Optimality of the Westfall-Young permutation procedure for multiple testing under dependence

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Abstract

Test statistics are often strongly dependent in large-scale multiple testing applications. Most corrections for multiplicity are unduly conservative for correlated test statistics, resulting in a loss of power to detect true positives. We show that the Westfall-Young permutation method has asymptotically optimal power for a broad class of testing problems with a block-dependence and sparsity structure among the tests, when the number of tests tends to infinity.

1 Introduction

We consider multiple hypothesis testing where the underlying tests are dependent. Such testing problems arise in many applications, in particular in the fields of genomics and genome-wide association studies (Hirschhorn and Daly, 2005; McCarthy et al., 2008; Dudoit and Van der Laan, 2008), but also astronomy and other fields (Liang et al., 2002; Meinshausen and Rice, 2006). Popular multiple-testing procedures include the Bonferroni-Holm method (Holm, 1979) which strongly controls the family-wise error rate (FWER), and the Benjamini-Yekutieli procedure (Benjamini and Yekutieli, 2001) which controls the false discovery rate (FDR), both under arbitrary dependence structures between test statistics. If test statistics are strongly dependent, these procedures have low power to detect true positives. The reasons for this loss of power are well known: loosely speaking, many strongly dependent test-statistics carry only the information equivalent to fewer "effective" tests. Hence, instead of correcting among many multiple tests, one would in principle only need to correct for the smaller number of "effective" tests. Moreover, when controlling some error measure of false positives, an oracle would only need to adjust among the tests corresponding to true negatives. In large-scale sparse multiple testing situations, this latter issue is usually less important since the number

*These authors contributed equally to this work of true positives is typically small and the number of true negatives is close to the overall number of tests.

The dependence among tests can be taken into account by using the permutation-based Westfall-Young method (Westfall and Young, 1993), already used widely in practice (e.g., Cheung et al., 2005; Winkelmann et al., 2007). Under the assumption of subset-pivotality (see Section 2.3 for a definition), this method strongly controls the FWER under any kind of dependence structure (Westfall and Young, 1989).

In this paper we show that the Westfall-Young permutation method is an optimal procedure in the following sense. We introduce a single-step oracle multiple testing procedure, by defining a single threshold such that all hypotheses with p-values below this threshold are rejected. The oracle threshold is the largest threshold that still guarantees the desired level of the testing procedure. The oracle threshold is unknown in practice if the dependence among test statistics and the set of true null hypotheses are unknown. We show that the single-step Westfall-Young threshold approximates the oracle threshold for a broad class of testing problems with a block-dependence and sparsity structure among the tests, when the number of tests tends to infinity. Our notion of optimality with an oracle threshold is on a general level and for any test statistic. The power of a multiple testing procedure depends also on the data generating distribution and the chosen individual test(s): we do not discuss this aspect here. Instead, our goal is to analyze optimality once the individual tests have been specified.

Our optimality result has an immediate consequence for large-scale multiple testing: it is not possible to improve on the power of the Westfall-Young permutation method while still controlling the FWER when considering single-step multiple testing procedures for a large number of tests and assuming only a block dependence and sparsity structure among the tests (and no additional modeling assumptions about the dependence or clustering/grouping). Hence, in such situations, there is no need to consider ad-hoc proposals that are sometimes used in practice, at least when taking the viewpoint that multiple testing adjusted p-values should be as model free as possible.

1.1 Related work

There is a small but growing literature on optimality in multiple testing under dependence. Sun and Cai (2009) studied and proposed optimal decision procedures in a two-state hidden Markov model. The effect of correlation between test statistics on the level of FDR control was studied in Benjamini and Yekutieli (2001) and Benjamini et al. (2006); see also Blanchard and Roquain (2009) for FDR control under dependence. Furthermore, Clarke and Hall (2009) discuss the effect of dependence and clustering when using the "wrong" methods based on independence assumptions for controlling the (generalized) FWER and FDR. The effect of dependence on the power of Higher Criticism was examined in Hall and Jin (2008, 2010). Another viewpoint is given in Efron (2007) who proposed a novel empirical choice of an appropriate null distribution for large-scale significance testing. We do not propose new methodology in this manuscript but study instead the optimality of the widely used Westfall-Young permutation method (Westfall and Young, 1993) for dependent test statistics.

2 Single-step oracle procedure and the Westfall-Young method

After introducing some notation, we define our notion of a single-step oracle threshold and describe the Westfall-Young permutation method.

2.1 Preliminaries and notation

Let W be a data matrix consisting of n independent realizations of an m-dimensional random variable $X = (X_1, \ldots, X_m)$ with distribution P_m. To make this more concrete, consider the following setting that fits the examples described in Section 3.2. Let y be a deterministic variable, and allow the distribution of $X = X_y$ to depend on y. For each value $y^{(i)}$, $i = 1, \ldots, n$, we observe an independent sample $X^{(i)} = (X_1^{(i)}, \ldots, X_m^{(i)})$ of $X = X_{y^{(i)}}$. We then define W to be an $(m+1) \times n$ dimensional matrix by setting $W_{1,i} = y^{(i)}$ for $i = 1, \ldots, n$ and $W_{j+1,i} = X_j^{(i)}$ for $j = 1, \ldots, m$ and $i = 1, \ldots, n$. Thus, the first row of W contains the y-variables, and the ith column of W corresponds to the ith data sample $(y^{(i)}, X^{(i)})$.

Based on W, we want to test m null hypotheses H_j, $j = 1, \ldots, m$, concerning the m components $X_1, \ldots, X_m$ of X. Let $I(P_m) \subseteq \{1, \ldots, m\}$ be the indices of the true null hypotheses, and let $I'(P_m)$ be the indices of the true alternative hypotheses, that is, $I'(P_m) = \{1, \ldots, m\} \setminus I(P_m)$. Let P_0 be a distribution under the complete null hypothesis, i.e., $I(P_0) = \{1, \ldots, m\}$. We denote the class of all distributions under the complete null hypothesis by $\mathcal{P}_0$.

Suppose that the same test is applied for all hypotheses, and let $S_n \subseteq [0, 1]$ be the set of possible p-values this test can take. Thus, $S_n = [0, 1]$ for t-tests and related approaches, while S_n is discrete for permutation tests and rank-based tests. Let $p_j(W)$, $j = 1, \ldots, m$, be the p-values for the m hypotheses, based on the chosen test and the data W.

2.2 Single-step oracle multiple testing procedure

Suppose that we knew the true set of null hypotheses $I(P_m)$ and the distribution of $\min_{j \in I(P_m)} p_j(W)$ under P_m (which is of course not true in practice). Then we could define the following single-step oracle multiple testing procedure: reject H_j if $p_j(W) \le c_{m,n}(\alpha)$, where $c_{m,n}(\alpha)$ is the α-quantile of $\min_{j \in I(P_m)} p_j(W)$ under P_m:

$$c_{m,n}(\alpha) = \max\{s \in S_n : P_m(\min_{j \in I(P_m)} p_j(W) \le s) \le \alpha\}. \tag{1}$$

Throughout, we define the maximum of the empty set to be zero, corresponding to a threshold $c_{m,n}(\alpha)$ that leads to zero rejections.

This oracle procedure controls the FWER at level α, since by definition:

$$\begin{aligned} &P_m(H_j \text{ is rejected for at least one } j \in I(P_m)) \\ &= P_m(\min_{j\in I(P_m)} p_j(W) \le c_{m,n}(\alpha)) \ \le \ \alpha, \end{aligned}$$

and it is optimal in the sense that values $c \in S_n$ with $c > c_{m,n}(\alpha)$ no longer control the FWER at level α.

2.3 Single-step Westfall-Young multiple testing procedure

The Westfall-Young permutation method is based on the idea that under the complete null hypothesis, the distribution of W is invariant under a certain group of transformations $\mathcal{G}$, i.e., for every $g \in \mathcal{G}$, gW and W have the same distribution under $P_0 \in \mathcal{P}_0$. Romano and Wolf (2005) refer to this as the "randomization hypothesis". In the examples in Section 3.2, we let $\mathcal{G}$ be the collection of all permutations g of $(1, \dots, n)$, so that the number of elements $|\mathcal{G}|$ equals $n!$, and we let gW be the matrix obtained by permuting the *first* row of W (i.e., permuting the y-variables). Under the complete null hypothesis $P_0 \in \mathcal{P}_0$, the distribution of gW is then identical to the distribution of W for all $g \in \mathcal{G}$, so that the randomization hypothesis is satisfied. We suppress the dependence of $|\mathcal{G}|$ on the sample size n for notational simplicity.

The single-step Westfall-Young critical value is a random variable, defined as follows:

$$\begin{aligned} \hat{c}_{m,n}(\alpha) &= \max\left\{ s \in S_n : \frac{1}{|\mathcal{G}|}\sum_{g\in\mathcal{G}} 1\{\min_{j=1,\dots,m} p_j(gW) \le s\} \le \alpha \right\} \\ &= \max\left\{ s \in S_n : P^*(\min_{j=1,\dots,m} p_j(W) \le s) \le \alpha \right\}, \end{aligned}$$

where $1\{\cdot\}$ denotes the indicator function and P^* represents the permutation distribution:

$$P^*(f(W) \le x) = \frac{1}{|\mathcal{G}|}\sum_{g\in\mathcal{G}} 1\{f(gW) \le x\}, \tag{2}$$

for any function $f(\cdot)$ mapping W into $\mathbb{R}$. In other words, $\hat{c}_{m,n}(\alpha)$ is the α-quantile of the permutation distribution of $\min_{j=1,\dots,m} p_j(W)$. Our main result (Theorem 1) shows that under some conditions, the Westfall-Young threshold $\hat{c}_{m,n}(\alpha)$ approaches the oracle threshold $c_{m,n}(\alpha)$.

It is easy to see that the Westfall-Young permutation method provides weak control of the FWER, i.e., control of the FWER under the complete null hypothesis. Under the assumption of subset-pivotality, it also provides strong control of the FWER (Westfall and Young, 1993), i.e., control of the FWER under any set $I(P_m)$ of true null hypotheses. Subset-pivotality means that the distribution of $\{p_j(W) : j \in K\}$ is identical under the restrictions $\cap_{j\in K} H_j$ and $\cap_{j\in I(P_0)} H_j$ for all possible subsets $K \subseteq I(P_m)$ of true null hypotheses. Subset-pivotality is not a necessary condition for strong control, see, e.g., Romano and Wolf (2005), Westfall and Troendle (2008), and Goeman and Solari (2010).

3 Optimality of Westfall-Young

We consider the setting where the number of hypotheses m tends to infinity. This framework is suitable for high-dimensional settings arising for example in microarray experiments or genome-wide association studies.

3.1 Assumptions

(A1) Block independence: the p-values of all true null hypotheses adhere to a block independence structure that is preserved under permutations in $\mathcal{G}$. Specifically, there exists a partition $A_1, \ldots, A_{B_m}$ of $\{1, \ldots, m\}$ such that for any pair of permutations $g, g' \in \mathcal{G}$,

$$\min_{\tilde{g} \in \{g, g'\}} \min_{j \in A_b \cap I(P_m)} p_j(\tilde{g}W), \qquad b = 1, \ldots, B_m,$$

are mutually independent under P_m. Here, the number of blocks is denoted by $B = B_m$. (We assume without loss of generality that $A_b \cap I(P_m) \neq \emptyset$ for all $b = 1, \ldots, B$, meaning that there is at least one true null hypothesis in each block; otherwise, the condition would be required only for blocks with $A_b \cap I(P_m) \neq \emptyset$.)

(A2) Sparsity: The number of alternative hypotheses that are true under P_m is small compared to the number of blocks, i.e., $|I'(P_m)|/B_m \to 0$ as $m \to \infty$.

(A3) Block size: The maximum size of a block, $m_B := \max_{b=1,\ldots,B_m} |A_b|$, is of smaller order than the square root of the number of blocks, i.e., $m_B = o(\sqrt{B})$ as $m \to \infty$.

(B1) Let G be a random permutation taken uniformly from $\mathcal{G}$. Under P_m, the joint distribution of $\{p_j(W) : j \in I(P_m)\}$ is identical to the joint distribution of $\{p_j(GW) : j \in I(P_m)\}$

(B2) Let P^* be the permutation distribution (2). There exists a constant $r < \infty$ such that for $s = c_{m,n}(\alpha) \in S_n$ and all W,

$$r^{-1}s \;\leq\; P^*\big(p_j(W) \leq s\big) \;\leq\; rs \qquad \text{for all } j = 1, \ldots, m. \tag{3}$$

(B3) The p-values corresponding to true null hypotheses are uniformly distributed, i.e., for all $j \in I(P_m)$ and $s \in S_n$, we have $P_m(p_j(W) \leq s) = s$.

A sufficient condition for the block independence assumption (A1) is that for every fixed pair of permutations $g, g' \in \mathcal{G}$ the blocks of random variables $\{p_j(gW), p_j(g'W) : j \in A_b \cap I(P_m)\}$ are mutually independent for $b = 1, \ldots, B_m$. This condition is implied by block independence of the m last rows of W for the examples discussed in Section 3.2. The block independence assumption captures an essential characteristic of large-scale testing problems: a test statistic is often strongly correlated with a number of other test statistics but not at all with the remaining tests. The block-size assumption (A3) requires that the size of the blocks grows slower than the square root of the number of blocks. The sparsity assumption (A2) is also appropriate in many contexts. Most genome-wide association studies, for example, aim to discover just a few of locations on the genome that are associated with prevalence of a certain disease (Kruglyak, 1999; Marchini et al., 2005).

We now consider assumptions (B1)-(B3), supposing that we work with a data matrix W and a group of transformations $\mathcal{G}$ as described in Sections 2.1 and 2.3. Assumption (B1) is satisfied if each p-value $p_j(W)$ only depends on the 1st and $(j+1)$th rows of W. Moreover, subset-pivotality is satisfied in this setting. Assumption (B3) is satisfied for any test with valid type I error control. Assumption (B2) is fulfilled with $r = 1$ if for all W

$$P_G(p_j(GW) \leq s|W) = s, \quad j = 1, \dots, m, s \in S_n \tag{4}$$

where P_G is the probability with respect to a random permutation G taken uniformly from $\mathcal{G}$, so that the left hand side of (4) equals $P^*\big(p_j(W) \leq s\big)$ in (3). Note that assumptions (B1) and (B3) together imply that

$$P_{m,G}(p_j(GW) \leq s) = s, \quad j \in I(P_m), s \in S_n \tag{5}$$

where the probability $P_{m,G}$ is with respect to a random draw of the data W and a random permutation G taken uniformly from $\mathcal{G}$. Thus, assumption (B2) holds if (5) is true for all $j = 1, \dots, m$ and if conditioned on the observed data. Section 3.2 discusses three concrete examples that satisfy assumptions (B1)-(B3) and subset-pivotality.

Remark For our theorems in Section 3.3, it were sufficient if (3) were holding only with probability converging to 1 when sampling a random W, but we leave a deterministic bound since it is easier notationally, the extension is direct, and we are mostly interested in rank-based and conditional tests for which the deterministic bound holds.

3.2 Examples

We now give three examples that satisfy assumptions (B1)-(B3), as well as subset-pivotality. As in Section 2.1, let y be a deterministic scalar class variable and $X = (X_1, \dots, X_m)$ an m-dimensional vector of random variables, where the distribution of $X = X_y$ can depend on y. Let the data matrix W and the group of permutations $\mathcal{G}$ be defined as in Section 2.1 and Section 2.3, respectively. In all examples, we work with tests with valid type I error control, and each p-value $p_j(W)$ only depends on the 1st and $(j+1)$th rows of W. Hence, assumptions (B1), (B3) and subset-pivotality are satisfied, and we focus on assumption (B2) in the remainder.

For the examples in Sections 3.2.1 and 3.2.2, we assume that there exists a $\mu(y) \in \mathbb{R}^m$ and a m-dimensional random variable $Z = (Z_1, \dots, Z_m)$ such that

$$X = X_y = \mu(y) \ + \ Z. \tag{6}$$

We omit the dependence of $X = X_y$ on y in the following for notational simplicity.

3.2.1 Location-shift models

We consider two-sample testing problems for location shifts, similar to Example 5 of Romano and Wolf (2005). Using the notation in (6), $y \in \{1, 2\}$ is a binary class variable and the marginal distributions of Z are assumed to have a median of 0.

We are interested in testing the null hypotheses

$$H_j: \ \mu_j(1) = \mu_j(2), \quad j = 1, \ldots, m,$$

versus the corresponding two-sided alternatives:

$$H'_j: \ \mu_j(1) \neq \mu_j(2), \quad j = 1, \ldots, m.$$

We now discuss location-shift tests that satisfy assumption (B2) when used in the Westfall-Young permutation procedure. First, note that all permutation tests satisfy (B2) with $r = 1$, since the p-values in a permutation test are defined to fulfill $P^*\big(p_j(W) \leq s\big) = s$ for all $s \in S_n$. Permutation tests are often recommended in biomedical research (Ludbrook and Dudley, 1998) and other large scale location-shift testing applications due to their robustness with respect to the underlying distributions. For example, one can use the Wilcoxon test. Another example is a "permutation t-test": choose the p-value $p_j(W)$ as the proportion of permutations for which the absolute value of the t-test statistic is larger than or equal to the observed absolute value of the t-test statistic for H_j. Then condition (B2) is fulfilled with $r = 1$ with the added advantage that inference is exact and the type I error is guaranteed even if the distributional Gaussian assumption for the t-test is not fulfilled (Good, 2000). Computationally, such a "permutation t-test" procedure seems to involve two rounds of permutations: one for the computation of the marginal p-value and one for the Westfall-Young method, see (2). However, the computation of the marginal permutation p-value can be inferred from the permutations in the Westfall-Young method, as in Meinshausen (2006), and just a single round of permutations is thus necessary.

3.2.2 Marginal association

Suppose that we have a continuous variable y in formula (6). Based on the observed data, we want to test the null hypotheses of no association between variable X_j and y, that is,

$$H_j: \ \mu_j(y) \text{ is constant in } y, \qquad j = 1, \ldots, m,$$

versus the corresponding two-sided alternatives. A special case is the test for linear marginal association, where the functions $\mu_j(y)$ for $j = 1, \ldots, m$ are assumed to be of the form $\mu_j(y) = \gamma_j + \beta_j y$ and the test of no linear marginal association is based on the null hypotheses

$$H_j: \ \beta_j = 0, \qquad j = 1, \ldots, m.$$

Rank-based correlation test like Spearman's or Kendall's correlation coefficient are examples of tests that fulfill assumption (B2). Alternatively, a "permutation correlation-test" could be used, analogous to the "permutation t-test" described in Section 3.2.1.

3.2.3 Contingency tables

Contingency tables are our final example. Let $y \in \{1, 2, \ldots, K_y\}$ be a class variable with K_y distinct values. Likewise, assume that the random variable X is discrete and that each component of X can take K_x distinct values, $X = (X_1, \ldots, X_m) \in \{1, 2, \ldots, K_x\}^m$.

As an example, in many genome-wide association studies, the variables of interest are single nucleotide polymorphisms (SNPs). Each SNP j (denoted by X_j) can take three distinct values in general and it is of interest to see whether there is a relation between the occurrence rate of these categories and a category of a person's health status y (Kruglyak, 1999; Goode et al., 2002; Bond et al., 2005).

Based on the observed data, we want to test the null hypothesis for $j = 1, \ldots, m$ that the distribution of X_j does not depend on y,

$$H_j: \ P(X_j = k|y) = P(X_j = k) \text{ for all } k \in \{1, \ldots, K_x\} \text{ and } y \in \{1, \ldots, K_y\}.$$

The available data for hypothesis H_j is contained in the 1st and $(j+1)$th rows of W. These data can be summarized in a contingency table and Fisher's exact test can be used. Since the test is conditional on the marginal distributions, we have that $P(p_j(GW) \leq s|W) = s$ for a random permutation $G \in \mathcal{G}$ and (B2) is fulfilled.

3.3 Main result

We now look at the properties of the Westfall-Young permutation method and show asymptotic optimality in the sense that the estimated Westfall-Young threshold $\hat{c}_{m,n}(\alpha)$ is at least as large as the optimal oracle threshold $c_{m,n}(\alpha - \delta)$, where $\delta > 0$ can be arbitrarily small. This implies that the power of the Westfall-Young permutation method approaches the power of the oracle test, while providing strong control of the FWER under subset-pivotality (Westfall and Young, 1993). All proofs are given in Section 5.

Theorem 1. *Assume (A1)-(A3) and (B1)-(B3). Then for any $\alpha \in (0,1)$ and any $\delta \in (0, \alpha)$*

$$P_m\{\hat{c}_{m,n}(\alpha) \geq c_{m,n}(\alpha - \delta)\} \to 1 \quad \text{as } m \to \infty. \tag{7}$$

We note that the sample size n can be fixed and does not need to tend to infinity. However, if S_n is discrete, the sample size must increase with m to avoid a trivial result where the oracle threshold $c_{m,n}(\alpha - \delta)$ vanishes; see also Theorem 2 where this is made explicit for the Wilcoxon test in the location-shift model of Section 3.2.1.

Theorem 1 implies that the actual level of the Westfall-Young procedure converges to the desired level (up to possible discretization effects; see Section 3.4). To appreciate the statement in Theorem 1 in terms of power gain, consider a simple example. Assume that the m hypotheses form B blocks. In the most extreme scenario, test statistics are perfectly dependent within each block. Under the made assumptions, the oracle threshold (1) for each individual p-value is then

$$1 - \sqrt[B]{1 - \alpha},$$

which is larger than, but very closely approximated by α/B for large values of B. Thus, when controlling the FWER at level α, hypotheses can be rejected when their p-values are less than $1 - \sqrt[B]{1-\alpha}$ and certainly when their p-values are less than α/B. The value of B is, however, unknown in practice and the same holds for the block dependence structure between hypotheses. With a Bonferroni correction for the FWER at level α, hypotheses can be rejected when their p-values are less than α/m. If $m \gg B$, the power loss compared to the procedure with the oracle threshold is substantial, since the Bonferroni method is really controlling at an effective level of size $\alpha B/m$ instead of α. Theorem 1, in contrast, implies that the effective level under the Westfall-Young procedure converges to the desired level (again up to possible discretization effects).

3.4 Discretization effects with Wilcoxon test

We showed in the last section that the Westfall-Young permutation method is asymptotically equivalent to the oracle threshold under the made assumptions. In this section we look in more detail at the difference between the nominal and effective levels of the oracle multiple testing procedure. Controlling at nominal level α, the effective oracle level is defined as

$$\alpha_- = P_m\big\{ \min_{j \in I(P_m)} p_j(W) \leq c_{m,n}(\alpha) \big\}. \tag{8}$$

By definition, α_- is less than or equal to α. We now examine under which assumptions the effective level α_- can be replaced by the nominal level α. As a concrete example, we work with the following assumptions:

(W) The test is a two-sample Wilcoxon test with equal sample sizes $n_1 = n_2 = n/2$, applied to a location-shift model as defined in Section 3.2.1.

(A3') Block size: The maximum size of a block satisfies $m_B = O(1)$ as $m \to \infty$.

The restriction to equal sample sizes in (W) is only for technical simplicity. We then obtain the following result about the discretization error.

Theorem 2. *Assume (W). Then the oracle critical value $c_{m,n}(\alpha)$ is strictly positive when*

$$n \geq 2\log_2(m/\alpha) + 2.$$

When assuming in addition (A1), (A2) and (A3'), then the results of Theorem 1 hold, and for any $\alpha \in (0, 1)$ we have

$$\alpha_- \to \alpha,$$

as $m, n \to \infty$ such that $n/\log(m) \to \infty$.

The first result in Theorem 2 says that the oracle critical value for the test defined in (W) is non-trivial, even when the number of tests grows almost exponentially with sample size. Hence, in this setting the result from Theorem 1 still applies in a non-trivial way.

The second result in Theorem 2 gives sufficient criteria for the effective oracle level α_- to converge to α. It is conceivable that this result can also be obtained under a milder assumption than (A3'), but this requires a detailed study of the Wilcoxon p-values and we leave this for future work. The main takeaway message is that discreteness of the p-values does not change the optimality result fundamentally.

4 Discussion

We considered optimality of large-scale multiple testing under dependence within a non-parametric framework. We showed that, under certain assumptions, the Westfall-Young permutation method is optimal in the following sense: with probability converging to 1 as the number of tests increases, the Westfall-Young critical value for multiple testing at nominal level α is greater than or equal to the unknown oracle threshold at level $\alpha - \delta$ for any $\delta > 0$. This implies that the actual level of the Westfall-Young procedure converges to the effective oracle level α_-. To investigate the possible impact of discrete p-values, we studied a specific example and provided sufficient conditions that ensure that α_- converges to α.

We gave several examples that satisfy subset-pivotality and our assumptions (A1)-(A3) and (B1)-(B3). Most of these examples involve rank-based or permutation tests. These tests are appropriate for very high-dimensional testing problems. If the number of tests is in the thousands or even millions, extreme tail probabilities are required to claim significance, and these tail probabilities are more trustworthy under a non-parametric test than under a parametric test.

If the hypotheses are strongly dependent, the gain in power of the Westfall-Young method compared to a simple Bonferroni correction can be very substantial. This is a well-known empirical fact, and we have established here that this improvement is also optimal in the asymptotic framework we considered.

Our study and results could be expanded to include step-down procedures like Bonferroni-Holm (Holm, 1979) and the step-down Westfall-Young method (Westfall and Young, 1993; Ge et al., 2003). The distinction between a single-step and step-down procedures will be very marginal though in our sparse high-dimensional framework, since the number of rejected hypotheses will always be orders of magnitudes less than the total number of hypotheses.

5 Proofs

After introducing some additional notation in Section 5.1, the proof of Theorem 1 is in Section 5.2 and the proof of Theorem 2 is in Section 5.3.

5.1 Additional notation

Let $p^{(b)}(W)$ be the minimum p-value over all true null hypotheses in the bth block:

$$p^{(b)}(W) = \min_{j \in A_b \cap I(P_m)} p_j(W), \qquad b = 1, \ldots, B,$$

and let $\pi_b(c)$ denote the probability under P_m that $p^{(b)}(W)$ is less than or equal to a constant $c \in [0,1]$:

$$\pi_b(c) = P_m(p^{(b)}(W) \leq c), \qquad b = 1, \ldots, B.$$

Throughout, we denote the expected value, the variance, and the covariance under P_m by E_m, Var_m and Cov_m, respectively.

5.2 Proof of Theorem 1

Let $\alpha' \in (0,1)$ and $\delta' \in (0, \alpha')$. Let $\delta = \delta'/2$ and $\alpha = \alpha' - \delta'$. Then writing expression (7) in terms of α' and δ' is equivalent to

$$P_m\Big\{\hat{c}_{m,n}(\alpha + 2\delta) \geq c_{m,n}(\alpha)\Big\} \to 1, \qquad \text{as } m \to \infty.$$

By definition,

$$\hat{c}_{m,n}(\alpha + 2\delta) = \max\Big\{s \in S_n : P^*\big(\min_{j \in \{1,\ldots,m\}} p_j(W) \leq s\big) \leq \alpha + 2\delta\Big\}.$$

We thus have to show that

$$P_m\Big\{P^*\big(\min_{j \in \{1,\ldots,m\}} p_j(W) \leq c_{m,n}(\alpha)\big) \;\leq\; \alpha + 2\delta\Big\} \;\to\; 1 \tag{9}$$

as $m \to \infty$.

First, we show in Lemma 1 that there exists an $M < \infty$ such that

$$P^*\big(\min_{j \in \{1,\ldots,m\}} p_j(W) \leq c_{m,n}(\alpha)\big) \;\leq\; P^*\big(\min_{j \in I(P_m)} p_j(W) \leq c_{m,n}(\alpha)\big) + \delta$$

for all $m > M$ and for all W. This result is mainly due to the sparsity assumption (A2). Second, we show in Lemma 2 that

$$P_m\Big\{P^*\big(\min_{j \in I(P_m)} p_j(W) \leq c_{m,n}(\alpha)\big) \;\leq\; \alpha + \delta\Big\} \;\to\; 1 \qquad \text{for } m \to \infty. \tag{10}$$

Theorem 1 follows by combining these two results.

Lemma 1. *Let $\alpha \in (0,1)$, $\delta \in (0, \alpha)$, and assume (A1), (A2), (B2) and (B3). Then there exists an $M < \infty$ such that*

$$P^*\big(\min_{j \in \{1,\ldots,m\}} p_j(W) \leq c_{m,n}(\alpha)\big) \;\leq\; P^*\big(\min_{j \in I(P_m)} p_j(W) \leq c_{m,n}(\alpha)\big) + \delta$$

for all $m > M$ and for all W.

Proof. Note that $c_{m,n}(\alpha) \in S_n$ by definition. Using the union bound, we have for all $s \in S_n$ and all W:

$$P^*(\min_{j\in\{1,\dots,m\}} p_j(W) \le s) \;\le\; P^*(\min_{j\in I(P_m)} p_j(W) \le s) \;+\; \sum_{j\in I'(P_m)} P^*(p_j(W) \le s). \tag{11}$$

Hence, we only need to show that there exists an $M < \infty$ such that

$$\sum_{j\in I'(P_m)} P^*(p_j(W) \le c_{m,n}(\alpha)) \le \delta \tag{12}$$

for all $m > M$ and all W. By assumption (B2) with constant r,

$$\sum_{j\in I'(P_m)} P^*\left(p_j(W) \le c_{m,n}(\alpha)\right) \;\le\; |I'(P_m)| r c_{m,n}(\alpha) = r\frac{|I'(P_m)|}{B} B c_{m,n}(\alpha). \tag{13}$$

Since $|I'(P_m)|/B \to 0$ as $m \to \infty$ by assumption (A2), and $Bc_{m,n}(\alpha)$ is bounded above by $-\log(1-\alpha)$ under assumptions (A1) and (B3) (see Lemma 3), we can choose a $M < \infty$ such that the right hand side of (13) is bounded above by δ for all $m > M$. This proves the claim in (12) and completes the proof. □

Lemma 2. *Let $\alpha > 0$ and $\delta > 0$ and assume (A1), (A3), and (B1)-(B3). Then*

$$P_m\Big\{P^*\big(\min_{j\in I(P_m)} p_j(W) \le c_{m,n}(\alpha)\big) \;\le\; \alpha + \delta\Big\} \;\to\; 1 \qquad \text{as } m \to \infty.$$

Proof. Let $\epsilon > 0$. The statement in the lemma is equivalent to showing that there exists an $M < \infty$ such that

$$P_m\Big\{P^*\big(\min_{j\in I(P_m)} p_j(W) > c_{m,n}(\alpha)\big) < 1 - \alpha - \delta\Big\} < \epsilon \tag{14}$$

for all $m > M$. By definition,

$$\begin{aligned} P^*(\min_{j\in I(P_m)} p_j(W) > c_{m,n}(\alpha)) &= \frac{1}{|\mathcal{G}|}\sum_{g\in\mathcal{G}} 1\{\min_{j\in I(P_m)} p_j(gW) > c_{m,n}(\alpha)\} \\ &= \frac{1}{|\mathcal{G}|}\sum_{g\in\mathcal{G}} R(g,W), \end{aligned} \tag{15}$$

where

$$R(g,W) := 1\big\{\min_{j\in I(P_m)} p_j(gW) > c_{m,n}(\alpha)\big\}.$$

(We suppress the dependence on m, n, P_m and α for notational simplicity.)

Let G be a random permutation, chosen uniformly in $\mathcal{G}$, and let 1 denote the identity permutation. Then, by assumption (B1), it follows that

$$E_m\Big(\frac{1}{|\mathcal{G}|}\sum_{g\in\mathcal{G}} R(g,W)\Big) = E_{m,G}R(G,W) = E_m R(1,W).$$

By definition of $c_{m,n}(\alpha)$ (see (1)),

$$E_m R(1,W) = P_m(\min_{j\in I_{P_m}} p_j(W) > c_{m,n}(\alpha)) \geq 1-\alpha.$$

Hence, the desired result (14) follows from a Markov inequality as soon as one can show that the variance of (15) vanishes as $m\to\infty$, i.e., if

$$\mathrm{Var}_m\Big(\frac{1}{|\mathcal{G}|}\sum_{g\in\mathcal{G}} R(g,W)\Big) = \frac{1}{(|\mathcal{G}|)^2}\sum_{g,g'\in\mathcal{G}} \mathrm{Cov}_m\big(R(g,W),R(g',W)\big) = o(1) \tag{16}$$

as $m\to\infty$.

Let G,G' be two random permutations, drawn independently and uniformly from $\mathcal{G}$. Then

$$\mathrm{Cov}_{m,G,G'}\big(R(G,W),R(G',W)\big) = \frac{1}{(|\mathcal{G}|)^2}\sum_{g,g'\in\mathcal{G}} \mathrm{Cov}_m\big(R(g,W),R(g',W)\big).$$

Hence, in order to show (16), we only need to show that

$$\mathrm{Cov}_{m,G,G'}\big(R(G,W),R(G',W)\big) = o(1) \qquad \text{for } m\to\infty.$$

Define

$$R_b(g,W) := 1\{p^{(b)}(gW) > c_{m,n}(\alpha)\}, \tag{17}$$

so that $R(g,W) := \prod_{b=1}^B R_b(g,W)$. We then need to prove that, as $m\to\infty$,

$$E_{m,G,G'}\Big(\prod_{b=1}^B R_b(G,W)R_b(G',W)\Big) - \Big(E_{m,G}\big(\prod_{b=1}^B R_b(G,W)\big)\Big)^2 = o(1). \tag{18}$$

Using assumption (A1), the left hand side in (18) can be written as

$$\prod_{b=1}^B E_{m,G,G'}\{R_b(G,W)R_b(G',W)\} - \prod_{b=1}^B \left[E_{m,G}\{R_b(G,W)\}\right]^2.$$

Note that $E_{m,G,G'}\{R_b(G,W)R_b(G',W)\}$ and $[E_{m,G}\{R_b(G,W)\}]^2$ are bounded between 0 and 1. For sequences of numbers $a_1,\ldots,a_B$ and $b_1,\ldots,b_B$ that are bounded between 0 and 1, the following inequality holds:

$$\left|\prod_{j=1}^B a_j - \prod_{j=1}^B b_j\right| = \left|\sum_{j=1}^B \left\{(a_j-b_j)\left(\prod_{k<j} b_k\right)\left(\prod_{k>j} a_k\right)\right\}\right| \leq \sum_{j=1}^B |a_j-b_j|.$$

Hence, in order to show (18) it is sufficient to show that

$$\max_{b=1,\dots,B} \left| E_{m,G,G'}\{R_b(G,W)R_b(G',W)\} - \big[E_{m,G}\{R_b(G,W)\}\big]^2 \right| = o(B^{-1}) \tag{19}$$

as $m \to \infty$.

Conditional on W,

$$R_b(G,W), R_b(G',W) \overset{i.i.d}{\sim} \textit{Bernoulli}(\mu_b(W)),$$

where $\mu_b(W)$ is the proportion of all permutations $g \in \mathcal{G}$ for which $R_b(g,W) = 1$ or, equivalently,

$$\mu_b(W) \;=\; P_{m,G}\big\{p^{(b)}(GW) > c_{m,n}(\alpha)|W\big\} \;=\; P^*\big\{p^{(b)}(W) > c_{m,n}(\alpha)\big\}. \tag{20}$$

Thus, the random proportion $\mu_b(W)$ is a function of W. Denote its distribution by F_b. Using Lemma 4, the support of F_b is contained in the interval $[1 - \log\{1/(1-\alpha)\}\alpha r^2 m_B B^{-1}, 1]$ under assumptions (A1), (B1) and (B2). Hence, using Lemma 5, it follows that

$$\begin{aligned} 0 &\le E_{m,G,G'}\{R_b(G,W)R_b(G',W)\} - \big[E_{m,G}\{R_b(G,W)\}\big]^2 \\ &\le \Big(\log\{1/(1-\alpha)\}\alpha r^2 m_B B^{-1}\Big)^2. \end{aligned}$$

Since $m_B = o(\sqrt{B})$ under assumption (A3), the claim (19) follows. □

Lemma 3. *Under assumptions (A1) and (B3), we have*

$$Bc_{m,n}(\alpha) \le \sum_{b=1}^{B} \pi_b(c_{m,n}(\alpha)) \le \log\{1/(1-\alpha)\}. \tag{21}$$

Proof. Let $b \in \{1,\dots,B\}$ and $j_b \in I(P_m) \cap A_b$. Then

$$\pi_b\{c_{m,n}(\alpha)\} \ge P_m\Big(p_{j_b}(W) \le c_{m,n}(\alpha)\Big) = c_{m,n}(\alpha), \tag{22}$$

where the inequality follows from the definition of $\pi_b(\cdot)$, and the equality follows from assumption (B3) and the fact that $c_{m,n}(\alpha) \in S_n$. Summing (22) over $b = 1,\dots,B$ yields the first inequality of (21).

To prove the second inequality of (21), note that assumption (A1) and the definition of $c_{m,n}(\alpha)$ imply that

$$1 - \prod_{b=1}^{B}[1 - \pi_b\{c_{m,n}(\alpha)\}] \le \alpha. \tag{23}$$

The maximum of $\sum_{b=1}^{B} \pi_b\{c_{m,n}(\alpha)\}$ under constraint (23) is obtained when

$$\pi_1\{c_{m,n}(\alpha)\} = \cdots = \pi_B\{c_{m,n}(\alpha)\}.$$

This implies $\pi_b\{c_{m,n}(\alpha)\} \leq 1-(1-\alpha)^{1/B}$ for all $b = 1,\ldots,B$, so that

$$\sum_{b=1}^{B} \pi_b\{c_{m,n}(\alpha)\} \leq B - B(1-\alpha)^{1/B},$$

and this is bounded above by $-\log(1-\alpha)$ for all values of B. □

Lemma 4. *Assume (A1), (B1) and (B2). Let F_b be the distribution of $\mu_b(W)$, where $\mu_b(W)$ is defined in* (20)*. Then*

$$\textit{support}(F_b) \subseteq [1 - \log\{1/(1-\alpha)\}\alpha r^2 m_B B^{-1}, 1].$$

Proof. Using assumption (B2) with constant r and the union bound, it holds that

$$1 - \mu_b(W) \;=\; P^*\big\{p^{(b)}(W) \leq c_{m,n}(\alpha)\big\} \;\leq\; r|A_b|c_{m,n}(\alpha).$$

Since $m_B = \max_{b=1,\ldots,B}|A_b|$, the support of F_b is thus in the interval $[1 - m_B r c_{m,n}(\alpha), 1]$.

Hence, the proof is completed if we show that

$$c_{m,n}(\alpha) \leq -\log(1-\alpha)\alpha r B^{-1}. \tag{24}$$

To see that (24) holds, we first show that

$$1-\alpha \;\leq\; P_m\{\min_{j\in I(P_m)} p_j(W) > c_{m,n}(\alpha)\} \;\leq\; (1 - c_{m,n}(\alpha)/r)^B. \tag{25}$$

The first inequality in (25) follows directly from the definition of $c_{m,n}(\alpha)$; see (1). To prove the second inequality, note that assumption (A1) implies that

$$P_m\{\min_{j\in I(P_m)} p_j(W) > c_{m,n}(\alpha)\} \;=\; \prod_{b=1}^{B} P_m\{p^{(b)}(W) > c_{m,n}(\alpha)\}. \tag{26}$$

By assumption (B1) and the law of iterated expectations,

$$\begin{aligned} P_m\{p^{(b)}(W) > c_{m,n}(\alpha)\} &= P_{m,G}\{p^{(b)}(GW) > c_{m,n}(\alpha)\} \\ &= E_m\big\{P_{m,G}\{p^{(b)}(GW) > c_{m,n}(\alpha)|W\}\big\}. \end{aligned} \tag{27}$$

By assumption (B2), the conditional probability within each block satisfies

$$\begin{aligned} P_{m,G}\{p^{(b)}(GW) > c_{m,n}(\alpha)|W\} &= P^*\{p^{(b)}(W) > c_{m,n}(\alpha)\} \\ &\leq 1 - P^*\{p_{j_b}(W) \leq c_{m,n}(\alpha)\} \\ &\leq 1 - c_{m,n}(\alpha)/r, \end{aligned} \tag{28}$$

where $j_b \in I(P_m) \cap A_b$. Since the right hand side of (28) does not depend on W, the same bound holds for (27), where we also take the expectation over W. Using this result in (26), the second inequality in (25) follows. Finally, (25) implies

$$c_{m,n}(\alpha) \leq r\{1 - (1-\alpha)^{1/B}\}.$$

Since $B(1-(1-\alpha)^{1/B}) \leq -\log(1-\alpha)$ for all values of B, it follows that $1-(1-\alpha)^{1/B} \leq -\log(1-\alpha)B^{-1}$. This proves (24) and completes the proof. □

Lemma 5. *Let U be a real-valued random variable with support $[a, b] \subset [0, 1]$. Suppose that the distribution of the two random variables X_1 and X_2, conditional on $U = u$, is given by*

$$X_1, X_2 \overset{i.i.d.}{\sim} \textit{Bernoulli}(u).$$

Then $0 \leq E(X_1 X_2) - E(X_1)E(X_2) \leq (b - a)^2$.

Proof. By the assumption that X_1 and X_2 are Bernoulli conditional on U, it follows that $E(X_1|U) = E(X_2|U) = U$. Combining this with the law of iterated expectation and the fact that X_1 and X_2 are conditionally independent given U, we obtain

$$E(X_1 X_2) = E_U\{E(X_1 X_2|U)\} = E_U\{E(X_1|U)E(X_2|U)\} = E(U^2).$$

Moreover, we have $E(X_1) = E_U\{E(X_1|U)\} = E(U)$ and similarly $E(X_2) = E(U)$. Hence,

$$E(X_1 X_2) - E(X_1)E(X_2) = E(U^2) - \{E(U)\}^2 = \text{Var}(U).$$

Finally, $0 \leq \text{Var}(U) \leq (b - a)^2$ by the assumption on the support of U. □

5.3 Proof of Theorem 2

First, note that (W) implies (B1)-(B3). Using the union bound and assumption (B3), it holds for any $s \in S_n$ that ms is an upper bound for $P_m(\min_{j \in I(P_m)} p_j(W) \leq s)$. Hence,

$$\begin{aligned} c_{m,n}(\alpha) &= \max\{s \in S_n : P_m(\min_{j \in I(P_m)} p_j(W) \leq s) \leq \alpha\} \\ &\geq \max\{s \in S_n : ms \leq \alpha\}. \end{aligned} \tag{29}$$

This implies that the oracle critical value is larger than zero if the set $\{s \in S_n : ms \leq \alpha\}$ is non-empty, which is the case if $\min(S_n) \leq \alpha/m$. The smallest possible two-sided Wilcoxon p-value is $\min(S_n) = 2\frac{(n/2)!(n/2)!}{n!} \leq 2^{-n/2+1}$. Hence, it is sufficient to require that $2^{-n/2+1} \leq \alpha/m$, or equivalently, that $n \geq 2\log_2(m/\alpha) + 2$.

Note that (A3') implies (A3). Hence, under assumptions (W), (A1), (A2) and (A3'), the result in Theorem 1 applies.

Let $\alpha \in (0, 1)$. We will now show that under assumptions (W), (A1) and (A3'),

$$\alpha_- \to \alpha,$$

as $m, n \to \infty$ such that $n/\log(m) \to \infty$, where α_- was defined in (8). Define $c^+_{m,n}(\alpha) := \min\{s \in S_n : s > c_{m,n}(\alpha)\}$. Using the definition of α_- and assumption (A1), we have

$$\begin{aligned} \alpha_- &= P_m(\min_{j \in I(P_m)} p_j(W) \leq c_{m,n}(\alpha)) \\ &= 1 - \prod_{b=1}^{B}[1 - \pi_b\{c_{m,n}(\alpha)\}] \\ &= 1 - \prod_{b=1}^{B}[1 - \pi_b\{c^+_{m,n}(\alpha)\} + \pi_b\{c^+_{m,n}(\alpha)\} - \pi_b\{c_{m,n}(\alpha)\}]. \end{aligned} \tag{30}$$

Define the function $g_{m,n} : \prod_{b=1}^{B}[0, \pi_b\{c^+_{m,n}(\alpha)\}] \to \mathbb{R}$ by

$$g_{m,n}(u) := g_{m,n}(u_1, \ldots, u_B) := 1 - \prod_{b=1}^{B} \big[1 - \pi_b\{c^+_{m,n}(\alpha)\} + u_b\big],$$

so that the right hand side of (30) equals $g_{m,n}(w)$, where $w_b := \pi_b\{c^+_{m,n}(\alpha)\} - \pi_b\{c_{m,n}(\alpha)\}$ for $b = 1, \ldots, B$. A first order Taylor expansion of $g_{m,n}(w)$ around $(0, \ldots, 0)$ yields

$$\alpha_- = g_{m,n}(w) = g_{m,n}(0) + \sum_{b=1}^{B} w_b \left.\frac{\partial g_{m,n}(u)}{\partial u_b}\right|_{u=0} + R, \tag{31}$$

where $R = o(\sum_{b=1}^{B} w_b)$. For all $b = 1, \ldots, B$, we have

$$\begin{aligned}\left.\frac{\partial g_{m,n}(u)}{\partial u_b}\right|_{u=0} &= - \prod_{j=1, j\neq b}^{B} [1 - \pi_j\{c^+_{m,n}(\alpha)\}] \\ &= -\frac{1 - g_{m,n}(0)}{1 - \pi_b\{c^+_{m,n}(\alpha)\}} \geq -\frac{1 - g_{m,n}(0)}{1 - m_B c^+_{m,n}(\alpha)},\end{aligned}$$

where the inequality follows from $\pi_b\{c^+_{m,n}(\alpha)\} \leq m_B c^+_{m,n}(\alpha)$ for $b = 1, \ldots, B$, by the union bound and assumption (B3). Plugging this into (31) yields

$$\begin{aligned}\alpha_- &\geq g_{m,n}(0) - \frac{1 - g_{m,n}(0)}{1 - m_B c^+_{m,n}(\alpha)} \sum_{b=1}^{B} w_b + R \\ &= g_{m,n}(0) \left(1 + \frac{\sum_{b=1}^{B} w_b}{1 - m_B c^+_{m,n}(\alpha)}\right) - \frac{\sum_{b=1}^{B} w_b}{1 - m_B c^+_{m,n}(\alpha)} + R. \qquad (32)\end{aligned}$$

The definition of $c^+_{m,n}(\alpha)$ implies that $g_{m,n}(0) > \alpha$ for all m and n. Hence, if

$$\sum_{b=1}^{B} w_b \to 0 \qquad \text{and} \qquad m_B c^+_{m,n}(\alpha) \to 0 \tag{33}$$

as $m, n \to \infty$ such that $n/\log(m) \to \infty$, then the right hand side of (32) converges to α and the proof is complete.

We first consider $\sum_{b=1}^{B} w_b$. By definition, there is no value $s' \in S_n$ such that $c_{m,n}(\alpha) < s' < c^+_{m,n}(\alpha)$. Hence,

$$\begin{aligned}w_b &= P_m\big\{\min_{j\in A_b\cap I(P_m)} p_j(W) = c^+_{m,n}(\alpha)\big\} \\ &\leq m_B \max_{j\in A_b\cap I(P_m)} P_m\{p_j(W) = c^+_{m,n}(\alpha)\} \\ &= m_B\{c^+_{m,n}(\alpha) - c_{m,n}(\alpha)\},\end{aligned}$$

where the inequality follows from the union bound, and the last equality is due to assumption (B3). This implies

$$\sum_{b=1}^{B} w_b \le B m_B \{c^+_{m,n}(\alpha) - c_{m,n}(\alpha)\} = B c_{m,n}(\alpha) m_B \left(\frac{c^+_{m,n}(\alpha)}{c_{m,n}(\alpha)} - 1 \right).$$

Similarly, we have

$$m_B c^+_{m,n}(\alpha) = B c_{m,n}(\alpha) \frac{m_B}{B} \frac{c^+_{m,n}(\alpha)}{c_{m,n}(\alpha)}.$$

Note that $B c_{m,n}(\alpha) \le \log\{1/(1-\alpha)\}$ by Lemma 3 and $m_B = O(1)$ (and hence $B \to \infty$) by assumption (A3'). Hence, in order to prove (33), it suffices to show that $c^+_{m,n}(\alpha)/c_{m,n}(\alpha) \to 1$ as $m, n \to \infty$ such that $n/\log(m) \to \infty$.

$$c^+_{m,n}(\alpha)/c_{m,n}(\alpha) \to 1 \text{ as } m, n \to \infty,\ n/\log(m) \to \infty. \tag{34}$$

Let the ordered p-values in S_n, based on a two-sided Wilcoxon test with equal sample sizes $n/2$ in both classes, be denoted by $s_0 < s_1 < \cdots < s_{r_n}$, where $r_n = \lfloor n^2/8 + 1 \rfloor$. It is well known that

$$s_i = 2\frac{(n/2)!(n/2)!}{n!} \sum_{j=0}^{i} q_{n/2}(j) \quad \text{for } i = 0, \ldots, r_n - 1$$

and $s_{r_n} = 1$, where $q_n(j)$ is the number of integer partitions of j such that neither the number of parts nor the part magnitudes exceed n (and $q_n(0) = 1$) (Wilcoxon, 1945). Let $i_{m,n}$ satisfy $s_{i_{m,n}} = c_{m,n}(\alpha)$. Then

$$\frac{c^+_{m,n}(\alpha)}{c_{m,n}(\alpha)} = \frac{\sum_{j=0}^{i_{m,n}+1} q_{n/2}(j)}{\sum_{j=0}^{i_{m,n}} q_{n/2}(j)}.$$

This ratio converges to 1 if $i_{m,n} \to \infty$. Recall that $c_{m,n}(\alpha) \ge \max\{s \in S_n : s \le \alpha/m\}$ (see (29)). Hence,

$$c^+_{m,n}(\alpha) = 2\frac{(n/2)!(n/2)!}{n!} \sum_{j=0}^{i_{m,n}+1} q_{n/2}(j) > \alpha/m.$$

Since $2m\{(n/2)!(n/2)!\}/n! \le m2^{-n/2} \to 0$ as $m, n \to \infty$ such that $n/\log(m) \to \infty$, we have that under these conditions $i_{m,n} \to \infty$ and $c^+_{m,n}(\alpha)/c_{m,n}(\alpha) \to 1$. Thus (34) holds and hence implies (33), which completes the proof.

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