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► **To cite this version:**

| Etienne Roquain, Mark van de Wiel. Multi-weighting for FDR control. 2008. hal-00306219v1

HAL Id: hal-00306219

<https://hal.science/hal-00306219v1>

Preprint submitted on 25 Jul 2008 (v1), last revised 13 Jul 2009 (v3)

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Multi-weighting for FDR control

Étienne Roquain, Mark A. van de Wiel

July 25, 2008

Abstract

In the context of multiple hypothesis testing, we propose a new method of p -value weighting when controlling the false discovery rate (FDR). To deal with all the possible rejection numbers in the FDR, we consider a matrix of weights and we integrate it in a new class of procedures, called the “multi-weighted” procedures. First, we propose multi-weighted step-up and step-down procedures which control rigorously the FDR under independence, positive dependence (PRDS) and general dependence. Second, we propose a way to derive a weight matrix which is optimal in the sense of power. When the optimal weight matrix is reasonably well approached, we demonstrate in a simulation study that the corresponding multi-weighted procedures outperform the standard uniformly-weighted Benjamini-Hochberg procedure. Finally, we apply our method to the two sample multiple comparison problem, and we demonstrate its interest in practice with an application to microarray experiments.

1 Introduction

1.1 Generalities

In high dimensional data, e.g. functional Magnetic Resonance Imaging (fMRI) or microarray data, thousands of null hypotheses have to be tested at the same time. Therefore, many researches have focused on building multiple testing procedures. The *false discovery rate* (FDR) i.e. the expected proportion of erroneously rejected hypotheses among the rejected ones is the most popular one in practice because of its “scale-invariant” property.

The first proposed procedure that has a provably controlled FDR is the procedure of Benjamini-Hochberg (1995), also called the *linear step-up procedure* (**LSU**) [1]. The control was proved when the p -values p_1, \dots, p_m are assumed to be independent. Later, this procedure was proved to control the FDR under positive dependencies (PRDS, see [4]) and some other works show that this should also be the case under “realistic” general dependencies (see e.g. [10] and [18]). However, power is always a concern, so an important research field aims to increase power of the **LSU** procedure, while maintaining the FDR control.

1.2 The p -value weighting problem

In many practical situations, the p -values cannot be considered interchangeably, because we know *a priori* (e.g. from previous independent experiments) that some nulls are more likely to be rejected than others. A major problem is thus to find a convenient way to capture this prior information in order to improve the performance of the **LSU** procedure. Therefore, p -value weighting is currently an active research topic (see e.g. [27], [15]).

The idea of p -value weighting can be traced back to [16]. In general, any multiple testing procedure has a “ p -value weighted version”, defined as the original procedure but taking in input a set of the weighted p -values $(p'_1, \dots, p'_m) = (p_1/w_1, \dots, p_m/w_m)$ instead of the initial set of p -values (p_1, \dots, p_m) . For normalization, the possible weight vectors $\mathbf{w} = (w_1, \dots, w_m)$ are assumed to sum up to m , $\sum_{i=1}^m w_i = m$. Weighted procedures that will be studied in this paper are the weighted linear step-up procedures: for a given weight vector \mathbf{w} , the corresponding weighted linear step-up procedure $\mathbf{LSU}(\mathbf{w})$ procedure rejects the nulls with weighted p -value upper bounded by

$$\max\{p'_{(i)} \mid p'_{(i)} \leq \alpha i/m\}.$$

An important property of such p -value weighting principle is that this transformation maintains the desired type I error control for many classical multiple testing procedures. Recently, [15] and [7] have proved that for any weight vector \mathbf{w} , $\mathbf{LSU}(\mathbf{w})$ controls the FDR at level α , when the p -values are supposed independent or PRDS. When the p -values have unspecified dependencies, [5] and [7] proved that the FDR control is still provided for the weighted version of the Benjamini Yekutieli (2001) procedure.

Since it is possible to use *any* weight vector \mathbf{w} in $\mathbf{LSU}(\mathbf{w})$ for FDR control at a given level α , a main issue is to find the best weight vector, i.e. the one which maximizes the *power* of $\mathbf{LSU}(\mathbf{w})$, where the power is defined as the expected number of true discoveries. For multiple testing procedures using *deterministic* thresholds, [20] addressed this maximization problem in a quite general framework. However, such a power computation is very difficult to make for weighted step-wise procedures, even in the asymptotic framework where the number of p -values m tends to infinity (see [15]).

1.3 Contributions of the paper

In this paper, we propose new weighted procedures which optimize power while maintaining FDR control. Initially, our multi-weighted procedure simply replaces the ordinary weights \mathbf{w} by multi-weights $\mathbf{w}(r)$. We develop weight vectors $\mathbf{w}(r)$ that maximize the power of $\mathbf{LSU}(\mathbf{w})$ for a given rejection volume parameter r , and we collect all these optimal weight vectors in an *optimal weight matrix* $\mathbf{W} = (\mathbf{w}(r))_{1 \leq r \leq m}$. Both in the independent and dependent case it is necessary to adjust \mathbf{W} to $\widetilde{\mathbf{W}}$ somewhat in order to provide FDR control. The resulting weighted p -values $p'_i = p_i/\widetilde{w}_i(r)$ are integrated recursively into a linear step-up or step-down procedure, denoted by $\mathbf{LSU}(\widetilde{\mathbf{W}})$ and $\mathbf{LSD}(\widetilde{\mathbf{W}})$ respectively, which will be detailed later. Hence, we modify weighted linear step-wise procedures by introducing multi-weights that depend on the rejection volume.

When the p -values are independent, we first prove that both $\mathbf{LSU}(\widetilde{\mathbf{W}})$ and $\mathbf{LSD}(\widetilde{\mathbf{W}})$ control rigorously the FDR. Under positive regression dependency (PRDS), the FDR control will be still provided up to a more conservative modification for $\widetilde{\mathbf{W}}$ which is proven to be less conservative than the “Benjamini-Yekutieli (2001) correction”. Under unspecified dependencies, the FDR control is provided by replacing the conventional threshold $\alpha r/m$ by $\alpha\beta(r)/m$ where β is a function of a specific form. The proofs use recent techniques developed in [7], [11] and [12]. In particular, we will use that all the above procedures satisfy a “self-consistency” condition.

An important part of the present work will be to derive in a general setting an explicit formula for the weight vectors $\mathbf{w}(r)$, $r = 1, \dots, m$ defined above. The corresponding weight

matrix will be referred as the optimal weight matrix. We will then demonstrate the interest of the Gaussian case, by proving that it can be seen as the limit case of several non-Gaussian setting. This will allow us to use our new procedure for the two-sample multiple comparison problem using Mann-Whitney test statistics. When the sample sizes available to test each hypothesis are different, our new procedures will improve substantially the **LSU** procedure, as we will see on an application to microarray data.

Finally, an important property of the new procedures **LSU**($\widetilde{\mathbf{W}}$) and **LSD**($\widetilde{\mathbf{W}}$) will be that they behave like the best procedure among $\{\mathbf{LSU}(\mathbf{w}(r)), r = 1, \dots, m\}$, up to some remaining term (close to 0 when α is small). This means in other words that they are *adaptive* to the parameter r . We will exhibit this property on simulations.

The paper is organized as follows: Section 2 presents some preliminary definitions, and introduces multi-weighted procedures. The FDR control of the multi-weighted procedures is stated in Section 3 for a general form of weight matrix. Section 4 then deals with the weight matrix choice in the Gaussian and asymptotically Gaussian cases. The performances of the new procedures are exhibited in Section 5 using a simulation study. Our method is then extended to the random effects model in Section 6, to be applied to the two sample multiple comparison problem in Section 7, where an application to microarray data is also given. Several discussions and a conclusion are given in Section 8, while we gathered the technical proofs in Section 9. All computer programs are written in *R* and are available upon request.

2 Preliminaries

2.1 Setting

We consider the classical statistical multiple testing framework: let be $(\mathcal{X}, \mathfrak{X}, P)$ a probability space and let be a random variable X taking values in $(\mathcal{X}, \mathfrak{X})$ such that $X \sim P$. Let $(\mathcal{H}, \mathfrak{H})$ be a finite set of null hypotheses $(H_i, i \in \{1, \dots, m\})$ for the underlying distribution P . Each hypothesis is formally defined as a subset of distributions on $(\mathcal{X}, \mathfrak{X})$, and we say that this hypothesis is true if P belongs to the corresponding distribution set. We denote by $\mathcal{H}_0 = \{i \in \{1, \dots, m\} \mid H_i \text{ is true}\}$ the set corresponding to the true null hypotheses and by $m_0 = |\mathcal{H}_0|$ its cardinal. Analogously, we define $\mathcal{H}_1 = \{i \in \{1, \dots, m\} \mid H_i \text{ is false}\}$ and $m_1 = |\mathcal{H}_1|$ for the alternative hypotheses. Since \mathcal{H}_1 is the complement of \mathcal{H}_0 in $\{1, \dots, m\}$, we have $m_1 = m - m_0$.

We suppose that for any null hypothesis H_i , it is given a *p-value* p_i , i.e. a measurable function from $(\mathcal{X}, \mathfrak{X}, P)$ to $[0, 1]$ such that the distribution of $p_i(X)$ is uniform on $[0, 1]$ as soon as H_i is true:

$$\forall i \in \mathcal{H}_0, \forall t \in [0, 1], \mathbb{P}(p_i(X) \leq t) = t. \quad (1)$$

Under the alternative i.e. for i in \mathcal{H}_1 , we denote by F_i the cumulative distribution function of $p_i(X)$: $\forall t \in [0, 1], F_i(t) = \mathbb{P}(p_i(X) \leq t)$. In our setting, the F_i 's are allowed to be different.

A *multiple testing procedure* R is defined as an algorithm which, from the data, aims to reject part of the null hypotheses. Formally, a multiple testing procedure is defined as a function $R : x \in \mathcal{X} \mapsto R(x) \subset \{1, \dots, m\}$ such that for each i , $\mathbf{1}\{i \in R\}$ is measurable. The rejected null hypotheses are then the hypotheses H_i , for i in R . Below, we will consider, as is usually the case, multiple testing procedure R which can be written as function $\widetilde{R}(\mathbf{p})$ of the

family of p -values $\mathbf{p} = (p_i, i \in \{1, \dots, m\})$. We will always identify R and \tilde{R} in our notations, writing e.g. $R(\mathbf{p})$.

As introduced by [1], the false discovery rate (FDR) of a multiple testing procedure is defined as the average proportion of true hypotheses in the set of the rejected hypotheses:

$$\text{FDR}(R) = \mathbb{E} \left[\frac{|\mathcal{H}_0 \cap R(X)|}{|R(X)| \vee 1} \right]. \quad (2)$$

In the notations below, we will always drop the explicit dependency in X for short.

The problem of finding procedures that control the above quantities has been widely studied in the multiple testing literature (see e.g. [1, 4, 23, 14, 20, 3]). For this, various conditions on the p -values $(p_i, i \in \{1, \dots, m\})$ have been considered. In this paper, we will restrict our attention to the three following cases: the p -values are mutually independent; the p -values are PRDS on \mathcal{H}_0 ; the p -values have unspecified dependencies. One way to establish FDR control is to consider step-up and step-down procedures. They are defined in the following section.

2.2 Weighted step-up and step-down procedures

In this paper, we will use a general definition of a step-up and step-down procedures. First, define a *thresholding-based multiple testing procedure* as a level set of the p -values

$$L_\Delta(r) := \{i \mid p_i \leq \Delta(i, r)\}, \quad (3)$$

where r represents a *rejection volume* and $\Delta : (i, r) \in \{1, \dots, m\} \times \{0, 1, \dots, m\} \mapsto \Delta(i, r)$ is a *threshold collection*, assumed nonnegative and nondecreasing in its second variable. The general definition of a step-up procedure with a threshold collection Δ is given by

$$\mathbf{SU}(\Delta) = L_\Delta(\hat{r}), \text{ where } \hat{r} = \max\{r \in \{0, 1, \dots, m\} \mid |L_\Delta(r)| \geq r\}. \quad (4)$$

On the other hand, the general definition of a step-down procedure with a threshold collection Δ is given by

$$\mathbf{SD}(\Delta) = L_\Delta(\tilde{r}), \text{ where } \tilde{r} = \max\{r \in \{0, 1, \dots, m\} \mid \forall r' \leq r, |L_\Delta(r')| \geq r'\}. \quad (5)$$

Of course, we classically have that for the same threshold collection Δ , $\mathbf{SU}(\Delta)$ rejects always more hypotheses than $\mathbf{SD}(\Delta)$. However, $\mathbf{SD}(\Delta)$ has a more constrained form which can be useful in some situations, as we will see later.

Remark 2.1 *From the nondecreasing property of $r \mapsto \Delta(i, r)$, note that $r \mapsto L_\Delta(r)$ is non-decreasing (as set), which implies that a step-wise procedure R satisfies the following self-consistency property:*

$$R \subset L_\Delta(|R|). \quad (6)$$

[7] have shown this condition to be crucial for FDR control. The main reason is that it allows to bound the false discovery proportion $\frac{|R \cap \mathcal{H}_0|}{|R|}$ by the ratio $\frac{|L_\Delta(|R|) \cap \mathcal{H}_0|}{|R|}$, which is more simple to bound (on average), because the numerator becomes a function of the denominator. Note also that the number of rejections of a step-wise procedure is exactly \hat{r} (resp. \tilde{r}), which means that (6) is in fact an equality.

Particular step-up and step-down procedures are defined with a threshold collection $\Delta(i, r)$ which is *factorized* with respect to i and r , that is, with Δ of the form

$$\Delta(i, r) = \alpha w_i \beta(r) / m,$$

where $\mathbf{w} = (w_i)_i$ are non negative weights summing up to m and β is some nonnegative nondecreasing function called the *shape function*. The latter name comes from the fact that $\beta(r)$ gives the “shape” of the threshold collection with respect to the rejection volume. We will refer the corresponding step-up procedure as *the weighted β -step-up procedure* with weight vector \mathbf{w} , denoted by $\mathbf{SU}(\beta, \mathbf{w})$. In the case $\beta(r) = r$ the latter is called the *weighted linear step-up procedure* and is simply denoted by $\mathbf{LSU}(\mathbf{w})$. Analogously, we define $\mathbf{SD}(\beta, \mathbf{w})$ and $\mathbf{LSD}(\mathbf{w})$ for step-down procedures.

The above definitions are equivalent to the classical re-ordering based definition of the weighted step-up and step-down procedure: consider the weighted p -values $p'_i = p_i / w_i$, ordered in the following way

$$p'_{(1)} \leq \dots \leq p'_{(m)}.$$

Since for any integer $r \in \{1, \dots, m\}$, we have

$$|L_\Delta(r)| \geq r \iff p'_{(r)} \leq \alpha \beta(r) / m, \quad (7)$$

$\mathbf{SU}(\beta, \mathbf{w})$ rejects the H_i such that $p'_i \leq \alpha \beta(\hat{r}) / m$, with

$$\hat{r} = \max\{r \in \{0, 1, \dots, m\} \mid p'_{(r)} \leq \alpha \beta(r) / m\},$$

with the convention $p_{(0)} = 0$. Similarly, $\mathbf{SD}(\beta, \mathbf{w})$ rejects H_i for which $p'_i \leq \alpha \beta(\tilde{r}) / m$, with

$$\tilde{r} = \max\{r \in \{0, 1, \dots, m\} \mid \forall r' \leq r, p'_{(r')} \leq \alpha \beta(r') / m\}.$$

Remark 2.2 *Since w_i is allowed to be equal to zero, we must define p_i / w_i in this particular case. We will suppose the latter ratio is equal to zero when both $w_i = 0$ and $p_i = 0$, and to ∞ when $w_i = 0$ and $p_i > 0$, implying $p_i \leq \alpha w_i \beta(r) / m \Leftrightarrow p_i / w_i \leq \alpha \beta(r) / m$.*

2.3 Multi-weighted procedures

To integrate several weight vector $\mathbf{w}(r)$, $r = 1, \dots, m$ in a step-wise procedure, we consider weight vector \mathbf{w} which can depend on r . This extension is directly possible using the general definitions of a step-up and step-down procedures presented in previous section, by considering (non factorized) threshold collections of the form

$$\Delta(i, r) = \alpha w_i(r) \beta(r) / m, \quad (8)$$

where $\mathbf{W} = (w_i(r))_{i,r}$ is a *weight matrix* i.e. is such that $\forall r, \sum_{i=1}^m w_i(r) = m$. We also make the following convention: $\forall i, w_i(0) = 0$.

Definition 2.3 *Consider a weight matrix $\mathbf{W} = (w_i(r))_{i,r}$ and a shape function β such that*

$$\forall i \in \{1, \dots, m\}, \quad r \mapsto w_i(r) \beta(r) \text{ is nondecreasing.} \quad (9)$$

Then the step-up procedure $\mathbf{SU}(\Delta)$ defined in (4) using the threshold collection (8) is called the multi-weighted β -step-up procedure with weight matrix $\mathbf{W} = (w_i(r))_{i,r}$, and is denoted by $\mathbf{SU}(\beta, \mathbf{W})$. When $\beta(r) = r$, the procedure is called the multi-weighted linear step-up procedure, and is simply denoted by $\mathbf{LSU}(\mathbf{W})$. In the multi-weighted step-down case, we define similarly $\mathbf{SD}(\beta, \mathbf{W})$ and $\mathbf{LSD}(\mathbf{W})$.

As for the standard weighted procedures, the multi-weighted procedures can be derived from a re-ordering based algorithm. The main difference is that the original p -values are ordered in several ways, because several weighting are used. Namely, if for $r \geq 1$, q_r denotes the r -th smallest $\mathbf{w}(r)$ -weighted p -value i.e. is equal to $p'_{(r)}$ where $\forall i, p'_i = p_i/w_i(r)$, then the multi-weighted β -step-up procedure rejects the hypotheses with a p -value p_i smaller than $\alpha w_i(\hat{r})\beta(\hat{r})/m$, where

$$\hat{r} = \max\{r \in \{0, 1, \dots, m\} \mid q_r \leq \alpha\beta(r)/m\},$$

(using (4), (7), and putting $q_0 = 0$). Equivalently, the multi-weighted step-up procedure is obtained using the following algorithm:

Algorithm 2.4 (*Step-up algorithm for $\mathbf{SU}(\beta, \mathbf{W})$*)

- *Step 1: compute for each i the weight vector $(w_i(m))_i$ and the weighted p -values $p'_i = p_i/w_i(m)$. If all the weighted p -values are less than or equal to $\alpha\beta(m)/m$, then reject all the null hypotheses. Otherwise go to step 2.*
- *Step j ($j \geq 2$): put $r = m - j + 1$ and compute for each i the weight vector $(w_i(r))_i$ and the weighted p -values $p'_i = p_i/w_i(r)$. Order the weighted p -values following $p'_{(1)} \leq \dots \leq p'_{(m)}$. If $p'_{(r)} \leq \alpha\beta(r)/m$, then reject the r null hypotheses corresponding to the smaller weighted p -values $p'_{(i)}$, $1 \leq i \leq r$. Otherwise go to step $j + 1$ (if $j = m$ stop and reject no null hypothesis).*

Similarly, the multi-weighted β -step-down procedure rejects the hypotheses with a p -value p_i smaller than $\alpha w_i(\tilde{r})\beta(\tilde{r})/m$, where

$$\tilde{r} = \max\{r \in \{0, 1, \dots, m\} \mid \forall r' \leq r, q_{r'} \leq \alpha\beta(r')/m\},$$

and is obtained using the following algorithm:

Algorithm 2.5 (*Step-down algorithm for $\mathbf{SD}(\beta, \mathbf{W})$*)

- *Step 1: compute for each i the weight vector $(w_i(1))_i$ and the weighted p -values $p'_i = p_i/w_i(1)$. If the smallest weighted p -values is strictly larger than $\alpha\beta(1)/m$, then reject no null hypothesis. Otherwise go to step 2.*
- *Step j ($j \geq 2$): put $r = j$ and compute for each i the weight vector $(w_i(r))_i$ and the weighted p -values $p'_i = p_i/w_i(r)$. Order the weighted p -values following $p'_{(1)} \leq \dots \leq p'_{(m)}$. If $p'_{(r)} > \alpha\beta(r)/m$, then reject the $r - 1$ null hypotheses corresponding to the smaller weighted p -values $p'_{(i)}$, $1 \leq i \leq r - 1$. Otherwise go to step $j + 1$ (if $j = m$ stop and reject all the null hypotheses).*

3 FDR control for multi-weighted procedures

In this section, we state the main results of this paper, which provides FDR control for quite general multi-weighted procedures. Since particular multi-weighted β -step-up procedures $\mathbf{SU}(\beta, \mathbf{W})$ are just the standard weighted β -step-up procedures $\mathbf{SU}(\beta, \mathbf{w})$ (by taking a matrix

$\mathbf{W} = (\mathbf{w}(r))_r$ such that $\forall r, \mathbf{w}(r) = \mathbf{w}$, it can be helpful to recall first what are the known results for $\mathbf{SU}(\beta, \mathbf{w})$.

Recent works (see [15, 5, 7]) showed that for any choices of weight vector $\mathbf{w} = (w_1, \dots, w_m)$ with $\sum_i w_i = m$, the weighted β -step-up procedures $\mathbf{SU}(\beta, \mathbf{w})$ with weight vector \mathbf{w} controls the FDR at level α in the three following cases :

- with $\beta(r) = r$, when the p -values are independent,
- with $\beta(r) = r$, when the p -values are PRDS on \mathcal{H}_0 (which is a form of positive dependency, see definition in Section 3.2),
- with β of the form $\beta(r) = \sum_{1 \leq i \leq r} i\nu_i$, where $\nu = (\nu_i)_i$ is a probability distribution on $\{1, \dots, m\}$ i.e. is a family of nonnegative real numbers such that $\sum_i \nu_i = 1$.

In the case (iii), no assumption is made on the dependencies between the p -values. Note also that $\nu_i \propto i^{-1}$ gives the Benjamini-Yekutieli correction $\beta(r) = r/(1 + 1/2 + \dots + 1/m)$.

3.1 Independent case

First assume that the p -values are independent. Even under this assumption, $\mathbf{LSU}(\mathbf{W})$ does not rigorously control the FDR for any choice of weight matrix \mathbf{W} and for any value of m (see Appendix B for a counterexample in the case $m = m_0 = 2$). Therefore, in order to get a rigorous FDR control for each m , we need to slightly correct $\mathbf{LSU}(\mathbf{W})$. We first propose the following step-up modification:

Theorem 3.1 Fix $\mathbf{W} = (w_i(r))_{i,r}$ a weight matrix such that (9) holds, and denote by $\widetilde{\mathbf{W}}$ the modified weight matrix with coefficient $\widetilde{w}_i(r) = \frac{w_i(r)}{1 + \alpha w_i(m)}$. Then, when the p -values of $\mathbf{p} = (p_i, i \in \{1, \dots, m\})$ are independent, $\mathbf{LSU}(\widetilde{\mathbf{W}})$ has a FDR less than or equal to α .

The threshold collection used in $\mathbf{LSU}(\widetilde{\mathbf{W}})$ is equal to the one of $\mathbf{LSU}(\mathbf{W})$ up to a factor smaller than $(1 + \alpha \max_i w_i(m))^{-1}$. Therefore, provided that for all i , $w_i(m)$ is at most of order 1, the two latter procedures are close when α is small.

The proof of Theorem 3.1 is given in Section 9.1. Intuitively, the main difficulty to bound the FDR of a multi-weighted procedure is that the weights depend on the rejection volume, so that we need this rejection volume to not change when we remove a given p -value $p_i \in \mathcal{H}_0$. For a step-up procedure of threshold collection Δ , this is true if the p -value p_i is larger than $\Delta(i, m)$ (because it does not affect the variables $|L_\Delta(r)|$, $r = 1, \dots, m$), which occurs with probability $1 - \Delta(i, m)$. Therefore, this leads to the step-up procedure with the modification $\widetilde{w}_i(r) = w_i(r)(1 - \Delta(i, m))$ and $\Delta(i, m) = \widetilde{w}_i(m)\alpha$, which is exactly the procedure of Theorem 3.1.

On the other hand, for a step-down procedure of threshold collection Δ which rejects \widetilde{r} hypotheses, remove a true p -value $p_i \in \mathcal{H}_0$ larger than $\Delta(i, \widetilde{r})$ does not change the final number of rejections (because this operation does not change the variables $|L_\Delta(r)|$, $r \leq \widetilde{r} + 1$). This leads to consider the modification $\widetilde{w}_i(r) = w_i(r)(1 - \Delta(i, r))$ and $\Delta(i, r) = \widetilde{w}_i(r)\alpha r/m$ i.e. $\widetilde{w}_i(r) = \frac{w_i(r)}{1 + \alpha w_i(r)r/m}$. This leads to the following result:

Theorem 3.2 Fix $\mathbf{W} = (w_i(r))_{i,r}$ a weight matrix such that (9) holds, and denote by $\widetilde{\mathbf{W}}$ the modified weight matrix with coefficient $\widetilde{w}_i(r) = \frac{w_i(r)}{1 + \alpha w_i(r)r/m}$. Then, when the p -values of $\mathbf{p} = (p_i, i \in \{1, \dots, m\})$ are independent, $\mathbf{LSD}(\widetilde{\mathbf{W}})$ has a FDR less than or equal to α .

The proof of Theorem 3.2 is given in Section 9.2. Since from (9), $\forall r, w_i(r)r/m \leq w_i(m)$, the threshold proposed in Theorem 3.1 is more conservative than the one of Theorem 3.2. However, the second result uses a step-down algorithm while the first one is step-up. Therefore, no procedure dominates a priori the other. However, we will see on simulations (Section 5) and on real data sets (Section 7) that the step-down modification is generally better.

3.2 Dependent case

We propose in this section to deal with the FDR control of the multi-weighted procedure in the case where the p -values have some dependencies. We consider first the case where the p -values are PRDS, which is a form of positive dependencies, defined as follows (see e.g. [4]). A set $D \subset [0, 1]^m$ is said to be *non-decreasing* if for all $x, y \in [0, 1]^m$, with $x \leq y$ coordinate-wise, $x \in D$ implies $y \in D$. Then, the p -values $\mathbf{p} = (p_i, i \in \{1, \dots, m\})$ are said *positively regressively dependent on each from \mathcal{H}_0* (PRDS on \mathcal{H}_0) if for any non-decreasing measurable set $D \subset [0, 1]^{\mathcal{H}}$ and for all $h \in \mathcal{H}_0, u \in [0, 1] \mapsto \mathbb{P}(\mathbf{p} \in D \mid p_h = u)$ is non-decreasing.

Theorem 3.3 *Fix $\mathbf{W} = (w_i(r))_{i,r}$ a weight matrix such that (9) holds, and put*

$$\gamma(\mathbf{W}) = \min \left\{ \frac{1}{m} \sum_{i=1}^m \max_r \{w_i(r)\}, 1 + \frac{1}{m} \sum_{i=1}^m \sum_{r=2}^m [w_i(r-1) - w_i(r)]_+ \right\}.$$

Then, when the p -values of $\mathbf{p} = (p_i, i \in \{1, \dots, m\})$ are PRDS on \mathcal{H}_0 , $\mathbf{LSU}(\mathbf{W}/\gamma(\mathbf{W}))$ has a FDR less than or equal to α .

Compared to $\mathbf{LSU}(\mathbf{W})$, the above procedure loses a factor $\gamma(\mathbf{W}) \geq 1$ in order to get a provable FDR control in the PRDS case. Interestingly, when \mathbf{W} is such that for all $i, r \mapsto w_i(r)$ is constant, we have $\gamma(\mathbf{W}) = 1$, so that the above result recovers the uni-weighted result in the PRDS case without any loss. Moreover, for any choice \mathbf{W} of weight matrix satisfying (9), we have

$$\gamma(\mathbf{W}) \leq 1 + 1/2 + \dots + 1/m, \tag{10}$$

so that $\gamma(\mathbf{W})$ is always smaller than the ‘‘Benjamini-Yekutieli correction’’ (see end of Section 9.3 for a proof).

Consider now the case where the p -values have some unspecified dependencies. The following result states that the procedure $\mathbf{SU}(\beta, \mathbf{W})$ controls the FDR for a shape function β of the same form than in the uni-weighted case and without any modification of the weight matrix.

Theorem 3.4 *Fix $\mathbf{W} = (w_i(r))_{i,r}$ a weight matrix such that (9) holds and consider a shape function β of the form $\beta(r) = \sum_{1 \leq i \leq r} i\nu_i$, where $\nu = (\nu_i)_i$ is a family of nonnegative real numbers such that $\sum_i \nu_i = 1$. Then $\mathbf{SU}(\beta, \mathbf{W})$ has a FDR less than or equal to α for any dependency structure on the p -values.*

Of course, as in the uni-weighted or uniformly-weighted case, the latter procedure will be quite conservative, because it controls the FDR for any dependency structure. However, interestingly, the above result states that our multi-weighting method can be generalized to this general dependent case without further correction.

Note that using the above theorem with $\nu_i \propto 1/i$ gives $\beta(r) = r/(1+1/2+\dots+1/m)$. Compared to the PRDS result, (10) states that the procedure of Theorem 3.3 makes always more discoveries; this is desirable because the latter uses the more restrictive PRDS assumption.

4 Choice for the weight matrix

The theorems in Section 3 allow to use any weight matrix we want (satisfying (9)). This section presents a way to choose the weight matrix from power considerations. The weights are chosen for the multi-weighted procedures using the non-corrected weight matrix \mathbf{W} , so that, in what concerns the weights choice, we forget about the light corrections introduced in the previous section.

4.1 Optimal choice for a fixed volume rejection

The way in which the procedures $\mathbf{SU}(\beta, \mathbf{W})$ and $\mathbf{SD}(\beta, \mathbf{W})$ are defined (see Algorithm 2.4 and Algorithm 2.5) suggests to choose the weight matrix $\mathbf{W} = (w_i(r))_{i,r}$ such that each weight vector $\mathbf{w}(r) = (w_i(r))_i$ maximizes the “power at volume rejection r ”:

$$\mathbf{w} = (w_i)_i \mapsto \text{Pow}_r(\mathbf{w}) := \sum_{i \in \mathcal{H}_1} F_i(w_i \alpha \beta(r) / m), \quad (11)$$

The following proposition solves the above maximization problem.

Proposition 4.1 *Assume that for each $i \in \mathcal{H}_1$, the cumulative distribution function F_i of the p -value p_i is twice differentiable and strictly concave on $(0, 1)$ and denote by f_i its derivative. Suppose that the supremum (resp. infimum) values of the f_i 's are constant over i and equal to $\ell^+ = f_i(0^+)$ (resp. $\ell^- = f_i(1^-)$). Consider β a nondecreasing function on \mathbb{R}_+ with $\beta(1) > 0$. Then for any $r \in \{1, \dots, m\}$, with $\beta(r) < m_1/\alpha$, the weight vector maximizing $\text{Pow}_r(\cdot)$ is unique and given by:*

$$w_i^*(r) = \frac{m}{\alpha \beta(r)} f_i^{-1}(y^*(r)) \mathbf{1}\{i \in \mathcal{H}_1\}, \quad (12)$$

where $y^*(r) = \Psi^{-1}(m\beta(r))$ and for any $y \in (\ell^-, \ell^+)$, $\Psi(y) = \frac{m}{\alpha} \sum_{j \in \mathcal{H}_1} f_j^{-1}(y)$.

The proof, which is based on similar arguments than those proposed in [22] and [27], is given in Section 9.5. In all what follows, the weight matrix $\mathbf{W}^* = (w_i^*(r))_{i,r}$ will be called the *optimal weight matrix* (for each fixed rejection volume). It is worth noting that the optimal weight matrix satisfies the assumption (9) (page 5) and thus can be used in the results of Section 3.

4.2 Optimal weight matrix in the Gaussian case

We detail here the optimal weight matrix when the p -values are generated from a Gaussian model. We focus on the one-sided case (a similar reasoning can be applied for the two-sided-case).

Consider the multiple testing problem $H_i : “\mu_i \leq 0”$ against $A_i : “\mu_i > 0”$ from Gaussian observations $X_i, i = 1, \dots, m$ of mean $\mu = (\mu_i)_i$ and of variance 1. We use the p -values $p_i = \overline{\Phi}(X_i)$, where $\overline{\Phi}(z) = \mathbb{P}(Z \geq z)$, with $Z \sim \mathcal{N}(0, 1)$, is the standard Gaussian distribution tail. Here, $\mathcal{H}_1 = \{i \mid \mu_i > 0\}$ and for all i ,

$$F_i(x) = \overline{\Phi}(\overline{\Phi}^{-1}(x) - \mu_i) \quad \text{and} \quad f_i(x) = \exp \left\{ \mu_i \left(\overline{\Phi}^{-1}(x) - \frac{\mu_i}{2} \right) \right\}. \quad (13)$$

The p -values assumptions of Proposition 4.1 with $\ell^+ = +\infty$ and $\ell^- = 0$ hold. Therefore, the optimal weight matrix is given by

$$w_i^*(r) = \frac{m}{\alpha\beta(r)} \bar{\Phi}\left(\frac{\mu_i}{2} + \frac{c(r)}{\mu_i}\right) \mathbf{1}_{\{\mu_i > 0\}}, \quad (14)$$

where $c(r)$ is the unique element of \mathbb{R} such that

$$\frac{m}{\alpha} \sum_{i | \mu_i > 0} \bar{\Phi}\left(\frac{\mu_i}{2} + \frac{c(r)}{\mu_i}\right) = \beta(r)m.$$

Figure 1 displays the weight vectors $\mathbf{w}^*(r) = (w_i^*(r))_i$ coming from the optimal weight matrix (14) for a particular choice of non-zero means and different values of r . This illustrates why it is interesting to use our multi-weights (Algorithm 2.4): for $r = m$, the p -value considered in the algorithm is large, that is, corresponds to small means (with high probability). Hence, in order to maximize the chance of rejection, it is better to choose large weights for small means, as $\mathbf{w}^*(m)$ does. Then, as r decreases, the p -values considered are smaller i.e. correspond to larger means. Hence it is better to choose weights larger on the large means, as $\mathbf{w}^*(r)$ does. Of course, the same reasoning can be applied for the step-down algorithm (Algorithm 2.5).

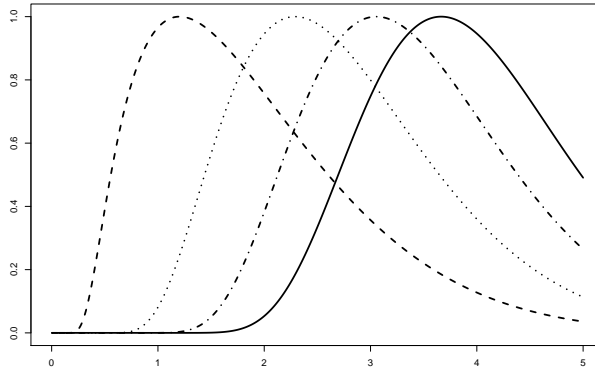


Figure 1: Plot of several optimal weights $(w_i^*(r))_i$ in function of μ_i and for $r = 1$ (solid), $r = 10$ (dashed-dotted), $r = 100$ (dotted), $r = 1000$ (dashed). Gaussian one-sided case with $\beta(r) = r$, $m = 1000$, $\alpha = 0.05$, $\mu_i = 5i/m$ for $i = 1, \dots, m$. Here $c(1) = 6.71$, $c(10) = 4.67$, $c(100) = 2.62$, $c(1000) = 0.72$. Each curve is normalized to have a maximum equal to 1.

The next section demonstrates that the Gaussian computations are useful in a general asymptotic framework, even if the underlying data distributions are not Gaussian.

4.3 Optimal weight matrix in asymptotically Gaussian cases

We expose here situations where the p -values p_i have a c.d.f. asymptotically equal to (13) under local alternatives. In these asymptotically Gaussian cases, the formula (14) thus gives the weights maximizing the asymptotic power (at each rejection volume r). The asymptotic considered here concerns the sample size n available to test each hypothesis H_i . We emphasize that the number of hypotheses to test m is maintained fixed here.

Suppose that each p -value $p_i = p_{i,n}$ tests the null $H_i : \theta_i = 0$ against the alternative $A_i : \theta_i > 0$ for a given parameter θ_i . Assume that each p -value is built from a test statistic $S_{i,n}$, i.e. $p_{i,n} = \zeta_{i,n}(S_{i,n})$, where $\zeta_{i,n}$ is the upper tail function of $S_{i,n}$ under the null distribution i.e. $\forall t, \zeta_{i,n}(t) = \mathbb{P}_{H_i}(S_{i,n} \geq t)$. Then, the following proposition holds (proof given in Section 9.5):

Proposition 4.2 Fix $i \in \{1, \dots, m\}$. Let τ_i and σ_i be two functions from \mathbb{R}_+ to $(0, \infty)$ respectively differentiable in 0 and continuous in 0. Assume that for all $\theta_{i,n}$ of the form $\theta_{i,n} = h_i/\sqrt{n}$ (with $h_i \geq 0$), we have:

$$\sqrt{n} \frac{S_{i,n} - \tau_i(\theta_{i,n})}{\sigma_i(\theta_{i,n})} \overset{\theta_{i,n}}{\rightsquigarrow} \mathcal{N}(0, 1). \quad (15)$$

Then, considering alternatives such that $\forall i \in \mathcal{H}_1, \theta_{i,n} = h_i/\sqrt{n}$ (with $h_i > 0$), for any $r \geq 0$ and weight vector $\mathbf{w} = (w_i)_i$, the power $\text{Pow}_r(\mathbf{w})$ defined in (11) converges to

$$\sum_{i \in \mathcal{H}_1} \bar{\Phi} \left(\bar{\Phi}^{-1}(w_i \alpha \beta(r)/m) - h_i \frac{\tau_i'(0)}{\sigma_i(0)} \right). \quad (16)$$

In particular, under these local alternatives, the weight matrix which maximizes the asymptotic power (16) are given by (14) with $\mu_i = h_i \frac{\tau_i'(0)}{\sigma_i(0)}$.

The assumption (15) is sometimes referred as ‘‘locally uniform’’ asymptotic normality. In Chapter 14 of [26], several explicit instances of statistics $S_{i,n}$ and functions τ_i and σ_i that satisfy (15) are exhibited e.g. the sign test, the Mann-Whitney test and the one and two-sample t -tests. For all these classical (multiple) tests, Proposition 4.2 establishes an asymptotically optimal way to choose the weight matrix in the multi-weighted procedures. We focus in Section 7 on the Mann-Whitney test in the two-sample (multiple) comparison problem.

Remark 4.3 In this approach, while the weight choice is motivated from asymptotic considerations, we emphasize that the FDR control of the resulting multi-weighted procedure is still non-asymptotic.

4.4 Weighting from prior guess

The optimal weight matrix (12) is of course an *oracle* weight matrix, in the sense that it depends on the unknown underlying distribution P , or more precisely on:

- The ‘‘location information’’: the set of the false null hypotheses \mathcal{H}_1 ,
- The ‘‘distribution information’’: the alternative distributions of the p -values $\{F_i, i \in \mathcal{H}_1\}$.

The two latter informations are of a different nature: the first information separates the true nulls from the false nulls; this is a strong information because directly related to the ideal output of a multiple testing procedure. The second information is more subtle; it separates the nulls among the false nulls.

In order to get computable weights, both of the above informations have to be *guessed* from prior information, e.g. from independent previous experiments. Formally, the prior information is given by the guesses $\tilde{\mathcal{H}}_1$ and $\{\tilde{F}_i, i \in \tilde{\mathcal{H}}_1\}$ of \mathcal{H}_1 and $\{F_i, i \in \mathcal{H}_1\}$, respectively.

In the (asymptotically) Gaussian case, the latter information is more handy because it is reduced to the guessed means $\tilde{\mu}_i, i = 1, \dots, m$. Namely, in the one-sided case, the guessed set \mathcal{H}_1 is $\tilde{\mathcal{H}}_1 = \{i \mid \tilde{\mu}_i > 0\}$ and the guessed alternative distributions $\tilde{F}_i(x) = \bar{\Phi}(\bar{\Phi}^{-1}(x) - \tilde{\mu}_i)$, for $\tilde{\mu}_i > 0$. Our optimal weight matrix can thus be guessed by plugging directly the guessed means $\tilde{\mu}_i$ in formula (14). When $\tilde{\mu}_i$ is “close enough” to μ_i , we will show that this way to guess the optimal weight matrix has good performance (see simulations in Section 5).

As a consequence, the prior guess can be simply seen as a family of guessed means $\tilde{\mu}_i$. The ‘best’ way to derive these means may dependent on the application; we discuss several options in Sections 7 and 8.1.

5 Simulation study

5.1 Simulations framework

We consider the one-sided Gaussian testing framework, where we want to test for each $i \in \{1, \dots, m\}$, the null $H_i : “\mu_i = 0”$ against the alternative $A_i : “\mu_i > 0”$ from the observation of a m -dimensional Gaussian vector $(X_i)_i$ of vector mean μ . For the sake of simplicity, we will only consider the independent case, i.e. we consider a covariance matrix equal to the identity.

In this section, the number of tests is $m = 1000$. We suppose that the $0 < m_0 < m$ first components of μ are equal to zero: $\mu_i = 0, 1 \leq i \leq m_0$. The $m_1 = m - m_0$ remaining non-zero means are taken in the two following ways:

- Case 1: the non-zero means increase linearly from $\frac{3}{m_1}\bar{\mu}$ to $3\bar{\mu}$: for $m_0 + 1 \leq i \leq m$,

$$\mu_i = 3\bar{\mu} \frac{i - m_0}{m_1}, \quad (17)$$

- Case 2: the non-zero means are gathered in three groups of different values $\bar{\mu}, 2\bar{\mu}$ and $3\bar{\mu}$: for $m_0 + 1 \leq i \leq m$,

$$\mu_i = \begin{cases} \bar{\mu} & m_0 + 1 \leq i \leq m_0 + 0.4m_1 \\ 2\bar{\mu} & m_0 + 1 + 0.4m_1 \leq i \leq m_0 + 0.8m_1 \\ 3\bar{\mu} & m_0 + 1 + 0.8m_1 \leq i \leq m \end{cases} . \quad (18)$$

In both cases $\bar{\mu}$ is an “effect size” parameter taking values in the range $0.5 + 0.25k, k \in \{0, \dots, 10\}$. The proportion $\pi_0 = m_0/m$ of zeros in the mean vector is taken equal to 0.7, which is a quite common value in real datasets. We performed the following procedures:

- [MW-Step-up-oracle] the multi-weighted linear step-up procedure $\mathbf{LSU}(\widetilde{\mathbf{W}}^*)$ of Theorem 3.1, using the optimal weight matrix \mathbf{W}^* given in (14),
- [MW-Step-down-oracle] the multi-weighted linear step-down procedure $\mathbf{LSD}(\widetilde{\mathbf{W}}^*)$ of Theorem 3.2, using the same optimal weight matrix as [MW-Step-up-oracle],
- [Unif-oracle] the weighted linear step-up procedure $\mathbf{LSU}(\mathbf{w})$ using a weight vector uniform on \mathcal{H}_1 : $w_i^* = 0$ for $\mu_i = 0$ and $w_i^* = m/m_1$ for $\mu_i > 0$,

- [WLSU(r)-oracle] the weighted linear step-up procedure $\mathbf{LSU}(\mathbf{w}(r))$ where the weight vector $\mathbf{w}(r) = (w_i^*(r))_i$ is the r -th column of the optimal weight matrix given in (14),
- [WLSU-oracle-best] the procedure which is the most powerful among the procedures [WLSU(r)-oracle], $1 \leq r \leq m$,
- [WLSU-oracle-worst] the procedure which is the least powerful among the procedures [WLSU(r)-oracle], $1 \leq r \leq m$.

These procedures correspond to the case where we have a perfect prior guess of the mean vector μ , hence the name “oracle”. In situations where we replace μ by a guess $\tilde{\mu}$ in the weights, the procedures are called “guessed” and are denoted by [MW-Step-up-guess], [MW-Step-down-guess], [Unif-guess], [WLSU(r)-guess], [WLSU-guess-best] and [WLSU-guess-worst] respectively. The procedure [Unif-oracle/guess] gives a uniform weighting over the (guessed) false nulls and is close in spirit to the approach of [15]. It takes only into account the subset $\mathcal{H}_1 \subset \mathcal{H}$ where the hypotheses are false (location information), but not the values of each non zero means. The procedures [WLSU-oracle/guess-best] and [WLSU-oracle/guess-worst] are used to evaluate the adaptivity range in which the multi-weighted procedures are expected to fluctuate. To compare with quite recent developments on π_0 -adaptive procedures (see e.g. [2]), we also performed the step-up procedure with threshold collection $\alpha i/m_0$, denoted by [LSU*]. Since it uses a perfect estimation of π_0 , it represents the best theoretical π_0 -adaptive modification of the LSU that we can build. For clarity reasons, we avoid the problem of choosing a particular estimator of π_0 and we only considered [LSU*]. For coherence of notations, the standard \mathbf{LSU} is also denoted [LSU].

All the latter procedures have provable FDR control (see Section 3) under independence, so that it is relevant to compare them in terms of power. In all experiments the targeted FDR level is either $\alpha = 0.01$ or $\alpha = 0.05$. The different performed procedures will be compared in terms of relative power (RelPow) with respect to the LSU procedure, defined as the expected surplus proportion of correct rejections among the false nulls: for a multiple testing procedure R ,

$$\text{RelPow}(R) = (m_1)^{-1} \left(\mathbb{E}(|R \cap \mathcal{H}_1|) - \mathbb{E}(|\mathbf{LSU} \cap \mathcal{H}_1|) \right) \quad (19)$$

Roughly speaking, this relative power represents the surplus “probability” of a false null to be rejected with respect to the LSU. This power will be estimated using Monte-Carlo simulations.

5.2 Results with perfect prior guess

We consider first the ideal situation where we have a perfect prior guess of the mean vector μ , so that we may use oracle procedures. We computed in Figure 2 the relative power (19) of [LSU] (solid), [LSU*] (short-dashed), [MW-Step-up-oracle] (dotted-dashed), [MW-Step-down-oracle] (long-dashed) and [Unif-oracle] (dotted) against the parameter $\bar{\mu}$ (1000 simulations). The gray area represents the range between [WLSU-oracle-best] and [WLSU-oracle-worst].

The conclusions of this experiment are :

- [MW-Step-up-oracle] and [MW-Step-down-oracle] seems adaptive over the range of [WLSU(r)-oracle] procedures with respect to the parameter r , that is, they have a power close to [WLSU-oracle-best], up to a small remaining term. However, the latter remaining term is growing with α .

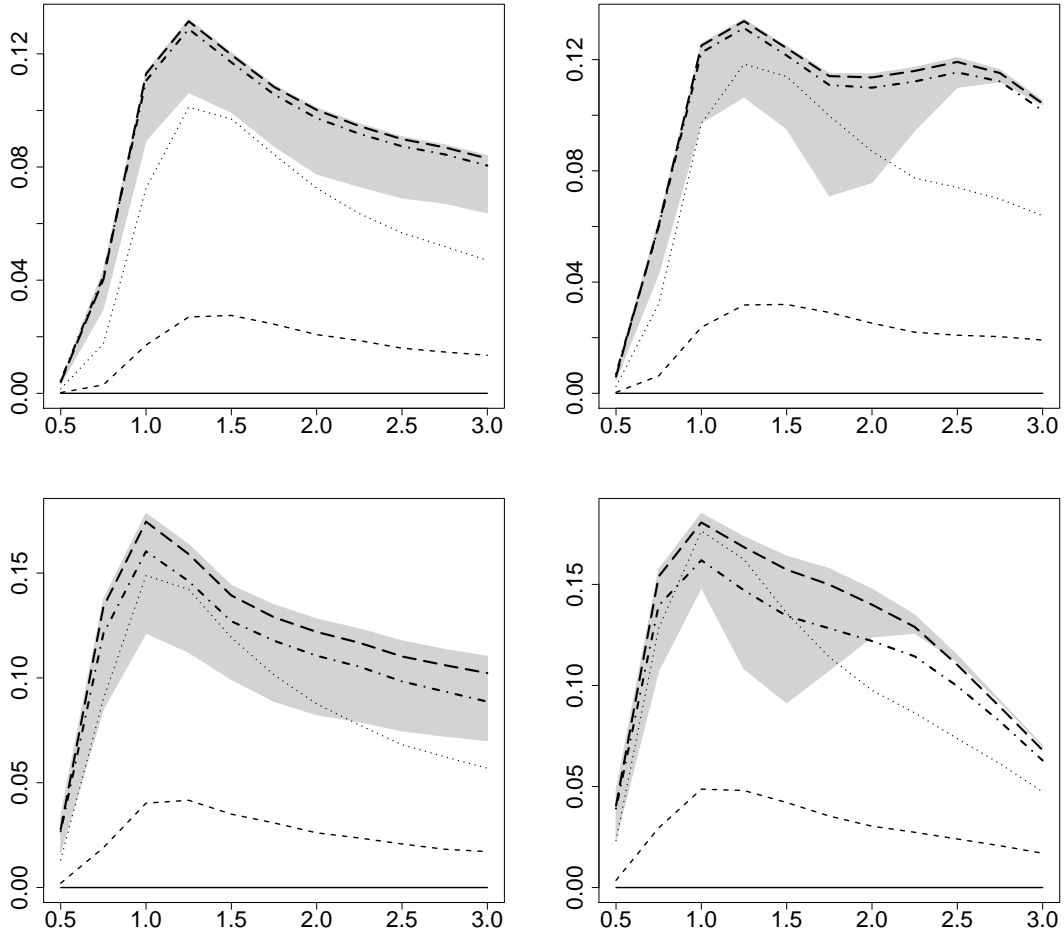


Figure 2: Case with perfect prior guess. Relative power of the different procedures in function of $\bar{\mu}$ (see text). $m = 1\,000$; 1 000 simulations; $\pi_0 = 0.7$. Left: type 1 of means, right: type 2 of means. Top $\alpha = 0.01$; bottom $\alpha = 0.05$.

- [MW-Step-down-oracle] performs here better than [MW-Step-up-oracle] (especially for $\alpha = 0.05$), so that the loss in the threshold of [MW-Step-up-oracle] seems significantly larger than the loss in the threshold of [MW-Step-down-oracle].
- The gray area measuring the adaptivity range is sometimes wide, so that a bad choice of r potentially leads to bad performance of the corresponding procedure [WLSU(r)-oracle]. Hence the adaptive property of the multi-weighted procedures is useful.
- [MW-Step-down-oracle] is more powerful than LSU* (actually, this is still true using a smaller π_0 , e.g. $\pi_0 = 0.5$).
- [MW-Step-down-oracle] is always better than [Unif-oracle], and allows sometimes for much more discoveries. This seems coherent because [MW-Step-down-oracle] takes into account more (correct) prior informations than [Unif-oracle] (namely, [MW-Step-down-oracle] uses both the values and the location of the non-zero means, while [Unif-oracle]

only uses the location information).

5.3 Results with non-perfect prior guess

We consider here the same experiment as before, except that we take into account the “randomness” due to the prior guesses. For this, we add a misspecification parameter σ and we suppose that the guessed means are of the form: $\forall i \in \{1, \dots, m\}$,

$$\tilde{\mu}_i = \mu_i + \varepsilon_i,$$

where ε_i are i.i.d with distribution $\mathcal{N}(0, \sigma^2)$ and independent of the p_i 's. The misspecification parameter (standard deviation) σ is taken in the range $\{j/4, j = 0, \dots, 12\}$. Figure 3 shows the relative power (19) of [LSU] (solid), [LSU*] (short-dashed), [MW-Step-up-guess] (dotted-dashed), [MW-Step-down-guess] (long-dashed) and [Unif-guess] (dotted) with respect to σ . The gray area represents the range between [WLSU-guess-best] and [WLSU-guess-worst]. We performed 100 simulations to compute the relative power and the latter is moreover averaged over 10 generated values of the $\tilde{\mu}_i$'s (for each values of σ).

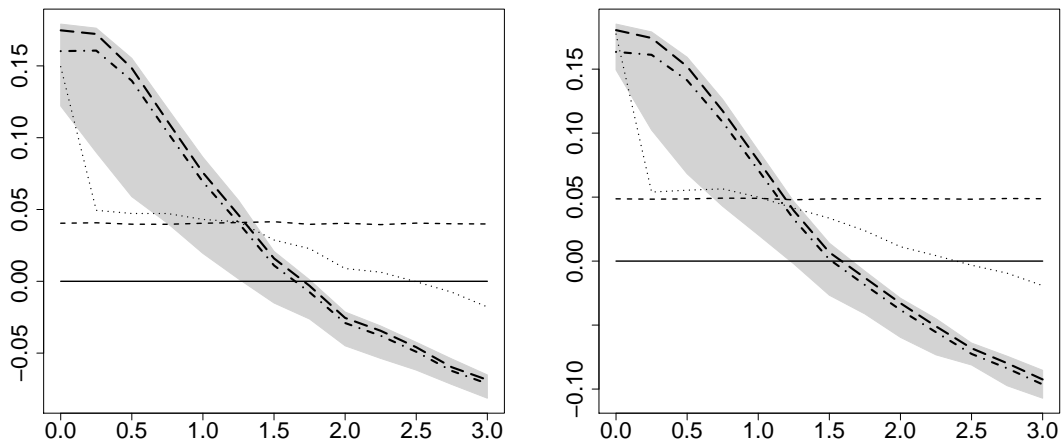


Figure 3: Case with non-perfect prior guess. Relative power of the different procedures in function of the misspecification parameter σ (see text). Left: type 1 of means, right: type 2 of means (see text). $\bar{\mu} = 1$; $\alpha = 0.05$; $\pi_0 = 0.7$. Each curve is averaged on 10 simulations of the $\tilde{\mu}_i$'s. We used 100 simulations to estimate the power.

In these experiments, the three first conclusions of the previous section are maintained (adaptivity, [MW-Step-down-guess] better than [MW-Step-up-guess], range of adaptivity wide), but the two last points become:

- The multi-weighted procedures are better than other procedures when the guesses are good i.e. over the range $\sigma \in [0, 1.2]$, but can be worst than the simple [LSU] procedure when σ is large.
- [Unif-guess] only proposes a slight improvement of [LSU] (or [LSU*]) when the guesses are good, but is “less risky” than the mutli-weighted procedures otherwise.

Therefore, the overall conclusion is that multi-weighted procedures can improve significantly the power in situations where the guesses are good enough.

5.4 The positive dependent case

We also performed simulations under the Gaussian positive equi-correlation case, with $\rho = 0.5$. We studied the performance of the multi-weighted linear step-up procedure with weights as in Theorem 3.3, denoted here by [MW-Step-up- γ]. The power of this procedure was compared with [WLSU-best], [WLSU-worst] and [MW-Step-down], both with a perfect guess and a non-perfect guess. From Section 3, remember that under positive dependencies, except for [MW-Step-down], all the above procedures have a provable FDR control. We report here only the conclusions of these simulations. First, we observed that in terms of power [MW-Step-down] is close to [WLSU-best] which on its turns dominates [MW-Step-down- γ]. Second, [WLSU-worst] is almost always better than [MW-Step-down- γ], which means that considering the uni-weighted LSU procedure with the optimal weight vector $\mathbf{w} = \mathbf{w}(r)$ at an arbitrary volume rejection r leads almost always to a better result than [MW-Step-down- γ]. This is a serious drawback of [MW-Step-down- γ]. On the other hand, we observed that the effective FDR of [MW-Step-down] was still well below the targeted level, which is not guaranteed by our theory for this procedure. This means that the correction of 3.3 is probably too much conservative. Therefore, in practical cases, [MW-Step-down] or any weighted LSU procedure using $\mathbf{w}(r)$, $1 \leq r \leq m$ should be preferred over [MW-Step-up- γ].

6 Extension to a random effects model

In this short section, we describe how our approach can be used when we have only a prior guess on the alternative distributions of the p -values ($F_i, i \in \{1, \dots, m\}$), without any guess on which hypotheses are false or true (using the terms of Section 4.4, this section deals with “distribution informations” without “location informations”). In such situation, each hypothesis has a priori the same “prior chance” to be true, so that using a random effects model is particularly relevant. This approach will be applied in Section 7.

6.1 Description of the model

Consider a random effects model (see e.g. [9, 24, 14]), where the null hypotheses of ($H_i, i \in \{1, \dots, m\}$) are generated – previously and independently from all other random variables – as i.i.d. random variables with outcomes in $\{0, 1\}$ (0 codes for “ H_i is true” whereas 1 codes for “ H_i is false”). We denote $\pi_0 = \mathbb{P}(H_i = 0)$. In this model, note that the number of the true hypotheses $|\mathcal{H}_0| = \sum_{i=1}^m (1 - H_i)$ is not deterministic anymore, but is a random variable. The marginals of the p -values are defined as in Section 2.1 but with a probability operator taken *conditionally* to ($H_i, i \in \{1, \dots, m\}$). That is, for any $i \in \mathcal{H}$, $\forall t \in [0, 1]$, $\mathbb{P}(p_i \leq t \mid H_i = 0) = t$ and $\mathbb{P}(p_i \leq t \mid H_i = 1) = F_i(t)$. In what concerns the p -value joint distribution, we assume for the sake of simplicity that the p -values of ($p_i, i \in \{1, \dots, m\}$) are independent conditionally to ($H_i, i \in \{1, \dots, m\}$) (a generalization to the case of “conditional dependent” p -values is straightforward).

As a consequence, unconditionally, the p -values are independent and for $i \in \{1, \dots, m\}$, each p -value p_i has a c.d.f. written as the mixture

$$G_i(t) = \pi_0 t + (1 - \pi_0) F_i(t). \quad (20)$$

6.2 FDR control and power maximization

In this model, the conclusion $\text{FDR} \leq \alpha$ of Theorems 3.1 and 3.2 holds conditionally to $(H_i, i \in \{1, \dots, m\})$, and therefore also unconditionally. As a consequence, given a correct weight matrix, the step-up and step-down multi-weighted procedures described in Section 3.1 control the FDR at level α in this model as well.

In such a random effects model, several notions of power can be used, for instance: the averaged number of rejections, the averaged number of correct rejections, the averaged number of rejected hypotheses given that they were false. Conveniently, all these quantities are equal up to some affine transformation: for any weight vector $\mathbf{w} = (w_i)_i$, $\sum_i w_i = m$, the averaged number of rejections of the procedure “at volume rejection r ” $\{i \mid p_i \leq w_i \alpha r / m\}$ is

$$\begin{aligned} \sum_{i=1}^m \mathbb{P}(p_i \leq w_i \alpha r / m) &= \sum_{i=1}^m \left[\pi_0 w_i \alpha r / m + (1 - \pi_0) F_i(w_i \alpha r / m) \right] \\ &= \pi_0 \alpha r + (1 - \pi_0) \sum_{i=1}^m F_i(w_i \alpha r / m). \end{aligned}$$

Therefore, following the maximization approach of Section 4, we have to maximize in $\mathbf{w} = (w_i)_i$, $\sum_i w_i = m$, the quantity $\sum_{i=1}^m F_i(w_i \alpha r / m)$. Since the latter is exactly the “power at volume rejection r ” of equation (11) used with “ $\mathcal{H}_1 = \mathcal{H}$ ”, this maximization problem is directly solved by Proposition 4.1. Furthermore, the exact expression of the optimal weight matrix in this random effects model is simply obtained by taking “ $\mathcal{H}_1 = \mathcal{H}$ ” in the formulas of Section 4 (formula (12) for the general case and (14) for the Gaussian case).

7 Application: increasing the power using sample sizes

In this Section, we present a direct application of our adaptive-weighting approach for the two-sample multiple comparison problem when the data are vectors of potentially high dimension. Our new approach allows for integrating the sample sizes into a FDR controlling procedure. The resulting improvement will be illustrated on a microarray application.

7.1 The two-sample multiple comparison problem

For each $i = 1, \dots, m$, suppose that we observe two independent i.i.d. samples $X_i = (X_{i,1}, \dots, X_{i,k_i})$ and $Y_i = (Y_{i,1}, \dots, Y_{i,\ell_i})$ from respective distribution $G(x)$ and $G(y - \theta_i)$. We denote by $n = k_i + \ell_i$ the sample size available to test each hypothesis. The density of G w.r.t. the Lebesgue measure on \mathbb{R} is denoted by g and is assumed bounded. We moreover assume that the data are row-wise independent, i.e. that $\{(X_i, Y_i), i = 1, \dots, m\}$ is a family of independent random variables. Our goal is to test simultaneously for each i the null $H_i : “\theta_i = 0”$ against the alternative $A_i : “\theta_i > 0”$, while controlling the FDR. To test each null, we use the distribution-free *Mann-Whitney* test statistic $S_i = \frac{1}{k_i \ell_i} \sum_{u,v} \mathbf{1}\{X_{i,u} \leq Y_{i,v}\}$, because it is ultimately robust to outliers, which is desirable in microarray studies. Denoting by ζ_i the upper-tail distribution function of S_i under the null, a p -value for H_i equals $p_i = \zeta_i(S_i)$.

In all what follows, we will focus on the case where the sample sizes can be different, that is, where $k_i \neq k_j$ for some (i, j) with $i \neq j$ (although the total sample size n does not depend on i). This situation occurs in specific practical cases, as we will see in Section 7.3. In order to control the FDR in such a multiple testing setting, we can use the **LSU** procedure. However,

since the sample sizes are not all equal, the p -values can not be considered interchangeably: when the proportions k_i/n and ℓ_i/n are far from 0.5 (unbalanced case), the corresponding p -value p_i will be less able to make a rejection. The idea here is thus to use this sample size information as a *prior guess* on each hypothesis in order to increase the power of the global multiple testing procedure.

We aim to consider as prior only the sample size information, without any guess on which hypotheses are false or true (i.e. without “location information”). Therefore, we consider the random effects model described in Section 6: we suppose that $\theta_i, i = 1, \dots, m$ are i.i.d. random variable (independent of all other variables), such that $\mathbb{P}(\theta_i = 0) = \pi_0$ and $\mathbb{P}(\theta_i = \theta) = 1 - \pi_0$, for an (unknown) probability $\pi_0 \in (0, 1)$ and an (unknown) “global effect size” $\theta > 0$. The variables $H_i = \mathbf{1}\{\theta_i = 0\}$ are then Bernoulli variables with success probability $1 - \pi_0$, as required by the random effects model.

7.2 Applying the multi-weighted procedures

From Section 6.2, the FDR control is provided by the procedures $\mathbf{LSU}(\widetilde{\mathbf{W}})$ and $\mathbf{LSD}(\widetilde{\mathbf{W}})$, for any choice of weight matrix \mathbf{W} satisfying (9). Moreover, the optimal weight matrix is derived from (12), applied with “ $\mathcal{H}_1 = \mathcal{H}$ ”. However, for the test statistic considered here, the exact p -value distribution is complex and discrete, and hence we choose the weights from the asymptotic approach of Section 4.3 (even if, again, the FDR control is non-asymptotic i.e. holds for any values of $(k_i, \ell_i), i = 1, \dots, m$).

As a consequence, the weight matrix maximizing the asymptotic power when $n \rightarrow \infty$ with $k_i/n \rightarrow \lambda_i \in (0, 1)$, and under the alternative $\theta = \theta_n = h/\sqrt{n}$ is: for all $i \in \{1, \dots, m\}$ and $r \in \{1, \dots, m\}$,

$$w_i^*(r) = \frac{m}{\alpha r} \overline{\Phi} \left(\frac{\delta}{2} [\lambda_i(1 - \lambda_i)]^{1/2} + \frac{c(r)}{\delta} [\lambda_i(1 - \lambda_i)]^{-1/2} \right), \quad (21)$$

where $c(r)$ is the unique element of \mathbb{R} such that

$$\frac{m}{\alpha} \sum_{i=1}^m \overline{\Phi} \left(\frac{\delta}{2} [\lambda_i(1 - \lambda_i)]^{1/2} + \frac{c(r)}{\delta} [\lambda_i(1 - \lambda_i)]^{-1/2} \right) = rm,$$

and where $\delta = 2\sqrt{3}h \int_{\mathbb{R}} g^2(x) dx$. To prove this, we have to check the condition (15) and to compute the corresponding functions τ_i and σ_i , for which we refer to Example 14.11 of [26]. Note that for standard Gaussian data, we have $\delta = h\sqrt{3/\pi} = \sqrt{3n/\pi} \theta$.

From the practical point of view, while the λ_i are known, the parameter θ is unknown and must be evaluated in order to compute the optimal weight matrix. To adress this issue, one solution could be to consider θ as a part of the prior information and we could propose a guess $\tilde{\theta}$ on θ , for instance $\tilde{\theta} = 1$. Although mathematically totally convenient, this could be a bit dangerous solution in practice, especially when the true value of θ is far away from the guessed value $\tilde{\theta}$: the misspecification of θ and thus of the optimal weight matrix can make decrease the power of the overall procedure (as it was point out in simulations of Section 5). Therefore, we chose a different approach: we propose to estimate θ with the simple estimator:

$$\hat{\theta}_m = (1 - \widehat{\pi}_0)^{-1} m^{-1} \sum_{i=1}^m Z_i, \quad (22)$$

where $Z_i = \frac{1}{\ell_i} \sum_{v=1}^{\ell_i} Y_{i,v} - \frac{1}{k_i} \sum_{u=1}^{k_i} X_{i,u}$ and where $\widehat{\pi}_0$ is an estimator of π_0 . We emphasize that, in order to provide the correct FDR control, our multi-weighted procedure should in principle be used with a weight matrix fixed or independent of the data used to compute the p -values. Therefore, in principle, the FDR control holds only if $\widehat{\theta}_m$ is computed with independent data. However, taking for instance for $\widehat{\pi}_0$ the Storey estimator (see [23, 25]), $\widehat{\theta}_m$ converges in probability when m grows to infinity, so that the fluctuations of $\widehat{\theta}_m$ in the weights will have a marginal effect on the effective FDR of the so multi-weighted procedures when m becomes large.

7.3 Application to microarray experiments

In a typical microarray experiment, we want to find the differentially expressed genes between two groups of individuals. For the i -th gene, the level expression is of the form $X_{i,1}, \dots, X_{i,k_i}$ for group 1 and $Y_{i,1}, \dots, Y_{i,\ell_i}$ for group 2, where k_i (resp. ℓ_i) is the number of individuals in group 1 (resp. group 2). Multiple testing procedures (e.g. the **LSU** procedure) are widely used to find the differentially expressed genes while controlling a given type I error rate (see e.g. [8]).

In some microarray experiments, the sample sizes (k_i, ℓ_i) available to assess the differential expression of gene i may strongly depend on i . For instance, this is the case when the groups are built from the same fixed set of n individuals, following the values of a *deterministic* binary covariate $A_{i,j}$, $j \in \{1, \dots, n\}$, $i \in \{1, \dots, m\}$. In this situation, the variables $X_{i,1}, \dots, X_{i,k_i}$ correspond to the expression level of gene i for individual j such that $A_{i,j} = 0$ (“zero’s group”) (with $k_i = |\{j \mid A_{i,j} = 0\}|$), and the variable $Y_{i,1}, \dots, Y_{i,\ell_i}$ correspond to the expression level of gene i for individual j such that $A_{i,j} = 1$ (“one’s group”) (with $\ell_i = |\{j \mid A_{i,j} = 1\}|$).

In our application, the response measurements are classical mRNA gene expressions, while the covariates are the DNA copy number statuses of the same genes on the same samples. These are obtained from an independent array CGH experiment, after a few pre-processing steps (see e.g. [21]). Hence, we focus on the covariate $A_{i,j}$ which is equal to 1 when gene i is *gained* for individual j (i.e. when sample j has an abnormally high DNA copy number of gene i), and 0 otherwise. The biological goal behind this is to find the genes for which the mRNA expression is induced by the DNA copy number. This is particularly useful to study cancer pathologies (see e.g. [17]).

Using the above framework, we analyse microarray lymphoma cancer data of [19]. In these data $m = 11\,169$ genes and $n = 42$ individuals are studied. The p -value of each gene was computed using a Mann-Whitney test. We performed the **LSU** procedure and the step-up and step-down multi-weighted procedures described in Section 7.2, using the estimator $\widehat{\theta}_m \simeq 0.98$ of the global effect size θ . We also performed the LSU weighted procedure **LSU(w)**, using the natural, although mathematically unfounded, weight vector $\mathbf{w} = (w_i)_i$, $w_i \propto \sqrt{\lambda_i(1 - \lambda_i)}$. For different values of α , the number of rejections of the four procedures are given in Table 1. Note that all these procedures control the FDR at the targeted level. For our new procedures, this holds because m is large (see end of Section 7.2).

We observe that our new step-down procedure allows to discover more differentially expressed genes when $\alpha \in \{0.005, 0.01, 0.05\}$. When $\alpha = 0.1$, the benefit due to the weighting in **LSD($\widetilde{\mathbf{W}}$)** is not large enough to compensate the correction term in the optimal weight matrix (and also the possible bias in the θ -estimation). For what concerns the “naturally weighted **LSU(w)**”, it seems correctly adjusted sometimes (here, $\alpha = 0.05$) but less relevant otherwise. The improvement of our procedures is surprisingly strong when the number of rejection of

α	LSU	Natural LSU(\mathbf{w})	LSU($\widetilde{\mathbf{W}}$)	LSD($\widetilde{\mathbf{W}}$)
0.005	33	48	83	83
0.01	112	118	136	137
0.05	436	453	433	452
0.1	797	805	738	790

Table 1: Number of discoveries of each procedure. See text.

the LSU is small ($\alpha = 0.005$). This is in accordance with our intuition: the prior information (here the sample sizes) is particularly useful when the number of rejections is expected to be small. Finally, let us mention that these positive results on the sample size problem have been corroborated in a specific simulation study (not reported here).

8 Discussions and conclusion

8.1 Discussion: informative guessing of the weights in applications

A crucial part in any weighted multiple testing procedure is the choice of the weights. In our application, we showed that in a case where the known sample sizes are integrated into the weights, even a relatively uninformative estimate of the effect size per test item, namely the global effect size, results in a powerful procedure. We believe even more powerful weights can be estimated from related studies. For example, microarray studies are very often used for studying several types of cancer. Now, suppose one wants to study a relatively rare type of cancer for a which limited amount of samples is available. Hence, it is crucial in this case to use a powerful multiple testing procedure to be able to discover anything. Nowadays, microarray profiles of many common cancers are publicly available. It is known that several genes, for example those involved in cell proliferation, play an important role in many types of cancer. Moreover, biologists probably know to which more common cancer the rare one is alike in terms of biological parameters (e.g. tissue type). Therefore, it can be very beneficial to guess the weights from the common cancer data to obtain a more powerful multiple testing procedure for the rare cancers.

When we have no prior information, we can still use our multi-weighted procedure by splitting the data sample X in two parts $(X^{(1)}, X^{(2)})$, estimating the weights from $X^{(1)}$ and computing the p -values from $X^{(2)}$. We performed simulations with the “naive” plug in approach, which estimates the optimal weight matrix by computing all the $\widehat{\mu}_i$ ’s from $X^{(1)}$. This does not work: our simulations showed that the loss in power due to the splitting approach is not compensated by the gain resulting from the weighting. This is in accordance with the findings in [27] and [22] (related to the FWER control). Furthermore, our simulations showed that using the data twice is really not allowed: by computing both the p -values and the weights from the whole sample X the effective FDR of this procedure may be twice larger than the targeted level.

However, as suggested in [22], this splitting approach can be useful in situation where we know a *prior structure* on the data. For instance, if we know that the non-zero means are smooth or organized in clusters, we need just few parameters in order to approach well the non-zero means, so that we can use a sample $X^{(1)}$ very small with respect to $X^{(2)}$. For ex-

ample, in microarray studies it is known that genes act together in so-called pathways. These pathways are known a priori, and it may be reasonable to use one parameter per pathway and estimate these parameters from $X^{(1)}$, thereby hoping for more informative weights since external information has been used.

8.2 Discussion: power properties of the multi-weighted procedures

Our simulations showed that the new multi-weighted procedures are *adaptive* in the sense that its power is close to the one of the (unknown) best procedure among $\{\mathbf{LSU}(\mathbf{w}^*(r)), 1 \leq r \leq m\}$. Furthermore, we observed in all our experiments that the two above powers are very close, as soon as we forget the correction of Section 3 in the multi-weighted procedure. We thus conjecture that an oracle inequality holds, taking the form:

$$\text{Pow}(\mathbf{LSU}(\mathbf{W}^*)) \geq (1 - C) \max_{\mathbf{w}} \{\text{Pow}(\mathbf{LSU}(\mathbf{w}))\} - \varepsilon, \quad (23)$$

for some constants $C \geq 0$ and $\varepsilon \geq 0$, possibly depending on many parameters (e.g. m). In what follows, we give a simple but informal argument establishing that (23) should hold asymptotically in m with $C = 0$ and $\varepsilon = 0$. Consider a random effects model, with nulls asymptotically gathered in two clusters $\{A, B\}$ with proportion q_A and q_B , and with associated guessed alternative distribution F_A and F_B , respectively. In this situation we should consider simple weight vector \mathbf{w} taking values w_A on A and w_B on B and such that $q_A w_A + q_B w_B = 1$. Following the asymptotic theory developed in [13, 14], we believe that under some well chosen regularity assumptions, the asymptotic rejection numbers (rescaled by α/m) of the $\mathbf{LSU}(\mathbf{w})$ and $\mathbf{LSU}(\mathbf{W})$ are asymptotically

$$T(\mathbf{w}) = \sup\{t \mid \pi_0 t + (1 - \pi_0)[q_A F_A(w_A t) + q_B F_B(w_B t)] \geq t/\alpha\},$$

and

$$T(\mathbf{W}) = \sup\{t \mid \pi_0 t + (1 - \pi_0)[q_A F_A(w_A(t)t) + q_B F_B(w_B(t)t)] \geq t/\alpha\},$$

respectively. The latter formulas come directly from the definition (4) of a step-up procedure, by taking the expectation inside the maximum and by substituting the random effects model (with two clusters). If these formulas hold, then the optimal weight matrix $\mathbf{W}^* = \{w_A^*(t), w_B^*(t)\}_t$ (i.e. maximizing the asymptotic power at each (rescaled) rejection number t) satisfies by definition $\forall \mathbf{w}, T(\mathbf{w}) \leq T(\mathbf{W}^*)$. Therefore, in this situation, (23) holds asymptotically with $C = 0$ and $\varepsilon = 0$.

8.3 Conclusion

This paper proposed a generic method to weight the Benjamini-Hochberg procedure from a prior knowledge on the p -value distributions. From a power maximization argument, we aimed to integrate in a step-up procedure a whole weight matrix instead of a single weight vector. We showed that the resulting multi-weighted step-up procedure can be easily computed in practice thanks to algorithms, which take sequentially into account the different weight vectors contained in the weight matrix.

Under various dependency conditions on the p -values, we proposed several multi-weighted procedures which control rigorously the FDR for a general class of weight matrix. We then investigated the general computation of the optimal weight matrix, and we obtained a closed formula in the Gaussian case and in the asymptotically Gaussian case, which covers a wide

range of non-Gaussian (multiple) testing situations (e.g. Mann-Whitney test in a distribution-free framework). We illustrated the interest of the resulting “optimal multi-weighted procedure” in the two-sample multiple comparison problem, where an application to microarray is also given. Our procedure was able to discover more than conventional state-of-the art FDR procedures.

An interesting direction for future works will be to investigate FDR bounds sharper than the one proposed in Section 3. First, we would like to find a way to remove (or reduce) the correction of the weight matrix in our procedure while still providing the FDR control. For $m = 2$, results in Appendix B shows that the required correction is 0 for the step-down case while it stay quite small for the step-up case. Furthermore, we believe in both cases that the correction is unnecessary when m grows to infinity. Second, our FDR bounds are certainly too conservative when the proportion π_0 of true nulls is small e.g. $\pi_0 \leq 0.5$ (this situation may arises in some applications although it is quite rare). In this cases, it would be useful to prove that the FDR of our procedures are upper bounded by $\pi_0\alpha$ instead of α (using for e.g. a random effects model). In the same spirit, it would be useful to combine our new procedures with a π_0 estimator, so building π_0 -adaptive and multi-weighted procedures (using for instance techniques developed in [2] and [6]).

9 Proofs

9.1 Proof of Theorem 3.1

First, remark that a procedure R satisfying the “self-consistency condition” $R = \{i \mid p_i \leq \Delta(i, |R|)\}$ has a FDR equal to

$$\begin{aligned} \text{FDR}(R) &= \mathbb{E} \left[\frac{|R \cap \mathcal{H}_0|}{|R| \vee 1} \right] = \sum_{i \in \mathcal{H}_0} \mathbb{E} \left[\frac{\mathbf{1}\{i \in R\}}{|R|} \right] \\ &= \sum_{i \in \mathcal{H}_0} \sum_{k=1}^m \frac{1}{k} \mathbb{P} [p_i \leq \Delta(i, k), |R| = k], \end{aligned} \quad (24)$$

Consider now the multi-weighted step-up procedure R of Theorem 3.1. Since any step-up procedure satisfies the “self consistency condition” (see Remark 2.1) we can use (24). From Lemma A.1 (first statement), if $|R| = k$, the assertion $p_i \leq \tilde{w}_i(k)\alpha k/m$ is equivalent to $|R'_{-i}| + 1 = k$, where R'_{-i} is the step-up procedures associated to the threshold collection $\forall r \leq m - 1, \Delta'(i, r) = \tilde{w}_i(r+1)\alpha[r+1]/m$ (and $\Delta'(i, m) = \Delta'(i, m - 1)$), restricted to the null hypotheses $H_j, j \neq i$. Note that from the definition, R'_{-i} only depends on the p -values

of $(p_j, j \neq i)$. Therefore, the FDR can be rewritten as follows:

$$\begin{aligned}
\text{FDR}(R) &= \sum_{i \in \mathcal{H}_0} \sum_{k=1}^m \frac{1}{k} \mathbb{P} [p_i \leq \tilde{w}_i(k) \alpha k / m, |R| = k] \\
&= \sum_{i \in \mathcal{H}_0} \sum_{k=1}^m \frac{1}{k} \mathbb{P} [p_i \leq \tilde{w}_i(k) \alpha k / m, |R'_{-i}| + 1 = k] \\
&= \frac{\alpha}{m} \sum_{i \in \mathcal{H}_0} \sum_{k=1}^m \tilde{w}_i(k) \mathbb{P} [|R'_{-i}| + 1 = k] \\
&= \frac{\alpha}{m} \sum_{i \in \mathcal{H}_0} \sum_{k=1}^m w_i(k) (1 - \Delta'(i, m)) \mathbb{P} [|R'_{-i}| + 1 = k] \\
&= \frac{\alpha}{m} \sum_{i \in \mathcal{H}_0} \sum_{k=1}^m w_i(k) \mathbb{P} [p_i > \Delta'(i, m), |R'_{-i}| = k - 1],
\end{aligned} \tag{25}$$

where we used twice the independence between p_i and $|R'_{-i}|$ and the fact that p_i has a uniform distribution on $[0, 1]$ (see (1)). Now, denoting by R' the step-up procedures associated to the threshold collection Δ' over the whole set of hypotheses \mathcal{H} , Lemma A.1 (second statement) states that $p_i > \Delta'(i, m) \geq \Delta'(i, |R'|)$ implies $|R'| = |R'_{-i}|$. Therefore,

$$\begin{aligned}
\text{FDR}(R) &\leq \frac{\alpha}{m} \sum_{i \in \mathcal{H}_0} \sum_{k=1}^m w_i(k) \mathbb{P} [p_i > \Delta'(i, m), |R'| = k - 1] \\
&\leq \frac{\alpha}{m} \sum_{i \in \mathcal{H}_0} \sum_{k=1}^m w_i(k) \mathbb{P} [|R'| = k - 1] \\
&\leq \frac{\alpha}{m} \sum_{k=1}^m \left[\sum_{i \in \mathcal{H}} w_i(k) \right] \mathbb{P} [|R'| = k - 1] \\
&\leq \alpha,
\end{aligned}$$

because for all k , $\sum_{i=1}^m w_i(k) = m$.

9.2 Proof of Theorem 3.2

First, let us prove that for any step-down procedure R with threshold collection Δ we have:

$$\text{FDR}(R) \leq \sum_{i \in \mathcal{H}_0} \sum_{k=1}^m \frac{1}{k} \mathbb{P} [|R_{-i}| = k - 1, p_i \leq \Delta(i, k)], \tag{26}$$

where R_{-i} is the step-down procedure associated to Δ and restricted to the hypotheses of $H_j, j \neq i$. This result has been implicitly proved in [12] (Section 3), using a specific non-weighted step-down procedure. We state (26) in a more general framework. For this, we

apply the two first points of Lemma A.2 to show that for any $i \in \mathcal{H}$,

$$\begin{aligned}
& \sum_{k=1}^m \frac{1}{k} \mathbb{P}[|R| = k, p_i \leq \Delta(i, k)] \\
&= \sum_{k=1}^m \frac{1}{k} \left[\mathbb{P}[|R| = k, p_i \leq \Delta(i, k-1)] + \mathbb{P}[|R| = k, \Delta(i, k-1) < p_i \leq \Delta(i, k)] \right] \\
&= \sum_{k=1}^m \frac{1}{k} \mathbb{P}[|R| \geq k, \Delta(i, k-1) < p_i \leq \Delta(i, k)] - \sum_{k=1}^m \left[\frac{\mathbf{1}\{k > 1\}}{k-1} - \frac{1}{k} \right] \mathbb{P}[|R| \geq k, p_i \leq \Delta(i, k-1)] \\
&\leq \sum_{k=1}^m \frac{1}{k} \mathbb{P}[|R_{-i}| \geq k-1, \Delta(i, k-1) < p_i \leq \Delta(i, k)] - \sum_{k=1}^m \left[\frac{\mathbf{1}\{k > 1\}}{k-1} - \frac{1}{k} \right] \mathbb{P}[|R_{-i}| \geq k-1, p_i \leq \Delta(i, k-1)] \\
&= \sum_{k=1}^m \frac{1}{k} \mathbb{P}[|R_{-i}| = k-1, p_i \leq \Delta(i, k)].
\end{aligned}$$

As a consequence, the latter combined with (24) states (26). Now, considering the step-down procedure R of Theorem 3.2, we use the independence between the p -values to show

$$\begin{aligned}
\text{FDR}(R) &\leq \sum_{i \in \mathcal{H}_0} \sum_{k=1}^m \frac{1}{k} \mathbb{P}[|R_{-i}| = k-1, p_i \leq \Delta(i, k)] \\
&= \frac{\alpha}{m} \sum_{i \in \mathcal{H}_0} \sum_{k=1}^m w_i(k) (1 - \Delta(i, k)) \mathbb{P}[|R_{-i}| = k-1] \\
&= \frac{\alpha}{m} \sum_{i \in \mathcal{H}_0} \sum_{k=1}^m w_i(k) \mathbb{P}[|R_{-i}| = k-1, p_i > \Delta(i, k)].
\end{aligned}$$

The third point of Lemma A.2 thus implies

$$\begin{aligned}
\text{FDR}(R) &\leq \frac{\alpha}{m} \sum_{i \in \mathcal{H}_0} \sum_{k=1}^m w_i(k) \mathbb{P}[|R| = k-1, p_i > \Delta(i, k)] \\
&\leq \frac{\alpha}{m} \sum_{k=1}^m \left[\sum_{i \in \mathcal{H}_0} w_i(k) \right] \mathbb{P}[|R| = k-1],
\end{aligned}$$

and the result follows because for all fixed k we have $\sum_{i \in \mathcal{H}_0} w_i(k) \leq \sum_{i \in \mathcal{H}} w_i(k) = m$.

9.3 Proof of Theorem 3.3

Put $\tilde{w}_i(r) = \gamma^{-1} w_i(r)$. Remember that from the PRDS assumption and because $|R|$ is nonincreasing in each p -value, we get for any $i \in \mathcal{H}_0$ and for all $r \in \{1, \dots, m\}$ and $0 \leq u \leq u' \leq 1$,

$$\mathbb{P}[|R| \leq r \mid p_i \leq u] \leq \mathbb{P}[|R| \leq r \mid p_i \leq u']. \quad (27)$$

Using (24), we get

$$\begin{aligned}
\text{FDR}(R) &= \sum_{i \in \mathcal{H}_0} \sum_{k=1}^m \frac{1}{k} \mathbb{P}[|R| = k, p_i \leq \alpha w_i(k) k \gamma^{-1} / m] \\
&= \frac{\alpha}{\gamma m} \sum_{i \in \mathcal{H}_0} \sum_{k=1}^m w_i(k) \mathbb{P}[|R| = k \mid p_i \leq \alpha w_i(k) k \gamma^{-1} / m]. \quad (28)
\end{aligned}$$

On the first hand, denoting $w'_i = \max_r \{w_i(r)\}$,

$$\begin{aligned} & \sum_{i \in \mathcal{H}_0} \sum_{k=1}^m w_i(k) \mathbb{P} [|R| = k \mid p_i \leq \alpha w_i(k) k \gamma^{-1} / m] \leq \sum_{i \in \mathcal{H}_0} w'_i \sum_{k=1}^m \mathbb{P} [|R| = k \mid p_i \leq \alpha w_i(k) k \gamma^{-1} / m] \\ & = \sum_{i \in \mathcal{H}_0} w'_i \sum_{k=1}^m \left[\mathbb{P} [|R| \leq k \mid p_i \leq \alpha w_i(k) k \gamma^{-1} / m] - \mathbb{P} [|R| \leq k-1 \mid p_i \leq \alpha w_i(k) k \gamma^{-1} / m] \right], \end{aligned}$$

so that, by using (27) and (9), the latter quantity is smaller than or equal to

$$\begin{aligned} & \sum_{i \in \mathcal{H}_0} w'_i \sum_{k=1}^m \left[\mathbb{P} [|R| \leq k \mid p_i \leq \alpha w_i(k) k \gamma^{-1} / m] - \mathbb{P} [|R| \leq k-1 \mid p_i \leq \alpha w_i(k-1) (k-1) \gamma^{-1} / m] \right] \\ & = \sum_{i \in \mathcal{H}_0} w'_i \leq \sum_{i=1}^m w'_i = \sum_{i=1}^m \max_r \{w_i(r)\}. \end{aligned}$$

On the other hand, we have similarly

$$\begin{aligned} & \sum_{i \in \mathcal{H}_0} \sum_{k=1}^m w_i(k) \mathbb{P} [|R| = k \mid p_i \leq \alpha w_i(k) k \gamma^{-1} / m] \\ & \leq \sum_{i \in \mathcal{H}_0} \sum_{k=1}^m \left[w_i(k) \mathbb{P} [|R| \leq k \mid p_i \leq \alpha w_i(k) k \gamma^{-1} / m] \right. \\ & \quad \left. - w_i(k) \mathbb{P} [|R| \leq k-1 \mid p_i \leq \alpha w_i(k-1) (k-1) \gamma^{-1} / m] \right], \\ & \leq \sum_{i \in \mathcal{H}_0} \sum_{k=1}^m \left[w_i(k) \mathbb{P} [|R| \leq k \mid p_i \leq \alpha w_i(k) k \gamma^{-1} / m] \right. \\ & \quad \left. - w_i(k-1) \mathbb{P} [|R| \leq k-1 \mid p_i \leq \alpha w_i(k-1) (k-1) \gamma^{-1} / m] \right] + \sum_{i \in \mathcal{H}_0} \sum_{k=1}^m (w_i(k-1) - w_i(k))_+ \\ & = |\mathcal{H}_0| + \sum_{i \in \mathcal{H}_0} \sum_{k=2}^m (w_i(k-1) - w_i(k))_+ \leq m + \sum_{i=1}^m \sum_{k=2}^m (w_i(k-1) - w_i(k))_+ \end{aligned}$$

Finally, we conclude by combining (28) and the two last displays. ■

Let us prove (10): from assumption (9), we have $(r-1)w_i(r-1) - rw_i(r) \leq 0$ and then:

$$\begin{aligned} \frac{1}{m} \sum_{i=1}^m \sum_{r=2}^m [w_i(r-1) - w_i(r)]_+ & = \frac{1}{m} \sum_{i=1}^m \sum_{r=2}^m \frac{1}{r} [(r-1)w_i(r-1) - rw_i(r) + w_i(r-1)]_+ \\ & \leq \frac{1}{m} \sum_{i=1}^m \sum_{r=2}^m \frac{w_i(r-1)}{r} = \sum_{r=2}^m \frac{1}{r}. \end{aligned}$$

9.4 Proof of Theorem 3.4

Using that for all $x > 0$, $\frac{1}{x} = \int_{y \geq x} y^{-2} dy$ and Fubini's theorem, we get

$$\begin{aligned}
& \sum_{i \in \mathcal{H}_0} \mathbb{E} \left[\frac{\mathbf{1}\{p_i \leq \alpha w_i(|R|)\beta(|R|)/m\}}{|R|} \right] \\
&= \sum_{i \in \mathcal{H}_0} \mathbb{E} \left[\int_0^\infty y^{-2} \mathbf{1}\{y \geq |R|\} \mathbf{1}\{p_i \leq \alpha w_i(|R|)\beta(|R|)/m\} dy \right] \\
&\leq \sum_{i \in \mathcal{H}_0} \mathbb{E} \left[\int_0^\infty y^{-2} \mathbf{1}\{p_i \leq \alpha w_i(y)\beta(y)/m\} dy \right] = \sum_{i \in \mathcal{H}_0} \int_0^\infty y^{-2} \mathbb{P}[p_i \leq \alpha w_i(y)\beta(y)/m] dy \\
&\leq \frac{\alpha}{m} \int_0^\infty \sum_{i \in \mathcal{H}_0} w_i(y) y^{-2} \beta(y) dy \leq \alpha \int_0^\infty y^{-2} \beta(y) dy,
\end{aligned}$$

where we used (9) in the first inequality. We conclude because $\int_0^\infty y^{-2} \beta(y) dy = 1$.

9.5 Proofs for Section 4

The Proposition 4.1 is proved using the following lemma with $C = \alpha\beta(r)/m$:

Lemma 9.1 *Suppose that the assumptions of Proposition 4.1 hold. Let $\mathcal{S} = \{\mathbf{w} = (w_i)_i \in [0, m]^m \mid \sum_{i=1}^m w_i = m\}$ and let be C a positive constant such that $C < m_1/m$. Then the function*

$$\Lambda : \mathbf{w} = (w_i)_i \in \mathcal{S} \mapsto \sum_{i \in \mathcal{H}_1} F_i(w_i C),$$

has a unique maximum given by $w_i^ = C^{-1} f_i^{-1}(y^*) \mathbf{1}\{i \in \mathcal{H}_1\}$, where $y^* = \Psi^{-1}(mC)$ and for any $y \in (\ell^-, \ell^+)$, $\Psi(y) = \sum_{j \in \mathcal{H}_1} f_j^{-1}(y)$.*

Remark 9.2 *All the quantities defined in the above theorem exist : for each i , the function $f_i : (0, 1) \rightarrow \mathbb{R}^+$ is continuous decreasing, so that f_i^{-1} is well defined, decreasing and one to one from (ℓ^-, ℓ^+) to $(0, 1)$. Therefore, Ψ is continuous decreasing from (ℓ^-, ℓ^+) to $(0, m_1)$, so that Ψ^{-1} exists and is one to one from $(0, m_1)$ to (ℓ^-, ℓ^+) . Hence, from assumption $mC < m_1$, $y^* = \Psi^{-1}(mC)$ is well defined. We can finally check that the w_i^* 's sum to m : $\sum_{i=1}^m w_i^* = C^{-1} \sum_{i \in \mathcal{H}_1} f_i^{-1}(y^*) = C^{-1} \Psi(y^*) = C^{-1} mC = m$.*

Proof of Lemma 9.1. Let us solve the maximization problem of Λ under the linear constraint $\sum_{i=1}^m w_i = m$. Trivially, we can restrict the study on the set $\mathcal{S}_1 = \{\mathbf{w} = (w_i)_i \in [0, C^{-1}]^{\mathcal{H}_1} \mid \sum_{i \in \mathcal{H}_1} w_i = m\}$, by letting $w_i = 0$ for all $i \in \mathcal{H}_0$ and because $F_i(w_i C) = 1$ for any $w_i > C^{-1}$. Following the constrained Lagrange multiplier method, the problem is to maximize in $(\lambda, \mathbf{w}) \in \mathbb{R} \times \mathcal{S}_1$ the function:

$$L(\lambda, \mathbf{w}) = \sum_{i \in \mathcal{H}_1} F_i(w_i C) - \lambda \left(\sum_{i \in \mathcal{H}_1} w_i - m \right).$$

First assume that $(w_i)_i$ is a critical point, i.e. that for each i : $\frac{\partial L}{\partial w_i}(\lambda, \mathbf{w}) = C f_i(w_i C) - \lambda = 0$, so that $w_i = C^{-1} f_i^{-1}(\lambda C^{-1})$. Then, λ is chosen such that $\sum_i w_i = m$ i.e. $\Psi(\lambda C^{-1}) = mC$, which gives $\lambda C^{-1} = \Psi^{-1}(mC)$ and we find that the only possible critical point is $\forall i, w_i = w_i^*$.

To conclude, it is sufficient to prove that $(w_i^*)_i$ is a maximum. The latter holds because for each i , f_i is decreasing : $\frac{\partial^2 L}{\partial w_i^2}(\lambda, \mathbf{w}) = C^2 f_i'(w_i C) < 0$. ■

The proof of Proposition 4.2 is a direct consequence of the next lemma, which gives a sufficient condition to provide that $p_{i,n}$ has a c.d.f. asymptotically equal to the left-hand side of (13).

Lemma 9.3 *Suppose that condition (15) of Proposition 4.2 holds, then we have*

$$\zeta_{i,n}(S_{i,n}) \stackrel{\theta_{i,n}}{\rightsquigarrow} \bar{\Phi} \left(Z + h_i \frac{\tau_i'(0)}{\sigma_i(0)} \right),$$

where $Z \sim \mathcal{N}(0, 1)$ and $\bar{\Phi}$ is the standard Gaussian distribution tail. In particular, under the local alternative $\theta_{n,i} = h_i/\sqrt{n}$, the c.d.f. of $p_{i,n}$ converge (uniformly) to the function (13) with $\mu_i = h_i \frac{\tau_i'(0)}{\sigma_i(0)}$.

Note that the latter Lemma is similar to Theorem 14.7 of [26], which was stated to study the asymptotic relative efficiency of tests.

Proof of Lemma 9.3. Put $Z_n = \sqrt{n} \frac{S_{i,n} - \tau_i(0)}{\sigma_i(0)}$ and denote by $\xi_n(t) = \mathbb{P}_{H_i}(Z_n \geq t)$ the upper tail function of Z_n under the null. From (15) with $h = 0$, we get that Z_n converges in distribution under the null to a standard Gaussian variable, so that ξ_n converge to $\bar{\Phi}$ uniformly over \mathbb{R} . Moreover, since $Z_n = \frac{\sigma_i(\theta_{i,n})}{\sigma_i(0)} \sqrt{n} \frac{S_{i,n} - \tau_i(\theta_{i,n})}{\sigma_i(\theta_{i,n})} + \sqrt{n} \frac{\tau_i(\theta_{i,n}) - \tau_i(0)}{\sigma_i(0)}$, we have from (15) and Slutsky lemma, $Z_n \stackrel{\theta_{i,n}}{\rightsquigarrow} Z + h_i \frac{\tau_i'(0)}{\sigma_i(0)}$, where $Z \sim \mathcal{N}(0, 1)$. Therefore, since ξ_n converge uniformly to $\bar{\Phi}$, we apply Lemma A.3 and conclude $\zeta_{i,n}(S_{i,n}) = \xi_n(Z_n) \stackrel{\theta_{i,n}}{\rightsquigarrow} \bar{\Phi} \left(Z + h_i \frac{\tau_i'(0)}{\sigma_i(0)} \right)$. ■

Appendix

A Technical lemmas

The two following lemmas are easy to check from the definition of a step-up and a step-down procedure:

Lemma A.1 *Let R be a step-up procedure associated to a threshold collection Δ . For any i , denote by R' the step-up procedure associated to the threshold collection $\Delta'(i, r) = \Delta(i, r + 1)$ ($\Delta'(i, m) = \Delta(i, m)$). Denote by R'_{-i} the same step-up procedure but restricted to the null hypotheses $H_j, j \neq i$. Then we get for any set of p -values:*

1. $i \in R \Leftrightarrow R = R'_{-i} \cup \{i\} \Leftrightarrow p_i \leq \Delta'(i, |R'_{-i}|)$
2. $i \notin R' \Leftrightarrow R' = R'_{-i} \Leftrightarrow p_i > \Delta'(i, |R'|)$

Lemma A.2 *Let R be a step-down procedure associated to a threshold collection Δ . For any i , denote by R_{-i} the same step-down procedure but restricted to the null hypotheses $H_j, j \neq i$. Then we get for any set of p -values:*

1. $|R| \geq k$ and $p_i > \Delta(i, k-1) \Rightarrow |R_{-i}| \geq k-1$
2. $|R_{-i}| \geq k-1$ and $p_i \leq \Delta(i, k-1) \Rightarrow |R| \geq k$
3. $|R_{-i}| = k-1$ and $p_i > \Delta(i, k) \Rightarrow |R| = |R_{-i}|$

Lemma A.3 *Let $f_n, f : \mathbb{R} \rightarrow \mathbb{R}$ such that $\sup_{x \in \mathbb{R}} |f_n(x) - f(x)| \rightarrow 0$, suppose that f is continuous on \mathbb{R} and that f_n is measurable for all n . If $Z_n \rightsquigarrow Z$, then $f_n(Z_n) \rightsquigarrow f(Z)$.*

B FDR bounds for LSU(W) and LSD(W)

B.1 Step-up case

Lemma B.1 *Assume the p -values independent and consider the situation where only two true hypotheses are tested, that is, $\mathcal{H} = \{1, 2\} = \mathcal{H}_0$. Then, the step-up procedure R using a given threshold collection $(\Delta(i, r))_{i \in \{1, 2\}, r \in \{1, 2\}}$ has a FDR equal to*

$$\mathbb{P}[|R| > 0] = \Delta(1, 1) + \Delta(2, 1) + \Delta(1, 2)\Delta(2, 2) - \Delta(1, 2)\Delta(2, 1) - \Delta(1, 1)\Delta(2, 2).$$

In particular, when $m = m_0 = 2$, the (non-corrected) **LSU(W)** procedure has a FDR equal to $\alpha + \alpha^2(1 - w_1(2))(w_1(2) - w_1(1))$, which has a maximum equal to $\alpha + \alpha^2/4$, attained e.g. for the weight matrix

$$\mathbf{W} = \begin{pmatrix} 0 & 0.5 \\ 2 & 1.5 \end{pmatrix}.$$

B.2 Step-down case

Lemma B.2 *Assume the p -values independent. Then the (non-corrected) **LSD(W)** procedure controls the FDR at level α in the two following cases:*

- (i) *when all the hypotheses are true, that is $\mathcal{H}_0 = \mathcal{H}$,*
- (ii) *when $m = 2$ (and m_0 is unspecified).*

To prove (i), we easily check that, when all the hypotheses are true, the FDR of **LSD(W)** is $1 - \mathbb{P}[|L_\Delta(1)| = 0]$ and is thus equal to the FDR of **LSD(w(1))**, which is equal to α from standard results on uni-weighted procedure (see the beginning of Section 3). For point (ii), using point (i), we just have to check the case $m_0 = 1$. And this trivially holds from (25) (which also holds in the step-down case) because all the weights are smaller than $m = 2$.

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