

Journal of Statistical Software

MMMMMM YYYY, Volume VV, Issue II.

doi: 10.18637/jss.v000.i00

SIHR: An R Package for Statistical Inference in High-dimensional Linear and Logistic Regression Models

Prabrisha Rakshit

T. Tony Cai

Zijian Guo

Rutgers University

University of Pennsylvania

Rutgers University

Abstract

We introduce and illustrate through numerical examples the R package SIHR which handles the statistical inference for (1) linear and quadratic functionals in the high-dimensional linear regression and (2) linear functional in the high-dimensional logistic regression. The focus of the proposed algorithms is on the point estimation, confidence interval construction and hypothesis testing. The inference methods are extended to multiple regression models. We include real data applications to demonstrate the package's performance and practicality.

Keywords: Hypothesis testing, confidence interval, R package.

1. Introduction

In a wide range of applications, we are confronted with high-dimensional problems where the number of feature or covariates p exceeds the sample size n. Much progress has been made in the estimation and support recovery under the high-dimensional generalized linear models (Tibshirani 1996; Fan and Li 2001; Negahban, Yu, Wainwright, and Ravikumar 2009; Meinshausen and Yu 2009; Zhang 2010; Sun and Zhang 2012; Belloni, Chernozhukov, and Wang 2011; Bühlmann and van de Geer 2011; Huang and Zhang 2012, e.g.). Starting from Zhang and Zhang (2014); van de Geer, Bühlmann, Ritov, and Dezeure (2014); Javanmard and Montanari (2014), a fast growing research area is on confidence interval construction and hypothesis testing for low-dimensional objects in high-dimensional generalized linear models; see for examples Athey, Imbens, and Wager (2016); Cai and Guo (2017); Ning and Liu (2017); Chernozhukov, Chetverikov, Demirer, Duflo, Hansen, Newey, and Robins (2017); Zhu and Bradic (2018); Cai, Guo, and Ma (2020).

In the current paper, we demonstrate the R package SIHR, which targets at a series of inference problems in high-dimensional linear and logistic models. Specifically, we consider the high-dimensional linear regression

$$y_i = X_i^{\mathsf{T}} \beta + \epsilon_i, \quad \text{for } 1 \le i \le n$$
 (1)

where $\beta \in \mathbb{R}^p$ is the high-dimensional regression vector, $\{X_i\}_{1 \leq i \leq n}$ are i.i.d. p-dimensional random vectors with $\Sigma = \mathbf{E} X_i X_i^{\mathsf{T}}$ and $\{\epsilon_i\}_{1 \leq i \leq n}$ are i.i.d. sub-Gaussian random errors, independent of X_i , with mean zero and variance σ^2 . Under (1), we study confidence interval construction and hypothesis testing related to the following low-dimensional targets:

- 1. The linear functional $x_{\text{new}}^{\mathsf{T}}\beta$ with $x_{\text{new}} \in \mathbb{R}^p$. When x_{new} is taken as the j-th Euclidean basis, then $x_{\text{new}}^{\mathsf{T}}\beta$ becomes the individual regression coefficient, β_j , which can be viewed as the treatment effect of the j-th variable on the response (Zhang and Zhang 2014; van de Geer et al. 2014; Javanmard and Montanari 2014). If x_{new} denotes a further observation's covariates, then the linear functional is closely related to the outcome prediction (Zhu and Bradic 2018; Tripuraneni and Mackey 2019; Cai, Cai, and Guo 2019). Inference for the linear functional is also closely related to inference for the average treatment effect (Athey et al. 2016) and individualized treatment effect (Cai et al. 2019).
- 2. The quadratic functional $\beta_G^{\mathsf{T}} A \beta_G$ with $G \subset \{1, 2, \dots, p\}$ and $A \in \mathbb{R}^{|G| \times |G|}$. The quadratic functional $\beta_G^{\mathsf{T}} A \beta_G$ can be viewed a total measure of all effects of variables in the group G. Inference for $\beta_G^{\mathsf{T}} A \beta_G$ is closely connected to the group significance test, (local) heritability, heterogeneous effect test, hierarchical testing, prediction loss evaluation and confidence ball construction; see Cai and Guo (2020); Guo, Wang, Cai, and Li (2019c); Guo, Renaux, Buhlmann, and Cai (2019b) for detailed discussion.

We further consider the following high-dimensional logistic regression model:

$$\mathbb{P}(y_i = 1|X_i) = h(X_i^{\mathsf{T}}\beta) \quad \text{with} \quad h(z) = \exp(z)/[1 + \exp(z)], \quad \text{for } 1 \le i \le n,$$
 (2)

where $\beta \in \mathbb{R}^p$ denotes the high-dimensional vector of odds ratio parameters, $X_i \in \mathbb{R}^p$ denotes the observed high-dimensional covariates and $y_i \in \{0,1\}$ denotes the binary response for i^{th} observation. The quantity of the interest is the case probability for a new observation $x_{\text{new}} \in \mathbb{R}^p$,

$$h(x_{\text{new}}^{\mathsf{T}}\beta) = \exp(x_{\text{new}}^{\mathsf{T}}\beta)/[1 + \exp(x_{\text{new}}^{\mathsf{T}}\beta)].$$

The case probability is closely connected to the linear functional $x_{\text{new}}^{\intercal}\beta$, which includes the single regression coefficient β_j as a special case. In health applications, an interesting problem is to test the following null hypothesis,

$$H_0: h(x_{\text{new}}^{\mathsf{T}}\beta) < 1/2.$$
 (3)

Personalized medicine requires to predict individualized treatment effects (ITEs) based on a given patient's profile. In consideration of two high-dimensional regressions with regression vectors $\beta_1 \in \mathbb{R}^p$ and $\beta_2 \in \mathbb{R}^p$, the quantity $x_{\text{new}}^{\dagger}(\beta_1 - \beta_2)$ can be viewed as an individualized treatment effect (ITE) for a patient with covariates $x_{\text{new}} \in \mathbb{R}^p$ (Cai et al. 2019; Guo,

Rakshit, Herman, and Chen 2019a). We extend our proposed inference methods from a single linear/logistic regression to multiple regression settings and make inference for the ITE $x_{\text{new}}^{\dagger}(\beta_1 - \beta_2)$ in both high-dimensional linear and logistic regression models.

For broader use of these methods, we introduce the nuanced and user friendly R package SIHR in this paper. This package consists of main functions LF, QF, ITE, LF_logistic and ITE_logistic, with the usage detailed in Section 3.

In the remaining of the paper, we review the inference methods in Section 2 and introduce the main package functions in Section 3 along with illustrative examples. We illustrate our proposed methods with real data applications in Section 4.

2. Methodological Background

In Sections 2.1 and 2.2 we present inference methods for $x_{\text{new}}^{\intercal}\beta$ and $\beta_G^{\intercal}A\beta_G$ under the high-dimensional linear regression model (1). In Section 2.3 we present the inference method for the case probability under high-dimensional logistic regression model. We discuss inference for ITEs in Section 2.4.

2.1. Inference For $x_{\text{new}}^{\intercal}\beta$ in High-dimensional Linear Model (1)

For a given $x_{\text{new}} \in \mathbb{R}^p$, we construct the point estimator and confidence interval for $x_{\text{new}}^{\intercal}\beta$. We also consider the hypothesis testing problem,

$$H_0: x_{\text{new}}^{\mathsf{T}} \beta \le 0 \quad \text{vs.} \quad H_1: x_{\text{new}}^{\mathsf{T}} \beta > 0.$$
 (4)

We will review the estimation and inference procedures proposed in Cai *et al.* (2019). With $Y \in \mathbb{R}^n$ and $X \in \mathbb{R}^{n \times p}$, we estimate β with the Lasso estimator (Tibshirani 1996)

$$\widehat{\beta} = \arg\min_{\beta \in \mathbb{R}^p} \frac{\|Y - X\beta\|_2^2}{2n} + \lambda \sum_{j=1}^p \frac{\|X_{j}\|_2}{\sqrt{n}} |\beta_j|,$$
 (5)

where $\lambda > 0$ is the tuning parameter and $X_{\cdot j}$ denotes the j-th column of X. We estimate $\sigma^2 = \operatorname{Var}(\epsilon_i)$ by $\widehat{\sigma}^2 = \frac{1}{n} \|Y - X\widehat{\beta}\|_2^2$.

A natural way of estimating $x_{\text{new}}^{\intercal} \beta$ is to plug in the LASSO estimator $\widehat{\beta}$ defined in (5). However, this plug-in estimator $x_{\text{new}}^{\intercal} \widehat{\beta}$ is known to suffer from the bias induced by the penalty in the LASSO estimator. We correct the bias of the plug-in estimator through identifying an effective projection direction $\widehat{u} \in \mathbb{R}^p$. Our proposed bias corrected estimator for $x_{\text{new}}^{\intercal} \beta$ is

$$\widehat{x_{\text{new}}^{\mathsf{T}}} \, \widehat{\beta} = x_{\text{new}}^{\mathsf{T}} \, \widehat{\beta} + \widehat{u}^{\mathsf{T}} \frac{1}{n} \sum_{i=1}^{n} X_i \left(Y_i - X_i^{\mathsf{T}} \widehat{\beta} \right). \tag{6}$$

To effectively de-bias for an arbitrary x_{new} , we construct \widehat{u} as

$$\widehat{u} = \arg\min u^{\mathsf{T}} \widehat{\Sigma} u \quad \text{s.t.} \quad \max_{w \in \mathcal{C}} \left\langle w, \widehat{\Sigma} u - x_{\text{new}} \right\rangle \le \|x_{\text{new}}\|_2 \lambda_n$$
 (7)

where $\lambda_n \asymp \sqrt{\log p/n}$, $\widehat{\Sigma} = \frac{1}{n} \sum_{i=1}^n X_i X_i^{\mathsf{T}}$ and

$$C = \left\{ e_1, \cdots, e_p, \frac{1}{\|x_{\text{new}}\|_2} x_{\text{new}} \right\}.$$

More detailed discussion about this bias correction step can be found in Cai *et al.* (2019). This debiased estimator in (6) has been shown to be asymptotically normal in Cai *et al.* (2019). Based on the asymptotic normality, we construct a CI for the $x_{\text{new}}^{\dagger}\beta$ as

$$CI = \left(\widehat{x_{\text{new}}^{\mathsf{T}}\beta} - z_{\alpha/2}\sqrt{\widehat{V}}, \quad \widehat{x_{\text{new}}^{\mathsf{T}}\beta} + z_{\alpha/2}\sqrt{\widehat{V}}\right) \quad \text{with} \quad \widehat{V} = \frac{\widehat{\sigma}^2}{n}\widehat{u}^{\mathsf{T}}\widehat{\Sigma}\widehat{u}, \tag{8}$$

where $z_{\alpha/2}$ is the upper $\alpha/2$ quantile for the standard normal distribution.

For the hypothesis testing problem (4), we propose the testing procedure

$$\phi_{\alpha} = 1\left(\widehat{x_{\text{new}}^{\mathsf{T}}\beta} - z_{\alpha}\sqrt{\widehat{V}} > 0\right),\tag{9}$$

with $\widehat{x_{\text{new}}^{\mathsf{T}}\beta}$ and \widehat{V} defined in (6) and (8), respectively.

2.2. Inference For $\beta_G^{\mathsf{T}} A \beta_G$ in High-dimensional Linear Model (1)

We consider $G \subset \{1, 2, ..., p\}$ and $A \in \mathbb{R}^{|G| \times |G|}$ being a positive definite matrix. In this case, the group significance test $H_0: \beta_G = 0$ can be recast as

$$H_{0,A}: \beta_C^{\mathsf{T}} A \beta_G = 0. \tag{10}$$

The matrix A can be either known or unknown. When the matrix A is unknown, we also need to quantify the uncertainty of estimating A. Particularly, we focus on two cases:

- 1. A is known (e.g. A = I). When A = I, the quadratic form $\|\beta_G\|_2^2$ is the sum of the square of regression coefficients inside G.
- 2. $A = \Sigma_{G,G}$ where $\Sigma_{G,G}$ is unknown. In this case, $\beta_G^{\mathsf{T}} \Sigma_{G,G} \beta_G = \mathsf{E} |X_{i,G}^{\mathsf{T}} \beta_G|$ is the explained variance for variables inside group G.

We now introduce the estimation and inference methods proposed in Guo *et al.* (2019b). For estimating the quantity $Q = \beta_G^{\mathsf{T}} A \beta_G$, we start with the plug-in estimator $\hat{\beta}_G \hat{A}_{G,G} \hat{\beta}_G$ where $\hat{\beta}$ is the LASSO estimator given by (5) and

$$\widehat{A} = \begin{cases} A & \text{if A is known;} \\ \widehat{\Sigma} & \text{if } A = \Sigma \text{ is unknown.} \end{cases}$$

We propose the bias-corrected estimator as

$$\widehat{\mathbf{Q}} = \widehat{\beta}_G^{\mathsf{T}} \widehat{A}_{G,G} \widehat{\beta}_G + \frac{2}{n} \widehat{u}^{\mathsf{T}} X^{\mathsf{T}} (y - X \widehat{\beta}), \tag{11}$$

where $\hat{u} \in \mathbb{R}^p$ is the projection direction to be constructed in the following.

To de-bias for arbitrary G, we introduce the following projection direction,

$$\widehat{u} = \arg\min \ u^{\mathsf{T}} \widehat{\Sigma} u \quad \text{ s.t. } \max_{w \in \mathcal{C}} \left\langle w, \widehat{\Sigma} u - \left(\widehat{\beta}_{G}^{\mathsf{T}} \widehat{A}_{G,G} \quad \mathbf{0} \right)^{\mathsf{T}} \right\rangle \leq \left\| \widehat{A}_{G,G} \widehat{\beta}_{G} \right\|_{2} \lambda_{n}, \tag{12}$$

where
$$\lambda_n = C\sqrt{\log p/n}$$
 and $C = \left\{e_1, \cdots, e_p, \frac{1}{\|\widehat{A}_{G,G}\widehat{\beta}_G\|_2} \begin{pmatrix} \widehat{\beta}_G^{\mathsf{T}} \widehat{A}_{G,G} & 0 \end{pmatrix}^{\mathsf{T}} \right\}$.

In Guo *et al.* (2019b), the asymptotic normality of the estimator \hat{Q} defined in (11) has been established under regularity conditions. We estimate the variance of the proposed estimator \hat{Q} by

$$\widehat{\mathbf{V}}(\tau) = \begin{cases} \frac{4\widehat{\sigma}^2}{n} \widehat{u}_{\Sigma}^{\mathsf{T}} \widehat{\Sigma} \widehat{u}_{\Sigma} + \frac{\tau}{n} & \text{if } A \text{ is known} \\ \frac{4\widehat{\sigma}^2}{n} \widehat{u}_{\Sigma}^{\mathsf{T}} \widehat{\Sigma} \widehat{u}_{\Sigma} + \frac{1}{n^2} \sum_{i=1}^{n} \left(\widehat{\beta}_{G}^{\mathsf{T}} X_{iG} X_{iG}^{\mathsf{T}} \widehat{\beta}_{G} - \widehat{\beta}_{G}^{\mathsf{T}} \widehat{\Sigma}_{G,G} \widehat{\beta}_{G} \right)^2 + \frac{\tau}{n} & \text{if } A = \Sigma \text{ is unknown} \end{cases}$$

$$\tag{13}$$

where $\tau > 0$ is some positive constant with default value 0.5. Here, the term τ/n is introduced to address the super-efficiency issue of the bias-corrected estimator when $Q = \beta_G^{\dagger} A \beta_G$ is near zero; see Guo *et al.* (2019b) for more detailed discussion.

Having introduced the point estimator and the estimated variance, we construct confidence intervals for Q and propose the testing procedure for (10) as follows:

$$CI(\tau) = \left(\widehat{Q} - z_{\frac{\alpha}{2}}\sqrt{\widehat{V}(\tau)}, \widehat{Q} + z_{\frac{\alpha}{2}}\sqrt{\widehat{V}(\tau)}\right), \ \phi_{\alpha}(\tau) = 1\left(\widehat{Q} \ge z_{\alpha}\sqrt{\widehat{V}(\tau)}\right), \tag{14}$$

where \hat{Q} and $\hat{V}(\tau)$ are defined in (11) and (13), respectively.

2.3. Inference For Case Probabilities in Logistic Model (2)

The negative log-likelihood function for the data $\{(X_i, y_i)\}_{1 \leq i \leq n}$ under the logistic regression model (2) is

$$\ell(\beta) = \sum_{i=1}^{n} \left[\log \left(1 + \exp \left(X_i^{\mathsf{T}} \beta \right) \right) - y_i \cdot \left(X_i^{\mathsf{T}} \beta \right) \right].$$

The penalized log-likelihood estimator $\hat{\beta}$ (Bühlmann and van de Geer 2011) is defined as,

$$\widehat{\beta} = \arg\min_{\beta} \ell(\beta) + \lambda \|\beta\|_{1}, \tag{15}$$

where $\lambda \simeq \sqrt{\log p/n}$ is a tuning parameter.

We now introduce a bias-corrected estimator of $x_{\text{new}}^{\intercal}\beta$ proposed in Guo *et al.* (2019a). Specifically, we propose the following weighted bias-corrected estimator:

$$\widehat{x_{\text{new}}^{\mathsf{T}}\beta} = x_{\text{new}}^{\mathsf{T}}\widehat{\beta} + \widehat{u}^{\mathsf{T}}\frac{1}{n}\sum_{i=1}^{n}W_{i}X_{i}\left(y_{i} - h(X_{i}^{\mathsf{T}}\widehat{\beta})\right). \tag{16}$$

where $x_{\text{new}}^{\intercal}\widehat{\beta}$ is the plug-in estimator with $\widehat{\beta}$ defined in (15), $\{W_i\}_{1\leq i\leq n}$ are the weights to be determined and $\widehat{u}\in\mathbb{R}^p$ is the projection direction to be determined.

For the high-dimensional logistic regression, we shall choose $W_i = 1/h'(X_i^{\mathsf{T}}\widehat{\beta})$. Define $\widehat{\Sigma} = n^{-1} \sum_{i=1}^n X_i X_i^{\mathsf{T}}$. Then we construct projection direction \widehat{u} as in (7). Subsequently we estimate the case probability $\mathbb{P}(y_i = 1 | X_i = x_{\text{new}})$ by

$$\widehat{\mathbb{P}}(y_i = 1 | X_i = x_{\text{new}}) = h(\widehat{x_{\text{new}}^{\mathsf{T}}}\beta). \tag{17}$$

We construct the confidence interval for $h(x_{\text{new}}^{\intercal}\beta)$ as

$$CI = \left[h\left(\widehat{x_{\text{new}}^{\mathsf{T}}\beta} - z_{\alpha/2}\widehat{V}^{1/2}\right), h\left(\widehat{x_{\text{new}}^{\mathsf{T}}\beta} + z_{\alpha/2}\widehat{V}^{1/2}\right) \right] \text{ with } \widehat{V} = \widehat{u}^{\mathsf{T}} \left[\frac{1}{n^2} \sum_{i=1}^n h'(X_i^{\mathsf{T}}\widehat{\beta}) X_i X_i^{\mathsf{T}} \right] \widehat{u}.$$

$$(18)$$

We conduct the test (3) as follows

$$\phi_{\alpha}(x_{\text{new}}) = \mathbf{1}\left(\widehat{x_{\text{new}}^{\dagger}\beta} - z_{\alpha}\widehat{V}^{1/2} \ge 0\right).$$
 (19)

All other technical details for the above procedures can be found in Guo et al. (2019a).

Our proposed methods can be extended to incorporate other weights W_i . For any weight W_i , define $\widehat{\Gamma} = n^{-1} \sum_{i=1}^n W_i \cdot h'(X_i^{\mathsf{T}} \widehat{\beta}) X_i X_i^{\mathsf{T}}$ and construct the projection direction \widehat{u} as

$$\widehat{u} = \arg\min \ u^{\mathsf{T}}\widehat{\Gamma}u \quad \text{s.t.} \ \max_{w \in \mathcal{C}} \left\langle w, \widehat{\Gamma}u - x_{\text{new}} \right\rangle \le \|x_{\text{new}}\|_2 \lambda_n$$
 (20)

where $\lambda_n \simeq (\log p/n)^{1/2}$ and $C = \left\{e_1, \cdots, e_p, \frac{1}{\|x_{\text{new}}\|_2} x_{\text{new}}\right\}$.

Accordingly, we replace \hat{V} in (18) and (19) by

$$\widehat{\mathbf{V}} = \widehat{u}^{\mathsf{T}} \left[\frac{1}{n^2} \sum_{i=1}^n W_i^2 h(X_i^{\mathsf{T}} \widehat{\beta}) (1 - h(X_i^{\mathsf{T}} \widehat{\beta})) X_i X_i^{\mathsf{T}} \right] \widehat{u}.$$

As an example, Cai et al. (2020) propose an inference procedure for the regression coefficient β_i using the constant weight $W_i = 1$.

2.4. Inference for the Individualized Treatment Effects

Linear Regression

Consider high-dimensional linear regression models for the outcomes in two groups:

$$\mathbf{Y}_k = X_k \beta_k + \epsilon_k, \quad k = 1, 2 \tag{21}$$

where $\mathbf{Y}_k = (Y_{k,1}, \dots, Y_{k,n_k})^{\mathsf{T}} \in \mathbb{R}^{n_k}$ and $X_k = (X_{k,1}, \dots, X_{k,n_k})^{\mathsf{T}} \in \mathbb{R}^{n_k \times p}$ are the response and covariates observed independently for the n_k subjects in the group k respectively, $\epsilon_k = (\epsilon_{k,1}, \dots, \epsilon_{k,n_k})^{\mathsf{T}} \in \mathbb{R}^{n_k}$ is the error vector with constant variance $\sigma_k^2 = \text{var}(\epsilon_{k,i})$ and $\beta_k \in \mathbb{R}^p$ is the regression vector for the k^{th} group.

The bias-correction procedures in sections 2.1 can be easily extended to perform inference for the individualized treatment effect $\Delta_{\text{new}} := x_{\text{new}}^{\intercal} \beta_1 - x_{\text{new}}^{\intercal} \beta_2$.

For k=1,2, we construct a bias-corrected estimator of $x_{\text{new}}^{\intercal}\beta_k$ by applying the procedure (6) to the data in the k^{th} group. Specifically, for k=1,2, define $\widehat{\Sigma}_k = \frac{1}{n_k} \sum_{i=1}^{n_k} X_{k,i} X_{k,i}^{\intercal}$ and $\widehat{\beta}_k$ as the LASSO estimator in (5) applied to the data in the k^{th} group. We construct the projection direction \widehat{u}_k as in (7) with replacing $\widehat{\Sigma}$ by $\widehat{\Sigma}_k$. By modifying (6), we construct the bias-corrected estimator of $x_{\text{new}}^{\intercal}\beta_k$ as

$$\widehat{x_{\text{new}}^{\mathsf{T}}}\widehat{\beta}_{k} = x_{\text{new}}^{\mathsf{T}}\widehat{\beta}_{k} + \widehat{u}_{k}^{\mathsf{T}}\frac{1}{n_{k}}\sum_{i=1}^{n_{k}}X_{k,i}\left(Y_{k,i} - X_{k,i}^{\mathsf{T}}\widehat{\beta}_{k}\right).$$

Then we estimate Δ_{new} by

$$\widehat{\Delta_{\text{new}}} = \widehat{x_{\text{new}}^{\mathsf{T}}} \widehat{\beta_1} - \widehat{x_{\text{new}}^{\mathsf{T}}} \widehat{\beta_2}. \tag{22}$$

For k = 1, 2, we estimate $\sigma_k^2 = \operatorname{Var}(\epsilon_{k,i})$ by $\widehat{\sigma}_k^2 = \frac{1}{n_k} \|\mathbf{Y}_k - X_k \widehat{\beta}_k\|_2^2$. The corresponding confidence interval can then be constructed as

$$CI = \left(\widehat{\Delta_{\text{new}}} - z_{\alpha/2}\sqrt{\widehat{V}_{\text{new}}}, \quad \widehat{\Delta_{\text{new}}} + z_{\alpha/2}\sqrt{\widehat{V}_{\text{new}}}\right) \quad \text{with} \quad \widehat{V}_{\text{new}} = \sum_{k=1}^{2} \frac{\widehat{\sigma}_{k}^{2}}{n_{k}} \widehat{u}_{k}^{\mathsf{T}} \widehat{\Sigma}_{k} \widehat{u}_{k}. \quad (23)$$

For the hypothesis testing problem $H_0: \Delta_{\text{new}} \leq 0 \text{ v.s. } H_1: \Delta_{\text{new}} > 0$, we propose the test

$$\phi_{\alpha} = 1 \left(\widehat{\Delta_{\text{new}}} - z_{\alpha} \sqrt{\widehat{V}_{\text{new}}} > 0 \right)$$
 (24)

Logistic Regression

We consider two sample logistic regression models. For k = 1, 2, let $\mathbf{Y}_k = (y_{k,1}, \dots, y_{k,n_k})^{\mathsf{T}} \in \mathbb{R}^{n_k}$ and $X_k = (X_{k,1}, \dots, X_{k,n_k})^{\mathsf{T}} \in \mathbb{R}^{n_k \times p}$ denote the outcome and covariates for the group k. For the kth group with k = 1, 2, we consider the following conditional outcome model,

$$\mathbb{P}(\mathbf{Y}_{k,i} = 1 \mid X_{k,i}) = h(X_{k,i}^{\mathsf{T}}\beta_k), \quad \text{for} \quad 1 \le i \le n_k$$
 (25)

where $\beta_k \in \mathbb{R}^p$ is the regression vector for the k^{th} group.

For the two sample setting, we introduce the individualized treatment effect $\Delta_{\text{new}} := h(x_{\text{new}}^{\dagger}\beta_1) - h(x_{\text{new}}^{\dagger}\beta_2)$, which is the difference between two case probabilities. The bias-correction procedures in sections 2.3 can be easily extended to perform inference for Δ_{new} .

For k = 1, 2, we construct a bias-corrected estimator of $x_{\text{new}}^{\intercal}\beta_k$ by applying the procedure (16) to the data in the k^{th} group. We construct the projection direction \hat{u}_k as in (7) with replacing $\hat{\Sigma}$ by $\hat{\Sigma}_k := \frac{1}{n_k} \sum_{i=1}^{n_k} X_{k,i} X_{k,i}^{\intercal}$. Be defining $\hat{\beta}_k$ as the penalized maximum likelihood estimator in (15) applied to the data in the k^{th} group, we construct the bias-corrected estimator of $x_{\text{new}}^{\intercal}\beta_k$ as

$$\widehat{x_{\text{new}}^{\mathsf{T}}}\widehat{\beta}_{k} = x_{\text{new}}^{\mathsf{T}}\widehat{\beta}_{k} + \widehat{u}_{k}^{\mathsf{T}}\frac{1}{n_{k}}\sum_{i=1}^{n_{k}}W_{k,i}X_{k,i}\left(y_{k,i} - h(X_{k,i}^{\mathsf{T}}\widehat{\beta}_{k})\right).$$

with $W_{k,i} = h'(X_{k,i}^{\mathsf{T}} \widehat{\beta}_k)$. Then Δ_{new} is estimated by

$$\widehat{\Delta}_{\text{new}} = h(\widehat{x_{\text{new}}} \widehat{\beta}_1) - h(\widehat{x_{\text{new}}} \widehat{\beta}_2).$$
(26)

The asymptotic variance of $\widehat{x_{\text{new}}} \beta_1 - \widehat{x_{\text{new}}} \beta_2$ is estimated by

$$\widehat{V}_{\text{new}} = \sum_{k=1}^{2} \widehat{u}_{k}^{\mathsf{T}} \frac{1}{n_{k}^{2}} \sum_{i=1}^{n_{k}} h'(X_{k,i}^{\mathsf{T}} \widehat{\beta}_{k}) X_{k,i} X_{k,i}^{\mathsf{T}} \widehat{u}_{k}.$$
(27)

Consider the hypothesis testing

$$H_0: x_{\text{new}}^{\mathsf{T}}(\beta_1 - \beta_2) \le 0 \quad \text{vs.} \quad H_1: x_{\text{new}}^{\mathsf{T}}(\beta_1 - \beta_2) > 0,$$
 (28)

we propose the following test

$$\phi_{\alpha} = 1 \left(\widehat{x_{\text{new}}^{\mathsf{T}} \beta_1} - \widehat{x_{\text{new}}^{\mathsf{T}} \beta_2} - z_{\alpha} \sqrt{\widehat{V}_{\text{new}}} > 0 \right)$$
 (29)

That is, if $\widehat{x_{\text{new}}^{\intercal}\beta_1} - \widehat{x_{\text{new}}^{\intercal}\beta_2}$ is sufficiently larger than zero, we would reject the null hypothesis $H_0: x_{\text{new}}^{\intercal}(\beta_1 - \beta_2) \leq 0$.

2.5. Construction of Projection Direction

The construction of projection directions in (7), (12) and (20) are key to the bias correction step. In the following, we introduce the equivalent dual problem of constructing the projection direction. The constrained optimizer $\hat{u} \in \mathbb{R}^p$ can be computed in the form of $\hat{u} = -\frac{1}{2} \left[\hat{\mathbf{v}}_{-1} + \frac{x_*}{\|x_*\|_2} \hat{\mathbf{v}}_1 \right]$, where, $\hat{\mathbf{v}} \in \mathbb{R}^{p+1}$ is defined as

$$\widehat{\mathbf{v}} = \underset{\mathbf{v} \in \mathbb{R}^{p+1}}{\operatorname{arg \, min}} \left\{ \frac{1}{4} \mathbf{v}^{\mathsf{T}} \mathbb{H}^{\mathsf{T}} \widehat{\Sigma} \mathbb{H} \mathbf{v} + \mathbf{x}_{*}^{\mathsf{T}} \mathbb{H} \mathbf{v} + \lambda_{n} \|\mathbf{x}_{*}\|_{2} \cdot \|\mathbf{v}\|_{1} \right\}$$
(30)

with $\mathbb{H} = \left[\frac{x_{\text{new}}}{\|x_{\text{new}}\|_2}, \mathbb{I}_{p \times p}\right] \in \mathbb{R}^{p \times (p+1)}$ and

$$x_* = \begin{cases} x_{\text{new}} & \text{for } (7), (20) \\ (\widehat{\beta}_G^{\mathsf{T}} \widehat{A}_{G,G} & \mathbf{0})^{\mathsf{T}} & \text{for } (12) \end{cases}$$

We refer to Proposition 2 in Cai et al. (2019) for the detailed derivation of the dual problem (30). In this dual problem, when $\hat{\Sigma}$ is singular and the tuning parameter $\lambda_n > 0$ in (30) gets sufficiently close to 0, the dual problem cannot be solved as the minimum value converges to negative infinity. Hence we choose the smallest $\lambda_n > 0$ such that the dual problem has a finite minimum value. Such selection of the tuning parameter dated at least back to Javanmard and Montanari (2014).

3. Package

3.1. Inference for High-dimensional Linear Regression

LF

The function LF, shorthanded for Linear Functional, performs inference for $x_{\text{new}}^{\intercal}\beta$ under the high-dimensional linear regression (1). The function can be called with the following arguments

LF(X, y, loading, intercept = TRUE, init.Lasso = NULL, lambda = NULL, mu = NULL, step = NULL, resol = 1.5, maxiter = 6, alpha = 0.05, verbose = TRUE)

 $\mathtt{X} \in \mathbb{R}^{n \times p}$ and $\mathtt{y} \in \mathbb{R}^n$ are the design matrix and response vector in (1) respectively. loading denotes the observation vector $x_{\mathrm{new}} \in \mathbb{R}^p$. The intercept is not included in the design matrix X and the loading x_{new} . intercept is a logical argument specifying whether the intercept should be fitted (TRUE) or not (FALSE) and the default value is TRUE. The init.Lasso argument allows the user to supply the initial estimator $\widehat{\beta}$ of the regression vector. If init.Lasso is set to NULL, the initial estimator $\widehat{\beta}$ in (5) is computed using cv.glmnet. lambda denotes the tuning parameter used for computing $\widehat{\beta}$ in (5) which can either be pre-specified or can be set to NULL whence LF uses cv.glmnet to compute it.

The main step of computing the debiased estimator is to construct the projection direction \hat{u} specified in (7). In that context we need to solve the optimization problem in (30) with $x_* = x_{\text{new}}$. mu denotes the dual tuning parameter λ_n in (30). When mu is set as NULL, it is computed as the smallest λ_n such that (30) has a finite optimum value. LF is also flexibly designed to work with user-specified mu. Arguments step, resol (default = 1.5) and maxiter (default = 6) denote the number of steps, the resolution factor and the maximum number of iterations respectively used to search for λ_n . Part of the code for selecting mu is adopted from the publicly available code at https://web.stanford.edu/~montanar/sslasso/code.html. Lastly alpha denotes the level of significance α in (8).

Example 1. In the following code, we make inference for $x_{\text{new}}^{\mathsf{T}}\beta$ with a simulated dataset. Set n=100 and p=400. For $1\leq i\leq n$, the covariates $X_i\in\mathbb{R}^p$ are independently generated from the multivariate normal distribution with mean 0 and covariance $\Sigma=\mathbf{I}_{400}$, where \mathbf{I}_p denotes the identity matrix of dimension p. We generate the outcome following the model $Y=X\beta+\epsilon$, where $\{\epsilon_i\}_{1\leq i\leq n}$ are independently generated from the standard normal distribution and β is generated as $\beta_j=j/20$ for $1\leq j\leq 10$ and $\beta_j=0$ for $11\leq j\leq 500$. We generate $x_{\text{basis}}\in\mathbb{R}^{500}$ following $N(0,\Sigma/2)$ with with $\Sigma=\mathbf{I}_{400}$ and generate x_{new} as

$$x_{\text{new},j} = \begin{cases} x_{\text{basis},j} & \text{for } 1 \le j \le 10\\ \frac{1}{25} \cdot x_{\text{basis},j} & \text{for } 11 \le j \le 401 \end{cases}$$
 (31)

```
R> n = 100
R> p = 400
R> Cov = diag(p)
R> mu <- rep(0,p)
R> beta <- rep(0,p)
R> beta[1:10] <- c(1:10)/5
R> X <- MASS::mvrnorm(n,mu,Cov)
R> y = X%*%beta + rnorm(n)
R> loading <- MASS::mvrnorm(1,mu,Cov/2)
R> loading[11:p] <- loading[11:p]/25
R> Est <- SIHR::LF(X = X, y = y, loading = loading)</pre>
```

The outputs from implementing LF are shown below. prop.est and se denote the debiased estimator $\widehat{x_{\text{new}}^{\mathsf{T}}\beta}$ and the corresponding estimated standard error $\sqrt{\widehat{\mathsf{V}}}$, as proposed in (6) and (8), respectively. CI gives the confidence interval in (8); decision denotes the hypothesis test proposed in (9) with respect to the hypothesis in (4): decision taking a value of 1 implies $x_{\text{new}}^{\mathsf{T}}\beta > 0$.

```
R> Est$prop.est
          [,1]
[1,] 3.625
R> Est$se
[1] 0.163
R> Est$CI
[1] 3.304741 3.945416
R> Est$decision
[1] 1
```

ITE

The function ITE, shorthanded for Individualised Treatment Effect, conducts inference for $x_{\text{new}}^{\dagger}(\beta_1 - \beta_2)$ under the high-dimensional linear regression models (21). The function can be called with the following arguments:

```
ITE(X1, y1, X2, y2, loading, intercept = TRUE, init.Lasso1 = NULL,
init.Lasso2 = NULL,lambda1 = NULL, lambda2 = NULL, mu1 = NULL, mu2 = NULL,
step1 = NULL, step2 = NULL, resol = 1.5, maxiter = 10, alpha = 0.05)
```

Here, X1 and y1 denote respectively the design matrix and the response vector for the first group of data while X2 and y2 denote those for the second group of data. alpha denotes the level of significance α in (24). All other arguments are similarly defined as for the function LF.

Example 2. In the following code, we make inference for $x_{\text{new}}^{\intercal}(\beta_1 - \beta_2)$ with a simulated dataset. Set $n_1 = n_2 = 100$ and p = 400. For k = 1, 2 and $1 \le i \le 100$, we generate the covariates $X_{k,i} \in \mathbb{R}^p$ independently from the same multivariate normal distribution with mean 0 and covariance $\Sigma = \mathbf{I}_{400}$; generate the errors $\epsilon_{k,i}$ from the standard normal distribution. Generate the sparse regression vectors β_1 and β_2 as $\beta_{1,j} = j/5 \cdot \mathbf{1}\{1 \le j \le 10\}$ and $\beta_{2,j} = j/10 \cdot \mathbf{1}\{1 \le j \le 10\}$, for $1 \le j \le p$. The loading x_{new} is generated as in **Example 1**.

```
R > n1 = 100
R > n2 = 100
R > p = 400
R> mu <- rep(0,p)
R> Cov <- diag(p)
R> beta1 <- rep(0,p)</pre>
R > beta1[1:10] <- c(1:10)/5
R> beta2 <- rep(0,p)</pre>
R > beta2[1:5] <- c(1:5)/10
R> X1 <- MASS::mvrnorm(n1,mu,Cov)</pre>
R> X2 <- MASS::mvrnorm(n2,mu,Cov)
R> y1 = X1\%*\%beta1 + rnorm(n1)
R > y2 = X2\%*\%beta2 + rnorm(n2)
R> loading <- MASS::mvrnorm(1,mu,Cov/2)</pre>
R> loading[11:p] <- loading[11:p]/25</pre>
R> Est <- SIHR::ITE(X1 = X1, y1 = y1, X2 = X2, y2 = y2,loading = loading)
```

The main outputs from implementing ITE are shown below. prop.est denotes the debiased estimator $\widehat{\Delta}_{\text{new}}$ as proposed in (22). se and CI give the corresponding estimated standard error $\sqrt{\widehat{V}_{\text{new}}}$ and the confidence interval in (23), respectively. decision denotes the hypothesis test proposed in (24): decision taking a value of 1 implies $x_{\text{new}}^{\mathsf{T}}(\beta_1 - \beta_2) > 0$.

```
[1] 0.316
R> Est$CI
[1] -2.898 -1.658
R> Est$decision
[1] 0
```

QF

The function QF, abbreviated for Quadratic Functional, conducts inference for $\beta_G^{\mathsf{T}} A \beta_G$ under the high-dimensional linear regression (1). The function can be called with the following arguments.

```
QF(X, y, G, Cov.weight = TRUE, A = NULL, intercept = TRUE, tau.vec = c(1), init.Lasso = NULL, lambda = NULL, mu = NULL, step = NULL, resol = 1.5, maxiter = 10, alpha = 0.05)
```

The argument G denotes the set of indices $G \subset \{1,2,\ldots,p\}$. When Cov.weight is set as TRUE, the inference target is $\beta_G^{\mathsf{T}}\Sigma_{G,G}\beta_G$ where Σ is unknown; when Cov.weight is set as FALSE we need to provide a $|G| \times |G|$ -dimensional matrix A to conduct the inference for $\beta_G^{\mathsf{T}}A\beta_G$, otherwise QF stops with the error message "Please provide the matrix A". Specifically when Cov.weight is set as TRUE, QF solves the optimization problem in (30) with $x_* = \left(\widehat{\beta}_G^{\mathsf{T}}\widehat{\Sigma}_{G,G} - \mathbf{0}\right)^{\mathsf{T}}$; if FALSE, QF solves the optimization problem in (30) with $x_* = \left(\widehat{\beta}_G^{\mathsf{T}}A - \mathbf{0}\right)^{\mathsf{T}}$. tau.vec allows the user to supply with a vector of possible values for τ in (13) and the default value is 1. alpha denotes the level of significance α in (14). All other arguments for QF are defined similarly as

Example 3(a). In the following code, we make inference for $\beta_G^{\mathsf{T}} \Sigma_{G,G} \beta_G$ with a simulated dataset. The design matrix X, the response vector y and the vector of regression coefficients β are generated as in Example 1. We consider $G = \{1, \ldots, 200\}$.

```
R> n = 100
R> p = 400
R> Cov = diag(p)
R> mu <- rep(0,p)
R> beta <- rep(0,p)
R> beta[1:10] <- c(1:10)/5
R> X <- MASS::mvrnorm(n,mu,Cov)
R> y = X%*%beta + rnorm(n)
R> test.set =c(1:200)
R> Est <-SIHR::QF(X = X, y = y, G = test.set)</pre>
```

the function LF detailed in Section 3.1.1.

QF returns prop.est and se which denote the debiased estimator $\beta_G^\mathsf{T}\widehat{\Sigma_{G,G}}\beta_G$ and the corresponding standard error as proposed in (11) and (13), respectively. CI and decision refer to the confidence interval and the hypothesis test with respect to the hypothesis (10) respectively. They are computed using (14). Both the outputs CI and decision are in matrix form where the rows correspond to different values of τ in tau.vec. For any value of τ , decision taking a value of 1 implies $\beta_G^\mathsf{T}\Sigma_{G,G}\beta_G>0$.

Example 3(b). In the following code, we make inference for $\|\beta_G\|_2^2$ with a simulated dataset. The design matrix X, the response vector y and the vector of regression coefficients β are generated as in Example 1. We consider $G = \{1, \ldots, 200\}$.

```
R> n = 100
R> p = 400
R> Cov = diag(p)
R> mu <- rep(0,p)
R> beta <- rep(0,p)
R> beta[1:10] <- c(1:10)/5
R> X <- MASS::mvrnorm(n,mu,Cov)
R> y = X%*%beta + rnorm(n)
R> test.set =c(1:200)
R> A=diag(length(test.set))
R> Est <-SIHR::QF(X = X, y = y, G = test.set, Cov.weight = FALSE,A = A)</pre>
```

The main outputs from implementing QF in this scenario are presented below. The interpretation is the same as those for the output of Example 3(b).

```
R> Est$prop.est
        [,1]
[1,] 11.738
R> Est$se
[1] 0.400
R> Est$CI
        [,1]        [,2]
[1,] 10.95494 12.52195
R> Est$decision
[1] 1
```

3.2. Inference for High-dimensional Logistic Regression

 $LF_logistic$

The function LF_logistic performs inference for $x_{\text{new}}^{\intercal}\beta$ and the case probability $h(x_{\text{new}}^{\intercal}\beta)$ under the high-dimensional logistic regression model (2). The function can be called with the following arguments

```
LF_logistic(X, y, loading, weight = NULL, trans = TRUE, intercept = TRUE, init.Lasso = NULL, lambda = NULL, mu = NULL, step = NULL, resol = 1.5, maxiter = 10, alpha = 0.05)
```

X and y are the design matrix and response vector in (2) respectively. loading denotes the observation vector x_{new} . weight allows the user to supply the weight vector $W = (W_i)_{i=1}^n$ in (16) used for correcting the plug-in estimator. If weight is set as NULL, it is set as $W_i = \left(h(X_i^{\mathsf{T}}\widehat{\beta})\left(1-h(X_i^{\mathsf{T}}\widehat{\beta})\right)\right)^{-1}$. trans is a logical argument for the inference target: if trans is TRUE, then the target is the case probability $h(x_{\text{new}}^{\mathsf{T}}\beta)$; if FALSE, the target is the linear functional $x_{\text{new}}^{\mathsf{T}}\beta$. The default value of trans is TRUE. Lastly alpha denotes the level of significance α in (19). All other arguments are defined similarly as the LF function.

Example 4. The application of LF_logistic is explained in the following code. We set trans = TRUE thereby performing inference for $h(x_{\text{new}}^{\dagger}\beta)$. Set n=200 and p=400. For $1 \leq i \leq n$, the covariates $X_i \in \mathbb{R}^p$ are independently generated from the multivariate normal distribution with mean 0 and covariance $\Sigma = \mathbf{I}_{400}$. We generate the outcome following the model $y_i \sim \text{Bernoulli}(h(X_i^{\dagger}\beta))$, for $1 \leq i \leq n$ where the sparse regression vector β is generated as $\beta_j = 1/20 \cdot \mathbf{1}\{1 \leq j \leq 10\}$. The loading x_{new} is generated as in **Example 1**.

```
R> n = 200
R> p = 400
R> Cov = diag(p)
R> mu <- rep(0,p)
R> beta <- rep(0,p)
R> beta[1:5] <- c(1:5)/10
R> X <- MASS::mvrnorm(n,mu,Cov)
R> prob <- exp(X%*%beta)/(1+exp(X%*%beta))
R> y <- rbinom(n,1,prob)
R> loading <- MASS::mvrnorm(1,mu,Cov/2)
R> loading[11:p] <- loading[11:p]/25
R> Est <- SIHR::LF_logistic(X = X, y = y, loading = loading)</pre>
```

We present the output in the following. prop.est refers to the debiased estimator $h(x_{\text{new}}^{\intercal}\beta)$ proposed in (17). se and CI give the corresponding standard error $\sqrt{\hat{V}}$ and the confidence interval in (18), respectively. decision denotes the hypothesis test proposed in (19) with respect to the hypothesis in (3). decision taking a value of 1 implies $h(x_{\text{new}}^{\intercal}\beta) > 1/2$.

```
R> Est$prop.est
[1] 0.714
R> Est$se
     [,1]
[1,] 0.068
```

```
R> Est$CI
[1] 0.5655807 0.8271722
R> Est$decision
[1] 1
```

ITE Logistic

The function ITE_Logistic performs inference for $h(x_{\text{new}}^{\dagger}\beta_1) - h(x_{\text{new}}^{\dagger}\beta_2)$ or $x_{\text{new}}^{\dagger}(\beta_1 - \beta_2)$ under (25). The function can be called with the following arguments:

```
ITE_Logistic(X1, y1, X2, y2, loading, weight = NULL, trans = TRUE, intercept =
TRUE, init.Lasso1 = NULL, init.Lasso2 = NULL, lambda1 = NULL, lambda2 = NULL,
mu1 = NULL, mu2 = NULL, step1 = NULL, step2 = NULL, resol = 1.5, maxiter = 10,
alpha = 0.05)
```

X1 and y1 denote respectively the design matrix and the response vector for the first group while X2 and y2 denote those for the second group. alpha denotes the level of significance α in (29). All other arguments are similarly defined as for the function LF_logistic.

Example 5. The application of ITE_Logistic is explained in the following simulation study. Set $n_1 = n_2 = 400$ and p = 500. We set trans = FALSE thereby performing inference for $x_{\text{new}}^{\mathsf{T}}(\beta_1 - \beta_2)$. For k = 1, 2 and $1 \le i \le 100$, we generate the covariates $X_{k,i} \in \mathbb{R}^p$ independently from the same multivariate normal distribution with mean $\mathbf{0}$ and covariance $\Sigma = \mathbf{I}_{400}$. We set the regression vectors β_1 and β_2 as $\beta_{1,j} = j/5 \cdot \mathbf{1}\{1 \le j \le 10\}$ and $\beta_{2,j} = j/10 \cdot \mathbf{1}\{1 \le j \le 10\}$ and generate the binary outcomes as $y_{k,i} \sim \text{Bernoulli}\left(h(X_{k,i}^{\mathsf{T}}\beta_k)\right)$, for $1 \le i \le 100$ and k = 1, 2. The loading x_{new} is generated as in **Example 1**.

```
R > n1 = 400
R > n2 = 400
R > p = 500
R> mu <- rep(0,p)
R > Cov < - diag(p)
R > beta1 <- rep(0,p)
R > beta1[1:10] <- c(1:10)/5
R > beta2 <- rep(0,p)
R > beta2[1:5] <- c(1:5)/10
R> X1 <- MASS::mvrnorm(n1,mu,Cov)</pre>
R> X2 <- MASS::mvrnorm(n2,mu,Cov)</pre>
R > prob1 <- exp(X1%*%beta1)/(1+exp(X1%*%beta1))
R > prob2 <- exp(X2\%*\%beta2)/(1+exp(X2\%*\%beta2))
R > y1 < - rbinom(n1,1,prob1)
R > y2 < - rbinom(n2, 1, prob2)
R> loading <- MASS::mvrnorm(1,mu,Cov/2)</pre>
R> loading[11:p] <- loading[11:p]/25</pre>
R > Est <- SIHR::ITE\_Logistic(X1 = X1, y1 = y1, X2 = X2,
                                y2 = y2, loading = loading, trans = FALSE)
```

We present the algorithm output in the following. prop.est and se below denote the debiased estimator for $x_{\text{new}}^{\intercal}(\beta_1 - \beta_2)$ and the corresponding estimated standard error proposed in (27), respectively. CI gives the confidence interval. decision denotes the hypothesis test (29) with respect to the hypothesis (28). decision taking a value of 1 implies $x_{\text{new}}^{\intercal}\beta_1 - x_{\text{new}}^{\intercal}\beta_2 > 0$.

```
R> Est$prop.est
[1] 1.476
R> Est$se
       [,1]
[1,] 0.587
R> Est$CI
[1] 0.3248793 2.6262071
R> Est$decision
[1] 1
```

4. Applications

4.1. Motif Regression

We demonstrate the use of LF and QF function on a motif regression problem for predicting transcription factor binding sites (TFBS, also called 'motifs') in DNA sequences. The data set consists of a univariate response variable measuring the binding intensity of the transcription factor on coarse DNA segments. The data consists of n = 2587 genes (samples). Moreover, for each of the n genes, a score describing the abundance of occurrence, is available for each of the p = 666 candidate motifs. This data set has been previously explored in Yuan, Lei, Shen, and Liu (2007). To summarize we have the following data:

```
Y_i: the binding intensity of the transcription factor on coarse DNA segment i X_{i,j}: the abundance score of candidate motif j in DNA segment i i = 1, \dots, n; \quad j = 1, \dots, p
```

Inference for single regression coefficients

We apply the package function SIHR::LF and construct confidence intervals for the first 30 regression coefficients in Fig. 1. Out of 30, 12 CIs (marked red) are found to be lying completely below 0 implying that the corresponding motif contributes negatively to the binding intensity of the transcription factor.

Group Test

In this section we test the significance of the first 200 motifs in explaining the binding intensity of the transcription factor. We test the equivalent hypothesis $H_0: \|\beta_G\|_2 = 0$ using the QF function. Specifically we set Cov.weight = FALSE and A = diag(200). The code returned decision = 1 which implies $\|\beta_G\|_2 \neq 0$; in words, this implies that the first 200 covariates are significantly associated with the binding intensity of the transcription factor.

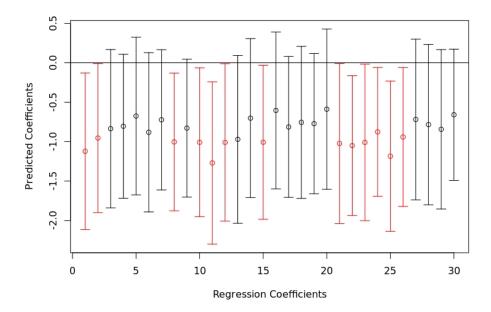


Figure 1: Constructed confidence intervals for the first 30 regression coefficients. The red CIs lie completely below 0.

Further to conduct the inference for $\beta_G^{\mathsf{T}} \Sigma_{G,G} \beta_G$ we use the function QF with Cov.weight = TRUE. The code returned decision = 1, which indicates that $\beta_G^{\mathsf{T}} \Sigma_{G,G} \beta_G > 0$.

Linear Combination

The package SIHR enables to perform inference for arbitrary linear combination of regression coefficients. We illustrate the procedure by randomly sampling 30 genes and then considering the corresponding covariate vectors as x_{new} . We use LF on the entire data to learn the unknown parameters β . The confidence intervals constructed for the linear combinations are plotted in Fig. 2.

4.2. Fasting Glucose Level Data

The aim is to analyze the effect of polymorphic genetic markers on the glucose level in a stock mice population using the LF_logistic function. The data set is available at https://wp.cs.ucl.ac.uk/outbredmice/heterogeneous-stock-mice/. Since fasting glucose level is an important indicator of type—2 diabetes, the fasting glucose level dichotomized at 11.1 (unit: mmol/L) is taken as the response variable. Specifically, glucose level below 11.1 is taken as normal and above 11.1 is as high (pre-diabetic and diabetic). The covariates consist of 10, 346 polymorphic genetic markers and the sample size is 1,269. We include "gender" and "age" as baseline covariates. The polymorphic markers and baseline covariates are standardized before analysis. However the number of polymorphic markers is large and there exist high correlation among some of them. To address this issue, we select a subset of polymorphic markers such that the maximum of the absolute correlation among the markers is below 0.75.

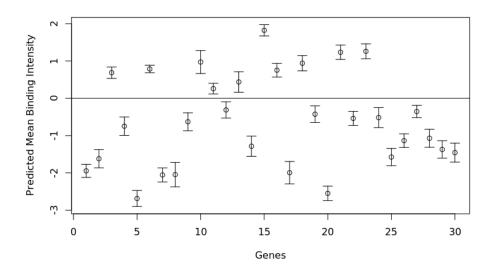


Figure 2: Constructed confidence intervals for the mean binding intensity corresponding to the 30 genes (samples).

Eventually, we select a subset of 2,270 polymorphic markers. In our analysis, we secured the first 30 subjects as the test sample, then their predictor vectors were treated as x_{new} . A prediction model for each outcome variable was developed using the remaining 1,239 subjects and then applied to the test sample to obtain bias-corrected estimates of the case probabilities LF_logistic. Figure 3 presents confidence intervals constructed using our method for the case probabilities.

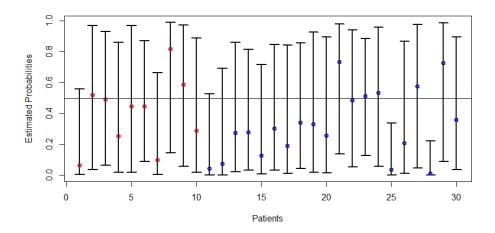


Figure 3: Confidence interval construction: indices 1 to 10 (the point estimators colored in red) correspond to observations with high glucose level; indices 11 to 30 (the point estimators colored in blue) correspond to those with normal glucose level.

5. Conclusion

High-dimensional statistical inference is immensely useful in a wide range of applications. We developed the R package SIHR to provide user-friendly algorithms for inference procedures for high-dimensional linear and logistic regression models. This article demonstrates the usage of the R package SIHR with both simulated and real data.

Acknowledgement

Dr. Tony Cai's research was supported in part by NSF grant DMS-2015259 and NIH grants R01-GM129781 and R01-GM123056. Dr. Zijian Guo's research was supported in part by NSF grants DMS-1811857 and DMS-2015373 and NIH grants R01-GM140463 and R01-LM013614. Dr. Zijian Guo is grateful to Dr. Lukas Meier for sharing the motif regression data used in Section 4.1.

References

- Athey S, Imbens GW, Wager S (2016). "Approximate residual balancing: De-biased inference of average treatment effects in high dimensions." arXiv preprint arXiv:1604.07125.
- Belloni A, Chernozhukov V, Wang L (2011). "Square-root LASSO: pivotal recovery of sparse signals via conic programming." *Biometrika*, **98**(4), 791–806.
- Bühlmann P, van de Geer S (2011). Statistics for high-dimensional data: methods, theory and applications. Springer Science & Business Media.
- Cai T, Cai TT, Guo Z (2019). "Optimal Statistical Inference for Individualized Treatment Effects in High-dimensional Models." Journal of the Royal Statistical Society: Series B (Statistical Methodology).
- Cai TT, Guo Z (2017). "Confidence intervals for high-dimensional linear regression: Minimax rates and adaptivity." The Annals of statistics, 45(2), 615–646.
- Cai TT, Guo Z (2020). "Semisupervised inference for explained variance in high dimensional linear regression and its applications." *Journal of the Royal Statistical Society: Series B* (Statistical Methodology), 82(2), 391–419.
- Cai TT, Guo Z, Ma R (2020). "Statistical Inference for High-Dimensional Generalized Linear Models with Binary Outcomes." Research Manuscript.
- Chernozhukov V, Chetverikov D, Demirer M, Duflo E, Hansen C, Newey W, Robins J (2017). "Double/debiased machine learning for treatment and causal parameters." *Technical report*.
- Fan J, Li R (2001). "Variable Selection via Nonconcave Penalized Likelihood and its Oracle Properties." *Journal of the American Statistical Association*, **96**, 1348–1360.
- Guo Z, Rakshit P, Herman DS, Chen J (2019a). "Inference for Case Probability in High-dimensional Logistic Regression." *Unknown*.

- Guo Z, Renaux C, Buhlmann P, Cai TT (2019b). "Group Inference in High Dimensions with Applications to Hierarchical Testing." *Unknown*.
- Guo Z, Wang W, Cai TT, Li H (2019c). "Optimal estimation of genetic relatedness in high-dimensional linear models." *Journal of the American Statistical Association*, **114**, 358–369.
- Huang J, Zhang CH (2012). "Estimation and selection via absolute penalized convex minimization and its multistage adaptive applications." *Journal of Machine Learning Research*, **13**(Jun), 1839–1864.
- Javanmard A, Montanari A (2014). "Confidence intervals and hypothesis testing for high-dimensional regression." The Journal of Machine Learning Research, 15(1), 2869–2909.
- Meinshausen N, Yu B (2009). "LASSO-type recovery of sparse representations for high-dimensional data." *The Annals of Statistics*, **37**(1), 246–270.
- Negahban S, Yu B, Wainwright MJ, Ravikumar PK (2009). "A unified framework for high-dimensional analysis of *M*-estimators with decomposable regularizers." In *Advances in Neural Information Processing Systems*, pp. 1348–1356.
- Ning Y, Liu H (2017). "A general theory of hypothesis tests and confidence regions for sparse high dimensional models." *The Annals of Statistics*, **45**(1), 158–195.
- Sun T, Zhang CH (2012). "Scaled Sparse Linear Regression." Biometrika, 99(4), 879–898.
- Tibshirani R (1996). "Regression shrinkage and selection via the LASSO." Journal of the Royal Statistical Society: Series B (Statistical Methodology), 58(1), 267–288.
- Tripuraneni N, Mackey L (2019). "Debiasing linear prediction." arXiv preprint arXiv:1908.02341.
- van de Geer S, Bühlmann P, Ritov Y, Dezeure R (2014). "On asymptotically optimal confidence regions and tests for high-dimensional models." *The Annals of Statistics*, **42**(3), 1166–1202.
- Yuan Y, Lei G, Shen L, Liu JS (2007). "Predicting Gene Expression from Sequence: A Reexamination." *PLOS Computational Biology*, **11**(3).
- Zhang CH (2010). "Nearly Unbiased Variable Selection under Minimax Concave Penalty." *The Annals of Statistics*, **38**(2), 894–942.
- Zhang CH, Zhang SS (2014). "Confidence intervals for low dimensional parameters in high dimensional linear models." Journal of the Royal Statistical Society: Series B (Statistical Methodology), 76(1), 217–242.
- Zhu Y, Bradic J (2018). "Linear hypothesis testing in dense high-dimensional linear models." Journal of the American Statistical Association, 113(524), 1583–1600.

Affiliation:

Zijian Guo Department of Statistics Rutgers, the State University of New Jersey

E-mail: zijguo@stat.rutgers.edu

URL: https://statistics.rutgers.edu/home/zijguo/

http://www.jstatsoft.org/

http://www.foastat.org/

Submitted: yyyy-mm-dd

Accepted: yyyy-mm-dd