FALSE DISCOVERY AND FALSE NONDISCOVERY RATES IN SINGLE-STEP MULTIPLE TESTING PROCEDURES[1]

BY SANAT K. SARKAR

Temple University

Results on the false discovery rate (FDR) and the false nondiscovery rate (FNR) are developed for single-step multiple testing procedures. In addition to verifying desirable properties of FDR and FNR as measures of error rates, these results extend previously known results, providing further insights, particularly under dependence, into the notions of FDR and FNR and related measures. First, considering fixed configurations of true and false null hypotheses, inequalities are obtained to explain how an FDR- or FNR-controlling single-step procedure, such as a Bonferroni or Šidák procedure, can potentially be improved. Two families of procedures are then constructed, one that modifies the FDR-controlling and the other that modifies the FNR-controlling Šidák procedure. These are proved to control FDR or FNR under independence less conservatively than the corresponding families that modify the FDR- or FNR-controlling Bonferroni procedure. Results of numerical investigations of the performance of the modified Šidák FDR procedure over its competitors are presented. Second, considering a mixture model where different configurations of true and false null hypotheses are assumed to have certain probabilities, results are also derived that extend some of Storey's work to the dependence case.

1. Introduction. The false discovery rate (FDR) and related measures have been receiving considerable attention due to their relevance as measures of the overall error rate in multiple testing problems that arise in many scientific investigations, particularly in the context of DNA microarray analysis. Consider Table 1, which summarizes the outcomes in multiple testing of n null hypotheses $H_1, \ldots, H_n$. Let $Q = V/R$ if $R > 0$ and $= 0$ if $R = 0$, that is, the proportion of false positives (Type I errors) among the rejected null hypotheses. Genovese and Wasserman [9] called this the false discovery proportion (FDP). The FDR is defined by $E(Q)$. It was first introduced in multiple testing by Benjamini and Hochberg [1], who provided a step-up procedure that controls the FDR with independent test statistics. Later, Benjamini and Liu [4] offered a step-down FDR procedure under independence. The FDR-controlling property of the Benjamini–Hochberg (BH) procedure was extended by Benjamini and Yekutieli [5] to some

	Rejected	**Accepted**	**Total**
True null	V	U	n_0
False null	S	T	n_1
Total	R	A	n

positively dependent multivariate distributions. Sarkar [14] proved that the critical values of the BH procedure can be used in a more general stepwise procedure to provide control of the FDR not only under independence, but also when the test statistics have the same type of positive dependence property as considered by Benjamini and Yekutieli [5]. In addition, he established the FDR-controlling property of the Benjamini–Liu step-down procedure for some positively dependent test statistics. Genovese and Wasserman [8, 9] investigated some operating characteristics of the BH procedure asymptotically under independence and further extended the theory of FDR by taking a stochastic process approach.

A slightly different concept of FDR, called the positive false discovery rate (pFDR), was considered by Storey [17]. It is defined as the conditional FDR given at least one rejection, that is, pFDR $= E(V/R|R > 0)$, and it has the interpretation of a Bayesian Type I error rate under a mixture model involving i.i.d. p-values when a single-step multiple testing procedure is used; see also [18]. Storey [17] provided estimates of FDR and pFDR under the above mixture model for a single-step procedure that are related to the empirical Bayes FDR of Efron, Tibshirani, Storey and Tusher [7]; see also [6]. A new family of FDR procedures based on estimates of FDR was suggested by Storey [17] and Storey, Taylor and Siegmund [19].

An analog of FDR in terms of false negatives (Type II errors) was introduced by Genovese and Wasserman [8] and Sarkar [15]. It is the FNR, called false nondiscovery rate by Genovese and Wasserman [8] and the false negatives rate by Sarkar [15]. It is defined by $E(N)$, where $N = T/A$ if $A > 0$ and $= 0$ if $A = 0$ is the proportion of false negatives among the accepted null hypotheses or the false nondiscovery proportion (FNP) [9]. Storey [18] defined the pFNR (positive false nondiscovery rate), the conditional expectation $E(T/A|A > 0)$, as an analog of his pFDR. While Genovese and Wasserman [8] considered new methods that incorporate both FDR and FNR, Storey [18] established a connection between multiple testing and classification theory in terms of a combination of pFDR and pFNR. Sarkar [15] proved that the FNR can be controlled by a step-down analog of the BH procedure. He also introduced a concept of unbiasedness of an FDR- or FNR-controlling multiple testing procedure and established this property for a generalized stepwise procedure under independence.

In this article we mainly concentrate on single-step multiple testing procedures, and we develop new results on FDR and FNR with dependent test statistics both

under a model where the configuration of true and false null hypotheses is assumed fixed, yet unknown, and under the so-called mixture model where different configurations of true and false null hypotheses are assumed to have certain probabilities. The intent of these results is to verify some desirable properties of FDR and FNR and to extend some previously known results, thereby providing further insights into the notions of FDR and FNR and related measures, particularly under dependence.

Suppose that $\mathbf{X} = (X_1, \ldots, X_n)$ has a joint distribution indexed by the set of parameters $\boldsymbol{\theta} = (\theta_1, \ldots, \theta_n)$. Let $H_i : \theta_i \leq \theta_{i0}$ be tested against $K_i : \theta_i > \theta_{i0}$, for some given θ_{i0}, $i = 1, \ldots, n$. Let $\{H_i : i \in J_0\}$ and $\{H_i : i \in J_1\}$ be the sets of true and false null hypotheses, respectively. It will be assumed that J_0 is nonempty. Consider a single-step procedure that rejects H_i in favor of K_i if $X_i \geq t$ for some fixed t. Two of our main results with fixed J_0 and J_1 (Theorems 1 and 3) are that if $\mathbf{X}$ is stochastically increasing in each θ_i, which is typically the case in many multiple testing problems, then the maximum values of FDR and FNR of a single-step procedure are $(n_0/n)P\{R > 0\}$ and $(n_1/n)P\{A > 0\}$, respectively, where the probabilities are evaluated at $\theta_0 = (\theta_{10}, \ldots, \theta_{n0})$ and $\mathbf{X}$ is assumed exchangeable under these null hypothesis values. In addition to representing more precise versions of the results that state that Šidák and Bonferroni single-step procedures control FDR or FNR, these theorems show how these procedures can potentially be improved in terms of having better control of FDR or FNR borrowing information about n_0 or n_1 from the data in the spirit of Benjamini and Hochberg [2], Benjamini, Krieger and Yekutieli [3], Storey [17] and Storey, Taylor and Siegmund [19]. Storey, Taylor and Siegmund [19] provided procedures for modifying the BH procedure using a family of estimates of n_0 and proved that they control FDR under independence. We obtain new families of procedures: one to modify the FDR-controlling and the other to modify the FNR-controlling Šidák procedure. Considering independent test statistics, we prove that they control FDR or FNR. The modified Šidák FDR procedures are less conservative under independence than the corresponding family that modifies the Bonferroni procedure obtained by using the estimates of n_0 considered in [19]. An analogous result is true for modified Šidák FNR procedures. Our method of modifying the Šidák FDR and the Šidák FNR procedures relies directly on two new results, Theorems 2 and 4, which extend inequalities given by Theorems 1 and 3, respectively, under independence from a single-step to a two-step procedure.

Next, we derive certain results that extend Storey's [17, 18] work to the dependent case. Storey obtained expressions for the FDR and FNR of a single-step procedure under a mixture model where, given any configuration of true and false null hypotheses, the X_i's are assumed to be independent, providing useful Bayesian interpretations to his notions of pFDR and pFNR. More specifically, he proved: pFDR $= P\{H_1 \text{ is true} | X_1 \geq t\}$ and pFNR $= P\{H_1 \text{ is false} | X_1 < t\}$, irrespective of the number of tests. Assuming a more general mixture model in

which the X_i's are assumed to be dependent with a location family of distributions and to have a certain type of positive dependence structure, we prove in Theorems 5 and 6, respectively, that pFDR $\leq \max_{1 \leq i \leq n} P\{H_i \text{ is true}|X_i \geq t\}$ and pFNR $\leq \max_{1 \leq i \leq n} P\{H_i \text{ is false}|X_i < t\}$, with the equalities holding under independence. An important implication of the first inequality is that Storey's [17] q-value for a single-step multiple test under certain commonly encountered types of dependence is more conservative, as one would desire, than that under independence.

The paper is organized as follows. In Section 2 we formally define the stochastic increasing property we need for **X** to obtain the maximum values of FDR and FNR for fixed J_0 and J_1. Section 3 reports the results related to FDR for fixed J_0 and J_1, and some numerical results that show the performance of the modified Šidák procedure in controlling FDR compared to the modified Bonferroni and the original Bonferroni and Šidák procedures. Similar results related to FNR are presented in Section 4, of course without showing any additional numerical evidence. Section 5 numerically compares the Bonferroni and Šidák procedures with their modified versions in terms of a concept of power involving both FDR and FNR. Section 6 presents the results on FDR and FNR under the aforementioned mixture model with dependent **X**. Proofs are given in Section 7. The paper concludes with some final remarks in Section 8.

2. Stochastically increasing family of distributions. This section defines a type of stochastic increasing property of a family of distributions that will be required to establish our results on FDR and FNR. Whenever an increasing or decreasing condition or property in terms of **X** or θ is mentioned, it is to be understood as being coordinatewise.

DEFINITION 1. An n-dimensional random vector $\mathbf{X} = (X_1, \ldots, X_n)$ or the corresponding family of distributions $\{P_\theta\}$, where $\theta = (\theta_1, \ldots, \theta_n)$, is said to be stochastically increasing in θ if $P_\theta\{\mathbf{X} \in \mathbf{C}\}$ is increasing in θ for any set **C** that is increasing.

EXAMPLE 1 (Random variables with mixtures of independent stochastically increasing distributions). In multiple testing, the X_i's often have distributions that are mixtures of independent stochastically increasing distributions. That is, the density of P_θ is often of the form

$$f_\theta(\mathbf{x}) = \int \prod_{i=1}^{n} f_{i\theta_i}(x_i, y) \, dG(y),$$

where $f_{i\theta_i}(x, y)$ is stochastically increasing in θ_i for each y and G is a probability distribution independent of θ. A stronger condition—which is that for any $\theta_i < \theta_i'$, $f_{i\theta_i'}(x, y)/f_{i\theta_i}(x, y)$ is increasing in x for each i, the monotone likelihood ratio (MLR) condition of Lehmann [12] satisfied by many of the commonly used

distributions—is often useful to check for the stochastic increasing property of $f_{i\theta_i}(x, y)$ in θ_i. The multivariate distribution of such random variables is stochastically increasing in θ.

EXAMPLE 2 (Multivariate location family of distributions). Let the density of P_θ be of the form $f_\theta(\mathbf{x}) \equiv f(\mathbf{x} - \theta)$. Distributions of this type are stochastically increasing. This is because, for any $\theta < \theta'$, we have

$$P_{\theta'}\{\mathbf{X} \in C\} = P_\theta\{\mathbf{X} \in C - (\theta' - \theta)\} \ge P_\theta\{\mathbf{X} \in C\}.$$

Many of the distributions that arise in multiple testing are of the type in Example 1 or 2. For instance, (i) independent normals with θ_i's representing the means, (ii) absolute values of independent normals with θ_i's representing the absolute means, (iii) independent chi-squares where θ_i's are the scale parameters or (iv) scaled mixtures of all these distributions, are of the type in Example 1. They arise in simultaneous testing of means or variances of independent normals against one- or two-sided alternatives. Multivariate $\ln F$ that arises in many-to-one comparisons of variances against one-sided alternatives is another distribution of the type in Example 1. Multivariate normal and multivariate t are distributions of the type in Example 2, arising, for instance, in Dunnett's many-to-one comparisons of means against one-sided alternatives in a one-way layout with a known or unknown common variance.

3. Results on FDR for fixed J_0 and J_1. In this section we derive results on the FDR of a single-step procedure, assuming fixed, but unknown, J_0 and J_1. We use the following notation here and in the rest of the paper. Define $J = \{1, \ldots, n\}$ and $J_{(-i)} = J - \{i\}$. Define $X_{(1)} \le \cdots \le X_{(n)}$ as the ordered components of the set $\{X_j : j \in J\}$ and $X_{(1)}^{(-i)} \le \cdots \le X_{(n-1)}^{(-i)}$ as those of the subset $\{X_j : j \in J_{(-i)}\}$. We assume that the marginal distribution of any X_i depends on θ only through the corresponding θ_i.

First, we have the following lemma.

LEMMA 1. *The FDR of the single-step procedure with fixed critical value t is given by*

$$\text{FDR}_\theta(t; J_0, J_1)$$

$$(3.1) \qquad = \sum_{i \in J_0} \left[P_{\theta_i}\{X_i \ge t\} - \sum_{j=1}^{n-1} \frac{P_\theta\{X_{(j)}^{(-i)} \ge t, X_i \ge t\}}{(n-j)(n-j+1)} \right]$$

$$= P_\theta\{X_{(n)} \ge t\} - \sum_{i \in J_1} \left[P_{\theta_i}\{X_i \ge t\} - \sum_{j=1}^{n-1} \frac{P_\theta\{X_{(j)}^{(-i)} \ge t, X_i \ge t\}}{(n-j)(n-j+1)} \right].$$

Now suppose that $\mathbf{X}$ is stochastically increasing in θ. Then, since the set $\{X_{(j)}^{(-i)} \geq t, X_i \geq t\}$ is increasing in $\mathbf{X}$, the probability $P_\theta\{X_{(j)}^{(-i)} \geq t, X_i \geq t\}$ is increasing in θ. The probability $P_\theta\{X_{(n)} \geq t\}$ is also increasing in θ because $\{X_{(n)} \geq t\}$ is an increasing set. Thus, using the first expression of the FDR in (3.1), we notice that it is decreasing in θ and, hence, in $\{\theta_i : i \in J_1\}$ for fixed $\{\theta_i : i \in J_0\}$, whereas from the the second expression we see that it is increasing in $\{\theta_i : i \in J_0\}$ for fixed $\{\theta_i : i \in J_1\}$. In other words, $\text{FDR}_\theta(t; J_0, J_1)$ decreases as θ_i moves away from θ_{i0} for at least one $i \in J_0$ or at least one $i \in J_1$, with

$$(3.2) \qquad \sup_\theta \text{FDR}_\theta(t; J_0, J_1) = \text{FDR}_{\theta_0}(t; J_0, J_1),$$

where $\theta_0 = (\theta_{10}, \ldots, \theta_{n0})$. If $\mathbf{X}$ is exchangeable when $\theta = \theta_0$ with the common marginal c.d.f. F_0, the right-hand side of (3.2) reduces to

$$
\begin{aligned}
(3.3) \qquad & n_0\left[\bar{F}_0(t) - \sum_{j=1}^{n-1} \frac{P_{\theta_0}\{X_{(j)}^{(-1)} \geq t, X_1 \geq t\}}{(n-j)(n-j+1)} \right] \\
& = \frac{n_0}{n} \text{FDR}_{\theta_0}(t; J, \phi) \\
& = \frac{n_0}{n} P_{\theta_0}\{R > 0\},
\end{aligned}
$$

where $\bar{F}_0 = 1 - F_0$ and ϕ represents a null set. Thus, we have the following theorem, which is one of the main results of this article.

THEOREM 1. *If $\mathbf{X}$ is stochastically increasing in θ, then $\text{FDR}_\theta(t, J_0, J_1)$ decreases as θ_i moves away from θ_{i0} for at least one $i \in J_0$ or for at least one $i \in J_1$. Furthermore, if $\mathbf{X}$ is exchangeable when $\theta = \theta_0$, then*

$$(3.4) \qquad \sup_\theta \text{FDR}_\theta(t; J_0, J_1) = \frac{n_0}{n} P_{\theta_0}\{R > 0\}.$$

Theorem 5.3 of [5] gives the above decreasing property of FDR with respect to only $\{\theta_i, i \in J_1\}$ under the assumptions that $\{X_i, i \in J_0\}$ and $\{X_i, i \in J_1\}$ are jointly independent and $\{X_i, i \in J_1\}$ is stochastically increasing in $\{\theta_i, i \in J_1\}$. Theorem 1 is a version of this for single-step procedures with dependent $\mathbf{X}$ and one-sided null hypotheses.

As a corollary to Theorem 1, if the critical value t provides a level α test for the overall null hypothesis $\bigcap_{i=1}^n H_i$, that is, if t satisfies $P_{\theta_0}\{R > 0\} = P_{\theta_0}\{\max_{i \in J} X_i \geq t\} \leq \alpha$, then we have

$$(3.5) \qquad \text{FDR}_\theta(t; J_0, J_1) \leq \frac{n_0}{n}\alpha,$$

implying that the FDR is controlled at α. Inequality (3.5) is interesting in that it represents a single-step analog of the same inequality known to hold for stepwise

procedures with Simes [16] critical values providing an α-level test for $\bigcap_{i=1}^{n} H_i$ [1, 5, 14]. Regarding the choice for t, if one does not want to utilize the distributional form of $\mathbf{X}$ or if it is unknown, the Bonferroni critical value that satisfies

$$(3.6) \qquad F_0(t) = 1 - \frac{\alpha}{n}$$

can be used. If, however, $\mathbf{X}$ is known to be positively dependent so that the inequality $P_{\theta_0}\{\max_{i \in J} X_i < t\} \geq F_0^n(t)$ holds under the null hypothesis values with the equality holding under independence, as in the case of many distributions that arise in multiple testing, the Šidák critical value t that satisfies the equation

$$(3.7) \qquad F_0(t) = (1 - \alpha)^{1/n}$$

offers a less conservative choice.

We should point out that there is no surprise that the Bonferroni and Šidák single-step procedures control FDR, because they are known to control the family-wise error rate (FWER). It is also known that, given n_0, it can be incorporated in the Bonferroni and other procedures to improve their FWER control [10]. What is new here is that Bonferroni and Šidák procedures can be further improved in terms of having better control of FDR using an estimate of n_0, in the spirit of Benjamini and Hochberg [2], Benjamini, Krieger and Yekutieli [3], Storey [17] and Storey, Taylor and Siegmund [19]. For instance, since $\sup_\theta \mathrm{FDR}_\theta(t; J_0, J_1) \leq n_0\{1 - F_0(t)\}$, as we see from Theorem 1, rather than controlling $n\{1 - F_0(t)\}$, which the Bonferroni method does, a better control of FDR can be achieved if we control $\hat{n}_0\{1 - F_0(t)\}$ for some appropriately chosen estimate $\hat{n}_0$ of n_0. To estimate n_0, Storey [17] suggested using the ratio $K_\tau/F_0(\tau)$, where $K_\tau = \sum_{i=1}^{n} I(X_i < \tau)$, for some well-chosen τ. However, Storey, Taylor and Siegmund [19] slightly modified it and used

$$(3.8) \qquad \hat{n}_0(\tau) = \frac{K_\tau + 1}{F_0(\tau)}$$

to obtain a new class of BH-type FDR-controlling procedures under independence. We use this $\hat{n}_0$ in our modification to the Bonferroni procedure. Also, the X_i's that are small compared to τ should not be declared large when modified Bonferroni is used. Thus, our modified Bonferroni procedure rejects H_i whenever

$$(3.9) \qquad X_i \geq \max\left\{\tau, F_0^{-1}\left(1 - \frac{\alpha F_0(\tau)}{K_\tau + 1}\right)\right\}.$$

We prove later in this section that our modified Bonferroni procedure controls FDR under independence and we provide numerical evidence showing that quite often this control can be achieved much less conservatively. However, when $\mathbf{X}$ is known to be independent or at least positively dependent, a modification to the Šidák procedure is expected to produce a better performing procedure than the modified Bonferroni procedure. So, we first modify the Šidák procedure. The following theorem suggests how the idea of modifying the Bonferroni procedure can

be extended to that for the Šidák procedure. It extends the inequality for the FDR under independence, given by Theorem 1, from a single-step to a two-step procedure that, for some fixed $\tau \in (-\infty, \infty)$ and a predetermined function $t_\tau(k) \geq \tau$, $k = 0, 1, \ldots, n$, first finds $k = \max_{0 \leq i \leq n}\{i : X_{(i)} < \tau\}$ (note that $X_{(0)} = -\infty$), then rejects all H_i for which $X_i \geq t_\tau(k)$.

THEOREM 2. *Let* $\mathbf{X}$ *be independent with the distribution of* X_i, *indexed by the parameter* θ_i, *belonging to an MLR family and having identical marginals when* $\theta = \theta_0$. *Then, for a two-step procedure with* $t_\tau(k) \geq \tau$, *for all* $k = 0, 1, \ldots, n$, *the FDR satisfies the inequality*

$$\mathrm{FDR}_\theta^{(2)}(t_\tau \geq \tau; J_0, J_1)$$

$$(3.10) \qquad \leq \bar{F}_0(\tau) \sum_{i \in J_0} \sum_{k=0}^{n-1} \frac{1}{n-k}\left[1 - \left(1 - \frac{\bar{F}_0(t_\tau(k))}{\bar{F}_0(\tau)}\right)^{n-k}\right]$$

$$\times P_\theta\{X_{(k)}^{(-i)} < \tau \leq X_{(k+1)}^{(-i)}\}$$

(*with* $X_{(0)}^{(-i)} = -\infty$ *and* $X_{(n)}^{(-i)} = \infty$).

When $\tau = -\infty$, $k = 0$ with probability 1 and (3.10) reduces to the one given by Theorem 1 under independence with $t = t_{-\infty}(0)$. It is interesting to see that $\mathrm{FDR}_\theta^{(2)}(t_\tau \geq \tau; J_0, J_1) \leq \mathrm{FDR}_\theta(\tau; J_0, J_1)$.

The modified Bonferroni procedure is a two-step procedure with $t_\tau(k)$ given by the right-hand side of (3.9) given $K_\tau = k$; that is, $t_\tau(k)$ is such that $\bar{F}_0(t_\tau(k)) = \min\{\bar{F}_0(\tau), \alpha F_0(\tau)/(k+1)\}$. We propose to modify the Šidák procedure using a two-step procedure where $t_\tau(k)$ is such that

$$(3.11) \quad \bar{F}_0(t_\tau(k)) = \bar{F}_0(\tau)\left[1 - \left(1 - \min\left\{1, \frac{\alpha(n-k)F_0(\tau)}{(k+1)\bar{F}_0(\tau)}\right\}\right)^{1/(n-k)}\right]$$

with $t_\tau(n) = \infty$. The right-hand side of (3.10) for this modified Šidák procedure is less than or equal to

$$\alpha \sum_{i \in J_0} \sum_{k=0}^{n-1} \frac{F_0(\tau)}{k+1} P_\theta\{X_{(k)}^{(-i)} < \tau \leq X_{(k+1)}^{(-i)}\}$$

$$(3.12) \qquad \leq \alpha \sum_{i \in J} \sum_{k=1}^{n} \frac{1}{k} P_\theta\{X_i < \tau, X_{(k-1)}^{(-i)} < \tau \leq X_{(k)}^{(-i)}\}$$

$$= \alpha \sum_{k=1}^{n} P_\theta\{X_{(k)} < \tau \leq X_{(k+1)}\}$$

$$= \alpha P_\theta\{X_{(1)} < \tau\};$$

see, for example, [13], page 497, for the first equality in (3.12). Thus, we see that our modified Šidák procedure controls FDR under independence.

The right-hand side of (3.10) is less than or equal to

$$(3.13) \qquad \sum_{i \in J_0} \sum_{k=0}^{n-1} \bar{F}_0(t_\tau(k)) P_\theta \{ X_{(k)}^{(-i)} < \tau \leq X_{(k+1)}^{(-i)} \},$$

which, for the modified Bonferroni procedure, is less than or equal to the first expression in (3.12). Thus, the FDR of the modified Bonferroni procedure is also less than or equal to $\alpha P_\theta \{ X_{(1)} < \tau \}$ and, hence, is controlled; of course, it is controlled more conservatively than the modified Šidák procedure.

We conducted a numerical study to investigate the extent of improvement offered by our modified Šidák procedure in controlling FDR over the modified Bonferroni and the original Bonferroni and Šidák procedures. We generated $n = 100$ dependent random variables $X_i \sim N(\mu_i, 1)$, $i = 1, \ldots, 100$, with the same variance 1 and a common correlation ρ, and performed 100 hypothesis tests of $\mu = 0$ against $\mu > 0$, each using first the Bonferroni critical value and then the Šidák critical value corresponding to $\alpha = 0.05$. The value of Q was then calculated for each procedure by setting n_0 of the μ_i's to zero and the remaining μ_i's to a positive value δ. The FDR then was estimated by averaging the Q values over 5000 iterations. Thus, we have the simulated FDR of the Bonferroni and Šidák procedures. We chose $F_0(\tau) = 1/2$ and similarly calculated the FDR of the modified Bonferroni and Šidák procedures corresponding to this τ. Table 2 compares the FDRs of the Bonferroni and Šidák procedures and their modification for $n_0 = 30, 50, 70$ and 90, $\rho = 0$ (independent) and 0.5 (dependent), and for different values of δ. The last row of this table gives the maximum of the standard errors of the estimated (simulated) FDRs in each column.

As we expected, the modified Šidák procedure provided the least conservative control of FDR under independence. Since the Bonferroni and Šidák procedures are relatively more conservative when the actual proportion of true null hypotheses is small, the idea of improving them using an estimate of n_0 should work well in this situation. This idea is confirmed by our numerical study. Both modified Bonferroni and modified Šidák procedures are seen to control FDR much less conservatively than their unmodified versions under independence. In the dependent case, however, the idea of improving the Bonferroni and Šidák procedures may not work unless n_0 is small and the dependence is weak.

Having found more than one procedure that can control the FDR under independence (e.g., the Bonferroni, Šidák and their modifications), comparing them further in terms of *power* seems to be the next important objective. While the idea of power can be conceptualized in terms of Type II errors (false negatives) in several different ways, extending it from single testing to multiple testing, one particular concept, which is the average power [i.e., $\frac{1}{n_1} E(S)$], has been used in a

TABLE 2
Simulated values of the FDR of the Bonferroni and Šidák procedures and their modifications
with $\alpha = 0.05$

| | | Independent ($\rho = 0$) | | | | Dependent ($\rho = 0.5$) | | | |
| | | Bonferroni | | Šidák | | Bonferroni | | Šidák | |
n_0	δ	Original	Modified	Original	Modified	Original	Modified	Original	Modified
30	0.5	0.0118	0.0150	0.0119	0.0167	0.0048	0.0167	0.0049	0.0332
	1.5	0.0045	0.0073	0.0045	0.0079	0.0006	0.0066	0.0006	0.0412
	2.5	0.0008	0.0019	0.0008	0.0022	0.0002	0.0054	0.0002	0.0412
50	0.5	0.0218	0.0259	0.0222	0.0276	0.0092	0.0307	0.0093	0.0493
	1.5	0.0103	0.0147	0.0106	0.0149	0.0015	0.0116	0.0015	0.0455
	2.5	0.0021	0.0031	0.0021	0.0033	0.0006	0.0093	0.0006	0.0441
70	0.5	0.0315	0.0349	0.0319	0.0359	0.0141	0.0488	0.0144	0.0667
	1.5	0.0187	0.0237	0.0189	0.0232	0.0034	0.0196	0.0034	0.0494
	2.5	0.0052	0.0061	0.0052	0.0061	0.0013	0.0154	0.0014	0.0463
90	0.5	0.0414	0.0423	0.0423	0.0434	0.0234	0.0734	0.0240	0.0903
	1.5	0.0351	0.0382	0.0359	0.0393	0.0108	0.0414	0.0111	0.0642
	2.5	0.0173	0.0180	0.0175	0.0189	0.0045	0.0311	0.0046	0.0554
	MaxSE	0.0028	0.0028	0.0028	0.0029	0.0020	0.0034	0.0021	0.0038

number of recent papers to compare FDR-controlling procedures [4, 17, 19]. However, it is argued in [15] that since the FDR is a measure of false positives, it seems more appropriate to compare different FDR-controlling procedures using a similar measure in terms of false negatives, the FNR [8, 15]. It will be interesting to see how the different FDR-controlling procedures in this paper compare in terms of measures involving FNR under the same distributional setting. This will be carried out in Section 5 after deriving some results on FNR in the next section.

4. Results on FNR for fixed J_0 and J_1. We will derive in this section some results on FNR of a single-step procedure, analogous to those on FDR, again assuming a fixed configuration of true and false null hypotheses. First, we have the following lemma.

LEMMA 2. *An explicit expression of FNR is*

$$\text{FNR}_\theta(t; J_0, J_1)$$

$$(4.1) \qquad = \sum_{i \in J_1} \left[P_{\theta_i}\{X_i < t\} - \sum_{j=1}^{n-1} \frac{P_\theta\{X_{(j)}^{(-i)} < t, X_i < t\}}{j(j+1)} \right]$$

$$= P_\theta\{X_{(1)} < t\} - \sum_{i \in J_0} \left[P_{\theta_i}\{X_i < t\} - \sum_{j=1}^{n-1} \frac{P_\theta\{X_{(j)}^{(-i)} < t, X_i < t\}}{j(j+1)} \right].$$

Making the same kind of arguments as we made before for the monotonicity property of the FDR, we notice that if $\mathbf{X}$ is stochastically increasing in θ, the FNR is increasing in $\{\theta_i : i \in J_0\}$ for fixed $\{\theta_i : i \in J_1\}$ and is decreasing in $\{\theta_i : i \in J_1\}$ for fixed $\{\theta_i : i \in J_0\}$. In other words, $\text{FNR}_\theta(t; J_0, J_1)$ decreases as θ_i moves away from θ_{i0} for at least one $i \in J_0$ or at least one $i \in J_1$, with

$$(4.2) \qquad \sup_\theta \text{FNR}_\theta(t; J_0, J_1) = \text{FNR}_{\theta_0}(t; J_0, J_1).$$

Since, when $\theta = \theta_0$, $\mathbf{X}$ is exchangeable, the right-hand side in (4.2) reduces to

$$(4.3) \qquad n_1 \left[F_0(t) - \sum_{j=1}^{n-1} \frac{P_{\theta_0}\{X_{(j)}^{(-1)} < t, X_1 < t\}}{j(j+1)} \right] = \frac{n_1}{n} P_{\theta_0}\{A > 0\}.$$

The equality in (4.3) follows from (4.1); see also [13]. This gives the next main result of this article.

THEOREM 3. *If $\mathbf{X}$ is stochastically increasing in θ, then $\text{FNR}_\theta(t, J_0, J_1)$ decreases as θ_i moves away from θ_{i0} for at least one $i \in J_0$ or for at least one $i \in J_1$. Furthermore, if $\mathbf{X}$ is exchangeable when $\theta = \theta_0$, then*

$$(4.4) \qquad \sup_\theta \text{FNR}_\theta(t; J_0, J_1) = \frac{n_1}{n} P_{\theta_0}\{A > 0\}.$$

Clearly, the FNR of a single-step procedure can be controlled at a level β under the condition stated in the above theorem by choosing a fixed t subject to the condition $P_{\theta_0}\{A > 0\} = P_{\theta_0}\{\min_{i \in J} X_i \le t\} \le \beta$. If the dependence structure of $\mathbf{X}$ is not utilized, the equation $F_0(t) = \beta/n$ provides a Bonferroni-type choice for t. When $\mathbf{X}$ is known to be positively dependent so that the inequality $P_{\theta_0}\{\min_{i \in J} X_i \ge t\} \ge \bar{F}_0^n(t)$ is true, with the equality holding under independence, Šidák-type t can be determined from the equation $F_0(t) = 1 - (1 - \beta)^{1/n}$. These procedures can potentially be improved in terms of having better control of FNR by borrowing information from the X_i's exceeding an appropriately chosen value τ.

The following theorem is a FNR analog of Theorem 2 that extends the inequality on FNR given by Theorem 3 from a single-step to a two-step procedure and suggests how to modify the above single-step FNR-controlling procedures.

THEOREM 4. *Under the conditions stated in Theorem 2, the FNR of a two-step procedure with $t_\tau(k) \le \tau$ for all $k = 0, 1, \ldots, n$ satisfies the inequality*

$$\text{FNR}_\theta^{(2)}(t_\tau \le \tau; J_0, J_1)$$

$$(4.5)$$

$$\le F_0(\tau) \sum_{i \in J_1} \sum_{k=1}^{n} \frac{1}{k} \left[1 - \left(1 - \frac{F_0(t_\tau(k))}{F_0(\tau)} \right)^k \right] P_\theta\{X_{(k-1)}^{(-i)} < \tau \le X_{(k)}^{(-i)}\}.$$

When $\tau \to \infty$, $k = n$ with probability 1 and the above inequality reduces to that given by Theorem 3 under independence with $t = t_\infty(n)$. We modify the Šidák procedure using a two-step procedure with $t_\tau(k) \le \tau$ satisfying

$$(4.6) \qquad F_0(t_\tau(k)) = F_0(\tau)\left[1 - \left(1 - \min\left\{1, \frac{\beta k \bar{F}_0(\tau)}{(n-k+1)F_0(\tau)}\right\}\right)^{1/k}\right]$$

and $t_\tau(0) = -\infty$. For this modified Šidák procedure,

$$\mathrm{FNR}_\theta^{(2)}(t_\tau \le \tau; J_0, J_1)$$

$$(4.7) \quad \begin{aligned}
&\le \beta \sum_{i \in J_1} \sum_{k=1}^{n} \frac{\bar{F}_0(\tau)}{n-k+1} P_\theta\{X_{(k-1)}^{(-i)} < \tau \le X_{(k)}^{(-i)}\} \\
&\le \beta \sum_{i \in J_1} \sum_{k=0}^{n-1} \frac{1}{n-k} P_\theta\{X_i \ge \tau, X_{(k)}^{(-i)} < \tau \le X_{(k+1)}^{(-i)}\} \\
&\le \beta \sum_{i \in J} \sum_{k=0}^{n-1} \frac{1}{n-k} P_\theta\{X_i \ge \tau, X_{(k)}^{(-i)} < \tau \le X_{(k+1)}^{(-i)}\} \\
&= \beta \sum_{k=0}^{n-1} P_\theta\{X_{(k)} < \tau \le X_{(k+1)}\} \\
&= \beta P_\theta\{X_{(n)} \ge \tau\}.
\end{aligned}$$

The second inequality in (4.7) follows from the fact that $\bar{F}_0(\tau) \le \bar{F}_{\theta_i}(\tau)$; for the first equality, see [13]. Thus, the above modified Šidák procedure controls FNR under independence.

The right-hand side of (4.5) is less than or equal to

$$(4.8) \qquad \sum_{i \in J_1} \sum_{k=1}^{n} F_0(t_\tau(k)) P_\theta\{X_{(k-1)}^{(-i)} < \tau \le X_{(k)}^{(-i)}\}.$$

This is less than or equal to the right-hand side of the first inequality in (4.7), which is less than or equal to β, if we choose $t_\tau(k) \le \tau$ satisfying

$$(4.9) \qquad F_0(t_\tau(k)) = \min\left\{F_0(\tau), \frac{\beta \bar{F}_0(\tau)}{n-k+1}\right\}.$$

This gives us our FNR-controlling modified Bonferroni procedure, which is of course more conservative than the modified Šidák procedure in the sense that it allows less nondiscoveries.

REMARK 1. It is important to note that the above results on FNR have been developed with the idea of controlling false nondiscoveries of any set of true alternatives (or false nulls). However, one is often interested in controlling false

nondiscoveries of a prespecified set of true alternatives. These results can be easily modified in such a situation. Let $\theta_i = \theta_{i1}$ for some specified $\theta_{i1} > \theta_{i0}$, $i \in J_1$. Assume that $\mathbf{X}$ is exchangeable under $\theta = \theta_1 = (\theta_{11}, \ldots, \theta_{n1})$. Then Theorem 3 can be modified to

$$(4.10) \qquad \sup_{\theta} \text{FNR}(t; J_0, J_1) = \frac{n_1}{n} P_{\theta_1}\{A > 0\}$$

and Theorem 4 can be modified to

$$\text{FNR}_{\theta}^{(2)}(t_\tau \leq \tau; J_0, J_1)$$

$$(4.11) \qquad \leq F_1(\tau) \sum_{i \in J_1} \sum_{k=1}^{n} \frac{1}{k}\left[1 - \left(1 - \frac{F_1(t_\tau(k))}{F_1(\tau)}\right)^k\right]$$

$$\times P_{\theta}\{X_{(k-1)}^{(-i)} < \tau \leq X_{(k)}^{(-i)}\},$$

where F_1 is the common c.d.f. of X_i under θ_{i1}. The Bonferroni and Šidák procedures as well as their two-step modifications using critical values based on F_1 will provide better control of FNR in this case than values based on F_0.

We conducted a numerical study to investigate how well these different FNR procedures control FNR under a specified set of true alternatives. We noticed, as in the case of controlling FDR, that although both modified Bonferroni and Šidák procedures often control FNR much less conservatively than their unmodified versions, the modified Šidák procedure provides the best control of FNR.

5. A numerical study. In this section we compare the different FDR-controlling procedures under independence discussed in Section 3 in terms of a concept of power that relates to the unbiasedness condition Sarkar [15] introduced. Since the FDR measures the expected proportion of incorrect decisions, a good multiple testing procedure must ensure that it does not exceed the expected proportion of correct decisions. The quantity $1 - \text{FNR}$, which Genovese and Wasserman [8] called the correct nondiscovery rate, is a measure of correct decisions. In situations where controlling false negatives is of primary importance, the FNR provides a measure of incorrect decisions with the corresponding measure of correct decisions being $1 - \text{FDR}$. Whether we have a multiple testing procedure designed to control FDR or FNR, the inequality $\text{FDR} + \text{FNR} \leq 1$ represents a desirable property for any such multiple testing procedure. This is referred to as the unbiasedness condition of an FDR- or FNR-controlling multiple testing procedure. A natural way to compare different FDR- or FNR-controlling procedures would be to see how they perform in terms of a measure that reflects the strength of unbiasedness. This leads us to the consideration of the quantity

$$(5.1) \qquad \pi_\theta = 1 - \text{FDR}_\theta - \text{FNR}_\theta.$$

It is also related to the idea of Genovese and Wasserman [8], who suggested using $1 - \pi_\theta$ as a risk function to compare multiple testing procedures. This is our concept of power.

We investigated how the different FDR procedures in Section 3 perform in terms of the aforementioned concept of power. We computed the FNR and then the power $1 - \text{FNR} - \text{FDR}$ for the Bonferroni and Šidák procedures and their modified versions [with $F_0(\tau) = 1/2$] based on the normal data that have been simulated before for FDR calculations. These simulated powers are displayed in Figure 1. As we see from this figure, the modified Šidák procedure is often the most powerful under independence, especially, as one would expect, when the proportion of true null hypotheses is relatively small. The unmodified Bonferroni and Šidák procedures, not surprisingly, are practically indistinguishable in terms of their power performance. One should, however, be cautious in interpreting this graph in the dependent case (particularly, the upper right two panels), in light of Table 1, which indicates that the modified Bonferroni and Šidák procedures may fail to control FDR unless the dependence is weak and n_0 is small.

We should point out that the unbiasedness property of the single-step procedures, which is numerically seen to hold, can be theoretically proved easily from
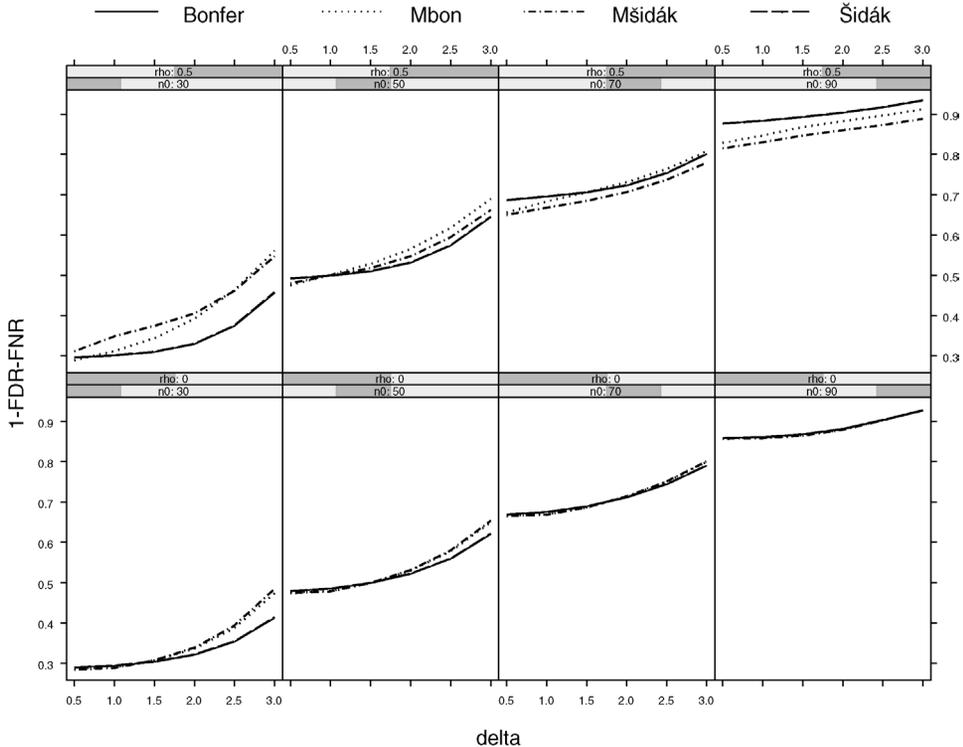

FIG. 1. *Comparison of Bonferroni and Šidák procedures with their modified versions in terms of* $1 - FDR - FNR$.

Theorems 1 and 3. However, a theoretical justification of the same property for the two-step procedures, which appears to be also true from Figure 1, is an interesting and a more challenging theoretical problem. Also, the same concept of power could be used to compare different FNR-controlling procedures.

6. Results on FDR and FNR under a mixture model. In this section, we present appropriate modifications to Lemmas 1 and 2 when a mixture approach is taken as in [7, 17]. We will, however, assume a slightly more general mixture model in the sense that it does not assume independence of the test statistics. More specifically, we first let $\mathbf{H} = (H_1, \ldots, H_n)$, with $H_i = 0$ indicating that H_i is true and $H_i = 1$ indicating that it is false. Then we assume that (X_i, H_i), $i = 1, \ldots, n$, have the distribution

$$\mathbf{X}|\mathbf{H} \sim f(\mathbf{x}, \theta_{\mathbf{H}}) \qquad \text{where } \theta_{\mathbf{H}} = (\theta_{H_1}, \ldots, \theta_{H_n}), \theta_{H_i} = (1 - H_i)\theta_i' + H_i\theta_i'',$$

$$\text{with } \theta_i' \leq \theta_{i0}, \theta_i'' > \theta_{i0}, i = 1, \ldots, n,$$

(6.1)

and $\quad \mathbf{H} \sim \pi_{\mathbf{h}}$, where $\pi_{\mathbf{h}}$ are some probabilities defined on

$$\mathcal{H} = \{\mathbf{h} = (h_1, \ldots, h_n) : h_i = 0 \text{ or } 1\}.$$

Regarding f, we assume that it belongs to a location family of distributions; that is, $f(\mathbf{x}, \theta_{\mathbf{H}}) = f(\mathbf{x} - \theta_{\mathbf{H}})$, with a positive dependence structure that ensures that, for any increasing (or decreasing) function ϕ of $\mathbf{X}$, the expectation $E\{\phi(\mathbf{X})|X_i, \mathbf{H}\}$ is increasing (or decreasing) in X_i. This is true if, for instance, $\mathbf{X}$ is positive regression dependent on subset (PRDS) under the density $f(\mathbf{x})$, as in the case of multivariate normal with positive correlations and many other multivariate distributions encountered in multiple testing; see, for example, [5, 14]. Of course, when (X_i, H_i), $i = 1, \ldots, n$, are independent, we assume no particular form for the density f; that is, we simply assume that $X_i|H_i \sim f(x, \theta_{H_i})$. Since we assume that θ_i takes the value θ_i' when $H_i = 0$ and the value θ_i'' when $H_i = 1$, the probabilities in the following discussion are all evaluated under these fixed $\theta' = (\theta_1', \ldots, \theta_n')$ and $\theta'' = (\theta_1'', \ldots, \theta_n'')$.

THEOREM 5. *Under the above mixture model and the conditions assumed therein,*

(6.2)
$$\text{FDR}(t, n) \leq \sum_{i=1}^{n} \delta_i P\{H_i = 0 | X_i \geq t\},$$

where

$$\delta_i = P\{X_i \geq t\} - \sum_{j=1}^{n-1} \frac{P\{X_{(j)}^{(-i)} \geq t, X_i \geq t\}}{(n-j)(n-j+1)} \quad and$$

(6.3)
$$\sum_{i=1}^{n} \delta_i = P\{R > 0\},$$

with the equality holding when the (X_i, H_i)'s are independent.

When (X_i, H_i), $i = 1, \ldots, n$, are identically distributed, Theorem 5 reduces to

$$(6.4) \qquad \text{FDR}(t, n) \leq P\{H_1 = 0 | X_1 \geq t\} P\{R > 0\}.$$

The equality in (6.4) holds when (X_i, H_i), $i = 1, \ldots, n$, are i.i.d., which is Storey's [17, 18] result, providing a "Bayesian Type I error rate" interpretation to his notion of pFDR $= \text{FDR}/P\{R > 0\}$. Thus, the following corollary to Theorem 5 is an extension of his result to the dependent case.

COROLLARY 1. *Under the above mixture model and the conditions assumed therein,*

$$(6.5) \qquad \text{pFDR}(t, n) \leq \max_{1 \leq i \leq n} P\{H_i = 0 | X_i \geq t\}.$$

When the (X_i, H_i)'s are identically distributed, we have

$$(6.6) \qquad \text{pFDR}(t, n) \leq P\{H_1 = 0 | X_1 \geq t\},$$

with the equality holding when the (X_i, H_i)'s are i.i.d.

Storey [17] introduced a pFDR analog of the p-value, called the q-value, that provides a measure of the strength of the tests in a multiple testing procedure with respect to pFDR. For a single-step multiple testing procedure of n hypotheses with a rejection region of the form $X_i \geq t$ for each H_i, it is defined as

$$(6.7) \qquad q_n(t) = \inf_{x \leq t} \text{pFDR}(x, n).$$

Storey [17], however, considered this quantity when (X_i, H_i), $i = 1, \ldots, n$, are i.i.d., which is

$$(6.8) \qquad q(t, H_1) = \inf_{x \leq t} P\{H_1 = 0 | X_1 \geq x\}.$$

Corollary 1 says that when the (X_i, H_i)'s are dependent with common marginals, in the sense assumed in that corollary, we have $q_n(t) \leq q(t, H_1)$. That is, the q-value of a single-step multiple test procedure obtained under certain commonly encountered types of dependence is more conservative, as one would want, compared to the corresponding i.i.d. case.

THEOREM 6. *Under the conditions stated in Theorem 5,*

$$(6.9) \qquad \text{FNR} \leq \sum_{i=1}^{n} \gamma_i P\{H_i = 1 | X_i < t\},$$

where

$$(6.10) \qquad \gamma_i = P\{X_i < t\} - \sum_{j=1}^{n-1} \frac{P\{X_{(j)}^{(-i)} < t, X_i < t\}}{j(j+1)} \quad and$$

$$\sum_{i=1}^{n} \gamma_i = P\{A > 0\},$$

with the equality holding when the (X_i, H_i)'s are independent.

This theorem can be proved following arguments similar to those used to prove Theorem 5 and with the help of an identity for $P(A > 0)$ given by Sarkar [13].

COROLLARY 2. *Under the conditions stated in Theorem 5,*

$$(6.11) \qquad \text{pFNR} \leq \max_{1 \leq i \leq n} P\{H_i = 1 | X_i < t\}.$$

When the (X_i, H_i)'s are identically distributed, we have

$$(6.12) \qquad \text{pFNR} \leq P\{H_1 = 1 | X_1 < t\},$$

with the equality holding when the (X_i, H_i)'s are i.i.d.

7. Proofs.

PROOF OF LEMMA 1.   The FDP is given by

$$(7.1) \qquad Q(t; J_0, J_1) = \sum_{i \in J_0} \sum_{j=0}^{n-1} \frac{1}{n-j} I\{R = n - j, X_i \geq t\}.$$

Since $\{R = n - j\} = \{X_{(j)} < t \leq X_{(j+1)}\}$, with $X_{(0)} = -\infty$ and $X_{(n+1)} = \infty$, we have

$$\{R = n - j, X_i \geq t\} = \{X_{(j)}^{(-i)} < t \leq X_{(j+1)}^{(-i)}, X_i \geq t\}.$$

Therefore,

$$Q(t; J_0, J_1) = \sum_{i \in J_0} \sum_{j=0}^{n-1} \frac{1}{n-j} I\{X_{(j)} < t \leq X_{(j+1)}, X_i \geq t\}$$

$$(7.2) \qquad = \sum_{i \in J_0} \sum_{j=0}^{n-1} \frac{1}{n-j} [I\{X_{(j+1)}^{(-i)} \geq t, X_i \geq t\} - I\{X_{(j)}^{(-i)} \geq t, X_i \geq t\}]$$

$$= \sum_{i \in J_0} I\{X_i \geq t\} - \sum_{i \in J_0} \sum_{j=1}^{n-1} \frac{I\{X_{(j)}^{(-i)} \geq t, X_i \geq t\}}{(n-j)(n-j+1)}.$$

Taking the expectation in (7.2), we get the first expression of the FDR in Lemma 1. The second expression follows from the fact that Q reduces to $I\{R > 0\} = I\{X_{(n)} \geq t\}$ if we consider the first summation in (7.2) over all $i \in J$.   □

PROOF OF THEOREM 2.   First note that

$$\text{FDR}_\theta^{(2)}(t_\tau \geq \tau; J_0, J_1)$$

$$(7.3) \qquad = \sum_{k=0}^{n} E_\theta\{Q(t_\tau(k); J_0, J_1) I\{X_{(k)} < \tau \leq X_{(k+1)}\}\}.$$

Since $t_\tau(k) \geq \tau$ for all k, when $k = n$ (i.e., when $X_{(n)} < \tau$), there is no rejection of null hypotheses, implying that $Q = 0$.

Let $F_{\theta_i}(x)$ and $f_{\theta_i}(x)$, respectively, be the c.d.f. and the density of X_i under any alternative θ_i for $i = 1, \dots, n$. Since the X_i's are assumed to be independent, the conditional expectation of $Q(t_\tau(k); J_0, J_1)$, given $\{X_{(k)} < \tau \leq X_{(k+1)}\}$ for $k = 0, 1, \dots, n-1$, is the FDR of the single-step procedure based on $n - k$ independent random variables $Y_1, \dots, Y_{n-k}$ with $Y_i \sim f_{\theta_i}(x) I(x \geq \tau) / \bar{F}_{\theta_i}(\tau)$ and critical value $t_\tau(k)$. Since the density of Y_i has the MLR property, implying that $(Y_1, \dots, Y_{n-k})$ is stochastically increasing, we have from Theorem 1 that this conditional expectation is

$$
\begin{aligned}
(7.4) \qquad & \leq \frac{n_0(\tau)}{n-k} P_{\theta_0} \left\{ \max_{1 \leq j \leq n-k} Y_j \geq t_\tau(k) \right\} \\
& = \frac{n_0(\tau)}{n-k} \left[1 - \left(1 - \frac{\bar{F}_0(t_\tau(k))}{\bar{F}_0(\tau)} \right)^{n-k} \right],
\end{aligned}
$$

where $n_0(\tau) = \sum_{i \in J_0} I(X_i \geq \tau)$. Going back to (7.3), we then have

$$
\begin{aligned}
& \mathrm{FDR}_\theta^{(2)}(t_\tau \geq \tau; J_0, J_1) \\
(7.5) \qquad & \leq \sum_{k=0}^{n-1} \sum_{i \in J_0} E_\theta \left\{ \frac{1}{n-k} \left[1 - \left(1 - \frac{\bar{F}_0(t_\tau(k))}{\bar{F}_0(\tau)} \right)^{n-k} \right] \right. \\
& \qquad\qquad \left. \times I\{X_i > \tau, X_{(k)} < \tau \leq X_{(k+1)}\} \right\} \\
& = \sum_{i \in J_0} \sum_{k=0}^{n-1} \frac{1}{n-k} \left[1 - \left(1 - \frac{\bar{F}_0(t_\tau(k))}{\bar{F}_0(\tau)} \right)^{n-k} \right] \\
& \qquad\qquad \times P_\theta \{ X_i > \tau, X_{(k)}^{(-i)} < \tau \leq X_{(k+1)}^{(-i)} \},
\end{aligned}
$$

which is the required inequality in Theorem 2. $\quad\square$

PROOF OF LEMMA 2. The FNP is given by

$$
\begin{aligned}
N(t; J_0, J_1) & = \sum_{i \in J_1} \sum_{j=1}^{n} \frac{1}{j} I\{A = j, X_i < t\} \\
& = \sum_{i \in J_1} \sum_{j=1}^{n} \frac{1}{j} I\{X_{(j)} < t \leq X_{(j+1)}, X_i < t\} \\
(7.6) \qquad & = \sum_{i \in J_1} \sum_{j=1}^{n} \frac{1}{j} \left[I\{X_{(j-1)}^{(-i)} < t, X_i < t\} - I\{X_{(j)}^{(-i)} < t, X_i < t\} \right] \\
& = \sum_{i \in J_1} I\{X_i < t\} - \sum_{i \in J_1} \sum_{j=1}^{n-1} \frac{I\{X_{(j)}^{(-i)} < t, X_i < t\}}{j(j+1)}.
\end{aligned}
$$

Taking the expectation of (7.6), we get the first expression of the FNR. The second expression follows from the fact that

$$N(t; J_0, J_1) = I\{A > 0\} - I\{UI(A > 0)/A\}$$

(7.7)
$$= I\{X_{(1)} < t\} - \sum_{i \in J_0} \sum_{j=1}^{n} \frac{1}{j} I\{A = j, X_i < t\}. \qquad \square$$

PROOF OF THEOREM 4. We have

$$\mathrm{FNR}_\theta^{(2)}(t_\tau \leq \tau; J_0, J_1)$$

$$= \sum_{k=1}^{n} E_\theta \big\{ \big[N(t_\tau(k); J_0, J_1) | X_{(k)} < \tau \leq X_{(k+1)} \big]$$

(7.8)
$$\times I\{X_{(k)} < \tau \leq X_{(k+1)}\} \big\}$$

$$\leq \sum_{i \in J_1} \sum_{k=1}^{n} \Bigg\{ \frac{1}{k} \bigg[1 - \bigg(1 - \frac{F_0(t_\tau(k))}{F_0(\tau)} \bigg)^k \bigg]$$

$$\times P_\theta \big\{ X_i < \tau, X_{(k-1)}^{(-i)} < \tau \leq X_{(k)}^{(-i)} \big\} \Bigg\}.$$

The inequality in (7.8) follows from Theorem 3, noting that the conditional expectation of $N(t_\tau(k); J_0, J_1)$, given $\{X_{(k)} < \tau \leq X_{(k+1)}\}$, is the FNR of the single-step procedure based on independent $Z_1, \ldots, Z_k$ with $Z_i \sim f_{\theta_i}(x) I(x < \tau)/F_{\theta_i}(\tau)$. The required inequality in Theorem 4 then follows from (7.8) because $F_{\theta_i}(\tau)$ is decreasing in θ_i for $i \in J_1$. $\square$

PROOF OF THEOREM 5. Since $V = \sum_{i=1}^{n} I(X_i \geq t) I(H_i = 0)$, we first note from Lemma 1 that the FDR under the mixture model is given by

$$\mathrm{FDR}(t, n) = \sum_{i=1}^{n} E_{\mathbf{H}} \Bigg[P\{X_i \geq t | H_i = 0\}$$

$$- \sum_{j=1}^{n-1} \frac{P\{X_{(j)}^{(-i)} \geq t, X_i \geq t | \mathbf{H} \text{ with } H_i = 0\}}{(n-j)(n-j+1)} \Bigg]$$

(7.9)
$$= \sum_{i=1}^{n} \Bigg[P\{X_i \geq t, H_i = 0\} - \sum_{j=1}^{n-1} \frac{P\{X_{(j)}^{(-i)} \geq t, X_i \geq t, H_i = 0\}}{(n-j)(n-j+1)} \Bigg]$$

$$= \sum_{i=1}^{n} \Bigg[P\{X_i \geq t, H_i = 0\}$$

$$\times \Bigg\{ 1 - \sum_{j=1}^{n-1} \frac{P\{X_{(j)}^{(-i)} \geq t | X_i \geq t, H_i = 0\}}{(n-j)(n-j+1)} \Bigg\} \Bigg].$$

We now prove that

(7.10) $$P\{X_{(j)}^{(-i)} \geq t | X_i \geq t, H_i = 0\} \geq P\{X_{(j)}^{(-i)} \geq t | X_i \geq t\}$$

under the assumed positive dependence condition of the density f of **X**.

Let $\psi(X_i) = P\{X_{(j)}^{(-i)} \geq t | X_i, \theta_i = 0\}$. Then the conditional probability $P\{X_{(j)}^{(-i)} \geq t | X_i \geq t, \theta_i\}$ can be written as

(7.11) $$\frac{E\{\psi(X_i)I(X_i \geq t - \theta_i)\}}{E\{I(X_i \geq t - \theta_i)\}},$$

with the expectations taken with respect to X_i under $\theta_i = 0$. Note that $\psi(x)$ is an increasing function of x under the assumed positive dependence condition of f. Also, $I(x \geq t)$ is a totally positive of order two (TP$_2$) function of (x, t) (see, e.g., [11]). Therefore, the ratio

(7.12) $$\frac{E\{\psi(X_i)I(X_i \geq t)\}}{E\{I(X_i \geq t)\}}$$

is increasing in t, because it is the expectation of an increasing function of a random variable whose distribution is stochastically increasing in t. This proves that $P\{X_{(j)}^{(-i)} \geq t | X_i \geq t, H_i = 0\} \geq P\{X_{(j)}^{(-i)} \geq t | X_i \geq t, H_i = 1\}$, implying that the probability $P\{X_{(j)}^{(-i)} \geq t | X_i \geq t\}$, being a convex combination of $P\{X_{(j)}^{(-i)} \geq t | X_i \geq t, H_i = 0\}$ and $P\{X_{(j)}^{(-i)} \geq t | X_i \geq t, H_i = 1\}$, is less than or equal to $P\{X_{(j)}^{(-i)} \geq t | X_i \geq t, H_i = 0\}$. Thus the required inequality (7.10) follows.

Applying (7.10) to (7.9), we get the inequality (6.2) to be proved in the theorem. The fact that

(7.13) $$\sum_{i=1}^{n} \delta_i = P\left\{\max_{1 \leq i \leq n} X_i \geq t\right\} = P\{R > 0\}$$

follows from [13]. Furthermore, it is clear that the equality in (6.2) holds under independence of (X_i, H_i). Thus, the theorem is proved. $\square$

8. Concluding remarks. We have obtained in this article some theoretical results that extend previous work done under the assumption of independent tests. Two of these set the stage for developing our idea to modify the FDR- and FNR-controlling Bonferroni and Šidák procedures and obtaining wider families of FDR- and FNR-controlling procedures. We developed this idea by extending inequalities for FDR and FNR under independence from single-step to two-step procedures. In the case of the Bonferroni procedures, it is somewhat similar to what Storey, Taylor and Siegmund [19] used to modify the FDR-controlling BH procedure (which is, of course, a stepwise procedure) under independence. In the case of

Šidák procedures, however, it is stronger in that we consider modifying less conservative procedures. It is important to point out that modifying the Šidák procedure by simply finding t that controls $(\hat{n}_0/n)\{1 - F_0^n(t)\}$ (the estimated maximum FDR, which is basically the idea in modifying the FDR-controlling Bonferroni procedure), does not seem to provide much improvement to the Šidák procedure. The same is true for the FNR-controlling Šidák procedure. This is what we have noticed based on additional simulations not reported here. Also, as is seen from Table 2, we need to be cautious using the present modifications when there is too much dependence in the tests; they may become anticonservative. Procedures that control FDR are different from those that control FNR. It will be interesting to see if procedures that control both FDR and FNR can be developed using the results discussed in this paper.

REFERENCES

[1] BENJAMINI, Y. and HOCHBERG, Y. (1995). Controlling the false discovery rate: A practical and powerful approach to multiple testing. *J. Roy. Statist. Soc. Ser. B* **57** 289–300. MR1325392

[2] BENJAMINI, Y. and HOCHBERG, Y. (2000). On the adaptive control of the false discovery rate in multiple testing with independent statistics. *J. Educational and Behavioral Statistics* **25** 60–83.

[3] BENJAMINI, Y., KRIEGER, A. M. and YEKUTIELI, D. (2002). Adaptive linear step-up false discovery rate controlling procedures. Unpublished manuscript.

[4] BENJAMINI, Y. and LIU, W. (1999). A step-down multiple hypotheses testing procedure that controls the false discovery rate under independence. *J. Statist. Plann. Inference* **82** 163–170. MR1736441

[5] BENJAMINI, Y. and YEKUTIELI, D. (2001). The control of the false discovery rate in multiple testing under dependence. *Ann. Statist.* **29** 1165–1188. MR1869245

[6] EFRON, B. (2003). Robbins, empirical Bayes and microarrays. *Ann. Statist.* **31** 366–378. MR1983533

[7] EFRON, B., TIBSHIRANI, R., STOREY, J. D. and TUSHER, V. (2001). Empirical Bayes analysis of a microarray experiment. *J. Amer. Statist. Assoc.* **96** 1151–1160. MR1946571

[8] GENOVESE, C. and WASSERMAN, L. (2002). Operating characteristics and extensions of the false discovery rate procedure. *J. R. Stat. Soc. Ser. B Stat. Methodol.* **64** 499–517. MR1924303

[9] GENOVESE, C. and WASSERMAN, L. (2004). A stochastic process approach to false discovery control. *Ann. Statist.* **32** 1035–1061. MR2065197

[10] HOCHBERG, Y. and BENJAMINI, Y. (1990). More powerful procedures for multiple significance testing. *Statistics in Medicine* **9** 811–818.

[11] KARLIN, S. (1968). *Total Positivity* **1**. Stanford Univ. Press. MR0230102

[12] LEHMANN, E. (1986). *Testing Statistical Hypotheses*, 2nd ed. Wiley, New York. MR0852406

[13] SARKAR, S. K. (1998). Some probability inequalities for ordered MTP_2 random variables: A proof of the Simes conjecture. *Ann. Statist.* **26** 494–504. MR1626047

[14] SARKAR, S. K. (2002). Some results on false discovery rate in stepwise multiple testing procedures. *Ann. Statist.* **30** 239–257. MR1892663

[15] SARKAR, S. K. (2004). FDR-controlling stepwise procedures and their false negatives rates. *J. Statist. Plann. Inference* **125** 119–137. MR2086892

[16] SIMES, R. J. (1986). An improved Bonferroni procedure for multiple tests of significance. *Biometrika* **73** 751–754. MR0897872

[17] STOREY, J. D. (2002). A direct approach to false discovery rates. *J. R. Stat. Soc. Ser. B Stat. Methodol.* **64** 479–498. MR1924302

[18] STOREY, J. D. (2003). The positive false discovery rate: A Bayesian interpretation and the q-value. *Ann. Statist.* **31** 2013–2035. MR2036398

[19] STOREY, J. D., TAYLOR, J. E. and SIEGMUND, D. (2004). Strong control, conservative point estimation and simultaneous conservative consistency of false discovery rates: A unified approach. *J. R. Stat. Soc. Ser. B Stat. Methodol.* **66** 187–205. MR2035766

FOX SCHOOL OF BUSINESS AND MANAGEMENT
TEMPLE UNIVERSITY
SPEAKMAN 319
1810 NORTH 13TH STREET
PHILADELPHIA, PENNSYLVANIA 19122-6083
USA
E-MAIL: sanat@temple.edu