Robust estimation of sparse precision matrix using adaptive weighted graphical lasso approach

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ABSTRACT
Estimation of a precision matrix (i.e. inverse covariance matrix) is widely used to exploit conditional independence among continuous variables. The influence of abnormal observations is exacerbated in a high dimensional setting as the dimensionality increases. In this work, we propose robust estimation of the inverse covariance matrix based on an $l_1$ regularised objective function with a weighted sample covariance matrix. The robustness of the proposed objective function can be justified by a nonparametric technique of the integrated squared error criterion. To address the non-convexity of the objective function, we develop an efficient algorithm in a similar spirit of majorisation-minimisation. Asymptotic consistency of the proposed estimator is also established. The performance of the proposed method is compared with several existing approaches via numerical simulations. We further demonstrate the merits of the proposed method with application in genetic network inference.

1. Introduction
Estimation of the inverse covariance matrix has attracted wide attention in various applications such as genetic network inference. Under the assumption of Gaussian distribution, it is well known that the estimation of undirected Gaussian graphs is equivalent to the estimation of inverse covariance matrices (Whittaker 1990; Lauritzen 1996). Let $x = (X^{(1)}, \ldots, X^{(p)})^T \sim N_p(\mu, \Sigma)$ be a $p$-dimensional Gaussian random vector with mean $\mu$ and covariance matrix $\Sigma$. The inverse covariance matrix $\Omega = \Sigma^{-1} = (c_{ij})_{1 \leq i, j \leq p}$ contains information related to the conditional dependency between variables, which are referred to as nodes in a graph representation. Each off-diagonal entry of $\Omega$ represents an edge of two nodes in the corresponding graph. If $c_{ij} = c_{ji} = 0$, then $X^{(i)}$ and $X^{(j)}$ are conditionally independent given the other variables $X^{(k)}$, $k \neq i, j$; otherwise, $X^{(i)}$ and $X^{(j)}$ are conditionally dependent.

Various estimation methods for a sparse inverse covariance matrix have been proposed in the literature. One direction is to exploit the connections between entries of the inverse covariance matrix and coefficients of the corresponding multivariate linear regressions.
(Pourahmadi 2000; Huang, Liu, Pourahmadi, and Liu 2006). For example, Meinshausen and Bühlmann (2006) applied a neighbourhood selection scheme by regressing each variable on the remaining variables. Recently, regularised likelihood-based approaches have been proposed by different researchers, see Banerjee, El Ghaoui, and Georges (2006), Yuan and Lin (2007), Friedman, Hastie, and Tibshirani (2008), Lam and Fan (2009), Deng and Yuan (2009), and Kang and Deng (2020), among many others. These methods identify zeros in the inverse covariance matrix through the penalised log-likelihood functions. Rather than directly using the likelihood function, Cai, Liu, and Luo (2011) investigated a constrained $l_1$ minimisation method to estimate the sparse inverse covariance matrix as well as its convergence properties.

The aforementioned approaches often can work effectively when there are no outliers in the observations. However, when abnormal observations contaminate the data, the estimation of inverse covariance matrix can be sensitive to the presence of outliers. Especially in the high-dimensional setting, where dimension $p$ is relatively large compared to the sample size $n$, it is non-trivial to check whether the observations follow the underlying model assumptions. Several methods were proposed to address this concern. Peña and Prieto (2001) presented a robust estimator for the covariance matrix based on the analysis of the projected data. Miyamura and Kano (2006) introduced a robustified likelihood function to estimate the inverse covariance matrix, and they also proposed corresponding test statistics associated with the robustified estimators. The above two methods did not consider the sparsity in the estimates. Later, Finegold and Drton (2011) proposed a so-called tlasso method by adopting multivariate $t$-distribution for robust inferences of graphical models. Sun and Li (2012) developed an $l_1$ regularisation procedure based on density power divergence and used coordinate descent algorithms for robust estimation of the inverse covariance matrix. Other robust approaches (Öllerer and Croux 2015; Tarr, Müller, and Weber 2016; Loh and Tan 2018) consider to use a robust estimate of the covariance matrix to replace the sample covariance matrix in solving the glasso (Friedman et al. 2008).

In this work, we propose robust estimation of a sparse precision matrix via maximising an $l_1$ regularised objective function with weighted sample covariance matrix. The robustness of our proposed method can be justified from a nonparametric perspective. Specifically, the proposed loss function can be viewed as approximation of the integrated squared error (ISE) criterion, which aims at minimising the $L_2$ distance between the probability densities using the estimated and true inverse covariance matrices. This property naturally enables the proposed estimate more resistant to outliers compared to likelihood-based approaches. Moreover, we encourage the sparsity by adding an $l_1$ penalty in the objective function, in a similar spirit as the Lasso (Tibshirani 1996) for sparse regression. Note that the proposed objective function is not convex and thus can be computationally inefficient. To address this challenge, we develop an efficient algorithm from the majorisation-minimisation (Hunter and Lange 2004) aspects to find an upper bound for the original objective function. Consequently, the estimation problem can be transformed into an iterative estimation procedure in the content of graphical lasso (Friedman et al. 2008) with an appropriate weighting scheme on observations. The sequence of weights in each iteration is adaptively updated to automatically account for potential abnormal observations. We call the proposed method ‘weighted Graphical Lasso’ (WGLasso).

The rest of the work is organised as follows. In Section 2, we introduce the robust inverse covariance matrix estimate and develop a computationally efficient algorithm for
it. Section 3 provides a series of simulations to evaluate the performance of the proposed
method. We continue in Section 4 with a real application using the proposed robust esti-
mate. A discussion and concluding remarks are given in Section 5. The proof of the theorem
is deferred to Appendix.

2. Robust estimation for sparse precision matrix

In this section, we describe in details the proposed robust estimator of the sparse inverse
covariance matrix. Suppose that \( x_1, \ldots, x_n \) are a random sample of \( n \) observations on
\( x = (X^{(1)}, \ldots, X^{(p)})^T \), each of which follows a multivariate normal distribution \( N_p(\mu, \Sigma) \)
with mean \( \mu \) and nonsingular covariance matrix \( \Sigma \). Without loss of generality, we assume that \( \mu = 0 \).

2.1. Proposed weighted graphical lasso

To estimate the inverse covariance matrix \( \Omega = \Sigma^{-1} \equiv (c_{ij})_{p \times p} \), we consider a minimisation
problem as

\[
\min_{\Omega} \left[ -\log |\Omega| + \text{tr}[\Omega S^*] + \rho \| \Omega \|_1 \right],
\]

where \( \rho \geq 0 \) is a tuning parameter, which is to balance the goodness of fit and the sparsity
of the estimate. Note that \( S^* = S^*(\Omega^{(0)}) \equiv \frac{1}{n} \sum_{i=1}^{n} w_i x_i x_i^T \) can be viewed as a weighted
sample covariance matrix given an initial estimate \( \Omega^{(0)} \). Here the weight \( w_i \) can be written as

\[
w_i = w_i(\Omega^{(0)}) \equiv \frac{\exp(-\frac{1}{2} x_i^T \Omega^{(0)} x_i)}{\frac{1}{n} \sum_{j=1}^{n} \exp(-\frac{1}{2} x_j^T \Omega^{(0)} x_j)}.
\]

The form of the objective function in (1) is similar to the negative log-likelihood function
but with a weighted sample covariance matrix. The optimisation of (1) can be efficiently
solved using the glasso algorithm developed by Friedman et al. (2008). Therefore, we refer
to the solution of (1) as the weighted Graphical Lasso (WGLasso). It is worth pointing
out that the derived objective function in (1) bears some similarity to the objective function in the M-step of the EM algorithm of the lasso method (Finegold and Drton 2011).
The lasso considered the weighted sample covariance with the weights derived based on
the EM algorithm, whereas the proposed method provides a weighted Graphical Lasso
algorithm with the weights derived based on the ISE criterion (Rudemo 1982) as discussed
in Section 2.2.

The weight in (2) also has a meaningful interpretation. One can see that the weights \( w_i \) can be rewritten as \( w_i = f(x_i)/\left[\frac{1}{n} \sum_{j=1}^{n} f(x_j)\right] \), where \( f(x_i) \) is the probability density
function (pdf) of \( N_p(0, (\Omega^{(0)})^{-1}) \) when \( x = x_i \). The form of \( S^* \) assigns different weights to
the observations \( x_i \) based on the ratio of its pdf value relative to the average density. If an
observation is an outlier from the underlying distribution, its pdf value tends to be smaller
compared to that of the average; thus its assigned weight would be smaller. This helps us
to reduce the influence from outliers on the proposed estimate.

Note that the expression in (1) depends on the initial estimate \( \Omega^{(0)} \) in order to calculate
the weights and corresponding \( S^* \). We iteratively minimise the objective function (1) to
obtain the estimate of \( \Omega \). The detailed description of the iterative algorithm is as follows:
Algorithm 2.1:
Step 1: Obtain an initial estimate \( \Omega^{(0)} \), a positive definite matrix, and set the stopping threshold \( \delta = 10^{-6} \).
Step 2: Compute \( w_i \) according to (2) and obtain \( S^* = \frac{1}{n} \sum_{i=1}^{n} w_i x_i x_i^T \).
Step 3: Estimate \( \Omega \) by minimising (1), i.e.,
\[
\hat{\Omega} = \arg\min_{\Omega} \left[ -\log |\Omega| + \text{tr}(\Omega S^*) + \rho \| \Omega \|_1 \right].
\]
Step 4: Stop if the Frobenius norm \( \| \hat{\Omega} - \Omega^{(0)} \|_F^2 \leq \delta \); otherwise, set \( \Omega^{(0)} = \hat{\Omega} \) and go back to Step 2.

We generally take the inverse of the sample covariance matrix as an initial estimate \( \Omega^{(0)} \). If \( p > n \), the sample covariance matrix is singular, and we add a small perturbation to its diagonal elements.

2.2. Justification of robustness via integrated squared error

In this section, we provide some justification of robustness for the proposed estimate from the scope of using the ISE as a loss function. The ISE criterion (Rudemo 1982) is to measure the \( L_2 \) distance between the estimated probability density function and the true density. Scott (2001) investigated various parametric statistical models by using this criterion as a theoretical and practical estimation tool. The key idea in Scott (2001) is to apply nonparametric techniques to parametric models for the robustness of the estimation. Based on the ISE as a loss function, one can consider the following minimisation for the estimation of the inverse covariance matrix.

\[
\int (f(x|\Omega) - f(x|\Omega_*))^2 \, dx = \int f^2(x|\Omega) \, dx - 2 \int f(x|\Omega)f(x|\Omega_*) \, dx + \int f^2(x|\Omega_*) \, dx,
\]

where \( f(x|\Omega) \) is the pdf of the normal distribution \( N_p(0, \Omega^{-1}) \) and \( \Omega_* \) is the true but unknown inverse covariance matrix. Note that the third term on the right hand side of (3) does not depend on \( \Omega \). Additionally, the second integral in (3) can be viewed as \( E(f(x|\Omega)) \) with respect to \( x \). With the observed data available, one can approximate \( E(f(x|\Omega)) \) by the empirical mean \( \frac{1}{n} \sum_{i=1}^{n} f(x_i|\Omega) \) (Scott 2001; Chi and Scott 2014). Now we reformulate the ISE as

\[
L_n(\Omega) \equiv \int f^2(x|\Omega) \, dx - 2 \int f(x|\Omega)f(x|\Omega_*) \, dx
\]

\[
\approx \int f^2(x|\Omega) \, dx - \frac{2}{n} \sum_{i=1}^{n} f(x_i|\Omega)
\]

\[
= \frac{1}{2p/2} \| \Omega \|_1^{1/2} - \frac{2}{n} \| \Omega \|_1^{1/2} \sum_{i=1}^{n} \exp \left( -\frac{1}{2} x_i^T \Omega x_i \right),
\]

up to constant \( (2\pi)^{-p/2} \). To encourage the sparsity in the estimate, one can consider the \( l_1 \) regularisation for estimating \( \Omega \) as

\[
L_{n,\rho}(\Omega) \equiv L_n(\Omega) + \rho \| \Omega \|_1
\]
\[ \alpha - \frac{2}{n} |\Omega|^{1/2} \sum_{i=1}^{n} \exp \left( -\frac{1}{2} x_i^T \Omega x_i \right) + \tau |\Omega|^{1/2} + \rho \| \Omega \|_1, \tag{5} \]

where \( \| \Omega \|_1 = \sum_{i,j} |c_{ij}| \) is the \( l_1 \) penalty for \( \Omega = (c_{ij})_{p \times p} \). Here \( \tau = 2^{-p/2} \).

It is also feasible to convert the problem into a constrained optimisation by the use of Lagrange multiplier. That is, we can reformulate the above optimisation in (5) as

\[
\min_{\Omega} \quad - \frac{2}{n} |\Omega|^{1/2} \sum_{i=1}^{n} \exp \left( -\frac{1}{2} x_i^T \Omega x_i \right), \\
\text{s.t.} \quad |\Omega|^{1/2} \leq M_1, \\
\quad \| \Omega \|_1 \leq M_2. \tag{6}
\]

The following lemma provides an inequality between the matrix determinant and its \( l_1 \) norm.

**Lemma 2.1**: For a positive definite matrix \( \Omega \) with dimension \( p \), the relationship between its determinant value and \( l_1 \) norm can be described in the following inequality

\[ |\Omega|^{1/2} \leq \left( \frac{\| \Omega \|_1}{p} \right)^{p/2}. \]

The proof of Lemma 2.1 is based on Gershgorin’s circle theorem (Horn and Johnson 1996). Using Lemma 2.1, we can transform the nonlinear constraint on matrix determinant to a linear constraint. Specifically, the minimisation under consideration becomes

\[
\min_{\Omega} \quad - \frac{2}{n} |\Omega|^{1/2} \sum_{i=1}^{n} \exp \left( -\frac{1}{2} x_i^T \Omega x_i \right), \\
\text{s.t.} \quad \left( \frac{\| \Omega \|_1}{p} \right)^{p/2} \leq M_1, \\
\quad \| \Omega \|_1 \leq M_2, \tag{7}
\]

where \( M_1 \geq 0 \) and \( M_2 \geq 0 \). This is a commonly used technique in optimisation for formulating the constraints (Boyd and Vandenberghe 2004). The optimisation in (7) can be written as

\[
\min_{\Omega} \quad - \frac{2}{n} |\Omega|^{1/2} \sum_{i=1}^{n} \exp \left( -\frac{1}{2} x_i^T \Omega x_i \right), \\
\text{s.t.} \quad \| \Omega \|_1 \leq M_*, \tag{8}
\]

where \( M_* = \min\{M_1^{-p/2}, M_2\} \) is a tuning parameter, which will be determined by proper cross-validation as described in Section 2.4. We remark that the problems (5) and (8) are not equivalent since the matrix determinant constraint in (6) is approximated by the linear
constraint via the use of Lemma 1. The underlying reasoning for approximating (5) by (8) is to mitigate the nonlinear constraint of the matrix determinant term.

From the fact that the logarithm is a monotonically increasing function, solving (8) is equivalent to minimising the objective function in (9) as

$$\min_{\Omega} - \log |\Omega|^{1/2} \times \frac{1}{n} \sum_{i=1}^{n} \exp \left( -\frac{1}{2} x_i^T \Omega x_i \right)$$

s.t. $\|\Omega\|_1 \leq M_\ast$. (9)

Note that the objective function (9) is to take logarithm of the objective function in (8) up to some constant. Here the $l_1$ constraint is to encourage the sparsity for inverse covariance matrix estimate (Tibshirani 1996; Yuan and Lin 2007).

To shed some lights on the robustness of the proposed method, we note that since the pdf of a normal distribution is proportional to $|\Omega|^{1/2} \exp(-\frac{1}{2} x^T \Omega x)$ up to some constant, the proposed method by solving (9) essentially attempts to maximise the summation of the probabilities. In contrast, the traditional likelihood-based approach attempts to maximise the product of the probabilities. As an objective function, the summation of probabilities can be more resistant than the product to outliers.

Converting the constraint in (9) to a penalty term in the minimisation, we have

$$\min_{\Omega} \left[ -\frac{1}{2} \log |\Omega| - \log \left( \frac{1}{n} \sum_{i=1}^{n} \exp \left( -\frac{1}{2} x_i^T \Omega x_i \right) \right) + \rho \|\Omega\|_1 \right].$$ (10)

To further facilitate the computational advantage of the proposed method, we adopt a first-order approximation (Zou and Li 2008) to the second term in (10), denoted as $g(\Omega)$, with respect to the initial estimate $\Omega^{(0)}$. Taking the first-order Taylor expansion on $g(\Omega)$ leads to $g(\Omega) = g(\Omega^{(0)}) + \frac{1}{2n} \sum_{i=1}^{n} w_i x_i^T \Omega x_i - \frac{1}{2n} \sum_{i=1}^{n} w_i x_i^T \Omega^{(0)} x_i$. Such an approximation strategy leads us to the WGLasso optimisation problem (1).

### 2.3. Asymptotic property

We derive an asymptotic property of the proposed estimator, which is analogous to the property for the likelihood-based estimator with $l_1$ penalty in Yuan and Lin (2007). For simplicity as in Yuan and Lin (2007), we assume that $\rho$ is fixed as the sample size $n \to \infty$.

**Theorem 2.1**: Let $\hat{\Omega}$ denote the final output of Algorithm 2.1 with an initial estimator $\Omega^{(0)}$ which is a consistent estimator of $\Omega$. If $\sqrt{n} \rho \to \rho_0 \geq 0$ as $n \to \infty$,

$$\sqrt{n} (\hat{\Omega} - \Omega) \to_d \text{argmin}_U V(U),$$

where $V(U) = \text{tr}(U \Sigma U \Sigma) + \text{tr}(U Q) + \rho_0 \sum_{i,j} \{u_{ij} \text{sign}(c_{ij})I(c_{ij} \neq 0) + |u_{ij}|I(c_{ij} = 0)\}$, where $Q$ is a random symmetric $p \times p$ matrix such that $\text{vec}(Q) \sim N(0, \Lambda)$, and $\Lambda$ is such that $\text{cov}(q_{ij}, q_{i'j'}) = \left( \frac{2}{\sqrt{3}} \right)^p \text{cov}(X^{(i)} X^{(j)}, X^{(i')} X^{(j')})$.

Theorem 2.1 implies the $\sqrt{n}$-consistency of $\hat{\Omega}$. The proof of Theorem 2.1 is provided in Appendix 1. We remark that there can be other ways to prove the above result. For instance,
the above asymptotic property can be achieved by using a similar technique as that of Lam and Fan (2009).

It is also worth to pointing out that, due to the non-convexity of the objective function in (1), there would be multiple local optima. Different settings of initial estimate or threshold value $\delta$ could potentially lead to the algorithm numerically converging to different estimates or local optima. The asymptotic result here is established for a certain local optimum.

### 2.4. Selection of tuning parameter

Note that $\rho$ is a tuning parameter in the proposed method. Common methods for tuning parameter selection include cross-validation (Finegold and Drton 2011), a validation-set approach (Levina, Rothman, and Zhu 2008) and information-based criteria such as the Bayesian information criterion (Yuan and Lin 2007). Since the proposed method is based on a nonparametric criterion, the cross-validation or validation-set approaches are more appropriate in our situation. However, the conventional cross-validation assumes data in every fold follow the same distribution. This assumption may no longer be valid with outliers presented in the data. When randomly partitioning the data into $k$ folds for cross-validation, outlier observations may not be uniformly allocated into each fold.

To address this issue, we adopt a revised cross-validation so that the observations in every fold are more likely to be uniformly distributed with respect to the likelihood. Specifically, we sort the observations based on the values of their likelihood functions with respect to $\Omega$. Suppose that there are $n$ observations for $k$-fold cross-validation. The ordered observations are grouped into $\lceil n/k \rceil$ blocks, each of which contains $k$ observations. Then every fold for cross validations is formed by randomly drawing one observation from each block without replacement. Consequently, the data points in each fold tend to be uniformly distributed in terms of the likelihood values. For the cross-validation score, the values of ISE in (4) are used for the proposed method. The optimal tuning parameter is the one associated with the smallest ISE value.

### 3. Simulation

To assess the performance of the proposed method, we conduct a set of simulation studies to compare the proposed method with several existing methods for estimating the inverse covariance matrix. In particular, we compare the proposed estimates with the LW estimator (Ledoit and Wolf 2004), glasso (Friedman et al. 2008), tlasso (Finegold and Drton 2011), spearman (Öllerer and Croux 2015) and cellwise (Tarr et al. 2016).

Ledoit and Wolf (2004) proposed to estimate $\Sigma$ by a linear combination of the sample covariance matrix $S$ and the identity matrix $I$, i.e.

$$\hat{\Sigma}_{LW} = \nu \tau S + (1 - \nu)I,$$

where the optimal values of $\tau$ and $\nu$ are obtained by minimising the expected quadratic loss $E(\|\hat{\Sigma}_{LW} - \Sigma\|_2)$. The corresponding estimator of $\Omega$ is $\hat{\Omega}_{LW} = \hat{\Sigma}_{LW}^{-1}$. Here we include the LW estimator in comparison because it is not a likelihood-based approach; therefore,
it can be robust to the model assumption. The glasso estimates $\Omega$ by solving

$$
\min_{\Omega} \ - \log |\Omega| + \text{tr}[\Omega S] + \lambda \sum_{i \neq j} |v_{ij}|,
$$

where $\Omega = (v_{ij})_{p \times p}$ and $\lambda$ is a tuning parameter. The tlasso estimates $\Omega$ by modelling the data with a multivariate $t$-distribution and solving

$$
\min_{\Omega} \frac{n}{2} \log |\Omega| - \frac{1}{2} \text{tr} \left( \Omega \sum_{i=1}^{n} \tau_i y_i y_i^T \right) + \mu^T \Omega \sum_{i=1}^{n} \tau_i y_i - \frac{1}{2} \mu^T \Omega \mu \sum_{i=1}^{n} \tau_i,
$$

where $y_i$’s are observed data following a multivariate $t$-distribution $t_{p, \nu}(\mu, \Omega^{-1})$ and $\tau_i$’s are an associated sequence of hidden gamma random variables assigned to the observations. An EM algorithm is applied to minimise the objective function to obtain the estimator. The tuning parameters in glasso and tlasso are selected using cross-validation. The R codes of tlasso are provided by the authors of lasso (Finegold and Drton 2011).

Another widely studied class of robust and sparse precision matrix estimator (Liu, Han, Yuan, Lafferty, and Larry Wasserman 2012; Öllerer and Croux 2015; Tar et al. 2016) is to take a robust correlation/covariance matrix as an initial, such as spearman correlation matrix, to convert into robust and sparse precision matrix via regularisation routines, such as the graphical lasso, QUIC and CLIME.

We evaluate and compare the performance of the proposed method and existing methods via (i) selection accuracy measured by $F_1$ score ($F_1$), and (ii) estimation accuracy measured by Frobenius norm ($F_{norm}$) and Kullback-Leibler loss ($KL$). Specifically, the $F_1$ score, a measure of selection accuracy of $\Omega$, is defined as

$$
F_1 = \frac{2PR}{P + R},
$$

where $P = tp/(tp + fp)$ is the precision and $R = tp/(tp + fn)$ is the recall. The larger $F_1$ score implies more selection accuracy for the estimate. Here $tp$ is the true positive, $fp$ is the false positive, and $fn$ is the false negative (Davis and Goadrich 2006). The $F_{norm}$ is a metric to measure the distance between the estimated and true inverse covariance matrices, and is defined as

$$
F_{norm} = ||\hat{\Omega} - \Omega||_F = \sqrt{\sum_{i,j} (c_{ij} - \hat{c}_{ij})^2},
$$

where $\Omega = (c_{ij})_{p \times p}$. The KL loss is a likelihood-based measurement for the accuracy of the estimate, and is defined as

$$
KL = - \log(|\hat{\Omega}|) + \text{tr}(\hat{\Omega} \Omega^{-1}) - (- \log(|\hat{\Omega}|) + p).
$$

Clearly, smaller $F_{norm}$ and $KL$ loss indicate better estimation accuracy for the estimate.

### 3.1. Estimation accuracy evaluation

In this simulation, we consider that observations with sample size $n_1$ are generated from a multivariate normal $N_p(0, \Omega^{-1})$ but they are contaminated by $n_2$ outlier observations generated from $N_p(\mu, I)$. That is, the total sample size of the data set is $n = n_1 + n_2$. Here we
fix \( n_1 = 50 \) and vary the outlier-to-signal ratios \( \gamma \equiv \frac{n_2}{n_1} = 0\%, 6\%, \) and \( 10\% \). Two different cases of the dimensionality \( p \) are considered: \( p = 55 \) and \( p = 100 \). Moreover, we investigate the performance of the proposed method under two different scenarios of mean shifts: \( \mu = 2 \) and \( 5 \). Three inverse covariance matrices for \( \Omega \) are considered as follows.

**Model 1.** Identity matrix, i.e. \( \Omega = I \). Denote by M1-I and M1-II the models under the mean shifts of \( \mu = 2 \) and \( 5 \), respectively.

**Model 2.** Autoregressive covariance AR(1), i.e. \( \Omega = (c_{ij})_{p \times p} \) with \( c_{ii} = 1, c_{i+1,i} = c_{i,i+1} = 0.2, c_{ij} = 0 \), where \( |i - j| > 1 \). Denote by M2-I and M2-II the models under the mean shifts of \( \mu = 2 \) and \( 5 \), respectively.

**Model 3.** Randomly permuted AR(1), i.e. \( \Omega = QMQ^T \), where \( M \) is the inverse covariance matrix defined in Model 2, and \( Q \) is a \( p \times p \) matrix obtained by randomly permuting the rows of a \( p \times p \) identity matrix. Denote by M3-I and M3-II the models under the mean shifts of \( \mu = 2 \) and \( 5 \), respectively.

The numerical results based on 100 simulation runs are reported in Tables 1–3, corresponding to 0%, 6%, and 10% outlier-to-signal ratios, respectively. The standard errors are in parentheses. Overall, the simulation results show that our proposed method outperforms the other five methods in most cases when outliers are present.

Table 1 reports the situation of no-outlier observations. From the results in Table 1, it can be seen that the performance of our proposed method is comparable to the glasso method in terms of the selection accuracy and estimation accuracy. Compared with the LW method, the proposed method gives better selection accuracy, while the LW method
Table 2. Simulation results under outlier-to-signal ratio = 6%.

| p   | Method  | $F_1$ | $F_{norm}$ | $KL$ | $F_1$ | $F_{norm}$ | $KL$ | $F_1$ | $F_{norm}$ | $KL$ |
|-----|---------|-------|------------|------|-------|------------|------|-------|------------|------|
| 55  | WGLasso | 0.31  | 8.78       | 6.26 | 0.31  | 8.72       | 6.24 | 0.39  | 4.10       | 3.92 |
|     |         | (0.03) | (1.10)     | (0.58) | (0.04) | (0.85)     | (0.49) | (0.06) | (0.76)     | (0.48) |
|     | glasso  | 0.16  | 10.21      | 6.62 | 0.16  | 9.93       | 6.41 | 0.12  | 5.61       | 4.43 |
|     |         | (0.01) | (1.37)     | (0.80) | (0.01) | (0.77)     | (0.52) | (0.01) | (1.21)     | (0.51) |
|     | lasso   | 0.28  | 40.11      | 61.37| 0.22  | 45.02      | 63.06| 0.21  | 44.68      | 62.24|
|     |         | (0.02) | (0.10)     | (0.28) | (0.01) | (0.11)     | (0.31) | (0.01) | (0.13)     | (0.31) |
|     | LW      | 0.10  | 8.81       | 5.76 | 0.10  | 8.80       | 5.74 | 0.04  | 8.19       | 4.89 |
|     |         | (0.00) | (0.76)     | (0.51) | (0.00) | (0.77)     | (0.50) | (0.00) | (1.63)     | (0.68) |
|     | spearman| 0.12  | 9.16       | 4.29 | 0.16  | 20.80      | 9.92 | 0.16  | 11.49      | 7.55 |
|     |         | (0.01) | (4.56)     | (1.47) | (0.01) | (6.01)     | (2.22) | (0.01) | (5.63)     | (2.08) |
|     | cellwise| 0.11  | **6.42**   | **5.04** | 0.16  | 11.83      | 7.77 | 0.16  | 11.49      | 7.55 |
|     |         | (0.01) | (1.13)     | (0.61) | (0.01) | (2.68)     | (1.49) | (0.01) | (2.49)     | (1.42) |

| 100 | WGLasso | 0.25  | 16.10      | 10.80| 0.25  | **16.20**  | **10.80** | 0.30  | **7.10**  | **6.50** |
|     |         | (0.04) | (1.27)     | (0.68) | (0.04) | (1.31)     | (0.73) | (0.06) | (1.36)     | (0.77) |
|     | glasso  | 0.12  | 17.90      | 11.41| 0.12  | 17.83      | 11.38| 0.10  | 9.21       | 7.52 |
|     |         | (0.01) | (0.86)     | (0.36) | (0.01) | (0.88)     | (0.35) | (0.01) | (1.25)     | (0.56) |
|     | lasso   | **0.61** | 87.25     | 180.61| **0.41** | 95.76     | 180.87| **0.41** | 95.75     | 180.94|
|     |         | (0.02) | (0.04)     | (0.19) | (0.01) | (0.02)     | (0.11) | (0.01) | (0.02)     | (0.12) |
|     | LW      | 0.06  | 20.95      | 14.06| 0.06  | 20.75      | 13.92| 0.02  | 23.14      | 14.47|
|     |         | (0.00) | (1.91)     | (1.03) | (0.00) | (2.10)     | (1.20) | (0.00) | (3.33)     | (1.18) |
|     | spearman| 0.09  | 16.80      | **8.25** | 0.12  | 26.13      | 14.44| 0.12  | 26.21      | 14.47|
|     |         | (0.00) | (1.47)     | (0.54) | (0.00) | (1.06)     | (0.44) | (0.00) | (1.12)     | (0.45) |
|     | cellwise| 0.10  | **12.21**  | 9.98 | 0.13  | 21.67      | 13.69| 0.13  | 21.66      | 13.68|
|     |         | (0.00) | (0.71)     | (0.60) | (0.00) | (0.85)     | (0.57) | (0.00) | (0.86)     | (0.56) |

provides best estimation accuracy in $F_{norm}$ and $KL$ loss among all methods. The lasso method performs well in selection accuracy but worst in estimation accuracy among all methods. The two robust initialisation methods (spearman and cellwise) have highest selection accuracy in most cases.
Table 3. Simulation results under outlier-to-signal ratio = 10%.

| Method  | $p$ | $F_1$ | $F_{norm}$ | $CL$ | $F_1$ | $F_{norm}$ | $CL$ | $F_1$ | $F_{norm}$ | $CL$ |
|---------|----|-------|------------|------|-------|------------|------|-------|------------|------|
| wGLasso | 255 | 0.30  | 9.01       | 6.42 | 0.31  | 9.03       | 6.46 | 0.35  | 4.44       | 4.27 |
| glasso  | 255 | 0.14  | 10.44      | 7.12 | 0.14  | 10.27      | 7.05 | 0.11  | 5.99       | 5.06 |
| tlasso  | 255 | 0.10  | 39.26      | 60.82| 0.15  | 44.14      | 61.91| 0.15  | 43.99      | 61.61|
| LW      | 255 | 0.10  | 21.49      | 11.61| 0.15  | 31.26      | 13.79| 0.15  | 11.74      | 8.10 |
| spearman| 255 | 0.10  | 19.91      | 7.50 | 0.15  | 11.74      | 8.10 | 0.15  | 11.74      | 8.10 |
| cellwise| 255 | 0.11  | 6.57       | 5.67 | 0.15  | 11.74      | 8.10 | 0.15  | 11.74      | 8.10 |
| WGLasso | 55  | 0.27  | 11.27      | 8.12 | 0.26  | 11.71      | 8.45 | 0.25  | 4.64       | 4.67 |
| glasso  | 55  | 0.10  | 18.23      | 13.51| 0.10  | 18.23      | 13.52| 0.04  | 17.73      | 12.26|
| tlasso  | 55  | 0.09  | 86.88      | 182.64| 0.12  | 95.25      | 183.38| 0.12  | 95.32      | 183.78|
| LW      | 55  | 0.06  | 54.61      | 32.67| 0.06  | 54.18      | 32.22| 0.02  | 56.82      | 29.25|
| spearman| 55  | 0.11  | 40.12      | 16.37| 0.11  | 40.12      | 16.37| 0.11  | 40.12      | 16.37|
| cellwise| 55  | 0.09  | 86.84      | 185.19| 0.11  | 86.84      | 185.19| 0.11  | 86.84      | 185.19|

Table 2 shows the results for the 6% outlier-to-signal ratio case. When the dimension is $p = 55$ and the mean shift is $\mu = 2$, the proposed method has comparable performance to the LW method in terms of KL loss for Models 1 and 2. However, the $F_1$ score of the proposed method is much larger than that of the LW method, indicating its superiority in...
terms of selection accuracy. When the dimension $p$ increases, as in the case of $p = 100$, the lasso method has larger $F_1$ scores than the other five methods, but worst prediction accuracy indicated by the $F_{\text{norm}}$ and $KL$ loss values. Our proposed method has highest prediction accuracy for M2 and M3 while the two robust initialisation methods, spearman and cellwise, perform best in prediction accuracy for M1. For the case of large mean shift, i.e. $\mu = 5$, the proposed method in general outperforms all other methods in both selection and prediction accuracy except for M1 where two robust initialisation methods perform best in prediction accuracy.

As an example of which abnormal observations become more significant, the results of the 10% outlier-to-signal ratio case are reported in Table 3. In this case, the proposed method always yields the largest $F_1$ score among the six methods under comparison. For M1 model, the values of $KL$ loss and $F_{\text{norm}}$ of our method are close to the cellwise method for $p = 100$ but the cellwise method performs better when $p = 55$. For M2 and M3 models, the overall prediction accuracy of our proposed method is superior to other competing methods.

To further validate our method, we also checked whether the final weights of outliers are much smaller than the weights of the normal observations. Under the Model 2 setting with $p = 55$ and 6% outliers, the average of final weights of the normal observations and outliers were 1.06 and $7.10 \times 10^{-3}$, respectively, over 100 iterations. This indicates that the normal observations dominate the fitting procedure.

### 3.2. Numerical study of convergence

The proposed WGLasso objective function in (1) is nonconvex and nonsmooth, and the weights are a complicated function of the observations and the inverse covariance matrix. To confirm the asymptotic properties derived in Section 2.3, we use Monte Carlo simulations to investigate the convergence performance of the proposed estimator. In the meantime, we also compare the proposed method with the glasso method, of which the objective function is convex and known to converge. We utilise our previous three numerical simulation settings in which the true inverse covariance matrices are the identity matrix, banded-structured matrix, and random banded-structured matrix. We consider a lower dimension $p = 55$ and a higher dimension $p = 100$ under three outlier-to-signal ratios 0%, 6% and 10%, where the mean of the outliers is $\mu = 5$.

To study the performance of the two methods as the total sample size $n$ increases, we increase the sample size $n$ while fixing the outlier-to-signal ratio. As expected in the asymptotic situations, the sample size $n$ will become much larger than the dimension $p$ eventually. Here we set the largest sample size $n$ to be roughly at the scale of $p^2$. In particular, for the lower dimension $p = 55$, the value of $n$ ranges from 20 to 2500; for the higher dimension $p = 100$, the value of $n$ ranges from 30 to 10,000. To measure the distance between the estimate and the true inverse covariance matrix, we use the matrix Frobenius norm ($F_{\text{norm}}$) as the metric. All the results are based on 100 independent replications.

Figures 1–3 depict the convergence performance results of the proposed method and the glasso methods under three numerical models, respectively. It is seen that as the total sample size $n$ increases, the $F_{\text{norm}}$ distances of the two estimates from the true inverse covariance matrix decrease gradually and become stable in the later stages. Under the no-outlier situation, the glasso method yields a smaller distance to the true inverse covariance matrix.
| outlier-to-signal ratio | \( p = 55 \) | \( p = 100 \) |
|------------------------|--------------|--------------|
| 0%                     | ![Graph](image1) | ![Graph](image2) |
| 6%                     | ![Graph](image3) | ![Graph](image4) |
| 10%                    | ![Graph](image5) | ![Graph](image6) |

**Figure 1.** Convergence of the WGLasso and glasso under the Model 1 setting.
| outlier-to-signal ratio | $p = 55$ | $p = 100$ |
|-------------------------|---------|---------|
| 0%                      | ![Graph](image1) | ![Graph](image2) |
| 6%                      | ![Graph](image3) | ![Graph](image4) |
| 10%                     | ![Graph](image5) | ![Graph](image6) |

**Figure 2.** Convergence of the WGLasso and glasso under the Model 2 setting.
outlier-to-signal ratio

| $p = 55$ | $p = 100$ |
| --- | --- |
| ![Graph for $p = 55$, 0% outlier ratio](image1) | ![Graph for $p = 55$, 0% outlier ratio](image2) |
| ![Graph for $p = 100$, 0% outlier ratio](image3) | ![Graph for $p = 100$, 0% outlier ratio](image4) |
| ![Graph for $p = 55$, 6% outlier ratio](image5) | ![Graph for $p = 55$, 6% outlier ratio](image6) |
| ![Graph for $p = 100$, 6% outlier ratio](image7) | ![Graph for $p = 100$, 6% outlier ratio](image8) |
| ![Graph for $p = 55$, 10% outlier ratio](image9) | ![Graph for $p = 55$, 10% outlier ratio](image10) |
| ![Graph for $p = 100$, 10% outlier ratio](image11) | ![Graph for $p = 100$, 10% outlier ratio](image12) |

**Figure 3.** Convergence of the WGLasso and glasso under the Model 3 setting.
matrix than the WGLasso does. In the cases of positive outlier-to-signal ratios, the average distance between the WGLasso estimate and the true inverse covariance matrix is smaller than that of the glasso estimate. This suggests that the WGLasso estimate converges to a better position in the neighbourhood of the true inverse covariance matrix when the data are noisy. The glasso estimate has a sharper decrease in the $F_{\text{norm}}$ value than the WGLasso estimate, especially at the beginning stages where the total sample size $n$ is much smaller than the dimension $p$. This illustrates the robustness of the WGLasso in a high-dimensional situation.

From the above Monte Carlo simulations and in comparison with the glasso estimate, it appears that the estimate from the proposed method converges a bit more slowly to the true inverse covariance matrix, and has a smaller $F_{\text{norm}}$ distance to the true one when outliers are present.

### 3.3. Numerical study on initial estimators

For the proposed method and other robust methods using adaptive weighting, an initial estimator can play an important role in the final solution for both computation convergence and estimation and selection performances. Note that for the proposed method, we take the inverse of the sample covariance matrix as an initial estimator. When $p > n$, the sample covariance matrix is singular, and we add a small perturbation to its diagonal elements.

To evaluate the role of the initial estimator for the proposed method, we consider two alternatives of initial estimators. The first one, denoted as ‘robust initial’, uses the robust covariance matrix in Öllerer and Croux (2015) as an initial estimator for our Algorithm 2.1. The second one, denoted as ‘one-step further’, considers using the estimator from currently proposed method as an initial estimator for Algorithm 2.1 (i.e. re-conducting the iteratively weighted graphical lasso method). Table 4 reports the performance results under the setting of 8% outliers and $p = 80$ based on 100 simulations. The standard errors are in parentheses.

![Table 4. Simulation results for the proposed method under different initial estimators under outlier-to-signal ratio = 8%](image-url)
From the results (i.e. the mean value and standard error of performance measures) in the table, it is seen that the proposed method under robust initial estimators generally have a comparable performance with the original proposed method using the sample covariance matrix as an initial estimator.

4. Case study

In this section, we illustrate the merits of the proposed method through a real-world application on gene network inference for breast cancer data.

The estimation of inverse covariance matrix is widely used in gene network applications to identify important relationships among genes. Here we adopt the gene expression data provided by Hess et al. (2006) to perform inference on the genetic networks. This data set contains 133 patients with stage I–III breast cancer, who were treated with chemotherapy. Two clusters are defined based on the patient responses to the treatment: pathologic complete response (pCR) and residual disease (not-pCR). Hess et al. (2006) and Natowicz et al. (2008) identified 26 key genes important for the treatment. A detailed description of these genes is listed in Appendix 2. As suggested by Ambroise, Chiquet, and Matias (2009), cases from the two classes of pCR (34 patients) and not-pCR (99 patients) do not have the same distribution since they were treated under different experimental conditions. Thus we apply the proposed inverse covariance matrix estimation procedure on each cluster separately. The proposed method of estimating $\Omega$ is compared with the glasso and the tlasso methods. Here the LW method is not included for comparison since it would not produce a sparse graph for the gene network. The hub genes, those with most connected edges are potentially most significant for breast cancer and would be emphasised in a further genetic study.

Figure 4 shows the inferred networks of the three methods for studying pCR and not-pCR classes. The penalty values are chosen by the revised cross-validation discussed in Section 2.4. The results of the proposed WGLasso method indicate that the structure of the not-pCR network is more centred than that of the pCR-network. All the edges in the network from not-pCR connect with SCUBE2, which implies its significant role in the study. The network for the pCR case involves more genes and the pairwise relations are discovered between BTG3, METRN and MELK, also among BTG3, SCUBE2 and IGFBP4, to name a few. Our findings confirm the results in Ambroise et al. (2009), where SCUBE2 is also identified as a hub gene for the not-pCR class and the cluster structure is discovered for the pCR class. In contrast, results from the glasso and the lasso methods tend to give less sparse structures, where more gene connections are identified in either the pCR or not-pCR networks. Moreover, in this case study, we have an example of a mixed data set with non-pCR class as the majority portion (more than 75%) of the data. To verify whether our proposed method can be well suited to identify the largest portion of the data that ‘matches’ the model, we tried our method on the complete data (both pCR and non-pCR classes) as well. As expected, it successfully recovered the same findings as we applied our method to non-pCR class only, i.e. SCUBE2 was identified as the hub gene.

To further elaborate the usefulness of the proposed method in exploring the gene network structure, we report in Figure 5 the estimated gene networks under low ($\rho = 0.1$), middle ($\rho = 0.6$) and high-level ($\rho = 0.9$) values of the tuning parameter $\rho$ for both pCR and non-pCR. For the pCR cluster, gene BTG3 consistently shows its importance to the
network for all levels of penalty values. This further validates the significance of BTG3, as indicated in Ambroise et al. (2009). For the non-pCR cluster, we observe that genes MAPT, METRN, and MELK tend to be more significant in the low and middle penalised networks, and gene SCUBE2 is identified as the key one in the high level network. This may provide additional information on potentially important genes when further investigating the network structure of the two classes.

5. Discussion

In this work, we proposed robust estimation for sparse precision matrix by maximising an $l_1$ regularised objective function with weighted sample covariance matrix. The robustness
of our proposed objective function can be justified from a nonparametric perspective of the ISE criterion. Adopting a majorisation-minimisation technique, we solved a relaxed optimisation problem and developed an iteratively weighted graphical lasso estimation procedure. Under such a formulation, the weights can be updated automatically in each iteration, which effectively reduces the influence of potential abnormal observations. This opens up a new possibility to better infer graphical models. Note that we adopt the $l_1$ penalty on the objective function to pursue the sparse structure of the graphical model. Other penalties can also be considered into the proposed method, such as the elastic net (Zou and Hastie 2005), which is a mixture of $l_1$ and $l_2$ penalties.

We show that the proposed estimator is asymptotically consistent, which is confirmed in the numerical experiments. Additionally, an extensive simulation study is conducted to show that the proposed estimate is robust to abnormal observations in comparison with conventional methods. In terms of computational efficiency, our simulation experience is that the computation time of the proposed algorithm is similar to that of the glasso method, but much faster than the tlasso method. Note that the tlasso method appears to require more computational time because it uses the EM algorithm.

Finally, the current theoretical results are not very surprising since the approximated objective function can be considered as likelihood based weighted graphical lasso. However, the original optimisation problem is not a likelihood based function as it considers the summation of probabilities. The theoretical investigation will be much more challenging. A possible direction is to connect the summation of probabilities to the density power

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**Figure 5.** Results of proposed WGLasso in gene expressions data under three levels of penalty values.
divergence (Basu, Harris, Hjort, and Jones 1998). It will be also interesting to investigate asymptotic results on the direction of characterising the break-down behaviour of the estimator as in Öllerer and Croux (2015). However, in our method of weighted graphical lasso, weights keep changing over iterations, which requires some new tools for investigating the break-down properties. Loh and Tan (2018) has investigated the break-down behaviour of a one-step robust graphical lasso. Their theoretical techniques could be helpful for further investigating theoretical properties of our proposed method.

**Disclosure statement**

No potential conflict of interest was reported by the author(s).

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Appendices

Appendix 1. The Proof of Theorem 2.1

To prove Theorem 2.1, we first establish the asymptotic property of the solution of the objective function in (1) as in Lemma A.1 below.

Lemma A.1: Let \( \hat{\Omega} \) denote the solution of the objective function in (1) with an initial estimator \( \Omega^{(0)} \) which is a consistent estimator of \( \Omega \). If \( \sqrt{n} \rho \rightarrow \rho \geq 0 \) as \( n \rightarrow \infty \),

\[
\sqrt{n}(\hat{\Omega} - \Omega) \rightarrow_d \text{arg min } V(U),
\]

where \( V(U) = \text{tr}(U\Sigma U\Sigma) + \text{tr}(UQ) + \rho_0 \sum_{i,j} \{u_{ij} \text{sign}(c_{ij})I(c_{ij} \neq 0) + |u_{ij}|I(c_{ij} = 0)\} \), where \( Q \) is a random symmetric \( p \times p \) matrix such that \( \text{vec}(Q) \sim N(0, \Lambda) \), and \( \Lambda \) is such that \( \text{cov}(q_{ij}, q_{ij'}) = \left( \frac{2}{\sqrt{3}} \right)^p \text{cov}(X^{(i)}X^{(j)}, X^{(i')}X^{(j')}) \).

Proof: Define \( V_n(U) \) as

\[
V_n(U) = -\log \left| \Omega + \frac{U}{\sqrt{n}} \right| + \text{tr} \left\{ \left( \Omega + \frac{U}{\sqrt{n}} \right) S^* \right\} + \rho \left\| \Omega + \frac{U}{\sqrt{n}} \right\|_1
\]

\[+ \log |\Omega| - \text{tr}(\Omega S^*) - \rho \|\Omega\|_1.\]

Note that \( \text{arg min } V_n(U) = \sqrt{n}(\hat{\Omega} - \Omega) \). Using similar arguments as in the proof of Theorem 1 in Yuan and Lin (2007), it follows that

\[
\log \left| \Omega + \frac{U}{\sqrt{n}} \right| - \log |\Omega| = \frac{\text{tr}(U\Sigma)}{\sqrt{n}} - \frac{\text{tr}(U\Sigma U\Sigma)}{n} + o\left( \frac{1}{n} \right), \tag{A1}
\]

\[
\text{tr} \left\{ \left( \Omega + \frac{U}{\sqrt{n}} \right) S^* \right\} - \text{tr}(\Omega S^*) = \frac{\text{tr}(U\Sigma)}{\sqrt{n}} = \frac{\text{tr}(U\Sigma)}{\sqrt{n}} + \frac{\text{tr}(U(S^* - \Sigma))}{\sqrt{n}}, \tag{A2}
\]

and

\[
\rho \left\| \Omega + \frac{U}{\sqrt{n}} \right\|_1 - \rho \|\Omega\|_1 = \rho \sum_{i,j} \left( |c_{ij} + \frac{u_{ij}}{\sqrt{n}}| - |c_{ij}| \right)
\]

\[= \frac{\rho}{\sqrt{n}} \sum_{i,j} \{u_{ij} \text{sign}(c_{ij})I(c_{ij} \neq 0) + |u_{ij}|I(c_{ij} = 0)\}, \tag{A3}\]

where \( c_{ij} \) is the \((i, j)\)th entry of \( \Omega \). Note that equation (A3) holds only when \( n \) is sufficiently large. Then, combining (A1), (A2), and (A3), we have

\[
nV_n(U) = \text{tr}(U\Sigma U\Sigma) + \text{tr}(UQ_n) + \sqrt{n} \rho \sum_{i,j} \{u_{ij} \text{sign}(c_{ij})I(c_{ij} \neq 0) + |u_{ij}|I(c_{ij} = 0)\} + o(1),
\]

where \( Q_n = \sqrt{n}(S^* - \Sigma) \). Let \( q_{n,i,j} \) denote the element of the matrix \( Q_n \). Then,

\[
\text{cov}(q_{n,i,j}, q_{n,i,j'}) = \frac{\sum_{k=1}^n w_k^2}{n} \text{cov}(X^{(i)}X^{(j)}, X^{(i')}X^{(j')}),
\]

where \( \sum_{k=1}^n w_k^2 \rightarrow \left( \frac{2}{\sqrt{3}} \right)^p \) as \( n \rightarrow \infty \) due to Lemma A.2 below. Also note that \( E(S^*) = \Sigma \). Therefore, \( Q_n \rightarrow_d N(0, \Lambda) \) by the central limit theorem, and thus \( nV_n(U) \rightarrow_d V(U) \). Since \( nV_n(U) \) and \( V(U) \) are both convex and \( V(U) \) has a unique minimum, \( \text{arg min } nV_n(U) \rightarrow_d \text{ arg min } V(U) \). Since \( \text{arg min } V_n(U) = \sqrt{n}(\hat{\Omega} - \Omega) \), it follows that \( \sqrt{n}(\hat{\Omega} - \Omega) \rightarrow_d \text{ arg min } V(U) \). \( \blacksquare \)

A careful examination of the proof of Lemma A.1 shows that the required condition to generalise the result for solving a single WGLasso problem in (1) to a sequence of WGLasso problems in
Algorithm 2.1 is the consistency of \( \hat{\Omega} \) in Step 3. The proof of the consistency of \( \hat{\Omega} \) is straightforward from the result of Lemma A.1.

**Lemma A.2:** With an initial estimator \( \Omega^{(0)} \) which is a consistent estimator of \( \Omega \), we have

\[
\frac{1}{n} \sum_{i=1}^{n} w_i^2 \rightarrow \left( \frac{2}{\sqrt{3}} \right)^p \text{ as } n \rightarrow \infty,
\]

where \( w_i = f(x_i) / \left( \frac{1}{n} \sum_{j=1}^{n} f(x_j) \right) \), where \( f(x) \) is the pdf of \( N_p(0, \Omega^{(0)}^{-1}) \) when \( x = x_i \).

**Proof:**

\[
\frac{1}{n} \sum_{i=1}^{n} w_i^2 = \frac{1}{n} \sum_{i=1}^{n} \left( \frac{f(x_i)}{\frac{1}{n} \sum_{j=1}^{n} f(x_j)} \right)^2 = \frac{1}{\left( \frac{1}{n} \sum_{j=1}^{n} f(x_j) \right)^2} \left( \frac{1}{n} \sum_{i=1}^{n} (f(x_i))^2 \right).
\]

By the law of large numbers and \( \Omega^{(0)} \rightarrow \Omega \),

\[
\frac{1}{n} \sum_{j=1}^{n} f(x_j) \rightarrow \mathbb{E} f(x | \Omega) = \int_{\mathbb{R}^p} [f(x)]^2 \, dx = 2^{-p} \pi^{-p/2} |\Sigma|^{-1/2}
\]

and

\[
\frac{1}{n} \sum_{i=1}^{n} (f(x_i))^2 \rightarrow \mathbb{E} (f(x) | \Omega)^2 = \int_{\mathbb{R}^p} [f(x)]^3 \, dx = 2^{-p} 3^{-p/2} \pi^{-p} |\Sigma|^{-1}.
\]

Therefore,

\[
\frac{1}{n} \sum_{i=1}^{n} w_i^2 \rightarrow \left( 2^{-p} \pi^{-p/2} |\Sigma|^{-1/2} \right)^2 2^{-p} 3^{-p/2} \pi^{-p} |\Sigma|^{-1} = 2^p 3^{-p/2} = \left( \frac{2}{\sqrt{3}} \right)^p.
\]

\[\blacksquare\]

**Appendix 2. The 26 key genes used in Section 4.1**

| Gene symbol | Gene name |
|-------------|-----------|
| AMFR        | Autocrine motility factor receptor |
| BBS4        | Bardet-Biedl syndrome 4 |
| BECN1       | Beclin 1 (coiled-coil, myosin-like BCL2 interacting protein) |
| BTG3        | BTG family, member 3 |
| CA12        | Carbonic anhydrase XII |
| CTNND2      | Catenin, delta 2 |
| E2F3        | E2F transcription factor 3 |
| ERBB4       | Verba erythroblastic leukemia viral oncogene homolog 4 (avian) |
| FGFR1OP     | FGFR1 oncogene partner |
| FLJ10916    | Hypothetical protein FLJ10916 |
| FLJ12650    | Hypothetical protein FLJ12650 |
| GAMT        | Guanidinoacetate N-methyl transferase |
| GFRA1       | GDNF family receptor 1 |
| IGFBP4      | Insulin-like growth factor binding protein 4 |
| JMJD2B      | Jumonji domain containing 2B |
| KIAA1467    | KIAA1467 protein |
| MAPT        | Microtubule-associated protein |
| MBTP-S1     | Hypothetical protein |
| MELK        | Maternal embryonic leucine zipper kinase |
| MTRN        | Meteorin, glial cell differentiation regulator |
| PDGFRA      | Human clone 23, 948 mRNA sequence |
| Gene symbol | Gene name                                           |
|-------------|----------------------------------------------------|
| RAMP1       | Receptor (calcitonin) activity modifying protein 1 |
| RRM2        | Ribonucleotide reductase M2 polypeptide             |
| SCUBE2      | Signal peptide, CUB domain EGF-like 2              |
| THRAP2      | Thyroid hormone receptor associated protein 2      |
| ZNF552      | Zinc finger protein 552                            |