Composite Expectile Regression with
Gene-environment Interaction

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Abstract

If error distribution has heteroscedasticity, it violates the assumption of linear regression. Expectile regression is a powerful tool for estimating the conditional expectiles of a response variable in this setting. Since multiple levels of expectile regression model has been well studied, we propose composite expectile regression by combining different levels of expectile regression to improve the efficacy. In this paper, we study the sparse composite expectile regression under high dimensional setting. It is realized by implementing a coordinate descent algorithm. We also prove its selection and estimation consistency. Simulations are conducted to demonstrate its performance, which is comparable to or better than the alternatives. We apply the proposed method to analyze Lung adenocarcinoma(LUAD) real data set, investigating the G-E interaction.

Keywords: Composite expectile regression, Gene-environment interaction, High dimension, Sparse

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1 Introduction

Linear regression minimizes the squared error with one assumption: the variance of the noise terms is constant over all observations. In the real world data, the magnitude of the noise is not constant and the data are heteroskedastic. Heteroscedasticity often exists due to heterogeneity in measurement units or accumulation of outlying observations from numerous sources of variables. Heteroscedasticity exists in biological data. For example, by implementing the genomics experiments, tens of thousands of genes are often analyzed simultaneously by microarrays and occasional outlying measurements appearing in numerous experimental and data preprocessing steps can accumulate to form heteroscedasticity in the data obtained.

When we have heteroskedasticity in the error distribution, expectile regression with an asymmetric least squares (ALS) is proposed as a solution to it by Newey and Powell (1987). The main idea in expectile regression is to assign different squared error loss to the positive and negative residuals, respectively. By doing so, one can explores a complete relationship between the conditional expectile of a response variable and a set of predictor variables. Similar work has been done in quantile regression (Zou and Yuan (2008)). By adapting this composite loss function, composite quantile regression (CQR) is much more efficient than the LS estimator under many heavy-tailed error. Zhao and Xiao (2014) show that if we combine information over multiple quantiles, an upper bound on the distance between the efficiency of the estimator and the Fisher information decreases as the number of quantiles increases. Motivated by composite quantile regression and related works, we proposed the composite expectile regression (CER) by combining information over different expectiles via a mix of ALS loss functions. The idea of CER is straightforward: if more expectiles are used, we have more distributional information and can obtain more efficient estimation.
In this paper, we develop sparse CER model under high dimensional setting since G-E interaction analysis is included. When fitting a sparse CQR model, it is natural to adopt some classical penalties, such as minmax concave penalty (MCP) by Zhang (2010). Coordinate descent, the most popular algorithm for solving the least squares lasso, is used to this optimization problem. We derive the consistency of CER and show its application in detecting heteroscedasticity under high dimensional setting. For G-E interaction analysis, we assume that interaction term can not be identified if the corresponding main G effect is not identified. We decompose the G-E interaction coefficients to respect the ”main effects, interactions” hierarchy. Minimax concave penalty (MCP) is applied to penalize genetic coefficient and G-E interaction coefficient.

The structure of the paper is as follows: In Section 2, we briefly introduced expectile regression (ER) and composite expectile regression (CER). The selection and estimation consistency of CER is presented in Section 3. We give a coordinate descent algorithm and run simulations to demonstrate its performance in Section 4. As an application, we apply CER and alternatives into analyzing lung adenocarcinoma data in section 5. Section 6 gives the summary and discussion.

2 Methods

In this section, we briefly introduce expectile regression and composite expectile regression under G-E interaction scenarios.

2.1 Expectile regression

Consider a dataset with \( n \) iid subjects. For the \( i \)th subject, let \( Y_i \) be the response of interest, and \( Z_i = (Z_{i1}, ..., Z_{iq}) \) and \( X_i = (X_{i1}, ..., X_{ip}) \) be the \( q \)- and \( p \)-dimensional
vectors of Environmental (E) and Genetic (G) measurements. We consider the scenario with a continuous outcome and a expectile regression model with the joint effects of all E and G effects and their interactions:

\[ Y_i = b + \sum_{k=1}^{q} Z_{ik} \alpha_k + \sum_{j=1}^{p} X_{ij} \beta_j + \sum_{k=1}^{q} \sum_{j=1}^{p} Z_{ik} X_{ij} \eta_{kj} + \epsilon_i \]  \hspace{1cm} (1)

where \( b \) is intercept, \( \{ \alpha_k \}_{k=1,..,q} \), \( \{ \beta_j \}_{j=1,..,p} \) and \( \{ \eta_{kj} \}_{k=1,..,q,j=1,..,p} \) are the regression coefficients for the main E, main G, and G-E interactions, respectively, and \( \{ \epsilon_i \}_{i=1,..,n} \) are the random errors.

To get the hierarchical constraint between main effects and interactions, we conduct the decomposition of \( \eta_{kj} \)

\[ Y_i = b + \sum_{k=1}^{q} Z_{ik} \alpha_k + \sum_{j=1}^{p} X_{ij} \beta_j + \sum_{k=1}^{q} \sum_{j=1}^{p} Z_{ik} X_{ij} \beta_j \gamma_{kj} + \epsilon_i \]  \hspace{1cm} (2)

\[ = b + Z_i \alpha + X_i \beta + \sum_{k=1}^{q} M_i^{(k)} (\beta \odot \gamma_k) + \epsilon_i \]  \hspace{1cm} (3)

where \( \alpha = (\alpha_1,..,\alpha_q)^T \), \( \beta = (\beta_1,..,\beta_p)^T \), \( \gamma_k = (\gamma_{k1},..,\gamma_{kp})^T \), \( M_i^{(k)} = (Z_{ik} X_{i1},..,Z_{ik} X_{ip}) \).

And \( \odot \) is the component-wise product. The coefficients of main G effects and G-E interaction effects are \( \beta \) and \( \beta \odot \gamma_k \). By adopting the decomposition technique of \( \eta_{kj} \), we could guarantee that G-E interactions will not be identified if the corresponding main G effects are not identified. In other words, if \( \beta_j = 0 \), then \( \eta_{kj} = 0 \).

Let \( Y = (Y_1,..,Y_n)^T \) be \( n \times 1 \) vector, \( b = (b,..,b)^T \) be \( n \times 1 \) vector, \( Z = (Z_1^T,..,Z_n^T)^T \) be \( n \times q \) matrix, \( X = (X_1^T,..,X_n^T)^T \) be \( n \times p \) matrix, \( M^{(k)} = ((M_1^{(k)})^T,..,(M_n^{(k)})^T)^T \) be \( n \times p \) matrix. We have the following matrix form:

\[ Y = b + Z \alpha + X \beta + \sum_{k=1}^{q} M^{(k)} (\beta \odot \gamma_k) + \epsilon, \]
where \( \epsilon = (\epsilon_1, ..., \epsilon_n)^T \) is the vector of random error.

Here we consider the asymmetric square loss function. To get the estimators, we minimize the following empirical risk function

\[
Q_n(\tau, \theta) = \frac{1}{2n} \sum_{i=1}^{n} L_\tau(y_i, f(X_i, Z_i)) + \sum_{j=1}^{p} \rho(|\beta_j|; \lambda_1, r) + \sum_{j=1}^{p} \sum_{k=1}^{q} \rho(|\gamma_{kj}|; \lambda_2, r), \quad 0 < \tau < 1,
\]

where \( \theta = (b^T, \alpha^T, \beta^T, \gamma_1^T, ..., \gamma_q^T)^T \). \( \rho(v; \lambda, r) = \lambda \int_0^{|v|} (1 - \frac{x}{r})_+ dx \) is the minimax concave penalty (MCP), where \( r > 1 \) is regularization parameter. \( \lambda_1, \lambda_2 \) are two tuning parameters. And

\[
L_\tau(Y, f(X, Z)) = \begin{cases} 
(1 - \tau)(Y - f(X, Z))^2, & \text{if } Y < f(X, Z) \\
\tau(Y - f(X, Z))^2, & \text{if } Y \geq f(X, Z).
\end{cases}
\]

Expectile regression can be regarded as weighted linear regression, but expectile regression has only two possible weight \( \tau \) and \( 1 - \tau \).

**2.2 Composite expectile regression**

To combine the strength across multiple expectile regression models, we propose composite expectile regression (CER) inspired by composite quantile regression (CQR) by Zou and Yuan (2008). Denote \( 0 < \tau_1 < ... < \tau_L < 1 \). Specifically, we use the equally spaced expectiles: \( \tau_l = \frac{l}{L+1}, 1 \leq l \leq L \). \( L \) is a positive constant and can be taken as 9 or 19. By adopting this strategy, we could improve the efficiency. We minimize the following objective function:

\[
\overline{Q}_n(\theta) = \frac{1}{2n} \sum_{i=1}^{n} \sum_{l=1}^{L} L_\tau(Y_i, f(X_i, Z_i)) + \sum_{j=1}^{p} \rho(|\beta_j|; \lambda_1, r) + \sum_{j=1}^{p} \sum_{k=1}^{q} \rho(|\gamma_{kj}|; \lambda_2, r),
\]
where \(f(X_i, Z_i) = b_i + Z_i\alpha + X_i\beta + \sum_{k=1}^{q} M_i^{(k)}(\beta \odot \gamma_k)\),

\[
L_{\tau_i}(Y_i, f(X_i, Z_i)) = \begin{cases} 
(1 - \tau_i)(Y_i - f(X_i, Z_i))^2, & \text{if } Y_i < f(X_i, Z_i) \\
\tau_i(Y_i - f(X_i, Z_i))^2, & \text{if } Y_i \geq f(X_i, Z_i).
\end{cases}
\]  

(9)

Note that the regression coefficients are the same across different expectile regression models, but intercepts are varied across different expectile regression models. Let \(Y = (Y_1, ..., Y_n)^T\) be \(n \times 1\) vector, \(b_i = (b_{l_i}, ..., b_{l_T})^T\) be \(n \times 1\) vector, \(Z = (Z_1^T, ..., Z_n^T)^T\) be \(n \times q\) matrix, \(X = (X_1^T, ..., X_n^T)^T\) be \(n \times p\) matrix, \(M^{(k)} = ((M_1^{(k)})^T, ..., (M_n^{(k)})^T)^T\) be \(n \times p\) matrix. We get \(\theta = (b_1^T, ..., b_p^T, \alpha^T, \beta^T, \gamma_1^T, ..., \gamma_q^T)^T\) by minimizing the penalized objective function in a matrix form:

\[
\mathcal{Q}_n(\theta) = \frac{1}{2n} \sum_{l=1}^{L} \| W_{\tau_i}^{1/2}(Y - b_l - Z\alpha - X\beta - \sum_{k=1}^{q} M^{(k)}(\beta \odot \gamma_k)) \|^2_2
\]

\[+ \sum_{j=1}^{p} \rho(|\beta_j|; \lambda_1, r) + \sum_{j=1}^{p} \sum_{k=1}^{q} \rho(|\gamma_{kj}|; \lambda_2, r),\]

\[(11)\]

where \(W_{\tau_i}\) is \(n \times n\) diagonal matrix with two possible elements \(\tau_i, 1 - \tau_i\). For each element \(w_i\) of \(W_{\tau_i}\), \(w_i = \tau_i\) if \(Y_i > b_l + Z_i\alpha + X_i\beta + \sum_{k=1}^{q} M_i^{(k)}(\beta \odot \gamma_k)\), otherwise \(w_i = 1 - \tau_i\).

If G-E interaction coefficients are not decomposed, we denote it as non-hierarchical CER.

### 3 Statistical analysis

In the section, we explore the consistency of CER with interaction term. We consider this scenario: when the sample size increases, the number of G factor increases and the number of E factor is finite. Let \(\theta^0 = ((b_0^T), ..., (b_p^T), (\alpha^0)^T, (\beta^0)^T, (\gamma_1^0)^T, ..., (\gamma_q^0)^T)^T\) be true parameter values. All \(\{\alpha_k\}_{k=1,...,q}\) are not subjected to penalized and are nonzero.
With hierarchical structure, we are only interested in those \( \{ \gamma_{kj} \}_{k=1,\ldots,q; j=1,\ldots,p} \) whose corresponding \( \{ \beta_j \}_{j=1,\ldots,p} \) are nonzero. Let \( \mathcal{A}_1 = \{ j : \beta_j^0 \neq 0 \} \) be nonzero parameter of G effect, \( \mathcal{A}_2^k = \{ j : \gamma_{kj}^0 \neq 0 \text{ and } \beta_j^0 \neq 0 \} \) be nonzero parameter of \( k \)-interaction effect. With hierarchical structure, in each \( \mathcal{A}_2^k \), \( \gamma_{kj} \) is zero if the corresponding \( \beta_j \) is zero too. For some \( k \), if \( j \in \mathcal{A}_2^k \), then we have \( j \in \mathcal{A}_1 \). Let \( \mathcal{A}_2 = \mathcal{A}_1^1 \cup \ldots \cup \mathcal{A}_1^p \), \( \mathcal{A} = \mathcal{A}_1 \cup \mathcal{A}_2 \) and \( s = |\mathcal{A}_1| + |\mathcal{A}_2^1| + \cdots + |\mathcal{A}_2^p| \). \( \theta_0^G = \left((\beta_1^0)^T, \ldots, (\beta_p^0)^T, (\alpha^0)^T, (\beta_{\mathcal{A}_1}^0)^T, (\gamma_{\mathcal{A}_2}^0)^T, \ldots, (\gamma_{\mathcal{A}_2^p}^0)^T \right)^T \) is the true parameter indexed by \( \mathcal{A} \).

Denote \( \hat{\theta}_G = \left((\hat{b}_1)^T, \ldots, (\hat{b}_p)^T, (\hat{\alpha})^T, (\hat{\beta}_{\mathcal{A}_1})^T, (\hat{\gamma}_{\mathcal{A}_2})^T, \ldots, (\hat{\gamma}_{\mathcal{A}_2^p})^T \right)^T \) as the minimizer of

\[
\overline{\mathcal{Q}}_n(\hat{\theta}_G) = \frac{1}{2n} \sum_{l=1}^L \| W^{1/2} (Y - b_l - Z\alpha - X_{\mathcal{A}_1}\beta_{\mathcal{A}_1} - \sum_{k=1}^q M_{\mathcal{A}_2^k}(\beta_{\mathcal{A}_2^k} \odot \gamma_{k,A_2^k}) ) \|_2^2 
+ \sum_{j=1}^p \rho(|\beta_j|; \lambda_1, r) + \sum_{j=1}^p \sum_{k=1}^q \rho(|\gamma_{kj}|; \lambda_2, r),
\]

where \( X_{\mathcal{A}_1}, \beta_{\mathcal{A}_1} \) denote the components of \( X, \beta \) indexed by \( \mathcal{A}_1 \), and \( M_{\mathcal{A}_2^k}, \beta_{\mathcal{A}_2^k}, \gamma_{k,A_2^k} \) denote the components of \( M^{(k)}, \beta, \gamma \) indexed by \( \mathcal{A}_2^k \) for each \( k \).

Suppose that we have the following conditions:

1. \( \varepsilon \) are i.i.d and sub-Gaussian with noise level \( \sigma \). That is, for any vector \( \mathbf{v} \) with \( \| \mathbf{v} \|_2 = 1 \) and any constant \( t > 0 \), \( P(|\mathbf{v}^T \varepsilon| \geq t) \leq 2 \exp\left(-\frac{t^2}{2\sigma^2}\right) \).

2. Let \( b_0 = \min\{||\beta_j^0| : j \in \mathcal{A}_1\}, \{||\gamma_{kj}^0| : j \in \mathcal{A}_2^k, k = 1, \ldots, q\} \), we have \( b_0 > a(\lambda_1 \lor \lambda_2), a > 0 \) and \( \lambda_1 \lor \lambda_2 \gg \sqrt{s/n} \).

3. We use \( \lambda_{\min}(\cdot) \) and \( \lambda_{\max}(\cdot) \) to represent the smallest and largest eigenvalues of a symmetric matrix, respectively. Then

\[
\max_{\hat{\theta}_G \in N_0} \max_{l \in \{1, \ldots, L\}} \lambda_{\max} \left( \frac{1}{n} G(\beta_{\mathcal{A}_2}, \gamma_{\mathcal{A}_1})^T G(\beta_{\mathcal{A}_2}, \gamma_{\mathcal{A}_1}) \right) \leq s \bar{C},
\]
\[
\min_{\theta_A} \min_{t_A \in \mathcal{N}_0} \lambda_{min} \left( \frac{1}{n} G(\beta_{A_2}, \gamma_{A_1})^T G(\beta_{A_2}, \gamma_{A_1}) + \frac{1}{n} F(\theta_A) \right) \geq \zeta,
\]
where \( \gamma_{A_1} = (\gamma_{1,A_1}^T, \ldots, \gamma_{q,A_1})^T \) with \( \gamma_{kj} = 0 \), if \( j \in A_1 \) but \( j \notin A_2^k \),
\[
G(\beta_{A_2}, \gamma_{A_1}) = W_{\theta_A}^{1/2} \left( 1_{n \times 1}, Z, U(\gamma_{A_1}), V^{(1)}(\beta_{A_2}), \ldots, V^{(q)}(\beta_{A_2}) \right)_{n \times (q+s+1)},
\]
with
\[
U(\gamma_{A_1}) = X_{A_1} + \sum_{k=1}^{q} M^{(k)}(I_{n \times 1}(\gamma_{k,A_1})^T), V^{(k)}(\beta_{A_2}) = M^{(k)}(I_{n \times 1}(\beta_{k,A_2})^T).
\]
\[
F_{\tau_i}(\theta_A) = (f_{jh}(\theta_A))_{(q+s) \times (q+s)} \text{ with } f_{jh}(\theta_A) = -W_{\theta_A}(M^{(k)}(Y - b_l - Z\alpha - X_{A_1} \beta_{A_1} - \sum_{g=1}^{q} M^{(q)}(\beta_{A_2} \odot \gamma_{g,A_2})) \text{ if both } j \text{ and } h \text{ correspond to the } \zeta \text{th element of } A_2^k \text{, and } 0 \text{ otherwise. For each element } w_i \text{ of } W_{\theta_A}, w_i = \tau_i \text{ if } i \text{-th element } (Y - b_l - Z\alpha - X_{A_1} \beta_{A_1} - \sum_{g=1}^{q} M^{(q)}(\beta_{A_2} \odot \gamma_{g,A_2})) > 0, \text{ otherwise } w_i = 1 - \tau_i. \text{ And } \bar{\tau} \text{ and } \zeta \text{ are positive constants, } \mathcal{N}_0 = \{ \theta_A : ||\theta_A - \theta_A^0||_\infty \leq \frac{b_0}{2} \}.
\]

4. Suppose \( ||U(\gamma_{A_1}^0)^T G(\beta_{A_2}^0, \gamma_{A_1}^0)||_{2,\infty} = O(n) \), \( ||V^{(k)}(\beta_{A_2}^0)^T G(\beta_{A_2}^0, \gamma_{A_1}^0)||_{2,\infty} = O(n) \), \( ||U(\gamma_{A_1}^0)^T W_{\tau_1}||_2 = O(\sqrt{n}) \), \( ||V^{(k)}(\beta_{A_2}^0)^T W_{\tau_1}||_2 = O(\sqrt{n}) \), \( j = 1, \ldots, p \), where each element \( w_i \) of \( W_{\tau_1}, w_i = \tau_i \) if \( i \)-th element \( \left( Y - b_l - Z\alpha - X_{A_1} \beta_{A_1} - \sum_{g=1}^{q} M^{(q)}(\beta \odot \gamma_{g}) \right) > 0 \), otherwise \( w_i = 1 - \tau_i \). For \( Q, ||Q||_{2,\infty} = \max_{||v||_2 = 1} ||Qv||_\infty, A_1^c = \{j : \beta_{j}^0 = 0\} \text{ and } (A_2^k)^c = \{j : \gamma_{kj}^0 = 0 \text{ and } \beta_{j}^0 \neq 0\}. \max_{\theta_A \in \mathcal{N}_0} \max_{j} \lambda_{\max} \left( T_{1}^{(j)}(\gamma_{j}) \right) = O(n) \), where \( T_{1}^{(j)}(\gamma_{j}) = \left( t_{jh}(\gamma_{j}) \right)_{(q+s) \times (q+s)} \text{ with } t_{jh}(\gamma_{j}) = \sum_{l=1}^{L} \left( X_{j} + \sum_{g=1}^{q} M^{(q)}(\gamma_{g}) \right)^T W_{\tau_1} \odot M^{(k)} \), if both \( f \) and \( h \) correspond to the \( \zeta \)th element of \( A_2^k \), and 0 otherwise. \( T_{2}^{(j)}(\beta_{j}) = \left( t_{jh}(\beta_{j}) \right)_{(q+s) \times (q+s)} \text{ with } t_{jh}(\beta_{j}) = \left( M^{(k)}(\beta_{j}) \right)^T M^{(k)} \), if both \( f \) and \( h \) correspond to the \( \zeta \)th element of \( A_2^k \), and 0 otherwise.

5. \( \log(p) = O(n^a), a \in (0, 1/2) \).

6. \( \frac{\lambda_i}{\sqrt{s/n}} \to \infty, \frac{\lambda_i}{n^{u/2-1/2}\sqrt{\log n}} \to \infty, i = 1, 2 \).
7. \( \frac{b_0}{\lambda_1} \to \infty. \)

Condition 1 is commonly assumed in the literature of high dimensional statistics. See for example Fa and Lv(2010). Condition 2 supposes that a smallest signal of genetic coefficient and G-E interaction coefficient with a rate that is not faster than \( \sqrt{n/s} \). Condition 3 assumes that the eigenvalue of design matrix is bounded, away from zero and infinity. The form of condition 3 is more complicated because of the decomposition technique to satisfy the hierarchy situation. Without decomposition of \( \eta_{kj} \), condition 3 will be simpler with \( F(\theta_A) = 0 \). Condition 4 is similar to Condition 6 in Wu, Zhang and Ma(2020). The first two equations assume a relationship between negligible variables(in \( \mathcal{A}_1^c \) and \( (\hat{\mathcal{A}}_2^c)^c \)) and significant variables(in \( \mathcal{A}_1 \) and \( \mathcal{A}_2 \)). Condition 5 assumes that the number of genetic coefficient has nonpolynomial dimensionality. See Fan and Lv(2010) for an overview of Variable Selection in high dimensional feature space. Condition 6 restricts the order of tuning parameters \( \lambda_1, \lambda_2 \). Condition 7 restricts the nonzero coefficients away from zero(Huang et al., 2017).

Next, we want to establish estimation consistency when the true sparsity structures are known.

**Theorem 1.** Under condition 1-3, there exists a local minimizer \( \hat{\theta}_A \) of \( \overline{Q}_n(\theta_A) \) such that for any constant \( C > 0 \),

\[
P(||\hat{\theta}_A - \theta_0^A||_2 \leq \delta_n) > 1 - \eta_1.
\]

where \( \delta_n = C \sqrt{s/n} \), \( \eta_1 = L \cdot \exp \left( -\frac{C \sqrt{s/n \sigma^2}}{2 \lambda_2 \sigma^2} \right) \), \( L \) is specified as a constant in loss function.

Proof: it is sufficient to prove

\[
P \left\{ \inf_{\theta_A \in \mathcal{N}_1} \overline{Q}_n(\theta_A) > \overline{Q}_n(\theta_0^A) \right\} \geq 1 - \eta_1,
\]

where \( \mathcal{N}_1 = \{ \theta_A : ||\theta_A - \theta_0^A||_2 = \delta_n \} \).
Let \( \omega = (e_{1,nx1})^T, \ldots, (e_{Lnx1})^T, (g_{qnx1})^T, (u_{1|A_1x1})^T, (v_{1|A_2x1})^T, \ldots, (v_{q|A_3x1})^T \) with \( \|\omega\|_2 = 1 \) and \( \theta_A = \theta_A^0 + \delta_n \omega \).

Suppose \( L_{\eta}(\theta_A) = \|W_{\eta}^{1/2}(Y - b_l - Za - X_{A_1}\beta_{A_1} - \sum_{k=1}^q M_{A_2^k}(\beta_{A_2^k} \circ \gamma_{k,A_2^k}) \|_2 \), then we have

\[
D_n(\omega) = G_{\tilde{\eta}(\theta_A)}(\beta_{A_2}, \gamma) = \frac{1}{2n} \sum_{l=1}^L L_{\eta}(\theta_A^l + \delta_n \omega) - \frac{1}{2n} \sum_{l=1}^L L_{\tilde{\eta}(\theta_A^l)}
\]

\[
= \frac{1}{2n} \sum_{l=1}^L \delta_n \omega^T \left( \nabla L_{\eta}(\theta_A)|_{\theta_A^l} \right) + \frac{1}{4n} \sum_{l=1}^L \delta^2_n \omega^T \left( \nabla^2 L_{\eta}(\theta_A)|_{\theta_A^l} \right) \omega
\]

\[
= \delta_n \omega^T \sum_{l=1}^L \left[ -\frac{1}{n} G_{\eta_l}(\beta_{A_2}, \gamma_{A_1})^T \epsilon_l \right] + \frac{1}{2} \delta^2_n \omega^T \sum_{l=1}^L \left[ \frac{1}{n} G_{\eta_l}(\tilde{\beta}_{A_2}, \tilde{\gamma}_{A_1})^T G_{\eta_l}(\tilde{\beta}_{A_2}, \tilde{\gamma}_{A_1}) + \frac{1}{n} F_{\eta_l}(\theta_A) \right] \omega
\]

\[
= T_1 + T_2,
\]

where \( \epsilon_l = W_{\theta_A}^{1/2} \left[ Y - b_l^0 - Zo - X_{A_1}\beta_{A_1} - \sum_{k=1}^q M_{A_2^k}(\beta_{A_2^k} \circ \gamma_{k,A_2^k}) \right], \gamma_{A_1} = (\gamma_{1,A_1}, \ldots, \gamma_{q,A_1})^T \)

with \( \gamma_{kj} = 0 \), if \( j \in A_1 \) but \( j \not\in A_2^k \),

\[
\begin{align*}
G_{\eta_l}(\beta_{A_2}, \gamma_{A_1}) &= W_{\theta_A}^{1/2} \left( 1_{n\times1}, Z, U(\gamma_{A_1}), V^{(1)}(\beta_{A_2}), \ldots, V^{(q)}(\beta_{A_2}) \right)_{n \times (q + s + 1)} ;
\end{align*}
\]

and

\[
U(\gamma_{A_1}) = \begin{bmatrix} \sum_{k=1}^q M_{A_2^k} \circ (1_{n \times 1}(\gamma_{k,A_1}))^T \end{bmatrix} \quad V^{(k)}(\beta_{A_2}) = M_{A_2^k}^\text{\(k\)} \circ (1_{n \times 1}(\beta_{A_2}))^T .
\]

\[
F_{\eta_l}(\theta_A) = (f_{jh}(\theta_A))_{(q+s) \times (q+s)} \text{ with } f_{jh}(\theta_A) = -W_{\theta_A}(M_{A_2^k}^\text{\(k\)})^T (Y - b_l - Za - X_{A_1}\beta_{A_1} - \sum_{g=1}^q M_{A_2^g}^\text{\(g\)}(\beta_{A_2^g} \circ \gamma_{g,A_2^g})) \text{ if both } j \text{ and } h \text{ correspond to the } c\text{th element of } A_2^k \text{, and } 0 \text{ otherwise. And } \tilde{\theta}_A \text{ lies on the line segment connecting } \theta_A^0 + \delta_n \omega \text{ and } \theta_A^0. \text{ For each element } w_i \text{ of } W_{\theta_A}, w_i = \tau_l \text{ if } i\text{-th element } (Y - b_l - Za - X_{A_1}\beta_{A_1} - \sum_{k=1}^q M_{A_2^k}(\beta_{A_2^k} \circ \gamma_{k,A_2^k})) \text{, otherwise } w_i = 1 - \tau_l .
\]

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Let $T_1 = \sum_{l=1}^{L} T_{1,l} = \sum_{l=1}^{L} \delta_n \omega^T \left[ -\frac{1}{n} G_{\gamma_l}(\beta_{A_2}^0, \gamma_{A_1}^0)^T \epsilon_l \right]$. For $\epsilon_1 > 0$, with condition 1 about tail distribution of subgaussian variable and condition 3, we have

$$P(T_{1,l} < -\delta_n \epsilon_1) = P(\delta_n \omega^T \left[ -\frac{1}{n} G_{\gamma_l}(\beta_{A_2}^0, \gamma_{A_1}^0)^T \epsilon_l \right] < -\delta_n \epsilon_1)
\leq P \left( \left\| \delta_n \omega^T \left[ -\frac{1}{n} G_{\gamma_l}(\beta_{A_2}^0, \gamma_{A_1}^0)^T \epsilon_l \right] \right\|_2 < -\frac{\epsilon_1}{\left\| \delta_n \omega^T \left[ -\frac{1}{n} G_{\gamma_l}(\beta_{A_2}^0, \gamma_{A_1}^0)^T \right] \right\|_2} \right)
\leq \exp(-\frac{n\epsilon_1^2}{2cs\sigma^2}).$$

Set $\epsilon_1 = \frac{1}{4L}\sqrt{\delta_n}$. With the Bonferroni’s inequality, we have

$$P(T_1 < -\frac{1}{4} \sum_{l=1}^{L} \epsilon_n^2 \delta_n^2) \leq \sum_{l=1}^{L} P(T_{1,l} < -\frac{1}{4} \epsilon_n^2 \delta_n^2) \leq L \exp \left(-\frac{n\epsilon_1^2 \delta_n}{32\sigma^2} \right).$$

Then

$$P(T_1 > -\frac{1}{4} L \epsilon_n^2 \delta_n^2) > 1 - L \exp \left(-\frac{n\epsilon_1^2 \delta_n}{32\sigma^2} \right).$$

For $T_2$, with condition 2, we have

$$||\hat{\theta}_A - \theta_A^0||_{\infty} \leq ||\theta_A - \theta_A^0||_{\infty} \leq \delta_n < b_0/2.$$

By condition 3, we have

$$T_2 \geq \frac{1}{2} L \delta_n^2 \epsilon > 0.$$

Let $\delta_n = C \sqrt{s/n}$, we have probability $1 - L \cdot \exp \left(-\frac{C \sqrt{n/s\epsilon^2}}{32\sigma^2} \right)$ such that $D_n(\omega) \geq \frac{1}{4} L \delta_n^2 \epsilon.$

Then

$$P\left\{ \inf_{\theta_A \in N_1} \overline{Q}_n(\theta_A) > \overline{Q}_n(\theta_A^0) \right\} \geq P(D_n(\omega) > 0)
\geq P\left( -\frac{1}{4} L \delta_n^2 \epsilon \geq 0 \right)
\geq P(T_1 \geq -\frac{1}{4} L \delta_n^2 \epsilon)
\geq 1 - L \cdot \exp \left(-\frac{C \sqrt{n/s\epsilon^2}}{32\sigma^2} \right).$$
Therefore, we prove the theorem 1. With Theorem 1, we have \(|\hat{\theta}_A - \theta_A^0|_2 = O_p(\sqrt{s/n})\).

The order \(O_p(\sqrt{s/n})\) is same to the existing result by Wu, Zhang and Ma(2020). This theorem establishes estimation consistency of \(\hat{\theta}_A\).

Next, we establish the oracle selection and estimation consistency properties of the proposed method. We check three condition in Theorem 1 in Fan and Lv (2011)[5]. Let \(A_1^c = \{j : \beta_j^0 = 0\}\) and \((\hat{A}_2^c)^c = \{j : \gamma_{k_j}^0 = 0\} \text{ and } \beta_j^0 \neq 0\}.\) We have \((\hat{A}_2^c)\cup A_1^c = \{j : \eta_{k_j}^0 = 0\}\). Consider the oracle estimator \(\hat{\theta}^0\) with \(\hat{\theta}_A^0 = \hat{\theta}_A^0 = 0\). Theorem 2 provides sufficient conditions to ensure that \(\hat{\theta}^0\) is a local minimizer of \(Q_n(\theta)\) with a high probability.

**Theorem 2.** Suppose \(\hat{\beta}_A^0 = 0, \hat{\gamma}_{k,(\hat{A}_2^c)^c} = 0\). Under condition 1-8, \(\hat{\theta}\) is a strict local minimizer of \(Q_n(\theta)\) with probability approaching 1.

**Proof:** We follow Theorem 1 in Fan and Lv (2011)[5] to prove theorem 2. With Theorem 1 we have proven, it is sufficient to check condition (8) in the literature of Fan and Lv, which is equivalent to check Karush-Kuhn-Tucher(KKT) condition.

First, we consider \(\hat{\beta}_{A_1^c}\). Suppose

\[
h_1 = (n\lambda_1)^{-1} \left[ \frac{1}{2} \sum_{l=1}^L \nabla \beta_{A_1^c} L_{\tau_l}(\theta) | \hat{\theta} \right].
\]

Since \(\hat{\beta}_{A_1^c} = 0\), by Taylor expansion, we have

\[
h_1 = (n\lambda_1)^{-1} \left[ \sum_{l=1}^L -U(\gamma_{A_1^c})^T W_{\tau_l} \left( Y - \hat{b}_l - Z\hat{\alpha} - X\hat{\beta} - \sum_{k=1}^q M^{(k)}(\hat{\beta} \odot \hat{\gamma}_k) \right) \right]
\]

\[
= (n\lambda_1)^{-1} \left[ \sum_{l=1}^L -U(\gamma_{A_1^c})^T W_{\tau_l} e_l + \left( \sum_{l=1}^L U(\gamma_{A_1^c})^T W_{\tau_l} G(\beta_{A_1^c}, \gamma_{A_1^c})^T (\hat{\theta}_A - \theta_A^0) + \kappa \right) \right]
\]

\[
= (n\lambda_1)^{-1} [I + II],
\]

where each element \(w_i\) of \(W_{\tau_l}, w_i = \tau_l\) if \(i\)-th element \((Y - \hat{b}_l - Z\hat{\alpha} - X\hat{\beta} - \sum_{k=1}^q M^{(k)}(\hat{\beta} \odot \hat{\gamma}_k))_i \geq 0\), otherwise, \(w_i = 1 - \tau_l\). And \(e_l = Y - \hat{b}_l - Z\alpha^0 - X_{A_1}\beta_{A_1}^0 - \sum_{k=1}^q M^{(k)}(\beta_{A_2^k} \odot \gamma_{k,A_2^k})\).
For II, let \( m_j(\theta_A) = \sum_{i=1}^{L} \left( X_j + \sum_{k=1}^{q} M_j^{(k)} \gamma_{kj} \right)^T \hat{W}_\tau \left( b_i + Z \alpha + X_A \beta_A + \sum_{k=1}^{q} M_{A_l}^{k} (\beta_{A_{l2}} \circ \gamma_{k,A_{l2}}) \right) \). Then \( \kappa = (\kappa_j, j \in A_2^c)^T \) with
\[
\kappa_j = \frac{1}{2} (\hat{\theta}_A - \theta_A^0) \left( \nabla_{\theta_A} m_j(\theta_A) \mid \hat{\theta}_A \right) (\hat{\theta}_A - \theta_A^0) \\
\leq \frac{1}{2} \max_j \lambda_{\max}(T^{(j)} \hat{\gamma}_j) ||\hat{\theta}_A - \theta_A^0||_2,
\]
where \( \hat{\theta}_A \) lies on the line segment between \( \hat{\theta}_A \) and \( \theta_A^0 \). And \( T^{(j)} \hat{\gamma}_j = \left( t^{(j)}_{fh}(\gamma_{ij}) \right)_{(q+s) \times (q+s)} \) with \( t^{(j)}_{fh}(\gamma_{ij}) = \sum_{i=1}^{L} \left( X_j + \sum_{g=1}^{q} M_j^{(g)} \gamma_{gj} \right)^T \hat{W}_\tau M^{(g)}_c \), if both \( f \) and \( h \) correspond to the \( \zeta \)th element of \( A_2^c \), and 0 otherwise. With condition 4 and condition 6,
\[
(n \lambda_1)^{-1} \|II\|_\infty = (n \lambda_1)^{-1} \left( \| \sum_{i=1}^{L} U(\gamma_{Ai})^T \hat{W}_\tau G(\beta_{A_{i1}}, \gamma_{Ai})^T (\hat{\theta}_A - \theta_A^0) + \kappa \|_\infty \right) \\
= (n \lambda_1)^{-1} \left( O(n \|\hat{\theta}_A - \theta_A^0\|_2 + O(n \|\hat{\theta}_A - \theta_A^0\|_2^2) \right) \\
= O(\lambda_1^{-1} \sqrt{s/n}) = o(1).
\]

For I, consider the event
\[
\Omega_1 = \{ \| U(\gamma_{Ai})^T \hat{W}_\tau \epsilon_1 \| \infty \leq \zeta_n \sqrt{n} \}
\]
with \( \zeta_n = n^a(log(n))^{1/2} \). With Condition 4 and Condition 5, we have
\[
P(\Omega_1) = 1 - P\{ \| U(\gamma_{Ai})^T \hat{W}_\tau \epsilon_1 \| \infty > \zeta_n \sqrt{n} \} \\
\geq 1 - \sum_{j \in A_1^c} P\{ \| U(\gamma_{Ai})^T \hat{W}_\tau \epsilon_1 \| \infty > \zeta_n \sqrt{n} \} \\
\geq 1 - 2p \times \exp \left( - \frac{\zeta_n^2 n}{2 \sigma^2 \max_{j \in A_1^c} \| U(\gamma_{Ai})^T \hat{W}_\tau \epsilon_1 \|_2^2} \right) \rightarrow 1.
\]
as \( log(p) = O(n^a) \) and \( \| U(\gamma_{Ai})^T \hat{W}_\tau \|_2 = O(\sqrt{n}) \). We have
\[
\| U(\gamma_{Ai})^T \hat{W}_\tau \epsilon_1 \|_\infty = O(n^{a/2+1/2} \sqrt{\log n}).
\]

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We use triangle inequality of maximal norm and $L$ is a constant. Then

$$
\left\lVert \sum_{l=1}^{L} U(\gamma_{A_l}^0)^T \tilde{W}_{\tau} \epsilon_1 \right\rVert_{\infty} \leq \sum_{l=1}^{L} \left\lVert U(\gamma_{A_l}^0)^T \tilde{W}_{\tau} \epsilon_1 \right\rVert_{\infty} = O(n^{\alpha/2+1/2} \sqrt{\log n}).
$$

With condition 6, we have

$$(n\lambda_1)^{-1} \left\lVert \sum_{l=1}^{L} U(\gamma_{A_l}^0)^T \tilde{W}_{\tau} \epsilon_1 \right\rVert_{\infty} = o(1).$$

Next, we consider $\gamma_{k,(\hat{A}_2)^c}$. The steps are similar to $\hat{\beta}_{A_1}$. Suppose

$$h_2 = (n\lambda_2)^{-1} \left[ \frac{1}{2} \sum_{l=1}^{L} \nabla_{(\hat{A}_2)^c} \lambda L_{\tau} (\theta) \bigg| \theta \right],$$

Since $\gamma_{k,(\hat{A}_2)^c} = 0$ and $\hat{\beta}_{(\hat{A}_2)^c} \neq 0$, by Taylor expansion, we can get

$$h_2 = (n\lambda_2)^{-1} \left[ \sum_{l=1}^{L} -V^{(k)}(\beta_{(\hat{A}_2)^c})^T \tilde{W}_{\tau} \left( Y - \hat{b}_t - Z\hat{\alpha} - X^T \hat{\beta} - \sum_{k=1}^{q} M^{(k)}(\beta \odot \gamma_k) \right) \right]$$

$$= (n\lambda_2)^{-1} \left[ \sum_{l=1}^{L} -V^{(k)}(\beta_{(\hat{A}_2)^c})^T \tilde{W}_{\tau} \epsilon_1 + \left( \sum_{l=1}^{L} V^{(k)}(\beta_{(\hat{A}_2)^c})^T \tilde{W}_{\tau} \epsilon_1 G(\beta_{A_2}, \gamma_{A_1})^T (\hat{\beta}_{A} - \theta_{A}) + \tilde{\kappa} \right) \right]$$

$$= IV + V.$$

For $V$, let $\tilde{m}_j(\theta_A) = \sum_{l=1}^{L} \left( M^{(k)}_{j} \beta_j \right)^T \tilde{W}_{\tau} \left( b_t + Z\alpha + X_{A_1} \beta_{A_1} + \sum_{k=1}^{q} M^{(k)}_{A_2} (\beta_{A_2} \odot \gamma_{k,A_2}) \right)$, then $\tilde{\kappa} = (\tilde{\kappa}_j, j \in (\hat{A}_2)^c)^T$ with

$$\tilde{\kappa}_j = \frac{1}{2} \left( \hat{\theta}_A - \theta_{A}^0 \right) \left( \nabla_{\hat{\theta}_A} m_j(\theta_A) \bigg| \hat{\theta}_A \right) \left( \hat{\theta}_A - \theta_{A}^0 \right)$$

$$\leq \frac{1}{2} \max_j \lambda_{max}(T^{(j)}(\tilde{\beta}_j)) \lVert \hat{\theta}_A - \theta_{A}^0 \rVert_2,$$

where $\hat{\theta}_A$ lies on the line segment between $\hat{\theta}_A$ and $\theta_{A}^0$. $T^{(j)}(\beta_j) = \left( t^{(j)}_{f_h}(\beta_j) \right)_{(q+s) \times (q+s)}$ with $t^{(j)}_{f_h}(\beta_j) = \sum_{l=1}^{L} \left( M^{(k)}_{j} \beta_j \right)^T \tilde{W}_{\tau} \epsilon_1 M^{(k)}_{\zeta}$, if both $f$ and $h$ correspond to the $\zeta$th element of $A_k$.
and 0 otherwise.

\[(n\lambda_2)^{-1}\|V\|_\infty = (n\lambda_2)^{-1} \left( \| \sum_{l=1}^{L} V^{(k)}(\beta_{\hat{A}_2}^{0})^T W_{\pi_l} G(\beta_{\hat{A}_2}, \gamma_{\hat{A}_1})^T (\hat{\theta}_A - \theta_{A}^0) + \kappa \|_\infty \right) \]
\[\leq (n\lambda_2)^{-1} \left( O(n)\|\hat{\theta}_A - \theta_{A}^0\|_2 + O(n)\|\hat{\theta}_A - \theta_{A}^0\|_2 \right) \]
\[\leq O(\lambda_2^{-1}\sqrt{s/n}) = o(1). \]

For IV, we consider the event

\[\Omega_2 = \{ \| V^{(k)}(\beta_{\hat{A}_2}^{0})^T \hat{W}_\pi \epsilon \|_\infty \leq \zeta_n \sqrt{n} \}, \]

where \( \zeta_n = n^{a}(\log(n))^{1/2} \). Then,

\[P(\Omega_2) = 1 - P\{\| V^{(k)}(\beta_{\hat{A}_2}^{0})^T \hat{W}_\pi \epsilon \|_\infty > \zeta_n \sqrt{n} \} \]
\[\geq 1 - \sum_{i \in (\hat{A}_2)^c} P\{\| V^{(k)}(\beta_i^0)^T \hat{W}_\pi \epsilon \|_\infty > \zeta_n \sqrt{n} \} \]
\[\geq 1 - 2p \exp \left( - \frac{\zeta_n^2 n}{2\sigma^2 \max_{i \in (\hat{A}_2)^c} || V^{(k)}(\beta_i^0)^T \hat{W}_\pi \epsilon ||_2^2} \right) \rightarrow 1. \]

as \( \log(p) = O(n^a) \) and \( || V^{(k)}(\beta_i^0)^T \hat{W}_\pi ||_2 = O(\sqrt{n}) \). Then we have, with probability approaching 1,

\[|| V^{(k)}(\beta_{\hat{A}_2}^{0})^T \hat{W}_\pi \epsilon ||_\infty = O(n^{a/2+1/2} \sqrt{\log n}). \]

Since \( L \) is a constant and triangle inequality of maximal norm, we have

\[\| \sum_{l=1}^{L} V^{(k)}(\beta_{\hat{A}_2}^{0})^T \hat{W}_\pi \epsilon \|_\infty \leq \sum_{l=1}^{L} || V^{(k)}(\beta_{\hat{A}_2}^{0})^T \hat{W}_\pi \epsilon ||_\infty = O(n^{a/2+1/2} \sqrt{\log n}). \]

By condition 6, we could get

\[(n\lambda_2)^{-1}\| \sum_{l=1}^{L} V^{(k)}(\beta_{\hat{A}_2}^{0})^T \hat{W}_\pi \epsilon \|_\infty = o(1). \]
Next, we check the KKT condition of non-zero estimator.

For \( j \in A_1 \), with probability tending to 1,

\[
|\hat{\beta}_j| \geq |\beta_j^0| - |\hat{\beta}_j - \beta_j^0| \geq |\beta_j^0| - ||\hat{\theta}_A - \theta_A^0||_\infty \geq |\beta_j^0| - ||\hat{\theta}_A - \theta_A^0||_2 > b_0 > a\lambda_1,
\]

then \( \min_{j \in A_1} |\hat{\beta}_j| > a\lambda_1 \).

Similarly, we can also show that for each \( k \in \{1, \ldots, q\} \), \( \min_{j \in A_k} |\gamma_{kj}| > a\lambda_2 \) when \( n \) is sufficiently large.

Therefore, we have shown that the corresponding KKT conditions are satisfied. This completes the proof.

4 Simulation

In this section, we give an iterative coordinate descent algorithm for composite expectile regression. To demonstrate the performance of the proposed approach, we simulate two settings: homoscedastic setting and heteroscedastic setting.

4.1 Algorithm

We use an iterative coordinate descent (CD) algorithm, which optimizes the objective function (8) with respect to one of the four types of parameters \( b_l, \alpha, \beta, \gamma \).

1. Initialization: Let \( t = 0, b_l = 0, \beta^{(t)} = 0, \gamma^{(t)} = 0, \alpha^{(t)} = (Z^T Z)^{-1}Z^T Y \) for \( l = 1, \ldots, L \), and \( \text{res}_{i}^{(t)} = Y - b_l^{(t)} - Z\alpha^{(t)} - X\beta^{(t)} - \sum_{k=1}^{q} M^{(k)}(\beta^{(t)} \odot \gamma^{(t)}_k) \), where \( b_l^{(t)}, \alpha^{(t)}, \beta^{(t)}, \gamma^{(t)}, \text{res}_{i}^{(t)} \) are the estimates of \( b_l, \alpha, \beta, \gamma \) and residual vector at iteration \( t \) respectively.
2. Update \( t = t + 1 \). With fixed \( \boldsymbol{b}_t, \gamma \) and \( \alpha \) at \( \boldsymbol{b}^{(t-1)}_t, \gamma^{(t-1)} \) and \( \alpha^{(t-1)} \), \( l = 1, \ldots, L \),
we optimize \( \mathcal{O}_n(\theta) \) with respect to \( \beta \). Let \( \hat{Y}^{(t)}_t = Y - \hat{b}^{(t-1)}_t - Z\alpha^{(t-1)} \) and \( \tilde{X}^{(t)} = X + \sum_{k=1}^q M^{(k)} \odot (1_{n \times 1}(\gamma^{(t-1)}_k)^T) \) with \( 1_{n \times 1} = (1, \ldots, 1)_{n \times 1} \). Then
\[
\beta^{(t)} = \arg\min \frac{1}{2n} \sum_{l=1}^L ||W^{1/2}_{\tau_l} (\hat{Y}^{(t)}_l - \tilde{X}^{(t)} \beta) ||^2 + \sum_{j=1}^p \rho(||\beta_j||; \lambda_1, r) \quad (13)
\]
For \( j = 1, \ldots, p \), we run the following steps sequentially. \( W_{\tau_l} \) is defined according to \( \hat{Y}^{(t)}_l - \tilde{X}^{(t)} \beta \) in each optimization steps with two possible elements \( \tau_l, 1 - \tau_l \). \( W_{\tau_l} \) is defined differently under varied squared loss function.

(a) Compute \( \text{res}^{(t)}_{l-j} = \hat{Y}^{(t)}_l - \sum_{l=1}^{j-1} \hat{X}^{(t)}_l \beta^{(t)}_l - \sum_{l=j+1}^{p} \hat{X}^{(t)}_l \beta^{(t-1)}_l = \text{res}^{(t-1)}_l + \tilde{X}^{(t)}_j \beta^{(t-1)}_j \),
\[
\phi^{(t)}_j = \frac{1}{n} \sum_{l=1}^L (\hat{X}^{(t)}_j)^T W_{\tau_l} \text{res}^{(t)}_{l-j}, \psi^{(t)}_j = \frac{1}{n} \sum_{l=1}^L (\tilde{X}^{(t)}_j)^T W_{\tau_l} \tilde{X}^{(t)}_j, \quad W_{\tau_l} \text{ is } n \times n \text{ diagonal matrix with two possible elements } \tau_l, 1 - \tau_l \text{ and } W_{\tau_l} \text{ is updated at each step.}
\]

(b) Update the estimate of \( \beta_j \) as
\[
\beta^{(t)}_j = \begin{cases} 
\frac{ST(\phi^{(t)}_j, \lambda_1)}{\psi^{(t)}_j - \frac{1}{r}}, & |\phi^{(t)}_j| \leq \lambda_1 r \psi^{(t)}_j \\
\phi^{(t)}_j, & |\phi^{(t)}_j| > \lambda_1 r \psi^{(t)}_j.
\end{cases} \quad (14)
\]
where \( ST(v, \lambda_1) = \text{sgn}(v)(|v| - \lambda_1)_+ \) is the soft-thresholding operator.

(c) Update \( \text{res}^{(t-1)}_l = \text{res}^{(t-1)}_l + \tilde{X}^{(t)}_j \beta^{(t-1)}_j - \tilde{X}^{(t)}_j \beta^{(t)}_j \)

3. With fixed \( \boldsymbol{b}_t, \beta \) and \( \alpha \) at \( \hat{b}^{(t-1)}_t, \beta^{(t)} \) and \( \alpha^{(t-1)} \), optimize equation (10) with respect to \( \gamma \). Let \( \hat{Y}^{(t)}_t = Y - \hat{b}^{(t-1)}_t - Z\alpha^{(t-1)} - X\beta^{(t)} \) and \( \hat{M}^{(i)}_j \equiv \hat{M}^{(i)}_j \odot (1_{n \times 1}(\beta_j^{(t)})^T) \).
Then
\[
(\gamma^{(t)}_1, \ldots, \gamma^{(t)}_q) = \arg\min \frac{1}{2n} \sum_{l=1}^L ||W^{1/2}_{\tau_l} (\hat{Y}^{(t)}_l - \sum_{k=1}^q (\hat{M}^{(k)}_j)^T \gamma_k) ||^2 + \sum_{j=1}^p \sum_{k=1}^q \rho(||\gamma_k||; \lambda_2, r)
\]
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For \( k = 1, \ldots, q \) and \( j \in \{ j : \beta_j^{(t)} \neq 0, j = 1, \ldots, p \} \), conduct estimation similar to step 2.

4. With fixed \( \beta, \gamma \) at \( b_l^{(t-1)}, \beta(t) \) and \( \gamma(t) \), we optimize equation (10) with respect to \( \alpha \). Let \( \hat{Y}_l^{(t)} = Y - b_l^{(t-1)} - X \beta(t) - \sum_{k=1}^{q} M^{(k)}(\beta(t) \odot \gamma_k^{(t)}) \). Then

\[
\hat{\alpha}^{(t)} = \arg \min \frac{1}{2n} \sum_{l=1}^{L} ||W_{n_l}^{1/2} \left( \text{hat}Y_l^{(t)} - Z\alpha \right)||^2
\]

We can get \( \alpha^{(t)} = (\sum_{l=1}^{L} Z^T W_{n_l} Z)^{-1}(\sum_{l=1}^{L} Z^T W_{n_l} \hat{Y}_l^{(t)}) \), where \( \hat{Y}_l^{(t)} = \text{res}_l^{(t-1)} + Z\alpha^{(t-1)} \). Then we update \( \text{res}_l^{(t)} = \text{res}_l^{(t-1)} + Z\alpha^{(t-1)} - Z\alpha^{(t)} \) for each \( l \) from 1 to \( L \).

5. With fixed \( \alpha, \beta \) and \( \gamma \) at \( \alpha^{(t)}, \beta(t) \) and \( \gamma(t) \), we optimize equation (10) with respect to \( \beta_l \). Let \( \hat{Y}^{(t)} = Y - Z\alpha^{(t)} - X \beta(t) - \sum_{k=1}^{q} M^{(k)}(\beta(t) \odot \gamma_k^{(t)}) \). Then

\[
(b_1, \ldots, b_L) = \arg \min \frac{1}{2n} \sum_{l=1}^{L} ||W_{n_l}^{1/2} (\hat{Y}^{(t)} - b_l)||^2
\]

This is a convex optimization problem with respect to \( b_l \). A build-in function ‘optimise’ in R is used to get the solution. Then we update \( \text{res}_l^{(t)} = \text{res}_l^{(t-1)} + b_l^{(t-1)} - b_l^{(t)} \).

6. Repeat step 2 to step 5 until convergence:

\[
\frac{|Q_n(\theta^{(t)}) - Q_n(\theta^{(t-1)})|}{|Q_n(\theta^{(t-1)})|} < 10^{-4}
\]

4.1.1 Details of step 2 for proposed algorithm

For \( j = 1, \ldots, p \), the CD algorithm optimizes the objective function with respect to \( \beta_j \) while fixing the other parameters \( \beta_l(l \neq j) \) at their current estimates \( \beta_l^{(t)} \) for \( l < j \) or \( \beta_l^{(t-1)} \) for
Consider the following simplified objective function in step 2:

$$Q_s(\beta_j) = \frac{1}{2n} \sum_{l=1}^L \|W_{\tau_l}^{1/2}(\text{res}_{-j,l}^{(t)} - \bar{X}_j^{(t)} \beta_j))\|^2 + \rho(|\beta_j|; \lambda_1, r)$$  \hspace{1cm} (15)

where \(\text{res}_{-j,l}^{(t)} = \tilde{Y}_l^{(t)} - \sum_{i=1}^{j-1} \tilde{X}_i^{(t)} \beta_i^{(t)} - \sum_{i=j+1}^p \bar{X}_i^{(t-1)} \beta_i^{(t-1)} = \text{res}_i^{(t-1)} + \bar{X}_j^{(t)} \beta_j^{(t-1)}\) with \(\text{res}_{-j,l}^{(t)} = \tilde{Y}_l^{(t)} - \sum_{i=1}^{j-1} \tilde{X}_i^{(t)} \beta_i^{(t)} - \sum_{i=j}^p \bar{X}_i^{(t-1)} \beta_i^{(t-1)}\), \(W_{\tau_l}\) is \(n \times n\) diagonal matrix with two possible elements \(\tau_l, 1 - \tau_l\)

We take derivative with respective to \(\beta_j\)

$$\frac{\partial Q_s(\beta)}{\partial \beta_j} = -\frac{1}{n} \sum_{l=1}^L (\bar{X}_j^{(t)})^T W_{\tau_l} \text{res}_{-j,l}^{(t)} + \frac{1}{n} \sum_{l=1}^L (\bar{X}_j^{(t)})^T W_{\tau_l} \bar{X}_j^{(t)} \beta_j$$

$$+ \lambda_1 \text{sgn}(\beta_j) \begin{cases} 1 - \frac{|\beta_j|}{\lambda_1 r}, & |\beta_j| \leq \lambda_1 r \\ 0, & |\beta_j| > \lambda_1 r \end{cases}$$

$$= -\phi_j^{(t)} + \psi_j^{(t)} \beta_j + \frac{1}{n} \sum_{l=1}^L (\bar{X}_j^{(t)})^T W_{\tau_l} \bar{X}_j^{(t)}.$$  \hspace{1cm} (16)

By setting \(\frac{\partial Q_s(\beta)}{\partial \beta_j} = 0\), we have

$$\beta_j^{(t)} = \begin{cases} \frac{\text{ST}(\phi_j^{(t)}, \lambda_1)}{\psi_j^{(t)}}, & |\phi_j^{(t)}| \leq \lambda_1 r \psi_j^{(t)} \\ \frac{\phi_j^{(t)}}{\psi_j^{(t)}}, & |\phi_j^{(t)}| > \lambda_1 r \psi_j^{(t)} \end{cases}$$

where \(\text{ST}(v, \lambda_1) = \text{sgn}(v)(|v| - \lambda_1)_+\) is the soft-thresholding operator.
4.2 Simulation setting

We choose n = 500, q = 5 and p = 500. Thus, there are a total of 5,05 main effects and 25,000 interactions. The true genetic estimators and G-E interaction estimators are fixed.

- For G effect, we simulate gene expression data coded from a multivariate Normal distribution.

- For E factors, we first generate five continuous variables from a multivariate Normal distribution with marginal mean 0, marginal variance 1, and correlation structure $AR(0.3)$, and then dichotomize two of them at 0 to create two binary variables. There are thus three continuous and two binary E factors.

- For E factors, their coefficients $\alpha$ are generated from Uniform (0.8, 1.2) with 5 non-zero value.

- For G factors, their coefficients $\beta$ are filled in sparse form, with 20 non-zero value.

- For G-E interaction effects, their coefficients $\gamma_{kj}$ are also filled in sparse uniform, with 40 non-zero value.

- We simulate y as a continuous response based on model (1)

To find optimal tuning parameters($\lambda_1, \lambda_2, r$), we use grid search method through a specified subset. For example, $\lambda_1 = (0.1, 0.5, 1, 1.5, 2), \lambda_2 = (0.1, 0.5, 1, 1.5, 2)$ and $r = 3$. 1000 iterations are used to train both ER and CER. To measure the model performance, we define absolute estimation error(AE) and Square estimation error(SE)

- Absolute estimation error:

$$AE=(\sum_{k=1}^q |\hat{\alpha}_k - \alpha^0_k| + \sum_{j=1}^p |\hat{\beta}_j - \beta^0_j| + \sum_{k=1}^q \sum_{j=1}^p |\hat{\gamma}_{kj} - \gamma^0_{kj}|)$$

20
• Square estimation error:
\[
SE = \sqrt{\left(\sum_{k=1}^{q} (\hat{\alpha}_k - \hat{\alpha}_k^0)^2 + \sum_{j=1}^{p} (\hat{\beta}_j - \hat{\beta}_j^0)^2 + \sum_{k=1}^{q} \sum_{j=1}^{p} (\hat{\gamma}_{kj} - \hat{\gamma}_{kj}^0)^2\right)}
\]

• Mean Absolute Deviation:
\[
MAD = \frac{1}{nL} \sum_{l=1}^{L} ||(Y - \hat{b}_l - Z\hat{\alpha} - X_{A_1}\hat{\beta}_{A_1} - \sum_{k=1}^{q} M_{A_2}(\hat{\beta}_{A_2^k} \odot \hat{\gamma}_{k,A_2^k}))||_1
\]

as criterion to measure the model’s estimation performance. True positive (TP) and False positive (FP) are also proposed to measure the model’s selection performance. We use
\[
BIC = \frac{C}{nL} \sum_{l=1}^{L} ||W_{n_l}^{1/2}(Y - \hat{b}_l - Z\hat{\alpha} - X_{A_1}\hat{\beta}_{A_1} - \sum_{k=1}^{q} M_{A_2}(\hat{\beta}_{A_2^k} \odot \hat{\gamma}_{k,A_2^k}))||_2^2 + s\frac{C_n\log(v)}{n}
\]
to select models, where \(C\) is a constant, \(v = p \times q + p + q\), \(C_n = \log(\log(n))\), \(s = DF\). This data-driven BIC criterion is motivated by Gu and Zou[10]. In composite expectile regression, we choose \(L\) as 9 or 19 to combine the strength of multiple expectile regressions. DF is the total number of non-zero estimator of G effect and G-E interaction effect.

Simulation studies were conducted to compare the performance of CER, ER under different settings: homoscedastic setting and heteroscedastic setting. Totally 200 replicates were simulated for each simulation setting. In each replicate, we measure the model performance in term of selection and estimation in high dimensional statistics,

### 4.3 Setting I: homoscedastic setting

In this section, we consider two types of error distribution:

1. Normal distribution: \(\epsilon \sim N(0,1)\)

2. Student’s t distribution with degree of freedom 4: \(\epsilon \sim \frac{1}{\sqrt{2}} t(4)\)

Since \(\tau\) - expectile quantifies different "location" of a distribution, we use 5 different \(\tau = 0.1, 0.25, 0.5, 0.75, 0.9\) to get a comprehensive view of relationship between covariate and
response. If $\tau = 0.5$, expectile regression is degenerate to mean regression. Therefore, expectile regression can be regarded as a generalization of the mean and an alternative measure of "location" of a distribution (Gu and Zou 2020).

Table 1: Error distribution is normal model under 200 replicates

| Method                | AE     | SE     | TP     | FP     | MAD   |
|-----------------------|--------|--------|--------|--------|-------|
| ER with $\tau = 0.10$ | 22.38(6.52) | 3.44(0.89) | 50.53(2.54) | 8.76(8.27) | 1.41(0.21) |
| ER with $\tau = 0.25$ | 15.57(2.88) | 2.53(0.39) | 52.98(1.75) | 7.12(6.71) | 1.17(0.11) |
| ER with $\tau = 0.50$ | 14.35(2.88) | 2.38(0.36) | 53.30(1.57) | 6.22(7.82) | 1.14(0.11) |
| ER with $\tau = 0.75$ | 15.65(2.78) | 2.57(0.39) | 52.87(1.48) | 6.60(5.47) | 1.18(0.11) |
| ER with $\tau = 0.90$ | 22.24(6.26) | 3.41(0.80) | 50.76(2.28) | 9.79(8.92) | 1.39(0.19) |
| CER                   | 10.69(2.02) | 1.69(0.35) | 57.59(1.16) | 8.45(3.97) | 1.09(0.12) |
| non-hierarchical CER  | 17.64(2.7)  | 2.95(0.47) | 55.20(2.08) | 8.49(3.51) | 1.31(0.07) |

Based on results from table 1, CER has smaller AE and SE value than ER and non-hierarchical CER under different $\tau$ value. Total 60 fixed G effect estimators and G-E interaction estimators are simulated. CER tends to identify more main G effects and G-E interaction effects while achieve comparable more TP. It also have comparable FP. The proposed approach has better prediction performance in term of MAD.

In table 2, we have similar result in table 1. CER outperforms ER and non-hierarchical CER in term of AE and SE. The proposed method also has better identification performance to choose more fixed G-effect estimators and G-E interaction estimators. In the meantime, the number of false positives is smaller. MAD of CER are comparable to ER.
Table 2: Error distribution is $t/\sqrt{2}$ distribution under 200 replicates

| Method          | AE       | SE       | TP       | FP       | MAD      |
|-----------------|----------|----------|----------|----------|----------|
| ER with $\tau = 0.10$ | 23.43(6.40) | 3.58(0.85) | 50.24(2.68) | 9.61(8.27) | 1.44(0.24) |
| ER with $\tau = 0.25$ | 16.49(3.67) | 2.68(0.46) | 52.49(1.55) | 7.28(8.11) | 1.16(0.14) |
| ER with $\tau = 0.50$ | 14.89(3.34) | 2.46(0.41) | 52.99(1.45) | 8.70(10.97) | 1.07(0.15) |
| ER with $\tau = 0.75$ | 16.65(3.56) | 2.69(0.45) | 52.31(1.45) | 8.24(8.85) | 1.17(0.13) |
| ER with $\tau = 0.90$ | 23.82(7.35) | 3.62(0.96) | 50.11(2.76) | 11.38(11.42) | 1.42(0.21) |
| CER              | 9.63(1.74)  | 1.53(0.30) | 57.73(1.07) | 6.22(2.48) | 1.01(0.12) |
| non-hierarchical CER | 16.93(2.76) | 2.94(0.52) | 55.65(2.04) | 10.43(4.66) | 1.23(0.10) |

4.4 Setting II: Heteroscedastic setting

We adopt a model from Wang, Wu and Li (2012). In the model, the covariates are generated in two steps. First, we generate copies of $Z_{n \times q} = (Z_1^c, ..., Z_q^c)$ and $X_{n \times p} = (X_1^c, ..., X_p^c)$. In the second step, for each copy of $(Z_1^c, ..., Z_q^c)$ and $(X_1^c, ..., X_p^c)$, we set $Z_1 = \Phi(Z_1^c)$, $Z_j = Z_j^c$, $X_1 = \Phi(X_1^c)$ and $X_j = X_j^c$ for $j = 2, 3, ..., q$, where $\Phi(\cdot)$ is the standard normal CDF. To include heteroscedastic error, we generate the data in this form:

$$Y_i = Z_i\alpha + X_i\beta + \sum_{k=1}^{q} M_i^{(k)}(\beta \odot \gamma_k) + |\sigma(Z_i, X_i)|\epsilon_i$$  \hspace{1cm} (17)

$|\sigma(Z_i, X_i)| = Z_1 + X_1, \epsilon_i \sim N(0, 1)$.

From table 3, the proposed approach has better estimation and selection performance than ER with different $\tau$ levels and CER without hierarchy.
Table 3: Error distribution is heteroscedastic under 200 replicates

| Method                  | AE     | SE     | TP     | FP     | MAD    |
|-------------------------|--------|--------|--------|--------|--------|
| ER with $\tau = 0.10$  | 19.96(6.84) | 3.12(0.90) | 51.04(2.71) | 8.65(9.77) | 1.17(0.29) |
| ER with $\tau = 0.25$  | 14.32(3.29) | 2.42(0.46) | 52.74(1.49) | 5.66(7.74) | 0.92(0.13) |
| ER with $\tau = 0.50$  | 12.92(2.63) | 2.23(0.31) | 53.48(1.30) | 6.59(8.79) | 0.85(0.10) |
| ER with $\tau = 0.75$  | 14.13(2.60) | 2.41(0.35) | 52.81(1.35) | 5.22(6.17) | 0.92(0.12) |
| ER with $\tau = 0.90$  | 20.36(6.65) | 3.19(0.89) | 50.85(2.77) | 9.12(9.73) | 1.17(0.27) |
| CER                     | 7.77(1.36) | 1.48(0.3) | 58.21(0.85) | 3.21(1.94) | 0.44(0.11) |
| non-hierarchical CER   | 12.38(3.71) | 2.32(0.57) | 57.35(2.25) | 4.78(3.54) | 0.65(0.2) |

5 Real data analysis

Lung adenocarcinoma (LUAD) occurs due to abnormal and uncontrolled cell growth in the lungs, which is a subtype of non-small cell lung cancer that is often diagnosed in an outer area of the lung [https://rarediseases.info.nih.gov/diseases/5742/lung-adenocarcinoma]. LUAD evolves from the mucosal glands and represents about 40% of all lung cancers. This rare disease is the most common disease to be diagnosed in people who have never smoked. LUAD usually occurs in the lung periphery, and in many cases, may be found in scars or areas of chronic inflammation (Myers and Wallen, 2021).

In this section, we applied composite expectile regression as well as the alternative to lung adenocarcinoma. We select age, gender, patient smoking history, and pathologic tumor stage as environmental variables, all of which have been suggested to be potentially associated with LUAD (Du, Liu and Wu (2021)). There are 522 subjects in this study. The FEV1 is response which measures how much air you can exhale in one second and can be used in the diagnosis of obstructive and restrictive lung disease. We match the mRNA
gene expression measurements with the clinical/environmental variables and response. For genetic effects, after some preprocessing procedures including matching subjects and imputing missing data, 232 subjects and 20097 mRNA measurements are chosen. Here, we select 791 mRNA with marginal screening. We examine prediction performance using a resampling-based approach. Specifically, subjects are randomly split into a training and a testing set with a ratio of 7:3. Then we estimate parameters using the training set and make prediction for the testing set subjects. With 50 resamplings, we compute the mean of all MADs. CER with MAD = 0.823. ER with MAD=0.857(τ = 0.5), MAD = 0.858(τ = 0.25), MAD = 0.868(τ = 0.75), MAD = 0.889(τ = 0.1), MAD = 0.885(τ = 0.9)

The proposed approach identified genes with implications of LUAD. 281 of main effects and interactions are identified. The details of coefficients can be found in appendix, table 4. The current study demonstrated that AATK, a radiosensitization-associated gene, is a target of miR-558 in lung cancer cells, using in silico analysis and a luciferase reporter system(Zhu ect,2016). High gene ABCG4 expression is associated with poor prognosis in non-small-cell lung cancer patients treated with cisplatin-based chemotherapy(Yang ect,2015). Gene ADAMTS20 mutations and high amplification of NKX2-1 may be related to brain metastases of lung cancer(Li ect, 2020). Gene AGFG1 is prognostic, high expression is unfavorable in lung cancer, which is associated with severity of airway responsiveness(Himes, 2013). Gene ALG13 were significantly associated with lymph node status of patients with non-small-cell lung cancer(Deng ect, 2019). Gene ARL2 induces rapid release of deltarasin from phosphodiesterase 6 delta subunit, resulting in the impairment of KRAS-dependent lung cancer cell growth(Leung ect, 2018). ATG16L1 is associated with decreased risk of brain metastasis in patients with non-small cell lung cancer(Li ect, 2017). Targeted gene BMI1 inhibition impairs tumor growth in lung adenocarcinomas with low CEBPα expression(Yong ect, 2016).
6 Summary and discussion

In this article, we have studied the sparse penalized CER with G-E interaction. In particular, we establish the selection and estimation consistency of the CER estimator. By implementing coordinate descent algorithm, we have shown that CER has superior or comparable model performance, compared to alternatives. Under heteroscedastic setting, simulations show that CER has better selection and estimation performance. A real data is analyzed to demonstrate the performance of proposed approach.

For CER, it is computational expensive compared to expectile regression since we integrate multiple expectile regression in the loss function. It is worthwhile to explore if an efficient algorithm could be implemented to speed up the computation. We investigate the selection and estimation consistency of CER. It is natural to explore the normality of CER in the future under high dimensional statistics. Some theoretical works has been done in quantile regression scenario. For example, if $L$ goes to infinity, the estimators by combining quantile regressions are asymptotically efficient. We fixed $L$ in our loss function, it is also worth to investigate the theoretical properties if $L$ goes to infinity.

7 Appendix
Table 4: Analysis of the LUAD data using CER: identified main effects and interactions

| Gene            | Sex  | Patient Smoking History | Diagnosis Age | Cancer.Tumor.Stage |
|-----------------|------|-------------------------|---------------|-------------------|
| VLOC645851      | 0.0616 | 0.1235                  | -0.0216       | 0.1120            |
| TMPRSS11E2      | -0.4068 | 0.0434                  | 0.0060        | 0.0587            |
| AATK            | -0.0135 |                          | -0.0022       |                   |
| ABCG4           | 0.0156 |                          | 0.0038        |                   |
| ASIC4           | -0.0206 |                          | -0.0036       |                   |
| ADAM3A          | -0.0074 |                          | -0.0025       |                   |
| ADAMTS1         | -0.0079 |                          | -0.0040       |                   |
| ADAMTS20        | -0.0012 |                          |               |                   |
| AGFG1           | -0.7800 | 0.1285                  | 0.0117        | 0.1708            |
| AKR1D1          | -0.0137 |                          | -0.0039       |                   |
| ALG10           | 0.0117 |                          | 0.00190       |                   |
| ALG13           | -0.3321 | -0.0131                 | 0.0097        |                   |
| ANKRD55         | -0.5915 | 0.0706                  | -0.0036       | 0.2206            |
| AQP8            | -0.0088 |                          | -0.0012       |                   |
| ARL2            | -0.0082 |                          | -0.0023       |                   |
| ATG16L1         | -0.0176 |                          | -0.0045       |                   |
| BMI1            | -0.0017 |                          |               |                   |
| BMX             | 0.6888 | -0.0279                 | -0.0136       | -0.0446           |
| DEPP1           | 0.0112 |                          | 0.0037        |                   |
| DDIAS           | 0.0182 |                          | 0.0072        |                   |
| GPATCH2L        | -0.0294 |                          | -0.0029       |                   |
| C14orf178       | 0.0050 |                          | 0.0004        |                   |
Table 5: Continued analysis of the LUAD data using CER: identified main effects and interactions

| Gene         | Sex | Patient Smoking History | Diagnosis Age | Cancer.Tumor.Stage |
|--------------|-----|-------------------------|---------------|-------------------|
| SLC25A47     | 0.0116 |                       | 0.0022 |          |
| C16orf92    | 0.0162 |                       | 0.0012 |          |
| SPATA46      | -0.0025 |                       |               |          |
| METTL18      | -0.0117 |                       | -0.0008 |          |
| C3orf49      | -0.0117 |                       | -0.0015 |          |
| NADK2        | -0.0141 |                       | -0.0035 |          |
| FAM225B      | -0.0082 |                       | -0.0039 |          |
| CARD18       | -0.0063 |                       | -0.0001 |          |
| CATSPER2P1   | -0.0107 |                       | -0.0005 |          |
| CCDC163P     | -0.0166 |                       | -0.0031 |          |
| CCDC91       | -0.0124 |                       | -0.0046 |          |
| ACKR4        | -0.0141 |                       | -0.0020 |          |
| CD36         | -0.0074 |                       | -0.0051 |          |
| CDC42SE1     | -0.0208 |                       | -0.0062 |          |
| CEP72        | -0.0103 |                       | -0.0035 |          |
| CLCN4        | 0.0102 |                       | 0.0010 |          |
| CLDN10       | 0.0131 |                       | 0.0010 |          |
| CLN3         | -0.0094 |                       | -0.0039 |          |
| COLEC10      | -0.0001 |                       |          |          |
| CRISPLD1     | -0.1900 | 0.0309 | -0.0014 |          |
| CSF3R        | 0.0191 |                       | 0.0042 |          |
| CYMP         | -0.0107 |                       | -0.0034 |          |
Table 6: Continued analysis of the LUAD data using CER: identified main effects and interactions

| Gene      | Sex | Patient Smoking History | Diagnosis Age | Cancer.Tumor.Stage |
|-----------|-----|-------------------------|---------------|--------------------|
| CYP27C1   | -0.0163 | -0.0023 |               |                    |
| DCAF16    | -0.0128 | -0.0030 |               |                    |
| DEPDC4    | 0.0113   | 0.0018   |               |                    |
| DGKG      | 0.0348   | 0.0024   |               |                    |
| DHRS4     | 0.0065   |          |               |                    |
| DSPP      | 0.0061   | 0.0010   |               |                    |
| EAF2      | -0.0024  |          |               |                    |
| ECM1      | 0.0416   | 0.0011   |               |                    |
| EIF1AD    | -0.0241  | -0.0043  |               |                    |
| ETV5      | 0.0070   | 0.0007   |               |                    |
| FAH       | 0.0042   |          |               |                    |
| FAM48B2   | 0.0324   | 0.0054   |               |                    |
| FIP1L1    | 0.0709   | 0.0053   |               |                    |
| FOS       | 0.0189   | 0.0039   |               |                    |
| GALNT13   | -0.0106  | -0.0010  |               |                    |
| FLJ21230  | 0.0375   | 0.0016   |               |                    |
| GPD1      | -0.0014  |          |               |                    |
| GRHL3     | 0.0101   | 0.0046   |               |                    |
| GSTT2     | -0.0256  | -0.0013  |               |                    |
| HEPN1     | -0.0429  | -0.0047  | -0.0053       |                    |
| HMGN4     | -0.0145  | -0.0055  |               |                    |
| HMHB1     | 0.0444   | 0.0168   | 0.0023        |                    |
Table 7: Continued analysis of the LUAD data using CER: identified main effects and interactions

| Gene       | Sex  | Patient Smoking History | Diagnosis Age | Cancer.Tumor.Stage |
|------------|------|-------------------------|---------------|-------------------|
| HNRNPR     | -0.0601 |                         |               | -0.0072           |
| HPR        | -0.0252 |                         |               | -0.0017           |
| HSD3B2     | 0.01560 |                         |               | 0.0056            |
| IL31RA     | -0.0115 |                         |               | -0.0013           |
| IWS1       | 0.0022  |                         |               |                   |
| KCNA5      | 0.0088  |                         |               | 0.0047            |
| KCNT1      | 0.0089  |                         |               | 0.00113           |
| KDM2A      | 0.0185  |                         |               | 0.0037            |
| ATG13      | -0.0117 |                         |               | -0.0044           |
| ICE1       | 0.0481  |                         |               | 0.0037            |
| KIF5A      | 0.0136  |                         |               | 0.0040            |
| KLC3       | -0.0146 |                         |               | -0.0023           |
| KRT72      | 0.0040  |                         |               |                   |
| KRTAP4-11  | -0.026  |                         |               | -0.0076           |
| LGALS9C    | -0.0352 |                         |               | -0.0016           |
| EPT        | 0.0225  |                         |               | 0.0083            |
| LHX9       | -0.0141 |                         |               | -0.0055           |
| LIPL4      | 0.0192  |                         |               | 0.0035            |
| LOC100240726 | 0.0799 |                        |               | -0.0063           |
| PACRG-AS1  | 0.0024  |                         |               |                   |
| LY6E       | 0.0186  |                         |               | 0.0036            |
| LYPD2      | 0.0154  |                         |               | 0.0007            |
Table 8: Continued analysis of the LUAD data using CER: identified main effects and interactions

| Gene           | Sex    | Patient Smoking History | Diagnosis Age | Cancer.Tumor.Stage |
|----------------|--------|-------------------------|---------------|-------------------|
| EEF1AKNMT      | -0.0131|                         |               | -0.0019           |
| STEAP1B        | -0.0091|                         |               | -0.0007           |
| MKRN2          | -0.0146|                         |               | -0.0027           |
| DLG6           | -0.0071|                         |               | -0.0042           |
| NAP1L2         | -0.0162|                         |               | -0.0056           |
| LINC00032      | 0.0102 |                         |               | 0.0019            |
| LINC00114      | 0.0007 |                         |               |                   |
| ANKRD30BL      | 0.0147 |                         |               | 0.0045            |
| NNMT           | 0.0142 |                         |               | 0.0060            |
| NOL11          | 0.0215 |                         |               | 0.0018            |
| NPAS2          | 0.0117 |                         |               | 0.0008            |
| FLJ22583       | -0.0180|                         |               | -0.0018           |
| OMG            | -0.0121|                         |               | -0.0016           |
| OR2A17P        | -0.0081|                         |               | -0.0027           |
| OR4C6          | 0.0177 |                         |               | 0.0027            |
| OR4D1          | 0.0058 |                         |               | 0.0005            |
| ORMDL1         | -0.0110|                         |               | -0.0017           |
| OVCH2          | 0.0170 |                         |               | 0.0008            |
| OXCT2          | -0.0537| -0.021602955            | -0.0013       |
| CNRS7          | 0.0275 |                         |               | 0.0007            |
| PCDHA2         | 0.0411 |                         |               | 0.0010            |
| PDIK1L         | 0.0075 |                         |               | 0.0029            |
Table 9: Continued analysis of the LUAD data using CER: identified main effects and interactions

| Gene    | Sex   | Patient Smoking History | Diagnosis Age | Cancer.Tumor.Stage |
|---------|-------|-------------------------|---------------|-------------------|
| PF4     | 0.0023|                         |               |                   |
| PGK2    | -0.0077|                        | -0.0042       |                   |
| PHF7    | 0.0172|                         | 0.0022        |                   |
| PIGQ    | 0.0171|                         | 0.0016        |                   |
| PREP    | 0.0086|                         | 0.0031        |                   |
| PSAPL1  | 0.0149|                         | 0.0007        |                   |
| RAB20   | -0.0090|                        | -0.0065       |                   |
| RASL11A | 0.0112|                         | 0.0010        |                   |
| RFPL1   | -0.0138|                        | -0.0033       |                   |
| RGPD5   | -0.0084|                        | -0.0058       |                   |
| RIMS2   | 0.0069|                         | 0.0041        |                   |
| RLF     | 0.01192|                         | 0.0037        |                   |
| RRAGB   | 0.0350|                         | 0.00978       |                   |
| SCGB2A1 | 0.0133|                         | 0.0023        |                   |
| PLI     | 0.0044|                         |               |                   |
| SH2D7   | 0.0088|                         |               |                   |
| SKAP2   | -0.0165|                        | -0.0048       |                   |
| SLC25A43| -0.0155|                        | -0.0021       |                   |
| SLC7A8  | -0.0118|                        | -0.0029       |                   |
| SMARCD3 | -0.0144|                        | -0.0074       |                   |
| SPAG16  | -0.0115|                        | -0.0023       |                   |
| TAAR8   | 0.0036|                         | 0.0002        |                   |
Table 10: Continued analysis of the LUAD data using CER: identified main effects and interactions

| Gene    | Sex    | Patient Smoking History | Diagnosis Age | Cancer.Tumor.Stage |
|---------|--------|-------------------------|---------------|-------------------|
| TGM7    | -0.0064| -0.0014                 |               |                   |
| TMEM182 | 0.0114 | 0.0049                  |               |                   |
| TRIM63  | -0.0128| -0.0034                 |               |                   |
| TRIT1   | -0.0082| -0.0046                 |               |                   |
| UNC5D   | -0.0002| -0.0062                 |               |                   |
| VEGFC   | -0.0086| -0.0007                 |               |                   |
| ZNF641  | -0.0090| -0.0070                 |               |                   |
| ZRANB2  | 0.0104 | 0.0070                  |               |                   |

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