Estimation and Inference for High Dimensional Generalized Linear Models: A Splitting and Smoothing Approach

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Abstract

For a better understanding of the molecular causes of lung cancer, the Boston Lung Cancer Study (BLCS) has generated comprehensive molecular data from both lung cancer cases and controls. It has been challenging to model such high dimensional data with non-linear outcomes, and to give accurate uncertainty measures of the estimators. To properly infer cancer risks at the molecular level, we propose a novel inference framework for generalized linear models and use it to estimate the high dimensional SNP effects and their potential interactions with smoking. We use multi-sample splitting and smoothing to reduce the high-dimensional problem to low-dimensional maximum likelihood estimations. Unlike other methods, the proposed estimator does not involve penalization/regularization and, thus, avoids its drawbacks in making inferences. Our estimator is asymptotically unbiased and normal, and gives confidence intervals with proper coverage. To facilitate hypothesis testing and drawing inferences on predetermined contrasts, our method can be applied to infer any fixed low-dimensional parameters in the presence of high dimensional nuisance parameters. To demonstrate the advantages of the method, we conduct extensive simulations, and analyze the BLCS SNP data and obtain some biologically meaningful results.

Keywords: High Dimensional GLMs; High Dimensional Inference; Hypothesis Testing; P-values; SSGLM.

1. Introduction

Lung cancer is the leading cause of cancer-related deaths in the United States, among both men and women (US Department of Health and Human Services, 2004; Parkin et al., 2005). Understanding the molecular mechanisms of lung cancer is a focus of current basic and translational research. The Boston Lung Cancer Study (BLCS) (Christiani, 2017) is a cancer epidemiology cohort of over 11,000 lung cancer cases enrolled at Massachusetts General Hospital and the Dana-Farber Cancer Institute from 1992 to present. In addition, controls are recruited at the hospital from healthy friends and non-blood-related family members (usually spouses) of the patients. This is the first and most comprehensive lung cancer survivor cohort with a long follow-up period, which has been growing with more...
patients recruited every year. For both groups, large scale data of various types, including gene expression, methylation, SNP, and CT imaging, have been measured and recorded. The rich data generated from the BLCS cohort allow powerful translational research and exploration of potential predictors for lung cancer.

Using a target gene approach, this paper analyzes high dimensional SNP data from 708 lung cancer patients and 751 controls, with more than 6,800 SNPs from 15 cancer related genes, along with important demographic variables, such as age, gender, race, education level, and smoking status. Our goal is to model the binary lung cancer indicator as the outcome and to estimate and test the effects of the potential predictors that could explain the differences between the cases and controls. Since smoking plays a vital role in lung cancer, we are especially interested in the interaction terms between SNPs and the smoking status in addition to their main effects.

It has been challenging to construct confidence intervals, perform statistical tests and assign uncertainty measures in sparse high dimensional models (Dezeure et al., 2015). The high dimensionality impedes accurate estimation of all the potential predictors, and evaluation of the uncertainty of the estimators. The high dimensionality considered in this paper includes but is not limited to the usual case of “p > n,” such as n = 500 samples with p = 1000 covariates. Even in a “p < n” setting such as n = 1000 samples with p = 500 covariates, direct applications of the GLM framework would lead to ambiguous and meaningless estimations and inferences. Alternatively, penalized regressions have been widely used to deal with high dimensionality (Friedman et al., 2010; Van de Geer, 2008; Candès and Tao, 2007; Lv and Fan, 2009; Huang et al., 2008; Zou and Hastie, 2005). The estimators from penalized regressions are shrunk and thus “irregular” as their asymptotics become difficult to track. There has been considerable success in drawing inferences based on penalized regressions, mostly for linear models (Zhang and Zhang, 2014; Javanmard and Montanari, 2014; Bühlmann et al., 2014; Dezeure et al., 2015). Meanwhile, there are limited works in the GLM settings. In sparse high dimensional GLMs, Bühlmann et al. (2014) offered the generalization of de-sparsified LASSO, while Ning and Liu (2017) proposed the decorrelated score tests for penalized M-estimators. In the presence of high dimensional controls, Belloni et al. (2014, 2016) proposed a post double selection procedure for estimation and inference; Lee et al. (2016) characterized the distribution of a post-LASSO-selection estimator conditioned on the selected variables, but only for linear regressions. The performance of most of these methods depends heavily on multiple tuning parameters, and their optimal choices are often not apparent in practice. As we will see in the data analysis, the application of existing works is also limited to the scale of data due to computation burdens.

We propose a novel approach of simultaneous estimation and inference for high dimensional generalized linear models that aims to resolve the aforementioned limitations. We first introduce a one-time estimator by splitting the data into two halves, using one half to select a subset of important variables as the “candidates.” On the other half, we fit a low dimensional GLM with the union of the parameter of interest (or a low dimensional subset of the coefficient vector) and the candidate set of variables (Belloni et al., 2016). The one-time estimator for the parameter of interest is then from the fitted low dimensional GLM. While the one-time estimator is unbiased and asymptotically normal under mild conditions, it is highly variable, and heavily dependents on the specific one-time selection. Therefore, we further propose the smoothed estimator by repeating the previous procedure a large
number of times and averaging the resulting estimators. The smoothed estimator is proved to possess the same desired theoretical properties with improved efficiency and practical performance. Our approach is shortened as SSGLM, where “SS” stands for “splitting and smoothing.” Thus, our idea takes advantage of the multi sample-splitting method in Meinshausen et al. (2009), and the bagging idea (Bühlmann and Yu, 2002; Friedman and Hall, 2007; Efron, 2014), and is therefore fundamentally different from penalized regressions. In this way, we reduce the high dimensional inference problem into low dimensional estimations that are free of penalization/regularization. As variable/model selection only plays an assistive role, our procedure is not sensitive to the tuning parameters, which is a major drawback of the existing methods (Bühlmann et al., 2014; Ning and Liu, 2017). Furthermore, we derive the variance estimator using the non-parametric delta method adapted to the splitting and smoothing procedure (Efron, 2014; Wager and Athey, 2017), which is free of the parametric model (GLM in this case) and achieves variance reduction from the effect of bagging (Bühlmann and Yu, 2002). Our framework also facilitates hypothesis testing or drawing inferences on predetermined contrasts in the presence of high dimensional nuisance parameters.

The rest of the paper is organized as follows. Section 2 describes the SSGLM and Section 3 introduces the theoretical properties. Section 4 describes the inferential procedure and Section 5 extends it to accommodate any subvectors of parameters of interest. Section 6 provides simulations and comparisons with the existing methods. Section 7 reports the results of the analysis of the BLCS SNP data. We conclude the paper with a brief discussion.

2. Method

2.1 Notation

We denote the observations as \((Y_i, \mathbf{x}_i)\) for \(i = 1, 2, \ldots, n\), where \(\mathbf{x}_i = (x_{i1}, x_{i2}, \ldots, x_{ip})\) is the \(1 \times p\) covariate vector and the outcome distribution belongs to a linear exponential family, which includes Normal, Bernoulli, Poisson, and other distributions,

\[
f(Y_i | \theta_i) = \exp \left\{ Y_i \theta_i - A(\theta_i) + c(Y_i) \right\},
\]

where \(\theta_i\) is the parameter relating to the mean. In this paper, we consider the canonical link with \(\theta_i = \mathbf{x}_i \beta\), where \(\mathbf{x}_i = (1, \mathbf{x}_i)\) and \(\beta = (\beta_0, \beta_1, \ldots, \beta_p)^T\) includes an intercept term. Specifically,

\[
\mathbf{E}(Y_i) = \mu_i = A'(\theta_i) = g^{-1}(\mathbf{x}_i \beta),
\]

and \(\mathbf{V}(Y_i) = A''(\theta_i) = \nu(\mu_i)\), where \(\mu_i\)'s are the mean of the responses \(Y_i\)'s and \(g\) is the link function. The collection of all \(n\) observations is denoted as \((Y, X)\), where \(Y = (Y_1, \ldots, Y_n)^T\) and \(X = (\mathbf{x}_1^T, \ldots, \mathbf{x}_n^T)^T\). In addition, we write \(X = (X_1, \ldots, X_p)\) with \(p\) column vectors and \(\mathbf{1} = (1, X)\) to include the \(1 \times n\) column vector \(\mathbf{1}\).

In the BLCS SNP data, the outcome of interest is the binary lung cancer indicator, and the covariate vector \(\mathbf{x}_i\) includes the demographic variables, the SNP variables, and the interactions between the SNPs and smoking. The parameterization of the assumed logistic regression is

\[
g(\mu_i) = \logit(\mu_i) = \log \left( \frac{\mu_i}{1 - \mu_i} \right), \quad \text{with} \quad A(\theta_i) = \log \left(1 + e^{\theta_i} \right).
\]
We write the full log-likelihood of model (1) and (2) as
\[
\ell(\beta) = \ell(\beta; Y, X) = \frac{1}{n} \sum_{i=1}^{n} \{Y_i \theta_i - A(\theta_i)\} = \frac{1}{n} \sum_{i=1}^{n} \{Y_i(\mathbf{x}_i\beta) - A(\mathbf{x}_i\beta)\} .
\]

The score and the observed information are
\[
U(\beta) = \frac{1}{n} \mathbf{X}^T \{Y - A'(\mathbf{X}\beta)\} , \quad \hat{I}(\beta) = \frac{1}{n} \mathbf{X}^T \mathbf{X},
\]
where \(V = \text{diag}\{\nu(\mu_1), \ldots, \nu(\mu_n)\}\), and whenever a univariate function such as \(A(\cdot)\) is applied to a vector, it denotes the vector of values of the function applied to each entry of the argument.

As our method involves low-dimensional estimation based on subsets of the covariates, we introduce some notation with respect to an index set \(S \subset [p] = \{1, 2, \ldots, p\}\). We write the subvectors \(\mathbf{x}_{iS} = (x_{ij})_{j \in S}\) and \(\mathbf{x}_{iS} = (1, \mathbf{x}_{iS})\), and submatrices \(X_S = (X_j)_{j \in S}\) and \(X_{\hat{S}} = (1, X_{S})\). Given a set \(S \subset [p]\) and an index \(j \in [p]\), we define \(S_{+j} = \{j\} \cup S\) and \(S_{-j} = S \setminus \{j\}\). In addition, we let \(S_{+0} = S_{-0} = S\) when concerning the intercept. Furthermore, we write \(\beta_S = (\beta_0, \beta_j)_{j \in S}\), which always includes the intercept and thus is of length \(1 + |S|\).

The working log-likelihood with respect to \((Y, X_S)\) and \(\beta_S\) is
\[
\ell_S(\beta_S) = \ell(\beta_S; Y, X_S) = \frac{1}{n} \sum_{i=1}^{n} \{Y_i(\mathbf{x}_{iS}\beta_S) - A(\mathbf{x}_{iS}\beta_S)\} .
\]

Similarly, \(U_S(\beta_S) = \frac{1}{n} \mathbf{X}_{S}^T (Y - A'(\mathbf{X}_{S}\beta_S))\); \(\hat{I}_S(\beta_S) = \frac{1}{n} \mathbf{X}_{S}^T V_S \mathbf{X}_{S}\), where \(V_S = \text{diag}\{A''(\mathbf{x}_{iS}\beta_S), \ldots, A''(\mathbf{x}_{iS}\beta_S)\}\). Now we write out the expected information with respect to \(\beta\) as \(I = \mathbf{E}_\beta (\nabla^2 \ell(\beta))\), and the sub-information \(I_S\) is the submatrix of \(I\) with rows and columns corresponding to \(S\). Note \(I_S\) can also be written as \(I_{SS}\) so that the subscripts reflect both rows and columns. The truth of \(\beta\) is denoted as \(\beta^* = (\beta^*_0, \beta^*_1, \ldots, \beta^*_p)\), \(I^* = \mathbf{E}_{\beta^*} (\nabla^2 \ell(\beta^*))\), and \(I^*_S\) is the submatrix of \(I^*\) analog to \(I_S\). Lastly, we define the partial information for \(j \in [p]\) and given \(S \subset [p]\) as
\[
I_{jiS} = I_{jj} - I_{jS-j} I^{-1}_{S-jS-j} I_{S-jj}, \quad (3)
\]
where \(I_{jj}, I_{jS-j}, \) and \(I_{S-jS-j}\) are the entry, subvector, and submatrix of \(I\) with respect to the respective subscripts.

### 2.2 Proposed SSGLM estimator

Assume the data \((Y, X)\) follows the generalized linear model (1) and (2) with the true parameter vector \(\beta = \beta^*\). We first define the one-time SSGLM estimator \(\tilde{\beta} = (\tilde{\beta}_j)_{j=0,1,\ldots,p}\) based on a single data split (Algorithm 1). We split the data into two halves \(D_1\) and \(D_2\), with sample sizes \(|D_1| = n_1, |D_2| = n_2, n_1 + n_2 = n\). For example, \(n_1 = n_2 = n/2\). Next on \(D_2\), we select a subset of important covariates \(S \subset [p], s = |S| < n_1 - 1\) via a selection scheme \(S_\lambda\), where \(\lambda\) is the regularization parameter. The selected set \(S\) is used as the candidate set of covariates for performing low dimensional estimation on \(D_1\). On \(D_1 = (Y_1, X_1)\), and
for each $j \in [p]$, we fit a low dimensional GLM by regressing $Y^1$ on $X_{S+j}^1$, where the set $S_{+j} = \{j\} \cup S$ is as defined before. Denoting the Maximum Likelihood Estimator (MLE) of the fitted model as $\tilde{\beta}^1$, we define the one-time estimator as $\tilde{\beta}_j = \left(\tilde{\beta}^1\right)_j$, which is the entry of $\tilde{\beta}^1$ corresponding to covariate $X_j$. Meanwhile, we denote $\tilde{\beta}_0$ as the intercept estimator from the MLE of $Y^1 \sim X_0^1$. With some abuse of notation that $S_{+0} = \{0\} \cup S = S$, the one-time SSGLM estimator is

$$\tilde{\beta}^1 = \arg\min_{\beta_{S_{+j}}} \ell_{S_{+j}}(\beta_{S_{+j}}) = \arg\min_{\beta} \ell(\beta_{S_{+j}}; Y^1, X_{S_{+j}}^1);$$

$$\tilde{\beta}_j = \left(\tilde{\beta}^1\right)_j; \quad \tilde{\beta} = (\tilde{\beta}_0, \tilde{\beta}_1, \ldots, \tilde{\beta}_p).$$

If the outcome is linear (Fei et al., 2018), (4) and (5) have an explicit form

$$\tilde{\beta}_j = \left\{\left(X_{S_{+j}}^1 X_{S_{+j}}^1\right)^{-1} X_{S_{+j}}^1 X_{S_{+j}}^1 Y^1\right\}_j.$$  

The SSGLM estimator is defined by repeating the previous procedure $B$ times and averaging over the $B$ estimates from (4 5) (Algorithm 2). More specifically, for each $b = 1, 2, \ldots, B$, we randomly split the data into two halves $D_1^b$ and $D_2^b$, with fixed sample sizes $|D_1^b| = n_1$ and $|D_2^b| = n_2$. In other words, the data splitting proportion $q = n_1/n$, $0 < q < 1$ is a fixed constant. Denote the selected candidate set of variables by $S_X$ on $D_2^b$ as $S^b$, and the one-time estimator by (4 5) as $\beta^b = (\tilde{\beta}_0^b, \tilde{\beta}_1^b, \ldots, \tilde{\beta}_p^b)$. The smoothed estimator is

$$\hat{\beta} = (\hat{\beta}_0, \hat{\beta}_1, \ldots, \hat{\beta}_p),$$

where $\hat{\beta}_j = \frac{1}{B} \sum_{b=1}^B \beta_j^b$.  

Algorithm 1 One-time SSGLM Estimator

Require: A GLM regression model, a selection procedure $S_X$
Input: Data $(Y, X)$, split proportion $q \in (0, 1)$
Output: Coefficient estimator $\hat{\beta}$
1: Split the data into two halves $D_1$ and $D_2$, with sample sizes $|D_1| = qn$, $|D_2| = (1 - q)n$
2: Apply $S_X$ on $D_2$ to select a subset of important covariates $S \subset [p]$
3: for $j = 0, 1, \ldots, p$ do
4: Define $S_{+j} = \{j\} \cup S$, and fit the GLM of $Y^1$ regressing on $X_{S_{+j}}^1$, where $D_1 = (Y^1, X^1)$
5: Denote the coefficient estimator in previous step as $\tilde{\beta}^1$
6: Define $\tilde{\beta}_j = \left(\tilde{\beta}^1\right)_j$, which is the coefficient for covariate $X_j$ ($\tilde{\beta}_0$ represents the intercept)
7: end for
8: Define $\hat{\beta} = (\hat{\beta}_0, \hat{\beta}_1, \ldots, \hat{\beta}_p)$

3. Theoretical results

3.1 One-time estimator

We first establish the asymptotic property of the one-time estimator under the following assumptions.
Algorithm 2 SSGLM Estimator

Require: A GLM regression model, a selection procedure $S_{\lambda}$
Input: Data $(Y, X)$, split proportion $q \in (0, 1)$, number of re-samples $B$
Output: Coefficient estimator $\hat{\beta}$

1: for $b = 1, 2, \ldots, B$ do
2: Run Algorithm 1 with random data split
3: Denote the output estimator as $\tilde{\beta}^b = (\tilde{\beta}_0^b, \tilde{\beta}_1^b, \ldots, \tilde{\beta}_p^b)$
4: end for
5: Define $\hat{\beta} = (\hat{\beta}_0, \hat{\beta}_1, \ldots, \hat{\beta}_p)$, where $\hat{\beta}_j = \frac{1}{B} \sum_{b=1}^{B} \tilde{\beta}_j^b$

(A1). The eigenvalues of the expected information matrix at $\beta^*$ are bounded:

$$0 < c_{\min} \leq \lambda_{\min}(I^*) \leq \lambda_{\max}(I^*) \leq c_{\max} < \infty.$$  

In addition, for any $i \in [n]$, $j \in [p]$, $|x_{ij}| \leq \rho_0$, $E|Y_i|^3 \leq \rho_1$.

(A2). Order of Model Parameters: There exist constants $0 < c_1 \leq 1, c_\beta > 0$ such that $s_0 = |S_0| = O(n^{c_1}), \max_j |\beta_j^*| \leq c_\beta$.

(A3). Sure Screening Property: There exist a sequence $\{\lambda_n\}_{n \geq 1}$ and constants $0 < \eta < 1$, $c_2 > 2c_\beta$ such that $|\hat{S}_{n,\lambda_n}|/n \leq \eta$, and

$$P(\hat{S}_{n,\lambda_n} \supset S_0) \geq 1 - o(n^{-c_2-1}) \quad \text{as} \quad n \to \infty.$$  

Here $\hat{S}_{n,\lambda_n}$ denotes the selected set of variables with sample size $n$ and tuning parameter $\lambda_n$.

Remark 1 The sure screening property for GLMs has been established in Fan et al. (2009); Fan and Song (2010). In addition to (A1) and (A2), the following conditions are sufficient for the sure screening property by Theorem 4 in Fan and Song (2010):

- The second derivative of $A(\theta)$ is continuous and positive;
- There exists $c_0, \kappa > 0$, such that for $j \in S_0$, $|\text{cov}(A'(\theta), X_j)| \geq c_0 n^{-\kappa}$;

It is worth pointing out that the aforementioned conditions imply that the order of $p$ can be as large as $\log p = o(n^{1-2\kappa})$, while providing a stronger tail probability (exponentially small in $n$) than what is required in assumption (A3).

Assumption (A1) is a standard condition on the eigenvalues and norms of the observed data. Assumption (A2) specifies the order of the sparsity and the effect sizes. While there is no direct assumption on the order of $p$, it is implied through Assumption (A3) as stated in Remark 1.

Theorem 2 Given model (1,2) and assumptions (A1)-(A3), consider the one-time estimator $\hat{\beta} = (\hat{\beta}_0, \hat{\beta}_1, \ldots, \hat{\beta}_p)^T$ as defined in (4-5). For any $j \in \{0\} \cup [p]$, denote $\hat{\sigma}_j^2 = \{I^{-1}_{S_{n,\lambda_n}}\}_{jj}$, as $n_1, n \to \infty$,

$$\sqrt{n_1}(\hat{\beta}_j - \beta_j^*)/\hat{\sigma}_j \to N(0,1).$$
3.2 SSGLM estimator

In practice, the one-time estimator is highly variable as \( p \) increases, making it difficult to separate signals from noise variables in the inferential step. In contrast, the smoothed estimator is much more consistent as it averages over both estimation and selection. However, it introduces dependency among the selected \( S^b \)'s. The following condition, which is stronger than “sure screening,” is required for the desired theoretical property.

(B3). Selection Consistency: There exists a sequence \( \{\lambda_n\}_{n \geq 1} \) and constants \( 0 < \eta < 1 \), \( c_2 > 2c_1 \) such that \( |\hat{S}_{n,\lambda_n}|/n \leq \eta \), and

\[
P(\hat{S}_{n,\lambda_n} = S_0) \geq 1 - o(n^{-c_2-1}) \quad \text{as} \quad n \to \infty.
\]

**Theorem 3** Given model (1,2) and assumptions (A1,A2,B3), consider the smoothed estimator \( \hat{\beta} = (\hat{\beta}_0, \hat{\beta}_1, \ldots, \hat{\beta}_p)^T \) as defined in (6). For each \( j \), as \( n,B \to \infty \),

\[
\sqrt{n}(\hat{\beta}_j - \beta^*)/\sqrt{I_{j|S_0}^*} \to N(0,1),
\]

where \( I_{j|S_0}^* \) is defined as in (3) with the truth \( \beta^* \), which is bounded away from both zero and infinity.

4. Inference by SSGLM

As shown in Theorem (3), \( \hat{\beta}_j \) converges to a normal distribution with the variance depending on the unknown active set \( S_0 \). We can accurately estimate the variance using the infinitesimal jackknife developed by Efron (2014); Wager et al. (2014); Wager and Athey (2017). For \( i = 1, 2, \ldots, n \) and \( b = 1, 2, \ldots, B \), let \( J_{bi} \in \{0,1\} \) denote whether the \( i^{th} \) observation appears in the \( b^{th} \) sub-sample \( D_1^b \), and \( J_i = \left( \sum_{b=1}^{B} J_{bi} \right)/B \) is the average. Then the variance estimator for \( \hat{\beta}_j \) is

\[
\hat{V}_j = \frac{n-1}{n} \left( \frac{n}{n-n_1} \right)^2 \sum_{i=1}^{n} \hat{\text{cov}}_{i,j}^2,
\]

where

\[
\hat{\text{cov}}_{i,j} = \frac{1}{B} \sum_{b=1}^{B} (J_{bi} - J_i) \left( \hat{\beta}_j^b - \hat{\beta}_j \right).
\]

The term \( n(n-1)/(n-n_1)^2 \) is a finite-sample correction regarding the sub-sampling scheme (Wager and Athey, 2017). They have shown that the variance estimator is consistent as \( B \to \infty \), in the sense that \( \hat{V}_j/V \left( \hat{\beta}_j \right) \overset{p}{\to} 1 \).

Moreover, with finite \( B \), we propose the bias corrected version of the variance estimator:

\[
\hat{V}_j^B = \hat{V}_j - \frac{n}{B^2} \frac{n_1}{n-n_1} \sum_{b=1}^{B} (\hat{\beta}_j^b - \hat{\beta}_j)^2.
\]
The derivation is analogous to that in Section 4.1 of Wager et al. (2014). The advantage of using (8) instead of (7) is that (7) requires $B = O(n^{1.5})$ to reduce the Monte Carlo noise down to the sampling noise level, while (8) only requires $B = O(n)$ (Wager et al., 2014).

Thus the asymptotic 100$(1 - \alpha)$% confidence interval for each $\beta_j^*$ is given by

$$
\left( \hat{\beta}_j - \Phi^{-1}(1 - \alpha/2)\sqrt{\hat{V}_{jj}}, \hat{\beta}_j + \Phi^{-1}(1 - \alpha/2)\sqrt{\hat{V}_{jj}} \right),
$$

where $\Phi$ is the CDF of the standard normal distribution. The p-value of testing $H_0 : \beta_j^* = 0$ is

$$
2 \times \left\{ 1 - \Phi \left( |\hat{\beta}_j|/\sqrt{\hat{V}_{jj}} \right) \right\}.
$$

5. Extension to a subvector of coefficients with a fixed dimension

An extension of SSGLM to estimating a subvector $\beta^{(1)}$ of $\beta^*$ with a fixed dimension allows us to derive confidence regions for a subset of covariates and to test for contrasts of interest. Denote $\beta^{(1)} = \beta^*_{S^{(1)}}$ with $|S^{(1)}| = p_1 \geq 2$, which is finite and does not increase with $n$ and $p$. Accordingly, the SSGLM estimator for $\beta^{(1)}$ is presented in Algorithm 3, and the extension of Theorem 3 is stated below.

**Theorem 4** Given model (1,2) under assumptions (A1,A2,B3), and a fixed finite subset $S^{(1)} \subset \{1,2,\ldots,p\}$ with $|S^{(1)}| = p_1$. Let $\hat{\beta}^{(1)}$ be the smoothed estimator for $\beta^{(1)} = \beta^*_{S^{(1)}}$ as defined in (3). Then as $n,B \to \infty$,

$$
\sqrt{n} \left\{ I_{S^{(1)}|S_0}^{*} \right\}^{-1/2} (\hat{\beta}^{(1)} - \beta^{(1)}) \to N(0,I_{p_1}),
$$

where $I_{S^{(1)}|S_0}^{*} = I_{S^{(1)}S^{(1)}}^{*} - I_{S^{(1)}S_{01}}^{*} \left\{ I_{S_{01}S_{01}}^{*} \right\}^{-1} I_{S_{01}S^{(1)}}^{*}; \quad S_{01} = S_0 \setminus S^{(1)}$.

There is a direct extension of the one-dimensional nonparametric delta method for estimating the variance-covariance matrix of $\hat{\beta}^{(1)}$, $\Sigma^{(1)} = \hat{COV}^{T}_{(1)} \hat{COV}^{(1)}$, where

$$
\hat{COV}^{(1)} = \left( \hat{cov}_{1}^{(1)}, \hat{cov}_{2}^{(1)}, \ldots, \hat{cov}_{n}^{(1)} \right)^{T}, \quad \text{with}
$$

$$
\hat{cov}_{i}^{(1)} = \sum_{b=1}^{B} (J_{bi} - \bar{J}_i)(\hat{\beta}_{S^{(1)}}^{b} - \hat{\beta}^{(1)})/B.
$$

Therefore, we are equipped to test the following hypothesis, where $Q$ is a $q \times p_1$ matrix and $r$ is a $q \times 1$ vector, $H_0 : Q\beta^{(1)} = r$. The Wald type test statistic is

$$
T = \left( Q\hat{\beta}^{(1)} - r \right)^{T} \left[ Q\Sigma^{(1)}Q^{T} \right]^{-1} \left( Q\hat{\beta}^{(1)} - r \right),
$$

which follows the Chi-square distribution with degree of freedom $q$ under the null. We would reject $H_0$ if $T$ is larger than the critical value.
Algorithm 3 SSGLM for Subvector $\beta^{(1)}$

**Require:** A GLM regression model, a selection procedure $\mathcal{S}_\lambda$

**Input:** Data $(Y, X)$, split proportion $q \in (0, 1)$, number of re-samples $B$, subvector $\beta^{(1)}$ with support $S^{(1)}$

**Output:** Coefficient estimator $\hat{\beta}^{(1)}$

1. for $b = 1, 2, \ldots, B$ do
   1. Split the data into two halves $D_1$ and $D_2$, with sample sizes $|D_1| = qn$, $|D_2| = (1 - q)n$
   2. Apply $\mathcal{S}_\lambda$ on $D_2$ to select a subset of important covariates $S \subset [p]$
   3. Fit the GLM of $Y^1$ regressing on $X^1_{S^{(1)} \cup S}$, where $D_1 = (Y^1, X^1)$
   4. Denote the coefficient estimator in previous step as $\tilde{\beta}_S^{(1)}$
   5. Define $\tilde{\beta}_S^{b} = \left(\tilde{\beta}_S^{(1)}\right)_S$, which is the part estimating $\beta^{(1)}$
   6. end for
7. Define $\hat{\beta}^{(1)} = \left(\sum_{b=1}^{B} \tilde{\beta}^{b}_S \right) / B$

6. Simulations

We have conducted numerical studies to investigate the performance of the proposed SSGLM procedure under various settings, and to compare with two existing methods, the de-biased LASSO for GLMs (Van de Geer et al., 2014; Dezeure et al., 2015) and the decorrelated score test (Ning and Liu, 2017). We investigated the role of $q = n_1/n$, the split proportion, in fitting SSGLM; we explored various selection methods used in SSGLM and their effects on the estimation and inference; we implemented SSGLM for both logistic and Poisson regressions; and we assessed its performance through calculating the power and type I errors. Some of the most challenging simulation settings (Bühlmann et al., 2014) were examined, as both the indexes in the active set and the non-zero effect sizes were randomized, and different covariance structures were used.

**Example 1** investigates the performance of SSGLM while tuning the split proportion in the procedure. We make data splitting with $n_1 = qn$, $q = 0.1, 0.2, \ldots, 0.9$. We set $n = 500$, $p = 1000$, $s_0 = 10$ with the identity covariance matrix. The indexes in the active set $S_0$ are randomly pick from $[p]$, and the non-zero effects $\beta_j^*, j \in S_0$ are generated from Unif$([-1.5, -0.5) \cup (0.5, 1.5])$. For each $q$, the objective function is defined by the mean squared errors (MSE), denote $\tilde{\beta}^{(k)}_j$ as the smoothed estimator for $\beta_j$ from $k$-th simulation, $k = 1, 2, \ldots, K$,

$$\text{MSE}_j = \frac{1}{K} \sum_{k=1}^{K} (\tilde{\beta}^{(k)}_j - \beta_j^*)^2, \quad \text{MSE}_{\text{avg}} = \frac{1}{p} \sum_{j=1}^{p} \text{MSE}_j.$$  

From Figure (1), the minimum MSE is achieved around $q = 0.5$, recommending half-sample in practice.

**Example 2** implements a number of selection methods in SSGLM and their impacts on the estimation and inference. There are five procedures being compared: LASSO, SCAD, MCP, Elastic net, and Bayesian LASSO. Five-fold cross-validation is used for the parameter tuning in each selection procedure. We assume a Poisson model with $n = 300$, $p = 400$, and $s_0 = 5$. The results are summarized in Table (1). By comparing the bias, the coverage
probability, and the mean squared error, we conclude that while the average selected set sizes might differ among the selection methods, there is little impact on the smoothed estimators and the resulting inferences.

**Example 3** assumes the following Poisson model for count data, for \( i = 1, 2, \ldots, n \):

\[
\log \left( \mathbb{E}(Y_i|\mathbf{x}_i) \right) = \beta_0 + \mathbf{x}_i \beta.
\]

We set \( n = 400, p = 500, s_0 = 6 \), with non-zero coefficients between 0.5 and 1, and three different correlation structures: Identity; AR(1) with \( \Sigma_{ij} = \rho^{\vert i-j \vert}, \rho = 0.5 \); Compound Symmetry with \( \Sigma_{ij} = \rho^{(i\neq j)}, \rho = 0.5 \). The results are summarized in Table (2), as SSGLM provides nearly unbiased component-wise estimation and accurate standard errors, which leads to coverage probabilities that are close to the nominal level. Meanwhile, the non-zero signals are selected with a very high probability in the procedure, suggesting our assumptions (A3) or (B3) are well met in this case.

**Example 4** assumes the following logistic regression for binary outcomes, with \( n = 400, p = 500 \), and \( s_0 = 4 \).

\[
\text{logit} \left( \mathbb{P}(Y_i = 1|\mathbf{x}_i) \right) = \beta_0 + \mathbf{x}_i \beta.
\]

We show the performance of SSGLM when estimating and drawing inferences for the sub-vector \( \beta^{(1)} = \beta_{\mathcal{S}_0} \), as a whole. The results are summarized in Tables (3,4). Our method gives nearly unbiased estimates under different correlation structures and reliable testing power of the low-dimensional contrasts.

**Example 5** compares our method with the de-biased LASSO estimator (Van de Geer et al., 2014) and the decorrelated score test (Ning and Liu, 2017) through the testing power and the type I error. We again assume the logistic model (10) with \( n = 200, p = 300, s_0 = 3, \beta^*_{\mathcal{S}_0} = (2, -2, 2) \) with AR(1) correlation structures. From Table (5), our method gives the highest testing power while maintaining the type I error around the nominal 0.05 level, while the de-biased LASSO estimators outperform the decorrelated score tests to some extent.

In summary, we have provided numerical evidence that SSGLM performs well when using half sample split, and is robust to various selection methods. We have illustrated its performance under both Poisson and Logistic regressions, and for either single \( \beta_j \)'s or a subvector \( \beta^{(1)} \). More importantly, the comparison with existing methods shows the clear advantage of our method in terms of the power and the type I error.

### 7. Data example

A number of studies have aimed to understand the molecular causes of the lung cancer heterogeneity. Identifying the genes and pathways involved, determining how they relate to the biologic behavior of lung cancer and their utility as diagnostic and therapeutic targets are important basic and translational research issues (Larsen and Minna, 2011). Recent studies have revealed extensive genetic diversity both between and within tumors. This heterogeneity affects key cancer pathways, driving phenotypic variation, and poses a significant challenge to personalized cancer medicine (Burrell et al., 2013; Fisher et al., 2013).
A subset of the Boston Lung Cancer Study (BLCS, Christiani (2017)) contains of \(n = 1,459\) individuals, among which 708 are lung cancer patients and 751 are controls. The cleaned data consists of 6,829 SNPs, along with important demographic variables including age, gender, race, education level, and smoking status (Table 6). Since smoking plays a vital role in lung cancer, we are particularly interested in the interactions between the SNPs and smoking status, in addition to the main effects.

We assumed a high-dimensional logistic model with the binary lung cancer indicator as the outcome; the demographic variables, the SNPs and the interactions between all SNPs and the smoking status give a total of \(p = 13,663\) covariates. The SSGLM is fitted with \(B = 1,000\) re-samples. The partial result is shown in Table (7), as we list the top coefficients sorted by their p-values. The SNP names starting with “AX,” and the prefix “SAX” indicates the covariate is the interaction between the SNP “AX.xxx” and the smoking status.

We identified 9 significant coefficients after Bonferroni correction, all of which are interaction terms (Table (7)). This result provides strong evidence of the gene-environmental interactions in addition to the main SNP effects among the lung cancer patients that has rarely been reported before. These nine SNPs come from three genes, TUBB, ERBB2, and TYMS. The presence of TUBB mutations has been associated with both poor treatment response to paclitaxel-containing chemotherapy and shortened overall survival in patients with advanced non-small-cell lung cancer (NSCLC) (Monzó et al., 1999; Kelley et al., 2001). Rosell et al. (2001) has proposed using the presence of TUBB mutations as a basis for selecting initial chemotherapy for patients with advanced NSCLC. In contrast, intragenic ERBB2 kinase mutations occur more often in the adenocarcinoma subtype of lung cancer (Stephens et al., 2004; Beer et al., 2002). Finally, advanced NSCLC patients with low/negative thymidylate synthase (TYMS) have better response to Pemetrexed-Based Chemotherapy and longer progression free survival (Wang et al., 2013).

For comparisons, we applied the de-sparsified estimator for GLM (Bühlmann et al., 2014). Direct applications of the “lasso.proj” function in the “hdi” R package (Dezeure et al., 2015) were not feasible given the size of the data. Instead, we used a shorter sequence of the candidate \(\lambda\) values and 5-fold instead of 10-fold cross validation for the node-wise LASSO in the procedure, which still cost about one day of CPU time. After correcting for multiple testing, there were two significant coefficients, both of which were interaction terms corresponding to SNPs AX.35719413\(C\) and AX.83477746\(A\). Both SNPs were from the TUBB gene and the first SNP was also identified by our method.

To validate our findings, we applied the prediction accuracy measures for nonlinear models proposed in Li and Wang (2018). We calculated the \(R^2\), the proportion of variation in \(Y\) explained, for the models we chose to compare. The five models chosen and their respective \(R^2\)’s were: **Model 1.** \((R^2 = 0.0938)\) the baseline model including only the demographic variables; **Model 2.** \((R^2 = 0.1168)\) the baseline model plus the significant interactions after Bonferroni correction as the top ones from Table (7); **Model 3.** \((R^2 = 0.1181)\) the baseline model plus the iterations in Model 2 and their corresponding main effects; **Model 4.** \((R^2 = 0.1018)\) the baseline model plus the significant interactions from the de-sparsified LASSO method; **Model 5.** \((R^2 = 0.1076)\) Model 4 plus the corresponding main effects. In summary, Model 2 based on our method would explain 25% more variation in \(Y\) (from 0.0938 to 0.1168), while Model 4 based on the de-sparsified LASSO method only...
explains 8.5% more variation (from 0.0938 to 0.1018). We also plotted the ROC curves of models 1, 2, and 4 (Figure 2) and their AUCs were 0.645, 0.69, 0.668, respectively.

Our method also provides estimation and uncertainty measures for any pre-specified subvectors of parameters. Past literature has identified several SNPs as potential risk factors for lung cancer. We studied a controversial SNP, rs3117582 from the TUBB gene on chromosome 6. This SNP was identified in association with lung cancer risk in a case/control study by Wang et al. (2008), while on the other hand, Wang et al. (2009) found no evidence of association between the SNP and risk of lung cancer among never-smokers. Our goal was to test this SNP and its interaction with smoking together with all the other covariates under the high dimensional logistic model. Without loss of generality, we denoted the coefficients corresponding to rs3117582 and its interaction term as $\beta^{(1)} = (\beta_1, \beta_2)$. To test the overall effect of rs3117582, the null hypothesis was $H_0 : \beta_1 = \beta_2 = 0$. From the proposed method, we got 

$$
(\hat{\beta}_1, \hat{\beta}_2) = (-0.067, 0.005), \quad \text{COV} (\beta_1, \beta_2) = \begin{pmatrix} 0.44 & -0.43 \\ -0.43 & 0.50 \end{pmatrix}.
$$

While the main effect of the SNP rs3117582 was small, the interaction with smoking was even more negligible. The test statistic of the overall effect was $T = 0.062 \sim \chi^2(2)$ by (9), and the p-value is 0.97. We conclude that rs3117582 is not significantly related to lung cancer regardless of smoking status in this dataset.

8. Conclusions

We have proposed a novel procedure for estimation and inference in high dimensional generalized linear models. We have shown the SSGLM estimator is asymptotically unbiased and normal, which leads to reliable inferences for any low dimensional parameters. Our method utilizes the partial regression idea, which estimates the parameter of interest together with a subset of important covariates, to avoid the common disadvantages caused by penalized regression approaches. Furthermore, our estimator is based on multi-sample splitting and smoothing so that it is robust to the selection variability and enjoys the variance reduction from the bagging effect. Unlike the existing methods (Belloni et al. (2014); Van de Geer et al. (2014); Javanmard and Montanari (2014); Ning and Liu (2017)) that require certain conditions on more than one tuning parameters, our method is not sensitive to the $\lambda$ used for the selection. Hence, our method has minimal requirements on extra model parameters. For the same reason, we have shown that our method is adaptive to a wide range of model selection procedures that gives robust estimation and inferential results. The variance of the proposed estimator is derived from the non-parametric delta method applied to the re-samples, which is free of the regression model and is consistent both theoretically and in simulations. The assumptions on the selection may limit our approach to sparse models and certain data structures. Weakening such conditions has great potential to broaden the applications and is our future work.

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9. Appendix

We present proofs to Theorems 1-3 and some useful lemmas and corollaries.

**Proof** [Proof of Theorem 1] From the data split, $D_1$ and $D_2$ are mutually exclusive, thus $S$, from $D_2$, is independent of $D_1 = (Y^1, X^1)$. Given $X^1$ and for $S \supset S_0$ under assumption (A3), the MLE $\bar{\beta}^1$ in (4) follows the classic low dimensional convergence. So does its scalar component $\tilde{\beta}_j$. Thus the key is to show the asymptotic normality is uniform with respect to $S$, $X^1$ and $j$. We reiterate that

$$\bar{\beta}^1 = \arg\min_{S \supset S_0} \ell_{S^1}(\beta_{S^1}) = \arg\min \ell(\beta_{S^1}; Y^1, X_{S^1}^1);$$

$$\tilde{\beta}_j = \left(\bar{\beta}^1\right)_j; \quad \tilde{\beta} = (\tilde{\beta}_0, \ldots, \tilde{\beta}_p).$$

When $S \supset S_0$, $\bar{\beta}^1$ satisfies $\sqrt{n_1}I_{S^1}^{1/2} \left(\bar{\beta}^1 - \beta^*_{S^1}\right) \mid S, X^1 \to N(0, I)$, where $I_{S^1} = X_{S^1}^TX_{S^1}X_{S^1}/n_1$, with $V_S = \text{diag}(A''(\overline{x}_iS\beta_S), \ldots, A''(\overline{x}_iS\beta_S))$. Thus its component $\tilde{\beta}_j$ follows $\sqrt{n_1} \left(\tilde{\beta}_j - \beta^*_j\right) / \sigma_j \mid S, X^1 \to N(0, 1)$, where $\sigma^2_j = \left\{I_{S^1}^{-1}\right\}_{jj}$.

To derive the uniform convergence in $j$ and $S$, we refer to Theorem 5 of Niemiro (1992), which gives a precise approximation of the convergence of M-estimators. Treating $\bar{\beta}^1$ as the M-estimator, with our notations, there exists $0 \leq t < 1$,

$$\sqrt{n_1} \left(\bar{\beta}^1 - \beta^*_S\right) = - \left\{I_{S^1}\right\}^{-1} \sqrt{n_1}U_{S^1} \beta^*_S + O \left(n_1^{-(1+t)/4}(\log n_1)^{1/2}(\log \log n_1)^{(1+t)/4}\right).$$

Furthermore, in the GLM case, $t$ can approach 1, meaning the remainder term can be of order close to $O(n_1^{-1/2})$. More importantly, the order of this remainder term only depends on the sample size $n_1$, but not on $j$ or $S$.

Now we write

$$\sqrt{n_1} \left(\tilde{\beta}_j - \beta^*_j\right) / \sigma_j = \phi_{n_1} + \xi_{n_1},$$

where $\phi_{n_1}$ corresponds to the first term on the right hand side in (11) and $\xi_{n_1}$ is the remainder term. When $S \supset S_0$, by assumption (A1) and Lemma (5), $\sigma_j$ is bounded away from zero and infinity with probability going to 1 uniformly in $j$ and $S$.

By the Berry-Esseen Theorem, under assumptions (A1) and (A2), $\left|F_{n_1}(x) - \Phi(x)\right| \leq C / \sqrt{n_1}$, where $F_{n_1}(x)$ is the CDF of $\phi_{n_1}$, $\Phi(x)$ is the CDF of the stand normal, and $C$ only depends on $c_{\min}, c_{\max}, \rho_0$, and $\rho_1$. Together with $\xi_{n_1} = O(n_1^{-t'})$ for some $t' < 1/2$, $t' \to 1/2$, we have

$$\sqrt{n_1} \left(\tilde{\beta}_j - \beta^*_j\right) / \sigma_j \to N(0, 1).$$

**Proof** [Proof of Theorem 3]

We define the oracle estimators of $\beta^*_j$ on the full data $(Y, X)$ and the $b$-th subsample $D^b_1$ respectively, where the candidate set is the true set $S_0$:

$$\beta_{S_0+j}^0 = \arg\min_{S_0+j} \ell_{S_0+j}(\beta_{S_0+j}) = \arg\min \ell(\beta_{S_0+j}; Y, X_{S_0+j}); \quad \beta_{S_0+j}^0 = \{\beta_{S_0+j}^0\}_j;$$

$$\beta_{S_0+j}^b = \arg\min_{S_0+j} \ell_{S_0+j}^b(\beta_{S_0+j}) = \arg\min \ell(\beta_{S_0+j}; Y^{1(b)}, X_{S_0+j}^{1(b)}); \quad \beta_{S_0+j}^b = \{\beta_{S_0+j}^b\}_j.$$
For each $j \in [p]$,
\[
W_j^* = \sqrt{n}(\beta_j^b - \beta_j^o) / \sqrt{I_{j|i}^*} \xrightarrow{d} N(0,1) \quad \text{as} \quad n \to \infty,
\]
where $I_{j|i}^*$ is defined as in (3). By Cauchy’s interlacing theorem, $c_{\min} \leq I_{j|i}^* \leq c_{\max}$, and thus it is bounded away from zero and infinity.

With the oracle estimates $\beta_j^b$’s, we have the following decomposition:
\[
\sqrt{n}(\beta_j - \beta_j^* ) = \frac{1}{B} \sum_{b=1}^{B} \sqrt{n}(\beta_j^b - \beta_j^* ) + \frac{1}{B} \sum_{b \in S^b \neq S_0} \sqrt{n}(\beta_j^b - \beta_j^o) \equiv Z_j^* + \Delta_j.
\]

First we show $\Delta_j = o_p(1)$ by writing $\Delta_j = \frac{1}{B} \sum_{b=1}^{B} \delta_b$; $\delta_b \equiv 1(S^b \neq S_0) \sqrt{n}(\beta_j^b - \beta_j^o)$. By Corollary (6), $E\delta_b = P(S^b \neq S_0) E\sqrt{n}(\beta_j^b - \beta_j^o) = o \left( n^{-c_2 - 1/2} C_\beta n^{c_1 + 1/2} \right) \to 0$ as $n \to \infty$. Similarly, $V\delta_b = P(S^b \neq S_0) E\sqrt{n}(\beta_j^b - \beta_j^o)^2 = o \left( n^{-c_2 - 4 C_\beta^2 n^{c_1 + 1}} \right) \to 0$ as $n \to \infty$. Thus $\delta_b = o_p(1)$ for all $b \in [B]$. Furthermore, since $E\Delta_j = E\delta_b$ and $V\Delta_j \leq V\delta_b$, we have $\Delta_j = o_p(1)$.

Next, we show the convergence of $Z_j^*$. Notice that
\[
Z_j^*/\sqrt{I_{j|i}^*} = W_j^* + \sqrt{n} \left( \frac{1}{B} \sum_{b=1}^{B} \beta_j^b - \beta_j^o \right) / \sqrt{I_{j|i}^*} \xrightarrow{d} W_j^* + T_n^B / \sqrt{I_{j|i}^*}.
\]

By (12) and that $I_{j|i}^*$ is bounded, we are only left to show $T_n^B = o_p(1)$. Define $t_{n,b} = \sqrt{n}(\beta_j^b - \beta_j^o)$, then $T_n^B = (\sum_{b=1}^{B} t_{n,b}) / B$. Since $\beta_j^b$ is estimated on the random subsample $D_{j|i}^b$, its conditional mean is $\beta_j^o$ and conditional variance is $\hat{I}_{j|i}^{-1}/n_1$. Thus, conditional on the data $(Y, X) = (X^{(n)}, Y^{(n)})$, $\{t_{n,b}\}_{b=1,2,..,B}$ are i.i.d. with
\[
E(t_{n,b}|(X^{(n)}, Y^{(n)})) = 0, \quad V(t_{n,b}|(X^{(n)}, Y^{(n)})) = \frac{n}{n_1} \hat{I}_{j|i}^{-1} = \hat{I}_{j|i}^{-1}/q.
\]

By Lemma (5), with probability at least $1 - 2 \exp(-\varepsilon^2 n C_K)$ for some constant $C_K$ and $\varepsilon = \min(1/2, c_{\min}/2)$, $c_{\min}/2 \leq \hat{I}_{j|i} \leq c_{\max} + (1 + c_{\min})/2$.

Therefore, $\hat{I}_{j|i}^{-1} \leq 2/c_{\min}$ with probability going to 1 exponentially fast in $n$. Now define
\[
\Omega_n = \{(X^{(n)}, Y^{(n)}) = (x_i, y_i)_{i=1,2,..,n} : \hat{I}_{j|i}^{-1} \leq 2/c_{\min}, \forall j \in [p]\}.
\]

Since $p = O(n^{\gamma_1})$ for some $\gamma_1 > 1$, $P\{ (X^{(n)}, Y^{(n)}) \in \Omega_n \} \to 1$ as $n \to \infty$. Thus $\forall (X^{(n)}, Y^{(n)}) \in \Omega_n$, $V\{t_{n,b}|(X^{(n)}, Y^{(n)})\} \leq 2/c_{\min}$. Furthermore,
\[
V\{T_n^B|(X^{(n)}, Y^{(n)})\} = \frac{1}{B^2} \sum_{b=1}^{B} V\{t_{n,b}|(X^{(n)}, Y^{(n)})\} \leq \frac{2}{B q c_{\min}}.
\]
Thus, \( \forall \delta, \zeta > 0, \exists N_0, B_0 > 0 \) such that \( \forall n > N_0, B > B_0, \)
\[
\mathbf{P}( |T_n^B| \geq \delta ) \\
\leq \frac{\sqrt{\mathbf{V}(X(n), Y(n))}}{\delta^2} + \frac{\mathbf{P}(X(n), Y(n) \notin \Omega_n)}{\delta^2} \\
\leq \frac{2}{B_0 \delta^2 q_{\min}} \int_{\Omega_n} \mathbf{dP}(X(n), Y(n)) + \mathbf{P}(X(n), Y(n) \notin \Omega_n) \\
\leq \zeta / 2 + \zeta / 2 \\
\leq \zeta.
\]

Finally, combining this with (12), we have
\[
Z_j^* / \sqrt{I_j^* | S_0} = W_j^* + T_n^B / \sqrt{I_j^* | S_0} \overset{d}{\to} N(0, 1) \quad \text{as} \quad B, n \to \infty.
\]

**Proof** [Proof of Theorem 3] Follow the previous proof, we replace the arguments in \( j \) with those in \( S(1) \). The *oracle* estimators are
\[
\beta_{S(1) \cup S_0}^o = \arg\min \ell_{S(1) \cup S_0}(\beta_{S(1) \cup S_0}; Y, X_{S(1) \cup S_0}), \quad \beta_{S(1)}^o = \{ \beta_{S(1) \cup S_0}^o \}_{S(1)};
\]
\[
\beta_{S(1) \cup S_0}^b = \arg\min \ell_{S(1) \cup S_0}(\beta_{S(1) \cup S_0}; Y^{1(b)}, X_{S(1) \cup S_0}^{1(b)}), \quad \beta_{S(1)}^b = \{ \beta_{S(1) \cup S_0}^b \}_{S(1)}.
\]
Notice that \( |S(1)| = p_1 = O(1), \) as \( n \to \infty, |S_0 \cup S(1)| = O(|S_0|) = o(n), \) so that the above quantities are well-defined. The oracle estimator satisfies
\[
W^{(1)} = \sqrt{n} \{ I_{S(1) \cup S_0}^o \}^{-1/2} (\beta_{S(1)}^o - \beta_{S(1)}^*) \overset{d}{\to} N(0, I_{p_1}) \quad \text{as} \quad n \to \infty,
\]

Similar to (13, 14), we decompose \( \sqrt{n}(\hat{\beta}_{S(1)} - \beta_{S(1)}^*) \) into three parts:
\[
\sqrt{n}(\hat{\beta}_{S(1)} - \beta_{S(1)}^*) \simeq W^{(1)} + \Delta_0^{(1)} + \Delta_1^{(1)}.
\]
For the interest of space, we do not spell out these quantities and the derivations, but it is straightforward to show that \( |\Delta_0^{(1)}|_1 = |\Delta_1^{(1)}|_1 = o_p(1), \) which completes the proof.

**Lemma 5** Given model (1, 2), and the corresponding information matrix at the truth \( \beta^* \),
\[ I^* = \mathbf{E}_{\beta^*}(\nabla^2 \ell(\beta^*)) \]. Assume \( 0 < c_{\min} \leq \lambda_{\min}(I^*) \leq \lambda_{\max}(I^*) \leq c_{\max} < \infty. \) For any subset \( S \subset \{ 1, 2, \ldots, p \} \) with \( |S| \leq \eta n, 0 < \eta < 1, \) and \( \forall j \in S, \) define the partial information as \( I_{j|S} = I_{jj} - I_{jS} I_{Sj}^{-1} I_{Sj} \), where \( S_j = S \setminus j. \) Denote its empirical estimator as \( \hat{I}_{j|S} \). Then with probability at least \( 1 - 2 \exp\left( -\frac{c_{\min}^2}{2 \varepsilon^2} n \right), \)
\[
\frac{c_{\min}}{2} \leq \hat{I}_{j|S} \leq c_{\max} + \frac{1 + c_{\min}}{2}
\]
where \( \varepsilon = \min(\frac{1}{2}, \frac{c_{\min}}{2}). \)
Corollary 6 Given model (1, 2) and assumptions (A1, A2), consider the one-time estimator as defined in (4, 5). If $|S| \leq \eta n$, $0 < \eta < 1$, then with probability at least $1 - 2 \exp(-\frac{\epsilon^{2}n}{C_{K}})$,

$$\widetilde{\beta}_{j} \leq C_{\beta}n^{c_{1}},$$

where $C_{\beta}$ depends on $c_{\min}, c_{\max}, c_{\beta}$. 
Figure 1: Average MSEs of all covariates at split proportions $q$'s from 0.1 to 0.9.

Figure 2: ROC curves of the three selected models.
Table 1: Comparisons of different selection procedures to implement our proposed method. First column is the indexes of the non-zero signals. Last row for the selection frequency is the average number of covariates being selected by each procedure. Last row for the coverage probability is the average coverage probability of all covariates.

| Bias | \( \beta^* \) | LASSO | SCAD | MCP | EN | Bayesian |
|------|----------------|-------|------|-----|----|----------|
| 12   | 0.4            | 0.003 | 0.003| 0.003| 0.003| 0.001    |
| 71   | 0.6            | 0.007 | 0.008| 0.008| 0.008| -0.010   |
| 351  | 0.8            | -0.001| 0.001| 0   | 0   | 0.001    |
| 377  | 1.0            | -0.005| -0.005| -0.006| -0.005| 0.001    |
| 386  | 1.2            | 0.002 | 0.001| 0.001| 0.001| 0.004    |

| Selection frequency | LASSO | SCAD | MCP | EN | Bayesian |
|---------------------|-------|------|-----|----|----------|
| 12                  | 0.59  | 0.55 | 0.49| 0.60| 0.60     |
| 71                  | 0.93  | 0.92 | 0.90| 0.95| 0.94     |
| 351                 | 0.99  | 0.99 | 0.99| 1.00| 1.00     |
| 377                 | 1.00  | 1.00 | 1.00| 1.00| 1.00     |
| 386                 | 1.00  | 1.00 | 1.00| 1.00| 1.00     |

| Average # | 23.12 | 13.15 | 10.89 | 10.31 | 7.98    |

| Coverage Prob | LASSO | SCAD | MCP | EN | Bayesian |
|---------------|-------|------|-----|----|----------|
| 12            | 0.90  | 0.90 | 0.91| 0.91| 0.95     |
| 71            | 0.94  | 0.94 | 0.95| 0.94| 0.94     |
| 351           | 0.95  | 0.95 | 0.95| 0.94| 0.95     |
| 377           | 0.94  | 0.93 | 0.93| 0.94| 0.92     |
| 386           | 0.94  | 0.95 | 0.95| 0.95| 0.94     |

| Average       | 0.93  | 0.94 | 0.94| 0.94| 0.94     |

| MSE           | LASSO | SCAD | MCP | EN | Bayesian |
|---------------|-------|------|-----|----|----------|
| 12            | 0.111 | 0.110| 0.110| 0.109| 0.106    |
| 71            | 0.104 | 0.103| 0.102| 0.102| 0.101    |
| 351           | 0.103 | 0.103| 0.103| 0.103| 0.100    |
| 377           | 0.101 | 0.100| 0.100| 0.100| 0.109    |
| 386           | 0.097 | 0.096| 0.096| 0.096| 0.102    |

| Average       | 0.105 | 0.104 | 0.103 | 0.103 | 0.102 |
Table 2: SSGLM under Poisson regression and three correlation structures. The last column summarizes the average of all noise variables.

| Index     | Int  | 74   | 109  | 347  | 358  | 379  | 438  | -   |
|-----------|------|------|------|------|------|------|------|-----|
| $\beta^*$ | 1.000| 0.810| 0.595| 0.545| 0.560| 0.665| 0.985| 0   |
| Identity  | Bias | -0.010| 0    | 0    | 0.001| 0.005| 0.005| 0.006| 0   |
|           | Avg SE | 0.050| 0.035| 0.034| 0.035| 0.035| 0.034| 0.034|     |
|           | Emp SE  | 0.064| 0.036| 0.038| 0.031| 0.033| 0.038| 0.036|     |
|           | Cov prob | 0.870| 0.920| 0.900| 0.960| 0.990| 0.910| 0.950| 0.936|
|           | Sel freq | 1.000| 1.000| 1.000| 1.000| 1.000| 1.000| 1.000| 0.015|
| AR(1)     | Bias | 0.006| 0.003| -0.002| -0.001| -0.001| -0.005| 0.003| 0   |
|           | Avg SE | 0.052| 0.035| 0.035| 0.035| 0.035| 0.035| 0.035|     |
|           | Emp SE  | 0.056| 0.031| 0.041| 0.035| 0.037| 0.037| 0.037|     |
|           | Cov prob | 0.930| 0.970| 0.890| 0.960| 0.950| 0.930| 0.960| 0.937|
|           | Sel freq | 1.000| 1.000| 1.000| 1.000| 1.000| 1.000| 1.000| 0.015|
| CS        | Bias | -0.003| -0.005| 0.004| -0.002| 0.005| -0.004| -0.001| 0.001|
|           | Avg SE | 0.033| 0.043| 0.043| 0.042| 0.043| 0.043| 0.044|     |
|           | Emp SE  | 0.038| 0.046| 0.044| 0.052| 0.040| 0.047| 0.043| 0.044|
|           | Cov prob | 0.960| 0.900| 0.930| 0.900| 0.970| 0.910| 0.950| 0.934|
|           | Sel freq | 1.000| 1.000| 0.999| 0.997| 0.998| 0.999| 1.000| 0.016|
Table 3: SSGLM under Logistic regression, with estimation and inference for the subvector \( \beta^{(1)} = \beta_{S_0} \). The oracle estimator is from the low dimensional GLM knowing the true set \( S_0 \). The empirical covariance matrix is with respect to the simulation replications.

| Index  | 218 | 242 | 269 | 517 | Truth | -2 | -1 | 1 | 2 | Index  | 218 | 242 | 269 | 517 | Truth | -2 | -1 | 1 | 2 |
|--------|-----|-----|-----|-----|-------|----|----|---|---|-------|----|----|----|----|-------|----|----|---|---|
|        |     |     |     |     |       |    |    |   |   |       |    |    |    |    |       |    |    |   |   |
| \( \beta^{(1)} \) | -2.048 | -1.043 | 0.999 | 2.096 | Oracle | -1.995 | -1.026 | 0.973 | 2.043 |
| \( \Sigma^{(1)} \) | 0.146 | 0.010 | -0.009 | -0.020 | Empirical | 0.155 | 0.006 | -0.009 | -0.027 |
|        | 0.010 | 0.134 | -0.004 | -0.011 |          | 0.006 | 0.129 | -0.011 | -0.015 |
|        | -0.009 | -0.004 | 0.134 | 0.009 |          | -0.009 | -0.011 | 0.152 | 0.010 |
|        | -0.020 | -0.011 | 0.009 | 0.143 |          | -0.027 | -0.015 | 0.010 | 0.134 |
|        |       |       |       |       | Identity |       |       |       |       |
|        |       |       |       |       | AR(1) |       |       |       |       |
|        |       |       |       |       | CS    |       |       |       |       |

Table 4: SSGLM under Logistic regression, with rejection rates of testing the contrasts.

| \( H_0 \) | Truth | Identity | AR(1) | CS |
|-----------|-------|----------|-------|----|
| \( \beta_{218}^* + \beta_{517}^* = 0 \) | 0 | 0.05 | 0.04 | 0.03 |
| \( \beta_{242}^* + \beta_{269}^* = 0 \) | 0 | 0.06 | 0.04 | 0.025 |
| \( \beta_{218}^* + \beta_{269}^* = 0 \) | -1 | 0.56 | 0.57 | 0.42 |
| \( \beta_{242}^* + \beta_{517}^* = 0 \) | 1 | 0.55 | 0.58 | 0.48 |
| \( \beta_{242}^* = 0 \) | -1 | 0.83 | 0.80 | 0.61 |
| \( \beta_{269}^* = 0 \) | 1 | 0.74 | 0.81 | 0.70 |
| \( \beta_{218}^* = 0 \) | -2 | 1 | 1 | 1 |
| \( \beta_{517}^* = 0 \) | 2 | 1 | 1 | 1 |
Table 5: Comparisons of SSGLM, Lasso-pro, and Decorrelated score in power and Type I error. AR(1) correlation structure with different $\rho$’s are examined.

| $\rho$ | Power | Type I error |
|--------|-------|--------------|
|        | Index | 10 | 20 | 30 | 0's |
| $\rho = 0.25$ | Proposed | 0.920 | 0.930 | 0.950 | 0.049 |
|          | Lasso-pro | 0.900 | 0.930 | 0.900 | 0.042 |
|          | Dscore | 0.790 | 0.880 | 0.890 | 0.177 |
| $\rho = 0.4$ | Proposed | 0.940 | 0.960 | 0.965 | 0.049 |
|          | Lasso-pro | 0.920 | 0.910 | 0.920 | 0.043 |
|          | Dscore | 0.770 | 0.905 | 0.840 | 0.175 |
| $\rho = 0.6$ | Proposed | 0.940 | 0.950 | 0.880 | 0.054 |
|          | Lasso-pro | 0.850 | 0.750 | 0.850 | 0.045 |
|          | Dscore | 0.711 | 0.881 | 0.647 | 0.268 |
| $\rho = 0.75$ | Proposed | 0.863 | 0.847 | 0.923 | 0.060 |
|          | Lasso-pro | 0.690 | 0.670 | 0.650 | 0.053 |
|          | Dscore | 0.438 | 0.843 | 0.530 | 0.400 |

Table 6: Demographic characteristics of the BLCS SNP data.

| Case | 0 | 1 |
|------|---|---|
| Race |   |   |
| White | 726 | 668 |
| Black | 5  | 22 |
| Other | 20 | 18 |
| Education |    |   |
| <High school | 64 | 97 |
| High school | 211 | 181 |
| >High school | 476 | 430 |
| Age | Mean(sd) | 59.7(10.6) | 60(10.8) |
| Gender |   |   |
| Female | 460 | 437 |
| Male | 291 | 271 |
| Pack years | Mean(sd) | 18.8(25.1) | 46.1(38.4) |
| Smoking |   |   |
| Ever | 498 | 643 |
| Never | 253 | 65 |
Table 7: SSGLM fitted to the BLCS SNP data. SNP variables start with “AX”; interaction terms start with “SAX”; “Smoke” is the binary smoking status indicator. Rows are sorted by p-values.

| Variable         | \( \hat{\beta} \) | SE  | T     | P-value | Adjusted P | Sel freq |
|------------------|---------------------|-----|-------|---------|------------|----------|
| SAX.88887606_T   | 0.33                | 0.02| 17.47 | < 10^{-3} | < 0.01     | 0.08     |
| SAX.11279606_T   | 0.53                | 0.06| 8.23  | < 10^{-3} | < 0.01     | 0.00     |
| SAX.88887607_T   | 0.29                | 0.04| 6.97  | < 10^{-3} | < 0.01     | 0.01     |
| SAX.15352688_C   | 0.56                | 0.08| 6.90  | < 10^{-3} | < 0.01     | 0.01     |
| SAX.88900908_T   | 0.54                | 0.09| 5.95  | < 10^{-3} | < 0.01     | 0.02     |
| SAX.88900909_T   | 0.51                | 0.09| 5.69  | < 10^{-3} | < 0.01     | 0.02     |
| SAX.32543135_C   | 0.78                | 0.14| 5.49  | < 10^{-3} | < 0.01     | 0.25     |
| SAX.11422900_A   | 0.32                | 0.06| 5.24  | < 10^{-3} | < 0.01     | 0.09     |
| SAX.35719413_C   | 0.47                | 0.10| 4.63  | < 10^{-3} | 0.049      | 0.00     |
| SAX.8894133_C    | 0.43                | 0.10| 4.53  | < 10^{-3} | 0.08       | 0.00     |
| SAX.11321564_T   | 0.47                | 0.11| 4.44  | < 10^{-3} | 0.12       | 0.00     |
| ...              |                     |     |       |         |            |          |
| AX.88900908_T    | 0.40                | 0.11| 3.84  | < 10^{-3} | 1.00       | 0.00     |
| Smoke            | 0.89                | 0.23| 3.82  | < 10^{-3} | 1.00       | -        |
| ...              |                     |     |       |         |            |          |