Heterogeneity-Aware Gaussian Graphical Models for High-Dimensional Omics: A Narrative Review

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Abstract In high-dimensional omics data, sparse precision matrices of Gaussian graphical models (GGMs) can be used to encode conditional dependence among molecular features to allow for interpretable network inference. This narrative review integrates some of the heterogeneity-aware extensions of GGMs and categorizes them based on the way in which the information on heterogeneity is incorporated into the model. The review takes into account joint estimation of networks in known groups or conditions, covariate-indexed networks or individualized networks, as well as latent-subgroup models for unobserved groups. Known-group approaches use information from other networks of the same kind of groups, covariate-indexed approaches model variation in networks as a function of observed covariates, and latent-subgroup approaches infer both the network structure and the group membership. This review shows how each representation relates to its information requirements and limitations, leading to the choice of models and prioritisation of scalable inference, uncertainty quantification and external biological validation. This review establishes a unified tripartite taxonomy based on the observability of heterogeneity drivers, which systematically compares methodological trade-offs absent from prior fragmented reviews of Gaussian graphical models.

Keywords Gaussian graphical models, high-dimensional omics, network heterogeneity, joint graphical models, precision matrix estimation

1. Introduction

To capture conditional dependence among genes, proteins, metabolites, and other molecular features in high dimensional omics data, one can use Gaussian graphical models (GGMs). A GGM has nonzero off-diagonal entries of its precision matrix that correspond to edges of conditional dependence between pairs of variables [1]. When the number of molecular features exceeds the number of samples, early partial correlation methods based on genome and sparse inverse covariance (SIC) methods like graphical lasso enable GGM estimation to be feasible [2, 3]. The following applications and methodological reviews have demonstrated that GGMs can assist in the reconstruction of a network in the field of Gene Expression and in metabolomics studies [1, 4].

However, traditional GGM analyses often take one overall average network for all samples as the estimation target. This goal may be limiting since molecular relationships can vary from disease subtype, time point, clinical covariate, experimental condition or even individual patient. It is important to note that if the cancer or other heterogeneous system contains an edge, it might not refer to a correlation that holds true for all of the samples, but rather to a conditionally specific association only present for a certain subtype or cellular context [5, 7]. So aggregating all observations may mask the biologically-important differences between networks and may provide a structure that is not adequately representative of any sub-population. The problem of inference is therefore not just to know whether there is an edge in the population but also when and for whom it arises.

This shift has motivated several interrelated heterogeneous GGM inference strategies. Joint GGM approaches infer networks of interest for each condition or group, as well as sharing information between them [5, 6]. The latent subgroup methods simultaneously estimate the unobserved subgroups and the networks of these subgroups, and the number of subgroups can be identified based on the data using penalized fusion [7]. Covariate-dependent graphical regression models, however, provide a precision matrix that is a function of observed covariates, providing gradual or continuous network variation [8]. Although the

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strategies differ in some respects, they both have the same central tension, that information sharing can stabilize high dimensional estimates, but in specific cases, it can also prevent edges. The strategies are commonly addressed in different methodological literatures and so the assumptions, inferential targets and practical trade-offs are not easily compared.

To provide this comparison, the present narrative review uses network heterogeneity as the organizing principle. It queries what the target of inference is in GGMs when they are derived from a heterogeneous network and what trade-offs are made when using existing methods for sharing information, network specificity, scalability and biological interpretability. Such a comparison is especially relevant in the field of omics, where small sample sizes, large numbers of molecular features and clinically heterogeneous patient groups may hinder the estimation of networks both in pooled and separate analyses. Hence, the review looks at forms of known groups, covariate indexes, and latent subgroup with respect to aspects of inputs to heterogeneity, targets to the network, mechanisms of information sharing, and main limitations.

2. Literature Review

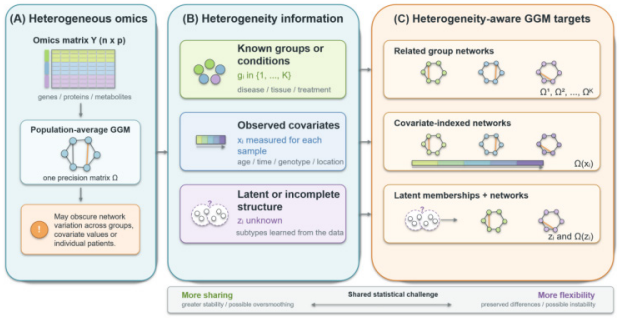

Figure 1. Network heterogeneity in GGMs.

2.1 Joint Network Estimation Across Known Groups and Conditions

Network heterogeneity can be captured by specifying precision matrix for each group of samples, where each group is defined by some disease, tissue type or experimental conditions. Combining all observations can lead to the loss of group specificity edges while estimating networks separately can result in the loss of shared biological structure and instability for small group samples. Joint estimation addresses this statistical tension by borrowing information across related groups while retaining meaningful network differences [5, 9].

For K groups, a broad class of frequentist joint estimators can be written as the following general penalized form, in which the constant terms that do not affect optimization are omitted [5, 9]:

$$\min_{\{\Omega^{(k)}\succ 0\}} \sum_{k=1}^{K} n_k \ell_k\left(\Omega^{(k)}\right) + P\left(\Omega^{(1)},\ldots,\Omega^{(K)}\right), \tag{1}$$

where the group-specific loss function is

$$\ell_k(\Omega) = \mathrm{tr}\left(S^{(k)}\Omega\right) - \log\det(\Omega). \tag{2}$$

Here, $S^{(k)}$ and $\Omega^{(k)}$ are the sample covariance and precision matrices for group k, respectively. The penalty $\mathcal{P}$ applies sparse constraints within each network and decides how similarity is encouraged across networks. Therefore, the main modeling choice is how the penalty structure encodes the information sharing between groups. Early methods shared information across networks, but generally adopted broad and unified penalties. Guo et al. decomposed each off-diagonal element of the precision matrix into the product form of a shared component and a group specific component. The hierarchical penalty encourages corresponding entries to be zero across all classes while allowing class-specific departures [9]. Danaher et al. made within-network sparsity and between-network similarity separately tunable in the joint graphical lasso. The fused graphical lasso (FGL) penalizes differences between corresponding entries, thereby encouraging similar sparsity and similar edge values. By contrast, the group graphical lasso (GGL) mainly encourages the corresponding edge to share a sparsity pattern without forcing their nonzero values to be the same [5]. Thus, FGL targets agreement in two edge-level aspects, edge inclusion and edge magnitude, whereas GGL primarily targets shared edge inclusion patterns. Using ADMM and block diagonal screening, FGL was applied to 17,772 genes and estimated shared and class-specific conditional dependence structures in airway epithelial samples from patients with lung cancer and controls [5]. However, these formulations largely apply a common similarity rule across edges and population pairs [6, 10].

Later research has gradually relaxed this uniformity by making information sharing more selective. Saegusa and Shojaie used a Laplacian penalty based on a weighted population-similarity graph, coupling more closely related populations more strongly. They applied the method to gene expression networks from three breast cancer subtypes [10]. At the edge level, CFGL used a data-driven screening matrix to decide which edges should be fused between each pair of conditions [6]. Bayesian approaches further introduce components shared across selected subsets of networks and edges [11], or use local, edge-specific shrinkage to borrow information while retaining network differences [12].

Their main value is that they can improve network estimation when several related groups have limited group-specific samples.

2.2. Covariate-indexed and Individualized Network Estimation

Joint estimation gives all subjects in a predefined group the same precision matrix. This setting becomes restrictive when networks vary with continuous or multivariate char-

acteristics, such as age, genotype, tumor purity, disease severity and spatial location. Covariate-indexed GGMs instead assume that

$$\mathbf{Y}_i | \ \mathbf{x}_i \sim \mathcal{N}_p\left(\mu(\mathbf{x}_i), \mathbf{\Omega}^{-1}(\mathbf{x}_i)\right). \quad (3)$$

Here, $\mathbf{x}_i$ denotes the covariate profile of subject i, and $\mathbf{\Omega}(\mathbf{x}_i)$ determines the network for subject i. Methods differ in their treatment of $\mu(\mathbf{x}_i)$, but they all allow covariates to change the precision matrix. Since each subject only provides one multivariate observation, the subject-specific graph must be obtained from a shared mapping $\mathbf{\Omega}(\cdot)$ learned across subjects.

One strategy borrows information along an ordered index. Zhou et al. used kernel weights to combine observations near a target time point, estimate a time-specific covariance matrix, and recover the corresponding precision matrix through an l_1-penalized Gaussian likelihood [13]. This assumes smooth evolution, whereas the group-fused graphical lasso estimates piecewise-constant precision matrices and accommodates abrupt changes [14]. These two ordered-index approaches exploit ordering but do not directly attribute edge-specific variation to multiple covariates. Covariate-indexed networks also differ from covariate-adjusted GGMs, in which covariates affect the mean while the precision matrix remains common across subjects [15].

Graphical regression models network structure directly as a function of observed covariates. An early Bayesian formulation allowed graph topology to vary with subject characteristics, although the developed methodology primarily targeted directed graphs [16]. GGMx extended this perspective to undirected GGMs by mapping covariates to sparse positive-definite precision matrices, allowing both edge inclusion and magnitude to vary [17]. A representative high-dimensional linear specification is [18]:

$$\Omega(\mathbf{x}_i) = \mathbf{B}_0 + \sum_{h=1}^{q} x_{ih}\mathbf{B}_h, \quad (4)$$

where $\mathbf{B}_0$ represents the population level precision structure and $\mathbf{B}_h$ captures the effect of covariate h. Zhang and Li imposed group and element-wise sparsity to select influential covariates and affected edges [18]. Wang et al. modeled edge-specific conditional precision functions using global-local shrinkage and Bayesian false discovery rate control [19]. Applications related individualized networks to prognostic factors in multiple myeloma [17], SNPs and clinical variables in brain cancer [18], and disease severity in hepatocellular carcinoma plasma-protein networks [19].

To relax fixed functional forms, Niu et al. used a covariate-dependent product partition, under which subjects with similar covariate profiles were more likely to share a graph [20]. GraphR accommodated categorical, continuous, and spatial heterogeneity within a graphical regression framework and used variational Bayes for scalable estimation in proteogenomic and spatial transcriptomics applications [21]. These approaches broaden covariate-dependent modeling while retaining information sharing across related subjects.

As the numbers of nodes and covariates increase, estimation shifts toward controlling the large array of edge-specific effects. Dual-group spike-and-slab priors select effects at covariate, node, and local levels [22]. Multitask learning jointly estimates node-wise regressions and shares information across related tasks [8], whereas debiased estimators enable asymptotically valid inference on covariate effects [23].

2.3 Network Estimation with Latent Subgroups

Observed group labels and measured covariates do not exhaust all biologically significant heterogeneity. After known-group and covariate-indexed GGMs, a third setting arises when subgroup attribution itself cannot be observed. A typical latent subgroup formulation assumes

$$Y_i \sim \sum_{k=1}^{K} \pi_k N_p\left(\mu_k, \Omega_k^{-1}\right) \quad (5)$$

where the membership variable z_i, the subgroup means and the subgroup-specific precision matrices are all unknown [24, 25]. The inferential target therefore shifts from estimating networks conditional on labels or covariates to jointly learning latent memberships and subgroup-specific conditional-dependence structures.

Gao et al. placed multiple-network estimation in this Gaussian-mixture framework, enabling unknown disease subtype discovery and differential gene-network analysis within the same model [24]. Hao et al. developed SCAN to learn cluster structure while estimating heterogeneous graphical models through a high-dimensional ECM algorithm and a joint graphical lasso penalty [25]. These methods show that clustering and network estimation need not be separated into two independent steps when heterogeneity is discrete but unlabelled.

Ren et al. addressed a further limitation of mixture-based approaches: the number of subgroups often has to be fixed in advance. Their penalized-fusion GGM applies regularization to both mean and precision-matrix parameters and uses a fusion penalty to determine the subgroup number in a data-dependent way [7]. Applications to non-small-cell lung cancer single-cell expression data and lung adenocarcinoma histopathological imaging data illustrate the value of this framework for unsupervised heterogeneity analysis [7].

3. Discussion

3.1 Comparing Three Representations of Network Heterogeneity

Previous omics-oriented GGM reviews have laid an important conceptual and practical foundation for omics network analysis, including conditional dependence

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interpretation, sparse precision matrix estimation, implementation workflows, and uncertainty assessment [1]. Bayesian graphical model reviews have further extended this landscape to non-standard biological settings, including multiple related graphs, networks that change with covariates, and other complex sampling or structural settings [26]. The present review builds on these foudations by taking the source of heterogeneity information as the organizing principle. This framewprk clarifies the point that is often implicit in method-centered reviews: known labels, measured covariates and latent subgroup not only correspond to different algorithms, but also define different network targets, information sharing assumptions and validation risks. The three representations primarily differ in how heterogeneity information enters the model. Their boundaries can overlap: encoding subtype or treament as a categorical covaraite can yield the same finite set of networks as a known-group model. Their inferential focus still differs: multi-network methods compare shared and condition-specific edges across supplied groups [5, 6], graphical regression estimates covariate effects or individualized networks [17, 21], and latent subgroup models infer memberships with specific networks [7, 25]. Representation therefore depends on the biological question, observed information, and whether variation is expected to be discrete or gradual. Table 1 summarizes the three representations in terms of the heterogeneity information they require, the network target they estimate, and the main validation risk.

Table 1. Comparison of three representations of network heterogeneity.

Representation	Heterogeneity information	Network target	Main strength	Main risk
Known-group multi-network models [5, 6, 10-12]	Given group or condition labels	Group specific networks; shared or condition specific edges	Direct group comparison	Label sensitivity; sharing strength
Covariate-indexed models [13, 14, 17-23]	Measured covariates or ordered indices	Covariate varying or sample specific networks	Gradual or context dependent variation	Functional form; covariate coverage; positive definiteness
Latent-subgroup models [7, 24, 25]	Unobserved group membership	Subgroup memberships; subgroup networks	Hidden class discovery without labels	Subgroup number; initialization; biological interpretation

In 902 tumor infiltrating regulatory T cells, penalized fusion identified three latent subgroups of 409, 316, and 177 cells whose networks contained 51, 87, and 276 edges; all pairwise network comparisons were significant ($p < 0.001$) [7]. Together, the unequal subgroup sizes, divergent edge counts, and significant pairwise tests indicate statistical network heterogeneity. Biological interpretation of these subgroups still requires external evidence, such as marker expression, pathway enrichment or sample annotation.

3.2 Methodological Trade-Offs and Model Selection

Model selection depends on the information available and the expected pattern of change. Known labels with small groups favor joint multi-network estimation; when heterogeneity is driven by continuous or multiple factors, the covariate-indexed model is more suitable; and unknown but plausibly discrete classes opt for latent subgroup models.

Frequentist penalized estimators often have good scalability and possess consistency or asymptotic theory, but it is still difficult to quantify uncertainty effectively after regularization; a debiased procedure can solve this partly [23]. Bayesian formulations can provide posterior edge integration into probabilities and structured shrinkage, but the inference based on MCMC can be computationally demanding [19]. Posterior-mode approximation such as jointGHS improve scalability but does not provide fully Bayesian uncertainty quantification [12]. GraphR uses variational Bayes for scalable approximate inference [21]. Covariate-indexed models must ensure positive definiteness, mixture models face uncertainty about the number of initialization and subgroups, while the multi-network models need to control the sharing parameter. Edge complexity increases quadratically with and will further multiplies across groups, covariates or latent components.

3.3 Scope Boundaries and Future Directions

3.3.1 General Limitations of Existing Heterogeneity-Aware GGM Frameworks

Several limitations cut across all three representations. First, a GGM edge records conditional dependence under the fitted distribution; Additional biological evidence is required to interpret these edges as regulatory relationships or physical interactions [1]. Secondly, the Gaussian assumptions can be inadequate for the omics measurements of heavy tail, mixed type or zero expansion [27-29]. In rBGR studies, the expression of Akt and PTEN in lung adenocarcinoma and E-cadherin and Rb in ovarian cancer still showed heavy tail and non-normal characteristics after logarithm conversion, and the H-score was higher

than 0.999 [27]. Third, unmeasured common factors may affect multiple nodes at the same time, making the estimated biological attribution of network differences more difficult [1]. Finally, the differences in simulation design and parameter adjustment procedures limit the numerical comparison across studies.

3.3.2 A Hierarchical Research Agenda

Recent methodological advances show that heterogeneity and departures from Gaussian assumption can be addressed jointly, but are still limited to specific data situations [27-29]. There is still an important research gap in integrating heterogeneity with missing data and nominal data [28] and with composition constraints [30]. At the structural level, GraphR incorporates group, sample and spatial heterogeneity within a covaraite-indexed regression framework [21]. A valuable expansion direction is to further incorporate covaraite-indexed models with latent subgroup models within the same framework, while also taking dependence across layers into consideration. Future models could also allow the degree of information sharing to change with different edges and samples. Inferential priorities include scalable uncertainty quantification, stability diagnostics, and benchmarks that vary subgroup imbalance, network similarity, covariate dimension, and model misspecification. External cohorts can test reproducibility; pathway agreement can evaluate whether the results are consistent with existing knowledge; perturbation studies can probe mechanisms; and outcome data can assess clinical relevance.

4. Conclusion

This narrative review examined how network heterogeneity changes the inferential target of Gaussian graphical models in high-dimensional omics. Based on the relevant literature of known groups, observed covariates and latent subgroups, it can be seen that the available heterogeneous information will affect the network inference target. Depending on the scientific question, an overall average GGM is sufficient if the conditional dependence structure of interest is the same for all networks; known labels can be used for joint multi-network estimation; if the driving variables can be measured, then a basis for covariate-indexed models; and if discrete subgroups are reasonable but not labeled, then a latent subgroup model can be used.

In all three settings, the general methodological issue is to borrow sufficiently to produce stable estimates and to not obscure the edge of the network in a particular context. Overall, the examined approach captures the shift from global merging to more targeted information sharing, which can happen at a population, edges, covariate profiles, and latent components. The present review makes a structured comparison of these options with respect to the heterogeneity input, the target of the inference, the stability, the computational requirements, the uncertainty quantification and the validation requirements. Estimating a more individual network or dividing a more refined subgroup does not in itself strengthen scientific interpretation. Conditional dependent edges depend on external biological evidence and statistically separated networks could be an effect of model assumptions, factors or parameter instability.

One of the keys is to achieve methodological flexibility while simultaneously enhancing validation. Applied methodology aspects involve models for non-Gaussian, mixed, compositional and incomplete measurements, locally adaptive information sharing and scalable uncertainty quantification and stability diagnostics. Common benchmarks of evaluation priorities are those that vary subgroup imbalance, network similarity, covariate dimension, and model misspecification. Estimated differences can be assessed in terms of biological significance and reproducibility using external cohorts, pathway concordance and perturbation studies, and clinical outcomes. If the network estimates are statistically valid, its assumptions and justification are clearly communicated, and appropriate verification is performed, it can be used to convey useful information for biological or clinical reasoning in the case of heterogeneous GGMs.

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