Using the Partitioning Principle to Control Generalized Familywise Error Rate

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Error Rates

- Familywise Error Rate
  - $FWER = P(V>0)$
- False Discovery Rate
  - $FDR = E(V/R * I(R>0))$
  - Good for sparse situations
  - Inappropriate when k_1/k known to be large
- Generalized Familywise Error Rate
  - $gFWER = Pr(V>m),\ 0 \leq m < k$
  - FWER is a **special** case of gFWER when $m=0$
  - Controls **number** of false findings

V=number of false findings; R=total number of findings

k_1=number of truly significant hypotheses; k=total number of hypotheses

Multiple Testing Issues in Clinical Trials

- Control FWER, FDR, or gFWER?
  - Finner & Roter example of how to manipulate FDR
- Set critical values at $\mu_1 = \mu_2 = \ldots = \mu_k$?
  - $\mu_1 = \mu_2 = \ldots \mu_2 \neq \mu_k$ less favorable for joint-ranking methods (e.g., Kruskal-Wallis type)
  - Partition testing is conditional testing
- Step-up always more powerful than step-down?
  - No!

Issues in Analysis of Gene Expressions

- Control FDR or gFWER?
  - Is FDR inappropriate if target genes are pre-selected?
- Set critical values at complete null $\theta_1 = \ldots = \theta_k = 0$?
- Test $F_1 = F_2$ or $\mu_{g1} = \mu_{g2}$?
  - Depends on use
  - Permutation tests not valid for testing $\mu_{g1} = \mu_{g2}$

Uses of gene expression profiling

- Designer medicine (CDRH)
  - Screen genes to build diagnostic/prognostic chip
- Patient targeting (CDER)
  - Find patient subgroup responsive to compound
  - Eliminate patient subgroup prone to serious AE
- Drug discovery (pre-clinical)
  - Find co-regulated genes
  - Find transcription factor co-regulating genes
  - Find pathways

Classical Partitioning Testing

- Form all possible hypotheses

  H_{0I}: $\theta_i = 0$ for $i \in I$ and $\theta_i \neq 0$ for $i \notin I$

- Test each H_{0I} at level-α
- Infer $\theta_i \neq 0$ iff all H_{0J} with $i \in J$ is rejected

Partition+Bonferroni=Holm's Stepdown

$$H_{01}: \theta_1 \le 0, \quad H_{02}: \theta_2 \le 0$$

A: reject $H^*_{0\{12\}}: \theta_1 \le 0$ and $\theta_2 \le 0$

if $\hat\theta_1 > Z_{\alpha/2}$ or $\hat\theta_2 > Z_{\alpha/2}$

B: reject $H^*_{0\{1\}}: \theta_1 \le 0$

if $\hat\theta_1 > Z_\alpha$

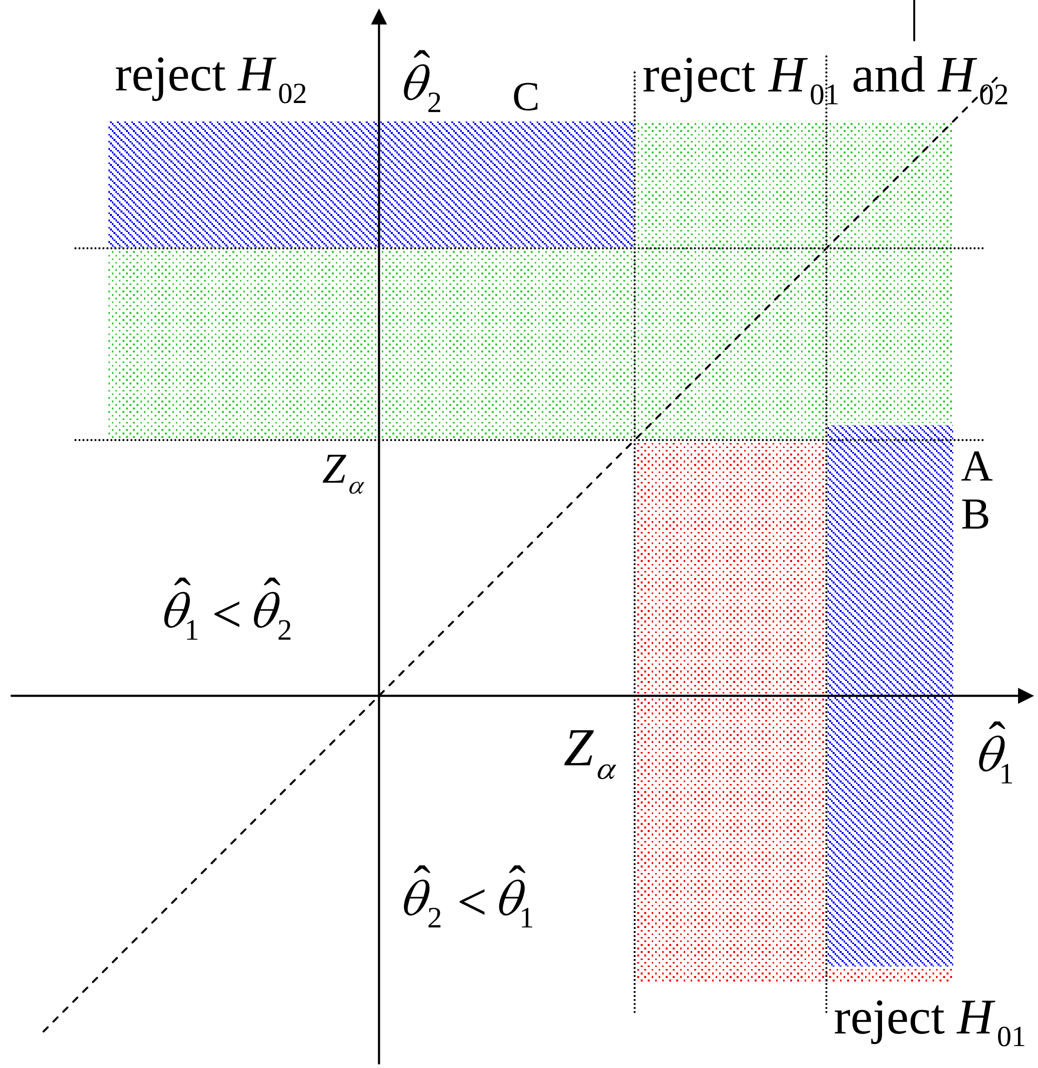
C: reject $H^*_{0\{2\}}: \theta_2 \le 0$

if $\hat\theta_2 > Z_\alpha$

$\mathrm{A}+\mathrm{B}+\mathrm{C} =$ reject H_{01} and H_{02}

$\mathrm{A}+\mathrm{B}-\mathrm{C} =$ reject H_{01}

$\mathrm{A}+\mathrm{C}-\mathrm{B} =$ reject H_{02}



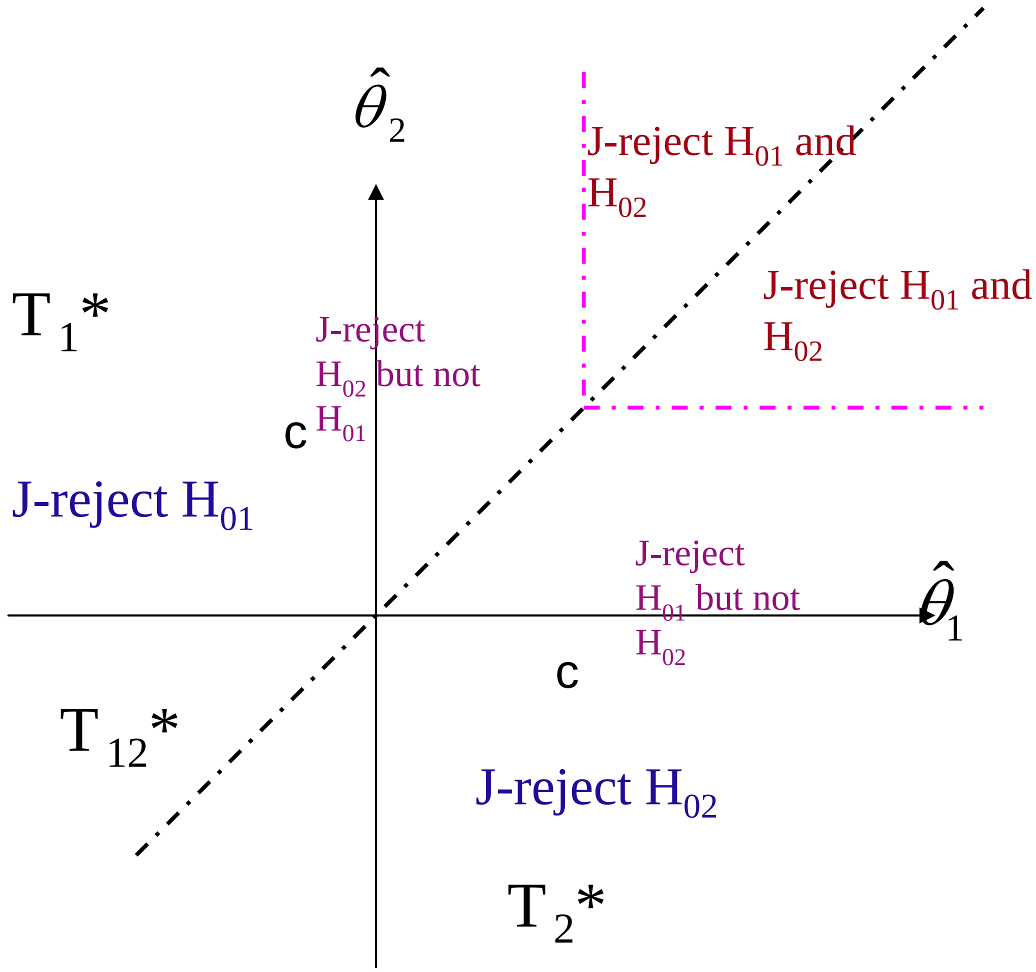
Single-step control of gFWER

- Single-step test based on adjusted p-values

$$\text{reject } H_{0i} \text{ if adjusted p-value } \tilde{p_i} = \sum_{j=m+1}^{k} \binom{k}{j} p_i^j (1-p_i)^{k-j} \leq \alpha.$$

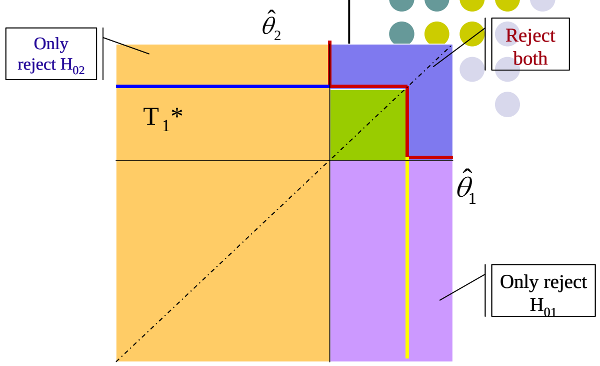
- Partially simultaneous confidence intervals
  - At least k-m confidence intervals cover true parameters with chance higher than (1-α)

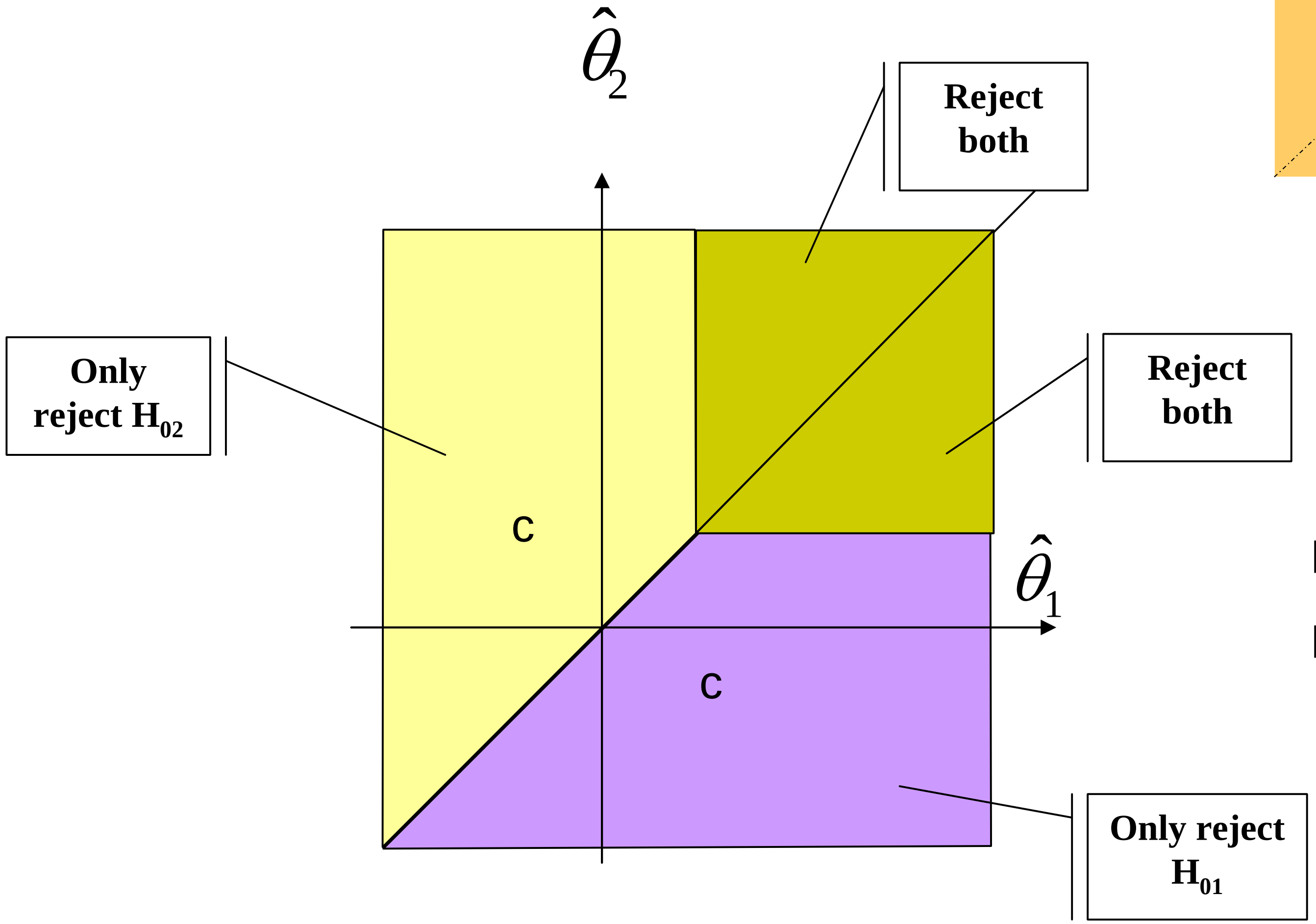
gFWER (k=2, m=1)



$\hat{\theta}_2$
J-reject H_{01} and H_{02}
J-reject H_{01} and H_{02}
T_1^*
J-reject H_{02} but not H_{01}
c
J-reject H_{01}
J-reject H_{01} but not H_{02}
$\hat{\theta}_1$
c
T_{12}^*
J-reject H_{02}
T_2^*

gFWER (k=2, m=1)





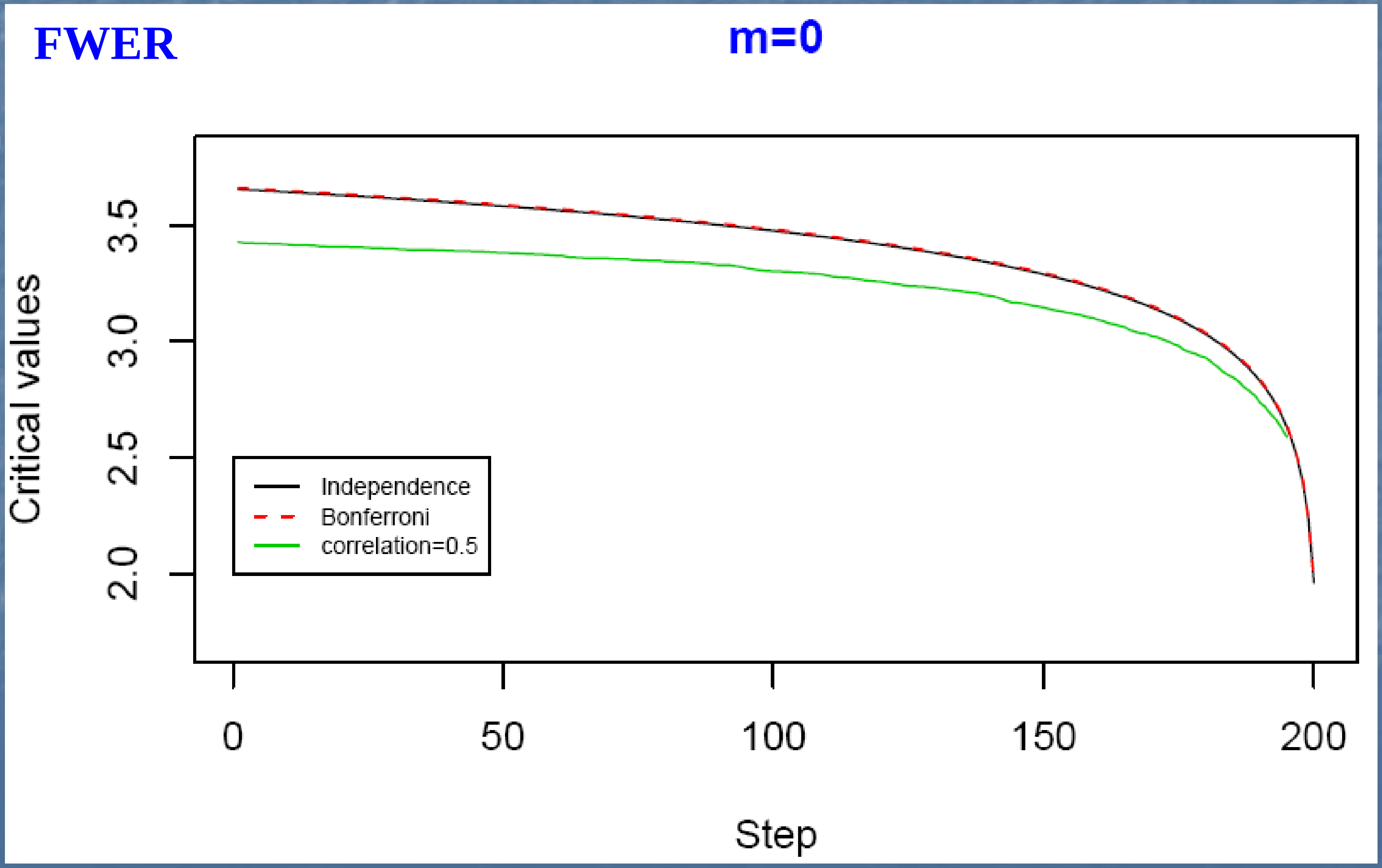
H_{01}: $?_1 = 0$

H_{02}: $?_2 = 0$

Other gFWER-controlling Methods

- van der Laan, Dudoit, and Pollard (2004)
  - Augmentation method
- Korn, Troendle, McShane, and Simon (2004)
  - Permutation test
- Lehmann and Romano (2005)
  - Step-down method
  - based on Markov's inequality

Comparison of Bonferroni vs. Independence vs. Modeling FWER-control



Comparison of Bonferroni vs. Independence vs. Modeling gFWER-control