The Sequential Rejection Principle

Livio Finos

I thank Aldo Solari, Jelle Goeman and Florian KlingImueller for the ideas and the materials we shared along these years. The material is the result of all this resoning together.

Outline

Some Multiple Testing Procedures

The sequential rejection principle

Inheritance procedure

- Application: Genomics
- Application: Neurotoxicity assay

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Some Multiple Testing Procedures

The sequential rejection principle

Inheritance procedure

- Application: Genomics
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Familywise Error Rate

$\mathcal{T} \subseteq \mathcal{H}$: set of true null hypotheses

Strong control of the familywise error rate

$$\text{FWE} = \Pr(\text{at least one type I error}) \leq \alpha \quad \forall\, \mathcal{T} \subseteq \mathcal{H}$$

Multiple testing procedures

- Bonferroni and Holm
- Closed testing
- Gatekeeping
- Stepdown $S_{\max}$
- ...

Bonferroni and Holm

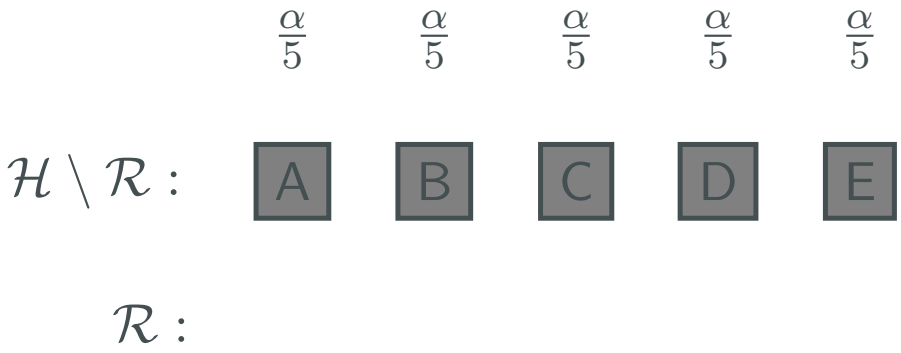
Bonferroni Inequality

$$\text{FWE} = \Pr\left(\bigcup_{H\in\mathcal{T}}\left\{p_H \le \frac{\alpha}{|\mathcal{H}|}\right\}\right) \le \sum_{H\in\mathcal{H}} \Pr\left(p_H \le \frac{\alpha}{|\mathcal{H}|}\right) \le \alpha$$

Holm's sequential procedure

1. Start testing at $\alpha/|\mathcal{H}|$
2. After $|\mathcal{R}|$ hypotheses have been rejected, test at $\alpha/|\mathcal{H}\setminus\mathcal{R}|$
3. Stop at the first failure to reject a hypothesis

Start at $\alpha/5$



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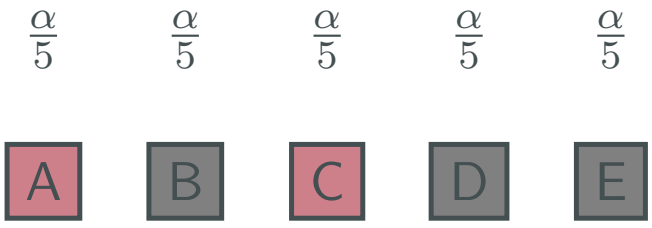
Suppose p_A and p_C significant



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Holm's sequential procedure Go on at $\alpha/3$

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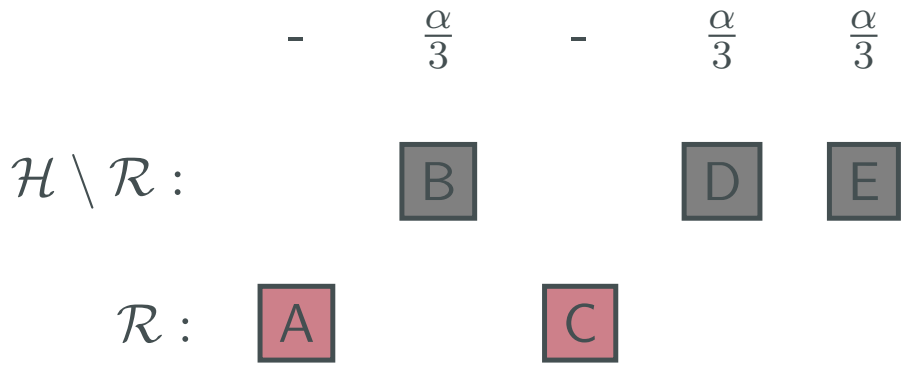

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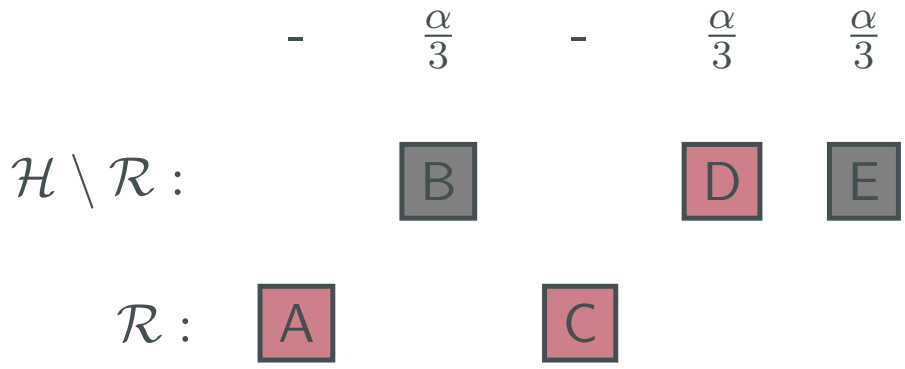
Suppose p_D significant



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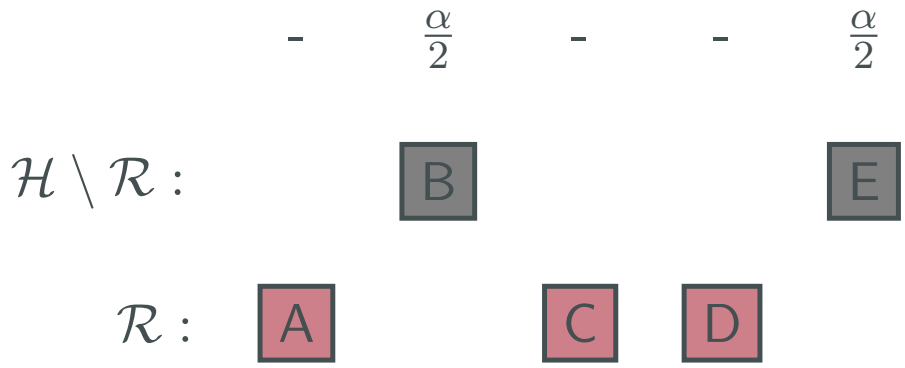

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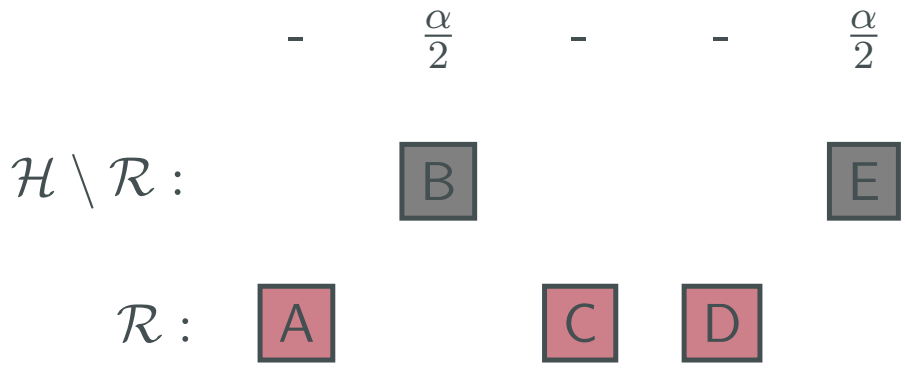
No more rejections. Stop



Closed Testing

Make use of the dependence structure of test statistics

Closed Testing

1. Make $\mathcal{H}$ closed, i.e. $A, B \in \mathcal{H} \Rightarrow AB \equiv A \cap B \in \mathcal{H}$
2. Start testing the top node
3. At each step, test all child nodes of which all ancestors are significant at α

Starting hypotheses

Closed Testing

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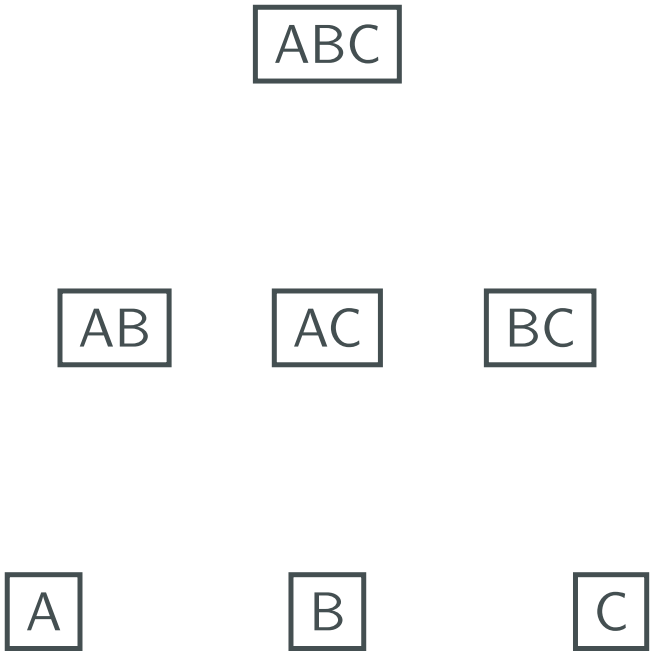
Make $\mathcal{H}$ closed w.r. to intersection



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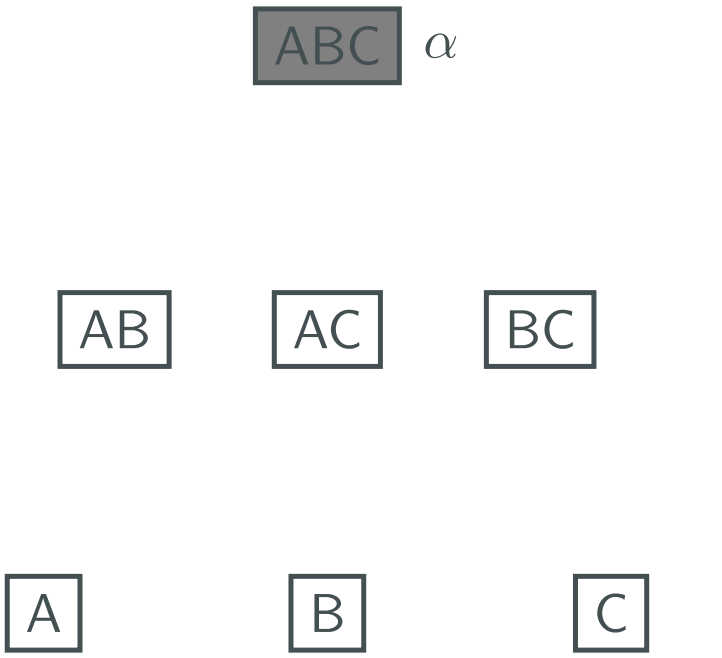
Start testing the top node at α



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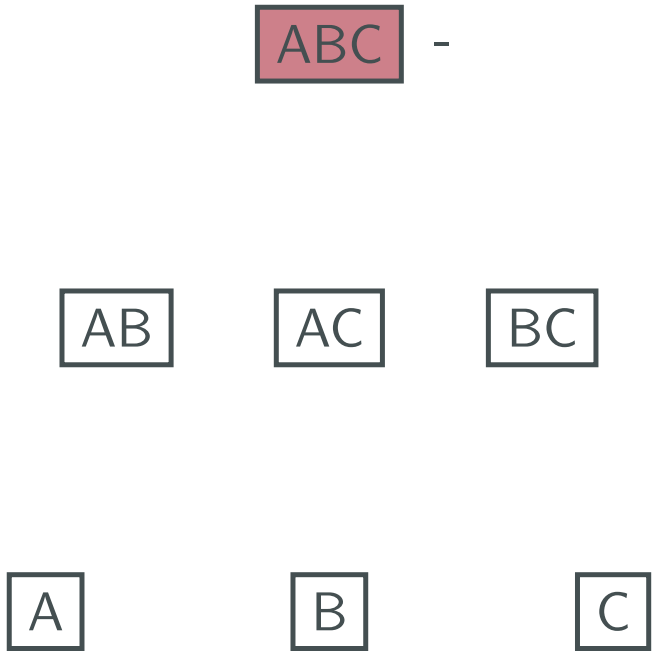
Suppose the top node is significant



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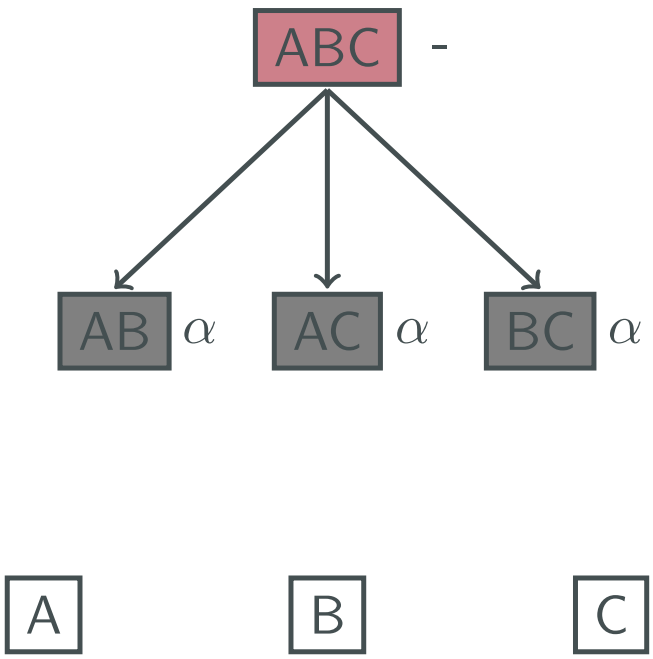
Go down



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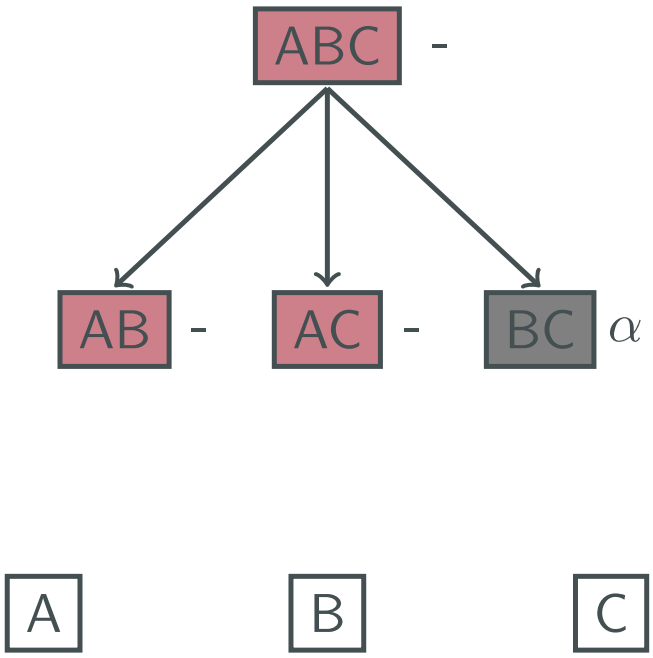
Find those are significant



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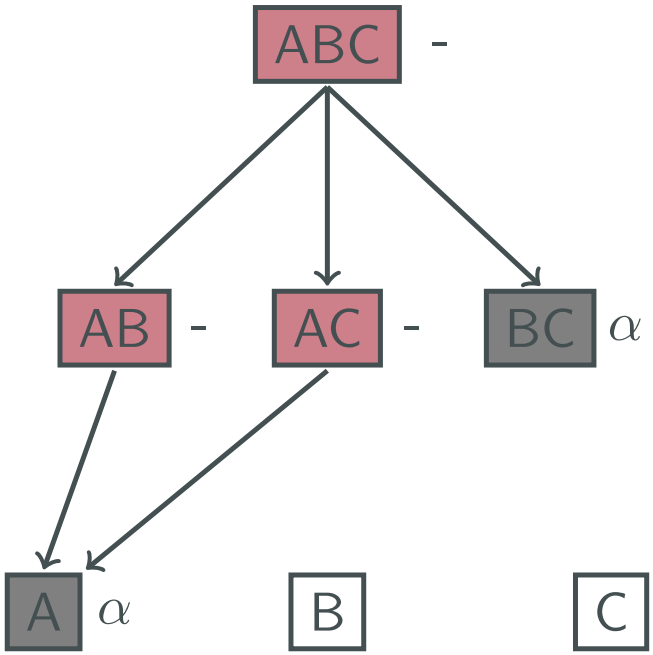

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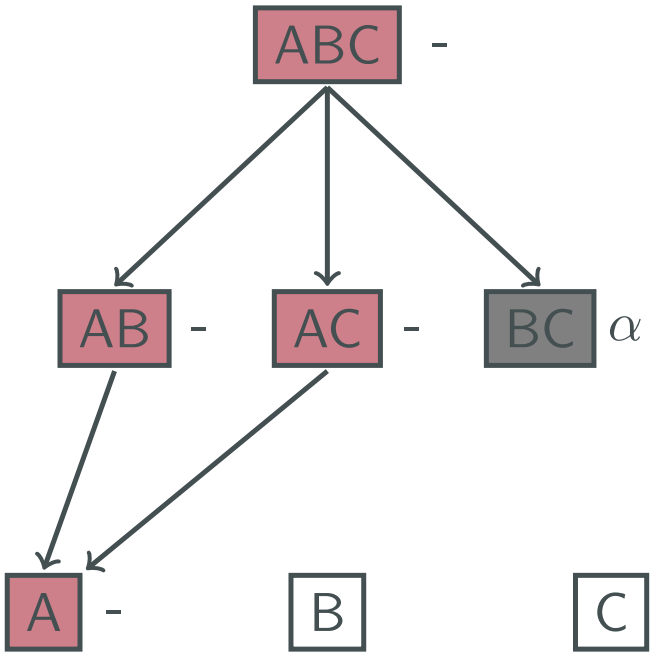
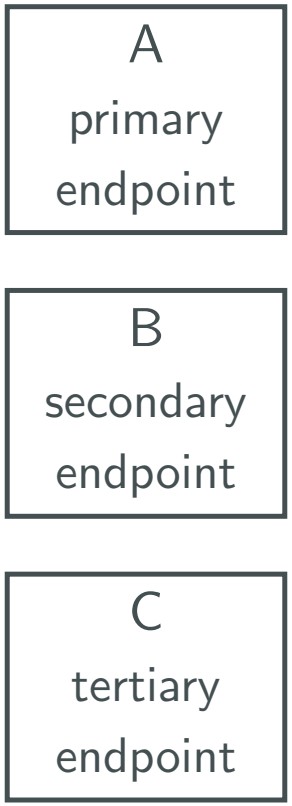


Gatekeeping Procedures

Ordered Testing

(three ordered endpoints)

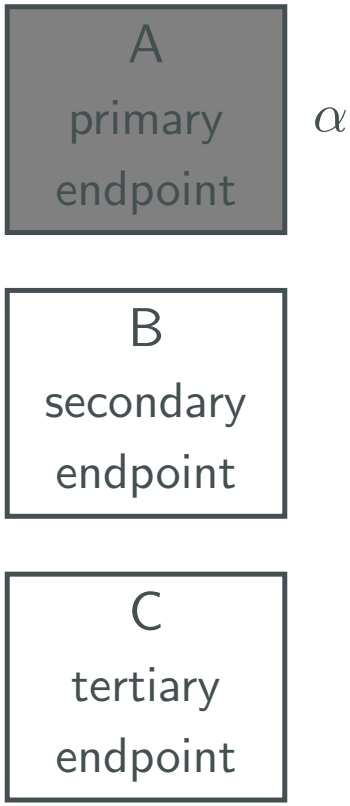


Gatekeeping Procedures

Ordered Testing

(three ordered endpoints)

Start test A at α

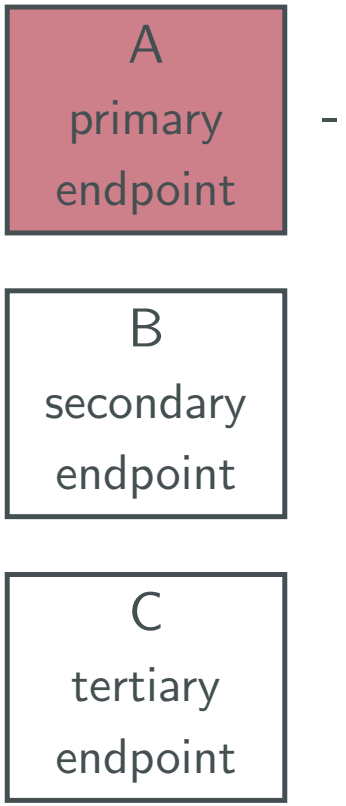


Gatekeeping Procedures

Ordered Testing

(three ordered endpoints)

Suppose $p_A < \alpha$

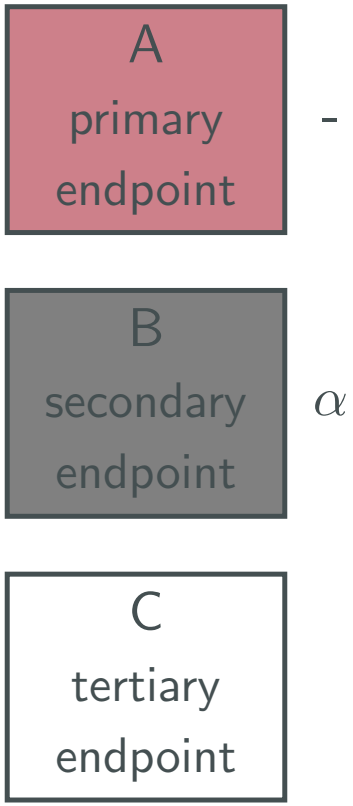


Gatekeeping Procedures

Ordered Testing

(three ordered endpoints)

Go on to test B at α

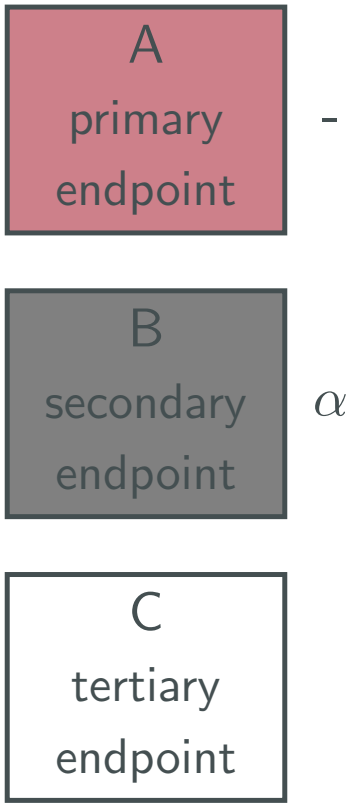


Gatekeeping Procedures

Ordered Testing

(three ordered endpoints)

Suppose $p_B > \alpha$. Stop

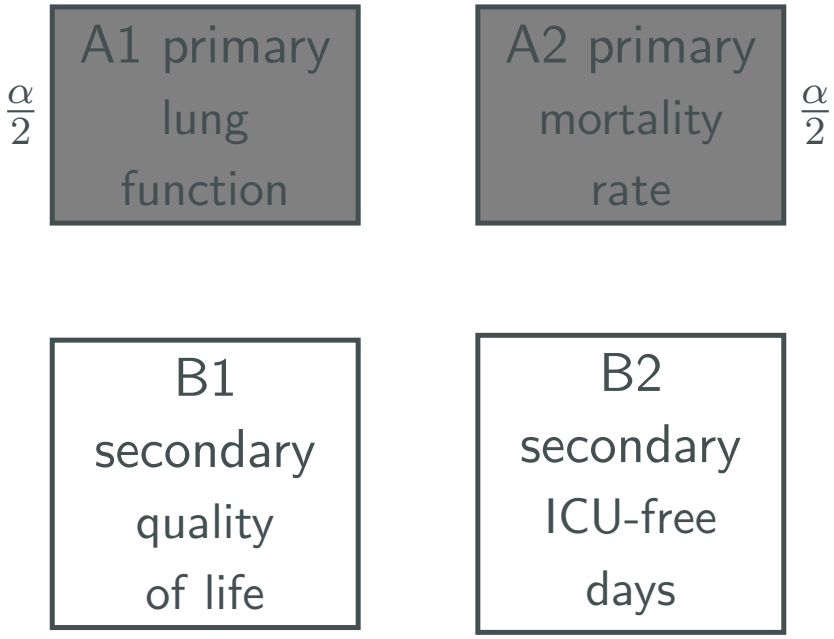


Gatekeeping Procedures

Parallel strategy

(Acute lung injury)

Start test A and B at $\alpha/2$



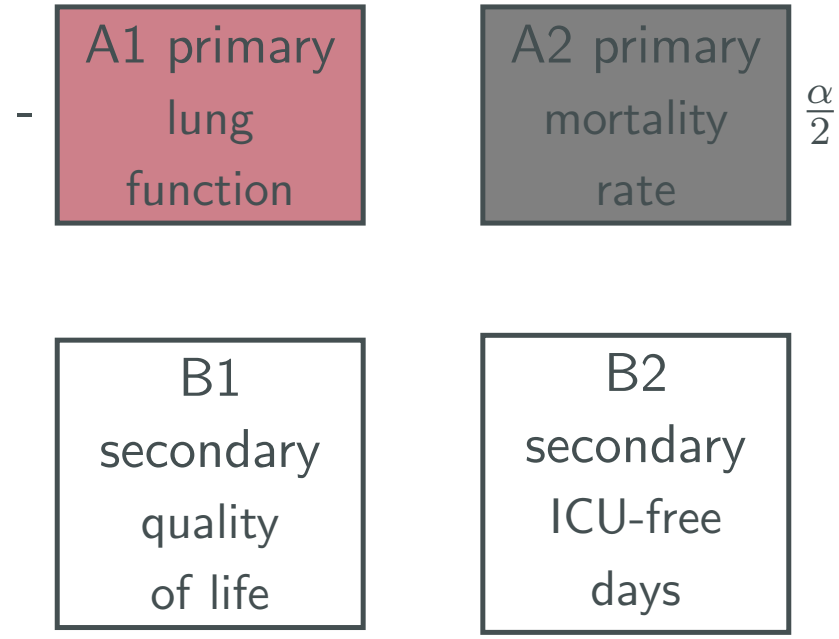
secondary endpoints are tested if at least one primary test is significant

Gatekeeping Procedures

Parallel strategy

(Acute lung injury)

Suppose $p_A < \alpha/2$



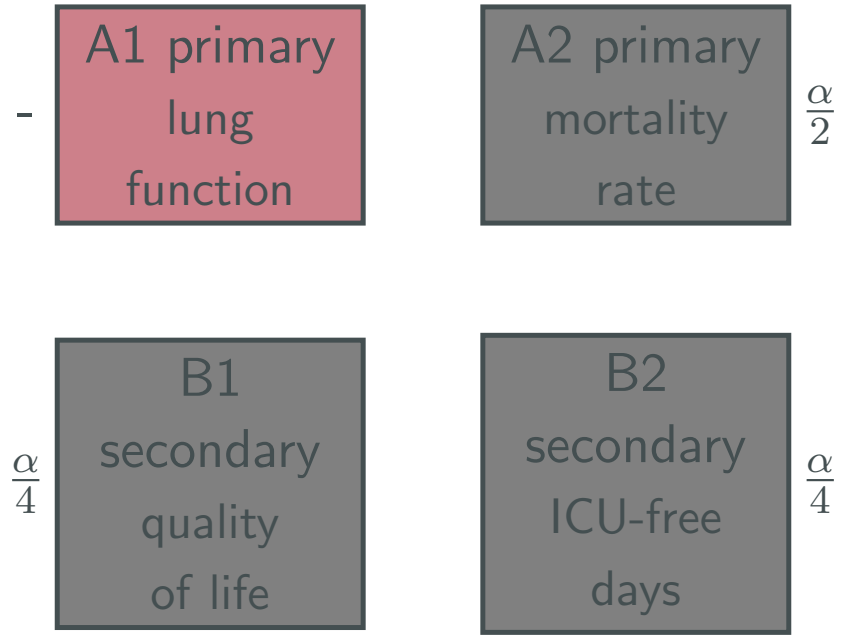
secondary endpoints are tested if at least one primary test is significant

Gatekeeping Procedures

Parallel strategy

(Acute lung injury)

Test C and D at $\alpha/4$



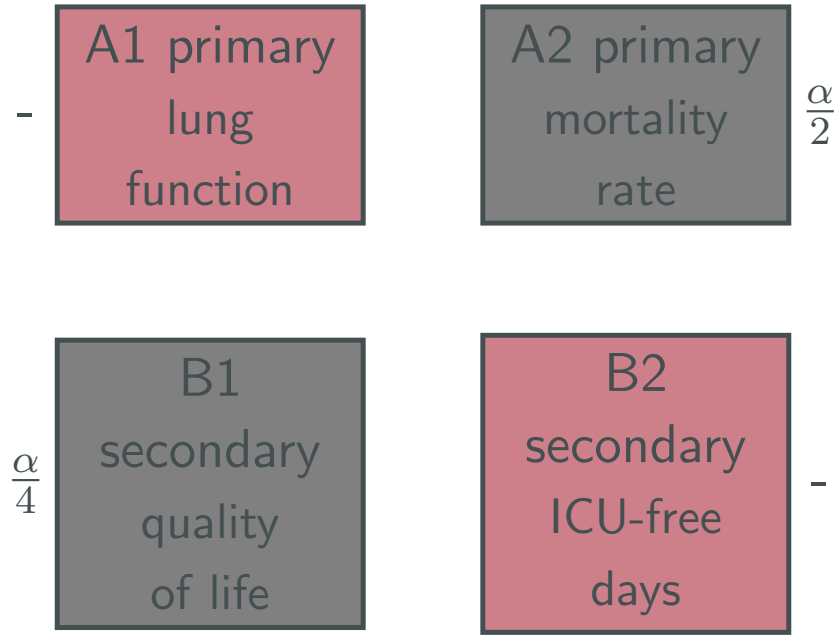
secondary endpoints are tested if at least one primary test is significant

Gatekeeping Procedures

Parallel strategy

(Acute lung injury)

Suppose $p_D < \alpha/4$



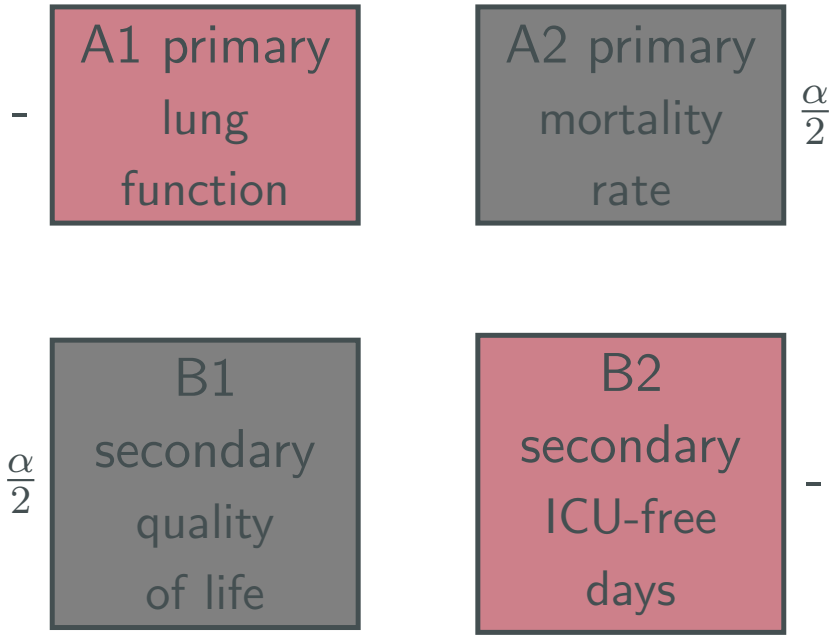
secondary endpoints are tested if at least one primary test is significant

Gatekeeping Procedures

Parallel strategy

(Acute lung injury)

Test C at $\alpha/2$



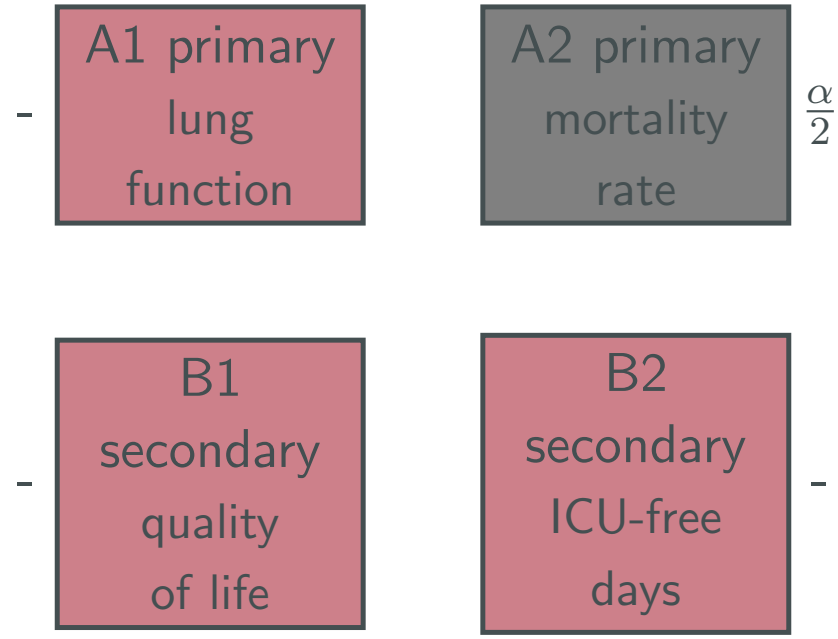
secondary endpoints are tested if at least one primary test is significant

Gatekeeping Procedures

Parallel strategy

(Acute lung injury)

Suppose $p_C < \alpha/2$

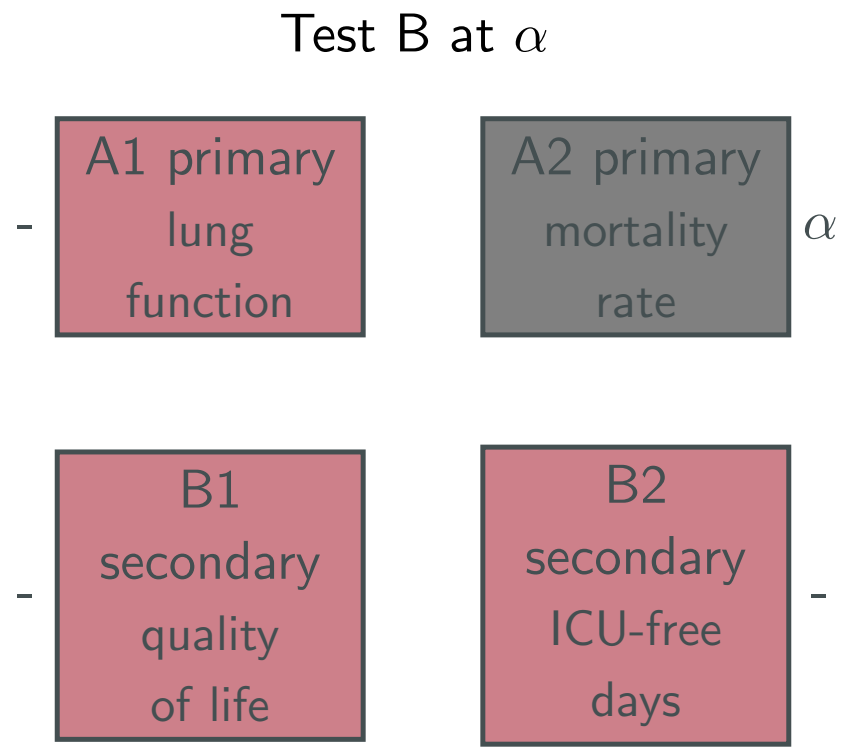


secondary endpoints are tested if at least one primary test is significant

Gatekeeping Procedures

Parallel strategy

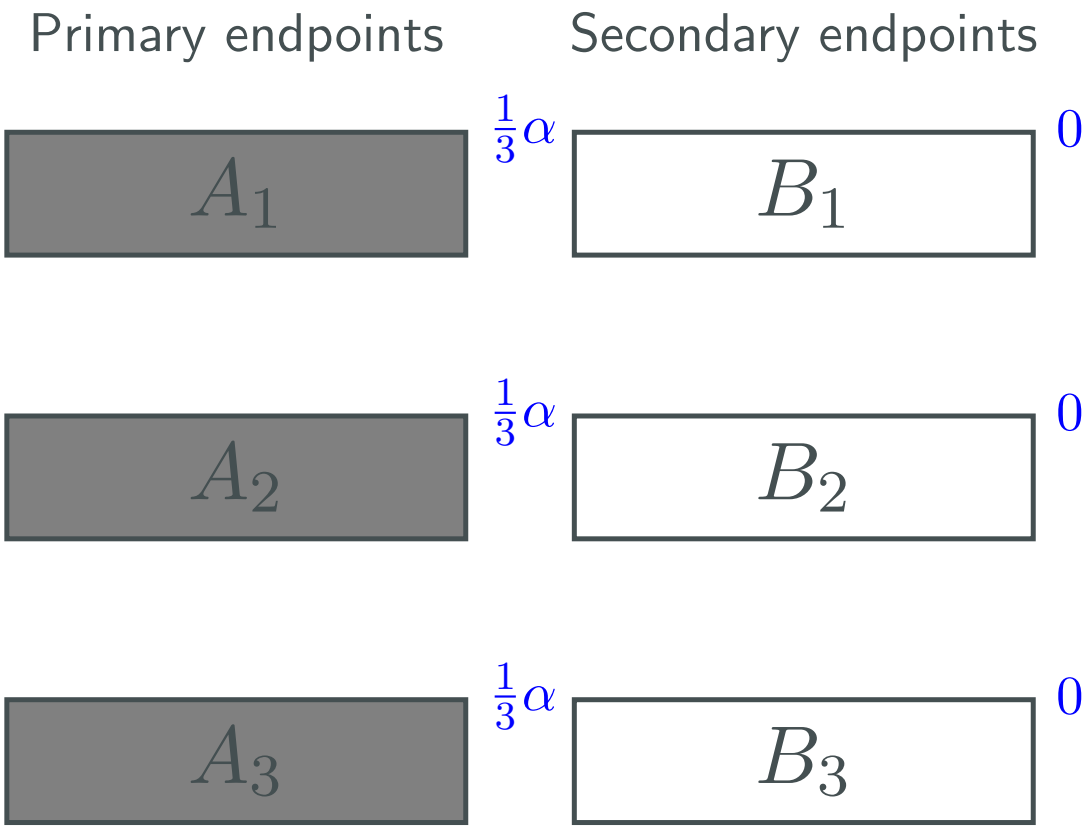
(Acute lung injury)



secondary endpoints are tested if at least one primary test is significant

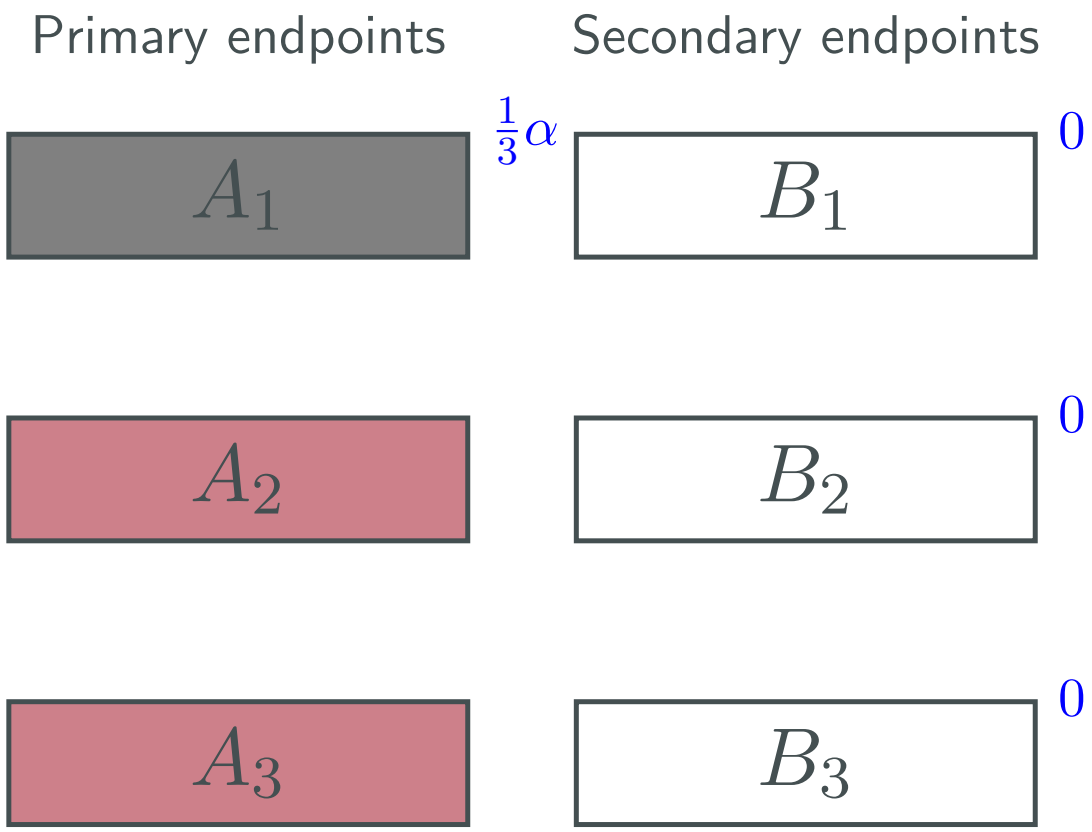
Serial gatekeeping

Test all primary endpoints at $\alpha/3$



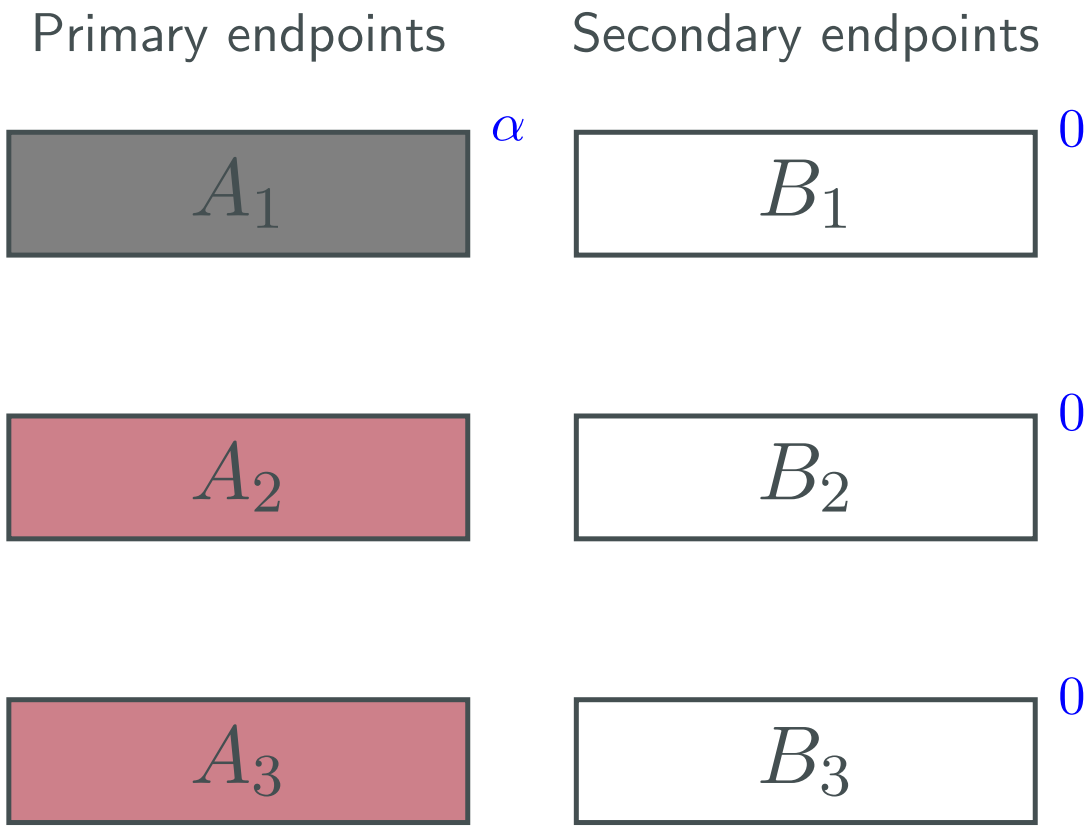
Serial gatekeeping

If we reject a few...



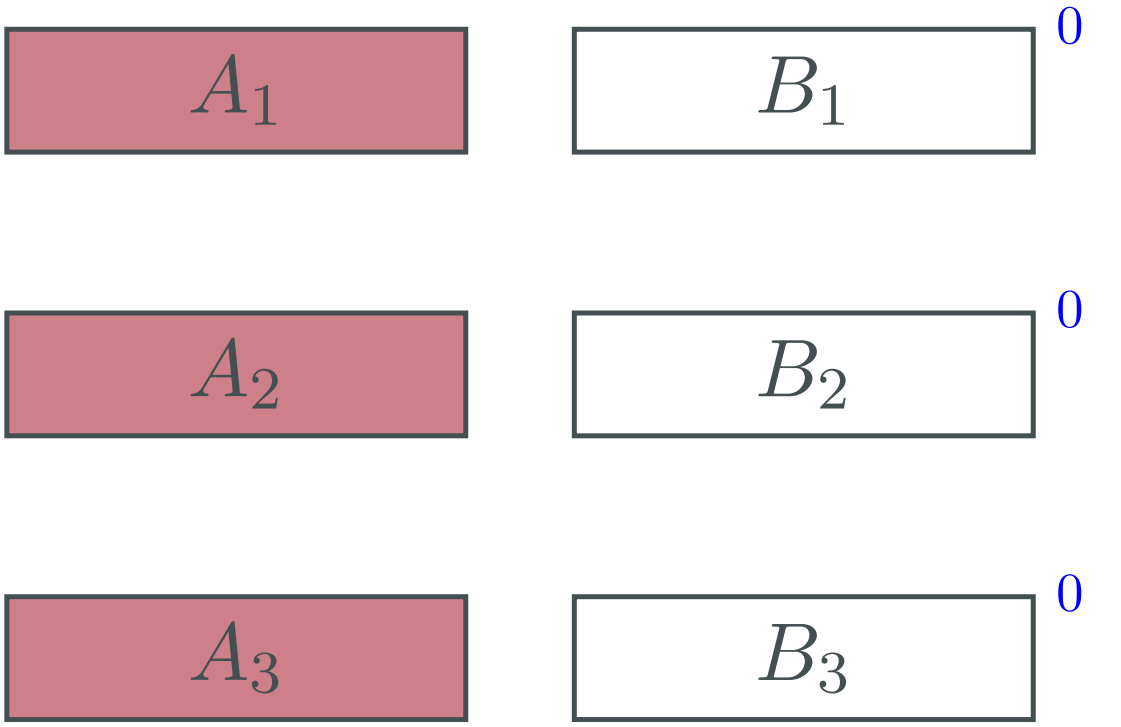
Serial gatekeeping

Go on with the other primary endpoints as in Holm's procedure



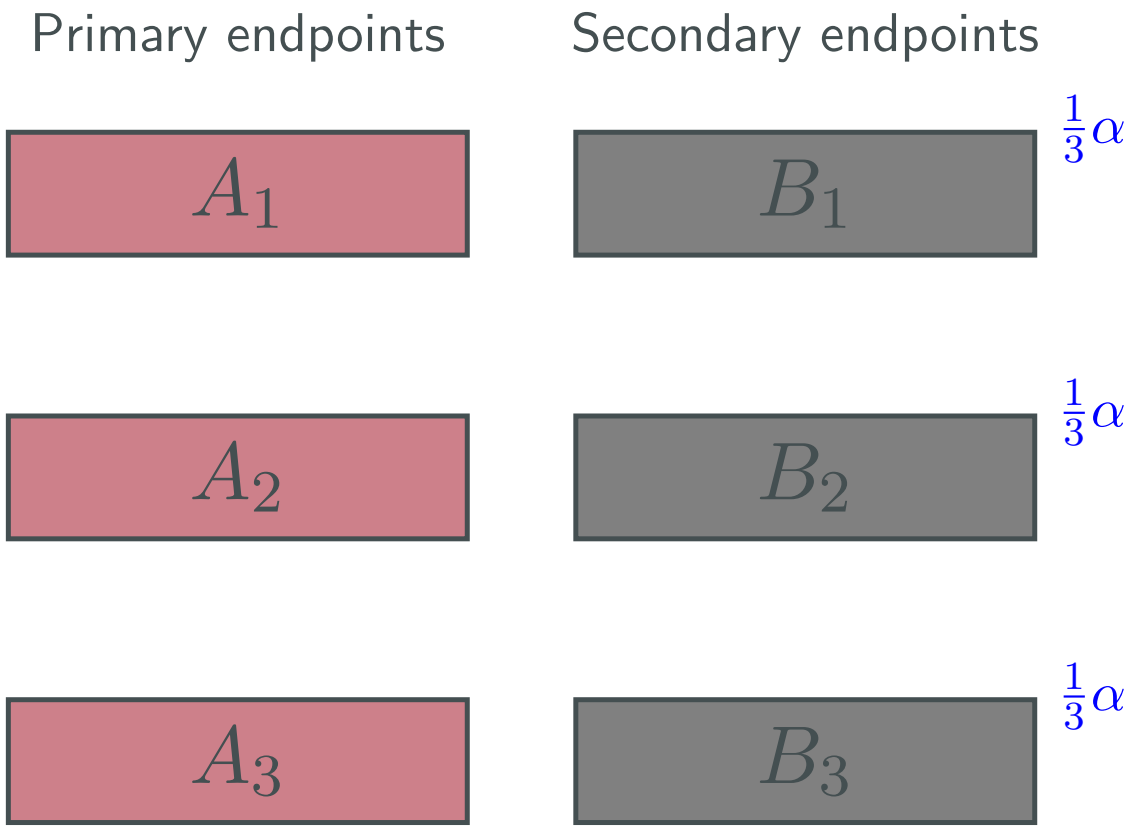
Serial gatekeeping

Suppose we are able to reject all primary endpoints...



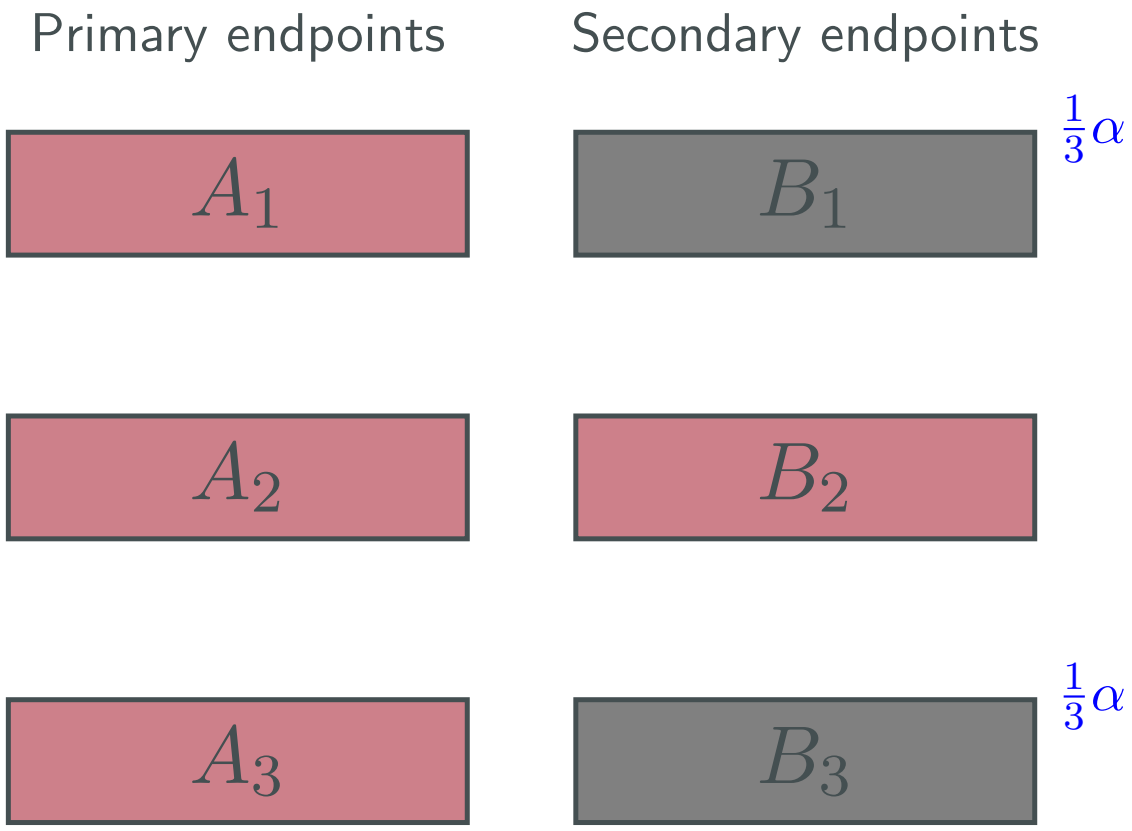
Serial gatekeeping

Go on testing the secondary endpoints at $\alpha/3$



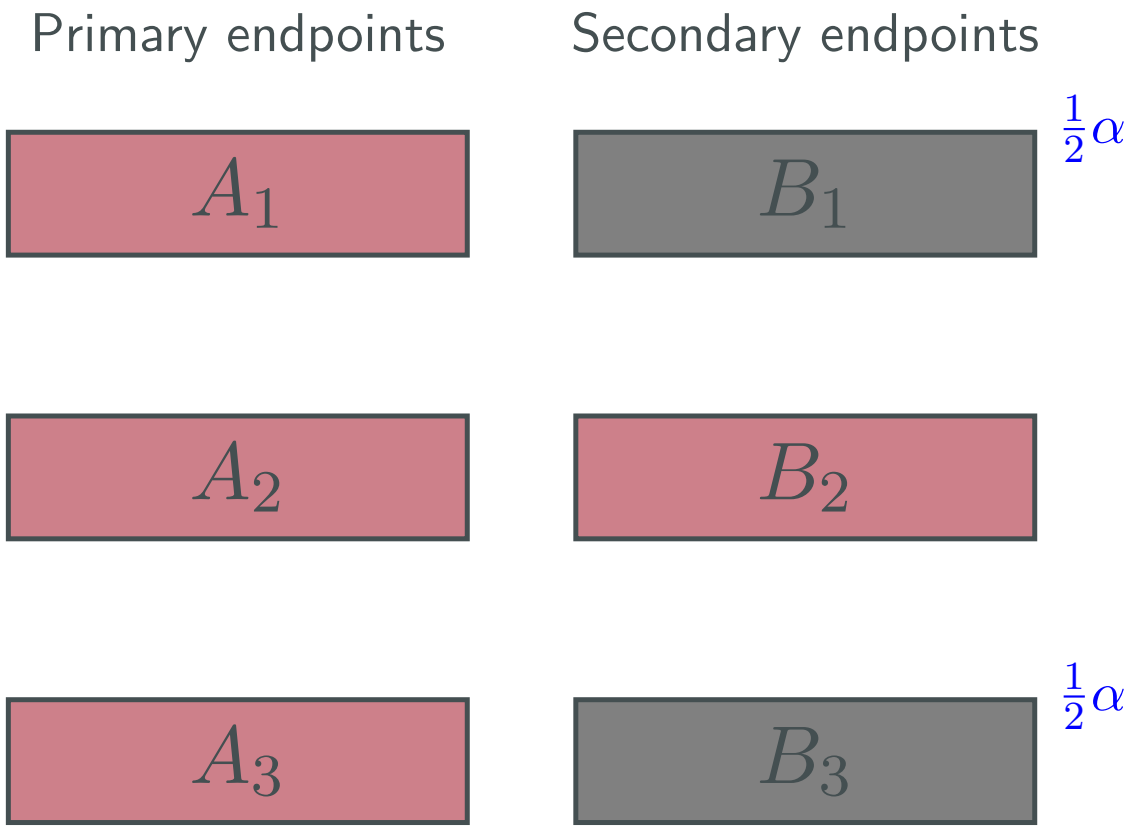
Serial gatekeeping

And if we reject some of those...



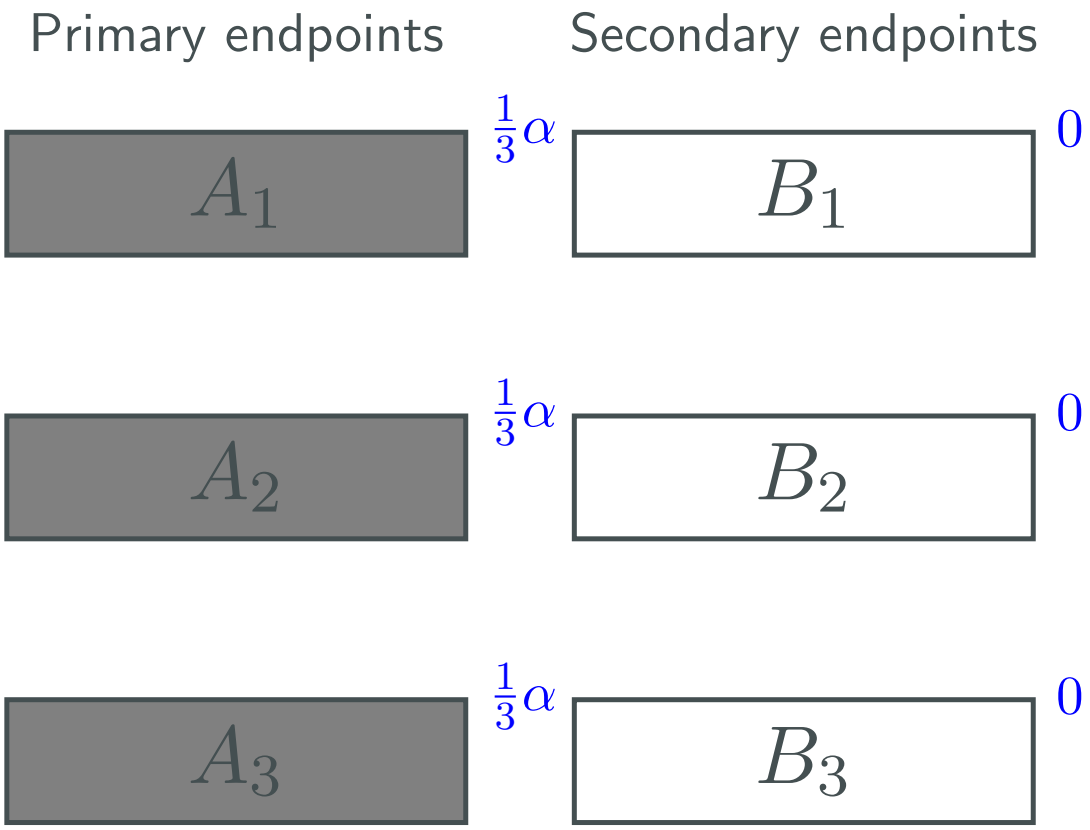
Serial gatekeeping

Go on doing Holm for the secondary endpoints



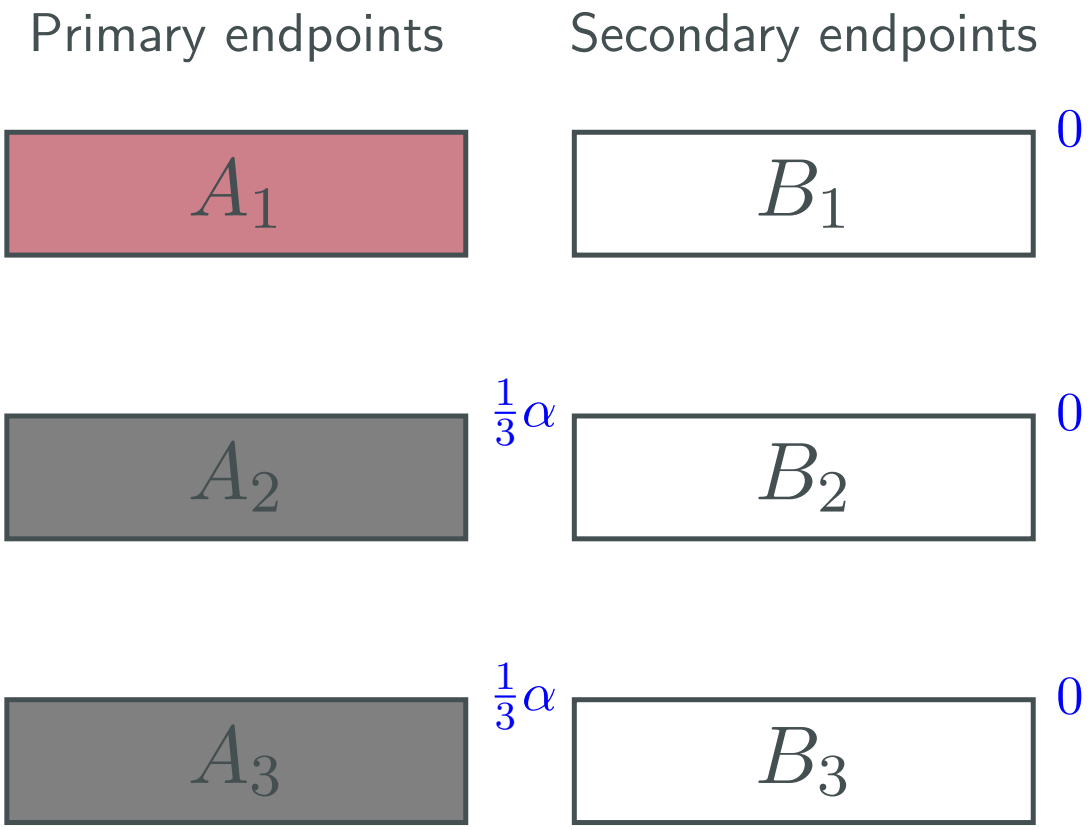
Parallel gatekeeping

Test all primary endpoints at $\alpha/3$



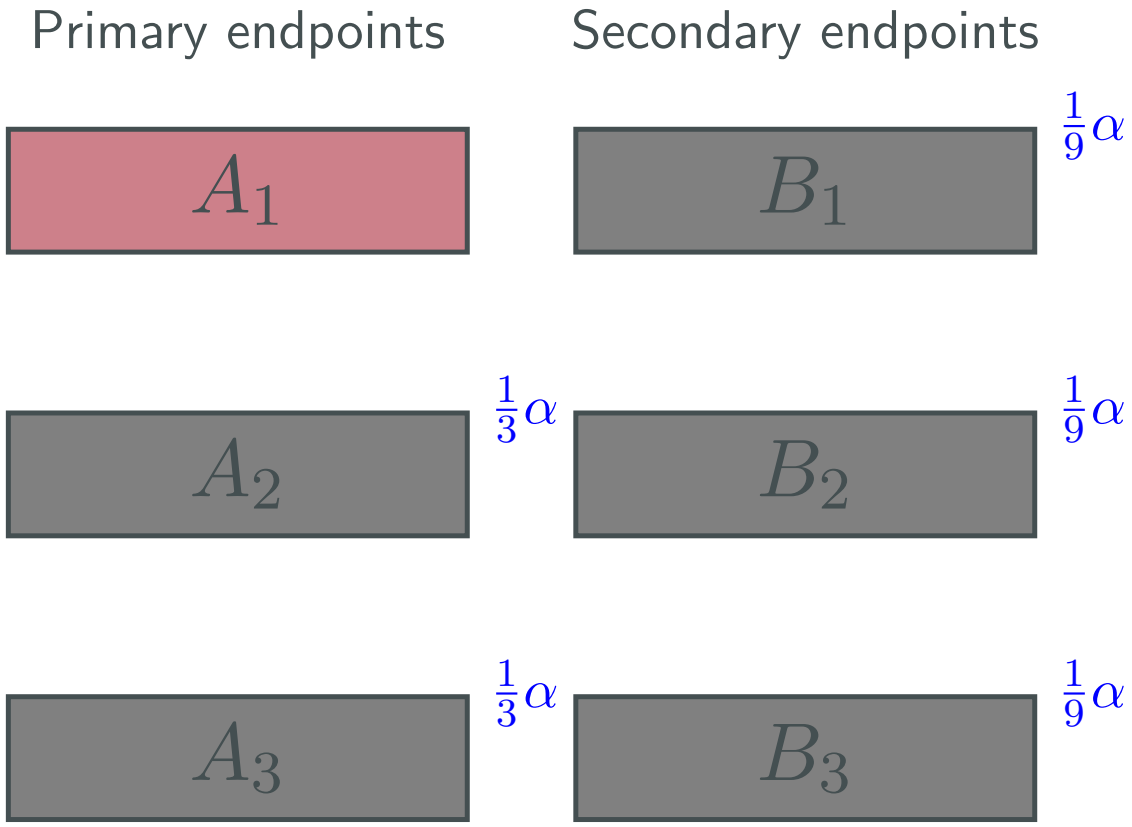
Parallel gatekeeping

If we reject a few...



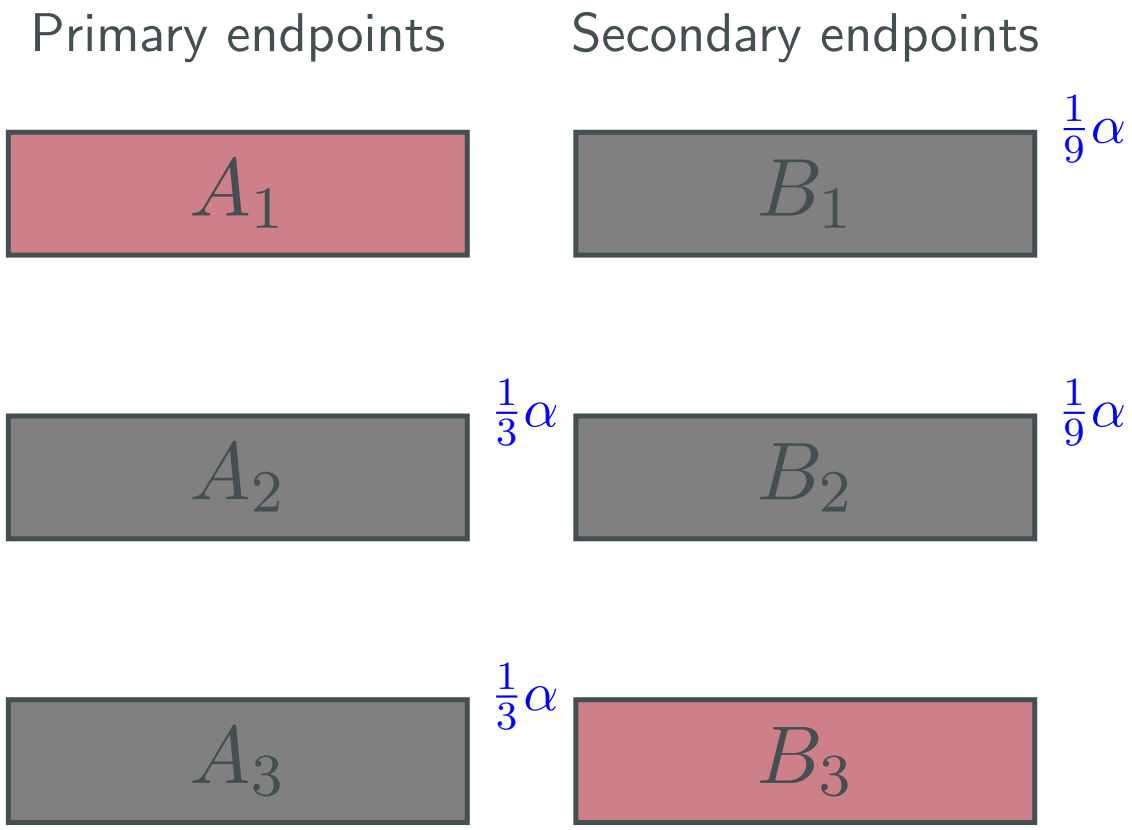
Parallel gatekeeping

Go on with the secondary endpoints with the available α



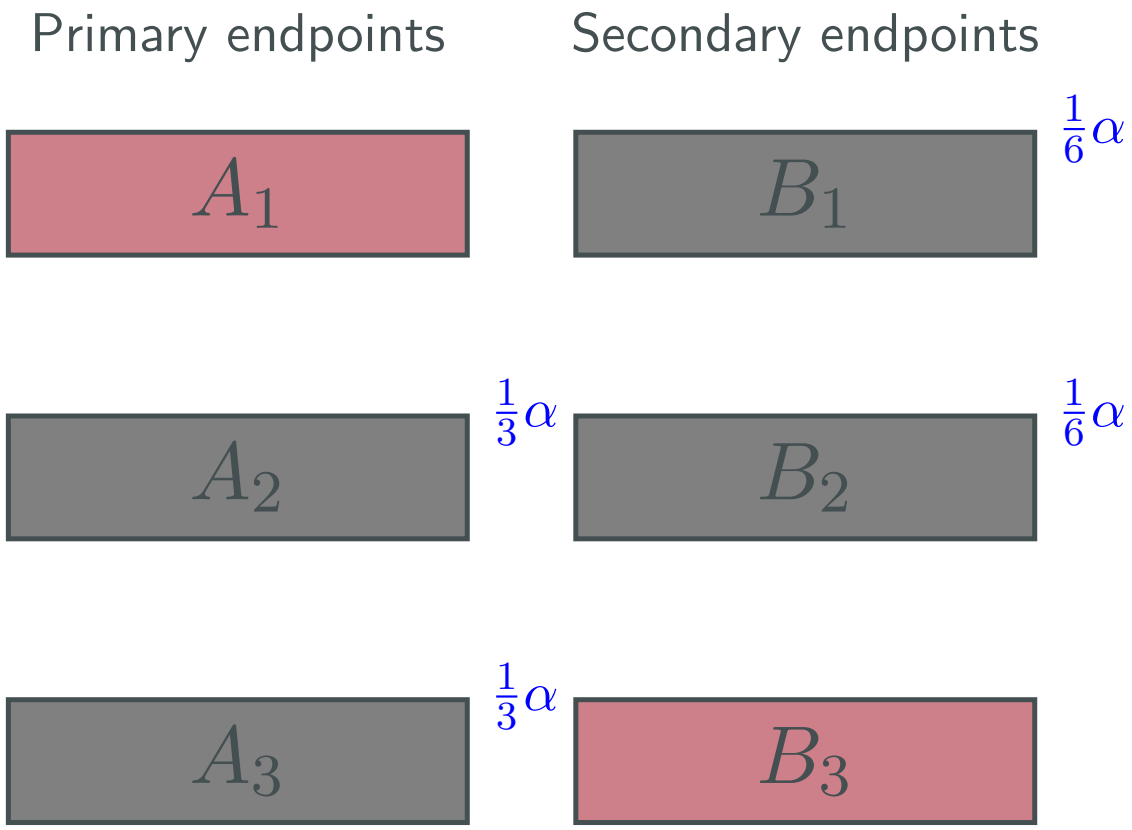
Parallel gatekeeping

Suppose we are able to reject some of the secondary endpoints...



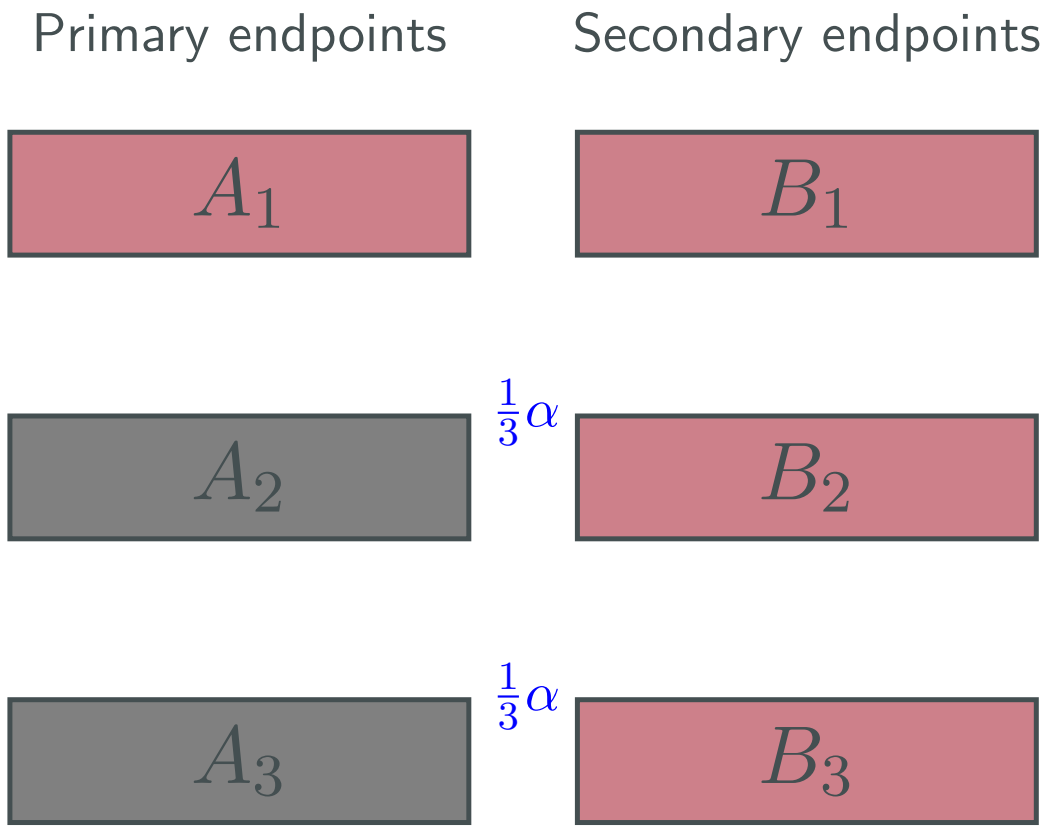
Parallel gatekeeping

Go on doing Holm for the secondary endpoints



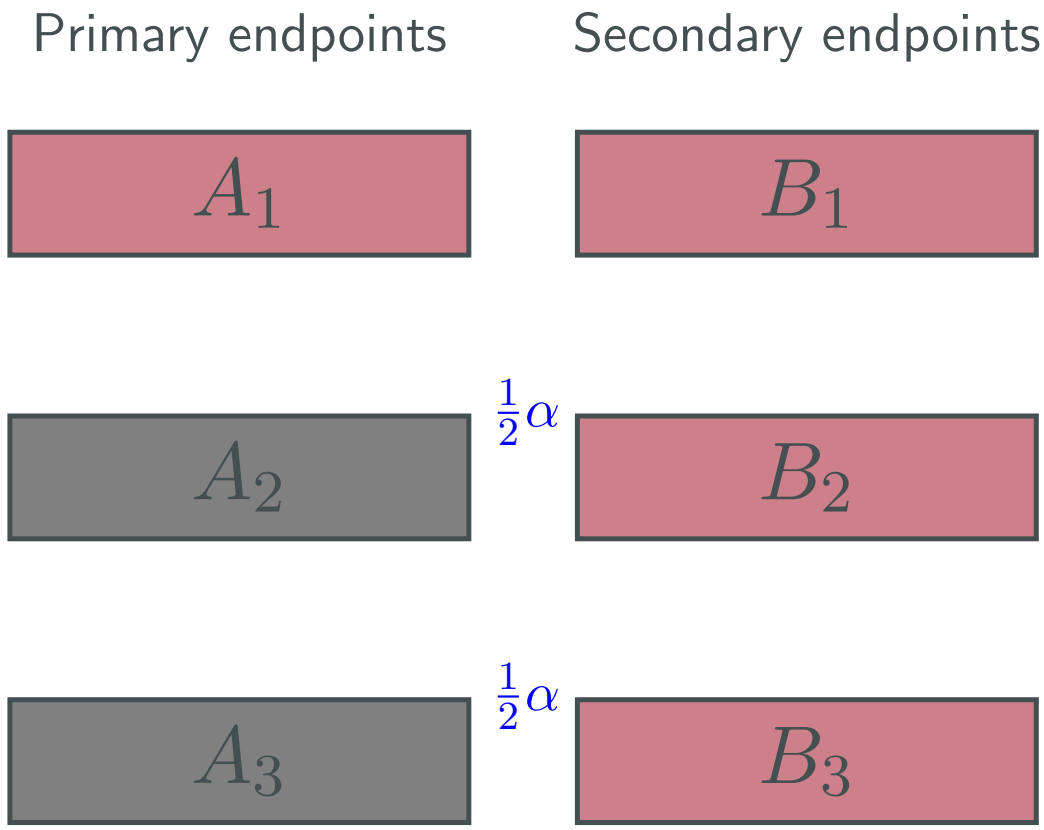
Parallel gatekeeping

And if we reject all secondary ones...



Parallel gatekeeping

Go on doing Holm for the primary endpoints



Example: clinical trial in patients with hypertension

Study design: two doses versus placebo

$$
\begin{aligned}
X_1, \ldots, X_m &\overset{\text{i.i.d.}}{\sim} N(\psi_x, 1) \quad \text{Placebo} \\
Y_1, \ldots, Y_n &\overset{\text{i.i.d.}}{\sim} N(\psi_y, 1) \quad \text{Low dose} \\
Z_1, \ldots, Z_n &\overset{\text{i.i.d.}}{\sim} N(\psi_z, 1) \quad \text{High dose}
\end{aligned}
$$

Primary endpoint: reduction in diastolic blood pressure

$$
\begin{aligned}
A &: \psi_x = \psi_y \quad \text{versus} \quad \tilde{A} : \psi_x > \psi_y \\
B &: \psi_x = \psi_z \quad \text{versus} \quad \tilde{B} : \psi_x > \psi_z
\end{aligned}
$$

Statistics: marginal and joint null distributions

$$
\begin{aligned}
S_A &= \sqrt{\tfrac{mn}{m+n}}(\bar{X} - \bar{Y}) \overset{A}{\sim} N(0,1) \\
S_B &= \sqrt{\tfrac{mn}{m+n}}(\bar{X} - \bar{Z}) \overset{B}{\sim} N(0,1)
\end{aligned}
\qquad
\begin{pmatrix} S_A \\ S_B \end{pmatrix} \overset{A,B}{\sim} N_2\left(\begin{bmatrix} 0 \\ 0 \end{bmatrix}, \begin{bmatrix} 1 & \lambda \\ \lambda & 1 \end{bmatrix} \right)
$$

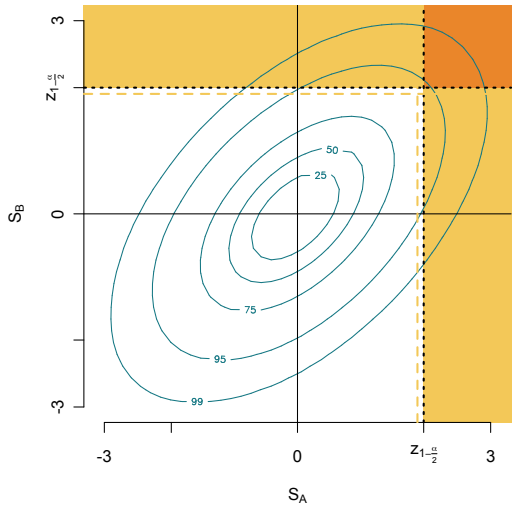
$\lambda = \frac{n}{n+m}$ nuisance parameter

Bonferroni's bound: positive dependence

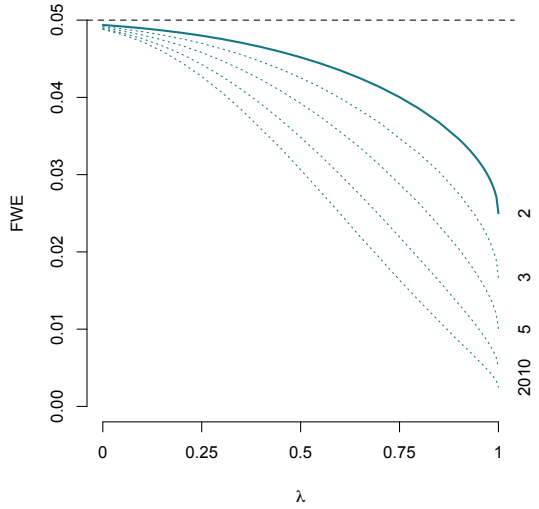
$\mathrm{FWE} = \Pr\left(\{S_A > c\} \cup \{S_B > c\}\right)$ using $c = z_{1-\frac{\alpha}{2}}$ (Bonferroni) is equal

$$\underbrace{\Pr\left(S_A > z_{1-\frac{\alpha}{2}}\right)}_{\alpha/2} + \underbrace{\Pr\left(S_B > z_{1-\frac{\alpha}{2}}\right)}_{\alpha/2} - \underbrace{\Pr\left(\left\{S_A > z_{1-\frac{\alpha}{2}}\right\} \cap \left\{S_B > z_{1-\frac{\alpha}{2}}\right\}\right)}_{\alpha(\lambda)}$$

$n = 3m$, $\lambda = 3/4$,
$\mathrm{FWE} = 0.04$



$0 < \lambda < 1$, ↑ dose levels



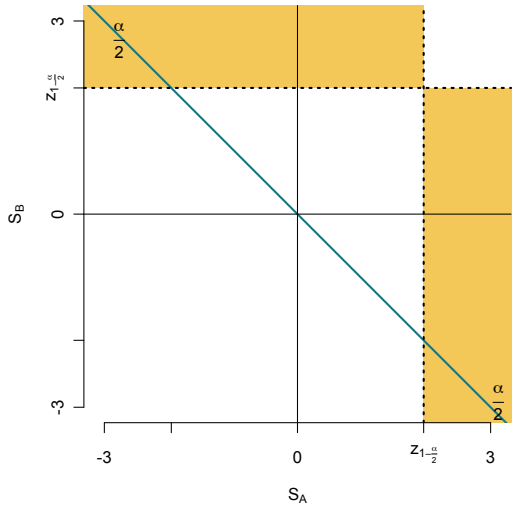
Bonferroni's bound: worst dependence case

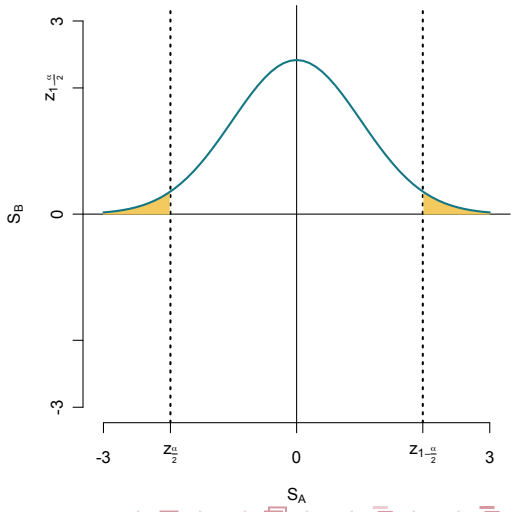
Two-sided testing

$$A : \psi = 0 \quad \text{versus} \quad \tilde{A} : \psi > 0$$
$$B : \psi = 0 \quad \text{versus} \quad \tilde{B} : \psi < 0$$

$S_B \equiv -S_A \Rightarrow \lambda = -1$ (disjoint rejection regions)

$$\text{FWE} = \Pr\left(S_A > z_{1-\frac{\alpha}{2}}\right) + \Pr\left(-S_A > z_{1-\frac{\alpha}{2}}\right) = \alpha$$





Stepdown $S_{\max}$ (parametric)

Make use of the dependence structure of test statistics

Stepdown procedure

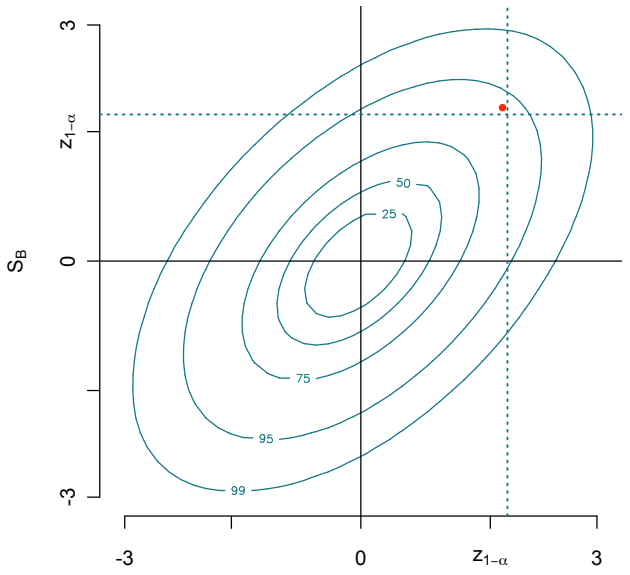
1. Find the null distribution of $S_{\max} = \max_{H \in \mathcal{H}}(S_H)$
2. Reject H if $S_H > c_{1-\alpha}$, the $(1-\alpha)$-quantile of $\mathrm{d}_{S_{\max}}$
3. Recompute the distribution of $S_{\max} = \max_{H \in \mathcal{H} \setminus \mathcal{R}}(S_H)$
4. Repeat

Find $c_{1-\alpha}$ from $\mathrm{d}_{S_{\max}} = \mathrm{d}_{\max(S_A, S_B)}$

$c_{1-\alpha}$ $c_{1-\alpha}$

$\mathcal{H} \setminus \mathcal{R}$: A B

$\mathcal{R}$:



Stepdown $S_{\max}$ (parametric)

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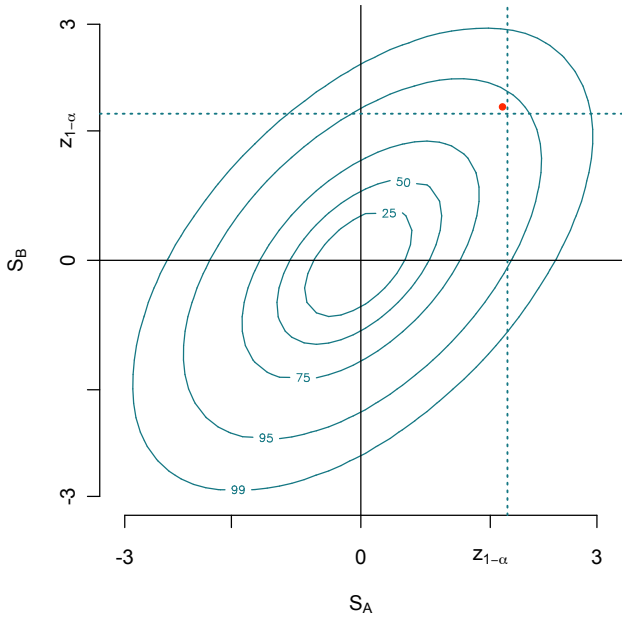
4. Repeat

Suppose $S_B > c_{1-\alpha}$

	$c_{1-\alpha}$	$c_{1-\alpha}$
$\mathcal{H} \setminus \mathcal{R}$:	A	B
$\mathcal{R}$:		



Stepdown $S_{\max}$ (parametric)

Make use of the dependence structure of test statistics

Stepdown procedure

1. Find the null distribution of $S_{\max} = \max_{H \in \mathcal{H}}(S_H)$
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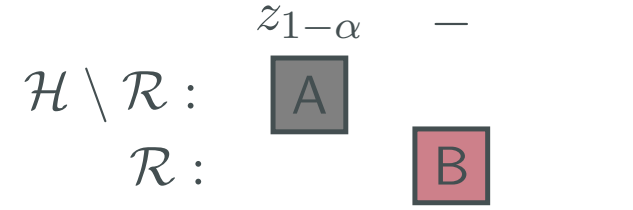
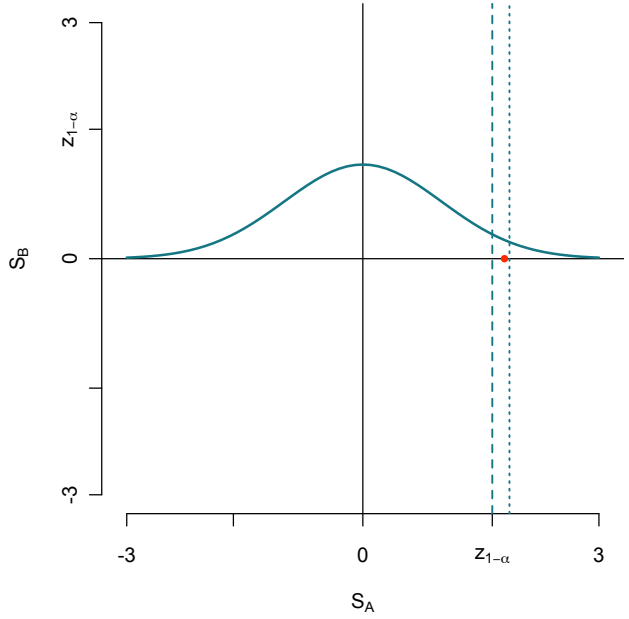
4. Repeat

Find $z_{1-\alpha}$ from $\mathrm{d}_{S_{\max}} = \mathrm{d}_{S_A}$





Stepdown $S_{\max}$ (parametric)

Make use of the dependence structure of test statistics

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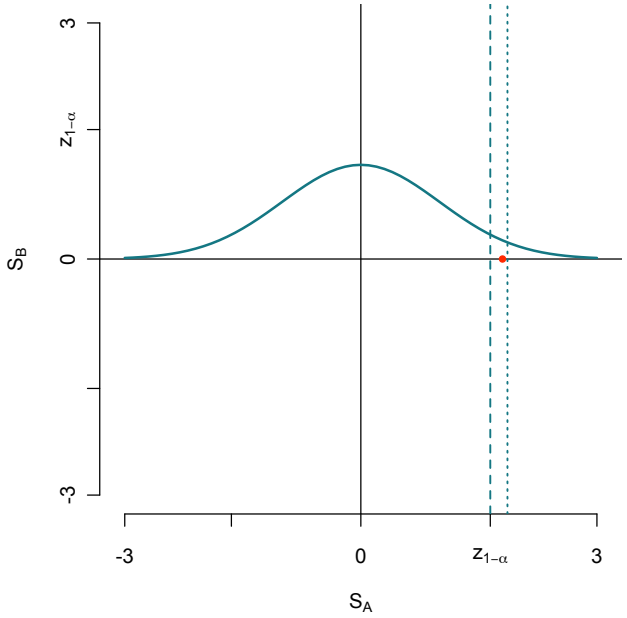
3. Recompute the distribution of $S_{\max} = \max_{H \in \mathcal{H} \setminus \mathcal{R}}(S_H)$
4. Repeat

Suppose $S_A > z_{1-\alpha}$

$\mathcal{H} \setminus \mathcal{R}$: — —

$\mathcal{R}$: A B



Stepdown $S_{\max}$ (resampling based)

Make use of the dependence structure of test statistics

Stepdown procedure

1. Find the null distribution* of $S_{\max} = \max_{H \in \mathcal{H}}(S_H)$
2. Reject H if $S_H > c^*_{1-\alpha}$, the $(1-\alpha)$-quantile of $\mathrm{d}^*_{S_{\max}}$
3. Recompute the distribution* of $S_{\max} = \max_{H \in \mathcal{H} \setminus \mathcal{R}}(S_H)$
4. Repeat

* bootstrap (parametric and non-), permutations

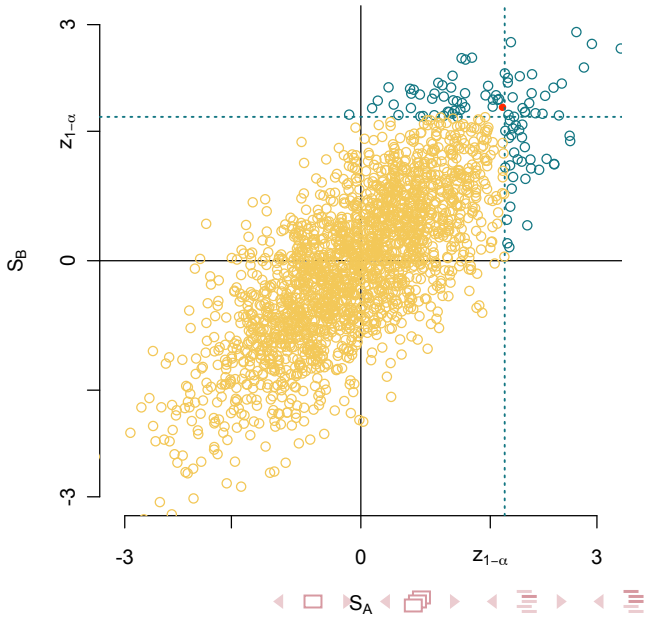
Assumption: "subset pivotality", exchangeability

Find $c^*_{1-\alpha}$ from $\mathrm{d}^*_{S_{\max}} = \mathrm{d}^*_{\max(S_A, S_B)}$

$c^*_{1-\alpha}$ $c^*_{1-\alpha}$

$\mathcal{H} \setminus \mathcal{R}$: A B

$\mathcal{R}$:



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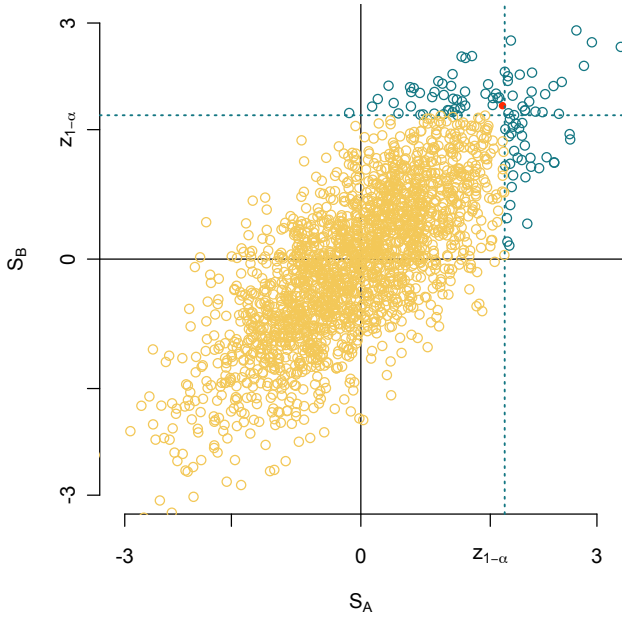
Suppose $S_B > c^*_{1-\alpha}$

	$c^*_{1-\alpha}$	$-$
$\mathcal{H} \setminus \mathcal{R}$:	A	
$\mathcal{R}$:		B



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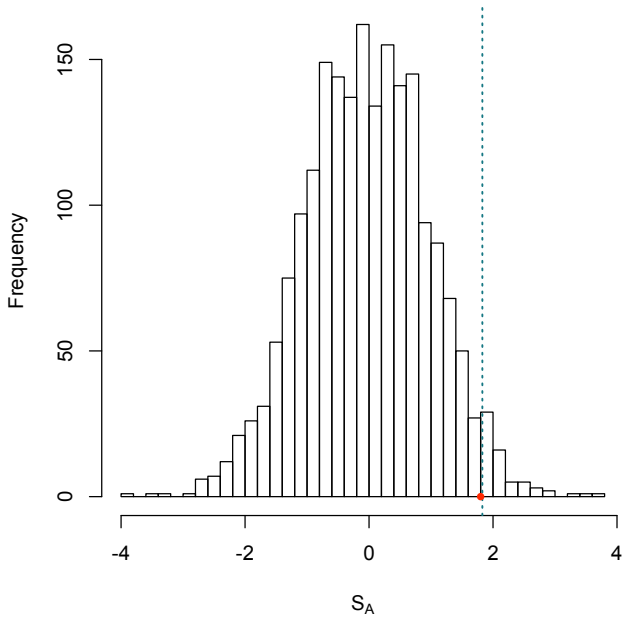
* bootstrap (parametric and non-), permutations

Assumption: "subset pivotality", exchangeability

Find $z^*_{1-\alpha}$ from $\mathrm{d}^*_{S_{\max}} = \mathrm{d}^*_{S_A}$

	$z^*_{1-\alpha}$	$-$
$\mathcal{H} \setminus \mathcal{R}$:	A	
$\mathcal{R}$:		B



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4. Repeat

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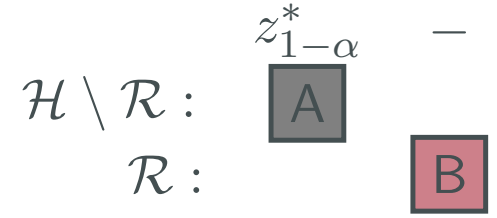
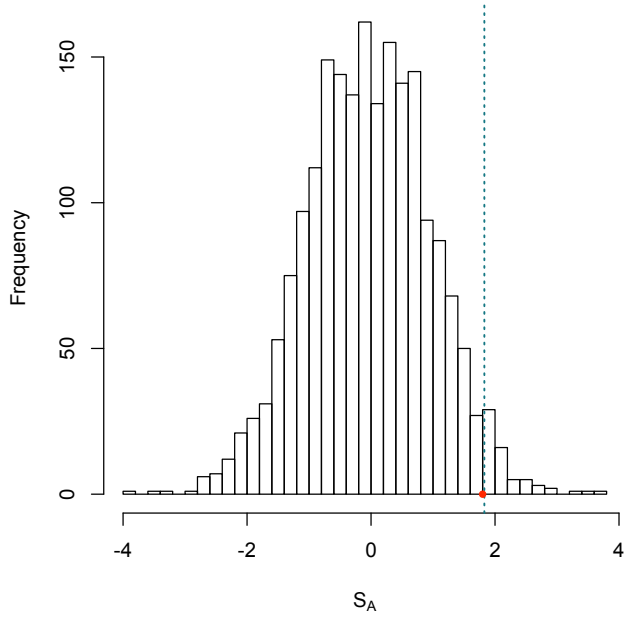
Assumption: "subset pivotality", exchangeability

Suppose $S_A \leq z^*_{1-\alpha}$. Stop





Outline

Some Multiple Testing Procedures

The sequential rejection principle

Inheritance procedure

Application: Genomics

Application: Neurotoxicity assay

All similar methods

1. Start testing hypotheses at some significance criterion
2. If any hypotheses rejected, set new significance criterion for unrejected hypotheses
3. Possibly new rejections
4. Stop if no new rejections occur

Are these all examples of the same procedure?

The general procedure

$\mathcal{R}_i \subseteq \mathcal{H}$: the rejected hypotheses after step i

$$\begin{aligned} \mathcal{R}_0 &= \emptyset \\ \mathcal{R}_{i+1} &= \mathcal{R}_i \cup \{H \in \mathcal{H} : S_H > c_H(\mathcal{R}_i)\} \end{aligned}$$

After every step the procedure adjusts the critical values on the basis of the new rejected set

The Sequential Rejection Principle

Theorem[1]

If a general sequentially rejective procedure fulfills two conditions

1. Monotonicity
2. Single step control

Then it controls the FWE

Monotonicity condition: for every $\mathcal{S} \subseteq \mathcal{R} \subset \mathcal{H}$ and every $H \in \mathcal{H} \setminus \mathcal{R}$,

$$c_H(\mathcal{S}) \geq c_H(\mathcal{R})$$

In words: critical values of unrejected null hypotheses never increase with more rejections

Note: monotonicity implies $c_H(\mathcal{R}_i) \geq c_H(\mathcal{R}_{i+1})$, but this is too weak to guarantee FWE control

[1] J.J. Goeman and A. Solari (2008) The sequential rejection principle of familywise error control. *Submitted*

The Sequential Rejection Principle

Theorem[1]

If a general sequentially rejective procedure fulfills two conditions

1. Monotonicity
2. Single step control

Then it controls the FWE

Single step condition: for every $\mathcal{R} \subset \mathcal{H}$ and $\mathcal{T} = \mathcal{H} \setminus \mathcal{R}$,

$$\Pr\left(\bigcup_{H \in \mathcal{T}} \{S_H > c_H(\mathcal{R})\}\right) \leq \alpha$$

In words: FWE weak control is guaranteed at each single step. It may be assumed that all previous rejections were correct rejections

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The Sequential Rejection Principle

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A unifying approach:

- Facilitates formulation of FWE controlling procedures
- Facilitates proof of FWE control
- Makes connections between methods more obvious

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Outline

Some Multiple Testing Procedures

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Problems with a natural tree structure

Genetic association studies

-○ Whole genome

—○ chromosomes

——○ genes

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Self Report psychological/sociological questionnaires

-○ investigated concepts

—○ different aspects

——○ single items (questions)

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Genetic association studies

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Self Report psychological/sociological questionnaires

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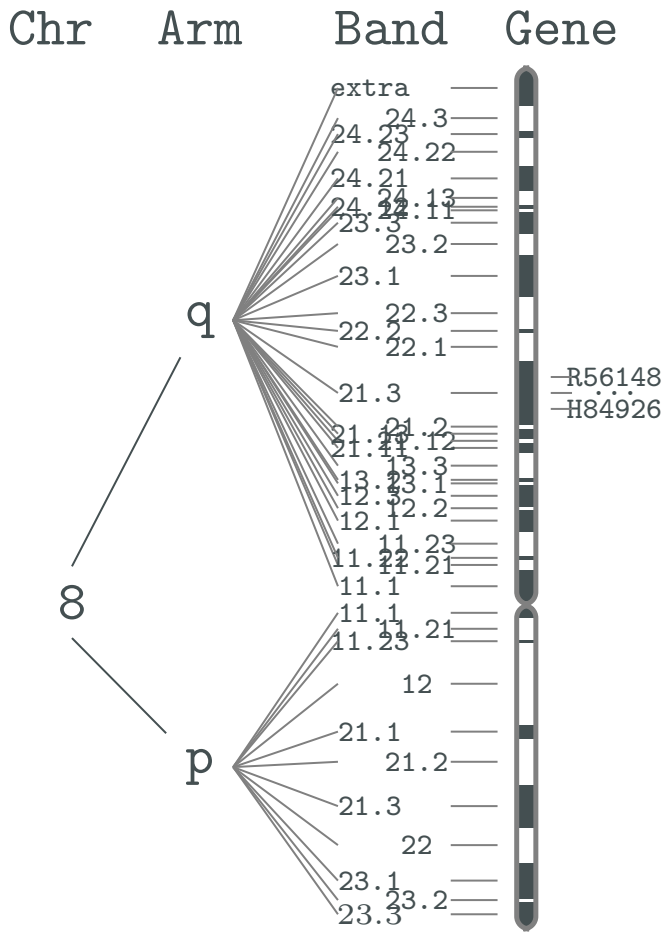
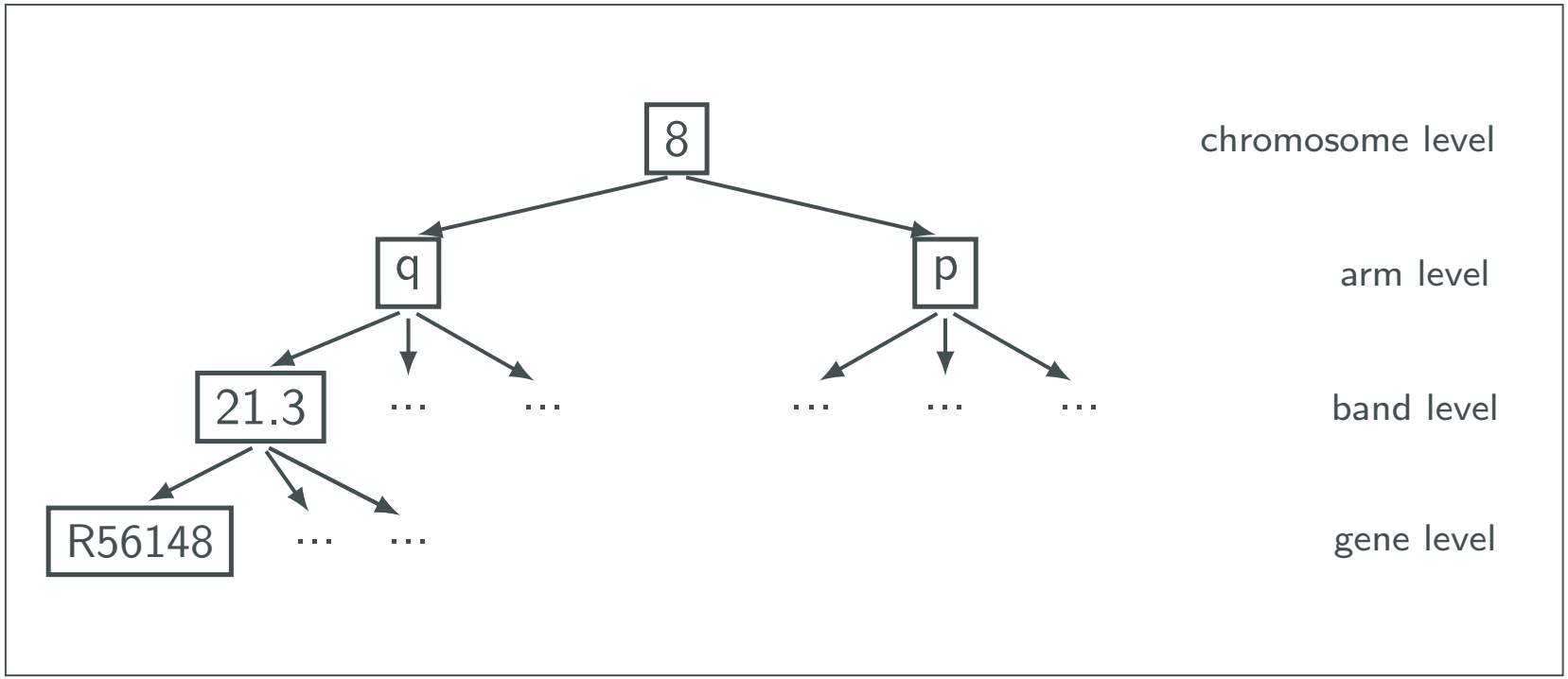
——○ single items (questions)

Alternative

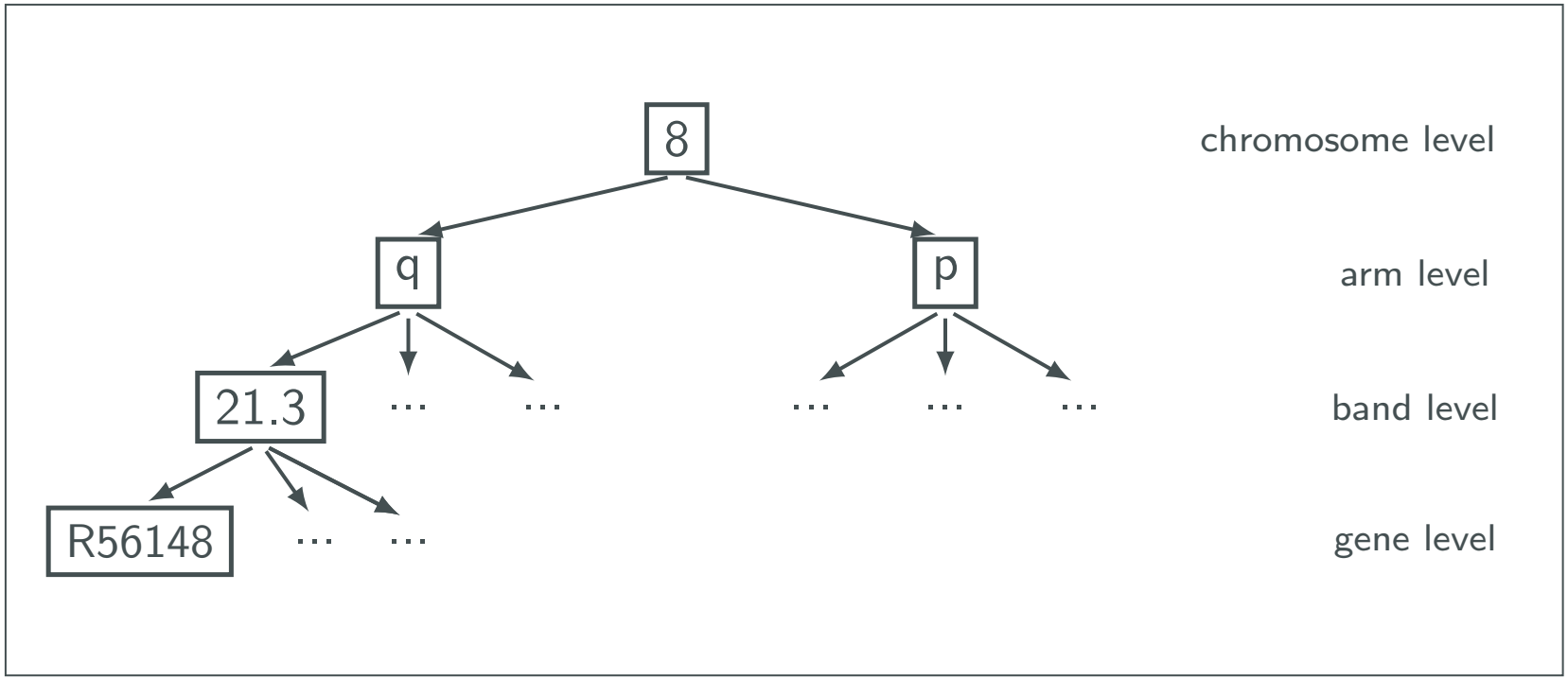
Make a tree structure from the data by hierarchical clustering

Example of Tree-Structured Hypotheses: Genes





root = general question, $\downarrow$ = more specific follow-up questions



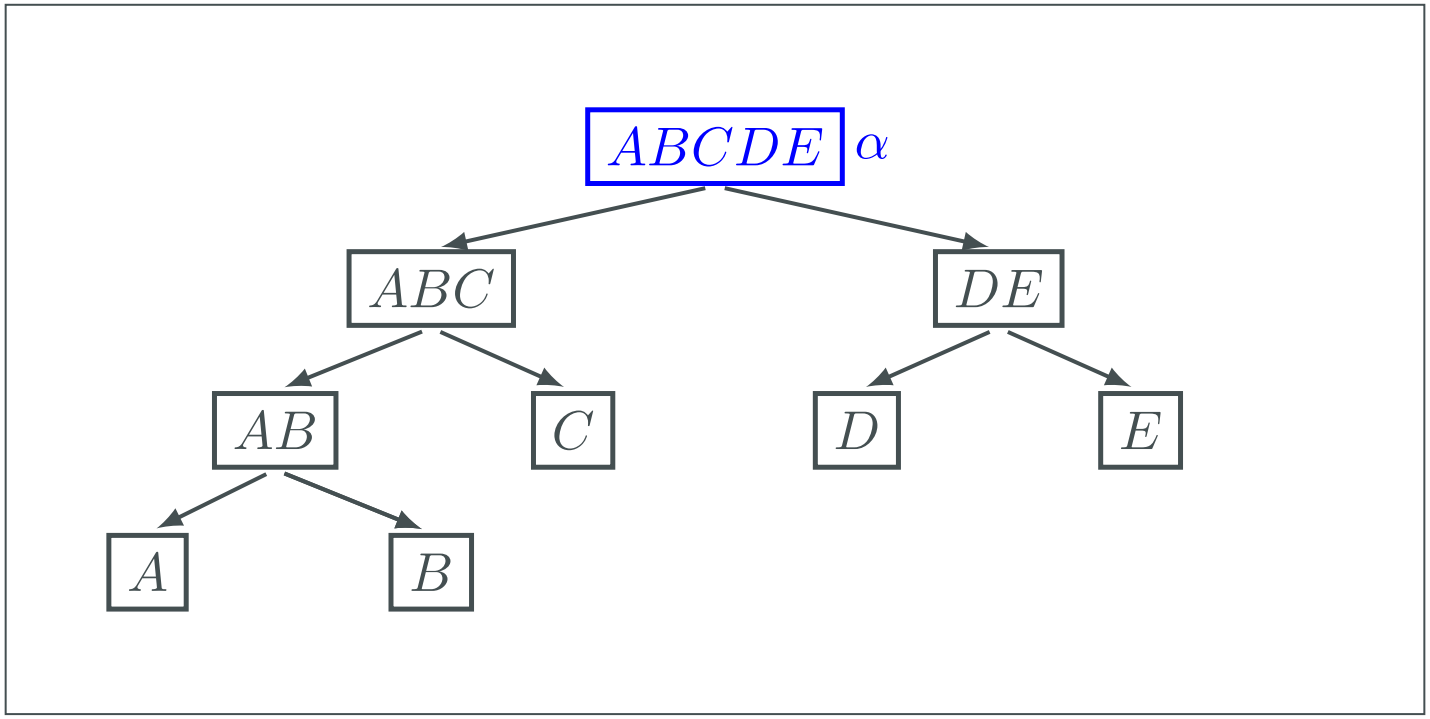
$\boxed{8}$: at least one of the genes in chr 8 is DE ? If yes,

$\boxed{p}$: at least one of the genes in arm p is DE ?

$\boxed{q}$: at least one of the genes in arm q is DE ? etc.

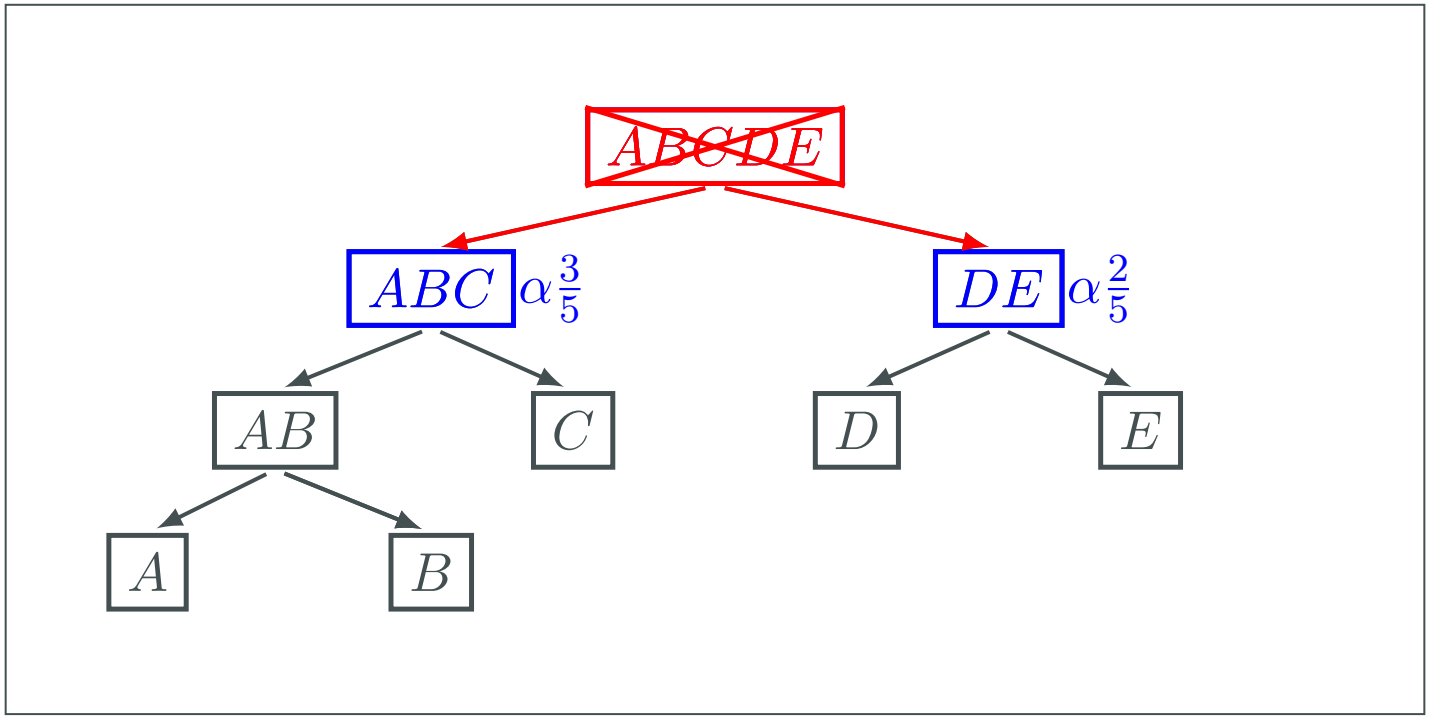
Meinshausen's procedure (BMK 2008)

start from the top:
test $ABCDE$ at level α



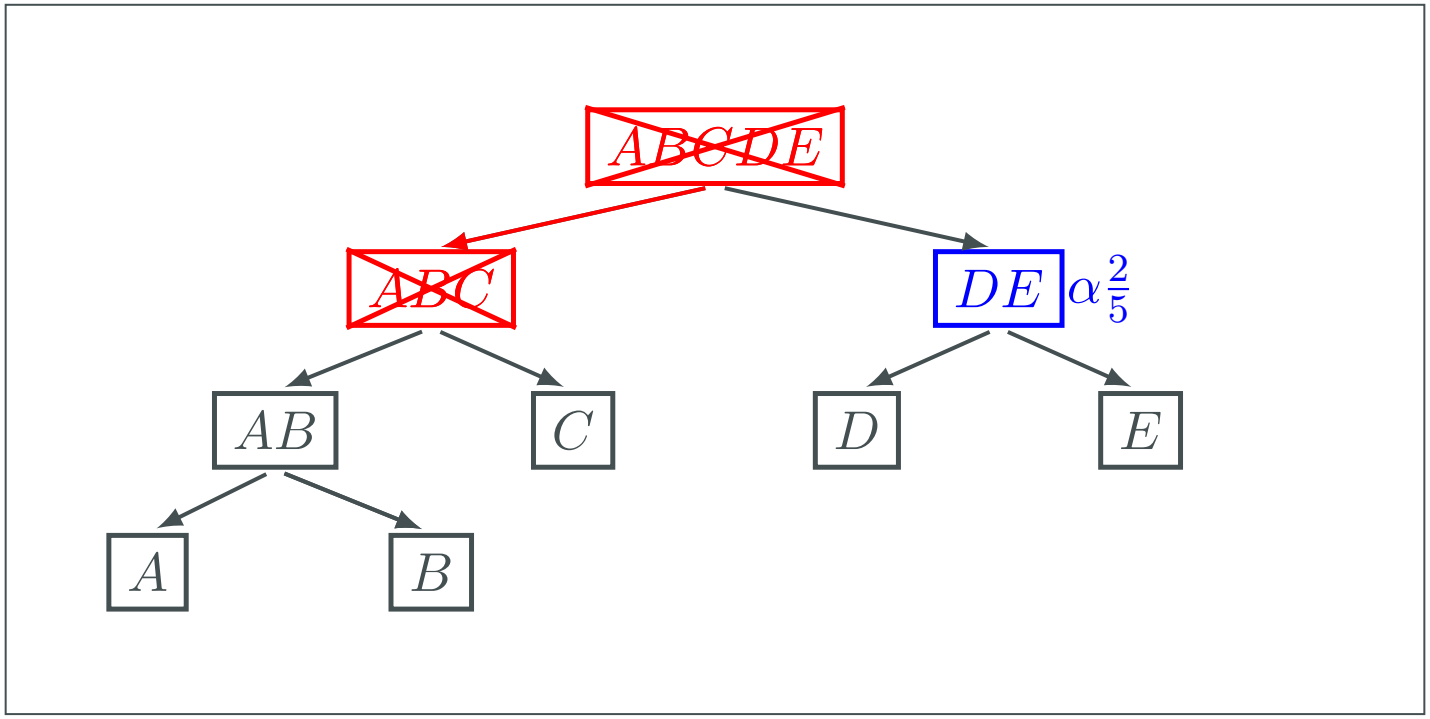
Meinshausen's procedure (BMK 2008)

suppose $p_{ABCDE} \leq \alpha$,
test ABC at $\frac{3}{5}\alpha$ and DE at $\frac{2}{5}\alpha$



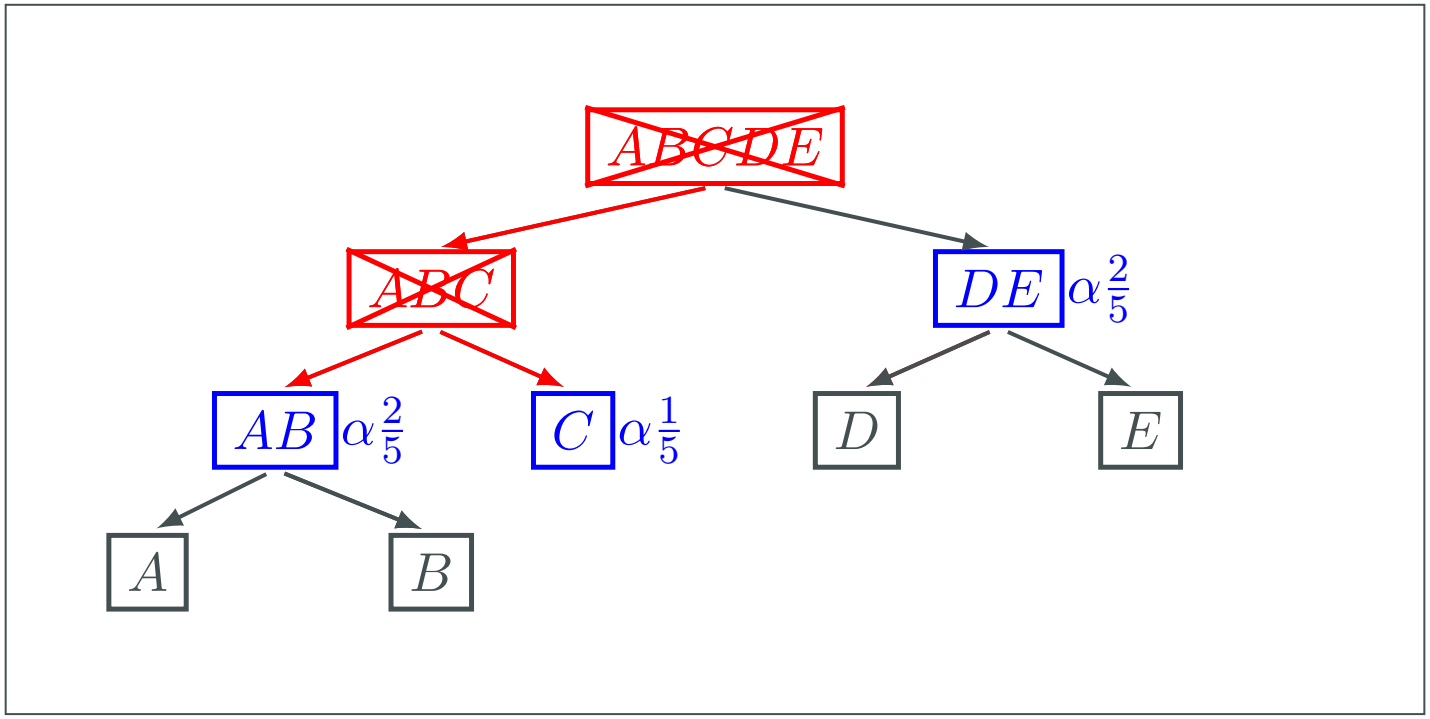
Meinshausen's procedure (BMK 2008)

suppose $p_{ABC} \leq \frac{3}{5}\alpha$ and $p_{DE} > \frac{2}{5}\alpha$



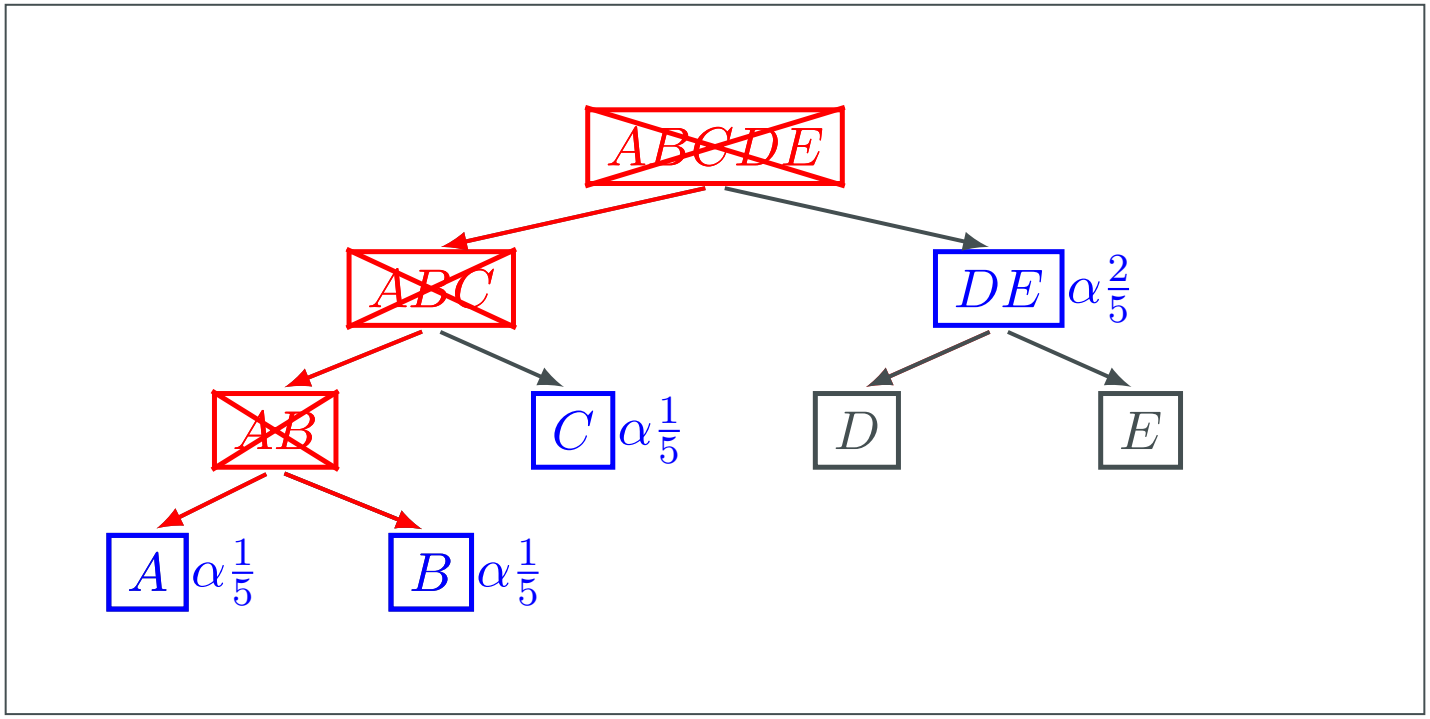
Meinshausen's procedure (BMK 2008)

test AB at $\frac{2}{5}\alpha$ and C at $\frac{1}{5}\alpha$



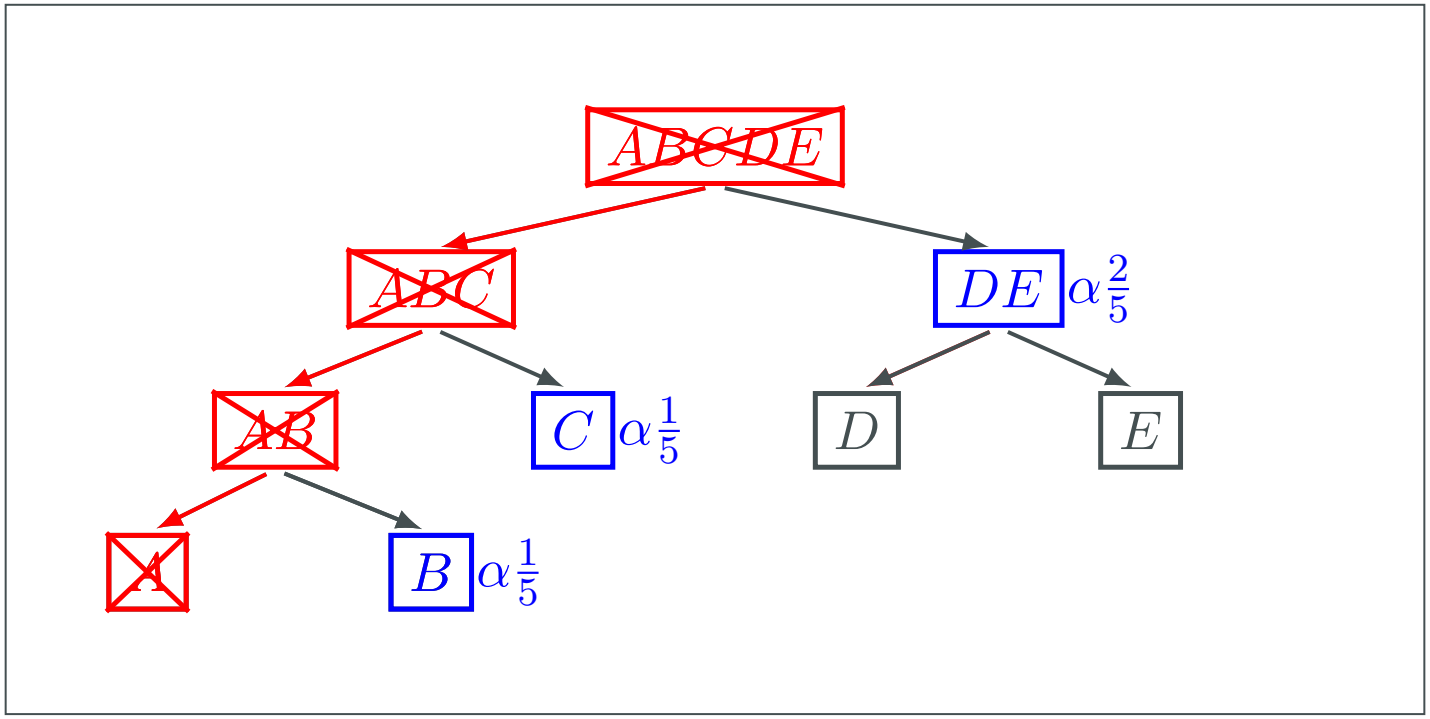
Meinshausen's procedure (BMK 2008)

suppose $p_{AB} \leq \frac{2}{5}\alpha$ and $p_C > \frac{1}{5}\alpha$,
test A at $\frac{1}{5}\alpha$ and B at $\frac{1}{5}\alpha$



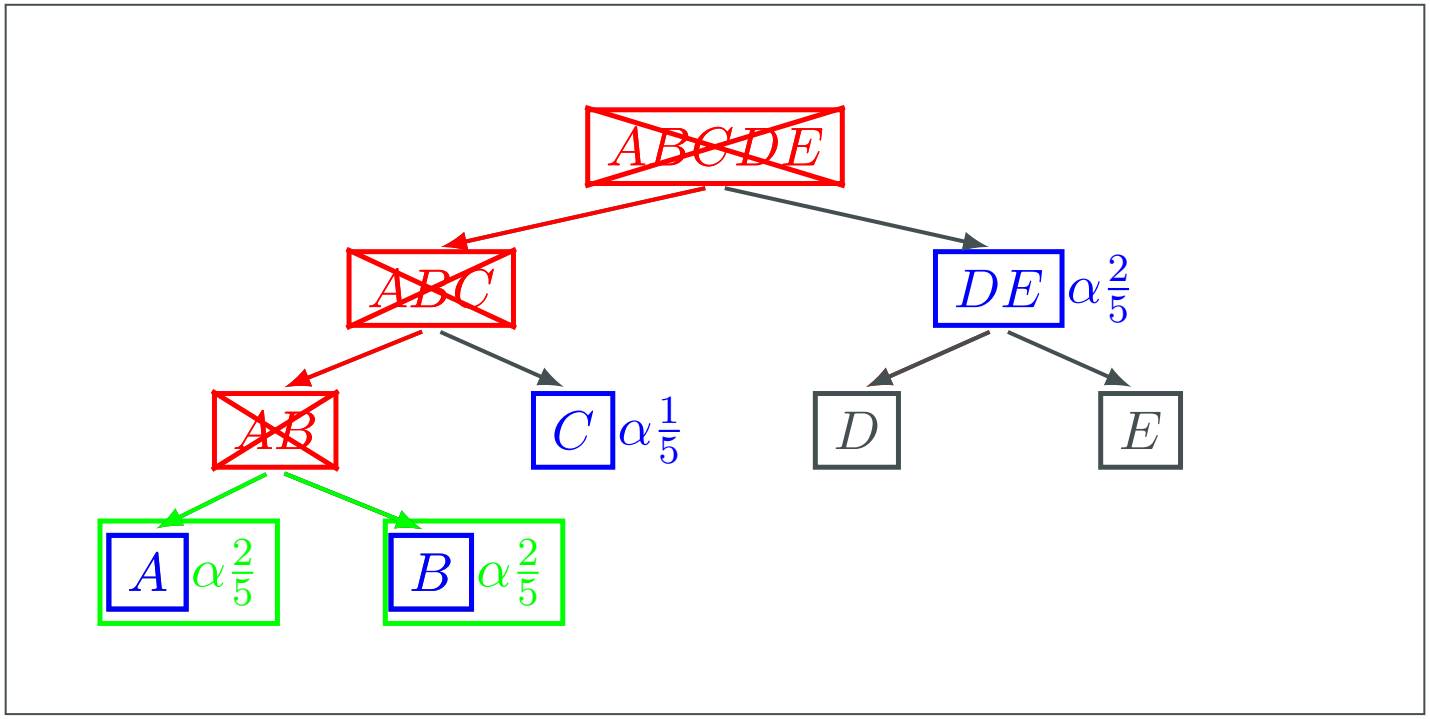
Meinshausen's procedure (BMK 2008)

suppose $p_A \leq \frac{1}{5}\alpha$ and $\frac{1}{5}\alpha < p_B < \frac{2}{5}\alpha$
STOP?



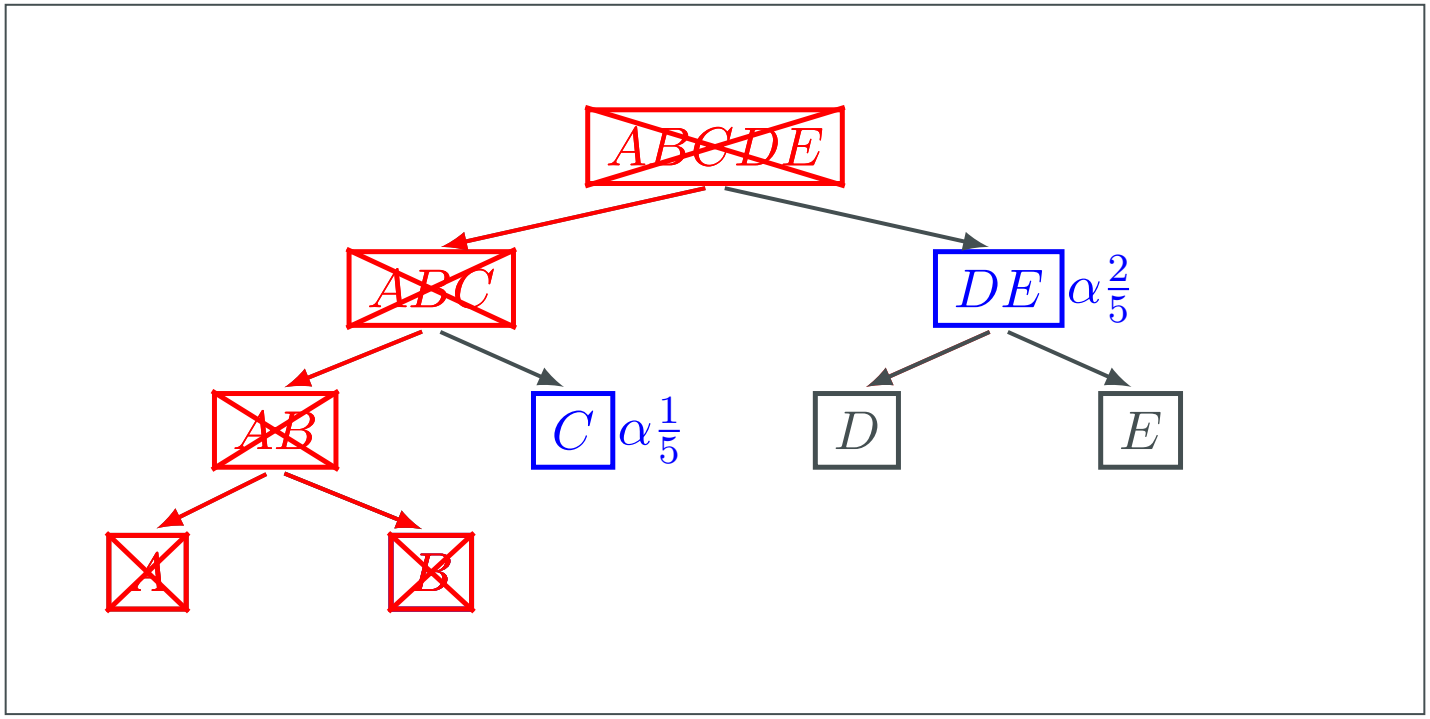
Meinshausen's procedure (BMK 2008)

Shaffer's improvement: if $A \cap B$ is a correct rejection, at least one hypothesis is false: test A and B at level $\frac{2}{5}\alpha$



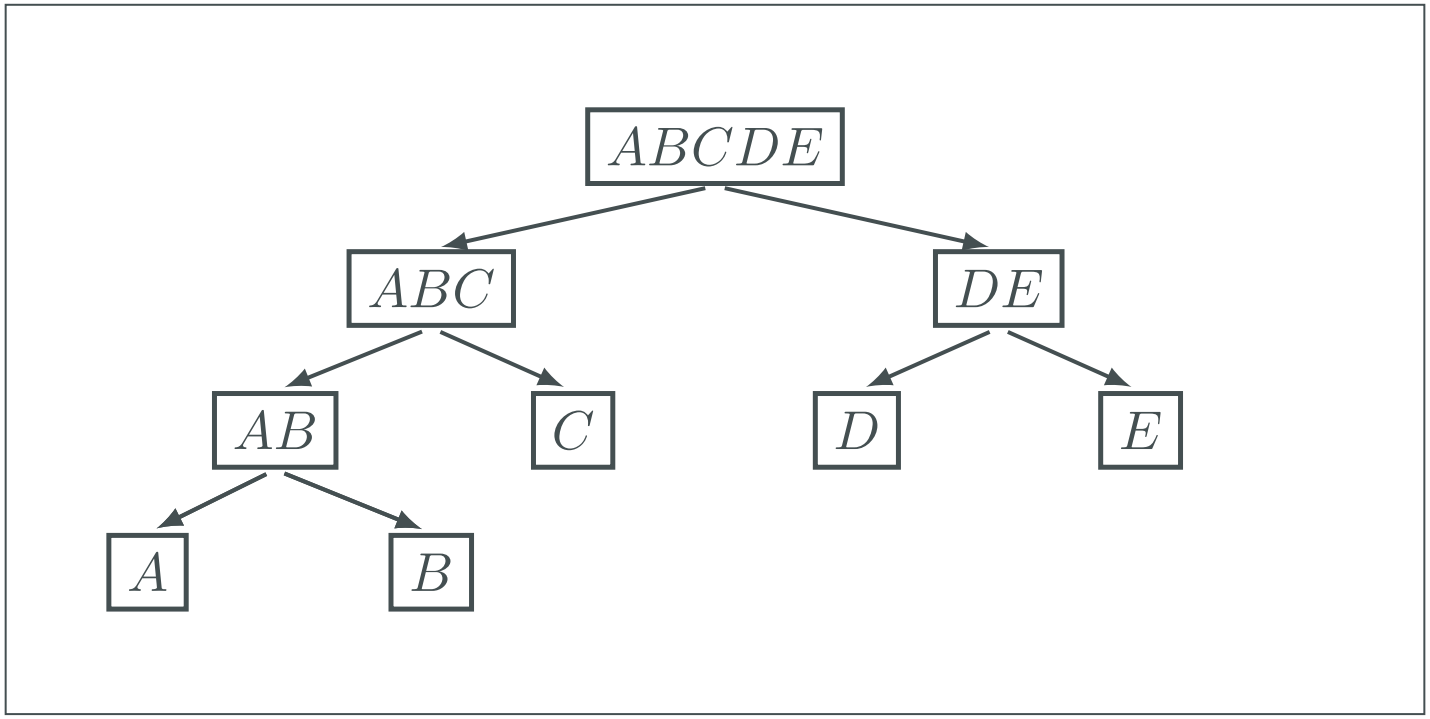
Meinshausen's procedure (BMK 2008)

reject A and B.
STOP!



Inheritance procedure (Goeman & Finos 2009)

Perform Meinshausen's procedure



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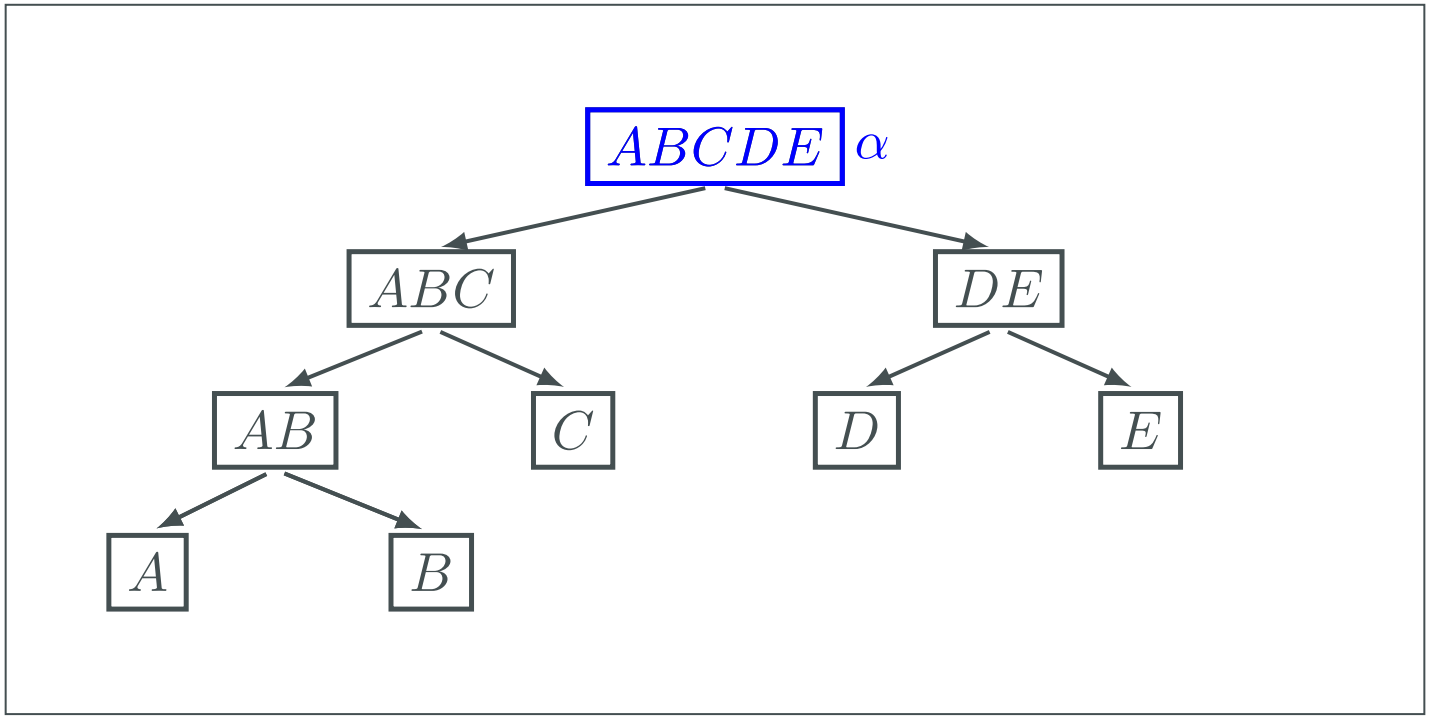

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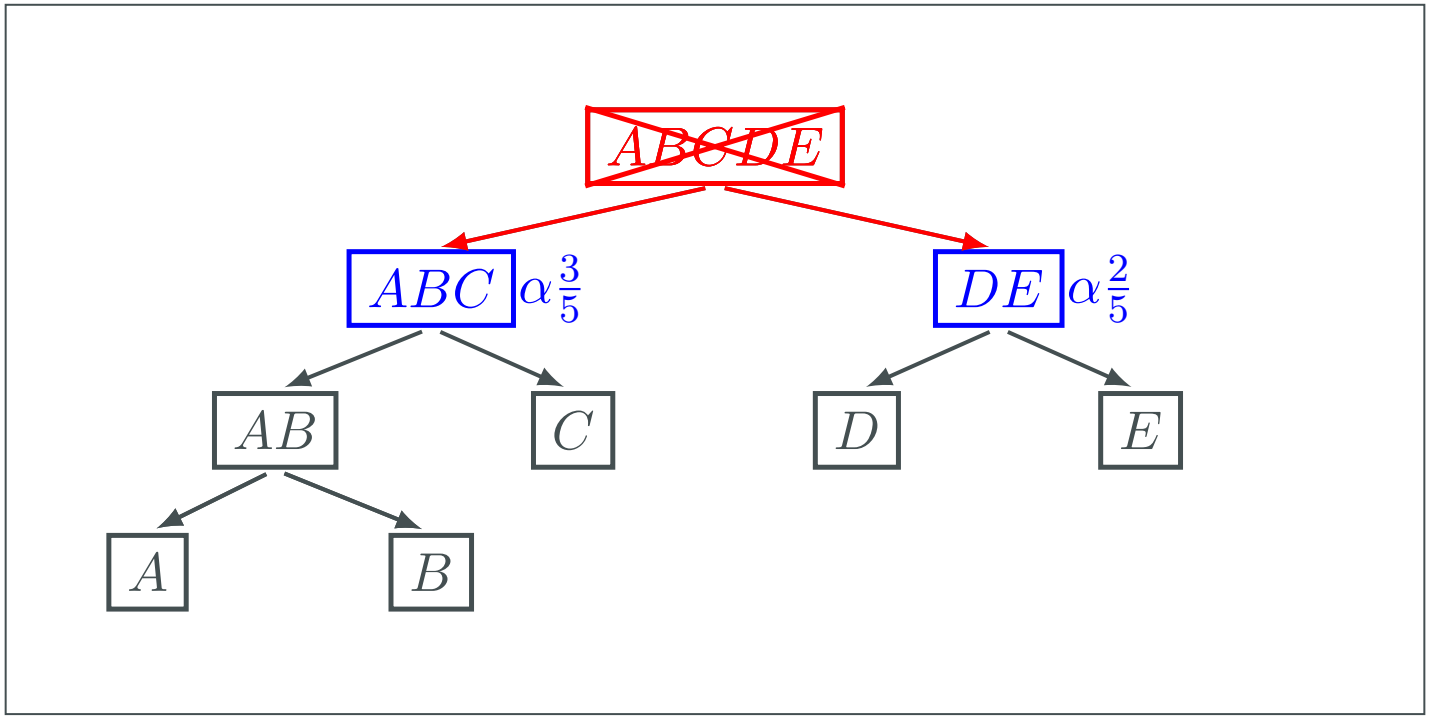
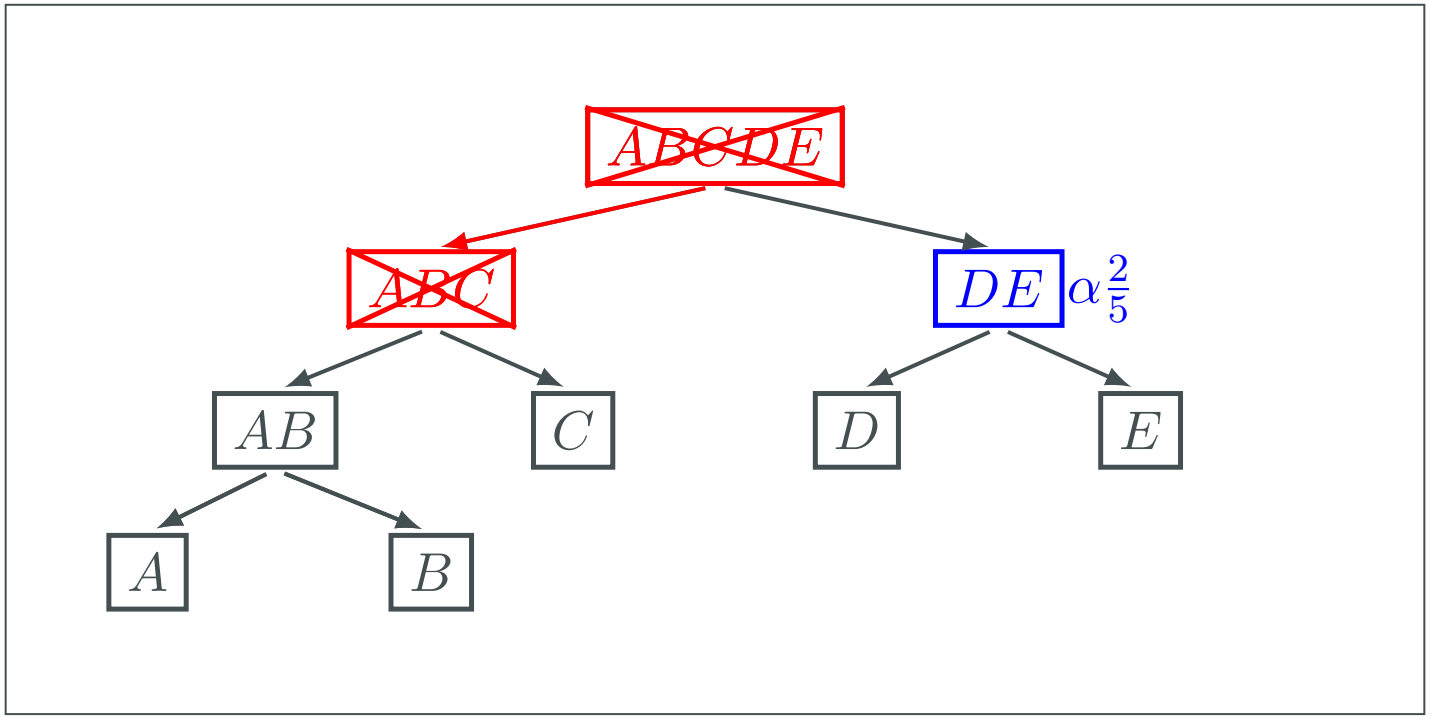


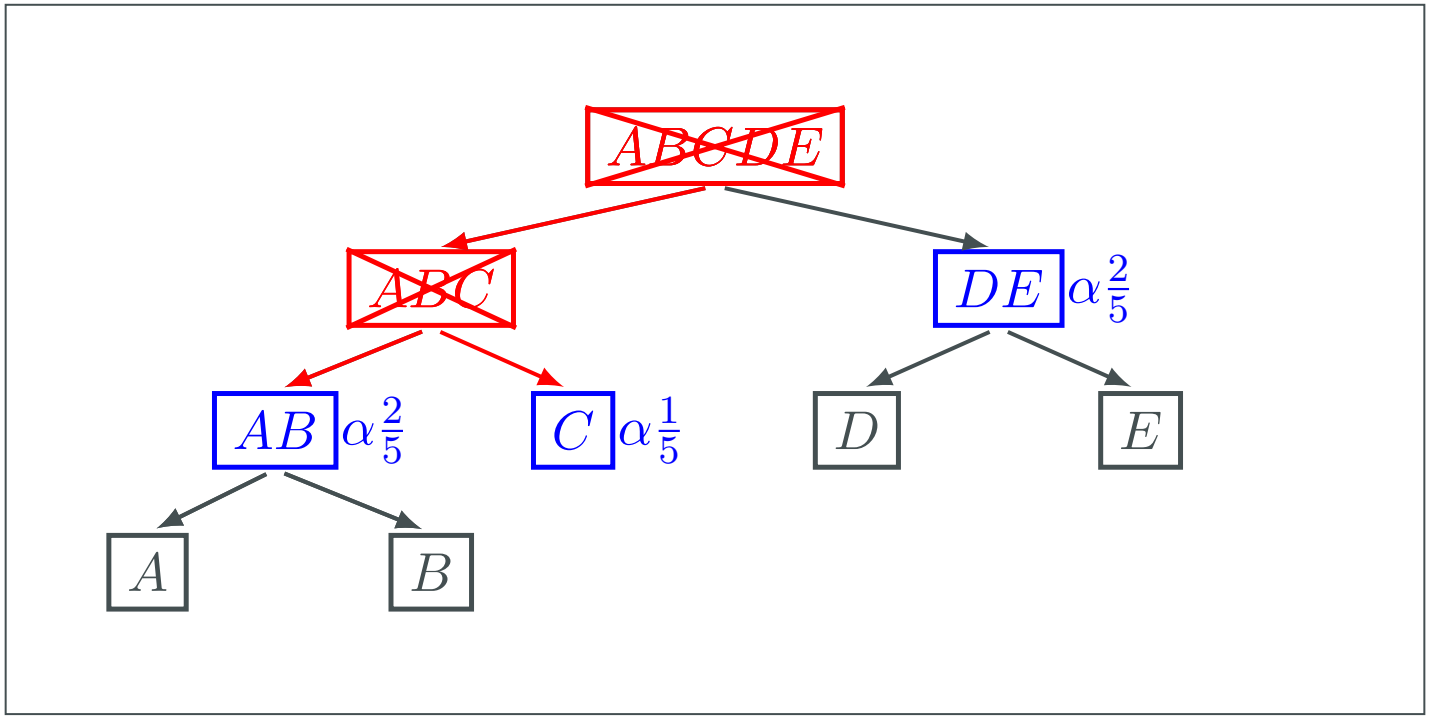
Inheritance procedure (Goeman & Finos 2009)

Perform Meinshausen's procedure



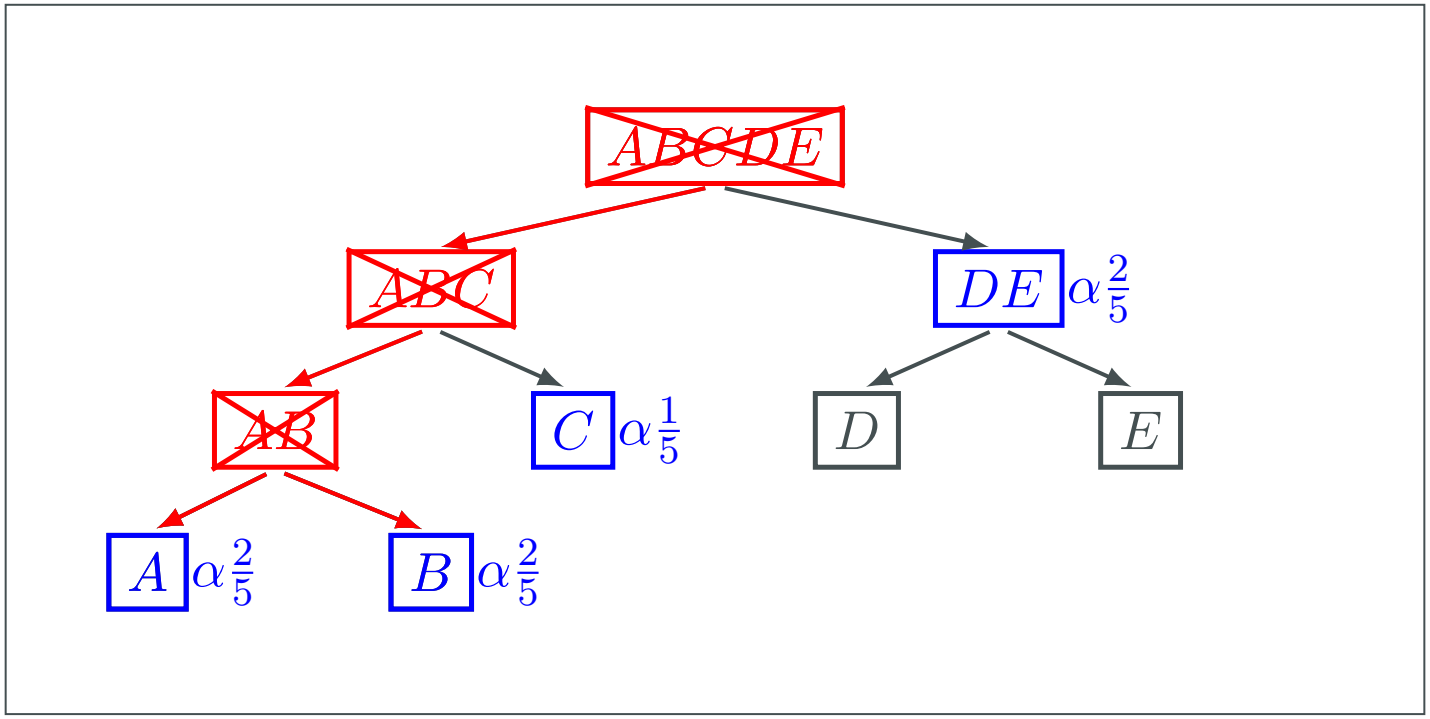
Inheritance procedure (Goeman & Finos 2009)

Perform Meinshausen's procedure



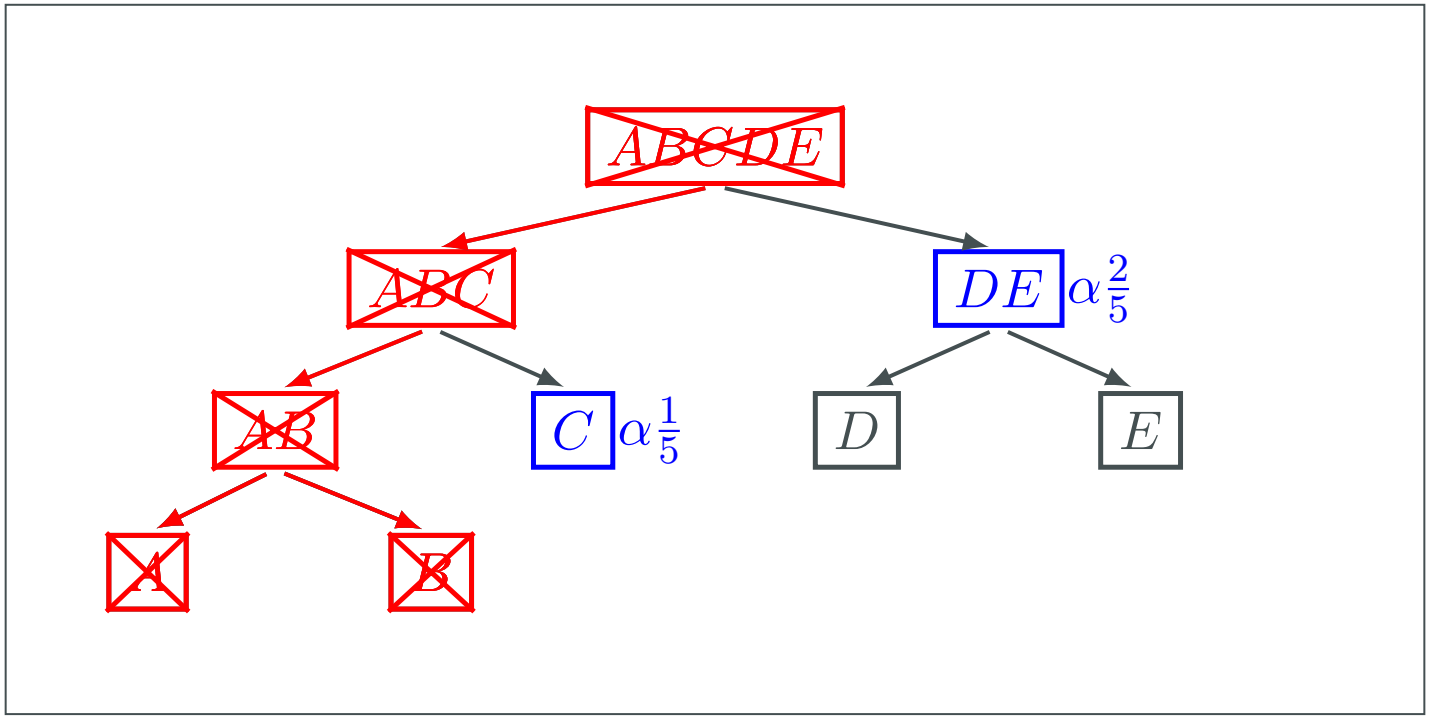
Inheritance procedure (Goeman & Finos 2009)

Perform Meinshausen's procedure



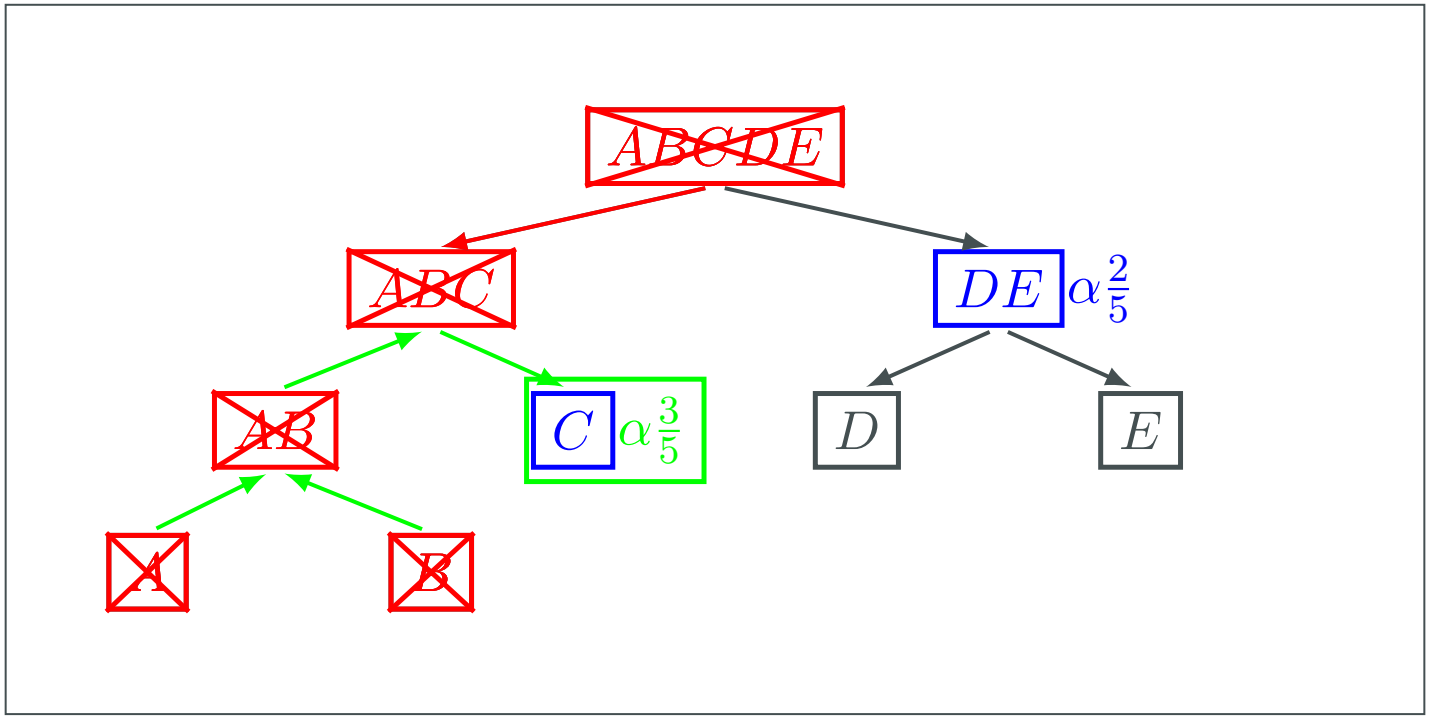
Inheritance procedure (Goeman & Finos 2009)

All leaf nodes in AB are rejected



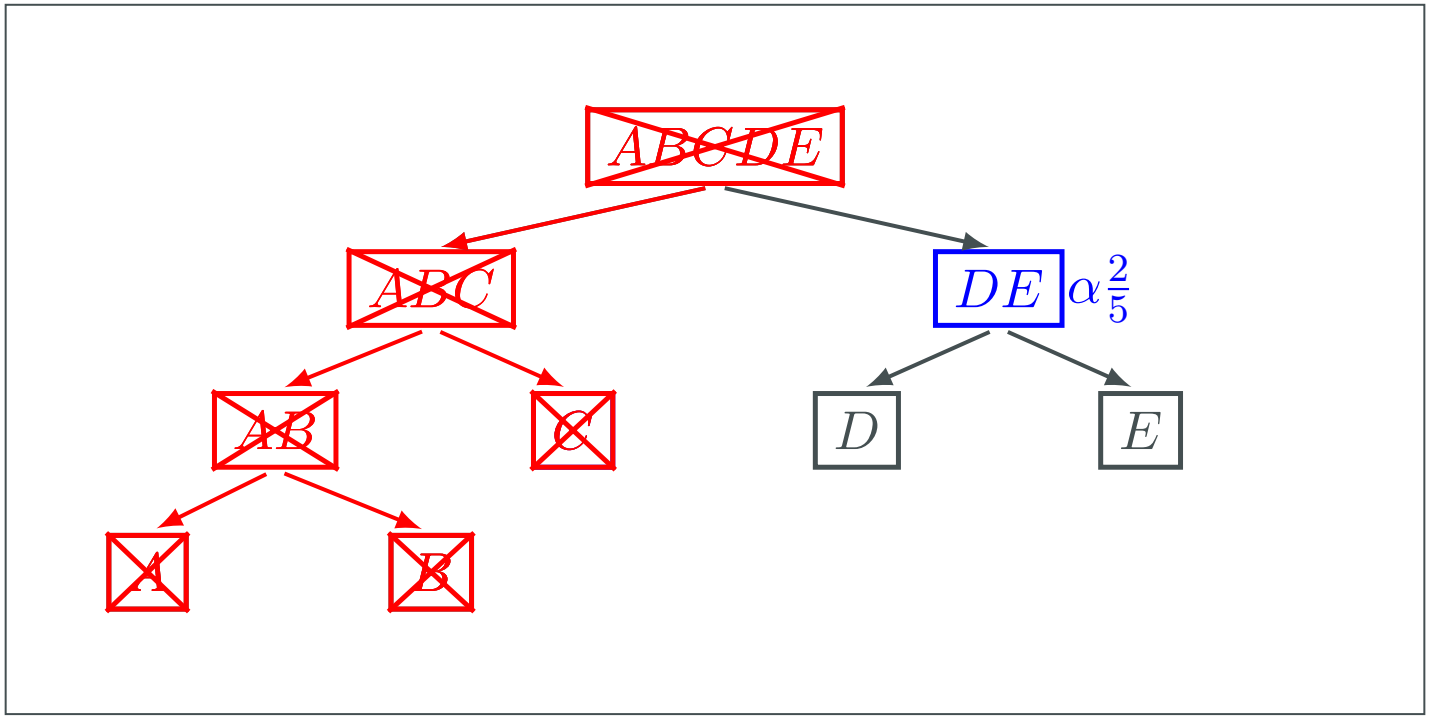
Inheritance procedure (Goeman & Finos 2009)

$\frac{2}{5}\alpha$ from AB is inherited to C (i.e. the closest relative)
test C at $(\frac{1}{5} + \frac{2}{5})\alpha$



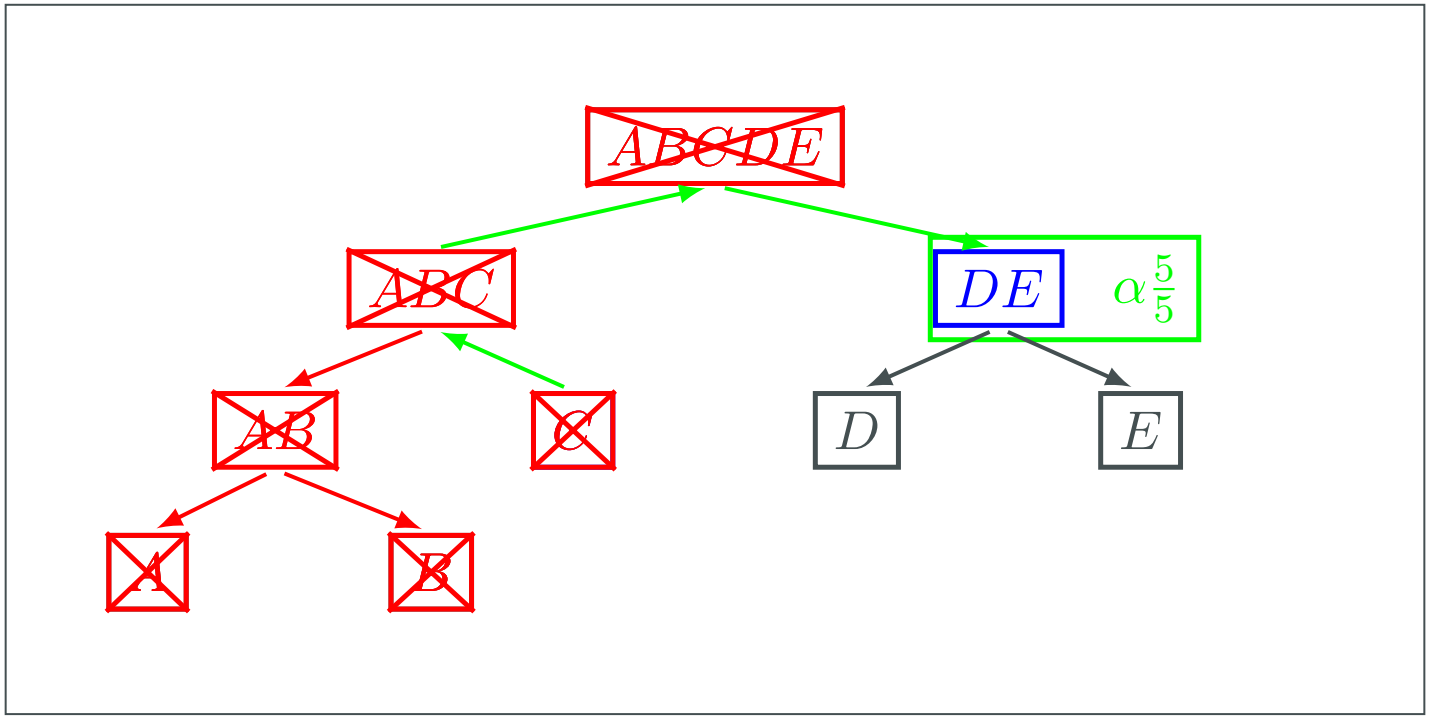
Inheritance procedure (Goeman & Finos 2009)

suppose $p_C \leq \frac{3}{5}\alpha$



Inheritance procedure (Goeman & Finos 2009)

$\frac{3}{5}\alpha$ from C is inherited to DE



Microarray-based comparative genomic hybridization (aCGH) Modena et al., 2006

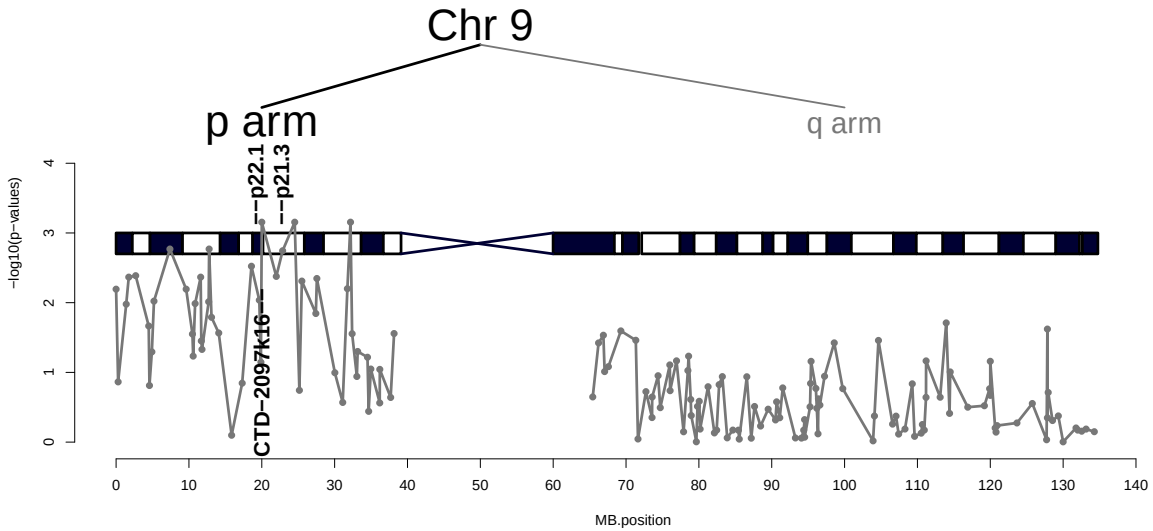
Data

- 2 samples:
  infratentorial tumors (14 patients) versus
  supratentorial tumors (8 patients).
- chromosome 9 (147 probes)

Inference

- for each probe (univariate): two sample t-test
- The signal is very weak and sparse among probes:
  Holm ($\alpha = .05$): no rejections

Results: Inheritance



Significant differences ($\alpha = .05$):

- arm: p
- band: p22.1 and p.21.3
- gene: CTD 2097k16

Software (bioconductor.org)

Inheritance procedure

R package *globaltest*

Authors: Goeman & Finos

```
> library(globaltest)
> inheritance()
```

Neurotoxicity screening assay (FOB; Moser, 1989)

Goal: Evaluation of neurotoxic effects of perchlorethylene

Data: The United States Enviromental Protection Agency published a guideline (FOB) to assess behavioural and neurologic functions in rats

- treatment (1.5g/kg exposure level) versus control (no exposure)
- 8 rats at each group
- 21 endpoints encompassing a wide spectrum of neurologic effects, grouped into 6 domains
- at each endpoint, the response is ordinal on a scale from 1 (absence of adverse effect) to 4 (most severe reaction)

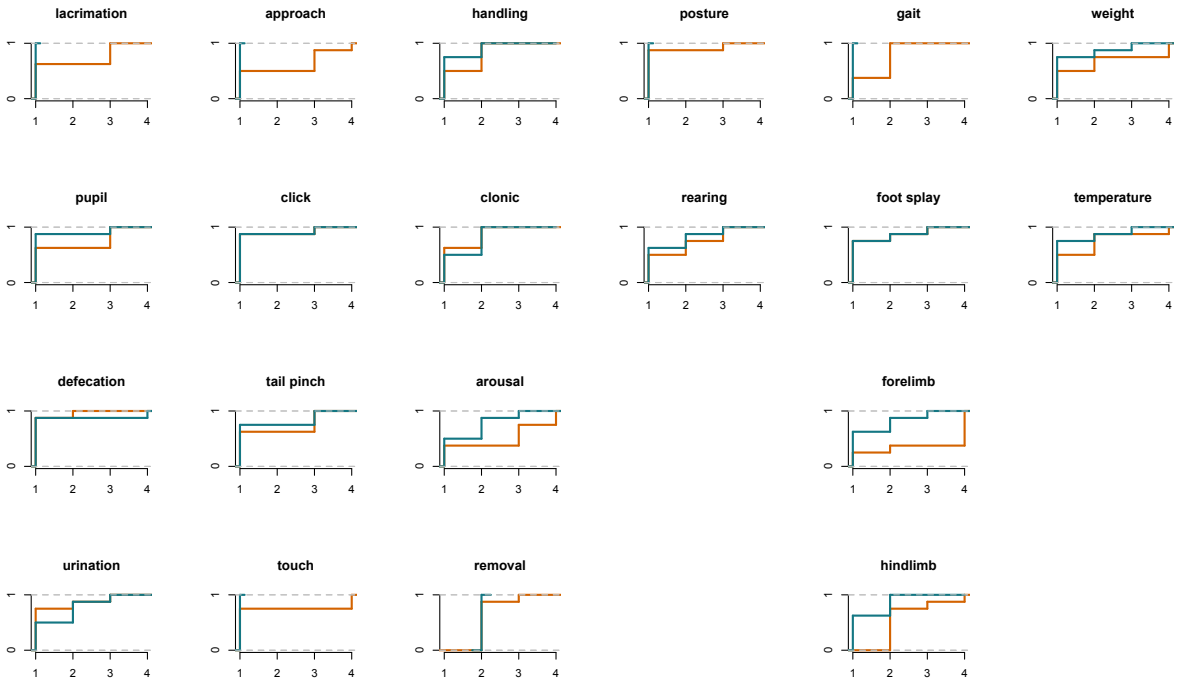
Challenging statistical problem: A large number of outcomes for a small sample of subjects

Data

Domain	Endpoint	Exposure (g/kg) 0 (control)				1.5 (treatment)			
		1	2	3	4	1	2	3	4
Autonomic	Lacrimation	8	0	0	0	5	0	3	0
	Pupil	7	0	1	0	5	0	3	0
	Defecation	7	0	0	1	7	1	0	0
	Urination	4	3	1	0	6	1	1	0
Sensorimotor	Approach	8	0	0	0	4	0	3	1
	Click	7	0	1	0	7	0	1	0
	Tail pinch	6	0	2	0	5	0	3	0
	Touch	8	0	0	0	6	0	0	2
CNS excitability	Handling	6	2	0	0	4	4	0	0
	Clonic	4	4	0	0	5	3	0	0
	Arousal	4	3	1	0	3	0	3	2
	Removal	0	8	0	0	0	7	1	0
CNS activity	Posture	8	0	0	0	7	0	1	0
	Rearing	5	2	1	0	4	2	2	0
Neuromuscolar	Gait	8	0	0	0	3	5	0	0
	Foot splay	6	1	1	0	6	1	1	0
	Forelimb	5	2	1	0	2	1	0	5
	Hindlimb	5	3	0	0	0	6	1	1
	Righting	8	0	0	0	5	2	1	0
Psysicological	Weight	6	1	1	0	4	2	0	2
	Temperature	6	1	1	0	4	3	0	1

Multiple hypotheses

$$H : Y_H \stackrel{\mathrm{d}}{=} X_H \quad \text{versus} \quad \tilde{H} : Y_H \stackrel{\mathrm{st}}{\geq} X_H, \qquad H \in \mathcal{H}$$



Test statistics

Ordinal measurement: distances between categories are unknown

Mantel's test $S_H(\mathbf{w})$ depends on nondecreasing scores $\mathbf{w}$ assigned to categories.

To overcome this problem, consider as the test statistic

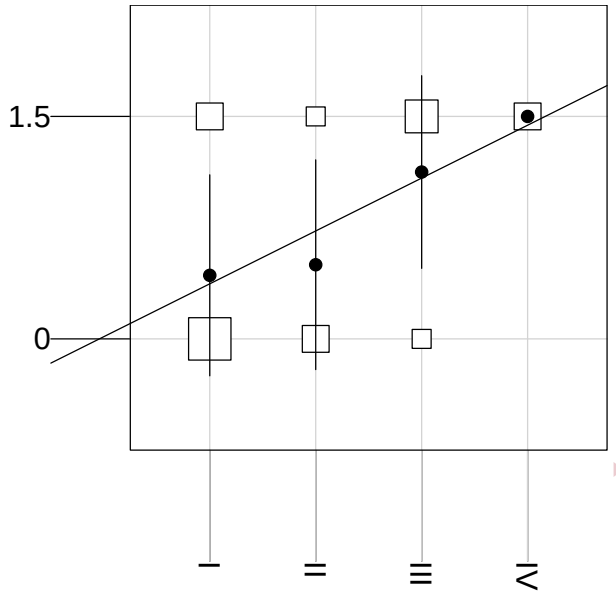
$$S_H^{\max} = \max_{\mathbf{w}}\{S_H(\mathbf{w})\}$$

where $\mathbf{w}^{\max}$ maximizing $S_H(\mathbf{w})$ can be found by isotonic regression (adaptive test)

Arousal	I	II	III	IV	
1.5 g/kg	2	1	3	2	8
0 g/kg	5	2	1	0	8

$\mathbf{w}^{\text{es}} = (0, 1/3, 2/3, 1)$

$S_H(\mathbf{w}^{\text{es}}) = 2.07$



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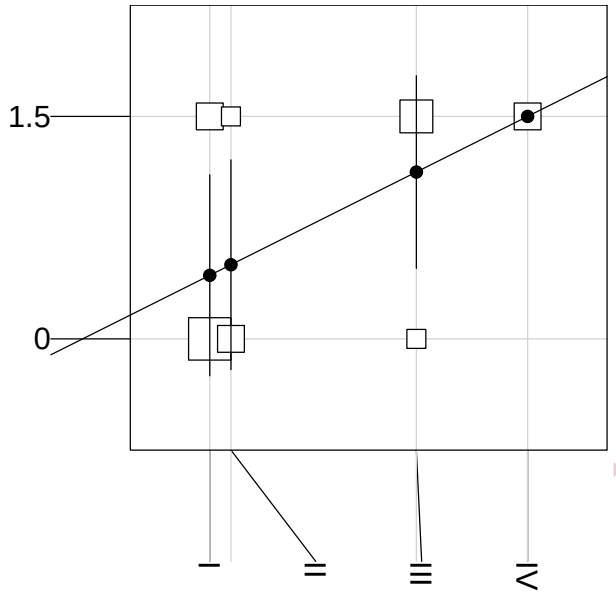
Arousal	I	II	III	IV	
1.5 g/kg	2	1	3	2	8
0 g/kg	5	2	1	0	8

$$\mathbf{w}^{\max} = (0, 0.07, 0.65, 1)$$

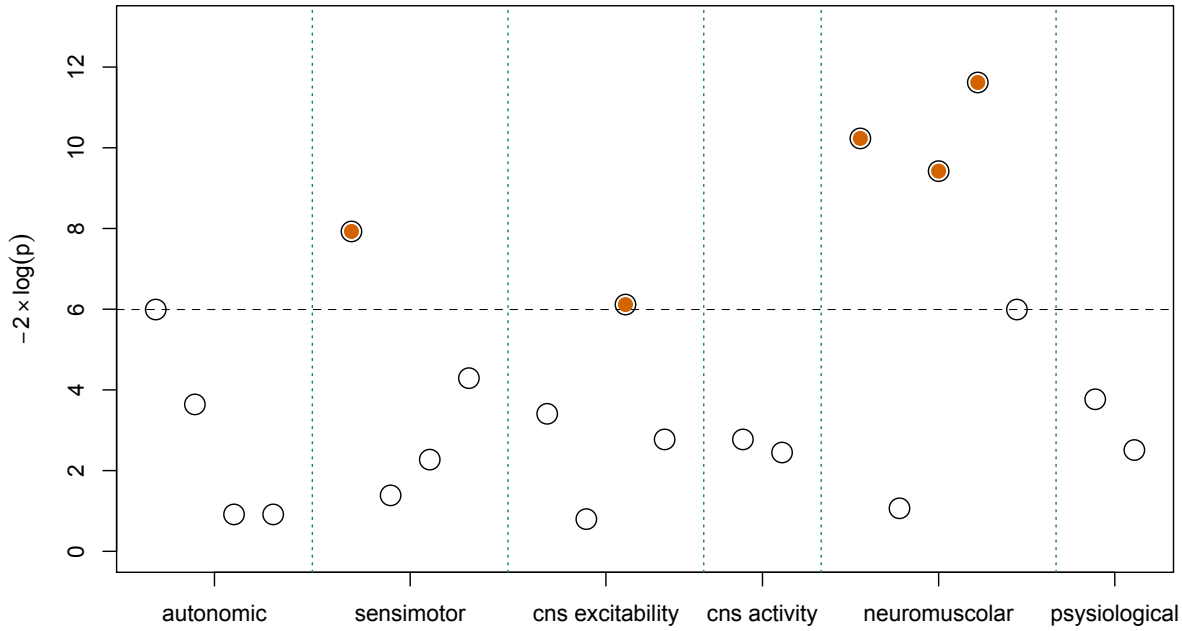
$$S_H^{\max} = S_H(\mathbf{w}^{\max}) = 2.15$$



Inference

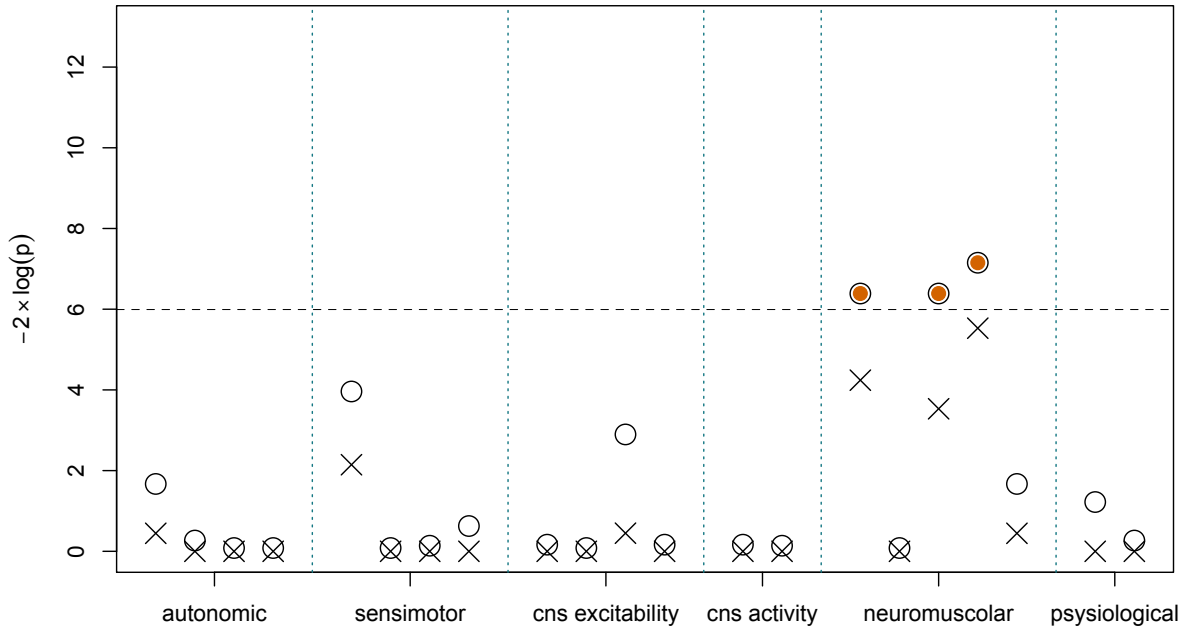
p-values for Endpoints (i.e. univariate test) are found by permutation approach (i.e. resampling based)
p-values for Domains (i.e. multivariate test) are found by combination of univariate ones (Pesarin 2001, klingenberg et al. 2009)

Results: endpoint level



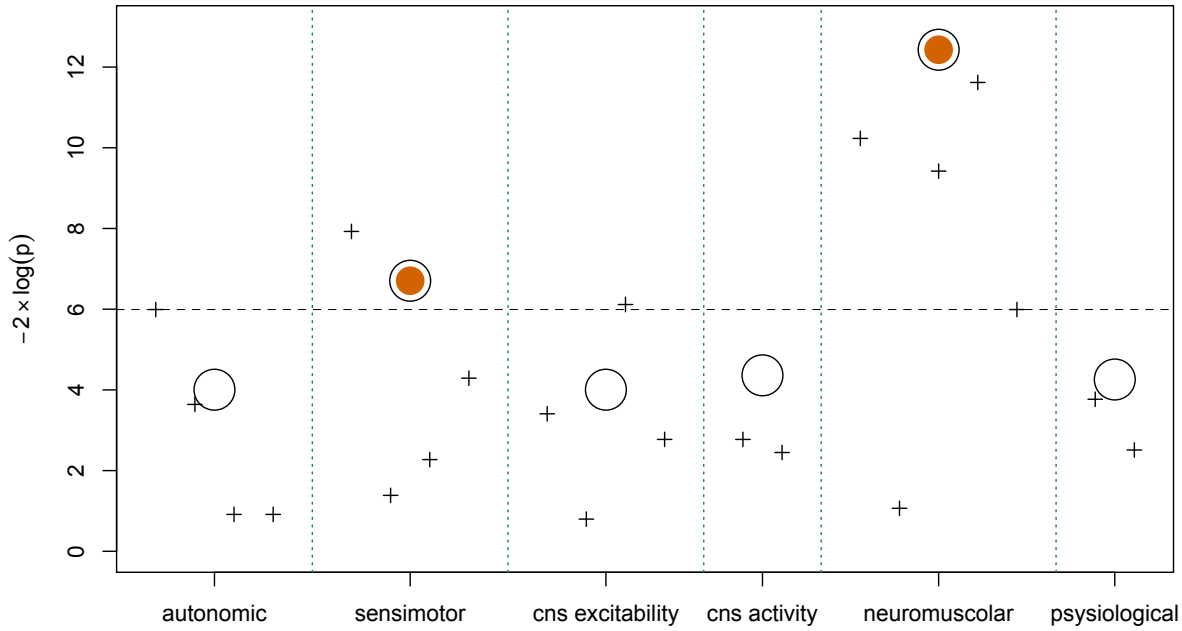
⊙ = raw p-values

Results: endpoint level



adjusted p-values: $\odot$ = Inheritance, x = Holm

Results: domain level



adjusted p-values: ◯ = Inheritance

Take-home message

Inheritance procedure

- Allows inference on tree-structured hypotheses
- Improves Meinshausen
- Available in the R package *globaltest*

Furthermore

- Extention to general graphs
- Extention to high dimension

Take-home message

Sequential Rejection principle

- A unifying approach,
  it includes other methods (Shaffer's, fallback, focus level, Meinshausen's, Rosenbaum's, etc.)
  Some other FWE controlling procedures do not fit (Sidak, Hochberg)
- Easy-to-check conditions of FWER control
- Useful tool to formulate procedures