correction

Adaptive Designs and Multiple Testing Procedures for Clinical Trials

October 2019

Outline

- 1 Hierarchical testing
- 2 Semi-parametric procedures
- 3 Closed testing
- 4 Graphical approaches
- 5 Multiplicity in practice

Hierarchical testing

Hierarchical test procedures

- Suppose hypotheses can be ordered into a *pre-specified* hierarchy H_1, \dots, H_K , before the data are observed
 - ▶ Clinical relevance
 - ▶ Dose concentration
 - ▶ Time sequence
- Hierarchical test procedures: tests the hypotheses in the pre-defined hierarchical order
 - ▶ Fixed sequence procedure
 - ▶ Fallback procedure

Fixed sequence procedure

- Each hypothesis is tested in the pre-specified sequence at level α until the first non-rejection

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- *Rejection rule*
 - ▶ if $p_1 \leq \alpha$, reject H_1 and continue; else stop
 - ▶ if $p_2 \leq \alpha$ reject H_2 and continue; else stop
 - ▶ ...
 - ▶ if $p_k \leq \alpha$ reject H_k and continue; else stop

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 - ▶ ...
 - ▶ if $p_k \leq \alpha$ reject H_k and continue; else stop
- As soon as a hypothesis H_i cannot be rejected, $p_i > \alpha$, the procedure stops and all remaining hypotheses H_{i+1}, \dots, H_K are not rejected

Fixed sequence procedure

Advantages

- Simple procedure
- Optimal (maximises power) if previous hypotheses rejected

Disadvantages

- Ordering of testing sequence is critically important, and may be based on subjective information
- Minimises power if a previous hypothesis is not rejected
- Once a hypothesis is not rejected, no further testing is allowed

Fallback procedure

- Again test each hypothesis in the pre-specified sequence, but split the α between hypotheses
- Assign α_i to hypothesis H_i , where $\sum_i^k \alpha_i = \alpha$
- H_1 is tested at level $\alpha'_1 = \alpha_1$
- For $i \geq 2$, H_i is tested at level α'_i , where

$$\alpha'_i = \begin{cases} \alpha_i & \text{if } H_{i-1} \text{ is not rejected} \\ \alpha_i + \alpha'_{i-1} & \text{if } H_{i-1} \text{ is rejected} \end{cases}$$

- Test all hypotheses even if initial hypotheses are not rejected
- Fallback procedure is implemented in the `multxpert` R package

Example

- $\alpha = 0.025$
- p-values $p_1 = 0.03$, $p_2 = 0.004$, $p_3 = 0.01$
- For fallback procedure, suppose α split equally:
 $\alpha_1 = \alpha_2 = \alpha_3 = 0.025/3$

p-value	Fixed sequence	Fallback procedure
0.03	$\alpha = 0.025$	$\alpha'_1 = 0.025/3$

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Semi-parametric procedures

Šidák procedure

- Hypotheses H_1, \dots, H_K
- Aim to control the FWER at level α

Šidák procedure

- Hypotheses H_1, \dots, H_K
- Aim to control the FWER at level α
- Šidák (also known as Dunn–Šidák) procedure uses the adjusted significance level

$$\alpha_S = 1 - (1 - \alpha)^{1/K}$$

- More powerful than Bonferroni for $K > 1$
- However, only guaranteed to control the FWER for **independent** or **positively correlated** test statistics
 - ▶ e.g. appropriate for **many-to-one comparisons**, where a positive correlation is induced by the control group

Hochberg

- **Ordered** p -values $p_{(1)} < \dots < p_{(K)}$ with corresponding hypotheses $H_{(1)}, \dots, H_{(K)}$
- Uses same significance thresholds as the Holm procedure, but reversed (step-up rather than step-down)
- *Rejection rule*
 - ▶ If $p_{(K)} \leq \alpha$, reject $H_{(1)}, \dots, H_{(K)}$ and stop; else continue
 - ▶ If $p_{(K-1)} \leq \alpha/2$, reject $H_{(1)}, \dots, H_{(K-1)}$ and stop; else continue
 - ▶ ...
 - ▶ If $p_{(1)} \leq \alpha/K$, reject $H_{(1)}$ and stop
- Find largest i such that $p_{(i)} \leq \alpha/(K - i + 1)$ and reject all hypotheses $H_{(i)}, H_{(i+1)}, \dots, H_{(1)}$

Hochberg

- More powerful than Bonferroni and Holm
- Again, only guaranteed to control FWER under certain **correlation assumptions**
 - ▶ e.g. When test statistics are independent or positively correlated

Hommel

- *Rejection rule*

- ▶ Let j be the largest integer for which

$$p_{(K-j+i)} > \frac{i\alpha}{j}$$

for all $i = 1, \dots, j$

- ▶ If no such j exists, reject all hypotheses
- ▶ Otherwise, reject all $H_{(i)}$ with $p_{(i)} \leq \alpha/j$
- More powerful than Hochberg, but needs same distributional assumptions
- Hommel and Hochberg procedures are implemented in the `multxpt` R package

Closed testing

Closed test procedures

- General methodology to construct multiple testing procedures which strongly control the FWER
- Includes many well-known procedures as special cases

Closed test procedures

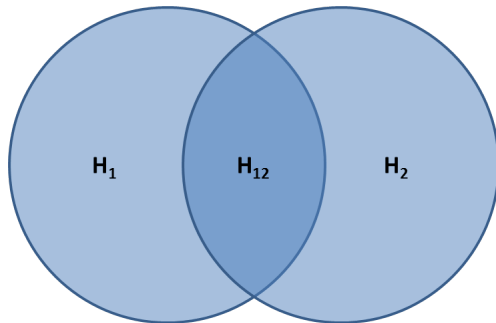
- General methodology to construct multiple testing procedures which strongly control the FWER
- Includes many well-known procedures as special cases
- Closed test procedures consider all *intersection hypotheses*

$$H_J = \bigcap_{i \in J} H_i, \quad J \subseteq \{1, \dots, K\}$$

- **Closure principle**: An individual hypothesis H_i is rejected at familywise level α only if every intersection hypothesis H_J with $i \in J$ is rejected at local level α

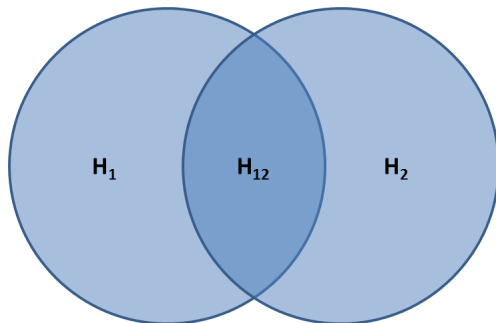
Closure principle

Venn diagram for $K = 2$ hypotheses



Closure principle

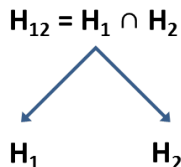
Venn diagram for $K = 2$ hypotheses



- Test $H_{12} = H_1 \cap H_2$ using Bonferroni or Dunnett etc. at level α
- Test H_1 and H_2 using a level α test

Closure principle

$K = 2$ hypotheses



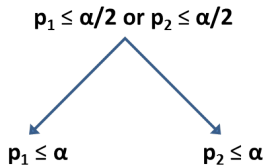
- Reject H_1 overall if H_{12} and H_1 are rejected locally at level α
- If $K > 2$, several intersection hypotheses have to be tested
- Different tests can be chosen for each (intersection) hypothesis

Closure principle

Holm

Holm's procedure is the closure principle applied to Bonferroni:

H_{12} is rejected if either $p_1 \leq \alpha/2$ **or** $p_2 \leq \alpha/2$

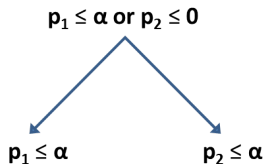


Closure principle

Fixed sequence procedure

Bonferroni could also be applied with unequal splitting of the significance level into α_1 and α_2 , where $\alpha_1 + \alpha_2 = \alpha$

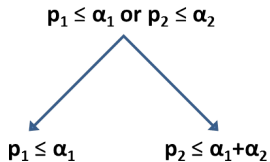
Setting $\alpha_1 = \alpha$ and $\alpha_2 = 0$ gives the *fixed sequence procedure*:



Closure principle

Fallback procedure

In general, we recover the *fallback procedure*:



Closure principle

$k = 3$ hypotheses

$$H_1 \cap H_2 \cap H_3$$

$$H_1 \cap H_2$$

$$H_1 \cap H_3$$

$$H_2 \cap H_3$$

$$H_1$$

$$H_2$$

$$H_3$$

Closure principle

Fixed sequence procedure with a-priori fixed order

$$H_1 \rightarrow H_2 \rightarrow H_3$$

$$H_1 \cap H_2 \cap H_3$$

$$p_1 \leq \alpha$$

$$H_1 \cap H_2$$

$$p_1 \leq \alpha$$

$$H_1 \cap H_3$$

$$p_1 \leq \alpha$$

$$H_2 \cap H_3$$

$$p_2 \leq \alpha$$

$$H_1$$

$$p_1 \leq \alpha$$

$$H_2$$

$$p_2 \leq \alpha$$

$$H_3$$

$$p_3 \leq \alpha$$

Closure principle

Holm

$$\begin{array}{c} H_1 \cap H_2 \cap H_3 \\ p_1 \leq \alpha/3 \text{ or } p_2 \leq \alpha/3 \text{ or } p_3 \leq \alpha/3 \end{array}$$

$$\begin{array}{c} H_1 \cap H_2 \\ p_1 \leq \alpha/2 \text{ or } p_2 \leq \alpha/2 \end{array}$$

$$\begin{array}{c} H_1 \cap H_3 \\ p_1 \leq \alpha/2 \text{ or } p_3 \leq \alpha/2 \end{array}$$

$$\begin{array}{c} H_2 \cap H_3 \\ p_2 \leq \alpha/2 \text{ or } p_3 \leq \alpha/2 \end{array}$$

$$\begin{array}{c} H_1 \\ p_1 \leq \alpha \end{array}$$

$$\begin{array}{c} H_2 \\ p_2 \leq \alpha \end{array}$$

$$\begin{array}{c} H_3 \\ p_3 \leq \alpha \end{array}$$

Closed test procedures

Advantages

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- Closed test procedures are more powerful than the procedures they are derived from

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- Any coherent multiple test controlling FWER is a closed test

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Disadvantages

- No natural point estimates or confidence intervals
- Can be a very large number of intersection hypotheses to test as k increases: worst-case is $2^K - 1$. However, shortcuts exist

Graphical approaches

Motivating example: Diabetes trial

- Trial compares two doses D_1 or D_2 against placebo in diabetes patients for two endpoints
 - ▶ Primary endpoint: HbA1c
 - ▶ Secondary endpoint: Body weight
- There is a natural order: a primary endpoint is more important than a secondary endpoint
 - ▶ We test the primary null hypothesis first; only if this is rejected do we test the secondary hypothesis

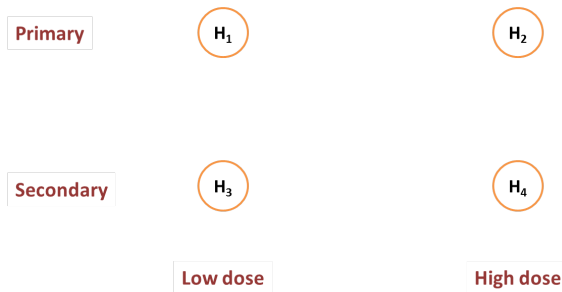
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 - ▶ We test the primary null hypothesis first; only if this is rejected do we test the secondary hypothesis
- Both doses are equally important

Motivating example: Diabetes trial

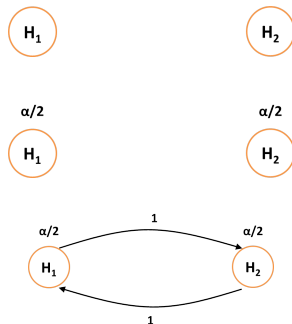
- *Objective*: test all four hypotheses under strong FWER while reflecting clinical objectives
- Standard multiple testing procedures do not reflect the relative importance of the two endpoints or the underlying structure
- In general, need test procedures that can deal with complex trial objectives and multiple structured hypotheses: **Graphical approaches** (also known as chain or sequentially rejective procedures)

Diabetes example



Graphical approaches

- 1 Hypotheses H_1, \dots, H_K represented as nodes
- 2 Split of significance level α into $(\alpha_1, \dots, \alpha_K)$
- 3 “ α propagation” through weighted, directed edges



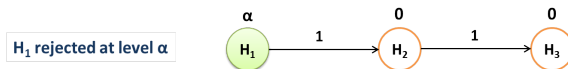
Graphical approaches

- Technical basis of the graphical approach: the graph defines a closed testing procedure with weighted Bonferroni tests for each intersection hypothesis
- Equivalent formulation of split of α using **weights** (w_1, \dots, w_K) where $\sum_{i=1}^K w_i = 1$ and $\alpha_i = \alpha w_i$.
- α -propagation: If a hypothesis H_i can be rejected at level α_i (i.e. $p_i \leq \alpha_i$), propagate its level α_i to the remaining (not yet tested) hypotheses, according to a prefixed rule, and continue testing with the updated α levels.

Examples

Fixed sequence procedure

- Assume $H_1 \rightarrow H_2 \rightarrow H_3$
- Example fixed sequence procedure:

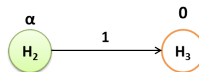


Examples

Fixed sequence procedure

- Assume $H_1 \rightarrow H_2 \rightarrow H_3$
- Example fixed sequence procedure:

H_2 rejected at level α



Examples

Fixed sequence procedure

- Assume $H_1 \rightarrow H_2 \rightarrow H_3$
- Example fixed sequence procedure:

H_3 not rejected at level α (stop)



Examples

- *Bonferroni*: no α -propagation (no edges between nodes)

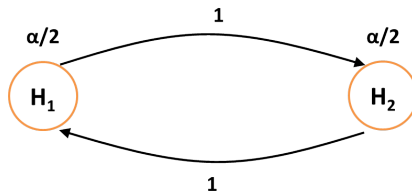


Examples

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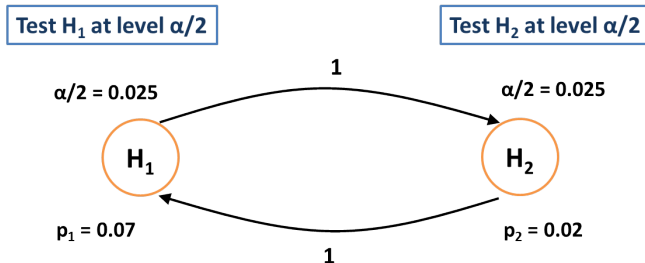


- *Holm*: includes α -propagation \rightarrow more powerful



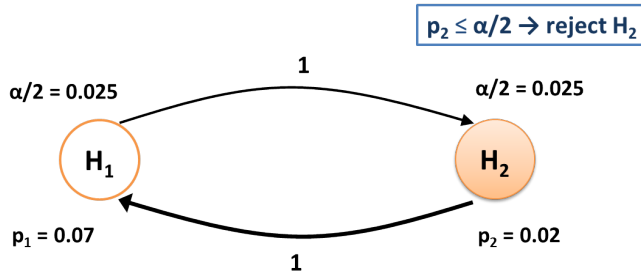
Examples

Holm procedure with $\alpha = 0.05$



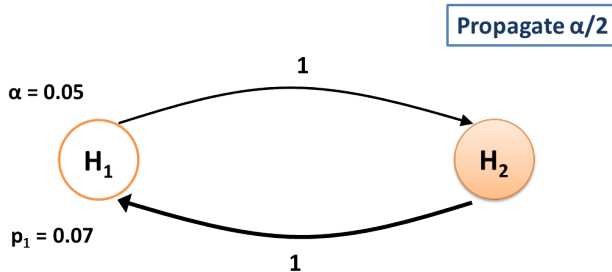
Examples

Holm procedure with $\alpha = 0.05$



Examples

Holm procedure with $\alpha = 0.05$



Examples

Holm procedure with $\alpha = 0.05$

Remove node for H_2

$\alpha = 0.05$



$p_1 = 0.07$

Examples

Holm procedure with $\alpha = 0.05$

Test H_1 at level α
 $p_1 > \alpha \rightarrow$ do not reject H_1

$\alpha = 0.05$

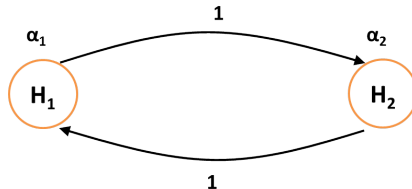


$p_1 = 0.07$

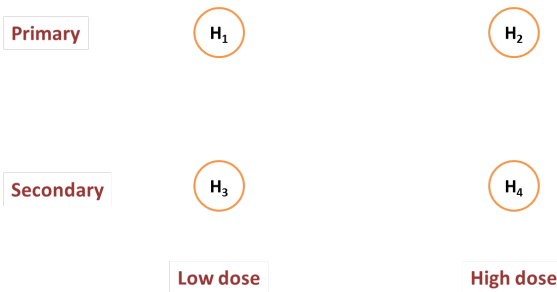
Examples

Weighted Holm procedure

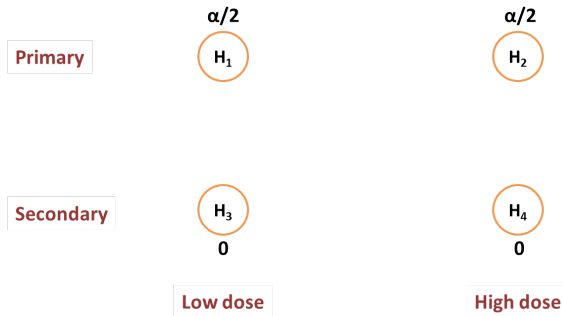
Use α_1, α_2 (where $\alpha_1 + \alpha_2 = \alpha$) instead of $\alpha_1 = \alpha_2 = \alpha/2$



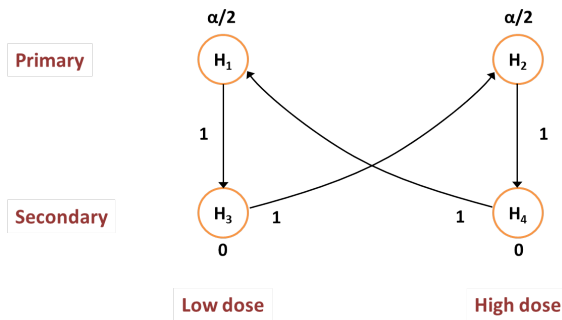
Diabetes example



Diabetes example



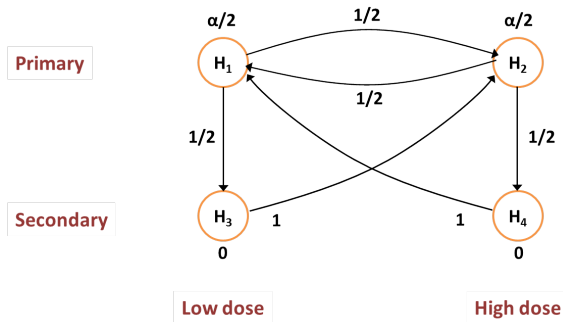
Diabetes example



$$\alpha = \begin{pmatrix} \frac{\alpha}{2} & \frac{\alpha}{2} & 0 & 0 \end{pmatrix} \quad \mathbf{G} = \begin{pmatrix} 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 1 \\ 0 & 1 & 0 & 0 \\ 1 & 0 & 0 & 0 \end{pmatrix}$$

(Based on the graphs in Maurer et al., 2011)

Diabetes example



$$\alpha = \begin{pmatrix} \frac{\alpha}{2} & \frac{\alpha}{2} & 0 & 0 \end{pmatrix} \quad \mathbf{G} = \begin{pmatrix} 0 & 1/2 & 1/2 & 0 \\ 1/2 & 0 & 0 & 1/2 \\ 0 & 1 & 0 & 0 \\ 1 & 0 & 0 & 0 \end{pmatrix}$$

(Based on the graphs in Maurer et al., 2011)

Update algorithm

Transition matrix $\mathbf{G} = (g_{ij})$, where g_{ij} is the fraction of α_i allocated to H_j if H_i is rejected.

Require $0 \leq g_{ij} \leq 1$, $g_{ii} = 0$ and $\sum_{k=1}^K g_{ik} = 1$ for $i, j = 1, \dots, K$.

- 0 Set $J = \{1, \dots, K\}$
- 1 Select a $j \in J$ such that $p_j \leq \alpha_j$ and reject H_j ; otherwise stop
- 2 Update the graph:

$$J \rightarrow J \setminus \{j\}$$

$$\alpha_\ell \rightarrow \begin{cases} \alpha_\ell + \alpha_j g_{j\ell} & \text{for } \ell \in J \\ 0 & \text{otherwise} \end{cases}$$

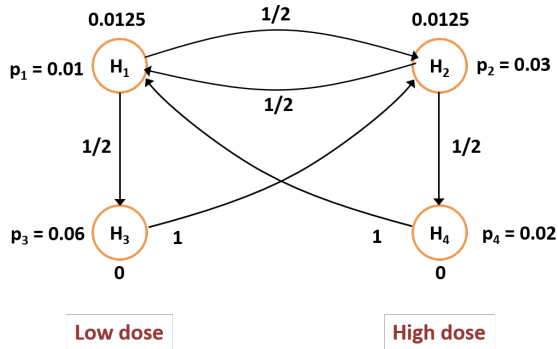
$$g_{\ell k} \rightarrow \begin{cases} \frac{g_{\ell k} + g_{\ell j} g_{jk}}{1 - g_{\ell j} g_{j\ell}} & \text{for } \ell, k \in J, \ell \neq k, g_{\ell j} g_{j\ell} < 1 \\ 0 & \text{otherwise} \end{cases}$$

- 3 If $|J| \geq 1$, go to Step 1; otherwise stop

(Bretz et al., 2009)

Diabetes example

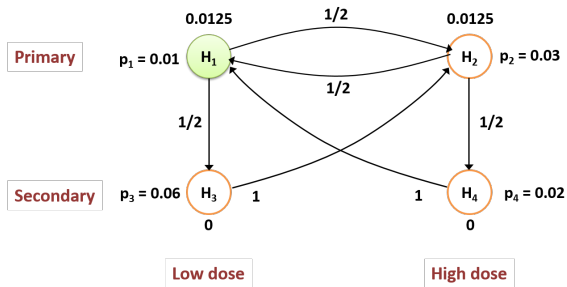
$$\alpha = 0.025$$



(Based on the graphs in Maurer et al., 2011)

Diabetes example

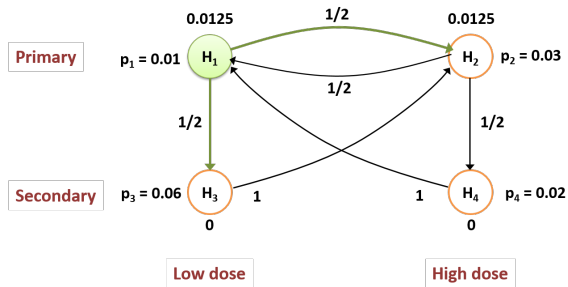
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Diabetes example

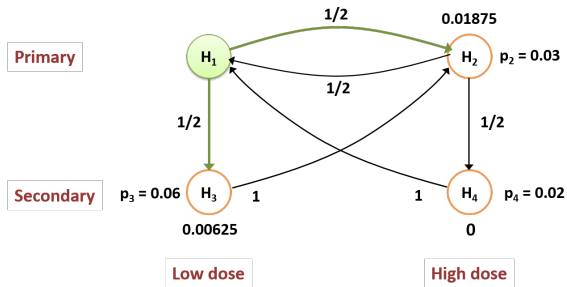
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Diabetes example

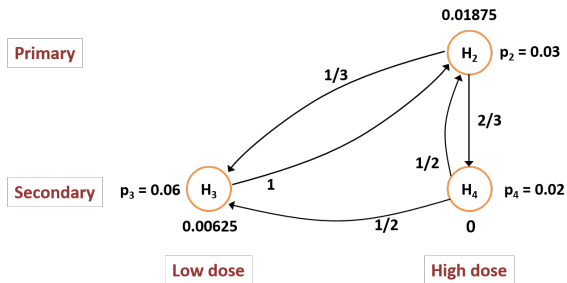
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(Based on the graphs in Maurer et al., 2011)

Diabetes example

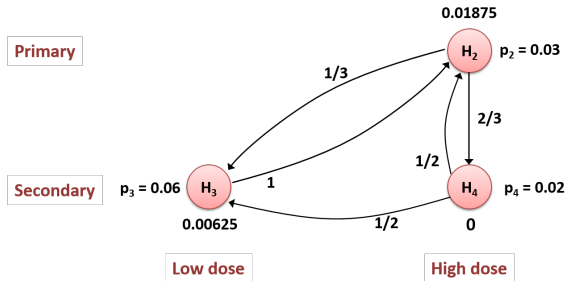
$$\alpha = 0.025$$



(Based on the graphs in Maurer et al., 2011)

Diabetes example

$$\alpha = 0.025$$



(Based on the graphs in Maurer et al., 2011)

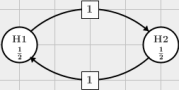
gMCP package

gMCP GUI 0.8.10

File Example graphs Analysis Extras Help

Place new nodes and edges or start the test procedure

Graph



```

graph LR
    H1((H1  
1/2)) -- 1 --> H2((H2  
1/2))
    H2 -- 1 --> H1
  
```

Description Analysis

Graph representing the (unweighted) Bonferroni-Holm-Procedure

The graph is a complete graph, where all nodes have the same weights and each edge weight is $1/(n-1)$.

Literature: Holm, S. (1979). A simple sequentially

Transition Matrix

	H1	H2
H1	0	1
H2	1	0

Hypothesis Weights P-Value

H1 0.5 0.015 Reject and pass α

H2 0.5 0.097 Reject and pass α

Sum of weights: 1

Total α : 0.025

Load p-values from R

☒ No information about correlations (Bonferroni based weighted tests)

☐ Select an R correlation matrix No 2x2-matrices found. Refresh Create Matrix

☐ Use Simes test

Summary

- Graphical approach allows the following (Bretz et al. 2015):
 - ▶ Tailor advanced multiple test procedures to a structured families of hypotheses
 - ▶ Visualise complex decision strategies in an efficient and easily communicable way
 - ▶ Ensure strong FWER control
- Approach covers many common multiple test procedures as special cases
- Many possible extensions as well

Multiplicity in practice

Choosing a multiple testing procedure

A lot of advice available!

- Dmitrienko and D'Agostino (2013) Traditional multiplicity adjustment methods in clinical trials. *Stat Med* 32:5172-5218.
- Dmitrienko and D'Agostino (2018) Multiplicity Considerations in Clinical Trials. *NEJM* 378:2115-2122.
- Howard *et al.* (2018) Recommendations on multiple testing adjustment in multi-arm trials with a shared control group. *SMMR* 27(5):1513-1530.
- Li *et al.* (2017) An introduction to multiplicity issues in clinical trials: the what, why, when and how. *Int J Epi* 46(2):746-55
- Wang *et al.* (2011) Regulatory Perspectives on Multiplicity in Adaptive Design Clinical Trials throughout a Drug Development Program. *J Biopharm Stat* 21:846-59.
- Wason *et al.* (2014) Correcting for multiple-testing in multi-arm trials: is it necessary and is it done? *Trials* 15:364.

Choosing a multiple testing procedure

- Need to identify the adjustment method aligned with the structure of the clinical objectives, that provides highest statistical power.
- Use all available clinical and statistical information to arrive at the most appropriate and efficient method.
- Often need to do a simulation-based assessment of operating characteristics of procedures under trial-specific assumptions.
- Helpful to classify methods (see Dmitrienko and D'Agostino, 2013)
 - ▶ Logical restrictions
 - ▶ Distributional information

Choosing a multiple testing procedure

Logical restrictions

- Group procedures into three classes:
 - ▶ Single-step that test all hypotheses simultaneously (e.g. Bonferroni)
 - ▶ Stepwise that rely on data-driven ordering (e.g. Holm and Hochberg)
 - ▶ Stepwise that rely on pre-specified ordering. (e.g. Fixed-sequence or Fallback)
- Single-step most basic. Stepwise more powerful; easier to tailor.

Choosing a multiple testing procedure

Distributional information

- Again group into three classes:
 - ▶ Non-parametric procedures: without distributional assumptions (e.g. Bonferroni, Holm, Fixed-sequence, Fallback)
 - ▶ Semi-parametric methods: control under e.g. independence or positive correlation, but not full specification of a joint distribution (e.g. Hochberg and Hommel)
 - ▶ Parametric methods: control FWER only when joint distribution of test statistics fully specified (e.g. Dunnett)
- In general, power increases as more distributional assumptions are added

Regulatory view

- So far, we have been assuming that we have to adjust for multiplicity.
- Often we will need to, but not always.
- Latest (draft) regulatory guidance from the FDA and EMA:
 - ▶ EMA: *Guideline on multiplicity issues in clinical trials* (2016)
 - ▶ FDA: *Multiple Endpoints in Clinical Trials* (2017)

Software

R

- **multxpert** package for common adjustments in single family (non-parametric, semi-parametric and parametric procedures) and multiple families (gatekeeping procedures).
 - ▶ <http://multxpert.com/wiki/Software>
 - ▶ “Multiple Testing Problems in Pharmaceutical Statistics” by Dmitrienko *et al.* (2009)
- **gMCP** for graph based multiple test procedures.
- **multcomp** package addresses multiplicity issues in general linear and non-linear models.
 - ▶ Adjustments for ANOVA, ANCOVA, regression models, and more.
 - ▶ “Multiple Comparisons Using R” by Bretz *et al.* (2016)

Software

Stata

- Several commands support correcting for multiple comparisons.
- oneway (one-way ANOVA) commands
- Powerful test command for testing linear hypotheses from regress, stcox, logit, svy has an mtest option that supports Bonferroni, Holm, etc.

Summary

- There is a lot of advice available on how to choose a multiple testing procedure.
- But no golden rule: have to tailor to your trial.
- Important as often required by regulatory authorities.
- Much software out there to do this in practice.

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