Distance-based regression analysis for measuring associations^{*}

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DOI:

Received: x x 20xx / Revised: x x 20xx © The Editorial Office of JSSC & Springer-Verlag GmbH Germany 2018

Abstract Distance-based regression model, as a nonparametric multivariate method, has been widely used to detect the association between variations in a distance or dissimilarity matrix for outcomes and predictor variables of interest in genetic association studies, genomic analyses, and many other research areas. Based on it, a pseudo-F statistic which partitions the variation in distance matrices is often constructed to achieve the aim. To the best of our knowledge, the statistical properties of the pseudo-F statistic has not yet been well established in the literature. To fill this gap, we study the asymptotic null distribution of the pseudo-F statistic and show that it is asymptotically equivalent to a mixture of chi-squared random variables. Given that the pseudo-F test statistic has unsatisfactory power when the correlations of the response variables are large, we propose a square-root F-type test statistic which replaces the similarity matrix with its square root. The asymptotic null distribution of the new test statistic and power of both tests are also investigated. Simulation studies are conducted to validate the asymptotic distributions of the tests and demonstrate that the proposed test has more robust power than the pseudo-F test. Both test statistics are exemplified with a gene expression dataset for a prostate cancer pathway.

Keywords Asymptotic distribution, Chi-squared-type mixture, Nonparametric test, Pseudo-F test, Similarity matrix.

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*This work was partially supported by Beijing Natural Science Foundation (Z180006).

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1 Introduction

Distance-based regression model, as a multivariate method testing the relationship between variation in a distance or dissimilarity matrix of outcomes and predictor variables of interest, has been widely used in a variety of applications including genetics [8], genomics [15, 26], microbiome [12, 16, 20, 24], and other research area such as geoscience [14], environmental science [22], and oceanography [1, 4]. Unlike conventional multivariate methods, the starting point of distance-based regression model is pairwise distance or dissimilarity of subjects instead of individuals' observations. This model was originally introduced by McArdle and Anderson [13] to analyze simultaneous responses of multiple species to several factors in ecological experimental designs. Subsequently, with the development of high-throughput technologies, it has been received considerable attentions in high-dimensional data analysis. For example, Wessel and Schork [21] applied distance-based regression model to relate variations measured by a genomic distance for multiple phenotypes with multiple variants; Zapala and Schork [26] proposed a multivariate regression approach based on a distance matrix to detect associations between expression patterns on groups of genes and related predictor variables; Chen et al. [3] developed a distance-based statistical test based on generalized UniFrac distances to detect the association of microbiome composition and environment covariates. Gambi et al. [5] applied it to detect the impaction of historical sulfide mine tailings discharge on meiofaunal assemblages.

By partitioning the variation in a distance or dissimilarity matrix, a pseudo-F test statistic, analogous to the conventional univariate F statistic in ANOVA or general linear models, is constructed to detect the association between multiple response and predictor variables [18]. However, to the best of our knowledge, the distribution or asymptotic distribution of the pseudo-F test statistic is unknown with only some results under normal assumption and Euclidean or Mahalanobis distance measures [9]. For the general cases, it has not been studied yet in the literature. Resampling procedures are often used to calculate the statistical significance of the pseudo-F test statistic [3, 8, 11, 13, 21, 26]. However, they are generally computationally intensive, especially for high-dimensional data.

To address this problem, we study the asymptotic distribution of the pseudo-F statistic. We show that under the null hypothesis, the pseudo-F statistic is asymptotically equivalent to a mixture of Chi-squared random variables, with the weights proportional to the eigenvalues of the similarity matrix. Such Chi-squared-type mixture variables could have a large critical value when the correlation coefficients of the response variables are large, since in this case the eigenvalues of the similarity matrix vary widely. Thus the pseudo-F statistic may suffer from a substantial power loss. So we propose a square-root F-type test statistic, which reduces the difference in the eigenvalues of the similarity matrix by replacing the similarity matrix with its square root. The asymptotic null distribution is also established for the new test statistic.

The rest of the article is organized as follows. We introduce the pseudo-F test statistic and the proposed test statistic in Section 2. Main theoretical results for the test statistics are given in Section 3. Simulation studies are conducted to validate the asymptotic distribution of the pseudo-F and square-root F-type test statistics in Section 4. In Section 5, we illustrate the two tests with gene expression data from a prostate cancer pathway study. Some conclusions are drawn in Section 6. Technical details are relegated to the Appendix.

2 Test statistics

We introduce the pseudo-F test statistic by taking a similarity matrix as the starting point since the distance matrix can be easily transferred to a similarity matrix. Let $S = (s_{ij})_{n \times n}$ be a similarity matrix for k response variables among n subjects, where s_{ij} is the pairwise similarity between the subjects i and j constructed based on a positive definite kernel $\psi(y_i, y_j)$, and y_i and y_j are two high-dimensional independent observations of the responses variable \mathbb{Y} , i, j = $1, \dots, n$. Let $\mathbb{X} = (\mathbb{X}_1, \dots, \mathbb{X}_m)^\top$ be m predictor variables of interest. Denote the observation of \mathbb{X} for the *i*th subject by $x_i = (x_{i1}, \dots, x_{im})^\top$, $i = 1, \dots, n$. Write $X = (x_1, \dots, x_n)^\top$. We refer to the regression model relating S and X as a distance-based regression model, denoted by $S \sim X$. Our interest is in testing the null hypothesis H_0 : there is no association between \mathbb{Y} and \mathbb{X} . A F-type test statistic proposed by McArdle and Anderson [13, page. 3] can be used to do it, which is given by

$$T_{pseudo} = \frac{\operatorname{tr}(H_X \mathbf{H} S \mathbf{H}/m)}{\operatorname{tr}((\mathbf{I}_n - H_X) \mathbf{H} S \mathbf{H}/(n-m))}$$

where $H_X = X(X^{\top}X)^{-1}X^{\top}$ is the traditional hat" matrix, $\mathbf{H} = \mathbf{I}_n - \mathbf{1}_n \mathbf{1}_n^{\top}/n$, \mathbf{I}_n is the $n \times n$ identity matrix, $\mathbf{1}_n$ is an *n*-dimensional column vector with all elements being 1, and $\operatorname{tr}(\cdot)$ represents the trace of a matrix. Since the distribution or asymptotic distribution of T_{pseudo} is unknown, its statistical significance is conventionally calculated using resampling procedures, which is usually computationally intensive, especially when *n* is large. One of the goals of this article is to establish the asymptotic distribution for the pseudo-*F* test statistic T_{pseudo} .

The numerical results in Section 4 below show that T_{pseudo} is sensitive to the correlation matrix of the response variables. To boost the power when the response variables are moderately or highly correlated, we propose a square-root F-type test statistic, which uses the square root of the similarity matrix. The square-root F-type statistic is defined as

$$T_{sqrt} = \frac{\operatorname{tr}(H_X(\mathbf{H}S\mathbf{H})^{1/2}/m)}{\operatorname{tr}((\mathbf{I}_n - H_X)(\mathbf{H}S\mathbf{H})^{1/2}/(n-m))}$$

where the square root B of a matrix A means $A = B \times B$. Consider the eigenvalues $\{\lambda_i\}_{i=1}^n$ and eigenfunctions $\{v_i\}_{i=1}^n$ of $\tilde{S} = \mathbf{H}S\mathbf{H}$ and $\tilde{S}^{1/2} = (v_1, \dots, v_n)diag(\lambda_1^{1/2}, \dots, \lambda_n^{1/2})(v_1, \dots, v_n)^\top$. The numerator of T_{pseudo} and T_{sqrt} now can be intuitively expressed as $\sum_{i=1}^n \lambda_i v_i^\top \tilde{v}_i/m$ and $\sum_{i=1}^n \lambda_i^{1/2} v_i^\top \tilde{v}_i/m$ where the eigenvalues of H_x are all 1 and the eigenfunctions of H_x are $\{\tilde{v}_i\}_{i=1}^n$. Superficially, when the response variables are moderately correlated, our square-root method may increase the weight of valuable factors to boost the power.

3 Theoretic properties and implementation

In this section, we derive the asymptotic distributions of the pseudo-F and the proposed test statistics. Assume that $E(\mathbb{X}) = \mu$ and $\operatorname{cov}(\mathbb{X}) = \Delta = (\delta_{ij})_{m \times m}$. It thus follows that $E(\mathbb{X}\mathbb{X}^{\top}) =$

 $\Delta + \mu \mu^{\top} \triangleq \widetilde{\Delta} = (\widetilde{\delta}_{ij})_{m \times m}.$ Denote the eigenvalues of $\widetilde{S} = \mathbf{H}S\mathbf{H}$ by $\lambda_1 \geq \lambda_2 \geq \cdots \geq \lambda_n \geq 0.$ Besides, let $\lambda_1^* \geq \cdots \geq \lambda_n^* \geq 0$ be the solutions to the equation $\int \psi_0(y_1, y_2) u_i(y_1) p(y_1) dy_1 = \lambda_i^* u_i(y_2)$, where $\psi_0(y_1, y_2) = \psi(y_1, y_2) - E_{y_1}(\psi(y_1, y_2)) - E_{y_2}(\psi(y_1, y_2)) + E_{y_1, y_2}(\psi(y_1, y_2)))$ and $u_i(y_1)$ is the eigenfunction of the kernel $\psi_0(y_1, y_2)$ corresponding to λ_i^* for $i = 1, \cdots, n$. Throughout, we assume that there exists positive values c_0 and c_1 , such that $E(\mathbb{X}_j^4) \leq c_0$ and $E(s_{ii}^2) \leq c_1$ for $j = 1, \cdots, m$ and $i = 1, \cdots, n$. The symbol " $\overset{d}{\longrightarrow}$ " represents "converges in distribution to" and " $\overset{p}{\longrightarrow}$ " means "converges in probability to".

3.1 Asymptotical null distributions

In the following two lemmas, we give the asymptotic null distribution of the numerator and denominator of the pseudo-F test statistic, respectively.

Lemma 3.1 Under the null hypothesis H_0 , the numerator of T_{pseudo} , $tr(H_X HSH)$, has the same asymptotic distribution as $\frac{1}{n} \sum_{i=1}^{n} \lambda_i \xi_i$ when $n \to \infty$, where $\xi_i = \varpi_i + \varrho_i / (1 + \mu^\top \Delta^{-1} \mu)$, $\varpi_1, \ldots, \varpi_n$ are independently identical distributed (iid) chi-squared random variables with m-1degrees of freedom, $\varrho_1, \cdots, \varrho_n$ are iid chi-squared random variables with 1 degrees of freedom, *i.e.*, $\varpi_i \stackrel{iid}{\sim} \chi^2_{m-1}$ and $\varrho_i \stackrel{iid}{\sim} \chi^2_1$, and ϖ_i and ϱ_i are independent, $i = 1, \cdots, n$. In particular, when $\mu = \mathbf{0}_m$ an m-dimensional column vector with all 0 units, $\xi_i \stackrel{iid}{\sim} \chi^2_m$.

Lemma 3.2 As $n \to \infty$, the denominator of T_{pseudo} ,

$$tr((\mathbf{I}_n - H_X)\mathbf{H}S\mathbf{H}/(n-m)) \xrightarrow{p} E(s_{11}) - E(s_{12}),$$

where $E(s_{11}) = E(\psi(y_1, y_1))$, $E(s_{12}) = E(\psi(y_1, y_2))$, and y_1 and y_2 are two independent observations of \mathbb{Y} .

All those proofs are presented in Appendix. Both lemmas lead to the following theorem concerning the asymptotic distribution of the pseudo-F test statistic.

Theorem 3.3 Under the null hypothesis H_0 , T_{pseudo} has the same asymptotic distribution with $m^{-1}\sum_{i=1}^n w_i\xi_i$ when $n \to \infty$, where $\xi_i = \varpi_i + \varrho_i/(1 + \mu^{\top}\Delta^{-1}\mu)$, $\varpi_i \stackrel{iid}{\sim} \chi^2_{m-1}$ and $\varrho_i \stackrel{iid}{\sim} \chi^2_1$ are mutually independent, $w_i = \lambda_i / \sum_{j=1}^n \lambda_j$, and $\{\lambda_1, \dots, \lambda_n\}$ are eigenvalues of **HSH** in descending order, $i = 1, \dots, n$. In particular, when $\mu = \mathbf{0}_m$, $\xi_i \stackrel{iid}{\sim} \chi^2_m$, $i = 1, \dots, n$.

This theorem shows that the pseudo-F test statistic has the same asymptotic distribution as the random variable of Chi-squared-type mixtures. From the proofs presented in the Appendix, we can see that the asymptotic results do not depend on the dimension of response variables and are valid for high-dimensional data. To derive the asymptotic distribution of the proposed test statistic T_{sqrt} , we need the following assumption.

Assumption 1 $\sum_{i=1}^{\infty} (\lambda_i^*)^{1/2} < \infty$ and $\sum_{i=1}^{\infty} \left| (\lambda_i/n)^{1/2} - (\lambda_i^*)^{1/2} \right| \xrightarrow{P} 0.$

Note that Gretton et al. [7] also assumed that $\sum_{i=1}^{\infty} (\lambda_i^*)^{1/2} < \infty$ and Zhang [27] shows that $(\lambda_i/n)^{1/2} \xrightarrow{P} (\lambda_i^*)^{1/2}$ for $i = 1, 2, \cdots$. It implies that the assumption can be easily satisfied when the number of eigenvalues of kernel $\psi(\cdot, \cdot)$ are finite, such as linear kernel. By the Theorem 1 of Gretton et al. [7] and Assumption 1, we have the following proposition.

Proposition 3.4 Assume that $\{z_1, z_2, \dots\}$ is an infinite sequence of *i.i.d.* standard Gaussian variables and Assumption 1 holds. Then $\sum_{i=1}^{\infty} ((\lambda_i/n)^{1/2} - (\lambda_i^*)^{1/2}) z_i^2 \xrightarrow{p} 0$ as $n \to \infty$.

Lemma 3.5 For any symmetric semidefinite matrices $\mathbf{D_1}$ and $\mathbf{D_2}$ of n dimension, the eigenvalues of $\mathbf{D} = \mathbf{D_1}\mathbf{D_2}$ are nonnegative such that $tr(\mathbf{D}^{\top}\mathbf{D}) \leq tr(\mathbf{D})^2$.

When \mathbf{D} is a symmetric semidefinite matrix, the result in 3.5 naturally holds, since the sum of squares of the nonnegative eigenvalues should be smaller than the squares of the sum of them. Lemma 3.5 is vital to show that a matrix formed by the product of two symmetric semidefinite matrices still have the same property. Based on it and proposition 3.4, the asymptotic null distribution of the proposed test statistic thus follows.

Theorem 3.6 When Assumptions 1 holds, T_{sqrt} has the same asymptotic distribution with $m^{-1}\sum_{i=1}^{n} \eta_i \xi_i$ when $n \to \infty$, where $\xi_i = \varpi_i + \varrho_i/(1 + \mu^{\top} \Delta^{-1} \mu)$, $\varpi_i \stackrel{iid}{\sim} \chi^2_{m-1}$ and $\varrho_i \stackrel{iid}{\sim} \chi^2_1$ are mutually independent, and $\eta_i = \lambda_i^{1/2} / \sum_{j=1}^{n} \lambda_j^{1/2}$, and $\{\lambda_1, \dots, \lambda_n\}$ are eigenvalues of **HSH** in descending order, $i = 1, \dots, n$. In particular, when $\mu = \mathbf{0}_m$, $\xi_i \stackrel{iid}{\sim} \chi^2_m$, $i = 1, \dots, n$.

3.2 Computation issue

 T_{pseudo} and T_{sqrt} have asymptotical null distribution of the same form with two mixtures of Chi-squared random variables, whose density functions involve multiple integrations. To ease computation and increase efficiency, we employ a parameter bootstrap procedure to approximate them in finite-sample cases as the explicit formulas of the distributions of T_{pseudo} , T_{sqrt} and the two mixtures are all intricate.

A parameter bootstrap procedure

Step 1. Set a large B, for example B = 1000.

Step 2. Randomly generate *n* pairs of observations from the Chi-squared distributions with m-1 and 1 degrees of freedom, denoted by $\{(\varpi_i, \varrho_i)|i = 1, \dots, n\}$. Let $T_1 = m^{-1} \sum_{i=1}^n w_i [\varpi_i + \varrho_i/(1 + \mu^\top \Delta^{-1} \mu)]$ and $T_2 = m^{-1} \sum_{i=1}^n \eta_i [\varpi_i + \varrho_i/(1 + \mu^\top \Delta^{-1} \mu)]$.

Step 3. Repeat Step 2 B times and denote the obtained statistics T_1 and T_2 by T_{11}, \dots, T_{1B} and T_{21}, \dots, T_{2B} .

Step 4. By the law of large numbers, the p-values of T_{pseudo} and T_{sqrt} can be empirically estimated by

$$p_{pseudo} = \frac{1}{B} \sum_{i=1}^{B} I\{T_{1i} \ge t_{pseudo}\}$$

and

$$p_{sqrt} = \frac{1}{B} \sum_{i=1}^{B} I\{T_{2i} \ge t_{sqrt}\},$$

where t_{pseudo} and t_{sqrt} is the observed value of T_{pseudo} and T_{sqrt} respectively and $I\{\cdot\}$ is an indicator function.

It is worth pointing out that the proposed parameter bootstrap procedure is much faster than the original bootstrap procedure. For a sample of size n, the bootstrap procedure needs to generate n individual observations, perform n(n-1)/2 calculations to obtain the similarity matrix and conduct two matrix multiplications, while the proposed procedure just needs to generate 2n random samples and calculate some summations, which runs ver fast. For example, it takes 0.57 seconds to implement a parameter bootstrap for B = 1000 and n = 500 using Inter Core (TM) i9-9900 CPU, and takes 246.85 seconds to implement the original bootstrap procedure under the same setting.

In addition to the parameter bootstrap procedure, one can use the Box scaled χ^2 -approximation [2] or the generalized gamma distribution approximation [10] by matching several cumulants of them. Based on Theorems 1 and 2, the cumulants of T_{pseudo} and T_{sqrt} can be estimated easily. In particular, the *l*th cumulant of T_{pseudo} and T_{sqrt} are estimated as $b_l = 2^{l-1}(l - 1)!m_0 \sum_{i=1}^n (w_i/m)^l$ and $h_l = 2^{l-1}(l-1)!m_0 \sum_{i=1}^n (\eta_i/m)^l$ respectively, l = 1, 2, 3, 4, where $m_0 = m - 1 + 1/(1 + \mu^T \Delta^{-1}\mu), w_i = \lambda_i / \sum_{j=1}^n \lambda_j, \eta_i = \lambda_i^{1/2} / \sum_{j=1}^n \lambda_j^{1/2}, \text{ and } \{\lambda_1, \dots, \lambda_n\}$ are eigenvalues of **HSH** in a descending order, $i = 1, \dots, n$. Let a random variable X_g follow a generalized gamma distribution with the density function being

$$f_{g}(x) = \frac{v_{g} x^{v_{g} w_{g} - 1}}{\sigma_{g}^{v_{g} w_{g}} \Gamma(w_{g})} \exp\{-(\frac{x}{\sigma_{g}})^{v}\}, x > 0$$

where v_g , w_g and σ_g are the parameters. We recommend to use the distribution of $X_g + \theta_g$ to approximate those of T_{pseudo} and T_{sqrt} , where θ_g is a location parameter. The unknown parameters v_g , w_g , σ_g , and θ_g can be obtained by solving the equations

$$\begin{cases}
b_1 (\text{or } h_1) &= m_1 + \theta_g \\
b_2 (\text{or } h_2) &= m_2 - m_1^2 \\
b_3 (\text{or } h_3) &= m_3 - 3m_2m_1 + 2m_1^3 \\
b_4 (\text{or } h_4) &= m_4 - 4m_3m_1 - 3m_2^2 + 12m_2m_1^2 - 6m_1^4,
\end{cases}$$

where $m_l = E(X_g^l) = \sigma_g^l \Gamma(v_g^{-1}l + w_g) / \Gamma(w_g)$ is the *l*th moment of X_g , l = 1, 2, 3, 4, and $\Gamma(\cdot)$ is a Gamma function.

3.3 Power analysis

To study the asymptotic power of the pseudo-F test, we consider the multivariate linear model $Y = X\beta + \varepsilon$, where $Y = (y_1, \ldots, y_n)^{\top}$ with $y_i = (y_{i1}, \cdots, y_{iq})^{\top}$, $\beta = (\beta_{ij})_{m \times q}$ is the effect of the predictor variables X on the responses variables Y and $\varepsilon = (\varepsilon_1, \cdots, \varepsilon_n)^{\top}$ are random errors with $E(\varepsilon_i) = \mathbf{0}_{n \times q}$ and $\operatorname{cov}(\varepsilon_i) = \Delta_{\varepsilon}$ for $i = 1, \cdots, n$. Then for a linear kernel ψ , i.e., $s_{ij} = \psi(\mathbf{y}_i, \mathbf{y}_j)$, we have the following theorem.

Theorem 3.7 Assume that for $0 < \iota < 0.5$, $\max_{1 \le i \le m, 1 \le j \le q} n^{0.5-\iota} |\beta_{ij}| = \tilde{c} \neq 0$ as $n \to \infty$, then for the linear kernel $\psi(\cdot, \cdot)$ and $\tilde{\tau}_0 > 0$, we have

$$\lim_{n \to \infty} P\Big(\Big|\frac{T_{pseudo}}{n^{2\iota}} - \frac{1}{m} \frac{tr(\tilde{\Delta}^{-1}\Delta \tilde{\boldsymbol{\beta}} \tilde{\boldsymbol{\beta}}^{\top} \Delta^{\top})}{tr(\Delta_{\varepsilon})}\Big| > \tilde{\tau}_0\Big) = 0.$$

It thus follows that $P(T_{pseudo} > F_1^{-1}(1-\alpha)) \xrightarrow{p} 1$ as $n \to \infty$, where F_1 is the asymptotic distribution function of T_{pseudo} , $F_1^{-1}(1-\alpha)$ is the $(1-\alpha)$ -quantile of F_1 and α is the nominal significance level.

Theorem 3.7 shows that when the effect β is relatively small, even as small as $n^{\iota-0.5}$ with tiny ι , the power of the pseudo-F test still converges to one in probability as $n \to \infty$. Actually, when β is fixed, the asymptotic power of the square-root F-type test statistic has the same performance.

Theorem 3.8 For the linear kernel $\psi(\cdot, \cdot)$, $P(T_{sqrt} > F_2^{-1}(1-\alpha)) \xrightarrow{p} 1$ as $n \to \infty$, where F_2 is the asymptotic distribution function of T_{sqrt} , $F_2^{-1}(1-\alpha)$ is the $(1-\alpha)$ -quantile of F_2 , and α is the nominal significance level.

4 Simulation studies

4.1 Accuracy of p-value calculation

We evaluate through simulation studies the p-value calculation accuracy of the asymptotic distributions of the pseudo- $F(T_{pseudo})$ and square-root F-type (T_{sqrt}) test statistics for various correlation matrices. The similarity matrix for the response variables is constructed based on the measure of inner product, that is, $S = YY^{\top}$. The observations for the predictor variables \mathbb{X} are generated from the *m*-dimensional normal distribution $N(\mathbf{1}_m, \Theta_x)$ with mean vector $\mathbf{1}_m = (1, \dots, 1)^{\top}$ and covariance matrix $\Theta_x = (\theta_{ij}^{(x)})_{m \times m}$, where $\theta_{ij}^{(x)} = \rho_x^{|i-j|}$ with $\rho_x = 0.5$. The observations for \mathbb{Y} are generated from $N_k(\mathbf{0}_k, \Theta_y)$. We consider the following two correlation models for $\Theta_y = (\theta_{ij}^{(y)})_{k \times k}$.

- Model 1 (AR(1) correlation): Let $\theta_{ij}^{(y)} = \rho_y^{|i-j|}$ for $1 \le i, j \le k$, where $\rho_y = 0.3, 0.8$.
- Model 2 (Equal correlation): Let $\theta_{ij}^{(y)} = \rho_y$ for $1 \le i \ne j \le k$ and $\theta_{ii}^{(y)} = 1$ for $1 \le i \le k$, where $\rho_y = 0.3, 0.8$.

Thus there are a total of four correlation matrices for the outcome variables \mathbb{Y} . We set the sample size *n* to be 500. Let m = 5 and k = 10. For each correlation setting, 10000 simulation replicates are performed to evaluate the empirical size of the tests at significance levels ranging from 0 to 1. In each simulation, the p-values of the T_{pseudo} and T_{sqrt} are calculated based on the asymptotic distribution and Monte Carlo method with B = 2000 replicates.

Figures 1 and 2 below display the empirical sizes of T_{pseudo} and T_{sqrt} based on the asymptotic distribution against significance levels under various correlation matrix settings. The figures show that the empirical sizes of T_{pseudo} and T_{sqrt} are always very close to the corresponding significance levels, even in the case of small significance levels. It indicates good accuracy of the asymptotic distributions derived in Theorems 3.3 and 3.6 and such accuracy is not sensitive to the correlation structure and magnitude.



Figure 1: Empirical sizes $(-\log_{10})$ of the pseudo-F test statistic (T_{pseudo}) based on the asymptotic distribution against the significance levels $(-\log_{10})$ for two correlation models.



Figure 2: Empirical sizes $(-\log_{10})$ of the proposed square-root *F*-type test statistic (T_{sqrt}) based on the asymptotic distribution against the significance levels $(-\log_{10})$ for two correlation models.

4.2 Power comparison

Next we compare the type I error rates and powers of T_{pseudo} and T_{sqrt} . The multivariate response data are generated based on the linear model $Y = X\beta + \varepsilon$, where $\varepsilon \sim N_k(\mathbf{0}_k, \Theta_{\varepsilon})$. The correlation matrix $\Theta_{\varepsilon} = (\theta_{ij}^{(\varepsilon)})_{k \times k}$ is set to have the following two correlation structures.

- Model 1 (AR(1) correlation): Let $\theta_{ij}^{(\varepsilon)} = \rho_{\varepsilon}^{|i-j|}$ for $1 \le i, j \le k$, where $\rho_{\varepsilon} = 0.3, 0.8$.
- Model 2 (Equal correlation): Let $\theta_{ij}^{(\varepsilon)} = \rho_{\varepsilon}$ for $1 \le i \ne j \le k$ and $\sigma_{ii}^{(\varepsilon)} = 1$ for $1 \le i \le k$, where $\rho_{\varepsilon} = 0.3, 0.8$.

The observations X for the predictor variables are generated from the multivariate normal distribution $N(\mathbf{1}_m, \Theta_x)$ with $\Theta_x = (\theta_{ij}^{(x)})_{m \times m}$ and $\theta_{ij}^{(x)} = 0.5^{|i-j|}$. For the two tests, we define

the similarity matrix as $S = YY^{\top}$. To investigate the performance of the two tests under different sparsity of the "signals", we choose the percentage τ of nonzero elements of β from $\{0\%, 20\%, 40\%, 60\%, 80\%, 100\%\}$. The null hypothesis corresponds to the case $\tau = 0\%$. The signals (i.e., nonzero elements of β) are set to be $\{\log(k)/(25\tau km)\}^{1/2} + (1/k) \times N(0, 0.01),$ to make the powers comparable in different settings, where N(0, 0.01) is the normal distribution with mean 0 and variance 0.01 and τkm is the total number of signals. We set k = 10, m = 5and n = 500. The empirical type I error rates and powers of the tests are calculated based on 1000 simulation replicates; in each simulation, 2000 Monte Carlo samples are drawn to calculate the p-values of the tests based on the asymptotic distributions. The nominal significance level is 0.05.

Correlation	Precentage	$\rho = 0$	$\rho = 0.3$		$\rho = 0.8$	
Model	of nonzeros	T_{pseudo}	T_{sqrt}	T_{pseudo}	T_{sqrt}	
1	0%	0.057	0.054	0.051	0.048	
	20%	0.909	0.886	0.507	0.940	
	40%	0.825	0.741	0.395	0.663	
	60%	0.874	0.794	0.463	0.603	
	80%	0.884	0.778	0.478	0.597	
	100%	0.881	0.803	0.469	0.493	
2	0%	0.051	0.053	0.051	0.049	
	20%	0.787	0.957	0.306	1.000	
	40%	0.669	0.810	0.249	0.980	
	60%	0.706	0.778	0.280	0.930	
	80%	0.683	0.652	0.305	0.718	
	100%	0.710	0.571	0.305	0.390	

Table 1: Type I error rates and powers of the pseudo- $F(T_{pseudo})$ and square-root F-type (T_{sqrt}) test statistics <u>under two correlation models</u>.

Table 1 presents the empirical type I error rates and powers of the two tests for various Σ_x and τ . It can be seen from the table that both tests can control the type I error rates adequately and the proposed test T_{sqrt} is generally more powerful than T_{pseudo} , especially when the correlation coefficients of the response variables are large. For example, under the AR(1) correlation model with $\rho = 0.8$, the powers of T_{pseudo} and T_{sqrt} for $\tau = 20\%$ are 0.507 and 0.940. The superiority of T_{sqrt} diminishes as the sparsity level of signals increases, but can still outperform T_{pseudo} when the correlation coefficient is large. This implies that the proposed test tends to gain more power than T_{pseudo} when the signals are sparse. T_{pseudo} is slightly more powerful than T_{sqrt} when the response variables are weakly dependent with decaying correlation (e.g., AR(1) correlation model with $\rho = 0.3$). For example, under the AR(1) correlation model with $\rho = 0.3$. For example, under the AR(1) correlation model with $\rho = 0.3$. For example, under the AR(1) correlation model with $\rho = 0.3$. For example, under the AR(1) correlation model with $\rho = 0.3$. For example, under the AR(1) correlation model with $\rho = 0.3$. For example, under the AR(1) correlation model with $\rho = 0.3$. For example, under the AR(1) correlation model with $\rho = 0.3$.

sparsity levels of signals and correlation magnitudes; it performs consistently well across all settings.

5 Applications

We exemplify the tests using the gene expression data from a prostate cancer study [19], whose aim is to investigate whether gene expression differences underlie common clinical and pathological features of prostate cancer. This can be achieved by comparing gene expression differences between tumor and normal prostate samples. The data of expression profiles of approximately 12,600 genes from 52 tumor and 50 normal prostate specimens were collected. We confine our analysis to the genes of 10 pathways: Alanine, aspartate and glutamate metabolism (map00250); Pathogenic Escherichia coli infection (map05130); Viral myocarditis (map05416); PPAR signaling pathway (map03320); Rheumatoid arthritis (map05323); Tight junction (map04530); Regulation of actin cytoskeleton (map04810); Hypertrophic cardiomyopathy (map04350). Detailed descriptions of these pathways are available in [23], [28], [17], and among others.

Here for illustration, we consider using the gene expression patterns as the response variables and the status of tumor as the predictor variable. Likewise, the measure of inner product is used to construct the similarity matrix, that is, $S = YY^{\top}$. We are interested in whether the expression patterns of the genes in a pathway are associated with prostate tumor. Table 2 presents the p values of the pseudo F and square-root F-type test statistics for testing the association between gene expression patterns and prostate tumor. The p value results are calculated based on 10000 Monte Carlo replicates. This table shows that, the p values of the pseudo F test are always larger than those of the square-root F-type test for the 10 pathways, indicating that the proposed test is more powerful than the pseudo F test. Moreover, for some pathways such as map05130 and map04810, the pseudo F test fails to detect any expression pattern difference between the normal and tumor samples under the significance level of 0.05, while the proposed test can detect a difference.

Pathway	Numbers of genes	T_{pseudo}	T_{sqrt}
map00250	33	0.0396	0.0130
map05130	80	0.1797	0.0134
map05416	98	0.0738	0.0155
map03320	66	0.0055	0.0025
map05323	118	0.0097	0.0010
map04530	160	0.0564	0.0072
map04810	279	0.2297	0.0121
map05410	118	0.2385	0.0185
map04260	72	0.0007	0.0002
map04350	128	0.0478	0.0034

Table 2: P values of the pseudo F (T_{pseudo}) and square-root F-type (T_{sqrt}) test statistics for the association between gene expression patterns and prostate tumor.

6 Conclusion

Distance-based regression model is very effective to detect the relationship between highdimensional response variables and predictor variables of interest. It has a wide applications in many research fields related to statistics. One drawback is the intensive computation for the calculation of statistical significance, due to the lack of asymptotic null distribution. In this work, we establish the asymptotic distribution for the pseudo-F test statistic based on the distance-based regression model and propose a new test which is more powerful than the original pseudo-F test when the correlation coefficient of the outcomes for measuring the similarity is relatively large. The proposed theory is anticipated to further broaden the application of distance-based regression model.

The asymptotic property of the pseudo-F test only requires that the kernel for the similarity matrix is a positive definite and does not impose any restrictions on the dimension of outcomes. So it is free to handle high-dimensional data and is expected to have a wide application in high-dimensional association studies.

Acknowledgement

We would like to thank the editor and two anonymous reviewers for their insighful comments.

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Appendix

Proof of Lemma 3.1.

Denote $\Omega = X \widetilde{\Delta}^{-1} X^{\top}$. Note that Ω can be regarded as a random variable constructed based on a weighted inner product, which is a positive definite kernel. Then the numerator of T_{pseudo} can be written as

$$\operatorname{tr}(H_X\widetilde{S}) = \frac{1}{n}\operatorname{tr}(\Omega\widetilde{S}) + \operatorname{tr}((H_X - \frac{1}{n}\Omega)\widetilde{S}).$$

We first show that $\frac{1}{n} \operatorname{tr}(\Omega \mathbf{H}S\mathbf{H})$ has the same asymptotical distribution with $\frac{1}{n} \sum_{i=1}^{n} \lambda_i \xi_i$ under H_0 . To this end, we denote the eigenvalues of $X\widetilde{\Delta}^{-1}X^{\top}$ by $\widetilde{\lambda}_1 \geq \cdots \geq \widetilde{\lambda}_m \geq 0$ and $\widetilde{\lambda}_{m+1} = \cdots = \widetilde{\lambda}_n = 0$. Let $\widetilde{\lambda}_1^* \geq \cdots \geq \widetilde{\lambda}_n^* \geq 0$ be the solutions to the equation

$$\int \widetilde{\psi}(x_1, x_2) \widetilde{u}_i(x_1) p(x_1) dx_1 = \widetilde{\lambda}_i^* \widetilde{u}_i(x_2) \tag{1}$$

with $\tilde{\psi}(x_1, x_2) = x_1^{\top} \tilde{\Delta}^{-1} x_2 - E_{x_1}(x_1^{\top} \tilde{\Delta}^{-1} x_2) - E_{x_2}(x_1^{\top} \tilde{\Delta}^{-1} x_2) + E_{x_1, x_2}(x_1^{\top} \tilde{\Delta}^{-1} x_2) = (x_1 - \mu)^{\top} \tilde{\Delta}^{-1}(x_2 - \mu)$, where $\tilde{u}_i(x_1)$ is the eigenfunction of the kernel $\tilde{\psi}(x_1, x_2)$ corresponding to $\tilde{\lambda}_i^*$. Note that eigenfunctions are orthonormal with respect to the probability measure $p(x_1)$, i.e.,

$$\int \widetilde{u}_i(x_1)\widetilde{u}_j(x_1)p(x_1)dx_1 = \mathbb{I}_{i=j},$$
(2)

where $\mathbb{I}_{\mathbf{E}}$ denoting the indicator function of **E**. Zhang [27] shows that $\frac{1}{n} \widetilde{\lambda}_i \longrightarrow \widetilde{\lambda}_i^*$, for i =1, \cdots , *n*. Then $\widetilde{\lambda}_{m+1}^* = \cdots = \widetilde{\lambda}_n^* = 0$.

When $\mu = \mathbf{0}$, it then follows that $E_{x_1}(e_i^{\top} \Delta^{-1/2} x_1 x_1^{\top} \widetilde{\Delta}^{-1} x_2) = e_i^{\top} \Delta^{-1/2} x_2$ and $E_{x_1}(e_i^{\top}\Delta^{-1/2}x_1x_1^{\top}\Delta^{-1/2}e_j) = \mathbb{I}_{i=j}$, where $\Delta^{-1/2}\Delta^{-1/2} = \Delta$. This implies that $\widetilde{\lambda}_i^* = 1$ and $\widetilde{u}_i(x_1) = e_i^{\top} \Delta^{-1/2} x_1$ for $i = 1, \cdots, m$. When $\mu \neq \mathbf{0}$, for $i, j = 1, \cdots, m-1$, it can be proved that $\widetilde{\lambda}_i^* = 1$ and $\widetilde{\lambda}_m^* = 1/(1+\mu^\top \Delta^{-1}\mu)$ corresponding to $\widetilde{u}_i(x_1) = v_i^\top(x_1-\mu)$ and $\widetilde{u}_m(x_1) = v_m^{\top}(x_1 - \mu)$ satisfy the equations (1) and (2), where $v_m = \Delta^{-1} \mu / \mu^{\top} \Delta^{-1} \mu$ and v_1, \cdots, v_{m-1} are the solutions to the equations $v_i^\top \mu = 0$ and $v_i^\top \Delta v_j = \mathbb{I}_{i=j}$.

We now show that $\widetilde{\lambda}_1^* = \cdots = \widetilde{\lambda}_{m-1}^* = 1$, $\widetilde{\lambda}_m^* = 1/(1 + \mu^\top \Delta^{-1} \mu)$ and $\widetilde{\lambda}_{m+1}^* = \cdots = 1$ $\widetilde{\lambda}_n^* = 0$. By Theorem 3 in Zhang [27], under H_0 , $\frac{1}{n} \operatorname{tr}(\Omega \mathbf{H} S \mathbf{H})$ has the same asymptotic distribution as $\sum_{i,j=1}^{n} \lambda_i^* \tilde{\lambda}_j^* z_{ij}^2 = \sum_{i=1}^{n} \lambda_i^* \xi_i$, where z_{ij} are *iid* standard Gaussian variables and $\xi_i = \sum_{j=1}^m \tilde{\lambda}_j^* z_{ij}^2 = \overline{\omega}_i + \varrho_i / (1 + \mu^\top \Delta^{-1} \mu)$. In addition, by Theorem 1 in Gretton et al. [7], we have $\sum_{i=1}^{\infty} (\frac{1}{n}\lambda_i - \lambda_i^*)\xi_i \xrightarrow{p} 0$. That is, $\sum_{i=1}^{n} \frac{1}{n}\lambda_i\xi_i$ has the same asymptotic distribution as $\sum_{i=1}^{n} \lambda_i^* \xi_i$. It thus follows that $\frac{1}{n} \operatorname{tr}(\Omega \mathbf{H} S \mathbf{H})$ has the same asymptotic distribution as $\frac{1}{n}\sum_{i=1}^n \lambda_i \xi_i.$

Next we show that $\operatorname{tr}\left((H_X - \frac{1}{n}\Omega)\widetilde{S}\right)$ converges to 0 in probability. Write

$$\operatorname{tr}\left((H_X - \frac{1}{n}\Omega)\widetilde{S}\right) = \operatorname{tr}(AB) = \sum_{i=1}^m \sum_{j=1}^m a_{ij}b_{ij},$$

where $A = (a_{ij})_{m \times m} = (\frac{1}{n}X^{\top}X)^{-1} - \widetilde{\Delta}^{-1}$ and $B = (b_{ij})_{m \times m} = \frac{1}{n}X^{\top}\widetilde{S}X$. By the law of large numbers, it can be obtained that the (i, j)th entry of $\frac{1}{n}X^{\top}X = \frac{1}{n}\sum_{i=1}^{n}x_ix_i^{\top}$ converges in probability to $\widetilde{\delta}_{ij}$, that is $a_{ij} \xrightarrow{p} 0, i, j = 1, \cdots, m$. Note that $(e_i - e_j)^\top S(e_i - e_j) \ge 0$ and $(e_i + e_j)^{\top} S(e_i + e_j) \ge 0$ for a positive definite kernel matrix S. Then we have $2|s_{ij}| \le s_{ii} + s_{jj}$ and $|E(s_{ij})| \leq E(s_{ii}), i, j = 1, \cdots, m$. It follows that

$$E(s_{ij}^2) \le \frac{1}{4}E((s_{ii} + s_{jj})^2) = \frac{1}{2}E(s_{ii}^2) + \frac{1}{2}E(s_{ii}s_{jj}) \le E(s_{ii}^2),$$
$$|E(s_{ij}s_{lk})| \le \frac{1}{2}E(s_{ij}^2) + \frac{1}{2}E(s_{lm}^2) \le E(s_{ii}^2) = c_1,$$

for $i, j, l, k = 1, \dots, m$. Similarly, we can obtain that $|E(x_{j_1 i_1} x_{j_2 i_1} x_{j_3 i_2} x_{j_4 i_2})| \leq \frac{1}{4} E(x_{j_1 i_1}^4 + x_{j_1 i_2}^4)$ $x_{j_2i_1}^4 + x_{j_3i_2}^4 + x_{j_4i_2}^4 \le c_0 \text{ for } i_1, i_2 = 1, \cdots, m \text{ and } j_1, j_2, j_3, j_4 = 1, \cdots, n.$

Define $\overline{x} = \frac{1}{n} \sum_{j=1}^{n} x_j$ and $\overline{x} = (\overline{x}_1, \cdots, \overline{x}_m)$. Then we can write

$$B = \frac{1}{n} \sum_{i=1}^{n} \sum_{j=1}^{n} (x_i - \overline{x}) s_{ij} (x_j - \overline{x})^{\top}.$$

Owing to $x_i - \overline{x} = (x_i - \mu) - (\overline{x} - \mu)$, we can assume that $E(\mathbb{X}) = \mathbf{0}_m$ to estimate the

expectation and variance of b_{ij} under H_0 ,

$$|E(B)| = \left|\frac{1}{n}\sum_{i=1}^{n}\sum_{j=1}^{n}E(s_{ij})E\left((x_i-\overline{x})(x_j-\overline{x})^{\top}\right)\right|$$

$$\leq E(s_{ii})\frac{1}{n}\sum_{i=1}^{n}\left|E\left((x_i-\overline{x})(x_i-\overline{x})^{\top}\right)\right| + E(s_{ii})\frac{1}{n}\sum_{i\neq j=1}^{n}\left|E\left((x_i-\overline{x})(x_j-\overline{x})^{\top}\right)\right|$$

$$\leq E(s_{ii})|\Delta| + E(s_{ii})|\Delta| = 2E(s_{ii})|\Delta|,$$

implying that $E(b_{i_1i_2})$ is finite, $i_1, i_2 = 1, \dots, n$. Through some algebraic manipulations, it can be obtained that

$$\begin{split} E(b_{i_{1}i_{2}}^{2}) &= \frac{1}{n^{2}} \sum_{j_{1}, j_{2}, j_{3}, j_{4}=1}^{n} c_{s} E\left((x_{j_{1}i_{1}} - \overline{x}_{i_{1}})(x_{j_{2}i_{1}} - \overline{x}_{i_{1}})(x_{j_{3}i_{2}} - \overline{x}_{i_{2}})\right) (x_{j_{4}i_{2}} - \overline{x}_{i_{2}}) \Big) \\ &= \frac{1}{n^{2}} \sum_{j_{1}, j_{2}, j_{3}, j_{4}=1}^{n} c_{s} E\left(x_{j_{1}i_{1}}x_{j_{2}i_{1}}x_{j_{3}i_{2}}x_{j_{4}i_{2}}\right) - \frac{4}{n^{2}} \sum_{j_{1}, j_{2}, j_{3}, j_{4}=1}^{n} c_{s} E\left(x_{j_{1}i_{1}}x_{j_{2}i_{1}}\overline{x}_{i_{2}}\overline{x}_{i_{2}}\right) \\ &+ \frac{2}{n^{2}} \sum_{j_{1}, j_{2}, j_{3}, j_{4}=1}^{n} c_{s} E\left(x_{j_{1}i_{1}}x_{j_{2}i_{1}}\overline{x}_{i_{2}}\overline{x}_{i_{2}}\right) + \frac{4}{n^{2}} \sum_{j_{1}, j_{2}, j_{3}, j_{4}=1}^{n} c_{s} E\left(x_{j_{1}i_{1}}\overline{x}_{i_{1}}\overline{x}_{i_{2}}\overline{x}_{i_{2}}\right) \\ &- \frac{4}{n^{2}} \sum_{j_{1}, j_{2}, j_{3}, j_{4}=1}^{n} c_{s} E\left(x_{j_{1}i_{1}}\overline{x}_{i_{1}}\overline{x}_{i_{2}}\overline{x}_{i_{2}}\right) + \frac{1}{n^{2}} \sum_{j_{1}, j_{2}, j_{3}, j_{4}=1}^{n} c_{s} E\left(\overline{x}_{i_{1}}\overline{x}_{i_{1}}\overline{x}_{i_{2}}\overline{x}_{i_{2}}\right) \\ &\triangleq \kappa_{1} + \kappa_{2} + \kappa_{3} + \kappa_{4} + \kappa_{5} + \kappa_{6}, \end{split}$$

where $c_s = E(s_{j_1j_2}s_{j_3j_4})$. Then using the assumptions $E(\mathbb{X}_1^4) \leq c_0$ and $E(s_{11}^2) \leq c_1$, we have

$$\begin{aligned} |\kappa_1| &\leq \frac{c_1}{n^2} \sum_{j_1, j_2, j_3, j_4=1}^n \left| E\left(x_{j_1 i_1} x_{j_2 i_1} x_{j_3 i_2} x_{j_4 i_2}\right) \right| \\ &\leq \frac{c_1}{n} \max_{i_1, i_2} E\left(x_{1 i_1}^2 x_{1 i_2}^2\right) + c_1 \max_{i_1, i_2} E\left(x_{1 i_1}^2 x_{2 i_2}^2\right) + 2c_1 \max_{i_1, i_2} \left| E\left(x_{1 i_1} x_{2 i_1} x_{1 i_2} x_{2 i_2}\right) \right| \\ &\leq \left(\frac{1}{n} c_0 c_1 + c_0 c_1 + 2c_0 c_1\right) \leq 4c_0 c_1. \end{aligned}$$

Similarly,

$$\begin{split} |\kappa_{2}| &\leq \frac{4}{n^{2}} \sum_{j_{1}, j_{2}, j_{3}, j_{4}=1}^{n} |c_{s}| |E(x_{j_{1}i_{1}}x_{j_{2}i_{1}}x_{j_{3}i_{2}}\overline{x}_{i_{2}})| \\ &\leq \frac{4c_{1}}{n^{2}} \sum_{j_{1}, j_{2}, j_{3}, j_{4}=1}^{n} |E(x_{j_{1}i_{1}}x_{j_{2}i_{1}}x_{j_{3}i_{2}}x_{j_{4}i_{2}})| \leq 16c_{0}c_{1}, \\ |\kappa_{3}| &\leq \frac{2}{n^{2}} \sum_{j_{1}, j_{2}, j_{3}, j_{4}=1}^{n} |c_{s}| |E(x_{j_{1}i_{1}}x_{j_{2}i_{1}}\overline{x}_{i_{2}}\overline{x}_{i_{2}})| \\ &\leq \frac{2c_{1}}{n^{2}} \sum_{j_{1}, j_{2}, j_{3}, j_{4}=1}^{n} |c_{s}| |E(x_{j_{1}i_{1}}x_{j_{3}i_{2}}\overline{x}_{j_{4}i_{2}})| \leq 8c_{0}c_{1}, \\ |\kappa_{4}| &\leq \frac{4}{n^{2}} \sum_{j_{1}, j_{2}, j_{3}, j_{4}=1}^{n} |c_{s}| |E(x_{j_{1}i_{1}}\overline{x}_{i_{1}}\overline{x}_{j_{3}i_{2}}\overline{x}_{j_{4}i_{2}})| \leq 16c_{0}c_{1}, \\ |\kappa_{5}| &\leq \frac{4}{n^{2}} \sum_{j_{1}, j_{2}, j_{3}, j_{4}=1}^{n} |E(x_{j_{1}i_{1}}\overline{x}_{i_{1}}\overline{x}_{i_{2}}\overline{x}_{i_{2}})| \\ &\leq \frac{4c_{1}}{n^{2}} \sum_{j_{1}, j_{2}, j_{3}, j_{4}=1}^{n} |c_{s}| |E(x_{j_{1}i_{1}}\overline{x}_{i_{1}}\overline{x}_{i_{2}}\overline{x}_{i_{2}})| \\ &\leq \frac{4c_{1}}{n^{2}} \sum_{j_{1}, j_{2}, j_{3}, j_{4}=1}^{n} |c_{s}| |E(x_{j_{1}i_{1}}\overline{x}_{i_{1}}\overline{x}_{i_{2}}\overline{x}_{i_{2}})| \\ &\leq \frac{4c_{1}}{n^{2}} \sum_{j_{1}, j_{2}, j_{3}, j_{4}=1}^{n} |c_{s}| |E(\overline{x}_{i_{1}}\overline{x}_{i_{1}}\overline{x}_{i_{2}}\overline{x}_{i_{2}})| \\ &\leq \frac{4c_{1}}{n^{2}} \sum_{j_{1}, j_{2}, j_{3}, j_{4}=1}^{n} |c_{s}| |E(\overline{x}_{i_{1}}\overline{x}_{i_{1}}\overline{x}_{i_{2}}\overline{x}_{i_{2}})| \\ &\leq \frac{c_{1}}{n^{2}} \sum_{j_{1}, j_{2}, j_{3}, j_{4}=1}^{n} |c_{s}| |E(\overline{x}_{i_{1}}\overline{x}_{i_{1}}\overline{x}_{i_{2}}\overline{x}_{i_{2}})| \\ &\leq \frac{c_{1}}{n^{2}} \sum_{j_{1}, j_{2}, j_{3}, j_{4}=1}^{n} |E(x_{j_{1}i_{1}}x_{j_{2}i_{1}}x_{j_{3}i_{2}}x_{j_{4}i_{2}})| \leq 4c_{0}c_{1}. \end{split}$$

It thus follows that $E(b_{i_1i_2}^2) \leq 4c_0c_2(1+4+6+4+1) = 64c_0c_1$ for $i_1, i_2 = 1, \dots, m$ and $j_1, j_2, j_3, j_4 = 1, \dots, n$. Then $E(b_{i_1i_2})$ and $\operatorname{var}(b_{i_1i_2})$ are finite. Further by the Chebyshev's inequality, $b_{i_1i_2}$ is bounded in probability. Therefore, $\operatorname{tr}\left((H_X - \frac{1}{n}\Omega)\widetilde{S}\right)$ converges to 0 in probability. This completes the proof.

Proof of Lemma 3.2.

Let \mathbb{H} be a reproducing kernel Hilbert space on \mathbb{X} , with a continuous feature mapping $\phi(x)$. With the positive definite kernel function $s_{ij} = \psi(y_i, y_j) = \langle \phi(y_i), \phi(y_j) \rangle_{\mathbb{H}}$, it can be obtained that

$$\frac{1}{n^2} \mathbf{1}_n^\top S \mathbf{1}_n = \langle \frac{1}{n} \sum_{i=1}^n \phi(y_i), \frac{1}{n} \sum_{j=1}^n \phi(y_j) \rangle_{\mathbb{H}} \xrightarrow{p} E(\langle \phi(y_i), \phi(y_j) \rangle_{\mathbb{H}}) = E(s_{ij}).$$

By the law of large numbers, we have

$$\frac{1}{n}\sum_{i=1}^{n}\lambda_{i} = \frac{1}{n}\operatorname{tr}(\widetilde{S}) = \frac{1}{n}\operatorname{tr}(S) - \frac{1}{n^{2}}\mathbf{1}_{n}^{\top}S\mathbf{1}_{n} \xrightarrow{p} E(s_{ii}) - E(s_{ij}).$$

By Lemma 3.1, $\operatorname{tr}(H_X \widetilde{S}) / \sum_{i=1}^n \frac{\lambda_i}{n}$ has the same asymptotic distribution as $\sum_{i=1}^n w_i \xi_i$, where $w_i = \lambda_i / \sum_{j=1}^n \lambda_j$. Since $\sum_{i=1}^n w_i = 1$ and $0 \le w_i \le 1, i = 1, \dots, n$, it then follows that

$$E\left(\sum_{i=1}^{n} w_i \xi_i\right) = m_0 \sum_{i=1}^{n} w_i = m_0 \text{ and } \operatorname{var}\left(\sum_{i=1}^{n} w_i \xi_i\right) = 2m_0 \sum_{i=1}^{n} w_i^2 \le 2m_0 \sum_{i=1}^{n} w_i = 2m_0,$$

where $m_0 = 1/(1 + \mu^{\top} \Delta^{-1} \mu) + m - 1$. Hence, by Chebyshev's inequality, for any $\tau_0 > 0$,

$$P\left(\left|\frac{1}{n}\sum_{i=1}^{n}w_{i}\xi_{i}\right| \geq \tau_{0} + \frac{m_{0}}{n}\right) \leq P\left(\left|\frac{1}{n}\sum_{i=1}^{n}w_{i}\xi_{i} - \frac{m_{0}}{n}\right| \geq \tau_{0}\right)$$
$$\leq \frac{2m_{0}}{n^{2}\tau_{0}^{2}}.$$

Then for any $\tau_1 = 2\tau_0 > 0$,

$$\lim_{n \to \infty} P\left(\left| \frac{1}{n} \sum_{i=1}^n w_i \xi_i \right| \ge \tau_1 \right) = 0.$$

It follows that $\operatorname{tr}(H_X \widetilde{S}) / \sum_{i=1}^n \lambda_i$ converges in distribution to zero, that is, $\operatorname{tr}(H_X \widetilde{S}) / \sum_{i=1}^n \lambda_i$ converges in probability to zero. Then we conclude that

$$\frac{1}{n-m}\operatorname{tr}\left((\mathbf{I}_n - H_X)\widetilde{S}\right) = \frac{\operatorname{tr}\left((\mathbf{I}_n - H_X)\widetilde{S}\right)}{\sum_{i=1}^n \lambda_i} \frac{1}{n-m} \sum_{i=1}^n \lambda_i \xrightarrow{p} E(s_{ii}) - E(s_{ij}).$$

Proof of Theorem 3.3.

Theorem 3.3 is a direct consequence of Lemma 3.1 and Lemma 3.2.

Proof of Proposition 3.4.

When Assumption 1 holds, by Theorem 1 of Gretton et al. [7] and the Chebyshev's inequality, we have $\sum_{i=1}^{\infty} (\frac{\lambda_i}{n})^{1/2} z_i^4$ and $\sum_{i=1}^{\infty} (\lambda_i^*)^{1/2} z_i^4$ are bounded in probability, as $n \to \infty$. Combining this and the Cauchy-Schwarz inequality leads to

$$\begin{split} \left|\sum_{i=1}^{\infty} \left(\left(\frac{\lambda_{i}}{n}\right)^{1/2} - \left(\lambda_{i}^{*}\right)^{1/2}\right) z_{i}^{2} \right| &\leq \left\{\sum_{i=1}^{\infty} \left(\frac{\lambda_{i}}{n}\right)^{1/2} z_{i}^{4} \right\}^{1/2} \left\{\sum_{i=1}^{\infty} \left| \left(\frac{\lambda_{i}}{n}\right)^{1/4} - \left(\lambda_{i}^{*}\right)^{1/4} \right|^{2} \right\}^{1/2} \\ &+ \left\{\sum_{i=1}^{\infty} \left(\frac{\lambda_{i}}{n}\right)^{1/2} z_{i}^{4} \right\}^{1/2} \left\{\sum_{i=1}^{\infty} \left| \left(\frac{\lambda_{i}}{n}\right)^{1/4} - \left(\lambda_{i}^{*}\right)^{1/4} \right|^{2} \right\}^{1/2} \\ &\leq \left\{\sum_{i=1}^{\infty} \left(\frac{\lambda_{i}}{n}\right)^{1/2} z_{i}^{4} \right\}^{1/2} \left\{\sum_{i=1}^{\infty} \left| \left(\frac{\lambda_{i}}{n}\right)^{1/2} - \left(\lambda_{i}^{*}\right)^{1/2} \right| \right\}^{1/2} \\ &+ \left\{\sum_{i=1}^{\infty} \left(\lambda_{i}^{*}\right)^{1/2} z_{i}^{4} \right\}^{1/2} \left\{\sum_{i=1}^{\infty} \left| \left(\frac{\lambda_{i}}{n}\right)^{1/2} - \lambda_{i}^{*1/2} \right| \right\}^{1/2} \xrightarrow{P} 0 \end{split}$$

Proof of Lemma 3.5.

For any symmetric semidefinite matrices \mathbf{D}_1 , there exits a symmetric matrices \mathbf{P} , so that $\mathbf{D}_1 = \mathbf{P}\mathbf{P}^{\top}$. For any n dimension vector \mathbf{x} , we have $\mathbf{x}^{\top}\mathbf{P}^{\top}\mathbf{D}_2\mathbf{P}\mathbf{x} \ge 0$. It follows that $\mathbf{P}^{\top}\mathbf{D}_2\mathbf{P}$ is a symmetric semidefinite matrice. Thus $\mathbf{D} = \mathbf{D}_1\mathbf{D}_2 = \mathbf{P}\mathbf{P}^{\top}\mathbf{D}_2$ has the same eigenvalues as $\mathbf{P}^{\top}\mathbf{D}_2\mathbf{P}$ whose eigenvalues are nonnegative. Consequently, $\operatorname{tr}(\mathbf{D}^{\top}\mathbf{D}) = \sum_{i=1}^n \lambda_{i,D}^2 \le \left(\sum_{i=1}^n \lambda_{i,D}\right)^2 = \operatorname{tr}(\mathbf{D})^2$, where $\lambda_{i,D}$ is eigenvalue of \mathbf{D} , $i = 1, \dots, n$.

Proof of Theorem 3.6.

For $\Omega = X\widetilde{\Delta}^{-1}X^{\top}$, it can be obtained that

$$n^{1/2} \operatorname{tr} \left(H_X \widetilde{S}^{1/2} \right) = \operatorname{tr} \left(\Omega(\widetilde{S}/n)^{1/2} \right) + n^{1/2} \operatorname{tr} \left((H_X - \frac{1}{n} \Omega) \widetilde{S}^{1/2} \right).$$

We first show that $\operatorname{tr}\left(\Omega(\widetilde{S}/n)^{1/2}\right)$ has the same asymptotical distribution with $\sum_{i=1}^{n} (\lambda_i/n)^{1/2} \xi_i$ under H_0 . By extending the proof of Theorem 3 in Zhang [27], under H_0 , $\operatorname{tr}\left(\Omega(\widetilde{S}/n)^{1/2}\right)$ has the same asymptotic distribution as $\sum_{i,j=1}^{n} (\lambda_i^*)^{1/2} \widetilde{\lambda}_j^* z_{ij}^2 = \sum_{i=1}^{n} (\lambda_i^*)^{1/2} \xi_i$. In addition, by proposition 3.4, we have $\sum_{i=1}^{n} ((\lambda_i/n)^{1/2} - (\lambda_i^*)^{1/2}) \xi_i \xrightarrow{p} 0$. It thus follows that $\operatorname{tr}\left(\Omega(\widetilde{S}/n)^{1/2}\right)$ has the same asymptotic distribution as $\sum_{i=1}^{n} (\lambda_i/n)^{1/2} \xi_i$.

Next we show that $n^{1/2} \operatorname{tr} \left((H_X - \frac{1}{n} \Omega) \widetilde{S}^{1/2} \right)$ converges to 0 in probability. Write

$$n^{1/2}\operatorname{tr}\left((H_X - \frac{1}{n}\Omega)\widetilde{S}^{1/2}\right) = \operatorname{tr}(A\widetilde{B}) = \sum_{i=1}^m \sum_{j=1}^m a_{ij}\widetilde{b}_{ij},$$

where $A = (a_{ij})_{m \times m} = (\frac{1}{n}X^{\top}X)^{-1} - \widetilde{\Delta}^{-1} \xrightarrow{p} 0$ and $\widetilde{B} = (\widetilde{b}_{ij})_{m \times m} = X^{\top}(\widetilde{S}/n)^{1/2}X$. Denote $B_0 = \widetilde{\Delta}^{-1/2}\widetilde{B}\widetilde{\Delta}^{-1/2}$ and by Lemma 3.5

$$\operatorname{tr}(B_0^{\top}B_0) = \operatorname{tr}\left(\widetilde{\Delta}^{-1}\widetilde{B}\widetilde{\Delta}^{-1}\widetilde{B}\right) = \operatorname{tr}\left(\Omega(\widetilde{S}/n)^{1/2}\Omega(\widetilde{S}/n)^{1/2}\right) \leq \left(\operatorname{tr}\left(\Omega(\widetilde{S}/n)^{1/2}\right)\right)^{1/2},$$

where $\operatorname{tr}(\Omega(\widetilde{S}/n)^{1/2})$ tends to $\sum_{i=1}^{\infty} (\lambda_i^*)^{1/2} \xi_i$ who is bounded in probability. It implies that $\operatorname{tr}(B_0^{\top}B_0)$, i.e., the (i,j)th entry of B_0 is bounded in probability such that the (i,j)th entry of $\widetilde{B} = \widetilde{\Delta}^{1/2} B_0 \widetilde{\Delta}^{1/2}$ is as well bounded, $i, j = 1, \cdots, m$. One can derive that $n^{1/2} \operatorname{tr}((H_X - \frac{1}{n}\Omega)\widetilde{S}^{1/2})$ converges to 0 in probability. It follows that $\operatorname{tr}(H_X(n\widetilde{S})^{1/2})$ has the same asymptotic distribution as $\sum_{i=1}^n (\lambda_i/n)^{1/2} \xi_i$ as $n \to \infty$.

By the extension of Lemma 3.2, we have $\operatorname{tr}\left((\mathbf{I}_n - H_X)\widetilde{S}^{1/2}\right) / \sum_{i=1}^n \lambda_i^{1/2} \xrightarrow{p} 1$ as $n \to \infty$. Consequently, T_{sqrt} has the same asymptotic distribution with $m^{-1}\sum_{i=1}^n \eta_i \xi_i$.

Proof of Theorem 3.7.

For the linear kernel $\psi(\cdot, \cdot)$, it follows that

$$\frac{1}{n}X^{\top}\widetilde{S}X = \frac{1}{n}\sum_{i=1}^{n}\sum_{j=1}^{n}(x_i-\overline{x})s_{ij}(x_j-\overline{x})^{\top}$$
$$= \left[(n)^{-1}\sum_{i=1}^{n}(x_i-\overline{x})(x_i^{\top}\boldsymbol{\beta}+\varepsilon_i^{\top})\right] \left[\sum_{j=1}^{n}(\boldsymbol{\beta}^{\top}x_j+\varepsilon_j)(x_j-\overline{x})^{\top}\right].$$

Let $G = (n)^{-1/2} \sum_{i=1}^{n} (x_i - \overline{x}) (x_i^{\top} \beta + \varepsilon_i^{\top}) = \frac{1}{n^{1-\iota}} \sum_{i=1}^{n} (x_i - \overline{x}) x_i^{\top} \widetilde{\beta}_n + (n)^{-1/2} \sum_{i=1}^{n} (x_i - \overline{x}) \varepsilon_i^{\top} \triangleq G_1 + G_2$, where G_2 is bounded in probability by the Chebyshev's inequality and then G_2/n^{ι} are converge in probability to zero. By the law of large numbers, it can be obtained that

$$Q_1 = \frac{1}{n} \sum_{i=1}^n s_{ij} = \frac{1}{n} \sum_{i=1}^n (x_i^\top \beta + \varepsilon_i^\top) (\beta^\top x_i + \varepsilon_i) \xrightarrow{p} \Delta_{\varepsilon} \text{ and } Q_2 = \frac{1}{n^2} \sum_{i=1}^n \sum_{j=1}^n s_{ij} \xrightarrow{p} 0$$

and the (i, j)th entry of G_1/n^i converges in probability to the (i, j)th entry of $\Delta \tilde{\beta}$ for $i = 1, \dots, m$ and $j = 1, \dots, q$. Then we have the numerator of T,

$$\frac{1}{n^{2\iota}} \operatorname{tr} \left(H_X \widetilde{S} \right) = \frac{1}{n^{2\iota}} \operatorname{tr} \left(\left(\frac{1}{n} X^\top X \right)^{-1} G G^\top \right) \xrightarrow{p} \operatorname{tr} \left(\widetilde{\Delta}^{-1} \Delta \widetilde{\beta} \widetilde{\beta}^\top \Delta^\top \right) > 0.$$

and the denominator of T_{pseudo} , $\operatorname{tr}(\widetilde{S}/n) = \operatorname{tr}(Q_1 - Q_2) \xrightarrow{p} \operatorname{tr}(\Delta_{\varepsilon}) > 0$. It follows that

$$\frac{T_{pseudo}}{n^{2\iota}} = \frac{n-m}{mn} \frac{\operatorname{tr}(H_X \widetilde{S}/n^{2\iota})}{\operatorname{tr}((\mathbf{I}_n - H_X)\widetilde{S}/n)} \xrightarrow{p} \frac{1}{m} \frac{\operatorname{tr}(\widetilde{\Delta}^{-1} \Delta \widetilde{\boldsymbol{\beta}} \widetilde{\boldsymbol{\beta}}^\top \Delta^\top)}{\operatorname{tr}(\Delta_{\varepsilon})} > 0$$

and then for any $\tilde{\tau}_0 > 0$,

$$\lim_{n \to \infty} P\Big(\Big| \frac{T_{pseudo}}{n^{2\iota}} - \frac{1}{m} \frac{\operatorname{tr}(\widetilde{\Delta}^{-1} \Delta \widetilde{\boldsymbol{\beta}} \widetilde{\boldsymbol{\beta}}^\top \Delta^\top)}{\operatorname{tr}(\Delta_{\varepsilon})} \Big| > \widetilde{\tau}_0 \Big) = 0$$

Now we show that $P(T_{pseudo} > F_1^{-1}(1-\alpha)) = P(T_{pseudo}/n^{2\iota} > F_1^{-1}(1-\alpha)/n^{2\iota}) \xrightarrow{p} 1$ as $n \to \infty$.

Proof of Theorem 3.8.

Denote $A_0 = H_X(\widetilde{S}/n)^{1/2}$ whose eigenvalues are nonnegative by Lemma 3.5 and then $\operatorname{tr}(H_X(\widetilde{S}/n)^{1/2}) = \operatorname{tr}(A_0) \geq \operatorname{tr}(A_0^{\top}A_0)^{1/2} = \operatorname{tr}(H_X\widetilde{S}/n)$ where $\operatorname{tr}(H_X\widetilde{S}/n)$ converges to a positive constant in probability by Theorem 3.7. It follows that

$$\frac{T_{sqrt}}{n} = \frac{\operatorname{tr}(H_X \widetilde{S}^{1/2}/mn)}{\operatorname{tr}((\mathbf{I}_n - H_X) \widetilde{S}^{1/2}/(n-m))} \ge \frac{n-m}{n} \frac{\operatorname{tr}(A_0^\top A_0)^{1/2}}{\sum_{i=1}^n (\lambda_i/n)^{1/2}} > 0.$$

Consequently, we have $P(T_{sqrt} > F_2^{-1}(1-\alpha)) = P(T_{sqrt}/n > F_2^{-1}(1-\alpha)/n) \xrightarrow{p} 1$ as $n \to \infty$.