# Networks and Sparse Graphical Models

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21 January, 2014

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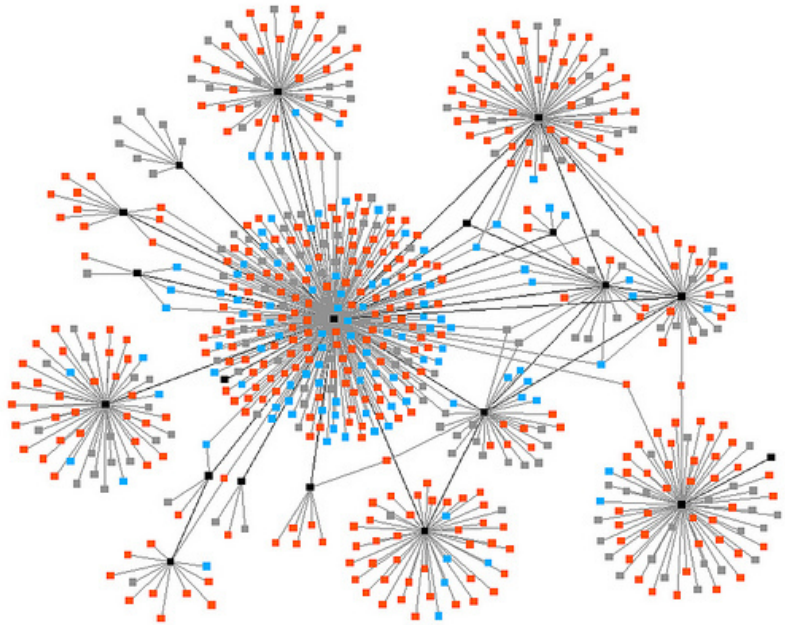
# Motivation: Features of a Dynamic Genomic Process

- "**p** >> **n**":
  - Number of observations smaller than number of variables.
  - Thousands of variables and hundreds of observations.
- **Structure:**
  - Highly complex and structured phenomenon.
  - Possibly with additional topographical structure (small world).
- **Sparsity:** only small number of links between nodes.



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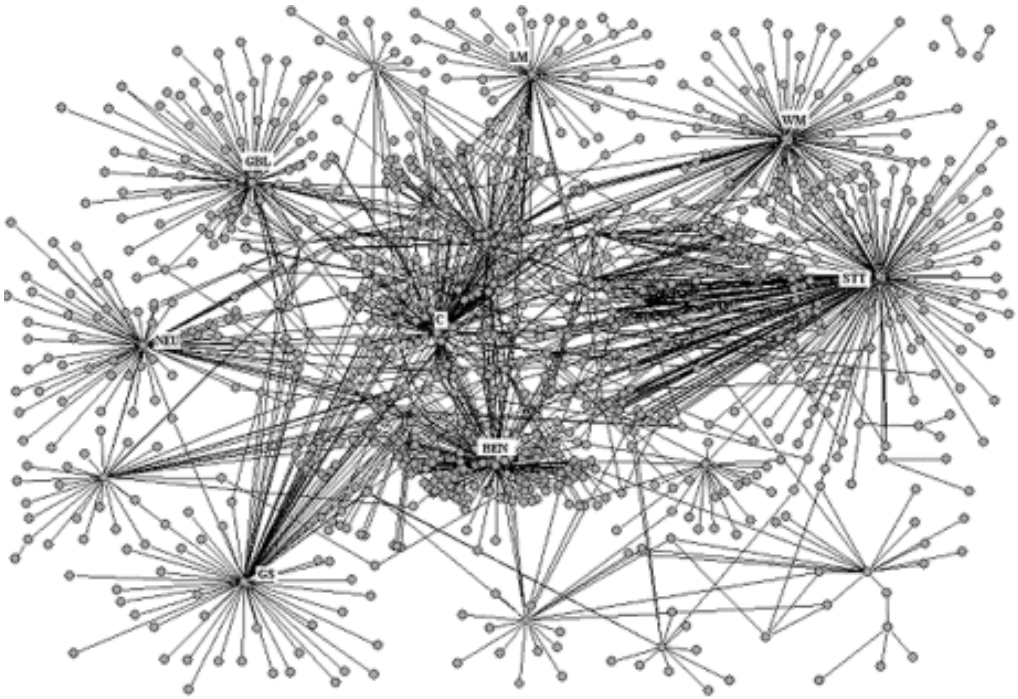
# "Network" as Graphical Model

**In Genomics:** typically have measurements of nodes
**Examples:** RNA-seq, GWAS, proteomics




**Proposal:** interpret network as *conditional independence* relations.

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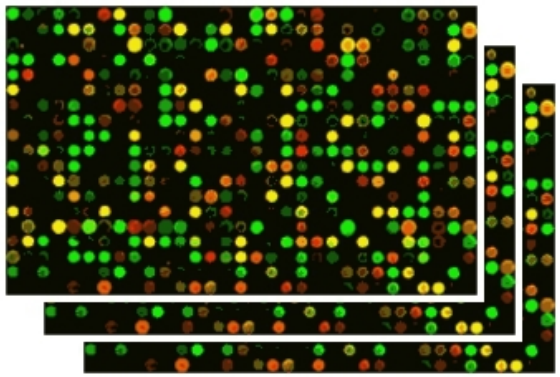
# Motivation: Dynamic Genomic Networks

- Transcription: snap-shot of gene activity in time and space.
- Microarray and RNA-seq data measure gene activity.



**Running example: T-cell time-series dataset.**

- Temporal expression of 58 genes for 10 spaced time points.
- At each time point there are 44 separate measurements.

## Definition (Aim)

Determine dynamic genomic graph $G$ on basis of $\{Y_{gt}^{(i)}\}_{gti}$.

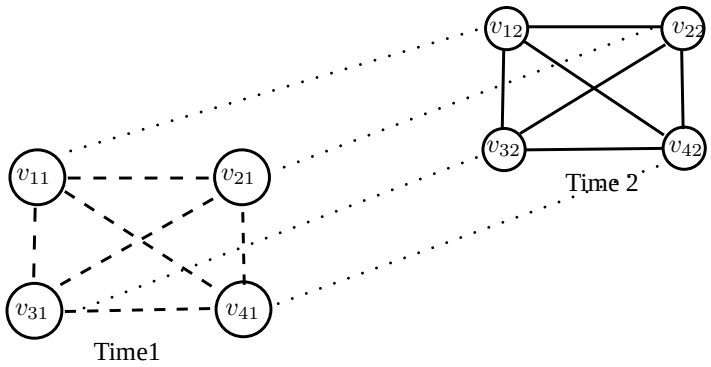
# Dynamic Genomic Graphs

- $\Gamma$ be a set of "genes".
- $T$ be a set of ordered "time points".

## Definition (Dynamic genomic graph)

A dynamic genomic graph is a pair $G = (V, E)$.

- Vertices: $V = \{v_{ij}\}_{i \in \Gamma, j \in T}$, where $\Gamma$ and $T$ are finite sets.
- Links: ordered pair of elements $E \subseteq V \times V$.

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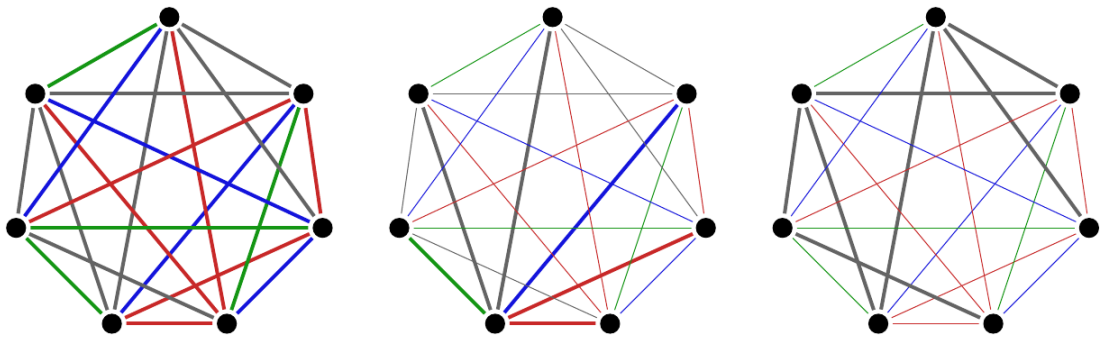
# Coloured graphs

## Definition (Coloured graph)

A coloured graph is a triplet $G_F = (V, E, F)$, where $G = (V, E)$ is a graph and $F$ is a mapping on the links, i.e.:

$$F : E \to C,$$

where $C$ is a finite set of colours.

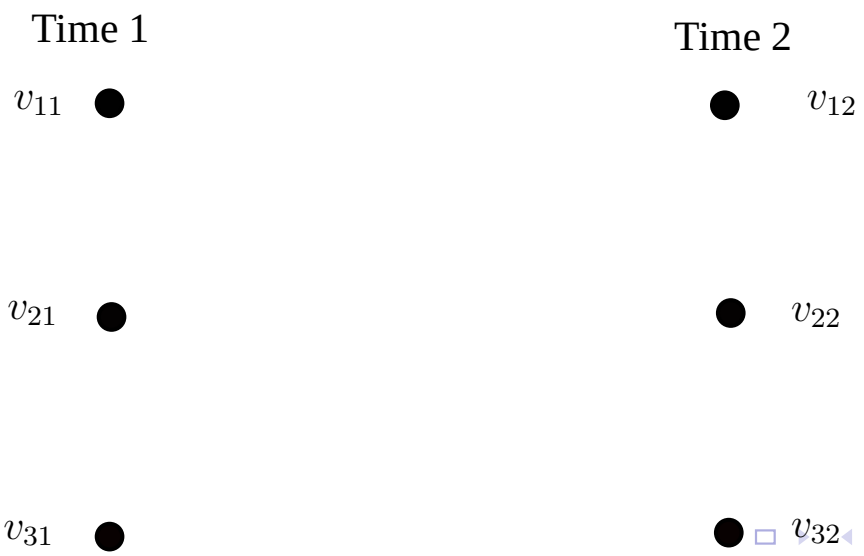


# Special kind of coloured graphs: Factorial Graphs

Denote mapping $F : E \to C$ by $E \prec F$.

In analogy with ANOVA, we define the following colouring:

- $\boxed{E \prec 0 \Rightarrow \text{an empty graph.}}$
- $E \prec F_1$.
- $E \prec F_T$.
- $E \prec F_\Gamma$.
- $E \prec F_{\Gamma T}$.



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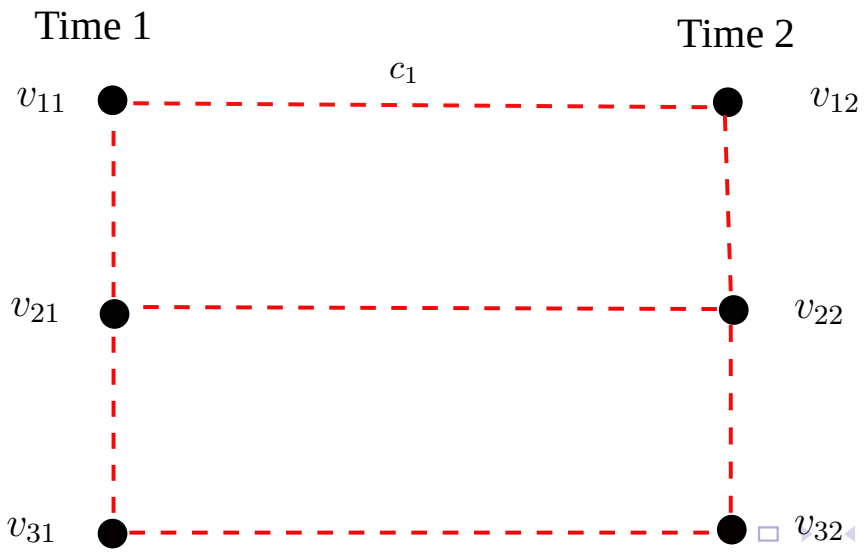


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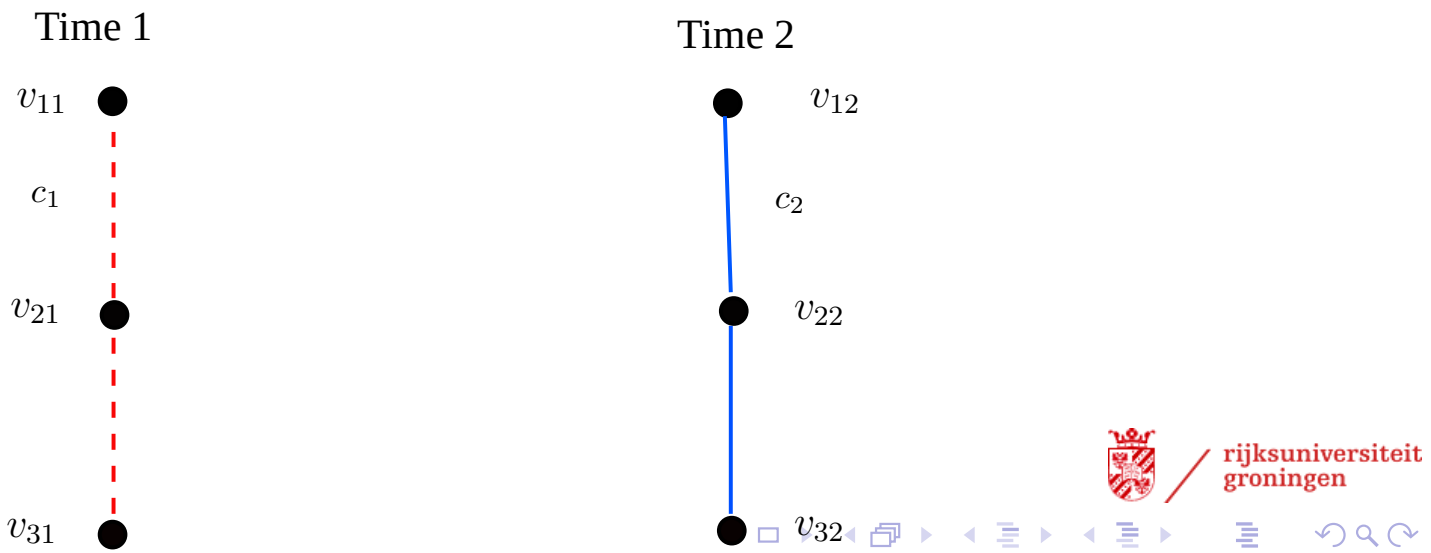


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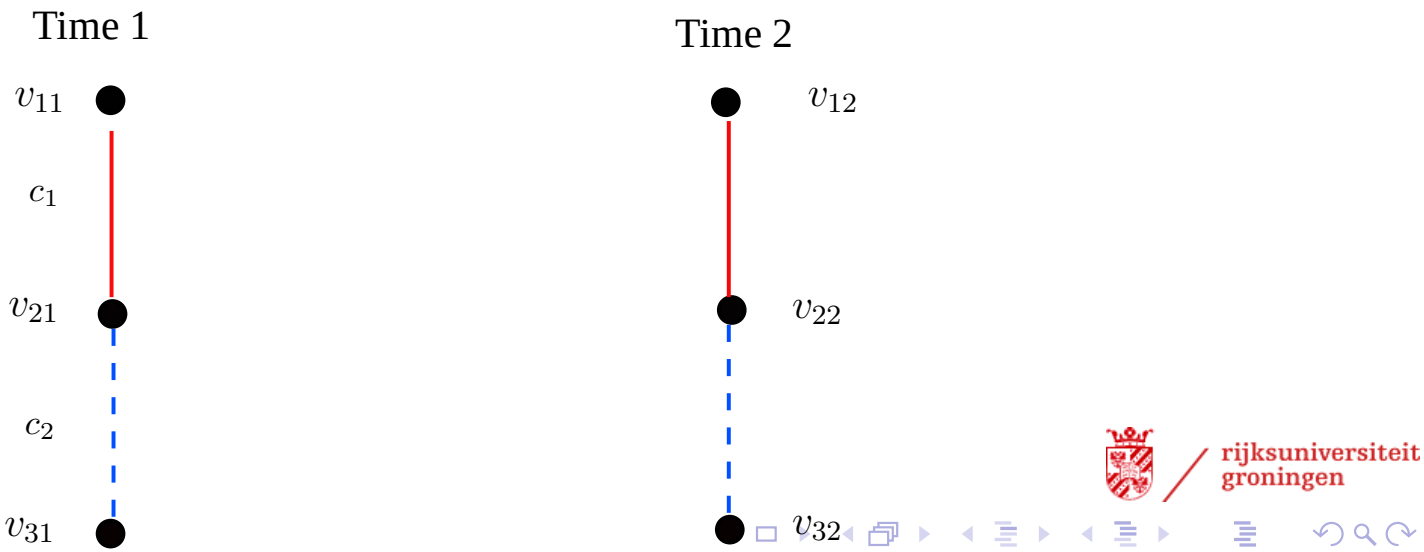

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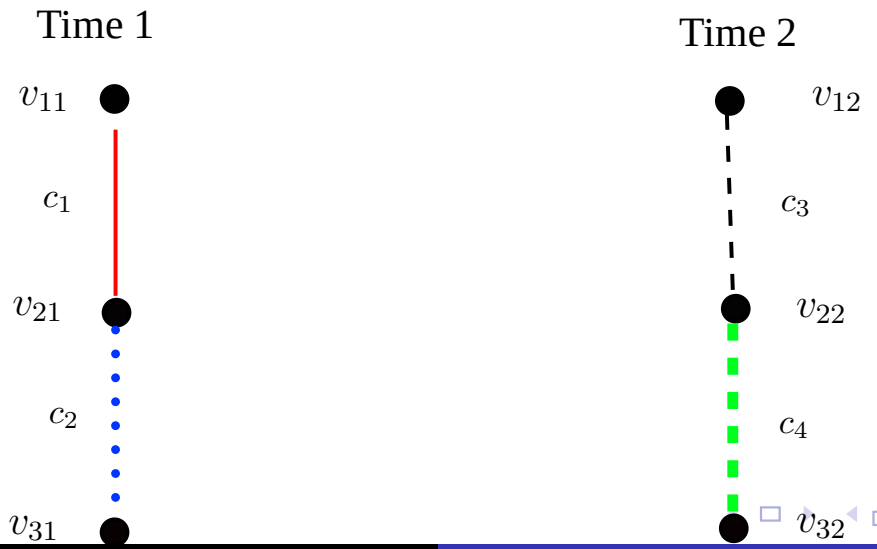
- $E \prec F_T$.
- $E \prec F_\Gamma$.
- $\boxed{E \prec F_{\Gamma T}\text{: all different colours}}$



# Natural Partitions

## Definition (Natural partition)

Let $E = \{S_i, N_i\}_{i=0}^{n_T-1}$ be subsets of links where $S_i, N_i$ are defined as follows:

$$S_i = \{\{(v_{jt}, v_{j,t+i}), (v_{j,t+i}, v_{jt})\} | j \in \Gamma, t = 1, \ldots, n_T - i\},$$

and

$$N_i = \{\{(v_{jt}, v_{k,t+i}), (v_{k,t+i}, v_{jt})\} | \forall j \neq k \in \Gamma, t = 1, \ldots, n_T - i\}.$$

The natural partitions imply subgraphs of $G$ and imply partions of $\mathbf{\Theta}$ for GGMs:

$$\mathbf{\Theta} = \left[\begin{array}{cc|cc|cc|cc} S_0 & N_0 & S_1 & N_1 & S_2 & N_2 & \ldots & \ldots \\ & S_0 & N_1 & S_1 & N_2 & S_2 & \ldots & \ldots \\ \hline & & S_0 & N_0 & S_1 & N_1 & S_2 & N_2 \\ & & & S_0 & N_1 & S_1 & N_2 & S_2 \\ \hline & & & & S_0 & N_0 & S_1 & N_1 \\ & & & & & S_0 & N_1 & S_1 \end{array}\right]$$

# Factorial Graphical Models

## Definition (Gaussian graphical models for factorially coloured graphs)

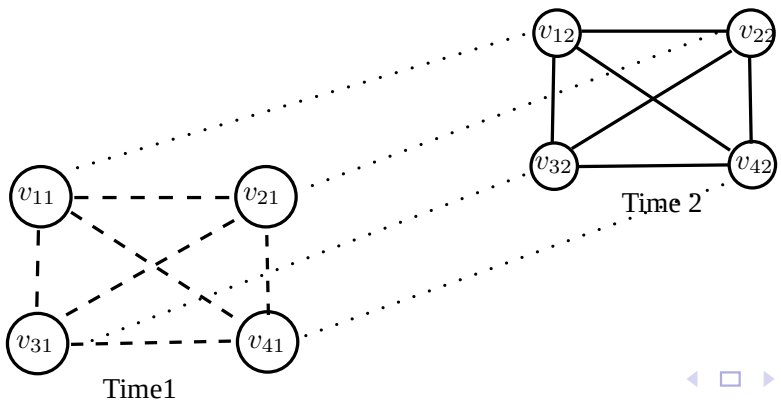
A factorial Gaussian graphical model is a graphical model defined on:

- a dynamic factorial graph $G = (V, E, F)$, where
- a factorial colouring $F$ is applied *separately* to natural partitions

$$S_i \prec F_{S_i}, \quad N_i \prec F_{N_i}, \quad i = 0, \ldots, n_T - 1$$

- which determines $\Theta$ in

$$\mathbf{Y} \sim N(\boldsymbol{\mu}, \boldsymbol{\Theta}^{-1}).$$

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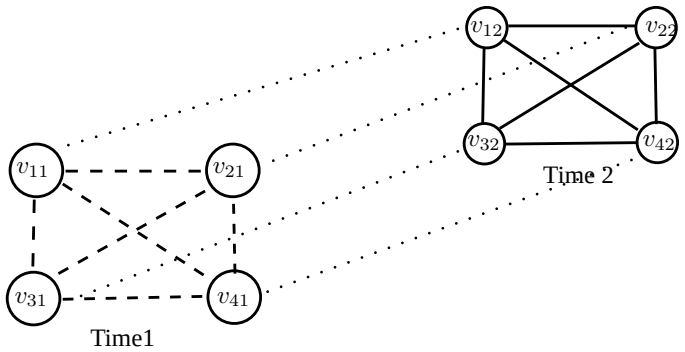
# Example: Factorial Gaussian Graphical Model

**Model:**

$$(S_0 \prec 1), \quad N_0 \prec F_T, \quad S_1 \prec 1, \quad N_1 \prec 0.$$

**Factorial coloured graph:**




**Precision Matrix:**

$$\boldsymbol{\Theta} = \left[\begin{array}{cccc|cccc} \theta_1 & \theta_2 & \theta_2 & \theta_2 & \theta_4 & 0 & 0 & 0 \\ & \theta_1 & \theta_2 & \theta_2 & 0 & \theta_4 & 0 & 0 \\ & & \theta_1 & \theta_2 & 0 & 0 & \theta_4 & 0 \\ & & & \theta_1 & 0 & 0 & 0 & \theta_4 \\ \hline & & & & \theta_1 & \theta_3 & \theta_3 & \theta_3 \\ & & & & & \theta_1 & \theta_3 & \theta_3 \\ & & & & & & \theta_1 & \theta_3 \\ & & & & & & & \theta_1 \end{array}\right]$$

# Penalized likelihood for GGMs

- Consider an experiment: $|\Gamma|$ genes measured across $|T|$ time points.
- Assume $n$ iid samples $\mathbf{y}^{(1)}, \ldots, \mathbf{y}^{(n)}$, where $\mathbf{y}^{(i)} = (y_1^{(i)}, \ldots, y_{\Gamma T}^{(i)})$.
- Assume $\mathbf{Y}^{(i)} \sim N(\mathbf{0}, \mathbf{\Theta}^{-1})$, then

**Likelihood:**

$$l(\mathbf{\Theta}|\mathbf{y}) \propto \log(|\Theta|) - \mathrm{tr}(\mathbf{S\Theta}).$$

**AIM:** Optimization of penalized likelihood:

$$\hat{\mathbf{\Theta}} := \mathrm{argmax}_{\mathbf{\Theta}}\{l(\mathbf{\Theta}|\mathbf{y})\}$$

subject to

- $\mathbf{\Theta} \succeq 0$;
- $||\mathbf{\Theta}||_1 \leq 1/\lambda$;
- some factorial colouring $F$.

# *Numquam ponenda est pluralitas sine necessitate*

William Occam (1288-1348) proposed a meta-theory of knowledge:

> *"For nothing ought to be posited without necessity."*

Can be interpreted *statistically* as a

- **Aesthetic principle:** enhances model interpretability through parsimonious representation
- **Pragmatic principle:** computability.
- **Ontological principle:** represents expectation about nature of solution.
- **Prediction principle:** bias-variance trade-off

# Inferring penalized factorial Gaussian graphical models

**LogdetPPA.** Newton-CG primal proximal point algorithm (*Wang et al., 2010*, including Kim Toh and Defeng Sun) is used to solve optimization:

$$\hat{\boldsymbol{\Theta}} := \underset{\boldsymbol{\Theta}}{\operatorname{argmin}} -\{\log|\boldsymbol{\Theta}| - \operatorname{tr}(\boldsymbol{\Theta}\mathbf{S}) + \boldsymbol{\lambda}'\boldsymbol{\theta}^{+} + \boldsymbol{\lambda}'\boldsymbol{\theta}^{-} : A(\boldsymbol{\Theta}) = \mathbf{0},$$

$$B(\boldsymbol{\Theta}) - \boldsymbol{\theta}^{+} + \boldsymbol{\theta}^{-} = \mathbf{0}, \boldsymbol{\Theta} \succeq 0, \boldsymbol{\theta}^{+}, \boldsymbol{\theta}^{-} \geq 0\}$$

- $A(\boldsymbol{\Theta})$: linear constraints which depend on coloured graph.
- $B(\boldsymbol{\Theta})$: $\ell_1$-norm penalty on elements of precision matrix.
- $\boldsymbol{\theta}^{+}$ and $\boldsymbol{\theta}^{-}$ are additional variables (slack variables).
- $\boldsymbol{\Theta} \succeq 0$: semi-positive definite constraint.

**Solves $\hat{\Theta}$ up to** $2000 \times 2000$ .

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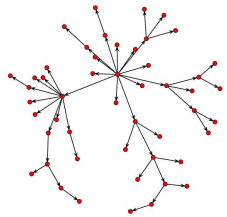
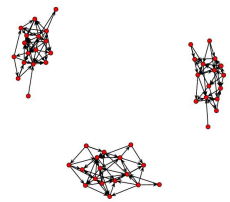
# Simulations: Lag 0 network identification

Table : $n = 50$ and $t = 10$ for various number of genes (p)

| | | $p = 50$ | $p = 100$ | $p = 50$ | $p = 100$ |
|---|---|---|---|---|---|
| SCAD | SEN | 0.987 | 0.957 | 0.992 | 0.971 |
| | SPE | 0.990 | 0.989 | 0.945 | 0.946 |
| | Distance | 6.289 | 7.484 | 9.576 | 30.192 |
| GLASSO | SEN | 0.930 | 0.946 | 0.975 | 0.923 |
| | SPE | 0.989 | 0.967 | 0.944 | 0.942 |
| | Distance | 6.821 | 13.67 | 9.641 | 30.517 |

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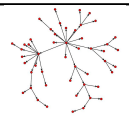
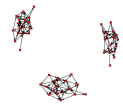
| | |  | |  | |
|---|---|---|---|---|---|
| | | $p = 50$ | $p = 100$ | $p = 50$ | $p = 100$ |
| SCAD | SEN | 0.998 | 0.948 | 0.989 | 0.993 |
| | SPE | 0.985 | 0.899 | 0.977 | 0.959 |
| | Distance | 0.602 | 1.665 | 0.452 | 3.254 |
| EBDBN | SEN | 0.343 | 0.195 | 0.394 | 0.226 |
| | SPE | 0.615 | 0.793 | 0.599 | 0.787 |
| | Distance | 37.910 | 52.048 | 59.730 | 80.722 |
| GeneNet | SEN | 0.000 | 0.000 | 0.000 | 0.000 |
| | SPE | 0.969 | 0.971 | 0.997 | 0.999 |
| | Distance | 10.607 | 15.092 | 19.414 | 31.197 |

# T-cell data

**Aim.** Use large time-course experiment to characterize response of human T-cell line (Jurkat) to PMA and ionomycin treatment.

**T-cell time-series dataset**

- Temporal expression of 58 genes for 10 unequally spaced time points.
- At each time point there are 44 separate measurements.
- See Rangel et al. (2004) for more details.

# Application to T-cell data

$$S_0 \prec F_1, \mathbf{N_0} \prec \mathbf{F_\Gamma}, S_1 \prec F_T, \mathbf{N_1} \prec \mathbf{F_\Gamma}$$

$$\mathbf{\Theta} = \left[\begin{array}{cc|cc|cc|cc} S_0^1 & N_0^1 & S_1^1 & N_1^1 & 0 & 0 & \dots & \dots \\ & S_0^1 & N_1^1 & S_1^1 & 0 & 0 & \dots & \dots \\ \hline & & S_0^2 & N_0^2 & S_1^2 & N_1^2 & 0 & 0 \\ & & & S_0^2 & N_1^2 & S_1^2 & 0 & 0 \\ \hline & & & & S_0^3 & N_0^3 & S_1^3 & N_1^3 \\ & & & & & S_0^3 & N_1^3 & S_1^3 \end{array}\right]$$

$N_0^1 = N_0^2 = \ldots = N_0^{10}$

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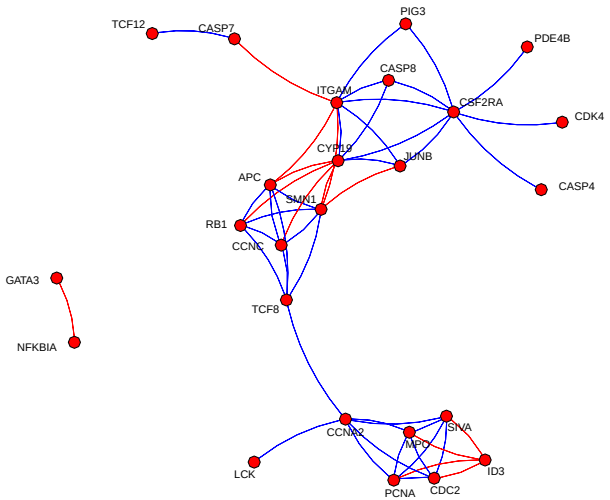


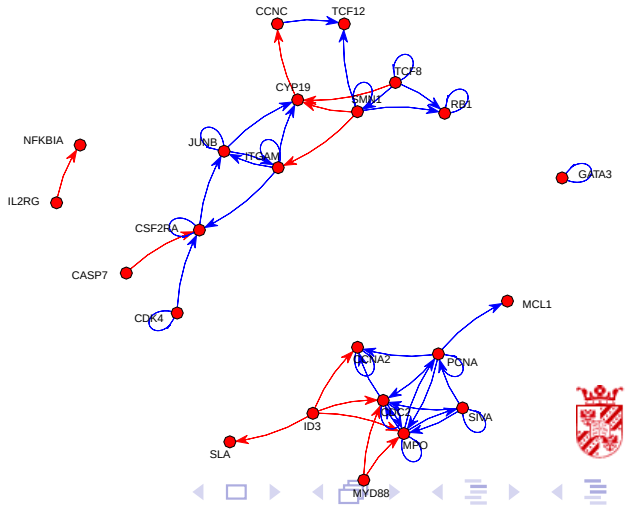


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# What have we achieved so far? And problems!

**Summary:**

- Penalized Gaussian graphical models
- Coloured graphs
- Natural partitions
- Factorially coloured Gaussian graphical models

**Problems:**

1. Factorial colouring not particularly flexible in modeling time dynamics.
2. Gaussian assumption may be too restrictive for realistic genomic data.

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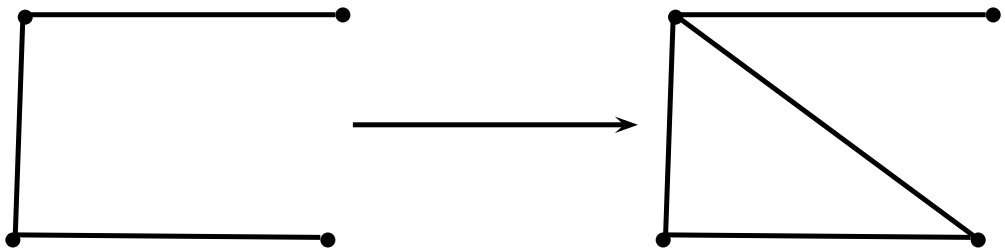
# 1. Extension: Slowly changing graphical models

- Problem: Estimate changes in the dynamic of the network.

**Main Idea:** Penalize changes between graphs at different time points

$$||\Delta\Theta||_1 = \sum_{s=0}^{t-1}\sum_{k=0}^{t-1} ||N_s^k - N_s^{k+1}||_1.$$




- Solution: Penalized maximum likelihood subject to constraints.

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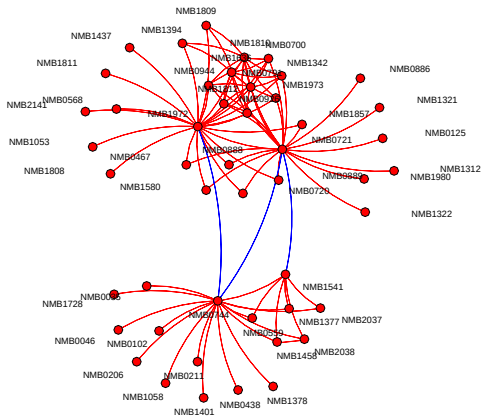
# Application to a time-course dataset

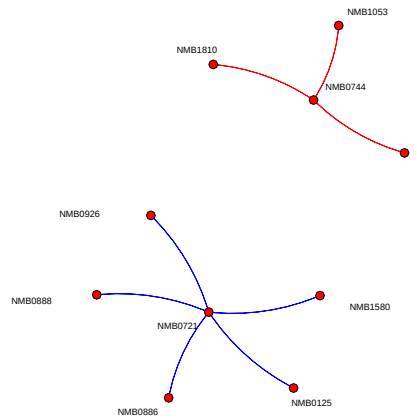
$$\mathbf{S_0} \prec F_{\Gamma T}, \mathbf{N_0} \prec 1, \mathbf{N_1} \prec 1, \mathbf{N_2} \prec 0$$

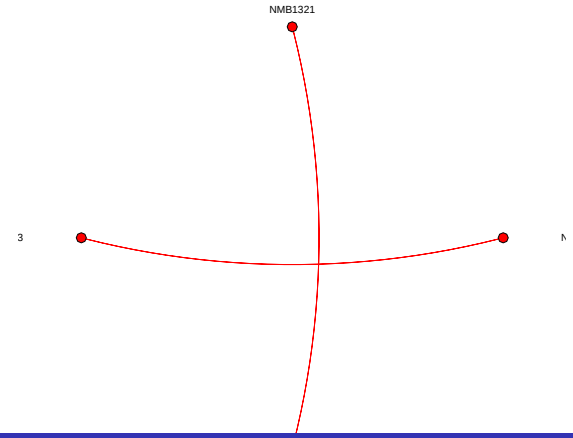
$$\Theta = \left[\begin{array}{cc|cc|cc|cc} S_0^1 & N_0^1 & S_1^1 & N_1^1 & 0 & 0 & \cdots & \cdots \\ & S_0^1 & N_1^1 & S_1^1 & 0 & 0 & \cdots & \cdots \\ \hline & & S_0^2 & N_0^2 & S_1^2 & N_1^2 & 0 & 0 \\ & & & S_0^2 & N_1^2 & S_1^2 & 0 & 0 \\ \hline & & & & S_0^3 & N_0^3 & S_1^3 & N_1^3 \\ & & & & & S_0^3 & N_1^3 & S_1^3 \end{array}\right]$$

$N_0^1$ | $|N_0^1| - |N_0^2|$ | $|N_0^2| - |N_0^3|$

N0 at time 1 | 1 | 7

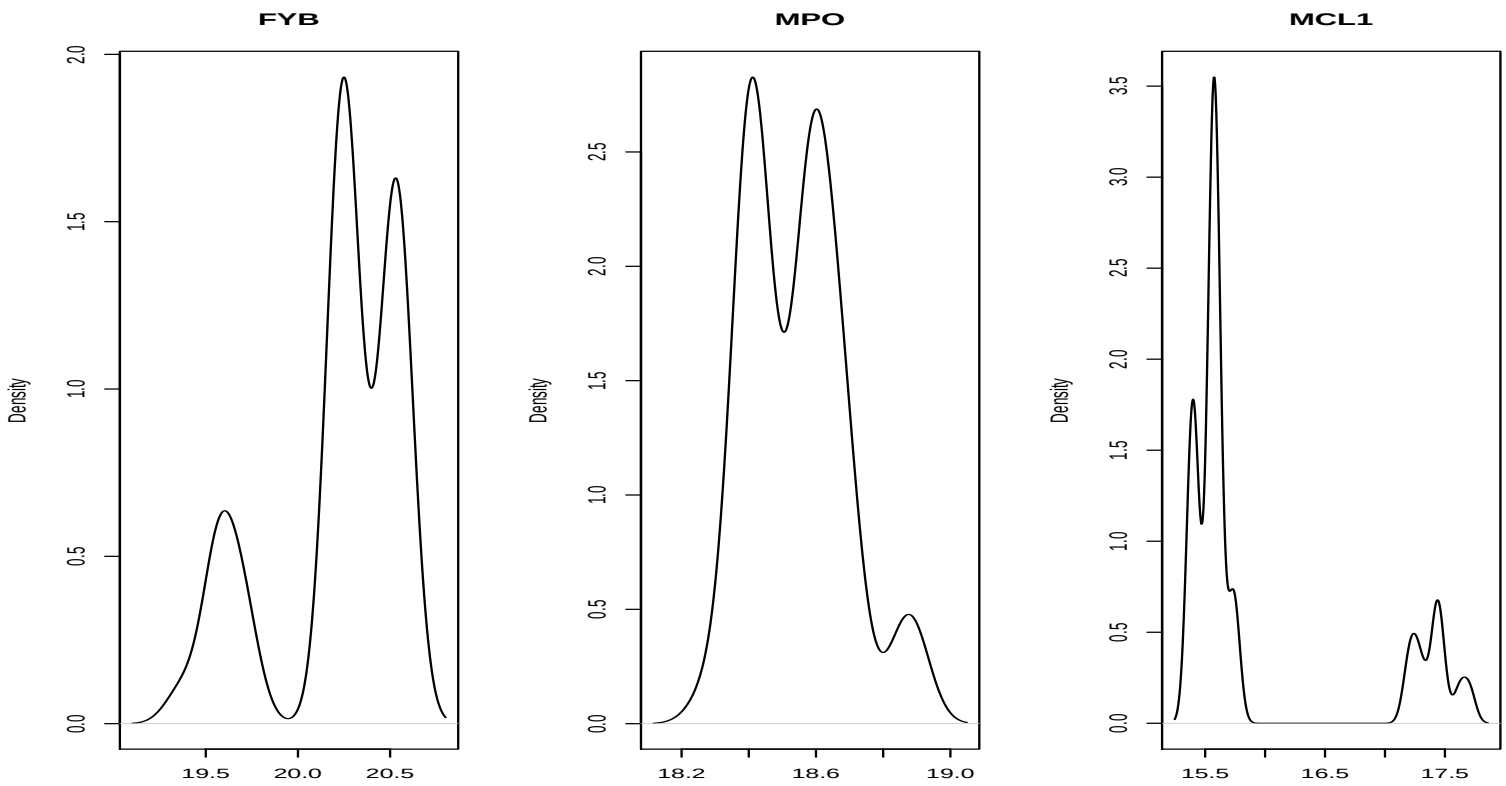


# 2. Extension: Non-Normality

- Problem: Non-Normality of the data (e.g. T-cell).




- Solution: Copula Gaussian graphical models

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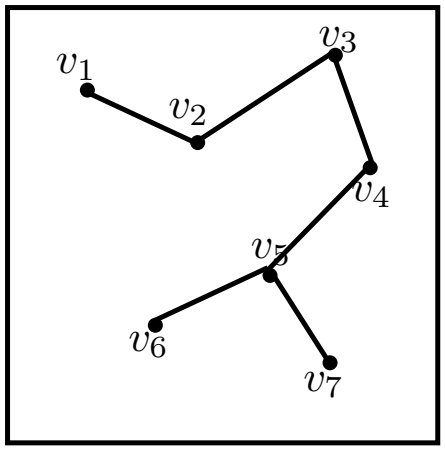
# Copula Gaussian graphical models

**IDEA:**

- Graph exists on a hidden Gaussian variable $\mathbf{Z} \sim N(0, \Theta)$,
- $\mathbf{Z}$ gives rise to observed non-Gaussian data $\mathbf{Y}$.




Latent Variable: $\mathbf{Z} \sim N(\mu, \mathbf{\Theta}^{-1})$

$$F_1$$
$$F_2$$
$$\vdots$$
$$F_7$$

Marginal Distribution: $\mathbf{F}$

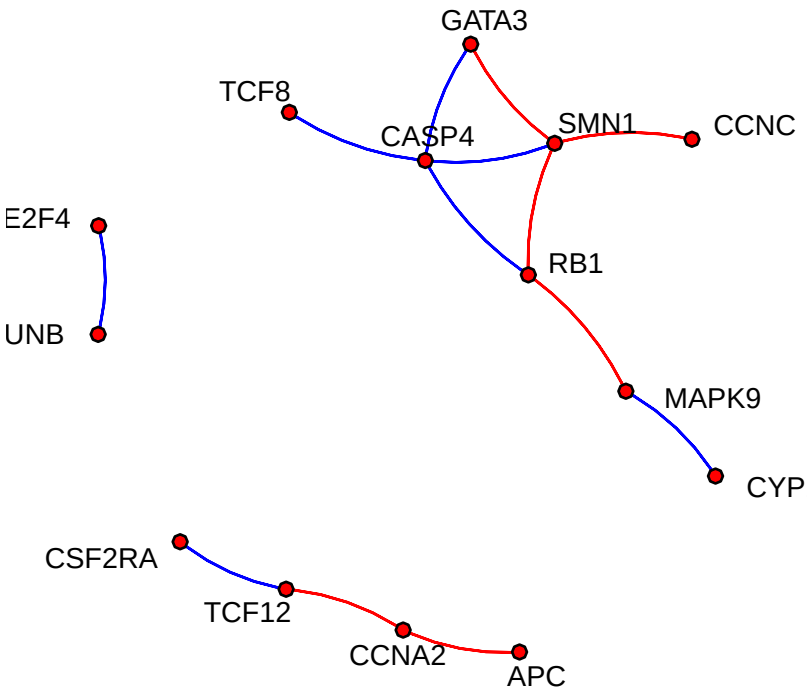
$$Y_1 = F_1^{-1}(\phi(Z_1))$$
$$Y_2 = F_2^{-1}(\phi(Z_2))$$
$$\vdots$$
$$Y_7 = F_p^{-1}(\phi(Z_7))$$

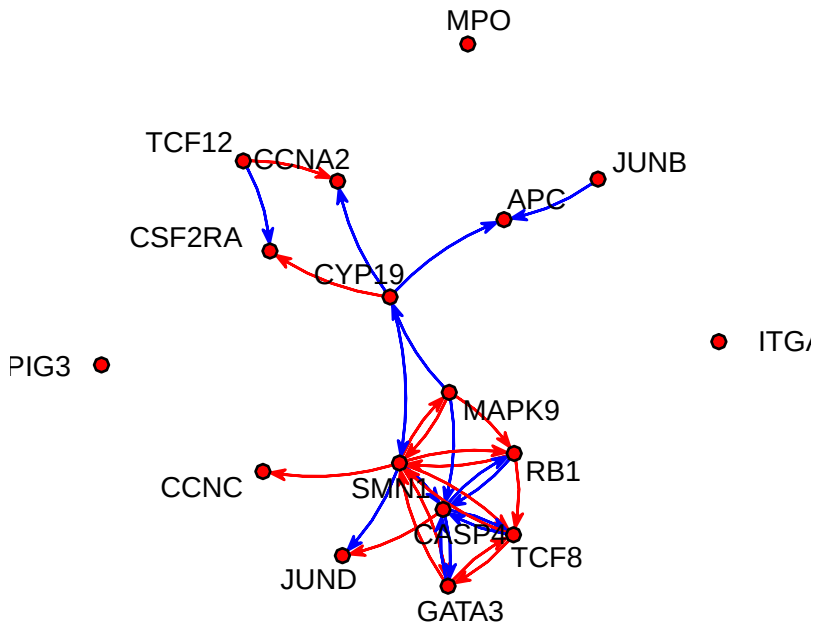
Observed: $\mathbf{Y}$

- We consider the $F_i$ as nuisance parameters.
- For continuous variables: 1-to-1 relationship between $Z$ and $Y$.
  For discrete variables, relationship is more complicated!

# Application of Gaussian copula graphical models to T-cell

$$S_0 \prec F_1, \mathbf{N_0} \prec \mathbf{F_\Gamma}, S_1 \prec F_T, \mathbf{N_1} \prec \mathbf{F_\Gamma}$$




$N_0^1 = N_0^2 = \ldots = N_0^{10}$

$N_1^1 = N_1^2 = \ldots = N_1^{10}$

# Dynamical mammary gland application

Mammary gland gene expression data:

- Microarray experiment
- using mammary tissue from female mice
- across 4 different developmental stages
- for 8,600 genes.
- 3 replicates on each of 18 time points.

30 genes have been identified as activators for developmental stages (Wit and McClure, 2004).

**Objective:**

Study interactions between these crucial mice genes.

# Inference

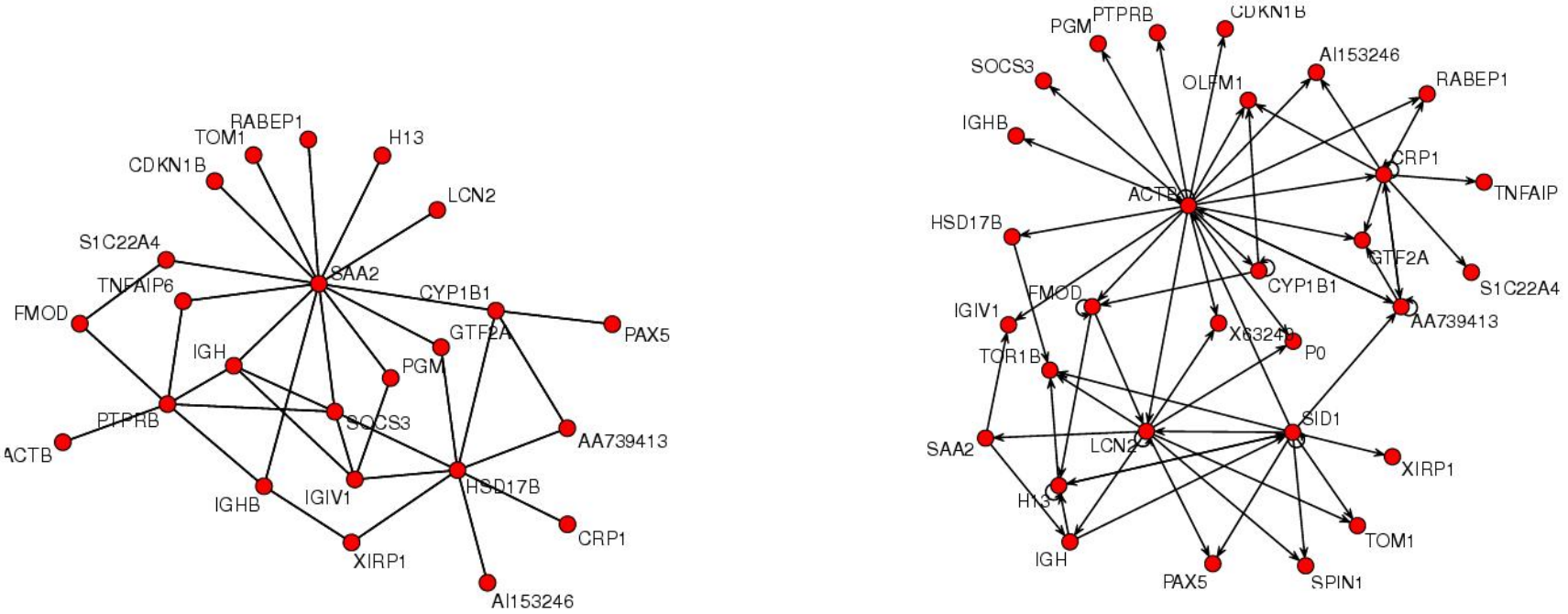



Figure : Undirected $N_0$ (left) and directed $N_1$ (right) time series chain graphical model networks inferred from mammary gland time course gene expression data.

Abegaz and Wit. "Sparse time series chain graphical models for reconstructing genetic networks". Biostatistics. 2013

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# Conclusions

- Graphical models are a convenient formulation of many genomic networks.
- Static boolean networks:
  - Sparse GLM inference via dglars.
  - Software: R package `dglars`.
- Dynamic continuous networks:
  - Chain graphical models infer sparse time dynamics.
  - Software: R package `SparseTSCGM`.