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RESEARCH ARTICLE

Hierarchy-assisted gene expression regulatory network analysis

Han Yan[1,2,3] | **Sanguo Zhang**[1,2,4] | **Shuangge Ma**[3]

[1]School of Mathematical Sciences, University of Chinese Academy of Sciences, Beijing, China

[2]Key Laboratory of Big Data Mining and Knowledge Management, Chinese Academy of Sciences, Beijing, China

[3]Department of Biostatistics, Yale School of Public Health, New Haven, Connecticut, USA

[4]Pazhou Lab, Guangzhou, China

Correspondence
Shuangge Ma, Department of Biostatistics, Yale School of Public Health, New Haven, CT 06520, USA.
Email: shuangge.ma@yale.edu

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Abstract

Gene expressions have been extensively studied in biomedical research. With gene expression, network analysis, which takes a system perspective and examines the interconnections among genes, has been established as highly important and meaningful. In the construction of gene expression networks, a commonly adopted technique is high-dimensional regularized regression. Network construction can be unadjusted (which focuses on gene expressions only) and adjusted (which also incorporates regulators of gene expressions), and the two types of construction have different implications and can be equally important. In this article, we propose a variable selection hierarchy to connect the unadjusted regression-based network construction with the adjusted construction that incorporates two or more types of regulators. This hierarchy is sensible and amounts to additional information for both constructions, thus having the potential of improving variable selection and estimation. An effective computational algorithm is developed, and extensive simulation demonstrates the superiority of the proposed construction over multiple closely relevant alternatives. The analysis of TCGA data further demonstrates the practical utility of the proposed approach.

KEYWORDS

gene expression network, hierarchy, high-dimensional regression, penalized estimation

1 | INTRODUCTION

Gene expressions have been extensively studied in biomedical research. The significance of gene expression analysis has been well established through a large number of studies [20, 23, 25] and does not need to be reiterated here. Early gene expression studies are individual-gene-based and treat genes as "exchangeable." Genes are functionally and statistically interconnected. Accordingly, pathway- and network-based analyses have been developed [18, 22, 31], which can accommodate the interconnections among genes. The power of gene expression network analysis has been well demonstrated. In this article, we focus on gene expression network construction, which has its own important implications and can also serve as the basis for downstream analysis such as clustering, regression, and others.

Gene expression network construction can be roughly classified as unconditional and conditional [9]. In an unconditional construction, when evaluating whether two genes are interconnected, the other genes are "ignored." In contrast, in a conditional construction, information on

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all the other genes is accounted for. The two types of construction serve different purposes. In this article, we conduct conditional construction, which can be statistically more challenging. There are quite a few methods for constructing conditional networks [4, 11, 21, 37]. The "simplest" method may be the Gaussian Graphical Model (GGM) [11]. Under the joint normality assumption, network construction amounts to a sparse estimation of the precision matrix. Graphical modeling methods have also been developed to relax the normality assumption. A limitation of the GGM methods is that operation of large matrices is needed. We refer to the literature [7] for comprehensive discussions on the available conditional constructions.

In the literature, a family of methods that has attracted broad interest is based on regression [21, 36]. With such methods, for a gene expression, its network connections with the other gene expressions are obtained by regressing this specific gene expression on the others. Regression-based constructions may enjoy multiple advantages. For example, they can take advantage of many existing regression methods and software. Second, they enjoy lucid interpretations. Third, they can be directly extended to other data distributions. For example, SNP networks can be constructed by replacing linear regression (for gene expressions) with logistic regression. Fourth, they can be conducted in a highly parallel manner (one gene expression at a time), leading to significantly reduced computer time. Last but not least, regression-based construction can have direct connections to, for example, GGM [11].

Network construction can be unadjusted and adjusted. In an unadjusted construction, only gene expressions are considered (that is, one gene expression ~ the other gene expressions). Gene expressions are regulated, and multiple types of regulators have been identified that can regulate gene expressions, including SNPs, methylation, microRNAs, and others [26, 27, 33]. Here we note that we use the terminology "regulator" (or regulate) in a somewhat loose sense. In an adjusted construction, regulators are incorporated (that is, one gene expression ~ the other gene expressions + regulators). Here we note that some studies have also used the terminology "conditional" to refer to adjusted construction (see, e.g., conditional GGM [35]). We use "adjusted" as opposed to "conditional" to distinguish from the aforementioned conditional analysis. An adjusted network reflects the interconnections among genes after removing the effects attributable to one type or multiple types of regulators. It is noted that, under the GGM and other frameworks, both unadjusted and adjusted constructions have also been conducted. The unadjusted and adjusted networks have different implications and serve different purposes, and we refer to the literature for relevant discussions. In the past decade, we have witnessed a significant growth in multi-omics studies [17, 19, 32]. With this growth, many multi-omics data analysis methods have been developed. Accordingly, adjusted network construction is getting increasingly popular and important, and we focus on it in this study.

In studies, such as The Cancer Genome Atlas (TCGA), multiple types of regulators are measured along with gene expressions [24]. When constructing an adjusted gene expression network with such data, the common practice in the literature is to focus on either a single type of regulator (often with some ad hoc justifications) or all available regulators [5, 13, 16]. To the best of our knowledge, *there has been a lack of study that jointly considers multiple adjusted networks that involve different sets of regulators*. To fill this knowledge gap, in this article, we propose a biologically sensible hierarchy that can link the sparsity structures of multiple adjusted networks. To fix ideas, consider a study with two types of regulators (along with gene expressions). The proposed hierarchy links the adjusted network involving both types of regulators (the "child" network) with those involving only a single type of regulator (the "parent" networks). By incorporating this hierarchy and simultaneously estimating three networks (one child and two parent networks), our analysis has the potential to improve estimation for all networks. We note that, beyond gene expression network construction, the proposed hierarchy and estimation strategy may also be applied to other types of omics data and other regression analysis settings, enjoying much broader applicability.

2 | METHODS

Denote n as the number of iid samples and p as the number of gene expressions. Denote $\mathbf{Y}$ as the $n \times p$ matrix of gene expression measurements. In a regression-based unadjusted network construction, to identify the edges for node (gene expression) i, we regress $Y_{\cdot,i}$ (the ith column of $\mathbf{Y}$) onto $\mathbf{Y}$, under the constraint that the ith coefficient is fixed at zero. To obtain a sparse network (which is usually the case for gene expressions) and regularize estimation, we often apply regularization techniques. For such a purpose, penalization has been a popular choice. With a penalized estimation, a nonzero coefficient suggests an edge (i.e., an interconnection between the corresponding gene expressions). We refer to published literature for more information on this analysis.

We now consider regression-based adjusted network construction. Assume that there are two types of regulators (for example, methylation and microRNA). Note that the proposed analysis can be directly extended to more than two types of regulators - as such, it can be broadly applied

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to multi-omics analysis. Denote $\mathbf{W}$ and $\mathbf{X}$ as the $n \times q$ and $n \times r$ matrices of regulator measurements, respectively. To further simplify notations, assume that all measurements have been properly centered (as such, no intercepts are needed) and scaled. Consider node (gene expression) $i(=1, \ldots, p)$. For the network construction that incorporates $\mathbf{W}$ only, the lack-of-fit function is:

$$(2n)^{-1}\left\|Y_{\cdot,i} - \mathbf{Y}\theta^{(1)} - \mathbf{W}\gamma^{(1)}\right\|_2^2,$$

where $\|\cdot\|_2$ denotes the ℓ_2 norm, $\theta^{(1)}$ is the length p vector of regression coefficients with the constraint that $\theta_i^{(1)} = 0$, and $\gamma^{(1)}$ is the length q vector of regression coefficients. The nonzero components of $\theta^{(1)}$ correspond to the gene expression network edges. Similarly, for the network construction that incorporates $\mathbf{X}$ only, the loss function is:

$$(2n)^{-1}\left\|Y_{\cdot,i} - \mathbf{Y}\theta^{(2)} - \mathbf{X}\eta^{(1)}\right\|_2^2,$$

where $\theta^{(2)}$ and $\eta^{(1)}$ are the vectors of regression coefficients under the constraint that $\theta_i^{(2)} = 0$. Now, for the network construction that incorporates both $\mathbf{W}$ and $\mathbf{X}$, the lack-of-fit function is:

$$(2n)^{-1}\left\|Y_{\cdot,i} - \mathbf{Y}\theta^{(3)} - \mathbf{W}\gamma^{(2)} - \mathbf{X}\eta^{(2)}\right\|_2^2,$$

where the implications of notations and constraints are similar to the above.

Consider gene expressions i and j. Their interconnection can be attributed to: (i) co-regulation by $\mathbf{W}$, (ii) co-regulation by $\mathbf{X}$, and (iii) co-regulation by other mechanisms and a direct interconnection between the two gene expressions. The child network (that incorporates both $\mathbf{W}$ and $\mathbf{X}$) only contains type (iii) interconnections. In contrast, the parent network that incorporates only $\mathbf{W}$ contains both types (iii) and (ii) interconnections; and the parent network that incorporates only $\mathbf{X}$ contains both the type (iii) and (i) interconnections. As such, the edge set of a child network is expected to be a subset of that of a parent network; note that this should hold for both parents. That is, the sparsity structures of the child and parent networks have a hierarchical structure.

Remarks. Under the GGM paradigm, a similar hierarchy has been proposed for linking an unadjusted network with an adjusted one [34]. It has been argued that this type of hierarchy is highly sensible and can assist estimation. The proposed hierarchy shares some similar spirit with the existing one. On the other hand, this study advances from the existing literature in multiple important ways. First, regression-based construction is conducted, which can be more easily extendable and may demand weaker data assumptions. Second, the existing analysis has been designed to accommodate a single type of regulator. In this study, we consider accommodating multiple types of regulators; this advancement is nontrivial. Third, with two or more types of regulators, there are multiple parents, and hence the proposed hierarchy is more complicated than the existing one.

It has been argued that counter examples can be developed under which the hierarchy is violated [34]. However, as discussed in the literature, such models may only be mathematically, but not biologically, sensible. In addition, scenarios under which the hierarchy is violated are expected to be limited.

With the hierarchy linking the three networks, for gene expression $i(=1, \ldots, p)$, we propose the following joint estimation:

$$\begin{aligned}\underset{\theta^{(k)}:\theta_i^{(k)}=0}{\arg\min}\, & (2n)^{-1}\sum_{k=1,2}\left\|\widetilde{Y}_{\cdot,i}^{(k)} - \mathbf{Y}\theta^{(k)}\right\|_2^2 \\ & + (2n)^{-1}\left\|\widetilde{Y}_{\cdot,i}^{(3)} - \mathbf{Y}\left(\theta^{(1)}\odot\theta^{(2)}\odot\delta\right)\right\|_2^2 \\ & + \lambda_1\left(\sum_{k=1,2}\sum_j|\theta_j^{(k)}|\right) + \lambda_2\left(\sum_j|\delta_j|\right) \\ & + \lambda_3\left(\sum_{k=1,2}\sum_j|\gamma_j^{(k)}| + \sum_{k=1,2}\sum_j|\eta_j^{(k)}|\right). \end{aligned} \quad (1)$$

Here, $\widetilde{Y}_{\cdot,i}^{(1)} = Y_{\cdot,i} - \mathbf{W}\gamma^{(1)}$, $\widetilde{Y}_{\cdot,i}^{(2)} = Y_{\cdot,i} - \mathbf{X}\eta^{(1)}$ and $\widetilde{Y}_{\cdot,i}^{(3)} = Y_{\cdot,i} - \mathbf{W}\gamma^{(2)} - \mathbf{X}\eta^{(2)}$, $\odot$ is the component-wise product, δ is a vector of unknown regression coefficients, and λ_1, λ_2, λ_3 are tuning parameters. The edges of the two parent networks correspond to the nonzero components of the estimates of $\theta^{(1)}$ and $\theta^{(2)}$. The edges of the child network correspond to the nonzero components of the estimate of $\theta^{(1)}\odot\theta^{(2)}\odot\delta$. In addition, the nonzero estimates of $\gamma^{(1)}$ and $\eta^{(1)}$ can reveal the interconnections between gene expressions and regulators.

2.1 | Rationale

We apply Lasso penalization for identifying important interconnections and regularizing estimates and note that it can be replaced by other penalties. For the child network, the regression coefficients are decomposed as $\theta^{(1)}\odot\theta^{(2)}\odot\delta$. This guarantees that, if a coefficient in a parent network is zero, then its counterpart in the child network is automatically zero. And, if a coefficient in the child network is nonzero, then its counterparts in both parent networks are nonzero. A similar decomposition strategy has been popular in genetic interaction analysis to ensure a variable selection hierarchy [38]. However, this is the first time it is used in regression-based network analysis. For genetic interaction analysis, hierarchy can also be ensured using other penalization strategies, for example,

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composite penalization [38]. However, our exploration suggests that, with two parents, such strategies are unlikely to be applicable.

In this article, we mainly focus on methodological and numerical developments. Heuristic discussions on theoretical properties are provided in Appendix 1.

2.2 | Computation

The proposed approach has a "least squares lack-of-fit + Lasso" form and is computationally highly feasible. We adopt an iterative algorithm and optimize one vector of unknown regression coefficients at a time. With each vector, we adopt the coordinate descent technique to optimize under the Lasso penalization. We repeat the iterations until the estimates from two consecutive iterations are close enough. More details on the computational algorithm are available from the authors. Convergence properties for a least squares lack-of-fit and Lasso penalty have been well studied in the literature [10]. Convergence is satisfactorily achieved in all of our numerical studies with a moderate number of iterations. For the tuning parameters $\lambda_1, \lambda_2, \lambda_3$, we conduct a three-dimensional grid search and use BIC to select the optimal tunings. To reduce computer time, the p gene expressions are analyzed in a parallel manner, and their tuning parameters are individually selected. It is also possible to jointly select so that all gene expressions share the same tuning. To facilitate implementation, an R code is developed and made publicly available at github.com/shuanggema/HierNetwork.

3 | SIMULATION

Simulation is conducted to gauge the performance of the proposed approach and compare it against the following alternatives: (a) SepLasso (separate Lasso), which takes a similar Lasso penalized regression strategy as the proposed approach and conducts the three sets of network construction separately; (b) GLasso (graphical Lasso), which is perhaps the most popular approach for network construction and can be realized using the R package *glasso* [12]. This approach constructs the three networks separately; (c) FGL (fused graphical Lasso [15]), which is based on the graphical Lasso approach and applies a fusion penalty to promote similarity between the three networks; (d) GGL (group graphical Lasso [15]), which is also based on the graphical Lasso approach and applies a group Lasso penalty that achieves the same sparsity structure for the three networks. Both FGL and GGL are realized using R package *JGL* [6]; (e) SSGL (spike-and-slab group Lasso), which fuses the Bayesian spike and slab technique with the group Lasso approach. It is realized using the R package *SSGL* [1]; (f) SepBoost, which conducts separate network constructions using the generalized boosted regression technique, an extension of the AdaBoost algorithm and gradient boosting machine. This approach is realized using the R package *gbm* [14]; and (g) SepThreshold, which combines the nearest positive definite and thresholding techniques. Specifically, for each network, it computes the nearest positive definite matrix of the empirical covariance matrix and thresholds its inverse matrix. This approach is realized using the R package *Matrix* [2]. For SepLasso, tuning parameter selection is conducted in a similar way as for the proposed approach. For SepThreshold, it follows [3]. For the other alternatives, it is conducted using the defaults in the packages. We note that there may be other approaches that can also be applied to analyze the simulated data. However, to the best of our knowledge, there is a lack of approaches that can jointly construct three networks in a way comparable to the proposed. Comparing the separate constructions can directly establish the merit of joint analysis under the proposed hierarchy, while the graphical Lasso-based approaches are state-of-the-art and perhaps the most popular for network construction. In particular, FGL, GGL, and SSGL also conduct joint estimation. For evaluating the performance of identifying edges, we use the true positive rate (TPR), the true discovery rate (TDR), and the Matthews correlation coefficient (MCC). It is noted that, with the proposed and alternative approaches, three networks are estimated, corresponding to three $\theta^{(k)}$'s. As such, there are three TPR and TDR measures. In addition, we also consider the number of hierarchies that are violated (N_VIO).

3.1 | Settings

We consider two types of regulators and generate gene expressions from the regression model:

$$\mathbf{Y} = \mathbf{W}\boldsymbol{\alpha} + \mathbf{X}\boldsymbol{\beta} + \boldsymbol{\varepsilon}.$$

Similar linear regression models have been adopted in the literature [28]. We set sample size $n = 200$ and dimensions of gene expressions $p = 40$, 60, and 100. We consider the setting with $q = r = p$, noting that, in practice, the three dimensions are often of the same order. For coefficient matrices α and β, we consider a block-diagonal structure, with blocks having sizes 20×20. For α, for each block, elements $\{6{:}\ 12\} \times \{6{:}\ 12\}$ (that is, those in rows 6 to 12 and columns 6 to 12) are randomly generated from a uniform distribution with support $[0.4, 1]$. The rest of the elements are 0. For β, we consider three scenarios: (Scenario 1) elements $\{6{:}\ 12\} \times \{6{:}\ 12\}$ are randomly generated from a

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uniform distribution with support $[-1, -0.4]$; (Scenario 2) the same as Scenario 1, with elements $\{8{:}\,14\} \times \{8{:}\,14\}$ being nonzero; and (Scenario 3) the same as Scenario 1, with elements $\{10{:}\,16\} \times \{10{:}\,16\}$ being nonzero. Under Scenario 1, the two types of regulators have the strongest overlapping effects, while under Scenario 3, the overlapping effects are the weakest. The $n \times p$ design matrices $\mathbf{W}$ and $\mathbf{X}$ are generated from a p-dimensional standard normal distribution. Our exploration suggests that correlations among $\mathbf{W}$ and $\mathbf{X}$ may have a limited impact on performance. The "residual" matrix ϵ is generated from $N_p(0, (\Theta_{\mathbf{E}})^{-1})$. As noted in the literature [28], ϵ may include "random errors" as well as regulatory effects not included in $\mathbf{W}$ and $\mathbf{X}$.

The design of the precision matrix $\Theta_{\mathbf{E}}$ should ensure hierarchy. It reflects the conditional dependence relationships among gene expressions after accounting for the two types of regulators. We set the "region" of the nonzero off-diagonal elements of $\Theta_{\mathbf{E}}$ to be the overlapping nonzero regions of α and β. Further, we consider the following three popular network structures and two signal strength levels.

1. *Power law structure*: Each nonzero block of $\Theta_{\mathbf{E}}$ is generated by a power law degree distribution, and each node is connected to two other nodes. For the elements corresponding to connections, their values are generated from a uniform distribution with support $\{[-0.5, -0.2] \cup [0.2, 0.5]\}$ or $\{[-1, -0.5] \cup [0.5, 1]\}$, which represents two signal strengths.
2. *Nearest neighbor structure*: For each node in each nonzero block of $\Theta_{\mathbf{E}}$, m other nodes in the same nonzero block are randomly selected as its neighbors. The neighboring nodes are connected, and we consider $m = 3, 2, 1$ for Scenarios 1–3, respectively. The nonzero elements are randomly generated from a uniform distribution with support $\{[-0.4, -0.2] \cup [0.2, 0.4]\}$ or $\{[-0.8, -0.6] \cup [0.6, 0.8]\}$, corresponding to two signal levels.
3. *Banded structure*: Let $AR(\rho)$ represent an autoregressive matrix, whose (i, j) th element is $\rho^{|i-j|}$. The nonzero elements of $\Theta_{\mathbf{E}}$ are set as their counterparts of $AR^{-1}(\rho)$. We set $\rho = 0.6$ and -0.6.

For all three structures, the diagonal elements of the precision matrices are set as 1. To ensure positive definiteness of the first two structures, the diagonal elements within the blocks are further adjusted as $\theta_{E,ii} = \sum_{i \neq j} |\theta_{E,ij}| + 0.1$. Two hundred replicates are generated under each simulation setting.

3.2 | Results

Simulation results for the power law structure are summarized in Tables A1 and A2 for the low and high signal levels, respectively. Results for the other two structures are summarized in Table B1–B4 in Appendix B. Overall, it is observed that the proposed approach has competitive performance. For all approaches, when p increases, performance in general deteriorates, which is as expected. Signal level has some impact on performance; however, not as prominent. Under simulation Scenario 1 where the two types of regulators have highly overlapping effects, the alternatives, especially FGL, may have superior performance, while the proposed approach has acceptable performance. Consider, for example, Table A1, Scenario 1, and $p = 60$. The mean MCC values, which reflect the overall identification performance, are 0.611 (GLasso), 0.520 (SepLasso), 0.810 (FGL), 0.804 (GGL), 0.542 (SSGL), 0.317 (SepBoost), 0.287 (SepThreshold), and 0.742 (proposed). When the overlapping effects of the two types of regulators diminish, the superiority of the proposed approach gets more prominent. Consider, for example, Table A1, Scenario 3, and $p = 100$. The mean MCC values are 0.384 (GLasso), 0.309 (SepLasso), 0.429 (FGL), 0.435 (GGL), 0.328 (SSGL), 0.193 (SepBoost), 0.142 (SepThreshold), and 0.507 (proposed). Under all the simulation settings, the hierarchy is satisfied. However, the alternative approaches, especially GLasso, SepLasso, SSGL, SepBoost, and SepThreshold, can lead to serious violations of the hierarchy. In addition, in Figure B1 (Appendix B), we also plot the ROC curves (which are generated based on a sequence of tuning parameter values) for a representative setting. This figure can provide a "global view" of identification performance. Similar plots for the other settings are available from the authors.

4 | DATA ANALYSIS

Lung cancer is the leading cause of cancer death worldwide, and non-small cell lung cancer (NSCLC) accounts for approximately 85% of all lung cancer cases [8, 30]. Lung adenocarcinoma (LUAD) is a major subtype of NSCLC. Extensive gene expression research has been conducted on NSCLC and LUAD in particular. In some of the published studies [34], network analysis has been conducted.

Here we analyze The Cancer Genome Atlas (TCGA) data on LUAD. TCGA is a collaborative effort organized by NIH and has published high-quality genetic data on more than 30 cancer types. It is especially noted that gene expression analysis, including network analysis, has been conducted with the TCGA LUAD data [29]. We refer to the literature for details on the collection and processing of TCGA gene expression data. For our analysis, Level 3 preprocessed data is downloaded from cBioPortal (www.cbioportal.org/). Data is available on 20,082 gene

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expressions and 481 samples. Network analysis concerns the interconnections among genes, which are “localized”, that is, for any specific gene, the number of interconnected genes is expected to be limited. In addition, network analysis involves a much larger number of parameters than “ordinary” analysis. Thus, we first use the KEGG (Kyoto Encyclopedia of Genes and Genomes, www.genome.jp/kegg/) pathway information to identify 67 genes that have functions relevant to lung cancer. The list of genes is available from the authors. For regulators, we identify 66 methylation loci and also select 67 microRNAs based on marginal screening. We note that, although seemingly not large, the number of unknown parameters is in fact much larger than the sample size.

Data analysis results are summarized in Figure A1. For the three networks, the proposed approach identifies 61, 60, and 46 edges. The hierarchy is satisfied. More detailed results on the interconnections are available from the authors. In Figure A2, we examine the distribution of the degree of edges. It is observed that the networks roughly satisfy the power law property, and the biological implication of this finding is worth further investigation. Data is additionally analyzed using the alternative approaches. The differences are summarized in Figures A3 and A4. It is observed that the alternatives lead to significantly different findings. In addition, they violated the hierarchy multiple times.

5 | DISCUSSION

Gene expression regulatory networks, both unadjusted and adjusted, have been established to have important implications. As there are often a large number of parameters to be estimated but limited sample sizes, the existing gene expression regulatory networks still have room for improvement, and there is still a strong demand for novel methods. In this article, we have focused on adjusted networks, developed an assisted strategy, linked multiple adjusted networks with a novel variable selection hierarchy, and effectively and cost-effectively improved estimation accuracy. Simulation has demonstrated improved practical performance. And in the analysis of TCGA data, networks different from the competing alternatives have been obtained. Overall, this study can deliver a new and effective tool for gene expression network analysis.

Network analysis is not limited to gene expression data, and the proposed analysis can be directly extended to other omics data and data in other domains as long as there exist similar regulating relationships. In addition, it can be extended to data with other distributions and other regression models (e.g., SNP data and logistic regression).

Regression-based network analysis has been commonly conducted. It has been shown that, for example, it is connected to GGM under certain conditions. It may be of interest to extend this work to GGM-based analysis. The proposed variable selection hierarchy is conceptually sensible and shares some similar spirit with the existing ones. However, mathematically, it is possible to construct counterexamples under which it fails. It may be of interest to identify the sufficient conditions under which it holds. However, this may demand considerable mathematical investigation and will be deferred to future research.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are openly available in The Cancer Genome Atlas at https://portal.gdc.cancer.gov/.

ORCID

Han Yan https://orcid.org/0000-0002-8460-9504
Shuangge Ma https://orcid.org/0000-0001-9001-4999

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APPENDIX A: HEURISTIC DISCUSSIONS ON THEORETICAL PROPERTIES

In this article, the focus is on methodological and numerical developments. It is conjectured that, following the literature, certain consistency properties can be established. For simplification, we assume that p, q, and r have the same order, which can match practical settings. As in [21], the following assumptions may be needed. (a) Dimensionality. There exists $\gamma > 0$ such that $p = O(n^{\gamma})$, as $n \to \infty$. (b) Nonsingularity. For all the networks, the conditional variance of any gene expression (conditional on the other gene expressions and regulators when applicable) is bounded below. (c) Sparsity I. For all the networks and for all the gene expressions, the maximum numbers of edges are bounded by $O(n^{\kappa})$ where $0 \leq \kappa < 1$. (d) Sparsity II. For all the networks and any gene expression, the l_1 norm of regression coefficients corresponding to the neighboring edges is bounded. (e) For all the networks and all the gene expressions, the absolute partial correlations corresponding to the edges are bounded below by $n^{-(1-\xi)/2}$, where ξ is a constant. (f) The neighborhood stability condition in [21] holds. Additional assumptions on the tuning parameters (as polynomials of n) are needed. It is noted that, in the existing network/regression analysis literature, there are alternative assumptions.

By the design of the penalty, the hierarchy in the sparsity structures automatically holds. It has been recognized that Lasso-based penalizations sometimes do not lead to consistent estimation. However, variable selection consistency may still hold. For a specific network and node i, consider E_i, its true set of connecting edges, and $\widehat{E}_i$, the estimate of E_i. The goal is to show that both $\widehat{E}_i \subseteq E_i$ and $E_i \subseteq \widehat{E}_i$ hold with a high probability (at least $1 - O(\exp(-cn^{\varphi}))$, where c, φ are positive constants). It is conjectured that the probability of $\widehat{E}_i \subseteq E_i$ can be established by combining Lemma A.2 of [21], the Bonferroni inequality, Assumption (a), and the Bernstein's inequality. Additionally, the probability of $E_i \subseteq \widehat{E}_i$ can be established also following Lemma A.2 of [21]. Overall, it is expected that sparsity structures can be consistently identified with probability at least $1 - O(\exp(-cn^{\varphi}))$.

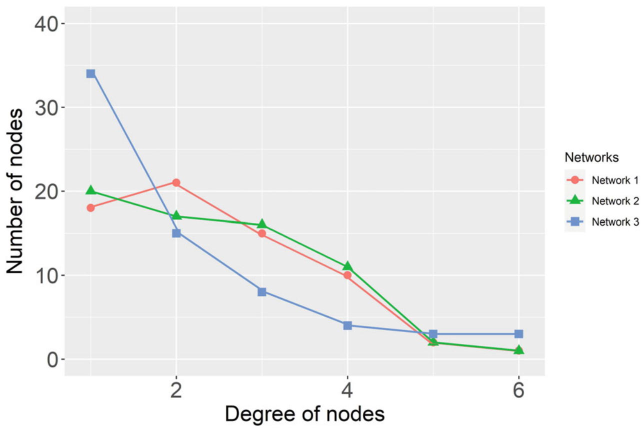

FIGURE A2 Data analysis: degree of nodes estimated by the proposed method

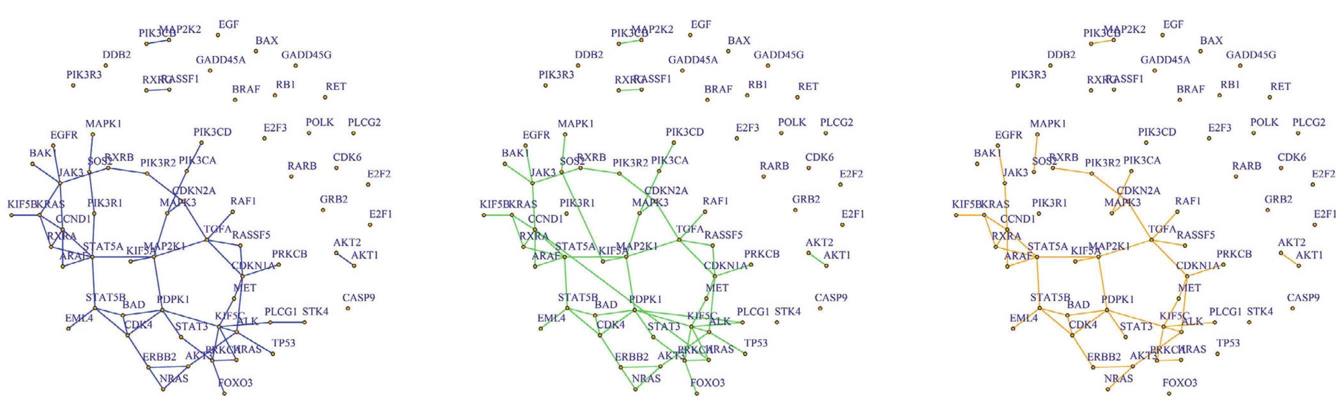

FIGURE A1 Data analysis: gene expression networks constructed using the proposed method. Left: incorporating microRNA only; Middle: incorporating methylation only; Right: incorporating both microRNA and methylation

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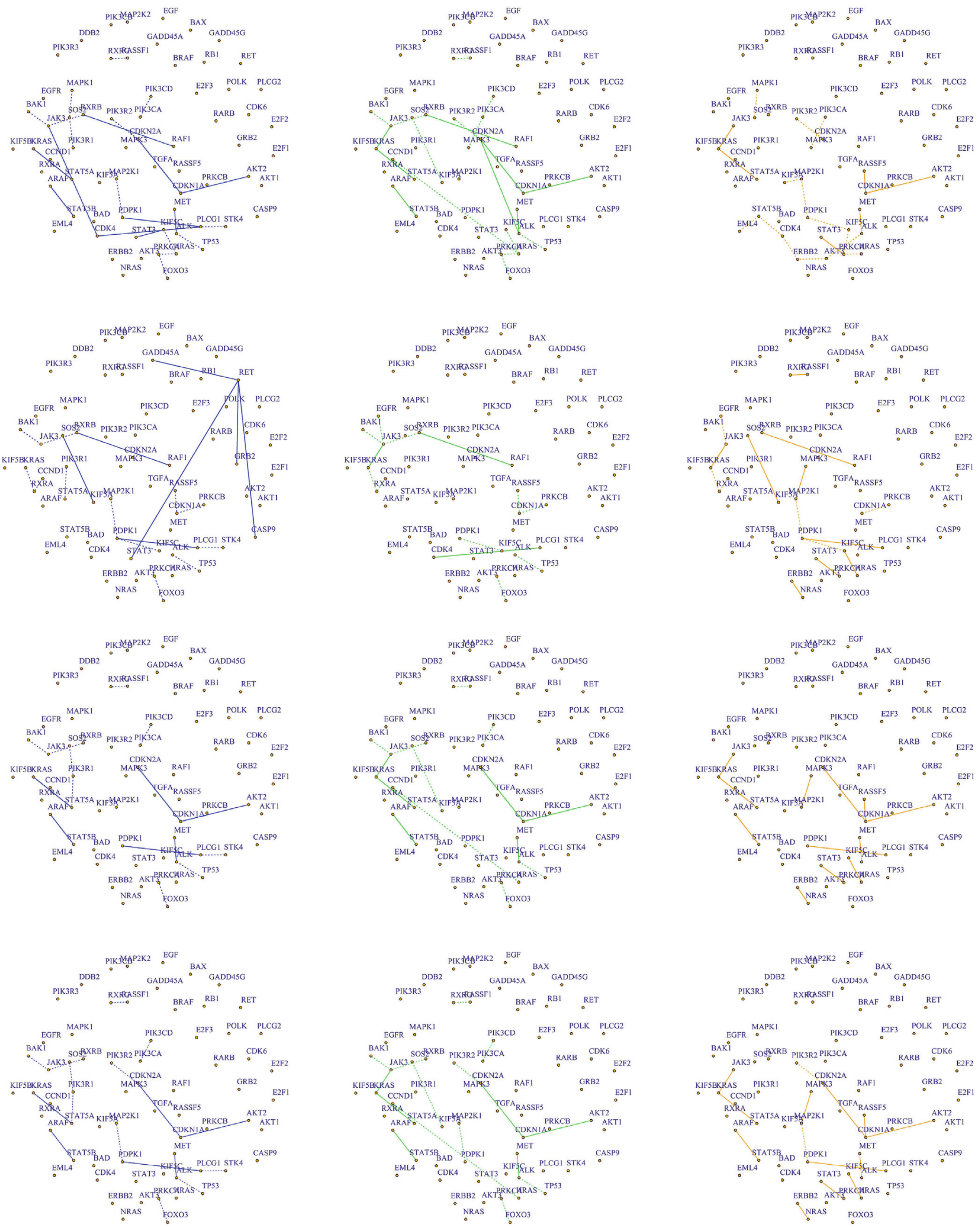

FIGURE A3 Data analysis: gene expression networks constructed using the alternative methods. Left: incorporating microRNA only; Middle: incorporating methylation only; Right: incorporating both microRNA and methylation. From top to bottom: GLasso, SepLasso, FGL, and GGL. Solid lines: edges identified by the alternative method but not by the proposed method. Dotted lines: edges not identified by the alternative method but by the proposed method

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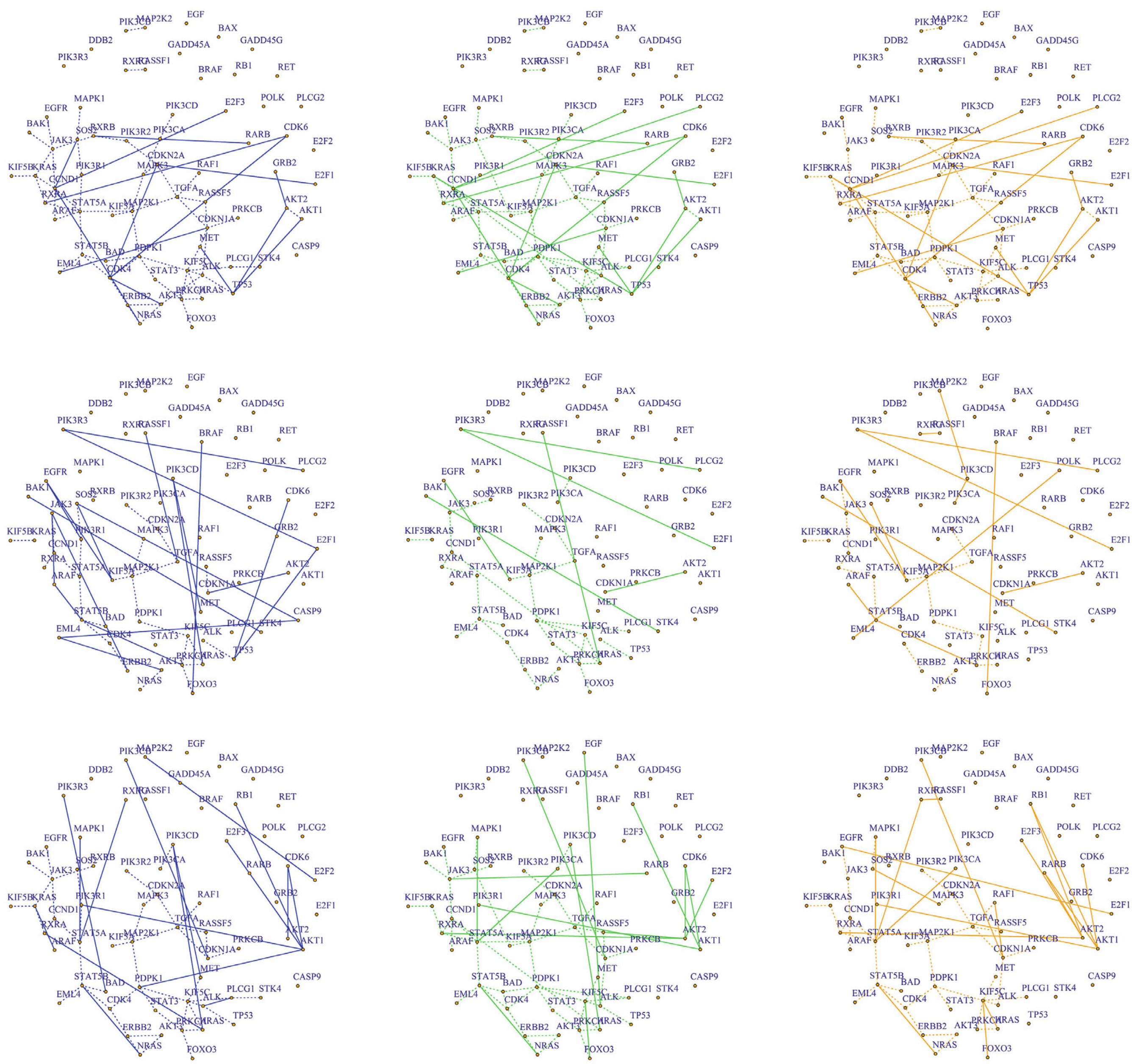

FIGURE A4 Data analysis: gene expression networks constructed using the alternative methods (cont.). Left: incorporating microRNA only; Middle: incorporating methylation only; Right: incorporating both microRNA and methylation. From top to bottom: SSGL, SepBoost, and SepThrehold. Solid lines: edges identified by the alternative method but not by the proposed method. Dotted lines: edges not identified by the alternative method but by the proposed method

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TABLE A1 Simulation results for the power law networks with low signal strengths. In each cell, mean (sd) based on 200 replicates

Method	TPR1	TDR1	TPR2	TDR2	TPR3	TDR3	MCC	N_VIO
Scenario 1	$p = 40$							
GLasso	0.691 (0.045)	0.957 (0.022)	0.663 (0.083)	0.937 (0.044)	0.327 (0.070)	0.702 (0.130)	0.720 (0.031)	11.7 (16.9)
SepLasso	0.695 (0.047)	0.576 (0.030)	0.740 (0.044)	0.562 (0.038)	0.609 (0.089)	0.376 (0.037)	0.617(0.026)	62.2 (9.7)
FGL	0.891 (0.055)	0.932 (0.043)	0.883 (0.051)	0.942 (0.034)	0.836 (0.069)	0.484 (0.029)	0.823 (0.025)	0.1 (0.4)
GGL	0.886 (0.032)	0.938 (0.026)	0.878 (0.035)	0.911 (0.030)	0.873 (0.049)	0.506 (0.016)	0.822 (0.015)	0.0 (0.0)
SSGL	0.510 (0.039)	0.605 (0.094)	0.552 (0.041)	0.590 (0.063)	0.636 (0.057)	0.516 (0.040)	0.649 (0.039)	31.9 (56.3)
SepBoost	0.989 (0.011)	0.253 (0.018)	0.994 (0.012)	0.247 (0.017)	1.000 (0.000)	0.106 (0.003)	0.377 (0.005)	31.9 (56.3)
SepThreshold	0.878 (0.038)	0.285 (0.018)	0.861 (0.044)	0.284 (0.019)	0.944 (0.032)	0.242 (0.009)	0.341 (0.059)	105.3 (79.4)
proposed	0.692 (0.060)	0.982 (0.013)	0.655 (0.023)	0.987 (0.015)	0.659 (0.060)	0.630 (0.088)	0.761 (0.077)	–
	$p = 60$							
GLasso	0.476 (0.048)	0.970 (0.028)	0.475 (0.043)	0.966 (0.042)	0.473 (0.089)	0.519 (0.081)	0.611 (0.039)	32.0 (36.0)
SepLasso	0.720 (0.021)	0.418 (0.032)	0.733 (0.029)	0.489 (0.044)	0.612 (0.034)	0.266 (0.012)	0.520 (0.089)	100.5 (11.2)
FGL	0.920 (0.031)	0.847 (0.019)	0.924 (0.039)	0.866 (0.012)	0.897 (0.056)	0.454 (0.015)	0.810 (0.019)	1.9 (2.5)
GGL	0.869 (0.043)	0.914 (0.088)	0.844 (0.036)	0.931 (0.051)	0.817 (0.030)	0.466 (0.028)	0.804 (0.041)	2.2 (1.5)
SSGL	0.508 (0.043)	0.505 (0.099)	0.497 (0.044)	0.598 (0.062)	0.697 (0.057)	0.297 (0.040)	0.542 (0.040)	137.5 (80.1)
SepBoost	0.984 (0.009)	0.147 (0.007)	0.982 (0.014)	0.150 (0.006)	0.997 (0.002)	0.045 (0.001)	0.317 (0.002)	96.9 (146.2)
SepThreshold	0.794 (0.036)	0.260 (0.019)	0.806 (0.039)	0.261 (0.016)	0.879 (0.047)	0.228 (0.008)	0.287 (0.035)	222.1 (202.7)
proposed	0.695 (0.045)	0.956 (0.044)	0.740 (0.036)	0.934 (0.031)	0.561 (0.048)	0.530 (0.084)	0.742 (0.058)	–
	$p = 100$							
GLasso	0.394 (0.105)	0.964 (0.023)	0.389 (0.117)	0.950 (0.052)	0.476 (0.083)	0.613 (0.090)	0.564 (0.052)	65.3 (45.8)
SepLasso	0.733 (0.030)	0.315 (0.021)	0.741 (0.042)	0.326 (0.027)	0.675 (0.034)	0.168 (0.014)	0.421 (0.075)	191.2 (38.3)
FGL	0.875 (0.015)	0.767 (0.047)	0.872 (0.019)	0.756 (0.039)	0.824 (0.058)	0.403 (0.024)	0.737 (0.022)	7.2 (4.7)
GGL	0.861 (0.048)	0.729 (0.024)	0.869 (0.054)	0.724 (0.025)	0.812 (0.038)	0.377 (0.014)	0.716 (0.033)	9.6 (3.7)
SSGL	0.317 (0.051)	0.726 (0.057)	0.291 (0.031)	0.594 (0.107)	0.655 (0.087)	0.232 (0.057)	0.444 (0.041)	205.5 (179.7)
SepBoost	0.971 (0.008)	0.080 (0.002)	0.977 (0.016)	0.079 (0.003)	0.987 (0.002)	0.024 (0.001)	0.265 (0.002)	286.6 (464.9)
SepThreshold	0.649 (0.027)	0.242 (0.012)	0.642 (0.034)	0.242 (0.013)	0.660 (0.063)	0.212 (0.011)	0.249 (0.018)	602.6 (620.6)
proposed	0.594 (0.047)	0.973 (0.029)	0.581 (0.043)	0.983 (0.022)	0.482 (0.048)	0.726 (0.084)	0.687 (0.033)	–
Scenario 2	$p = 40$							
GLasso	0.390 (0.046)	0.977 (0.023)	0.386 (0.063)	0.957 (0.040)	0.614 (0.057)	0.725 (0.020)	0.605 (0.044)	19.9 (20.0)
SepLasso	0.722 (0.073)	0.448 (0.026)	0.741 (0.022)	0.461 (0.016)	0.614 (0.114)	0.286 (0.012)	0.521 (0.098)	63.2 (10.6)
FGL	0.810 (0.037)	0.525 (0.035)	0.835 (0.043)	0.543 (0.045)	0.905 (0.044)	0.208 (0.019)	0.607 (0.016)	0.2 (0.6)
GGL	0.813 (0.019)	0.545 (0.083)	0.813 (0.021)	0.542 (0.070)	0.829 (0.029)	0.191 (0.023)	0.579 (0.039)	0.6 (0.9)
SSGL	0.500 (0.036)	0.629 (0.077)	0.375 (0.040)	0.640 (0.060)	0.786 (0.143)	0.270 (0.032)	0.505 (0.032)	47.6 (23.0)
SepBoost	0.980 (0.011)	0.193 (0.009)	0.979 (0.018)	0.191 (0.009)	1.000 (0.000)	0.072 (0.001)	0.293 (0.009)	31.5 (47.5)
SepThreshold	0.925 (0.018)	0.278 (0.016)	0.933 (0.025)	0.279 (0.015)	0.996 (0.011)	0.222 (0.010)	0.340 (0.052)	113.8 (93.4)
proposed	0.738 (0.033)	0.681 (0.018)	0.787 (0.056)	0.670 (0.022)	0.964 (0.057)	0.300 (0.043)	0.644 (0.037)	–
	$p = 60$							
GLasso	0.323 (0.041)	0.970 (0.026)	0.331 (0.034)	0.962 (0.011)	0.676 (0.081)	0.601 (0.031)	0.572 (0.025)	36.4 (34.3)
SepLasso	0.689 (0.051)	0.325 (0.020)	0.715 (0.022)	0.322 (0.027)	0.586 (0.064)	0.271 (0.005)	0.450 (0.090)	140.6 (35.7)
FGL	0.792 (0.038)	0.594 (0.033)	0.782 (0.071)	0.583 (0.072)	0.834 (0.117)	0.219 (0.034)	0.588 (0.047)	4.1 (1.4)
GGL	0.793 (0.028)	0.504 (0.019)	0.803 (0.038)	0.510 (0.012)	0.829 (0.124)	0.184 (0.025)	0.549 (0.024)	4.8 (2.3)
SSGL	0.385 (0.046)	0.565 (0.075)	0.405 (0.052)	0.542 (0.071)	0.643 (0.080)	0.227 (0.033)	0.478 (0.039)	123.0 (74.1)
SepBoost	0.960 (0.012)	0.127 (0.002)	0.965 (0.017)	0.127 (0.005)	1.000 (0.000)	0.032 (0.001)	0.236 (0.008)	97.9 (150.2)
SepThreshold	0.823 (0.033)	0.259 (0.015)	0.815 (0.028)	0.258 (0.014)	0.910 (0.073)	0.167 (0.012)	0.265 (0.029)	266.3 (239.2)
proposed	0.716 (0.051)	0.654 (0.037)	0.658 (0.065)	0.581 (0.051)	0.786 (0.052)	0.264 (0.062)	0.592 (0.069)	–

(Continues)

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TABLE A1 (Continued)

Method	TPR1	TDR1	TPR2	TDR2	TPR3	TDR3	MCC	N_VIO
	$p = 100$							
GLasso	0.218 (0.025)	0.957 (0.030)	0.223 (0.028)	0.971 (0.009)	0.343 (0.071)	0.571 (0.027)	0.432 (0.024)	73.8 (54.4)
SepLasso	0.661 (0.023)	0.199 (0.006)	0.685 (0.032)	0.204 (0.017)	0.623 (0.085)	0.173 (0.009)	0.347 (0.074)	231.5 (30.3)
FGL	0.821 (0.020)	0.476 (0.065)	0.787 (0.077)	0.456 (0.059)	0.799 (0.085)	0.160 (0.024)	0.523 (0.042)	7.2 (2.7)
GGL	0.816 (0.057)	0.499 (0.023)	0.819 (0.057)	0.478 (0.026)	0.798 (0.118)	0.170 (0.019)	0.539 (0.023)	11.2 (2.8)
SSGL	0.230 (0.034)	0.534 (0.109)	0.242 (0.017)	0.516 (0.108)	0.557 (0.037)	0.219 (0.055)	0.386 (0.052)	104.0 (83.4)
SepBoost	0.934 (0.017)	0.096 (0.003)	0.935 (0.018)	0.097 (0.003)	1.000 (0.000)	0.024 (0.001)	0.208 (0.004)	287.7 (467.5)
SepThreshold	0.632 (0.053)	0.238 (0.012)	0.659 (0.032)	0.222 (0.013)	0.706 (0.073)	0.108 (0.012)	0.229 (0.018)	599.2 (582.2)
proposed	0.790 (0.067)	0.474 (0.071)	0.779 (0.053)	0.486 (0.059)	0.900 (0.042)	0.193 (0.060)	0.547 (0.015)	–
Scenario 3	$p = 40$							
GLasso	0.417 (0.095)	0.495 (0.079)	0.420 (0.104)	0.482 (0.071)	0.970 (0.054)	0.307 (0.021)	0.441 (0.039)	16.4 (18.4)
SepLasso	0.757 (0.038)	0.346 (0.022)	0.737 (0.052)	0.338 (0.018)	0.817 (0.070)	0.142 (0.009)	0.404 (0.106)	91.9 (25.2)
FGL	0.839 (0.033)	0.382 (0.037)	0.832 (0.053)	0.376 (0.062)	0.733 (0.067)	0.049 (0.005)	0.460 (0.041)	0.3 (0.7)
GGL	0.859 (0.071)	0.400 (0.054)	0.861 (0.069)	0.394 (0.023)	0.767 (0.090)	0.053 (0.017)	0.460 (0.029)	0.6 (0.9)
SSGL	0.471 (0.053)	0.518 (0.089)	0.440 (0.048)	0.510 (0.082)	0.833 (0.144)	0.120 (0.031)	0.422 (0.045)	38.5 (24.4)
SepBoost	0.973 (0.026)	0.192 (0.009)	0.981 (0.018)	0.191 (0.011)	1.000 (0.000)	0.018 (0.000)	0.251 (0.007)	32.6 (49.3)
SepThreshold	0.906 (0.024)	0.273 (0.013)	0.925 (0.036)	0.254 (0.014)	1.000 (0.000)	0.010 (0.001)	0.270 (0.047)	123.3 (111.0)
proposed	0.621 (0.059)	0.626 (0.050)	0.613 (0.074)	0.543 (0.051)	0.618 (0.033)	0.262 (0.064)	0.542 (0.031)	–
	$p = 60$							
GLasso	0.385 (0.079)	0.399 (0.099)	0.576 (0.086)	0.585 (0.110)	0.933 (0.049)	0.146 (0.042)	0.410 (0.033)	43.6 (44.6)
SepLasso	0.757 (0.038)	0.296 (0.022)	0.737 (0.052)	0.288 (0.018)	0.817 (0.070)	0.092 (0.009)	0.354 (0.106)	131.0 (25.2)
FGL	0.816 (0.056)	0.360 (0.026)	0.823 (0.036)	0.351 (0.020)	0.700 (0.074)	0.046 (0.006)	0.436 (0.013)	3.2 (2.7)
GGL	0.828 (0.027)	0.364 (0.015)	0.822 (0.026)	0.362 (0.013)	0.711 (0.061)	0.045 (0.005)	0.442 (0.008)	3.6 (1.7)
SSGL	0.418 (0.052)	0.420 (0.062)	0.429 (0.053)	0.429 (0.065)	0.722 (0.144)	0.186 (0.031)	0.375 (0.034)	106.4 (62.2)
SepBoost	0.965 (0.014)	0.137 (0.009)	0.957 (0.015)	0.127 (0.009)	1.000 (0.000)	0.014 (0.000)	0.214 (0.008)	98.2(147.3)
SepThreshold	0.803 (0.058)	0.205 (0.014)	0.814 (0.036)	0.184 (0.013)	0.994 (0.018)	0.007 (0.000)	0.191 (0.024)	321.8 (303.1)
proposed	0.635 (0.077)	0.504 (0.079)	0.624 (0.078)	0.433 (0.085)	0.537 (0.030)	0.176 (0.043)	0.519 (0.032)	–
	$p = 100$							
GLasso	0.361 (0.066)	0.568 (0.107)	0.427 (0.063)	0.439 (0.086)	0.956 (0.099)	0.171 (0.069)	0.384 (0.052)	108.2 (60.9)
SepLasso	0.742 (0.017)	0.206 (0.012)	0.713 (0.017)	0.202 (0.010)	0.693 (0.095)	0.082 (0.005)	0.309 (0.110)	233.4 (34.3)
FGL	0.791 (0.032)	0.354 (0.016)	0.798 (0.052)	0.347 (0.019)	0.733 (0.069)	0.046 (0.011)	0.429 (0.022)	10.5 (4.3)
GGL	0.818 (0.015)	0.346 (0.017)	0.782 (0.040)	0.338 (0.020)	0.689 (0.038)	0.041 (0.002)	0.435 (0.019)	8.3 (4.5)
SSGL	0.293 (0.034)	0.491 (0.086)	0.291 (0.038)	0.468 (0.084)	0.800(0.114)	0.124 (0.023)	0.328 (0.033)	123.6 (127.5)
SepBoost	0.933 (0.012)	0.077 (0.006)	0.928 (0.020)	0.077 (0.005)	1.000 (0.000)	0.009 (0.000)	0.193 (0.005)	287.1 (433.7)
SepThreshold	0.645 (0.040)	0.135 (0.013)	0.630 (0.043)	0.175 (0.012)	0.640 (0.018)	0.012 (0.000)	0.142 (0.019)	589.6 (594.8)
proposed	0.714 (0.038)	0.508 (0.038)	0.768 (0.064)	0.534 (0.027)	0.836 (0.026)	0.092 (0.007)	0.507 (0.016)	–

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TABLE A2 Simulation results for the power law networks with high signal strengths. In each cell, mean (sd) based on 200 replicates

Method	TPR1	TDR1	TPR2	TDR2	TPR3	TDR3	MCC	N_VIO
Scenario 1	$p = 40$							
GLasso	0.533 (0.090)	0.985 (0.033)	0.535 (0.094)	0.969 (0.028)	0.518 (0.107)	0.501 (0.061)	0.634 (0.079)	20.9 (12.0)
SepLasso	0.715 (0.017)	0.574 (0.079)	0.730 (0.050)	0.545 (0.065)	0.709 (0.093)	0.380 (0.035)	0.621 (0.090)	81.9 (13.8)
FGL	0.879 (0.069)	0.928 (0.030)	0.865 (0.084)	0.903 (0.034)	0.864 (0.125)	0.483 (0.046)	0.810 (0.059)	0.0 (0.0)
GGL	0.854 (0.025)	0.899 (0.051)	0.860 (0.029)	0.878 (0.046)	0.799 (0.069)	0.448 (0.022)	0.781 (0.026)	0.0 (0.0)
SSGL	0.524 (0.035)	0.662 (0.111)	0.492 (0.036)	0.588 (0.061)	0.705 (0.049)	0.201 (0.036)	0.570 (0.048)	99.2 (31.5)
SepBoost	0.975 (0.020)	0.192 (0.009)	0.969 (0.022)	0.192 (0.008)	0.892 (0.062)	0.087 (0.003)	0.274 (0.009)	31.4 (47.9)
SepThreshold	0.860 (0.027)	0.313 (0.023)	0.890 (0.023)	0.309 (0.019)	0.986 (0.024)	0.138 (0.012)	0.303 (0.058)	88.4 (56.1)
proposed	0.785 (0.061)	0.880 (0.050)	0.806 (0.059)	0.906 (0.057)	0.651 (0.047)	0.511 (0.056)	0.764 (0.064)	–
	$p = 60$							
GLasso	0.414 (0.087)	0.981 (0.019)	0.388 (0.101)	0.979 (0.021)	0.297 (0.076)	0.788 (0.062)	0.558 (0.054)	31.6 (32.8)
SepLasso	0.728 (0.035)	0.393 (0.039)	0.718 (0.025)	0.428 (0.021)	0.685 (0.066)	0.259 (0.021)	0.499 (0.076)	132.4 (27.2)
FGL	0.865 (0.019)	0.911 (0.059)	0.861 (0.022)	0.919 (0.071)	0.850 (0.058)	0.482 (0.053)	0.797 (0.039)	2.7 (1.5)
GGL	0.875 (0.037)	0.827 (0.045)	0.866 (0.049)	0.834 (0.041)	0.909 (0.055)	0.443 (0.030)	0.765 (0.033)	3.8 (1.3)
SSGL	0.397 (0.039)	0.586 (0.073)	0.360 (0.056)	0.498 (0.049)	0.803 (0.061)	0.130 (0.023)	0.464 (0.031)	179.6 (83.7)
SepBoost	0.946 (0.022)	0.147 (0.008)	0.940 (0.021)	0.148 (0.008)	0.761 (0.049)	0.055 (0.003)	0.241 (0.006)	98.0 (148.4)
SepThreshold	0.794 (0.020)	0.204 (0.018)	0.799 (0.019)	0.214 (0.015)	0.865 (0.063)	0.132 (0.013)	0.251 (0.044)	173.4 (131.5)
proposed	0.626 (0.105)	0.881 (0.066)	0.693 (0.094)	0.882 (0.082)	0.443 (0.099)	0.522 (0.074)	0.685 (0.083)	–
	$p = 100$							
GLasso	0.318 (0.077)	0.945 (0.033)	0.262 (0.044)	0.952 (0.024)	0.402 (0.060)	0.564 (0.099)	0.541 (0.066)	44.4 (48.4)
SepLasso	0.695 (0.025)	0.330 (0.027)	0.687 (0.054)	0.318 (0.025)	0.596 (0.031)	0.177 (0.010)	0.414 (0.081)	253.8 (36.3)
FGL	0.904 (0.069)	0.844 (0.077)	0.896 (0.048)	0.832 (0.079)	0.885 (0.050)	0.438 (0.031)	0.773 (0.055)	7.2 (3.2)
GGL	0.805 (0.039)	0.843 (0.030)	0.798 (0.032)	0.856 (0.029)	0.779 (0.071)	0.458 (0.039)	0.741 (0.031)	10.3 (5.4)
SSGL	0.381 (0.063)	0.456 (0.057)	0.367 (0.047)	0.445 (0.059)	0.709 (0.061)	0.145 (0.023)	0.396 (0.016)	316.4 (124.2)
SepBoost	0.909 (0.020)	0.117 (0.009)	0.911 (0.019)	0.117 (0.008)	0.700 (0.061)	0.034 (0.002)	0.210 (0.005)	290.0 (437.5)
SepThreshold	0.652 (0.036)	0.175 (0.016)	0.676 (0.033)	0.176 (0.016)	0.667 (0.063)	0.112 (0.013)	0.180 (0.012)	627.9 (618.4)
proposed	0.707 (0.055)	0.661 (0.057)	0.719 (0.071)	0.660 (0.054)	0.561 (0.083)	0.605 (0.073)	0.646 (0.078)	–
Scenario 2	$p = 40$							
GLasso	0.416 (0.090)	0.977 (0.020)	0.477 (0.062)	0.983 (0.030)	0.672 (0.058)	0.719 (0.014)	0.578 (0.046)	17.7 (17.8)
SepLasso	0.711 (0.035)	0.422 (0.021)	0.675 (0.030)	0.421 (0.021)	0.671 (0.132)	0.281 (0.016)	0.490 (0.075)	88.7 (25.1)
FGL	0.824 (0.022)	0.565 (0.017)	0.829 (0.019)	0.555 (0.014)	0.952 (0.016)	0.224 (0.013)	0.610 (0.015)	0.2 (0.9)
GGL	0.774 (0.043)	0.560 (0.014)	0.754 (0.048)	0.536 (0.031)	0.872 (0.059)	0.214 (0.027)	0.560 (0.021)	0.4 (1.0)
SSGL	0.433 (0.048)	0.620 (0.077)	0.400 (0.027)	0.586 (0.077)	0.750 (0.086)	0.220 (0.041)	0.512 (0.046)	75.5 (29.0)
SepBoost	0.989 (0.007)	0.181 (0.011)	0.984 (0.015)	0.186 (0.010)	1.000 (0.000)	0.030 (0.000)	0.248 (0.007)	30.2 (46.3)
SepThreshold	0.898 (0.035)	0.292 (0.016)	0.894 (0.025)	0.273 (0.020)	0.989 (0.000)	0.123 (0.000)	0.285 (0.051)	101.5 (76.1)
proposed	0.707 (0.057)	0.744 (0.057)	0.700 (0.058)	0.709 (0.043)	0.964 (0.101)	0.351 (0.103)	0.653 (0.071)	–

(Continues)

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TABLE A2 (Continued)

Method	TPR1	TDR1	TPR2	TDR2	TPR3	TDR3	MCC	N_VIO
	$p = 60$							
GLasso	0.316 (0.077)	0.951 (0.042)	0.337 (0.064)	0.979 (0.029)	0.565 (0.070)	0.717 (0.055)	0.534 (0.063)	34.1 (31.3)
SepLasso	0.714 (0.034)	0.324 (0.015)	0.715 (0.059)	0.311 (0.022)	0.695 (0.092)	0.180 (0.015)	0.410 (0.076)	149.2 (29.7)
FGL	0.849 (0.037)	0.587 (0.059)	0.806 (0.050)	0.545 (0.041)	0.943 (0.078)	0.225 (0.043)	0.597 (0.031)	2.2 (2.3)
GGL	0.800 (0.065)	0.533 (0.044)	0.788 (0.079)	0.524 (0.042)	0.867 (0.123)	0.195 (0.028)	0.528 (0.040)	5.0 (3.7)
SSGL	0.348 (0.043)	0.597 (0.057)	0.330 (0.039)	0.516 (0.052)	0.762 (0.104)	0.161 (0.021)	0.392 (0.036)	165.1 (96.8)
SepBoost	0.978 (0.014)	0.143 (0.009)	0.981 (0.012)	0.149 (0.009)	1.000 (0.000)	0.020 (0.000)	0.218 (0.006)	97.9 (145.4)
SepThreshold	0.786 (0.024)	0.180 (0.017)	0.791 (0.030)	0.171 (0.015)	0.881 (0.050)	0.079 (0.011)	0.204 (0.034)	214.3 (169.7)
proposed	0.678 (0.047)	0.684 (0.042)	0.675 (0.033)	0.669 (0.038)	0.833 (0.077)	0.299 (0.079)	0.610 (0.068)	–
	$p = 100$							
GLasso	0.379 (0.095)	0.901 (0.030)	0.375 (0.068)	0.942 (0.029)	0.314 (0.031)	0.706 (0.037)	0.477 (0.064)	46.0 (41.4)
SepLasso	0.678 (0.029)	0.262 (0.017)	0.689 (0.019)	0.249 (0.016)	0.651 (0.043)	0.124 (0.006)	0.353 (0.073)	270.4 (31.4)
FGL	0.794 (0.036)	0.454 (0.020)	0.805 (0.039)	0.463 (0.026)	0.848 (0.070)	0.166 (0.011)	0.522 (0.017)	8.2 (4.6)
GGL	0.772 (0.013)	0.470 (0.025)	0.781 (0.037)	0.474 (0.036)	0.838 (0.072)	0.175 (0.019)	0.487 (0.029)	9.7 (3.3)
SSGL	0.327 (0.024)	0.525 (0.100)	0.358 (0.010)	0.474 (0.090)	0.643 (0.052)	0.137 (0.037)	0.336 (0.035)	250.5 (168.9)
SepBoost	0.968 (0.021)	0.118 (0.009)	0.959 (0.016)	0.118 (0.009)	1.000 (0.000)	0.020 (0.000)	0.206 (0.005)	290.0 (474.3)
SepThreshold	0.664 (0.031)	0.158 (0.015)	0.694 (0.042)	0.160 (0.014)	0.691 (0.090)	0.018 (0.001)	0.181 (0.014)	563.4 (562.7)
proposed	0.743 (0.042)	0.641 (0.055)	0.678 (0.067)	0.597 (0.053)	0.886 (0.085)	0.265 (0.056)	0.567 (0.045)	–
Scenario 3	$p = 40$							
GLasso	0.326 (0.078)	0.503 (0.052)	0.388 (0.058)	0.654 (0.075)	0.939 (0.058)	0.147 (0.014)	0.422 (0.050)	10.1 (12.3)
SepLasso	0.762 (0.064)	0.405 (0.020)	0.787 (0.054)	0.391 (0.046)	0.700 (0.045)	0.185 (0.002)	0.453 (0.128)	80.7 (12.0)
FGL	0.807 (0.053)	0.461 (0.039)	0.837 (0.036)	0.464 (0.055)	0.848 (0.046)	0.171 (0.049)	0.489 (0.059)	0.7 (1.5)
GGL	0.813 (0.010)	0.489 (0.062)	0.795 (0.009)	0.479 (0.075)	0.771 (0.029)	0.160 (0.021)	0.487 (0.039)	0.5 (1.3)
SSGL	0.444 (0.049)	0.493 (0.070)	0.453 (0.054)	0.512 (0.082)	0.917 (0.111)	0.134 (0.029)	0.454 (0.042)	52.7 (28.0)
SepBoost	0.983 (0.012)	0.183 (0.010)	0.978 (0.017)	0.183 (0.010)	0.988 (0.040)	0.030 (0.000)	0.231 (0.011)	33.7 (54.9)
SepThreshold	0.900 (0.037)	0.283 (0.015)	0.899 (0.028)	0.282 (0.016)	1.000 (0.000)	0.010 (0.000)	0.244 (0.046)	113.5 (94.0)
proposed	0.701 (0.069)	0.534 (0.071)	0.720 (0.075)	0.546 (0.076)	0.917 (0.059)	0.216 (0.028)	0.547 (0.025)	–
	$p = 60$							
GLasso	0.347 (0.083)	0.444 (0.068)	0.430 (0.080)	0.631 (0.068)	0.933 (0.049)	0.216 (0.080)	0.393 (0.041)	36.9 (39.6)
SepLasso	0.782 (0.042)	0.306 (0.020)	0.765 (0.043)	0.316 (0.018)	0.800 (0.092)	0.135 (0.006)	0.396 (0.106)	140.0 (27.5)
FGL	0.894 (0.053)	0.350 (0.027)	0.866 (0.046)	0.350 (0.016)	0.889 (0.036)	0.052 (0.010)	0.449 (0.025)	4.0 (2.8)
GGL	0.837 (0.042)	0.368 (0.027)	0.855 (0.056)	0.372 (0.021)	0.845 (0.068)	0.055 (0.013)	0.453 (0.025)	5.2 (3.6)
SSGL	0.500 (0.067)	0.433 (0.042)	0.448 (0.052)	0.429 (0.064)	0.944 (0.164)	0.085 (0.016)	0.364 (0.030)	129.5 (73.5)
SepBoost	0.972 (0.020)	0.142 (0.007)	0.977 (0.016)	0.149 (0.009)	1.000 (0.000)	0.025 (0.000)	0.213 (0.010)	94.4 (156.7)
SepThreshold	0.782 (0.037)	0.209 (0.015)	0.812 (0.033)	0.213 (0.014)	0.933 (0.090)	0.018 (0.001)	0.180 (0.026)	261.3 (241.8)
proposed	0.765 (0.051)	0.483 (0.054)	0.788 (0.069)	0.469 (0.056)	0.815 (0.070)	0.153 (0.041)	0.530 (0.046)	–
	$p = 100$							
GLasso	0.435 (0.054)	0.522 (0.046)	0.379 (0.034)	0.526 (0.045)	0.956 (0.059)	0.152 (0.049)	0.387 (0.053)	44.3 (48.5)
SepLasso	0.739 (0.023)	0.254 (0.012)	0.731 (0.041)	0.258 (0.021)	0.746 (0.055)	0.084 (0.004)	0.345 (0.107)	249.1 (41.2)
FGL	0.835 (0.033)	0.357 (0.020)	0.806 (0.032)	0.351 (0.024)	0.743 (0.016)	0.045 (0.013)	0.424 (0.010)	8.4 (2.7)
GGL	0.809 (0.055)	0.396 (0.027)	0.791 (0.046)	0.393 (0.055)	0.803 (0.067)	0.057 (0.012)	0.435 (0.031)	10.6 (4.9)
SSGL	0.248 (0.026)	0.509 (0.083)	0.246 (0.025)	0.489 (0.083)	0.833 (0.116)	0.100 (0.025)	0.367 (0.035)	130.8 (82.6)
SepBoost	0.962 (0.018)	0.113 (0.009)	0.959 (0.015)	0.113 (0.009)	1.000 (0.000)	0.020 (0.000)	0.194 (0.05)	291.9 (440.2)
SepThreshold	0.633 (0.041)	0.142 (0.013)	0.645 (0.039)	0.132 (0.013)	0.674 (0.090)	0.013 (0.001)	0.169 (0.016)	640.1 (631.2)
proposed	0.605 (0.051)	0.521 (0.058)	0.677 (0.069)	0.512 (0.062)	0.772 (0.045)	0.157 (0.030)	0.514 (0.046)	–

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APPENDIX B: ADDITIONAL NUMERICAL RESULTS

TABLE B1 Simulation results for the nearest-neighbor networks with low signal strengths. In each cell, mean (sd) based on 200 replicates

Method	TPR1	TDR1	TPR2	TDR2	TPR3	TDR3	MCC	N_VIO
Scenario 1	$p = 40$							
GLasso	0.863 (0.057)	0.900 (0.074)	0.856 (0.065)	0.879 (0.074)	0.811 (0.076)	0.548 (0.044)	0.799 (0.037)	14.4 (12.9)
SepLasso	0.764 (0.047)	0.598 (0.034)	0.757 (0.056)	0.574 (0.030)	0.678 (0.038)	0.435 (0.027)	0.660 (0.079)	61.7 (16.8)
FGL	0.901 (0.034)	0.937 (0.011)	0.912 (0.040)	0.943 (0.009)	0.876 (0.048)	0.600 (0.021)	0.857 (0.021)	0.0 (0.0)
GGL	0.854 (0.025)	0.899 (0.051)	0.860 (0.029)	0.878 (0.046)	0.799 (0.069)	0.448 (0.022)	0.781 (0.026)	0.0 (0.0)
SSGL	0.666 (0.045)	0.570 (0.111)	0.716 (0.036)	0.513 (0.061)	0.611 (0.049)	0.452 (0.036)	0.591 (0.048)	131.1 (11.4)
SepBoost	0.954 (0.027)	0.242 (0.016)	0.956 (0.029)	0.243 (0.012)	0.975 (0.025)	0.099 (0.009)	0.303 (0.033)	30.9 (43.2)
SepThreshold	0.922 (0.029)	0.279 (0.015)	0.917 (0.030)	0.230 (0.014)	0.974 (0.036)	0.142 (0.012)	0.316 (0.057)	105.0 (79.0)
proposed	0.940 (0.053)	0.798 (0.086)	0.929 (0.068)	0.748 (0.082)	0.926 (0.047)	0.759 (0.046)	0.815 (0.054)	–
	$p = 60$							
GLasso	0.865 (0.065)	0.858 (0.042)	0.866 (0.073)	0.847 (0.047)	0.823 (0.110)	0.534 (0.050)	0.788 (0.051)	28.6 (15.7)
SepLasso	0.761 (0.026)	0.500 (0.049)	0.750 (0.034)	0.495 (0.042)	0.583 (0.100)	0.328 (0.028)	0.574 (0.102)	101.5 (22.2)
FGL	0.891 (0.029)	0.886 (0.038)	0.885 (0.035)	0.877 (0.027)	0.840 (0.060)	0.553 (0.007)	0.820 (0.018)	4.5 (2.1)
GGL	0.875 (0.037)	0.827 (0.045)	0.866 (0.049)	0.834 (0.041)	0.909 (0.055)	0.443 (0.030)	0.765 (0.033)	5.0 (2.3)
SSGL	0.627 (0.039)	0.412 (0.059)	0.670 (0.040)	0.497 (0.063)	0.762 (0.099)	0.250 (0.029)	0.545 (0.033)	220.5 (70.6)
SepBoost	0.871 (0.029)	0.185 (0.015)	0.891 (0.034)	0.194 (0.018)	0.956 (0.020)	0.075 (0.008)	0.263 (0.016)	95.4 (164.5)
SepThreshold	0.825 (0.035)	0.265 (0.015)	0.798 (0.043)	0.241 (0.014)	0.867 (0.064)	0.133 (0.014)	0.291 (0.034)	212.4 (208.1)
proposed	0.873 (0.091)	0.805 (0.077)	0.852 (0.072)	0.813 (0.080)	0.786 (0.071)	0.532 (0.056)	0.771 (0.064)	–
	$p = 100$							
GLasso	0.844 (0.052)	0.838 (0.011)	0.845 (0.046)	0.843 (0.023)	0.797 (0.063)	0.524 (0.023)	0.772 (0.024)	41.1 (28.6)
SepLasso	0.718 (0.013)	0.391 (0.024)	0.727 (0.023)	0.388 (0.010)	0.630 (0.028)	0.274 (0.019)	0.499 (0.063)	196.7 (30.3)
FGL	0.815 (0.015)	0.942 (0.049)	0.814 (0.027)	0.931 (0.034)	0.747 (0.061)	0.543 (0.028)	0.793 (0.018)	14.4 (4.2)
GGL	0.805 (0.039)	0.843 (0.030)	0.798 (0.032)	0.856 (0.029)	0.779 (0.071)	0.458 (0.039)	0.741 (0.031)	15.5 (6.7)
SSGL	0.539 (0.064)	0.363 (0.034)	0.549 (0.071)	0.368 (0.032)	0.821 (0.099)	0.149 (0.029)	0.462 (0.033)	458.1 (198.9)
SepBoost	0.747 (0.014)	0.177 (0.010)	0.744 (0.022)	0.171 (0.009)	0.935 (0.018)	0.060 (0.000)	0.240 (0.011)	290.6 (429.3)
SepThreshold	0.663 (0.043)	0.192 (0.012)	0.666 (0.042)	0.173 (0.012)	0.697 (0.048)	0.115 (0.011)	0.254 (0.029)	585.6 (569.6)
proposed	0.928 (0.071)	0.672 (0.061)	0.937 (0.069)	0.665 (0.045)	0.864 (0.068)	0.461 (0.044)	0.751 (0.053)	–
Scenario 2	$p = 40$							
GLasso	0.785 (0.094)	0.501 (0.042)	0.813 (0.057)	0.531 (0.064)	0.774 (0.107)	0.154 (0.021)	0.544 (0.034)	17.7 (12.5)
SepLasso	0.722 (0.086)	0.436 (0.016)	0.738 (0.077)	0.461 (0.015)	0.664 (0.108)	0.282 (0.018)	0.517 (0.094)	91.8 (9.3)
FGL	0.820 (0.103)	0.590 (0.010)	0.804 (0.083)	0.576 (0.038)	0.813 (0.048)	0.193 (0.030)	0.585 (0.045)	0.8 (0.5)
GGL	0.774 (0.043)	0.560 (0.014)	0.754 (0.048)	0.536 (0.031)	0.872 (0.059)	0.214 (0.027)	0.560 (0.021)	0.4 (0.3)
SSGL	0.793 (0.069)	0.323 (0.035)	0.864 (0.064)	0.313 (0.52)	0.758 (0.099)	0.356 (0.029)	0.442 (0.033)	132.4 (10.4)
SepBoost	0.953 (0.030)	0.231 (0.017)	0.941 (0.026)	0.226 (0.016)	0.993 (0.015)	0.061 (0.006)	0.283 (0.015)	32.4 (44.5)
SepThreshold	0.926 (0.018)	0.278 (0.014)	0.930 (0.032)	0.273 (0.013)	1.000 (0.000)	0.120 (0.001)	0.312 (0.053)	117.0 (99.3)
proposed	0.714 (0.063)	0.697 (0.066)	0.684 (0.062)	0.643 (0.056)	0.844 (0.084)	0.261 (0.059)	0.607 (0.043)	–

(Continues)

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TABLE B1 (Continued)

Method	TPR1	TDR1	TPR2	TDR2	TPR3	TDR3	MCC	N_VIO
	$p = 60$							
GLasso	0.797 (0.033)	0.487 (0.023)	0.834 (0.028)	0.518 (0.037)	0.764 (0.108)	0.151 (0.030)	0.533 (0.031)	32.3 (27.0)
SepLasso	0.702 (0.039)	0.361 (0.011)	0.707 (0.040)	0.376 (0.030)	0.650 (0.056)	0.220 (0.005)	0.452 (0.084)	144.0 (38.4)
FGL	0.813 (0.027)	0.561 (0.025)	0.805 (0.045)	0.535 (0.036)	0.847 (0.050)	0.185 (0.012)	0.575 (0.030)	6.1 (2.2)
GGL	0.800 (0.065)	0.533 (0.044)	0.788 (0.079)	0.524 (0.042)	0.867 (0.123)	0.195 (0.028)	0.538 (0.040)	7.0 (3.2)
SSGL	0.653 (0.053)	0.357 (0.047)	0.631 (0.054)	0.342 (0.071)	0.650 (0.043)	0.267 (0.033)	0.397 (0.042)	224.5 (96.0)
SepBoost	0.895 (0.028)	0.183 (0.010)	0.887 (0.021)	0.174 (0.012)	0.969 (0.034)	0.048 (0.003)	0.250 (0.017)	91.3 (146.5)
SepThreshold	0.819 (0.049)	0.207 (0.014)	0.789 (0.036)	0.205 (0.014)	0.884 (0.055)	0.075 (0.006)	0.246 (0.053)	262.7 (248.4)
proposed	0.744 (0.076)	0.602 (0.074)	0.693 (0.081)	0.641 (0.060)	0.808 (0.070)	0.253 (0.056)	0.588 (0.079)	–
	$p = 100$							
GLasso	0.778 (0.035)	0.503 (0.034)	0.775 (0.039)	0.497 (0.027)	0.776 (0.060)	0.157 (0.013)	0.493 (0.028)	57.1 (46.6)
SepLasso	0.649 (0.022)	0.288 (0.004)	0.672 (0.020)	0.298 (0.018)	0.593 (0.094)	0.165 (0.016)	0.384 (0.078)	227.5 (28.2)
FGL	0.800 (0.044)	0.528 (0.056)	0.766 (0.044)	0.502 (0.042)	0.808 (0.073)	0.169 (0.024)	0.557 (0.061)	17.1 (5.0)
GGL	0.772 (0.013)	0.470 (0.025)	0.781 (0.037)	0.474 (0.036)	0.838 (0.072)	0.175 (0.019)	0.487 (0.029)	15.5 (4.7)
SSGL	0.562 (0.058)	0.453 (0.102)	0.529 (0.028)	0.435 (0.103)	0.576 (0.056)	0.255 (0.061)	0.377 (0.042)	397.2 (189.3)
SepBoost	0.757 (0.023)	0.164 (0.007)	0.767 (0.015)	0.165 (0.006)	0.914 (0.039)	0.044 (0.003)	0.229 (0.012)	292.7 (441.0)
SepThreshold	0.650 (0.044)	0.137 (0.013)	0.638 (0.035)	0.127 (0.014)	0.685 (0.066)	0.027 (0.002)	0.178 (0.026)	619.4 (602.8)
proposed	0.732 (0.051)	0.602 (0.050)	0.722 (0.047)	0.574 (0.034)	0.787 (0.052)	0.184 (0.075)	0.551 (0.038)	–
Scenario 3	$p = 40$							
GLasso	0.669 (0.061)	0.391 (0.012)	0.690 (0.073)	0.412 (0.018)	0.700 (0.109)	0.033 (0.012)	0.396 (0.018)	15.8 (14.4)
SepLasso	0.641 (0.076)	0.458 (0.029)	0.635 (0.056)	0.447 (0.022)	0.925 (0.068)	0.230 (0.003)	0.473 (0.095)	82.8 (8.2)
FGL	0.713 (0.048)	0.442 (0.018)	0.746 (0.068)	0.464 (0.018)	0.333 (0.088)	0.017 (0.006)	0.428 (0.026)	0.8 (1.2)
GGL	0.813 (0.010)	0.489 (0.062)	0.795 (0.009)	0.446 (0.075)	0.771 (0.029)	0.160 (0.021)	0.487 (0.039)	0.6 (1.1)
SSGL	0.710 (0.049)	0.280 (0.056)	0.733 (0.056)	0.278 (0.051)	0.875 (0.056)	0.149 (0.061)	0.386 (0.037)	97.9 (15.6)
SepBoost	0.960 (0.028)	0.225 (0.013)	0.955 (0.017)	0.218 (0.009)	0.983 (0.035)	0.036 (0.002)	0.278 (0.027)	30.7 (45.7)
SepThreshold	0.901 (0.035)	0.274 (0.016)	0.924 (0.027)	0.245 (0.005)	1.000 (0.000)	0.117 (0.004)	0.263 (0.048)	120.1 (110.2)
proposed	0.679 (0.058)	0.533 (0.081)	0.643 (0.062)	0.545 (0.073)	0.619 (0.079)	0.496 (0.058)	0.576 (0.062)	–
	$p = 60$							
GLasso	0.607 (0.058)	0.356 (0.029)	0.614 (0.028)	0.374 (0.014)	0.533 (0.104)	0.023 (0.006)	0.360 (0.014)	26.2 (19.3)
SepLasso	0.562 (0.032)	0.373 (0.005)	0.559 (0.043)	0.379 (0.020)	0.943 (0.108)	0.178 (0.003)	0.404 (0.076)	129.3 (24.6)
FGL	0.576 (0.020)	0.414 (0.017)	0.606 (0.019)	0.420 (0.016)	0.444 (0.093)	0.022 (0.010)	0.380 (0.012)	5.3 (2.7)
GGL	0.837 (0.042)	0.368 (0.027)	0.855 (0.056)	0.372 (0.021)	0.845 (0.068)	0.055 (0.013)	0.453 (0.025)	4.9 (2.3)
SSGL	0.608 (0.047)	0.309 (0.074)	0.578 (0.047)	0.348 (0.067)	0.750 (0.133)	0.108 (0.030)	0.353 (0.038)	204.6 (89.2)
SepBoost	0.881 (0.029)	0.184 (0.016)	0.881 (0.032)	0.186 (0.009)	0.978 (0.039)	0.028 (0.002)	0.249 (0.027)	100.2 (151.3)
SepThreshold	0.809 (0.035)	0.213 (0.016)	0.817 (0.038)	0.215 (0.009)	0.967 (0.058)	0.105 (0.010)	0.228 (0.021)	250.6 (228.6)
proposed	0.582 (0.079)	0.518 (0.077)	0.571 (0.067)	0.526 (0.068)	0.685 (0.042)	0.276 (0.079)	0.543 (0.055)	–
	$p = 100$							
GLasso	0.508 (0.038)	0.395 (0.047)	0.528 (0.056)	0.386 (0.060)	0.467 (0.108)	0.022 (0.012)	0.353 (0.029)	39.0 (29.6)
SepLasso	0.462 (0.025)	0.306 (0.008)	0.459 (0.022)	0.319 (0.019)	0.810 (0.114)	0.125 (0.002)	0.330 (0.071)	234.0 (19.3)
FGL	0.520 (0.016)	0.384 (0.032)	0.502 (0.018)	0.382 (0.035)	0.367 (0.106)	0.045 (0.016)	0.343 (0.029)	12.8 (4.9)
GGL	0.809 (0.055)	0.396 (0.027)	0.791 (0.046)	0.393 (0.055)	0.803 (0.067)	0.057 (0.012)	0.435 (0.031)	11.3 (3.6)
SSGL	0.585 (0.034)	0.330 (0.085)	0.552 (0.030)	0.257 (0.067)	0.600 (0.066)	0.171 (0.017)	0.317 (0.023)	375.2.6 (205.7)
SepBoost	0.768 (0.031)	0.155 (0.009)	0.762 (0.036)	0.153 (0.009)	0.927 (0.049)	0.030 (0.002)	0.234 (0.022)	293.7 (445.5)
SepThreshold	0.644 (0.048)	0.135 (0.012)	0.632 (0.043)	0.135 (0.012)	0.705 (0.119)	0.082 (0.007)	0.177 (0.012)	639.1 (645.9)
proposed	0.533 (0.068)	0.562 (0.076)	0.495 (0.059)	0.511 (0.072)	0.644 (0.043)	0.182 (0.067)	0.505 (0.048)	–

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TABLE B2 Simulation results for the nearest-neighbor networks with high signal strengths. In each cell, mean (sd) based on 200 replicates

Method	TPR1	TDR1	TPR2	TDR2	TPR3	TDR3	MCC	N_VIO
Scenario 1	$p = 40$							
GLasso	0.443 (0.090)	0.978 (0.038)	0.436 (0.073)	0.967 (0.058)	0.508 (0.052)	0.661 (0.010)	0.616 (0.048)	15.2 (10.7)
SepLasso	0.705 (0.041)	0.572 (0.074)	0.695 (0.063)	0.569 (0.082)	0.611 (0.065)	0.403 (0.032)	0.618 (0.097)	73.6 (17.2)
FGL	0.665 (0.096)	0.912 (0.023)	0.662 (0.077)	0.935 (0.017)	0.880 (0.106)	0.531 (0.032)	0.729 (0.042)	0.0 (0.0)
GGL	0.611 (0.083)	0.850 (0.055)	0.622 (0.073)	0.868 (0.047)	0.869 (0.031)	0.500 (0.026)	0.698 (0.041)	0.0 (0.0)
SSGL	0.711 (0.037)	0.382 (0.058)	0.733 (0.031)	0.347 (0.057)	0.737 (0.046)	0.358 (0.029)	0.427 (0.023)	89.2 (16.5)
SepBoost	0.901 (0.022)	0.303 (0.026)	0.887 (0.036)	0.300 (0.021)	0.980 (0.023)	0.104 (0.004)	0.257 (0.016)	33.2 (50.9)
SepThreshold	0.868 (0.041)	0.320 (0.024)	0.876 (0.032)	0.326 (0.024)	0.990 (0.016)	0.248 (0.013)	0.350 (0.062)	88.3 (52.4)
proposed	0.605 (0.048)	0.903 (0.055)	0.617 (0.045)	0.916 (0.054)	0.823 (0.065)	0.530 (0.037)	0.679 (0.069)	–
	$p = 60$							
GLasso	0.169 (0.066)	0.957 (0.037)	0.185 (0.060)	0.962 (0.039)	0.455 (0.053)	0.604 (0.040)	0.412 (0.064)	36.5 (24.2)
SepLasso	0.730 (0.047)	0.491 (0.031)	0.724 (0.064)	0.461 (0.038)	0.673 (0.041)	0.347 (0.030)	0.469 (0.070)	130.0 (29.5)
FGL	0.493 (0.060)	0.843 (0.046)	0.502 (0.071)	0.854 (0.062)	0.885 (0.053)	0.540 (0.063)	0.626 (0.011)	4.8 (2.9)
GGL	0.501 (0.084)	0.885 (0.042)	0.507 (0.086)	0.894 (0.050)	0.888 (0.048)	0.551 (0.045)	0.643 (0.058)	3.9 (2.3)
SSGL	0.600 (0.050)	0.411 (0.102)	0.582 (0.036)	0.383 (0.098)	0.573 (0.056)	0.357 (0.063)	0.369 (0.058)	234.6 (105.5)
SepBoost	0.783 (0.039)	0.275 (0.022)	0.771 (0.032)	0.274 (0.024)	0.971 (0.029)	0.081 (0.005)	0.232 (0.015)	95.7 (147.4)
SepThreshold	0.774 (0.028)	0.259 (0.023)	0.770 (0.029)	0.246 (0.017)	0.873 (0.036)	0.139 (0.013)	0.269 (0.047)	266.1 (220.4)
proposed	0.658 (0.055)	0.708 (0.037)	0.673 (0.070)	0.717 (0.041)	0.824 (0.057)	0.603 (0.041)	0.614 (0.061)	–
	$p = 100$							
GLasso	0.192 (0.041)	0.949 (0.033)	0.182 (0.033)	0.978 (0.028)	0.316 (0.041)	0.633 (0.042)	0.396 (0.038)	57.9 (43.6)
SepLasso	0.663 (0.021)	0.385 (0.027)	0.689 (0.026)	0.387 (0.032)	0.652 (0.031)	0.262 (0.012)	0.483 (0.058)	266.1 (45.6)
FGL	0.396 (0.032)	0.872 (0.033)	0.395 (0.039)	0.882 (0.029)	0.859 (0.053)	0.530 (0.036)	0.575 (0.029)	15.4 (7.5)
GGL	0.359 (0.045)	0.853 (0.026)	0.379 (0.022)	0.857 (0.014)	0.856 (0.064)	0.518 (0.031)	0.559 (0.034)	12.1 (6.5)
SSGL	0.582 (0.103)	0.312 (0.052)	0.581 (0.096)	0.331 (0.054)	0.762 (0.086)	0.116 (0.031)	0.297 (0.046)	427.1 (179.2)
SepBoost	0.607 (0.011)	0.254 (0.012)	0.596 (0.029)	0.243 (0.012)	0.950 (0.032)	0.062 (0.003)	0.212 (0.017)	288.9 (461.4)
SepThreshold	0.672 (0.037)	0.192 (0.019)	0.662 (0.031)	0.191 (0.016)	0.743 (0.045)	0.116 (0.011)	0.182 (0.023)	601.3 (676.7)
proposed	0.391 (0.053)	0.898 (0.040)	0.358 (0.057)	0.907 (0.049)	0.722 (0.068)	0.497 (0.044)	0.543 (0.037)	–
Scenario 2	$p = 40$							
GLasso	0.324 (0.070)	0.978 (0.028)	0.315 (0.072)	0.965 (0.031)	0.871 (0.048)	0.664 (0.030)	0.572 (0.064)	17.3 (10.9)
SepLasso	0.739 (0.079)	0.418 (0.021)	0.674 (0.069)	0.406 (0.015)	0.672 (0.051)	0.275 (0.016)	0.483 (0.076)	87.3 (25.8)
FGL	0.829 (0.049)	0.583 (0.066)	0.812 (0.059)	0.575 (0.050)	0.863 (0.098)	0.196 (0.023)	0.588 (0.060)	0.2 (0.6)
GGL	0.804(0.040)	0.489 (0.039)	0.799 (0.049)	0.489 (0.039)	0.860 (0.076)	0.171 (0.017)	0.547 (0.039)	0.2 (0.6)
SSGL	0.592 (0.033)	0.283 (0.052)	0.623 (0.034)	0.282 (0.047)	0.708 (0.067)	0.252 (0.029)	0.367 (0.046)	89.0 (14.2)
SepBoost	0.900 (0.034)	0.275 (0.015)	0.890 (0.024)	0.276 (0.015)	0.950 (0.030)	0.063 (0.003)	0.233 (0.025)	31.4 (48.6)
SepThreshold	0.892 (0.044)	0.286 (0.027)	0.907 (0.038)	0.288 (0.017)	1.000 (0.000)	0.121 (0.012)	0.284 (0.052)	105.8 (80.5)
proposed	0.744 (0.073)	0.670 (0.088)	0.768 (0.079)	0.663 (0.080)	0.846 (0.087)	0.242 (0.040)	0.618 (0.065)	–
	$p = 60$							
GLasso	0.325 (0.045)	0.968 (0.033)	0.326 (0.058)	0.955 (0.048)	0.819 (0.031)	0.583 (0.059)	0.551 (0.069)	35.5 (27.4)
SepLasso	0.725 (0.028)	0.381 (0.015)	0.720 (0.049)	0.353 (0.019)	0.758 (0.077)	0.228 (0.011)	0.464 (0.071)	158.2 (19.6)
FGL	0.773 (0.056)	0.568 (0.022)	0.762 (0.062)	0.552 (0.036)	0.839 (0.043)	0.198 (0.012)	0.567 (0.023)	7.2 (5.1)
GGL	0.805 (0.046)	0.479 (0.045)	0.807 (0.081)	0.481 (0.035)	0.831 (0.116)	0.154 (0.023)	0.531 (0.045)	5.5 (4.5)
SSGL	0.562 (0.052)	0.264 (0.052)	0.557 (0.053)	0.317 (0.057)	0.786 (0.098)	0.131 (0.031)	0.324 (0.032)	195.1 (81.0)
SepBoost	0.810 (0.013)	0.218 (0.012)	0.818 (0.031)	0.234 (0.012)	0.986 (0.020)	0.068 (0.003)	0.213 (0.017)	97.8 (155.1)
SepThreshold	0.780 (0.022)	0.233 (0.011)	0.790 (0.021)	0.224 (0.017)	0.915 (0.052)	0.118 (0.012)	0.229 (0.031)	245.2 (204.0)
proposed	0.758 (0.085)	0.639 (0.066)	0.701 (0.062)	0.572 (0.053)	0.830 (0.064)	0.234 (0.046)	0.587 (0.063)	–

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TABLE B2 (Continued)

Method	TPR1	TDR1	TPR2	TDR2	TPR3	TDR3	MCC	N_VIO
	$p = 100$							
GLasso	0.333 (0.037)	0.956 (0.039)	0.335 (0.031)	0.974 (0.025)	0.743 (0.035)	0.643 (0.052)	0.530 (0.024)	70.3 (47.4)
SepLasso	0.653 (0.041)	0.294 (0.011)	0.625 (0.041)	0.281 (0.017)	0.593 (0.095)	0.159 (0.011)	0.373 (0.077)	261.0 (39.1)
FGL	0.774 (0.035)	0.561 (0.021)	0.769 (0.039)	0.561 (0.027)	0.817 (0.064)	0.177 (0.019)	0.545 (0.022)	15.6 (7.1)
GGL	0.779 (0.032)	0.513 (0.043)	0.766 (0.033)	0.506 (0.032)	0.800 (0.078)	0.164 (0.007)	0.528 (0.020)	13.8 (6.7)
SSGL	0.456 (0.041)	0.309 (0.042)	0.455 (0.036)	0.308 (0.047)	0.621 (0.070)	0.155 (0.038)	0.295 (0.032)	322.3 (165.3)
SepBoost	0.664 (0.017)	0.188 (0.020)	0.654 (0.026)	0.187 (0.016)	0.971 (0.025)	0.049(0.003)	0.189 (0.013)	288.6 (449.9)
SepThreshold	0.642(0.034)	0.149(0.013)	0.661(0.042)	0.151(0.013)	0.721(0.085)	0.028 (0.004)	0.162 (0.010)	611.6 (611.3)
proposed	0.778 (0.073)	0.506 (0.050)	0.789 (0.064)	0.462 (0.059)	0.906 (0.055)	0.155 (0.035)	0.546 (0.057)	–
Scenario 3	$p = 40$							
GLasso	0.353 (0.098)	0.617 (0.076)	0.334 (0.113)	0.552 (0.075)	0.917 (0.044)	0.094 (0.006)	0.386 (0.035)	14.4 (7.7)
SepLasso	0.591 (0.085)	0.332 (0.012)	0.575 (0.077)	0.333 (0.010)	0.975 (0.055)	0.132 (0.004)	0.353 (0.073)	95.1 (9.5)
FGL	0.628 (0.095)	0.430 (0.034)	0.648 (0.060)	0.456 (0.058)	0.417 (0.044)	0.023 (0.009)	0.399 (0.013)	0.1 (0.4)
GGL	0.630 (0.033)	0.431 (0.050)	0.588 (0.038)	0.406 (0.029)	0.750 (0.053)	0.039 (0.018)	0.380 (0.021)	0.0 (0.0)
SSGL	0.584 (0.054)	0.245 (0.044)	0.618 (0.041)	0.246 (0.059)	0.875 (0.067)	0.153 (0.029)	0.335 (0.032)	77.9 (9.9)
SepBoost	0.939 (0.032)	0.240 (0.009)	0.928 (0.030)	0.218 (0.009)	0.983 (0.035)	0.047 (0.003)	0.222 (0.023)	32.1 (44.6)
SepThreshold	0.901 (0.046)	0.275 (0.025)	0.924 (0.029)	0.266 (0.017)	1.000 (0.000)	0.096 (0.007)	0.232 (0.043)	123.7 (108.1)
proposed	0.634 (0.061)	0.505 (0.059)	0.610 (0.067)	0.485 (0.066)	0.832 (0.047)	0.316 (0.062)	0.539 (0.027)	–
	$p = 60$							
GLasso	0.358 (0.106)	0.548 (0.052)	0.208 (0.077)	0.473 (0.074)	0.778 (0.104)	0.067 (0.058)	0.367 (0.031)	28.6 (19.4)
SepLasso	0.553 (0.027)	0.279 (0.017)	0.545 (0.052)	0.276 (0.019)	0.900 (0.108)	0.077 (0.004)	0.300 (0.079)	149.2 (24.9)
FGL	0.549 (0.032)	0.424 (0.010)	0.544 (0.040)	0.430 (0.026)	0.389 (0.055)	0.021 (0.015)	0.368 (0.018)	3.6 (2.2)
GGL	0.574 (0.028)	0.392 (0.020)	0.565 (0.048)	0.384 (0.018)	0.667 (0.034)	0.031 (0.017)	0.362 (0.033)	3.3 (1.9)
SSGL	0.509 (0.037)	0.300 (0.051)	0.509 (0.052)	0.288 (0.048)	0.817 (0.041)	0.149 (0.012)	0.301 (0.034)	124.8 (75.5)
SepBoost	0.870 (0.026)	0.199 (0.016)	0.866 (0.036)	0.209 (0.012)	0.972 (0.039)	0.031 (0.003)	0.198 (0.017)	97.9 (155.5)
SepThreshold	0.801 (0.031)	0.207 (0.013)	0.795 (0.041)	0.196 (0.009)	0.983 (0.053)	0.090 (0.007)	0.181 (0.023)	303.9 (271.8)
proposed	0.565 (0.052)	0.583 (0.061)	0.508 (0.042)	0.504 (0.065)	0.676 (0.063)	0.216 (0.042)	0.506 (0.025)	–
	$p = 100$							
GLasso	0.311 (0.116)	0.532 (0.060)	0.273 (0.124)	0.453 (0.088)	0.680 (0.058)	0.036 (0.026)	0.319 (0.025)	46.8 (32.0)
SepLasso	0.402 (0.023)	0.211 (0.016)	0.397 (0.041)	0.200 (0.010)	0.910 (0.089)	0.028 (0.003)	0.217 (0.047)	247.3 (55.6)
FGL	0.446 (0.031)	0.407 (0.023)	0.443 (0.020)	0.408 (0.030)	0.609 (0.050)	0.030 (0.006)	0.335 (0.024)	10.2 (7.7)
GGL	0.468 (0.021)	0.363 (0.033)	0.490 (0.028)	0.373 (0.028)	0.534 (0.048)	0.022 (0.008)	0.325 (0.017)	10.3 (7.3)
SSGL	0.395 (0.037)	0.269 (0.051)	0.374 (0.064)	0.251 (0.029)	0.600 (0.118)	0.098 (0.014)	0.278 (0.023)	393.0 (135.6)
SepBoost	0.729 (0.030)	0.166 (0.015)	0.737 (0.026)	0.166 (0.008)	0.957 (0.055)	0.024 (0.003)	0.183 (0.018)	291.8 (433.9)
SepThreshold	0.635 (0.031)	0.136 (0.012)	0.623 (0.053)	0.136 (0.012)	0.625 (0.127)	0.022 (0.005)	0.161 (0.016)	623 (616.4)
proposed	0.682 (0.068)	0.492 (0.035)	0.663 (0.061)	0.463 (0.040)	0.650 (0.026)	0.112 (0.038)	0.465 (0.033)	–

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TABLE B3 Simulation results for the banded networks with low signal strengths. In each cell, mean (sd) based on 200 replicates

Method	TPR1	TDR1	TPR2	TDR2	TPR3	TDR3	MCC	N_VIO
Scenario 1	$p = 40$							
GLasso	0.536 (0.212)	0.972 (0.032)	0.519 (0.202)	0.929 (0.060)	0.609 (0.161)	0.318 (0.053)	0.604 (0.126)	15.7 (7.4)
SepLasso	0.705 (0.056)	0.323 (0.037)	0.737 (0.060)	0.375 (0.053)	0.973 (0.047)	0.170 (0.014)	0.427 (0.068)	79.0 (17.4)
FGL	0.878 (0.044)	0.973 (0.019)	0.881 (0.053)	0.989 (0.025)	0.975 (0.024)	0.324 (0.011)	0.820 (0.013)	0.0 (0.0)
GGL	0.911 (0.034)	0.889 (0.029)	0.919 (0.031)	0.876 (0.051)	0.986 (0.017)	0.289 (0.012)	0.787 (0.010)	0.0 (0.0)
SSGL	0.633 (0.030)	0.455 (0.099)	0.679 (0.053)	0.410 (0.090)	1.000 (0.000)	0.233 (0.055)	0.460 (0.051)	91.6 (34.3)
SepBoost	0.952 (0.026)	0.241 (0.021)	0.953 (0.025)	0.253 (0.020)	0.984 (0.025)	0.123 (0.012)	0.357 (0.027)	33.3 (44.5)
SepThreshold	0.880 (0.033)	0.310 (0.011)	0.853 (0.036)	0.303 (0.019)	1.000 (0.000)	0.111 (0.012)	0.337 (0.052)	134.7 (69.4)
proposed	0.951 (0.061)	0.897 (0.042)	0.986 (0.064)	0.807 (0.045)	0.958 (0.031)	0.279 (0.028)	0.794 (0.047)	–
	$p = 60$							
GLasso	0.575 (0.145)	0.729 (0.012)	0.577 (0.148)	0.736 (0.054)	0.695 (0.153)	0.227 (0.042)	0.546 (0.163)	27.7 (13.9)
SepLasso	0.711 (0.018)	0.306 (0.051)	0.716 (0.033)	0.297 (0.011)	0.957 (0.038)	0.126 (0.019)	0.405 (0.053)	133.7 (17.8)
FGL	0.901 (0.053)	0.917 (0.014)	0.891 (0.038)	0.886 (0.020)	0.926 (0.024)	0.273 (0.030)	0.793 (0.032)	3.6 (1.7)
GGL	0.891 (0.051)	0.803 (0.038)	0.887 (0.042)	0.902 (0.026)	0.973 (0.039)	0.295 (0.018)	0.732 (0.026)	3.7 (1.7)
SSGL	0.640 (0.046)	0.341 (0.041)	0.634 (0.051)	0.339 (0.039)	1.000 (0.000)	0.173 (0.024)	0.415 (0.029)	187.3 (68.5)
SepBoost	0.870 (0.034)	0.187 (0.010)	0.866 (0.039)	0.188 (0.013)	0.960 (0.032)	0.095 (0.012)	0.307 (0.024)	98.0 (165.6)
SepThreshold	0.783 (0.020)	0.245 (0.016)	0.776 (0.034)	0.251 (0.020)	0.914 (0.082)	0.115 (0.009)	0.310 (0.038)	312.5 (206.2)
proposed	0.934 (0.062)	0.792 (0.049)	0.950 (0.066)	0.803 (0.048)	0.963 (0.014)	0.255 (0.058)	0.759 (0.051)	–
	$p = 100$							
GLasso	0.387 (0.110)	0.927 (0.072)	0.398 (0.131)	0.913 (0.084)	0.467 (0.140)	0.320 (0.130)	0.502 (0.021)	47.2 (19.6)
SepLasso	0.705 (0.043)	0.261 (0.027)	0.704 (0.030)	0.275 (0.050)	0.924 (0.034)	0.121 (0.012)	0.391 (0.049)	242.1 (22.0)
FGL	0.912 (0.042)	0.830 (0.023)	0.909 (0.043)	0.804 (0.020)	0.959 (0.028)	0.268 (0.008)	0.733 (0.016)	11.9 (4.1)
GGL	0.873 (0.044)	0.788 (0.009)	0.880 (0.032)	0.779 (0.015)	0.926 (0.012)	0.265 (0.026)	0.715 (0.015)	12.6 (5.2)
SSGL	0.584 (0.078)	0.281 (0.035)	0.544 (0.063)	0.265 (0.033)	1.000 (0.000)	0.111 (0.019)	0.365 (0.033)	340.8 (177.1)
SepBoost	0.756 (0.025)	0.179 (0.013)	0.744 (0.024)	0.168 (0.009)	0.947 (0.028)	0.077 (0.006)	0.286 (0.018)	290.1 (445.7)
SepThreshold	0.664 (0.041)	0.176 (0.015)	0.655 (0.037)	0.175 (0.015)	0.775 (0.102)	0.108 (0.008)	0.271 (0.012)	602.1 (588.2)
proposed	0.823 (0.032)	0.811 (0.056)	0.835 (0.034)	0.802 (0.058)	0.833 (0.017)	0.183 (0.052)	0.712 (0.036)	–
Scenario 2	$p = 40$							
GLasso	0.344 (0.112)	0.961 (0.045)	0.348 (0.114)	0.991 (0.029)	0.887 (0.181)	0.418 (0.023)	0.543 (0.052)	19.0 (13.1)
SepLasso	0.740 (0.025)	0.263 (0.029)	0.741 (0.029)	0.260 (0.043)	0.968 (0.032)	0.077 (0.003)	0.348 (0.072)	87.2 (10.5)
FGL	0.827 (0.040)	0.581 (0.025)	0.806 (0.036)	0.610 (0.024)	0.657 (0.057)	0.096 (0.022)	0.568 (0.025)	0.2 (0.6)
GGL	0.789 (0.029)	0.506 (0.027)	0.777 (0.045)	0.488 (0.037)	0.550 (0.041)	0.067 (0.020)	0.511 (0.036)	0.0 (0.0)
SSGL	0.607 (0.046)	0.388 (0.075)	0.552 (0.042)	0.395 (0.074)	1.000 (0.000)	0.172 (0.032)	0.423 (0.042)	84.2 (30.1)
SepBoost	0.946 (0.019)	0.218 (0.015)	0.952 (0.018)	0.222 (0.016)	0.988 (0.026)	0.090 (0.005)	0.309 (0.027)	30.8 (47.0)
SepThreshold	0.869 (0.030)	0.275 (0.010)	0.891 (0.039)	0.285 (0.015)	1.000 (0.000)	0.100 (0.008)	0.310 (0.043)	134.7 (69.4)
proposed	0.527 (0.069)	0.780 (0.061)	0.512 (0.061)	0.788 (0.048)	0.688 (0.041)	0.478 (0.032)	0.612 (0.048)	–
	$p = 60$							
GLasso	0.362 (0.068)	0.968 (0.046)	0.358 (0.077)	0.946 (0.062)	0.833 (0.184)	0.406 (0.014)	0.532 (0.084)	39.1 (28.8)
SepLasso	0.722 (0.050)	0.225 (0.014)	0.717 (0.040)	0.245 (0.024)	0.967 (0.031)	0.076 (0.004)	0.341 (0.061)	129.2 (21.6)
FGL	0.803 (0.029)	0.570 (0.023)	0.783 (0.039)	0.547 (0.020)	0.676 (0.043)	0.093 (0.016)	0.547 (0.023)	6.9 (4.0)
GGL	0.777 (0.040)	0.488 (0.034)	0.781 (0.039)	0.478 (0.035)	0.425 (0.052)	0.052 (0.021)	0.476 (0.037)	6.5 (3.4)
SSGL	0.585 (0.050)	0.307 (0.048)	0.552 (0.044)	0.316 (0.051)	1.000 (0.000)	0.102 (0.019)	0.387 (0.028)	229.8 (91.3)
SepBoost	0.896 (0.020)	0.185 (0.012)	0.900 (0.021)	0.181 (0.016)	0.950 (0.045)	0.060 (0.007)	0.286 (0.021)	95.6 (144.6)
SepThreshold	0.804 (0.025)	0.214 (0.013)	0.766 (0.041)	0.228 (0.018)	0.954 (0.054)	0.073 (0.008)	0.270 (0.028)	322.3 (245.5)
proposed	0.600 (0.052)	0.605 (0.056)	0.597 (0.054)	0.733 (0.041)	0.292 (0.043)	0.412 (0.045)	0.582 (0.041)	–

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TABLE B3 (Continued)

Method	TPR1	TDR1	TPR2	TDR2	TPR3	TDR3	MCC	N_VIO
	$p = 100$							
GLasso	0.290 (0.110)	0.906 (0.072)	0.311 (0.131)	0.909 (0.084)	0.650 (0.053)	0.397 (0.010)	0.498 (0.019)	86.2 (47.7)
SepLasso	0.712 (0.026)	0.197 (0.014)	0.692 (0.032)	0.197 (0.009)	0.949 (0.032)	0.063 (0.002)	0.315 (0.053)	275.7 (13.0)
FGL	0.782 (0.073)	0.555 (0.021)	0.742 (0.056)	0.533 (0.058)	0.550 (0.168)	0.078 (0.024)	0.513 (0.032)	16.9 (9.1)
GGL	0.733 (0.028)	0.423 (0.017)	0.825(0.026)	0.500 (0.016)	0.417 (0.053)	0.048 (0.010)	0.446 (0.019)	15.7 (8.9)
SSGL	0.562 (0.066)	0.283 (0.073)	0.547 (0.064)	0.395 (0.068)	1.000 (0.000)	0.087 (0.031)	0.353 (0.038)	448.9 (222.1)
SepBoost	0.782 (0.038)	0.147 (0.012)	0.768 (0.027)	0.147 (0.010)	0.884 (0.071)	0.049 (0.003)	0.260 (0.016)	292.8 (441.8)
SepThreshold	0.658 (0.035)	0.159 (0.015)	0.664 (0.028)	0.160 (0.014)	0.713 (0.054)	0.035 (0.008)	0.227 (0.010)	580.2 (563.6)
proposed	0.758 (0.048)	0.526 (0.058)	0.739 (0.051)	0.481 (0.044)	0.192 (0.037)	0.459 (0.049)	0.536 (0.037)	–
Scenario 3	$p = 40$							
GLasso	0.409 (0.067)	0.628 (0.099)	0.295 (0.051)	0.571 (0.082)	0.987 (0.013)	0.173 (0.091)	0.378 (0.031)	12.7 (7.3)
SepLasso	0.768 (0.034)	0.277 (0.038)	0.746 (0.021)	0.253 (0.011)	0.973 (0.024)	0.036 (0.003)	0.326 (0.111)	83.2 (17.5)
FGL	0.821 (0.031)	0.461 (0.033)	0.811 (0.035)	0.449 (0.034)	0.982 (0.021)	0.055 (0.007)	0.505 (0.019)	0.0 (0.0)
GGL	0.860 (0.038)	0.382 (0.025)	0.831 (0.058)	0.369 (0.019)	0.983 (0.017)	0.045 (0.004)	0.445 (0.015)	0.0 (0.0)
SSGL	0.625 (0.036)	0.421 (0.075)	0.600 (0.050)	0.437 (0.072)	1.000 (0.000)	0.130 (0.016)	0.422 (0.042)	62.5 (25.0)
SepBoost	0.967 (0.037)	0.228 (0.019)	0.944 (0.031)	0.212 (0.009)	0.975 (0.040)	0.082 (0.004)	0.279 (0.029)	29.8 (46.8)
SepThreshold	0.907 (0.035)	0.264 (0.015)	0.911 (0.028)	0.252 (0.014)	1.000 (0.000)	0.060 (0.006)	0.268 (0.041)	127.4 (107.7)
proposed	0.783 (0.059)	0.569 (0.039)	0.728 (0.044)	0.559 (0.066)	0.987 (0.051)	0.235 (0.070)	0.585 (0.033)	–
	$p = 60$							
GLasso	0.350 (0.069)	0.559 (0.106)	0.338 (0.093)	0.545 (0.092)	0.973 (0.016)	0.125 (0.050)	0.349 (0.065)	23.2 (14.4)
SepLasso	0.749 (0.013)	0.227 (0.016)	0.741 (0.039)	0.230 (0.023)	0.966 (0.026)	0.034 (0.002)	0.312 (0.100)	119.7 (30.7)
FGL	0.813 (0.033)	0.408 (0.039)	0.835 (0.034)	0.415 (0.031)	0.966 (0.024)	0.052 (0.005)	0.467 (0.022)	4.0 (2.9)
GGL	0.857 (0.042)	0.353 (0.020)	0.843 (0.046)	0.355 (0.014)	0.984 (0.016)	0.042 (0.002)	0.422 (0.018)	4.4 (3.3)
SSGL	0.525 (0.036)	0.421 (0.075)	0.550 (0.052)	0.417 (0.066)	1.000 (0.000)	0.091 (0.016)	0.392 (0.040)	175.5 (73.3)
SepBoost	0.905 (0.025)	0.178 (0.011)	0.895 (0.034)	0.179 (0.015)	0.992 (0.026)	0.027 (0.002)	0.256 (0.023)	98.1 (169.6)
SepThreshold	0.780 (0.038)	0.216 (0.014)	0.798 (0.032)	0.225 (0.014)	0.967 (0.056)	0.037 (0.003)	0.232 (0.026)	347.2 (289.7)
proposed	0.770 (0.045)	0.564 (0.033)	0.730 (0.042)	0.528 (0.046)	0.988 (0.026)	0.179 (0.015)	0.530 (0.028)	–
	$p = 100$							
GLasso	0.347 (0.066)	0.573 (0.109)	0.357 (0.072)	0.467 (0.083)	0.889 (0.140)	0.100 (0.130)	0.333 (0.040)	43.8 (20.9)
SepLasso	0.734 (0.025)	0.219 (0.013)	0.731 (0.013)	0.224 (0.021)	0.928 (0.045)	0.034 (0.001)	0.315 (0.101)	214.8 (13.7)
FGL	0.818 (0.016)	0.361 (0.049)	0.824 (0.026)	0.399 (0.051)	0.965 (0.017)	0.046 (0.009)	0.439 (0.032)	10.7 (5.3)
GGL	0.849 (0.032)	0.360 (0.020)	0.840 (0.033)	0.361 (0.016)	0.964 (0.024)	0.043 (0.003)	0.404 (0.021)	12.2 (7.6)
SSGL	0.444 (0.055)	0.447 (0.087)	0.467 (0.031)	0.449 (0.073)	1.000 (0.000)	0.075 (0.019)	0.340 (0.034)	300.0 (167.3)
SepBoost	0.777 (0.021)	0.147 (0.008)	0.762 (0.025)	0.147 (0.008)	0.920 (0.071)	0.024 (0.002)	0.241 (0.014)	293.2 (442.1)
SepThreshold	0.642 (0.032)	0.132 (0.010)	0.649 (0.032)	0.138 (0.014)	0.805 (0.096)	0.023 (0.002)	0.207 (0.019)	586.9 (579.2)
proposed	0.703 (0.021)	0.565 (0.033)	0.713 (0.025)	0.469 (0.032)	0.970 (0.015)	0.156 (0.026)	0.512 (0.019)	–

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TABLE B4 Simulation results for the banded networks with high signal strengths. In each cell, mean (sd) based on 200 replicates

Method	TPR1	TDR1	TPR2	TDR2	TPR3	TDR3	MCC	N_VIO
Scenario 1	$p = 40$							
GLasso	0.465 (0.256)	0.973 (0.021)	0.462 (0.254)	0.988 (0.026)	0.583 (0.261)	0.278 (0.064)	0.565 (0.126)	16.6 (8.8)
SepLasso	0.739 (0.041)	0.317 (0.041)	0.759 (0.065)	0.299 (0.032)	0.341 (0.119)	0.037 (0.008)	0.314 (0.179)	99.0 (22.8)
FGL	0.785 (0.051)	0.989 (0.025)	0.785 (0.039)	0.971(0.020)	0.267 (0.171)	0.094 (0.059)	0.689 (0.037)	0.0 (0.0)
GGL	0.801 (0.033)	0.904 (0.066)	0.789 (0.031)	0.909 (0.056)	0.267 (0.109)	0.088 (0.035)	0.661 (0.044)	0.0 (0.0)
SSGL	0.642 (0.054)	0.493 (0.104)	0.727 (0.053)	0.507 (0.090)	0.642 (0.123)	0.193 (0.016)	0.445 (0.041)	77.5 (37.9)
SepBoost	0.864 (0.025)	0.333 (0.023)	0.868 (0.029)	0.343 (0.021)	0.985 (0.020)	0.102 (0.002)	0.277 (0.014)	32.0 (48.9)
SepThreshold	0.915 (0.032)	0.290 (0.017)	0.922 (0.020)	0.295 (0.016)	1.000 (0.000)	0.122 (0.004)	0.340 (0.071)	73.9 (51.6)
proposed	0.881 (0.061)	0.895 (0.035)	0.879 (0.071)	0.872 (0.027)	0.583 (0.048)	0.171 (0.063)	0.731 (0.045)	–
	$p = 60$							
GLasso	0.416 (0.153)	0.967 (0.012)	0.413 (0.149)	0.990 (0.019)	0.479 (0.214)	0.264 (0.042)	0.526 (0.114)	33.0 (19.5)
SepLasso	0.725 (0.042)	0.263 (0.039)	0.707(0.013)	0.307 (0.051)	0.116 (0.041)	0.013 (0.003)	0.284 (0.102)	126.5 (28.5)
FGL	0.817 (0.040)	0.934 (0.016)	0.816 (0.036)	0.923 (0.015)	0.334 (0.040)	0.112 (0.033)	0.649 (0.017)	4.0 (2.9)
GGL	0.810 (0.049)	0.823 (0.020)	0.821 (0.045)	0.817 (0.022)	0.333 (0.044)	0.097 (0.025)	0.634 (0.017)	4.4 (2.9)
SSGL	0.548 (0.083)	0.444 (0.067)	0.552 (0.079)	0.433 (0.066)	0.667 (0.189)	0.114 (0.008)	0.383 (0.021)	212.9 (115.6)
SepBoost	0.756 (0.020)	0.210 (0.014)	0.739 (0.020)	0.210(0.015)	0.984 (0.016)	0.102 (0.008)	0.235 (0.014)	96.4 (149.9)
SepThreshold	0.870 (0.024)	0.229 (0.016)	0.816 (0.020)	0.228 (0.016)	0.836 (0.095)	0.097 (0.005)	0.267 (0.040)	246.1 (174.4)
proposed	0.845 (0.066)	0.826 (0.050)	0.846 (0.077)	0.807 (0.029)	0.540 (0.060)	0.151 (0.053)	0.679 (0.051)	–
	$p = 100$							
GLasso	0.383 (0.163)	0.973 (0.024)	0.392 (0.167)	0.993 (0.014)	0.358 (0.191)	0.265 (0.029)	0.521 (0.104)	59.2 (29.2)
SepLasso	0.681 (0.010)	0.286 (0.024)	0.669 (0.031)	0.292 (0.013)	0.020 (0.018)	0.002 (0.002)	0.279 (0.112)	212.3 (14.8)
FGL	0.746 (0.026)	0.870 (0.010)	0.758 (0.027)	0.868 (0.016)	0.111 (0.024)	0.037 (0.017)	0.618 (0.016)	14.9 (6.0)
GGL	0.798 (0.030)	0.776 (0.017)	0.790 (0.023)	0.776 (0.014)	0.267 (0.026)	0.075 (0.013)	0.621 (0.015)	15.9 (6.5)
SSGL	0.604 (0.101)	0.355 (0.052)	0.595 (0.129)	0.340 (0.045)	0.800 (0.164)	0.036 (0.002)	0.308 (0.028)	471.7 (292.5)
SepBoost	0.581 (0.016)	0.284 (0.009)	0.583 (0.024)	0.273 (0.015)	0.974 (0.016)	0.104 (0.008)	0.205 (0.013)	284.3 (437.4)
SepThreshold	0.646 (0.022)	0.235 (0.015)	0.646 (0.017)	0.244 (0.013)	0.708 (0.095)	0.067 (0.005)	0.187 (0.047)	609.0 (590.5)
proposed	0.694 (0.055)	0.687 (0.026)	0.688 (0.059)	0.687 (0.049)	0.473 (0.017)	0.159 (0.004)	0.612 (0.036)	–
Scenario 2	$p = 40$							
GLasso	0.398 (0.085)	0.989 (0.020)	0.397 (0.088)	0.977 (0.038)	0.896 (0.153)	0.391 (0.013)	0.574 (0.066)	23.1 (17.4)
SepLasso	0.698 (0.064)	0.221 (0.027)	0.690 (0.053)	0.229 (0.029)	0.237 (0.142)	0.015 (0.009)	0.234 (0.057)	100.2 (32.5)
FGL	0.786 (0.050)	0.573 (0.035)	0.806 (0.046)	0.584 (0.038)	0.655 (0.067)	0.091 (0.024)	0.566 (0.016)	0.0 (0.0)
GGL	0.751 (0.051)	0.499 (0.033)	0.737 (0.047)	0.492 (0.029)	0.405 (0.046)	0.052 (0.032)	0.471 (0.019)	0.0 (0.0)
SSGL	0.504 (0.043)	0.409 (0.084)	0.542 (0.051)	0.461 (0.069)	0.538 (0.119)	0.138 (0.010)	0.391 (0.034)	59.4 (30.9)
SepBoost	0.911 (0.035)	0.303 (0.016)	0.912 (0.032)	0.307 (0.018)	0.989 (0.026)	0.100 (0.004)	0.259 (0.017)	31.7 (47.7)
SepThreshold	0.924 (0.037)	0.282 (0.014)	0.920 (0.040)	0.284 (0.016)	1.000 (0.000)	0.104 (0.005)	0.273 (0.055)	94.7 (72.1)
proposed	0.786 (0.057)	0.771 (0.054)	0.762 (0.056)	0.743 (0.047)	0.367 (0.053)	0.308(0.043)	0.621 (0.038)	–
	$p = 60$							
GLasso	0.402 (0.083)	0.942 (0.031)	0.403 (0.084)	0.945 (0.034)	0.866 (0.211)	0.379 (0.044)	0.570 (0.068)	45.8 (26.6)
SepLasso	0.676 (0.023)	0.221 (0.025)	0.670 (0.035)	0.211 (0.026)	0.050 (0.034)	0.003 (0.002)	0.225 (0.075)	111.9 (18.8)
FGL	0.823 (0.043)	0.609 (0.028)	0.790 (0.049)	0.576 (0.038)	0.656 (0.046)	0.094 (0.048)	0.547 (0.020)	6.3 (3.1)
GGL	0.774 (0.038)	0.522 (0.034)	0.780 (0.034)	0.500 (0.035)	0.471 (0.076)	0.054(0.020)	0.443 (0.033)	8.2 (4.6)
SSGL	0.486 (0.048)	0.429 (0.066)	0.421 (0.063)	0.389 (0.059)	0.583 (0.128)	0.090 (0.007)	0.361 (0.030)	192.1 (117.1)
SepBoost	0.824 (0.013)	0.285 (0.018)	0.835 (0.028)	0.221 (0.008)	0.949 (0.035)	0.095(0.006)	0.244 (0.012)	97.9 (147.6)
SepThreshold	0.810 (0.046)	0.243 (0.016)	0.822 (0.047)	0.245 (0.015)	0.892 (0.000)	0.082 (0.005)	0.219 (0.034)	153.4 (144.6)
proposed	0.713 (0.051)	0.799 (0.037)	0.687 (0.050)	0.772 (0.055)	0.394 (0.052)	0.277 (0.041)	0.603 (0.034)	–

(Continues)

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TABLE B4 (Continued)

Method	TPR1	TDR1	TPR2	TDR2	TPR3	TDR3	MCC	N_VIO
	$p = 100$							
GLasso	0.387 (0.110)	0.927 (0.072)	0.398 (0.131)	0.913 (0.084)	0.467 (0.140)	0.320 (0.130)	0.502 (0.021)	88.7 (33.3)
SepLasso	0.625 (0.015)	0.184 (0.014)	0.656 (0.037)	0.199 (0.011)	0.020 (0.020)	0.002(0.001)	0.214 (0.065)	232.6 (26.5)
FGL	0.798 (0.029)	0.552 (0.019)	0.776 (0.027)	0.559 (0.023)	0.550 (0.041)	0.077 (0.010)	0.532 (0.022)	17.4 (4.4)
GGL	0.762 (0.023)	0.479 (0.019)	0.760 (0.022)	0.473 (0.011)	0.550 (0.061)	0.066 (0.018)	0.433 (0.021)	18.4 (6.4)
SSGL	0.470 (0.057)	0.336 (0.088)	0.416 (0.041)	0.325 (0.089)	0.525 (0.146)	0.060 (0.006)	0.306 (0.041)	408.0 (247.0)
SepBoost	0.755 (0.032)	0.152 (0.010)	0.757 (0.021)	0.146 (0.010)	0.910 (0.065)	0.060 (0.003)	0.232 (0.016)	293.2 (441.2)
SepThreshold	0.681 (0.029)	0.146 (0.016)	0.665 (0.043)	0.145 (0.015)	0.770 (0.000)	0.104 (0.009)	0.186 (0.011)	628.0 (618.6)
proposed	0.644 (0.041)	0.687 (0.048)	0.638 (0.042)	0.677 (0.046)	0.352 (0.053)	0.104 (0.042)	0.567 (0.047)	–
Scenario 3	$p = 40$							
GLasso	0.487 (0.084)	0.530 (0.084)	0.435 (0.092)	0.568 (0.107)	0.986 (0.010)	0.229 (0.054)	0.405 (0.022)	20.1 (10.6)
SepLasso	0.781 (0.013)	0.224 (0.010)	0.803 (0.033)	0.237 (0.017)	0.700 (0.068)	0.019 (0.001)	0.281 (0.074)	119.3 (19.0)
FGL	0.888 (0.043)	0.455 (0.014)	0.910 (0.042)	0.414 (0.015)	0.980 (0.014)	0.050 (0.003)	0.514 (0.010)	0.0 (0.0)
GGL	0.885 (0.020)	0.362 (0.031)	0.912 (0.016)	0.377 (0.028)	0.974 (0.020)	0.040 (0.003)	0.493 (0.024)	0.0 (0.0)
SSGL	0.544 (0.051)	0.385 (0.071)	0.538 (0.053)	0.404 (0.081)	0.500 (0.121)	0.140 (0.016)	0.409 (0.045)	44.2 (26.3)
SepBoost	0.940 (0.017)	0.242 (0.015)	0.938 (0.029)	0.242 (0.016)	0.983 (0.053)	0.090 (0.005)	0.268 (0.018)	35.5 (46.0)
SepThreshold	0.915 (0.036)	0.276 (0.016)	0.936 (0.29)	0.279 (0.014)	1.000 (0.000)	0.071 (0.009)	0.284 (0.048)	103.6 (88.1)
proposed	0.800 (0.059)	0.588 (0.050)	0.825 (0.066)	0.584 (0.039)	0.914 (0.035)	0.222 (0.016)	0.603 (0.032)	–
	$p = 60$							
GLasso	0.446 (0.079)	0.559 (0.076)	0.400 (0.074)	0.476 (0.085)	0.974 (0.016)	0.132 (0.055)	0.385 (0.011)	35.6 (18.9)
SepLasso	0.766 (0.014)	0.227 (0.010)	0.773 (0.040)	0.224 (0.011)	0.283 (0.091)	0.008 (0.005)	0.266 (0.071)	116.3 (13.6)
FGL	0.861 (0.027)	0.405 (0.034)	0.831 (0.024)	0.404 (0.026)	0.952 (0.021)	0.045 (0.004)	0.486 (0.014)	5.1(3.0)
GGL	0.852 (0.017)	0.371 (0.017)	0.846 (0.054)	0.369 (0.023)	0.958 (0.015)	0.040 (0.002)	0.454 (0.016)	5.8 (4.8)
SSGL	0.494 (0.055)	0.375 (0.074)	0.447 (0.040)	0.362 (0.068)	0.593 (0.121)	0.091 (0.012)	0.381 (0.039)	119.4 (72.6)
SepBoost	0.884 (0.023)	0.173 (0.012)	0.883 (0.013)	0.175 (0.012)	0.975 (0.040)	0.050 (0.004)	0.242 (0.017)	99.4 (149.6)
SepThreshold	0.775 (0.038)	0.208 (0.016)	0.804 (0.36)	0.211 (0.014)	0.883 (0.153)	0.081 (0.007)	0.245 (0.025)	263.6 (247.6)
proposed	0.810 (0.049)	0.531 (0.030)	0.831 (0.054)	0.493 (0.032)	0.878 (0.029)	0.220 (0.012)	0.557 (0.018)	–
	$p = 100$							
GLasso	0.386 (0.077)	0.537 (0.075)	0.373 (0.071)	0.507 (0.080)	0.936 (0.031)	0.096 (0.033)	0.310 (0.031)	63.2 (28.1)
SepLasso	0.771 (0.025)	0.220 (0.010)	0.765 (0.022)	0.208 (0.014)	0.380 (0.097)	0.011 (0.003)	0.275 (0.060)	234.8 (52.9)
FGL	0.803 (0.031)	0.413 (0.042)	0.812 (0.044)	0.412 (0.031)	0.944 (0.026)	0.046 (0.005)	0.456 (0.018)	15.2 (5.2)
GGL	0.816 (0.010)	0.3650 (0.029)	0.834 (0.025)	0.346 (0.018)	0.923 (0.016)	0.040 (0.003)	0.430 (0.016)	17.3 (6.5)
SSGL	0.398 (0.038)	0.441 (0.089)	0.362 (0.042)	0.437 (0.077)	0.601 (0.153)	0.080 (0.021)	0.358 (0.034)	221.4 (118.5)
SepBoost	0.753 (0.025)	0.146 (0.008)	0.760 (0.029)	0.156 (0.009)	0.915 (0.063)	0.040 (0.005)	0.215 (0.012)	290.7 (438.3)
SepThreshold	0.630 (0.047)	0.140 (0.013)	0.623 (0.37)	0.142 (0.008)	0.675 (0.103)	0.072 (0.006)	0.183 (0.017)	630.2 (611.2)
proposed	0.756 (0.062)	0.496 (0.074)	0.742 (0.060)	0.476 (0.061)	0.907 (0.036)	0.104 (0.012)	0.511 (0.038)	–

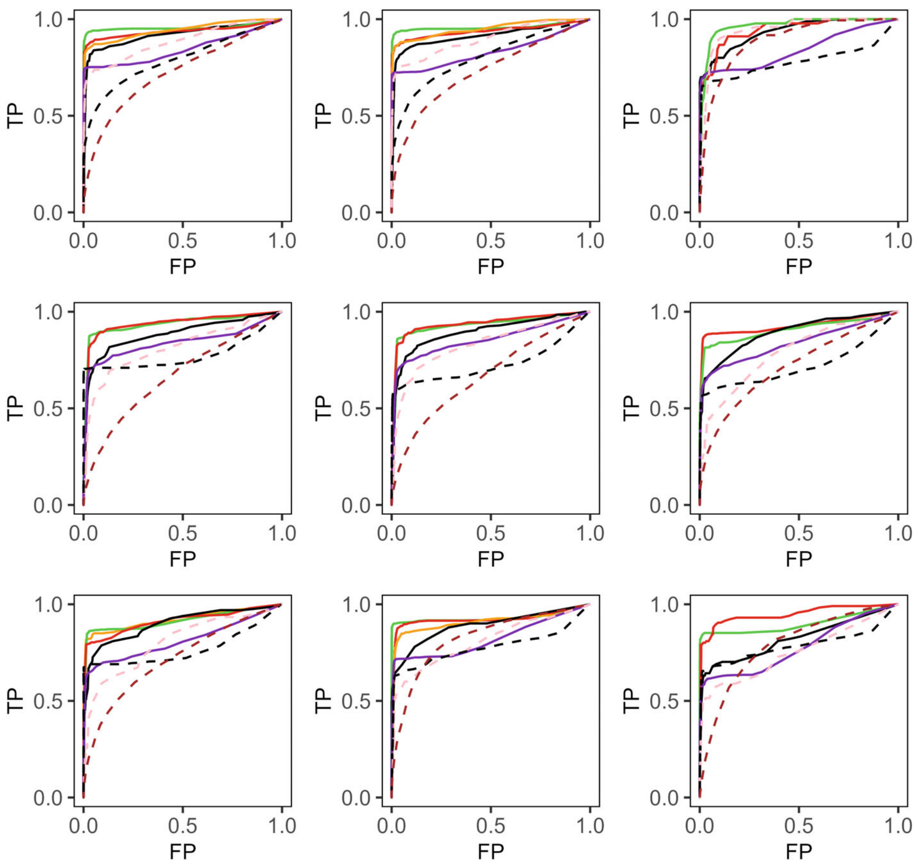

FIGURE B1 Simulation: ROC curves for the setting with power law networks, low signal strengths, and $p = 60$, $n = 200$: (—) GLasso; (—) SepLasso; (—) FGL; (—) GGL; (- - -) SSGL; (- - -) SepBoost; (- - -) SepThreshold; (—) proposed. Upper/Middle/Lower: Scenario 1/2/3

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