Ecological network reconstruction from count data

Raphaëlle Momal
Supervision: S. Robin[1] and C. Ambroise[2]

[1]UMR AgroParisTech / INRA MIA-Paris
[2]LaMME, Evry

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Context

Rising interest in jointly analysed species abundances:

- Metagenomics
- Microbiology
- Ecology

Ecological network

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

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

Example

Data:

- Species: bacteria, fungi...
- Abundances: read counts from Next-Generation Sequencing technologies (metabarcoding) $\Rightarrow$ $n \times p$ matrix Y
- Covariates: temperature, water depth... $\Rightarrow$ $n \times d$ matrix X
- Offsets: species-specific, sample-specific $\Rightarrow$ $p \times p$ matrix O

Goal:

Infer the species interaction network $\widehat{G}$ from count data Y, accounting for X and O :

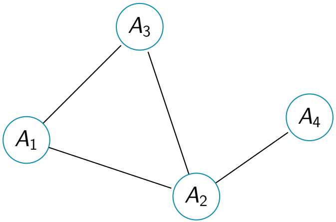
$$\widehat{G} = f(Y, X, O)$$

Challenges

- Statistical network inference
- Count data
- Offsets and covariates

Graphical models: a statistical framework for network inference

Example:



- Connected: all variables are dependant
- Some are conditionally independent (i.e. indirectly dependant)

  A_4 is independent from (A_1, A_3) conditionally on A_2

Graphical models: a statistical framework for network inference

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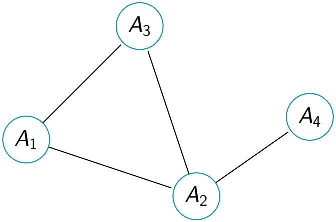

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$$P(A_1, \dots, A_p) \propto \prod_{C \in \mathcal{C}_G} \psi_C(A_C)$$

PLN model

Poisson log-Normal distribution (Aitchison and Ho, 1989)

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

- Dependency structure in the Gaussian latent layer
- Easy handling of multi-variate data

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

PLN model + Graphical model

Poisson log-Normal distribution (Aitchison and Ho, 1989)

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Proposed method: PLN + Spanning trees

Tree structure on PLN latent layer

EMtree model

$$\left.\begin{array}{rl} T & \sim \prod_{kl} \beta_{kl}/B \\ Z_i|T \;\; iid & \sim \mathcal{N}_d(0, \Sigma_T) \\ & (Y_{ij})_j \perp\!\!\!\perp |Z_i|T \\ Y_{ij}|Z_{ij}, T & \sim \mathcal{P}(e^{o_{ij}+x_i^\intercal \Theta_j + Z_{ij}}) \end{array}\right\} Y \sim \mathcal{P}\ell\mathcal{N}(O + X^\intercal \Theta, \Sigma_T)$$

$$Z_i \sim \sum_{T \in \mathcal{T}} P(T)\mathcal{N}(0, \Sigma_T)$$

Why Spanning trees

Sparse structures:

$$\#\mathcal{G}_p = 2^{\frac{p(p-1)}{2}} \text{ reduced to } \#\mathcal{T}_p = p^{(p-2)}$$

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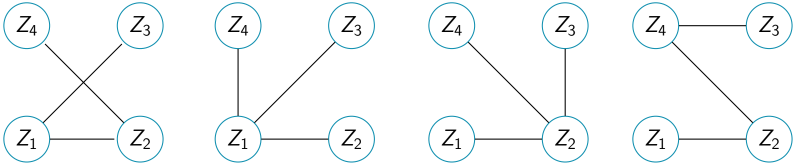
Suitable algebraic tool:

Matrix tree theorem (Chaiken and Kleitman, 1978)

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

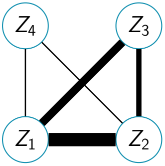
Approach: infer the network by averaging spanning trees

Tree averaging



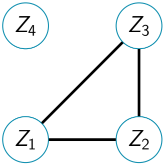
$P\{T = T_1|Z\}$ $P\{T = T_2|Z\}$ $P\{T = T_3|Z\}$ $P\{T = T_4|Z\}$ ...

Compute edge probabilities:



$P\{(j, k) \in T|Z\}$

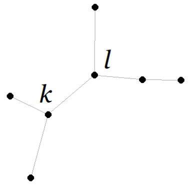
Thresholding probabilities:



$P\{(j, k) \in T|Z\}$

Tree structured data

- Data dependency structure relies on a tree



- Likelihood factorizes on nodes and edges (Chow and Liu, 1968):

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

Where

$$\psi_{kl}(Z) = \frac{\mathbb{P}(Z_k, Z_l)}{\mathbb{P}(Z_k) \times \mathbb{P}(Z_l)}.$$

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

Direct EM algorithm ?

- Complete likelihood :

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

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

Direct EM algorithm ?

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

- Conditional expectation :

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

Two steps solution

The PLNmodels package approximates the distribution parameters:

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

Simplified conditional expectation writing:

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

$\Rightarrow$ **EM algorithm** (E: Kirshner (2008), M: Meilă and Jaakkola (2006))

EMtree algorithm

Input: Abundance data, covariates, offsets

1rst step: VEM algorithm to fit PLN model $\Rightarrow \hat{\theta}, \hat{\Sigma}_Z$.

2nd step: EM algorithm to update the β_{jk} $\Rightarrow$ conditional probabilities for all edges.

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Thresholding: Select edges with probability above the probability of edges in a tree drawn uniformly ($2/p$)

Resampling: Strengthen the results: only edges selected in more than 80% of S sub-samples are kept.

Available for download at `https://github.com/Rmomal/EMtree`

Evaluation strategy

Alternatives:

Two methods on transformed counts, no covariates:

- SpiecEasi algorithm Kurtz et al. (2015)
- gCoda Fang et al. (2017)

One taking raw counts and covariates:

- MInt Biswas et al. (2016) (uses PLN model)

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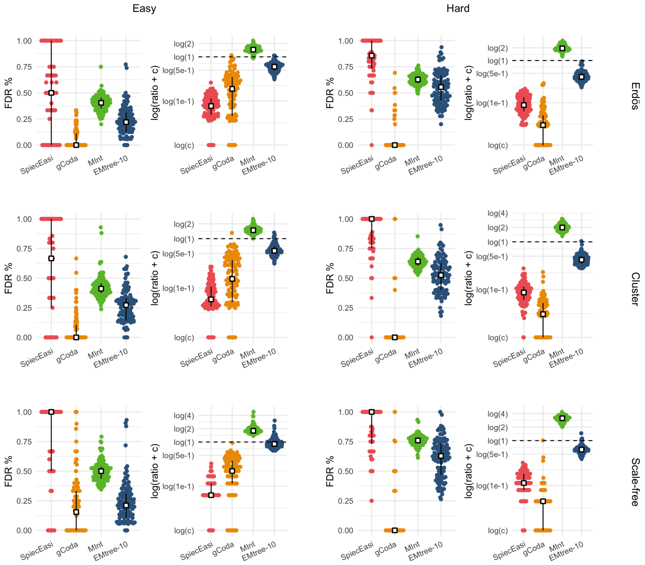
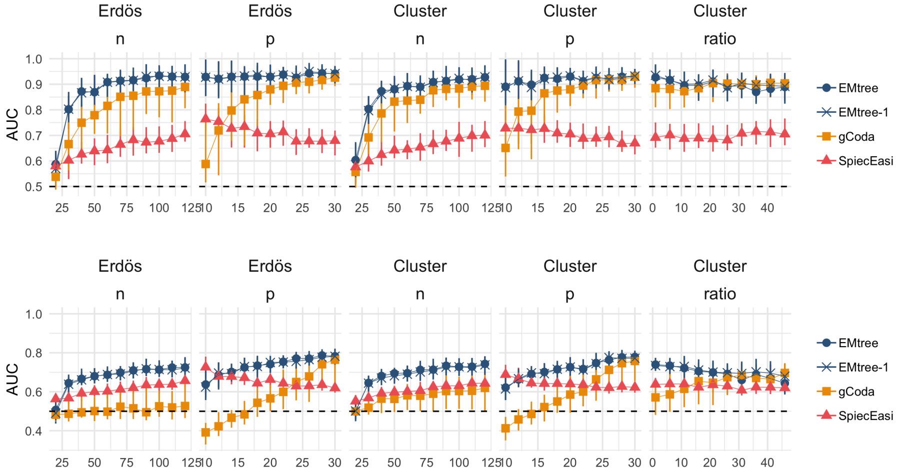
Simulation design:

1. Choose G and define Σ_G accordingly
2. Sample count data Y from $\mathcal{P}\ell\mathcal{N}(X, \Sigma_G)$
3. Infer the network with EMtree, SpiecEasi, gCoda, and MInt
4. Compare results with presence/absence of edges (FDR, AUC)

Difficulty level

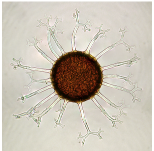


Network density



Effect of Erdös and Cluster structures on the evolutions of AUC median and inter-quartile intervals for parameters n, p and *ratio*. *Top*: densities set to $2/p$, *bottom*: densities set to $5/p$.

Oak Mildew



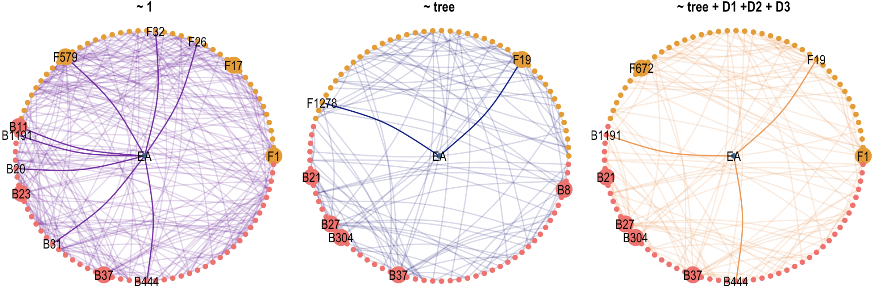
Pathogen Erysiphe alphitoides (EA).

Oak leaf with powdery mildew.

Metabarcoding of oak tree leaves microbiome (Jakuschkin et al., 2016).

- 114 sample of 94 bacterial/fungal-OTUs
- Different read depth for bacteria and fungi
- covariates: tree status; distance to ground, to trunk and to base of the branch.

Inferred networks



Conclusion

Contributions:

- Formal probabilistic model for network inference with count data
- Inclusion of offsets and covariates
- Variational estimation algorithm

Perspectives:

- Network comparison
- Missing major actor (species/covariates)
- Model for the inference in the observed counts layer

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Data Corinne Vacher (INRA Bordeaux)

Contact :

email raphaelle.momal@agroparistech.fr

Web Rmomal.github.io

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:

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

Then for all u et v:

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

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

M step

Goal : optimization of weights β_{kl}.

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

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

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

β_{kl} update

A result from Meilă Meilă and Jordan (2000)

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

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

On peut montrer que :

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

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

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

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