A direct approach to false discovery rates by decoy permutations

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April 24, 2018

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Abstract

The current approaches to false discovery rates (FDRs) in multiple hypothesis testing are usually based on the null distribution of a test statistic. However, all types of null distributions, including the theoretical, permutation-based and empirical ones, have some inherent drawbacks. For example, the theoretical null might fail because of improper assumptions on the sample distribution. In addition, many existing approaches to FDRs need to estimate the ratio of true null hypotheses, which is difficult and unsatisfactorily addressed. In this paper, we propose the target-decoy procedure, a different approach to FDRs for search of random variables different between cases and controls in general case-control study. Our approach is free of estimation of the null distribution and the ratio of true null hypotheses. The target-decoy procedure simply builds on the ordering of hypotheses by some statistic, and directly estimates the false target discoveries using the competing decoy hypotheses constructed by permutation. We prove that this approach can control the FDR. Simulation demonstrates that it is more stable and powerful than two most popular approaches. We also evaluate our approach on a real microarray data for identifying differential gene expression.

Keywords: False discovery rate control; Multiple testing; Target-decoy procedure; Null distribution free methods
1 Introduction

Controlling the false discovery rate (FDR, i.e., the expected proportion of incorrect rejections among all rejections) is a powerful and popular way to do multiple testing. FDR was firstly introduced by Benjamini and Hochberg (1995) (BH). Let $H_j (j = 1, ..., m)$ be the tested null hypotheses, $m_0$ of which are true and the remaining are false. Let $V$ denote the number of true null hypotheses that are erroneously rejected and $R$ be the total number of hypotheses that are rejected. Then the false discovery rate is $FDR = \mathbb{E}(Q)$ where the proportion of false discoveries, $Q$, is $V/R$ if $R > 0$ and 0 if $R = 0$. BH also provided a $p$-value based sequential method to control the FDR. FDR control is to search for a significance threshold of $p$-values or other test statistics such that the real FDR of all rejections does not exceed a given level. Since then, many FDR control methods have been developed, e.g., Benjamini and Yekutieli (2001); Sarkar (2002); Storey (2002, 2003); Benjamini et al. (2006); Basu et al. (2017).

The Bayes method (Storey, 2002, 2003) is one of the most popular approaches to FDRs. This method does not only provide a Bayesian interpretation for FDR, but also improves the power of FDR control by estimating the ratio of true null hypotheses. The ratio estimation, which was absent in the original BH procedure, is now widely used in current FDR methods to enhance the power, such as the Bayes and the empirical Bayes methods (Storey, 2002; Benjamini et al., 2006; Efron, 2008; Strimmer, 2008).

Current canonical approaches to FDRs are based on the null distribution of a test statistic (Benjamini and Hochberg, 1995; Storey, 2002; Benjamini et al., 2006). However, it is usually difficult to obtain the proper null distribution. Popular null distributions include the theoretical null, permutation null, bootstrap null and empirical null (Efron, 2008, 2012). Though the theoretical null is most popularly used, it might fail in practice
for many reasons, such as improper mathematical assumptions or unobserved covariates (Efron, 2007, 2008). For example, if the real null distribution is not normal, the p-values calculated by Student’s t-test are not uniform (0, 1) distributed for true null hypotheses. The permutation null is also widely used. There are mainly two different permutation methods, i.e., the permutation tests and the pooled permutation (Kerr, 2009). The permutation tests are a class of widely applicable non-parametric tests to calculate p-values, and are most useful when the information about the data distribution is insufficient. However, the p-values reported by permutation tests are discretely distributed and their precision is limited by the sample size of a test. Low precision may reduce the statistical power (Tusher et al., 2001). Instead of estimating a null distribution for each test separately, the pooled permutation in multiple testing estimates an overall null distribution for all tests (Efron et al., 2001). However, it has been found that the pooling permutation null distributions across hypotheses can produce invalid p-values, since even true null hypotheses can have different permutation distributions (Kerr, 2009). Bootstrap is another popular method for calculating p-value, but it is not applicable to the cases where the number of tests is much larger than the sample size of a test (Fan et al., 2007; Efron, 2012; Liu and Shao, 2014).

To overcome the shortcomings of the theoretical and permutation null distributions, new methods were proposed to estimate an empirical null distribution from a large number of tests (Efron et al., 2001; Efron and Tibshirani, 2002; Efron, 2008; Scott and Berger, 2010). For example, the empirical Bayes method estimates the empirical null distribution by decomposing the mixture of null and alternative distributions. However, decomposing the mixture distribution is intrinsically a difficult problem. For example, if the empirical distribution has a strong peak, the decomposing may fail (Strimmer, 2008).

As far as we know, almost all methods with the proof of FDR control depend exclusively on the accurate null distribution, no matter the required inputs are proper p-values (Storey, 2003).
2002 Benjamini et al., 2006 Gavrilov et al., 2009 Sarkar et al., 2013) or z-values (Sun and Cai, 2007, Tansey et al., 2017). Some methods do not need the accurate null distribution, but additional assumptions about the null distribution are still necessary, such as the null distribution is normal (Efron, 2007, Strimmer, 2008) and the null distributions of all statistics are the same and symmetric about 0 (Arias-Castro and Chen, 2017). Meanwhile, to enhance the power of FDR control, most popular methods estimate the ratio of true null hypotheses (Storey, 2002, Benjamini et al., 2006, Efron, 2008, Strimmer, 2008). However, these estimates often have considerable biases (Hansen and Kerr, 2012).

In this paper, we propose a direct approach to FDR control, named target-decoy procedure, which is free of the null distribution and the ratio of true null hypotheses. In this approach, a target score and a number of decoy scores are calculated for each hypothesis. The target score is calculated with regard to the original samples. The decoy scores are calculated with regard to randomly permuted samples. Based on the target score and decoy scores, a label and a final score are calculated as follows. If the target score is more significant than half of decoy scores, the hypothesis is labeled as target and the final score is set as the target score. Otherwise, the hypothesis is labeled as decoy and the final score is set as the decoy score with a specific rank mapped from the rank of the target score. Then the hypotheses are sorted by their final scores and the ratio of decoy to target hypotheses beyond a threshold is directly used for FDR control. Our approach to FDRs is exclusively based on these scores and their labels. Unlike p-values or other test statistics with clear null distributions, the score used in our approach can be any measure of the (dis)similarity of two groups of samples. Therefore, our approach is very flexible and can be more powerful than traditional approaches that are limited by the precision of p-values or the sample size of each test. Importantly, we establish the theoretical foundation of the target-decoy procedure by proving that it can rigorously control the FDR when the scores
are independent between different tests.

Monte-Carlo simulations demonstrate that our approach is more stable and powerful than two popular methods, i.e., the Bayes method (Storey, 2002; Storey et al., 2004) and the empirical Bayes method (Efron et al., 2001; Efron and Tibshirani, 2002; Efron, 2008). The performances of the three methods were also compared on a real data set. Because our procedure is more straightforward and can be used with arbitrary scores, we believe that it will have many practical applications.

Our approach was inspired by the target-decoy protein database search strategy widely used to estimate the FDR of peptide identifications by tandem mass spectrometry (Elias and Gygi, 2007). A modified version of this strategy (addition of one to the number of decoys) was proved to control the FDR by us (He, 2013; He et al., 2015). The similar approach has been used for FDR control in the setting of variable selection of classical linear regression model (Barber and Candès, 2015). To our knowledge, our approach presents a first attempt to establish a distribution-free framework for search of random variables different between cases and controls in general case-control study. We will discuss the difference of our approach from previous related work at the end of the paper.

The rest of the paper is organized as follows. Section 2 discusses a general model for case-control study. Our target-decoy procedure is presented in Section 3. Section 4 establishes the theoretical foundation of our procedure. Numerical results are given in Section 5. In Section 6 we show an application of the target-decoy procedure on an Arabidopsis microarray data set. Section 7 concludes the paper with a discussion of related and future works. Proofs of theoretical results are provided in the Supplementary Materials.
2 Problem Formulation

Consider a case-control study involving \( m \) random variables, \( X_1, X_2, \ldots, X_m \). For each random variable \( X_j \) where \( j \in [m] \), there are \( n \) random samples \( X_{j_1}, X_{j_2}, \ldots, X_{j_n} \), where \( X_{j_1}, X_{j_2}, \ldots, X_{j_n} \) are from the \( n_1 \) cases and \( X_{j_{n_1+1}}, \ldots, X_{j_n} \) are from the \( n_0 = n - n_1 \) controls.

The goal is to search for random variables different between cases and controls. The null hypothesis for random variable \( X_j \) used here is the ‘symmetrically distributed’ hypothesis \( H_{j0} \): the joint distribution of \( X_{j_1}, X_{j_2}, \ldots, X_{j_n} \) is symmetric. In other words, the joint probability density function of \( X_{j_1}, X_{j_2}, \ldots, X_{j_n} \) (or the joint probability mass function if \( X_{j_1}, X_{j_2}, \ldots, X_{j_n} \) are discrete) satisfies
\[
f_{X_{j_1}, \ldots, X_{j_n}}(x_{j_1}, \ldots, x_{j_n}) = f_{X_{j_1}, \ldots, X_{j_n}}(\pi_n(x_{j_1}, \ldots, x_{j_n}))
\]
for any possible \( x_{j_1}, \ldots, x_{j_n} \) and any permutation \( \pi_n \) of \( x_{j_1}, \ldots, x_{j_n} \). If \( X_{j_1}, \ldots, X_{j_n} \) are independent, this hypothesis is equivalent to that \( X_{j_1}, \ldots, X_{j_n} \) are identically distributed. Here we use the ‘symmetrically distributed’ hypothesis to deal with the case where \( X_{j_1}, \ldots, X_{j_n} \) are related but still an exchangeable sequence of random variables (Chow and Teicher, 2012).

Let \( S(x_1, x_2, \ldots, x_n) \) be some score to measure the difference between \( x_1, x_2, \ldots, x_{n_1} \) and \( x_{n_1+1}, x_{n_1+2}, \ldots, x_n \). Without loss of generality, we assume that large scores indicate significance and \( S(x_1, \ldots, x_n) = S(\pi_{n_1}(x_1, \ldots, x_{n_1}), \pi_{n_0}(x_{n_1+1}, \ldots, x_n)) \) holds for any possible \( x_1, \ldots, x_n \) where \( \pi_{n_1}(x_1, \ldots, x_{n_1}) \) is any permutation of \( x_1, \ldots, x_{n_1} \) and \( \pi_{n_0}(x_{n_1+1}, \ldots, x_n) \) is any permutation of \( x_{n_1+1}, \ldots, x_n \). Note that neither the null distributions of scores nor the distributions of random variables are required to be known.

3 The target-decoy procedure

Our procedure for FDR control is as follows.
Algorithm: the target-decoy procedure

1. For each test \( j \), calculate the target score \( S^T_j = S(X_{j_1}, X_{j_2}, \ldots, X_{j_n}) \). Permute the case and control status randomly for \( t - 1 \) times and calculate the \( t - 1 \) scores of the permutations. Sort these \( t \) scores in descending order. For equal scores, sort them randomly with equal probability.

2. For each test \( j \), calculate a final score \( S_j \) and assign it a label \( L_j \in \{T, D\} \), where \( T \) and \( D \) stand for target and decoy, respectively. Assume that the rank of \( S^T_j \) is \( i \). If \( i < (t + 1)/2 \), let \( L_j = T \) and set \( S_j = S^T_j \). If \( i > (t + 1)/2 \), let \( L_j = D \) and set \( S_j \) as the score ranking \( i - \lceil t/2 \rceil \). Otherwise, \( i = (t + 1)/2 \), let \( L_j \) be \( T \) or \( D \) randomly with equal probability and set \( S_j \) as \( S^T_j \).

3. Sort the \( m \) tests in descending order of the final scores. For tests with equal scores, sort them randomly with equal probability. Let \( L_{(1)}, L_{(2)}, \ldots, L_{(m)} \) denote the sorted labels and \( S_{(1)}, S_{(2)}, \ldots, S_{(m)} \) denote the sorted scores.

4. If the specified FDR control level is \( \alpha \), let

\[
K = \max \left\{ k \in \{0, 1, \ldots, m\} \mid \frac{\#\{L_{(j)} = D, j \leq k\} + 1}{\#\{L_{(j)} = T, j \leq k\} \lor 1} \leq \alpha \right\} \tag{1}
\]

and reject the hypothesis with rank \( j \) if \( L_{(j)} = T \) and \( j \leq K \).

Section 4 will show the target-decoy procedure can control the FDR. The random permutation used in our procedure can be generated by simple random sampling either with or without replacement, just as in the permutation tests. Similarly, with larger sampling number \( t - 1 \), the power of our procedure will be a little stronger as shown in Section 5. We can set \( t \) as \( \min \{n_0, \tau\} \), where \( \tau \) is the maximum number of permutations we would perform.
Table 1. Possible values of $Z_j$ for the target-decoy procedure.

| $L_j$ = $T$ | $L_j$ = $D$ |
|------------|------------|
| $H_j = 0$  | 1          | $-1$       |
| $H_j = 1$  | 0          | $-2$       |

Unlike other FDR control methods, our target-decoy procedure does not depend on the null distribution. The sampling number of permutations, $t - 1$, used in our procedure can be much smaller than that used in permutation tests. In our simulations, $t - 1$ was set as 49 or 1, while in the real data experiments, $t - 1$ was set as 19. Simulations demonstrate that our target-decoy procedure can still control the FDR even if $t - 1$ was set as 1 and then little information about the null distributions was revealed.

4 Theoretic Analysis

In this section, we will show that equation (1) can control the FDR. Let $H_j = 0$ and $H_j = 1$ denote that the null hypothesis for random variable $j$ is true and false, respectively. Note that $H_1, H_2, \cdots, H_m$ are constants in the setting of hypothesis testing. Define $Z_j$ where $1 \leq j \leq m$ as follows. If $H_j = 0$, let $Z_j$ be 1 if $L_j = T$ and be $-1$ if $L_j = D$. Otherwise, $H_j = 1$, let $Z_j$ be 0 if $L_j = T$ and be $-2$ if $L_j = D$. Table 1 summarizes the possible situations. Let $Z_{(1)}, Z_{(2)}, \cdots, Z_{(m)}$ denote the sorted sequence of $Z_1, Z_2, \cdots, Z_m$.

Let $\overrightarrow{S}$ and $\overrightarrow{S}_{\neq j}$ denote $S_1, \cdots, S_m$ and $S_1, \cdots, S_{j-1}, S_{j+1}, \cdots, S_m$, respectively. Let $\overrightarrow{S}_{(\cdot)}$ and $\overrightarrow{S}_{(\neq j)}$ denote $S_{(1)}, \cdots, S_{(m)}$ and $S_{(1)}, \cdots, S_{(j-1)}, S_{(j+1)}, \cdots, S_{(m)}$, respectively. We define $\overrightarrow{s}$, $\overrightarrow{s}_{\neq j}$, $\overrightarrow{s}_{(\cdot)}$ and $\overrightarrow{s}_{(\neq j)}$ similarly. For example, we will use $\overrightarrow{s}_{(\cdot)}$ to denote a sequence of $m$ constants, $s_{(1)}, s_{(2)}, \cdots, s_{(m)}$, which is one of the observed values of $S_{(\cdot)}$. We will also
define $\tilde{L}, \tilde{Z}, \tilde{H}, \tilde{L}_{(\neq j)}$, etc. Then we have the following theorem, the proof of which is given in the Supplementary Materials.

**Theorem 1.** In the target-decoy procedure, if the $m$ random variables are independent, then for any fixed $j \in [m]$ and any possible $s(\cdot)$ and $\tilde{z}(\cdot)$, we have

$$
\Pr \left( Z(j) = 1 \mid s(\cdot) = \tilde{s}(\cdot), Z(\neq j) = \tilde{z}(\neq j) \right) = \Pr \left( Z(j) = -1 \mid s(\cdot) = \tilde{s}(\cdot), Z(\neq j) = \tilde{z}(\neq j) \right). \quad (2)
$$

From Table 1, we have $Z(j) \geq 0$ if $L(j) = T$ and $Z(j) < 0$ if $L(j) = D$. Thus, equation (1) is equivalent to $K = \max\{k \in \{0, 1, \ldots, m\} \mid \frac{\# \{ Z(j) < 0, j \leq k \} + 1}{\# \{ Z(j) \geq 0, j \leq K \} \vee 1} \leq \alpha \}$. Meanwhile, the total number of rejected hypotheses is $\# \{ L(j) = T, j \leq K \} = \# \{ Z(j) \geq 0, j \leq K \}$, and the number of falsely rejected hypotheses is $\# \{ L(j) = T, H(j) = 0, j \leq K \} = \# \{ Z(j) = 1, j \leq K \}$. Therefore, the false discovery proportion (FDP) is $\frac{\# \{ Z(j) = 1, j \leq K \}}{\# \{ Z(j) \geq 0, j \leq K \} \vee 1}$ and the real FDR is $\mathbb{E} \left( \frac{\# \{ Z(j) = 1, j \leq K \}}{\# \{ Z(j) \geq 0, j \leq K \} \vee 1} \right)$. To prove that equation (1) can control the FDR, we only need to prove the following theorem, and the proof is given in the Supplementary Materials.

**Theorem 2.** Let random variables $S(1), S(2), \ldots, S(m), Z(1), Z(2), \ldots, Z(m), K$ be defined as in Section 3. Then for any $\alpha \in [0, 1]$, we have

$$
\mathbb{E} \left( \frac{\# \{ Z(j) = 1, j \leq K \}}{\# \{ Z(j) \geq 0, j \leq K \} \vee 1} \right) < \alpha. \quad (3)
$$

**Remark.** The most intuitive way for FDR control is to set $K$ as

$$
K = \max \left\{ k \in \{0, 1, \ldots, m\} \mid \frac{\# \{ Z(j) < 0, j \leq k \}}{\# \{ Z(j) \geq 0, j \leq k \} \vee 1} \leq \alpha \right\}. \quad (4)
$$

However, this way cannot control the FDR. Consider a case-control study where the specified FDR control level is 0.1 and all hypotheses are true null. From Theorem 1, we have $\Pr(Z(1) = 1) = \Pr(Z(1) = -1) = 0.5$. If $Z(1) = 1$, we have $\frac{\# \{ Z(j) < 0, j \leq 1 \}}{\# \{ Z(j) \geq 0, j \leq 1 \} \vee 1} = 0$. Therefore, $K > 1$ and at least one hypothesis will be rejected. Then the FDP when $Z(1) = 1$ is 1. Thus, the FDR is no less than $0.5 \times 1 = 0.5 > 0.1$, which is not controlled.
5 Simulation Studies

We used Monte-Carlo simulations to study the performance of our method. We considered the case-control studies in which the random variables follow the normal distribution, the gamma distribution and the Cauchy distribution, respectively. In addition to the normal distribution, we did simulation experiments for the gamma distribution because many random variables in real world are gamma-distributed. Moreover, to test the multiple testing methods with a heavy-tailed distribution, we did simulation experiments for the Cauchy distribution.

Recall that the case-control study consists of \( m \) random variables. For each random variable, there are \( n \) random samples, \( n_1 \) of which are from the cases and the other \( n_0 = n - n_1 \) are from the controls. Let \( X_{j_1}, X_{j_2}, \ldots, X_{j_n} \) be the \( n \) random samples for random variable \( X_j \).

The observation values from the normal distribution were generated in a way similar to Benjamini, Krieger, and Yekutieli (2006). First, let \( \zeta_0, \zeta_{11}, \ldots, \zeta_{1n}, \ldots, \zeta_{m1}, \ldots, \zeta_{mn} \) be independent and identically distributed random variables following the \( N(0,1) \) distribution. Next, let \( X_{ji} = \sqrt{\rho} \zeta_0 + \sqrt{\rho} \zeta_{ji} + \mu_{ji} \) for \( j = 1, \ldots, m \) and \( i = 1, \ldots, n \). We used \( \rho = 0, 0.4 \) and \( 0.8 \) corresponding to independence and \( \rho = 0.4 \) and 0.8 corresponding to typical moderate and high correlation values estimated from real microarray data, respectively (Almudevar et al., 2006). The values of \( \mu_{ji} \) are zero for \( i = n_1 + 1, n_1 + 2, \ldots, n \), the \( n_0 \) controls. For the \( n_1 \) cases where \( i = 1, 2, \ldots, n_1 \), the values of \( \mu_{ji} \) are also zero for \( j = 1, 2, \ldots, m_0 \), the \( m_0 \) hypotheses that are true null. The values of \( \mu_{ji} \) for \( i = 1, 2, \ldots, n_1 \) and \( j = m_0 + 1, \ldots, m \) are set as follows. We let \( \mu_{ji} = 1, 2, 3 \) and 4 for \( j = m_0 + 1, m_0 + 2, m_0 + 3, m_0 + 4 \), respectively. Similarly, we let \( \mu_{ji} = 1, 2, 3 \) and 4 for \( j = m_0 + 5, m_0 + 6, m_0 + 7, m_0 + 8 \), respectively. This cycle was repeated to produce
\(\mu_{(m_0+1)1}, \cdots, \mu_{(m_0+1)n_1}, \cdots, \mu_{m1}, \cdots, \mu_{mn} \) for the false null hypotheses.

The observation values from the gamma distribution, which is characterized using shape and scale, were generated in the following way. First, let \(\Gamma_0, \Gamma_{11}, \cdots, \Gamma_{1n}, \cdots, \Gamma_{m1}, \cdots, \Gamma_{mn} \) be independent random variables where \(\Gamma_0 \) follows the \(\Gamma(k_0, 1)\) distribution and \(\Gamma_{ji} \) follows the \(\Gamma(k_{ji}, 1)\) distribution for any \(j = 1, \cdots, m\) and \(i = 1, \cdots, n\). Next, let \(X_{ji} = \Gamma_{ji}\) for \(j = 1, \cdots, m\) and \(i = 1, \cdots, n\) in the simulation study for independent random variables and let \(X_{ji} = \Gamma_0 + \Gamma_{ji}\) for dependent random variables. To obtain reasonable correlation values, \(k_0\) was set as 4 and \(k_{ji}\) was set as 1 for \(i = n_1 + 1, n_1 + 2, \cdots, n\), the \(n_0\) controls. For the \(n_1\) cases where \(i = 1, 2, \cdots, n_1\), \(k_{ji}\) was set as 1 for \(j = 1, \cdots, m_0\), the \(m_0\) hypotheses that are true null. The values of \(k_{ji}\) for \(i = 1, 2, \cdots, n_1\) and \(j = m_0 + 1, \cdots, m\) are set as follows. We let \(k_{ji} = 2, 3, 4\) and 5 for \(j = m_0 + 1, m_0 + 2, m_0 + 3, m_0 + 4\), respectively. Similarly, we let \(k_{ji} = 2, 3, 4\) and 5 for \(j = m_0 + 5, m_0 + 6, m_0 + 7, m_0 + 8\), respectively. This cycle was repeated to produce \(k_{(m_0+1)1}, \cdots, k_{(m_0+1)n_1}, \cdots, k_{m1}, \cdots, k_{mn} \) for the false null hypotheses. The observation values from the Cauchy distribution were generated in a similar way and the details are given in the Supplementary Materials.

The specified FDR control levels were 5\% and 10\%, respectively. The total number of tests, \(m\), was set as 10000. The ratio of false null hypotheses was either 1\% or 10\%. The total sample size, \(n\), was set as 20, 60 or 100, and the number of cases and that of controls were always set to the same. We only present the results of experiments for normal and gamma distributions where \(n\) was 20 in the main text. Other results are given in the Supplementary Materials.

Three different approaches to FDRs were compared in our simulations, i.e., the Bayes method ([Storey] 2002, 2003, [Storey et al.] 2004), the empirical Bayes method ([Efron et al.] 2001, [Efron and Tibshirani] 2002, [Efron] 2008) and our target-decoy procedure. The Bayes method and the empirical Bayes method are among the most remarkable multiple testing
methods. To compare the power of these methods, we rejected the hypotheses against specified FDR control levels, $\alpha$. The rejection threshold, $s$, for the Bayes method was set as the largest $p$-value such that $q$-value(s) is no more than $\alpha$ (Storey 2002, 2003). The rejection threshold, $s$, for the empirical Bayes method was set as the minimum $z$-value such that $\text{Efdr}(s)$ is no more than $\alpha$, where $\text{Efdr}(s)$ is the expected fdr of hypotheses with $z$-values no smaller than $s$ (Efron 2007, 2004). Specifically, the R packages ”locfdr” version 1.1-8 (Efron 2004), and ”qvalue” version 2.4.2 (Storey and Tibshirani 2003) were used. Each simulation experiment was repeated for 1000 times. We calculated the mean number of rejected hypotheses to value the power of each method. The FDRs of rejected hypotheses were calculated by the means of FDPs. Note that the variance of the mean of FDPs of 1000 repetitions is one thousandth of the variance of FDPs. We can also estimate the standard deviation of the mean of FDPs from the sample standard deviation of FDPs.

The $p$-values of the Bayes method and the $z$-values of the empirical Bayes method were calculated with the Student’s $t$-test, Wilcoxon rank sum test, the Student’s $t$-test with permutation, or the Student’s $t$-test with bootstrap. For the permutation and bootstrap methods, we sampled the cases and the controls for each test, calculated the $z$-values for sampled data by $t$-test, and calculated the $p$-values with the null distribution of pooled $z$-values (Xie et al. 2005; Liu and Shao 2014). For the bootstrap method, the resampling was within the groups. The sampling number of permutations was set as 10 (Efron 2012) and that of bootstrap was set as 200.

For our target-decoy procedure, the cases and the controls of each test were permuted for 49 times or only once and the $t$-values and the test statistics of the Wilcoxon rank sum test were used. We did the one permutation experiments where little information about the null distributions was revealed to demonstrate that our procedure does not rely on the null distribution. Because the permutation is performed inherently in our target-decoy
procedure, the extra permutation and bootstrap are unnecessary.

We will use abbreviations to represent the experiments. For example, Bayes, permutation, Normal, 10%, $\rho = 0.8$ represents the simulation experiment where the Bayes method combined with the pooled permutation is used, the random variables follow the normal distribution, the ratio of false null hypotheses is as high as 10% and the correlation values are 0.8. For our target-decoy procedure, $t$-value, 49, Gamma, 1% represents the simulation experiment where the $t$-value is used as the score, 49 permutations are performed for each test, the random variables follow the gamma distribution and the ratio of false null hypotheses is as low as 1%.

5.1 Independent random variables
Table 2. Real FDRs with independent random variables. The sample size is 20. The FDRs were calculated by the means of FDPs of 1000 repetitions. The standard deviations of the means of FDPs are less than 0.0020 for all the experiments. All the cases where FDRs exceed $\alpha$ are labeled with $\ast$.

|                  | Normal,1% | Normal,10% | Gamma,1% | Gamma,10% |
|------------------|-----------|------------|----------|-----------|
| $\alpha$         | 0.05      | 0.10       | 0.05     | 0.10      |
| **Bayes**        |           |            |          |           |
| t-test           | 0.050     | 0.100      | 0.050    | 0.100     |
| permutation      | 0.048     | 0.099      | 0.048    | 0.098     |
| rank-sum         | 0.039     | 0.088      | 0.039    | 0.087     |
| bootstrap        | 0.012     | 0.035      | 0.034    | 0.080     |
| **Empirical Bayes** |        |            |          |           |
| t-test           | 0.044     | 0.092      | 0.040    | 0.084     |
| permutation      | 0.039     | 0.078      | 0.039    | 0.086     |
| rank-sum         | 0.046     | 0.092      | 0.037    | 0.078     |
| bootstrap        | 0.005     | 0.015      | 0.022    | 0.060     |
| **Target-decoy** |           |            |          |           |
| t-value,49       | 0.041     | 0.094      | 0.049    | 0.099     |
| t-value,1        | 0.044     | 0.093      | 0.048    | 0.097     |
| rank-sum,49      | 0.042     | 0.096      | 0.049    | 0.099     |
| rank-sum,1       | 0.042     | 0.093      | 0.048    | 0.097     |
Table 3. Power with independent random variables. The sample size is 20. All the cases where FDRs exceed $\alpha$ as shown in Table 2 are labeled with *.

|                  | Normal,1% | Normal,10% | Gamma,1% | Gamma,10% |
|------------------|-----------|------------|----------|-----------|
| $\alpha$        | 0.05 0.10 | 0.05 0.10  | 0.05 0.10 | 0.05 0.10 |
| Bayes            |           |            |          |           |
| $t$-test         | 71 80     | 845 937    | 40 50    | 687 798   |
| permutation      | 71 80     | 842 933    | 41 55    | 737 861*  |
| rank-sum         | 67 76     | 813 906    | 48 59    | 734 836   |
| bootstrap        | 60 68     | 808 902    | 0 1      | 494 673   |
| Empirical Bayes  |           |            |          |           |
| $t$-test         | 70 78     | 823 909    | 23 32    | 534 650   |
| permutation      | 69 76     | 821 913    | 49 66*   | 755* 891* |
| rank-sum         | 69 77     | 806 889    | 47 59    | 715 823   |
| bootstrap        | 53 61     | 772 863    | 0 0      | 10 221    |
| Target-decoy     |           |            |          |           |
| $t$-value,49     | 69 79     | 843 935    | 45 60    | 743 853   |
| $t$-value,1      | 69 79     | 841 931    | 45 60    | 736 845   |
| rank-sum,49      | 67 77     | 834 926    | 42 60    | 755 872   |
| rank-sum,1       | 66 77     | 831 922    | 42 60    | 751 865   |

*FDR Control.* Table 2 shows the real FDRs of different methods with independent random variables while the specified FDR control level $\alpha$ was 5% or 10%. The results show that the $t$-test with Bayes or empirical Bayes overestimated the FDRs for the gamma
distribution. The real FDRs of pooled permutation can significantly exceed $\alpha$ when the random variables follow the gamma distribution. The Wilcoxon rank-sum test with Bayes or empirical Bayes overestimated the FDRs. The real FDRs of bootstrap were much smaller than $\alpha$. The target-decoy procedure always controlled the FDR.

Statistical power. Table 3 shows the statistical power of different methods with independent random variables. Bootstrap is less powerful than all the other methods, especially when the random variables follow the gamma distribution.

When the random variables follow the normal distribution, the Bayes method is a little more powerful than the target-decoy procedure while $t$-test is used. However, it is much less powerful than the target-decoy procedure while the Wilcoxon rank-sum test is used. The empirical Bayes method is less powerful than the Bayes method and our target-decoy procedure, especially for the Normal,10% experiments.

When the random variables follow the gamma distribution, the target-decoy procedure is much more powerful than the Bayes and empirical Bayes methods, even if only one permutation was performed. Though the pooled permutation seems to be powerful, the FDRs were not controlled.

In our experiments, the target-decoy procedure always controlled the FDR. Meanwhile, our procedure is very powerful and does not rely on the null distribution. Even if only one permutation was performed, many hypotheses were still rejected while the FDRs were controlled.

5.2 Dependent random variables
Table 4. Real FDRs with dependent random variables. The sample size is 20. The FDRs were calculated by the means of FDPs of 1000 repetitions. The standard deviations of the means of FDPs are less than 0.0021 for all the experiments. All the cases where FDRs exceed $\alpha$ are labeled with $\ast$.

| Normal, $\rho = 0.4$ | Normal, $\rho = 0.8$ | Gamma |
|----------------------|----------------------|-------|
| 1%                   | 1%                   | 1%    |
| 10%                  | 10%                  | 10%   |
| \(\alpha\)           | \(\alpha\)           | \(\alpha\) |
| 0.05 0.10            | 0.05 0.10            | 0.05 0.10 |
| 0.05 0.10            | 0.05 0.10            | 0.05 0.10 |

| Bayes |
|-------|
| \(t\)-test | 0.052* 0.102* 0.050 0.100 | 0.050 0.101* 0.050 0.100 | 0.023 0.048 0.031 0.072 |
| permutation | 0.050 0.100 0.048 0.098 | 0.049 0.099 0.047 0.098 | 0.026 0.067 0.047 0.103* |
| rank-sum | 0.046 0.088 0.044 0.085 | 0.038 0.092 0.039 0.083 | 0.043 0.085 0.042 0.082 |
| bootstrap | 0.014 0.039 0.034 0.081 | 0.015 0.041 0.035 0.083 | 0.000 0.000 0.005 0.027 |

| Empirical Bayes |
|-----------------|
| \(t\)-test | 0.047 0.097 0.044 0.090 | 0.048 0.100 0.047 0.097 | 0.006 0.013 0.008 0.023 |
| permutation | 0.042 0.083 0.043 0.093 | 0.041 0.084 0.045 0.099 | 0.048 0.123* 0.055* 0.121* |
| rank-sum | 0.049 0.095 0.042 0.086 | 0.048 0.094 0.046 0.095 | 0.045 0.090 0.037 0.077 |
| bootstrap | 0.006 0.020 0.026 0.067 | 0.008 0.024 0.029 0.074 | 0.000 0.000 0.000 0.001 |

| Target-decoy |
|---------------|
| \(t\)-value,49 | 0.047 0.097 0.050 0.100 | 0.047 0.095 0.049 0.100 | 0.043 0.094 0.048 0.099 |
| \(t\)-value,1 | 0.046 0.096 0.048 0.098 | 0.045 0.096 0.049 0.100 | 0.042 0.092 0.047 0.096 |
| rank-sum,49 | 0.049 0.099 0.049 0.099 | 0.045 0.096 0.050 0.100 | 0.042 0.090 0.050 0.100 |
| rank-sum,1 | 0.048 0.100 0.049 0.099 | 0.048 0.097 0.050 0.100 | 0.040 0.089 0.047 0.096 |
Table 5. Power with dependent random variables. The sample size is 20. All the cases where FDRs exceed $\alpha$ as shown in Table 4 are labeled with $\ast$.

|                | Normal, $\rho = 0.4$ | Normal, $\rho = 0.8$ | Gamma |
|----------------|----------------------|----------------------|-------|
|                | 1% 10%               | 1% 10%               | 1% 10%|
| $\alpha$      | 0.05 0.10 0.05 0.10  | 0.05 0.10 0.05 0.10  | 0.05 0.10 0.05 0.10 |
| $t$-test       |                      |                      |       |
| permutation    | 82 90 927 1016       | 101 108* 1047 1109   | 40 50 687 797 |
| rank-sum       | 82 90 922 1012       | 101 108 1043 1106    | 42 55 737 861* |
| bootstrap      | 74 80 893 984        | 93 99 1028 1087      | 0 1 493 673 |
| Empirical Bayes|                      |                      |       |
| $t$-test       | 81 90 914 999        | 100 108 1043 1105    | 23 32 536 652 |
| permutation    | 81 87 912 1003       | 99 106 1041 1108     | 49 66* 757* 893* |
| rank-sum       | 80 88 900 984        | 99 107 1040 1102     | 47 59 716 823 |
| bootstrap      | 69 75 871 958        | 90 96 1020 1077      | 0 0 10 221 |
| Target-decoy   |                      |                      |       |
| $t$-value,49   | 81 90 926 1015       | 100 108 1046 1109    | 44 60 741 852 |
| $t$-value,1    | 81 89 923 1013       | 100 108 1046 1109    | 45 60 735 845 |
| rank-sum,49    | 80 89 917 1007       | 99 107 1045 1108     | 42 59 756 870 |
| rank-sum,1     | 80 89 916 1005       | 99 107 1044 1108     | 41 59 749 863 |
Similar results are found for dependent random variables.

**FDR Control.** Table 4 shows the real FDRs of different methods with dependent random variables while the specified FDR control level, \(\alpha\), was 5% or 10%. The results show that with the Bayes method, the real FDRs of \(t\)-test may slightly exceed \(\alpha\) in the Normal, 1% experiments. Meanwhile, the \(t\)-test with Bayes or empirical Bayes overestimated the FDRs for the gamma distribution. The real FDRs of pooled permutation can significantly exceed \(\alpha\) when the random variables follow the gamma distribution. The Wilcoxon rank-sum test with Bayes or empirical Bayes overestimated the FDRs. The real FDRs of bootstrap were much smaller than \(\alpha\). The target-decoy procedure always controlled the FDR.

**Statistical power.** Table 5 shows the statistical power of different methods with dependent random variables. Bootstrap is less powerful than all the other methods, especially when the random variables follow the gamma distribution.

When the random variables follow the normal distribution, the Bayes method is less powerful than the target-decoy procedure while the Wilcoxon rank-sum test is used. Though the Bayes method seems to be a little more powerful than the target-decoy procedure while the \(t\)-test is used, the real FDR of this method may exceed the specified FDR control level. The empirical Bayes method is less powerful than the Bayes method and our target-decoy procedure in the Normal, 10%, \(\rho = 0.4\) experiments.

When the random variables follow the gamma distribution, the target-decoy procedure is much more powerful than the Bayes and empirical Bayes methods, even if only one permutation was performed. Though the pooled permutation seems to be powerful, the FDRs were not controlled.

In our experiments, the target-decoy procedure controlled the FDRs with dependent random variables in all cases. Meanwhile, the target-decoy procedure is very powerful.
6 An Application

In this section, we apply the target-decoy procedure to an Arabidopsis microarray data set. To determine whether Arabidopsis genes respond to oncogenes encoded by the transfer-DNA (T-DNA) or to bacterial effector proteins codelivered by Agrobacteria into the plant cells, Lee et al. (2009) conducted microarray experiments at 3 h and 6 d after inoculating wounded young Arabidopsis plants with two different Agrobacterium strains, C58 and GV3101. Strain GV3101 is a cognate of strain C58, which only lacks T-DNA, but possesses proteinaceous virulence (Vir) factors such as VirD2, VirE2, VirE3 and VirF (Vergunst et al., 2003). Wounded, but uninfected, stalks were served as control. Here we just use the 6d postinoculation data as an example (downloaded from http://www.ncbi.nlm.nih.gov/geo/, GEO accession: GSE14106). The data consisting of 22810 genes were obtained from the C58 infected and control stalks. Both infected and control stalks are with three replicates.

Similar to the simulation experiments, the Bayes method, the empirical Bayes method and our target-decoy procedure are compared here. The p-values in the Bayes method and the z-values in the empirical Bayes method were calculated with the Student’s t-test, Wilcoxon rank sum test, and the Student’s t-test with permutation, respectively. The bootstrap method is not compared because the number of tests, 22810, is much larger than the sample size of a test, i.e., 6. For the Bayes method, two-tailed tests were used. For the empirical Bayes method, we first transformed the FDR control level to the threshold of local fdr and then identified differentially expressed genes according to the threshold. For the target-decoy procedure, the absolute t-values and the test statistics of the Wilcoxon rank sum test were used.

Because it is unknown which genes are really differentially expressed, the real FDRs can not be computed here. The power of these methods are compared. In fairness, the
Table 6. Power of different methods for *Arabidopsis* microarray data (Lee et al., 2009).

|        | 0.01 | 0.02 | 0.03 | 0.04 | 0.05 | 0.06 | 0.07 | 0.08 | 0.09 | 0.10 |
|--------|------|------|------|------|------|------|------|------|------|------|
| **Bayes** |      |      |      |      |      |      |      |      |      |      |
| t-test  | 0    | 5    | 5    | 171  | 322  | 712  | 1108 | 1469 | 1875 | 2208 |
| permutation | 0    | 0    | 0    | 0    | 251  | 1266 | 2035 | 2816 | 3499 | 4150 |
| rank-sum test | 0    | 0    | 0    | 0    | 0    | 0    | 0    | 0    | 0    | 0    |
| **Empirical Bayes** |      |      |      |      |      |      |      |      |      |      |
| t-test  | 0    | 0    | 0    | 0    | 0    | 0    | 0    | 0    | 0    | 0    |
| permutation | 0    | 0    | 0    | 0    | 0    | 0    | 0    | 0    | 0    | 0    |
| rank-sum test | *    | *    | *    | *    | *    | *    | *    | *    | *    | *    |
| **Target-decoy** |      |      |      |      |      |      |      |      |      |      |
| t-value | 0    | 0    | 0    | 1026 | 1481 | 1824 | 2204 | 2951 | 3506 | 3820 |
| rank-sum test | 0    | 0    | 0    | 0    | 0    | 0    | 0    | 0    | 0    | 0    |

* The R package ‘locfdr’ crashed while the Wilcoxon rank-sum test is used.
sampling numbers were set as $19 = \binom{6}{3} - 1$ in all the experiments, including the pooled permutation and the target-decoy procedure. In other words, all the permutated null scores were generated for each gene.

As shown in Table 6, no differentially expressed genes were found by the empirical Bayes method or the Wilcoxon rank-sum test. For the Bayes method, the $t$-test is more powerful than the pooled permutation for small $\alpha \leq 0.05$ while the pooled permutation is more powerful for large $\alpha \geq 0.06$. The target-decoy procedure with $t$-test is most powerful for $0.04 \leq \alpha \leq 0.09$. The additional genes identified by the target-decoy procedure are reliable, because similar numbers, i.e., 785 genes for FDR 0.034, 1427 genes for FDR 0.050 and 2071 genes for FDR 0.065, were reported by a more specific analysis \cite{Tan and Xu 2014}.

7 Discussion

In this paper, we proposed the target-decoy procedure, a direct approach to FDRs, which is free of the null distribution. We theoretically prove that this approach can control the FDR for independent statistics, and experimentally demonstrate that it is more stable and powerful than two most popular methods. Our procedure can also be extended to the pair-matched case-control study by adjusting the permutation sub-procedure. Actually, we need to randomly exchange the paired observed values just as the permutation tests for pair-matched study instead of permuting them in Step 1. The other steps and analyses are the same. In the target-decoy procedure, the scores are only used to determine the labels and ranks of tests, and the statistical meaning of the scores is not required. Similar to permutation tests, the target-decoy procedure can be used for any test statistic, regardless of whether or not its null distribution is known.
The decoy method was also used in the field of variable selection with a different name “knockoff” for FDR control without null distribution (Barber and Candès, 2015). Given response and covariates, variable selection aims at removing redundant or irrelevant covariates without incurring much loss of information in model construction for response, which is different from the multiple testing problem we discussed here. In the original paper of knockoff, Barber and Candès (Barber and Candès, 2015) considered a Gaussian linear regression model where the number of covariates is no more than the number of observations. Since then, this method has been extended to a wide range of variable selection problems, such as the high dimensional setting where the number of covariates is more than the number of observations (Barber and Candes, 2016) and a nonparametric setting with random covariates (Candes et al., 2018).

The knockoff filter and our target-decoy procedure are both for FDR control without null distribution. But they aim at different multiple testing problems. The knockoff filter is for variable selection which removes the redundant covariates. Thus, permutation is not suitable for constructing knockoff variables because it cannot maintain the correlation between the original variables (Barber and Candès, 2015). Meanwhile, the FDR control by knockoff filter is based on the normal stochastic error, which is a fundamental assumption of classic linear regression model. However, for search of random variables different between the cases and controls, the impact of correlation on FDR control is greatly reduced. Constructing the decoy scores by permutation results in good performance as shown in our simulations. Meanwhile, the target-decoy procedure makes use of the natural symmetry of case-control study, i.e., the exchangeability between observations of each random variable, and is free of additional assumptions.

The following are some detailed differences between these two methods. Firstly, only one knockoff counterpart is generated for each original variable in knockoff filter and the
“antisymmetry property” of statistics is necessary for FDR control. Whereas many decoy scores are generated for a hypothesis in the target-decoy procedure and the “antisymmetry property” is not required. As shown in our simulation, the target-decoy procedure is a little more powerful if more decoy scores than one are generated for a hypothesis. Secondly, in the knockoff filter method the expectation of FDP is taken over the stochastic error, which is the only randomness, and the variables with identical original and knockoff statistics will never be selected. Whereas the expectation of FDP is taken over at least four kinds of randomness in our target-decoy procedure. The first two are the randomness of $X_1, X_2, \ldots, X_m$ and the randomness of permutations. The last two are from two special situations, including the randomness of labeling hypotheses with target scores ranking in the middle, i.e., $i = (t + 1)/2$ in Step 2, and the randomness of sorting identical scores. The hypotheses with middle target scores are still possible to be rejected. Thirdly, the construction of knockoff variables with the necessary properties for FDR control is usually difficult and the construction methods can be complex, such as in Candes et al. (2018). Our procedure constructs the decoy scores simply by permutation.

The model-X knockoffs also tried to release the constrains of having valid $p$-values and can control the FDR of high-dimensional variable selection for a nonparametric setting in which the conditional distribution of the response is arbitrary (Candes et al., 2018). This approach requires the covariates be random with a distribution that is known or can be estimated. However, the distribution estimation is unpractical in some studies if the number of observations for each covariate is limited. Our approach is free of this constraint.

There were many studies on the FDR control in multiple testing under dependency (Benjamini and Yekutieli, 2001; Efron, 2007; Ghosal and Roy, 2011; Kang, 2016). In this paper, we only experimentally verify the performance of our target-decoy procedure on dependent test statistics. The theoretic analysis under dependency needs further research.
Moreover, our theoretic analysis is based on the ‘symmetrically distributed’ hypothesis. This null hypothesis is stronger than the hypothesis that the two groups have the same means. The performance of our procedure for the ‘equality of means’ hypothesis needs further studies.

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Supplementary Materials
to
A direct approach to false discovery rates by decoy permutations
Proof of Theorem \[\text{Proof} \text{ Case 1: permutations sampled with replacement.}\] Our proof is divided into four steps. In the first three steps, we concentrate on the \(j'\)-th test (before sorting the tests) where \(j' \in [m]\) and the \(j'\)-th null hypothesis is true. For simplicity, we will omit the index \(j'\) in these three steps if there is no confusing. For example, \(X\) is short for \(X_j = [X_{j1}, X_{j2}, \cdots, X_{jn}]\), \(x_1, x_2, \cdots, x_n\) are short for \(x_{j1}, x_{j2}, \cdots, x_{jn}\) and \(x\) is short for \(x = [x_1, x_2, \cdots, x_n]\).

**Step 1. Analysis of the permutation subroutine of each test.**

In our proof, we will use pdf to denote the probability density function of continuous random variable and the probability mass function of discrete random variable.

If the \(j'\)-th null hypothesis is true, the joint distribution of \(X = [X_{j1}, X_{j2}, \cdots, X_{jn}]\) is symmetric. Therefore, for any permutation \(\pi_n\) of \(n\) elements and any \(x = [x_1, x_2, \cdots, x_n]\), we have the pdf \(f_X\) of \(X\) satisfies that \(f_X(x) = f_X(\pi_n(x))\). Let the \(t - 1\) random permutations for the \(j'\)-th test are \(\hat{\pi}_1, \hat{\pi}_2, \cdots, \hat{\pi}_{t - 1}\) and corresponding decoy scores are \(S_{j1}^D, S_{j2}^D, \cdots, S_{jt - 1}^D\). Let \(\hat{Y}\) be the result obtained by sorting \(X\) in descending order. For any fixed \(\hat{x}\), let \(\tilde{\pi}_0\) be the random variable of permutation such that \(\hat{x} = \tilde{\pi}_0(\hat{y})\). If there is more than one permutation meeting the condition, \(\tilde{\pi}_0\) is set as one of these permutations randomly with equal probability. Let \(\Pi_n^0\) be the permutation such that \(\hat{X} = \Pi_n^0[\hat{Y}]\). Let \(\Pi_n^1, \cdots, \Pi_n^{t - 1}\) denote \(\Pi_n^0, \Pi_n = \hat{\pi}_n \Pi_n^0, \cdots, \Pi_n^{t - 1} = \hat{\pi}_n^{t - 1} \Pi_n^0\). Note that there are three kinds of randomnesses here. The first one is the randomness of \(\hat{X}\), the second one is the randomness introduced in Step 1 of the target-decoy procedure for permuting case and control status, and the last one is the random choice of multiple possible permutations for recovering \(\hat{x}\) from \(\hat{y}\). In our definition, \(\hat{\pi}_n, \hat{\pi}_n^2, \cdots, \hat{\pi}_n^{t - 1}\) only involve the second kind of randomness, \(\tilde{\pi}_n^0\) only involves the third kind of randomness, \(\Pi_n^0\)
involves the first and third kind of randomness and \( \Pi_{n_1}, \Pi_{n_2}, \cdots, \Pi_{n_t-1} \) involve all of the three kinds of randommesses.

For any possible \( \pi_0 \) and \( \bar{y} = [y_1, y_2, \cdots, y_n] \) where \( y_1 \geq y_2 \geq \cdots \geq y_n \), the pdf \( f_{\Pi_n, \bar{Y}} \) of \( \Pi_n, \bar{Y} \) satisfies
\[
f_{\Pi_n, \bar{Y}}(\pi_0, \bar{y}) = \frac{f_X(\pi_0[\bar{y}])}{|\{\pi_n | \pi_n[\bar{y}] = \pi_0[\bar{y}]\}|}.
\] (5)

For any possible \( \bar{y} \) and \( \bar{\pi}_n = \pi_0^1, \pi_0^2, \cdots, \pi_0^{n-1} \), we have the pdf \( f_{\Pi_n, \bar{Y}} \) of \( \bar{\Pi}_n, \bar{Y} \) satisfies that
\[
f_{\Pi_n, \bar{Y}}(\bar{\pi}_n, \bar{y}) = \left( \begin{array}{c} n \\ n_1 \end{array} \right)^{1-t} f_{\Pi_n, \bar{Y}}(\pi_0, \bar{y}) = \left( \begin{array}{c} n \\ n_1 \end{array} \right)^{1-t} \frac{f_X(\pi_0[\bar{y}])}{|\{\pi_n | \pi_n[\bar{y}] = \pi_0[\bar{y}]\}|},
\] (6)
because the probability that the randomly chosen \( t-1 \) random permutations are exactly \( \pi_0^1, \cdots, \pi_0^{n-1} \) is \( \left( \begin{array}{c} n \\ n_1 \end{array} \right)^{1-t} \). For any permutation \( \pi_t \) of \( t \) elements and any possible \( \bar{\pi}_n \), let \( (\pi_t, \bar{\pi}_n)_i \) denote the \( i \)-th element of \( \pi_t \bar{\pi}_n = \pi_t[\pi_0^1, \pi_0^2, \cdots, \pi_0^{n-1}] \). We also have
\[
f_{\Pi_n, \bar{Y}}(\pi_t \bar{\pi}_n, \bar{y}) = \left( \begin{array}{c} n \\ n_1 \end{array} \right)^{1-t} \frac{f_X((\pi_t \bar{\pi}_n)_1[\bar{y}])}{|\{\pi_n | \pi_n[\bar{y}] = (\pi_t \bar{\pi}_n)_1[\bar{y}]\}|}.
\] (7)

Because \( f_X \) is symmetric, we have for permutation \( \pi_0 \) and \( (\pi_t \bar{\pi}_n)_1 \),
\[
f_X(\pi_0[\bar{y}]) = f_X((\pi_t \bar{\pi}_n)_1[\bar{y}]).
\] (8)

Moreover, note that \( |\{\pi_n | \pi_n[\bar{y}] = \pi_0[\bar{y}]\}| = |\{\pi_n | \pi_n[\bar{y}] = (\pi_t \bar{\pi}_n)_1[\bar{y}]\}| \), because for every permutation \( \pi_n' \), \( |\{\pi_n | \pi_n[\bar{y}] = \pi_n'[\bar{y}]\}| \) is the same since it is determined by the multiplicities of elements in multiset \( y_1, y_2, \cdots, y_n \). Therefore, from equations (6), (7), and (8) we have for any \( \pi_t \),
\[
f_{\Pi_n, \bar{Y}}(\bar{\pi}_n, \bar{y}) = f_{\Pi_n, \bar{Y}}(\pi_t \bar{\pi}_n, \bar{y}).
\] (9)

\textit{Step 2. Analysis of the sorting subroutine of each test.}
Note that the target-decoy procedure sorts \( S_{j_1}^T, S_{j_1}^{D_1}, \ldots, S_{j_1}^{D_{t-1}} \) in descending order and sorts equal scores randomly. Let \( \Pi_t \) denote the used permutation for sorting \( S_{j_1}^T, S_{j_1}^{D_1}, \ldots, S_{j_1}^{D_{t-1}} \) in the procedure. Thus, \( \Pi_t \) involves three kinds of randomnesses, i.e., the randomness of \( \widetilde{X} \), the randomness for permuting case and control status, and the randomness for sorting equal scores. For any possible \( \vec{Y} \) and \( \vec{\pi}_n \), \( \Pi_t \) can only take values in \( \mathcal{A}(\vec{\pi}_n, \vec{y}) = \{ \pi_t | \pi_t [S(\pi_n^0[\vec{y}]), S(\pi_n^1[\pi_n^0[\vec{y}]], \ldots, S(\pi_n^{t-1}[\pi_n^0[\vec{y}]])) \} \) is in descending order if \( \Pi_n = \vec{\pi}_n \) and \( \vec{Y} = \vec{y} \). Thus, for any fixed \( \pi_t \) in \( \mathcal{A}(\vec{\pi}_n, \vec{y}) \), we have the pdf \( f_{\Pi_t, \Pi_n, \vec{y}}(\pi_t, \vec{\pi}_n, \vec{y}) \) of \( \Pi_t, \Pi_n, \vec{y} \) satisfies that

\[
    f_{\Pi_t, \Pi_n, \vec{y}}(\pi_t, \vec{\pi}_n, \vec{y}) = \frac{f_{\Pi_t, \vec{y}}(\pi_t, \vec{\pi}_n, \vec{y})}{|\mathcal{A}(\vec{\pi}_n, \vec{y})|},
\]

because \( \Pi_t \) sorts equal scores randomly and all permutations in \( \mathcal{A}(\vec{\pi}_n, \vec{y}) \) can sort \( S(\pi_n^0[\vec{y}]), S(\pi_n^1[\pi_n^0[\vec{y}]], \ldots, S(\pi_n^{t-1}[\pi_n^0[\vec{y}]])) \) in descending order. From \( \pi_t \in \mathcal{A}(\vec{\pi}_n, \vec{y}) \), we have \( \pi_t(\pi_t)^{-1} \in \mathcal{A}(\pi_t^1, \pi_t^0, \vec{y}) \) for any fixed \( \pi_t^1 \). Therefore, from equation (10) we have for any possible \( \pi_t \) and any fixed \( \pi_t^1 \),

\[
    f_{\Pi_t, \Pi_n, \vec{y}}(\pi_t(\pi_t)^{-1}, \pi_t^1, \vec{\pi}_n, \vec{y}) = \frac{f_{\Pi_t, \vec{y}}(\pi_t(\pi_t)^{-1}, \pi_t^1, \vec{\pi}_n, \vec{y})}{|\mathcal{A}(\pi_t^1, \pi_t^0, \vec{y})|} = \frac{f_{\Pi_t, \vec{y}}(\pi_t, \vec{\pi}_n, \vec{y})}{|\mathcal{A}(\vec{\pi}_n, \vec{y})|} = f_{\Pi_t, \Pi_n, \vec{y}}(\pi_t, \vec{\pi}_n, \vec{y}).
\]

The second equality is from equation (9) and \(|\{\mathcal{A}(\vec{\pi}_n^*, \vec{y})\}| = |\{\mathcal{A}(\pi_t^1, \vec{\pi}_n^*, \vec{y})\}| \), because for every permutation \( \pi_t^1 \), \( |\{\mathcal{A}(\pi_t^1, \vec{\pi}_n, \vec{y})\}| \) is the same since it is determined by the multiplicities of elements in multiset \( \{S(\pi_n^0[\vec{y}]), S(\pi_n^1[\pi_n^0[\vec{y}]], \ldots, S(\pi_n^{t-1}[\pi_n^0[\vec{y}]])) \} \). Therefore, from equation (11) we have for any possible \( \pi_t, \vec{\pi}_n^* \) and any fixed \( \pi_t^1 \),

\[
    \sum_{\pi_t^1} f_{\Pi_t, \Pi_n, \vec{y}}(\pi_t, \pi_t^1, \vec{\pi}_n^*, \vec{y}) = \sum_{\pi_t^1} f_{\Pi_t, \Pi_n, \vec{y}}(\pi_t(\pi_t)^{-1}, \pi_t^1, \pi_t^1, \pi_t^0, \vec{y})
    = \sum_{\pi_t^1 \pi_t^0} f_{\Pi_t, \Pi_n, \vec{y}}(\pi_t(\pi_t)^{-1}, \pi_t^1, \pi_t^0, \vec{y})
    = \sum_{\pi_t^1 \pi_t^0} f_{\Pi_t, \Pi_n, \vec{y}}(\pi_t^2, \pi_t^1, \pi_t^0, \vec{y}),
\]

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where \( \pi_2^t = \pi_t(\pi_1^t)^{-1} \) and \( \pi_t' \) takes values in all possible permutations of \( t \) elements. The last equality is obtained by substituting \( \pi_1^t \pi_t' \) and \( \pi_t(\pi_1^t)^{-1} \) with \( \pi_t' \) and \( \pi_2^t \), respectively. Since \( \pi_1^t \) can be any permutation of \( t \) elements for every fixed \( \pi_t \), we have \( \pi_2^t \) can also be any permutation.

**Step 3. Analysis of the labeling subroutine of each test.**

Let \( [\pi_t]_{i_1} = i_2 \) denote that the original \( i_2 \)-th element is the \( i_1 \)-th element after permutation \( \pi_t \). Consider all permutations \( \{\pi_t\} \) of \( t \) elements, we have for any \( i_1 \),
\[
|\{\pi_t | [\pi_t]_{i_1} = 1\}| = \frac{|\{\pi_t\}|}{t} = (t-1)!. \tag{13}
\]

Note that the original first element is the \([\Pi_t]^{-1}_{i_1} = i \)-th element after permutation \( \Pi_t \), because \( [\Pi_t]_{i_1} = 1 \) is equivalent to \([\Pi_t]^{-1}_{i_1} = i \). Thus, for any fixed permutation \( \pi_2^t \), the pdf \( f_{\{\Pi_t\}^{-1}_{i_1}, \Pi_n, \vec{Y}} \) of \([\Pi_t]^{-1}_{i_1}, \Pi_n, \vec{Y} \) satisfying that
\[
\sum_{\pi_t'} f_{\{\Pi_t\}^{-1}_{i_1}, \Pi_n, \vec{Y}}(i_1, \pi_t' \Pi_n, \vec{Y}) = \sum_{[\pi_t]_{i_1} = 1} \sum_{\pi_t'} f_{\Pi_t, \Pi_n, \vec{Y}}(\pi_t, \pi_t' \Pi_n, \vec{Y})
= \sum_{[\pi_t]_{i_1} = 1} \sum_{\pi_t'} f_{\Pi_t, \Pi_n, \vec{Y}}(\pi_t^2, \pi_t' \Pi_n, \vec{Y}) \tag{14}
= (t-1)! \sum_{\pi_t'} f_{\Pi_t, \Pi_n, \vec{Y}}(\pi_t^2, \pi_t' \Pi_n, \vec{Y})
\]

The penultimate equality is due to equation (12) and the last equality is due to equation (13). From equation (14) we have for any \( i_1, i_2 \in [t] \),
\[
\sum_{\pi_t'} f_{\{\Pi_t\}^{-1}_{i_1}, \Pi_n, \vec{Y}}(i_1, \pi_t' \Pi_n, \vec{Y}) = (t-1)! \sum_{\pi_t'} f_{\Pi_t, \Pi_n, \vec{Y}}(\pi_t^2, \pi_t' \Pi_n, \vec{Y})
= \sum_{\pi_t'} f_{\{\Pi_t\}^{-1}_{i_1}, \Pi_n, \vec{Y}}(i_2, \pi_t' \Pi_n, \vec{Y}) \tag{15}
\]

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Thus, we have for any positive integer $i < \frac{t+1}{2}$,

\[
\sum_{\pi'_t} f_{[(\Pi_t)^{-1}]_1, \Pi_n^*, \bar{Y}}(i, \pi'_t \tilde{\pi}_n, \vec{y}) = \sum_{\pi'_t} f_{[(\Pi_t)^{-1}]_1, \Pi_n^*, \bar{Y}}(i + \left\lceil \frac{t}{2} \right\rceil, \pi'_t \tilde{\pi}_n, \vec{y})
\]  

(16)

Therefore, the pdf $f_{[(\Pi_t)^{-1}]_1, \Pi_n^*, \bar{Y}, S_j'}$ of $[(\Pi_t)^{-1}]_1, \Pi_n^*, \bar{Y}, S_j'$ satisfies that

\[
\sum_{\pi'_t} f_{[(\Pi_t)^{-1}]_1, \Pi_n^*, \bar{Y}, S_j'}(i, \pi'_t \tilde{\pi}_n, \vec{y}, s_j') = \sum_{\pi'_t} f_{[(\Pi_t)^{-1}]_1, \Pi_n^*, \bar{Y}, S_j'}(i + \left\lceil \frac{t}{2} \right\rceil, \pi'_t \tilde{\pi}_n, \vec{y}, s_j')
\]

(17)

because for any possible $\vec{y}, \tilde{\pi}_n, i < \frac{t+1}{2}$ and any fixed $\pi'_t, S_j'$ is set as the score ranking $i$-th in $S((\pi'_t \tilde{\pi}_n)_1[\vec{y}]), \cdots, S((\pi'_t \tilde{\pi}_n)_1[\vec{y}])$ no matter $[(\Pi_t)^{-1}]_1 = i$ or $i + \left\lceil \frac{t}{2} \right\rceil$. Therefore, the pdf $f_{L_j', \Pi_n^*, \bar{Y}, S_j'}$ of $L_j', \Pi_n^*, \bar{Y}, S_j'$ satisfies that

\[
\sum_{\pi'_t} f_{L_j', \Pi_n^*, \bar{Y}, S_j'}(T, \pi'_t \tilde{\pi}_n, \vec{y}, s_j')
\]

\[
= \sum_{i \leq \frac{t}{2}} \sum_{\pi'_t} f_{[(\Pi_t)^{-1}]_1, \Pi_n^*, \bar{Y}, S_j'}(i, \pi'_t \tilde{\pi}_n, \vec{y}, s_j') + \frac{1}{2} \sum_{\pi'_t} f_{[(\Pi_t)^{-1}]_1, \Pi_n^*, \bar{Y}, S_j'}(\frac{t+1}{2}, \pi'_t \tilde{\pi}_n, \vec{y}, s_j')
\]

\[
= \sum_{i \leq \frac{t}{2}} \sum_{\pi'_t} f_{[(\Pi_t)^{-1}]_1, \Pi_n^*, \bar{Y}, S_j'}(i + \left\lceil \frac{t}{2} \right\rceil, \pi'_t \tilde{\pi}_n, \vec{y}, s_j') + \frac{1}{2} \sum_{\pi'_t} f_{[(\Pi_t)^{-1}]_1, \Pi_n^*, \bar{Y}, S_j'}(\frac{t+1}{2}, \pi'_t \tilde{\pi}_n, \vec{y}, s_j')
\]

\[
= \sum_{\pi'_t} f_{L_j', \Pi_n^*, \bar{Y}, S_j'}(D, \pi'_t \tilde{\pi}_n, \vec{y}, s_j')
\]

(18)

Note that if $t$ is odd, $f_{[(\Pi_t)^{-1}]_1, \Pi_n^*, \bar{Y}, S_j'}(\frac{t+1}{2}, \pi'_t \tilde{\pi}_n, \vec{y}, s_j')$ is zero for any $\pi'_t$ in the above equation. The first and last equalities is due to Step 2 of the target-decoy procedure. From
From equation (19), we have for any \( j \) fixed in descending order. Therefore, whether 
\[ \pi \]
the second equality is due to that for any given \( f \), cause \( \Pi \) dominance introduced by Step 3 of the target-decoy procedure for sorting equal scores. Because \( \Pi \) is determined given \( Z \), i.e., \( S(j) \) is from \( S_j' \). Let \( A(s(\cdot), z(\cdot), j') \) denote the event \( S(\cdot) = s(\cdot), Z(\cdot) = z(\cdot), [\Pi_m]_j = j' \).

Note that whether \( A(s(\cdot), z(\cdot), j') \) happens is fully determined by \( S, L_{\neq j}' \) and the randomness introduced by Step 3 of the target-decoy procedure for sorting equal scores. Because \( \Pi_m \) is determined given \( S = \vec{s} \) and the random choice of permutations which sort \( \vec{s} \) in descending order. Therefore, whether \( S(\cdot) = s(\cdot), [\Pi_m]_j = j' \) holds is determined. For any fixed \( \pi_m \) where \( [\pi_m]_j = j' \), whether \( Z(\neq j) = z(\neq j) \) holds only depends on \( L_{\neq j}' \) if \( \Pi_m = \pi_m \). Since \( Z(\neq j) \) is determined by \( L_{\neq j}' \) and \( H_{\neq j}' \) for the fixed \( \pi_m \), and \( H_{\neq j}' \) is a constant vector.

Because \( S_{\neq j}', L_{\neq j}' \) and the randomness for sorting equal scores are independent of \( L_j' \), we have that \( S, L_{\neq j}' \) and the randomness are independent of \( L_j' \) given \( S_j' = s_j' \). Thus,

Step 4. Analysis of the sorting subroutine for all the \( m \) tests.

Let \( \Pi_m \) denote the permutation for sorting \( \vec{S} \). Let \( [\Pi_m]_j = j' \) denote that the original \( j' \)-th element is the \( j \)-th element after sorting with permutation \( \Pi_m \), i.e., \( S(j) \) is from \( S_j' \).

Let \( A(s(\cdot), z(\cdot), j') \) denote the event \( S(\cdot) = s(\cdot), Z(\cdot) = z(\cdot), [\Pi_m]_j = j' \).

Pr \((L_j' = T|S_j' = s_j') = Pr(L_j' = D|S_j' = s_j'). \)
whether the event $A(s_i, Z_{(\neq j)}, j')$ happens is also independent of $L_{j'}$ given $S_{j'} = s_{j'}$. Therefore, we have for any possible $j'$,

$$
\Pr \left( L_{j'} = T \mid A(s_i, Z_{(\neq j)}, j'), S_{j'} = s_{j'} \right) \Pr \left( A(s_i, Z_{(\neq j)}, j') \mid S_{j'} = s_{j'} \right) \\
= \Pr \left( L_{j'} = T, A(s_i, Z_{(\neq j)}, j') \mid S_{j'} = s_{j'} \right) \\
= \Pr \left( L_{j'} = T \mid S_{j'} = s_{j'} \right) \Pr \left( A(s_i, Z_{(\neq j)}, j') \mid S_{j'} = s_{j'} \right). \quad (21)
$$

The first equality is due to the chain rule and the second equality is due to the independence. From equation (21) we have

$$
\Pr \left( L_{j'} = T \mid A(s_i, Z_{(\neq j)}, j'), S_{j'} = s_{j'} \right) = \Pr \left( L_{j'} = T \mid S_{j'} = s_{j'} \right). \quad (22)
$$

From the definition of $A(s_i, Z_{(\neq j)}, j')$, we have

$$
\Pr \left( L_{j'} = T \mid A(s_i, Z_{(\neq j)}, j'), S_{j'} = s_{j'} \right) = \Pr \left( L_{j'} = T \mid A(s_i, Z_{(\neq j)}, j') \right). \quad (23)
$$

Thus, from equations (22) and (23) we have

$$
\Pr \left( L_{j'} = T \mid A(s_i, Z_{(\neq j)}, j') \right) = \Pr \left( L_{j'} = T \mid S_{j'} = s_{j'} \right). \quad (24)
$$

Similarly, we can also prove

$$
\Pr \left( L_{j'} = D \mid A(s_i, Z_{(\neq j)}, j') \right) = \Pr \left( L_{j'} = D \mid S_{j'} = s_{j'} \right). \quad (25)
$$

Thus, from equations (20), (24) and (25) we have

$$
\Pr \left( L_{j'} = T \mid A(s_i, Z_{(\neq j)}, j') \right) = \Pr \left( L_{j'} = D \mid A(s_i, Z_{(\neq j)}, j') \right). \quad (26)
$$
Note that
\[
\Pr \left( Z_{(j)} = 1 \big| \overrightarrow{S}_{(\cdot)} = \overrightarrow{s}_{(\cdot)}, \overrightarrow{Z}_{(\cdot \setminus j)} = \overrightarrow{z}_{(\cdot \setminus j)} \right) = \Pr \left( L_{(j)} = T, H_{(j)} = 0 \big| \overrightarrow{S}_{(\cdot)} = \overrightarrow{s}_{(\cdot)}, \overrightarrow{Z}_{(\cdot \setminus j)} = \overrightarrow{z}_{(\cdot \setminus j)} \right)
\]
\[
= \sum_{j': H_{j'} = 0} \Pr \left( L_{j'} = T, \Pi_m \big| \overrightarrow{S}_{(\cdot)} = \overrightarrow{s}_{(\cdot)}, \overrightarrow{Z}_{(\cdot \setminus j)} = \overrightarrow{z}_{(\cdot \setminus j)} \right) \Pr \left( \Pi_m = j', \overrightarrow{S}_{(\cdot)} = \overrightarrow{s}_{(\cdot)}, \overrightarrow{Z}_{(\cdot \setminus j)} = \overrightarrow{z}_{(\cdot \setminus j)} \right)
\]
\[
= \sum_{j': H_{j'} = 0} \Pr \left( L_{j'} = T \big| A(\overrightarrow{s}_{(\cdot)}, \overrightarrow{z}_{(\cdot \setminus j)}, j') \right) \Pr \left( \Pi_m = j', \overrightarrow{S}_{(\cdot)} = \overrightarrow{s}_{(\cdot)}, \overrightarrow{Z}_{(\cdot \setminus j)} = \overrightarrow{z}_{(\cdot \setminus j)} \right) \tag{27}
\]
where the last equality is due to the chain rule and the definition of \( A(\overrightarrow{s}_{(\cdot)}, \overrightarrow{z}_{(\cdot \setminus j)}, j') \). Similarly, we also have
\[
\Pr \left( Z_{(j)} = -1 \big| \overrightarrow{S}_{(\cdot)} = \overrightarrow{s}_{(\cdot)}, \overrightarrow{Z}_{(\cdot \setminus j)} = \overrightarrow{z}_{(\cdot \setminus j)} \right) = \sum_{j': H_{j'} = 0} \Pr \left( L_{j'} = D \big| A(\overrightarrow{s}_{(\cdot)}, \overrightarrow{z}_{(\cdot \setminus j)}, j') \right) \Pr \left( \Pi_m = j', \overrightarrow{S}_{(\cdot)} = \overrightarrow{s}_{(\cdot)}, \overrightarrow{Z}_{(\cdot \setminus j)} = \overrightarrow{z}_{(\cdot \setminus j)} \right) \tag{28}
\]
Thus, from equations (26), (27) and (28) we have for any fixed \( j \in \mathbb{N} \),
\[
\Pr \left( Z_{(j)} = 1 \big| \overrightarrow{S}_{(\cdot)} = \overrightarrow{s}_{(\cdot)}, \overrightarrow{Z}_{(\cdot \setminus j)} = \overrightarrow{z}_{(\cdot \setminus j)} \right) = \Pr \left( Z_{(j)} = -1 \big| \overrightarrow{S}_{(\cdot)} = \overrightarrow{s}_{(\cdot)}, \overrightarrow{Z}_{(\cdot \setminus j)} = \overrightarrow{z}_{(\cdot \setminus j)} \right) \tag{29}
\]

**Case 2: permutations sampled without replacement.** The idea is similar to the proof for the case with replacement. Only the following two differences merit attention. Firstly, the permutations \( \pi^1_n, \ldots, \pi^{t-1}_n \) should be different and cannot be the identical permutation which does not exchange any element. Secondly, the term \( \binom{n}{m_i}^{1-t} \) in equations (6) and (7) should be replaced with \( (\Pi_{i=1}^{t-1}(\binom{n}{m} - i))^{-1} \). Because the probability that the randomly chosen \( t - 1 \) permutations are exactly \( \pi^n_1, \ldots, \pi^{t-1}_n \), which are different and are not the identical permutation, is \( (\Pi_{i=1}^{t-1}(\binom{n}{m} - i))^{-1} \).  

\(\square\)
Proof of Theorem 2

The proof of Theorem 2 is based on the following three lemmas.

Lemma 1. Let \( Z(i_1), Z(i_2), \ldots, Z(i_{m'}) \) be independent random variables such that \( \Pr(Z(i_j) = -1) = \Pr(Z(i_j) = 1) = 1/2 \) for any fixed \( j \in \{1, 2, \ldots, m'\} \). Let \( L = \max\{j : Z(i_1) = Z(i_2) = \cdots = Z(i_j) = 1\} \) if \( Z(i_1) = 1 \). Otherwise, let \( L = 0 \). Then \( E(L) < 1 \).

Proof of Lemma 1. For any \( j < m' \), the probability that \( Z(i_1) = Z(i_2) = \cdots = Z(i_j) = 1 \) and \( Z(i_{j+1}) = -1 \) is \( 1/(2^{j+1}) \). The probability that \( Z(i_1) = Z(i_2) = \cdots = Z(i_{m'}) = 1 \) is \( 1/2^{m'} \). Then we have
\[
E(L) = \sum_{j=0}^{m'-1} \frac{j}{2^{j+1}} + \frac{m'}{2^{m'}} < 1.
\] (30)

Lemma 2. Let \( p \) be a positive constant and \( Z(i_1), Z(i_2), \ldots, Z(i_{m'}) \) be independent random variables such that \( \Pr(Z(i_j) = -1) = p, \Pr(Z(i_j) = 1) = 1 - p \) for any fixed \( j \in [m'] \). Let \( L = \max\{j : Z(i_1) = Z(i_2) = \cdots = Z(i_j) = 1\} \) if \( Z(i_1) = 1 \). Otherwise, let \( L = 0 \). Then for any nonnegative constants \( c_1 \) and \( c_2 \) satisfying \( c_1 + c_2 \leq m' \),
\[
E(L|\#\{Z(i_j) = 1, j \leq c_1 + c_2\} = c_1) \geq \frac{c_1}{c_2 + 1}.
\] (31)

Proof of Lemma 2. If \( c_2 = 0 \), the lemma is immediate. Consider the case \( c_2 > 0 \). Under the condition \( \#\{Z(i_j) = 1, j \leq c_1 + c_2\} = c_1 \), the probabilities for \( Z(i_1), Z(i_2), \ldots, Z(i_{c_1+c_2}) \) being all sequences consisting of \( c_1 \) elements equal to 1 and \( c_2 \) elements equal to \(-1\) are the same because \( Z(i_1), Z(i_2), \ldots, Z(i_{m'}) \) are independent and identically distributed. Then the \( c_2 \) elements equal to \(-1\) separate the \( c_1 \) elements equal to 1 into \( c_2 + 1 \) intervals, and every element equal to 1 falls into each interval with the same probability. Then the probability is \( 1/(c_2 + 1) \), and the expected number of elements falling into each interval is \( c_1/(c_2 + 1) \).
L is the number of elements equal to 1 which fall into the interval before the first $-1$, then the expectation of $L$ is also $c_1/(c_2 + 1)$.

Lemma 3. Let $p$ be a positive constant and $Z_{(i_1)}, Z_{(i_2)}, \ldots, Z_{(i_{m'})}$ be random variables taking values in $\{1, -1\}$. If for any $j \in [m']$ and any possible $\overrightarrow{z_{(i_j)}}$,

\[
\Pr \left( Z_{(i_j)} = 1 \left| \overrightarrow{Z_{(i_{\neq j})}} = \overrightarrow{z_{(i_{\neq j})}} \right. \right) = p,
\]

then $Z_{(i_1)}, Z_{(i_2)}, \ldots, Z_{(i_{m'})}$ are independent.

Proof of Lemma 3. We will prove the following claim: for any integer constant $2 \leq C \leq m'$, any $C$ random variables in $Z_{(i_1)}, Z_{(i_2)}, \ldots, Z_{(i_{m'})}$ are independent. Lemma 3 is a special case of this claim where $C = m'$. If $c_1 = 2$, the claim is immediate. Now we will prove that the claim holds for $C = c \leq m'$ based on the inductive assumption that any $c - 1$ variables in $Z_{(i_1)}, Z_{(i_2)}, \ldots, Z_{(i_{m'})}$ are independent. From equation (32) we have

\[
\Pr \left( Z_{(i_1)} = 1 \right) = \sum \Pr \left( Z_{(i_1)} = 1, \overrightarrow{Z_{(i_{\neq 1})}} = \overrightarrow{z_{(i_{\neq 1})}} \right)
\]

\[
= \sum \Pr \left( Z_{(i_1)} = 1 \left| \overrightarrow{Z_{(i_{\neq 1})}} = \overrightarrow{z_{(i_{\neq 1})}} \right. \right) \Pr \left( \overrightarrow{Z_{(i_{\neq 1})}} = \overrightarrow{z_{(i_{\neq 1})}} \right)
\]

\[
= p \sum \Pr \left( \overrightarrow{Z_{(i_{\neq 1})}} = \overrightarrow{z_{(i_{\neq 1})}} \right)
\]

\[
= p.
\]

Similarly, we also have

\[
\Pr \left( Z_{(i_1)} = 1 \left| Z_{(i_2)} = z_{(i_2)}, \ldots, Z_{(i_c)} = z_{(i_c)} \right. \right) = p.
\]

(34)

Thus,

\[
\Pr \left( Z_{(i_1)} = 1 \left| Z_{(i_2)} = z_{(i_2)}, \ldots, Z_{(i_c)} = z_{(i_c)} \right. \right) = \Pr \left( Z_{(i_1)} = 1 \right).
\]

(35)
Similarly, we also have
\[
\Pr\left( Z_{(i_1)} = -1 \mid Z_{(i_2)} = z_{(i_2)}, \ldots, Z_{(i_c)} = z_{(i_c)} \right) = 1 - p = \Pr\left( Z_{(i_1)} = -1 \right). \tag{36}
\]
Then, we have
\[
\Pr\left( Z_{(i_1)} = z_{(i_1)} \mid Z_{(i_2)} = z_{(i_2)}, \ldots, Z_{(i_c)} = z_{(i_c)} \right) = \Pr\left( Z_{(i_1)} = z_{(i_1)} \right). \tag{37}
\]
Therefore,
\[
\begin{align*}
\Pr\left( Z_{(i_1)} = z_{(i_1)}, Z_{(i_2)} = z_{(i_2)}, \ldots, Z_{(i_c)} = z_{(i_c)} \right) &= \Pr\left( Z_{(i_1)} = z_{(i_1)} \mid Z_{(i_2)} = z_{(i_2)}, \ldots, Z_{(i_c)} = z_{(i_c)} \right) \Pr\left( Z_{(i_2)} = z_{(i_2)}, \ldots, Z_{(i_c)} = z_{(i_c)} \right) \\
&= \Pr\left( Z_{(i_1)} = z_{(i_1)} \right) \prod_{j=2}^{c} \Pr\left( Z_{(i_j)} = z_{(i_j)} \right) \\
&= \prod_{j=1}^{c} \Pr\left( Z_{(i_j)} = z_{(i_j)} \right). \tag{38}
\end{align*}
\]
The penultimate equality is due to the inductive assumption that $Z_{i_2}, Z_{i_3}, \ldots, Z_{i_c}$ are independent. Similarly, we can also prove that all the other $c$ variables in $Z_{i_1}, Z_{i_2}, \ldots, Z_{i_{m'}}$ are independent.  

\textbf{Proof of Theorem 3} Let $V = \#\{Z_{(j)} = 1, j \leq K\}$, $\tilde{V} = \#\{Z_{(j)} < 0, j \leq K\}$, $\tilde{V}' = \#\{Z_{(j)} = -1, j \leq K\}$ and $R = \#\{Z_{(j)} \geq 0, j \leq K\}$. Note that for any $j \in [m]$, we have $|Z_{(j)}|$ is 0, 1 or 2. Let $|\overrightarrow{Z_{(c)}}|$ denote $|Z_{(1)}|, |Z_{(2)}|, \ldots, |Z_{(m)}|$. Let $\overrightarrow{a}$ denote $a_1, \ldots, a_m$ where $a_j \in \{0, 1, 2\}$ for any $j \in [m]$. If for any possible $\overrightarrow{a}$ and $\overrightarrow{s_{(c)}}$,
\[
\mathbb{E}\left( \frac{V}{R \vee 1} \mid |\overrightarrow{Z_{(c)}}| = \overrightarrow{a}, S_{(c)} = \overrightarrow{s_{(c)}} \right) \leq \alpha, \tag{39}
\]

\textbf{42}
then from the law of total expectation, we have

$$\mathbb{E}
\left(\frac{V}{R \lor 1}\right) = \mathbb{E}
\left(\mathbb{E}
\left(\frac{V}{R \lor 1} \bigg| Z_{(i)} = \vec{a}, \vec{S}_{(i)} = \vec{s}_{(i)}\right)\right) \leq \alpha. \quad (40)$$

Therefore, we only need to prove equation (39) for any possible \( \vec{a} \) and \( \vec{s}_{(i)} \).

Let \( \vec{a}_{\neq j} \) denote \( a_1, \ldots, a_{j-1}, a_{j+1}, \ldots, a_m \). For any possible \( \vec{a} \), \( \vec{z}_{(\neq j)} \) and \( \vec{s}_{(i)} \) where \( z_{(\neq j)} = \vec{a}_{\neq j} \), if \( a_j \neq 1 \) we have

$$\Pr\left(Z_{(j)} = -1\big| \vec{S}_{(i)} = \vec{s}_{(i)}, Z_{(\neq j)} = \vec{z}_{(\neq j)}, |Z_{(i)}| = \vec{a}\right)$$
$$= \Pr\left(Z_{(j)} = 1\big| \vec{S}_{(i)} = \vec{s}_{(i)}, Z_{(\neq j)} = \vec{z}_{(\neq j)}, |Z_{(i)}| = \vec{a}\right) = 0. \quad (41)$$

If \( a_j = 1 \), from Theorem 1 we have

$$\Pr\left(Z_{(j)} = -1\big| \vec{S}_{(i)} = \vec{s}_{(i)}, Z_{(\neq j)} = \vec{z}_{(\neq j)}, |Z_{(i)}| = \vec{a}\right)$$
$$= \Pr\left(Z_{(j)} = 1\big| \vec{S}_{(i)} = \vec{s}_{(i)}, Z_{(\neq j)} = \vec{z}_{(\neq j)}, |Z_{(i)}| = \vec{a}\right)$$
$$= \frac{\Pr\left(|Z_{(j)}| = 1\big| \vec{S}_{(i)} = \vec{s}_{(i)}, Z_{(\neq j)} = \vec{z}_{(\neq j)}\right)}{\Pr\left(|Z_{(j)}| = 1\big| \vec{S}_{(i)} = \vec{s}_{(i)}, Z_{(\neq j)} = \vec{z}_{(\neq j)}\right)}$$
$$= \frac{\Pr\left(Z_{(j)} = 1\big| \vec{S}_{(i)} = \vec{s}_{(i)}, Z_{(\neq j)} = \vec{z}_{(\neq j)}\right)}{\Pr\left(Z_{(j)} = 1\big| \vec{S}_{(i)} = \vec{s}_{(i)}, Z_{(\neq j)} = \vec{z}_{(\neq j)}\right)} = 1. \quad (42)$$

In summary, we have for any fixed \( j \in [m] \) and any possible \( \vec{a} \), \( \vec{z}_{(\neq j)} \) and \( \vec{s}_{(i)} \) where \( z_{(\neq j)} = \vec{a}_{\neq j} \),

$$\Pr\left(Z_{(j)} = -1\big| \vec{S}_{(i)} = \vec{s}_{(i)}, Z_{(\neq j)} = \vec{z}_{(\neq j)}, |Z_{(i)}| = \vec{a}\right)$$
$$= \Pr\left(Z_{(j)} = 1\big| \vec{S}_{(i)} = \vec{s}_{(i)}, Z_{(\neq j)} = \vec{z}_{(\neq j)}, |Z_{(i)}| = \vec{a}\right) \quad (43)$$
always holds. In other words, \( \Pr \left( Z(j) = -1 \mid Z(\neq j) = \bar{z}(\neq j) \right) = \Pr \left( Z(j) = 1 \mid Z(\neq j) = \bar{z}(\neq j) \right) \) holds under the condition \( S_{(j)} = \bar{s}_{(j)}, |Z(\cdot)| = \bar{\alpha} \).

In the following we will assume that \( S_{(j)} = \bar{s}_{(j)} \) and \( |Z(\cdot)| = \bar{\alpha} \) always hold for some fixed \( \bar{s}_{(j)} \) and \( \bar{\alpha} \), and omit this condition in equations. Moreover, all the random variables and expectations are considered under this condition. Let \( m' = \# \{ a_i \mid a_i = 1 \} \). Then there are in total \( m' \) elements, \( Z(i_1), Z(i_2), \ldots, Z(i_{m'}) \), equal to 1 or -1. Note that \( i_1, i_2, \ldots, i_{m'} \) are constants because \( |Z(j)| = \bar{\alpha} \) for some fixed \( \bar{\alpha} \).

For any fixed \( j \in [m'] \) and any possible \( \bar{z}(i_{\neq j}) \) where \( |z(i_{j'})| = 1 \) for all \( j' \in [m'] \setminus \{ j \} \), we have

\[
\Pr \left( Z(i_j) = -1 \mid Z(i_{\neq j}) = \bar{z}(i_{\neq j}) \right) = \Pr \left( Z(i_j) = 1 \mid Z(i_{\neq j}) = \bar{z}(i_{\neq j}) \right).
\]

Because \( |Z(i_j)| = 1 \), we have

\[
\Pr \left( Z(i_j) = 1 \mid Z(i_{\neq j}) = \bar{z}(i_{\neq j}) \right) + \Pr \left( Z(i_j) = -1 \mid Z(i_{\neq j}) = \bar{z}(i_{\neq j}) \right) = 1.
\]

Therefore, we have

\[
\Pr \left( Z(i_j) = 1 \mid Z(i_{\neq j}) = \bar{z}(i_{\neq j}) \right) = \frac{1}{2}.
\]

Therefore, from Lemma 3, we have \( Z(i_1), Z(i_2), \ldots, Z(i_{m'}) \) are independent.

Let \( L = \max \{ j : Z(i_1) = Z(i_2) = \cdots = Z(i_j) = 1 \} \) if \( Z(i_1) = 1 \). Otherwise, let \( L \) be 0. Note that there are \( V \) elements equal to 1 and \( \bar{V}' \) elements equal to -1 in \( Z(i_1), Z(i_2), \ldots, Z(i_{V + \bar{V}'}) \). Therefore,

\[
\# \{ Z_{i_j} = 1, j \leq V + \bar{V}' \} = V.
\]

By applying Lemma 2 to \( Z(i_1), Z(i_2), \ldots, Z(i_{m'}) \), we have

\[
\mathbb{E}(L \mid V = c_1, \bar{V}' = c_2) = \mathbb{E}(L \# \left\{ Z_{i_j} = 1, j \leq c_1 + c_2 \right\} = c_1) = c_1 \frac{c_1}{c_2 + 1}.
\]
Therefore,
\[ \mathbb{E}(L) = \sum_{c_1,c_2} \mathbb{E}(L | V = c_1, \hat{V}' = c_2) \Pr(V = c_1, \hat{V}' = c_2) \]
\[ \geq \sum_{c_1,c_2} \frac{c_1}{c_2+1} \Pr(V = c_1, \hat{V}' = c_2) = \mathbb{E}\left(\frac{V}{\hat{V}'+1}\right). \tag{49} \]

By applying Lemma 1 to \( Z_{(i_1)}, Z_{(i_2)}, \ldots, Z_{(i_m)} \), we have \( \mathbb{E}(L) < 1 \). Then
\[ \mathbb{E}\left(\frac{V}{\hat{V}'+1}\right) \leq \mathbb{E}(L) < 1. \tag{50} \]

From the definitions of \( \hat{V}' \) and \( \hat{V} \), we have \( \hat{V}' \leq \hat{V} \) and
\[ \mathbb{E}\left(\frac{V}{\hat{V}+1}\right) \leq \mathbb{E}\left(\frac{V}{\hat{V}'+1}\right) < 1. \tag{51} \]

Recall that \( \hat{V} = \# \{ Z(j) < 0, j \leq K \} \) and \( R = \# \{ Z(j) \geq 0, j \leq K \} \). If \( R > 0 \), from the definition of \( K \), we have
\[ \frac{\hat{V}+1}{R \lor 1} \leq \alpha. \tag{52} \]

Thus,
\[ R \geq \frac{\hat{V}+1}{\alpha}, \tag{53} \]
and then
\[ \frac{V}{R \lor 1} \leq \frac{\alpha V}{\hat{V}+1}. \tag{54} \]
If \( R = 0 \), we have \( V \leq R = 0 \) and \( V/(R \lor 1) = 0 = \alpha V/(\hat{V}+1) \). Thus, equation \( 54 \) always holds no matter \( R > 0 \) or \( R = 0 \). Then from equations \( 51 \) and \( 54 \) we have
\[ \mathbb{E}\left(\frac{V}{R \lor 1}\right) \leq \mathbb{E}\left(\frac{\alpha V}{\hat{V}+1}\right) < \alpha. \tag{55} \]
Results for Normal and Gamma distributions

Sample size is 60

The simulation results are similar when sample size was set as 60 or 20. Firstly, the target-decoy procedure controlled the FDRs in all cases. Meanwhile, the target-decoy procedure is very powerful. When the random variables follow the gamma distribution, the target-decoy procedure is more powerful than the Bayes and empirical Bayes methods. Finally, the pooled permutation and the empirical Bayes with rank-sum test cannot control the FDR.

As the sample size increased from 20 to 60, the power of different methods became very close, especially for the normal distribution. The power of these methods was also enhanced.

The detailed results are listed in Tables 7, 8, 9 and 10.
Table 7. Real FDRs with independent normal and gamma random variables. The sample size is 60. The FDRs were calculated by the means of FDPs of 1000 repetitions. The standard deviations of the means of FDPs are less than 0.0027 for all the experiments. All the cases where FDRs exceed $\alpha$ are labeled with $\ast$.

|                | Normal,1% | Normal,10% | Gamma,1% | Gamma,10% |
|----------------|-----------|------------|----------|-----------|
| $\alpha$       | 0.05 0.10 | 0.05 0.10  | 0.05 0.10| 0.05 0.10 |

Bayes

|                | Bayes     | Bayes     | Bayes     | Bayes     |
|----------------|-----------|-----------|-----------|-----------|
| $t$-test       | 0.050 0.100 | 0.050 0.100 | 0.030 0.066 | 0.041 0.089 |
| permutation    | 0.049 0.098 | 0.049 0.099 | 0.041 0.099 | 0.060$^*$ 0.121$^*$ |
| rank-sum       | 0.048 0.097 | 0.048 0.096 | 0.048 0.098 | 0.048 0.096 |
| bootstrap      | 0.042 0.089 | 0.048 0.098 | 0.012 0.035 | 0.035 0.082 |

Empirical Bayes

|                | Empirical Bayes | Empirical Bayes | Empirical Bayes | Empirical Bayes |
|----------------|-----------------|-----------------|-----------------|-----------------|
| $t$-test       | 0.048 0.100     | 0.047 0.098     | 0.017 0.043     | 0.028 0.065     |
| permutation    | 0.043 0.085     | 0.046 0.097     | 0.185$^*$ 0.349$^*$ | 0.119$^*$ 0.202$^*$ |
| rank-sum       | 0.049 0.103$^*$ | 0.045 0.091     | 0.048 0.101$^*$ | 0.045 0.093     |
| bootstrap      | 0.036 0.074     | 0.045 0.096     | 0.005 0.017     | 0.025 0.065     |

Target-decoy

|                | Target-decoy | Target-decoy | Target-decoy | Target-decoy |
|----------------|--------------|--------------|--------------|--------------|
| $t$-value,49   | 0.045 0.095  | 0.049 0.099  | 0.044 0.098  | 0.049 0.100  |
| $t$-value,1    | 0.045 0.097  | 0.049 0.099  | 0.044 0.095  | 0.050 0.100  |
| rank-sum,49    | 0.044 0.095  | 0.049 0.100  | 0.044 0.096  | 0.049 0.099  |
| rank-sum,1     | 0.047 0.097  | 0.049 0.099  | 0.044 0.096  | 0.049 0.099  |
Table 8. Power with independent normal and gamma random variables. The sample size is 60. All the cases where FDRs exceed $\alpha$ as shown in Table 7 are labeled with $\ast$.

|                | Normal,1% | Normal,10% | Gamma,1% | Gamma,10% |
|----------------|-----------|------------|----------|-----------|
| $\alpha$       | 0.05 0.10 | 0.05 0.10  | 0.05 0.10| 0.05 0.10 |

**Bayes**

|                | t-test     | permutation | rank-sum  | bootstrap |
|----------------|------------|-------------|-----------|-----------|
|                | 96 104     | 1024 1094   | 87 93     | 969 1046  |
|                | 96 104     | 1022 1093   | 89 98     | 1000* 1093*|
|                | 95 103     | 1016 1086   | 93 101    | 1006 1078 |
|                | 95 102     | 1021 1091   | 82 88     | 957 1036  |

**Empirical Bayes**

|                | t-test     | permutation | rank-sum  | bootstrap |
|----------------|------------|-------------|-----------|-----------|
|                | 96 104     | 1019 1092   | 84 89     | 942 1009  |
|                | 95 102     | 1018 1090   | 112* 146* | 1091* 1223*|
|                | 95 104*    | 1011 1079   | 93 102*   | 1001 1073 |
|                | 94 100     | 1017 1089   | 79 84     | 935 1008  |

**Target-decoy**

|                | t-value,49 | t-value,1   | rank-sum,49 | rank-sum,1 |
|----------------|------------|-------------|--------------|------------|
|                | 95 103     | 1023 1093   | 89 98        | 983 1061   |
|                | 95 103     | 1023 1093   | 89 98        | 984 1061   |
|                | 94 103     | 1018 1090   | 92 101       | 1007 1082  |
|                | 95 103     | 1018 1089   | 92 101       | 1007 1081  |
Table 9. Real FDRs with dependent normal and gamma random variables. The sample size is 60. The FDRs were calculated by the means of FDPs of 1000 repetitions. The standard deviations of the means of FDPs are less than 0.0027 for all the experiments. All the cases where FDRs exceed $\alpha$ are labeled with $\ast$.

|               | Normal, $\rho = 0.4$ |         | Normal, $\rho = 0.8$ |         | Gamma          |
|---------------|----------------------|---------|----------------------|---------|----------------|
|               | 1%       | 10%     | 1%       | 10%     | 1%       | 10%     |
| $\alpha$      | 0.05     | 0.10    | 0.05     | 0.10    | 0.05     | 0.10    |
| Bayes         |          |         |          |         |          |         |
| t-test        | 0.050    | 0.101   | 0.050    | 0.100   | 0.050    | 0.100   |
| permutation   | 0.049    | 0.100   | 0.048    | 0.098   | 0.049    | 0.099   |
| rank-sum      | 0.049    | 0.098   | 0.048    | 0.097   | 0.048    | 0.096   |
| bootstrap     | 0.043    | 0.090   | 0.048    | 0.098   | 0.042    | 0.090   |
| Empirical Bayes|         |         |          |         |          |         |
| t-test        | 0.047    | 0.099   | 0.047    | 0.098   | 0.048    | 0.102   |
| permutation   | 0.043    | 0.088   | 0.046    | 0.097   | 0.045    | 0.089   |
| rank-sum      | 0.050    | 0.105   | 0.046    | 0.094   | 0.054    | 0.109   |
| bootstrap     | 0.036    | 0.077   | 0.046    | 0.096   | 0.039    | 0.080   |
| Target-decoy  |          |         |          |         |          |         |
| t-value, 49   | 0.046    | 0.096   | 0.050    | 0.100   | 0.046    | 0.095   |
| t-value, 1    | 0.046    | 0.094   | 0.050    | 0.100   | 0.046    | 0.095   |
| rank-sum, 49  | 0.048    | 0.099   | 0.049    | 0.100   | 0.047    | 0.096   |
| rank-sum, 1   | 0.047    | 0.097   | 0.050    | 0.100   | 0.047    | 0.097   |

49
Table 10. Power with dependent normal and gamma random variables. The sample size is 60. All the cases where FDRs exceed \( \alpha \) as shown in Table 9 are labeled with \(*\).

|                  | Normal, \( \rho = 0.4 \) | Normal, \( \rho = 0.8 \) | Gamma  |
|------------------|--------------------------|--------------------------|--------|
|                  | 1%  10%                  | 1%  10%                  | 1%  10%|
| \( \alpha \)     | 0.05 0.10 0.05 0.10      | 0.05 0.10 0.05 0.10      | 0.05 0.10 0.05 0.10 |

|                  | Bayes                     | Empirical Bayes          | Target-decoy |
|------------------|---------------------------|--------------------------|---------------|
|                  |                           |                          |               |
| \( t \)-test     | 103 110* 1050 1110        | 105 111 1053 1111        | 103 110 1050 1110 |
| permutation      | 103 110 1048 1108         | 105 111 1050 1108        | 105 110 1050 1108 |
| rank-sum         | 103 110 1047 1105         | 105 111 1050 1106        | 103 109 1048 1107 |
| bootstrap        | 103 109 1048 1107         | 104 110 1051 1108        | 104 109 1051 1108 |

|                  |                           |                          |               |
|                  | 103 109 1046 1107         | 105 110 1045 1099        | 103 107 1046 1106 |
| rank-sum         | 103 110* 1045 1102        | 106* 112* 1049 1103      | 104 109 1047 1101 |
| bootstrap        | 102 107 1046 1106         | 104 109 1047 1101        | 79  84 934 1006  |

|                  |                           |                          |               |
|                  | 103 110 1050 1110         | 105 111 1052 1111        | 90  98 983 1062 |
| t-value,49       | 103 109 1050 1110         | 105 111 1052 1111        | 89  98 983 1061 |
| rank-sum,49      | 103 110 1048 1110         | 105 111 1052 1110        | 92  101 1008 1083 |
| rank-sum,1       | 103 109 1049 1110         | 105 111 1052 1110        | 92  101 1008 1082 |

|                  |                           |                          |               |
|                  | 103 109 1046 1106         | 104 109 1047 1101        | 79  84 934 1006 |
| rank-sum,1       | 103 109 1046 1106         | 104 109 1047 1101        | 79  84 934 1006 |

|                  |                           |                          |               |
|                  | 103 109 1046 1106         | 104 109 1047 1101        | 79  84 934 1006 |
| rank-sum,1       | 103 109 1046 1106         | 104 109 1047 1101        | 79  84 934 1006 |

|                  |                           |                          |               |
|                  | 103 109 1046 1106         | 104 109 1047 1101        | 79  84 934 1006 |
| rank-sum,1       | 103 109 1046 1106         | 104 109 1047 1101        | 79  84 934 1006 |
Sample size is 100

The simulation results are similar when sample size was set as 100 or 60. Firstly, the target-decoy procedure controlled the FDRs in all cases. Meanwhile, the target-decoy procedure is very powerful. When the random variables follow the gamma distribution, the target-decoy procedure is more powerful than the Bayes method with $t$-test and empirical Bayes method. Finally, the pooled permutation and the empirical Bayes with rank-sum test cannot control the FDR.

As the sample size increased from 60 to 100, the power of different methods became closer. The power of these methods was also enhanced slightly.

The detailed results are listed in Tables 11, 12, 13, and 14.
Table 11. Real FDRs with independent normal and gamma random variables. The sample size is 100. The FDRs were calculated by the means of FDPs of 1000 repetitions. The standard deviations of the means of FDPs are less than 0.0026 for all the experiments. All the cases where FDRs exceed $\alpha$ are labeled with $\ast$.

|       | Normal,1% | Normal,10% | Gamma,1% | Gamma,10% |
|-------|-----------|------------|----------|-----------|
| $\alpha$ | 0.05 0.10 | 0.05 0.10  | 0.05 0.10 | 0.05 0.10 |
| **Bayes** |           |            |          |           |
| $t$-test | 0.051 $\ast$ 0.101 $\ast$ | 0.050 0.100 | 0.036 0.077 | 0.044 0.093 |
| permutation | 0.050 0.100 | 0.049 0.099 | 0.049 0.114 $\ast$ | 0.063 $\ast$ 0.124 $\ast$ |
| rank-sum | 0.050 0.100 | 0.049 0.099 | 0.051 $\ast$ 0.100 | 0.049 0.099 |
| bootstrap | 0.048 0.097 | 0.050 0.099 | 0.026 0.062 | 0.043 0.093 |
| **Empirical Bayes** |           |            |          |           |
| $t$-test | 0.046 0.097 | 0.047 0.098 | 0.025 0.059 | 0.037 0.084 |
| permutation | 0.045 0.088 | 0.047 0.097 | 0.233 $\ast$ 0.404 $\ast$ | 0.134 $\ast$ 0.220 $\ast$ |
| rank-sum | 0.051 $\ast$ 0.104 $\ast$ | 0.046 0.094 | 0.050 0.103 $\ast$ | 0.046 0.094 |
| bootstrap | 0.043 0.085 | 0.048 0.099 | 0.018 0.044 | 0.037 0.086 |
| **Target-decoy** |           |            |          |           |
| $t$-value,49 | 0.048 0.096 | 0.050 0.100 | 0.047 0.097 | 0.049 0.099 |
| $t$-value,1 | 0.048 0.098 | 0.050 0.100 | 0.046 0.095 | 0.049 0.099 |
| rank-sum,49 | 0.048 0.097 | 0.050 0.100 | 0.049 0.099 | 0.050 0.099 |
| rank-sum,1 | 0.046 0.096 | 0.049 0.100 | 0.049 0.097 | 0.050 0.100 |
Table 12. Power with independent normal and gamma random variables. The sample size is 100. All the cases where FDRs exceed $\alpha$ as shown in Table 11 are labeled with *.

|      | Normal,1% | Normal,10% | Gamma,1% | Gamma,10% |
|------|-----------|------------|----------|-----------|
| $\alpha$ | 0.05 0.10 | 0.05 0.10  | 0.05 0.10 | 0.05 0.10 |
| Bayes |           |            |          |           |
| $t$-test | 104* 110* | 1051 1110 | 98 104   | 1030 1094 |
| permutation | 104 110  | 1049 1109 | 100 109* | 1055* 1135* |
| rank-sum | 104 110  | 1049 1109  | 103* 109 | 1047 1107 |
| bootstrap | 104 110 | 1050 1109 | 96 102 | 1028 1093 |
| Empirical Bayes |           |            |          |           |
| $t$-test | 103 110  | 1047 1107 | 96 101  | 1020 1082 |
| permutation | 103 109 | 1047 1107  | 129* 169* | 1149* 1279* |
| rank-sum | 104* 111* | 1046 1103 | 103 110* | 1043 1102 |
| bootstrap | 103 108  | 1048 1109 | 94 99 | 1021 1084 |
| Target-decoy |           |            |          |           |
| $t$-value,49 | 104 110 | 1050 1110 | 99 107  | 1037 1102 |
| $t$-value,1 | 104 110 | 1051 1111 | 99 106 | 1037 1101 |
| rank-sum,49 | 103 110 | 1049 1111 | 102 109 | 1047 1108 |
| rank-sum,1 | 103 110 | 1049 1110 | 102 109 | 1047 1108 |
Table 13. Real FDRs with dependent normal and gamma random variables. The sample size is 100. The FDRs were calculated by the means of FDPs of 1000 repetitions. The standard deviations of the means of FDPs are less than 0.0026 for all the experiments. All the cases where FDRs exceed $\alpha$ are labeled with $\ast$.

| Normal, $\rho = 0.4$ | Normal, $\rho = 0.8$ | Gamma |
|----------------------|----------------------|-------|
|                      | 1%       | 10%    | 1%       | 10%    | 1%       | 10%    |
| $\alpha$             | 0.05 0.10 | 0.05 0.10 | 0.05 0.10 | 0.05 0.10 | 0.05 0.10 | 0.05 0.10 |
| **Bayes**            |          |        |          |        |          |        |
| $t$-test             | 0.050 0.101* 0.050 0.100 | 0.050 0.100 0.050 0.101* | 0.034 0.076 0.044 0.092 |
| permutation          | 0.049 0.101* 0.048 0.099 | 0.049 0.099 0.047 0.099 | 0.047 0.114* 0.063* 0.124* |
| rank-sum             | 0.050 0.098 0.049 0.099 | 0.050 0.098 0.049 0.099 | 0.050 0.099 0.049 0.098 |
| bootstrap            | 0.047 0.097 0.049 0.099 | 0.047 0.097 0.049 0.100 | 0.024 0.060 0.043 0.092 |
| **Empirical Bayes**  |          |        |          |        |          |        |
| $t$-test             | 0.047 0.100 0.047 0.099 | 0.047 0.096 0.046 0.096 | 0.024 0.058 0.036 0.083 |
| permutation          | 0.045 0.089 0.045 0.093 | 0.046 0.090 0.043 0.090 | 0.230* 0.402* 0.134* 0.219* |
| rank-sum             | 0.054* 0.110* 0.048 0.096 | 0.051* 0.103* 0.047 0.093 | 0.050 0.104* 0.046 0.093 |
| bootstrap            | 0.043 0.086 0.047 0.095 | 0.045 0.087 0.047 0.094 | 0.017 0.042 0.037 0.084 |
| **Target-decoy**     |          |        |          |        |          |        |
| $t$-value,49         | 0.046 0.095 0.049 0.099 | 0.046 0.095 0.050 0.100 | 0.044 0.094 0.049 0.099 |
| $t$-value,1          | 0.046 0.095 0.050 0.100 | 0.046 0.095 0.050 0.100 | 0.045 0.095 0.049 0.099 |
| rank-sum,49          | 0.047 0.095 0.050 0.100 | 0.047 0.096 0.050 0.100 | 0.046 0.095 0.049 0.099 |
| rank-sum,1           | 0.048 0.097 0.050 0.100 | 0.048 0.096 0.049 0.100 | 0.047 0.096 0.049 0.099 |

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Table 14. Power with dependent normal and gamma random variables. The sample size is 100. All the cases where FDRs exceed $\alpha$ as shown in Table 13 are labeled with $\ast$.

|                  | Normal, $\rho = 0.4$ | Normal, $\rho = 0.8$ | Gamma          |
|------------------|-----------------------|-----------------------|----------------|
|                  | 1% 10%                | 1% 10%                | 1% 10%         |
| $\alpha$         | 0.05 0.10 0.05 0.10   | 0.05 0.10 0.05 0.10   | 0.05 0.10 0.05 0.10 |
| Empirical Bayes  |                       |                       |                |
| $t$-test         | 105 111$^\ast$ 1053 1111 | 105 111 1053 1112$^\ast$ | 97 104 1030 1092 |
| permutation      | 105 111$^\ast$ 1051 1109 | 105 111 1050 1109 | 99 109$^\ast$ 1055$^\ast$ 1134$^\ast$ |
| rank-sum         | 105 111 1052 1110     | 105 111 1052 1110     | 103 109 1046 1106 |
| bootstrap        | 105 111 1052 1110     | 105 111 1052 1111     | 96 101 1028 1092 |
| Target-decoy     |                       |                       |                |
| $t$-value,49     | 105 111 1051 1110     | 105 111 1052 1112     | 99 106 1037 1101 |
| $t$-value,1      | 105 111 1053 1111     | 105 111 1052 1111     | 99 107 1036 1101 |
| rank-sum,49      | 105 111 1052 1111     | 105 111 1052 1112     | 102 109 1046 1107 |
| rank-sum,1       | 105 111 1052 1111     | 105 111 1052 1111     | 102 109 1046 1107 |
Results for Cauchy distribution

Recall that the case-control study consists of $m$ random variables. For each random variable, there are $n$ random samples, $n_1$ of which are from the cases and the other $n_0 = n - n_1$ are from the controls. Let $X_{j1}, X_{j2}, \cdots, X_{jn}$ be the $n$ random samples for random variable $X_j$. The observation values from the Cauchy distribution were generated in the following way. First, let $C_0, C_{11}, \cdots, C_{1n}, \cdots, C_{m1}, \cdots, C_{mn}$ be independent random variables where $C_0$ follows the Cauchy($\mu_0, 1$) distribution and $C_{ji}$ follows the Cauchy($\mu_{ji}, 1$) distribution for any $j = 1, \cdots, m$ and $i = 1, \cdots, n$. Next, let $X_{ji} = C_{ji}$ for $j = 1, \cdots, m$ and $i = 1, \cdots, n$ in the simulation study for independent random variables and let $X_{ji} = C_0 + C_{ji}$ for dependent random variables. In our simulation, $\mu_0$ was set as 0 and $\mu_{ji}$ was also set as 0 for $i = n_1 + 1, n_1 + 2, \cdots, n$, the $n_0$ controls. For the $n_1$ cases where $i = 1, 2, \cdots, n_1$, $\mu_{ji}$ was set as 0 for $j = 1, \cdots, m_0$, the $m_0$ hypotheses that are true null. The values of $\mu_{ji}$ for $i = 1, 2, \cdots, n_1$ and $j = m_0 + 1, \cdots, m$ are set as follows. We let $\mu_{ji} = 2, 3, 4$ and 5 for $j = m_0 + 1, m_0 + 2, m_0 + 3, m_0 + 4$, respectively. Similarly, we let $\mu_{ji} = 2, 3, 4$ and 5 for $j = m_0 + 5, m_0 + 6, m_0 + 7, m_0 + 8$, respectively. This cycle was repeated to produce $\mu_{(m_0+1)1}, \cdots, \mu_{(m_0+1)n_1}, \cdots, \mu_{m1}, \cdots, \mu_{mn_1}$ for the false null hypotheses.

Sample size is 20

The simulation results are as follows. Firstly, the target-decoy procedure controlled the FDRs in all cases. Meanwhile, the target-decoy procedure is more powerful than the Bayes and empirical Bayes methods for the Cauchy, 10% cases. For the Cauchy, 1% cases, it is also more powerful for $t$-test but less powerful for rank-sum test. Finally, the empirical Bayes with rank-sum test cannot control the FDR.

The detailed results are listed in Tables 15, 16, 17 and 18.
Table 15. Real FDRs with independent Cauchy random variables. The sample size is 20. The FDRs were calculated by the means of FDPs of 1000 repetitions. The standard deviations of the means of FDPs are less than 0.0029 for all the experiments. All the cases where FDRs exceed $\alpha$ are labeled with $\ast$.

| $\alpha$ | Cauchy,1% | Cauchy,10% |
|----------|-----------|------------|
| 0.05     | 0.002     | 0.004      |
| 0.10     | 0.003     | 0.011      |

**Bayes**

| Method    | Cauchy,1% | Cauchy,10% |
|-----------|-----------|------------|
| $t$-test  | 0.024     | 0.041      |
| permutation | 0.061     | 0.087      |
| rank-sum  | 0.040     | 0.041      |
| bootstrap | 0.000     | 0.000      |

**Empirical Bayes**

| Method    | Cauchy,1% | Cauchy,10% |
|-----------|-----------|------------|
| $t$-test  | 0.000     | 0.000      |
| permutation | 0.008     | 0.006      |
| rank-sum  | 0.050     | 0.025      |
| bootstrap | 0.000     | 0.000      |

**Target-decoy**

| Method    | Cauchy,1% | Cauchy,10% |
|-----------|-----------|------------|
| $t$-value,49 | 0.022     | 0.048      |
| $t$-value,1  | 0.022     | 0.043      |
| rank-sum,49  | 0.022     | 0.049      |
| rank-sum,1   | 0.021     | 0.046      |
Table 16. Power with independent Cauchy random variables. The sample size is 20. All the cases where FDRs exceed $\alpha$ as shown in Table 15 are labeled with $\ast$.

|                  | Cauchy,1% | Cauchy,10% |
|------------------|-----------|------------|
| $\alpha$        | 0.05 0.10 | 0.05 0.10  |
| *Bayes*          |           |            |
| $t$-test         | 6 8       | 145 190    |
| permutation      | 13 17     | 250 321    |
| rank-sum         | 14 19     | 427 566    |
| bootstrap        | 0 0       | 0 0        |
| *Empirical Bayes*|           |            |
| $t$-test         | 0 0       | 2 18       |
| permutation      | 9 11      | 157 216    |
| rank-sum         | 15 21*    | 336 469    |
| bootstrap        | 0 0       | 0 0        |
| *Target-decoy*   |           |            |
| $t$-value,49     | 5 18      | 274 345    |
| $t$-value,1      | 5 17      | 266 334    |
| rank-sum,49      | 5 18      | 449 603    |
| rank-sum,1       | 5 18      | 440 589    |
Table 17. Real FDRs with dependent Cauchy random variables. The sample size is 20. The FDRs were calculated by the means of FDPs of 1000 repetitions. The standard deviations of the means of FDPs are less than 0.0027 for all the experiments. All the cases where FDRs exceed $\alpha$ are labeled with *.

|               | Cauchy,1% | Cauchy,10% |
|---------------|-----------|------------|
| $\alpha$     | 0.05 0.10 | 0.05 0.10  |

|                | Bayes     |
|----------------|-----------|
|                |           |
| $t$-test       | 0.000 0.002 | 0.004 0.012 |
| permutation    | 0.027 0.063 | 0.034 0.079 |
| rank-sum       | 0.040 0.084 | 0.042 0.088 |
| bootstrap      | 0.000 0.000 | 0.000 0.000 |

|                | Empirical Bayes     |
|----------------|----------------------|
|                |                      |
| $t$-test       | 0.000 0.000 | 0.000 0.000 |
| permutation    | 0.007 0.016 | 0.006 0.020 |
| rank-sum       | 0.053* 0.104* | 0.025 0.056 |
| bootstrap      | 0.000 0.000 | 0.000 0.000 |

|                | Target-decoy     |
|----------------|------------------|
|                |                   |
| $t$-value,49   | 0.021 0.077 | 0.048 0.097 |
| $t$-value,1    | 0.021 0.077 | 0.044 0.091 |
| rank-sum,49    | 0.020 0.080 | 0.050 0.100 |
| rank-sum,1     | 0.019 0.082 | 0.046 0.094 |
Table 18. Power with dependent Cauchy random variables. The sample size is 20. All the cases where FDRs exceed $\alpha$ as shown in Table 17 are labeled with $\ast$.

|                | Cauchy,1% | Cauchy,10% |
|----------------|-----------|------------|
| $\alpha$       | 0.05 0.10 | 0.05 0.10  |
| Bayes          |           |            |
| $t$-test       | 6 8       | 145 191    |
| permutation    | 13 18     | 251 322    |
| rank-sum       | 14 19     | 428 568    |
| bootstrap      | 0 0       | 0 0        |
| Empirical Bayes|           |            |
| $t$-test       | 0 0       | 3 19       |
| permutation    | 9 11      | 159 217    |
| rank-sum       | 15$^*$ 21$^*$ | 341 474 |
| bootstrap      | 0 0       | 0 0        |
| Target-decoy   |           |            |
| $t$-value,49   | 5 17      | 275 345    |
| $t$-value,1    | 5 17      | 267 336    |
| rank-sum,49    | 4 18      | 452 607    |
| rank-sum,1     | 5 18      | 438 586    |
Sample size is 60

The simulation results are similar when sample size was set as 60 or 20. Firstly, the target-decoy procedure controlled the FDRs in all cases. Meanwhile, the target-decoy procedure is more powerful than the Bayes and empirical Bayes methods for the Cauchy,10% cases.

As the sample size increased from 20 to 60, the power of all the methods, especially the Wilcoxon rank-sum test, was enhanced.

The detailed results are listed in Tables 19, 20, 21 and 22.
Table 19. Real FDRs with independent Cauchy random variables. The sample size is 60. The FDRs were calculated by the means of FDPs of 1000 repetitions. The standard deviations of the means of FDPs are less than 0.0026 for all the experiments.

|                | Cauchy,1% | Cauchy,10% |
|----------------|-----------|------------|
| α              | 0.05 0.10 | 0.05 0.10  |

Bayes

|                |          |            |
|----------------|----------|------------|
| t-test         | 0.001 0.002 | 0.003 0.011 |
| permutation    | 0.020 0.053 | 0.033 0.079 |
| rank-sum       | 0.048 0.098 | 0.048 0.097 |
| bootstrap      | 0.000 0.000 | 0.000 0.000 |

Empirical Bayes

|                |          |            |
|----------------|----------|------------|
| t-test         | 0.000 0.000 | 0.000 0.000 |
| permutation    | 0.003 0.006 | 0.003 0.013 |
| rank-sum       | 0.044 0.096 | 0.046 0.096 |
| bootstrap      | 0.000 0.000 | 0.000 0.000 |

Target-decoy

|                |          |            |
|----------------|----------|------------|
| t-value,49     | 0.030 0.085 | 0.048 0.098 |
| t-value,1      | 0.029 0.082 | 0.046 0.093 |
| rank-sum,49    | 0.044 0.097 | 0.050 0.100 |
| rank-sum,1     | 0.045 0.098 | 0.049 0.100 |
Table 20. Power with independent Cauchy random variables. The sample size is 60.

|                | Cauchy,1% | Cauchy,10% |
|----------------|-----------|-------------|
| **α**          | 0.05 0.10 | 0.05 0.10   |
| **Bayes**      |           |             |
| t-test         | 10 12     | 186 227     |
| permutation    | 17 21     | 282 349     |
| rank-sum       | 88 97     | 992 1069    |
| bootstrap      | 0 0       | 0 0         |
| **Empirical Bayes** |       |             |
| t-test         | 1 2       | 42 58       |
| permutation    | 12 14     | 183 233     |
| rank-sum       | 87 97     | 987 1067    |
| bootstrap      | 0 0       | 0 0         |
| **Target-decoy** |       |             |
| t-value,49     | 11 23     | 307 372     |
| t-value,1      | 11 23     | 303 366     |
| rank-sum,49    | 86 97     | 994 1073    |
| rank-sum,1     | 86 97     | 993 1072    |

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Table 21. Real FDRs with dependent Cauchy random variables. The sample size is 60. The FDRs were calculated by the means of FDPs of 1000 repetitions. The standard deviations of the means of FDPs are less than 0.0027 for all the experiments.

|                | Cauchy,1% | Cauchy,10% |
|----------------|-----------|------------|
| **α**          | 0.05 0.10 | 0.05 0.10  |
| **Bayes**      |           |            |
| t-test         | 0.001 0.002 | 0.003 0.011 |
| permutation    | 0.019 0.054 | 0.033 0.080 |
| rank-sum       | 0.048 0.098 | 0.048 0.096 |
| bootstrap      | 0.000 0.000 | 0.000 0.000 |
| **Empirical Bayes** |          |            |
| t-test         | 0.000 0.000 | 0.000 0.000 |
| permutation    | 0.003 0.006 | 0.003 0.013 |
| rank-sum       | 0.044 0.094 | 0.046 0.096 |
| bootstrap      | 0.000 0.000 | 0.000 0.000 |
| **Target-decoy** |          |            |
| t-value,49     | 0.029 0.081 | 0.049 0.098 |
| t-value,1      | 0.033 0.088 | 0.046 0.094 |
| rank-sum,49    | 0.045 0.098 | 0.050 0.099 |
| rank-sum,1     | 0.045 0.098 | 0.049 0.099 |
Table 22. Power with dependent Cauchy random variables. The sample size is 60.

|                  | Cauchy,1% | Cauchy,10% |
|------------------|-----------|------------|
| \( \alpha \)     | 0.05 0.10 | 0.05 0.10  |
| Bayes            |           |            |
| \( t \)-test     | 10 12     | 186 228    |
| permutation      | 17 21     | 283 350    |
| rank-sum         | 88 97     | 992 1069   |
| bootstrap        | 0 0       | 0 0        |
| Empirical Bayes  |           |            |
| \( t \)-test     | 1 2       | 42 58      |
| permutation      | 12 14     | 183 233    |
| rank-sum         | 87 97     | 988 1068   |
| bootstrap        | 0 0       | 0 0        |
| Target-decoy     |           |            |
| \( t \)-value,49 | 11 23     | 307 372    |
| \( t \)-value,1  | 12 23     | 304 367    |
| rank-sum,49      | 86 97     | 994 1073   |
| rank-sum,1       | 87 97     | 993 1072   |
Sample size is 100

The simulation results are similar when sample size was set as 100 or 60. Firstly, the target-decoy procedure controlled the FDRs in all cases. Meanwhile, the target-decoy procedure is powerful. Finally, the empirical Bayes with rank-sum test cannot control the FDR.

As the sample size increased from 60 to 100, the power of all the methods was enhanced slightly.

The detailed results are listed in Tables 23, 24, 25 and 26.
Table 23. Real FDRs with independent Cauchy random variables. The sample size is 100. The FDRs were calculated by the means of FDPs of 1000 repetitions. The standard deviations of the means of FDPs are less than 0.0026 for all the experiments. All the cases where FDRs exceed $\alpha$ are labeled with $\ast$.

|         | Cauchy,1% | Cauchy,10% |
|---------|-----------|------------|
| $\alpha$ | 0.05 0.10 | 0.05 0.10  |
| Bayes   |           |            |
|         |           |            |
| t-test  | 0.001 0.002 | 0.003 0.011 |
| permutation | 0.020 0.052 | 0.032 0.078 |
| rank-sum| 0.049 0.099 | 0.049 0.099 |
| bootstrap | 0.000 0.000 | 0.000 0.000 |
| Empirical Bayes | |            |
|         |           |            |
| t-test  | 0.000 0.000 | 0.000 0.000 |
| permutation | 0.003 0.006 | 0.003 0.012 |
| rank-sum| 0.049 0.103$^*$ | 0.047 0.097 |
| bootstrap | 0.000 0.000 | 0.000 0.000 |
| Target-decoy | |            |
|         |           |            |
| $t$-value,49 | 0.035 0.088 | 0.049 0.098 |
| $t$-value,1 | 0.034 0.083 | 0.046 0.093 |
| rank-sum,49  | 0.046 0.094 | 0.050 0.099 |
| rank-sum,1  | 0.045 0.094 | 0.049 0.099 |
Table 24. Power with independent Cauchy random variables. The sample size is 100. All the cases where FDRs exceed $\alpha$ as shown in Table 23 are labeled with $\ast$.

|                | Cauchy,1% | Cauchy,10% |
|----------------|-----------|------------|
| $\alpha$       | 0.05 0.10 | 0.05 0.10  |
| **Bayes**      |           |            |
| $t$-test       | 11 13     | 193 235    |
| permutation    | 18 22     | 288 354    |
| rank-sum       | 102 109   | 1045 1106  |
| bootstrap      | 0 0       | 0 0        |
| **Empirical Bayes** |       |            |
| $t$-test       | 2 2       | 50 66      |
| permutation    | 12 14     | 188 237    |
| rank-sum       | 102 109*  | 1042 1104  |
| bootstrap      | 0 0       | 0 0        |
| **Target-decoy** |       |            |
| $t$-value,49   | 13 24     | 314 377    |
| $t$-value,1    | 13 24     | 310 371    |
| rank-sum,49    | 101 108   | 1045 1107  |
| rank-sum,1     | 101 108   | 1045 1106  |
Table 25. Real FDRs with dependent Cauchy random variables. The sample size is 100. The FDRs were calculated by the means of FDPs of 1000 repetitions. The standard deviations of the means of FDPs are less than 0.0025 for all the experiments. All the cases where FDRs exceed $\alpha$ are labeled with $\ast$.

|          | Cauchy,1% | Cauchy,10% |
|----------|-----------|------------|
| $\alpha$ | 0.05      | 0.10       |
|          | 0.05      | 0.10       |
| **Bayes**|           |            |
| $t$-test | 0.001     | 0.002      |
| permutation | 0.020    | 0.054      |
| rank-sum  | 0.049     | 0.099      |
| bootstrap | 0.000     | 0.000      |
|          | 0.003     | 0.011      |
|          | 0.033     | 0.079      |
|          | 0.050     | 0.099      |
|          | 0.000     | 0.000      |
| **Empirical Bayes**| | |
| $t$-test | 0.000     | 0.000      |
| permutation | 0.003    | 0.006      |
| rank-sum  | 0.049     | 0.104$\ast$|
| bootstrap | 0.000     | 0.000      |
|          | 0.000     | 0.000      |
|          | 0.003     | 0.012      |
|          | 0.047     | 0.097      |
|          | 0.000     | 0.000      |
| **Target-decoy**| | |
| $t$-value,49 | 0.034    | 0.086      |
| $t$-value,1 | 0.032     | 0.084      |
| rank-sum,49 | 0.046    | 0.096      |
| rank-sum,1 | 0.046     | 0.096      |
|          | 0.048     | 0.097      |
|          | 0.046     | 0.094      |
|          | 0.050     | 0.100      |
|          | 0.050     | 0.100      |

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Table 26. Power with dependent Cauchy random variables. The sample size is 100. All the cases where FDRs exceed $\alpha$ as shown in Table 25 are labeled with $\ast$.

|       | Cauchy,1% | Cauchy,10% |
|-------|-----------|------------|
| $\alpha$ | 0.05    | 0.10      |
| Bayes |           |           |
| $t$-test | 11      | 13        |
| permutation | 18      | 22        |
| rank-sum | 102     | 109*      |
| bootstrap | 0       | 0         |
| Empirical Bayes | |           |
| $t$-test | 2       | 2         |
| permutation | 12      | 15        |
| rank-sum | 102     | 109*      |
| bootstrap | 0       | 0         |
| Target-decoy |         |           |
| $t$-value,49 | 13      | 24        |
| $t$-value,1 | 12      | 24        |
| rank-sum,49 | 101     | 108       |
| rank-sum,1 | 101     | 108       |