A Model-free Approach for Testing Association

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Abstract

The question of association between outcome and feature is generally framed in the context of a model on functional and distributional forms. Our motivating application is that of identifying serum biomarkers of angiogenesis, energy metabolism, apoptosis, and inflammation, predictive of recurrence after lung resection in node-negative non-small cell lung cancer patients with tumor stage T2a or less. We propose an omnibus approach for testing association that is free of assumptions on functional forms and distributions and can be used as a black box method. This proposed maximal permutation test is based on the idea of thresholding, is readily implementable and is computationally efficient. We illustrate that the proposed omnibus tests maintain their levels and have strong power as black box tests for detecting linear, nonlinear and quantile-based associations, even with outlier-prone and heavy-tailed error distributions and under nonparametric setting. We additionally illustrate the use of this approach in model-free feature screening and further examine the level and power of these tests for binary outcome. We compare the performance of the proposed omnibus tests with comparator methods in our motivating application to identify preoperative serum biomarkers associated with non-small cell lung cancer recurrence in early stage patients.

Keywords: Feature screening, Lung Cancer, Maximal test, Permutation test, Thresholding.

1 Introduction

The question of association between outcome and feature is of interest in most scientific investigations. This association is usually explored within the framework of an appropriate statistical model depending on the scale of the outcome, such as a linear model, a generalized linear model or a time-to-event response model. Nonparametric regression models provide flexibility from the constraints of specified functional forms of these parametric models. In most cases, the primary objective of such analysis is to model the functional relationship. Instead, our objective here is to provide a decision on the association without necessarily modeling the functional relation.

Our motivation for this work comes from our longtime association with Non-Small Cell Lung Cancer (NSCLC) research. Lung cancer is the leading cause of cancer mortality in the United States and NSCLC

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accounts for about 85% of the lung cancer cases. National Comprehensive Cancer Network and Medicare and Medicaid services are supporting widespread implementation of lung cancer screening programs for identification of early stage lung cancers. Unfortunately, approximately 1 in 5 patients with pathologic stage IA NSCLC die of disease recurrence within 5 years of tumor resection. A recent study focused on identifying serum biomarkers for predicting recurrence after lung resection in node-negative NSCLC patients with tumor stage T2a or less (tumors less than 4 cm). Preoperative serum specimens of the patients were evaluated in a blinded manner for biomarkers of angiogenesis, energy metabolism, apoptosis, and inflammation; biological processes known to be associated with metastatic progression. From a statistical perspective, the popular approach for assessing association with the binary outcome of recurrence within 5 years is a binary regression analysis within the parametric framework of a logistic regression model. However, none of the biomarkers are found to be marginally significantly associated with recurrence in logistic regression framework (see Table 5). Penalized variable selection approaches such as Lasso (Tibshirani 1996), Elastic Net (Zou and Hastie 2005) and Surely Independent Screening (Fan et al. 2010) all yield the null model as the selected model.

Our primary objective in this article is to develop a general framework for providing a decision about the association between outcome and feature without necessarily modeling their functional relation. Towards this goal, we propose an omnibus test for association that can be used as a general black box tool. This omnibus test is based on thresholding and is computationally efficient. Thresholding is a popular approach to provide flexibility from or within parametric models. Recursive partitioning models (Trees (Breiman et al. 1984), Random Forests (Breiman 2001)) extend thresholding to model-free approaches. Even within parametric models, thresholding provides robustness from outlying values and assumed functional forms.

Thresholding can be based on scientific knowledge and historical knowledge from previous studies. For example, Carcino Embryonic Antigen (CEA) in Table 5 is a common prognostic and predictive biomarker for NSCLC (Grunnet and Sorensen 2012; Dong et al. 2016). However, there is no strong biological evidence that supports a single threshold for CEA (Grunnet and Sorensen 2012). In absence of prior scientific knowledge, thresholds are often determined empirically. Data dependent threshold selection approaches include splits at arbitrary percentiles (such as median). A popular method, as reviewed in Mazumdar and Glassman (2000), is an empirical systematic search for an optimal threshold which, using statistical criterion, maximizes the measure of differences between low and high groups with respect to an outcome. This method is associated with the minimum p-value approach. A well documented issue of this approach is the significant inflation of type I error and the resulting overstatement of significance of the relationship between the prognostic and the outcome variable (Mazumdar and Glassman 2000). In our simulation studies we found that the inflation of type-I error can be as high as 0.30 from the target value of 0.05.

Several methods have been proposed for adjustment of chi-square tests under threshold selection. Lausen and Schumacher (1992) proposed the maximally selected rank statistic which is the maximum of the absolute value of the standardized two sample linear rank statistic obtained through empirical process. They also derived the asymptotic null distribution of the statistic and showed that the result is similar to the asymptotic distribution of the maximum chi-square as derived by Miller and Siegmund (1982). Based on this asymptotic distribution Miller and Siegmund (1982) derived p-value adjustment in the setting of binary outcome variables; this approach works best when number of potential cutpoints is large (Mazumdar and Glassman 2000). For small minimum p-values, Altman et al. (1994) provided
a simplified formula for adjustment of the minimum p-value. Lausen and Schumacher (1996) derived a modified version of the Bonferroni correction which incorporates the dependencies among the test statistics for adjacent thresholds. The alternative adjustments of the minimum p-value suggested by Altman et al. (1994) and Lausen and Schumacher (1996) work for smaller number of thresholds.

Each of these methods has its own complexities and remains infrequently used. Further, we find that many of these proposed adjustments result in substantial loss of power. In this article, we instead propose a test based on the concept of permutation distribution of the maximal test statistic which can successfully capture the dependencies among the tests at individual thresholds. The simplicity of this method is in its generality. We illustrate that the proposed method can be used as a general black box test for association and does not require complex analytic adjustments. Further, being based on the permutation distribution, this method is free of distributional assumptions. The proposed approach is based on thresholding of the feature variable. There is often concern that thresholding may result in loss of information. Our simulation studies, however, show that the proposed method based on repeated thresholding of the feature variable provides comparable power under correct model specifications and superior power under model mis-specifications compared to standard methods that utilize original feature values.

The rest of the article is organized as follows. In section 2 we develop the general framework for testing the association hypothesis. The maximal permutation test is proposed and described in section 3. Section 4 develops and illustrates the utility of the test as a black box test for association in the setting of binary outcome and compares with standard and other existing methods. We illustrate the model-free performance of the test in section 5 in a wide range of settings ranging from quantile regression to heavy-tailed and outlier-prone cases. We additionally illustrate performance of the proposed approach in feature screening and compare with screening based on distance correlation (Li et al., 2012). In section 6 we illustrate the performance of our proposed method in establishing association of NSCLC recurrence with preoperative serum biomarkers and conclude with a brief discussion in section 7.

2 Formulation

We are interested in exploring the association between outcome Y and feature X. The null hypothesis of no association between Y and X is reformulated in our thresholding approach as \( \bigcap_c H_{0c} \) for threshold \( c \) in the feature space of \( X \) and where each \( H_{0c} \) represents the two-group null hypothesis of no difference between \( Y|X \leq c \) and \( Y|X > c \).

While our approach is completely model-free, to fix ideas, consider the case when the association between \( Y \) ans \( X \) is expressed by a function \( h(x) \). The function \( h(x) \) may be linear, nonlinear, or could, for example be expressed as a nonparametric regression model. The association with the stochastic outcome \( Y \) is expressed in terms of a quantity \( \eta Y|X \) associated with the probability distribution \( F_{Y|X} = x \) via the regression model \( \eta Y|X = h(x) \). Examples of \( \eta Y|X \) include \( E[Y|X = x] \) or a quantile of \( F_{Y|X} = x \) as in quantile regression. Within this regression framework, the no association null hypothesis is usually formulated as the regression function \( h(x) \) being constant in \( x \), namely \( H_0 : \eta Y|x \equiv h_0 \). In the thresholding approach, we formulate this no association hypothesis as \( \bigcap_c H_{0c} \) where \( H_{0c} : \eta Y|x \leq c = \eta Y|x > c \).

To put this in a more concrete setting, popular regression models, such as generalized linear models and others, can be put in the framework where \( Y_1, \ldots, Y_n|X \) are independent and \( Y_i|X = x \sim f(y_i|\theta_i, \phi) \) with \( \theta_i = h(x_i) \), \( i = 1, \ldots, n \). Within this framework, the no association null hypothesis of \( H_0 : h(x) \equiv h_0 \)
implies that $Y_1, \ldots, Y_n$ are i.i.d. Under the alternative $H_a: h(x) \neq h_0$, $Y_1, \ldots, Y_n$, however, are no longer exchangeable.

We note here that one can also formulate the no association hypothesis in a nonparametric testing formulation as $\bigcap_{c} H_{0c}^{NP}$ where $H_{0c}^{NP}: F_{Y|X \leq c} = F_{Y|X > c}$. Tests focusing on $H_{0c}^{NP}$ may check for association beyond the specified regression model structure.

Permutation tests were introduced by Fisher (1936). The theoretical properties of these tests were studied in Pitman (1937), Lehmann et al. (1949), Hoeffding (1952), among others. Permutation tests are generally considered when the null hypothesis $H_0$ under consideration is a subset of an exchangeable specification for the outcomes $Y_1, \ldots, Y_n$,

$$H_0 \subseteq \{Y_1, \ldots, Y_n \text{ are i.i.d.}\} \quad (1)$$

Let $T_n(Y) = T_n(Y_1, \ldots, Y_n)$ be a test statistic for testing $H_0$. Also, let $(\pi(1), \ldots, \pi(n))$ denote a permutation of $(1, \ldots, n)$ and let $\Pi_n = \{\text{the group of all such permutations } \pi\}$. The permutation distribution of the test statistic is usually constructed as $\{T_n(\pi(Y)) = T_n(Y_{\pi(1)}, \ldots, Y_{\pi(n)}), \pi \in \Pi_n\}$ with equal probability of $1/n!$ and the $p$-value under the permutation distribution can be roughly computed as the tail area probability of $T_n(Y)$ under this permutation distribution (The permutation test statistic is usually defined as a randomization test to account for the discreteness).

Under the i.i.d. hypothesis, the permutation test is of exact level for each sample size $n$ (Janssen et al., 2003). The book by Good (2013) provides a practical review of permutation tests. There is an extensive literature on permutations and other resampling tests (see Janssen et al., 2003) and studentized permutation tests when $H_0$ is strictly bigger than the i.i.d structure (Chung and Romano, 2013; Janssen, 1997). The i.i.d. structure may be violated when the null hypothesis implies equality of a functional (such as mean or quantile) of the distributions, but not the distributions themselves. This, for example, may arise in the presence of nuisance parameters, such as, with heteroscedastic variances (Janssen, 1997; Chung and Romano, 2013).

The power of the permutation test has been extensively investigated. Hoeffding (1952) established general conditions under which permutation tests are asymptotically as powerful as corresponding standard parametric tests. See also Lehmann et al. (1949); Wald and Wolfowitz (1944) and Lehman (1986, p230).

3 An Omnibus test for association

For a response $Y$ and a continuous predictor $X$, we describe here a model-free omnibus test for testing their association. The proposed test procedure can be applied when $Y$ is treated as measured in a continuous scale, or when $Y$ is binary or when $Y$ is a time-to-event, though we do not consider the last case in this article. The test procedure also does not depend on the modeled functional relation between the predictor $X$ and response $Y$ and thus can be applied blindly irrespective of whether the functional relation is linear or nonlinear, or whether it is specified in terms of $E[Y|X]$, quantile of $F_{Y|X}$ or something else.

The concept of the test procedure is based on the observation that the hypothesis of no association typically results in $Y_1, \ldots, Y_n$ being exchangeable. For the test statistic, we use a repeated thresholding approach. In particular, let $C$ denote the class of thresholds considered and for $c \in C$, let $T_n^c(Y)$ denote the test statistic for either the parametric hypothesis $H_{0c}: \eta_{Y|X \leq c} = \eta_{Y|X > c}$ or the nonparametric hypothesis $H_{0c}^{NP}: F_{Y|X \leq c} = F_{Y|X > c}$. We consider the test statistic $T_n(Y) = \max\{T_n^c(Y): c \in C\}$ and next apply
the permutation test procedure to this test statistic $T_n(Y)$. In particular, the permutation distribution of this test statistic is given by $\{\max_c T_n(\pi(Y)) : \pi \in \Pi_n\}$ where $\max_c T_n(\pi(Y)) = \max_c T_n(Y_{\pi(1)}, \ldots, Y_{\pi(n)})$ for a permutation $\pi$ in permutation group $\Pi_n$.

Procedurally, the proposed test is based on the following steps

0. Select a two-group test statistic $T_n(Y)$ for comparing $\{Y|X \leq c\}$ and $\{Y|X > c\}$.

1. Obtain

$$\max_c T_n^c(Y) = \max_c \{T_n^c(Y) : c \in C\}$$

for the class of thresholds $C$.

2. Repeat 1. for $\pi(Y)$ and over the class of permutations $\pi \in \Pi_n$ to obtain the permutation distribution

$$\{\max_c T_n^c(\pi(Y)), \pi \in \Pi_n\}.$$  \hspace{1cm} (3)

As is apparent from the above description, this proposed test is completely model-free and can be applied as a black box test without modeling the functional relation between $Y$ and $X$. The test is also free of distributional assumptions.

The computational complexity of the test arises from the repeated computation of the test statistic over the class of thresholds $C$ and then the repetitions over the class of permutations $\Pi_n$. However, several simplifications are possible. The indexing of $\{X \leq c\}$ and $\{X > c\}$ are invariant to permutation of $Y$ and thus can be done swiftly based on ordered $X$’s outside the repetitions over $\Pi_n$. Computational simplifications are also possible for some test statistics $T_n^C(Y)$, for example, when $T_n^C(Y)$ is chosen as the Mann-Whitney statistic, the mapping from $Y$ to rank($Y$) is invariant to permutations and thus need to be done only once for the original $Y$. In our implementation in the R software on a personal laptop without utilizing parallel computing, for $n = 400$, the whole computation for 1000 random permutations from $\Pi_n$ was completed in 0.09 seconds. The procedure above is, of course, ideally suited for distributing the computation of each permutation over parallel nodes.

We now discuss the choice of the two-group test statistic $T_n^c(Y)$ for comparing $\{Y|X \leq c\}$ and $\{Y|X > c\}$. When $Y$ is treated as measured in continuous scale, and the regression model between $Y$ and $X$ is modeled via $E(Y|X = x)$, we have $H_{0c} : E[Y|X \leq c] = E[Y|X > c]$ and one choice for $T_n^c(Y)$ is the two-sample t-statistic based on $\{Y_i : x_i \leq c\}$ and $\{Y_i : x_i > c\}$. The choice of Welch type studentization may provide additional robustness to the permutation test procedure (see Chung and Romano [2013]; Janssen (1997)) which is further discussed in section 6.1. Alternatively, and for testing $H_0^{NP} : F_{Y|X \leq c} = F_{Y|X > c}$, one can use the Mann-Whitney/Wilcoxon test statistic. For binary $Y$, $H_{0c} : P(Y = 1|X \leq c) = P(Y = 1|X > c)$ and $T_n^c(Y)$ can be chosen to be the chi-square or Fisher’s exact statistics. For time-to-event $Y$, $T_n^c(Y)$ can be selected to be the log-rank or similar test statistics.

The proposed test is of exact level by the usual theory of permutation tests as long as $Y_1, \ldots, Y_n$ are i.i.d under the no association hypothesis. The i.i.d. assumption does not hold, for example, when errors are heteroscedastic, this case is explored in section [5.1]. In the following sections, we examine the power of the proposed test with its comparators in different scenarios.
4 Association with a binary outcome

Consider the setting when we have observations \((y_i, x_i) = \{(y_i, x_i), \ i = 1, \ldots, n\}\) where \(y\) is treated as measured in binary scale while \(x\) is continuous and the scientific question of interest is to make a decision on the association between outcome \(Y\) and feature \(X\). Following our approach discussed above, we reformulate the null hypothesis of \(H_0\) of no association as \(\bigcap_{c} H_{0c}\) for threshold \(c\) in the feature space of \(X\) and where each \(H_{0c}\) represents the two-group null hypothesis of no difference between \(Y|X \leq c\) and \(Y|X > c\). We can construct a \(2 \times 2\) table (see Table 1) based on the observed \(\{x_i, y_i\}\) values and let \(T_n^c(y)\) be the \(\chi^2\) test statistic based on Table 1 for \(H_{0c}\). Operationally, the statistic remains constant in between ordered \(x\)-values \(x^{(i)} \leq c < x^{(i+1)}\), so it suffices to consider the observed \(\{x_i\}\) as possible choices at threshold \(c\). The maximal test statistic is given as before \(\max_{c} T_n^c(y) = \max_{c} \{T_n^c(y) : c \in C\}\)

|          | \(x_i \leq c\) | \(x_i > c\) |
|----------|----------------|-------------|
| \(y_i = 0\) | \(n_{11c}\)   | \(n_{12c}\) |
| \(y_i = 1\)  | \(n_{21c}\)   | \(n_{22c}\) |

There is a substantial literature on the maximal \(\chi^2\) test statistic based on thresholding of the feature space. Halpern (1982) considered the maximal \(\chi^2\) statistic over the central \((1 - 2\epsilon)\) proportion of \(\{x_i\}\) as \(\chi^2_{max} = \max_{\lceil n \rceil + 1 \leq c \leq n - \lfloor n \rfloor - 1} T_n^c(y)\) where \(0 \leq \epsilon < \frac{1}{2}\) and \([\ell]\) denotes 'the largest integer \(\leq \ell\)'. This method of maximal test statistics has been referred to as the equivalent minimum \(p\)-value approach by Altman et al. (1994) to highlight the associated multiple testing (Mazumdar and Glassman 2000). We have observed that when \(\alpha\) is controlled at 0.05 for testing each individual \(H_{0c}\) by the usual \(\chi^2\) test, the family wise error rate (FWER, Hochberg and Tamhane (1987)) for \(\bigcap H_{0c}\) can inflate to as high as 0.30. There is an extensive literature and extensive list of general approaches for controlling the FWER (see, for example, Hochberg and Tamhane (1987), Dudoit and Van Der Laan (2007)), however these general purpose methods may not incorporate the specific structure of repeated thesholding. Miller and Siegmund (1982) considered a similar problem, however, in their framework, \(Y = 0\) and \(Y = 1\) groups are treated as fixed whereas \(X|Y = j \sim F_j,\ j = 0, 1\) and the null hypothesis of interest is \(F_0 = F_1\). In particular, they addressed the question of two sample comparison by the maximally selected \(\chi^2\) statistic rather than the question of association between the outcome \(Y\) and predictor \(X\) that we are interested in. A detailed review of these approaches and many other methods are discussed in Mazumdar and Glassman (2000).

We compare the performance of our maximal permutation test with Miller and Siegmund (1982), Altman et al. (1994) and modified Bonferroni (Lausen and Schumacher 1996) in simulation studies. For the first simulation study, we consider a data generating model where the association between binary outcome \(Y\) and predictor \(x\) is described by logistic regression

\[
\text{logit}(P(Y_i = 1)) = \beta_0 + \beta_1 x_i,
\]

For the analysis methods for evaluating the association between \(X\) and \(Y\), we consider (1) logistic regression, (2) maximal \(\chi^2\) statistic based on thresholding which is then compared with \(\chi^2\) distribution without any adjustments (maximal), (3) Miller and Siegmund (1982), (4) Altman et al. (1994), (5) modified Bonferroni (Lausen and Schumacher 1996) and (6) the proposed maximal permutation approach. We examine the
level (type 1 error) and power of these approaches by repeated data simulations from the data generating model in [4].

Table 2: Sizes (Type-I errors) of tests. Target level is 0.05,

| Data Generation | Analysis methods |
|-----------------|------------------|
| Logistic        | Logistic | Maximal | Miller-Siegmund | Altman | Modified Bonferroni | Permutation |
| Linear          | 0.04     | 0.32    | 0.02           | 0.02   | 0.03                | 0.04        |
| Quadratic       | 0.040    | 0.358   | 0.024          | 0.024  | 0.018               | 0.036       |

Table 2 shows that the maximal-unadjusted approach severely inflate the Type-1 error to 0.32 from the target 0.05 level. The previously proposed approaches of Miller and Siegmund (1982), Altman et al. (1994) and Lausen and Schumacher (1996), on the other hand, are overly conservative in maintaining their levels.

Figure 1a plots the empirically estimated power curves of these six methods. The maximal-unadjusted approach depicts highest power but, as noted before, has substantially inflated type-I error. Among the remaining five methods which maintain their levels, the logistic regression analysis model utilizes the correct specified model here and shows highest power. The proposed maximal permutation approach displays the next best power curve.

![Figure 1a: Empirically estimated power curves under different data generation models](image)

Figure 1: Empirically estimated power curves under different data generation models: (a) binary response with logistic linear regression and (b) logistic quadratic regression.

We explore robustness to model misspecification under with a quadratic logistic regression as the data generating model

\[
\text{logit}\{P(Y_i = 1)\} = \beta_0 + \beta_1 x_i + \beta_1 x_i^2.
\]

We consider the same set of analysis methods as in the previous simulation study. We continue to use logistic linear regression as an analysis model to mimic common practice of considering only linear relations. The maximal permutation test is used as a black box test without any modifications. The type I error reported in Table 2 show that the maximal unadjusted method again results in a severely inflated type 1 error. The power curves in Figure 1b show that the linear-logistic method has relatively low power under this model mispecification, The maximal permutation test shows strong power in detecting association while maintaining the level of the test whereas the previously proposed methods are conservative and have lower power compared to the maximal permutation test.
5 Association with outcome measured on continuous scale

In this section, we consider the setting when we have observations \((y, x) = \{(y_i, x_i), \ i = 1, \ldots, n\}\) where \(Y\) is treated as measured on continuous scale. The proposed maximal permutation test can again be used as a completely general blackbox method to make a decision on the association between \(Y\) and \(X\). We consider variants of the proposed test in \((3)\) based on three different choices of \(T^n(Y)^\pi\), namely the two-sample t-statistic, the Welch t-statistic and the Mann-Whitney statistic. For the two-sample t-statistic, we take a permutation \(\pi \in \Pi_n\) and a cutpoint \(c \in \mathcal{C}\) and calculate the two-sample t-statistic

\[
T^n_\pi(Y) = \frac{\bar{Y}_{\pi,1} - \bar{Y}_{\pi,2}}{\sqrt{\left(\frac{(n_{\pi,1} - 1)s^2_{\pi,1} + (n_{\pi,2} - 1)s^2_{\pi,2}}{(n_{\pi,1} + n_{\pi,2} - 2)}\right)}}
\]

where \((n_{\pi,1}, \bar{Y}_{\pi,1}, s_{\pi,1})\) and \((n_{\pi,2}, \bar{Y}_{\pi,2}, s_{\pi,2})\) are the sample sizes, means and standard deviations of \(\{Y_{\pi(i)} : x_i \leq c\}\) and \(\{Y_{\pi(i)} : x_i > c\}\) respectively. We next obtain \(\max_c T^n_\pi(Y)\) and its permutation distribution over permutations \(\pi \in \Pi_n\).

There has been extensive research on two-sample permutation tests when the null hypothesis specifies equality of two population quantities (such as means) but may not result in the two population distributions being the same. One prominent example is testing for equality of means under unequal variances. \cite{Janssen1997} and \cite{Chung2013} established that even though the exchangeable assumption does not hold in this setting, permutation test using studentized statistics, especially the Welch’s t-statistic, given by \(T^n_{MW}(\pi(Y)) = \frac{\bar{Y}_{\pi,1} - \bar{Y}_{\pi,2}}{\sqrt{n_{\pi,1}s^2_{\pi,1} + n_{\pi,2}s^2_{\pi,2}}\)}\) asymptotically maintains the level of the test.

A third alternative test statistic that we consider is the Mann-Whitney statistic which considers the nonparametric hypothesis \(H^NP_0 : F_{Y|X \leq c} = F_{Y|X > c}\) and is given by \(T^n_{MW}(\pi(Y)) = \sum_{x_i \leq c} R_{\pi(i)} - \{n_{\pi,1}(n_{\pi,1} + 1)/2\}\) where, \(\{R_{\pi(i)}\}\) are the ranks associated with \(\{Y_{\pi(i)}\}\). Usually, rank based statistics are computationally more expensive compared to their parametric counterparts. In our setting however, the Monte Carlo permutation distribution of \(\max_c T^n_{MW}(\pi(Y))\) can be obtained substantially more efficiently than, for example, the t-statistics based counterparts. This substantial gain in computational efficiency is obtained from the simple observation that the mapping of rank \(R_i\) to observation \(Y_i\) remains invariant under a permutation, so the ranks only needs to be computed once and then reused in each permutation.

5.1 Linear model

We consider a linear regression model for data generation where we treat \(Y\) as measured in continuous scale and the regression model between outcome \(Y\) and predictor \(X\) is described by

\[
Y_i = \beta_0 + \beta_1 x_i + \varepsilon_i, \ i = 1, \ldots, n
\]  

(5)

where \(\varepsilon_1, \ldots, \varepsilon_n \overset{i.i.d.}{\sim} F_0\). This results in \(h(x) = \beta_0 + \beta_1 x\) and the hypothesis of no association is \(H_0 : h(x) \equiv \beta_0 \text{ or } \beta_1 = 0\). When \(F_0\) is Normal, the model can also be expressed as \(E[Y|x] = \eta_{Y|x} = \beta_0 + \beta_1 x\).

We examine the level (type 1 error) and power of the maximal permutation test based on the two-sample t-statistic, the Welch t-statistic and the Mann-Whitney statistic by repeated data simulations from the data generating model in \((5)\) with \(n = 50\). As comparators, we consider the usual linear regression test for \(H_0 : \beta_1 = 0\) (denoted as LM) and a robust test using the sandwich estimator of \(\text{Var} (\hat{\beta}_1)\) \cite{Zeileis2006} that may provide consistent estimator of variance of parameter estimates even under violation of model
Table 3: Sizes (Type-1 errors) of tests. Target level is 0.05.

| Data Generation       | Unadjusted methods | Maximal permutation statistics |
|-----------------------|--------------------|--------------------------------|
|                       | LM | Sandwich | T | Welch | Mann-Whitney | T \( (T_T) \) | Welch \( (T_W) \) | Mann-Whitney \( T_{MW} \) |
| Linear Regression     | 0.04 | 0.06 | 0.27 | 0.27 | 0.27 | 0.05 | 0.04 | 0.05 |
| Heteroscedastic       | 0.05 | 0.08 | 0.28 | 0.28 | 0.28 | 0.05 | 0.05 | 0.05 |
| Quadratic Reg         | 0.05 | 0.06 | 0.27 | 0.28 | 0.27 | 0.05 | 0.05 | 0.04 |
| Nonparametric Reg     | 0.05 | 0.06 | 0.31 | 0.32 | 0.31 | 0.06 | 0.06 | 0.06 |
| Outliers              | 0.04 | 0.03 | 0.27 | 0.31 | 0.18 | 0.05 | 0.04 | 0.04 |
| t-errors, df=1        | 0.03 | 0.03 | 0.27 | 0.36 | 0.14 | 0.05 | 0.05 | 0.05 |
| t-errors, df=2        | 0.04 | 0.04 | 0.33 | 0.32 | 0.26 | 0.05 | 0.05 | 0.04 |
| t-errors, df=8        | 0.04 | 0.04 | 0.33 | 0.32 | 0.31 | 0.04 | 0.05 | 0.04 |
| Quantile Reg, p=0.25  | 0.047 | 0.046 | 0.327 | 0.368 | 0.328 | 0.053 | 0.048 | 0.051 |
| Quantile Reg, p=0.5   | 0.042 | 0.053 | 0.297 | 0.281 | 0.296 | 0.053 | 0.046 | 0.057 |
| Quantile Reg, p=0.75  | 0.064 | 0.069 | 0.342 | 0.412 | 0.339 | 0.062 | 0.056 | 0.053 |

assumptions. We also include results from the often used unadjusted maximal test statistics methods where the maximum value of the test statistic over the set of cutpoints \( T(Y) = \max T_c(Y) \) is compared with the null distribution of the test statistic \( T_c(Y) \) (such as the appropriate t-distribution for the t-statistics \( T_c(T) \) or \( T_c(W) \)). As expected, the unadjusted methods result in inflation of Type-1 error. What is surprising is the level of this inflation; as we note in Table 3 the Type-1 error gets inflated to as high as 0.27 from the nominal 0.05 level. In contrast, the permutation tests maintain their level as prescribed by theory.

![Figure 2: Empirically estimated power curves under linear regression data generating model](image)

Figure 2 displays the power curves of the eight methods. The unadjusted methods have higher power curves as expected, but their power curves begin with excessively inflated levels (Type-1 error rates). The permutation based methods have only marginally lower power than the standard linear regression and sandwich methods but they provide the often sought categorization of the prognostic variable. They
also provide substantial robustness (as we illustrate below) at the expense of marginal loss of power. We also note that the Mann-Whitney based permutation test maintains almost the same power as its t-test equivalent. As we noted before, the Mann-Whitney based permutation test can be computed efficiently and it is also found to be the most robust as illustrated in the following.

**Heteroscedasticity:** If the variances $\text{Var}(Y_i|x_i)$ in the linear regression model (5) are not equal, then even under the null hypothesis of $H_0: \beta_1 = 0$, $Y_1, \ldots, Y_n$ are no longer exchangeable and the basic setting under which permutation tests function do not hold. As noted before, the properties of two-sample permutation tests in this setting has been studied in Janssen (1997) and Chung and Romano (2013). We investigate a specific setting where $\text{Var}(Y|x)$ increases with increase in the value of the predictor $x$, in particular $\text{Var}(Y|x) = \sigma^2(1 + x), x > 0$. As we notice in Table 3 the permutation based tests, in fact, maintain their levels even under violation of the exchangeable assumption. The estimated power curves in Figure 4a shows that the permutation tests also maintain good power.

**Quadratic regression:** We explore the wide scale applicability of the proposed test in the setting of a quadratic regression data generating model

$$Y_i = \beta_0 + \beta_1(x_i - 2)^2 + \epsilon_i, \ i = 1, \ldots, n$$

In common practice of statistical analysis, only linear functional forms are explored in analysis models to test for association and we mimic this case by considering the linear functional form based tests (LM and sandwich) as tests for association. In addition we investigate the unadjusted and permutation based maximal test statistics. Table 3 shows that the unadjusted tests severely inflate the Type-1 error as before. The power curve estimates in Figure 4b illustrate that due to the misspecification of the functional form, the linear functional form based tests (LM and sandwich) have almost no power at all in detecting the association. The maximal test statistics based permutation tests, on the other hand, display strong power for detecting association while maintaining the level of the tests. We want to emphasize that the permutation tests were used completely as generic black box tests without any modifications to reflect the structure of the data generating model.

**Nonparametric Regression:** We also explore the applicability of the proposed approach in the setting of a nonparametric regression model

$$Y_i = f(x_i) + \epsilon_i, \ i = 1, \ldots, n$$

for a function $f(\cdot)$ defined on $x$-space. We model the function $f(\cdot)$ using a basis expansion as $f(\cdot) = \sum \beta_j f_j(\cdot)$ where $\{f_j(\cdot)\}$ are the basis functions.
For our numerical study, we consider the cubic B-spline basis; the first few B-spline basis functions are shown in Figure 3. We vary the $\beta_j$ coefficients to consider a range of increasing signal to noise ratios in the nonparametric regression model and generate replicated datasets from each of these settings. As before, we apply the tests as blackbox association tests without any input about the data generating model. The power curve estimates in Figure 4c illustrate that the linear functional form based tests (LM and sandwich) again suffer from model misspecification and yield almost zero power. The maximal permutation tests, on the other hand, provide sufficient power in this nonparametric regression setting while having comparable type-I error (Table 3).

Figure 4: Empirically estimated power curves under different data generation models: (a) heteroscedastic errors; (b) quadratic regression; (c) nonparametric regression and (d) presence of outliers

5.2 Outliers

The robustness of the proposed tests in presence of outliers is investigated by considering a contaminated distribution (Tukey, 1960) for data generation from the model in (5) where $\text{Var}(Y|x)$ is taken to be $= 1$ with probability 0.9 and $= 100$ with probability 0.1; the large variance case allowing the potential of outliers. As in the previous cases, the permutation tests as well as the LM and sandwich tests maintain level $\leq 0.05$ whereas the levels of the unadjusted tests are severely inflated. In Figure 4d, we note that the permutation adjusted rank based maximally selected Mann-Whitney test statistic outperforms the other
methods. This is expected as rank based methods are resistant to outliers. We also note that the robust sandwich method outperforms the LM method.

5.3 Heavy tailed error distributions

The robustness of the proposed tests is further investigated by considering heavy tailed error distributions in data generation from the model in (5). We considered t-distributions with 1, 2 and 8 degrees of freedom (df) respectively for the error distribution. Note that for df = 1, E(Y|x) does not exist and the regression model can only be specified in terms of median (Y|x). As seen in Figure 5a-5c, the LM and sandwich methods as well as t-test based permutation methods perform poorly in this case whereas permutation adjusted rank based maximally selected Mann-Whitney test statistic significantly outperforms all other methods. For t-distribution with df = 2, Var(y|x) does not exist. The LM, sandwich and t-test based permutation methods perform better here but the permutation adjusted Mann-Whitney test statistic continues to outperform other methods. For df = 8, the estimated power curves reflect an ordering similar to the nominal case (df = ∞) where the permutation test based methods have power slightly below the LM and sandwich methods.

5.4 Quantile Regression

We also investigated the robustness of our proposed test methodology in exploring the association between the outcome and predictors in the framework of quantile regression (Yu and Moyeed, 2001). The p\(^{th}\) quantile (0 < p < 1) of Y conditional on X, denoted by q\(_p\) (Y|X), is regressed on a set of predictors X

\[ q_p (Y|X) = X \beta_p, \quad (6) \]

where \( \beta_p \) is the set of regression coefficients corresponding to the p\(^{th}\) quantile of the outcome. The estimate of \( \beta_p, \hat{\beta}_p, \) is the solution to the minimization of the loss function

\[ \min_{\beta_p} \sum \rho_p (y_t - x_t' \beta_p), \quad (7) \]

where \( \rho_p (u) = u (p - I (u < p)) \). The loss function in (7) is considered to be robust compared to the quadratic loss function in linear regression. The quantile regression problem can equivalently be formulated
Figure 6: Empirically estimated power curves under different data generation models: (a) quantile regression with 0.25<sup>th</sup> quantile; (b) quantile regression with 0.50<sup>th</sup> quantile; (c) quantile regression with 0.75<sup>th</sup> quantile.

In terms of the asymmetric Laplace distribution (Yu and Moyeed, 2001) and in our data generation model, we generate \( Y_i \sim \text{Asymmetric Laplace} (\mu_i, \sigma) \) with \( g(\mu_i) = x_i \beta_p \). We generate \( X \) from \( \text{Uniform} (0, 4) \), consider values of \( \beta \) in \([0, 2.5]\) and further considered \( p = 0.25, 0.5 \) and 0.75 quantiles. In Figure 6a-6c we observe that for \( p = 0.25 \) the permutation adjusted rank based Mann-Whitney test outperforms the rest of the methods giving maximum power while simultaneously maintaining the estimated type-I error at 0.05. However, the power of the permutation adjusted two sample T test and Welch test are observed to be less than that of the LM and Sandwich test. Similar results are obtained for \( p = 0.75 \) too. Also, the ordering of the performance of the methods remains unchanged for \( p = 0.5 \); permutation based Mann-Whitney still outperforms other methods.

5.5 Feature screening

In recent years, there has been increased interest in feature screening or filtering while modeling association with a number of predictor variables. Screening is often used to reduce the dimensionality of the feature space so that it is amenable for the next step of the analysis. Screening approaches in the setting of linear models include the sure independent screening (SIS) method proposed in Fan and Lv (2008) and the forward regression in Wang (2009). Fan et al. (2009) proposed screening in generalized linear models whereas Fan et al. (2011) considered feature screening in nonlinear additive models.

Consider the case when we have a number of \( X \)-variable \( X_1, \ldots, X_p \) but the data-generating model is postulated to be sparse in which only a few of these \( X \)-variables are postulated to be associated with outcome \( Y \). Sparsity is a frequently assumed framework in high dimensional data. Screening in this context is often done using a marginal utility or a marginal measure of association. In particular, let \( T_j = T(Y, X_j) \) denote a measure of marginal association between \( Y \) and variable \( X_j \). Features \( \{X_j\}_{j=1}^p \) are then screened based on \( \{T_j\}_{j=1}^p \) values, and for a pre-specified integer \( k \), a screening approach proposes the reduced set of \( X \) variables

\[
X_R = \{1 \leq j \leq p : T_j \text{ is among the top } k \text{ values}\}
\]

for consideration in the next stage of the analysis. Alternative strategy for constructing \( X_R \) may consist of including variables which are within a pre-specified threshold.

Fan and Lv (2008) considered screening with \( T(Y, X_j) \) being the marginal correlation between outcome
Y and feature $X_j$ and established sure independent screening property in the setting of linear regression. In the setting of generalized linear models, Fan et al. (2009) proposed independence screening with maximum marginal likelihood estimators. Fan et al. (2011) considered the context of nonparametric additive model where screening is performed by fitting marginal non-parametric regression to each of the features and then thresholding the utility of the predictors.

In this numerical study, we propose feature screening using the proposed maximal permutation test statistic as the marginal screening statistic $T(Y, X_j)$. As we have argued, the maximal permutation statistic is model-free and can be used as a blackbox approach for testing association. We have also illustrated strong performance of this statistic in detecting linear and nonlinear associations.

We explore screening performance in an example considered in Meier et al. (2009) and Fan et al. (2011). In this setting of a sparse additive model, out of features $\{1, \ldots, p\}$, the sparse data generating model only includes predictors $D = \{j_1, \ldots, j_d\}$ which are associated with outcome $Y$ via an additive model

$$Y_i = \sum_{j \in D} g_j(x_{ij}) + \varepsilon_i, \ i = 1, \ldots, n$$

where $g_j(\cdot)$ are functions of the respective predictors. Following Meier et al. (2009) and Fan et al. (2011), we take $d = 4$, $D = \{1, 2, 3, 4\}$ and $g_1(x) = \beta_1 x$, $g_2(x) = \beta_2 (2x - 1)^2$, $g_3(x) = \beta_3 \frac{\sin(2\pi x)}{(2-\sin(2\pi x))}$ and $g_4(x) = \beta_4 \{0.1\sin(2\pi x) + 0.2\cos(2\pi x) + 0.3\sin(2\pi x)^2 + 0.4\cos(2\pi x)^3 + 0.5\sin(2\pi x)^3\}$. We consider the case of $p = 100$, where the remaining 96 $X$-variables do not contribute in the data generating model.

Li et al. (2012) proposed use of the distance correlation for general feature screening that may not require a model specification. The distance covariance (Székely et al., 2007) Székely and Rizzo (2009) between two random vectors is a weighted $L^2$-distance between the joint characteristic function and the product of the marginal characteristic functions. The distance correlation is the ratio of the distance covariance to the product of the distance standard deviations. It is a measure of dependence between the random vectors and equals zero if and only if the random vectors are independent (Székely et al., 2007).

Following the distance correlation based screening in Li et al. (2012) and other works, we consider $T(Y, X_j) = \text{distance correlation}(Y, X_j)$ as a comparator screening method.

We follow the simulation framework in Meier et al. (2009) and Fan et al. (2011) and consider $n = 400$, $p = 100$, $\varepsilon_i \overset{i.i.d.}{\sim} N(0, \text{variance}=1.74)$, and $\beta = (\beta_1, \ldots, \beta_4) = (5, 3, 4, 6)$. We additionally include $\beta = (0, 0, 0, 0)$, $(1, 1, 1, 1)$ and $(2.5, 1.5, 2.3)$ to consider cases of no and weak associations. We compute \{T_l(Y, X_j), \ j = 1, \ldots, p, \ l = 1, 2\} where $T_1(\cdot)$ and $T_2(\cdot)$ are respectively the maximal permutation test statistic and the distance correlation. For each $T_l$, we perform marginal screening by keeping only those $X_j$ having the top $k$ $T_l(Y, X_j)$ values. We consider three choices, $k = 4, 10$ and 20. The results in Table \ref{table:screening} are based on 100 replications.

For the null case of $\beta = (0, 0, 0, 0)$, the chance of an individual feature $j$ being among the top $k$ is completely random and we notice that the empirical inclusion probabilities from permutation screening closely align with these values. For the non-null cases, screening performances improve as signal-to-noise increases in $\beta$ ranging among $(1, 1, 1, 1)$, $(2.5, 1.5, 2.3)$ and $(5, 3, 4, 6)$. We notice that associations with predictors 1 and 2 are easier to detect by screening whereas that of predictor 3 is more difficult to screen. In general, Table \ref{table:screening} illustrates that the maximal permutation based screening performs comparatively, and often in a superior fashion in including relevant predictors in the screening set. We also note that computation time for maximal permutation based screening was in the same scale as that of distance correlation based screening.
Table 4: Empirical inclusion probabilities of individual predictors and all predictors in the data generating model after screening

| \( \beta = (0, 0, 0, 0) \) | \( \beta = (1, 1, 1, 1) \) | \( \beta = (2.5, 1.5, 2, 3) \) | \( \beta = (5, 3, 4, 6) \) |
|-----------------|-----------------|-----------------|-----------------|
| Screening       | 1                | 2                | 3                | 4                |
|                 | 1 2 3 4 All 4   | 1 2 3 4 All 4   | 1 2 3 4 All 4   | 1 2 3 4 All 4   |
| Top 4 Permutation | .02 .02 .01 .04 .00 | .97 .56 .45 .22 | .97 .63 .99 .60 | .98 .76 .1 .75 |
| Dist. Corr.     | .07 .07 .05 .04 .00 | .96 .39 .30 .09 | .96 .49 .91 .36 | .92 .59 .98 .52 |
| Top 10 Permutation | .11 .10 .10 .16 .00 | 1 .85 .80 .66 | 1 .89 1 .08 .88 | 1 .94 1 .94 .94 |
| Dist. Corr.     | .12 .13 .09 .12 .00 | 1 .73 .56 .43 | 1 .82 .99 .81 | 1 .98 .91 1 .90 |
| Top 20 Permutation | .17 .19 .17 .27 .00 | 1 .89 .93 .82 | 1 .95 1 .95 1 1 | 1 1 1 1 1     |
| Dist. Corr.     | .23 .21 .20 .24 .00 | 1 .89 .79 .70 | 1 .92 1 .92 .92 | 1 1 1 1 1     |

6 NSCLC recurrence and baseline biomarker levels

A primary motivation for the statistical methodological development in this article is based on our work in NSCLC research. Lung cancer is the leading cause of cancer deaths in the United States, with approximately 222,500 new diagnoses and 157,600 deaths estimated in 2017. A large proportion of patients who undergo lung resection for non-small cell lung cancer dies of disease recurrence within 5 years. Numerous observational studies have shown low-dose computed tomography (LDCT) of the lung to be an effective method for screening lung cancer, especially in the early stage in high-risk patient population (Doria-Rose and Szabo, 2010). The National Comprehensive Cancer Network recently recommended such screening for appropriately selected high-risk patients (Aberle DR, 2011) and the Centers for Medicare and Medicaid Services have approved payment screening in these patients (Mulshine and D’Amico, 2014). Nevertheless, there is a concern over the accuracy of lung cancer screening as it involves moderately high number of false positives and consequent morbidity. Unfortunately, approximately 1 in 5 patients with pathologic stage IA NSCLC die of disease recurrence within 5 years of tumor resection. Blood and serum-based biomarkers, including EarlyCDT-lung and microRNA based biomarkers, serve as potentially useful supplements to LDCT for lung cancer screening, by further evaluating patient risk prior to LDCT, or assessing malignant risk of positive LDCT findings (Kanodra et al., 2015). The identification of prognostic biomarkers of NSCLC patients is crucial from both clinical and therapeutic decision perspectives. Clinical and demographic variables such as male gender, age, non-squamous histology, are known to have negative prognostic effects for NSCLC patients (Williams et al., 1981; Charloux et al., 1997). We consider data from a recent NSCLC study on \( n = 123 \) early stage (Stage 1A and 1B) patients who underwent lung resection and the objective is to identify serum biomarkers predictive of recurrence after lung resection. Preoperative serum specimens of the patients are evaluated in a blinded manner for biomarkers of angiogenesis, energy metabolism, apoptosis, and inflammation; biological processes known to be associated with metastatic progression. Biomarker levels were measured using the Luminex system. Recurrence was considered as that occurring within 5 years from the date of surgery. The median follow up was 58.2 months and 23 patients had NSCLC recurrences during follow-up.

One of the biomarkers measured in this study is human epididymis secretory protein 4 (HE4), which is a secretory protein known to be a prognostic factor for NSCLC patients (Iwahori et al., 2012; Lamy et al., 2015; Lan et al., 2016). Figure 7a shows a scatterplot of the measured HE4 levels and the outcome variable of recurrence status for the 123 patients. A logistic regression based estimated probability of recurrence curve is overlaid on the scatterplot. This estimated curve does not display a significant slope and both logistic and asymmetric complementary log-log link models for association of HE4 levels with NSCLC
recurrence yield $p$-values higher than 0.4 (Table 5). Another common prognostic marker for NSCLC is Carcino Embryonic Antigen (CEA) (Grunnet and Sorensen, 2012; Dong et al., 2016). Shintani et al. (2017) reported that Stage 1 NSCLC patients with high level of CEA have a higher risk of regional or systemic relapse. In Table 5, however, both logistic and complementary log-log link models for association of CEA levels with NSCLC recurrence yield $p$-values higher than 0.6. The $p$-values for marginal association from logistic regression model for some of the other important serum biomarkers are listed in Table 5. In fact, none of the markers meets the ubiquitous $p < 0.05$ threshold. Exploration of joint association via forward and backward selection by AIC (Venables and Ripley, 2002) both returned the null model. Penalized variable selection via Elastic Net (Zou and Hastie, 2005) and Lasso (Tibshirani, 1996), utilizing different recommended choices of the penalty parameters, also yield the null as the selected model. We further explore Surely Independent Screening (Fan et al., 2010), which iterates between screening based on marginal association and selection by joint association using the ‘SCAD’ penalty. After many iterations, this approach also returns the null model as the selected model.

Table 5: Comparison of $p$-values of marginal biomarker associations. The $p$-values from univariable binary regression using logit and cloglog links, and the corrections by Miller-Siegmund, Altman, Modified Bonferroni and the proposed Permutation test are reported. For each $p$-value, the FDR corrected $p$-value adjustments are provided in the parentheses.

| Predictor       | logistic | cloglog | Permutation | Miller-Siegmund | Altman | Modified Bonferroni |
|-----------------|----------|---------|-------------|-----------------|--------|---------------------|
| HE4             | 0.47(0.76) | 0.49(0.74) | 0.01(0.08) | 0.08(0.54) | 0.08(0.54) | 0.03(0.32) |
| CEA             | 0.68(0.76) | 0.67(0.74) | 0.05(0.16) | 0.32(0.54) | 0.32(0.54) | 0.21(0.5)  |
| beta.HCG        | 0.41(0.76) | 0.43(0.74) | 0.08(0.16) | 0.39(0.54) | 0.39(0.54) | 0.25(0.5)  |
| IGFBP.2         | 0.44(0.76) | 0.47(0.74) | 0.08(0.16) | 0.39(0.54) | 0.39(0.54) | 0.27(0.5)  |
| IGFBP.4         | 0.35(0.76) | 0.37(0.74) | 0.08(0.16) | 0.3(0.54)   | 0.3(0.54)  | 0.22(0.5)  |
| TNFRI           | 0.64(0.76) | 0.67(0.74) | 0.1(0.16)  | 0.36(0.54) | 0.36(0.54) | 0.31(0.5)  |
| FGF.1           | 0.67(0.76) | 0.67(0.74) | 0.11(0.16) | 0.67(0.67) | 0.67(0.67) | 0.5(0.5)   |
| IGFBP.3         | 0.1(0.76)  | 0.09(0.74) | 0.14(0.17) | 0.49(0.54) | 0.49(0.54) | 0.48(0.5)  |
| Angiopoietin.2  | 0.99(0.99) | 0.99(0.99) | 0.16(0.17) | 0.46(0.54) | 0.46(0.54) | 0.44(0.5)  |
| TNF.alpha       | 0.61(0.76) | 0.63(0.74) | 0.17(0.17) | 0.44(0.54) | 0.44(0.54) | 0.42(0.5)  |

These results are clearly negative to the objectives and hypotheses of the study. The Hosmer-Lemeshow test (Hosmer and Lemeshow, 1980) for goodness-of-fit of the marginal logistic model with HE4 however yields a rather small $p$-value of 0.005 suggesting issues with the logistics regression model. The scatter plot in Figure 7a highlights a few large outlying HE4 values that may be influencing the regression model fit. A scatter plot with CEA (not shown) also displays a few outlying values, however, they represent a different set of patients than the outlying values for HE4. A panel of ROC curves for four biomarkers are shown in Figure 7c-7e. In contrast to the weak $p$-values from the logistic regression analyses, these ROC curves show strong to moderate sensitivity and specificity for NSCLC recurrence.

Statistical analysis with many features is an increasingly common practice. It is tedious to perform model diagnostics when association with a large number of features are being explored and for this reason, model diagnostics is often overlooked. As we have illustrated in sections 4 and 5, the proposed maximal permutation test can be robust to outliers and offers a general blackbox method for making a decision about association without necessarily performing such diagnostics. We employed the maximal permutation test
Figure 7: (a) HE4 biomarker levels versus NSCLC recurrence and the fitted logistic regression curve; (b) $p$-values from Chi-square test using different cut-points for HE4, (c)-(f) ROC curves for top 4 biomarkers

here using chi-square test as the underlying test at each cutpoint. For association of NSCLC recurrence with preoperative levels of the HE4 marker, Figure 7b shows a plot of $p$-values obtained at different cut points for the original sequence of the data. This process is repeated for the permuted sequences to obtain the permutation distribution of the test statistic. For comparison, we also report $p$-values based on Miller and Siegmund (1982); Altman et al. (1994) and modified Bonferroni (Lausen and Schumacher, 1996) approaches. Note that the Altman et al. (1994) adjustment is known to be similar to the Miller and Siegmund (1982) adjustment for larger $p$-values. As we noted in our simulation studies, these adjustments are often overly conservative and have less power. For association with NSCLC recurrence, the proposed maximal permutation test reports a $p$-value of 0.008 for human epididymis secretory protein 4 (HE4) and $p$-value of 0.05 for Carcino Embryonic Antigen (CEA), respectively. After adjusting for multiplicity by the Benjamini and Hochberg (1995) False Discovery Rate (FDR) approach, these $p$-values are respectively 0.08 and 0.16 but the multiplicity adjustment maintains the ordering of the $p$-values, and biomarkers HE4 and CEA still remain at the top among 10 markers ranked by adjusted $p$-value.

7 Concluding Remarks

The question of association is of prime importance in modern scientific research. Categorization of a predictor is a popular practice because of its easy interpretability and probably also because we, as humans, process binary information more effectively. From statistical point of view, thresholding a predictor has its own advantages as it provides flexibility from parametric models and robustness from outliers. However, systematic search of optimal threshold can strikingly inflate type-1 error.
In this article, we propose a test for association that is free of functional form and distributional assumptions. We illustrate the strong performance of this test as a black box tool for detecting association in diverse settings. We provide an extensive set of simulation studies and real data analysis to establish the strong performance of the proposed test. In addition, we propose an innovative application of the proposed methodology in feature screening under sparsity.

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