

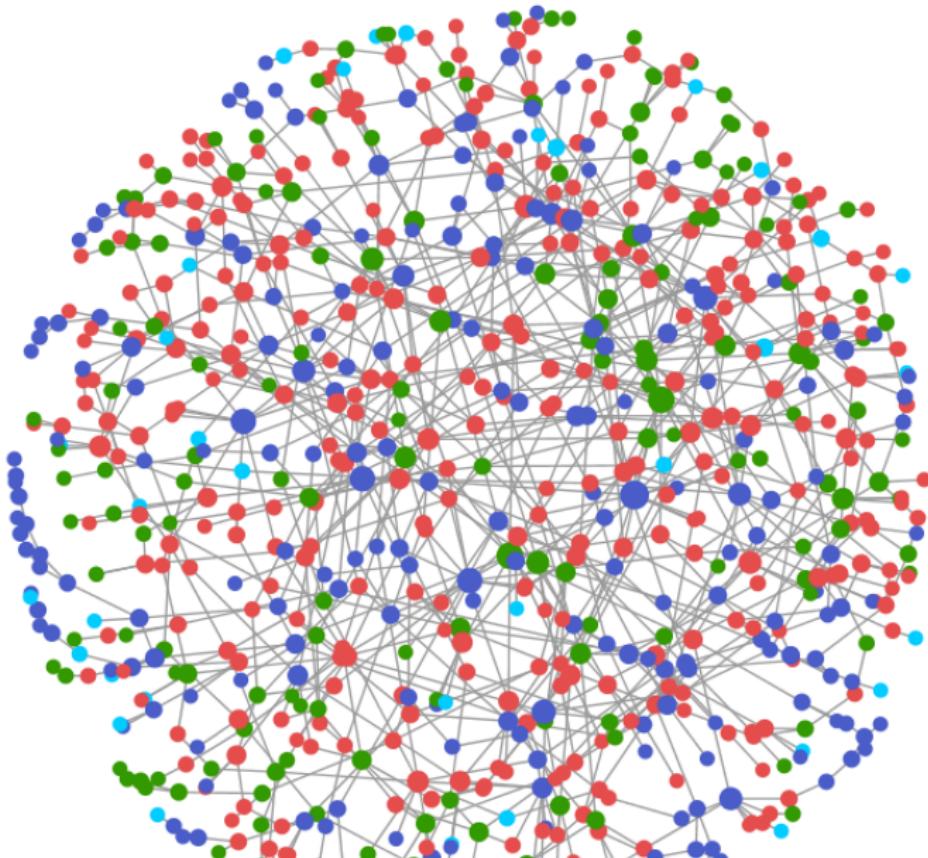
Mixed Graphical Models with Applications to Integrative Cancer Genomics

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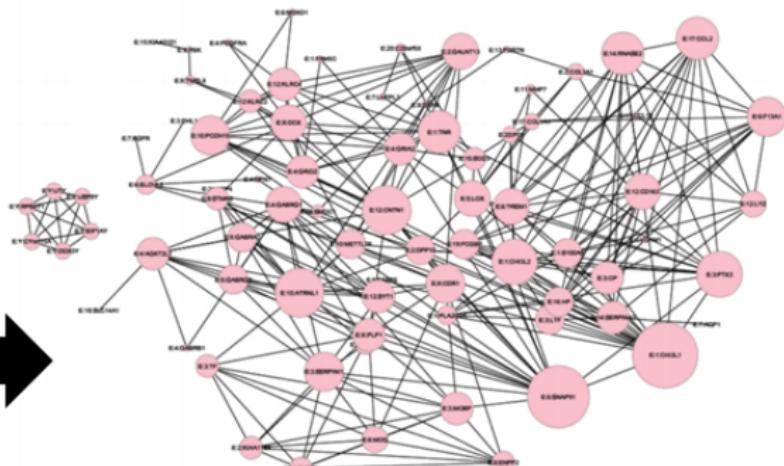
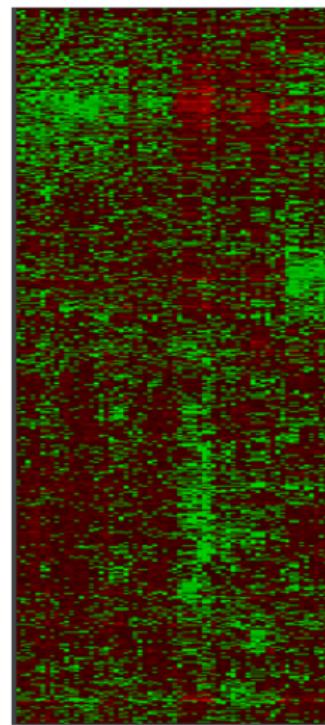
June 27, 2018

Genomic Networks from High-Throughput Data



Motivation: Gene Expression Networks

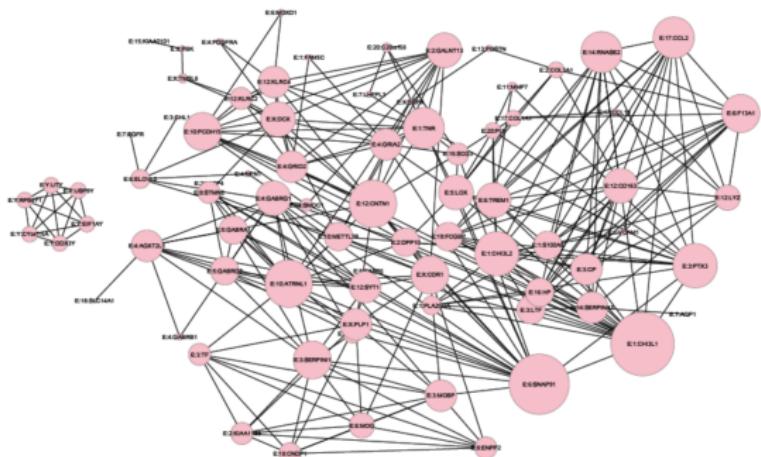
Subjects



Glioblastoma gene expression network estimated from microarrays using a Gaussian Graphical Model.

Motivation: Gene Expression Networks

- Visualize data.
 - Infer pathways.
 - Discover biomarkers.
 - Guide Experimentalists.
 - Generate Hypotheses.



Motivation: The Cancer Genome Atlas (TCGA)

THE CANCER GENOME ATLAS
National Cancer Institute
National Human Genome Research Institute

Launch Data Portal | Contact Us | For the Media

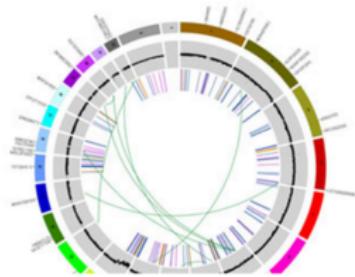
Search

Home About Cancer Genomics Cancers Selected for Study Research Highlights Publications News and Events About TCGA

Program Overview

Explore how The Cancer Genome Atlas works, the components of the TCGA Research Network and TCGA's place in the cancer genomics field in the Program Overview.

[Learn More ▶](#)



 Analysis of Adrenocortical Carcinoma

 TCGA's Study of Prostate Cancer

 Cancers Selected for Study

 About TCGA

Launch Data Portal ▶

The Cancer Genome Atlas (TCGA) Data Portal provides a platform for researchers to search, download, and analyze data sets generated by TCGA.

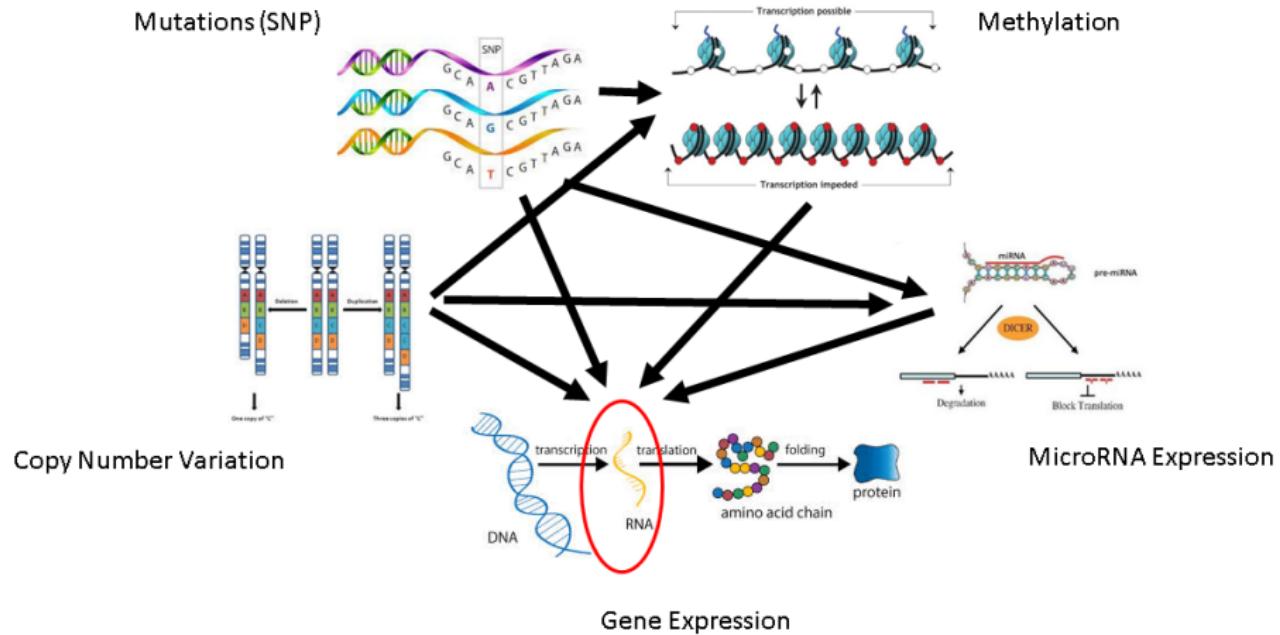
Questions About Cancer

Visit www.cancer.gov
Call 1-800-4-CANCER
Use [LiveHelp Online Chat](#)

Multimedia Library

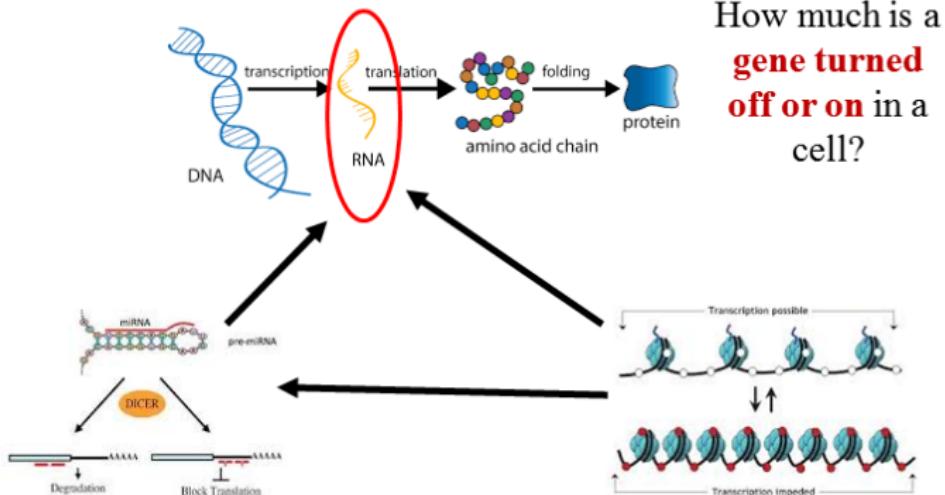
- 33 different cancer types.
- Over 11,000 patients!
- 7 different types of genetics data.
- 2.5 Petabytes worth of data.

Motivation: The Cancer Genome Atlas (TCGA)



Motivation: The Cancer Genome Atlas (TCGA)

Gene Expression



MicroRNA Expression

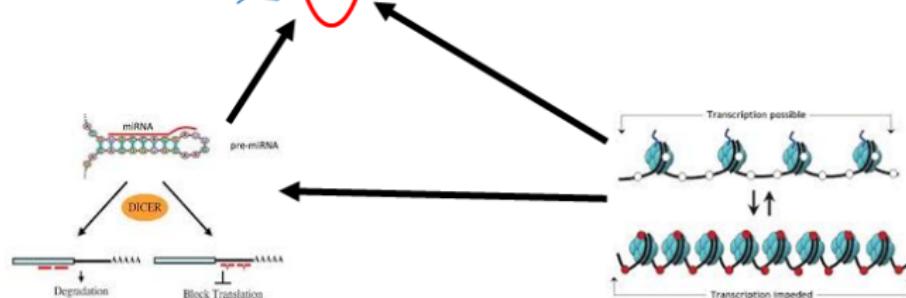
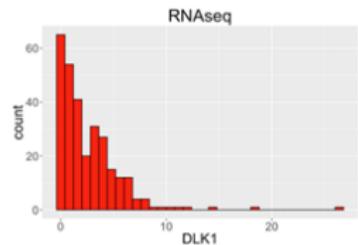
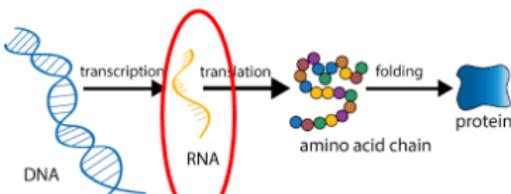
DNA Methylation

Epigenetics:

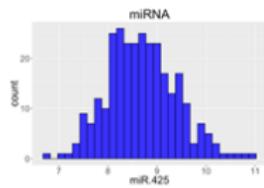
- Can turn off gene expression
- Changes with **Lifestyle & Environment**

Motivation: The Cancer Genome Atlas (TCGA)

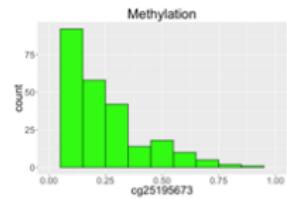
Gene Expression



MicroRNA Expression



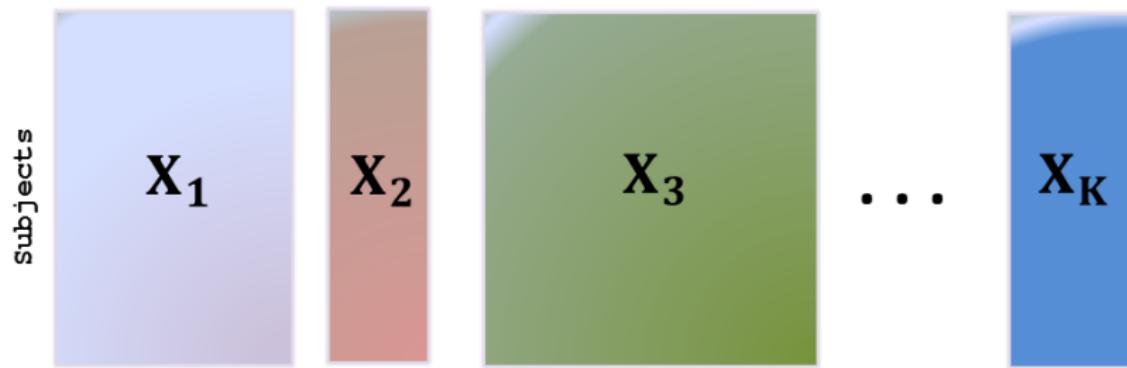
DNA Methylation



Data Integration & Multi-Modal Data

Mixed, Multi-Modal Data

Mixed or heterogeneous sources of data (sets of features) measured for the same set of subjects or observations.



Objective

Objectives

- Develop new families of graphical models that can integrate mixed, multi-modal data.
- Develop new statistical machine learning techniques to estimate integrative graphical models.

Why proper graphical models (Markov Networks)?

- Probabilistic interpretability.
- Statistical guarantees on network recovery.
- Characterize uncertainty.

Reproducible Data-Driven Discoveries.

1 Review: Markov Networks

2 Graphical Models via Exponential Families

- Motivation
- Graphical Models via Exponential Families

3 Mixed Graphical Models

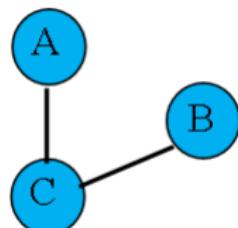
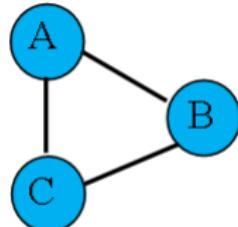
- Mixed MRFs
- Mixed Chain Graphical Models

4 Mixed Graphical Model Selection

5 Results

Markov Networks

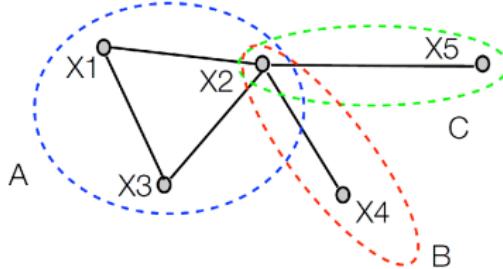
- Represent dependencies in multivariate distributions.
- Undirected graphical models or **pair-wise Markov Random Fields**.
- $X = (X_1, X_2, \dots, X_p)$ is a random vector.
- Denote the graph G by a set of vertices $V = 1, \dots, p$ and edges, $E \in V \times V$: $G = \{V, E\}$.
- Lack of edges denote conditional independence given all other nodes (pairwise conditional independence).
- Captures **direct dependencies** between random variables.



$$A \perp B \mid C$$

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.



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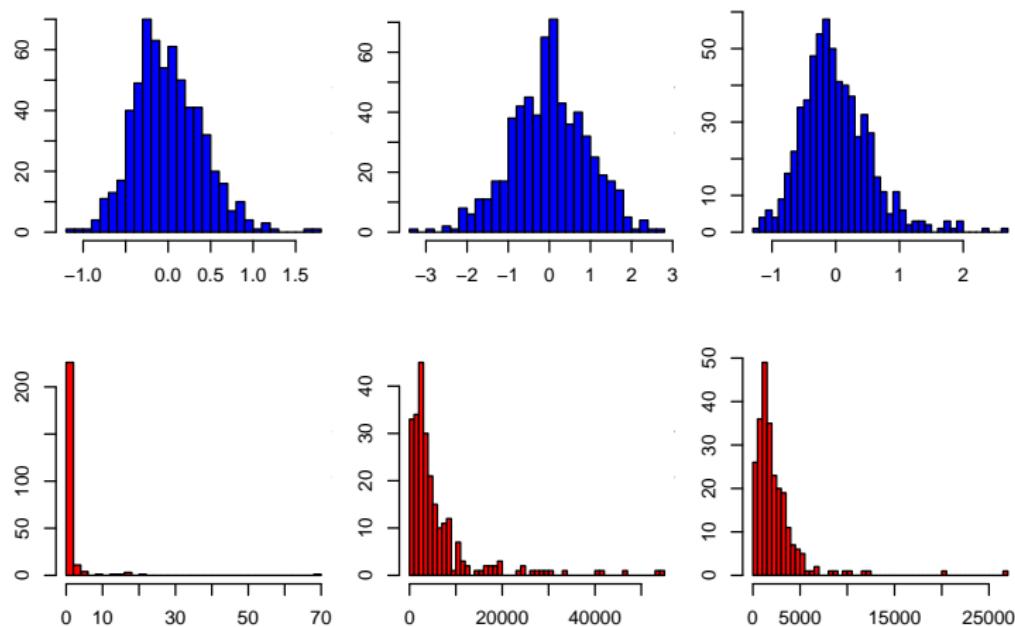
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Motivation: Networks from RNA-Sequencing Data

Gaussian Graphical Models have been widely used to infer **genomic networks** from microarray data:



Not appropriate for next generation sequencing (RNA-Seq) data!

Graphical Models from Count or Other Data Types?

- Gaussian Graphical Model.

- ▶ Conditional & marginal distributions are Gaussian, jointly multivariate Gaussian.
- ▶ Conditional independence given by zeros in inverse covariance matrix.
- ▶ Sparse Graphical Model Estimation. (Meinshaussen & Bühlmann, 2006; Yuan & Lin, 2007; Banerjee *et al.*, 2008; Friedman *et al.*, 2008)

- Ising & Potts Model.

- ▶ Assumes node-conditional distributions are binomial / multinomial.
- ▶ Sparse Graphical Model Estimation. (Ravikumar *et al.*, 2010)

Graphical Models from Count or Other Data Types?

- Mixed Conditional Gaussian Model & Chain Graphs.
 - ▶ Mixed Chain Graphical Models. (Lauritzen and Wermuth (1989); Frydenberg (1990); Lauritzen (1996)).
 - ★ Continuous variables conditioned on all combos discrete variables are multivariate Gaussian.
 - ★ Number of parameters scale exponentially.
 - ★ Can chain recursively.
 - ★ Have the block concentration Markov property.
 - ▶ Graph selection for Mixed Chain Graphs:
 - ★ Learning the Structure of Mixed Graphical Models (Lee and Hastie (2012)).
 - ★ High-Dimensional Mixed Graphical Model (Cheng, Levina, Zhu (2013)).

Only Gaussian & Discrete variables. . .

Review: Univariate Exponential Families

Key Idea: What if we can leverage univariate distributions appropriate for different data types?

Examples:

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

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

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

Graphical Models via Exponential Families

Assumption:

- Node-conditional distributions are univariate exponential family densities.

Theorem

Joint Density **necessarily** has the form:

$$P(X) = \exp \left\{ \sum_s \theta_s B(X_s) + \sum_{s \in V} \sum_{t \in N(s)} \theta_{st} B(X_s)B(X_t) \right. \\ \left. + \sum_{s \in V} \sum_{t_2, \dots, t_k \in N(s)} \theta_{s \dots t_k} B(X_s) \prod_{j=2}^k B(X_{t_j}) + \sum_s C(X_s) - A(\theta) \right\}$$

$N(s)$ denotes the neighborhood of node s & $A(\theta)$ is the log-normalization term.

(**YRAL**, 2012; **YRAL**, 2015)

Graphical Models via Exponential Families

Special Case:

- Pairwise interactions.
- Linear sufficient statistics $B(X_s) = X_s$.

Joint Density

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

Node-Conditional Density

$$P(X_s | X_{V \setminus s}) \propto \exp \left\{ \left(\theta_s + \sum_{t \in N(s)} \theta_{st} X_t \right) X_s + C(X_s) \right\},$$

i.e. a Generalized Linear Model with response X_s and predictors $X_{V \setminus s}$.

Graphical Models via Exponential Families

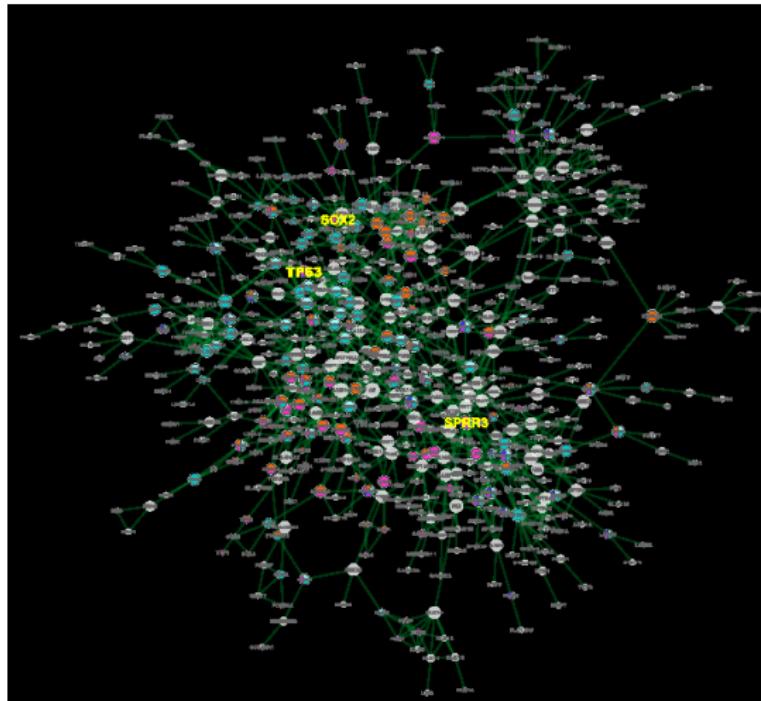
Example of Poisson Graphical Model (Count Data):

$$P(X) = \exp \left\{ \sum_s \theta_s X_s + \sum_{(s,t) \in E} \theta_{st} X_s X_t + \sum_s \log(X_s!) - A(\theta) \right\}.$$

- Technical conditions needed to ensure proper densities.
 - ▶ $\theta_{st} \leq 0$ (only negative conditional dependencies!)
- Variations that permit negative & positive dependencies:
 - ▶ Truncation, Sub-linear, Quadratic, and approximations to these.

(**YRAL**, 2013; **AL**, 2012; **AL**, 2013)

Results Preview: Graphical Models via Exponential Families



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

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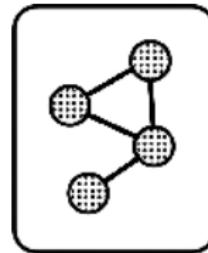
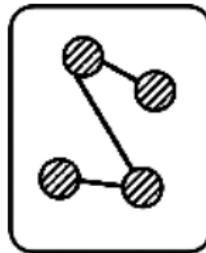
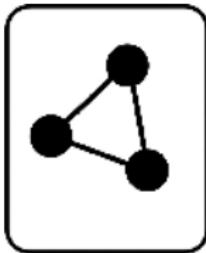
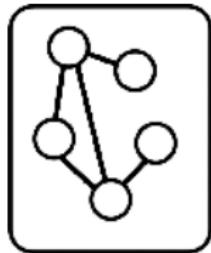
- Mixed MRFs
- Mixed Chain Graphical Models

4 Mixed Graphical Model Selection

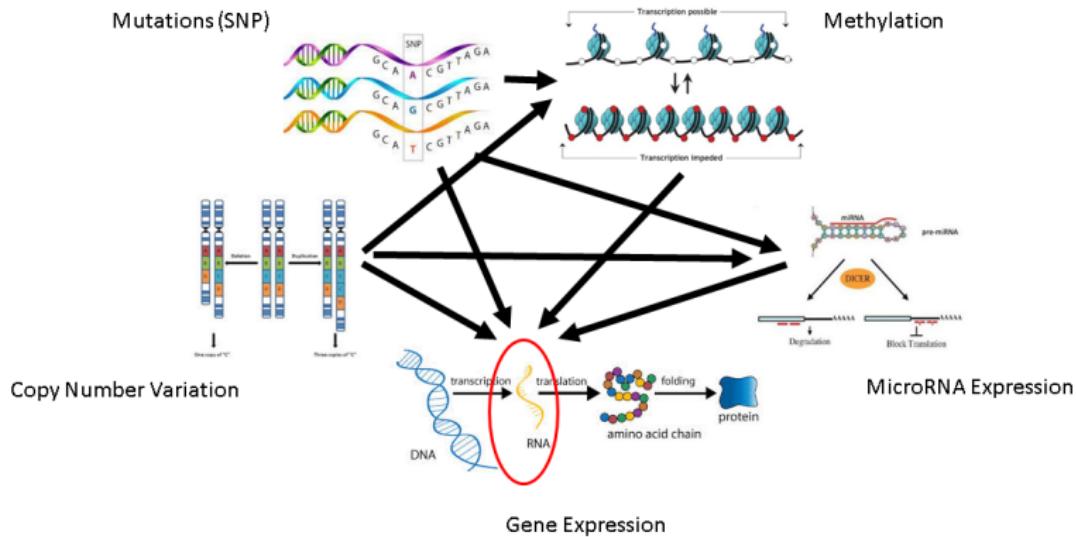
5 Results

Motivation: Integrative Genomics

Graphical Models via Exponential Families



Motivation: Integrative Genomics



No general multivariate density that directly parameterizes dependencies for mixed variables exists!

Mixed Graphical Models via Exponential Families

- Key Assumption: Conditional distributions are **different** Exponential Families.

Theorem

Joint Density necessarily has the form:

$$P(X) = \exp \left\{ \sum_s \theta_s B_s(X_s) + \sum_{s \in V} \sum_{t \in N(s)} \theta_{st} B_s(X_s) B_t(X_t) \right. \\ \left. + \sum_{s \in V} \sum_{t_2, \dots, t_k \in N(s)} \theta_{s \dots t_k} B_s(X_s) \prod_{j=2}^k B_t(X_{t_j}) + \sum_s C_s(X_s) - A(\theta) \right\}$$

(**YBRAL**, 2014; Chen et al., 2015)

Mixed Graphical Models via Exponential Families

Special Case: Two partitions of variables (\mathbf{X}, \mathbf{Y}) & pairwise graph.

$$\begin{aligned} P(\mathbf{X}, \mathbf{Y}; \theta) = & \exp \left\{ \sum_{s \in V_X} \theta_s B_X(X_s) + \sum_{s' \in V_Y} \theta_{s'} B_Y(Y_{s'}) \right. \\ & + \sum_{(s,t) \in E_X} \theta_{st} B_X(X_s) B_X(X_t) + \sum_{(s',t') \in E_Y} \theta_{s't'} B_Y(Y_{s'}) B_Y(Y_{t'}) \\ & \left. + \sum_{(s,s') \in E_{XY}} \theta_{ss'} B_X(X_s) B_Y(Y_{s'}) + \sum_{s \in V_X} C_X(X_s) + \sum_{s' \in V_Y} C_Y(Y_{s'}) - A(\theta) \right\} \end{aligned}$$

$$A(\theta) := \log \int_{\mathcal{X}^P} \exp \left\{ \sum_{s \in V_X} \theta_s B_X(X_s) + \sum_{s' \in V_Y} \theta_{s'} B_Y(Y_{s'}) + \dots + \sum_{s' \in V_Y} C_Y(Y_{s'}) \right\}$$

$B_X(\cdot), C_X(\cdot)$ sufficient stat. and base measure for node-conditional of X

$B_Y(\cdot), C_Y(\cdot)$ sufficient stat. and base measure for node-conditional of Y

$A(\theta)$ log-partition function

Mixed Graphical Models via Exponential Families

Advantage:

- General mixed multivariate distribution exists!

Problem:

- Stringent **Normalizability** Assumptions.
 - ▶ Example: No (non-trivial) distribution exists linking Poisson and Gaussian variables.

Solution:

- Chain rule of conditional probability: $P(X, Y) = P(Y|X)P(X)$.

Mixed Chain MRFs: Elementary Construction

Partition p variables into two groups: $X = \{Y, Z\}$:

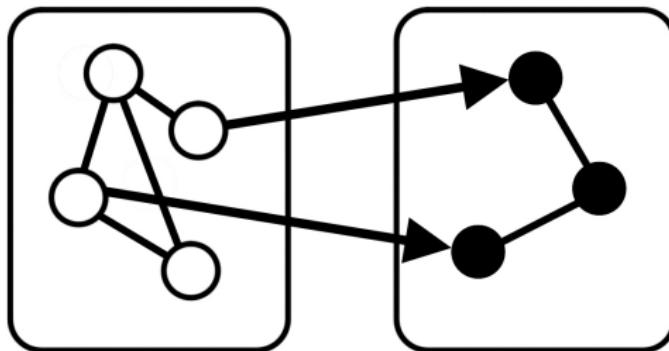
$$P(X) = P_1(Y|Z)P_2(Z)$$

- P_1 is a **Conditional Markov Random Field** constructed via node-conditional exponential families.
 - ▶ Heterogeneous (Mixed).
 - ▶ Homogeneous.
- P_2 is a **Markov Random Field** constructed via node-conditional exponential families.
 - ▶ Heterogeneous (Mixed).
 - ▶ Homogeneous.

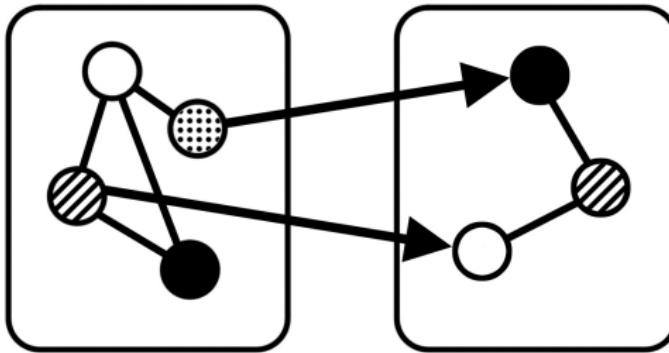
(YRABWL, 2015)

Mixed Chain MRFs: Elementary Construction

Homogeneous Elementary Mixed Chain MRF:



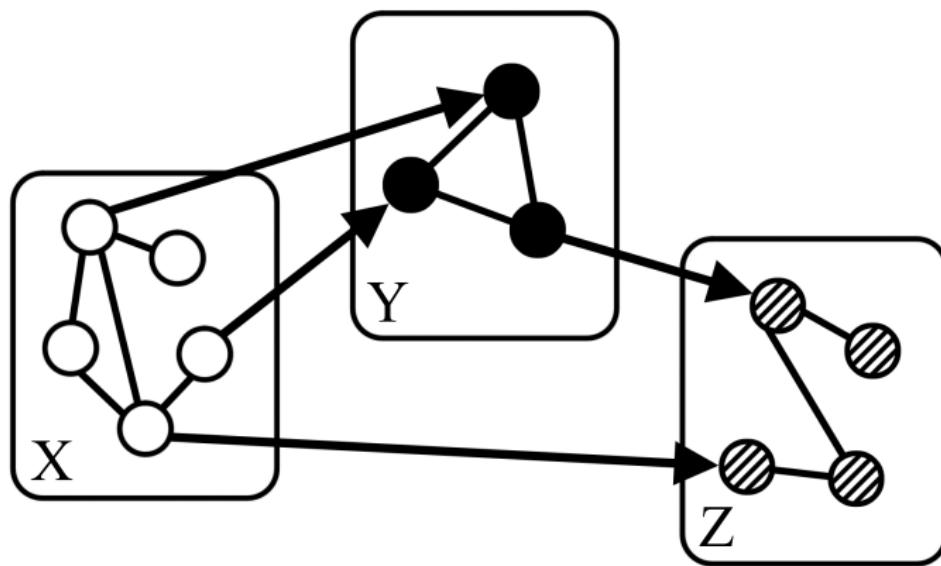
Heterogeneous Elementary Mixed Chain MRF:



Multiple Blocks: Recursive Mixed Chain Graphs

Idea: Recursively apply chain rule to blocks of variables.

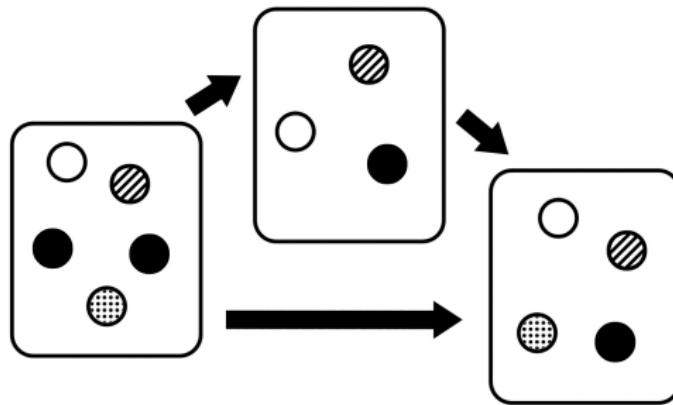
$$P(X, Y, Z) = P(Z|X, Y)P(Y|X)P(X)$$



Multiple Blocks: Recursive Mixed Chain Graphs

Will this yield a network with Markov properties?

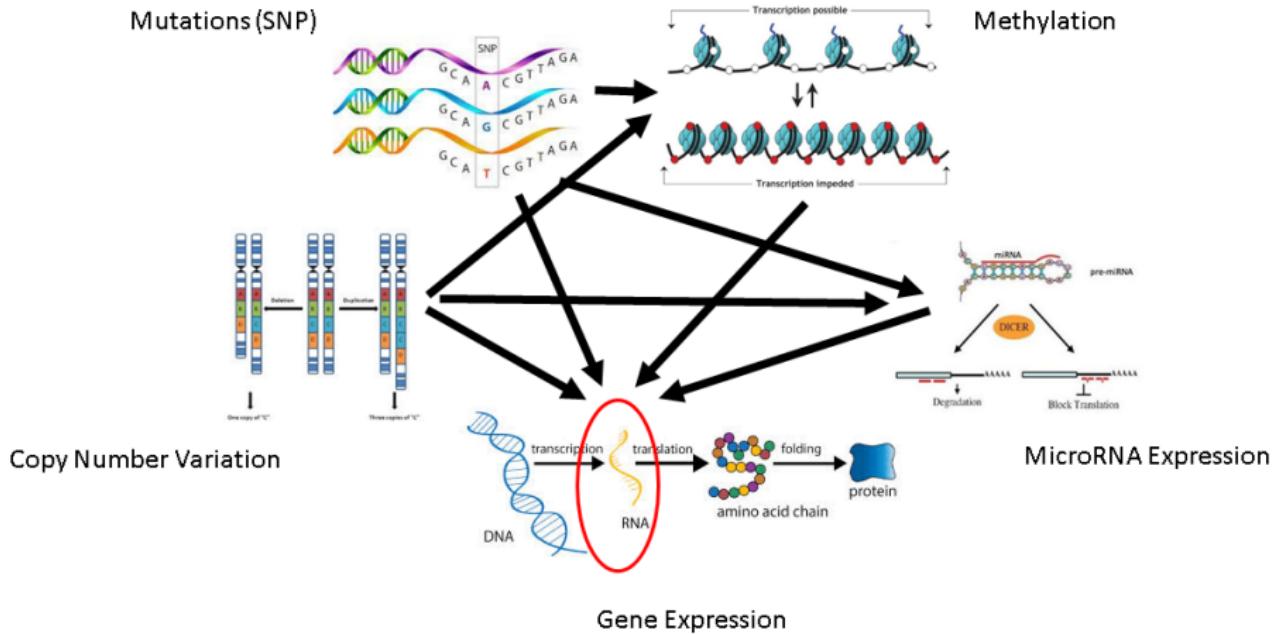
- Yes! Block concentration Markov property. (Lauritzen, 1996)
- Special cases - global Markov property for network skeleton.



Blocks known & Partial ordering of blocks known:

- Blocked Directed Acyclic Graph (DAG):
 - ▶ Within Block: Undirected edges.
 - ▶ Between Blocks: Directed edges (no cycles!).

Multiple Blocks: Recursive Mixed Chain Graphs



Mixed Chain MRFs: Properties

How does this compare to the Mixed MRF?

Example: $P(Y, X) = P(Y|X)P(X)$ for 2-block homogeneous, pairwise graphs.

$$\begin{aligned} P(X, Y; \theta) = & \exp \left\{ \sum_{s \in V_X} \theta_s B_X(X_s) + \sum_{s' \in V_Y} \theta_{s'} B_Y(Y_{s'}) \right. \\ & + \sum_{(s,t) \in E_X} \theta_{st} B_X(X_s) B_X(X_t) + \sum_{(s',t') \in E_Y} \theta_{s't'} B_Y(Y_{s'}) B_Y(Y_{t'}) \\ & + \sum_{(s,s') \in E_{XY}} \theta_{ss'} B_X(X_s) B_Y(Y_{s'}) + \sum_{s \in V_X} C_X(X_s) + \sum_{s' \in V_Y} C_Y(Y_{s'}) \\ & \left. - A_{Y|X}(\theta) - A_X(\theta) \right\} \end{aligned}$$

$A_{Y|X}(\theta)$ normalizability term for CRF.

$A_X(\theta)$ normalizability term for MRF.

Mixed Chain MRFs: Properties

What does this mean in terms of normalizability?

Theorems

- ① Normalizable if CRFs and MRFs are normalizable.
- ② Normalizability conditions strictly weaker than Mixed MRFs.

Implication: Dependencies permitted in Mixed Chain MRFs that are not in Mixed MRFs.

Mixed Chain MRFs: Properties

Gaussian-Poisson Chain MRF

Let \mathbf{X} be counts (Poisson) and \mathbf{Y} continuous (Gaussian).

- Mixed MRF does not permit dependencies between \mathbf{X} and \mathbf{Y} .
- Mixed Chain MRF $P(\mathbf{X}, \mathbf{Y}) = P(\mathbf{Y}|\mathbf{X})P(\mathbf{X})$ exists!
- Mixed Chain MRF $P(\mathbf{X}, \mathbf{Y}) = P(\mathbf{X}|\mathbf{Y})P(\mathbf{Y})$ exists!

$$\begin{aligned}\log P(\mathbf{X}, \mathbf{Y}) &= \sum_{s \in V_Y} \left(\theta_s + \sum_{t \text{ s.t } (s,t) \in E_{XY}} \theta_{st} X_t \right) \frac{Y_s}{\sigma_s} + \sum_{(s,s') \in E_Y} \theta_{ss'} \frac{Y_s Y_{s'}}{\sigma_s \sigma_{s'}} - \sum_{s \in V_Y} \frac{Y_s^2}{2\sigma_s^2} \\ &\quad + \sum_{X \in V_X} \theta_t X_t + \sum_{(t,t') \in E_X} \theta_{tt'} X_t X_{t'} - \sum_{t \in V_X} \log(X_t!) - A_{Y|X}(\theta(\mathbf{X})) - A_X(\theta).\end{aligned}$$

Mixed Chain MRFs: Properties

Implications:

- General, flexible class of MRF models.
 - ▶ Mixed variables.
 - ▶ Mixed edges (both directed and undirected).
- First multivariate density that directly parameterizes dependencies over mixed variables!

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Mixed Graph Selection and Estimation

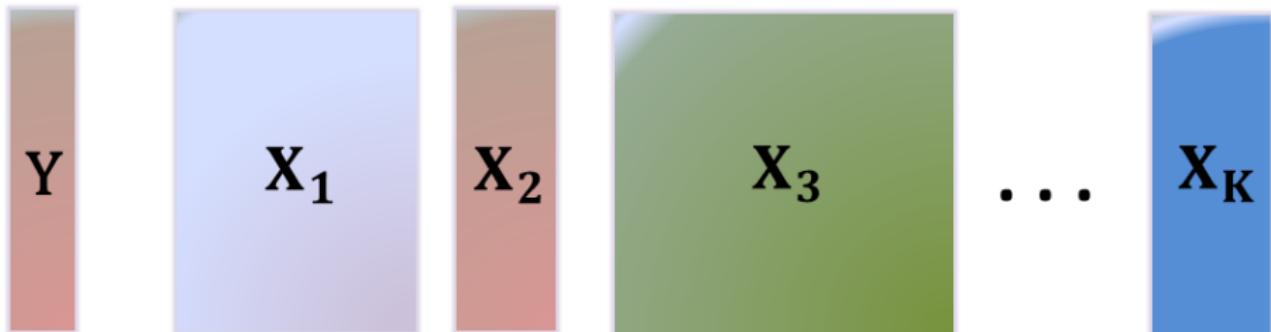
Objective: Given iid observations, seek to learn graph structure (selection) and parameters (estimation).

- Mixed Chain MRF density factorizes into products of CRFs.
 - ▶ \implies Can learn each CRF separately.
- Each CRF factorizes by node-neighborhood.
 - ▶ \implies Can learn each node neighborhood separately.
- **Neighborhood Selection** - For each node:
 - ▶ Maximize penalized conditional likelihood.
 - ▶ \implies Mixed, ℓ_1 penalized GLMs!

Mixed Graph Selection and Estimation

Neighborhood Selection for node $X_{k,j}$:

$$\underset{\alpha, \beta_1 \dots \beta_K}{\text{minimize}} \quad -\frac{1}{n} \ell \left(X_{k,j}; \quad \alpha + \mathbf{x}_{k, \neq j} \beta_k + \sum_{k' \neq k}^K \mathbf{x}_{k'} \beta_{k'} \right) + \sum_{k=1}^K \lambda_k \|\beta_k\|_1.$$



Mixed Graph Selection and Estimation

Theoretical Guarantees

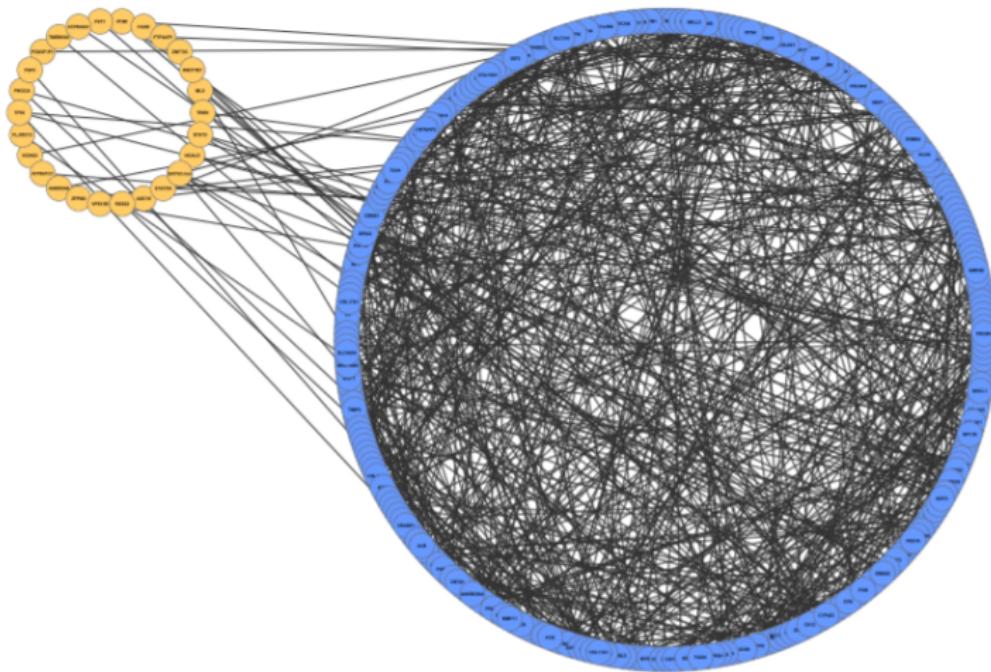
Assumptions:

- Restricted Eigenvalue condition (on Fisher Information matrix associated with each parent distribution).
- $\lambda_k \propto \sqrt{\log(p_k)/n}$ & $n \propto d^2 \log(\sum_{k=1}^K p_k)$ (degree squared).

Result:

- Unique solution.
- With high probability, exactly recover the true edge structure.
- Consistent parameter estimation.

Mixed Graph Selection and Estimation: Reality



Theory too restrictive!

Challenges

① Ultra high-dimensional problem.

- ▶ Variable selection for each data type may be in high-dimensional regime, but collectively in ultra high-dimensional regime.
- ▶ More samples are needed for selection consistency of non-Gaussian GLMs (esp. Poisson, Negative Binomial, etc.). [Yang et al., 2012, 2014; Chen et al., 2015]
- ▶ Need $n \propto d^2!$ (Huge n needed to select hub-like and scale-free graphs.) [Yang et al., 2014, 2017+]

② Strong and complex dependencies.

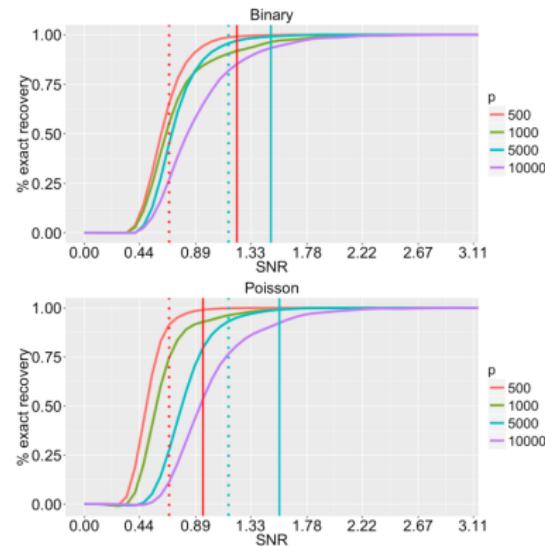
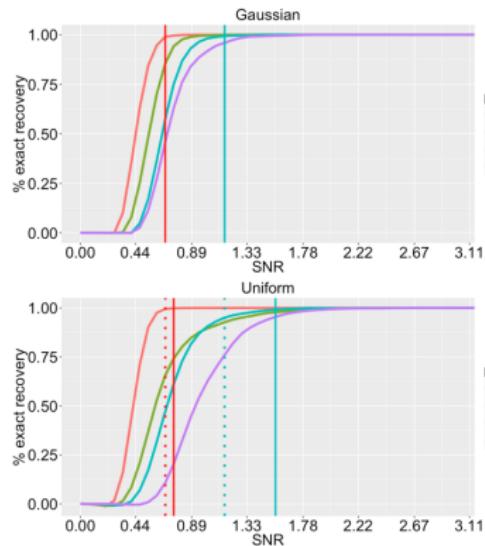
- ▶ Existing techniques known to perform poorly.

③ Different scale and signal strength between data types.

- ▶ Need different λ_k for each data type.
- ▶ How to choose λ_k ?

Challenges

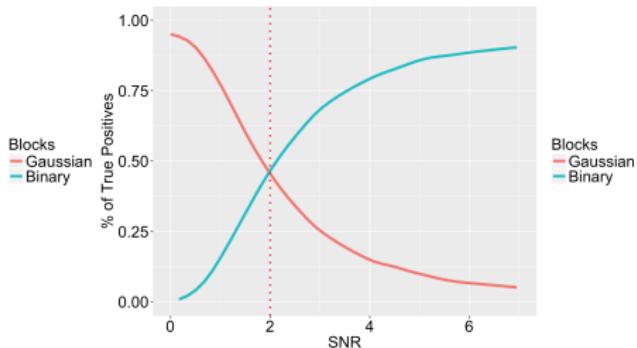
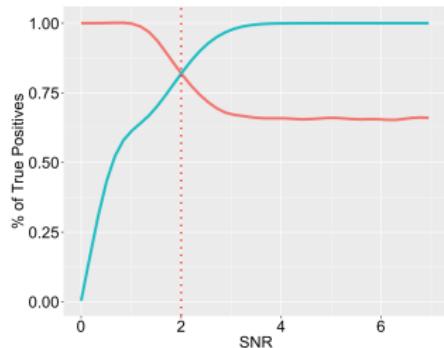
- ① Ultra high-dimensional problem.
- ② Strong and complex dependencies.
- ③ Different scale and signal strength between data types.



- ▶ Different signal strengths (β -mins) needed to select variables of different types.

Challenges

- ① Ultra high-dimensional problem.
- ② Strong and complex dependencies.
- ③ Different scale and signal strength between data types.



- ▶ Block Shrinkage Noise [Su et al., 2015].

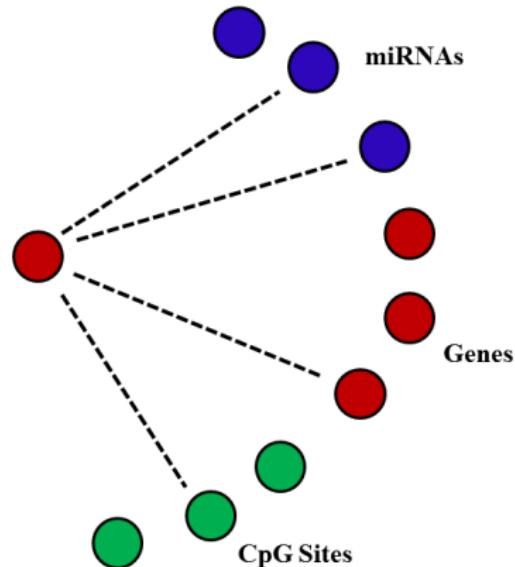
Block Randomized Adaptive Iterative Lasso (B-RAIL)

Idea:

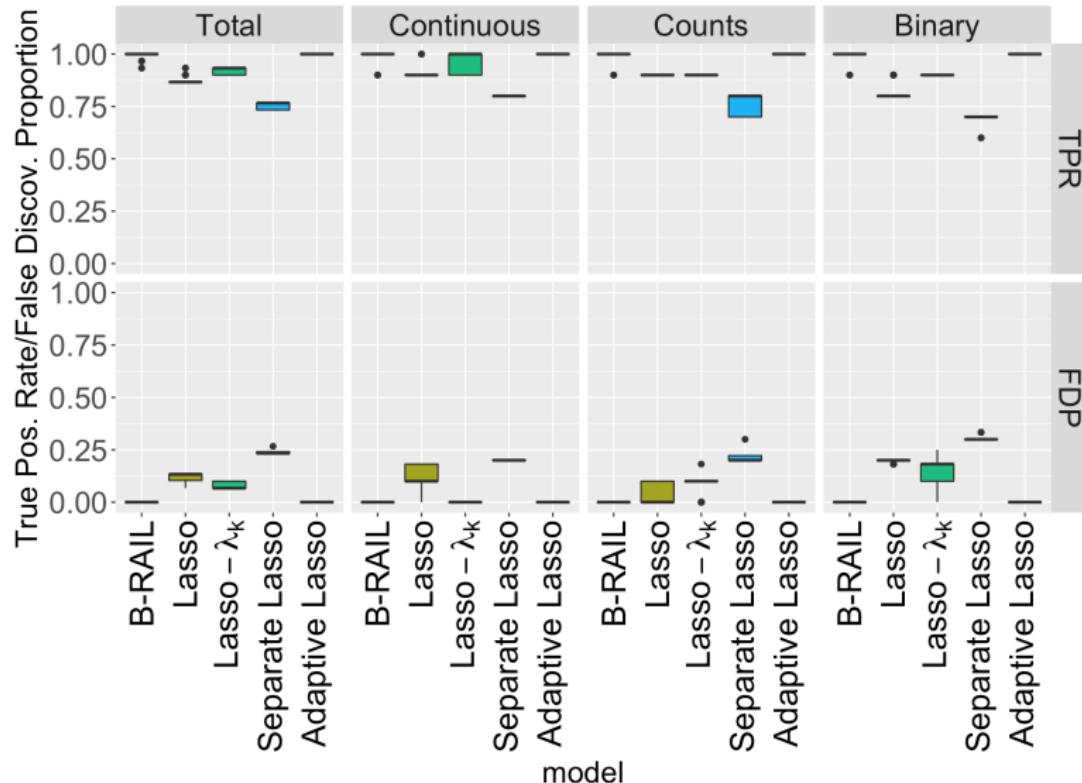
- Combine task of selection & estimation.
- Consider one block at a time.
- Adaptive regularization for each block.
- Randomized regularization.

Result:

- Automatically adjusts for differential scaling and SNR.
- Better handles complex dependencies.
- From ultra high-dimensional to high-dimensional.
- Fast, parallelizable algorithm.

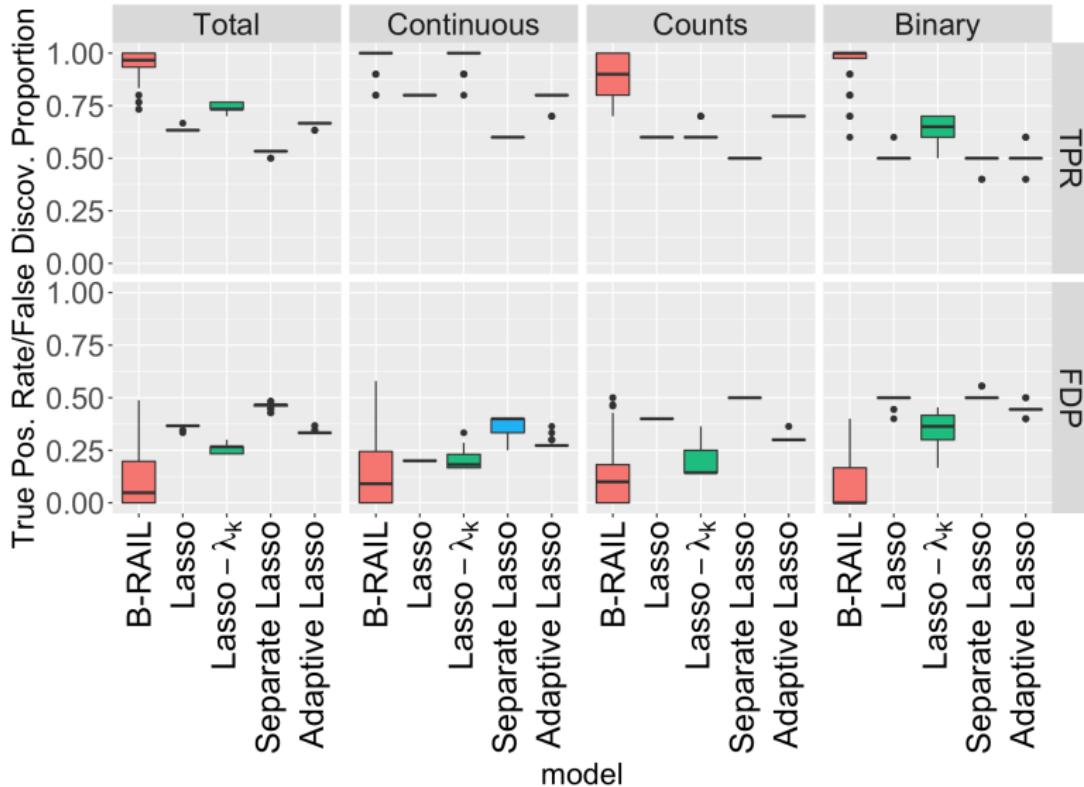


Simulation Studies



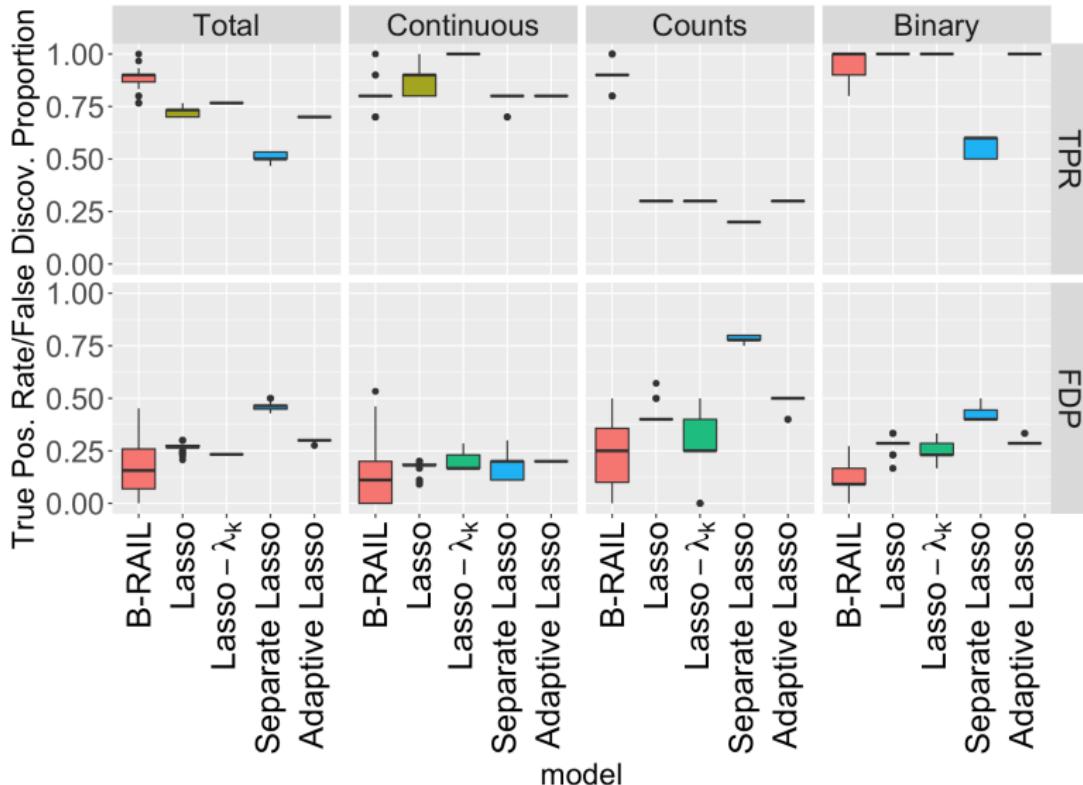
High-Dimensional Case; iid \mathbf{X} ; Gaussian GLM

Simulation Studies



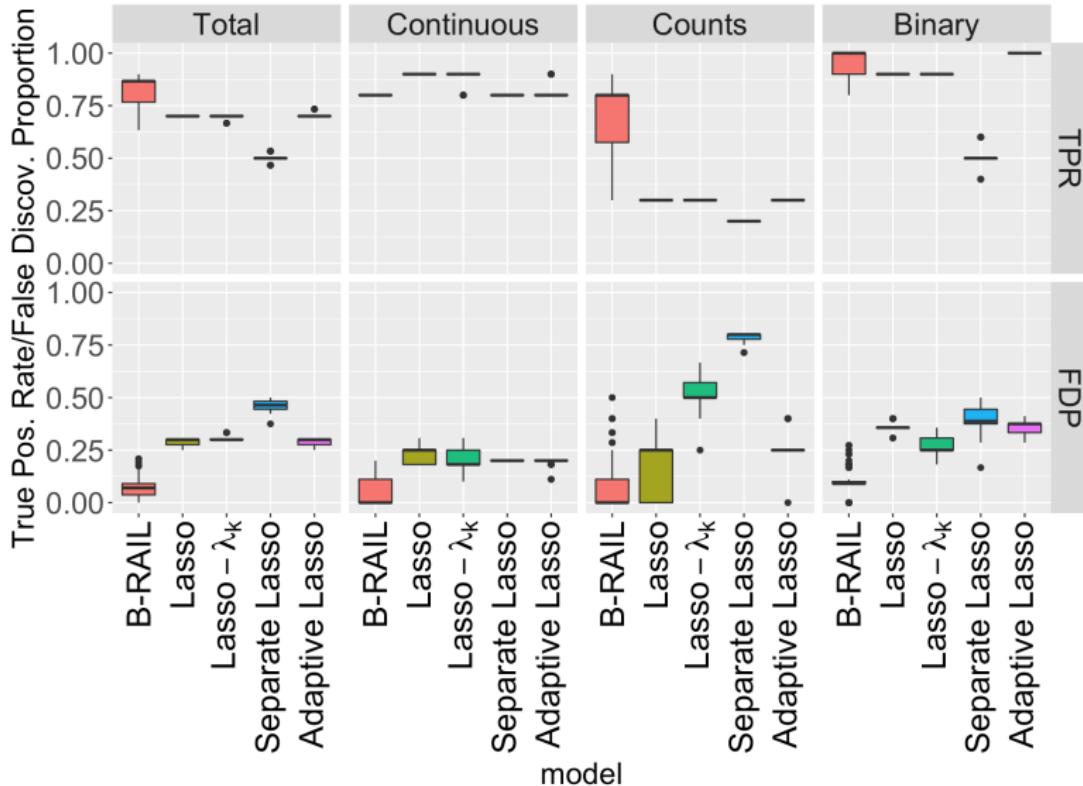
Ultra High-Dimensional Case; iid \mathbf{X} ; Gaussian GLM

Simulation Studies



Ultra High-Dimensional Case; Mixed Graphical Model X; Gaussian GLM

Simulation Studies



Ultra High-Dimensional Case; Mixed Graphical Model X; Logistic GLM

1 Review: Markov Networks

2 Graphical Models via Exponential Families

- Motivation
- Graphical Models via Exponential Families

3 Mixed Graphical Models

- Mixed MRFs
- Mixed Chain Graphical Models

4 Mixed Graphical Model Selection

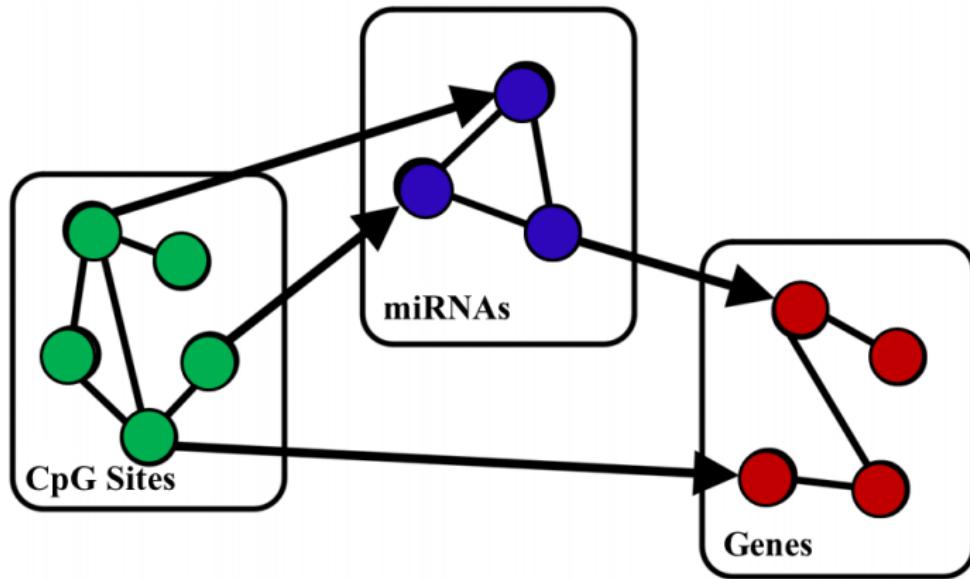
5 Results

Case Study: Ovarian Cancer Regulatory Network

TCGA Ovarian Cancer Data:

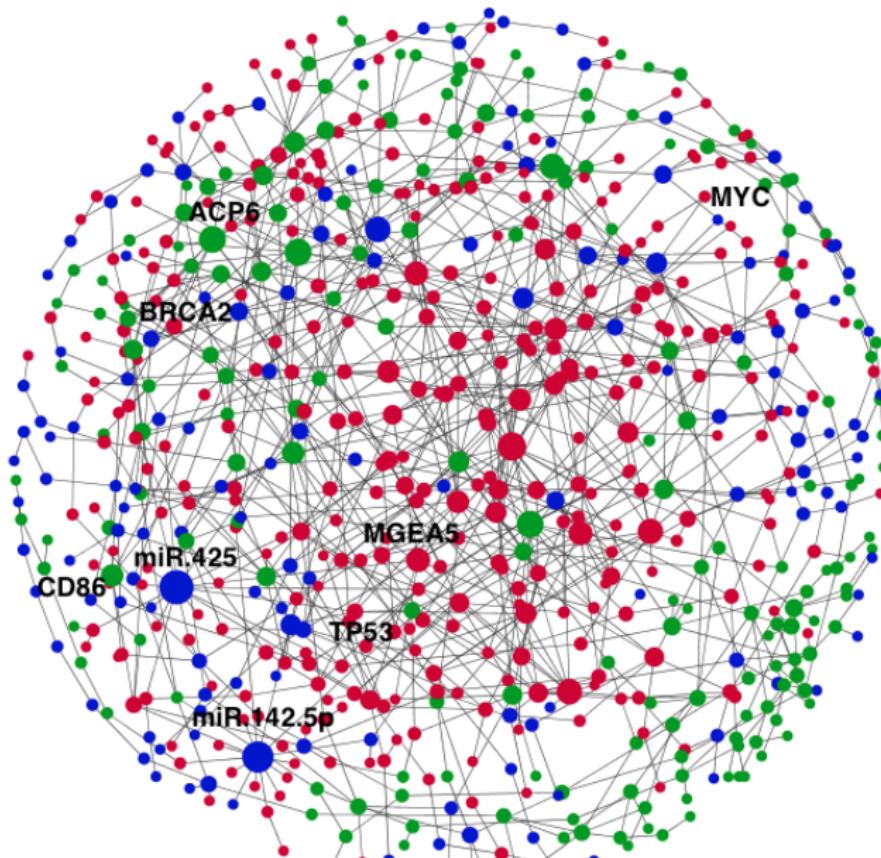
- Level III miRNA-array data.
- Level II Methylation data.
- Level III RNA-Seq data.
- $n = 293$ subjects (complete cases).
- Genes, miRNAs and CpG sites were filtered down to $p = 1016$ via association tests with survival, recurrence, chemoresistance, or mutation rate.
- Edges selected via stability selection threshold of 90%.

Case Study: Ovarian Cancer Regulatory Network

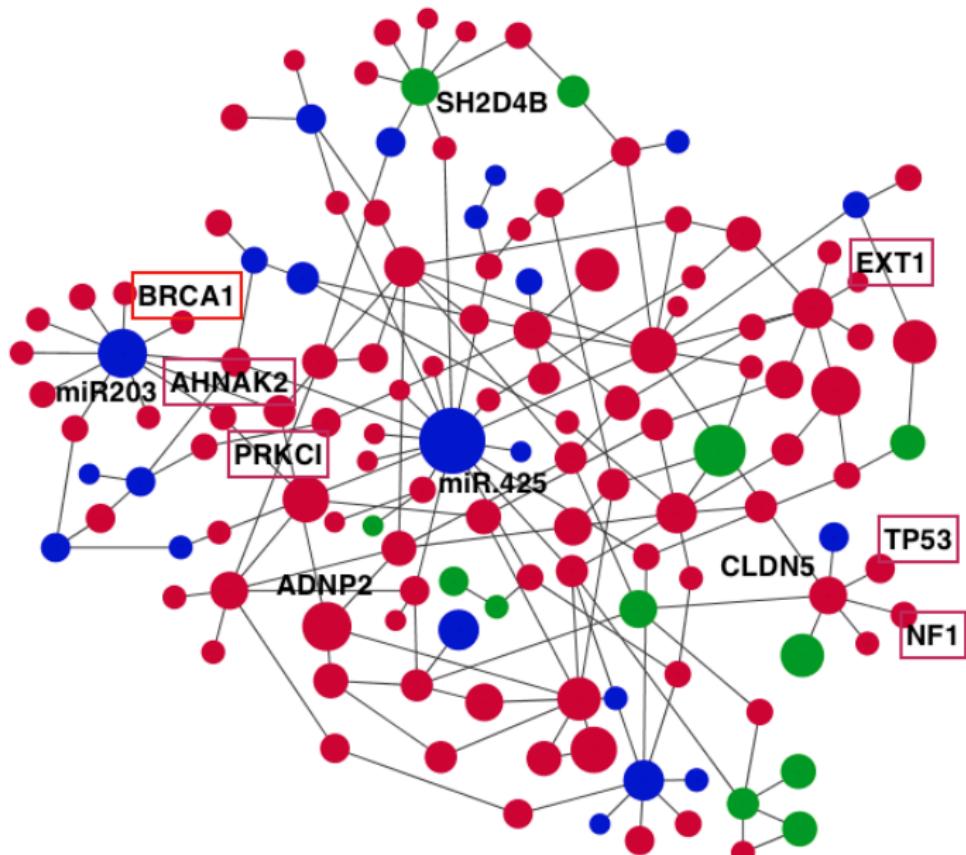


$$\mathbb{P}_{\text{Pois}}(\text{Genes} \mid \text{miRNAs}, \text{CpGs}) \quad \mathbb{P}_{\text{Gauss}}(\text{miRNAs} \mid \text{CpGs}) \quad \mathbb{P}_{\text{Ising}}(\text{CpGs})$$

Case Study: Ovarian Cancer Regulatory Network



Case Study: Ovarian Cancer Regulatory Network



Case Study: Ovarian Cancer Regulatory Network

Existing Literature on miR-425:

- Suggested as a diagnostic marker for ovarian cancer.
- PDGFC, a putative target, has been used as a prognostic marker for ovarian cancer survival.
- Up-regulated in ER+ breast cancers.
- Suggested as early stage marker of breast cancer.
- Implicated in other cancers such as prostate, renal, kidney, colorectal, lung, liver, bladder, etc.

Summary

Graphical Models via Exponential Families

- Stat: Extends Markov Networks for (almost) any data type!
- Application: Poisson Graphical Models for RNA-Sequencing data.

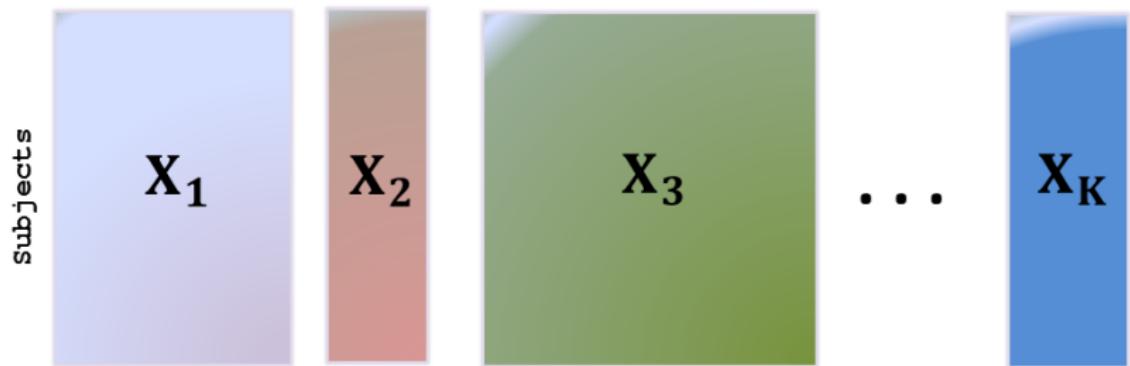
Mixed Graphical Models

- Stat: First direct multivariate density for mixed data types!
- Stat: Permits both directed AND undirected edges - flexible class of models.
- Application: Can model connections within and between multiple types of biomarkers.

Current & Future Work

Integrated Principal Components Analysis (iPCA)

- Dimension reduction for multi-modal data.
- Model-based, unique solution with statistical guarantees.
- Direct extension of classical PCA.
- Finds dimensions of joint variation across subjects.



Acknowledgments

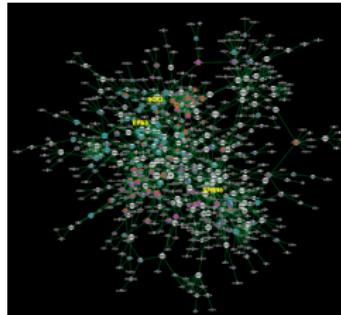
Collaborators:

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- Pradeep Ravikumar, Carnegie Mellon University.
- Eunho Yang, Korea Advanced Institute of Science and Technology.
- Zhandong Liu, Baylor College of Medicine.
- Ying-Wooi Wan, Baylor College of Medicine.
- Matthew Anderson, Baylor College of Medicine.



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.

MixedGraphs coming soon!

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Thank You!