Statistical network inference

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Outline

Statistics for networks

Network inference

Gaussian graphical models

Tree-based Bayesian inference

Extensions

Concluding remarks & questions

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Network: convenient way to describe

connexions / relations / interactions → links $i \sim j$

between

individuals / genes / species / entities → nodes i

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$$G = (V, E)$$

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Alternatively: Adjacency matrix

$$A = [A_{ij}] : \qquad A_{ij} = \begin{cases} 1 & \text{if } i \sim j, \\ 0 & \text{otherwise.} \end{cases}$$

Different questions

Understanding the network topology:

- Data = observed network
- Questions: central nodes? cluster structure? small-world property? ...

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Each to be combined with covariates, time, missing data, ...

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A brief review

Data. p species ($i = 1..p$), n replicates ($r = 1..n$)

$$\begin{aligned} Y_{ir} &= \text{abundance of species } i \text{ in replicate } r \\ Y_r = (Y_{ir})_{i=1..p} &= \text{vector of abundances in replicate } r \end{aligned}$$

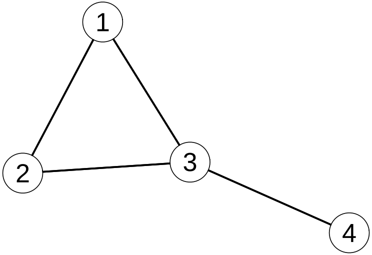
Goal. Infer the species interaction network from the set of Y_r? [15]

Remarks.

- Need to specify the type of interaction
- Need to distinguish between direct and indirect interactions

General framework: Graphical models [6]

Example: (undirected graph)



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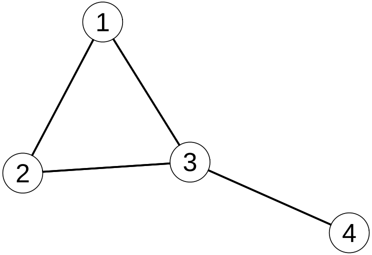

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All variables are dependent (connected graph).

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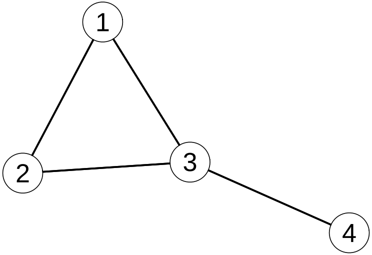

Properties:

All variables are dependent (connected graph).

Some are conditionally independent, e.g.

$$Y_4 \perp (Y_1, Y_2) | Y_3$$

Graphical models

More precisely. $P =$ joint distribution faithful to G iff

$$P(Y_1, \dots, Y_p) \propto \prod_{C \in \mathcal{C}_G} \psi_C(Y_C)$$

where $\mathcal{C}_G =$ set of cliques of G. [4]

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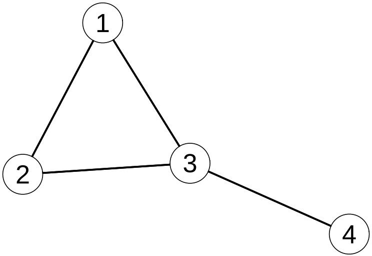

$$P(Y_1, Y_2, Y_3, Y_4) \propto$$

$$\psi_1(Y_1, Y_2, Y_3) \times \psi_2(Y_3, Y_4)$$

Network inference

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Generic statistical model.

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Critical issue. There are $2^{p(p-1)/2}$ possible graphs

p	5	10	20	50
# graphs	10^3	10^{14}	10^{57}	10^{369}

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Gaussian distribution.

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μ = vector of means, Σ = covariance matrix.

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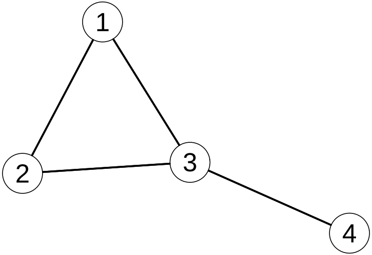
A nice property.



Adjacency matrix

$$A = \left[\begin{array}{cccc} 0 & 1 & 1 & 0 \\ 1 & 0 & 1 & 0 \\ 1 & 1 & 0 & 1 \\ 0 & 0 & 1 & 0 \end{array}\right]$$

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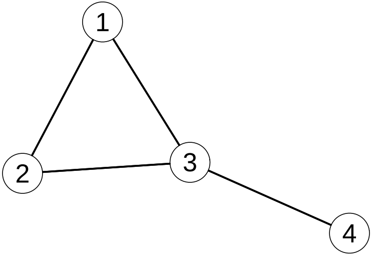

Covariance matrix

$$\Sigma \propto \begin{bmatrix} 1 & -.25 & -.41 & .25 \\ -.25 & 1 & -.41 & .25 \\ -.41 & -.41 & 1 & -.61 \\ .25 & .25 & -.61 & 1 \end{bmatrix}$$

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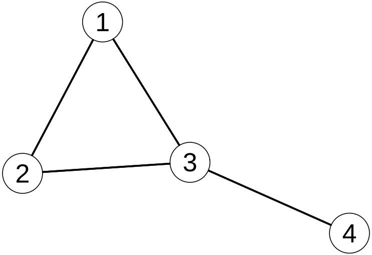

Inverse covariance matrix

$$\Sigma^{-1} \propto \begin{bmatrix} 1 & .5 & .5 & 0 \\ .5 & 1 & .5 & 0 \\ .5 & .5 & 1 & .5 \\ 0 & 0 & .5 & 1 \end{bmatrix}$$

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Gaussian distribution.

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$\mu =$ vector of means, $\Sigma =$ covariance matrix.

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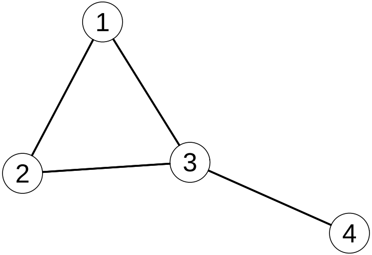

Estimated inverse covariance matrix

$$\widehat{\Sigma}^{-1} \propto \begin{bmatrix} 1 & .48 & .61 & .09 \\ .48 & 1 & .67 & .06 \\ .61 & .67 & 1 & .46 \\ .09 & .06 & .46 & 1 \end{bmatrix}$$

$(n = 100)$

Sparsity

Sparsity assumption:

$$\Omega = \Sigma^{-1} \text{ is sparse}$$

$=$ most entries of Ω are zeros.

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A series of approaches for Gaussian data

- Sparse regression of each species on the others:

$$Y_i = a_j + \sum_{j \neq i} b_{ij} Y_j + E_i \quad \text{forcing most } b_{ij} = 0 \text{ [8]}$$

- Directly estimate Ω forcing most $\omega_{ij} = 0$ [3]

using, e.g, Lasso penalty [14,2] or more refined [1].

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Same problem. Infer G based on an iid sample $(Y_r) \sim P$ faithful to G.

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Tree assumption: The network G is a spanning tree, i.e.

$$\left.\begin{array}{l} G \text{ is connected} \\ G \text{ has no cycle} \end{array}\right\} \rightarrow G \text{ has } p-1 \text{ edges (sparse)}$$

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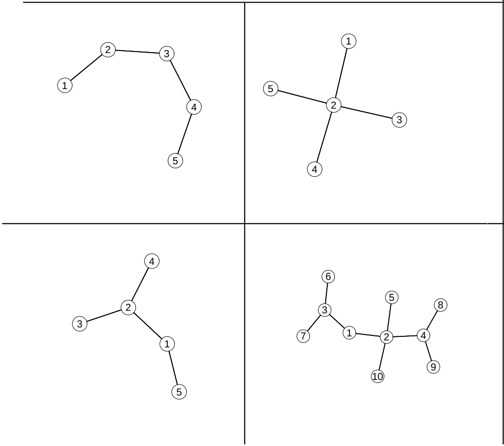
Bayesian inference: aim at providing

- the global posterior distribution of G given the data Y: $P(G|Y)$
- or edge probabilities:

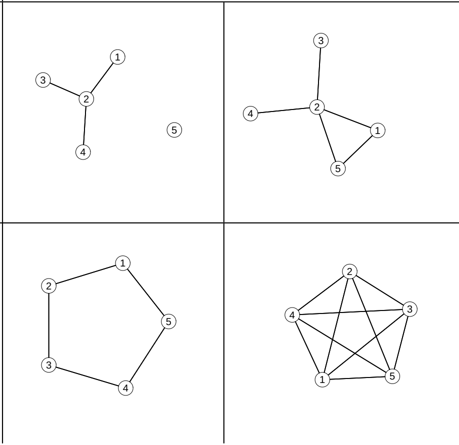
$$P(i \sim j|Y)$$

Tree-shaped network

Spanning trees



Non spanning trees



Exact Bayesian inference

Bayesian inference requires to sum over all possible graphs
$\rightarrow$ sum over all possible spanning trees ($\#\mathcal{T} = p^{p-2}$).

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An algebraic tool. w_{ij} = weight of (i, j)

- Score of a tree = product of the weights of its branches

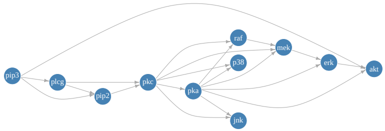
$$s(T) = \prod_{(i,j) \in T} w_{ij}$$

- Matrix-tree theorem:

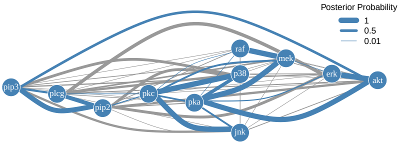
$$\sum_{T \in \mathcal{T}} s(T) \text{ is computable in } O(p^3)$$

Illustration: Raf pathway [13]

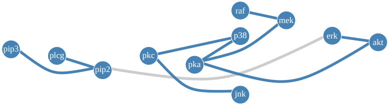
Flow cytometry data for $p = 11$ proteins from the Raf signaling pathway [11]



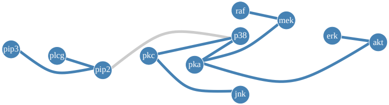
'ground truth'



posterior probabilities



most likely tree



second most likely tree

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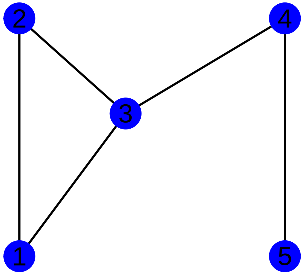
Removing nodes

Complete network (all nodes).

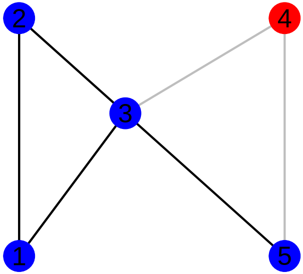
Graphical model



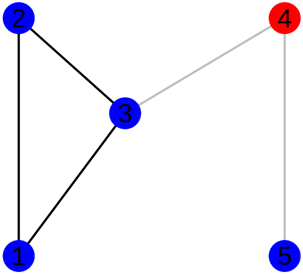
Removing nodes

Removing one node.

Marginal graph (missing node)



Conditional graph (observed node)



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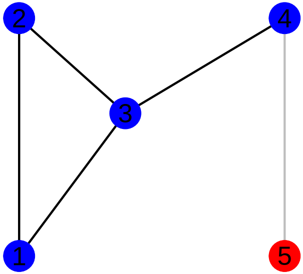

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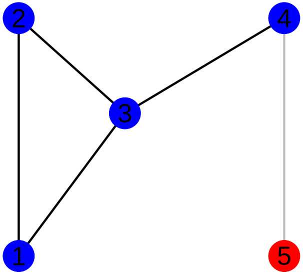

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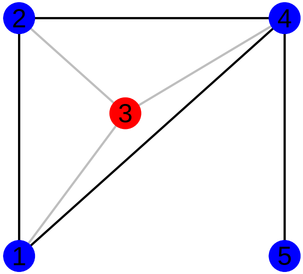

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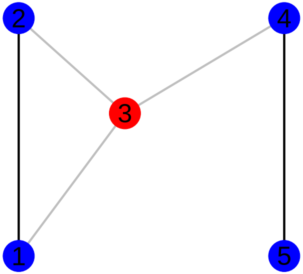

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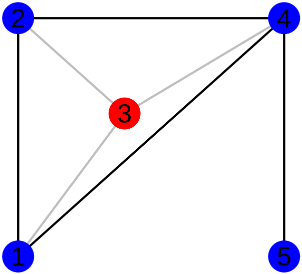

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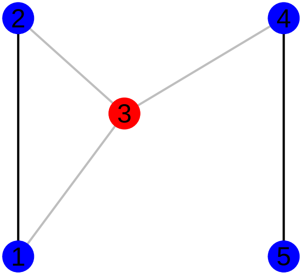

More complex patterns for directed graphical models.

Accounting for covariates (1/3)

Deciphering the pathobiome: Intra-and interkingdom interactions involving the pathogen *E. alphitoides*. [5]

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Data.

- 3 trees × few tens of leaves per tree
- Abundance of few tens of (fungal and bacterial) species on each leaves via NGS
- Few covariates describing both trees and leaves

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Questions.

- Infer the ecological network
- Account for covariates (to avoid spurious edges)
- Deal with NGS counts as (Y_{ir}) measurements

Accounting for covariates (2/3)

Proposed strategy.

1. Perform regression on the covariates x for each species i:

$$Y_{ir} \sim \mathcal{P}(\mu_{ir}), \qquad \log \mu_{ir} = x_r \beta_i \qquad \rightarrow \qquad \widehat{\mu}_{ir} = e^{x_r \widehat{\beta}_i}$$

2. Compute the Pearson residuals $\widetilde{Y}_{ir} = (Y_{ir} - \widehat{\mu}_{ir}) / \sqrt{\widehat{\mu}_{ir}}$
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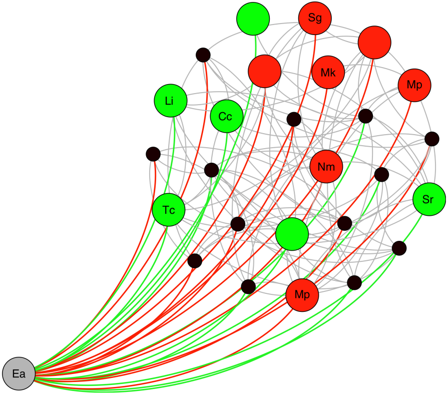
Still unsolved problem.

- How to account for the uncertainty of the $\widehat{\beta}_i$ in the inference of G?

Accounting for covariates (3/3)



●: *E. alphitoides*

🔴: positively correlated fungal OTUs

🟢: negatively correlated fungal OTUs

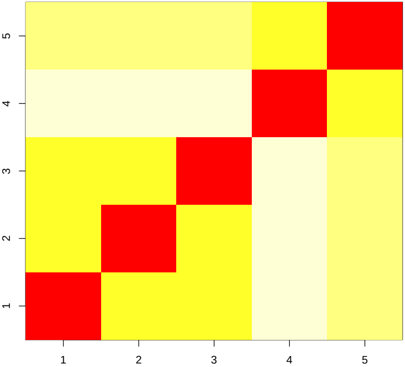
●: bacterial OTUs

Missing nodes (1/3)

Fact. Block-structured empirical correlation matrix.

→ Each block could be associated with an unobserved node.

→ Can we infer such missing nodes?



Missing nodes (2/3)

Problem statement. There exist a complete vector

$$(\underbrace{Y_1, \dots Y_p}_{O=\text{observed}}, \underbrace{Z_1, \dots Z_r}_{H=\text{hidden}})$$

the distribution P of which is faithful to a graph G.

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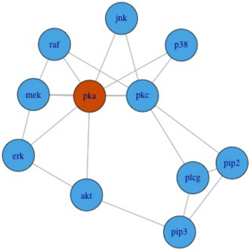
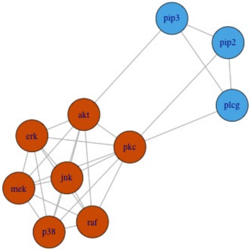
EM algorithm. [10]

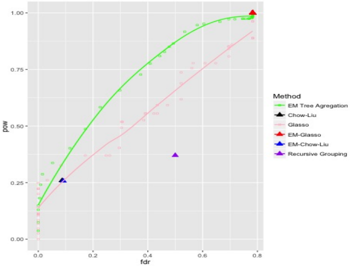
- E-step: infer H from O with current parameters $(\mu, \Sigma, G, ...)$
- M-step: update the parameters using O and $\widehat{H}$ (using [13] for G).

Missing nodes (3/3)





Accuracy for edge detection based on edge probability:



Change-point detection (1/2)

Data: $Y_t = (Y_{1t}, \dots Y_{pt})$ collected along time t.

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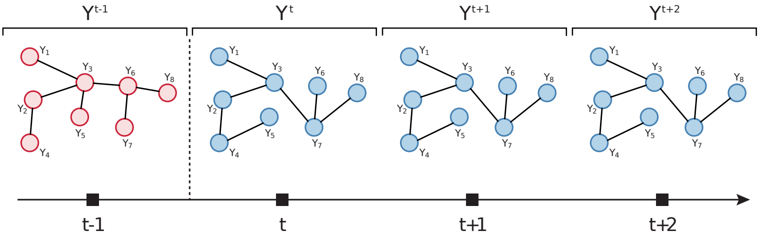
Problem: Suppose that Y_t is associated with graph G_t, that is affected by abrupt changes:



→ Infer both the change-points and the network associated with each period [9,12]

Change-point detection (2/2)

Data: $N = 67$ time points, $p = 11$ genes, four expected regions

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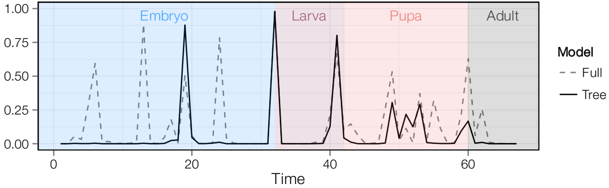
Posterior probability of change-points:



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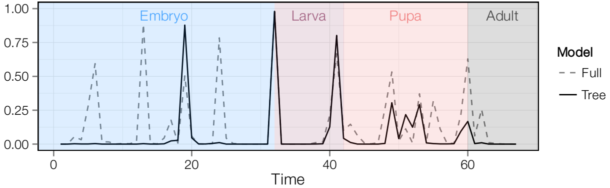
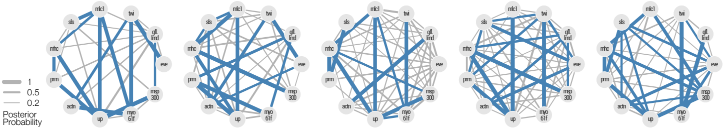


Inferred networks:



1 - 18 | 19 - 31 | 32 - 40 | 41 - 52 | 53 - 67

Concluding remarks & questions

A generic framework for network inference, with not completely solved problems:

- Deal with NGS counts (non Gaussian)
- Accounting for covariates
- Incompletely observed species and/or variables

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Questions & remarks.

- Network = set of binary interactions
- What is an ecological network?

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