

Implicitly adaptive FDR control based on the asymptotically optimal rejection curve

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Outline

Multiple Testing and the False Discovery Rate

Explicitly adaptive FDR control

Asymptotically Optimal Rejection Curve (AORC)



Multiple statistical decision problems

- Multiple comparisons (multiple tests)
- Simultaneous confidence regions
- Multiple power / sample size calculation
- Selection problems
- Ranking problems
- Partitioning problems



Prologue

We assume a statistical model (statistical experiment)

$$(\Omega, \mathcal{F}, (\mathbb{P}_\vartheta)_{\vartheta \in \Theta})$$

More concrete scenario (chosen for exemplary purposes):

Balanced ANOVA1 model:

$$X = (X_{ij})_{i=1,\dots,k, j=1,\dots,n}, \quad X_{ij} \sim \mathcal{N}(\mu_i, \sigma^2),$$

X_{ij} stochastically independent random variables on $\mathbb{R}$,
 $\mu_i \in \mathbb{R} \forall 1 \leq i \leq k$, $\sigma^2 > 0$ (known or unknown) variance
 $k \geq 3, n \geq 2$, $\nu = k(n-1)$ (degrees of freedom)

$$\Omega = \mathbb{R}^{k \cdot n}, \mathcal{F} = \mathbb{B}^{k \cdot n}$$

$$\vartheta = (\mu_1, \dots, \mu_k, \sigma^2) \in \mathbb{R}^k \times [0, \infty) = \Theta$$



Multiple comparisons (multiple tests)

$$(\Omega, \mathcal{F}, (\mathbb{P}_\vartheta)_{\vartheta \in \Theta})$$

Statistical model

$$\mathcal{H}_m = (H_i)_{i=1, \dots, m}$$

Family of null hypotheses with $\emptyset \neq H_i \subset \Theta$
and alternatives $K_i = \Theta \setminus H_i$

$$(\Omega, \mathcal{F}, (\mathbb{P}_\vartheta)_{\vartheta \in \Theta}, \mathcal{H}_m)$$

Multiple testing problem

$$\varphi = (\varphi_i : i = 1, \dots, m) \quad \text{multiple test for } \mathcal{H}_m$$

Hypotheses	Test decision		
	0	1	
true	U_m	V_m	m_0
false	T_m	S_m	m_1
	$m - R_m$	R_m	m



Multiple tests (II)

Wanted features of φ :

No (or only minor) **contradictions** among the individual test decisions

Control of the probability of **erroneous decisions**

(Type I) error measures / concepts:

$$\text{FWER}_m(\varphi) = \mathbb{P}_{\vartheta}(V_m > 0) \stackrel{!}{\leq} \alpha \quad \forall \vartheta \in \Theta$$

(Strong) control of the **Family-Wise Error Rate (FWER)**

$$\text{FDR}_m(\varphi) = \mathbb{E}_{\vartheta} \left[\frac{V_m}{R_m \vee 1} \right] \stackrel{!}{\leq} \alpha \quad \forall \vartheta \in \Theta$$

Control of the **False Discovery Rate (FDR)**



FWER control

FWER-controlling multiple testing principles:

- Historical single-step tests
(Bonferroni, Sidak, Tukey, Scheffé, Dunnett)
- Holm's (1979) stepwise rejective procedure
- Closed test principle (Marcus, Peritz, Gabriel (1969))
- Intersection-union principle (generalized closed testing)
- Partitioning principle
(Finner and Straßburger 2001, Hsu 1996)
- Projection methods under asymptotic normality
(Bretz, Hothorn and Westfall)
- Resampling-based multiple testing
(Westfall / Young 1992, Dudoit / van der Laan 2008)



Multiplicity of current applications

Due to rapid technical developments in many scientific fields, the number m of hypotheses to be tested simultaneously can nowadays become **almost arbitrary large**:

- Genetics, microarrays: $m \sim 30000$ genes / hypotheses
- Genetics, SNPs: $m \sim 500000$ SNPs / hypotheses
- Proteomics: $m \sim 5000$ proteine spots per gele sheet
- Cosmology: Signal detection, $m \sim 10^6$ pixels / hypotheses
- Neurology: Identification of active brain loci, $m \sim 10^3$ voxels
- Biometry: pairwise comparisons of many means,
tests for correlations

Analyses have (in a first step) typically **explorative character**.

⇒ **Control of the FWER much too conservative goal!**



Definition of the False Discovery Rate

 Θ

Parameter space

 $H_1, \dots, H_m$

Null hypotheses

 $\varphi = (\varphi_1, \dots, \varphi_m)$

Multiple test procedure

 $V_m = |\{i : \varphi_i = 1 \text{ and } H_i \text{ true}\}|$

Number of falsely rejected, true nulls

 $R_m = |\{i : \varphi_i = 1\}|$

Total number of rejections

$$\text{FDR}_{\vartheta}(\varphi) = \mathbb{E}_{\vartheta} \left[\frac{V_m}{R_m \vee 1} \right]$$

False Discovery Rate (FDR) given $\vartheta \in \Theta$

Definition: Let $\alpha \in (0, 1)$ fixed.

The multiple test φ controls the FDR at level α if

$$\text{FDR}(\varphi) = \sup_{\vartheta \in \Theta} \text{FDR}_{\vartheta}(\varphi) \leq \alpha.$$



The classical FDR theorem

Benjamini and Hochberg (1995)

$p_1, \dots, p_m$ (marginal) p -values for hypotheses $H_1, \dots, H_m$

H_i true for $i \in I_{m,0}$, H_i false for $i \in I_{m,1}$

$I_{m,0} + I_{m,1} = \mathbb{N}_m = \{1, \dots, m\}$, $m_0 = |I_{m,0}|$

$p_i \sim \text{UNI}[0, 1]$, $i \in I_{m,0}$ **stochastically independent** (I1)

$(p_i : i \in I_{m,0})$, $(p_i : i \in I_{m,1})$ **stoch. independent vectors** (I2)

$p_{1:m} \leq \dots \leq p_{m:m}$ **ordered p -values**

Linear step-up procedure φ^{LSU} with Simes' crit. values $\alpha_{i:m} = i\alpha/m$:

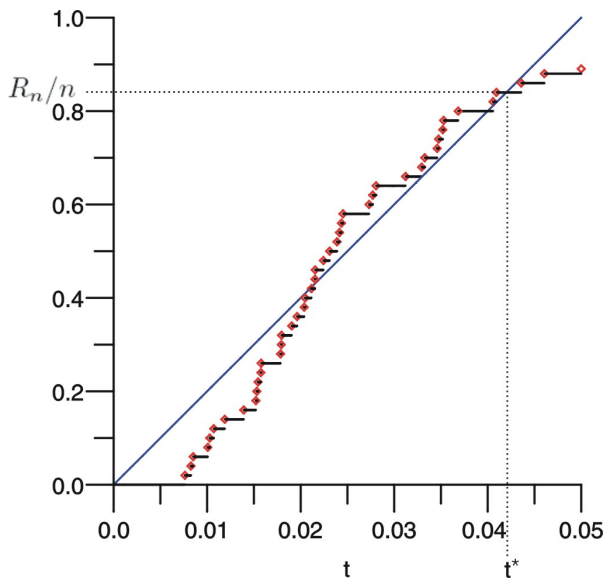
Reject all H_i with $p_i \leq \alpha_{\bar{m}:m}$, where $\bar{m} = \max\{j : p_{j:m} \leq j\alpha/m\}$.

Then it holds:

$$\text{FDR}_{\vartheta}(\varphi^{\text{LSU}}) = \mathbb{E}_{\vartheta}\left[\frac{V_m}{R_m \vee 1}\right] = \frac{m_0}{m}\alpha \quad \forall \vartheta \in \Theta.$$



Linear step-up in terms of Simes' rejection line



FDR control under positive dependency

Benjamini, Y. & Yekutieli, D. (2001) / Sarkar, S. K. (2002):

Proofs for FDR control in presence of special dependency structures:

$$\text{FDR}_{\vartheta}(\varphi) \leq \frac{m_0}{m} \alpha \quad \forall \vartheta \in \Theta$$

for stepwise test procedures employing Simes' critical values.

Model assumptions: **MTP₂ oder PRDS**

Examples:

Multivariate normal distributions with non-negative correlations,
multivariate (absolute) t -distributions

(Finner, Dickhaus, Roters (2007), The Annals of Statistics **35**, 1432-1455)



Explicit adaptation

Since under positive dependency the FDR of the LSU-procedure is bounded by

$$\frac{m_0}{m} \alpha$$

for any $m > 1$ and given $\alpha \in (0, 1)$, φ^{LSU} does **not exhaust** the FDR level α in case of $m_0 < m$.

Many modern FDR-controlling methods:

Pre-estimation of m_0 or $\pi_0 = m_0/m$ aiming at
tighter α -exhaustion and gain of power

(Explicit adaption)



Empirical stochastic processes

Interpret the number of rejections of (true / false) null hypotheses and the FDR of a **single-step test** with threshold $t \in [0, 1]$ for the p -values as empirical processes in t :

$$V(t) = \sum_{i \in I_{m,0}} \mathbf{1}_{[0,t]}(p_i),$$

$$S(t) = \sum_{i \in I_{m,1}} \mathbf{1}_{[0,t]}(p_i),$$

$$R(t) = V(t) + S(t) = \sum_{i=1}^m \mathbf{1}_{[0,t]}(p_i),$$

$$\text{FDR}(t) = \mathbb{E} \left[\frac{V(t)}{R(t) \vee 1} \right].$$



The adaptive procedure of Storey, Taylor and Siegmund (2004)

For a tuning parameter $\lambda \in (0, 1)$ is the following estimator $\hat{\pi}_0$ of π_0 reasonable (Schweder and Spjøtvoll (1982)):

$$\hat{\pi}_0 \equiv \hat{\pi}_0(\lambda) = \frac{m - R(\lambda) + 1}{m(1 - \lambda)} = \frac{1 - \hat{F}_m(\lambda) + 1/m}{1 - \lambda}$$

Under (I1) and (I2), we additionally obtain an estimator for the FDR of a single-step test with threshold $t \in [0, 1]$:

$$\widehat{\text{FDR}}_{\lambda}(t) = \frac{\hat{\pi}_0(\lambda)t}{(R(t) \vee 1)/m}$$

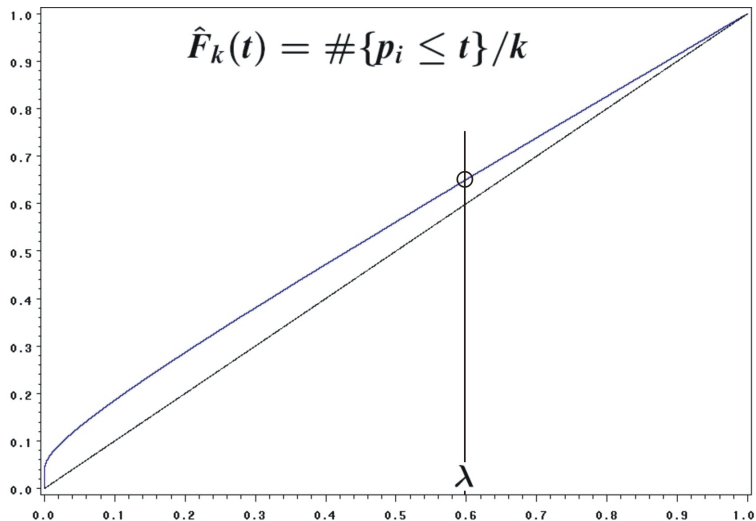
Resulting adaptive thresholding:

$$t_{\alpha}^{\lambda} = \sup\{0 \leq t \leq \lambda : \widehat{\text{FDR}}_{\lambda}(t) \leq \alpha\}$$



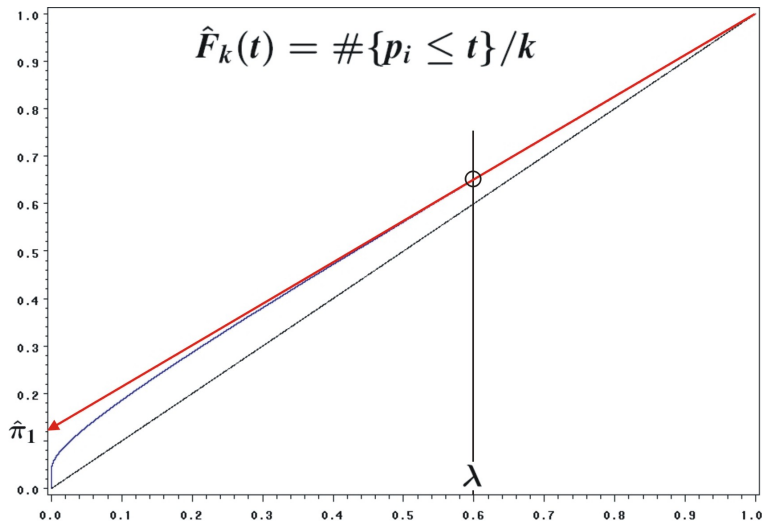
The estimator $\hat{\pi}_0$

Schweder and Spjøtvoll (1982)



The estimator $\hat{\pi}_0$

Schweder and Spjøtvoll (1982)



Martingale- and stopping time properties

Lemma: (Storey, Taylor and Siegmund (2004))

Assuming stochastically independent p -values under the m_0 null hypotheses, $V(t)/t$ is for $0 \leq t < 1$ a **reverse martingal** with respect to the filtration $\mathcal{F}_t = \sigma(\mathbf{1}_{[0,s]}(p_i), t \leq s \leq 1, i = 1, \dots, m)$, i. e., for $s \leq t$ it holds $\mathbb{E}[V(s)/s | \mathcal{F}_t] = V(t)/t$.

The random threshold t_α^λ is a stopping time with respect to $\mathcal{F}_{t \wedge \lambda}$.

$\implies$ FDR-proofs utilizing theory of **optimal stopping**



Proof of FDR-control of the adaptive test procedure by Storey et al.

Assumption: λ chosen such that $\widehat{\text{FDR}}_{\lambda}(\lambda) \geq \alpha$.

It follows: $\widehat{\text{FDR}}_{\lambda}(t_{\alpha}^{\lambda}) = \alpha \Leftrightarrow R(t_{\alpha}^{\lambda}) = m\hat{\pi}_0(\lambda)t_{\alpha}^{\lambda}/\alpha$.

Moreover, the process $V(t)/t$ stoppt at t_{α}^{λ} is bounded and

$$\begin{aligned}
 \text{FDR}(t_{\alpha}^{\lambda}) &= \mathbb{E} \left[\frac{V(t_{\alpha}^{\lambda})}{R(t_{\alpha}^{\lambda})} \right] = \mathbb{E} \left[\frac{\alpha}{m\hat{\pi}_0(\lambda)} \frac{V(t_{\alpha}^{\lambda})}{t_{\alpha}^{\lambda}} \right] \\
 &= \mathbb{E} \left[\alpha \frac{1 - \lambda}{m - R(\lambda) + 1} \frac{V(t_{\alpha}^{\lambda})}{t_{\alpha}^{\lambda}} \right] \\
 &= \mathbb{E} \left[\alpha \frac{1 - \lambda}{m - R(\lambda) + 1} \mathbb{E} \left[\frac{V(t_{\alpha}^{\lambda})}{t_{\alpha}^{\lambda}} \middle| \mathcal{F}_{\lambda} \right] \right] \\
 &= \mathbb{E} \left[\alpha \frac{1 - \lambda}{m - R(\lambda) + 1} \frac{V(\lambda)}{\lambda} \right].
 \end{aligned}$$

Noticing $V(\lambda) \sim \text{Bin}(n_0, \lambda)$, yields:

$$\begin{aligned}\text{FDR}(t_\alpha^\lambda) &= \mathbb{E} \left[\alpha \frac{1 - \lambda}{m - R(\lambda) + 1} \frac{V(\lambda)}{\lambda} \right] \\ &\leq \mathbb{E} \left[\alpha \frac{1 - \lambda}{m_0 - V(\lambda) + 1} \frac{V(\lambda)}{\lambda} \right] \\ &= \sum_{k=0}^{m_0} \alpha \frac{1 - \lambda}{m_0 - k + 1} \frac{k}{\lambda} \cdot \mathbb{P}(V(\lambda) = k) \\ &= \alpha \frac{1 - \lambda}{\lambda} \sum_{k=0}^{m_0} \frac{k}{m_0 - k + 1} \binom{m_0}{k} \lambda^k (1 - \lambda)^{m_0 - k} \\ &= \alpha \frac{1 - \lambda}{\lambda} \cdot \frac{\lambda - \lambda^{m_0+1}}{1 - \lambda} = \alpha(1 - \lambda^{m_0}) \\ &\leq \alpha \text{ for all } \lambda \in (0, 1) \text{ and } m_0 \geq 0. \quad \blacksquare\end{aligned}$$

Implicit adaptation

Alternatively to explicit adaptation, it may be asked:

**Is it possible to derive a better rejection curve
circumventing the factor m_0/m appearing in
the FDR of φ^{LSU} ?**

First step:

Identification of least favorable parameter configurations (LFCs) for the FDR.



Dirac-uniform models as LFCs

Theorem: (Benjamini & Yekutieli (2001))

If $p_i \sim U([0, 1])$, $i \in I_{m,0}$, **stochastically independent (I1)** and $(p_i : i \in I_{m,0})$, $(p_i : i \in I_{m,1})$ **stoch. independent vectors (I2)**, then a step-up procedure $\varphi_{(m)}^{\text{SU}}$ with critical values $\alpha_{1:m} \leq \dots \leq \alpha_{m:m}$ has the following properties: If

$\alpha_{i:m}/i$ is **increasing (decreasing)** in i

and the distribution of $(p_i : i \in I_{m,1})$ decreases stochastically, then the FDR of $\varphi_{(m)}^{\text{SU}}$ **increases (decreases)**.

If $\alpha_{i:m}/i$ is **increasing** in i , it follows that the FDR becomes largest for $p_i \sim \delta_0 \forall i \in I_{m,1}$ (Dirac-uniform model).

In DU-models, **analytic calculations** are possible!



Asymptotic Dirac-uniform model: $\text{DU}(\zeta)$

Assumptions:

Independent p -values $p_1, \dots, p_m$;

$m_0 = m_0(m)$ null hypotheses true with

$$\lim_{m \rightarrow \infty} \frac{m_0(m)}{m} = \zeta \in (0, 1],$$

m_0 p -values $\text{UNI}([0, 1])$ -distributed (corresp. hypotheses true)

$m_1 = m - m_0$ p -values δ_0 -distributed (corresp. hypotheses false)

Then the ecdf of the p -values F_m (say) converges (Glivenko-Cantelli) for $m \rightarrow \infty$ to

$$G_\zeta(x) = (1 - \zeta) + \zeta x \text{ for all } x \in [0, 1].$$



Heuristic for an asymptotically optimal rejection curve

Assume we reject all H_i with $p_i \leq x$ for some $x \in (0, 1)$.

Then the FDR (depending on ζ and x) under $\text{DU}(\zeta)$ is asymptotically given by

$$\text{FDR}_{\zeta}(x) = \frac{\zeta x}{(1 - \zeta) + \zeta x}.$$

Aim: Find an optimal threshold x_{ζ} (say), such that

$$\text{FDR} \equiv \alpha \text{ for all } \zeta \in (\alpha, 1).$$

We obtain:

$$\text{FDR}_{\zeta}(x_{\zeta}) = \alpha \iff x_{\zeta} = \frac{\alpha(1 - \zeta)}{\zeta(1 - \alpha)}.$$



Asymptotically optimal rejection curve

Ansatz: Rejection curve f_α and G_ζ shall cross each other
in x_ζ , i.e., $f_\alpha(x_\zeta) = G_\zeta(x_\zeta)$.

Plugging in x_ζ derived above yields

$$f_\alpha\left(\frac{\alpha(1-\zeta)}{\zeta(1-\alpha)}\right) = \frac{1-\zeta}{1-\alpha}.$$

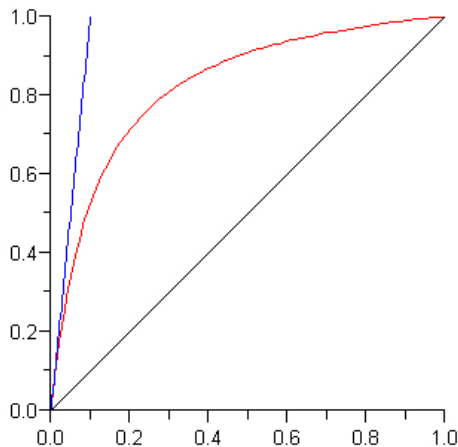
Substituting $t = \frac{\alpha(1-\zeta)}{\zeta(1-\alpha)} \iff \zeta = \frac{\alpha}{(1-\alpha)t + \alpha},$

we get that $f_\alpha(t) := \frac{t}{(1-\alpha)t + \alpha}, t \in [0, 1],$

is the curve solving the problem!



Asymptotically optimal rejection curve for $\alpha = 0.1$



Critical values, step-up-down procedure

The critical values induced by f_α are given by

$$\alpha_{i:m} = f_\alpha^{-1}(i/m) = \frac{i\alpha}{m - i(1 - \alpha)}, \quad i = 1, \dots, m. \quad (1)$$

Due to $\alpha_{m:m} = 1$, a **step-up** procedure based on f_α cannot work.

One possible solution:

Step-up-down procedure with parameter $\lambda \in (0, 1)$:

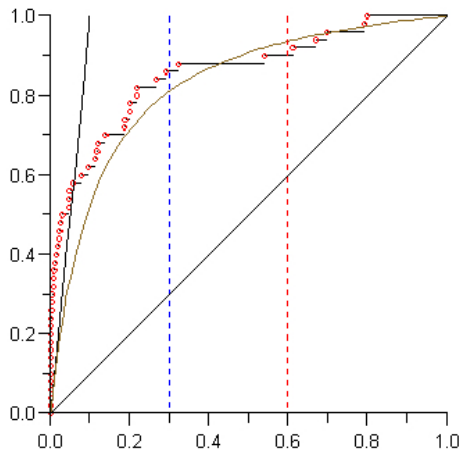
$F_m(\lambda) \geq f_\alpha(\lambda) \Rightarrow t^* = \inf\{p_i > \lambda : F_m(p_i) < f_\alpha(p_i)\}$ (SD-branch),

$F_m(\lambda) < f_\alpha(\lambda) \Rightarrow t^{**} = \sup\{p_i < \lambda : F_m(p_i) \geq f_\alpha(p_i)\}$ (SU-branch).

Reject all H_i with $p_i < t^*$ or $p_i \leq t^{**}$, respectively.



SUD-procedure for $\lambda = 0.3, 0.6$ ($m = 50, \alpha = 0.1$)



Refined results for SUD tests

Finner, Dickhaus, Roters (2009), Annals of Statistics 37, 596-618

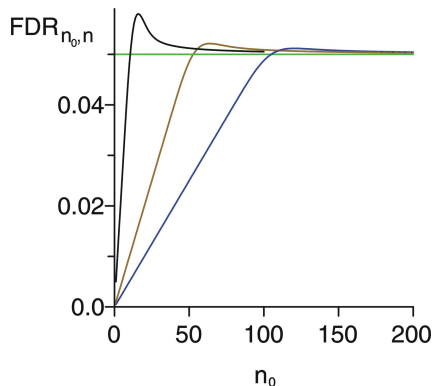
- AORC-based stepwise test procedures asymptotically keep the FDR level under (I1) und (I2).
- In the class of stepwise test procedures with fixed rejection curve asymptotically keeping the FDR level, AORC-based tests have largest power for $\zeta \in (\alpha, 1)$.

Technical results:

- New methodology of proof for stepwise test procedures with non-linear rejection curves resp. critical values
- Upper FDR bounds for step-up-down tests (asymptotically and finite)



SU-test with modified version of f_α , finite case ($m = 100, 500, 1000, \alpha = 0.05$)



For $m = 100$, maximum DU FDR is $FDR_{16,100} \approx 0.05801$.

$\Rightarrow$ **Adjustment** of critical values for finite cases necessary!



FDR control for step-up implies FDR control for step-up-down

Theorem:

Consider a SU test φ^m and a SUD(λ) test φ^λ for $\lambda \in \{1, \dots, m-1\}$ with the same set of critical values $(\alpha_{i:m})_{i=1}^m$ belonging to

$$\mathcal{M}_m = \{(c_{i:m})_{i=1}^m : 0 \leq c_{1:m} \leq \dots \leq c_{m:m} \leq 1, c_{i:m}/i \text{ increases in } i\}.$$

Then, under (I1) and (I2), it holds

$$\text{FDR}_\vartheta(\varphi^\lambda) \leq \text{FDR}_\vartheta(\varphi^m) \text{ for all } \vartheta \in \Theta.$$

Hence, if the FDR is controlled by the SU test, then the SUD(λ) test also controls the FDR.

Sketch of Proof: $\{R_m^{\lambda_1} \geq j, p_{i_0} \leq \alpha_{j:m}\} \subseteq \{R_m^{\lambda_2} \geq j, p_{i_0} \leq \alpha_{j:m}\}$ for any $1 \leq \lambda_1 \leq \lambda_2 \leq m$, which implies that

$P_\vartheta(R_m^\lambda \geq j | p_{i_0} \leq \alpha_{j:m})$ is non-decreasing in λ for each $j \in \mathbb{N}_m$.



Exact finite adjustment (for step-up)

(Slight) modification of f_α or its critical values, e. g.

$$\alpha_{i:m} = \frac{i\alpha}{m + \beta_m - i(1 - \alpha)}, \quad i = 1, \dots, m,$$

for a suitable adjustment constant $\beta_m > 0$.

(Same as: Use $\tilde{f}_\alpha(t) = (1 + \beta_m/m) f_\alpha(t)$, $t \in [0, \alpha/(\alpha + \beta/m)]$.)

$m = 100$ leads to $\beta_{100} \approx 1.76$.

Ray of light:

GAVRILOV, Y., BENJAMINI, Y. AND SARKAR, S. K. (2009).
An adaptive step-down procedure with proven FDR control.
Annals of Statistics **37**, 619-629:

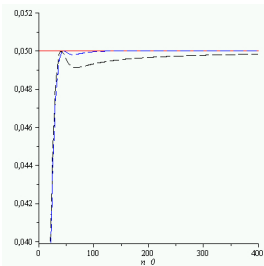
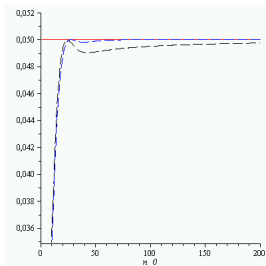
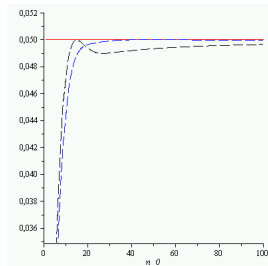
SD-procedure with $\beta_m \equiv 1.0$ controls FDR for every $m \in \mathbb{N}$.



Adjustment with three parameters

For $i = 1, \dots, m$, utilize adjusted critical values of the form

$$\alpha_{i:m} = \frac{i\alpha}{m + \beta_{1,m} + \beta_{2,m} \left(\frac{i}{m}\right)^{\beta_{3,m}} - i(1 - \alpha)}$$



Resulting FDRs for adjusted critical values with one (black) and **three** parameters, respectively, for $m = 100, 200, 400$, depending on m_0 .



Iterative method

Let $J \in \mathbb{N}$ be fixed and $\alpha_{1:m}^{(0)}, \dots, \alpha_{m:m}^{(0)} \in \mathcal{M}_m$ be start critical values, for instance adjusted AORC-based critical values, fulfilling that $\text{FDR}_{m,m_0} \approx \alpha$ for all $m_0 \geq k$.

Now, try to iteratively modify crit. values most influencing FDR_{m,m_0} for $k \leq m_0 \leq m$ to reduce $d(m_0, m) = \alpha - \text{FDR}_{m,m_0}$.

One possible iteration scheme:

For j from 1 to J do:

For i from 1 to $i^*(k)$ do:

1. Determine $\alpha_i^{(j-1)}$ from $\alpha_{i:m}^{(j-1)} = i\alpha_i^{(j-1)} / (m - i(1 - \alpha_i^{(j-1)}))$.
2. Put $\alpha_i^j = \alpha \alpha_i^{(j-1)} / \text{FDR}_{m,m_0(i)}(\alpha_i^{(j-1)})$.

Motivation: **Fixed-point iteration** for

$$f(\alpha_i) = \alpha \alpha_i / \text{FDR}_{m,m_0(i)}(\alpha_i).$$



Stepwise finding

Subsequently solve (for $\alpha_{m_1+1:m}$) the target equations

$$FDR_{m,m_0}(\alpha_{m_1+1:m}, \dots, \alpha_{m:m}) = \alpha, \quad m_0 \in \mathbb{N}_m. \quad (2)$$

$m_0 = 1 \Rightarrow \alpha_{m:m} = m\alpha$ for a fixed α , because $FDR_{m,1} = \alpha_{m:m}/m$.
It follows that $\alpha_{m:m} \geq 1$ for each $m \geq 1/\alpha$, which is unacceptable. We can try to fix that by replacing (2) by

$$FDR_{m,m_0}(\alpha_{m_1+1:m}, \dots, \alpha_{m:m}) = \min\left(\frac{m_0}{m}, \alpha\right), \quad m_0 \in \mathbb{N}_m. \quad (3)$$

If even (3) cannot be solved in $\mathcal{M}_m$, we further generalize the right-hand-side and solve

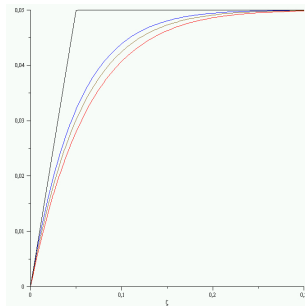
$$FDR_{m,m_0}(\alpha_{m_1+1:m}, \dots, \alpha_{m:m}) = g(\alpha, \zeta_m), \quad m_0 \in \mathbb{N}_m.$$



Flexible FDR-control

Candidates for $g(\alpha, \zeta_m)$:

$$g(\zeta|\gamma, \eta) = \begin{cases} \alpha(1 - (1 - \zeta/\gamma)^\eta), & 0 \leq \zeta < \gamma, \\ \alpha, & \gamma \leq \zeta \leq 1. \end{cases}$$



$g(\zeta|\gamma, \eta)$ for $\alpha = 0.05$ and $\gamma = 1$, $\eta =$ 20.0, 18.0, 16.0 together with $\min(\alpha, \zeta)$ for ζ ranging from 0 to 0.3.

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- Markus Roters

References:

- Benjamini, Y. & Yekutieli, D. (2001). The control of the false discovery rate in multiple testing under dependency. *Ann. Statist.* **29**, 1165-1188.
- Sarkar, S. K. (2002). Some results on false discovery rate in stepwise multiple testing procedures. *Ann. Statist.* **30**, 239-257.
- Storey, J. D., Taylor, J. E. & Siegmund, D. (2004). Strong control, conservative point estimation and simultaneous conservative consistency of false discovery rates: a unified approach. *J. R. Stat. Soc., Ser. B, Stat. Methodol.* **66**, 187-205.
- Schweder, T & Spjøtvoll, E. (1982). Plots of P -values to evaluate many tests simultaneously. *Biometrika* **69**, 493-502.

