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Conditional Screening for Ultra-high
Dimensional Covariates with Survival
Outcomes

Hyokyung Grace Hong*

Jian Kang†

Yi Li‡

*Michigan State University, hhong@stt.msu.edu

†University of Michigan Department of Biostatistics, jiankang@umich.edu

‡University of Michigan School of Public Health, yili@umich.edu

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Identifying important biomarkers that are predictive for cancer patients' prognosis is key in gaining better insights into the biological influences on the disease and has become a critical component of precision medicine. The emergence of large-scale biomedical survival studies, which typically involve excessive number of biomarkers, has brought high demand in designing efficient screening tools for selecting predictive biomarkers. The vast amount of biomarkers defies any existing variable selection methods via regularization. The recently developed variable screening methods, though powerful in many practical setting, fail to incorporate prior information on the importance of each biomarker and are less powerful in detecting marginally weak while jointly important signals. We propose a new conditional screening method for survival outcome data by computing the marginal contribution of each biomarker given priorly known biological information. This is based on the premise that some biomarkers are known to be associated with disease outcomes a priori. Our method possesses sure screening properties and a vanishing false selection rate. The utility of the proposal is further confirmed with extensive simulation studies and analysis of a Diffuse large B-cell lymphoma (DLBCL) dataset.

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Keywords: Conditional screening, Cox model, Diffuse large B-cell lymphoma, high-dimensional variable screening

*Hyokyoung Grace Hong is Assistant Professor in the Department of Probability and Statistics, Michigan State University, East Lansing, MI 48823. Jian Kang is Assistant Professor in the Department of Biostatistics, University of Michigan, Ann Arbor, MI 48019. Yi Li is Professor of Biostatistics, Director of Kidney Epidemiology and Cost Center, University of Michigan, Ann Arbor, MI 48019.

[†]To whom correspondence should be addressed: jiankang@umich.edu. This research was partially supported by a grant from NSA (H98230-15-1-0260, Hong), an NIH grant (R01MH105561, Kang) and Chinese Natural Science Foundation (11528102, Li).

1 Introduction

Despite much progress made in the past two decades, many cancers do not have a proven means of prevention or effective treatments. Precision medicine that takes into account individual susceptibility has become a valid approach to gaining better insights into the biological influences on cancers, which is expected to benefit millions of cancer patients. A critical component of precision medicine lies in detecting and identifying important biomarkers that are predictive for cancer patients' prognosis. The emergence of large-scale biomedical survival studies, which typically involve excessive number of biomarkers, has brought high demand in designing efficient screening tools for selecting predictive biomarkers. The presented work is motivated by a genomic study of Diffuse large B-cell lymphoma (DLBCL) Rosenwald et al. (2002), with the goal of identifying gene signatures out of 7399 genes for predicting survival among 240 DLBCL patients. The results may address whether the DLBCL patients' survival after chemotherapy could be regulated by the molecular features.

The recently developed variable screening methods, such as the sure independence screening proposed by Fan and Lv (2008), have emerged as a powerful tool to solve this problem, but their validity often hinges upon the partial faithfulness assumption, that is, the jointly important variables are also marginally important. Consequently, they will fail to identify the *hidden* variables that are jointly important but have weak marginal associations with the outcome, resulting in poor understanding of the molecular mechanism underlying or regulating the disease. To alleviate this problem, Fan and Lv (2008) further suggested an iterative procedure (ISIS) by repeatedly using the residuals from the previous iterations, which has gained much popularity. However, the required iterations have increased the computational burden, and the statistical properties are elusive.

On the other hand, intensive biomedical research has generated a large body

of biological knowledge. For example, several studies have confirmed AA805575, a Germinal-center B-cell signature gene, is relevant to DLBCL survival (Gui and Li 2005, Liu et al. 2013). Including such prior knowledge for improved accuracy in variable selection has drawn much interest. Barut et al. (2016) proposed a conditional screening (CS) approach in the framework of a generalized linear model (GLM) when some prior knowledge on feature selection is known, and showed that the CS approach provides a powerful means to identify jointly-informative but marginally weak associations, and Hong et al. (2016) further proposed to integrate prior information using data-driven approaches.

Development of high dimensional screening tools with survival outcome has been fruitful. Some related work includes an (iterative) sure screening procedure for Cox's proportional hazards model (Fan et al. 2010), a marginal maximum partial likelihood estimator (MPLE) based screening procedure (Zhao and Li 2012), a censored rank independence screening method which is robust to outliers and applicable to a general class of survival model (Song et al. 2014). But to the best of our knowledge, all these methods essentially posit the partial faithfulness assumption and do not incorporate the known prior biological information. As a result, they will be likely to suffer the inability to identify marginally weak but jointly important signals.

To fill the gap, we propose a new conditional screening method for the Cox proportional hazards model by computing the marginal contribution of each covariate given priorly known information. We refer to it as Cox conditional screening (CoxCS). As opposed to the conventional marginal screening methods, our method enables the detection of marginally weak but jointly important signals, which will have important biological applications as shown in the data example section. Moreover, in contrast with most screening methods that usually employ subjective thresholds for screening, we also propose a principled cut-off to govern the screening and control the false posi-

tives in light of Zhao and Li (2012). This will be especially important in the presence of hidden variables.

To demonstrate the utility of CoxCS in recovering important hidden variables, we consider an example with 100 subjects and 1,000 covariates, where the survival times were generated from a Cox model with baseline hazards function being 1, and the covariates being generated from the multivariate standard normal distribution with equal correlation 0.5. The true coefficients in the Cox model are set to be $\beta_1 = \dots = \beta_5 = 1$ and $\beta_6 = -2.5$ and $\beta_j = 0$ for $j \in \{7, \dots, 1000\}$. By design, variable 6 is the hidden variable in that it is marginally uncorrelated with survival times approximately; see Example 1 in Section 4 for more details. Let $\widehat{\beta}_{\mathcal{C},j}$ denote the screening statistics by the CoxCS approach (defined in Section 2), where \mathcal{C} indexes variables that are pre-included into the model. When $\mathcal{C} = \emptyset$, the CoxCS is equivalent to the marginal screening approach for the Cox proportional hazard model. Figure 1 summarizes the densities of the screening statistics for the hidden variable 6 and noisy variables 10 to 1,000 for different sets of conditional variables based on 400 simulated datasets. The results show that with a high probability the marginal screening statistic for hidden variable 6 is much smaller than those of noisy variables. When the conditioning set includes one truly active variable, the density plots show a clear separation between the hidden variables and the noisy variables. When we include more truly active variables, this separation becomes larger. Interestingly, when conditional on noisy variables that are correlated with both active and hidden variables in the model, the chance of identifying the hidden variable using CoxCS is still higher than the marginal screening. A similar phenomenon was observed in the GLM setting (Barut et al. 2016). This is because when such “noisy” variables are correlated with both marginally important variables and hidden variables, they may effectively function as surrogates for the active variables and conditioning on them can help detect

hidden variables.

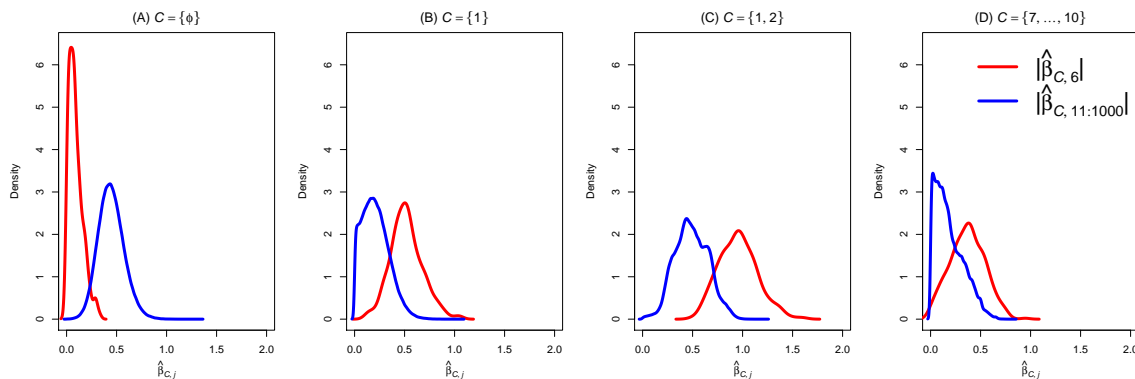


Figure 1: Density of the screening statistics $|\hat{\beta}_{C,6}|$ (red) for the hidden variable compared with a mixture of densities of screening statistics $|\hat{\beta}_{C,11:1000}|$ (blue) for the noise variables with different conditioning sets: (A) $\mathcal{C} = \{\emptyset\}$ which is equivalent to marginal screening; (B) $\mathcal{C} = \{1\}$ one truly active variables; (C) $\mathcal{C} = \{1, 2\}$ two truly active variables; (D) $\mathcal{C} = \{7, \dots, 10\}$ four noisy variables.

The theory of conditional screening for GLM has been established by Barut et al. (2016). But its extension to the survival context is challenging and elusive, calling for new techniques. To this end, we propose two new functional operators on random variables to characterize their linear associations given other random variables: the conditional linear expectation and the conditional linear covariance. Both are critical to formulate the regularity conditions for the population level properties of CoxCS with statistically meaningful interpretations, and facilitate the development of theory for conditional screening approaches in general settings. A similar concept of the conditional linear covariance has been introduced by Barut et al. (2016), but it can not be used for the survival outcome data. In summary, the proposed method is computationally efficient, adapts to sparse and weak signals, enjoys the good theoretical properties under weak regularity conditions, and works robustly in a variety of settings to identify hidden variables.

The remaining of this paper is organized as follows. In Section 2, we review the Cox proportional hazard model and present CoxCS approach with some alternatives. In

Section 3, we list the regularity conditions and establish the sure screening properties. In Section 4, we further conduct simulation studies to compare our method with the major competing methods under a number of scenarios. In Section 4, we apply our method to study the DLBCL data. We conclude with a brief discussion on the future work in Section 5.

2 Model

2.1 The Cox Proportional Hazard Model

Suppose we have n observations with p covariates. Let i and j respectively index subjects and covariates. Denote by $Z_{i,j}$ covariate j for subject i , write $\mathbf{Z}_i = (Z_{i,1}, \dots, Z_{i,p})^\top$. Let T_i be the underlying survival time and C_i be the censoring time. We observe $X_i = \min\{T_i, C_i\}$, and $\delta_i = I[T_i \leq C_i]$, where $I(\cdot)$ is the indicator function. Assume that there exists $\tau > 0$, such that $P(X_i > \tau | \mathbf{Z}_i) = 0$ and assume that the event time T_i and the censoring time C_i are independent. Suppose T_i follows a Cox proportional hazards model

$$\lambda(t; \mathbf{Z}_i) = \lambda_0(t) \exp(\boldsymbol{\alpha}^\top \mathbf{Z}_i), \quad (1)$$

where $\lambda_0(t)$ is an-unspecified baseline hazard and $\boldsymbol{\alpha} = (\alpha_1, \dots, \alpha_p)^\top$ is the true-coefficient. Let $\Lambda_0(t) = \int_0^t \lambda_0(s) ds$ be the cumulative hazard function. Suppose there is a set of covariates that are known a priori to be related to the survival outcome. Denote by \mathcal{C} the indices of these covariates. Let $q = |\mathcal{C}|$ be the number of covariates in \mathcal{C} . Write $\mathbf{Z}_{i,\mathcal{C}} = (Z_{i,j}, j \in \mathcal{C})^\top$, $\mathbf{Z}_{i,-\mathcal{C}} = (Z_{i,j}, j \notin \mathcal{C})^\top$, $\boldsymbol{\alpha}_{\mathcal{C}} = (\alpha_j, j \in \mathcal{C})^\top$ and $\boldsymbol{\alpha}_{-\mathcal{C}} = (\alpha_j, j \notin \mathcal{C})^\top$. Note that in our problem, \mathcal{C} is known but both $\boldsymbol{\alpha}_{\mathcal{C}}$ and $\boldsymbol{\alpha}_{-\mathcal{C}}$ are unknown. Then the true hazard function in (1) is equivalent to

$$\lambda(t; \mathbf{Z}_i) = \lambda_0(t) \exp(\boldsymbol{\alpha}_{\mathcal{C}}^\top \mathbf{Z}_{i,\mathcal{C}} + \boldsymbol{\alpha}_{-\mathcal{C}}^\top \mathbf{Z}_{i,-\mathcal{C}}), \quad (2)$$

To estimate $\boldsymbol{\alpha}_{\mathcal{C}}$ and $\boldsymbol{\alpha}_{-\mathcal{C}}$, we introduce the independent counting process $N_i(t) =$

$I(X_i \leq t, \delta_i = 1)$ and the at-risk process $Y_i(t) = I[X_i \geq t]$. When p is small, we can obtain the partial likelihood estimator $\hat{\boldsymbol{\alpha}} = (\hat{\boldsymbol{\alpha}}_{\mathcal{C}}^T, \hat{\boldsymbol{\alpha}}_{-\mathcal{C}}^T)^T$ by solving the estimation equation $\mathbf{U}(\boldsymbol{\alpha}) = \mathbf{0}_p$ with $\mathbf{U}(\boldsymbol{\alpha}) = (U_1(\boldsymbol{\alpha}), \dots, U_p(\boldsymbol{\alpha}))^T$ and

$$U_j(\boldsymbol{\alpha}) = \sum_{i=1}^n \int_0^\tau \left\{ Z_{i,j} - \frac{S_j^{(1)}(t, \boldsymbol{\alpha})}{S_j^{(0)}(t, \boldsymbol{\alpha})} dN_i(t) \right\}, \quad (3)$$

with

$$S_j^{(m)}(t, \boldsymbol{\alpha}) = \frac{1}{n} \sum_{i=1}^n Z_{i,j}^m Y_i(t) \exp(\boldsymbol{\alpha}_{\mathcal{C}}^T \mathbf{Z}_{i,\mathcal{C}} + \boldsymbol{\alpha}_{-\mathcal{C}}^T \mathbf{Z}_{i,-\mathcal{C}}), \quad (4)$$

for $m \in \{0, 1, 2, \dots\}$. When $p > n$, it is computationally and theoretically infeasible to directly solve the equation (6). By imposing sparsity on the coefficients, one may maximize the penalized partial likelihood to obtain solutions. However, when $p \gg n$, we need to employ a variable screening procedure first before performing regularized regression. We propose a new conditional screening procedure in the next section.

2.2 Cox Conditional Screening

We fit the marginal Cox regression by including the known covariates in \mathcal{C} . Specifically, for $j \notin \mathcal{C}$, we have the following marginal Cox regression model

$$\lambda_j(t; \mathbf{Z}_i) = \lambda_{j,0}(t) \exp(\boldsymbol{\beta}_{\mathcal{C}}^T \mathbf{Z}_{i,\mathcal{C}} + \beta Z_{i,j}), \quad (5)$$

from which the maximum partial likelihood estimation equation $(\hat{\boldsymbol{\beta}}_{\mathcal{C},j}^T, \hat{\beta}_j)^T$ can be obtained. It is given by the solution of the following equation:

$$\mathbf{V}_j(\boldsymbol{\beta}_{\mathcal{C}}, \beta) = [V_{j,k}(\boldsymbol{\beta}_{\mathcal{C}}, \beta), k \in \mathcal{C} \cup \{j\}]^T = \mathbf{0}_{q+1}, \quad (6)$$

with

$$V_{j,k}(\boldsymbol{\beta}_{\mathcal{C}}, \beta) = \sum_{i=1}^n \int_0^\tau \left\{ Z_{i,k} - \frac{R_{j,k}^{(1)}(\boldsymbol{\beta}_{\mathcal{C}}, \beta, t)}{R_{j,k}^{(0)}(\boldsymbol{\beta}_{\mathcal{C}}, \beta, t)} dN_i(t) \right\}, \quad (7)$$

and

$$R_{j,k}^{(m)}(\boldsymbol{\beta}_{\mathcal{C}}, \beta, t) = \frac{1}{n} \sum_{i=1}^n Z_{i,k}^m Y_i(t) \exp(\boldsymbol{\beta}_{\mathcal{C}}^T \mathbf{Z}_{i,\mathcal{C}} + \beta Z_{i,j}), \quad (8)$$

for $k \in \mathcal{C} \cup \{j\}$ and $m \in \{0, 1, 2, \dots\}$. For a given threshold $\gamma > 0$. The selected index set in addition to set \mathcal{C} is given by

$$\widehat{\mathcal{M}}_{-\mathcal{C}} = \{j \notin \mathcal{C} : |\widehat{\beta}_j| \geq \gamma\}. \quad (9)$$

Namely, we recruit variables with large additional contribution given $\mathbf{Z}_{\mathcal{C}}$. We refer to this method as Cox conditional screening (CoxCS).

3 Theoretical Results

We establish the theoretical properties of the proposed methods by introducing a few new definitions along with the basic properties.

3.1 Definitions and Basic Properties

Let (Ω, \mathcal{F}, P) be the probability space for all random variables introduced in this paper, where Ω is the sample space, \mathcal{F} is the σ -algebra as the set of events and P is the probability measure. Let \mathbb{R}^d be a d -dimensional Euclidean vector space, for positive integer d . Denote by $E[\bullet]$, $\text{Var}[\bullet]$ and $\text{Cov}[\bullet, \bullet]$ the commonly used expectation, variance and covariance operator in the probability theory, respectively. For any $d \geq 1$, any random variable $\boldsymbol{\xi} : \Omega \rightarrow \mathbb{R}^d$ and any operator A , denote by $A[\bullet \mid \boldsymbol{\xi}]$ conditional A of \bullet given $\boldsymbol{\xi}$. For any vector $\mathbf{a} = (a_1, \dots, a_p) \in \mathbb{R}^p$, let $\mathbf{a}_{\mathcal{C}} = (a_j, j \in \mathcal{C})^T$ be the sub vector where all its elements are indexed in \mathcal{C} . Let $\|\mathbf{a}\|_d = \sqrt[d]{\sum_{j=1}^p |a_j|^d}$ be the L- d norm for any vector $\mathbf{a} \in \mathbb{R}^p$. For a sequence of random variables indexed by $\{\xi_n\}$, $\xi_n = o_p(1)$ if and only if for any $\epsilon_1 > 0$ and $\epsilon_2 > 0$, there exists N such that for any $n > N$ $P[|\xi_n| > \epsilon_1] < \epsilon_2$.

For simplicity, let $T, C, X, Y(t), Z_j, \mathbf{Z}$ and δ represent $T_i, C_i, X_i, Y_i(t), Z_{i,j}, \mathbf{Z}_i$ and δ_i respectively, by removing the subject index i . Let $S_T(t \mid \mathbf{Z})$ and $S_C(t)$ represent the survival functions for the event time T and censored time C . Let $F_T(t \mid \mathbf{Z}) = 1 - S_T(t \mid \mathbf{Z})$.

Definition 1. Let $\mathcal{M}_{-\mathcal{C}} = \{j \notin \mathcal{C}, \alpha_j \neq 0\}$ and $w = \sum_{j \notin \mathcal{C}} I[\alpha_j \neq 0]$ be the true set of non-zero coefficients and its cardinality in model (1), aside from the important predictors known a priori.

To study the asymptotic property of $(\widehat{\boldsymbol{\beta}}_{\mathcal{C},j}^T, \widehat{\beta}_j)^T$, define the population level quantity as follows:

Definition 2. Let $(\boldsymbol{\beta}_{\mathcal{C},j}^T, \beta_j)^T$ be the solution of the following equations

$$\mathbf{v}_j(\boldsymbol{\beta}_{\mathcal{C}}, \beta) = [v_{j,k}(\boldsymbol{\beta}_{\mathcal{C}}, \beta), k \in \mathcal{C} \cup \{j\}]^T = \mathbf{0}_{q+1}, \quad (10)$$

with

$$v_{j,k}(\boldsymbol{\beta}_{\mathcal{C}}, \beta) = \int_0^\tau \left[s_k^{(1)}(t) - \frac{r_{j,k}^{(1)}(t, \boldsymbol{\beta}_{\mathcal{C}}, \beta)}{r_{j,k}^{(0)}(t, \boldsymbol{\beta}_{\mathcal{C}}, \beta)} s_k^{(0)}(t) \right] dt, \quad (11)$$

where $s_k^{(m)}(t) = \mathbb{E}[Z_k^m dN(t)]$ and $r_{j,k}^{(m)}(t, \boldsymbol{\beta}_{\mathcal{C}}, \beta) = \mathbb{E}[R_{j,k}^{(m)}(t, \boldsymbol{\beta}_{\mathcal{C}}, \beta)]$.

Definition 3. Let $\boldsymbol{\beta}_{\mathcal{C},0}$ be the solution of the following equations

$$\mathbf{v}_{\mathcal{C}}(\boldsymbol{\beta}_{\mathcal{C}}) = [v_{j,k}(\boldsymbol{\beta}_{\mathcal{C}}, 0), k \in \mathcal{C}]^T = \mathbf{0}_q. \quad (12)$$

Proposition 1. $\mathbf{v}_j(\boldsymbol{\beta}_{\mathcal{C},0}, 0) = \mathbf{0}_{q+1}$ if and only if $v_{j,j}(\boldsymbol{\beta}_{\mathcal{C},0}, 0) = 0$, for all $j \in \mathcal{C}$.

To understand the intuition of the population level properties for the Cox conditional screening, we need to define a conditional linear expectation. A similar concept has been used to study the conditional sure independence screening (CSIS) in the GLM setting by Barut et al. (2016). We provide a formal definition here.

Definition 4. For two random variables $\boldsymbol{\zeta} : \Omega \rightarrow \mathbb{R}^d$ and $\boldsymbol{\xi} : \Omega \rightarrow \mathbb{R}^p$. The conditional linear expectation of $\boldsymbol{\zeta}$ given $\boldsymbol{\xi}$ is defined as

$$\mathbb{E}^*(\boldsymbol{\zeta} \mid \boldsymbol{\xi}) = \mathbb{E}[\boldsymbol{\zeta}] + \mathbf{A}^T \{\boldsymbol{\xi} - \mathbb{E}(\boldsymbol{\xi})\}, \quad (13)$$

where $\mathbf{A} = \operatorname{argmin}_{\mathbf{B} \in \mathbb{R}^d \times \mathbb{R}^p} \mathbb{E}[(\boldsymbol{\zeta} - \mathbb{E}[\boldsymbol{\zeta}] - \mathbf{B}^T \{\boldsymbol{\xi} - \mathbb{E}(\boldsymbol{\xi})\})^2 \mid \boldsymbol{\xi}]$. Also, define notation $\mathbb{E}^*(\boldsymbol{\zeta}) = \mathbb{E}(\boldsymbol{\zeta})$.

The basic properties of the conditional linear expectation are listed in the following proposition.

Proposition 2. *Let ζ , ζ_1 , ζ_2 and ξ be any four random variables in the probability space (Ω, \mathcal{F}, P) . The following properties hold for the conditional linear expectation $E^*[\bullet | \xi]$ given ξ :*

1. *Closed form:* $E^*(\zeta | \xi) = E[\zeta] + \text{Cov}(\zeta, \xi)\text{Var}[\xi]^{-1}\{\xi - E(\xi)\}$.
2. *Stability:* $E^*[\xi | \xi] = \xi$.
3. *Linearity:* $E^*[\mathbf{A}_1\zeta_1 + \mathbf{A}_2\zeta_2 | \xi] = \mathbf{A}_1E^*[\zeta_1 | \xi] + \mathbf{A}_2E^*[\zeta_2 | \xi]$, where \mathbf{A}_1 and \mathbf{A}_2 are two matrices that are compatible with the equation.
4. *Law of total expectation:* $E^*[E^*(\zeta | \xi)] = E[E^*(\zeta | \xi)] = E[\zeta]$.

Remark 1. *In general, $E^*(\zeta | \xi) \neq E(\zeta | \xi)$. Also, ζ and ξ are independent does not imply $E^*(\zeta | \xi) = 0$, unless ζ and ξ are jointly normally distributed.*

Definition 5. *For any random variables $\zeta_1 : \Omega \rightarrow \mathbb{R}^{d_1}$, $\zeta_2 : \Omega \rightarrow \mathbb{R}^{d_2}$ and $\xi : \Omega \rightarrow \mathbb{R}^p$. The conditional linear covariance between ζ_1 and ζ_2 given ξ is defined as*

$$\text{Cov}^*(\zeta_1, \zeta_2 | \xi) = E^*[\{\zeta_1 - E^*(\zeta_1 | \xi)\}\{\zeta_2 - E^*(\zeta_2 | \xi)\} | \xi]. \quad (14)$$

Remark 2. *By Proposition 2, we can easily verify the following properties.*

Proposition 3. *The conditional linear covariance defined in definition 5 has the following properties*

1. *Linear independence and linear zero correlation:*

$$\text{Cov}^*(\zeta_1, \zeta_2 | \xi) = 0 \quad \Leftrightarrow \quad E^*(\zeta_1\zeta_2 | \xi) = E^*(\zeta_1 | \xi)E^*(\zeta_2 | \xi).$$

2. *Expectation of conditional linear covariance:*

$$E[\text{Cov}^*(\zeta_1, \zeta_2 | \xi)] = \text{Cov}(\zeta_1, \zeta_2) - \text{Cov}(\zeta_1, \xi)\text{Var}(\xi)^{-1}\text{Cov}(\xi, \zeta_2).$$

3. *Sign*: for any increasing function $h(\cdot) : \mathbb{R} \rightarrow \mathbb{R}$ and random variable $\eta : \Omega \rightarrow \mathbb{R}$, then

$$\text{Cov}^*(h(\eta), \eta \mid \boldsymbol{\xi}) \geq 0.$$

Definition 6. *Define*

$$v_j(\boldsymbol{\beta}_{\mathcal{C}}, \beta) = v_{j,j}(\boldsymbol{\beta}_{\mathcal{C}}, \beta) + \sum_{k \in \mathcal{C}} a_k v_{j,k}(\boldsymbol{\beta}_{\mathcal{C}}, \beta),$$

where vector $\mathbf{a}_{\mathcal{C}} = [a_k, k \in \mathcal{C}]^T$ such that $\mathbb{E}^*[Z_j \mid \mathbf{Z}_{\mathcal{C}}] = \sum_{k \in \mathcal{C}} a_k Z_k$.

Proposition 4. $v_{j,j}(\boldsymbol{\beta}_{\mathcal{C},0}, 0) = 0$ if and only if $v_j(\boldsymbol{\beta}_{\mathcal{C},0}, 0) = 0$.

3.2 Regularity Conditions

We list all conditions for the theoretical results.

Condition 1. For each $j \notin \mathcal{C}$ and $k \in \mathcal{C} \cup \{j\}$, there exists a neighborhood of $(\boldsymbol{\beta}_{\mathcal{C},j}^T, \beta_j)^T$, which is defined as

$$\mathcal{B}_j = \{(\boldsymbol{\beta}_{\mathcal{C}}^T, \beta)^T : \|(\boldsymbol{\beta}_{\mathcal{C}}^T, \beta)^T - (\boldsymbol{\beta}_{\mathcal{C},j}^T, \beta_j)^T\|_1 < \delta_j\}, \quad \text{with} \quad \delta_j > 0,$$

such that for each $\tau < \infty$,

1. For $m = 0, 1$,

$$\sup_{t \in [0, \tau], (\boldsymbol{\beta}_{\mathcal{C}}^T, \beta)^T \in \mathcal{B}_j} \|R_{j,k}^{(m)}(\boldsymbol{\beta}_{\mathcal{C}}, \beta) - r_{j,k}^{(m)}(\boldsymbol{\beta}_{\mathcal{C}}, \beta)\|_2 \rightarrow 0,$$

in probability as $n \rightarrow \infty$.

2. There exists a constant $L > 0$ such that

$$L = \min_{j \notin \mathcal{C}} \left[\inf_{t \in [0, \tau], (\boldsymbol{\beta}_{\mathcal{C}}^T, \beta)^T \in \mathcal{B}_j} \{r_{j,k}^{(0)}(\boldsymbol{\beta}_{\mathcal{C}}, \beta, t)\} \right].$$

Of note, $\{r_{j,k}^{(0)}(\boldsymbol{\beta}_{\mathcal{C}}, \beta, t)\}$ does not depend on k . Let $\delta = \max_{j \notin \mathcal{C}} \delta_j$.

Condition 2. *The covariates Z_j 's satisfy the following conditions*

1. For $j \in \{1, \dots, p\}$, $E[Z_j] = 0$ and there exists a constant K_0 such that $P(Z_j > K_0) = 0$.
2. Z_j is a time constant variable, for all j .
3. All Z_j 's, $j \in \mathcal{M}_{-c}$ are independent of all Z_k 's, $k \notin \mathcal{M}_{-c}$ given \mathbf{Z}_c .
4. For constant $c_1 > 0$ and $\kappa < 1/2$,

$$\min_{j \in \mathcal{M}_{-c}} |E[\text{Cov}^*(Z_j, P[\delta = 1 | \mathbf{Z}] | \mathbf{Z}_c)]| \geq c_1 n^{-\kappa}.$$

Condition 3. *There exists a constant K_1 such that*

$$\|\boldsymbol{\alpha}\|_1 < K_1 \text{ and } \|(\boldsymbol{\beta}_{c,j}^T, \beta_j)^T\|_1 < K_1,$$

for all $p > 0$.

Condition 4. *For all $j \notin \mathcal{C}$, there exists a constant $M > 0$ such that*

$$M \|(\widehat{\boldsymbol{\beta}}_{c,j}^T, \widehat{\beta}_j)^T - \boldsymbol{\beta}_{c,j}^T, \beta_j)^T\|_2 \leq \|\overline{\mathbf{V}}_j(\widehat{\boldsymbol{\beta}}_{c,j}, \widehat{\beta}_j) - \overline{\mathbf{V}}_j(\boldsymbol{\beta}_{c,j}, \beta_j)\|_2.$$

3.3 Properties on Population Level

Lemma 1. *The solution of $\mathbf{v}_j(\boldsymbol{\beta}_c, \beta) = \mathbf{0}_{q+1}$ and the solution of $\mathbf{v}_c(\boldsymbol{\beta}_c) = \mathbf{0}_q$ are both unique, for any $j \notin \mathcal{C}$.*

Theorem 1. *Suppose Condition 2 hold, $\beta_j = 0$ if and only if $\alpha_j = 0$ for all $j \notin \mathcal{C}$.*

Theorem 2. *Suppose Condition 2 holds. There exist constants $c_2 > 0$ and $\kappa < 1/2$ such that*

$$\min_{j \in \mathcal{M}_{-c}} |\beta_j| \geq c_2 n^{-\kappa}.$$

3.4 Properties on Sample Level

Theorem 3. *Suppose Conditions 1–4 hold. For any $\epsilon_1 > 0$ and any $\epsilon_2 > 0$, there exists positive constants c_3, c_4 and integer N such that for any $n > N$,*

1. *For any $0 < \kappa < 1/2$,*

$$\mathbb{P} \left[\max_{j \in \mathcal{M}_{-c}} |\widehat{\beta}_j - \beta_j| > \frac{c_2}{2}(n^{-\kappa} - \epsilon_1) \right] \leq 2w(q+1) \exp(-c_3 n^{1-2\kappa}) + \epsilon_2.$$

where w is the size of \mathcal{M}_{-c} , q is the size of \mathcal{C} and c_2 is the same value in Theorem 2 and c_3 does not depend on ϵ_1, ϵ_2 and κ , but N depends on ϵ_1 and ϵ_2 .

2. *If $\gamma_n = c_4 n^{-\kappa}$, where κ is the same number in Condition 2, then*

$$\mathbb{P} \left[\min_{j \in \mathcal{M}_{-c}} |\widehat{\beta}_j| > \gamma_n \right] \geq 1 - 2w(q+1) \exp(-c_3 n^{1-2\kappa}) - \epsilon_2. \quad (15)$$

where c_4 does not depend on ϵ_1, ϵ_2 and κ , thus

$$\lim_{n \rightarrow \infty} \mathbb{P} \left[\mathcal{M}_{-c} \subseteq \widehat{\mathcal{M}}_{-c} \right] = 1. \quad (16)$$

3.5 Controlling the False Discover Rate

Define the information matrix

$$\mathbf{I}_j(\beta_{\mathcal{C}}, \beta_j) = - \left(\frac{\partial V_{j,k}(\beta_{\mathcal{C}}, \beta_j)}{\partial \beta_{k'}} \right)_{k,k' \in \mathcal{C} \cup \{j\}}, \quad (17)$$

which is of $q+1$ dimension. Denote $\widehat{\sigma}_j^2 = [\mathbf{I}_j(\beta_{\mathcal{C},j}, \widehat{\beta}_j)]_{q+1,q+1}^{-1}$ be the variance estimate of $\widehat{\beta}_j$. For a given threshold $\gamma > 0$, we can have a different way to select the index which is given by

$$\widehat{\mathcal{M}}_{-c}^* = \left\{ j \notin \mathcal{C} : \frac{|\widehat{\beta}_j|}{\widehat{\sigma}_j} \geq \gamma \right\}, \quad (18)$$

as suggested by Zhao and Li (2012). We refer to (18) as ‘‘CS-Wald’’.

Another alternative to construct the screening statistics, which is also scale free, is to utilize the partial log likelihood ratio statistic. Specifically,

$$\ell(\boldsymbol{\beta}_C, \beta) = \sum_{i=1}^n \int_0^\tau \left\{ \boldsymbol{\beta}_C^T \mathbf{Z}_{i,c} + \beta Z_{i,j} - \log \left(R_{j,k}^{(0)}(\boldsymbol{\beta}_C, \beta, t) \right) dN_i(t) \right\}. \quad (19)$$

Suppose $(\hat{\boldsymbol{\beta}}_{C,j}^T, \hat{\beta}_j)^T$ maximizes (19) for a given j . Then, for a given threshold $\gamma > 0$, the index set can be chosen by considering the following likelihood ratio statistic.

$$\widehat{\mathcal{M}}_{-C}^* = \left\{ j \notin C : \ell(\hat{\boldsymbol{\beta}}_{C,j}, \hat{\beta}_j) - \ell(\hat{\boldsymbol{\beta}}_{C,0}, \beta = 0) \geq \gamma \right\}, \quad (20)$$

where $\hat{\boldsymbol{\beta}}_{C,0}$ maximizes $\ell(\boldsymbol{\beta}_C, 0)$. Hereafter (20) will be referred to as ‘‘CS-PLIK’’.

4 Simulation Studies

The utility of the proposed methods was evaluated via extensive simulations. Denote by CS-MPLE, a version of CoxCS that is based on the criteria of (9). For completeness, we considered two other variations of CoxCS, namely, CS-PLIK and CS-Wald. The finite sample performance of the proposed methods was compared with the following marginal screening methods designed for the survival data.

- CRIS: censored rank independence screening proposed by Song et al. (2014).
- CORS: correlation screening, which is an extension of sure independence screening to the censored outcome data by using inverse probability weighting; see Song et al. (2014).
- PSIS-Wald: Wald test based on the marginal Cox model fitted on each covariate; see Zhao and Li (2012).
- PSIS-PLIK: partial likelihood ratio test based on the marginal Cox model fitted on each covariate, which is asymptotically equivalent to Zhao and Li (2012).

We illustrated our methods and compared them with the competing methods on data simulated as below.

Example 1. The survival time was generated from a Cox model with baseline hazards function being set to be 1, i.e.,

$$\lambda(t | \mathbf{Z}) = \exp(\boldsymbol{\beta}^T \mathbf{Z}),$$

where \mathbf{Z} were generated from the standard normal distribution with equal correlation 0.5 and $\boldsymbol{\beta} = (\mathbf{1}_5^T, -2.5, \mathbf{0}_{p-6}^T)^T$.

Example 2. The survival time was generated from a Cox model with baseline hazards function being set to be 1, i.e.,

$$\lambda(t | \mathbf{Z}) = \exp(-1 + \boldsymbol{\beta}^T \mathbf{Z}),$$

where $\boldsymbol{\beta} = (10, \mathbf{0}_{p-2}^T, 1)^T$ and all covariates were generated from the independent standard normal distribution.

Example 3. The same as Example 2 except that the first $p - 1$ covariates were generated from the multivariate standard normal distribution with an equal correlation of 0.9.

The simulated data examples were designed in such a way that variables Z_6 in Example 1 and Z_p in Example in 3 possessed marginally weak but conditionally strong signals, which made marginal screening approaches not ideal for identifying them. For the GLM, Barut et al. (2016) provided a similar simulation design in the context of non-censored regression. Figure 3 depicted the distribution of the absolute correlation between the survival time and the covariate variables, where uncensored data were used to compute the marginal correlation between the event time and the covariate using an inverse probability weighting (Song et al. 2014). Clearly, in Example 1 the marginal signal strength of Z_6 was weaker than most noisy (inactive) variables

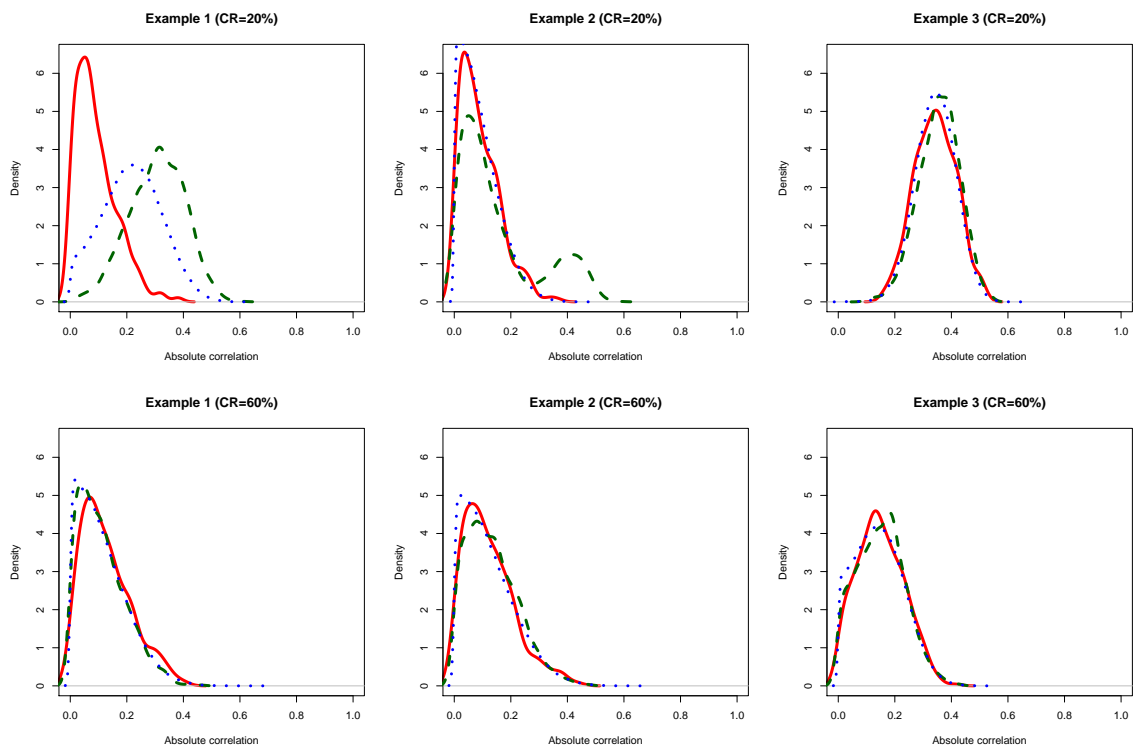


Figure 2: Absolute correlation of the survival time and the covariate variables. The blue short-dashed lines (\cdots) represents the distribution of the inactive variables; the green long-dashed ($---$) lines for the active variables with relatively strong signals; the red solid lines ($---$) for the hidden active variable.

$(Z_7 - Z_{1000})$, while the marginal signal strength of Z_{1000} in Examples 2 and 3 was similar or even lower than most noisy variables. The marginal correlation between the survival time and each variable was getting weaker with heavier censoring.

In all these examples, the censoring times C_i were independently generated from a uniform distribution $U[0, c]$, with c chosen to give approximately 20% and 60% of censoring proportions. We set $n = 100$ and varied p from 1000 (high-dimensional) to 10000 (ultrahigh-dimensional). For each configuration, a total of 400 simulated datasets were generated.

We considered two metrics to compare the performance between different methods: the minimum model size (MMS) which is the minimum number of variables that need to be selected in order to include all active variables, and the true positive rate (TPR) which is the proportion of active variables that are included in the first n selected variables. Hence, a method with small MMS and large TPR can be more efficient to discover true signals. To have a fair comparison, we added one (the number of conditioning variable in our examples) to MMS for the proposed methods (CS-MPLE, CS-Wald and CS-PLIK). In practice, identifying conditional sets normally requires some prior biological information. In our simulations, we simply choose the covariate Z_1 as the conditioning variable. In practice, we propose to choose the variable with the highest marginal signal strength as the conditioning variable, which can be a practical solution in the absence of prior biological knowledge. In Examples 1–3, $\mathcal{C} = \{1\}$ is the true conditioning set, the signal of which was strong enough to be easily selected by other marginal screening methods.

Table 1 demonstrated the superiority of our proposed methods under the difficult scenarios as reflected in Examples 1–3. Indeed, the proposed methods drastically reduced MMS in Examples 1–3 compared to the marginal approaches. Moreover, we noted that all the marginal screening methods had tremendous difficulties in identi-

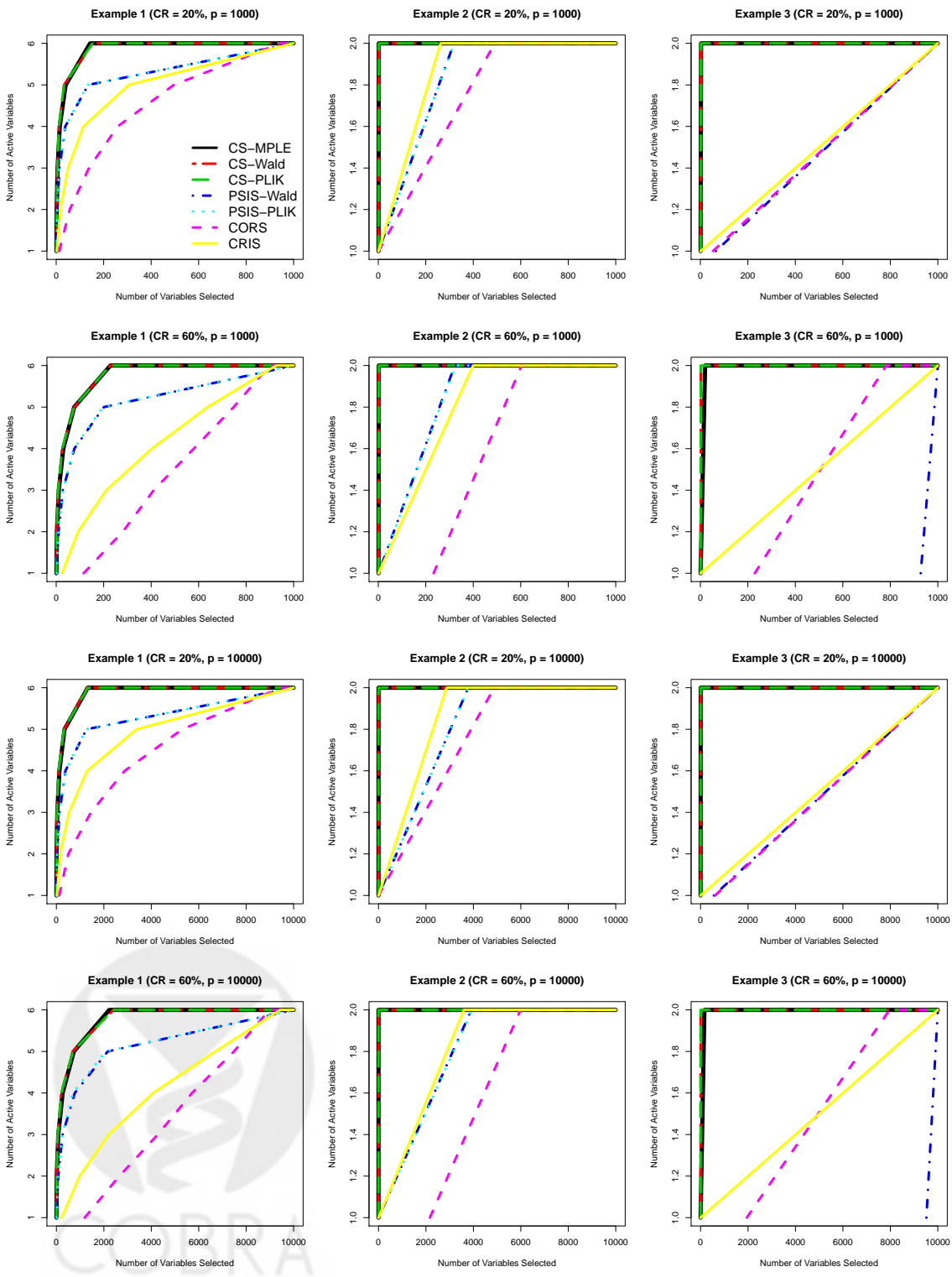


Figure 3: Median number of active variables that are included in the model with different thresholds by different methods

ying Z_6 in Example 1 and Z_{1000} in Examples 2–3. Indeed, these variables had the lowest priorities to be included by using the competing methods. On the other hand, the proposed approaches greatly outperformed the marginal approaches, as the conditioning approaches effectively boosted the signal strengths of the “hidden” variables. The performance by CS-MPLE, CS-Wald and CS-PLIK are quite similar in all the cases in Examples 1 and 2. In Example 3, there is a very high correlation among the covariate variables, CS-MPLE has a slightly larger MMS compared to the CS-Wald and CS-PLIK which well control the false discover rate in this cases.

5 Application

We illustrated the practical utility of the proposed method by applying it to analyze the diffuse large B-cell lymphoma (DLBCL) dataset of Rosenwald et al. (2002). The dataset, which was originally collected for identifying gene signatures relevant to the patient survival from time of chemotherapy, included a total of 240 DLBCL patients with 138 deaths observed during the followup and a median survival time of 2.8 years. Along with the clinical outcomes, the expression levels of 7,399 genes were available for analysis. In our subsequent analysis, each gene expression was standardized to have mean zero and variance 1.

To facilitate the use of our method, we identified the conditional set by resorting to the medical literature. As gene AA805575, a Germinal-center B-cell signature gene, has been known to be predictive to DCBCL patients’ survival in the literature (Liu et al. 2013, Gui and Li 2005), we used it as the conditional variable in our proposed procedure. For comparisons, we also analyzed the same data using various competing methods introduced in the simulation section and computed the corresponding concordance statistics (C-statistics) (Uno et al. 2011).

Specifically, we randomly assigned 160 patients to the training set and 80 patients

		$(n, p) = (100, 1000)$		$(n, p) = (100, 10000)$	
Method		MMS	TPR	MMS	TPR
Example 1 CR \approx 20%	CRIS	1000.0 (3.0)	0.50 (0.17)	9995.0 (37.0)	0.17 (0.17)
	CORS	944.0 (168.2)	0.33 (0.33)	9466.0 (1101.8)	0.00 (0.17)
	PSIS-PLIK	1000.0 (0.0)	0.67 (0.17)	10000.0 (2.2)	0.33 (0.17)
	PSIS-Wald	1000.0 (0.0)	0.67 (0.17)	10000.0 (2.2)	0.33 (0.17)
	CS-PLIK	152.5 (272.2)	0.83 (0.17)	1322.0 (2253.8)	0.67 (0.17)
	CS-Wald	154.5 (274.5)	0.83 (0.17)	1286.5 (2287.0)	0.67 (0.17)
	CS-MPLE	143.0 (249.0)	0.83 (0.17)	1321.0 (2305.8)	0.50 (0.17)
Example 1 CR \approx 60%	CRIS	926.5 (151.8)	0.33 (0.17)	9429.0 (1405.0)	0.00 (0.17)
	CORS	898.0 (152.2)	0.00 (0.17)	8976.0 (1610.0)	0.00 (0.00)
	PSIS-PLIK	1000.0 (2.0)	0.67 (0.17)	9999.0 (17.0)	0.33 (0.17)
	PSIS-Wald	1000.0 (2.0)	0.67 (0.17)	9999.0 (17.0)	0.33 (0.17)
	CS-PLIK	227.0 (351.2)	0.83 (0.17)	2383.5 (3331.5)	0.50 (0.33)
	CS-Wald	227.5 (348.2)	0.83 (0.17)	2403.5 (3233.2)	0.50 (0.33)
	CS-MPLE	228.5 (320.5)	0.83 (0.17)	2229.5 (3046.8)	0.50 (0.17)
Example 2 CR \approx 20%	CRIS	262.5 (401.8)	0.50 (0.00)	2871.0 (4314.0)	0.50 (0.00)
	CORS	490.5 (510.8)	0.50 (0.00)	4878.5 (5099.8)	0.50 (0.00)
	PSIS-PLIK	318.0 (492.8)	0.50 (0.00)	3777.0 (5690.8)	0.50 (0.00)
	PSIS-Wald	318.5 (494.2)	0.50 (0.00)	3786.5 (5707.8)	0.50 (0.00)
	CS-PLIK	2.0 (0.0)	1.00 (0.00)	2.0 (0.0)	1.00 (0.00)
	CS-Wald	2.0 (0.0)	1.00 (0.00)	2.0 (0.0)	1.00 (0.00)
	CS-MPLE	2.0 (0.0)	1.00 (0.00)	2.0 (0.0)	1.00 (0.00)
Example 2 CR \approx 60%	CRIS	399.5 (478.0)	0.50 (0.00)	3601.0 (4894.2)	0.50 (0.00)
	CORS	603.5 (390.5)	0.00 (0.00)	5988.0 (4353.0)	0.00 (0.00)
	PSIS-PLIK	325.0 (498.5)	0.50 (0.00)	3942.5 (5679.5)	0.50 (0.00)
	PSIS-Wald	322.0 (501.0)	0.50 (0.00)	3915.5 (5679.5)	0.50 (0.00)
	CS-PLIK	2.0 (0.0)	1.00 (0.00)	2.0 (1.0)	1.00 (0.00)
	CS-Wald	2.0 (0.0)	1.00 (0.00)	2.0 (2.0)	1.00 (0.00)
	CS-MPLE	2.0 (0.0)	1.00 (0.00)	2.0 (4.0)	1.00 (0.00)
Example 3 CR \approx 20%	CRIS	1000.0 (0.0)	0.50 (0.00)	10000.0 (0.0)	0.50 (0.00)
	CORS	1000.0 (0.0)	0.50 (0.50)	10000.0 (0.0)	0.00 (0.00)
	PSIS-PLIK	1000.0 (0.0)	0.50 (0.00)	10000.0 (0.0)	0.50 (0.00)
	PSIS-Wald	1000.0 (0.0)	0.50 (0.50)	10000.0 (0.0)	0.00 (0.50)
	CS-PLIK	2.0 (0.0)	1.00 (0.00)	2.0 (0.0)	1.00 (0.00)
	CS-Wald	2.0 (0.0)	1.00 (0.00)	2.0 (0.0)	1.00 (0.00)
	CS-MPLE	3.0 (4.0)	1.00 (0.00)	7.5 (33.0)	1.00 (0.00)
Example 3 CR \approx 60%	CRIS	1000.0 (0.0)	0.50 (0.00)	10000.0 (0.0)	0.50 (0.00)
	CORS	783.0 (463.8)	0.00 (0.50)	7967.0 (4972.2)	0.00 (0.00)
	PSIS-PLIK	1000.0 (0.0)	0.50 (0.00)	10000.0 (0.0)	0.50 (0.00)
	PSIS-Wald	1000.0 (0.0)	0.00 (0.00)	10000.0 (0.0)	0.00 (0.00)
	CS-PLIK	2.0 (0.0)	1.00 (0.00)	2.0 (0.0)	1.00 (0.00)
	CS-Wald	2.0 (0.0)	1.00 (0.00)	2.0 (0.0)	1.00 (0.00)
	CS-MPLE	20.0 (55.2)	1.00 (0.00)	161.5 (553.5)	0.50 (0.50)

Table 1: Median minimum model size (MMS) and median true positive rates (TPR) along with their corresponding IQRs (in the parentheses) based on 400 simulated data sets.

to the testing set, while maintaining the censoring proportion roughly the same in each set. For each split, we applied each method to select top 31(= 160/log(160)) variables using the training set. LASSO was performed subsequently for refined modeling, with the tuning parameter selected by the 10-fold cross-validation. The risk score for each subject was obtained by using the final model selected by LASSO in the training dataset and the C-statistics was obtained in the testing dataset. A total of 100 splits were made and the average C-statistics and the model size (MS) were reported in Table 2. By the criterion of C-statistics, the proposed method seemed to have more predictive power.

	CRIS	CORS	PSIS-PLIK	PSIS-Wald
C-statistics	0.54 (0.21)	0.58 (0.20)	0.58 (0.19)	0.55 (0.20)
Model size	14.41 (3.00)	6.83 (3.70)	15.22 (2.93)	15.65 (2.89)
	CS-MPLE	CS-PLIK	CS-Wald	
C-statistics	0.63 (0.18)	0.63 (0.18)	0.62 (0.19)	
Model size	16.74 (3.26)	15.90 (3.01)	16.28 (3.41)	

Table 2: Summary of C-statistics and the model size for different methods.

Our further scientific investigation focused on identifying the relevant genes by utilizing the full dataset. Applying our proposed method, we selected top 44 (= 240/log(240)) genes, before using LASSO to reach the final list. It follows that CS-MPLE, CS-PLIK and CS-Wald selected 20, 16 and 16 genes, respectively. Among the 22 uniquely selected genes by either of them, 14 genes were overlapped and were reported in Table 3. Twelve genes among these 22 genes belong to Lymph-node signature group, proliferation signature group, and Germinal-center B-cell group defined by Rosenwald et al. (2002). We observed that 13 of these 22 genes were chosen by at least one of CRIS, CORS, PSIS-PLIK, and PSIS-Wald. On the other hand, gene AB007866, Z50115, S78085, U00238, AL050283, J03040, U50196, and AA830781, and M81695 were only identified by using our methods.

In fact, only a few studies have suggested an important role of M81695 (Deb and Reddy 2003, Chow et al. 2001, Mikovits et al. 2001, Stewart and Schuh 2000) or AA830781 (Li and Luan 2005, Binder and Schumacher 2009, Schifano et al. 2010) in predicting DLBCL survival. Indeed, as the marginal correlation between M81695 and the survival time and between AA830781 and the survival time are markedly low at 0.008 and 0.097, respectively. Thus, it is highly likely to be missed by using the conventional screening approaches. Schifano et al. (2010) also commented their majorization-minimization algorithm selected AA830781 because of coexpression or correlation with other relevant genes. A more detailed investigation of its functions in the context of a broader class of blood cancers, including lymphoma, may shed light on preventing, treating and controlling the lethal blood cancers.



GenBank ID	Signature	Description	CS-MPLE	CS-PLIK	CS-Wald
LC_25054			✓	✓	✓
X77743	Proliferation	cyclin-dependent kinase 7	✓	✓	✓
U15552		acidic 82 kDa protein mRNA	✓	✓	✓
AB007866		KIAA0406 gene product	✓		
BC012161	Proliferation	septin 1	✓	✓	✓
AF134159	Proliferation	chromosome 14 open reading frame 1	✓	✓	✓
Z50115	Proliferation	thimet oligopeptidase 1	✓		
S78085	Proliferation	programmed cell death 2	✓		
M29536	Proliferation	eukaryotic translation initiation factor 2	✓	✓	✓
U00238	Proliferation	phosphoribosyl pyrophosphate amidotransferase		✓	✓
AL050283	Proliferation	sentrin/SUMO-specific protease 3	✓		
BF129543	Germinal-center-B-cell	ESTs, Weakly similar to A47224	✓	✓	✓
M81695		thyroxine-binding globulin precursor	✓	✓	✓
D13666	Lymph node	integrin, alpha X	✓	✓	✓
J03040	Lymph node	osteoblast specific factor 2 (fasciclin I-like)	✓	✓	✓
U50196		secreted protein		✓	✓
U28918	Proliferation	adenosine kinase	✓	✓	✓
AA721746		suppression of tumorigenicity 13	✓	✓	✓
AA830781		ESTs	✓	✓	✓
AF127481		lymphoid blast crisis oncogene	✓	✓	✓
M61906		phosphoinositide-3-kinase	✓	✓	✓
D42043		KIAA0084 protein	✓	✓	✓

Table 3: A comparison of genes that are selected by CS-MPLE, CS-PLIK and CS-Wald.

6 Discussion

In this paper, we have proposed a new conditional variable screening approach for the Cox proportional hazard model with ultra-high dimensional covariates. The proposed partial likelihood based conditional screening approaches are extremely computationally efficient, with a solid theoretical foundation. Our method and theory are extensions of the conditional sure independence screening (CSIS) Barut et al. (2016), which is designed for the GLM. In the development of theory, we introduce the new concept of the conditional linear covariance for the first time, which is useful to specify the regularity conditions for the model identifiability and the sure screening property. This also provides a solid building block for a general theoretical framework of conditional variable screening in the context of other semi-parametric models, such as the partially linear single-index model.

We have mainly focused on studying the theoretical properties of CS-MPLE, which extends the work of Barut et al. (2016) in the GLM setting, though development of the inference procedures for the two variants of the proposed method, namely, CS-PLIK and CS-Wald, will be more involved and out of scope of this paper. However, as indicated by the simulation studies, these two variants may induce substantial improvement especially when the variables are highly correlated. More research is warranted.

Our work also enlightens a few directions that are worth ensuing effort. First, as our proposal requires the prior information to be known and informative, it remains statistically challenging to develop efficient screening methods in the absence of such information. Recently, in the context of GLM, Hong et al. (2016) has proposed a data-driven alternative when a pre-selected set of variables is unknown. It is thus of substantial interest to develop a data-driven conditional screening for the survival model. Second, even with prior knowledge, an open question often lies in how to

balance it with the information extracted from the given data. There has been some recent work on how to incorporate prior information. For example, Wang et al. (2013) developed a LASSO method by assigning different prior distributions to each subset according to a modified Bayesian information criterion that incorporates prior knowledge on both the network structure and the pathway information, and Jiang et al. (2015) proposed “prior lasso” (plasso) to balance between the prior information and the data. A natural extension of the current work is to develop a variable screening approach that incorporates more complex prior knowledge, such as the network structure or the spatial information of the covariates. We will report the progress elsewhere.



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7 Appendix

7.1 Proof of Theorem 1

Proof. First we make the connection between β_j to the expected conditional linear covariance between Z_j and $P[\delta = 1 \mid \mathbf{Z}]$ given \mathbf{Z}_C , that is

$$E[\text{Cov}^*(Z_j, P[\delta = 1 \mid \mathbf{Z}] \mid \mathbf{Z}_C)],$$

then by Condition 2, we relate it to α_j . For any $j \notin \mathcal{C}$ and $k \in \mathcal{C}$, it is straightforward to see that

$$s_k^{(m)}(t) = E[Z_k^m \lambda_0(t) \exp(\mathbf{Z}^T \boldsymbol{\alpha}) S_T(t \mid \mathbf{Z}) S_C(t)], \quad (21)$$

and

$$r_{j,k}^{(m)}(t, \boldsymbol{\beta}_C, \beta) = E[Z_k^m \exp(\mathbf{Z}_C^T \boldsymbol{\beta}_C + Z_j \beta) S_T(t \mid \mathbf{Z}) S_C(t)], \quad (22)$$

for $m = 0, 1$. Then

$$v_{j,k}(\boldsymbol{\beta}_C, \beta) = \int_0^\tau E [W_{j,k}(t, \boldsymbol{\beta}_C, \beta) \exp(\mathbf{Z}^T \boldsymbol{\alpha}) S_T(t \mid \mathbf{Z}) S_C(t) \lambda_0(t)] dt, \quad (23)$$

where

$$W_{j,k}(t, \boldsymbol{\beta}_C, \beta) = Z_k - \frac{\mathbb{E}[Z_k \exp(\mathbf{Z}_C^T \boldsymbol{\beta}_C + Z_j \beta) S_T(t | \mathbf{Z}) S_C(t)]}{\mathbb{E}[\exp(\mathbf{Z}_C^T \boldsymbol{\beta}_C + Z_j \beta) S_T(t | \mathbf{Z}) S_C(t)]}.$$

By Proposition 2,

$$\begin{aligned} & \mathbb{E} [W_{j,k}(t, \boldsymbol{\beta}_C, \beta) \exp(\mathbf{Z}^T \boldsymbol{\alpha}) S_T(t | \mathbf{Z}) S_C(t)] \\ &= \mathbb{E} \{ \mathbb{E}^* [W_{j,k}(t, \boldsymbol{\beta}_C, \beta) \exp(\mathbf{Z}^T \boldsymbol{\alpha}) S_T(t | \mathbf{Z}) S_C(t)] \}. \end{aligned}$$

By Definition 6,

$$\begin{aligned} v_j(\boldsymbol{\beta}_C, \beta) &= v_{j,j}(\boldsymbol{\beta}_C, \beta) - \sum_{k \in C} a_k v_{j,k}(\boldsymbol{\beta}_C, \beta) \\ &= \mathbb{E} [\text{Cov}^*(Z_j, \mathbb{P}[\delta = 1 | \mathbf{Z}] | \mathbf{Z}_C)] - g(\boldsymbol{\beta}_C, \beta). \end{aligned}$$

where

$$\begin{aligned} & \mathbb{E} [\text{Cov}^*(Z_j, \mathbb{P}[\delta = 1 | \mathbf{Z}] | \mathbf{Z}_C)] \\ &= \int_0^\tau \mathbb{E} [(Z_j - \mathbb{E}^*[Z_j | \mathbf{Z}_C]) \exp(\mathbf{Z}^T \boldsymbol{\alpha}) S_T(t | \mathbf{Z}) S_C(t) \lambda_0(t)] dt, \end{aligned}$$

and

$$\begin{aligned} g_j(\boldsymbol{\beta}_C, \beta) &= \int_0^\tau \frac{\mathbb{E}[(Z_j - \mathbb{E}^*[Z_j | \mathbf{Z}_C]) \exp(\mathbf{Z}_C^T \boldsymbol{\beta}_C + Z_j \beta) S_T(t | \mathbf{Z}) S_C(t)]}{\mathbb{E}[\exp(\mathbf{Z}_C^T \boldsymbol{\beta}_C + Z_j \beta) S_T(t | \mathbf{Z}) S_C(t)]} \\ &\quad \times \mathbb{E} [\exp(\mathbf{Z}^T \boldsymbol{\alpha}) S_T(t | \mathbf{Z}) \lambda_0(t) S_C(t)] dt. \end{aligned}$$

By Definition 2, $\mathbf{v}_j(\boldsymbol{\beta}_{C,j}, \beta_j) = \mathbf{0}_{q+1}$,

$$g_j(\boldsymbol{\beta}_{C,j}, \beta_j) = \mathbb{E} [\text{Cov}^*(Z_j, \mathbb{P}[\delta = 1 | \mathbf{Z}] | \mathbf{Z}_C)].$$

When $\alpha_j = 0$, then $\mathbb{E} [\text{Cov}^*(Z_j, \mathbb{P}[\delta = 1 | \mathbf{Z}] | \mathbf{Z}_C)] = 0$. Thus $g_j(\boldsymbol{\beta}_{C,j}, \beta_j) = 0$. Also, by Propositions 1 and 2, $g_j(\boldsymbol{\beta}_{C,0}, 0) = 0$, then $\mathbf{v}_j(\boldsymbol{\beta}_{C,0}, 0) = \mathbf{0}_{q+1}$. By uniqueness in Lemma 1, $\beta_j = 0$.

When $\alpha_j \neq 0$, by Condition 2, we have

$$|g_j(\boldsymbol{\beta}_{C,j}, \beta_j)| = |\text{E}[\text{Cov}^*(Z_j, \text{P}[\delta = 1 | \mathbf{Z}] | \mathbf{Z}_C)]| > c_1 n^{-\kappa}.$$

This implies that $g_j(\boldsymbol{\beta}_{C,j}, \beta_j)$ and $\text{E}[\text{Cov}^*(Z_j, \text{P}[\delta = 1 | \mathbf{Z}] | \mathbf{Z}_C)]$ are both nonzero and have the same signs since they are equal. Next we show for any $\boldsymbol{\beta}_C$, $g_j(\boldsymbol{\beta}_C, 0)$ and $\text{E}[\text{Cov}^*(Z_j, \text{P}[\delta = 1 | \mathbf{Z}] | \mathbf{Z}_C)]$ have the opposite signs unless they are equal to zero. This fact implies that $\beta_j \neq 0$. Specifically, note that $\text{P}(\delta = 1 | \mathbf{Z})$ is the probability of occurring the event and $S_T(t | \mathbf{Z})S_C(t) = \text{P}(X > t | \mathbf{Z})$ represents the probability at risk at time t . Based on Model (1), for any t ,

$$\frac{\partial \text{P}(X > t | \mathbf{Z})}{\partial Z_j} \times \frac{\partial \text{P}(\delta = 1 | \mathbf{Z})}{\partial Z_j} \leq 0.$$

By Proposition 3, $\text{Cov}^*(Z_j, \text{P}[\delta = 1 | \mathbf{Z}] | \mathbf{Z}_C)$ and $\text{Cov}^*[Z_j, S_T(t | \mathbf{Z})S_C(t) | \mathbf{Z}_C]$ have the opposite signs unless they are zero. This further implies that for any $\boldsymbol{\beta}_C$,

$$g_j(\boldsymbol{\beta}_C, 0) = \int_0^\tau \frac{\text{E}[\exp(\mathbf{Z}_C^\top \boldsymbol{\beta}_C) \text{Cov}^*[Z_j, S_T(t | \mathbf{Z})S_C(t) | \mathbf{Z}_C]]}{\text{E}[\exp(\mathbf{Z}_C^\top \boldsymbol{\beta}_C) S_T(t | \mathbf{Z})S_C(t)]} \times \text{E}[\exp(\mathbf{Z}^\top \boldsymbol{\alpha}) S_T(t | \mathbf{Z}) \lambda_0(t) S_C(t)] dt.$$

and $\text{E}[\text{Cov}^*(Z_j, \text{P}[\delta = 1 | \mathbf{Z}] | \mathbf{Z}_C)]$ have opposite signs unless they are equal to zero. Therefore, $\beta_j \neq 0$. □

7.2 Proof of Theorem 2

Proof. For any $j \in \mathcal{M}_{-C}$, we have $\beta_j \neq 0$ by Theorem 1, by mean value theorem, for some $\tilde{\beta}_j \in (0, \beta_j)$,

$$|v_j(\boldsymbol{\beta}_{C,j}, 0)| = |v_j(\boldsymbol{\beta}_{C,j}, \beta_j) - v_j(\boldsymbol{\beta}_{C,j}, 0)| = \left| \frac{\partial v_j}{\partial \beta}(\boldsymbol{\beta}_{C,j}, \tilde{\beta}_j) \right| |\beta_j|,$$

Next we show that $\left| \frac{\partial v_j}{\partial \beta}(\boldsymbol{\beta}_{C,j}, \tilde{\beta}_j) \right|$ is bounded. For given any $\boldsymbol{\beta}_C$, consider $g_j(\boldsymbol{\beta}_C, \beta)$ as a function of β , Then

$$\frac{\partial g_j}{\partial \beta}(\boldsymbol{\beta}_C, \beta) = \text{E} \left[\int_0^\tau H_j(t, \boldsymbol{\beta}_C, \beta) S_C(t) dF_T(t | \mathbf{Z}) \right].$$

where

$$H_j(t, \boldsymbol{\beta}_C, \beta) = \frac{\mathbb{E}[\exp(\mathbf{Z}_C^T \boldsymbol{\beta}_C) \text{Cov}^*[Z_j^2 \exp(Z_j \beta), S_T(t | \mathbf{Z}) | \mathbf{Z}_C]]}{\mathbb{E}[\exp(\mathbf{Z}_C^T \boldsymbol{\beta}_C + Z_j \beta) S_T(t | \mathbf{Z})]} \\ - \frac{\mathbb{E}[\exp(\mathbf{Z}_C^T \boldsymbol{\beta}_C) \text{Cov}^*[Z_j \exp(Z_j \beta), S_T(t | \mathbf{Z}) | \mathbf{Z}_C]] \mathbb{E}[Z_j \exp(\mathbf{Z}_C^T \boldsymbol{\beta}_C + Z_j \beta) S_T(t | \mathbf{Z})]}{[\mathbb{E}[\exp(\mathbf{Z}_C^T \boldsymbol{\beta}_C + Z_j \beta) S_T(t | \mathbf{Z})]]^2}$$

By Condition 2.1, $\mathbb{P}(|Z| < K_0) = 1$, then $\sup_{\boldsymbol{\beta}_C, \beta} |H_j(t, \boldsymbol{\beta}_C, \beta)| \leq 2K_0^2$. Thus,

$$\left| \frac{\partial v_j}{\partial \beta}(\boldsymbol{\beta}_{C,j}, \tilde{\beta}_j) \right| \leq \sup_{\boldsymbol{\beta}_C, \beta} \left| \frac{\partial g_j}{\partial \beta}(\boldsymbol{\beta}_C, \beta) \right| \leq 2K_0^2 \mathbb{E}[\mathbb{E}[S_C(T) | \mathbf{Z}]] \leq 2K_0^2.$$

By the proof in Theorem 1, $g(\boldsymbol{\beta}_{C,j}, 0)$ and $\mathbb{E}[\text{Cov}^*(Z_j, \mathbb{E}\{F_T(C | \mathbf{Z}) | \mathbf{Z}\} | \mathbf{Z}_C)]$ have the opposite signs, and by Condition 2,

$$|v_j(\boldsymbol{\beta}_{C,j}, 0)| = |\mathbb{E}[\text{Cov}^*(Z_j, \mathbb{P}[\delta = 1 | \mathbf{Z}] | \mathbf{Z}_C])| + |g_j(\boldsymbol{\beta}_{C,j}, 0)| > c_1 n^{-\kappa}.$$

Taking $c_2 = 0.5K_0^{-2}c_1$, $\beta_j > 0.5K_0^{-2}|v_j(\boldsymbol{\beta}_{C,j}, 0)| > c_2 n^{-\kappa}$. This completes the proof. \square

7.3 Proof of Theorem 3

Proof. For any $j \notin \mathcal{C}$ and $k \in \mathcal{C} \cup \{j\}$, by Lin and Wei (1989), we have

$$\bar{\mathbf{V}}_j(\boldsymbol{\beta}_C, \beta) = \mathbb{E}_n\{\mathbf{W}_{i,j}(\boldsymbol{\beta}_C, \beta)\} + o_p(1),$$

where $\mathbb{E}_n[\cdot]$ denotes the empirical measure, which is defined as $\mathbb{E}_n[\boldsymbol{\xi}_i] = n^{-1} \sum_{i=1}^n \boldsymbol{\xi}_i$ for any random variables $\boldsymbol{\xi}_1, \dots, \boldsymbol{\xi}_n$, and $\mathbf{W}_{i,j}(\boldsymbol{\beta}_C, \beta)$ are independent over i , and write $\mathbf{W}_{i,j}(\boldsymbol{\beta}_C, \beta) = [W_{i,j,k}(\boldsymbol{\beta}_C, \beta), k \in \mathcal{C} \cup \{j\}]^T$ with

$$W_{i,j,k}(\boldsymbol{\beta}_C, \beta) = \int_0^\tau \left\{ Z_{i,k} - \frac{r_{j,k}^{(1)}(\boldsymbol{\beta}_C, \beta, t)}{r_{j,k}^{(0)}(\boldsymbol{\beta}_C, \beta, t)} \right\} dN_i(t) \\ - \int_0^\tau \frac{Y_i(t) \exp(\mathbf{Z}_{i,C} \boldsymbol{\beta}_C^T + Z_{i,j} \beta)}{r_{j,k}^{(0)}(\boldsymbol{\beta}_C, \beta, t)} \left\{ Z_{i,k} - \frac{r_{j,k}^{(1)}(\boldsymbol{\beta}_C, \beta, t)}{r_{j,k}^{(0)}(\boldsymbol{\beta}_C, \beta, t)} \right\} d\mathbb{E}[N_i(t)].$$

Note that given any i, j, k , with probability one $|W_{i,j,k}(\boldsymbol{\beta}_C, \beta)|$ are uniformly bounded. Specifically, by Conditions 1.2, 2.1 and 3, with probability one, for all $t \in [0, \tau]$, $(\boldsymbol{\beta}_C^T, \beta)^T \in \mathcal{B}_j$,

$$\left| Z_{i,k} - \frac{r_{j,k}^{(1)}(\boldsymbol{\beta}_C, \beta, t)}{r_{j,k}^{(0)}(\boldsymbol{\beta}_C, \beta, t)} \right| \leq |Z_{i,k}| + K_0,$$

$$\left| \frac{Y_i(t) \exp(\mathbf{Z}_{i,C} \boldsymbol{\beta}_C^T + Z_{i,j} \beta)}{r_{j,k}^{(0)}(\boldsymbol{\beta}_C, \beta, t)} \right| \leq \exp\{K_0(K_1 + \delta) - \log(L)\},$$

and

$$\left| \int_0^\tau dE[N_i(t)] \right| \leq \Lambda_0(\tau) \exp(K_0 K_1).$$

Thus, with probability one,

$$|W_{i,j,k}(\boldsymbol{\beta}_C, \beta)| \leq K_2,$$

where $K_2 = 2K_0(1 + \Lambda_0(\tau) \exp(2K_0 K_1 + K_0 \delta - \log L))$. By the fact that $E[W_{i,j,k}(\boldsymbol{\beta}_C, \beta)] = 0$,

$$\text{Var}[W_{i,j,k}(\boldsymbol{\beta}_C, \beta)] = E[|W_{i,j,k}(\boldsymbol{\beta}_C, \beta)|^2] < K_2^2$$

By Lemma 2.2.9 (Bernsterin's inequality) of Van Der Vaart and Wellner (1996), for any $t > 0$, for all $j, k, \boldsymbol{\beta}_C$ and β , we have

$$P\left(|E_n(W_{i,j,k}(\boldsymbol{\beta}_C, \beta))| > \frac{t}{n}\right) \leq 2 \exp\left(-\frac{1}{2} \frac{t^2}{nK_2^2 + K_2 t/3}\right).$$

Note that the above inequality holds for every $j \notin \mathcal{C}$ and $k \in \mathcal{C} \cup \{j\}$. By Bonferroni inequality,

$$P\left(\|E_n(\mathbf{W}_{i,j}(\boldsymbol{\beta}_C, \beta))\|_2 > \frac{t}{(q+1)n}\right) \leq 2(q+1) \exp\left(-\frac{1}{2} \frac{t^2}{nK_2^2 + K_2 t/3}\right).$$

Since,

$$\|\bar{\mathbf{V}}_j(\boldsymbol{\beta}_C, \beta) - E_n(\mathbf{W}_{i,j}(\boldsymbol{\beta}_C, \beta))\|_2 = o_p(1).$$

Then for any $\epsilon_1 > 0$ and $\epsilon_2 > 0$, there exists N_1 , such that for any $n > N_1$

$$P(\|\bar{\mathbf{V}}_j(\boldsymbol{\beta}_C, \beta) - E_n(\mathbf{W}_{i,j}(\boldsymbol{\beta}_C, \beta))\|_2 > M\epsilon_1/2) < \epsilon_2.$$

where M is the same value in Condition 4. By Triangle inequality and Bonferroni inequality, we have

$$\begin{aligned} & \mathbb{P} \left(\|\bar{\mathbf{V}}_j(\boldsymbol{\beta}_{\mathcal{C}}, \beta)\|_2 > \frac{t}{(q+1)n} \right) \\ & \leq \mathbb{P} \left(\|\mathbb{E}_n(\mathbf{W}_{i,j}(\boldsymbol{\beta}_{\mathcal{C}}, \beta))\|_2 > \frac{t}{(q+1)n} - M\epsilon_1/2 \right) + \mathbb{P}(\|\bar{\mathbf{V}}_j(\boldsymbol{\beta}_{\mathcal{C}}, \beta) - \mathbb{E}_n(\mathbf{W}_{i,j}(\boldsymbol{\beta}_{\mathcal{C}}, \beta))\|_2 > M\epsilon_2/2) \end{aligned}$$

When $n \rightarrow \infty$, take $t = c_2 M(q+1)n^{1-\kappa}/2 > 0$ on both side of the inequality, where c_2 is the same value in Theorem 2, we have

$$\mathbb{P} \left(\|\bar{\mathbf{V}}_j(\boldsymbol{\beta}_{\mathcal{C}}, \beta)\|_2 > \frac{Mc_2}{2}(n^{-\kappa} - \epsilon_1) \right) \leq 2(q+1) \exp \left(-\frac{M^2 c_2^2}{8(q+1)^2} \frac{n^{1-2\kappa}}{K_2^2 + K_2 n^{-\kappa}/3} \right) + \epsilon_2.$$

Take $N = \max\{\lceil (K_2/3)^{1/\kappa} \rceil, N_1\}$, then for any $n > N$, $n^{-\kappa} < 3/K_2$, and

$$\mathbb{P} \left(\|\bar{\mathbf{V}}_j(\boldsymbol{\beta}_{\mathcal{C}}, \beta)\|_2 > \frac{Mc_2}{2}(n^{-\kappa} - \epsilon_1) \right) \leq 2(q+1) \exp \left(-\frac{M^2 c_2^2}{8(q+1)^2} \frac{n^{1-2\kappa}}{K_2^2 + 1} \right) + \epsilon_2.$$

Note that the above inequality holds for all $(\boldsymbol{\beta}_{\mathcal{C}}^T, \beta)^T \in \mathcal{B}_j$, particularly for $(\boldsymbol{\beta}_{\mathcal{C},j}^T, \beta_j)^T$, $j \notin \mathcal{C}$. Also, we have $\bar{\mathbf{V}}_j(\hat{\boldsymbol{\beta}}_{\mathcal{C},j}, \hat{\beta}_j) = \mathbf{0}_{q+1}$. By Condition 4, we have

$$\begin{aligned} & \mathbb{P} \left(|\hat{\beta}_j - \beta_j| > \frac{c_2}{2}(n^{-\kappa} - \epsilon_1) \right) \\ & \leq \mathbb{P} \left(\|(\hat{\boldsymbol{\beta}}_{\mathcal{C},j}^T, \hat{\beta}_j)^T - (\boldsymbol{\beta}_{\mathcal{C},j}^T, \beta_j)^T\|_2 > \frac{c_2}{2}(n^{-\kappa} - \epsilon_1) \right) \\ & \leq 2(q+1) \exp \left(-\frac{M^2 c_2^2}{8(q+1)^2} \frac{n^{1-2\kappa}}{K_2^2 + 1} \right) + \epsilon_2. \end{aligned}$$

Taking $c_3 = \frac{M^2 c_2^2}{8(q+1)^2(K_2^2+1)}$ and by Bonferroni completes the proof for part 1.

For part 2, by Theorem 2,

$$\min_{j \in \mathcal{M}_{-\mathcal{C}}} |\beta_j| > c_2 n^{-\kappa}.$$

Note that, for any $j \in \mathcal{M}_{-\mathcal{C}}$, event

$$\begin{aligned} & \left\{ |\hat{\beta}_j - \beta_j| \leq c_2 n^{-\kappa}/2 - \epsilon_1 \right\} \\ & \subseteq \left\{ |\hat{\beta}_j| \geq |\beta_j| - c_2 n^{-\kappa}/2 + \epsilon_1 \right\} \\ & \subseteq \left\{ |\hat{\beta}_j| \geq c_2 n^{-\kappa}/2 + \epsilon_1 \right\}. \end{aligned}$$

Take $\gamma_n = c_4 n^{-\kappa}$ with $c_4 = c_2/4$,

$$\begin{aligned} & \left\{ \max_{j \in \mathcal{M}_{-c}} |\hat{\beta}_j - \beta_j| \leq c_2 n^{-\kappa}/2 - \epsilon_1 \right\} \\ & \subseteq \left\{ \min_{j \in \mathcal{M}_{-c}} |\hat{\beta}_j| \geq c_2 n^{-\kappa}/2 + \epsilon_1 \right\} \\ & \subseteq \left\{ \min_{j \in \mathcal{M}_{-c}} |\hat{\beta}_j| \geq \gamma_n + \epsilon_1 \right\}. \end{aligned}$$

Thus,

$$\begin{aligned} & \mathbb{P} \left[\mathcal{M}_{-c} \subseteq \widehat{\mathcal{M}}_{-c} \right] \\ & = \mathbb{P} \left[\min_{j \in \mathcal{M}_{-c}} |\hat{\beta}_j| > \gamma_n \right] \\ & \geq \mathbb{P} \left[\min_{j \in \mathcal{M}_{-c}} |\hat{\beta}_j| > \gamma_n + \epsilon_1 \right] \\ & \geq 1 - \mathbb{P} \left[\max_{j \in \mathcal{M}_{-c}} |\hat{\beta}_j - \beta_j| \leq c_2 n^{-\kappa}/2 - \epsilon_1 \right] \\ & \geq 1 - 2w(q+1) \exp(-c_3 n^{1-2\kappa}) - \epsilon_2. \end{aligned}$$

Let $n \rightarrow \infty$, we have for any $\epsilon_2 > 0$,

$$\lim_{n \rightarrow \infty} \mathbb{P} \left[\mathcal{M}_{-c} \subseteq \widehat{\mathcal{M}}_{-c} \right] \geq 1 - \epsilon_2.$$

Note that the left side of the above equation does not depend on n any more. Taking $\epsilon_2 \rightarrow 0$ completes proof.

□

