P-Values for High-Dimensional Regression

Abstract

Assigning significance in high-dimensional regression is challenging. Most computationally efficient selection algorithms cannot guard against inclusion of noise variables. Asymptotically valid p-values are not available. An exception is a recent proposal by Wasserman and Roeder (2008) which splits the data into two parts. The number of variables is then reduced to a manageable size using the first split, while classical variable selection techniques can be applied to the remaining variables, using the data from the second split. This yields asymptotic error control under minimal conditions. It involves, however, a one-time random split of the data. Results are sensitive to this arbitrary choice: it amounts to a 'p-value lottery' and makes it difficult to reproduce results. Here, we show that inference across multiple random splits can be aggregated, while keeping asymptotic control over the inclusion of noise variables. We show that the resulting p-values can be used for control of both family-wise error (FWER) and false discovery rate (FDR). In addition, the proposed aggregation is shown to improve power while reducing the number of falsely selected variables substantially.

Keywords: High-dimensional variable selection, Data splitting, Multiple comparisons, Family-wise error rate, False discovery rate.

1 Introduction

The problem of high-dimensional variable selection has received tremendous attention in the last decade. Sparse estimators like the Lasso (Tibshirani, 1996) and extensions thereof (Zou,

^{*}These authors contributed equally to this work

[†]Department of Statistics, University of Oxford, UK

[‡]Seminar für Statistik, ETH Zurich, Switzerland

2006; Meinshausen, 2007) have been shown to be very powerful because they are suitable for high-dimensional data sets and because they lead to sparse, interpretable results.

In the usual work-flow for high-dimensional variable selection problems, the user sets potential tuning parameters to their prediction optimal values and uses the resulting estimator as the final result. In the classical low-dimensional setup, some error control based on p-values is a widely used standard in all areas of sciences. So far, p-values were not available in high-dimensional situations, except for the proposal of Wasserman and Roeder (2008). An ad-hoc solution for assigning relevance is to use the bootstrap to analyze the stability of the selected predictors and to focus on those which are selected most often (or even always). Bach (2008) and Meinshausen and Bühlmann (2008) show for the Lasso that this leads to a consistent model selection procedure under fewer restrictions than for the non-bootstrap case.

More recently, some progress has been achieved to obtain error control (Wasserman and Roeder, 2008; Meinshausen and Bühlmann, 2008). Here, we build upon the approach of Wasserman and Roeder (2008) and show that an extension of their 'screen and clean' algorithm leads to a more powerful variable selection procedure. Moreover, family-wise error rate (FWER) and false discovery rate (FDR) can be controlled, while Wasserman and Roeder (2008) focus on variable selection rather than assigning significance via p-values. We also extend methodology to control of the false discovery rate (Benjamini and Hochberg, 1995) for high-dimensional data.

While the main application of the procedure are high-dimensional data, where the number p of variables can greatly exceed sample size n, we show that the method is also quite competitive with more standard error control for n > p settings, indeed often giving a better detection power in the presence of highly correlated variables.

This article is organized as follows. We discuss the single-split method of Wasserman and Roeder (2008) briefly in Section 2, showing that results can strongly depend on the arbitrary choice of a random sample splitting. We propose a multi-split method, removing this dependence. In Section 3 we prove FWER and FDR-control of the multi-split method, and we show in Section 4 numerically for simulated and real data-sets that the method is more powerful than the single-split version while reducing substantially the number of false discoveries. Some possible extensions of the proposed methodology are outlined in Section 5.

2 Sample Splitting and High-Dimensional Variable Selection

We consider the usual high-dimensional linear regression setup with a response vector $Y = (Y_1, \ldots, Y_n)$ and an $n \times p$ fixed design matrix X such that

$$Y = X\beta + \varepsilon$$
,

where $\varepsilon = (\varepsilon_1, \dots \varepsilon_n)$ is a random error vector with ε_i iid. $\mathcal{N}(0, \sigma^2)$ and $\beta \in \mathbb{R}^p$ is the parameter vector. Extensions to other models are outlined in Section 5.

Denote by

$$S = \{j; \, \beta_j \neq 0\}$$

the set of active predictors and similarly by $N = S^c = \{j; \beta_j = 0\}$ the set of noise variables. Our goal is to assign p-values for the null-hypotheses $H_{0,j}: \beta_j = 0$ versus $H_{A,j}: \beta_j \neq 0$ and to infer the set S from a set of n observations $(X_i, Y_i), i = 1, \ldots, n$. We allow for potentially high-dimensional designs, i.e. $p \gg n$. This makes statistical inference very challenging. An approach proposed by Wasserman and Roeder (2008) is to split the data into two parts, reducing the dimensionality of predictors on one part to a manageable size of predictors (keeping the important variables with high probability), and then to assign p-values and making a final selection on the second part of the data, using classical least squares estimation.

2.1 FWER control with the Single-Split Method

The procedure of Wasserman and Roeder (2008) attempts to control the family-wise error rate (FWER), which is defined as the probability of making at least one false rejection. The method relies on sample-splitting, performing variable selection and dimensionality reduction on one part of the data and classical significance testing on the remaining part. The data are splitted randomly into two disjoint groups $D_{in} = (X_{in}, Y_{in})$ and $D_{out} = (X_{out}, Y_{out})$ of equal size. Let \tilde{S} be a variable selection or screening procedure which estimates the set of active predictors. Abusing notation slightly, we also denote by \tilde{S} the set of selected predictors. Then variable selection and dimensionality reduction is based on D_{in} , i.e. we apply \tilde{S} only on D_{in} . This includes the selection of potential tuning parameters involved in \tilde{S} . The idea is to break down the large number p of potential predictor variables to a smaller number $k \ll p$ with k at most a fraction of n while keeping all relevant variables. The regression coefficients and the corresponding p-values $\tilde{P}_1, \ldots, \tilde{P}_p$ of the selected predictors are determined based on D_{out} by using ordinary least squares estimation on the set \tilde{S} and setting $\tilde{P}_j = 1$ for all

 $j \notin \tilde{S}$. If the selected model \tilde{S} contains the true model S, i.e. $\tilde{S} \supseteq S$, the p-values based on D_{out} are unbiased. Finally, each p-value \tilde{P}_j is adjusted by a factor $|\tilde{S}|$ to correct for the multiplicity of the testing problem.

The selected model is given by all variables in \tilde{S} for which the adjusted p-value is below a cutoff $\alpha \in (0,1)$,

$$\hat{S}_{single} = \left\{ j \in \tilde{S} : \tilde{P}_j | \tilde{S} | \le \alpha \right\}.$$

Under suitable assumptions discussed later, this yields asymptotic control against inclusion of variables in N (false positives) in the sense that

$$\limsup_{n \to \infty} \mathbb{P} \Big[|N \cap \hat{S}_{single}| \ge 1 \Big] \le \alpha,$$

i.e. control of the family-wise error rate. The method is easy to implement and yields the asymptotic control under weak assumptions. The single-split method relies, however, on an arbitrary split into D_{in} and D_{out} . Results can change drastically if this split is chosen differently. This in itself is unsatisfactory since results are not reproducible.

2.2 FWER control with the New Multi-Split Method

An obvious alternative to a single arbitrary split is to divide the sample repeatedly. For each split we end up with a set of p-values. It is not obvious, though, how to combine and aggregate the results.

In the remainder of the section, we will give a possible answer. For each hypothesis, a distribution of p-values is obtained for random sample splitting. We will propose that error control can be based on the quantiles of this distribution. We will show empirically that, maybe unsurprisingly, the resulting procedure is more powerful than the single-split method. The multi-split method also makes results reproducible, at least approximately if the number of random splits is chosen to be very large.

The multi-split method uses the following procedure:

For
$$b = 1, ..., B$$
:

- 1. Randomly split the original data into two disjoint groups $D_{in}^{(b)}$ and $D_{out}^{(b)}$ of equal size.
- 2. Using only $D_{in}^{(b)}$, estimate the set of active predictors $\tilde{S}^{(b)}$.
- 3. (a) Using only $D_{out}^{(b)}$, fit the selected variables in $\tilde{S}^{(b)}$ with ordinary least squares and calculate the corresponding p-values $\tilde{P}_{j}^{(b)}$ for $j \in \tilde{S}^{(b)}$.

(b) Set the remaining p-values to 1, i.e.

$$\tilde{P}_j^{(b)} = 1, j \notin \tilde{S}^{(b)}.$$

4. Define the adjusted (non-aggregated) p-values as

$$P_j^{(b)} = \min\left(\tilde{P}_j^{(b)}|\tilde{S}^{(b)}|, 1\right), \ j = 1, \dots, p$$
 (2.1)

Finally, aggregate over the B p-values $P_j^{(b)}$, as discussed below.

The procedure leads to a total of B p-values for each predictor j = 1, ..., p. It will turn out that suitable summary statistics are quantiles. For $\gamma \in (0, 1)$ define

$$Q_j(\gamma) = \min \left\{ 1, q_{\gamma} \left(\{ P_j^{(b)} / \gamma; b = 1, \dots, B \} \right) \right\},$$
 (2.2)

where $q_{\gamma}(\cdot)$ is the (empirical) γ -quantile function.

A p-value for each predictor j = 1, ..., p is then given by $Q_j(\gamma)$, for any fixed $0 < \gamma < 1$. We will show in Section 3 that this is an asymptotically correct p-value, adjusted for multiplicity. To give an example, for a choice of $\gamma = 0.5$, the quantity $Q_j(0.5)$ is twice the median of all p-values $P_j^{(b)}$, b = 1, ..., B.

A proper selection of γ may be difficult. Error control is not guaranteed anymore if we search for the best value of γ . We propose to use instead an adaptive version which selects a suitable value of the quantile based on the data. Let $\gamma_{\min} \in (0,1)$ be a lower bound for γ , typically 0.05, and define

$$P_j = \min \left\{ 1, \left(1 - \log \gamma_{\min} \right) \inf_{\gamma \in (\gamma_{\min}, 1)} Q_j(\gamma). \right\}$$
 (2.3)

The extra correction factor $1 - \log \gamma_{\min}$ ensures that the family-wise error rate remains controlled at level α despite of the adaptive search for the best quantile, see Section 3. For the recommended choice of $\gamma_{\min} = 0.05$, this factor is upper bounded by 4; in fact, $1 - \log(0.05) \approx 3.996$.

We comment briefly on the relation between the proposed adjustment to false discovery rate (Benjamini and Hochberg, 1995; Benjamini and Yekutieli, 2001) or family-wise error (Holm, 1979) controlling procedures. While we provide a family-wise error control and as such use union bound corrections as in Holm (1979), the definition of the adjusted p-values (2.3) and its graphical representation in Figure 1 are vaguely reminiscent of the false discovery rate procedure, rejecting hypotheses if and only if the empirical distribution of p-values crosses a certain linear bound. The empirical distribution in (2.3) is only taken

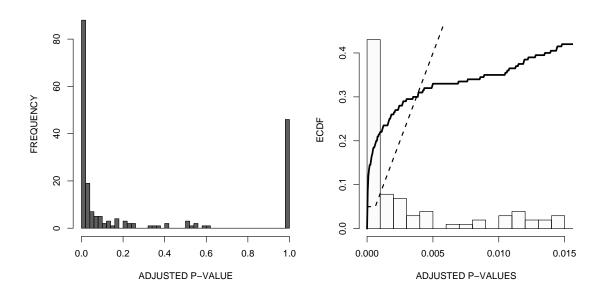


Figure 1: Left: a histogram of adjusted p-values $P_j^{(b)}$ for the selected variable in the motif regression data example of Section 4.3. The single split method picks randomly one of these p-values (a 'p-value lottery') and rejects if it is below α . For the multi-split method, we reject if and only if the empirical distribution function of the adjusted p-values crosses the broken line (which is $f(p) = \max\{0.05, (3.996/\alpha)p\}$) for some $p \in (0,1)$. This bound is shown as a broken line for $\alpha = 0.05$. For the given example, the bound is indeed exceeded and the variable is thus selected.

for one predictor variable, though, which is either in S or N. This would correspond to a multiple testing situation where we are testing a single hypothesis with multiple statistics. Figure 1 shows an example. The left panel contains the histogram of the adjusted p-values $P_j^{(b)}$ for $b=1,\ldots,B$ of the selected variable in the real data example in Section 4.3. The single split method is equivalent to picking one of these p-values randomly and selecting the variable if this randomly picked p-value is sufficiently small. To avoid this 'p-value lottery', the multi-split method computes the empirical distribution of all p-values $P_j^{(b)}$ for $b=1,\ldots,B$ and rejects if the empirical distribution crosses the broken line in the right panel of Figure 1. A short derivation of the latter is as follows. Variable j is selected if and only if $P_j \leq \alpha$, which happens if and only if there exists some $\gamma \in (0.05,1)$ such that $Q_j(\gamma) \leq \alpha/(1-\log 0.05) \approx \alpha/3.996$. Equivalently, using definition (2.2), the γ -quantile of the adjusted p-values, $q_{\gamma}(P_j^{(b)})$, has to be smaller than or equal to $\alpha\gamma/3.996$. This in turn is equivalent to the event that the empirical distribution of the adjusted p-values $P_j^{(b)}$ for $b=1,\ldots,B$ is crossing above the bound $f(p)=\max\{0.05,(3.996/\alpha)p\}$ for some $p\in(0,1)$. This bound is shown as a broken line in the right panel of Figure 1.

The resulting adjusted p-values P_j , j = 1, ..., p can then be used for both FWER and FDR control. For FWER control at level $\alpha \in (0, 1)$, simply all p-values below α are rejected and the selected subset is

$$\hat{S}_{multi} = \{ j : P_j \le \alpha \}. \tag{2.4}$$

We will show in Section 3.2 that indeed, asymptotically, $\mathbb{P}(V > 0) \leq \alpha$, where $V = |\hat{S}_{multi} \cap N|$ is the number of falsely selected variables under the proposed selection (2.4). Besides better reproducibility and asymptotic family-wise error control, the multi-split version is, maybe unsurprisingly, more powerful than the single-split selection method.

2.3 FDR control with the multi-split method

Control of the family-wise error rate is often considered as too conservative. If many rejections are made, Benjamini and Hochberg (1995) proposed to control instead the expected proportion of false rejections, the false discovery rate (FDR). Let $V = |\hat{S} \cap N|$ be the number of false rejections for a selection method \hat{S} and $R = |\hat{S}|$ the total number of rejections. The false discovery rate is defined as the expected proportion of false rejections

$$\mathbb{E}(Q), \quad \text{with} \quad Q = V/\max\{1, R\}. \tag{2.5}$$

For no rejections, R = 0, the denominator ensures that the false discovery proportion Q is 0, conforming with the definition in Benjamini and Hochberg (1995).

The original FDR controlling procedure in (Benjamini and Hochberg, 1995) first orders the

observed p-values as $P_{(1)} \leq P_{(2)} \leq \ldots \leq P_{(p)}$ and defines

$$k = \max\{i : P_{(i)} \le \frac{i}{p}q\}.$$
 (2.6)

Then all variables or hypotheses with the smallest k values are rejected and no rejection is made if the set in (2.6) is empty. FDR is controlled this way at level q under the condition that all p-values are independent. It has been shown in Benjamini and Yekutieli (2001) that the procedure is conservative under a wider range of dependencies between p-values; see also Blanchard and Roquain (2008) for related work. It would, however, require a big leap of faith to assume any such assumption for our setting of high-dimensional regression. For general dependencies, Benjamini and Yekutieli (2001) showed that control is guaranteed at level $q \sum_{i=1}^{p} i^{-1} \approx q(1/2 + \log(p))$.

The standard FDR procedure is working with the raw p-values, which are assumed to be uniformly distributed on [0,1] for true null hypotheses. The division by p in (2.6) is an effective correction for multiplicity. The proposed multi-split method, however, is producing already adjusted p-values, as in (2.3). Since we are working already with multiplicity-corrected p-values, the division by p in (2.6) turns out to be superfluous. Instead, we can order the corrected p-values P_j , $j=1,\ldots,p$ in increasing order $P_{(1)} \leq P_{(2)} \leq \ldots \leq P_{(p)}$ and select the p variables with the smallest p-values, where

$$h = \max\{i : P_{(i)} \le iq\}. \tag{2.7}$$

The selected set of variables is denoted, with the value of h given in (2.7), by

$$\hat{S}_{multi;FDR} = \{j : P_j \le P_{(h)}\},$$
 (2.8)

with no rejections, $\hat{S}_{multi;FDR} = \emptyset$, if $P_{(i)} > iq$ for all $i = 1, \ldots, p$.

The procedure (2.8) will achieve FDR control at level $q \sum_{i=1}^{p} i^{-1} \approx q(1/2 + \log p)$. To get FDR control at level q, we replace q in (2.7) by $q/(\sum_{i=1}^{p} i^{-1})$, completely analogous to the standard FDR-procedure under arbitrary dependence of the p-values in Benjamini and Yekutieli (2001). We will prove error control in the following section and show empirically the advantages of the proposed multi-split version over both the single-split and standard FDR controlling procedures in the later section with numerical results.

3 Error Control and Consistency

3.1 Assumptions

To achieve asymptotic error control, a few assumptions are made in Wasserman and Roeder (2008) regarding the crucial requirements for the variable selection procedure \tilde{S} .

- (A1) Screening property: $\lim_{n\to\infty} \mathbb{P}\left[\tilde{S} \supseteq S\right] = 1.$
- (A2) Sparsity property: $|\tilde{S}| < n/2$.

The screening property (A1) ensures that all relevant variables are retained. Irrelevant noise variables are allowed to be selected, too, as long as there are not too many as required by the sparsity property (A2). A violation of the sparsity property would make it impossible to apply classical tests on the retained variables.

The Lasso (Tibshirani, 1996) is an important example which satisfies (A1) and (A2) under appropriate conditions discussed in Meinshausen and Bühlmann (2006), Zhao and Yu (2006), van de Geer (2008), Meinshausen and Yu (2009) and Bickel et al. (2008). The adaptive Lasso (Zou, 2006; Zhang and Huang, 2008) satisfies (A1) and (A2) as well under suitable conditions. Other examples include, assuming appropriate conditions, L_2 Boosting (Friedman, 2001; Bühlmann, 2006), orthogonal matching pursuit (Tropp and Gilbert, 2007) or Sure Independence Screening (Fan and Lv, 2008).

We will typically use the Lasso (and extensions thereof) as screening method. Other algorithms would be possible. Wasserman and Roeder (2008) studied various scenarios under which these two properties are satisfied for the Lasso, depending on the choice of the regularization parameter. We refrain from repeating these and similar arguments, just working on the assumption that we have a selection procedure \tilde{S} at hand which satisfies both the screening property and the sparsity property.

3.2 FWER control

We proposed two versions for multiplicity-adjusted p-values. One is $Q_j(\gamma)$ as defined in (2.2) which relies on a choice of $\gamma \in (0,1)$. The second is the adaptive version P_j defined in (2.3) which makes an adaptive choice of γ . We show that both quantities are multiplicity-adjusted p-values providing asymptotic FWER-error control.

Theorem 3.1. Assume (A1) and (A2). Let $\alpha, \gamma \in (0,1)$. If the null-hypothesis $H_{0,j}: \beta_j = 0$ gets rejected whenever $Q_j(\gamma) \leq \alpha$, the family-wise error rate is asymptotically controlled at level α , i.e.

$$\limsup_{n \to \infty} \mathbb{P}\Big[\min_{j \in N} Q_j(\gamma) \le \alpha\Big] \le \alpha,$$

where \mathbb{P} is with respect to the data sample and the statement holds for any of the B random sample splits.

A proof is given in the appendix.

Theorem 3.1 is valid for any pre-defined value of the quantile γ . However, the adjusted p-values $Q_j(\gamma)$ involve the somehow arbitrary choice of γ which might pose a problem for practical applications. We therefore proposed the adjusted p-values P_j which search for the optimal value of γ adaptively.

Theorem 3.2. Assume (A1) and (A2). Let $\alpha \in (0,1)$. If the null-hypothesis $H_{0,j}: \beta_j = 0$ gets rejected whenever $P_j \leq \alpha$, the family-wise error rate is asymptotically controlled at level α , i.e.

$$\limsup_{n \to \infty} \mathbb{P} \Big[\min_{j \in N} P_j \le \alpha \Big] \le \alpha,$$

where the probability \mathbb{P} is as in Theorem 3.1.

A proof is given in the appendix.

A brief remark regarding the asymptotic nature of the results seems in order. The proposed error control relies on all truly important variables being selected in the screening stage with very high probability. This is our *screening property* (A1). Let \mathcal{A} be the event $S \subseteq \tilde{S}$. The results above for example in Theorem 3.2 can be formulated in a non-asymptotic way as $\mathbb{P}[\mathcal{A} \cap \{\min_{j \in N} P_j \leq \alpha\}] \leq \alpha$, and $P(\mathcal{A}) \to 1$, typically exponentially fast, for $n \to \infty$. Analogous remarks apply to Theorem 3.1 and 3.3 below.

3.3 FDR control

The adjusted p-values can be used for FDR control, as laid out in Section 2.3. The set of selected variables $\hat{S}_{multi;FDR}$ was defined in (2.8). Here, we show that FDR is indeed controlled at the desired rate with this procedure.

Theorem 3.3. Assume (A1) and (A2). Let $q \in (0,1)$. Let $\hat{S}_{multi;FDR}$ be the set of selected variables, as defined in (2.8) and $V = |\hat{S}_{multi;FDR} \cap N|$ and $R = |\hat{S}_{multi;FDR}|$. The false discovery rate (2.5) with $Q = V/\max\{1, R\}$ is then asymptotically controlled at level $q \sum_{i=1}^{p} i^{-1}$, i.e.

$$\limsup_{n \to \infty} \mathbb{E}(Q) \le q \sum_{i=1}^{p} \frac{1}{i}.$$

A proof is given in the appendix.

As with FWER-control, we could be using, for any fixed value of γ , the values $Q_j(\gamma)$, $j = 1, \ldots, p$ instead of P_j , $j = 1, \ldots, n$. We refrain from giving the full details since, in our experience, the adaptive version above works reliably and does not require an a-priori choice of the quantile γ that is necessary otherwise.

3.4 Model Selection Consistency

If we let level $\alpha = \alpha_n \to 0$ for $n \to \infty$, the probability of falsely including a noise variable vanishes because of the preceding results. In order to get the property of consistent model selection, we have to analyze the asymptotic behavior of the power. It turns out that this property is inherited from the single-split method.

Corollary 3.1. Let \hat{S}_{single} be the selected model of the single-split method. Assume that $\alpha_n \to 0$ can be chosen for $n \to \infty$ at a rate such that $\lim_{n\to\infty} \mathbb{P}[\hat{S}_{single} = S] = 1$. Then, for any γ_{\min} (see (2.3)), the multi-split method is also model selection consistent for a suitable sequence α_n , i.e. for $\hat{S}_{multi} = \{j \in \tilde{S}; P_j \leq \alpha_n\}$ it holds that

$$\lim_{n \to \infty} \mathbb{P}\Big[\hat{S}_{multi} = S\Big] = 1.$$

Wasserman and Roeder (2008) discuss conditions which ensure that $\lim_{n\to\infty} \mathbb{P}[\hat{S}_{single} = S] = 1$ for various variable selection methods such as the Lasso or some forward variable selection scheme.

The reverse of the Corollary above is not necessarily true. The multi-split method can be consistent if the single-split method is not. A necessary condition for consistency of the single-split method is $\limsup_{n\to\infty} \mathbb{P}[P_j^{(b)} \leq \alpha] = 1$ for all $j \in S$, where the probability is with respect to both the data and the random split-point, as there is a positive probability otherwise that variable j will not be selected with the single-split approach. For the multi-split method, on the other hand, we only need a bound on quantiles of $P_j^{(b)}$ over $b = 1, \ldots, B$. We refrain from going into more details here and rather show with numerical results that the multi-split method is indeed more powerful than the single-split analogue. We also remark that the Bonferroni correction in (2.1), multiplying the raw p-values with the number $|\tilde{S}^{(b)}|$ of selected variables, could possibly be improved upon by using ideas in Hothorn et al. (2008), further improving the power of the procedure.

4 Numerical Results

In this section we compare the empirical performance of the different estimators on simulated and real data sets. Simulated data allow a thorough evaluation of the model selection properties. The real data set shows that we can find signals in data with our proposed method that would not be picked up by the single-split method. We use a default value of $\alpha = 0.05$ everywhere.

4.1 Simulations

We use the following simulation settings:

- (A) Simulated data set with n = 100, p = 100 and a design matrix coming from a centered multivariate normal distribution with covariance structure $Cov(X_j, X_k) = \rho^{|j-k|}$ with $\rho = 0.5$.
- (B) As (A) but with n = 100 and p = 1000.
- (C) Real data set with n = 71 and p = 4088 for the design matrix X and artificial response Y.

The data set in (C) is from gene expression measurements in Bacillus Subtilis. The p=4088 predictor variables are log-transformed gene expressions and there is a response measuring the logarithm of the production rate of riboflavin in Bacillus Subtilis. The data is kindly provided by DSM (Switzerland). As the true variables are not known, we consider a linear model with design matrix from real data and simulating a sparse parameter vector β as follows. In each simulation run, a new parameter vector β is created by either 'uniform' or 'varying-strength' sampling. Under 'uniform' sampling, |S| randomly chosen components of β are set to 1 and the remaining p-|S| components to 0. Under 'varying-strength' sampling, |S| randomly chosen components of β are set to values $1, \ldots, |S|$. The error variance σ^2 is adjusted such that the signal to noise ratio (SNR) is maintained at a desired level at each simulation run. We perform 50 simulations for each setting.

The sample-splitting is done such that the model is trained on a data set of size $\lfloor (n-1)/2 \rfloor$ and the p-values are calculated on the remaining data set. This slightly unbalanced scheme prevents us from situations where the full model might be selected on the first data set. Calculations of p-values would not be possible on the remaining data in such a situation. We use a total of B=50 sample-splits for each simulation run. As in Wasserman and Roeder (2008), we compute p-values for all procedures using a normal approximation. Results are qualitatively similar when using a t-distribution instead.

We compare the average number of true positives and the family-wise error rate (FWER) for the single- and multi-split methods for all three simulation settings (A)–(C) and vary in each the SNR to 0.25, 1, 4 and 16 (which corresponds to population R^2 values of 0.2, 0.5, 0.8 and 0.94, respectively). The number |S| of relevant variables is either 5 or 10. As initial variable selection or screening method \tilde{S} we use three approaches, which are all based on the Lasso (Tibshirani, 1996). The first one, denoted by \tilde{S}_{fixed} , uses the Lasso and selects those $\lfloor n/6 \rfloor$ variables which appear most often in the regularization path when varying the penalty parameter. The constant number of $\lfloor n/6 \rfloor$ variables is chosen, somewhat arbitrarily, to ensure a reasonably large set of selected coefficients on the one hand and to ensure, on

the other hand, that least squares estimation will work reasonably well on the second half of the data with sample size $\lfloor n/2 \rfloor$. While the choice seems to work well in practice and can be implemented very easily and efficiently, it is still slightly arbitrary. Avoiding any such choices of non-data adaptive tuning parameters, the second method, \tilde{S}_{cv} , uses the Lasso with penalty parameter chosen by 10-fold cross-validation and selecting the variables whose corresponding estimated regression coefficients are different from zero. The third method, \tilde{S}_{adap} , is the adaptive Lasso of Zou (2006) where regularization parameters are chosen based on 10-fold cross-validation with the Lasso solution used as initial estimator for the adaptive Lasso. The selected variables are again the ones whose corresponding estimated regression parameters are different from zero.

Results are shown in Figures 2 and 3 for both the single-split method and the multi-split method with the default setting $\gamma_{\min} = 0.05$. Using the multi-split method, the average number of true positives (the variables in S which are selected) is typically slightly increased while the FWER (the probability of including variables in N) is reduced sharply. The single-split method has often a FWER above the level $\alpha = 0.05$ at which it is asymptotically controlled while for the multi-split method the FWER is above the nominal level only in few scenarios. The asymptotic control seems to give a good control in finite sample settings with the multi-split method, maybe apart from the method S_{fixed} on the very high-dimensional dataset (C). The single-split method, in contrast, selects in nearly all settings too many noise variables, exceeding the desired FWER sometimes substantially. This suggests that the asymptotic error control seems to work better for finite sample sizes for the multisplit method. Even though the multi-split method is more conservative than the single-split method (having substantially lower FWER), the number of true discoveries is often increased. We note that for data (C), with p = 4088, and in general for low SNR, the number of true positives is low since we control the very stringent family-wise error criterion at $\alpha = 0.05$ significance level. As an alternative, controlling less conservative error measures is possible and is discussed in Section 5.

We also experimented with using the value of $Q_j(\gamma)$ directly as an adjusted p-value, without the adaptive choice of γ but using a fixed value $\gamma = 0.5$ instead, i.e. looking at twice the median value of all p-values across multiple data splits, as suggested in a different context by van de Wiel et al. (2009). The results were not as convincing as for the adaptive choice and we recommend the adaptive version with $\gamma_{\min} = 0.05$ as a good default choice.

4.2 Comparisons with adaptive Lasso

Next, we compare the multi-split selector with the adaptive Lasso (Zou, 2006). We have used the adaptive Lasso previously as a variable selection method in our proposed multi-

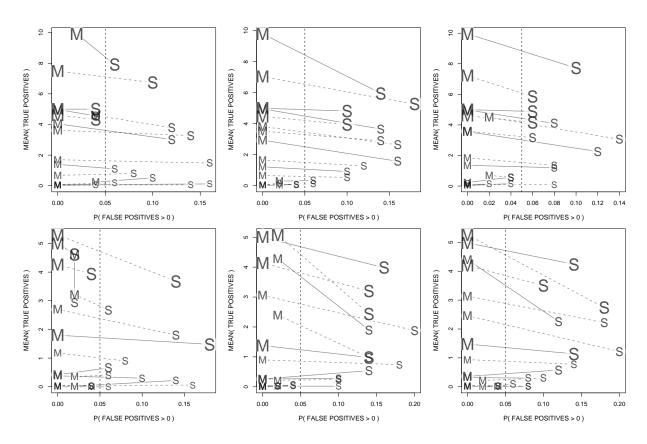


Figure 2: Simulation results for setting (A) in the top and (B) in the bottom row. Average number of true positives vs. the family-wise error rate (FWER) for the single split method ('S') against the multi-split version ('M'). FWER is controlled (asymptotically) at $\alpha = 0.05$ for both methods and this value is indicated by a broken vertical line. From left to right are results for \tilde{S}_{fixed} , \tilde{S}_{cv} and \tilde{S}_{adap} . Results of a unique setting of SNR, sparsity and design are joined by a line, which is solid if the coefficients follow the 'uniform' sampling and broken otherwise. Increasing SNR is indicated by increasing symbol size.

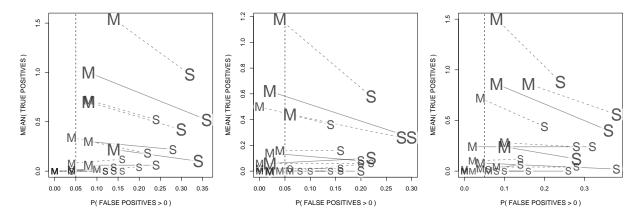


Figure 3: The results of simulation setup (C).

split method. The adaptive Lasso is usually employed on its own. There are a few choices to make when using the adaptive Lasso. We use the same choices as previously. The initial estimator is obtained as the Lasso solution with a 10-fold CV-choice of the penalty parameter. The adaptive Lasso penalty is also obtained by 10-fold CV.

Despite desirable asymptotic consistency properties (Huang et al., 2008), the adaptive Lasso does not offer error control in the same way as Theorem 3.1 does for the multi-split method. In fact, the FWER (the probability of selecting at least one noise variable) is very close to 1 with the adaptive Lasso in all the simulations we have seen. In contrast, our multi-split method offers asymptotic control, which was seen to be very well matched by the empirical FWER in the vicinity of $\alpha=0.05$. Table 1 shows the simulation results for the multi-split method using \tilde{S}_{adap} and the adaptive Lasso on its own side by side for a simulation setting with n=100, p=200 and the same settings as in (A) and (B) otherwise. The adaptive Lasso selects roughly 20 noise variables (out of p=200 variables), even though the number of truly relevant variables is just 5 or 10. The average number of false positives is at most 0.04 and often simply 0 with the proposed multi-split method.

			E(Tru	e Positives)	E(False Positives)		\mid P(False Positives > 0)	
Uniform			Multi	Adaptive	Multi	Adaptive	Multi	Adaptive
Sampling	S	SNR	Split	Lasso	Split	Lasso	Split	Lasso
NO	10	0.25	0.00	2.30	0	9.78	0	0.76
NO	10	1	0.58	6.32	0	20.00	0	1
NO	10	4	4.14	8.30	0	25.58	0	1
NO	10	16	7.20	9.42	0.02	30.10	0.02	1
YES	10	0.25	0.02	2.52	0	10.30	0	0.72
YES	10	1	0.10	7.46	0.02	21.70	0.02	1
YES	10	4	2.14	9.96	0	28.46	0	1
YES	10	16	9.92	10.00	0.04	30.66	0.04	1
NO	5	0.25	0.06	1.94	0	11.58	0	0.84
NO	5	1	1.50	3.86	0.02	19.86	0.02	1
NO	5	4	3.52	4.58	0.02	23.56	0.02	1
NO	5	16	4.40	4.98	0	27.26	0	1
YES	5	0.25	0.02	2.22	0	12.16	0	0.8
YES	5	1	0.82	4.64	0.02	22.18	0.02	1
YES	5	4	4.90	5.00	0	24.48	0	1
YES	5	16	5.00	5.00	0	28.06	0	1

Table 1: Comparing the multi-split method with CV-Lasso selection, \tilde{S}_{adap} , with the selection made when using the adaptive Lasso and a CV-choice of the involved penalty parameters for a setting with n = 100 and p = 200.

There is clearly a price to pay for controlling the family-wise error rate. Our proposed multisplit method detects on average less truly relevant variables than the adaptive Lasso. For very low SNR, the difference is most pronounced. The multi-split method selects in general neither correct nor wrong variables for SNR = 0.25, while the adaptive Lasso averages between 2 to 3 correct selections, among 9-12 wrong selections. Depending on the objectives of the study, one would prefer either of the outcomes. For larger SNR, the multi-split method detects almost as many truly important variables as the adaptive Lasso, while still reducing the number of falsely selected variables from 20 or above to roughly 0.

The multi-split method seems hence beneficial in settings where the cost of making an erroneous selection is rather high. For example, expensive follow-up experiments are usually required to validate results in bio-medical applications and a stricter error control will place more of the available resources into experiments which are likely to be successful.

4.3 Motif regression

We apply the multi-split method to a real data set about motif regression (Conlon et al., 2003). For a total of n=287 DNA segments we have the binding intensity of a protein to each of the segments. These will be our response values Y_1, \ldots, Y_n . Moreover, for p=195 candidate words ('motifs') we have scores x_{ij} which measure how well the jth motif is represented in the ith DNA sequence. The motifs are typically 5–15bp long candidates for the true binding site of the protein. The hope is that the true binding site is in the list of significant variables showing the strongest relationship between the motif score and the binding intensity. Using a linear model with \tilde{S}_{adap} , the multi-split method identifies one predictor variable at the 5% significance level. The single-split method is not able to identify a single significant predictor. In view of the asymptotic error control and the empirical results in Section 4 there is substantial evidence that the selected variable corresponds to a true binding site. For this specific application it seems desirable to pursue a conservative approach with low FWER. As mentioned above, we could control other, less conservative error measures as discussed in Section 5.

4.4 Comparison with standard low-dimensional FDR control

We mentioned that control of FDR can be an attractive alternative to FWER if we expect a sizable number of rejections. Using the corrected p-values P_1, \ldots, P_p , a simple FDR-controlling procedure was derived in Section 2.3 and its asymptotic control of FDR was shown in Theorem 3.3. We now look empirically at the behavior of the resulting method and its power to detect truly interesting variables. Turning again to the simulation setting

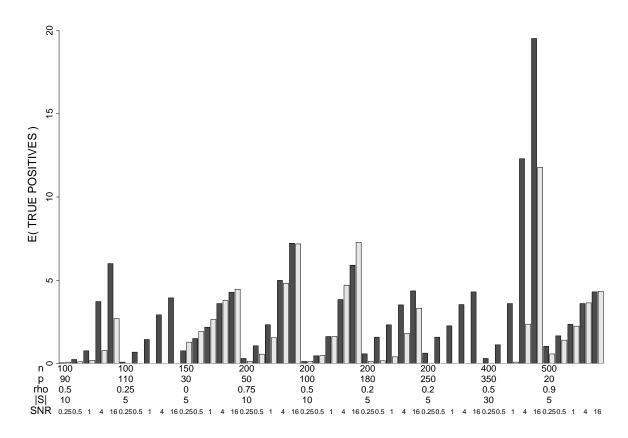


Figure 4: The results of FDR controlling simulations for the multi-split method (dark bar) and standard FDR control (light bar). The settings of $n, p, \rho, |S|$ and SNR are given below each simulation. The height of the bars corresponds to the average number of selected important variables. For p > n, the standard method breaks down and the corresponding bars are set to height 0.

(A), we vary the sample size n, the number of variables p, the signal to noise ratio SNR, the correlation ρ between neighboring variables and the number s of truly interesting variables.

It was shown already above extensively that the multi-split method is preferable to the single-split method. Here, we are more interested in comparison to well understood traditional FDR controlling procedures. For p < n, the standard approach would be to compute the least squares estimator once for the full dataset. For each variable a p-value is obtained and the FDR controlling procedure as in (2.6) can be applied. This approach obviously breaks down for p > n. Our proposed approach can be applied both to low-dimensional (p < n) and high-dimensional $(p \ge n)$ settings.

In all settings, the empirical FDR of our method (not shown) is below q = 0.05 and often close to zero. Results regarding power are shown in Figure 4 for control at q = 0.05.

It is maybe unexpected, but the multi-split method tracks the power of the standard FDR controlling procedure quite closely for low-dimensional data p < n. In fact, the multi-split method is doing considerably better if n/p is below, say, 1.5 or the correlation among the tests is large. An intuitive explanation for this behavior is that, as p approaches n, the variance in each estimated coefficient vector under the OLS estimate is increasing substantially. This in turn increases the variance of all OLS components $\hat{\beta}_j$, $j = 1, \ldots, p$ and reduces the ability to select the truly important variables. The multi-split method, in contrast, trims the total number of variables to a substantially smaller number on one half of the samples and suffers then less from an increased variance in the estimated coefficients on the second half of the samples. Repeating this over multiple splits leads thus to a surprisingly powerful variable selection procedure even for low-dimensional data. Nevertheless, we think that the main application will be high-dimensional data, where the standard approach breaks down completely.

5 Extensions

Due to the generic nature of our proposed methodology, extensions to any situation where (asymptotically valid) p-values \tilde{P}_j for hypotheses $H_{0,j}$ $(j=1,\ldots,p)$ are available are straightforward. An important class of examples are generalized linear models (GLMs) or Gaussian Graphical Models. The dimensionality reduction step would typically involve some form of shrinkage estimation. An example for Gaussian Graphical Models would be the recently proposed 'Graphical Lasso' (Friedman et al., 2008). The second step would rely on classical (e.g. likelihood ratio) tests applied to the selected submodel, analogous to the methodology proposed for linear regression.

In some settings, control of FWER at, say, $\alpha = 0.05$ is too conservative. One can either

resort to control of FDR, as alluded to above. Alternatively, FWER control can easily be adjusted to control the expected number of false rejections. Take as an example the adjusted p-value P_j , defined in (2.3). Variable j is rejected if and only if $P_j \leq \alpha$. (For the following, assume that adjusted p-values, as defined in (2.1), are not capped at 1. This is a technical detail only as it does not modify the proposed FWER controlling procedure.) Rejecting variable j if and only if $P_j \leq \alpha$ controls FWER at level α . Instead, one can reject variables if and only if $P_j/K \leq \alpha$, where K > 1 is a correction factor. Call the number of falsely rejected variables V,

$$V = \sum_{j \in N} 1\{P_j/K \le \alpha\}.$$

Then the expected number of false positives is controlled at level $\limsup_{n\to\infty} \mathbb{E}[V] \leq \alpha K$. A proof of this follows directly from the proof of Theorem 3.2. Of course, we can equivalently set $k = \alpha K$ and obtain a control $\limsup_{n\to\infty} \mathbb{E}[V] \leq k$. For example, setting k = 1 offers a much less conservative error control, if so desired, than control of the family-wise error rate.

6 Discussion

We proposed a multi-sample-split method for assigning statistical significance and constructing conservative p-values for hypothesis testing for high-dimensional problems where the number of predictor variables may be much larger than sample size. Our method is an extension of the single-split approach of Wasserman and Roeder (2008) and is extended to false discovery rate (FDR) control. Combining the results of multiple data-splits, based on quantiles as summary statistics, improves reproducibility compared to the single-split method. The multi-split method shares with the single-split method the property of asymptotic error control and model selection consistency. We argue empirically that the multi-split method usually selects much fewer false positives than the single-split method while the number of true positives is slightly increased. The main area of application will be high-dimensional data, where the number p of predictor variables exceeds sample size n, as standard approaches rely on least-squares estimation and thus fail in this setting. It was, however, shown that the method is also an interesting alternative to standard FDR and FWER control in lower-dimensional settings as the proposed FDR control can be more powerful if p is reasonably large but smaller than sample size n. The method is very generic and can be used for a broad spectrum of error controlling procedures in multiple testing, including linear and generalized linear models.

A Proofs

Proof of Theorem 3.1. For technical reasons we define

$$K_i^{(b)} = P_i^{(b)} 1\{S \subseteq \tilde{S}^{(b)}\} + 1\{S \not\subseteq \tilde{S}^{(b)}\}. \tag{A.9}$$

 $K_j^{(b)}$ are the adjusted p-values if the estimated active set contains the true active set. Otherwise, all p-values are set to 1. Because of assumption (A1) and for fixed B, $\mathbb{P}[K_j^{(b)} = P_j^{(b)}]$ for all $b = 1, \ldots, B$ on a set A_n with $\mathbb{P}[A_n] \to 1$. Therefore, we can define all the quantities involving $P_j^{(b)}$ also with $K_j^{(b)}$, and it is sufficient to show under this slightly altered procedure that

$$\mathbb{P}[\min_{j \in N} Q_j(\gamma) \le \alpha] \le \alpha.$$

In particular we can omit here the limes superior.

We also omit for the proofs the function $\min\{1,\cdot\}$ from the definitions of $Q_j(\gamma)$ and P_j in (2.2) and (2.3) respectively. The selected sets of variables are clearly unaffected and notation is simplifies considerably.

Define for $u \in (0,1)$ the quantity $\pi_j(u)$ as the fraction of bootstrap samples that yield $Kj^{(b)}$ less than or equal to u,

$$\pi_j(u) = \frac{1}{B} \sum_{b=1}^{B} 1\{K_j^{(b)} \le u\}.$$

Note that the events $\{Q_j(\gamma) \leq \alpha\}$ and $\{\pi_j(\alpha\gamma) \geq \gamma\}$ are equivalent. Hence,

$$\mathbb{P}\Big[\min_{j\in N} Q_j(\gamma) \le \alpha\Big] \le \sum_{j\in N} \mathbb{E}\Big[1\{Q_j(\gamma) \le \alpha\}\Big] = \sum_{j\in N} \mathbb{E}\Big[1\{\pi_j(\alpha\gamma) \ge \gamma\}\Big]. \tag{A.10}$$

Using a Markov inequality,

$$\sum_{j \in N} \mathbb{E} \Big[1 \big\{ \pi_j(\alpha \gamma) \ge \gamma \big\} \Big] \le \frac{1}{\gamma} \sum_{j \in N} \mathbb{E} [\pi_j(\alpha \gamma)].$$

By definition of $\pi_j(\cdot)$,

$$\frac{1}{\gamma} \sum_{j \in N} \mathbb{E}[\pi_j(\alpha \gamma)] = \frac{1}{\gamma} \frac{1}{B} \sum_{b=1}^B \sum_{j \in N \cap \tilde{S}^{(b)}} \mathbb{E}\left[1\left\{K_j^{(b)} \le \alpha \gamma\right\}\right].$$

Moreover, using the definition of $K_j^{(b)}$ in (A.9),

$$\mathbb{E}\Big[1\big\{K_j^{(b)} \leq \alpha\gamma\big\}\Big] \leq \mathbb{P}\Big[P_j^{(b)} \leq \alpha\gamma\,\big|\,S \subseteq \tilde{S}^{(b)}\Big] = \frac{\alpha\gamma}{|\tilde{S}^{(b)}|}.$$

This is a consequence of the uniform distribution of $\tilde{P}_j^{(b)}$ given $S \subseteq \tilde{S}^{(b)}$. Summarizing these results we get

$$\mathbb{P}\Big[\min_{j\in N} Q_j(\gamma) \le \alpha\Big] \le \frac{1}{\gamma} \frac{1}{B} \sum_{b=1}^B \mathbb{E}\Big[\sum_{j\in N\cap \tilde{S}^{(b)}} \frac{\alpha\gamma}{|\tilde{S}^{(b)}|}\Big] \le \alpha,$$

which completes the proof.

Proof of Theorem 3.2. As in the proof of Theorem 3.1 we will work with $K_j^{(b)}$ instead of $P_j^{(b)}$. Analogously, instead of $\tilde{P}_j^{(b)}$ we work with $\tilde{K}_j^{(b)}$.

For any $\tilde{K}_{j}^{(b)}$ with $j \in N$ and $\alpha \in (0,1)$,

$$\mathbb{E}\left[\frac{1\left\{\tilde{K}_{j}^{(b)} \leq \alpha \gamma\right\}}{\gamma}\right] \leq \alpha. \tag{A.11}$$

Furthermore,

$$\mathbb{E}\Big[\max_{j \in N} \frac{1\big\{K_j^{(b)} \leq \alpha\gamma\big\}}{\gamma}\Big] \leq \mathbb{E}\Big[\sum_{j \in N} \frac{1\big\{K_j^{(b)} \leq \alpha\gamma\big\}}{\gamma}\Big] \leq \mathbb{E}\Big[\sum_{j \in N \cap \tilde{S}^{(b)}} \frac{1\big\{K_j^{(b)} \leq \alpha\gamma\big\}}{\gamma}\Big]$$

and hence, with (A.11) and using the definition (A.9) of $K_i^{(b)}$,

$$\mathbb{E}\Big[\max_{j\in N} \frac{1\{K_j^{(b)} \le \alpha\gamma\}}{\gamma}\Big] \le \mathbb{E}\Big[\sum_{j\in N\cap \tilde{S}^{(b)}} \frac{\alpha}{|\tilde{S}^{(b)}|}\Big] \le \alpha. \tag{A.12}$$

For a random variable U taking values in [0, 1],

$$\sup_{\gamma \in (\gamma_{\min}, 1)} \frac{1\{U \le \alpha \gamma\}}{\gamma} = \begin{cases} 0 & U \ge \alpha, \\ \alpha/U & \alpha \gamma_{\min} \le U < \alpha, \\ 1/\gamma_{\min} & U < \alpha \gamma_{\min}. \end{cases}$$

Moreover, if U has a uniform distribution on [0,1],

$$\mathbb{E}\Big[\sup_{\gamma \in (\gamma_{\min}, 1)} \frac{1\{U \le \alpha \gamma\}}{\gamma}\Big] = \int_0^{\alpha \gamma_{\min}} \gamma_{\min}^{-1} dx + \int_{\alpha \gamma_{\min}}^{\alpha} \alpha x^{-1} dx = \alpha (1 - \log \gamma_{\min}).$$

Hence, by using that $\tilde{K}_{j}^{(b)}$ has a uniform distribution on [0,1] for all $j \in N$, conditional on $S \subseteq \tilde{S}^{(b)}$,

$$\mathbb{E}\Big[\sup_{\gamma \in (\gamma_{\min}, 1)} \frac{1\{\tilde{K}_j^{(b)} \le \alpha \gamma\}}{\gamma}\Big] \le \mathbb{E}\Big[\sup_{\gamma \in (\gamma_{\min}, 1)} \frac{1\{\tilde{K}_j^{(b)} \le \alpha \gamma\}}{\gamma} \, \big| \, S \subseteq \tilde{S}^{(b)}\Big] = \alpha(1 - \log \gamma_{\min}).$$

Analogously to (A.12), we can then deduce that

$$\sum_{j \in N} \mathbb{E} \Big[\sup_{\gamma \in (\gamma_{\min}, 1)} \frac{1\{K_j^{(b)} \le \alpha \gamma\}}{\gamma} \Big] \le \alpha (1 - \log \gamma_{\min}).$$

Averaging over all bootstrap samples yields

$$\sum_{j \in N} \mathbb{E} \Big[\sup_{\gamma \in (\gamma_{\min}, 1)} \frac{\frac{1}{B} \sum_{b=1}^{B} 1\{K_j^{(b)}/\gamma \le \alpha\}}{\gamma} \Big] \le \alpha (1 - \log \gamma_{\min}).$$

Using again a Markov inequality,

$$\sum_{j \in N} \mathbb{E} \Big[\sup_{\gamma \in (\gamma_{\min}, 1)} 1\{ \pi_j(\alpha \gamma) \ge \gamma \} \Big] \le \alpha (1 - \log \gamma_{\min}),$$

where we have used the same definition for $\pi_j(\cdot)$ as in the proof of Theorem 3.1.

Since the events $\{Q_j(\gamma) \leq \alpha\}$ and $\{\pi_j(\alpha\gamma) \geq \gamma\}$ are equivalent, it follows that

$$\sum_{j \in N} \mathbb{P} \Big[\inf_{\gamma \in (\gamma_{\min}, 1)} Q_j(\gamma) \le \alpha \Big] \le \alpha (1 - \log \gamma_{\min}),$$

implying that

$$\sum_{j \in N} \mathbb{P} \Big[\inf_{\gamma \in (\gamma_{\min}, 1)} Q_j(\gamma) (1 - \log \gamma_{\min}) \le \alpha \Big] \le \alpha.$$

Using the definition of P_j in (2.3),

$$\sum_{j \in N} \mathbb{P}\Big[P_j \le \alpha\Big] \le \alpha,\tag{A.13}$$

and thus, by the union bound,

$$\mathbb{P}\Big[\min_{j\in N} P_j \le \alpha\Big] \le \alpha,$$

which completes the proof.

Proof of Theorem 3.3. We use identical notation to the proof of Theorem 1.3 in Benjamini and Yekutieli (2001). An exception is that we use the value q instead of q/m in the FDR-controlling procedure since we are working with adjusted p-values. Let

$$p_{ijk} = \mathbb{P}(\{P_i \in [(j-1)q, jq]\} \text{ and } C_k^{(i)}),$$

where $C_k^{(i)}$ is the event that if variable i were rejected, then k-1 other variables were also rejected. Now, as shown in equation (10) and then again in (28) in Benjamini and Yekutieli (2001),

$$\mathbb{E}(Q) = \sum_{i \in N} \sum_{k=1}^{p} \frac{1}{k} \sum_{i=1}^{k} p_{ijk}.$$

Using this result, we use in the beginning a similar argument to Benjamini and Yekutieli (2001),

$$\mathbb{E}(Q) = \sum_{i \in N} \sum_{k=1}^{p} \frac{1}{k} \sum_{j=1}^{k} p_{ijk} = \sum_{i \in N} \sum_{j=1}^{p} \sum_{k=j}^{p} \frac{1}{k} p_{ijk}$$

$$\leq \sum_{i \in N} \sum_{j=1}^{p} \sum_{k=j}^{p} \frac{1}{j} p_{ijk} \leq \sum_{i \in N} \sum_{j=1}^{p} \frac{1}{j} \sum_{k=1}^{p} p_{ijk} = \sum_{j=1}^{p} \frac{1}{j} \sum_{i \in N} \sum_{k=1}^{p} p_{ijk} \qquad (A.14)$$

Let us denote

$$f(j) := \sum_{i \in N} \sum_{k=1}^{p} p_{ijk}, \quad j = 1, \dots, p$$

The last equation (A.14) can then be rewritten as

$$\mathbb{E}(Q) \leq \sum_{j=1}^{p} \frac{1}{j} f(j) = f(1) + \sum_{j=2}^{p} \frac{1}{j} \left(\sum_{j'=1}^{j} f(j') - \sum_{j'=1}^{j-1} f(j') \right)$$
(A.15)

$$= \sum_{j=1}^{p-1} \left(\frac{1}{j} - \frac{1}{j+1}\right) \sum_{j'=1}^{j} f(j') + \frac{1}{p} \sum_{j'=1}^{p} f(j')$$
 (A.16)

Note that, in analogy to (27) in Benjamini and Yekutieli (2001),

$$\sum_{k=1}^{p} p_{ijk} = P\left(\{P_i \in [(j-1)q, jq]\} \cap \left(\bigcup_{k=1}^{p} C_k^{(i)}\right)\right) = P\left(P_i \in [(j-1)q, jq]\right)$$

and hence

$$f(j) = \sum_{i \in N} \sum_{k=1}^{p} p_{ijk} = \sum_{i \in N} P(P_i \in [(j-1)q, jq]),$$

from which it follows by (A.13) in the proof of Theorem 3.2 that

$$\sum_{j'=1}^{j} f(j') = \sum_{i \in N} P(P_i \le jq) \le jq.$$

Using this in (A.17), we obtain

$$\mathbb{E}(Q) \leq \sum_{j=1}^{p-1} \left(\frac{1}{j} - \frac{1}{j+1}\right) jq + \frac{1}{p} pq = \left(\sum_{j=1}^{p-1} \frac{1}{j(j+1)} j + 1\right) q = q \sum_{j=1}^{p} \frac{1}{j}, \tag{A.17}$$

which completes the proof.

Proof of Corollary 3.1. Because the single-split method is model selection consistent, it must hold that $\mathbb{P}[\max_{j\in S} \tilde{P}_j | \tilde{S}| \leq \alpha_n] \to 1$ for $n \to \infty$. Using multiple data-splits, this property holds for each of the B splits and hence $\mathbb{P}[\max_{j\in S} \max_b \tilde{P}_j^{(b)} | \tilde{S}^{(b)}| \leq \alpha_n] \to 1$, which implies that, with probability converging to 1 for $n \to \infty$, the quantile $\max_{j\in S} Q_j(1)$ is bounded from above by α_n . The maximum over all $j \in S$ of the adjusted p-values $P_j = (1 - \log \gamma_{\min}) \inf_{\gamma \in (\gamma_{\min}, 1)} Q_j(\gamma)$ is thus bounded from above by $(1 - \log \gamma_{\min}) \alpha_n$, again with probability converging to 1 for $n \to \infty$.

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