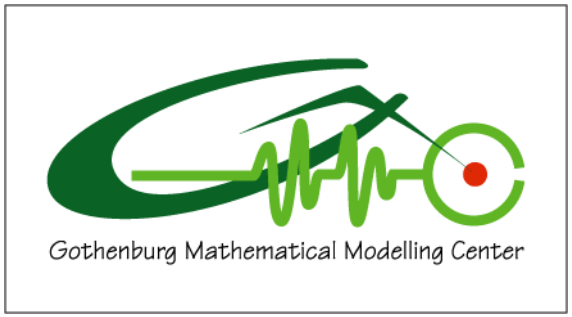
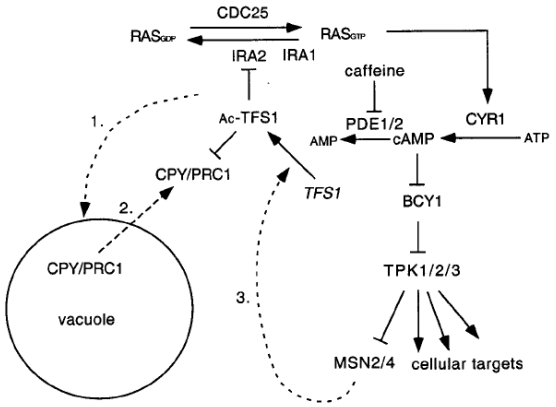
Tail estimation for false positives in high-throughput testing

Holger Rootzén & Dmitrii Zholud
GMMC & Stochastic Centre
Chalmers & Gothenburg University

www.math.chalmers.se/~rootzen/





Yeast
understanding basic life functions

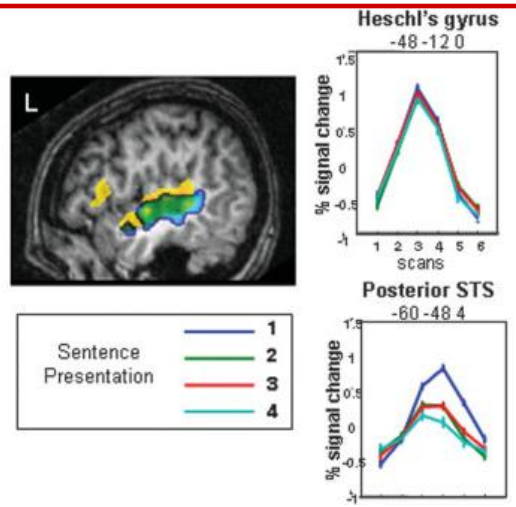
11,904 p-values

Blomberg et al. 2003, 2010

Arabidopsis Thaliana
association mapping

3,745 p-values

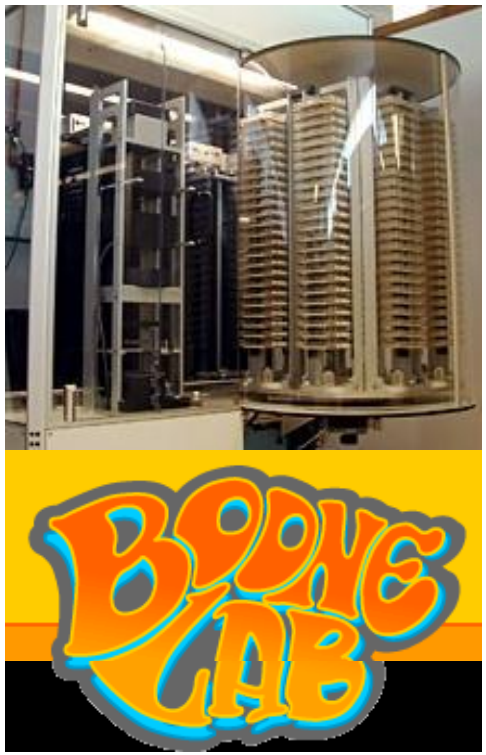
Zhao et al. 2007



fMRI brain scans
function of brain language network

appr. 3 mill. p-values

Taylor et al. 2006



27 millon p-values from study of interaction between pairs of genes in yeast, coming from 27 million experiments in 4 replications

→ very many tests at very low significance levels --- and this is the future!

EVS!

how many of the positive test results are false?

which pre-processing method is best? *)

*) typically true null distribution is different from the theoretical one

answers

- conditional distribution of #{false positives}, given that there are r positives, is approximately binomial

- methods to estimate the success probability parameter (=pFDR) of this binomial distribution

- estimates of the true null distribution of p-values resulting from a pre-processing method, and techniques to compare it with the theoretical uniform distribution

conditional binomial distribution of the number of false positives

m_0 = #{ true null hypotheses} m_1 = #{ false null hypotheses}

F_0 d.f. of p-values if H_0 true, F_1 d.f. of p-values if H_1 true,

#{ false positives} asymptotically Poisson with parameter $m_0 F_0(\alpha)$

#{ true positives} asymptotically Poisson with parameter $m_1 F_1(\alpha)$

(#{ false positives} | #{positives} = *r***)** ≈ Bin(r, pFDR)

$$\mathrm{pFDR} = \frac{m_0 F_0(\alpha)}{m_0 F_0(\alpha) + m_1 F_1(\alpha)} \approx \frac{\pi_0 F_0(\alpha)}{F(\alpha)}$$

power model for distribution of p-values

$$F_0(x) = \Pr(P \le x \mid H_0) = c_0 x^{1/\gamma_0} \qquad 0 \le x \le u$$

$$F_1(x) = \Pr(P \le x \mid H_1) = c_1 x^{1/\gamma_1} \qquad 0 \le x \le u$$

$$F(x) = \Pr(P \le x) = \pi_0 c_0 x^{1/\gamma_0} + \pi_1 c_1 x^{1/\gamma_1} \approx c x^{1/\gamma} \qquad 0 \le x \le u$$

u *threshold*: model assumed to hold for $x \le u << 1$

only p-values less than u are used for estimation

α *critical value*: null hypothesis "rejected" if $p\text{-value} \le \alpha$

- only trust model for $x \le u$, where u is chosen from data
- however u can be often be chosen much bigger than α

→ model-based estimates of $F_0(\alpha)$ and $F(\alpha)$ more accurate than empirical estimates

estimation of F (the TuT-method)

$p_1, \ldots, p_n$ observed p-values, $N = \#\{p_i \le u\}$

$$\Pr(-\log(P/u) > x \mid P \le u) = \frac{c(ue^{-x})^{1/\gamma}}{cu^{1/\gamma}} = e^{-x/\gamma}$$

$$\hat{\gamma} = \frac{1}{N} \sum_{p_i \le u} -\log(p_i/u)$$

$$\Pr(P \le \alpha) = \Pr(P \le u)\Pr(P \le \alpha \mid P \le u)$$

$$\hat{F}(\alpha) = \frac{N}{n}\left(\frac{\alpha}{u}\right)^{1/\hat{\gamma}}$$

this together with “the same” estimator for F_0, and “guesses” of π_0 directly gives estimates of

- FDR
- pFDR
- fdr(*x*)
- FWER
- k-FWER

motivation for power model

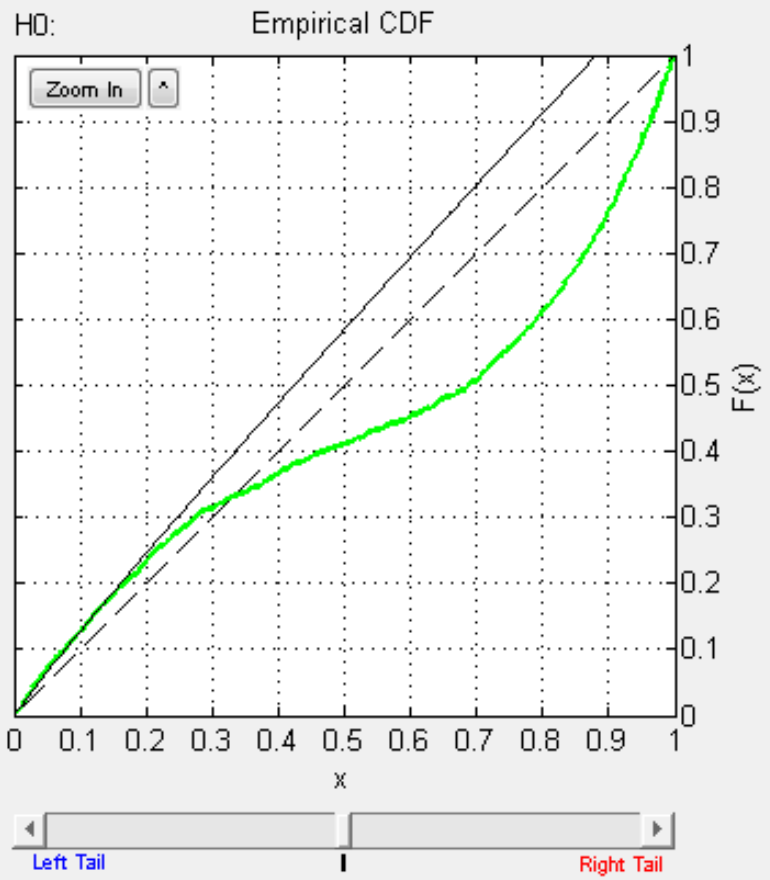
G_0 and G_h true and hypothetical null cdf-s of test statistic, respectively

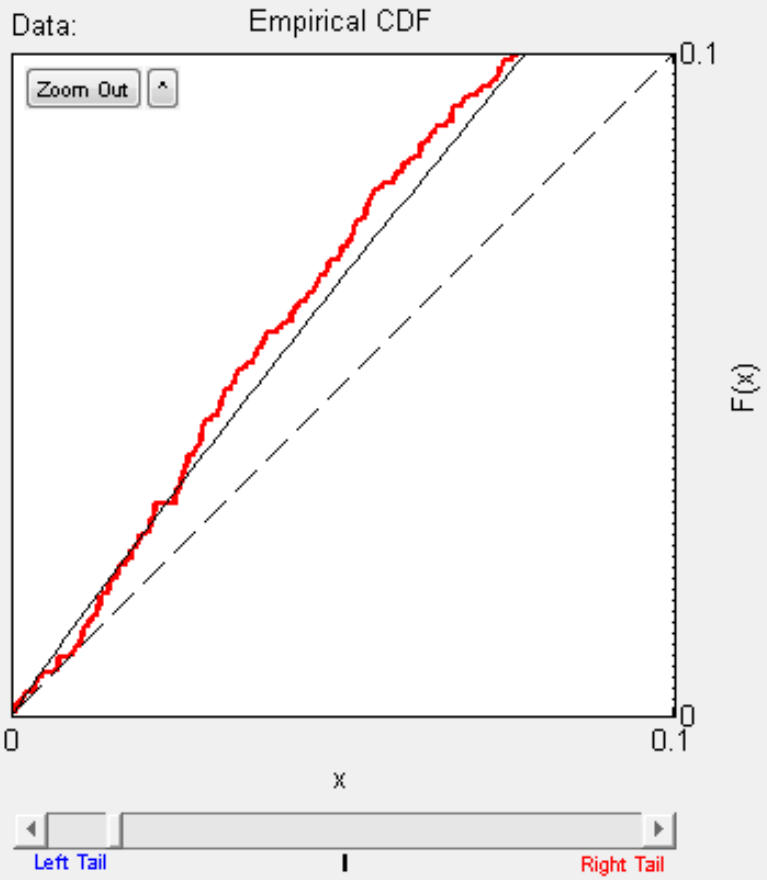
$$\overline{G}_0(\mathrm{x}) = 1 - G_0(\mathrm{x}) \approx \mathrm{C}_0 \frac{1}{\mathrm{x}^{1/\bar{\gamma}_0}} \quad \text{and} \quad \overline{G}_h(x) \approx \mathrm{C}_\mathrm{h} \frac{1}{\mathrm{x}^{1/\bar{\gamma}_\mathrm{h}}}, \qquad \mathrm{x} \downarrow 0$$

$$F_0(x) = G_0(\mathrm{G}_\mathrm{h}^{\leftarrow}(\mathrm{x})) \approx C_0 / ((x/C_h)^{-\bar{\gamma}_h})^{1/\bar{\gamma}_0} =: \mathrm{c}_0 x^{\gamma_0}, \qquad x \downarrow 0$$

- true for t- and F-statistics (paper by Zholud), more general motivation via extreme value theory
- same for F_1

SmartTail





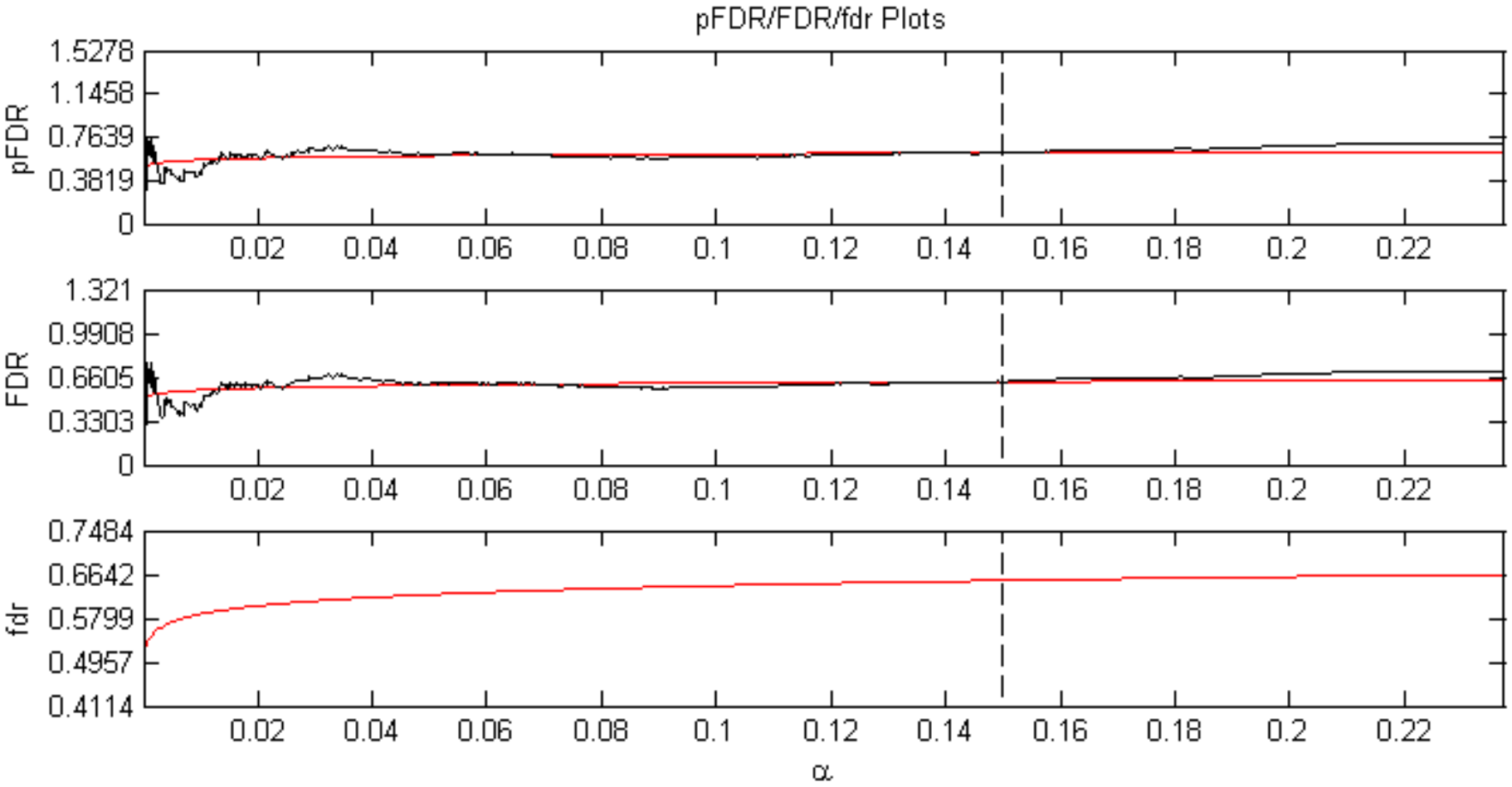
Statistics:

	Model	u	C	a	#{x less/above u}	y	$\hat{F}(y)$	CI
H0:	F(x)=cx^a, x<u.	0.100000	1.1259	0.9466	220 / 1508	0.01	-	-
Data:	F(x)=cx^a, x<u.	0.100000	1.1259	0.9466	220 / 1508	0.01	-	-

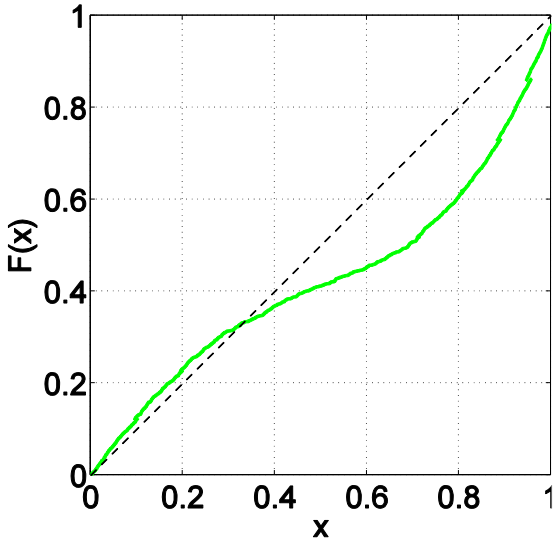
Bioscreen testing for gene expression in yeast: wildtype data

Binomial distribution of #{false positives}, given #{positives}, prob. parameter = pFDR

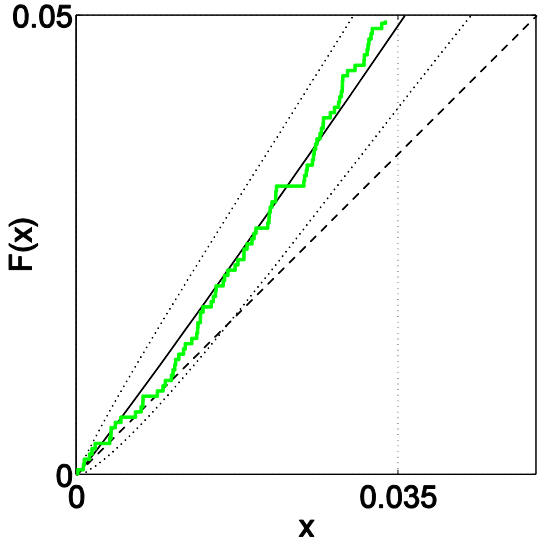
$$\mathrm{pFDR} = \frac{\pi_0 F_0(\alpha)}{F(\alpha)}, \qquad \mathrm{fdr}(x) = \frac{\pi_0 \frac{d}{dx} F_0(x)}{\frac{d}{dx} F(x)}$$



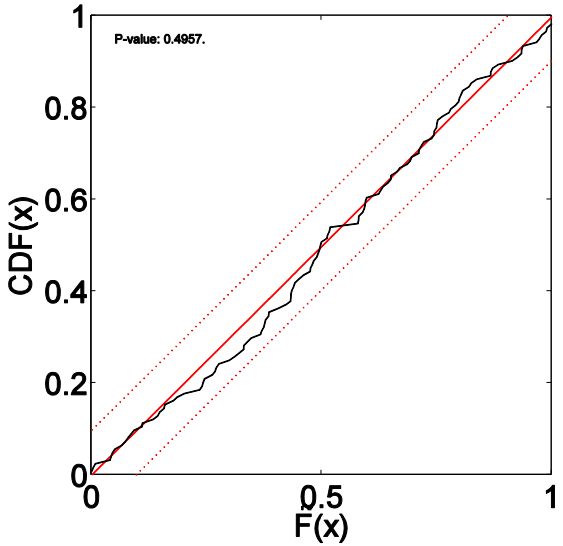
yeast: p-values for wildtype data set



empirical cdf of p-values (1728 p-values)

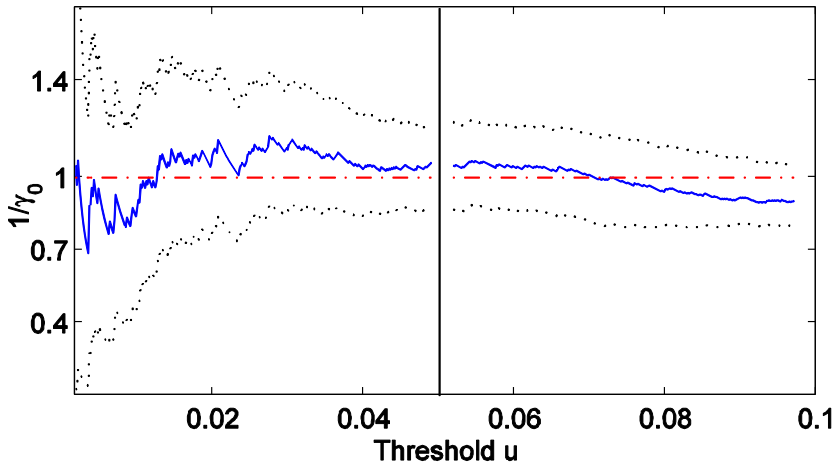


empirical cdf of p-values for p<0.05 with fitted model

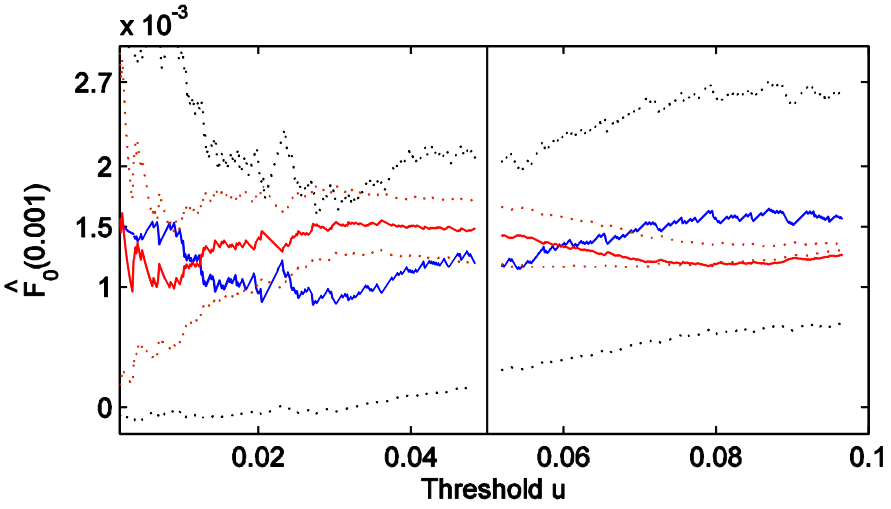


Kolmogorov - Smirnov 95% goodness of fit test (p=0.49)

yeast: choice of threshold u for wildtype data ("compromise between bias and varaince")



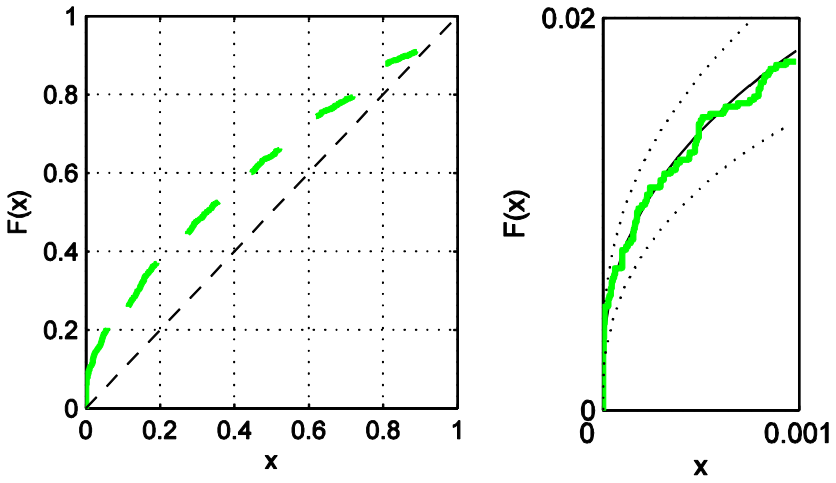
estimate of $1/\gamma_0$ as function of threshold u



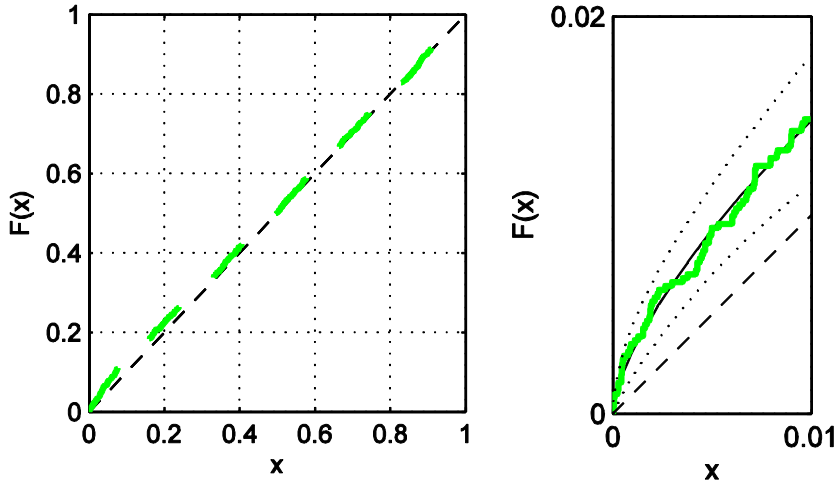
estimate of $F_0(\alpha)$ as function of threshold u, *for* $\alpha = 0.001$

red line: estimate for γ_0 equal to 1

Arabidopsis: comparing preprocessing methods

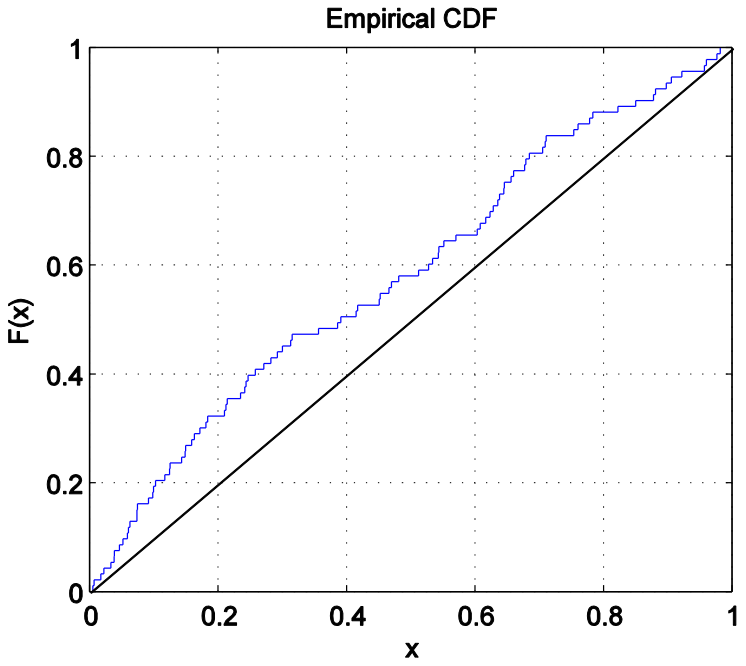


empirical cdf of p-values for Kruskal-Wallis test (3745 p-values)



empirical cdf of p-values for Q+K test which corrects for population structure

fMRI brain scans: accuracy of power model



Empirical cdf of 93 p-values from Kolmogorov-Smirnov goodness of fit tests of polynomial model, for 93 brain scans with each leading to appr. 35,000 p-values. The threshold was $u = 0.01$.

False Positives in high-throughput testing → it is tails (and not centers) of distributions of p-values which matter!

Extreme Value Statistics is *the* instrument for looking at tails.

Clarke, S. and Hall, P. (2009). Robustness of multiple testing procedures against dependence. *Ann. Statist*. **37**, 332–358.

Knijnenburg, T. A., Wessels, L. F. A., Reinders, J. T. M., and Shmulevich, I. (2009). Fewer permutations, more accurate P-values. *Bioinformatics* **25***, 161-168.*

Rootzén, H. and Zholud, D. (2010). Tail estimation methods for the number of false positives in high-throughput testing. *Submitted.*

Storey, J.D. (2002). A direct approach to false discovery rates. *J. R. Statist. Soc. B* **64**, *479-498.*

Taylor, J. E. and Worsley, K. J. (2006). Inference for magnitudes and delays of response in the FIAC data using BRAINSTAT/FMRISTAT. *Human Brain Mapping* **27***, 434-41.*

Zhao K., Aranzana M. J., Kim S, Lister C., Shindo C., et al. (2007). An Arabidopsis example of association mapping in structured samples. *PLoS Genet* **3***, 71-82.*

Zholud, D. (2010). Extremes of Student's one- and two-sample t-test, Welch's test, and F-test for non-normal and not necessarily i.i.d. random variables, *To be submitted.*