

# Mixture tree model for network inference

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Final internship, multi-OMICS data analysis (Jouy)  
avril 2017 - octobre 2017

Mathematical statistics Research MSc (Rennes)  
2016-2017

Preparation of biostatistician engineer diploma (Rennes)  
2014-2017

Prep school MPSI/MP, St Louis highschool (Paris)  
2012-2014

# Training courses

## Cross training 53h

- Basis for teaching
- Journées Carrières en Mathématiques
- Career plan definition (FEM and course)

## Pedagogical M2 "Mathématiques pour les Sciences du vivant", Orsay

- Statistiques en grande dimension - C.Giraud
- Models with Hidden Structure - S. RObin

# Doctoral mission

50% teaching - 50% scientific mediation:

**Teaching** Statistical data interpretation with R (26h, L3 MINT Orsay)

**Mediation** MISS - Maison d'Initiation et de Sensibilisation aux Sciences (12 days per year, 8-15 years-old)

- Mathématiques et botanique
- Histoire des nombres

# Talks

This work was presented in :

## Research schools:

- Scientific seminar, Rochebrune, 25-30 March
- Chaire MMB (Modélisation Mathématique et Biodiversité), Aussois, 12-16 May

**Conference:** JOBIM (Journées Ouvertes de Biologie Informatique & Mathématiques), 3-6 July

# The subject: preliminaries and general approach

# Context

Rising interest in **jointly analysed** species abundances:

- Metagenomics
- Microbiology
- Ecology

## Ecological network

Tool to better understand species interactions (direct/indirect), eco-systems organizations (clusters ?)

Allows for resilience analyses, pathogens control, ecosystem comparison, response prediction...

## Data example

- **Species:** bacteria, fungi...
- **Abundances:** read counts from Next-Generation Sequencing technologies (metabarcoding)
- **Covariates:** sequencing depth, temperature, water depth...

Repeated signal :  $n$  samples,  $p$  abundances.

### Data table

$$Y = [Y_{ij}]_{(i,j) \in \{1, \dots, n\} \times \{1, \dots, p\}}$$

- $Y_{ij}$ : abundance of the  $j^{th}$  species in the  $i^{th}$  sample

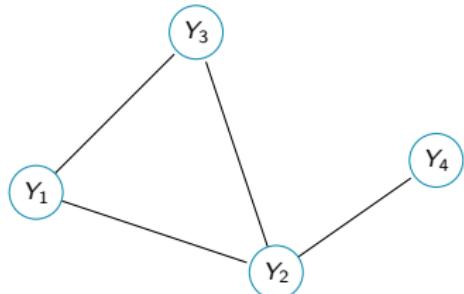
Infer the **species interaction network** from count data  $Y$

# Challenges

- Statistical network inference
- Count data
- Offsets and covariates

# Graphical models: a statistical framework for network inference

Example:



- All variables are dependant
- Some are **conditionally independent** (i.e. indirectly dependant)

$Y_4$  is independent from  $(Y_1, Y_3)$  conditionally on  $Y_2$

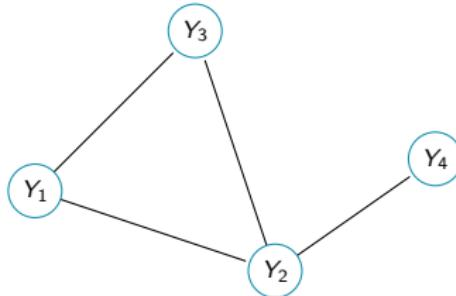
# Graphical models

Definition [Lauritzen, 1996]

The joint distribution  $P$  is faithful to the graph  $G$  iff

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

where  $\mathcal{C}_G = \text{set of maximal cliques of } G$ .



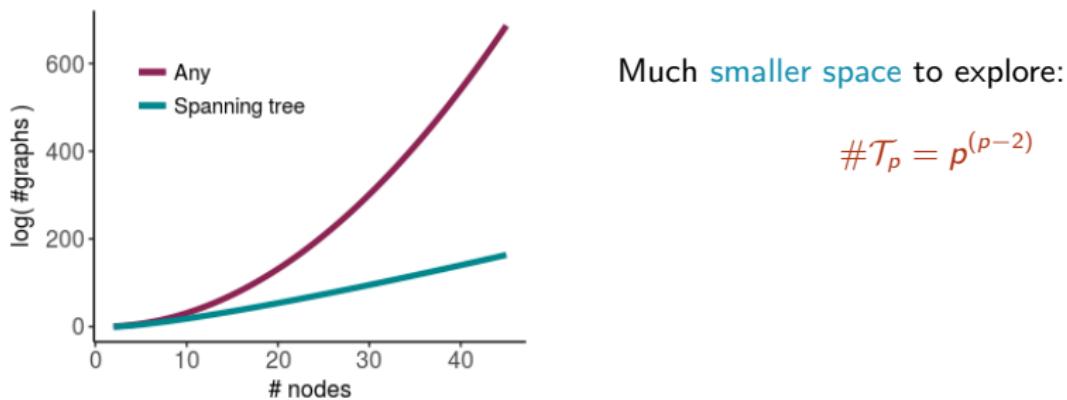
$$P(Y_1, Y_2, Y_3, Y_4) \propto \\ \psi_1(Y_1, Y_2, Y_3) \times \psi_2(Y_3, Y_4)$$

# Spanning trees

Unconstrained graph  $\Rightarrow$  very large space to explore:  $\#\mathcal{G}_p = 2^{\frac{p(p-1)}{2}}$

Spanning trees are a **sparse** solution :

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

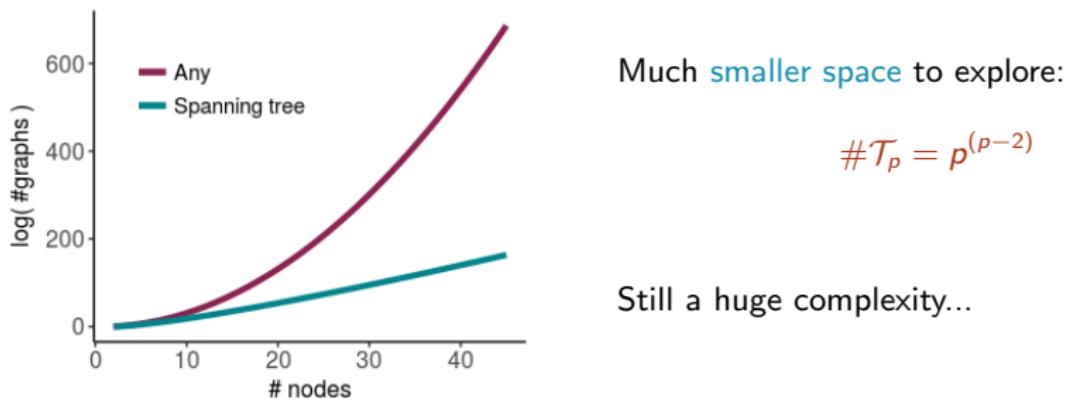


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# Maximizing and summing over spanning trees

Maximum spanning tree Kruskal's algorithm

$$\hat{T} = \underset{\mathcal{T}}{\operatorname{argmax}} \left\{ \prod_{(k,l) \in \mathcal{T}} \psi_{k,l}(Y) \right\} \rightarrow \Theta(p^2 \log(p))$$

Tree averaging Matrix tree theorem [Chaiken and Kleitman, 1978]

$$\sum_{\mathcal{T}} \prod_{(k,l) \in \mathcal{T}} \psi_{k,l}(Y) = \det(L(Y)) \rightarrow \Theta(p^3)$$

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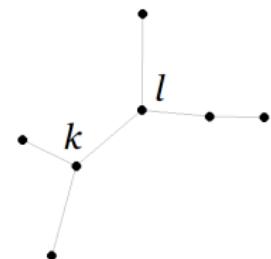
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**Approach:** infer the network by averaging spanning trees

# Tree structured data

- Data dependency structure relies on a tree



- Likelihood factorizes on nodes and edges  
[Chow and Liu, 1968]:

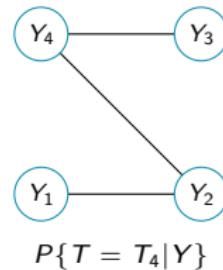
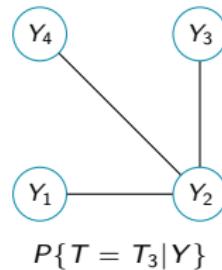
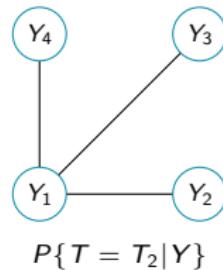
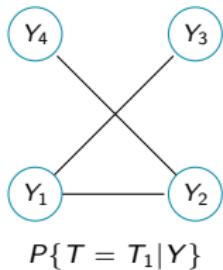
$$\mathbb{P}(Y|T) = \prod_{j=1}^d \mathbb{P}(Y_j) \prod_{k,l \in T} \psi_{kl}(Y) ,$$

Where

$$\psi_{kl}(Y) = \frac{\mathbb{P}(Y_k, Y_l)}{\mathbb{P}(Y_k) \times \mathbb{P}(Y_l)}.$$

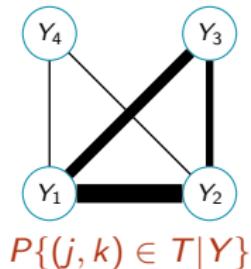
**Rmq** : with standardised gaussian data,  $\hat{\Psi} = [\hat{\psi}_{kl}] \propto (1 - \hat{\rho}^2)^{-1/2}$

# Tree averaging

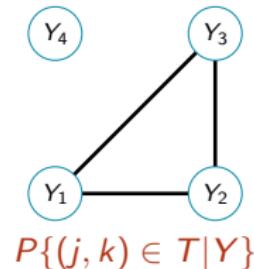


...

Compute edge probabilities:



Thresholding probabilities:



# PLN model

Poisson log-Normal distribution [Aitchison and Ho, 1989]

$$\left. \begin{array}{ll} Z_i \text{ iid} & \sim \mathcal{N}_d(0, \Sigma) \\ (Y_{ij})_j \perp\!\!\!\perp |Z_i & \\ Y_{ij}|Z_j & \sim \mathcal{P}(e^{Z_{ij}}) \end{array} \right\} Y \sim \mathcal{PLN}(0, \Sigma)$$

- Dependency structure in the Gaussian latent layer
- Easy handling of multi-variate data (contrary to Negative binomial distribution)

# PLN model

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- Dependency structure in the Gaussian latent layer
- Easy handling of multi-variate data (contrary to Negative binomial distribution)
- Allow adjustment for covariates and offsets
- Variational estimation algorithm [Chiquet et al., 2017]

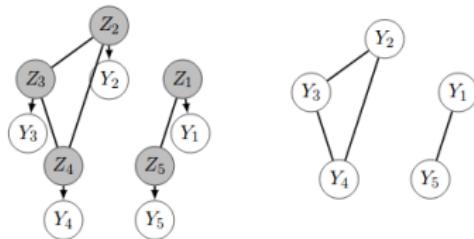
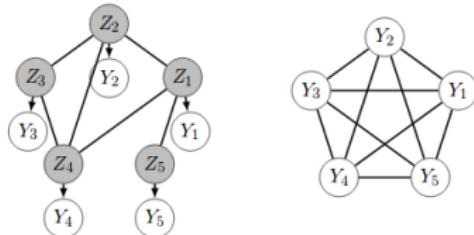


Figure 1: Two examples (top/bottom) of the PLN-network graphical representation. Left: joint distribution of  $p(Z_i, Y_i)$ . Right: marginal distribution  $p(Y_i)$ . The graph on the top right is a clique because the graph of the  $Z_i$ 's on the top left is connected.

Figure 1 from [Chiquet et al., 2018]

## PLN + mixture tree

$G$  is taken as a spanning tree  $T$ , the dependency structure is encoded in  $\Sigma_T$ .

$$Z_T \sim \mathcal{N}(0, \Sigma_T)$$

Tree averaging (mixture model):

$$Z \sim \sum_T w_T \mathcal{N}(0, \Sigma_T)$$

$$\Rightarrow \mathbb{P}(Z) \propto \sum_T \prod_{k,l \in T} \beta_{k,l} \psi_{k,l}(Z_T)$$

## Detailed inference

## Hierarchical model with latent tree

- 1 A spanning tree is drawn in a distribution decomposable on the edges:

Decomposable distribution for a tree  $T$  [Meilă and Jaakkola, 2006]

$$\mathbb{P}(T) = \frac{1}{B} \prod_{(k,l) \in T} \beta_{kl}, \text{ avec } B = \sum_{T \in \mathcal{T}} \prod_{(k,l) \in T} \beta_{kl}$$

- A weight  $\beta_{kl}$  is assigned to each edge  $(k, l)$
- The dependence tree probability is proportional to its weights product
- We consider **varying weights**

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$$Z|T \sim \mathcal{N}_d(0, \Sigma_Z)$$

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- 2 Data is simulated conditionally on the drawn tree :

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The data shaping tree is treated as a **latent variable**.

$$\mathbb{P}(Z) = \sum_{T \in \mathcal{T}} \mathbb{P}(T) \mathbb{P}(Z|T) : \text{mixture tree}$$

## E step

- Complete likelihood :

$$\mathbb{P}(Y, Z, T) = \mathbb{P}(T) \times \mathbb{P}(Z|T) \times \mathbb{P}(Y|Z)$$

$$\begin{aligned} \log(\mathbb{P}(Y, Z, T)) &= \sum_{k,l} \mathbb{1}_{\{(k,l) \in T\}} (\log(\beta_{kl}) + \log(\psi_{kl}(Z))) - \log(B) \\ &\quad + \sum_k (\log(\mathbb{P}(Z_k)) + \log(\mathbb{P}(Y_k|Z_k))) \end{aligned}$$

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- Conditional expectation :

$$\begin{aligned} \mathbb{E}_\theta[\log(\mathbb{P}(Y, Z, T))|Y] &= \sum_{k,l \in V} \mathbb{P}((k,l) \in T|Y) \log(\beta_{kl}) + \mathbb{E}[\mathbb{1}_{\{(k,l) \in T\}} \log(\psi_{kl}(Z)|Y)] \\ &\quad + \sum_k \mathbb{E}[\log(\mathbb{P}(Z_k))|Y] + \mathbb{E}[\log(\mathbb{P}(Y_k|Z_k))|Y] - \log(B) \end{aligned}$$

## Two steps solution

The PLNmodels package approximates the distribution parameters. Using PLNmodels:

- 1 Estimate  $\hat{\Sigma}_Z$
- 2 Apply EM mixture tree to  $Z \sim \mathcal{N}(0, \hat{\Sigma}_Z)$

Simplified conditional expectation writing:

$$\mathbb{E}_{\theta}[\log(\mathbb{P}(Z, T))|Z] = \sum_{k,l} \textcolor{red}{\mathbb{P}((k, l) \in T|Z)} (\log(\beta_{kl}) + \log(\psi_{kl})) - \log(B) + \sum_k \log(\mathbb{P}(Z_k))$$

## Conditional probability computation

Kirchhoff's theorem (matrix tree, [Aitchison and Ho, 1989])

For all  $W = (a_{kl})_{k,l}$  a symmetric matrix, the corresponding Laplacian  $Q(W)$  is defined as follows:

$$Q_{uv}(W) = \begin{cases} -a_{uv} & 1 \leq u < v \leq n \\ \sum_{i=1}^n a_{vi} & 1 \leq u = v \leq n. \end{cases}$$

Then for all  $u$  et  $v$ :

$$|Q_{uv}^*(W)| = \sum_{T \in \mathcal{T}} \prod_{\{k,l\} \in E_T} a_{kl}$$

$$\begin{aligned} \mathbb{P}((k,l) \in T | Z) &= \sum_{T \in \mathcal{T}: (k,l) \in T} \mathbb{P}(T | Z) = \frac{\sum_{(k,l) \in T} \mathbb{P}(T) \mathbb{P}(Z | T)}{\sum_T \mathbb{P}(T) \mathbb{P}(Z | T)} \\ &= 1 - \frac{|Q_{uv}^*(B\Psi^{-kl})|}{|Q_{uv}^*(B\Psi)|} \\ &= \tau_{kl} \end{aligned}$$

## M step

**Goal** : optimization of weights  $\beta_{kl}$ .

$$\operatorname{argmax}_{\beta_{kl}} \left\{ \sum_{k,l \in V} \tau_{kl} (\log(\beta_{kl}) + \log(\psi_{kl})) - \log(B) + \sum_k \log(\mathbb{P}(Z_k)) \right\}$$

With high combinatorial complexity of  $B = \sum_{T \in \mathcal{T}} \prod_{k,l \in T} \beta_{kl}$

How to compute  $\frac{\partial B}{\partial \beta_{kl}}$  ?

## $\beta_{kl}$ update

A result from Meilă [Meilă and Jordan, 2000]

Inverting a minor of the laplacien  $Q$ , we define  $M$  :

$$\begin{cases} M_{uv} = [Q^{*-1}]_{uu} + [Q^{*-1}]_{vv} - 2[Q^{*-1}]_{uv} & u, v < n \\ M_{nv} = M_{vn} = [Q^{*-1}]_{vv} & v < n \\ M_{vv} = 0. \end{cases}$$

On peut montrer que :

$$\frac{\partial |Q_{uv}^*(W)|}{\partial \beta_{kl}} = M_{kl} \times |Q_{uv}^*(W)|$$

$$\frac{\partial \mathbb{E}_\theta[\log(\mathbb{P}(Z, T))|Z]}{\partial \beta_{kl}} = \frac{1}{\beta_{kl}} \tau_{kl} - \frac{1}{B} \frac{\partial B}{\partial \beta_{kl}}$$

Update formula at iteration  $h+1$

$$\hat{\beta}_{kl}^{h+1} = \frac{\tau_{kl}^h}{M_{kl}^h}$$

## Simulation design

- 1 Choose  $G$  and define  $\Omega$  accordingly
- 2 Sample count data  $Y$  from  $\mathcal{PLN}(0, \Omega^{-1})$  with possible covariates
- 3 Infer the network with PLN + mixture tree EM and SpiecEasi
- 4 Compare results with AUC (presence/absence of edges)

⇒ 40 replicates for each setting ( $p, n, \text{edge probability}$ )

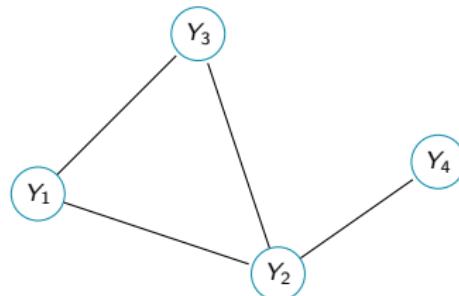
# Gaussian Graphical Models (GGM)

Gaussian distribution:

$Y_i \sim \mathcal{N}_p(\mu, \Omega^{-1})$ ,  $\mu$  = vector of means,  $\Omega^{-1}$  = precision matrix.

A nice property:

$$\begin{aligned} p(Y) &\propto \exp(-Y^T \Omega Y / 2) \\ &\propto \prod_{j,k, \omega_{jk} \neq 0} \exp(-Y_j \omega_{jk} Y_k / 2) \end{aligned}$$



Inverse covariance matrix

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

# Graphical LASSO

Glasso on gaussian data:

$$L(Y, \Omega) = \frac{n}{2} \log(\det(\Omega)) - \frac{n}{2} Y^T \Omega Y + cste$$

L1 penalization of the precision matrix:

$$\widehat{\Omega}_{glasso}(\lambda) = \arg \min_{\Omega \in \mathcal{S}_d^+} \left\{ L(Y, \Omega) + \lambda \sum_{i \neq j} |\omega_{ij}| \right\}$$

SpiecEasi method [Kurtz et al., 2015]

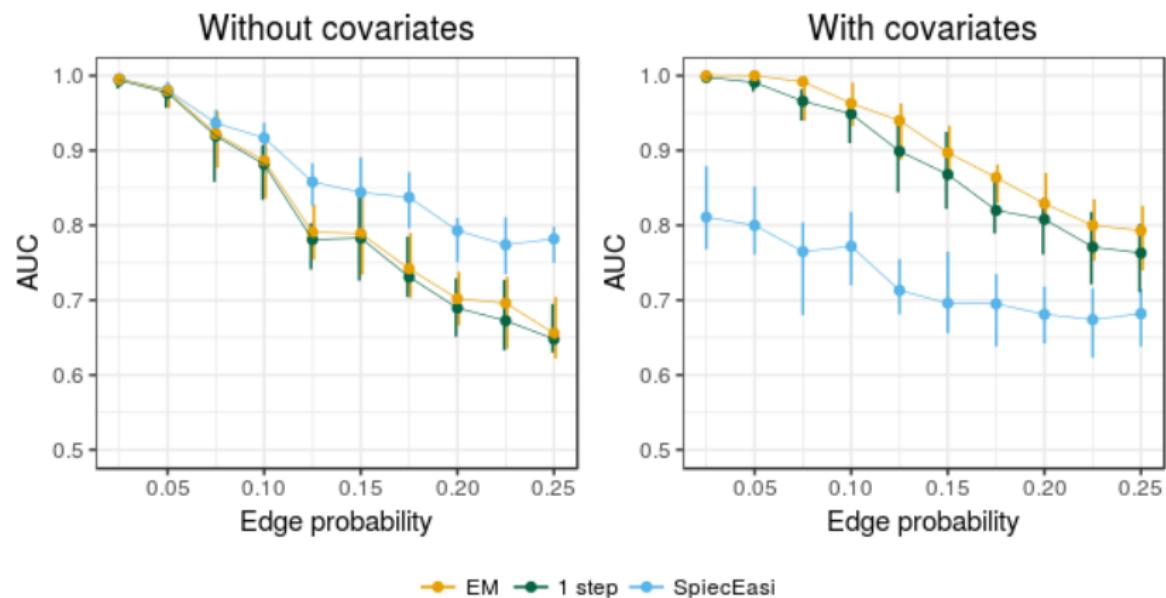
- 1 Count data centered log-ratio transformation:

$$clr(Y) = \left[ \log \left( \frac{Y_{ij}}{\left( \prod_{l=1}^p Y_{lj} \right)^{1/p}} \right) \right]_{i,j}$$

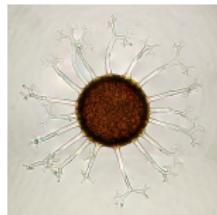
- 2 Glasso on transformed data

Output used : Matrix of first penalization constants removing each edge

## AUC curves with Erdös structure, 20 nodes



# Oak Mildew



Pathogen *Erysiphe alphitoides* (EA).



Oak leaf with powdery mildew.

Metabarcoding of oak tree leaves microbiome [Jakuschkin et al., 2016].

- 114 sample of 94 microbial species counts (bacteria/fungi)
- Different read depth for bacteria and fungi: unsuited for normalization with SpiecEasi
- 3 quantitative covariates

# Model with covariates

F19: a major fungi of the microbiome.

## Regression coefficients

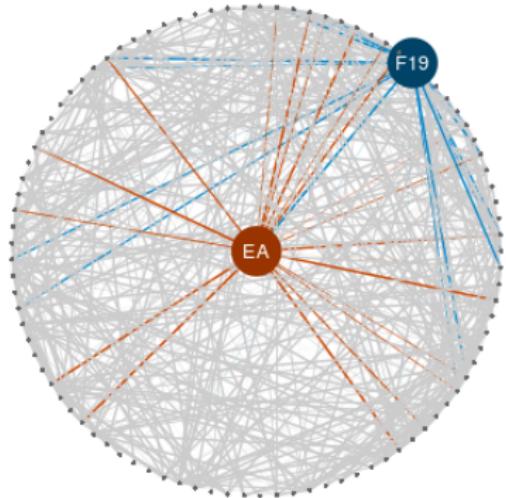
	Covariates ( $\times 10^{-2}$ )		
	to base	to trunk	to ground
EA	-2.00	2.15	-2.51
F19	2.19	-1.72	1.43

## Degree estimation

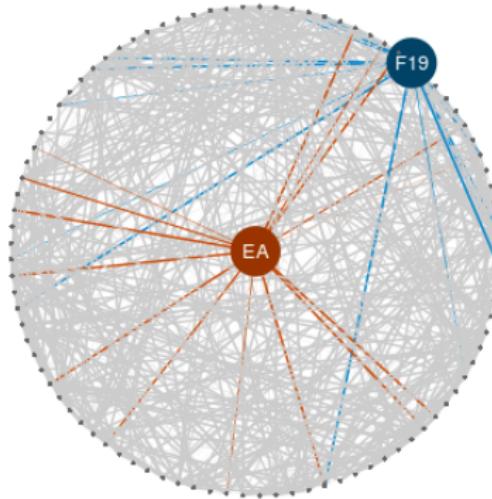
	Offset	Covariates
EA	2.20	1.86
F19	3.03	2.80

## Inferred networks

Offset only



With covariates



## Further developments

- ① Latent layer network inference
- ② Observed counts network inference
- ③ Thresholding the network
- ④ Missing actor
- ⑤ REMMOA data

# Latent network inference

- 2 steps inference:  $\hat{\Sigma}_Z$  with PLNmodels, and then network inference starting from  $\hat{\Sigma}_Z$ 
  - Formal probabilistic model for network inference with **count data**
  - Estimation algorithm (VEM and then EM)
  - Inclusion of **offsets** and **covariates**
  - Yet estimating with PLNmodels adds some variability
- VEM inference: rewrite the Variational EM used in PLNmodels, to incorporate the latent layer tree dependency structure.
  - Would allow to re-estimate  $\hat{\Sigma}_Z$  at each iteration

## Inference approach

$\psi_{kl}(Y) = \frac{\mathbb{P}(Y_k, Y_l)}{\mathbb{P}(Y_k) \times \mathbb{P}(Y_l)}$  are directly accessible

- The `poilog` R package computes the uni and bi-variate densities of the  $\mathcal{PLN}$  distribution
  - ⇒ Direct network inference in the  $Y$  space

### Direct inference

$$\mathbb{P}(Y|T) = \prod_k \mathbb{P}(Y_k) \prod_{kl \in T} \mathbb{P}(Y_k, Y_l)$$

# Pros and cons

## Pros

- Good news for ecologists/biologists
- Maximum likelihood
- Network comparison made possible (ex: likelihood ratio)
- No competitor

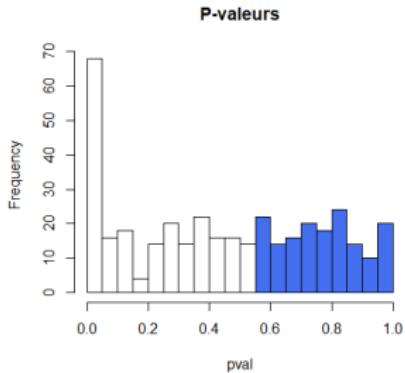
## Cons

- Recursive calls to `poilog`: might be long
- No straightforward to simulate (Metropolis-Hastings simulation strategy)

## Method for determining the threshold

$$Y_i \sim Y_{\setminus -i}$$

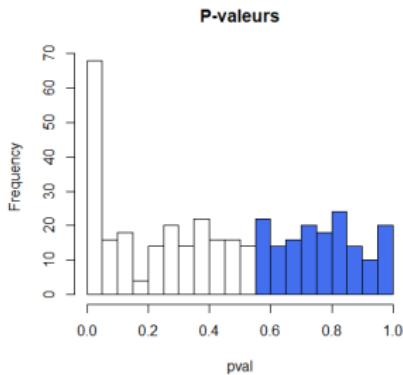
- Adjust each variable on all others
- Interpret coefficients tests in edges presence/absence:  
 $(\mathcal{H}_0) : c_{ij} = 0$  vs  $(\mathcal{H}_1) : c_{ij} \neq 0$
- Deduce from the p-values an estimator of the "non-edges" number



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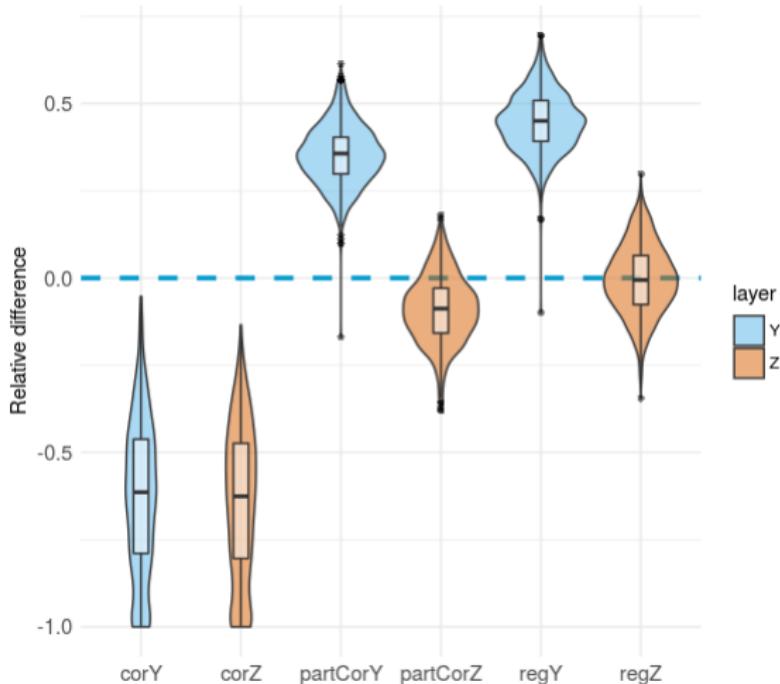


## $S$ and $S^*$

- $S^*(G)$  : number of absent edges in graph  $G$
- $S^*$  estimator:

$$S(Y_G) = 2 \sum \mathbb{1}\{pval(Y_G) \geq 0.5\}$$

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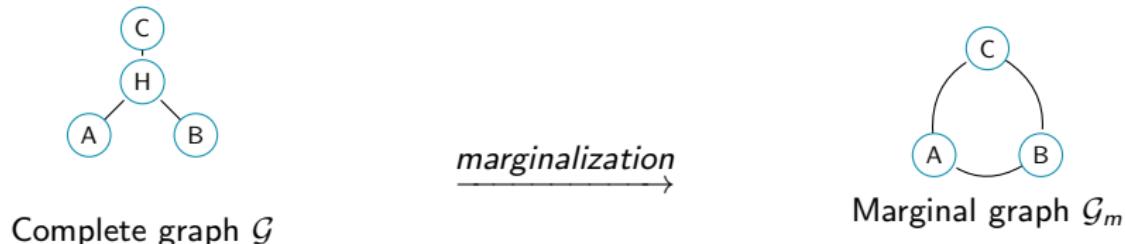


Switching from Gaussian data Z to count data Y: relative difference between  $S$  and  $S^*$ , related to tests of regression coefficients, correlations or partial correlations.

## Missing major actor (species/covariable)

In the latent layer :

Missing a major actor induces spurious edges, and distort the network interpretation  
 [Chandrasekaran et al., 2012] :



$$\mathcal{G} \Omega = \underbrace{\begin{pmatrix} \Omega_{OO} & \Omega_{OH} \\ \Omega_{HO} & \Omega_{HH} \end{pmatrix}}_{\text{edges from } E} \quad \Sigma = \begin{pmatrix} \Sigma_{OO} & \Sigma_{OH} \\ \Sigma_{HO} & \Sigma_{HH} \end{pmatrix}$$

$$\mathcal{G}_m : \Omega_m = \underbrace{\Omega_{OO} - \Omega_{OH}\Omega_{HH}^{-1}\Omega_{HO}}_{\text{edges from } E_m} \quad \Sigma_m = \Sigma_{OO}$$

# REMMOA data



## REcensement des Mammifères marins et autre Mégafaune pélagique par Observation Aérienne

- Count data from marine mega-fauna
- Network comparison between Nouvelle-Calédonie and Wallis-et-Futuna
- Collaboration to develop and highlight the benefits from ecological network study



Thank you for your attention!

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