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New adaptive step-up procedures that control the FDR under independence and dependence

Gilles Blanchard
Fraunhofer FIRST.IDA, Berlin, Germany,
blanchar@first.fraunhofer.de

Étienne Roquain
INRA Jouy-en-Josas, unité MIG,
78 352 Jouy-en-Josas Cedex, France,
etienne.roquain@jouy.inra.fr

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Abstract

The proportion π_0 of true null hypotheses is a quantity that often appears explicitly in the FDR control bounds. In order to obtain more powerful procedures, recent research effort has focussed on finding ways to estimate this quantity and incorporate it in a meaningful way in multiple testing procedures, leading to so-called "adaptive" procedures. We present here new adaptive multiple testing procedures with control of the false discovery rate (FDR), respectively in the independent, positive dependent and distribution-free context. In the independent context, we present a procedure that is less conservative than a recent adaptive procedure proposed by [BKY06]. In the positive dependence and distribution-free contexts, owing to Markov's inequality, we propose adaptive versions of the existing procedures of [BY01] and [BF07], which present an improvement of the power when a "large" number of hypotheses are expected to be rejected.

1 Introduction

Multiple testing is a topic coming from statistics that has generated growing attention in the recent years due to an increasing number of application fields

with a strong demand for powerful, large scale multiple testing procedures, in particular in bioinformatics. For example with microarray data, the goal is to detect which genes (among several ten of thousands) exhibit a significantly different level of expression in two different experimental conditions. Each gene represents a “hypothesis” to be tested in the statistical sense. The genes’ expression levels fluctuate naturally (not to speak of other sources of fluctuation introduced by the experimental protocol), and because they are so many to choose from it is important to control precisely what can be deemed a significant observed difference. Generally it is assumed that the natural fluctuation distribution of a *single* gene is known and the problem is to take into account the number of genes involved (for more details, see for instance [DSB03]).

In this work, we focus on building procedures that control the False Discovery Rate (FDR), which is defined as the expected proportion of rejected true hypotheses among all the rejected hypotheses. This global type I error has been introduced by [BH95] where they also propose a powerful procedure, called *the linear step-up* (LSU) procedure, that control the FDR under independence between the p -values. Later, [BY01] have proved that the LSU procedure still control the FDR under positive dependence. Under general dependence, the same authors show that the FDR control is still provided if the global threshold of the LSU procedure is divided by a factor $1 + 1/2 + \dots + 1/m$, where m is the total number of hypotheses to test. More recently, [BF07] have generalized the latter result, by showing that there exists a family of step-up procedures (depending on the choice of a prior distribution) that still control the FDR under general dependence between the p -values.

All these procedures, attempting to control the FDR at a level α , do finally have a FDR smaller than $\pi_0\alpha$, where π_0 is the proportion of true null hypotheses. Therefore, when most of the hypotheses are false, these procedure are inevitably conservative. The challenge of *adaptive control* of FDR (see [BH00] and [Bla04]) is then to integrate in the threshold of the previous procedures an estimation of the unknown proportion π_0 and to prove that the FDR is still rigorously controlled by α .

Recently, under independence, [BKY06] have shown that the Storey estimator (proposed in [Sto02]) can be used to build an adaptive procedure that control the FDR. They also give a new adaptive procedure (denoted here by “BKY06”) that control the FDR under independence and that seems robust to positive correlations. This adaptive procedure is said “two-stage” because it consists of two different steps: 1. Estimate π_0 . 2. Use this estimate in a new threshold to build a new multiple testing procedure.

In this paper, our main contributions are

1. To build a simple procedure with an explicit threshold more powerful than the LSU procedure that control the FDR under independence (this procedure is said "one-stage adaptive").
2. To build a new two-stage adaptive procedure more powerful than the BKY06 procedure that control the FDR under independence and that seems robust to positive correlations on simulations.
3. To propose a new two-stage adaptive version of the LSU procedure that control the FDR under positive dependence, resulting in an improvement of the power in a certain regime.
4. To propose new two-stage adaptive versions of all the procedures of [BF07] that control the FDR under general dependence, resulting in an improvement of the power in a certain regime.

In particular, we present in the two last points what we think are the first examples of adaptive multiple testing procedures that control the FDR when the p -values have dependencies. Although their interest is mainly theoretical, it shows in principle that adaptivity can improve performance in a theoretically rigorous way even under dependence.

The paper is organized as follows: in Section 2, we introduced the necessary mathematical notions, and we recall the existing non-adaptive results in FDR control. Section 3 states the existing and new adaptive results in the independence context, and compares them in a simulations study. The positive dependent and general dependent case are examined in Section 4. Section 5 contains the proofs of the new results and Section 6 presents technical lemmas.

2 Preliminaries

2.1 Multiple testing framework

In this paper we stick to the traditional statistical framework for multiple testing. Let $(\mathcal{X}, \mathfrak{X}, \mathbb{P})$ be a probability space and we want to infer a decision on \mathbb{P} from an observation x on \mathcal{X} . Let \mathcal{H} be a finite set of null hypotheses for \mathbb{P} , that is, each null hypothesis $h \in \mathcal{H}$ corresponds to some subset of distributions on $(\mathcal{X}, \mathfrak{X})$ and " \mathbb{P} satisfies h " means that \mathbb{P} belongs to this

subset of distributions. The number of null hypotheses $|\mathcal{H}|$ is denoted by m . The underlying probability \mathbb{P} being fixed, we note $\mathcal{H}_0 = \{h \in \mathcal{H} | \mathbb{P} \text{ satisfies } h\}$ the set of the true null hypotheses and $m_0 = |\mathcal{H}_0|$ the number of true null hypotheses. We let also $\pi_0 := m_0/m$ the proportion of true null hypotheses. Since \mathbb{P} is unknown, we remark that \mathcal{H}_0 and then m_0 and π_0 are unknown.

We suppose that there exists a set of *p-values* $\mathbf{p} = (p_h, h \in \mathcal{H})$, meaning that each $p_h : (\mathcal{X}, \mathfrak{X}) \mapsto [0, 1]$ is a measurable function and that for each $h \in \mathcal{H}_0$, p_h is bounded stochastically by a uniform distribution, that is,

$$\forall t \in [0, 1], \mathbb{P}(p_h \leq t) \leq t. \quad (1)$$

2.2 Multiple testing procedure and errors

A *multiple testing procedure* is a measurable function

$$R : [0, 1]^{\mathcal{H}} \mapsto \mathcal{P}(\mathcal{H}),$$

which takes as input a realisation of the *p-values* and returns a subset of \mathcal{H} , corresponding to the rejected hypotheses. From an observation $x \in \mathcal{X}$, the function $R(\mathbf{p})$ rejects then the null hypotheses which belongs to $R(\mathbf{p}(x))$. To clarify the notations in what follows, we will often write R instead of $R(\mathbf{p})$.

A multiple testing procedure R can make two kinds of errors: we said that a *type I error* occurs for h when h is true and is rejected by R , that is $h \in \mathcal{H}_0 \cap R$. The primary concern is to control the number of type I errors of a testing procedure. Conversely, a *type II error* occurs for h when h is false and is not rejected by R , that is $h \in \mathcal{H}_1 \cap R^c$.

The most traditional way to control type I error is to bound the “Family-wise error rate” which is the probability that one or more null hypotheses is wrongly rejected. However procedures with a controlled FWER are very “cautious” not to make a single error, and thus reject only few hypotheses. More recently, a more liberal measure of type I errors has been introduced in multiple testing (see [BH95]): the *false discovery rate*, which is the averaged proportion of true null hypotheses in the set of all the rejected hypotheses:

Definition 2.1 (False discovery rate). The *false discovery rate* of a multiple testing procedure R is given by

$$\text{FDR}(R) := \mathbb{E} \left(\frac{|R \cap \mathcal{H}_0|}{|R|} \mathbf{1}_{\{|R| > 0\}} \right),$$

where $|\cdot|$ is the cardinality function.

Remark 2.2. Throughout this paper we will use the following convention: whenever there is an indicator function inside an expectation, this has logical priority over any other factor appearing in the expectation. What we mean is that if other factors include expressions that may not be defined (such as the ratio $\frac{0}{0}$) outside of the set defined by the indicator, this is safely ignored. This results in more compact notations, such as in the above definition.

The goal is then to build procedures R with a FDR smaller than a given level α . Of course if we choose $R = \emptyset$, meaning that R rejects no hypotheses, $\text{FDR}(R) = 0 \leq \alpha$ trivially. Therefore, we want procedures R with $\text{FDR}(R) \leq \alpha$ and which have as small type II error as possible. Given two procedures R and R' that satisfy $\text{FDR}(R) \leq \alpha$ and $\text{FDR}(R') \leq \alpha$, we say that R is said *less conservative* than R' if $R' \cap \mathcal{H}_1 \subset R \cap \mathcal{H}_1$ pointwise (where $\mathcal{H}_1 = \mathcal{H} \setminus \mathcal{H}_0$). Hence, provided that $\text{FDR}(R), \text{FDR}(R') \leq \alpha$, R is less conservative than R' if $R \subset R'$, meaning that, provided that $\text{FDR}(R) \leq \alpha$, we want to build procedures that reject as many hypotheses as possible.

2.3 The step-up procedures in FDR control

Let us order the p -values $p_{(1)} \leq \dots \leq p_{(m)}$ and put $p_{(0)} = 0$.

Definition 2.3 (Step-up procedure). Given a level $\alpha \in (0, 1)$ and a non-decreasing function $\beta : \mathbb{R}_+ \rightarrow \mathbb{R}_+$. The *step-up procedure* at level α and of threshold function β , denoted by $R_{\alpha, \beta}$, is defined as

$$R_{\alpha, \beta} := \{h \in \mathcal{H} | p_h \leq p_{(k)}\}, \quad \text{where } k = \max\{i | p_{(i)} \leq \alpha\beta(i)/m\}.$$

The function $\alpha\beta(\cdot)/m$ is called the *global threshold* of the procedure. In the particular case where β is the identity function I on \mathbb{R}_+ , the procedure $R_{\alpha, I}$ is called the *linear step-up procedure* at level α . When this is not ambiguous, we suppose α fixed by advance, and we note R_β instead of $R_{\alpha, \beta}$.

Remark 2.4. In our setting, the "linear step-up procedure" should rather being called the "identity step-up procedure". However, for historical reason, we choose here to keep the usual name.

When the p -values are independent, the following theorem holds (the first part has been proved in [BH95] whereas the second part was proved in [FR01]):

Theorem 2.5. *Suppose that the p -values $(p_h)_{h \in \mathcal{H}}$ are independent. Then the linear step-up procedure R_I has a FDR smaller than $\pi_0\alpha$. Moreover, if the p -values associated to the true null hypotheses are exactly distributed like a uniform distribution, that is, if (1) is an equality for all $h \in \mathcal{H}_0$, we have the equality $\text{FDR}(R_I) = \pi_0\alpha$.*

The authors [BY01] extend the previous FDR control of the linear step-up procedure to the case of p -values with positive dependence: remember that a set $D \subset [0, 1]^{\mathcal{H}}$ is said to be *nondecreasing* if for all $x, y \in [0, 1]^{\mathcal{H}}$, $x \leq y$ coordinate-wise and $x \in D$ implies $y \in D$. Then, the p -values $\mathbf{p} = (p_h)_{h \in \mathcal{H}}$ are said *positively regressively dependent on each one from \mathcal{H}_0* (PRDS on \mathcal{H}_0 in short) if for all nondecreasing set $D \subset [0, 1]^{\mathcal{H}}$ and for all $h \in \mathcal{H}_0$, $u \in [0, 1] \mapsto \mathbb{P}(\mathbf{p} \in D | p_h = u)$ is nondecreasing. The authors [BY01] have proved the following result under the PRDS assumption:

Theorem 2.6. *Suppose that the p -values $(p_h)_{h \in \mathcal{H}}$ are PRDS on \mathcal{H}_0 . Then the linear step-up procedure R_I has a FDR smaller than $\pi_0 \alpha$.*

When no particular assumption can be made about the dependence structure of the p -values, it was proved in [BF07] extending a result in [BY01] that there is a class of step-up procedures that control the FDR:

Theorem 2.7. *Under general dependence between the p -values, let β be a threshold function of the form:*

$$\beta(r) = \int_0^r u d\nu(u), \quad (2)$$

where ν is some probability distribution on $(0, \infty)$. Then the step-up procedure R_β has a FDR smaller than $\alpha \pi_0$.

A direct corollary of Theorems 2.5, 2.6 and 2.7 is that the step-up procedure R_{β^*} with $\beta^* = \beta/\pi_0$ has a FDR smaller than α in either of the following situations:

- $\beta = I$ when the p -values are independent or PRDS
- β of the form (2) in the general dependent case.

Moreover, since $\pi_0 \leq 1$, the procedure R_{β^*} is always less conservative than procedure R_β , and then seems to be a better choice (especially when π_0 is small). However, since π_0 is unknown, the procedure R_{β^*} can not be only derived from the observations. Therefore, the procedure R_{β^*} is called the *oracle step-up procedure* of threshold function β (and level α).

The adaptive step-up procedures mimic the oracle and are defined as the oracle step-up procedures where π_0^{-1} has been replaced by an estimator F of this value:

Definition 2.8 ((two-stage) adaptive step-up procedure). Given a level $\alpha \in (0, 1)$, a non-decreasing *threshold function* $\beta : \mathbb{R}_+ \rightarrow \mathbb{R}_+$ and an estimator $G : [0, 1]^{\mathcal{H}} \rightarrow (0, \infty)$ of π_0^{-1} . The *(two-stage) adaptive step-up*

procedure at level α , of threshold function β and using estimator F , denoted by $R_{\alpha,\beta G}$, is defined as

$$R_{\alpha,\beta G} := \{h \in \mathcal{H} | p_h \leq p_{(k)}\}, \text{ where } k = \max\{i | p_{(i)} \leq \alpha\beta(i)G(\mathbf{p})/m\}.$$

The (data-dependent) function $r \mapsto \alpha\beta(r)G/m$ is called the *global threshold* of the adaptive procedure. In the particular case where β is the identity function I on \mathbb{R}_+ , the procedure $R_{\alpha,IG}$ is called the *adaptive linear step-up procedure* at level α and using estimator G .

Following the previous definition, an adaptive procedure is composed of two-steps:

1. Estimate π_0^{-1} with an estimator G
2. Take the step-up procedure of threshold function βG

The main theoretical task is to ensure that an adaptive procedure of this type still correctly controls the FDR at the desired level, this including of course the additional variations in the estimator G .

3 Adaptive step-up procedures that control the FDR under independence

We suppose in this section that the p -values $(p_h, h \in \mathcal{H})$ are independent. We introduce the following notation: for each $h \in \mathcal{H}$, we denote by \mathbf{p}_{-h} the collection of p -values $(p_{h'}, h' \neq h)$ and by $\mathbf{p}_{0,h} = (\mathbf{p}_{-h}, 0)$ the collection \mathbf{p} where p_h has been replaced by 0.

3.1 A general theorem and some previously known procedures

The theorem is strongly inspired from techniques developed in [BKY06]. It gives general conditions on the estimator to provided FDR control of adaptive procedure, with what we think is a more compact and synthetic proof that the one proposed in [BKY06].

Theorem 3.1. *Suppose that the p -values of $\mathbf{p} = (p_h, h \in \mathcal{H})$ are independent and consider a coordinate-wise non-increasing estimator $G : [0, 1]^{\mathcal{H}} \rightarrow \mathbb{R}^+$ such that for each $h \in \mathcal{H}_0$,*

$$\mathbb{E}G(\mathbf{p}_{0,h}) \leq \pi_0^{-1}. \tag{3}$$

Then, the linear adaptive step-up procedure $R_{\alpha,IG}$ of global threshold $\alpha IG/m$ has a FDR smaller than α .

Remark 3.2. If G is moreover supposed coordinate-wise left-continuous, we can moreover prove that the Theorem 3.1 still hold when the condition (3) is replaced by the slightly weaker condition:

$$\mathbb{E}G(\tilde{\mathbf{p}}_h) \leq \pi_0^{-1}, \quad (4)$$

where for each $h \in \mathcal{H}_0$, $\tilde{\mathbf{p}}_h = (\mathbf{p}_{-h}, \tilde{p}_h(\mathbf{p}_{-h}))$ is the collection of p -values \mathbf{p} where p_h has been replaced by $\tilde{p}_h(\mathbf{p}_{-h}) = \max\{p \in [0, 1] \mid p \leq \alpha\pi(h)|R((\mathbf{p}_{-h}, p))|G((\mathbf{p}_{-h}, p))\}$.

Following [BKY06], we can consider propose the following choices for G :

Corollary 3.3 (essentially proved in [BKY06]). *Assume that the p -values of $\mathbf{p} = (p_h, h \in \mathcal{H})$ are independent. The adaptive linear step-up procedure at level α has a FDR smaller than α for one of the following choices for the estimators G :*

- $G_1(\mathbf{p}) = \frac{(1-\lambda)m}{\sum_{h \in \mathcal{H}} \mathbf{1}_{\{p_h > \lambda\}} + 1}$, $\lambda \in [0, 1[$
- $G_2(\mathbf{p}) = \frac{1}{1+\alpha} \frac{m}{m - |R_0(\mathbf{p})| + 1}$, where R_0 is the linear step-up procedure at level $\alpha/(1 + \alpha)$.

Remark 3.4. To be more precise, in [BKY06] the result is proved using a slightly better version of G_2 without the “+1” in the denominator (this could be derived here from Remark 3.2). We forget about this refinement here, noting that it results only in a very slight improvement.

Remark 3.5. The estimator $\frac{\sum_{h \in \mathcal{H}} \mathbf{1}_{\{p_h > \lambda\}} + 1}{(1-\lambda)m}$ of π_0 is called the *modified Storey’s estimator* and was initially introduced in [Sto02] and [STS04] (initially without the “+1” in the numerator, hence the name “modified”). Note that G_1 is not necessarily larger than 1.

3.2 A new one-stage adaptive step-up procedure

We now introduce our main first contribution, a ”one-stage adaptive procedure”. This means that estimation step is directly includes in the threshold function β , and so does fall in the framework of Definition 2.3 (and not in the one of Definition 2.8).

Theorem 3.6. *Suppose that the p -values of $(p_h, h \in \mathcal{H})$ are independent. The step-up procedure with the global threshold*

$$\frac{\alpha}{1 + \alpha} \min \left(\frac{I}{m - I + 1}, 1 \right),$$

has a FDR smaller than α .

Remark 3.7. As Figure 1 illustrates,

this explicit new procedure is less conservative than the non-adaptive linear step-up procedure, since its global threshold is higher (except in the quite marginal cases where the proportion of hypotheses rejected by the linear step-up is more than a $(1 + \alpha)^{-1}$, or less than $1/|\mathcal{H}| + \alpha/(1 + \alpha)$).

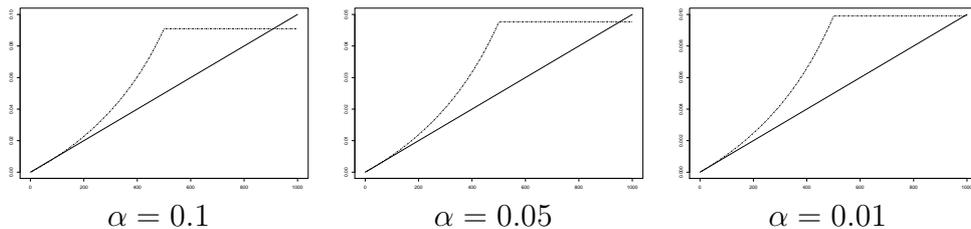


Figure 1: For $|\mathcal{H}| = 1000$ hypotheses. These graphs represent the global threshold of the new adaptive one-stage procedure of Theorem 3.6 (dashed line) and the global threshold of the linear procedure $\alpha I/|\mathcal{H}|$ (full line). The left (resp. center, right) graphs represent the case $\alpha = 0.1$ (resp. $\alpha = 0.05$, $\alpha = 0.01$).

3.3 A new adaptive two-stage procedure

We can now in turn use the previous one-stage procedure to estimate π_0^{-1} to build a two-stage procedure, exactly following the philosophy that led to proposing G_2 . That is, we can use the same function G_2 as proposed earlier, except we replace the first step using the standard step-up linear procedure by the above adaptive procedure. We obtain the following result:

Theorem 3.8. *Assume that the p -values of $\mathbf{p} = (p_h, h \in \mathcal{H})$ are independent and note R'_0 the new one-stage adaptive procedure of Theorem 3.6. Then the adaptive linear step-up procedure with the global threshold $\alpha \frac{1}{m} G_3(\mathbf{p})$, where*

$$G_3(\mathbf{p}) = \frac{1}{1 + \alpha} \frac{m}{m - |R'_0| + 1},$$

has a FDR less or equal to α .

3.4 Simulation study

How can we compare the different procedures defined above? Choosing $\lambda = \alpha/(1 + \alpha)$, we have pointwise $G_1 \geq G_3 \geq G_2$ which shows that the adaptive

procedure obtained using G_1 is always less conservative than the one derived from G_3 , itself less conservative than the one using G_2 (except in the marginal cases where the one-step adaptive procedure is more conservative than the standard step-up procedure, delineated earlier). It would therefore appear that one should always choose G_1 and disregard the other ones. Nevertheless, an argument made in [BKY06] for introducing G_2 as a better alternative to the (already known earlier) G_1 was that on simulations with positively dependent test statistics, the FDR of the adaptive procedure using G_1 with $\lambda = 1/2$ resulted in very bad control of the FDR, which was not the case for G_2 . While the positively dependent case is not covered by the theory, it is important to require that a multiple testing procedure is sufficiently robust in practice so that the FDR does not vary too much in this situation.

Therefore, to assess the quality of our new procedures, we propose here to evaluate the different methods on a simulation study following the setting used in [BKY06]: Let for $i, 1 \leq i \leq m$, $X_i = \mu_i + \varepsilon_i$, where ε is a \mathbb{R}^m -valued centred Gaussian random vector such that $\mathbb{E}(\varepsilon_i^2) = 1$ and for $i \neq j$, $\mathbb{E}(\varepsilon_i \varepsilon_j) = \rho$, where $\rho \in [0, 1]$ is a correlation parameter. Consequently, when $\rho = 0$ the X_i 's are independent whereas when $\rho > 0$ the X_i 's are positively correlated (with a constant correlation). For instance, the ε_i 's can be constructed by taking $\varepsilon_i := \sqrt{\rho}U + \sqrt{1-\rho}Z_i$, where $Z_i, 1 \leq i \leq m$ and U are all i.i.d $\sim \mathcal{N}(0, 1)$.

Considering the one-sided hypotheses $h_i : \mu_i \leq 0$ for $1 \leq i \leq m$, we define the p -values $p_i = \overline{\Phi}(X_i)$, for $1 \leq i \leq m$, where $\overline{\Phi}$ is the standard Gaussian distribution tail. For $i, 1 \leq i \leq m_0$, $\mu_i = 0$ and for $i, m_0 + 1 \leq i \leq m$, $\mu_i = 3$, providing that the p -values corresponding to the null mean follow exactly a uniform distribution. Recall that $\pi_0 = m_0/m$

We perform the following step-up multiple testing procedures:

- [LSU] the linear procedure as defined in Definition 2.3 i.e. with the global threshold $\alpha I/m$.
- [LSU Oracle] the procedure with the global threshold $\alpha I/m_0$.
- [Storey- λ] the two-stage procedures corresponding to G_1 in Corollary 3.3. The classical choice for λ is $1/2$. We try here also $\lambda = \alpha/(1 + \alpha)$.
- [BKY06] The two-stage procedures corresponding to G_2 in Corollary 3.3.
- [BR07-1S] The new one-stage adaptive procedure of Theorem 3.6.
- [BR07-2S] The new two-stage adaptive procedure of Theorem 3.8.

3.4.1 The independent case ($\rho = 0$)

Recall that under independence ($\rho = 0$), the *LSU* procedure has a FDR equal to $\alpha\pi_0$ and that the *LSU Oracle* procedure has a FDR equal to α (given that $\alpha \leq \pi_0$). The other procedures have their FDR bounded by α . We can then define the *power of a procedure* as the number of true rejections of the procedure divided by the number of true rejections of the *LSU Oracle* procedure.

Figure 2 represents the FDR and the Power of these procedures in function of the proportion of true null hypotheses π_0 . These simulations show that we can order the procedures in term of Power :

$$\textit{Storey-1/2} \gg \textit{Storey-}\alpha/(1 + \alpha) \gg \textit{BR07-2S} \gg \textit{BKY06},$$

the symbol " \gg " meaning "is (π_0 -uniformly) more powerful than". The procedure *BR07-1S* is between *BKY06* and *BR07-2S*. We see here that the choice $\lambda = 1/2$ seems to be better than $\lambda = \alpha/(1 + \alpha)$. However, as noticed by [BKY06], simulations when $\rho > 0$ will prove that the procedure with $\lambda = 1/2$ is not robust when there is positive dependence.

3.4.2 The positive dependent case ($\rho > 0$)

Under positive dependence ($\rho > 0$), the FDR of the procedure *LSU* (resp. *LSU Oracle*) is still bounded by $\alpha\pi_0$ (resp. α), but without equality. We do not know if the other procedures have a FDR smaller than α , so that we can not compare them in term of power.

Figure 3 shows that the FDR control is no more provided for the procedure *Storey-1/2*. The maximum FDR for *BR07-2S* is smaller than the one of *Storey-}\alpha/(1 + \alpha)*. Thus our new two-stage procedure seems more robust to positive correlations than *Storey-}\alpha/(1 + \alpha)* (for $\rho = 0.5$, the maximum FDR for *BR07-2S* is 0.0508 whereas the one of *Storey-}\alpha/(1 + \alpha)* is 0.0539). One explanation is that the procedure *BR07-2S* is more conservative than *Storey-}\alpha/(1 + \alpha)* in its estimation of π_0 . When the p -value are very positively correlated $\rho = 0.9$, both procedures control the FDR. One cause is that both procedures are based on the linear step-up procedure which is in this case very conservative.

4 New adaptive step-up procedures that control the FDR under dependence

When the p -values have a general dependency structure, we have to use another device than Lemma 6.4 to estimate π_0^{-1} , we propose here to use the

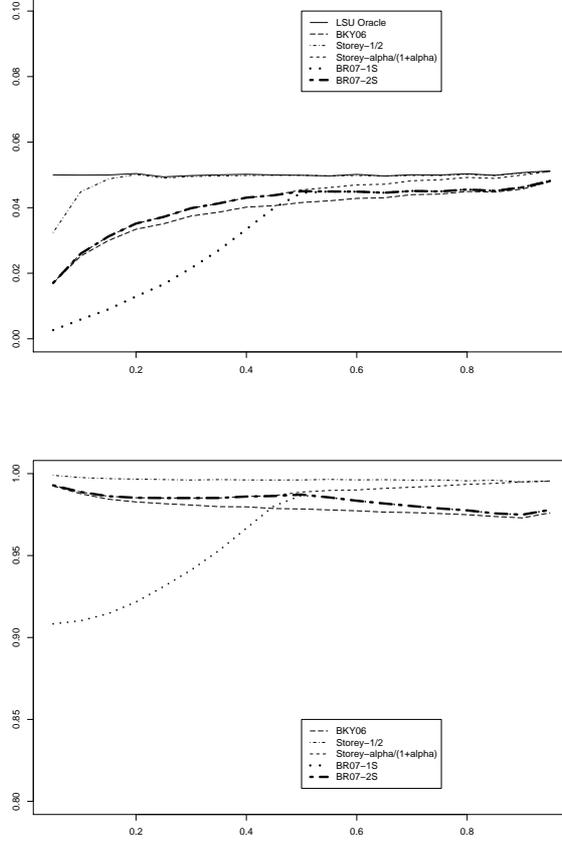


Figure 2: Independent case ($\rho = 0$), $m = 100$, left : FDR in function of π_0 ; right : Power in function of π_0 . Number of simulations : 10000.

Markov inequality. Obviously, because the Markov inequality is general but not extremely precise, the resulting procedure will be quite conservative and is arguably of a limited practical interest. However, we will show that it still provides an improvement, in a certain regime, with respect to the non-adaptive procedure proposed in Theorem 2.7. For a fixed constant $\kappa \geq 2$, define the following function:

$$F_\kappa(x) = \begin{cases} 1 & \text{if } x \leq \kappa^{-1} \\ \frac{2\kappa^{-1}}{1 - \sqrt{1 - 4(1-x)\kappa^{-1}}} & \text{otherwise.} \end{cases} \quad (5)$$

We can prove the following general theorem:

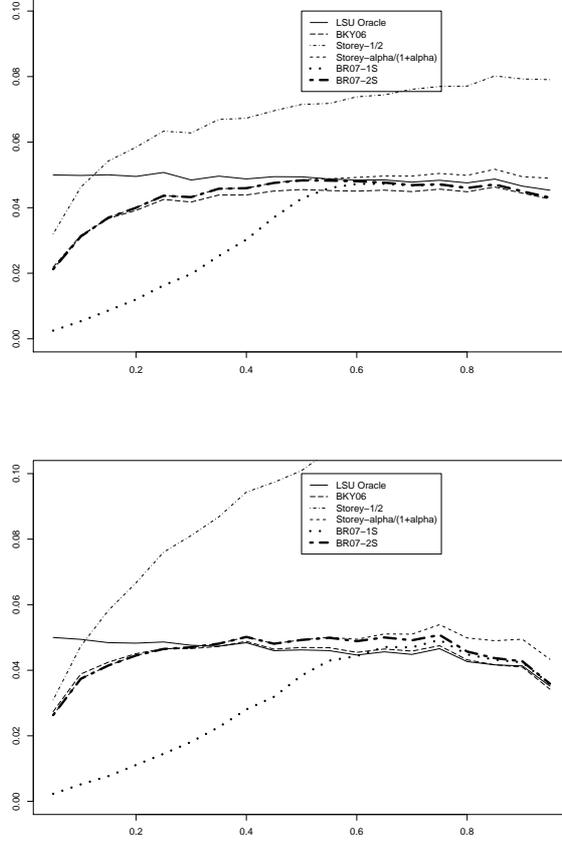


Figure 3: Positive dependent case (left: $\rho = 0.2$, right: $\rho = 0.5$), $m = 100$. FDR in function of π_0 . Number of simulations : 10000.

Theorem 4.1. Consider a threshold function β (that is, a non-decreasing function from \mathbb{R}_+ to \mathbb{R}_+) and fix α_0 and α_1 in $(0, 1)$ such that $\alpha_0 \leq \alpha_1$. Define R_0 is the step-up procedure with global threshold $\alpha_0\beta(\cdot)/m$ and R the adaptive step-up procedure with global threshold $\alpha_1\beta(\cdot)F_\kappa(|R_0|/m)/m$. Suppose moreover that $FDR(R_0) \leq \alpha_0\pi_0$ and that for each $h \in \mathcal{H}_0$ and any constant $c > 0$,

$$\mathbb{E}\left(\frac{\mathbf{1}\{p_h \leq c\beta(|R|)\}}{|R|}\mathbf{1}\{|R| > 0\}\right) \leq c. \quad (6)$$

Then R has a FDR smaller than $\alpha_1 + \kappa\alpha_0$.

Combining Theorem 4.1 with Theorems 2.6 and 2.7, we obtain the following corollary:

Corollary 4.2. Fix α_0 and α_1 in $(0, 1)$ such that $\alpha_0 \leq \alpha_1$ and let β be a threshold function. Define R_0 the step-up procedure with global threshold $\alpha_0\beta(\cdot)/m$. Then the adaptive step-up procedure with global threshold $\alpha_1\beta(\cdot)F_\kappa(|R_0|/m)/m$ has a FDR smaller than $\alpha_1 + \kappa\alpha_0$ in either of the following dependence situations:

- the p -values $(p_h)_{h \in \mathcal{H}}$ are PRDS on \mathcal{H}_0 and $\beta = I$
- the p -values are general dependent and β is a threshold function of the form (2)

Remark 4.3. If we choose $\kappa = 2$, $\alpha_0 = \alpha/4$ and $\alpha_1 = \alpha/2$, the adaptive procedure R of Corollary 4.2 has then a FDR smaller than α . We note that R is less conservative than the non-adaptive step-up procedure with global threshold $\alpha\beta(\cdot)F_c(|R_0|/m)/m$ if $F_2(|R_0|/|\mathcal{H}|) \geq 2$ or equivalently when R_0 rejects more than $F_2^{-1}(2) = 62, 5\%$ of the null hypotheses. Conversely, R is more conservative otherwise, and we can lose up to a factor 2 in the global threshold with respect to the standard one-stage version.

Therefore, this adaptive procedure is only useful in the cases where it is expected that a “large” proportion of hypotheses can easily be rejected.

Remark 4.4. In the PRDS case, and choosing $\kappa = 2$, $\alpha_0 = \alpha/4$ and $\alpha_1 = \alpha/2$, the procedure of Corollary 4.2 is the adaptive LSU procedure at level $\alpha/2$ with the estimator

$$\frac{1}{1 - \sqrt{(2|R_0|/m - 1)_+}},$$

where $|R_0|$ is the number of rejections of the LSU procedure at level $\alpha/4$ and $(\cdot)_+$ denotes the positive part. This procedure has been performed with in the simulation setting of section 3.4 with $\rho = 0.1$, $m_0 = 5$, $m = 100$ (see Figure 4). The common value μ of the positive means is taken in the range $[2, 5]$, so that large values for μ correspond to large rejection cases. We can notice that there exists a regime where the adaptive procedure out-performs the regular one.

Remark 4.5. In the general dependent case, to have a first step procedure that rejects sufficiently, we can choose a prior distribution ν (and then a threshold β of the form (2)) quite concentrate on the large numbers of $\{1, \dots, m\}$.

5 Proofs of the results

Proof. (of Theorem 3.1) By definition $R := R_{\alpha, IG}$ satisfies the following “self-bounding condition”:

$$R = \{h \in \mathcal{H} | p_h \leq \alpha|R|G/m\}. \quad (7)$$

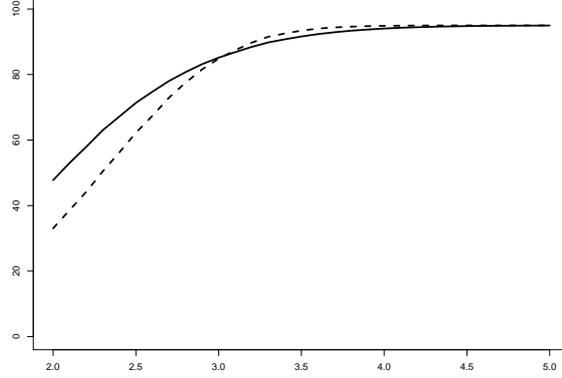


Figure 4: Y axis: the number of rejected false null hypotheses of different procedures, X axis: the common value of all the positive means. Number of simulations 10000, $m = 100$, $m_0 = 5$, $\rho = 0.1$. The full line corresponds to the LSU procedure. The dashed line corresponds to the two-stage adaptive procedure of Corollary 4.2 in the PRDS case with $\kappa = 2$, $\alpha_0 = \alpha/4$ and $\alpha_1 = \alpha/2$.

Therefore, the FDR has the following expression :

$$\text{FDR}(R) = \mathbb{E} \left(\frac{|R \cap \mathcal{H}_0|}{|R|} \mathbf{1}\{|R| > 0\} \right) = \sum_{h \in \mathcal{H}_0} \mathbb{E} \left(\frac{\mathbf{1}\{p_h \leq \alpha |R(\mathbf{p})| G(\mathbf{p})/m\}}{|R(\mathbf{p})|} \right).$$

Therefore, since G is non-increasing, we get:

$$\begin{aligned} \text{FDR}(R) &\leq \sum_{h \in \mathcal{H}_0} \mathbb{E} \left(\frac{\mathbf{1}\{p_h \leq \alpha |R(\mathbf{p})| G(\mathbf{p}_{0,h})/m\}}{|R(\mathbf{p})|} \right) \\ &= \sum_{h \in \mathcal{H}_0} \mathbb{E} \left(\mathbb{E} \left(\frac{\mathbf{1}\{p_h \leq \alpha |R(\mathbf{p})| G(\mathbf{p}_{0,h})/m\}}{|R(\mathbf{p})|} \middle| \mathbf{p}_{-h} \right) \right) \leq \frac{\alpha}{m} \sum_{h \in \mathcal{H}_0} \mathbb{E} G(\mathbf{p}_{0,h}). \end{aligned}$$

The last step is obtained with Lemma 6.1 with $Y = p_h$, $g(p_h) = |R(\mathbf{p}_{-h}, p_h)|$ and $c = \alpha G(\mathbf{p}_{0,h})/m$, because p_h conditionnally to \mathbf{p}_{-h} is stochastically bounded by a uniform distribution, because $|R|$ is coordinate-wise non-increasing and because $\mathbf{p}_{0,h}$ depend only on the p -values of \mathbf{p}_{-h} . We apply then (3) to conclude. \square

Proof. (of Corollary 3.3) By Theorem 3.1, it is sufficient to prove that the condition (3) holds for G_1 and G_2 . The bound for G_1 is obtained using lemma 6.4 with $k = m_0$ and $q = 1 - \lambda$: for all $h \in \mathcal{H}_0$,

$$\mathbb{E}[G_1(\mathbf{p}_{0,h})] \leq m(1 - \lambda) \mathbb{E} \left[\sum_{h' \in \mathcal{H}_0 \setminus \{h\}} \mathbf{1}\{p_{h'} > \lambda\} + 1 \right]^{-1} \leq \pi_0^{-1}.$$

The proof for G_2 is deduced from the one of G_1 with $\lambda = \alpha/(1 + \alpha)$ because in this case $G_2 \leq G_1$ pointwise. \square

Proof. (of Theorem 3.6) We denote by R the corresponding procedure. By definition of a step-up procedure, R satisfies the "cardinal control condition" $R = \{h \in \mathcal{H} | p_h \leq \frac{\alpha}{1+\alpha} \min(\frac{|R|}{m-|R|+1}, 1)\}$. Therefore, we have

$$\begin{aligned} \text{FDR}(R) &\leq \sum_{h \in \mathcal{H}_0} \mathbb{E} \left(\frac{\mathbf{1}\{p_h \leq \frac{\alpha}{1+\alpha} \frac{|R(\mathbf{p})|}{m-|R(\mathbf{p})|+1}\}}{|R(\mathbf{p})|} \right) \\ &\leq \sum_{h \in \mathcal{H}_0} \mathbb{E} \left(\frac{\mathbf{1}\{p_h \leq \frac{\alpha}{1+\alpha} \frac{|R(\mathbf{p}_0, h)|}{m-|R(\mathbf{p}_0, h)|+1}\}}{|R(\mathbf{p})|} \right) \\ &\leq \sum_{h \in \mathcal{H}_0} \mathbb{E} \left(\mathbb{E} \left(\frac{\mathbf{1}\{p_h \leq \frac{\alpha}{1+\alpha} \frac{|R(\mathbf{p})|}{m-|R(\mathbf{p}_0, h)|+1}\}}{|R(\mathbf{p})|} \middle| \mathbf{p}_{-h} \right) \right) \\ &\leq \frac{\alpha}{1+\alpha} \sum_{h \in \mathcal{H}_0} \mathbb{E} \left(\frac{1}{m - |R(\mathbf{p}_0, h)| + 1} \right), \end{aligned}$$

The last step is obtained with Lemma 6.1 with $Y = p_h$, $g(p_h) = |R(\mathbf{p}_{-h}, p_h)|$ and $c = \frac{\alpha}{1+\alpha} \frac{1}{m-|R(\mathbf{p}_0, h)|+1}$, because p_h conditionnally to \mathbf{p}_{-h} is stochastically bounded by a uniform distribution and because $\mathbf{p}_{0, h}$ depend only on the p -values of \mathbf{p}_{-h} .

Finally, we see that since the global threshold is smaller than $\alpha/(1 + \alpha)$,

$$\frac{\alpha}{1+\alpha} \mathbb{E} (1/(|\mathcal{H}| - |R(\mathbf{p}_0, h)| + 1)) \leq \mathbb{E} G_1,$$

where G_1 is the Storey Estimator with $\lambda = \alpha/(1 + \alpha)$. We then use that $\mathbb{E} G_1 \leq \pi_0^{-1}$ (see proof of Corollary 3.3) to conclude. \square

Proof. (of Theorem 3.8) By Theorem 3.1, it suffices to prove that $\mathbb{E} G_3(\mathbf{p}_{0, h}) \leq \pi_0^{-1}$, and this is the case because R'_0 has a global threshold smaller than $\alpha/(1 + \alpha)$. \square

Proof. (of Theorem 4.1) Assume $\pi_0 > 0$ (otherwise the result is trivial). Note first that since R is a step-up procedure, it satisfies the "cardinal control condition" $R = \{h \in \mathcal{H} | p_h \leq \alpha_1 \beta (|R|) F_c(|R_0|/m)/m\}$. Let us decompose

the final output of the two-stage procedure the following way:

$$\begin{aligned}
\text{FDR}(R) &\leq \sum_{h \in \mathcal{H}_0} \mathbb{E} \left[\frac{\mathbf{1}\{p_h \leq \beta(|R|)\alpha_1/m_0\}}{|R|} \mathbf{1}\{|R| > 0\} \right] \\
&\quad + \sum_{h \in \mathcal{H}_0} \mathbb{E} \left[\frac{\mathbf{1}\{\alpha_1\beta(|R|)/m_0 < p_h \leq \alpha_1\beta(|R|)F_c(|R_0|/m)/m\}}{|R|} \mathbf{1}\{|R| > 0\} \right] \\
&\leq \alpha_1 + m_0 \mathbb{E} \left[\frac{\mathbf{1}\{F_c(|R_0|/m) > \pi_0^{-1}\}}{|R_0|} \mathbf{1}\{|R_0| > 0\} \right]
\end{aligned}$$

For the last inequality, we have used (6) with $K = \alpha_1/m_0$ for the first term.

For the second term, we have used the two following facts:

- (i) $F_c(|R_0|/m) > \pi_0^{-1}$ implies $|R_0| > 0$
- (ii) Because of the assumption $\alpha_0 \leq \alpha_1$ and $F_c \geq 1$, the output of the second step is necessarily a set containing at least the output of the first step. Hence $|R| \geq |R_0|$.

Let us now concentrate on further bounding this second term. For this first consider the generalized inverse of F_c , $F_c^{-1}(t) = \inf \{x : F_c(x) > t\}$. Because F_c is a nondecreasing left-continuous function, we have $F_c(x) > t \Leftrightarrow x > F_c^{-1}(t)$. Furthermore, the expression of F_c^{-1} is given by: $\forall t \in [1, +\infty)$, $F_c^{-1}(t) = c^{-1}t^{-2} - t^{-1} + 1$ (providing in particular that $F_c^{-1}(\pi_0^{-1}) > 1 - \pi_0$). Hence

$$\begin{aligned}
m_0 \mathbb{E} \left[\frac{\mathbf{1}\{F_c(|R_0|/m) > \pi_0^{-1}\}}{|R_0|} \right] &\leq m_0 \mathbb{E} \left[\frac{\mathbf{1}\{|R_0|/m > F_c^{-1}(\pi_0^{-1})\}}{|R_0|} \right] \\
&\leq \frac{\pi_0}{F_c^{-1}(\pi_0^{-1})} \mathbb{P} [|R_0|/m \geq F_c^{-1}(\pi_0^{-1})] . \quad (8)
\end{aligned}$$

Now, by assumption the FDR of the first step R_0 is controlled at level $\pi_0\alpha_0$, so that

$$\begin{aligned}
\pi_0\alpha_0 &\geq \mathbb{E} \left[\frac{|R_0 \cap \mathcal{H}_0|}{|R_0|} \mathbf{1}\{|R_0| > 0\} \right] \\
&\geq \mathbb{E} \left[\frac{|R_0| + m_0 - m}{|R_0|} \mathbf{1}\{|R_0| > 0\} \right] \\
&= \mathbb{E} [[1 + (\pi_0 - 1)Z^{-1}] \mathbf{1}\{Z > 0\}] ,
\end{aligned}$$

where we denoted Z the random variable $|R_0|/m$. Hence by Markov's inequality, for each $t > 1 - \pi_0$,

$$\mathbb{P} [Z \geq t] \leq \mathbb{P} \left([1 + (\pi_0 - 1)Z^{-1}] \mathbf{1}\{Z > 0\} \geq 1 + (\pi_0 - 1)t^{-1} \right) \leq \frac{\pi_0\alpha_0}{1 + (\pi_0 - 1)t^{-1}} ;$$

choosing $t = F_c^{-1}(\pi_0^{-1})$ and using this into (8), we obtain

$$m_0 \mathbb{E} \left[\frac{\mathbf{1}\{F_c(|R_0|/m) > \pi_0^{-1}\}}{|R_0|} \right] \leq \alpha_0 \frac{\pi_0^2}{F_c^{-1}(\pi_0^{-1}) - 1 + \pi_0}.$$

If we want that this last quantity to be less than $c\alpha_0$, this yields the condition $F_c^{-1}(\pi_0^{-1}) \geq c^{-1}\pi_0^2 - \pi_0 + 1$, and this is true from the expression of F_c^{-1} . (Note that this is how the formula for F_c was determined in the first place). \square

Proof. (of Corollary 4.2) We have just to prove that (6) is true for any fixed $h \in \mathcal{H}_0$. In the general dependent case, this is a direct consequence of Lemma 6.3 with $X = p_h$ and $Y = \beta(|R|)$. For the PRDS case, we note that $|R|$ is coordinate-wise non-increasing in the p -values and then for any y , $\{\mathbf{p} \in [0, 1]^{\mathcal{H}} \mid \beta(|R(\mathbf{p})|) < y\}$ is a non-decreasing set, so that the PRDS property implies that the function $x \mapsto \mathbb{P}(\beta(|R(\mathbf{p})|) < y \mid p_h \leq x)$ is non-decreasing. We can then apply Lemma 6.2 with $X = p_h$ and $Y = \beta(|R|)$. \square

6 Technical lemmas

Lemma 6.1. *Let $g : [0, 1] \rightarrow (0, \infty)$ be a non-increasing function. Then for any random variable Y stochastically larger than a uniform distribution, and any constant $c > 0$,*

$$\mathbb{E} \left(\frac{\mathbf{1}\{Y \leq cg(Y)\}}{g(Y)} \right) \leq c.$$

of Lemma 6.1. We let $U = \{u : cg(u) \geq u\}$, $u^* = \sup U$ and $C^* = \inf\{g(u) \mid u \in U\}$. It is not difficult to check that $u^* \leq cC^*$, for example take any nondecreasing sequence $u_n \in U \nearrow u^*$, then we have $g(u_n) \searrow C^*$. If $C^* = 0$, the result is trivial. Otherwise, since g is non-increasing,

$$\mathbb{E} \left(\frac{\mathbf{1}\{Y \leq cg(Y)\}}{g(Y)} \right) \leq \frac{\mathbb{P}(Y \in U)}{C^*} \leq \frac{\mathbb{P}(Y \leq u^*)}{C^*} \leq \frac{u^*}{C^*} \leq c.$$

\square

Lemma 6.2. *Let X, Y be two positive real variables. Assume the following:*

1. *X is stochastically larger than a uniform variable in $[0, 1]$, that is $\forall x \in [0, 1], \mathbb{P}(X \leq x) \leq x$.*
2. *The conditional distribution of Y given $X \leq x$ is stochastically decreasing in x , that is,*

$$\forall y \geq 0 \quad \forall 0 \leq x \leq x', \quad \mathbb{P}(Y < y \mid X \leq x) \leq \mathbb{P}(Y < y \mid X \leq x').$$

Then for any constant $c > 0$:

$$\mathbb{E} \left(\frac{\mathbf{1}\{X \leq cY\}}{Y} \right) \leq c.$$

Proof. Fix some $\varepsilon > 0$ and some $\rho \in (0, 1)$ and choose K big enough so that $\rho^K < \varepsilon$. Put $y_0 = 0$ and $y_i = \rho^{K+1-i}$ for $1 \leq i \leq 2K + 1$.

Then

$$\begin{aligned} \mathbb{E} \left(\frac{\mathbf{1}\{X \leq cY\}}{Y \vee \varepsilon} \right) &\leq \sum_{i=1}^{2K+1} \frac{\mathbb{P}(X \leq cy_i; Y \in [y_{i-1}, y_i])}{y_{i-1} \vee \varepsilon} + \varepsilon \\ &\leq c \sum_{i=1}^{2K+1} \frac{\mathbb{P}(X \leq cy_i; Y \in [y_{i-1}, y_i])}{\mathbb{P}(X \leq cy_i)} \frac{y_i}{y_{i-1} \vee \varepsilon} + \varepsilon \\ &= c\rho^{-1} \sum_{i=1}^{2K+1} \mathbb{P}(Y \in [y_{i-1}, y_i] | X \leq cy_i) + \varepsilon \\ &= c\rho^{-1} \sum_{i=1}^{2K+1} (\mathbb{P}(Y < y_i | X \leq cy_i) - \mathbb{P}(Y < y_{i-1} | X \leq cy_i)) + \varepsilon \\ &\leq c\rho^{-1} \sum_{i=1}^{2K+1} (\mathbb{P}(Y \leq y_i | X \leq cy_i) - \mathbb{P}(Y \leq y_{i-1} | X \leq cy_{i-1})) + \varepsilon \\ &\leq c\rho^{-1} + \varepsilon. \end{aligned}$$

We obtain the conclusion by letting $\rho \rightarrow 1$, $\varepsilon \rightarrow 0$ and applying the monotone convergence theorem. \square

Lemma 6.3. *Let X, Y be two positive real variables and β be a function of the form (2). Assume that X is stochastically larger than a uniform variable in $[0, 1]$, that is $\forall x \in [0, 1], \mathbb{P}(X \leq x) \leq x$. Then, for any constant $c > 0$, we have*

$$\mathbb{E} \left(\frac{\mathbf{1}\{X \leq c\beta(Y)\}}{Y} \right) \leq c.$$

Proof. First note that since $\beta(0) = 0$, the expectation is always well defined. Next, since for any $z > 0$, $\int_0^{+\infty} y^{-2} \mathbf{1}\{y \geq z\} dy = 1/z$ and so using Fubini's

theorem:

$$\begin{aligned}
\mathbb{E}\left(\frac{\mathbf{1}\{X \leq c\beta(Y)\}}{Y}\right) &= \mathbb{E}\left(\int_0^{+\infty} y^{-2} \mathbf{1}\{y \geq Y\} \mathbf{1}\{X \leq c\beta(Y)\}\right) \\
&= \int_0^{+\infty} y^{-2} \mathbb{E}[\mathbf{1}\{y \geq Y\} \mathbf{1}\{X \leq c\beta(Y)\}] \\
&\leq \int_0^{+\infty} y^{-2} \mathbb{P}(X \leq c\beta(y)) \\
&\leq c \int_0^{+\infty} y^{-2} \beta(y),
\end{aligned}$$

and we conclude because any function β of the form (2) satisfies $\int_0^{+\infty} y^{-2} \beta(y) = 1$. \square

The following lemma was already propose in [BKY06], it is a central argument when we estimate π_0^{-1} in the independent case:

Lemma 6.4. *For all $k \geq 2$ and $q \in]0, 1]$, we have for any $Y \sim \mathcal{B}(k - 1, q)$,*

$$\mathbb{E}[1/(1 + Y)] \leq 1/kq, \tag{9}$$

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