Multiples Testen
-Graphische Prozeduren-

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MSc Medical Biometry/Biostatistics

WiSe 2019/2020

Idee: α-Recycling

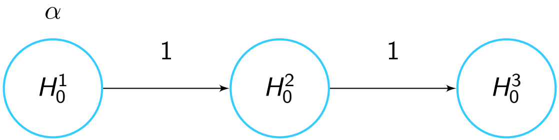
Notation

- Nullhypothesen $H_0^1, \ldots, H_0^h$
- $p_1, \ldots, p_h$: elementare p-Werte
- $\boldsymbol{\alpha} = (\alpha_1, \ldots, \alpha_h)$: anfängliche Zuordnung des Niveaus $\alpha = \sum_{i=1}^{h} \alpha_i$

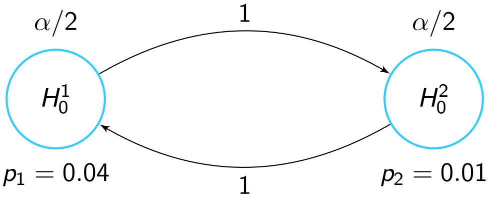
"α-Recycling"

1. Wenn eine Hypothese H_0^i verworfen wird, verteile ihr Niveau α_i auf andere noch nicht verworfene Hypothesen (einer bestimmten Regel folgend)
2. Teste mit den so erhaltenen Niveaus
3. Gehe zu Schritt 1 bis keine Hypothesen mehr verworfen werden können

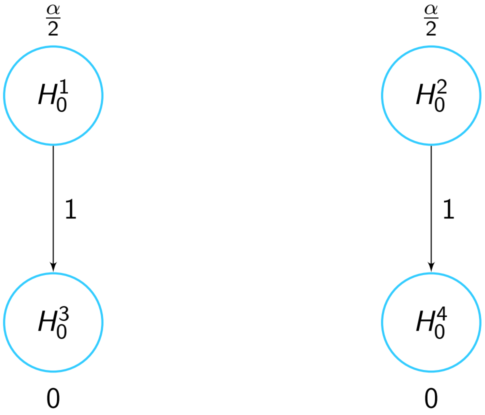
Hierarchischer Test



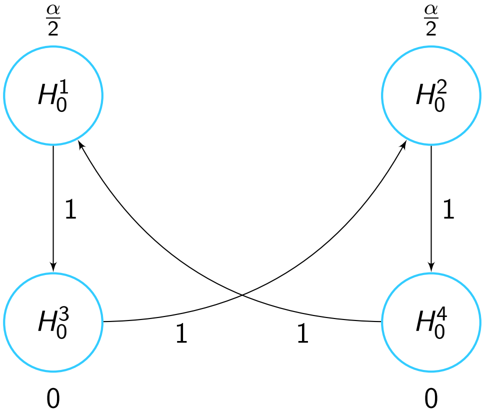
Bonferroni-Holm-Test (k=2, α=0.025)



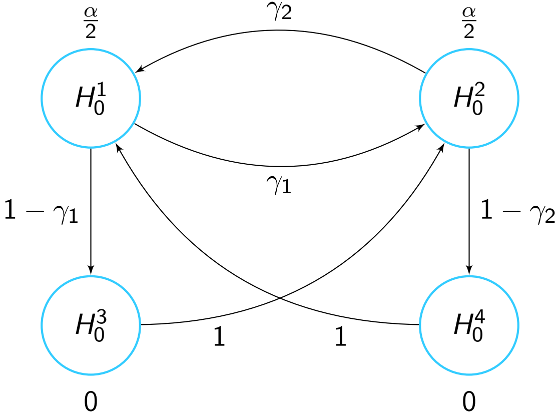
Einfaches paralleles Gatekeeping



Verbessertes paralleles Gatekeeping



Mehr Gewicht auf die primären Endpunkte



Definition der Prozedur

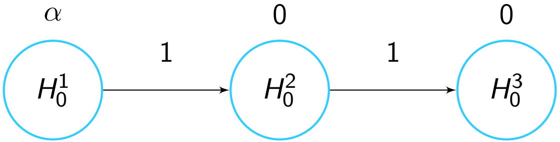
Allgemeine Defintion

- $\boldsymbol{\alpha} = (\alpha_1, \dots, \alpha_h)$, $\sum_{i=1}^{h}, \alpha_i = \alpha$, anfängliche Niveaus
- $\mathbf{G} = (g_{ij}) : h \times h$ Transitions-Matrix
  g_{ij} mit $0 \leq g_{ij} \leq 1$, $g_{ii} = 0$ und $\sum_{j=1}^{h} g_{ij} = 1$ für alle $i = 1, \dots, h$.

- g_{ij}, Anteil des Niveaus für H_0^i das nach H_0^j geschoben wird
- **G** bestimmt den Graphen vollständig
- **G** und $\boldsymbol{\alpha}$ bestimmen den multiplen Test

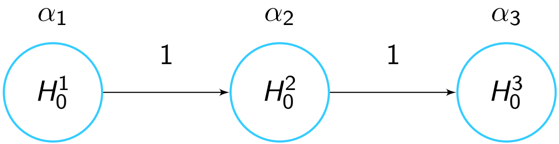
Hierarchischer Test

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



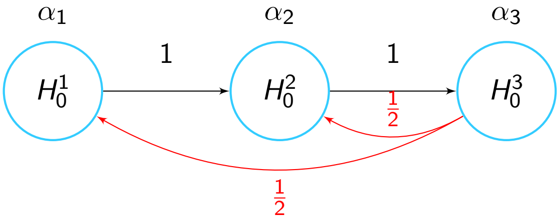
Fallback Procedure (Wiens, 2003)

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



Improved Fallback Procedure (Wiens & Dmitrienko, 2005)

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



Testprozedur

Definiere $J = \{1, \dots, h\}$

1. Setze $j = \text{argmin}_{i \in J} p_i / \alpha_i$
2. Wenn $p_j \leq \alpha_j$ verwerfe H_0^j und gehe zu 3.
   Ansonsten stoppe und akzeptiere alle H_0^i, $i \in J$.
3. Aktualisiere den Graphen:

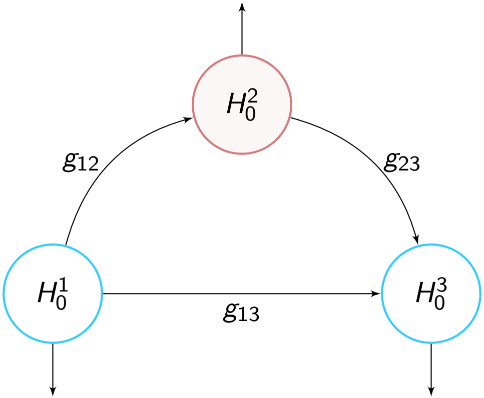
$$J \to J / \{j\}$$

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

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

   Konvention: Wenn kein Pfeil von H_0^j nach H_0^l, dann $g_{jl} = 0$.
4. Gehe zu Schritt 1.

Aktualisierung des Graphen – Fall 1



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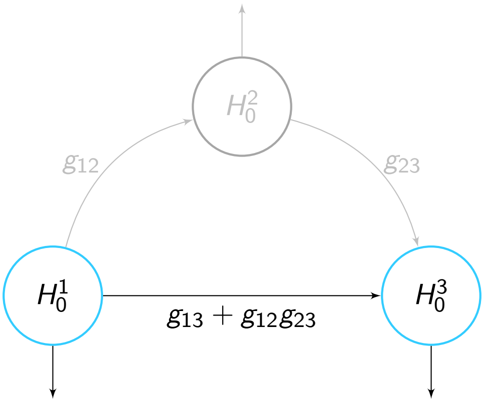
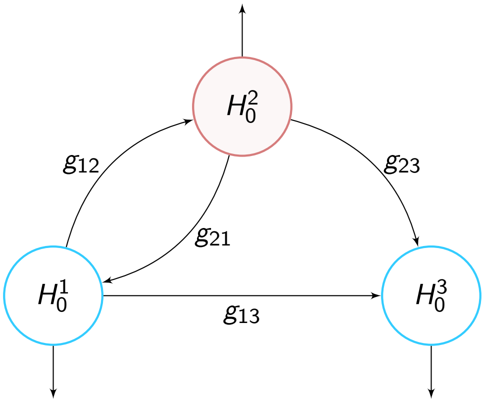


Aktualisierung des Graphen – Fall 2



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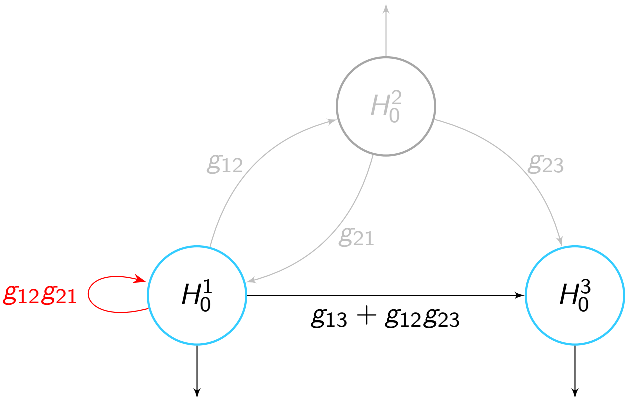

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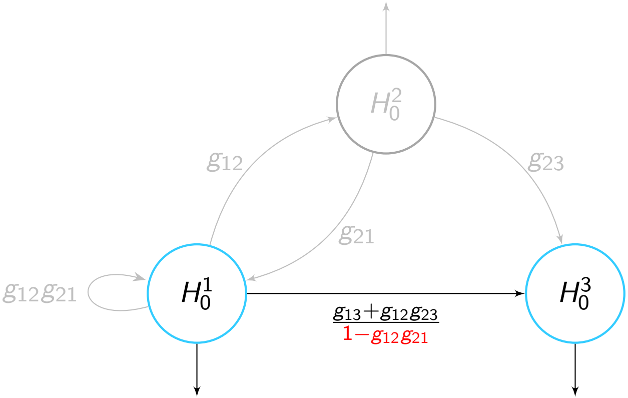


Kontrolle der FWER

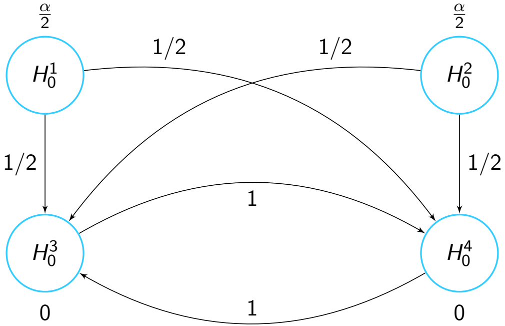
Satz.
Die Anfangsniveaus $\boldsymbol{\alpha}$, die Transitions-Matrix **G** und der Algorithmus definieren eindeutig eine multiple Testprozedur, die die FWER stark auf dem Niveau α kontrolliert.

Beweiskizze:

- Der Graph und der Algorithmus definieren einen lokal konsonanten verallgemeinerten Bonferroni- Abschluss-Test
- Der Algorithmus ist die Abkürzung des entsprechenden Abschlusstests

Paralleles Gatekeeping nach Dmitrienko et al. (2003)

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



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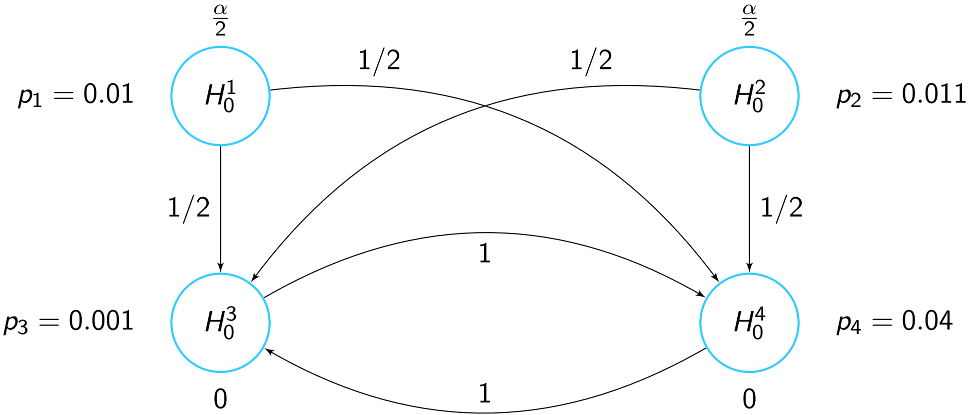

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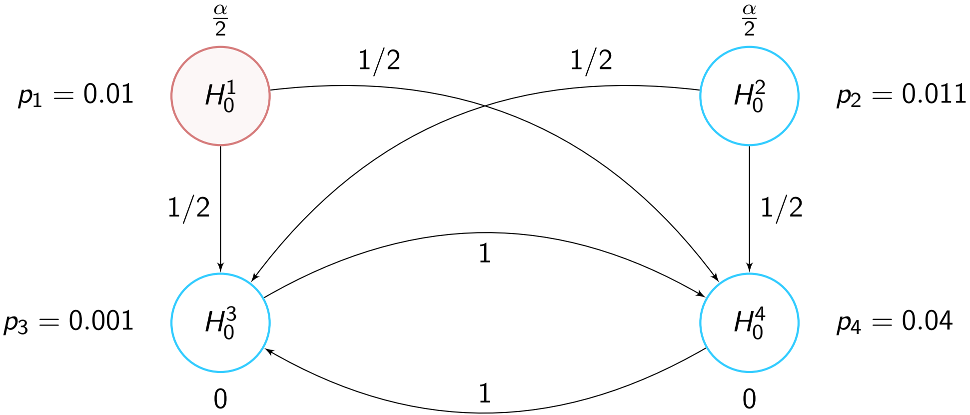

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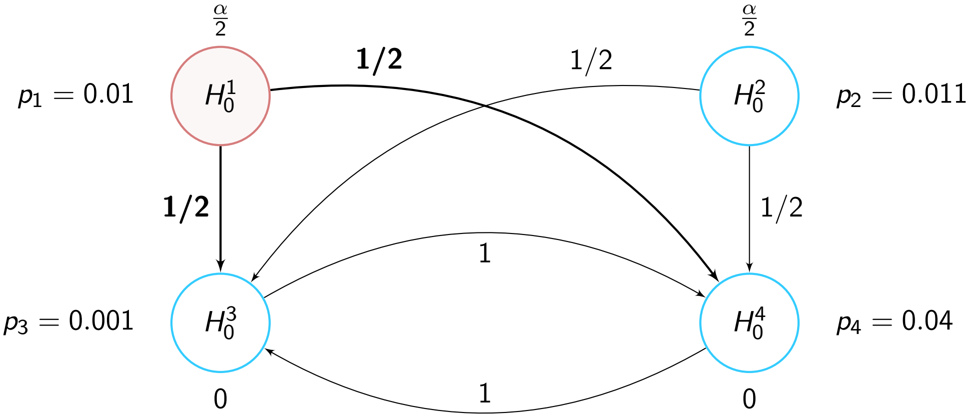

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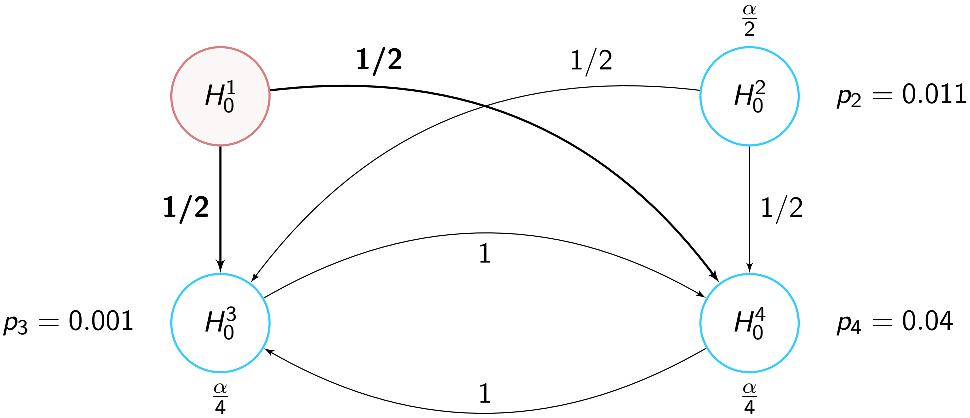

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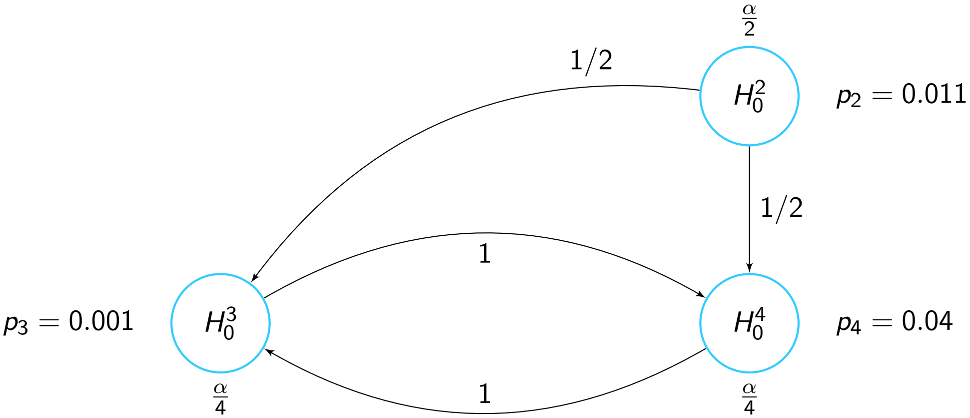

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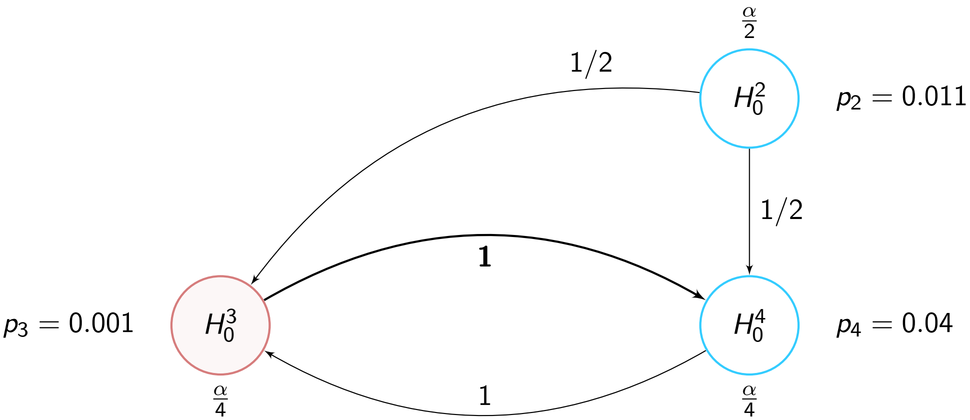

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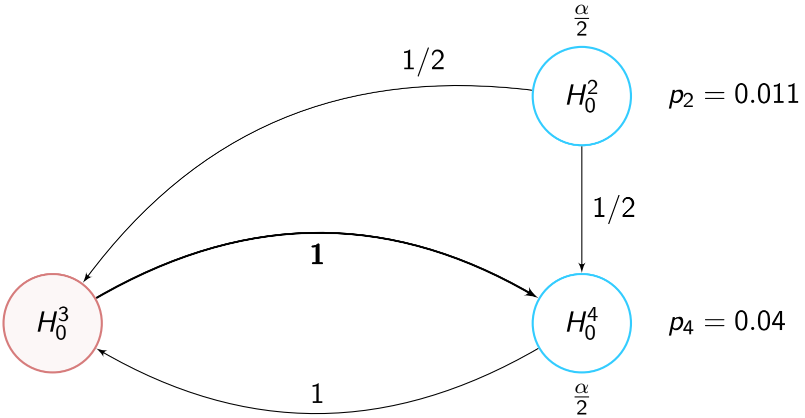

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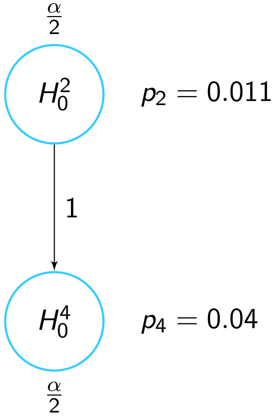

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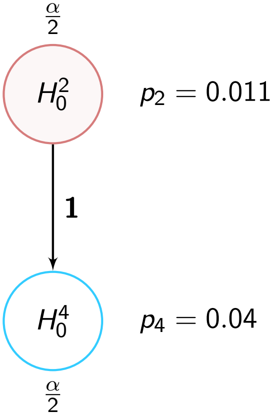

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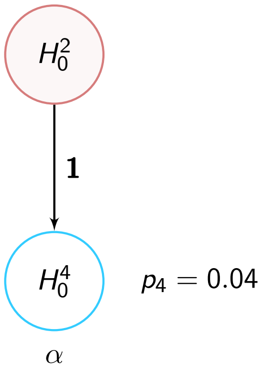

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H_0^4 $\quad p_4 = 0.04$

α

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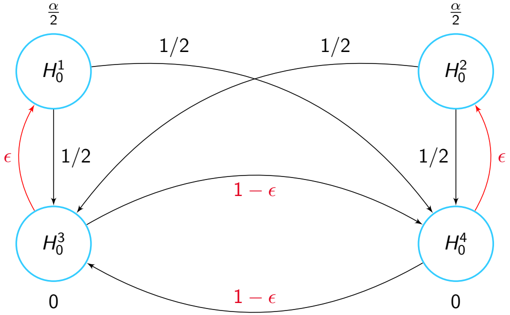
α

Verbessertes paralleles Gatekeeping (Hommel, Bretz & Maurer, 2007)

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



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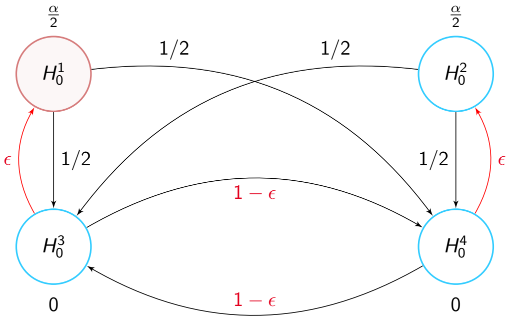

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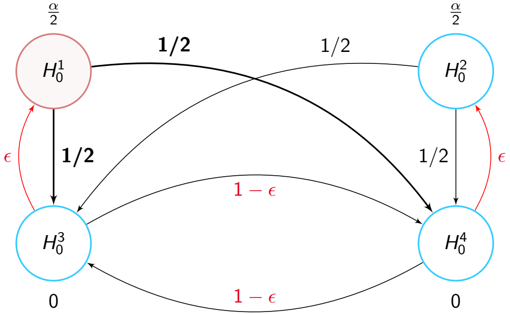

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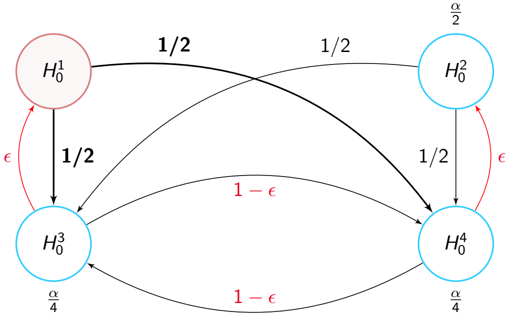

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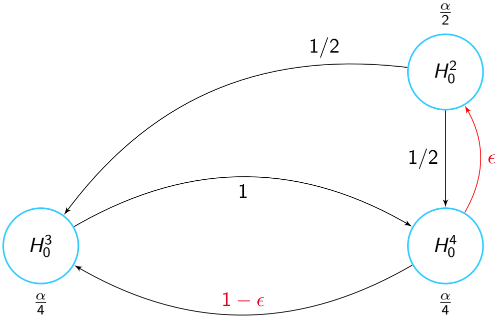

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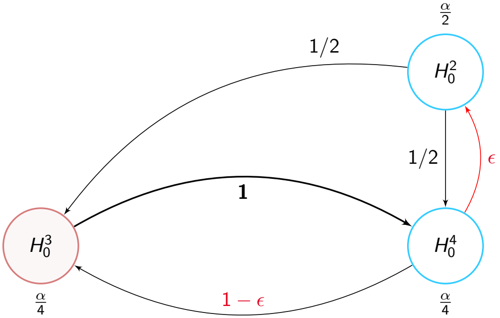

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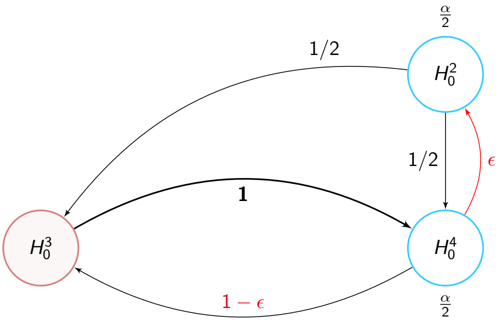

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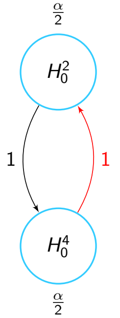


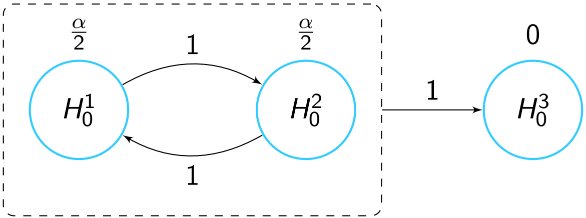
Wann ist der Graph vollständig und kann nicht verbessert werden?

Ein hinreichende Bedingung für Vollständigkeit ist:

- die Gewichte aller ausgehenden Pfeile einer Hypothese summieren sich auf 1 und
- jede Hypotheses ist von jeder aus erreichbar.

Wenn $\alpha_i > 0$ für alle $i = 1, \ldots, h$, dann ist das auch eine notwendige Bedingung.

Signifikanzniveauverschiebung zwischen Familien von Hypothesen



Teststrategie

- H_0^1, H_0^2 werden mit Bonferroni-Holm gestest
- H_0^3 wird nur dann (zum Niveau α) getestet, wenn H_0^1 **und** H_0^2 verworfen werden

Signifikanzniveauverschiebung zwischen Familien von Hypothesen

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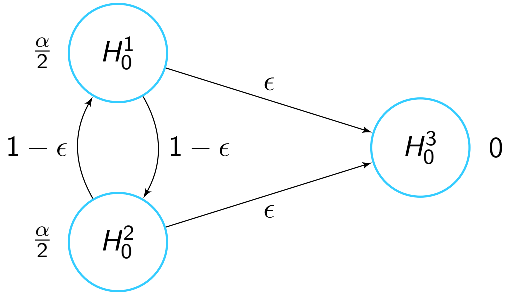

Wir lassen $\epsilon \to 0$.

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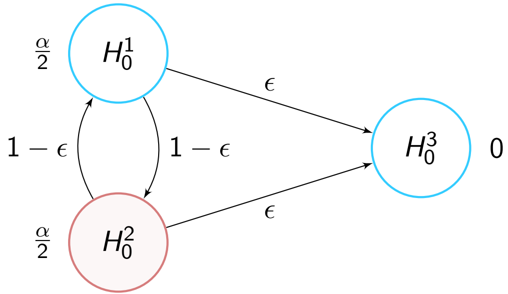

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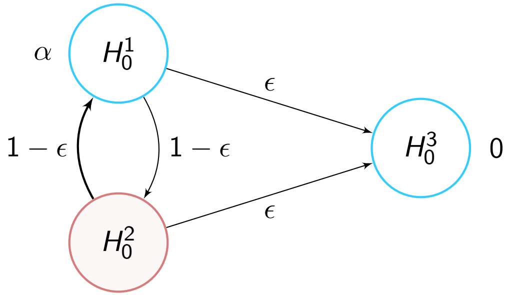

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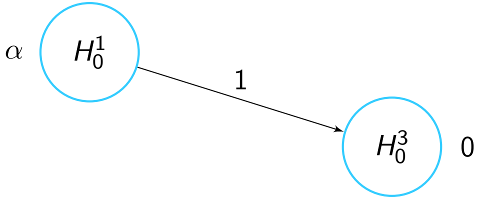

Erinnerung: Verbesserte Fallback Procedure (Wiens, 2003)

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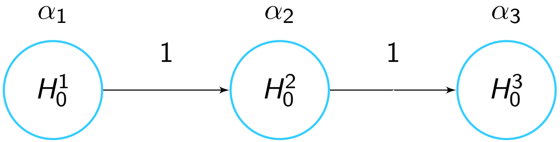

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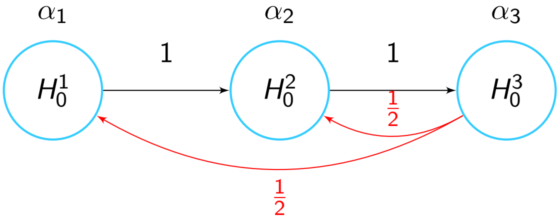
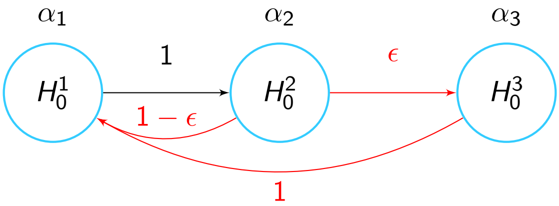


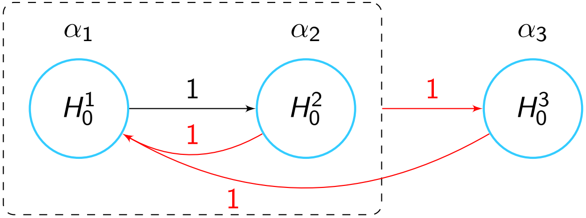
Eine andere Verbesserung der Fallback Procedure

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



Wenn $\epsilon \to 0$, dann ...

Eine andere Verbesserung der Fallback Procedure



Übung: Überlegen Sie sich, dass diese und die vorige Prozedur identisch sind.

Literatur zu graphischen Prozeduren

F. Bretz, W. Maurer, W. Brannath, and M. Posch.
A graphical approach to sequentially rejective multiple test procedures.
Statistics in Medicine, 28:586–604, 2008.

F. Bretz, W. Maurer, and G. Hommel.
Test and power considerations for multiple endpoint analyses using sequentially rejective graphical procedures.
Statistics in Medicine, 30:1489–1501, 2011.

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

F. Bretz, M. Posch, E. Glimm, F. Klinglmueller, W. Maurer, and K. Rohmeyer.
Graphical approaches for multiple endpoint problems using weighted Bonferroni, Simes or parametric tests.
Biometrical Journal, 6:894-913, 2011