

CRAMÉR-TYPE MODERATE DEVIATIONS FOR STUDENTIZED TWO-SAMPLE U -STATISTICS WITH APPLICATIONS

BY JINYUAN CHANG^{1,*,\dagger}, QI-MAN SHAO^{2,\ddagger} AND WEN-XIN ZHOU^{3,\S,\dagger}

Southwestern University of Finance and Economics, University of Melbourne,\dagger
 Chinese University of Hong Kong^{\ddagger} and Princeton University^{\S}*

Two-sample U -statistics are widely used in a broad range of applications, including those in the fields of biostatistics and econometrics. In this paper, we establish sharp Cramér-type moderate deviation theorems for Studentized two-sample U -statistics in a general framework, including the two-sample t -statistic and Studentized Mann–Whitney test statistic as prototypical examples. In particular, a refined moderate deviation theorem with second-order accuracy is established for the two-sample t -statistic. These results extend the applicability of the existing statistical methodologies from the one-sample t -statistic to more general nonlinear statistics. Applications to two-sample large-scale multiple testing problems with false discovery rate control and the regularized bootstrap method are also discussed.

1. Introduction. The U -statistic is one of the most commonly used nonlinear and nonparametric statistics, and its asymptotic theory has been well studied since the seminal paper of [Hoeffding \(1948\)](#). U -statistics extend the scope of parametric estimation to more complex nonparametric problems and provide a general theoretical framework for statistical inference. We refer to [Koroljuk and Borovskikh \(1994\)](#) for a systematic presentation of the theory of U -statistics, and to [Kowalski](#)

Tribute: Peter was a brilliant and prolific researcher, who has made enormously influential contributions to mathematical statistics and probability theory. Peter had extraordinary knowledge of analytic techniques that he often applied with ingenious simplicity to tackle complex statistical problems. His work and service have had a profound impact on statistics and the statistical community. Peter was a generous mentor and friend with a warm heart and keen to help the young generation. Jinyuan Chang and Wen-Xin Zhou are extremely grateful for the opportunity to learn from and work with Peter in the last two years at the University of Melbourne. Even in his final year, he had afforded time to guide us. We will always treasure the time we spent with him. Qi-Man Shao is so grateful for all the helps and supports that Peter had provided during the various stages of his career. Peter will be dearly missed and forever remembered as our mentor and friend.

Received June 2015.

¹Supported in part by the Fundamental Research Funds for the Central Universities (Grant No. JBK160159, JBK150501), NSFC (Grant No. 11501462), the Center of Statistical Research at SWUFE and the Australian Research Council.

²Supported by Hong Kong Research Grants Council GRF 603710 and 403513.

³Supported by NIH Grant R01-GM100474-4 and a grant from the Australian Research Council.

MSC2010 subject classifications. Primary 60F10, 62E17; secondary 62E20, 62F40, 62H15.

Key words and phrases. Bootstrap, false discovery rate, Mann–Whitney U test, multiple hypothesis testing, self-normalized moderate deviation, Studentized statistics, two-sample t -statistic, two-sample U -statistics.

and Tu (2007) for more recently discovered methods and contemporary applications of U -statistics.

Applications of U -statistics can also be found in high dimensional statistical inference and estimation, including the simultaneous testing of many different hypotheses, feature selection and ranking, the estimation of high dimensional graphical models and sparse, high dimensional signal detection. In the context of high dimensional hypothesis testing, for example, several new methods based on U -statistics have been proposed and studied in Chen and Qin (2010), Chen, Zhang and Zhong (2010) and Zhong and Chen (2011). Moreover, Li et al. (2012) and Li, Zhong and Zhu (2012) employed U -statistics to construct independence feature screening procedures for analyzing ultrahigh dimensional data.

Due to heteroscedasticity, the measurements across disparate subjects may differ significantly in scale for each feature. To standardize for scale, unknown nuisance parameters are always involved and a natural approach is to use Studentized, or self-normalized statistics. The noteworthy advantage of Studentization is that compared to standardized statistics, Studentized ratios take heteroscedasticity into account and are more robust against heavy-tailed data. The theoretical and numerical studies in Delaigle, Hall and Jin (2011) and Chang, Tang and Wu (2013, 2016) evidence the importance of using Studentized statistics in high dimensional data analysis. As noted in Delaigle, Hall and Jin (2011), a careful study of the moderate deviations in the Studentized ratios is indispensable to understanding the common statistical procedures used in analyzing high dimensional data.

Further, it is now known that the theory of Cramér-type moderate deviations for Studentized statistics quantifies the accuracy of the estimated p -values, which is crucial in the study of large-scale multiple tests for controlling the false discovery rate [Fan, Hall and Yao (2007), Liu and Shao (2010)]. In particular, Cramér-type moderate deviation results can be used to investigate the robustness and accuracy properties of p -values and critical values in multiple testing procedures. However, thus far, most applications have been confined to t -statistics [Cao and Kosorok (2011), Delaigle, Hall and Jin (2011), Fan, Hall and Yao (2007), Wang and Hall (2009)]. It is conjectured in Fan, Hall and Yao (2007) that analogues of the theoretical properties of these statistical methodologies remain valid for other resampling methods based on Studentized statistics. Motivated by the above applications, we are attempting to develop a unified theory on moderate deviations for more general Studentized nonlinear statistics, in particular, for two-sample U -statistics.

The asymptotic properties of the standardized U -statistics are extensively studied in the literature, whereas significant developments are achieved in the past decade for one-sample Studentized U -statistics. We refer to Wang, Jing and Zhao (2000) and the references therein for Berry–Esseen-type bounds and Edgeworth expansions. The results for moderate deviations can be found in Vandemaële and Veraverbeke (1985), Lai, Shao and Wang (2011) and Shao and Zhou (2016). The results in Shao and Zhou (2016) paved the way for further applications of statistical methodologies using Studentized U -statistics in high dimensional data analysis.

Two-sample U -statistics are also commonly used to compare the different (treatment) effects of two groups, such as an experimental group and a control group, in scientifically controlled experiments. However, due to the structural complexities, the theoretical properties of the two-sample U -statistics have not been well studied. In this paper, we establish a Cramér-type moderate deviation theorem in a general framework for Studentized two-sample U -statistics, especially the two-sample t -statistic and the Studentized Mann–Whitney test. In particular, a refined moderate deviation theorem with second-order accuracy is established for the two-sample t -statistic.

The paper is organized as follows. In Section 2, we present the main results on Cramér-type moderate deviations for Studentized two-sample U -statistics as well as a refined result for the two-sample t -statistic. In Section 3, we investigate statistical applications of our theoretical results to the problem of simultaneously testing many different hypotheses, based particularly on the two-sample t -statistics and Studentized Mann–Whitney tests. Section 4 shows numerical studies. A discussion is given in Section 5. All the proofs are relegated to the supplementary material [Chang, Shao and Zhou (2016)].

2. Moderate deviations for Studentized U -statistics. We use the following notation throughout this paper. For two sequences of real numbers a_n and b_n , we write $a_n \asymp b_n$ if there exist two positive constants c_1, c_2 such that $c_1 \leq a_n/b_n \leq c_2$ for all $n \geq 1$, we write $a_n = O(b_n)$ if there is a constant C such that $|a_n| \leq C|b_n|$ holds for all sufficiently large n , and we write $a_n \sim b_n$ and $a_n = o(b_n)$, respectively, if $\lim_{n \rightarrow \infty} a_n/b_n = 1$ and $\lim_{n \rightarrow \infty} a_n/b_n = 0$. Moreover, for two real numbers a and b , we write for ease of presentation that $a \vee b = \max(a, b)$ and $a \wedge b = \min(a, b)$.

2.1. A review of Studentized one-sample U -statistics. We start with a brief review of Cramér-type moderate deviation for Studentized one-sample U -statistics. For an integer $s \geq 2$ and for $n > 2s$, let $X_1, \dots, X_n$ be independent and identically distributed (i.i.d.) random variables taking values in a metric space $(\mathbb{X}, \mathcal{G})$, and let $h : \mathbb{X}^d \mapsto \mathbb{R}$ be a symmetric Borel measurable function. Hoeffding's U -statistic with a kernel h of degree s is defined as

$$U_n = \frac{1}{\binom{n}{s}} \sum_{1 \leq i_1 < \dots < i_s \leq n} h(X_{i_1}, \dots, X_{i_s}),$$

which is an unbiased estimate of $\theta = \mathbb{E}\{h(X_1, \dots, X_s)\}$. In particular, we focus on the case where $\mathbb{X}$ is the Euclidean space $\mathbb{R}^r$ for some integer $r \geq 1$. When $r \geq 2$, write $X_i = (X_i^1, \dots, X_i^r)^T$ for $i = 1, \dots, n$.

Let

$$h_1(x) = \mathbb{E}\{h(X_1, \dots, X_s) | X_1 = x\} \quad \text{for any } x = (x^1, \dots, x^r)^T \in \mathbb{R}^r$$

and

$$\sigma^2 = \text{var}\{h_1(X_1)\}, \quad v_h^2 = \text{var}\{h(X_1, X_2, \dots, X_s)\}.$$

Assume that $0 < \sigma^2 < \infty$, then the standardized nondegenerate U -statistic is given by

$$Z_n = \frac{n^{1/2}}{s\sigma}(U_n - \theta).$$

Because σ is usually unknown, we are interested in the following Studentized U -statistic:

$$(2.1) \quad \widehat{U}_n = \frac{n^{1/2}}{s\widehat{\sigma}}(U_n - \theta),$$

where $\widehat{\sigma}^2$ denotes the leave-one-out jackknife estimator of σ^2 given by

$$\widehat{\sigma}^2 = \frac{(n-1)}{(n-s)^2} \sum_{i=1}^n (q_i - U_n)^2 \quad \text{with}$$

$$q_i = \frac{1}{\binom{n-1}{s-1}} \sum_{\substack{1 \leq \ell_1 < \dots < \ell_{s-1} \leq n \\ \ell_j \neq i \text{ for each } j=1, \dots, s-1}} h(X_i, X_{\ell_1}, \dots, X_{\ell_{s-1}}).$$

Shao and Zhou (2016) established a general Cramér-type moderate deviation theorem for Studentized nonlinear statistics, in particular for Studentized U -statistics.

THEOREM 2.1. Assume that $v_p := [\mathbb{E}\{|h_1(X_1) - \theta|^p\}]^{1/p} < \infty$ for some $2 < p \leq 3$. Suppose that there are constants $c_0 \geq 1$ and $\kappa \geq 0$ such that for all $x_1, \dots, x_s \in \mathbb{R}$,

$$(2.2) \quad \{h(x_1, \dots, x_s) - \theta\}^2 \leq c_0 \left[\kappa \sigma^2 + \sum_{i=1}^s \{h_1(x_i) - \theta\}^2 \right].$$

Then there exist constants $C, c > 0$ depending only on d such that

$$\frac{\mathbb{P}(\widehat{U}_n \geq x)}{1 - \Phi(x)} = 1 + O(1) \{ (v_p/\sigma)^p (1+x)^p n^{1-p/2} + (a_s^{1/2} + v_h/\sigma)(1+x)^3 n^{-1/2} \}$$

holds uniformly for $0 \leq x \leq c \min\{(\sigma/v_p)n^{1/2-1/p}, (n/a_s)^{1/6}\}$, where $|O(1)| \leq C$ and $a_s = \max(c_0\kappa, c_0 + s)$. In particular, we have

$$\frac{\mathbb{P}(\widehat{U}_n \geq x)}{1 - \Phi(x)} \rightarrow 1$$

holds uniformly in $x \in [0, o(n^{1/2-1/p})]$.

Condition (2.2) is satisfied for a large class of U -statistics. Below are some examples.

Statistic	Kernel function	c_0	κ
t -statistic	$h(x_1, x_2) = 0.5(x_1 + x_2)$	2	0
Sample variance	$h(x_1, x_2) = 0.5(x_1 - x_2)^2$	10	$(\theta/\sigma)^2$
Gini's mean difference	$h(x_1, x_2) = x_1 - x_2 $	8	$(\theta/\sigma)^2$
One-sample Wilcoxon's statistic	$h(x_1, x_2) = I\{x_1 + x_2 \leq 0\}$	1	σ^{-2}
Kendall's τ	$h(x_1, x_2) = 2I\{(x_2^2 - x_1^2)(x_2^1 - x_1^1) > 0\}$	1	σ^{-2}

2.2. Studentized two-sample U -statistics. Let $\mathcal{X} = \{X_1, \dots, X_{n_1}\}$ and $\mathcal{Y} = \{Y_1, \dots, Y_{n_2}\}$ be two independent random samples, where $\mathcal{X}$ is drawn from a probability distribution P and $\mathcal{Y}$ is drawn from another probability distribution Q . With s_1 and s_2 being two positive integers, let

$$h(x_1, \dots, x_{s_1}; y_1, \dots, y_{s_2})$$

be a kernel function of order (s_1, s_2) which is real and symmetric both in its first s_1 variates and in its last s_2 variates. It is known that a nonsymmetric kernel can always be replaced with a symmetrized version by averaging across all possible rearrangements of the indices.

Set $\theta := \mathbb{E}\{h(X_1, \dots, X_{s_1}; Y_1, \dots, Y_{s_2})\}$, and let

$$U_{\bar{n}} = \frac{1}{\binom{n_1}{s_1}\binom{n_2}{s_2}} \sum_{1 \leq i_1 < \dots < i_{s_1} \leq n_1} \sum_{1 \leq j_1 < \dots < j_{s_2} \leq n_2} h(X_{i_1}, \dots, X_{i_{s_1}}; Y_{j_1}, \dots, Y_{j_{s_2}}),$$

be the two-sample U -statistic, where $\bar{n} = (n_1, n_2)$. To lighten the notation, we write $\mathbf{X}_{i_1, \dots, i_{\ell}} = (X_{i_1}, \dots, X_{i_{\ell}})$, $\mathbf{Y}_{j_1, \dots, j_k} = (Y_{j_1}, \dots, Y_{j_k})$ such that

$$h(\mathbf{X}_{i_1, \dots, i_{\ell}}; \mathbf{Y}_{j_1, \dots, j_k}) = h(X_{i_1}, \dots, X_{i_{\ell}}; Y_{j_1}, \dots, Y_{j_k}),$$

and define

$$(2.3) \quad \begin{aligned} h_1(x) &= \mathbb{E}\{h(\mathbf{X}_{1, \dots, s_1}; \mathbf{Y}_{1, \dots, s_2}) | X_1 = x\}, \\ h_2(y) &= \mathbb{E}\{h(\mathbf{X}_{1, \dots, s_1}; \mathbf{Y}_{1, \dots, s_2}) | Y_1 = y\}. \end{aligned}$$

Also let $v_h^2 = \text{var}\{h(\mathbf{X}_{1, \dots, s_1}; \mathbf{Y}_{1, \dots, s_2})\}$, $\sigma_1^2 = \text{var}\{h_1(X_i)\}$, $\sigma_2^2 = \text{var}\{h_2(Y_j)\}$ and

$$(2.4) \quad \sigma^2 = \sigma_1^2 + \sigma_2^2, \quad \sigma_{\bar{n}}^2 = s_1^2 \sigma_1^2 n_1^{-1} + s_2^2 \sigma_2^2 n_2^{-1}.$$

For the standardized two-sample U -statistic of the form $\sigma_{\bar{n}}^{-1}(U_{\bar{n}} - \theta)$, a uniform Berry–Esseen bound of order $O\{(n_1 \wedge n_2)^{-1/2}\}$ was obtained by [Helmers and Janssen \(1982\)](#) and [Borovskich \(1983\)](#). Using a concentration inequality approach, [Chen and Shao \(2007\)](#) proved a refined uniform bound and also established an optimal nonuniform Berry–Esseen bound. For large deviation asymptotics of two-sample U -statistics, we refer to [Nikitin and Ponikarov \(2006\)](#) and the references therein.

Here, we are interested in the following Studentized two-sample U -statistic:

$$(2.5) \quad \hat{U}_{\bar{n}} = \hat{\sigma}_{\bar{n}}^{-1}(U_{\bar{n}} - \theta) \quad \text{with } \hat{\sigma}_{\bar{n}}^2 = s_1^2 \hat{\sigma}_1^2 n_1^{-1} + s_2^2 \hat{\sigma}_2^2 n_2^{-1},$$

where

$$\hat{\sigma}_1^2 = \frac{1}{n_1 - 1} \sum_{i=1}^{n_1} \left(q_i - \frac{1}{n_1} \sum_{i=1}^{n_1} q_i \right)^2, \quad \hat{\sigma}_2^2 = \frac{1}{n_2 - 1} \sum_{j=1}^{n_2} \left(p_j - \frac{1}{n_2} \sum_{j=1}^{n_2} p_j \right)^2$$

and

$$q_i = \frac{1}{\binom{n_1-1}{s_1-1} \binom{n_2}{s_2}} \sum_{1 \leq i_2 < \dots < i_{s_1} \leq n_1} \sum_{\substack{1 \leq j_1 < \dots < j_{s_2} \leq n_2 \\ i_\ell \neq i, \ell=2, \dots, s_1}} h(\mathbf{X}_{i, i_2, \dots, i_{s_1}}; \mathbf{Y}_{j_1, \dots, j_{s_2}}),$$

$$p_j = \frac{1}{\binom{n_1}{s_1} \binom{n_2-1}{s_2-1}} \sum_{1 \leq i_1 < \dots < i_{s_1} \leq n_1} \sum_{\substack{1 \leq j_2 < \dots < j_{s_2} \leq n_2 \\ j_k \neq j, k=2, \dots, s_2}} h(\mathbf{X}_{i_1, \dots, i_{s_1}}; \mathbf{Y}_{j, j_2, \dots, j_{s_2}}).$$

Note that $\hat{\sigma}_1^2$ and $\hat{\sigma}_2^2$ are leave-one-out jackknife estimators of σ_1^2 and σ_2^2 , respectively.

2.2.1. *Moderate deviations for $\hat{U}_{\bar{n}}$.* For $p > 2$, let

$$(2.6) \quad v_{1,p} = [\mathbb{E}\{|h_1(X_1) - \theta|^p\}]^{1/p} \quad \text{and} \quad v_{2,p} = [\mathbb{E}\{|h_2(Y_1) - \theta|^p\}]^{1/p}.$$

Moreover, put

$$s = s_1 \vee s_2, \quad \bar{n} = (n_1, n_2), \quad n = n_1 \wedge n_2$$

and

$$\lambda_{\bar{n}} = v_h \left(\frac{n_1 + n_2}{\sigma_1^2 n_2 + \sigma_2^2 n_1} \right)^{1/2} \quad \text{with } v_h^2 = \text{var}\{h(\mathbf{X}_{1, \dots, s_1}; \mathbf{Y}_{1, \dots, s_2})\}.$$

The following result gives a Cramér-type moderate deviation for $\hat{U}_{\bar{n}}$ given in (2.5) under mild assumptions. A self-contained proof can be found in the supplementary material [Chang, Shao and Zhou (2016)].

THEOREM 2.2. Assume that there are constants $c_0 \geq 1$ and $\kappa \geq 0$ such that

$$(2.7) \quad \{h(\mathbf{x}; \mathbf{y}) - \theta\}^2 \leq c_0 \left[\kappa \sigma^2 + \sum_{i=1}^{s_1} \{h_1(x_i) - \theta\}^2 + \sum_{j=1}^{s_2} \{h_2(y_j) - \theta\}^2 \right]$$

for all $\mathbf{x} = (x_1, \dots, x_{s_1})$ and $\mathbf{y} = (y_1, \dots, y_{s_2})$, where σ^2 is given in (2.4). Assume that $v_{1,p}$ and $v_{2,p}$ are finite for some $2 < p \leq 3$. Then there exist constants $C, c > 0$

independent of n_1 and n_2 such that

$$(2.8) \quad \frac{\mathbb{P}(\widehat{U}_{\bar{n}} \geq x)}{1 - \Phi(x)} = 1 + O(1) \left\{ \sum_{\ell=1}^2 \frac{v_{\ell,p}^p (1+x)^p}{\sigma_{\ell}^p n_{\ell}^{p/2-1}} + (a_d^{1/2} + \lambda_{\bar{n}})(1+x)^3 \left(\frac{n_1 + n_2}{n_1 n_2} \right)^{1/2} \right\}$$

holds uniformly for

$$0 \leq x \leq c \min[(\sigma_1/v_{1,p})n_1^{p/2-1}, (\sigma_2/v_{2,p})n_2^{p/2-1}, a_s^{-1/6}\{n_1 n_2/(n_1 + n_2)\}^{1/6}],$$

where $|O(1)| \leq C$ and $a_s = \max(c_0 \kappa, c_0 + s)$. In particular, as $n \rightarrow \infty$,

$$(2.9) \quad \frac{\mathbb{P}(\widehat{U}_{\bar{n}} \geq x)}{1 - \Phi(x)} \rightarrow 1$$

holds uniformly in $x \in [0, o(n^{1/2-1/p})]$.

Theorem 2.2 exhibits the dependence between the range of uniform convergence of the relative error in the central limit theorem and the optimal moment conditions. In particular, if $p = 3$, the region becomes $0 \leq x \leq O(n^{1/6})$. See Theorem 2.3 in [Jing, Shao and Wang \(2003\)](#) for similar results on self-normalized sums. Under higher order moment conditions, it is not clear if our technique can be adapted to provide a better approximation for the tail probability $\mathbb{P}(\widehat{U}_{\bar{n}} \geq x)$ for x lying between $n^{1/6}$ and $n^{1/2}$ in order.

It is also worth noticing that many commonly used kernels in nonparametric statistics turn out to be linear combinations of the indicator functions and, therefore, satisfy condition (2.7) immediately.

2.2.2. Two-sample t -statistic. As a prototypical example of two-sample U -statistics, the two-sample t -statistic is of significant interest due to its wide applicability. The advantage of using t -tests, either one-sample or two-sample, is their high degree of robustness against heavy-tailed data in which the sampling distribution has only a finite third or fourth moment. The robustness of the t -statistic is useful in high dimensional data analysis under the sparsity assumption on the signal of interest. When dealing with two experimental groups, which are typically independent, in scientifically controlled experiments, the two-sample t -statistic is one of the most commonly used statistics for hypothesis testing and constructing confidence intervals for the difference between the means of the two groups.

Let $\mathcal{X} = \{X_1, \dots, X_{n_1}\}$ be a random sample from a one-dimensional population with mean μ_1 and variance σ_1^2 , and let $\mathcal{Y} = \{Y_1, \dots, Y_{n_2}\}$ be a random sample from another one-dimensional population with mean μ_2 and variance σ_2^2 independent of $\mathcal{X}$. The two-sample t -statistic is defined as

$$\widehat{T}_{\bar{n}} = \frac{\bar{X} - \bar{Y}}{\sqrt{\widehat{\sigma}_1^2 n_1^{-1} + \widehat{\sigma}_2^2 n_2^{-1}}},$$

where $\bar{n} = (n_1, n_2)$, $\bar{X} = n_1^{-1} \sum_{i=1}^{n_1} X_i$, $\bar{Y} = n_2^{-1} \sum_{j=1}^{n_2} Y_j$ and

$$\hat{\sigma}_1^2 = \frac{1}{n_1 - 1} \sum_{i=1}^{n_1} (X_i - \bar{X})^2, \quad \hat{\sigma}_2^2 = \frac{1}{n_2 - 1} \sum_{j=1}^{n_2} (Y_j - \bar{Y})^2.$$

The following result is a direct consequence of Theorem 2.2.

THEOREM 2.3. *Assume that $\mu_1 = \mu_2$, and $\mathbb{E}(|X_1|^p) < \infty$, $\mathbb{E}(|Y_1|^p) < \infty$ for some $2 < p \leq 3$. Then there exist absolute constants $C, c > 0$ such that*

$$\frac{\mathbb{P}(\hat{T}_{\bar{n}} \geq x)}{1 - \Phi(x)} = 1 + O(1)(1+x)^p \sum_{\ell=1}^2 (v_{\ell,p}/\sigma_{\ell})^p n_{\ell}^{1-p/2}$$

holds uniformly for $0 \leq x \leq c \min_{\ell=1,2} \{(\sigma_{\ell}/v_{\ell,p})n_{\ell}^{1/2-1/p}\}$, where $|O(1)| \leq C$ and $v_{1,p} = \{\mathbb{E}(|X_1 - \mu_1|^p)\}^{1/p}$, $v_{2,p} = \{\mathbb{E}(|Y_1 - \mu_2|^p)\}^{1/p}$.

Motivated by a series of recent studies on the effectiveness and accuracy of multiple-hypothesis testing using t -tests, we investigate whether a higher order expansion of the relative error, as in Theorem 1.2 of Wang (2005) for self-normalized sums, holds for the two-sample t -statistic, so that one can use bootstrap calibration to correct skewness [Delaigle, Hall and Jin (2011), Fan, Hall and Yao (2007)] or study power properties against sparse alternatives [Wang and Hall (2009)]. The following theorem gives a refined Cramér-type moderate deviation result for $\hat{T}_{\bar{n}}$, whose proof is placed in the supplementary material [Chang, Shao and Zhou (2016)].

THEOREM 2.4. *Assume that $\mu_1 = \mu_2$. Let $\gamma_1 = \mathbb{E}\{(X_1 - \mu_1)^3\}$ and $\gamma_2 = \mathbb{E}\{(Y_1 - \mu_2)^3\}$ be the third central moment of X_1 and Y_1 , respectively. Moreover, assume that $\mathbb{E}(|X_1|^p) < \infty$, $\mathbb{E}(|Y_1|^p) < \infty$ for some $3 < p \leq 4$. Then*

$$(2.10) \quad \frac{\mathbb{P}(\hat{T}_{\bar{n}} \geq x)}{1 - \Phi(x)} = \exp \left\{ -\frac{\gamma_1 n_1^{-2} - \gamma_2 n_2^{-2}}{3(\sigma_1^2 n_1^{-1} + \sigma_2^2 n_2^{-1})^{3/2}} x^3 \right\} \\ \times \left[1 + O(1) \sum_{\ell=1}^2 \left\{ \frac{v_{\ell,3}^3 (1+x)}{\sigma_{\ell}^3 n_{\ell}^{1/2}} + \frac{v_{\ell,p}^p (1+x)^p}{\sigma_{\ell}^p n_{\ell}^{p/2-1}} \right\} \right]$$

holds uniformly for

$$(2.11) \quad 0 \leq x \leq c \min_{\ell=1,2} \min \{(\sigma_{\ell}/v_{\ell,3})^3 n_{\ell}^{1/2}, (\sigma_{\ell}/v_{\ell,p}) n_{\ell}^{1/2-1/p}\},$$

where $|O(1)| \leq C$ and for every $q \geq 1$, $v_{1,q} = \{\mathbb{E}(|X_1 - \mu_1|^q)\}^{1/q}$, $v_{2,q} = \{\mathbb{E}(|Y_1 - \mu_2|^q)\}^{1/q}$.

A refined Cramér-type moderate deviation theorem for the one-sample t -statistic was established in Wang (2011), which to our knowledge, is the best result for the t -statistic known up to date, or equivalently, self-normalized sums.

2.2.3. *More examples of two-sample U -statistics.* Beyond the two-sample t -statistic, we enumerate three more well-known two-sample U -statistics and refer to Nikitin and Ponikarov (2006) for more examples. Let $\mathcal{X} = \{X_1, \dots, X_{n_1}\}$ and $\mathcal{Y} = \{Y_1, \dots, Y_{n_2}\}$ be two independent random samples from population distributions P and Q , respectively.

EXAMPLE 2.1 (The Mann–Whitney test statistic). The kernel h is of order $(s_1, s_2) = (1, 1)$, defined as

$$h(x; y) = I\{x \leq y\} - 1/2 \quad \text{with } \theta = \mathbb{P}(X_1 \leq Y_1) - 1/2,$$

and in view of (2.3),

$$h_1(x) = 1/2 - G(x), \quad h_2(y) = F(y) - 1/2.$$

In particular, if $F \equiv G$, we have $\sigma_1^2 = \sigma_2^2 = 1/12$.

EXAMPLE 2.2 (The Lehmann statistic). The kernel h is of order $(s_1, s_2) = (2, 2)$, defined as

$$h(x_1, x_2; y_1, y_2) = I\{|x_1 - x_2| \leq |y_1 - y_2|\} - 1/2$$

with $\theta = \mathbb{P}(|X_1 - X_2| \leq |Y_1 - Y_2|) - 1/2$. Then under $H_0 : \theta = 0$, $\mathbb{E}\{h(X_1, X_2; Y_1, Y_2)\} = 0$, and

$$h_1(x) = G(x)\{1 - G(x)\} - 1/6, \quad h_2(y) = F(y)\{F(y) - 1\} + 1/6.$$

In particular, if $F \equiv G$, then $\sigma_1^2 = \sigma_2^2 = 1/180$.

EXAMPLE 2.3 (The Kochar statistic). The Kochar statistic was constructed by Kochar (1979) to test if the two hazard failure rates are different. Denote by $\mathcal{F}$ the class of all absolutely continuous cumulative distribution functions (CDF) $F(\cdot)$ satisfying $F(0) = 0$. For two arbitrary CDF's $F, G \in \mathcal{F}$, and let $f = F'$, $g = G'$ be their densities. Thus, the hazard failure rates are defined by

$$r_F(t) = \frac{f(t)}{1 - F(t)}, \quad r_G(t) = \frac{g(t)}{1 - G(t)},$$

as long as both $1 - F(t)$ and $1 - G(t)$ are positive. Kochar (1979) considered the problem of testing the null hypothesis $H_0 : r_F(t) = r_G(t)$ against the alternative $H_1 : r_F(t) \leq r_G(t), t \geq 0$ with strict inequality over a set of nonzero measures. Observe that H_1 holds if and only if $\delta(s, t) = \bar{F}(s)\bar{G}(t) - \bar{F}(t)\bar{G}(s) \geq 0$ for $s \geq t \geq 0$ with strict inequality over a set of nonzero measures, where $\bar{F}(\cdot) := 1 - F(\cdot)$ for any $F \in \mathcal{F}$.

Recall that $X_1, \dots, X_{n_1}$ and $Y_1, \dots, Y_{n_2}$ are two independent samples drawn respectively from F and G . Following Nikitin and Ponikarov (2006), we see that

$$\begin{aligned} \eta(F; G) &= \mathbb{E}\{\delta(X \vee Y, X \wedge Y)\} \\ &= \mathbb{P}(Y_1 \leq Y_2 \leq X_1 \leq X_2) + \mathbb{P}(X_1 \leq Y_2 \leq Y_2 \leq X_2) \\ &\quad - \mathbb{P}(X_1 \leq X_2 \leq Y_1 \leq Y_2) - \mathbb{P}(Y_1 \leq X_1 \leq X_2 \leq Y_2). \end{aligned}$$

Under H_0 , $\eta(F; G) = 0$ while under H_1 , $\eta(F; G) > 0$. The U -statistic with the kernel of order $(s_1, s_2) = (2, 2)$ is given by

$$h(x_1, x_2; y_1, y_2) = I\{yyxx \text{ or } xyxy\} - I\{xxyy \text{ or } yxxy\}.$$

Here, the term “ $yyxx$ ” refers to $y_1 \leq y_2 \leq x_1 \leq x_2$ and similar treatments apply to $xxyy$, $xxyy$ and $yxxy$. Under $H_0 : r_F(t) = r_G(t)$, we have

$$h_1(x) = -4G^3(x)/3 + 4G^2(x) - 2G(x),$$

$$h_2(y) = 4F^3(y)/3 - 4F^2(y) + 2F(y).$$

In particular, if $F \equiv G$, then $\sigma_1^2 = \sigma_2^2 = 8/105$.

3. Multiple testing via Studentized two-sample tests. Multiple-hypothesis testing occurs in a wide range of applications including DNA microarray experiments, functional magnetic resonance imaging analysis (fMRI) and astronomical surveys. We refer to [Dudoit and van der Laan \(2008\)](#) for a systematic study of the existing multiple testing procedures. In this section, we consider multiple-hypothesis testing based on Studentized two-sample tests and show how the theoretical results in the previous section can be applied to these problems.

3.1. Two-sample t -test. A typical application of multiple-hypothesis testing in high dimensions is the analysis of gene expression microarray data. To see whether each gene in isolation behaves differently in a control group versus an experimental group, we can apply the two-sample t -test. Assume that the statistical model is given by

$$(3.1) \quad \begin{cases} X_{i,k} = \mu_{1k} + \varepsilon_{i,k}, & i = 1, \dots, n_1, \\ Y_{j,k} = \mu_{2k} + \omega_{j,k}, & j = 1, \dots, n_2, \end{cases}$$

for $k = 1, \dots, m$, where index k denotes the k th gene, i and j indicate the i th and j th array, and the constants μ_{1k} and μ_{2k} , respectively, represent the mean effects for the k th gene from the first and the second groups. For each k , $\varepsilon_{1,k}, \dots, \varepsilon_{n_1,k}$ (resp., $\omega_{1,k}, \dots, \omega_{n_2,k}$) are independent random variables with mean zero and variance $\sigma_{1k}^2 > 0$ (resp., $\sigma_{2k}^2 > 0$). For the k th marginal test, when the population variances σ_{1k}^2 and σ_{2k}^2 are unequal, the two-sample t -statistic is most commonly used to carry out hypothesis testing for the null $H_0^k : \mu_{1k} = \mu_{2k}$ against the alternative $H_1^k : \mu_{1k} \neq \mu_{2k}$.

Since the seminal work of [Benjamini and Hochberg \(1995\)](#), the Benjamini and Hochberg (B-H) procedure has become a popular technique in microarray data analysis for gene selection, which along with many other procedures depend on p -values that often need to be estimated. To control certain simultaneous errors, it has been shown that using approximated p -values is asymptotically equivalent to using the true p -values for controlling the k -familywise error rate (k -FWER) and false discovery rate (FDR). See, for example, [Kosorok and Ma \(2007\)](#), [Fan, Hall](#)

and Yao (2007) and Liu and Shao (2010) for one-sample tests. Cao and Kosorok (2011) proposed an alternative method to control k -FWER and FDR in both large-scale one- and two-sample t -tests. A common thread among the aforementioned literature is that theoretically for the methods to work in controlling FDR at a given level, the number of features m and the sample size n should satisfy $\log m = o(n^{1/3})$.

Recently, Liu and Shao (2014) proposed a regularized bootstrap correction method for multiple one-sample t -tests so that the constraint on m may be relaxed to $\log m = o(n^{1/2})$ under less stringent moment conditions as assumed in Fan, Hall and Yao (2007) and Delaigle, Hall and Jin (2011). Using Theorem 2.4, we show that the constraint on m in large scale two-sample t -tests can be relaxed to $\log m = o(n^{1/2})$ as well. This provides theoretical justification of the effectiveness of the bootstrap method which is frequently used for skewness correction.

To illustrate the main idea, here we restrict our attention to the special case in which the observations are independent. Indeed, when test statistics are correlated, false discovery control becomes very challenging under arbitrary dependence. Various dependence structures have been considered in the literature. See, for example, Benjamini and Yekutieli (2001), Storey, Taylor and Siegmund (2004), Ferreira and Zwiderman (2006), Leek and Storey (2008), Friguet, Kloareg and Causeur (2009) and Fan, Han and Gu (2012), among others. For completeness, we generalize the results to the dependent case in Section 3.1.3.

3.1.1. Normal calibration and phase transition. Consider the large-scale significance testing problem:

$$H_0^k : \mu_{1k} = \mu_{2k} \quad \text{versus} \quad H_1^k : \mu_{1k} \neq \mu_{2k}, \quad 1 \leq k \leq m.$$

Let V and R denote, respectively, the number of false rejections and the number of total rejections. The well-known false discovery proportion (FDP) is defined as the ratio $\text{FDP} = V / \max(1, R)$, and FDR is the expected FDP, that is, $\mathbb{E}\{V / \max(1, R)\}$. Benjamini and Hochberg (1995) proposed a distribution-free method for choosing a p -value threshold that controls the FDR at a prespecified level where $0 < \alpha < 1$. For $k = 1, \dots, m$, let p_k be the marginal p -value of the k th test, and let $p_{(1)} \leq \dots \leq p_{(m)}$ be the order statistics of $p_1, \dots, p_m$. For a predetermined control level $\alpha \in (0, 1)$, the B–H procedure rejects hypotheses for which $p_k \leq p_{(\hat{k})}$, where

$$(3.2) \quad \hat{k} = \max \left\{ 0 \leq k \leq m : p_{(k)} \leq \frac{\alpha k}{m} \right\}$$

with $p_{(0)} = 0$.

In microarray analysis, two-sample t -tests are often used to identify differentially expressed genes between two groups. Let

$$T_k = \frac{\bar{X}_k - \bar{Y}_k}{\sqrt{\hat{\sigma}_{1k}^2 n_1^{-1} + \hat{\sigma}_{2k}^2 n_2^{-1}}}, \quad k = 1, \dots, m,$$

where $\bar{X}_k = n_1^{-1} \sum_{i=1}^{n_1} X_{i,k}$, $\bar{Y}_k = n_2^{-1} \sum_{j=1}^{n_2} Y_{j,k}$ and

$$\hat{\sigma}_{1k}^2 = \frac{1}{n_1 - 1} \sum_{i=1}^{n_1} (X_{i,k} - \bar{X}_k)^2, \quad \hat{\sigma}_{2k}^2 = \frac{1}{n_2 - 1} \sum_{j=1}^{n_2} (Y_{j,k} - \bar{Y}_k)^2.$$

Here and below, $\{X_{i,1}, \dots, X_{i,m}\}_{i=1}^{n_1}$ and $\{Y_{j,1}, \dots, Y_{j,m}\}_{j=1}^{n_2}$ are independent random samples from $\{X_1, \dots, X_m\}$ and $\{Y_1, \dots, Y_m\}$, respectively, generated according to model (3.1), which are usually non-Gaussian in practice. Moreover, assume that the sample sizes of the two samples are of the same order, that is, $n_1 \asymp n_2$.

Before stating the main results, we first introduce a number of notation. Set $\mathcal{H}_0 = \{1 \leq k \leq m : \mu_{1k} = \mu_{2k}\}$, let $m_0 = \#\mathcal{H}_0$ denote the number of true null hypotheses and $m_1 = m - m_0$. Both $m = m(n_1, n_2)$ and $m_0 = m_0(n_1, n_2)$ are allowed to grow as $n = n_1 \wedge n_2$ increases. We assume that

$$\lim_{n \rightarrow \infty} \frac{m_0}{m} = \pi_0 \in (0, 1].$$

In line with the notation used in Section 2, set

$$\sigma_{1k}^2 = \text{var}(X_k), \quad \sigma_{2k}^2 = \text{var}(Y_k),$$

$$\gamma_{1k} = \mathbb{E}\{(X_k - \mu_{1k})^3\}, \quad \gamma_{2k} = \mathbb{E}\{(Y_k - \mu_{2k})^3\}$$

and $\sigma_{\bar{n},k}^2 = \sigma_{1k}^2 n_1^{-1} + \sigma_{2k}^2 n_2^{-1}$. Throughout this subsection, we focus on the normal calibration and let $\hat{p}_k = 2 - 2\Phi(|T_k|)$, where $\Phi(\cdot)$ is the standard normal distribution function. Indeed, the exact null distribution of T_k and thus the true p -values are unknown without the normality assumption.

THEOREM 3.1. *Assume that $\{X_1, \dots, X_m, Y_1, \dots, Y_m\}$ are independent non-degenerate random variables; $n_1 \asymp n_2$, $m = m(n_1, n_2) \rightarrow \infty$ and $\log m = o(n^{1/2})$ as $n = n_1 \wedge n_2 \rightarrow \infty$. For independent random samples $\{X_{i,1}, \dots, X_{i,m}\}_{i=1}^{n_1}$ and $\{Y_{j,1}, \dots, Y_{j,m}\}_{j=1}^{n_2}$, suppose that*

$$(3.3) \quad \min_{1 \leq k \leq m} \min(\sigma_{1k}, \sigma_{2k}) \geq c > 0, \quad \max_{1 \leq k \leq m} \max\{\mathbb{E}(\xi_k^4), \mathbb{E}(\eta_k^4)\} \leq C < \infty$$

for some constants C and c , where $\xi_k = \sigma_{1k}^{-1}(X_k - \mu_{1k})$ and $\eta_k = \sigma_{2k}^{-1}(Y_k - \mu_{2k})$. Moreover, assume that

$$(3.4) \quad \#\{1 \leq k \leq m : |\mu_{1k} - \mu_{2k}| \geq 4(\log m)^{1/2} \sigma_{\bar{n},k}\} \rightarrow \infty$$

as $n \rightarrow \infty$, and let

$$(3.5) \quad c_0 = \liminf_{n, m \rightarrow \infty} \left\{ \frac{n^{1/2}}{m_0} \sum_{k \in \mathcal{H}_0} \sigma_{\bar{n},k}^{-3} |\gamma_{1k} n_1^{-2} - \gamma_{2k} n_2^{-2}| \right\}.$$

(i) *Suppose that $\log m = o(n^{1/3})$. Then as $n \rightarrow \infty$, $\text{FDP}_\Phi \xrightarrow{P} \alpha \pi_0$ and $\text{FDR}_\Phi \rightarrow \alpha \pi_0$.*

(ii) Suppose that $c_0 > 0$, $\log m \geq c_1 n^{1/3}$ for some $c_1 > 0$ and that $\log m_1 = o(n^{1/3})$. Then there exists some constant $\beta \in (\alpha, 1]$ such that

$$\lim_{n \rightarrow \infty} \mathbb{P}(\text{FDP}_\Phi \geq \beta) = 1 \quad \text{and} \quad \liminf_{n \rightarrow \infty} \text{FDR}_\Phi \geq \beta.$$

(iii) Suppose that $c_0 > 0$, $(\log m)/n^{1/3} \rightarrow \infty$ and $\log m_1 = o(n^{1/3})$. Then as $n \rightarrow \infty$, $\text{FDP}_\Phi \xrightarrow{P} 1$ and $\text{FDR}_\Phi \rightarrow 1$.

Here, FDR_Φ and FDP_Φ denote, respectively, the FDR and the FDP of the B-H procedure with p_k replaced by $\hat{p}_k$ in (3.2).

Together, conclusions (i) and (ii) of Theorem 3.1 indicate that the number of simultaneous tests can be as large as $\exp\{o(n^{1/3})\}$ before the normal calibration becomes inaccurate. In particular, when $n_1 = n_2 = n$, the skewness parameter c_0 given in (3.5) reduces to

$$c_0 = \liminf_{m \rightarrow \infty} \left\{ \frac{1}{m_0} \sum_{k \in \mathcal{H}_0} \frac{|\gamma_{1k} - \gamma_{2k}|}{(\sigma_{1k}^2 + \sigma_{2k}^2)^{3/2}} \right\}.$$

As noted in Liu and Shao (2014), the limiting behavior of the FDR_Φ varies in different regimes and exhibits interesting phase transition phenomena as the dimension m grows as a function of (n_1, n_2) . The average of skewness c_0 plays a crucial role. It is also worth noting that conclusions (ii) and (iii) hold under the scenario $\pi_0 = 1$, that is, $m_1 = o(m)$. This corresponds to the sparse settings in applications such as gene detections. Under finite 4th moments of X_k and Y_k , the robustness of two-sample t -tests and the accuracy of normal calibration in the FDR/FDP control have been investigated in Cao and Kosorok (2011) when $m_1/m \rightarrow \pi_1 \in (0, 1)$. This corresponds to the relatively dense setting, and the sparse case that we considered above is not covered.

3.1.2. Bootstrap calibration and regularized bootstrap correction. In this subsection, we first use the conventional bootstrap calibration to improve the accuracy of FDR control based on the fact that the bootstrap approximation removes the skewness term that determines first-order inaccuracies of the standard normal approximation. However, the validity of bootstrap approximation requires the underlying distribution to be very light tailed, which does not seem realistic in real data applications. As pointed in the literature of gene study, many gene data are commonly recognized to have heavy tails which violates the assumption on underlying distribution used to make conventional bootstrap approximation work. Recently, Liu and Shao (2014) proposed a regularized bootstrap method that is shown to be more robust against the heavy tailedness of the underlying distribution and the dimension m is allowed to be as large as $\exp\{o(n^{1/2})\}$.

Let $\mathcal{X}_{k,b}^\dagger = \{X_{1,k,b}^\dagger, \dots, X_{n_1,k,b}^\dagger\}$, $\mathcal{Y}_{k,b}^\dagger = \{Y_{1,k,b}^\dagger, \dots, Y_{n_2,k,b}^\dagger\}$, $b = 1, \dots, B$, denote bootstrap samples drawn independently and uniformly, with replacement,

from $\mathcal{X}_k = \{X_{1,k}, \dots, X_{n_1,k}\}$ and $\mathcal{Y}_k = \{Y_{1,k}, \dots, Y_{n_2,k}\}$, respectively. Let $T_{k,b}^\dagger$ be the two-sample t -statistic constructed from $\{X_{1,k,b}^\dagger - \bar{X}_k, \dots, X_{n_1,k,b}^\dagger - \bar{X}_k\}$ and $\{Y_{1,k,b}^\dagger - \bar{Y}_k, \dots, Y_{n_2,k,b}^\dagger - \bar{Y}_k\}$. Following Liu and Shao (2014), we use the following empirical distribution:

$$F_{m,B}^\dagger(t) = \frac{1}{mB} \sum_{k=1}^m \sum_{b=1}^B I\{|T_{k,b}^\dagger| \geq t\}$$

to approximate the null distribution, and thus the estimated p -values are given by $\hat{p}_{k,B} = F_{m,B}^\dagger(|T_k|)$. Respectively, FDP_B and FDR_B denote the FDP and the FDR of the B-H procedure with p_k replaced by $\hat{p}_{k,B}$ in (3.2).

The following result shows that the bootstrap calibration is accurate provided $\log m$ increases at a strictly slower rate than $(n_1 \wedge n_2)^{1/2}$, and the underlying distribution has sub-Gaussian tails.

THEOREM 3.2. *Assume the conditions in Theorem 3.1 hold and that*

$$\max_{1 \leq k \leq m} \max\{\mathbb{E}(e^{t_0 \xi_k^2}), \mathbb{E}(e^{t_0 \eta_k^2})\} \leq C < \infty$$

for some constants $t_0, C > 0$.

(i) *Suppose that $\log m = o(n^{1/3})$. Then as $n \rightarrow \infty$, $\text{FDP}_B \xrightarrow{P} \alpha \pi_0$ and $\text{FDR}_B \rightarrow \alpha \pi_0$.*

(ii) *Suppose that $\log m = o(n^{1/2})$ and $m_1 \leq m^\rho$ for some $\rho \in (0, 1)$. Then as $n \rightarrow \infty$, $\text{FDP}_B \xrightarrow{P} \alpha$ and $\text{FDR}_B \rightarrow \alpha$.*

The sub-Gaussian condition in Theorem 3.2 is quite stringent in practice, whereas it can hardly be weakened in general when the bootstrap method is applied. In the context of family-wise error rate control, Fan, Hall and Yao (2007) proved that the bootstrap calibration is accurate if the observed data are bounded and $\log m = o(n^{1/2})$. The regularized bootstrap method, however, adopts the very similar idea of the trimmed estimators and is a two-step procedure that combines the truncation technique and the bootstrap method.

First, define the trimmed samples

$$\hat{X}_{i,k} = X_{i,k} I\{|X_{i,k}| \leq \lambda_{1k}\}, \quad \hat{Y}_{j,k} = Y_{j,k} I\{|Y_{j,k}| \leq \lambda_{2k}\}$$

for $i = 1, \dots, n_1, j = 1, \dots, n_2$, where λ_{1k} and λ_{2k} are regularized parameters to be specified. Let $\hat{\mathcal{X}}_{k,b}^\dagger = \{\hat{X}_{1,k,b}^\dagger, \dots, \hat{X}_{n_1,k,b}^\dagger\}$ and $\hat{\mathcal{Y}}_{k,b}^\dagger = \{\hat{Y}_{1,k,b}^\dagger, \dots, \hat{Y}_{n_2,k,b}^\dagger\}$, $b = 1, \dots, B$, be the corresponding bootstrap samples drawn by sampling randomly, with replacement, from

$$\hat{\mathcal{X}}_k = \{\hat{X}_{1,k}, \dots, \hat{X}_{n_1,k}\} \quad \text{and} \quad \hat{\mathcal{Y}}_k = \{\hat{Y}_{1,k}, \dots, \hat{Y}_{n_2,k}\},$$

respectively. Next, let $\hat{T}_{k,b}^\dagger$ be the two-sample t -test statistic constructed from $\{\hat{X}_{1,k,b}^\dagger - n_1^{-1} \sum_{i=1}^{n_1} \hat{X}_{i,k}, \dots, \hat{X}_{n_1,k,b}^\dagger - n_1^{-1} \sum_{i=1}^{n_1} \hat{X}_{i,k}\}$ and $\{\hat{Y}_{1,k,b}^\dagger - n_2^{-1} \sum_{j=1}^{n_2} \hat{Y}_{j,k}, \dots, \hat{Y}_{n_2,k,b}^\dagger - n_2^{-1} \sum_{j=1}^{n_2} \hat{Y}_{j,k}\}$.

$\sum_{j=1}^{n_2} \hat{Y}_{j,k}, \dots, \hat{Y}_{n_2,k,b}^\dagger - n_2^{-1} \sum_{j=1}^{n_2} \hat{Y}_{j,k}\}$. As in the previous procedure, define the estimated p -values by

$$\hat{p}_{k,\text{RB}} = \hat{F}_{m,\text{RB}}^\dagger(|T_k|) \quad \text{with } \hat{F}_{m,\text{RB}}^\dagger(t) = \frac{1}{mB} \sum_{k=1}^m \sum_{b=1}^B I\{|\hat{T}_{k,b}^\dagger| \geq t\}.$$

Let FDP_{RB} and FDR_{RB} denote the FDP and the FDR, respectively, of the B-H procedure with p_k replaced by $\hat{p}_{k,\text{RB}}$ in (3.2).

THEOREM 3.3. *Assume the conditions in Theorem 3.1 hold and that*

$$(3.6) \quad \max_{1 \leq k \leq m} \max\{\mathbb{E}(|X_k|^6), \mathbb{E}(|Y_k|^6)\} \leq C < \infty.$$

The regularized parameters $(\lambda_{1k}, \lambda_{2k})$ are such that

$$(3.7) \quad \lambda_{1k} \asymp \left(\frac{n_1}{\log m}\right)^{1/6} \quad \text{and} \quad \lambda_{2k} \asymp \left(\frac{n_2}{\log m}\right)^{1/6}.$$

(i) *Suppose that $\log m = o(n^{1/3})$. Then as $n \rightarrow \infty$, $\text{FDP}_{\text{RB}} \xrightarrow{P} \alpha\pi_0$ and $\text{FDR}_{\text{RB}} \rightarrow \alpha\pi_0$.*

(ii) *Suppose that $\log m = o(n^{1/2})$ and $m_1 \leq m^\rho$ for some $\rho \in (0, 1)$. Then as $n \rightarrow \infty$, $\text{FDP}_{\text{RB}} \xrightarrow{P} \alpha$ and $\text{FDR}_{\text{RB}} \rightarrow \alpha$.*

In view of Theorem 3.3, the regularized bootstrap approximation is valid under mild moment conditions that are significantly weaker than those required for the bootstrap method to work theoretically. The numerical performance will be investigated in Section 4. To highlight the main idea, a self-contained proof of Theorem 3.1 is given in the supplementary material [Chang, Shao and Zhou (2016)]. The proofs of Theorems 3.2 and 3.3 are based on straightforward extensions of Theorems 2.2 and 3.1 in Liu and Shao (2014), and thus are omitted.

3.1.3. FDR control under dependence. In this section, we generalize the results in previous sections to the dependence case. Write $\varrho = n_1/n_2$. For every $k, \ell = 1, \dots, m$, let $\sigma_k^2 = \sigma_{1k}^2 + \varrho\sigma_{2k}^2$ and define

$$(3.8) \quad r_{k\ell} = (\sigma_k\sigma_\ell)^{-1}\{\text{cov}(X_k, X_\ell) + \varrho\text{cov}(Y_k, Y_\ell)\},$$

which characterizes the dependence between (X_k, Y_k) and (X_ℓ, Y_ℓ) . Particularly, when $n_1 = n_2$ and $\sigma_{1k}^2 = \sigma_{2k}^2$, we see that $r_{k\ell} = \frac{1}{2}\{\text{corr}(X_k, X_\ell) + \text{corr}(Y_k, Y_\ell)\}$. In this subsection, we impose the following conditions on the dependence structure of $\mathbf{X} = (X_1, \dots, X_m)^\text{T}$ and $\mathbf{Y} = (Y_1, \dots, Y_m)^\text{T}$.

(D1) There exist constants $0 < r < 1$, $0 < \rho < (1-r)/(1+r)$ and $b_1 > 0$ such that

$$\max_{1 \leq k \neq \ell \leq m} |r_{k\ell}| \leq r \quad \text{and} \quad \max_{1 \leq k \leq m} s_k(m) \leq b_1 m^\rho,$$

where for $k = 1, \dots, m$,

$$s_k(m) = \{1 \leq \ell \leq m : \text{corr}(X_k, X_\ell) \geq (\log m)^{-2-\gamma} \\ \text{or } \text{corr}(Y_k, Y_\ell) \geq (\log m)^{-2-\gamma}\}$$

for some $\gamma > 0$.

(D2) There exist constants $0 < r < 1$, $0 < \rho < (1-r)/(1+r)$ and $b_1 > 0$ such that $\max_{1 \leq k \neq \ell \leq m} |r_{k\ell}| \leq r$ and for each X_k , the number of variables X_ℓ that are dependent of X_k is less than $b_1 m^\rho$.

The assumption $\max_{1 \leq k \neq \ell \leq m} |r_{k\ell}| \leq r$ for some $0 < r < 1$ imposes a constraint on the magnitudes of the correlations, which is natural in the sense that the correlation matrix $\mathbf{R} = (r_{k\ell})_{1 \leq k, \ell \leq m}$ is singular if $\max_{1 \leq k \neq \ell \leq m} |r_{k\ell}| = 1$. Under condition (D1), each (X_k, Y_k) is allowed to be “moderately” correlated with at most as many as $O(m^\rho)$ other vectors. Condition (D2) enforces a local dependence structure on the data, saying that each vector is dependent with at most as many as $O(m^\rho)$ other random vectors and independent of the remaining ones. The following theorem extends the results in previous sections to the dependence case. Its proof is placed in the supplementary material [Chang, Shao and Zhou (2016)].

THEOREM 3.4. *Assume that either condition (D1) holds with $\log m = O(n^{1/8})$ or condition (D2) holds with $\log m = o(n^{1/3})$.*

(i) *Suppose that (3.3) and (3.4) are satisfied. Then as $n \rightarrow \infty$, $\text{FDP}_\Phi \xrightarrow{P} \alpha\pi_0$ and $\text{FDR}_\Phi \rightarrow \alpha\pi_0$.*

(ii) *Suppose that (3.3), (3.6) and (3.7) are satisfied. Then as $n \rightarrow \infty$, $\text{FDP}_{\text{RB}} \xrightarrow{P} \alpha\pi_0$ and $\text{FDR}_{\text{RB}} \rightarrow \alpha\pi_0$.*

In particular, assume that condition (D2) holds with $\log m = o(n^{1/2})$ and $m_1 \leq m^c$ for some $0 < c < 1$. Then as $n \rightarrow \infty$, $\text{FDP}_{\text{RB}} \xrightarrow{P} \alpha\pi_0$ and $\text{FDR}_{\text{RB}} \rightarrow \alpha\pi_0$.

3.2. Studentized Mann–Whitney test. Let $\mathcal{X} = \{X_1, \dots, X_{n_1}\}$ and $\mathcal{Y} = \{Y_1, \dots, Y_{n_2}\}$ be two independent random samples from distributions F and G , respectively. Let $\theta = \mathbb{P}(X \leq Y) - 1/2$. Consider the null hypothesis $H_0 : \theta = 0$ against the one-sided alternative $H_1 : \theta > 0$. This problem arises in many applications including testing whether the physiological performance of an active drug is better than that under the control treatment, and testing the effects of a policy, such as unemployment insurance or a vocational training program, on the level of unemployment.

The Mann–Whitney (M–W) test [Mann and Whitney (1947)], also known as the two-sample Wilcoxon test [Wilcoxon (1945)], is prevalently used for testing equality of means or medians, and serves as a nonparametric alternative to the two-sample t -test. The corresponding test statistic is given by

$$(3.9) \quad U_{\bar{n}} = \frac{1}{n_1 n_2} \sum_{i=1}^{n_1} \sum_{j=1}^{n_2} I\{X_i \leq Y_j\}, \quad \bar{n} = (n_1, n_2).$$

The M–W test is widely used in a wide range of fields including statistics, economics and biomedicine, due to its good efficiency and robustness against parametric assumptions. Over one-third of the articles published in *Experimental Economics* use the Mann–Whitney test and Okeh (2009) reported that thirty percent of the articles in five biomedical journals published in 2004 used the Mann–Whitney test. For example, using the M–W U test, Charness and Gneezy (2009) developed an experiment to test the conjecture that financial incentives help to foster good habits. They recorded seven biometric measures (weight, body fat percentage, waist size, etc.) of each participant before and after the experiment to assess the improvements across treatments. Although the M–W test was originally introduced as a rank statistic to test if the distributions of two related samples are identical, it has been prevalently used for testing equality of medians or means, sometimes as an alternative to the two-sample t -test.

It was argued and formally examined recently in Chung and Romano (2016) that the M–W test has generally been misused across disciplines. In fact, the M–W test is only valid if the underlying distributions of the two groups are identical. Nevertheless, when the purpose is to test the equality of distributions, it is recommended to use a statistic, such as the Kolmogorov–Smirnov or the Cramér–von Mises statistic, that captures the discrepancies of the entire distributions rather than an individual parameter. More specifically, because the M–W test only recognizes deviation from $\theta = 0$, it does not have much power in detecting overall distributional discrepancies. Alternatively, the M–W test is frequently used to test the equality of medians. However, Chung and Romano (2013) presented evidence that this is another improper application of the M–W test and suggested to use the Studentized median test.

Even when the M–W test is appropriately applied for testing $H_0 : \theta = 0$, the asymptotic variance depends on the underlying distributions, unless the two population distributions are identical. As Hall and Wilson (1991) pointed out, the application of resampling to pivotal statistics has better asymptotic properties in the sense that the rate of convergence of the actual significance level to the nominal significance level is more rapid when the pivotal statistics are resampled. Therefore, it is natural to use the Studentized Mann–Whitney test, which is asymptotic pivotal.

Let

$$(3.10) \quad \widehat{U}_{\bar{n}} = \widehat{\sigma}_{\bar{n}}^{-1}(U_{\bar{n}} - 1/2)$$

denote the Studentized test statistic for $U_{\bar{n}}$ as in (3.9), where $\widehat{\sigma}_{\bar{n}}^2 = \widehat{\sigma}_1^2 n_1^{-1} + \widehat{\sigma}_2^2 n_2^{-1}$,

$$\widehat{\sigma}_1^2 = \frac{1}{n_1 - 1} \sum_{i=1}^{n_1} \left(q_i - \frac{1}{n_1} \sum_{i=1}^{n_1} q_i \right)^2, \quad \widehat{\sigma}_2^2 = \frac{1}{n_2 - 1} \sum_{j=1}^{n_2} \left(p_j - \frac{1}{n_2} \sum_{j=1}^{n_2} p_j \right)^2$$

with $q_i = n_2^{-1} \sum_{j=1}^{n_2} I\{Y_j < X_i\}$ and $p_j = n_1^{-1} \sum_{i=1}^{n_1} I\{X_i \leq Y_j\}$.

When dealing with samples from a large number of geographical regions (suburbs, states, health service areas, etc.), one may need to make many statistical inferences simultaneously. Suppose we observe a family of paired groups, that is, for $k = 1, \dots, m$, $\mathcal{X}_k = \{X_{1,k}, \dots, X_{n_1,k}\}$, $\mathcal{Y}_k = \{Y_{1,k}, \dots, Y_{n_2,k}\}$, where the index k denotes the k th site. Assume that $\mathcal{X}_k$ is drawn from F_k , and independently, $\mathcal{Y}_k$ is drawn from G_k .

For each $k = 1, \dots, m$, we test the null hypothesis $H_0^k : \theta_k = \mathbb{P}(X_{1,k} \leq Y_{1,k}) - 1/2 = 0$ against the one-sided alternative $H_1^k : \theta_k > 0$. If H_0^k is rejected, we conclude that the treatment effect (of a drug or a policy) is acting within the k th area. Define the test statistic

$$\widehat{U}_{\bar{n},k} = \widehat{\sigma}_{\bar{n},k}^{-1}(U_{\bar{n},k} - 1/2),$$

where $\widehat{U}_{\bar{n},k}$ is constructed from the k th paired samples according to (3.10). Let

$$F_{\bar{n},k}(t) = \mathbb{P}(\widehat{U}_{\bar{n},k} \leq t | H_0^k) \quad \text{and} \quad \Phi(t) = \mathbb{P}(Z \leq t),$$

where Z is the standard normal random variable. Then the true p -values are $p_k = 1 - F_{\bar{n},k}(\widehat{U}_{\bar{n},k})$, and $\widehat{p}_k = 1 - \Phi(\widehat{U}_{\bar{n},k})$ denote the estimated p -values based on normal calibration.

To identify areas where the treatment effect is acting, we can use the B-H method to control the FDR at α level by rejecting the null hypotheses indexed by $\mathcal{S} = \{1 \leq k \leq m : \widehat{p}_k \leq \widehat{p}_{(\hat{k})}\}$, where $\hat{k} = \max\{1 \leq k \leq m : \widehat{p}_{(k)} \leq \alpha k/m\}$, and $\{\widehat{p}_{(k)}\}$ denote the ordered values of $\{\widehat{p}_k\}$. As before, let FDR_Φ be the FDR of the B-H method based on normal calibration.

Alternative to normal calibration, we can also consider bootstrap calibration. Recall that $\mathcal{X}_{k,b}^\dagger = \{X_{1,k,b}^\dagger, \dots, X_{n_1,k,b}^\dagger\}$ and $\mathcal{Y}_{k,b}^\dagger = \{Y_{1,k,b}^\dagger, \dots, Y_{n_2,k,b}^\dagger\}$, $b = 1, \dots, B$, are two bootstrap samples drawn independently and uniformly, with replacement, from $\mathcal{X}_k = \{X_{1,k}, \dots, X_{n_1,k}\}$ and $\mathcal{Y}_k = \{Y_{1,k}, \dots, Y_{n_2,k}\}$, respectively. For each $k = 1, \dots, m$, let $\widehat{U}_{\bar{n},k,b}^\dagger$ be the bootstrapped test statistic constructed from $\mathcal{X}_{k,b}^\dagger$ and $\mathcal{Y}_{k,b}^\dagger$, that is,

$$\widehat{U}_{\bar{n},k,b}^\dagger = \widehat{\sigma}_{\bar{n},k,b}^{-1} \left[U_{\bar{n},k,b} - \frac{1}{n_1 n_2} \sum_{i=1}^{n_1} \sum_{j=1}^{n_2} I\{X_{i,k} \leq Y_{j,k}\} \right],$$

where $U_{\bar{n},k,b}$ and $\widehat{\sigma}_{\bar{n},k,b}$ are the analogues of $U_{\bar{n}}$ given in (3.9) and $\widehat{\sigma}_{\bar{n}}$ specified below (3.10) via replacing X_i and Y_j by $X_{i,k,b}^\dagger$ and $Y_{j,k,b}^\dagger$, respectively. Using the empirical distribution function

$$\widehat{G}_{m,B}^\dagger(t) = \frac{1}{mB} \sum_{k=1}^m \sum_{b=1}^B I\{|\widehat{U}_{\bar{n},k,b}^\dagger| \leq t\},$$

we estimate the unknown p -values by $\widehat{p}_{k,B} = 1 - \widehat{G}_{m,B}^\dagger(\widehat{U}_{\bar{n},k,b}^\dagger)$. For a pre-determined $\alpha \in (0, 1)$, the null hypotheses indexed by $\mathcal{S}_B = \{1 \leq k \leq m : \widehat{p}_{k,B} \leq$

$\widehat{p}_{(\widehat{k}_B),B}$ are rejected, where $\widehat{k}_B = \max\{0 \leq k \leq m : \widehat{p}_{k,B} \leq \alpha k/m\}$. Denote by FDR_B the FDR of the B–H method based on bootstrap calibration.

Applying the general moderate deviation result (2.9) to Studentized Mann–Whitney statistics $\widehat{U}_{\bar{n},k}$ leads to the following result. The proof is based on a straightforward adaptation of the arguments we used in the proof of Theorem 3.1, and hence is omitted.

THEOREM 3.5. *Assume that $\{X_1, \dots, X_m, Y_1, \dots, Y_m\}$ are independent random variables with continuous distribution functions $X_k \sim F_k$ and $Y_j \sim G_k$. The triplet (n_1, n_2, m) is such that $n_1 \asymp n_2$, $m = m(n_1, n_2) \rightarrow \infty$, $\log m = o(n^{1/3})$ and $m^{-1}\#\{k = 1, \dots, m : \theta_k = 1/2\} \rightarrow \pi_0 \in (0, 1]$ as $n = n_1 \wedge n_2 \rightarrow \infty$. For independent samples $\{X_{i,1}, \dots, X_{i,m}\}_{i=1}^{n_1}$ and $\{Y_{j,1}, \dots, Y_{j,m}\}_{j=1}^{n_2}$, suppose that $\min_{1 \leq k \leq m} \min(\sigma_{1k}, \sigma_{2k}) \geq c > 0$ for some constant $c > 0$ and as $n \rightarrow \infty$,*

$$\#\{1 \leq k \leq m : |\theta_k - 1/2| \geq 4(\log m)^{1/2} \sigma_{\bar{n},k}\} \rightarrow \infty,$$

where $\sigma_{1k}^2 = \text{var}\{G_k(X_k)\}$, $\sigma_{2k}^2 = \text{var}\{F_k(Y_k)\}$ and $\sigma_{\bar{n},k}^2 = \sigma_{1k}^2 n_1^{-1} + \sigma_{2k}^2 n_2^{-1}$. Then as $n \rightarrow \infty$, $\text{FDP}_\Phi, \text{FDP}_B \xrightarrow{P} \alpha \pi_0$ and $\text{FDR}_\Phi, \text{FDR}_B \rightarrow \alpha \pi_0$.

Attractive properties of the bootstrap for multiple-hypothesis testing were first noted by Hall (1990) in the case of the mean rather than its Studentized counterpart. Now it has been rigorously proved that bootstrap methods are particularly effective in relieving skewness in the extreme tails which leads to second-order accuracy [Delaigle, Hall and Jin (2011), Fan, Hall and Yao (2007)]. It is interesting and challenging to investigate whether these advantages of the bootstrap can be inherited by multiple U -testing in either the standardized or the Studentized case.

4. Numerical study. In this section, we present numerical investigations for various calibration methods described in Section 3 when they are applied to two-sample large-scale multiple testing problems. We refer to the simulation for two-sample t -test and Studentized Mann–Whitney test as Sim_1 and Sim_2 , respectively. Assume that we observe two groups of m -dimensional gene expression data $\{\mathbf{X}_i\}_{i=1}^{n_1}$ and $\{\mathbf{Y}_j\}_{j=1}^{n_2}$, where $\mathbf{X}_1, \dots, \mathbf{X}_{n_1}$ and $\mathbf{Y}_1, \dots, \mathbf{Y}_{n_2}$ are independent random samples drawn from the distributions of $\mathbf{X}$ and $\mathbf{Y}$, respectively.

For Sim_1 , let $\mathbf{X}$ and $\mathbf{Y}$ be such that

$$(4.1) \quad \mathbf{X} = \boldsymbol{\mu}_1 + \{\boldsymbol{\varepsilon}_1 - \mathbb{E}(\boldsymbol{\varepsilon}_1)\} \quad \text{and} \quad \mathbf{Y} = \boldsymbol{\mu}_2 + \{\boldsymbol{\varepsilon}_2 - \mathbb{E}(\boldsymbol{\varepsilon}_2)\},$$

where $\boldsymbol{\varepsilon}_1 = (\varepsilon_{1,1}, \dots, \varepsilon_{1,m})^T$ and $\boldsymbol{\varepsilon}_2 = (\varepsilon_{2,1}, \dots, \varepsilon_{2,m})^T$ are two sets of i.i.d. random variables. The i.i.d. components of noise vectors $\boldsymbol{\varepsilon}_1$ and $\boldsymbol{\varepsilon}_2$ follow two types of distributions: (i) the exponential distribution $\text{Exp}(\lambda)$ with density function $\lambda^{-1} e^{-x/\lambda}$; (ii) Student t -distribution $t(k)$ with k degrees of freedom. The exponential distribution has nonzero skewness, while the t -distribution is symmetric and heavy-tailed. For each type of error distribution, both cases of homogeneity and

TABLE 1
Distribution settings in Sim₁

	Homogeneous case	Heteroscedastic case
Exponential distributions	$\varepsilon_{1,k} \sim \text{Exp}(2)$ $\varepsilon_{2,k} \sim \text{Exp}(2)$	$\varepsilon_{1,k} \sim \text{Exp}(2)$ $\varepsilon_{2,k} \sim \text{Exp}(1)$
Student t -distributions	$\varepsilon_{1,k} \sim t(4)$ $\varepsilon_{2,k} \sim t(4)$	$\varepsilon_{1,k} \sim t(4)$ $\varepsilon_{2,k} \sim t(3)$

heteroscedasticity were considered. Detailed settings for the error distributions are specified in Table 1.

For Sim₂, we assume that **X** and **Y** satisfy

(4.2) $\mathbf{X} = \boldsymbol{\mu}_1 + \boldsymbol{\varepsilon}_1 \quad \text{and} \quad \mathbf{Y} = \boldsymbol{\mu}_2 + \boldsymbol{\varepsilon}_2,$

where $\boldsymbol{\varepsilon}_1 = (\varepsilon_{1,1}, \dots, \varepsilon_{1,m})^T$ and $\boldsymbol{\varepsilon}_2 = (\varepsilon_{2,1}, \dots, \varepsilon_{2,m})^T$ are two sets of i.i.d. random variables. We consider several distributions for the error terms $\varepsilon_{1,k}$ and $\varepsilon_{2,k}$: standard normal distribution $N(0, 1)$, t -distribution $t(k)$, uniform distribution $U(a, b)$ and Beta distribution $\text{Beta}(a, b)$. Table 2 reports four settings of $(\varepsilon_{1,k}, \varepsilon_{2,k})$ used in our simulation. In either setting, we know $\mathbb{P}(\varepsilon_{1,k} \leq \varepsilon_{2,k}) = 1/2$ holds. Hence, the power against the null hypothesis $H_0^k : \mathbb{P}(X_k \leq Y_k) = 1/2$ will generate from the magnitude of the difference between the k th components of $\boldsymbol{\mu}_1$ and $\boldsymbol{\mu}_2$.

In both Sim₁ and Sim₂, we set $\boldsymbol{\mu}_1 = \mathbf{0}$, and assume that the first $m_1 = \lfloor 1.6m^{1/2} \rfloor$ components of $\boldsymbol{\mu}_2$ are equal to $c\{(\sigma_1^2 n_1^{-1} + \sigma_2^2 n_2^{-1}) \log m\}^{1/2}$ and the rest are zero. Here, σ_1^2 and σ_2^2 denote the variance of $\varepsilon_{1,k}$ and $\varepsilon_{2,k}$, and c is a parameter employed to characterize the location discrepancy between the distributions of **X** and **Y**. The sample size (n_1, n_2) was set to be (50, 30) and (100, 60), and the discrepancy parameter c took values in {1, 1.5}. The significance level α in the B–H procedure was specified as 0.05, 0.1, 0.2 and 0.3, and the dimension m was set to be 1000 and 2000. In Sim₁, we compared three different methods to calculate the p -values in the B–H procedure: normal calibration given in Section 3.1.1, bootstrap cali-

TABLE 2
Distribution settings in Sim₂

	Identical distributions	Nonidentical distributions
Case 1	$\varepsilon_{1,k} \sim N(0, 1)$ $\varepsilon_{2,k} \sim N(0, 1)$	$\varepsilon_{1,k} \sim N(0, 1)$ $\varepsilon_{2,k} \sim t(3)$
Case 2	$\varepsilon_{1,k} \sim U(0, 1)$ $\varepsilon_{2,k} \sim U(0, 1)$	$\varepsilon_{1,k} \sim U(0, 1)$ $\varepsilon_{2,k} \sim \text{Beta}(10, 10)$

bration and regularized bootstrap calibration proposed in Section 3.1.2. For regularized bootstrap calibration, we used a cross-validation approach as in Section 3 of Liu and Shao (2014) to choose regularized parameters λ_{1k} and λ_{2k} . In Sim₂, we compared the performance of normal calibration and bootstrap calibration proposed in Section 3.2. For each compared method, we evaluated its performance via two indices: the empirical FDR and the proportion among the true alternative hypotheses was rejected. We call the latter correct rejection proportion. If the empirical FDR is low, the proposed procedure has good FDR control; if the correct rejection proportion is high, the proposed procedure has fairly good performance in identifying the true signals. For ease of exposition, we only report the simulation results for $(n_1, n_2) = (50, 30)$ and $m = 1000$ in Figures 1 and 2. The results for $(n_1, n_2) = (100, 60)$ and $m = 2000$ are similar, which can be found in the supplementary material [Chang, Shao and Zhou (2016)]. Each curve corresponds to the performance of a certain method and the line types are specified in the caption below. The horizontal ordinates of the four points on each curve depict the empirical FDR of the specified method when the pre-specified level α in the B–H procedure was taken to be 0.05, 0.1, 0.2 and 0.3, respectively, and the vertical ordinates indicate the corresponding empirical correct rejection proportion. We say that a method has good FDR control if the horizontal ordinates of the four points on its performance curve are less than the prescribed α levels.

In general, as shown in Figures 1 and 2, the B–H procedure based on (regularized) bootstrap calibration has better FDR control than that based on normal calibration. In Sim₁ where the errors are symmetric (e.g., $\varepsilon_{1,k}$ and $\varepsilon_{2,k}$ follow the Student t -distributions), the panels in the first row of Figure 1 show that the B–H procedures using all the three calibration methods are able to control or approximately control the FDR at given levels, while the procedures based on bootstrap and regularized bootstrap calibrations outperform that based on normal calibration in controlling the FDR. When the errors are asymmetric in Sim₁, the performances of the three B–H procedures are different from those in the symmetric cases. From the second row of Figure 1, we see that the B–H procedure based on normal calibration is distorted in controlling the FDR while the procedure based on (regularized) bootstrap calibration is still able to control the FDR at given levels. This phenomenon is further evidenced by Figure 2 for Sim₂. Comparing the B–H procedures based on conventional and regularized bootstrap calibrations, we find that the former approach is uniformly more conservative than the latter in controlling the FDR. In other words, the B–H procedure based on regularized bootstrap can identify more true alternative hypotheses than that using conventional bootstrap calibration. This phenomenon is also revealed in the heteroscedastic case. As the discrepancy parameter c gets larger so that the signal is stronger, the correct rejection proportion of the B–H procedures based on all the three calibrations increase and the empirical FDR is closer to the prescribed level.

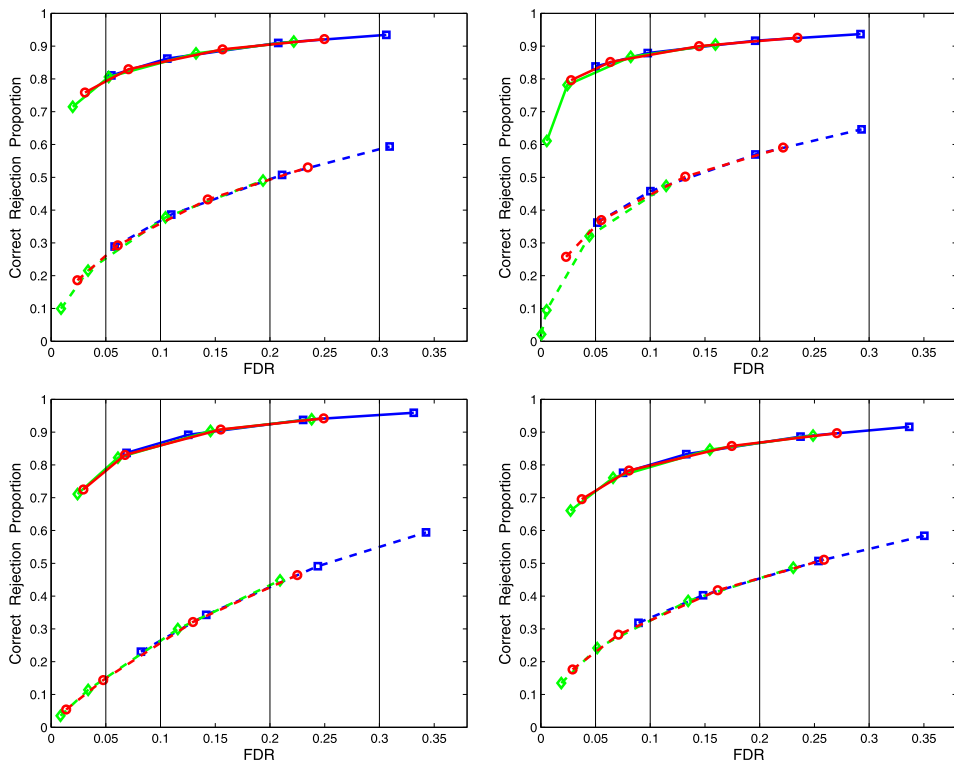


FIG. 1. Performance comparison of B - H procedures based on three calibration methods in Sim_1 with $(n_1, n_2) = (50, 30)$ and $m = 1000$. The first and second rows show the results when the components of noise vectors ε_1 and ε_2 follow t -distributions and exponential distributions, respectively; left and right panels show the results for homogeneous and heteroscedastic cases, respectively; horizontal and vertical axes depict empirical false discovery rate and empirical correct rejection proportion, respectively; and the prescribed levels $\alpha = 0.05, 0.1, 0.2$ and 0.3 are indicated by unbroken horizontal black lines. In each panel, dashed lines and unbroken lines represent the results for the discrepancy parameter $c = 1$ and 1.5 , respectively, and different colors express different methods employed to calculate p -values in the B - H procedure, where blue line, green line and red line correspond to the procedures based on normal, conventional and regularized bootstrap calibrations, respectively.

5. Discussion. In this paper, we established Cramér-type moderate deviations for two-sample Studentized U -statistics of arbitrary order in a general framework where the kernel is not necessarily bounded. Two-sample U -statistics, typified by the two-sample Mann–Whitney test statistic, have been widely used in a broad range of scientific research. Many of these applications rely on a misunderstanding of what is being tested and the implicit underlying assumptions, that were not explicitly considered until relatively recently by [Chung and Romano \(2016\)](#). More importantly, they provided evidence for the advantage of using the Studentized statistics both theoretically and empirically.

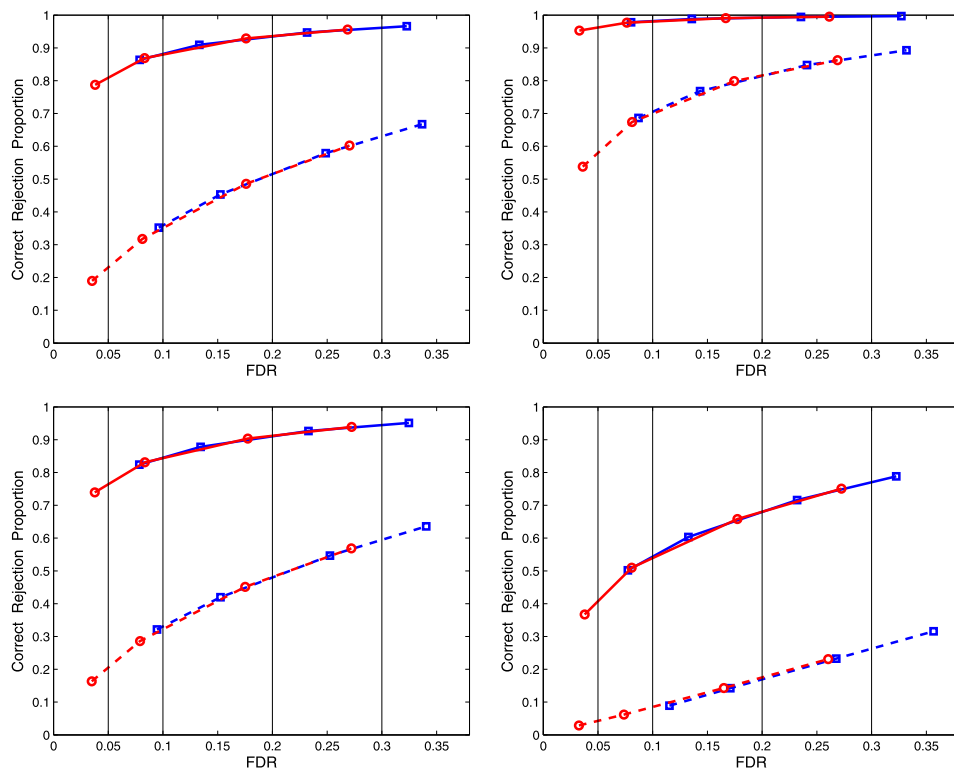


FIG. 2. Performance comparison of B-H procedures based on two different calibration methods in Sim_2 with $(n_1, n_2) = (50, 30)$ and $m = 1000$. The first and second rows show the results when the components of noise vectors $\mathbf{\varepsilon}_1$ and $\mathbf{\varepsilon}_2$ follow the distributions specified in cases 1 and 2 of Table 2, respectively; left and right panels show the results for the cases of identical distributions and non-identical distributions, respectively; horizontal and vertical axes depict empirical false discovery rate and empirical correct rejection proportion, respectively; and the prescribed levels $\alpha = 0.05, 0.1, 0.2$ and 0.3 are indicated by unbroken horizontal black lines. In each panel, dashed lines and unbroken lines represent the results for the discrepancy parameter $c = 1$ and 1.5 , respectively, and different colors express different methods employed to calculate p -values in the B-H procedure, where blue line and red line correspond to the procedures based on normal and bootstrap calibrations, respectively.

Unlike the conventional (one- and two-sample) U -statistics, the asymptotic behavior of their Studentized counterparts has barely been studied in the literature, particularly in the two-sample case. Recently, Shao and Zhou (2016) proved a Cramér-type moderate deviation theorem for general Studentized nonlinear statistics, which leads to a sharp moderate deviation result for Studentized one-sample U -statistics. However, extension from one-sample to two-sample in the Studentized case is totally nonstraightforward, and requires a more delicate analysis on the Studentizing quantities. Further, for the two-sample t -statistic, we proved moderate deviation with second-order accuracy under a finite 4th moment condition

(see Theorem 2.4), which is of independent interest. In contrast to the one-sample case, the two-sample t -statistic cannot be reduced to a self-normalized sum of independent random variables, and thus the existing results on self-normalized ratios [Jing, Shao and Wang (2003), Wang (2005, 2011)] cannot be directly applied. Instead, we modify Theorem 2.1 in Shao and Zhou (2016) to obtain a more precise expansion that can be used to derive a refined result for the two-sample t -statistic.

Finally, we show that the obtained moderate deviation theorems provide theoretical guarantees for the validity, including robustness and accuracy, of normal, conventional bootstrap and regularized bootstrap calibration methods in multiple testing with FDR/FDP control. The dependence case is also covered. These results represent a useful complement to those obtained by Fan, Hall and Yao (2007), Delaigle, Hall and Jin (2011) and Liu and Shao (2014) in the one-sample case.

Acknowledgements. The authors would like to thank Peter Hall and Aurore Delaigle for helpful discussions and encouragement. The authors sincerely thank the Editor, Associate Editor and three referees for their very constructive suggestions and comments that led to substantial improvement of the paper.

SUPPLEMENTARY MATERIAL

Supplement to “Cramér-type moderate deviations for Studentized two-sample U -statistics with applications” (DOI: [10.1214/15-AOS1375SUPP](https://doi.org/10.1214/15-AOS1375SUPP); .pdf). This supplemental material contains proofs for all the theoretical results in the main text, including Theorems 2.2, 2.4, 3.1 and 3.4, and additional numerical results.

REFERENCES

- BENJAMINI, Y. and HOCHBERG, Y. (1995). Controlling the false discovery rate: A practical and powerful approach to multiple testing. *J. R. Stat. Soc. Ser. B. Stat. Methodol.* **57** 289–300. [MR1325392](#)
- BENJAMINI, Y. and YEKUTIELI, D. (2001). The control of the false discovery rate in multiple testing under dependency. *Ann. Statist.* **29** 1165–1188. [MR1869245](#)
- BOROVSKICH, Y. V. (1983). Asymptotics of U -statistics and Von Mises’ functionals. *Soviet Math. Dokl.* **27** 303–308.
- CAO, H. and KOSOROK, M. R. (2011). Simultaneous critical values for t -tests in very high dimensions. *Bernoulli* **17** 347–394. [MR2797995](#)
- CHANG, J., SHAO, Q. and ZHOU, W.-X. (2016). Supplement to “Cramér-type moderate deviations for Studentized two-sample U -statistics with applications.” DOI:[10.1214/15-AOS1375SUPP](https://doi.org/10.1214/15-AOS1375SUPP).
- CHANG, J., TANG, C. Y. and WU, Y. (2013). Marginal empirical likelihood and sure independence feature screening. *Ann. Statist.* **41** 2123–2148. [MR3127860](#)
- CHANG, J., TANG, C. Y. and WU, Y. (2016). Local independence feature screening for nonparametric and semiparametric models by marginal empirical likelihood. *Ann. Statist.* **44** 515–539. [MR3476608](#)
- CHARNESS, G. and GNEEZY, U. (2009). Incentives to exercise. *Econometrica* **77** 909–931.
- CHEN, S. X. and QIN, Y.-L. (2010). A two-sample test for high-dimensional data with applications to gene-set testing. *Ann. Statist.* **38** 808–835. [MR2604697](#)

- CHEN, L. H. Y. and SHAO, Q.-M. (2007). Normal approximation for nonlinear statistics using a concentration inequality approach. *Bernoulli* **13** 581–599. [MR2331265](#)
- CHEN, S. X., ZHANG, L.-X. and ZHONG, P.-S. (2010). Tests for high-dimensional covariance matrices. *J. Amer. Statist. Assoc.* **105** 810–819. [MR2724863](#)
- CHUNG, E. and ROMANO, J. P. (2013). Exact and asymptotically robust permutation tests. *Ann. Statist.* **41** 484–507. [MR3099111](#)
- CHUNG, E. and ROMANO, J. (2016). Asymptotically valid and exact permutation tests based on two-sample U -statistics. *J. Statist. Plann. Inference.* **168** 97–105. [MR3412224](#)
- DELAIGLE, A., HALL, P. and JIN, J. (2011). Robustness and accuracy of methods for high dimensional data analysis based on Student's t -statistic. *J. R. Stat. Soc. Ser. B. Stat. Methodol.* **73** 283–301. [MR2815777](#)
- DUDOIT, S. and VAN DER LAAN, M. J. (2008). *Multiple Testing Procedures with Applications to Genomics*. Springer, New York. [MR3273771](#)
- FAN, J., HALL, P. and YAO, Q. (2007). To how many simultaneous hypothesis tests can normal, Student's t or bootstrap calibration be applied? *J. Amer. Statist. Assoc.* **102** 1282–1288. [MR2372536](#)
- FAN, J., HAN, X. and GU, W. (2012). Estimating false discovery proportion under arbitrary covariance dependence. *J. Amer. Statist. Assoc.* **107** 1019–1035. [MR3010887](#)
- FERREIRA, J. A. and ZWINDERMAN, A. H. (2006). On the Benjamini–Hochberg method. *Ann. Statist.* **34** 1827–1849. [MR2283719](#)
- FRIGUET, C., KLOAREG, M. and CAUSEUR, D. (2009). A factor model approach to multiple testing under dependence. *J. Amer. Statist. Assoc.* **104** 1406–1415. [MR2750571](#)
- HALL, P. (1990). On the relative performance of bootstrap and Edgeworth approximations of a distribution function. *J. Multivariate Anal.* **35** 108–129. [MR1084945](#)
- HALL, P. and WILSON, S. R. (1991). Two guidelines for bootstrap hypothesis testing. *Biometrics* **47** 757–762. [MR1132543](#)
- HELMERS, R. and JANSSEN, P. (1982). On the Berry–Esseen theorem for multivariate U -statistics. In *Math. Cent. Rep. SW* **90** 1–22. Mathematisch Centrum, Amsterdam.
- HOEFFDING, W. (1948). A class of statistics with asymptotically normal distribution. *Ann. Math. Statistics* **19** 293–325. [MR0026294](#)
- JING, B.-Y., SHAO, Q.-M. and WANG, Q. (2003). Self-normalized Cramér-type large deviations for independent random variables. *Ann. Probab.* **31** 2167–2215. [MR2016616](#)
- KOCHAR, S. C. (1979). Distribution-free comparison of two probability distributions with reference to their hazard rates. *Biometrika* **66** 437–441. [MR0556731](#)
- KOROLJUK, V. S. and BOROVSKICH, Y. V. (1994). *Theory of U -Statistics. Mathematics and Its Applications* **273**. Kluwer Academic, Dordrecht. [MR1472486](#)
- KOSOROK, M. R. and MA, S. (2007). Marginal asymptotics for the “large p , small n ” paradigm: With applications to microarray data. *Ann. Statist.* **35** 1456–1486. [MR2351093](#)
- KOWALSKI, J. and TU, X. M. (2007). *Modern Applied U -Statistics*. Wiley, Hoboken, NJ. [MR2368050](#)
- LAI, T. L., SHAO, Q.-M. and WANG, Q. (2011). Cramér type moderate deviations for Studentized U -statistics. *ESAIM Probab. Stat.* **15** 168–179. [MR2870510](#)
- LEEK, J. T. and STOREY, J. D. (2008). A general framework for multiple testing dependence. *Proc. Natl. Acad. Sci. USA* **105** 18718–18723.
- LI, R., ZHONG, W. and ZHU, L. (2012). Feature screening via distance correlation learning. *J. Amer. Statist. Assoc.* **107** 1129–1139. [MR3010900](#)
- LI, G., PENG, H., ZHANG, J. and ZHU, L. (2012). Robust rank correlation based screening. *Ann. Statist.* **40** 1846–1877. [MR3015046](#)
- LIU, W. and SHAO, Q.-M. (2010). Cramér-type moderate deviation for the maximum of the periodogram with application to simultaneous tests in gene expression time series. *Ann. Statist.* **38** 1913–1935. [MR2662363](#)

- LIU, W. and SHAO, Q.-M. (2014). Phase transition and regularized bootstrap in large-scale t -tests with false discovery rate control. *Ann. Statist.* **42** 2003–2025. [MR3262475](#)
- MANN, H. B. and WHITNEY, D. R. (1947). On a test of whether one of two random variables is stochastically larger than the other. *Ann. Math. Statistics* **18** 50–60. [MR0022058](#)
- NIKITIN, Y. and PONIKAROV, E. (2006). On large deviations of nondegenerate two-sample U - and V -statistics with applications to Bahadur efficiency. *Math. Methods Statist.* **15** 103–122. [MR2225432](#)
- OKEH, U. M. (2009). Statistical analysis of the application of Wilcoxon and Mann–Whitney U test in medical research studies. *Biotechnol. Molec. Biol. Rev.* **4** 128–131.
- SHAO, Q.-M. and ZHOU, W.-X. (2016). Cramér type moderate deviation theorems for self-normalized processes. *Bernoulli* **22** 2029–2079.
- STOREY, J. D., TAYLOR, J. E. and SIEGMUND, D. (2004). Strong control, conservative point estimation and simultaneous conservative consistency of false discovery rates: A unified approach. *J. R. Stat. Soc. Ser. B. Stat. Methodol.* **66** 187–205. [MR2035766](#)
- VANDEMAELE, M. and VERAVERBEKE, N. (1985). Cramér type large deviations for Studentized U -statistics. *Metrika* **32** 165–179. [MR0824452](#)
- WANG, Q. (2005). Limit theorems for self-normalized large deviation. *Electron. J. Probab.* **10** 1260–1285 (electronic). [MR2176384](#)
- WANG, Q. (2011). Refined self-normalized large deviations for independent random variables. *J. Theoret. Probab.* **24** 307–329. [MR2795041](#)
- WANG, Q. and HALL, P. (2009). Relative errors in central limit theorems for Student's t statistic, with applications. *Statist. Sinica* **19** 343–354. [MR2487894](#)
- WANG, Q., JING, B.-Y. and ZHAO, L. (2000). The Berry–Esseen bound for Studentized statistics. *Ann. Probab.* **28** 511–535. [MR1756015](#)
- WILCOXON, F. (1945). Individual comparisons by ranking methods. *Biometrics* **1** 80–83.
- ZHONG, P.-S. and CHEN, S. X. (2011). Tests for high-dimensional regression coefficients with factorial designs. *J. Amer. Statist. Assoc.* **106** 260–274. [MR2816719](#)

J. CHANG
SCHOOL OF STATISTICS
SOUTHWESTERN UNIVERSITY OF FINANCE
AND ECONOMICS
CHENGDU, SICHUAN 611130
CHINA
AND
SCHOOL OF MATHEMATICS AND STATISTICS
UNIVERSITY OF MELBOURNE
PARKVILLE, VICTORIA 3010
AUSTRALIA
E-MAIL: jingyuan.chang@unimelb.edu.au

Q.-M. SHAO
DEPARTMENT OF STATISTICS
CHINESE UNIVERSITY OF HONG KONG
SHATIN, NT
HONG KONG
E-MAIL: qmshao@cuhk.edu.hk

W.-X. ZHOU
DEPARTMENT OF OPERATIONS RESEARCH
AND FINANCIAL ENGINEERING
PRINCETON UNIVERSITY
PRINCETON, NEW JERSEY 08544
USA
AND
SCHOOL OF MATHEMATICS AND STATISTICS
UNIVERSITY OF MELBOURNE
PARKVILLE, VICTORIA 3010
AUSTRALIA
E-MAIL: wenzinx@princeton.edu