Optimal FDR control in the two-group model

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Abstract. The highly influential two group model in testing a large number of statistical hypothesis assumes that the test statistics come from a mixture of a high probability null distribution and a low probability alternative. Optimal control of the marginal false discovery rate (mFDR), in the sense that it provides maximal power (expected true discoveries) subject to mFDR control, is achieved by thresholding the local false discovery rate (locFDR) with a fixed threshold. In this paper we address the challenge of controlling the popular false discovery rate (FDR) rather than mFDR in the two group model. Since FDR is less conservative, this results in more rejections. We derive the optimal multiple testing (OMT) policy for this task, which turns out to be thresholding the locFDR with a threshold that is a function of the entire set of statistics. We show how to evaluate this threshold in time that is linear in the number of hypotheses, leading to an efficient algorithm for finding this policy. Thus, we can easily derive and apply the optimal procedure for problems with thousands of hypotheses. We show that for $K = 5000$ hypotheses there can be significant power gain in OMT with FDR versus mFDR control.

Keywords: Multiple testing; False discovery rate; Infinite linear programming.
1 Introduction

In large scale inference problems, hundreds or thousands of hypotheses are tested in order to discover the set of nonnull hypotheses. Such problems are ubiquitous in modern applications like medicine, genetics, particle physics, ecology, and psychology. Multiple testing procedures applied to these large scale problems should control for false discoveries, but they should not be over-conservative, since this limits the ability of scientists to make true discoveries. Thus it is natural to seek multiple testing procedures that control for false discoveries, while assuring as many discoveries as possible.

In order to guarantee that not too many false positives are among the discoveries, Benjamini and Hochberg (1995) introduced the false discovery rate (FDR). This error measure gained tremendous popularity in large scale testing, as it was less stringent than the familywise error rate. Given a rejection policy, denote the (random) number of rejected null hypotheses by $R$, and the number of falsely rejected hypotheses (true nulls) by $V$. The FDR is

$$\text{FDR}: \mathbb{E}\left(\frac{V}{\max(R, 1)}\right) = \mathbb{E}\left(\frac{V}{R} \mid R > 0\right) \Pr(R > 0).$$

In this paper, we assume that the test-statistics come from the “two-group model”, first introduced by Efron (2001). This model has been widely used in large scale inference problems (Efron, 2001; Genovese and Wasserman, 2002; Storey, 2003; Sun and Cai, 2007; Efron, 2008; Cai and Sun, 2017). The observed test statistics $Z_1, \ldots, Z_K$ are assumed to be generated independently from the mixture model

$$Z_k \mid h_k \sim (1 - h_k)F + h_kG, \ k = 1, \ldots, K, \quad (1.1)$$

where $h_1, \ldots, h_K$ are independent Bernoulli($\pi$) random variables, and $F$ and $G$ are the null and non-null distributions respectively. Here $h_k = 0$ and $h_k = 1$ indicate, respectively, whether the null hypothesis is true (so $Z_k$ has distribution $F$) or false (so $Z_k$ has distribution $G$).

Two measures that are similar to the FDR became popular within the framework of the two-
group model. The false positive rate (pFDR) was introduced in Storey (2003). The marginal FDR (mFDR) was introduced in Genovese and Wasserman (2002); Sun and Cai (2007). Their formulas are:

\[
pFDR: \mathbb{E} \left( \frac{V}{R} \mid R > 0 \right); \quad mFDR: \frac{\mathbb{E}V}{\mathbb{E}R}.
\]

These measures were considered briefly in Benjamini and Hochberg (1995), but since the pFDR and mFDR are identically 1 if all null hypotheses are true, it is not possible to design a multiple testing procedure that controls these measures at level \( \alpha < 1 \) for any fixed configuration \((h_1, \ldots, h_K)\) (including the complete null configuration \(\vec{0}\)) of null and nonnull hypothesis. Moreover, mFDR does not take the dependence between \(V\) and \(R\) into consideration. Therefore, Benjamini and Hochberg (1995) chose to control the FDR.

When test statistics come from the two group model, if the rejection policy is a fixed subset of the real line, then the pFDR and mFDR have been shown to be equivalent (Storey, 2003). Moreover, as \(K \to \infty\), all three measures are equivalent (Benjamini, 2008). According to Cai and Sun (2017), there is essentially no difference between the three measures in large-scale testing problems. They say the use of mFDR is mainly for technical considerations, since the ratio of two expectations is easier to handle. In this paper we show that for large values of \(K\) there can still be important differences when aiming at FDR control rather than at mFDR control. Moreover, the resulting rejection policy is such that the mFDR and pFDR do not coincide.

The test statistic that plays a central role for inference on which hypotheses are false is the locFDR, defined for a test statistic value \(z\) as \(T(z) = \frac{(1-\pi)f(z)}{(1-\pi)f(z) + \pi g(z)}\), where \(f\) and \(g\) are the densities under the null distribution \(F\) and the non-null distribution \(G\), respectively. This statistic was originally introduced by Efron (2001) as the a posteriori probability of a hypothesis being in the null group. Sun and Cai (2007) showed that the optimal multiple testing (OMT) procedure with mFDR control is to threshold the locFDR statistics.
In this paper, we consider OMT with FDR control rather than mFDR control for the two-group model. As Cai and Sun (2017) have noted, since mFDR is the ratio of two expectations, it is easier to handle when seeking an optimal policy. However, $V/R$ is the more fundamental quantity the investigator would like control over for finite $K$. Therefore a rejection policy that guarantees control over $V/R$ in expectation, while maximizing the expected number of true rejections, can be very useful. We can write the problem of finding the optimal rejection policy as an optimization problem. Briefly, let $\tilde{z} = (z_1, \ldots, z_K)$ be the test statistics for a family of $K$ hypotheses. Let $\tilde{D} : \mathbb{R}^K \to \{0, 1\}^K$ be the decision function based on $\tilde{z}$, so the $i$th coordinate $D_i(\tilde{z})$ receives the value of one if the $i$th null hypothesis is rejected, and zero otherwise. Then $R(\tilde{D}(\tilde{z})) = \sum_{k=1}^{K} D_k(\tilde{z})$ and $V(\tilde{D}(\tilde{z})) = \sum_{k=1}^{K} (1 - h_k)D_k(\tilde{z})$ are the number of rejected and falsely rejected hypotheses, respectively. We denote by $FDR(\tilde{D})$ the FDR for policy $\tilde{D}$. We seek to maximize the expected number of true discoveries,

$$E(R(\tilde{D}) - V(\tilde{D})),$$

subject to $FDR(\tilde{D}) \leq \alpha$. For $K = 1$, this problem reduces to the classic Neyman-Pearson (NP) problem,

$$\max_{D : \mathbb{R} \to \{0, 1\}} \int_{\mathbb{R}} D(z)g(z)dz \quad \text{s.t.} \quad \int_{\mathbb{R}} D(z)f(z)dz \leq \alpha.$$

The solution has a simple structure implied by the NP lemma because it has just one variable instead of $K$ variables in our setting.

In Rosset et al. (2018), we formulated the multiple testing problem as an infinite-dimensional optimization problem, seeking the most powerful rejection policy which guarantees strong control of frequentist error measures, which assume $h_1, \ldots, h_K$ are fixed but unknown. In this paper, we show that for $K > 1$, the resulting optimization problem for the two-group model can be solved by following the developments in Rosset et al. (2018). Specifically, as in Rosset et al. (2018) we have $K$ functions to optimize for every point in the domain. However, unlike in Rosset et al. (2018), we only have a single constraint. Therefore, in this work we are able to compute the optimal rejection policy essentially for any dimension $K$, whereas the optimal policies in Rosset et al. (2018) could
be computed only for a very low dimension $K$.

Although the notion of power we consider is the expected number of true discoveries $E(R - V)$, the results can easily be extended to minimize the expectation of various loss functions, e.g.,

$$L_\lambda(\vec{h}, \vec{D}) = \lambda \sum_{k=1}^{K} (1 - h_k) D_k(\vec{z}) + \sum_{k=1}^{K} h_k (1 - D_k(\vec{z}))$$

considered in Sun and Cai (2007). The chosen definition should capture the true “scientific” goal for inference and the type of discoveries we wish to make.

In § 2, we develop the OMT procedure with FDR control. We show that for FDR control, as for mFDR control, the optimal decision function can be defined in terms of the locFDR statistics. However, contrary to the optimal rejection policy for mFDR control, even when all parameters are assumed known, the threshold for selection depends on the other realized locFDRs. In § 3 we detail our efficient computational approach for implementing the OMT procedure with FDR control. With this approach, it is feasible to compute the optimal rejection region on a standard PC when $K$ is in the tens of thousands. In § 4 we provide numerical examples that demonstrate the potential power gain from controlling the FDR rather than the mFDR with an optimal rejection policy. We show that we have greater power for every sample size. Although it was argued that control of FDR and mFDR is more or less the same for large enough $K$, we see that we can have non-negligible higher power even when $K$ is in the thousands in our numerical examples.

In the last part of the introduction, we review the optimal procedure for mFDR control, and argue that it is sub-optimal for FDR control since by aiming at FDR rather than mFDR control we necessarily gain power.
1.1 Optimal procedure for mFDR control in the two-group model

Many multiple testing procedures threshold the test statistics $Z_1, \ldots, Z_K$ (or their respective $p$-values) instead of thresholding the locFDRs $T(Z_1), \ldots, T(Z_K)$, and these procedures can have much lower power than procedures that threshold the locFDRs (Sun and Cai, 2007; Storey, 2007).

Cai and Sun (2017) proved that the optimal mFDR controlling procedure is of the form $T \leq t$ for independent test statistics from the two group model (1.1). Specifically, in order to maximize the expected number of rejections with $mFDR \leq \alpha$, the optimal rejection policy is $T \leq t_{\text{oracle}}$, where $t_{\text{oracle}}$ is the largest value among all rejection policies of the form $T \leq t$ for which $mFDR(t) \leq \alpha$.

We provide an alternative proof in § C.

Storey (2003) showed that when the rejection policy is a fixed region of the real line, $pFDR = mFDR$. Therefore, the optimal rule has a nice Bayesian interpretation: by reporting a hypothesis as nonnull if $T \leq t_{\text{oracle}}$, then the mFDR is the chance that a false discovery was made, since pFDR can be written as the following posterior probability (Storey, 2003),

$$pFDR = \Pr(h = 0 \mid T \leq t_{\text{oracle}}).$$

It is easy to see that $\Pr(h = 0 \mid T \leq t_{\text{oracle}}) = \mathbb{E}(T \mid T \leq t_{\text{oracle}})$, where the expectation is taken over the marginal distribution of $T$ (or $Z$), so the computation of $t_{\text{oracle}}$ is straightforward (Efron, 2008).

Since $FDR = pFDR \times Pr(R > 0)$, it follows that the optimal procedure with mFDR control at level $\alpha$, also controls the FDR at level $\alpha$. Therefore, the optimal procedure with FDR control at level $\alpha$ will necessarily be at least as powerful as the optimal procedure with mFDR control at level $\alpha$. We formalize this in the following proposition.

**Proposition 1.1.** The OMT with FDR control at level $\alpha$ has at least as much power (expected number of true discoveries) as the OMT with mFDR control at level $\alpha$ for $K$ test statistics independently.
drawn from the two-group model (1.1).

2 Optimal procedure for FDR control in the two-group model

We formulate our problem in terms of the \( z \) scores of the \( K \) hypotheses:

\[
\max_{\vec{D} : \mathbb{R}^K \rightarrow \{0,1\}^K} \mathbb{E}(\vec{h}^t \vec{D}) = \int_{\mathbb{R}^K} \sum_{i=1}^{K} D_i(\vec{z}) \pi g(z_i) \sum_{\vec{h}(i) \neq i}^{K} \prod_{l=1}^{K} \left[ \pi g(z_l) \right]^{h_l} \left[ (1 - \pi) f(z_l) \right]^{1-h_l} d\vec{z} \quad (2.1)
\]

\[
= \int_{\mathbb{R}^K} \sum_{i=1}^{K} D_i(\vec{z}) \frac{\pi g(z_i)}{\pi g(z_i) + (1 - \pi) h(z_i)} \prod_{l=1}^{K} \left[ \pi g(z_l) + (1 - \pi) f(z_l) \right] d\vec{z}
\]

\[
= \int_{\mathbb{R}^K} \sum_{i=1}^{K} D_i(\vec{z})(1 - T(z_i)) \mathbb{P}(\vec{z}) d\vec{z}
\]

s.t. \( FDR(\vec{D}) = \int_{\mathbb{R}^K} \sum_{\vec{h}} \frac{(1 - \vec{h}^t) \vec{D}(\vec{z})}{\vec{1}^t \vec{D}(\vec{z})} \prod_{l=1}^{K} \left[ \pi g(z_l) \right]^{h_l} \left[ (1 - \pi) f(z_l) \right]^{1-h_l} d\vec{z} \quad (2.2) \]

\[
= \int_{\mathbb{R}^K} \left( \sum_{\vec{h}} \frac{(1 - \vec{h}^t) \vec{D}(\vec{z})}{\vec{1}^t \vec{D}(\vec{z})} \prod_{l=1}^{K} \left[ 1 - T(z_l) \right]^{h_l} T(z_l)^{1-h_l} \right) \mathbb{P}(\vec{z}) d\vec{z} \leq \alpha,
\]

where we expressed the objective and the constraints in terms of the locFDR values \( T(z_1), \ldots, T(z_K) \) and the probability of \( \vec{z} \) under the model

\[
\mathbb{P}(\vec{z}) = \prod_{i=1}^{K} \left( (1 - \pi) f(z_i) + \pi g(z_i) \right).
\]

Note that given \( \pi, f, g \), the locFDR values are monotone decreasing in the likelihood ratios \( g(z)/f(z) \).

To simplify the notation, we employ in our FDR calculations the convention \( 0/0 = 0 \).

Denote by \( \vec{D}^* \) an optimal solution of this problem. As written, this is an integer infinite program,
with objective that is linear but a constraint which is a non-linear function of \( \tilde{D} \). In this section, we prove that:

1. The optimal solution is symmetric, that is if \( \tilde{D}^* \) is a solution of Problem \((2.1,2.2)\) then for any permutation \( \sigma \) of \( 1, \ldots, K \) we have \( \tilde{D}^*(\sigma(\tilde{z})) = \sigma(\tilde{D}^*(\tilde{z})) \) (Lemma 2.4).

2. The optimal solution has a structure which allows us to write the constraint as a linear functional of \( \tilde{D} \) (Lemma 2.1).

3. Once the problem is written in this linear fashion, the infinite linear program relaxation of the infinite integer problem is guaranteed to have a solution that is integer almost everywhere under a non-redundancy condition (Lemma 2.2).

4. This infinite linear program is guaranteed to have zero duality gap, and hence its solution can be found by solving the Euler-Lagrange conditions, and a solution to these can be found via one-dimensional search (Lemma 2.3).

Taken together, these results establish a practical methodology to solve the two-group FDR control problem. In the next section, we discuss the algorithmic and computational aspects, establishing that this problem can be practically solved for high dimensional settings, yielding the optimal FDR controlling policy.

The results in this section are similar in nature, and employ similar techniques, to results in our previous work on multiple testing under strong control (Rosset et al., 2018), although some of the important details differ. We therefore give a relatively concise exposition of our mathematical results here, with proofs and further details deferred to Appendix A.

Our first Lemma states a monotonicity property of the optimal solution:

**Lemma 2.1.** An optimal solution to Problem \((2.1,2.2)\) is almost surely weakly monotone in the likelihood ratio:

\[
\frac{g(z_i)}{f(z_i)} \leq \frac{g(z_j)}{f(z_j)} \iff D^*_i(\tilde{z}) \leq D^*_j(\tilde{z}).
\]
The Problem (2.1,2.2) is symmetric between the $K$ hypotheses, so it is reasonable to assume that an optimal solution would also be symmetric. We start by assuming the solution we are looking for has this property, and once we derive the optimal solution under this assumption we confirm in Lemma 2.4 below that it is indeed optimal among all possible solutions, not only symmetric ones.

Using Lemma 2.1 and symmetry, we can define $\vec{D}^*$ fully by its behavior on the set $Q \in \mathbb{R}^K$ of ordered locFDR scores (or equivalently, likelihood ratio scores):

$$Q = \left\{ \vec{z} \in \mathbb{R}^K : \frac{g(z_1)}{f(z_1)} \geq \frac{g(z_2)}{f(z_2)} \geq \ldots \geq \frac{g(z_K)}{f(z_K)} \right\} = \left\{ \vec{z} \in \mathbb{R}^K : T(z_1) \leq T(z_2) \leq \ldots \leq T(z_K) \right\}.$$

Because the Lemma tells us that the optimal policy always rejects the largest likelihood ratios, for a point $\vec{z} \in Q$ we can characterize $\vec{D}^*(\vec{z})$ by the smallest likelihood ratio it rejects:

$$k^*(\vec{z}) = \max\{i : D^*_i(\vec{z}) = 1\}, \vec{z} \in Q.$$

For $\vec{z} \notin Q$, denote its sorting permutation by the likelihood ratios by $\sigma_{\vec{z}}$, so that $\sigma_{\vec{z}}(\vec{z}) \in Q$. By symmetry we have:

$$\vec{D}^*(\vec{z}) = \sigma_{\vec{z}}^{-1} \left( \vec{D}^*(\sigma_{\vec{z}}(\vec{z})) \right).$$

With this characterization of the optimal solution, we can rewrite Problem (2.1,2.2) as a linear integer program on $Q$, as follows:

$$\max_{\vec{D},Q \rightarrow \{0,1\}^K} \mathbb{E}(\vec{h}^T \vec{D}) = K! \int_Q \mathbb{P}(\vec{z}) \sum_{i=1}^K D_i(\vec{z})(1 - T(z_i)) d\vec{z}$$

s.t. $FDR(\vec{D}) = K! \int_Q \mathbb{P}(\vec{z}) \sum_{i=1}^K D_i(\vec{z})$ \hspace{1cm} (2.3)

$$\times \left[ \sum_{m=0}^{i-1} \left( \frac{T(z_i)}{i} - \frac{m}{i(i-1)} \right) \sum_{h \in \mathbb{P}(m)} \prod_{l=1}^{i-1} [1 - T(z_l)]^{h_l} T(z_l)^{1-h_l} \right] d\vec{z} \leq \alpha$$

$$D_1(\vec{z}) \geq D_2(\vec{z}) \geq \ldots \geq D_K(\vec{z}), \forall \vec{z} \in Q,$$
where we use the following notation:

\[ P_{i-1}^{(m)} = \{ \vec{h} \in \{0, 1\}^{i-1} : \sum_{j=1}^{i-1} (1 - h_j) = m \} \text{, } m = 0, \ldots, i - 1. \]

The linear representation in (2.3) is derived from the nonlinear one in (2.2) by noticing that on \( Q \), if \( D_i(\vec{z}) = 1 \) it implies that \( D_1 = D_2 = \ldots = D_{i-1} = 1 \) by Lemma 2.1. Since the number of true nulls in hypotheses 1, \ldots, i − 1 is \( m \), then the rejection of hypothesis \( i \) changes FDR by \( (m + 1)/i - m/(i - 1) \) if the null hypothesis \( i \) is true and by \( m/i - m/(i - 1) \) if it is false. Multiplying and dividing by \( \mathbb{P}(\vec{z}) \) gives the desired representation. See Appendix B for more details on deriving the formulation (2.3).

We can simplify this expression further by using Bernoulli calculations to notice that:

\[
\begin{align*}
\sum_{m=0}^{i-1} \sum_{\vec{h} \in P_{i-1}^{(m)}} \prod_{l=1}^{i-1} [1 - T(z_l)]^{h_l} T(z_l)^{1-h_l} &= 1 \\
\sum_{m=0}^{i-1} \frac{m}{i-1} \sum_{\vec{h} \in P_{i-1}^{(m)}} \prod_{l=1}^{i-1} [1 - T(z_l)]^{h_l} T(z_l)^{1-h_l} &= \frac{\sum_{l=1}^{i-1} T(z_l)}{i - 1} = \bar{T}_{i-1}(\vec{z}),
\end{align*}
\]

where we use \( \bar{T}_{i-1}(\vec{z}) \) in the obvious way to denote the average of the first \( i - 1 \) locFDR scores.

This yields:

\[
FDR(\vec{D}) = K! \int_Q \mathbb{P}(\vec{z}) \sum_{i=1}^K D_i(\vec{z}) \frac{1}{i} (T(z_i) - \bar{T}_{i-1}(\vec{z})).
\]

To emphasize the linearity of the objective and constraints, and simplify the followup, we rewrite our formulation in a generic form:

\[
\begin{align*}
\max_{\vec{D}:Q \to \{0, 1\}^K} & K! \int_Q \mathbb{P}(\vec{z}) \sum_{i=1}^K D_i(\vec{z}) a_i(\vec{z}) d\vec{z} \\
\text{s.t.} & K! \int_Q \mathbb{P}(\vec{z}) \sum_{i=1}^K D_i(\vec{z}) b_i(\vec{z}) d\vec{z} \leq \alpha, \\
& D_1(\vec{z}) \geq D_2(\vec{z}) \geq \ldots \geq D_K(\vec{z}), \forall \vec{z} \in Q,
\end{align*}
\]
where \( a_i(\vec{z}) = 1 - T(z_i), b_i(\vec{z}) = (T(z_i) - \bar{T}_{i-1}(\vec{z})) / i \) are fixed functions that depend on \( f, g, \pi \) only through the locFDR scores.

We now consider the relaxed linear program without the integer requirement on \( \vec{D} \), by writing the same problem, except optimizing over \( \vec{D} \in [0, 1]^K \):

\[
\max_{\vec{D}, \vec{z} \to [0,1]^K} K! \int_Q \mathbb{P}(\vec{z}) \sum_{i=1}^K D_i(\vec{z}) a_i(\vec{z}) d\vec{z} \\
\text{s.t.} \quad K! \int_Q \mathbb{P}(\vec{z}) \sum_{i=1}^K D_i(\vec{z}) b_i(\vec{z}) d\vec{z} \leq \alpha \\
D_1(\vec{z}) \geq D_2(\vec{z}) \geq \ldots \geq D_K(\vec{z}), \forall \vec{z} \in Q.
\]

To analyze this problem, we consider its Euler-Lagrange (EL) necessary optimality conditions (Korn and Korn, 2000). We derive the EL conditions for this problem in Appendix A, and also show there that they can be rephrased as requiring the following to hold almost everywhere for optimality, in addition to the (primal feasibility) constraints of Problem (2.5):

\[
a_i(\vec{z}) - \mu b_i(\vec{z}) - \lambda_i(\vec{z}) + \lambda_{i+1}(\vec{z}) = 0, \; \forall \vec{z} \in Q, i = 1, \ldots, K. \tag{2.6}
\]

\[
\mu \left\{ K! \int_Q \left( \sum_{i=1}^K b_i(\vec{z}) D_i(\vec{z}) \right) \mathbb{P}(\vec{z}) d\vec{z} - \alpha \right\} = 0, \tag{2.7}
\]

\[
\lambda_{K+1}(\vec{z}) D_K(\vec{z}) = 0 \; \forall \vec{z} \in Q \tag{2.8}
\]

\[
\lambda_j(\vec{z})(D_{j-1}(\vec{z}) - D_j(\vec{z})) = 0, \; \forall \vec{z} \in Q, \; j = 2, \ldots, K \tag{2.9}
\]

\[
\lambda_1(\vec{z})(D_1(\vec{z}) - 1) = 0, \; \forall \vec{z} \in Q, \tag{2.10}
\]

where \( \mu \) and \( \lambda_j(\vec{z}), \; j = 1, \ldots, K + 1, \; \vec{z} \in Q \) are non-negative Lagrange multiplies. In analogy to the Karush-Kuhn-Tucker (KKT) conditions in finite convex optimization, we can term condition (2.6) the stationarity condition, and conditions (2.7–2.10) the complementary slackness conditions.

The following result clarifies that for this problem, we can solve the linear program relaxation instead of the integer program, and get an integer solution:
Lemma 2.2. For the given functions $a_i, b_i$, assume the following non-redundancy condition:

$$
P(a_i(\vec{z}) - \mu b_i(\vec{z}) = 0) = 0 \forall \mu \geq 0, \ i = 1, \ldots, K
$$

where $\vec{z}$ has the joint mixture density $P(\vec{z})$. We note that this assumption is generally mild, given the highly non-linear nature of the functions $a_i, b_i$ in typical applications.

Under this assumption, any solution to the EL conditions (2.6)–(2.10) is integer almost everywhere on $Q$, and by extension on $\mathbb{R}^K$.

Our next result shows that for our problem, the EL conditions are in fact not only necessary, but also sufficient (like the KKT conditions in finite linear programs), and we can thus find the infinite linear program solution by finding any solution that complies with these conditions.

Lemma 2.3. The infinite linear program (2.5) has zero duality gap, and therefore the conditions (2.6)–(2.10) together with primal feasibility are also sufficient, and a solution complying with these conditions is optimal.

For brevity, we defer explicit derivation of the dual together with the proof to Appendix A.

Finally, we use this last result to confirm that the optimal symmetric solution we find on $Q$ is in fact the global solution to Problem (2.1,2.2).

Lemma 2.4. An optimal solution to Problem (2.3), extended to $\mathbb{R}^K$ using the symmetry property:

$$
\text{for } \vec{z} \in Q : \vec{D}^*(\sigma(\vec{z})) = \sigma\left(\vec{D}^*(\vec{z})\right),
$$

is optimal for the original Problem (2.1,2.2).

Putting our lemmas together, we obtain our main theoretical result:

Theorem 2.1. For the two-group FDR problem (2.1,2.2), an optimal solution can be found by
solving the EL conditions (2.6)–(2.10) together with primal feasibility of the infinite linear program (2.5).

We next show how this can be used to efficiently solve high-dimensional multiple testing problem with FDR control for the two-group model.

3 Algorithm

Following similar steps to Rosset et al. (2018), we first characterize a generic algorithm for using Theorem 2.1 to solve the OMT problem with FDR control. We then show how to use dynamic programming to efficiently implement this approach for high dimensional instances of the problem.

Given a candidate Lagrange multiplier $\mu \geq 0$, for $i = 1, \ldots, K$, define:

$$R_i(\mathbf{z}) = a_i(\mathbf{z}) - \mu b_i(\mathbf{z}) = 1 - (T(z_i) - \frac{\mu}{i}(T(z_i) - T_{i-1}(\mathbf{z})).$$

Denote by $\tilde{D}^{\mu}(\mathbf{z})$ a solution which complies with (2.6) and (2.8)–(2.10) for this value of $\mu$. It is easy to confirm that this dictates that almost surely:

$$D^{\mu}_i(\mathbf{z}) = \mathbb{I}\left\{ \bigcup_{l=1}^{K} \left( \sum_{k=1}^{l} R_k(\mathbf{z}) > 0 \right) \right\}, \quad i = 1, \ldots, K,$$

$$D^{\mu}_{i-1} \cap \bigcup_{l=1}^{K} \left( \sum_{k=1}^{l} R_k(\mathbf{z}) > 0 \right), \quad i = 2, \ldots, K,$$

where $\mathbb{I}\{\cdot\}$ is the indicator function. Now we have to ensure that primal feasibility and complementary slackness for $\mu$ hold, in other words find $\mu^* \geq 0$ such that the following holds:

$$K! \int_{Q} \mathbb{P}(\mathbf{z}) \left( \sum_{i=1}^{K} b_i(\mathbf{z}) D^{\mu*}_i(\mathbf{z}) \right) d\mathbf{z} = \alpha. \quad (3.3)$$

It is easy to confirm that if we find such a solution, then it is feasible, it complies with conditions
and it is obviously binary. Thus, finding the optimal solution amounts to searching the one-dimensional space of $\mu$ values for a solution of Eq. (3.3), using the characterization in Eqs. (3.1), (3.2).

When naively implemented, the calculation in Eqs. (3.1)(3.2) requires $O(K^2)$ operations to calculate all partial sums. However we can rephrase it using a recursive representation to require only $O(K)$ calculations. We first calculate, in decreasing order:

$$m_K(\vec{z}) = \max(0, R_k(\vec{z}))$$
$$m_i(\vec{z}) = \max(0, m_{i+1} + R_i(\vec{z}))$$

and then, in increasing order:

$$D^\mu_{i} = \mathbb{I}\{m_1 > 0\}$$
$$D^\mu_{i} = \mathbb{I}\{D^\mu_{i-1} \cap m_i > 0\}$$

We see from the algorithm that the OMT procedure with FDR control starts by determining whether the hypothesis with the smallest locFDR can be rejected, and proceeds to decide whether to reject the hypothesis with the second smallest locFDR only if the decision at the first step was to reject (i.e., $D^\mu_1 = 1$). Proceeding similarly, only if the hypothesis with the $l$th smallest locFDR is rejected, the hypothesis with the $(l + 1)$th smallest locFDR is tested, for $l = 1, \ldots, K - 1$. Thus, it is a step-down procedure (Lehmann and Romano, 2005). In contrast, the OMT procedure with mFDR control is a single step procedure since each hypothesis is rejected if its locFDR is less than a common cut-off value.

Implementing the algorithm allows us to find optimal solutions to two-group FDR problems with many thousands of hypotheses in minutes of CPU, as illustrated below.
4 Numerical Examples

We compare the performance of the OMT procedure with FDR control (henceforth, OMT-FDR) against two natural competitors: the OMT procedure with mFDR control (henceforth, OMT-mFDR), and the oracle BH procedure, which applies the BH procedure assuming the probability of a null hypothesis is known (so the threshold for significance of the $i$th largest $p$-value is $\frac{i\alpha}{K(1-\pi)}$ instead of the BH threshold $\frac{i\alpha}{K}$).

We generate test statistics from the following mixture model: with probability $1-\pi$, $Z$ is $N(0,1)$; with probability $\pi$, $Z$ is $N(\theta,1)$ with $\theta < 0$. We fix $K = 5000$ hypotheses, and experiment with a range of values for $\pi, \theta$. We note that we carried out additional simulations that led to qualitatively similar conclusions, so we omitted them from the manuscript. In the additional simulations, the alternative hypothesis signal is not fixed but instead it is sampled from a Gaussian centered at zero (the unimodal assumption of Stephens (2017), also known as the spike and slab model, which is popular in genomics research).

When the signal is weak the gain in using OMT-FDR versus the other two procedures is large. Our results in Table 1 show that for a fixed probability of nonnulls $\pi$, the power advantage is larger in configurations where $\theta$ is closer to zero. The power advantage of OMT-FDR is greater than 40% when the signal is $\theta = -1.5$. With $\theta = -2$, OMT-FDR still has a 5% power advantage when $\pi = 0.1$, but for $\pi = 0.3$ or $\theta = -2.5$ the advantage is negligible.

As expected, the FDR is always smaller than the mFDR. When the gain in power is small, the mFDR of the OMT-FDR procedure is only slightly above the nominal level. However, when the gain is large, the mFDR of the OMT-FDR procedure can be large. In Table 1 the mFDR of the OMT-FDR procedure is above 0.18 for $\theta = -1.5$, and 0.079 for $\theta = -2, \pi = 0.1$. It is close to the nominal level in the three other settings. Interestingly, when the gain is large the FDR of the OMT-mFDR procedure is not much smaller than the nominal level. So the OMT-mFDR has lower power, but approximately the same FDR level, as OMT-FDR. The Oracle BH procedure has FDR
level identical to the nominal level, as expected, and its mFDR is only slightly above the nominal level except in the rarest and weakest setting, where it is inflated to be 0.066.

Figure 1 sheds some light on the power advantage of OMT-FDR for rare and weak signals: the density of the number of true discoveries is bimodal in these settings, with the highest mode at zero. For the two other procedures, the density is unimodal. This suggests that in order to control the FDR, the OMT-FDR procedure either makes no rejections, or makes many rejections, when the signal is weak. As a consequence, the false discovery proportion (FDP) is either zero or much higher than the nominal level. In the first row, with $\theta = -1.5$, we clearly see this (perhaps unattractive) behavior of the optimal procedure. The distribution of the FDP for the OMT-FDR procedure for $\theta \geq -2$ is much more reasonable, in the sense that the probability of having a large FDP (say $FDP > 0.15$) is small.

Table 1: Results for $K = 5000$ $z$-scores generated independently from the two group model $(1 - \pi) \times N(0, 1) + \pi \times N(\theta, 1)$. For each $\theta \in \{-2.5, -2.0, -1.5\}$, we provide the FDR, mFDR, and expected number of true positives (TP=$E(R-V)$), for the OMT procedure with FDR control (OMT-FDR), for the OMT procedure with mFDR control (OMT-mFDR), and for oracle BH.

| $\theta$ | Procedure  | $\pi = 0.1$       |          | $\pi = 0.3$       |          |
|----------|------------|-------------------|----------|-------------------|----------|
|         |            | TP    | FDR   | mFDR | TP    | FDR   | mFDR |
| -1.5    | OMT-FDR    | 24.228 | 0.050 | 0.507 | 167.639 | 0.050 | 0.183 |
|         | OMT-mFDR   | 4.051  | 0.049 | 0.050 | 117.135 | 0.050 | 0.050 |
|         | Oracle BH  | 6.113  | 0.050 | 0.066 | 118.671 | 0.050 | 0.051 |
| -2      | OMT-FDR    | 60.215 | 0.050 | 0.079 | 499.940 | 0.050 | 0.050 |
|         | OMT-mFDR   | 56.367 | 0.050 | 0.050 | 499.499 | 0.050 | 0.050 |
|         | Oracle BH  | 57.343 | 0.050 | 0.052 | 499.667 | 0.050 | 0.050 |
| -2.5    | OMT-FDR    | 179.436 | 0.050 | 0.051 | 927.788 | 0.050 | 0.050 |
|         | OMT-mFDR   | 178.945 | 0.050 | 0.050 | 927.714 | 0.050 | 0.050 |
|         | Oracle BH  | 179.407 | 0.050 | 0.050 | 927.774 | 0.050 | 0.050 |

4.1 The effect of estimation of the mixture components

In practice, the distributions $F$ and $G$ and the mixture proportion $\pi$ are typically unknown. The estimation of the marginal density of the $z$-scores and of $\pi$ can be difficult, and there are many different approaches. We shall limit our investigation to fitting a bivariate mixture of normals using
\[ \pi = 0.1 \quad \text{and} \quad \pi = 0.3 \]

Figure 1: The density of the number of correct rejections (TP=\(R - V\)) and false discovery proportion, when the signal for the nonnull hypotheses is -1.5 (row 1), -2 (row 2) and -2.5 (row 3). In each panel, the OMT-FDR procedure is in solid blue, the OMT-mFDR procedure is in dash-dotted black, and the oracle BH procedure is in dashed red.
the R package *mixfdr* available from CRAN (Muralidharan, 2010). The estimation is done using
the EM algorithm with a penalization via a Dirichlet prior on \((1 - \pi, \pi)\). Estimation of the fraction
of nulls is most conservative if the Dirichlet prior parameters are \((1,0)\). In addition to this prior,
we also examined the results with the Dirichlet prior parameters \((1 - \hat{\pi}, \hat{\pi})\), where \(\hat{\pi}\) is estimated
by the method of Jin and Cai (2007), recommended in Sun and Cai (2007).

As in the known distribution case, est-OMT-FDR appears to have the most power, even though
it is no longer a necessary guarantee since the rejection region is computed using the estimated
parameters from the data. For example, in Table 2, with \(\pi = 0.3\) the procedure est-OMT-FDR
has an FDR level below the nominal level, and it rejects few more hypotheses on average if the
non-conservative method is used for estimating the fraction of nulls, and many more hypotheses if
the conservative method is used. However, the estimated OMT FDR can have an inflated FDR level
when the fraction of nulls is fairly small (making the estimation problem more difficult). In Table
2, with \(\pi = 0.1\) the procedure est-OMT-FDR has an FDR level of 0.123 if the non-conservative
method is used for estimating the fraction of nulls, and 0.057 if the conservative method is used.

Table 2: Results for \(K = 5000\) \(z\)-scores generated independently from the two group model
\((1 - \pi) \times N(0,1) + \pi \times N(-2,1)\). We provide the FDR, mFDR, and expected number of true
positives (\(\text{TP} = \mathbb{E}(R - V)\)), for the estimated OMT procedure with FDR control (est-OMT-FDR),
for the estimated OMT procedure with mFDR control (est-OMT-mFDR), and for adaptive BH.
The conservative estimation method uses the default prior \(\text{Dirichlet}(1,0)\) for \((1 - \pi, \pi)\); the non-
conservative estimation method uses the estimator of Jin and Cai (2007), which was recommended
in Sun and Cai (2007) with supplementary R code. The standard error of the estimated FDR is at
most 0.0025.

| \((1 - \pi)\) estimation method | Procedure  | \(\pi = 0.1\) |          | \(\pi = 0.3\) |          |
|---------------------------------|------------|---------------|----------|---------------|----------|
|                                 |            | TP  | FDR  | mFDR  | TP  | FDR  | mFDR  |
| non-conservative                | est-OMT-FDR| 117.986 | 0.123 | 0.273 | 499.887 | 0.049 | 0.050 |
|                                 | est-OMT-mFDR| 51.294 | 0.044 | 0.047 | 491.689 | 0.048 | 0.048 |
|                                 | Adaptive BH| 58.537 | 0.050 | 0.052 | 495.706 | 0.049 | 0.049 |
| conservative                    | est-OMT-FDR| 67.140 | 0.057 | 0.062 | 496.375 | 0.049 | 0.049 |
|                                 | est-OMT-mFDR| 48.382 | 0.041 | 0.041 | 387.820 | 0.036 | 0.036 |
|                                 | Adaptive BH| 55.006 | 0.048 | 0.049 | 452.535 | 0.043 | 0.043 |
5 Discussion

In this paper, we provide the first practical approach to the problem of maximizing an objective which is linear in the decision functions, subject to FDR control in the two group model. Similarly, it is possible to solve the optimization problem with FDR control replaced by other error measures such as FWER control ($Pr(V > 0) \leq \alpha$), or false discovery exceedance control ($Pr(FDP > \gamma) \leq \alpha$). As with FDR control, the solution will be a single threshold for rejection that depends on the $K$ realized locFDR statistics. The error measures $E(V)$ and mFDR result in a much simpler solution (see derivation in § C for mFDR control), where the threshold for rejection depends only on the mixture distribution.

We demonstrate the potential large power gain in aiming for optimal testing with FDR control, in comparison with the current state of the art of optimal testing with mFDR control. However, we observe that the optimal procedure for FDR control can be problematic when the signal is weak. At the extreme, it appears that the optimal policy is to either reject no hypotheses or to have a very high FDP. A similar behavior has been observed in Rosset et al. (2018), where in certain situations the optimal multiple testing policy with strong frequentist FDR control is to reject all hypotheses if the optimal test of the global null is rejected, and to reject none otherwise. This may indicate a potentially problematic aspect of the FDR error criterion.

The potential gain is maintained also when the parameters are estimated, but care has to be taken in proper estimation of the mixture parameters. In particular, it appears that the estimation of the fraction of nulls has to be conservative when the actual fraction is fairly small. Further research into estimation methods tailored towards est-OMT-FDR is needed.

We provide an efficient algorithm for computing the OMT-FDR policy for independent test statistics. While the theoretical results also work for exchangeable hypotheses, the efficient algorithm does not. In principle, we can find the optimal symmetric solution even without requiring exchangeability, but the computational complexity may be exponential in the number of hypotheses.
Deriving solutions for dependent test statistics with known local dependence (e.g., in genomic applications with known linkage disequilibrium) is an interesting direction for future work.

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A Proofs and additional mathematical details

Proof of Lemma 2.1:

Denote \( l(z_i) := \frac{g(z_i)}{f(z_i)} \), \( i = 1, \ldots, K \) the likelihood ratios for the observations.

Given a candidate solution \( \vec{D} \), we prove the lemma by constructing an alternative solution \( \vec{E} \) that complies with the condition and has no lower objective and no higher constraint than \( \vec{D} \).
For every pair of indexes $1 \leq i < j \leq K$, define:

$$A_{ij} = \{ \vec{z} : l(z_i) > l(z_j), \ D_i(\vec{z}) = 0, \ D_j(\vec{z}) = 1 \}.$$

We will now examine the solution $\vec{E}$ which is equal to $\vec{D}$ everywhere, except on the set $A_{ij}$, where it switches the value of coordinates $i, j$:

$$E_k(\vec{z}) = \begin{cases} D_k(\vec{z}) & \text{if } \vec{z} \notin A_{ij} \text{ or } k \notin \{i, j\} \\ 1 - D_k(\vec{z}) & \text{if } \vec{z} \in A_{ij} \text{ and } k \in \{i, j\} \end{cases}.$$ 

We now show the following:

1. For the integrated power in Eq. (2.1), $\Pi(\vec{E}) \geq \Pi(\vec{D})$.

2. For the FDR constraint in Eq. (2.2), $FDR(\vec{E}) \leq FDR(\vec{D})$.

Therefore $\vec{E}$ is an improved solution compared to $\vec{D}$. This can be done for all $i, j$ pairs repeatedly until $P(A_{ij}) = 0 \forall i, j$, and we end up with $\vec{E}$ which has the desired monotonicity property and is superior to $\vec{D}$. Since $\vec{D}^*$ the optimal solution cannot be improved, it must have this monotonicity property.

It remains to prove properties 1,2 above. For the power, we write the expression in Eq. (2.1) for $\vec{E}$ and $\vec{D}$ and subtract them:

$$\Pi(\vec{E}) - \Pi(\vec{D}) = \int_{\mathbb{R}^K} \sum_{i=1}^{K} E_i(\vec{z})(1 - T(z_i))P(\vec{z})d\vec{z} - \int_{\mathbb{R}^K} \sum_{i=1}^{K} D_i(\vec{z})(1 - T(z_i))P(\vec{z})d\vec{z} = \int_{A_{ij}} (T(z_j) - T(z_i))P(\vec{z})d\vec{z} \geq 0,$$

where the second equality uses the definition of $\vec{E}$, and the inequality uses the equivalence between the likelihood ratio relationship $l(z_i) > l(z_j)$ and locFDR scores relationship $T(z_i) < T(z_j)$. 

21
The same idea with slightly more complex algebra applies to the FDR constraint:

\[
\begin{align*}
FDR(\bar{D}) - FDR(\bar{E}) &= \int_{\mathbb{R}^K} \left( \sum_{\vec{h}} \left( \frac{(1 - \vec{h}^t \bar{D}(\vec{z}))}{\vec{1}^t \bar{D}(\vec{z})} - \frac{(1 - \vec{h}^t \bar{E}(\vec{z}))}{\vec{1}^t \bar{E}(\vec{z})} \right) \prod_{l=1}^{K} [1 - T(z_l)]^{h_l} T(z_l)^{1-h_l} \right) \mathbb{P}(\vec{z}) d\vec{z} = \\
\int_{A_{ij}} \left( \sum_{\vec{h}} \left( \frac{h_i - h_j}{\vec{1}^t \bar{D}(\vec{z})} \right) \prod_{l=1}^{K} [1 - T(z_l)]^{h_l} T(z_l)^{1-h_l} \right) \mathbb{P}(\vec{z}) d\vec{z} = \\
\int_{A_{ij}} \sum_{\vec{h} \in H_{ij}} \frac{1}{\vec{1}^t \bar{D}(\vec{z})} \left( \prod_{l=1,l \notin \{i,j\}}^{K} [1 - T(z_l)]^{h_l} T(z_l)^{1-h_l} \right) \times \\
([1 - T(z_i)] T(z_j) - [1 - T(z_j)] T(z_i)) \mathbb{P}(\vec{z}) d\vec{z} \geq 0,
\end{align*}
\]

where the second equality follows since the difference of the two ratios is nonzero only on \(A_{ij}\), and the difference is only in the numerator, with \((1 - \vec{h}^t) \bar{D}(\vec{z}) - (1 - \vec{h}^t) \bar{E}(\vec{z}) = (1 - h_i) - (1 - h_j)\). The last inequality follows since \(T(z_i) < T(z_j), \forall \vec{z} \in A_{ij}\).

**Derivation of Euler-Lagrange conditions for Problem (2.5)**

Our optimization problem is:

\[
\begin{align*}
\text{max} & \quad \int_Q \sum_k a_k(\vec{z}) D_k(\vec{z}) d\vec{z} \\
\text{s.t.} & \quad \int_Q \sum_k b_k(\vec{z}) D_k(\vec{z}) d\vec{z} \leq \alpha \\
& \quad 0 \leq D_K(\vec{z}) \leq \cdots \leq D_j(\vec{z}) \leq D_i(\vec{z}) \leq \cdots \leq D_1(\vec{z}) \leq 1 \quad \forall \vec{z} \in Q.
\end{align*}
\]
We eliminate the inequality constraints, by introducing non-negative auxiliary variables, and then square those variables to also eliminate non-negativity constraints:

\[
\begin{align*}
\max & \quad \int Q \sum_k a_k(\vec{z}) D_k(\vec{z}) d\vec{z} \\
\text{s.t.} & \quad \int Q \sum_k b_k(\vec{z}) D_k(\vec{z}) d\vec{z} + E^2 = \alpha \\
& \quad D_K(\vec{z}) = e_K^2(\vec{z}) \quad \forall \vec{z} \in Q \\
& \quad D_k(\vec{z}) - D_{k+1}(\vec{z}) = e_k^2(\vec{z}) \quad \forall 0 < k < K, \vec{z} \in Q \\
& \quad 1 - D_1(\vec{z}) = e_0^2(\vec{z}) \quad \forall \vec{z} \in Q 
\end{align*}
\] (A.1)

The Euler-Lagrange (EL) necessary conditions for a solution to this optimization problem may be obtained through calculus of variations (Korn and Korn, 2000). Let \(y_1(x), y_2(x), \ldots, y_n(x) : \mathbb{R} \to \mathbb{R}\) be a set of \(n\) functions and

\[
I = \int_{x_0}^{x_F} F(y_1(x), y_2(x), \ldots, y_n(x); y_1'(x), y_2'(x), \ldots, y_n'(x); x) dx
\] (A.2)

be a definite integral over fixed boundaries \(x_0, x_F\). Every set of \(y_1(x), y_2(x), \ldots, y_n(x)\) which maximize or minimize (A.2) must satisfy a set of \(n\) equations

\[
\frac{d}{dx} \left( \frac{\partial F}{\partial y'_i} \right) - \frac{\partial F}{\partial y_i} = 0 \quad i = 1, \ldots, n.
\] (A.3)

In addition, let

\[
\varphi_{j_1}(y_1(x), y_2(x), \ldots, y_n(x); x) = 0 \quad j_1 = 1, \ldots, m_1 < n,
\] (A.4)

be a set of \(m_1 < n\) point-wise equality constraints on \(y_1(x), y_2(x), \ldots, y_n(x)\) and

\[
\int_{x_0}^{x_F} \Psi_{j_2}(y_1(x), y_2(x), \ldots, y_n(x); y_1'(x), y_2'(x), \ldots, y_n'(x); x) = C_{j_2} \quad j_2 = 1, \ldots, m_2.
\] (A.5)
be a set of $m_2$ integral equality constraints on $y_1(x), y_2(x), \ldots, y_n(x)$. Then, every set of $n$ functions $y_1(x), y_2(x), \ldots, y_n(x)$ which maximize (A.2), subject to the constraints (A.4, A.5) must satisfy the EL equations,

$$\frac{d}{dx} \left( \frac{\partial \Phi}{\partial y_i} \right) - \frac{\partial \Phi}{\partial y_i} = 0 \quad i = 1, \ldots, n,$$

(A.6)

where

$$\Phi = F - \sum_{j_1=1}^{m_1} \lambda_{j_1}(x) \varphi_{j_1} - \sum_{j_2=1}^{m_2} \mu_{j_2} \Psi_{j_2}.$$  

(A.7)

The unknown functions $\lambda_{j_1}(x)$ and constants $\mu_{j_2}$ are called the Lagrange multipliers. The differential equations in (A.6) are necessary conditions for a maximum, provided that all the quantities on the left hand side of (A.6) exist and are continuous.

Hence, the set of $y_1(x), y_2(x), \ldots, y_n(x)$ which maximize (A.2) subject to the constraints (A.4,A.5), is to be determined, together with unknown Lagrange multipliers, from (A.4,A.5,A.6).

This derivation may also be extended to a higher dimensional case, $x, y_1(x), y_2(x), \ldots, y_n(x) \in \mathbb{R}^d$, as appears in Korn and Korn (2000). In this case the EL equations are

$$\sum_{k=1}^{d} \frac{\partial}{\partial x_k} \left( \frac{\partial \Phi}{\partial y_{i,k}} \right) - \frac{\partial \Phi}{\partial y_i} = 0 \quad i = 1, \ldots, n,$$

(A.8)

where $y_{i,k} \triangleq \frac{\partial y_i}{\partial x_k}$ and $\Phi$ follows the same definition as in (A.7), with

$$\int \Psi_{j_2}(y_1(x), y_2(x), \ldots, y_n(x); y_{1,1}(x), y_{1,2}(x), \ldots, y_{1,d}(x), \ldots, y_{n,1}(x), y_{n,2}(x), \ldots, y_{n,d}(x); x) = C_{j_2} \quad j_2 = 1, \ldots, m_2.$$
Therefore, the Lagrangian $\Phi$ for our optimization problem (A.1) is

$$
\Phi = \sum_k a_k(\vec{z}) D_k(\vec{z}) - \mu \left( \sum_k b_k(\vec{z}) D_k(\vec{z}) + E^2 \right) - 
\lambda_K(\vec{z}) \left( e_K^2(\vec{z}) - D_K(\vec{z}) \right) - \sum_{k=1}^{K-1} \lambda_k(\vec{z}) \left( e_k^2(\vec{z}) + D_{k+1}(\vec{z}) - D_k(\vec{z}) \right) - \lambda_0(\vec{z}) \left( D_1(\vec{z}) + e_0^2(\vec{z}) - 1 \right).
$$

(A.9)

The necessary conditions for the minimizers of (A.1) are that the original constraints are met with equality, and additionally

1. $\frac{\partial \Phi}{\partial D_k(\vec{z})} = a_k(\vec{z}) - \mu b_k(\vec{z}) + \lambda_k(\vec{z}) - \lambda_{k-1}(\vec{z}) = 0 \quad \forall 1 \leq k \leq K, \; \vec{z} \in QK$

2. $\frac{\partial \Phi}{\partial e_k(\vec{z})} = 2 e_k(\vec{z}) \lambda_k(\vec{z}) = 0 \quad \forall 0 \leq k \leq K, \; \vec{z} \in Q$

3. $\frac{\partial \Phi}{\partial E} = 2 \mu E = 0$

It is interesting to notice that these conditions are exactly the KKT conditions for the discrete optimization case, where $\vec{z}$ is over a finite grid. Specifically, the first condition corresponds to the derivatives of the Lagrangian, while conditions (2), (3), are equivalent to the complementary slackness property.

**Proof of Lemma 2.2**

Assume that for some $\vec{z} \in Q$ and index $j$ we have that $0 < D_j(\vec{z}) < 1$. Then it is easy to see that out of the $K + 1$ constraints implied by conditions (2.8)–(2.10), at least two will require $\lambda_i = 0$ to hold: for example, if $0 < D_1(\vec{z}) < 1$ and $D_2(\vec{z}) = \ldots = D_K(\vec{z}) = 0$, we will have that $\lambda_1(\vec{z}) = \lambda_2(\vec{z}) = 0$ to maintain complementary slackness.

Assume wlog that $\lambda_l(\vec{z}) = \lambda_j(\vec{z}) = 0$ for some $l < j$. Now we can sum the equations between $l$ and
j - 1 in the stationarity condition (2.6):

\[
\sum_{i=l}^{j-1} \left[ a_i(\vec{z}) - \mu b_i(\vec{z}) - \lambda_i(\vec{z}) + \lambda_{i+1}(\vec{z}) \right] = \\
\sum_{i=l}^{j-1} \left[ a_i(\vec{z}) - \mu b_i(\vec{u}) \right] = 0,
\]

where all the \( \lambda \) terms have cancelled out due to the telescopic nature of the sum, and \( \lambda_l = \lambda_j = 0 \).

Hence we have concluded that having any non-binary value in the optimal solution \( \vec{D}^*(\vec{z}) \) implies

\[
\sum_{i=l}^{j-1} \left[ a_i(\vec{z}) - \mu b_i(\vec{z}) \right] = 0,
\]

which has probability zero by our assumption.

Derivation of dual to Problem (2.5) and proof of Lemma 2.3

The result in Lemma 2.3 relies on explicit derivation of the dual to the infinite linear program (2.5) (see Anderson and Nash (1987) for details on derivation of dual to infinite linear programs):

\[
\begin{align*}
\min_{\mu, \lambda} \quad & \alpha \mu + \int_Q \lambda_1(\vec{z}) d\vec{z} \\
\text{s.t.} \quad & a_k(\vec{z}) - \mu b_k(\vec{z}) + \lambda_{k+1}(\vec{z}) - \lambda_k(\vec{z}) \leq 0, \forall k, \vec{z} \\
& \lambda_k(\vec{z}) \geq 0, \forall k, \vec{z}; \quad \mu \geq 0.
\end{align*}
\]

Proof of Lemma 2.3: Feasibility of dual solution holds by construction: \( \mu, \lambda \) are non-negative Lagrange multipliers by definition, and the EL conditions require that

\[
a_i(\vec{z}) - \mu^* b_i(\vec{z}) - \lambda_i^*(\vec{z}) + \lambda_{i+1}^*(\vec{z}) = 0, \forall i, \vec{z}.
\]
To calculate the dual objective, we explicitly derive the value of $\lambda^*_1(\vec{z})$ as a function of the other variables. If $D^*_K(\vec{z}) = 1$, then $\lambda^*_K(\vec{z}) = 0$ and it is easy to see from (2.6)–(2.10) that $\lambda^*_1(\vec{z})$ is equal to

$$
\sum_{i=1}^{K} (a_i(\vec{z}) - \mu^* b_i(\vec{z})).
$$

Similarly, if $D^*_{j-1}(\vec{z}) - D^*_j(\vec{z}) = 1$ for $j \in \{2, \ldots, K - 1\}$, then $\lambda^*_j(\vec{z}) = 0$ and $\lambda^*_1(\vec{z})$ is equal to

$$
\sum_{i=1}^{j-1} (a_i(\vec{z}) - \mu^* b_i(\vec{z})).
$$

It thus follows that

$$\lambda^*_1(\vec{z}) = \sum_{j=1}^{K} D^*_j(\vec{z}) (a_j(\vec{z}) - \mu^* b_j(\vec{z})).$$

Therefore,

$$
\int_Q \lambda^*_1(\vec{z}) d\vec{z} = \int_Q \left( \sum_{j=1}^{K} a_j(\vec{z}) D^*_j(\vec{z}) \right) d\vec{z} - \mu^* \int_Q \left( \sum_{j=1}^{K} b_j(\vec{z}) D^*_j(\vec{z}) \right) d\vec{z}.
$$

Therefore the dual objective is equal to the primal objective:

$$
\sum_{L=0}^{K-1} \mu^* \alpha + \int_Q \left( \sum_{j=1}^{K} a_j(\vec{z}) D^*_j(\vec{z}) \right) d\vec{z} - \mu^* \int_Q \left( \sum_{j=1}^{K} b_j(\vec{z}) D^*_j(\vec{z}) \right) d\vec{z}
$$

$$= \mu^* \left\{ \alpha - \int_Q \left( \sum_{j=1}^{K} b_j(\vec{z}) D^*_j(\vec{z}) \right) d\vec{z} \right\} + \int_Q \left( \sum_{j=1}^{K} a_j(\vec{z}) D^*_j(\vec{z}) \right) d\vec{z}
$$

$$= \int_Q \left( \sum_{j=1}^{K} a_j(\vec{z}) D^*_j(\vec{z}) \right) d\vec{z},
$$

where we have used the complementary slackness condition for the $\mu^*$ in the last equality.
Proof of Lemma 2.4

Let $S$ be the set of $K!$ permutations of the vector of indices $(1,\ldots,K)$, and let $Q\tilde{s} \subset \mathbb{R}^K$ be the “quadrant” where locFDR scores are ordered according to $\tilde{s} = (s_1,\ldots,s_K) \in S$:

$$Q\tilde{s} = \{ \vec{z} \in \mathbb{R}^K : T(z_{s_1}) \leq \ldots \leq T(z_{s_K}) \}.$$  

For the identity order $Q = Q_{1,\ldots,K}$, we proved in Lemma 2.3 that the infinite linear program Eq. (2.5), which assumes the decision rule is symmetric, has zero duality gap. Let $\vec{D}^*$ denote the optimal policy and $f^*_Q$ the corresponding optimal value of the objective in Eq. (2.5). We shall now show that this is the optimal solution also to the infinite linear program that does not restrict the decision rule to be symmetric.

Our optimization problem is

$$f^* = \max_{\vec{D} : K \rightarrow [0,1]^K} \sum_{\tilde{s} \in S} \int_{Q\tilde{s}} \mathbb{P}(\vec{z}) \sum_{i=1}^K D_i(\vec{z}) a_i(\vec{z}) d\vec{z} \quad (A.11)$$

subject to

$$\sum_{\tilde{s} \in S} \int_{Q\tilde{s}} \mathbb{P}(\vec{z}) \sum_{i=1}^K D_i(\vec{z}) b_i(\vec{z}) d\vec{z} \leq \alpha$$

$$D_{s_1}(\vec{z}) \geq D_{s_2}(\vec{z}) \geq \ldots \geq D_{s_K}(\vec{z}), \quad \forall \vec{z} \in Q\tilde{s}, \tilde{s} \in S.$$

Consider the Lagrangian

$$L(\vec{D}, \mu) = \sum_{\tilde{s} \in S} \int_{Q\tilde{s}} \mathbb{P}(\vec{z}) \sum_{i=1}^K D_i(\vec{z}) a_i(\vec{z}) d\vec{z} + \mu \left( \alpha - \sum_{\tilde{s} \in S} \int_{Q\tilde{s}} \mathbb{P}(\vec{z}) \sum_{i=1}^K D_i(\vec{z}) b_i(\vec{z}) d\vec{z} \right)$$

$$= \sum_{\tilde{s} \in S} \left\{ \int_{Q\tilde{s}} \mathbb{P}(\vec{z}) \sum_{i=1}^K D_i(\vec{z}) a_i(\vec{z}) d\vec{z} + \mu \left( \frac{\alpha}{K!} - \int_{Q\tilde{s}} \mathbb{P}(\vec{z}) \sum_{i=1}^K D_i(\vec{z}) b_i(\vec{z}) d\vec{z} \right) \right\} \quad (A.12)$$

The following optimization problem, which integrates the integral constraint into the objective, will
have a solution \( q(\mu) \geq f^* \) for any \( \mu > 0 \):

\[
q(\mu) = \max_{\tilde{D} : K \rightarrow [0,1]^K} L(\tilde{D}, \mu) \tag{A.13}
\]

\[
\text{s.t. } D_{s_1}(\tilde{z}) \geq D_{s_2}(\tilde{z}) \geq \ldots \geq D_{s_K}(\tilde{z}), \forall \tilde{z} \in Q_\tilde{s}, \tilde{s} \in S.
\]

Since expression (A.12) shows that problem (A.13) is separable, it can be written as follows:

\[
q(\mu) = \sum_{\tilde{s} \in S} \max_{\tilde{D}(\tilde{z}) \in [0,1]^K} \left\{ \int_{Q_\tilde{s}} \mathbb{P}(\tilde{z}) \sum_{i=1}^{K} D_i(\tilde{z})a_i(\tilde{z})d\tilde{z} + \mu \frac{\alpha}{K!} - \int_{Q_\tilde{s}} \mathbb{P}(\tilde{z}) \sum_{i=1}^{K} D_i(\tilde{z})b_i(\tilde{z})d\tilde{z} \right\}
\]

\[
\text{s.t. } D_{s_1}(\tilde{z}) \geq D_{s_2}(\tilde{z}) \geq \ldots \geq D_{s_K}(\tilde{z})
\]

\[
\forall \tilde{z} \in Q_\tilde{s}
\]

\[
= K! \max_{\tilde{D}(\tilde{z}) \in [0,1]^K} \left\{ \int_{Q} \mathbb{P}(\tilde{z}) \sum_{i=1}^{K} D_i(\tilde{z})a_i(\tilde{z})d\tilde{z} + \mu \frac{\alpha}{K!} - \int_{Q} \mathbb{P}(\tilde{z}) \sum_{i=1}^{K} D_i(\tilde{z})b_i(\tilde{z})d\tilde{z} \right\}
\]

\[
\text{s.t. } D_{1}(\tilde{z}) \geq D_{2}(\tilde{z}) \geq \ldots \geq D_{K}(\tilde{z})
\]

\[
\forall \tilde{z} \in Q
\]

\[
(A.14)
\]

where the last equality in (A.14) follows since the \( K! \) maximization problems have identical solutions by the symmetry of the problem. Let \( \tilde{D}^\mu \) be the (necessarily symmetric) optimal policy for problem (A.13) with solution \( q(\mu) = L(\tilde{D}^\mu, \mu) \). Then \( \min_{\mu > 0} q(\mu) \geq f^* \). The inequality is in fact an equality by the following argument. First, we note that the symmetric policy \( \tilde{D}^* \) achieves the value \( f_Q^* \) for the objective function in (A.11), so necessarily \( f_Q^* \leq f^* \). However, from (A.14) and the zero duality gap in Lemma (2.3), it follows that \( \min_{\mu > 0} q(\mu) = f_Q^* \), so \( \tilde{D}^* \) is the policy that attains a value at least as large as \( f^* \). Therefore, it follows that \( f_Q^* = f^* \) and that \( \tilde{D}^* \) is the optimal policy for the general problem (A.11), thus proving that the optimal policy is one with a symmetric decision rule.
B Derivation of the expression for $FDR(\vec{D})$ in (2.3)

The false discovery proportion (FDP) is linear in $\vec{D}$ for decision functions that are weakly monotone in the likelihood ratio\(^1\):

$$FDP = \sum_{i=1}^{K} D_i(\vec{z}) \left( \frac{\sum_{l=1}^{i} (1 - h_l)}{i} - \frac{\sum_{l=1}^{i-1} (1 - h_l)}{i - 1} \right).$$

For the two group model, the joint density of $(\vec{z}, \vec{h})$ can be expressed in terms of the locFDR values and $\mathbb{P}(\vec{z})$:

$$\Pi_{i=1}^{K} \{ (1 - \pi) f(z_i) \}^{(1-h_i)} \{ \pi g(z_i) \}^{h_i} = \mathbb{P}(\vec{z}) \Pi_{i=1}^{K} \{ T(z_i) \}^{(1-h_i)} \{ 1 - T(z_i) \}^{h_i}.$$ 

Therefore, $FDR(\vec{D}) = \mathbb{E} \left( FDP(\vec{D}) \right)$ is equal to

$$K! \int_{Q} \mathbb{P}(\vec{z}) \sum_{i=1}^{K} D_i(\vec{z}) \left[ \sum_{\tilde{h}} \Pi_{i=1}^{K} \{ T(z_i) \}^{(1-h_i)} \{ 1 - T(z_i) \}^{h_i} \left( \frac{\sum_{l=1}^{i} (1 - h_l)}{i} - \frac{\sum_{l=1}^{i-1} (1 - h_l)}{i - 1} \right) \right] d\vec{z}.$$ 

The expression in (2.3) follows by writing the internal sum using $P_{i-1}^{(m)}$ as defined in the main text:

$$\sum_{\tilde{h}} \Pi_{i=1}^{K} \{ T(z_i) \}^{(1-h_i)} \{ 1 - T(z_i) \}^{h_i} \left( \frac{\sum_{l=1}^{i} (1 - h_l)}{i} - \frac{\sum_{l=1}^{i-1} (1 - h_l)}{i - 1} \right)$$

$$\sum_{\tilde{h}} \Pi_{i=1}^{K} \{ T(z_i) \}^{(1-h_i)} \{ 1 - T(z_i) \}^{h_i} \left( \frac{(1 - h_i)}{i} - \frac{1}{i(i-1)} \sum_{l=1}^{i-1} (1 - h_l) \right)$$

$$= \sum_{(h_1, \ldots, h_{i-1})} \Pi_{i=1}^{i-1} \{ T(z_i) \}^{(1-h_i)} \{ 1 - T(z_i) \}^{h_i} \left( \frac{T(z_i)}{i} - \frac{1}{i(i-1)} \sum_{l=1}^{i-1} (1 - h_l) \right)$$

$$= \sum_{m=0}^{i-1} \sum_{(h_1, \ldots, h_{i-1}) \in P_{i-1}^{(m)}} \Pi_{i=1}^{i-1} \{ T(z_i) \}^{(1-h_i)} \{ 1 - T(z_i) \}^{h_i} \left( \frac{T(z_i)}{i} - \frac{m}{i(i-1)} \right).$$

\(^1\)This was first observed in Rosset et al. 2018, for decision functions that are weakly monotone in the p-values, see their § S2.
C An alternative proof of the rejection policy for OMT with mFDR control

We shall show that the solution to the optimization problem of finding the optimal decision rule with the expected number of true rejections as the objective and the mFDR at most level $\alpha$ as the constraint, coincides with the rule of Cai and Sun (2017) for the two group model. This is an alternative proof to the proof presented in Cai and Sun (2017) about the optimality of the rule that thresholds the locFDR using a fixed cut-off.

The constraint $mFDR \leq \alpha$ is equivalent to $\mathbb{E}(V(\tilde{D})) - \mathbb{E}(R(\tilde{D})) \alpha \leq 0$, where

$$
\mathbb{E}[V(\tilde{D}) - \alpha R(\tilde{D})] = \mathbb{E}\left(\sum_{i=1}^{K} (1 - h_i) D_i - \alpha \sum_{i=1}^{K} D_i\right) = \mathbb{E}\left(\sum_{i=1}^{K} ((1 - h_i) - \alpha) D_i\right)
$$

$$
= \int_{\mathbb{R}^K} \mathbb{P}(\tilde{z}) \sum_{i=1}^{K} D_i(\tilde{z}) \left[\sum_{\tilde{h}} \prod_{i=1}^{K} \{T(z_i)\}^{(1-h_i)}(1 - T(z_i))^{h_i} ((1 - h_i) - \alpha)\right] d\tilde{z}
$$

$$
= \int_{\mathbb{R}^K} \mathbb{P}(\tilde{z}) \sum_{i=1}^{K} D_i(\tilde{z}) [(1 - \alpha) - (1 - T(z_i))] d\tilde{z},
$$

(C.1)

where the last equality follows since $\sum_{\tilde{h}} \prod_{i=1}^{K} \{T(z_i)\}^{(1-h_i)}(1 - T(z_i))^{h_i} = 1$ and $\sum_{\tilde{h}} \prod_{i=1}^{K} \{T(z_i)\}^{(1-h_i)}(1 - T(z_i))^{h_i} = 1 - T(z_i)$.

Therefore, the linear program for maximizing the objective subject to mFDR control is:

$$
\max_{\tilde{D} : \mathbb{R}^K \rightarrow [0,1]^K} \int_{\mathbb{R}^K} \left(\sum_{i=1}^{K} a_i(z_i) D_i(\tilde{z})\right) \mathbb{P}(\tilde{z}) d\tilde{z}
$$

s.t. $\int_{\mathbb{R}^K} \mathbb{P}(\tilde{z}) \sum_{i=1}^{K} D_i(\tilde{z})b_i(z_i) d\tilde{z} \leq 0$,

(C.2)

where $b_i = (1 - \alpha) - (1 - T(z_i)) = T(z_i) - \alpha$ and $a_i = 1 - T(z_i)$.
As in the FDR proof, the EL necessary optimality conditions are:

\[ a_i(\vec{z}) - \mu b_i(\vec{z}) - \lambda_{i1}(\vec{z}) + \lambda_{i2}(\vec{z}) = 0, \quad \forall \vec{z} \in \mathbb{R}^K, \ i = 1, \ldots, K. \quad (C.3) \]

\[ \mu \left\{ \int_{\mathbb{R}^K} \mathbb{P}(\vec{z}) \sum_{i=1}^{K} D_i(\vec{z}) b_i(z_i) d\vec{z} \right\} = 0, \quad (C.4) \]

\[ \lambda_{i1}(\vec{z}) D_i(\vec{z}) = 0 \quad \forall \vec{z} \in \mathbb{R}^K, \ i = 1, \ldots, K. \quad (C.5) \]

\[ \lambda_{i2}(\vec{z})(D_i(\vec{z}) - 1) = 0, \quad \forall \vec{z} \in \mathbb{R}^K, \ i = 1, \ldots, K, \quad (C.6) \]

where \( \mu, \lambda_{ij}(\vec{z}), \ i = 1, \ldots, K, \ j = 1, 2, \ \vec{z} \in \mathbb{R}^K \) are non-negative Lagrange multiplies. The solution that satisfies (C.3),(C.5), and (C.6) is guaranteed to be an integer solution under the non-redundancy condition in Lemma 2.2, since if \( 0 < D_i(\vec{z}) < 1 \) it follows that \( \lambda_{i1}(\vec{z}) = \lambda_{i2}(\vec{z}) = 0 \) and therefore that \( a_i(\vec{z}) - \mu b_i(\vec{z}) = 0 \). Moreover, following steps similar to the ones in the FDR proof of Lemma 2.3, it can be shown that conditions (C.3)-(C.6) together with primal feasibility are sufficient.

Clearly, given \( \mu > 0 \), almost surely the rejection policy that satisfies (C.3),(C.5), and (C.6) is

\[ D_i^\mu(\vec{z}) = D_i^\mu(z_i) = \mathbb{I} \{ a_i(\vec{z}) - \mu b_i(\vec{z}) > 0 \} = \mathbb{I} \left\{ T(z_i) < \frac{1 + \mu \alpha}{1 + \mu} \right\}. \]

Therefore, all that remains is to find \( \mu \) that satisfies \( \int_{\mathbb{R}^K} \mathbb{P}(\vec{z}) \sum_{i=1}^{K} D_i^\mu(\vec{z}) b_i(z_i) d\vec{z} = 0 \), i.e., \( \mathbb{E}(V(\vec{D}^\mu)) - \mathbb{E}(R(\vec{D}^\mu)) \alpha = 0 \).