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# Adaptive FDR control under independence and dependence

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**Abstract.** In the context of multiple hypotheses testing, the proportion  $\pi_0$  of true null hypotheses in the pool of hypotheses to test often plays a crucial role, although it is generally unknown *a priori*. A testing procedure using an implicit or explicit estimate of this quantity in order to improve its efficiency is called *adaptive*. In this paper, we focus on the issue of False Discovery Rate (FDR) control and we present new adaptive multiple testing procedures with control of the FDR. First, in the context of assuming independent  $p$ -values, we present two new procedures and give a unified review of other existing adaptive procedures that have provably controlled FDR. We report extensive simulation results comparing these procedures and testing their robustness when the independence assumption is violated. The new proposed procedures appear competitive with existing ones. The overall best, though, is reported to be Storey’s estimator, but for a parameter setting that does not appear to have been considered before. Second, we propose adaptive versions of step-up procedures that have provably controlled FDR under positive dependences and unspecified dependences of the  $p$ -values, respectively. While simulations only show an improvement over non-adaptive procedures in limited situations, these are to our knowledge among the first theoretically founded adaptive multiple testing procedures that control the FDR when the  $p$ -values are not independent.

## 1 Introduction

### 1.1 Adaptive multiple testing procedures

Spurred by an increasing number of application fields, in particular bioinformatics, the topic of multiple testing (which enjoys a long history in the statistics literature) has generated a renewed, growing attention in the recent years. For example, using 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 genes 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 Dudoit et al., 2003).

In this work, we focus on building multiple testing procedures with a control of the false discovery rate (FDR). This quantity is defined as the expected proportion of type I errors, that is, the proportion of true null hypotheses among all the null hypotheses that have been rejected (i.e. declared as false) by the procedure. In their seminal work on this topic, Benjamini and Hochberg (1995) proposed the celebrated *linear step-up* (LSU) procedure, that is proved to control the FDR under independence between the  $p$ -values. Later, it was proved (Benjamini and Yekutieli, 2001) that the LSU procedure still controls the FDR when the  $p$ -values have positive dependences (or more precisely, a specific form of positive dependence called PRDS). Under unspecified dependences, the same authors have shown that the FDR control still holds if the threshold collection of the LSU procedure is divided by a factor  $1 + 1/2 + \dots + 1/m$ , where  $m$  is the total number of null hypotheses to test.

More recently, the latter result has been generalized (Blanchard and Fleuret, 2007; Blanchard and Roquain, 2008; Sarkar, 2008a), by showing that there is a family of step-up procedures (depending on the choice of a kind of prior distribution) that still control the FDR under unspecified dependences between the  $p$ -values.

However, all of these procedures, which are built in order to control the FDR at a level  $\alpha$ , can be showed to have actually their FDR upper bounded by  $\pi_0\alpha$ , where  $\pi_0$  is the proportion of true null hypotheses in the initial pool. Therefore, when most of the hypotheses are false (i.e.,  $\pi_0$  is small), these procedures are inevitably conservative, since their FDR is in actuality much lower than the fixed target  $\alpha$ . In this context, the challenge of *adaptive control* of the FDR (e.g., Benjamini and Hochberg, 2000; Black, 2004) is to integrate an estimation of the unknown proportion  $\pi_0$  in the threshold of the previous procedures and to prove that the FDR is still rigorously controlled by  $\alpha$ .

Adaptive procedures are therefore of practical interest if it is expected that  $\pi_0$  is, or can be, significantly smaller than 1. An example of such a situation occurs when using hierarchical procedures (e.g., Benjamini and Heller, 2007) which first selects some clusters of hypotheses that are likely to contain false nulls, and then apply a multiple testing procedure on the selected hypotheses. Since a large part of the true null hypotheses is expected to be false in the second step, an adaptive procedure is needed in order to keep the FDR close to the target level.

A number of adaptive procedures have been proposed in the recent literature and can loosely be divided into the following categories:

- *plug-in* procedures, where some initial estimator of  $\pi_0$  is directly plugged in as a multiplicative level correction to the usual procedures. In some cases (e.g. Storey’s estimator, see Storey, 2002), the resulting plug-in adaptive procedure (or a variation thereof) has been proved to control the FDR at the desired level (Benjamini et al., 2006; Storey et al., 2004). A variety of other estimators of  $\pi_0$  have been proposed (e.g. Meinshausen and Rice, 2006; Jin and Cai, 2007; Jin, 2008); while their asymptotic consistency (as the number of hypotheses tends to infinity) is generally established, their use in plug-in adaptive procedures has not always been studied.
- *two-stage* procedures: in this approach, a first round of multiple hypothesis testing is performed using some fixed algorithm, then the results of this first round are used in order to tune the parameters of a second round in an adaptive way. This can generally be interpreted as using the output of the first stage to estimate  $\pi_0$ . Different procedures following this general approach have been proposed (Benjamini et al., 2006; Sarkar, 2008a; Farcomeni, 2007); more generally, multiple-stage procedures can be considered.
- *one-stage* procedures, which perform a single round of multiple testing (generally step-up or step-down), based on a particular threshold collection that renders it adaptive (Finner et al., 2009; Gavrilov et al., 2009).

In addition, some other works (Genovese and Wasserman, 2004; Storey et al., 2004; Finner et al., 2009) have studied the question of adaptivity to the parameter  $\pi_0$  from an *asymptotic* viewpoint. In this framework, the more specific *random effects* model is – most generally, though not always – considered, in which  $p$ -values are assumed independent, each hypothesis has a probability  $\pi_0$  of being true, and all false null hypotheses share the same alternate distribution. The behavior of different procedures is then studied under the limit where the number of tested hypotheses grows to infinity. One advantage of this approach and specific model is that it allows to derive quite precise results (see Neuvial, 2008, for a precise study of limiting behaviors of central limit type under this model, including for some of the new procedures introduced in the present paper). However, we emphasize that in the present work our focus is decidedly on the nonasymptotic side, using finite samples and arbitrary alternate hypotheses.

To complete this overview, let us also mention another interesting and different direction opened up recently, that of adaptivity to the alternate distribution. If the alternate distribution is known *a priori*, it is well-known that the optimal testing statistics are likelihood ratios between the null and the alternate (which can then be transformed into  $p$ -values). When the alternate is unknown though, one can hope to estimate, implicitly or explicitly, the alternate distribution from the observed data, and consequently approximate the optimal test statistics (Sun and Cai, 2007

proposed an asymptotically consistent approach to this end; see also Spjøtvoll, 1972, Storey, 2007). Interestingly, this point of view is also intimately linked to some traditional topics in statistical learning such as classification and of optimal novelty detection (see, e.g., Scott and Blanchard, 2009). However, in the present paper we will focus on adaptivity to the parameter  $\pi_0$  only.

## 1.2 Overview of this paper

The contributions of the present paper are the following. A first goal of the paper is to introduce a number of novel adaptive procedures:

1. We introduce a new *one-stage* step-up procedure that is more powerful than the standard LSU procedure in a large range of situations, and provably controls the FDR under independence. This procedure is called one-stage adaptive, because the estimation of  $\pi_0$  is performed implicitly.
2. Based on this, we then build a new *two-stage* adaptive procedure, which is more powerful in general than the procedure proposed by Benjamini et al. (2006), while provably controlling the FDR under independence.
3. Under the assumption of positive or arbitrary dependence of the  $p$ -values, we introduce new two-stage adaptive versions of known step-up procedures (namely, of the LSU under positive dependences, and of the family of procedures introduced by Blanchard and Fleuret, 2007, under unspecified dependences). These adaptive versions provably control the FDR and result in an improvement of power over the non-adaptive versions in some situations (namely, when the number of hypotheses rejected in the first stage is large, typically more than 60%).

A second goal of this work is to present a review of several existing adaptive step-up procedures with provable FDR control under independence. For this, we present the theoretical FDR control as a consequence of a single general theorem for plug-in procedures, which was first established by Benjamini et al. (2006). Here, we give a short self-contained proof of this result that is of independent interest. The latter is based on some tools introduced earlier (Blanchard and Roquain, 2008; Roquain, 2007), that aim to unify FDR control proofs. Related results and tools also appear independently in Finner et al. (2009); Sarkar (2008b).

A third goal is to compare both the existing and our new adaptive procedures in an extensive simulation study under both independence and dependence, following the simulation model and methodology used by Benjamini et al. (2006). Concerning the new one- and two- step procedures with theoretical FDR control under independence, these are generally quite competitive in comparison to existing ones. However we also report that the best procedure overall (in terms of power, among procedures that are robust enough to the dependent case) appears to be the plug-in procedure based on the well-known Storey estimator (Storey, 2002) used with the somewhat nonstandard parameter  $\lambda = \alpha$ . This outcome was in part unexpected since to the best of our knowledge, this fact had never been pointed out so far (the usual default recommended choice is  $\lambda = \frac{1}{2}$  and turns out to be very unstable in dependent situations); this is therefore an important conclusion of this paper regarding practical use of these procedures.

Concerning the new two-step procedure with theoretical FDR control under dependence, simulations show an (admittedly limited) improvement over their non-adaptive counterpart in favorable situations which correspond to what was expected from the theoretical study (large proportion of false hypotheses). The observed improvement is unfortunately not striking enough to be able to recommend using these procedures in practice; their interest is therefore at this point mainly theoretical, in that these are to our knowledge among the first theoretically founded adaptive multiple testing procedures that control the FDR when the  $p$ -values are not independent.

The paper is organized as follows: in Section 2, we introduce the mathematical framework, and we recall the existing non-adaptive results in FDR control. In Section 3 we deal with the setup of independent  $p$ -values. We expose our new procedures and review the existing ones, and finally compare them in a simulation study. The case of positive dependent and arbitrarily dependent  $p$ -values is examined in Section 4 where we introduce our new adaptive procedures in this context.

A conclusion is given in Section 5. Section 6 and 7 contains proofs of the results and lemmas, respectively. Some technical remarks and discussions of links to other work are gathered at the end of each relevant subsection, and can be skipped by the non-specialist reader.

## 2 Preliminaries

### 2.1 Multiple testing framework

In this paper, we will stick to the traditional statistical framework for multiple testing. Let  $(\mathcal{X}, \mathfrak{X}, \mathbb{P})$  be a probability space; we want to infer a decision on  $\mathbb{P}$  from an observation  $x$  in  $\mathcal{X}$  drawn from  $\mathbb{P}$ . 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  $m$ , where  $|\cdot|$  is the cardinality function. The underlying probability  $\mathbb{P}$  being fixed, we denote  $\mathcal{H}_0 = \{h \in \mathcal{H} | \mathbb{P} \text{ satisfies } h\}$  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. We stress that  $\mathcal{H}_0$ ,  $m_0$ , and  $\pi_0$  are unknown and implicitly depend on the unknown  $\mathbb{P}$ . All the results to come are always implicitly meant to hold for any generating distribution  $\mathbb{P}$ .

We suppose further that there exists a set of *p-value* functions  $\mathbf{p} = (p_h, h \in \mathcal{H})$ , 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,

$$\forall h \in \mathcal{H}_0 \quad \forall t \in [0, 1], \quad \mathbb{P}(p_h \leq t) \leq t. \quad (1)$$

Typically, *p-values* are obtained from statistics that have a known distribution  $P_0$  under the corresponding null hypothesis. In this case, if  $F_0$  denotes the corresponding cumulative distribution function, applying  $1 - F_0$  to the observed statistic results in a random variable satisfying (1) in general. Here, we are however not concerned how these *p-values* are constructed and only assume that they exist and are known (this is the standard setting in multiple testing).

### 2.2 Multiple testing procedure and errors

A *multiple testing procedure* is a measurable function

$$R : x \in \mathcal{X} \mapsto R(x) \in \mathcal{P}(\mathcal{H}),$$

which takes as input an observation  $x$  and returns a subset of  $\mathcal{H}$ , corresponding to the rejected hypotheses. As it is commonly the case, we will focus here on multiple testing procedure based on *p-values*, that is, we will implicitly assume that  $R$  is of the form  $R(\mathbf{p})$ .

A multiple testing procedure  $R$  can make two kinds of errors: a *type I error* occurs for  $h$  when  $h$  is true and is rejected by  $R$ , that is,  $h \in \mathcal{H}_0 \cap R$ . Following the Neyman-Pearson general philosophy for hypothesis testing, 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  $h \in \mathcal{H}_0^c \cap R^c$ .

The most traditional way to control type I error is to upper bound the "Family-wise error rate" (FWER), which is the probability that one or more true null hypotheses are wrongly rejected. However, procedures with a controlled FWER are very "cautious" not to make a single error, and thus reject only few hypotheses. This conservative way of measuring the type I error for multiple hypothesis testing can be a serious hindrance in practice, since it requires to collect large enough datasets so that significant evidence can be found under this strict error control criterion. More recently, a more liberal measure of type I errors has been introduced in multiple testing (Benjamini and Hochberg, 1995): the *false discovery rate* (FDR), 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  $R$  for a generating distribution  $\mathbb{P}$  is given by*

$$\text{FDR}(R) := \mathbb{E} \left[ \frac{|R \cap \mathcal{H}_0|}{|R|} \mathbf{1}_{\{|R| > 0\}} \right]. \quad (2)$$

*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. Note also again that the dependence of the FDR on the unknown  $\mathbb{P}$  is implicit.

A classical aim, then, is to build procedures  $R$  with FDR upper bounded at a given, fixed level  $\alpha$ . Of course, if we choose  $R = \emptyset$ , meaning that  $R$  rejects no hypotheses, trivially  $\text{FDR}(R) = 0 \leq \alpha$ . Therefore, it is desirable to build procedures  $R$  satisfying  $\text{FDR}(R) \leq \alpha$  while at the same time having as few type II errors as possible. As a general rule, provided that  $\text{FDR}(R) \leq \alpha$ , we want to build procedures that reject as many false hypotheses as possible. The absolute power of a multiple testing procedure is defined as the average proportion of false hypotheses correctly rejected,  $\mathbb{E}[|R \cap \mathcal{H}_0^c| / |\mathcal{H}_0^c|]$ . Given two procedures  $R$  and  $R'$ , a particularly simple sufficient condition for  $R$  to be more powerful than  $R'$  is when  $R' \subset R$  holds pointwise. We will say in this case that  $R$  is (uniformly) less conservative than  $R'$ .

### 2.3 Self-consistency, step-up procedures, FDR control and adaptivity

We first define a general class of multiple testing procedures called *self-consistent procedures* (Blanchard and Roquain, 2008).

**Definition 2.3 (Self-consistency, non-increasing procedure).** *Let  $\Delta : \{0, 1, \dots, m\} \rightarrow \mathbb{R}$ ,  $\Delta(0) = 0$ , be a function called threshold collection; a multiple testing procedure  $R$  is said to satisfy the self-consistency condition with respect to  $\Delta$  if*

$$R \subset \{h \in \mathcal{H} \mid p_h \leq \Delta(|R|)\} \quad (3)$$

*holds almost surely. Furthermore, we say that  $R$  is non-increasing if for all  $h \in \mathcal{H}$  the function  $p_h \mapsto |R(\mathbf{p})|$  is non-increasing, that is if  $|R|$  is non-increasing in each  $p$ -value.*

The class of self-consistent procedures includes well-known types of procedures, notably step-up and step-down. The assumption that a procedure is non-increasing, which is required in addition to self-consistency in some of the results to come, is relatively natural as a lower  $p$ -value means we have more evidence to reject the corresponding hypothesis. We will mainly focus on the *step-up* procedure, which we define now. For this, we sort the  $p$ -values in increasing order using the notation  $p_{(1)} \leq \dots \leq p_{(m)}$  and put  $p_{(0)} = 0$ . This order is of course itself random since it depends on the observation.

**Definition 2.4 (Step-up procedure).** *The step-up procedure with threshold collection  $\Delta$  is defined as*

$$R = \{h \in \mathcal{H} \mid p_h \leq p_{(k)}\}, \quad \text{where } k = \max\{0 \leq i \leq m \mid p_{(i)} \leq \Delta(i)\}.$$

A trivial but important property of a step-up procedure is the following.

**Lemma 2.5.** *The step-up procedure with threshold collection  $\Delta$  is non-increasing and self-consistent with respect to  $\Delta$ .*

Therefore, a result valid for any non-increasing self-consistent procedure also holds for the corresponding step-up procedure. This will be used extensively through the paper and thus should be kept in mind by the reader.

Among all procedures that are self-consistent with respect to  $\Delta$ , the step-up is uniformly less conservative than any other (Blanchard and Roquain, 2008) and is therefore of primary interest. However, to recover procedures of a more general form (including step-down for instance), the statements of this paper will be preferably expressed in terms of self-consistent procedures when it is possible.

Threshold collections are generally scaled by the target FDR level  $\alpha$ . Once correspondingly rewritten under the normalized form  $\Delta(i) = \alpha\beta(i)/m$ , we will call  $\beta$  the *shape function* for threshold collection  $\Delta$ . In the particular case where the shape function  $\beta$  is the identity function, the procedure is called the *linear step-up (LSU) procedure* (at level  $\alpha$ ).

The LSU plays a prominent role in multiple testing under FDR control; it was the first procedure for which FDR control was proved and it is probably the most widely used procedure in this context. More precisely, when the  $p$ -values are assumed to be independent, the following theorem holds.

**Theorem 2.6.** *Suppose that the  $p$ -values of  $\mathbf{p} = (p_h, h \in \mathcal{H})$  are independent. Then any non-increasing self-consistent procedure with respect to threshold collection  $\Delta(i) = \alpha i/m$  has FDR upper bounded by  $\pi_0\alpha$ , where  $\pi_0 = m_0/m$  is the proportion of true null hypotheses. (In particular, this is the case for the linear step-up procedure). Moreover, if the  $p$ -values associated to true null hypotheses are exactly distributed like a uniform distribution, the linear step-up procedure has FDR equal to  $\pi_0\alpha$ .*

The first part of this result, in the case of the LSU, was proved in the landmark paper of Benjamini and Hochberg (1995); the second part (also for the LSU) was proved by Benjamini and Yekutieli (2001) and Finner and Roters (2001).

Benjamini and Yekutieli (2001) extended the previous result about FDR control of the linear step-up procedure to the case of  $p$ -values with a certain form of positive dependence called *positive regressive dependence from a subset* (PRDS). We skip a formal definition for now (we will get back to this topic in Section 4). The extension of this result to self-consistent procedures (in the independent as well as PRDS cases) was established by Blanchard and Roquain (2008) and Finner et al. (2009).

However, when no particular assumptions are made on the dependences between the  $p$ -values, it can be shown that the above FDR control is not generally true. This situation is called *unspecified* or *arbitrary* dependence. A modification of the LSU was first proposed in Benjamini and Yekutieli (2001) which was proved to have a controlled FDR under arbitrary dependence. This result was extended by Blanchard and Fleuret (2007) and Blanchard and Roquain (2008) (see also a related result of Sarkar, 2008a): it can be shown that self-consistent procedures (not necessarily non-increasing) based on a particular class of shape functions have controlled FDR:

**Theorem 2.7.** *Under unspecified dependences between the  $p$ -values of  $\mathbf{p} = (p_h, h \in \mathcal{H})$ , consider  $\beta$  a shape function of the form:*

$$\beta(r) = \int_0^r u d\nu(u), \quad (4)$$

where  $\nu$  is some fixed a priori probability distribution on  $(0, \infty)$ . Then any self-consistent procedure with respect to threshold collection  $\Delta(i) = \alpha\beta(i)/m$  has FDR upper bounded by  $\alpha\pi_0$ .

To recap, in all of the above cases, the FDR is actually controlled at the level  $\pi_0\alpha$  instead of the target  $\alpha$ . Hence, a direct corollary of both of the above theorems is that the step-up procedure with shape function  $\beta^*(x) = \pi_0^{-1}\beta(x)$  has FDR upper bounded  $\alpha$  in either of the following situations:

- $\beta(x) = x$  when the  $p$ -values are independent or PRDS,
- the shape function  $\beta$  is of the form (4) when the  $p$ -values have unspecified dependences.

Note that, since  $\pi_0 \leq 1$ , using  $\beta^*$  always gives rise to a less conservative procedure than using  $\beta$  (especially when  $\pi_0$  is small). However, since  $\pi_0$  is unknown, the shape function  $\beta^*$  is not directly accessible. We therefore will call the step-up procedure using  $\beta^*$  the *Oracle step-up procedure* based on shape function  $\beta$  (corresponding to one of the above cases).

Simply put, the role of adaptive step-up procedures is to mimic the latter oracle in order to obtain more powerful procedures. Adaptive procedures are often step-up procedures using the modified shape function  $G\beta$ , where  $G$  is some estimator of  $\pi_0^{-1}$ :

**Definition 2.8 (Plug-in adaptive step-up procedure).** *Given a level  $\alpha \in (0, 1)$ , a shape function  $\beta$  and an estimator  $G : [0, 1]^{\mathcal{H}} \rightarrow (0, \infty)$  of the quantity  $\pi_0^{-1}$ , the plug-in adaptive step-up procedure of shape function  $\beta$  and using estimator  $G$  (at level  $\alpha$ ) is defined as*

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

The (data-dependent) function  $\Delta(\mathbf{p}, i) = \alpha\beta(i)G(\mathbf{p})/m$  is called the adaptive threshold collection corresponding to the procedure. In the particular case where the shape function  $\beta$  is the identity function on  $\mathbb{R}^+$ , the procedure is called an adaptive linear step-up procedure using estimator  $G$  (and at level  $\alpha$ ).

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

1. Estimate  $\pi_0^{-1}$  with an estimator  $G$ .
2. Take the step-up procedure of shape function  $G\beta$ .

A subclass of plug-in adaptive procedures is formed by so-called *two-stage procedures*, when the estimator  $G$  is actually based on a first, non-adaptive, multiple testing procedure. This can obviously be possibly iterated and lead to multi-stage procedures. The distinction between generic plug-in procedures and two-stage procedures is somewhat informal and generally meant only to provide some kind of nomenclature between different possible approaches.

The main theoretical task is to ensure that an adaptive procedure of this type still correctly controls the FDR. The mathematical difficulty obviously comes from the additional random variations of the estimator  $G$  in the procedure.

### 3 Adaptive procedures with provable FDR control under independence

In this section, we introduce two new adaptive procedures that provably control the FDR under independence. The first one is one-stage and does not include an explicit estimator of  $\pi_0^{-1}$ , hence it is not a plug-in procedure. We then propose to use this as the first stage in a new two-stage procedure, which constitutes the second proposed method.

For clarity, we first introduce the new one-stage procedure; we then discuss several possible plug-in procedures, including our new proposition and several procedures proposed by other authors. FDR control for these various plug-in procedures can be studied using a general theoretical device introduced by Benjamini et al. (2006) which we reproduce here with a self-contained and somewhat simplified proof. Finally, to compare these different approaches, we close this section with extensive simulations which both examined the performance under independence and the robustness under (possibly strong) positive correlations.

#### 3.1 New adaptive one-stage step-up procedure

We present here our first main contribution, a one-stage adaptive step-up procedure. This means that the estimation step is implicitly included in the shape function  $\beta$ .

**Theorem 3.1.** *Suppose that the  $p$ -values of  $\mathbf{p} = (p_h, h \in \mathcal{H})$  are independent and let  $\lambda \in (0, 1)$  be fixed. Define the adaptive threshold collection*

$$\Delta(i) = \min\left(\left(1 - \lambda\right)\frac{\alpha i}{m - i + 1}, \lambda\right). \quad (5)$$

*Then any non-increasing self-consistent procedure with respect to  $\Delta$  has FDR upper bounded by  $\alpha$ . In particular, this is the case of the corresponding step-up procedure, denoted by BR-1S- $\lambda$ .*



The above result will be proved in Section 6. Our proof is in part based on Lemma 1 of Benjamini et al. (2006). Note that an alternate proof of Theorem 3.1 has been established in Sarkar (2008b) without using this lemma while nicely connecting the FDR upper-bound to the false non-discovery rate.

Below, we will focus on the choice  $\lambda = \alpha$ , leading to the threshold collection

$$\Delta(i) = \alpha \min \left( (1 - \alpha) \frac{i}{m - i + 1}, 1 \right). \quad (6)$$

For  $i \leq (m + 1)/2$ , the threshold (6) is

$$\alpha \frac{(1 - \alpha)i}{m - i + 1},$$

and thus our approach differs from the threshold collection of the standard LSU procedure threshold by the factor  $\frac{(1 - \alpha)m}{m - i + 1}$ .

It is interesting to note that the correction factor  $\frac{m}{m - i + 1}$  appears in Holm's step-down procedure (Holm, 1979) for FWER control. The latter is a well-known improvement of Bonferroni's procedure (which corresponds to the fixed threshold  $\alpha/m$ ), taking into account the proportion of true nulls, and defined as the step-down procedure<sup>3</sup> with threshold collection  $\alpha/(m - i + 1)$ . Here we therefore prove that this correction is suitable as well for the linear step-up procedure, in the framework of FDR control.

If  $r$  denotes the final number of rejections of the new one-stage procedure, we can interpret the ratio  $\frac{(1 - \lambda)m}{m - r + 1}$  between the adaptive threshold and the LSU threshold at the same point as an *a posteriori* estimate for  $\pi_0^{-1}$ . In the next section we propose to use this quantity in a plug-in, 2-stage adaptive procedure.

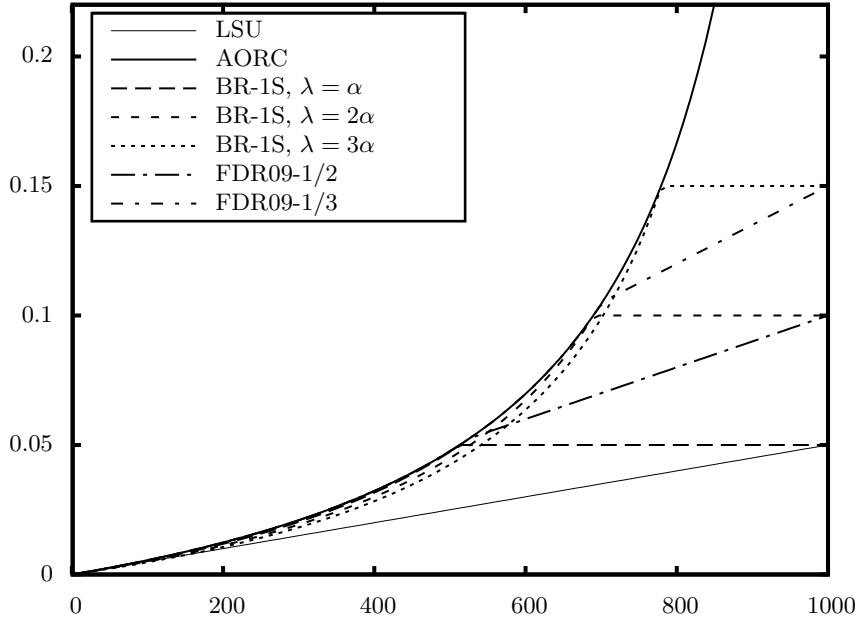
As Figure 1 illustrates, our procedure is generally less conservative than the (non-adaptive) linear step-up procedure (LSU). Precisely, the new procedure can only be more conservative than the LSU procedure in the marginal case where the factor  $\frac{(1 - \alpha)m}{m - i + 1}$  is smaller than one. This happens only when the proportion of null hypotheses rejected by the LSU procedure is positive but less than  $\alpha + 1/m$  (and even in this region the ratio of the two threshold collections is never less than  $(1 - \alpha)$ ). Roughly speaking, this situation with only few rejections can only happen if there are few false hypotheses to begin with ( $\pi_0$  close to 1) or if the false hypotheses are very difficult to detect (the distribution of false  $p$ -values is close to being uniform).

In the interest of being more specific, we briefly investigate this issue in the next lemma, considering the particular *Gaussian random effects* model (which is relatively standard in the multiple testing literature, see e.g. Genovese and Wasserman, 2004) in order to give a quantitative answer from an asymptotical point of view (when the number of tested hypotheses grows to infinity). In the random effect model, hypotheses are assumed to be randomly true or false with probability  $\pi_0$ , and the false null hypotheses share a common distribution  $P_1$ . Globally, the  $p$ -values then are i.i.d. drawn according to the mixture distribution  $\pi_0 U[0, 1] + (1 - \pi_0)P_1$ .

**Lemma 3.2.** *Consider the random effects model where the  $p$ -values are i.i.d. with common cumulative distribution function  $t \mapsto \pi_0 t + (1 - \pi_0)F(t)$ . Assume the true null hypotheses are standard Gaussian with zero mean and the alternative hypotheses are standard Gaussian with mean  $\mu > 0$ . In this case  $F(t) = \bar{\Phi}(\bar{\Phi}^{-1}(t) - \mu)$ , where  $\bar{\Phi}$  is the standard Gaussian upper tail function. Assuming  $\pi_0 < (1 + \alpha)^{-1}$ , define*

$$\mu^* = \bar{\Phi}^{-1}(\alpha^2) - \bar{\Phi}^{-1}\left(\frac{\alpha^{-1} - \pi_0}{1 - \pi_0} \alpha^2\right).$$

<sup>3</sup> The step-down procedure with threshold collection  $\Delta$  rejects the hypotheses corresponding to the  $k$  smallest  $p$ -values, where  $k = \max\{0 \leq i \leq m \mid \forall j \leq i \ p_{(j)} \leq \Delta(j)\}$ . It is self-consistent with respect to  $\Delta$  but uniformly more conservative than the step-up procedure with the same threshold collection, compare with Definition 2.4.



**Fig. 1.** For  $m = 1000$  null hypotheses and  $\alpha = 5\%$ : comparison of the new threshold collection  $BR-1S-\lambda$  given by (5) to that of the LSU, the AORC and  $FDR09-\eta$ .

Then if  $\mu > \mu^*$ , the probability that the LSU rejects a proportion of null hypotheses less than  $1/m + \alpha$  tends to 0 as  $m$  tends to infinity. On the other hand, if  $\pi_0 > (1 + \alpha)^{-1}$ , or  $\mu < \mu^*$ , then this probability tends to one.

For instance, taking in the above lemma the values  $\pi_0 = 0.5$  and  $\alpha = 0.05$ , results in the critical value  $\mu^* \simeq 1.51$ . This lemma delineates clearly in a particular case in which situation we can expect an improvement from the adaptive procedure over the standard LSU.

**Comparison to other adaptive one-stage procedures.** Very recently, other adaptive one-stage procedures with important similarities to  $BR-1S-\lambda$  have been proposed by other authors. (The present work was developed independently.)

Starting with some heuristic motivations, Finner et al. (2009) proposed the threshold collection  $t(i) = \frac{\alpha i}{m - (1 - \alpha)i}$ , which they dubbed the *asymptotically optimal rejection curve* (AORC). However, the step-up procedure using this threshold collection as is does not have controlled FDR (since  $t(m) = 1$ , the corresponding step-up procedure would always reject all the hypotheses), and several suitable modifications were proposed by Finner et al. (2009), the simplest one being

$$t'_\eta(i) = \min(t(i), \eta^{-1}\alpha i/m),$$

which is denoted by  $FDR09-\eta$  in the following.

The theoretical FDR control proved in Finner et al. (2009) is studied asymptotically as the number of hypotheses grows to infinity. In that framework, asymptotical control at level  $\alpha$  is shown to hold for any  $\eta < 1$ . On Figure 1, we represented the thresholds  $BR-1S-\lambda$  and  $FDR09-\eta$  for comparison, for several choices of the parameters. The two families appear quite similar, initially following the AORC curve then branching out or capping at a point depending on the parameter. One noticeable difference in the initial part of the curve is that while  $FDR09-\eta$  exactly coincides with the AORC,  $BR-1S-\lambda$  is arguably slightly more conservative. This reflects the nature of the corresponding theoretical result – non-asymptotic control of the FDR requires a somewhat

more conservative threshold as compared to the only asymptotic control of  $FDR\text{-}\eta$ . Moreover, we can use  $BR\text{-}1S\text{-}\lambda$  as a first step in a 2-step procedure, as will be argued in the next section.

The ratio between  $BR\text{-}1S\text{-}\lambda$  and the AORC (before the capping point) is a factor which, assuming  $\alpha \geq (m+1)^{-1}$ , is lower bounded by  $(1-\lambda)(1 - \frac{1}{m+1})$ . This suggests that the value for  $\lambda$  should be kept small, this is why we propose  $\lambda = \alpha$  as a default choice.

Finally, the *step-down* procedure based on the same threshold collection  $t(i)$  (without modification) is proposed and studied by Gavrilov et al. (2009). Using specific properties of step-down procedures, these authors proved the nonasymptotic FDR control of this procedure.

### 3.2 Adaptive plug-in methods

In this section, we consider different adaptive step-up procedures of the plug-in type, i.e. based on an explicit estimator of  $\pi_0^{-1}$ . We first review a general method proposed by Benjamini et al. (2006) in order to derive FDR control for such plug-in procedures (see also Theorem 4.3 of Finner et al., 2009). We propose here a self-contained proof of this result, which is somewhat more compact than the original one (and also extends the original result from step-up procedures to more generally self-consistent procedures). Based on this result, we review the different plug-in estimators considered by Benjamini et al. (2006) and add a new one to the lot, based on the one-stage adaptive procedure introduced in the previous section.

Let us first introduce the following notations: for each  $h \in \mathcal{H}$ , we denote by  $\mathbf{p}_{-h}$  the collection of  $p$ -values  $\mathbf{p}$  restricted to  $\mathcal{H} \setminus \{h\}$ , that is,  $\mathbf{p}_{-h} = (p_{h'}, h' \neq h)$ . We also denote  $\mathbf{p}_{0,h} = (\mathbf{p}_{-h}, 0)$  the collection  $\mathbf{p}$  where  $p_h$  has been replaced by 0.

**Theorem 3.3 (Benjamini, Krieger, Yekutieli 2006).** *Suppose that the family  $p$ -values  $\mathbf{p} = (p_h, h \in \mathcal{H})$  is independent. Let  $G : [0, 1]^{\mathcal{H}} \rightarrow (0, \infty)$  be a measurable, coordinate-wise non-increasing function. Consider a non-increasing multiple testing procedure  $R$  which is self-consistent with respect to the adaptive linear threshold collection  $\Delta(\mathbf{p}, i) = \alpha G(\mathbf{p})i/m$ . Then the following holds:*

$$\text{FDR}(R) \leq \frac{\alpha}{m} \sum_{h \in \mathcal{H}_0} \mathbb{E}[G(\mathbf{p}_{0,h})]. \quad (7)$$

*In particular, if for any  $h \in \mathcal{H}_0$ , it holds that  $\mathbb{E}[G(\mathbf{p}_{0,h})] \leq \pi_0^{-1}$ , then  $\text{FDR}(R) \leq \alpha$ .*

We will apply the above result to the following estimators, depending on a fixed parameter  $\lambda \in (0, 1)$  or  $k_0 \in \{1, \dots, m\}$ :

$$\begin{aligned} [\text{Storey-}\lambda] \quad G_1(\mathbf{p}) &= \frac{(1-\lambda)m}{\sum_{h \in \mathcal{H}} \mathbf{1}\{p_h > \lambda\} + 1}; \\ [\text{Quant-}\frac{k_0}{m}] \quad G_2(\mathbf{p}) &= \frac{(1-p_{(k_0)})m}{m - k_0 + 1}; \\ [\text{BKY06-}\lambda] \quad G_3(\mathbf{p}) &= \frac{(1-\lambda)m}{m - |R_0(\mathbf{p})| + 1}, \text{ where } R_0 \text{ is the standard LSU at level } \lambda; \\ [\text{BR-2S-}\lambda] \quad G_4(\mathbf{p}) &= \frac{(1-\lambda)m}{m - |R'_0(\mathbf{p})| + 1}, \text{ where } R'_0 \text{ is BR-1S-}\lambda \text{ (see Theorem 3.1)}. \end{aligned}$$

Above, the notations “Storey- $\lambda$ ”, “Quant- $\frac{k_0}{m}$ ”, “BKY06- $\lambda$ ” and “BR-2S- $\lambda$ ” refer to the plug-in adaptive linear step-up procedures associated to  $G_1$ ,  $G_2$ ,  $G_3$  and  $G_4$ , respectively.

Estimator  $G_1$  is usually called *modified Storey’s estimator* and was initially introduced by Storey (2002) from an heuristics on the  $p$ -values histogram (originally without the “+1” in the numerator, hence the name “modified”). Its intuitive justification is as follows: the set  $S_\lambda$  of  $p$ -values larger than the threshold  $\lambda$  contains on average at least a proportion  $(1-\lambda)$  of the true null hypotheses. Hence, a natural estimator of  $\pi_0^{-1}$  is  $(1-\lambda)m/|S_\lambda \cap \mathcal{H}_0| \leq (1-\lambda)m/|S_\lambda| \simeq G_1(\mathbf{p})$ . Therefore, we expect that Storey’s estimator is generally an overestimate of  $\pi_0^{-1}$ . A standard choice is  $\lambda = 1/2$

(as in the SAM software of Storey and Tibshirani, 2003). FDR control for the corresponding plug-in step-up procedure was proved by Storey et al. (2004) (actually, for the modification  $\tilde{\Delta}(\mathbf{p}, i) = \min(\alpha G_1(\mathbf{p})i/m, \lambda)$ ) and by Benjamini et al. (2006).

Estimator  $G_2$  was introduced by Benjamini and Hochberg (2000) and Efron et al. (2001), from a slope heuristics on the  $p$ -values c.d.f. Roughly speaking,  $G_2$  appears as a Storey's estimator with the data-dependent choice  $\lambda = p_{(k_0)}$ , and can therefore be interpreted as the quantile version of the Storey estimator. A standard value for  $k_0$  is  $\lfloor m/2 \rfloor$ , resulting in the so-called median adaptive LSU (see Benjamini et al. (2006) and the references therein).

Estimator  $G_3$  was introduced by Benjamini et al. (2006) for the particular choice  $\lambda = \alpha/(1+\alpha)$ . More precisely, a slightly less conservative version, without the "+1" in the denominator, was used in Benjamini et al. (2006). We forget about this refinement here, noting that it results only in a very slight improvement.

Finally, the estimator  $G_4$  is new and follows exactly the same philosophy as  $G_3$ , that is, uses a step-up procedure as a first stage in order to estimate  $\pi_0^{-1}$ , but this time based on our adaptive one-stage step-up procedure introduced in the previous section, rather than the standard LSU. Note that since  $R'_0$  is less conservative than  $R_0$  (except in marginal cases), we generally have  $G_2 \leq G_3$  pointwise and our estimator improves over the one of Benjamini et al. (2006).

These different estimators all satisfy the sufficient condition mentioned in Theorem 3.3, and we thus obtain the following corollary:

**Corollary 3.4.** *Assume that the  $p$ -values of  $\mathbf{p} = (p_h, h \in \mathcal{H})$  are independent. For  $i = 1, 2, 3, 4$ , and any  $h \in \mathcal{H}_0$ , it holds that  $\mathbb{E}[G_i(\mathbf{p}_{0,h})] \leq \pi_0^{-1}$ . Therefore, the plug-in adaptive linear step-up procedure at level  $\alpha$  using estimator  $G_i$  has FDR smaller than  $\alpha$ .*

The above result for  $G_1$ ,  $G_2$  and  $G_3$  (for  $\lambda = \alpha/(1+\alpha)$ ) was proved by Benjamini et al. (2006). For completeness, we reproduce shortly the corresponding arguments in the appendix.

In other words, Corollary 3.4 states that under independence, for any  $\lambda$  and  $k_0$ , the plug-in adaptive procedures Storey- $\lambda$ , Quant- $\frac{k_0}{m}$ , BKY06- $\lambda$  and BR-2S- $\lambda$  all control the FDR at level  $\alpha$ .

*Remark 3.5.* The result proved by Benjamini et al. (2006) is actually slightly sharper than Theorem 3.3. Namely, if  $G(\cdot)$  is moreover supposed to be coordinate-wise left-continuous, it is possible to prove that Theorem 3.3 still holds when  $\mathbf{p}_{0,h}$  in the RHS of (7) is replaced by the slightly better  $\tilde{\mathbf{p}}_h = (\mathbf{p}_{-h}, \tilde{p}_h(\mathbf{p}_{-h}))$ , defined as the collection of  $p$ -values  $\mathbf{p}$  where  $p_h$  has been replaced by  $\tilde{p}_h(\mathbf{p}_{-h}) = \max\{p \in [0, 1] \mid p \leq \alpha\pi(h)|R(\mathbf{p}_{-h}, p)|G(\mathbf{p}_{-h}, p)\}$ . This improvement then permits to get rid of the "+1" in the denominator of  $G_3$ . Here, we opted for simplicity and a more straightforward statement, noting that this improvement is not crucial.

*Remark 3.6.* The one-stage step-up procedure of Finner et al. (2009) (see previously the discussion at the end of Section 3.1) — for which there is no result proving non-asymptotic FDR control up to our knowledge — can also be interpreted intuitively as an adaptive version of the LSU using estimator  $G_2$ , where the choice of parameter  $k_0$  is data-dependent. Namely, assume we reject at least  $i$  null hypotheses whenever  $p_{(i)}$  is lower than the standard LSU threshold times the estimator  $G_2$  wherein parameter  $k_0 = i$  is used. This corresponds to the inequality  $p_{(i)} \leq \frac{(1-p_{(i)})k}{m-i+1}$ , which, solved in  $p_{(i)}$ , gives the threshold collection of Finner et al. (2009). Remember from Section 3.1 that this threshold collection must actually be modified in order to be useful, since it otherwise always leads to reject all hypotheses. The modification leading to  $FDR09$ - $\eta$  consists in capping the estimated  $\pi_0^{-1}$  at a level  $\eta$ , i.e. using  $\min(\eta, G_2)$  instead of  $G_2$  in the above reasoning. In fact, the proof of Finner et al. (2009) relies on a result which is essentially a reformulation of Theorem 3.3 for a specific form of estimator.

*Remark 3.7.* The estimators  $G_i$ ,  $i = 1, 2, 3, 4$  are not necessarily larger than 1, and to this extent can in some unfavorable cases result in the final procedure being actually more conservative than the standard LSU. This can only happen in the situation where either  $\pi_0$  is close to 1 ("sparse signal") or the alternative hypotheses are difficult to detect ("weak signal"); if such a situation is anticipated, it is more appropriate to use the regular non-adaptive LSU.

For the Storey- $\lambda$  estimator, we can control precisely the probability that such an unfavorable case arises by using Hoeffding's inequality (Hoeffding, 1963): assuming the true nulls are i.i.d. uniform on  $(0, 1)$  and the false nulls i.i.d. of c.d.f.  $F(\cdot)$ , we write by definition of  $G_1$

$$\begin{aligned} \mathbb{P}[G_1(\mathbf{p}) < 1] &= \mathbb{P}\left[\frac{1}{m} \sum_{h \in \mathcal{H}} (\mathbf{1}\{p_h > \lambda\} - \mathbb{P}[p_h > \lambda]) > (1 - \pi_0)(F(\lambda) - \lambda) - m^{-1}\right] \\ &\leq \exp(-2(mc^2 + 1)), \end{aligned} \quad (8)$$

where we denoted  $c = (1 - \pi_0)(F(\lambda) - \lambda)$ , and assumed additionally  $c > m^{-1}$ . The behavior of the bound mainly depends on  $c$ , which can get small only if  $\pi_0$  is close to 1 (sparse signal) or  $F(\lambda)$  is close to  $\lambda$  (weak signal), illustrating the above point. In general, provided  $c > 0$  does not depend on  $m$ , the probability that the Storey procedure fails to outperform the LSU vanishes exponentially as  $m \rightarrow \infty$ .

### 3.3 Theoretical robustness of the adaptive procedures under maximal dependence

For the different procedures proposed above, the theory only provides the correct FDR control under independence between the  $p$ -values. An important issue is to know how robust this control is when dependences are present (as it is often the case in practice). However, the analytic computation of the FDR under dependence is generally a difficult task, and this issue is often tackled empirically through simulations in a pre-specified model (we will do so in Section 3.4).

In this short section, we present theoretical computations of the FDR for the previously introduced adaptive step-up procedures, under the maximally dependent model where all the  $p$ -values are in fact equal, that is  $p_h \equiv p_1$  for all  $h \in \mathcal{H}$  (and  $m_0 = m$ ). It corresponds to the case where we perform  $m$  times the same test, with the same  $p$ -value. Albeit relatively trivial and limited, this case leads to very simple FDR computations and provides at least some hints concerning the robustness under dependence of the different procedures studied above.

**Proposition 3.8.** *Suppose that we observe  $m$  identical  $p$ -values  $\mathbf{p} = (p_1, \dots, p_m) = (p_1, \dots, p_1)$  with  $p_1 \sim U([0, 1])$  and assume  $m = m_0$ . Then, the following holds:*

$$\begin{aligned} \text{FDR}(BR-1S-\lambda) &= \min(\lambda, (1 - \lambda)\alpha m), \\ \text{FDR}(FDR09-\eta) &= \alpha\eta^{-1}, \\ \text{FDR}(Storey-\lambda) &= \min\left(\lambda, \alpha(1 - \lambda)m\right) + (\alpha(1 - \lambda)(1 + m^{-1}) - \lambda)_+, \\ \text{FDR}(Quant-k_0/m) &= \frac{\alpha}{(1 + \alpha) - (k_0 - 1)m^{-1}}, \\ \text{FDR}(BKY06-\lambda) &= \text{FDR}(BR-2S-\lambda) = \text{FDR}(Storey-\lambda). \end{aligned}$$

Interestingly, the above proposition suggests specific choices of the parameters  $\lambda$ ,  $\eta$  and  $k_0$  to ensure control of the FDR at level  $\alpha$  under maximal dependence:

- For BR-1S- $\lambda$ , putting  $\lambda_2 = \alpha/(\alpha + m^{-1})$ , Proposition 3.8 gives that  $\text{FDR}(BR-1S-\lambda) = \lambda$  whenever  $\lambda \leq \lambda_2$ . This suggests to take  $\lambda = \alpha$ , and is thus in accordance with the default choice proposed in Section 3.1.
- For FDR09- $\eta$ , no choice of  $\eta < 1$  will lead to the correct FDR control under maximal dependence. However, the larger  $\eta$ , the smaller the FDR in this situation. Note that  $\text{FDR}(FDR09-\frac{1}{2}) = 2\alpha$ .
- For Storey- $\lambda$ , BKY06- $\lambda$  and BR-2S- $\lambda$ , putting  $\lambda_1 = \alpha/(1 + \alpha + m^{-1})$ , we have  $\text{FDR} = \lambda$  for  $\lambda_1 \leq \lambda \leq \lambda_2$ . This suggests to choose  $\lambda = \alpha$  within these three procedures. Furthermore, note that the standard choice  $\lambda = 1/2$  for Storey- $\lambda$  leads to a very poor control under maximal dependence:  $\text{FDR}(Storey-1/2) = \min(\alpha m, 1)/2$ .

- For  $\text{Quant-}k_0/m$ , we see that the value of  $k_0$  maximizing the FDR while maintaining it below  $\alpha$  is  $k_0 = \lfloor \alpha m \rfloor + 1$ . Remark also that the standard choice  $k_0 = \lfloor m/2 \rfloor$  leads to  $\text{FDR}(\text{Quant-}k_0/m) = 2\alpha/(1 + 2\alpha + 2m^{-1}) \simeq 2\alpha$ .

Nevertheless, we would like to underline that the above computations should be interpreted with caution, as the maximal dependence case is very specific and cannot possibly give an accurate idea of the behavior of the different procedures when the correlation between the  $p$ -values are strong but not equal to 1. For instance, it is well-known that the LSU procedure has FDR far below  $\alpha$  for strong positive correlations, but its FDR is equal to  $\alpha$  in the above extreme model (see Finner et al., 2007, for a comprehensive study of the LSU under positive dependence). Conversely, the FDR of some adaptive procedures can be higher under moderate dependence than under maximal dependence. This behavior appears in the simulations of the next section, illustrating the complexity of the issue.

### 3.4 Simulation study

How can we compare the different adaptive procedures defined above? For a fixed  $\lambda$ , we have pointwise  $G_1 \geq G_4 \geq G_3$ , which shows that the adaptive procedure [Storey- $\lambda$ ] is always less conservative than [BR-2S- $\lambda$ ], itself less conservative than [BKY06- $\lambda$ ] (except in the marginal cases where the one-stage adaptive procedure is more conservative than the standard step-up procedure, as delineated earlier for example in Lemma 3.2). It would therefore appear that one should always choose [Storey- $\lambda$ ] and disregard the other ones. However, an important point made by Benjamini et al. (2006) for introducing  $G_3$  as a better alternative to the (already known earlier)  $G_1$  is that, on simulations with positively dependent test statistics, the plug-in procedure using  $G_1$  with  $\lambda = 1/2$  had very poor control of the FDR, while the FDR was still controlled for the plug-in procedure based on  $G_3$ . While the positively dependent case is not covered by the theory, it is of course very important to ensure that a multiple testing procedure is sufficiently robust in practice so that the FDR does not vary too much in this situation.

In order to assess the quality of our new procedures, we compare here the different methods on a simulation study following the setting used by Benjamini et al. (2006). Let  $X_i = \mu_i + \varepsilon_i$ , for  $i, 1 \leq i \leq m$ , where  $\varepsilon$  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. Thus, when  $\rho = 0$  the  $X_i$ 's are independent, whereas when  $\rho > 0$  the  $X_i$ 's are positively correlated (with a constant pairwise correlation). For instance, the  $\varepsilon_i$ '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 null hypotheses  $h_i : \mu_i \leq 0$  against the alternatives " $\mu_i > 0$ " for  $1 \leq i \leq m$ , we define the  $p$ -values  $p_i = \bar{\Phi}(X_i)$ , for  $1 \leq i \leq m$ , where  $\bar{\Phi}$  is the standard Gaussian distribution tail. We choose a common mean  $\bar{\mu}$  for all false hypotheses, that is, for  $i, 1 \leq i \leq m_0$ ,  $\mu_i = 0$  and for  $i, m_0 + 1 \leq i \leq m$ ,  $\mu_i = \bar{\mu}$ ; the  $p$ -values corresponding to the null means follow exactly a uniform distribution.

Note that the case  $\rho = 1$  and  $m = m_0$  (i.e.  $\pi_0 = 1$ ) corresponds to the maximally dependent case studied in Section 3.3.

We compare the following step-up multiple testing procedures: first, the one-stage step-up procedures defined in Section 3.1:

- [BR08-1S- $\alpha$ ] The new procedure of Theorem 3.1, with parameter  $\lambda = \alpha$ ,
- [FDR09- $\frac{1}{2}$ ] The procedure proposed in Finner et al. (2009) and described in Section 3.1, with  $\eta = \frac{1}{2}$ .

Second, the adaptive plug-in step-up procedure defined in Section 3.2:

- [Median LSU] The procedure [Quant- $\frac{k_0}{m}$ ] with the choice  $\frac{k_0}{m} = \frac{1}{2}$ ,
- [BKY06- $\alpha$ ] The procedure [BKY06- $\lambda$ ] with the parameter choice  $\lambda = \alpha$ ,
- [BR08-2S- $\alpha$ ] The procedure [BR08-2S- $\lambda$ ] with the parameter choice  $\lambda = \alpha$ ,
- [Storey- $\lambda$ ] With the choices  $\lambda = 1/2$  and  $\lambda = \alpha$ .

Finally, we used as oracle reference [*LSU Oracle*], the step-up procedure with the threshold collection  $\Delta(i) = \alpha i/m_0$ , using a perfect estimation of  $\pi_0$ .

The parameter choice  $\lambda = \alpha$  for [*Storey- $\lambda$* ] comes from the relationship of  $G_3, G_4$  to  $G_1$  in Section 3.1, and form the discussion of the maximally dependent case in Section 3.3. Note that the procedure studied by Benjamini et al. (2006) is actually [*BKY06- $\alpha/(1+\alpha)$* ] in our notation (up to the very slight modification explained in Remark 3.5). This means that the procedure [*BKY06- $\alpha$* ] used in our simulations is not exactly the same as in Benjamini et al. (2006), but it is very close.

The three most important parameters in the simulation are the correlation coefficient  $\rho$ , the proportion of true null hypotheses  $\pi_0$ , and the alternative mean  $\bar{\mu}$  which represents the signal-to-noise ratio, or how easy it is to distinguish alternative hypotheses. We present in Figures 2, 3, and 4 results of the simulations for one varying parameter ( $\pi_0$ ,  $\bar{\mu}$  and  $\rho$ , respectively), the others being kept fixed. Reported are, for the different methods: the average FDR, and the average power relative to the reference [*LSU-Oracle*]. The absolute power is defined as the average proportion of false null hypotheses rejected, and the relative power as the mean of the number of true rejections of the procedure divided by the number of true rejections of [*LSU-Oracle*]. Each point is an average of  $10^5$  simulations, with fixed parameters  $m = 100$  and  $\alpha = 5\%$ .

**Under independence ( $\rho = 0$ )** Remember that under independence of the  $p$ -values, the *LSU* procedure has FDR equal to  $\alpha\pi_0$  and that the *LSU Oracle* procedure has FDR equal to  $\alpha$  (provided that  $\alpha \leq \pi_0$ ). The other procedures have their FDR upper bounded by  $\alpha$  (in an asymptotical sense only for [*FDR09- $\frac{1}{2}$* ]).

The situation where the  $p$ -values are independent corresponds to the first row of Figures 2 and 3 and the leftmost point of each graph in Figure 4. It appears that in the independent case, the following procedures can be consistently ordered in terms of (relative) power over the range of parameters studied here:

$$[\textit{Storey-1/2}] \succ [\textit{Storey-}\alpha] \succ [\textit{BR08-2S-}\alpha] \succ [\textit{BKY06-}\alpha],$$

the symbol “ $\succ$ ” meaning “is (uniformly over our experiments) more powerful than”.

Next, the procedures [*median-LSU*] and [*FDR09- $\frac{1}{2}$* ] appear both consistently less powerful than [*Storey- $\frac{1}{2}$* ], and [*FDR09- $\frac{1}{2}$* ] is additionally also consistently less powerful than [*Storey- $\alpha$* ]. Their relation to the remaining procedures depends on the parameters; both [*median-LSU*] and [*FDR09- $\frac{1}{2}$* ] appear to be more powerful than the remaining procedures when  $\pi_0 > \frac{1}{2}$ , and less efficient otherwise. We note that [*median-LSU*] also appears to perform better when  $\bar{\mu}$  is low (i.e. the alternative hypotheses are harder to distinguish).

Concerning our one-stage procedure [*BR08-1S- $\alpha$* ], we note that it appears to be indistinguishable from its two-stage counterpart [*BR08-2S- $\alpha$* ] when  $\pi_0 > \frac{1}{2}$ , and significantly less powerful otherwise. This also corresponds to our expectations, since in the situation  $\pi_0 < \frac{1}{2}$ , there is a much higher likelihood that more than 50% hypotheses are rejected, in which case our one-stage threshold family hits its “cap” at level  $\alpha$  (see e.g. Fig. 1; a similar qualitative explanation applies to understand the behavior of *FDR09-1/2*). This is precisely to improve on this situation that we introduced the 2-stage procedure, and we see that does in fact improve substantially the 1-stage version in that specific region.

The fact that [*Storey- $\frac{1}{2}$* ] is uniformly more powerful than the other procedures in the independent case corroborates the simulations reported in Benjamini et al. (2006). Generally speaking, under independence we obtain a less biased estimate for  $\pi_0^{-1}$  when considering Storey’s estimator based on a “high” threshold like  $\lambda = \frac{1}{2}$ . Namely, higher  $p$ -values are less likely to be “contaminated” by false null hypotheses; conversely, if we take a lower threshold  $\lambda$ , there will be more false null hypotheses included in the set of  $p$ -values larger than  $\lambda$ , leading to a pessimistic bias in the estimation of  $\pi_0^{-1}$ . This qualitative reasoning is also consistent with the observed behavior of [*median-LSU*], since the set of  $p$ -values larger than the median is much more likely to be “contaminated” when  $\pi_0 < \frac{1}{2}$ .

However, the problem with [*Storey- $\frac{1}{2}$* ] is that the corresponding estimation of  $\pi_0^{-1}$  exhibits much more variability than its competitors when there is a substantial correlation between the

$p$ -values. As a consequence it is a very fragile procedure. This phenomenon was already pinpointed in Benjamini et al. (2006) and we study it next.

**Under positive dependences ( $\rho > 0$ )** Under positive dependences, remember that it is known theoretically from Benjamini and Yekutieli (2001) that the FDR of the procedure *LSU* (resp. *LSU Oracle*) is still bounded by  $\alpha\pi_0$  (resp.  $\alpha$ ), but without equality. However, we do not know from a theoretical point of view if the adaptive procedures have their FDR upper bounded by  $\alpha$ . In fact, it was pointed out by Farcomeni (2007), in another work reporting simulations on adaptive procedures, that one crucial point for these seems to be the variability of estimate of  $\pi_0^{-1}$ . Estimates of this quantity that are not robust with respect to positive dependence will result in failures for the corresponding multiple testing procedure.

The situation where the  $p$ -values are positively dependent corresponds to the second and third rows ( $\rho = 0.2, 0.5$ , respectively) of Figures 2 and 3 and to all the graphs of Figure 4.

The most striking fact is that [Storey- $\frac{1}{2}$ ] does not control the FDR at the desired level any longer under positive dependences, and can even be off by quite a large factor. This is in accordance with the experimental findings of Benjamini et al. (2006). Therefore, although this procedure was the favorite in the independent case, it turns out to be not robust, which is very undesirable for practical use where it is generally impossible to guarantee that the  $p$ -values are independent. The procedure [median-LSU] appears to have higher power than the remaining ones in the situations studied in Figure 3, especially with a low signal-to-noise ratio. Unfortunately, other situations appearing in Figures 2 and 4 show that [median-LSU] can exhibit a poor FDR control in some parameter regions, most notably when  $\pi_0$  is close to 1 and positive dependences are present (see, e.g., Fig. 4, bottom row). In a majority of practical situations, it is difficult to rule out *a priori* that  $\pi_0$  could be close to 1 (i.e., there is only a small proportion of false hypotheses), or that there are no dependences. For these reasons, our conclusion is that [median-LSU] is also not robust enough in general to be reliable.

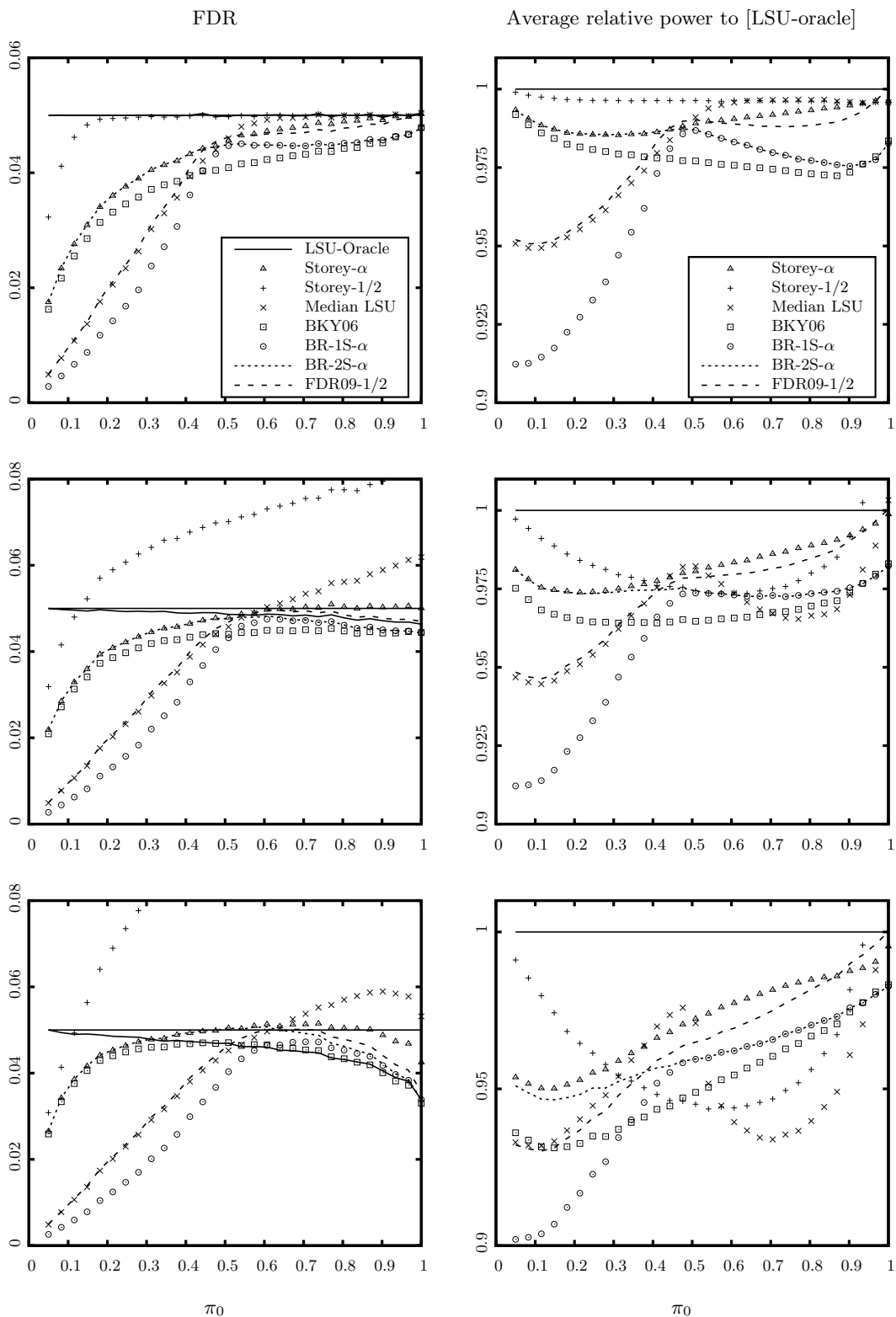
The other remaining procedures seem to still have a controlled FDR, or at least to be very close to the FDR target level (except for [FDR09- $\frac{1}{2}$ ] when  $\rho$  and  $\pi_0$  are close to 1). For these it seems that the qualitative conclusions concerning power comparison found in the independent case remain true. To sum up:

- the best overall procedure seems to be [Storey- $\alpha$ ]: its FDR seems to be under or only slightly over the target level in all situations, and it exhibits globally a power superior to other procedures.
- then come in order of power, our 2-stage procedure [BR08-2S- $\alpha$ ], then [BKY06- $\alpha$ ].
- like in the dependent case, [FDR09- $\frac{1}{2}$ ] ranks second when  $\pi_0 > \frac{1}{2}$  but tends to perform noticeably poorer if  $\pi_0$  gets smaller. Its FDR is also not controlled if very strong correlations are present.

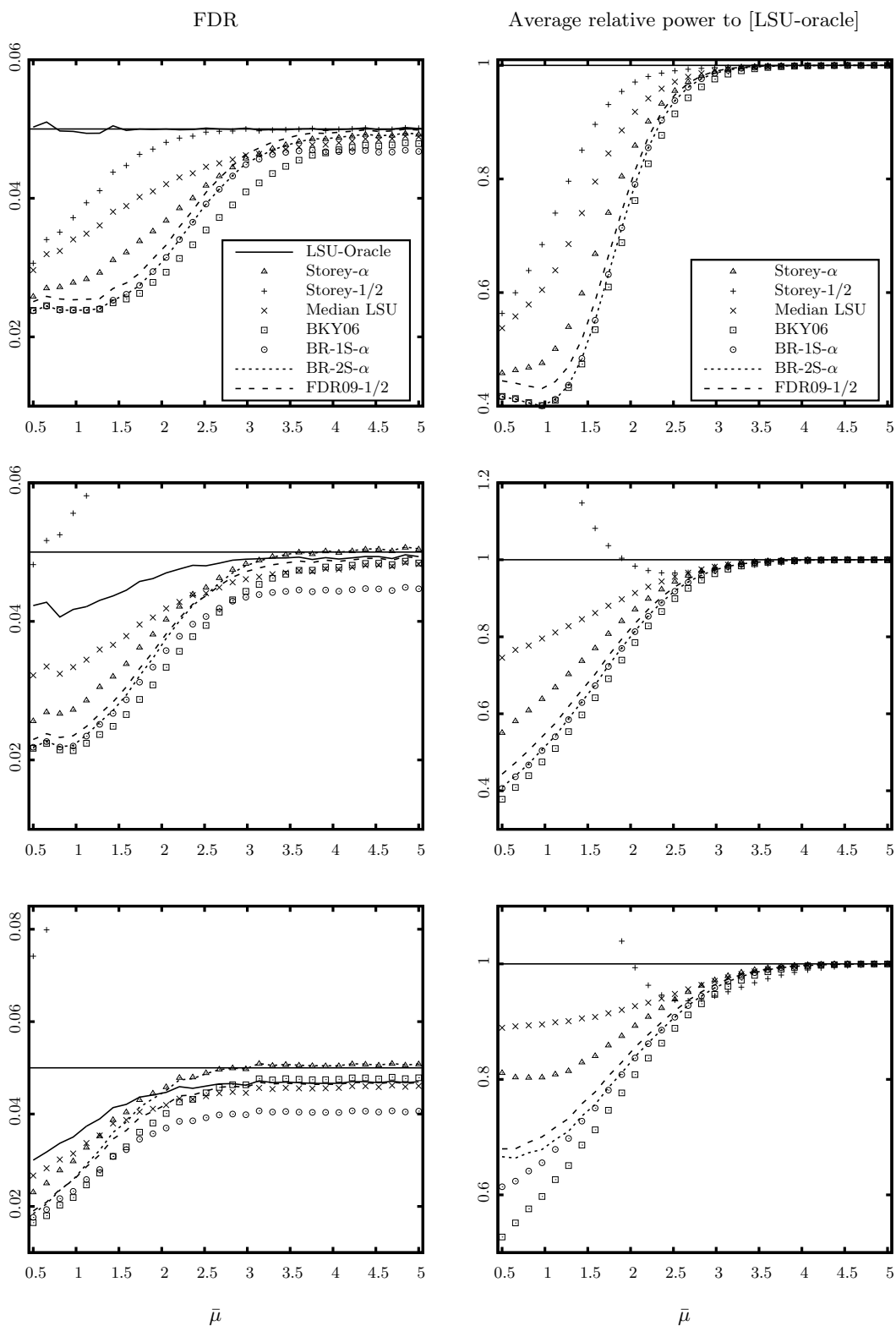
To conclude, the recommendation that we draw from these experiments is that for practical use, we recommend in priority [Storey- $\alpha$ ], then as close seconds [BR08-2S- $\alpha$ ] or [FDR09- $\frac{1}{2}$ ] (the latter when it is expected that  $\pi_0 > 1/2$ , and that there are no very strong correlations present). The procedure [BKY06- $\alpha$ ] is also competitive but appears to be in most cases noticeably outperformed by the above ones. These procedures all exhibit good robustness to dependence for FDR control as well as comparatively good power. The fact that [Storey- $\alpha$ ] performs so well and seems to hold the favorite position has up to our knowledge not been reported before (it was not included in the simulations of Benjamini et al., 2006) and came somewhat as a surprise to us.

*Remark 3.9.* As pointed out earlier, the fact that [FDR09- $\frac{1}{2}$ ] performs sub-optimally for  $\pi_0 < \frac{1}{2}$  appears to be strongly linked to the choice of parameter  $\eta = \frac{1}{2}$ . Namely, the implicit estimator of  $\pi_0^{-1}$  in the procedure is capped at  $\eta$  (see Remark 3.6). Choosing a higher value for  $\eta$  will reduce the sub-optimality region but increase the variability of the estimate and thus decrease the overall robustness of the procedure (if dependences are present; and also under independence if only a small number of hypotheses  $m$  are tested, as for this procedure the convergence of the FDR towards its asymptotically controlled value becomes slower as  $\eta$  grows towards 1).

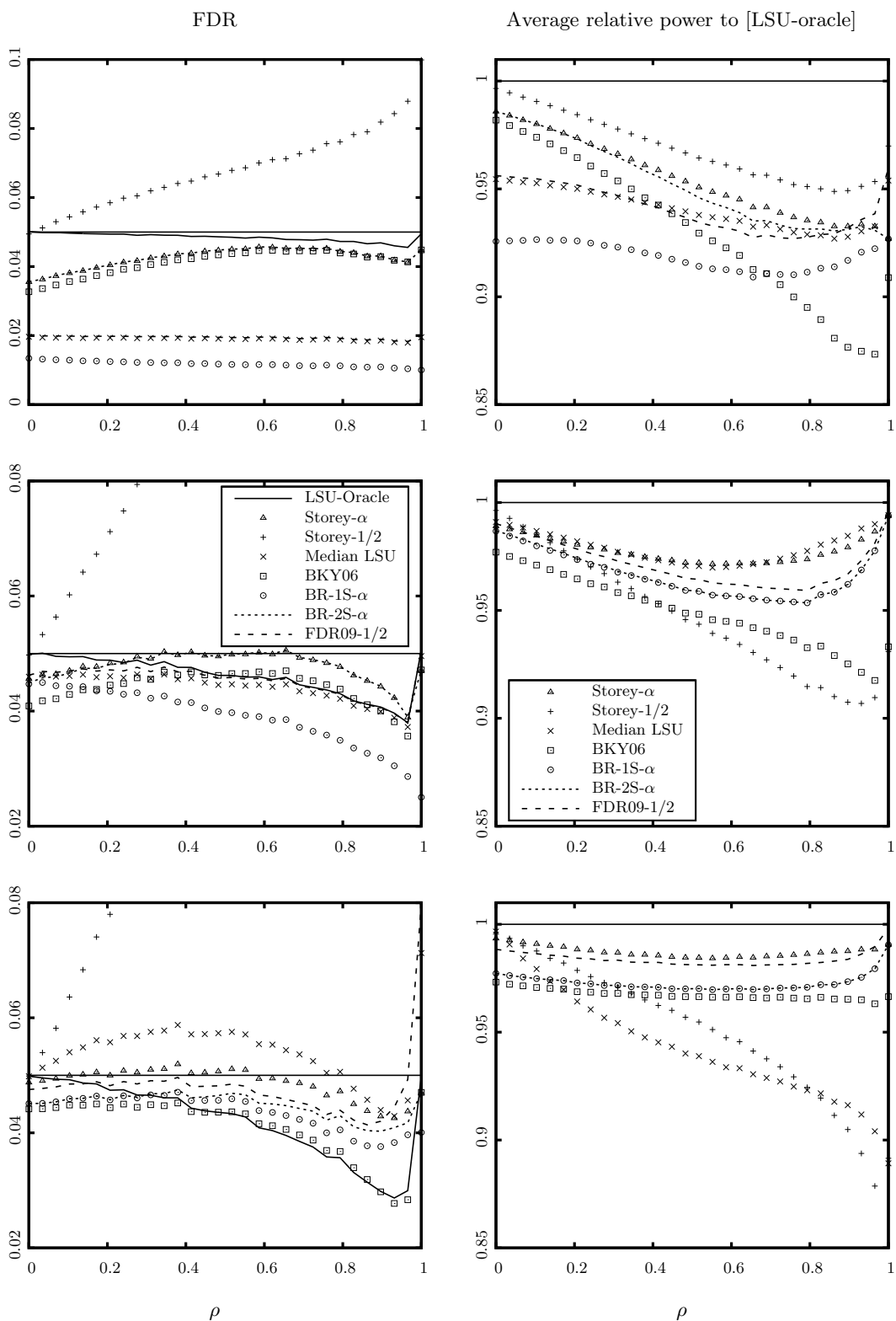




**Fig. 2.** FDR and power relative to oracle as a function of the true proportion  $\pi_0$  of null hypotheses. Target FDR is  $\alpha = 5\%$ , total number of hypotheses  $m = 100$ . The mean for the alternatives is  $\bar{\mu} = 3$ . From top to bottom: pairwise correlation coefficient  $\rho \in \{0, 0.2, 0.5\}$ .



**Fig. 3.** FDR and power relative to oracle as a function of the common alternative hypothesis mean  $\bar{\mu}$ . Target FDR is  $\alpha = 5\%$ , total number of hypotheses  $m = 100$ . The proportion of true null hypotheses is  $\pi_0 = 0.5$ . From top to bottom: pairwise correlation coefficient  $\rho \in \{0, 0.2, 0.5\}$ .



**Fig. 4.** FDR and power relative to oracle as a function of the pairwise correlation coefficient  $\rho$ . Target FDR is  $\alpha = 5\%$ , total number of hypotheses  $m = 100$ . The mean for the alternatives is  $\bar{\mu} = 3$ . From top to bottom: proportion of true null hypotheses  $\pi_0 \in \{0.2, 0.5, 0.8\}$ .

*Remark 3.10.* Another 2-stage adaptive procedure was introduced in Sarkar (2008a), which is very similar to a plug-in procedure using [Storey- $\lambda$ ]. In fact, in the experiments presented in Sarkar (2008a), the two procedures are almost equivalent, corresponding to  $\lambda = 0.995$ . We decided not to include this additional procedure in our simulations to avoid overloading the plots. Qualitatively, we observed that the procedures of Sarkar (2008a) or [Storey-0.995] are very similar in behavior to [Storey- $\frac{1}{2}$ ]: very performant in the independent case but very fragile with respect to deviations from independence.

*Remark 3.11.* One could formulate the concern that the observed FDR control for [Storey- $\alpha$ ] could possibly fail with other parameters settings, for example when  $\pi_0$  and/or  $\rho$  are close to one. We performed additional simulations to this regard, which we summarize briefly here. We considered the following cases:  $\pi_0 = 0.95$  and varying  $\rho \in [0, 1]$ ;  $\rho = 0.95$  and varying  $\pi \in [0, 1]$ ; finally  $(\pi_0, \rho)$  varying both in  $[0.8, 1]^2$ , using a finer discretization grid to cover this region in more detail. In all the above cases Storey- $\alpha$  still had its FDR very close to (or below)  $\alpha$ . Note also that the case  $\rho \simeq 1$  and  $\pi_0 \simeq 1$  is in accordance with the result of Section 3.3, stating that  $\text{FDR}(\text{Storey-}\alpha) = \alpha$  when  $\rho = 1$  and  $\pi_0 = 1$ . Finally, we also performed additional experiments for different choices of the number of hypotheses to test ( $m = 20$  and  $m = 10^4$ ) and different choices of the target level ( $\alpha = 10\%, 1\%$ ). In all of these cases were the results qualitatively in accordance with the ones already presented here.

## 4 New adaptive procedures with provable FDR control under arbitrary dependence

In this section, we consider from a theoretical point of view the problem of constructing multiple testing procedures that are adaptive to  $\pi_0$  under arbitrary dependence conditions of the  $p$ -values. The derivation of adaptive procedures that have provably controlled FDR under dependences appears to have been only studied scarcely (see Sarkar, 2008a, and Farcomeni, 2007). Here, we propose to use a 2-stage procedure where the first stage is a multiple testing with either controlled FWER or controlled FDR. The first option is relatively straightforward and is intended as a reference. In the second case, we use Markov's inequality to estimate  $\pi_0^{-1}$ . Since Markov's inequality is general but not extremely precise, the resulting procedures are obviously quite conservative and are arguably of a limited practical interest. However, we will show that they still provide an improvement, in a certain regime, with respect to the (non-adaptive) LSU procedure in the PRDS case and with respect to the family of (non-adaptive) procedures proposed in Theorem 2.7 in the arbitrary dependences case.

For the purposes of this section, we first recall the formal definition for PRDS dependence of Benjamini and Yekutieli (2001):

**Definition 4.1 (PRDS condition).** *Remember that a set  $D \subset [0, 1]^{\mathcal{H}}$  is said to be non-decreasing 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 any non-decreasing measurable 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 non-decreasing.*

On the one hand, it was proved by Benjamini and Yekutieli (2001) that the LSU still has controlled FDR at level  $\pi_0\alpha$  (i.e., Theorem 2.6 still holds) under the PRDS assumption. On the other hand, under totally arbitrary dependences this result does not hold, and Theorem 2.7 provides a family of threshold collection resulting in controlled FDR at the same level in this case.

Our first result concerns a two-stage procedure where the first stage  $R_0$  is any multiple testing procedure with controlled FWER, and where we (over-) estimate  $m_0$  via the straightforward estimator  $(m - |R_0|)$ . This should be considered as a form of baseline reference for this type of two-stage procedure.

**Theorem 4.2.** *Let  $R_0$  be a non-increasing multiple testing procedure and assume that its FWER is controlled at level  $\alpha_0$ , that is,  $\mathbb{P}[R_0 \cap \mathcal{H}_0 \neq \emptyset] \leq \alpha_0$ . Then the adaptive step-up procedure  $R$*

with data-dependent threshold collection  $\Delta(i) = \alpha_1(m - |R_0|)^{-1}\beta(i)$  has FDR controlled at level  $\alpha_0 + \alpha_1$  in either of the following dependence situations:

- the  $p$ -values  $(p_h, h \in \mathcal{H})$  are PRDS on  $\mathcal{H}_0$  and the shape function is the identity function.
- the  $p$ -values have unspecified dependences and  $\beta$  is a shape function of the form (4).

Here it is clear that the price for adaptivity is a certain loss in FDR control for being able to use the information of the first stage. If we choose  $\alpha_0 = \alpha_1 = \alpha/2$ , then this procedure will outperform its non-adaptive counterpart (using the same shape function) only if there are more than 50%, rejected hypotheses in the first stage. Only if it is expected that this situation will occur does it make sense to employ this procedure, since it will otherwise perform worse than the non-adaptive procedure.

Our second result is a two-stage procedure where the first stage has controlled FDR. First introduce, for a fixed constant  $\kappa \geq 2$ , the following function: for  $x \in [0, 1]$ ,

$$F_\kappa(x) = \begin{cases} 1 & \text{if } x \leq \kappa^{-1} \\ \frac{2\kappa^{-1}}{1 - \sqrt{1 - 4(1-x)\kappa^{-1}}} & \text{otherwise} \end{cases} \quad (9)$$

If  $R_0$  denotes the first stage, we propose using  $F_\kappa(|R_0|)$  as an (under-)estimation of  $\pi_0^{-1}$  at the second stage. We obtain the following result:

**Theorem 4.3.** *Let  $\beta$  be a fixed shape function, and  $\alpha_0, \alpha_1 \in (0, 1)$  such that  $\alpha_0 \leq \alpha_1$ . Denote by  $R_0$  the step-up procedure with threshold collection  $\Delta_0(i) = \alpha_0\beta(i)/m$ . Then the adaptive step-up procedure  $R$  with data-dependent threshold collection  $\Delta_1(i) = \alpha_1\beta(i)F_\kappa(|R_0|/m)/m$  has FDR upper bounded by  $\alpha_1 + \kappa\alpha_0$  in either of the following dependence situations:*

- the  $p$ -values  $(p_h, h \in \mathcal{H})$  are PRDS on  $\mathcal{H}_0$  and the shape function is the identity function.
- the  $p$ -values have unspecified dependences and  $\beta$  is a shape function of the form (4).

For instance, in the PRDS case, the procedure  $R$  of Theorem 4.3 with  $\kappa = 2$ ,  $\alpha_0 = \alpha/4$  and  $\alpha_1 = \alpha/2$ , is the adaptive linear step-up procedure at level  $\alpha/2$  with the following estimator for  $\pi_0^{-1}$ :

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

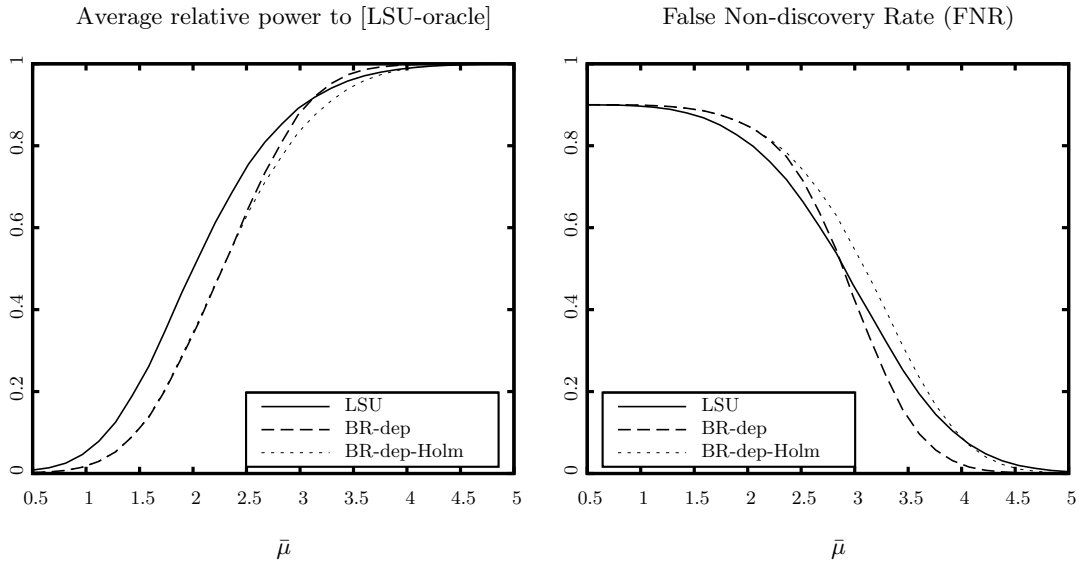
where  $|R_0|$  is the number of rejections of the LSU procedure at level  $\alpha/4$  and  $(\cdot)_+$  denotes the positive part.

Whether in the PRDS or arbitrary dependences case, with the above choice of parameters, we note that  $R$  is less conservative than the non-adaptive step-up procedure with threshold collection  $\Delta(i) = \alpha\beta(i)/m$  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 threshold collection with respect to the standard one-stage version. Therefore, here again this adaptive procedure is only useful in the cases where it is expected that a “large” proportion of null hypotheses can easily be rejected. In particular, when we use Theorem 4.3 in the distribution-free case, it is relevant to choose the shape function  $\beta$  from a prior distribution  $\nu$  concentrated on the large numbers of  $\{1, \dots, m\}$ . Finally, note that it is not immediate to see if this procedure will improve on the one of Theorem 4.2. Namely, with the above choice parameters, it has to reject more hypotheses in the first step than the procedure of Theorem 4.2 in order to beat the LSU, and the first step is performed at a smaller target level. However, since the first step only controls the FDR, and not the FWER, it can actually be much less conservative.

To explore this issue, we performed limited experiments in a favorable situation to test the two above procedures, i.e. with a small  $\pi_0$ . Namely, we considered the simulation setting of Section 3.4 with  $\rho = 0.1$ ,  $m_0 = 100$  and  $m = 1000$  (hence  $\pi_0 = 10\%$ ) and  $\alpha = 5\%$ . The common value  $\bar{\mu}$  of the positive means varies in the range  $[0, 5]$ . Larger values of  $\bar{\mu}$  correspond to a very large proportion of hypotheses that are easy to reject, which favors the first stage of the two above procedures.

A positively correlated family of Gaussians satisfies the PRDS assumption (see Benjamini and Yekutieli (2001)), so that we use the identity shape function (linear step-up), and compare our procedures against the standard LSU. For the FWER-controlled first stage of Theorem 4.2, we chose a standard Holm procedure Holm (1979), which is a step-down procedure with threshold family  $t(i) = \alpha m / (m - i + 1)$ . In Figure 5, we report the average relative power to the oracle LSU, and the False Non-discovery Rate (FNR), which is the converse of the FDR for type II errors, i.e., the average of the ratio of non-rejected false hypotheses over the total number of non-rejected hypotheses. Since we are in a situation where  $\pi_0$  is small, the FNR might actually be a more relevant criterion than the raw power: in this situation, because of the small number of non-rejected hypotheses, two different procedures could have their power very similar and close to 1, but noticeably different FNRs.

The conclusion is that there exists an (unfortunately relatively small) region where the adaptive procedures improve over the standard LSU in terms of power. In terms of FNR, the improvement is more noticeable and over a larger region. Finally, our two-step adaptive procedure of Theorem 4.3 appears to outperform consistently the baseline of Theorem 4.2. These results are still unsatisfying to the extent that the adaptive procedure improves over the non-adaptive one only in a region limited to some quite particular cases, and underperforms otherwise. Nevertheless, this demonstrates theoretically the possibility of provably adaptive procedures under dependence. Again, this theme appears to have been theoretically studied in only a handful of previous works until now, and improving significantly the theory in this setting is still an open challenge.



**Fig. 5.** Relative power to oracle and false non-discovery rate (FNR) of the different procedures, as a function of the common alternative hypothesis mean  $\bar{\mu}$ . Parameters are  $\alpha = 5\%$ ,  $m = 1000$ ,  $\pi_0 = 10\%$ ,  $\rho = 0.1$ . “BR08-dep-Holm” corresponds to the procedure of Theorem 4.2 using  $\alpha_1 = \alpha_0 = \alpha/2$  and Holm’s step-down for the first step, and “BR08-dep” to the procedure of Theorem 4.3 with  $\kappa = 2$ ,  $\alpha_0 = \alpha/4$  and  $\alpha_1 = \alpha/2$ . The shape function  $\beta$  is the identity function. Each point is an average over  $10^4$  independent repetitions.

*Remark 4.4.* Some theoretical results for two-stage procedures under possible dependences using a first stage with controlled FWER or controlled FDR appeared earlier (Farcomeni, 2007). However, it appears that in this reference, it is implicitly assumed that the two stages are actually independent, because the proof relies on a conditioning argument wherein FDR control for the

second stage still holds conditionally to the first stage output. This is the case for example if the two stages are performed on separate families of  $p$ -values corresponding to a new independent observation. Here we specifically wanted to take into account that we use the same collection of  $p$ -values for the two stages, and therefore that the two stages cannot assumed to be independent. In this sense our results are novel with respect to those of Farcomeni (2007).

*Remark 4.5.* The theoretical problem of adaptive procedures under arbitrary dependences was also considered by Sarkar (2008a) using two-stage procedures. However, the procedures proposed there were reported not to yield any significant improvement over non-adaptive procedures. In fact, in the explicit procedures proposed by Sarkar (2008a), it can be seen that there exists a function  $\beta$  of the form (4) such that the second stage is always more conservative (and sometimes by a large factor) than the non-adaptive step-up procedure with threshold collection  $\Delta(i) = \alpha\beta(i)/m$ , which has FDR bounded by  $\pi_0\alpha$  (see Theorem 2.7).

## 5 Conclusion and discussion

We proposed several adaptive multiple testing procedures that provably control the FDR under different hypotheses on the dependence of the  $p$ -values. Firstly, we introduced the one- and two-stage procedures *BR-1S* and *BR-2S* and we proved their theoretical validity when the  $p$ -values are independent. The procedure *BR-2S* is less conservative in general (except in marginal situations) than the adaptive procedure proposed by Benjamini et al. (2006). Extensive simulations showed that these new procedures appear to be robustly controlling the FDR even in a positive dependence situation, which is a very desirable property in practice. This is an advantage with respect to the [Storey- $\frac{1}{2}$ ] procedure, which is less conservative but breaks down under positive dependences. Moreover, our simulations showed that the choice of parameter  $\lambda = \alpha$  instead of  $\lambda = 1/2$  in the Storey procedure resulted in a much more robust procedure under positive dependences, at the price of being slightly more conservative. This fact is supported by a theoretical investigation of the maximally dependent case. These properties do not appear to have been reported before, and put forward Storey- $\alpha$  as a procedure of considerable practical interest.

Secondly, we presented what we think is among the first examples of adaptive multiple testing procedures with provable FDR control in the PRDS and distribution-free cases. An important difference with respect to earlier works on this topic is that the procedures we introduced here are both theoretically founded and can be shown to improve on non-adaptive procedures in certain (admittedly limited) circumstances. Although their interest at this point is mainly theoretical, this shows in principle that adaptivity can improve performance in a theoretically rigorous way even without the independence assumption.

The proofs of the results have been built upon the notion of *self-consistency* and other technical tools introduced in a previous work (Blanchard and Roquain, 2008). We believe these tools allow for a more unified approach than in the classical adaptive multiple testing literature, avoiding in particular to deal explicitly with the reordered  $p$ -values, which can be somewhat cumbersome.

Another advantage of this approach is that it can be extended in a relatively straightforward manner to the case of *weighted FDR*, that is, the quantity (2) where the cardinality measure  $|\cdot|$  has been replaced by a general measure  $W(R) = \sum_{h \in R} w_h$  (with  $W(\mathcal{H}) = \sum_{h \in \mathcal{H}} w_h = m$ ). This allows in particular to recover results very similar to those of Benjamini and Heller (2007) and can also be used to prove that a (generalized) Storey estimator can be used to control the weighted FDR. The modifications needed to include this generalizations are relatively minor; we omit the details here and refer the reader to Blanchard and Roquain (2008) to see how the case of weighted FDR can be handled using the same technical tools.

There remains a vast number of open issues concerning adaptive procedures. We first want to underline once more that the theory for adaptive procedures under dependence is still underdeveloped. It might actually be too restrictive to look for procedures having theoretically controlled FDR uniformly over arbitrary dependence situations such as what we studied in Section 4. An interesting future theoretical direction could be to prove that some of the adaptive procedures

showing good robustness in our simulations actually have controlled FDR under some types of dependence, at least when the  $p$ -values are in some sense not too far from being independent.

## 6 Proofs of the results

### 6.1 Proofs for Section 3

The following proofs use the notations  $\mathbf{p}_{0,h}$  and  $\mathbf{p}_{-h}$  defined at the beginning of Section 3.2.

**Proof of Theorem 3.1.** Let  $R$  denote a non-increasing self-consistent procedure with respect to  $\Delta$  defined in (5); by definition  $R$  satisfies

$$R \subset \left\{ h \in \mathcal{H} \mid p_h \leq \min \left( (1 - \lambda) \frac{\alpha |R|}{m - |R| + 1}, \lambda \right) \right\}.$$

Therefore, we have

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

The second inequality above comes from  $|R(\mathbf{p})| \leq |R(\mathbf{p}_{0,h})|$ , which itself holds because  $|R|$  is coordinate-wise non-increasing in each  $p$ -value. The last inequality is obtained with Lemma 7.1 of Section 7 with  $U = p_h$ ,  $g(U) = |R(\mathbf{p}_{-h}, U)|$  and  $c = \frac{(1-\lambda)\alpha}{m - |R(\mathbf{p}_{0,h})| + 1}$ , because the distribution of  $p_h$  conditionnally to  $\mathbf{p}_{-h}$  is stochastically lower bounded by a uniform distribution,  $|R|$  is coordinate-wise non-increasing and because  $\mathbf{p}_{0,h}$  depends only on the  $p$ -values of  $\mathbf{p}_{-h}$ . Finally, since the threshold collection of  $R$  is upper bounded by  $\lambda$ , we get

$$(1 - \lambda) \mathbb{E} [m / (m - |R(\mathbf{p}_{0,h})| + 1)] \leq \mathbb{E} G_1(\mathbf{p}_{0,h}),$$

where  $G_1$  is the Storey estimator with parameter  $\lambda$ . We then use  $\mathbb{E} G_1(\mathbf{p}_{0,h}) \leq \pi_0^{-1}$  (see proof of Corollary 3.4) to conclude.  $\blacksquare$

**Proof of Lemma 3.2.** Denote  $G(t) = \pi_0 t + (1 - \pi_0) F(t)$  the cdf of the  $p$ -values under the random effects mixture model. Let us denote by  $\hat{t}_m$  the threshold of the LSU procedure. The proportion of rejected hypotheses from the initial pool is then exactly  $\hat{G}_m(\hat{t}_m)$ , where  $\hat{G}_m$  is the empirical cdf of the  $p$ -values. It was proved by Genovese and Wasserman (2002) under the random effects model, that as  $m$  tends to infinity the LSU threshold  $\hat{t}_m$  converges in probability to  $t^*$ , which is the largest point  $t \in [0, 1]$  such that  $G(t) = \alpha^{-1} t$ . Since  $\hat{G}_m$  converges in probability uniformly to  $G$ , we deduce that the proportion of rejected hypotheses converges to  $\alpha^{-1} t^*$  in probability; hence, if  $t^* > \alpha^2$ , the probability that the proportion of rejected hypotheses is less than  $\alpha + 1/m$  converges to zero; and conversely converges to 1 if  $t^* < \alpha^2$ .



The definition of  $t^*$  and the expression for  $G$  in the Gaussian mean shift model imply the following relation whenever  $t^* > 0$ :

$$\mu = \bar{\Phi}^{-1}(t^*) - \bar{\Phi}^{-1}\left(\frac{\alpha^{-1} - \pi_0}{1 - \pi_0} t^*\right).$$

It is easily seen that if  $\pi_0 < (1 + \alpha)^{-1}$ , the quantity  $\mu^*$  in the statement of the lemma is well defined and we have  $t^* > \alpha^2$  for  $\mu > \mu^*$ . This gives the first part of the result.

Conversely, if  $\pi_0 > (1 + \alpha)^{-1}$  we have  $t^* = 0$ , and if  $\pi_0 < (1 + \alpha)^{-1}$  but  $\mu < \mu^*$ , we have  $t^* < \alpha^2$ ; this leads to the second part of the result.  $\blacksquare$

**Proof of Theorem 3.3.** By definition of self-consistency, the procedure  $R$  satisfies

$$R \subset \{h \in \mathcal{H} \mid p_h \leq \alpha |R| G(\mathbf{p})/m\}.$$

Therefore,

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

Since  $G$  is non-increasing, we get:

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

The last step is obtained with Lemma 7.1 of Section 7 with  $U = p_h$ ,  $g(U) = |R(\mathbf{p}_{-h}, U)|$  and  $c = \alpha G(\mathbf{p}_{0,h})/m$ , because the distribution of  $p_h$  conditionnally to  $\mathbf{p}_{-h}$  is stochastically lower bounded by a uniform distribution,  $|R|$  is coordinate-wise non-increasing and  $\mathbf{p}_{0,h}$  depends only on the  $p$ -values of  $\mathbf{p}_{-h}$ .  $\blacksquare$

**Proof of Corollary 3.4.** We prove that the sufficient condition of Theorem 3.3 holds for the nonincreasing estimators  $G_i$ ,  $i = 1, 2, 3, 4$ . To that end, we reproduce here without major changes the arguments used by Benjamini et al. (2006). The bound for  $G_1$  is obtained using Lemma 7.4 (see below) with  $k = m_0$  and  $q = 1 - \lambda$ : for all  $h \in \mathcal{H}_0$ ,

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

The proof for  $G_3$  and  $G_4$  is deduced from the one of  $G_1$  because  $G_3 \leq G_4 \leq G_1$  pointwise.

Let us prove that  $\mathbb{E}G_2(\mathbf{p}_{0,h}) \leq \pi_0^{-1}$ , for any  $h \in \mathcal{H}_0$  and any  $k_0 \in \{1, \dots, m\}$ . If  $k_0 \leq m_1 + 1$ , the result is trivial. Suppose now  $k_0 > m_1 + 1$ . Introduce the following auxiliary notation: for  $\mathbf{p}$  a family of  $p$ -values indexed by  $\mathcal{H}$ , and a subset  $B \subset \mathcal{H}$ , denote by  $S(i, \mathbf{p}, B)$  the  $i$ -th ordered  $p$ -value of the subfamily  $(x'_h)_{h' \in B}$ . Pointwise,  $G_2$  can be rewritten as:

$$\begin{aligned} G_2(\mathbf{p}_{0,h}) &= \frac{m}{m+1-k_0} \left( 1 - S(k_0, \mathbf{p}_{0,h}, \mathcal{H}) \right) \\ &= \frac{m}{m+1-k_0} \left( 1 - S(k_0 - 1, \mathbf{p}, \mathcal{H} \setminus \{h\}) \right) \\ &\leq \frac{m}{m+1-k_0} \left( 1 - S(k_0 - 1 - m + m_0, \mathbf{p}, \mathcal{H}_0 \setminus \{h\}) \right), \end{aligned}$$

the latter coming from the relation  $S(i, \mathbf{p}, A) \geq S(i - |A \setminus B|, \mathbf{p}, B)$ , for every finite sets  $B \subsetneq A$  and integer  $i > |A \setminus B|$ . Therefore, using that  $m_0 - 1$  independent random variables with marginal distributions stochastically lower bounded by a uniform law have a  $j$ -largest value on average larger than  $j/m_0$ , we obtain:

$$\mathbb{E}G_2(\mathbf{p}_{0,h}) \leq \frac{m}{m+1-k_0} \left( 1 - \frac{k_0 - 1 - m + m_0}{m_0} \right) = \pi_0^{-1}.$$

■

**Proof of Proposition 3.8.** Let us first consider adaptive one-stage procedures: for any step-up procedure  $R$  of threshold  $\Delta(i) = \alpha\beta(i)/m$  we easily derive that the probability that  $R$  makes any rejection is

$$\mathbb{P}[\exists i \mid p_i \leq \Delta(i)] = \mathbb{P}[\exists i \mid p_1 \leq \Delta(i)] = \mathbb{P}[p_1 \leq \Delta(m)] = \Delta(m),$$

which is  $\text{FDR}(R)$  because  $m_0 = m$ . The results for  $BR-1S-\lambda$  and  $FDR09-\eta$  follow.

With the same reasoning, we find that for any plug-in adaptive linear step-up procedure  $R$  that uses an estimator  $G(\mathbf{p})$ ,

$$\text{FDR}(R) = \mathbb{P}[p_1 \leq \alpha G(\mathbf{p})]. \quad (10)$$

Next, for the Storey plug-in procedure, we have  $G_1(p_1, \dots, p_1) = (1 - \lambda)m/(m\mathbf{1}\{p_1 > \lambda\} + 1)$ , so that applying (10), we get

$$\begin{aligned} \text{FDR}(\text{Storey-}\lambda) &= \mathbb{P}[p_1 \leq \alpha G_1(\mathbf{p})] \\ &= \mathbb{P}[p_1 \leq \lambda, p_1 \leq \alpha(1 - \lambda)m] + \mathbb{P}[p_1 > \lambda, p_1 \leq \alpha(1 - \lambda)m/(m + 1)] \\ &= \min\left(\lambda, \alpha(1 - \lambda)m\right) + \left(\frac{\alpha(1 - \lambda)m}{m + 1} - \lambda\right)_+. \end{aligned}$$

For the quantile procedure, we have

$$\mathbb{P}[p_1 \leq \alpha(1 - p_1)m/(m - k_0 + 1)] = \mathbb{P}[p_1((1 + \alpha)m - k_0 + 1) \leq \alpha m] = \frac{\alpha}{1 + \alpha - (k_0 - 1)/m}.$$

For the BKY06 procedure, we simply remark that since the linear step-up procedure of level  $\lambda$  rejects all the hypotheses when  $p_1 \leq \lambda$  and rejects no hypothesis otherwise, the estimator  $G_1$  and  $G_3$  are equal in this case. The proof for  $BR-2S-\lambda$  is similar. ■

## 6.2 Proofs for Section 4

We begin with a technical lemma that will be useful for proving both Theorem 4.2 and 4.3. It is related to techniques previously introduced by Blanchard and Roquain (2008).

**Lemma 6.1.** *Assume  $R$  is a multiple testing procedure satisfying the self-consistency condition:*

$$R \subset \{h \in \mathcal{H} \mid p_h \leq \alpha G(\mathbf{p})\beta(|R|)/m\},$$

where  $G(\mathbf{p})$  is a data-dependent factor. Then the following inequality holds:

$$\text{FDR}(R) \leq \alpha + \mathbb{E} \left[ \frac{|R \cap \mathcal{H}_0|}{|R|} \mathbf{1}\{|R| > 0\} \mathbf{1}\{G(\mathbf{p}) > \pi_0^{-1}\} \right], \quad (11)$$

under either of the following conditions:

- the  $p$ -values  $(p_h, h \in \mathcal{H})$  are PRDS on  $\mathcal{H}_0$ ,  $R$  is non-increasing and  $\beta$  is the identity function.
- the  $p$ -values have unspecified dependences and  $\beta$  is a shape function of the form (4).

**Proof.** We have

$$\begin{aligned}
\text{FDR}(R) &= \mathbb{E} \left[ \frac{|R \cap \mathcal{H}_0|}{|R|} \mathbf{1}_{\{|R| > 0\}} \right] \\
&= \mathbb{E} \left[ \frac{|R \cap \mathcal{H}_0|}{|R|} \mathbf{1}_{\{|R| > 0\}} \mathbf{1}_{\{G \leq \pi_0^{-1}\}} \right] + \mathbb{E} \left[ \frac{|R \cap \mathcal{H}_0|}{|R|} \mathbf{1}_{\{|R| > 0\}} \mathbf{1}_{\{G > \pi_0^{-1}\}} \right] \\
&\leq \sum_{h \in \mathcal{H}_0} \mathbb{E} \left[ \frac{\mathbf{1}_{\{p_h \leq \alpha \beta(|R|)/m_0\}}}{|R|} \right] + \mathbb{E} \left[ \frac{|R \cap \mathcal{H}_0|}{|R|} \mathbf{1}_{\{|R| > 0\}} \mathbf{1}_{\{G > \pi_0^{-1}\}} \right].
\end{aligned}$$

The desired conclusion will therefore hold if we establish that for any  $h \in \mathcal{H}_0$ , and  $c > 0$ :

$$\mathbb{E} \left[ \frac{\mathbf{1}_{\{p_h \leq c \beta(|R|)\}}}{|R|} \right] \leq c.$$

In the distribution-free case, this is a direct consequence of Lemma 7.3 of Section 7 with  $U = p_h$  and  $V = \beta(|R|)$ . For the PRDS case, we note that since  $|R(\mathbf{p})|$  is coordinate-wise nonincreasing in each  $p$ -value, for any  $v > 0$ ,  $D = \{\mathbf{z} \in [0, 1]^{\mathcal{H}} \mid |R(\mathbf{z})| < v\}$  is a measurable non-decreasing set, so that the PRDS property implies that  $u \mapsto \mathbb{P}(|R| < v \mid p_h = u)$  is non-decreasing. This implies that  $u \mapsto \mathbb{P}(|R| < v \mid p_h \leq u)$  by the following argument (see also Lehmann, 1966, cited by Benjamini and Yekutieli, 2001, and Blanchard and Roquain, 2008): putting  $\gamma = \mathbb{P}[p_h \leq u \mid p_h \leq u']$ ,

$$\begin{aligned}
\mathbb{P}[\mathbf{p} \in D \mid p_h \leq u'] &= \mathbb{E}[\mathbb{P}[\mathbf{p} \in D \mid p_h] \mid p_h \leq u'] \\
&= \gamma \mathbb{E}[\mathbb{P}[\mathbf{p} \in D \mid p_h] \mid p_h \leq u] + (1 - \gamma) \mathbb{E}[\mathbb{P}[\mathbf{p} \in D \mid p_h] \mid u < p_h \leq u'] \\
&\geq \mathbb{E}[\mathbb{P}[\mathbf{p} \in D \mid p_h] \mid p_h \leq u] = \mathbb{P}[\mathbf{p} \in D \mid p_h \leq u].
\end{aligned}$$

We can then apply Lemma 7.2 of Section 7 with  $U = p_h$  and  $V = |R|$ . ■

**Proof of Theorem 4.2.** By definition of a step-up procedure, the two-stage procedure  $R$  satisfies the assumption of Lemma 6.1 for  $G(\mathbf{p}) = (1 - \frac{|R_0|}{m})^{-1}$ , where  $R_0$  is the first stage with FWER controlled at level  $\alpha_0$ . Furthermore, it is easy to check that  $|R|$  is nonincreasing as a function of each  $p$ -value (since  $|R_0|$  is). Then, we can apply Lemma 6.1, and from inequality (11) we deduce

$$\begin{aligned}
\text{FDR}(R) &\leq \alpha_1 + \mathbb{E} \left[ \frac{|R \cap \mathcal{H}_0|}{|R|} \mathbf{1}_{\left\{1 - \frac{|R_0|}{m} < \pi_0\right\}} \right] \\
&\leq \alpha_1 + \mathbb{P}[R_0 \cap \mathcal{H}_0 \neq \emptyset] \\
&\leq \alpha_0 + \alpha_1.
\end{aligned}$$

In the case where  $R_0$  rejects all hypotheses, we assumed implicitly that the second stage also does. ■

**Proof of Theorem 4.3.** Assume  $\pi_0 > 0$  (otherwise the result is trivial). By definition of a step-up procedure, the two-stage procedure  $R$  satisfies the assumption of Lemma 6.1 for  $G(\mathbf{p}) = F_\kappa(|R_0|/m)$ , where  $R_0$  is the first stage. Furthermore, it is easy to check that  $|R|$  is nonincreasing as a function of each  $p$ -value (since  $|R_0|$  is). Then, we can apply Lemma 6.1, and from inequality (11) we deduce

$$\begin{aligned}
\text{FDR}(R) &\leq \alpha_1 + \mathbb{E} \left[ \frac{|R \cap \mathcal{H}_0|}{|R|} \mathbf{1}_{\{F_\kappa(|R_0|/m) > \pi_0^{-1}\}} \right] \\
&\leq \alpha_1 + m_0 \mathbb{E} \left[ \frac{\mathbf{1}_{\{F_\kappa(|R_0|/m) > \pi_0^{-1}\}}}{|R_0|} \right]
\end{aligned}$$

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

(i)  $F_\kappa(|R_0|/m) > \pi_0^{-1}$  implies  $|R_0| > 0$ ,

(ii) because of the assumption  $\alpha_0 \leq \alpha_1$  and  $F_\kappa \geq 1$ , 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  $F_\kappa$ ,  $F_\kappa^{-1}(t) = \inf \{x \mid F_\kappa(x) > t\}$ . Since  $F_\kappa$  is a non-decreasing left-continuous function, we have  $F_\kappa(x) > t \Leftrightarrow x > F_\kappa^{-1}(t)$ . Furthermore, the expression of  $F_\kappa^{-1}$  is given by:  $\forall t \in [1, +\infty)$ ,  $F_\kappa^{-1}(t) = \kappa^{-1}t^{-2} - t^{-1} + 1$  (providing in particular that  $F_\kappa^{-1}(\pi_0^{-1}) > 1 - \pi_0$ ). Hence

$$\begin{aligned} m_0 \mathbb{E} \left[ \frac{\mathbf{1} \{F_\kappa(|R_0|/m) > \pi_0^{-1}\}}{|R_0|} \right] &\leq m_0 \mathbb{E} \left[ \frac{\mathbf{1} \{|R_0|/m > F_\kappa^{-1}(\pi_0^{-1})\}}{|R_0|} \right] \\ &\leq \frac{\pi_0}{F_\kappa^{-1}(\pi_0^{-1})} \mathbb{P} [|R_0|/m \geq F_\kappa^{-1}(\pi_0^{-1})] . \end{aligned} \quad (12)$$

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

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

choosing  $t = F_\kappa^{-1}(\pi_0^{-1})$  and using this into (12), we obtain

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

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

## 7 Probabilistic lemmas

The three following lemmas have been established in a previous work (see Blanchard and Roquain, 2008, Lemma 3.2).

**Lemma 7.1.** *Let  $g : [0, 1] \rightarrow (0, \infty)$  be a non-increasing function. Let  $U$  be a random variable which has a distribution stochastically lower bounded by a uniform distribution, that is,  $\forall u \in [0, 1]$ ,  $\mathbb{P}(U \leq u) \leq u$ . Then, for any constant  $c > 0$ , we have*

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

**Lemma 7.2.** *Let  $U, V$  be two non-negative real variables. Assume the following:*

1. *The distribution of  $U$  is stochastically lower bounded by a uniform distribution, that is,  $\forall u \in [0, 1]$ ,  $\mathbb{P}(U \leq u) \leq u$ .*

2. The conditional distribution of  $V$  given  $U \leq u$  is stochastically decreasing in  $u$ , that is,

$$\forall v \geq 0 \quad \forall 0 \leq u \leq u', \quad \mathbb{P}(V < v \mid U \leq u) \leq \mathbb{P}(V < v \mid U \leq u').$$

Then, for any constant  $c > 0$ , we have

$$\mathbb{E} \left( \frac{\mathbf{1}\{U \leq cV\}}{V} \right) \leq c.$$

**Lemma 7.3.** Let  $U, V$  be two non-negative real variables and  $\beta$  be a function of the form (4). Assume that the distribution of  $U$  is stochastically lower bounded by a uniform distribution, that is,  $\forall u \in [0, 1], \mathbb{P}(U \leq u) \leq u$ . Then, for any constant  $c > 0$ , we have

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

The following lemma was stated by Benjamini et al. (2006). It is a major point when we estimate  $\pi_0^{-1}$  in the independent case. The proof is left to the reader.

**Lemma 7.4.** For any  $k \geq 2, q \in ]0, 1]$ , let  $Y$  be a binomial random variable with parameters  $(k - 1, q)$ ; then the following holds:

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

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