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On control of the false discovery rate under no assumption of dependency

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Abstract

Most false discovery rate (FDR) controlling procedures require certain assumptions on the joint distribution of p-values. Benjamini and Hochberg [1995. Controlling the false discovery rate: a practical and powerful approach to multiple testing. J. Roy. Statist. Soc. Ser. B 57, 289–300] proposed a step-up procedure with critical constants $\alpha_i = (i/m)\alpha$, $1 \leqslant i \leqslant m$, for a given level $0 < \alpha < 1$ and showed that $\text{FDR} \leqslant (m_0/m)\alpha$ under the assumption of independence of p-values, where m is the total number of null hypotheses and m_0 the number of true null hypotheses. Benjamini and Yekutieli [2001. The control of the false discovery rate in multiple testing under dependency. Ann. Statist. 29, 1165–1188] showed that for the same procedure $\text{FDR} \leqslant (m_0/m)\alpha \sum_{j=1}^{m} 1/j$, whatever may be the joint distribution of p-values. In one of the results in this paper, we show that this upper bound for FDR cannot be improved in the sense that there exists a joint distribution of p-values for which the upper bound is attained. A major thrust of this paper is to work in the realm of step-down procedures without imposing any condition on the joint distribution of the underlying p-values. As a starting point, we give an explicit expression for FDR specially tailored for step-down procedures. Using the same critical constants as those of the Benjamini–Hochberg procedure, we present a new step-down procedure for which the upper bound for FDR is much lower than what is given by Benjamini and Yekutieli. The explicit expression given for FDR and some optimization techniques stemming from the knapsack problem are instrumental in getting the main result. We also present some general results on stepwise procedures built on non-decreasing sequences of critical constants.

Keywords: Critical constants; False discovery rate; Knapsack problem; Multiple testing; Positive regression dependence; p-Value; Step-up procedure; Step-down procedure

1. Introduction

In this article, we consider the problem of simultaneously testing a finite number of null hypotheses H_i $(i = 1, \ldots, m)$. A main concern in multiple testing is the multiplicity problem. A traditional approach to solve this problem is to control the familywise error rate (FWER), which is the probability of one or more false rejections, at a desired level. However, when the number m of null hypotheses is large, very few false null hypotheses are rejected when one uses a multiple testing procedure that controls FWER. Consequently, alternative measures of error rates have been considered in the literature. Control of these measures purportedly leads to rejection of more false null hypotheses. One well-known

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measure is the false discovery rate (FDR), which is the expected proportion of Type I errors among the rejected hypotheses, proposed by Benjamini and Hochberg (1995).

In this paper, discussion is focused on multiple testing procedures controlling FDR. Benjamini and Hochberg (1995) proposed a simple linear step-up procedure with critical constants $\alpha_i = (i/m)\alpha$, $1 \leqslant i \leqslant m$ and showed that $\mathrm{FDR} \leqslant (m_0/m)\alpha$, where m_0 is the number of true null hypotheses, under the assumption of independence of the underlying test statistics. Subsequently, Benjamini and Liu (1999a) constructed a step-down procedure with the FDR-controlling property for independent test statistics. Benjamini and Yekutieli (2001) extended the FDR-controlling property of the Benjamini–Hochberg procedure to the case in which the test statistics have positive regression dependency on each of the test statistics corresponding to the true null hypotheses (the PRDS property). Sarkar (2002) strengthened the result of Benjamini and Yekutieli by showing that a more general step-down–step-up procedure with the same critical values as those of Benjamini–Hochberg procedure controls the FDR under the PRDS property. In addition, he also showed that the Benjamini–Liu step-down procedure has the FDR-controlling property under certain positive dependence requirements. In the absence of any knowledge of dependence among the test statistics, Benjamini and Yekutieli (2001) showed that for the Benjamini–Hochberg step-up procedure

$$\mathrm{FDR} \leqslant \frac{m_0}{m}\alpha D_1(m), \tag{1}$$

where $D_1 = D_1(m) = \sum_{j=1}^{m} 1/j$.

In view of (1), one can modify the Benjamini–Hochberg procedure in order to control FDR at level α. The critical constants have to be now $\alpha_i' = (i/m)\alpha \cdot 1/D_1$, $1 \leqslant i \leqslant m$. If we can lower the upper bound (1) from $(m_0\alpha/m)D_1$ to some $(m_0\alpha/m)D_1'$, then the modified critical constants based on D_1' will be larger leading to more power, i.e., rejection of more false hypotheses. However, we show that the upper bound (1) cannot be improved in the sense that there is a joint distribution of p-values for which the upper bound is attained (Theorem 5.1). Consequently, it is natural to look at step-down procedures and check whether the upper bound (1) can be lowered. This is our main pursuit in this paper. In fact, we propose a new step-down procedure using the same critical constants as those of the Benjamini–Hochberg procedure for which the upper bound is much less than (1) (Theorem 4.1). Most of the techniques used in the literature in deriving bounds for FDR rely on probability inequalities and an explicit expression of FDR due to Benjamini and Yekutieli (2001). See also Sarkar (2002). As a prelude to the main result, we fine-tune the expression for FDR specially tailored for step-down procedures. Using this expression and an optimization technique stemming from the knapsack problem, we achieve the desired upper bound, which is smaller than (1), for the new step-down procedure.

The FDR has been extensively used in many applications such as microarray data analysis (Reiner et al., 2003), clinical trials (Mehrotra and Heyse, 2004), model selection (Abramovich et al., 2006), and educational evaluation (Williams et al., 1999). A major impetus for this work comes from genome studies, in which a large number of null hypotheses are tested simultaneously. It is almost impossible to check from biological principles or real data sets whether the underlying test statistics satisfy the assumption of independence or positive dependence of some type, although based on simulation studies and general assumptions of weak dependence, it is well known among practitioners that the Benjamini–Hochberg procedure controls the FDR at α. Thus, it is important to seek multiple testing procedures which are operational whatever may be the joint distribution of the test statistics with a tight bound for FDR.

The paper is organized as follows. In Section 2, we describe our basic setting and terminology. We establish a finely tuned version of the standard expression of FDR for step-down procedures in Section 3. Step-down procedures for controlling FDR under arbitrary dependency are considered in Section 4. The first main result is presented in Theorem 4.1 and generalized in Theorem 4.2. In Section 5, step-up procedures for controlling FDR are discussed under no assumption on dependency. The second main result is presented in Theorem 5.1.

2. Basic setting

Consider the problem of testing simultaneously m null hypotheses $\mathrm{H}_1, \mathrm{H}_2, \ldots, \mathrm{H}_m$, of which m_0 are true and $m_1 = m - m_0$ are false. Assume, without loss of generality, that $\mathrm{H}_1, \ldots, \mathrm{H}_{m_0}$ are true. Let $I = \{1, 2, \ldots, m\}$ and $I_0 = \{1, \ldots, m_0\}$.

Suppose R is the total number of hypotheses rejected and V the number of true null hypotheses rejected. The proportion of false discoveries is defined to be $Q = V/R$ (and equal to 0 if $R = 0$) and the FDR is defined to be the expectation of Q, i.e.,

$$\mathrm{FDR} = E(Q) = E\left(\frac{V}{R}\right). \tag{2}$$

When testing $\mathrm{H}_1, \mathrm{H}_2, \ldots, \mathrm{H}_m$, the corresponding p-values $P_1, P_2, \ldots, P_m$ are available to us. Multiple testing procedures are usually built on the p-values. We assume that each of the p-values corresponding to true null hypotheses satisfies

$$\Pr\{P_i \leqslant x\} \leqslant x \quad \text{for any } 0 < x < 1 \text{ and } i \in I_0,$$

and the joint distribution is arbitrary. Let the ordered p-values be denoted by $P_{(1)} \leqslant P_{(2)} \leqslant \cdots \leqslant P_{(m)}$, and the associated hypotheses by $\mathrm{H}_{(1)}, \mathrm{H}_{(2)}, \ldots, \mathrm{H}_{(m)}$. Suppose $\alpha_1 \leqslant \alpha_2 \leqslant \cdots \leqslant \alpha_m$ is a non-decreasing sequence of critical constants.

The step-up procedure based on the constants proceeds as follows. If $P_{(m)} \leqslant \alpha_m$, then reject all null hypotheses; otherwise, reject hypotheses $\mathrm{H}_{(1)}, \ldots, \mathrm{H}_{(r)}$ where r is the smallest index satisfying $P_{(m)} > \alpha_m, \ldots, P_{(r+1)} > \alpha_{r+1}$. If, for all r, $P_{(r)} > \alpha_r$, then reject none of the hypotheses. A step-up procedure begins with the least significant hypothesis and continues accepting hypotheses as long as their corresponding p-values are greater than the corresponding critical values. Specially, the Benjamini–Hochberg procedure is a step-up procedure with critical constants $\alpha_i = (i/m)\alpha$, $i \in I$.

Similarly, the step-down procedure based on the constants $\alpha_1 \leqslant \alpha_2 \leqslant \cdots \leqslant \alpha_m$ proceeds as follows. If $P_{(1)} > \alpha_1$, reject none of the null hypotheses. Otherwise, reject hypotheses $\mathrm{H}_{(1)}, \ldots, \mathrm{H}_{(r)}$ where r is the largest index satisfying $P_{(1)} \leqslant \alpha_1, \ldots, P_{(r)} \leqslant \alpha_r$. A step-down procedure starts with the most significant hypothesis and continues rejecting hypotheses as long as their corresponding p-values are less than or equal to the corresponding critical values.

3. A refined expression for FDR

The following expression for the FDR is fundamental in deriving upper bounds for FDR.

Lemma 3.1 (Benjamini and Yekutieli, 2001; Sarkar, 2002). *The FDR of the step-up or step-down procedure based on any non-decreasing critical values α_i, $i \in I$ is given by*

$$\mathrm{FDR} = \sum_{i=1}^{m_0} \sum_{k=1}^{m} \frac{1}{k} \Pr(P_i \leqslant \alpha_k, R = k). \tag{3}$$

For convenience, let $\alpha_0 = 0$, and denote $S_j = (\alpha_{j-1}, \alpha_j]$ and $p_{ijk} = \Pr(P_i \in S_j, R = k)$ for $1 \leqslant i \leqslant m_0$ and $1 \leqslant j \leqslant k \leqslant m$. Observe that, from Lemma 3.1, FDR can be expressed as follows:

$$\mathrm{FDR} = \sum_{i=1}^{m_0} \sum_{k=1}^{m} \sum_{j=1}^{k} \frac{1}{k} p_{ijk} = \sum_{i=1}^{m_0} \sum_{j=1}^{m} \sum_{k=j}^{m} \frac{1}{k} p_{ijk}. \tag{4}$$

We now proceed to refine (4) by splitting p_{ijk} further. Note that p_{ijk} is the probability that k null hypotheses are being rejected with p-value P_i corresponding to the ith true null hypothesis lying in the jth interval S_j. We want to identify how many true null hypotheses are rejected and where the corresponding p-values are located in the event that defines p_{ijk}. Towards this goal, we introduce the entity (5) described below. Let k stand as a generic symbol for the number of null hypotheses rejected and l for the number of true null hypotheses rejected. Clearly, $1 \leqslant k \leqslant m$ and $1 \leqslant l \leqslant \min\{k, m_0\}$. For convenience of notation, we denote $\min\{k, m_0\} = k \wedge m_0$.

Consider the event $\{R = k \text{ and } V = l\}$ of rejecting k null hypotheses of which l many are true. The true null hypotheses could be any l of $\mathrm{H}_1, \ldots, \mathrm{H}_{m_0}$. Let $1 \leqslant i_1 < \cdots < i_l \leqslant m_0$, $1 \leqslant j_1, \ldots, j_l \leqslant k$, and

$$q^{(k)}_{(i_1, j_1), \ldots, (i_l, j_l)} = \Pr\{P_{i_1} \in S_{j_1}, \ldots, P_{i_l} \in S_{j_l}, R = k, V = l\}. \tag{5}$$

In (5), we are trying to identify the true null hypotheses that are rejected and the intervals at which the corresponding p-values are located in the make-up of the event $\{R = k \text{ and } V = l\}$. In other words, $q^{(k)}_{(i_1, j_1), \ldots, (i_l, j_l)}$ is the probability of rejecting k null hypotheses of which l many are true, and the indices of the l true null hypotheses are $1 \leqslant i_1 < \cdots < i_l \leqslant m_0$, and the corresponding p-values belong to $S_{j_1}, \ldots, S_{j_l}$, respectively.

As we want to tie up p_{ijk}'s with q's, we need to introduce two more symbols. For any $1 \leqslant i \leqslant m_0$, $1 \leqslant j \leqslant k \leqslant m$, and $1 \leqslant l \leqslant k \wedge m_0$, define

$$\begin{aligned}\Omega_l^{(k)}(i,j) = \{((i_1,j_1),\ldots,(i_l,j_l)) : 1 \leqslant i_1 < \cdots < i_l \leqslant m_0, 1 \leqslant j_1,\ldots,j_l \leqslant k \\ \text{and } (i_d,j_d)=(i,j) \text{ for some } 1 \leqslant d \leqslant l\}\end{aligned} \tag{6}$$

and

$$\begin{aligned}\Omega_l^{(k)} &= \{((i_1,j_1),\ldots,(i_l,j_l)) : 1 \leqslant i_1 < \cdots < i_l \leqslant m_0, 1 \leqslant j_1,\ldots,j_l \leqslant k\} \\ &= \bigcup_{\substack{1 \leqslant i \leqslant m_0 \\ 1 \leqslant j \leqslant k}} \Omega_l^{(k)}(i,j).\end{aligned} \tag{7}$$

Specially, observe that for $l=1$, $\Omega_1^{(k)}(i,j)=\{(i,j)\}$ and $\Omega_1^{(k)}=\{(i,j) : 1 \leqslant i \leqslant m_0, 1 \leqslant j \leqslant k\}$. Based on (6), the event $\{P_i \in S_j, R=k\}$ can be expressed as a union of events of the type involved in the definition of q's over $1 \leqslant l \leqslant k \wedge m_0$ and $((i_1,j_1),\ldots,(i_l,j_l)) \in \Omega_l^{(k)}(i,j)$. Consequently, p_{ijk} can be expressed by

$$p_{ijk} = \sum_{l=1}^{k \wedge m_0} \sum_{\Omega_l^{(k)}(i,j)} q^{(k)}_{(i_1,j_1),\ldots,(i_l,j_l)}, \tag{8}$$

where the summation $\sum_{\Omega_l^{(k)}(i,j)}$ is taken over all $((i_1,j_1),\ldots,(i_l,j_l)) \in \Omega_l^{(k)}(i,j)$.

Example 3.1. For $m=3$, $m_0=2$, $k=3$, and $i=1$,

$$\begin{aligned}p_{113} &= q^{(3)}_{(1,1)} + q^{(3)}_{(1,1),(2,1)} + q^{(3)}_{(1,1),(2,2)} + q^{(3)}_{(1,1),(2,3)}, \\ p_{123} &= q^{(3)}_{(1,2)} + q^{(3)}_{(1,2),(2,1)} + q^{(3)}_{(1,2),(2,2)} + q^{(3)}_{(1,2),(2,3)},\end{aligned}$$

and

$$p_{133} = q^{(3)}_{(1,3)} + q^{(3)}_{(1,3),(2,1)} + q^{(3)}_{(1,3),(2,2)} + q^{(3)}_{(1,3),(2,3)}.$$

We now present an explicit expression for the FDR, which is, in fact, a finely tuned version of (3) and (4) for any step-up or step-down procedure.

Lemma 3.2. *The FDR of the step-up or step-down procedure with any non-decreasing critical values* $\alpha_i, i \in I$ *is given by*

$$\mathrm{FDR} = \sum_{l=1}^{m_0} \sum_{k=l}^{m} \sum_{\Omega_l^{(k)}} \frac{l}{k} q^{(k)}_{(i_1,j_1),\ldots,(i_l,j_l)}. \tag{9}$$

Proof. Combining Eqs. (4) and (8), we have

$$\begin{aligned}\mathrm{FDR} &= \sum_{i=1}^{m_0} \sum_{j=1}^{m} \sum_{k=j}^{m} \sum_{l=1}^{k \wedge m_0} \sum_{\Omega_l^{(k)}(i,j)} \frac{1}{k} q^{(k)}_{(i_1,j_1),\ldots,(i_l,j_l)} \\ &= \sum_{k=1}^{m} \sum_{l=1}^{k \wedge m_0} \sum_{i=1}^{m_0} \sum_{j=1}^{k} \sum_{\Omega_l^{(k)}(i,j)} \frac{1}{k} q^{(k)}_{(i_1,j_1),\ldots,(i_l,j_l)} \\ &= \sum_{l=1}^{m_0} \sum_{k=l}^{m} \sum_{i=1}^{m_0} \sum_{j=1}^{k} \sum_{\Omega_l^{(k)}(i,j)} \frac{1}{k} q^{(k)}_{(i_1,j_1),\ldots,(i_l,j_l)}.\end{aligned} \tag{10}$$

The second equality in (10) is obtained by interchanging the first two summations and the last ones in the first equality, and the final equality is obtained by interchanging the first two summations in the second equality. For the final step, suppose $x = ((i_1, j_1), \ldots, (i_l, j_l)) \in \Omega_l^{(k)}$. Then, from (7), $x \in \Omega_l^{(k)}(i_1, j_1), \ldots, \Omega_l^{(k)}(i_l, j_l)$. Note that x belongs to only these l sets in view of the fact that $x \in \Omega_l^{(k)}(i, j)$ if and only if $(i_d, j_d) = (i, j)$ for some $1 \leqslant d \leqslant l$. Consequently,

$$\sum_{i=1}^{m_0} \sum_{j=1}^{k} \sum_{\Omega_l^{(k)}(i,j)} \frac{1}{k} q^{(k)}_{(i_1,j_1),\ldots,(i_l,j_l)} = \sum_{\Omega_l^{(k)}} \frac{l}{k} q^{(k)}_{(i_1,j_1),\ldots,(i_l,j_l)}. \tag{11}$$

Thus, (9) follows from (10) and (11). □

In the expression (9) for the FDR of the step-down procedure, not all q's are positive.

Example 3.2. This is a continuation of Example 3.1. For the step-down procedure based on the constants $\alpha_1 \leqslant \alpha_2 \leqslant \alpha_3$, $q^{(3)}_{(1,3),(2,3)} = 0$. Recall $q^{(3)}_{(1,3),(2,3)} = \Pr(P_1 \in (\alpha_2, \alpha_3], P_2 \in (\alpha_2, \alpha_3], R = 3, V = 2)$. The event $R = 3$ can occur if and only if the event $\{P_{(1)} \leqslant \alpha_1, P_{(2)} \leqslant \alpha_2, P_{(3)} \leqslant \alpha_3\}$ occurs. The later event is not compatible with $\{P_1 \in (\alpha_2, \alpha_3], P_2 \in (\alpha_2, \alpha_3], R = 3\}$. Also, it is true that $q^{(3)}_{(1,1)} = q^{(3)}_{(1,2)} = q^{(3)}_{(1,3)} = 0$.

More generally, we have the following result.

Lemma 3.3. *Consider the step-down procedure based on any non-decreasing critical constants $\alpha_i, i \in I$. For any $((i_1, j_1), \ldots, (i_l, j_l)) \in \Omega_l^{(k)}$ with $1 \leqslant k \leqslant m$ and $1 \leqslant l \leqslant k \wedge m_0$, $q^{(k)}_{(i_1,j_1),\ldots,(i_l,j_l)} = 0$ if either of the following inequalities is violated.*

$$k - l \leqslant m_1, \tag{12}$$

$$j_{(d)} \leqslant k - l + d \quad \text{for any } 1 \leqslant d \leqslant l, \tag{13}$$

where $j_{(1)} \leqslant \cdots \leqslant j_{(l)}$ is an ordered rearrangement of $j_1, \ldots, j_l$.

Proof. In the event $\{R = k, V = l\}$, $k - l$ is the number of false null hypotheses rejected and consequently $k - l \leqslant m_1$. Thus, if (12) does not hold, then $q^{(k)}_{(i_1,j_1),\ldots,(i_l,j_l)} = 0$. Note that, if the event $\{R = k, V = l\}$ occurs, then, for any $1 \leqslant d \leqslant l$, the largest possible index $j_{(d)}$ occurs when all the smallest p-values correspond to the $k - l$ false null hypotheses and the next l p-values correspond to the true null hypotheses; that is, $j_{(d)} \leqslant (k - l) + d$. So, if (13) does not hold, then $q^{(k)}_{(i_1,j_1),\ldots,(i_l,j_l)} = 0$. □

4. A new step-down procedure

In this section, we present a new step-down procedure, for which we obtain an upper bound for FDR under arbitrary dependency. The critical constants of the procedure are $\alpha_i = (i/m)\alpha, i \in I$, which are the same as those of the Benjamini–Hochberg step-up procedure. Later, more generally, we obtain an upper bound for a step-down procedure with any non-decreasing critical constants.

We first present a lemma, which is needed in the proof of the main result, Theorem 4.1.

Lemma 4.1. *Let the sequence of constants $\lambda_i, i = 1, \ldots, m$ be defined by*

$$\lambda_i = \begin{cases} \dfrac{1}{i} & \text{if } 1 \leqslant i \leqslant m_1 + 1, \\[2ex] \dfrac{m_1}{i(i-1)} & \text{if } m_1 + 2 \leqslant i \leqslant m. \end{cases} \tag{14}$$

Then, for any $((i_1, j_1), \ldots, (i_l, j_l)) \in \Omega_l^{(k)}$ *with* k, l *and* j*'s satisfying* (12) *and* (13), *we have*

$$\sum_{d=1}^{l} \lambda_{j_d} \geqslant \frac{l}{k}. \tag{15}$$

Proof. We use mathematical induction to prove (15). For $l = 1$, note that from (12) and (13), $j_1 \leqslant k \leqslant m_1 + 1$. Hence $\lambda_{j_1} = 1/j_1 \geqslant 1/k$. That is, (15) holds for $l = 1$.

Suppose that (15) holds for $l=s$. We now prove that it also holds for $l=s+1$. For any $((i_1, j_1), \ldots, (i_s, j_s), (i_{s+1}, j_{s+1})) \in \Omega_{s+1}^{(k)}$ with k, $s+1$ and j's satisfying (12) and (13). Assume, without loss of generality, that $j_{s+1} = \max\{j_1, \ldots, j_s, j_{s+1}\}$. Then, from (13) and (7), $((i_1, j_1), \ldots, (i_s, j_s)) \in \Omega_s^{(k-1)}$. It is easy to verify that $k-1$, s and $(j_1, \ldots, j_s)$ satisfy (12) and (13). By the induction hypothesis,

$$\sum_{d=1}^{s} \lambda_{j_d} \geqslant \frac{s}{k-1}. \tag{16}$$

Note that, from (12) and (13), $j_{s+1} \leqslant k \leqslant m_1 + s + 1$. Then, from (14) and (16), we have

$$\sum_{d=1}^{s+1} \lambda_{j_d} \geqslant \frac{s}{k-1} + \frac{1}{k} \geqslant \frac{s+1}{k} \quad \text{if } j_{s+1} \leqslant m_1 + 1 \tag{17}$$

and

$$\sum_{d=1}^{s+1} \lambda_{j_d} \geqslant \frac{s}{k-1} + \frac{m_1}{k(k-1)} \geqslant \frac{s+1}{k} \quad \text{if } j_{s+1} > m_1 + 1. \tag{18}$$

This completes the proof. □

In order to obtain an upper bound for the FDR of the proposed step-down procedure, we formulate a relevant optimization problem in (21). Note that, for any $i \in I_0$ and $j \in I$,

$$\sum_{k=j}^{m} p_{ijk} = \Pr\left\{P_i \in \left(\frac{j-1}{m}\alpha, \frac{j}{m}\alpha\right], j \leqslant R \leqslant m\right\} \leqslant \frac{\alpha}{m}. \tag{19}$$

Combining Eqs. (19) and (8), we have

$$\sum_{k=j}^{m} \sum_{l=1}^{k\wedge m_0} \sum_{\Omega_l^{(k)}(i,j)} q^{(k)}_{(i_1,j_1),\ldots,(i_l,j_l)} \leqslant \frac{\alpha}{m}. \tag{20}$$

Note that FDR as given in (9) is a linear function of q's. In order to obtain an upper bound for FDR as low as possible, we maximize FDR with respect to q's, since FDR's maximum value is FDR's least upper bound. Combining (9) and (20), we formulate an abstract optimization problem as follows:

$$\text{maximize FDR} = \sum_{l=1}^{m_0} \sum_{k=l}^{m} \sum_{\Omega_l^{(k)}} \frac{l}{k} q^{(k)}_{(i_1,j_1),\ldots,(i_l,j_l)}, \tag{21}$$

with respect to $q^{(k)}_{(i_1,j_1),\ldots,(i_l,j_l)}$'s $\geqslant 0$, subject to the constraints

$$\sum_{k=j}^{m} \sum_{l=1}^{k\wedge m_0} \sum_{\Omega_l^{(k)}(i,j)} q^{(k)}_{(i_1,j_1),\ldots,(i_l,j_l)} \leqslant \frac{\alpha}{m}, \quad i \in I_0, j \in I,$$

and those imposed by Lemma 3.3.

In (21), we want to maximize FDR (abuse of notation) with respect to q's whether or not q's come from a joint distribution of p-values. We split the objective function in (21) into two parts: $l=1$ and $l \geqslant 2$. Note that $\Omega_1^{(k)} = \{(i,j) : 1 \leqslant i \leqslant m_0 \text{ and } 1 \leqslant j \leqslant k\}$. Further, $q_{(i,j)}^{(k)} = 0$ if $k > m_1 + 1$ (Lemma 3.3). We remove these q's from consideration. The objective function in (21) is simplified as follows:

$$\mathrm{FDR} = \sum_{k=1}^{m_1+1} \sum_{i=1}^{m_0} \sum_{j=1}^{k} \frac{1}{k} q_{(i,j)}^{(k)} + \sum_{l=2}^{m_0} \sum_{k=l}^{m} \sum_{\Omega_l^{(k)}} \frac{l}{k} q_{(i_1,j_1),\ldots,(i_l,j_l)}^{(k)}. \tag{22}$$

We split the first sum in (22) into two parts: $j = k$ and $j \leqslant k-1$. That is,

$$\mathrm{FDR} = \sum_{k=1}^{m_1+1} \sum_{i=1}^{m_0} \frac{1}{k} q_{(i,k)}^{(k)} + \sum_{k=2}^{m_1+1} \sum_{i=1}^{m_0} \sum_{j=1}^{k-1} \frac{1}{k} q_{(i,j)}^{(k)} + \sum_{l=2}^{m_0} \sum_{k=l}^{m} \sum_{\Omega_l^{(k)}} \frac{l}{k} q_{(i_1,j_1),\ldots,(i_l,j_l)}^{(k)}. \tag{23}$$

The constraints in (21) are also split analogously: $l=1$ and $l \geqslant 2$. Note that $\Omega_1^{(k)}(i,j) = \{(i,j)\}$ and for $i \in I_0$ and $j \in I$,

$$\sum_{k=j}^{m} q_{(i,j)}^{(k)} + \sum_{k=j}^{m} \sum_{l=2}^{k \wedge m_0} \sum_{\Omega_l^{(k)}(i,j)} q_{(i_1,j_1),\ldots,(i_l,j_l)}^{(k)} \leqslant \frac{\alpha}{m}. \tag{24}$$

Split the first sum in (24) into two parts: $k=j$ and $k \geqslant j+1$. Exploit $q_{(i,j)}^{(k)} = 0$ if $k > m_1+1$. The constraint (24) now becomes

$$q_{(i,j)}^{(j)} + \sum_{k=j+1}^{m_1+1} q_{(i,j)}^{(k)} + \sum_{k=j}^{m} \sum_{l=2}^{k \wedge m_0} \sum_{\Omega_l^{(k)}(i,j)} q_{(i_1,j_1),\ldots,(i_l,j_l)}^{(k)} \leqslant \frac{\alpha}{m}, \tag{25}$$

for $i \in I_0$ and $1 \leqslant j \leqslant m_1+1$, and for $i \in I_0$ and $m_1 + 2 \leqslant j \leqslant m$,

$$\sum_{k=j}^{m} \sum_{l=2}^{k \wedge m_0} \sum_{\Omega_l^{(k)}(i,j)} q_{(i_1,j_1),\ldots,(i_l,j_l)}^{(k)} \leqslant \frac{\alpha}{m}. \tag{26}$$

In summary, the optimization problem stated in (21) is reformulated with the objective function now being (23) and the constraints are (25), (26), and those imposed by Lemma 3.3.

Theorem 4.1. *The FDR of the step-down procedure with critical values $\alpha_i = (i/m)\alpha$, $i \in I$ satisfies the following inequality*:

$$\mathrm{FDR} \leqslant \frac{m_0}{m} \alpha \left\{ \sum_{j=1}^{m_1+1} \frac{1}{j} + \frac{m_1}{m_1+1} - \frac{m_1}{m} \right\}. \tag{27}$$

Specifically, *let*

$$D_2 = D_2(m) = \max_{1 \leqslant m_0 \leqslant m} \frac{m_0}{m} \left\{ \sum_{j=1}^{m_1+1} \frac{1}{j} + \frac{m_1}{m_1+1} - \frac{m_1}{m} \right\}. \tag{28}$$

Now, the modified step-down procedure with critical constants $\alpha_i' = (i/m)\alpha/D_2$, $i \in I$ will always control the FDR at a level less than or equal to α.

Proof. The optimization problem posed as it is in (21) is not easy to solve. We consider a closely related optimization problem. Let $x_{ik} = q^{(k)}_{(i,k)}$, $i \in I_0$ and $1 \leqslant k \leqslant m_1 + 1$ and introduce new variables x_{ik}, $i \in I_0$ and $m_1 + 2 \leqslant k \leqslant m$. Let λ_k's be the same as those defined in (14).

$$\text{maximize } \widetilde{\text{FDR}} = \sum_{k=1}^{m} \sum_{i=1}^{m_0} \lambda_k x_{ik} + \sum_{k=2}^{m_1+1} \sum_{i=1}^{m_0} \sum_{j=1}^{k-1} \frac{1}{k} q^{(k)}_{(i,j)} + \sum_{l=2}^{m_0} \sum_{k=l}^{m} \sum_{\Omega_l^{(k)}} \frac{l}{k} q^{(k)}_{(i_1,j_1),\ldots,(i_l,j_l)}, \tag{29}$$

with respect to x_{ik}'s $\geqslant 0$ and q's $\geqslant 0$, subject to the constraints, for each $i \in I_0$,

$$x_{ij} + \sum_{k=j+1}^{m_1+1} q^{(k)}_{(i,j)} + \sum_{k=j}^{m} \sum_{l=2}^{k \wedge m_0} \sum_{\Omega_l^{(k)}(i,j)} q^{(k)}_{(i_1,j_1),\ldots,(i_l,j_l)} \leqslant \frac{\alpha}{m}, \quad 1 \leqslant j \leqslant m_1 + 1,$$

$$x_{ij} + \sum_{k=j}^{m} \sum_{l=2}^{k \wedge m_0} \sum_{\Omega_l^{(k)}(i,j)} q^{(k)}_{(i_1,j_1),\ldots,(i_l,j_l)} \leqslant \frac{\alpha}{m}, \quad m_1 + 2 \leqslant j \leqslant m.$$

There is one difference between the objective function in (29) and the objective function in (21), simplified in (23),

$$\widetilde{\text{FDR}} = \text{FDR} + \sum_{k=m_1+2}^{m} \sum_{i=1}^{m_0} \lambda_k x_{ik} \geqslant \text{FDR}.$$

We add an additional term x_{ij} on the left-hand side of (26). Consequently, any solution to the constraints (25) and (26) is also a solution to the constraint in (29) if we set $x_{ij} = 0$, for each $i \in I_0$ and $m_1 + 2 \leqslant j \leqslant m$. Hence, the maximum value of the objective function in (21) is less than or equal to the maximum value of the objective function in (29). We now proceed to obtain the maximum value of (29).

Let x's and q's be any solution to the constraints in (29) with $\widetilde{\text{FDR}} = u$, say. We give another solution x^*'s and q^*'s to the constraints in (29), whose value of $\widetilde{\text{FDR}}$ is at least u. Let $l \geqslant 2$ and $((i_1, j_1), \ldots, (i_l, j_l)) \in \Omega_l^{(k)}$. Suppose $q^{(k)}_{(i_1,j_1),\ldots,(i_l,j_l)} > 0$. Set $x^*_{i_d j_d} = x_{i_d j_d} + q^{(k)}_{(i_1,j_1),\ldots,(i_l,j_l)}$ for $1 \leqslant d \leqslant l$ and $q^{(k)*}_{(i_1,j_1),\ldots,(i_l,j_l)} = 0$. The other x's and q's remain the same. The new solution increases the value of $\widetilde{\text{FDR}}$ by $(\sum_{d=1}^{l} \lambda_{j_d} - l/k) q^{(k)}_{(i_1,j_1),\ldots,(i_l,j_l)} \geqslant 0$, since $\sum_{d=1}^{l} \lambda_{j_d} \geqslant l/k$ by Lemma 4.1. Thus, in the optimization problem (29),we can set each $q^{(k)}_{(i_1,j_1),\ldots,(i_l,j_l)} = 0$ for any $l \geqslant 2$. Similarly, for any $(i, j) \in \Omega_1^{(k)}$ with $1 \leqslant j < k \leqslant m_1 + 1$, we can also set $q^{(k)}_{(i,j)} = 0$, since $\lambda_j \geqslant 1/k$. The optimization problem in (29) simplifies to

$$\text{maximize } \widetilde{\text{FDR}} = \sum_{k=1}^{m} \sum_{i=1}^{m_0} \lambda_k x_{ik}, \tag{30}$$

with respect to x_{ik}'s $\geqslant 0$, and subject to $x_{ik} \leqslant \alpha/m$, for $i \in I_0$ and $k \in I$.

Obviously, the optimal solution to the problem (30) is $x^*_{ik} = \alpha/m$, $i \in I_0$ and $k \in I$, and the maximum value of $\widetilde{\text{FDR}}$ is

$$\begin{aligned} \widetilde{\text{FDR}}^* &= \sum_{k=1}^{m} \sum_{i=1}^{m_0} \frac{\alpha}{m} \lambda_k = \frac{m_0}{m} \alpha \left\{ \sum_{k=1}^{m_1+1} \frac{1}{k} + \sum_{k=m_1+2}^{m} \frac{m_1}{k(k-1)} \right\} \\ &= \frac{m_0}{m} \alpha \left\{ \sum_{k=1}^{m_1+1} \frac{1}{k} + \frac{m_1}{m_1+1} - \frac{m_1}{m} \right\}. \end{aligned} \tag{31}$$

This leads to

$$\text{FDR} \leqslant \frac{m_0}{m} \alpha \left\{ \sum_{j=1}^{m_1+1} \frac{1}{j} + \frac{m_1}{m_1+1} - \frac{m_1}{m} \right\}. \qquad \square$$

Remark 4.1. Sarkar (2002) showed that the step-down analog of the Benjamini–Hochberg procedure controls the FDR if the test statistics satisfy the PRDS property. One may contrast his result with the result stated in Theorem 4.1, in which no assumption is made on the joint distribution of p-values.

Remark 4.2. If $[m_0(m_1+2)-1]\alpha/m \leqslant 1$, we can construct a joint distribution of p-values so that for the step-down procedure with critical constants $\alpha_i = i\alpha/m$, $i \in I$, $\mathrm{FDR} = (m_0\alpha/m)\sum_{j=1}^{m_1+1} 1/j$. The construction of the joint distribution is as follows. Let $U_1, \ldots, U_{m+1}$ be $m+1$ uniformly distributed random variables such that $U_i \sim U[\alpha_{i-1}, \alpha_i]$, $i = 1, \ldots, m$, and $U_{m+1} \sim U[\alpha_m, 1]$. Let N be a random variable taking values $1, \ldots, m+1$ with the following probability distribution:

$$Pr\{N = n\} = \begin{cases} m_0(\alpha_n - \alpha_{n-1}) & \text{if } 1 \leqslant n \leqslant m_1 + 1, \\ \alpha_n - \alpha_{n-1} & \text{if } m_1 + 2 \leqslant n \leqslant m, \\ 1 - (m_0 - 1)\alpha_{m_1+1} - \alpha_m & \text{if } n = m + 1. \end{cases} \tag{32}$$

Suppose n is the realized value of N. For $n = 1, \ldots, m_1 + 1$, randomly pick one index from I_0 and $n-1$ indices from I_1 without replacement. Let the p-value associated with the index chosen from I_0 be U_n, each of the p-values associated with those $n-1$ indices chosen from I_1 be U_1, and each of the p-values associated with the remaining $m-n$ p-values equal to U_{m+1}. For $n = m_1 + 2, \ldots, m$, let all m_0 p-values from I_0 be equal to U_n and m_1 p-values from I_1 be equal to U_1. For $n = m + 1$, let all m p-values be equal to U_{m+1}. It is easy to verify that the p-values from I_0 are uniformly distributed on [0, 1] and the p-values from I_1 are stochastically smaller than $U[0, 1]$, and $p_{ijn} = \alpha_j - \alpha_{j-1}$, if $j = n$ and $1 \leqslant n \leqslant m_1 + 1$, and equals to 0, otherwise. From (4), we have $\mathrm{FDR} = (m_0\alpha/m)\sum_{j=1}^{m_1+1} 1/j$, which is close to the upper bound of the FDR in Theorem 4.1. For example, if $m = 100$, $m_0 = 80$, and $\alpha = 0.05$, then $m_0(m_1+1)\alpha/m = 0.84 \leqslant 1$, $\mathrm{FDR} = (m_0\alpha/m)\sum_{j=1}^{m_1+1} 1/j = 0.146$, and the upper bound in (27) is 0.176. The difference between these numbers relative to the upperbound is about 17%.

Theorem 4.1 can be generalized to the step-down procedure with any non-decreasing critical values α_i, $i \in I$. Let $\alpha_0 = 0$. Using ideas similar to the ones in the proof of Theorem 4.1, the following result holds.

Theorem 4.2. *The FDR of the step-down procedure with any non-decreasing critical values α_i, $i \in I$ satisfies the following inequality*:

$$\mathrm{FDR} \leqslant m_0 \left\{ \sum_{j=1}^{m_1+1} \frac{\alpha_j - \alpha_{j-1}}{j} + \sum_{j=m_1+2}^{m} \frac{m_1(\alpha_j - \alpha_{j-1})}{j(j-1)} \right\}.$$

Specifically, *let*

$$D_3 = D_3(m) = \max_{1 \leqslant m_0 \leqslant m} \frac{m_0}{\alpha} \left\{ \sum_{j=1}^{m_1+1} \frac{\alpha_j - \alpha_{j-1}}{j} + \sum_{j=m_1+2}^{m} \frac{m_1(\alpha_j - \alpha_{j-1})}{j(j-1)} \right\}. \tag{33}$$

Now, *the modified step-down procedure with critical constants $\alpha_i' = \alpha_i/D_3$, $i \in I$ will always control the FDR at a level less than or equal to α.*

We now contrast the Benjamini–Yekutieli step-up procedure and the new step-down procedure with respect to the constants $D_1(m)$ in (1) and $D_2(m)$ in (28). The values of $D_1(m)$ and $D_2(m)$ are tabulated along with $1 - D_2(m)/D_1(m)$ in Table 1. For the range of values of m considered, the difference between $D_1(m)$ and $D_2(m)$ relative to $D_1(m)$ is at least 20%. For lower values of m ($\leqslant 25$), the relative difference is at least 35%.

We now give a real data example illustrating the usefulness of the new step-down procedure. We revisit a clinical trial in patients with hypertension analyzed in Dmitrienko et al. (2007, Section 5). The trial is conducted to compare an experimental drug to an active control with respect to four endpoints: mean reductions in systolic and diastolic blood pressures, proportion of patients with controlled systolic/diastolic blood pressure, and average blood pressure based on ambulatory blood pressure monitoring. For each of the four endpoints, a non-inferiority and a superiority hypothesis

Table 1
The constants $D_1(m)$ and $D_2(m)$ based on (1) and (28)

m	$D_1(m)$	$D_2(m)$	$1 - D_2(m)/D_1(m)$
10	2.929	1.84	0.372
25	3.816	2.467	0.354
50	4.499	2.992	0.335
100	5.187	3.545	0.317
250	6.101	4.306	0.294
500	6.793	4.898	0.279
1000	7.486	5.499	0.265
2500	8.402	6.306	0.249
5000	9.095	6.924	0.239
10 000	9.788	7.547	0.229

are established, so there are eight null hypotheses of interest. For these hypotheses, the corresponding raw p-values are 0.001, 0.008, 0.026, 0.003, 0.208, 0.302, 0.010, and 0.578, respectively. By using our new step-down procedure in Theorem 4.1, which works for all joint distributions of p-values, four hypotheses are rejected at level 0.05. In contrast, the Benjamini–Yekutieli step-up procedure rejects only two hypotheses at level 0.05.

5. Step-up procedure

We now consider the problem of controlling FDR in step-up procedures. The following is the main result of this section. The first part of the result is due to Benjamini and Yekutieli (2001). We give an alternative proof of this result. Benjamini and Yekutieli (2001) used a certain probability inequality to establish their result. We use optimization techniques. Our technique provides a deeper insight when the upper bound is attained. In addition, we also construct a joint distribution of the p-values under which the upper bound is attained.

Theorem 5.1. (i) *For the step-up procedure with critical constants* $\alpha_i = (i/m)\alpha,\ i \in I$, *the following inequality holds*:

$$\mathrm{FDR} = \sum_{i=1}^{m_0} \sum_{j=1}^{m} \sum_{k=j}^{m} \frac{1}{k} p_{ijk} \leqslant \frac{m_0}{m} \alpha \sum_{j=1}^{m} \frac{1}{j}, \tag{34}$$

where m_0 *is the number of true null hypotheses.*

(ii) *Equality in* (34) *holds if and only if for each* $i \in I_0$, $p_{ijk} = \alpha/m$ *if* $j = k$ *and equal to 0 if* $j < k$.

(iii) *As long as* $\{m_1/m + (m_0/m)\sum_{j=1}^{m_0} 1/j\}\alpha \leqslant 1$, *there exists a joint distribution of the p-values for which the inequality in* (34) *is equality.*

Proof. (i) Combining (4) and (19), we consider the following optimization problem:

$$\text{maximize } \mathrm{FDR} = \sum_{i=1}^{m_0} \sum_{j=1}^{m} \sum_{k=j}^{m} \frac{1}{k} p_{ijk}, \tag{35}$$

with respect to p_{ijk}'s $\geqslant 0$ and subject to the constraints

$$\sum_{k=j}^{m} p_{ijk} \leqslant \frac{\alpha}{m} \quad \text{for } i \in I_0,\ j \in I.$$

Problem (35) can be decomposed into a family of sub-problems indexed by $i \in I_0$, $j \in I$ as follows:

$$\text{maximize } Q_{ij} = \sum_{k=j}^{m} \frac{1}{k} p_{ijk}, \tag{36}$$

with respect to p_{ijk}'s $\geqslant 0$, and subject to $\sum_{k=j}^{m} p_{ijk} \leqslant \alpha/m$.

Obviously, the maximum value of the objective function in (35) is the sum of the maximum values of all sub-problems (36), and its optimal solution is a combination of optimal solutions of the sub-problems.

Problem (36) has a simple unique solution $p^*_{ijk} = \alpha/m$ if $j = k$ and equal to 0 if $j < k$. This optimization problem is a special case of the general knapsack problem (see Martello and Toth, 1990). Consequently, the maximum value of FDR is

$$\mathrm{FDR}^* = \sum_{i=1}^{m_0} \sum_{j=1}^{m} \sum_{k=j}^{m} \frac{1}{k} p^*_{ijk} = \frac{m_0}{m} \alpha \sum_{j=1}^{m} \frac{1}{j}. \tag{37}$$

In view of the uniqueness of the solution p^*_{ijk} in (36), equality in (34) holds if and only if for $i \in I_0$, $1 \leqslant j \leqslant k \leqslant m$, $p_{ijk} = p^*_{ijk}$. This proves (i) and (ii).

To prove (iii), the construction of the joint distribution proceeds as follows: let $U_1, \ldots, U_m, U_{m+1}$ be $m+1$ uniformly distributed random variables such that $U_i \sim \mathrm{U}[(i-1)\alpha/m, i\alpha/m]$, $i = 1, \ldots, m$, and $U_{m+1} \sim \mathrm{U}[\alpha, 1]$. Let N be a random variable taking values $1, 2, \ldots, m+1$ with the following probability distribution:

$$\Pr\{N = n\} = \begin{cases} \dfrac{m_0}{m} \alpha \cdot \dfrac{1}{n} & \text{if } 1 \leqslant n \leqslant m_0, \\ \dfrac{\alpha}{m} & \text{if } m_0 + 1 \leqslant n \leqslant m, \\ 1 - \left\{ \dfrac{m_1}{m} + \dfrac{m_0}{m} \sum\limits_{j=1}^{m_0} \dfrac{1}{j} \right\} \alpha & \text{if } n = m+1. \end{cases} \tag{38}$$

We want to associate a p-value to each of the indices $1, 2, \ldots, m$. The association proceeds in three distinct phases.

Phase 1: For each given $N = n \in \{1, 2, \ldots, m_0\}$, choose n many indices $i_1, i_2, \ldots, i_n$ randomly without replacement from I_0. Each of these chosen indices has the same p-value $P_{i_j} = U_n$. Each of the indices s in $I - \{i_1, i_2, \ldots, i_n\}$ has the same p-value $P_s = U_{m+1}$.

Phase 2: For each given $N = n \in \{m_0 + 1, \ldots, m\}$, choose the indices $1, 2, \ldots, m_0$ and $(m - n)$ indices randomly without replacement from I_1. Each of these indices is associated with the same p-value U_n. Each of the remaining unaccounted indices from I_1 is associated with the same p-value U_{m+1}.

Phase 3: Given $N = m + 1$, each of the indices in I_0 is associated with the same p-value U_{m+1}, and each of the indices in I_1 is associated with the same p-value U_1. It is easy to verify that, for each $i \in I_0$, each p-value $P_i \sim \mathrm{U}[0, 1]$ and

$$\begin{aligned} p_{ijk} &= \Pr\left\{ P_i \in \left(\frac{(j-1)}{m}\alpha, \frac{j}{m}\alpha \right], R = k \right\} \\ &= \Pr\left\{ R = k \,\middle|\, P_i \in \left(\frac{(j-1)}{m}\alpha, \frac{j}{m}\alpha \right] \right\} \Pr\left\{ P_i \in \left(\frac{(j-1)}{m}\alpha, \frac{j}{m}\alpha \right] \right\}. \end{aligned} \tag{39}$$

Thus, for each $i \in I_0$, $p_{ijk} = \alpha/m$ if $j = k$ and equal to 0 if $j < k$. This proves part (iii). □

Remark 5.1. As pointed out by one referee, the above constructed example is very artificial as the distribution of the p-value corresponding to some index in I_1 may be stochastically greater than U[0, 1].

Remark 5.2. The upper bound (34) is useful only when $(m_0\alpha/m)\sum_{j=1}^{m} 1/j \leqslant 1$. In such a situation, the condition $\{m_1/m + m_0/m \sum_{j=1}^{m_0} 1/j\}\alpha \leqslant 1$ is easy to meet as it is close to $(m_0\alpha/m)\sum_{j=1}^{m} 1/j$ for large m_0 relative to m.

We generalize Theorem 5.1 for the step-up procedure with any non-decreasing critical constants α_i, $i \in I$. A proof can be fashioned along the lines of the proof of Theorem 5.1.

Theorem 5.2. (i) *For the step-up procedure with non-decreasing critical constants α_i, $i \in I$, the following inequality holds*:

$$\mathrm{FDR} = \sum_{i=1}^{m_0} \sum_{j=1}^{m} \sum_{k=j}^{m} \frac{1}{k} p_{ijk} \leqslant m_0 \sum_{j=1}^{m} \frac{\alpha_j - \alpha_{j-1}}{j}, \tag{40}$$

where m_0 is the number of true null hypotheses.

(ii) *Equality in* (40) *holds if and only if for each $i \in I_0$, $p_{ijk} = \alpha_j - \alpha_{j-1}$ if $j = k$ and equal to* 0 *if $j < k$*.

(iii) *As long as $\{(\alpha_m - \alpha_{m_0}) + m_0 \sum_{j=1}^{m_0} (\alpha_j - \alpha_{j-1})/j\} \leqslant 1$, there exists a joint distribution of the p-values for which the inequality in* (40) *is equality*.

6. Conclusion

In this paper, we have mainly focused on controlling the FDR under no assumption on dependency of the underlying *p*-values. Benjamini and Yekutieli (2001) have given an upper bound for the FDR of the Benjamini–Hochberg step-up procedure that is valid whatever may be the joint distribution of the *p*-values. We have shown that this upper bound is optimal in the sense that there is a joint distribution of *p*-values for which the upper bound is attained. We have proposed a new step-down procedure with the same critical constants as those of the Benjamini–Hochberg step-up procedure and provided an upper bound of its FDR. In the process, we have fine-tuned the standard expression for FDR specially tailored to step-down procedures. Using this expression and a certain optimization technique, we have established our upper bound. Through some numerical computations, we have shown that our upper bound is much less than that of Benjamini and Yekutieli (2001).

We point out that, in Hart and Weiss (1997), optimization techniques were used for solving some different multiple testing problems. Benjamini and Liu (1999b) introduced a step-down FDR controlling procedure and showed that the procedure can control the FDR at α under general dependence. However, Romano and Shaikh (2006) recently independently introduced the same step-down procedure, but by using a similar proof, they only showed the FDR controllability of the procedure under a weak condition (viz. the *p*-value corresponding to a true null hypothesis is dominated by the uniform distribution conditional on the observed *p*-values of the false null hypotheses). We checked carefully these two proofs, and it seems that there is a gap in the proof of Benjamini and Liu (1999b), but we may be wrong.

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