Conditional calibration for false discovery rate control under dependence

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Abstract

We introduce a new class of methods for finite-sample false discovery rate (FDR) control in multiple testing problems with dependent test statistics where the dependence is fully or partially known. Our approach separately calibrates a data-dependent p-value rejection threshold for each hypothesis, relaxing or tightening the threshold as appropriate to target exact FDR control. In addition to our general framework we propose a concrete algorithm, the dependence-adjusted Benjamini–Hochberg (dBH) procedure, which adaptively thresholds the q-value for each hypothesis. Under positive regression dependence the dBH procedure uniformly dominates the standard BH procedure, and in general it uniformly dominates the Benjamini–Yekutieli (BY) procedure (also known as BH with log correction). Simulations and real data examples illustrate power gains over competing approaches to FDR control under dependence.

1 Introduction

Despite the immense popularity of the false discovery rate (FDR) paradigm and the Benjamini–Hochberg (BH) method for large-scale multiple testing (Benjamini and Hochberg, 1995), the literature on FDR-controlling methods has long been dogged by their uncertain validity when applied to dependent p-values. In particular, the BH procedure is only known to control FDR under restrictive positive dependence assumptions, or after a severe correction to the significance level (Benjamini and Yekutieli, 2001). Apart from specific supervised learning settings where knockoff methods (Barber and Candès, 2015; Candès et al., 2018) can be applied, practitioners still commonly default to the uncorrected BH method, choosing to forego theoretical guarantees and hope for the best.

This article introduces new methods for finite-sample FDR control under dependence. Our key technical idea is to decompose the FDR according to the additive contribution of each hypothesis, and use conditional inference to adaptively calibrate a separate rejection rule for each hypothesis to directly control its FDR contribution. Equipped with this tool, we prove finite-sample FDR control for a broad class of multiple testing methods. We also propose a concrete algorithm, the *dependence-adjusted Benjamini–Hochberg procedure* (dBH), that operates by adaptively calibrating a separate BH q-value cutoff for each hypothesis. Specifically, our method rejects H_i if $q_i \leq \hat{c}_i$, where the calibrated threshold $\hat{c}_i$ may be larger or smaller than α. Although the dBH procedure can be applied in a wide variety of discrete and continuous, parametric and nonparametric models, the present work emphasizes multivariate Gaussian and linear regression models. We show empirically that our methods perform similarly to BH, but with provable FDR control.

Because $\hat{c}_i$ can be larger than α, the dBH procedure can be, and often is, somewhat more powerful than the usual BH procedure. We show that dBH is uniformly more powerful than BH under positive dependence, in the sense that it makes at least as many rejections, almost surely. In addition, versions of the method are uniformly more powerful than the corrected version of BH (known as the Benjamini–Yekutieli (BY) procedure), usually dramatically so.

1.1 Multiple testing and the false discovery rate

In a multiple testing problem, an analyst observes a data set $X \sim P$, and rejects a subset of null hypotheses $H_1, \ldots, H_m$. We assume $P \in \mathcal{P}$ for some parametric or non-parametric model $\mathcal{P}$, and each null hypothesis $H_i \subsetneq \mathcal{P}$ represents a submodel; without loss of generality, the ith alternative hypothesis is $\mathcal{P} \setminus H_i$. We assume the analyst computes a p-value $p_i(X)$ to test each H_i, where p_i is marginally *super-uniform* (i.e., stochastically larger than $\mathrm{Unif}(0,1)$) under H_i. Let $\mathcal{H}_0(P) = \{i : P \in H_i\}$ denote the set of true null hypotheses, and $m_0 = |\mathcal{H}_0|$. Much of our discussion will treat the parametric setting $\mathcal{P} = \{P_\theta : \theta \in \Theta \subseteq \mathbb{R}^d\}$, often parameterized so that H_i concerns only θ_i, for example $H_i : \theta_i = 0$ or $H_i : \theta_i \leq 0$.

A *multiple testing procedure* is a decision $\mathcal{R}(X) \subseteq [m] = \{1, \ldots, m\}$ designating the set of rejected hypotheses. An analyst who rejects H_i for each $i \in \mathcal{R}(X)$ makes $V = |\mathcal{R} \cap \mathcal{H}_0|$ false rejections (sometimes called "false discoveries"). If $R = |\mathcal{R}|$ is the number of total rejections, Benjamini and Hochberg (1995) define the *false discovery proportion* (FDP) as

$$\mathrm{FDP}(\mathcal{R}(X); P) = \frac{V}{R \vee 1},$$

where $a \vee b = \max\{a, b\}$ and $a \wedge b = \min\{a, b\}$. The *false discovery rate* (FDR) is defined as the expected FDP:

$$\mathrm{FDR}_P(\mathcal{R}) = \mathbb{E}_P\big[\mathrm{FDP}(\mathcal{R}(X); P)\big].$$

A standard goal in multiple testing is to maximize a procedure's power subject to constraining $\sup_{P \in \mathcal{P}} \mathrm{FDR}_P(\mathcal{R}) \leq \alpha$ at a pre-set significance level, typically 5%, 10%, or 20%.

The most widely used method for FDR control is the *Benjamini–Hochberg (BH) procedure*, an example of the more general class of *step-up procedures*. Let $p_{(1)} \leq \cdots \leq p_{(m)}$ denote the order statistics of the m p-values. Then the step-up procedure for an increasing sequence of thresholds $0 \leq \Delta(1) \leq \ldots \leq \Delta(m) \leq 1$ finds the largest index r for which $p_{(r)} \leq \Delta(r)$ and rejects all of the corresponding hypotheses up to that index. That is, we reject the hypotheses with the smallest $R(X)$ p-values, where

$$R(X) = \max\left\{r : p_{(r)}(X) \leq \Delta(r)\right\}. \tag{1}$$

The BH(α) procedure takes $\Delta_\alpha(r) = \alpha r / m$. For a general family of thresholds $\Delta_\alpha(r)$ that are non-decreasing in α and r, we denote the generic step-up procedure as $\mathrm{SU}_\Delta(\alpha)$. We denote the corresponding testing procedures as $\mathcal{R}^{\mathrm{BH}(\alpha)}$ and $\mathcal{R}^{\mathrm{SU}_\Delta(\alpha)}$ respectively.

As α increases, the BH(α) procedure becomes more liberal, with nested rejection sets. Storey (2003) defined the *q-value* as the level at which H_i is barely rejected:

$$q_i(X) = \min\left\{\alpha : i \in \mathcal{R}^{\mathrm{BH}(\alpha)}\right\}. \tag{2}$$

The same definition may be extended to any step-up procedure. If $\Delta_\alpha(r)$ is right-continuous in α, the rejection sets are right-continuous too, and the minimum is always well-defined.

Benjamini and Hochberg (1995) showed that the BH(α) procedure controls FDR at exactly $\alpha m_0 / m$ if the p-values are independent, but the picture for dependent p-values has been more complex.

1.2 FDR under dependence

We can begin to understand the role of dependence by first making a standard decomposition of the FDR according to the contribution of each true null hypotheses:

$$\mathrm{FDR} = \mathbb{E}\left[\frac{V}{R \vee 1}\right] = \sum_{i \in \mathcal{H}_0} \mathbb{E}\left[\frac{V_i}{R \vee 1}\right], \tag{3}$$

where $V_i = 1\{H_i \text{ rejected}\}$. Under independence, BH controls each term in the sum at α / m, attaining FDR control at level $\alpha m_0 / m$.

==Positive dependence between V_i and R tends to reduce each term in (3), making methods like BH conservative.== In particular, the BH procedure is known to be conservative under *positive regression dependence on a subset* (PRDS): For $a, b \in \mathbb{R}^d$, we say $a \preceq b$ if $a_i \leq b_i$ for all $i = 1$, and a set $A \subseteq \mathbb{R}^d$ is *increasing* if $a \in A$ and $a \preceq b$ implies $b \in A$. We say that $p_{-i} = (p_1, p_2, \ldots, p_{i-1}, p_{i+1}, \ldots, p_m)$ is *positive regression dependent* (PRD) on p_i if $\mathbb{P}(p_{-i} \in A \mid p_i)$ is increasing in p_i for any increasing set A. Benjamini and Yekutieli (2001) show that the BH(α) procedure controls FDR conservatively at $\alpha m_0/m$, provided that p_{-i} is PRD on p_i, for every $i \in \mathcal{H}_0$; this condition is called PRDS. Subsequently, many procedures designed to control FDR under independence have also been shown to control FDR under positive dependence as well. Notable exceptions include the Storey-BH method (Storey et al., 2004), whose estimate of m_0/m can fail badly under dependence[1], and adaptive weighting methods such as AdaPT (Lei and Fithian, 2018) and SABHA (Li and Barber, 2019), whose finite-sample FDR control may be threatened by local random effects that make a cluster of p-values smaller together.[2]

Unfortunately, the PRDS condition is quite restrictive. It does hold for one-sided testing with multivariate Gaussian test statistics whose pairwise correlations are all non-negative, or for one- or two-sided testing of uncorrelated multivariate t-test statistics. But p-values for one-sided testing with any negative pairwise correlations, or for two-sided testing with any correlations at all, no longer satisfy PRDS.

For general, unspecified dependence, Benjamini and Yekutieli (2001) also showed that the much more conservative BH(α/L_m) procedure controls FDR at level α under arbitrary dependence, where

$$L_m = \sum_{i=1}^m \frac{1}{i} = \log m + \mathcal{O}(1).$$

This method has become known as the *Benjamini–Yekutieli (BY)* procedure, or sometimes the *log-corrected BH* procedure. The proof technique was subsequently generalized in the *shape function* approach of Blanchard and Roquain (2008) who show that if ν is any probability measure on $\{1, \ldots, m\}$, then the step-up procedure with

$$\Delta_\alpha(r) = \frac{\alpha\beta(r)}{m}, \quad \text{where } \beta(r) = \sum_{i=1}^r i\nu(\{i\}) \tag{4}$$

also controls FDR under arbitrary dependence between the p-values. Taking $\nu(\{i\}) = (iL_m)^{-1}$ recovers the BY(α) procedure, but Blanchard and Roquain (2008) suggest other choices that sometimes improve on the BY procedure's power.

These methods control FDR under worst-case dependence assumptions, but their generality typically comes at a price of substantial conservatism and diminished power compared to the BH procedure. As a result the BH procedure is often still used in applications where PRDS does not hold. This "off-label" use of BH owes in part to a widely held belief that, under dependence typically arising in practice, BH is more often conservative than it is anti-conservative (e.g. Farcomeni, 2006; Kim and van de Wiel, 2008).

A second strategy is to prove asymptotic control in regimes where the limiting problem is simpler. For example, Genovese and Wasserman (2004) and Storey et al. (2004) study regimes where the empirical distributions of null and non-null p-values converge to limiting deterministic functions as $m \to \infty$; this line of analysis was developed further in Ferreira and Zwinderman (2006) and Farcomeni (2007). While these analyses provide valuable insights, the results hold only in the limit where $R \to \infty$; but FDR control is often desired in problems where R may be relatively small, even if m is large. Troendle (2000) and Romano et al. (2008) study resampling-based approaches in a different asymptotic regime where m is fixed but the non-null p-values converge in probability to zero; in finite samples this is likely an optimistic assumption.

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[1] Benjamini et al. (2006) propose another adaptive method that behaves better under positive dependence

[2] Li and Barber (2019) derive an upper bound for the FDR inflation in the multivariate Gaussian case, but the bound depends on unknown aspects of the data distribution.

Recently discovered knockoff methods (Barber and Candès, 2015) offer an alternative means of FDR control under dependence for testing coefficients in linear regression models, and have been extended to testing conditional independence in supervised learning settings where a model for the joint distribution of predictor variables is available (Candès et al., 2018). Knockoff methods, which operate by feeding synthetic noise variables to a supervised learning procedure, represent a sharp methodological departure from classical multiple testing procedures like BH. Knockoffs can be more or less powerful than the BH procedure for context-dependent reasons that are not yet fully understood. We discuss their relative strengths and weaknesses compared to classical procedures like BH in Section 7.1.

In this work, we propose a new methodological framework for controlling FDR under dependence in a wide variety of discrete and continuous, parametric and nonparametric models. Rather than assume worst-case dependence, we begin with a baseline procedure like BH or BY and calibrate its FDR by exploiting full or partial knowledge of the dependence.

2 FDR control by conditional calibration

2.1 Conditional calibration: a new strategy

Our method operates by adaptively calibrating a separate rejection threshold for each of the m p-values to control each term in (3), which we will call the *FDR contribution* of H_i. Let $\tau_i(c; X)$ be some possibly data-dependent rejection threshold for p_i, with *calibration parameter* $c \geq 0$. We assume τ_i is non-decreasing in c for all X, and $\tau_i(0; X) = 0$ almost surely. We will be primarily interested in the *effective* BH *threshold*, defined as the p-value rejection threshold that is "estimated" by the $\mathrm{BH}(c)$ procedure:

$$\tau^{\mathrm{BH}}(c; X) = \frac{cR^{\mathrm{BH}(c)}}{m}. \tag{5}$$

Because the BH q-value $q_i(X)$ is below α if and only if $p_i \leq \tau^{\mathrm{BH}}(\alpha)$, we can roughly interpret τ^{BH} as an inverse q-value transformation, and c as a q-value cutoff. More generally, we define the *effective* SU_Δ *threshold* as $\tau^{\mathrm{SU}_\Delta}(c) = \Delta_c(R^{\mathrm{SU}_\Delta(c)})$.

Taking the decomposition in (3) as our starting point, we will aim to calibrate the threshold for p_i, choosing $\hat{c}_i$ to directly control the ith term in the sum:

$$\mathbb{E}_{H_i}\left[\frac{V_i}{R \vee 1} \right] = \sup_{P \in H_i} \mathbb{E}_P\left[\frac{1\{p_i \leq \tau_i(\hat{c}_i)\}}{R \vee 1} \right] \leq \frac{\alpha}{m}. \tag{6}$$

We will use $\mathbb{E}_{H_i}[\cdot]$ as a shorthand notation for $\sup_{P \in H_i} \mathbb{E}_P[\cdot]$ throughout.

There are two main challenges in solving for $\hat{c}_i$ in (6). First, the expectation depends in a possibly complicated way on the entire distribution of X, whereas H_i typically only constrains the distribution of p_i. Our first idea is to achieve (6) by controlling a more tractable conditional expectation, given some *conditioning statistic* S_i that blocks most or all of the nuisance parameters from influencing the conditional analysis. Often S_i is independent of p_i, but we only require that p_i is conditionally superuniform given S_i:

$$\sup_{P \in H_i} \mathbb{P}_P(p_i \leq \alpha \mid S_i) \leq \alpha, \quad \text{for all } \alpha \in [0, 1]. \tag{7}$$

This style of conditioning is a well-established device for handling nuisance parameters in inference problems, especially for exponential family models and permutation tests, and has seen recent application in approaching complex decision problems like multiple testing (e.g. Weinstein et al., 2013; Barber and Candès, 2015; Candès et al., 2018) and post-selection inference (e.g. Tibshirani et al., 2016; Lee et al., 2016; Fithian et al., 2014).

Under independence, (7) is satisfied with $S_i = p_{-i}$. A standard FDR control proof for the BH procedure, introduced in Benjamini and Yekutieli (2001), conditions on p_{-i} and applies the following key lemma, whose proof is given in Appendix A:
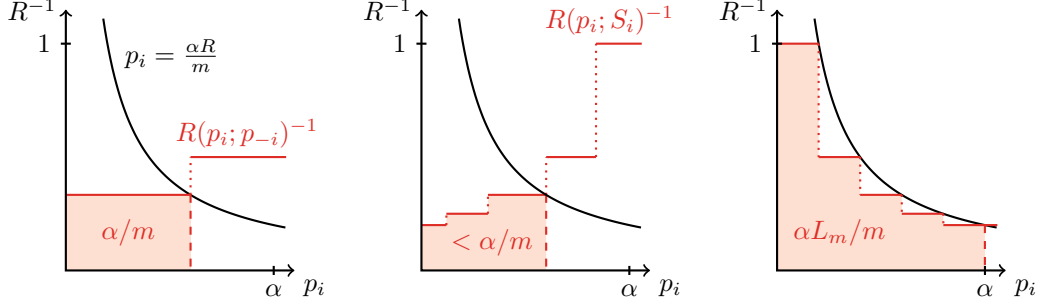
(a) Independent case: R is constant on $\{p_i \leq \alpha R/m\}$.

(b) Positive-dependent case: R is decreasing in p_i

(c) Worst-case: R is always just large enough to reject p_i.

Figure 1: Visualizing the conditional FDR contribution for BH(α) under two simplifying assumptions: (i) p_i is uniform under the null, and (ii) the rejection set is a function of p_i and S_i. R^{-1} is shown as the broken red line. The BH(α) procedure rejects H_i when (p_i, R^{-1}) is below the hyperbola $p_i = \alpha R/m$ and the conditional FDR contribution is given by $\mathbb{E}\left[\frac{V_i}{R \vee 1} \mid S_i\right] = \int_{u \leq \alpha R(u)/m} R^{-1}(u)\, du$, the area of the light red region.

Lemma 1. *Let $p^{(i \leftarrow 0)} = (p_1, \ldots, p_{i-1}, 0, p_{i+1}, \ldots, p_m)$. If $\mathcal{R}$ is a step-up procedure with threshold sequence $\Delta(1), \ldots, \Delta(m)$, then the following are equivalent:*

1. $p_i \leq \Delta(R(p^{(i \leftarrow 0)}))$,

2. $i \in \mathcal{R}(p)$, and

3. $\mathcal{R}(p) = \mathcal{R}(p^{(i \leftarrow 0)})$.

Let $R^0 = R(p^{(i \leftarrow 0)})$, which depends only on p_{-i}. Then for the standard BH procedure under independence, applying Lemma 1 gives

$$\mathbb{E}_{H_i}\left[\frac{V_i}{R \vee 1} \mid p_{-i}\right] = \mathbb{E}_{H_i}\left[\frac{1\{p_i \leq \alpha R^0/m\}}{R^0} \mid p_{-i}\right] \leq \frac{1}{R^0}\frac{\alpha R^0}{m} = \frac{\alpha}{m}.$$

Marginalizing over p_{-i} and summing over $i \in \mathcal{H}_0$ yields FDR $\leq \alpha m_0/m$.

For dependent p-values, p_{-i} will not in general satisfy (7). As a simple example, suppose $Z \sim N_m(\mu, \Sigma)$ where Σ is a known covariance matrix with diagonal entries $\Sigma_{ii} = 1$, and we wish to test $H_i : \mu_i = 0$ against a one- or two-sided alternative. If $\Sigma_{ij} \neq 0$ then p_i and p_j are not independent and the distribution of p_i given p_{-i} depends on μ_j. However, the conditioning statistic $S_i = Z_{-i} - \Sigma_{-i,i} Z_i$ is independent of Z_i, and after conditioning on S_i the data distribution depends only on μ_i, which is fixed at zero under the null.

In this example the data set can be reconstructed from S_i and Z_i, and if the p-values are one-sided then it can also be reconstructed from S_i and p_i. Figure 1 illustrates the conditional FDR contribution of H_i for one-sided testing under three conditions: independence ($\Sigma = I_m$), where the contribution is exactly α/m; positive-dependence ($\Sigma_{ij} \geq 0$ for all i, j), where the contribution is below α/m; and worst-case dependence, where the contribution can be as high as $\alpha L_m/m$. In Figure 1b, the red line $R(p_i; S_i)^{-1}$ is increasing in p_i because, fixing S_i, the other p-values are increasing functions of p_i.

The second main challenge is that the number of rejections R in the denominator depends on all of $\hat{c}_1, \ldots, \hat{c}_m$, so all m calibration problems are coupled to one another. To deal with this, we substitute an "estimator" $\widehat{R}_i(X) \geq 1$ of the eventual value of $R_i(X) = |\mathcal{R}(X) \cup \{i\}|$, the number of rejections if we also include H_i. Because $R_i = R$ for $i \in \mathcal{R}(X)$, we have $V_i/R_i = V_i/(R \vee 1)$ almost surely. Ideally, $\widehat{R}_i$ should be an accurate and easily computable lower-bound for R_i.

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2.2 Our method

We now present a generic two-step FDR-controlling method, possibly with a third randomization step to handle cases where $\widehat{R}_i$ fails to lower-bound R_i:

Step 1: Calibration. First, we use $\widehat{R}_i$ to estimate the conditional FDR contribution $\mathbb{E}_{H_i}[V_i/R_i \mid S_i]$ as a function of the calibration parameter, and recalibrate as appropriate to control the conditional expectation at α/m:

$$g_i^*(c\,;S_i) = \sup_{P \in H_i} \mathbb{E}_P \left[\frac{1\{p_i \le \tau_i(c)\}}{\widehat{R}_i} \,\Big|\, S_i \right] \le \frac{\alpha}{m}, \tag{8}$$

suppressing the dependence of p_i, $\tau_i(c)$, and $\widehat{R}_i$ on X for compactness of notation.

The function g_i^* is almost surely non-decreasing in c with $g_i^*(0) = 0$ because $\tau_i(0) = 0$ by assumption. Let $c_i^*(S_i) \le \infty$ denote the least upper bound for the set of allowed c values, which is either $[0, c_i^*]$ or $[0, c_i^*)$ (note that neither τ_i nor g_i^* is necessarily continuous in c). If $g_i^*(c_i^*) \le \alpha/m$, we can set $\hat{c}_i(S_i) = c_i^*$; otherwise we can take a non-decreasing sequence $(\hat{c}_{i,t}(S_i))_{t=1}^\infty$ converging to c_i^* from below, such as $\hat{c}_{i,t} = (c_i^* - 1/t) \vee 0$. We say $\hat{c}_i$ is *maximal* if, almost surely, either c_i^* satisfies (8) and $\hat{c}_i = c_i^*$, or c_i^* does not satisfy (8) and $\lim_t \hat{c}_{i,t} = c_i^*$. If $c_i^*(S_i)$ is difficult to calculate, it is enough to assume only that $\hat{c}_i(S_i)$ is any value satisfying (8) almost surely.

Step 2: Initial rejection. Next, we initialize the rejection set, via:

$$\mathcal{R}_+ = \{i : p_i \le \tau_i(\hat{c}_i)\}.$$

If $\hat{c}_i$ is a sequence, the condition $p_i \le \tau_i(\hat{c}_i)$ is understood to mean $p_i \le \tau_i(\hat{c}_{i,t})$ for some t (which is not equivalent to $p_i \le \tau_i(\lim_t \hat{c}_{i,t})$). To limit notational bloat in our prose, we will discuss $\hat{c}_i$ as though it is a single value, but our results all apply to the general case.

Let $R_+ = |\mathcal{R}_+|$. If $R_+ \ge \widehat{R}_i$ for all $i \in \mathcal{R}_+$, then we can halt the procedure with $\mathcal{R} = \mathcal{R}_+$. Otherwise, we may need to prune the rejection set further.

Step 3 (if necessary): Randomized pruning. If there is some $i \in \mathcal{R}_+$ for which $\widehat{R}_i > R_+$, then we must prune the rejection set via a secondary BH procedure. For user-generated uniform random variables $u_1, \dots, u_m \overset{\text{i.i.d.}}{\sim} \text{Unif}(0,1)$, let

$$R(X;u) = \max \left\{ r : \left| \{i \in \mathcal{R}_+ : u_i \le r/\widehat{R}_i\} \right| \ge r \right\}, \tag{9}$$

and reject H_i for the R indices with $i \in \mathcal{R}_+$ and $u_i \le R/\widehat{R}_i$. The procedure in (9) is equivalent to the BH(1) procedure on "p-values" $\tilde{p}_i = u_i \widehat{R}_i/R_+$ for $i \in \mathcal{R}_+$. We can skip this step if $R_+ \ge \widehat{R}_i$ for all $i \in \mathcal{R}_+$; in that case all $u_i \widehat{R}_i/R_+ \le 1$, so $R = R_+$.

We show next that this procedure controls FDR at the desired level.

Theorem 2 (FDR control). *Assume that (7) holds, and $\hat{c}_{i,t}(S_i)$ is chosen to guarantee (8), for all i and t. Then the three-step procedure defined above controls the FDR at or below level $\alpha m_0/m$.*

Proof. It is sufficient to show that $\mathbb{E}[V_i/R_i] \le \alpha/m$ for every $i \in \mathcal{H}_0$. For $i \in \mathcal{R}_+$ let $R_i^* = R(X; u^{(i \leftarrow 0)})$, which is independent of u_i. By Lemma 1 applied to the secondary BH

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procedure, $R_i^* = R$ on the event $\{V_i = 1\}$. As a result, we can write

$$\mathbb{E}\left[\frac{V_i}{R \vee 1}\right] = \mathbb{E}\left[\frac{1\{i \in \mathcal{R}_+\} \cdot 1\left\{u_i \le R/\widehat{R}_i\right\}}{R \vee 1}\right] \tag{10}$$

$$= \mathbb{E}\left[\frac{1\{i \in \mathcal{R}_+\} \cdot 1\left\{u_i \le R_i^*/\widehat{R}_i\right\}}{R_i^*}\right] \tag{11}$$

$$= \mathbb{E}\left[\mathbb{E}\left[\frac{1\{i \in \mathcal{R}_+\} \cdot 1\left\{u_i \le R_i^*/\widehat{R}_i\right\}}{R_i^*} \mid X, u_{-i}\right]\right] \tag{12}$$

$$\le \mathbb{E}\left[\frac{1\{i \in \mathcal{R}_+\}}{\widehat{R}_i}\right] \tag{13}$$

$$= \lim_{t \to \infty} \mathbb{E}\left[\frac{1\{p_i \le \tau_i(\hat{c}_{i,t})\}}{\widehat{R}_i}\right] \tag{14}$$

$$= \lim_{t \to \infty} \mathbb{E}\left[\mathbb{E}\left[\frac{1\{p_i \le \tau_i(\hat{c}_{i,t})\}}{\widehat{R}_i} \mid S_i\right]\right]. \tag{15}$$

We can move the limit outside the integral in (14) by monotone convergence. Under H_i, the last expression is no larger than α/m, completing the proof. $\qquad\square$

We pause to make several further observations:

Remark 2.1. If we modify the calibration step replacing α/m by a generic, possibly data-dependent upper bound $\kappa_i(S_i)$ in inequality (8), then the proof of Theorem 2 trivially generalizes to guarantee FDR control at level $\sum_{i \in \mathcal{H}_0} \mathbb{E}_P \kappa_i(S_i)$. Section 7 discusses two extensions of the procedure where this additional flexibility is useful: adaptive estimation of m_0/m and adaptive hypothesis weighting.

Remark 2.2. From the proof of Theorem 2 we see that there are three possible sources of conservatism in the above procedure. First, we typically have $m_0 < m$. Second, the inequality in (13) is the price we pay in conservatism when $\widehat{R}_i$ underestimates R_i. Third, the conditional expectation in (15) may not attain α/m, either because $\hat{c}_i$ is not maximal, because p_i has a discrete distribution, or because P does not attain the supremum in (8) (for example if P lies in the interior of H_i).

Remark 2.3. When we are forced to carry out the randomized pruning in Step 3, every rejection in $\mathcal{R}_+$ is at risk, and there is a real danger that we could prune even a hypothesis for which the p-value p_i is extremely small. Even if the number of pruned rejections is small in expectation, we believe it is scientifically preferable to use a procedure that obeys the sufficiency principle and avoids randomization, even if the randomization has a negligible effect on power calculations. We call a calibrated procedure *safe* if pruning is never necessary.

To operationalize our method, we must fill in the details of what threshold family τ_i and estimator $\widehat{R}_i$ we use, how we identify the conditioning statistic S_i, and how we calibrate the threshold in practice. The next sections address these issues in turn.

2.3 The dependence-adjusted BH and BY procedure

While Theorem 2 proves FDR control for a broad class of procedures, our empirical results focus on special cases of our method that are designed to couple tightly with the BH and BY procedures. If we use the three-step method of the previous section with the effective BH threshold $\tau_i = \tau^{\mathrm{BH}}$ and estimator $\widehat{R}_i = R_i^{\mathrm{BH}(\gamma\alpha)} = |\mathcal{R}^{\mathrm{BH}(\gamma\alpha)} \cup \{i\}|$, we call the resulting method the *dependence-adjusted BH procedure*, which we denote $\mathrm{dBH}_\gamma(\alpha)$. In the special

case where we take $\gamma = 1/L_m$, we call the resulting method the *dependence-adjusted BY procedure*, denoted $\mathrm{dBY}(\alpha)$. More generally, let the $\mathrm{dSU}_{\gamma,\Delta}(\alpha)$ procedure use threshold $\tau_i = \tau^{\mathrm{SU}_\Delta}$ and estimator $\widehat{R}_i = R_i^{\mathrm{SU}_\Delta(\gamma\alpha)}$. All of these definitionally use maximal $\hat{c}_i$.

We can interpret the $\mathrm{dBH}_\gamma(\alpha)$ calibration parameters $\hat{c}_1, \ldots, \hat{c}_m$ as calibrated q-value rejection thresholds for the respective hypotheses, since $q_i \leq c$ if and only if $p_i \leq \tau^{\mathrm{BH}}(c)$. As a result, we have

$$\mathcal{R}^{\mathrm{BH}(\min_i \hat{c}_i)} \subseteq \mathcal{R}_+ \subseteq \mathcal{R}^{\mathrm{BH}(\max_i \hat{c}_i)}. \tag{16}$$

Provided that $\min_i \hat{c}_i \geq \gamma\alpha$, the randomization step is avoided and we can replace $\mathcal{R}_+$ with $\mathcal{R}$ in (16). In our simulations we take $\gamma = 0.9$ as a conservative choice except in the positive-dependent case, where we take $\gamma = 1$. Figure 2 illustrates how conditional calibration operates for the dBH_1 and dBY procedures.

Under a slight strengthening of the PRDS condition, the $\mathrm{dBH}_1(\alpha)$ procedure is *uniformly more powerful* than the BH procedure, meaning $\mathcal{R}^{\mathrm{dBH}_1} \supseteq \mathcal{R}^{\mathrm{BH}}$ almost surely. For a given conditioning statistic S_i we say the p-values p_{-i} are *conditionally positive regression dependent* (CPRD) if $\mathbb{P}(p_{-i} \in A \mid p_i, S_i)$ is almost surely increasing in p_i for any increasing set A. If p_{-i} is CPRD on p_i for all $i \in \mathcal{H}_0$ we say the p-values are *CPRD on a subset* (CPRDS). Note CPRDS implies PRDS after marginalizing over S_i, but PRDS does not necessarily imply CPRDS.

Theorem 3. *Assume $\hat{c}_1, \ldots, \hat{c}_m$ are maximal. Then*

1. *If the p-values are independent with p_i uniform under H_i, then the $\mathrm{dBH}_1(\alpha)$ procedure with $S_i = p_{-i}$ is identical to the $\mathrm{BH}(\alpha)$ procedure.*

2. *If the p-values are CPRDS for all $P \in \mathcal{P}$, then the $\mathrm{dBH}_1(\alpha)$ procedure is safe, and uniformly more powerful than the $\mathrm{BH}(\alpha)$ procedure.*

3. *For arbitrary dependence, the $\mathrm{dBY}(\alpha)$ procedure is safe, and uniformly more powerful than the $\mathrm{BY}(\alpha)$ procedure.*

4. *Assume the thresholds Δ_α are of the form (4). Then for arbitrary dependence, the $\mathrm{dSU}_\Delta(\alpha)$ procedure is safe, and uniformly more powerful than the $\mathrm{SU}_\Delta(\alpha)$ procedure.*

The proof of Theorem 3 adapts and extends proofs in Benjamini and Yekutieli (2001) and Blanchard and Roquain (2008), and may be found in Appendix A.

Remark 2.4. The proof of Theorem 3 only involves values of p_i in the interval $p_i \in [0, \alpha]$, and the only increasing sets that appear in the proof are of the form $\{\widehat{R}_i \leq r\}$. For the purpose of applying Theorem 3, then, we could relax the definition of CPRD to require only that $\mathbb{P}(\widehat{R}_i \leq r \mid p_i, S_i)$ is increasing for $p_i \in [0, \alpha]$. As a result, the second conclusion of Theorem 3 applies to one-sided testing with uncorrelated multivariate t-statistics even though the p-values are neither PRDS nor CPRDS, as we show in Section 3.2.

Remark 2.5. In many of our examples, including one-sided multivariate Gaussian testing, the entire data set can be reconstructed from p_i and S_i. In that case, the conditional probability is always 0 or 1, and a sufficient condition for CPRD is that, fixing S_i, every other p_j is an increasing function of p_i.

Recognizing $\hat{c}_i$ as a q-value threshold has a convenient computational interpretation as well, because $i \in \mathcal{R}_+$ if and only if $g_i^*(q_i; S_i) \leq \alpha/m$. As a result, we usually do not need to calculate $\hat{c}_i$ explicitly, but can simply evaluate the conditional expectation plugging in $c = q_i(X)$. Section 4 discusses computational considerations in more detail.
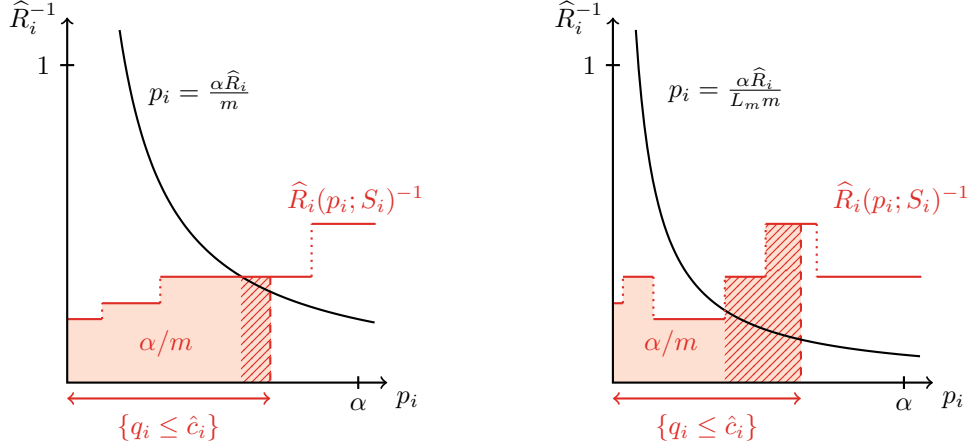
(a) The dBH$_1(\alpha)$ procedure in the positive-dependent case.

(b) The dBY(α) procedure, which is often much more powerful than BY(α).

Figure 2: Illustration of conditional calibration for the dBH$_1$ and dBY procedures. The red line in each plot represents the inverse of $\widehat{R}_i = |\mathcal{R}^{\mathrm{BH}(\gamma\alpha)} \cup \{i\}|$ (assumed here as in Figure 1 to be a deterministic function of p_i and S_i) for $\gamma = 1$ (left) and $\gamma = 1/L_m$ (right). If p_i is uniform under the null, the conditional FDR contribution is estimated as $\int_{u:\, q_i(u) \le \hat{c}_i} \widehat{R}_i^{-1}(u)\, du$. The hatched region is added in the calibration step to "top up" the FDR contribution to α/m. The set $\{u : q_i(u) \le \hat{c}_i\}$ is not always a contiguous interval.

2.4 Identifying the conditioning statistic S_i

There are several desiderata for a good conditioning statistic. Most importantly, recall that our method's validity depends on p_i being a valid conditional p-value, so that (7) holds. To facilitate calibration, S_i should also eliminate or mitigate the influence of nuisance parameters on the conditional distribution of X. Finally, the conditional distribution under H_i should be analytically and/or computationally tractable. Calibration is conceptually simplified if S_i is a sufficient statistic for the null submodel H_i, so that the conditional distribution of X is known under H_i. In that case, we say H_i is *conditionally simple*, and $g_i^*(c\,; S_i)$ is an integral we can directly evaluate. Otherwise, we say H_i is *conditionally composite*, and P_i^* is *least favorable* for calibrating $\hat{c}_i$ if it almost surely attains the supremum:

$$g_i^*(c\,; S_i) = \mathbb{E}_{P_i^*}\left[\frac{1\{p_i \le \tau_i(c)\}}{\widehat{R}_i} \;\Big|\; S_i \right], \quad \text{for all } c \ge 0. \tag{17}$$

We discuss two primary examples where the choice of conditioning statistic is fairly natural: parametric exponential family models and nonparametric models with constraints on the dependence graph.

Example 2.1 (Exponential families). In exponential family models, there is a natural choice of S_i which follows from the classical theory of conditional testing in the style of Lehmann and Scheffé (1955). Suppose our model arises from a full-rank exponential family in canonical form:

$$X \sim f_\theta(x) = e^{\theta' T(x) - A(\theta)} f_0(x), \quad \theta \in \Theta \subset \mathbb{R}^d, \tag{18}$$

and for $i = 1, \ldots, m \le d$, H_i takes the form $H_i : \theta_i = 0$ or $H_i : \theta_i \le 0$. In this setting, the uniformly most powerful unbiased (UMPU) test rejects H_i when $T_i(X)$ is extreme, conditional on the value of $S_i = T_{-i}(X)$; see e.g. Lehmann and Romano (2005). As a result, $T_{-i}(X)$ makes a natural choice of test statistic, because it eliminates nuisance parameters and because p_i is conditionally valid by construction, so the hypothesis H_i is

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conditionally simple and we can evaluate $g_i^*(c)$ directly. For one-sided testing, the null hypothesis $H_i : \theta_i \leq 0$ is conditionally composite, but we will see in Section 2.6 that under mild conditions setting $\theta_i = 0$ is least favorable.

Section 3 and Appendix B discuss a variety of multiple testing problems in this vein, including multivariate Gaussian test statistics, testing in linear models, multiple comparisons with binary responses, and conditional independence testing in Gaussian graphical models.

Example 2.2 (Nonparametric models with dependence constraints)**.** As a nonparametric example, consider observing only p-values $p \in [0,1]^m$, where the dependence is not parametrically specified but there are constraints on the dependence graph between p-values. Specifically, we assume that each p-value has a neighborhood $\mathcal{M}_i \subseteq [m]$ for which $S_i = p_{\mathcal{M}_i^c}$ is independent of p_i. We assume nothing else about p_i except that it is uniform or superuniform under H_i. In this case the null hypotheses are not conditionally simple since we cannot directly sample from the distribution of p given S_i. Instead, we must assume worst-case dependence of $p_{\mathcal{M}_i}$ on p_i: the least favorable distribution P_i^* adversarially configures $p_{\mathcal{M}_i \setminus \{i\}}$ to maximize the integrand in (8), conditional on p_i and $S_i = p_{\mathcal{M}_i^c}$. This may nevertheless allow for considerable improvement on the BY method or the shape function approach of Blanchard and Roquain (2008), which effectively assume worst-case dependence of *all* other p-values on p_i, corresponding to the special case where all $\mathcal{M}_i = [m]$. We defer further exploration of this example to future work.

2.5   Recursive refinement of $\widehat{R}_i$

The random variable $\widehat{R}_i(X)$ is an unusual estimator in that, by the time the procedure terminates, we will have computed the estimand $R_i(X)$. If they differ, it seems natural to re-run the procedure substituting the "correct value" for the inaccurate estimate. While we can start again at Step 1 with the same threshold family, we will still not have a perfect estimator because changing $(\widehat{R}_1, \ldots, \widehat{R}_m)$ will affect the entire procedure and change $(R_1, \ldots, R_m)$ in turn. Nevertheless, we may obtain a better procedure if the new $\widehat{R}_i$ is a better estimator of the new R_i. We call this process *recursive refinement* of the estimator.

We will denote the original estimator as $\widehat{R}_i^{(1)}$, which leads to original calibration parameter $\hat{c}_i^{(1)}$ and initial rejection set $\mathcal{R}_+^{(1)}$. We define the recursively refined estimator as

$$\widehat{R}_i^{(2)}(X) = \left| \mathcal{R}_+^{(1)}(X) \cup \{i\} \right|. \tag{19}$$

We can then calibrate new thresholds $\hat{c}_i^{(2)}$ solving (8) with respect to $\widehat{R}_i^{(2)}$, and proceed as before. In principle, we can repeat this refinement as many times as we want, defining $\widehat{R}_i^{(k)}(X) = \left| \mathcal{R}_+^{(k-1)}(X) \cup \{i\} \right|$ for all $k > 1$, but in most problems of moderate size the computational cost is prohibitive for $k > 2$, for reasons we explain in Section 4.

Recursive refinement is especially useful when we begin with a very conservative estimator, as we do when we use the dBY procedure. If we use the effective BH threshold with the $\mathrm{dBH}_\gamma(\alpha)$ estimator, we call the resulting procedure the $\mathrm{dBH}_\gamma^2(\alpha)$ procedure, or the $\mathrm{dBY}^2(\alpha)$ procedure if $\gamma = 1/L_m$. When the baseline procedure is safe, recursive refinement always yields another safe procedure that is uniformly more powerful:

Theorem 4. *Assume $\hat{c}_1^{(k)}, \ldots, \hat{c}_m^{(k)}$ are maximal for all i and k. If $\mathcal{R}^{(1)}$ is safe, then for every $k \geq 1$, $\mathcal{R}^{(k+1)}$ is safe and uniformly more powerful than $\mathcal{R}^{(k)}$.*

Proof. It is sufficient to prove the result for $k = 1$, since for any $k > 1$, $\mathcal{R}^{(k+1)}$ bears the same relationship to $\mathcal{R}^{(k)}$ that $\mathcal{R}^{(2)}$ bears to $\mathcal{R}^{(1)}$.

The safeness of $\widehat{R}_i^{(1)}$ implies that, almost surely, $\mathcal{R}_+^{(1)} = \mathcal{R}^{(1)}$ and

$$R_i^{(1)} = R_+^{(1)} \geq \widehat{R}_i^{(1)}, \text{ for all } i \in \mathcal{R}^{(1)}. \tag{20}$$

As a result, we have

$$\widehat{R}_i^{(2)} = |\mathcal{R}^{(1)} \cup \{i\}| = R_i^{(1)} \geq \widehat{R}_i^{(1)}, \text{ for all } i \in \mathcal{R}^{(1)}, \text{ almost surely.} \tag{21}$$

Because $\widehat{R}_i^{(2)} \geq \widehat{R}_i^{(1)}$, the integrand in (8) for $k = 2$ is almost surely smaller than the integrand for $k = 1$, so $\hat{c}_i^{(2)} \geq \hat{c}_i^{(1)}$ almost surely. If all the calibration parameters increase, then $\mathcal{R}_+^{(2)} \supseteq \mathcal{R}_+^{(1)}$ as well, so for all $i \in \mathcal{R}^{(2)}$,

$$\mathcal{R}_+^{(2)} \supseteq (\mathcal{R}^{(1)} \cup \{i\}) \implies R_+^{(2)} \geq \widehat{R}_i^{(2)}, \tag{22}$$

completing the proof. $\qquad\square$

2.6 One-sided testing in exponential family models

In this section we consider how to test the one-sided hypotheses $H_i : \theta_i \leq 0$ in exponential family models of the form (18). We assume throughout that $0 \in \Theta \cup \mathbb{R}^d$, and that the tests are right-tailed; otherwise we can reparameterize the family (possibly with different reparameterizations for each i).

If we were testing a single hypothesis, the UMPU test for H_i would reject for large values of T_i, conditional on the value of $S_i = T_{-i}$; these include the z-, t-, and Fisher exact tests we discuss in Section 3 and Appendix B (Lehmann and Romano, 2005). That is, the conditional test p-value is given by

$$p_i = 1 - \mathbb{P}_{\theta_i=0}(T_i < t \mid S_i) = \lim_{t \to T_i^-} 1 - F_{i,0}(t \mid S_i),$$

where the conditional distribution $F_{i,\theta_i}(t \mid S_i) = \mathbb{P}_{\theta_i}(T_i \leq t \mid S_i)$ depends only on θ_i.

Because the distribution of T_i is stochastically increasing in θ_i, only the boundary case $\theta_i = 0$ is relevant for calculating the p-value, but we cannot necessarily restrict our attention to the boundary when we calibrate $\hat{c}_i$, unless $\theta_i = 0$ is least favorable in the sense of (17). The next result gives a sufficient condition for least favorability:

Proposition 5. *Consider testing $H_i : \theta_i \leq 0$ for $i = 1, \ldots, m \leq d$ in an exponential family model of the form (18) with $0 \in \Theta^o \subseteq \mathbb{R}^d$. Assume for all i that p_i is given by the standard one-sided UMPU test, and that we have for some α' which is not necessarily the target FDR level, almost surely,*

(i) $\tau_i(c; X) \leq \alpha'$, and

(ii) Under $\theta_i = 0$, the conditional upper-α' quantile of T_i is above its conditional mean:

$$F_{i,0}(t \mid S_i) < 1 - \alpha', \quad \text{for all } t < \mu_{i,0}(S_i),$$

where $\mu_{i,\theta_i}(S_i) = \mathbb{E}_{\theta_i}[T_i \mid S_i]$.

Then, $\theta_i = 0$ is least favorable for H_i, for purposes of calibrating $\hat{c}_i$.

Proof. Let $f_{\theta_i}(t \mid s)$ denote the conditional density of $T_i(X)$ given $S_i(X) = s$, which is a one-parameter exponential family with respect to some base measure P_0:

$$f_{\theta_i}(t \mid s) = e^{\theta_i t - B(\theta_i \mid s)} f_0(t \mid s),$$

and let

$$h(t, s) = \mathbb{E}\left[\frac{1\{p_i \leq \tau_i(c)\}}{\widehat{R}_i} \mid S_i = s, T_i = t \right],$$

which does not depend on θ by sufficiency of (S_i, T_i).

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Finally, define

$$g_{i,\theta_i}(c\,;s) = \mathbb{E}_{\theta_i}\left[\frac{1\{p_i \leq \tau_i(c)\}}{\widehat{R}_i} \mid S_i = s\right]$$

$$= \int h(t,s)f_{\theta_i}(t \mid s)\,dP_0(t).$$

Because $h(t,s)$ takes values in $[0,1]$, by dominated convergence we can differentiate under the integral sign, giving

$$\frac{\partial}{\partial\theta_i}g_{i,\theta_i}(c\,;s) = \int h(t,s)(t - \mu_{i,\theta_i}(s))f_{\theta_i}(t \mid s)\,dP_0(t),$$

where $\mu_{i,\theta_i}(s) = \frac{d}{d\theta_i}B(\theta_i \mid s) = \mathbb{E}_{\theta_i}[T_i \mid S_i = s]$ is increasing in θ_i.

If $\theta_i \leq 0$ then our assumption (ii) ensures that $p_i > \alpha' \geq \tau_i(c)$, and therefore $h(T_i \mid S_i) = 0$, whenever $T_i < \mu_{i,\theta_i}(S_i) \leq \mu_{i,0}(S_i)$, so the integrand is non-negative for all t and s. As a result $g_{i,\theta_i}(c\,;s)$ is non-decreasing in θ_i for any $\theta_i \leq 0$, so it attains its maximum at 0. $\qquad\square$

Although there is no universal cap on the τ^{BH} threshold, in practice it very rarely exceeds α, and we can choose to modify it by capping it manually at some α'. In our implementation of dBH, we cap c at 2α, effectively capping τ^{BH} at $\alpha' = 2\alpha$, as discussed in Appendix C.2.2. In all examples discussed in Section 3, T_i is symmetrically distributed given S_i with $\mu_{i,0}(S_i) = 0$, so the assumptions of Proposition 5 hold for all $\alpha \leq 0.25$.

2.7   Two-sided testing and directional error control

We say a hypothesis is *two-sided* if it can be written as $H_i : \theta_i(P) = 0$, for some parameter θ_i mapping $\mathcal{P}$ to $\mathbb{R}$, where the range includes both positive and negative values. Because a two-sided hypothesis frequently represents a "measure-zero" set in the model $\mathcal{P}$, rejecting H_i is more meaningful when we can also draw an inference about the sign of θ_i. If we write H_i as the intersection of the one-sided hypotheses $H_i^{\leq} : \theta_i(P) \leq 0$ and $H_i^{\geq} : \theta_i(P) \geq 0$, a *directional inference* is one that rejects exactly one of $H_i^{\leq}$ and $H_i^{\geq}$ along with H_i.

For multiple testing of two-sided hypotheses with directional inferences, let $\mathcal{R}^+$ denote the set of indices for which we declare $\theta_i > 0$ (reject $H_i^{\leq}$) and $\mathcal{R}^-$ the set for which we declare $\theta_i < 0$ (reject $H_i^{\geq}$), with $\mathcal{R}$ the disjoint union of both sets. Let p_i^+ and p_i^- denote p-values for each of the two tests, which we assume are conditionally valid:

$$\sup_{P \in H_i^{\leq}} \mathbb{P}_P(p_i^+ \leq \alpha \mid S_i) \leq \alpha \quad \text{and} \quad \sup_{P \in H_i^{\geq}} \mathbb{P}_P(p_i^- \leq \alpha \mid S_i) \leq \alpha, \quad \forall\alpha \in [0,1]. \qquad (23)$$

We assume the two one-sided tests are based on a common test statistic T_i, with $H_i^{\leq}$ rejected when T_i is large and $H_i^{\geq}$ rejected when T_i is small, where the critical thresholds possibly depend on S_i. For the sake of simplicity we also assume the two-sided test is *equal-tailed*, in the sense that $p_i = 2\min\{p_i^+, p_i^-\}$.

In general, multiple testing procedures that are valid for two-sided hypotheses do not necessarily justify directional conclusions even if the constituent single hypothesis tests do (Shaffer, 1980; Finner, 1999). Testing two-sided hypotheses with directional inferences creates more opportunities to make errors: defining $\mathcal{H}_i^{\leq} = \{i : \theta_i \leq 0\}$ and likewise $\mathcal{H}_i^{\geq} = \{i : \theta_i \geq 0\}$, the number of directional errors is $V^{\mathrm{dir.}} = V^+ + V^-$, where

$$V^+ = \left|\mathcal{H}^{\leq} \cap \mathcal{R}^+\right|, \quad \text{and} \quad V^- = \left|\mathcal{H}^{\geq} \cap \mathcal{R}^-\right|.$$

The *directional FDP* is defined as $\mathrm{FDP}^{\mathrm{dir.}} = V^{\mathrm{dir.}}/(R \vee 1)$, and its expectation $\mathrm{FDR}^{\mathrm{dir.}}$ is the *directional FDR*. The next result gives a natural sufficient condition guaranteeing that our method with directional inferences controls the directional FDR:

Lemma 6. *Assume p_i^+ and p_i^- are valid in the sense of (23), and that the assumptions of Theorem 2 are satisfied for $S_i, \tau_i, \hat{c}_{i,t}$ and $\widehat{R}_i$, for $i = 1, \ldots, m$. Define*

$$g_{i,\theta}^a(c\,;S_i) \;=\; \sup_{P:\,\theta_i(P)=\theta} \mathbb{E}_P\left[\frac{1\{p_i^a \leq \tau_i(c)/2\}}{\widehat{R}_i} \mid S_i\right], \quad \text{for } a = +, -.$$

*If $g_{i,\theta}^+(c\,;S_i)$ is almost surely non-decreasing in θ for $\theta \leq 0$, and $g_{i,\theta}^-$ is non-*increasing* in θ for $\theta \geq 0$, then our three-step method controls the directional FDR.*

Proof. Define $V_i^a = 1\{p_i^a \leq \tau_i(c)/2\}$, so that $V_i = 1\{p_i \leq \tau_i(c)\} = V_i^+ + V_i^-$. Then

$$\text{FDR}^{\text{dir.}} = \sum_{i \in \mathcal{H}_0^{\leq}} \mathbb{E}\left[\frac{V_i^+}{R \vee 1}\right] + \sum_{i \in \mathcal{H}_0^{\geq}} \mathbb{E}\left[\frac{V_i^-}{R \vee 1}\right]$$

$$= \sum_{i:\,\theta_i=0} \mathbb{E}\left[\frac{V_i}{R \vee 1}\right] + \sum_{i:\,\theta_i<0} \mathbb{E}\left[\frac{V_i^+}{R \vee 1}\right] + \sum_{i:\,\theta_i>0} \mathbb{E}\left[\frac{V_i^-}{R \vee 1}\right].$$

Each term in the first sum is no larger than α/m, by the argument in Theorem 2. For a generic term in the second sum, we have almost surely

$$g_{i,\theta_i}^+(c\,;S_i) \;\leq\; g_{i,0}^+(c\,;S_i) \;\leq\; g_i^*(c\,;S_i).$$

Then we can likewise repeat the argument of Theorem 2 to obtain

$$\mathbb{E}\left[\frac{V_i^+}{R \vee 1}\right] \leq \lim_{t \to \infty} \mathbb{E}\left[\mathbb{E}\left[\frac{1\left\{p_i^+ \leq \tau_i(\hat{c}_{i,t})/2\right\}}{\widehat{R}_i} \mid S_i\right]\right]$$

$$\leq \lim_{t \to \infty} \mathbb{E}\left[g_{i,\theta_i}^+(\hat{c}_{i,t}\,;S_i)\right]$$

$$\leq \lim_{t \to \infty} \mathbb{E}\left[g_i^*(\hat{c}_{i,t}\,;S_i)\right],$$

which is no larger than α/m by assumption. Likewise, each term in the third sum is no larger than α/m, and there are m total terms among the three sums. $\square$

As an immediate consequence of Lemma 6 and Proposition 5, we see that we can draw directional conclusions for two-sided multiple testing in exponential family models:

Corollary 7. *Consider testing $H_i: \theta_i = 0$ for $i = 1, \ldots, m \leq d$ in an exponential family model of the form (18) with $0 \in \Theta^\circ \subseteq \mathbb{R}^d$. Assume for all i that $p_i = 2\min\{p_i^+, p_i^-\}$ where $p_i^\pm$ are given by the standard one-sided UMPU tests, and that we have, almost surely,*

(i) *$\tau_i(c\,;X) \leq \alpha$, and*

(ii) *Under $\theta_i = 0$, the conditional mean is between the conditional lower- and upper-$\alpha/2$ quantiles:*

$$F_{i,0}(t \mid S_i) < 1 - \alpha/2, \quad \text{for all } t < \mu_{i,0}(S_i), \quad \text{and}$$
$$F_{i,0}(t \mid S_i) > \alpha/2, \quad \text{for all } t > \mu_{i,0}(S_i),$$

where $\mu_{i,\theta_i}(S_i) = \mathbb{E}_{\theta_i}[T_i \mid S_i]$.

Then, our three-step method controls the directional FDR.

Proof. Applying Proposition 5 to the modified threshold $\tilde{\tau}_i(c) = \tau_i(c)/2$, we have the hypotheses of Lemma 6. $\square$

3   Examples

In this section we give additional details about several parametric examples arising from the multivariate Gaussian family. Appendix B discusses three further parametric examples — edge testing in Gaussian graphical models, post-selection z- and t-testing, and multiple comparisons to control for a one-way layout with binary outcomes — as well as a nonparametric example, multiple comparisons to control with in a one-way layout with generic responses and p-values arising from permutation tests.

Let $Z \sim N_d(\mu, \Sigma)$ with $\Sigma \succ 0$, an exponential family model with density

$$f_{\mu,\Sigma}(z) = \frac{1}{(2\pi)^{n/2}|\Sigma|} \exp\left\{-\frac{1}{2}(z-\mu)'\Sigma^{-1}(z-\mu)\right\} \tag{24}$$

$$= \frac{1}{(2\pi)^{d/2}|\Sigma|} \exp\left\{\mu'\Sigma^{-1}z - \frac{1}{2}z'\Sigma^{-1}z - \frac{1}{2}\mu'\Sigma^{-1}\mu\right\}. \tag{25}$$

Defining $A^i = (\Sigma^{-1})_{-i,-i}$, it will be useful to recall the formula

$$(\Sigma^{-1})_{-i,i} = -A^i\Sigma_{-i,i}\Sigma_{i,i}^{-1}. \tag{26}$$

3.1   Multivariate z-statistics

First assume Σ is known, with $\Sigma_{i,i} = 1$, so that each Z_i is a z-statistic for testing $H_i : \mu_i = 0$ or $H_i : \mu_i \leq 0$, for $i = 1, \ldots, m \leq d$, and p_i is the resulting one- or two-sided p-value. We can rewrite (25) as a full-rank d-parameter exponential family:

$$f_{\mu,\Sigma}(z) = \frac{1}{(2\pi)^{d/2}|\Sigma|} \exp\left\{\mu_i(\Sigma^{-1}z)_i + \mu'_{-i}(\Sigma^{-1}z)_{-i} - \frac{1}{2}z'\Sigma^{-1}z - \frac{1}{2}\mu'\Sigma^{-1}\mu\right\} \tag{27}$$

$$= \frac{1}{(2\pi)^{d/2}|\Sigma|} \exp\left\{\mu_i(\Sigma^{-1}z)_i + (A^i\mu_{-i})'(z_{-i} - \Sigma_{-i,i}z_i) - \frac{1}{2}z'\Sigma^{-1}z - \frac{1}{2}\mu'\Sigma^{-1}\mu\right\}. \tag{28}$$

To test H_i, the general proposal in Section 2.4 leads to the conditioning statistic $S_i = Z_{-i} - \Sigma_{-i,i}Z_i$. S_i is independent of Z_i and p_i since $\text{Cov}(Z_i, S_i) = 0$.

To carry out the $\text{dBH}_\gamma(\alpha)$ procedure, we must evaluate for each i whether

$$\mathbb{E}_0\left[\frac{1\{q_i \leq c\}}{R_i^{\text{BH}(\gamma\alpha)}} \mid S_i\right] \leq \frac{\alpha}{m}, \tag{29}$$

plugging in $c = q_i(Z)$, the observed BH q-value. Because $Z_{-i} = S_i + \Sigma_{-i,i}Z_i$, it is straightforward to evaluate the expectation in (29) by integrating over the set $\{(z, S_i + \Sigma_{i,-i}z) : z \in \mathbb{R}\}$. For one-sided p-values $p_i = 1 - \Phi(Z_i)$, p_{-i} is CPRD on p_i if and only if $\Sigma_{ij} \geq 0$ for all $j \leq m$, mirroring the condition for marginal PRD in Benjamini and Yekutieli (2001).

3.2   Multivariate t-statistics

A slightly harder case is to assume that $\Sigma = \sigma^2\Psi$ where $\Psi \succ 0$ is known but $\sigma^2 > 0$ is unknown. Assume we are still testing $H_i : \mu_i = 0$ for $i = 1, \ldots, m \leq d$, with an additional independent vector $W \sim N_{n-d}(0, \sigma^2 I_{n-d})$ available for estimating σ^2. Then the usual t-statistic for testing H_i is

$$T_i = \frac{Z_i}{\sqrt{\Psi_{i,i}\hat{\sigma}^2}} \overset{H_i}{\sim} t_{n-d}, \qquad \text{where} \quad (n-d)\hat{\sigma}^2 = \|W\|^2 \sim \sigma^2\chi_{n-d}^2.$$

Extending the density in (28) to include W, we obtain the $d+1$-parameter exponential family form

$$f_{\mu,\Psi,\sigma^2}(z,w) = \frac{1}{(2\pi\sigma^2)^{n/2}|\Psi|} \exp\left\{ \frac{\mu_i}{\sigma^2}(\Psi^{-1}z)_i + (A^i\mu_{-i})'(z_{-i} - \Psi_{-i,i}\Psi_{i,i}^{-1}z_i)) \right.$$
$$\left. - \frac{1}{2\sigma^2}(w'w + z'\Psi^{-1}z) - \frac{\mu'\Psi^{-1}\mu}{2\sigma^2} \right\},$$

Letting $U_i = Z_{-i} - \Psi_{-i,i}\Psi_{i,i}^{-1}Z_i$, the general proposal in Section 2.4 leads to the conditioning statistic $(U_i, \|W\|^2 + Z'\Psi^{-1}Z)$, or equivalently

$$S_i(Z,W) = (U_i, V_i), \quad \text{where } V_i = \|W\|^2 + \frac{Z_i^2}{\Psi_{i,i}}.$$

since

$$Z'\Psi^{-1}Z = \frac{Z_i^2}{\Psi_{i,i}} + U_i'(\Psi_{-i,-i} - \Psi_{-i,i}\Psi_{i,i}^{-1}\Psi_{i,-i})^{-1}U_i.$$

T_i, U_i, and V_i are mutually independent under H_i, and we can reconstruct the other t-statistics from their values:

$$V_i = \|W\|^2 + \frac{Z_i^2}{\Psi_{ii}} = \|W\|^2 \left(1 + \frac{T_i^2}{n-d}\right),$$

and

$$T_j = \frac{Z_j}{\sqrt{\Psi_{j,j}\hat{\sigma}^2}} = \frac{U_{ij}}{\sqrt{\Psi_{j,j}\hat{\sigma}^2}} + \frac{\Psi_{j,i}Z_i}{\Psi_{i,i}\sqrt{\Psi_{j,j}\hat{\sigma}^2}} = U_{ij}\sqrt{\frac{n-d+T_i^2}{\Psi_{j,j}V_i}} + \frac{\Psi_{j,i}}{\Psi_{i,i}}T_i$$

Hence, just as in the previous section we can evaluate $g_i^*(q_i)$ by integrating over reconstructed t-statistics:

$$\left\{ \left(t, \ \sqrt{\frac{n-d+t^2}{V_i}} \operatorname{diag}(\Psi_{-i,-i})^{-1/2} U_i + \frac{\Psi_{-i,i}}{\Psi_{i,i}} t \right) : t \in \mathcal{R} \right\},$$

where $t \sim t_{n-d}$. For two-sided testing with uncorrelated test statistics (diagonal Ψ), we see that T_j^2 is non-decreasing in t^2 for all values of t, so the test statistics are CPRDS. For one-sided right-tailed testing with uncorrelated test statistics, in light of Remark 2.4 we only need to consider values with $t > 0$ and the conditional probability of the event $R_i^{\mathrm{BH}(\alpha)} \leq r$, which only depends on p-values that are below $\alpha < 0.5$ and thus positive T_j values. Then, T_j is non-decreasing in t and positive provided that $\Psi_{j,i} = 0$ and $U_{ij} = Z_j > 0$. As a result, even though the one-sided test statistics are not CPRDS, the second claim of Theorem 3 holds. When the test statistics are correlated, even this relaxed version of the CPRDS condition does not hold for either one- or two-sided testing.

3.3 Testing coefficients in linear models

A third example is the Gaussian linear model in which we observe covariates $x_i \in \mathbb{R}^d$, with response

$$Y_i \sim x_i'\beta + \epsilon_i, \quad \text{for } \epsilon_i \stackrel{\mathrm{i.i.d.}}{\sim} N(0,\sigma^2), \quad i = 1, \dots, n,$$

with $\beta \in \mathbb{R}^d$ and $\sigma^2 > 0$ unknown. Typically we wish to test $H_j: \ \beta_j = 0$ (or analogous one-sided hypotheses), for $j = 1, \dots, m \leq d$.

If the design matrix $\mathbf{X} = (x_1, \ldots, x_n)' \in \mathbb{R}^{d \times n}$ has full column rank then a sufficiency reduction boils the data set down to ordinary least squares coefficients and residual sum of squares:

$$\hat{\beta} = (\mathbf{X}'\mathbf{X})^{-1}\mathbf{X}'Y \sim N_d(\beta,\, \sigma^2(\mathbf{X}'\mathbf{X})^{-1}), \quad \text{and} \quad \|Y - \mathbf{X}\hat{\beta}\|^2 \sim \sigma^2 \chi^2_{n-d}.$$

Thus we can reduce the linear model case to multivariate t-testing problem we discuss above, with $Z = \hat{\beta}$, $\Psi = (\mathbf{X}'\mathbf{X})^{-1}$ and $\|W\|^2 = \|Y - \mathbf{X}\hat{\beta}\|^2 = RSS$, the residual sum of squares.

Defining $\mathbf{X}_j$ as the jth column of $\mathbf{X}$, and $\mathbf{X}_{-j}$ as the remaining columns, let

$$\mathbf{b}^j(\mathbf{X}) \;=\; (\mathbf{X}'_{-j}\mathbf{X}_{-j})^{-1}\mathbf{X}'_{-j}\mathbf{X}_j \;=\; \Psi_{-j,j}\Psi_{j,j}^{-1}, \quad \text{and} \quad \mathbf{r}^j(\mathbf{X}) \;=\; \mathbf{X}_j - \mathbf{X}_{-j}\mathbf{b}^j$$

denote the coefficients and residuals from an OLS regression of $\mathbf{X}_i$ on $\mathbf{X}_{-i}$. Then we can write

$$U_j \;=\; \hat{\beta}_{-j} - \hat{\beta}_j\mathbf{b}^j, \quad \text{and} \quad V_j \;=\; RSS + \frac{\hat{\beta}_j^2}{((\mathbf{X}'\mathbf{X})^{-1})_{j,j}} \;=\; RSS + \hat{\beta}_j^2\,\|\mathbf{r}^j\|^2.$$

Applying the logic of the previous section, the one- and two-sided t-statistics are CPRDS if $\mathbf{X}'\mathbf{X}$ is diagonal. In many cases, only a subset of regression coefficients are of interest; for example we would rarely test for an intercept term. Assuming the coefficients are defined so that only the first $m < d$ are of interest, we use $\hat{\beta}_{[m]} \sim N_m(\beta_{[m]},\, \sigma^2[(\mathbf{X}'\mathbf{X})^{-1}]_{[m],[m]})$ and $\|Y - \mathbf{X}\hat{\beta}\|^2 \sim \sigma^2\chi^2_{n-d}$, which has the same structure as testing the full set of coefficients.

4 Computation

4.1 An exact homotopy algorithm for $\mathrm{dBH}_\gamma(\alpha)$

In this section we discuss an exact homotopy algorithm for $\mathrm{dBH}_\gamma(\alpha)$. It can be easily generalized to $\mathrm{dSU}_{\gamma,\Delta}(\alpha)$ at the cost of more complex notation; see Appendix C for details. Recalling the definition of $\mathrm{dBH}_\gamma(\alpha)$ in Section 2.3 and that of $\tau^{\mathrm{BH}}(c;X)$ in (5), g_i^* can be equivalently formulated as

$$g_i^*(c\,;S_i) = \sup_{P \in H_i} \mathbb{E}\left[\frac{1\{p_i \le cR^{\mathrm{BH}(c)}(X)/m\}}{R^{\mathrm{BH}(\gamma\alpha)}(X)} \,\Big|\, S_i\right].$$

For all examples discussed in Section 3, H_i is conditionally simple and $p_i = \eta_i(T_i)$ for some univariate transformation η_i of test statistic T_i, and there exists a bijective mapping ξ_i from (T_i, S_i) to $(T_1, T_2, \ldots, T_m)$. For the multivariate Gaussian case, $T_i = Z_i$, $\eta_i(t) = 1 - \Phi(t)$ for one-sided testing and $\eta_i(t) = 2(1 - \Phi(|t|))$ for two-sided testing, and $\xi_i(t; s) = (\xi_{i1}(t), \ldots, \xi_{im}(t))$ where $\xi_{ii}(t) = t$ and $\xi_{ij}(t) = s_j + \Sigma_{j,i}t$. Since T_i is independent of S_i, $g_i^*(c\,;S_i)$ can be equivalently formulated as the following univariate integral:

$$g_i^*(c\,;S_i) = \int_{\mathbb{R}} \frac{1\{\eta_i(t) \le cR_i^{(c)}(t)/m\}}{R_i^{(\gamma\alpha)}(t)}\,dP_i(t) \tag{30}$$

where $P_i(t)$ is the marginal distribution of T_i under H_i, and $R_i^{(c)}(t) = R^{\mathrm{BH}(c)}(\xi_i(t; S_i))$ denotes the number of rejections by $\mathrm{BH}(c)$ if the observed test statistics $\xi_i(T_i; S_i)$ are replaced by $\xi_i(t; S_i)$. As remarked at the end of Section 2.3, if q_i is the observed q-value then

$$\mathcal{R}_+ = \left\{i : g_i^*(q_i\,;S_i) \le \frac{\alpha}{m}\right\}.$$

Therefore, it is left to compute $R_i^{(c)}(t)$ with $c \in \{q_i, \gamma\alpha\}$.

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The test statistics $(T_1, \ldots, T_m)$ as well as the induced p-values $(p_1, \ldots, p_m)$ from the new dataset $\xi_i(t; S_i)$ are both functions of t: $T_j(t) = \xi_{ij}(t)$ and $p_j(t) = \eta_j(T_j(t)) = \eta_j(\xi_{ij}(t))$. Since $R_i^{(c)}(t)$ is an integer-valued function, it must be piecewise constant. We call each point at which $R_i^{(c)}(t)$ changes the value a *knot*. Then a point is a knot only if $p_j(t)$ crosses cr/m for some $j, r \in [m]$.

For all examples discussed in Section 3, the domain of T_i is $\mathbb{R}$, and η_i, ξ_{ij} are differentiable. Then the set of potential knots of $R_i^{(c)}(t)$ is

$$\mathcal{K}_i = \bigcup_{j,r \in [m]} \mathcal{K}_{i,j,r}, \quad \text{where } \mathcal{K}_{i,j,r} = \left\{ t : \eta_j(\xi_{ij}(t)) = \frac{cr}{m} \right\}, \tag{31}$$

For the one-sided multivariate Gaussian testing problem,

$$\mathcal{K}_{i,i,r} = \left\{ t : 1 - \Phi(t) = \frac{cr}{m} \right\} = \left\{ \Phi^{-1}\left(1 - \frac{cr}{m}\right) \right\},$$

and for each $j \neq i$,

$$\mathcal{K}_{i,j,r} = \left\{ t : 1 - \Phi(S_{ij} + \Sigma_{j,i} t) = \frac{cr}{m} \right\}$$
$$= \begin{cases} \left\{ (\Phi^{-1}\left(1 - \frac{cr}{m}\right) - S_{ij})/\Sigma_{j,i} \right\} & (\text{if } \Sigma_{j,i} \neq 0) \\ \emptyset & (\text{if } \Sigma_{j,i} = 0 \text{ and } 1 - \Phi(S_{ij}) \neq \frac{cr}{m}) \\ \mathbb{R} & (\text{otherwise}) \end{cases}.$$

Note that S_{ij} has an absolutely continuous density, $\mathbb{P}(\mathcal{K}_{i,j,r} = \mathbb{R} \text{ for any } j, r) = 0$. Thus, with probability 1,

$$\mathcal{K}_i = \bigcup_{r \in [m]} \bigcup_{j : \Sigma_{j,i} \neq 0} \mathcal{K}_{i,j,r}$$

where $\mathcal{K}_{i,j,r}$ is a singleton. Similarly, for the two-sided multivariate Gaussian testing problem, it is easy to verify that $\mathcal{K}_i$ has the same form as above except that each $\mathcal{K}_{i,j,r}$ has two elements. For multivariate t-statistics, $\mathcal{K}_{i,j,r}$ has a more complicated structure though it can still be computed efficiently; see Appendix C.3 for details.

Let $t_1 < t_2 < \ldots < t_N$ denote the elements of $\mathcal{K}$ with $(j_1, r_1), (j_2, r_2), \ldots, (j_N, r_N)$ denoting the indices such that $t_k \in \mathcal{K}_{i,j_k,r_k}$. Let

$$B_\ell^{(c)}(t) = \left| \left\{ \ell : p_\ell(t) \leq \frac{c\ell}{m} \right\} \right| - \ell, \quad (\ell = 0, \ldots, m).$$

By definition of BH(c),

$$R_i^{(c)}(t) = \max \left\{ \ell : B_\ell^{(c)}(t) = 0 \right\}. \tag{32}$$

As t moves from t_{k-1} to t_k, $B_\ell^{(c)}(t)$ remain the same for $\ell \neq r_k$ while $B_{r_k}^{(c)}(t_k)$ is incremented by $+1$ or -1, depending on whether $p_{j_k}(t)$ is increasing or decreasing at t_k. For all examples discussed in Section 3, $p_j(t)$ is differentiable, and thus

$$B_{r_k}^{(c)}(t_k) - B_{r_k}^{(c)}(t_{k-1}) = \text{sign}\left(p_{j_k}'(t_k)\right). \tag{33}$$

For one-sided multivariate Gaussian testing problems, $\eta_{j_k}'(z) = -\phi(z) < 0$ for any $z \in \mathbb{R}$ and $\xi_{ij_k}'(t) = \Sigma_{j_k,i}$. As a result,

$$B_{r_k}^{(c)}(t_k) - B_{r_k}^{(c)}(t_{k-1}) = \text{sign}(\Sigma_{j_k,i}).$$

This motivates a homotopy algorithm to calculate $B_\ell^{(c)}(t)$ sequentially based on (33) and $R_i^{(c)}(t)$ based on (32). It is not hard to see he computational cost of the homotopy algorithm for a single hypothesis H_i is $\mathcal{O}(|\mathcal{K}_i|)$. Therefore, the total cost for dBH$_\gamma(\alpha)$ is of order

$$\sum_i |\mathcal{K}_i| \leq \sum_i \sum_j \sum_r |\mathcal{K}_{i,j,r}|. \tag{34}$$

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Naively, it requires $\mathcal{O}(m^3)$ computation since there are m summands for i and j, corresponding to the hypotheses, and m summands for r, corresponding to the thresholds. Nonetheless, we can significantly reduce the size of each sum above by using a step-up method similar to BH, but with sparse increments so that there are only $\log_2 m$ distinct threshold values:

$$\Delta_\alpha(r) = \frac{\alpha\beta(r)}{m}, \quad \text{with } \beta(r) = 2^{\lfloor \log_2 r \rfloor}. \tag{35}$$

We define the *sparse* dBH$_\gamma$ (s-dBH$_\gamma$) method as the dSU$_{\gamma,\Delta}$ method with thresholds given in (35). In this case, even the naive method only requires $\mathcal{O}(m^2 \log m)$ computation.

With all the tricks that are detailed in Appendix C, the number of summands in all of the three sums can be further drastically reduced. For multivariate Gaussian testing problems, the number of i has the same order of $R_{\mathrm{BH}}(2\alpha)$, the number of j given i has the same order as the range of non-negligible correlation, and the number of r given i and j may be far lower than the total number of thresholds when $\Sigma_{j,i}$ is small. For the case with short-ranged dependence like in the autoregressive (AR) process, and a bounded number of signals, $R_{\mathrm{BH}}(2\alpha)$ is bounded with high probability and thus the computation cost of dBH$_\gamma(\alpha)$ is at most $\mathcal{O}(m)$. Thus, although the worst-case performance is poor, the cost is highly instance-specific and we find that the algorithm is reasonably fast in many cases.

4.2 An approximate numerical integration for dBH$_\gamma^2(\alpha)$

Similar to (30), the conditional expectation $g_i^*(c \mid S_i)$ in dBH$_\gamma^2(\alpha)$ can be formulated as

$$g_i^*(c\,;S_i) = \int_{\mathbb{R}} \frac{1\{\eta_i(t) \leq cR_i^{(c)}(t)/m\}}{\tilde{R}_i(t)} dP_i(t), \tag{36}$$

where $\tilde{R}_i(t) = R^{\mathrm{dBH}_\gamma(\alpha)}(\xi_i(t;S_i))$ denotes the number of rejections by dBH$_\gamma(\alpha)$ if the test statistics shift from $X = (T_i, S_i)$ to $\xi_i(t;S_i)$. Unlike dBH$_\gamma(\alpha)$, the denominator $\tilde{R}_i(t)$ has a much more complicated structure and we do not have an efficient homotopy algorithm to calculate the whole path. In principle, Monte-Carlo integration can guarantee almost sure convergence as the number of random samples grows to infinity because the integrand is bounded. However, it introduces extra randomness to the procedure which is undesirable. For this reason, we approximate (36) via a heuristic numerical integration method that has no guarantee in theory but works well in practice. For illustration, we focus on the one-sided multivariate Gaussian testing problem.

The first step is to reduce (36) to a finite-range integral. Since $R_i^{(c)}(t) \leq m$, the integrand is 0 whenever $\eta_i(t) > c$, or equivalently $t < t_{\mathrm{lo}} \triangleq \Phi^{-1}(1 - c)$. On the other hand, let $t_{\mathrm{hi}} \triangleq \Phi^{-1}(1 - \alpha\epsilon/m)$ for some $\epsilon < 1$, then the integral (36) from t_{hi} to ∞ is upper bounded by $\alpha\epsilon/m$ because the integrand is bounded by 1 and P_i is the standard Gaussian distribution. As a consequence, $\int_{t_{\mathrm{lo}}}^{t_{\mathrm{hi}}} r_i(t)dP_i(t) \leq g_i^*(c\,;S_i) \leq \int_{t_{\mathrm{lo}}}^{t_{\mathrm{hi}}} r_i(t)dP_i(t) + \frac{\alpha\epsilon}{m}$, where $r_i(t)$ denotes the integrand. If we take ϵ to be small, e.g. $\epsilon = 0.01$, then the approximation error of $\int_{t_{\mathrm{lo}}}^{t_{\mathrm{hi}}} r_i(t)dP_i(t)$ is negligible.

To compute $\int_{t_{\mathrm{lo}}}^{t_{\mathrm{hi}}} r_i(t)dP_i(t)$, a naive method is to approximate $r_i(t)$ by a piecewise constant function evaluated on an equi-spaced grid of $[t_{\mathrm{lo}}, t_{\mathrm{hi}}]$. However, it may be inefficient since $r_i(t) = 0$ whenever $\eta_i(t) > cR_i^{(c)}(t)/m$. A simple improved version is to find the region of t in which $\eta_i(t) \leq cR_i^{(c)}(t)/m$ using the exact homotopy algorithm for $R_i^{(c)}(t)$, and then discretize the resulting region to approximate $\int_{t_{\mathrm{lo}}}^{t_{\mathrm{hi}}} r_i(t)dP_i(t)$.

Naively, the computational cost is the product of the number of hypotheses m, the grid size and the cost of the homotopy algorithm to calculate a single $\tilde{R}_i(t)$. However, as with the homotopy algorithm, we discussed a few tricks in Appendix C that can drastically reduce the number of hypotheses for which the integral $g_i^*(q_i\,;S_i)$ needs to be computed. For instance, for a safe procedure, Theorem 4 guarantees that the hypotheses rejected by dBH$_\gamma(\alpha)$ are

also rejected by $\text{dBH}_\gamma^2(\alpha)$, for which the computation of $g_i^*(q_i\,;S_i)$ can be avoided. With all tricks discussed in Appendix C, it is even possible that no integral needs to be evaluated, in which case the computational cost of $\text{dBH}_\gamma^2(\alpha)$ reduces to that of $\text{dBH}_\gamma(\alpha)$. In a nutshell, the computational cost of the above algorithm is highly instance-specific.

4.3   Illustration of scalability

With all the tricks discussed in Appendix C, both algorithms are efficient and scalable to problems of reasonably large size. We illustrate it using a simple simulation study on multivariate z-statistics with an autoregressive covariance structure with autocorrelation 0.8. We consider the number of hypotheses $m \in \{10^2, 10^3, 10^4, 10^5, 10^6\}$. For each size m, we consider both one- and two-sided tests, with either 10 or 30 non-nulls in the front of the list with mean $\sqrt{2\log m}$. In each case, we implement $\text{dBH}_1(\alpha)$ and s-$\text{dBH}_1(\alpha)$ via the homotopy algorithm and implemented $\text{dBH}_1^2(\alpha)$ and s-$\text{dBH}_1^2(\alpha)$ via the approximate numerical integration with 20 knots and 40 knots for one- and two-sided tests, respectively. Figure 3 presents the median running time over 100 simulations of each method. For $\text{dBH}_1(\alpha)$ and s-$\text{dBH}_1(\alpha)$, the homotopy algorithm can handle 10^6 hypotheses in a few minutes, while for $\text{dBH}_1^2(\alpha)$ and s-$\text{dBH}_1^2(\alpha)$, the approximate numerical integration can handle 10^5 hypotheses in 20 minutes. The results corroborate the intuition in previous sections that (a) using a sparse threshold collection yields faster algorithms, and (b) both algorithms are more efficient for sparser problems.
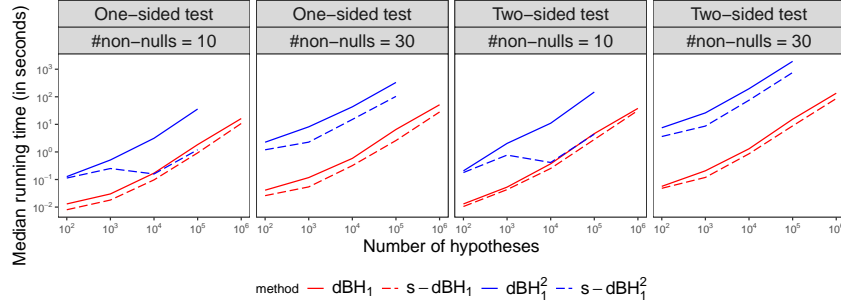

Figure 3: Median running time (in seconds) over 100 independent simulations.

5   Selected simulations

In Appendix D we provide extensive simulations to compare the power of our approach with the power of several competing procedures including the $\text{BH}(\alpha)$ and $\text{BH}(\alpha/L_m)$ procedures as well as the fixed-X knockoffs (Barber and Candès, 2015), where appropriate. This section includes some highlights from our simulation results.

We start from a multivariate Gaussian case with $m = 1000$ and $z \sim N_m(\mu, \Sigma)$ where

$$\mu_1 = \cdots = \mu_{10} = \mu^*, \quad \mu_{11} = \cdots = \mu_{1000} = 0,$$

We consider two types of covariance structures: (1) an autoregressive structure with $\Sigma_{ij} = (0.8)^{|i-j|}$; and (2) a block dependence structure with $\Sigma_{ii} = 1$ and $\Sigma_{ij} = 0.5 \cdot 1(\lceil i/20 \rceil = \lceil j/20 \rceil)$. We perform both one- and two-sided testing using $\text{BH}(\alpha)$, $\text{dBH}_\gamma(\alpha)$, $\text{dBH}_\gamma^2(\alpha)$, $\text{BY}(\alpha)$, $\text{dBY}(\alpha)$ and $\text{dBY}^2(\alpha)$. All these methods are implemented in the R package dbh. For one-sided testing, we choose $\gamma = 1$ because the p-values are CPRD, as shown in Section 3.1. For two-sided testing, we choose $\gamma = 0.9$. We set the level $\alpha = 0.05$ and tune the signal strength μ^* such that $\text{BH}(\alpha)$ has approximately 30% power in a separate Monte-Carlo simulation. We run each of the above 12 methods on 1000 independent samples of z-values and estimate the FDR and power, presented in Figure 4.
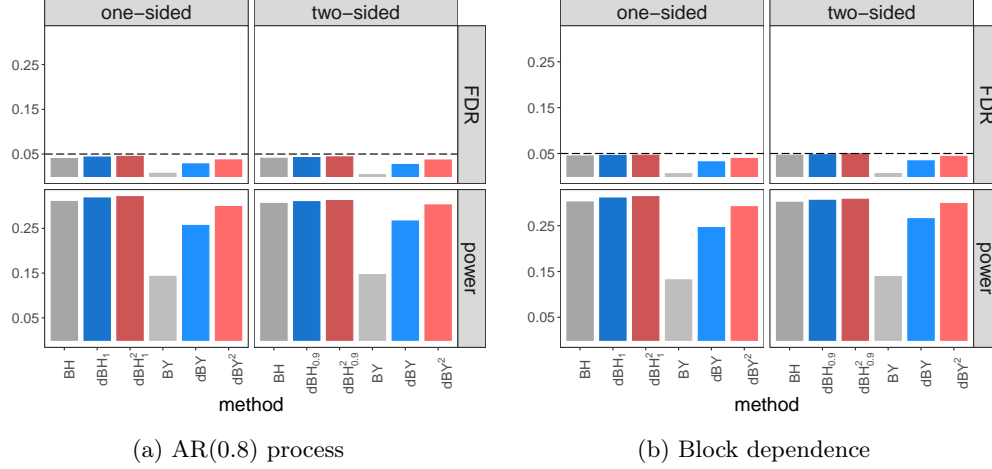
(a) AR(0.8) process

(b) Block dependence

Figure 4: Estimated FDR and power for multivariate z-statistics.

We observe that dBH and dBH^2 slightly improve the power of BH, while dBY and dBY^2 significantly improve the power of BY, for one- and two-sided testing with both covariance structures. For one-sided testing, the p-values are CPRD, so Theorem 4 guarantees that BH, dBH_1, and dBH_1^2 are all safe procedures with nested rejection sets. For two-sided testing, BH does not provably control the FDR, unlike the other five methods.

For two-sided testing, $BH(\alpha)$ does not provably control FDR, but the other five methods do. Although the $dBY_{0.9}^2(\alpha)$ procedure is not safe, the randomized pruning is never invoked over 1000 realizations of each simulation scenario. In all four scenarios, the power of dBY^2 is comparable to that of BH.

(a) $m = 100, \ n - d = 5$
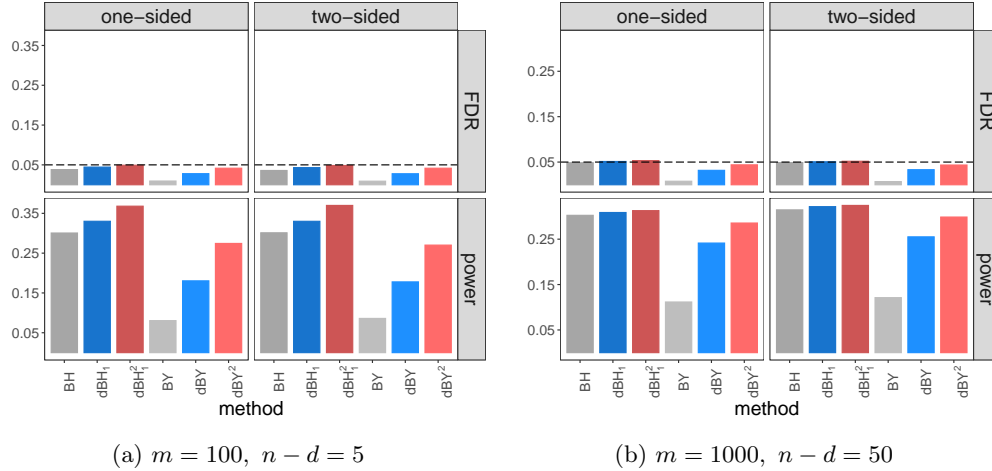
(b) $m = 1000, \ n - d = 50$

Figure 5: Estimated FDR and power for multivariate t-statistics.

Figure 5 shows results for uncorrelated multivariate t-statistics with either $m = 100, n - m = 5$ (Figure 5a) or $m = 1000, n - m = 50$ (Figure 5b). In the first case, the marginal null distribution of each test statistic is heavy-tailed, and very large values tend to be observed together due to the common variance estimate. In both cases we set the first 10 hypotheses as alternatives with an equal signal strength, tuned so that BH(0.05) has approximately 30% power. We evaluate the same six methods as in the multivariate Gaussian case, except that γ is taken as 1 for both one- and two-sided testing because both are CPRD. The results are qualitatively similar to the multivariate Gaussian results. Notably, the power gains of dBH_1 and dBH_1^2 over BH are more pronounced for heavier-tailed t-statistics.

Finally, we consider two linear modeling scenarios, for which we evaluate the fixed-X knockoff method as an extra competitor. To apply the knockoff method, we always consider two-sided testing problems with $n > 2d$. In this section we simulate the fixed design matrix $\mathbf{X}$ as one realization of a random matrix with i.i.d. Gaussian entries with $n = 3000$ and $d = 1000$, and simulate 1000 independent copies of homoscedastic Gaussian error vectors with $\sigma^2 = 1$, each generating an outcome vector $Y = \mathbf{X}\beta + \epsilon$ with $\beta_1 = \cdots = \beta_{10} = \beta^*$ and $\beta_{11} = \cdots = \beta_{1000} = 0$. Again, β^* is tuned so that BH(0.05) has approximately 30% power. For all dBH$_\gamma$ procedures, we choose $\gamma = 0.9$ and find that the randomized pruning step is never invoked for any method in the 1000 simulations. For the knockoff method, we generate the knockoff matrix via the default semidefinite programming procedure and choose the knockoff statistics as the maximum penalty level at which the variable is selected (Barber and Candès, 2015). We use the knockoff+ method in all cases to ensure FDR control at the advertised level. The estimated FDR and power with $\alpha = 0.05$ and $\alpha = 0.2$ are shown in Figure 6a. The comparison between the dBH (dBY) procedures and BH (BY) procedure is qualitatively similar to the previous examples. The fixed-X knockoff has much higher power than all other methods when $\alpha = 0.2$, but has near-zero power when $\alpha = 0.05$. The former may result from the knockoff method's use of the lasso for variable selection (Tibshirani, 1996), while the latter is due to the small-sample issue discussed in Section 7.1. Appendix B gives several more linear modeling examples showing the same qualitative pattern for random design matrices with different correlation structures.

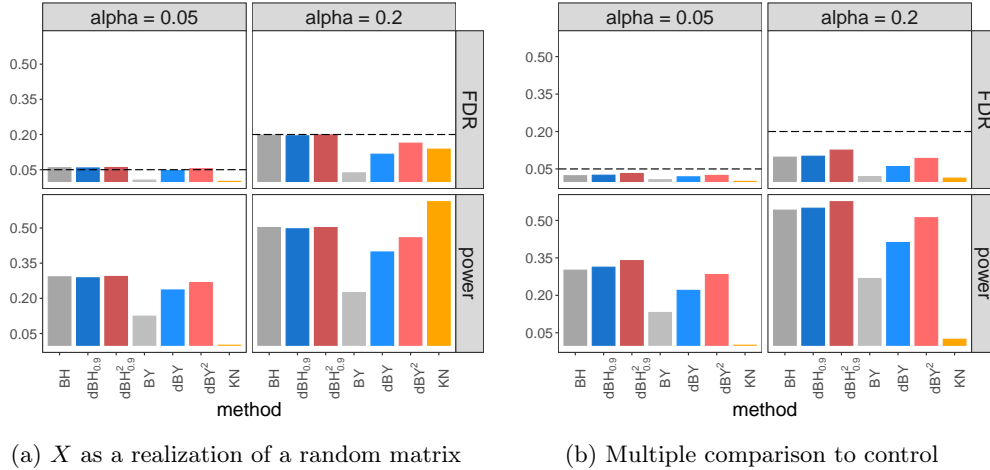(a) X as a realization of a random matrix   (b) Multiple comparison to control

Figure 6: Estimated FDR and power for two types of linear models.

While the knockoffs method often outperform the others when α is large enough, the reverse can also occur, as we illustrate in a second linear modeling example: the problem of multiple comparisons to control (MCC) in a one-way layout. For each of 100 treatment groups, we sample 30 independent replicates from $N(\mu_i, \sigma^2)$, and a control group with 30 independent replicates sampled from $N(\mu_0, \sigma^2)$. We then test $H_i : \mu_i = \mu_0$ based on the two-sample t-statistics. In this case, the test statistics are positively equi-correlated. By coding dummy variables this MCC problem is equivalent to a homoscedastic Gaussian linear model with a design matrix $\mathbf{X} \in \{0, 1\}^{3030 \times 101}$ and a coefficient vector $(\mu_1 - \mu_0, \ldots, \mu_{100} - \mu_0, \mu_0)$. To ameliorate the small-sample issue of the knockoff method, we set the first 30 hypotheses to be non-nulls with an equal μ_i that is tuned so that BH(α) has approximately 30% power. All of the coefficients are inferential targets except μ_0, which is effectively an intercept term. For fixed-X knockoffs, we follow Barber and Candès (2015) to generate a knockoff matrix that is orthogonal to the column corresponding to μ_0, which is a vector with all entries 1 in this case. The results are presented in Figure 6b. In this case, the fixed-X knockoff is almost powerless for either $\alpha = 0.05$ or $\alpha = 0.2$. In contrast to the previous case, the lack of power

is caused by the huge amount of noise generated by knockoffs to handle the equi-correlated covariance structure. The other six methods are less sensitive to this correlation.

6   HIV drug resistance data

This section compares our method's performance against the BH, BY, and knockoff procedures on the Human Immunodeficiency Virus (HIV) drug resistance data of Rhee et al. (2006), reproducing and extending the analysis of Barber and Candès (2015). In each of three separate data sets, we test for associations between mutations present in different HIV samples and resistance to each of 16 different drugs. The data come from three experiments, each for a different drug category: protease inhibitors (PIs), nucleoside reverse transcriptase inhibitors (NRTIs), and nonnucleoside reverse transcriptase inhibitors (NNRTIs).

Following Barber and Candès (2015), we encode mutations as binary with $x_{ij} = 1$ if the jth mutation is present in the ith sample, discard mutations that occur fewer than three times, and remove duplicated columns in the resulting design matrix $\mathbf{X} \in \{0, 1\}^{n \times d}$. For each drug there is a different response vector $Y \in \mathbb{R}^n$ representing a measure of drug resistance. As in Barber and Candès (2015) we do not include an intercept in the model. We also evaluate replicability in the same way as Barber and Candès (2015), by comparing the rejection set to the set of mutations identified in the treatment-selected mutation (TSM) panel of Rhee et al. (2005). We refer to Section 4 of Barber and Candès (2015) for further details.

Figure 7 shows results comparing results for the fixed-X knockoffs, BH, $\mathrm{dBH}^2_{0.9}$, and dBY^2, at significance level $\alpha = 0.2$, as used in Barber and Candès (2015). For the knockoff method, we generate equi-correlated knockoff copies and use as the knockoff statistic the maximum penalty level at which the variable is selected, following the vingette of the `knockoff` package (Patterson and Sesia, 2018). The latter three have similar power for all seven responses, with the behavior of $\mathrm{dBH}^2_{0.9}$ nearly identical to BH and dBY^2 very slightly less powerful. By contrast, the knockoffs method makes somewhat fewer rejections overall than the other methods, but the differences are modest for most drugs. Knockoffs appears to have a higher replicability rate for the TSM panel, possibly because the method is achieving a better tradeoff between Type I and Type II error by using the lasso algorithm to select variables. Alternatively, it may be that the other methods are better able to detect weak signals which are less likely to be replicated in an independent experiment. The $\mathrm{dBH}^2_{0.9}$ method does not require randomization for any of the 16 drugs.

Figure 8 shows the same results at the more conservative significance level $\alpha = 0.05$, where knockoffs suffers from the small-sample issues discussed in Section 7.1. The relationships between the other three methods are qualitatively the same. Again, $\mathrm{dBH}^2_{0.9}$ does not require randomization for any of the drugs.

7   Discussion

We have presented a new approach for controlling FDR in dependent settings, and proposed new dependence-adjusted step-up methods including the dBH_γ, dBY, and dSU_Δ procedures. The dBH_1 procedure uniformly improves on the BH procedure under (conditional) positive dependence, while the dBY procedure uniformly improves on the BY procedure. Likewise, our dSU method can uniformly improve on any shape function method in the style of Blanchard and Roquain (2008).

Practically speaking, our methods offer an alternative to the BH and BY procedures in applications where theoretical FDR control guarantees are attractive. In particular, dBY^2 improves dramatically on the BY procedure and is often competitive even with BH. The $\mathrm{dBH}^2_{0.9}$ procedure offers a balanced approach that is commonly more powerful than BH, and requires randomization only very rarely.
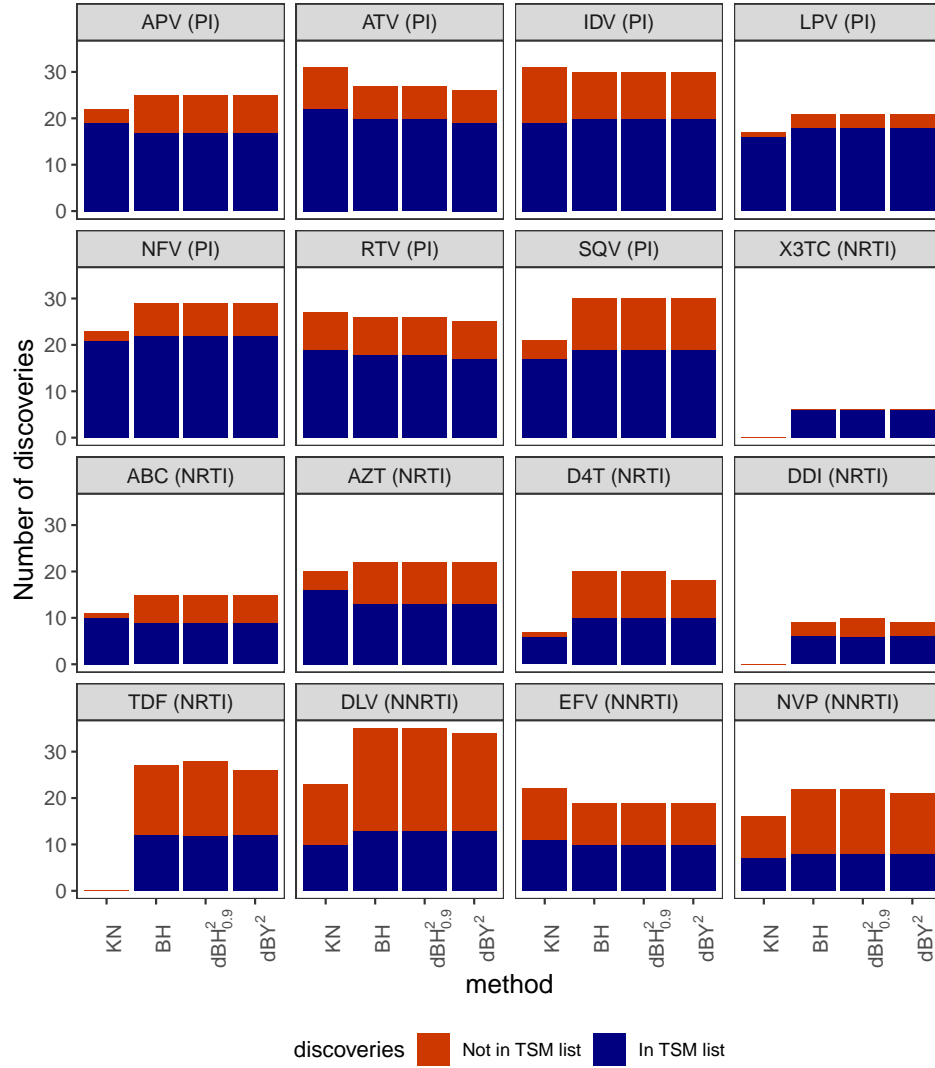
Figure 7: Results on the HIV drug resistance data with $\alpha = 0.2$. The blue segments represent the number of discoveries that were replicated in the TSM panel, while the orange segments represent the number that were not. Results are shown for the fixed-X knockoffs, BH, $\mathrm{dBH}_{0.9}^2$, and dBY.
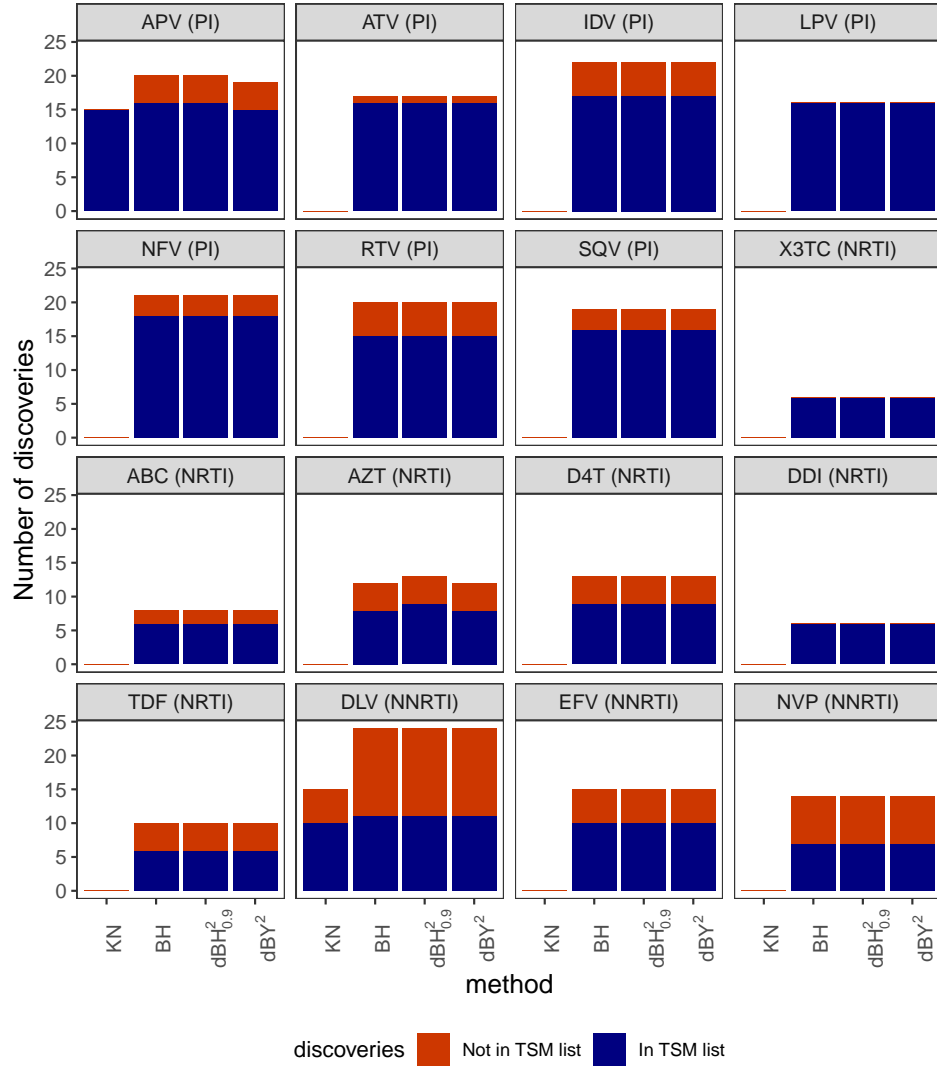
Figure 8: Results on the HIV drug resistance data with $\alpha = 0.05$. The blue segments represent the number of discoveries that were replicated in the TSM panel, while the orange segments represent the number that were not. Results are shown for the fixed-X knockoffs, BH, $\text{dBH}_{0.9}^2$, and dBY.

More generally, conditional calibration as proposed here is a general-purpose technical device that may prove useful for supplying FDR control proofs in other contexts like grouped, hierarchical, multilayer, or partial conjunction hypothesis testing (e.g. Benjamini and Bogomolov, 2014; Barber and Ramdas, 2016; Lynch and Guo, 2016; Benjamini and Heller, 2008).

Numerous challenges remain for future work, including investigation into models that constrain the dependence graph, as in Example 2.2. In addition, further development is needed to produce algorithms and software for some of the models we did not implement in this work. Finally, the next sections suggest directions of further methodological innovation.

7.1 Comparison with knockoffs

Both the dBH method and the knockoff filter offer finite-sample FDR control for linear models, but with very different statistical tools and methods of proof. In our simulation experiments neither method is a clear overall winner, but some qualitative trends emerge. First, as expected, the dBH procedure performs similarly to BH in power comparisons, so any comparison between knockoffs and dBH is also a comparison between knockoffs and BH. Second, the dBH and BH procedures consistently enjoy better power in experiments where the total number of rejections is relatively small, either because there are very few non-null coefficients to find, the signals are weak, or the FDR significance level is small. This pattern has a clear theoretical explanation: to make rejections, the knockoff+ method requires $(1 + A_t)/R_t \leq \alpha$, where A_t is the count of W_j-values smaller than $-t$ and R_t is the count above t. As a result the method cannot make any rejections unless it makes at least $1/\alpha$, and it can be unstable if the number of rejections is on the order of $1/\alpha$.

Apart from small-sample issues, it remains unclear in which contexts we should expect one method to outperform the other, and this is an interesting question for future research. Because the knockoffs framework is very general and allows the analyst to bring a great deal of prior knowledge to bear, we expect it can enjoy substantial advantages over BH and dBH in problems where the jth t-statistic carries only a small fraction of the total evidence against $H_j : \beta_j = 0$. In particular, $U_j = \hat{\beta}_{-j} - \hat{\beta}_j \mathbf{b}^j$ is independent of the t-statistic and p-value for H_j, but it may hold a wealth of information about β_j, especially if we reasonably expect that β is approximately sparse. In our view, it is an important open problem to develop methods that can likewise exploit this kind of information, for example by using adaptive weights as proposed below, while avoiding the randomization and binarization inherent to knockoff methods.

Our method is also extensible to many settings where no knockoff method has been proposed, for example edge testing in the Gaussian graphical model and the discrete and nonparametric examples discussed in Appendix B. Because our method operates directly on p-values it is easily extensible to testing composite hypotheses about parameters, for example to test $H_j : |\beta_j| \leq \delta$ for a fixed $\delta > 0$. Finally, in regression problems, there is no requirement that $n \geq 2d$; we require only that $n \geq d + 1$, the same dimension required to test individual regression coefficients. Conversely, we have not extended our framework to conditional randomization tests as proposed in Candès et al. (2018), and this may be very challenging in general. Computationally, our method is more scalable for some problems because it avoids solving a semidefinite program or eigendecomposing a large matrix, but the recursively refined variants of our method pose substantial computational challenges of their own. Nevertheless, computational efficiency depends on problem specifics.

7.2 Extension: adapting to the non-null proportion

One arguable weakness of the present work is its conservative control of the FDR at level $\alpha m_0/m$. In some problems it would be very useful to correct for this conservatism; for example, in post-screening or other post-selection inference, we may expect $\pi_0 = m_0/m$ to be substantially smaller than 1. For independent p-values, various plug-in methods apply

a standard method such as BH at an adjusted level $\alpha \hat{\pi}_0^{-1}$, for some estimator $\hat{\pi}_0(X)$. (e.g. Genovese and Wasserman, 2002; Storey, 2002; Storey et al., 2004; Benjamini et al., 2006; Blanchard and Roquain, 2009).

Inspired by this approach, we can modify our calibration procedure as discussed in Remark 2.1 to use the calibration constraint $\kappa_i(S_i) = \alpha \hat{\pi}_{0,i}(S_i)^{-1}/m$ in place of α/m in (8). The resulting method would control FDR at level α provided that

$$\sum_{i \in \mathcal{H}_0} \mathbb{E} \hat{\pi}_{0,i}(S_i)^{-1} \leq \pi_{0,i}^{-1} m_0 = m,$$

for which a sufficient condition is that $\mathbb{E}_{H_i} \hat{\pi}_0(S_i)^{-1} \leq \pi_0^{-1}$ for each $i = 1, \ldots, m$. Given any pre-existing estimator $\tilde{\pi}_0(X)$ for which $\mathbb{E} \tilde{\pi}_0(X)^{-1} \leq \pi_0^{-1}$, we can construct such an estimator by Rao-Blackwellization:

$$\hat{\pi}_{0,i}(S_i) = \left(\mathbb{E}_{H_i} \left[\tilde{\pi}_0(X)^{-1} \mid S_i \right] \right)^{-1},$$

which amounts to a simple calculation if H_i is conditionally simple.

7.3   Extension: adaptive weights

Another promising extension, the full exploration of which is outside the scope of this work, is to use adaptive weights that exploit side information about the hypotheses. There are a variety of setting where p-value weights w_i can substantially improve the power of multiple-testing methods (Benjamini and Hochberg, 1997; Genovese et al., 2006; Dobriban et al., 2015). For fixed weights $w_1, \ldots, w_m$ that sum to one, it is straightforward to generalize our framework by replacing α/m by αw_i in the right-hand side of (8).

More interestingly, however, we might wish to use learn the weights from the data, adaptively allowing for some hypotheses to contribute more to the FDR than others. While there is a robust literature on adaptive p-value weighting for independent hypotheses (e.g. Ignatiadis et al., 2016; Boca and Leek, 2017; Li and Barber, 2019; Lei and Fithian, 2018; Ignatiadis and Huber, 2017; Xia et al., 2017; Tansey et al., 2018), there is very little work on adaptive weighting for dependent p-values. This is a major gap in the literature, since true independence between p-values is rare in applied problems

Similarly to the strategy described above for estimating π_0, we can accommodate data-adaptive weights by using $\kappa_i(S_i) = \alpha w_i(S_i)$, provided that $\sum_{i \in \mathcal{H}_0} \mathbb{E} w_i(S_i) \leq 1$. As above, we can Rao-Blackwellize initial weights $\tilde{w}$ by setting $w_i(S_i) = \mathbb{E}_{H_i} \left[\tilde{w}_i \mid S_i \right]$. If $\sum_i \tilde{w}_i(X) \leq 1$ almost surely, then

$$\sum_{i \in \mathcal{H}_0} \mathbb{E} \kappa_i(S_i) = \alpha \sum_{i \in \mathcal{H}_0} \mathbb{E} \tilde{w}_i \leq \alpha.$$

We defer exploration of this idea to future work.

Reproducibility

Our R package dbh is available to download at `https://github.com/lihualei71/dbh`. A public github repo accompanying the paper with code to reproduce the figures herein can be found at `https://github.com/lihualei71/dbhPaper`.

Acknowledgments

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A Proofs

We restate and prove several of the technical results from the paper.

Lemma 1. *Let $p^{(i\leftarrow 0)} = (p_1, \ldots, p_{i-1}, 0, p_{i+1}, \ldots, p_m)$. If $\mathcal{R}$ is a step-up procedure with threshold sequence $\Delta(1), \ldots, \Delta(m)$, then the following are equivalent:*

1. $p_i \leq \Delta(R(p^{(i\leftarrow 0)}))$,

2. $i \in \mathcal{R}(p)$, and

3. $\mathcal{R}(p) = \mathcal{R}(p^{(i\leftarrow 0)})$.

Proof. Let $p^0 = p^{(i\leftarrow 0)}$, $R^0 = R(p^{(i\leftarrow 0)})$, $R = R(p)$. By the properties of step-up procedures, we always have $p^0_{(R^0)} \leq \Delta(R^0)$ and $p_{(R)} \leq \Delta(R)$, and $j \in \mathcal{R}(p)$ iff $p_j \leq \Delta(R)$. By monotonicity, we have $R^0 \geq R$ and $\Delta(R^0) \geq \Delta(R)$.

$(1 \Rightarrow 2)$. Assume $p_i \leq \Delta(R^0)$. Because $p^0_{(R^0)} \leq \Delta(R^0)$, and p and p^0 only differ in their ith coordinate, we have $p_{(R^0)} \leq p_i \vee p^0_{(R^0)} \leq \Delta(R^0)$. As a result, $R \geq R^0$ and $\Delta(R) \geq \Delta(R^0) \geq p_i$.

$(2 \Rightarrow 3)$. Assume $i \in \mathcal{R}(p)$. Then $p_i \leq p_{(R)} \leq \Delta(R)$, and $p_{(r)} > \Delta(r)$ for $r > R$. Because $p^0_{(r)} = p_{(r)}$ for all order statistics with $p_{(r)} \geq p_i$, we have $R^0 = R$ as well. As a result,

$$\mathcal{R}(p) = \{j : p_j \leq \Delta(R)\} = \{j : p_j \leq \Delta(R^0)\} = \mathcal{R}(p^0)$$

$(3 \Rightarrow 1, 2)$. Assume $\mathcal{R}(p) = \mathcal{R}(p^{(i \leftarrow 0)})$. Because $p_i^0 = 0$, $i \in \mathcal{R}(p^{(i \leftarrow 0)}) = \mathcal{R}(p)$, so we must have $p_i \leq \Delta(R) = \Delta(R^0)$. $\qquad \square$

Theorem 3. *Assume $\hat{c}_1, \ldots, \hat{c}_m$ are maximal. Then*

1. *If the p-values are independent with p_i uniform under H_i, then the $\mathrm{dBH}_1(\alpha)$ procedure with $S_i = p_{-i}$ is identical to the $\mathrm{BH}(\alpha)$ procedure.*

2. *If the p-values are CPRDS for all $P \in \mathcal{P}$, then the $\mathrm{dBH}_1(\alpha)$ procedure is safe, and uniformly more powerful than the $\mathrm{BH}(\alpha)$ procedure.*

3. *For arbitrary dependence, the $\mathrm{dBY}(\alpha)$ procedure is safe, and uniformly more powerful than the $\mathrm{BY}(\alpha)$ procedure.*

4. *Assume the thresholds Δ_α are of the form (4). Then for arbitrary dependence, the $\mathrm{dSU}_\Delta(\alpha)$ procedure is safe, and uniformly more powerful than the $\mathrm{SU}_\Delta(\alpha)$ procedure.*

Proof.
Claim 1. If $R_i^0 = R^{\mathrm{BH}(\alpha)}(p^{(i \leftarrow 0)})$, then by Lemma 1 we have

$$p_i \leq \frac{\alpha R_i^0}{m} \iff i \in \mathcal{R}^{\mathrm{BH}(\alpha)},$$

with $\widehat{R}_i = R^{\mathrm{BH}(\alpha)} = R_i^0$ on the same set. As a result,

$$g_i^*(\alpha; p_{-i}) = \mathbb{E}_{H_i} \left[\frac{1\{p_i \leq \alpha R_i^0/m\}}{R_i^0} \mid p_{-i} \right] = \frac{\alpha}{m}.$$

For $c > \alpha$, we have $c R_i^0/m \leq \tau^{\mathrm{BH}}(c)$, so

$$g_i^*(c; p_{-i}) \geq \frac{\alpha}{m} + \mathbb{E}_{H_i} \left[\frac{1\{\alpha R_i^0/m < p_i \leq c R_i^0/m\}}{m} \mid p_{-i} \right] > \frac{\alpha}{m}$$

As a result, $\hat{c}_i = 1$ for all $i = 1, \ldots, m$, so $\mathcal{R} = \mathcal{R}_+ = \mathcal{R}^{\mathrm{BH}(\alpha)}$.

Claim 2. Because $\{\widehat{R}_i \leq r\}$ is a non-decreasing set for all $r \leq m$ we have for $P \in H_i$,

$$\mathbb{P}_P \left[\widehat{R}_i \leq r \mid p_i \leq \frac{\alpha r}{m}, S_i \right] + \mathbb{P}_P \left[\widehat{R}_i = r + 1 \mid p_i \leq \frac{\alpha(r+1)}{m}, S_i \right] \tag{37}$$

$$\leq \mathbb{P}_P \left[\widehat{R}_i \leq r \mid p_i \leq \frac{\alpha(r+1)}{m}, S_i \right] + \mathbb{P}_P \left[\widehat{R}_i = r + 1 \mid p_i \leq \frac{\alpha(r+1)}{m}, S_i \right] \tag{38}$$

$$= \mathbb{P}_P \left[\widehat{R}_i \leq r + 1 \mid p_i \leq \frac{\alpha(r+1)}{m}, S_i \right]. \tag{39}$$

Beginning with $\{\widehat{R}_i \leq 1\} = \{\widehat{R}_i = 1\}$ and then iteratively applying the above inequality, we obtain

$$\sum_{r=1}^m \mathbb{P}_P \left[\widehat{R}_i = r \mid p_i \leq \frac{\alpha r}{m}, S_i \right] \leq \mathbb{P}_P \left[\widehat{R}_i \leq m \mid p_i \leq \alpha, S_i \right] = 1, \tag{40}$$

and

$$\mathbb{E}_P \left[\frac{1\left\{p_i \leq \alpha \widehat{R}_i/m\right\}}{\widehat{R}_i} \mid S_i \right] = \sum_{r=1}^m \frac{1}{r} \mathbb{P}_P \left[\widehat{R}_i = r, p_i \leq \frac{\alpha r}{m} \mid S_i \right] \tag{41}$$

$$\leq \sum_{r=1}^m \frac{\alpha}{m} \mathbb{P}_P \left[\widehat{R}_i = r \mid p_i \leq \frac{\alpha r}{m}, S_i \right] \tag{42}$$

$$\leq \frac{\alpha}{m}, \tag{43}$$

so $g_i^*(\alpha\,;S_i) \le \alpha/m$ and $\hat{c}_i \ge \alpha$. As a result, $\mathcal{R}_+ \supseteq \mathcal{R}^{\mathrm{BH}(\alpha)}$, so $R_+ \ge \widehat{R}_i$ for all $i \in \mathcal{R}_+$.

Claim 4. Define $R^\alpha = R^{\mathrm{SU}_\Delta(\alpha)}$, $\Delta_\alpha(0) = 0$, and the intervals $I_k = (\Delta_\alpha(k-1), \Delta_\alpha(k)]$ for $k = 1, \ldots, m$. By the nature of step-up procedures, $i \in \mathcal{R}^{\mathrm{SU}_\Delta(\alpha)}$ and $R^\alpha = \widehat{R}_i$ on the set $\{p_i \le \Delta_\alpha(R^\alpha)\}$. Then we have for $P \in H_i$,

$$\mathbb{E}_P\left[\frac{1\{p_i \le \tau_i(\alpha)\}}{\widehat{R}_i} \mid S_i\right] = \mathbb{E}_P\left[\frac{1\{p_i \le \alpha\beta(R^\alpha)/m\}}{R^\alpha} \mid S_i\right] \tag{44}$$

$$= \sum_{k=1}^m \mathbb{E}_P\left[\frac{1\{p_i \le \alpha\beta(R^\alpha)/m\}}{R^\alpha} \cdot 1\{p_i \in I_k\} \mid S_i\right] \tag{45}$$

$$\le \sum_{k=1}^m \frac{1}{k}\, \mathbb{P}_P\left[p_i \in I_k \mid S_i\right] \tag{46}$$

$$\le \sum_{k=1}^m \frac{1}{k} \cdot (\Delta_\alpha(k) - \Delta_\alpha(k-1)) \tag{47}$$

$$= \frac{\alpha}{m} \sum_{k=1}^m \nu(\{k\}) = \frac{\alpha}{m}. \tag{48}$$

The inequality in (46) follows from the fact that

$$p_i \in I_k \text{ and } p_i \le \frac{\alpha\beta(R^\alpha)}{m} \implies R^\alpha \ge k.$$

Because $1/k$ is decreasing in k, the uniform distribution maximizes the sum in (46) among all superuniform distributions, leading to the inequality in (47).

Claim 3. If we define $\tau^{\mathrm{BY}}(c) = \tau^{\mathrm{BH}}(c/L_m)$, a rescaled version of the effective BH threshold, then the claim follows as a special case of Claim 4, with $\nu(\{k\}) = (kL_m)^{-1}$. $\qquad\square$

B   Further examples

B.1   Edge testing in Gaussian graphical models

In the usual Gaussian graphical model (GGM) setting, we observe $X_1, \ldots, X_n \overset{\text{i.i.d.}}{\sim} N_d(\mu, \Sigma)$, and attempt to reconstruct the partial dependence graph $\mathcal{G}$ of pairs (j, k) for which X_{ij} and X_{ik} are not independent conditional on $X_{i,-(jk)}$. As a hypothesis testing problem, the edge (j, k) is not present if and only if $\Theta_{ij} = 0$, where $\Theta = \Sigma^{-1}$; thus

$$H_{jk}: \ \Theta_{ij} = 0 \iff (i, j) \notin \mathcal{G}.$$

We begin by constructing the sample covariance matrix

$$V(X) = \frac{1}{n-1}\sum_i (X_i - \overline{X})(X_i - \overline{X})', \quad \text{with } (n-1)V \sim \text{Wishart}(\Sigma, n-1).$$

The Wishart distribution is an exponential family with complete sufficient statistic $T(X) = (\overline{X}, V)$, and the standard test for H_{jk} is simply the t-test for the coefficient of X_j in a multiple regression of X_k on the other $d-1$ variables.

A homotopy algorithm for the Wishart problem is more complex than the homotopy algorithm for the other Gaussian-derived problems discussed above.

B.2 Post-selection z- and t-tests

Another potentially interesting application of our work is in post-selection multiple testing of regression coefficients after some . The post-selection distribution of regression coefficients follows a truncated multivariate Gaussian leading to post-selection z- and t-tests depending on whether the error variance is known or unknown, as investigated in various works including Tibshirani et al. (2016); Lee et al. (2016); Fithian et al. (2014); Tian and Taylor (2018). Because the post-selection distribution is a continuous exponential family, methods closely related to the ones discussed above may be used, with more computational effort. We leave full investigation of these examples to future work.

B.3 Multiple comparisons to control for binary outcomes

Our methods extend to discrete as well as continuous models. For example, consider a clinical trial or A/B test with binary outcomes, in which m different treatments are compared in the same experiment to a common control treatment, known as the *multiple comparisons to control* (MCC) problem in multiple testing. Let n_i denote the number of experimental subjects in the ith treatment group, and let $X_i \sim \text{Binom}(n_i, \theta_i)$ denote the number whose binary response is positive. In addition, let $X_0 \sim \text{Binom}(n_0, \theta_0)$ denote the number of positive responses in the control group. Assume that $n_0, \dots, n_m$ are fixed and known.

To test $H_i : \theta_i = \theta_0$ (or $H_i : \theta_i \leq \theta_0$), we can reject for extreme values (respectively large values) of the statistic X_i, whose null distribution is hypergeometric conditional on $S_i = (X_0 + X_i, X_{-i})$. The resulting p-values are correlated with each other through their common dependence on X_0, since larger values of X_0 shift the null distributions of all X_i to the right, increasing the tests' critical values.

Conditional expectations given S_i in this model can be evaluated exactly, since X_i is conditionally supported on the finite set $\{0 \vee (X_0 + X_i - n_0), \dots, n_i \wedge (X_0 + X_i)\}$.

B.4 Nonparametric multiple comparisons to control

Conditionally simple models can arise in other contexts than exponential families; for example, consider a nonparametric one-way layout problem with real-valued observations:

$$X_{ij} \stackrel{\text{i.i.d.}}{\sim} F_i, \quad \text{for } i = 0, \dots, m, \ j = 1, \dots, n_i.$$

Such a model might arise in an A/B testing context where we wish to compare each F_i for $i \geq 1$ with a common control distribution F_0, a nonparametric version of the MCC problem. A complete sufficient statistic for the full model $\mathcal{P}$ is the set of order statistics for each of the $m + 1$ samples, or equivalently the empirical distributions of each sample $T(X) = (\widehat{F}_0, \dots, \widehat{F}_m)$, where

$$\widehat{F}_i(x) = \frac{1}{n_i} \sum_j 1\{X_{ij} \leq x\}.$$

The null hypothesis $H_i : F_i = F_0$ defines a submodel with complete sufficient statistic

$$S_i = \left(\frac{n_0 \widehat{F}_0 + n_i \widehat{F}_i}{n_0 + n_i}, \ \widehat{F}_1, \dots, \widehat{F}_{i-1}, \widehat{F}_{i+1}, \dots, \widehat{F}_m \right),$$

or equivalently the pooled order statistics of sample i and the control sample, as well as the separate order statistics of each of the other samples. Under H_i, every permutation of the order statistics is equally likely, and the p-value any two-sample permutation test of H_i will be uniformly distributed on $\left\{ \frac{1}{B+1}, \dots, \frac{B}{B+1}, 1 \right\}$ where B is the number of random permutations used (ruling out ties).

C   Algorithmic Details

In this Appendix we discuss the algorithmic details as well as the computational tricks of both the homotopy algorithm and approximate numerical integration.

C.1   Useful subclasses of $\mathrm{dSU}_{\gamma,\Delta}$

For any threshold collection $\{\Delta_\alpha(r) : r \in [m]\}$, the homotopy algortihm in Section 4.1 can be applied to $\mathrm{dSU}_{\gamma,\Delta}$ with slight modification. Here we introduce several subclasses of sparse threshold collections that can reduce computational cost without losing nice theoretical guarantees. Given any integers $1 \leq a_1 < a_2 < \cdots < a_L \leq m$, define

$$\Delta_\alpha(r) = \frac{\alpha\beta(r)}{m} = \frac{\alpha a_\ell}{m}, \quad (r \in [a_\ell, a_{\ell+1}),\ \ell = 0, 1, \ldots, L), \tag{49}$$

where $a_0 = 0$ and $a_{L+1} = m + 1$ for convenience. Note that $\beta(r) \leq r$. Using the same argument as in the proof of Theorem 3 Claim 1 and 2, we can prove that $\mathrm{dSU}_{\gamma,\Delta}$ with (49) controls FDR at level α in finite samples when the p-values are independent or CPRDS. Further, we can define the safe version by setting $\gamma = 1/L_{m,a}$ where

$$L_{m,a} = \sum_{\ell=1}^{L} \frac{a_\ell - a_{\ell-1}}{a_\ell}.$$

This is safe because $\beta(r)/L_{m,a}$ can be rewritten as $\sum_{i=1}^{r} i\nu(\{i\})$ where

$$\nu(\{a_\ell\}) = (a_\ell - a_{\ell-1})/a_\ell L_{m,a}, \text{ and } \nu(\{i\}) = 0,\ (i \notin \{a_1, \ldots, a_L\}).$$

It is easy to verify that ν is a density function on $[m]$ and thus the proof of Theorem 3 Claim 4 guarantees that $\mathrm{dSU}_{1/L_{m,a},\Delta}$ is safe.

Indeed, (49) includes various interesting cases.

- When $L = 1$ and $a_1 = 1$, (49) recovers the Bonferroni correction. Moreover $L_{m,a} = 1$, implying that the Bonferroni correction is safe without correcting α.

- When $L = m$ and $a_\ell = \ell$, (49) recovers $\mathrm{BH}(\alpha)$. In this case, $L_{m,a} = \sum_{\ell=1}^{m}(1/\ell)$ so the safe version recovers the $\mathrm{BY}(\alpha)$ procedure.

- When $L = \lfloor \log_2 m \rfloor$ and $a_\ell = 2^\ell$, (49) recovers the setting (35) and $L_{m,a} = L/2$.

Motivated by (35), we design a class of "geometrically increasing" integer sequences with simple analytical forms as follows:

$$a_\ell = \left\lceil \frac{\beta^{\ell-1} - 1}{\beta - 1} + 1 \right\rceil,\ \ell \in [L] \text{ where } L = \left\lfloor \frac{\log\{(\beta - 1)(m - 1) + 1\}}{\log \beta} \right\rfloor \tag{50}$$

It is easy to see that (35) is a special case of (50) with $\beta = 2$. Since $a_1 = 1$, $\mathrm{dSU}_{1,\Delta}(\alpha)$ is never less powerful than the Bonferroni correction.

As for power, $\mathrm{dSU}_{1,\Delta}(\alpha)$ is strictly dominated by $\mathrm{dBH}_1(\alpha)$ since $\beta(r) \leq r$. However, $\mathrm{dSU}_{1/L_{m,a},\Delta}(\alpha)$ may be more powerful than $\mathrm{dBH}_{1/L_m}(\alpha)$ when $L_{m,a} \leq L_m$. For instance, $L_m = \log m + \mathcal{O}(1)$ while $L_{m,a} = (\log m)((\beta - 1)/\beta \log \beta) + \mathcal{O}(1)$ for Δ defined in (50). As long as $\beta > 1$, $L_{m,a} < L_m$ for sufficiently large m. Furthermore, it is easy to verify that the mapping $\beta \mapsto (\beta - 1)/\beta \log \beta$ is decreasing in β. Thus a higher β would produce a smaller correction factor $L_{m,a}$.

As for computational efficiency, $\mathrm{dSU}_{\gamma,\Delta}(\alpha)$ may be faster than $\mathrm{dBH}_\gamma(\alpha)$, when the number of distinct positive thresholds is L is much smaller than m, in which case the number of potential knots is reduced as discussed in Section 4. For the class (50), the number of distinct thresholds is $\log m / \log \beta + \mathcal{O}(1)$.

C.2 Computation tricks

C.2.1 Efficient update of $R_i^{(c)}(t)$

In principle, $R_i^{(c)}(t)$ can be recovered from $\{B_\ell^{(c)}(t) : \ell = 0, \ldots, m\}$ by (32). However, this naive method involves a search with computational cost up to m for each knot. Indeed, $R_i^{(c)}(t_k)$ can also be updated sequentially as follows:

$$
R_i^{(c)}(t_k) = \begin{cases}
R_i^{(c)}(t_{k-1}) & (\text{if } r_k < R_i^{(c)}(t_{k-1})) \\
R_i^{(c)}(t_{k-1}) & (\text{if } r_k \geq R_i^{(c)}(t_{k-1}) \text{ and } B_{r_k}^{(c)}(t_k) \neq 0) \\
r_k & (\text{if } r_k > R_i^{(c)}(t_{k-1}) \text{ and } B_{r_k}^{(c)}(t_k) = 0) \\
\max \left\{ \ell < r_k : B_\ell^{(c)}(t) = 0 \right\} & (\text{if } r_k = R_i^{(c)}(t_{k-1}) \text{ and } B_{r_k}^{(c)}(t_k) = 0)
\end{cases} .
$$

In all but the last scenario, the search cost is zero. Only when the value of $R_i^{(c)}(t)$ decreases, the search cost is nonzero and equal to $R_i^{(c)}(t^-) - R_i^{(c)}(t)$. For the independent and CPRDS case, $R_i^{(c)}(t)$ is strictly increasing and thus no search is needed at all. For other cases, we observe that in most cases $R_i^{(c)}(t)$ is strictly increasing or has occasional drops by a small amount. Therefore, the search cost of updating $R_i^{(c)}(t)$ is negligible.

C.2.2 Q-value capping to reduce $\sum_i$

As discussed in Section 4.1, the first determinant of the computational cost is the size of $\sum_i$ in (34), namely the number of hypotheses for which $g_i^*(q_i \, ; S_i)$ needs to be evaluated. Intuitively, the maximal $\hat{c}_i$ cannot be much larger than α. For $\mathrm{dBH}_1(\alpha)$ on independence p-values, $g_i^*(\alpha \mid S_i) = \alpha/m$ and thus $\hat{c}_i = \alpha$. For CPRDS cases, although $\hat{c}_i \geq \alpha$, we observed that it is always below 2α in all our pilot numerical studies. Of course there is no theoretical guarantee that $\hat{c}_i \leq 2\alpha$. Nonetheless, if we cap $\hat{c}_i$ at 2α, the dBH procedures still control FDR in finite samples because this operation is equivalent to modifying $\tau_i(c; X)$ as $\tau_i(c \wedge 2\alpha; X)$ which is still non-decreasing in c for all X. This trick excludes all hypotheses with q-values above 2α, without the need to compute g_i^*. As a result, the size of $\sum_i$ is reduced to $R_{\mathrm{BH}}(2\alpha)$, which is usually a few orders of magnitude smaller than m. Meanwhile, as we observed, it is typical that $\hat{c}_i < 2\alpha$ and so this capping step does not lose power.

C.2.3 Screening to reduce $\sum_j$ and $\sum_r$

For a given hypothesis H_i, we need to find $\mathcal{K}_{i,j,r}$ defined in (31). As discussed in Section 4.2, for one-sided testing, we can also reduce the range of the integral (30) from $\mathbb{R}$ to a finite interval $[t_{\mathrm{lo}}, t_{\mathrm{hi}}]$ with a tiny approximation error $\alpha\epsilon/m$. Similarly, the range can be reduced into $[-t_{\mathrm{hi}}, -t_{\mathrm{lo}}] \cup [t_{\mathrm{lo}}, t_{\mathrm{hi}}]$ for two-sided testing considered in Section 3. For simplicity, we only discuss one-sided testing in this subsection and discuss a shortcut to handle two-sided testing in the next subsection. For this reason, we only need to find knots lying in this interval. Our goal is to find an efficient way to identify pairs (j, r) for which $\mathcal{K}_{i,j,r} \cap [t_{\mathrm{lo}}, t_{\mathrm{hi}}]$ is empty and to ignore them in the computation.

The idea is to compute the minimum $p_{j,\min}$ and maximum $p_{j,\max}$ of $p_j(t)$ over $[t_{\mathrm{lo}}, t_{\mathrm{hi}}]$ and to find all thresholds between $[p_{j,\min}, p_{j,\max}]$. As a result, those with no thresholds in the interval can be excluded directly, thereby reducing the size of $\sum_j$, while given j, the thresholds outside the interval can be excluded, thereby reducing the size of $\sum_r$. It can be implemented efficiently if $p_{j,\min}$ and $p_{j,\max}$ have analytical forms.

For the one-sided multivariate Gaussian testing problem, since η_i is increasing and ξ_{ij} is linear, the minimum and maximum are achieved at t_{lo} (resp. t_{hi}) and t_{hi} (resp. t_{lo}) if $\Sigma_{j,i} > 0$ (resp. $\Sigma_{j,i} < 0$). For short-ranged covariance structures like in the AR process, $\Sigma_{j,i}$ is tiny for most j's. For such a j, $p_{j,\min}$ is very close to $p_{j,\max}$ and it is likely that $\mathcal{K}_{i,j,r} \cap [t_{\mathrm{lo}}, t_{\mathrm{hi}}]$ is empty. So the screening step can adaptively remove the hypotheses with low correlation with H_i.

C.2.4 A shortcut for two-sided testing

For all examples considered in Section 3, $\xi_{ij}(t)$ is identical for one- and two-sided testing. For the latter, $f_j(t) = 2(1 - F(|t|))$ where F is the marginal distribution function. In addition, since the effective range of the integral (30) can be reduced to $[-t_{\mathrm{hi}}, -t_{\mathrm{lo}}] \cup [t_{\mathrm{lo}}, t_{\mathrm{hi}}]$, it remains to compute

$$\mathcal{K}_{i,j,r} \cap ([-t_{\mathrm{hi}}, -t_{\mathrm{lo}}] \cup [t_{\mathrm{lo}}, t_{\mathrm{hi}}]) = \left\{ t \in [-t_{\mathrm{hi}}, -t_{\mathrm{lo}}] \cup [t_{\mathrm{lo}}, t_{\mathrm{hi}}] : \xi_{ij}(t) = \pm F^{-1}\left(1 - \frac{cr}{2m}\right) \right\}.$$

This can be written as the union of four sets $\mathcal{K}_{i,j,r}^{++} \cup \mathcal{K}_{i,j,r}^{+-} \cup \mathcal{K}_{i,j,r}^{-+} \cup \mathcal{K}_{i,j,r}^{--}$ where

$$\mathcal{K}_{i,j,r}^{++} = \left\{ t : t \in [t_{\mathrm{lo}}, t_{\mathrm{hi}}], \xi_{ij}(t) = F^{-1}\left(1 - \frac{cr}{2m}\right) \right\}$$

$$\mathcal{K}_{i,j,r}^{+-} = \left\{ t : t \in [t_{\mathrm{lo}}, t_{\mathrm{hi}}], -\xi_{ij}(t) = F^{-1}\left(1 - \frac{cr}{2m}\right) \right\}$$

$$\mathcal{K}_{i,j,r}^{-+} = \left\{ -t : t \in [t_{\mathrm{lo}}, t_{\mathrm{hi}}], \xi_{ij}(-t) = F^{-1}\left(1 - \frac{cr}{2m}\right) \right\}$$

$$\mathcal{K}_{i,j,r}^{--} = \left\{ -t : t \in [t_{\mathrm{lo}}, t_{\mathrm{hi}}], -\xi_{ij}(-t) = F^{-1}\left(1 - \frac{cr}{2m}\right) \right\}.$$

Each of them has the same structure as in the one-sided testing counterpart, with $\xi_{ij}(t)$ replaced by $\xi_{ij}(t), \xi_{ij}(-t), -\xi_{ij}(t), -\xi_{ij}(-t)$, and we compute each of the four sets separately.

C.2.5 Screening for $\mathrm{dBH}_\gamma^2(\alpha)$

Denote by $g_i^{(1)}$ and $g_i^{(2)}$ the conditional expectations $g_i^*(q_i\,;S_i)$ in $\mathrm{dBH}_\gamma(\alpha)$ and $\mathrm{dBH}_\gamma^2(\alpha)$, respectively. Note that $g_i^{(2)}$ is much more expensive to compute than $g_i^{(1)}$. When the procedure is safe, Theorem 4 guarantees that $g_i^{(2)} \le g_i^{(1)}$ almost surely. As a consequence, $g_i^{(2)}$ is below α/m whenever $g_i^{(1)}$ is and thus we can avoid computing $g_i^{(2)}$ for all rejected hypotheses by $\mathrm{dBH}_\gamma(\alpha)$.

When the procedure is not safe, through extensive numerical studies, we observed that $g_i^{(1)}$ and $g_i^{(2)}$ are typically not significantly different for any given i. Thus we can view $g_i^{(1)}$ as a proxy for $g_i^{(2)}$. Since it is only necessary to decide whether $g_i^{(2)} \le \alpha/m$, we avoid the computation if $g_i^{(1)} \le C\alpha/m$ for some constant $C < 1$. In particular, we choose $C = 0.9$ in our implementation as the default.

C.3 Finding knots for multivariate t-statistics

Recall the definitions of η_i and ξ_{ij} from Section 4.1. For multivariate t-statistics, as shown in Section 3.2,

$$\xi_{ij}(t) = a_{ij}\sqrt{n - d + t^2} + b_{ij}t, \text{ where } a_{ij} = \frac{U_i}{\sqrt{V_i \Psi_{j,j}}}, \text{ and } b_{ij} = \frac{\Psi_{j,i}}{\Psi_{i,i}}.$$

Note that $\xi_{ij}(t), \xi_{ij}(-t), -\xi_{ij}(t), -\xi_{ij}(-t)$ all have this form. Recalling the definition of $\mathcal{K}_{i,j,r}$ and the discussion in Appendix C.2.4, we need to solve equations in the following form (after transforming t to $t\sqrt{n - d}$):

$$a\sqrt{1 + t^2} + bt = c. \tag{51}$$

Moreover, if $\alpha < 0.5$, we only need to find *positive* solutions in $[t_{\mathrm{lo}}, t_{\mathrm{hi}}]$ and we know that $c > 0$. Nonetheless, the solution of (51) is more complicated than it appears to be. Although it is attempting to solve the induced quadratic equation $a^2(1 + t^2) = (c - bt)^2$, the solution of the latter may not satisfy (51) since we need $\mathrm{sign}(c - bt) = \mathrm{sign}(a)$. Moreover, as shown in (33) in Section 4.1, we also need to compute $\mathrm{sign}(p_j'(t))$. In this case,

$$\mathrm{sign}(p_j'(t)) = \mathrm{sign}(\eta_j'(\xi_{ij}(t))\xi_{ij}'(t)) = \mathrm{sign}(\xi_{ij}'(t)).$$

With a generic form (51), $\xi'_{ij}(t) = at/\sqrt{1+t^2} + b$.

In order to apply the screening step discussed in Appendix C.2.3, we need analytical formulae for the minimum and maximum of the function $t \mapsto a\sqrt{1+t^2} + bt$.

Proposition 8. *Write $m(t)$ for $a\sqrt{1+t^2} + bt$. Given any $0 < t_{\mathrm{lo}} < t_{\mathrm{hi}}$, let $m_- = \min\{m(t_{\mathrm{lo}}), m(t_{\mathrm{hi}})\}$ and $m_+ = \max\{m(t_{\mathrm{lo}}), m(t_{\mathrm{hi}})\}$.*

- *If $|a| \leq |b|$ or $\mathrm{sign}(a) = \mathrm{sign}(b)$,*

$$\min_{t \in [t_{\mathrm{lo}}, t_{\mathrm{hi}}]} m(t) = m_-, \qquad \max_{t \in [t_{\mathrm{lo}}, t_{\mathrm{hi}}]} m(t) = m_+.$$

- *If $|a| > |b|$ and $\mathrm{sign}(a) = \mathrm{sign}(b)$. Let $t^* = \sqrt{b^2/(a^2 - b^2)}$.*

  - *If $t^* \notin [t_{\mathrm{lo}}, t_{\mathrm{hi}}]$,*

$$\min_{t \in [t_{\mathrm{lo}}, t_{\mathrm{hi}}]} m(t) = m_-, \qquad \max_{t \in [t_{\mathrm{lo}}, t_{\mathrm{hi}}]} m(t) = m_+.$$

  - *If $t^* \in [t_{\mathrm{lo}}, t_{\mathrm{hi}}]$,*

$$\min_{t \in [t_{\mathrm{lo}}, t_{\mathrm{hi}}]} m(t) = \min\{m_-, m(t^*)\}, \qquad \max_{t \in [t_{\mathrm{lo}}, t_{\mathrm{hi}}]} m(t) = \max\{m_+, m(t^*)\}.$$

Proof. Note that $m'(t) = at/\sqrt{1+t^2} + b$. If $|a| \leq |b|$,

$$m'(t)\mathrm{sign}(b) \geq |b|\left(1 - \frac{t}{\sqrt{1+t^2}}\right) \geq 0.$$

As a result, $m(t)$ is either non-decreasing or non-increasing. Thus the extremes are achieved at the boundaries. Similarly, if $\mathrm{sign}(a) = \mathrm{sign}(b)$, $m'(t)$ has the same sign with b on $[0, \infty)$, implying that the extremes are also achieved at the boundaries.

If $|a| > |b|$ and $\mathrm{sign}(a) \neq \mathrm{sign}(b)$, $m'(t^*) = 0$. Without loss of generality we assume $b > 0$ and $a < 0$. Then $m'(t) > 0$ for $t < t^*$ and $m'(t) < 0$ for $t > t^*$. Thus $m(t)$ is increasing on $[0, t^*]$ and decreasing on $[t^*, \infty)$. This proves the second case. The case with $b < 0$ and $a > 0$ can be proved similarly. $\square$

The screening step guarantees that each equation of concern in the form of (51) has at least one positive solution. The following proposition provides neat analytical formulae for the solutions of (51) as well as $m'(t)$ for each solution. Albeit straightforward, it avoids unnecessary algebraic operations and thus is important for an efficient implementation of the homotopy algorithm.

Proposition 9. *Assume that $c > 0$ and $m(t) = c$ has at least one positive root.*

(1) If $a = 0$, $m(t) = c$ has only one positive root $t_1 = \frac{c}{b}$ with $m'(t_1) > 0$.

(2) If $b = 0$, $m(t) = c$ has only one positive root $t_1 = \sqrt{\frac{c-a}{c}}$ with $m'(t_1) > 0$.

(3) If $a > 0$ and $b = \pm a$, $m(t) = c$ has only one positive root $t_1 = \frac{c^2 - b^2}{2bc}$ with $\mathrm{sign}(m'(t)) = \mathrm{sign}(b)$.

(4) If $a < |b|$ or $a > b > 0$, $m(t) = c$ has only one positive root $t_1 = \frac{bc - \mathrm{sign}(b)a\sqrt{b^2 + c^2 - a^2}}{b^2 - a^2}$ with $\mathrm{sign}(m'(t_1)) = \mathrm{sign}(b)$.

(5) If $c > a > -b > 0$, $m(t) = c$ has only one positive root $t_1 = \frac{bc - a\sqrt{b^2 + c^2 - a^2}}{b^2 - a^2}$ with $m'(t_1) > 0$.

(6) If $a > -b > 0$ and $a \geq c$, $m(t) = c$ has two positive roots $t_1 = \frac{bc - a\sqrt{b^2 + c^2 - a^2}}{b^2 - a^2}$ and $t_2 = \frac{bc + a\sqrt{b^2 + c^2 - a^2}}{b^2 - a^2}$ with $m'(t_1) > 0$ and $m'(t_2) < 0$.

Furthermore, these are all settings in which $m(t) = c$ can have at least one positive root.

Proof. In case (1), $m(t) = c$ reduces to a linear function with root c/b. Since we assume $m(t) = c$ has at least one positive solution, it must be the positive solution and thus $b > 0$ and $m'(t_1) = b > 0$. The case (2) can be proved similarly. For the remaining cases, note that

$$m(t) = c \iff a^2(1 + t^2) = (c - bt)^2 \text{ and } \text{sign}(c - bt) = \text{sign}(a)$$

$$\iff (b^2 - a^2)t^2 - 2bct + (c^2 - a^2) = 0 \text{ and } \frac{c - bt}{a} \geq 0. \tag{52}$$

When $b^2 - a^2 = 0$, (52) reduces to a linear equation with solution $t = (c^2 - b^2)/2bc$. Since we assume $m(t) = c$ has at least one positive solution, it must be the positive solution. Moreover, as shown in the proof of Proposition 8, when $|b| = |a|$, $\text{sign}(m'(t)) = \text{sign}(b)$. Thus, (3) is proved.

When $b^2 - a^2 \neq 0$, the first equation in (52) is quadratic. Thus,

$$m(t) = c \iff t = \frac{bc \pm a\sqrt{b^2 + c^2 - a^2}}{b^2 - a^2} \text{ and } \frac{c - bt}{a} \geq 0.$$

For each of the two potential solutions,

$$\frac{c - bt}{a} = \frac{c(b^2 - a^2) - b(bc \pm a\sqrt{b^2 + c^2 - a^2})}{(b^2 - a^2)a} = \frac{-ca \mp b\sqrt{b^2 + c^2 - a^2}}{b^2 - a^2}$$

$$= \frac{b^2 + c^2}{ca \mp b\sqrt{b^2 + c^2 - a^2}}.$$

Therefore,

$$m(t) = c \iff t = \frac{bc \pm a\sqrt{b^2 + c^2 - a^2}}{b^2 - a^2} \text{ and } ca \mp b\sqrt{b^2 + c^2 - a^2} \geq 0. \tag{53}$$

First we prove the part for $m'(t)$ in case (4) – (6). If $t = \frac{bc + a\sqrt{b^2 + c^2 - a^2}}{b^2 - a^2} > 0$ is the solution of (53), then $c - bt = a\sqrt{1 + t^2}$ and

$$\text{sign}(m'(t)) = \text{sign}\left(\frac{at}{\sqrt{1 + t^2}} + b\right) = \text{sign}(at + b\sqrt{1 + t^2})$$

$$= \text{sign}\left(at + \frac{b(c - bt)}{a}\right) = \text{sign}(a)\text{sign}((a^2 - b^2)t + bc)$$

$$= \text{sign}(a)\text{sign}(-a\sqrt{b^2 + c^2 - a^2}) = -1.$$

Similarly, if $t = \frac{bc - a\sqrt{b^2 + c^2 - a^2}}{b^2 - a^2} > 0$ is the solution of (53), then $\text{sign}(m'(t)) = 1$. This derivation covers case (4) – (6).

Next we compute the solutions (53) in case (4) – (6). We consider each case separately.

- If $a < |b|$,

$$(b^2 - a^2)(b^2 + c^2) > 0 \implies b^2(b^2 + c^2 - a^2) > a^2c^2 \implies ca - |b|\sqrt{b^2 + c^2 - a^2} < 0$$

$$\implies ca - \text{sign}(b)b\sqrt{b^2 + c^2 - a^2} < 0$$

$$\implies \frac{b^2 + c^2}{ca - \text{sign}(b)b\sqrt{b^2 + c^2 - a^2}} < 0.$$

This means $t = \frac{bc + a\text{sign}(b)\sqrt{b^2 + c^2 - a^2}}{b^2 - a^2}$ does not satisfy the second condition of (53). By the assumption that $m(t) = c$ has at least one positive solution, $t = \frac{bc - a\text{sign}(b)\sqrt{b^2 + c^2 - a^2}}{b^2 - a^2}$ must be the only positive solution.

- If $a > b > 0$, $\frac{bc+a\sqrt{b^2+c^2-a^2}}{b^2-a^2} < 0$ and thus cannot be the positive solution of (53). By the assumption that $m(t) = c$ has at least one positive solution and (53), $t = \frac{bc-a\sqrt{b^2+c^2-a^2}}{b^2-a^2} = \frac{bc-a\,\mathrm{sign}(b)\sqrt{b^2+c^2-a^2}}{b^2-a^2}$ must be the only positive solution.

- If $c > a > -b > 0$,

$$\frac{bc + a\sqrt{b^2 + c^2 - a^2}}{b^2 - a^2} = \frac{c^2 - a^2}{bc - a\sqrt{b^2 + c^2 - a^2}} < 0.$$

Similar to the last case, $t = \frac{bc-a\sqrt{b^2+c^2-a^2}}{b^2-a^2}$ must be the only positive solution.

- If $a > -b > 0$ and $a \geq c$, we can easily verify that $\frac{bc\pm a\sqrt{b^2+c^2-a^2}}{b^2-a^2}$ both satisfy (53).

Finally, it is not hard to see that the only scenario that is not covered by case (1) – (6) is that $a < 0$ and $b \leq |a|$. In this case, $m(t) < a(\sqrt{1+t^2} - t) < 0$ and thus $m(t) = c$ cannot have any solution. $\square$

D   Full simulation results

This section includes a fuller description of our simulation results. All experimental settings are listed below.

- Multivariate z-statistics drawn from $N(\mu, \Sigma)$ with $m = 1000$ and 10 non-nulls in the top of the list with equal mean. We consider three types of covariance matrices:
    - the AR(0.8) process, i.e. $\Sigma_{ij} = (0.8)^{|i-j|}$. In this case, one-sided p-values are CPRD while two-sided p-values are not.
    - the AR(-0.8) process, i.e. $\Sigma_{ij} = (-0.8)^{|i-j|}$. In this case, neither one- nor two-sided p-values are not CPRD.
    - the block dependent structure with $\Sigma_{ii} = 1$ and $\Sigma_{ij} = 0.5 \cdot 1(\lceil i/20 \rceil = \lceil j/20 \rceil)$. In this case, one-sided p-values are CPRD while two-sided p-values are not.

- Multivariate t-statistics with degree-of-freedom $n - d \in \{5, 50\}$. The null distribution is heavy-tailed for the former and is light-tailed for the latter. The z-statistics are drawn from $N(\mu, \Sigma)$ with $m = 100$ when $n - d = 5$ and $m = 1000$ when $n - d = 50$, and with 10 non-nulls in the top of the list with equal mean. We consider three types of covariance matrices:
    - the AR(0.8) process, i.e. $\Sigma_{ij} = (0.8)^{|i-j|}$. In this case, one-sided p-values are CPRD while two-sided p-values are not.
    - uncorrelated structure, i.e. $\Sigma_{ij} = 1(i \neq j)$. In this case, both one- and two-sided p-values are CPRD.
    - the block dependent structure with $\Sigma_{ii} = 1$ and $\Sigma_{ij} = 0.5 \cdot 1(\lceil i/20 \rceil = \lceil j/20 \rceil)$. In this case, one-sided p-values are CPRD while two-sided p-values are not.

- Fixed-design homoscedastic Gaussian linear models with $n = 3000$ and $d = 1000$. The first 10 coefficients are set to be non-zero with a equal size and the intercept is set to be 0. As with Section 5, we only consider two-sided testing with $\alpha \in \{0.05, 0.2\}$ for a fair comparison with the fixed-X knockoffs. The design matrix is generated as a realization of a random Gaussian matrix with i.i.d. rows drawn from $N(0, \Sigma)$, where Σ takes one of the three form as in the multivariate-t case. The p-values are not CPRD in any case.

- Multiple comparisons to control for Gaussian outcomes with $m = 100$ groups with either 3 or 30 replicates in each group. In both cases, we set the first 30 groups as non-nulls with equal effect sizes. The p-values are not CPRD in any case.

For all above settings, the signal strength is tuned such that BH(0.05) has approximately 30% power through a separate Monte-Carlo simulation. As with Section 5, the FDR and power are estimated on 1000 independent simulations for each setting. Apart from the methods considered in Section 5, we also include their sparse counterparts with threshold collection defined in (35), denoted by s-BH, s-dBH, s-dBH^2, s-BY, s-dBY, and s-dBY^2. For all CPRD cases we take $\gamma = 1$ in dBH, dBH^2, s-dBH and s-dBH^2, while in all other cases γ is set to be 0.9. For the knockoffs method, we generate the knockoff matrix using both the equicorrelated and semi-definite programming-based constructions. As in Section 5, the intercept term is not included for the linear models but is included for the multiple comparisons to control for knockoffs. All experimental results are qualitatively the same as those in Section 5.

D.1 Testing on multivariate z-statistics

(a) One-sided testing

(b) Two-sided testing
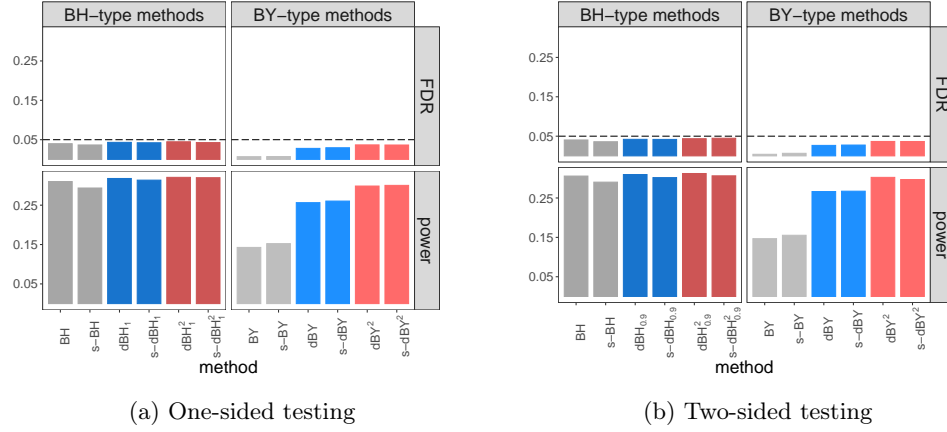
Figure 9: Multivariate z-statistics with AR(0.8) covariance structure.

(a) One-sided testing

(b) Two-sided testing
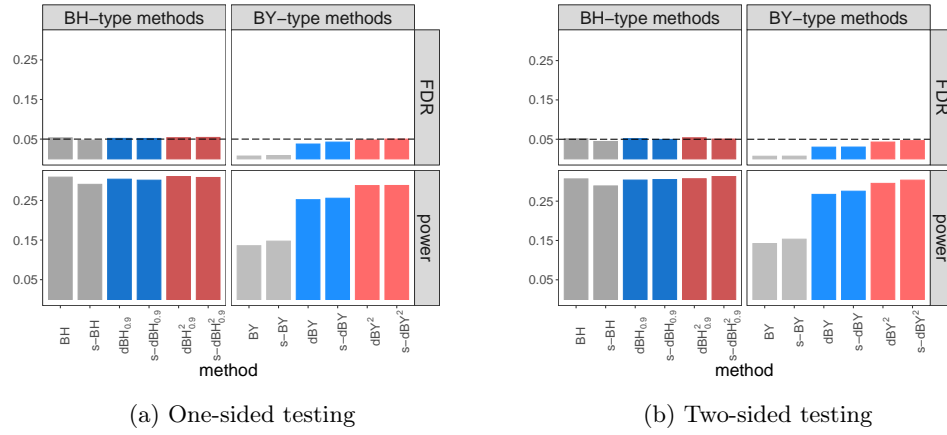
Figure 10: Multivariate z-statistics with AR(−0.8) covariance structure.
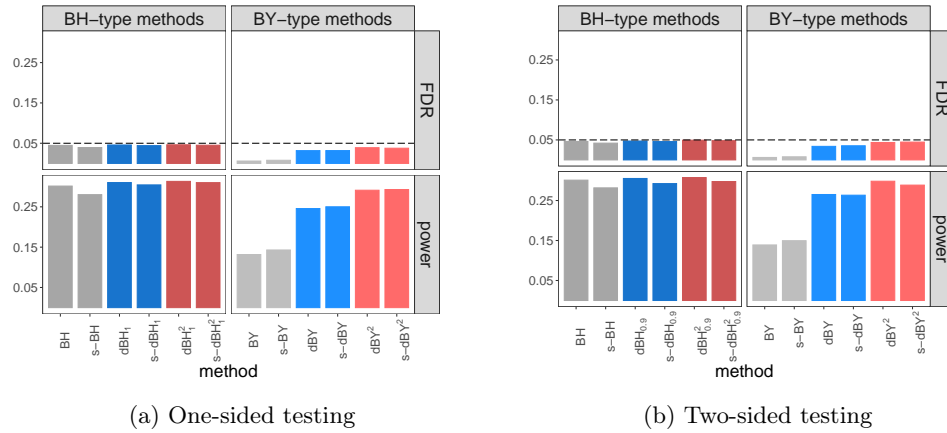

(a) One-sided testing

(b) Two-sided testing

Figure 11: Multivariate z-statistics with block covariance structure.
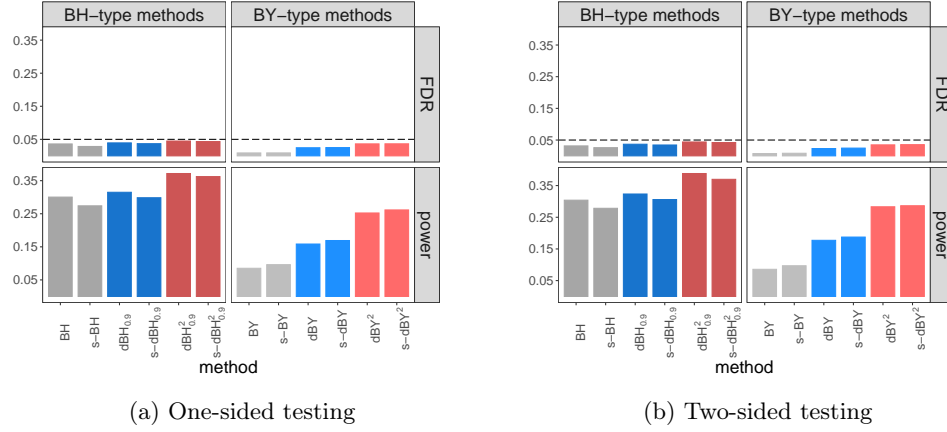
D.2   Testing on heavy-tailed multivariate t-statistics

(a) One-sided testing

(b) Two-sided testing

Figure 12: Heavy-tailed multivariate t-statistics with AR(0.8) z-statistics.

(a) One-sided testing

(b) Two-sided testing
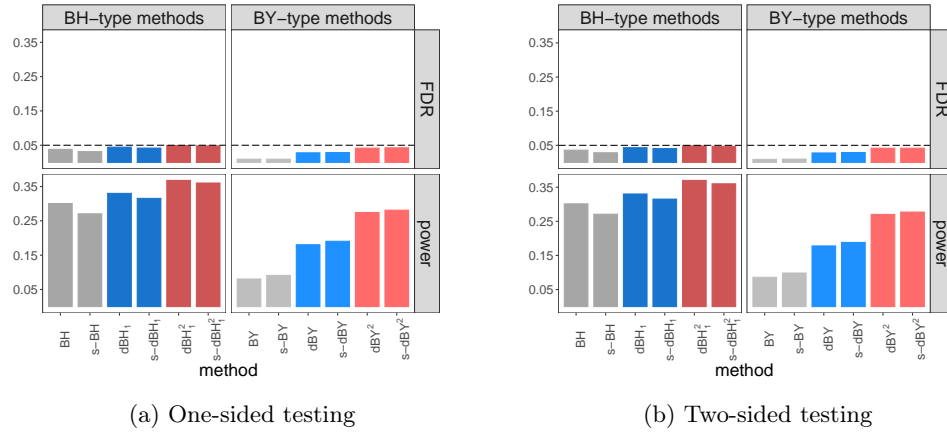
Figure 13: Heavy-tailed multivariate t-statistics with uncorrelated z-statistics.

(a) One-sided testing

(b) Two-sided testing
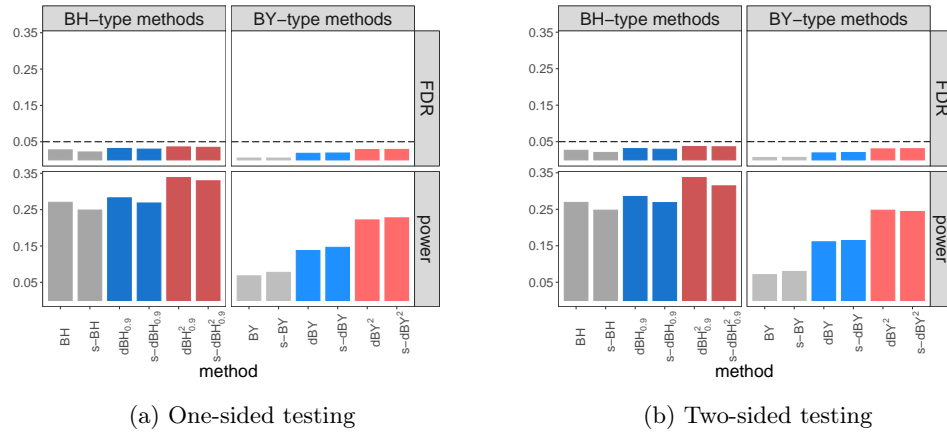
Figure 14: Heavy-tailed multivariate t-statistics with block dependent z-statistics.

D.3 Testing on light-tailed multivariate t-statistics

(a) One-sided testing

(b) Two-sided testing
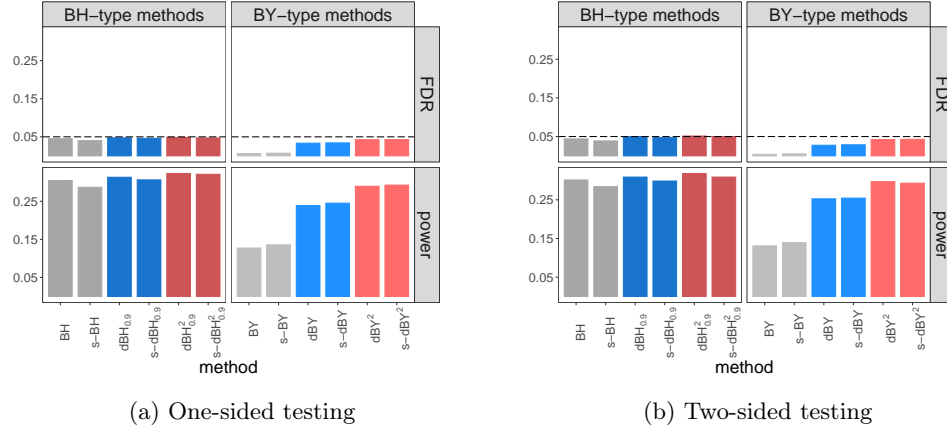
Figure 15: Light-tailed multivariate t-statistics with AR(0.8) z-statistics

(a) One-sided testing

(b) Two-sided testing
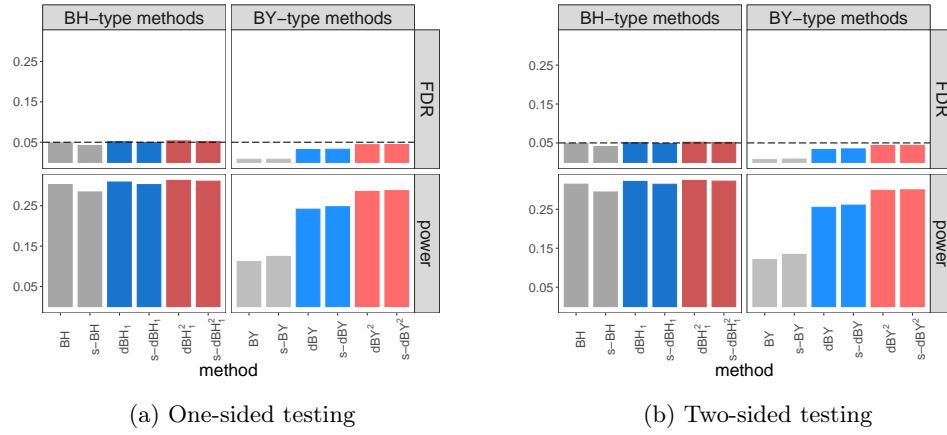
Figure 16: Light-tailed multivariate t-statistics with uncorrelated z-statistics

(a) One-sided testing

(b) Two-sided testing
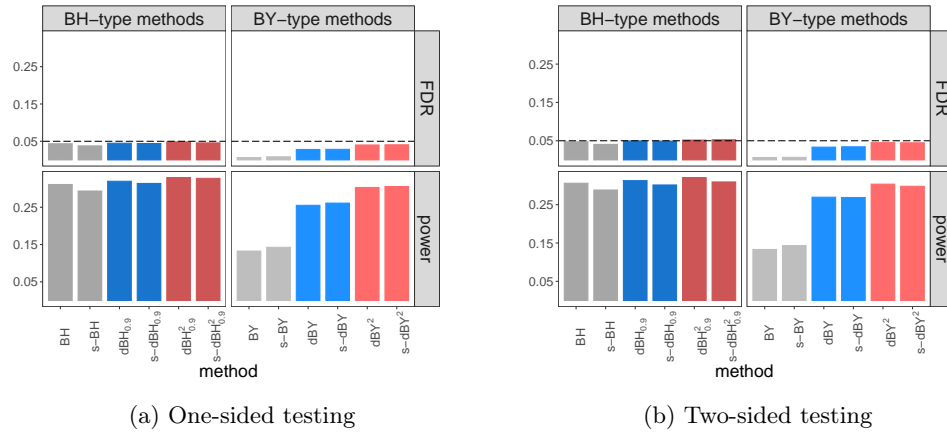
Figure 17: Light-tailed multivariate t-statistics with block dependent z-statistics

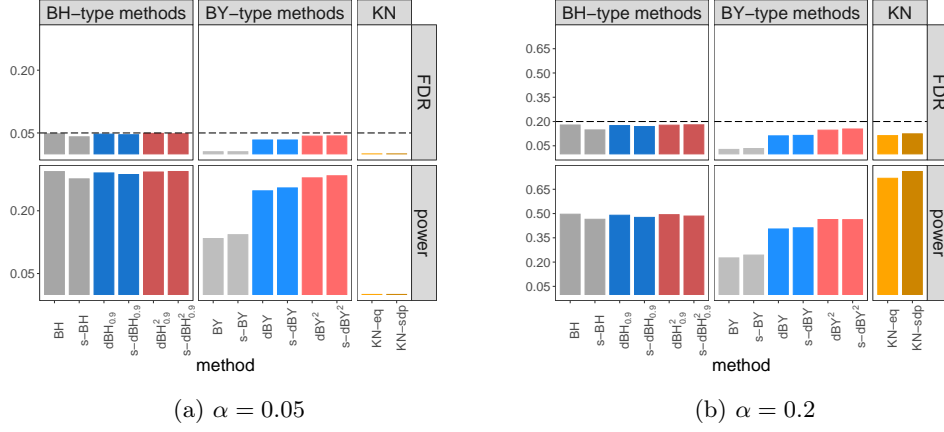## D.4 Testing on fixed-design homoscedastic Gaussian linear models

(a) $\alpha = 0.05$

(b) $\alpha = 0.2$

Figure 18: X as a realization of a random Gaussian matrix with AR(0.8) rows

(a) $\alpha = 0.05$

(b) $\alpha = 0.2$
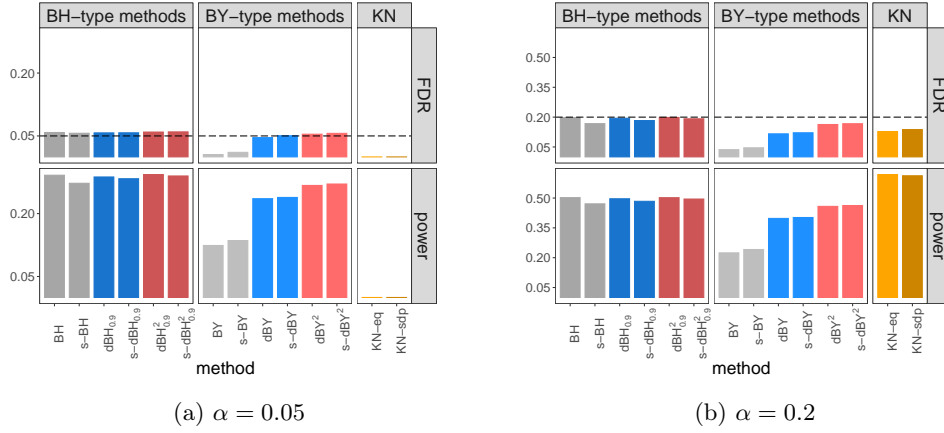
Figure 19: X as a realization of a random Gaussian matrix with i.i.d. entries
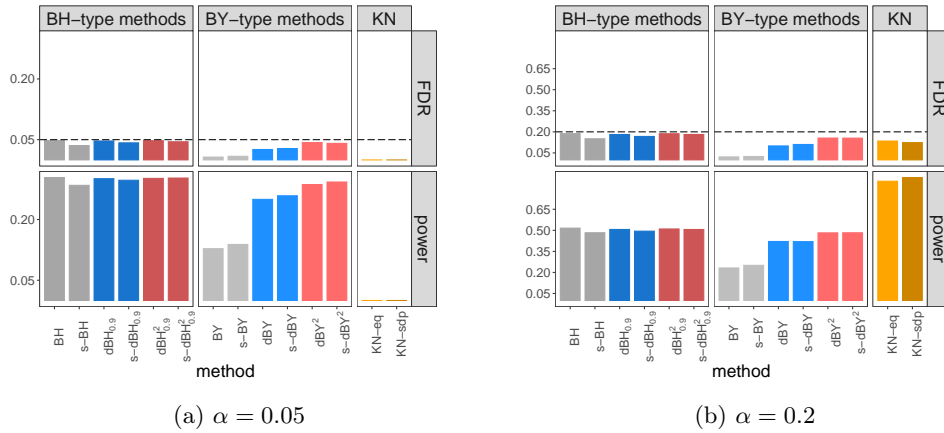

(a) $\alpha = 0.05$

(b) $\alpha = 0.2$

Figure 20: X as a realization of a random Gaussian matrix with block dependent rows

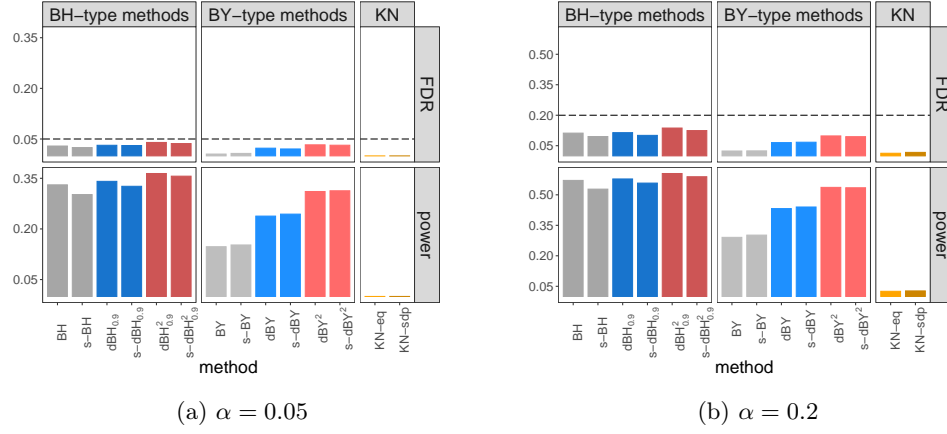## D.5   Multiple comparisons to control for Gaussian outcomes

(a) $\alpha = 0.05$ (b) $\alpha = 0.2$

Figure 21: Multiple comparisons to control with 3 replicates in each group
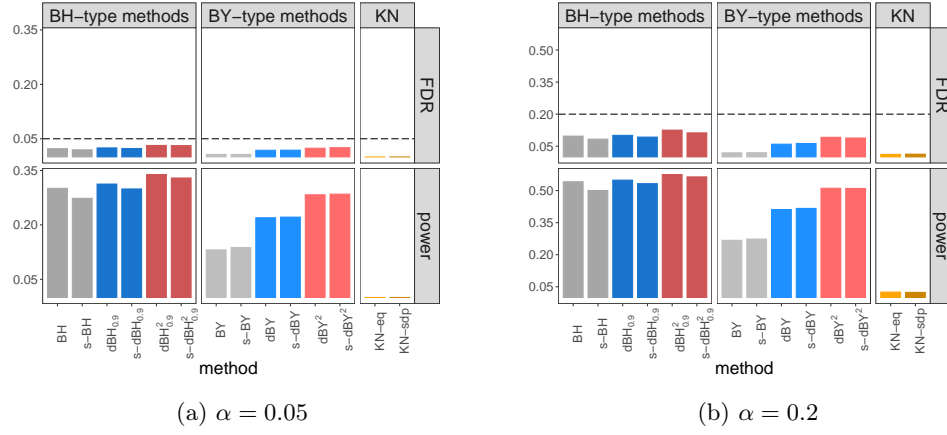

(a) $\alpha = 0.05$ (b) $\alpha = 0.2$

Figure 22: Multiple comparisons to control with 30 replicates in each group

D.6 Estimated probability of the randomized pruning step

In principle, the randomized pruning step may be invoked for dBH, s-dBH, dBH^2, and s-dBH^2, if the procedures are not safe. We summarize the fraction of simulations in which it is invoked for each case below. As desired, the chance of the randomized pruning step is extremely low.

			dBH$_{0.9}$	s-dBH$_{0.9}$	dBH$^2_{0.9}$	s-dBH$^2_{0.9}$
Multivariate z-statistics	One-sided	AR(0.8)	0	0	0	0
		AR(-0.8)	0.012	0.002	0.001	0
		block	0	0	0	0
	Two-sided	AR(0.8)	0	0	0	0
		AR(-0.8)	0.002	0	0.001	0
		block	0	0	0	0
Multivariate t-statistics	One-sided	AR(0.8)	0	0	0	0
		uncorrelated	0	0	0	0
		block	0	0	0	0
	Two-sided	AR(0.8)	0	0	0	0
		uncorrelated	0	0	0	0
		block	0	0	0	0
Linear models	$\alpha = 0.05$	AR(0.8)	0	0	0	0
		uncorrelated	0	0	0	0
		block	0	0	0	0
	$\alpha = 0.2$	AR(0.8)	0	0	0	0
		uncorrelated	0	0	0	0
		block	0	0	0	0
Multiple comparisons to control	$\alpha = 0.05$	3 replicates	0	0	0.001	0
		30 replicates	0	0	0	0
	$\alpha = 0.2$	3 replicates	0.012	0.004	0.001	0.001
		30 replicates	0.016	0.004	0.003	0.003

Table 1: Estimated probability of the randomized pruning step.