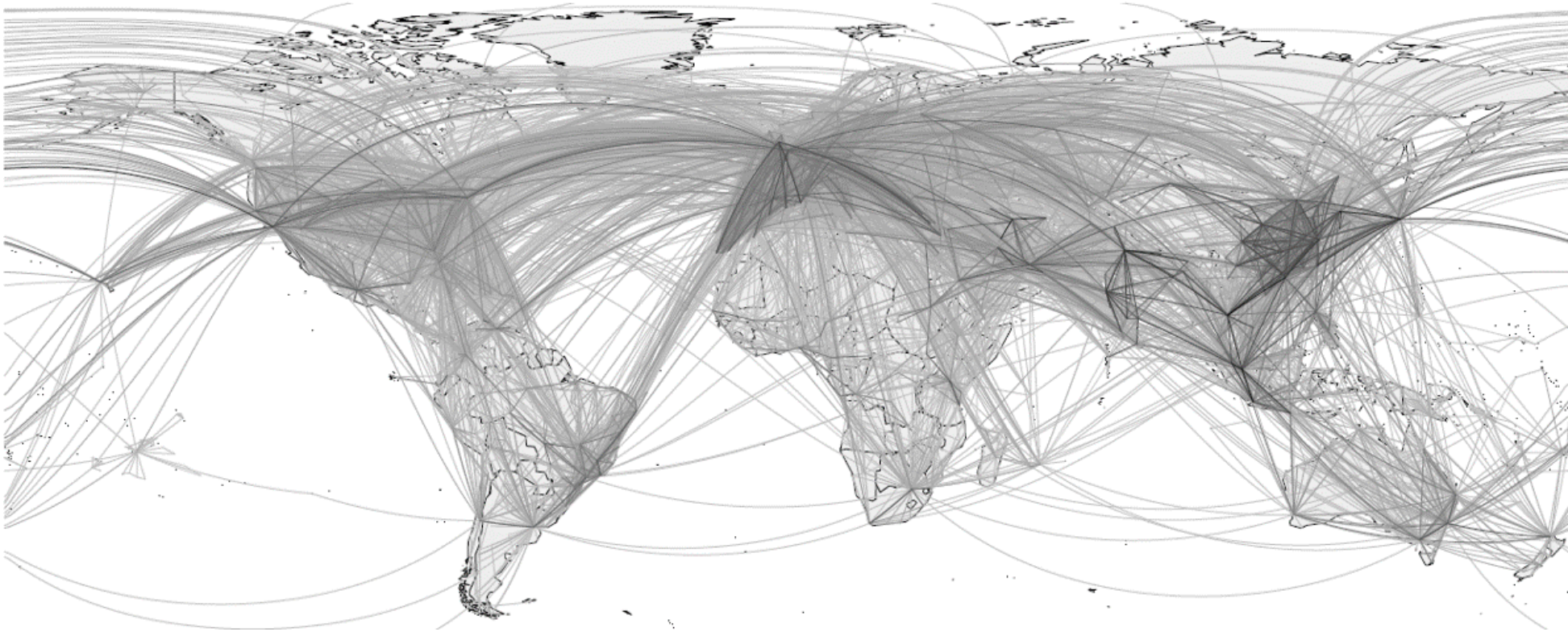
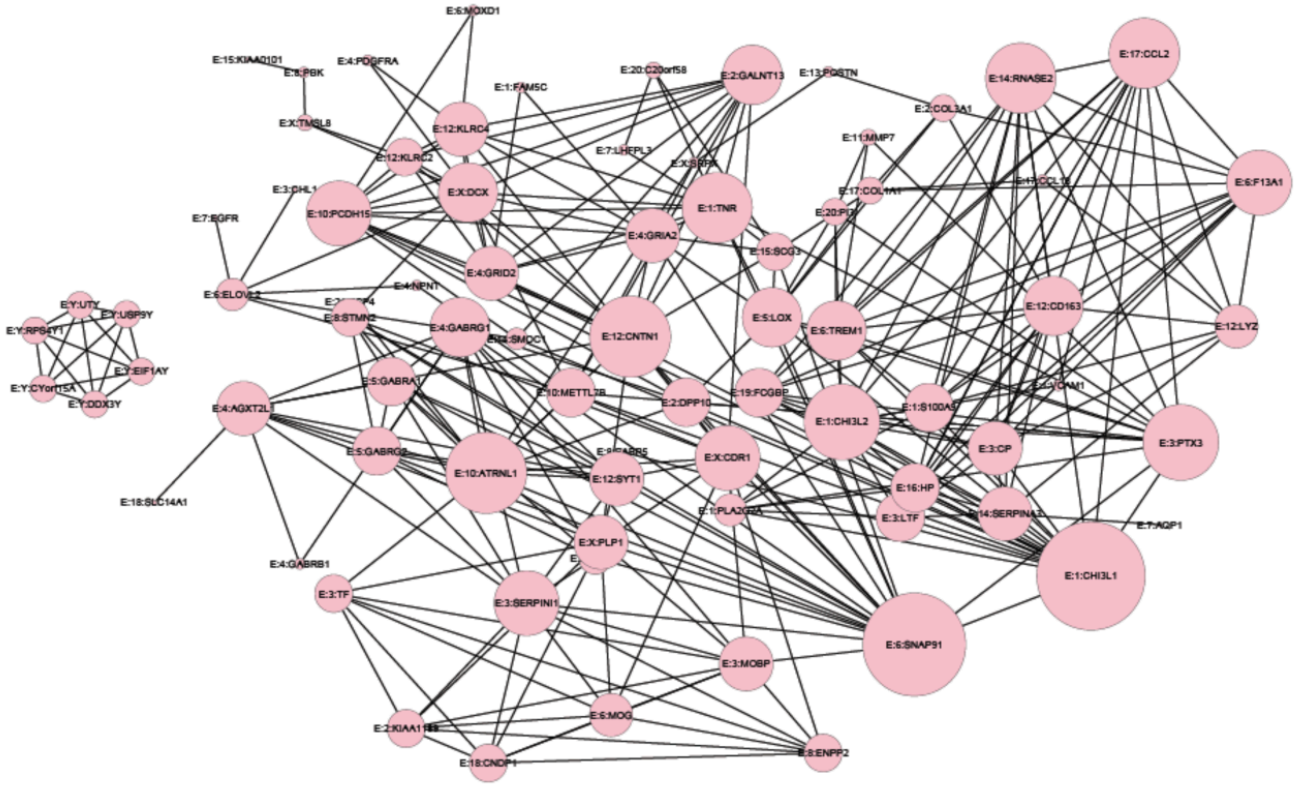
Unsupervised Learning: Graphical Models

Networks



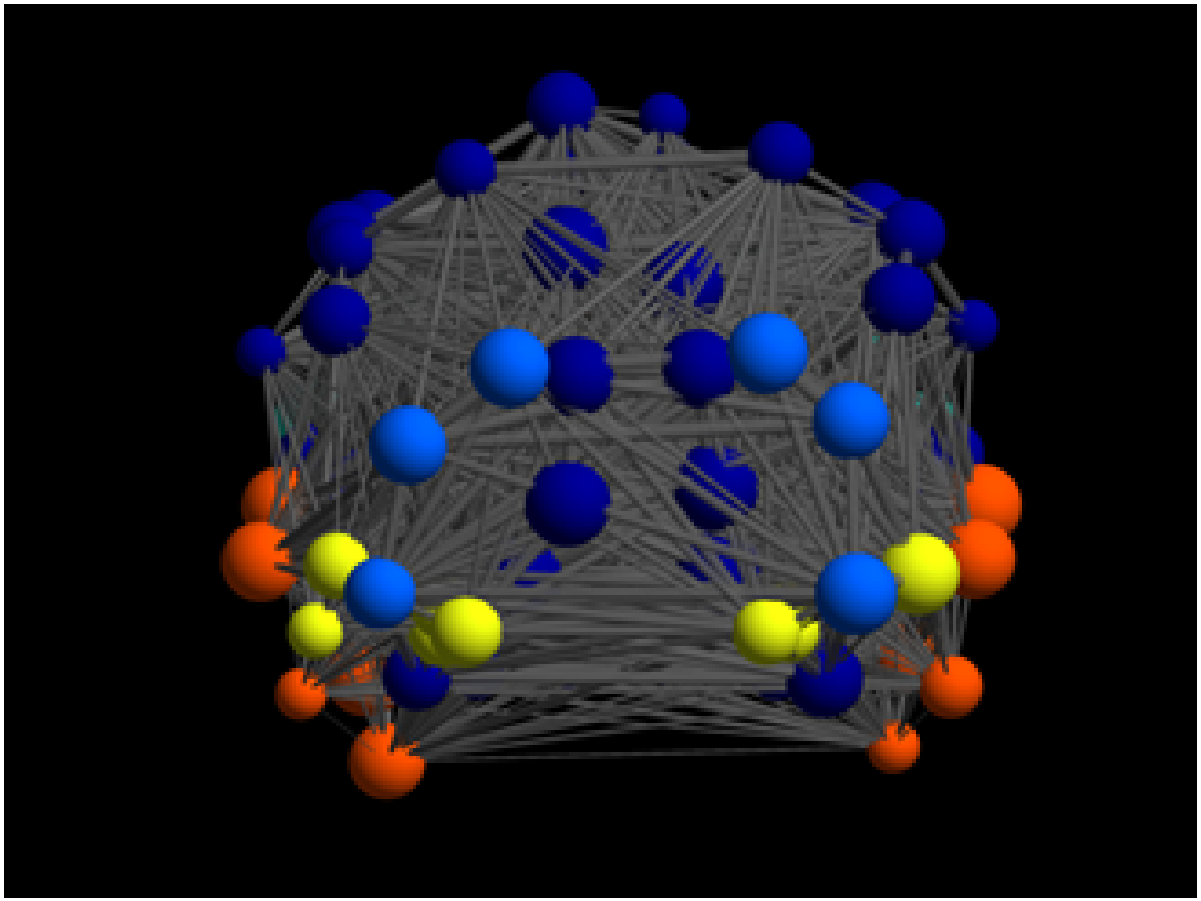
Depicts relationships (edges) between features (nodes).

Networks



Genomics: Relationships between genes.

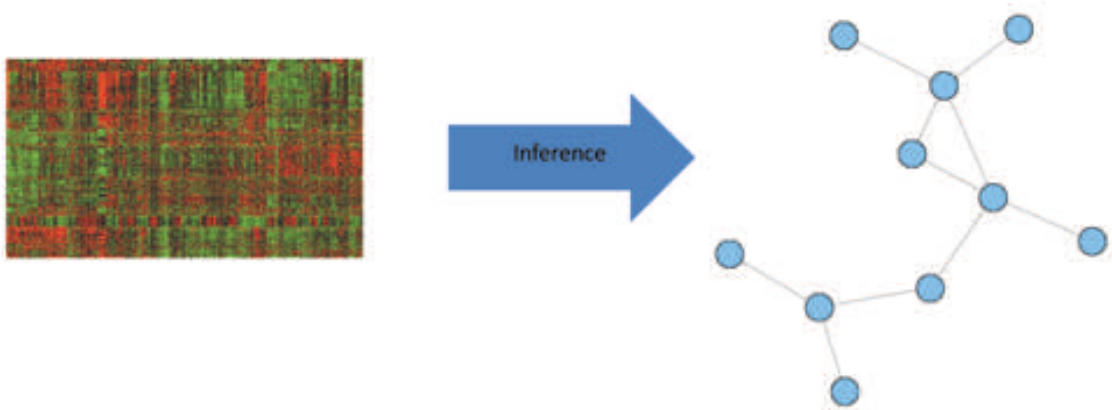
Networks



Neuroimaging: Relationships between brain regions.

Networks in Unsupervised Learning

1. Network Data.
   - Examples: Social networks, twitter, citations, surveillance, web links, etc.
2. **Our focus**: Learn network from data (structural network learning).
   - Data matrix: $\boldsymbol{X}_{n\times p}$.
   - Features form p nodes.
   - Goal: Learn edges between nodes $\equiv$ learn the relationships between features.



Network Data

- Network data have arisen as one of the most common forms of information collection.
- Networks consist of two components:
  1. nodes or vertices corresponding to basic units of a system;
  2. edges representing connections between nodes.
- Examples:
  1. Nodes might be humans in social networks; molecules, genes, or neurons in biology networks, or web pages in information networks.
  2. Edges could be friendships, alliances, URLs, or citations.
- A network can be represented by an adjacency matrix.

Stochastic Block Models

- There are different statistical models for network data, and the stochastic block model (SBM) is very popular.
- In a SBM, the nodes are partitioned into $K < n$ disjoint groups, or *communities*, according to some latent random mechanism.
- A stochastic block model with n nodes and K communities is parameterized by a pair of matrices (Θ, B), where $\Theta \in \mathbb{M}_{n,K}$ is the membership matrix (each row has exactly one 1 and $(K-1)$ 0 's) and $B \in \mathbb{R}^{K \times K}$ is a symmetric connectivity matrix with edge probabilities.
- The adjacency matrix $A = (a_{ij})_{1 \le i,j \le n}$ is generated as

$$a_{ij} = \begin{cases} \text{independent Bernoulli}\left(B_{g_i g_j}\right), & \text{if } i \le j \\ a_{ji}, & \text{if } i > j \end{cases}$$

  where $g_i \, (1 \le g_i \le K)$ is the community label.
- Variants of block models: degree-corrected SBM, dynamic SBM, etc.

Community Detection

- The basic goal of community detection is to partition the vertices of a graph into clusters that are more densely connected.
- In SBMs, community detection aims to recover the membership matrix Θ up to column permutations.
- Assuming K is known, different procedures are proposed to solve the problem, including likelihood methods, spectral clustering, modularity maximization, etc.

Community Detection and Stochastic Block Models

Example of one spectral clustering algorithm in SBM (Lei and Rinaldo, 2015)

Algorithm 1: Spectral clustering with approximate k-means

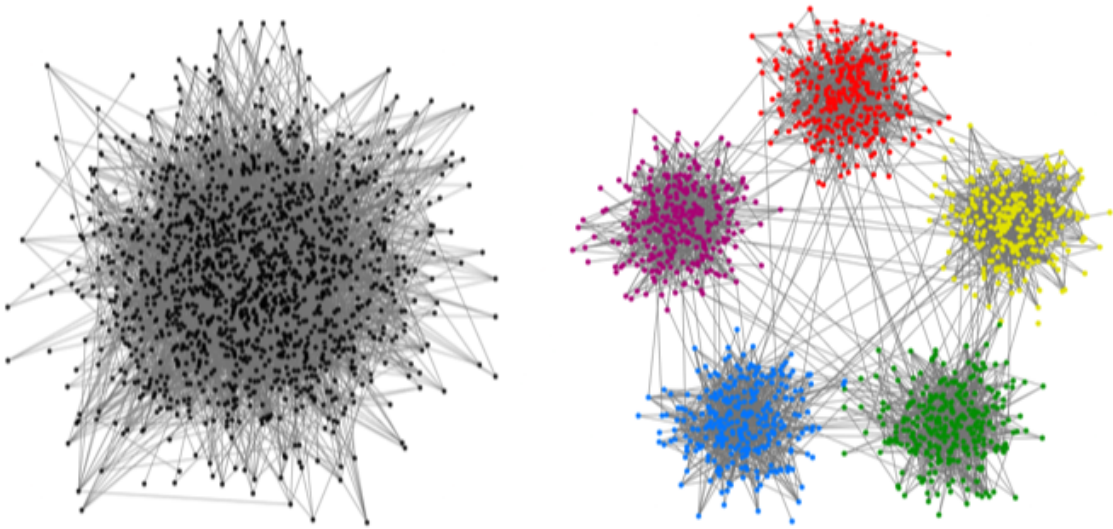
Input : Adjacency matrix A; number of communities K; approximation parameter ε.

Output: Membership matrix $\widehat{\Theta} \in \mathbb{M}_{n,K}$.

1. Calculate $\widehat{U} \in \mathbb{R}^{n \times K}$ consisting of the leading k eigenvectors (ordered in absolute eigenvalue) of A.
2. Let $(\widehat{\Theta}, \widehat{X})$ be an $(1+\varepsilon)$ -approximate solution to the k -means problem with K clusters and input matrix $\widehat{U}$.
3. Output $\widehat{\Theta}$.

Community Detection and Stochastic Block Models

- The following two graphs are the same graph re-organized and drawn from the SBM model with 1000 vertices, 5 balanced communities, within-cluster probability of $1/50$ and across-cluster probability of $1/1000$.
- The goal of community detection in this case is to obtain the right graph (with the true communities) from the left graph (scrambled) up to some level of accuracy.



Networks in Unsupervised Learning

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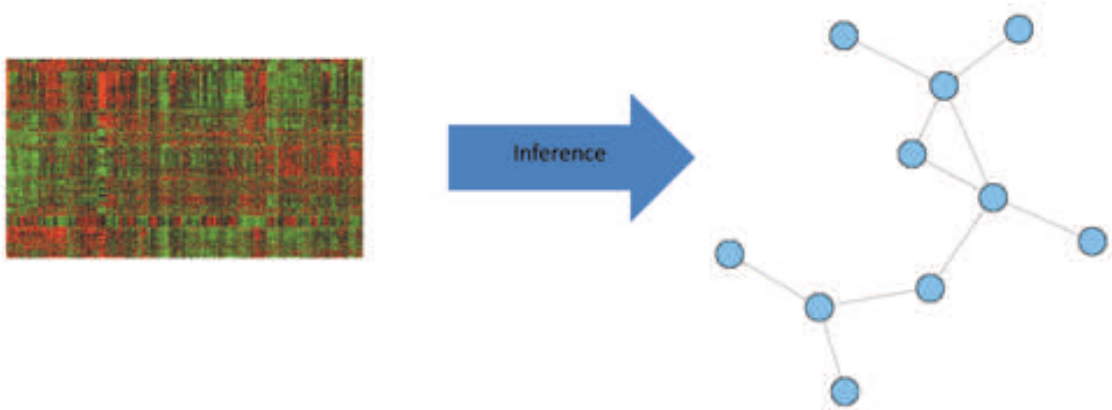
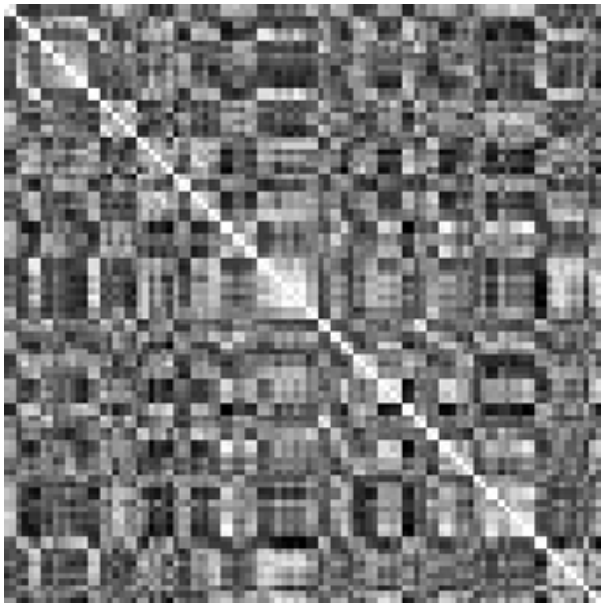
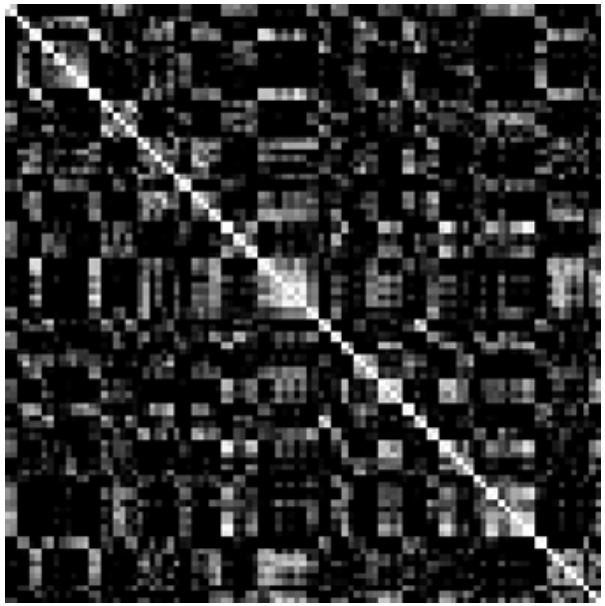


Correlation Networks (Association Networks)

- Simplest (and most-widely used!) method for estimating networks; assumes that edges correspond to large correlation magnitudes.
- Let $r(i, j)$ be correlation between X_i and X_j; we claim an edge between i and j if $|r(i, j)| > \tau$.
  - τ: a user-specified threshold (tuning parameter).



Correlation matrix.



Thresholded correlation matrix.

Limitations of Correlation Networks

1. The estimation is highly dependent on the choice of τ.
2. Correlation captures **linear** associations, but many real-world relationships are nonlinear.
3. Large correlations can occur due to confounding.

Limitations of Correlation Networks

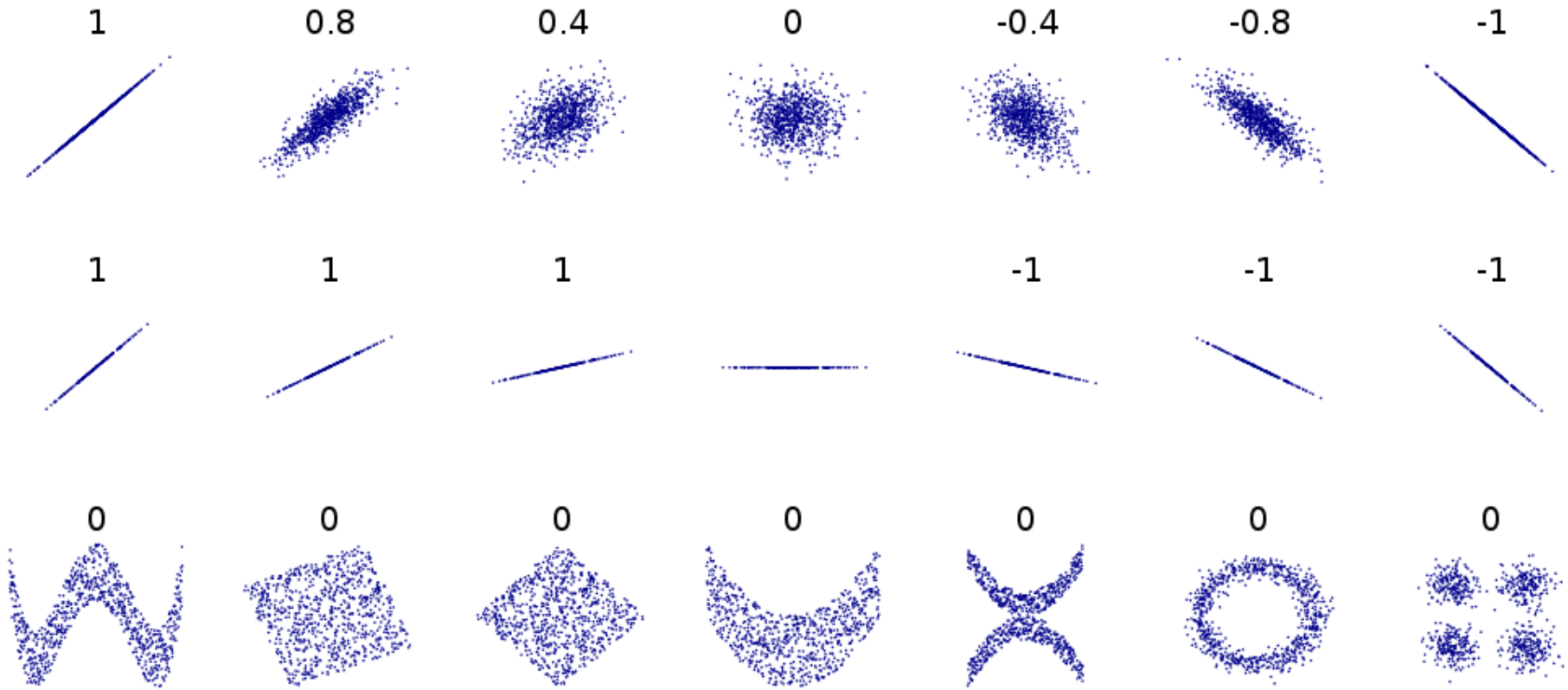
The estimation is highly dependent on the choice of τ.

- We can instead test $H_0 : r_{xy} = 0$
- A commonly used test is given by the Fisher transformation

$$Z = \frac{1}{2} \ln \left(\frac{1+r}{1-r} \right) = \operatorname{artanh}(r) \sim_{H_0} N \left(0, \frac{1}{\sqrt{n-3}} \right)$$

Limitations of Correlation Networks

Correlation captures **linear** associations, but many real-world relationships are nonlinear.



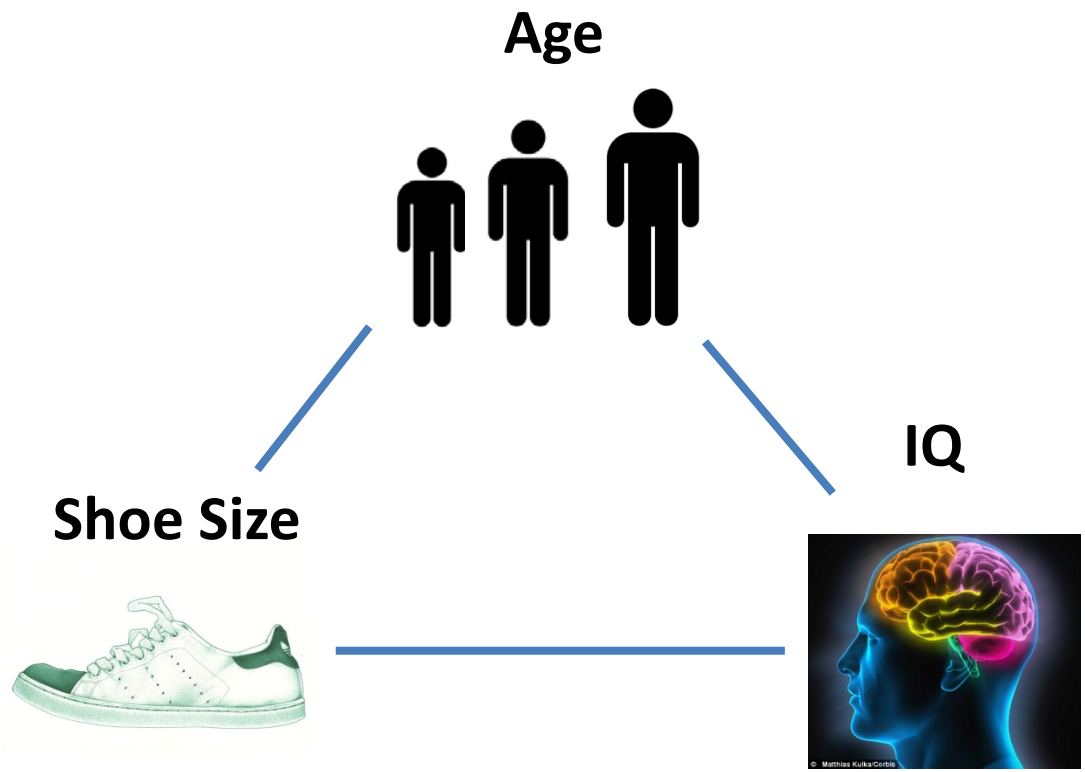
Limitations of Correlation Networks

Correlation captures **linear** associations, but many real-world relationships are nonlinear.

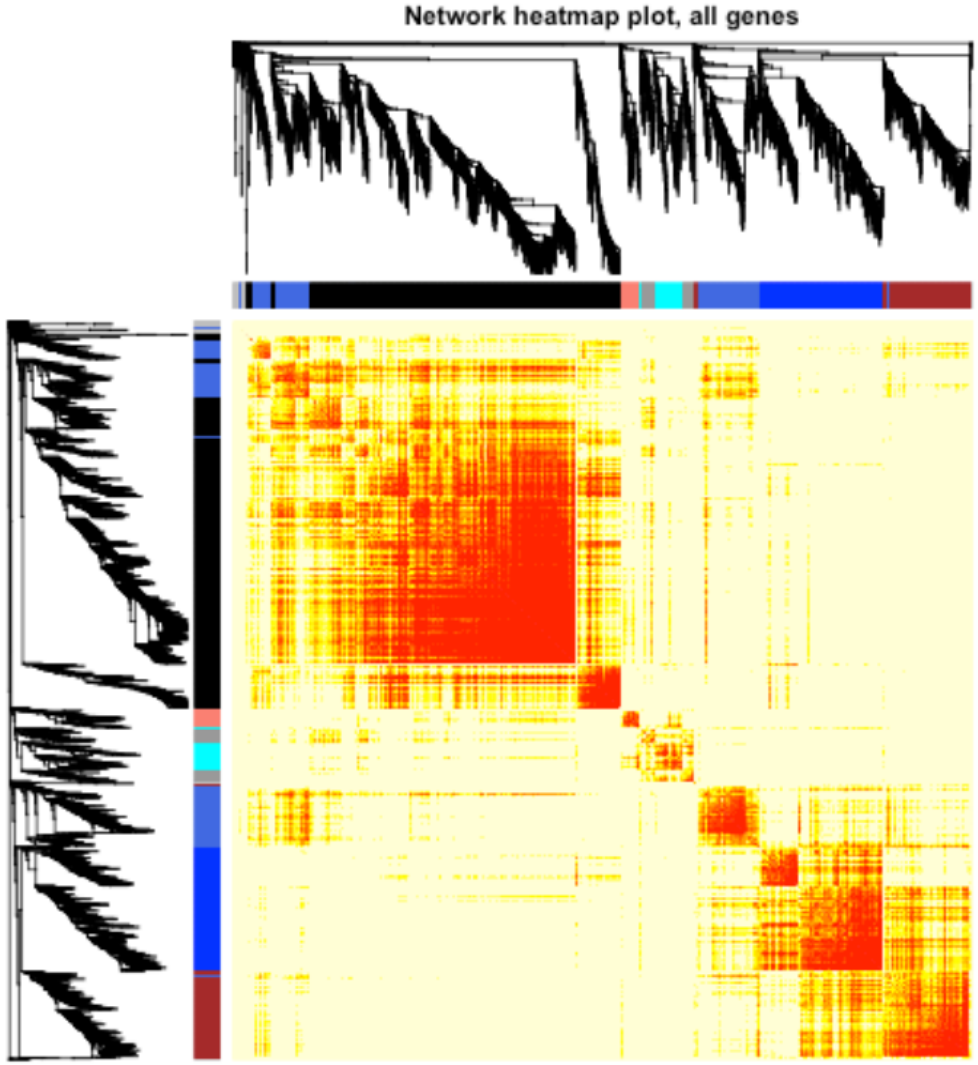
- We can use other measures of association, for instance, Spearman correlation or Kendal's τ.
  - These methods define correlation between two variables, based on the ranking of observations, and not their exact values.
  - They can better capture non-linear associations.
- We can instead use mutual information; this has been used in many algorithm, e.g. ARACNE.

Limitations of Correlation Networks

Large correlations can occur due to confounding.



Correlation Network Example: WGCNA



Weighted Gene Co-Expression Network Analysis

Popular R Package

Correlation Network Example: WGCNA

WGCNA Approach:

1. Thresholds the correlation matrix.
2. Raises this to an even-integer power (usually 6).
3. Measures modularity via a topological approach.
4. Finds modules (clusters) using hierarchical clustering of co-modularity.
5. Analyzes modules.

Strengths?
Weaknesses?

Graphical Models

Probabilistic Graphical Models

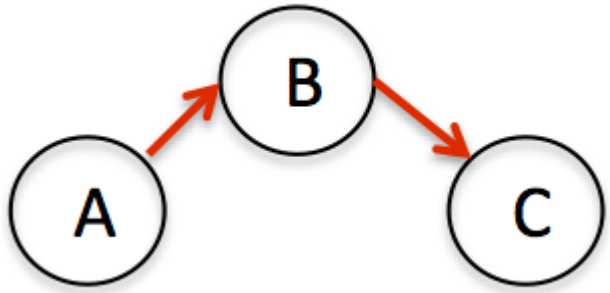
Joint multivariate probability distribution where dependencies can be represented as a network.

Advantages:

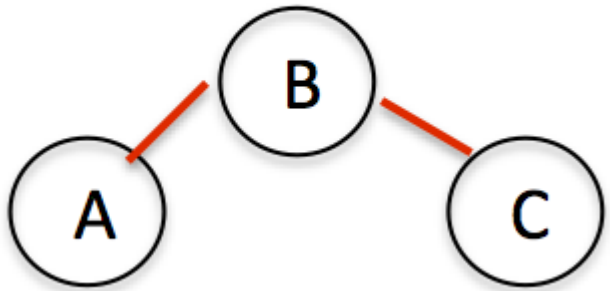
- Graphical models offer efficient factorized forms for joint distributions with easily interpretable dependencies.
  - **Conditional dependencies** denoted via an edge in network.
- Convenient visual representation.

Two Major Types of Graphical Models

1. Directed - Bayesian Networks.
   - Directed Acyclic Graphs.



2. Undirected - Markov Networks.
   - **Our Focus!**

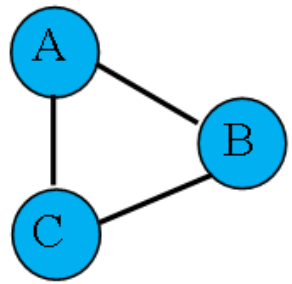


Markov Networks

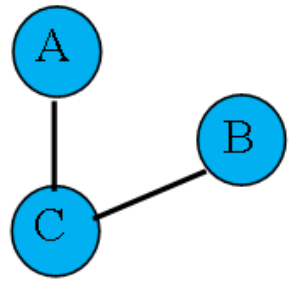
Markov Network

An *undirected graphical model* that characterizes conditional dependence ($\equiv$ direct relationships).

- *Edge*: Two nodes are **conditionally dependent**.
- *No edge*: Two nodes are **conditionally independent**.
- Conditions on all other nodes.



$$A \perp B \mid C$$



Markov Networks — Conditional Dependence

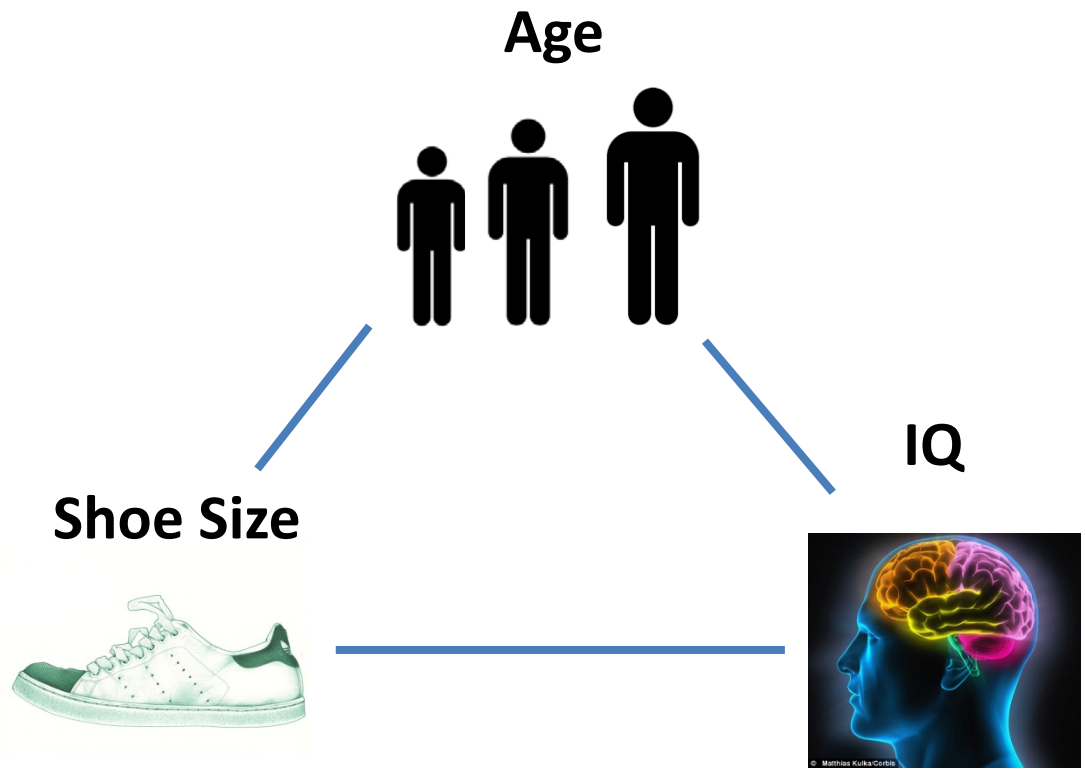
Regression Interpretation:

- Imagine trying to predict the observations in Node A (response) by the observations of all other nodes (predictors).

- Node B predictive of Node A (with all other nodes in model).
  - A is conditionally dependent on B.
  - Edge.

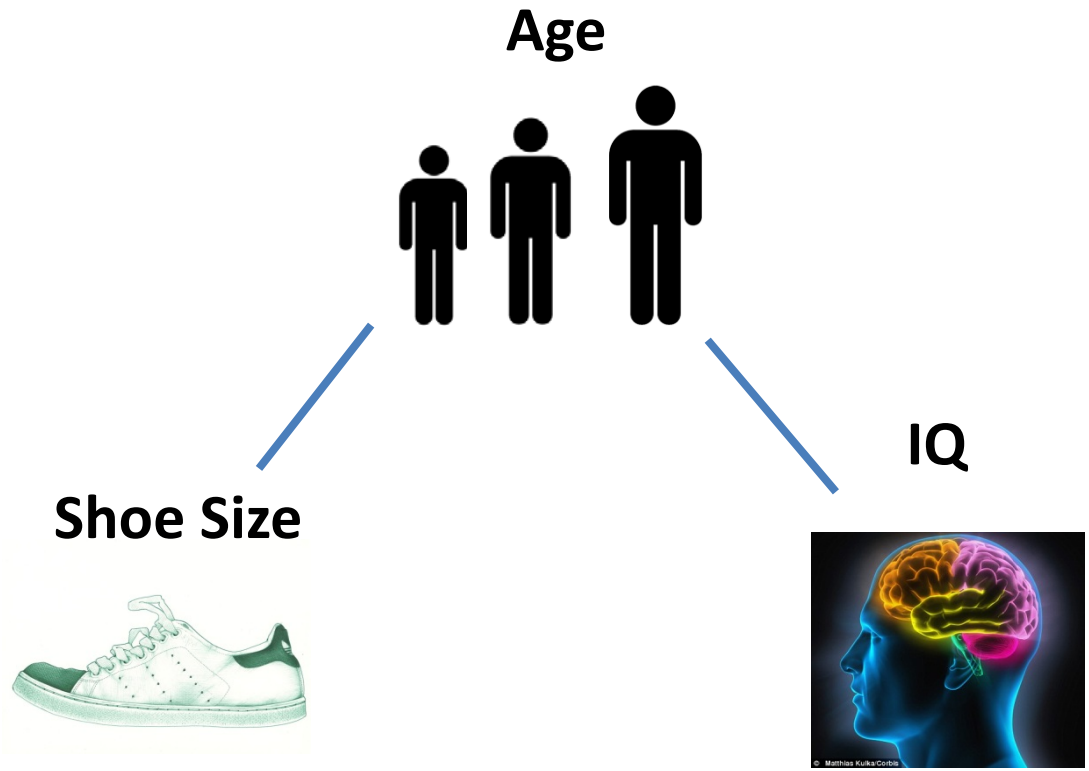
- Because of other nodes in model, Node B does not add any predictive value for Node A.
  - A is conditionally independent of B.
  - No Edge.

Markov Networks — Conditional Dependence



Correlation.

Markov Networks — Conditional Dependence



Conditional Dependence.

Markov Networks — Conditional Dependence

How can we learn conditional dependencies?

- A and B are conditionally independent given C if

$$P(A, B \mid C) = P(A \mid C)P(B \mid C)$$

  - Generally difficult (need to estimate multivariate densities).
- Alternatively, can use nonparametric approaches, e.g. conditional mutual information, but not easy in high dimensions.
- Often resort to models, or simple measures, such as partial correlations...

Partial Correlation

- Partial correlation measures the correlation between A and B after the effect of the other variables are removed.
  - In our example, this means correlation between shoe size and IQ, after adjusting for age.
- The partial correlation between A and B given C is given by:

$$\rho_{AB \cdot C} \equiv \rho(A, B|C) = \frac{\rho_{AB} - \rho_{AC}\rho_{BC}}{\sqrt{1-\rho_{AC}^2}\sqrt{1-\rho_{BC}^2}}.$$

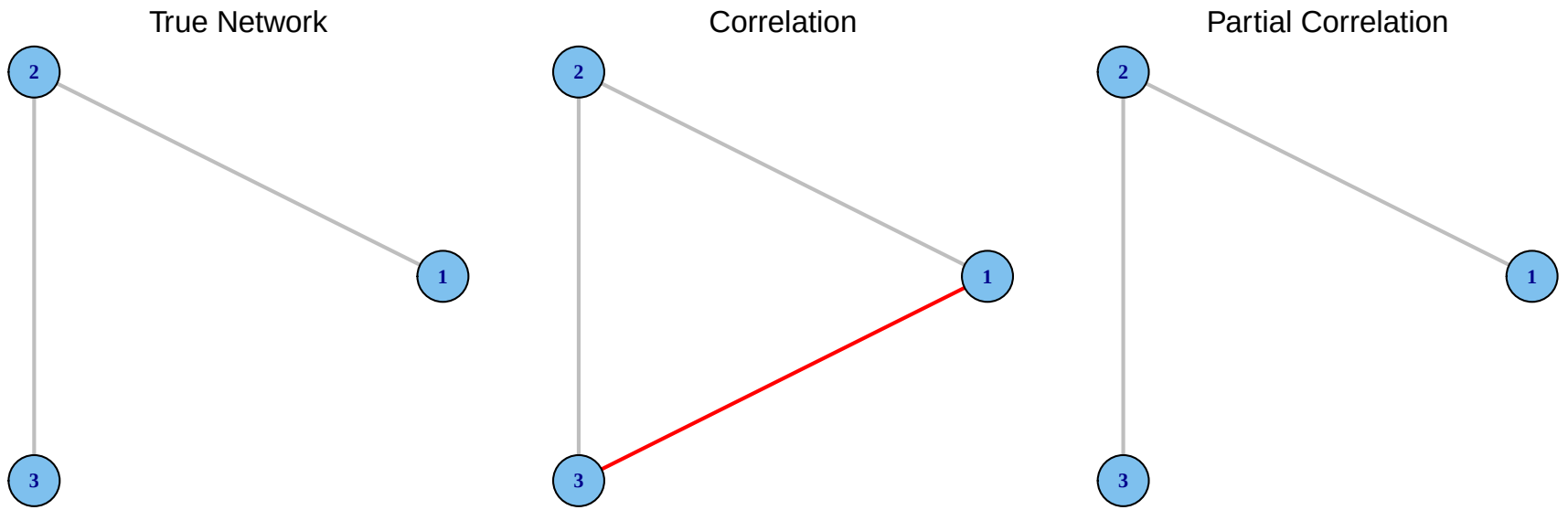
- Alternatively, regress A on C and get the residual, r_A; do the same for B to get r_B. The partial correlation between A and B give C is $\text{Cor}(r_A, r_B)$.

Partial Correlation

- Partial correlation is symmetric $\Rightarrow$ undirected network
- Partial correlation is a number between -1 and 1
- In partial correlation networks, we draw an edge between A and B, if the partial correlation between them is large
- Calculation of partial correlation is more difficult

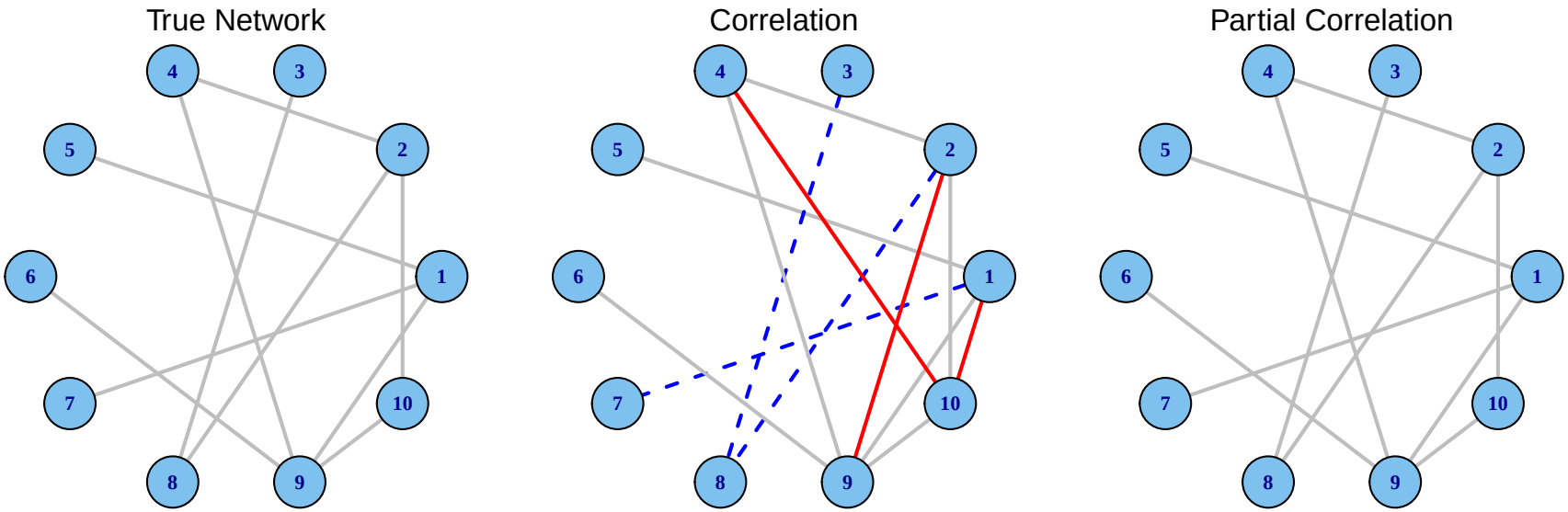
A Simple Example

$$Correlation = \begin{bmatrix} 1 & -.8 & .7 \\ -.8 & 1 & -.8 \\ .7 & -.8 & 1 \end{bmatrix} \quad PartialCorr = \begin{bmatrix} 1 & .6 & 0 \\ .6 & 1 & .6 \\ 0 & .6 & 1 \end{bmatrix}$$



A Larger Example

- A network with 10 nodes and 20 edges
- $n = 100$ observations
- Estimation using correlation & partial correlation (20 edges)

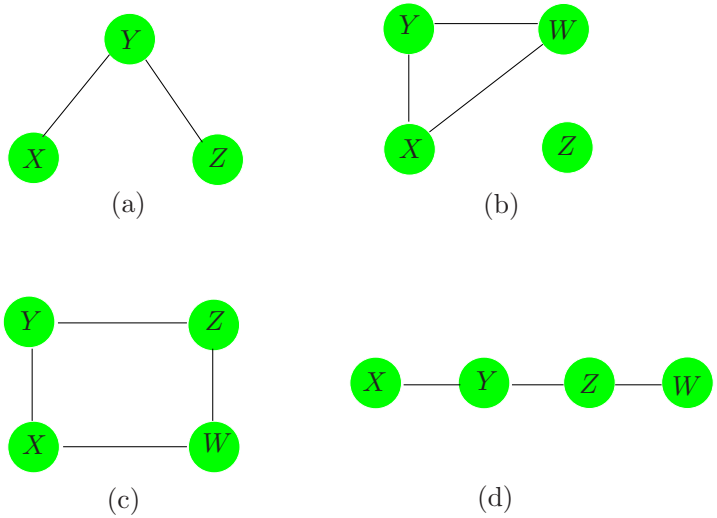


Gaussian Graphical Models (GGMs)

Partial Correlation for Gaussian Random Variables

- For Gaussian (multivariate normal) random variables, partial correlation between X_i and X_j given all other variables is given by the inverse of the (standardize) covariance matrix $\mathbf{\Sigma}$.
  - The (i, j) entry in $\mathbf{\Sigma}^{-1}$ gives the partial correlation between X_i and X_j given all other variables $X_{\setminus i,j}$.
- Gaussian Graphical Model (GGM):
  - Multivariate normal: $\boldsymbol{X} \sim N(0, \mathbf{\Sigma})$
  - $\mathbf{\Theta} = \mathbf{\Sigma}^{-1} =$ inverse covariance/precision/concentration matrix.
  - Zeros in $\mathbf{\Theta} \implies$ conditional independence!
  - Edges correspond to non-zeros in $\mathbf{\Theta}$.

Partial Correlation for Gaussian Random Variables



$$\begin{pmatrix} - & \times & 0 \\ \times & - & \times \\ 0 & \times & - \end{pmatrix} \qquad \begin{pmatrix} - & \times & \times & 0 \\ \times & - & \times & 0 \\ \times & \times & - & 0 \\ 0 & 0 & 0 & - \end{pmatrix}$$

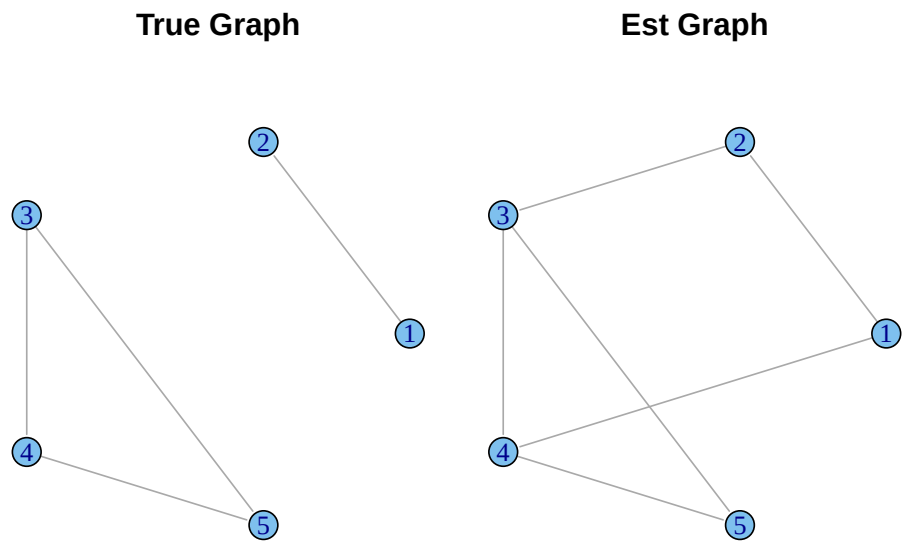
$$\begin{pmatrix} - & \times & 0 & \times \\ \times & - & \times & 0 \\ 0 & \times & - & \times \\ \times & 0 & \times & - \end{pmatrix} \qquad \begin{pmatrix} - & 0 & 0 & \times \\ 0 & - & \times & 0 \\ 0 & \times & - & \times \\ \times & 0 & \times & - \end{pmatrix}$$

Estimating GGMs

From our discussions so far, to estimate the network, we can

1. Calculate the empirical covariance matrix: for (centered) $n \times p$ data matrix X, $\boldsymbol{S} = (n-1)^{-1} X^\intercal X$.
2. Find the inverse of $\boldsymbol{S}$. Non-zero values of $\boldsymbol{S}^{-1}$ give the edges.

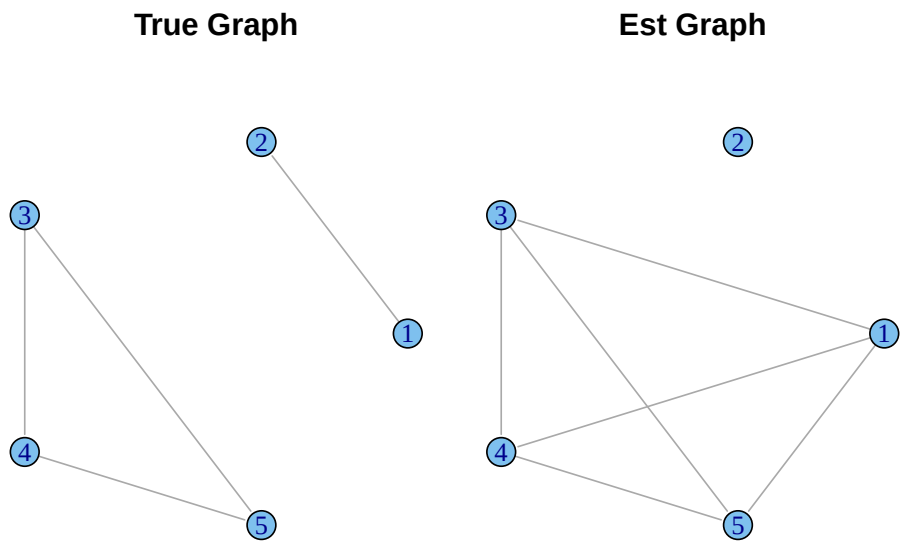
While simple, this may not work well in practice, even with large samples!



Estimating GGMs in High Dimensions

Many problems arise in high-dimensional settings, when $p \gg n$.

- First, $\boldsymbol{S}$ is not invertible if $p > n$!
- Even if $p < n$, but n is not very large, we may still get poor estimates, and many false positives/negatives.



Estimating GGMs in High Dimensions

- A number of methods have been recently proposed for estimating GGMs in high dimensions.
- The main idea in most of these methods is to use a regularization penalty, like the lasso.
- We discuss two approaches:
  - neighborhood selection
  - graphical lasso

Estimating GGMs in High Dimensions – Method 1

The idea behind neighborhood selection, is to estimate the graph by fitting a penalized regression of each variable on all other variables.

- Find neighbors of each node X_j by l_1-penalized regression or lasso:

$$\underset{\beta^j}{\text{minimize}} \quad \|X_j - \boldsymbol{X}_{\neq j}\beta^j\|_2^2 + \lambda \sum_{k \neq j} |\beta_k^j|$$

- The final estimate is found by combining all of the edges from these individual regression problems.
  - Symmetry — β_k^j not always same as β_j^k.
  - Use min or max rule.

Estimating GGMs in High Dimensions – Method 2

Estimate a sparse $\mathbf{\Theta}$ via penalized maximum likelihood estimation (MLE).

Graphical Lasso (glasso)

$$\underset{\mathbf{\Theta}}{\text{maximize}} \quad \log\det(\mathbf{\Theta}) - \text{tr}(S\mathbf{\Theta}) - \lambda\|\mathbf{\Theta}\|_1$$

- Blue: Log-likelihood; $\log\det$ is log-determinant and tr is matrix trace.
- Red: Penalty that encourages zeros in off-diagonal elements of $\mathbf{\Theta}$.

Comparing the Two Approaches

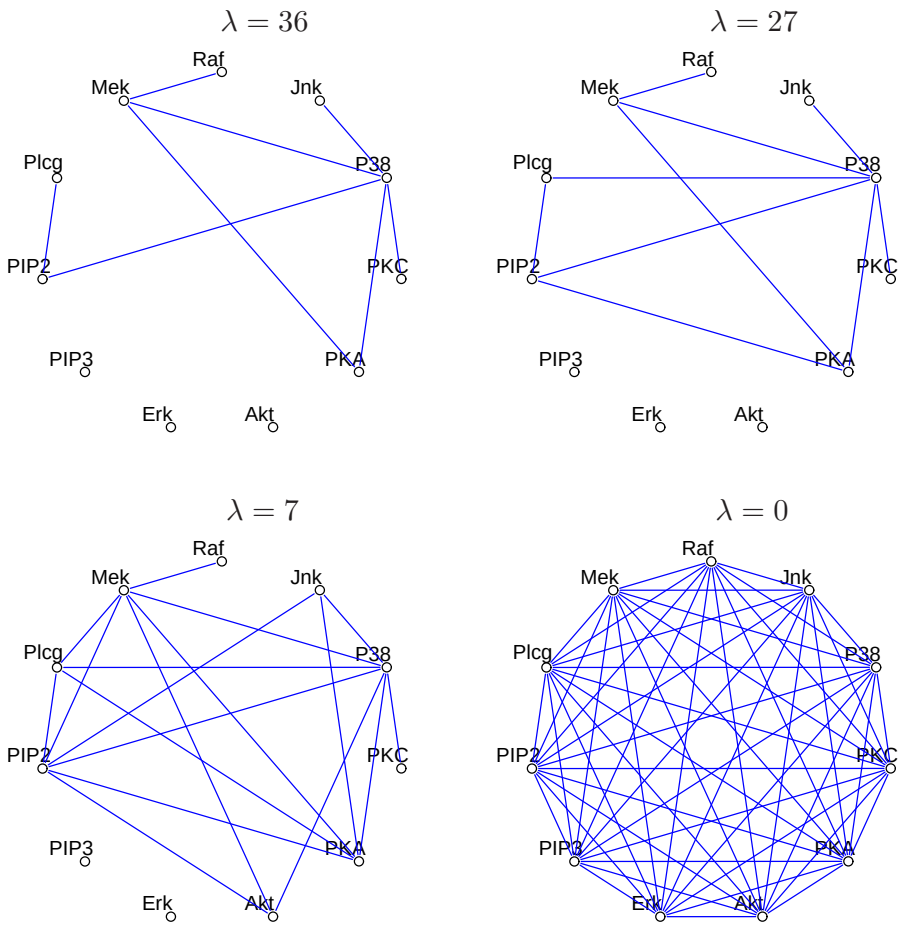
- Neighborhood selection is an approximation to the graphical lasso:
  - Consider regression of X_j on $X_k, j \neq k$
  - Then the regression coefficient for neighborhood selection is related to the j, k element of $\mathbf{\Theta}$:

$$\beta_k^j = -\frac{\mathbf{\Theta}_{jk}}{\mathbf{\Theta}_{jj}}$$

- Neighborhood selection is computationally more efficient, and may give better graph estimates, but does not give an estimate of $\mathbf{\Theta}$!

A Real Example

- Flow cytometry proteomics in single cells (Sachs et al, 2003).
- $p = 11$ proteins measured in $n = 7466$ cells



How to Choose λ?

- λ modulates trade-off between model fit and network sparsity:
  - $\lambda = 0$ gives a dense network (no sparsity).
  - As λ increases, network becomes more sparse.

- A number of approaches available

  1. Cross-Validation — tends to yield overly dense networks.
  2. Extended BIC — adjusted BIC for high dimensions.
  3. Controlling the probability of falsely connecting disconnected components at level α (Banerjee et al, 2008):

$$\lambda(\alpha) = \frac{t_{n-2}(\alpha/2p^2)}{\sqrt{n-2+t_{n-2}(\alpha/2p^2)}},$$

  ($t_{n-2}(\alpha)$ is the $(100-\alpha)\%$ quantile of t-distribution with $n-2$ d.f.)

  4. Stability selection — Choose λ that gives the most **stable network** (`R`: `huge` package)

Other Types of Graphical Models

Nonparanormal (Gaussian Copula) Models

- Suppose $X \nsim N(0, \Sigma)$, but there exists monotone functions $f_j, j = 1, \ldots p$ such that $[f_1(X_1), \ldots f_p(X_p)] \sim N(0, \Sigma)$
  - X has a nonparanormal distribution $X \sim NPN_p(f, \Sigma)$.
  - f and Σ are parameters of the distribution, and estimated from data.
  - For continuous distributions, the nonparanormal family is the same as the Gaussian copula family
- To estimate the nonparanomal network:
  i) transform the data: $[f_1(X_1), \ldots f_p(X_p)]$
  ii) estimate the network of the transformed data (e.g. calculate the empirical covariance matrix of the transformed data, and apply glasso or neighborhood selection)

A Related Procedure

- Liu et al (2012) and Xue & Zou (2012) proposed a closely related idea using rank-based correlation
  - Let r_j^i be the rank of x_j^i among $x_j^1, \ldots, x_j^n$ and $\bar{r}_j = (n+1)/2$ be the average rank
  - Calculate Spearman's ρ or Kendall's τ

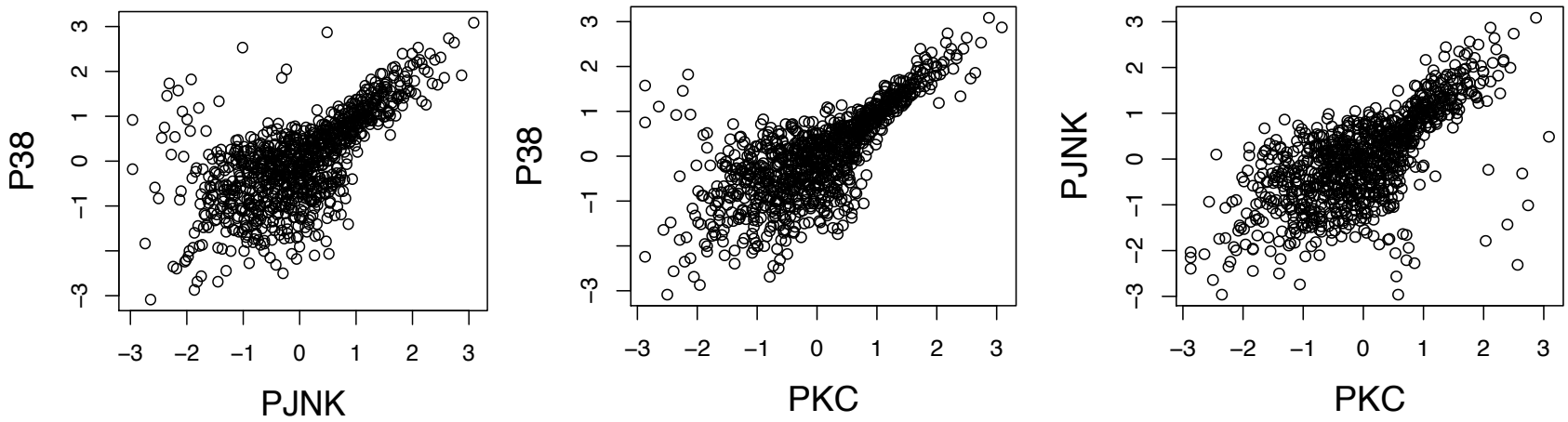
$$\hat{\rho}_{jk} = \frac{\sum_{i=1}^n (r_j^i - \bar{r}_j)(r_k^i - \bar{r}_k)}{\sqrt{\sum_{i=1}^n (r_j^i - \bar{r}_j)^2 \sum_{i=1}^n (r_k^i - \bar{r}_k)^2}}$$

$$\hat{\tau}_{jk} = \frac{2}{n(n-1)} \sum_{1 \le i < i' \le n} \text{sign}\left((x_j^i - x_j^{i'})(x_k^i - x_k^{i'})\right)$$

- If $X \sim NPN_p(f, \Sigma)$, then $\Sigma_{jk} = 2\sin(\rho_{jk}\pi/6) = \sin(\tau_{jk}\pi/2)$
- Therefore, we can estimate Σ^{-1} by plugging in rank-based correlations into graphical lasso (R-package `huge`)

A Real Data Example

- Protein cytometry data for cell signaling (Sachs et al, 2005)
- Transform the data using Gaussian copula (Liu et al, 2009), giving marginal normality
- Pairwise relationships still seem non-linear



- Shapiro-Wilk test rejects multivariate normality: $p < 2 \times 10^{-16}$

Graphical Models for Discrete Random Variables

- In many cases, biological data are not Gaussian: SNPs, RNAseq, etc
- Need to estimate CIG for other distributions: binomial, poisson, etc
- In this case, the estimators do not have a closed-form!
- A special case, which is computationally more tractable, is the class of pairwise MRFs

Pairwise Markov Random Fields

- The idea of pairwise MRFs is to "assume" that only two-way interactions among variables exist
  - The pairwise MRF associated with the graph G over the random vector X is the family of probability distributions $P(X)$ that can be written as

$$P(X) \propto \exp \sum_{(j,k) \in E} \phi_{jk}(x_j, x_k)$$

  - For each edge $(j, k) \in E$, ϕ_{jk} is called the edge potential function
- For discrete random variables, any MRF can be transformed to an MRF with pairwise interactions by introducing additional variables[1]

[1] Wainwright & Jordan, 2008

Graphical Models for Binary Random Variables

- Suppose $X_1, \ldots, X_p$ are binary random variables, e.g. corresponding to SNPs, or DNA methylation
- A special case of discrete graphical models is the Ising model for binary random variables

$$P_\theta(x) = \frac{1}{Z(\theta)} \exp\left\{ \sum_{(j,k)\in E} \theta_{jk} x_j x_k \right\}$$

  - A pairwise MRF for binary data, with $\phi_{jk}(x_j, x_k) = \theta_{jk} x_j x_k$
  - $x^i \in \{-1, +1\}^p$
  - The partition function $Z(\theta)$ ensures that distribution sums to 1
  - $(j,k) \in E$ iff $\theta_{jk} \neq 0$!

Graphical Models for Binary Random Variables

- We can consider a neighborhood selection[2] approach with an ℓ_1 penalty to find the neighborhood of each node $N(j) = \{k \in V : (j,k) \in E\}$
- For $j = 1, \ldots, p$, need to solve (after some algebra)

$$\min_{\theta} \left\{ n^{-1} \sum_{i=1}^{n} \left[f(\theta; x^i) - \sum_{k \neq j} \theta_{jk} x_j^i x_k^i + \lambda \|\theta_{-j}\|_1 \right] \right\}$$

  - $f(\theta; x) = \log \left\{ \exp\left(\sum_{k \neq j} \theta_{jk} x_k \right) + \exp\left(- \sum_{k \in -j} \theta_{jk} x_k \right) \right\}$
- This is equivalent to solving p penalized logistic regression problems, which is straightforward (R-package `glmnet`)

[2] Ravikumar et al (2010)

Other Non-Gaussian Distributions

- Assume a pairwise graphical model

$$P(X) \propto \exp\left\{\sum_{j\in V}\theta_j\phi_j(X_j) + \sum_{(j,k)\in E}\theta_{jk}\phi_{jk}(X_j, X_k)\right\}$$

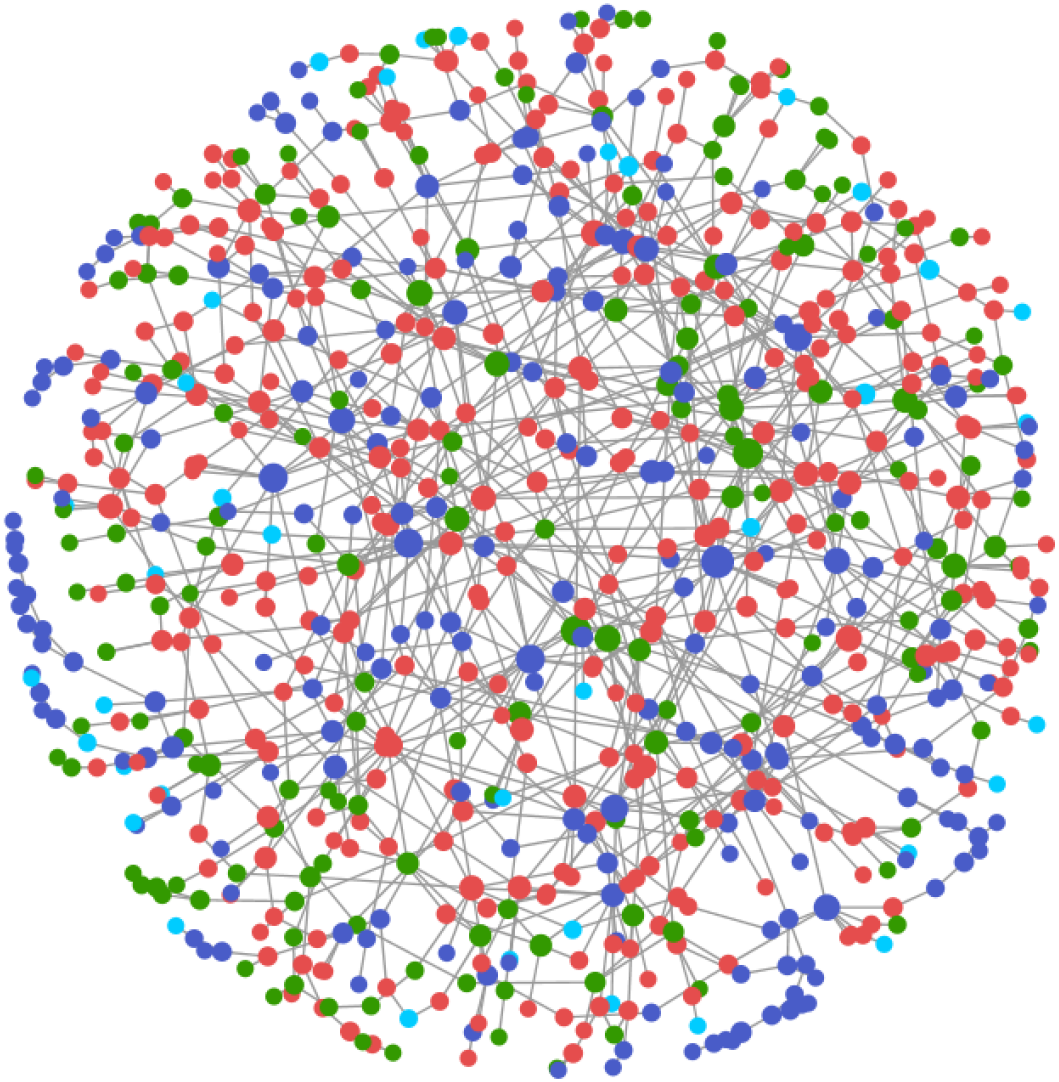
- Then, similar to the Ising model, graphical models can be learned for other members of the exponential family
  - Poisson graphical models (for e.g. RNAseq), Multinomial graphical models, etc
  - All of these can be learned using a neighborhood selection approach, using the `glmnet` package[3]
  - We can even learn networks with multiple types of nodes (gene expression, SNPs, and CNVs)[4]

[3] Yang et al (2012)

[4] Yang et al (2014), Chen et al (2015)

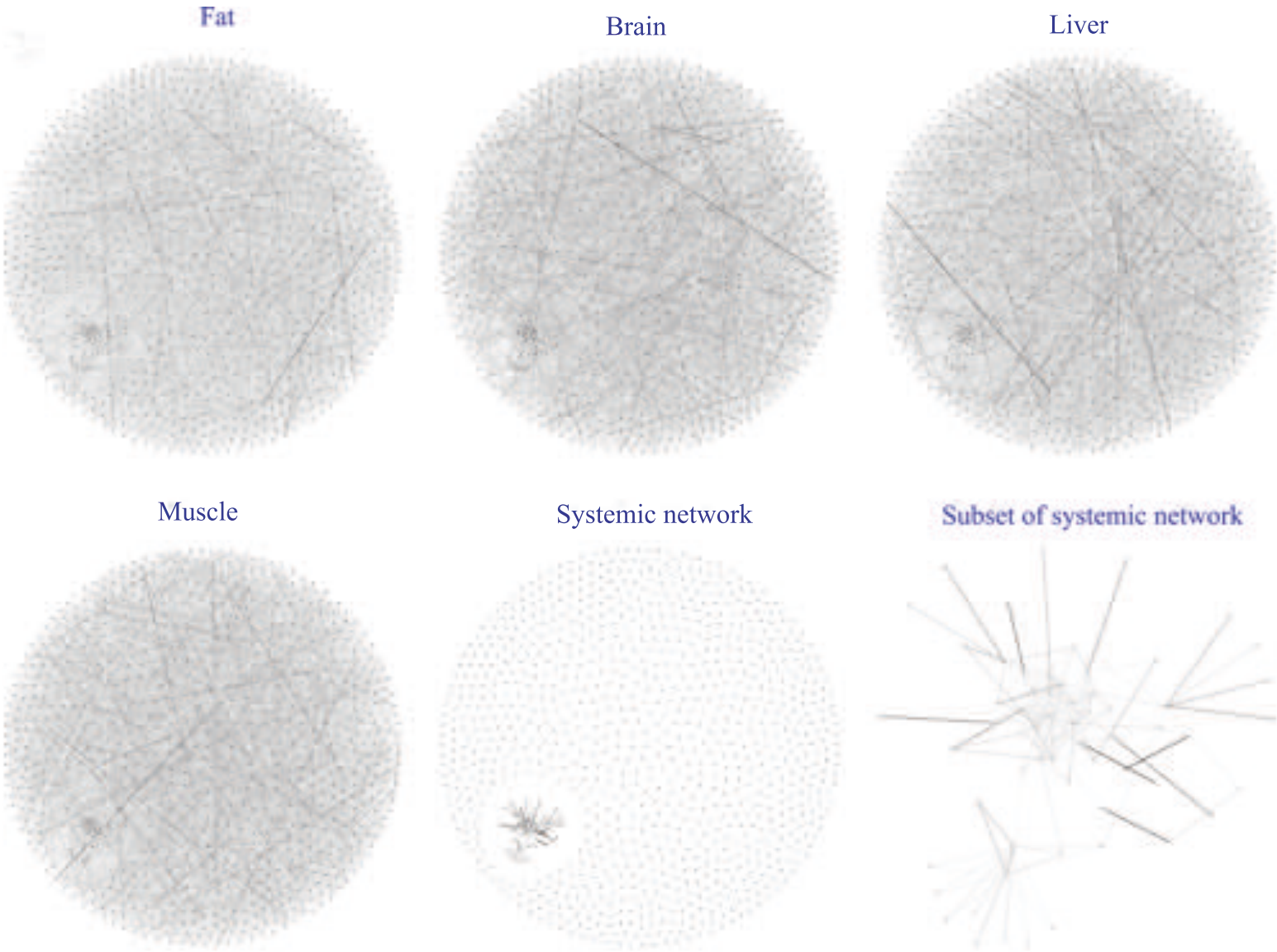
Research Highlight

Mixed Graphical Models



Research Highlight

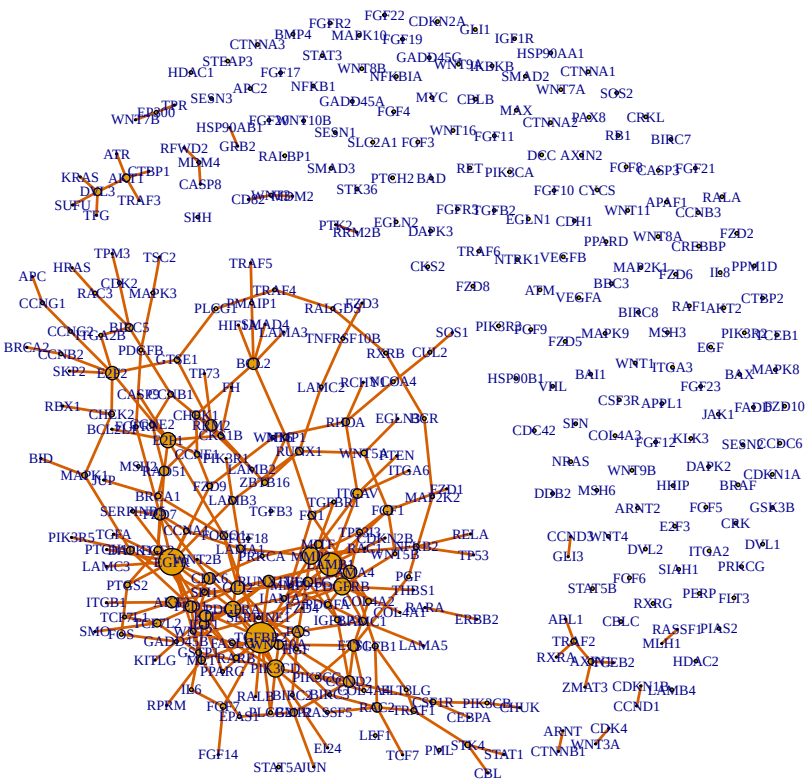
Multiple Gaussian Graphical Models



Research Highlight

Testing Differences in Networks

Edges in the Positive but not the Negative Group



Edges in the Negative but not the Positive Group