The Holdout Randomization Test: 
Principled and Easy Black Box Feature Selection

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Abstract

We consider the problem of feature selection using black box predictive models. For example, high-throughput devices in science are routinely used to gather thousands of features for each sample in an experiment. The scientist must then sift through the many candidate features to find explanatory signals in the data, such as which genes are associated with sensitivity to a prospective therapy. Often, predictive models are used for this task: the model is fit, error on held out data is measured, and strong performing models are assumed to have discovered some fundamental properties of the system. A model-specific heuristic is then used to inspect the model parameters and rank important features, with top features reported as “discoveries.” However, such heuristics provide no statistical guarantees and can produce unreliable results. We propose the holdout randomization test (HRT) as a principled approach to feature selection using black box predictive models. The HRT is model agnostic and produces a valid \( p \)-value for each feature, enabling control over the false discovery rate (or Type I error) for any predictive model. Further, the HRT is computationally efficient and, in simulations, has greater power than a competing knockoffs-based approach. Code is available at https://github.com/tansey/hrt.

1 Introduction

We consider the task of selecting the subset of features (\( X \)) that are relevant to an outcome (\( Y \)). Formally, the inferential goal is to conduct a conditional independence test for each feature \( X_j \), with the null hypothesis:

\[
H_0: X_j \perp Y | X_{-j},
\]

where \( X_{-j} \) is every column in the feature matrix \( X \) except \( X_j \). Under \( H_0 \), the feature contains no additional information about \( Y \) that is not contained in the other features. Features where the null hypothesis is rejected are labeled as discoveries (i.e., potential drivers of the observed response). Controlling the rate of false discoveries is crucial to ensuring analysis results are reliable. Yet in many scientific studies, feature selection is performed

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heuristically (e.g. using the lasso), without any statistical guarantees or control over the error rate.

This paper introduces the holdout randomization test (HRT) as a new approach to feature selection. At a high level, the HRT works by repeatedly evaluating a predictive model \( \pi \) on test data. The prediction quality of \( \pi(X) \) is compared to \( \pi(\tilde{X}) \), where \( \tilde{X} \) is a copy of \( X \) that replaces the feature \( X_j \) to be tested with a null sample \( \tilde{X}_j \), that is, one where \( \tilde{X}_j \) is conditionally independent of \( Y \). This null sample is drawn from the complete conditional \( P(X_j|X_{-j}) \), the distribution of the \( j \)th feature given all other features. The complete conditional serves as a valid null model for Eq. (1) by preserving the joint dependency structure of \( P(X) \) and removing any dependency between \( X_j \) and \( Y \). Intuitively, if \( X_j \) actually has predictive power for \( Y \) then replacing it with a null sample \( \tilde{X}_j \) is likely to lead to worse predictions. A \( p \)-value for the hypothesis test is then approximated by repeatedly resampling \( \tilde{X}_j \) and comparing predictive performance under the null with performance using the original data.

The HRT and the predictor are decoupled. The HRT works with any choice of predictor \( \pi \) and returns a valid \( p \)-value for each feature. The scientist does not need to consider the HRT when designing the predictive model, and the HRT does not need any knowledge of the model internals. The scientist is responsible only for constructing a strong predictor, with the understanding that a better model will typically lead to more discoveries. The HRT only needs to be able to query the model for predictions in order to perform feature selection. This decoupling enables the scientist to easily add the HRT to their analysis pipeline, making it a drop-in replacement for heuristic feature selection procedures.

The majority of the paper is dedicated to three aspects of the HRT:

**Power** Any predictive model can be used with the HRT, but empirically its power increases with the quality of the predictor. Scientists can therefore focus on building the best predictive model they can. A better predictor will tend to yield more discoveries.

**Robustness** In practice, the conditional null distribution is unknown and must be estimated from data. The HRT is theoretically robust to estimation errors. Empirically, it produces conservative \( p \)-values when the null distribution is poorly estimated.

**Computational efficiency** The HRT is tailored to machine learning models where prediction is faster than model fitting. In particular, the HRT requires only a single model fit. By only relying on test error, the HRT is computationally less expensive than feature selection methods that rely on model refitting.

1.1 Connections to existing work

Most classical work on feature selection relies on strong parametric assumptions. For instance, the train-test splitting procedure of the HRT resembles the data splitting procedure of Wasserman and Roeder [2009] for high-dimensional feature selection in linear models, with the cross-validation HRT extension (Section 3.2) then mirroring the multiple re-splitting extension of Meinshausen et al. [2009]. However, the HRT is focused on the case where no simple parametric model is assumed. A flurry of recent techniques have been proposed to extract information from such black box predictive models. We contextualize the HRT in relation to these methods.
Many approaches are model-specific. Examples include iterative random forests [Basu et al., 2018], Bayesian kernel regression [Crawford et al., 2018], and Bayesian neural networks [Liang et al., 2018]. These approaches constrain the scientist to a specific modeling choice, rather than allowing the scientist to choose the best model or build a custom one specific for their problem. An advantage of the HRT is that it maximizes the freedom of the scientist to build the best predictive model they can, with reassurance that strong-performing models are likely to have high power.

Other methods focus on interpretation of the model, rather than testing for conditional independence. These include LIME [Ribeiro et al., 2016], DeepLIFT [Shrikumar et al., 2017], SHAP [Lundberg and Lee, 2017], and L2X [Chen et al., 2018]. The latter two methods, SHAP and L2X, are related to the HRT in that they measure the conditional mutual information between each feature and the response. This can be seen as an optimization variant of the HRT where the statistic is change in prediction rather than prediction accuracy; however, for computational purposes both methods make simplifying independence assumptions between covariates that may lead to false positives. Even with a correct model for measuring mutual information, interpretability of the model is a related but different question. A poor model may use some true-null feature to make its predictions, in which case a correct interpretation would be to flag that variable as important to the model’s prediction, even though it is independent of the true label. An incorrect model is not a problem for the HRT; it will simply have low power to detect the true signals. See [Fisher et al., 2018] for an in-depth discussion on different notions of variable importance.

Only a handful of methods exist for feature selection in arbitrary black box models. We describe and compare the HRT against these methods in detail below.

**Conditional randomization tests (CRTs)** [Candes et al., 2018] proposed CRTs as a generic approach for performing the conditional independence test in Eq. (1) using any test statistic and any predictive model. A CRT repeatedly samples from the conditional null for the feature being tested and compares the test statistic under the null with the test statistic of the original data. Unfortunately, this generality comes at a computational cost: refitting the model. For instance, the example test statistic in [Candes et al., 2018] was the feature coefficient magnitude in a lasso regression. In order to calculate the test statistic under a null sample, the regression must be re-run using the null data. Repeating this many times to approximate the feature \( p \)-value is prohibitively expensive computationally. The basic HRT is a special case of the CRT, where the test statistic is carefully chosen to avoid the need to refit after every null sample.

**Model-X knockoffs** Although [Candes et al., 2018] originally proposed the CRT procedure, they discarded it in favor of the *model-X knockoffs* approach, to avoid the computational issues outlined above. In the model-X knockoffs framework, a “knockoff” feature is generated for every feature in the dataset and the model is fit using both the original and knockoff features. Generating the knockoffs requires knowing (or estimating) the joint distribution over the features; selection is performed by a model-specific variable importance function for the original and knockoff features. The knockoffs procedure has been extended to different feature distributions than the original multivariate normal (e.g. hidden Markov models [Sesia et al., 2017], Gaussian mixture models [Gimenez et al., 2018]). Others have suggested altering certain black box models to support knockoffs, such as using a special input layer in neural networks [Lu et al., 2018]. While knockoffs have an appealing computational efficiency, they
also have several drawbacks for scientific pipelines: i) a valid model of the joint distribution of the covariates must be obtainable, though recent work [Barber et al., 2018] shows knockoffs have similar robustness properties to CRTs; ii) a knockoff statistic must be chosen, which is model-specific and requires knowing something about the model internals; and iii) they require the scientist to design the analysis procedure around knockoffs. This last point is worth stressing.

The scientist must decide before any predictive modeling is done that feature selection will be carried out via knockoffs. The knockoff variables must be included in the covariate set and screened similarly to the real covariates, which complicates leveraging external data sources (e.g. gene regulatory pathway information in predicting drug response from expression data). Even if knockoffs can be incorporated, it is unclear whether doubling the covariates will have an impact on the performance of the trained model, presenting a possible trade-off between predictive performance and feature selection power. Finally, if the scientist wishes to use the trained model to make any prediction on new data, corresponding knockoff samples must be generated for every prediction, which makes model usage awkward. The HRT, by contrast, enables the scientist to build a model that maximizes predictive performance without considering feature selection.

Mimic and Classify [Sen et al., 2018] propose an approach inspired by generative adversarial networks [Goodfellow et al., 2014]. Mimic and Classify fits a conditional model of the feature, similarly to a CRT, but then also fits a “discriminator” model to distinguish between samples from the true dataset and samples from the null model, with the difference in error magnitude as the test statistic. This is conceptually similar to the HRT but differs in key ways: i) it does not leverage a pre-built predictive model at all, ii) it does not provide direct p-value calculation, iii) it requires fitting a discriminator per hypothesis test, each of which may be as difficult to build as a predictive model for the response, and iv) it implicitly ties the magnitude of the dependency between \( X \) and \( Y \) to the test statistic, whereas the HRT is able to detect small but consistent performance differences between the original data and the null samples.

Conditional permutation tests (CPTs) [Berrett et al., 2018] propose the CPT as a robust choice of CRT. In addition to conditioning on the other features, the CPT also conditions on the order statistics when drawing randomizations. Thus, rather than randomly shuffling the order statistics like in a classical permutation test, each feature is shuffled in a non-uniform way. CPTs are an interesting approach and are complementary to the HRT. In particular, they are more robust than vanilla CRTs and may increase the robustness of the HRT even further.

Recent work [Shah and Peters, 2018] has also shown that there is no free lunch for conditional independence testing. That is, conditional independence testing is essentially impossible without some assumption on the joint distribution of \( (Y, X) \). Neither the HRT nor the above methods avoid this result. The assumption made in the HRT is that a reasonable approximation to the complete conditional distribution of \( X_j \) given \( X_{-j} \) can be obtained. [Berrett et al., 2018] provide a theoretical investigation under this assumption for CPTs.
2 The Holdout Randomization Test

2.1 Setup and notation

Throughout the paper, upper case symbols (e.g. $X$) denote matrix variables; the first subscript indexes the row ($X_i$) and the second indexes columns ($X_{\cdot j}$); negation indicates every element except the one(s) specified ($X_{\cdot -j}$). Let $P_{j\mid -j} = P(X_j \mid X_{\cdot-j})$ denote the complete conditional of the $j^{th}$ feature.

Consider the following predictive modeling scenario:

- We receive a dataset $D^* = \{(X_i, Y_i)\}_{i=1}^{n^*}$ of $n^*$ samples where $(X_i, Y_i) \overset{iid}{\sim} P$.
- The scientist specifies a predictive model class $\pi_\theta(X) \rightarrow \hat{Y}$ with parameters $\theta$.
- Data is split into train and test sets, $D$ and $D'$ of $n$ and $n'$ samples, respectively.
- $D$ is used to fit $\hat{\theta}$ by optimizing an objective function $L_{\pi}(D, \theta)$.
- $D'$ is held out for evaluating the empirical risk $G(D', \pi_{\hat{\theta}}) = \frac{1}{n'} \sum_{i=1}^{n'} g(X_i, Y_i, \pi_{\hat{\theta}}(X_i))$.
- The inferential goal is to use $\pi_{\hat{\theta}}$ to conduct a conditional independence test for feature $X_{\cdot,j}$ as in Eq. (1).

Fitting a single model may take hours or even days for large datasets and complicated models. Evaluating the model on the test set, however, is much faster and it is computationally feasible to perform many evaluations. We assume the scientist chooses their predictive model without looking at the test set.

2.2 Basic Method

The HRT procedure is presented in Algorithm 1. The HRT algorithm first fits the predictive model using the training dataset and the fitting procedure supplied by the scientist (Line 2). Arbitrary fitting procedures and model choices are allowed. For instance, the scientist is free to use cross-validation of the training set to select model hyperparameters, bootstrap and aggregate multiple model fits, or add sparsity-inducing regularizers. Moreover, the scientist is encouraged to build the best predictive model they can. As we show in Section 5.3 there is a strong correlation between model quality and the power of the HRT when using the model.

Once fit, Algorithm 1 evaluates the empirical risk of the model (Line 3). This establishes a baseline for model performance on the original data. The HRT algorithm then repeatedly resamples $X_{\cdot,j}$, the feature being tested, from the null distribution $P_{j\mid -j}$ (Line 5). This sampling procedure breaks any possible dependence between $X_j$ and $Y$, but preserves the joint distribution structure of $P(X)$. Consequently, the samples are valid draws from the null distribution where $X_{\cdot,j}$ has no predictive power. For each null sample, the algorithm replaces the real feature values with the sampled null values (Line 6) and evaluates the empirical risk of the model on the new dataset (Line 7).

Empirical risk functions as a test statistic in the HRT. Algorithm 1 compares the risk $(t)$ on the original data with risk $(\tilde{t})$ under the null. It then uses the null samples to estimate the likelihood of observing an empirical risk as low as $t$, if $H_0$ were true. Adding 1 to the numerator and denominator in the average (Line 8) corrects for finite sampling; the result is a valid one-sided $p$-value for testing the null hypothesis in Eq. (1).
Algorithm 1 Holdout Randomization Test

1: procedure HRT(training data $D$, test data $D'$, model $\pi$, training objective $L_\pi$, empirical risk function $G$, sample size $K$)
2: Fit $\hat{\theta}$ by optimizing $L_\pi(D, \theta)$.
3: Compute the empirical risk on held out data, $t \leftarrow G(D', \pi_{\hat{\theta}})$.
4: for $k \leftarrow 1, \ldots, K$ do
5: Sample $\tilde{X}'_j \sim P_{j | -j}$.
6: Create a new dataset $\tilde{D}$ by replacing $X'_j$ in $D'$ with $\tilde{X}'_j$.
7: Compute the empirical risk, $\tilde{t}(k) \leftarrow G(\tilde{D}, \pi_{\hat{\theta}})$.
8: return A (one-sided) $p$-value,

$$\hat{p}_j = \frac{1}{K + 1} \left( 1 + \sum_{k=1}^{K} \mathbb{I}[t \geq \tilde{t}(k)] \right)$$

The validity of the $p$-value derives from the fact that it is a specialized version of a conditional randomization test [Candes et al., 2018]. In CRTs, any test statistic and predictive model represent a valid conditional independence test. The key separator between the HRT and generic CRTs is in the construction of the test statistic. In the original construction, the test statistic is assumed to be a function of the entire dataset $D^*$ and the parameters $\hat{\theta}$ after fitting to the dataset. Evaluating a null sample then requires refitting the model to obtain a sample from the null distribution over $\theta$. This makes CRTs prohibitively expensive to compute in practice. By defining the test statistic to focus only on predictive performance of a fixed model, the HRT requires no refitting at all. Only model evaluation is necessary, which is cheap enough in many machine learning models to make the HRT feasible for a large class of predictive models.

Algorithm 1 focuses on simple scalar regression. In general, the HRT is valid for a much broader class of methods—effectively any predictive modeling scenario. In fact, the model fit need not even be very good and can be chosen by an adversary in the worst case. Poorly chosen models may have zero power, but Type I error will still be conserved.

The remainder of the paper addresses several pragmatic questions regarding the HRT:

- If we estimate the conditional $P_{j | -j}$ from data, will the HRT be robust to estimation errors? If not, can we somehow err on side of caution and produce conservative $p$-values? (Section 3.1)

- Is it possible to use the entire dataset, rather than splitting it into train and test, so as to maximize power? (Section 3.2)

- Can we speed up the algorithm further? (Section 3.3 and Section 4)

- How does model predictive performance relate to feature selection power? (Section 5.3)
3 Modeling details: making the HRT more robust, powerful, and efficient

3.1 Conservative estimation by bootstrap sample reweighting

CRT procedures—such as the HRT—provide valid p-values under the assumption that we have access to the true complete conditional distributions $P_{j \mid j} = \mathbb{P}(X_j \mid X_{-j})$. In practice, these distributions must be estimated from data. The error in the estimated complete conditional, $Q_{j \mid j}$, can lead to inflated tails of the null p-values, causing a violation of the Type I or FDR error threshold. Here we develop a calibration technique that aims to produce conservative p-values by pessimistically weighting each null sample comparison.

We begin by casting Algorithm 1 as an importance sampling scheme with $Q_{j \mid j}$ as a proposal distribution,

$$
\hat{p}_j \approx \frac{1}{1 + \sum_{k=1}^{K} W^{(k)}} \left( 1 + \sum_{k=1}^{K} \mathbb{1} \left\{ G(D', \pi_\theta) \geq G(\tilde{D}^{(k)}, \pi_\theta) \right\} W^{(k)} \right),
$$

(2)

$$
\tilde{D}^{(k)} = [\tilde{X}_j^{(k)}, X_{-j}'], \quad \tilde{X}_j^{(k)} \sim Q_{j \mid j},
$$

where $W^{(k)}$ is the importance weight,

$$
W^{(k)} = \frac{P_{j \mid j}(\tilde{X}_j^{(k)})}{Q_{j \mid j}(\tilde{X}_j^{(k)})}.
$$

(3)

The estimate in (2) is consistent, but it still relies on the unknown true conditional $P_{j \mid j}$, making it impossible to compute in practice.

Let $f_{j \mid j}$ and $h_{j \mid j}$ be functions that bound the true probability of the null sample: $0 \leq f_{j \mid j}(\tilde{X}_j) \leq P_{j \mid j}(\tilde{X}_j) \leq h_{j \mid j}(\tilde{X}_j)$. If we have access to such a function, we can then bound $p_j$ in expectation by biasing the importance weights to be conservative. This works by choosing the importance weight dynamically based on the outcome of each test statistic comparison,

$$
\tilde{W}^{(k)} = \begin{cases} 
    f_{j \mid j}(\tilde{X}_j^{(k)}) & \text{if } G(D', \pi_\theta) < G(\tilde{D}^{(k)}, \pi_\theta) \\
    Q_{j \mid j}(\tilde{X}_j^{(k)}) & \text{otherwise.}
\end{cases}
$$

(4)

Under this conservative weighting, $\mathbb{E} [\tilde{p}_j] \leq p_j$. The tighter the bound from $(f_{j \mid j}, h_{j \mid j})$, the less conservative the p-value estimate and thus the more powerful the test statistic. Trivially, for any true $P_{j \mid j}$, we can always choose $f_{j \mid j} = 0$ and guarantee $\hat{p}$ will be conservative. It will always be 1, however, so the method will be without power. To be effective, the bound must be relatively tight.

A natural way to generate approximate bounds on $P_{j \mid j}$ is to use a conditional density estimation (CDE) method that quantifies uncertainty. For instance, when using a Bayesian method, quantiles can be derived either analytically or approximately by sampling from the posterior via Markov chain Monte Carlo. Since we wish to remain maximally flexible to the form of $P_{j \mid j}$, we treat the CDE model as a black box and use the bootstrap to generate quantiles [see Efron and Tibshirani 1998 for a discussion on the technical issues with using the bootstrap for confidence intervals].
We create \( b \) bootstrap resamples of the dataset and fit \( b \) corresponding CDE models \( B_{j|\cdot} = (Q_{j|\cdot}^{(1)}(X_{j|\cdot}), \ldots, Q_{j|\cdot}^{(b)}(X_{j|\cdot})) \), with \( Q_{j|\cdot}^{(1)} \) used as the proposal distribution. Given a choice of lower and upper quantile, \((l, u)\), we can replace the reweighting scheme in (4) with an approximate one,

\[
\tilde{W}^{(k)} = \begin{cases} 
\frac{B_{j|\cdot}^{(i)}(\tilde{X}^{(k)}_{ij})}{Q_{j|\cdot}^{(i)}(\tilde{X}^{(k)}_{ij})} & \text{if } \mathcal{G}(\mathcal{D}', \pi_{\hat{\theta}}) < \mathcal{G}(\tilde{\mathcal{D}}^{(k)}, \pi_{\hat{\theta}}) \\
\frac{B_{j|\cdot}^{(n)}(\tilde{X}^{(k)}_{ij})}{Q_{j|\cdot}^{(n)}(\tilde{X}^{(k)}_{ij})} & \text{otherwise.}
\end{cases}
\]

where \( B_{j|\cdot}^{(i)} \) denotes the \( i \)th quantile of the estimates in \( B_{j|\cdot} \).

In practice, \( X_{\cdot\cdot} \) is a vector of conditionally-independent (given \( X_{\cdot\cdot} \)) variables and the conditional density estimates are made on a per-sample basis. We take the geometric mean of lower and upper quantile, \((l, u)\), as defined in Eq. (4), relatively little is required for the upper and lower quantiles. For this, we leverage the IID property of the conditional CDF values for each sample.

If a sampling distribution \( Q_{j|\cdot} \) is well-calibrated, the distribution of CDF values for all samples should be uniform. In practice, this does not happen when using highly-flexible black box conditional density estimators trained via maximum likelihood estimation. While many approaches to recalibration have been explored in the literature, most tend to apply to classification or regression models (e.g. Platt scaling [Platt 1999]). It is not immediately clear how one can calibrate quantiles for black box conditional density estimates. We use a data-adaptive strategy described in Appendix A for continuous random variables; for other data types, we recommend simply using \((l, u) = (5, 95)\) as a conservative choice.

**Proof of Conservatism**  With \( \tilde{W}^{(k)} \) as defined in Eq. (4), relatively little is required for conservativism of the estimator of \( p_j \) (the true \( p \)-value),

\[
\hat{p}_j^K \approx \frac{1}{1 + \sum_{k=1}^{K} \tilde{W}^{(k)}} \left( 1 + \sum_{k=1}^{K} \mathbb{1} \left\{ \mathcal{G}(\mathcal{D}', \pi_{\hat{\theta}}) \geq \mathcal{G}(\tilde{\mathcal{D}}^{(k)}, \pi_{\hat{\theta}}) \right\} \tilde{W}^{(k)} \right),
\]

\[
\tilde{\mathcal{D}}^{(k)} = [\tilde{X}^{(k)}_{j}, X'_{\cdot\cdot}], \quad \tilde{X}^{(k)}_{j} \sim Q_{j|\cdot}.
\]

In particular, the functions \( f_{j|\cdot} \) and \( h_{j|\cdot} \) only need to bound \( P_{j|\cdot} \) in a very crude sense. Let \( E_j = \left\{ \mathcal{G}(\mathcal{D}', \pi_{\hat{\theta}}) \geq \mathcal{G}(\tilde{\mathcal{D}}^{(k)}, \pi_{\hat{\theta}}) \right\} \) be the event that the empirical risk of a null sampler is less than the observed empirical risk. Then,
Algorithm 2  Cross-Validation Holdout Randomization Test

1: procedure CV-HRT(training data split into $M$ folds: $\mathcal{D} = \{\mathcal{D}^{(1)}, \mathcal{D}^{(2)}, \ldots, \mathcal{D}^{(M)}\}$, model $\pi$, training objective $\mathcal{L}_{\pi}$, empirical risk function $\mathcal{G}$, sample size $K$)

2: Initialize $t \leftarrow 0$

3: for $m \leftarrow 1, \ldots, M$ do

4:  Fit $\hat{\theta}^{(m)}$ by optimizing $\mathcal{L}_{\pi}(\mathcal{D}^{(-m)}, \theta)$.

5:  Add the fold empirical risk, $t \leftarrow t + (1/M)\mathcal{G}(\mathcal{D}^{(m)}, \pi_{\hat{\theta}^{(m)}})$.

6: for $k \leftarrow 1, \ldots, K$ do

7:  Sample $\bar{X}_j' \sim P_{j|\cdot}$.

8:  Create a new dataset $\bar{\mathcal{D}}$ by replacing $X_j'$ in $\mathcal{D}'$ with $\bar{X}_j'$.

9:  Initialize $\bar{t}^{(k)} \leftarrow 0$

10: for $m \leftarrow 1, \ldots, M$ do

11:  Add the fold empirical risk on the randomized data, $\bar{t}^{(k)} \leftarrow \bar{t}^{(k)} + (1/M)\mathcal{G}(\bar{\mathcal{D}}^{(m)}, \pi_{\hat{\theta}^{(m)}})$.

12: return A (one-sided) $p$-value,

$$\hat{p}_j = \frac{1}{K+1} \left(1 + \sum_{k=1}^{K} \mathbb{I}[t \geq \bar{t}^{(k)}]\right)$$

Theorem 1. If $E_{P_{j|\cdot}} \left[ \frac{f_{j|\cdot}(\bar{X}_j^{(k)})}{P_{j|\cdot}(X_j^{(k)})} (1 - \mathbb{I}\{E_j\}) \right] \leq 1 - p_j$ and $E_{P_{j|\cdot}} \left[ \frac{h_{j|\cdot}(\bar{X}_j^{(k)})}{P_{j|\cdot}(X_j^{(k)})} \mathbb{I}\{E_j\} \right] \geq p_j$
then, almost surely, $\lim_{K \to \infty} \hat{p}_j^K \geq p_j$.

The proof is in Appendix [3]. Theorem [1] shows that, because the test statistic is fixed, we require only that the upper and lower bounds are valid on average over the events $E_j$ and $1 - E_j$.

3.2 Higher power via a cross-validation extension

Modeling pipelines typically allocate the bulk of the total data to the training set, leaving only 10–20% for testing. Since the HRT only uses the test set and the trained model, the majority of the data will not be used for testing. In scientific settings where sample sizes are small-to-moderate, discarding this much data may result in the HRT having low power. Here we show how the train-test paradigm of the basic HRT can be extended to a cross-validation paradigm that uses the entire dataset.

The cross-validation holdout randomization test (CV-HRT) is presented in Algorithm 2. The CV-HRT splits the data into $M$ folds, rather than the train-test split of the basic HRT. The algorithm fits $M$ models, with the $m$th model trained using the $m$th fold as the holdout set. Predictions are made across the entire dataset, but only model $m$ is used to make predictions for samples in the $m$th fold. The test statistic is then the average empirical risk across all folds. In effect, the CV-HRT performs $M$ basic HRTs. This leads to a higher-power, lower-variance estimate of the usefulness of the $j$th feature in predicting $Y$.

The CV-HRT is an extension of the basic HRT procedure in Algorithm 1, and again inherits validity from being a CRT. Unlike the basic HRT, however, the CV-HRT takes
Algorithm 3: Fast Holdout Randomization Test

1: procedure Fast-HRT(training data $D$, test data $D'$, model $\pi$, training objective $L_\pi$, empirical risk function $G$, sample size $K$, grid size $S$)
2: \hspace{1cm} Fit $\hat{\theta}$ by optimizing $L_\pi(D, \theta)$.
3: \hspace{1cm} Compute the empirical risk on held out data, $t \leftarrow G(D', \pi_{\hat{\theta}})$.
4: \hspace{1cm} Construct $S$-grid approximations, $Z$ and $\tilde{P}_{j|\cdot}$ for $X'_i$ and $P_{j|\cdot}$, respectively.
5: \hspace{2cm} for $i \leftarrow 1, \ldots, n'$ do
6: \hspace{3cm} for $s \leftarrow 1, \ldots, s$ do
7: \hspace{4cm} Create a new sample $(\tilde{X}_i, Y'_i)$ by replacing $X'_{ij}$ in $D'$ with grid point $Z_{is}$.
8: \hspace{4cm} Compute sample risk, $T_{is} \leftarrow g(\tilde{X}_i, Y'_i, \pi_{\hat{\theta}}(\tilde{X}_i))$.
9: \hspace{2cm} for $k \leftarrow 1, \ldots, K$ do
10: \hspace{3cm} Sample grid points $\{z_i\}_{i=1}^{n'}$ proportional to their weight in $\tilde{P}_{j|\cdot}(i)$.
11: \hspace{3cm} Compute the empirical risk, $\tilde{t}(k) \leftarrow \frac{1}{n'} \sum_{i=1}^{n'} T_{is, z_i}$.
12: return A (one-sided) $p$-value, $\hat{p}_j = \frac{1}{K + 1} \left( 1 + \sum_{k=1}^{K} I[t \geq \tilde{t}(k)] \right)$

full advantage of the dataset by building multiple models, with one valid test model per sample. This takes the CV-HRT closer to the original CRT procedure, which also uses the full dataset. The key difference is that CRTs as originally conceived would train a single model on the entire dataset, whereas the CV-HRT trains multiple models on subsets of the data. As with the basic HRT, this specialization enables the CV-HRT to avoid refitting the predictive models after every null sample.

Stronger predictive models in any HRT procedure are likely to capture more of the dependency structure between $X$ and $Y$. Consequently, more folds leads to more training data per model, which in turn should lead to better predictive performance per model. In the extreme, leave-one-out cross-validation will maximize power, but this comes at the computational expense of fitting $n$ models, which may be prohibitive. In practice, we observe much higher power from as few as 5 folds.

3.3 Faster $p$-value approximation by empirical risk decomposition

The HRT relies on random sampling to approximate the expectation of the indicator function in Algorithm 1. Unlike other randomization tests, however, the HRT assumes a fixed model and a test statistic that is a summation of independent components. These two properties can be leveraged to substantially speed up the computation of the $p$-value approximation.

Algorithm 3 presents the fast approximation algorithm. The Fast-HRT first creates finite grid approximations $\tilde{P}_{j|\cdot}$ to $P_{j|\cdot}$. It then queries the model at each point to create a matrix $T$ of cached component risk scores. In the test statistic computation loop (Lines 9–11), the cached component scores are sampled proportional to their likelihood in the complete conditional. The Fast-HRT then averages these cached component scores rather than querying the predictive model. This lowers the computational complexity from $O(Kn')$ to $O(Sn')$. Empirically, when $K$ is large (e.g. in the case of many candidate features being
tested) the Fast-HRT is 1–2 orders of magnitude faster than the basic HRT.

The discretization step is unnecessary when dealing with discrete data. The Fast-HRT would still benefit computationally from the caching strategy, however. Similarly, if one were to use an HRT version of a conditional permutation test [Berrett et al., 2018], a similar caching strategy could be employed with a modification to the sampling strategy to ensure valid permutation draws.

3.4 Putting it all together: a fast, calibrated, cross-validation HRT

All three of the HRT enhancements above were described independently but are fully compatible with each other. Combining them together yields a faster, more powerful, robust HRT that takes between seconds and a few minutes to calculate a precise, conservative \( p \)-value on a laptop.

Fig. 1 shows a visual example of the combined algorithm. The calibration method from Section 3.1 returns bootstrapped upper and lower bound estimates for \( P_{j|j} \) in each sample (left column). The per-sample empirical risk for the model can be evaluated for any arbitrary value of the target feature (middle column). Gray bars in both the left and middle columns indicate the finite grid points used in the fast approximation; the bounds and empirical risk are evaluated at each grid point and cached. Null samples are then drawn from the grid approximation, proportional to the likelihood in the proposal distribution \( Q_{j|j} \).

The test statistic is calculated by summing over the cached component risk values for the sampled grid points (top right panel). Each null sample is associated with a likelihood weight corresponding to its lower (blue) or upper (orange) bounds for the sampled grid points (middle right panel). In the example, the first null sample has lower empirical risk than the original data (top right, dashed red line) and the other two null samples have higher empirical risk. Null samples where the empirical risk is below the threshold set by the original data are assigned the weight from the upper bound; other null samples are assigned the lower bound weight. Upper bound weights are added to the numerator and denominator in the final \( p \)-value calculation, causing the \( p \)-value to increase; lower bound

Figure 1: Visual depiction of the HRT with all enhancements described in Section 3, applied to a dataset of three samples with three null samples.
Algorithm 4: Empirical Risk One-Sample Selection

1: procedure ERK(training data \( D \), test data \( D' \), model \( \pi \), training objective \( \mathcal{L}_\pi \), empirical risk function \( \mathcal{G} \), FDR threshold \( \alpha \))
2: 
3: Fit \( \hat{\theta} \) by optimizing \( \mathcal{L}_\pi(D, \theta) \).
4: Compute the empirical risk on held out data, \( t \leftarrow \mathcal{G}(D', \pi_{\hat{\theta}}) \).
5: for each feature \( j \) do
6: Sample \( \tilde{X}'_j \sim P_{j|\cdot} \).
7: Create a new dataset \( \tilde{D} \) by replacing \( X'_j \) in \( D' \) with \( \tilde{X}'_j \).
8: Compute the change in empirical risk, \( \tilde{w}(j) \leftarrow \mathcal{G}(\tilde{D}, \pi_{\hat{\theta}}) - t \).
9: \( \omega^* \leftarrow \min_{\omega \geq 0} \omega, \text{subject to } \left[ \frac{1+\# w(j) \leq \omega}{\# w(j) \geq \omega} \leq \alpha \right] \).
10: return discoveries at the \( \alpha \) level: \( \{ j : w(j) \geq \omega^* \} \).

weights are added only to the denominator, lowering the \( p \)-value estimation; we refer to this as the sample impact (bottom right panel).

4 A hybrid knockoff-like alternative

Some models may be too compute intensive for the HRT, even when applying the speedup trick from Section 3.3. For instance, if the predictive model is a kernel method, it may require \( O(np) \) operations (where \( n \) is the number of training examples and \( p \) is the number of features) to make a single prediction. Similarly, if the predictor is a fully Bayesian model, it may require approximate posterior inference (e.g. MCMC) for every randomization. In other cases, the conditional model may be expensive to run, making generation of the nulls too costly.

Here we present a computationally inexpensive algorithm that is a hybrid between the HRT and ‘model-X’ knockoffs [Candes et al., 2018]. The algorithm uses the same held out empirical risk test statistic from the HRT, but only evaluates a single null sample per feature. Feature selection is then performed simultaneously using a step-up procedure to guarantee FDR control. Algorithm 4 presents the full algorithm, which we call Empirical Risk One-Sample Selection (EROSS).

**Theorem 2.** Algorithm 4 controls the false discovery rate at level \( \alpha \).

**Proof.** First note that the selection procedure in Algorithm 4 and admission criterion for \( \omega^* \) are the same as for the knockoffs multiple testing procedure of Barber and Candès [2015]. Theorems 1 and 2 of Barber and Candès [2015] guarantee FDR control using the knockoffs selection procedure at the \( \alpha \) level as long as the sign of the difference statistics \( w(j) \) are i.i.d. coin flips under the null. In Algorithm 4, test statistics \( t \) and \( \tilde{t}(j) = \mathcal{G}(\tilde{D}, \pi_{\hat{\theta}}) \) are identically distributed under the null (by assumption that \( P_{j|\cdot} \) is the true complete conditional). The distribution of \( w(j) \) under the null is therefore symmetric about the origin. Thus, the sign of every \( w(j) \) is an independent coin flip. \( \Box \)

EROSS is closely related the “swap” knockoff statistic [Gimenez et al., 2018]. The primary difference, as with the HRT, is that the algorithm is carefully constructed so as to not require any modifications to the predictive model. That is, there are no extra knockoff features for the predictive model to consider. The scientist can perform selection with their pre-trained model without considering the testing procedure.
While EROSS is faster than the HRT, there are several reasons to prefer the HRT in practice. First, for most models the cost of prediction is not prohibitively high. Second, EROSS only controls the FDR; in settings where family-wise error or another p-value-based selection is required, EROSS will not be applicable. Finally, although the cross-validation HRT extension carries over to EROSS, the calibration approach does not. Adapting the bootstrap reweighting procedure to the knockoff-style selection procedure in EROSS is difficult as there is only a single sample to consider. This makes EROSS more brittle, as it relies on accurate estimates of the complete conditionals. In our simulations, we find EROSS often fails to control FDR when the conditionals are fit empirically (see Section 5.4). Thus, it is best used only when there is an accurate set of complete conditional estimates but expensive predictive models.

5 Benchmarks

5.1 Setup

We benchmark the HRT on a variant of a benchmark from a recent paper on feature selection in Bayesian neural networks [Liang et al., 2018]. We generate 100 independent datasets of 500 samples each with a nonlinear ground truth regression model,

\[ y = \sum_{j=0}^{9} \left[ w_{4j}x_{4j} + w_{4j+1}x_{4j+1} + \tanh(w_{4j+2}x_{4j+2} + w_{4j+3}x_{4j+3}) \right] + \sigma \epsilon, \quad (7) \]

where \( \sigma = 0.5 \) and \( \epsilon \sim \mathcal{N}(0, 1) \). The 500 features are generated to have 0.5 correlation coefficient with each other,

\[ x_j = (\rho + z_j)/2, \quad j = 1, \ldots, 500, \quad (8) \]

where \( \rho \) and \( z_j \) are independently generated from \( \mathcal{N}(0, 1) \).

The ground truth in (7) uses the first 40 features, representing true signals; each sample also contains 460 null features. We note that [Liang et al., 2018] only had 4 signal features in their simulation. In preliminary simulations, the HRT had nearly 100% power and 0% FDR in this setting; we extend the experiment to 40 features to make the benchmark more challenging and model comparisons more informative.

We choose this setup for several reasons: (i) it is a nonlinear ground truth, (ii) most features are not involved in the response, (iii) all features are highly correlated, and (iv) it is compatible with the available implementation of model-X knockoffs [Candes et al., 2018] for the lasso; we compare to this implementation in Section 5.3.

For all experiments, we use a mixture density network [Bishop, 1994] with 5 components as the conditional density estimator in the HRT. For each feature, we fit a bag of \( b = 100 \) bootstrap estimators and use the data-adaptive calibration technique in Appendix A to choose the approximate lower and upper bounds. We use mean-squared error (MSE) as the empirical risk function. We select significant features with a target FDR of 10%, using the Benjamini-Hochberg procedure [Benjamini and Hochberg, 1995] for multiple testing correction.
5.2 Comparing the basic and enhanced HRT variants

We first compare several variants of the HRT procedure to investigate the effect of each component. For each dataset, the predictive model is a neural network with 2 hidden layers of 200 nodes each and ReLU activation functions; we fit the model using RMSprop with fixed learning rate $3 \times 10^{-5}$. We use an 80%/20% train/test split for the basic HRT and 5-fold cross-validation for the CV-HRT. Fig. 2 shows the power and FDR results for the different variants. We discuss the individual variants and results below.

![Figure 2: Power and FDR results for each HRT variant on the benchmark simulation. The calibration technique from Section 3.1 adjusts the sample weights to achieve tighter control over the FDR at the specified 10% level (dashed red line). Using cross-validation for predictive modeling increases power and reduces variance by using the entire dataset rather than just a held out subset.](image)

Marginal Permutation. A common approach to testing for feature importance in many applications is the classical permutation test, where the values of a given feature are shuffled. Combining this with empirical risk on held out data was suggested by Breiman [2001] as a feature selection technique. To be valid, permutation testing requires that features are independent, which is explicitly not the case in the benchmark nor in many—if not most—real world datasets. The two left-most results in Fig. 2 show performance using a permutation approach, rather than the complete conditional, in both the basic and cross-validation HRT. The misspecified independence assumption causes an extreme inflation in the false discovery rate to nearly 80% instead of the target 10%.

Calibration. The middle two results in Fig. 2 show performance using a single, uncalibrated estimation of $P_{j\mid j}$ in the basic and cross-validation HRT. The estimated conditional is a much better approximation of the true feature distribution than the marginal permutation above, but is still insufficient to control FDR at the target level. By contrast, the two right-most results show that the calibrated model better conserves FDR, with minimal impact on power compared to the uncalibrated model.

Fig. 3 provides a closer look at the calibration procedure results for the cross-validation HRT. The top two panels show a sweep of possible choices of the upper and lower bounds.
for both power and FDR. Even at a stringent 90% confidence interval (top right corner of both heat maps), power is still 28%; FDR declines relatively rapidly, being only $\approx 5\%$ at a 90% interval. The bottom left panel shows the the CDF values of the $p$-values for the null features using different bounds. The panel is zoomed in to show the $[0, 0.1]$ region where $p$-values may be rejected under the target FDR threshold. Without any calibration, even the bootstrapped median (i.e. the $[50, 50]$ interval) still shows an inflation in the lower portion of the CDF, leading to invalid null $p$-values. A 20–30% confidence interval biases the null $p$-values down sufficiently to control the empirical FDR near the target level. The bottom right panel shows the distribution of bounds chosen by the data-adaptive procedure in each of the 100 independent trials; the procedure chooses roughly a 25% confidence region for most trials.

**Basic HRT vs. CV-HRT.** The right-most results in Fig. 2 demonstrate the effect of using a basic train-test split HRT versus a 5-fold cross-validation HRT. Cross-validation has the effect of boosting power and reducing variance compared to the basic HRT.
5.3 Model selection and knockoffs comparison

We next compare several choices of predictive model on the same benchmark task as above. Specifically, we ran the CV-HRT procedure with the neural network model from the previous section and the following alternative predictive models:

- Ordinary least squares (OLS)
- Partial least squares (PLS) with 10 components.
- Lasso with penalty parameter chosen via 5-fold cross-validation on each training set.
- Elastic net with both penalty parameters chosen via 5-fold cross-validation on each training set.
- Bayesian ridge with normal-inverse-gamma priors for coefficients and weakly informative scale hyperpriors.
- Kernel ridge with cubic polynomial kernel with a fixed penalty weight of 1.
- Support vector with radial basis function (RBF) kernel.
- Random forest with 20 trees.

All model hyperparameters not specified were set to their default in the scikit-learn Python package. We also compare to a lasso knockoff model using coefficient difference statistic; we use the implementation provided in the knockoffs R package.

Fig. 4 (top) shows the power and FDR results for each model. The predictive models are ordered by average cross-validation $r^2$ across all trials. CV-HRT power roughly increases with the quality of the predictive model, with the lasso model producing the highest power results. Fig. 4 (bottom right) demonstrates this with more granularity. It shows the power for each individual model on each trial as a function of the individual model $r^2$. Even within the same model class, the models that generalize better tend to have higher power in the CV-HRT.

A notable exception is the random forest model, which has low power across all trials. This may be due to the nature of the model. Random forests average predictions from an ensemble of decision trees. Each tree predicts by recursively dividing into a series of half-planes, with each half-plane based on a single feature. Most null samples in the HRT are near, but slightly different than, the original data. It is likely that a small change to the original data will not change the random forest prediction, since it may not cause the feature to cross any half-plane. Since the comparison of the test statistic under the original model with each null sample statistic is not strict in the HRT, the insensitivity of random forests to small data changes leads to lower power. One solution to this is to use more trees in the forest, with data subsampling or bootstrapping to produce many different half-planes for each feature. Alternatively, switching to a conditional permutation HRT may boost power by generating more null samples where some feature values cross a hyperplane.

Fig. 4 also presents the results of a lasso knockoffs model using the coefficient magnitude as a test statistic, as proposed by Candes et al. [2018]. The power of the CV-HRT lasso model is approximately 3x more than knockoffs (45% versus 15% on average). There are two possible causes here: i) the knockoff procedure itself is underpowered compared to the HRT or ii) the lasso coefficient test statistic is underpowered compared to empirical risk. The EROSS benchmarks in the next section investigate this.
Figure 4: Top: Power and FDR for different choices of predictive model used in the CV-HRT, ordered by empirical risk of the predictive model. The right-most result is for a lasso model using model-X knockoffs for feature selection. Bottom left: distribution of p-values for signal features using each predictive model. Bottom right: predictive model performance versus feature selection power for each model and independent trial. Colors in the bottom right plot correspond to those in the bottom left.

5.4 EROSS performance

Fig. 5 shows the results of the same simulations, but using the hybrid EROSS procedure from Section 4 instead of the HRT. EROSS combines the selection procedure of knockoffs with the held out empirical risk statistic of the HRT. EROSS maintains the correlation between predictive performance and power, as shown in Fig. 4, and achieves similar power to the HRT. This suggests (at least for this simulation) the low power of lasso coefficient knockoffs is likely due to the choice of test statistic. However, unlike the HRT, EROSS is unable to control FDR in all predictive models as it lacks a way to calibrate of the complete conditional.
Figure 5: Power and FDR for different choices of predictive model used with EROSS, ordered by empirical risk of the predictive model.

6 Case studies from the scientific literature

6.1 Reporting features chosen by heuristics

We demonstrate the usefulness of the HRT on two datasets from real experiments. The first dataset measures the genomic profile of hundreds of cancer cell lines and their response to an anti-cancer drug. The second measures the molecular structure of hundreds of chemicals and their perceived olfactory properties. In both experiments, the original scientific analyses followed the same template: (i) a large number of features were gathered about the target, (ii) a predictive model was fit, (iii) a model-specific feature importance heuristic was used to rank features, and (iv) top-ranked features were reported as discoveries.

In both case studies, we followed the same procedures for steps (i) and (ii), but then replaced (iii) and (iv) with the calibrated CV-HRT. We use the same conditional estimator as in Section 5, but for numerical stability take the first 100 principal components as inputs rather than raw features. We briefly describe each experiment and the original analysis approach, then present a comparison of the heuristics employed with the discoveries made by the HRT.

Drug response experiment The first dataset is a study of anti-cancer drug response in cancer cell lines [Barretina et al., 2012]. Multiple drugs were tested against hundreds of cell lines; phenotypic response was measured as the area under the dose-response curve (AUC). Each cell line was analyzed to obtain gene mutation and expression features. The scientific goal is to discover the genomic features associated with drug response. Genomic features were first screened to filter out features with less than 0.1 magnitude Pearson correlation to the AUC. An elastic net model was fit for each drug, with hyperparameters chosen via 10-fold cross-validation. Features were then ranked by average coefficient magnitude. We choose a single drug, PLX4720, as an illustrative example. The results presented are similar to the original publication results for PLX4720, though not identical. We followed the analysis to the best of our ability, but the publicly available data is newer than the dataset.
used in the original publication. Our results are therefore different than those published, but not meaningfully so.

Olfactory perception experiment The second dataset is a study of the perceived fragrant properties of various molecules [Keller et al., 2017]. Several hundred human subjects smelled and rated each molecule across 20 different categories. For each molecule, several thousand descriptive features about its chemical structure were measured. A random forest model was fit for each category to predict the average human rating given the features for a molecule. Different types of molecular descriptors were tried, with two sets (Dragon and Morgan descriptors) being selected based on performance on a held out test set. Features were then ranked by the random forest feature importance heuristic in scikit-learn. This heuristic estimates the expected number of samples in which a feature is used, based on how often and how deep it appears in the constituent trees. We again choose a single illustrative example, the Bakery category.

To increase power, we use the heuristics as a filter on which features to test in both case studies. Features with less than $10^{-3}$ heuristic importance (coefficient magnitude in elastic net and expected usage in random forests) are ignored. This leaves 873 features for the drug response dataset and 93 features for the olfactory perception dataset. This filtering step does not affect the statistical guarantees of the HRT since it is not based on any of the held out test data. It only avoids testing features that are completely ignored by the model and which the HRT will have no power to detect, if they are signals.

Table 1 shows the top 10 ranked features in both datasets, following their respective heuristics. Beside each feature, we report its heuristic importance score and the $p$-value assigned by the HRT. The heuristic rankings correlate poorly with the (theoretically grounded) $p$-value assigned by the HRT. Features with an asterisk denote those selected by the HRT with Benjamini-Hochberg correction at a 20% FDR threshold. It is impossible to know whether these features are all true positives, but the HRT demonstrates that the statistical

Figure 6: Predictive model performance versus feature selection power for each model and independent trial using EROSS.
evidence from the model does not match with the ranking heuristics.

6.2 Additional discoveries by the HRT

In the drug response experiment, the HRT selected additional features. Table 2 shows all discoveries by the HRT at a 20% FDR threshold that were not ranked in the top 10 by the heuristic. Alongside each feature we show its p-value estimate, heuristic score, and heuristic ranking. Several features were found to have significant predictive power despite their estimated model effect size being relatively low. This suggests there may be new potential targets of therapy worthy of follow-up investigation.

7 Discussion

When Leo Breiman wrote about the two cultures in statistics [Breiman, 2001], he divided statisticians into the data modelers and the algorithmic modelers. Data modelers relied on inflexible, idealized parametric models that make unrealistic assumptions about the true data generating distribution in order to gain the mathematical convenience of verification tools like goodness-of-fit tests. Algorithmic modelers chose to treat the latent function mapping features to response as a black box. In this latter paradigm, predictive performance on held out data was the only way to truly measure the strength of a model. Breiman estimated at the time that 98% of the mainstream analyst world fell into the data modeling crowd, while a mere 2% were algorithmic modelers.

Nearly 20 years later, the tables have turned. A confluence of factors (better numerical computing tools, the rise of Computer Science as one of the most popular majors in university, the dawn of the “Big Data” era, high throughput screening techniques in science, and the practical successes of machine learning) has led us to a world where algorithmic modeling is the norm and test error is the gold standard for model evaluation. The gravity of algorithmic

### Table 1: Two examples of predictive modeling with heuristic post-hoc feature importance ranking in scientific studies. 

| Genomic Feature | Imp. score | Est. p-value | Molecular Feature | Imp. score | Est. p-value |
|-----------------|------------|--------------|-------------------|------------|--------------|
| BRAF V600E Mut  | 0.0975     | ≤ 10^{-5}*   | Isovanillin       | 0.2629     | 0.0012*      |
| RP11-208G20.3   | 0.0715     | 0.0065*      | Vanillin isobutyrate | 0.0528 | 0.2553      |
| RP6-149D17.1    | 0.0665     | 0.2108       | Ethyl vanillin    | 0.0481     | 0.0430       |
| RNU6-104P       | 0.0652     | 0.9970       | Ethyl vanillin acetate | 0.0258 | 0.0666      |
| RNA5SP184       | 0.0634     | 0.3359       | Protocatechualdehyde | 0.0236 | 0.1515      |
| VPS13B Mut      | 0.0557     | 0.0042*      | Vanillin acetate | 0.0232     | 0.2845       |
| RP11-567M16.3   | 0.0535     | 0.0079*      | 2-Formylimidazole | 0.0186 | 0.8132      |
| MTMR11 Mut      | 0.0525     | 0.0821       | R7e+              | 0.0179     | 0.5806       |
| ZNF549          | 0.0524     | 0.1915       | Ethyl Isovalerate | 0.0123     | 0.7837       |
| HIP1 Mut        | 0.0519     | ≤ 10^{-5}*   | SM05 AEA(ri)      | 0.0099     | 0.2751       |

(a) Elastic net for cancer drug response

(b) Random forests for olfactory perception

Table 2: Two examples of predictive modeling with heuristic post-hoc feature importance ranking in scientific studies. 

| Genomic Feature | Imp. score | Est. p-value |
|-----------------|------------|--------------|
| BRAF V600E Mut  | 0.0975     | ≤ 10^{-5}*   |
| RP11-208G20.3   | 0.0715     | 0.0065*      |
| RP6-149D17.1    | 0.0665     | 0.2108       |
| RNU6-104P       | 0.0652     | 0.9970       |
| RNA5SP184       | 0.0634     | 0.3359       |
| VPS13B Mut      | 0.0557     | 0.0042*      |
| RP11-567M16.3   | 0.0535     | 0.0079*      |
| MTMR11 Mut      | 0.0525     | 0.0821       |
| ZNF549          | 0.0524     | 0.1915       |
| HIP1 Mut        | 0.0519     | ≤ 10^{-5}*   |

Table 1: Two examples of predictive modeling with heuristic post-hoc feature importance ranking in scientific studies. a) Genomic features were used to predict cell line response to treatment with the drug PLX-4720 [Barretina et al., 2012]. b) Molecular features were used to predict perceived fragrant properties of molecules [Keller et al., 2017]. Asterisks indicate features selected by the HRT at a 20% FDR threshold.
| Genomic Feature | Heuristic ranking | Coefficient magnitude | Est. p-value |
|-----------------|-------------------|-----------------------|--------------|
| CNTN1 Mut       | 11                | 0.0512                | 0.0059       |
| RNU6-448P       | 12                | 0.0486                | 0.0000       |
| MIR4482-1       | 14                | 0.0474                | 0.0004       |
| MTND4P25        | 19                | 0.0457                | 0.0010       |
| RP11-585F1.8    | 20                | 0.0451                | 0.0058       |
| RN7SL528P       | 21                | 0.0433                | 0.0034       |
| KRTAP23-1       | 25                | 0.0384                | 0.0006       |
| GS1-24F4.3      | 29                | 0.0372                | 0.0000       |
| FLT3 Mut        | 31                | 0.0363                | 0.0000       |
| RNU6-1287P      | 32                | 0.0360                | 0.0000       |
| RP11-575H3.1    | 44                | 0.0294                | 0.0035       |
| SNAPC3          | 51                | 0.0268                | 0.0012       |
| RP11-541E12.1   | 55                | 0.0251                | 0.0000       |
| RP11-488I4.2    | 70                | 0.0225                | 0.0012       |
| RNA5SP234       | 72                | 0.0224                | 0.0000       |
| CDC42BPA Mut    | 76                | 0.0213                | 0.0000       |
| NEURL           | 79                | 0.0205                | 0.0000       |
| RP11-481A12.2   | 82                | 0.0203                | 0.0002       |
| HCP5            | 86                | 0.0200                | 0.0011       |
| CTC-539A10.7    | 91                | 0.0190                | 0.0062       |
| PIK3R4 Mut      | 98                | 0.0183                | 0.0025       |
| SLC35G6         | 115               | 0.0165                | 0.0008       |
| PIP5K1A Mut     | 122               | 0.0162                | 0.0002       |
| CCND2 Mut       | 171               | 0.0123                | 0.0026       |
| CDC37L1         | 178               | 0.0121                | 0.0000       |
| CSPG4 Mut       | 211               | 0.0094                | 0.0003       |
| RP5-1195D24.1   | 213               | 0.0094                | 0.0000       |
| DIP2C Mut       | 256               | 0.0081                | 0.0003       |
| RIOK3 Mut       | 358               | 0.0055                | 0.0049       |
| POLR2J4         | 401               | 0.0047                | 0.0031       |
| CACNA2D2        | 409               | 0.0046                | 0.0060       |
| RNA5SP280       | 420               | 0.0044                | 0.0020       |
| NTSR1 Mut       | 672               | 0.0018                | 0.0002       |

Table 2: Additional genomic features selected by the HRT at a 20% false discovery rate threshold in the drug response study, but not in the top 10 ranking of coefficient magnitude.
modeling has grown so strong that it has even pulled in many scientific fields, leading to prediction challenges like the DREAM series [Stolovitzky et al., 2007]. These challenges publicly release scientific data and teams compete to build the best model based solely on performance on held out test data. One would be hard pressed to argue that the algorithmic modelers are in the minority today.

Yet as we have shown, this shift has come at the cost of reliably extracting understanding from the data, what Breiman called the information goal. Articles in premier scientific journals now commonly use machine learning methods to build predictive models then derive scientific conclusions from ad-hoc model interpretation. These heuristic approaches rest on unstable ground that may lead scientists astray by convincing them that a strong signal exists where there is only noise. Breiman himself nearly solved this by effectively proposing to use what we call the marginal permutation HRT (Section 5.2) as a means for interpreting random forests, but he failed to consider the need to account for feature dependency structure in his test. It is fitting then that rigorously extracting information from black box models, as the HRT does, requires using more black box modeling (i.e. conditional density estimators) to disentangle the features and perform a reliable conditional independence test.

There are several additional directions to explore for extending the HRT to other analysis settings. In some models, such as empirical Bayes models that use predictive models for prior estimation, inference is still too expensive to run the HRT. Efficiently searching over the space of potential features to test, using an approach like Bayesian optimization [Shahriari et al., 2016] or multi-armed bandit learning [Gandy and Hahn, 2017], would make applying the HRT to compute-intensive models feasible. In other scenarios, such as image classification, language modeling, and time series analysis, the features themselves have a more complicated structure and selecting an individual feature is not necessarily the inferential goal. For example, a pixel location being significant is not usually an interesting discovery in image classification. A conceptual layer needs to be added to extract meaningful insight in these types of models.

Finally, the HRT has the added benefit of allowing arbitrarily fine-grained questions to be asked. For instance, the scientist can partition the dataset based on some other feature, at which point the null hypothesis is \(X_j \perp \perp Y | X_k = x, X_\setminus(j,k)\). This is a common test in biology, where predictive models are often trained on all of the data but questions are then asked about feature dependencies for specific samples, such as a specific type of cancer or class of drug. We plan to explore these data-partitioning scenarios in future work.

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A Approximate calibration via a one-way KS statistic

For continuous random variables, we propose a one-way Kolmogorov-Smirnov (KS) statistic to choose the lower and upper quantiles of the bootstrapped models. An adaptation to discrete random variables is also available in our implementation. For other types of features, we recommend a conservative bound of \((l, u) = (5, 95)\); we find this is sufficient to control FDR in preliminary experiments.

We describe the approach in terms of finding a lower bound; the upper bound is determined analogously. To choose a lower quantile, we start with the median \((l = 50)\) and iteratively lower it until the CDF estimates dominate the uniform CDF from above in a Q-Q plot. Let \(C_{j|j} \) be the CDF for \(B_{j|j} \). The one-way lower-KS statistic for \(l \) is then,

\[
KS^+(l) = \max_{c \in [0, 1]} \left( 0, c - \frac{1}{n} \sum_{i=1}^{n} I \left[ C_{j|j}^{(l)}(X_{ij}) \leq c \right] \right).
\]

We then check if the current choice of \(l \) yields a sufficiently-small test statistic. Specifically, we conduct a hypothesis test by Monte Carlo, where we repeatedly draw samples from \(U(0, 1)\) and only accept \(l \) if it is smaller than \(10^5 \) draws from a true \(U(0, 1)\). This corresponds to solving the following optimization problem:

\[
\arg\max_l \quad \max(0, KS^+(l)) \quad \text{subject to} \quad KS^+(l) < \tau^+,
\]

where \(\tau^+ \) is the MC-derived threshold; the upper quantile is found analogously. While the calibration procedure may seem very conservative, in practice it yields reasonable bounds even for the high-dimensional datasets in Section 5.
B Proof of Theorem 1

Proof. By the law of large numbers, almost surely,

\[
\lim_{K \to \infty} \hat{p}_j^K = \frac{\mathbb{E}_Q[\hat{W}^{(k)} \mathbbm{1}\{E_j\}]}{\mathbb{E}_Q[\hat{W}^{(k)}]} \tag{11}
\]

\[
= 1/(1 + \frac{\mathbb{E}_Q[\hat{W}^{(k)}(1 - \mathbbm{1}\{E_j\})]}{\mathbb{E}_Q[\hat{W}^{(k)} \mathbbm{1}\{E_j\}]}) \tag{12}
\]

where the second line is an algebraic manipulation. Notice that

\[
\mathbb{E}_Q[\hat{W}^{(k)} \mathbbm{1}\{E_j\}] = \mathbb{E}_Q[\frac{h_{j|j}}{Q_{j|j}(\hat{X}_j^{(k)})} \mathbbm{1}\{E_j\}]
\]

\[
= \mathbb{E}_{P_{j|j}}[\frac{h_{j|j}}{P_{j|j}(\hat{X}_j^{(k)})} \mathbbm{1}\{E_j\}]
\]

\[
\geq p_j,
\]

where the last line is by assumption. Similarly, \(\mathbb{E}_Q[\hat{W}^{(k)}(1 - \mathbbm{1}\{E_j\})] \leq 1 - p_j\). The result then follows by comparing \(p_j = 1/(1 - \frac{1-p_j}{p_j})\) and Eq. (12). \(\square\)