University of Bremen

Faculty 03
Mathematics and
Computer Science

Online closed procedures

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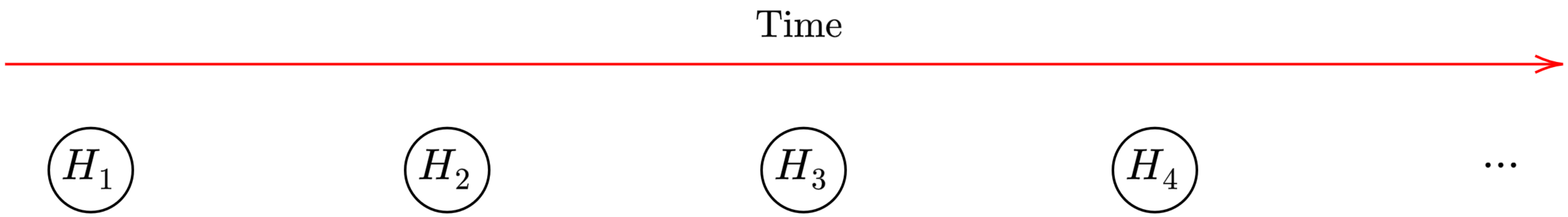
General concepts



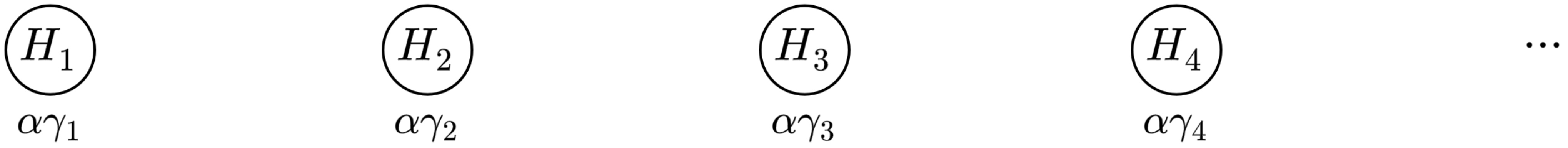
- In online multiple testing we only have access to the previous hypotheses and decisions.
  - Decisions made by an online procedure cannot be reversed based on future information.
- Familywise error rate (FWER) is the probability of committing at least one type I error.

Motivational applications

- Public databases
- Platform trials
- Modification of machine learning algorithms
- ...

Alpha-Spending (Foster & Stine, 2008)

→ Weight each hypothesis H_i with a predefined γ_i such that $\sum_{i \in \mathbb{N}} \gamma_i \leq 1$.

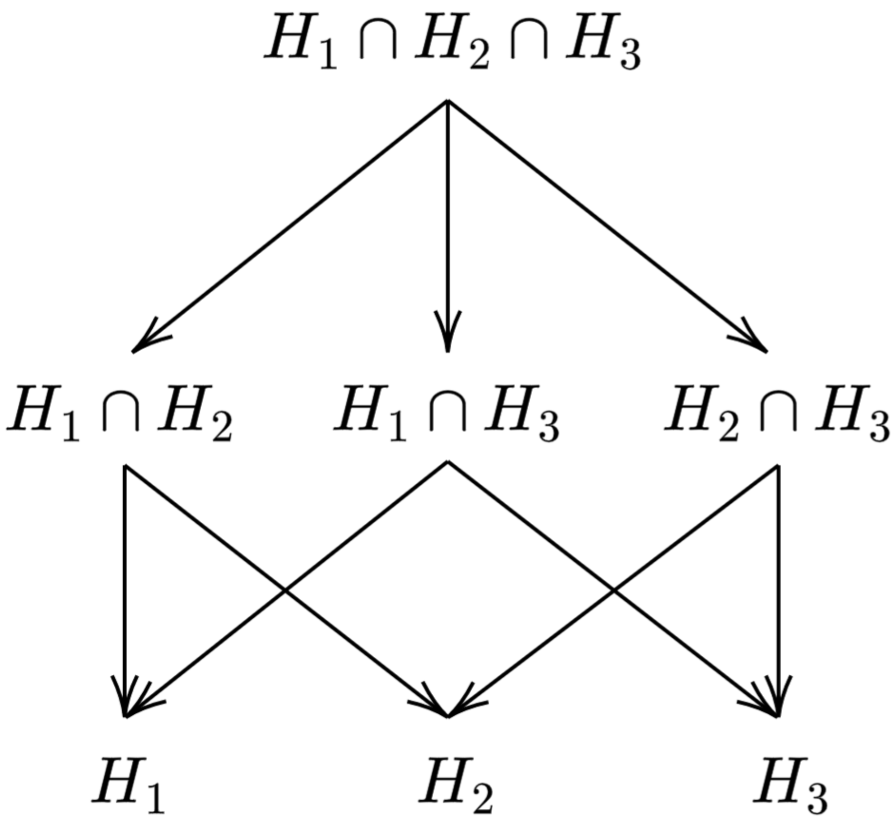


→ Strongly controls FWER by the Bonferroni inequality.

→ As Bonferroni, generally a conservative procedure.

Closure Principle

- Reject H_i, $i \in \{1,2,3\}$, if all $H_I = \bigcap_{i \in I} H_i$ with $I \subseteq \{1,2,3\}$ and $i \in I$ are rejected, each at level α.
- Not admissible in online multiple testing!



Online intersection test

An online intersection test ϕ_I, $I \subseteq \mathbb{N}$ is based on an online multiple test $(\phi_i^I)_{i \in I}$ such that $\phi_I = 1$ if and only if $\phi_i^I = 1$ for at least one $i \in I$.

→ Restricting to online intersection tests is not sufficient to obtain online closed procedures.

Example (Alpha-Spending):

$$\phi_{\{1\}} = \begin{cases} 1, & P_1 \leq \alpha \\ 0, & \text{otherwise} \end{cases} \qquad \phi_{\{1,2\}} = \begin{cases} 1, & P_1 \leq \frac{\alpha}{2} \text{ or } P_2 \leq \frac{\alpha}{2} \\ 0, & \text{otherwise} \end{cases}$$

→ If $\frac{\alpha}{2} < P_1 \leq \alpha$ and $P_2 > \frac{\alpha}{2} \implies \phi_{\{1\}} = 1$ and $\phi_{\{1,2\}} = 0$.

Predictability condition

A family of online intersection tests $(\phi_I)_{I\subseteq\mathbb{N}}$ is called *predictable*, if for all $i \in \mathbb{N}$ and $I \subseteq \{1, \ldots, i\}$ holds that:

$$\phi_I = 1 \text{ implies } \phi_K = 1 \text{ for all } K = I \cup J \text{ with } J \subseteq \{j \in \mathbb{N} : j > i\}.$$

→ The condition ensures that if a finite intersection hypothesis H_I, $I \subseteq \{1, \ldots, i\}$, is rejected, it remains rejected when future hypotheses H_j, $j > i$, are added.

Example:

$H_1 \cap H_2$ rejected $\implies$ $H_1 \cap H_2 \cap H_3$ rejected.

$H_1 \cap H_3$ rejected $\not\Longrightarrow$ $H_1 \cap H_2 \cap H_3$ rejected.

Online Closure Principle

1. Define the closure set $\overline{\mathcal{H}} = \left\{ H_I = \bigcap_{i \in I} H_i : I \subseteq \mathbb{N}, H_I \neq \emptyset \right\}$.
2. Identify an online α-level intersection test ϕ_I for each intersection hypothesis $H_I \in \overline{\mathcal{H}}$.
3. Reject H_i, if all $H_I \in \overline{\mathcal{H}}$ with $i \in I$ are rejected by its intersection test ϕ_I.

→ Every closed procedure controls the FWER in the strong sense.

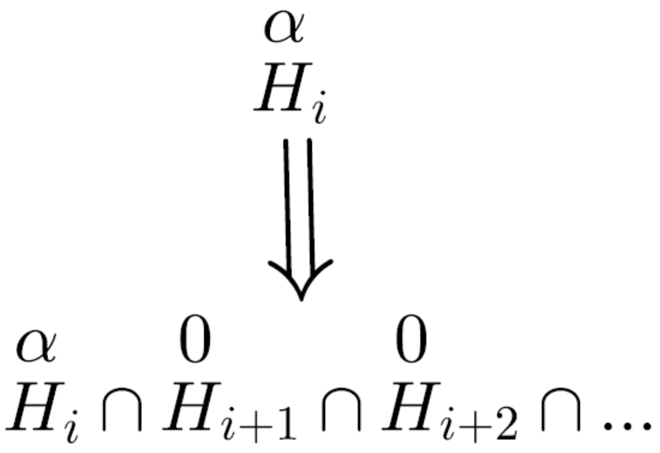
→ The resulting closed procedure is an **online procedure**, iff the family of online intersection tests $(\phi_I)_{I \subseteq \mathbb{N}}$ is **predictable**.

All online procedures are online closed procedures

→ If Q is a strong FWER controlling online procedure, then there exists an online closed procedure Q_c such that Q and Q_c are equivalent.

Exhaustive Alpha-Spending based online closed procedures

- → $\sum_{i \in I} \alpha_i^I = \alpha$.
- → We end up with fixed sequence procedure: reject H_i, if $P_1 \leq \alpha, \dots, P_i \leq \alpha$.
- → To derive Alpha-Spending based online closed procedures $\sum_{i \in I} \alpha_i^I < \alpha$ for some $I \subseteq \mathbb{N}$.



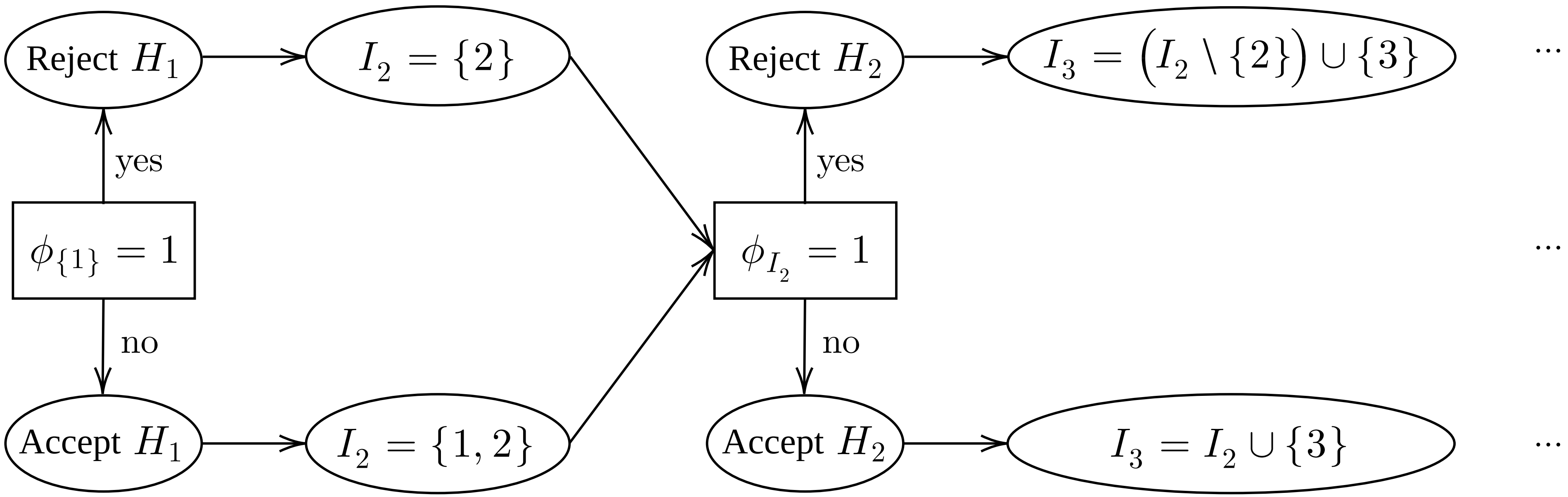
Consonance property

Problem: At each step $i \in \mathbb{N}$ we need to consider up to 2^{i-1} intersection hypotheses.

Solution: $(\phi_I)_{I \subseteq \mathbb{N}}$ has the **consonance property**, if $\phi_I = 1$, $I \subseteq \mathbb{N}$, implies that there exists at least one $i \in I$ such that $\phi_J = 1$ for all $J \subseteq I$ with $i \in J$.

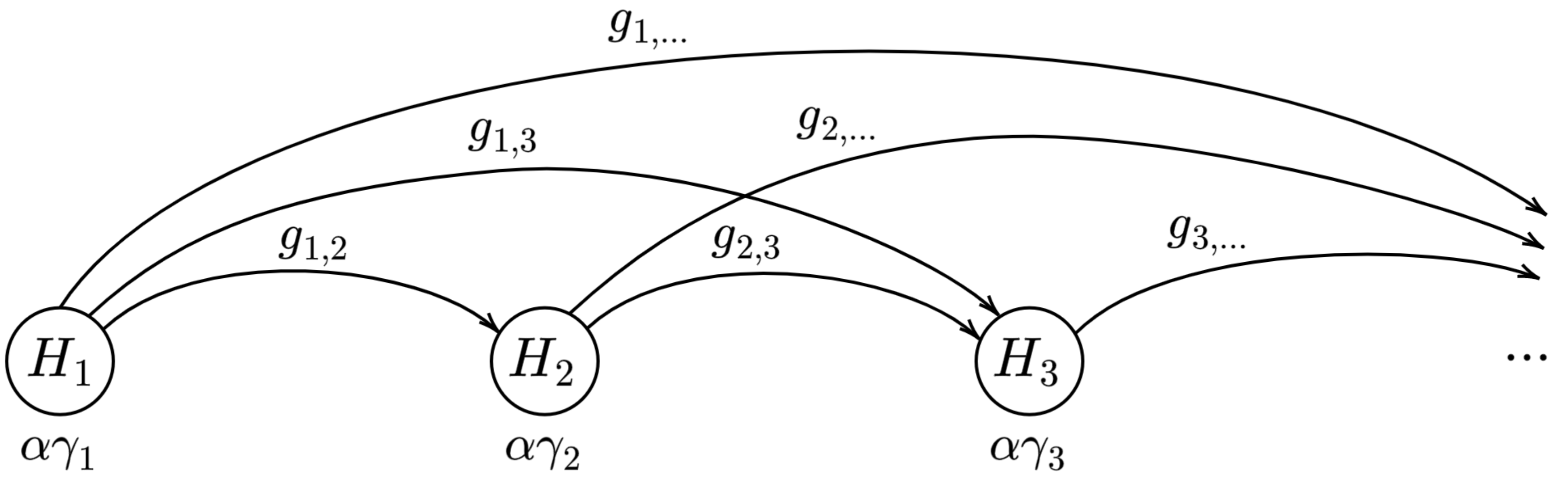
→ If $(\phi_I)_{I \subseteq \mathbb{N}}$ is a predictable family of online intersection tests with the consonance property, only one intersection test per individual hypothesis is needed.

Short-cuts of online closed procedures



Online-Graph

- Can be derived as Alpha-Spending based online closed procedure.
- Online version of the graphical procedure by (Bretz et al., 2009).



- In contrast to the classical graphical procedure, the weights $(g_{j,i})_{j\geq 1, i>j}$ are not updated during the testing process.

Closures of existing online procedures

→ Applying the **same** online procedure to each intersection hypothesis ensures predictability.

$$\overset{\alpha_1}{H_1} \cap \overset{\alpha_4}{H_4} \cap \overset{\alpha_6}{H_6}$$

$$\Downarrow$$

$$\overset{\alpha_1}{H_1} \cap \overset{\alpha_4}{H_4} \cap \overset{\alpha_6}{H_6} \cap \overset{\alpha_8}{H_8} \cap \overset{\alpha_9}{H_9}$$

→ Can often be used to construct improvements of existing FWER controlling online procedures.

→ Every weak FWER controlling online procedure (e.g. FDR procedure) defines a (new) strong FWER controlling online procedure.

Summary

- The predictability condition ensures that the resulting closed procedure is indeed an online procedure.
- All FWER controlling online procedures are online closed procedures.
- Due to restricted information, online procedures are often conservative.
- Short-cuts of online closed procedures are available under consonance.
- Applying the same online procedure to every intersection hypothesis satisfies the predictability condition.

Discussion

- When is FWER control desirable in online multiple testing?
  - Except for unrealistic extreme cases, the individual significance levels of FWER controlling online procedures tend to 0 for i to infinity ("alpha-death").

- In practice, the number of hypotheses is not necessarily extremely large.
- Some problems might require FWER control (e.g. modification of machine learning algorithms).
- Other approaches control the error rate over some time window (Feng et al., 2021).

- The closure principle is not limited to FWER control.
  - E.g. the closure principle can be used to construct confidence bounds on the false discovery proportion (Goeman & Solari, 2011).

References - Thank you!

- Bretz, F., Maurer, W., Brannath, W. & Posch, M. (2009). A graphical approach to sequentially rejective multiple test procedures. *Statistics in Medicine*, *28*, 586–604.
- Foster, D. P. & Stine, R. A. (2008). α-Investing: A Procedure for Sequential Control of Expected False Discoveries. *Journal of the Royal Statistical Society*, *70*(2), 429–444.
- Fischer, L., Roig, M. B., & Brannath, W. (2022). *The online closure principle*. *arXiv preprint arXiv:2211.11400*.
- Fischer, L., Roig, M. B., & Brannath, W. (2023). *An adaptive-discard-graph for online error control*. *arXiv preprint arXiv:2301.11711*.
- Hommel, G., Bretz, F. & Maurer, W. (2007). *Powerful short-cuts for multiple testing procedures with special reference to gatekeeping strategies*. *Statistics in Medicine*, *26*, 4063–4073.
- Tian, J. & Ramdas, A. (2021). Online control of the familywise error rate. *Journal of Biopharmaceutical Statistics*, *15*, 929–942.