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SURE INDEPENDENCE SCREENING ADJUSTED FOR CONFOUNDING COVARIATES WITH ULTRAHIGH DIMENSIONAL DATA

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Abstract: Detecting candidate genetic variants in genomic studies often encounters the confounding problems, particularly when the data are ultrahigh dimensional. Confounding covariates, such as age and gender, not only can reduce the statistical power, but also will introduce spurious genetic association. How to control for the confounders in ultrahigh dimensional data analysis is critical yet challenging issues. In this paper, we propose a novel sure independence screening method based on conditional distance correlation under the ultrahigh dimensional model setting. Our proposal accomplishes the adjustment by conditioning on the confounding variables. With the model-free feature of conditional distance correlation, our method does not need any parametric modeling assumptions and is thus quite flexible in practice. In addition, it is naturally applicable to data with multivariate response. We show that under some mild technical conditions, the proposed method enjoys the sure screening property even when the dimensionality is an exponential order of the sample size. The simulation studies and a real data analysis demonstrate that the proposed procedure has competitive performance.

Key words and phrases: Confounding; Feature Screening; Model Free; Multivariate Response; Ultrahigh Dimension.

1. Introduction

Identifying variants associated with common complex disease in ultrahigh dimensional data is a central goal of genome-wise association studies (GWAS). The genetic disease effects are potentially confounded by covariates such as age, gender or education levels, which not only could reduce the statistical power, but also will cause spurious genetic associations (Glorioso and Sibille, 2011; Wang et al., 2012). As a motivating example, consider a study of the association between copy number changes and gene expression levels in breast cancer. In this

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study, there were a total of 88 subjects with 19672 genes and 2149 measurements of copy number changes after preprocessing. Age at diagnosis as well as other covariates has been found to be confounders of the cancer effect with significant interaction term in some biomarkers (Stephens et al., 2012). Genetic variants identification without proper adjustment for confounders could yield to spurious associated genetic detections. In addition, the response variable is multivariate and thus traditional feature selection techniques cannot be directly utilized.

In the last two decades, variable selection plays an prominent role in high-dimensional statistical modeling especially for genetic variants detection, see Fan and Li (2006) and Fan and Lv (2010) for a comprehensive overview. Yet it is challenged with ultrahigh dimensional data for computational cost and estimation accuracy.

Fan and Lv (2008) introduced the concept of sure screening and proposed the Sure Independent Screening (SIS) method to select important variables in ultra-high dimensional linear models. They showed that this correlation-ranking procedure enjoys a sure screening property in linear models with Gaussian error; that is, with probability close to 1, the SIS procedure retains all of the important variables. Later, the SIS method has been extended by relaxing the model assumptions or the error distribution assumption, see Fan and Song (2010), Hall and Miller (2009), Fan et al. (2011) and Zhu et al. (2011). In particular, Li et al. (2012) proposed a model-free screening procedure called DC-SIS by ranking the marginal utility measure based on distance correlation, which is an efficient measure of dependence. The distance correlation of two random vectors equals to zero if and only if they are independent (Székely et al., 2007; Székely and Rizzo, 2009), a property that is not shared by other correlations. Furthermore, due to the nature of distance correlation, DC-SIS can be directly applied in cases with multivariate responses. However, these approaches undoubtedly ignored effects from confounding covariates, which calls for research on SIS procedures to take the confounders into account.

In this paper, we propose a novel model-free feature screening procedure by ranking the conditional distance correlation of the response and each predictor on confounding covariates. The conditional distance correlation was proposed by Wang et al. (2015) and possesses an appealing property analogous to the distance

correlation, i.e., the conditional distance correlation of two random vectors given a random vector equals to zero if and only if they are conditionally independence. Compared with DC-SIS, the most distinguishable feature of our proposal is that the confounding covariates are incorporated into the feature screening process and hence can increase the statistical power. Furthermore, our proposed method does not require to specify the distribution or the regression model. This nice property makes our proposed procedure particularly flexible in feature screening. In addition, our method is applicable to multivariate response by the virtue of conditional distance correlation.

Theoretically, we establish the sure screening property for the proposed procedure under the ultrahigh dimensional model setting. The sure screening property guarantees that our screening procedure will include the true model with probability tends to 1 in an exponential rate of the sample size n. This property is valid provided that the dimensionality of the predictors p grows slightly slower than $\exp(an)$ for any fixed $a > 0$. This rate is comparable to those achieved by DC-SIS and SIS. In simulation studies, we demonstrate that our method possesses the sure screening property, and has superior performance than DC-SIS and SIS under a variety of settings.

The rest of this paper is organized as follows. In Section 2, we develop a novel feature screening approach corrected for confounding covariate. The sure screening property of the proposed procedure is established in Section 3. Section 4 illustrates its finite performance by Monte Carlo simulations and a real data analysis in breast cancer. A brief discussion is provided in Section 5. All technical proofs can be found in the online Supplementary Materials.

2. Independence Screening using Conditional Distance Correlation

Let Y be the q_y-dimensional response variable, which can be either univariate or multivariate. Let $(X_1, \ldots, X_p)$ be predictor vectors, and Z be the q_z-dimensional confounding covariates such as age and education. The predictor $X_r, r = 1, \ldots, p$, is p_r-dimensional to allow categorical or grouped variable. We allow p to grow with n and denote it by p_n whenever necessary. Next we introduce the notation of active predictors and inactive predictors conditioning on Z. Without specifying a regression model, we define the index sets of active

and inactive predictors given Z by

$$\mathcal{A} = \{r : \text{ Some } Y \text{ depends on } X_r \text{ given } Z\},$$
$$\mathcal{I} = \{r : \text{ Any } Y \text{ does not depend on } X_r \text{ given } Z\}.$$

Note that the intersection of $\mathcal{A}$ and $\mathcal{I}$ is empty set. The predictors whose index set in $\mathcal{A}$ is referred to the active predictors. Our primary interest is to identify all the active predictors given the confounding covariates. When there is no confounding effects, sure independence screening procedure based on distance correlation (DC-SIS, Li et al. (2012)) is desirable for its model-free property and flexible application to grouped predictor variables and multivariate response variables. The distance correlation works by measuring a weighted $L_q(0 < q \leq 2)$ distance between the joint characteristic function and the product of the two marginal characteristic functions. A suitable weight is selected to make the distance correlation a proper and scale invariant correlation measurement. This type of weight function leads to a simple product-average form of the covariance analogous to Pearson covariance (Székely et al., 2007; Székely and Rizzo, 2009). This motivates us to extend the DC-SIS feature screening procedure to take the confounding effects into account.

Test of conditional dependence is one of the most widely used statistical method for controlling the confounding effect. Therefore, measurement of conditional dependence is of increasing interest. In the literature, a series of conditional dependence measures have been developed using a generalization of empirical distribution function (Linton and Gozalo, 1996), smoothing empirical likelihood (Su and White, 2003), a normalized conditional cross-covariance operator in reproducing kernel Hilbert space (Gretton et al., 2005) , conditional characteristic function (Su and White, 2007), weighted Hellinger distance (Su and White, 2008) and the Hibert-Schmidt norm with Copula transformation (J Reddi and Póczos, 2013). Inspired by the great success of distance correlation (Székely et al., 2007), several conditional measurements are proposed based on the distance correlation. Póczos and Schneider (2012) replaced the characteristic function with conditional characteristic function and derived the estimation based on the k-nearest neighbour method. Fan et al. (2015) proposed a conditional independence measure based on the distance covariance between the residuals after adjusting the covariates. Recently, Wang et al. (2015) proposed a novel conditional dependence

measure called conditional distance correlation (CDC). It was shown to enjoy the desirable property analogous to the distance correlation; that is, the conditional distance correlation of two random vectors given a random vector equals to zero if and only if they are conditionally independence. It guarantees the conditional distance correlation can describe exactly the relationship between two variables given a third variable. Furthermore, they derived the corresponding statistic for test of conditional dependence.

Given the confounding covariate Z, the conditional distance correlation between the response variable Y and each predictor variable $X_r, r = 1, \ldots, p$, is defined by

$$\rho_r(Z) = \mathrm{CDCor}^2(X_r, Y \mid Z) = \frac{\mathrm{CDCov}^2(X_r, Y \mid Z)}{\sqrt{\mathrm{CDCov}^2(X_r, X_r \mid Z)\mathrm{CDCov}^2(Y, Y \mid Z)}},$$

if $\mathrm{CDCov}^2(X_r, X_r \mid Z)\mathrm{CDCov}^2(Y, Y \mid Z) > 0$, and 0 otherwise. $\mathrm{CDCov}^2(\cdot, \cdot \mid \cdot)$ is the conditional distance covariance defined through characteristic function. To be precise, the conditional distance covariance between X_r and Y given Z is

$$\begin{aligned} & \mathrm{CDCov}^2(X_r, Y \mid Z) \\ = \; & \|\phi_{X_r,Y|Z}(t,s) - \phi_{X_r|Z}(t)\phi_{Y|Z}(s)\|^2 \\ = \; & \frac{1}{c_{p_r}c_{q_y}} \int_{\mathbb{R}^{p_r+q_y}} \frac{|\phi_{X_r,Y|\mathbf{z}}(t,s) - \phi_{X_r|Z}(t)\phi_{Y|\mathbf{z}}(s)|^2}{|t|_{p_r}^{1+p_r}|s|_{q_y}^{1+q_y}} dtds, \end{aligned}$$

where $c_{p_r} = \pi^{(1+p_r)/2}/\Gamma((1+p_r)/2)$ and $c_{q_y} = \pi^{(1+q_y)/2}/\Gamma((1+q_y)/2)$ are constants related to p_r and q_y. $\phi_{X_r,Y|Z}(t,s)$ is the joint conditional characteristic function X_r and Y given Z. $\phi_{X_r|Z}(t)$ and $\phi_{Y|Z}(s)$ are the marginal conditional characteristic functions for $X_r \mid Z$ and $Y \mid Z$, respectively. The conditional distance variance $\mathrm{CDCov}^2(X_r, X_r \mid Z)$ and $\mathrm{CDCov}^2(Y, Y \mid Z)$ are defined similarly.

From the definition, $\rho_r(Z)$ is a function of Z and therefore not yet ready for ranking. Hence here we consider defining a marginal utility to screen features as

$$\rho_r^* = E(\rho_r(Z)) = E\{\mathrm{CDCor}^2(X_r, Y \mid Z)\}.$$

To estimate ρ_r^*, let us first proceed with the estimation of $\mathrm{CDCov}^2(X_r, Y \mid Z)$. It essentially requires the estimation of $\phi_{X_r,Y|Z}(t,s)$, $\phi_{X_r|Z}(t)$ and $\phi_{Y|Z}(s)$, which can be estimated from their empirical versions, respectively. In particular,

we use the Gaussian kernel smoothing method to estimate the characteristic functions.

Suppose $\mathbf{W} = (\mathbf{X}_1, \ldots, \mathbf{X}_p, \mathbf{Y}, \mathbf{Z}) = \{(X_{k1}, \ldots, X_{kp}, Y_k, Z_k) : k = 1, \ldots, n\}$ is a random sample from the joint distribution of random vectors X, Y and Z. For the rth predictor, let $d^X_{ij,r} = d(X_{ir}, X_{jr})$ be the Euclidean distance of X_{ir} and X_{jr}, $i, j = 1, \ldots, n$. Similarly, let $d^Y_{ij} = d(Y_i, Y_j)$ denote the Euclidean distance of Y_i and Y_j, $i, j = 1, \ldots, n$. Define the distance function as

$$d^s_{ijkl,r} = (d_{ijkl,r} + d_{ijlk,r} + d_{ilkj,r})/3,$$

where $d_{ijkl,r} = (d^X_{ij,r} + d^X_{kl,r} - d^X_{ik,r} - d^X_{jl,r})(d^Y_{ij} + d^Y_{kl} - d^Y_{ik} - d^Y_{jl})$.

Given Z, the sample conditional distance covariance $\mathrm{CDCov}^2(X_r, Y \mid Z)$ is

$$\widehat{\mathrm{CDCov}}^2(\mathbf{X}_r, \mathbf{Y}, \mathbf{Z} \mid Z) = n^{-4} \sum_{i,j,k,l} \psi_n(\mathbf{W}_i, \mathbf{W}_j, \mathbf{W}_k, \mathbf{W}_l; Z),$$

with the symmetric random kernel of degree 4,

$$\psi_n(\mathbf{W}_i, \mathbf{W}_j, \mathbf{W}_k, \mathbf{W}_l; Z) = \frac{n^4 \omega_i(Z)\omega_j(Z)\omega_k(Z)\omega_l(Z)}{4\omega^4(Z)} d^s_{ijkl,r},$$

where $\omega_i(Z)$ is an estimate for the density function in Z_i and $\omega(Z)$ is $n^{-1}\sum \omega_i(Z)$. Wang et al. (2015) showed that $\widehat{\mathrm{CDCov}}^2(\mathbf{X}_r, \mathbf{Y}, \mathbf{Z} \mid Z)$ is actually a V process, which has well-established asymptotical framework (Lee, 1990). The sample conditional distance variances $\widehat{\mathrm{CDCov}}^2(\mathbf{X}_r, \mathbf{X}_r, \mathbf{Z} \mid Z)$ and $\widehat{\mathrm{CDCov}}^2(\mathbf{Y}, \mathbf{Y}, \mathbf{Z} \mid Z)$ can be defined similarly. Thus the sample conditional distance correlation $\hat{\rho}_r(Z)$ is defined as

$$\hat{\rho}_r(Z) = \widehat{\mathrm{CDCor}}^2(\mathbf{X}_r, \mathbf{Y}, \mathbf{Z} \mid Z) = \frac{\widehat{\mathrm{CDCov}}^2(\mathbf{X}_r, \mathbf{Y}, \mathbf{Z} \mid Z)}{\sqrt{\widehat{\mathrm{CDCov}}^2(\mathbf{X}_r, \mathbf{X}_r, \mathbf{Z} \mid Z)\widehat{\mathrm{CDCov}}^2(\mathbf{Y}, \mathbf{Y}, \mathbf{Z} \mid Z)}}.$$

A plug-in estimate of ρ^*_r is given by

$$\hat{\rho}^*_r = n^{-1} \sum_{k=1}^{n} \hat{\rho}_r(Z_k).$$

Using $\hat{\rho}^*_r$ as a marginal utility, we propose a new screening procedure for ultrahigh dimensional data with the control of confounding as follows:

$$\hat{\mathcal{M}}_{d_n} = \{r : \hat{\rho}^*_r \text{ is among the first } d_n \text{ largest of all, } r = 1, \ldots, p\}.$$

where the submodel size d_n is predefined to be smaller than the sample n. This reduces the full model of size $p \gg n$ to a submodel with size d_n. This proposed procedure is referred as conditional distance correlation sure independence screening (CDC-SIS for short).

3. Theoretical Properties

In this section, we establish the asymptotical property of the proposed CDC-SIS procedure. To derive the sure screening property for CDC-SIS, we impose some regularity conditions on X, Y and Z as following

(C1): The kernel function $K(\cdot)$ is bounded uniformly such that $K(u) \geq 0$, $\int K(u)du = 1$, $\int uK(u)du = 0$ and $\int \|u\|^2 K(u)du < \infty$.

(C2): The random vectors X and Y satisfy the sub-exponential tail probability uniformly in p. That is, there exists a positive constant s_0 such that for all $0 < s \leq s_0$,

$$\sup_p \max_{1\leq r\leq p} E(\exp(s\|X_r\|_p^2)) < \infty, \quad E(\exp(s\|Y\|_{q_y}^2)) < \infty,$$

where p and q_y are the dimensions of the predictor X_r and the response variable Y, respectively.

(C3): Suppose Z_1, Z_2, Z_3, Z_4 are independent copies of Z. Then for $1 \leq r \leq p$, $E(d_{1234,r} \mid Z_1, Z_2, Z_3, Z_4)$ marginally satisfies the Lipschitz condition uniformly in p. That is, there exists a positive constant L, such that

$$\sup_r |E(d_{1234,r}|Z_1, Z_2, Z_3, Z_4) - E(d_{1234,r}|Z_1', Z_2, Z_3, Z_4)| \leq L|Z_1 - Z_1'|.$$

(C4): There exist some constants $c > 0$ and $0 \leq \kappa < 1/2$ such that

$$\min_{r\in\mathcal{A}} \rho_r^* \geq 2cn^{-\kappa}.$$

Condition (C1) contains mild conditions on the density function $f(z)$ and kernel function $K(\cdot)$, which can be guaranteed by most commonly used distributions and kernels including the Gaussian kernel. Condition (C2) is satisfied

if X and Y are uniformly bounded. This condition puts an exponential bound on the tails of X and Y. Similar condition is widely used in Fan and Lv (2008) and Li et al. (2012). Condition (C3) can be satisfied when the first order partial derivative of $E(d_{1234,r} \mid Z_1, Z_2, Z_3, Z_4)$ is bounded. This condition is used to control the change rate of Z. Condition (C4) requires the true CDCor between the active predictors and the response must be large enough. This assumption is fundamental and intuitive in the area of high-dimensional feature selection and ultrahigh dimensional feature screening.

In the following theorem, we will present the uniform convergence rate for the proposed method and then show the CDC-SIS procedure possesses the sure screening property. The proof is left to the Appendix of the Supplementary Materials.

Theorem 1 *Under Conditions (C1)-(C3) and the assumption of the bandwidth for kernel estimation of Z satisfies $h = O(n^{-\kappa/(2q_z)})$, then for any $0 < \gamma < 1/2 - \kappa$, there exists positive constants $c_1 > 0$ and $c_2 > 0$ such that*

$$\mathrm{pr}(\max_{1\le r\le p} |\hat{\rho}_r^* - \rho_r^*| \ge cn^{-\kappa}) \le p[\exp(-c_1 n^{1-2(\gamma+\kappa)}) + n^4 \exp(-c_2 n^{\gamma})] + o(1).$$

Furthermore, if Condition (C4) holds, we have

$$\begin{aligned}\mathrm{pr}(\mathcal{A} \subseteq \hat{\mathcal{M}}_{d_n}) \ge & 1 - n|\mathcal{A}|[\exp(-c_1 n^{1-2(\kappa+\gamma)}) + n^4 \exp(-c_2 n^{\gamma})] \\ & - |\mathcal{A}| \exp(-c_3 n^{1-2\kappa}) + o(1).\end{aligned}$$

where $|\mathcal{A}|$ is the size of the set $\mathcal{A}$ and c_3 is a positive constant.

Theorem 1 requires that the bandwidth of kernel estimation of Z satisfies $h = O(n^{-\kappa/(2q_z)})$, where q_z is the dimension of Z, and $0 < \kappa < 1/2$. Similar conditions can be found in Liu et al. (2014). This rate obviously satisfies the general rate in the kernel density estimation ($n \to \infty, h \to 0$ and $nh^{q_z} \to \infty$), where density estimate is consistent. This rate could be faster or slower than the theoretical optimal rate of kernel density estimation, depending on the choice of κ and γ. It is easy to see that when γ is fixed, the right side of $\mathrm{pr}(\mathcal{A} \subseteq \hat{\mathcal{M}}_{d_n})$ increases as κ decreases. This indicates that oversmoothing could benefit the screening performance in terms of the probability of true active predictors.

Note that the convergence rate of the sure property depends only on $|\mathcal{A}|$ rather than the dimensionality p. This result is remarkable since the size of $\mathcal{A}$

is smaller than the sample size n and much smaller than p. Thus, CDC-SIS is an effective and general alternative as a sure screening procedure adjusted for confounding covariates.

4. Numerical Studies

4.1 General Setting

We conducted three simulation studies and a real data analysis in genetical application to evaluate the finite sample performance of CDC-SIS, and compared its performance with those of SIS (Fan and Lv, 2008) and DC-SIS (Li et al., 2012). The bandwidth parameter of $\hat{\rho}_r^*$ in the CDC-SIS method is determined by optimizing the conditional distance correlation. If the bandwidth is too close to zero, we select the bandwidth with the plug-in method.

To assess the feature screening performance, we consider the following two criteria adopted from Li et al. (2012).

$\mathcal{S}$ the minimum model size to include all active predictors for a specific method. We report the median of $\mathcal{S}$ and draw a boxplot of $\log \mathcal{S}$ out of 100 replications

$\mathcal{P}_d$ the proportion that all active predictors are selected by a screening procedure for a given model size d in the 100 replications.

The $\mathcal{S}$ is used to measure the model complexity of the resulting model for an underlying screening procedure. The closer to the size of active predictors the $\mathcal{S}$ is, the better the screening procedure performs. The sure screening property ensures that $\mathcal{P}_d$ is close to one when the estimated model size d is sufficiently large. Li et al. (2012) suggested setting $d = \gamma\lceil n/\log(n)\rceil$, where $\lceil a\rceil$ refers to the integer part of a and γ is an integer number. To examine the overall performance on the choice of d, we consider a plot of $\mathcal{P}_d$ with $d = \gamma\lceil n/\log(n)\rceil$ as the y coordinate versus γ as the x coordinate.

For all examples in the simulation studies section, we generate $U = \{Z, X\} = (Z, X_1, \ldots, X_p)^T$ from normal distribution with zero mean and covariance matrix $\Sigma = (\sigma_{ij})_{(p+1)\times(p+1)}$, which is characterized by ρ. The ρ are set to be 0, 0.5 and 0.8 to examine the impact of correlation to the screening performance. The

sample size n is fixed to be 100 and the dimensionality p varies from 1000 to 5000. All simulations are replicated for 100 times.

4.2 Simulation Studies

EXAMPLE 1 In this example, we consider the following four models:

$$\text{(1.a):} \quad Y = 2.5Z + 3X_1 + 1.5X_2 + 2X_5 + \epsilon,$$

$$\text{(1.b):} \quad Y = 2.5Z + 3X_1 + 1.5X_2 + 2X_5^2 + \epsilon,$$

$$\text{(1.c):} \quad Y = 2.5Z + 3X_1 + 1.5X_2 + 2\sin(0.5\pi X_5) + \epsilon,$$

$$\text{(1.d):} \quad Y = 3X_1 + 1.5X_2 + 4ZX_5 + \epsilon.$$

where ϵ's are i.i.d. standard normal random variables. Note that for X_5, the regression function is linear in model (1.a), but nonlinear in all others. Specifically, the regression function of X_5 is non-monotonous in model (1.b), and periodic in model (1.c). In model (1.d), there is an interaction term involving the confounding covariate Z, i.e., ZX_5. The effect of X_5 to the response Y depends on the values of the confounding covariate Z and vice versa. Two kinds of covariance matrix Σ are considered: (i) compound symmetric (CS); (ii) first-order autoregressive (AR). The CS covariance matrix Σ has entries $\sigma_{ii} = 1, i = 1, \ldots, p+1$, and $\sigma_{ij} = \rho, i \neq j$. The AR matrix covariance Σ has entries $\sigma_{ij} = \rho^{|i-j|}, i, j = 1, \ldots, p+1$.

To save space, we report only the summary results with compound symmetric covariance matrix of X and $p = 1000$ in Table 4.1 and Figures 4.1-4.2. The summary results for other situations are put in Table S1 and Figures S1-S6 of the online Supplementary Material.

Obviously, DC-SIS and CDC-SIS outperform SIS in all models except for (1.a) where a linear regression model is assumed, which was also revealed in Li et al. (2012). More specifically, the performance of CDC-SIS is slightly better than those of SIS and much better than those of DC-SIS in model (1.a), indicating that CDC-SIS has a robust performance if the working models is linear.

Compared with DC-SIS, CDC-SIS shrinks the full model down to a much smaller scale by taking account for the confounding covariate Z in models (1.b)-(1.d). In particular, in model (1.d) with the CS covariance matrix, while other

Table 4.1: Example 1: Median of the minimum model size S for the SIS, DC-SIS and CDC-SIS methods for different values of p and ρ based on 100 replications under different modelswith compound symmetric (CS) covariance matrix

Model	p	ρ	SIS	DC-SIS	CDC-SIS
(1.a)	1000	0	6	8	5
		0.5	18	48	6
		0.8	40	67	16
	5000	0	16	28	9
		0.5	114	208	18
		0.8	189	292	40
(1.b)	1000	0	273	16	13
		0.5	598	404	82
		0.8	454	384	70
	5000	0	1261	58	30
		0.5	2630	1655	344
		0.8	2604	2040	370
(1.c)	1000	0	83	40	25
		0.5	94	43	12
		0.8	132	62	18
	5000	0	234	60	82
		0.5	558	324	72
		0.8	804	472	76
(1.d)	1000	0	312	128	5
		0.5	498	218	17
		0.8	661	283	33
	5000	0	1818	694	27
		0.5	2915	1331	66
		0.8	2654	1225	139

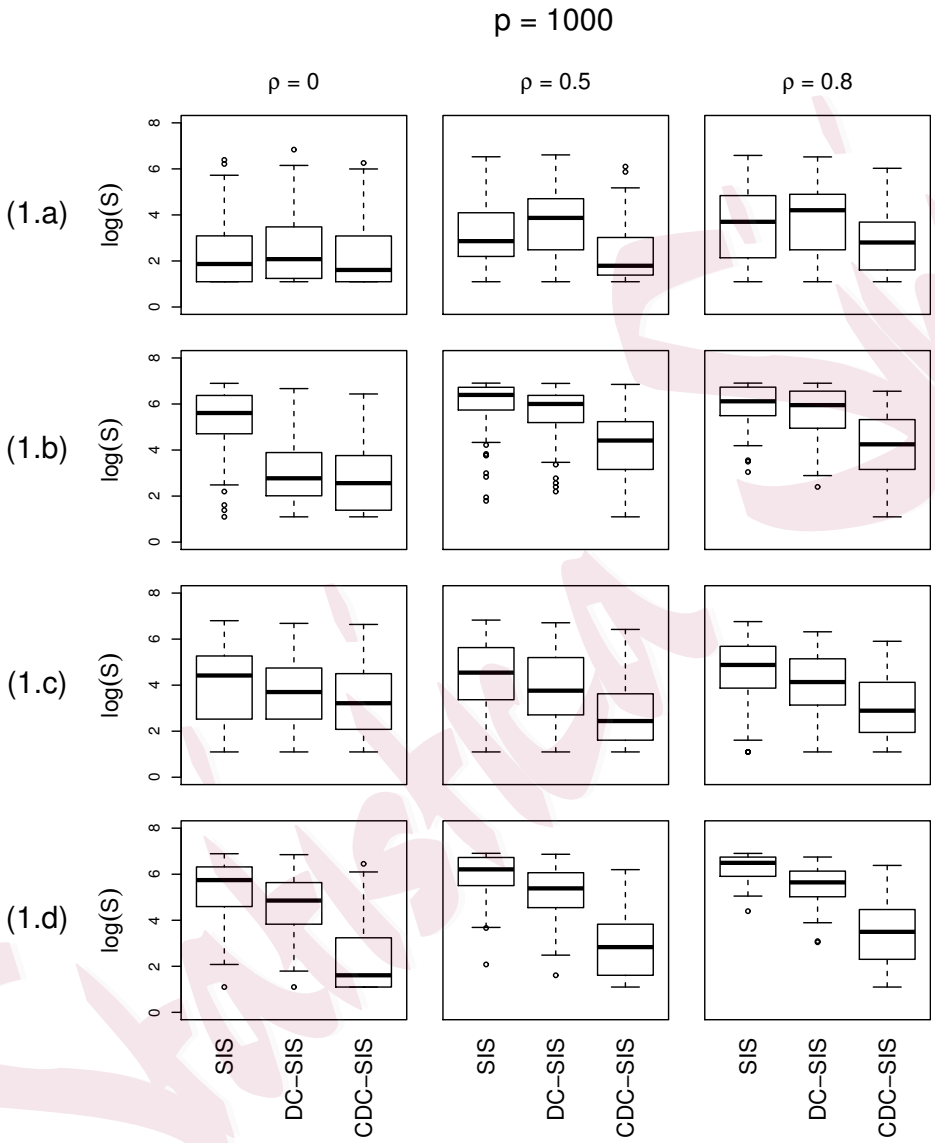

Figure 4.1: Example 1: Boxplots of $\log(\mathcal{S})$ for the SIS, DC-SIS and CDC-SIS methods for different values of ρ based on 100 replications under different models with $p = 1000$ and compound symmetric (CS) covariance matrix.

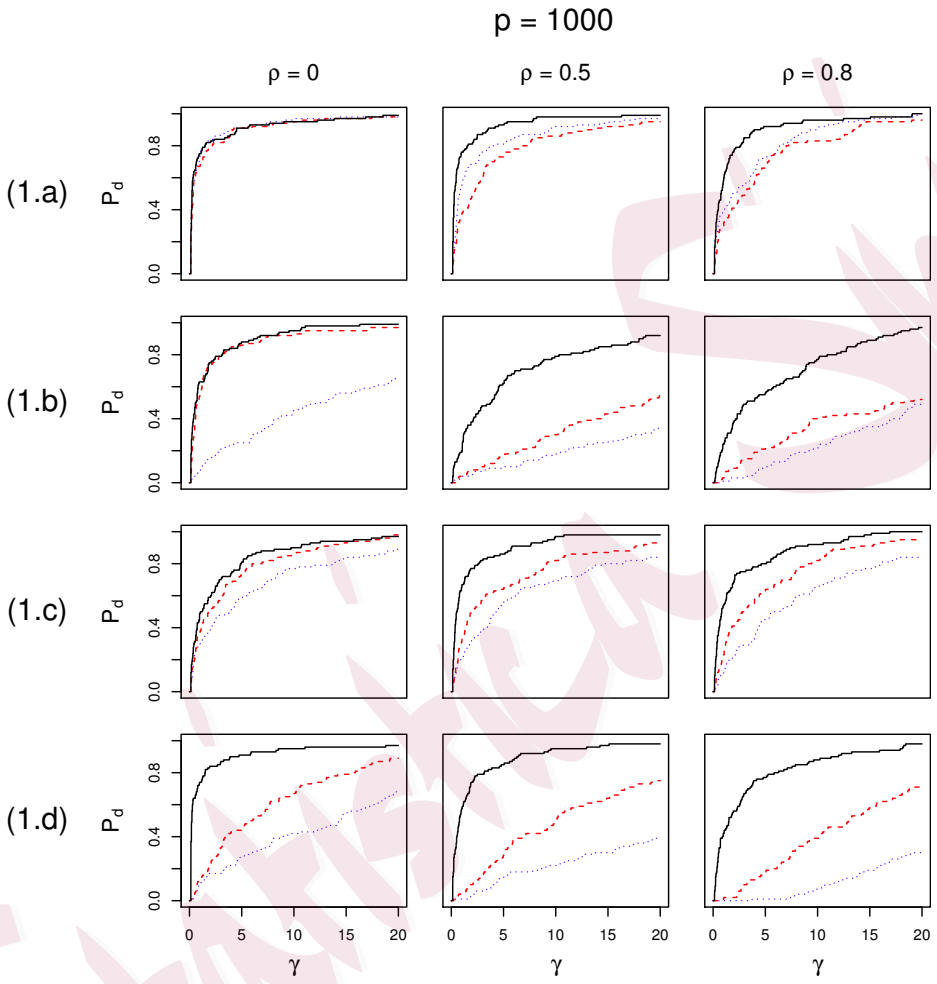

Figure 4.2: Examples 1: Summary results of the proportion of $\mathcal{P}_d$ for the SIS (dotted line), DC-SIS (dashed line) and CDC-SIS (solid line) methods for different values of ρ based on 100 replications under different models with $p = 1000$ and compound symmetric (CS) covariance matrix.

two screening procedures fail to identify the active predictor even with the threshold d being n $(= 100)$, CDC-SIS ranks all the active predictors at the top positions for $p = 1000$ and $\rho = 0.5$. In addition, the proportions $\mathcal{P}_d$ of our proposed method are close to one, which supports the assertion that it processes the sure screening property. Compared to other screening methods, CDC-SIS has significant better performance with the curves of $\mathcal{P}_d^{\gamma}$ being the one at the most upper left, especially in models (1.b)-(1.d). The effect is more pronounced for higher values of ρ and higher dimensionality. It suggests that adjusting for the confounding covariate(s) helps reduce false selection and might improve the prediction accuracy subsequently.

Furthermore, CDC-SIS is less sensitive to the change in the correlation ρ than SIS. While the median $\mathcal{S}$ of SIS at least doubles with ρ increasing from 0.5 to 0.8, those of CDC-SIS almost remains the same. This phenomenon is exemplified in Fan and Lv (2008) for the SIS with the Pearson correlation. When the confounding covariates are highly correlated with the predictors, the dimensionality and thus the correlation increases. Since the conditional distance correlation can remove the confounding effect by its essence, it can be less influenced by the correlation between the confounding covariates and the predictors variables.

We include comparison results for ISIS, an iterative version of SIS to variable selection. The threshold is set to be $d = \lceil n/\log(n) \rceil$ for all methods. For ISIS, the SCAD variable selection method with regularization parameter tuning by Bayesian information criterion was used after the SIS screening step and we kept on collecting variables until we obtained $\lceil n/\log(n) \rceil$ variables. Table 4.2 and Table S2 in the online Supplementary Material report the percentages of SIS, ISIS, DC-SIS and the prosed CDC-SIS that include the true model $\{X_1, X_2, X_5\}$, an index also used in Fan and Lv (2008). From Table 4.2 and Table S2, ISIS always improves the performance of SIS especially with larger value of ρ, which confirms the findings in Fan and Lv (2008). Yet compared with SIS and ISIS, CDC-SIS always has the best performance except for Model (1.a) where a linear model is assumed.

EXAMPLE 2 As suggested by one of the reviewers, we examined the effect of confounding covariate to the performance of CDC-SIS. Three models are considered: (2.a) the univariate covariate Z is not directly related to the response; (2.b)

Table 4.2: Example 1: Accuracy of SIS, ISIS, DC-SIS, CDC-SIS in including the true model $\{X_1, X_2, X_5\}$ for different values of ρ and p with compound symmetric (CS) covariance matrix.

Model	p	ρ	SIS	ISIS	DC-SIS	CDC-SIS
(1.a)	1000	0	0.73	0.97	0.67	0.75
		0.5	0.55	0.91	0.37	0.76
		0.8	0.39	0.88	0.30	0.58
	5000	0	0.53	0.78	0.45	0.61
		0.5	0.23	0.67	0.17	0.52
		0.8	0.16	0.54	0.08	0.43
(1.b)	1000	0	0.07	0.12	0.54	0.63
		0.5	0.04	0.04	0.04	0.19
		0.8	0.01	0	0.03	0.24
	5000	0	0.03	0.03	0.33	0.45
		0.5	0.01	0.01	0.01	0.14
		0.8	0	0	0	0.08
(1.c)	1000	0	0.3	0.49	0.37	0.49
		0.5	0.22	0.44	0.31	0.65
		0.8	0.11	0.19	0.23	0.54
	5000	0	0.15	0.21	0.27	0.31
		0.5	0.01	0.09	0.08	0.31
		0.8	0.03	0.05	0.08	0.16
(1.d)	1000	0	0.11	0.09	0.13	0.74
		0.5	0.01	0.03	0.05	0.57
		0.8	0	0	0.01	0.42
	5000	0	0.01	0	0.01	0.46
		0.5	0.01	0	0.03	0.34
		0.8	0	0	0	0.20

the confounding covariate $Z = (Z_1, Z_2)$ is two-dimensional and only Z_1 is related to the response; (2.c) the confounding covariate $Z = (Z_1, Z_2)$ is two-dimensional and both of Z_1 and Z_2 are related to the response. The response are generated respectively by

$$\text{(2.a):} \quad Y = 3X_1 + 1.5X_2 + 2X_5^2 + \epsilon,$$

$$\text{(2.b):} \quad Y = 2.5Z_1 + 3X_1 + 1.5X_2 + 2X_5^2 + \epsilon,$$

$$\text{(2.c):} \quad Y = 2.5Z_1 + 2.5Z_2 + 3X_1 + 1.5X_2 + 2X_5^2 + \epsilon,$$

where ϵ's are i.i.d. standard normal random variables. For Model (2.a), the covariance matrix of $U = \{Z, X\}$ is a block diagonal matrix with the first block having $\sigma_{ii} = 1, i = 1, \ldots, 3$, and $\sigma_{ij} = \rho, i \neq j$ and the second block $\sigma_{ii} = 1, i = 4, \ldots, p+1$, and $\sigma_{ij} = \rho, i \neq j$. Note that the confounding covariate Z is strongly correlated with X_1 and X_2. However, X_5 belongs to a group of strongly correlated variables $\{X_3, \cdots, X_p\}$ that are independent of Z, X_1 and X_2. For Models (2.b) and (2.c), the covariance matrix of $U = \{Z, X\}$ has entries $\sigma_{ii} = 1$ and $\sigma_{ij} = \rho, i \neq j$. The results for $p = 1000$ are summarized in Table 4.3 and Figures 4.3-4.4. The results for $p = 5000$ are summarized in Table S3 and Figures S7-S8 of the online Supplementary Material.

It is no surprised that the DC-SIS and CDC-SIS methods significantly outperform SIS since the model is non-linear in X_5, which again support the finding in Li et al. (2012). The results in Table 4.3 present interesting patterns. For the low correlation setting in Model (2.a), i.e., $\rho = 0$, the minimum model size of including all the active predictors for the proposal is slightly larger than those of DC-SIS on average. When $\rho = 0.8$, the medians $\mathcal{S}$ of the CDC-SIS are half of those of the DC-SIS. It suggests that when the confounding variable is not directly related to the response, CDC-SIS has competitive performance to DC-SIS although it might lose some power. For Models (2.b) and (2.c) where multivariate confounding covariates are considered, CDC-SIS performs best no matter whether Z is partially or all related with the response. Overall, taking account for the confounding covariates in the feature screening process may help reduce false selection even when the confounding variable is not directly related to the response or only partially correlated with the response.

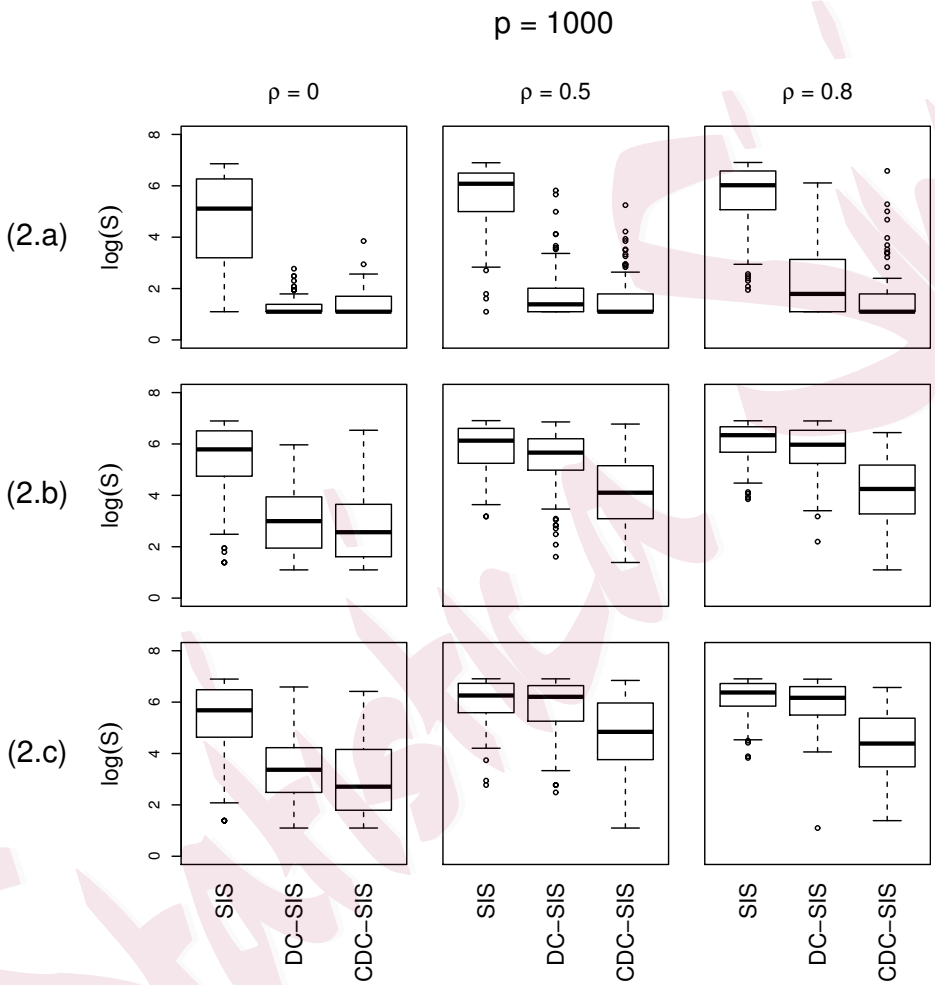

Figure 4.3: Example 2: Boxplots of $\log(\mathcal{S})$ for the SIS, DC-SIS and CDC-SIS methods for different values of ρ based on 100 replications under different models with $p = 1000$.

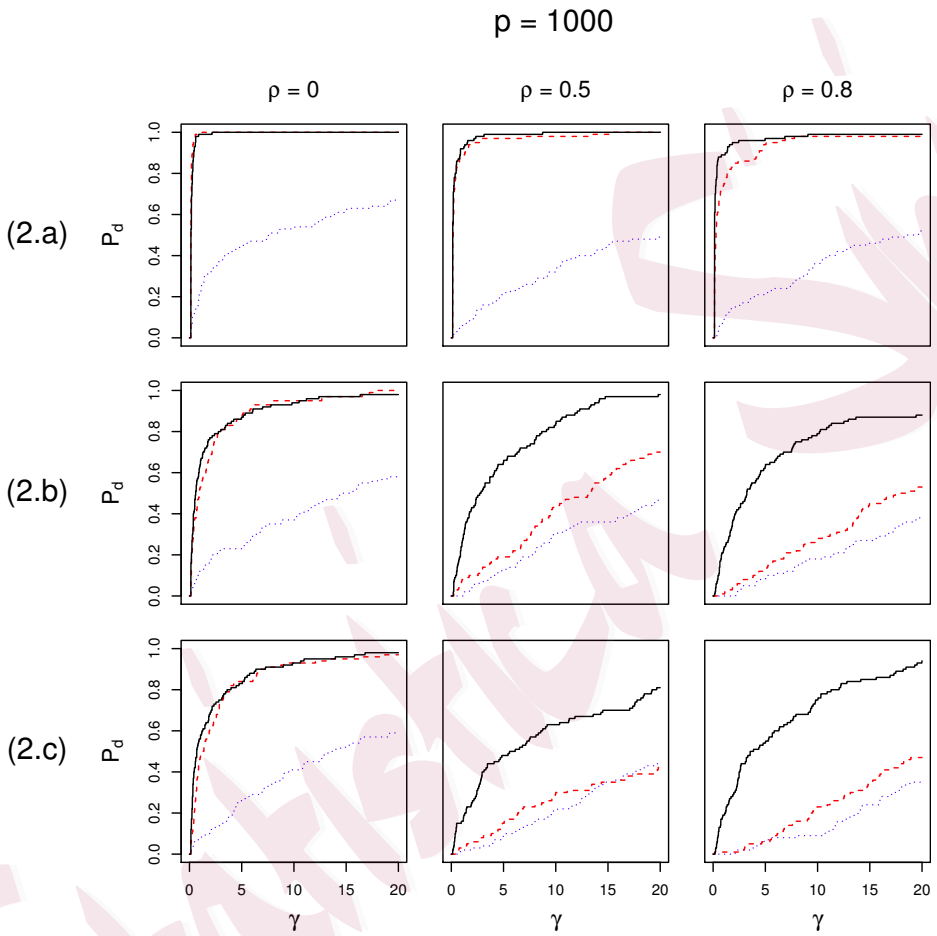

Figure 4.4: Examples 2: Summary results of the proportion of $\mathcal{P}_d$ for the SIS (dotted line), DC-SIS (dashed line) and CDC-SIS (solid line) methods for different values of ρ based on 100 replications under different models with $p = 1000$.

Table 4.3: Example 2: Median of the minimum model size S for the SIS, DC-SIS and CDC-SIS methods for different values of p and ρ based on 100 replications under different models.

Model	p	ρ	SIS	DC-SIS	CDC-SIS
(2.a)	1000	0	166	3	3
		0.5	437	4	3
		0.8	413	6	3
	5000	0	1843	5	6
		0.5	1536	5	4
		0.8	1570	14	3
(2.b)	1000	0	327	20	13
		0.5	459	288	60
		0.8	568	392	70
	5000	0	2147	130	75
		0.5	2582	1340	474
		0.8	2570	1882	330
(2.c)	1000	0	294	29	15
		0.5	522	496	127
		0.8	587	478	80
	5000	0	2154	184	84
		0.5	2292	1870	510
		0.8	3010	2774	884

In the next example, we will consider data with multivariate response. Since the SIS cannot deal with this kind of data directly, we will focus on the results from the DC-SIS and CDC-SIS methods.

EXAMPLE 3 In this example, we explore the performance of the proposal in dealing data with multivariate response. Two scenarios are considered, the first one simulated two dimensional response and the second one simulated high dimensional response. To make the simulation mimic the motivating data, the dimension in the second scenario is the same with that in the motivating data. In this example, the covariance matrix Σ of $U = \{Z, X\}$ has entries $\sigma_{ii} = 1, i = 1, \ldots, p+1$, and $\sigma_{ij} = \rho, i \neq j$.

(3.a): The two-dimensional response $Y = (Y_1, Y_2)^\top$ was generated by

$$Y = Z\beta_Z + X\beta_X + E,$$

where E is generated from normal distribution with mean zero and covariance matrix $\Sigma_{y|x} = I_{2\times 2}$. We choose a pair of (β_Z, β_X) such that Y_1 and Y_2 share the same association with X_1, i.e., $\beta_Z = (-1.6\sqrt{\rho},\ 1.6,\ 0, \ldots, 0)^\top$ and $\beta_X = (0,\ 1.6,\ -1.6\sqrt{\rho}, 0, \ldots, 0)^\top$.

(3.b): The 136-dimensional response Y is generated by

$$Y = Z\beta_Z + X_1\beta_1 + X_2\beta_2 + E,$$

where $E^{(2)}$ is generated from normal distribution with mean zero and covariance matrix $\Sigma_{y|x} = I_{136\times 136}$. In this model, the response Y is related with the first three predictors $\{X_1, X_2\}$ and confounding covariate Z. The nonzero regression coefficients, i.e., the first four column of $B^{(2)}$, are drawn from standard normal distribution independently.

Table 4.4: Example 3: Median of the minimum model size S for DC-SIS and CDC-SIS methods for different values of p and ρ based on 100 replications under different models.

		$p = 1000$		$p = 5000$	
Model	ρ	DC-SIS	CDC-SIS	DC-SIS	CDC-SIS
(3.a)	0*	1	1	1	1
	0.5	3	2	6	2
	0.8	15	2	102	2
(3.b)	0	3	3	3	3
	0.5	3	3	3	3
	0.8	6	3	18	3

*: When $\rho = 0$, only X_1 is correlated with Y. So the true active predictors set is $\{X_1\}$.

Comparison results are summarized in Table 4.4 and Figures 4.5-4.6, from which it can be seen that the benefit of adjusting for the confounding effect is significant. Compared to DC-SIS, CDC-SIS needs a much smaller model to include all the true active predictors. CDC-SIS performs very well in terms of model complexity, while DC-SIS performs unsatisfactorily especially when $\rho =$

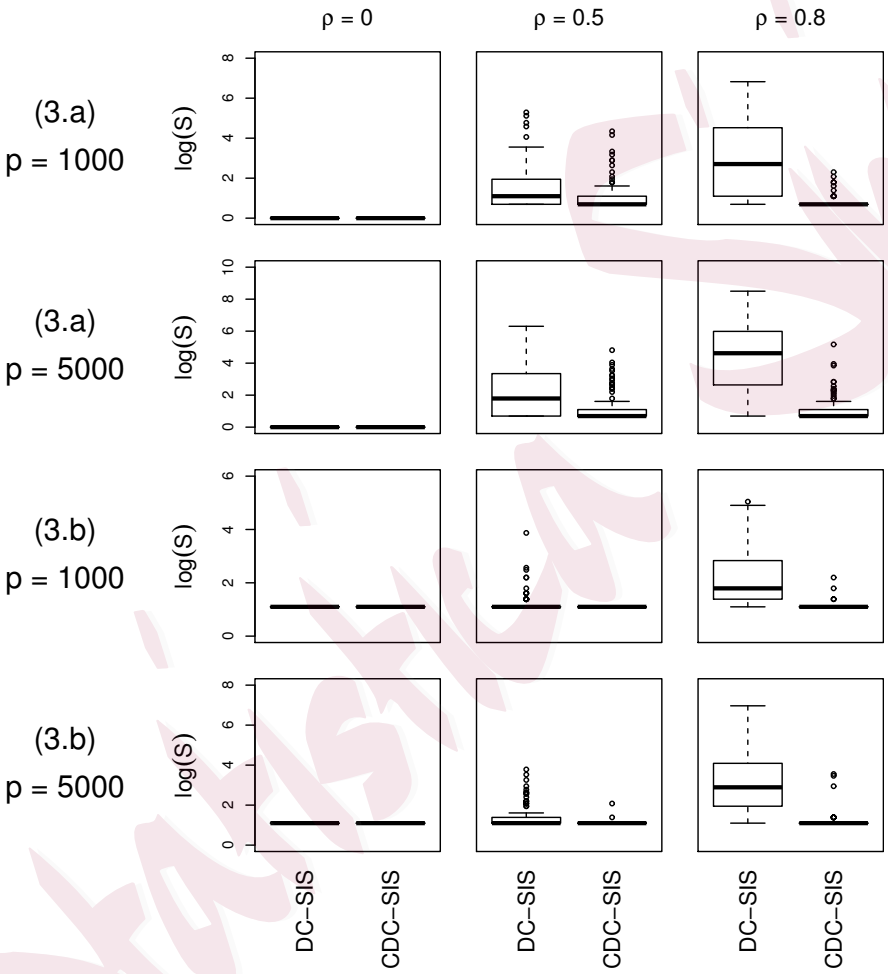

Figure 4.5: Example 3: Boxplots of $\log(\mathcal{S})$ for the DC-SIS(dashed line) and CDC-SIS(solid line) methods for different values of p and ρ based on 100 replications under different models.

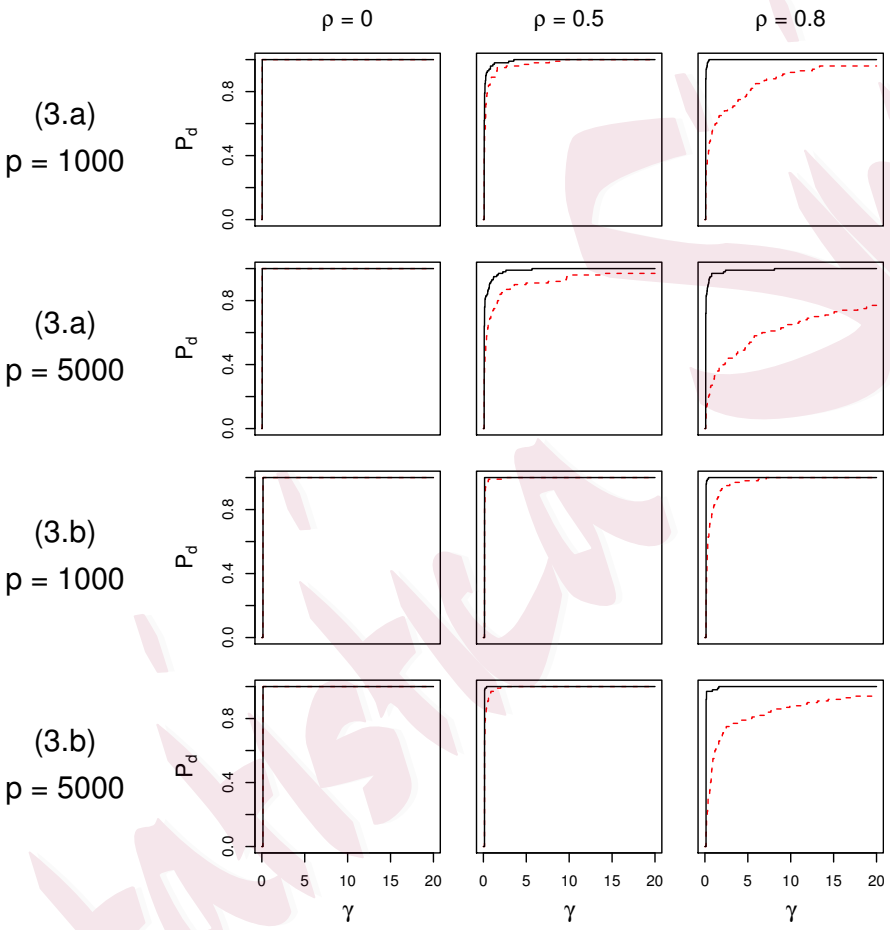

Figure 4.6: Examples 3: Summary results of the proportion of $\mathcal{P}_d$ for the DC-SIS (dashed line) and CDC-SIS (solid line) methods for different values of p and ρ based on 100 replications under different models.

0.8. In addition, CDC-SIS is robust to the correlation between predictors, while the proportions for DC-SIS drop dramatically as ρ increases.

4.3. Real Data Analysis in Breast Cancer

We illustrate our proposed method using the public breast cancer data set reported by Chin et al. (2006) and re-analyzed by Witten et al. (2009) and Ma and Sun (2014). The data set includes the gene expression, comparative genomic hybridization (CGH) measurements and clinical characteristics for a set of breast cancer patient samples. Note that CGH measures genome copy number variation along each chromosome in cancer samples, which can be helpful in characterizing certain types of cancers and understanding how the genome aberrations influence cancer pathophysiologies (Chin et al., 2006). Our goal is to identify a set of genes that are related to the copy number changes with or without adjustment to potential confounding covariates. In the literature, age at diagnosis (AGE for short) as well as other covariates has been found to be confounders of the disease effect with significant interaction term in some biomarkers (Stephens et al., 2012). Here we consider AGE as a potential confounding covariate.

We extract both the gene expression and CGH measurements data from the R package PMA (Witten et al., 2009) and download the clinical data from `http://www.ebi.ac.uk/arrayexpress/experiments/E-TABM-158/`. After removing missing data in AGE, the data set consists of $n = 88$ samples, $p = 19672$ gene expression measurements and 2149 CGH measurements on 23 chromosomes. Following Witten et al. (2009), we performed the screening methods for chromosome 1 using CGH measurements on chromosome 1 and all the available gene expression data. Chromosome 1 includes 136 CGH measurements in total. To assess the stability of the screening results, we adopt the idea of stability selection (Meinshausen and Bühlmann, 2010). For each fixed threshold value d, we compute the selection probability of each gene over the 500 sub-samples of size $\lceil n/2 \rceil$.

Table 4.5 lists the top $d = \lceil n/\log(n) \rceil = 20$ genes that were identified by the DC-SIS and CDC-SIS procedures. It also includes the selection probability for these selected genes. As can be seen from Table 4.5, 16 genes are identified by both the two screening methods. It is interesting to see that the first ten

ranking of CDC-SIS is almost the same with those of DC-SIS, which shows the competitiveness of the proposed method.

Table 4.5: Breast cancer data: The top d ($= \lceil n/\log(n) \rceil = 20$) genes identified by DC-SIS or CDC-SIS using the CGH spots on chromosome 1 and gene expression measurements on all chromosomes. Their ranks are shown on the second and third column for the DC-SIS and CDC-SIS, respectively. Their corresponding selection probability over the 500 sub-samples of size $\lceil n/2 \rceil$ with $d = 20$ are presented on the fourth and fifth column.

			Selection Probability	
Gene	DC-SIS	CDC-SIS	DC-SIS	CDC-SIS
TPR	13		.382	.144
GNPAT	3	3	.894	.784
NDUFS2	12	13	.494	.354
NUP133		19	.248	.240
GGPS1	14	8	.408	.552
RAB3-GAP150	16	20	.346	.198
PEX11B	8	10	.574	.322
PIGC	7	5	.786	.826
TBCE	6	6	.674	.636
RABIF		15	.116	.244
PPOX	17	18	.318	.294
SF3B4	4	4	.790	.688
DEGS		17	.184	.336
VPS45A	20	16	.304	.310
B4GALT3	15		.408	.220
FLJ12671	5	7	.728	.522
HSPC155	10	11	.522	.386
LGTN		14	.136	.254
MRPL24	2	2	.830	.784
HSPC003	1	1	.966	.868
FLJ10876	19		.240	.164
LOC51107	18		.244	.158
C1orf27	9	9	.474	.468
MY014	11	12	.482	.324

To gain further insight into the screening results, we fit generalized additive models(GAM) using the first sparse principle component (Witten et al., 2009) of Y with or without AGE. Here we take gene "HSPC003" and "B4GALT3" for

example. Note that "HSPC003" is ranked the first by both two methods, while "B4GALT3" is only identified by DC-SIS. The two models we considered are (1) $V = Cont_1 + f_1(gene)$ and (2) $V = Cont_2 + f_2(gene) + g(gene, \log(age))$, where V is the first principle component of Y, $Cont_i, i = 1, 2$ are the intercept terms and $f_i, i = 1, 2, g$ are unknown functions.

The fitted curve plots are displayed in Figure 4.7 and Figure 4.8. Leaving AGE out of account, both "HSPC003" and "B4GALT3" are highly correlated with V, as one can seen from the left panels of Figures 4.7-4.8. However, when including AGE as an interaction effect with the gene, they have quite different performance. As for "HSPC003", the interaction term is insignificant with p-value equal to 0.205 and the fitted curve looks like a cylindrical surface. However, the interaction term for "B4GALT3" is significant with p-value equal to 0.0282 and the fitted curve has non-smooth surface as shown in Figure 4.8. It means that "B4GALT3" has different correlation with V at different values of AGE.

5. Discussion

This paper studies the problem of ultra high dimensional feature screening with adjustment for the confounding effects. We propose a novel model-free screening method based on conditional distance correlation. The proposed method provides a powerful approach to effectively screening variables with potential confounding effects correction, which is of great importance for ultra-high dimensional genomic data analysis. In both the theoretical analysis and numerical study, the proposed approach has been shown to be capable of reducing the exponentially growing dimensionality of the model to a scale smaller than the sample size with probability tending to 1, i.e, the sure screening property. Although we are primarily motivated by genomic applications, the methodology is in fact very general and likely to find a wide range of applications in econometrics, clinical studies, and many other fields.

Some issues deserve further study. The threshold used in the proposed method is adopted from those in Fan and Lv (2008) and Li et al. (2012). It would be of interest to develop a criterion to determine the threshold for finite samples. We opt not to pursue this further and leave it to be a topic for future research. In addition, more refined model building and selection methods could

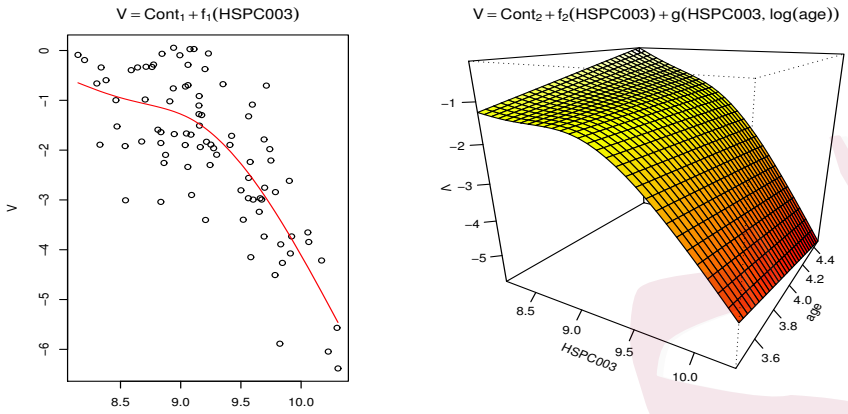

Figure 4.7: Real Data Analysis: The left panel displays the scatterplot of Y versus the expression of gene "HSPC003" well as the GAM fitting $V = Cont_1 + f_1(HSPC003)$. The right panel displays the perspective view of the GAM model $V = Cont_2 + f_2(HSPC003) + g(HSPC003, \log(age))$.

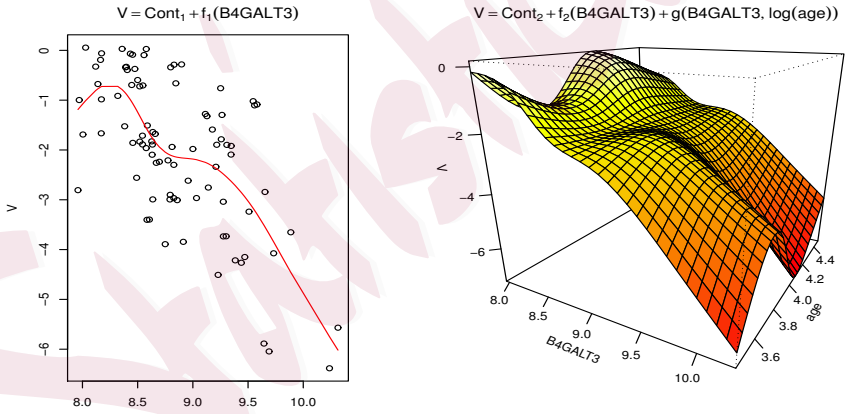

Figure 4.8: Real Data Analysis: The left panel displays the scatterplot of Y versus the expression of gene "B4GALT3" as well as the GAM fitting $V = Cont_1 + f_1(B4GALT3)$. The right panel displays the perspective view of the GAM model $V = Cont_2 + f_2(B4GALT3) + g(B4GALT3, \log(age))$.

be employed after feature screening, while the model-free nature of our screening method grants full flexibility in subsequent modeling.

Similar with other existing feature screening methods, the CDC-SIS procedure may fail to identify some important predictors which are marginally unrelated with the response. Thus it is an interesting problem to develop an iterative version of CDC-SIS to address such an issue. The essence of iterative procedure is to apply iteratively a large-scale variable screening followed by a moderate-scale careful variable selection. The proposed CDC-SIS procedure is model-free and thus a model-free variable selection procedure is prefered after screening. Yet most of the existing variable selection methods are based on a parametric regression model. Furthermore, in the case of multivariate response, the variable selection method should be able to handle multivariate response. It is quite challenging to simultaneously fix both problems in theory and computation. We have an ongoing research project on this issue and some preliminary Monte Carlo simulations show that iterative CDC-SIS may improve performance over the CDC-SIS procedure under univariate response setting. Similar idea on the iterative version of DC-SIS can be found in Zhong and Zhu (2014). However, there is no theoretic properties of the proposed iterative sure screening approach. Theoretical analysis of both the iterative DC-SIS and iterative CDC-SIS deserves further study. We leave it for future investigation.

A R package implementing the CDC-SIS method, called **cdcsis**, is publicly available on CRAN.

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