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CONFIDENCE INTERVALS FOR HIGH-DIMENSIONAL COX MODELS

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Abstract: We provide a theoretical justification for post-selection inference in high-dimensional Cox models, based on the celebrated debiased Lasso procedure. Our generic model setup allows time-dependent covariates and an unbounded time interval, which is unique among post-selection inference studies on high-dimensional survival analysis. In addition, we adopt a novel proof technique to replace the use of Rebolledo's central limit theorem. Our theoretical results provide conditions under which our confidence intervals are asymptotically valid, and are supported by extensive numerical experiments.

Key words and phrases: Debiased Lasso, High-dimension statistical inference, survival analysis.

1. Introduction

Since its introduction, the Cox proportional hazards model (Cox (1972)) has become central to the analysis of censored survival data. The model posits that the conditional hazard rate at time $t \in \mathcal{T}$ for the survival time $\tilde{T}$ of an individual, given their p-variate covariate vector $\boldsymbol{Z}(t)$, can be expressed as

$$\lambda(t) := \lambda_0(t) \exp\bigl\{\boldsymbol{\beta}^{o\top} \boldsymbol{Z}(t)\bigr\}, \tag{1.1}$$

where $\boldsymbol{\beta}^o \in \mathbb{R}^p$ is an unknown vector of regression coefficients, and $\lambda_0(\cdot)$ is an unknown baseline hazard function. With n individuals from a population, we assume that for each $i = 1, \ldots, n$, we observe a (possibly right-censored) survival time T_i, an indicator δ_i of whether or not failure is observed, and the corresponding covariate processes $\{\boldsymbol{Z}_i(t) : t \in \mathcal{T}\}$.

When $p < n$, the maximum partial likelihood estimator (MPLE) (Cox (1975)) may be used to estimate $\boldsymbol{\beta}^o$. In the classical setting, the dimension p is assumed to be fixed and the sample size n is allowed to diverge to infinity. In

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such a setting, and under a strong (and difficult to check) condition on the weak convergence of the sample covariance processes, Andersen and Gill (1982) derived the asymptotic normality of the MPLE using counting process arguments and Rebolledo's martingale central limit theorem. This result can be used to provide asymptotically valid confidence intervals for components of $\boldsymbol{\beta}^o$ (or, more generally, for linear combinations $\mathbf{c}^\top\boldsymbol{\beta}^o$, for some fixed $\mathbf{c} \in \mathbb{R}^p$).

Our interest lies in providing corresponding confidence intervals in the high-dimensional regime, where p may be much larger than n. The motivation for such a methodology arises from many different application areas, but particularly those in biomedicine. Here, Cox models are ubiquitous, and data on each individual, which may arise from combinations of genetic information, greyscale values for each pixel in a scan, and many other types, are often plentiful. Our construction begins with the Lasso penalized partial likelihood estimator $\widehat{\boldsymbol{\beta}}$ studied in Huang et al. (2013), which is sparse, and is used here as an initial estimator. We then seek a sparse estimator of the inverse of the negative Hessian matrix, which we refer to as a *sparse precision matrix estimator*. In Zhang and Zhang (2014) and van de Geer et al. (2014), who consider similar problems in linear and generalized linear model settings, respectively, this sparse precision matrix estimator is constructed using a nodewise Lasso regression (Meinshausen and Bühlmann (2006)). In contrast, Javanmard and Montanari (2014) derived their precision matrix estimators by minimizing the trace of the product of the sample covariance matrix and the precision matrix, where the covariates are assumed to be centered. However, in the Cox model setting, the counterpart of the design matrix is a mean-shifted design matrix, where the mean is based on a set of tilting weights. This destroys the necessary independence structure. Instead, we adopt a modification of the CLIME estimator (Cai, Liu and Luo (2011)) as the sparse precision matrix estimator, which allows us to handle the mean subtraction. Adjusting $\widehat{\boldsymbol{\beta}}$ by the product of our sparse precision matrix estimator and the score vector yields a debiased estimator $\widehat{\boldsymbol{b}}$. Our main theoretical result (Theorem 1) provides conditions under which $\boldsymbol{c}^\top\widehat{\boldsymbol{b}}$ is asymptotically normally distributed around $\boldsymbol{c}^\top\boldsymbol{\beta}^o$. The desired confidence intervals can then be obtained straightforwardly. Recent applications of the debiasing idea, although not within the context of regression problems, can be found in, for example, Janková and van de Geer (2018).

The success of the debiased Lasso approach for high-dimensional post-selection inference means it has received a great deal of attention in recent years. However, ours is the first attempt to provide a theoretical justification for the method in the important area of survival analysis. In addition to this main contribution, we believe that our novel proof techniques provide the survival analysis community with new tools that can be applied in other related problems. Our list three technical contributions are as follows:

- We avoid the difficult assumption on the weak convergence of sample covariance processes inherent in the martingale central limit theorem approach (Bradic, Fan and Jiang (2011)). This entails a different approach, which provides new insights, even in low-dimensional settings. In particular, we introduce a new finite-sample concentration inequality (Lemma **S**2), which controls the largest deviations from its population analogue of the weighted sample covariate process.

- We allow the upper limit t_+ of the time index set $\mathcal{T}$ to be infinite, and do not assume that each subject has a constant, positive probability of remaining in the at-risk set at time t_+. This differs from the approach of, for example, Fang, Yang and Liu (2017), who propose hypothesis tests based on decorrelated scores and decorrelated partial likelihood ratios. Because our concentration inequality is useful only when sufficiently many individuals remain under study, this feature of the problem necessitates a novel truncation argument.

- Our theory handles settings where p may be much larger than n; in fact, we assume only that $p = o(\exp(n^a))$, for every $a > 0$; this is sometimes called the ultrahigh-dimensional setting (e.g. Fan, Samworth and Wu (2009)).

Our estimators and inference procedure are given in Section 2, and our theoretical arguments are presented in Section 3. Section 4 is devoted to extensive numerical studies of our methdology on both simulated and real data. These reveal, in particular, that valid p-values and confidence intervals for the noise variables can be obtained with a relatively small sample size, whereas a larger sample size is needed for good coverage of signal variables. Various auxiliary results and proofs are given in the Supplementary Material (Yu, Bradic and Samworth (2021)).

We conclude this section by introducing the notation used throughout the remainder of this paper. For any set S, let $|S|$ denote its cardinality. For a vector $\boldsymbol{v} = (v_1, \ldots, v_m)^\top \in \mathbb{R}^m$, let $\|\boldsymbol{v}\|_1$, $\|\boldsymbol{v}\|$, and $\|\boldsymbol{v}\|_\infty$ denote its ℓ_1, ℓ_2, and ℓ_∞ norms, respectively; we also write $\boldsymbol{v}^{\otimes 2} := \boldsymbol{v}\boldsymbol{v}^\top$. Given a set $J \subseteq \{1, \ldots, m\}$, we write $\boldsymbol{v}_J := (v_j)_{j \in J} \in \mathbb{R}^{|J|}$. For a matrix $\boldsymbol{A} = (A_{ij})_{i,j=1}^m \in \mathbb{R}^{m \times m}$, let

$\|\boldsymbol{A}\|_\infty := \max_{i,j=1,\ldots,m} |A_{ij}|$ be the entrywise maximum absolute norm, and let $\|\boldsymbol{A}\|_{\mathrm{op},\infty} := \sup_{\boldsymbol{v}\neq 0}(\|\boldsymbol{A}\boldsymbol{v}\|_\infty/\|\boldsymbol{v}\|_\infty)$ and $\|\boldsymbol{A}\|_{\mathrm{op},1} := \sup_{\boldsymbol{v}\neq 0}(\|\boldsymbol{A}\boldsymbol{v}\|_1/\|\boldsymbol{v}\|_1)$ denote its operator ℓ_∞ and operator ℓ_1 norms, respectively. In Lemma **S**1 in the Supplementary Material, we show that $\|\boldsymbol{A}\|_{\mathrm{op},\infty}$ and $\|\boldsymbol{A}\|_{\mathrm{op},1}$ are the maximum of the ℓ_1 norms of the rows of $\boldsymbol{A}$, and the maximum of the ℓ_1 norms of its columns, respectively. Given two real sequences (a_n) and (b_n), we write $a_n \asymp b_n$ to mean $0 < \liminf_{n\to\infty} |a_n/b_n| \leq \limsup_{n\to\infty} |a_n/b_n| < \infty$. Given a distribution function F, we write $\bar{F} := 1 - F$. All probabilities and expectations are taken under the true model with baseline hazard λ_0 and regression parameter $\boldsymbol{\beta}^o$, though we suppress this in our notation.

2. Methodology

Recall that $\mathcal{T} \subseteq [0,\infty)$ denotes our time index set. We assume that, for $i = 1,\ldots,n$, there exist independent triples $\big(\tilde{T}_i, U_i, \{\boldsymbol{Z}_i(t) : t \in \mathcal{T}\}\big)$, where $\tilde{T}_i$ is a nonnegative random variable indicating failure time, U_i is a nonnegative random variable indicating a censoring time, and $\{\boldsymbol{Z}_i(t) : t \in \mathcal{T}\}$ is a p-variate, predictable time-varying covariate process. We further assume that $\tilde{T}_i$ and U_i are conditionally independent, given $\{\boldsymbol{Z}_i(t) : t \in \mathcal{T}\}$. Writing $T_i := \min(\tilde{T}_i, U_i)$ and $\delta_i := \mathbb{1}_{\{\tilde{T}_i \leq U_i\}}$, our observations are $\big\{\big(T_i, \delta_i, \{\boldsymbol{Z}_i(t) : t \in \mathcal{T}\}\big) : i = 1,\ldots,n\big\}$. We regard these observations as independent copies of a generic triple $\big(T, \delta, \{\boldsymbol{Z}(t) : t \in \mathcal{T}\}\big)$.

Let F_T denote the distribution function of T, and let $t_+ := \inf\{t \geq 0 : F_T(t) = 1\}$ denote the upper limit of the support of T. If $t_+ < \infty$, we assume that $\mathcal{T} = [0, t_+]$; if $t_+ = \infty$, then we assume $\mathcal{T} = [0,\infty)$. In this sense, we assume that $\mathcal{T}$ covers the entire support of the distribution of T. Therefore, in particular, there are no individuals in the at-risk set at time t_+.

For $i = 1,\ldots,n$, define processes $\{N_i(t) : t \in \mathcal{T}\}$ and $\{Y_i(t) : t \in \mathcal{T}\}$ by $N_i(t) := \mathbb{1}_{\{T_i \leq t, \delta_i = 1\}}$ and $Y_i(t) := \mathbb{1}_{\{T_i \geq t\}}$, respectively. We regard these as independent copies of processes $\{N(t) : t \in \mathcal{T}\}$ and $\{Y(t) : t \in \mathcal{T}\}$, respectively. Let $\bar{N}(t) := n^{-1}\sum_{i=1}^n N_i(t)$. Therefore, the natural σ-field at time $t \in \mathcal{T}$ is $\mathcal{F}_t := \sigma(\{(N_i(t), Y_i(t), \{\boldsymbol{Z}_i(s) : s \in [0,t]\}) : i = 1,\ldots,n\})$. In the Cox model (1.1), $N_i(t)$ has predictable compensator

$$\Lambda_i(t, \boldsymbol{\beta}^o) := \int_0^t Y_i(s) \exp\big\{\boldsymbol{\beta}^{o\top} \boldsymbol{Z}_i(t)\big\} \lambda_0(s)\, ds,$$

with respect to the filtration $(\mathcal{F}_t : t \in \mathcal{T})$.

Define the log-partial likelihood function, divided by n, at $\boldsymbol{\beta} \in \mathbb{R}^p$ by

$$\begin{aligned}\ell(\boldsymbol{\beta}) &= \ell_n(\boldsymbol{\beta}) \\ &:= \frac{1}{n}\sum_{i=1}^{n}\int_{\mathcal{T}}\boldsymbol{\beta}^\top \boldsymbol{Z}_i(s)\,dN_i(s) - \int_{\mathcal{T}}\log\left[\sum_{j=1}^{n} Y_j(s)\exp\{\boldsymbol{\beta}^\top \boldsymbol{Z}_j(s)\}\right] d\bar{N}(s).\end{aligned}$$

Inspired by Zhang and Zhang (2014) and van de Geer et al. (2014), our main object of interest is the one-step-type estimator

$$\widehat{\boldsymbol{b}} := \widehat{\boldsymbol{\beta}} + \widehat{\boldsymbol{\Theta}}\dot{\ell}(\widehat{\boldsymbol{\beta}}), \tag{2.1}$$

where $\widehat{\boldsymbol{\beta}} = (\hat{\beta}_1, \ldots, \hat{\beta}_p)^\top$ is an initial estimator of $\boldsymbol{\beta}^o$, $\widehat{\boldsymbol{\Theta}} = (\hat{\Theta}_{ij})_{i,j=1}^{p}$ is a sparse precision matrix estimator that approximates the inverse of the negative Hessian $-\ddot{\ell}(\boldsymbol{\beta}^o)$, and $\dot{\ell}(\widehat{\boldsymbol{\beta}})$ is the score function evaluated at the initial estimator. In the rest of this section, we discuss the definition and rationale for our choices of $\widehat{\boldsymbol{\beta}}$ and $\widehat{\boldsymbol{\Theta}}$. Note that our proposals for $\widehat{\boldsymbol{\beta}}$ and $\widehat{\boldsymbol{\Theta}}$ depend on certain tuning parameters; this dependence is suppressed in our notation. However, in our theoretical results, we provide explicit conditions on these tuning parameters. Note that a similar construction has also been proposed in a later submission Kong et al. (2018), which focuses on the utility of such a construction under model misspecification.

2.1. Initial estimator

Following Huang et al. (2013), for $\lambda > 0$, let

$$\widehat{\boldsymbol{\beta}} = \widehat{\boldsymbol{\beta}}(\lambda) := \operatorname*{argmin}_{\boldsymbol{\beta}\in\mathbb{R}^p}\bigl\{-\ell(\boldsymbol{\beta}) + \lambda\|\boldsymbol{\beta}\|_1\bigr\}. \tag{2.2}$$

For $i = 1, \ldots, n$ and $t \in \mathcal{T}$, let $\tilde{w}_i(t, \boldsymbol{\beta}) := Y_i(t)\exp\{\boldsymbol{\beta}^\top \boldsymbol{Z}_i(t)\}$ be the ith weight, and let

$$w_i(s, \boldsymbol{\beta}) := \frac{\tilde{w}_i(s, \boldsymbol{\beta})}{\sum_{j=1}^{n}\tilde{w}_j(s, \boldsymbol{\beta})}$$

be the ith normalized weight, with the convention that $0/0 := 0$. The weighted average of the covariate processes is defined by

$$\bar{\boldsymbol{Z}}(s, \boldsymbol{\beta}) := \sum_{i=1}^{n}\boldsymbol{Z}_i(s)w_i(s, \boldsymbol{\beta}).$$

Then, it follows from the subgradient conditions for optimality (i.e., the Karush–Kuhn–Tucker conditions) that there exists $\hat{\boldsymbol{\tau}} = (\hat{\tau}_1, \ldots, \hat{\tau}_p)^\top$, such that

$$0 = -\dot{\ell}(\widehat{\boldsymbol{\beta}}) + \lambda\widehat{\boldsymbol{\tau}} = -\frac{1}{n}\sum_{i=1}^{n}\int_{\mathcal{T}}\bigl\{\boldsymbol{Z}_i(s) - \bar{\boldsymbol{Z}}(s,\widehat{\boldsymbol{\beta}})\bigr\}\,dN_i(s) + \lambda\widehat{\boldsymbol{\tau}},$$

where $\|\widehat{\boldsymbol{\tau}}\|_\infty \leq 1$ and $\hat{\tau}_j = \mathrm{sgn}(\hat{\beta}_j)$ if $\hat{\beta}_j \neq 0$.

2.2. The estimator of the precision matrix

For $\boldsymbol{\beta} \in \mathbb{R}^p$, we have

$$\ddot{\ell}(\boldsymbol{\beta}) = -\sum_{i=1}^{n}\int_{\mathcal{T}}\bigl\{\boldsymbol{Z}_i(s) - \bar{\boldsymbol{Z}}(s,\boldsymbol{\beta})\bigr\}^{\otimes 2} w_i(s,\boldsymbol{\beta})\,d\bar{N}(s).$$

However, the presence of the weights in this integral makes it difficult to analyze directly. As a first step toward obtaining a more tractable expression, we rewrite this equation as

$$\ddot{\ell}(\boldsymbol{\beta}) = -\frac{1}{n}\sum_{i=1}^{n}\int_{\mathcal{T}}\bigl\{\boldsymbol{Z}_i(s) - \bar{\boldsymbol{Z}}(s,\boldsymbol{\beta})\bigr\}^{\otimes 2}\tilde{w}_i(s,\boldsymbol{\beta})\,d\widehat{\Lambda}(s,\boldsymbol{\beta}),$$

where we define $\widehat{\Lambda}(t,\boldsymbol{\beta}) := n\int_0^t \bigl\{\sum_{j=1}^n \tilde{w}_j(s,\boldsymbol{\beta})\bigr\}^{-1}\,d\bar{N}(s)$ to be the Breslow estimator of $\int_0^t \lambda_0(s)\,ds$ (Breslow (1972)). Now, recall from, among others, Andersen et al. (1993, p. 66) that the process $\{N(t) : t \in \mathcal{T}\}$ has the Doob–Meyer decomposition

$$N(t) = M(t) + \int_0^t \tilde{w}(s,\boldsymbol{\beta}^o)\lambda_0(s)\,ds, \tag{2.3}$$

where $\{M(t) : t \in \mathcal{T}\}$ is a mean-zero martingale. This motivates us to define a population approximation to $-\ddot{\ell}(\boldsymbol{\beta}^o)$ by

$$\begin{aligned}\boldsymbol{\Sigma} &:= \mathbb{E}\int_{\mathcal{T}}\{\boldsymbol{Z}(s) - \boldsymbol{\mu}(s,\boldsymbol{\beta}^o)\}^{\otimes 2}\,dN(s)\\ &= \mathbb{E}\int_0^{t_+}\bigl\{\boldsymbol{Z}(s) - \boldsymbol{\mu}(s,\boldsymbol{\beta}^o)\bigr\}^{\otimes 2}\tilde{w}(s,\boldsymbol{\beta}^o)\lambda_0(s)\,ds,\end{aligned}$$

where, for $t \in \mathcal{T}$ and $\boldsymbol{\beta} \in \mathbb{R}^p$,

$$\boldsymbol{\mu}(t,\boldsymbol{\beta}) := \frac{\mathbb{E}\{\boldsymbol{Z}(t)Y(t)\exp(\boldsymbol{\beta}^\top\boldsymbol{Z}(t))\}}{\mathbb{E}\{Y(t)\exp(\boldsymbol{\beta}^\top\boldsymbol{Z}(t))\}}.$$

Our goal in this subsection is to define an estimator of $\boldsymbol{\Sigma}^{-1}$ with properties that we can analyze. To this end, observe that an oracle, with knowledge of $\boldsymbol{\beta}^o$, could estimate $\boldsymbol{\Sigma}$ by

$$\begin{aligned}\widehat{\mathcal{V}}(\boldsymbol{\beta}^o) &:= \frac{1}{n}\sum_{i=1}^{n}\int_{\mathcal{T}}\big\{\boldsymbol{Z}_i(s) - \bar{\boldsymbol{Z}}(s,\boldsymbol{\beta}^o)\big\}^{\otimes 2}\,dN_i(s)\\ &= \frac{1}{n}\sum_{i=1}^{n}\delta_i\big\{\boldsymbol{Z}_i(T_i) - \bar{\boldsymbol{Z}}(T_i,\boldsymbol{\beta}^o)\big\}^{\otimes 2}.\end{aligned}$$

This suggests the genuine estimator

$$\widehat{\mathcal{V}}(\widehat{\boldsymbol{\beta}}) = \frac{1}{n}\sum_{i=1}^{n}\delta_i\big\{\boldsymbol{Z}_i(T_i) - \bar{\boldsymbol{Z}}(T_i,\widehat{\boldsymbol{\beta}})\big\}^{\otimes 2}. \tag{2.4}$$

Whereas both $-\ddot{\ell}(\widehat{\boldsymbol{\beta}})$ and $\widehat{\mathcal{V}}(\widehat{\boldsymbol{\beta}})$ can be considered as estimators of $\boldsymbol{\Sigma}$, it turns out that the latter is a much more convenient expression to study, from a theoretical perspective.

As mentioned in the introduction, both Zhang and Zhang (2014) and van de Geer et al. (2014) employ a nodewise regression to obtain a sparse precision matrix estimator $\widehat{\boldsymbol{\Theta}}$. In those cases, the design matrices consist of independent rows, which facilitate the adoption of Lasso-type methods; in the Cox model, however, we do not have the luxury of row independence, because $\widehat{\mathcal{V}}$, defined in (2.4), involves $\bar{\boldsymbol{Z}}(T_i,\widehat{\boldsymbol{\beta}})$.

As an alternative, we adapt the CLIME estimator of Cai, Liu and Luo (2011), originally proposed in the context of precision matrix estimation. Let $\widehat{\boldsymbol{\Theta}} = (\widehat{\boldsymbol{\Theta}}_1,\ldots,\widehat{\boldsymbol{\Theta}}_p)^\top$ be defined by

$$\widehat{\boldsymbol{\Theta}}_j \in \operatorname*{argmin}_{\boldsymbol{b}_j\in\mathbb{R}^p}\Big\{\|\boldsymbol{b}_j\|_1 : \big\|\widehat{\mathcal{V}}(\widehat{\boldsymbol{\beta}})\boldsymbol{b}_j - \boldsymbol{e}_j\big\|_\infty \le \lambda_n\Big\}, \tag{2.5}$$

where $\boldsymbol{e}_j^\top := (\mathbb{1}_{\{j=l\}})_{l=1}^p \in \mathbb{R}^p$, for $j = 1,\ldots,p$. The original proposal of Cai, Liu and Luo (2011) symmetrized $\widehat{\boldsymbol{\Theta}}$ by taking both the (i,j)th and (j,i)th off-diagonal entries as the corresponding entry of $\widehat{\boldsymbol{\Theta}}$ with the smaller absolute value. In our theoretical analysis, it turned out to be convenient not to symmetrize in this way. In practice, we found the difference to be negligible; see Section 4.1.

For $j = 1,\ldots,p$, let $\dot{\ell}_j(\boldsymbol{\beta})$ denote the jth component of the score vector at $\boldsymbol{\beta}$, and let $\ddot{\ell}_j(\boldsymbol{\beta}) \in \mathbb{R}^p$ have lth component $\partial^2\ell(\boldsymbol{\beta})/\partial\beta_l\partial\beta_j$. By a Taylor expansion, for each $j = 1,\ldots,p$, there exists $\widetilde{\boldsymbol{\beta}}_j$ on the line segment between $\widehat{\boldsymbol{\beta}}$ and $\boldsymbol{\beta}^o$, such that

$$\dot{\ell}_j(\widehat{\boldsymbol{\beta}}) = \dot{\ell}_j(\boldsymbol{\beta}^o) + \ddot{\ell}_j(\widetilde{\boldsymbol{\beta}}_j)^\top(\widehat{\boldsymbol{\beta}} - \boldsymbol{\beta}^o). \tag{2.6}$$

Now, let $\boldsymbol{M}(\widetilde{\boldsymbol{\beta}}) \in \mathbb{R}^{p\times p}$ be the matrix with jth row $\ddot{\ell}_j(\widetilde{\boldsymbol{\beta}}_j)^\top$. It follows that with $\widehat{\boldsymbol{b}}$ defined as in (2.1), and for any $\mathbf{c} \in \mathbb{R}^p$ with $\|\mathbf{c}\|_1 = 1$, we can write

$$\begin{aligned}
\mathbf{c}^\top(\widehat{\boldsymbol{b}} - \boldsymbol{\beta}^o) &= \mathbf{c}^\top\big\{\widehat{\boldsymbol{\beta}} + \widehat{\boldsymbol{\Theta}}\dot{\ell}(\widehat{\boldsymbol{\beta}}) - \boldsymbol{\beta}^o\big\} \\
&= \mathbf{c}^\top\boldsymbol{\Sigma}^{-1}\dot{\ell}(\boldsymbol{\beta}^o) + \mathbf{c}^\top\big(\widehat{\boldsymbol{\Theta}} - \boldsymbol{\Sigma}^{-1}\big)\dot{\ell}(\boldsymbol{\beta}^o) \\
&\quad + \mathbf{c}^\top\widehat{\boldsymbol{\Theta}}\big\{\dot{\ell}(\widehat{\boldsymbol{\beta}}) - \dot{\ell}(\boldsymbol{\beta}^o)\big\} + \mathbf{c}^\top(\widehat{\boldsymbol{\beta}} - \boldsymbol{\beta}^o) \\
&= \mathbf{c}^\top\boldsymbol{\Sigma}^{-1}\dot{\ell}(\boldsymbol{\beta}^o) + \mathbf{c}^\top(\widehat{\boldsymbol{\Theta}} - \boldsymbol{\Sigma}^{-1})\dot{\ell}(\boldsymbol{\beta}^o) + \mathbf{c}^\top\{\widehat{\boldsymbol{\Theta}}\boldsymbol{M}(\widetilde{\boldsymbol{\beta}}) + \boldsymbol{I}\}(\widehat{\boldsymbol{\beta}} - \boldsymbol{\beta}^o).
\end{aligned} \tag{2.7}$$

In Section 3, we provide conditions under which, when both sides of (2.7) are rescaled by $n^{1/2}$, the first, dominant term is asymptotically normal, and the second and third terms are asymptotically negligible. This is the main step in deriving asymptotically valid confidence intervals for $\mathbf{c}^\top\boldsymbol{\beta}^o$.

3. Theory

3.1. Assumptions and main result

Recall that our underlying processes are n independent copies of the triple $\big(\tilde{T}, U, \boldsymbol{\mathcal{Z}}\big)$, where $\boldsymbol{\mathcal{Z}} := \{\boldsymbol{Z}(t) : t \in \mathcal{T}\}$, and that we assume $\tilde{T}$ and U are conditionally independent, given $\boldsymbol{\mathcal{Z}}$. Our observations are n independent copies of $\big(T, \delta, \{\boldsymbol{Z}(t) : t \in \mathcal{T}\}\big)$, and we assume that the conditional hazard function of $\tilde{T}$ at time t, given $\boldsymbol{\mathcal{Z}}$, satisfies (1.1)[1], for some $\boldsymbol{\beta}^o \in \mathbb{R}^p$. We use the following assumptions:

(A1) **(a)** The process $\{\boldsymbol{Z}(t) : t \in \mathcal{T}\}$ is predictable, and there exists a deterministic $K_Z > 0$, with $\sup_{t\in\mathcal{T}} \mathbb{P}\{\|\boldsymbol{Z}(t)\|_\infty \leq K_Z\} = 1$.

(b) The process $\{\boldsymbol{Z}(t) : t \in \mathcal{T}\}$ is uniformly Lipschitz in the sense that there exists a deterministic $L > 0$, such that

$$\mathbb{P}\bigg\{\sup_{s,t\in\mathcal{T}, s\neq t} \frac{\|\boldsymbol{Z}(s) - \boldsymbol{Z}(t)\|_\infty}{|s-t|} \leq L\bigg\} = 1.$$

(A2) **(a)** The random variable T has a bounded density f_T with respect to the Lebesgue measure.

(b) $\int_0^{t_+} t^\alpha f_T(t)\, dt < \infty$, for some $\alpha > 0$.

[1] In the terminology of, e.g., Kalbfleisch and Prentice (2002, Sec. 6.3), this means that all time-dependent covariates are *external*.

(A3) **(a)** $p = p_n = o(e^{n^a})$, for every $a > 0$.

(b) $d_o := |\{j : \beta^o_j \neq 0\}|$ satisfies $d_o = o\big(n^{1/2}/\log^{1/2}(np)\big)$.

(A4) **(a)** Writing $\mathcal{S} := \{j : \beta^o_j \neq 0\}$, $\mathcal{N} := \{j : \beta^o_j = 0\}$, and

$$\kappa := \inf_{\{\mathbf{v}\in\mathbb{R}^p\setminus\{0\}:\|\mathbf{v}_{\mathcal{N}}\|_1\leq 2\|\mathbf{v}_{\mathcal{S}}\|_1\}} \frac{d_o^{1/2}\{\mathbf{v}^\top\ddot{\ell}(\boldsymbol{\beta}^o)\mathbf{v}\}^{1/2}}{\|\mathbf{v}_{\mathcal{S}}\|_1},$$

we have that $1/\kappa = O_p(1)$.

(b) $\max_{j=1,\ldots,p}\Sigma_{jj} = O(1)$ as $n \to \infty$.

(c) $\liminf_{n\to\infty}\|\boldsymbol{\Sigma}^{-1}\|_{\mathrm{op},1} > 0$, and writing $r_j := \sum_{i=1}^p \mathbb{1}_{\{(\boldsymbol{\Sigma}^{-1})_{ij}\neq 0\}}$, for $j = 1,\ldots,p$, there exists $\delta_0 > 0$, such that

$$\|\boldsymbol{\Sigma}^{-1}\|^2_{\mathrm{op},1}\max\left\{\frac{d_o^2\log(np)}{n^{1/2}}\,,\, d_o n^{-(1/3-\delta_0)}\right\}\max_{j=1,\ldots,p} r_j$$
$$=o\left(\frac{1}{\log^{1/2}(np)}\right).$$

A discussion of these assumptions is in order. Condition **(A1)** concerns the boundedness and Lipschitz continuity of the covariate process. It is likely that the first of these conditions could be replaced with a tail condition, at the expense of further complicating the theoretical analysis. Indeed, in our simulations in Section 4, we explore settings in which $\|\boldsymbol{Z}(t)\|_\infty$ is unbounded. Condition **(A2)** consists of two mild and interpretable conditions on the distribution of the observed failure times. Condition **(A3)(a)** controls the rate of growth of the dimensionality as the sample size increases, and, in particular, allows super-polynomial growth. However, the sparsity assumption **(A3)(b)** ensures that the number of important variables (those with nonzero regression coefficients) is more tightly controlled. Condition **(A4)(a)** is a high-level condition on the so-called compatibility factor of $\ddot{\ell}(\boldsymbol{\beta}^o)$; in the presence of our other assumptions, we find that this essentially amounts to a condition on the smallest eigenvalue of $\boldsymbol{\Sigma}$; see the discussion following Lemma 1. The other parts of **(A4)** imposes further conditions on $\boldsymbol{\Sigma}$, and, in the case of**(A4)(c)**, the way its properties interact with the sparsity level of $\boldsymbol{\beta}^o$.

The confidence intervals for the regression coefficients are constructed based on the results derived in the following theorem.

Theorem 1. *Assume* **(A1)**–**(A4)**, *and let* $\boldsymbol{c} \in \mathbb{R}^p$ *be such that* $\|\boldsymbol{c}\|_1 = 1$ *and*

$\boldsymbol{c}^\top \boldsymbol{\Sigma}^{-1}\boldsymbol{c} \to \nu^2 \in (0,\infty)$. *For* $\widehat{\boldsymbol{\beta}}$ *in* (2.2)*, let* $\lambda \asymp n^{-1/2}\log^{1/2}(np)$*, and for* $\widehat{\boldsymbol{\Theta}}$ *in* (2.5)*, let*

$$\lambda_n \asymp \left\{\max\left(\|\boldsymbol{\Sigma}^{-1}\|_{\mathrm{op},1}\frac{d_o\log(np)}{n^{1/2}}\,,\ \|\boldsymbol{\Sigma}^{-1}\|_{\mathrm{op},1}n^{-(1/3-\delta_0)}\right)\right\}.$$

Then, for $\widehat{\boldsymbol{b}}$ *defined in* (2.7)*, we have*

$$n^{1/2}\boldsymbol{c}^\top(\widehat{\boldsymbol{b}} - \boldsymbol{\beta}^o) \xrightarrow{d} \mathcal{N}(0,\nu^2),$$

as $n \to \infty$*. Moreover,*

$$n^{1/2}\frac{\boldsymbol{c}^\top(\widehat{\boldsymbol{b}} - \boldsymbol{\beta}^o)}{(\boldsymbol{c}^\top\widehat{\boldsymbol{\Theta}}\boldsymbol{c})^{1/2}} \xrightarrow{d} \mathcal{N}(0,1).$$

Remark 1. Theorem 1 can be extended to include testing a hypothesis about a fixed-dimensional sub-vector of $\boldsymbol{\beta}^o$, such as $H_0 : \beta_1^o = \beta_2^o = \beta_3^o = 0$, by choosing an appropriate matrix $\boldsymbol{C}$ in place of the vector $\mathbf{c}$. However, for simplicity of exposition, we state the result in terms of a single linear combination of the components of $\boldsymbol{\beta}^o$.

It follows immediately from Theorem 1 that for any $q \in (0,1)$, an asymptotic $(1-q)$-level confidence interval for $\boldsymbol{c}^\top\boldsymbol{\beta}^o$ is given by

$$\big[\boldsymbol{c}^\top\widehat{\boldsymbol{b}} - z_{q/2}n^{-1/2}(\boldsymbol{c}^\top\widehat{\boldsymbol{\Theta}}\boldsymbol{c})^{1/2}, \boldsymbol{c}^\top\widehat{\boldsymbol{b}} + z_{q/2}n^{-1/2}(\boldsymbol{c}^\top\widehat{\boldsymbol{\Theta}}\boldsymbol{c})^{1/2}\big],$$

where z_q is the $(1-q)$th quantile of the standard normal distribution. In particular, for each $j = 1,\ldots,p$, an asymptotic $(1-q)$-level confidence interval for β_j^o is provided by

$$[\hat{b}_j - z_{q/2}n^{-1/2}(\widehat{\Theta}_{jj})^{1/2}, \hat{b}_j + z_{q/2}n^{-1/2}(\widehat{\Theta}_{jj})^{1/2}]. \tag{3.1}$$

3.2. Proof of theorem 1

The proof of Theorem 1 contains three main steps: a) provide the properties of the initial estimator $\widehat{\boldsymbol{\beta}}$; b) show the asymptotic normality of the first term in (2.7); and c) show that the remainder terms in (2.7) are negligible. These steps are tackled using the intermediate results in the following three subsections (the proofs are deferred to the Supplementary Material). The final subsection completes the proof.

First, in step b), note that the first term in (2.7) is split in two by subtracting and adding the population quantity $\boldsymbol{\mu}(s, \boldsymbol{\beta}^o)$ in the integrand of the expression for the score function $\dot{\ell}(\boldsymbol{\beta}^o)$ at $\boldsymbol{\beta}^o$. This allows us to apply the Lindeberg–Feller central limit theorem to the first (dominant) term to obtain its limiting distribution. The remainder term is a normalized sum of mean-zero, exchangeable random variables, the variances of which are controlled by weighted integrals over $\mathcal{T}$ of $\|\bar{\boldsymbol{Z}}(\cdot, \boldsymbol{\beta}^o) - \boldsymbol{\mu}(\cdot, \boldsymbol{\beta}^o)\|_\infty^2$. We expect this term to be small when the at-risk set size is reasonably large. However, because we allow this at-risk set to be empty at t_+, we adopt a novel truncation technique in which we set $t_* := F_T^{-1}(1 - n^{-1/2})$, and treat the time intervals from zero to t_* and from t_* to t_+ separately. For the former interval, we develop a new finite-sample concentration inequality (Lemma **S**2) to control $\sup_{t \in [0, t_*)} \|\bar{\boldsymbol{Z}}(\cdot, \boldsymbol{\beta}^o) - \boldsymbol{\mu}(\cdot, \boldsymbol{\beta}^o)\|_\infty$. In the latter case, we exploit the boundedness of the process $\bar{\boldsymbol{Z}}(\cdot, \boldsymbol{\beta}^o)$, together with Jensen's inequality, to argue that the weighted integral over this region is also asymptotically negligible.

For step c), we derive a special form of the martingale concentration inequality using the decoupling techniques of de la Peña (1999), and concentration inequalities for sub-gamma random variables.

3.2.1. The initial estimator

The following lemma gives the required properties for the score function at $\boldsymbol{\beta}^o$ and the initial estimator. The first result is proved in Lemma 3.3 of Huang et al. (2013). The second combines Theorem 3.2 and Theorem 4.1 of the same study.

Lemma 1. *(i) Assume* **(A1)(a)**. *Then, for each* $x > 0$,

$$\mathbb{P}\{\|\dot{\ell}(\boldsymbol{\beta}^o)\|_\infty > x\} \leq 2pe^{-nx^2/(8K_Z^2)}.$$

(ii) Assume **(A1)(a)**, **(A3)(b)**, *and* **(A4)(a)**, *and take* $\lambda \asymp n^{-1/2} \log^{1/2}(np)$ *in* (2.2). *Then,*

$$\|\widehat{\boldsymbol{\beta}} - \boldsymbol{\beta}^o\|_1 = O_p\left(\frac{d_o \log^{1/2}(np)}{n^{1/2}}\right).$$

Remark 2. More generally, if we take a sequence (a_n) diverging to infinity arbitrarily slowly, and set $\lambda \asymp n^{-1/2} \log^{1/2}(a_n p)$ in (2.2), then under the conditions of Lemma 1(ii), we have $\|\widehat{\boldsymbol{\beta}} - \boldsymbol{\beta}^o\|_1 = O_p(d_o \log^{1/2}(a_n p)/n^{1/2})$. In fact, if we further assume that $p = p_n \to \infty$ as $n \to \infty$, then we may take $\lambda = An^{-1/2} \log^{1/2} p$ in (2.2), and for sufficiently large $A > 0$, conclude that $\|\widehat{\boldsymbol{\beta}} - \boldsymbol{\beta}^o\|_1 = O_p(d_o \log^{1/2} p/n^{1/2})$.

We now discuss **(A4)(a)** in greater depth. For arbitrary finite $t^* \in \mathcal{T}$ and $M > 0$, let $C_1 := 1 + \Lambda_0(t^*)$, and let $C_2 := 2\Lambda_0(t^*)/r_*$, where $r_* := \mathbb{E}\bigl[Y(t^*)\min\{M, e^{\boldsymbol{\beta}^{o\top}\boldsymbol{Z}(t^*)}\}\bigr]$. Further, let

$$\boldsymbol{\Sigma}(t^*; M) := \mathbb{E}\int_0^{t^*}\bigl\{\boldsymbol{Z}(s) - \boldsymbol{\mu}(s, \boldsymbol{\beta}^o; M)\bigr\}^{\otimes 2} Y(s)\min\{M, e^{\boldsymbol{\beta}^{o\top}\boldsymbol{Z}(t^*)}\}\lambda_0(s)\,ds,$$

where

$$\boldsymbol{\mu}(t, \boldsymbol{\beta}^o; M) := \frac{\mathbb{E}\bigl[\boldsymbol{Z}(t)Y(t)\min\{M, e^{\boldsymbol{\beta}^{o\top}\boldsymbol{Z}(t)}\}\bigr]}{\mathbb{E}\bigl[Y(t)\min\{M, e^{\boldsymbol{\beta}^{o\top}\boldsymbol{Z}(t)}\}\bigr]}.$$

Write ρ^* for the smallest eigenvalue of $\boldsymbol{\Sigma}(t^*; M)$, and let

$$t_{n,p,\epsilon} := \max\biggl\{\frac{4}{3n}\log\biggl(\frac{2.221p(p+1)}{\epsilon}\biggr), \frac{2}{n^{1/2}}\log^{1/2}\biggl(\frac{2.221p(p+1)}{\epsilon}\biggr)\biggr\}.$$

Then, the proof of Huang et al. (2013, Theorem 4.1) states that, for each $\epsilon \in (0, 1/3)$,

$$\mathbb{P}\left[\kappa < \rho^* - 36 d_o K_Z^2\left\{\frac{2^{1/2}C_1}{n^{1/2}}\log^{1/2}\left(\frac{p(p+1)}{\epsilon}\right) + C_2 t_{n,p,\epsilon}^2\right\}\right] \le 3\epsilon + e^{-nr_*^2/(8M^2)}.$$

Because t^* and M are considered fixed, it is natural to assume that both $\limsup_{n\to\infty}\max(C_1, C_2) < \infty$ and $\liminf_{n\to\infty}\min(\rho^*, r_*) > 0$. In that case, under **(A3)(b)**, we have $\mathbb{P}(\kappa < \liminf_{n\to\infty}\rho^*/2) \le 4\epsilon$ for sufficiently large n; thus, **(A4)(a)** holds.

3.2.2. The dominant and remainder terms

Here, we will describe the limiting behavior of the dominant term in Proposition 1, and the limiting behavior of the remainder terms in Propositions 2 and 3. All proofs can be found in the Supplementary Material.

After rescaling by $n^{1/2}$, the leading term in (2.7) is

$$n^{1/2}\boldsymbol{c}^\top\boldsymbol{\Sigma}^{-1}\dot{\ell}(\boldsymbol{\beta}^o) = \frac{1}{n^{1/2}}\sum_{i=1}^n\int_{\mathcal{T}}\boldsymbol{c}^\top\boldsymbol{\Sigma}^{-1}\bigl\{\boldsymbol{Z}_i(s) - \bar{\boldsymbol{Z}}(s, \boldsymbol{\beta}^o)\bigr\}\,dN_i(s).$$

We prove that its limiting distribution is Gaussian.

Proposition 1. *Assume* **(A1)**, **(A2)**, **(A3)(a)**, *and* **(A4)(c)**, *and let* $\boldsymbol{c} \in \mathbb{R}^p$ *be such that* $\|\boldsymbol{c}\|_1 = 1$ *and* $\boldsymbol{c}^\top\boldsymbol{\Sigma}^{-1}\boldsymbol{c} \to \nu^2 \in (0, \infty)$. *Then,*

$$n^{1/2}\boldsymbol{c}^\top\boldsymbol{\Sigma}^{-1}\dot{\ell}(\boldsymbol{\beta}^o) \xrightarrow{d} \mathcal{N}(0, \nu^2),$$

as $n \to \infty$.

The two remainder terms in (2.7) are controlled in Propositions 2 and 3, respectively.

Proposition 2. *Assume conditions* **(A4)**, **(A2)(a)**, **(A3)(b)**, **(A4)(a)**, *and* **(A4)(c)**. *For* $\widehat{\boldsymbol{\beta}}$ *in* (2.2), *let* $\lambda \asymp n^{-1/2}\log^{1/2}(np)$, *and for* $\widehat{\boldsymbol{\Theta}}$ *in* (2.5), *let*

$$\lambda_n \asymp \max\biggl(\|\boldsymbol{\Sigma}^{-1}\|_{\mathrm{op},1}\frac{d_o\log(np)}{n^{1/2}}\,,\,\|\boldsymbol{\Sigma}^{-1}\|_{\mathrm{op},1}n^{-(1/3-\delta_0)}\biggr).$$

Then, for $\boldsymbol{c} \in \mathbb{R}^p$, *with* $\|\boldsymbol{c}\|_1 = 1$, *we have*

$$\boldsymbol{c}^\top\bigl(\widehat{\boldsymbol{\Theta}} - \boldsymbol{\Sigma}^{-1}\bigr)\dot{\ell}(\boldsymbol{\beta}^o) = o_p(n^{-1/2}).$$

Recall the definition of the matrix $\boldsymbol{M}(\widetilde{\boldsymbol{\beta}})$, which is defined just after (2.6), and appears in (2.7).

Proposition 3. *Assume* **(A1)**, **(A2)(a)**, **(A3)(b)**, *and* **(A4)**. *For* $\widehat{\boldsymbol{\beta}}$ *in* (2.2), *let* $\lambda \asymp n^{-1/2}\log^{1/2}(np)$, *and for* $\widehat{\boldsymbol{\Theta}}$ *in* (2.5), *let*

$$\lambda_n \asymp \max\biggl(\|\boldsymbol{\Sigma}^{-1}\|_{\mathrm{op},1}\frac{d_o\log(np)}{n^{1/2}}\,,\,\|\boldsymbol{\Sigma}^{-1}\|_{\mathrm{op},1}n^{-(1/3-\delta_0)}\biggr).$$

Then, for $\boldsymbol{c} \in \mathbb{R}^p$, *with* $\|\boldsymbol{c}\|_1 = 1$, *we have*

$$\boldsymbol{c}^\top(\widehat{\boldsymbol{\Theta}}\boldsymbol{M}(\widetilde{\boldsymbol{\beta}}) + \boldsymbol{I})(\widehat{\boldsymbol{\beta}} - \boldsymbol{\beta}^o) = o_p(n^{-1/2}).$$

3.2.3. Completion of the proof

We now summarize all the results from the previous three subsections.

Proof of Theorem 1. From (2.7) and Propositions 1–3, we deduce from Slutsky's theorem that under the stated assumptions, the first claim follows. To prove the second claim, note that

$$\bigl|\boldsymbol{c}^\top\widehat{\boldsymbol{\Theta}}\boldsymbol{c} - \boldsymbol{c}^\top\boldsymbol{\Sigma}^{-1}\boldsymbol{c}\bigr| \le \bigl\|\widehat{\boldsymbol{\Theta}} - \boldsymbol{\Sigma}^{-1}\bigr\|_\infty = o_p(1),$$

where the final claim follows from (S2.5), Lemma **S**3, and **(A4)(c)**. A further application of Slutsky's theorem yields the second claim.

4. Numerical Experiments

In this section, we investigate the numerical performance of our proposed method. We begin by discussing various practical implementation issues in Section sec-pracissue. In Sections 4.2 and 4.3, we present analyses of simulated data and real data, respectively.

4.1. Practical issues

4.1.1. Software

Recall that the debiased estimator $\widehat{\boldsymbol{b}}$ is obtained from a Lasso estimator $\widehat{\boldsymbol{\beta}}$ of the vector of true regression coefficients $\boldsymbol{\beta}^o = (\beta_1^o, \ldots, \beta_p^o)^\top$, as well as a CLIME-type estimator $\widehat{\boldsymbol{\Theta}}$ of $\boldsymbol{\Sigma}^{-1}$, the population version of the inverse of the negative Hessian matrix. We use the R (R Core Team (2017)) package GLMNET (Friedman, Hastie and Tibshirani (2010); Simon et al. (2011)) to compute $\widehat{\boldsymbol{\beta}}$, and adapt the CLIME (Cai, Liu and Luo (2012)) and FLARE (Li et al. (2014)) packages to obtain $\widehat{\boldsymbol{\Theta}}$. The CLIME package is more accurate, but is slow to compute for high-dimensional data; the FLARE algorithm computes only an approximate solution, but is faster. For simplicity, we refer to the modified CLIME and FLARE algorithms as the CLIME and FLARE packages, respectively. We also conducted analyses based on unmodified CLIME and FLARE (with `sym = 'or'`) packages; the differences were negligible.

4.1.2. Tuning parameters

Our theoretical results provide conditions on the tuning parameters λ and λ_n, under which our confidence intervals are asymptotically valid. However, in practice, the unknown population quantities and the unspecified constants mean that these conditions do not provide a practical algorithm for choosing these tuning parameters. Therefore, to choose λ, we use the default 10-fold cross-validation algorithm implemented in the GLMNET package, with a grid of 100 different tuning parameters, equally spaced on the log scale. When using the CLIME and FLARE packages to compute $\widehat{\boldsymbol{\Theta}}$, the default 10-fold cross-validation algorithms were used to compute λ_n, with $\mathrm{tr}\big(\mathrm{diag}\big((\widehat{\boldsymbol{\Sigma}}\widehat{\boldsymbol{\Theta}} - \boldsymbol{I})^2\big)\big)$ as the cross-validation criterion.

4.1.3. Covariates

Assumption **(A1)**(i) asks that the covariate process $\boldsymbol{\mathcal{Z}}$ be bounded. However, in our numerical results, we generate the covariate processes from a multivariate Gaussian distribution, owing to the convenience of generating different correlation structures. A simulation setting based on uniformly distributed covariates can be found in the Supplementary Material. We also focus on time-independent covariates, for simplicity.

Note that even if $\boldsymbol{Z} = (Z_1, \ldots, Z_p)^\top$ has the identity covariance matrix, this does not necessarily mean that $\boldsymbol{\Sigma} = (\Sigma_{ij})$ is the identity matrix. We can illustrate this for $\boldsymbol{Z} \sim \mathcal{N}_p(\mathbf{0}, \boldsymbol{\Sigma}^Z)$, as follows: suppose that $(\boldsymbol{\Sigma}^Z)_{ij} = 0$ whenever $\beta_i^o \neq 0$ and $\beta_j^o = 0$. Then,

- for any i, j with $\beta_i^o \neq 0$ and $\beta_j^o = 0$, we have $\Sigma_{ij} = 0$;
- for any i, j with $\beta_i^o = 0$ and $\beta_j^o = 0$, we have
$$\Sigma_{ij} = \mathbb{E}(Z_i Z_j)\mathbb{E}\int_0^{t_+} Y(s) \exp\left(\sum_{l:\beta_l^o \neq 0} \beta_l^o Z_l\right) \lambda_0(s)\, ds;$$
- for any i, j with $\beta_i^o \neq 0$ and $\beta_j^o = 0$, we have
$$\Sigma_{ij} = \mathbb{E}\int_0^{t_+} c_i(s) c_j(s) Y(s) \exp\left(\sum_{l:\beta_l^o \neq 0} \beta_l^o Z_l\right) \lambda_0(s)\, ds,$$
where
$$c_i(s) := Z_i - \frac{\mathbb{E}\Big\{Z_i Y(s) \exp\Big(\sum_{l:\beta_l^o \neq 0} \beta_l^o Z_l\Big)\Big\}}{\mathbb{E}\Big\{Y(s) \exp\Big(\sum_{l:\beta_l^o \neq 0} \beta_l^o Z_l\Big)\Big\}}.$$

In order to satisfy the sparse precision matrix conditions, we consider the following two choices of $\boldsymbol{\Sigma}^Z$ in our simulations in Section 4.2.

a. $\boldsymbol{\Sigma}_a^Z = \boldsymbol{I}$;

b. $\boldsymbol{\Sigma}_b^Z = (\Sigma_b^Z)_{ij}$, with
$$(\Sigma_b^Z)_{ij} = \begin{cases} 1, & \text{if } i = j, \\ 0.5, & \text{if } i \neq j,\ \beta_i^o \neq 0, \beta_j^o \neq 0, \\ 0, & \text{if } i \neq j, \beta_i^o \beta_j^o = 0, |\beta_i^o| + |\beta_j^o| > 0, \\ 0.5^{|i-j|}, & \text{if } i \neq j, \beta_i^o = 0, \beta_j^o = 0. \end{cases}$$

4.1.4. A simple preliminary example

To illustrate several of the features that arise in more complicated settings, we consider the following two scenarios: let $n = 1{,}000$; $p = 10$; $\boldsymbol{Z} \sim \mathcal{N}_p(\mathbf{0}, \boldsymbol{I})$; $\beta_1^o = \cdots = \beta_d^o = 1$, and $\beta_{d+1}^o = \cdots = \beta_p^o = 0$, for $d = 1, 3$; $\lambda_0(t) = 1$, for all $t > 0$; and $U_i = 3$ when $d_o = 1$, and $U_i = 5$ when $d_o = 3$. Given these settings, the average censoring rate is around 15%. In the top-left blocks of Tables 1 and 2, we report the average initial estimator error $\hat{\beta}_j - \beta_j^o$ for each index $j = 1, \ldots, p$, the average debiased estimator error $\hat{b}_j - \beta_j^o$, the average empirical coverage (EC) of the 95% confidence intervals, their average widths, and the average p-values, based on 400 repetitions. Standard errors for all quantities are given in parentheses.

Here, the results are quite encouraging: the biases of the estimates $\hat{\beta}_j$ of the signal variables are corrected substantially by the debiased estimator $\hat{b}_j$, the coverage probabilities are satisfactory (certainly in the $d_o = 1$ case), and the p-values for the noise variables appear to be approximately uniformly distributed (note that, under uniformity, the standard errors should be close to $1/(400 \times 12)^{1/2} \approx 0.014$). Of course, this is a setting in which the usual inference for the MPLE is also valid, as illustrated in the bottom-right blocks of Tables 1 and 2 (for ease of exposition, the MPLE estimators are collected in the $\hat{b}_j - \beta_j^o$ columns). The MPLE was computed using the package SURVIVAL (Therneau (2015)).

Closer inspection, however, reveals that the situation is not perhaps as ideal as it first seemed. First, although the bias correction works very well for the noise variables, it slightly under-corrects for the signal variables. Second, the widths of the confidence intervals are slightly smaller than those for the MPLE, which is an efficient estimator. These issues both arise from our choice of precision matrix estimator $\widehat{\boldsymbol{\Theta}}$, which aims to provide a good approximation to $\boldsymbol{\Sigma}^{-1}$ in different matrix norms. To attempt to address this, we widened the intervals by replacing the diagonal entries of $\widehat{\boldsymbol{\Theta}}$ in (3.1) with the diagonal entries of $\widetilde{\boldsymbol{\Theta}}$, where $\widetilde{\boldsymbol{\Theta}} = (\widetilde{\Theta}_{ij}) \in \mathbb{R}^{p \times p}$ is given by

$$\widetilde{\Theta}_{ij} = \begin{cases} \widehat{\Theta}_{ij} & \text{if } i \neq j; \\ \max\left\{\frac{1}{\widehat{\mathcal{V}}(\widehat{\boldsymbol{\beta}})_{jj}}, \widehat{\Theta}_{jj}\right\} & \text{if } i = j. \end{cases} \tag{4.1}$$

The rationale behind our definition of $\widetilde{\boldsymbol{\Theta}}$ is that, in an extreme case, when $\widehat{\mathcal{V}}(\widehat{\boldsymbol{\beta}})$ is a diagonal matrix, $\widehat{\boldsymbol{\Theta}}$ is still a biased estimator of $\boldsymbol{\Sigma}^{-1}$. Because our precision matrix estimators are also potentially sensitive to the choice of tuning parameter, and the default choice tends to over-penalize, we consider alternative options to the 10-fold cross-validation choice λ_{CV} in the other blocks of Tables 1 and 2:

(1) Top-right: $\widehat{\boldsymbol{\Theta}}, 0.1\lambda_{\mathrm{CV}}$: confidence interval constructed based on (3.1), with $0.1\lambda_{\mathrm{CV}}$ used in $\widehat{\boldsymbol{\Theta}}$, which is provided by the CLIME package;

(2) Middle-left: $\widetilde{\boldsymbol{\Theta}}$: confidence interval replaces $\widehat{\boldsymbol{\Theta}}$ in (3.1) with $\widetilde{\boldsymbol{\Theta}}$, computed using (4.1) with λ_{CV} in the CLIME package;

(3) Middle-right: $\widehat{\boldsymbol{\Theta}}$, FLARE: confidence interval based on (3.1), and $\widehat{\boldsymbol{\Theta}}$ is computed using the FLARE package;

(4) Bottom-left: Merge: confidence interval constructed based on (3.1), the tuning parameter for the sparse precision matrix is provided by the FLARE package using cross-validation, and $\widehat{\boldsymbol{\Theta}}$ is optimized by the CLIME package using the aforementioned tuning parameter.

Comparing the columns of $\hat{\beta}_j - \beta_j^o$ and $\hat{b}_j - \beta_j^o$, we can see that our proposed methods indeed correct the bias due to the shrinkage introduced by the Lasso estimators. However, the biases for the signal variables are not fully corrected, and the signs of the errors all tend to be under-corrected, except for the $\widehat{\boldsymbol{\Theta}}, 0.1\lambda_{\text{CV}}$ blocks. A comparison of the $\widehat{\boldsymbol{\Theta}}, \lambda_{\text{CV}}$ and $\widehat{\boldsymbol{\Theta}}, 0.1\lambda_{\text{CV}}$ blocks show that the tuning parameter chosen using 10-fold cross-validation still over-penalizes the sparse precision matrix estimation, leading to an under-correction of $\widehat{\boldsymbol{b}}$. From the EC and Width columns in the $\widehat{\boldsymbol{\Theta}}, \lambda_{\text{CV}}$ and $\widetilde{\boldsymbol{\Theta}}$ blocks, we can see that in some cases, using $\widetilde{\boldsymbol{\Theta}}$ indeed helps to improve the coverages (naturally, the confidence intervals are a little wider). We can also see that the FLARE package does not produce identical solutions to those of the CLIME package, even in this relatively simple context. Note that the $\widehat{\boldsymbol{\Theta}}$, FLARE, and Merge blocks have the same initial estimators, the same tuning parameter grids for $\widehat{\boldsymbol{\Theta}}$, and the same cross-validation algorithms. Further investigation in the case $d_o = 1$ reveals that the FLARE package tends to choose slightly larger tuning parameters, which explains the better centering and coverage of the CLIME confidence intervals; see Table 3.

4.2. Further simulated examples

In order to provide a deeper understanding of our proposed method, we consider the following 16 simulation settings, where CT is the censoring time, and CR is the censoring rate:

(1) $n = 1{,}000$; $p = 10$; $\beta_j^o = 1$, $j = 1, 2, 3$; $\beta_j^o = 0$, $j = 4, \ldots, 10$; $\boldsymbol{Z} \sim \mathcal{N}(0, \boldsymbol{\Sigma}_a^Z)$; CT $= 5$; and CR $\approx 15\%$;

(2) $n = 1{,}000$; $p = 10$; $\beta_j^o = 1$, $j = 1, 2, 3$; $\beta_j^o = 0$, $j = 4, \ldots, 10$; $\boldsymbol{Z} \sim \mathcal{N}(0, \boldsymbol{\Sigma}_a^Z)$; CT $= 2$; and CR $\approx 30\%$;

(3) $n = 1{,}000$; $p = 10$; $(\beta_1^o, \beta_2^o, \beta_3^o) = (1.2, 1, 0.8)$; $\beta_j^o = 0$, $j = 4, \ldots, 10$; $\boldsymbol{Z} \sim \mathcal{N}(0, \boldsymbol{\Sigma}_a^Z)$; CT $= 5$; and CR $\approx 15\%$;

Table 1. Simple preliminary example, $d_o = 1$.

β_j^o	$\hat{\beta}_j - \beta_j^o$	$\hat{b}_j - \beta_j^o$	EC	Width	p-value	$\hat{b}_j - \beta_j^o$	EC	Width	p-value
			$\widehat{\mathbf{\Theta}}$, λ_{CV}				$\widehat{\mathbf{\Theta}}$, $0.1\lambda_{\text{CV}}$		
1	-0.051(0.002)	-0.003(0.002)	0.937(0.012)	0.157(0.000)	0.000(0.000)	0.000(0.002)	0.940(0.011)	0.159(0.000)	0.000(0.000)
0	0.000(0.001)	0.000(0.001)	0.966(0.009)	0.123(0.000)	0.539(0.014)	0.000(0.001)	0.961(0.009)	0.125(0.000)	0.532(0.014)
0	0.000(0.001)	0.001(0.001)	0.952(0.010)	0.123(0.000)	0.520(0.014)	0.000(0.001)	0.952(0.010)	0.125(0.000)	0.510(0.014)
0	0.001(0.001)	0.001(0.001)	0.955(0.010)	0.124(0.000)	0.522(0.014)	0.001(0.002)	0.952(0.010)	0.125(0.000)	0.518(0.014)
0	-0.001(0.001)	-0.001(0.001)	0.943(0.011)	0.123(0.000)	0.532(0.014)	-0.002(0.002)	0.943(0.011)	0.125(0.000)	0.528(0.014)
0	0.001(0.001)	0.001(0.001)	0.943(0.011)	0.123(0.000)	0.514(0.014)	0.000(0.002)	0.947(0.011)	0.125(0.000)	0.509(0.014)
0	-0.002(0.001)	-0.003(0.001)	0.955(0.010)	0.123(0.000)	0.539(0.014)	-0.003(0.001)	0.950(0.010)	0.125(0.000)	0.529(0.014)
0	0.000(0.001)	-0.001(0.001)	0.934(0.012)	0.123(0.000)	0.532(0.014)	-0.001(0.002)	0.933(0.012)	0.125(0.000)	0.517(0.014)
0	0.000(0.001)	-0.001(0.002)	0.930(0.012)	0.123(0.000)	0.523(0.014)	-0.001(0.002)	0.929(0.012)	0.125(0.000)	0.513(0.014)
0	0.000(0.001)	-0.001(0.001)	0.957(0.010)	0.123(0.000)	0.520(0.014)	-0.001(0.002)	0.959(0.010)	0.125(0.000)	0.514(0.014)
			$\widetilde{\mathbf{\Theta}}$				$\widehat{\mathbf{\Theta}}$, FLARE		
1	-0.051(0.002)	-0.003(0.002)	0.961(0.009)	0.171(0.000)	0.000(0.000)	-0.007(0.002)	0.925(0.013)	0.153(0.000)	0.000(0.000)
0	0.000(0.001)	0.000(0.001)	0.972(0.008)	0.134(0.000)	0.564(0.013)	0.000(0.001)	0.965(0.009)	0.121(0.000)	0.544(0.014)
0	0.000(0.001)	0.000(0.001)	0.975(0.008)	0.134(0.000)	0.547(0.013)	0.001(0.001)	0.953(0.010)	0.121(0.000)	0.529(0.014)
0	0.001(0.001)	0.001(0.001)	0.968(0.008)	0.134(0.000)	0.548(0.014)	0.001(0.001)	0.948(0.011)	0.121(0.000)	0.526(0.014)
0	-0.001(0.001)	-0.002(0.001)	0.970(0.008)	0.134(0.000)	0.559(0.014)	-0.002(0.001)	0.948(0.011)	0.121(0.000)	0.539(0.014)
0	0.001(0.001)	0.001(0.001)	0.959(0.010)	0.134(0.000)	0.543(0.014)	0.001(0.001)	0.948(0.011)	0.121(0.000)	0.522(0.014)
0	-0.002(0.001)	-0.003(0.001)	0.968(0.008)	0.134(0.000)	0.560(0.014)	-0.003(0.001)	0.955(0.010)	0.121(0.000)	0.541(0.014)
0	0.000(0.001)	-0.001(0.001)	0.968(0.008)	0.134(0.000)	0.551(0.013)	-0.001(0.001)	0.937(0.012)	0.121(0.000)	0.534(0.014)
0	0.000(0.001)	-0.001(0.002)	0.952(0.010)	0.134(0.000)	0.544(0.014)	-0.001(0.002)	0.930(0.012)	0.121(0.000)	0.524(0.015)
0	0.000(0.001)	-0.001(0.001)	0.968(0.008)	0.134(0.000)	0.547(0.014)	-0.001(0.001)	0.958(0.010)	0.121(0.000)	0.527(0.014)
			Merge				MPLE		
1	-0.051(0.002)	-0.004(0.002)	0.938(0.012)	0.157(0.000)	0.000(0.000)	0.007(0.002)	0.950(0.011)	0.173(0.000)	0.000(0.000)
0	0.000(0.001)	0.000(0.001)	0.964(0.009)	0.123(0.000)	0.541(0.014)	0.000(0.002)	0.967(0.009)	0.136(0.000)	0.519(0.014)
0	0.000(0.001)	0.001(0.001)	0.955(0.010)	0.123(0.000)	0.525(0.014)	0.001(0.002)	0.953(0.010)	0.135(0.000)	0.497(0.014)
0	0.001(0.001)	0.001(0.002)	0.950(0.011)	0.123(0.000)	0.522(0.014)	0.001(0.002)	0.957(0.010)	0.136(0.000)	0.497(0.014)
0	-0.001(0.001)	-0.002(0.001)	0.948(0.011)	0.123(0.000)	0.536(0.014)	-0.002(0.002)	0.950(0.011)	0.136(0.000)	0.510(0.014)
0	0.001(0.001)	0.000(0.001)	0.948(0.011)	0.123(0.000)	0.518(0.014)	0.000(0.002)	0.950(0.011)	0.135(0.000)	0.493(0.014)
0	-0.002(0.001)	-0.003(0.001)	0.953(0.010)	0.123(0.000)	0.539(0.014)	-0.003(0.002)	0.962(0.009)	0.135(0.000)	0.516(0.014)
0	0.000(0.001)	-0.001(0.001)	0.941(0.012)	0.123(0.000)	0.529(0.014)	0.000(0.002)	0.945(0.011)	0.136(0.000)	0.504(0.014)
0	0.000(0.001)	-0.001(0.002)	0.927(0.013)	0.123(0.000)	0.518(0.015)	-0.001(0.002)	0.924(0.013)	0.135(0.000)	0.494(0.015)
0	0.000(0.001)	-0.001(0.001)	0.957(0.010)	0.123(0.000)	0.526(0.014)	-0.001(0.002)	0.960(0.010)	0.135(0.000)	0.501(0.014)

Table 2. Simple preliminary example, $d_o = 3$.

β^o_j	$\hat{\beta}_j - \beta^o_j$	$\hat{b}_j - \beta^o_j$	EC	Wid	pvals	$\hat{b}_j - \beta^o_j$	EC	Width	p-value
			$\widehat{\mathbf{\Theta}}$, λ_{CV}				$\widehat{\mathbf{\Theta}}$, $0.1\lambda_{\text{CV}}$		
1	-0.040(0.002)	-0.003(0.002)	0.917(0.013)	0.153(0.000)	0.000(0.000)	0.000(0.002)	0.919(0.013)	0.157(0.000)	0.000(0.000)
1	-0.041(0.002)	-0.005(0.002)	0.932(0.012)	0.153(0.000)	0.000(0.000)	-0.001(0.002)	0.940(0.011)	0.157(0.000)	0.000(0.000)
1	-0.042(0.002)	-0.006(0.002)	0.924(0.012)	0.153(0.000)	0.000(0.000)	-0.002(0.002)	0.930(0.012)	0.157(0.000)	0.000(0.000)
0	0.000(0.001)	0.000(0.001)	0.943(0.011)	0.123(0.000)	0.505(0.013)	0.000(0.002)	0.934(0.011)	0.125(0.000)	0.499(0.013)
0	0.000(0.001)	0.000(0.001)	0.941(0.011)	0.123(0.000)	0.505(0.014)	0.000(0.002)	0.938(0.011)	0.125(0.000)	0.499(0.014)
0	0.001(0.001)	0.001(0.001)	0.930(0.012)	0.123(0.000)	0.501(0.014)	0.001(0.002)	0.928(0.012)	0.125(0.000)	0.494(0.014)
0	-0.001(0.001)	-0.002(0.001)	0.932(0.012)	0.123(0.000)	0.520(0.014)	-0.001(0.002)	0.932(0.012)	0.125(0.000)	0.513(0.014)
0	-0.002(0.001)	-0.003(0.002)	0.936(0.011)	0.123(0.000)	0.510(0.014)	-0.003(0.002)	0.928(0.012)	0.125(0.000)	0.503(0.014)
0	0.000(0.001)	0.000(0.002)	0.928(0.012)	0.123(0.000)	0.497(0.014)	0.000(0.002)	0.928(0.012)	0.125(0.000)	0.491(0.014)
0	0.000(0.001)	0.000(0.001)	0.938(0.011)	0.123(0.000)	0.506(0.014)	0.000(0.002)	0.938(0.011)	0.125(0.000)	0.500(0.014)
			$\widetilde{\mathbf{\Theta}}$				$\widehat{\mathbf{\Theta}}$, FLARE		
1	-0.040(0.002)	-0.004(0.002)	0.919(0.013)	0.154(0.000)	0.000(0.000)	-0.008(0.002)	0.899(0.015)	0.148(0.000)	0.000(0.000)
1	-0.041(0.002)	-0.005(0.002)	0.932(0.012)	0.154(0.000)	0.000(0.000)	-0.009(0.002)	0.923(0.013)	0.149(0.000)	0.000(0.000)
1	-0.042(0.002)	-0.006(0.002)	0.923(0.012)	0.154(0.000)	0.000(0.000)	-0.010(0.002)	0.891(0.015)	0.148(0.000)	0.000(0.000)
0	0.000(0.001)	0.000(0.001)	0.962(0.009)	0.135(0.000)	0.535(0.013)	-0.001(0.002)	0.944(0.011)	0.121(0.000)	0.511(0.014)
0	0.000(0.001)	0.000(0.001)	0.957(0.009)	0.135(0.000)	0.534(0.013)	-0.001(0.002)	0.940(0.012)	0.121(0.000)	0.500(0.015)
0	0.001(0.001)	0.001(0.001)	0.962(0.009)	0.135(0.000)	0.530(0.014)	0.000(0.002)	0.923(0.013)	0.121(0.000)	0.511(0.015)
0	-0.001(0.001)	-0.001(0.001)	0.953(0.010)	0.135(0.000)	0.549(0.013)	-0.002(0.002)	0.935(0.012)	0.121(0.000)	0.524(0.015)
0	-0.002(0.001)	-0.003(0.002)	0.955(0.010)	0.135(0.000)	0.537(0.014)	-0.003(0.002)	0.937(0.012)	0.121(0.000)	0.514(0.015)
0	0.000(0.001)	0.000(0.002)	0.947(0.010)	0.135(0.000)	0.526(0.014)	-0.002(0.002)	0.935(0.012)	0.121(0.000)	0.497(0.015)
0	0.000(0.001)	0.000(0.001)	0.966(0.008)	0.135(0.000)	0.535(0.014)	0.001(0.002)	0.935(0.012)	0.121(0.000)	0.511(0.015)
			Merge				MPLE		
1	-0.040(0.002)	-0.004(0.002)	0.910(0.014)	0.153(0.000)	0.000(0.000)	0.006(0.002)	0.940(0.012)	0.172(0.000)	0.000(0.000)
1	-0.041(0.002)	-0.006(0.002)	0.928(0.013)	0.154(0.000)	0.000(0.000)	0.005(0.002)	0.958(0.010)	0.172(0.000)	0.000(0.000)
1	-0.042(0.002)	-0.006(0.002)	0.918(0.014)	0.154(0.000)	0.000(0.000)	0.005(0.002)	0.942(0.012)	0.171(0.000)	0.000(0.000)
0	0.000(0.001)	-0.002(0.002)	0.952(0.011)	0.123(0.000)	0.510(0.015)	-0.002(0.002)	0.955(0.010)	0.137(0.000)	0.495(0.014)
0	0.000(0.001)	-0.001(0.002)	0.942(0.012)	0.123(0.000)	0.497(0.015)	-0.001(0.002)	0.948(0.011)	0.136(0.000)	0.480(0.014)
0	0.001(0.001)	0.000(0.002)	0.925(0.013)	0.123(0.000)	0.506(0.015)	0.000(0.002)	0.945(0.011)	0.136(0.000)	0.493(0.015)
0	-0.001(0.001)	-0.002(0.002)	0.935(0.012)	0.123(0.000)	0.524(0.015)	-0.002(0.002)	0.940(0.012)	0.137(0.000)	0.511(0.015)
0	-0.002(0.001)	-0.003(0.002)	0.942(0.012)	0.123(0.000)	0.512(0.015)	-0.003(0.002)	0.950(0.011)	0.137(0.000)	0.500(0.015)
0	0.000(0.001)	-0.002(0.002)	0.935(0.012)	0.123(0.000)	0.499(0.015)	-0.002(0.002)	0.932(0.013)	0.136(0.000)	0.486(0.014)
0	0.000(0.001)	0.001(0.002)	0.932(0.013)	0.123(0.000)	0.509(0.015)	0.001(0.002)	0.948(0.011)	0.136(0.000)	0.493(0.014)

Table 3. Selected tuning parameter comparisons.

Packages	Mean	Median
CLIME	0.022	0.015
FLARE	0.026	0.025

(4) $n = 1{,}000$; $p = 10$; $(\beta_1^o, \beta_2^o, \beta_3^o) = (1.2, 1, 0.8)$; $\beta_j^o = 0$, $j = 4, \ldots, 10$; $\boldsymbol{Z} \sim \mathcal{N}(0, \boldsymbol{\Sigma}_a^Z)$; CT $= 2$; and CR $\approx 30\%$;

$(5-8)$ As for (1)–(4), but with $\boldsymbol{Z} \sim \mathcal{N}(0, \boldsymbol{\Sigma}_b^Z)$; and CT $= 10, 2.5, 10, 2.5$;

$(9-10)$ As for (1)–(2), but with $p = 300$; $\beta_j^o = 1$, $j = 1, \ldots, 6$; $\beta_j^o = 0$, $j = 7, \ldots, 300$; and CT $= 9, 2.5$;

$(11-12)$ As for (3)–(4), but $p = 300$; $(\beta_1^o, \ldots, \beta_6^o) = (0.5, 0.7, 0.9, 1.1, 1.3, 1.5)$; $\beta_j^o = 0$, $j = 7, \ldots, 300$; and CT $= 10, 3$;

$(13-16)$ As for (9)–(12), but with $\boldsymbol{Z} \sim \mathcal{N}(0, \boldsymbol{\Sigma}_b^Z)$; and CT $= 100, 7, 100, 7$.

In Table 4, we report the averaged results for the signal and noise variables separately, with $\widehat{\boldsymbol{\Theta}}$ and $\widetilde{\boldsymbol{\Theta}}$ chosen using 10-fold cross-validation. The simulations were run on a cluster, each node of which is an Intel(R) Xeon(R) CPU E5-2670 0@2.60GHz machine, with 16 CPUs. One repetition of an $(n, p) = (1{,}000,\ 300)$ setting, 32 minutes, on average. This is why we limit our simulations to $p = 300$, even though our theory can handle $p \gg n$ settings.

It is reassuring to see that, in all cases, the confidence intervals for the noise variables have close to nominal coverage, and the p-values for the noise variables appear to be uniformly distributed. Thus, our methodology is providing a reliable method for identifying signal variables, with uncertainty quantification. On the other hand, although the confidence intervals for the signal variables have good coverage when $p = 10$ (particularly with $\widetilde{\boldsymbol{\Theta}}$), it is much more challenging to ensure adequate coverage for the signal variables in the $p = 300$ case. Apparently, the sample size needs to be very large for the asymptotics to have an effect, to the extent that we can think, for instance, that **(A4)(c)** is satisfied. The greater width of the intervals when using $\widetilde{\boldsymbol{\Theta}}$ yields improved coverage for the signal variables, but leads to some over-coverage for the noise variables.

One approach in high-dimensional settings, then, is to use our methodology as a screening method to identify signal variables (with false discovery guarantees). Then use the standard MPLE inference to obtain confidence intervals for the signal variables at a second stage. Further discussion can be found in the Supplementary Material.

Table 4. Simulation settings (1)–(16). S and N rows show the results for the signal and noise variables respectively.

				$\widehat{\boldsymbol{\Theta}}$			$\widetilde{\boldsymbol{\Theta}}$	
	$\hat{b}_j - \beta_j^o$	$\hat{\beta}_j - \beta_j^o$	EC	Width	p-values	EC	Width	p-values
(1) S	-0.003(0.001)	-0.038(0.001)	0.933(0.008)	0.153(0.000)	0.000(0.000)	0.933(0.008)	0.154(0.000)	0.000(0.000)
(1) N	-0.001(0.001)	-0.001(0.001)	0.929(0.008)	0.123(0.000)	0.491(0.010)	0.956(0.006)	0.135(0.000)	0.521(0.009)
(2) S	-0.009(0.001)	-0.039(0.001)	0.907(0.009)	0.150(0.000)	0.000(0.000)	0.940(0.008)	0.165(0.000)	0.000(0.000)
(2) N	-0.002(0.001)	-0.001(0.001)	0.921(0.008)	0.123(0.000)	0.503(0.010)	0.957(0.006)	0.147(0.000)	0.556(0.009)
(3) S	-0.003(0.001)	-0.038(0.001)	0.940(0.007)	0.154(0.000)	0.000(0.000)	0.940(0.007)	0.155(0.000)	0.000(0.000)
(3) N	-0.002(0.001)	-0.001(0.001)	0.933(0.008)	0.123(0.000)	0.497(0.010)	0.951(0.007)	0.135(0.000)	0.527(0.009)
(4) S	-0.009(0.001)	-0.039(0.001)	0.883(0.010)	0.150(0.000)	0.000(0.000)	0.913(0.009)	0.166(0.000)	0.000(0.000)
(4) N	-0.002(0.001)	-0.001(0.001)	0.914(0.009)	0.123(0.000)	0.510(0.010)	0.957(0.006)	0.147(0.000)	0.565(0.010)
(5) S	-0.004(0.002)	-0.036(0.002)	0.937(0.008)	0.177(0.000)	0.000(0.000)	0.953(0.006)	0.194(0.000)	0.000(0.000)
(5) N	0.000(0.001)	0.000(0.001)	0.933(0.008)	0.152(0.000)	0.496(0.009)	0.937(0.008)	0.152(0.000)	0.496(0.009)
(6) S	-0.008(0.002)	-0.035(0.002)	0.887(0.010)	0.174(0.000)	0.000(0.000)	0.950(0.007)	0.211(0.000)	0.000(0.000)
(6) N	0.000(0.001)	0.000(0.001)	0.913(0.009)	0.151(0.000)	0.495(0.01)	0.921(0.008)	0.154(0.000)	0.508(0.010)
(7) S	-0.003(0.002)	-0.036(0.002)	0.930(0.008)	0.177(0.000)	0.000(0.000)	0.940(0.007)	0.194(0.000)	0.000(0.000)
(7) N	0.000(0.001)	0.000(0.001)	0.936(0.008)	0.152(0.000)	0.496(0.009)	0.936(0.008)	0.152(0.000)	0.494(0.009)
(8) S	-0.007(0.002)	-0.033(0.002)	0.903(0.009)	0.175(0.000)	0.000(0.000)	0.940(0.007)	0.212(0.000)	0.000(0.000)
(8) N	-0.001(0.001)	0.000(0.001)	0.917(0.009)	0.151(0.000)	0.496(0.010)	0.920(0.009)	0.154(0.000)	0.504(0.010)
(9) S	-0.169(0.005)	-0.264(0.005)	0.290(0.026)	0.242(0.001)	0.000(0.000)	0.322(0.027)	0.268(0.001)	0.000(0.000)
(9) N	0.000(0.002)	0.000(0.001)	0.984(0.006)	0.218(0.001)	0.625(0.014)	0.992(0.004)	0.251(0.001)	0.663(0.014)
(10) S	-0.078(0.002)	-0.155(0.002)	0.415(0.016)	0.138(0.000)	0.000(0.000)	0.495(0.016)	0.159(0.000)	0.000(0.000)
(10) N	0.000(0.001)	0.000(0.000)	0.976(0.004)	0.120(0.000)	0.609(0.008)	0.992(0.002)	0.149(0.000)	0.668(0.007)
(11) S	-0.063(0.002)	-0.150(0.002)	0.553(0.016)	0.143(0.000)	0.000(0.000)	0.612(0.015)	0.149(0.000)	0.000(0.000)
(11) N	0.000(0.001)	0.000(0.000)	0.977(0.004)	0.120(0.000)	0.586(0.008)	0.988(0.003)	0.136(0.000)	0.621(0.008)
(12) S	-0.081(0.002)	-0.154(0.002)	0.413(0.016)	0.141(0.000)	0.000(0.000)	0.485(0.016)	0.158(0.000)	0.000(0.000)
(12) N	0.000(0.001)	0.000(0.000)	0.976(0.005)	0.120(0.000)	0.608(0.008)	0.991(0.002)	0.147(0.000)	0.665(0.007)
(13) S	-0.034(0.002)	-0.122(0.002)	0.848(0.011)	0.178(0.000)	0.000(0.000)	0.895(0.010)	0.198(0.000)	0.000(0.000)
(13) N	0.000(0.001)	0.000(0.000)	0.985(0.003)	0.150(0.000)	0.593(0.008)	0.985(0.003)	0.150(0.000)	0.593(0.008)
(14) S	-0.052(0.002)	-0.126(0.002)	0.745(0.014)	0.177(0.000)	0.000(0.000)	0.852(0.011)	0.219(0.000)	0.000(0.000)
(14) N	0.000(0.001)	0.000(0.000)	0.988(0.003)	0.149(0.000)	0.624(0.008)	0.989(0.003)	0.151(0.000)	0.628(0.008)
(15) S	-0.028(0.002)	-0.122(0.002)	0.863(0.011)	0.180(0.000)	0.000(0.000)	0.897(0.009)	0.198(0.000)	0.000(0.000)
(15) N	0.000(0.001)	0.000(0.000)	0.985(0.003)	0.151(0.000)	0.593(0.008)	0.985(0.003)	0.151(0.000)	0.593(0.008)
(16) S	-0.046(0.002)	-0.126(0.002)	0.772(0.013)	0.178(0.000)	0.000(0.000)	0.845(0.011)	0.219(0.000)	0.000(0.000)
(16) N	0.000(0.001)	0.000(0.000)	0.987(0.003)	0.149(0.000)	0.624(0.008)	0.988(0.003)	0.151(0.000)	0.628(0.008)

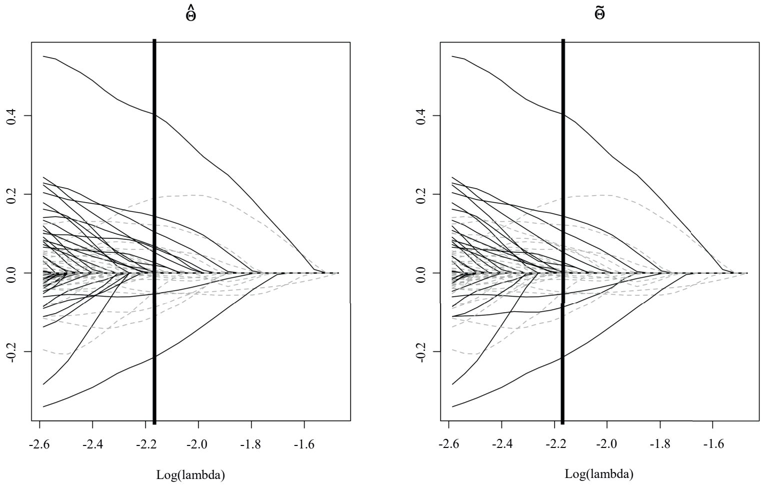

Figure 1. Solution paths

4.3. Real-data analysis

In this section, we apply our method to a diffuse large B-cell lymphoma (DLBCL) data set, comprising survival times of 240 DLBCL patients and gene expression data for 7,399 genes (Rosenwald et al. (2002)). To reduce the dimensionality, we computed the Lasso path, noting that the cross-validation algorithm picked the 16th largest value of λ on our grid of size 100. In total, 84 variables were selected at some stage in the first 25 λ values. Thus, we retain these 84 variables in our subsequent analysis.

In Figure 1, we plot the glmnet solution paths, with solid and black paths denoting variables deemed to be significant, according to our methodology, and dashed and grey paths denoting variables deemed nonsignificant. The left and right panels correspond to the use of $\widehat{\mathbf{\Theta}}$ and $\widetilde{\mathbf{\Theta}}$, respectively, and the vertical lines indicate the regularization parameter values chosen using cross-validation. The only difference between the inferences drawn from the two precision matrix estimates is the confidence interval widths; thus, the variables selected when using $\widehat{\mathbf{\Theta}}$ are a proper subset of those obtained using $\widetilde{\mathbf{\Theta}}$.

Some variables enter the model fairly early along the path, but appear not to be statistically significant, according to our methods. These variables are often omitted from the model at a later stage along the path, as other variables enter. This observation is demonstrated in Table 5, which presents the median life spans of the corresponding variables, where a life span is defined as the proportion of

Table 5. Median life spans for variables deemed significant and nonsignificant.

	$\widehat{\mathbf{\Theta}}$			$\widetilde{\mathbf{\Theta}}$	
No.	Significant	Insignificant	No.	Significant	Insignificant
41	0.78	0.26	32	0.78	0.35

the locations on the solution paths for which a certain variable is chosen.

Supplementary Material

The online Supplementary Material contains auxiliary results, remaining proofs. and further numerical results.

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