Proportion Of True Null Hypotheses In Non High-Dimensional Multiple Testing Problems: Procedures And Comparison

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Introduction

Starting Point

consider simultaneous testing of m null hypotheses $H_1, \dots, H_m$

$\Rightarrow$ possible outcome (Benjamini & Hochberg, 1995):

	Declared non-significant	*Declared significant*	Σ
True null hypotheses	$m_0 - V$	V	m_0
False null hypotheses	$(m - m_0) - (R - V)$	$R - V$	$m - m_0$
Σ	$m - R$	R	m

e. g.: $\mathrm{FDR}^{\mathrm{BH}} := \mathbb{E}(\frac{V}{R} 1_{\{R>0\}}) \leq \pi_0\, \alpha$ with $\pi_0 := \frac{m_0}{m}$

Motivation

Reason for Estimating π_0

- improving type I error rates controlling procedures, which make use of π_0
- estimating FDR, pFDR or Storey's q-value
- microarray experiments, proteomics, fMRI, astrophysics etc.
- π_0 is a quantity of interest of its own right

Object

- investigate and evaluate methods for estimating π_0
- here: in case of non high-dimensional problems, i. e. $m \approx 100 - 500$.

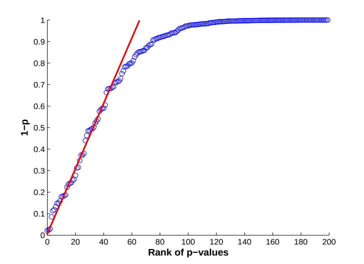
Classification of Estimating Procedures

1. Classical Approach

apply a multiple testing procedure (FWE, FDR, ...) and count the number of non-significant hypotheses $\Rightarrow \hat{\pi}_0$

e.g.: Holm (1979), Benjamini-Hochberg (1995), Benjamini-Krieger-Yekutieli (2006), Farcomeni (2006)

2. Graphical Approach



$\hat{\pi}_0 \hat{=}$ slope of the red line

e.g.: Schweder-Spjøtvoll (1982)
Brown-Russell (1997)
Benjamini-Hochberg (2000)
Turkheimer-Smith-Schmidt (2001)
Hsueh-Chen-Kodell (2003)

3. Density estimation

Mixture model: p-value's density is of the form

$$f(p) = \pi_0 f_0(p) + (1 - \pi_0) f_1(p)\,, \quad p \in [0,1]\,.$$

Assumption: $\pi_0 \leq \inf_{p \in [0,1]} f(p)$

(3a) non-parametric density estimation (incl. kernel estimation, histogram based estimation)

e.g.: Swanepoel (1999), Efron *et al.* (2001, 2002), Cannoun *et al.* (2004), Langaas-Ferkingstad-Lindquist (2005), Lai (2006), Pawitan *et al.* (2006), Tang *et al.* (2006), Pounds-Cheng (2006)

(3b) (semi-)parametric density estimation

e.g.: Allison *et al.* (2002), Pounds-Morris (2003), Ruppert *et al.* (2006)

4. Confidence Estimation (Meinshausen)

For $t \in [0,1]$ let

$$\begin{aligned} V(t) &:= \sharp\{\text{true } P_i \ (i=1,\ldots,m) : P_i \le t\} \\ R(t) &:= \sharp\{P_i \ (i=1,\ldots,m) : P_i \le t\} \end{aligned}$$

Idea: For a given $\alpha \in (0,1)$ find a bounding function $G_{m,\alpha}(t)$ with

$$\mathbb{P}\big(\sup_{t\in[0,1]} \{V(t) - G_{m,\alpha}(t)\} > 0\big) < \alpha\,.$$

Estimator: $$1 - \hat{\pi}_0 = \frac{1}{m} \cdot \sup_{t\in[0,1]} \{R(t) - G_{m,\alpha}(t)\}$$

$$\Rightarrow \mathbb{P}(\hat{\pi}_0 \ge \pi_0) \ge 1-\alpha$$

e. g.: Meinshausen (2006), Meinshausen-Rice (2006), Meinshausen-Bühlmann (2004), Genovese-Wasserman (2004)

5. Threshold Method

Let:

$$W(\lambda) := \sharp\{P_i \ (i = 1, \ldots, m) \, : \, P_i \in (\lambda, 1]\} \quad (\lambda \in [0, 1])\,.$$

$$\Rightarrow \hat{\pi}_0(\lambda) = \frac{W(\lambda)}{m(1-\lambda)} \quad (\lambda \in [0, 1])$$

Idea: as long as each test has a reasonable power, then most of the *p*-values near 1 should be corresponding to true null hypotheses

$$\Rightarrow \mathbb{E}(W(\lambda)) \approx m \, \pi_0 \, (1 - \lambda) \quad (\lambda \in [0, 1])$$

e. g.: Storey (2002), Storey-Tibshirani (2003), Storey-Taylor-Siegmund (2004), Efron *et al.* (2001)

6. Moment based Method

Methods are based on estimation of first and/or second moments of (transformed) p-values.

e. g.: Benjamini-Hochberg (2000), Broberg (2005), Dalmasso-Broët-Moreau (2005), Pounds-Cheng (2006), Lai (2007), Muino-Krajewski (unpublished)

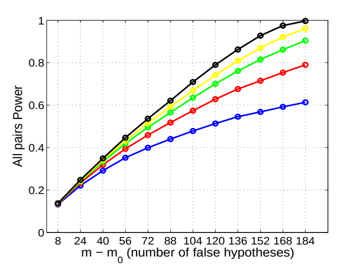
Problem and Criterion

Question: What is a „good“ estimator for π_0 ?

most used comparison criteria:

- mean, standard deviation, (R)MSE, bias, Boxplots
- gain in power of a multiple testing procedure (FWE, FDR, . . .)

Motivation for a new criterion



1. π_0 should be estimated as exactly as possible
2. π_0 should be overestimated

$$\Downarrow$$

$$P_\gamma := \mathbb{P}(\{\pi_0 \leq \hat{\pi}_0 \leq \pi_0 + \gamma(1 - \pi_0)\})$$

for $\gamma \in \{0, 0.05, 0.1, \ldots, 0.95, 1\}$

Results

Simulation

Generate n m-dimensional random vectors

$$X_j \sim \mathcal{N}(\mu, \Sigma) \quad (j = 1, \ldots, n)$$

with mean vector

$$\mu_1 = \ldots = \mu_{m_0} = 0 \quad \text{and} \quad \mu_{m_0+1} = \ldots = \mu_m = \Delta$$

and covariance matrix

$$\Sigma = \begin{pmatrix} 1 & \rho_{12} & \cdots & \rho_{1m} \\ \rho_{21} & 1 & \cdots & \rho_{2m} \\ \vdots & \vdots & \ddots & \vdots \\ \rho_{m1} & \rho_{m2} & \cdots & 1 \end{pmatrix}.$$

Special Correlation Structure

constant correlation

$\rho_{ik} = \rho$ for $i \neq k$ with $\rho = 0, 0.2, 0.5, 0.8$

mixed correlation

$$\Sigma_{R_1 R_2} = \begin{pmatrix} R_1 & R_2 & R_2 \\ R_2 & R_1 & R_2 \\ R_2 & R_2 & R_1 \end{pmatrix} \quad \text{where}$$

$$R_1 = \begin{pmatrix} 1 & 2/3 & \cdots & 2/3 \\ 2/3 & 1 & \cdots & 2/3 \\ \vdots & \vdots & \ddots & \vdots \\ 2/3 & 2/3 & \cdots & 1 \end{pmatrix} \quad \text{and} \quad R_2 = (-1) \cdot \begin{pmatrix} 1/3 & 1/3 & \cdots & 1/3 \\ 1/3 & 1/3 & \cdots & 1/3 \\ \vdots & \vdots & \ddots & \vdots \\ 1/3 & 1/3 & \cdots & 1/3 \end{pmatrix}$$

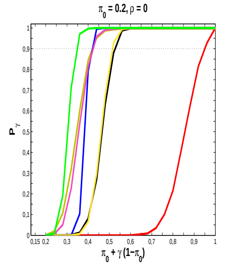
Configuration

- $n = 15$
- $m = 200$
- $\pi_0 = 0.2,\ 0.5,\ 0.8$
- $\Delta = 0.5,\ 1.5$
- number of simulations: 5000
- *p*-values calculated based on one sample t-test

Measurement

$$P_\gamma := \mathbb{P}(\{\pi_0 \leq \hat{\pi}_0 \leq \pi_0 + \gamma(1 - \pi_0)\}) \quad (\gamma \in \{0, 0.05, 0.1, \ldots, 0.95, 1\})$$

$\Delta = 0.5, m = 200$, constant correlation $\rho = 0$



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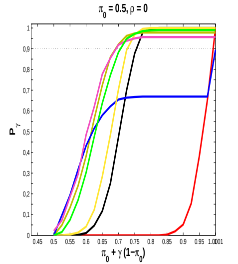

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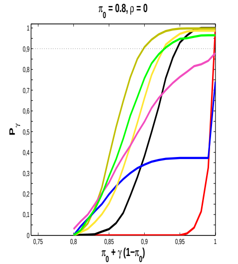

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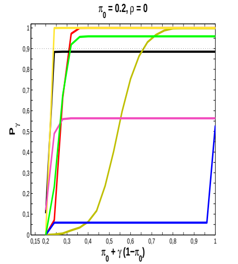

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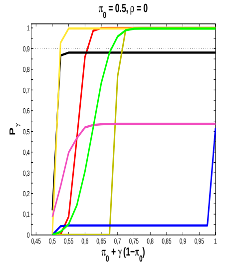

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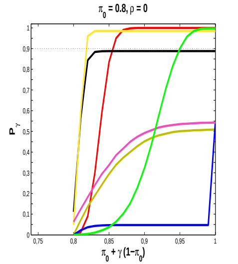

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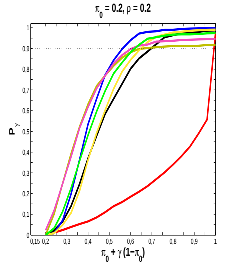

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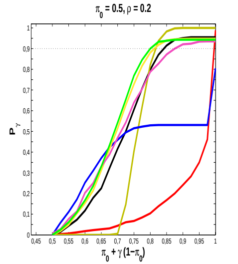

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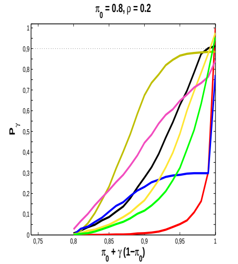

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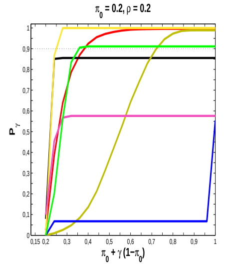

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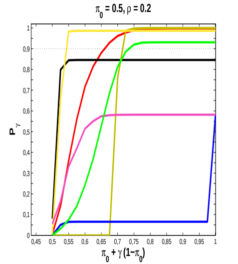

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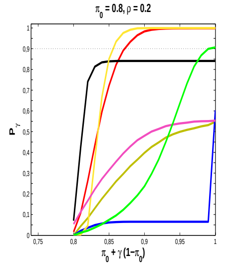

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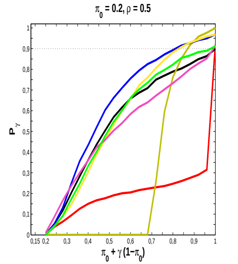

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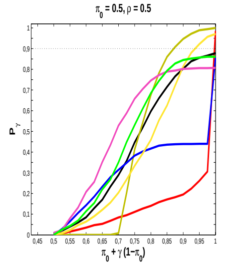

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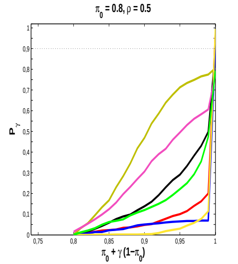

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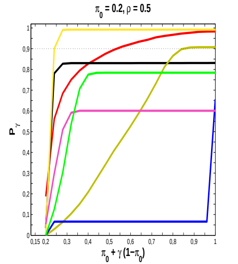

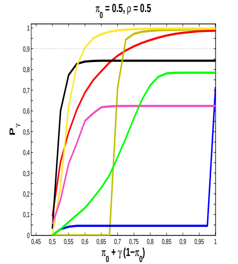

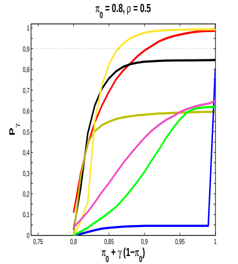

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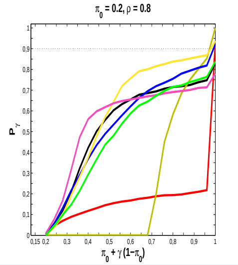

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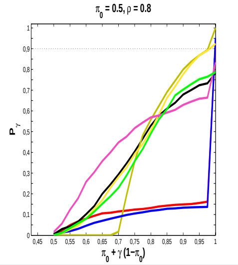

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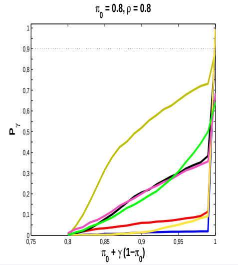

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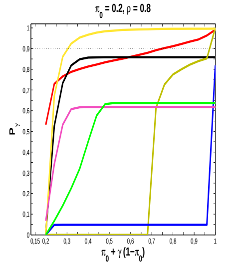

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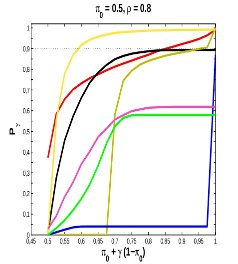

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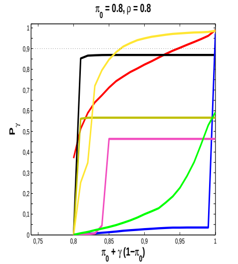
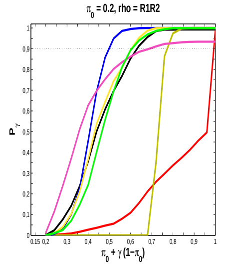
- — Swanepoel (2*s*-spacing) (3a)
- — Pounds-Morris (BUM-MM) (3b)
- — Meinshausen (ind. case) (4)
- — Quantile Method (SAM) (5)
- — Lai (moment based) (6)



$P_\gamma := \mathbb{P}(\{\pi_0 \leq \hat{\pi}_0 \leq \pi_0 + \gamma(1-\pi_0)\})$

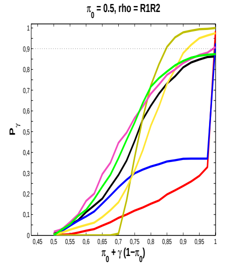
- — simple Holm (1)
- — Benjamini-Hochberg (MD) (2)
- — Langaas *et al.* (convex, decr.) (3a)
- — Pounds-Morris (BUM-MM) (3b)
- — Meinshausen (ind. case) (4)
- — Storey (bootstrapping) (5)
- — Lai (moment based) (6)

$\Delta = 0.5, m = 200$, mixed correlation $\rho = R1R2$



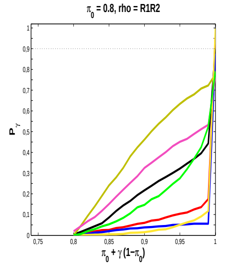
$P_\gamma := \mathbb{P}(\{\pi_0 \leq \hat{\pi}_0 \leq \pi_0 + \gamma(1-\pi_0)\})$

- iterated BH-FDR (1)
- Turkheimer (2)
- Swanepoel (2*s*-spacing) (3a)
- Pounds-Morris (BUM-MLE) (3b)
- Meinshausen (ind. case) (4)
- Storey ($\lambda = 0.5$) (5)
- Broberg (moment generating f.) (6)



$P_\gamma := \mathbb{P}(\{\pi_0 \leq \hat{\pi}_0 \leq \pi_0 + \gamma(1-\pi_0)\})$

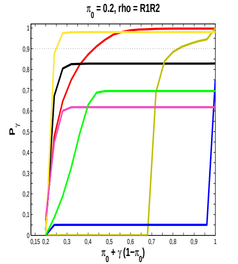
- iterated BH-FDR (1)
- Turkheimer (2)
- Swanepoel (2*s*-spacing) (3a)
- Pounds-Morris (BUM-MM) (3b)
- Meinshausen (dep. case) (4)
- Quantile Method (SAM) (5)
- Broberg (moment generating) (6)



$P_\gamma := \mathbb{P}(\{\pi_0 \leq \hat{\pi}_0 \leq \pi_0 + \gamma(1-\pi_0)\})$

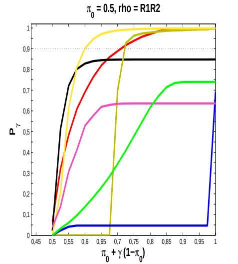
- simple BH-FDR (1)
- Benjamini-Hochberg (LSL) (2)
- Swanepoel (2*s*-spacing) (3a)
- Pounds-Morris (BUM-MM) (3b)
- Meinshausen (ind. case) (4)
- Quantile Method (SAM) (5)
- Muino-Krajewskie (6)

$\Delta = 1.5, m = 200$, mixed correlation $\rho = R1R2$



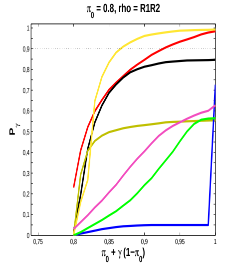
$P_\gamma := \mathbb{P}(\{\pi_0 \le \hat{\pi}_0 \le \pi_0 + \gamma(1-\pi_0)\})$

- — simple Holm (1)
- — Benjamini-Hochberg (LSL) (2)
- — Swanepoel (2s-spacing) (3a)
- — Pounds-Morris (BUM-MM) (3b)
- — Meinshausen (dep. case) (4)
- — Quantile Method (SAM) (5)
- — Muino-Krajewski (6)



$P_\gamma := \mathbb{P}(\{\pi_0 \le \hat{\pi}_0 \le \pi_0 + \gamma(1-\pi_0)\})$

- — simple Holm (1)
- — Benjamini-Hochberg (LSL) (2)
- — Swanepoel (2s-spacing) (3a)
- — Pounds-Morris (BUM-MM) (3b)
- — Meinshausen (ind. case) (4)
- — Quantile Method (SAM) (5)
- — Muino-Krajewski (6)



$P_\gamma := \mathbb{P}(\{\pi_0 \le \hat{\pi}_0 \le \pi_0 + \gamma(1-\pi_0)\})$

- — simple Holm (1)
- — Benjamini-Hochberg (LSL) (2)
- — Pounds-Cheng (LOESS) (3a)
- — Pounds-Morris (BUM-MM) (3b)
- — Meinshausen (ind. case) (4)
- — Quantile Method (SAM) (5)
- — Lai (moment based) (6)

Summary

- for $\Delta = 1.5$ the methods of Meinshausen seem to be the best one in all configurations concerning π_0 and ρ
- but within the category (4) the „best“ methods differ
- for $\Delta = 0.5$ there is no category which dominates all each other
- for $\Delta = 0.5$ most procedures have high probability of overestimating π_0, but they are not closed to π_0
- there is need for improvements of estimating procedures for small Δ
- theoretical investigations of several procedures concerning the introduced measure

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