Networks effectively capture interactions among components of complex systems, and have thus become a mainstay in many scientific disciplines. Growing evidence, especially from biology, suggest that networks undergo changes over time, and in response to external stimuli. In biology and medicine, these changes have been found to be predictive of complex diseases. They have also been used to gain insight into mechanisms of disease initiation and progression. Primarily motivated by biological applications, this article provides a review of recent statistical machine learning methods for inferring networks and identifying changes in their structures.

This article is categorized under:
Data: Types and Structure > Graph and Network Data
Statistical Models > Graphical Models

**KEYWORDS**
differential network analysis, graphical modeling, high-dimensional statistics, network inference

**1 INTRODUCTION**

Networks are ubiquitous in many scientific disciplines. They are widely used to capture interactions among components of complex systems, and to glean insight into how these interactions shape the system's behavior. The latter is often achieved by comparing networks over time and/or in different states, a task referred to as **differential network analysis** (Ideker & Krogan, 2012).

Differential network analysis has become particularly popular in biological studies, where growing evidence suggests that interactions among components of biological systems can vastly change over (evolutionary) time (Borneman et al., 2007; Schmidt et al., 2010), when the system responds to external stimuli (Bar-Yam & Epstein, 2004; Luscombe et al., 2004), or in disease conditions (Goh et al., 2007; Hussain & Harris, 2006). For instance, changes in gene, protein, and metabolite networks have been found to be associated with the onset and progression of various diseases (J. Ma, Karnovsky, et al., 2019; West, Bianconi, Severini, & Teschendorff, 2012; X.-F. Zhang, Ou-Yang, Zhao, & Yan, 2016; Zhong et al., 2009). Similarly, changes in brain connectivity networks have been successfully used as predictive biomarkers for neurodegenerative diseases (Chuang, Lee, Liu, Lee, & Ideker, 2007; Taylor et al., 2009).

Let $G = (V, E)$ be a network with nodes $V = \{1, 2, ..., m\}$ and edge set $E \subseteq V \times V$. Changes in $G$ can be due to changes in its nodes, $V$, its edges, $E$, or both. Changes in the node set are common in social and communication networks, where both $V$ and $E$ can change as the network grows over time. In these settings, network edges—for example, social interactions or internet connections—are directly observed and the primary goal is to understand the mechanisms of network growth (Durrett, 2007). In contrast, in this paper we focus on the setting where the node set $V$ is fixed and the goal is to identify changes in network edges, $E$. Identifying such changes is of primary interest in the study of biological systems, where network nodes—for example, genes or brain regions—can be measured, but network edges are often
not directly observed. In fact, despite recent progress in developing assays for identifying interactions among genes and proteins (Krogan et al., 2006; Stelzl et al., 2005; Tarassov et al., 2008), and changes in interactions in different biological conditions (Barrios-Rodiles et al., 2005), interactions in biological systems and changes in those interactions are commonly inferred from measurements on the nodes. Primarily motivated by the challenges in biological applications, this paper reviews statistical methods for identifying changes in the edge set, $E$, inferred from $n$ observations on each node $j \in V$. To this end, we first briefly review probabilistic graphical models (Lauritzen, 1996), which are the primary building blocks for inferring network edges. We then review statistical methods for differential network analysis.

Throughout the paper, random variables are denoted by capital letters (e.g., $X$ and $X_j$), scalar parameters are denoted by lower case Greek letters (e.g., $\theta$) and parameter vectors/matrices are denoted by uppercase Greek letters (e.g., $\Theta$). Matrices of observations are denoted by Calligraphic letters (e.g., $X'$) and single observations are denoted by the corresponding lower case letters (e.g., $x_j$).

## 2 BACKGROUND: LEARNING NETWORK STRUCTURES

Probabilistic graphical models are widely used to summarize dependency relationships among random variables (Lauritzen, 1996), and to learn such dependencies from observations on the variables (Drton & Maathuis, 2017). For a graph $G = (V, E)$, the set of nodes $V = \{1, \ldots, m\}$ is associated with random variables $X_1, \ldots, X_m$, and the edge set $E$ captures dependency relationships among the variables. The edges in $E$ can be directed or undirected.

Directed graphical models are often used to capture causal relationships among random variables, with a directed edge $j \to k$ representing a direct causal effect of $X_j$ on $X_k$. The special case of directed acyclic graphs (DAGs)—where there are no directed cycles in $G$—corresponds to well-known Bayesian networks (Pearl, 2009), which have found many applications in biological (Markowetz & Spang, 2007) and social (Babin & Svensson, 2012) sciences, as well as machine learning (Koller & Friedman, 2009).

As expected, learning directed causal graphs from observational data is challenging and often impossible, or only possible under (uncheckable) identifiability assumptions (Peters & Bühlmann, 2013). This is because multiple DAGs may have the same likelihood and may thus be indistinguishable from data. Instead, the completed partially directed acyclic graph representing the class of Markov equivalent DAGs is often estimated from observational data. Despite recent progress (Ghoshal & Honorio, 2019; Manzour, Küçükyavuz, & Shojaie, 2019; Shojaie & Michailidis, 2010; Y. Wang, Squires, Belyaeva, & Uhler, 2018), existing methods for differential analysis of directed networks are in their infancy. As such, this review primarily focuses on differential analysis of undirected networks; references to recent work on differential analysis of directed networks are given in the Further Reading section.

Methods for learning the structure of undirected networks can be broadly categorized into methods based on (a) marginal and (b) conditional associations among variables, $X_1, \ldots, X_m$. These two classes of methods are reviewed in the remainder of this section.

### 2.1 Learning networks from marginal associations

Marginal inference procedures declare an (undirected) edge between two variables $X_j$ and $X_k$ if and only if they are dependent on each other. In practice, the dependence is often characterized by a marginal association measure, $\rho(X_j, X_k)$. In that case, two nodes $j$ and $k$ are connected in $G$, that is, $j \sim k \in E$, if and only if $\rho(X_j, X_k) \neq 0$.

In the simplest case, the marginal association network is defined based on the (Pearson) correlation between $X_j$ and $X_k$. In practice, this simple approach, which is widely used in biological settings (Junker & Schreiber, 2008), amounts to calculating the sample correlation coefficient between each pair of variables, $X_j$ and $X_k$, or, equivalently, the $(j, k)$ entry of the empirical correlation matrix of $X_1, \ldots, X_m$, denoted $S$. Learning the network structure then corresponds to selecting a subset of nondiagonal entries of $S$. This can be achieved by testing whether each $\rho(X_j, X_k)$ is zero, using, for example, the Fisher's transformation of sample correlations (Fisher, 1921), which can be used to test the hypothesis of no correlation, $H_0: \rho(X_j, X_k) = 0$. As an alternative, the network structure can be learned by identifying the set of correlations that are larger in magnitude than a prespecified threshold $\kappa$. The threshold $\kappa$ plays the role of a tuning parameter, and can be selected to achieve a certain level of sparsity in the network (Y. Wang, Joshi, Zhang, Xu, & Chen, 2006), or to obtain a network that satisfies a certain degree distribution (Langfelder & Horvath, 2008).
While simple, the Pearson correlation in the above procedure only captures linear dependencies. This is appropriate if \( X_1, \ldots, X_m \) are jointly normally distributed. However, multivariate normality (or presence of linear dependencies; C. Khatri & Rao, 1976) is a stringent assumption that may not hold in practice. As an alternative, rank-based correlation measures, such as Spearman correlation or Kendal’s-\( \tau \), or nonparametric measures of marginal association, such as mutual information (Margolin et al., 2006) or kernel-based measures of dependence (Yamanishi, Vert, & Kanehisa, 2004) can be used to test whether each pair of variables, \( X_j \) and \( X_k \), are independent. The network structure can then be learned by from \( p \)-values for testing independence among variables from each of these approaches, or by applying a prespecified threshold.

Regardless of the choice of association measure, the above network learning procedures have another limitation: marginal measures of associations cannot distinguish between direct and indirect relationships. As a simple example, consider three normally distributed variables \( X_1, X_2, \) and \( X_3 \). Suppose the true network \( G \) consists of two edges, \( 1 \rightarrow 2 \) and \( 1 \rightarrow 3 \). Furthermore, suppose the true correlation between \( X_1 \) and both \( X_2 \) and \( X_3 \) is 0.8. In other words, \( \rho(X_1, X_2) = \rho(X_1, X_3) = 0.8 \). But this implies that \( \rho(X_2, X_3) = 0.64 \) ! Thus, with enough observations, the network learned from the (correctly specified) marginal association measure would incorrectly include the edge \( 2 \rightarrow 3 \).

Despite its simplicity, the above example illustrates a major limitation of network inference based on marginal associations. Unfortunately, the same issue also arises with other distributions and other measures of associations. Network learning procedures based on conditional measures of associations, discussed next, try to address this limitation.

2.2 Learning networks from conditional associations

Undirected graphical models, also known as Markov random fields (MRF), represent conditional dependence relationships between a set of random variables. For random variables \( \{X_1, X_2, \ldots, X_m\} \), an MRF is associated with an undirected graph \( G = (V, E) \) with vertex set \( V = \{1, 2, \ldots, m\} \) and undirected edges \( E \subseteq V \times V \), such that the absence of an edge between nodes \( j \) and \( k \) indicates that \( X_j \) and \( X_k \) are conditionally independent given all other variables, that is, \( X_{\{j, k\}} \) (Lauritzen, 1996). In the smallest such graph \( G \), known as the conditional independence graph (CIG), there is an edge between \( j \) and \( k \), that is, \( j - k \in E \), if and only if \( X_j \) and \( X_k \) are conditionally dependent given all other variables (Lauritzen, 1996).

Given \( n \) observations from each random variable \( X_j \), \( j \in V \), learning the CIG corresponds to identifying pairs of random variables that are independent given all other variables. While learning networks from conditional associations, and in particular the CIG, is more challenging than learning based on marginal associations, edges in a CIG capture unconfounded associations among variables and may thus be more scientifically meaningful. For instance, in the simple example of the previous section, the partial correlation between \( X_2 \) and \( X_3 \) after adjusting for \( X_1 \) is indeed zero. Thus, the CIG correctly captures the association among variables.

When \( m = |V| \) is small compared to \( n \), the CIG can be learned nonparametrically, using, for example, nonparametric procedures for testing conditional independences, such as conditional mutual information (Margolin et al., 2006), or kernel-based procedures (Yamanishi et al., 2004). However, nonparametric procedures become computationally challenging, if not prohibitive, when \( m \) is large. Moreover, it is not straightforward to extend such nonparametric procedures to high-dimensional settings, that is, when \( m > n \). In contrast, characterizing conditional independence is often easier if the family of probability distributions corresponding to \( G \) is represented by finite-dimensional parameters. Such parametric models can also be more easily extended to high-dimensional settings. Finally, existing procedures for differential network analysis mainly consider parametric graphical models. Therefore, the rest of this section is primarily focused on parametric models, and we only provide a brief review of semiparametric and nonparametric graphical modeling approaches.

2.2.1 Gaussian graphical models

The most well-known, and most widely studied, example of probabilistic graphical models is the class of Gaussian graphical models (GGMs), wherein \( \{X_1, X_2, \ldots, X_m\} \) are jointly Gaussian. Formally, in a GGM, \( (X_1, X_2, \ldots, X_m) \sim N(\mu, \Sigma) \), where \( \mu \in \mathbb{R}^m \), \( \Sigma \in S^m_+ \), and \( S^m_+ \) denote the set of symmetric positive definite matrices. In this case, any two variables \( X_j \) and \( X_k \) are conditionally independent, given all other variables \( X_{\{j, k\}} \), if and only if the \((j, k)\) entry of the inverse covariance, or precision, matrix, \( \Omega = \Sigma^{-1} \), is zero (Lauritzen, 1996). Formally,
Equation (1) implies that in the Gaussian case, the CIG is fully characterized by the precision matrix, $\Omega$. This characterization suggests the following simple estimation strategy: Let $\mathcal{X}$ be the $n \times m$ data matrix corresponding to $n$ i.i.d. observations for centered variables $\{X_1, X_2, ..., X_m\}$ (so, $\sum_{i=1}^{n} x_{ij} = 0$). Then, calculate the empirical covariance matrix, $S = (n-1)^{-1} \mathcal{X}^T \mathcal{X}$, and estimate the CIG based on nonzero entries of $S^{-1}$, by applying a threshold (similar to $\kappa$ discussed earlier for marginal association networks) or using an inference procedure (Drton & Perlman, 2004).

While the above strategy is straightforward, the inverse of the empirical covariance matrix, $S^{-1}$, may not be well conditioned even when $n > m$ (Dempster, 1972). Moreover, the inverse does not even exist in the high-dimensional setting, where $m > n$. An alternative strategy is to directly calculate the partial correlations among pairs of variables, which are well known measures of conditional independence for Gaussian random variables. The partial correlation conditioned even when $\kappa$ may not coincide, leading to (asymptotically) equivalent estimates of the CIG.

A potential drawback of regressions-based estimation of the CIG in (2) is that, given a fixed sample size $n$, estimated conditional independences between $X_j$ and $X_k$ given $X_{\{i, k\}}$ may not coincide. Nonetheless, this regression-based strategy can be easily generalized to high-dimensional settings, by, for example, utilizing a sparsity-inducing penalty such as the lasso (Tibshirani, 1996). This approach, known as neighborhood selection, was first considered in the seminal work of Meinshausen and Bühlmann (2006), who also established the consistency of the estimated CIG in high-dimensional sparse settings. In this approach, the “neighborhood” of each node $j \in V$ is defined as variables with nonzero coefficients in $m$ penalized regressions of the form

$$\hat{\beta}_{jk} = \arg\min_{\beta_{jk}} \left\| X_j - \sum_{k \neq j} \beta_{jk} X_k + \delta_j \right\|_2^2 + \lambda \sum_{k \neq j} |\beta_{jk}|, \quad j = 1, ..., m. \quad (3)$$

Here, the tuning parameter $\lambda$ controls the sparsity of the estimated neighborhoods, defined as $\bar{\Omega}_{jk} = \{k : \hat{\beta}_{jk} \neq 0\}$. To mitigate the potential discrepancy between the neighborhoods (e.g., those estimated based on $\hat{\beta}_{jk}$ and $\hat{\beta}_{kj}$), the authors then propose constructing the CIG based on either the intersection or the union of the estimated neighborhoods.

To estimate the precision matrix $\Omega$, in this approach, first considered by M. Yuan and Lin (2007) and Banerjee, Ghaoui, and d’Aspremont (2008), and popularized by the efficient graphical lasso algorithm (Friedman, Hastie, & Tibshirani, 2008), $\Omega$ is estimated by minimizing the $\ell_1$-penalized negative log likelihood

$$\hat{\Omega} = \arg\min_{\Omega \in \mathbb{S}^m_{++}} \left\{ \text{trace}(S\Omega) - \log\det(\Omega) + \lambda \|\Omega\|_1 \right\}, \quad (4)$$

where, as before, $S$ is the empirical covariance matrix, and for a square matrix $M$, trace($M$) and logdet($M$) denote the sum of its diagonal entries and the logarithm of its determinant, respectively. In graphical modeling applications, the $\ell_1$ penalty $\|\Omega\|_1 = \sum_{k \neq l} |\Omega_{kl}|$ is often replaced by the sum of absolute values of the off-diagonal entries of $\Omega$, $\sum_{k \neq l} |\Omega_{kl}|$.

Since their introductions, various authors have considered other penalties for both neighborhood selection and penalized likelihood estimation approaches, and have also investigated asymptotic properties of these estimators.
Graphical models for other probability distributions

A key reason for the popularity of GGMs and the extensive recent work in this area is the convenient characterization of conditional independence relations for Gaussian random variables by the inverse covariance, or precision, matrix. However, joint normality is a stringent assumption that may not be satisfied in many real data applications (Voorman, Shojaie, & Witten, 2013). In particular, GGMs are not appropriate when the observations are discrete (e.g., binary or Poisson), have heavy-tail distributions (e.g., exponential), or their support is a subset of the real line (e.g., nonnegative).

The main challenge in estimating CIGs for other distributions is that unlike in the Gaussian case, conditional independence relations between pairs of variables are not necessarily characterized by a single parameter. Instead, conditional independence relations are more generally characterized by the Hammersley–Clifford theorem (Besag, 1975), which states that a probability distribution \( P \) with a strictly positive density defines a MRF over a graph \( G \) if and only if its density, \( f \), can be factorized over complete subgraphs, or cliques, of \( G \). While elegant and general, this characterization does not necessarily lead to tractable algorithms for estimating CIGs given observations from \( \{X_1, \ldots, X_m\} \). That is because one would need to search over all possible subsets of the variables to find the cliques that define the MRF.

In the special case of GGMs, the Hammersley–Clifford theorem is considerably simplified: In this case, it suffices to only consider pairwise interactions among variables, which is efficiently learned from the precision matrix of \( \{X_1, \ldots, X_m\} \). Motivated by this property, graphical models for other distributions have also been defined based on pairwise interactions among variables. Denoting by \( f_j(X_j) \) and \( f_{jk}(X_j, X_k) \) the node and edge potentials, respectively, the density \( f(x) \) for such a pairwise MRF is proportional to

\[
\exp \left( \sum_{j=1}^{m} f_j(X_j) + \frac{1}{2} \sum_{(j,k) \in E} f_{jk}(X_j, X_k) \right). \tag{5}
\]

Importantly, (5) implies that \( f_{jk} = 0 \) for \( j - k \notin E \). Thus, the CIG can be estimated by identifying nonzero edge potentials. This characterization can be further simplified by parametrizing the edge potentials by, for example, assuming

\[
f_{jk}(X_j, X_k) = \theta_{jk} X_j X_k = \theta_{kj} X_k X_j, \tag{6}
\]

for parameters \( \theta_{jk} \in \mathbb{R} \). Let \( \Theta \in \mathbb{R}^m \) be the matrix with zero diagonal entries and off diagonal entries equal to \( \theta_{jk} \). Then, similar to GGMs, conditional independence relations for this family can be simply learned from the entries of \( \Theta \): \( j - k \in E \) if and only if \( \theta_{jk} = \theta_{kj} = 0 \) (Wainwright & Jordan, 2008).

With the parametrization in (6), a key remaining challenge in estimating CIGs for exponential families is computing the normalizing constant to ensure that the distribution specified in (5) is well defined. To overcome this challenge, Yang, Allen, Liu, and Ravikumar (2012) consider the case where conditional distributions for each node, given all other nodes, are generalized linear models (GLMs). More specifically, setting \( f_j(X_j) = \theta_j X_j \), they consider conditionally specified graphical models, where node-conditional distributions are GLMs proportional to

\[
\exp \left( \theta_j X_j + \sum_{k \in \text{ne}(j)} \theta_{kj} X_k X_j + g(X_j) \right), \tag{7}
\]

\( \text{ne}(j) = \{k : k - j \in E\} \) is the neighborhood of \( j \) in \( G \), and \( g(\cdot) \) is a function that specifies different GLM distributions.

Yang et al. (2012) show that the conditionally specified model (7) leads to a unique joint probability distribution of the form
\[
\exp \left( \sum_{j} \theta_j x_j + \sum_{(j,k) \in E} \theta_{jk} x_k x_j + \sum_{j} g(x_j) - h(\Theta) \right),
\]

where \( h(\Theta) \) is the normalizing constant. Various GLM distributions are then obtained by considering different functions \( g(\cdot) \). For instance, \( g(x) = -x^2/2 \) corresponds to the Gaussian distribution, while \( g(x) = 0 \) corresponds to the Bernoulli distribution (Ravikumar, Wainwright, & Lafferty, 2010). Chen, Witten, & Shojaie (2014), Yang, Baker, Ravikumar, Allen, & Liu (2014), and Cheng, Li, Levina, & Zhu (2017) further extend this approach to estimate CIGs from mixed data, where node-conditional distributions are specified by multiple GLM distributions, for instance, binary, Poisson, and Gaussian.

A key advantage of the conditionally specified model (7) is that it allows bypassing the computation of the normalizing constant, and facilitates computationally efficient estimation of CIGs for a broad class of distributions. In fact, for GLMs, estimating the pairwise MRF amounts to solving \( m \) GLM regressions—\( m \) logistic regressions for binary data (similar to Ravikumar et al., 2010), and \( m \) Poisson regressions for Poisson variables (similar to Allen & Liu, 2013; Yang, Ravikumar, Allen, & Liu, 2013). High-dimensional pairwise MRF for these and other distributions can then be estimated by augmenting the conditional negative log-likelihoods corresponding to (7) with a sparsity inducing penalty on \( \Theta \), such as lasso. This approach is thus a natural extension of the neighborhood selection estimator of Meinshausen and Bühlmann (2006) for other distributions in the exponential family.

While computationally convenient, conditionally specified models are not guaranteed to result in a symmetric network estimate (as discussed in the case of GGMs). To circumvent the latter shortcoming, few authors have proposed estimation strategies similar to conditionally specified models that result in symmetric network estimates (see, e.g., Drton & Maathuis, 2017). An alternative strategy for bypassing the computation of the normalizing constant, which can be used to directly obtain symmetric network estimates, is the score matching approach of Lin, Drton, & Shojaie (2016). In this approach, the loss function is defined as the Fisher information distance between the gradients, with respect to observations \( x \), of true and candidate log densities. Using integration-by-parts, Hyvärinen (2005) showed that under mild conditions, the empirical loss for a candidate density \( f \) can be written as the average, over \( n \) observations, of

\[
\frac{1}{2} \| \nabla_x \log f(x) \|^2_2 + \Delta_x \log f(x),
\]

where \( \nabla_x \) and \( \Delta_x \) denote the gradient and Laplace operators, respectively with respect to \( x \).

Lin et al. (2016) equipped the score matching loss with an \( \ell_1 \) penalty to obtain estimates of high-dimensional graphical models for distributions in the exponential family with absolutely continuous densities. Using the generalized score matching loss of Hyvärinen (2007), they also extended this approach to distributions with densities supported over a subset of \( \mathbb{R} \). See S. Yu, Drton, and Shojaie (2018) and S. Yu, Drton, & Shojaie (2019) for further generalizations of this approach.

### 2.2.3 Semiparametric and nonparametric graphical models

While computationally attractive and statistically efficient, parametric graphical models can lead to biased and incorrect CIG estimates if their underlying model does not hold. As an alternative to parametric models, few authors have recently considered semiparametric and nonparametric estimation of graphical models. Early work in this area considered the Gaussian copula or nonparanormal distribution (Dobra & Lenkoski, 2011; H. Liu, Lafferty, & Wasserman, 2009); instead of assuming multivariate normality, the nonparanormal model posits that for some (unknown) monotone functions \( h_1, \ldots, h_m \), the transformed variables \( h_1(x_1), \ldots, h_m(x_m) \) have a multivariate normal distribution with mean zero and precision matrix \( \Omega \). While estimating the unknown functions \( h_j, j = 1, \ldots, m \) seems difficult at first glance, H. Liu, Han, Yuan, Lafferty, & Wasserman (2012) and Xue & Zou (2012) show that this approach is equivalent to estimating the CIG by plugging in a rank-based correlation matrix, such as Spearman correlation or Kendall’s \( \tau \) into the graphical lasso optimization problem (4).

The nonparanormal graphical model can be efficiently estimated and provides a natural generalization of the graphical lasso estimator. However, Voorman et al. (2013) show that the nonparanormal model can be restrictive, and propose, as an alternative, conditionally-specified additive graphical models, by assuming
\[ X_j | X_{\neq j} = \sum_{k \in \text{ne}(j)} f_{jk}(X_k) + \epsilon_j, \]

where \( \epsilon_j \) is a mean-zero noise variable. In this model, \( X_j \perp X_{\neq j} \) given other variables if and only if \( f_{jk} = f_{kj} = 0 \). Thus, in high dimensions, the CIG can be estimated by fitting \( m \) penalized nonparametric regressions. Voorman et al. (2013) consider a basis expansion approach and use a joint standardized group lasso penalty (Simon & Tibshirani, 2012) to enforce both \( f_{jk} \) and \( f_{kj} \) to zero in order to estimate the neighborhood of each node in \( G \). Other related ideas include the graphical random forest estimator of Fellinghauer, Bühlmann, Ryffel, Von Rhein, & Reinhardt (2013), the kernel-based estimator of Lee, Li, & Zhao (2016), as well as nonparametric approaches for exponential densities in Sun, Kolar, & Xu (2015) and Suggala, Kolar, & Ravikumar (2017).

3 | STATISTICAL METHODS FOR DIFFERENTIAL NETWORK ANALYSIS

Before reviewing recent developments in statistical methods for differential network analysis, we discuss relevant hypotheses and measures of difference between networks. For simplicity, we restrict the discussion to comparing two networks, \( G^1 \) and \( G^2 \) with the same node set \( V \) and edges sets \( E^1 \) and \( E^2 \), or, equivalently, adjacency matrices \( A^1 \) and \( A^2 \). In general, \( E^1 \) and \( E^2 \) may have been directly observed, obtained from experiments, or learned from observations on the nodes via graphical modeling approaches. However, as mentioned in Section 1, we focus primarily on networks inferred using graphical modeling methods. For instance, in the case of GGMs, \( A^s, s \in \{1, 2\} \) may correspond to estimated partial correlation matrices, \( \hat{\Omega}^s, s \in \{1, 2\} \).

Various notions of difference between \( A^1 \) and \( A^2 \) can be considered. For instance, we may be interested in identifying global differences between \( A^1 \) and \( A^2 \), that is, whether \( A^1 = A^2 \). However, similar to testing for equality of vectors of parameters, different norms or distance measures can be used to assess whether \( A^1 \) and \( A^2 \) are the same. For instance, one can examine the difference between weighted adjacency matrices, by examining the value of \( \|A^1 - A^2\| \) for some matrix norm. In the case of GGMs, this can be achieved by examining \( ||\hat{\Omega}^1 - \hat{\Omega}^2|| \).

Alternatively, one can consider the structural Hamming distance (Diestel, 2012) between \( A^1 \) and \( A^2 \), which counts the total number of edge differences between the two networks. Compared to the norm-based approach, which takes the quantitative values of estimated parameters into account, this approach assesses qualitative differences between the two networks. Finally, the topology of the space of networks offers additional measures of differences between \( A^1 \) and \( A^2 \), including (potentially vector-valued) summary measures of the two networks, such as the size and/or number of clusters, the average connectivity, or the degree distribution; see Shojaie & Sedaghat (2017) for examples of such measures.

In many applications, local differences between the two networks, including differences in individual edges, neighborhoods, or subnetworks, can also be of interest. This is especially the case in biological applications, where network-based biomarkers can be used to interrogate mechanisms of diseases initiation and progression (Erler & Linding, 2010; Gomez-Ramirez & Wu, 2014; Z.-P. Liu, 2016). Identifying local differences between networks can also be of interest following an affirmative global test of difference between the two networks. As in the case of global differences, local differences between two networks can be assessed qualitatively or quantitatively. For instance, in the case of GGMs, one may be interested in identifying node pairs \((j, k)\) such that \( \hat{\Omega}^1_{jk} \neq \hat{\Omega}^2_{jk} \). Alternatively, instead of looking at quantitative differences between parameters, we may want to identify node pairs \((j, k)\) such that \( j - k \in G^1 \) but \( j - k \notin G^2 \). In the Gaussian case, such qualitative differences can be identified by comparing the zero/nonzero patterns of \( \hat{\Omega}^1 \) and \( \hat{\Omega}^2 \); for instance, by identifying node-pairs \((j, k)\) such that \( \text{supp}(\hat{\Omega}^1_{jk}) \neq \text{supp}(\hat{\Omega}^2_{jk}) \), where \( \text{supp}(\omega) = 1 \) if \( \omega \neq 0 \) and 0 otherwise.

Examples of quantitative and qualitative differences in networks are depicted in Figure 1. This simple example highlights different insights and conclusions based on different notions of network difference: the differential network based on values of partial correlations (\( A^2 - A^1 \), bottom-left) captures differences in signs and magnitudes of model parameters; the differential network based on supports of \( A^2 \) and \( A^1 \) (bottom-center) captures differences in edge structures; and the differential network based on differences in signs (bottom-right) captures both support and sign differences between. The choice of the appropriate notion of difference depends on the application. In particular, as discussed in the remainder of this section, qualitative methods/tests may better capture differences in the structures of underlying networks, while quantitative methods could offer higher power for identifying differences in parameters of graphical models used to learn the networks.
In the following, we discuss existing statistical approaches that examine various notions of difference between two networks (global vs. local and qualitative vs. quantitative). Given the current state of the literature, we focus primarily on methods for Gaussian observations, and briefly review methods for other graphical models at the end.

### 3.1 Global tests of network differences

Naturally, the global null hypothesis of no difference between two GGMs, that is, $H_0 : E^1 = E^2$, can be tested by examining whether correlation, or partial correlation, matrices in the two populations are different. Formally, two GGMs are the same if $H_0 : \Sigma^1 = \Sigma^2$, or, equivalently, $H_0 : \Omega^1 = \Omega^2$, holds. However, as mentioned earlier, these matrix-based hypotheses can be tested using different matrix norms and summaries. Regardless of the choice of norm/summary, a key challenge arises from high-dimensionality: When $m \gg n$ classical estimates of $\Sigma^s$, $s \in \{1, 2\}$ may be too noisy for an unbiased tests, and estimating $\Omega^s$, $s \in \{1, 2\}$ requires regularization methods that rely on sparsity.

Motivated by classical multivariate methods, early tests of difference between high-dimensional correlation matrices (Li & Chen, 2012; Schott, 2007) were based on the Frobenius norm, $\|\Sigma^1 - \Sigma^2\|_F^2 = \sum_{k=1}^m \sum_{j=1}^m (\Sigma_{jk}^1 - \Sigma_{jk}^2)^2$. These tests are sensitive to orchestrated weak changes in entries of the correlation matrices, but may have low power if few correlations are significantly different, but the majority are similar. In contrast, methods based on maximum entries of matrices (T. T. Cai & Zhang, 2016; Chang, Zhou, Zhou, & Wang, 2017) are sensitive to large differences between individual correlations, that is, sparse but large differences. Other approaches have utilized eigen-structures (Srivastava & Yanagihara, 2010) and random matrix projections (Wu & Li, 2015). In a recent work, L. Zhu, Lei, Devlin, and Roeder (2017) proposed a test based on sparse leading eigenvectors that can detect both sparse and weak differences.

A potential advantage of the above methods for testing differences in covariance matrices is that they can also be applied to prespecified subsets of nodes. More specifically, for a subset $U \subseteq V$ of nodes, the above methods can test $H_0 : \Sigma_{U,U}^1 = \Sigma_{U,U}^2$. Such tests are particularly relevant in pathway enrichment analysis (P. Khatri, Sirola, & Butte, 2012), where $U$ is the set of nodes corresponding to a biological pathway, and the goal is to determine whether the distributions of random variables $X_j$ for $j \in U$ are the same across two populations. Similar problems also arise in other applications, for instance, when interrogating composite brain regions (Tryputsen et al., 2015). Both nonparametric methods, such as the energy statistic (Székely & Rizzo, 2013), and permutation-based approaches (Subramanian et al., 2005; Tian et al., 2005) have been used to test for differences in distributions. However, more recent approaches have focused on accounting for the topology of the underlying networks (P. Khatri et al., 2012) by utilizing the full power of graphical models. For instance, assuming normality, the topologyGSA method (Massa, Chiogna, & Romualdi, 2010) first tests for
equality of covariance matrices, $\Sigma_1 = \Sigma_2$. Depending on the outcome of this test, pathway enrichment is determined by testing for differences in means, that is, $\mu_1 = \mu_2$: if equality of covariances is not rejected, a multivariate analysis of variance (Smith, Gnanadesikan, & Hughes, 1962) is used, whereas the Behrens–Fisher method (Anderson, 2003) is used if covariances are found to be different. Similarly, DEGraph (Jacob, Neuvial, & Dudoit, 2012) also starts with testing $\Sigma_1 = \Sigma_2$. If this hypothesis is rejected, then the pathway is declared to be enriched. If not, differences in means are tested using a Hotelling’s $T^2$ statistic (Hotelling, 1931) using the pooled estimate of the covariance matrix. The NetGSA framework (J. Ma, Shojaie, & Michailidis, 2016; Shojaie & Michailidis, 2009, 2010) is also related, but takes a different perspective; it combines differences in mean and covariance matrices between the two populations by considering a latent variable model, and defines a contrast vector based on covariances. Aside from details of testing procedures, another key difference between NetGSA and other methods is that it uses the observations in each population to learn/update the estimated network in each condition, and thus accounts for differential connectivity in the two networks. See J. Ma, Shojaie, et al. (2019) for more discussions and a recent review of topology-based pathway enrichment methods.

### 3.2 Estimating multiple GGMs and their differences

Biological systems are inherently robust (Kitano, 2004). Therefore, despite potential differences, networks in similar conditions or populations are expected to share many common edges. For instance, gene regulatory networks in different cancer subtypes, for instance ER+ and ER− subtypes of breast cancer in Figure 2, are expected to share many edges. It therefore makes sense to account for these common edges. This is particularly the case when estimating high-dimensional graphical models, where the small sample size, compared to the number of variables/features, is a key challenge. Recent graphical modeling approaches that try to account for common edges in networks in order to better delineate their differences can be broadly categorized into two classes: joint estimation of multiple graphical models and direct estimation of differences between graphical models.

In joint estimation of multiple graphical models, the goal is to borrow information across populations/conditions in order to better estimate the networks in each condition. For instance, when estimating two GGMs, this can be achieved by encouraging the entries of the precision matrices to be similar to each other. More specifically, let $\Omega_{1jk}$ and $\Omega_{2jk}$ be $(j, k)$ entries of precision matrices in two populations. Then, joint estimation strategies encourage the estimates of $\Omega_{1jk}$ and

![Figure 2](image_url) Differential network analysis in subtypes of breast cancer. The two networks show edges identified as significant in only one breast cancer subtypes (left: ER+; right: ER−). They correspond to interactions among a subset of $m = 358$ cancer-related genes, and are inferred using gene expression measurements from the Cancer Genome Atlas (TCGA)
to define the similarity structure among (sub)populations. The idea of combining clustering and estimation of multiple graphical models was also considered in Hao, Sun, Liu, and Cheng (2017), wherein clustering and graphical model estimation differences between networks in different populations. However, when the primary scientific focus is on differences between networks, learning their common structures may be unnecessary and inefficient. As an alternative, authors utilize the CLIME estimation framework (T. Cai, Liu, & Luo, 2011) to estimate the sparse difference of two precision matrices, \( \Omega_k \), to be similar to each other. To achieve this goal, Guo, Levina, Michailidis, & Zhu (2011) proposed to reparametrize the entries of the precision matrices as the product of a common parameter (for both populations) and a population-specific parameter. Formally, for \( s \in \{1, 2\} \), they let \( \Omega_{jsk} = \Theta_{js} \Gamma_{sk} \), where to avoid sign ambiguity, \( \Theta_{js} \) is restricted to be nonnegative. The graphical models are then jointly estimated by replacing the \( \ell_1 \) penalty in the graphical lasso problem (4) with two penalties on \( \Theta_{js} \) and \( \Gamma_{sk} \):

\[
\lambda_1 \sum_{j \neq k} \Theta_{js} + \lambda_2 \sum_{j \neq k} \sum_{s} \Gamma_{sk}.
\]

The first penalty encourages sparsity in both \( \Omega_{js} \) and \( \Omega_{sk} \), and hence improves the selection of common zero coefficients in the precision matrices. If \( \Theta_{js} \neq 0 \), then the second penalty induces condition-specific sparsity in each of the precision matrices.

The proposal of Guo et al. (2011) leads to a non-convex optimization problem, and potential challenges in large-scale networks. As an alternative, Danaher, Wang, and Witten (2014) proposed to directly augment the graphical lasso problem (4) with a second penalty to encourage similarity among \( \Omega_{jsk}, s \in \{1, 2\} \) coefficients. In particular, they proposed two penalties: a group lasso penalty (M. Yuan & Lin, 2006), \( \sum_{s} \sqrt{\left( \Omega_{jk}^1 \right)^2 + \left( \Omega_{jk}^2 \right)^2} \), and a fused lasso penalty (Tibshirani, Saunders, Rosset, Zhu, & Knight, 2005), \( \sum_{s} \left| \Omega_{jk}^1 - \Omega_{jk}^2 \right| \). The group lasso penalty encourages similar sparsity patterns across the two populations, whereas the fused lasso penalty encourages the coefficients across the two populations to be equal to each other.

While effective for jointly learning two networks, the strategies described above may not work well for learning multiple GGMs. This is because they inherently assume that the networks in multiple (sub)populations are equally similar to each other. Addressing this shortcoming is the primary focus of a number of recent papers, including Y. Zhu, Shen, & Pan (2014), Peterson, Stingo, & Vannucci (2015), J. Ma and Michailidis (2016), and Saegusa and Shojaie (2016). To achieve this goal, Y. Zhu et al. (2014) and J. Ma and Michailidis (2016) generalize the fused and group lasso penalties, respectively, to account for the known similarity structure among multiple networks. The methods by Peterson et al. (2015) and Saegusa and Shojaie (2016) focus instead on the setting where the similarity structure is unknown. In particular, Peterson et al. (2015) propose a Bayesian approach by using a MRF prior to learn the precision matrices in a mixture of Gaussian distributions. To overcome the computational challenges of Bayesian estimation of GGMs, this approach assumes that network edges are formed independently. Saegusa and Shojaie (2016) instead propose to use a Laplacian shrinkage penalty (Huang, Ma, Li, & Zhang, 2011) based on a similarity structure learned from data. More specifically, instead of a fused or group lasso penalty, the authors propose to use \( \sum_{s,s'} \pi_{s,s'} \left( \Omega_{jk}^s - \Omega_{jk}^{s'} \right)^2 \), where the data-driven weights \( \pi_{s,s'} \) capture the similarity among (sub)populations \( s \) and \( s' \). To justify this data-driven penalty, the authors establish the consistency of hierarchical clustering in high-dimensional settings and use the resulting clustering to define the similarity structure among (sub)populations. The idea of combining clustering and estimation of multiple graphical models was also considered in Hao, Sun, Liu, and Cheng (2017), wherein clustering and graphical model estimation are combined into a single problem, which is solved using an expectation conditional maximization algorithm.

Methods for joint estimation of multiple graphical models provide valuable insight into commonalities and differences between networks in different populations. However, when the primary scientific focus is on differences between networks, learning their common structures may be unnecessary and inefficient. As an alternative, S. D. Zhao, Cai, and Li (2014) proposed to directly estimate the difference of two GGMs. More specifically, the authors utilize the CLIME estimation framework (T. Cai, Liu, & Luo, 2011) to estimate the sparse difference of two precision matrices, \( \Delta = \Omega^2 - \Omega^1 \) subject to a constraint motivated by the observation that the true covariance and precision matrices must satisfy

\[
\Sigma^1 \Delta \Sigma^2 - (\Sigma^2 - \Sigma^1) = 0.
\]

The key advantage of this approach is it only assumes that the difference of the precision matrices, \( \Delta \), is sparse, and not each of the precision matrices. However, solving the optimization problem for direct estimation of differences
introduces additional challenges. To overcome these, the authors also propose an alternative formulation based on neighborhood selection. H. Yuan, Xi, Chen, and Deng (2017) have recently proposed a more computationally-appealing alternative based on the D-trace loss (T. Zhang & Zou, 2014), which is a special case of the score matching loss (Lin et al., 2016) discussed earlier; see also Na, Kolar, and Koyejo (2019) for a related approach to learn differences in networks with latent (hidden) nodes.

### 3.3 Testing for differences in network edges

Unlike global tests of network differences, methods for joint estimation of multiple graphical models and their differences do not provide measures of uncertainty, such as confidence intervals and \( p \)-values. Thus, although they provide powerful tools for exploratory analysis and hypothesis generation, the methods discussed in the previous section have limited utility in scientific applications. In contrast, recent hypothesis testing procedures for single precision matrices (Janková & van de Geer, 2015, 2017; Ren, Sun, Zhang, & Zhou, 2015; Xia & Li, 2017) offer confidence intervals for entries of each precision matrix, \( \Omega^1 \), and/or \( p \)-values for the null hypothesis \( H_0 : \Omega^j_{jk} = 0 \) for \( j \neq k \). M. Yu, Gupta, & Kolar (2019) have further generalized this idea for inference in non-GGMs using the framework for generalized score matching (S. Yu, Drton, et al., 2019).

Equipped with a multiple comparison adjustment procedure (e.g., Benjamini & Hochberg, 1995), the above inference methods can be used to (asymptotically) control the probability of falsely detecting nonexistent network edges in each (sub)population. However, these inference procedures are not guaranteed to control the probability of false positives when testing differences between networks. To see this, consider testing the difference between the \((j, k)\) entry in two precision matrices, that is, \( \Omega^1_{jk} \) and \( \Omega^2_{jk} \). Suppose we obtain confidence intervals for these parameters, using, for example, the method of Janková and van de Geer (2015). These confidence intervals can be used to test the difference in support of the two networks with respect to the \( j-k \) edge, as illustrated in Figure 1. (The confidence intervals can also be used to test for differences in signs and values of the precision matrices, but, for simplicity, here we focus only on the support.) If both confidence intervals cover zero, or if both do not overlap with zero, then we conclude, with high confidence, that the two networks are not differentially connected at this edge. However, things become complicated if one confidence interval covers zero and the other does not. In this case, the optimistic conclusion is that the difference in coverage of confidence intervals points to differential connectivity between the two networks. However, that is not necessarily the case! The fact that one of the confidence intervals covers zero may simply be due to the low power of the inference procedure, especially if the true parameter or the sample size is small. This simple example highlights the primary limitation of single network inference for inferring differential connectivity between networks.

Inference procedures for detecting differences in two GGMs directly examine whether the entries in the two precision matrices are equal. For instance, Xia, Cai, and Cai (2015) tests whether \( \Omega^1_{jk} = \Omega^2_{jk} \) using the connection between the entries of the precision matrix and the regression coefficients obtained from neighborhood selection (Meinshausen & Bühlmann, 2006). Alternatively, He et al. (2019) test the same hypothesis directly based on estimates of precision matrices using graphical lasso (Friedman et al., 2008). As yet another alternative, Belilovsky, Varoquaux, and Blaschko (2016) propose a test by directly estimating the difference between two vectors of regression coefficients using a multitask fused lasso penalty. This approach offers an efficient framework for testing the difference between partial correlations, which may be of interest in some applications.

As an alternative perspective to the above procedures, S. Zhao, Ottinger, Peck, Mac Donald, and Shojaie (2019) have recently argued that quantitative tests for differential analysis of undirected networks, for example, tests based on differences between entries of precision matrices (or partial correlations) may not be desirable. In making this argument, they first point out that while GGMs are used for network inference, differences in parameter values (e.g., differences in partial correlations) may not be scientifically meaningful. Rather, the scientists are often interested in whether connectivity patterns are different. They also point out that because of their complex dependence patterns, GGM parameters corresponding to other edges may change if few edges in the network are rewired. As a result, tests based on quantitative differences between GGM parameters could result in uncontrollable false positives if the goal is to identify differences in network structures. To circumvent these issues, S. Zhao et al. (2019) propose a new framework, termed differential connectivity analysis (DCA), for testing qualitative differences in patterns of connectivity between two GGMs. However, testing qualitative hypotheses is more challenging and DCA requires additional assumptions.
4 | CONCLUSIONS

Differential network analysis is a promising new field with diverse biological applications (Cabusora, Sutton, Fulmer, & Forst, 2005; Gambardella et al., 2013; C. Ma, Xin, Feldmann, & Wang, 2014; Sas et al., 2018; Troy, Hollams, Holt, & Bosco, 2016). Given that networks are often not directly observed in biological settings, statistical methods for identifying differences between networks will continue to be essential tools in this area. With few exceptions (see Further Reading), existing statistical and computational approaches have thus far primarily focused on undirected GGMs. Differential network analysis for non-Gaussian data and directed networks offer fruitful opportunities of future research. Addressing the limitations of quantitative tests of differences between networks, discussed in S. Zhao et al. (2019) and briefly reviewed in the previous section, would also be an important direction of future research.

In addition to inferring networks based on activities of components of biological systems, a number of experimental platforms, such as ChIP-Seq and ChIP-chip assays (Landt et al., 2012), have also been developed to interrogate the interactions among these components as well as changes in these interactions (Barrios-Rodiles et al., 2005). These emerging assays offer the opportunity to more directly observe network edges or changes in the network structures. They may also be able to validate the findings from statistical/computational approaches, which is currently a key challenge. Designing efficient experiments based on these new assays (Kerr & Churchill, 2001) and accounting, and adjusting for batch effects (Leek et al., 2010) are challenging but impactful areas of future research.

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CONFLICT OF INTEREST

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FURTHER READING

Recent developments on statistical approaches for differential network analysis have started to focus on directed networks, and, in particular, directed acyclic graphs (DAGs) (Ghoshal & Honorio, 2019; Y. Wang et al., 2018), as well as graphical models for other data types (T. Cai, Li, Ma, & Xia, 2018; He et al., 2019; Kim, Liu, & Kolar, 2019; M. Yu, Gupta, et al., 2019; S. Zhao et al., 2019). A number of software tools have also been developed that provide tests of differential connectivity based on permutation approaches (Gill, Datta, & Datta, 2014), or by considering differences in marginal associations based on correlations, instead of conditional dependencies (Fukushima, 2013; McKenzie, Katsyv, Song, Wang, & Zhang, 2016). While these tools may not have strong theoretical support, or may test different hypotheses, they provide more convenient user interfaces and may be more computationally amenable for analysis of large networks.

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