Derandomized knockoffs: leveraging e-values for false discovery rate control

Zhimei Ren
Department of Statistics and Data Science, Wharton School, University of Pennsylvania, PA, USA.
E-mail: zren@wharton.upenn.edu
Rina Foygel Barber
Department of Statistics, University of Chicago, IL, USA.
E-mail: rina@uchicago.edu

Summary. Model-X knockoffs is a flexible wrapper method for high-dimensional regression algorithms, which provides guaranteed control of the false discovery rate (FDR). Due to the randomness inherent to the method, different runs of model-X knockoffs on the same dataset often result in different sets of selected variables, which is undesirable in practice. In this paper, we introduce a methodology for derandomizing model-X knockoffs with provable FDR control. The key insight of our proposed method lies in the discovery that the knockoffs procedure is in essence an e-BH procedure. We make use of this connection, and derandomize model-X knockoffs by aggregating the e-values resulting from multiple knockoff realizations. We prove that the derandomized procedure controls the FDR at the desired level, without any additional conditions (in contrast, previously proposed methods for derandomization are not able to guarantee FDR control). The proposed method is evaluated with numerical experiments, where we find that the derandomized procedure achieves comparable power and dramatically decreased selection variability when compared with model-X knockoffs.

Keywords: Multiple hypothesis testing; Knockoffs; Variable selection; Stability; False discovery rate.

1. Introduction

In high-dimensional datasets, it is common to have measurements of a large number of potential explanatory features, of which relatively few are informative for predicting the target response. The problem of identifying these few relevant features among the many candidates, also known as the variable selection problem, is often framed as a test of conditional independence: for which features $X_j$ is it true that $Y \notin X_j | X_{-j}$? Here, $Y$ denotes the response variable and $X_{-j}$ denotes all measured features aside from $X_j$—effectively, this question asks whether $X_j$ carries information for predicting $Y$, beyond what is already contained in the set of remaining features $X_{-j}$.

The knockoff filter (Barber and Candès, 2015; Candès et al., 2018) is a framework for selecting a set of $X_j$’s that are likely relevant, with guaranteed control of the false discovery rate (FDR). It operates by constructing a knockoff copy $\hat{X}_j$ of each candidate feature $X_j$, after which the response $Y$ and (original and knockoff) features $X_1, \ldots, X_p, \hat{X}_1, \ldots, \hat{X}_p$ are given as input to an arbitrary variable selection procedure. By examining whether the procedure chooses substantially more original variables (the $X_j$’s) than knockoffs (the $\hat{X}_j$’s), we may infer whether the procedure is successfully controlling the FDR.

Since the $\hat{X}_j$’s are drawn randomly, the resulting output $S_{kn}$ of the method is random as well—that is, multiple runs of knockoffs on the same observed dataset can in general lead to different selected sets $S_{kn}$. Empirically, it has been observed that the output can be highly
variable from one run to another, which is potentially an undesirable property. To address this, Ren et al. (2021) propose the “derandomized knockoffs”. After running knockoffs $M$ times on the given dataset, their procedure computes

$$
\Pi_j = \frac{1}{M} \sum_{m=1}^{M} \mathbf{1}\{j \in S_{kn}^{(m)}\}
$$

for each feature $X_j$, where $S_{kn}^{(m)}$ is the selected set of features on the $m$-th run of the knockoffs method. The final selected set is then given by $S_{kn-derand} = \{j : \Pi_j \geq \eta\}$, all features $X_j$ exceeding some threshold probability of selection for a random run of knockoffs. For this method, Ren et al. (2021) establish a guaranteed bound on the expected number of false discoveries, but it appears impossible to prove a bound directly on the FDR.

Our contributions

In this work, we find that, with a simple and natural modification in the construction of the derandomized knockoffs procedure, we can restore the guarantee of FDR control. Specifically, we will consider a weighted probability of selection, replacing $\Pi_j$ with

$$
\frac{1}{M} \sum_{m=1}^{M} \text{weight}_j^{(m)} \cdot \mathbf{1}\{j \in S_{kn}^{(m)}\},
$$

where, informally, we choose a lower weight if many features were selected in the $m$-th run. In the case of a single run of knockoffs ($M = 1$), our new procedure reduces to the original knockoff filter, while for large $M$, the output is derandomized (i.e., as $M \to \infty$, the set $S_{kn-derand}$ becomes a deterministic function of the observed data). Our method builds on the recent e-BH procedure of Wang and Ramdas (2022) (a generalization of the Benjamini–Hochberg algorithm for FDR control (Benjamini and Hochberg, 1995)), which allows us to find an adaptive, FDR-controlling threshold for the weighted selection probabilities computed in (2). By leveraging these tools, we are able to provide a version of the knockoff filter that offers derandomization without losing the benefit of a rigorous guarantee on the FDR.

1.1. Problem setup

Suppose there are $p$ explanatory variables $X = (X_1, X_2, \ldots, X_p)$ and a response $Y$, where $(X, Y)$ are jointly sampled from some distribution $P_{XY}$. For each $j \in [p] := \{1, 2, \ldots, p\}$, we wish to test the hypothesis

$$
H_j : Y \perp \!\!\!\!\perp X_j | X_{-j}.
$$

We call a feature $j$ a null if $H_j$ is true, and a non-null otherwise. We will write $\mathcal{H}_0 = \{j : H_j \text{ is true}\}$ and $\mathcal{H}_1 = [p] \setminus \mathcal{H}_0$ to denote the set of nulls and the set of non-nulls, respectively.

Imagine now we have $n$ samples $(X_i, Y_i) \overset{\text{iid}}{\sim} P_{XY}$, and we assemble the covariates into a matrix $X \in \mathbb{R}^{n \times p}$ and the responses into a vector $Y \in \mathbb{R}^n$. A multiple testing procedure applied to $(X, Y)$ then produces a set $S$ of selected variables. The goal here is to include in this set as many non-nulls as possible while controlling the false discovery rate

$$
\text{FDR} := \mathbb{E}\left[\frac{|S \cap \mathcal{H}_0|}{|S| \lor 1}\right],
$$

where $a \lor b = \max(a, b)$. In this work, we consider the model-X framework, where we (approximately) know the marginal distribution $P_X$ of the covariates $X$, but do not assume any knowledge of the model of $Y | X$. For example, in many applications, we may have ample unlabeled data (i.e., observations of $X = (X_1, \ldots, X_p)$) which may be used for estimating $P_X$, but relatively little labeled data (i.e., observations of labeled pairs $(X, Y)$); see Candes et al. (2018) for more discussion of this framework.
1.2. Background: model-X knockoffs

The model-X knockoff filter, or knockoffs for short, is a multiple testing procedure that provably controls the FDR under the model-X framework. Given the dataset \((X, Y)\) as well as knowledge of \(P_X\), the knockoffs procedure starts by generating a knockoff copy \(\tilde{X}\) satisfying

\[
(X_j, \tilde{X}_j, \tilde{X}_{-j}) \overset{d}{=} (\tilde{X}_j, X_j, \tilde{X}_{-j})
\]

for each \(j\), where \(\overset{d}{=}\) denotes equality in distribution. This condition requires \(\tilde{X}\) to depend on \(X\) (so that any dependence between features \(X_j\) and \(X_k\) is mimicked by dependence between, e.g., \(\tilde{X}_j\) and \(X_k\)), but \(\tilde{X}\) is constructed independently of \(Y\), i.e., \(Y \perp \tilde{X} | X\). (See Candès et al. (2018); Sesia et al. (2019); Romano et al. (2020); Bates et al. (2021); Spector and Janson (2022) for discussion and examples of knockoff generation.) Having sampled \(\tilde{X}\), the knockoffs procedure proceeds to compute feature importance statistics \(W \in \mathbb{R}^p\) using the augmented dataset \(((X, \tilde{X}), Y)\):

\[
W = W((X, \tilde{X}), Y),
\]

where \(W(\cdot)\) is an algorithm evaluating the importance of the features, with the property that swapping \(X_j\) and \(\tilde{X}_j\) flips the sign of \(W_j\), and a larger value of \(W_j\) suggests evidence against the null. For instance, to compute the Lasso coefficient-difference (LCD) statistic proposed by Candès et al. (2018), \(\beta_j\) denote the resulting coefficient of \(X_j\) and \(\tilde{\beta}_j\) that of \(\tilde{X}_j\), and define \(W_j = |\beta_j| - |\tilde{\beta}_j|\) for each \(j \in [p]\). Since the knockoffs act as a control group for the real features, if \(X_j\) is a null then the Lasso is equally likely to select \(X_j\) or \(\tilde{X}_j\), and moreover, \(W_j\)'s distribution is symmetric around 0.

The final selected set of features is then given by

\[
S_{kn} := \{j : W_j \geq T\} \text{ where } T := \inf\left\{ t > 0 : \frac{1 + \sum_{j \in [p]} 1\{W_j \leq -t\}}{\sum_{j \in [p]} 1\{W_j \geq t\}} \leq \alpha \right\}.
\]

Barber and Candès (2015); Candès et al. (2018) prove that this selected set satisfies FDR \(\leq \alpha\).

1.3. Background: e-values and the e-BH procedure

The concept of e-values (Vovk and Wang, 2021) is another useful tool for statistical inference and multiple testing in general. Given a null hypothesis, we call a non-negative random variable \(E\) an “e-value” if \(\mathbb{E}[E] \leq 1\) under the null (in contrast, a p-value is a random variable \(P \in [0,1]\) such that \(\mathbb{P}(P \leq t) \leq t\) for any \(t \in [0,1]\) under the null). For the e-value, a large value shows evidence against the null, and hence the null hypothesis is rejected when the e-value exceeds a threshold. For example, if the goal is to test a hypothesis at level \(\alpha\), we can reject the null hypothesis when \(E \geq 1/\alpha\). The probability of making a type-I error is then

\[
\mathbb{P}(E \geq 1/\alpha) \leq \alpha \cdot \mathbb{E}[E] \leq \alpha,
\]

where the first step applies Markov’s inequality and the second follows from the definition of e-values.

In the context of multiple hypothesis testing, let \(e_j\) be an e-value associated with a null hypothesis \(H_j\). With e-values \(e_1, e_2, \ldots, e_p\), Wang and Ramdas (2022) propose the e-BH procedure that achieves FDR control when testing \(H_1, H_2, \ldots, H_p\) simultaneously. The e-BH procedure operates in a similar way to the BH procedure (Benjamini and Hochberg, 1995): the rejection set (i.e., the selected set of discoveries) is given by

\[
S_{ebh} = \left\{ j : e_j \geq \frac{p}{\alpha \hat{k}} \right\} \text{ where } \hat{k} = \max \left\{ k \in [p] : e_{(k)} \geq \frac{p}{\alpha \hat{k}} \right\},
\]

where \(e_{(k)}\) denotes the \(k\)-th largest e-value.
where $e_{(1)} \geq \cdots \geq e_{(p)}$ denotes the order statistics of the $e_j$’s, and where we take the convention that if this latter set is empty then we set $\hat{k} = 0$ (and so $S_{ebh} = \emptyset$). Wang and Ramdas (2022) prove that the e-BH procedure satisfies $FDR \leq \alpha \cdot |\mathcal{H}_0|/p \leq \alpha$. Importantly, this result allows for arbitrary dependence among the $e_j$’s.

1.4. Additional related work

Previously, many attempts have been made to derandomize knockoffs. As mentioned earlier, Ren et al. (2021) propose a derandomizing scheme controlling the expected number of false discoveries; Nguyen et al. (2020) introduce a aggregation method aiming at FDR control, but under strong assumptions such as that the null feature importance statistics are i.i.d. In a parallel line of work, Emery and Keich (2019); Gimenez and Zou (2019) consider constructing multiple simultaneous knockoffs to improve the stability of knockoffs—this is in contrast to our attempt to aggregate multiple independent knockoff copies. The idea of using e-values for derandomization can also be found in Vovk (2020); Wasserman et al. (2020).

Broadly speaking, the process of derandomization via computing each feature’s selection probability over random runs of the knockoffs method, can be viewed as a special case of stability selection (Meinshausen and Bühlmann, 2010) (see also Liu et al. (2010); Shah and Samworth (2013) for related methods). More recently, Dai et al. (2022, 2023) also consider derandomization (over multiple sample splits) with FDR control via computing each feature’s weighted selection frequency (this is termed the “inclusion rate” in their paper). Their procedure also takes the form of (2) but with a different choice of the weight terms, weight$^{(m)}_j$, and with asymptotic rather than finite-sample FDR control guarantees (we will compare the definitions of the procedures, and the different results, in more detail in Section 3.1 below).

2. Knockoffs as an e-BH procedure

Our first main result shows that the two multiple testing procedures introduced in Section 1 can be unified through a certain perspective—the knockoffs procedure is in fact equivalent to a (relaxed) e-BH procedure with a class of properly defined e-values.

2.1. The equivalence between the knockoffs and the e-BH

To see why knockoffs is equivalent to an e-BH procedure, we first define a set of relaxed e-values. Recall that in the knockoffs procedure, we have the feature importance statistics $W$ and the stopping time $T$. For each $j \in [p]$, define

$$e_j := p \cdot \frac{1\{W_j \geq T\}}{1 + \sum_{k \in [p]} 1\{W_k \leq -T\}}.$$ (7)

We will now see that running e-BH on the $e_j$’s is exactly equivalent to running knockoffs.

**Theorem 1.** Let $S_{kn}$ be the set of selected features for the knockoff procedure (5), and let $S_{ebh}$ be the set of selected features for the e-BH procedure (6) applied to $e_1, \ldots, e_p$, where $e_j$ is defined in (7). Then $S_{kn} = S_{ebh}$.

**Proof.** Taking $K = |S_{kn}| = \sum_{k \in [p]} 1\{W_k \geq T\}$, we see that $\frac{1+\sum_{k \in [p]} 1\{W_k \leq -T\}}{K} \leq \alpha$ by definition of the knockoffs threshold $T$ (5), and so for all $j \in S_{kn}$, $e_j$ takes the value $\frac{1}{1+\sum_{k \in [p]} 1\{W_k \leq -T\}} \geq p/(\alpha K)$. Therefore, $e_{(K)} \geq p/(\alpha K)$, and so we must have $\hat{k} \geq K$ when we run the e-BH procedure (6). This proves that $j \in S_{ebh}$ for all $j \in S_{kn}$. Conversely, if $j \notin S_{kn}$, then $W_j < T$ and so $e_j = 0$, which means that $j$ cannot be selected by the e-BH procedure, i.e., $j \notin S_{ebh}$. 

2.2. A relaxation of the e-BH procedure

While the theorem above shows that knockoffs gives identical output to the e-BH procedure, we note that it does not yet give an alternative explanation for why knockoffs controls the FDR—this is because the quantities \( e_j \) defined in (7) have not been shown to be e-values. Indeed, while \( e_j \geq 0 \) holds by definition, it may not be the case that \( \mathbb{E}[e_j] \leq 1 \) for all \( j \in \mathcal{H}_0 \). Instead, the \( e_j \)'s satisfy a more relaxed criterion. A key step in the proof of the FDR control property of the knockoff filter is the bound (Barber and Candès, 2015; Candès et al., 2018)

\[
\mathbb{E} \left[ \frac{\sum_{j\in \mathcal{H}_0} \mathbb{I}\{W_j \geq T\}}{1 + \sum_{j\in \mathcal{H}_0} \mathbb{I}\{W_j \leq -T\}} \right] \leq 1. \tag{8}
\]

Intuitively, this arises from the fact that each null \( j \in \mathcal{H}_0 \) is equally likely to have \( W_j \geq T \) as to have \( W_j \leq -T \), because the knockoff copy \( \bar{X}_j \) acts as a control group for the null feature \( X_j \). As a result, we can immediately see that the \( e_j \)'s defined in (7) satisfy

\[
\sum_{j\in \mathcal{H}_0} \mathbb{E}[e_j] \leq p. \tag{9}
\]

Clearly, this condition is strictly weaker than requiring \( \mathbb{E}[e_j] \leq 1 \) for all \( j \in \mathcal{H}_0 \). Nonetheless, as pointed out by Wang and Ramdas (2022), this condition is sufficient to bound FDR in the e-BH procedure: the \( e_j \)'s satisfying (9) can be thought of as weighted e-values; that is, we can write \( e_j = \mathbb{E}[e_j] \cdot \bar{e}_j \), where \( \bar{e}_j \)'s are strict e-values with \( \mathbb{E}[\bar{e}_j] = 1 \) and \( \mathbb{E}[e_j]'s \) are weights. This is summarized in the following theorem.

**Theorem 2 (Wang and Ramdas 2022).** Suppose the values \( e_1, e_2, \ldots, e_p \) satisfy condition (9). Then the selected set \( \mathcal{S}_{ebh} \) of the e-BH procedure (6) satisfies FDR \( \leq \alpha \).

From this point on, then, we will refer to any \( e_1, \ldots, e_p \) satisfying (9) as e-values, even though the original condition (i.e., \( \mathbb{E}[e_j] \leq 1 \) for \( j \in \mathcal{H}_0 \)) is strictly stronger and may not be satisfied.

Before proceeding, we remark that the knockoff e-values are close to sharp in the following sense.

**Remark 1 (Sharpness of the knockoff e-values).** Given e-values \( e_1, e_2, \ldots, e_p \), let \( \mathcal{S}_{ebh} \) denote the set of features selected by the e-BH procedure, and its FDR is given by

\[
\text{FDR} = \mathbb{E} \left[ \frac{\sum_{j\in \mathcal{H}_0} \mathbb{I}\{e_j \geq \frac{p}{\alpha|\mathcal{S}_{ebh}|}\}}{\sum_{j\in \mathcal{H}_0} \mathbb{I}\{e_j \geq \frac{p}{\alpha|\mathcal{S}_{ebh}|}\} + \sum_{j\not\in \mathcal{H}_0} \mathbb{I}\{e_j \geq 0\}} \right].
\]

The proof of FDR control for the e-BH procedure makes use of the inequality

\[
\mathbb{I}\{e_j \geq \frac{p}{\alpha|\mathcal{S}_{ebh}|}\} \leq \frac{e_j \alpha|\mathcal{S}_{ebh}|}{p}, \tag{10}
\]

which is tight when \( e_j \in \{p/(\alpha|\mathcal{S}_{ebh}|), 0\} \). Meanwhile, the knockoff e-values defined in (7) are either 0 or

\[
\frac{p}{1 + \sum_{j\in \mathcal{S}_{kn}} \mathbb{I}\{W_j \leq -T\}} \geq \frac{p}{\alpha|\mathcal{S}_{kn}|} = \frac{p}{\alpha|\mathcal{S}_{ebh}|}, \tag{11}
\]

where the first inequality is by the definition of \( T \). For any \( t < T \), again by the definition of \( T \), we have that

\[
\frac{p}{1 + \sum_{j\in \mathcal{S}_{kn}} \mathbb{I}\{W_j \leq -t\}} < \frac{p}{\alpha|\mathcal{S}_{kn}|} \leq \frac{p}{\alpha|\mathcal{S}_{ebh}|}. \tag{12}
\]

Combining (11) and (12), we can see when \( \sum_{j\in \mathcal{S}_{kn}} \mathbb{I}\{W_j \leq -T\} \) is reasonably large, the nonzero e-values will be close to \( p/(\alpha|\mathcal{S}_{ebh}|) \), and therefore the inequality in (10) is close to tight.
3. Derandomizing knockoffs

One major advantage of using e-values for multiple testing is that validity depends only on the expected values $E[e_j]$—in particular, no assumptions are needed on the dependence structure among the $e_j$’s (Wang and Ramdas, 2022). As observed by Vovk and Wang (2021), the fact that the average of multiple e-values is still an e-value is a very favorable property, as it allows us to pool results from multiple runs or multiple analyses of an experiment. Since Theorem 1 finds an equivalent e-value based formulation of the knockoffs method, we can therefore combine results from different knockoff realizations by averaging the corresponding e-values, to achieve a derandomized procedure.

3.1. The procedure

Suppose we have used our knowledge of $P_X$ to construct a valid distribution for $\tilde{X} | X$, i.e., so that (4) is satisfied for each $j$. We then generate $M$ copies of the knockoff matrix, drawing $\tilde{X}^{(1)}, \tilde{X}^{(2)}, \ldots, \tilde{X}^{(M)}$ from this distribution (drawn i.i.d. conditional on the observed data $(X, Y)$). Let $W^{(m)}$ denote the feature importance statistics computed with the $m$-th knockoff matrix, $W^{(m)} = W([X, \tilde{X}^{(m)}], Y)$. Choosing some $\alpha_{kn} \in (0, 1)$, we compute the threshold

$$T^{(m)} = \inf \left\{ t > 0 : \frac{1 + \sum_{j \in [p]} I\{W^{(m)}_j \leq -t\}}{\sum_{k \in [p]} I\{W^{(m)}_k \geq t\}} \leq \alpha_{kn} \right\} \quad (13)$$

for each $m$, so that $S^{(m)}_{kn} = \{ j : W^{(m)}_j \geq T^{(m)} \}$ is the selected set for the knockoff filter when run with the $m$-th copy $\tilde{X}^{(m)}$ of the knockoff matrix. Let

$$e^{(m)}_j = p \cdot \frac{I\{W^{(m)}_j \geq T^{(m)}\}}{1 + \sum_{k \in [p]} I\{W^{(m)}_k \leq -T^{(m)}\}}$$

be the corresponding e-value, so that as proved in Theorem 1, the $m$-th selected set $S^{(m)}_{kn}$ is equivalent to running e-BH on the e-values $e^{(m)}_1, \ldots, e^{(m)}_p$. For each $j \in [p]$, we aggregate the e-values obtained from these $M$ knockoff copies by taking the average

$$e^{avg}_j = \frac{1}{M} \sum_{m=1}^{M} e^{(m)}_j.$$

Finally, we obtain the selected set of discoveries, $S_{kn-derand}$, by applying the e-BH procedure at level $\alpha_{ebh}$ to the e-values $e^{avg}_1, \ldots, e^{avg}_p$. Note that the parameters $\alpha_{kn}$ and $\alpha_{ebh}$ may be different—we will discuss this more below.

The following theorem proves that this derandomized procedure controls the FDR at level $\alpha_{ebh}$.

**Theorem 3.** For any $\alpha_{kn}, \alpha_{ebh} \in (0, 1)$, and any number of knockoff copies $M \geq 1$, the selected set $S_{kn-derand}$ computed in Algorithm 1 satisfies $\text{FDR} \leq \alpha_{ebh}$.

**Proof.** Applying the bound (8) with the $m$-th knockoff copy $\tilde{X}^{(m)}$ in place of $\tilde{X}$, and with the threshold $\alpha_{kn}$ in place of $\alpha$, we see that $E \left[ \frac{\sum_{j \in H_0} I\{W^{(m)}_j \geq T^{(m)}\}}{1 + \sum_{j \in H_0} I\{W^{(m)}_j \leq -T^{(m)}\}} \right] \leq 1$. This implies that the $m$-th set of e-values satisfies $\sum_{j \in H_0} E[e^{(m)}_j] \leq p$, for each $m$. Taking the average over $m = 1, \ldots, M$, we have $\sum_{j \in H_0} E[e^{avg}_j] \leq p$ as well. The result then follows from Theorem 2.
Remark 2. A special case of Algorithm 1 is when $\alpha_{kn} = \alpha_{ebh} = \alpha$ and $M = 1$. In this case, the derandomized procedure reduces to the original knockoffs procedure at level $\alpha$, and $\alpha_{ebh}$ is also the optimal choice for $\alpha_{kn}$.

To see the optimality, let $T(\alpha)$ and $S(\alpha)$ denote the selection threshold and the selection set of knockoffs with target FDR level $\alpha$; let $e_j(\alpha)$ be the $e$-value by plugging $T(\alpha)$ in (7). When $\alpha_{kn} < \alpha_{ebh}$, we have by construction that $|\{ j : e_j(\alpha_{kn}) > 0 \}| = |S(\alpha_{kn})| \leq |S(\alpha_{ebh})|$. Since only positive $e$-values can possibly be selected, the number of selections made by $e$-BH applied to $\{ e_j(\alpha_{kn}) \}_{j \in [p]}$ is no larger than $|S(\alpha_{ebh})|$. On the other hand, when $\alpha_{kn} > \alpha_{ebh}$, we assume $|S(\alpha_{kn})| > |S(\alpha_{ebh})|$, since otherwise $e_j(\alpha_{kn}) \leq e_j(\alpha_{ebh})$ for any $j \in [p]$ and the result is immediate. By the definition of $T(\alpha_{kn})$, 

$$\frac{1 + \sum_{j \in [p]} 1 \{ W_j \leq -T(\alpha_{kn}) \}}{\sum_{j \in [p]} 1 \{ W_j \geq T(\alpha_{kn}) \}} > \alpha_{ebh}.$$ 

As an implication, for any integer $K$ such that $|S(\alpha_{ebh})| + 1 \leq K \leq |S(\alpha_{kn})|$, the $K$-th largest element in $\{ e_j(\alpha_{kn}) \}_{j \in [p]}$ is 

$$\frac{p}{1 + \sum_{j \in [p]} 1 \{ W_j \leq -T(\alpha_{kn}) \}} < \frac{p}{\alpha_{ebh} \cdot |S(\alpha_{kn})|} \leq \frac{p}{\alpha_{ebh} \cdot K}.$$ 

By definition, the $e$-BH procedure cannot make more than $|S(\alpha_{ebh})|$ selections. Collectively, we show that $\alpha_{kn} = \alpha_{ebh}$ is optimal.

Remark 3. In fact, we are allowed to use different methods for constructing the knockoffs $\tilde{X}^{(m)}$ and/or different functions $W$ for defining the feature importance statistics $W^{(m)}$, for each run $m = 1, \ldots, M$; the FDR control result will still hold as long as the conditions for validity of the knockoff procedure are satisfied for each $m$. This could be the case when two different labs are using different knockoffs generating mechanisms and/or different $W$ for their data analysis and wish to combine their results. More generally, combining different knockoff configurations across multiple runs can potentially improve the robustness of our procedure, and this is an interesting direction for future research.

Remark 4 (Generalization of $T^{(m)}$). More generally, we are free to choose the $m$-th threshold $T^{(m)}$ in a different way as long as it is still a stopping time with respect to the filtration generated by a masked version of $W^{(m)}$, and the FDR guarantee for derandomized knockoffs will still hold.

To be specific, for each run $m$ of knockoffs, the values $e_j^{(m)}$ defined in (14) are valid $e$-values (according to the relaxed definition (9)), as long as $T^{(m)}$ is a stopping time with respect to the filtration generated by a masked version of $W^{(m)}$, meaning that for each $t > 0$, the event $1 \{ T^{(m)} \geq t \}$ is determined by (1) the magnitudes $|W_j^{(m)}|$ for all $j$, (2) the values $W_j^{(m)}$ for all $j$ with $|W_j^{(m)}| < t$, and (3) $\sum_{j : |W_j^{(m)}| \geq t} 1 \{ W_j^{(m)} > 0 \}$. For example, for any $c \geq 0$, one can define 

$$T^{(m)} := \inf \left\{ t > 0 : \frac{c + \sum_{j \in [p]} 1 \{ W_j^{(m)} \leq -t \}}{\sum_{k \in [p]} 1 \{ W_k^{(m)} \geq t \}} \leq \alpha_{kn} \right\}.$$ 

Remark 5. In practice, we recommend letting $M$ be the largest acceptable number given the computational constraint of the user.

A uniform improvement on $T^{(m)}$ in (13) For any choice of $\alpha_{kn}$, we can uniformly improve the power of our procedure by slightly modifying the stopping time defined in (13). This
Zhimei Ren and Rina Foygel Barber

improvement is inspired by Luo et al. (2022), and specifically, we define an alternative stopping time as

\[
T^{(m)} := \inf \left\{ t > 0 : \frac{1 + \sum_{j \in [p]} \mathbb{I}\{W_j^{(m)} \leq -t\} + \sum_{k \in [p]} \mathbb{I}\{W_k^{(m)} \geq t\}}{\sum_{k \in [p]} \mathbb{I}\{W_k^{(m)} \leq t\}} \leq \alpha_{kn} \right\} \quad \text{(15)}
\]

Note that (15) differs from (13) only when

\[
\inf \left\{ t > 0 : \frac{1 + \sum_{j \in [p]} \mathbb{I}\{W_j \leq -t\}}{\sum_{k \in [p]} \mathbb{I}\{W_k \geq t\}} \leq \alpha_{kn} \right\} > \inf \left\{ t > 0 : \sum_{j \in [p]} \mathbb{I}\{W_j^{(m)} \geq t\} < 1/\alpha_{kn} \right\},
\]

that is, the “hopeless” case where (13) gives an infinite stopping time and all the corresponding e-values are 0’s. The alternative definition of \( T^{(m)} \) only increases the value of e-values by stopping earlier in the powerless case, therefore leading to a uniformly more powerful procedure. Plugging (15) in (7) still yields valid e-values as a result of Remark 4. The improvement is particularly significant when \( \alpha_{kn} \) and/or the fraction of non-nulls is small. The complete procedure with the improved stopping time is described in Algorithm 1.

3.1.1. Comparison to Ren et al. (2021)

Recall that the procedure of Ren et al. (2021) computes the (unweighted) selection probability defined in (1), then picking the features whose selection probability passes a constant threshold. In contrast, our procedure instead computes a weighted selection probability, and then thresholding it with a data-dependent cutoff—here, the weight corresponding to the \( m \)-th run is given by

\[
\frac{1}{\alpha_{kn}} \cdot \frac{1}{\sum_{k \in [p]} \mathbb{I}\{W_k^{(m)} \leq -T^{(m)}\}}.
\]

3.1.2. Comparison to Dai et al. (2022, 2023)

Our procedure uses e-values of the form

\[
e_j = \frac{1}{M} \sum_{m=1}^{M} \text{weight}_j^{(m)} \cdot \mathbb{1}\{j \in S_{kn}^{(m)}\},
\]

where we have now seen that the weights are chosen as

\[
\text{weight}_j^{(m)} = \frac{1}{1 + \sum_{k \in [p]} \mathbb{I}\{W_k^{(m)} \leq -T^{(m)}\}}.
\]

In contrast, the method proposed in Dai et al. (2022, 2023) can be rewritten in our notation by taking

\[
\text{weight}_j^{(m)} = \frac{1}{\alpha_{kn}} \cdot \frac{1}{\sum_{k \in [p]} \mathbb{I}\{W_k^{(m)} \geq t\}}.
\]

By definition of the knockoff procedure, comparing the denominators, the weights used by Dai et al. (2022, 2023) are always less than or equal to the weights in our proposed method; consequently, our method is strictly more powerful. In addition, the results of Dai et al. (2022, 2023) establish asymptotic control of the FDR and require additional strong conditions (e.g., an assumption that the ranking of the baseline algorithm is consistent asymptotically). In contrast, our result in Theorem 3 offers finite-sample FDR control without any additional assumptions. (Indeed, since the key to establish finite-sample FDR control is showing that the weighted selection frequencies we construct in (2) is a class of (relaxed) e-values, and since this is also true when the weights \( \text{weight}_j^{(m)} \) are chosen according to Dai et al. (2022, 2023)’s more conservative rule (16), our analysis can also be applied to show a finite-sample FDR control result for their method.)
investigate the power of our proposed procedure with different choices of defining the knockoff threshold. To provide a guidance on parameter selection, we numerically power. As pointed out by Remark 4, we also have the freedom to tune the offset parameter $c$ in Theorem 3), the parameter $\alpha$ reduces to the original knockoffs method when $\alpha > M > 1$? In fact, it turns out that choosing $\alpha_{kn} < \alpha_{ebh}$ is preferable when $M > 1$. To understand why, we will sketch a simple scenario where choosing $\alpha_{kn} = \alpha_{ebh}$ might lead to zero power, while choosing a smaller value of $\alpha_{kn}$ can lead to high power. Suppose that the data contains $s$ many non-nulls, which each have extremely strong signals, so that any single run of the knockoff filter is highly likely to select all $s$ non-nulls. For each run $m$, we will expect a false discovery proportion of approximately $\alpha_{kn}$, meaning that we have $|S_{kn}^{(m)} \cap H_0| \approx \frac{\alpha_{kn}}{1 - \alpha_{kn}} s$ false discoveries together with the $\approx s$ true discoveries. In particular, should then have

$$1 + \sum_{j \in H_0} \mathbf{1}_{\{W_j^{(m)} \leq -T^{(m)}\}} \approx \sum_{j \in H_0} \mathbf{1}_{\{W_j^{(m)} \geq T^{(m)}\}} = |S_{kn}^{(m)} \cap H_0| \approx \frac{\alpha_{kn}}{1 - \alpha_{kn}} s,$$

where the first step holds since null features $j$ have statistics $W_j^{(m)}$ that are symmetric around zero. Since each non-null $j$ is selected in (nearly) every run of knockoffs, while for a null $j \in H_0$ it may be the case that $j$ is selected for only a small proportion of the runs, we therefore expect to see

$$e_j^{avg} \approx \frac{p}{\alpha_{kn}} \frac{\alpha_{kn}}{1 - \alpha_{kn}} s \quad \text{for } j \in H_1, \quad e_j^{avg} \approx 0 \quad \text{for } j \in H_0.$$

Applying the e-BH procedure at level $\alpha_{ebh}$ to these e-values, we see that power can be high only if $p/(\frac{\alpha_{kn}}{1 - \alpha_{kn}} s) \gtrsim p/(\alpha_{ebh} s)$, while otherwise power will be zero as we will not be able to make any discoveries. In other words, $\alpha_{kn} = \alpha_{ebh}$ will likely lead to zero power but $\alpha_{kn} \lesssim \frac{\alpha_{ebh}}{1 + \alpha_{ebh}}$ will lead to (nearly) perfect recovery.

The above derivation provides some intuition for choosing $\alpha_{kn} < \alpha_{ebh}$ in order to obtain high power. As pointed out by Remark 4, we also have the freedom to tune the offset parameter $c$ in defining the knockoff threshold. To provide a guidance on parameter selection, we numerically investigate the power of our proposed procedure with different choices of $\alpha_{kn}$ and $c$ in the simulated experiments (see Section 4 and Section C of the appendix). Empirically, we find that the combination of $c = 1$ and $\alpha_{kn} = \alpha_{ebh}/2$ consistently works well in different scenarios; whether these parameters are optimal, or can be chosen in a better way, remains an open question for future work.

**Algorithm 1** Derandomized knockoffs with e-values

**Input:** Data $(X, Y)$; parameters $\alpha_{kn}, \alpha_{ebh} \in (0, 1)$, $M \in \mathbb{N}_+$.

1: for $m = 1, \ldots, M$ do
2: Sample the knockoff copy $\tilde{X}^{(m)}$.
3: Compute the feature importance statistics: $W^{(m)} = \mathcal{W}(X, \tilde{X}^{(m)}, Y)$.
4: Compute the knockoffs threshold $T^{(m)}$ according to (15).
5: Compute the e-values $e_j^{(m)}$ according to (14) for each $j \in [p]$.
6: end for
7: Compute the averaged e-values $e_j^{avg} = \frac{1}{M} \sum_{m=1}^{M} e_j^{(m)}$ for each $j \in [p]$.
8: Compute $\hat{k} = \max\{k : e_j^{avg} \geq p/(\alpha_{ebh} k)\}$, or $\hat{k} = 0$ if this set is empty.

**Output:** The selected set of discoveries $S_{kn-derand} := \{j \in [p] : e_j^{avg} \geq p/(\alpha_{ebh} \hat{k})\}$.

### 3.2. Choices of parameters

In Algorithm 1, we have the freedom to choose two potentially different parameters $\alpha_{ebh}$ and $\alpha_{kn}$. While $\alpha_{ebh}$ determines the ultimate FDR guarantee of the procedure (as established in Theorem 3), the parameter $\alpha_{kn}$ does not affect this FDR guarantee, but may instead affect the power of the method. Should we simply choose $\alpha_{kn} = \alpha_{ebh}$ (particularly given that this choice reduces to the original knockoffs method when $M = 1$)?

While $\alpha_{ebh}$ and $\alpha_{kn}$ are both $< 1$, $\alpha_{kn}$ is preferable when $\alpha_{kn} < \alpha_{ebh}$. In particular, should then have

$$1 + \sum_{j \in H_0} \mathbf{1}_{\{W_j^{(m)} \leq -T^{(m)}\}} \approx \sum_{j \in H_0} \mathbf{1}_{\{W_j^{(m)} \geq T^{(m)}\}} = |S_{kn}^{(m)} \cap H_0| \approx \frac{\alpha_{kn}}{1 - \alpha_{kn}} s,$$

where the first step holds since null features $j$ have statistics $W_j^{(m)}$ that are symmetric around zero. Since each non-null $j$ is selected in (nearly) every run of knockoffs, while for a null $j \in H_0$ it may be the case that $j$ is selected for only a small proportion of the runs, we therefore expect to see

$$e_j^{avg} \approx \frac{p}{\alpha_{kn}} \frac{\alpha_{kn}}{1 - \alpha_{kn}} s \quad \text{for } j \in H_1, \quad e_j^{avg} \approx 0 \quad \text{for } j \in H_0.$$

Applying the e-BH procedure at level $\alpha_{ebh}$ to these e-values, we see that power can be high only if $p/(\frac{\alpha_{kn}}{1 - \alpha_{kn}} s) \gtrsim p/(\alpha_{ebh} s)$, while otherwise power will be zero as we will not be able to make any discoveries. In other words, $\alpha_{kn} = \alpha_{ebh}$ will likely lead to zero power but $\alpha_{kn} \lesssim \frac{\alpha_{ebh}}{1 + \alpha_{ebh}}$ will lead to (nearly) perfect recovery.

The above derivation provides some intuition for choosing $\alpha_{kn} < \alpha_{ebh}$ in order to obtain high power. As pointed out by Remark 4, we also have the freedom to tune the offset parameter $c$ in defining the knockoff threshold. To provide a guidance on parameter selection, we numerically investigate the power of our proposed procedure with different choices of $\alpha_{kn}$ and $c$ in the simulated experiments (see Section 4 and Section C of the appendix). Empirically, we find that the combination of $c = 1$ and $\alpha_{kn} = \alpha_{ebh}/2$ consistently works well in different scenarios; whether these parameters are optimal, or can be chosen in a better way, remains an open question for future work.
3.3. Derandomization: a closer look

In Algorithm 1, conditional on the data \((X, Y)\), for each feature \(j\) the \(e_j^{(m)}\)'s are i.i.d. for \(m = 1, \ldots, M\). By the strong law of large numbers, we then have

\[
e_j^{\text{avg}} = \frac{1}{M} \sum_{m=1}^{M} e_j^{(m)} \to e_j^{\infty} := \mathbb{E}[e_j^{(1)} | X, Y],
\]  

almost surely as \(M \to \infty\). Let \(S_{kn-\infty}\) denote the selected set obtained by applying e-BH to these limiting e-values \(e_1^{\infty}, \ldots, e_p^{\infty}\). Note that \(S_{kn-\infty}\) is now a deterministic function of the data \((X, Y)\). By (17), we would then expect that the selected set \(S_{kn-\text{derand}}\) obtained by averaging over \(M\) runs of knockoffs, should eventually stabilize to this completely derandomized selected set \(S_{kn-\infty}\).

To quantify this intuition, let \(\Delta = \min_{k \in [p]} |e_{(k)}^{\infty} - p/(\alpha k)|\). Applying Hoeffding’s inequality, we have with probability at least 1 \(- 2p \cdot \exp(-2\Delta^2 M/p^2)\) that \(\max_{k \in [p]} |e_k^{\text{avg}} - e_k^{\infty}| < \Delta\), which implies \(\max_{k \in [p]} |e_k^{\text{avg}} - e_k^{(1)}| < \Delta\). On this event, then, the definition of the e-BH procedure implies that \(S_{kn-\text{derand}} = S_{kn-\infty}\).

4. Simulations

We next illustrate the performance of our proposed derandomized knockoffs method, and compare to the original knockoffs procedure, with numerical experiments.

**Settings** We generate data for two different models: the Gaussian linear model and the logistic model. In both settings, we choose sample size \(n = 1000\). In the linear case, the feature dimension \(p = 800\) with \(|H_1| = 80\) non-nulls, and in the logistic case, \(p = 600\) with \(|H_1| = 50\) non-nulls. The marginal distribution \(P_X\) of the feature vector \(X \in \mathbb{R}^p\) is given by \(X \sim \mathcal{N}(0, \Sigma)\), where the covariance matrix has entries \(\Sigma_{jk} = 0.5^{|j-k|}\). The distribution of \(Y | X\) is defined as follows for our two models:

- **Gaussian linear model:** \(Y | X \sim \mathcal{N}(X^\top \beta, 1)\)
- **Logistic model:** \(Y | X \sim \text{Bernoulli}\left(\frac{e^{X^\top \beta}}{1 + e^{X^\top \beta}}\right)\)

where \(\beta \in \mathbb{R}^p\) is the coefficient vector. To determine \(\beta\), we first construct \(\tilde{\beta} \in \mathbb{R}^{|H_1|}\), where each entry of \(\tilde{\beta}\) is independently generated from \(\mathcal{N}(A, 1)\), with \(A\) denoting the overall signal amplitude. Once generated, \(\tilde{\beta}\) is fixed across the experiments. We then determine the coefficient vector \(\beta\) by letting

\[
\beta = \left(0, \ldots, 0, \frac{\beta_1}{\sqrt{n}}, 0, \ldots, 0, -\frac{\beta_2}{\sqrt{n}}, \ldots\right),
\]

where \(z = 9\) in the linear case and \(z = 11\) in the logistic case. The signal amplitude \(A \in \{4, 5, 6, 7, 8\}\) for the Gaussian linear model or \(A \in \{10, 15, 20, 25, 30, 35\}\) for the logistic model.

**Methods** For the original model-X knockoff filter, the knockoffs \(\tilde{X}\) are constructed using the multivariate Gaussian distribution \(P_X\) of the features, as in Candes et al. (2018, Eqn. (3.2), (3.13)), and the feature importance statistics \(W \in \mathbb{R}^p\) are computed via the Lasso coefficient-difference (LCD) statistic as in Candes et al. (2018, Eqn. (3.7)). Finally, the selection set \(S_{kn}\) is computed via the knockoff filter run with target FDR level \(\alpha = 0.1\).

†Code to reproduce all experiments on simulated and real data is available at [https://github.com/zhimeir/derandomized_knockoffs_fdr](https://github.com/zhimeir/derandomized_knockoffs_fdr). The knockoffs method is implemented via the R-package knockoff (Patterson and Sesia, 2018).
For the derandomized knockoffs method (Algorithm 1), we draw $M = 50$ copies of the knockoffs, and compute the $m$-th selected set $S_{kn}^{(m)}$ using the selection threshold defined in (15) with $\alpha_{kn} \in \{0.01, 0.02, \ldots, 0.2\}$, and then apply e-BH with target FDR level $\alpha_{ebh} = 0.1$. When compared with the original knockoffs, $\alpha_{kn}$ is taken to be 0.05.

**Measures of performance** For each model and each signal amplitude setting, the data set $(X, Y)$ is generated independently 100 times. For each draw of the dataset $(X, Y)$, we also replicate the knockoffs procedure (i.e., original or derandomized) 20 times. (When investigating the effect of different parameters, the derandomized knockoffs procedure is implemented once for each draw of the dataset.) For each model, each signal amplitude, and each of the two methods, we measure performance in several different ways. First, we estimate the power and FDR as

\[
\text{Power} = \frac{1}{100 \cdot 20} \sum_{d=1}^{100} \sum_{k=1}^{20} \frac{|S_{d,k} \cap H_1|}{|H_1|} \quad \text{and} \quad \text{FDR} = \frac{1}{100 \cdot 20} \sum_{d=1}^{100} \sum_{k=1}^{20} \frac{|S_{d,k} \cap H_0|}{|S_{d,k}| \vee 1},
\]

where $S_{d,k}$ denotes the selected set for the $d$-th draw of the dataset $(X, Y)$ and the $k$-th run of (original or derandomized) knockoffs for this dataset.

Next, we would like to quantify the “randomness” of each selection procedure. Note that there are two sources of variability: the randomness conditional on the dataset (i.e., arising from the knockoffs construction), and that from the dataset itself. We define two different measures, to capture the overall (“marginal”) variability, and to capture the “conditional” variability that arises from the knockoffs construction (note that it is this latter measure that derandomized knockoffs aims to reduce). Define

\[
\hat{p}_j = \frac{1}{100 \cdot 20} \sum_{d=1}^{100} \sum_{k=1}^{20} \mathbb{I}\{j \in S_{d,k}\} \quad \text{and} \quad \hat{p}_{j,d} = \frac{1}{20} \sum_{k=1}^{20} \mathbb{I}\{j \in S_{d,k}\}
\]

for each $j \in p$, where $\hat{p}_j$ is the empirical probability of selection on average over a random draw of the datasets and the knockoffs, while $\hat{p}_{j,d}$ is the empirical probability of selection conditional on the $d$-th draw of the dataset. Let $\tilde{s}$ be the average number of selections over all $d, k$, and let $\tilde{s}_d$ be the average number over all runs $k$ of knockoffs for a fixed dataset $d$. We then define

\[
\text{Marginal selection variability} = \frac{\sum_{j \in [p]} \hat{p}_j (1 - \hat{p}_j)}{p \cdot \frac{\tilde{s}}{p} (1 - \frac{\tilde{s}}{p})}.
\]

To motivate this definition, if the selected set $S_{d,k}$ contains the same $\tilde{s}$ features for each $d, k$ then we will have $\hat{p}_j \in \{0, 1\}$ for all $j$ and so $\text{Var}_{\text{marg}} = 0$, while if $S_{d,k}$ contains a random selection of $\tilde{s}$ features for each $d, k$, then we will have $\hat{p}_j \approx \tilde{s}/p$ for all $j$ and so $\text{Var}_{\text{marg}} \approx 1$. Similarly, we define

\[
\text{Conditional selection variability} = \frac{\sum_{d=1}^{100} \sum_{j \in [p]} \hat{p}_{j,d} (1 - \hat{p}_{j,d})}{\sum_{d=1}^{100} p \cdot \frac{\tilde{s}_d}{p} (1 - \frac{\tilde{s}_d}{p})}.
\]

**Results** Figure 1 plots the power and FDR of derandomized knockoffs as a function of $\alpha_{kn}$ under both models with different signal amplitude. For the Gaussian linear model, the low, medium and high signal amplitude correspond to $A = 4, 6$ and 8, respectively; for the logistic model, the three cases correspond to $A = 10, 20$ and 30, respectively. In all the settings, we observe that derandomized knockoffs consistently performs well with $\alpha_{kn} = \alpha_{ebh}/2 = 0.05$. 

Fig. 1. Realized power (left) and FDR (right) of derandomized knockoffs as a function of the parameter $\alpha_{kn}$ for the simulation data experiments. The offset parameter $c = 1$. Shading for the power and FDR plots indicates error bars. The target FDR level $\alpha_{ebh} = 0.1$. Results are averaged over 100 independent trials.

Figure 2 plots the power, FDR, and selection variability as functions of the signal amplitude, for both settings. We see that derandomized knockoffs achieves comparable power as the original knockoffs method when the signal strength is reasonably large, while there is some power loss when the signal strength is weak (as we shall see in Figure 3 and 4, the original knockoffs achieves higher power in this scenario with an increased chance of selecting null features). For logistic regression, derandomized knockoffs achieves a slightly higher power than the original knockoffs method in the strong-signal setting. In all cases, both methods have FDR bounded by the target level $\alpha = 0.1$, whereas derandomized knockoffs consistently achieves an FDR substantially lower than the original knockoffs. Finally, derandomized knockoffs in general exhibits lower selection variability, both marginally and conditionally. In particular, the conditional variability (that is, the variability arising from the randomness in the knockoffs method, while conditioning on a fixed dataset) is substantially decreased for the derandomized method, as expected.

In Figure 3 and 4, we take a closer look at the marginal and conditional selection probability of individual features by the two methods. Especially in weak-signal settings, we can see that the original knockoffs often has a high selection probability for the nulls that are rarely selected by derandomized knockoffs (i.e., many red points are above the 45-degree line); this phenomenon is more pronounced when we focus on the conditional selection probability.

5. Application to HIV mutation data

We next compare original and derandomized knockoffs on a study of detecting mutations associated with drug resistance in Human Immunodeficiency Virus Type 1 (HIV-1) (Rhee et al., 2006).

Data The dataset‡ documents drug resistance measurements (for several classes of drugs) and genotype information on samples of HIV-1. Our analysis focuses on a particular protease inhibitor (PI) named lopinavir. For sample $i$ and mutation $j$, $Y_i$ denotes the log-fold increase

‡Available at https://hivdb.stanford.edu/download/GenoPhenodatasets/PI_dataset.txt
in resistance to the drug, and $X_{ij}$ is a binary variable indicating whether or not mutation $j$ is present in sample $i$.

**Methods** After cleaning the data (removing rows with missing values and mutations that appear less than three times in the data), we have a dataset of $n = 1840$ samples and $p = 219$ mutations. The data matrix $X$ is normalized such that each column has zero mean and unit variance. We use the second-order method (Candès et al., 2018, Sec. 3.4.2) to generate knockoffs via the first and second moments of $X$ (as discussed in Romano et al. (2020) and the references therein, it is empirically observed that this approximate knockoffs construction often affects the power but leaves the FDR intact). The original and derandomized knockoffs methods are implemented with the LCD as the feature importance statistic, as for our simulations. We set $\alpha = 0.1$ for knockoffs, and $\alpha_{kn} = 0.05$ and $\alpha_{ebh} = 0.1$ for derandomized knockoffs, so that the target FDR level is 0.1 for both methods. The derandomized method is run with $M = 100$ copies of the knockoff matrix. For both original and derandomized knockoffs, we repeat the experiment 50 times in order to examine the variability of the selected set across different generations of the knockoffs.

**Results** The results of this experiment are shown in Figure 5, summarizing the results from 50 independent runs of both methods. In the histograms, we display the selection frequency (across the 50 trials) for each mutation $j \in [p]$, for both methods. For the original knockoffs method, we see that a substantial number of mutations have selection probability bounded away from 0 and from 1, exhibiting some instability. For derandomized knockoffs, on the other hand, nearly all the mass is at 0 and 1, meaning that each mutation is either (almost) always selected or (almost) never selected. In the boxplot, we see that the original knockoffs method makes more discoveries on average than derandomized knockoffs, but the number of discoveries is quite variable. When the discoveries from each method are cross-referenced with the verified discoveries reported at https://hivdb.stanford.edu/dr-summary/comments/PI/, we find evidence of a higher FDR for the original knockoff method, indicating that derandomized knockoffs may retain the
Fig. 3. Top: the marginal selection probability $\hat{p}_j$ by original knockoffs versus that by derandomized knockoffs. Bottom: the conditional selection probability $\hat{p}_{j,1}$ by original knockoffs versus that by derandomized knockoffs. The results are from simulations under the Gaussian linear model. Each point corresponds to a feature, where the blue ones are non-nulls and the red ones are nulls. For the given dataset, many null features never selected by derandomized knockoffs have large selection probability by the original knockoffs.

same power despite the lower average number of discoveries (see Appendix D for a more detailed analysis, including which specific mutations were selected).

6. Discussion

In this work, we discover a connection between knockoffs and e-values, showing that the knockoff filter can be reframed as an e-BH procedure. This equivalence in turn allows us to pool information across multiple runs of knockoffs to achieve a derandomized procedure without compromising the guarantee of FDR control. Our method shows desirable performance in practice, retaining the power of the original method while reducing variability. Additionally, derandomized knockoffs achieves an empirical FDR that is lower than the target level in our experiments; as an open question for future work, it would be interesting to see under what mild conditions can we derive a sharper FDR bound (for example, as in Meinshausen and Bühlmann (2010); Shah and Samworth (2013) for stability selection, or as in Ren et al. (2021) for the previously proposed version of derandomized knockoffs).

Many variants and extensions of the knockoffs method have appeared in the literature, including the “fixed-X” setting (Barber and Candés, 2015), robustness results for the model-X setting when $P_X$ is not known exactly (Barber et al., 2020), a multi-environment knockoff filter (Li et al., 2021), and knockoffs that incorporate side information (Ren and Candès, 2020). In Appendix A, we give derandomized versions of each of these, together with accompanying theoretical guarantees. In addition to these extensions, our proposed derandomization scheme could potentially also be combined with other existing extensions of the knockoffs methodology—for example, the group knockoff filter (Dai and Barber, 2016) for discovering a group-sparse structure, or the missing value knockoffs method (Koyuncu and Yener, 2022) to handle the presence of missing data.
Fig. 4. The results are from simulations under the logistic model. The other details are the same as in Figure 4.

Fig. 5. Results for the HIV data experiment. Left: boxplot of the number of discoveries for original and derandomized knockoffs, over 50 independent trials. Right: histogram of the selection probability for each feature $j \in [p]$, over 50 independent trials, for original and derandomized knockoffs.

Data availability statement
The code for reproducing the numerical results in this paper can be found at https://github.com/zhimeir/derandomized_knockoffs_fdr.

Acknowledgment
Z.R. and R.F.B were supported by the Office of Naval Research via grant N00014-20-1-2337. R.F.B. was additionally supported by the National Science Foundation via grants DMS-1654076 and DMS-2023109.

A. Extensions
A.1. Fixed-X knockoffs
The derandomization procedure can also be applied to aggregating multiple runs of the fixed-X knockoffs procedure (Barber and Candès, 2015). The fixed-X knockoffs procedure considers a
setting where the design matrix $X$ is fixed and the response is generated from a Gaussian linear model:

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

where $\beta \in \mathbb{R}^p$ is an unknown coefficient vector and $\varepsilon \sim \mathcal{N}(0, I_n)$. The test of conditional independence (defined in (3)) is equivalent to testing if $\beta_j = 0$. The (fixed-X) knockoffs $\tilde{X}$ for $X$ is any matrix $\tilde{X} \in \mathbb{R}^{n \times p}$ satisfying

$$\tilde{X}^\top \tilde{X} = \Sigma, \quad X^\top \tilde{X} = \Sigma - \text{diag}\{s\},$$

where $\Sigma = X^\top X$ is the gram matrix, and $s$ is a $p$-dimensional nonnegative vector; given $\tilde{X}$, one can compute the feature importance statistics with $([X, \tilde{X}], Y)$ and apply the knockoffs filter as in the model-X case. Specifically, $\tilde{X}$ can be generated as

$$\tilde{X} = X(I_p - \Sigma^{-1}\text{diag}\{s\}) - U(2\text{diag}\{s\} - \text{diag}\{s\}\Sigma^{-1}\text{diag}\{s\})^{1/2},$$

where $U \in \mathbb{R}^{n \times p}$ is an orthonormal matrix orthogonal to $X$ (i.e., $U^\top U = I_p$ and $U^\top X = 0$). When generating $\tilde{X}$, the choice of $U$ is arbitrary, and may be constructed deterministically or randomly (c.f. Barber and Candès (2015, Section 2))—in either case, this arbitrary choice will generally affect the set of discoveries, and thus it might be desirable to derandomize in order to obtain a more stable and meaningful selected set. Our derandomization scheme can be applied here to aggregating results from fixed-X knockoffs with different methods of implementation, and the resulting set of discoveries has guaranteed FDR control (the proof is exactly the same as in the model-X case). The complete procedure for derandomized fixed-X knockoffs is described in Algorithm 1.1, and its validity proved in the following theorem.

**Theorem A.1.** For any $\alpha_{\text{kn}}, \alpha_{\text{ebh}} \in (0, 1)$, and any number of knockoff copies $M \geq 1$, the selected set offered by Algorithm A.1 satisfies $FDR \leq \alpha_{\text{ebh}}$.

**Proof.** By Barber and Candès (2015, Lemma A1), $\sum_{j \in H_0} \mathbb{E}[e_j^{(m)}] \leq p$, and by the linearity of expectation, $\sum_{j \in H_0} \mathbb{E}[e_j^{\text{avw}}] \leq p$. The result follows immediately from Theorem 2.

### A.2. Robust knockoffs

The validity of the model-X knockoffs frame relies crucially on the knowledge of $P_X$, but in practice, this distribution might be estimated rather than known exactly. In this section, we investigate the robustness of the derandomized knockoffs procedure when the knockoff copies are sampled without exact knowledge of $P_X$. In this section, we will show that when the knockoffs are constructed using approximate knowledge of $P_X$, Algorithm 1 achieves approximate FDR control.

The setting of our discussion follows that of Barber et al. (2020). Formally, suppose for each $j \in [p]$, the researcher only has access to an estimated conditional distribution for $X_j | X_{-j}$, denoted by $Q_j'(\cdot | X_{-j})$ (instead of the ground truth $P_j(\cdot | X_{-j}) = P_{X_j | X_{-j}}$). Based on these $Q_j$’s, the researcher samples the knockoffs with $\tilde{X} | X \sim P_{\tilde{X} | X}$, such that for any $j \in [p]$, $P_{\tilde{X} | X}$ is pairwise exchangeable w.r.t. $Q_j$. The definition of pairwise exchangeability w.r.t. $Q_j$ is as follows.

**Definition A.1.** $P_{\tilde{X} | X}$ is pairwise exchangeable with respect $Q_j$ if for any distribution $D^{(j)}$ on $\mathbb{R}^p$ with the $j$-th conditional distribution $Q_j$, and $(X, \tilde{X}) \sim D^{(j)} \times P_{\tilde{X} | X}$, it holds that

$$(X_j, \tilde{X}_j, X_{-j}, \tilde{X}_{-j}) \overset{d}{=} (\tilde{X}_j, X_j, X_{-j}, \tilde{X}_{-j}).$$

Algorithm A.1 Derandomized fixed-X knockoffs

**Input:** Data \((X, Y)\); nonnegative \(s\) satisfying \(2\text{diag}\{s\} - \text{diag}\{s\}\Sigma^{-1}\text{diag}\{s\} \geq 0\); parameters \(\alpha_{\text{ehh}}, \alpha_{\text{kn}} \in (0, 1)\) and \(M \in \mathbb{N}_+\).

1: for \(m = 1, \ldots, M\) do
2: Construct the knockoff copy
   \[
   \tilde{X}^{(m)} = X(I_p - \Sigma^{-1}\text{diag}\{s\}) - U^{(m)}(2\text{diag}\{s\} - \text{diag}\{s\}\Sigma^{-1}\text{diag}\{s\})^{1/2},
   \]
   where \(U^{(m)}\) is drawn uniformly at random from the set of orthonormal \(n \times p\) matrices orthogonal to \(X\).
3: Compute the feature importance statistics: \(W^{(m)} = \mathcal{W}^{(m)}([X, \tilde{X}^{(m)}], Y)\).
4: Compute the stopping time \(T^{(m)}\) according to (15).
5: Compute the e-value \(e_j\) according to (14), for all \(j \in [p]\).
6: end for
7: Compute the average e-value \(e_j^{\text{avg}} = \frac{1}{M} \sum_{m=1}^{M} e_j^{(m)}\) for each \(j \in [p]\).
8: Compute \(\hat{k} = \max\{k : e_j^{\text{avg}} \geq p/(\alpha_{\text{ehh}}k)\}\), or \(\hat{k} = 0\) if this set is empty.

**Output:** The selected set of discoveries \(S_{\text{kn-derand}} := \{j \in [p] : e_j^{\text{avg}} \geq p/(\alpha_{\text{ehh}}\hat{k})\}\).

As remarked in Barber et al. (2020), when the conditional distributions \(Q_j\)’s are mutually compatible, i.e. there exists a joint distribution \(Q_X\) on \(\mathbb{R}^p\) whose \(j\)-th conditional distribution coincides with \(Q_j\), then the knockoff construction algorithm (Cand` es et al., 2018, Algorithm 1) with \(Q_X\) as the input produces knockoffs satisfying Definition A.1. When the \(Q_j\)’s are not mutually compatible, Barber et al. (2020, Section 4) provide examples in which knockoffs satisfying Definition A.1 can be produced. Moving on, we work under the premise that we can generate knockoffs obeying Definition A.1.

To measure the deviation of \(Q_j\) from the ground truth, we follow Barber et al. (2020) and define the “empirical KL divergence” quantity for any \(j \in [p]\) and for each run \(m\) of knockoffs:

\[
\hat{\text{KL}}_j^{(m)} = \sum_i \log \left( \frac{P_j(X_{ij} \mid X_{i,-j})}{Q_j(X_{ij} \mid X_{i,-j})} \cdot \frac{Q_j(X_{ij}^{(m)} \mid X_{i,-j})}{P_j(X_{ij}^{(m)} \mid X_{i,-j})} \right), \quad m \in [M].
\]

We then take the maximum over the \(M\) runs of knockoffs,

\[
\hat{\text{KL}}_j^{\text{max}} = \max_{m \in [M]} \hat{\text{KL}}_j^{(m)}.
\]

Clearly, the smaller \(\hat{\text{KL}}_j^{\text{max}}\) is, the closer \(Q_j\) is to \(P_j\), and \(\hat{\text{KL}}_j^{\text{max}} = 0\) when \(P_j = Q_j\). Intuitively, the better \(Q_j\) approximated \(P_j\), the more likely it is to control the FDR (when \(P_j = Q_j\) for all \(j \in [p]\), the FDR is controlled at the desired level). Such an intuition is formalized by the following theorem which shows that Algorithm 1 controls the FDR among the features with small values of \(\hat{\text{KL}}_j^{\text{max}}\).

**Theorem A.2.** Fix any \(\alpha_{\text{kn}}, \alpha_{\text{ehh}} \in (0, 1)\), and any number of knockoff copies \(M \geq 1\). For any \(\varepsilon \geq 0\), consider the null variables for which \(\hat{\text{KL}}_j^{\text{max}} \leq \varepsilon\). The fraction of the rejections made by Algorithm 1 that correspond to such nulls obeys

\[
\mathbb{E} \left[ \left\{ \frac{1}{|S|} \sum_{j \in S \cap H_0} \hat{\text{KL}}_j^{\text{max}} \leq \varepsilon \right\} \right] \leq e^{\varepsilon} \cdot \alpha.
\]
As a result, the FDR can be controlled as

$$\text{FDR} \leq \min_{\varepsilon > 0} \left\{ e^\varepsilon \cdot \alpha + \mathbb{P} \left( \max_j K_{L,j}^{\text{max}} \geq \varepsilon \right) \right\}.$$  

The proof of Theorem A.2 can be found in Appendix B.1. Note that the FDR inflation depends directly on the $K_{L,j}^{\text{max}}$'s, which take the form of the maximum of $M$ conditional independent objects. Consequently, when $K_{L,j}^{(m)}$ is bounded almost surely, the FDR inflation is bounded for any choices of $M$. In the numerical experiments to be presented in the next section, we will see that we generally observe controlled FDR even with estimated $P_X$.

### A.3. Multi-environment knockoffs

For the purpose of making scientific conclusions, it is sometimes not sufficient to find associations that are significant in only one environment—here, environments can refer to subpopulations, experimental settings or data sources (see more discussion in Li et al. (2021)). Intuitively, if an association is found to be significant in all environments (e.g., a genetic variant found to be associated with a certain disease in all subpopulations), it is more likely to be the “true” driving factor and less prone to the impact of unobserved confounders.

Formally, suppose there are $E$ environments, and in each environment $e \in [E]$, the data vector $(X, Y) \sim P_{X,Y}$ (we work again in the model-X framework, and so $P_X$ is assumed known). We write the conditional independence hypothesis in environment $e$ as

$$H_{j,e}^{\text{ci}} : Y_e \perp X^e_j | X^e_{-j}.$$  

(A.1)

To find the association that is consistently true across all the environments (i.e., robust association) is equivalent to testing the following consistent conditional independence hypothesis:

$$H_j^{\text{ci},e} : \exists e \in [E] \text{ such that the null } H_{j,e}^{\text{ci}} \text{ defined in (A.1) is true.}$$  

(A.2)

By definition, rejecting $H_j^{\text{ci}}$ suggests an association between $X_j$ and $Y$ across all the environments. In practice, (A.2) may be hard to reject especially as the number of environments increases. Li et al. (2021) also propose a relaxed version of (A.2) that tests for partial consistency. For any fixed number $r \in [E]$, the partial consistency null hypothesis is defined as

$$H_j^{\text{pcc},r} : \left\{ e \in [E] : H_{j,e}^{\text{ci}} \text{ is true} \right\} > E - r.$$  

(A.3)

Rejecting (A.3) then means that the association is true in at least $r$ environments.

To proceed, we let the set of nulls $\mathcal{H}_0 = \{ j : H_j^{\text{ci}} \text{ is true} \}$ when testing $H_j^{\text{ci}}$’s or $\mathcal{H}_0 = \{ j : H_j^{\text{pcc}} \text{ is true} \}$ when testing $H_j^{\text{pcc}}$’s. Previously, Li et al. (2021) proposed a variant of knockoffs called the multi-environment knockoff filter (MEKF) to simultaneously test $H_j^{\text{ci}}$’s or $H_j^{\text{pcc}}$’s with guaranteed FDR control. To be specific, suppose we have independent datasets $(X^1, Y^1), \ldots, (X^E, Y^E)$ where $(X_e, Y_e)$ is obtained from environment $e$. For each $e \in [E]$, the MEKF generates a knockoff copy $X^e$ for $X^e$; it then takes $([X^e, X^e, Y^e])_{e \in [E]}$ as input and computes the multi-environment feature importance statistic $W \in \mathbb{R}^{E \times p}$, whose definition is given as follows.

**Definition A.2** (Definition 1 of Li et al. (2021)). $W \in \mathbb{R}^{E \times p}$ are valid multi-environment knockoff statistics if they satisfy $W \overset{d}{=} W \odot \varepsilon$ and $\varepsilon \in \{ \pm 1 \}^{E \times p}$ is a random matrix with independent entries and rows $\varepsilon^e$ such that $\varepsilon^e_j = \pm 1$ with probability $1/2$ if $H_{j,e}^{\text{ci}}$ is true and $\varepsilon^e_j = +1$ otherwise, for all $j \in [p]$ and $e \in [E]$. 


To construct such $W$, one can simply compute $W^e = \mathcal{W}(X^e, \mathbf{X}^e, Y^e)$ for all $e \in [E]$ and assemble the $W$’s into a $E \times p$ matrix. More methods for constructing $W$ can be found in Li et al. (2021, Section 4.2). With $W$, we define for each $j \in [p]$ the (normal) feature importance statistic for testing $H_{j}^{\text{est}}$ to be

$$W_j = \min_{e \in [E]} \left( \text{sign}(W^e_j) \right) \cdot \prod_{e \in [E]} |W^e_j|,$$

(A.4)

and that for testing $H_{j}^{\text{est}, r}$ to be

$$W_j = \text{sign}\left( \frac{1}{2} - p_j \right) \cdot \prod_{e=1}^r |W^e_j|^{(E-e+1)}.$$

(A.5)

Above, $|W_j|^{(k)}$ denotes the $k$-th largest element among $\{|W^e_j|\}_{e \in [E]}$, and

$$p_j = \Psi\left(n_j^- - 1, (E - r + 1 - n_j^0) \vee 0, \frac{1}{2}\right) + U_j \cdot \psi\left(n_j^-, (E - r + 1 - n_j^0) \vee 0, \frac{1}{2}\right),$$

where $\Psi(x, m, \pi)$ is the binomial cumulative distribution function evaluated at $x$, $\psi(x, m, \pi)$ is the corresponding probability mass, and $U_j \sim \text{Uniform}[0,1]$ that is independent of everything else; $n_j^-$ and $n_j^0$ denote the number of negative signs and zeros in the $j$-th column of $W$, respectively. Finally, applying the knockoff filter to the $W_j$’s produces a selected set controlling FDR.

The MEKF procedure is random since it depends on the one-time construction of knockoffs (and the auxiliary $U_j$’s); we can again derandomize it with the assistance of e-values. Specifically, for each $m \in [M]$, we construct the feature importance statistics $W^{(m)}$ as in (A.4) or (A.5) (based on the $m$-th draw of knockoffs, $\mathbf{X}^{(m)}$); define then the stopping time and e-values according to (15) and (14) respectively. For each $j \in [p]$, we aggregate the e-values from different runs by taking their average. The selected set is obtained by applying e-BH to the $e_j$’s. We summarize the complete derandomized MEKF in Algorithm A.2; the following theorem verifies the validity of the derandomized MEKF.

**Theorem A.3.** Consider testing consistent conditional independence hypotheses defined in (A.2) or partial consistent conditional independence hypotheses defined in (A.3) for any $r \in [E]$. For any $\alpha_{\text{kn}}, \alpha_{\text{ebh}} \in (0, 1)$, any number of knockoff copies $M \geq 1$, and any number of environments $E \geq 1$, the selected set offered by Algorithm A.2 satisfies FDR $\leq \alpha_{\text{ebh}}$.

**Proof.** When testing $H_{j}^{\text{est}}$’s, by Theorem 1 of Li et al. (2021), we have for any $m \in [M]$ that $\sum_{j \in H_0} \mathbb{E}[e_j^{(m)}] \leq p$. When testing $H_{j}^{\text{est}, r}$’s, by Proposition 7 of Li et al. (2021), we have for any $m \in [M]$ that $\sum_{j \in H_0} \mathbb{E}[e_j^{(m)}] \leq p$. In either case, by the linearity of expectation, $\sum_{j \in H_0} \mathbb{E}[e_j^{\text{avg}}] \leq p$. Applying Theorem 2 completes the proof.

### A.4. Knockoffs with side information

Imagine a situation where each hypothesis $H_j$ is associated with some prior/side information $u_j \in \mathbb{R}^r$. For example, in a genome-wide association study (GWAS), $H_j$ corresponds to the association between genetic variant $j$ and the response; $u_j$ can be the prior knowledge of this genetic variant a scientist has from previous related work. For structured hypothesis testing, $u_j$ can be the physical location corresponding to the hypothesis, and scientists know a priori that signals are sparse/clustered. In these examples, incorporating prior information in the multiple testing procedure can potentially boost the detecting power.
Input: Data \((X, Y)\); parameters \(\alpha_{\text{ebh}}, \alpha_{\text{kn}} \in (0, 1)\) and \(M \in \mathbb{N}_+\).

1: for \(m = 1, \ldots, M\) do
2:   Construct the knockoff copy \(\tilde{X}^{(e,m)}\) for all \(e \in [E]\).
3:   Compute the multi-environment feature importance statistics: \(W^{(m)} = \mathcal{W}(X, \tilde{X}^{(m)}), Y)\).
4: Transform the multi-environment feature importance statistics \(W^{(m)}\) into the feature importance statistics \(W_j^{(m)}\) according to (A.4) when testing \(H_j^{\text{res}}\)'s or to (A.5) when testing \(H_j^{\text{res}}\)'s.
5: Compute the stopping time \(T^{(m)}\) according to (15).
6: Compute the e-value \(e_j^{(m)}\) according to (14), for all \(j \in [p]\).
7: end for
8: Compute the average e-value \(e_j^{\text{avg}} = \frac{1}{M} \sum_{m=1}^{M} e_j^{(m)}\) for each \(j \in [p]\).
9: Compute \(\hat{k} = \max \{k : e_j^{\text{avg}} \geq p/(\alpha_{\text{ebh}}k)\}\), or \(k = 0\) if this set is empty.

Output: The selected set of discoveries \(S_{\text{kn-derand}} := \{j \in [p] : e_j^{\text{avg}} \geq p/(\alpha_{\text{ebh}}\hat{k})\}\).

Consider first a special case where \(u_j \in \mathbb{R}_+\) reflects the possibility of \(j\) being a non-null (a higher value suggests an increased chance). We explicitly make use of \(u_j\) when constructing the e-values: for each \(j \in [p]\) and \(m \in [M]\), define

\[
e_j^{(m)} := \frac{pu_j \cdot \mathbb{I}\{W_j^{(m)} \geq T^{(m)}\}}{u_j + \sum_{k \in [p]} u_k \cdot \mathbb{I}\{W_k^{(m)} \leq -T^{(m)}\}}, \tag{A.6}
\]

and aggregate the e-values across \(m \in [M]\) by taking their average. We then apply e-BH to the newly defined e-values and obtain a selected set of discoveries. Intuitively, a large value of \(u_j\) can boost the e-value of hypothesis \(j\), thereby increasing the chance of selecting \(j\) and improving the power of our procedure. We refer to this weight-assisted multiple testing procedure the \textit{weighted version} of derandomized knockoffs with side information.

Alternatively, we may have side information \(u_j\) that is of higher dimensions, or it may not be explicit how the side information helps selection (it needs to be learned from the data). We can apply the adaptive knockoff procedure (Ren and Candès, 2020) and similarly aggregate the e-values associated with different knockoff copies. Concretely, the adaptive knockoffs procedure generates knockoffs and computes feature importance statistics as in the original knockoffs procedure; it then sequentially screens the hypotheses in an order determined by the side information and the partially masked feature importance statistics. At each step \(k \in \{0, 1, \ldots, p\}\), let \(P(k)\) denote the set of unscreened features (there are in all \(p - k\) of them) with positive feature importance statistics and \(N(k)\) those with negative feature importance statistics. Define

\[
T = \inf \left\{k \in \{0, 1, \ldots, p\} : \frac{1 + |N(k)|}{|P(k)|} \leq \alpha_{\text{kn}}\right\}, \tag{A.7}
\]

and the selected set of adaptive knockoffs is \(P(T)\). When there are \(M\) knockoff runs, we define for any \(m \in [M]\) correspondingly the set of unscreened features with positive \(W_j\)'s to be \(P_m(k)\), the set of those with negative \(W_j\)'s to be \(N_m(k)\), and the stopping time to be \(T^{(m)}\). The e-value for this \(m\) and \(j\) can be constructed as

\[
e_j^{(m)} = \frac{p \cdot \mathbb{I}\{j \in P_m(T^{(m)})\}}{1 + |N_m(T^{(m)})|}, \tag{A.8}
\]
Observe that when \( W \) side information. As such, it remains interesting to investigate the pros and cons of these two
versions in different scenarios.

The complete procedure of both versions for derandomized knockoffs with side information is
summarized in Algorithm A.3. The following theorem establishes the validity of both versions.

**Theorem A.4.** For any \( \alpha_{\text{kn}}, \alpha_{\text{ebh}} \in (0, 1) \), any number of knockoff copies \( M \geq 1 \), and
any fixed side information \( u \in \mathbb{R}_+^p \), the selected set offered by both versions described in Algo-

The proof of Theorem A.4 can be found in Appendix B.2. Intuitively, the weighted version makes explicit use of the side information but only applies in a special case; on the other hand, the adaptive version is more general, but need to pay the price of learning when utilizing the
side information. As such, it remains interesting to investigate the pros and cons of these two
versions in different scenarios.

**Algorithm A.3** Derandomized knockoffs with side information

**Input:** Data \((X, Y)\); parameters \( \alpha_{\text{ebh}}, \alpha_{\text{kn}} \in (0, 1) \), \( M \in \mathbb{N}_+ \) and \( u \in \mathbb{R}_+^p \).

1: for \( m = 1, \ldots, M \) do
2: Sample the knockoff copy \( \tilde{X}^{(m)} \).
3: Compute the feature importance statistics: \( W^{(m)} = W([X, \tilde{X}^{(m)}], Y) \).
4: Weighted version: compute the stopping time \( T^{(m)} \) according to (15), and the e-values
   according to (A.6).
   Adaptive version: compute the stopping time \( T^{(m)} \) according to (A.7), and the e-values
   according to (A.8).
5: end for
6: Compute the average e-value \( e_{j}^{\text{avg}} = \frac{1}{M} \sum_{m=1}^{M} e_{j}^{(m)} \) for each \( j \in [p] \).
7: Compute \( \hat{k} = \max \{ k : e_{j}^{\text{avg}} \geq p/(\alpha_{\text{ebh}} k) \} \), or \( \hat{k} = 0 \) if this set is empty.

**Output:** The selected set of discoveries \( S^{\text{kn-derand}} := \{ j \in [p] : e_{j}^{\text{avg}} \geq p/(\alpha_{\text{ebh}} \hat{k}) \} \).

**B. Proofs for Section A**

**B.1. Proof of Theorem A.2**

Fix \( m \in [M] \). For any \( j \in \mathcal{H}_0 \), we additionally define the “masked” feature importance statistics
\( W^{(m, j)} = (W^{(m, j)}_1, \ldots, W^{(m, j)}_p) \), and the stopping time induced by \( W^{(m, j)} \) as

\[
T^{(m,j)} = \inf \left\{ t > 0 : \frac{1 + \sum_{k \in [p]} I \{ W_k^{(m,j)} \leq \ell \}}{\sum_{\ell \in [p]} I \{ W_{\ell}^{(m,j)} \geq \ell \}} \leq \alpha_{\text{kn}} \right\}.
\]

Observe that when \( W_j^{(m)} \geq 0 \), it holds that \( T^{(m)} = T^{(m,j)} \). Consequently,

\[
\mathbb{E}[e_j^{(m)} \cdot I \{ \hat{\text{KL}}_{\ell}^{\text{max}} \leq \varepsilon \} \mid W^{(m,j)}] = p \cdot \mathbb{E}\left[ I \{ W_j^{(m)} \geq T^{(m,j)}, \hat{\text{KL}}_{\ell}^{\text{max}} \leq \varepsilon \} \mid W^{(m,j)} \right] \]

\[
= p \cdot \mathbb{E}\left[ I \{ W_j^{(m)} \geq T^{(m,j)}, \hat{\text{KL}}_{\ell}^{\text{max}} \leq \varepsilon \} \right] \frac{1}{1 + \sum_{k \neq j} I \{ W_k^{(m)} \leq -T^{(m,j)} \}} \cdot P(W_j^{(m)} > 0, \hat{\text{KL}}_{\ell}^{\text{max}} \leq \varepsilon \mid W^{(m,j)}),
\]

\[
\mathbb{E}[e_j^{(m)} \cdot I \{ W_j^{(m)} \geq T^{(m,j)} \}] \leq p \cdot \frac{1}{1 + \sum_{k \neq j} I \{ W_k^{(m)} \leq -T^{(m,j)} \}} \cdot P(W_j^{(m)} > 0, \hat{\text{KL}}_{\ell}^{\text{max}} \leq \varepsilon \mid W^{(m,j)}),
\]
where step (a) follows from the fact that $T^{(m, j)}$ is a function of $W^{(m, j)}$. Define now $\{X_j^{(m,+)}, X_j^{(m,-)}\}$ the unordered set of $(X_j, \tilde{X}_j^{(m)})$ such that when $X_j = X_j^{(m,+)}$ and $\tilde{X}_j^{(m)} = X_j^{(m,-)}$, $W_j > 0$ and vice versa. Let

$$
\rho_j^{(m)} = \sum_{i=1}^{n} \log \left( \frac{P_j(X_{ij}^{(m,+)} | X_i, j)}{Q_j(X_{ij}^{(m,+)} | X_i, j)}, \frac{Q_j(X_{ij}^{(m,-)} | X_i, j)}{P_j(X_{ij}^{(m,-)} | X_i, j)} \right).
$$

Then

$$
P(W_j^{(m)} > 0, \tilde{KL}_j^{\max} \leq \varepsilon | \{X_j^{(m,+)}, X_j^{(m,-)}\}, X_{-j}, \tilde{X}_j^{(m)}, Y) \leq P(W_j^{(m)} > 0, \tilde{KL}_j^{(m)} \leq \varepsilon | \{X_j^{(m,+)}, X_j^{(m,-)}\}, X_{-j}, \tilde{X}_j^{(m)}, Y)
$$

$$= P(X_j = X_j^{(m,+)}, \tilde{X}_j = X_j^{(m,-)}, \rho_j^{(m)} \leq \varepsilon | \{X_j^{(m,+)}, \tilde{X}_j^{(m,-)}\}, X_{-j}, \tilde{X}_j^{(m)}, Y)
$$

$$\overset{(a)}{=} e^{\rho_j^{(m)} - \varepsilon} \cdot 1\{\rho_j^{(m)} \leq \varepsilon\} \cdot P(X_j = X_j^{(m,+)}, \tilde{X}_j = X_j^{(m,+)} | \{X_j^{(m,+)}, \tilde{X}_j^{(m,-)}\}, X_{-j}, \tilde{X}_j^{(m)}, Y)
$$

$$\leq e^{\varepsilon} \cdot P(W_j^{(m)} < 0 | \{X_j^{(m,+)}, \tilde{X}_j^{(m,-)}\}, X_{-j}, \tilde{X}_j^{(m)}, Y),$$

where step (a) follows from Lemma 1 of Barber et al. (2020). Next, we shall make use of the following lemma that connects $T^{(m, j)}$ to $T^{(m, \ell)}$, whose proof is exactly the same as Lemma 6 of Barber et al. (2020), so we omit the proof here.

**Lemma B.1.** For any $j, \ell$, if $W_j^{(m)} \leq -\min(T^{(m, j)}, T^{(m, \ell)})$ and $W_{\ell}^{(m)} \leq -\min(T^{(m, j)}, T^{(m, \ell)})$, then $T^{(m, j)} = T^{(m, \ell)}$.

Using the above and the tower property, we have

$$
E[e_j^{(m)} \cdot 1\{\tilde{KL}_j^{\max} \leq \varepsilon\}] \leq p \cdot e^{\varepsilon} \cdot E\left[ 1\{W_j^{(m)} \leq -T_j^{(m)}\} \cdot \frac{1}{1 + \sum_{k \neq j} 1\{W_k^{(m)} \leq -T_k^{(m)}\}} \right] = p \cdot e^{\varepsilon} \cdot E\left[ 1\{W_j^{(m)} \leq -T_j^{(m)}\} \cdot \frac{1}{1 + \sum_{k \neq j} 1\{W_k^{(m)} \leq -T_k^{(m)}\}} \right].
$$

The last equality is due to Lemma B.1. Summing over $m \in [M]$ and $j \in \mathcal{H}_0$, we have

$$
\sum_{j \in \mathcal{H}_0} E[e_j^{avg} \cdot 1\{\tilde{KL}_j^{\max} \leq \varepsilon\}] = \frac{1}{M} \sum_{j \in \mathcal{H}_0} \sum_{m=1}^{M} E[e_j^{(m)} \cdot 1\{\tilde{KL}_j^{\max} \leq \varepsilon\}] \leq \frac{P}{M} \sum_{m=1}^{M} e^{\varepsilon} \cdot E\left[ 1\{W_j^{(m)} \leq -T_j^{(m)}\} \cdot \frac{1}{1 + \sum_{k \neq j} 1\{W_k^{(m)} \leq -T_k^{(m)}\}} \right] \leq p \cdot e^{\varepsilon}.
$$
Finally,

\[
\mathbb{E}\left[\left\{ j : j \in \mathcal{S}_{\text{ebh}} \cap \mathcal{H}_0, \hat{K}_{L,j}^{\max} \leq \varepsilon \right\}\right] = \sum_{j \in \mathcal{H}_0} \mathbb{E}\left[\mathbb{1}\left\{ e_j^{av} \geq \frac{p}{\alpha|\mathcal{S}_{\text{ebh}}|} \cdot \mathbb{1}\{ \hat{K}_{L,j}^{\max} \leq \varepsilon \}\right\}\right]
\]

\[
= \sum_{j \in \mathcal{H}_0} \sum_{k=1}^{p} \mathbb{E}\left[\mathbb{1}\left\{ e_j^{av} \geq \frac{p}{\alpha k} \cdot |\mathcal{S}_{\text{ebh}}| = k \right\} \cdot \mathbb{1}\{ \hat{K}_{L,j}^{\max} \leq \varepsilon \}\right]
\]

\[
\leq \frac{1}{p} \sum_{j \in \mathcal{H}_0} \sum_{k=1}^{p} \mathbb{E}\left[e_j^{av} \cdot \mathbb{1}\{ |\mathcal{S}_{\text{ebh}}| = k \} \cdot \mathbb{1}\{ \hat{K}_{L,j}^{\max} \leq \varepsilon \}\right]
\]

\[
\leq \frac{1}{p} \sum_{j \in \mathcal{H}_0} \mathbb{E}\left[e_j^{av} \cdot \mathbb{1}\{ \hat{K}_{L,j}^{\max} \leq \varepsilon \}\right]
\]

\[
\leq \varepsilon^{2} \cdot \alpha,
\]

completing the proof.

### B.2. Proof of Theorem A.4

By Theorem 2, for both versions of the algorithm it suffices to check that the \( e_j \)'s satisfy the relaxed e-value condition (9).

**Weighted version** We continue using the notation for masked feature importance statistics and the corresponding stopping time. For any \( m \in [M], j \in \mathcal{H}_0 \) and the e-value defined in (A.6), we have

\[
e_j^{(m)} = \frac{p u_j \cdot \mathbb{1}\{ W_j^{(m)} \geq T^{(m)} \}}{u_j + \sum_{\ell \neq j} u_\ell \cdot \mathbb{1}\{ W_\ell^{(m)} \leq -T^{(m)} \}} = \frac{p u_j \cdot \mathbb{1}\{ W_j^{(m)} \geq T^{(m,j)} \}}{u_j + \sum_{\ell \neq j} u_\ell \cdot \mathbb{1}\{ W_\ell^{(m)} \leq -T^{(m,j)} \}}
\]

Since \( T^{(m,j)} \) is fully deterministic given \( W^{(m,j)} \), we have

\[
\mathbb{E}[e_j^{(m)} \mid W^{(m,j)}] = \mathbb{P}(W_j^{(m)} > 0 \mid W^{(m,j)}) \cdot \frac{p u_j \cdot \mathbb{1}\{ |W_j^{(m)}| \geq T^{(m,j)} \}}{u_j + \sum_{\ell \neq j} u_\ell \cdot \mathbb{1}\{ W_\ell^{(m)} \leq -T^{(m,j)} \}}
\]

\[\overset{(a)}{=} \mathbb{P}(W_j < 0 \mid W^{(m,j)}) \cdot \frac{p u_j \cdot \mathbb{1}\{ |W_j^{(m)}| \geq -T^{(m,j)} \}}{u_j + \sum_{\ell \neq j} u_\ell \cdot \mathbb{1}\{ W_\ell^{(m)} \leq -T^{(m,j)} \}}
\]

\[= \mathbb{E}\left[ \frac{p u_j \cdot \mathbb{1}\{ W_j^{(m)} \leq -T^{(m,j)} \}}{u_j + \sum_{\ell \neq j} u_\ell \cdot \mathbb{1}\{ W_\ell^{(m)} \leq -T^{(m,j)} \}} \mid W^{(m,j)} \right], \tag{B.1}
\]

where step (a) uses the property of knockoffs that conditional on the magnitudes \( (|W_1|, |W_2|, \ldots, |W_p|) \), the signs of the null \( W_j \)'s are i.i.d. coin flips (c.f. Candès et al. (2018, Lemma 3.3)). By Lemma B.1,

\[
(B.1) = \mathbb{E}\left[ \frac{p u_j \cdot \mathbb{1}\{ W_j^{(m)} \leq -T^{(m,j)} \}}{u_j + \sum_{\ell \neq j} u_\ell \cdot \mathbb{1}\{ W_\ell^{(m)} \leq -T^{(m,j)} \}} \mid W^{(m,j)} \right] = \mathbb{E}\left[ \frac{p u_j \cdot \mathbb{1}\{ W_j^{(m)} \leq -T^{(m,j)} \}}{\sum_{\ell \in [p]} u_\ell \cdot \mathbb{1}\{ W_\ell^{(m)} \leq -T^{(m,j)} \}} \mid W^{(m,j)} \right].
\]

Summing over \( j \in \mathcal{H}_0 \), we have

\[
\sum_{j \in \mathcal{H}_0} \mathbb{E}[e_j^{(m)}] = p \cdot \mathbb{E}\left[ \sum_{j \in \mathcal{H}_0} u_j \cdot \mathbb{1}\{ W_j^{(m)} \leq -T^{(m,j)} \} \right] \leq p \cdot \mathbb{E}\left[ \sum_{j \in \mathcal{H}_0} u_j \cdot \mathbb{1}\{ W_j \leq -T^{(m,j)} \} \right] = p.
\]
We then average over \( m \in [M] \) and obtain that
\[
\sum_{j \in H_0} \mathbb{E}[e^\text{avg}_j] = \sum_{j \in H_0} \mathbb{E}\left[ \frac{1}{M} \sum_{m=1}^M e_j^{(m)} \right] = \frac{1}{M} \sum_{m=1}^M \sum_{j \in H_0} \mathbb{E}[e_j^{(m)}] \leq p.
\]

**Adaptive version**  
For any \( m \in [M] \) and the e-value defined in (A.8),
\[
\sum_{j \in H_0} \mathbb{E}[e_j^{(m)}] = p \cdot \sum_{j \in H_0} \mathbb{E}\left[ \frac{\mathbb{1}\{j \in P_m(T^{(m)})\}}{1 + |N_m(T^{(m)})|} \right] \leq p \cdot \mathbb{E}\left[ \frac{\mathbb{1}\{j \in H_0, j \in P_m(T^{(m)})\}}{1 + \{\mathbb{1}\{j \in H_0, j \in N_m(T^{(m)})\}\}} \right] \leq p,
\]
where the last inequality follows from Theorem 1 of Ren and Candès (2020). We then have \( \sum_{j \in H_0} \mathbb{E}[e^\text{avg}_j] \leq p \) by linearity of expected value.

### C. Additional simulations

In this section, we collect results from additional simulations to evaluate our proposed method under a variety of scenarios.

#### C.1. The effect of \( c \) and \( \alpha_{kn} \)

Under the two simulation settings in Section 4, we additionally investigate the joint effect of \( c \) and \( \alpha_{kn} \) on the performance of derandomized knockoffs. Here, we consider \( \alpha_{ehb} = 0.1 \) and 0.2; for the former choice, we let \( \alpha_{kn} \) range in \( \{0.01, 0.02, \ldots, 0.2\} \) and in \( \{0.02, 0.04, \ldots, 0.4\} \) for the latter. In both cases, \( c \in \{0.1, 0.2, \ldots, 2\} \). Figure C.1 and C.2 are heatmaps of the proposed procedure’s power resulting from different choices of \((c, \alpha_{kn})\) with \( \alpha_{ehb} = 0.1 \) and \( \alpha_{ehb} = 0.2 \), respectively. Figure C.3 further plots the power and FDR as functions of \( \alpha_{kn} \) when \( \alpha_{ehb} = 0.2 \). In all cases, we observe that derandomized knockoffs consistently performs well with the choice \( c = 1 \) and \( \alpha_{kn} = \alpha_{ehb}/2 \), justifying our intuition that \( \alpha_{kn} = \alpha_{ehb}/2 \) is a good default choice.

---

**Fig. C.1.** Heatmaps of the power of derandomized knockoffs with different choices of \((c, \alpha_{kn})\). The left, middle and right columns correspond to low, medium and high signal amplitude, respectively. A darker color represents a higher value. In these experiments, we set \( \alpha_{ehb} = 0.1 \), and we observe that power is consistently high around \( \alpha_{kn} = 0.05 \), justifying our intuition that \( \alpha_{kn} = \alpha_{ehb}/2 \) is a good default setting.
C.2. A high-dimensional setting

Consider \( n = 800 \) samples and \( p = 1000 \) features, with \( |H_0| = 100 \). The marginal distribution of the features \( P_X = \mathcal{N}(0, \Sigma) \) where \( \Sigma_{jk} = 0.5^{j-k} \) for all \( j, k \in [p] \). The model of \( Y \mid X \) is the same Gaussian linear model as in Section 4; the coefficient vector \( \beta \) is given by

\[
\beta = \left( 0, \ldots, 0, \frac{\bar{\beta}_1}{\sqrt{n}}, 0, \ldots, 0, \frac{\bar{\beta}_2}{\sqrt{n}}, \ldots, 0, \ldots, 0, \frac{\bar{\beta}_{99}}{\sqrt{n}}, 0, \ldots, 0, -\frac{\bar{\beta}_{100}}{\sqrt{n}} \right),
\]

where as before \( \bar{\beta} \) is sampled from \( \mathcal{N}(A, I_{100}) \) and fixed throughout the trials. The signal amplitude \( A \) ranges in \( \{4, 5, 6, 7, 8, 9\} \), and the implementation of original and derandomized knockoffs is the same as that in Section 4. Figure C.4 and C.5 present the results under the high-dimensional setting, where we see a similar pattern: derandomized knockoffs exhibits comparable (or even slightly higher) power when the signal strength is moderately strong, while there is some power loss in the weak-signal regime. Derandomized knockoffs achieves lower FDR, and decreased variability (especially for the conditional variability). When we compare the marginal and conditional selection probability of individual hypotheses by both methods, we can also observe that the original knockoffs tends to have a higher selection probability for the null features that are rarely selected by the original knockoffs.

C.3. Comparison under simulation settings in Candès et al. (2018)

We now compare our proposed method with the original knockoffs method under two simulation settings considered in Candès et al. (2018). In both settings, there are \( n = 3000 \) samples. For the low-dimensional setting, there are \( p = 1000 \) features and in the high-dimensional setting, \( p = 6000 \). The marginal distribution of the features is \( P_X = \mathcal{N}(0, I_p) \) and the model \( Y \mid X \) is the same Gaussian linear model as in Section 4, where the coefficient vector \( \beta \) contains 60 nonzero entries whose location and signs are randomly determined and fixed throughout the trials. The nonzero entries all have the same magnitude \( \frac{A}{\sqrt{n}} \), where \( A \in \{2, 3, 4, 5\} \) in the low-dimensional setting and \( A \in \{3, 4, 5, 6\} \) in the high-dimensional one. The implementation of original and
Fig. C.3. Realized power (left) and FDR (right) of derandomized knockoffs as a function of the parameter $\alpha_{kn}$ for the simulation data experiments. The target FDR level $\alpha_{ebh} = 0.2$. The details are otherwise the same as in Figure 1.

Fig. C.4. Power, FDR, and selection variability, for the high-dimensional simulated data experiment. The other details are the same as in Figure 2.

derandomized knockoffs is the same as in Section 4, and that of original knockoffs also coincides with Candès et al. (2018), except that Candès et al. (2018) use a selection threshold slightly different from (5) and is designed for controlling a relaxed version of FDR.

Figure C.6 shows the power and FDR of the two methods under the two settings. We again see that derandomized knockoffs exhibits comparable power as original knockoffs when the signals are reasonably strong, and there is some power loss in the weak-signal regime. The realized FDR of derandomized knockoffs is consistently lower than that of original knockoffs.

C.4. Comparison with the derandomization scheme of Ren et al. (2021)

As discussed earlier, Ren et al. (2021) propose a scheme for derandomizing the knockoffs by thresholding the (unweighted) selection frequency. The algorithm proposed there is designed for the purpose of per family-wise error (PFER) control; it is nevertheless of interest to compare the two methods empirically. Hereafter, we refer to the method of Ren et al. (2021) as the PFER version, and the method proposed in this paper the FDR version. We compare the two methods under the Gaussian linear model defined in Section 4. For both methods, we generate $M = 50$ knockoff copies given the dataset $(X, Y)$. In the $m$-th run of the PFER version, we generate a knockoff copy $\tilde{X}^{(m)}$ and compute the feature importance statistics $W^{(m)} = W([X, \tilde{X}^{(m)}], Y)$.
Derandomized knockoffs

Fig. C.5. Top: the marginal selection probability $\hat{p}_j$ by original knockoffs versus that by derandomized knockoffs. Bottom: the conditional selection probability $\hat{p}_{j,1}$ by original knockoffs versus that by derandomized knockoffs. The results are from simulations under the high-dimensional setting. The details are otherwise the same as in Figure 3.

as in the FDR version. We then apply the filter of Janson and Su (2016) (designed for the PFER control) to $W^{(m)}$ with a sequence of parameters $v \in \mathcal{V} := \{1, 2, 3, 4\}$. Here, the parameter $v$ suggests the target PFER level the filter controls (i.e., $E[\left|S^{(m)} \cap \mathcal{H}_0\right|] \leq v$), and with each $v$, we obtain a selected set $\hat{S}^{(v,m)}$. Next, we compute $\Pi_j^{(v)} = \frac{1}{M} \sum_{m=1}^M 1\{j \in \hat{S}^{(v,m)}\}$ for all $v \in \mathcal{V}$ and $j \in [p]$. Finally, the set of discoveries corresponding to a parameter $v$ is given by $\hat{S}^{(v)} = \{j : \Pi_j^{(v)} \geq 0.5\}$. For each $v$, the aggregated selected set $\hat{S}^{(v)}$ has PFER controlled at level $2v$, but is not guaranteed to control the FDR; in order to compare it with our proposed method, we compute the realized power and the realized FDR of these selected sets, plotting the power as a function of the FDR (i.e., the ROC curve) in Figure C.7. We implement the derandomized knockoffs in the same way as in Section 4, where we take $\alpha_{ebh} = 0.05$ and $\alpha_{kn} = 0.05$. The realized power and FDR of the derandomized knockoffs is marked as a rectangle in Figure C.7. We can see from the figures that at the same level of realized FDR, the FDR version (i.e., the derandomized procedure proposed in our present work) achieves comparable power with the previous version of Ren et al. (2021).

C.5. Robustness to the estimation error of $P_X$

We empirically evaluate the robustness of the derandomized knockoffs procedure. In this experiment, $n = 600$ and $p = 100$; the covariate distribution $P_X = N(0, \Sigma)$, where $\Sigma_{ij} = 0.5^{|i-j|}$, $Y \mid X$ follows a Gaussian linear model, with the coefficient vector being

$$\beta = \left(\frac{A}{\sqrt{n}}, 0, -\frac{A}{\sqrt{n}}, 0, \ldots\right),$$

and $A \in \{4.5, 5, 5.5, 6, 6.5\}$. The implementation of derandomized knockoffs is the same as in Section 4, except that now we assume no knowledge of covariance matrix $\Sigma$; instead, to estimate $\Sigma$, we are given an additional $n_0$ many unlabeled samples (i.e., we observe $X$ but do not observe $Y$). We construct knockoffs with $Q_X = N(0, \bar{\Sigma})$, where $\bar{\Sigma}$ is the sample covariance matrix computed with the $n_0$ unlabeled samples; we then apply the original knockoffs and derandomized
knockoffs, where the derandomized version is implemented according to Algorithm 1 with the same parameters used in Section 4. Figure C.8 describes the realized power and FDR achieved by the original knockoffs and the proposed method under the Gaussian linear model setting. In particular, the covariance matrix is estimated with \( n_0 \in \{600, 700, 800, 900, 1000\} \). Here, we observe the FDR to be controlled at the desired level for both methods, with lower FDR for derandomized knockoffs as before. Derandomized knockoffs shows power that is comparable to the original method across most settings, although the power is lower in one setting (the smallest value of \( n_0 \), where the estimated distribution of \( X \) is most unreliable).

C.6. A multiple-environment setting

We evaluate the performance of the algorithm proposed in Section A.3 in a multi-environment simulation setting. Suppose \( p = 100 \), and there are two environments. In environment \( e \in [2] \), we assume \( X^e \sim \mathcal{N}(0, \Sigma) \), where \( \Sigma_{jk} = 0.5^{|j-k|} \) for all \( j, k \in [p] \); the response follows from a environment-specific linear model: \( Y^e \sim \mathcal{N}((X^e)^T \beta^{(e)}, \Sigma) \), where \( \beta^{(e)} \) is the coefficient vector.
We construct the coefficient vectors as:

$$\beta^{(1)} = \left( \frac{A}{\sqrt{n}}, \frac{A}{\sqrt{n}}, \ldots, \frac{A}{\sqrt{n}}, 0, \ldots, 0 \right), \quad \beta^{(2)} = \left( \frac{A}{\sqrt{n}}, \frac{A}{\sqrt{n}}, \ldots, \frac{A}{\sqrt{n}}, 0, \ldots, 0 \right),$$

and the signal amplitude $A$ ranges in $\{3, 3.5, 4, 4.5, 5, 5.5\}$. Here, $\{1, 2, \ldots, 50\}$ is the set of nonnulls, and the FDR target is 0.1. We implement MEKF with the code from https://github.com/lsn235711/MEKF_code, where the empirical prior is used when constructing the multi-environment feature importance statistics. The derandomized MEKF is implemented with the same details, and we take $\alpha_{ehb} = 0.1$ and $\alpha_{kn} = 0.05$. Figure C.9 shows the power and FDR resulting from MEKF and the derandomized MEKF in this simulated setting—the derandomized version shows higher power and lower FDR.
C.7. Side information

We set up an experiment to illustrate how side information can help improve the power of derandomized knockoffs. The simulation setting is the same as the Gaussian linear model in Section C.5 with a few changes. Here, we assume known $\Sigma$, and $A \in \{3,3.5,4,4.5,5,5.5\}$; the nonnulls are placed on $\{1,2,\ldots,50\}$ while the remaining features $\{51,\ldots,100\}$ are null (the index hence carries information, with lower values of $j$ corresponding to signals). We apply the weighted version of derandomized knockoffs with side information, using $u_j = \exp(-j)$. The other implementation details are exactly the same as in Section 4. Figure C.10 plots the power and FDR from the original knockoffs, derandomized knockoffs, and the weighted version of derandomized knockoffs with side information. Clearly, the weighted version achieves a significantly higher power by incorporating side information, while still controlling FDR.

![Fig. C.10. Power and FDR, for the simulated experiments with side information. The other details are the same as in Figure 2.](image)

D. Additional results from the analysis of the HIV dataset

For the HIV dataset, over 50 independent runs of both methods, the average number of discoveries made by the derandomized knockoffs procedure is 63.5, and the average number of discoveries made by the original knockoffs is 77.0. As we have observed in the simulations, the derandomized knockoffs procedure often shows a lower FDR while achieving comparable power with the original knockoffs—in other words, the original knockoffs would often make more (false) discoveries to achieve the same detecting power as the derandomized knockoffs. To examine whether this may be the case in our real data example as well, we compare the discoveries made by both methods with the reference found at [https://hivdb.stanford.edu/dr-summary/comments/PI/](https://hivdb.stanford.edu/dr-summary/comments/PI/). To be specific, for each method we take the set of mutations selected for more than half of the times; this results in a set of 63 discoveries for the derandomized knockoffs, and a set of 74 discoveries for the original version (which includes all 63 of the discoveries made by derandomized knockoffs).

Table D.1 contains a complete list of the 63 mutations selected in at least 50% of the runs of the derandomized knockoffs procedure, and Table D.2 shows the list of the 74 mutations selected in at least 50% of the runs of the original knockoffs procedure. In each table, the column “Annotation” contains the comments on the corresponding mutations from the reference, where “Major”, “Accessory” and “Other” refer to major effect, accessory effect and other effect on the drug resistance to PI (i.e., the discovery is confirmed); “NA” means no comments are found from the reference. We say a mutation is “verified” by the reference if the annotation is not “NA”. For derandomized knockoffs, Out of the 63 discoveries, 38 mutations are verified. For original knockoffs, out of the 74 discoveries, 39 are verified. We thus see approximately the same number of verified mutations made by the two methods, even though the original knockoffs
Table D.1. The complete list of mutations discovered by derandomized knockoffs at FDR level 0.1. The annotation is the reported effect from https://hivdb.stanford.edu/dr-summary/comments/PI/.

| Mutation | Annotation | Mutation | Annotation |
|----------|------------|----------|------------|
| 6W       | NA         | 54M      | Major      |
| 10F      | Accessory  | 54S      | Major      |
| 10I      | Other      | 54T      | Major      |
| 10L      | NA         | 54V      | Major      |
| 10V      | Other      | 58E      | Accessory  |
| 12P      | NA         | 61D      | NA         |
| 14R      | NA         | 62V      | NA         |
| 16A      | NA         | 63P      | NA         |
| 20F      | Other      | 64L      | NA         |
| 20R      | Other      | 69K      | NA         |
| 20T      | Accessory  | 71A      | NA         |
| 20V      | Other      | 71T      | Other      |
| 22V      | NA         | 71V      | Other      |
| 24I      | Accessory  | 72L      | NA         |
| 32I      | Major      | 73T      | Accessory  |
| 33F      | Accessory  | 76V      | Major      |
| 33L      | NA         | 77I      | NA         |
| 34Q      | NA         | 82A      | Major      |
| 36I      | NA         | 82F      | Major      |
| 36L      | NA         | 82S      | Major      |
| 36M      | NA         | 82T      | Major      |
| 37Q      | NA         | 84A      | Major      |
| 43T      | Accessory  | 84V      | Major      |
| 46I      | Major      | 88D      | Accessory  |
| 46L      | Major      | 89I      | NA         |
| 47V      | Major      | 89V      | Accessory  |
| 48M      | Major      | 90M      | Major      |
| 48V      | Major      | 92K      | NA         |
| 50L      | Major      | 92Q      | NA         |
| 50V      | Major      | 93I      | NA         |
| 53L      | Accessory  | 95F      | NA         |
| 54L      | Accessory  |           |            |

Method makes substantially more discoveries overall—this can be viewed as evidence that the derandomized knockoffs procedure maintains comparable detection power while decreasing FDR and decreasing variability.
Table D.2. The complete list of mutations selected for more than 50% times (out of 50 independent runs) by the original knockoffs procedure at FDR level 0.1. The annotation is the reported effect from https://hivdb.stanford.edu/dr-summary/comments/PI/.

| Mutation | Annotation |
|----------|------------|
| 6W       | NA         |
| 10F      | Accessory  |
| 10I      | Other      |
| 10L      | NA         |
| 10V      | Other      |
| 12P      | NA         |
| 14R      | NA         |
| 16A      | NA         |
| 20I      | Other      |
| 20K      | NA         |
| 20R      | Other      |
| 20T      | Accessory  |
| 20V      | Other      |
| 22V      | NA         |
| 24I      | Accessory  |
| 32I      | Major      |
| 33F      | Accessory  |
| 33L      | NA         |
| 34Q      | NA         |
| 35D      | NA         |
| 36I      | NA         |
| 36L      | NA         |
| 36M      | NA         |
| 37Q      | NA         |
| 39Q      | NA         |
| 43T      | Accessory  |
| 46I      | Major      |
| 46L      | Major      |
| 47V      | Major      |
| 48M      | Major      |
| 48V      | Major      |
| 50L      | Major      |
| 50V      | Major      |
| 53L      | Accessory  |
| 54L      | Major      |
| 54M      | Major      |
| 54S      | Major      |

| Mutation | Annotation |
|----------|------------|
| 54T      | Major      |
| 54V      | Major      |
| 58E      | Accessory  |
| 61D      | NA         |
| 61E      | NA         |
| 62V      | NA         |
| 63P      | NA         |
| 64L      | NA         |
| 67C      | NA         |
| 67E      | NA         |
| 67Y      | NA         |
| 69K      | NA         |
| 71A      | NA         |
| 71I      | Other      |
| 71T      | Other      |
| 71V      | Other      |
| 72L      | NA         |
| 72M      | NA         |
| 73T      | Accessory  |
| 76V      | Major      |
| 77I      | NA         |
| 82A      | Major      |
| 82F      | Major      |
| 82S      | Major      |
| 82T      | Major      |
| 84A      | Major      |
| 84V      | Major      |
| 88D      | Accessory  |
| 89I      | NA         |
| 89V      | Accessory  |
| 90M      | Major      |
| 91S      | NA         |
| 92K      | NA         |
| 92Q      | NA         |
| 93I      | NA         |
| 93L      | NA         |
| 95F      | NA         |
References

Barber, R. F. and Candès, E. J. (2015) Controlling the false discovery rate via knockoffs. The Annals of Statistics, 43, 2055–2085.

Barber, R. F., Candès, E. J. and Samworth, R. J. (2020) Robust inference with knockoffs. The Annals of Statistics, 48, 1409–1431.

Bates, S., Candès, E., Janson, L. and Wang, W. (2021) Metropolized knockoff sampling. Journal of the American Statistical Association, 116, 1413–1427.

Benjamini, Y. and Hochberg, Y. (1995) Controlling the false discovery rate: a practical and powerful approach to multiple testing. Journal of the Royal Statistical Society: Series B (Methodological), 57, 289–300.

Candès, E., Fan, Y., Janson, L. and Lv, J. (2018) Panning for gold: ‘model-x’ knockoffs for high dimensional controlled variable selection. Journal of the Royal Statistical Society: Series B (Statistical Methodology), 80, 551–577.

Dai, C., Lin, B., Xing, X. and Liu, J. S. (2022) False discovery rate control via data splitting. Journal of the American Statistical Association, 1–18.

— (2023) A scale-free approach for false discovery rate control in generalized linear models. Journal of the American Statistical Association, 1–31.

Dai, R. and Barber, R. (2016) The knockoff filter for fdr control in group-sparse and multitask regression. In International conference on machine learning, 1851–1859. PMLR.

Emery, K. and Keich, U. (2019) Controlling the fdr in variable selection via multiple knockoffs. arXiv preprint arXiv:1911.09442.

Gimenez, J. R. and Zou, J. (2019) Improving the stability of the knockoff procedure: Multiple simultaneous knockoffs and entropy maximization. In The 22nd International Conference on Artificial Intelligence and Statistics, 2184–2192. PMLR.

Janson, L. and Su, W. (2016) Familywise error rate control via knockoffs. Electronic Journal of Statistics, 10, 960–975.

Koyuncu, D. and Yener, B. (2022) Missing value knockoffs. arXiv preprint arXiv:2202.13054.

Li, S., Sesia, M., Romano, Y., Candès, E. and Sabatti, C. (2021) Searching for robust associations with a multi-environment knockoff filter. Biometrika.

Liu, H., Roeder, K. and Wasserman, L. (2010) Stability approach to regularization selection (stars) for high dimensional graphical models. Advances in neural information processing systems, 23.

Luo, Y., Fithian, W. and Lei, L. (2022) Improving knockoffs with conditional calibration. arXiv preprint arXiv:2208.09542.

Meinshausen, N. and Bühlmann, P. (2010) Stability selection. Journal of the Royal Statistical Society: Series B (Statistical Methodology), 72, 417–473.

Nguyen, T.-B., Chevalier, J.-A., Thirion, B. and Arlot, S. (2020) Aggregation of multiple knockoffs. In International Conference on Machine Learning, 7283–7293. PMLR.

Patterson, E. and Sesia, M. (2018) knockoff: The knockoff filter for controlled variable selection. R package version 0.3, 2.
Ren, Z. and Candès, E. (2020) Knockoffs with side information. *arXiv preprint arXiv:2001.07835*.

Ren, Z., Wei, Y. and Candès, E. (2021) Derandomizing knockoffs. *Journal of the American Statistical Association*, 1–11.

Rhee, S.-Y., Taylor, J., Wadhera, G., Ben-Hur, A., Brutlag, D. L. and Shafer, R. W. (2006) Genotypic predictors of human immunodeficiency virus type 1 drug resistance. *Proceedings of the National Academy of Sciences*, **103**, 17355–17360.

Romano, Y., Sesia, M. and Candès, E. (2020) Deep knockoffs. *Journal of the American Statistical Association*, **115**, 1861–1872.

Sesia, M., Sabatti, C. and Candès, E. J. (2019) Gene hunting with hidden markov model knockoffs. *Biometrika*, **106**, 1–18.

Shah, R. D. and Samworth, R. J. (2013) Variable selection with error control: another look at stability selection. *Journal of the Royal Statistical Society: Series B (Statistical Methodology)*, **75**, 55–80.

Spector, A. and Janson, L. (2022) Powerful knockoffs via minimizing reconstructability. *The Annals of Statistics*, **50**, 252–276.

Vovk, V. (2020) A note on data splitting with e-values: online appendix to my comment on glenn shafer’s” testing by betting”. *arXiv preprint arXiv:2008.11474*.

Vovk, V. and Wang, R. (2021) E-values: Calibration, combination and applications. *The Annals of Statistics*, **49**, 1736–1754.

Wang, R. and Ramdas, A. (2022) False discovery rate control with e-values. *Journal of the Royal Statistical Society: Series B (Statistical Methodology)*. URL: [https://rss.onlinelibrary.wiley.com/doi/abs/10.1111/rssb.12489](https://rss.onlinelibrary.wiley.com/doi/abs/10.1111/rssb.12489).

Wasserman, L., Ramdas, A. and Balakrishnan, S. (2020) Universal inference. *Proceedings of the National Academy of Sciences*, **117**, 16880–16890.

**List of figure legends**

- Figure 1: Realized power (left) and FDR (right) of derandomized knockoffs as a function of the parameter $\alpha_{kn}$ for the simulation data experiments. The offset parameter $c = 1$. Shading for the power and FDR plots indicates error bars. The target FDR level $\alpha_{ebh} = 0.1$. Results are averaged over 100 independent trials.

- Figure 2: Power, FDR, and selection variability, for the simulated data experiments. Shading for the power and FDR plots indicates error bars. Results are averaged over 100 independent trials.

- Figure 3: Top: the marginal selection probability $\hat{p}_j$ by original knockoffs versus that by derandomized knockoffs. Bottom: the conditional selection probability $\hat{p}_{j,1}$ by original knockoffs versus that by derandomized knockoffs. The results are from simulations under the Gaussian linear model. Each point corresponds to a feature, where the blue ones are non-nulls and the red ones are nulls. For the given dataset, many null features never selected by derandomized knockoffs have large selection probability by the original knockoffs.
• Figure 4: The results are from simulations under the logistic model. The other details are the same as in Figure 4.

• Figure 5: Results for the HIV data experiment. Left: boxplot of the number of discoveries for original and derandomized knockoffs, over 50 independent trials. Right: histogram of the selection probability for each feature \( j \in [p] \), over 50 independent trials, for original and derandomized knockoffs.

• Figure C.1: Heatmaps of the power of derandomized knockoffs with different choices of \( (c, \alpha_{kn}) \). The left, middle and right columns correspond to low, medium and high signal amplitude, respectively. A darker color represents a higher value. In these experiments, we set \( \alpha_{ebh} = 0.1 \), and we observe that power is consistently high around \( \alpha_{kn} = 0.05 \), justifying our intuition that \( \alpha_{kn} = \alpha_{ebh}/2 \) is a good default setting.

• Figure C.2: Heatmaps of the power of derandomized knockoffs with different choices of \( (c, \alpha_{kn}) \). The target FDR level \( \alpha_{ebh} = 0.2 \), and the power is consistently high around \( \alpha_{kn} = 0.1 \). The other details are the same as in Figure C.1.

• Figure C.3: Realized power (left) and FDR (right) of derandomized knockoffs as a function of the parameter \( \alpha_{kn} \) for the simulation data experiments. The target FDR level \( \alpha_{ebh} = 0.2 \). The details are otherwise the same as in Figure 1.

• Figure C.4: Power, FDR, and selection variability, for the high-dimensional simulated data experiment. The other details are the same as in Figure 2.

• Figure C.5: Top: the marginal selection probability \( \hat{p}_j \) by original knockoffs versus that by derandomized knockoffs. Bottom: the conditional selection probability \( \hat{p}_{j,1} \) by original knockoffs versus that by derandomized knockoffs. The results are from simulations under the high-dimensional setting. The details are otherwise the same as in Figure 3.

• Figure C.6: Power and FDR under the low-dimensional simulation setting (top) and the high-dimensional simulation setting (bottom) considered in Candès et al. (2018). Shading indicates error bars, and the results are averaged over 100 independent trials.

• Figure C.7: The dashed line represents the realized power of the PFER version as a function of the realized FDR; the rectangle represents the realized power and FDR resulting from the FDR version (with the target FDR level \( \alpha_{ebh} = 0.1 \)).

• Figure C.8: Power (top) and FDR (bottom), for the Gaussian linear simulation data experiments with estimated \( P_X \). Each panel corresponds to a size of unlabeled data for estimating \( P_X \).

• Figure C.9: Power and FDR, for the multi-environment simulated setting. The other details are the same as in Figure 2.

• Figure C.10: Power and FDR, for the simulated experiments with side information. The other details are the same as in Figure 2.