A graphical approach to sequentially rejective multiple test procedures

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μToss, Berlin 2010

Sequentially rejective, weighted Bonferroni type tests

- Applied in clinical trials with multiple treatment arms, subgroups and endpoints
- Bonferroni-Holm Test, Fixed Sequence Test, Fallback Test, Gatekeeping Tests, ...
- Allow to map the difference in importance as well as the relationship between research questions onto the multiple test procedure.
- However: The testing procedure can be technical and often hard to communicate.

Parallell gatekeeping: Testing $\mathcal{F}_1 = \{H_1, H_2\}$, $\mathcal{F}_2 = \{H_3, H_4\}$

Rejection of hypotheses in the family $\mathcal{F}_2 = \{H_3, H_4\}$ is only of interest if at least one of the hypotheses in the family $\mathcal{F}_1 = \{H_1, H_2\}$ can be rejected

Parallel Gatekeeping (Dmitrienko, Offen & Westfall, 2003)

Table II. Decision matrix for the parallel Bonferroni gatekeeping procedure.

Intersection hypothesis	P-values for intersection hypotheses	Original hypotheses			
		H_1	H_2	H_3	H_4
H_{1111}	$p_{1111} = \min(p_1/0.9, p_2/0.1)$	p_{1111}	p_{1111}	p_{1111}	p_{1111}
H_{1110}	$p_{1110} = \min(p_1/0.9, p_2/0.1)$	p_{1110}	p_{1110}	p_{1110}	0
H_{1101}	$p_{1101} = \min(p_1/0.9, p_2/0.1)$	p_{1101}	p_{1101}	0	p_{1101}
H_{1100}	$p_{1100} = \min(p_1/0.9, p_2/0.1)$	p_{1100}	p_{1100}	0	0
H_{1011}	$p_{1011} = \min(p_1/0.9, p_3/0.05, p_4/0.05)$	p_{1011}	0	p_{1011}	p_{1011}
H_{1010}	$p_{1010} = \min(p_1/0.9, p_3/0.1)$	p_{1010}	0	p_{1010}	0
H_{1001}	$p_{1001} = \min(p_1/0.9, p_4/0.1)$	p_{1001}	0	0	p_{1001}
H_{1000}	$p_{1000} = p_1$	p_{1000}	0	0	0
H_{0111}	$p_{0111} = \min(p_2/0.1, p_3/0.45, p_4/0.45)$	0	p_{0111}	p_{0111}	p_{0111}
H_{0110}	$p_{0110} = \min(p_2/0.1, p_3/0.9)$	0	p_{0110}	p_{0110}	0
H_{0101}	$p_{0101} = \min(p_2/0.1, p_4/0.9)$	0	p_{0101}	0	p_{0101}
H_{0100}	$p_{0100} = p_2$	0	p_{0100}	0	0
H_{0011}	$p_{0011} = \min(p_3/0.5, p_4/0.5)$	0	0	p_{0011}	p_{0011}
H_{0010}	$p_{0010} = p_3$	0	0	p_{0010}	0
H_{0001}	$p_{0001} = p_4$	0	0	0	p_{0001}

Note: The table shows p-values associated with the intersection hypotheses. The adjusted p-values for the original hypotheses H_1, H_2, H_3 and H_4 are defined as the largest p-value in the corresponding column in the right-hand panel of the table (see equation (1)).

Heuristics

Notation

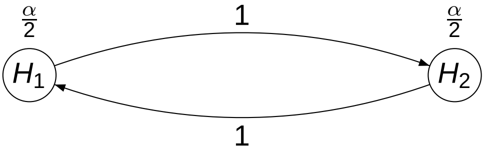
- $H_1, \ldots, H_m$: m null hypotheses.
- $p_1, \ldots, p_m$: m elementary p-values
- $\boldsymbol{\alpha} = (\alpha_1, \ldots, \alpha_m)$: initial allocation of the type I error rate $\alpha = \sum_{i=1}^{m} \alpha_i$.

"α Reshuffling"

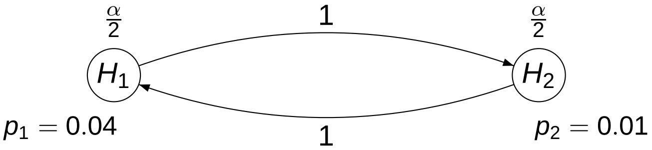
1. If a hypothesis H_i can be rejected at level α_i, reallocate its level to one of the other hypotheses (according to a prefixed rule)
2. Repeat the testing with the resulting α levels.
3. Go to step 1 until no hypothesis can be rejected anymore.

Does this lead to a FWE-controlling test?

Example: Bonferroni-Holm Test



Example: Bonferroni-Holm Test ($\alpha = 0.025$)



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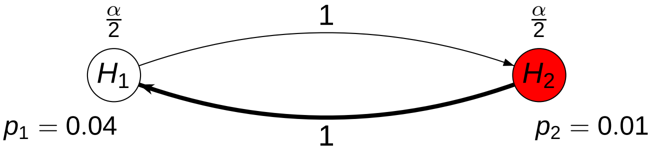

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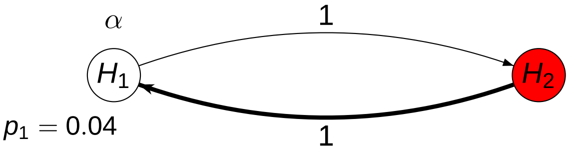

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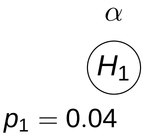
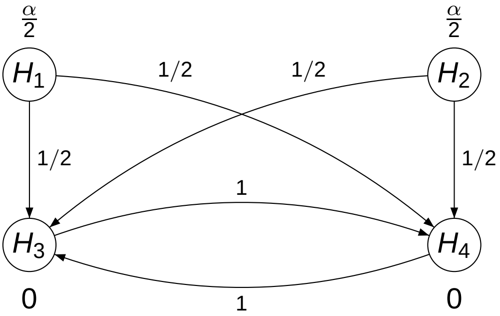


Example: Parallel Gatekeeping



To the procedure of Dmitrienko et al. (2003)

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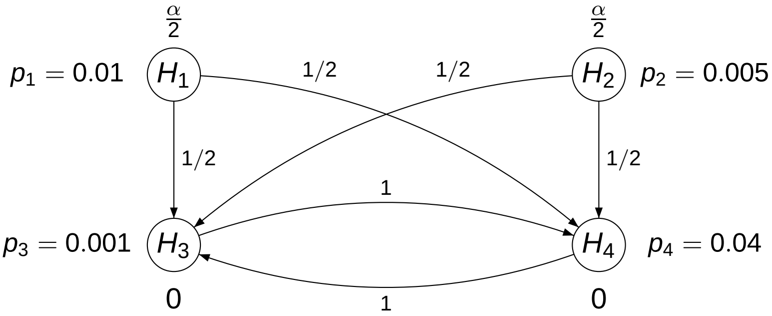

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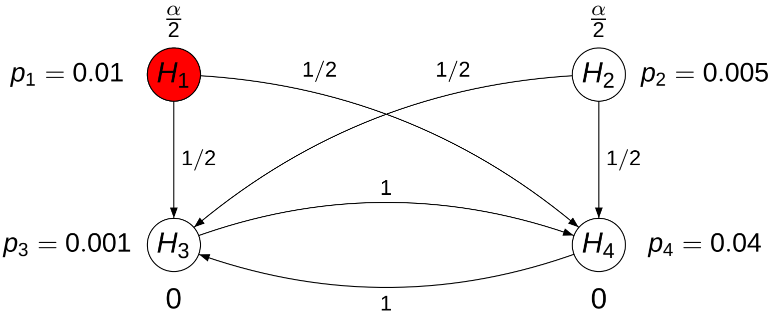

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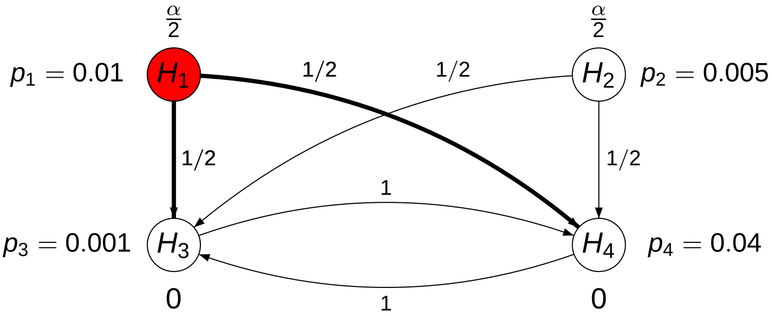

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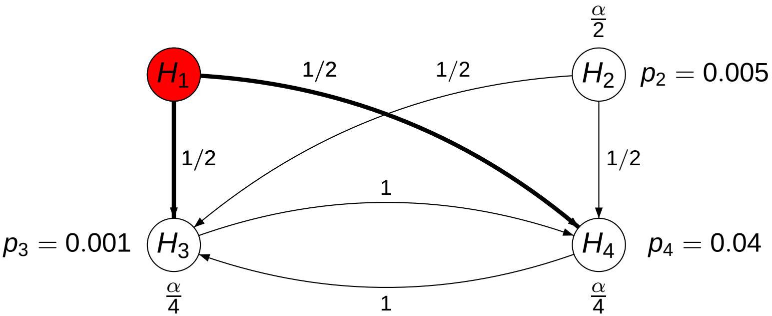

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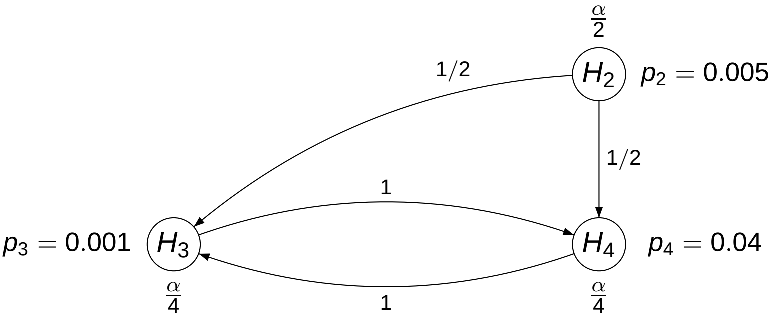

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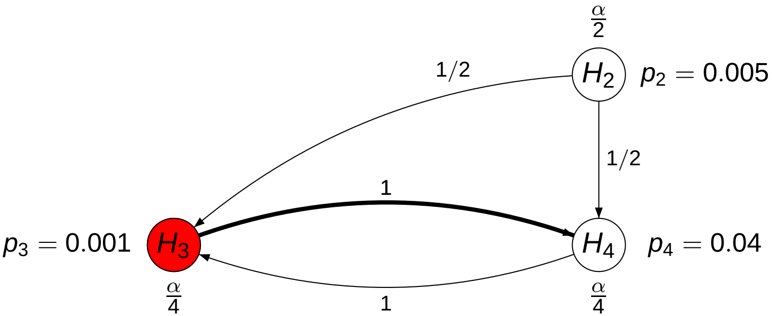

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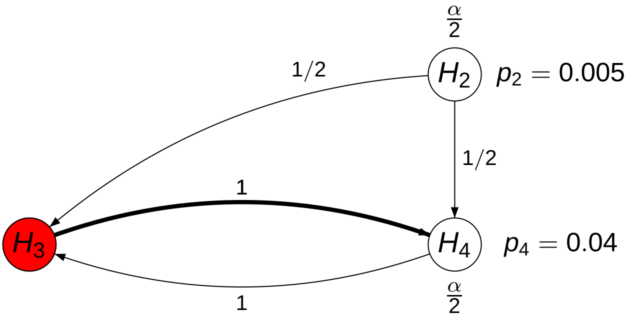

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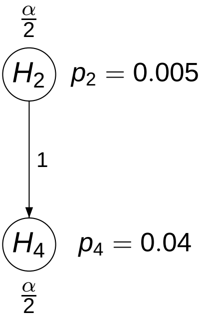

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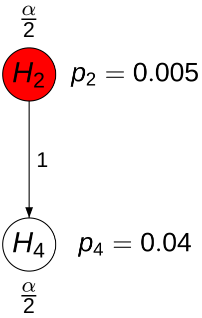

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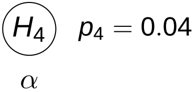

General Definition of the Multiple Test Procedure

General definition of the multiple test

- $\boldsymbol{\alpha} = (\alpha_1, \ldots, \alpha_m)$, $\sum_{i=1}^{m}, \alpha_i = \alpha$, initial levels
- $\mathbf{G} = (g_{ij})$: $m \times m$ transition matrix
  g_{ij} with $0 \leq g_{ij} \leq 1$, $g_{ii} = 0$ and $\sum_{j=1}^{m} g_{ij} \leq 1$ for all $i = 1, \ldots, m$.

- $g_{ij}\ldots$fraction of the level of H_i that is allocated to H_j.
- $\mathbf{G}$ and α determine the graph and the multiple test.

The Testing Procedure

Set $J = \{1, \ldots, m\}$.

1. Select a j such that $p_j \leq \alpha_j$.
   If no such j exists, stop, otherwise reject H_j.
2. Update the graph:
$$J \to J / \{j\}$$
$$\alpha_\ell \to \begin{cases} \alpha_\ell + \alpha_j g_{j\ell}, & \ell \in J \\ 0, & \text{otherwise} \end{cases}$$
$$g_{\ell k} \to \begin{cases} \frac{g_{\ell k} + g_{\ell j} g_{jk}}{1 - g_{\ell j} g_{j\ell}}, & \ell, k \in J, \ell \neq k \\ 0, & \text{otherwise} \end{cases}$$
3. Go to step 1.

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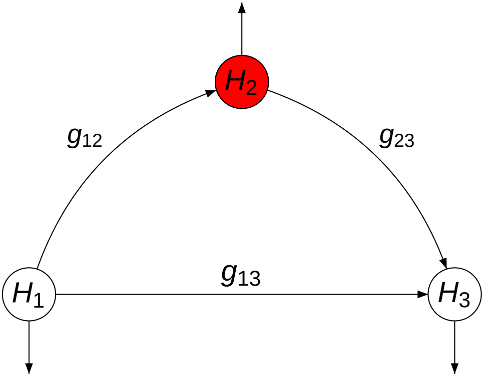
Updating the Graph



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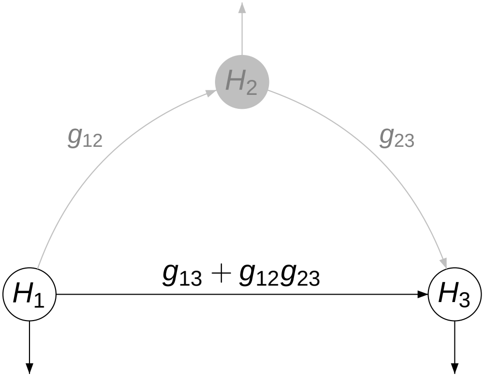

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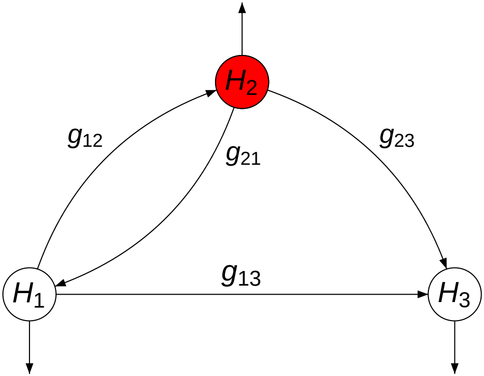

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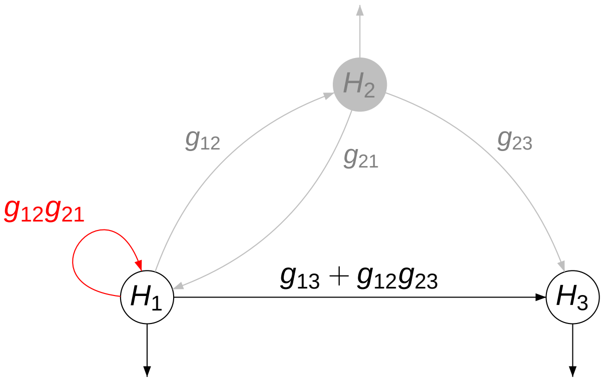

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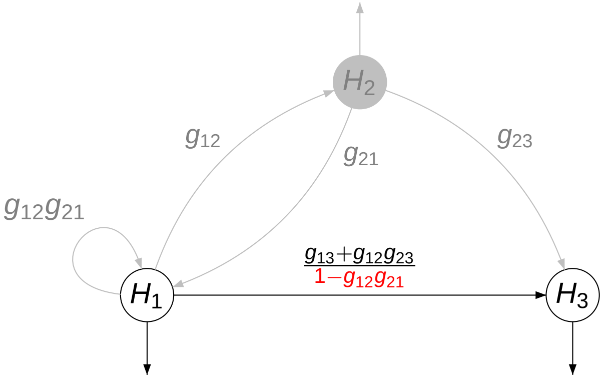


Control of the FWE

Theorem

The initial levels α, the transition matrix $\mathbf{G}$ and the algorithm define a unique multiple testing procedure controlling strongly the FWER at level α.

Proof:

- The graph and algorithm define weighted Bonferroni tests for all intersection hypotheses.
- The algorithm is a short cut for the resulting closed test.

Closed Testing with Weighted Bonferroni Tests

Closed Testing Procedure:

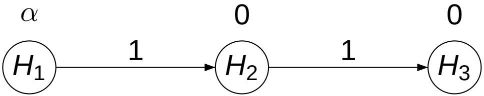
1. Define level α tests for all intersection hypotheses $H_J = \cap_{i \in J} H_i, J \subseteq \{1, \ldots, m\}$.
2. Reject H_j, at multiple level α, if for all $J \subseteq \{1, \ldots, m\}$ that contain j the intersection hypotheses H_J can be rejected at level α.

Weighted Bonferroni Test.

1. For each $J \subseteq \{1, \ldots, m\}$ define α_j^J such that $\sum_{j \in J} \alpha_j^J = \alpha$.
2. Reject H_J, if $p_j \leq \alpha_j^J$ for some $j \in J$.

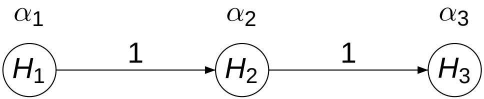
Fixed Sequence Test

$$\boldsymbol{\alpha} = (\alpha, 0, 0), \quad \mathbf{G} = \begin{pmatrix} 0 & 1 & 0 \\ 0 & 0 & 1 \\ 0 & 0 & 0 \end{pmatrix}$$



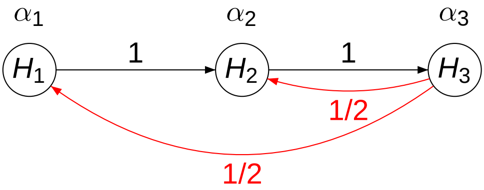
Fallback Procedure (Wiens, 2003)

$$\boldsymbol{\alpha} = (\alpha_1, \alpha_2, \alpha_3), \quad \mathbf{G} = \begin{pmatrix} 0 & 1 & 0 \\ 0 & 0 & 1 \\ 0 & 0 & 0 \end{pmatrix}$$



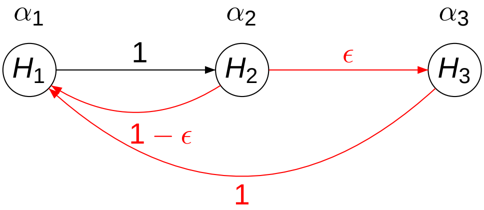
Improved Fallback Procedure (Wiens & Dmitrienko, 2005)

$$\boldsymbol{\alpha} = (\alpha_1, \alpha_2, \alpha_3), \quad \mathbf{G} = \begin{pmatrix} 0 & 1 & 0 \\ 0 & 0 & 1 \\ 1/2 & 1/2 & 0 \end{pmatrix}$$



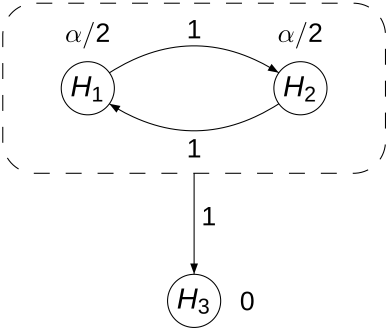
Yet another improved Fallback Procedure

$$\boldsymbol{\alpha} = (\alpha_1, \alpha_2, \alpha_3), \quad \mathbf{G} = \begin{pmatrix} 0 & 1 & 0 \\ 1-\epsilon & 0 & \epsilon \\ 1 & 0 & 0 \end{pmatrix}$$



Let $\epsilon \longrightarrow 0$, see explanation below.

Shifting level between families of hypotheses (1)

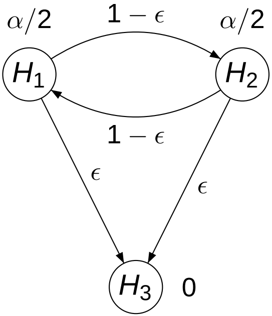


Test strategy

- H_1, H_2 tested with Bonferroni-Holm
- H_3 tested (at level α) only if H_1 and H_2 are rejected

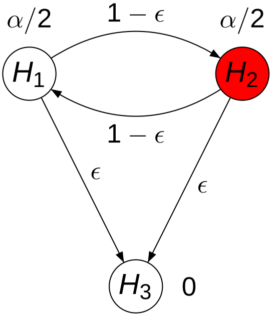
Shifting level between families of hypotheses (2)

$$\boldsymbol{\alpha} = \left(\frac{\alpha}{2}, \frac{\alpha}{2}, 0\right), \quad \mathbf{G} = \begin{pmatrix} 0 & 1-\epsilon & \epsilon \\ 1-\epsilon & 0 & \epsilon \\ 0 & 0 & 0 \end{pmatrix}$$



Let $\epsilon \to 0$.

Shifting level between families of hypotheses (2)



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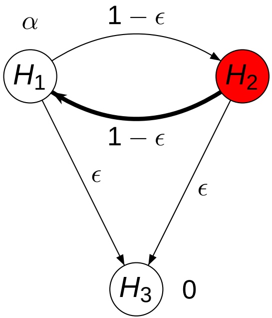
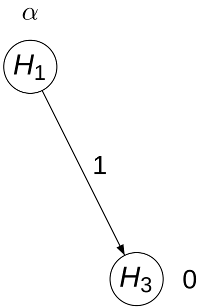


Let $\epsilon \longrightarrow 0$.

Shifting level between families of hypotheses (2)

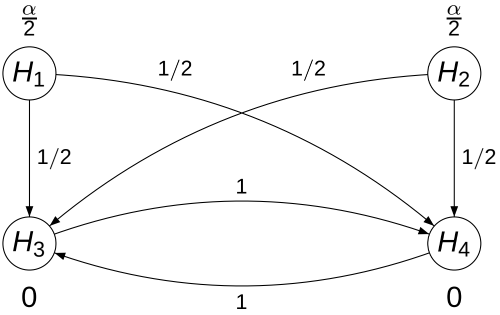
$$\boldsymbol{\alpha} = (\alpha, 0, 0)\,, \quad \mathbf{G} = \begin{pmatrix} 0 & 0 & 1 \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{pmatrix}$$



Let $\epsilon \to 0$.

Parallel Gatekeeping (Dmitrienko, Offen & Westfall, 2003)

$$\boldsymbol{\alpha} = \left(\tfrac{\alpha}{2}, \tfrac{\alpha}{2}, 0, 0\right), \quad \mathbf{G} = \begin{pmatrix} 0 & 0 & 0.5 & 0.5 \\ 0 & 0 & 0.5 & 0.5 \\ 0 & 0 & 0 & 1 \\ 0 & 0 & 1 & 0 \end{pmatrix}$$



Improved Parallel Gatekeeping (Hommel, Bretz & Maurer, 2007)

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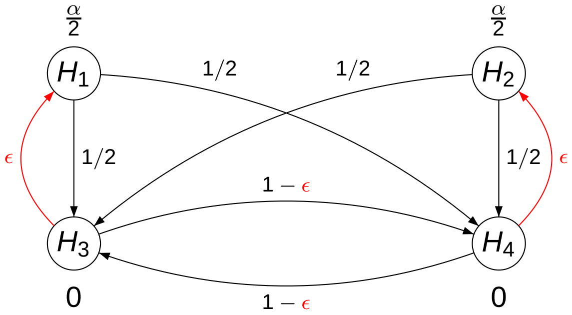

When is a graph complete?

... and cannot be improved by adding additional edges?

A sufficient condition for completeness:

- the weights of outgoing edges sum to one at each node and
- every node is accessible from any of the other nodes

If $\alpha_i > 0, i = 1, \ldots, m$, this is also a necessary condition for completeness.

How general is the procedure?

Can all consonant closed test procedures using weighted Bonferroni Tests for the intersection hypotheses be constructed with the graphical procedure?

No:

- For the general procedure we can choose weights for 2^{m-1} intersection hypotheses.
- The graphical procedure is defined by $m^2 + m$ parameters.

Extensions

- Multiplicity adjusted confidence bounds (Guilbaud (2008) and Strassburger and Bretz (2008))
- Adjusted p-values

Construction of Adjusted Confidence Bounds

Assumptions:

- Test for $H_i : \theta_i \leq 0$ v.s. $H_i' : \theta_i > 0$
- Let $p_i(\mu)$ denote a p-value for $H_i(\mu) : \theta_i \leq \mu$.
- $p_i(\mu)$ is increasing in μ.
- $b_i(\gamma) = \inf\{\mu | p_i(\mu) > \gamma)\}$ (local level γ confidence bound)
- $I \subseteq \{1, \ldots, m\} \ldots$ index set of rejected hypotheses H_i.

The adjusted bounds

- If $I = \{1, \ldots, m\}$: $b_i^{adj} = \max\{0, b_i(\alpha_i)\}$.
- Otherwise:

$$b_i^{adj} = \begin{cases} 0 & \text{if } i \in I \\ b_i(\alpha_i') & \text{otherwise.} \end{cases}$$

$\alpha_i' \ldots$ level of hypothesis H_i in the final graph.

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$$b_i^{adj} = \begin{cases} 0 & \text{if } i \in I \\ b_i(\alpha_i') & \text{otherwise.} \end{cases}$$

$\alpha_i' \ldots$ level of hypothesis H_i in the final graph.

Construction of Adjusted Confidence Bounds

Assumptions:

- Test for $H_i : \theta_i \leq 0$ v.s. $H_i' : \theta_i > 0$
- Let $p_i(\mu)$ denote a p-value for $H_i(\mu) : \theta_i \leq \mu$.
- $p_i(\mu)$ is increasing in μ.
- $b_i(\gamma) = \inf\{\mu | p_i(\mu) > \gamma)\}$ (local level γ confidence bound)
- $I \subseteq \{1, \ldots, m\} \ldots$ index set of rejected hypotheses H_i.

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Construction of adjusted p-values

Let $\mathbf{w} = (w_1, \dots, w_m) = (\alpha_1, \dots, \alpha_m)/\alpha$

$J = \{1, \dots, m\}$ and $p_{\max} = 0$

1. Let $j = \text{argmin}_{i \in J} p_i / w_i$
2. $p_j^{adj} = \max\{p_j/w_j, p_{\max}\}$
3. $p_{\max} = p_j^{adj}$
4. Update the graph:

$$J \rightarrow J/\{j\}$$

$$w_\ell \rightarrow \begin{cases} w_\ell + w_j g_{j\ell}, & \ell \in J \\ 0, & \text{otherwise} \end{cases}$$

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

5. Goto step 1.

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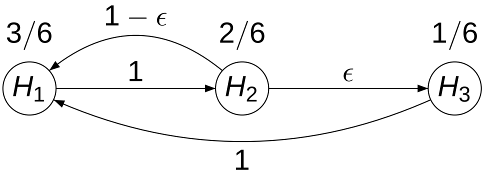
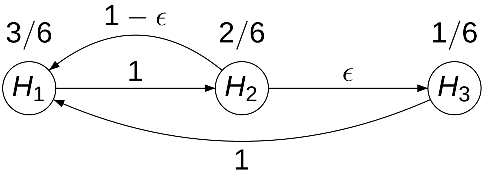
5. Goto step 1.

Example: Improved Fallback Procedure



$p_1 = 0.02$ $p_2 = 0.01$ $p_3 = 0.06$

Example: Improved Fallback Procedure



$p_1 = 0.02$ $\quad$ $p_2 = 0.01$ $\quad$ $p_3 = 0.06$

$\frac{p_1}{w_1} = 0.036$ $\quad$ $\frac{p_2}{w_2} = 0.03$ $\quad$ $\frac{p_3}{w_3} = 0.36$

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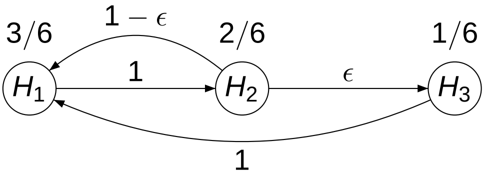

$p_1 = 0.02$ $\quad$ $p_2 = 0.01$ $\quad$ $p_3 = 0.06$

$\frac{p_1}{w_1} = 0.036$ $\quad$ $p_2^{adj} = 0.03$ $\quad$ $\frac{p_3}{w_3} = 0.36$

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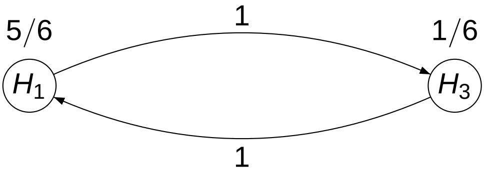

$p_1 = 0.02$ $\quad$ $p_2 = 0.01$ $\quad$ $p_3 = 0.06$

$\frac{p_1}{w_1} = 0.024$ $\quad$ $p_2^{adj} = 0.03$ $\quad$ $\frac{p_3}{w_3} = 0.36$

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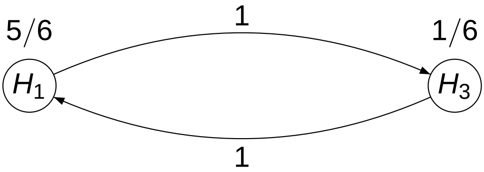

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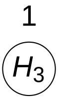

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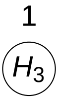

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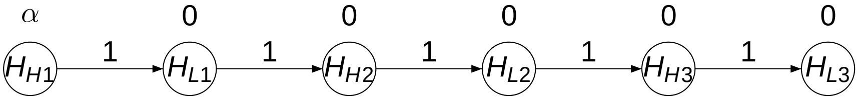
$p_1^{adj} = 0.03$ $p_2^{adj} = 0.03$ $p_3^{adj} = 0.06$

- Two dose levels
- Three hierarchically ordered endpoints:
  annualized relapse rate, number of lesions in the brain, and disability progression.
- Six elementary hypotheses $H_{ij} : \theta_{ij} \leq 0$

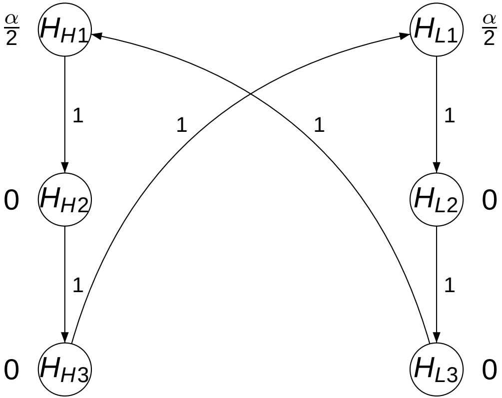
  $i =$H(igh dose), L(ow dose)

  $j = 1, 2, 3 \ldots$ endpoints

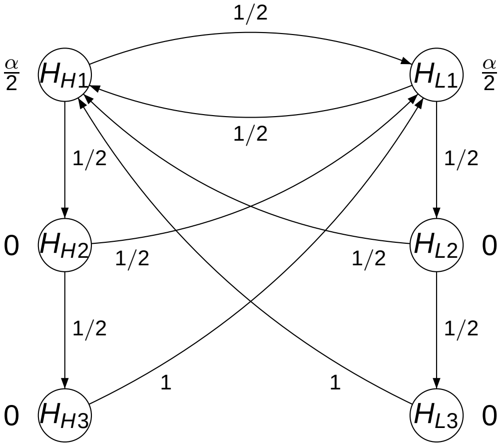
Strategy 1: Fixed Sequence Test



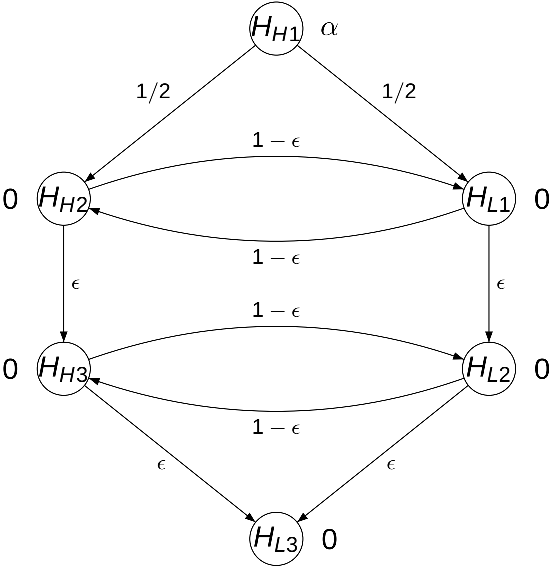
Strategy 2: Fixed Sequence Test per Dose



Strategy 3: More weight to the Primary Endpoints



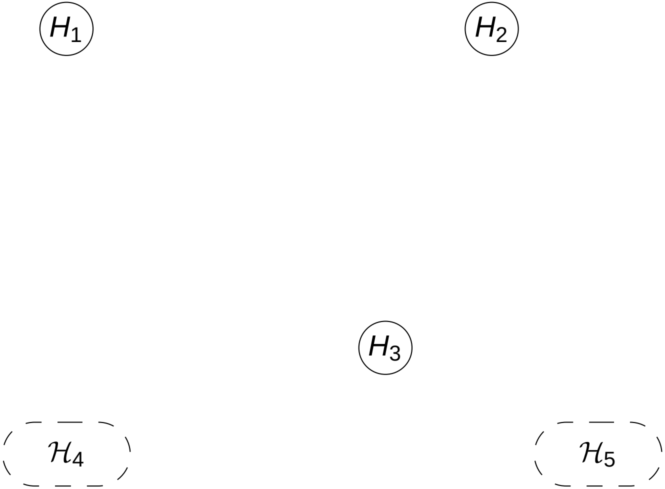
Strategy 4 : Gatekeeper



- Combination (AB) and mono therapy (B) compared with comparator(A)
- Superiority and non-inferiority tests for primary and multiple secondary endpoints.
- Three elementary hypotheses and two families of hypotheses:
    - H_1: superiority of AB vs. A
    - H_2: non-inferiority of B vs. A
    - H_3: superiority of B vs. A
    - $\mathcal{H}_4$: multiple secondary variables for AB vs. A
    - $\mathcal{H}_5$: multiple secondary variables for B vs. A

Multiple Test Procedure

Multiple Test Procedure



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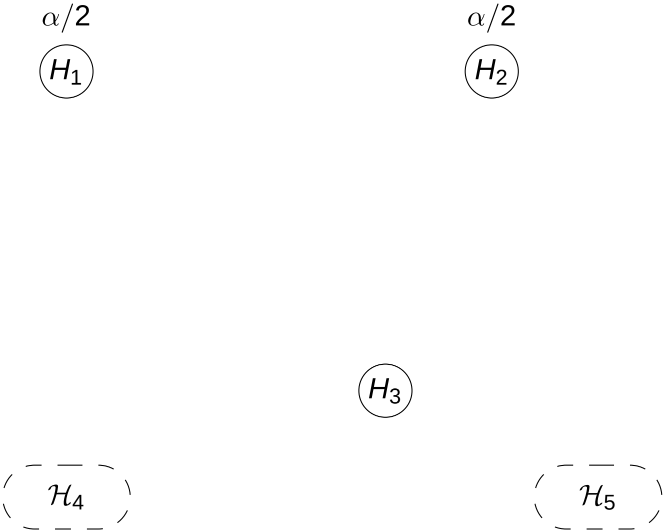

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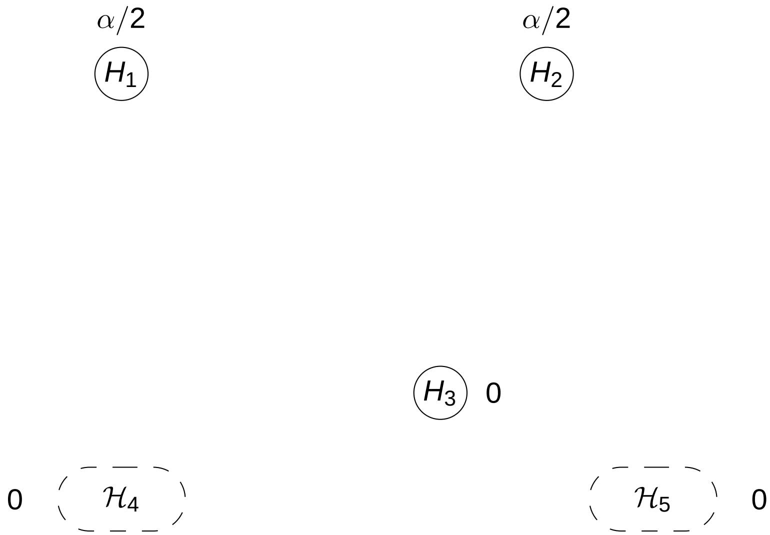
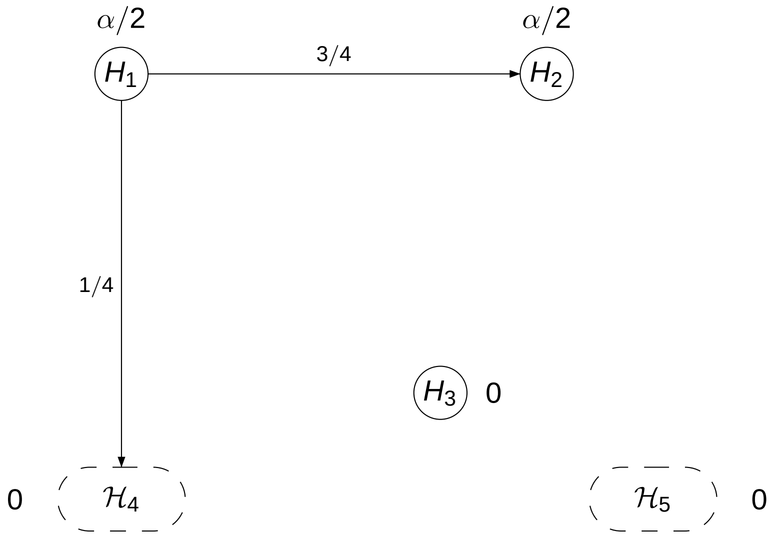


Multiple Test Procedure



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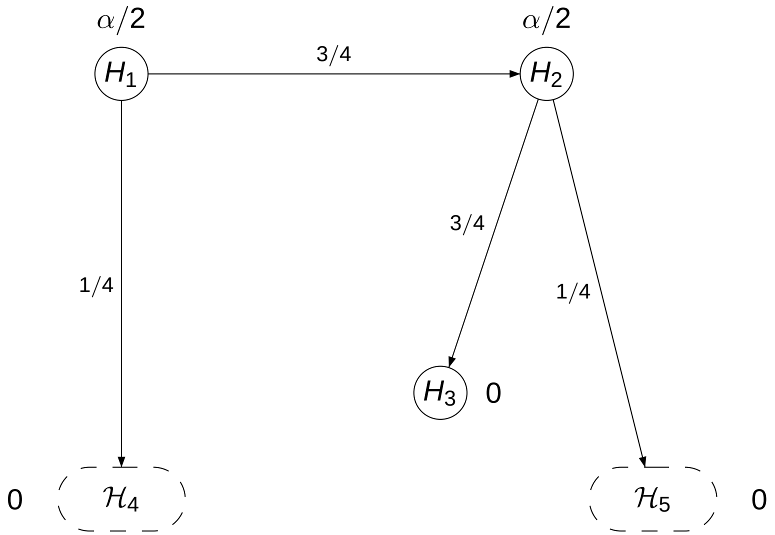
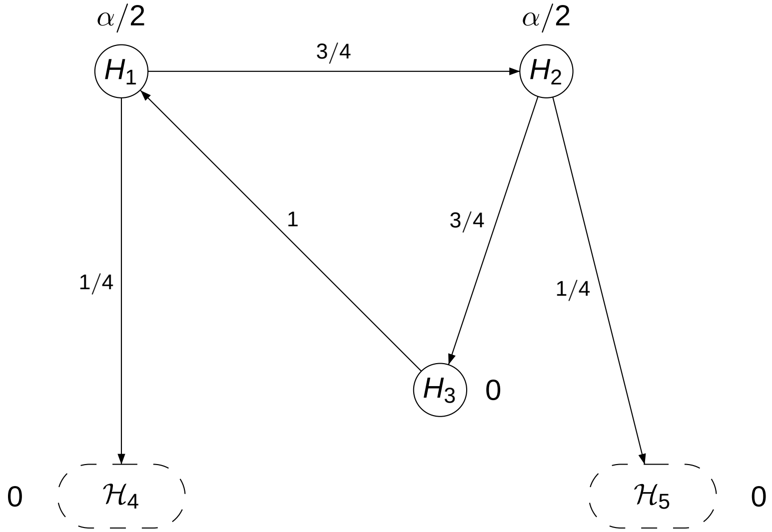
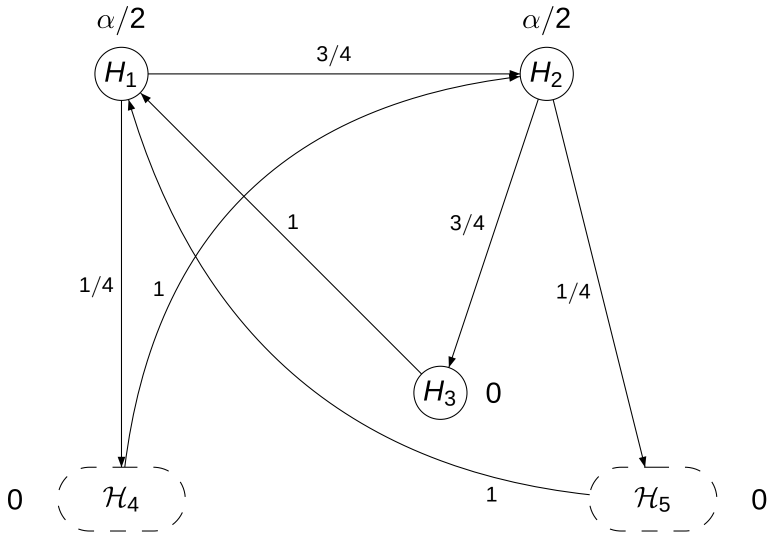


Multiple Test Procedure



Multiple Test Procedure

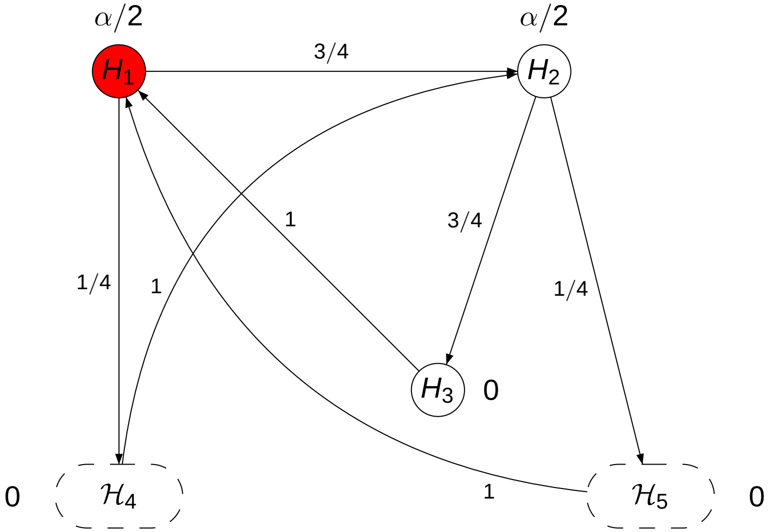


Multiple Test Procedure

$$\boldsymbol{\alpha} = \left(\frac{\alpha}{2}, \frac{\alpha}{2}, 0, 0, 0\right)$$

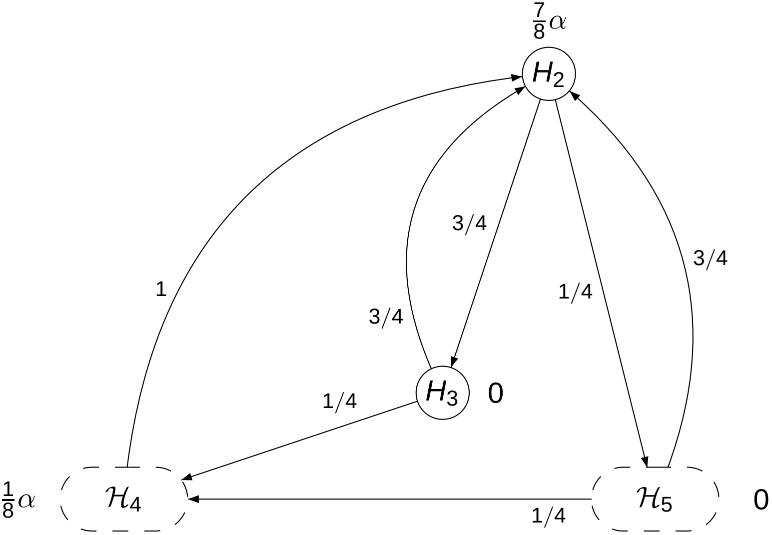
$$\mathbf{G} = \begin{pmatrix} 0 & 3/4 & 0 & 1/4 & 0 \\ 0 & 0 & 3/4 & 0 & 1/4 \\ 1 & 0 & 0 & 0 & 0 \\ 0 & 1 & 0 & 0 & 0 \\ 1 & 0 & 0 & 0 & 0 \end{pmatrix}$$

Example



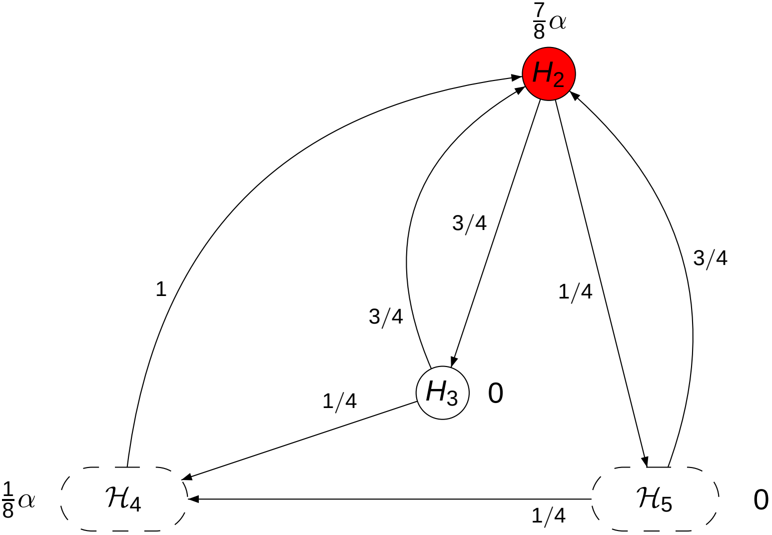
$\alpha/2$
$\alpha/2$
$3/4$
H_1
H_2
1
$3/4$
$1/4$
1
$1/4$
H_3
0
0
$\mathcal{H}_4$
1
$\mathcal{H}_5$
0

Example



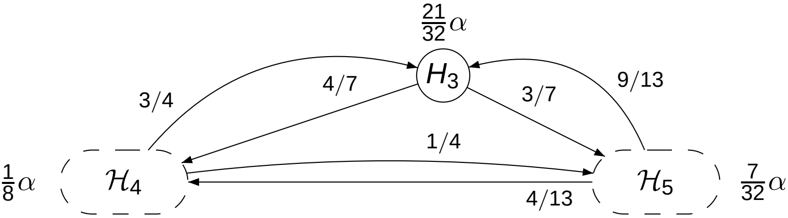
$\frac{7}{8}\alpha$
H_2
$3/4$
$3/4$
$1/4$
$3/4$
1
H_3
0
$1/4$
$\frac{1}{8}\alpha$
$\mathcal{H}_4$
$\mathcal{H}_5$
0
$1/4$

Example



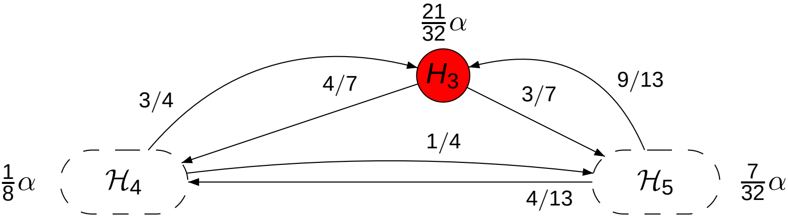
$\frac{7}{8}\alpha$
H_2
3/4
3/4
1
1/4
3/4
H_3
0
1/4
$\frac{1}{8}\alpha$
$\mathcal{H}_4$
$\mathcal{H}_5$
0
1/4

Example



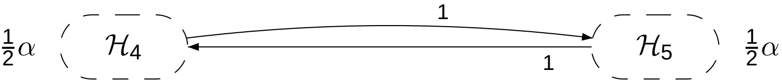
$\frac{21}{32}\alpha$
H_3
3/4
4/7
3/7
9/13
1/4
$\frac{1}{8}\alpha$
$\mathcal{H}_4$
$\mathcal{H}_5$
$\frac{7}{32}\alpha$
4/13

Example



$\frac{21}{32}\alpha$
H_3
3/4
4/7
3/7
9/13
1/4
$\frac{1}{8}\alpha$
$\mathcal{H}_4$
$\mathcal{H}_5$
$\frac{7}{32}\alpha$
4/13

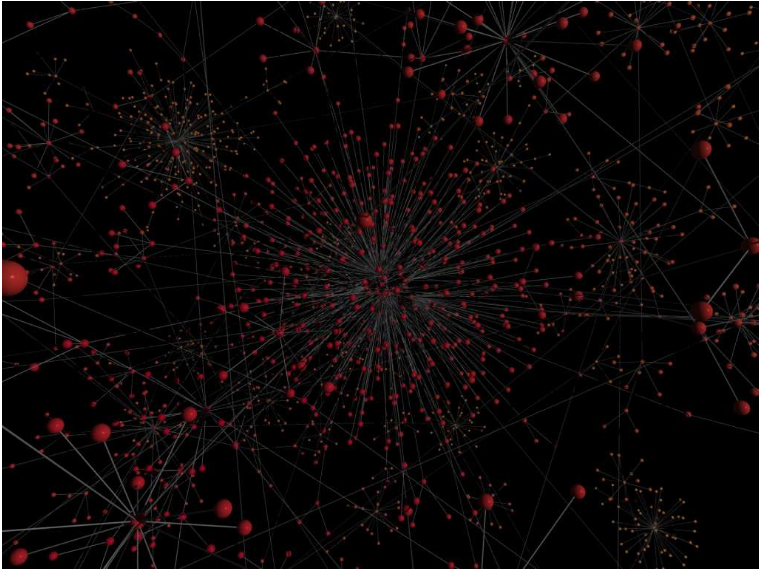
Example



Summary and Extensions

- Intuitive graphical procedure to construct multiple tests
- Easy to communicate the testing strategy
- Easy to implement in software
- Adjusted p-values available
- Multiplicity adjusted confidence intervals can be constructed based on Strassburger and Bretz (2008), Guilbaud (2008)
- Adjusted p-values
- Interpretation as Finite Markov Chain
- Similar approach published by Burman (2009)

Aesthetics...



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