

BONuS: Multiple multivariate testing with a data-adaptive test statistic

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Abstract

We propose a new adaptive empirical Bayes framework, the Bag-Of-Null-Statistics (BONuS) procedure, for multiple testing where each hypothesis testing problem is itself multivariate or nonparametric. BONuS is an adaptive and interactive knockoff-type method that helps improve the testing power while controlling the false discovery rate (FDR), and is closely connected to the “counting knockoffs” procedure analyzed in Weinstein et al. (2017). Contrary to procedures that start with a p -value for each hypothesis, our method analyzes the entire data set to adaptively estimate an optimal p -value transform based on an empirical Bayes model. Despite the extra adaptivity, our method controls FDR in finite samples even if the empirical Bayes model is incorrect or the estimation is poor. An extension, the Double BONuS procedure, validates the empirical Bayes model to guard against power loss due to model misspecification.

1 Introduction

1.1 Multiple multivariate testing

In the literature of multiple testing, it is customary to begin with one p -value for each of n null hypotheses as the primitive inputs and then focus on designing or analyzing methods for processing them. In many scientific problems, however, each of the n experiments yields multivariate data, and it is unclear *a priori* how best to summarize each one with a univariate p -value. As a result, the ultimate power of the full procedure may depend much more on how the p -values are calculated than on what procedure we apply after calculating them. Typical examples of multivariate or nonparametric testing problems that we may encounter include large scale A/B testing, genome-wide association studies (GWAS) with multivariate phenotypes, and analysis of dose-response curves in high-throughput toxicology experiments. In such problems, as the dimension of each problem grows, an agnostic p -value transformation may yield little power unless an exceptionally strong signal is present.

In most multivariate hypothesis testing problems, there is no uniformly most powerful (UMP) test that is efficient against all alternatives. For example, the generalized likelihood ratio test (GLRT) searches over all possible directions in which the true parameter $\theta \in \mathbb{R}^d$ might differ from some hypothesized θ_0 , but is not asymptotically efficient against local alternatives in any given

direction. In high-dimensional or nonparametric settings, the power tradeoff between different possible alternatives becomes especially pressing: Janssen (2000) shows that for a Gaussian shift experiment in a real Hilbert space, for any test there exists a finite-dimension subspace outside of which the power curve is essentially flat. The same problem exists in nonparametric goodness-of-fit testing, where methods like Pearson’s χ^2 test, Neyman’s smooth test, and the Kolmogorov–Smirnov test all represent different compromises across the many different ways that the true distribution might differ from the hypothesized distribution. Even in relatively low-dimensional multivariate settings, a well-chosen test statistic that focuses on the right alternatives can substantially improve a method’s power.

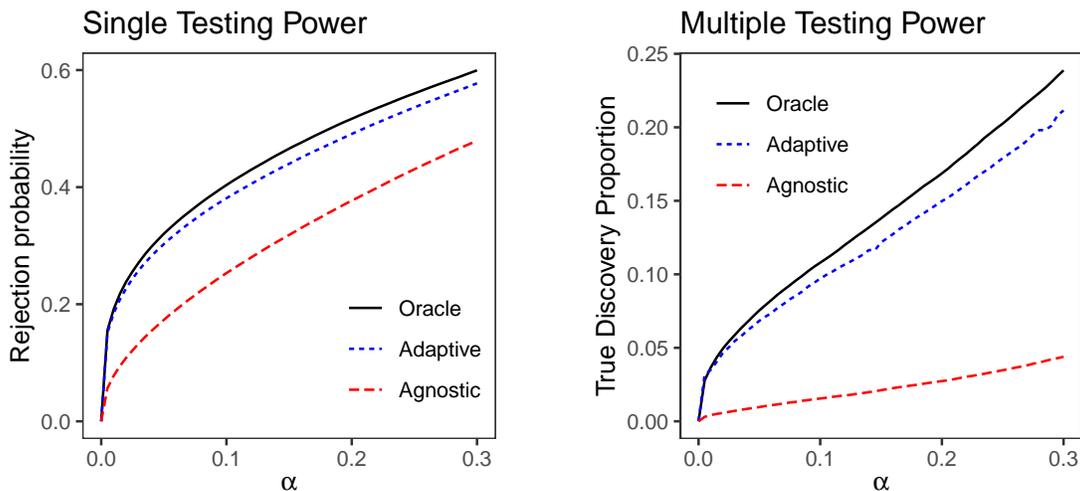
In a single multivariate testing problem, we cannot avoid paying the price of agnosticism without prior knowledge of which alternatives are more likely to occur. By contrast, when testing many multivariate hypotheses at once, we can pool information across hypotheses to *learn* the requisite prior knowledge to craft a more powerful test for each hypothesis. This article proposes an interactive empirical Bayes testing framework that uses a partially masked version of the entire data set to jointly estimate a prior distribution over the alternative. Our method, which we call the *Bag of Null Statistics* (BONuS) procedure, controls the *false discovery rate* (FDR) criterion proposed by Benjamini and Hochberg (1995): if R is the number of rejections and V is the number of false rejections, the *false discovery proportion* (FDP) is defined as $V/(1 \vee R)$ and the FDR is defined as its expectation, $\text{FDR} = \mathbb{E}[\text{FDP}]$. The BONuS procedure adaptively estimates an optimal sequence of nested rejection regions, selecting the largest region for which an estimator of the FDP is below a prespecified significance level α . It achieves robust finite-sample control of the FDR at level α whether or not the empirical Bayes working model for the prior is correctly specified.

To illustrate the cost of using an inefficient agnostic test, we consider a rudimentary multivariate Gaussian simulation with

$$\mathbf{X}^{(i)} \stackrel{\text{ind.}}{\sim} \mathcal{N}_{10}(\boldsymbol{\theta}^{(i)}, I_{10}), \quad \text{for } i = 1, \dots, n = 10,000,$$

where we wish to test $\boldsymbol{\theta}^{(i)} = \mathbf{0}$ against $\boldsymbol{\theta}^{(i)} \neq \mathbf{0}$ for each i . We generate $n_1 = 500$ non-null statistics with mean parameters drawn independently from $\boldsymbol{\theta}^{(i)} \sim \mathcal{N}_{10}(\mathbf{0}, 4\mathbf{v}\mathbf{v}')$, and the remaining $n_0 = n - n_1$ parameters are set to $\mathbf{0}$. In this problem the GLRT statistic is (equivalent to) $T_{\text{GLRT}}(\mathbf{X}^{(i)}) = \|\mathbf{X}^{(i)}\|_2^2$, while the Bayes-optimal test statistic is $T(\mathbf{X}^{(i)}) = (\mathbf{v}'\mathbf{X}^{(i)})^2$, which focuses all of its power in a single dimension of \mathbb{R}^{10} .

Figure 1 compares the single- and multiple-hypothesis testing power of three test statistics: the GLRT test, the oracle test, and an adaptive test statistic using an estimator $\hat{\mathbf{v}}$ fitted on the full data set using EM-PCA (Roweis, 1998). Figure 1a shows the average power for a level- α hypothesis test on a new problem with parameter $\boldsymbol{\theta}^{(n+1)}$ drawn at random from the alternative. Even in a relatively low-dimensional setting with $d = 10$, we see that there are substantial power gains to be had by substituting the oracle test for the agnostic test, especially for small values of α . The adaptive estimate of the oracle test statistic, obtained by plugging in $\hat{\mathbf{v}}$ for \mathbf{v} , nearly recovers the power of the oracle test. These differences are magnified in multiple testing, as shown in Figure 1b, where we compare the true discovery proportion of the Benjamini-Hochberg (BH) procedure (Benjamini and Hochberg, 1995) with the GLRT and oracle test statistics, as well as our BONuS procedure which also uses the plug-in estimator $\hat{\mathbf{v}}$.



(a) Average power for a single level- α hypothesis test using each of three test statistics: The GLRT statistic $T_{\text{GLRT}}(\mathbf{X}^{(i)}) = \|\mathbf{X}^{(i)}\|_2^2$, the oracle test statistic $T(\mathbf{X}^{(i)}) = (\mathbf{v}'\mathbf{X}^{(i)})^2$, and an adaptive test statistic that estimates \mathbf{v} .

(b) True discovery proportion for three FDR-controlling multiple testing procedures: the BH(α) procedure using the GLRT statistic, the BH(α) procedure using the oracle test statistic, and our BONuS procedure, which estimates \mathbf{v} .

Figure 1: Motivating Gaussian example, where $\boldsymbol{\theta}^{(i)} \sim \mathcal{N}_{10}(\mathbf{0}, 4\mathbf{v}\mathbf{v}')$ under the alternative. The Bayes-optimal oracle test dramatically outperforms the agnostic GLRT test, but requires prior knowledge of \mathbf{v} . Pooling information across all n hypotheses allows estimation of \mathbf{v} using EM-PCA on the full data set, nearly recovering the oracle performance.

1.2 Multiple testing and the two-groups model

We consider testing the null hypothesis $H_0^{(i)} : \boldsymbol{\theta}^{(i)} = \mathbf{0}$ against $H_1^{(i)} : \boldsymbol{\theta}^{(i)} \neq \mathbf{0}$ in n independent experiments

$$\mathbf{X}^{(i)} \stackrel{\text{ind.}}{\sim} f_{\boldsymbol{\theta}^{(i)}}(\mathbf{X}) \text{ for } i = 1, \dots, n, \quad (1)$$

with possibly infinite-dimensional parameter $\boldsymbol{\theta}^{(i)} \in \Theta$. Let $\mathcal{H}_0 = \{i : H_0^{(i)} \text{ is true}\}$, and $n_0 = \#\mathcal{H}_0$, the number of true null hypotheses.

We assume throughout that we are testing a simple null against a composite alternative, but it is possible to extend the analysis to some problems with nuisance parameters; for example we could take $\mathbf{X}^{(i)}$ to be a multivariate score statistic for the parameter of interest, calculated at a maximum likelihood estimate for the nuisance parameters. The data $\mathbf{X}^{(i)}$ may represent the entire data set for the i th experiment or a d -variate sufficient statistic summarizing it; we let \mathcal{X} represent the sample space for a generic experiment and assume all distributions under consideration have densities with respect to a common measure μ on \mathcal{X} .

Because the null hypothesis is simple, we can define a valid hypothesis test and calculate p -values using any (fixed) univariate transformation $T : \mathcal{X} \rightarrow \mathbb{R}$ as our test statistic, rejecting for large values of $T(\mathbf{X}^{(i)})$; likewise, we could test all $H_0^{(i)}$ using the BH, Storey-BH Storey et al. (2004), or other multiple testing procedure that accepts independent p -values as input. We say another

test statistic $\tilde{T}(\mathbf{x})$ is *monotonically equivalent* to $T(\mathbf{x})$ if it can be written as a strictly increasing function of $T(\mathbf{x})$; if \tilde{T} and T are monotonically equivalent then they yield identical p -values.

If we take a Bayesian perspective and assume that $\boldsymbol{\theta} \sim \Lambda$ under the alternative, then the test with highest average power rejects for large values of $\text{LR}_\Lambda(\mathbf{X}) = \bar{f}_\Lambda(\mathbf{X})/f_0(\mathbf{X})$, where the mixture density $\bar{f}_\Lambda(\mathbf{X}) = \int_{\Theta} f_{\boldsymbol{\theta}}(\mathbf{X}) d\Lambda(\boldsymbol{\theta})$ represents the marginal distribution of \mathbf{X} under the alternative. By contrast, the GLRT rejects for large values of $T_{\text{GLRT}}(\mathbf{X}) = \sup_{\boldsymbol{\theta} \in \Theta \setminus \{0\}} f_{\boldsymbol{\theta}}(\mathbf{X})/f_0(\mathbf{X})$. If the prior Λ is relatively concentrated around a lower-dimensional region of $\Theta \setminus \{0\}$ then the test based on LR_Λ may have much higher power, as illustrated in Figure 1, but we must know Λ to use it.

In real applications we typically have no access to Λ , but when we test many hypotheses simultaneously, we can hope to reap many of the gains by jointly estimating Λ in a hierarchical Bayesian working model. Defining the Bernoulli indicator $H^{(i)} = 0$ if $H_0^{(i)}$ is true and $H^{(i)} = 1$ if false, we may introduce a version of the *two-groups model* Efron (2005, 2008) as follows:

$$\begin{aligned} H^{(i)} &\stackrel{\text{i.i.d.}}{\sim} \text{Bern}(1 - \pi_0) \\ \boldsymbol{\theta}^{(i)} \mid H^{(i)} = 1 &\stackrel{\text{i.i.d.}}{\sim} \Lambda \\ \mathbf{X}^{(i)} \mid \boldsymbol{\theta}^{(1)}, \dots, \boldsymbol{\theta}^{(n)} &\stackrel{\text{ind.}}{\sim} f_{\boldsymbol{\theta}^{(i)}}(\mathbf{x}). \end{aligned} \tag{2}$$

We emphasize here that (2) is merely a “working model” in the sense that Λ need not exist at all for our methods to control FDR: finite-sample control is guaranteed under the *fixed effects model* (1) where $\boldsymbol{\theta}^{(1)}, \dots, \boldsymbol{\theta}^{(n)}$ take arbitrary fixed values. Because (1) can be obtained by conditioning on the latent parameters in (2), the tower rule implies that FDR control is also marginally guaranteed under the working two-groups model for any π_0 and Λ ; in particular, FDR is controlled both conditionally and marginally regardless of whether the analyst specifies a correct model for Λ .

Under the working model, the data follow a closely related mixture density with

$$\mathbf{X}^{(i)} \stackrel{\text{i.i.d.}}{\sim} f_{\text{mix}}(\mathbf{x}) = \pi_0 f_0(\mathbf{x}) + (1 - \pi_0) \bar{f}_\Lambda(\mathbf{x}). \tag{3}$$

The posterior probability that $H_0^{(i)}$ is true, called the *local FDR* or *lfdr* (Efron, 2005), is given by

$$\text{lfdr}_{\pi_0, \Lambda}(\mathbf{x}) = \mathbb{P}_{\pi_0, \Lambda} \left(H^{(i)} = 0 \mid \mathbf{X}^{(i)} = \mathbf{x} \right) = \frac{\pi_0 f_0(\mathbf{x})}{f_{\text{mix}}(\mathbf{x})} = \left(1 + \frac{1 - \pi_0}{\pi_0} \cdot \text{LR}_\Lambda(\mathbf{x}) \right)^{-1}.$$

Thus, from either a Bayesian or frequentist perspective, any optimal decision rule should reject for large values of $f_{\text{mix}}(\mathbf{x})/f_0(\mathbf{x})$, the ratio of the observable mixture density to the null density, which is always identifiable and monotonically equivalent to the likelihood ratio $\text{LR}_\Lambda(\mathbf{x})$ and the local FDR $\text{lfdr}_{\pi_0, \Lambda}(\mathbf{x})$. In other words, optimal rejection regions are super-level sets of $f_{\text{mix}}(\mathbf{x})/f_0(\mathbf{x})$. Calculating LR_Λ or $\text{lfdr}_{\pi_0, \Lambda}$ is more challenging because π_0 is nearly unidentifiable: without strong assumptions it is very difficult to disentangle the proportion π_0 of exact nulls from the proportion of non-nulls with parameter values very close to $\mathbf{0}$. Fortunately, it is sufficient for purposes of testing to remain agnostic about π_0 and estimate $f_{\text{mix}}(\mathbf{x})/f_0(\mathbf{x})$ instead.

A natural empirical Bayes idea is to estimate either Λ or f_{mix} directly from the data, calculate p -values with respect to the plug-in test statistic $\text{LR}_{\hat{\Lambda}}(\mathbf{x})$ or $\hat{f}_{\text{mix}}(\mathbf{x})/f_0(\mathbf{x})$, and then use a method like BH to control the FDR. The main difficulty with this plan is that we must account properly for its using the same data twice. If we implement it with no safeguards, we could very easily arrive at an anticonservative procedure, for example by overestimating $f_{\text{mix}}(\mathbf{x})$ at the observed values

of $\mathbf{X}^{(i)}$. Furthermore, expecting consistent estimation of Λ is highly dubious for several reasons: first, the space of priors over the alternative is very large, and the number of clearly discernible observations from the alternative is most often relatively small; second, π_0 is difficult to estimate for the reason given above; and finally, density de-convolution is a hard statistical problem even without these challenges. As a result, we should demand that any adaptive procedure robustly account for its own adaptivity without relying on consistent estimation or even correct specification of the prior Λ . As we will see, our method meets these demands.

1.3 Related Work

As an adaptive procedure for multiple testing, BONuS is motivated by several papers on adaptive inference. In particular, the idea of creating synthetic controls is inspired by the knockoff procedure Barber et al. (2015), where one constructs synthetic nulls mimicking the original covariance structure and use the synthetic controls as a natural way to provide FDR control. Both AdaPT Lei and Fithian (2016) and STAR Lei et al. (2020) perform adaptive inference in multiple testing and are closely related to the knockoff methods as well. BONuS is especially closely related to the “counting knockoffs” method of Weinstein et al. (2017), which uses the same martingale structure to perform multiple testing in a linear regression setting with i.i.d. design matrix. By contrast, our focus here is to learn a prior distribution over a multivariate parameter space.

BONuS attempts to improve the power by using a better test statistic and the motivation comes from the empirical Bayes model introduced by Efron (2005).

In BONuS, the objective is to adaptively learn the structure of the problem from the data and use the structure to construct a more powerful test statistics. Similar in spirit, many recent methodology papers in post-selective inference have explored the use of structural information to improve testing power when certain prior information is available. For example, Li and Barber (2017); Lei and Fithian (2016); G’Sell et al. (2016) studied a common type of structure that comes up in dosage response experiment and LASSO solution path, where the hypotheses are ranked in a order such that a hypothesis can be rejected only if its preceding hypotheses have been rejected. In gene expression data, Guo et al. (2018); Ramdas et al. (2017) studied another structure represented by a directed acyclic graph (DAG). In Li and Barber (2016), a generalization of utilizing prior information is proposed. Finally, Lei and Fithian (2018); Ignatiadis et al. (2016) studied how to exploit covariates independent of p -values when they are available.

In applications of genome wide association studies (GWAS), there are many situations where researchers are interested in diseases related to multiple endophenotypes, which naturally motivates the study of quantitative trait loci (QTL) that have a joint impact on these endophenotypes. Following this motivation, practitioners proposed various methods for solving multivariate GWAS problems. For example, in Ferreira and Purcell (2008), the authors used canonical correlation analysis to extract linear combinations of traits that explains the most correlation with the markers. Another approach is given by O’Reilly et al. (2012), where in testing the regression coefficients of genotypes for some quantitative phenotypes, the authors proposed to use multiple phenotypes jointly to test the coefficients, different from the traditional approach that adopts a T -test for each genotype-phenotype pair. There is also a principle component based dimension reduction method in multivariate GWAS Liu and Lin (2019). However, the aforementioned methods are often nonadaptive and rely on strong modelling assumptions. There has also been some study of optimizing multivariate test statistics without much modeling assumption, such as Alishahi et al. (2016) in high dimensional setting and Fithian and Ting (2017) in the setting of nonparametric

permutation testing. However, neither method achieves finite-sample FDR control.

2 The Bag of Null Statistics (BONuS) procedure

2.1 Definition of the procedure

The BONuS procedure begins by either generating a set of \tilde{n} synthetic controls drawn from the null distribution,

$$\widetilde{\mathbf{X}}^{(1)}, \dots, \widetilde{\mathbf{X}}^{(\tilde{n})} \stackrel{\text{i.i.d.}}{\sim} f_{\mathbf{0}}(\mathbf{x}),$$

and then hiding them among the real statistics $\mathbf{X}^{(1)}, \dots, \mathbf{X}^{(n)}$, without revealing to the analyst which test statistics are real samples and which are synthetic nulls. Formally, the analyst observes a permuted version of the data set,

$$\mathbf{Z} = \left(\mathbf{Z}^{(1)}, \dots, \mathbf{Z}^{(n+\tilde{n})} \right) = \Pi \left(\mathbf{X}^{(1)}, \dots, \mathbf{X}^{(n)}, \widetilde{\mathbf{X}}^{(1)}, \dots, \widetilde{\mathbf{X}}^{(\tilde{n})} \right),$$

where Π is a uniformly random permutation on $n_+ = n + \tilde{n}$ elements. Equivalently, the analyst observes the pooled empirical distribution of synthetic null and real test statistics. We will use the variable j to refer to indices of the permuted vector, so that if $j = \Pi(i)$ for $i \in [n]$, then $\mathbf{Z}^{(j)} = \mathbf{X}^{(i)}$, and likewise $\mathbf{Z}^{(j)} = \widetilde{\mathbf{X}}^{(i)}$ if $j = \Pi(i + n)$.

Under the working Bayesian model (2), the permuted values $\mathbf{Z}^{(j)}$ are exchangeable (but not quite independent) with a marginal distribution closely related to f_{mix} :

$$\mathbf{Z}^{(j)} \sim \tilde{f}_{\text{mix}}(\mathbf{x}) = \frac{\tilde{n}}{n_+} f_{\mathbf{0}}(\mathbf{x}) + \frac{n}{n_+} f_{\text{mix}}(\mathbf{x}) = \frac{\tilde{n} + \pi_0 n}{n_+} f_{\mathbf{0}}(\mathbf{x}) + \frac{(1 - \pi_0)n}{n_+} \bar{f}_{\Lambda}(\mathbf{x}).$$

Because \tilde{n}/n_+ and $f_{\mathbf{0}}$ are known, estimating \tilde{f}_{mix} is equivalent to estimating f_{mix} .

The BONuS method proceeds iteratively, gradually revealing more information to the analyst, who continually updates an estimator $\hat{T} : \mathcal{X} \rightarrow \mathbb{R}$ of either $\text{LR}_{\Lambda}(\mathbf{x})$ or $f_{\text{mix}}(\mathbf{x})/f_{\mathbf{0}}(\mathbf{x})$ as new information arrives. This estimator may be based on plugging in a parametric estimate for the prior Λ , or on estimating f_{mix} directly; our notation is meant to capture either. The analyst uses the evolving estimator \hat{T} to construct a shrinking sequence of candidate rejection regions $\mathcal{X} \supseteq \mathcal{R}_1 \supseteq \mathcal{R}_2 \supseteq \dots$. As soon as an estimator of FDP falls below a pre-specified significance level α , the analyst halts the procedure and rejects all null hypotheses $H^{(i)}$ for which $\mathbf{X}^{(i)}$ is in the current rejection region.

To formally define the procedure, it will be convenient to define the binary indicator $B^{(j)} = 1$ if $\mathbf{Z}^{(j)}$ is real (i.e., if $\Pi^{-1}(j) \leq n$) and $B^{(j)} = 0$ if it is a synthetic control, and let $B(\mathcal{A}) = (B^{(j)} : \mathbf{Z}^{(j)} \in \mathcal{A})$ denote the real/synthetic identities for all observations in a set $\mathcal{A} \subseteq \mathcal{X}$. In addition define the counting processes

$$N(\mathcal{A}) = \#\{i : \mathbf{X}^{(i)} \in \mathcal{A}\}, \quad \text{and} \quad \tilde{N}(\mathcal{A}) = \#\{i : \widetilde{\mathbf{X}}^{(i)} \in \mathcal{A}\},$$

representing respectively the number of real and synthetic observations in $\mathcal{A} \subseteq \mathcal{X}$.

At step $t = 0$, the analyst uses the permuted data to calculate an initial estimator $\hat{T}_0(\mathbf{x}; \mathbf{Z})$, and an initial rejection region $\mathcal{R}_1 \subseteq \mathcal{X}$. \mathcal{R}_1 will typically be a super-level set of $\hat{T}_0(\mathbf{x})$, which is

a (random) real-valued function defined on \mathcal{X} . In the Storey-BONuS version of our procedure, the analyst also selects a *correction set* $\mathcal{A} \subseteq \mathcal{R}_1^c$, typically a sub-level set of $\widehat{T}_0(\mathbf{x})$. At step $t = 1, \dots, 1 + n_+$, the analyst is allowed to observe $B(\mathcal{R}_t^c)$, “unmasking” the real/synthetic identities of all observations excluded from the current rejection region, and then calculates an estimator $\widehat{\text{FDP}}_t$ (defined below) for the rejection region \mathcal{R}_t . The analyst either halts the procedure or proposes a new candidate rejection region $\mathcal{R}_{t+1} \subsetneq \mathcal{R}_t$, typically \mathcal{R}_t intersected with a super-level set of an updated estimator $\widehat{T}_t(\mathbf{x}; \mathbf{Z}, B(\mathcal{R}_t^c))$. Figure 2 illustrates how information gradually accrues to the analyst as more observations are unmasked. We finally reject all $H_0^{(i)}$ with $\mathbf{X}^{(i)} \in \mathcal{R}_{\hat{t}}$, where

$$\hat{t} = \min \left\{ t \geq 0 : \widehat{\text{FDP}}_t \leq \alpha \text{ or } N(\mathcal{R}_t) = 0 \right\}.$$

To ensure that the method terminates after at most $1 + n_+$ steps, we require that at least one new observation be excluded from the rejection region at every step. This requirement is without loss of generality because the analyst observes no new information unless a new $B^{(i)}$ is revealed. Otherwise, there are no restrictions at all on how the analyst may choose \mathcal{R}_{t+1} , provided it depends only on \mathbf{Z} and $B(\mathcal{R}_t^c)$.

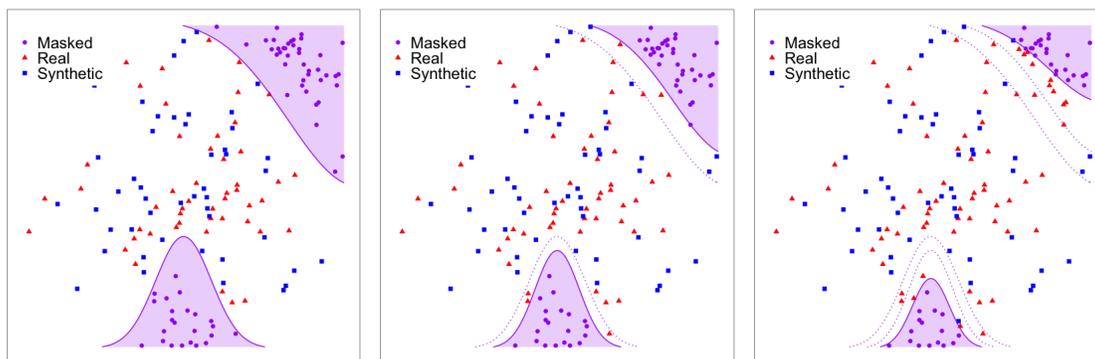


Figure 2: Schematic illustration of the BONuS procedure as the candidate rejection region shrinks. Each point represents either a two-dimensional test statistic for one of the real hypotheses (red triangles), or a synthetic test statistic generated from the null distribution (blue squares). The points in the rejection region are “masked” in the sense that the analyst does not observe whether each one is real or synthetic.

We consider two versions of the above procedure, the *BH-BONuS procedure* and the *Storey-BONuS procedure*, which respectively use the FDP estimators

$$\widehat{\text{FDP}}_t^{\text{BH}} = \frac{n}{\tilde{n} + 1} \cdot \frac{\tilde{N}(\mathcal{R}_t) + 1}{1 \vee N(\mathcal{R}_t)}, \quad \text{and} \quad \widehat{\text{FDP}}_t^{\text{St}} = \frac{N(\mathcal{A}) + 1}{\tilde{N}(\mathcal{A})} \cdot \frac{\tilde{N}(\mathcal{R}_t) + 1}{1 \vee N(\mathcal{R}_t)},$$

To understand the motivation for these estimators, note that $\tilde{N}(\mathcal{R}_t)/\tilde{n}$ acts as an estimator of $N_0(\mathcal{R}_t)/n_0$, where $N_0(\mathcal{R}) = \{i \in \mathcal{H}_0 : \mathbf{X}^{(i)} \in \mathcal{R}\}$ is the number of false rejections we would make if we used \mathcal{R} as our rejection set. As a result, for large rejection regions, we have

$$\widehat{\text{FDP}}_t^{\text{BH}} \approx \frac{n}{n_0} \cdot \frac{N_0(\mathcal{R}_t)}{1 \vee N(\mathcal{R}_t)} = \frac{n}{n_0} \text{FDP}(\mathcal{R}_t).$$

The extra factor of n/n_0 makes the BH-BONuS procedure conservative in the same way the usual BH procedure is. The Storey-BONuS procedure attempts to adjust for this conservatism using the correction set \mathcal{A} . If nulls predominate in \mathcal{A} , we have $N(\mathcal{A})/\tilde{N}(\mathcal{A}) \approx N_0(\mathcal{A})/\tilde{N}(\mathcal{A}) \approx n_0/\tilde{n}$, so $\widehat{\text{FDP}}_t^{\text{St}} \approx \text{FDP}(\mathcal{R}_t)$.

To avoid $\tilde{N}(\mathcal{A}) = 0$, in which case $\widehat{\text{FDP}}_t^{\text{St}} = +\infty$, we should be sure to choose \tilde{n} and \mathcal{A} large enough that $\mathbb{P}(\tilde{N}(\mathcal{A}) = 0) = \left(\int_{\mathcal{A}^c} f_0(\mathbf{x}) d\mathbf{x}\right)^{\tilde{n}} \approx 0$. Since f_0 is known, we can easily ensure this.

Algorithm 1 summarizes the Storey-BONuS procedure; the BH-BONuS procedure is identical except that there is no \mathcal{A} , and we substitute $\widehat{\text{FDP}}_t^{\text{BH}}$ for $\widehat{\text{FDP}}_t^{\text{St}}$.

Algorithm 1: The Storey-BONuS procedure

Input : Real statistics $\mathbf{X}^{(1)}, \dots, \mathbf{X}^{(n)}$, synthetic statistics $\tilde{\mathbf{X}}^{(1)}, \dots, \tilde{\mathbf{X}}^{(\tilde{n})}$, FDR level α .
Output: Rejection set

- 1 Generate random permutation Π ;
- 2 Reveal $\mathbf{Z} = \Pi\left(\mathbf{X}^{(1)}, \dots, \mathbf{X}^{(n)}, \tilde{\mathbf{X}}^{(1)}, \dots, \tilde{\mathbf{X}}^{(\tilde{n})}\right)$;
- 3 Select initial rejection region $\mathcal{R}_1 \subseteq \mathcal{X}$ and correction set $\mathcal{A} \subseteq \mathcal{R}_1^c$;
- 4 **for** $t = 1, \dots, 1 + n_+$ **do**
- 5 Reveal $B(\mathcal{R}_t^c)$;
- 6 **if** $\widehat{\text{FDP}}_t^{\text{St}} \leq \alpha$ **or** $N(\mathcal{R}_t) = 0$ **then**
- 7 | Stop procedure and reject $H^{(i)}$ if $\mathbf{X}^{(i)} \in \mathcal{R}_t$;
- 8 **end**
- 9 Select new rejection region $\mathcal{R}_{t+1} \subsetneq \mathcal{R}_t$;
- 10 **end**

To prove finite-sample control we rely on an optional stopping argument. Both $\widehat{\text{FDP}}_t^{\text{BH}}$ and $\widehat{\text{FDP}}_t^{\text{St}}$ can be computed from \mathbf{Z} and $B(\mathcal{R}_t^c)$, since

$$N(\mathcal{R}_t) = n - \sum_{\mathbf{Z}^{(j)} \in \mathcal{R}_t^c} B^{(j)}, \quad \text{and} \quad N(\mathcal{A}) = \sum_{\mathbf{Z}^{(j)} \in \mathcal{A} \subseteq \mathcal{R}_t^c} B^{(j)},$$

and likewise for $\tilde{N}(\mathcal{R}_t)$ and $\tilde{N}(\mathcal{A})$ after replacing n with \tilde{n} and $B^{(j)}$ with $1 - B^{(j)}$. As a result, for either estimator, \hat{t} is a stopping time with respect to the filtration defined by $\mathcal{F}_t = \sigma(\mathbf{Z}, B(\mathcal{R}_t^c))$, the information available to the analyst at step t . We show next that both variants of our method control FDR in finite samples. Our results rely on a lemma regarding the expectations of two functions of a hypergeometric random variable:

Lemma 1. *Let $V \sim \text{Hypergeom}(a + b, a, k)$, and define $U = k - V$. Then*

$$\mathbb{E} \left[\frac{V}{1 + U} \right] \leq \frac{a}{1 + b}, \quad \text{and} \quad \mathbb{E} \left[\frac{V}{1 + U} \cdot \frac{b - U}{1 + a - V} \right] \leq 1. \quad (4)$$

The inequalities in (4) are standard results in the FDR control literature used in Storey et al. (2004), Barber et al. (2015), Weinstein et al. (2017) and Lei and Fithian (2018), but we include a proof for completeness in Appendix A.1.

Theorem 2. Assume that the null test statistics $(\mathbf{X}^{(i)} : i \in \mathcal{H}_0)$ are drawn i.i.d. from f_0 conditional on the non-null test statistics $(\mathbf{X}^{(i)} : i \in \mathcal{H}_0^c)$. Then the BH-BONuS procedure controls FDR at level $\alpha n_0/n$ and the Storey-BONuS procedure controls FDR at level α .

Proof. For our optional stopping arguments, we will use the augmented filtration that also unmask the identities of all real, non-null observations:

$$\mathcal{F}_t^+ = \sigma\left(\mathbf{Z}, B(\mathcal{R}_t^c), (B^{(\Pi(i))} : i \in \mathcal{H}_0^c)\right).$$

We also define the σ -fields $\mathcal{F}_0 = \sigma(\mathbf{Z})$ and $\mathcal{F}_0^+ = \sigma(\mathbf{Z}, (B^{(\Pi(i))} : i \in \mathcal{H}_0^c))$. Conditional on \mathcal{F}_0^+ , the $n_0 + \tilde{n}$ unmasked observations are exchangeable, so that each of the $\binom{n_0 + \tilde{n}}{n_0}$ configurations of their $B^{(j)}$ values is equally likely. Recall that \mathcal{A} and \mathcal{R}_1 are data dependent subsets chosen by the analyst after observing $\mathcal{F}_0 \subseteq \mathcal{F}_0^+$.

As the procedure unfolds, each time more $B^{(j)}$ values are unmasked, the remaining masked values remain conditionally exchangeable. As a result, defining $V_t = N_0(\mathcal{R}_t)$ and $U_t = \tilde{N}(\mathcal{R}_t)$, and $V_0 = n_0, U_0 = \tilde{n}$, we have for $t \geq 1$

$$V_t \mid \mathcal{F}_{t-1}^+ \sim \text{Hypergeom}(V_{t-1} + U_{t-1}, V_t + U_t, V_{t-1}).$$

Note that $V_t + U_t$ is \mathcal{F}_{t-1}^+ -measurable since the analyst chooses \mathcal{R}_t knowing how many total observations are in $\mathcal{R}_{t-1} \setminus \mathcal{R}_t$ (or in $\mathcal{X} \setminus \mathcal{R}_1$, for $t = 1$). As a result, by the first inequality in Lemma 1 the quotient $V_t/(1+U_t)$ is a super-martingale with respect to the filtration $\mathcal{F}^+ = (\mathcal{F}_t^+)_{t=0}^{1+n_0}$. Moreover, because both estimators $\widehat{\text{FDP}}_t^{\text{BH}}$ and $\widehat{\text{FDP}}_t^{\text{St}}$ are measurable with respect to $\mathcal{F}_t \subseteq \mathcal{F}_t^+$, \hat{t} is a stopping time with respect to \mathcal{F}^+ .

We are now ready to prove the result for the BH-BONuS method:

$$\text{FDR} = \mathbb{E}\left[\frac{N_0(\mathcal{R}_{\hat{t}})}{1 \vee N(\mathcal{R}_{\hat{t}})}\right] \tag{5}$$

$$= \mathbb{E}\left[\widehat{\text{FDP}}_{\hat{t}}^{\text{BH}} \cdot \frac{\tilde{n} + 1}{n} \cdot \frac{N_0(\mathcal{R}_{\hat{t}})}{1 + \tilde{N}(\mathcal{R}_{\hat{t}})}\right] \tag{6}$$

$$\leq \alpha \cdot \frac{\tilde{n} + 1}{n} \cdot \mathbb{E}\left[\frac{N_0(\mathcal{R}_{\hat{t}})}{1 + \tilde{N}(\mathcal{R}_{\hat{t}})}\right] \tag{7}$$

$$\leq \alpha \cdot \frac{\tilde{n} + 1}{n} \cdot \mathbb{E}\left[\frac{N_0(\mathcal{X})}{1 + \tilde{N}(\mathcal{X})}\right] \tag{8}$$

$$= \alpha \cdot \frac{n_0}{n}. \tag{9}$$

The inequality in (7) follows from the fact that either $\widehat{\text{FDP}}_{\hat{t}}^{\text{BH}} \leq \alpha$ or $N_0(\mathcal{R}_{\hat{t}}) = N(\mathcal{R}_{\hat{t}}) = 0$. The

inequality in (8) follows from the optional stopping theorem. For the Storey-BONuS method:

$$\text{FDR} = \mathbb{E} \left[\frac{N_0(\mathcal{R}_{\hat{t}})}{1 \vee N(\mathcal{R}_{\hat{t}})} \right] \quad (10)$$

$$= \mathbb{E} \left[\widehat{\text{FDP}}_{\hat{t}}^{\text{St}} \cdot \frac{N_0(\mathcal{R}_{\hat{t}})}{1 + \tilde{N}(\mathcal{R}_{\hat{t}})} \cdot \frac{\tilde{N}(\mathcal{A})}{1 + N(\mathcal{A})} \right] \quad (11)$$

$$\leq \alpha \cdot \mathbb{E} \left[\frac{N_0(\mathcal{R}_{\hat{t}})}{1 + \tilde{N}(\mathcal{R}_{\hat{t}})} \cdot \frac{\tilde{N}(\mathcal{A})}{1 + N_0(\mathcal{A})} \right] \quad (12)$$

$$\leq \alpha \cdot \mathbb{E} \left[\frac{N_0(\mathcal{R}_1)}{1 + \tilde{N}(\mathcal{R}_1)} \cdot \frac{\tilde{N}(\mathcal{A})}{1 + N_0(\mathcal{A})} \right] \quad (13)$$

$$\leq \alpha. \quad (14)$$

For the expectation in (11), we define the integrand as 0 if $\tilde{N}(\mathcal{A}) = 0$; in that case it coincides with the integrand in (10) because $\widehat{\text{FDP}}_t^{\text{St}} = +\infty$ for all t so the method makes no rejections. The inequality in (13) follows from the optional stopping theorem, applied conditional on \mathcal{F}_1^+ since $\tilde{N}(\mathcal{A})$ and $N_0(\mathcal{A})$ are \mathcal{F}_1^+ -measurable (but not \mathcal{F}_0^+ -measurable).

To justify step (14), define $A = N_0(\mathcal{A} \cup \mathcal{R}_1)$ and $B = \tilde{N}(\mathcal{A} \cup \mathcal{R}_1)$. Since the masked $B^{(j)}$ values in $\mathcal{A} \cup \mathcal{R}_1$ are exchangeable, we have

$$V_1 \mid \mathcal{F}_0^+, A, B \sim \text{Hypergeom}(A + B, V_1 + U_1, A),$$

and we apply the second inequality in Lemma 1. □

The martingales that appear in our method are very similar to those in Section 3 of Weinstein et al. (2017). With a different focus, their paper studies the power-FDR tradeoff of a knockoff procedure for linear models with i.i.d. Gaussian design and this martingale structure is used to calibrate the FDR for their knockoff procedure. Although our procedure has a very similar martingale structure and shares the use of FDR calibration with the null statistics, we use this martingale for a different purpose, namely, to adaptively use the data to design a better test statistic for multiple testing problems with a multivariate structure.

We emphasize once again that Theorem 2 controls FDR in the fixed-effects model (1), and also in the two-groups model (2) for any π_0 and Λ , whether or not the analyst uses a correctly specified model for the prior.

2.2 Asymptotic Power

In this section we show under the Bayesian two-groups model (2) that, if we can consistently estimate the optimal test statistic, then the BH-BONuS and Storey-BONuS procedures asymptotically match the power of the BH and Storey-BH procedures respectively. We adopt the empirical process perspective common in the literature (e.g. Genovese and Wasserman, 2002, 2004; Storey et al., 2004; Ferreira and Zwiderman, 2006) with the added twist that the test statistic is estimated.

Let $T : \mathcal{X} \rightarrow \mathbb{R}$ denote some version of the optimal test statistic, either the likelihood ratio statistic $\text{LR}_{\Lambda}(\mathbf{x})$ or any monotonically equivalent proxy such as $f_{\text{mix}}(\mathbf{x})/f_0(\mathbf{x})$ or $1 - \text{lfdr}(\mathbf{x})$. To avoid technicalities around randomized p -values, we assume that under sampling from f_{mix} , $T(\mathbf{X})$ is

a continuous random variable, equivalent to assuming the corresponding p -value $p(\mathbf{X})$ is continuous, and that $T(\mathbf{X})$ has bounded density under sampling from f_{mix} .

Further, let the random function $\widehat{T}_n(\mathbf{x})$ denote an estimator of the function $T(\mathbf{x})$ calculated by the analyst using n real experiments and \tilde{n} synthetic nulls. We define the estimation errors

$$e_n(\mathbf{x}) = T(\mathbf{x}) - \widehat{T}_n(\mathbf{x}),$$

and show next that if most of the e_n values are small, the BH-BONuS procedure and the BH procedure differ on $o_p(n)$ rejections.

Theorem 3. *Assume that $T(\mathbf{x})$ is monotonically equivalent to $f_{\text{mix}}(\mathbf{x})/f_0(\mathbf{x})$, and that it is continuously distributed with bounded density under sampling \mathbf{X} from f_{mix} . Assume further that $\pi_0 > 0$ and \tilde{n}/n converges to a nonzero constant.*

Further, assume that for any $\delta > 0$,

$$\#\{j : |e_n(\mathbf{Z}^{(j)})| > \delta\} = o_p(n).$$

Then the set difference between the rejection sets for the BH method using test statistic $T(\mathbf{x})$ and the BH-BONuS method has cardinality $o_p(n)$. Likewise, the set difference between the rejection sets for the Storey-BH method using test statistic $T(\mathbf{x})$ and the Storey-BONuS method has cardinality $o_p(n)$.

The proof is given in the appendix.

2.3 Double BONuS

The BONuS method guarantees FDR control while learning an adaptive test statistic from the data, but there is no guarantee that it will improve the power in any given example. In particular, if we specify an inappropriate empirical Bayes model or overfit the data, BONuS may underperform relative to a method that uses an agnostic test. As a result, it is appealing to have a way to try out several different competing models, perhaps including the agnostic method as a competitor, and assess which yields the best power. Even if we choose an appropriate model for the prior, our estimation method may involve tuning parameters that we will need to choose in a principled way. However, if we naively run many different variants of our method on the same data set and keep the one that makes the most rejections, we will violate the FDR control guarantee.

To allow for data-driven choices that make the procedure's power more robust, this section proposes a validation scheme for assessing the power gain of different variants of the BONuS procedure, based on introducing a second group of synthetic nulls and running an initial stage of each BONuS variant. The method, which we call *Double BONuS*, has three steps:

1. Create a set $\widetilde{\mathbf{X}}$ of \tilde{n} number of synthetic samples, and mix them with n real statistics to get a mixed sample \mathbf{Z} with size and $n_+ = n + \tilde{n}$. Then, generate another set $\widetilde{\mathbf{Z}}$ of synthetic samples with size \tilde{n}_+ .
2. Run each variant of BONuS on \mathbf{Z} and $\widetilde{\mathbf{Z}}$, treating the first group as the “real” observations and the second group as the synthetic nulls.
3. Apply BONuS to \mathbf{Z} with the variant that makes the most rejections in Step 2 (or a mixture of several competitive options from Step 2).

The above may be applied for either the Storey-BONuS or BH-BONuS method (or to choose between the BH-BONuS and Storey-BONuS methods). Using Double BONuS does not violate the FDR guarantee of Theorem 2 because the results of Step 2 are all \mathcal{F}_0 -measurable, i.e. they can all be calculated from \mathbf{Z} without knowing anything about which observations in \mathbf{Z} correspond to real observations and which correspond to (the first group of) synthetic nulls. We recommend always including a non-adaptive, agnostic test as a competitor in case there is very little structure to find; this will tend to guard against the BONuS method actively harming the power relative to the BH or Storey-BH procedures. The Double BONuS method is defined formally in Algorithm 2.

Algorithm 2: The Double BONuS procedure

Input : \mathbf{X} , \tilde{n} , \tilde{n}_+ , updating rules $\{\mathcal{M}_1, \dots, \mathcal{M}_k\}$
Output: The rejection region

- 1 generate \tilde{n} null statistics and mix them with \mathbf{X} to get \mathbf{Z} , and generate another \tilde{n}_+ null statistics to be mixed with \mathbf{Z} to get $\tilde{\mathbf{Z}}$;
- 2 LR **for** $i \in \{1, \dots, k\}$ **do**
- 3 Run algorithm 1 with $\mathbf{Z} \cup \tilde{\mathbf{Z}}$ as input and \mathcal{M}_i as the updating rule for the rejection region, where \mathbf{Z} is treated as real and $\tilde{\mathbf{Z}}$ is treated as synthetic in the computation of FDP estimator
- 4 **end**
- 5 analyze the results of updating rules to finalize a updating rule \mathcal{M}^* and then run algorithm 1 with \mathbf{Z} and use \mathcal{M}^* to update the rejection region. Return the final rejection region.

Besides the additional computational cost from the additional modeling assumptions, there is no extra cost in the use of double BONuS. We note that the intention of double BONuS is to help the analyst select the most reasonable modeling assumptions among the several competitors, but not to exhaust the space of all possible modeling assumptions, where they can always find one, among the astronomical number of options, that generates high power in step 2 as a result of overfitting. In Section 3, we demonstrate the use of the double BONuS extension, where we also discuss strategies of finalizing \mathcal{M}^* in Section 3.2.

3 Data Experiment

In this section we discuss implementation techniques, some simulation results, and a real data experiment.

3.1 Choosing the Number of Synthetic Controls

In choosing the number \tilde{n} of synthetic nulls, the main tradeoff to consider is that larger values of \tilde{n} improve the accuracy of our FDP estimates, but also make it more difficult to estimate the alternative density \bar{f}_Λ : as $\tilde{n} \rightarrow \infty$, the signal from the alternative hypotheses is lost in the sea of synthetic nulls. The other downside of picking a large \tilde{n} is the additional computational cost, which may be burdensome in extremely large scale experiments.

In particular, for problems where one expects the final number of rejections to be very small, it is important to choose a value \tilde{n} large enough to mitigate the finite sample correction that arises

in the computation of $\widehat{\text{FDP}}$. For example, in the BH-BONuS procedure, unless the procedure can reject at least $n/\alpha(\tilde{n} + 1)$ hypotheses, it cannot reject any at all; the minimum number of rejections for the Storey-BONuS method is roughly the same. As a result, picking \tilde{n} in the order of n/α is a natural choice in problems where there is a chance we will make very few rejections. Iterative techniques such as the EM algorithm may be employed in the case where we need to adopt a large \tilde{n} .

Although the analyst is certainly free to attempt any choice or even a multiple-layer BONuS that allows them to experiment with different numbers of synthetic controls, hereby we make a general recommendation as follows. First, we choose \tilde{n} in the order of n/α , unless constraint in computational power or storage forbids us from doing so, in which case we may choose \tilde{n} as large as possible. Then, we choose \tilde{n}_+ , the number of second layer synthetic controls in double BONuS, to be any sufficiently large number. Note that \tilde{n}_+ is only used in the double BONuS phase where one wants to compare different candidate models so its value does not need to match $n_+ = n + \tilde{n}$ in order. If the analyst expects the problem to come with many discoveries, they can adjust \tilde{n} to the order of n instead of n/α .

3.2 Ensemble Method in Double BONuS

Double BONuS attempts to cherry pick the optimal model from a pool of candidates. However, there are often situations where none of the candidate models is exactly the same as the true model and several models pick up different subsets of alternative hypotheses. The traditional wisdom from ensemble learning instructs one to use multiple models' result, and we recommend a similar approach as well.

Specifically, at the stage of double BONuS and before we decide the model to be used in BONuS, we assess the performance of different candidate models and check if, besides the winning model's discoveries, there is a significant number of discoveries from other candidate models. For example, suppose the winning model makes 200 discoveries while another candidate model only makes 100 discoveries but many of these 100 discoveries are not in the set of 200 discoveries from the winning model, we may want to pick them up as well. Essentially, we want to combine the candidate models when they happen to detect different perspectives of the problem.

There is no consensus on how to use the multiple candidate models and combine their results, so we encourage the analyst to exploit domain knowledge to make an appropriate judgement. In addition, we recommend an approach based on p -values' ranking: among the candidate models, we can compute the (empirical) p -values of each of these models and use the minimum of them as the new p -value. If this new p -value, equivalent to a test statistic, turns out to perform even better in the double BONuS step, we can adopt it as the test statistic in the final step.

3.3 Multivariate Gaussian simulation

In this simulation, we use a sample size $n = 5,000$ with the number of true positives being $n_1 = 500$ and choose the dimension d to be 50. The distribution of the summary statistic \mathbf{X} is:

$$\mathbf{X}^{(i)}|H^{(i)} = 0 \sim \mathcal{N}_d(\mathbf{0}, I_d) \tag{15}$$

$$\mathbf{X}^{(i)}|H^{(i)} = 1 \sim \mathcal{N}_d(\mathbf{0}, I_d + \mathbf{M}) \tag{16}$$

where \mathbf{M} is a fixed matrix of rank 5. In our double BONuS experiment, we use a principal component analysis (PCA) approach with k principal components, where k ranges from 1 to d .

Besides the set of real statistics \mathbf{X} , we create a set $\widetilde{\mathbf{X}}$ of $\tilde{n} = n$ synthetic controls for BONuS and mix them to get $S = \mathbf{X} \cup \widetilde{\mathbf{X}}$. Then, we create another set \widetilde{S} of $2n$ synthetic samples as the second layer synthetic nulls for double BONuS. We perform PCA with different choices of k on $S \cup \widetilde{S}$ to cherry pick the optimal model. The result, for a level 0.05 FDR control, is shown in Figure 3.

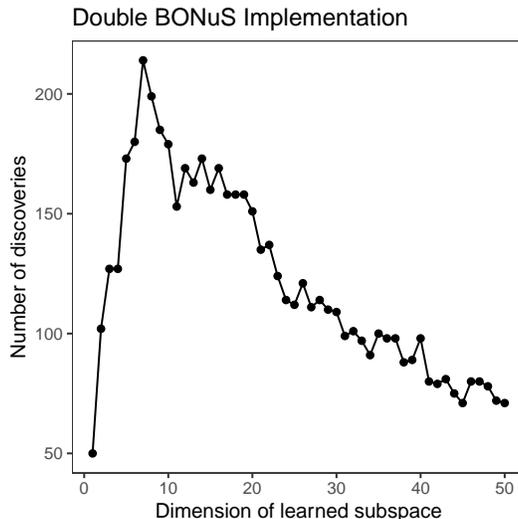


Figure 3: Numerical simulation for multivariate Gaussian with low rank signals, $\alpha = 0.05$

The optimal choice is the model with 7 components, where we attained 214 ‘discoveries’ in S . After the screening, we pick this model, with which we apply BONuS to the mixture of \mathbf{X} and $\widetilde{\mathbf{X}}$.

To see the effect, we also run the same set of data with different choices of α , ranging from 0.01 to 0.2. In Figure 4, we compare the false discovery proportion and empirical power of the three approaches: the agnostic (Chi-squared) test, the double BONuS procedure, and the oracle procedure. All three procedures used the same Storey correction, and the oracle procedure is computed with knowledge of M . As expected, the double BONuS procedure is able to capture much of the low rank structure in the problem and thus much more powerful than the agnostic test.

3.4 Multiple Multinomial Testing

BONuS is especially suitable for a high dimensional setting where an appropriate test statistic is typically not available and the cost of an agnostic test is huge. To illustrate this point, we run a simulation of multinomial tests with varying dimensions.

We consider the case where each $\mathbf{X}^{(i)}$ follows a multinomial distribution $\text{MultiNom}(N, \boldsymbol{\theta})$, with $\boldsymbol{\theta} = \boldsymbol{\theta}_0$ under the null and $\boldsymbol{\theta} = \boldsymbol{\theta}_1$ under the alternative, where we know $\boldsymbol{\theta}_0$ but not $\boldsymbol{\theta}_1$. For the simulation, we choose $\boldsymbol{\theta}_0$ to be $(1/d, \dots, 1/d)$ and add normalized Rademacher perturbation to $\boldsymbol{\theta}_0$ to obtain $\boldsymbol{\theta}_1$, a setting from Balakrishnan and Wasserman (2017a). We repeat this simulation with 120 independent runs for each $d \in \{6, \dots, 30\}$ and $N = 2000$, where in each run the number of hypotheses is $n = 3000$ and the number of alternative hypotheses is $n_1 = 300$. Note that we generate a new $\boldsymbol{\theta}_1$ for each run as well.

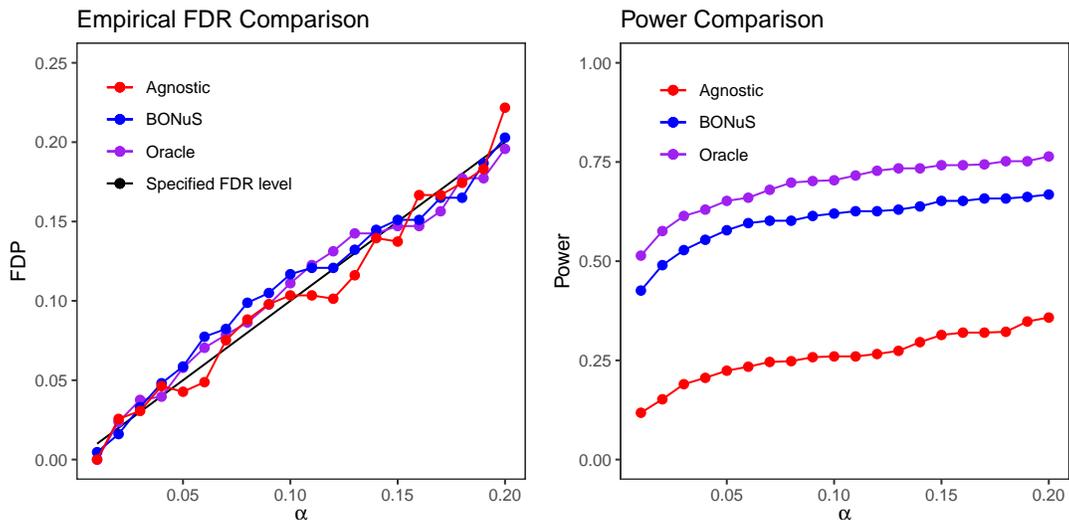


Figure 4: Comparison of false discovery proportions and powers of agnostic, double BONuS, and oracle procedure for the multivariate normal testing problem.

We compare BONuS with the oracle test and an agnostic test, where the oracle procedure assumes the knowledge of θ_1 and uses the corresponding likelihood ratio test statistic. For the agnostic test, we use the χ_2 test statistics and note that although it is suboptimal for multinomial test in general, but for the case of uniform null, the χ_2 test is equivalent to the truncated χ_2 test, which was shown to be minimax Balakrishnan and Wasserman (2017a,b). We include the result in Figure 5.

3.5 The Metabolic Syndrome GWAS

In many GWAS experiments, scientists are interested in identifying the SNPs related to certain diseases, whose severity can be characterized by multiple phenotypes. In this section, we apply BONuS to study the SNPs associated with metabolic syndrome, a problem studied by Liu and Lin (2019) with a different focus.

Metabolic syndromes refer to a medical condition found to be associated with a higher risk in cardiovascular disease and type-II diabetes. In this experiment, we want to identify the SNPs related to the metabolic syndrome, which in turn is linked to the following list of quantitative phenotypes: BMI, waist-hip ratio adjusted for BMI, high-density lipoprotein cholesterol (HDL), low-density lipoprotein cholesterol (LDL), Triglycerides (TG), fasting glucose, and fasting insulin. Although it is more likely for a SNP to be related to only one or few phenotypes, scientists speculate about detecting the SNPs with a weak effect on any single phenotype but a non-negligible joint effect.

For our experiment, we have z -scores for each of the phenotypes from several different medical research projects: Locke et al. (2015); Shungin et al. (2015); Teslovich et al. (2010); Manning et al. (2012). Since these projects study slightly different sets of SNPs, we choose to focus only on the

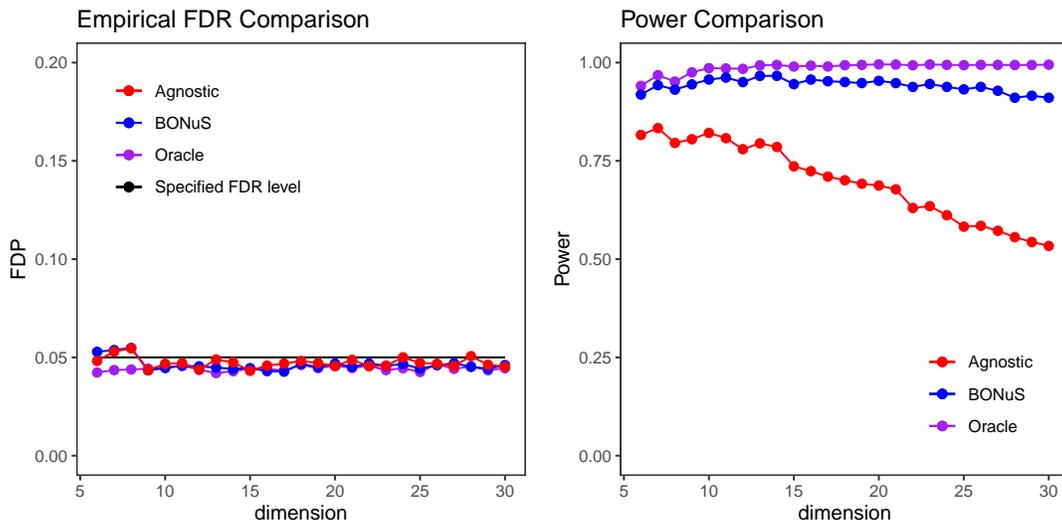


Figure 5: FDR and power of agnostic, double BONuS, and oracle procedures for the multinomial testing problem.

intersection of SNPs in all studies.

Before running the experiment, we use LD-pruning, a method described in Purcell et al. (2007), to prune SNPs such that the remaining SNPs can be considered approximately independent under the null. After the preprocessing, there are about 1.8 million SNPs left.

One challenge is in the specification of the null. Under the null, a SNP is not associated with the metabolic syndrome so we expect its z-score vector to have mean 0. However, the z-scores of different phenotypes are correlated so the covariance matrix of the z-score vector is not the identity matrix: for example, the z-scores for SNPs in the fasting glucose study and the fasting insulin study have a 0.26 correlation coefficient. To create synthetic controls, we use a robust covariance matrix estimation on the z-score matrix \mathbf{X} , and then transform \mathbf{X} to have a identity covariance matrix, after which we may assume that under the null, the z-score vector for a SNP follows a standard multivariate Gaussian distribution and thus create the synthetic controls.

In Figure 6, we show the number of discoveries as a function of α for both BONuS and agnostic approaches. One may observe that the power gain here is less than those in the previous experiments, but in this study one actually expects a large fraction of discoveries to be related to only one phenotype so it is the marginal gain that matters.

4 Discussion

The BONuS procedure is a novel method for multiple testing in multivariate or nonparametric settings. By learning an empirical Bayes prior from a joint analysis of all the data, it estimates a test statistic to optimize the average power across all hypotheses. By using a data masking scheme, it prevents the analyst from violating its finite-sample FDR control guarantee even when the analyst

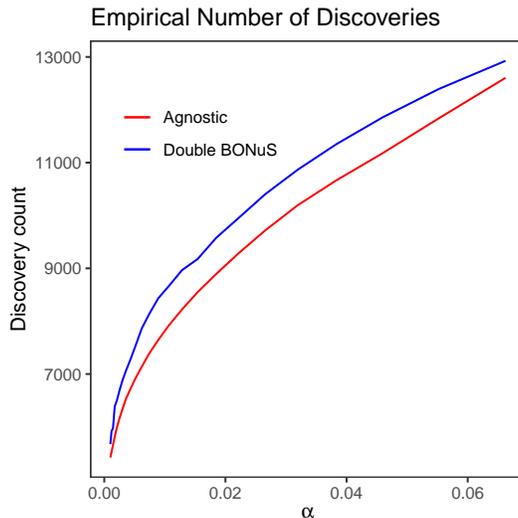


Figure 6: Metabolic syndrome GWAS experiment.

has full access to the synthetic controls. While BONuS is especially useful in high-dimensional cases where agnostic testing has very low power, we have seen that it is possible to attain significant power improvements even in relatively low dimensions. Besides the BONuS procedure, we also presented its extension, the double BONuS procedure, a cross-validation-like scheme that robustly gains power by allowing the user to test several models and choose the best-performing one.

For future work, there are two remaining issues with the work that we feel it is especially pressing to resolve. First, like many other FDR-controlling multiple testing methods, BONuS assumes independence across the hypotheses, an unrealistic assumption in many of the most popular applications of multiple testing in genetics and medical imaging. Second, BONuS requires the null hypotheses to be simple rather than composite, and does not allow for incorporating covariates. Both of these are important topics for future work.

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A FDR Control and Power

A.1 Proof to Lemma 1

Proof. The probability mass function for (V, U) is:

$$\mathbb{P}(V = v, U = k - v) = \frac{\binom{a}{v} \binom{b}{k-v}}{\binom{a+b}{k}},$$

where we define the binomial term $\binom{a}{k}$ and $\binom{b}{k-v}$ to be 0 when $k > a$ and $k - v > b$.

Let V^-, V^+ be the minimum and maximum numbers such that $\mathbb{P}(V = v, U = k - v) > 0$. Then we have:

$$\begin{aligned} \mathbb{E}\left[\frac{V}{1+U}\right] &= \sum_{v=V^-}^{V^+} \frac{v}{1+k-v} \cdot \frac{\binom{a}{v} \binom{b}{k-v}}{\binom{a+b}{k}} \\ &= \frac{a}{1+b} \cdot \left(1\{V^- > 0\} \frac{\binom{a-1}{V^- - 1} \binom{b+1}{k-v+1}}{\binom{a+b}{k}} + \sum_{v=V^-+1}^{V^+} \frac{\binom{a-1}{v-1} \binom{b+1}{k-v+1}}{\binom{a+b}{k}}\right) \\ &\leq \frac{a}{1+b}, \end{aligned}$$

and thus we complete the first part, where we note that the result is not contingent on the choice of k , which can be any of $\{0, \dots, a+b\}$. With a similar approach,

$$\mathbb{E}\left[\frac{V}{1+U} \cdot \frac{b-U}{1+a-V}\right] = \sum_{v=V^-}^{V^+} \frac{v \cdot (b - (k - v))}{(1+k-v) \cdot (1+a-v)} \cdot \mathbb{P}(V = v) \quad (17)$$

$$= \sum_{v=V^-}^{V^+} \frac{v \cdot (b - (k - v))}{(1+k-v) \cdot (1+a-v)} \cdot \frac{\binom{a}{v} \binom{b}{k-v}}{\binom{a+b}{k}} \quad (18)$$

$$= \sum_{v=V^-+1}^{V^+} \frac{\binom{a}{v-1} \binom{b}{k-v+1}}{\binom{a+b}{k}} \quad (19)$$

$$\leq 1, \quad (20)$$

where in (19) the term corresponding to V^- is 0 since either V^- is 0 or $b - (k - V^-)$ is 0. Thus the proof is complete. \square

Theorem 3. *Assume that $T(\mathbf{x})$ is monotonically equivalent to $f_{\text{mix}}(\mathbf{x})/f_0(\mathbf{x})$, and that it is continuously distributed with bounded density under sampling \mathbf{X} from f_{mix} . Assume further that $\pi_0 > 0$ and \tilde{n}/n converges to a nonzero constant.*

Further, assume that for any $\delta > 0$,

$$\#\{j : |e_n(\mathbf{Z}^{(j)})| > \delta\} = o_p(n).$$

Then the set difference between the rejection sets for the BH method using test statistic $T(\mathbf{x})$ and the BH-BONuS method has cardinality $o_p(n)$. Likewise, the set difference between the rejection sets

for the Storey-BH method using test statistic $T(\mathbf{x})$ and the Storey-BONuS method has cardinality $o_p(n)$.

Proof. The maximum density for $T(\mathbf{X})$ under sampling from f_0 is no more than $1/\pi_0$ times the maximum density under sampling from f_{mix} ; let g^* be the maximum of either of the two densities.

Define the following functions of $\zeta \geq 0$:

$$\tilde{Q}_n(\zeta) = \frac{1 + \#\{i : \hat{T}_n(\tilde{\mathbf{X}}^{(i)}) \geq \zeta\}}{1 + \tilde{n}}$$

$$\tilde{P}_n(\zeta) = \frac{1 + \#\{i : T(\tilde{\mathbf{X}}^{(i)}) \geq \zeta\}}{1 + \tilde{n}}$$

$$Q_n(\zeta) = \frac{\#\{i : \hat{T}_n(\mathbf{X}^{(i)}) \geq \zeta\}}{n}$$

$$P_n(\zeta) = \frac{\#\{i : T(\mathbf{X}^{(i)}) \geq \zeta\}}{n}$$

$$P_0(\zeta) = \mathbb{P}_{\mathbf{X} \sim f_0}(T(\mathbf{X}) \geq \zeta)$$

$$P(\zeta) = \mathbb{P}_{\mathbf{X} \sim f_{\text{mix}}}(T(\mathbf{X}) \geq \zeta)$$

Then BH-BONuS rejects all hypotheses with

$$\hat{T}_n(\mathbf{X}^{(i)}) \geq \hat{\zeta}_n = \min \left\{ \zeta : \hat{G}_n(\zeta) \leq \alpha \right\}, \quad \text{where } \hat{G}_n(\zeta) = \frac{\tilde{Q}_n(\zeta)}{Q_n(\zeta)}.$$

The BH procedure with test statistic $T(\mathbf{x})$, on the other hand, rejects all hypotheses with

$$T(\mathbf{X}^{(i)}) \geq \hat{\zeta}_n^{\text{BH}} = \min \left\{ \zeta : \hat{G}_n^{\text{BH}}(\zeta) \leq \alpha \right\}, \quad \text{where } \hat{G}_n^{\text{BH}}(\zeta) = \frac{P_0(\zeta)}{P_n(\zeta)}.$$

Define the idealized BH threshold to be the same expression as above but with P_n replaced with its population counterpart P :

$$\zeta^* = \min \left\{ \zeta : G(\zeta) \leq \alpha \right\}, \quad \text{where } G(\zeta) = \frac{P_0(\zeta)}{P(\zeta)}.$$

If no such ζ satisfies the inequality, define ζ^* or $\hat{\zeta}_n^{\text{BH}}$ to be the supremum of $\text{supp}(T(\mathbf{X}))$, and $\hat{\zeta}_n$ to be the supremum of $\text{supp}(\hat{T}_n(\mathbf{X}))$; either of these suprema could be infinite. If $T(\mathbf{x})$ is monotonically equivalent to $f_{\text{mix}}(\mathbf{x})/f_0(\mathbf{x})$, and its distribution is continuous, then $G(\zeta)$ must be strictly decreasing in ζ .

Next, fix ζ_0 with $P(\zeta_0) > 0$. Our next goal is to show that

$$\sup_{\zeta \leq \zeta_0} \left| \hat{G}_n(\zeta) - G(\zeta) \right|, \quad \sup_{\zeta \leq \zeta_0} \left| \hat{G}_n^{\text{BH}}(\zeta) - G(\zeta) \right| \xrightarrow{P} 0. \quad (21)$$

For $\delta > 0$ define E_δ to be the event under which:

$$\max \left\{ \frac{\#\{i : |e_n(\widetilde{\mathbf{X}}^{(i)})| > \delta\}}{\widetilde{n}}, \frac{\#\{i : |e_n(\mathbf{X}^{(i)})| > \delta\}}{n}, \right. \\ \left. \sup_{\zeta} |\widetilde{P}_n(\zeta) - P_0(\zeta)|, \sup_{\zeta} |P_n(\zeta) - P(\zeta)| \right\} < \delta.$$

The probability of E_δ tends to one, by assumption for the first two expressions and by the Glivenko-Cantelli Theorem for the other two. Then for sufficiently small δ , on E_δ we have for all $\zeta \leq \zeta_0$:

$$\begin{aligned} \widehat{G}_n(\zeta) &= \frac{\widetilde{Q}_n(\zeta)}{Q_n(\zeta)} \leq \frac{\widetilde{P}_n(\zeta - \delta) + \delta}{P_n(\zeta + \delta) - \delta} \leq \frac{\widetilde{P}_n(\zeta) + \delta g^* + \delta}{P_n(\zeta) - \delta g^* - \delta} \leq \frac{P_0(\zeta) + \delta + \delta g^* + \delta}{P(\zeta) - \delta - \delta g^* - \delta} \\ &\leq \frac{P_0(\zeta)}{P(\zeta)} + \frac{2(P_0(\zeta) + P(\zeta))}{(P(\zeta) - (2 + g^*)\delta)^2} \cdot (2 + g^*)\delta \leq G(\zeta) + C(P(\zeta_0), g^*)\delta, \end{aligned}$$

where we have used in the last step that $P(\zeta)$ is decreasing in ζ , and $P_0(\zeta) \leq P(\zeta) \leq 1$. By similar means we can establish bounds in the other direction, as well as bounds in both directions for the difference between $\widehat{G}_n^{\text{BH}}$ and G , so we have (21) because δ is arbitrary.

Now there are two cases: $P(\zeta^*) = 0$, and $P(\zeta^*) > 0$. In the first case, choose ζ_0 and sufficiently small δ so that $P(\zeta_0) < P(\zeta_0 - \delta) < 1/M$. Then by our uniform convergence result we must have $\mathbb{P}(\widehat{\zeta}_n, \widehat{\zeta}_n^{\text{BH}} > \zeta_0) \rightarrow 1$, and we will therefore have $o_p(n)$ rejections for either procedure.

In the second case, we can choose any ζ_0 with $0 < P(\zeta_0) < P(\zeta^*)$, and it will follow by the definitions of $\widehat{\zeta}_n$, $\widehat{\zeta}_n^{\text{BH}}$, and ζ^* that

$$\widehat{\zeta}_n, \widehat{\zeta}_n^{\text{BH}} \xrightarrow{p} \zeta^*. \quad (22)$$

Because $G(\zeta)$ is strictly decreasing in ζ , the result follows. \square

B Linear Multivariate Gaussian Testing

As we have proved above, the FDR control of BONuS does not rely on specific model assumptions. However, the gain in power depends on the model we choose. In the following, we demonstrate a particular theoretical example in multiple testing for multivariate Gaussian distributions, first illustrating how problems can arise in a high dimensional testing and then demonstrating that the parameters are learnable via an maximum likelihood estimator (MLE) approach, where we also give a nonasymptotic upper bound on the error of the MLE.

B.1 Problem Statement and Result

Consider the Bayes two-group model with:

$$\boldsymbol{\mu}^{(i)} | H^{(i)} \sim H^{(i)} \cdot \mathcal{N}_d(0, \boldsymbol{\Psi}) \quad (23)$$

$$X^{(i)} | \boldsymbol{\mu}^{(i)}, H^{(i)} \sim \mathcal{N}_d(\boldsymbol{\mu}^{(i)}, I_d) \quad (24)$$

An important case is that $\boldsymbol{\Psi}$ is a diagonal matrix that has only k nonzero terms, which corresponds to a feature selection problem, and when $k \ll d$, it reduces to a sparse problem. Here we consider a more general version where $\boldsymbol{\Psi}$ is a rank k matrix.

In this case, we have $\mathbf{X}^{(i)}|H^{(i)} = 1 \sim \mathcal{N}_d(0, \Psi + I_d)$, so we may derive the likelihood ratio as:

$$\frac{f_\Lambda(\mathbf{x})}{f_0(x)} \propto \mathbf{x}'\mathbf{x} - \mathbf{x}'(\Psi + I_d)^{-1}\mathbf{x} \quad (25)$$

$$= \mathbf{x}'\left(I_d - (\Psi + I_d)^{-1}\right)\mathbf{x} \quad (26)$$

If we know the matrix Ψ , then we can use $\mathbf{X}'\left(I_d - (\Psi + I_d)^{-1}\right)\mathbf{X}$ as an oracle test statistic. Hence, the problem reduces to finding the matrix Ψ from the data mixed with the synthetic samples. To formulate our problem more precisely, note that the data $\mathbf{X}^{(1)}, \dots, \mathbf{X}^{(n)}$ can be thought to be i.i.d. samples from two-components mixture models with true density function $p_{G_*} := (1 - \lambda^*)N(0, I_d) + \lambda^*N(0, I_d + \Psi^*)$ where $G_* := (\lambda^*, \Psi^*)$ such that $\lambda^* \in (0, 1)$ and $\Psi^* \in \Omega$ are unknown parameters. Here, Ω is a set of positive definite matrices whose eigenvalues are upper bounded by some fixed constant. If we mix a fixed proportion of synthetic samples with the true samples, the resulting mixture is still a Gaussian mixture, so without loss of generality we may just ignore the synthetic samples here.

In this case of Gaussian 2-mixture model, we can show that the maximum likelihood estimator for Ψ is rate-optimal up to a $(\log(n))^{1/2}$ factor. We use MLE to obtain an estimation of G_* , i.e., we have the following estimator

$$\hat{G}_n := \arg \min_{G \in (0,1) \times \Omega} \sum_{i=1}^n \log(p_G(\mathbf{X}^{(i)})) \quad (27)$$

To talk about density estimation from MLE method, we will utilize the classical result from van de Geer (2000). In particular, we have the following result regarding the density estimation $p_{\hat{G}_n}$.

Proposition 4. *There exist some positive constants C and c depending only on d, Ω such that*

$$P\left(h(p_{\hat{G}_n}, p_{G_*}) > C\left(\frac{\log n}{n}\right)^{1/2}\right) \leq \exp(-c \log n).$$

The proof of the above proposition is a direct application of Theorem 7.14 in van de Geer (2000). Note that the standard result holds that the optimal convergence rate for parameter estimation in finite mixture model with a known number of component is $n^{-1/2}$, so MLE is rate optimal up to a $(\log(n))^{1/2}$ factor.

Convergence rates of MLE Given the setup of MLE in equation (27), we have the following result regarding the convergence rates of \hat{G}_n .

Theorem 5. *Assume that \hat{G}_n is given as in equation (27). Then, the following holds:*

- (a) $\mathbb{P}\left(|\hat{\lambda}_n - \lambda^*| \|\hat{\Psi}_n\| \|\Psi^*\| > C_1\left(\frac{\log n}{n}\right)^{1/2}\right) \leq \exp(-c_1 \log n),$
- (b) $\mathbb{P}\left(\lambda^* \|\Psi^*\| \|\hat{\Psi}_n - \Psi^*\| > C_1\left(\frac{\log n}{n}\right)^{1/2}\right) \leq \exp(-c_1 \log n).$

Here, the probability \mathbb{P} is taken with respect to density function p_{G_*} . Furthermore, C_1, c_1 are positive constants depending only on d and Ω .

The interesting feature in Theorem 5 is that both constants C_1 and c_1 are independent of λ^* and Ψ^* . Therefore, the above results give a rigorous way to evaluate the convergence rates of $\hat{\lambda}_n$ and $\hat{\Psi}_n$ when either λ^* goes to 0 or Ψ^* goes to $\vec{0}$ with the sample size. To further obtain the sole dependence of the convergence rate of $\hat{\lambda}_n$ on $\|\Psi^*\|$ in part (a) of Theorem 5, we will need to enforce more conditions on λ^* and $\|\Psi^*\|$. In particular, we denote

$$\Theta_n(l_n) = \left\{ G = (\lambda, \Psi) : \frac{l_n}{\|\Psi\|^2 \sqrt{n}} \leq \lambda \right\}.$$

We have the following convergence result of $\hat{\lambda}_n$ when $G_* \in \Theta_n(l_n)$:

Proposition 6. *Assume that the sequence l_n is chosen such that $l_n/\sqrt{\log(n)} \rightarrow \infty$ as $n \rightarrow \infty$. Then, as n is sufficiently large such that $C_1\sqrt{\log n}/l_n < 1/2$, we obtain*

$$P\left(\left|\hat{\lambda}_n - \lambda^*\right| \|\Psi^*\|^2 > 2C_1 \left(\frac{\log n}{n}\right)^{1/2}\right) \leq 2 \exp(-c_1 \log n)$$

as long as $G_* \in \Theta_n(l_n)$ where C_1, c_1 are two positive constants defined in Theorem 5.

Note that, the condition of $\Theta(l_n)$ is to guarantee that $\hat{\Psi}_n$ is the consistent estimator of Ψ^* . The detail proof of Proposition 6 is deferred to Section B.2. A minimax result is also available but not related to our discussion here.

B.2 Proof of Theorem 5

Our approach to obtain the convergence rate of \hat{G}_n to G_* is based on the comparison between density estimation and parameter estimation, i.e., we would like to see how close \hat{G}_n to G_* as long as $p_{\hat{G}_n}$ is close to p_{G_*} . In particular, we have the following result regarding such approach.

Theorem 7. *For any $G = (\lambda, \Psi)$ and $G_* = (\lambda^*, \Psi^*)$, we denote*

$$\mathcal{D}(G, G_*) := l\|\Psi\|^2 + \lambda^*\|\Psi^*\|^2 - \min\{\lambda, \lambda^*\} \left(\|\Psi\|^2 + \|\Psi^*\|^2 \right) + \left(\lambda\|\Psi\| + \lambda^*\|\Psi^*\| \right) \|\Psi - \Psi^*\|.$$

Then, there exists a positive constant C depending only on d and Ω such that

$$\|p_G - p_{G_*}\|_1 \geq C \cdot \mathcal{D}(G, G_*)$$

for all G and G_* .

Remark: We can verify that

$$\mathcal{D}(G, G_*) \asymp \mathcal{D}_1(G, G_*) = |\lambda - \lambda^*| \|\Psi\| \|\Psi^*\| + \left(\lambda\|\Psi\| + \lambda^*\|\Psi^*\| \right) \|\Psi - \Psi^*\|$$

for any Ψ and Ψ^* . Therefore, we also can obtain the lower bound of L_1 norm between p_G and p_{G_*} in terms of $\mathcal{D}_1(G, G_*)$. This particular lower bound is useful for deriving the convergence rates of MLE estimation later.

To achieve the conclusion of the theorem, we firstly demonstrate the following result

Proposition 8. Denote $\bar{G} = (\bar{\lambda}, \bar{\Psi})$ such that $\bar{\lambda} \in [0, 1]$ and $\bar{\Psi}$ can be identical to $\vec{0}$ where $\vec{0}$ denotes matrix with all elements to be 0. Then, the following holds

$$\liminf_{\epsilon \rightarrow 0} \inf_{G, G_*} \left\{ \frac{\|p_G - p_{G_*}\|_\infty}{\mathcal{D}(G, G_*)} : \mathcal{D}(G, \bar{G}) \vee \mathcal{D}(G_*, \bar{G}) \leq \epsilon \right\} > 0.$$

Proof. Throughout this proof, we denote $f_1(\mathbf{x}|\Psi)$ to be the density of $N(0, I_d + \Psi)$. Here, we only consider the most challenging setting that $\bar{\Psi} = \vec{0}$ as the proof for other possibilities of $\bar{\Psi}$ and $\bar{\lambda}$ can be argued in the similar fashion. Assume that the conclusion of Proposition 8 does not hold. It implies that we can find two sequences $G_n = (\lambda_n, \Psi_n)$ and $G_{*,n} = (\lambda_n^*, \Psi_n^*)$ such that $\mathcal{D}(G_n, \bar{G}) = \lambda_n \|\Psi_n\|^2 \rightarrow 0$, $\mathcal{D}(G_{*,n}, \bar{G}) = \lambda_n^* \|\Psi_n^*\|^2 \rightarrow 0$, and $\|p_{G_n} - p_{G_{*,n}}\|_\infty / \mathcal{D}(G_n, G_{*,n}) \rightarrow 0$ as $n \rightarrow \infty$. For the transparency of presentation, we denote $A_n = \|\Psi_n\|$, $B_n = \|\Psi_n^*\|$, and $C_n = \|\Psi_n - \Psi_n^*\|$. Now, we have three main cases regarding the convergence behaviors of Ψ_n and Ψ_n^*

Case 1: Both $A_n \rightarrow 0$ and $B_n \rightarrow 0$, i.e., Ψ_n and Ψ_n^* vanish to $\vec{0}$ as $n \rightarrow \infty$. Due to the symmetry between λ_n and λ_n^* , we assume without loss of generality that $\lambda_n^* \geq \lambda_n$ for infinite values of n . Without loss of generality, we replace these subsequences of $G_n, G_{*,n}$ by the whole sequences of G_n and $G_{*,n}$. Now, the formulation of $\mathcal{D}(G_n, G_{*,n})$ is

$$\mathcal{D}(G_n, G_{*,n}) = (\lambda_n^* - \lambda_n) B_n^2 + (\lambda_n A_n + \lambda_n^* B_n) C_n.$$

Now, by means of Taylor expansion up to the second order, we get

$$\begin{aligned} \frac{p_{G_n}(\mathbf{x}) - p_{G_{*,n}}(\mathbf{x})}{\mathcal{D}(G_n, G_{*,n})} &= \frac{(\lambda_n^* - \lambda_n)[f_1(\mathbf{x}|\vec{0}) - f_1(\mathbf{x}|\Psi_n^*)] + \lambda_n[f_1(\mathbf{x}|\Psi_n) - f_1(\mathbf{x}|\Psi_n^*)]}{\mathcal{D}(G_n, G_{*,n})} \\ &= \frac{(\lambda_n^* - \lambda_n) \left(\sum_{|\alpha|=1}^2 \frac{(-\Psi_n^*)^\alpha}{\alpha!} \frac{\partial^{|\alpha|} f_1}{\partial \Psi^\alpha}(\mathbf{x}|\Psi_n^*) + R_1(\mathbf{x}) \right)}{\mathcal{D}(G_n, G_{*,n})} \\ &\quad + \frac{\lambda_n \left(\sum_{|\alpha|=1}^2 \frac{(\Psi_n - \Psi_n^*)^\alpha}{\alpha!} \frac{\partial^{|\alpha|} f_1}{\partial \Psi^\alpha}(\mathbf{x}|\Psi_n^*) + R_2(\mathbf{x}) \right)}{\mathcal{D}(G_n, G_{*,n})}, \end{aligned}$$

where $R_1(\mathbf{x})$ and $R_2(\mathbf{x})$ are Taylor remainders that satisfy $R_1(\mathbf{x}) = O(B_n^{2+\gamma})$ and $R_2(\mathbf{x}) = O(C_n^{2+\gamma})$ for some positive number γ due to the smoothness of Gaussian kernel. From the formation of $\mathcal{D}(G_n, G_{*,n})$, since $A_n + B_n \geq C_n$ (triangle inequality), as $A_n \rightarrow 0$ and $B_n \rightarrow 0$ it is clear that

$$\begin{aligned} (\lambda_n - \lambda_n^*) |R_1(\mathbf{x})| / \mathcal{D}(G_n, G_{*,n}) &\leq |R_1(\mathbf{x})| / B_n^2 = O(B_n^\gamma) \rightarrow 0, \\ \lambda_n |R_2(\mathbf{x})| / \mathcal{D}(G_n, G_{*,n}) &\leq |R_2(\mathbf{x})| / \{(\lambda_n + \lambda_n^*) C_n\} = O\left(C_n^{2+\gamma} / C_n^2\right) = O(C_n^\gamma) \rightarrow 0, \end{aligned}$$

as $n \rightarrow \infty$ for all $\mathbf{x} \in \mathcal{X}$. Therefore, we achieve for all $\mathbf{x} \in \mathcal{X}$ that

$$\left((\lambda_n - \lambda_n^*) |R_1(\mathbf{x})| + \lambda_n |R_2(\mathbf{x})| \right) / \mathcal{D}(G_n, G_{*,n}) \rightarrow 0.$$

Hence, we can treat $[p_{G_n}(\mathbf{x}) - p_{G_{*,n}}(\mathbf{x})]/\mathcal{D}(G_n, G_{*,n})$ as a linear combination of $\frac{\partial^{|\alpha|} f_1}{\partial \Psi^\alpha}(\mathbf{x}|\Psi_n^*)$ for all \mathbf{x} and $\alpha \in \mathbb{N}^{d \times d}$ such that $1 \leq |\alpha| \leq 2$. Assume that all the coefficients of these terms go to 0 as $n \rightarrow \infty$. By studying the vanishing behaviors of the coefficients of $\frac{\partial^{|\alpha|} f_1}{\partial \Psi^\alpha}(\mathbf{x}|\Psi_n^*)$ as $|\alpha| = 1$, we achieve the following limits

$$\left(\lambda_n(\Psi_n)_{uv} - \lambda_n^*(\Psi_n^*)_{uv} \right) / \mathcal{D}(G_n, G_{*,n}) \rightarrow 0$$

for all $1 \leq u, v \leq d$ where A_{uv} denotes the (u, v) -th element of matrix A . For any two pairs $(u_1, v_1), (u_2, v_2)$ (not necessarily distinct) such that $1 \leq u_1, u_2, v_1, v_2 \leq d$, the coefficients of $\frac{\partial^{|\alpha|} f_1}{\partial \Psi^\alpha}(\mathbf{x}|\Psi_n^*)$ when $(\alpha)_{u_1 v_1} = (\alpha)_{u_2 v_2} = 1$ leads to

$$\left[(\lambda_n^* - \lambda_n)(-\Psi_n^*)_{u_1 v_1}(-\Psi_n^*)_{u_2 v_2} + \lambda_n(\Psi_n - \Psi_n^*)_{u_1 v_1}(\Psi_n - \Psi_n^*)_{u_2 v_2} \right] / \mathcal{D}(G_n, G_{*,n}) \rightarrow 0. \quad (28)$$

When $(u_1, v_1) \equiv (u_2, v_2)$, the above limits lead to

$$\left[(\lambda_n^* - \lambda_n)(\Psi_n^*)_{u_1 v_1}^2 + \lambda_n(\Psi_n - \Psi_n^*)_{u_1 v_1}^2 \right] / \mathcal{D}(G_n, G_{*,n}) \rightarrow 0.$$

Therefore, we would have that

$$\left[(\lambda_n^* - \lambda_n)\|\Psi_n^*\|^2 + \lambda_n\|\Psi_n - \Psi_n^*\|^2 \right] / \mathcal{D}(G_n, G_{*,n}) \rightarrow 0. \quad (29)$$

Now, as $\left(\lambda_n(\Psi_n)_{uv} - \lambda_n^*(\Psi_n^*)_{uv} \right) / \mathcal{D}(G_n, G_{*,n}) \rightarrow 0$ for all $1 \leq u, v \leq d$, we obtain that

$$\begin{aligned} \left(\lambda_n(\Psi_n)_{u_1 v_1}(\Psi_n)_{u_2 v_2} - \lambda_n^*(\Psi_n^*)_{u_1 v_1}(\Psi_n)_{u_2 v_2} \right) / \mathcal{D}(G_n, G_{*,n}) &\rightarrow 0, \\ \left(\lambda_n(\Psi_n)_{u_1 v_1}(\Psi_n^*)_{u_2 v_2} - \lambda_n^*(\Psi_n^*)_{u_1 v_1}(\Psi_n^*)_{u_2 v_2} \right) / \mathcal{D}(G_n, G_{*,n}) &\rightarrow 0 \end{aligned}$$

for any two pairs $(u_1, v_1), (u_2, v_2)$. The above results imply that

$$\begin{aligned} \left[(\lambda_n^* - \lambda_n)(-\Psi_n^*)_{u_1 v_1}(-\Psi_n^*)_{u_2 v_2} + \lambda_n(\Psi_n - \Psi_n^*)_{u_1 v_1}(\Psi_n - \Psi_n^*)_{u_2 v_2} \right. \\ \left. + (\lambda_n - \lambda_n^*)(\Psi_n^*)_{u_1 v_1}(\Psi_n)_{u_2 v_2} \right] / \mathcal{D}(G_n, G_{*,n}) \rightarrow 0. \end{aligned} \quad (30)$$

By combining the results from (28) and (30), we ultimately achieve for any two pairs (u_1, v_1) and (u_2, v_2) that

$$(\lambda_n - \lambda_n^*)(\Psi_n^*)_{u_1 v_1}(\Psi_n)_{u_2 v_2} / \mathcal{D}(G_n, G_{*,n}) \rightarrow 0. \quad (31)$$

Using the results from equation (28) and (31), we have

$$\begin{aligned}\frac{\lambda_n(\Psi_n)_{u_1 v_1}(\Psi_n - \Psi_n^*)_{u_2 v_2}}{\mathcal{D}(G_n, G_{*,n})} &\rightarrow \frac{(\lambda_n^* - \lambda_n)(\Psi_n)_{u_1 v_1}(\Psi_n^*)_{u_2 v_2}}{\mathcal{D}(G_n, G_{*,n})} \rightarrow 0, \\ \frac{\lambda_n^*(\Psi_n^*)_{u_1 v_1}(\Psi_n - \Psi_n^*)_{u_2 v_2}}{\mathcal{D}(G_n, G_{*,n})} &\rightarrow \frac{(\lambda_n^* - \lambda_n)(\Psi_n^*)_{u_1 v_1}(\Psi_n)_{u_2 v_2}}{\mathcal{D}(G_n, G_{*,n})} \rightarrow 0\end{aligned}$$

for any two pairs (u_1, v_1) and (u_2, v_2) . Therefore, it leads to

$$\begin{aligned}\frac{\sum_{(u_1, v_1), (u_2, v_2)} \lambda_n |(\Psi_n)_{u_1 v_1}| |(\Psi_n - \Psi_n^*)_{u_2 v_2}|}{\mathcal{D}(G_n, G_{*,n})} &= \frac{\lambda_n \sum_{(u_1, v_1)} |(\Psi_n)_{u_1 v_1}| \sum_{(u_2, v_2)} |(\Psi_n - \Psi_n^*)_{u_2 v_2}|}{\mathcal{D}(G_n, G_{*,n})} \rightarrow 0, \\ \frac{\sum_{(u_1, v_1), (u_2, v_2)} \lambda_n^* |(\Psi_n^*)_{u_1 v_1}| |(\Psi_n - \Psi_n^*)_{u_2 v_2}|}{\mathcal{D}(G_n, G_{*,n})} &= \frac{\lambda_n^* \sum_{(u_1, v_1)} |(\Psi_n^*)_{u_1 v_1}| \sum_{(u_2, v_2)} |(\Psi_n - \Psi_n^*)_{u_2 v_2}|}{\mathcal{D}(G_n, G_{*,n})} \rightarrow 0.\end{aligned}$$

The above results indicate that

$$\lambda_n \|\Psi_n\| \|\Psi_n - \Psi_n^*\| / \mathcal{D}(G_n, G_{*,n}) \rightarrow 0, \quad \lambda_n^* \|\Psi_n^*\| \|\Psi_n - \Psi_n^*\| / \mathcal{D}(G_n, G_{*,n}) \rightarrow 0. \quad (32)$$

Combining the results from (29) and (32), we have

$$1 = \mathcal{D}(G_n, G_{*,n}) / \mathcal{D}(G_n, G_{*,n}) \rightarrow 0,$$

which is a contradiction. As a consequence, not all the coefficients of $\frac{\partial^{|\alpha|} f_1}{\partial \Psi^\alpha}(\mathbf{x} | \Psi_n^*)$ go to 0 as $1 \leq |\alpha| \leq 2$. By denoting m_n to be the maximum of the absolute values of the coefficients of $\frac{\partial^{|\alpha|} f_1}{\partial \Psi^\alpha}(\mathbf{x} | \Psi_n^*)$ we achieve for all \mathbf{x} that

$$\frac{1}{m_n} \frac{p_{G_n}(\mathbf{x}) - p_{G_{*,n}}(\mathbf{x})}{\mathcal{D}(G_n, G_{*,n})} \rightarrow \sum_{|\alpha|=1}^2 \tau_\alpha \frac{\partial^{|\alpha|} f_1}{\partial \Psi^\alpha}(\mathbf{x} | 0) = 0$$

where $\tau_\alpha \in \mathbb{R}$ are some coefficients such that not all of them are 0. We can check that the previous equation only holds when $\tau_\alpha = 0$ for all $1 \leq |\alpha| \leq 2$, which is a contradiction. As a consequence, Case 1 cannot happen.

Case 2: Exactly one of A_n and B_n goes to 0, i.e., there exists at least one component among Ψ_n and Ψ_n^* that does not converge to $\vec{0}$ as $n \rightarrow \infty$. Due to the symmetry of A_n and B_n , we assume without loss of generality that $A_n \not\rightarrow 0$ and $B_n \rightarrow 0$, which is equivalent to $\Psi_n \rightarrow \Psi' \neq \vec{0}$ while $\Psi_n^* \rightarrow \vec{0}$ as $n \rightarrow \infty$. We denote

$$\mathcal{D}'(G_n, G_{*,n}) = |\lambda_n^* - \lambda_n| B_n + \lambda_n A_n + \lambda_n^* B_n.$$

Since $[p_{G_n}(\mathbf{x}) - p_{G_{*,n}}(\mathbf{x})] / \mathcal{D}(G_n, G_{*,n}) \rightarrow 0$, we achieve that $[p_{G_n}(\mathbf{x}) - p_{G_{*,n}}(\mathbf{x})] / \mathcal{D}'(G_n, G_{*,n}) \rightarrow 0$ for all \mathbf{x} as $\mathcal{D}(G_n, G_{*,n}) \lesssim \mathcal{D}'(G_n, G_{*,n})$. By means of Taylor expansion up to the first order,

we have

$$\begin{aligned}
\frac{p_{G_n}(\mathbf{x}) - p_{G_{*,n}}(\mathbf{x})}{\mathcal{D}'(G_n, G_{*,n})} &= \frac{(\lambda_n^* - \lambda_n)[f_1(\mathbf{x}|\vec{0}) - f_1(\mathbf{x}|\Psi_n^*)] + \lambda_n f_1(\mathbf{x}|\Psi_n) - \lambda_n f_1(\mathbf{x}|\Psi_n^*)}{\mathcal{D}'(G_n, G_{*,n})} \\
&= \frac{(\lambda_n^* - \lambda_n) \left(\sum_{|\alpha|=1} \frac{(-\Psi_n^*)^\alpha}{\alpha!} \frac{\partial^{|\alpha|} f_1}{\partial \Psi^\alpha}(\mathbf{x}|\Psi_n^*) + R_1'(\mathbf{x}) \right)}{\mathcal{D}'(G_n, G_{*,n})} \\
&\quad + \frac{\lambda_n f_1(\mathbf{x}|\Psi_n) - \lambda_n f_1(\mathbf{x}|\Psi_n^*)}{\mathcal{D}'(G_n, G_{*,n})}
\end{aligned}$$

where $R_1'(\mathbf{x})$ is Taylor remainder that satisfies $(\lambda_n^* - \lambda_n)|R_1'(\mathbf{x})|/\mathcal{D}'(G_n, G_{*,n}) = O(B_n^{\gamma'}) \rightarrow 0$ for some positive number $\gamma' > 0$. Since Ψ_n and Ψ_n^* do not have the same limit, they will be different when n is large enough, i.e., $n \geq M'$ for some value of M' . Now, as $n \geq M'$, $[p_{G_n}(\mathbf{x}) - p_{G_{*,n}}(\mathbf{x})]/\mathcal{D}'(G_n, G_{*,n})$ becomes a linear combination of $\frac{\partial^{|\alpha|} f_1}{\partial \Psi^\alpha}(\mathbf{x}|\Psi_n^*)$ for all $|\alpha| \leq 1$ and $f_1(\mathbf{x}|\Psi_n)$. If all of the coefficients of these terms go to 0, we would have $\lambda_n/\mathcal{D}'(G_n, G_{*,n}) \rightarrow 0$ and $(\lambda_n^* - \lambda_n)(-\Psi_n^*)_{uv}/\mathcal{D}'(G_n, G_{*,n}) \rightarrow 0$ for all $1 \leq u, v \leq d$. It implies that $(\lambda_n^* - \lambda_n)B_n/\mathcal{D}'(G_n, G_{*,n}) \rightarrow 0$, $\lambda_n A_n/\mathcal{D}'(G_n, G_{*,n}) \rightarrow 0$, and $\lambda_n B_n/\mathcal{D}'(G_n, G_{*,n}) \rightarrow 0$. These results lead to

$$1 = \left(|\lambda_n^* - \lambda_n|B_n + \lambda_n A_n + \lambda_n^* B_n \right) / \mathcal{D}'(G_n, G_{*,n}) \rightarrow 0,$$

a contradiction. Therefore, not all the coefficients of $\frac{\partial^{|\alpha|} f_1}{\partial \Psi^\alpha}(\mathbf{x}|\Psi_n^*)$ and $f_1(\mathbf{x}|\Psi_n)$ go to 0. By defining m'_n to be the maximum of these coefficients, we achieve for all \mathbf{x} that

$$\frac{1}{m'_n} \frac{p_{G_n}(\mathbf{x}) - p_{G_{*,n}}(\mathbf{x})}{\mathcal{D}'(G_n, G_{*,n})} \rightarrow \eta' f_1(\mathbf{x}|\vec{0}) + \sum_{|\alpha|=0}^1 \tau'_\alpha \frac{\partial^{|\alpha|} f_1}{\partial \Psi^\alpha}(\mathbf{x}|\Psi') = 0,$$

where η' and τ'_α are coefficients such that not all of them are 0, which is a contradiction to the first order identifiability of Gaussian distribution with only covariance parameter. As a consequence, Case 2 cannot hold.

Case 3: Both A_n and B_n do not go to 0, i.e., Ψ_n and Ψ_n^* do not converge to $\vec{0}$ as $n \rightarrow \infty$. Since $\mathcal{D}_n(G_n, G_{*,n}) \lesssim \mathcal{K}(G_n, G_{*,n}) = |\lambda_n - \lambda_n^*| + (\lambda_n + \lambda_n^*)C_n$ and $[p_{G_n}(\mathbf{x}) - p_{G_{*,n}}(\mathbf{x})]/\mathcal{D}(G_n, G_{*,n}) \rightarrow 0$, we achieve that $[p_{G_n}(\mathbf{x}) - p_{G_{*,n}}(\mathbf{x})]/\mathcal{K}(G_n, G_{*,n}) \rightarrow 0$ for all \mathbf{x} . From here, by using the same argument as that of Case 1 and Case 2, we also reach the contradiction. Therefore, Case 3 cannot happen.

In sum, we achieve the conclusion of the proposition. \square

Now, assume that the conclusion of Theorem 7 does not hold. It implies that we can find two sequences G'_n and $G'_{*,n}$ such that $F_n = \|p_{G'_n} - p_{G'_{*,n}}\|_1/\mathcal{D}(G'_n, G'_{*,n}) \rightarrow 0$ as $n \rightarrow \infty$. Since Ω is bounded set of positive definite matrices, we can find subsequences of G'_n and $G'_{*,n}$ such that $\mathcal{D}(G'_n, \bar{G}_1)$ and $\mathcal{D}(G'_{*,n}, \bar{G}_2)$ vanish to 0 as $n \rightarrow \infty$ where \bar{G}_1, \bar{G}_2 are some parameters in $[0, 1] \times \Omega$. Because $F_n \rightarrow 0$, we obtain $\|p_{G'_n} - p_{G'_{*,n}}\|_1 \rightarrow 0$ as $n \rightarrow \infty$. By means of Fatou's lemma, we have

$$0 = \lim_{n \rightarrow \infty} \int |p_{G'_n}(x) - p_{G'_{*,n}}(x)| dx \geq \int \liminf_{n \rightarrow \infty} |p_{G'_n}(\mathbf{x}) - p_{G'_{*,n}}(\mathbf{x})| d\mathbf{x} = \|p_{\bar{G}_1} - p_{\bar{G}_2}\|_1.$$

Due to the fact that Gaussian is identifiable, the above equation implies that $\overline{G}_1 \equiv \overline{G}_2$. However, from the result of Proposition 8, regardless of the value of \overline{G}_1 we would have $F_n \not\rightarrow 0$ as $n \rightarrow \infty$, which is a contradiction. Therefore, we obtain the conclusion of the theorem.

B.3 Proof of Proposition 6

Let n be such that $C_1\sqrt{\log n}/l_n < 1/2$ where C_1 is positive constant in Theorem 5. Then, we obtain that

$$\begin{aligned}
P\left(\|\widehat{\Psi}_n\| < \frac{\|\Psi^*\|}{2}\right) &= P\left(\|\Psi^*\| - \|\widehat{\Psi}_n\| > \frac{\|\Psi^*\|}{2}\right) \leq P\left(\|\Psi^* - \widehat{\Psi}_n\| > \frac{\|\Psi^*\|}{2}\right). \\
&\leq P\left(\|\Psi^* - \widehat{\Psi}_n\| > \frac{C_1\sqrt{\log n}\|\Psi^*\|}{l_n}\right) \\
&\leq P\left(\|\Psi^* - \widehat{\Psi}_n\| > \frac{C_1\sqrt{\log n}\|\Psi^*\|}{\lambda^*\|\Psi^*\|^2\sqrt{n}}\right) \\
&= P\left(\lambda^*\|\Psi^*\|\|\widehat{\Psi}_n - \Psi^*\| > C_1\left(\frac{\log n}{n}\right)^{1/2}\right) \leq \exp(-c_1 \log n)
\end{aligned}$$

where c_1 is positive constant defined in Theorem 5. The above inequality leads to

$$\begin{aligned}
P\left(|\widehat{\lambda}_n - \lambda^*|\|\Psi^*\|^2 > 2C_1\left(\frac{\log n}{n}\right)^{1/2}\right) &= P\left(|\widehat{\lambda}_n - \lambda^*|\|\Psi^*\|^2 > 2C_1\left(\frac{\log n}{n}\right)^{1/2}, \|\widehat{\Psi}_n\| \geq \frac{\|\Psi^*\|}{2}\right) \\
&+ P\left(|\widehat{\lambda}_n - \lambda^*|\|\Psi^*\|^2 > 2C_1\left(\frac{\log n}{n}\right)^{1/2}, \|\widehat{\Psi}_n\| < \frac{\|\Psi^*\|}{2}\right) \\
&\leq P\left(|\widehat{\lambda}_n - \lambda^*|\|\widehat{\Psi}_n\|\|\Psi^*\|^2 > C_1\left(\frac{\log n}{n}\right)^{1/2}\right) \\
&+ P\left(\|\widehat{\Psi}_n\| < \frac{\|\Psi^*\|}{2}\right) \\
&\leq 2\exp(-c_1 \log n).
\end{aligned}$$

We obtain the conclusion of the proposition.