# Empirical Likelihood Ratio Tests for Coefficients in High Dimensional Heteroscedastic Linear Models

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**Abstract**

This paper considers hypothesis testing problems for a low-dimensional coefficient vector in a high-dimensional linear model with heteroscedastic variance. Heteroscedasticity is a commonly observed phenomenon in many applications including finance and genomic studies. Several statistical inference procedures have been proposed for low-dimensional coefficients in a high-dimensional linear model with homoscedastic variance. However, existing procedures designed for homoscedastic variance are not applicable for models with heteroscedastic variance and the heterscedasticity issue has been rarely investigated and studied. We propose a simple inference procedure based on empirical likelihood to overcome the heteroscedasticity issue. The proposed method is able to make valid inference even when the conditional variance of random error is an unknown function of high-dimensional predictors. We apply our inference procedure to three recently proposed estimating equations and establish the asymptotic distributions of the proposed methods. Simulation studies and real data analyses are conducted to demonstrate the proposed methods.

# 1 Introduction

In the last two decades, rapid progress has been made in high dimensional statistics. In particular, high-dimensional linear regression models have received tremendous attention. Many regularization methods have been proposed for simultaneous estimation and variable selection in linear models which include LASSO (Tibshirani, 1996), SCAD (Fan and Li, 2001), MCP (Zhang, 2010), among others. A vast majority of existing literature has focused on the estimation for coefficients in linear models with homoscedastic random errors. An excellent review can be found in Bühlmann and Van De Geer (2011).

The issue of heteroscedasticity is commonly seen in practice. However, it has not received much attention in high dimensional statistics literature. Wang et al. (2012) analyzed the heteroscedasticity in high dimensional case by using quantile regression. Daye et al. (2012) proposed a method that allows nonconstant error variances for high dimensional estimation but with a parametric form of the variance function. More recently, Belloni et al. (2014) came up with a self-tuning square root Lasso estimation method that solved this important problem in high dimensional regression analysis.

Although significant advancements have been made towards understanding the estimation theory for high dimensional models, less has been done for statistical inference for regression coefficients in a high dimensional model. Recently, important progresses have been achieved

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for the inference about low dimensional parameters in a high dimensional model, including Zhang and Zhang (2014), Bühlmann (2013), Javanmard and Montanari (2013), van de Geer et al. (2013), Lan et al. (2016), and Ning and Liu (2014).

All the above inference procedures assume homoscedasticity for the error term. More specifically, the conditional variance of the error is a constant. This is essential for their inference procedure to be valid since most existing methods require an accurate estimation of the variance of the proposed estimators. However, we find that, the variances of these existing estimators are very complex and difficult to estimate under the heteroscedasticity case. In addition, homoscedasticity hardly holds in practice. Similarly there is rarely sufficient information to accurately specify a correct variance function. Using incorrect variance models will, in general, lead to inferences that are not asymptotically valid (Belsley, 2002). Wagener and Dette (2012) generalized the asymptotic results of Knight and Fu (2000) for the case of a fixed dimension under heteroscedasitic errors. But there is little work in statistical inference dealing with heteroscedasticity under the high dimensional setting except that Dezeure et al. (2016) recently proposed bootstrap methods for inference under high dimensional linear models with heteroscedastic errors.

This paper proposes to use Empirical Likelihood (EL) to test statistical hypotheses and construct confidence regions for low dimensional components in high dimensional liner models with heteroscedastic noise. EL (Owen, 2001) is a nonparametric approach for deriving estimations and confidence regions for unknown parameters, which shares the most well known merit of parametric likelihood, the Wilks property (Owen, 1990, 2001). Professor Peter Hall made fundamental contribution to EL. He showed that EL is Bartlett correctable (Hall, 1990; DiCiccio et al., 1991) and produces confidence regions with natural shape and orientation (Hall and La Scala, 1990). As EL is a data-driven nonparametric method, it does not need distribution assumptions except some moment conditions. EL based methods have been used for statistical inferences with heteroscedasiticity in low dimensional case. Tsao and Wu (2006) conducted EL inference for a common mean in the presence of heteroscedasticity. Chen and Qin (2003) considered the EL based point-wise confidence intervals for a nonparametric regression function with the heteroscedastic errors. Lu (2009) and Zhou et al. (2012) discussed EL analysis for heteroscedastic partially linear models and heteroscedastic accelerated failure time models respectively. However, EL based method has not been used for the problem considered in this paper. A comprehensive overview of the EL methods can be found in Owen (2001) and a survey of recent developments is referred to Chen and Van Keilegom (2009).

Different from the existing methods, our proposed procedure does not need to estimate the variance explicitly due to the internal studentizing ability of EL. This makes our procedure attractive especially under the heteroscedasticity setting, even when the conditional variance of the error term is an unknown function of high dimensional predictors. The proposed EL-based method is a general unified framework suitable for various estimating equations as long as they satisfy some conditions specified later. Thus our EL-based inference procedure is widely applicable and hence useful in practice.

The paper is organized as follows. In section 3, we study the asymptotic normality of Wald type statistic for the existing methods under the heteroscedastic noise. In section

4, we introduce a general empirical likelihood based method for the problems considered in this paper. In addition, we provide explicit examples of the general EL-based method. Section 5 provides numerical results and Section 6 shows some real data analysis, followed by discussions in Section 7. We relegate all the technical proofs to the Appendix.

# 2 Basic setup and notations

We consider the following linear regression model,

$$\mathbb{Y} = \mathbb{X}\boldsymbol{\beta}^0 + \boldsymbol{\epsilon}, \tag{2.1}$$

where $\mathbb{Y} = (Y_1, Y_2, \cdots, Y_n)^\intercal \in \mathbb{R}^n$ is the response vector, $\boldsymbol{\epsilon} = (\epsilon_1, \epsilon_2, \cdots, \epsilon_n)^\intercal \in \mathbb{R}^n$ is the vector of noise, $\mathbb{X} = ((X_{ij})) \in \mathbb{R}^{n\times p}$ is the random design matrix with $p$ columns $\{\mathbb{X}_j \in \mathbb{R}^{n\times 1}\}_{j=1}^p$ and $n$ rows $\{\mathbf{X}_i^\intercal \in \mathbb{R}^{1\times p}\}_{i=1}^n$. The row vectors are assumed to be independent and identically distributed (IID) with $\mathrm{E}(\mathbf{X}_i) = \mathbf{0}$ and $\mathrm{Var}(\mathbf{X}_i) = \boldsymbol{\Sigma} = ((\sigma_{jl}))_{1\le j,l\le p}$, and $\boldsymbol{\beta}^0 \in \mathbb{R}^p$ is a vector of unknown true regression coefficients. The independent error terms satisfy $\mathrm{E}(\epsilon_i|\mathbf{X}_i) = 0$, and $\mathrm{Var}(\epsilon_i) = \sigma_i^2$. This is the commonly seen heteroscedastic model (White, 1980; Li and Yao, 2015; Daye et al., 2012; Bai et al., 2016; Dezeure et al., 2016). Let $\mathbf{Z}_i = \epsilon_i\mathbf{X}_i$ be a random vector. Note that with these assumptions, $\mathbf{X}_i$ and $\epsilon_i$ are uncorrelated, i.e., $\mathrm{E}(\mathbf{Z}_i) = \mathbf{0}$. In addition, marginally we assume $\mathrm{Var}(\epsilon_i^2) = \kappa_i$. We denote the covariance matrix of $\mathbf{Z}_i$ by $\boldsymbol{\Theta}_i = ((\theta_{i;jk}))$.

In practice, among thousands of regressors, investigators might want to test whether some target coefficients are significant or not. For example, one may want to know if treatment effects are significant after accounting for the effects of many other variables. This paper focuses on assessing the significance of a single coefficient. We test the following hypothesis for any given $j \in \{1, 2, \cdots, p\}$,

$$H_0 : \beta_j^0 = 0 \quad \text{vs.} \quad H_1 : \beta_j^0 \neq 0, \tag{2.2}$$

in (2.1) with $p \gg n$ assuming heteroscedastic errors.

The following notations are adopted throughout the paper. For $\mathbf{v} = (v_1, v_2, \cdots, v_d)^\intercal \in \mathbb{R}^d$, we define $\|\mathbf{v}\|_q = (\sum_{i=1}^d |v_i|^q)^{1/q}$ for $0 < q < \infty$, $\|\mathbf{v}\|_0 = |\mathrm{supp}(\mathbf{v})|$ where $\mathrm{supp}(\mathbf{v}) = \{j : v_j \neq 0\}$ and $|A|$ is the cardinality of a set $A$, and $\|\mathbf{v}\|_\infty = \max_{1\le j\le d}|v_i|$. We denote $\mathbf{I}_d$ as a $d \times d$ identity matrix. If the dimension is obvious from the context, we just omit the subscript $d$. For $\mathcal{S} \subseteq \{1, 2\cdots, d\}$, let $\mathbf{v}_\mathcal{S} = \{v_j : j \in \mathcal{S}\}$ be a subvector of $\mathbf{v}$. And for any $k \in \{1, 2, \cdots, d\}$, let $\mathbf{M}_{j\mathcal{S}} = \{M_{jl}, l \in \mathcal{S}\}$ as a row vector and $\mathbf{M}_{\mathcal{S}j} = \{M_{lj} : l \in \mathcal{S}\}$ as a column vector. Denote $\backslash k = \{1, 2, \cdots, k-1, k+1, \cdots, d\}$ as the $(d-1)$-dim vector with the $k-$th component removed. For a sequence of random variables $X_n$, we use $X_n \xrightarrow{d} X$ to denote the convergence in distribution, and use $X_n \xrightarrow{p} a$ to denote convergence in probability. Let $s = \|\boldsymbol{\beta}^0\|_0$ be the number of non-zeros of $\boldsymbol{\beta}^0$ and we assume sparsity with $s < n$.

# 3 Asymptotic properties of some existing methods under heteroscedasticity

To motivate our proposed method, we first study three existing methods and derive their asymptotic properties for these estimators under the heteroscedastic linear model (2.1). Note that these methods were only studied under the homogeneous linear models, i.e. $\mathrm{Var}(\epsilon_i|\mathbf{X}_i) = \sigma_\epsilon^2$ for all $i = 1, 2, \cdots, n$. We generalize these results to the heteroscedasticity case.

## 3.1 Low-dimensional projection method

In this subsection, we introduce the low dimensional projection method proposed by Zhang and Zhang (2014). Under model (2.1) and the low dimensional scenario with $p < n$, the ordinary least square (OLS) estimator for $\beta_j^0$,

$$\hat{\beta}_j = \frac{(\mathbb{X}_j^\perp)^\intercal \mathbb{Y}}{(\mathbb{X}_j^\perp)^\intercal \mathbb{X}_j} = \frac{(\mathcal{Q}_{\setminus j}\mathbb{X}_j)^\intercal \mathbb{Y}}{(\mathcal{Q}_{\setminus j}\mathbb{X}_j)^\intercal \mathbb{X}_j} = \frac{(\mathcal{Q}_{\setminus j}\mathbb{X}_j)^\intercal (\mathcal{Q}_{\setminus j}\mathbb{Y})}{(\mathcal{Q}_{\setminus j}\mathbb{X}_j)^\intercal (\mathcal{Q}_{\setminus j}\mathbb{X}_j)} = \frac{\mathbb{X}_j^\intercal \mathcal{Q}_{\setminus j}\mathbb{Y}}{\mathbb{X}_j^\intercal \mathcal{Q}_{\setminus j}\mathbb{X}_j}, \tag{3.1}$$

where $\mathbb{X}_j^\perp$ is the projection of $\mathbb{X}_j$ to the orthogonal complement of the column space spanned by $\{\mathbb{X}_{\setminus j}\}$, and $\mathcal{Q}_{\setminus j}$ is defined below for any general $\mathcal{Q}_\mathcal{S}$ with $\mathcal{S} \subseteq \{1, 2 \cdots, p\}$ and $|\mathcal{S}| < n$, $\mathcal{Q}_\mathcal{S} = \mathbf{I} - \mathcal{P}_\mathcal{S} = \mathbf{I} - \mathbb{X}_\mathcal{S}(\mathbb{X}_\mathcal{S}^\intercal \mathbb{X}_\mathcal{S})^- \mathbb{X}_\mathcal{S}^\intercal \in \mathbb{R}^{n\times n}$, where $(\mathbb{X}_\mathcal{S}^\intercal \mathbb{X}_\mathcal{S})^-$ is a generalized inverse of $\mathbb{X}_\mathcal{S}^\intercal \mathbb{X}_\mathcal{S}$.

In the high-dimensional linear model with $p > n$, the OLS estimator in (3.1) is no longer valid because $\mathcal{Q}_{\setminus j}\mathbb{Y}$ and $\mathcal{Q}_{\setminus j}\mathbb{X}_j$ are always 0. To resolve the issue in the high-dimensional case, Zhang and Zhang (2014) proposed a de-biased estimator. We briefly introduce their idea here. Let $\mathbb{Z}_j$ be an $n \times 1$ projection vector. A simple estimate of $\beta_j^0$ is

$$\hat{\beta}_j^{(\mathrm{lin})} = \frac{\mathbb{Z}_j^\intercal \mathbb{Y}}{\mathbb{Z}_j^\intercal \mathbb{X}_j} = \beta_j^0 + \frac{\mathbb{Z}_j^\intercal \boldsymbol{\epsilon}}{\mathbb{Z}_j^\intercal \mathbb{X}_j} + \mathrm{Bias}(\hat{\beta}_j^{(\mathrm{lin})}), \tag{3.2}$$

where $\mathrm{Bias}(\hat{\beta}_j^{(\mathrm{lin})}) = \sum_{k\neq j} \mathbb{Z}_j^\intercal \mathbb{X}_k \beta_k^0 / \mathbb{Z}_j^\intercal \mathbb{X}_j$ is a bias term. The second term in (3.2) has mean zero and at the order $1/\sqrt{n}$. Because of the bias term is not ignorable, $\hat{\beta}_j^{(\mathrm{lin})}$ is not directly useful for inference. To make $\hat{\beta}_j^{(\mathrm{lin})}$ useful for inference, we need to reduce the order of the bias term $\mathrm{Bias}(\hat{\beta}_j^{(\mathrm{lin})})$ to $o_p(1/\sqrt{n})$. To reduce the order of the bias of $\hat{\beta}_j^{(\mathrm{lin})}$, Zhang and Zhang (2014) proposed the following de-biased estimator,

$$\hat{\beta}_j^{(\mathrm{de})} = \frac{\mathbb{Z}_j^\intercal \mathbb{Y} - \sum_{k\neq j} \mathbb{Z}_j^\intercal \mathbb{X}_k \hat{\beta}_k^{(0)}}{\mathbb{Z}_j^\intercal \mathbb{X}_j}, \tag{3.3}$$

where $\hat{\boldsymbol{\beta}}^{(0)}$ is some initial regularized estimator of $\boldsymbol{\beta}^0$ so that $\|\hat{\boldsymbol{\beta}}^{(0)} - \boldsymbol{\beta}^0\|_1 = o(a_n)$ for some $a_n \to 0$. Then the bias of $\hat{\beta}_j^{(\mathrm{de})}$ is controlled by

$$|\sum_{k\neq j} \mathbb{Z}_j^\intercal \mathbb{X}_k (\beta_k^0 - \hat{\beta}_k^{(0)}) / \mathbb{Z}_j^\intercal \mathbb{X}_j| \leq \|\hat{\boldsymbol{\beta}}^{(0)} - \boldsymbol{\beta}^0\|_1 \max_{k\neq j} |\mathbb{Z}_j^\intercal \mathbb{X}_k / \mathbb{Z}_j^\intercal \mathbb{X}_j|.$$

Note that, to make the right hand side of the above inequality to be of order $o_p(1/\sqrt{n})$, only removing the bias using $\hat{\boldsymbol{\beta}}^{(0)} - \boldsymbol{\beta}^0$ is not enough because $\|\hat{\boldsymbol{\beta}}^0 - \boldsymbol{\beta}^0\|_1$ is typically of order $O_p(s\sqrt{\log p/n})$ (Belloni et al., 2014). Therefore, we need to make $\max_{k\neq j} |\mathbb{Z}_j^\intercal \mathbb{X}_k|$ small enough. Ideally, if $\mathbb{Z}_j$ is orthogonal to all $\mathbb{X}_k, k \neq j$, then $\max_{k\neq j} |\mathbb{Z}_j^\intercal \mathbb{X}_k|$ is 0. However, this is impossible if $p > n$. Therefore, a key problem is on selecting projection vector $\mathbb{Z}_j$.

In Zhang and Zhang (2014), van de Geer et al. (2013), and Ning and Liu (2014), they used the linear sparse regularized regression procedure such as LASSO to select the projection vector. Define $\eta_{ij} := X_{ij} - \mathbf{X}_{i,\backslash j}^\intercal \boldsymbol{\Sigma}_{\backslash j,\backslash j}^{-1} \boldsymbol{\Sigma}_{\backslash j,j}$, that is

$$X_{ij} = \mathbf{X}_{i,\backslash j}^\intercal \mathbf{w}_j^0 + \eta_{ij}, \text{ with } \mathbf{w}_j^0 = \boldsymbol{\Sigma}_{\backslash j,\backslash j}^{-1} \boldsymbol{\Sigma}_{\backslash j,j}, \text{ for } i = 1, 2, \cdots, n.$$

This leads to a de-biased version of (3.3) with $\mathbb{Z}_j = \mathbb{X}_j - \mathbb{X}_{\backslash j} \hat{\mathbf{w}}_j$ with $\hat{\mathbf{w}}_j$ as an regularized estimator of $\mathbf{w}_j^0$.

Under the homoscedastic case, as discussed in Zhang and Zhang (2014) and van de Geer et al. (2013), the inference procedure can be bulit on asymptotic normality of $\hat{\beta}_j^{(\mathrm{de})}$, which requires to estimate the asymptotic variance $\sigma_\epsilon^2/(\sigma_{jj} - \boldsymbol{\Sigma}_{j,\backslash j} \boldsymbol{\Sigma}_{\backslash j,\backslash j}^{-1} \boldsymbol{\Sigma}_{\backslash j,j})$. In Zhang and Zhang (2014) and Dezeure et al. (2016), they used $\hat{\sigma}_\epsilon^2 \|\mathbb{Z}_j\|_2^2 / |\mathbb{Z}_j^\intercal \mathbb{X}_j|^2$ with $\hat{\sigma}_\epsilon^2$ estimated from scaled LASSO-LSE (Zhang and Zhang, 2014) or from the recommended method in Reid et al. (2016). Under the heteroscedastic noise, we can also establish the asymptotic normality but with much more complicated asymptotic variance than the homoscedastic case. Let us firstly define the asymptotic variance of $\hat{\beta}_j^{(\mathrm{de})}$ as following

$$\sigma_{n,\mathrm{lasso}}^2 = \frac{1}{n} \sum_{i=1}^n \frac{\theta_{i;jj} - 2\boldsymbol{\Sigma}_{j,\backslash j} \boldsymbol{\Sigma}_{\backslash j,\backslash j}^{-1} \boldsymbol{\Theta}_{i;j,\backslash j} + \boldsymbol{\Sigma}_{j,\backslash j} \boldsymbol{\Sigma}_{\backslash j,\backslash j}^{-1} \boldsymbol{\Theta}_{i;\backslash j,\backslash j} \boldsymbol{\Sigma}_{\backslash j,\backslash j}^{-1} \boldsymbol{\Sigma}_{\backslash j,j}}{(\sigma_{jj} - \boldsymbol{\Sigma}_{j,\backslash j} \boldsymbol{\Sigma}_{\backslash j,\backslash j}^{-1} \boldsymbol{\Sigma}_{\backslash j,j})^2}. \tag{3.4}$$

As a special case, if $\epsilon_i$ and $\mathbf{X}_i$ are independent and the error term is homoscedastic, then $\sigma_{n,\mathrm{lasso}}^2$ can be simplified to $\sigma_\epsilon^2/\{\sigma_{jj} - \boldsymbol{\Sigma}_{j,\backslash j} \boldsymbol{\Sigma}_{\backslash j,\backslash j}^{-1} \boldsymbol{\Sigma}_{\backslash j,j}\}$, which is the same as the result obtained by Zhang and Zhang (2014).

**Proposition 1.** *Under model (2.1) with heteroscedastic noise, if Assumption 1 in the appendix holds, we have*

$$\sqrt{n}(\hat{\beta}_j^{(de)} - \beta_j^0) \xrightarrow{d} N(0, \sigma_{lasso}^2), \tag{3.5}$$

*where $\sigma_{lasso}^2$ is the asymptotic variance and $\sigma_{lasso}^2 = \lim_{n\to\infty} \sigma_{n,lasso}^2$.*

The complex asymptotic variance (3.4) makes it hard to use Wald type inference procedure in practice since it is difficult to get a good estimate for the asymptotic variance. Thus, using the Wald type test procedure proposed by Zhang and Zhang (2014) in the heteroscedastic case will lead to invalid results, which will be demonstrated in the simulation study in Section 5.

## 3.2 KFC projection

Lan et al. (2016) proposed another way to construct an asymptotically unbiased estimator. The idea is similar to the low dimensional projection method proposed by Zhang and Zhang (2014). In the estimator considered in (3.1), one project $\mathbb{X}_j$ to all the variables except the $j$-th variable. The main idea of Lan et al. (2016) is to project $\mathbb{X}_j$ onto the so-called KFC set $\mathcal{S} = \{l \neq j : |\sigma_{jl}| > c\}$ for some pre-specified threshold value $c > 0$. That is essentially the set of all key confounders associated with $X_j$. Assume $|\mathcal{S}| \leq m$ for some $m$ depending on the sample size $n$. After excluding the covariates that are highly correlated with $\mathbb{X}_j$, an approximate estimate of $\beta_j$ can be obtained by the marginal regression of the profiled response $\tilde{\mathbb{Y}} = \mathcal{Q}_{\mathcal{S}}\mathbb{Y}$ on the profiled covariates $\tilde{\mathbb{X}}_j = \mathcal{Q}_{\mathcal{S}}\mathbb{X}_j$, namely

$$\hat{\beta}_j^{(\text{kfc})} = \frac{\tilde{\mathbb{X}}_j^\intercal \tilde{\mathbb{Y}}}{\tilde{\mathbb{X}}_j^\intercal \tilde{\mathbb{X}}_j} = \frac{\mathbb{X}_j^\intercal \mathcal{Q}_{\mathcal{S}} \mathbb{Y}}{\mathbb{X}_j^\intercal \mathcal{Q}_{\mathcal{S}} \mathbb{X}_j}. \tag{3.6}$$

Based on the de-biasing idea, we propose the following de-biased KFC estimator

$$\hat{\beta}_j^{(\text{kfc-de})} = \frac{\mathbb{X}_j^\intercal \mathcal{Q}_{\mathcal{S}} \mathbb{Y} - \sum_{k \in \mathcal{S}^*} \mathbb{X}_j^\intercal \mathcal{Q}_{\mathcal{S}} \mathbb{X}_k \hat{\beta}_k}{\mathbb{X}_j^\intercal \mathcal{Q}_{\mathcal{S}} \mathbb{X}_j}, \tag{3.7}$$

where $\mathcal{S}^* = \mathcal{S}^{+c}$, i.e., the complement of $\mathcal{S}^+ := \{j\} \cup \mathcal{S}$, and $\hat{\boldsymbol{\beta}}_{\mathcal{S}^*}$ is an initial estimator. The key difference between $\hat{\beta}_j^{(\text{kfc-de})}$ and $\hat{\beta}_j^{(\text{de})}$ is the selection approach of the low dimensional projection space spanned by the subsets of covariates. $\hat{\beta}_j^{(\text{de})}$ is based on the lasso approach while $\hat{\beta}_j^{(\text{kfc-de})}$ is based on the screening approach to find the low dimensional projection space.

If we assume $\epsilon_i$ and $\mathbf{X}_i$ are independent, the simple asymptotic variance of $\hat{\beta}_j^{(\text{kfc-de})}$ is $\sigma_\epsilon^2/(\sigma_{jj} - \boldsymbol{\Sigma}_{j\mathcal{S}}\boldsymbol{\Sigma}_{\mathcal{S}\mathcal{S}}^{-1}\boldsymbol{\Sigma}_{\mathcal{S}j})$ as discussed in Lan et al. (2016). Under model (2.1) with heteroscedastic errors, the following Proposition 2 proves the asymptotic normality of the de-biased estimator $\hat{\beta}_j^{(\text{kfc-de})}$,

**Proposition 2.** *Under the Assumption 3 in the appendix, we have*

$$\sqrt{n}(\hat{\beta}_j^{(kfc\text{-}de)} - \beta_j^0) \xrightarrow{d} N(0, \sigma_{kfc}^2), \tag{3.8}$$

*where the asymptotic variance is defined as*

$$\sigma_{kfc}^2 = \lim_{n\to\infty} \frac{1}{n} \sum_{i=1}^{n} \frac{\theta_{i;jj} - 2\boldsymbol{\Sigma}_{j\mathcal{S}}\boldsymbol{\Sigma}_{\mathcal{S}\mathcal{S}}^{-1}\boldsymbol{\Theta}_{i;j\mathcal{S}} + \boldsymbol{\Sigma}_{j\mathcal{S}}\boldsymbol{\Sigma}_{\mathcal{S}\mathcal{S}}^{-1}\boldsymbol{\Theta}_{i;\mathcal{S}\mathcal{S}}\boldsymbol{\Sigma}_{\mathcal{S}\mathcal{S}}^{-1}\boldsymbol{\Sigma}_{\mathcal{S}j}}{(\sigma_{jj} - \boldsymbol{\Sigma}_{j\mathcal{S}}\boldsymbol{\Sigma}_{\mathcal{S}\mathcal{S}}^{-1}\boldsymbol{\Sigma}_{\mathcal{S}j})^2}. \tag{3.9}$$

Note that if we assume independence between $\epsilon_i$ and $\mathbf{X}_i$ and homoscedasticity for the error terms, we have $\sigma_{\text{kfc}}^2 = \lim_{n\to\infty} \sigma_\epsilon^2/\{\sigma_{jj} - \boldsymbol{\Sigma}_{j\mathcal{S}}\boldsymbol{\Sigma}_{\mathcal{S}\mathcal{S}}^{-1}\boldsymbol{\Sigma}_{\mathcal{S}j}\}$, whose consistent estimator is discussed in Lan et al. (2016). However, based on the findings in Proposition 2, we can see that the adjusted KFC estimator is not easy to be implemented under the heteroscedastic linear models. This again motivates us to develop new methods under heteroscedastic linear models.

### 3.3 Inverse projection

In the last two subsections, the test statistics are constructed based on the asymptotically unbiased estimator for $\beta_j^0$. However, to conduct the hypothesis testing problem (2.2), Liu and Luo (2014) proposed an equivalent test based on the projection of $X_{ij}$ onto $(Y_i, \mathbf{X}_{i,\setminus j}^\intercal)^\intercal$,

$$X_{ij} = (Y_i, \mathbf{X}_{i,\setminus j}^\intercal)\boldsymbol{\gamma}_j^0 + \eta_{ij,y}, \tag{3.10}$$

where $\eta_{ij,y}$ satisfies $\mathrm{E}\eta_{ij,y} = 0, \mathrm{Cov}\{\eta_{ij,y}, (Y_i, \mathbf{X}_{i,\setminus j}^\intercal)\} = \mathbf{0}$. Under the linear model (2.1) with heteroscedastic noise, as long as $\mathrm{Cov}(\mathbf{X}_i, \epsilon) = \mathbf{0}$, we can still show that the vector $\boldsymbol{\gamma}_j^0$ satisfies $\boldsymbol{\gamma}_j^0 = -\sigma_{\eta_{j,y}}^2\big(-\beta_j^0/\sigma_\epsilon^2, \beta_j^0\boldsymbol{\beta}_{\setminus j}^{0\intercal}/\sigma_\epsilon^2 + \boldsymbol{\Omega}_{\setminus j,j}\big)^\intercal$, where $\sigma_{\eta_{j,y}}^2 = \mathrm{Var}(\eta_{ij,y}) = \{(\beta_j^0)^2 + w_{jj}\}^{-1}$ with $\boldsymbol{\Omega} = \boldsymbol{\Sigma}^{-1} = ((w_{jk}))$. Because $\mathrm{Cov}(\epsilon_i, \mathbf{X}_i) = \mathbf{0}$, with $\gamma_{j1}^0$ as the first element of $\boldsymbol{\gamma}_j^0$, we have

$$\mathrm{Cov}(\epsilon_i, \eta_{ij,y}) = \gamma_{j1}^0\mathrm{Cov}(\epsilon_i, -Y_i) = -\sigma_{\eta_{j,y}}^2\beta_j^0 := -\mathfrak{b}_j^0. \tag{3.11}$$

Hence to test (2.2) is equivalent to test $H_0 : \mathfrak{b}_j^0 = 0$ because $\sigma_{\eta_{j,y}}^2 > 0$. Based on the idea proposed in Liu and Luo (2014), we can estimate $\mathfrak{b}_j^0$ using

$$\hat{\mathfrak{b}}_j = -\frac{1}{n}\sum_{i=1}^n \big\{Y_i - \mathbf{X}_i^\intercal\hat{\boldsymbol{\beta}}\big\}\big\{X_{ij} - (Y_i, \mathbf{X}_{i,\setminus j}^\intercal)\hat{\boldsymbol{\gamma}}_j\big\}, \tag{3.12}$$

where $\hat{\boldsymbol{\beta}}$ and $\hat{\boldsymbol{\gamma}}_j$ are some initial regularized estimators of $\boldsymbol{\beta}^0$ and $\boldsymbol{\gamma}_j^0$.

The asymptotic normality with possibly heteroscedastic noise is stated in the following proposition, although the asymptotic variance is difficult to estimate. Define

$$\begin{aligned}\sigma_{i;n,\mathrm{inv}}^2 = {} & \theta_{i;jj} + (\gamma_{j1}^0)^2\boldsymbol{\beta}^{0\intercal}\boldsymbol{\Theta}_i\boldsymbol{\beta}^0 + (\gamma_{j1}^0)^2\kappa_i + \boldsymbol{\gamma}_{j,\setminus 1}^{0\intercal}\boldsymbol{\Theta}_{i;\setminus j,\setminus j}\boldsymbol{\gamma}_{j,\setminus 1}^0 - 2\gamma_{j1}^0\boldsymbol{\beta}^{0\intercal}\boldsymbol{\Theta}_{i;\cdot,j} - 2\gamma_{j1}^0\varpi_{i;j} \\ & - 2\boldsymbol{\gamma}_{j,\setminus 1}^{0\intercal}\boldsymbol{\Theta}_{i;\setminus j,j} + 2(\gamma_{j1}^0)^2\boldsymbol{\beta}^{0\intercal}\boldsymbol{\varpi}_i + 2\gamma_{j1}^0\boldsymbol{\beta}^{0\intercal}\boldsymbol{\Theta}_{i;\cdot,\setminus j}\boldsymbol{\gamma}_{j,\setminus 1}^0 + 2\gamma_{j1}^0\boldsymbol{\gamma}_{j,\setminus 1}^{0\intercal}\boldsymbol{\varpi}_{i;\setminus j},\end{aligned}$$

where $\boldsymbol{\varpi}_i = \mathrm{Cov}(\epsilon_i^2, \mathbf{Z}_i)$ with $\mathbf{Z}_i = \epsilon_i\mathbf{X}_i$.

**Proposition 3.** *Under Assumption 2 in the appendix, we have*

$$\sqrt{n}(\hat{\mathfrak{b}}_j - \mathfrak{b}_j^0) \xrightarrow{d} N(0, \sigma_{inv}^2), \tag{3.13}$$

*where* $\sigma_{inv}^2 = \lim_{n\to\infty}(1/n)\sum_{i=1}^n \sigma_{i;n,inv}^2$.

# 4 EL based approaches

The key of our proposed method is based on the fact that all the estimators in Section 3 can be considered as the solution of estimating equations $\sum_{i=1}^n m_{ni}(\beta_j) = 0$. In addition, $m_{ni}(\beta_j^0)$ admits the following asymptotic decompositions when it is evaluated at the true value $\beta_j^0$:

$$m_{ni}(\beta_j^0) := m_n(\mathbf{X}_i, Y_i, \beta_j^0, \hat{\boldsymbol{\beta}}_{\setminus j}, \hat{\boldsymbol{\theta}}) := W_{ni} + R_{ni}, \tag{4.1}$$

where the nuisance parameters $\boldsymbol{\beta}_{\setminus j}$ and the other nuisance parameters denoted as $\boldsymbol{\theta}$ are replaced by their estimators $\hat{\boldsymbol{\beta}}_{\setminus j}$ and $\hat{\boldsymbol{\theta}}$. Moreover, $\{W_{ni}\}_{i=1}^n$ are independent random variables, and $\{R_{ni}\}_{i=1}^n$ satisfy the following conditions:

(C0) $\mathrm{P}\big(\min_{1\le i\le n} m_{ni} < 0 < \max_{1\le i\le n} m_{ni}\big) \to 1$;

(C1) $W_{ni}$'s are independent with mean 0 and finite variance $\sigma_{i;n}^2$ such that $s_n^2/n \to \sigma_w^2$ where $s_n^2 = \sum_{i=1}^n \sigma_{i;n}^2$;

(C2) $n^{-1/2}\sum_{i=1}^n R_{ni} = o_p(1)$ and $\max_{1\le i\le n}|R_{ni}| = o_p(n^{1/2})$.

Condition (C0) implies that 0 is inside of the convex hull of "data points" $m_{ni}$'s, which ensures EL can be appropriately defined and computed. Condition (C1) and (C2), respectively, impose some conditions on the leading order term $W_{ni}$ and small order term $R_{ni}$ in the decomposition of $m_{ni}(\beta_j^0)$ so that the Wilks' theorem can be established for the EL ratio statistic based on $m_{ni}$'s. In particular, the condition (C2) implies that the errors due to the plug-in estimators of nuisance parameters $\hat{\boldsymbol{\beta}}_{\setminus j}, \hat{\boldsymbol{\theta}}$ are ignorable.

According to Owen (2001), with estimating equations, we can construct EL statistic to make the inference. Define the following EL ratio function for the target parameter $\beta_j$

$$\mathrm{EL}_n(\beta_j) = \max\Big\{\prod_{i=1}^n np_i : p_i > 0, \sum_{i=1}^n p_i = 1, \sum_{i=1}^n p_i m_{ni}(\beta_j) = 0\Big\}. \tag{4.2}$$

Under this unified framework with the above general conditions, we have the following powerful Wilks' theorem.

**Theorem 1.** *If (C0)-(C2) hold, then* $-2\log EL_n(\beta_j^0) \xrightarrow{d} \chi_1^2$.

Based on Theorem 1, an asymptotic $\alpha$ level test is given by rejecting $H_0$ if $-2\log \mathrm{EL}_n(\beta_j^0) > \chi_{1,\alpha}^2$ where $\chi_{1,\alpha}^2$ is the upper $\alpha$ quantile of $\chi_1^2$. We can also construct a $(1-\alpha)100\%$ confidence interval for $\beta_j$ as $\mathrm{CI}_\alpha = \{\beta_j : -2\log \mathrm{EL}_n(\beta_j) < \chi_{1,\alpha}^2\}$. Based on Proposition 1, 2 and 3, we see that Wald type inference procedure is hard to implement due to the complex asymptotic variance. Since the asymptotic distribution is chi-square, we do not need to estimate any additional parameters, such as the asymptotic variance. This is a great advantage of the proposed method, especially under the heteroscedastic linear regression models.

To apply Theorem 1 in practice, we need to find estimating equations $m_{ni}(\beta_j^0)$ for $\beta_j^0$ that admit the decompositions that satisfied the conditions in Theorem 1. The following subsections outline three EL methods based on the estimators proposed in Sections 3.1, 3.2 and 3.3.

## 4.1 EL method based on low dimensional projection

In fact, the de-biased estimator (3.3) can be regarded as the solution to the following estimating equation

$$\sum_{i=1}^n m_{ni}^{(\mathrm{lasso})}(\beta_j) := \sum_{i=1}^n \big\{X_{ij} - \mathbf{X}_{i,\setminus j}^\intercal \hat{\mathbf{w}}_j\big\}\big\{Y_i - X_{ij}\beta_j - \mathbf{X}_{i,\setminus j}^\intercal \hat{\boldsymbol{\beta}}_{\setminus j}\big\} = 0. \tag{4.3}$$

Here $\hat{\beta}^0_{\setminus j}$ is the estimation of $p-1$ dimensional vector with all its elements from the initial estimator $\hat{\beta}$ except the $j$-th one. Note that the corresponding population counterpart of (4.3) is $\eta_{ij}\epsilon_i = \{X_{ij} - \mathrm{E}(X_{ij}|\mathbf{X}_{i,\setminus j})\}\{Y_i - \mathbf{X}_i^\intercal \boldsymbol{\beta}^0\}$. Simple algebra implies that $m_{ni}^{(\mathrm{lasso})}(\beta_j)$ has the following decomposition

$$m_{ni}^{(\mathrm{lasso})}(\beta_j^0) = \underbrace{\epsilon_i\eta_{ij}}_{W_{ni}^{(\mathrm{lasso})}} + \underbrace{\eta_{ij}(\boldsymbol{\beta}^0_{\setminus j} - \hat{\boldsymbol{\beta}}_{\setminus j})^\intercal \mathbf{X}_{i,\setminus j} + (\mathbf{w}_j^0 - \hat{\mathbf{w}}_j)^\intercal \mathbf{X}_{i,\setminus j}\{Y_i - X_{ij}\beta_j^0 - \mathbf{X}_{i\setminus j}\hat{\boldsymbol{\beta}}_{\setminus j}\}}_{R_{ni}^{(\mathrm{lasso})}}.$$

For a fully understanding of the effect of heteroscedasticity, we study the asymptotics of $m_{ni}^{(\mathrm{lasso})}(\beta_j^0)$ in the following. The following proposition provides the asymptotic variance of the leading term $W_{ni}^{(\mathrm{lasso})}$.

**Proposition 4.** *Under model (2.1), $W_{ni}^{(lasso)}$ has mean 0 and variance*

$$E[(W_{ni}^{(lasso)})^2] = \theta_{i;jj} - 2\boldsymbol{\Sigma}_{j,\setminus j}\boldsymbol{\Sigma}^{-1}_{\setminus j,\setminus j}\boldsymbol{\Theta}_{i;j,\setminus j} + \boldsymbol{\Sigma}_{j,\setminus j}\boldsymbol{\Sigma}^{-1}_{\setminus j,\setminus j}\boldsymbol{\Theta}_{i;\setminus j,\setminus j}\boldsymbol{\Sigma}^{-1}_{\setminus j,\setminus j}\boldsymbol{\Sigma}_{\setminus j,j}. \tag{4.4}$$

*Here $\theta_{i;jj}$, $\boldsymbol{\Theta}_{i;j,\setminus j}$ and $\boldsymbol{\Theta}_{i;\setminus j,\setminus j}$ are from the covariance matrix $\boldsymbol{\Theta}_i = ((\theta_{i;jk}))$ of $\mathbf{Z}_i = \epsilon_i\mathbf{X}_i$. Furthermore, if $\epsilon_i$ and $\mathbf{X}_i$ are independent and the error term is homoscedastic, then $E[(W_{ni}^{(lasso)})^2] = \sigma_\epsilon^2(\sigma_{jj} - \boldsymbol{\Sigma}_{j,\setminus j}\boldsymbol{\Sigma}^{-1}_{\setminus j,\setminus j}\boldsymbol{\Sigma}_{\setminus j,j})$.*

The comparison of the variances in Proposition 4 shows the difference between our heteroscedastic case and the homoscedastic case.

Let $\mathrm{EL}_n^{(\mathrm{lasso})}(\beta_j)$ be the EL ratio test statistic defined by (4.2) using $m_{ni}^{(\mathrm{lasso})}(\beta_j)$ to replace $m_{ni}(\beta_j)$. The following Theorem demonstrates that the EL ratio test statistic $\mathrm{EL}_n^{(\mathrm{lasso})}(\beta_j)$ constructed based on the estimating equations (4.3) is asymptotically chi-square distributed.

**Theorem 2.** *Under some regularity conditions for the initial estimators as in Assumption 1 in the appendix and assume that $\mathbf{X}_i$ and $\epsilon_i$ are both sub-Gaussian. As long as $s\log p/\sqrt{n} = o(1)$, the conditions (C0)-(C2) are satisfied. Assume $\sigma^2_{n,lasso} \to \sigma^2_{lasso}$ for some $\sigma^2_{lasso} < \infty$, and then we have $-2\log EL_n^{(lasso)}(\beta_j^0) \xrightarrow{d} \chi^2_1$.*

**Remark 1.** *Assumption 1 is needed to control the order of the remainder term $R_{ni}^{(lasso)}$ so that it satisfies the condition (C2). By applying appropriate inequalities, the order of remainder term is dominated by the orders of estimation errors of initial estimators, and some quantities related to $\epsilon_i$ and $\mathbf{X}_i$, which can be, respectively, controlled by choosing appropriate initial regularized estimators (such as LASSO, SCAD and MCP) for $\boldsymbol{\beta}^0$ and $\mathbf{w}_j^0$, and the sub-Gaussian assumptions for $\epsilon_i$ and $\mathbf{X}_i$. For details, please refer to the proof of Theorem 2.*

Notice that under the homoscedastic noise case, Zhang and Zhang (2014) and van de Geer et al. (2013) used the Wald type test statistic for testing $H_0$ based on the de-biased estimator $\hat{\beta}_j^{(\mathrm{de})}$. Ning and Liu (2014) consider the Score test statistic for testing $H_0$ based on the same estimating equation (4.3). The Score test statistic and the Wald type test statistics are asymptotically equivalent. There still exist some differences between these two methods as pointed out by Ning and Liu (2014). Our method constructs likelihood ratio tests

based on the same estimating equation, thus it enjoys the nice properties of likelihood based methods. Since we are using empirical likelihood, it not only enjoys the Wilk's phenomenon, but also has other nice properties, such as the shape of the confidence interval is data driven and our procedure is more robust to the distribution assumption for the error term since it only requires moment assumptions. The key advantage of our method is that the proposed method can be easily implemented under heteroscedasticity linear models due to the self studentization property of EL. Please refer to the empirical studies in the simulation section for the performance comparison of our method with the Wald type test and Score test.

## 4.2 EL method based on KFC method

The de-biased KFC estimator can be also represented as the solution to the estimating equation based on the population subject $\eta_{ij,\mathcal{S}}\epsilon_i := \{X_{ij} - \mathrm{E}(X_{ij}|\mathbf{X}_{i\mathcal{S}})\}\{Y_i - \mathbf{X}_i^\intercal \boldsymbol{\beta}^0\}$, that is

$$\sum_{i=1}^{n} m_{ni}^{(\mathrm{kfc})}(\beta_j) := \sum_{i=1}^{n} (\tilde{Y}_i - \tilde{X}_{ij}\beta_j - \tilde{\mathbf{X}}_{i\mathcal{S}^*}^\intercal \hat{\boldsymbol{\beta}}_{\mathcal{S}^*})\tilde{X}_{ij} = 0, \tag{4.5}$$

where $m_n^{(\mathrm{kfc})}(\beta_j^0)$ can be decomposed as, asymptotically,

$$\begin{aligned} m_{ni}^{(\mathrm{kfc})}(\beta_j^0) = {} & \epsilon_i \eta_{ij,\mathcal{S}} + \{\boldsymbol{\Sigma}_{j\mathcal{S}}\boldsymbol{\Sigma}_{\mathcal{S}\mathcal{S}}^{-1}\mathbf{X}_{i\mathcal{S}} - X_{ij}\}\mathbf{X}_{i\mathcal{S}}^\intercal (\mathbb{X}_{\mathcal{S}}^\intercal \mathbb{X}_{\mathcal{S}})^{-1}\mathbb{X}_{\mathcal{S}}^\intercal \boldsymbol{\epsilon} \\ & + \{\epsilon_i - \mathbf{X}_{i\mathcal{S}}^\intercal (\mathbb{X}_{\mathcal{S}}^\intercal \mathbb{X}_{\mathcal{S}})^{-1}\mathbb{X}_{\mathcal{S}}^\intercal \boldsymbol{\epsilon}\}\{\boldsymbol{\Sigma}_{j\mathcal{S}}\boldsymbol{\Sigma}_{\mathcal{S}\mathcal{S}}^{-1}\mathbf{X}_{i\mathcal{S}} - \mathbb{X}_j^\intercal \mathbb{X}_{\mathcal{S}}(\mathbb{X}_{\mathcal{S}}^\intercal \mathbb{X}_{\mathcal{S}})^{-1}\mathbf{X}_{i\mathcal{S}}\} \\ & + \{X_{ij} - \mathbb{X}_j^\intercal \mathbb{X}_{\mathcal{S}}(\mathbb{X}_{\mathcal{S}}^\intercal \mathbb{X}_{\mathcal{S}})^{-1}\mathbf{X}_{i\mathcal{S}}\}\{\mathbf{X}_{i\mathcal{S}^*}^\intercal - \mathbf{X}_{i\mathcal{S}}^\intercal (\mathbb{X}_{\mathcal{S}}^\intercal \mathbb{X}_{\mathcal{S}})^{-1}\mathbb{X}_{\mathcal{S}}^\intercal \mathbb{X}_{\mathcal{S}^*}\}[\boldsymbol{\beta}_{\mathcal{S}^*}^0 - \hat{\boldsymbol{\beta}}_{\mathcal{S}^*}]. \end{aligned}$$

We denote the first term as $W_{ni}^{(\mathrm{kfc})}$ and all the others are denoted by $R_{ni}^{(\mathrm{kfc})}$. For simplicity we assume the normality of $\mathbf{X}_i \sim \mathrm{N}(\mathbf{0}, \boldsymbol{\Sigma})$ for the KFC projection section. Now $W_{ni}^{(\mathrm{kfc})} = \{\epsilon_i(X_{ij} - \boldsymbol{\Sigma}_{j\mathcal{S}}\boldsymbol{\Sigma}_{\mathcal{S}\mathcal{S}}^{-1}\mathbf{X}_{i\mathcal{S}})\}_{i=1}^n$ are independent with $\mathrm{E}W_{ni}^{(\mathrm{kfc})} = 0$, and similarly as Proposition 4, it follows that $\mathrm{E}[(W_{ni}^{(\mathrm{kfc})})^2] = \theta_{i;jj} - 2\boldsymbol{\Sigma}_{j\mathcal{S}}\boldsymbol{\Sigma}_{\mathcal{S}\mathcal{S}}^{-1}\boldsymbol{\Theta}_{i;j\mathcal{S}} + \boldsymbol{\Sigma}_{j\mathcal{S}}\boldsymbol{\Sigma}_{\mathcal{S}\mathcal{S}}^{-1}\boldsymbol{\Theta}_{i;\mathcal{S}\mathcal{S}}\boldsymbol{\Sigma}_{\mathcal{S}\mathcal{S}}^{-1}\boldsymbol{\Sigma}_{\mathcal{S}j}$. Note that if we assume independence between $\epsilon_i$ and $\mathbf{X}_i$ and homoscedasticity for the error terms, we have $\mathrm{E}[(W_{ni}^{(\mathrm{kfc})})^2] = \sigma_\epsilon^2(\sigma_{jj} - \boldsymbol{\Sigma}_{j\mathcal{S}}\boldsymbol{\Sigma}_{\mathcal{S}\mathcal{S}}^{-1}\boldsymbol{\Sigma}_{\mathcal{S}j})$.

Let $\mathrm{EL}_n^{(\mathrm{kfc})}(\beta_j)$ be the empirical likelihood ratio test statistic defined by 4.2 with $m_{ni}^{(\mathrm{kfc})}(\beta_j)$ replaced by $m_{ni}(\beta_j)$. The following Theorem demonstrates that the EL ratio test statistic $\mathrm{EL}_n^{(\mathrm{kcf})}(\beta_j)$ constructed based on the estimating equations (4.5) is asymptotically chi-square distributed.

**Theorem 3.** *Under Assumption 3 in the appendix, the conditions (C0)-(C2) can be verified. Assume $\sigma_{n,kfc}^2 \to \sigma_{kfc}^2$ for some $\sigma_{kfc}^2 < \infty$, and then we have $-2\log EL_n^{(kfc)}(\beta_j^0) \xrightarrow{d} \chi_1^2$.*

**Remark 2.** *Similar to the discussion in Remark 1, to make the remainder term $R_{ni}^{(kfc)}$ satisfies (C2), we need to control the error due to the initial estimators and assume sub-Gaussianian for both $\epsilon$ and $\mathbf{X}$. In addition, for the KFC method, we need to control the partial correlation between $X_j$ and any covariates that are not in the KFC set.*

One of the key steps in the above procedure is the selection of the KFC set, we propose the following procedure. Based on normality assumption of the predictors, we have the well known conditional distribution result for any give subset $\mathcal{S}$:

$$\rho_{jk}(\mathcal{S}) := \mathrm{Corr}(X_{ij}, X_{ik}|\mathbf{X}_{i\mathcal{S}}) = \sigma_{jk} - \mathbf{\Sigma}_{\mathcal{S}j}^{\intercal}\mathbf{\Sigma}_{\mathcal{S}\mathcal{S}}^{-1}\mathbf{\Sigma}_{\mathcal{S}k}.$$

The sample partial correlation can be evaluated by, $\hat{\rho}_{jk}(\mathcal{S}) = \tilde{\mathbb{X}}_j^{\intercal}\tilde{\mathbb{X}}_k/n$. For testing whether a partial correlation is zero or not, we could apply Fisher's z-transformation

$$\hat{F}_{jk} = \frac{1}{2}\log\left\{\frac{1+\hat{\rho}_{jk}(\mathcal{S})}{1-\hat{\rho}_{jk}(\mathcal{S})}\right\}.$$

Classical decision theory yields then the following rule when using the significance level $\alpha$. Reject the null hypothesis $H_0 : \rho_{jk}(\mathcal{S}) = 0$ against the two-sided alternative $H_a : \rho_{jk}(\mathcal{S}) \neq 0$ if

$$\sqrt{n - |\mathcal{S}| - 3}|\hat{F}_{jk}| > z_{\alpha/2}.$$

So we could then select the smallest size of $\mathcal{S}$ such that

$$\max_{k\in\mathcal{S}^*}\sqrt{n - |\mathcal{S}| - 3}|\hat{F}_{jk}| < z_{\alpha/2}.$$

And in order to make this KFC set selection more stable, we adopt the stability selection proposed by Meinshausen and Bühlmann (2010) and Shah and Samworth (2013). According to Shah and Samworth (2013), we split the data into half for $B$ times and select the final KFC set with variables shown at least 50% of those $2B$ KFC sets.

## 4.3 EL method based on the inverse method

Note that $\hat{\mathfrak{b}}_j$ is the solution to the following estimating equation

$$\sum_{i=1}^{n} m_{ni}^{(\mathrm{inv})}(\mathfrak{b}_j) := \sum_{i=1}^{n}\left\{Y_i - \mathbf{X}_i^{\intercal}\hat{\boldsymbol{\beta}}\right\}\left\{X_{ij} - (Y_i, \mathbf{X}_{i,\setminus j}^{\intercal})\hat{\boldsymbol{\gamma}}_j\right\} + n\mathfrak{b}_j = 0. \tag{4.6}$$

Simple algebra immediately yields the following decomposition of $m_{ni}^{(\mathrm{inv})}(\mathfrak{b}_j)$,

$$m_{ni}^{(\mathrm{inv})}(\mathfrak{b}_j^0) = \underbrace{\{\epsilon_i\eta_{ij,y} + \mathfrak{b}_j^0\}}_{W_{ni}^{(\mathrm{inv})}} + \underbrace{\epsilon_i(Y_i, \mathbf{X}_{i,\setminus j}^{\intercal})(\boldsymbol{\gamma}_j^0 - \hat{\boldsymbol{\gamma}}_j) + \mathbf{X}_i^{\intercal}(\boldsymbol{\beta}^0 - \hat{\boldsymbol{\beta}})\left\{X_{ij} - (Y_i, \mathbf{X}_{i,\setminus j}^{\intercal})\hat{\boldsymbol{\gamma}}_j\right\}}_{R_{ni}^{(\mathrm{inv})}}.$$

The following proposition about the variance of the dominant term $W_{ni}^{(\mathrm{inv})}$ under different situations shows the complexity brought by the heteroscedastic noise.

**Proposition 5.** *Under model (2.1), we have $W_{ni}^{(inv)}$ mean 0 and $E[(W_{ni}^{(inv)})^2] = \sigma_{i;n,inv}^2$. Furthermore, if $\epsilon_i$ and $\mathbf{X}_i$ are independent, then $E[(W_{ni}^{(inv)})^2] = Var(\epsilon_i)\,Var(\eta_{ij,y}) + (\gamma_{j1}^0)^2\{\,Var(\epsilon_i^2) - Var^2(\epsilon_i)\}$. With additional assumption of homoscedasticity and normality for $\epsilon_i$, we further have $E[(W_{ni}^{(inv)})^2] = \sigma_\epsilon^2\sigma_{\eta_j,y}^2 + (\beta_j^0)^2\sigma_{\eta_j,y}^4$.*

Let $\mathrm{EL}_n^{(\mathrm{inv})}(\beta_j)$ be the empirical likelihood ratio test statistic defined by 4.2 with $m_{ni}^{(\mathrm{inv})}(\beta_j)$ replaced by $m_{ni}(\beta_j)$. The following Theorem demonstrates that the EL ratio test statistic $\mathrm{EL}_n^{(\mathrm{inv})}(\beta_j)$ constructed based on the estimating equations (4.6) is asymptotically chi-square distributed.

**Theorem 4.** *Under some conditions for the initial estimators as in Assumption 2 in the appendix, and assume* $(\mathbf{X}_i^\intercal, \epsilon_i)^\intercal$ *is sub-Gaussian. As long as* $s \log p/\sqrt{n} = o(1)$*, the conditions (C0)-(C2) are satisfied. Assume* $(1/n)\sum_{i=1}^n \sigma_{i;n,inv}^2 \to \sigma_{inv}^2$ *for some* $\sigma_{inv}^2 < \infty$*, then we have* $-2\log EL_n^{(inv)}(\mathfrak{b}_j^0) \xrightarrow{d} \chi_1^2$.

# 5 Simulation studies

In this section, we conducted simulation studies to investigate the finite sample performance of the proposed EL ratio tests, as well as comparing the performance with methods proposed in the existing literature.

We generated random samples according to model (2.1). The covariates were generated from a multivariate Gaussian distribution with mean $\mathbf{0}$ and covariance $\mathbf{\Sigma}$. To compare the performance under different dependence structures, we considered three different covariance matrices for $\mathbf{\Sigma} = ((\sigma_{jk}))$: banded matrix with $\sigma_{jk} = \rho^{|j-k|}\mathbb{1}(|j-k| < 2)$, Toeplitz matrix with $\sigma_{jk} = \rho^{|j-k|}$ and block diagonal matrix with $\mathbf{\Sigma} = \mathbf{I}_{[p/3]} \otimes \mathbf{B}(\rho)$ where $\mathbf{B}(\rho)$ is a $3 \times 3$ matrix with the $(i,j)$ component $\rho^{|i-j|}$. We set $\rho = 0.2$ and 0.5 in our simulation.

We also considered five scenarios for the error distribution: standard normal $\mathrm{N}(0,1)$, mixture normal distribution $0.7\mathrm{N}(0,1) + 0.3\mathrm{N}(0,5^2)$, $t$ distribution with degrees of freedom 3, and two heteroscedastic distributions $0.7X_1Z$ and $X_1Z\sum_{j=2}^p X_{j-1}X_j/(p-1)$ where $Z \sim \mathrm{N}(0,1)$ independent of $\mathbf{X}$. Note that for the two heteroscedastic distributions, $\epsilon$ is not independent of $\mathbf{X}$. For the first heteroscedastic case the conditional variance only depends on a low dimensional covariate (the first component of the covariates $\mathbf{X}$). But the conditional variance for the second heteroscedastic case depends on the the entire vector of covariates. Our goal is to test if the first coefficient is zero or not. Namely,

$$H_0 : \beta_1^0 = 0, \quad \text{v.s.} \quad H_1 : \beta_1^0 \neq 0.$$

The first component of the true coefficients $\boldsymbol{\beta}_1^0$ was set to $0, 0.1, 0.2, 0.3, 0.4$ and $0.5$. Here 0 was used to evaluate the empirical size and the non-zero values were used to evaluate the power of the proposed methods. In addition, we set $\beta_4^0 = 1.5, \beta_7^0 = 2$ and all others are 0. We chose $p = 100, 200, 500$ and $n = 200, 400$. The number of simulation replicates was 500.

We compared five methods: three proposed methods and two existing methods. Specifically, we considered three EL based methods proposed in Section 4. In particular, "EL-LASSO", "EL-KFC" and "EL-INV", respectively, corresponds to the proposed method introduced in Section 4.1, 4.2 and 4.3. We compared them with two existing methods: the Wald type test proposed in Zhang and Zhang (2014) and and van de Geer et al. (2013) (denoted by "Wald") and the Score type test (denoted by "Score") proposed in Ning and Liu (2014) with Lasso estimation for $\hat{\mathbf{w}}_1$. For the initial estimators such as $\hat{\boldsymbol{\beta}}$, $\hat{\boldsymbol{\gamma}}_1$ and $\hat{\mathbf{w}}_1$,

we applied the scaled Lasso proposed by Sun and Zhang (2012), which has the advantage of being tuning insensitive. And for the "EL-KFC", in order to stabilize the KFC set selection, we used the stability selection procedure through sub-sampling proposed by Meinshausen and Bühlmann (2010) and Shah and Samworth (2013). According to Shah and Samworth (2013), we splited the data into half for 10 times and select the final KFC set with variables shown at least 50% of those 20 KFC sets.

For the scenarios with normally distributed random errors, we observed that all the procedures were able to control type I error around nominal level at 5%. The proposed EL based approach with different estimating equations had very similar power. In general, the EL based tests had better power performance than the existing methods, especially in the low sample size situation. Due to the limited space, please refer to the Supplemental material for the simulation results in these cases.

Our main interest is to evaluate the performance of the proposed methods and some existing methods under the heteroscedastic linear regression model. Table 1 summarizes the results for the scenario with $\mathbf{X}$ generated by multivariate normal distribution with the Toeplitz covariance matrix ($\rho = 0.2$) and the heteroscedastic error distribution $0.7X_1\mathrm{N}(0,1)$. Under this case, it is clear that all of the EL based inference procedures, namely "EL- KFC", " EL- INV" and "EL-LASSO" were asymptotically valid because they can control the type I errors reasonably well. But for the existing methods "Wald" and "Score", their type I errors were largely inflated, which indicates that these two procedures are invalid. This is not surprising because these two procedures were designed for linear models with homogeneous variance. Similarly, in Table 2, we summarize the empirical size and power under another scenario with heteroscedastic error distribution whose conditional error variance depends on high dimensional covariates generated according to $X_1 \sum_{j=2}^{p} X_{j-1}X_j\mathrm{N}(0,1)/(p-1)$. Although the error variance depends on a high dimensional covariates, our proposed methods were still able to control the type I error well under the null hypothesis. However, the existing methods "Wald" and "Score" had size distortion under the heteroscedastic error distribution. This further confirms the advantages of our proposed EL based inference procedures.

# 6 An empirical study

We applied the proposed methods to study the association between gene expression and copy number alternation using a real data set collected at multiple cancer centers (Feng et al., 2010). The data set contains gene expression and copy number alternation measured through primary breast tumor specimens in a few recent breast cancer cohort studies. In cells with cancer, mutations can cause a gene to be either deleted or duplicated on a chromosome, which leads to loss or gain of DNA copies of a gene. Comparative Genomic Hybridization (CGH) is a technique for measuring DNA copy numbers of genes of interest on the genome. The CGH array experiments return $log_2$ ratio between the number of DNA copies of a gene in the tumor cells and that in the reference cells. A positive (negative) measurement suggests a possible copy number gain (loss). After proper normalization, among a number of algorithms, `cghFLasso` (Tibshirani and Wang, 2008) was used to estimate the underlying

Table 1: Empirical size and power of the proposed EL-based test procedures and two existing procedures under the heteroscedastic error case. In this table, covariates are generated by a multivariate normal distribution with covariance given by a Toeplitz matrix with $\rho = 0.2$, and the random error are generated according to $0.7X_1\mathrm{N}(0,1)$.

| | | | $\beta_1^0$ | | | | | |
|---|---|---|---|---|---|---|---|---|
| Method | p | n | 0 | 0.1 | 0.2 | 0.3 | 0.4 | 0.5 |
| EL-KFC | 100 | 200 | 0.062 | 0.244 | 0.624 | 0.924 | 0.986 | 1.000 |
| | | 400 | 0.040 | 0.366 | 0.916 | 0.998 | 1.000 | 1.000 |
| | 200 | 200 | 0.070 | 0.230 | 0.652 | 0.920 | 0.990 | 1.000 |
| | | 400 | 0.076 | 0.350 | 0.890 | 0.990 | 1.000 | 1.000 |
| | 500 | 200 | 0.060 | 0.254 | 0.636 | 0.900 | 0.986 | 0.996 |
| | | 400 | 0.058 | 0.402 | 0.902 | 0.992 | 1.000 | 1.000 |
| EL-INV | 100 | 200 | 0.058 | 0.230 | 0.620 | 0.910 | 0.986 | 1.000 |
| | | 400 | 0.040 | 0.356 | 0.918 | 0.998 | 1.000 | 1.000 |
| | 200 | 200 | 0.058 | 0.222 | 0.652 | 0.910 | 0.988 | 1.000 |
| | | 400 | 0.066 | 0.342 | 0.880 | 0.990 | 1.000 | 1.000 |
| | 500 | 200 | 0.060 | 0.236 | 0.624 | 0.898 | 0.980 | 0.996 |
| | | 400 | 0.050 | 0.402 | 0.902 | 0.992 | 1.000 | 1.000 |
| EL-LASSO | 100 | 200 | 0.056 | 0.244 | 0.634 | 0.922 | 0.988 | 1.000 |
| | | 400 | 0.046 | 0.376 | 0.926 | 1.000 | 1.000 | 1.000 |
| | 200 | 200 | 0.062 | 0.232 | 0.668 | 0.926 | 0.990 | 1.000 |
| | | 400 | 0.072 | 0.356 | 0.890 | 0.988 | 1.000 | 1.000 |
| | 500 | 200 | 0.068 | 0.250 | 0.640 | 0.912 | 0.986 | 0.996 |
| | | 400 | 0.052 | 0.412 | 0.902 | 0.992 | 1.000 | 1.000 |
| Wald | 100 | 200 | 0.256 | 0.496 | 0.860 | 0.986 | 1.000 | 1.000 |
| | | 400 | 0.210 | 0.706 | 0.986 | 1.000 | 1.000 | 1.000 |
| | 200 | 200 | 0.234 | 0.464 | 0.848 | 0.980 | 1.000 | 1.000 |
| | | 400 | 0.236 | 0.680 | 0.968 | 1.000 | 1.000 | 1.000 |
| | 500 | 200 | 0.208 | 0.516 | 0.874 | 0.978 | 1.000 | 1.000 |
| | | 400 | 0.234 | 0.736 | 0.986 | 1.000 | 1.000 | 1.000 |
| Score | 100 | 200 | 0.256 | 0.490 | 0.860 | 0.986 | 1.000 | 1.000 |
| | | 400 | 0.218 | 0.700 | 0.986 | 1.000 | 1.000 | 1.000 |
| | 200 | 200 | 0.234 | 0.470 | 0.846 | 0.980 | 1.000 | 1.000 |
| | | 400 | 0.234 | 0.672 | 0.968 | 1.000 | 1.000 | 1.000 |
| | 500 | 200 | 0.204 | 0.518 | 0.870 | 0.978 | 1.000 | 1.000 |
| | | 400 | 0.230 | 0.728 | 0.984 | 1.000 | 1.000 | 1.000 |

DNA copy numbers based on array outputs. Then, the copy number alteration intervals (CNAIs), which are defined as basic CNA units (genome regions) in which all genes tend to be duplicated or deleted simultaneously, were estimated by using some clustering method

Table 2: Empirical size and power of the proposed EL-based test procedures and two existing procedures under the heteroscedastic error case. In this table, covariates are generated by a multivariate normal distribution with covariance given by a Toeplitz matrix with $\rho = 0.2$, and the random error are generated according to $X_1 \sum_{j=2}^{p} X_{j-1} X_j \mathrm{N}(0,1)/(p-1)$.

| | | | $\beta_1^0$ | | | | | |
|---|---|---|---|---|---|---|---|---|
| Method | p | n | 0 | 0.1 | 0.2 | 0.3 | 0.4 | 0.5 |
| EL-KFC | 100 | 200 | 0.066 | 0.886 | 0.998 | 1.000 | 1.000 | 1.000 |
| | | 400 | 0.048 | 0.988 | 1.000 | 1.000 | 1.000 | 1.000 |
| | 200 | 200 | 0.076 | 0.932 | 1.000 | 1.000 | 1.000 | 1.000 |
| | | 400 | 0.068 | 0.988 | 1.000 | 1.000 | 1.000 | 1.000 |
| | 500 | 200 | 0.060 | 0.942 | 1.000 | 1.000 | 1.000 | 1.000 |
| | | 400 | 0.054 | 1.000 | 1.000 | 1.000 | 1.000 | 1.000 |
| EL-INV | 100 | 200 | 0.062 | 0.872 | 0.998 | 1.000 | 1.000 | 1.000 |
| | | 400 | 0.038 | 0.988 | 1.000 | 1.000 | 1.000 | 1.000 |
| | 200 | 200 | 0.074 | 0.936 | 1.000 | 1.000 | 1.000 | 1.000 |
| | | 400 | 0.064 | 0.988 | 1.000 | 1.000 | 1.000 | 1.000 |
| | 500 | 200 | 0.056 | 0.938 | 1.000 | 1.000 | 1.000 | 1.000 |
| | | 400 | 0.042 | 1.000 | 1.000 | 1.000 | 1.000 | 1.000 |
| EL-LASSO | 100 | 200 | 0.066 | 0.876 | 0.998 | 1.000 | 1.000 | 1.000 |
| | | 400 | 0.046 | 0.988 | 1.000 | 1.000 | 1.000 | 1.000 |
| | 200 | 200 | 0.078 | 0.934 | 1.000 | 1.000 | 1.000 | 1.000 |
| | | 400 | 0.064 | 0.988 | 1.000 | 1.000 | 1.000 | 1.000 |
| | 500 | 200 | 0.064 | 0.944 | 1.000 | 1.000 | 1.000 | 1.000 |
| | | 400 | 0.046 | 1.000 | 1.000 | 1.000 | 1.000 | 1.000 |
| Wald | 100 | 200 | 0.222 | 0.982 | 1.000 | 1.000 | 1.000 | 1.000 |
| | | 400 | 0.214 | 1.000 | 1.000 | 1.000 | 1.000 | 1.000 |
| | 200 | 200 | 0.244 | 0.990 | 1.000 | 1.000 | 1.000 | 1.000 |
| | | 400 | 0.214 | 0.998 | 1.000 | 1.000 | 1.000 | 1.000 |
| | 500 | 200 | 0.260 | 0.990 | 1.000 | 1.000 | 1.000 | 1.000 |
| | | 400 | 0.240 | 1.000 | 1.000 | 1.000 | 1.000 | 1.000 |
| Score | 100 | 200 | 0.226 | 0.984 | 1.000 | 1.000 | 1.000 | 1.000 |
| | | 400 | 0.208 | 1.000 | 1.000 | 1.000 | 1.000 | 1.000 |
| | 200 | 200 | 0.236 | 0.990 | 1.000 | 1.000 | 1.000 | 1.000 |
| | | 400 | 0.206 | 0.998 | 1.000 | 1.000 | 1.000 | 1.000 |
| | 500 | 200 | 0.260 | 0.990 | 1.000 | 1.000 | 1.000 | 1.000 |
| | | 400 | 0.232 | 1.000 | 1.000 | 1.000 | 1.000 | 1.000 |

based on the DNA copy numbers estimation. The gene expression data were collected by microarray expression experiments.

In our study, we used data collected from a total of 172 specimens with both cDNA

expression microarray and CGH array measurements. For each CNAI, the mean value of the estimated copy numbers of the genes falling into this CNAI was calculated. This resulted in a 172 (samples) by 384 (CNAIs) numeric matrix. We focused on a set of 654 breast cancer related genes, which was derived based on seven published breast cancer gene lists. This resulted in a 172 (samples) by 654 (genes) numeric matrix. Please refer to Peng et al. (2010) for more details about the data preprocessing.

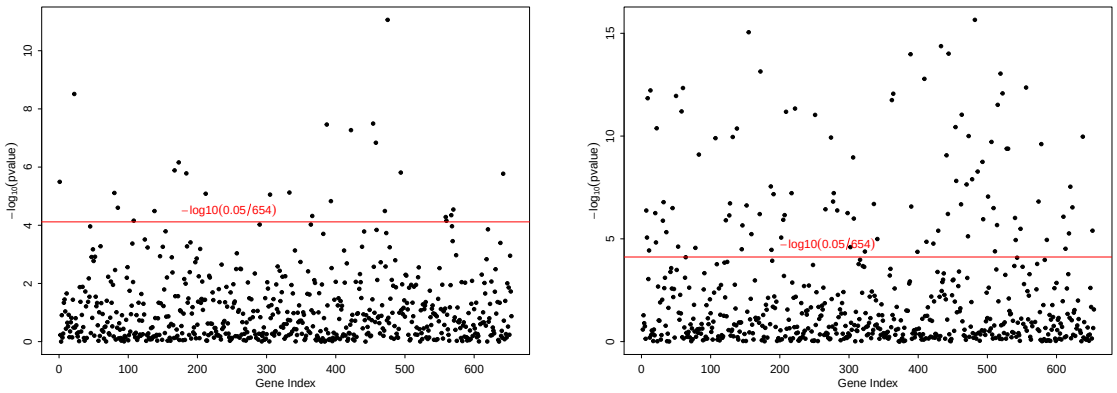
We studied the association between gene expression and DNA copy numbers through a high dimensional linear regression model. In the linear regression model, gene expression data for a given gene were used as response, and the DNA copy numbers were used as predictors. Namely, each of the 654 gene expression was used as response variable, and the DNA copy numbers were used as predictors. For illustration purpose, we focused on the genes with heteroscedastic error variance. To this end, we first conducted a test to identify genes with heteroscedastic variance.

We tested for the presence of heteroscedasticity for each of the 654 genes using two test procedures proposed by Li and Yao (2015), i.e. the approximate likelihood-ratio test (ALRT) and coefficient-of-variation test (CVT). These two test procedures were constructed using the residuals obtained by $\mathbb{Y} - \mathbb{X}\hat{\boldsymbol{\beta}}^0$ where $\hat{\boldsymbol{\beta}}^0$ is the ordinary least squares (OLS) estimate of $\boldsymbol{\beta}^0$. Although both the dimension of covariates and the sample size are allowed to grow to infinity simultaneously in their proposed test procedures, the covariates dimension needs to be less than the sample size. In our data set, the sample size is $n = 172$ and covariates dimension is $p = 384$. As a result, their proposed procedure was not directly applicable.

In order to apply the above test procedures, for each of the 654 gene expressions, we first selected variables by feature screening via distance correlation learning approach proposed by Li et al. (2012), which was implemented in package *grpss*. This procedure was demonstrated nice performance under heteroscedastic setting in Li et al. (2012) The p-values obtained by the above two test procedures are summarized, respectively, in Figure 1 (a) and (b). To adjust for the multiplicity, we applied the Bonferroni method to control the family-wise error rate. After the Bonferroni correction, 33 genes were declared to have significant heteroscedasticity based on the ALRT procedure, and 155 genes had significant heteroscedasticity based on the CVT procedure. These results demonstrate that heteroscedasticity exists for many genes in this data set.

For further analysis and illustration purpose, we selected the top four genes with significant heteroscedasticity from the ALRT procedure among the common genes selected by both of ALRT and CVT for further analysis. The reason to choose ALRT here is due its robustness which has been confirmed in Li and Yao (2015). The four selected genes are the 279-th gene named "SEMA3C" on Chr7, the 433-th gene named "POLR2F" on Chr22, the 493-th gene named "C18orf21" on Chr18 and the 610-th gene called "FOXA1" on Chr14.

We applied the proposed EL based approaches to the four genes selected above, and compared them with the "Wald" test and the "Score" test described in the simulation studies. The results are demonstrated in Figure 2. For each test procedure (EL-bassed approaches, "Wald" and "Score"), we can obtain a sequence of p-values $\{p_j\}_{j=1}^p$, where $p_j$ is the p-value for testing $H_{0j} : \beta_j^0 = 0$ vs $H_{1j} : \beta_j^0 \neq 0$ for $j = 1, \cdots, p$. Then we ordered p-values in an increasing order, $p_{(1)} \leq p_{(2)} \leq \cdots \leq p_{(j)} \leq \cdots \leq p_{(p)}$, and applied

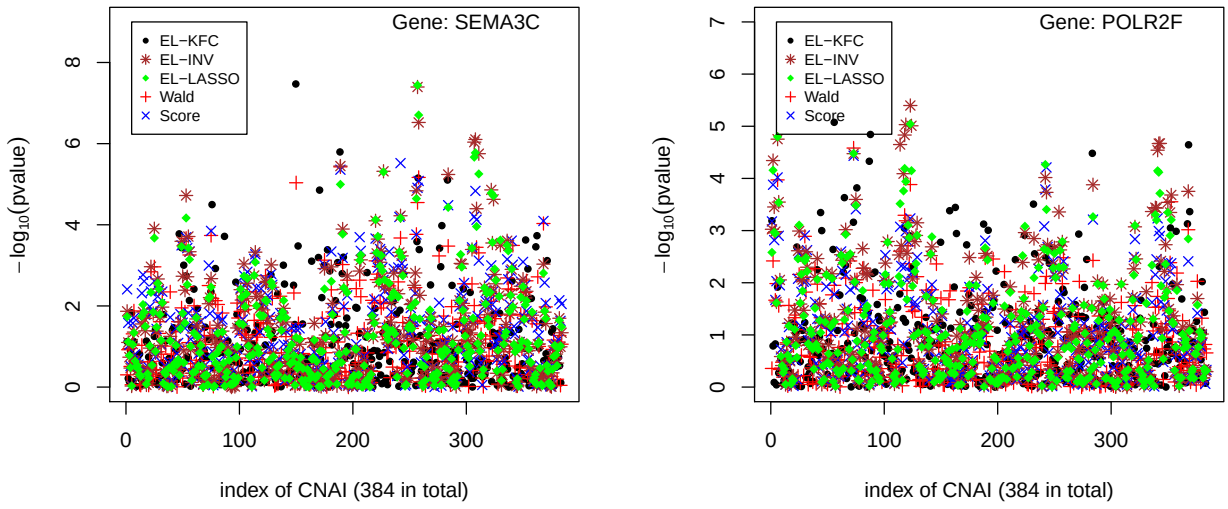



(a) ALRT (b) CVT

Figure 1: **p values for testing heteroscedasticity.** From ALRT, we got 33 genes with significant heteroscedasticity. And from CVT, we got 155 genes with significant heteroscedasticity. The horizontal red line represents the Bonferoni threshold.

the Benjamini-Hochberg (BH) to identify the significant hypotheses. Rejecting the null hypotheses $H_{0j} : \beta_j^0 = 0$ means that the $j$-th CNAI are significantly associated with the gene expression.

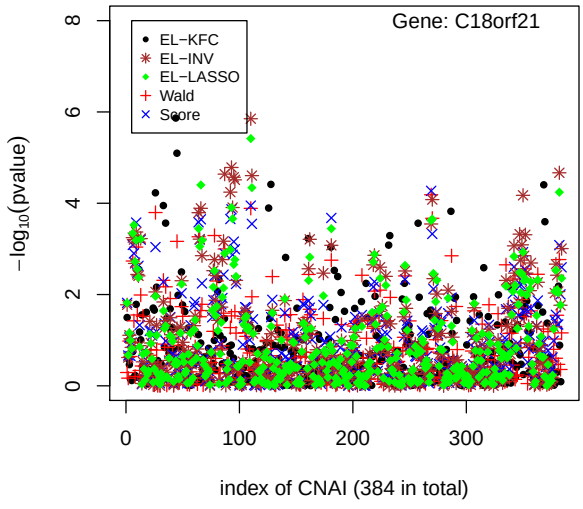
It is interesting to find that as shown in Figure 2d, for the gene "FOXA1" on chromosome 14, the 114-th and 258-th CNAIs were significant using all the EL-based test procedures and the existing "Wald" and "Score" test procedures. However, for the gene "C18orf21" on chromosome 18, the 161-th CNAI was detected by all the EL based methods as illustrated in Figure (2c) but not detected by the "Score" test and "Wald" tests. The 161-th CNAI corresponds to Cytoband 8p22. In the studies conducted by Tsuneizumi et al. (2002) and Voeghtly et al. (2012), it was found that the allelic loss in Cytoband 8p22 is closely related to the risk of breast cancer. Specifically, patients with tumors lost an allele at 8p22 had significantly higher risks of mortality than those with tumors retaining both alleles at those loci. In another study on the Human Protein Atlas (`http://www.proteinatlas.org/ENSG00000141428-C18orf21/cancer`), it was found that several cases of breast cancers exhibited moderate nuclear/nucleolar positivity of the gene "C18orf21". Finding the significant association between the expression of gene "C18orf21" and the CNA in Cytoband 8p22 can improve our understanding of the relationship between the discoveries in above studies. More importantly, it provided us some insight about the underlying disease mechanism of breast cancer. This shows the advantage of the EL based proposed methods, and the necessarily of considering heteroscedasticity in this data set.



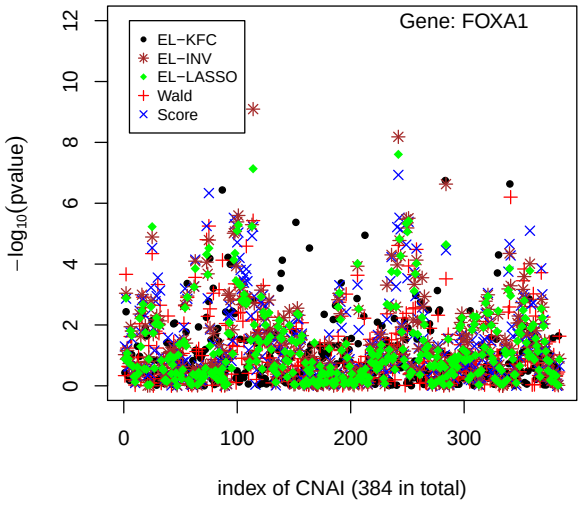

(a)




(b)




(c)




(d)

Figure 2: **Manhattan Plot for Top 4 Genes with heteroscedastic.**

# 7 Discussion

In this paper, we studied inference problem for low-dimensional parameters in a high-dimensional heteroscedastic linear model. The asymptotic normalities of the existing es-

timators were established under the heteroscedastic linear model. However, the asymptotic normalities were found to be difficult to be used in practice due to the complicated asymptotic variance. To address the issue, we proposed three EL based approaches, which avoids the explicit estimation of the variance. The key advantage of our proposed EL based methods comparing with others such as Wald type method and Score based method is that it can allow heteroscedastic error noise. This is largely due to the self normalization property of the empirical likelihood. More interestingly, the conditional variance of random error is allowed to depend on the high dimensional covariates. It can be used to test statistical hypothesis and construct confidence intervals, which have more natural data driven shape. Moreover, we do not need to assume independence between the error term and the covariates, which is a common assumption in the existing literature. We only required the error term and the covariates to be uncorrelated. The method we proposed provides a unified framework for testing low-dimensional coefficients in high dimensional linear models when the estimating equations can be established and satisfy the conditions specified in Theorem 1. Our procedure is simple to apply in practice because we do not need to derive the asymptotic variances for estimators based on different estimating equations.

# A Technical assumptions

For a symmetric matrix $\mathbf{M} = ((M_{jk}))$, $\lambda_{\min}(\mathbf{M})$ and $\lambda_{\max}(\mathbf{M})$ are the minimal and maximal eigenvalues of $\mathbf{M}$. For any matrix $\mathbf{M} = ((M_{jk}))$, let $\|\mathbf{M}\|_{\max} = \max_{j,k} |M_{jk}|$, $\|\mathbf{M}\|_1 = \max_k \sum_j |M_{jk}|$, $\|\mathbf{M}\|_2 = \sqrt{\lambda_{\max}(\mathbf{M}^\intercal \mathbf{M})}$, and $\|\mathbf{M}\|_\infty = \max_j \sum_k |M_{jk}|$.

**Assumption 1.** *(1) Assume the initial estimator $\hat{\boldsymbol{\beta}}$ satisfying $\|\hat{\boldsymbol{\beta}} - \boldsymbol{\beta}^0\|_1 = O_p(s\sqrt{\log p/n})$.*

*(2) Suppose the initial estimators $\hat{\mathbf{w}}_j$ satisfy $\max_{1\le j\le p} \|\hat{\mathbf{w}}_j - \mathbf{w}_j^0\|_1 = O_p(a_n)$, where $a_n = o(1/\sqrt{\log p})$.*

*(3) The prediction errors satisfy $\|\mathbb{X}(\hat{\boldsymbol{\beta}} - \boldsymbol{\beta}^0)\|_2^2/n = O_p(s \log p/n)$ and $\max_{1\le j\le p} \|\mathbb{X}_{\setminus j}(\hat{\mathbf{w}}_j - \mathbf{w}_j^0)\|_2^2/n = O_p(b_n)$, where $\mathbb{X}_{\setminus j}$ is the design matrix $\mathbb{X}$ with the $j$-th column deleted and $b_n = o(1/\sqrt{n})$.*

*(4) $\mathbf{X}_i$ and $\epsilon_i$ are all sub-Gaussian.*

*(5) $s \log p/\sqrt{n} = o(1)$.*

**Remark 3.** *1. With (4) that $\mathbf{X}_i$ and $\epsilon_i$ are all sub-Gaussian, we have $X_{ik}\epsilon_i$ sub-exponential with $E(\epsilon_i X_{ik}) = 0$. By Bernstein inequality Vershynin (2010) and union bound inequality, we have*

$$P(\Big\|\frac{1}{n}\sum_{i=1}^n \mathbf{X}_i\epsilon_i\Big\|_\infty \ge t) \le C_1 p \exp(-C\min(t^2/C_2, t/C_3)n).$$

*By taking* $t = C'\sqrt{\log p/n}$ *for some positive constant* $C'$ *such that* $CC'^2 > C_2$*, we have*

$$\|\frac{1}{n}\sum_{i=1}^{n}\mathbf{X}_i\epsilon_i\|_\infty = O_p(\sqrt{\log p/n}). \tag{A.1}$$

2. *For* $\eta_{ij} = X_{ij} - E(X_{ij}|\mathbf{X}_{i,\backslash j})$*, we have* $\eta_{ij}$ *sub-gaussian since* $\mathbf{X}_i$ *is sub-gaussian. And for any* $k \neq j$*, we have* $E(X_{ik}\eta_{ij}) = E\{X_{ik}[X_{ij} - E(X_{ij}|\mathbf{X}_{i,\backslash j})]\} = E\{X_{ik}X_{ij} - E[X_{ik}X_{ij}|\mathbf{X}_{i,\backslash j}]\} = 0$*. Similarly, we have for any* $t > 0$ *and* $1 \leq j \neq k \leq p$*,*

$$P(\big|\frac{1}{n}\sum_{i=1}^{n}X_{ik}\eta_{ij}\big| \geq t) \leq C_1 p\exp(-C\min(t^2/C_2, t/C_3)n),$$

*which leads to*

$$\Big\|\frac{1}{n}\sum_{i=1}^{n}\eta_{ij}\mathbf{X}_{i,\backslash j}\Big\|_\infty = O_p(\sqrt{\log p/n}). \tag{A.2}$$

3. *For the properties of the initial estimators in (1), (2) and (3) under the heteroscedasitic noise case, we can use the* $\sqrt{Lasso}$ *estimator as in Belloni et al. (2014). According to Theorem 7 in Belloni et al. (2014), we have that the* $\sqrt{Lasso}$ *estimators under certain conditions have these properties satisfied.*

**Assumption 2.** *(1) Assume the same assumption as Lasso projection case for the initial estimator* $\|\hat{\boldsymbol{\beta}} - \boldsymbol{\beta}^0\|_1 = O_p(s\sqrt{\log p/n})$*.*

*(2) Assume similar assumption as Lasso projection case for the initial estimators* $\hat{\boldsymbol{\gamma}}_j$*, i.e.,* $\max_{1\leq j\leq p}\|\hat{\boldsymbol{\gamma}}_j - \boldsymbol{\gamma}_j^0\|_1 = O_p(a_n)$*, where* $a_n = o(1/\sqrt{\log p})$*.*

*(3) Assume similar assumption as Lasso projection case for the prediction errors, i.e.,* $\|\mathbb{X}(\hat{\boldsymbol{\beta}} - \boldsymbol{\beta}^0)\|_2^2/n = O_p(s\log p/n)$ *and* $\max_{1\leq j\leq p}\|(\mathbb{Y}, \mathbb{X}_{\backslash j})(\hat{\boldsymbol{\gamma}}_j - \boldsymbol{\gamma}_j^0)\|_2^2/n = O_p(b_n)$ *and* $b_n = o(1/\sqrt{n})$*.*

*(4)* $(\mathbf{X}_i^\intercal, \epsilon_i)^\intercal$ *is sub-Gaussian.*

*(5)* $s\log p/\sqrt{n} = o(1)$*.*

**Remark 4.** *For the condition (2) above, if we assume* $a = \max_{1\leq j\leq p}s_j$ *with* $s_j = \|\boldsymbol{\gamma}_j^0\|_0$ *and then the* $\sqrt{Lasso}$ *estimators for* $\boldsymbol{\gamma}_j^0$ *satisfy this condition with* $a_n = a\sqrt{\log p/n}$*. For the condition (3) above, since we assume that* $(\mathbf{X}_i^\intercal, \epsilon_i)^\intercal$ *is sub-Gaussian (which makes* $\boldsymbol{\beta}^{0\intercal}\mathbf{X}_i$ *also sub-Gaussian), then due to* $Cov(\boldsymbol{\beta}^{0\intercal}\mathbf{X}_i, \epsilon_i) = E(\epsilon_i\boldsymbol{\beta}^{0\intercal}\mathbf{X}_i) = 0$*, we have* $\epsilon_i\boldsymbol{\beta}^{0\intercal}\mathbf{X}_i$ *sub-exponential and by the Bernstein inequality, we have for any* $t > 0$*,*

$$P(\big|\frac{1}{n}\sum_{i=1}^{n}\mathbf{X}_i^\intercal\boldsymbol{\beta}^0\epsilon_i\big| \geq t) \leq 2\exp\{-C_1 n\min(t^2/C_2^2, t/C_2)\}.$$

*This also leads to*

$$\frac{1}{n}\sum_{i=1}^{n}\mathbf{X}_i^\intercal\boldsymbol{\beta}^0\epsilon_i = O_p(\sqrt{\log p/n}), \tag{A.3}$$

*as long as* $\log p/n \to 0$. *And with the same argument, we have*

$$\frac{1}{n}\sum_{i=1}^{n}X_{ik}\eta_{ij,y} = O_p(\sqrt{\log p/n}), \tag{A.4}$$

$$\frac{1}{n}\sum_{i=1}^{n}(Y_i, \mathbf{X}_{i,\setminus j}^\intercal)\boldsymbol{\gamma}_j^0\eta_{ij,y} = O_p(\sqrt{\log p/n}). \tag{A.5}$$

**Assumption 3.** *(1) For the eigenvalues of* $\boldsymbol{\Sigma}$, *there exist some constants* $\lambda_{\min}$ *and* $\lambda_{\max}$ *such that* $0 < \lambda_{\min} < \lambda_{\min}(\boldsymbol{\Sigma}) \leq \lambda_{\max}(\boldsymbol{\Sigma}) < \lambda_{\max} < \infty$.

*(2) Assume* $\mathbf{X}_i \sim N(\mathbf{0}, \boldsymbol{\Sigma})$ *and* $\epsilon_i$ *to be sub-Gaussian.*

*(3) The initial estimator* $\hat{\boldsymbol{\beta}}$ *(e.g., LASSO) satisfies* $\|\hat{\boldsymbol{\beta}} - \boldsymbol{\beta}^0\|_1 = O_p(s\sqrt{\log p/n})$.

*(4)* $s\sqrt{(\log p)^2 m^3/n} = o(1)$ *and* $s\sqrt{(\log p)^3 m^2/n^2} = o(1)$ *where* $m$ *is the upper bound of the size of KFC set* $|\mathcal{S}|$.

*(5) Assume* $s\sqrt{\log p}\sup_{\mathcal{S}:|\mathcal{S}|\leq m}\max_{k\in\mathcal{S}^*}\left|\sigma_{jk} - \boldsymbol{\Sigma}_{j\mathcal{S}}\boldsymbol{\Sigma}_{\mathcal{S}\mathcal{S}}^{-1}\boldsymbol{\Sigma}_{\mathcal{S}k}\right| = o(1)$.

**Remark 5.** *Condition (1) is a mild condition that assures the asymptotic identifiability of the model (Fan and Lv, 2008; Wang, 2009, 2012). Condition (2) is a common condition used for simplification of theoretical proofs in high dimensional setup; see for example, Wang (2009) and Zhang and Zhang (2014). Condition (3) was also used in Assumptions 1 and 2. Condition (4) is for controlling the size of the KFC set* $|\mathcal{S}|$, *and Condition (5) controls the partial correlation between the target covariate* $X_{ij}$ *and* $\mathbf{X}_{i\mathbf{S}^*}$.

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# Supplemental material

In this supplemental file, we provide technical proofs to all the theoretical results presented in the paper, and some additional simulation results.

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