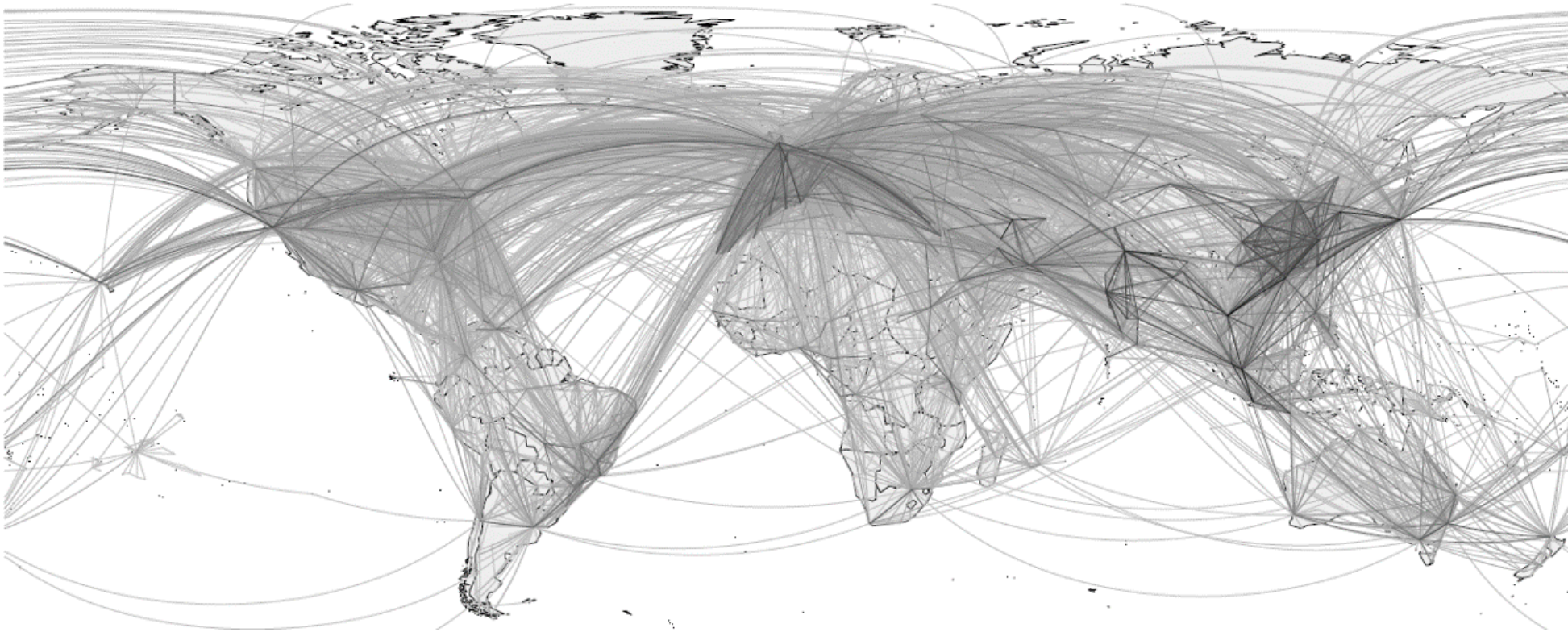
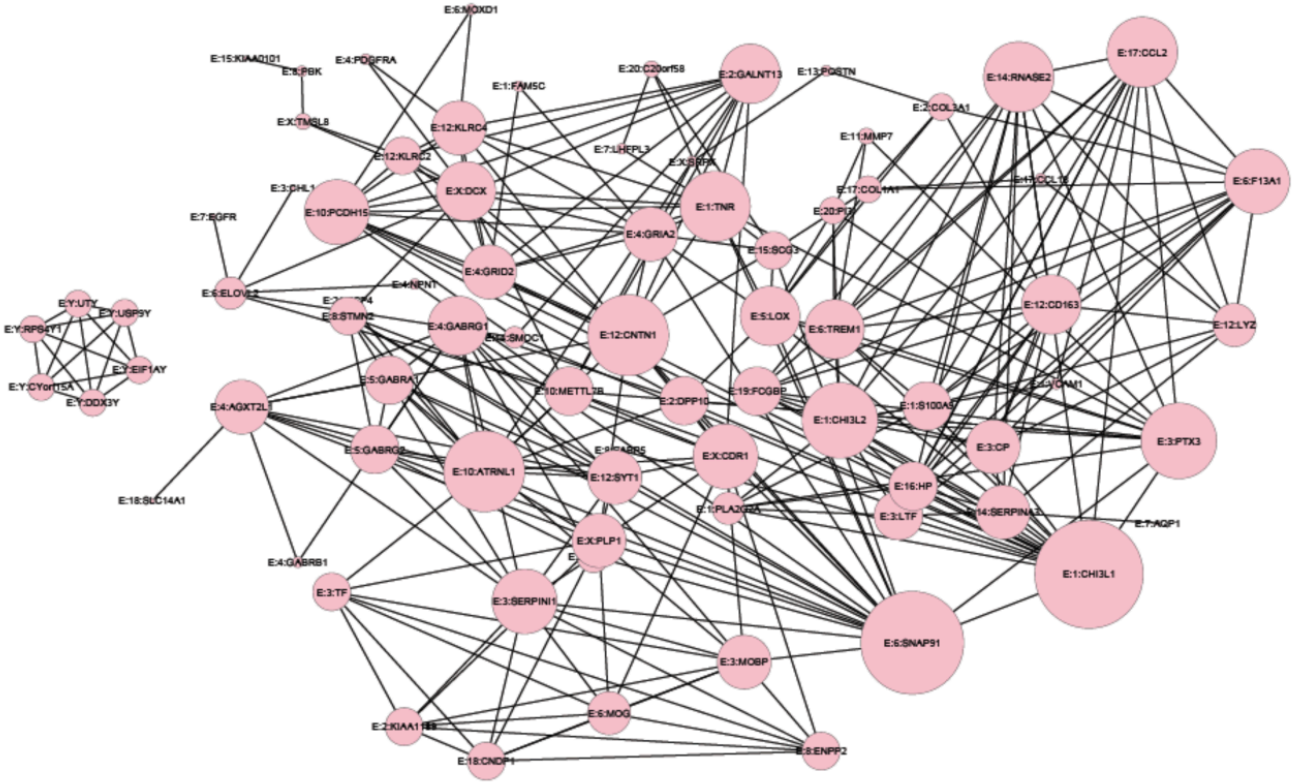
Unsupervised Analysis: Graphical Models

Why Graphical Models?



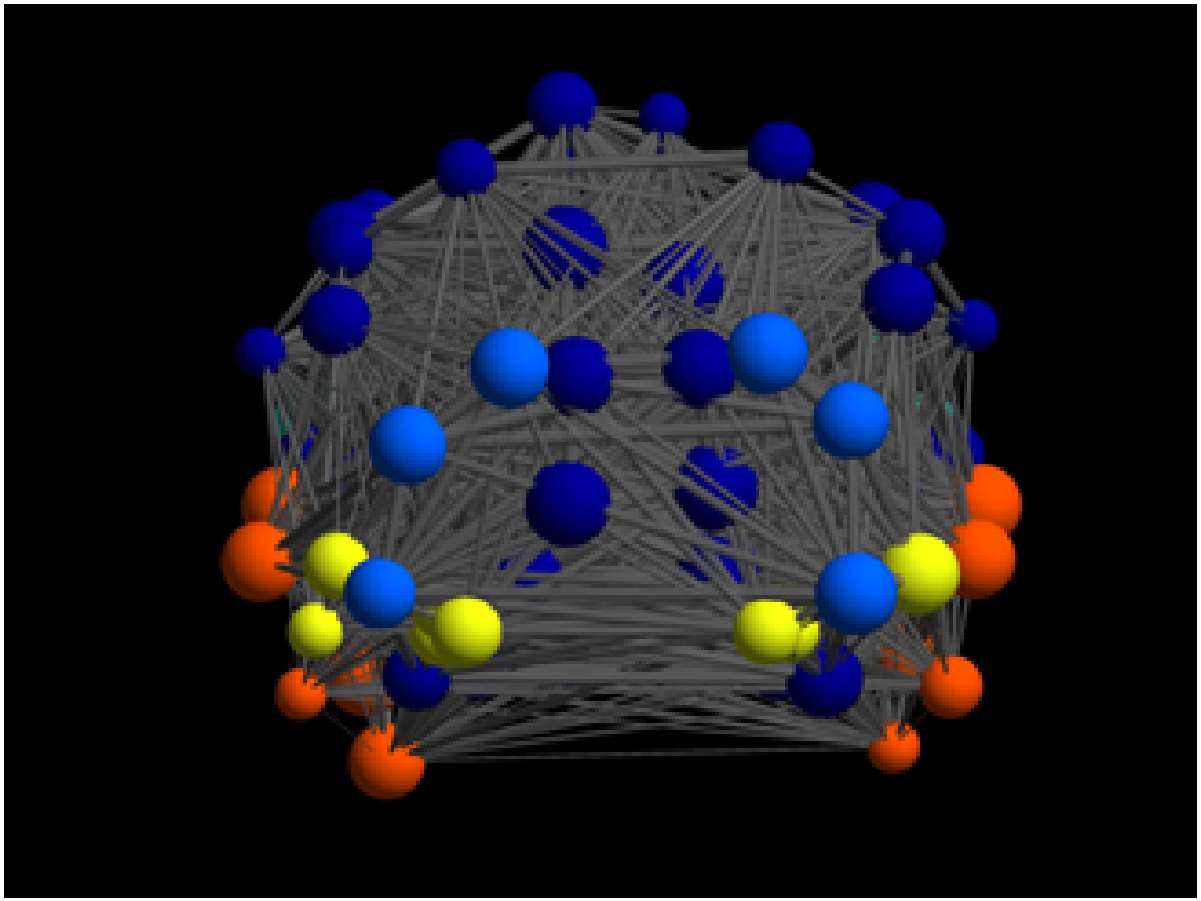
Depicts relationships (edges) between features (nodes).

Why Graphical Models?



Genomics: Relationships between genes.

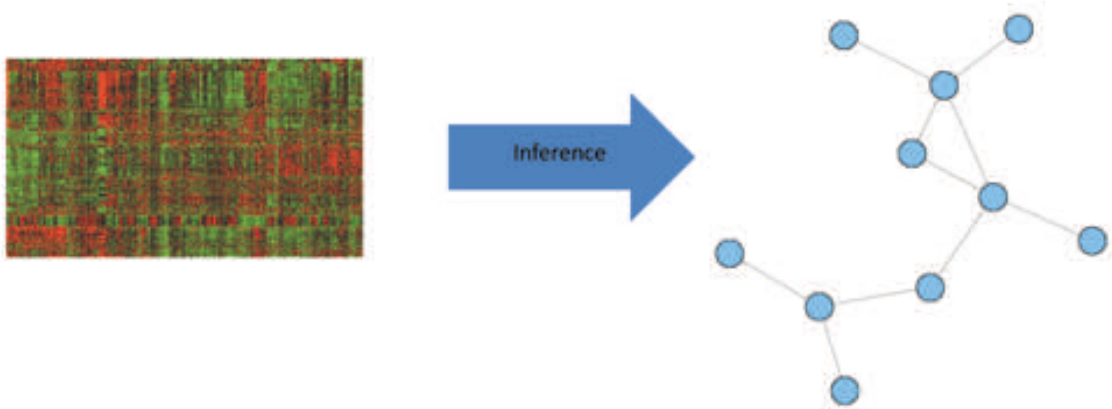
Why Graphical Models?



Neuroimaging: Relationships between brain regions.

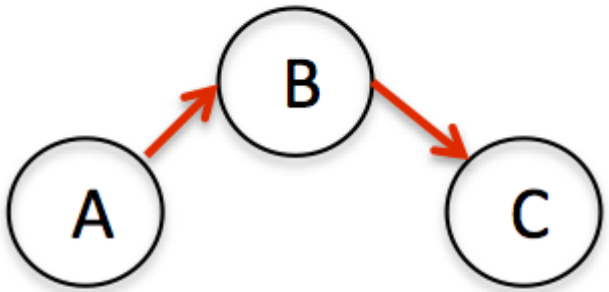
Graphical Models in Unsupervised Learning

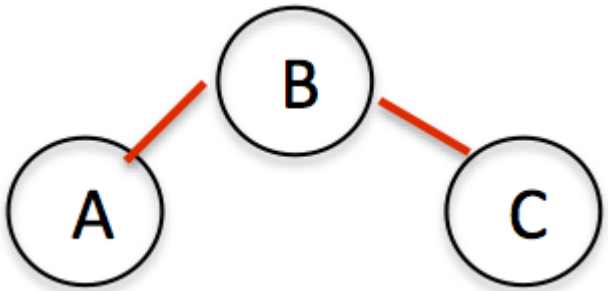
1. Network Data.
   - Examples: Social networks, twitter, citations, surveillance, web links, etc.
2. **Our focus**: Learn network from data.
   - Data matrix: $\boldsymbol{X}_{n \times p}$.
   - Features form p nodes.
   - Goal: Learn edges between nodes (i.e. learn the relationships between features).



Major Types of Graphical Models

Undirected vs. Directed Graphs.





Major Types of Graphical Models

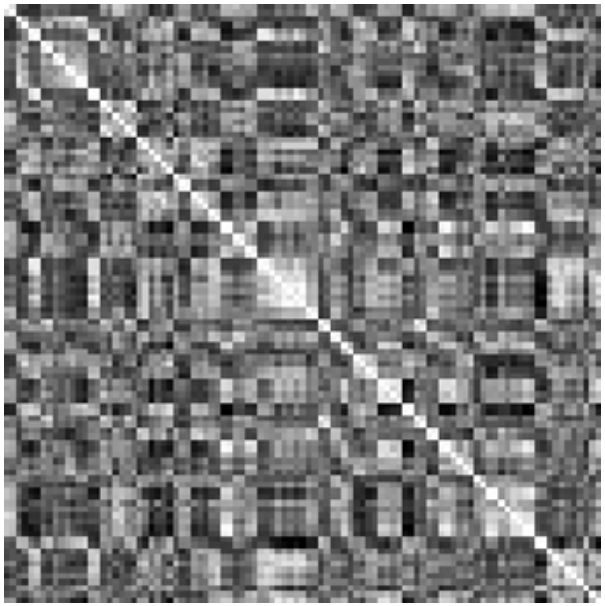
Undirected Graphical Models:

- Most common: Correlation Networks (association networks).
- **Our Focus**: Markov Networks.
- Others: Mutual information networks.

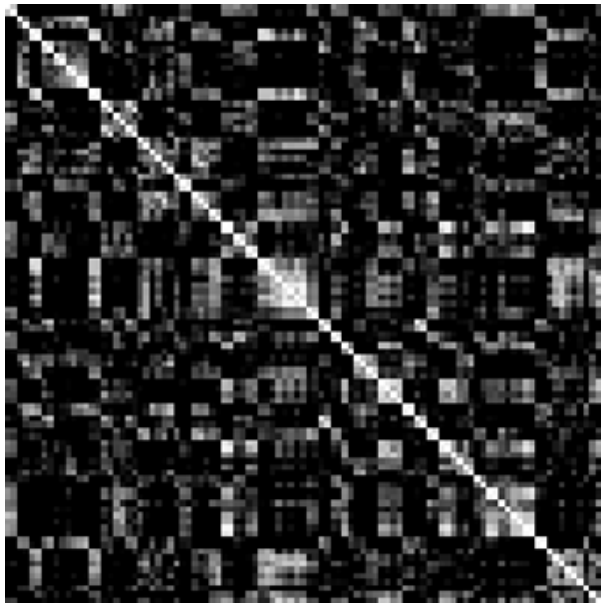
Directed Graphical Models:

- Bayesian Networks (DAG - Directed Acyclic Graphs).

Correlation Networks



Correlation matrix.



Thresholded correlation matrix.

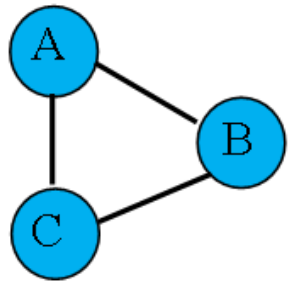
- Correlation matrix - $\mathbf{C} = \text{Cor}(\boldsymbol{X})$: $\mathbf{C}_{ij} = \text{Cor}(\boldsymbol{x}_i, \boldsymbol{x}_j)$.
- Measures linear associations between features.

Markov Networks

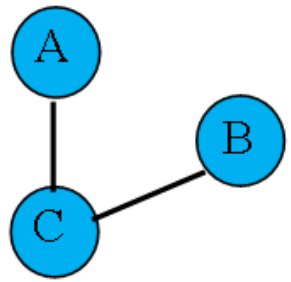
Markov Network

An *undirected graphical model* that characterizes conditional dependence (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

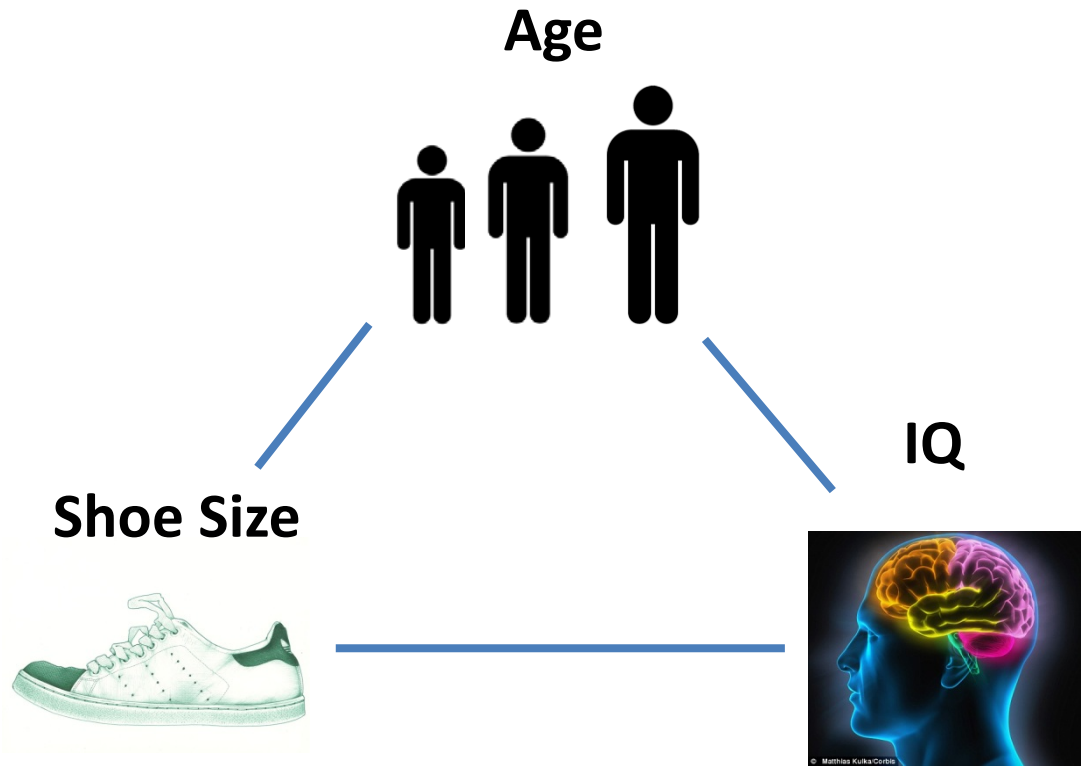
Regression Interpretation:

- 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.

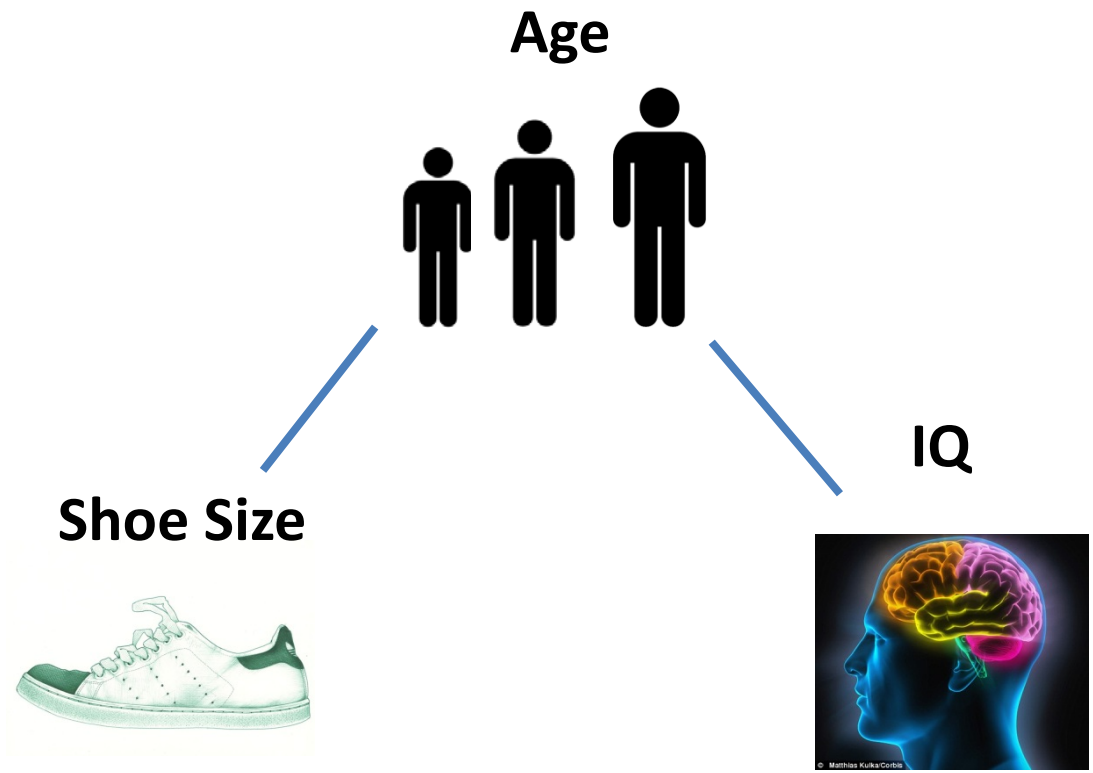
- Because of other nodes in model, Node B does not add any predictive value for Node A.
  - A is conditionally independent of B.
  - No Edge.

Markov Networks - Conditional Dependence



Correlation.

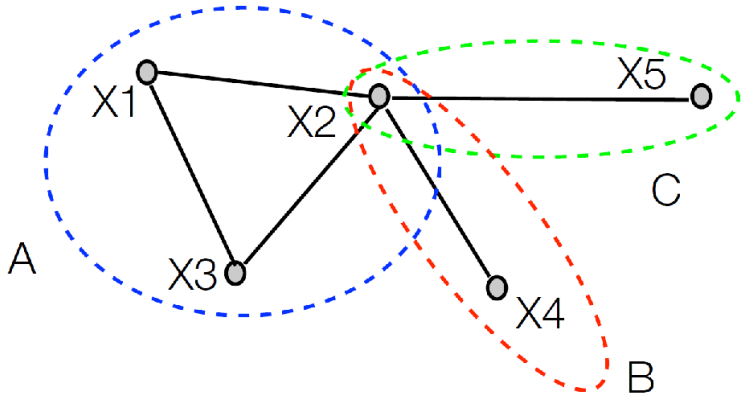
Markov Networks - Conditional Dependence



Conditional Dependence (Partial Correlation).

Markov Networks

- Local Markov Property: Conditional dependencies defined by node-neighborhoods, or the set of nodes connected to a given node via an edge.
- Global Markov Property: Pairwise conditional dependencies and neighborhoods jointly define the global dependence structure (formally defined by separators).
- Hammersley-Clifford Theorem: Density on graph factorizes according to sufficient statistics on cliques. (Probabilistic model!)



Gaussian Graphical Models

Gaussian Graphical Models

GGM:

- Multivariate normal: $\boldsymbol{X} \sim N(0, \boldsymbol{\Theta}^{-1})$
- $\boldsymbol{\Theta}$ the inverse covariance matrix.
- If data standardized, $\boldsymbol{\Theta}$ the partial correlation matrix.
- Zeros in $\boldsymbol{\Theta} \Longrightarrow$ conditional independence!
  - Edges correspond to non-zeros in $\boldsymbol{\Theta}$.
- Inference Goal: Estimate a sparse $\boldsymbol{\Theta}$.

Algorithms:

1. Graphical Lasso - penalized maximum likelihood estimation.
2. Neighborhood Selection - penalized conditional maximum likelihood estimation.

Graphical Lasso

Estimate sparse $\mathbf{\Theta}$ via Penalized Maximum Likelihood Estimation (MLE).

Graphical Lasso (Glasso)

$$\underset{\mathbf{\Theta}}{\text{maximize}} \quad \log|\mathbf{\Theta}| - \text{tr}(\boldsymbol{X}^T\boldsymbol{X}\mathbf{\Theta}) - \lambda||\mathbf{\Theta}||_1$$

- Blue: Log-likelihood.
- Red: Penalty that encourages zeros in $\mathbf{\Theta}$.

[Yuan and Lin (2007), Banerjee et al. (2007), d'Aspremont et al., 2006; Friedman et al., 2008; and many others]

R: `glasso` package.

Neighborhood Selection

- Estimate sparse $\boldsymbol{\Theta}$ via penalized conditional MLE - by estimating zeros in one row / column of $\boldsymbol{\Theta}$ at a time.
- For each node $\boldsymbol{x}_j$, find it's node-neighbors (L_1-penalized regression or Lasso):

$$\underset{\beta^j}{\text{minimize}} \quad ||\boldsymbol{x}_j - \boldsymbol{X}_{\neq j}\beta^j||_2^2 + \lambda||\beta^j||_1$$

- Symmetry - β_i^j not always same as β_j^i.
  - Min or max rule.
- Meinshausen and Buhlmann (2006).

Network Sparsity

λ Controls Sparsity.

$$\underset{\boldsymbol{\Theta}}{\text{maximize}} \quad \log|\boldsymbol{\Theta}| - \text{tr}(\boldsymbol{X}^T\boldsymbol{X}\boldsymbol{\Theta}) - \lambda||\boldsymbol{\Theta}||_1$$

- $\lambda = 0$ gives a dense network (no sparsity).
- As λ increases, network becomes more sparse.

- Modulates trade-off between model fit and network sparsity.

How to Choose λ?

- Cross-Validation - tends to yield overly dense networks.
- Extended BIC - adjusted BIC for high-dimensional settings.

Stability Selection.

- Idea: Choose λ that gives the most **stable network**.

Procedure:

1. Repeatedly re-sample (bootstrapping or sub-sampling) observations.
2. Choose λ that results in the smallest network variability across re-samples.
3. *Stability Score*: For each edge, the proportion of re-samples in which edge was selected.

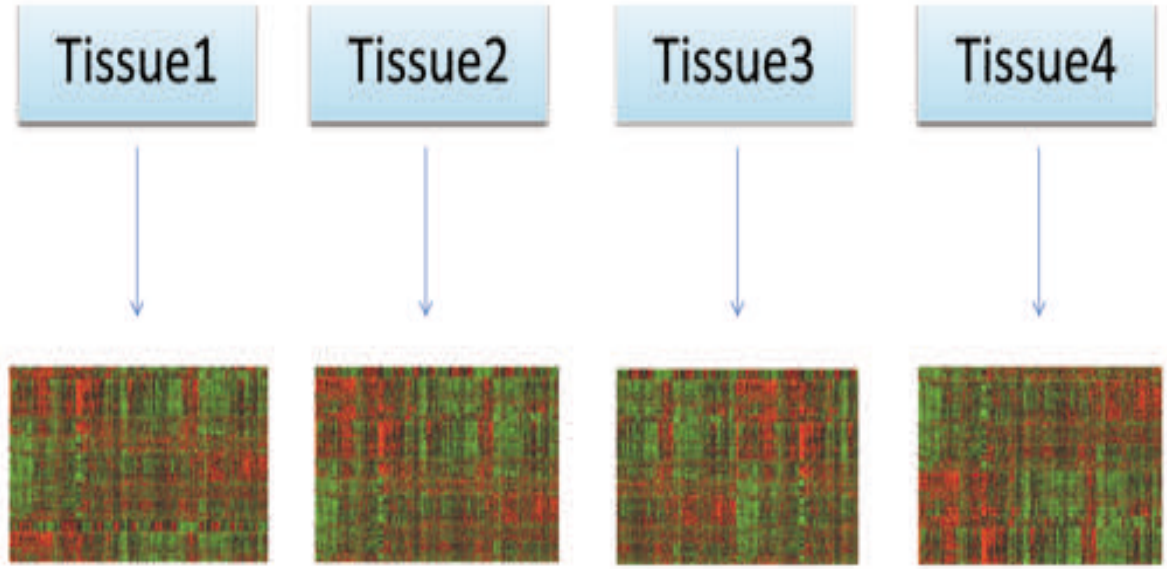
[Meinshausen & Buhlmann, 2011]

R: `huge` package.

Multiple Gaussian Graphical Models

Multiple Gaussian Graphs

- Multiple data sets available.
- Share common structure.
- Gene networks describing different tissues.



Joint Estimation of Multiple Graphical Models

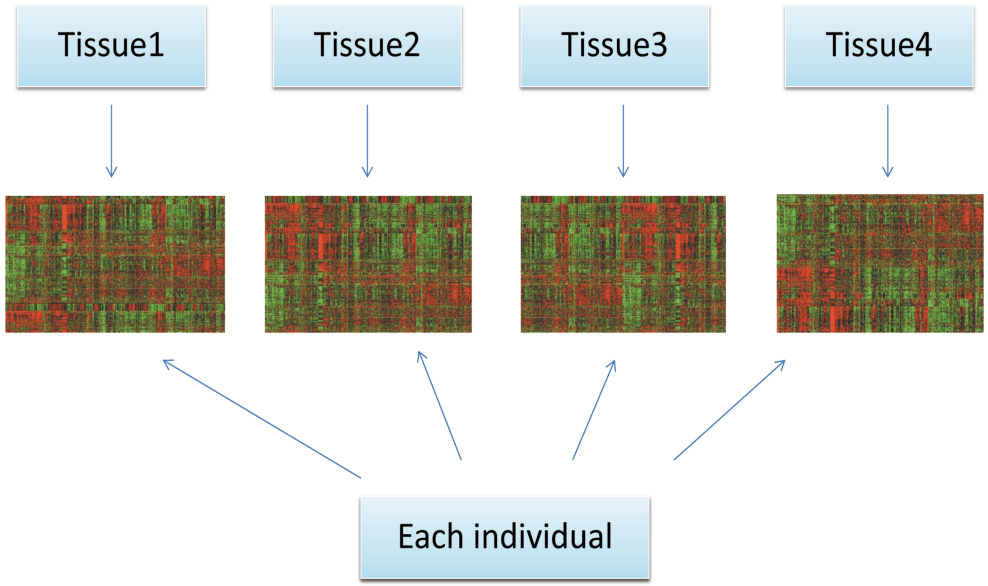
- Independence assumption for multiple data sets; Share common structure.
- Gene networks describing different sources.

$$\text{argmin}\, \mathbf{\Omega}^{(k)} \sum_{k=1}^{K} [\text{trace}(\hat{\mathbf{\Sigma}}^{(k)} \mathbf{\Omega}^{(k)}) - \log\det(\mathbf{\Omega}^{(k)})] + P(\mathbf{\Omega})$$

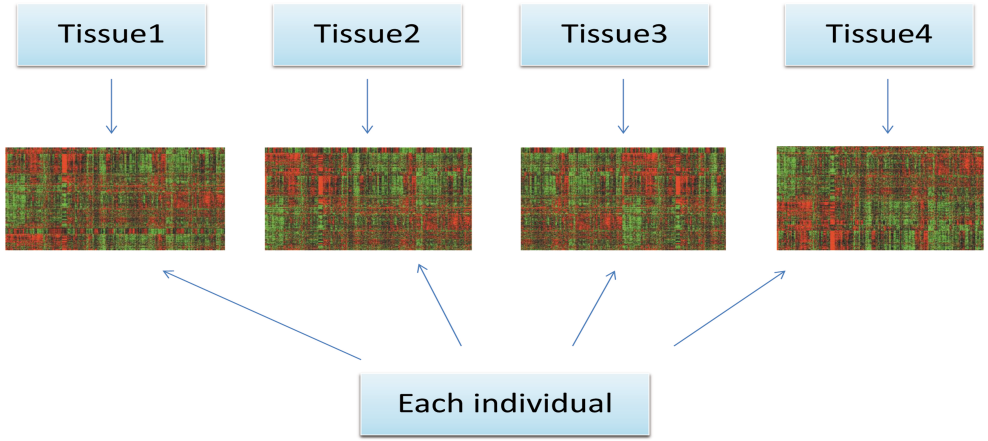
- Encourage common structure through joint regularization (Varoquaux et al, 2007; Guo et al., 2011; Chiquet et al., 2011; Danaher et al., 2012; etc)
  - Guo et al.: Encourage both group sparsity and within group sparsity
    $P(\mathbf{\Omega}) = \lambda \sum_{i \neq j} \sum_{\ell=1}^{k} \sqrt{|\omega_{i,j}^{(\ell)}|}$.
  - Danaher et al.: Graphical group lasso penalty
    $\lambda_1 \sum_{\ell=1}^{k} \sum_{i \neq j} |\omega_{i,j}^{(\ell)}| + \lambda_2 \sum_{\ell=1}^{k} \sqrt{\sum_{i \neq j} \omega_{i,j}^{(\ell)2}}$
    Fused graphical lasso penalty
    $\lambda_1 \sum_{\ell=1}^{k} \sum_{i \neq j} |\omega_{i,j}^{(\ell)}| + \lambda_2 \sum_{\ell < \ell'} \sum_{i,j} |\omega_{i,j}^{(\ell)} - \omega_{i,j}^{(\ell')}|$

Joint Estimation of Dependent Graphical Models

- Multiple data available.
- Data sets from multiple tissues for a group of mice.
- Tissues are the categories.
- Gene expression for four tissues: fat, brain, liver, and muscle.
- Individual is the system.
- Independent assumption is invalid: Related to existing time varying graphs (Zhou et al.; Kolar et al., 2010), but different.



Dependent Graphical Models: Problem Formulation



Xie, Liu, Valdar (2014) considered two layers of graphs:

1. Category specific layer: tissue-specific graphs
2. Systemic layer: whole-body systemic graph

- Let $\mathbf{y}_{k,i} = (y_{k,i1}, ..., y_{k,ip})^T$ be the i-th observed data vector for the k-th category.
- For given i-th mouse, $\mathbf{y}_{k,i}$ are not independent among different tissues k.

Dependent Graphical Models: Problem Formulation

- We model

$$\mathbf{y}_{k,i} = \mathbf{x}_{k,i} + \mathbf{z}_i, \quad i = 1, ..., n \;\; k = 1, ..., K$$

  where $\mathbf{z}_i$ is the shared systemic random effect, and $\mathbf{x}_{k,i}$ is the random effect for k-th category.

- $\mathbf{x}_{k,i} \overset{\text{i.i.d.}}{\sim} \mathbf{N}(0, \mathbf{\Sigma}_k)$, $\mathbf{z}_i \overset{\text{i.i.d.}}{\sim} \mathbf{N}(0, \mathbf{\Sigma}_0)$ and $\mathbf{x}_{k,i} \perp\!\!\!\perp \mathbf{z}_i$.
- Only $\mathbf{y}_{k,i}$'s are available.
- Although $\mathbf{x}_k$ and $\mathbf{z}$ are latent variables, $\mathbf{\Omega}_k = \mathbf{\Sigma}_k^{-1}; k = 1, \ldots, K$ are identifiable with $K \geq 2$.
- Terminologies
  systemic network: $\mathbf{\Omega}_0 = \mathbf{\Sigma}_0^{-1}$
  category-specific network: $\mathbf{\Omega}_k = \mathbf{\Sigma}_k^{-1}$
  aggregate network: $\mathbf{\Omega}_{Y_k} = (\mathbf{\Omega}_k^{-1} + \mathbf{\Omega}_0^{-1})^{-1}$

Sparsity Notion for Dependent Graphical Models

- Sparse systemic network $\mathbf{\Omega}_0$: whole-body systemic graph characterizes the body wide dependence structure among genes.
- Sparse category-specific network $\mathbf{\Omega}_k$: tissue-specific graphs characterize the dependence structure among genes within each tissue, after removing the common systemic variation.
- Aggregate network $\mathbf{\Omega}_{Y_k} = (\mathbf{\Omega}_k^{-1} + \mathbf{\Omega}_0^{-1})^{-1}$ may not be sparse, given sparse $\mathbf{\Omega}_0$, $\mathbf{\Omega}_k; k = 1, \ldots, K$.
- Goal: Estimate sparse $\mathbf{\Omega}_0$, $\mathbf{\Omega}_k; k = 1, \ldots, K$.

Application to Mouse Gene Expression Data

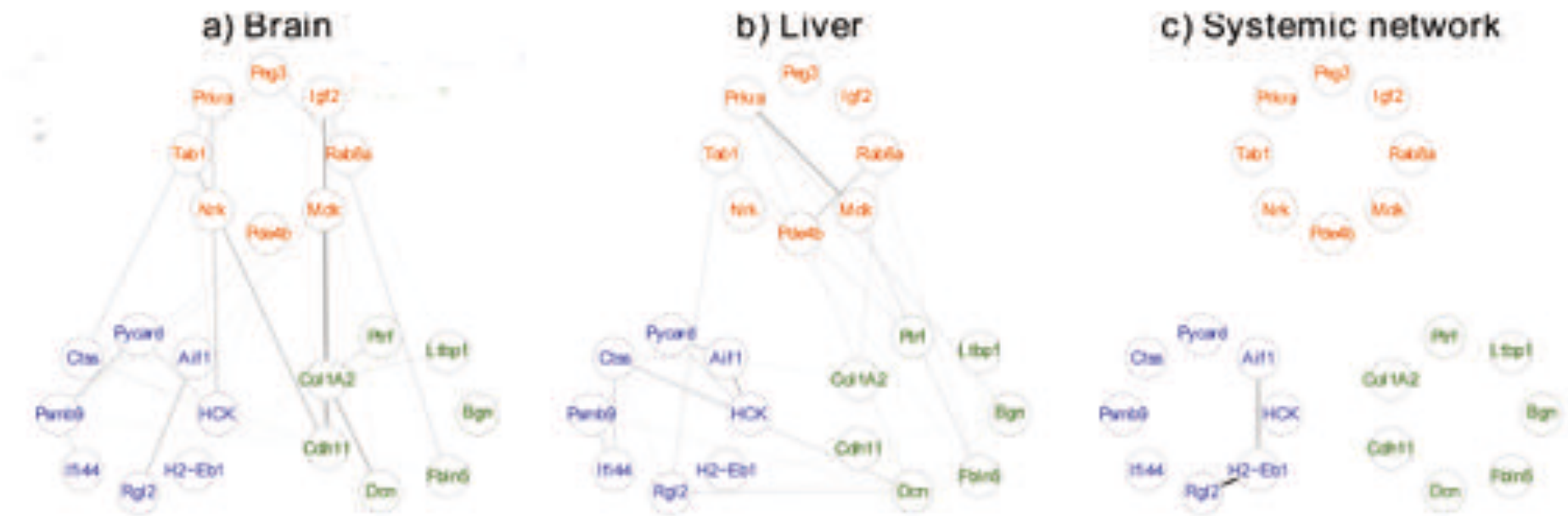
- 301 mice from F_2 cross, varying genes for fat composition (Dobrin et al. 2009).
- Acts like randomized allocation of fat-inducing treatment.
- Gene expression for fat, brain, liver, and muscle.
- For each tissue, over 20,000 gene expression values.
- Three groups of gene networks: the obesity-related network, the imprinting related-network, and the extracellular matrix (ECM)-related network.

Application to Mouse Gene Expression Data

Systemic network should has links that:

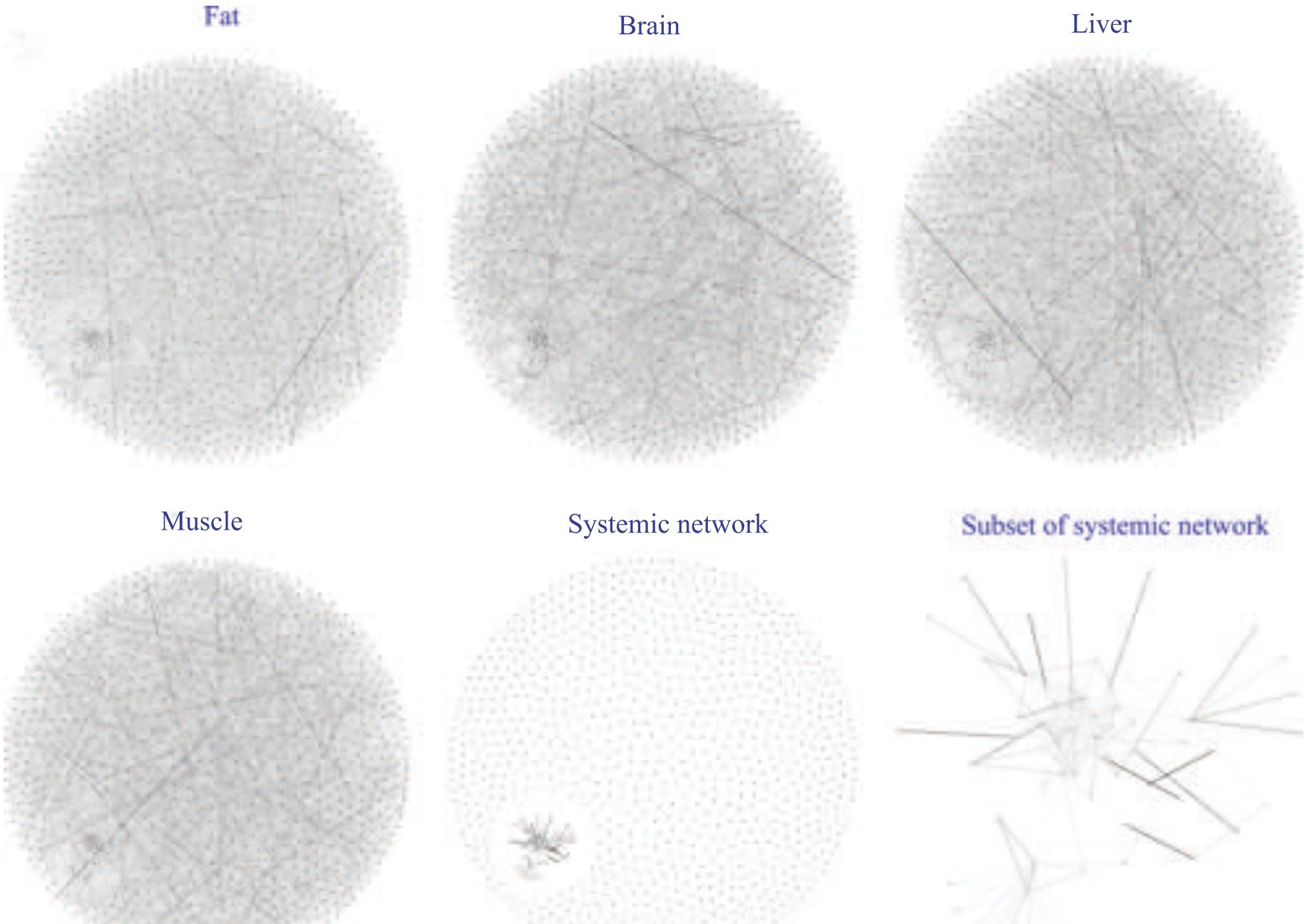
1. affect the whole individual
2. reflect the treatment allocation.

Systemic network only has edges for obesity-related network.



Obesity-related network Imprinted network ECM network

Application to Mouse Gene Expression Data: P = 1000

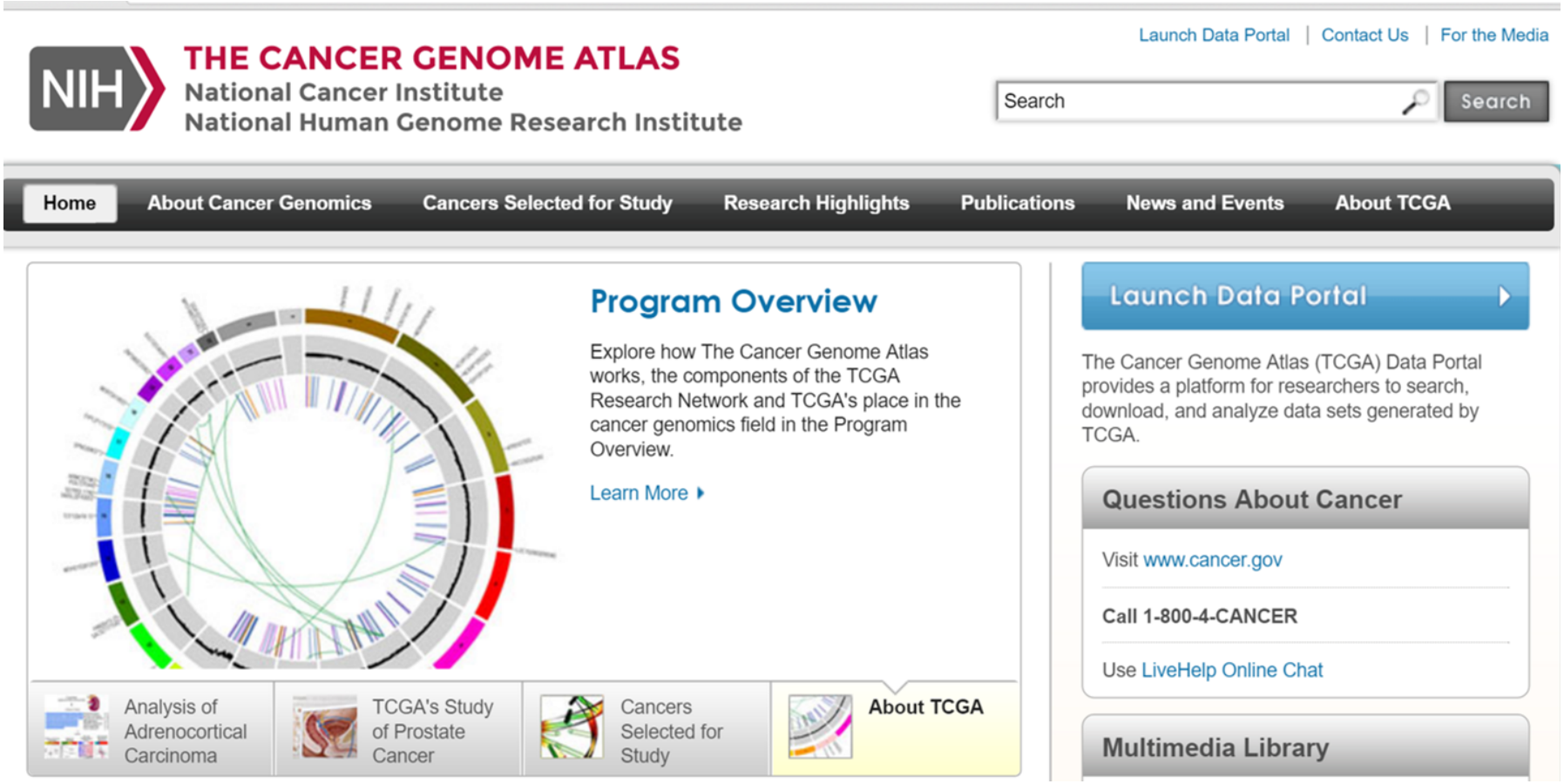


Application to Mouse Gene Expression Data: P = 1000

- Systemic network is sparse (249 edges among 62 genes)
- These 62 genes include some obesity-related genes
- Analysis of gene ontology (GO) enrichment on the systemic network: the network is significantly enriched for genes associated with immune and metabolic processes, consistent with recent studies linking obesity to strong negative impacts on immune response to infection
- Tissue-specific networks are much denser

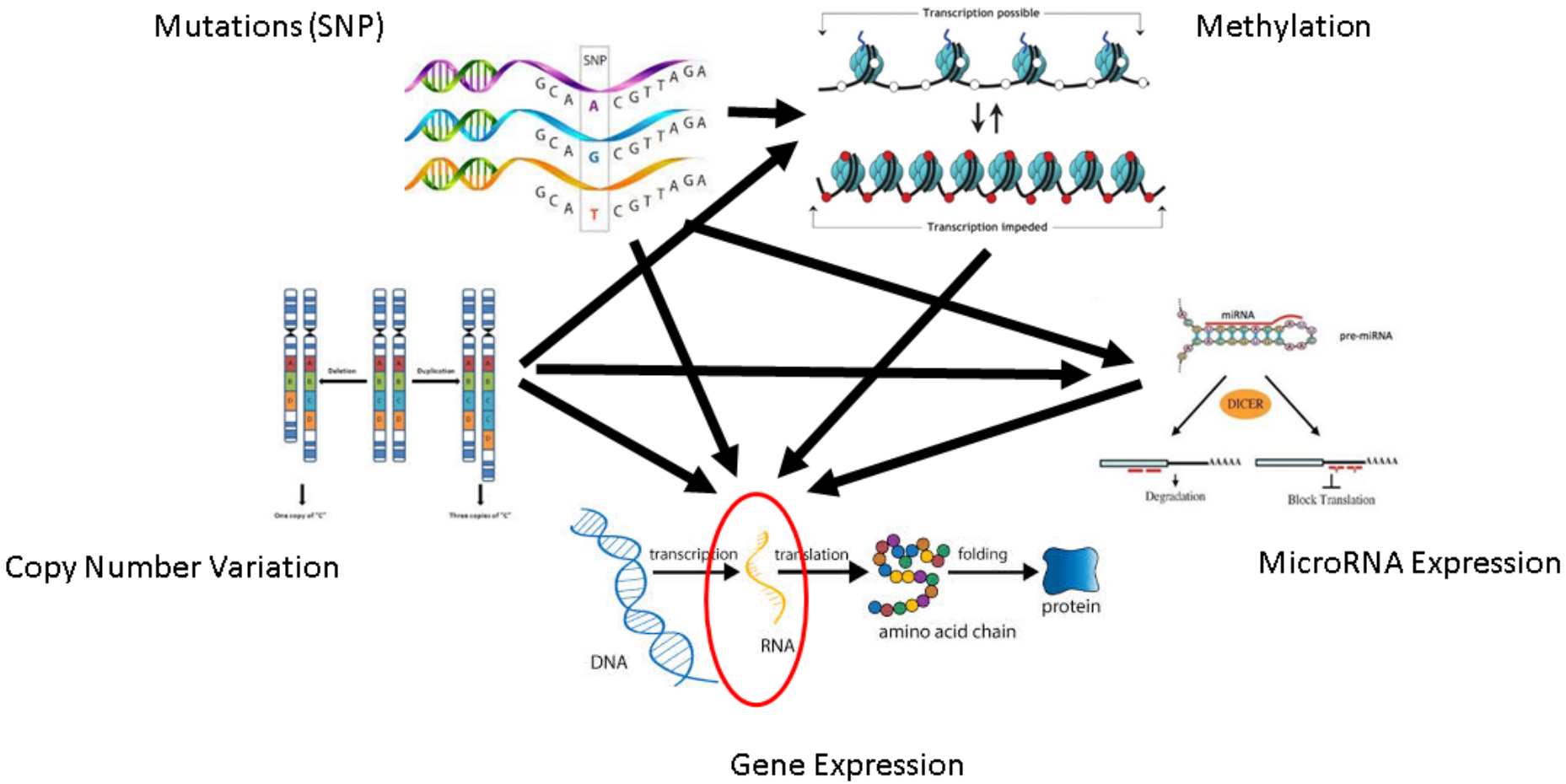
(Mixed) Graphical Models via Exponential Families

Motivation - TCGA



- 33 different cancer types.
- Over 11,000 patients!
- 7 different types of genetics data.
- 2.5 Petabytes worth of data.

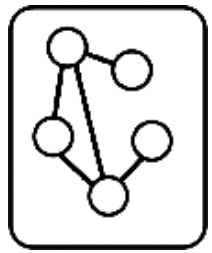
Motivation - Integrated Networks



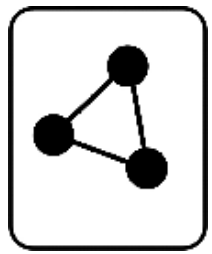
Networks for Different Data Types

Existing Markov Network Types:

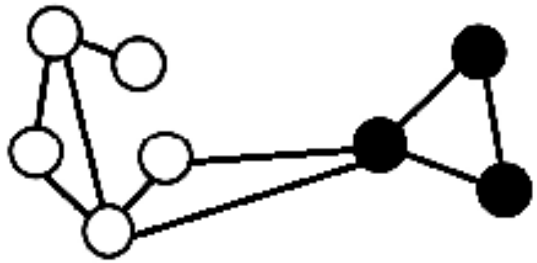
1. Gaussian Graphical Models.



2. Ising Models (Binary-Valued).
   - Estimated via L_1 penalized logistic regression - neighborhood selection.



3. Gaussian-Ising Models.



What about other data types?

- Counts? Skewed Continuous? Bounded? Etc.

Networks for Different Data Types

Review: Exponential Family Distributions.

- Examples: Gaussian, Bernoulli, Poisson, Binomial, Negative Binomial, Exponential, ...

$$P(Z) = \exp\left(\theta\, B(Z) + C(Z) - D(\theta)\right)$$

- θ is the canonical parameter.
- $B(Z)$ is the sufficient statistic.
- $C(Z)$ is the base measure.
- $D(\theta)$ is the log-partition function.

Networks for Different Data Types

Our Framework: Graphical Models via Exponential Families.

Assume: All conditional distributions are Exponential Families.

$$P(X_s|X_{\neq s}) = \exp\left(\theta(X_{\neq s})\, B(X_s) + C(X_s) - D(\theta(X_{\neq s}))\right)$$

Theorem

Joint Density necessarily has the form:

$$P(X) = \exp\left\{ \sum_s \theta_s B(X_s) + \sum_{s \in V} \sum_{t \in N(s)} \theta_{st}\, B(X_s) B(X_t) + \sum_s C(X_s) - A(\theta) \right\}$$

Networks for Different Data Types

Our Framework: Graphical Models via Exponential Families.

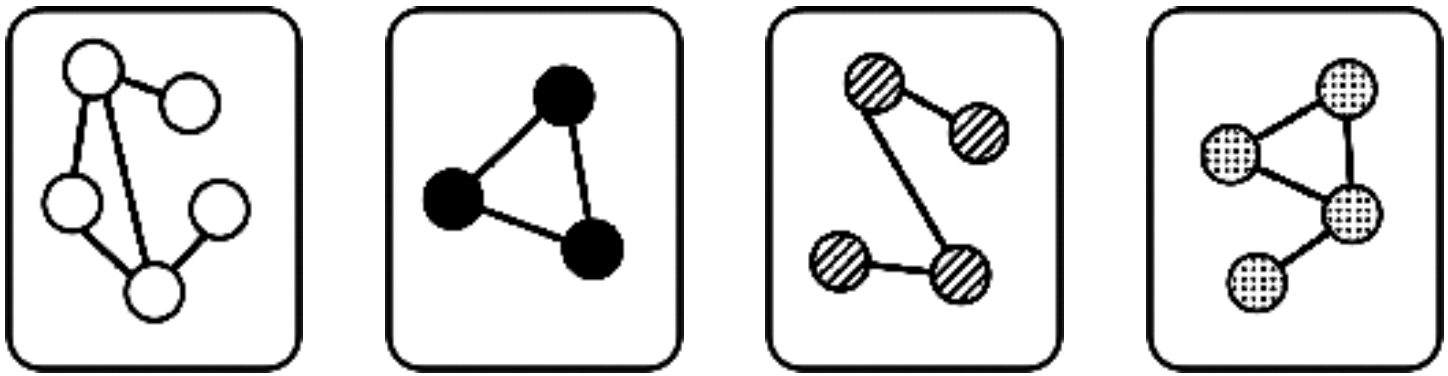
Network Selection & Estimation via Penalized Conditional MLEs.

$$\underset{\alpha,\theta}{\text{minimize}} \quad -\frac{1}{n}\ell(X_s^{(i)}; \alpha_s + \sum_{t \neq s} B(X_t^{(i)})\theta_t) + \lambda||\theta||_1$$

- Neighborhood Selection via penalized GLMs!
- Strong statistical guarantees.
- Fast, parallelizable algorithms.

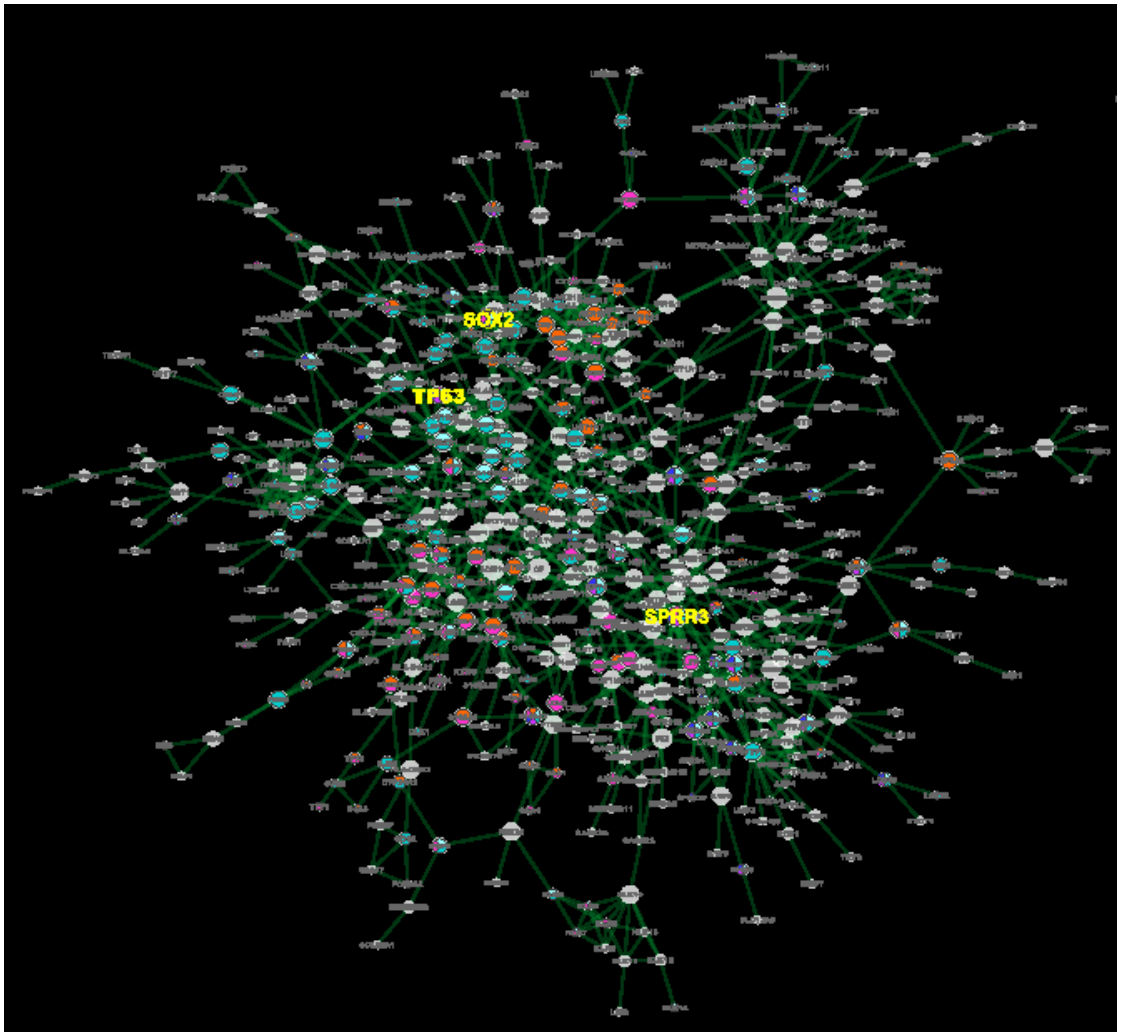
Networks for Different Data Types

Our Framework: Graphical Models via Exponential Families.



Networks for Different Data Types

Our Framework: Graphical Models via Exponential Families.



Lung Cancer Gene Expression Network (RNA-Seq via Poisson Graphical Models).

Integrated Network Models

Mixed Chain Graphical Models via Exponential Families.

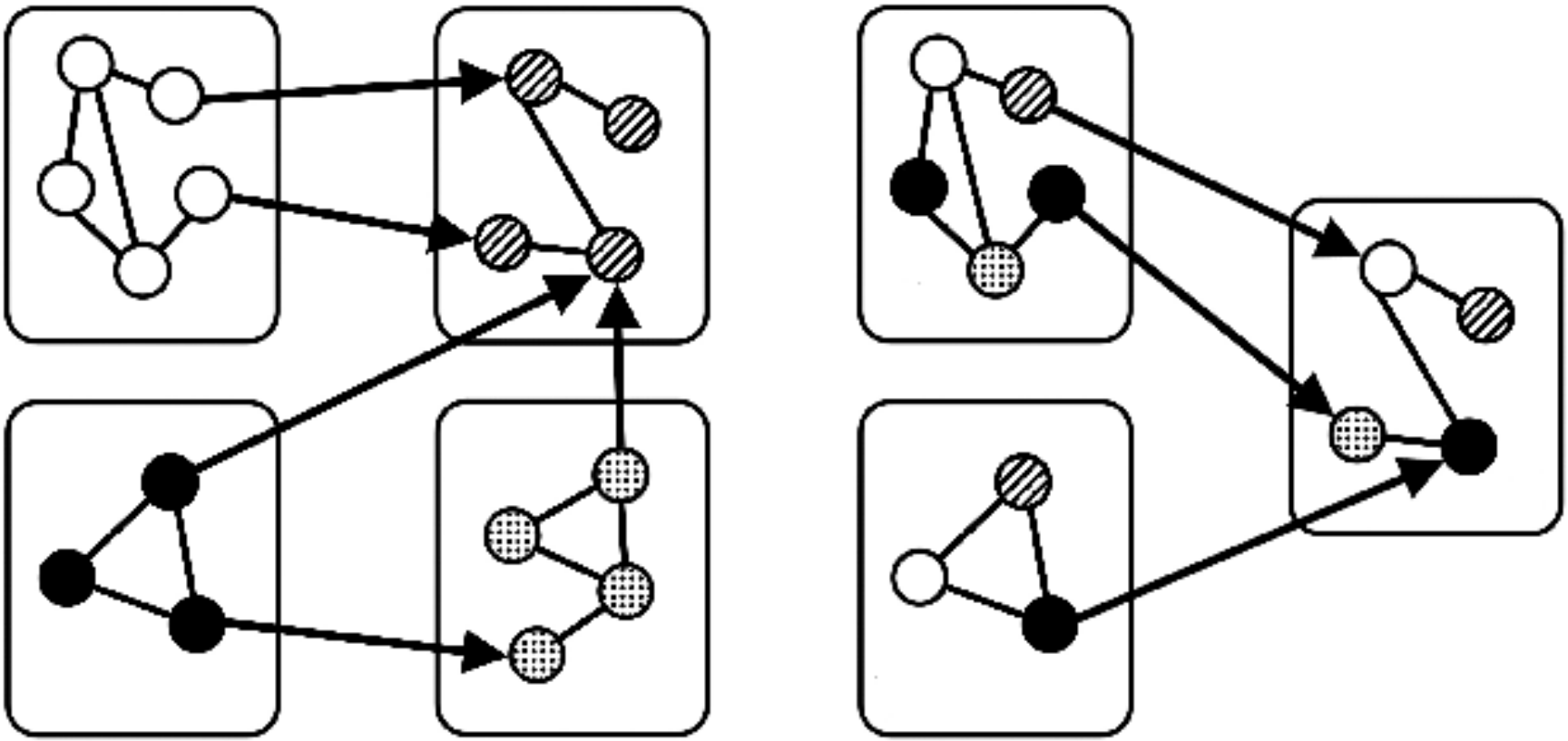
- Assumptions:
  - Conditional distributions are different Exponential Families.
  - Variables belong to known groups and the directionality of dependencies between groups is known.

[Skipping the math . . .]

- Theorem: Joint integrated network distribution exists and has a closed form!
  - Dependencies parameterized by products of sufficient statistics from different distributions.
  - Strong statistical guarantees for network inference.
  - Fast, parallelizable algorithm to learn network structure.

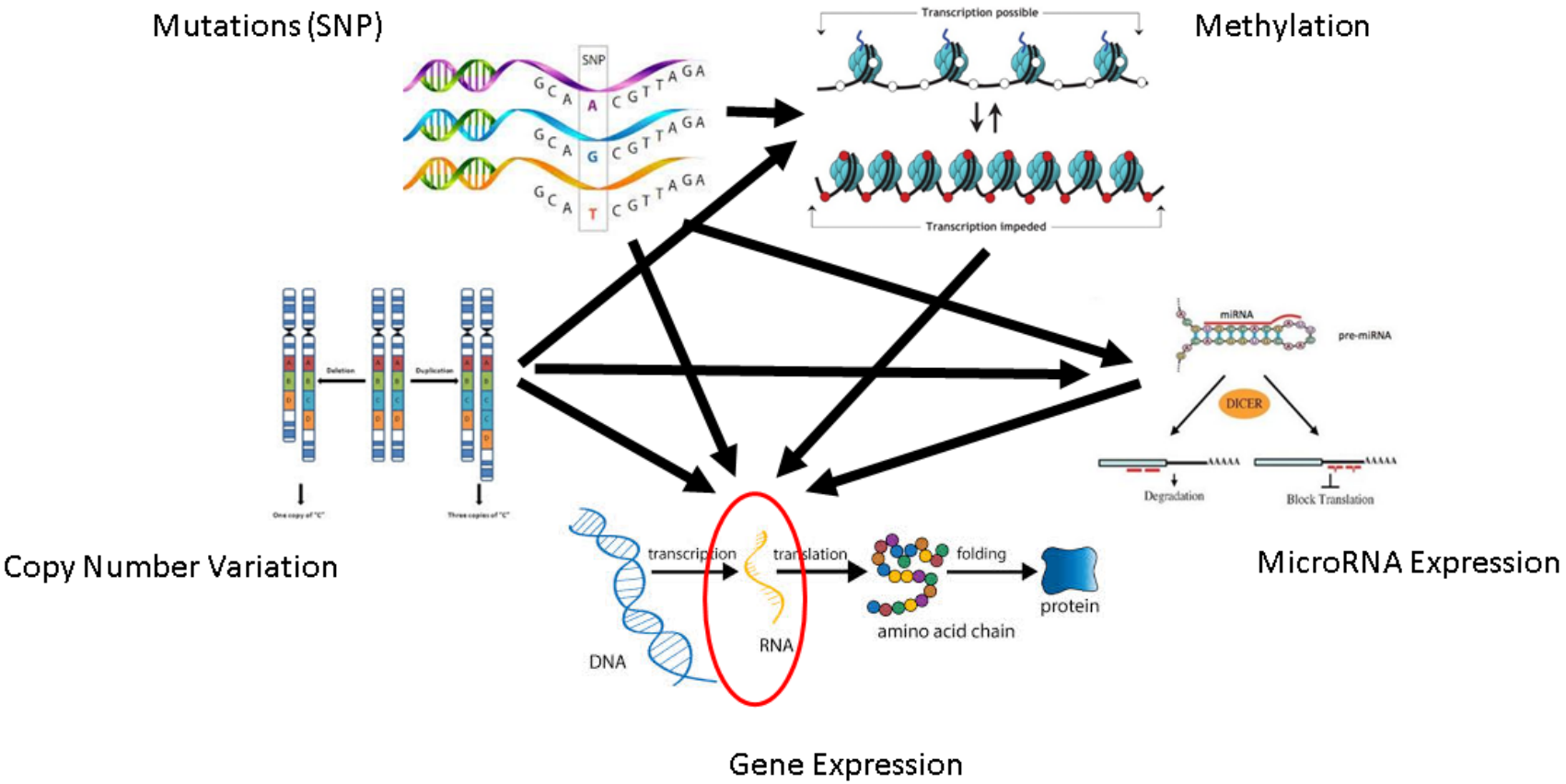
Integrated Network Models

Mixed Chain Graphical Models via Exponential Families.



Integrated Network Models

Mixed Chain Graphical Models via Exponential Families.



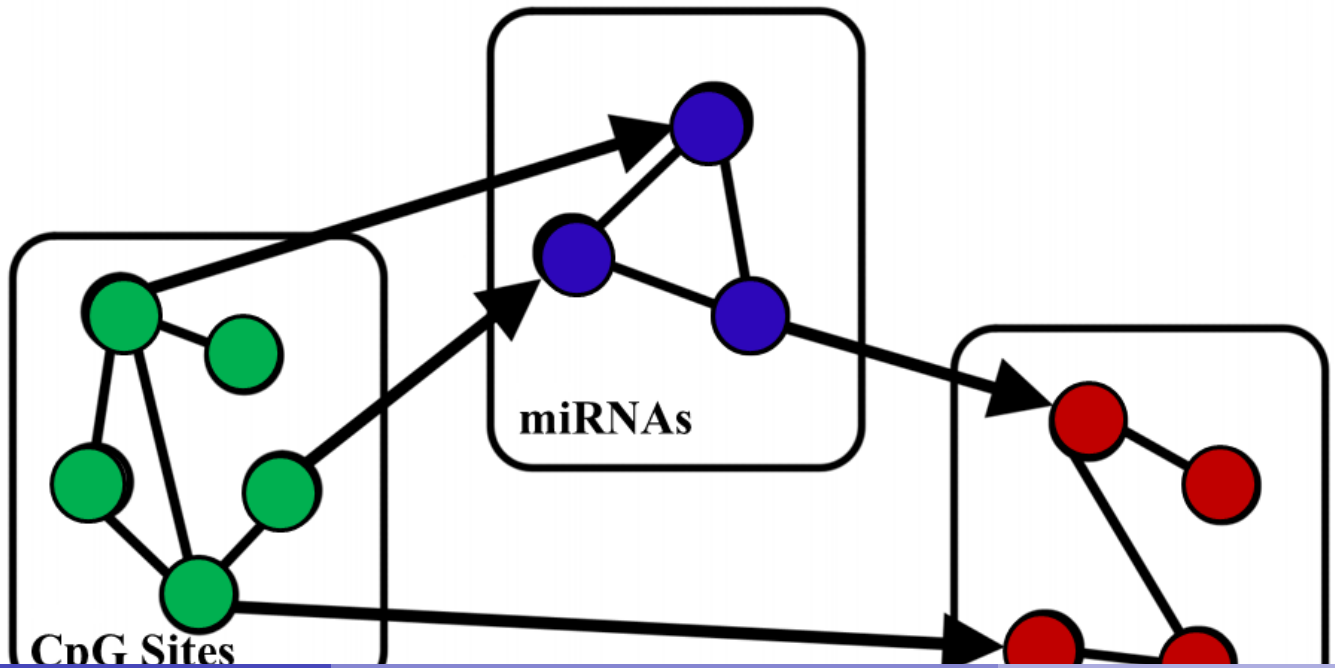
Integrated Network Models

Mixed Chain Graphical Models via Exponential Families.

Implication

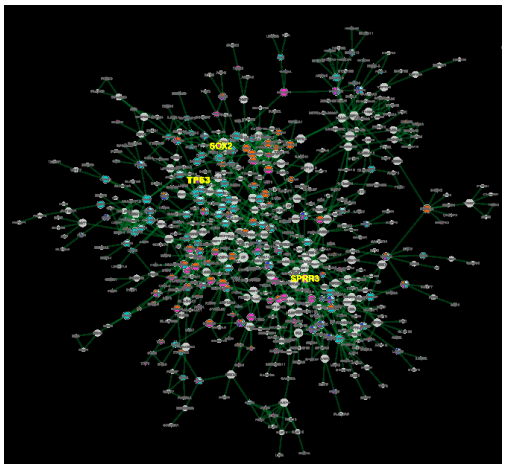
First multivariate distribution for mixed data types (that directly parameterizes a rich set of dependencies).

Case Study: Ovarian Cancer Gene Regulatory Network



Software

XMRF: An R Package to Fit Markov Networks to High-Throughput Genomics Data.



TCGA2STAT: Simple TCGA Data Access for Integrated Statistical Analysis in R.