On efficient estimators of the proportion of true null hypotheses in a multiple testing setup

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Journées MAS - Août 2014.

Outline

Context: multiple testing procedures

Semiparametric mixture model

Asymptotic efficiency theory [van der Vaart, 1998]

Parametric rate estimators

Simulations

Conclusions

Multiple testing procedures (MTP)

- MT appears in many applications: microarray analysis, signal detection, astrophysics, ...
- Controlling the type I error of each test (e.g. nominal level α) may result in a large number of false positives.
- MTP aim at controlling global quantities, such as
  - Family-wise error rate: FWER=$\mathbb{P}(\text{FP} \geq 1)$ (too stringent)
  - False discovery rate:
    $\text{FDR} = \mathbb{E}\left(\frac{\text{FP}}{\max(\text{R},1)}\right) = \mathbb{E}\left(\frac{\text{FP}}{\text{R}}\middle|\text{R} > 0\right)\mathbb{P}(\text{R} > 0)$
  - Positive FDR: pFDR=$\mathbb{E}\left(\frac{\text{FP}}{\text{R}}|\text{R} > 0\right)$
  - ...

	Accept H^i	Reject H^i	Total
H^i true	TN	FP	n_0
H^i false	FN	TP	n_1
Total	W	R	n

Table : Possible outcomes from testing n hypotheses $H^1, \ldots, H^n$

Error control vs error estimation

Two points of view on MTP

- Either estimate the error (FDR or pFDR or . . .) for some fixed rejection region;
- Or, fix an a priori upper bound on the error and find a rejection region with controlled error.

Equivalent issues

- In fact these two points of view merge, as most of the MTP may be viewed as threshold procedures applied to estimates of FDR, pFDR . . ..
- Thus estimating FDR or pFDR is of major interest in MT.
- These quantities are closely related to the proportion of true null hypotheses and the density under the alternative hypothesis.

Outline

Semi-parametric mixture model

Notation

- Consider n identical hypotheses with test statistics $T_1, \dots, T_n$ and p-values $P_1, \dots, P_n$
- Let $H^i = 0$ if the i-th null hypothesis is true, and 1 otherwise. Assume H^i are i.i.d. variables.
- If $T_i | H^i = 0$ has a continuous distribution, then $P_i | H^i = 0 \sim \mathcal{U}([0,1])$
- Then the P_i are i.i.d. and follow a mixture distribution $g(x) = \theta 1_{[0,1]}(x) + (1-\theta) f(x),\ x \in [0,1]$
- $\theta \in [0,1]$ is the unknown proportion of true null hypotheses
- f is the unknown density of P_i under the alternative $H^i = 1$.

The model is parametrized by (θ, f).

Identifiability

Proposition

The parameter (θ, f) is identifiable on a set $(0,1) \times \mathcal{F}$ if and only if for all $f \in \mathcal{F}$ and for all $c \in (0,1)$, we have $c + (1-c)f \notin \mathcal{F}$.

Examples of sets $\mathcal{F}$

- Purity condition [Genovese & Wasserman, 2004]: $\inf_{x \in [0,1]} f(x) = 0$
- [Langaas *et al.*, 2005]: f is non-increasing with $f(1) = 0$
- [Pounds & Cheng, 2006, Celisse & Robin, 2010]: f vanishes in a neighborhood of 1 or an open interval in $(0,1)$.

In the following, we work on the set

$$\mathcal{F}_\lambda = \{f : [0,1] \mapsto \mathbb{R}^+, \text{ continuously non increasing density, positive on } [0,\lambda) \text{ and such that } f_{|[\lambda,1]} = 0\}.$$

Estimation of the proportion θ

Many proposals in the literature.

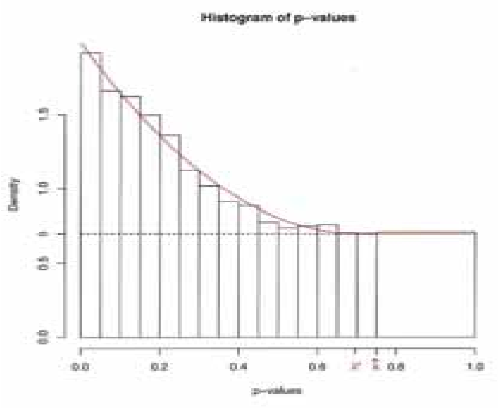
3 main types of estimators

- Histogram based estimators;
- Monotone density estimators;
- Regular density estimators.

Histogram based estimators I

Underlying assumption

f vanishes on some neighborhood of 1. *E.g.* [Schweder & Spjøtvoll, 1982]'s estimator



$$\hat{\theta}_n(\lambda) = \frac{\sharp\{P_i > \lambda, 1 \leq i \leq n\}}{n(1-\lambda)}$$

Choice of λ

- Fixed value: $\lambda = 1/2$ most popular choice;
- Adaptive choices. Many references, among which:
  - [Benjamini & Hochberg 2000]: detection of a change of slope;
  - [Storey 2002]: bootstrap procedure;
  - [Celisse & Robin, 2010]: cross-validation (LpO) procedure;

Histogram based estimators II

Convergence properties

- Very few convergence results have been established;
- [Celisse & Robin, 2010]'s estimator is proved to convergent in probability;
- Properties of [Schweder & Spjøtvoll, 1982]'s oracle version: if $f_{|[\lambda^\star,1]} = 0$ and $\lambda = \lambda^\star$ then $\sqrt{n}(\hat{\theta}_n(\lambda^\star) - \theta) \rightarrow^d_{n\rightarrow\infty} \mathcal{N}(0, \theta(\frac{1}{1-\lambda^\star} - \theta))$.

Monotone density and regular densities estimators

Other estimators

- Grenander's estimate is proposed by [Langaas *et al.*, 2005]; Converges at nonparametric rate $(\log n)^{1/3} n^{-1/3}$;
- Regular density estimators: [Neuvial, 2013] proposed a kernel based estimator; Converges at nonparametric rate $n^{-k/(2k+1)}\eta_n$, where $\eta_n \to \infty$ and k controls regularity of f near $x = 1$.

Issues

- When is it possible to construct an estimator converging at parametric rate?
- What is the optimal asymptotic variance of a parametric estimator and are there efficient estimators?

Results

Let us recall that we work on

$$f \in \mathcal{F}_\lambda = \{f : [0,1] \mapsto \mathbb{R}^+, \text{ continuously non increasing density,} \\ \text{positive on } [0,\lambda) \text{ and such that } f_{|[\lambda,1]} = 0\}.$$

2 different cases occur

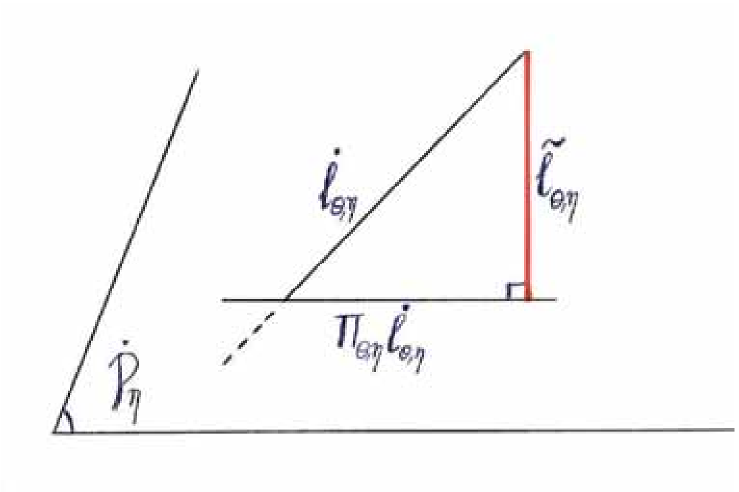
- When $\lambda = 1$: any estimator of θ cannot converge at parametric rate.
- When $\lambda < 1$: we can construct estimators converging at parametric rate but they are not asymptotically efficient (except for irregular models).

Outline

Asymptotic efficiency theory in semi-parametric models I

Let $\mathcal{P} = \{\mathbb{P}_{\theta,\eta} : \theta \in \Theta, \eta \in \mathcal{F}\}$, with $\Theta \subset \mathbb{R}$ an open set and $\mathcal{F}$ an infinite dimensional set.
We aim at estimating $\psi(\theta)$.

- The ordinary score function: $\dot{l}_{\theta,\eta} = \frac{\partial}{\partial\theta} \log d\mathbb{P}_{\theta,\eta}$.
- A tangent set for η:
  $$\dot{\mathcal{P}}_\eta = \left\{ \frac{\partial}{\partial t}\Big|_{t=0} \log d\mathbb{P}_{\theta,\eta_t} : \text{ for suitable paths } t \mapsto \eta_t \text{ in } \mathcal{F} \right\}$$
- The efficient score function: $\tilde{l}_{\theta,\eta} = \dot{l}_{\theta,\eta} - \Pi_{\theta,\eta}\dot{l}_{\theta,\eta}$, where $\Pi_{\theta,\eta}$ is the orthogonal projection onto $\overline{\text{lin}}\dot{\mathcal{P}}_\eta$ in $\mathbb{L}_2(\mathbb{P}_{\theta,\eta})$.
- The efficient information: $\tilde{I}_{\theta,\eta} = \mathbb{E}_{\theta,\eta}\tilde{l}^2_{\theta,\eta}$



Asymptotic efficiency theory in semi-parametric models II

Definition. An estimator $\hat{\theta}_n$ is asymptotically efficient if and only if it satisfies

$$\sqrt{n}(\hat{\theta}_n - \theta) = \frac{1}{\sqrt{n}} \sum_{i=1}^n \tilde{I}_{\theta,\eta}^{-1} \tilde{l}_{\theta,\eta}(X_i) + o_{\mathbb{P}_{\theta,\eta}}(1).$$

As a consequence,

- By the central limit theorem and Slutsky's theorem,

$$\sqrt{n}(\hat{\theta}_n - \theta) \overset{\mathbb{P}_{\theta,\eta}}{\rightsquigarrow} N(0, \tilde{I}_{\theta,\eta}^{-1}).$$

- By the LAM theorem: the optimal variance is $\tilde{I}_{\theta,\eta}^{-1}$.

Efficient score and information in our case

$$\mathcal{P}_{\lambda^*} = \left\{\mathbb{P}_{\theta,f}; \frac{d\mathbb{P}_{\theta,f}}{d\mu} = \theta + (1-\theta)f; (\theta,f) \in (0,1) \times \mathcal{F}_{\lambda^*}\right\}.$$

Proposition. The efficient score function $\tilde{l}_{\theta,f}$ and the efficient information $\tilde{I}_{\theta,f}$ for estimating θ in model $\mathcal{P}_{\lambda^*}$ are given by

$$\tilde{l}_{\theta,f}(x) = \frac{1}{\theta} - \frac{1}{\theta[1-\theta(1-\lambda^*)]}\mathbf{1}_{[0,\lambda^*)}(x) \text{ and } \tilde{I}_{\theta,f} = \frac{1-\lambda^*}{\theta[1-\theta(1-\lambda^*)]}.$$

Corollary.

- When $\lambda^* = 1$, we have $\tilde{I}_{\theta,f} = 0$, then there is no estimator of θ converging at parametric rate.
- When $\lambda^* < 1$, an estimator $\hat{\theta}_n$ of θ is asympt. eff. if and only if it satisfies

$$\hat{\theta}_n = \frac{\#\{X_i > \lambda^* : 1 \leq i \leq n\}}{n(1-\lambda^*)} + o_{\mathbb{P}_{\theta,f}}(n^{-1/2}),$$

with the optimal variance equal to $\theta\left(\frac{1}{1-\lambda^*} - \theta\right)$.

Case $\lambda^* < 1$

Let us further investigate what may be obtained in this case:

- Can we exhibit $\sqrt{n}$-consistent estimators?
- If yes, do they asymptotically achieve the optimal variance?

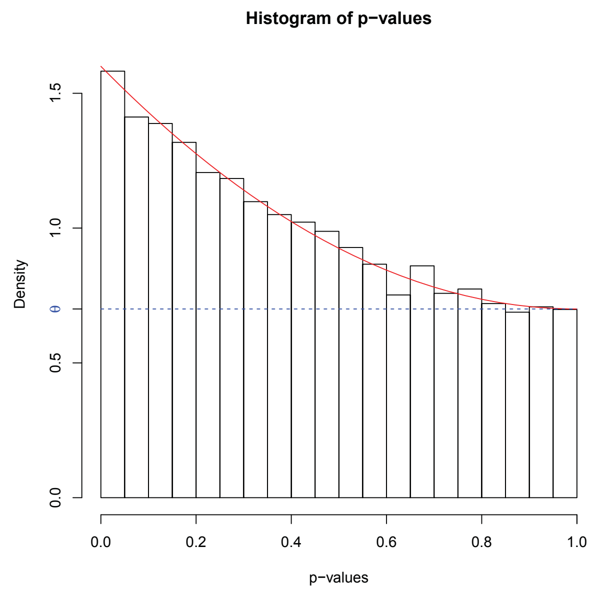
Outline

Case $\lambda^* < 1$: estimators with parametric rate I

A histogram based estimator

$\hat{f}_I$: a histogram estimator of f.
Define an estimator of θ as

$$\hat{\theta}_{I,n} = \min_{x \in [0,1]} \hat{f}_I(x)$$



Theorem

Suppose that $f \in \mathcal{F}_\lambda^*$ with $\lambda^* < 1$ and I is fine enough, then the estimator $\hat{\theta}_{I,n}$ has the following properties

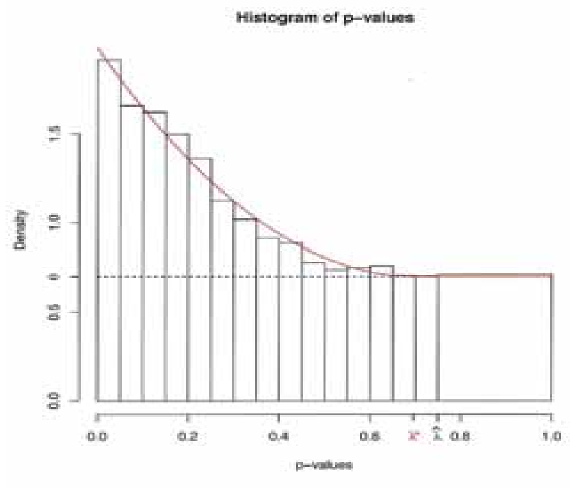
i) $\hat{\theta}_{I,n}$ *converges almost surely to* θ,

ii) $\limsup_{n \to \infty} n\mathbb{E}\left[(\hat{\theta}_{I,n} - \theta)^2\right] < +\infty$.

Case $\lambda^* < 1$: estimators with parametric rate II

Celisse & Robin [2010]'s procedure

$\hat{\theta}_n^{CR}$: estimator proposed by [Celisse & Robin, 2010]
$\hat{\lambda}$: chosen adaptively based on cross-validation method.



Theorem

Under some assumptions, the estimator $\hat{\theta}_n^{CR}$ has the following properties

i) $\hat{\theta}_n^{CR}$ *converges almost surely to* θ,

ii) $\hat{\theta}_n^{CR}$ *is* $\sqrt{n}$*-consistent, i.e.* $\sqrt{n}(\hat{\theta}_n^{CR} - \theta) = O_{\mathbb{P}}(1)$,

iii) *If the parameter* p *in leave-p-out estimator is fixed then* $\limsup_{n\to\infty} n\mathbb{E}\left[(\hat{\theta}_n^{CR} - \theta)^2\right] < +\infty$.

Case $\lambda^* < 1$: estimators with parametric rate III

Additional remarks

- We did not succeed in computing the asymptotic variance of these estimators;
- In the simulations, we further study this point.

"One-step" estimator

- The one-step procedure is a general method for constructing an asymptotically efficient estimator starting from a $\sqrt{n}$-convergent one.

One step procedure

Construction

Let $\hat{\theta}_n$ a $\sqrt{n}$-consistent estimator of θ and $\hat{l}_{n,\theta}(\cdot) = \hat{l}_{n,\theta}(\cdot; X_1, \dots, X_n)$ an estimator of $\tilde{l}_{\theta,f}$. Denoting $m = \lfloor n/2 \rfloor$, we let

$$\hat{l}_{n,\theta,i}(\cdot) = \begin{cases} \hat{l}_{m,\theta}(\cdot; X_1, \dots, X_m) & \text{if} \quad i > m, \\ \hat{l}_{n-m,\theta}(\cdot; X_{m+1}, \dots, X_n) & \text{if} \quad i \leq m. \end{cases}$$

Then, a one-step estimator is constructed as

$$\tilde{\theta}_n = \hat{\theta}_n - \Big(\sum_{i=1}^{n} \hat{l}^2_{n,\hat{\theta}_n,i}(X_i) \Big)^{-1} \sum_{i=1}^{n} \hat{l}_{n,\hat{\theta}_n,i}(X_i).$$

Existence of asympt. eff. estimators

For an estimator $\hat{l}_{n,\theta}(\cdot) = \hat{l}_{n,\theta}(\cdot; X_1, \ldots, X_n)$ of $\tilde{l}_{\theta,f}$ and every sequence $\theta_n = \theta + O(n^{-1/2})$, introduce the following conditions

$$\sqrt{n}\mathbb{P}_{\theta_n,f}\hat{l}_{n,\theta_n} \xrightarrow[n\to\infty]{\mathbb{P}_{\theta,f}} 0, \qquad (1)$$

$$\mathbb{P}_{\theta_n,f}\|\hat{l}_{n,\theta_n} - \tilde{l}_{\theta_n,f}\|^2 \xrightarrow[n\to\infty]{\mathbb{P}_{\theta,f}} 0 \qquad (2)$$

Proposition (▸ Recall)

- *The existence of asympt. eff. estimator of $\theta \iff$ the existence of estimator $\hat{l}_{n,\theta}$ of $\tilde{l}_{\theta,f}$ satisfying (1) and (2).*
- *If $\tilde{l}_{\theta,f}$ is estimated through a plug-in estimate $\hat{\lambda}_n$ of λ^*, then this condition is equivalent to $\sqrt{n}(\hat{\lambda}_n - \lambda^*) = o_{\mathbb{P}}(1)$.*

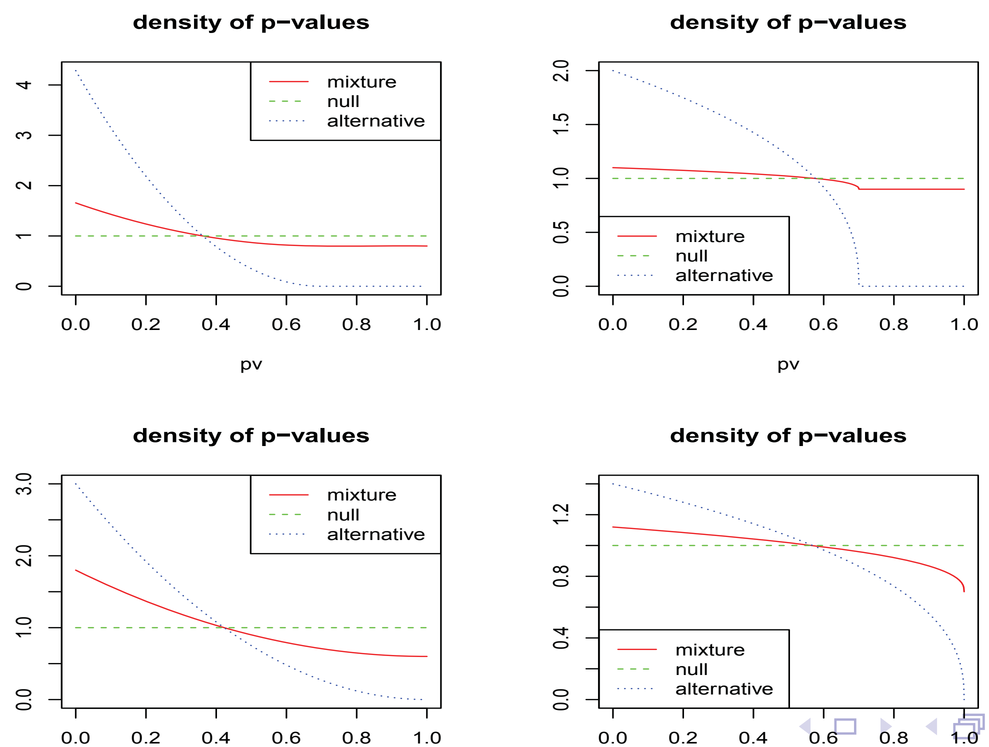
Existence

- Irregular models: f has a jump point at λ^*, YES
- Regular models: conjecture that NO

Outline

Simulations setup

- Consider the alternative density
$$f_1(x) = \frac{s}{\lambda^*}\left(1 - \frac{x}{\lambda^*}\right)^{s-1} \mathbf{1}_{[0,\lambda^*]}(x)$$
- Different parameter values: $s \in \{1.4; 3\}, \lambda^* \in \{0.7; 1\}, \theta \in \{0.6; 0.7; 0.8; 0.9\}$
- Sample size $n \in \{5000; 7000; 9000; 10000; 12000; 14000; 15000\}$ and $S = 100$ repetitions.



Simulations

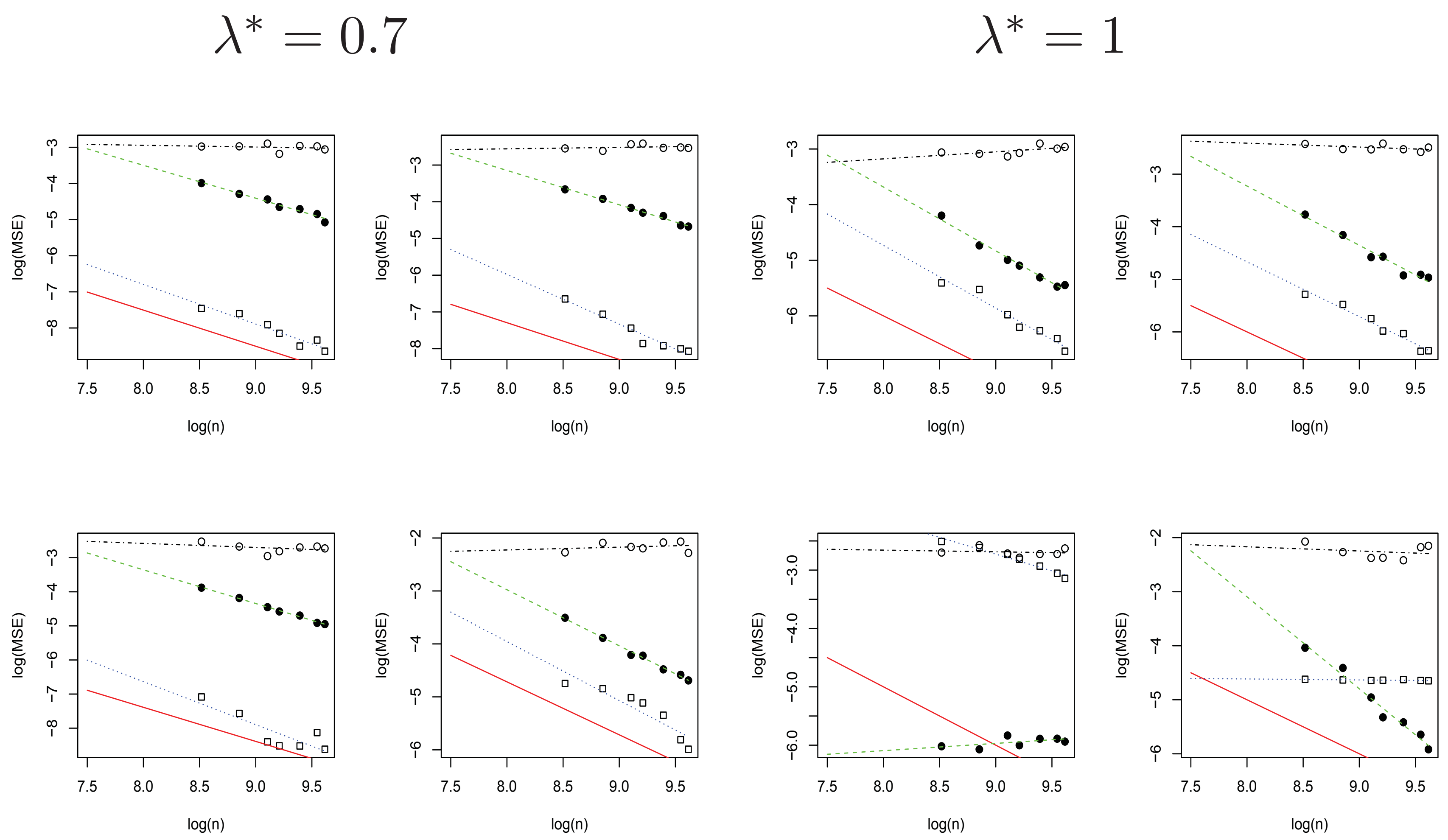


Figure : Logarithm of MSE as a function of $\log(n)$ and linear regression for $\hat{\theta}_n^L$ (black line), $\hat{\theta}_n^{CR}$ (blue line) and $\hat{\theta}_{I,n}$ (green line). Red line: $y = -\log(n) + \log[\theta((1-\lambda^*)^{-1} - \theta)]$ (oracle version).

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Consider a mixture $g(x) = \theta \mathbf{1}_{[0,1]}(x) + (1-\theta) f(x)$, where the density f is non-increasing and its support stops at λ^*.

- $\lambda^* = 1$: there is no estimator of θ converging at parametric rate
- $\lambda^* < 1$:
  - Two estimators of θ converging at parametric rate
  - Irregular model: it is possible to construct an asymptotically efficient estimator of θ.
  - Regular models: we conjecture that asymptotically efficient estimators of θ do not exist.

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