Lecture 2: Advanced multiplicity correction

Adaptive Designs and Multiple Testing Procedures for Clinical Trials

October 2019

Outline

Hierarchical testing

Hierarchical test procedures

- Suppose hypotheses can be ordered into a *pre-specified* hierarchy $H_1, \ldots, H_K$, 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

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  - 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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- As soon as a hypothesis H_i cannot be rejected, $p_i > \alpha$, the procedure stops and all remaining hypotheses $H_{i+1}, \ldots, H_K$ 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 $H_1, \ldots, H_K$
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Šidák procedure

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- 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 $p_{(1)} < \cdots < p_{(K)}$ with corresponding hypotheses $H_{(1)}, \ldots, H_{(K)}$
- Uses same significance thresholds as the Holm procedure, but reversed (step-up rather than step-down)
- *Rejection rule*
  - If $p_{(K)} \leq \alpha$, reject $H_{(1)}, \ldots, H_{(K)}$ and stop; else continue
  - If $p_{(K-1)} \leq \alpha/2$, reject $H_{(1)}, \ldots, H_{(K-1)}$ and stop; else continue
  - $\ldots$
  - 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 $H_{(i)}, H_{(i+1)}, \ldots, H_{(1)}$

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 $i = 1, \ldots, j$
  - 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 `multxpert` 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

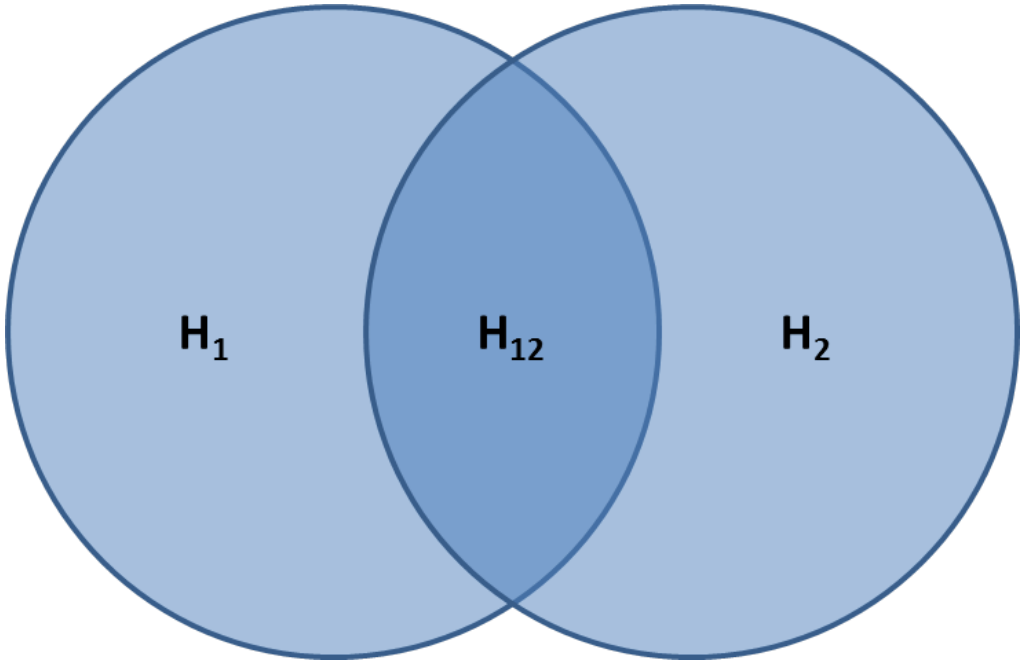
- General methodology to construct multiple testing procedures which strongly control the FWER
- Includes many well-known procedures as special cases
- Closed test procedures consider all *intersection hypotheses*

$$H_J = \bigcap_{i \in J} H_i, \qquad J \subseteq \{1, \ldots, K\}$$

- 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



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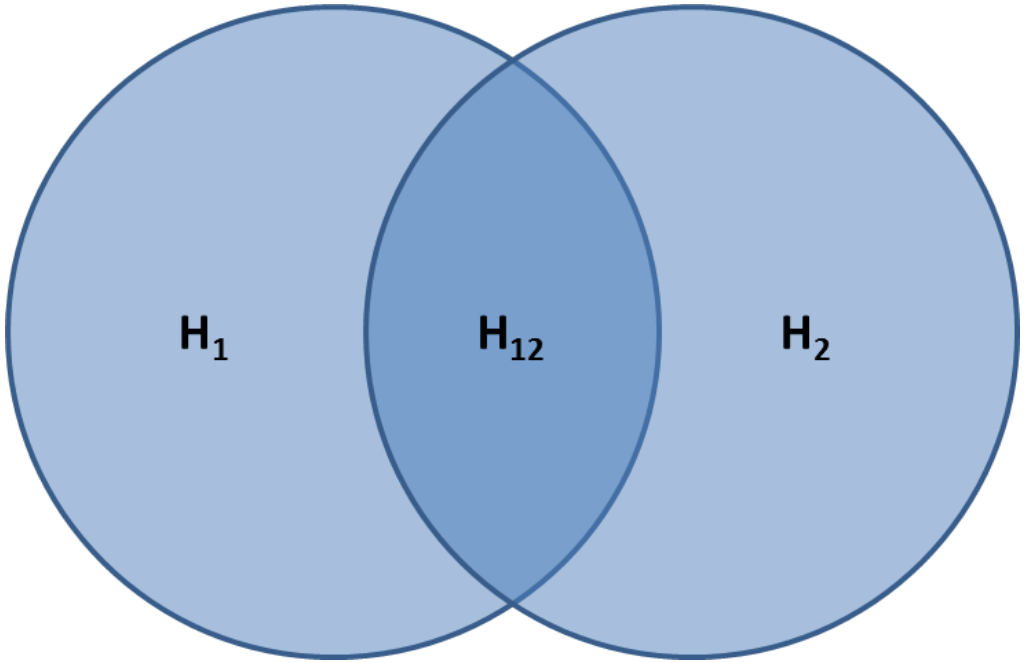
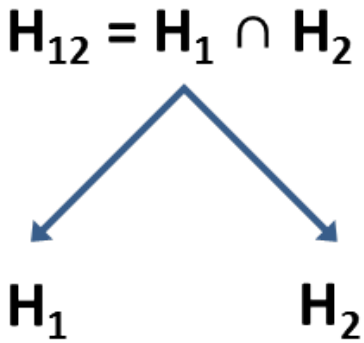


- Test $H_{12} = H_1 \cap H_2$ using Bonferroni or Dunnett etc. at level α
- Test H_1 and H_2 using a level α test

Closure principle

$K = 2$ hypotheses

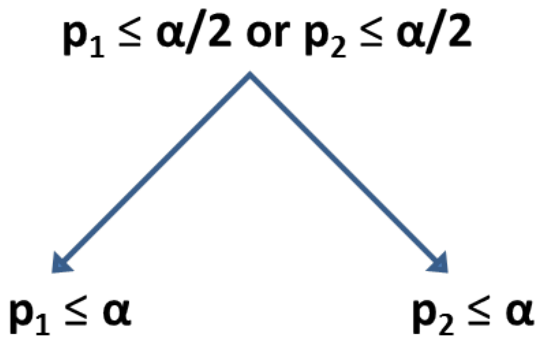


- Reject H_1 overall if H_{12} and H_1 and are rejected locally at level α
- If $K > 2$, several intersection hypotheses have to be tested
- Different tests can be chosen for each (intersection) hypothesis

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 $p_2 \leq \alpha/2$

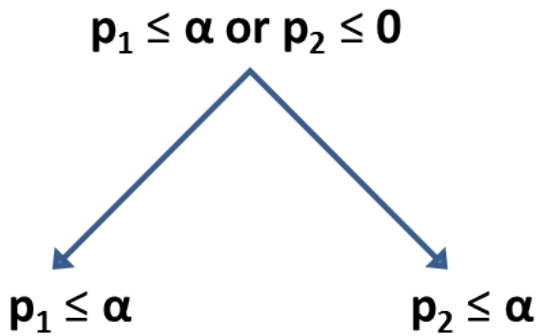


Closure principle

Fixed sequence procedure

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

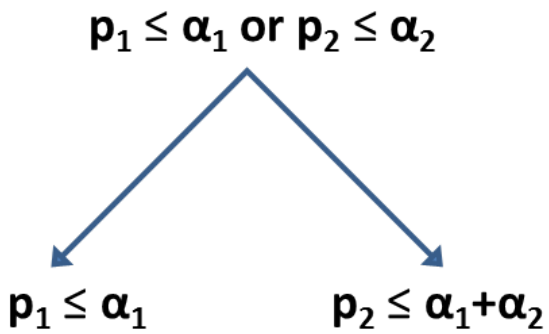
Setting $\alpha_1 = \alpha$ and $\alpha_2 = 0$ gives the *fixed sequence procedure*:



Closure principle

Fallback procedure

In general, we recover the *fallback procedure*:



Closure principle

$k = 3$ hypotheses

$$H_1 \cap H_2 \cap H_3$$

$$H_1 \cap H_2 \qquad H_1 \cap H_3 \qquad H_2 \cap H_3$$

$$H_1 \qquad H_2 \qquad H_3$$

Closure principle

Fixed sequence procedure with a-priori fixed order $H_1 \to H_2 \to H_3$

$$H_1 \cap H_2 \cap H_3$$
$$p_1 \leq \alpha$$

$$H_1 \cap H_2 \qquad H_1 \cap H_3 \qquad H_2 \cap H_3$$
$$p_1 \leq \alpha \qquad p_1 \leq \alpha \qquad p_2 \leq \alpha$$

$$H_1 \qquad H_2 \qquad H_3$$
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Closure principle

Holm

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

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$$H_2 \cap H_3$$
$$p_2 \leq \alpha/2 \text{ or } p_3 \leq \alpha/2$$

$$H_1$$
$$p_1 \leq \alpha$$

$$H_2$$
$$p_2 \leq \alpha$$

$$H_3$$
$$p_3 \leq \alpha$$

Closed test procedures

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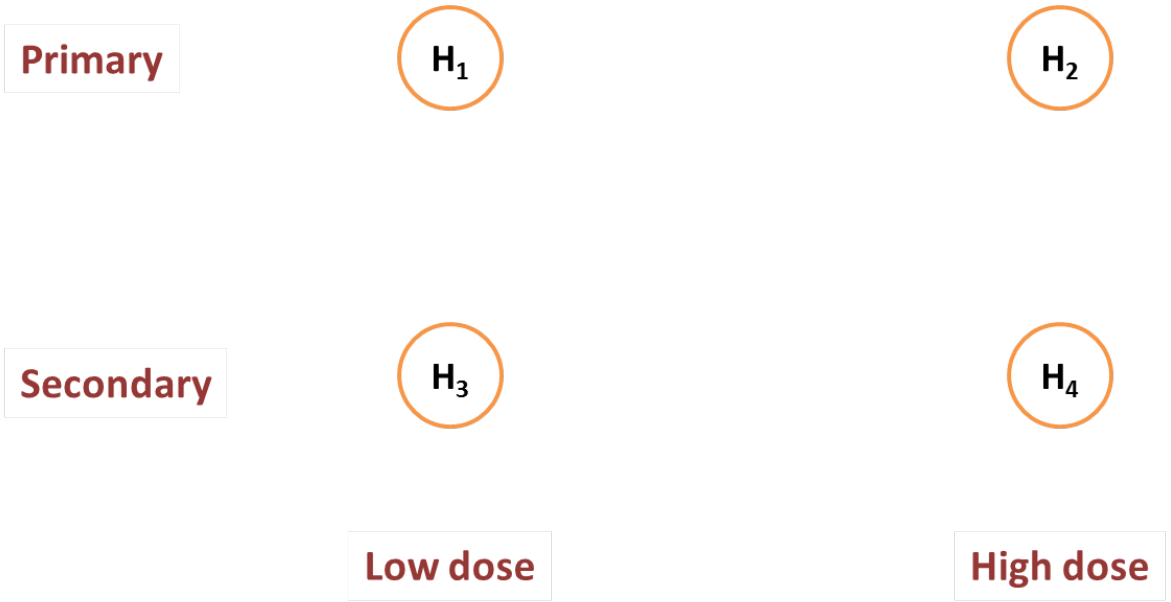
  - We test the primary null hypothesis first; only if this is rejected do we test the secondary hypothesis
- Both doses are equally important

Motivating example: Diabetes trial

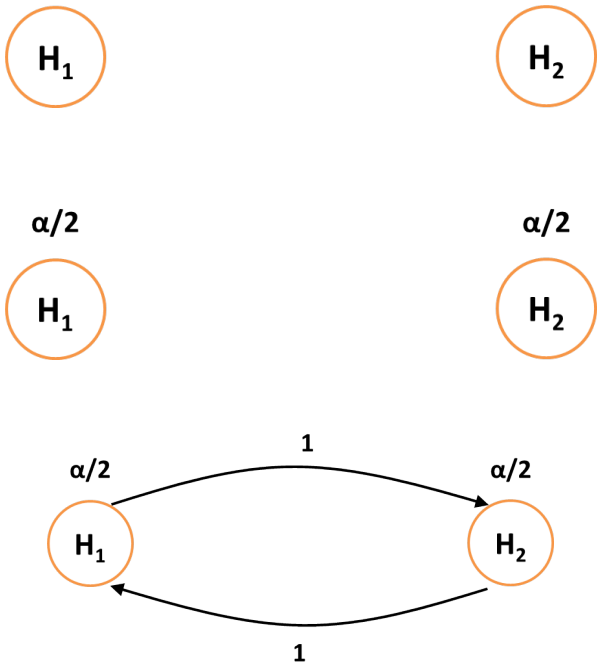
- *Objective*: test all four hypotheses under strong FWER while reflecting clinical objectives
- Standard multiple testing procedures do not reflect the relative importance of the two endpoints or the underlying structure
- In general, need test procedures that can deal with complex trial objectives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

Diabetes example



Graphical approaches

1. Hypotheses $H_1, \ldots, H_K$ represented as nodes
2. Split of significance level α into $(\alpha_1, \ldots, \alpha_K)$
3. "α propagation" through weighted, directed edges



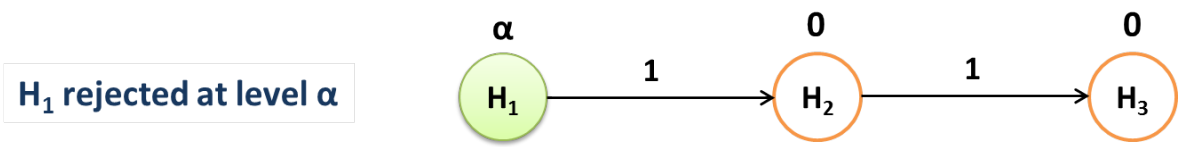
Graphical approaches

- 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** $(w_1, \ldots, w_K)$ 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

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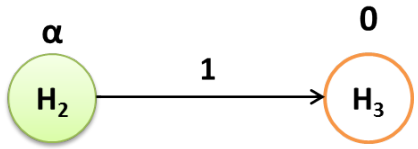
- Example fixed sequence procedure:

H_2 rejected at level α

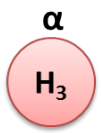


Examples

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)

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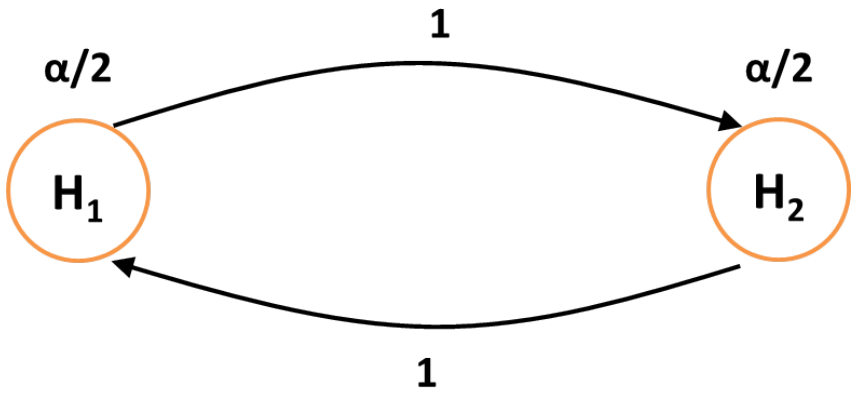
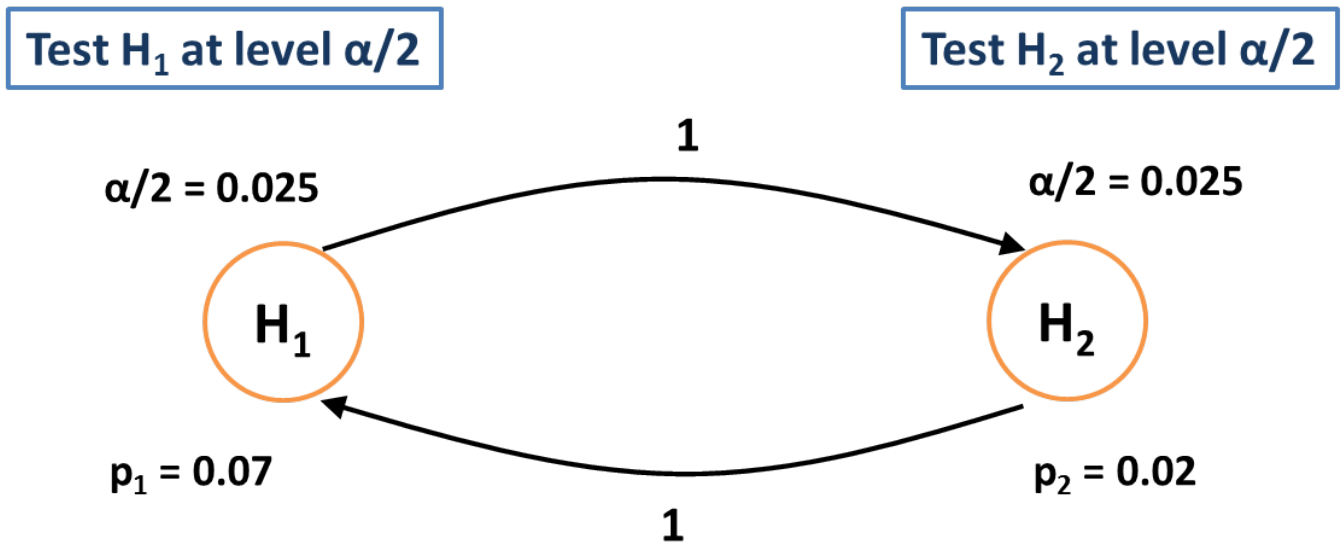
- *Holm*: includes α-propagation $\rightarrow$ more powerful



Examples

Holm procedure with $\alpha = 0.05$



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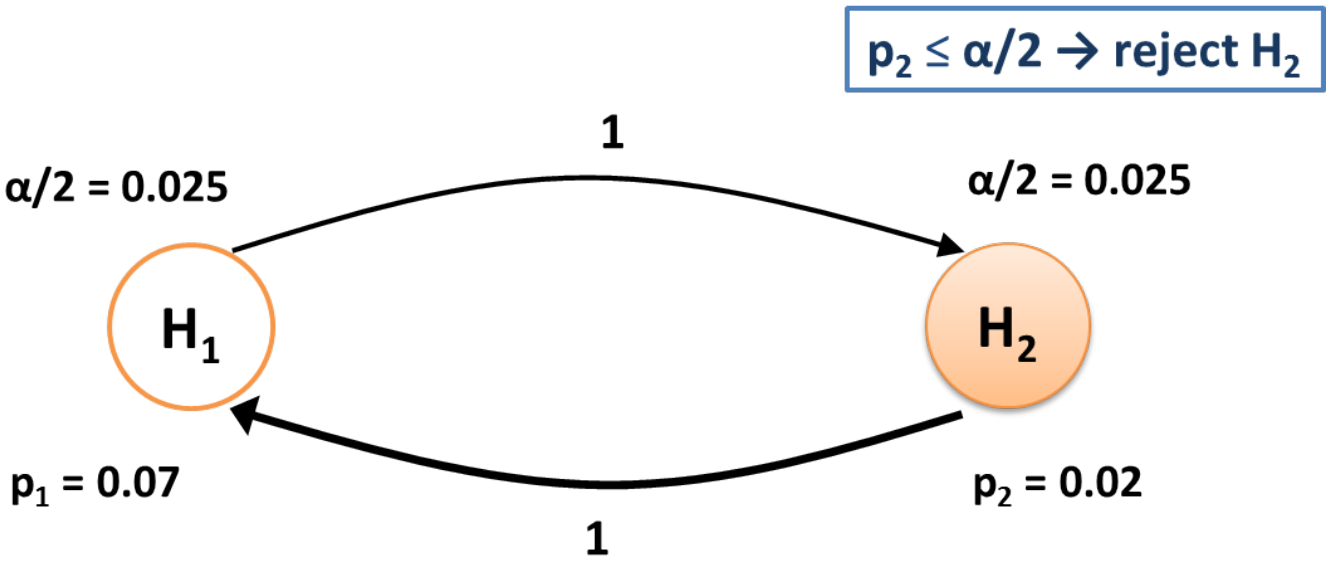
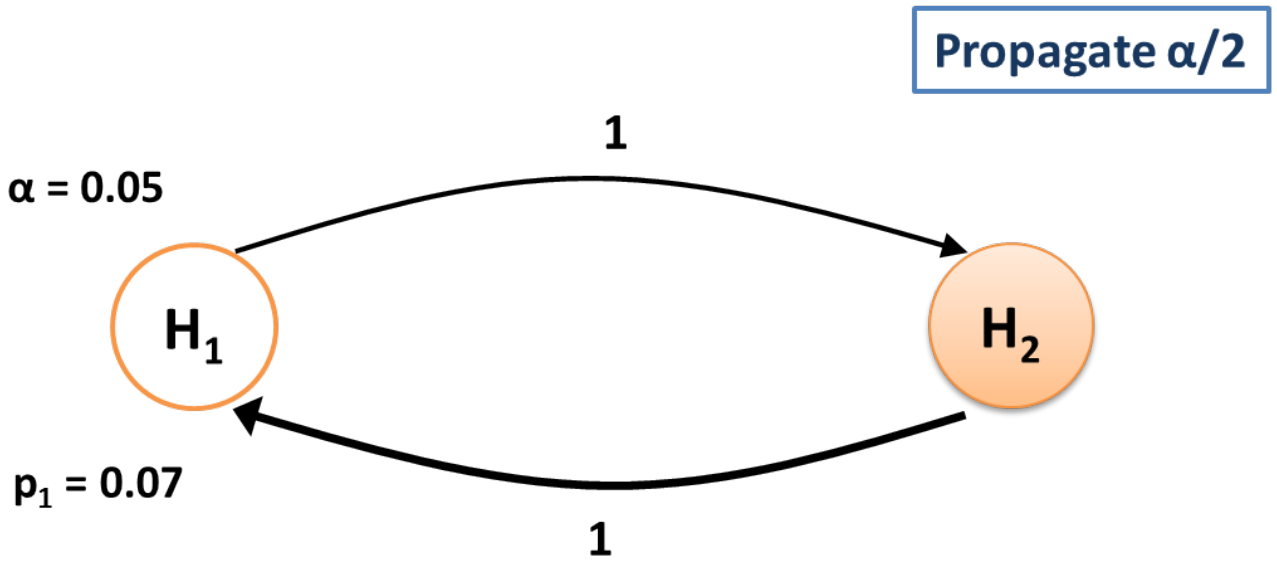


Examples

Holm procedure with $\alpha = 0.05$



Examples

Holm procedure with $\alpha = 0.05$

Remove node for H_2

$\alpha = 0.05$

H_1

$p_1 = 0.07$

Examples

Holm procedure with $\alpha = 0.05$

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

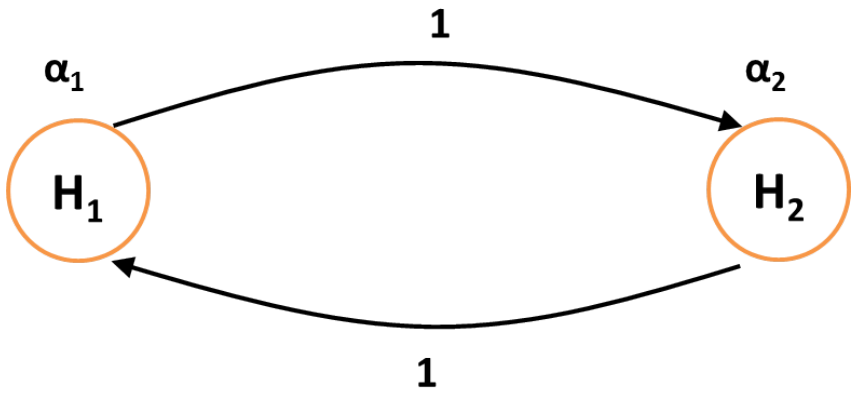
α = 0.05

$p_1 = 0.07$

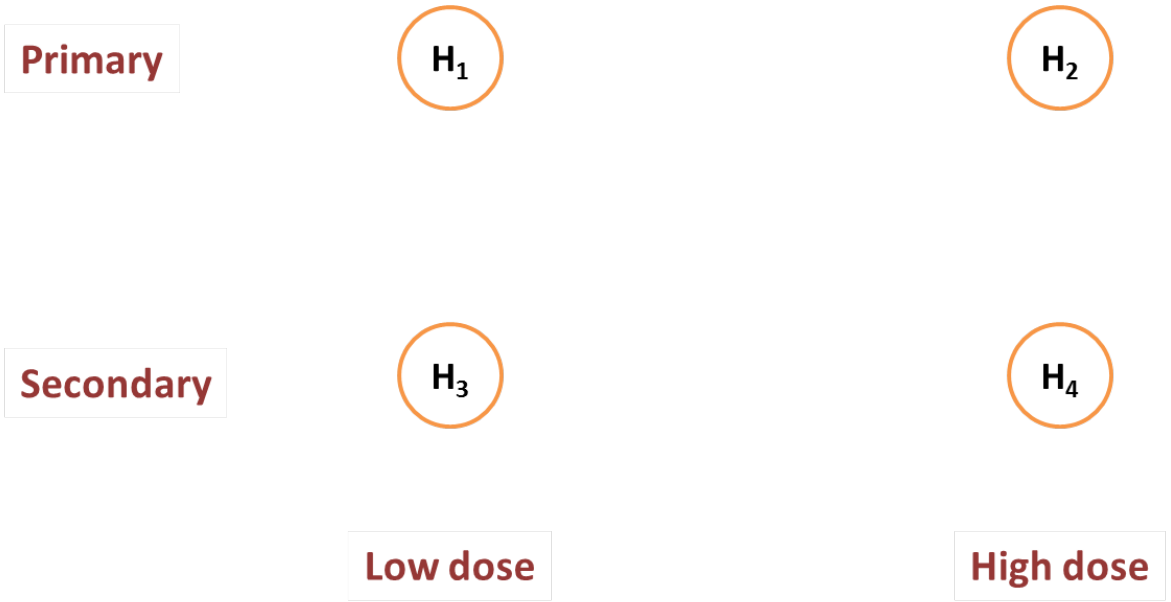
Examples

Weighted Holm procedure

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



Diabetes example



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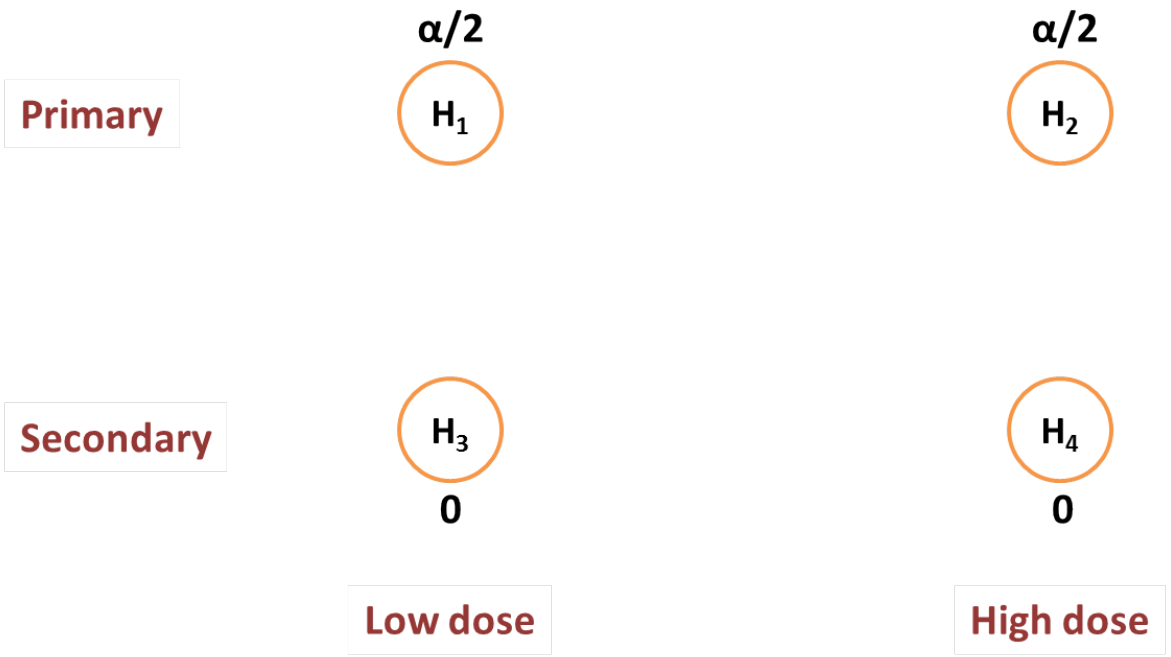

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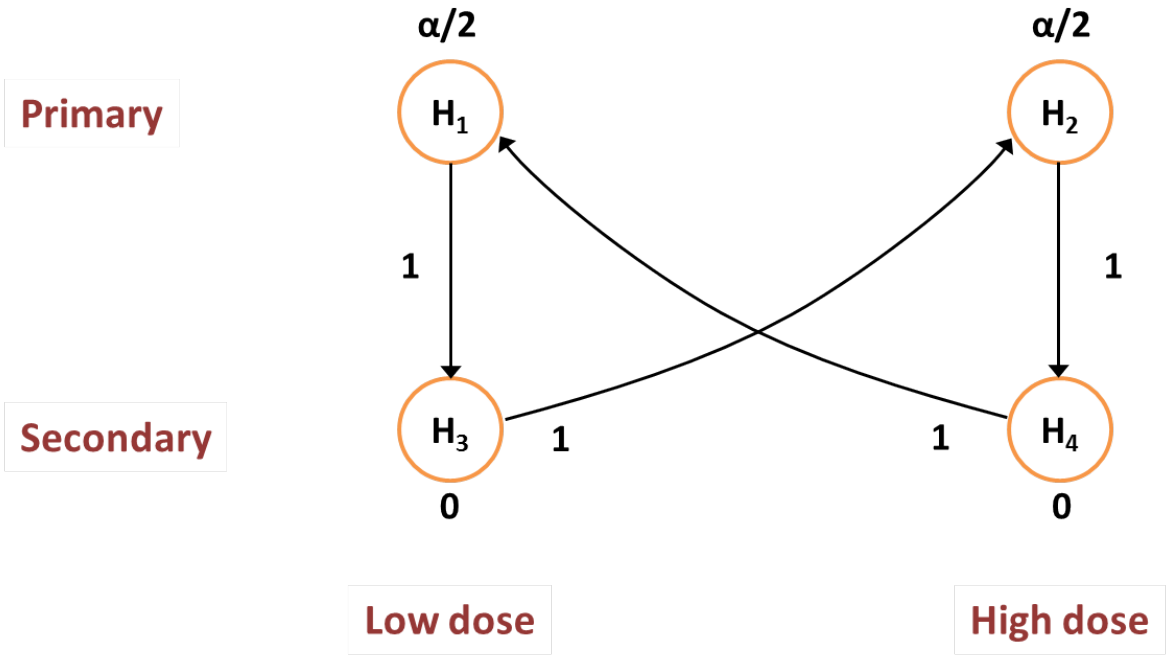
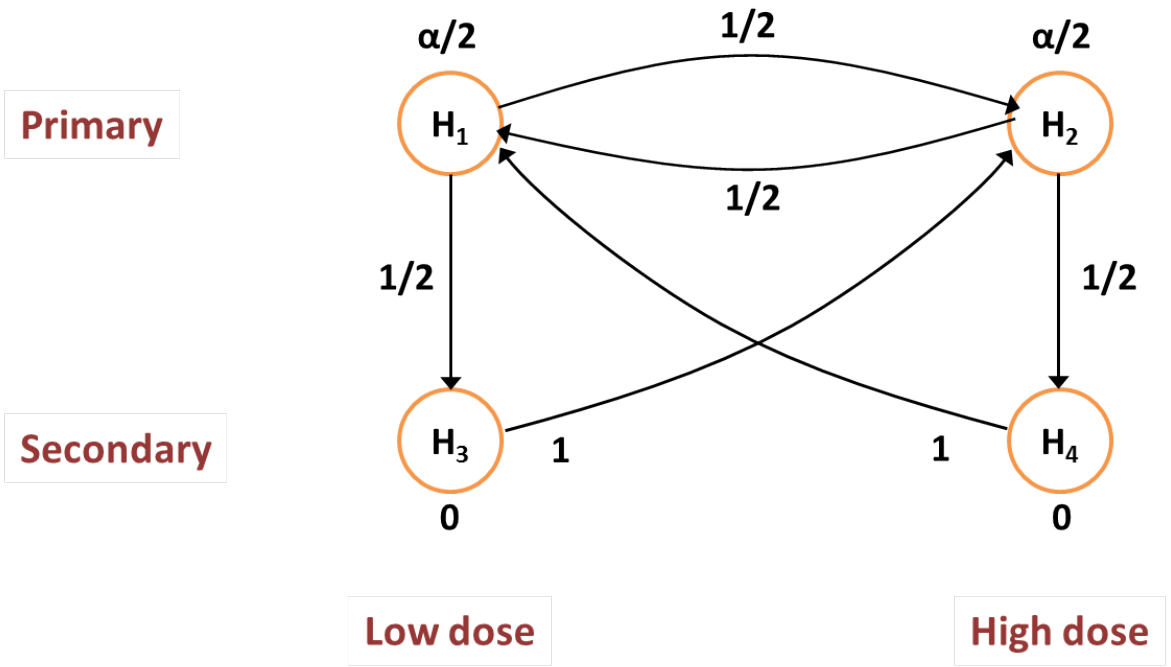


$$\boldsymbol{\alpha} = \begin{pmatrix} \frac{\alpha}{2} & \frac{\alpha}{2} & 0 & 0 \end{pmatrix} \qquad \boldsymbol{G} = \begin{pmatrix} 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 1 \\ 0 & 1 & 0 & 0 \\ 1 & 0 & 0 & 0 \end{pmatrix}$$

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

Diabetes example



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

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

Update algorithm

Transition matrix $\boldsymbol{G} = (g_{ij})$, 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 $i, j = 1, \ldots, K$.

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

$$J \to J \setminus \{j\}$$

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

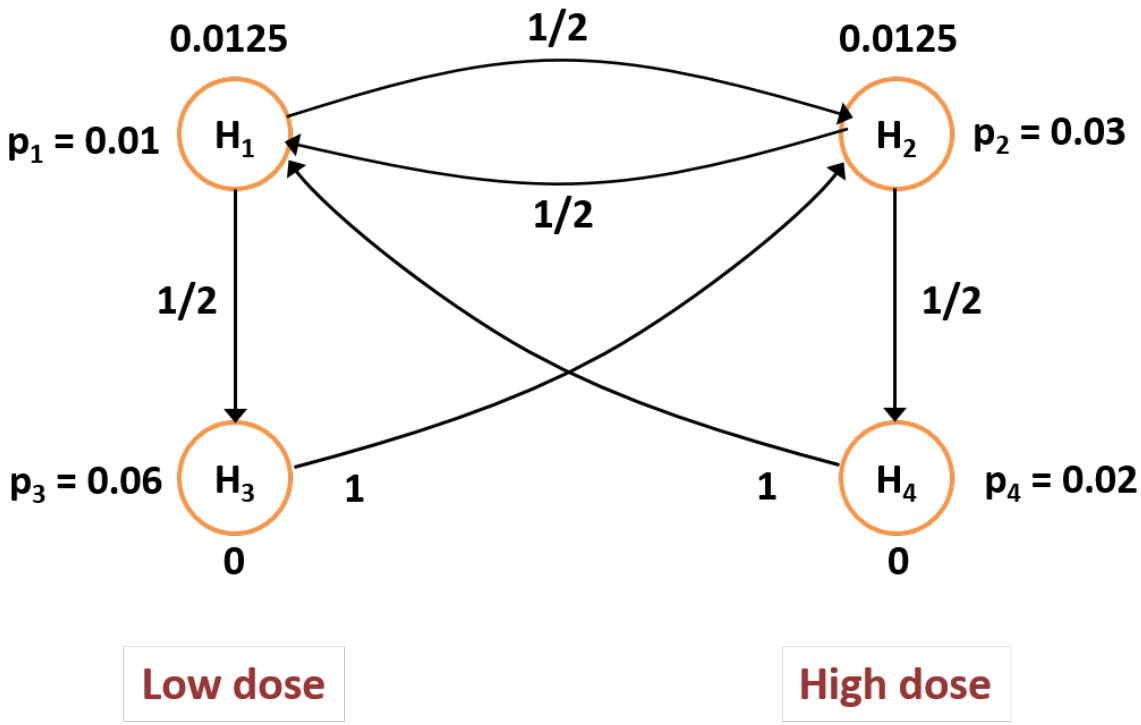
$$g_{\ell k} \to \begin{cases} \frac{g_{\ell k} + g_{\ell j} g_{jk}}{1 - g_{\ell j} g_{j\ell}} & \text{for } \ell, k \in J, \ell \neq k, g_{\ell j} g_{j\ell} < 1 \\ 0 & \text{otherwise} \end{cases}$$

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

(Bretz et al., 2009)

Diabetes example

$\alpha = 0.025$



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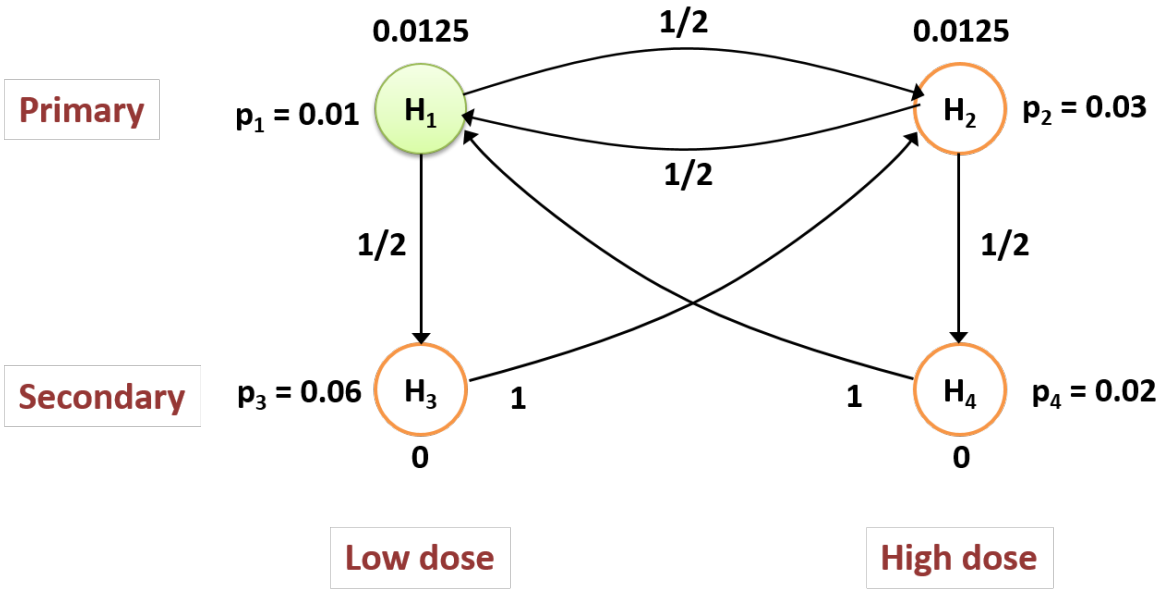

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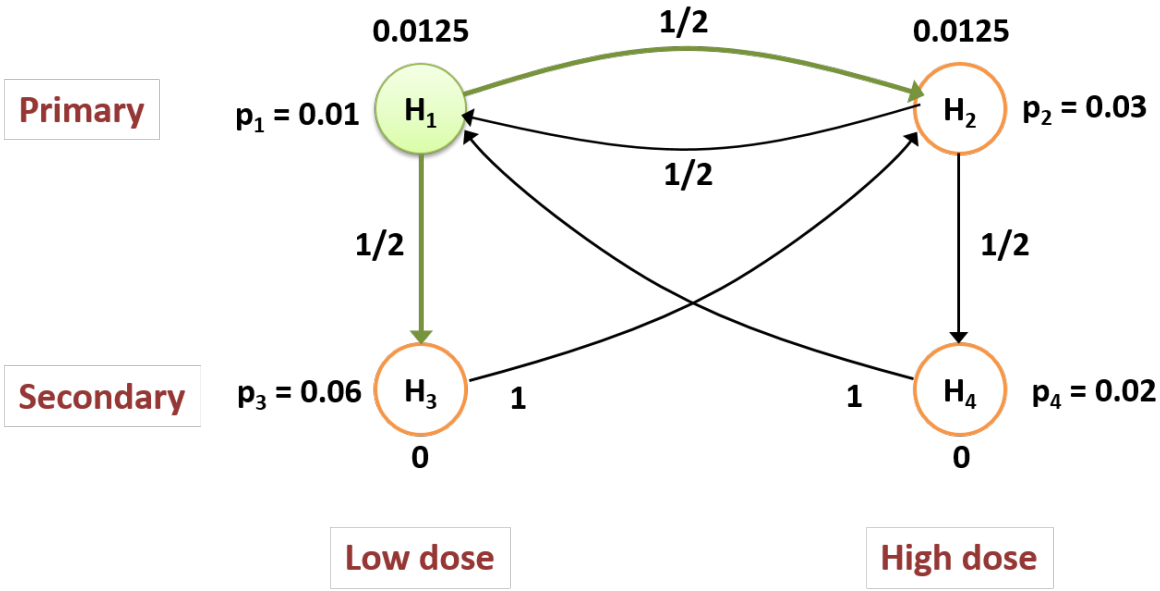

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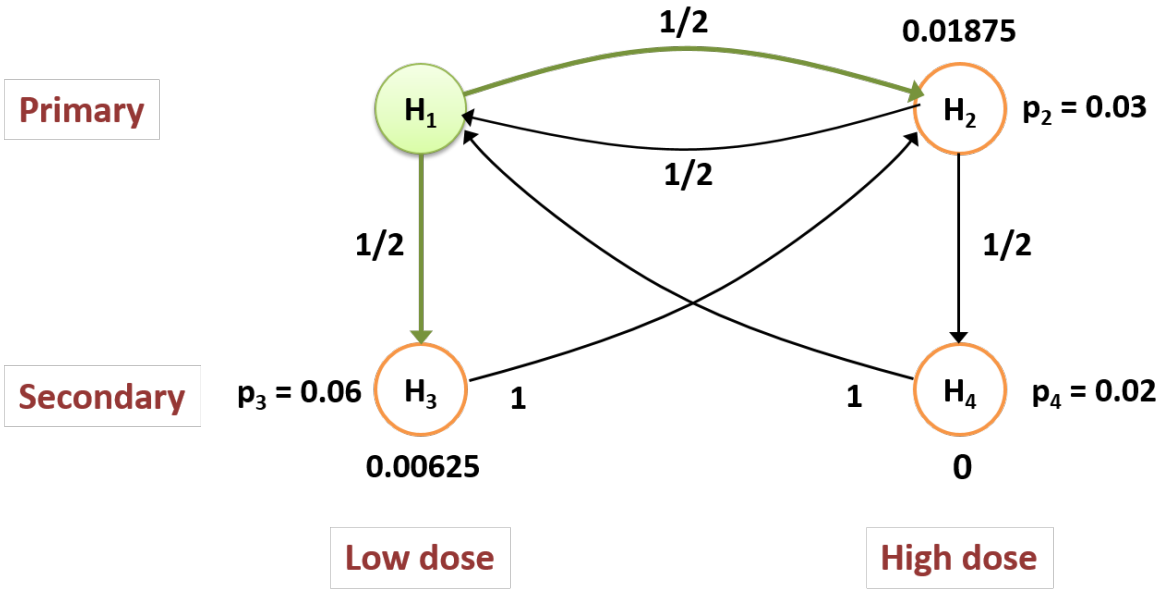
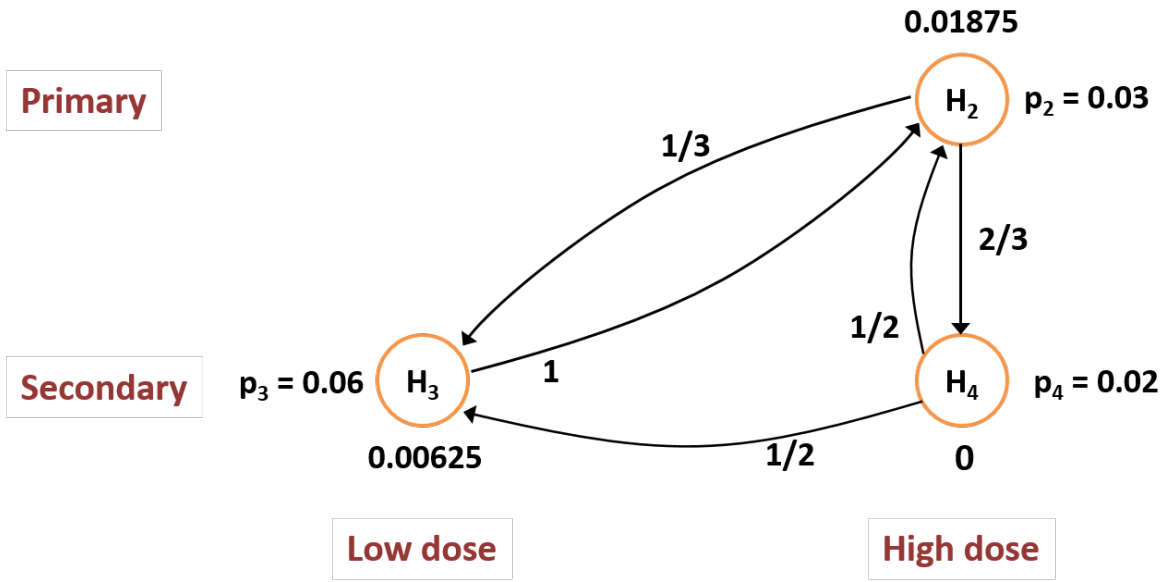


(Based on the graphs in Maurer et al., 2011)

Diabetes example

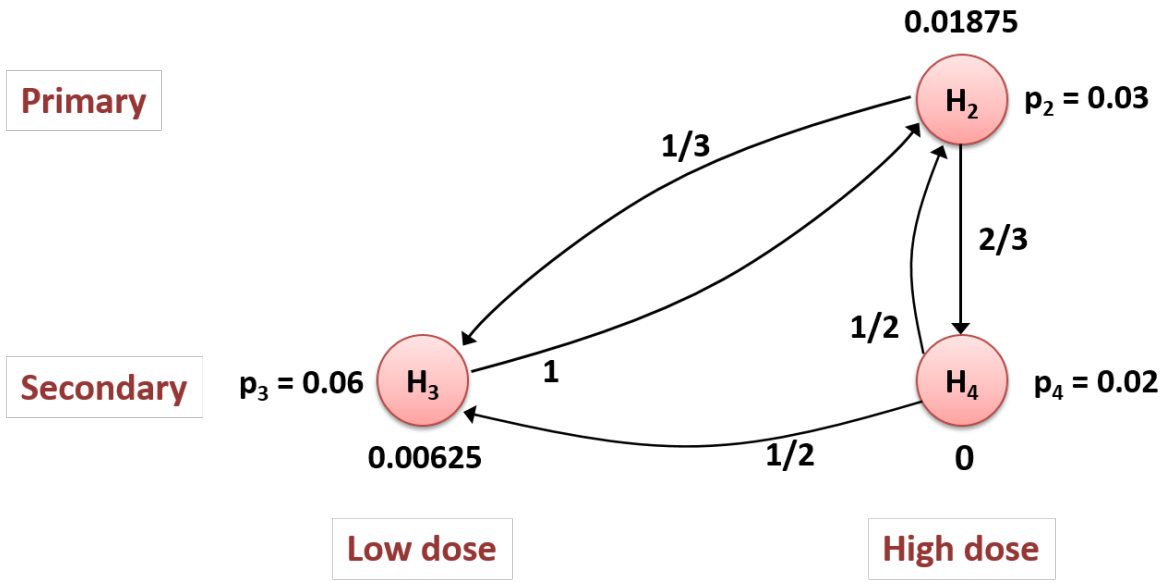
$\alpha = 0.025$



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

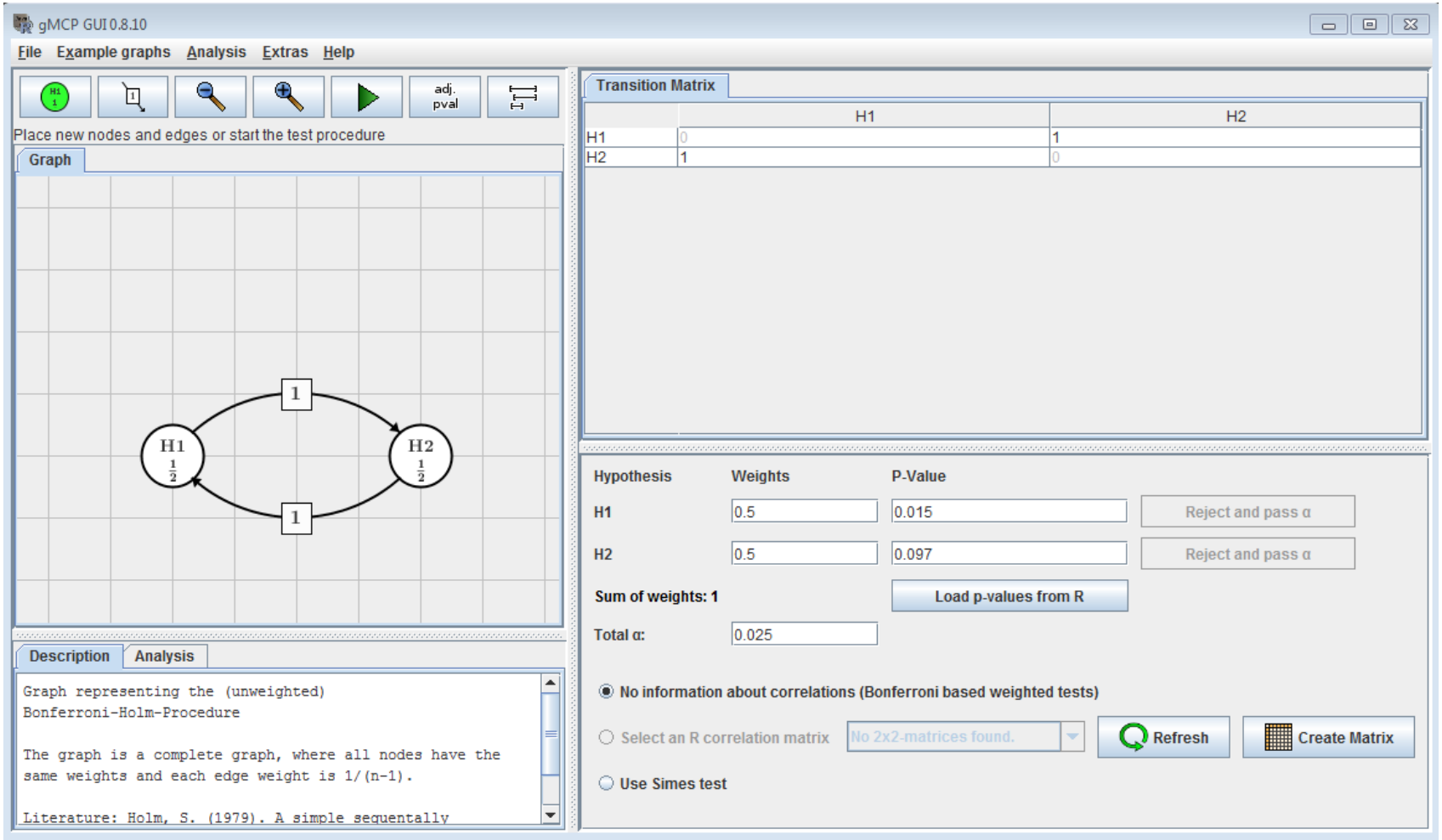
Diabetes example

$\alpha = 0.025$



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

gMCP package



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.

References I

M. Alosh, F. Bretz and M. Huque
Advanced multiplicity adjustment methods in clinical trials
Statistics in Medicine, 33:693–713, 2011.

A. Dmitrienko, A. C. Tamhane and F. Bretz
Multiple testing problems in pharmaceutical statistics, CRC Press, 2009.

F. Bretz et al.
Confirmatory Seamless Phase II/III Clinical Trials with Hypotheses Selection at Interim: General Concepts
Biometrical Journal, 48:623–634, 2006.

F. Bretz et al.
Adaptive designs for confirmatory clinical trials
Statistics in Medicine, 28:1181–1217, 2009.

F. Bretz, T. Hothorn, P. Westfall
Multiple comparisons using R, CRC Press, 2016.

F. Bretz, W. Maurer W. Brannath and M. Posch
A graphical approach to sequentially rejective multiple test procedures
Statistics in Medicine, 28:586–604, 2009.

References II

F. Bretz, W. Maurer and J. Maca
Graphical approaches to multiple testing
in *Clinical Trial Biostatistics and Biopharmaceutical Applications*, CRC Press, 2015.

W. Maurer, E. Glimm and F. Bretz
Multiple and repeated testing of primary, coprimary, and secondary hypotheses
Statistics in Biopharmaceutical Research, 3(2):336–352, 2011.

H. Schmidli et al.
Confirmatory Seamless Phase II/III Clinical Trials with Hypotheses Selection at Interim: Applications and Practical Considerations
Biometrical Journal, 48:635–643, 2006.

J.P. Shaffer
Multiple Hypothesis Testing
Annual Review Psychology, 46:561-84, 1995.