Adaptive Dunnett Tests
based on conditional-rejection-probabilities

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TOPIC OF THIS TALK

- König et al. 2008: *Adaptive Dunnett Test*

  Assumption: Mean in control group known,
  or allocation ratios identical in both stages

- Motivation: response-adaptive multi-armed designs

CRP principle (Müller & Schäfer, 2001, 2004)

- Preplanned test φ
- Design modification after observing interim data D
- Adapted test $\tilde{\varphi}$
- If $E(\varphi \mid D) = E(\tilde{\varphi} \mid D)$, then $E(\varphi) = E(\tilde{\varphi})$

Nuisance parameters (Timmesfeld, 2007, 2008)

- Assume data depend on nuisance parameter(s) λ
- If there exists an adapted test $\tilde{\varphi}$, so that

$$E_{\lambda}(\tilde{\varphi} \mid D) = E_{\lambda}(\varphi \mid D), \quad \text{for all } \lambda,$$

then φ and $\tilde{\varphi}$ have the same level.

Numeric approach (Gutjahr, 2011)

$\tilde{\varphi}$ solution of semi-infinite linear program

$$\begin{aligned} \text{maximize} \quad & \int E_\lambda(\tilde{\varphi} \mid D)\, d\pi(\lambda) \\ \text{subject to} \quad & E_\lambda(\tilde{\varphi} \mid D) \leq E_\lambda(\varphi \mid D) \quad \text{for all } \lambda, \end{aligned}$$

with π the posterior of λ after observing D.

MULTIPLE HYPOTHESES

- Consider hypotheses $H_1, \ldots, H_k$
- Define intersection hypotheses $H_J = \bigcap_{j \in J} H_j$
- Preplanned test φ_J for H_J
- Closure principle: Reject H_j,
  if every H_J with $j \in J$ is rejected by φ_J.
- After interim analysis with data D,
  we can use adapted test $\tilde{\varphi}_J$.

Setup for the Dunnett test

- k treatments versus single control
- In control, observations are $N(\lambda, 1)$
- In treatment j, observations are $N(\lambda + \delta_j, 1)$
- $H_j : \delta_j = 0$
- Interim analysis with sample-size reassessment (and, as special case, treatment selection)

WE ARE DONE ...

- 1-dimensional nuisance parameter
- Calculate the φ_J's numerically

Explicit solution (1/3)

- Fix J; we want a test for H_J.
- Preplanned Dunnett test

$$\varphi = \mathbb{1}\{\max_{j \in J} Z_j > c\}$$

  with Z_j the preplanned z-statistic for j-th comparison
  (the Z_j's are not observable)

- After sample-size modification, we want to apply a test

$$\tilde{\varphi} = \mathbb{1}\{\max_{j \in J} \tilde{Z}_j > \tilde{c}\}$$

  with $\tilde{Z}_j$ the j-th z-statistic from the actual data.

Explicit solution (2/3)

- Conditional error of preplanned test

$$E_{\lambda}(\varphi \mid D) = 1 - \Phi_{\eta,\Sigma}(\lambda \mathbf{1}),$$

  with known values $\eta = \eta(D) \in \mathbb{R}^k$ and $\Sigma \in \mathbb{R}^{k,k}$.

- Let $\bar{X}$ denote the sample mean from actual second-stage observations (all groups).

- Let m denote the total second-stage sample size (all groups).

- Define $\tilde{\Sigma} = \Sigma - \frac{1}{m}\mathbf{1}\mathbf{1}^{\top}$

Explicit solution (3/3)

- If $\det(\tilde{\Sigma}) \geq 0$, we can select a critical value for $\tilde{\varphi}$ so that

$$E(\tilde{\varphi} \mid D, \bar{X}) = 1 - \Phi_{\eta,\tilde{\Sigma}}(\bar{X}\mathbf{1}).$$

  Integration over $\bar{X}$ gives

$$E_{\lambda}(\tilde{\varphi} \mid D) = 1 - \Phi_{\eta,\Sigma}(\lambda\mathbf{1}) = E_{\lambda}(\varphi \mid D) \quad \text{for all } \lambda.$$

- If $\det(\tilde{\Sigma}) < 0$, then simultaneous exhaustion is not possible. However, there still is a test that exhausts the conditional error rates most efficiently.

SUMMARY

- Closure principle—test each intersection hypothesis before rejecting an elementary hypothesis
- To correct for the data-dependent modification, use the CRP principle
- Calculate the adapted test analytically (if possible), or find numerically the test that exhaust the conditional error rates most efficiently.