Detection of Gene-Gene Interactions by Multistage Sparse and Low-Rank Regression

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Abstract

A daunting challenge faced by modern biological sciences is finding an efficient and computationally feasible approach to deal with the curse of high dimensionality. The problem becomes even more severe when the research focus is on interactions. To improve the performance, we propose a low-rank interaction model, where the interaction effects are modeled using a low-rank matrix. With parsimonious parameterization of interactions, the proposed model increases the stability and efficiency of statistical analysis. Built upon the low-rank model, we further propose an Extended Screen-and-Clean approach, based on the Screen and Clean (SC) method (Wasserman and Roeder, 2009; Wu \textit{et al}., 2010), to detect gene-gene interactions. In particular, the screening stage utilizes a combination of a low-rank structure and a sparsity constraint in order to achieve higher power and higher selection-consistency probability. We demonstrate the effectiveness of the method using simulations and apply the proposed procedure on the warfarin dosage study. The data analysis identified main and interaction effects that would have been neglected using conventional methods.

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1 Introduction

Modern biological researches deal with high-throughput data and encounter the curse of high-dimensionality. The problem is further exacerbated when the question of interest focuses on gene-gene interactions ($G \times G$). Due to the extremely high-dimensionality for modeling $G \times G$, many $G \times G$ methods are multi-staged in nature that rely on a screening step to reduce the number of loci (Cordell 2009; Wu et al. 2010). Joint screening based on the multi-locus model with all main effect and interactions terms is preferred over marginal screening based on single-locus tests — it improves the ability to identify loci that interact with each other but exhibit little marginal effect (Wan et al. 2010) and improves the overall screening performance by reducing the unexplained variance in the model (Wu et al. 2010). However, joint screening imposes statistical and computational challenges due to the ultra-large number of variables. To tackle this problem, one promising method that has good results is the Screen and Clean (SC) procedure (Wasserman and Roeder, 2009; Wu et al. 2010). The SC procedure first uses Lasso to pre-screen candidate loci where only main effects are considered. Next, the expanded covariates are constructed to include the selected loci and their corresponding pairwise interactions, and another Lasso is applied to identity important terms. Finally, in the cleaning stage with an independent data set, the effects of the selected terms are estimated by least squares estimate (LSE) method, and those terms that pass $t$-test cleaning are identified to form the final model.

A crucial component of the SC procedure is the Lasso step in the screening process for interactions. Let $Y$ be the response of interest and $G = (g_1, \cdots, g_p)^T$ be the genotypes at the $p$ loci. A typical model, which is also the model considered in SC, for $G \times G$ detection is

$$E(Y|G) = \gamma + \sum_{j=1}^{p} \xi_j \cdot g_j + \sum_{j<k} \eta_{jk} \cdot (g_j g_k), \quad (1)$$

where $\xi_j$ is the main effect of the $j^{th}$ loci, and $\eta_{jk}, j < k$, is the $G \times G$ corresponding to the $j^{th}$ and $k^{th}$ loci. The Lasso step of SC then fits model (1) to reduce the model size from

$$m_p = 1 + p + \left(\binom{p}{2}\right)$$

(2)

to a number relatively smaller than sample size, $n$, based on which the validity of the subsequent LSE cleaning can be guaranteed. The performance of Lasso is known to depend on the involved number of parameters $m_p$ and the available sample size $n$. Although Lasso has been verified to perform well for large $m_p$, caution should be used when $m_p$ is ultra-large such as in the order of $\exp\{O(n^{\delta})\}$ for some $\delta > 0$ (Fan and Lv, 2008). In addition, the $m_p$ encountered in modern biomedical study is usually greatly larger than $n$ even for a moderate size of $p$. In this situation, statistical inferences can become unstable and inefficient, which
would impact the screening performance and consequently affect the selection-consistency of
the SC procedure or reduce the power in the \( t \)-tests cleaning.

To improve the exhaustive screening involving all main and interaction terms, we consider
a reduced model by utilizing the matrix nature of interaction terms. Observing model (1)
that \((g_j g_k)\) is the \((j, k)^{th}\) element of the symmetric matrix \( J = GG^T \), it is natural to treat \( \eta_{jk} \) as the \((j, k)^{th}\) entry of the symmetric matrix \( \eta \), which leads to an equivalent expression of model (1) as

\[
E(Y|G) = \gamma + \xi^T G + \text{vecp}(\eta)^T \text{vecp}(J),
\]

where \( \xi = (\xi_1, \ldots, \xi_p)^T \) and \( \text{vecp}(\cdot) \) denotes the operator that stacks the lower half (excluding diagonals) of a symmetric matrix columnwisely into a long vector. With the model expression (3), we can utilize the structure of the symmetric matrix \( \eta \) to improve the inference procedure. Specifically, we posit the condition for the interaction parameters

\[
\eta: \text{being sparse and low-rank.}\]  

Condition (4) is typically satisfied in modern biomedical research. First, in a \( G \times G \) scan, it is reasonable to assume most elements of \( \eta \) are zeros because only a small portion of the terms are related to the response \( Y \). This sparsity assumption is also the underlying rationale for applying Lasso for variable selection in conventional approaches (e.g., Wu’s SC procedure).

Second, if the elements of \( \eta \) are sparse, the matrix \( \eta \) is also likely to be low-rank. Displayed below is an example of \( \eta \) with \( p = 10 \) that contains three pairs of non-zero interactions, and hence has rank 3 only:

\[
\eta = \begin{bmatrix}
0 & \star & \diamond & \fa & \mathbf{0}_{3 \times 7} \\
\star & 0 & \diamond & \fa & \fa \\
\fa & \fa & \fa & 0 \\
\mathbf{0}_{7 \times 3} & \mathbf{0}_{7 \times 7}
\end{bmatrix}.
\]  

One key characteristic in our proposed method is the consideration of the sparse and low-rank condition (4), which allows us to express \( \eta \) with much fewer parameters. In contrast, Lasso does not utilize the matrix structure but only assumes the sparsity of \( \eta \) and, hence, still involves \( \left(\frac{p}{2}\right) \) parameters in \( \eta \). From a statistical viewpoint, parsimonious parameterizations can improve the efficiency of model inferences. Our aims of this work are thus twofold. First, using model (3) and condition (4), we propose an efficient screening procedure referred to as the sparse and low-rank screening (SLR-screening). Second, we demonstrate how the SLR-screening can be incorporated into existing multi-stage \( G \times G \) methods to enhance the power and selection-consistency. Based on the promise of the SC procedure, we illustrate the concept by proposing the Extended Screen-and-Clean (ESC) procedure, which replaces the Lasso screening with SLR-screening in the standard SC procedure.
Some notation is defined here for reference. Let \( \{(Y_i, G_i)\}_{i=1}^n \) be random copies of \((Y, G)\), and let \( J_i = G_i G_i^T \). Let \( Y = (Y_1, \cdots, Y_n)^T \) be an \( n \)-vector of observed responses, and let \( X = [X_1, \cdots, X_n]^T \) be the design matrix with \( X_i = [1, G_i^T, \text{vecp}(J_i)^T]^T \). For any square matrix \( M, M^- \) is its Moore-Penrose generalized inverse. \( \text{vec}(\cdot) \) is the operator that stacks a matrix columnwisely into a long vector. \( K_{p,k} \) is the commutation matrix such that \( K_{p,k} \text{vec}(M) = \text{vec}(M^T) \) for any \( p \times k \) matrix \( M \) (Henderson and Searle, 1979; Magnus and Neudecker, 1979). \( P \) is the matrix satisfying \( P \text{vec}(M) = \text{vecp}(M) \) for any \( p \times p \) symmetric matrix \( M \). \( P \) can be chosen such that \( PK_{p,p} = P \). For a vector, \( \| \cdot \| \) is its Euclidean norm (2-norm), and \( \| \cdot \|_1 \) is its 1-norm. For a set, \(| \cdot |\) denotes its cardinality.

2 Inference Procedure for Low-Rank Model

2.1 Model specification and estimation

To incorporate the low-rank property (4) into model building, for a pre-specified positive integer \( r \leq p \), we consider the following rank-\( r \) model

\[
E(Y|G) = \gamma + \xi^T G + \text{vecp}(\eta)^T \text{vecp}(J), \quad \text{rank}(\eta) \leq r.
\]

Although the above low-rank model expression is straightforward, it is not convenient for numerical implementation. In view of this point, we adopt an equivalent parameterization \( \eta(\phi) \) for \( \eta \) that directly satisfies the constraint \( \text{rank}(\eta) \leq r \). Consider the case with the minimum rank \( r = 1 \) (the rank-1 model), we use the parameterization

\[
\eta(\phi) = u\alpha \alpha^T, \quad \phi = (\alpha^T, u)^T, \quad \alpha \in \mathbb{R}^p, \quad u \in \mathbb{R}.
\]

For the case of higher rank, we consider the parameterization

\[
\eta(\phi) = AB^T + BA^T, \quad \phi = \text{vec}(A, B)^T, \quad A, B \in \mathbb{R}^{p \times k},
\]

which gives \( r = 2k \) (the rank-2\( k \) model), since the maximum rank attainable by \( \eta(\phi) \) in (8) is \( 2k \). Note that in either cases of (7) or (8), the number of parameters required for interactions \( \eta(\phi) \) can be largely smaller than \( \binom{p}{2} \). See Remark 1 for more explications. Thus, when model (6) is true, standard MLE arguments show that statistical inference based on model (6) must be the most efficient. Even if model (6) is incorrectly specified, when the sample size is small, we are still in favor of the low-rank model. In this situation, model (6) provides a good “working” model. It compromises between the model approximation bias and the efficiency of parameters estimation. With limited sample size, instead of unstably estimating the full model, it is preferable to more efficiently estimate the approximated low-rank model. As will be shown later, a low-rank approximation of \( \eta \) with parsimonious parameterization suffices to more efficiently screen out relevant interactions.
Let the parameters of interest in the rank-$r$ model (6) be

$$\beta(\theta) = [\gamma, \xi^T, \text{vecp}\{\eta(\phi)\}^T]^T \quad \text{with} \quad \theta = (\gamma, \xi^T, \phi^T)^T,$$

(9)

which consist of intercept, main effects, and interactions. Under model (6) and assuming i.i.d. errors from a normal distribution $N(0, \sigma^2)$, the log-likelihood function (apart from constant term) is derived to be

$$\ell(\theta) = -\frac{1}{2} \sum_{i=1}^{n} \{Y_i - \gamma - \xi^T G_i - \text{vecp}\{\eta(\phi)\}^T \text{vecp}(J_i)\}^2 = -\frac{1}{2} \|Y - X \beta(\theta)\|^2.$$

(10)

To further stabilize the maximum likelihood estimation MLE, a common approach is to append a penalty on $\theta$ to the log-likelihood function. We then propose to estimate $\theta$ through maximizing the penalized log-likelihood function

$$\ell_{\lambda}(\theta) = \ell(\theta) - \frac{\lambda}{2} \|\theta\|^2,$$

(11)

where $\lambda$ is the penalty (the subscript $\ell$ is for low-rank). Denote the penalized MLE as

$$\hat{\theta}_{\lambda} = \left(\hat{\gamma}_{\lambda}, \hat{\xi}_{\lambda}, \hat{\phi}_{\lambda}^T\right)^T = \arg\max_{\theta} \ell_{\lambda}(\theta).$$

(12)

The parameters of interest $\beta(\theta)$ are then estimated by

$$\hat{\beta}_{\lambda} = \beta(\hat{\theta}_{\lambda}),$$

(13)

on which subsequent analysis for main and $G \times G$ effects can be based. In practical implementation, we use $K$-fold cross-validation ($K = 10$ in this work) to select $\lambda$.  

**Remark 1.** We only need $pr - r^2/2 + r/2$ parameters to specify a $p \times p$ rank-$r$ symmetric matrix, and the number of parameters required for model (6) is

$$d_r = 1 + p + (pr - r^2/2 + r/2).$$

(14)

However, adding constraints makes no difference to our inference procedures, but only increases the difficulty in computation. For convenience, we keep this simple usage of $\phi$ without imposing any identifiability constraint.

### 2.2 Implementation algorithm

#### 2.2.1 The case of rank-1 model

For the rank-1 model $\eta(\phi) = u \alpha \alpha^T$, it suffices to maximize (11) using Newton method under both $u = +1$ and $u = -1$. The one from $u = \pm 1$ with the larger value of penalized log-likelihood will be used as the estimate of $\theta$. For any fixed $u$, maximizing (11) is equivalent to the minimization problem:

$$\min_{\theta_u} \frac{1}{2} \|Y - X_u \beta_u(\theta_u)\|^2 + \frac{\lambda\ell}{2} \|\theta_u\|^2,$$

(15)
where $X_u = [X_{u1}, \cdots, X_{un}]^T$ with $X_{ui} = [1, G_i^T, u \cdot \text{vecp}(J_i)^T]^T$ is the design matrix, and 
$\beta_u(\theta_u) = \{\gamma, \xi^T, \text{vecp}(\alpha \alpha^T)^T\}^T$ with $\theta_u = (\gamma, \xi^T, \alpha^T)^T$. Define

$$W_u(\theta_u) = X_u \frac{\partial \beta_u(\theta_u)}{\partial \theta_u} \quad \text{with} \quad \frac{\partial \beta_u(\theta_u)}{\partial \theta_u} = \begin{bmatrix} I_{p+1} & 0 \\ 0 & 2P(\alpha \otimes I_p) \end{bmatrix}.$$ 

The gradient and Hessian matrix (ignoring the zero expectation term) of (15) are

$$g_u(\theta_u) = -\{W_u(\theta_u)\}^T\{Y - X_u \beta_u(\theta_u)\} + \lambda_t \theta_u,$$

$$H_u(\theta_u) = \{W_u(\theta_u)\}^T\{W_u(\theta_u)\} + \lambda_t I_{2p+1}.$$ 

Then, given an initial $\theta_u^{(0)}$, the minimizer $\hat{\theta}_u$ of (15) can be obtained through the iteration

$$\hat{\theta}_u^{(t+1)} = \theta_u^{(t)} - \{H_u(\theta_u^{(t)})\}^{-1}g_u(\theta_u^{(t)}), \quad t = 0, 1, 2, \ldots,$$ 

until convergence, and output $\hat{\theta}_u = \theta_u^{(t+1)}$. Let $u^*$ correspond to the optimal $u$ from $u = \pm 1$. The final estimate is defined to be $\hat{\theta}_\lambda = (\hat{\theta}_u^*, u^*)^T$.

### 2.2.2 The case of rank-$2k$ model

When $\eta(\phi) = AB^T + BA^T$, we use the alternating least squares (ALS) method to maximize (11). By fixing $A$, the problem of solving $B$ becomes a standard penalized least squares problem. This can be seen from

$$\text{vecp}(AB^T + BA^T) = 2P \text{vec}(AB^T) = 2P(B \otimes I_p)\text{vec}(A),$$

where the second equality holds by $PK_{p,p} = P$. Hence, maximizing (11) with fixed $B$ is equivalent to the minimization problem:

$$\min_{\theta_B} \frac{1}{2} \|Y - X_B \theta_B\|^2 + \frac{\lambda_t}{2} \|\theta_B\|^2,$$ 

where $X_B = [X_{B1}, \cdots, X_{Bn}]^T$ with $X_{Bi} = [1, G_i^T, 2\text{vecp}(J_i)^T P(B \otimes I_p)]^T$ being the design matrix when $B$ is fixed, and $\theta_B = [\gamma, \xi^T, \text{vec}(A)^T]^T$. It can be seen that (17) is the penalized least squares problem with data design matrix $X_B$ and parameters $\theta_B$, which is solved by

$$\hat{\theta}_B = (X_B^TX_B + \lambda_t I_{1+p+pk})^{-1}X_B^TY.$$ 

Similarly, the maximization problem with fixed $A$ is equivalent to the minimization problem

$$\min_{\theta_A} \frac{1}{2} \|Y - X_A \theta_A\|^2 + \frac{\lambda_t}{2} \|\theta_A\|^2,$$

where $X_A = [X_{A1}, \cdots, X_{nA}]^T$ with $X_{Ai} = [1, G_i^T, 2\text{vecp}(J_i)^T P(A \otimes I_p)]^T$ being the design matrix when $A$ is fixed, and $\theta_A = [\gamma, \xi^T, \text{vec}(B)^T]^T$. Thus, when $A$ is fixed, $\theta_A$ is solved by

$$\hat{\theta}_A = (X_A^TX_A + \lambda_t I_{1+p+pk})^{-1}X_A^TY.$$ 

(19)
The ALS algorithm then iteratively and alternatively changes the roles of $A$ and $B$ until convergence. Detailed algorithm is summarized below.

**Alternating Least Squares (ALS) Algorithm:**

1. Set initial $B^{(0)}$. For $t = 0, 1, 2, \ldots$

   (1) Fix $B = B^{(t)}$, obtain $\hat{\theta}_{B^{(t)}} = \{\gamma^{(t)}, \xi^{(t)}, \text{vec}(A^{(t+1)})^T\}^T$ from (18).

   (2) Fix $A = A^{(t+1)}$, obtain $\hat{\theta}_{A^{(t+1)}} = \{\gamma^{(t+1)}, \xi^{(t+1)}, \text{vec}(B^{(t+1)})^T\}^T$ from (19).

2. Repeat Step-1 until convergence. Output $(\gamma^{(t+1)}, \xi^{(t+1)}, A^{(t+1)}, B^{(t+1)})$ to form $\hat{\theta}_{\lambda^t}$.

Note that the objective function value increases in each iteration of the ALS algorithm. In addition, the penalized log-likelihood function is bounded above by zero, which ensures that the ALS algorithm converges to a stationary point. We found in our numerical studies that a random initial $B^{(0)}$ will converge quickly and produce a good solution.

### 2.3 Asymptotic properties

This subsection devotes to derive the asymptotic distribution of $\hat{\beta}_{\lambda^t}$ defined in (13), which is the core to propose our SLR-screening in the next section. Assume that the parameter space $\Theta$ of $\theta$ is bounded, open and connected, and define $\Xi = \beta(\Theta)$ be the induced parameter space. Let $\beta_0 = \{\gamma_0, \xi_0^T, \text{vec}(\eta_0)^T\}^T$ be the true parameter value of the low-rank model (6) and define

$$\Delta(\theta) = \frac{\partial}{\partial \theta} \beta(\theta).$$

We need the following regularity conditions for deriving asymptotic properties.

(C1) Assume $\beta_0 = \beta(\theta_0)$ for some $\theta_0 \in \Theta$.

(C2) Assume that $\beta(\theta)$ is locally regular at $\theta_0$ in the sense that $\Delta(\theta)$ has the same rank as $\Delta(\theta_0)$ for all $\theta$ in a neighborhood of $\theta_0$. Further assume that there exists neighborhoods $\mathcal{U}$ and $\mathcal{V}$ of $\theta_0$ and $\beta_0$ such that $\Xi \cap \mathcal{V} = \beta(\mathcal{U})$.

(C3) Let $V_n = \frac{1}{n}X^TX$. Assume that $V_n \xrightarrow{p} V_0$ and that $V_0$ is strictly positive definite.

The main result is summarized in the following theorem.

**Theorem 2.** Assume model (6) and conditions (C1)-(C3). Assume also $\lambda_\ell = o(\sqrt{n})$. Then, as $n \to \infty$, we have

$$\sqrt{n}(\hat{\beta}_{\lambda^t} - \beta_0) \xrightarrow{d} N(0, \Sigma_0),$$

where $\Sigma_0 = \sigma^2 \Delta_0 (\Delta_0^T V_0 \Delta_0)^{-1} \Delta_0^T$ with $\Delta_0 = \Delta(\theta_0)$. 

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To estimate the asymptotic covariance $\Sigma_0$, we need to estimate $(\sigma^2, \Delta_0)$. The error variance $\sigma^2$ can be naturally estimated by

$$\hat{\sigma}^2 = \frac{\|Y - X\hat{\beta}_n\|^2}{n - d_r}, \quad (22)$$

where $d_r$ is defined in (14). We propose to estimate $\Delta_0$ by $\Delta_n = \Delta(\hat{\theta}_{\lambda_n})$. Finally, the asymptotic covariance matrix in Theorem 2 is estimated by

$$\hat{\Sigma}_0 = \hat{\sigma}^2 \hat{\Delta}_n \left\{ U \left( \Lambda + \frac{\lambda_n}{n} I_{d_r} \right) U^T \right\}^{-1} \hat{\Delta}_n^T, \quad (23)$$

where $U\Lambda U^T$ is the singular value decomposition of $\Delta_n^T V_n \Delta_n$, $\Lambda \in \mathbb{R}^{d_r \times d_r}$ is the diagonal matrix consisting of $d_r$ nonzero singular values with the corresponding singular vectors in $U$. We note that adding $\frac{\lambda_n}{n} I_{d_r}$ to $\Lambda$ in (23) aims to stabilize the estimator $\hat{\Sigma}_0$, and will not affect its consistency to $\Sigma_0$.

**Remark 3.** The number $d_r$ in (22) can be used as a guide in determining how large the model rank is allowed with the given data size $n$. That is, the value $n - d_r$ should be adequate for error variance estimation.

### 3 Multistage Variable Selection for Genetic Main and G×G Effects

By the developed inference procedure of low-rank model, we introduce in Section 3.1 the SLR-screening. In Section 3.2, the SLR-screening is incorporated into the conventional SC procedure to propose ESC for G×G detection.

#### 3.1 Sparse and low-rank screening

Due to the extremely high dimensionality for G×G, a single-stage Lasso screening is not adequately flexible enough for variable selection. To improve the performance, it is helpful to reduce the model size from $m_p$ to a smaller number. The main idea of SLR-screening is to fit a low-rank model to filter out insignificant variables first, followed by implementing Lasso screening on the survived variables. The algorithm is summarized below.

**Sparse and Low-Rank Screening (SLR-Screening):**

1. **Low-Rank Screening:** Fit the low-rank model (6). Based on the test statistics for $\beta_0$, screen out variables to obtain the index set $I_{LR}$. 

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### Sparse (Lasso) Screening

Fit Lasso on $\mathcal{I}_{LR}$. Those variables with non-zero estimates are identified in $\mathcal{I}_{SLR}$.

The goal of Stage-1 in SLR-screening is to screen out important variables by utilizing the low-rank property of $\eta$. To achieve this task, we propose to fit the low-rank model (6) to obtain $\hat{\beta}_{\lambda}$ and $\hat{\Sigma}_0$. Based on Theorem 2, it is then reasonable to screen out variables as

$$\mathcal{I}_{LR} = \left\{ j : \frac{|\hat{\beta}_{\lambda,j}|}{\sqrt{n^{-1} \hat{\Sigma}_{0,j}}} > \alpha_\ell \right\}$$

for some $\alpha_\ell > 0$, where $\hat{\beta}_{\lambda,j}$ is the $j^{th}$ element of $\hat{\beta}_{\lambda}$, and $\hat{\Sigma}_{0,j}$ is the $j^{th}$ diagonal element of $\hat{\Sigma}_0$. Here the threshold value $\alpha_\ell$ controls the power of the low-rank screening.

The goal of Stage-2 in SLR-screening is to enforce sparsity. Based on the selected index set $\mathcal{I}_{LR}$, we refit the model with 1-norm penalty through minimizing

$$\frac{1}{2} \| Y - X_{\mathcal{I}_{LR}} \beta_{\mathcal{I}_{LR}} \|^2 + \lambda_s \| \beta_{\mathcal{I}_{LR}} \|_1,$$

where $X_{\mathcal{I}_{LR}}$ and $\beta_{\mathcal{I}_{LR}}$ are, respectively, the selected variables and parameters in $\mathcal{I}_{LR}$, and $\lambda_s$ is a penalty parameter for sparsity constraint. Let the minimizer of (25) be $\hat{\beta}_{\mathcal{I}_{LR}}$, and define

$$\mathcal{I}_{SLR} = \left\{ j \in \mathcal{I}_{LR} : \hat{\beta}_{\mathcal{I}_{LR},j} \neq 0 \right\}$$

(26)

to be the final identified main effects and interactions from the screening stage, where $\hat{\beta}_{\mathcal{I}_{LR},j}$ is the $j^{th}$ element of $\hat{\beta}_{\mathcal{I}_{LR}}$. To determine $\lambda_s$, the $K$-fold cross-validation ($K = 10$ in this work) is applied. Subsequent analysis can then be conducted on those variables in $\mathcal{I}_{SLR}$.

### 3.2 Extended Screen-and-Clean for G x G

Screen-and-Clean (SC) of Wasserman and Roeder (2009) is a novel variable selection procedure. Firstly, the data are split into two parts, one for screening and the other for cleaning. The main reason of using two independent data sets is to control the type-I errors while maintaining high detection power. In the screening stage, Lasso is used to fit all covariates, of which zero estimates are dropped. The threshold for passing the screening is determined by cross-validation. In the cleaning stage, a linear regression model with variables passing the screening process is fitted, which leads to the LSE to identify significant covariates via hypothesis testing. A critical assumption for the validity of SC is the sparsity of effective covariates. As a consequence, by using Lasso to reduce the model size, the success of the cleaning stage in identifying relevant covariates is guaranteed.

Recently, SC has been modified by Wu et al. (2010) to detect $G \times G$ as described in Section 1. This procedure has been shown to perform well through simulation studies. However,
the procedure can be less efficient when the number of genes is large. For instance, there could be many genes remain after the first screening and, hence, a rather large number of parameters is required to fit model (1) for the second screening. As the performance of Lasso depends on the model size, a further reduction of model size can be helpful to increase the detection power. To achieve this aim, unlike standard SC that fits the full model (1) with Lasso screening, we propose to fit the low-rank model (6) with SLR-screening instead. We call this procedure Extended Screen-and-Clean (ECS). Let \( G^* \) be the set of all genes under consideration. Given a random partition \( D_1 \) and \( D_2 \) of the original data \( D \), the ESC procedure for detecting \( G \times G \) is summarized below.

**Extended Screen-and-Clean (ESC):**

1. Based on \( D_1 \), fit Lasso on \((Y, G^*)\) to obtain \( \tilde{\xi}_{G^*} \) with the 1-norm penalty \( \lambda_m \). Let \( G \) consist of genes in \( \{j : \tilde{\xi}_{G^*, j} \neq 0\} \). Obtain \( E(G) = G \cup \{\text{all interactions of } G\} \).

2. Based on \( D_1 \), implement SLR-screening on \((Y, E(G))\) to obtain \( I_{SLR} \). Let \( S \) consist of main and interaction terms in \( I_{SLR} \).

3. Based on \( D_2 \), fit LSE on \((Y, S)\) to obtain estimates of main effects and interactions \( \hat{\xi}_S \) and \( \hat{\eta}_S \). The chosen model is

\[
\mathcal{M} = \left\{ g_j, g_k g_l \in S : \left| T_j \right| > t_{n-1-|S|, \frac{\alpha}{2|S|}}, \left| T_{kl} \right| > t_{n-1-|S|, \frac{\alpha}{2|S|}} \right\},
\]

where \( T_j \) and \( T_{kl} \) are the t-statistics based on elements of \( \tilde{\xi}_S \) and \( \tilde{\eta}_S \), respectively.

For the determination of \( \lambda_m \) in Step-1 of ESC, in Wu et al. (2010) they use cross-validation. Later, Liu, Roeder and Wasserman (2010) introduce StARS (Stability Approach to Regularization Selection) for \( \lambda_m \) selection, and this selection criterion is adopted in the R code of Screen & Clean (available at http://wpicr.wpic.pitt.edu/WPICCompGen/). Note that the intercept will be included in the model all the time. Note also that the proposed ESC is exactly the same with Wu’s SC, except SLR-screening is implemented in Step-2 instead of Lasso screening. See Figure 1 for the flowchart of ESC.

### 4 Simulation Studies

Our simulation studies are based on the design considered in Wu et al. (2010) with some extensions. In each simulated dataset, we generated genotype and trait values of 400 individuals. For genotypes, we generated 1000 SNPs, \( G = [g_1, \cdots, g_{1000}]^T \) with \( g_j \in \{0, 1, 2\} \), from a discretization of normal random variable satisfying \( P(g_j = 0) = P(g_j = 2) = 0.25 \)
and $P(g_j = 1) = 0.5$. The 1000 SNPs can be grouped into 200 5-SNP blocks, with which SNPs from different blocks are independent and SNPs within the same block are correlated with $R^2 = 0.3^2$. Conditional on $G$, we generate $Y$ using the following 4 models, where $\beta$ is the effect size and $\varepsilon \sim N(0, 1)$:

M1: $Y = \beta(g_5 g_6 + 0.8 g_{10} g_{11} + 0.6 g_{15} g_{16} + 0.4 g_{20} g_{21} + 0.2 g_{25} g_{26}) + \varepsilon$.

M2: $Y = \beta(g_5 g_6 + 0.8 g_{10} g_{11} + 0.6 g_{15} g_{16} + 2 g_{20} + 2 g_{21}) + \varepsilon$.

M3: $Y = \beta \text{vecp}(\eta)^T \text{vecp}(J) + \varepsilon$, where we randomly generate $\eta_{jk} = \text{sign}(u_1) \cdot u_2$ with $u_1 \sim U(-0.1, 0.9)$ and $u_2 \sim U(0.5, 1)$ for $1 \leq j \neq k \leq 6$, and $\eta_{jk} = 0$ for $j, k > 6$.

M4: $Y = \beta \text{vecp}(\eta)^T \text{vecp}(J) + \varepsilon$, where we randomly generate $\eta_{jk} = \text{sign}(u_1) \cdot u_2$ with $u_1 \sim U(-0.1, 0.9)$ and $u_2 \sim U(0.5, 1)$ for $1 \leq j \neq k \leq 8$, and $\eta_{jk} = 0$ for $j, k > 8$.

To compare the performances, let $M_0$ denote the index set of nonzero coefficients of the true model, and let $M$ be the estimated model. Define the power to be $E(|M \cap M_0|/|M_0|)$, the exact discovery to be $P(M = M_0)$, the false discovery rate (FDR) to be $E(|M \cap M_0^c|/|M|)$, and the type-I error to be $P(M \cap M_0^c \neq \emptyset)$. These quantities are reported with 100 replicates for each model.

Simulation results under different model settings are placed in Figures 2-5. It can be seen that both ESC(1) and ESC(2) can control FDR and type-I error adequately in all settings. In the pure interaction model M1, ESC(1) is the best performer, while the performances of SC and ESC(2) are comparable. Interestingly, when the true model contains main effects (M2, Figure 3), both ESC(1) and ESC(2) do outperform SC obviously for every effect size $\beta$. It indicates that conventional SC using model (1) is not able to identify main effects efficiently. We found SC procedure is more likely to wrongly filter out the true main effects in the second Lasso screening stage. However, with the low-rank screening to reduce the model size, these true main effects have higher chances to enter the final LSE cleaning and, hence, a higher power of ESC is reasonably expected. The superiority of ESC procedure can be more obviously observed under models M3-M4 (Figures 4-5), where the powers and exact discovery rates of ESC(1) and ESC(2) dominate that of SC for every effect size $\beta$. One reason is that there are many significant interactions involved in M3-M4, and ESC with a low-rank model is able to correctly filter out insignificant interactions in $\eta$ to achieve better performances. In contrast, directly using Lasso screening does not utilize the matrix structure of $\eta$. On one side, it tends to wrongly filter out significant interactions. On the other side, it tends to leave too many insignificant terms in the screening stage. Consequently, the subsequent LSE does not have enough sample size to clean the model well, and results in lower detection powers.

We note that although the rank of $\eta$ in models M1-M4 ranges from 6 to 8, ESC with rank-1 and rank-2 models suffice to achieve good performances. It indicates the robustness and applicability of the low-rank model (6), even with an incorrectly specified rank $r$. Moreover,
we observe that ESC(1) outperforms ESC(2) in most of the settings. Given that the aim of low-rank screening in SLR-screening is to reduce the model size, a good approximation of $\eta$ is capable to remove non-important terms. In contrast, while the rank-2 model approximates $\eta$ more precisely, it also requires more parameters in model fitting. With limited sample size, the gain in approximation accuracy from rank-2 model cannot compensate the loss in estimation efficiency and, hence, ESC(2) may not have a better performance than ESC(1) does. See also Remark 3 for the discussion of selecting $r$ in ESC procedure.

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Extended Screen-and-Clean

Figure 1: Flowchart of ESC for detecting $G \times G$. The arrow indicates which part of the data is used. The case of SC replaces SLR-screening by Lasso screening.
Figure 2: Simulation results under M1.

Figure 3: Simulation result under M2.
Figure 4: Simulation result under M3.

Figure 5: Simulation result under M4.