université PARIS-SACLAY

Discovering multi-scale metagenomic signatures through hierarchical organization of species

PhD defense

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LaMME – Enterome
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MaIAGE

enterome

Context

Microbiota

Ecological community of microorganisms that reside in an environmental niche.

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For human gut

- 10^{14} bacterial cells in one gut...
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- More than 10 millions unique genes.
- Helpful for nutrient absorption and anti inflammatory properties.

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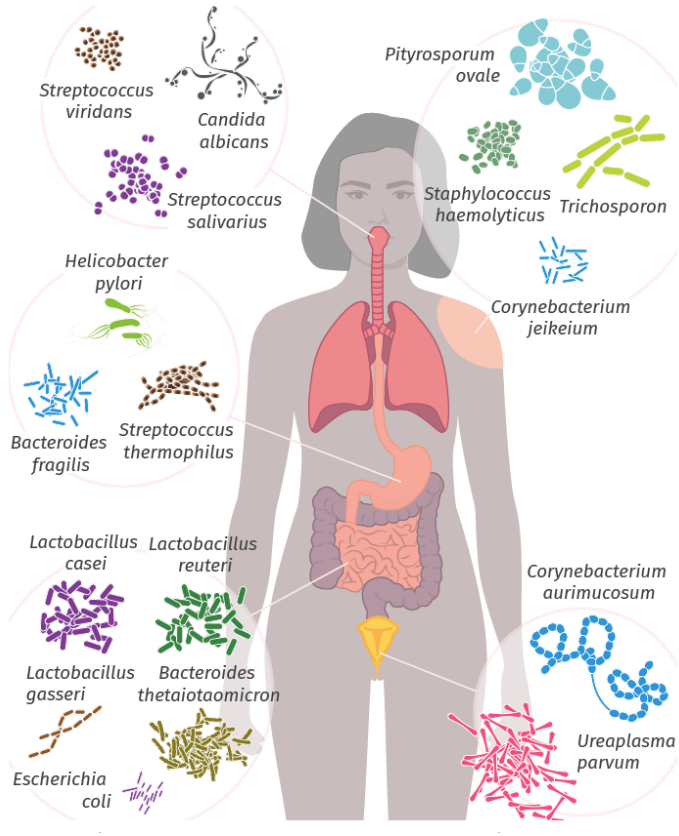

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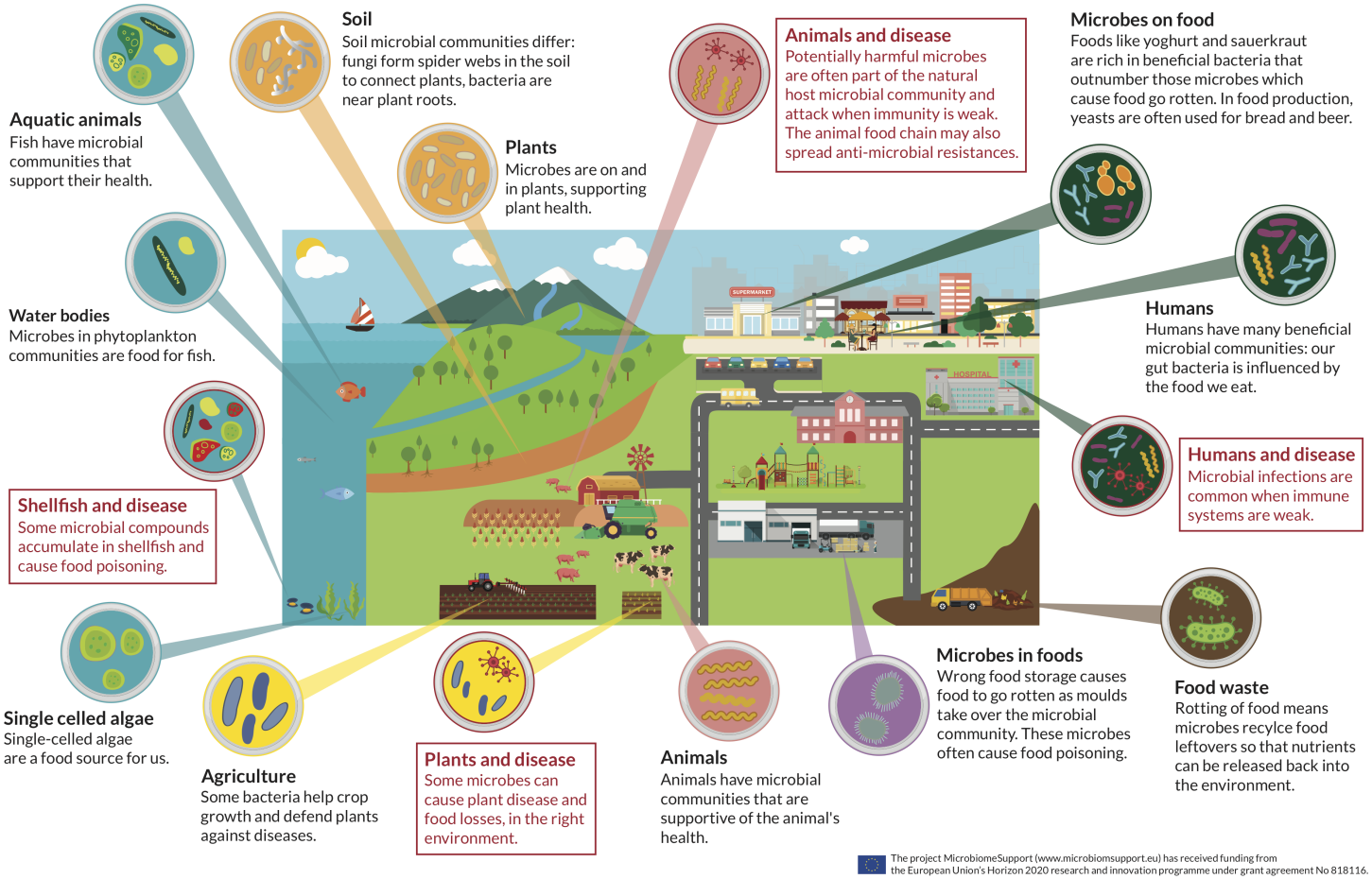
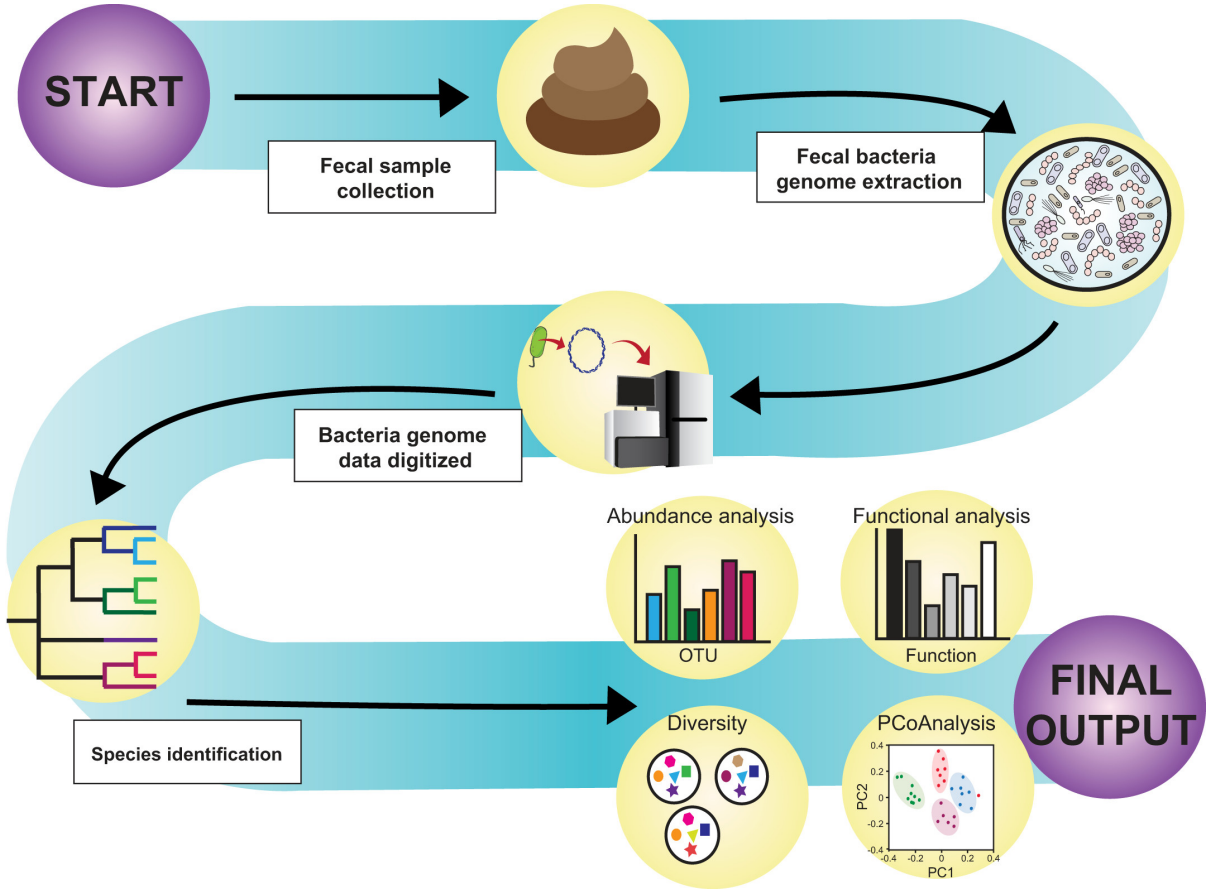
Microbiota everywhere



The project MicrobiomeSupport (www.microbiomsupport.eu) has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 818116.

Sequencing



Cryan O'Riordan, et al. [Cry+19]

Abundance table

- Matrix with m taxa and p samples.
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Bacteroides dorei	89893	2567192	648639	0	0	8498
Bifidobacterium longum	376119	0	30671	0	1292193	1830318
Enterobacter cloacae	756064	12234	142652	2186	238175	535786
Escherichia coli	256424	5551041	9905179	76052	70234	79805
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Megamonas hypermegale	0	0	0	0	0	27317
Streptococcus anginosus	0	0	0	985	0	19134

Brito Yilmaz, et al. [Bri+16]

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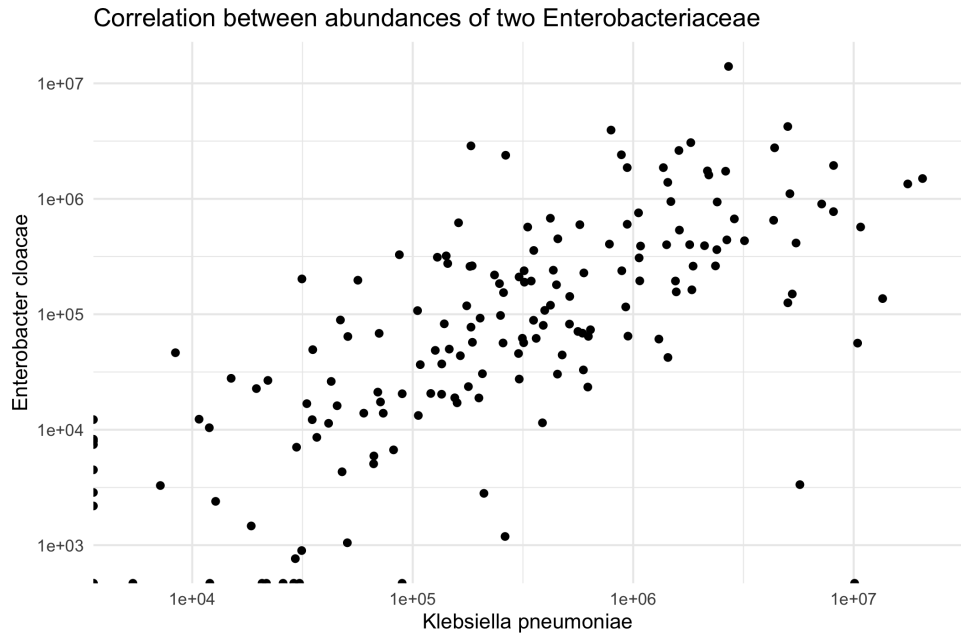

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Phylogeny

- Tree with m leaves which describes the evolutionary history of the taxa.

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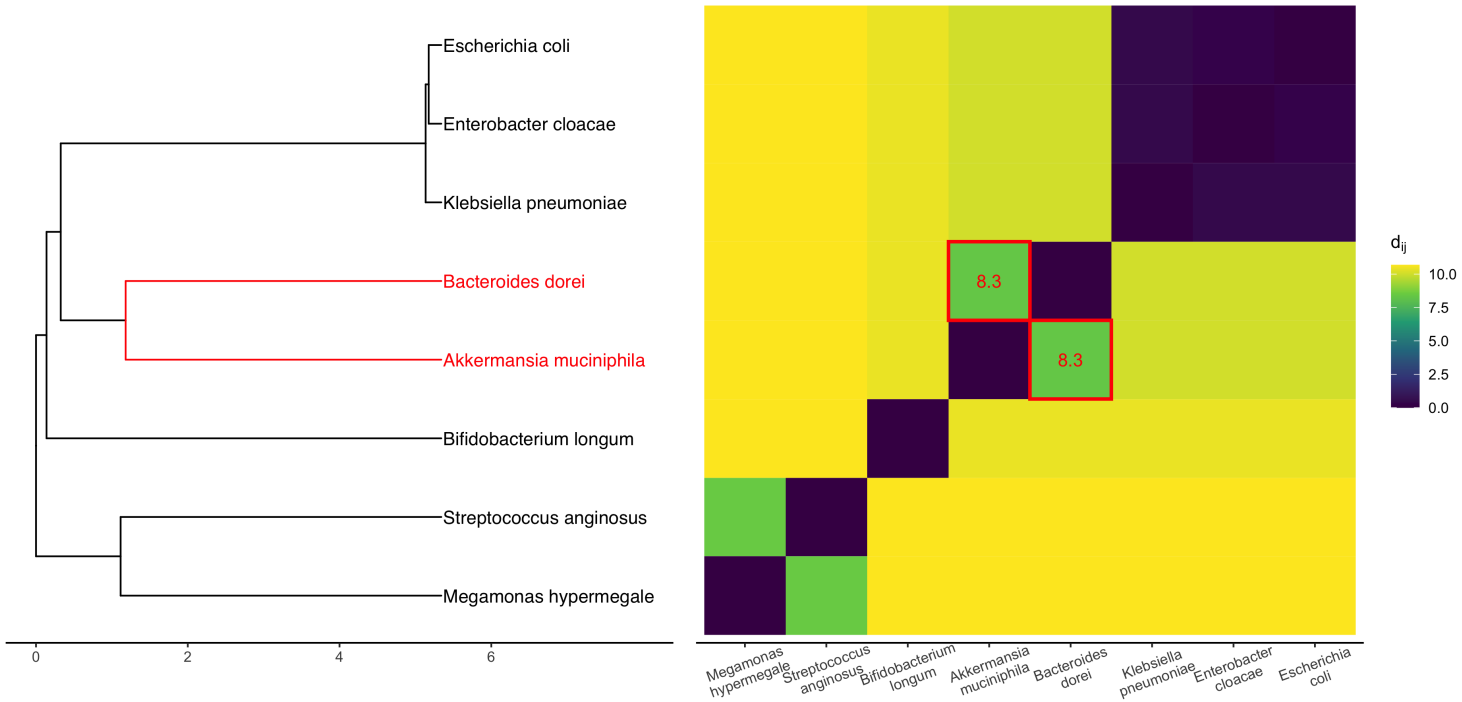
- Associated with a patristic distance matrix $\left(d_{i,j}\right)_{i,j}$.



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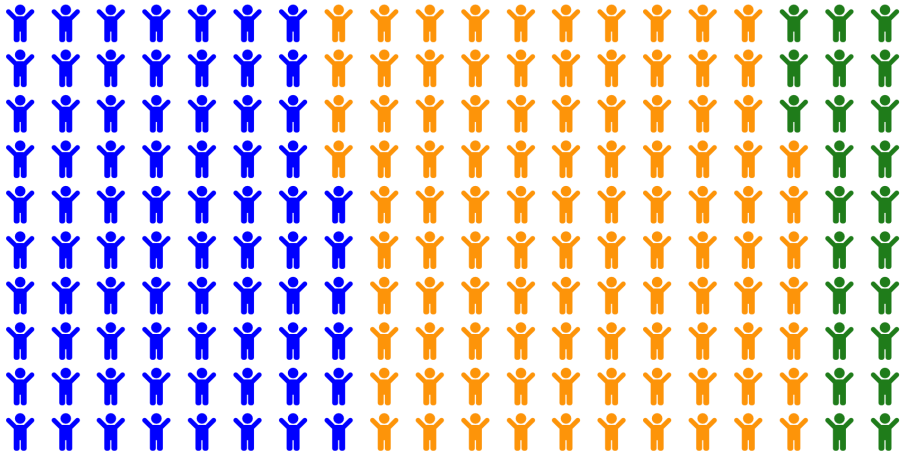
Differential abundance studies



Used to find **associations** between microbiota and

- diet [Dav+14],
- birth mode [Bok+16],
- age [Yat+12],
- pet owning [Kat+20],
- tobacco [Ops+16],
- antibiotics [Pal+18],
- Crohn's disease [Mor+12],
- cirrhosis [Qin+14]
- schizophrenia [Zhe+19]...

Classical approach

Vector $\mathfrak{p} \in [0, 1]^m$ of p-values, computed on each taxa independently.

Wilcoxon and Kruskal-Wallis non-parametric tests can be used.

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Each taxon fall into one class of the confusion matrix:

		True condition	
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Detection	Positive	TP	FP
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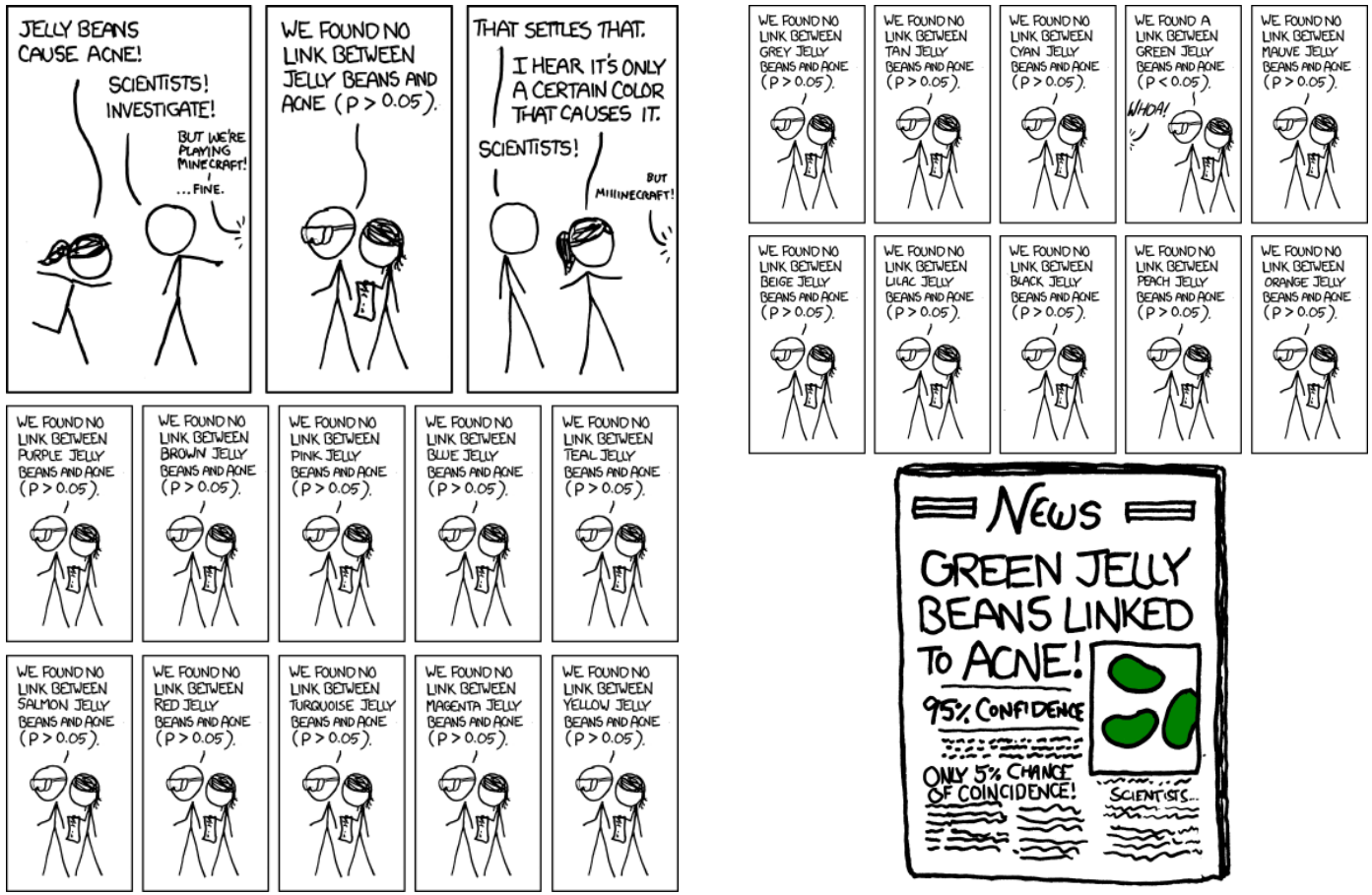
Under $\mathbb{H}_0$, $\mathfrak{p}_i \sim \mathcal{U}([0,1])$.

Multiple testing problem



XKCD

TPR and FDR

		True condition: Positive	True condition: Negative
Detection	Positive	TP	FP
	Negative	FN	TN

True Positive Rate:

$$\mathrm{TPR} = \frac{\mathrm{TP}}{\mathrm{TP} + \mathrm{FN}}.$$

False Discovery Rate:

$$\mathrm{FDP} = \frac{\mathrm{FP}}{\mathrm{TP} + \mathrm{FP}}, \mathrm{FDR} = \mathbb{E}[\mathrm{FDP}].$$

Multiple testing problem correction

Correction with Benjamini-Hochberg procedure to respect an *a priori* FDR : q^{bh}.

Benjamini and Hochberg [BH95]

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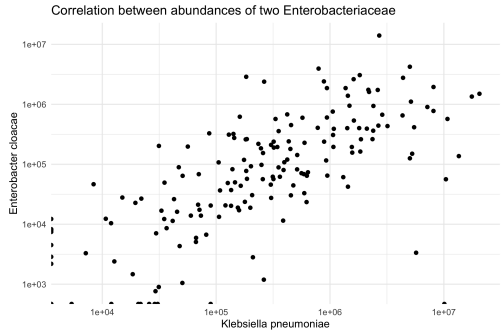

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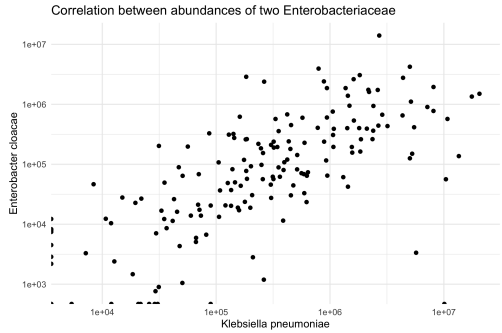

One can use Benjamini-Yekutieli correction which does not make any assumption about dependence between taxa but

- it's too conservative,
- we want to correct explicitly for correlation between taxa.

Benjamini and Hochberg [BH95]; Benjamini and Yekutieli [BY01]

Incorporation of hierarchical information

Goal

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- Increase power.

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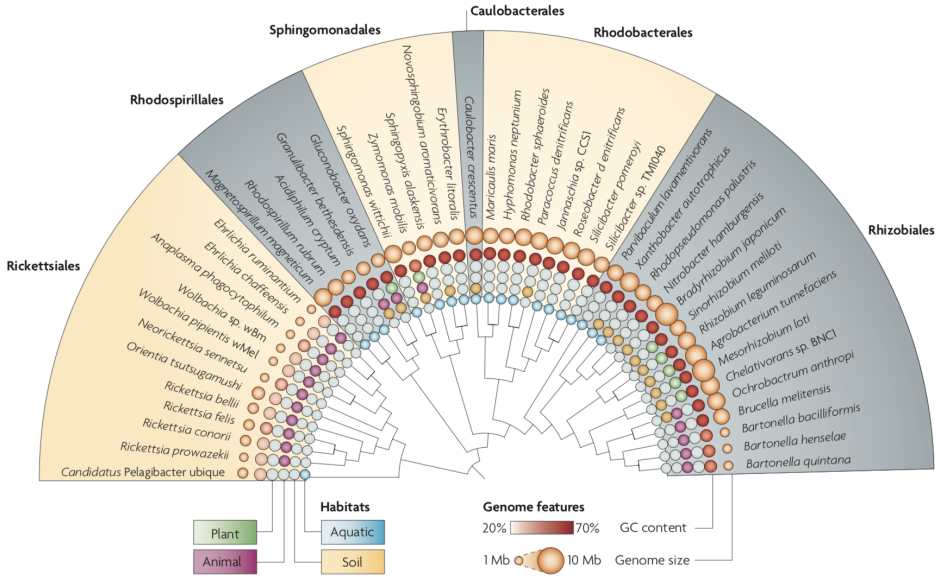
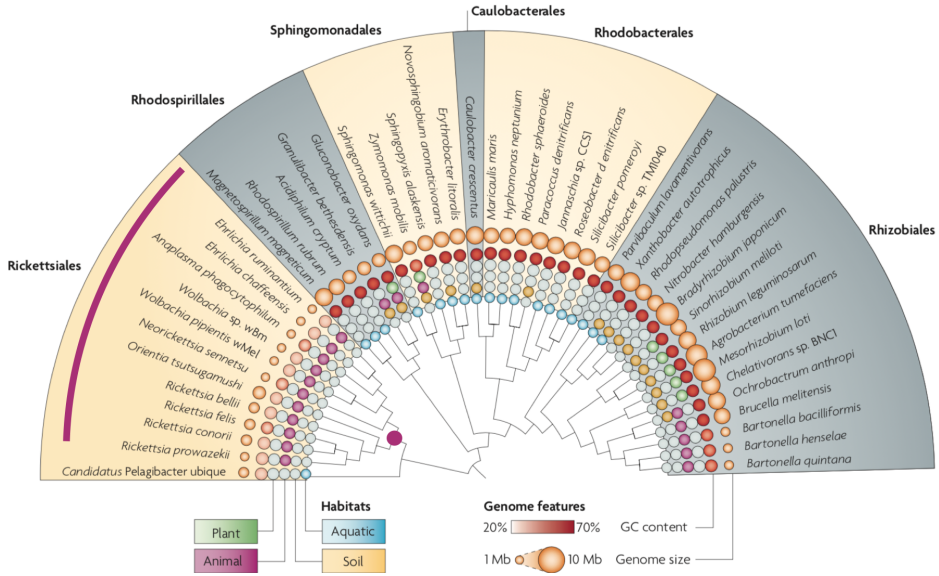
- Increase power.
- Keep FDR under a desired level.

Rationale



Philippot Andersson, et al. [Phi+10]

Rationale



These species are associated with animals.

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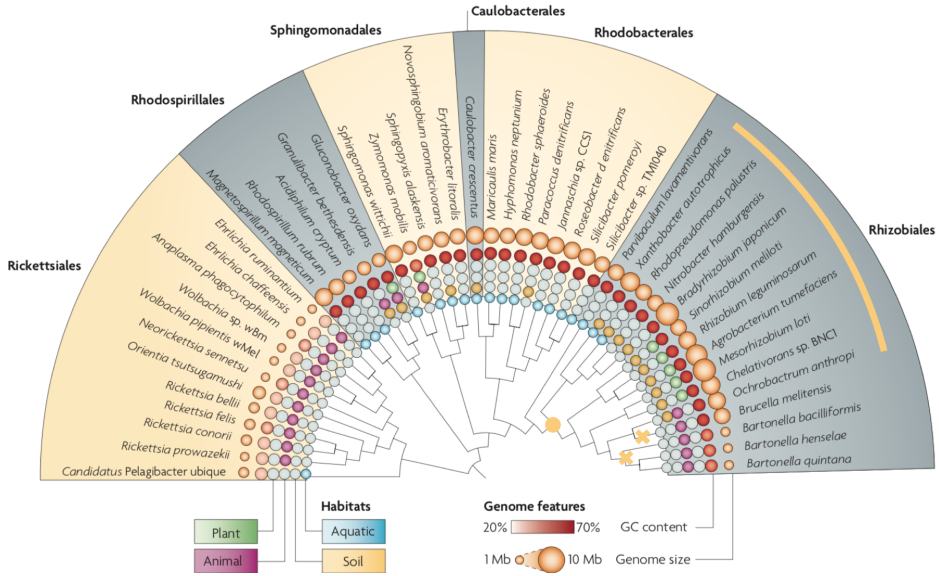

These species are associated with soil.

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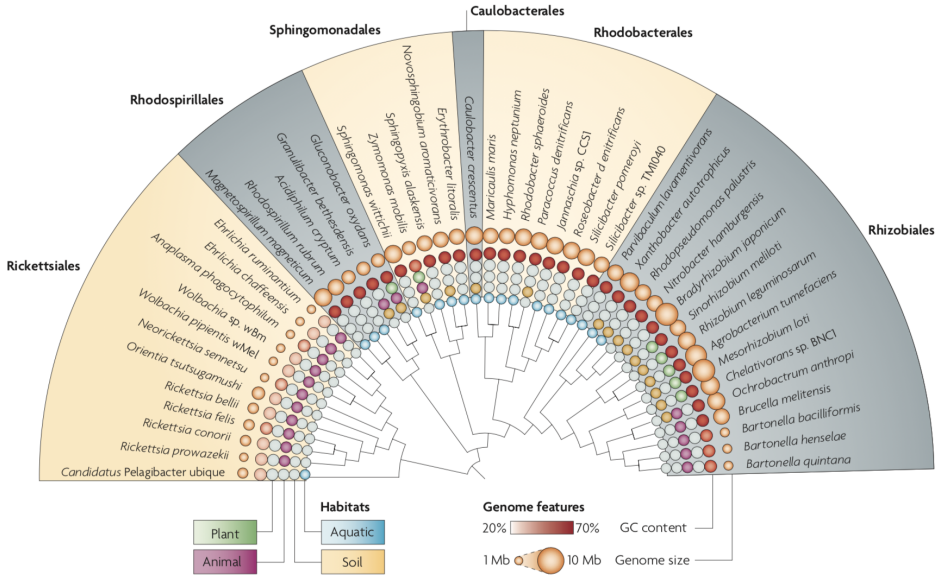

Already used in

- Hierarchical FDR [Yek08; SH14],
- **TreeFDR [XCC17]**.

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z-scores smoothing with TreeFDR

$\mathfrak{z} = \Phi^{-1}(\mathfrak{p})$ is the vector of observed z-scores and μ the vector of "true" z-scores.

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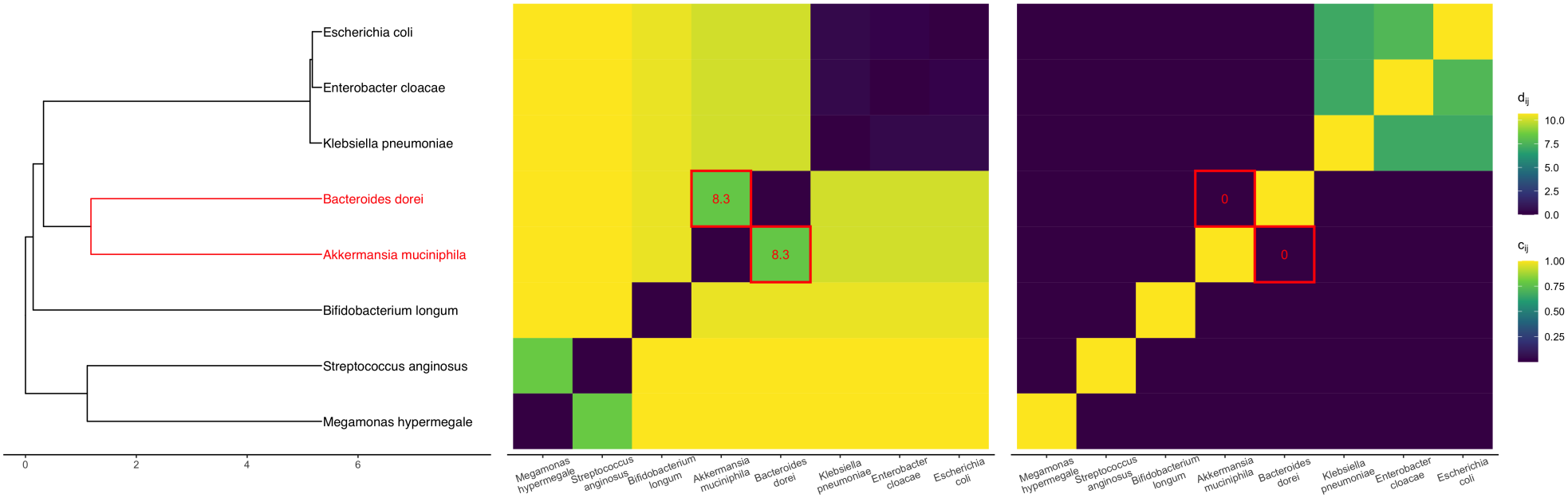
Assume a hierarchical model: $\mathfrak{z} \mid \mu \sim \mathcal{N}_m(\mu, \sigma^2 \mathbf{I}_m)$ and $\mu \sim \mathcal{N}_m(\gamma \mathbf{1}_m, \tau^2 C_\rho)$ with $C_\rho = \left(\exp\left(-2\rho d_{i,j}\right)\right)_{i,j}$.



z-scores smoothing with TreeFDR

Then $\mathcal{z} \sim \mathcal{N}_m\left(\gamma \mathbf{1}_m, \tau^2 C_\rho + \sigma^2 \mathbf{I}_m\right)$ by Bayes formula and the maximum a posteriori gives

$$\mu^* = \left(\mathbf{I}_m + k^2 C_\rho^{-1}\right)\left(k^2 C_\rho^{-1}\gamma \mathbf{1}_m + \mathcal{z}\right),$$

with $k = \frac{\sigma}{\tau}$ and ρ_0 hyperparameters to optimize.

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At the end, a multiple testing correction by resampling is done on smoothed values.

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- Phylogeny? Taxonomy?

😀 Proxy for correlations at high-level niches.

☹️ Not so much for low-level niches?

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- Correlation tree?

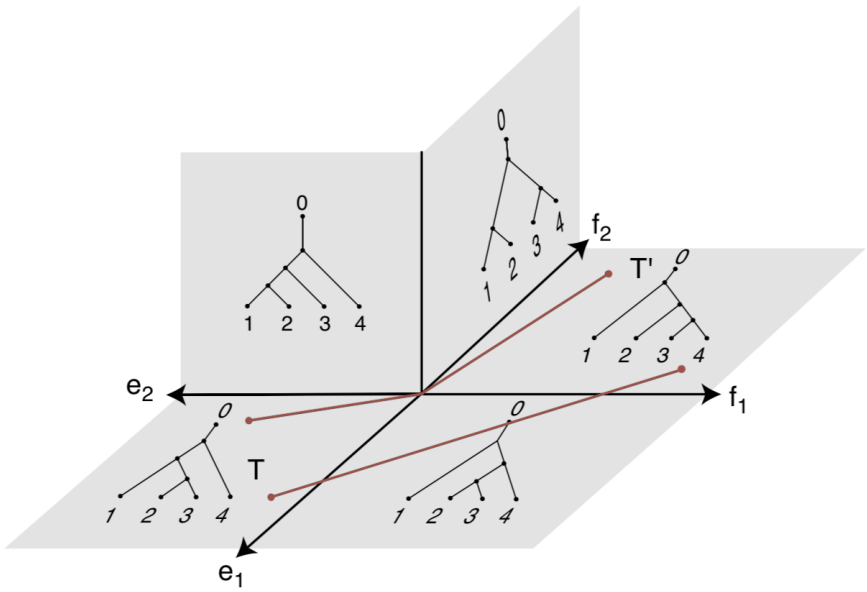
😀 Actual correlation between taxa.

😀 Always available.

☹ Risk of overfitting.

Bichat Plassais, et al. [Bic+20]

Billera-Holmes-Vogtmann distance



- Each tree is mapped into a space composed by merged orthants.
- An orthant corresponds to a topology.
- The BHV distance is the length of the unique shortest path between the trees on treespace.
- It can be computed with a $O\left(m^4\right)$ algorithm.

Billera Holmes, et al. [BHV01]

Quantifying distance between trees

- Trees of primary interest:
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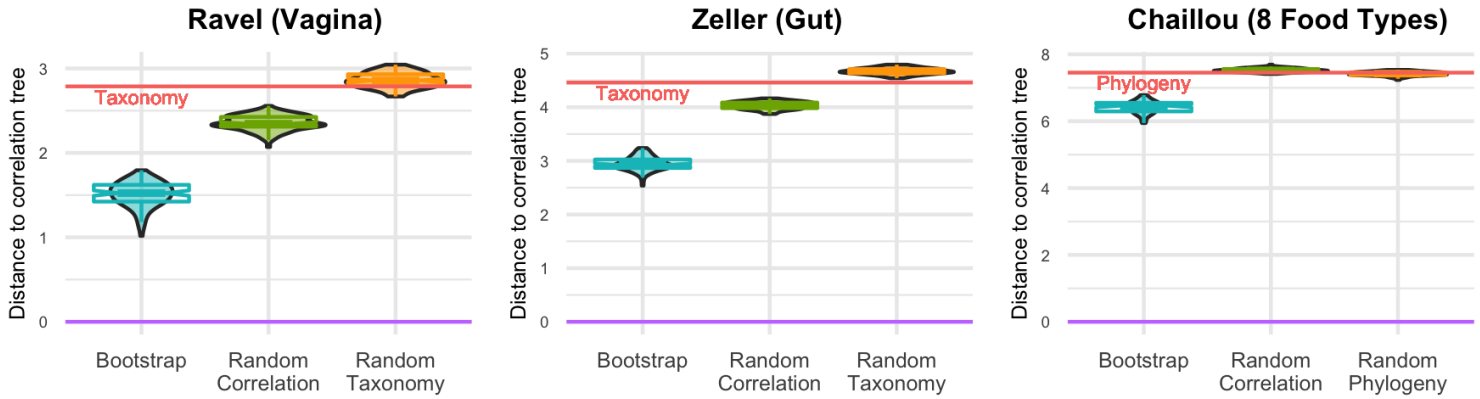
We compute all pairwise distances between these trees.

Comparisons between trees

Neither phylogeny nor taxonomy is in the confident region of the correlation tree.



[Bic+20; Rav+11; Zel+14; Cha+15]

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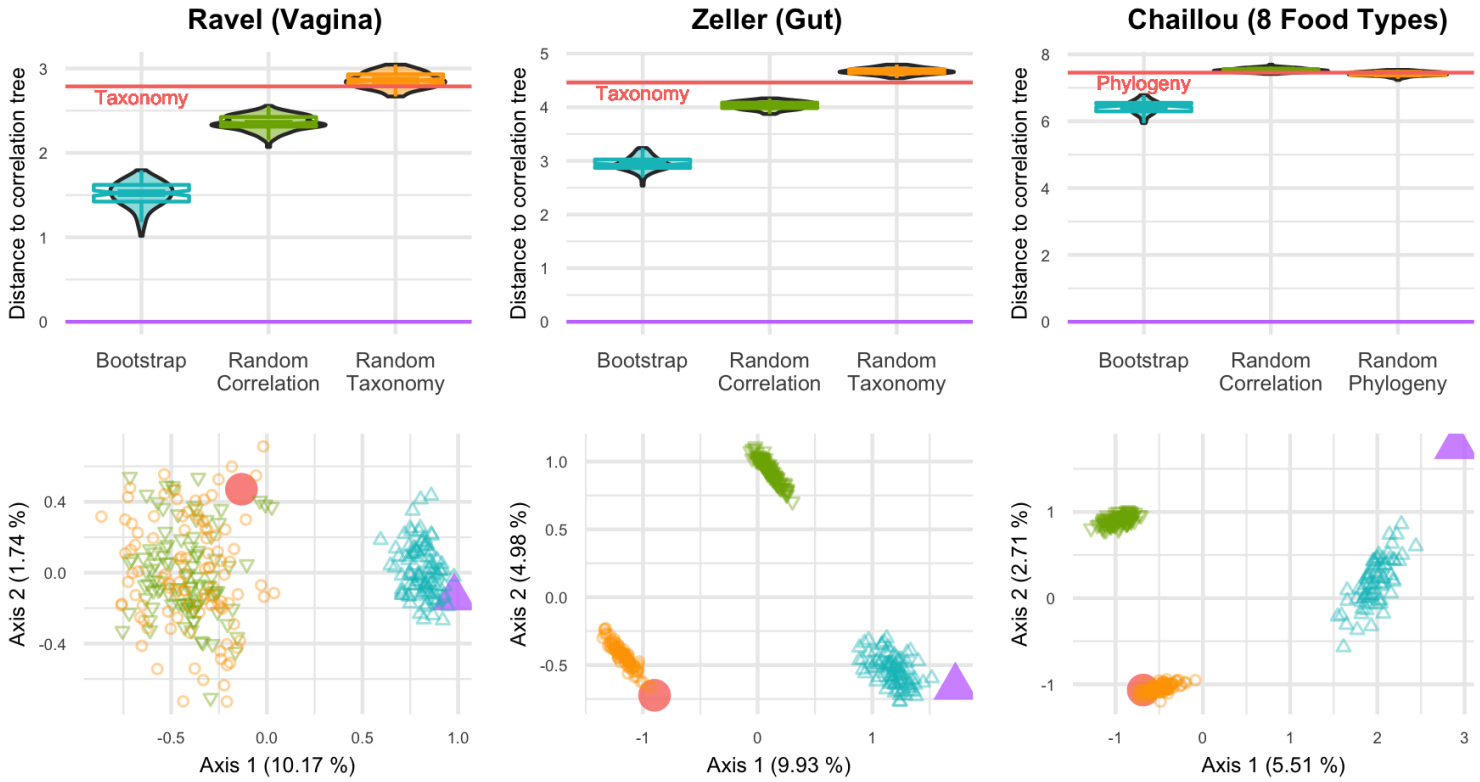

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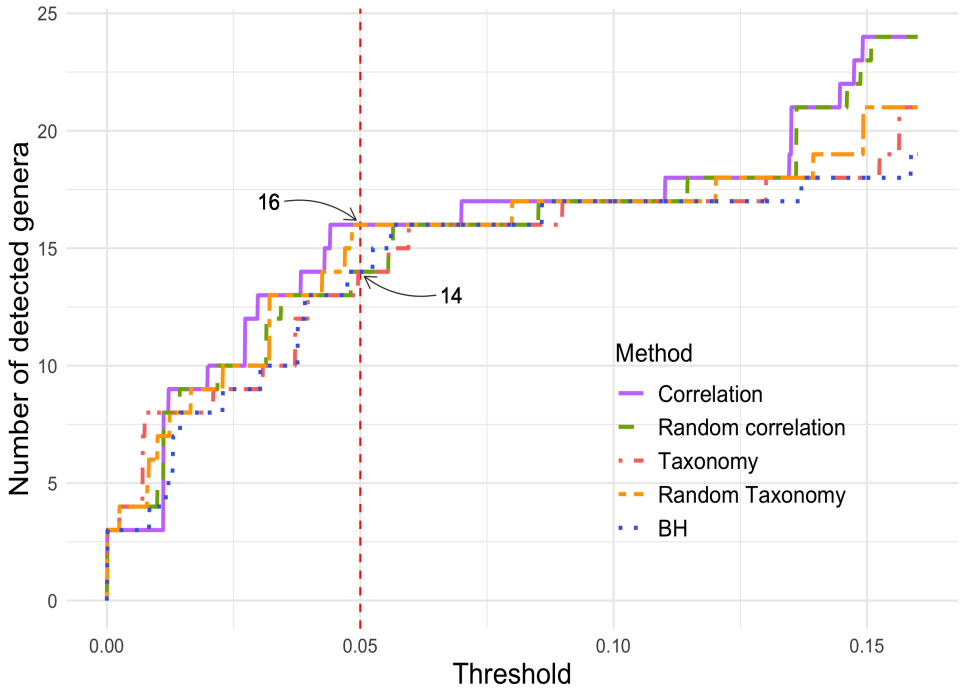
Impact of the tree with Zeller dataset

All hierarchies give highly similar results.



- 119 genera
- 199 patients
  - 66 healthy
  - 42 adenoma
  - 91 colorectal cancer

Bichat Plassais, et al. [Bic+20]; Zeller Tap, et al. [Zel+14]

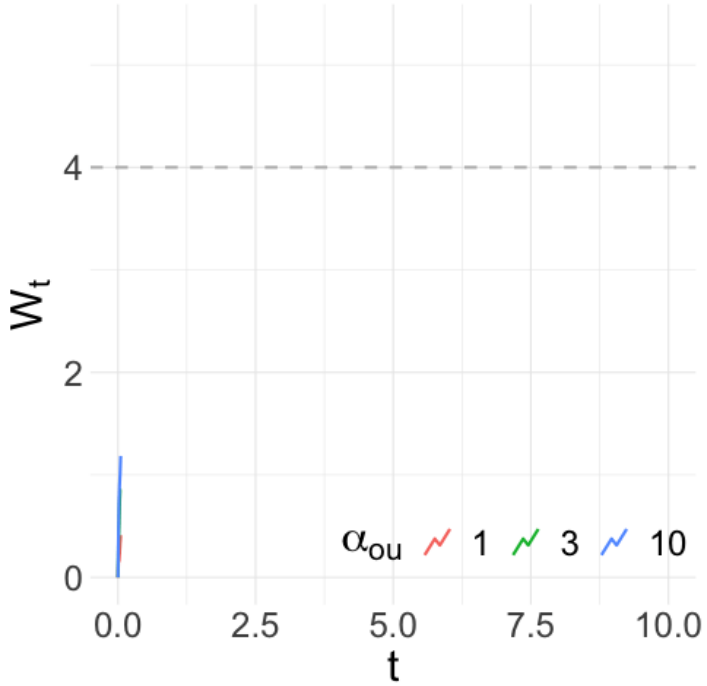
zazou

Z-scores AZ Ornstein-Uhlenbeck

Ornstein-Uhlenbeck process

An Ornstein-Uhlenbeck (OU) process with an optimal value of β_{ou} and a strength of selection $\alpha_{\text{ou}} > 0$ is a Gaussian process that satisfies the SDE

$$\mathrm{d}W_t = -\alpha_{\text{ou}}(W_t - \beta_{\text{ou}})\mathrm{d}t + \sigma_{\text{ou}}\mathrm{d}B_t.$$



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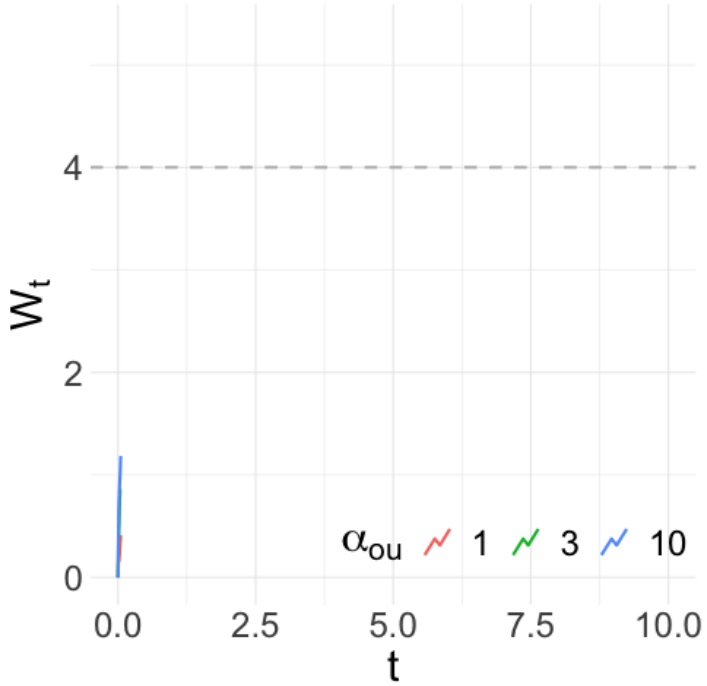
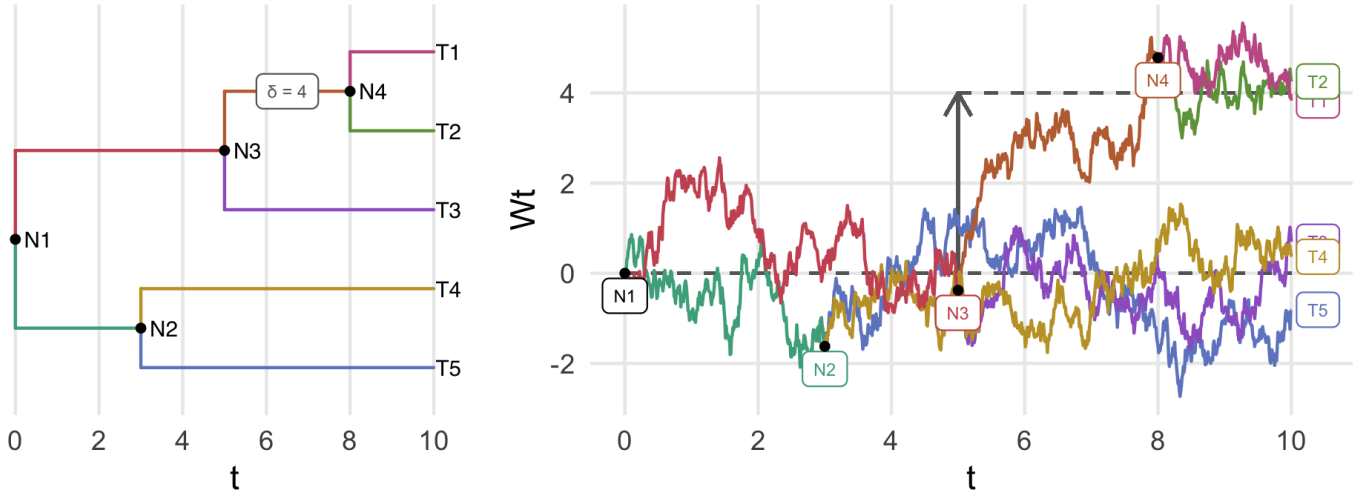


W_t is Gaussian with bounded variance and

$$W_t \xrightarrow[t\to\infty]{} \mathcal{N}\left(\beta_{\text{ou}}, \frac{\sigma_{\text{ou}}^2}{2\alpha_{\text{ou}}}\right).$$

OU process on a tree with shifts δ



Bastide Mariadassou, et al. [BMR17]

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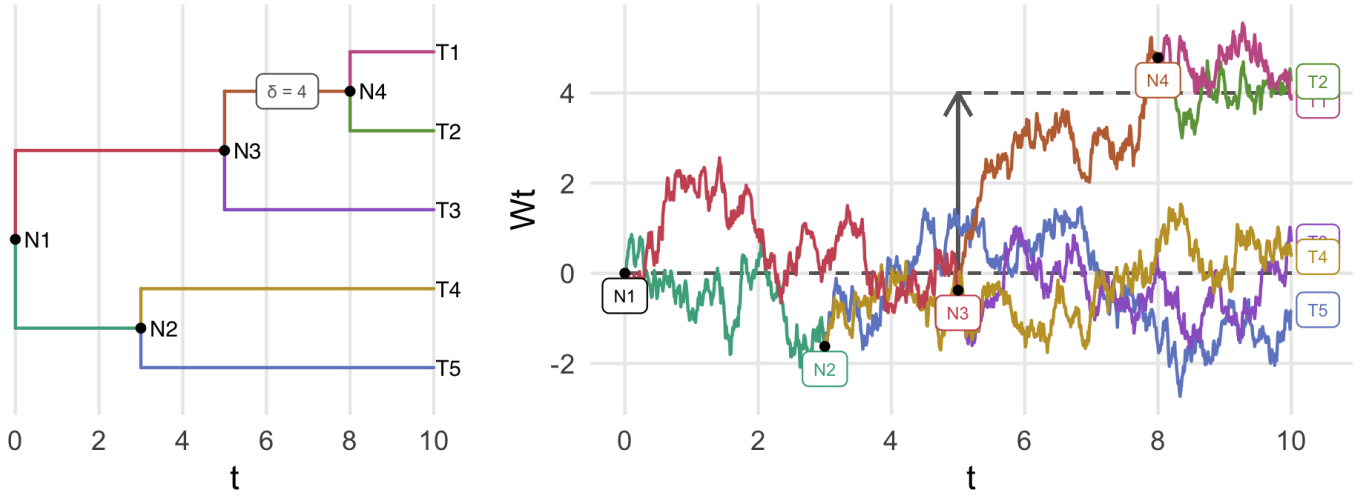

- On a branch, the process behaves like on $\mathbb{R}_+$.

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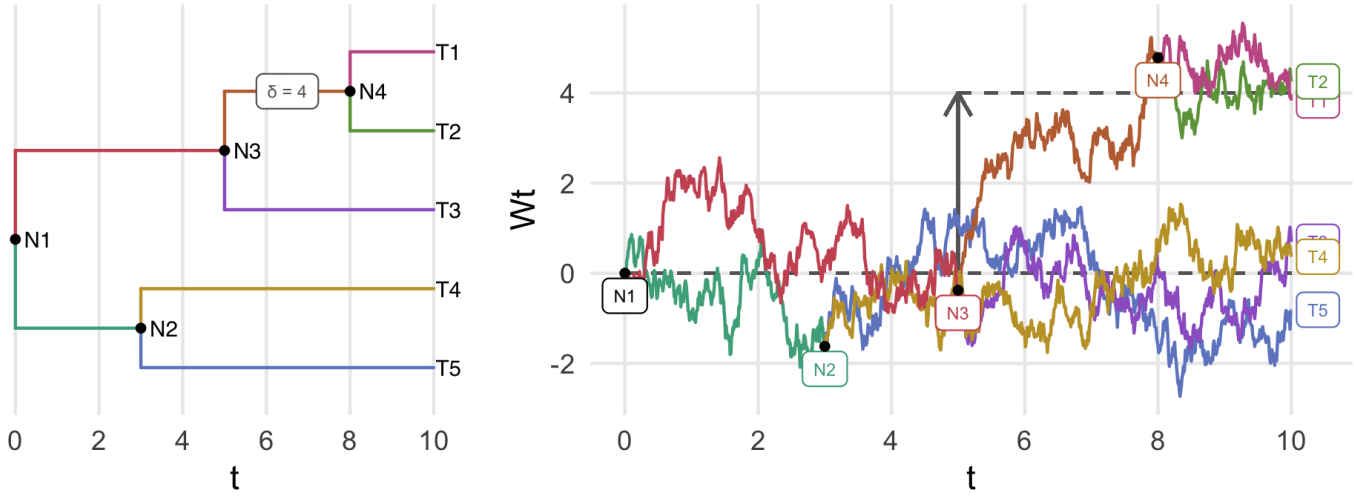

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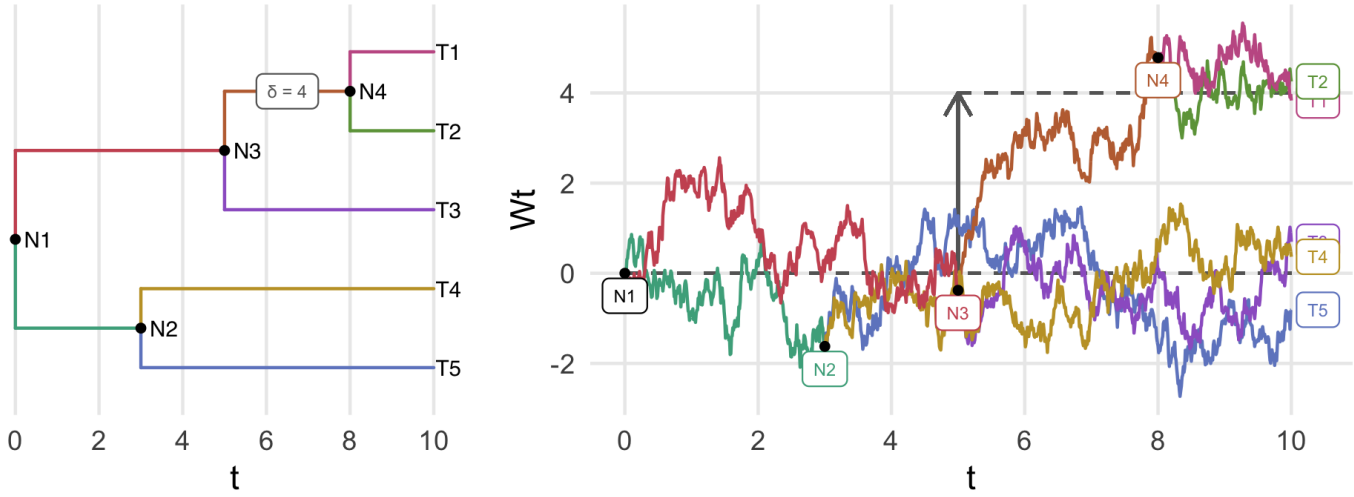
OU process on a tree with shifts δ



- On a branch, the process behaves like on $\mathbb{R}_+$.
- At each node, the process splits into two independent processes with the same initial value.
- The optimal value can shift at a node.

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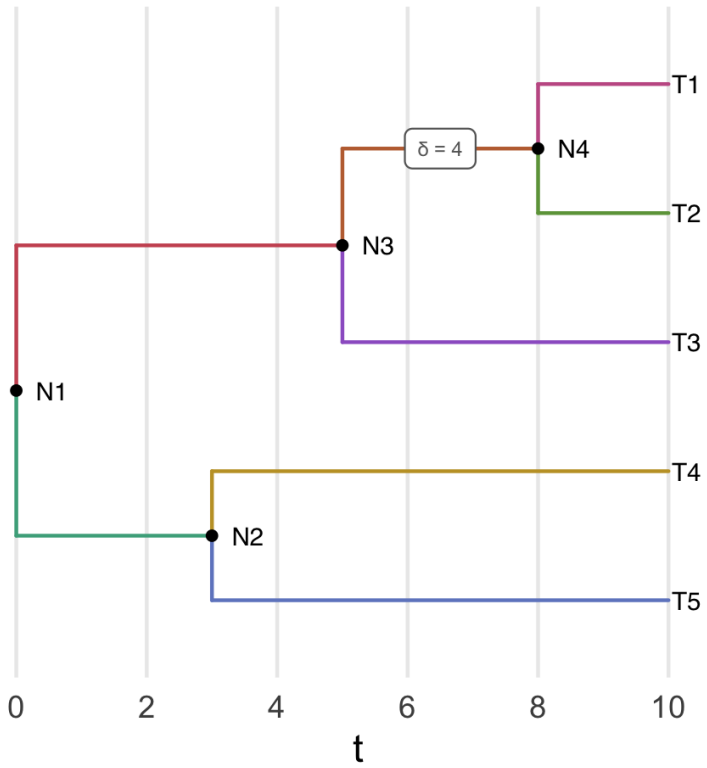
Incidence matrix and vector of shifts



$T = (\mathbb{1}_{\{i \in \mathrm{desc}(j)\}})_{ij} \in \{0,1\}^{m \times n}$ is the incidence matrix of the tree:

$$\begin{bmatrix} 1 & 0 & 1 & 1 & 1 & 0 & 0 & 0 & 0 \\ 1 & 0 & 1 & 1 & 0 & 1 & 0 & 0 & 0 \\ 1 & 0 & 1 & 0 & 0 & 0 & 1 & 0 & 0 \\ 1 & 1 & 0 & 0 & 0 & 0 & 0 & 1 & 0 \\ 1 & 1 & 0 & 0 & 0 & 0 & 0 & 0 & 1 \end{bmatrix}$$

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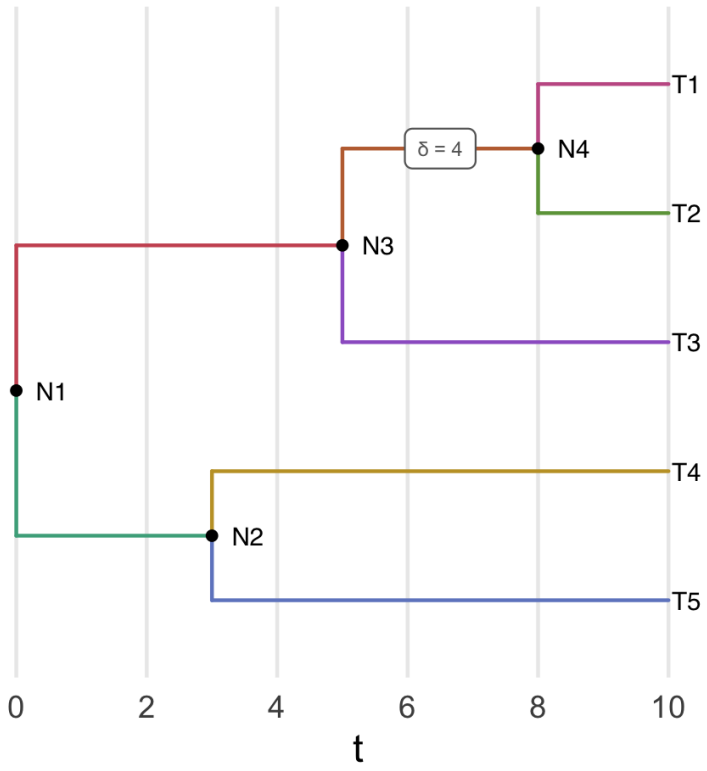

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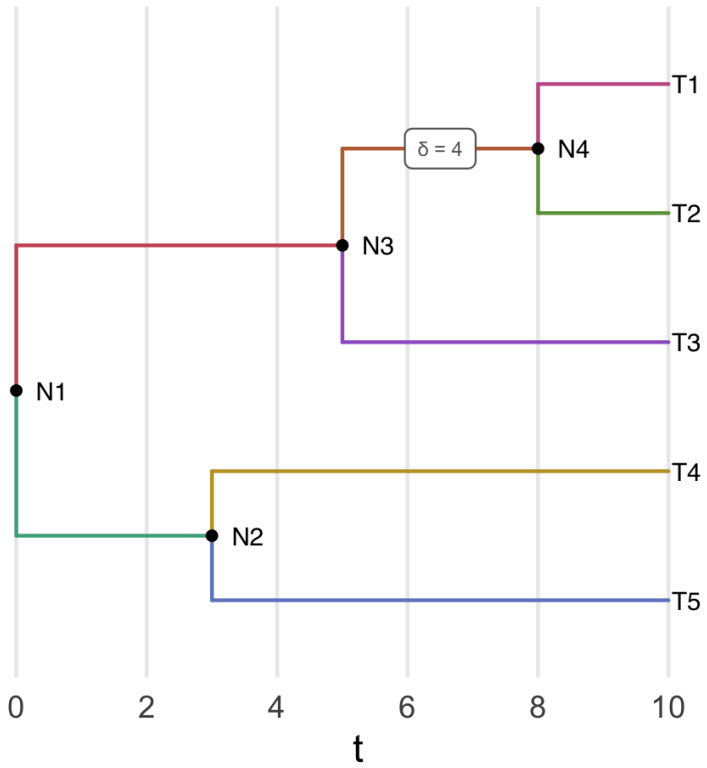
and δ the vector of shifts:

$$\begin{bmatrix} 0 & 0 & 0 & 4 & 0 & 0 & 0 & 0 & 0 \end{bmatrix}^T.$$

Incidence matrix and vector of shifts



$T = (\mathbb{1}_{\{i \in \mathrm{desc}(j)\}})_{ij} \in \{0,1\}^{m \times n}$ is the incidence matrix of the tree:

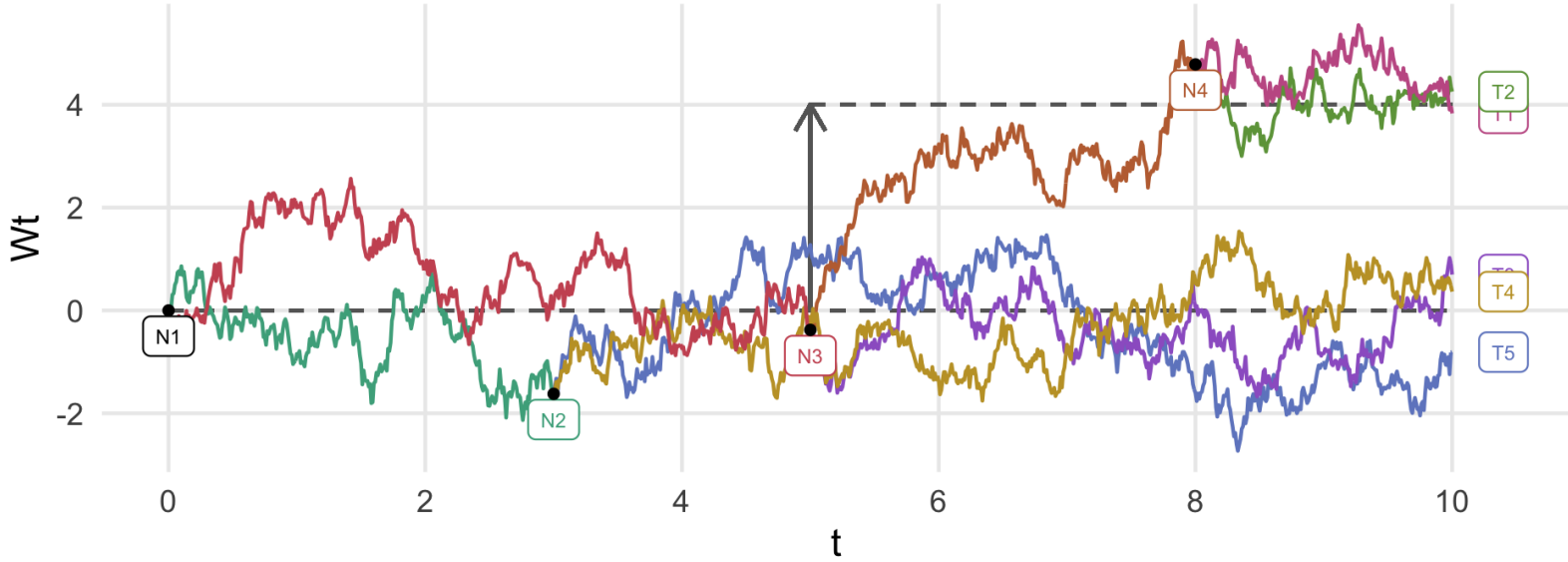
$$\begin{bmatrix} 1 & 0 & 1 & 1 & 1 & 0 & 0 & 0 & 0 \\ 1 & 0 & 1 & 1 & 0 & 1 & 0 & 0 & 0 \\ 1 & 0 & 1 & 0 & 0 & 0 & 1 & 0 & 0 \\ 1 & 1 & 0 & 0 & 0 & 0 & 0 & 1 & 0 \\ 1 & 1 & 0 & 0 & 0 & 0 & 0 & 0 & 1 \end{bmatrix}$$

and δ the vector of shifts:

$$\begin{bmatrix} 0 & 0 & 0 & 4 & 0 & 0 & 0 & 0 & 0 \end{bmatrix}^T.$$

The product $T\delta$ is the vector of optimal values on leaves.

Random variables on leaves



The random variables on leaves are jointly Gaussian $\mathcal{N}_m(T\delta, \Sigma)$ with

$$\Sigma_{i,j} = \frac{\sigma^2_{\text{ou}}}{2\alpha_{\text{ou}}}\left(1 - e^{-2\alpha_{\text{ou}} t_{i,j}}\right) \times e^{-\alpha_{\text{ou}} d_{i,j}}.$$

First assumption

z is the realization of an OU on a tree with shifts δ.

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$\mathfrak{z}$ is the realization of an OU on a tree with shifts δ.

Then,

$$\mathfrak{z} \sim \mathcal{N}_m(\mu, \Sigma)$$

with $\mu = T\delta$ and Σ depends on α_{ou} and σ_{ou} by

$$\Sigma_{i,j} = \frac{\sigma^2_{\text{ou}}}{2\alpha_{\text{ou}}}\left(e^{-\alpha_{\text{ou}} d_{i,j}} - e^{-2\alpha_{\text{ou}} h}\right)$$

for a tree with total height h.

Second assumption

For a taxa i,

- if $\mathcal{H}_i \in \mathbb{H}_0$, $\mathfrak{p}_i \sim \mathcal{U}([0,1])$ so $\mathfrak{z}_i \sim \mathcal{N}(0,1)$,
- if $\mathcal{H}_i \notin \mathbb{H}_0$, $\mathfrak{p}_i \preccurlyeq \mathcal{U}([0,1])$ so $\mathfrak{z}_i \sim \mathcal{N}(\mu_i, 1)$ with $\mu_i < 0$.

McLachlan and Peel [MP04]

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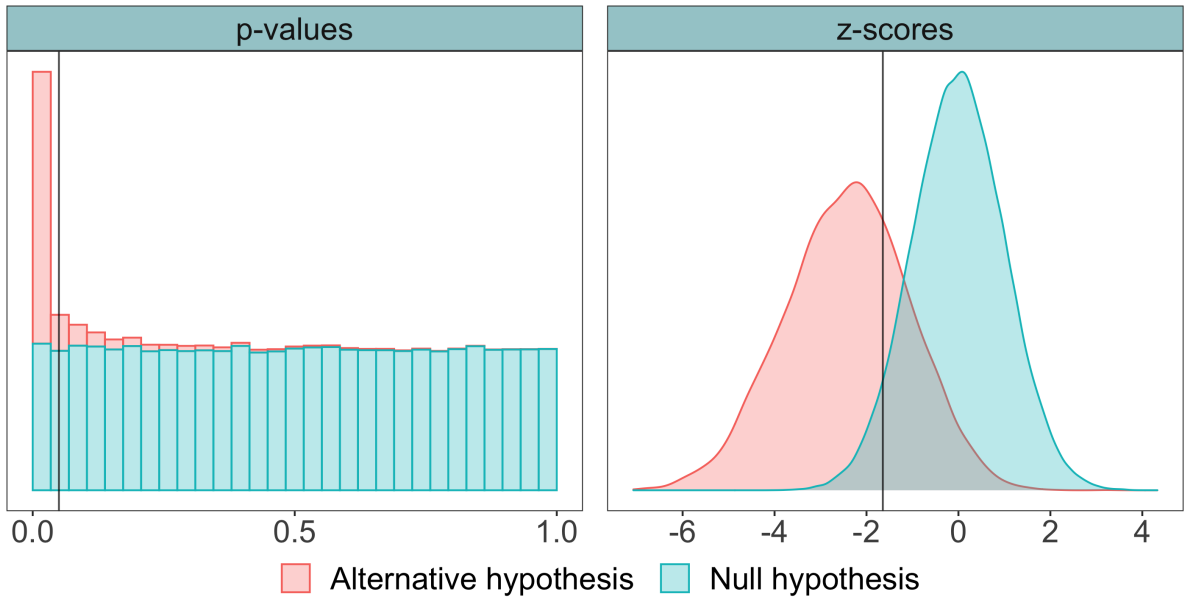

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Then,

$$\mathfrak{z} \sim \mathcal{N}_m\left(\mu \in \mathbb{R}_-^m, \Sigma\right).$$

One will find **differentially abundant** taxa by finding the **non-zero elements** of μ.

This impose $\Sigma_{i,i} = 1$ so $\sigma_{\text{ou}} = \frac{2\alpha_{\text{ou}}}{1-e^{-2\alpha_{\text{ou}}h}}$.

McLachlan and Peel [MP04]

Estimation of μ

With Σ known, a naive ML estimator gives

$$\hat{\mu} = \underset{\mu \in \mathbb{R}^m}{\operatorname{argmin}} \|\mathfrak{z} - \mu\|^2_{\Sigma^{-1},2}.$$

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To add hierarchically coherent sparsity in our estimate

$$\hat{\delta} = \underset{\delta \in \mathbb{R}^n / T\delta \in \mathbb{R}_-^m}{\operatorname{argmin}} \|\mathfrak{z} - T\delta\|^2_{\Sigma^{-1},2} + \lambda\|\delta\|_1.$$

Estimation of μ (bis)

By Cholesky decomposition, $\Sigma^{-1} = R^T R$

$$\begin{aligned}
\|z - T\delta\|^2_{\Sigma^{-1},2} &= (z - T\delta)^T \Sigma^{-1} (z - T\delta) \\
&= (z - T\delta)^T R^T R (z - T\delta) \\
&= (Rz - RT\delta)^T (Rz - RT\delta) \\
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with $y = R\mathfrak{z}$ and $X = RT$.

Finally, we fall back to a constrained lasso problem:

$$\hat{\delta} = \underset{\delta \in \mathbb{R}^n / T\delta \in \mathbb{R}^m_-}{\operatorname{argmin}} \|y - X\delta\|_2^2 + \lambda \|\delta\|_1.$$

Numerical resolution

The previous problem could be numerically solved by the shooting algorithm, **iterating unidirectional updates** form the associated problem:

$$\begin{cases} \underset{\theta \in \mathbb{R}}{\operatorname{argmin}}\, h(\theta) = \dfrac{1}{2}\|y - z - x\theta\|_2^2 + \lambda|\theta| \\ \text{s.t. } u + v\theta \leq 0. \end{cases}$$

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But Σ and λ are not yet known.

Fu [98]

Estimation of Σ and choice of λ

$\widehat{\Sigma} = \left(\frac{e^{-\hat{\alpha}_{\text{ou}} d_{ij}} - e^{-2\hat{\alpha}_{\text{ou}} h}}{1 - e^{-2\hat{\alpha}_{\text{ou}} h}} \right)_{i,j}$ is determined by $\hat{\alpha}_{\text{ou}}$.

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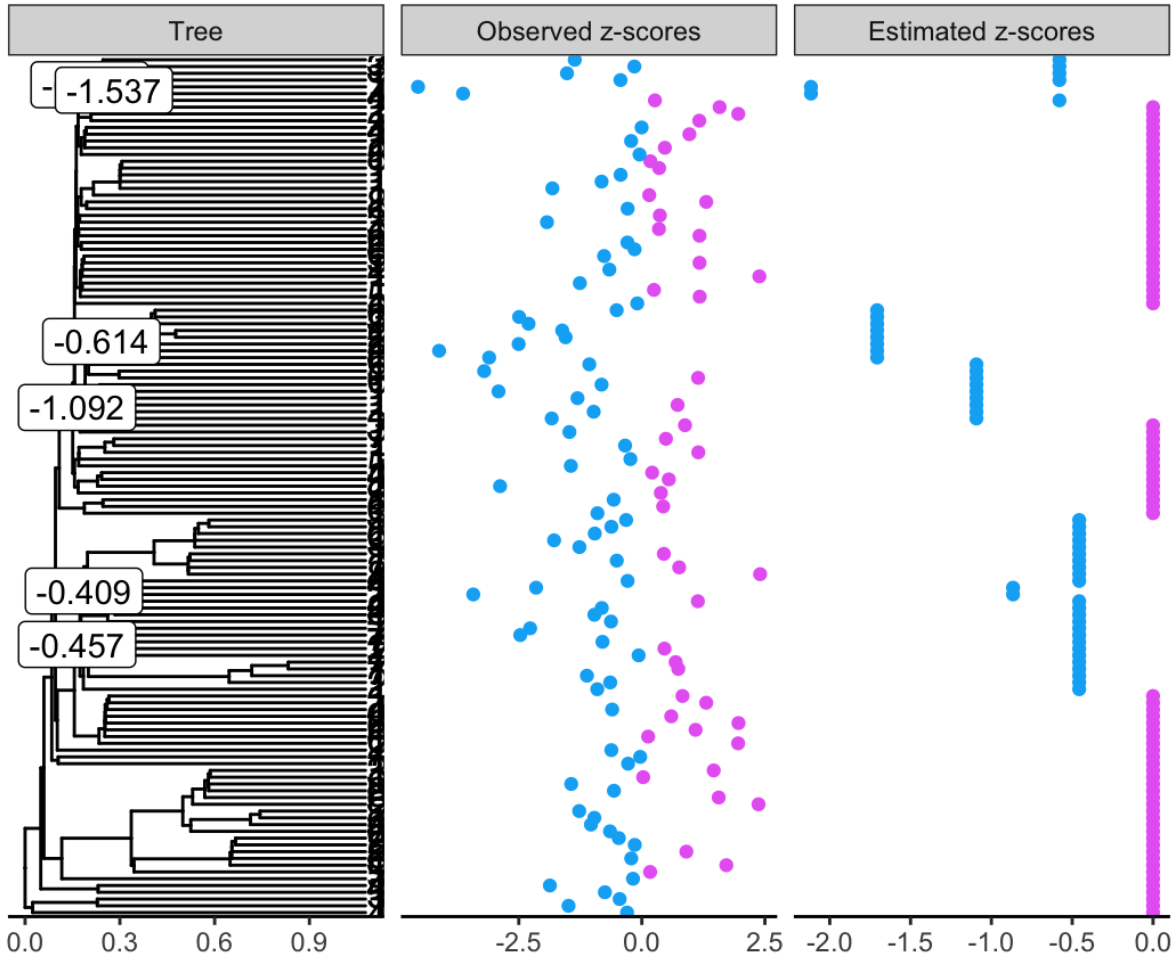
The optimal $(\alpha_{\text{ou}}, \lambda)$, is chosen on a bidimensional grid as the argmin of the BIC

$$\|\mathfrak{z} - T\delta_{\alpha_{\text{ou}},\lambda}\|^2_{\Sigma(\alpha_{\text{ou}})^{-1},2} + \log|\Sigma(\alpha_{\text{ou}})| + \|\delta_{\alpha_{\text{ou}},\lambda}\|_0 \log m.$$

Effect of hierarchical smoothing



Find non zero values

Estimation from lasso provides biased estimators without confidence intervals.

We need confidence intervals on $\hat{\delta}$ and $\hat{\mu}$.

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Use of a debiasing procedure

- **score system (ss) [ZZ14],**
- column-wise inverse (ci) [JM13; JM14].

Scaled lasso

The debiasing procedure requires a **initial joint estimator** of $\delta^{(\text{init})}$ and its associated standard error σ.

This can be done with a scaled lasso

$$\left(\hat{\delta}^{(\text{init})}, \hat{\sigma}\right) = \underset{\delta,\sigma}{\text{argmin}} \frac{\|y - X\delta\|_2^2}{2\sigma n} + \frac{\sigma}{2} + \lambda\|\delta\|_1.$$

Sun and Zhang [SZ12]

Score system

The **score system** $S \in \mathbb{R}^{n \times p}$ associated with X and y where s_j is the residual of the (classical) lasso regression of y against X_{-j}:

$$s_j = y - \delta_{\text{lasso}}^{-j} X_{-j}.$$

S is as **weak orthogonalisation** of X.

Debiasing procedure

From the initial estimator $\hat{\delta}_j^{(\text{init})}$ of the scaled lasso, one can do a **one-step correction**

$$\hat{\delta}_j = \hat{\delta}_j^{(\text{init})} + \frac{\langle s_j, y - X\hat{\delta}^{(\text{init})} \rangle}{\langle s_j, x_j \rangle}.$$

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Asymptotically, $\hat{\delta} \sim \mathcal{N}_n(\delta, V)$ with

$$v_{i,j} = \hat{\sigma} \frac{\langle s_i, s_j \rangle}{\langle s_i, x_i \rangle \langle s_j, x_j \rangle}.$$

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Then the **bilateral confidence interval** for a shift $\hat{\delta}_j$ is

$$\left[\hat{\delta}_j \pm \phi^{-1}\left(1 - \frac{\alpha}{2}\right) \sqrt{v_{j,j}} \right].$$

Smoothed p-values

To have the **unilateral hierarchically smoothed p-values** $\mathfrak{p}^{\mathrm{h}}$, we need to propagate the shifts with the incidence matrix T

$$\mathfrak{p}_i^{\mathrm{h}} = \Phi\left(\frac{t_{i.}^T \hat{\delta}}{\left(t_{i.}^T V t_{i.}\right)^{1/2}}\right)$$

with $t_{i.}$ the i^{th} row of T.

Multiple testing correction

Let $\mathrm{t}_i = \frac{t_{i.}^T \hat{\delta}}{\left(t_{i.}^T V t_{i.}\right)^{1/2}}$ be the t-scores, $t_{\max} = \sqrt{2\log m - 2\log\log m}$ and

$$t^\star = \inf\left\{0 \leq t \leq t_{\max} : \underbrace{\frac{2m(1-\Phi(t))}{R(t) \vee 1}}_{\widehat{\mathrm{FDR}}(t)} \leq \alpha\right\}$$

with $R(t) = \sum_{i=1}^m \mathbb{1}_{\{\mathrm{t}_i \leq -t\}}$.

Javanmard Javadi, et al. [JJ19]

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One reject if $\mathrm{t}_i \leq -t^\star$ and the associated **hierarchical q-values** are

$$\mathrm{q}_i^{\mathrm{h}} = \frac{\mathrm{p}_i^{\mathrm{h}} \alpha}{\Phi(-t^\star)}.$$

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zazou overview

zazou is a recipe with four steps:

- a modeling of z-scores by an Ornstein-Uhlenbeck process on a tree with shifts,

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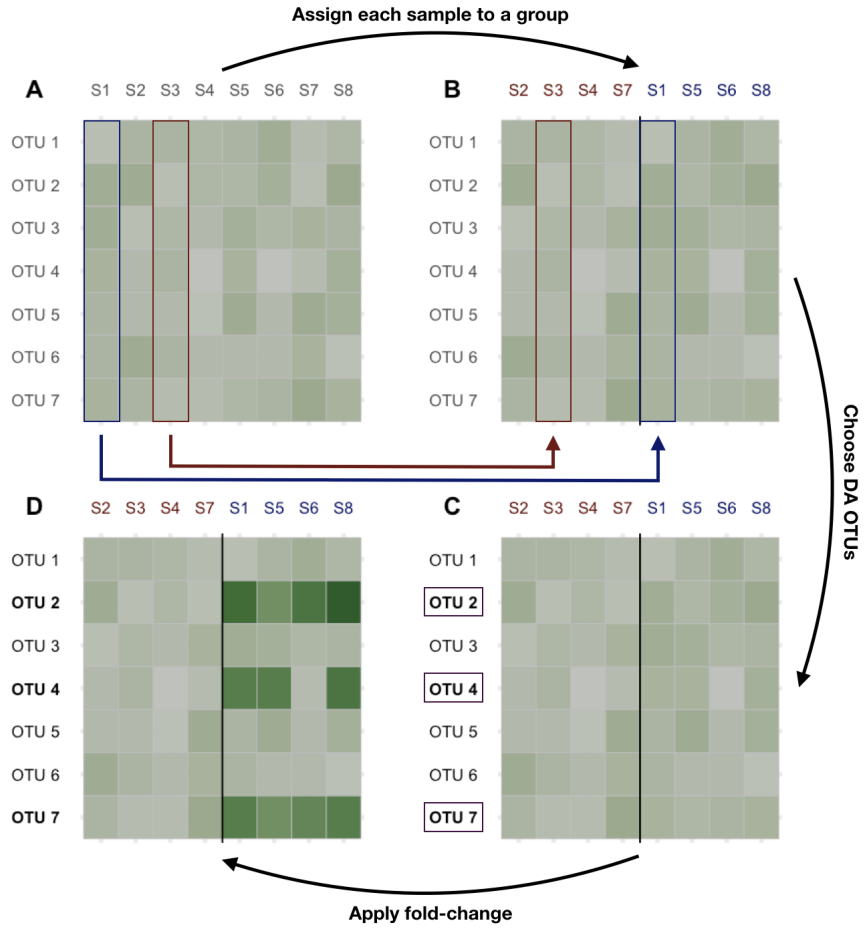
- a debiasing procedure for the scaled lasso,
- a debiased lasso designed multiple testing procedure.

Evaluation of zazou

Simulations



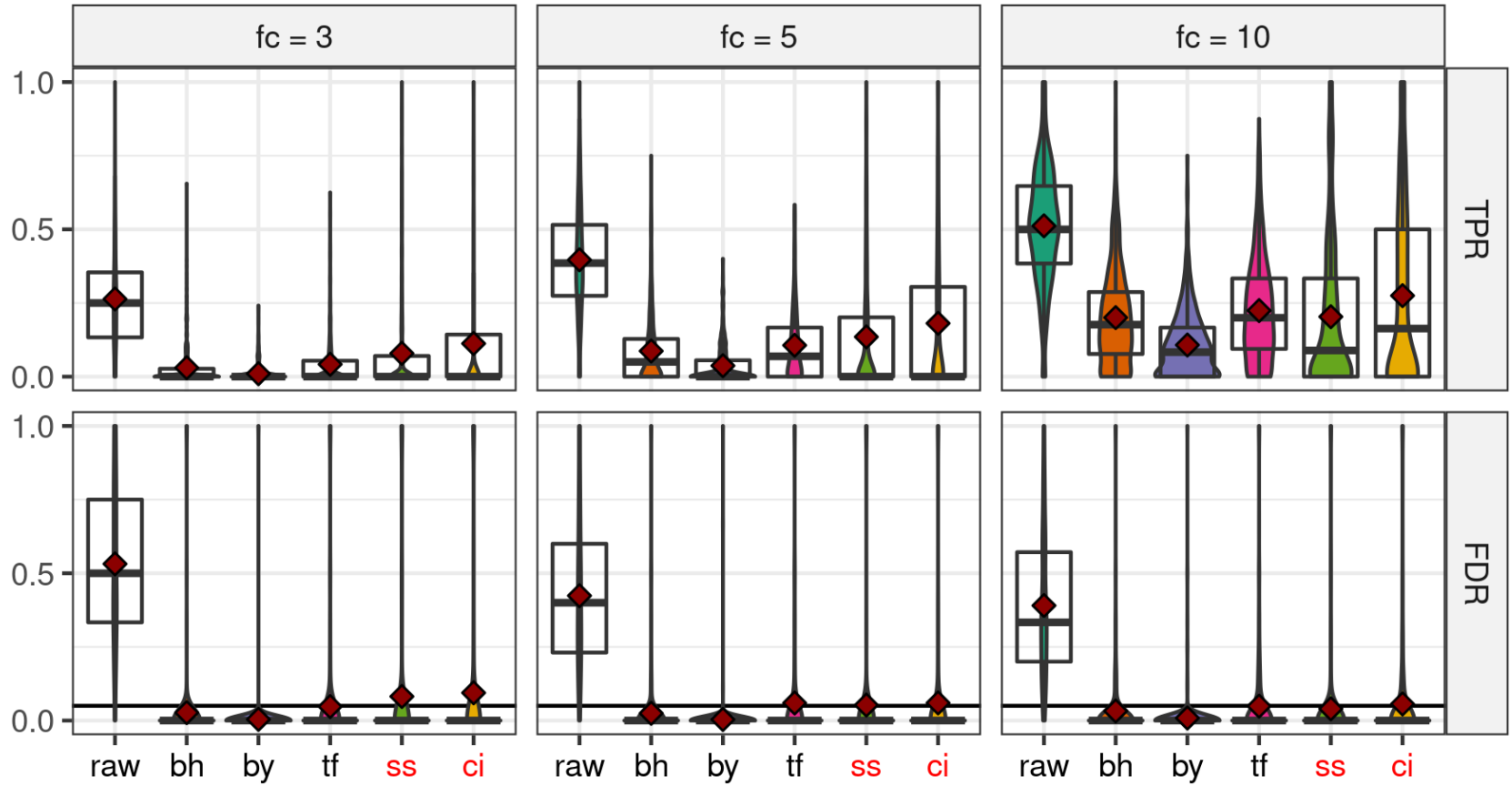
The choice of differentially abundant taxa is done in a hierarchically consistent manner.

- $m = 127, p = 49$ split into two groups.
- Fold-changes of 3, 5 and 10.
- 5 estimated proportions of π_1.
- 100 replicates for each parameters.

Bichat Plassais, et al. [Bic+20]

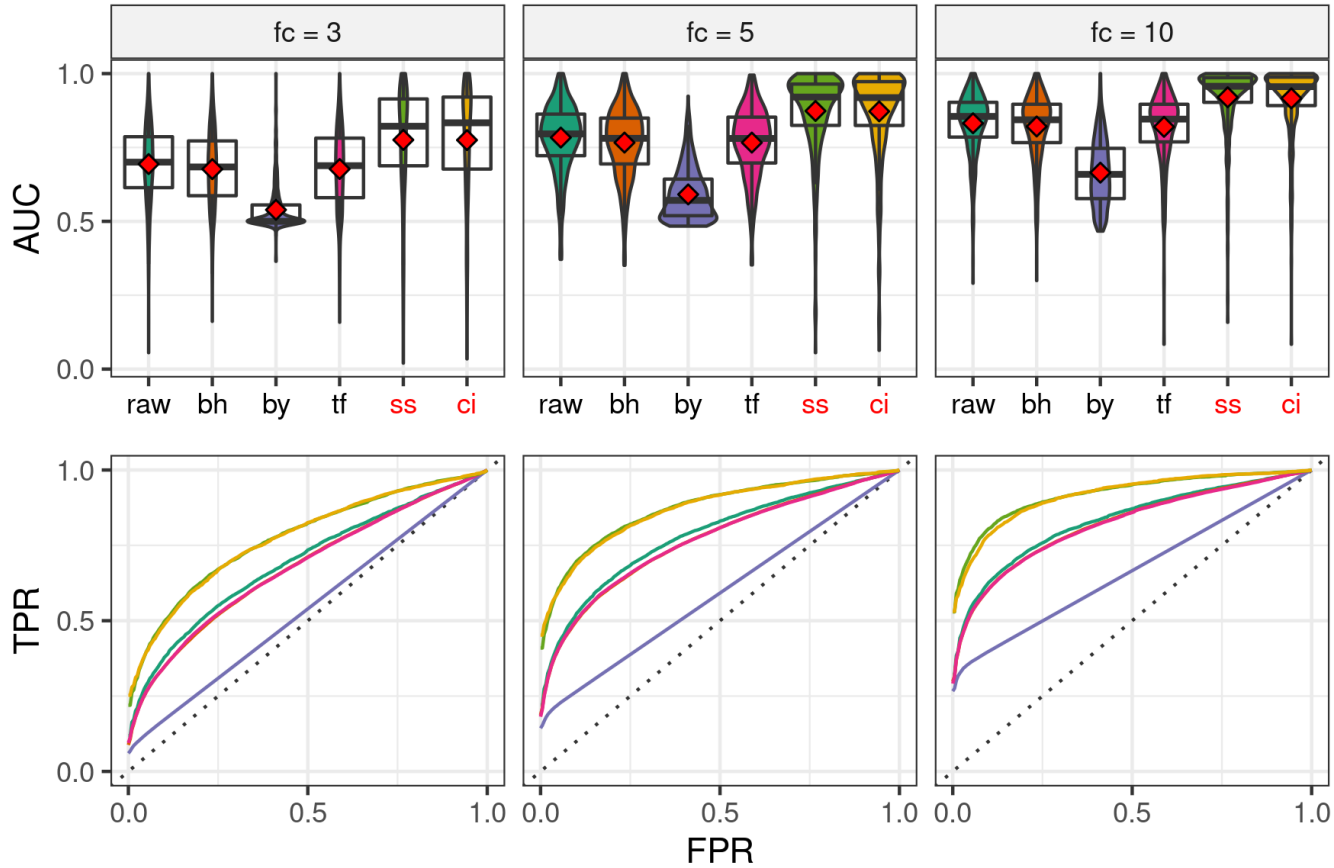
Results

zazou increases the TPR but does not always control the FDR.



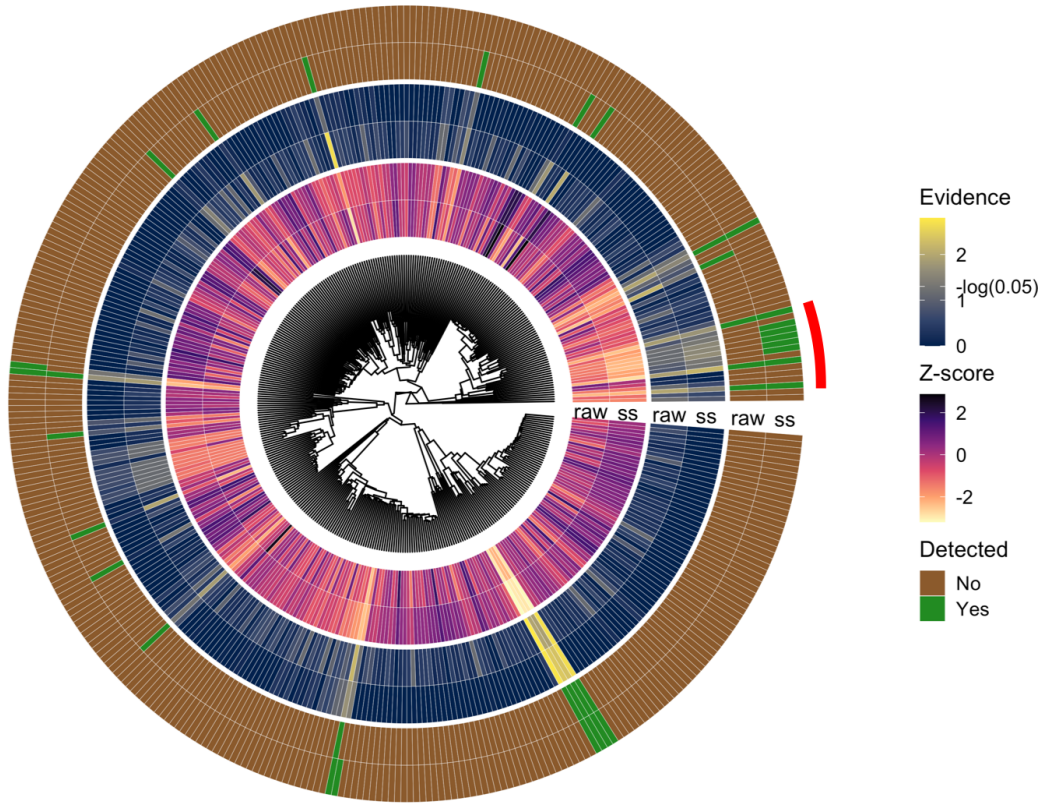
Results

zazou has better AUC and ROC curves.



Association with age

zazou identifies phylogenetically coherent taxa.



Brito Yilmaz, et al. [Bri+16]

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- Articles published in Frontiers in Microbiology and submitted in Statistics and Computing.

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- Use hierarchical information during testing step, and not only correction step.
- Use the framework of prediction instead of association.

Thanks!

Manuscript

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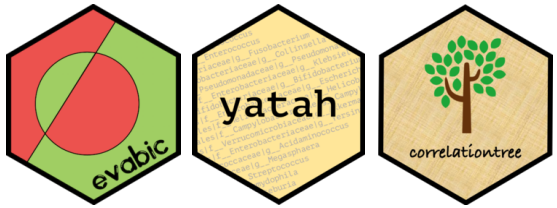
R packages



evabic evaluates the performance of binary classifiers. It can compute compute 19 different measures with tidy outputs.

yatah provides functions to manage taxonomy when lineages are described like `k__Bacteria|p__Proteobacteria|c__Gammaproteobacteria`.

correlationtree computes correlation trees.

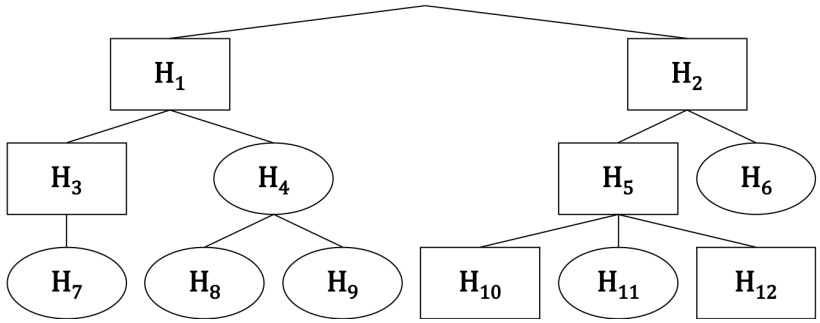
zazou implements the zazou procedure.

hadamardown contains the Université Paris-Saclay PhD manuscript template for bookdown.

Hierarchical FDR

This procedure inscreases statistical power by lessening the number of test to do with a descending method:

- test the family $\mathcal{T}_0$,
- if node t is rejected, test $\mathcal{T}_t = \{H_i \mid \mathrm{Par}(i) = t\}$ with a BH procedure at level α.



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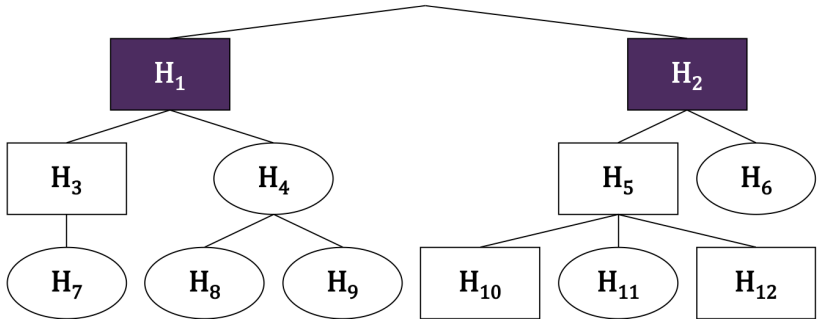

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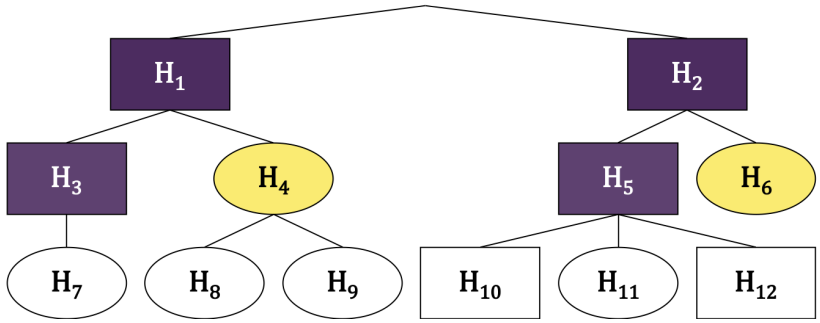

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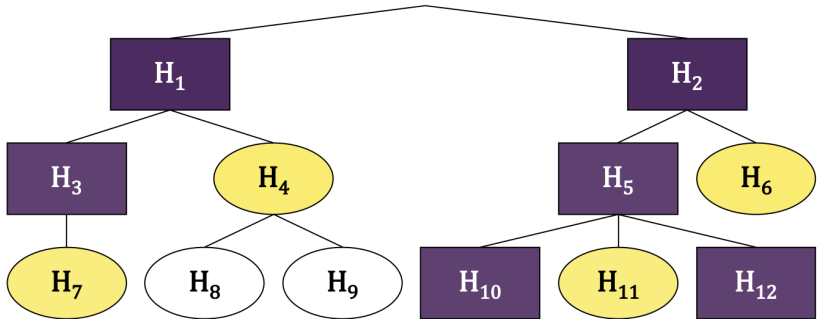

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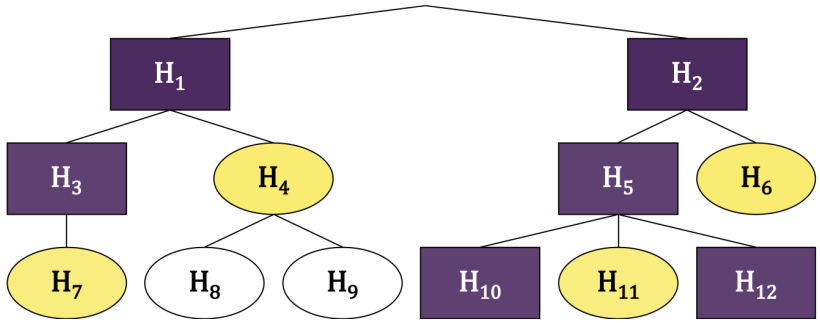
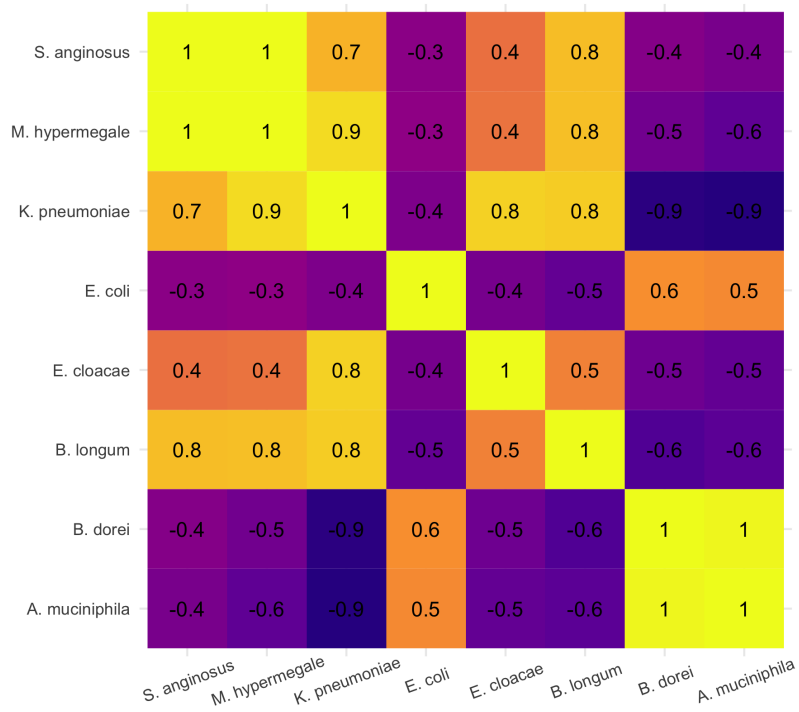


The FDR is controlled at level $\alpha' = 1.44 \times \alpha \times \frac{\#\text{discoveries} + \#\text{families tested}}{\#\text{discoveries} + 1}$.

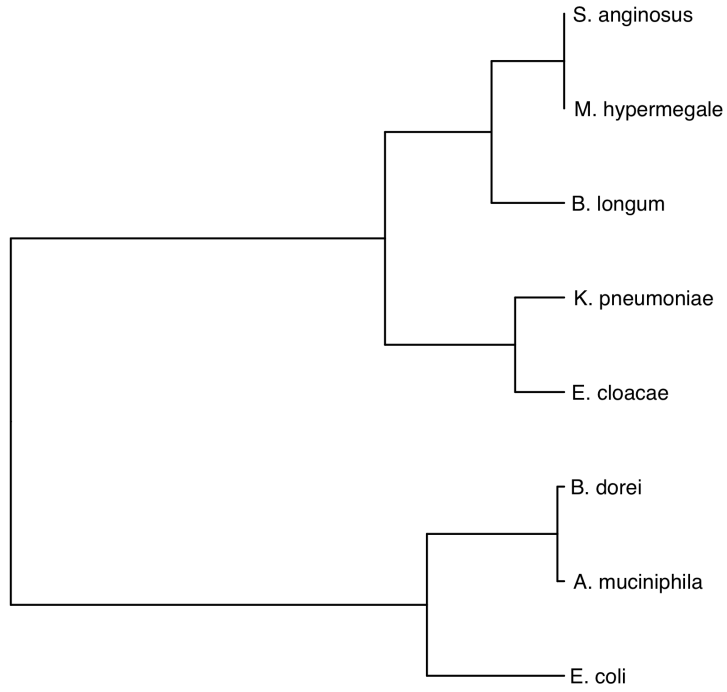
Yekutieli [Yek08]; Sankaran and Holmes [SH14]

Correlation tree

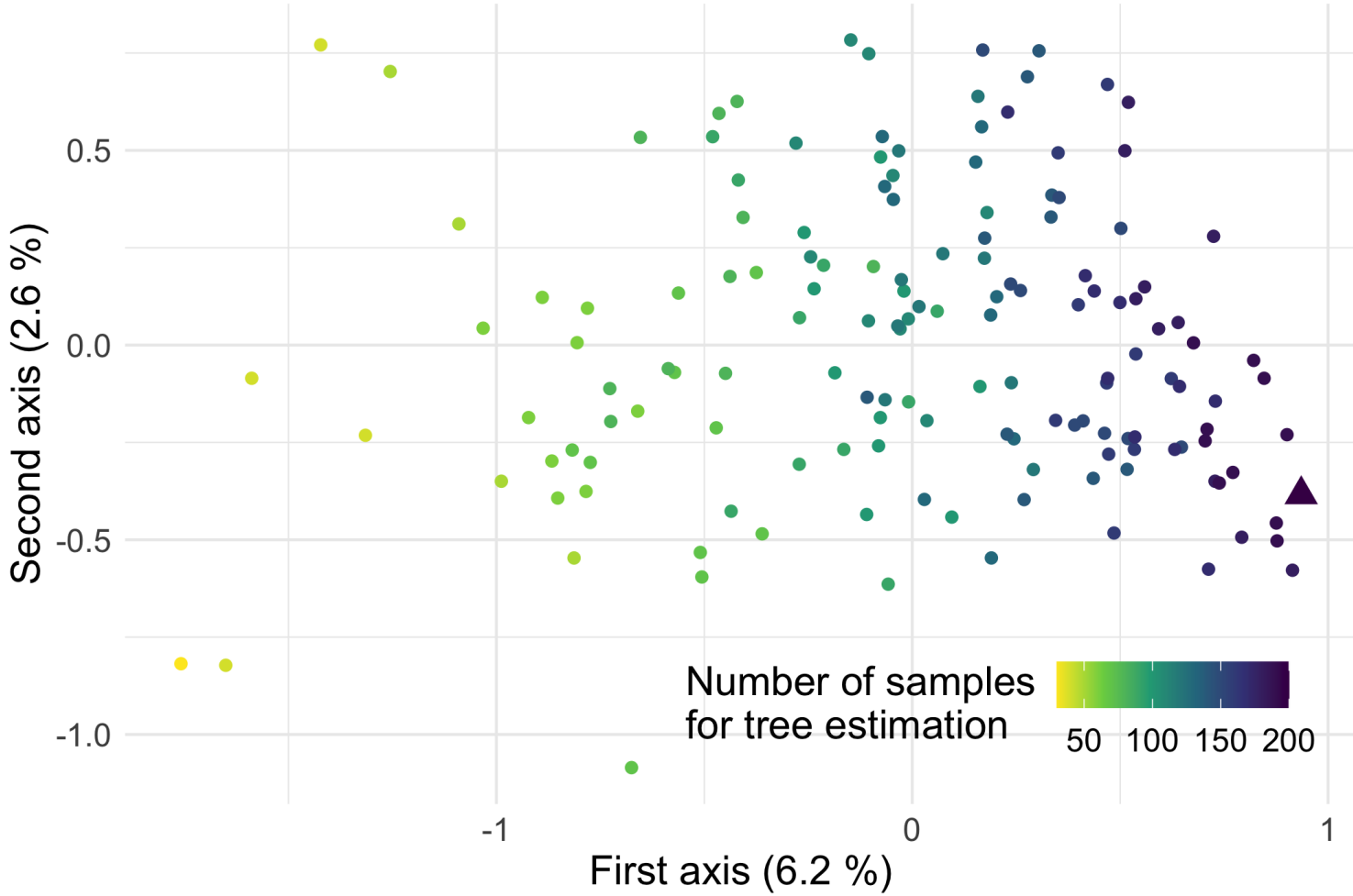
Matrix of pairwise correlation C



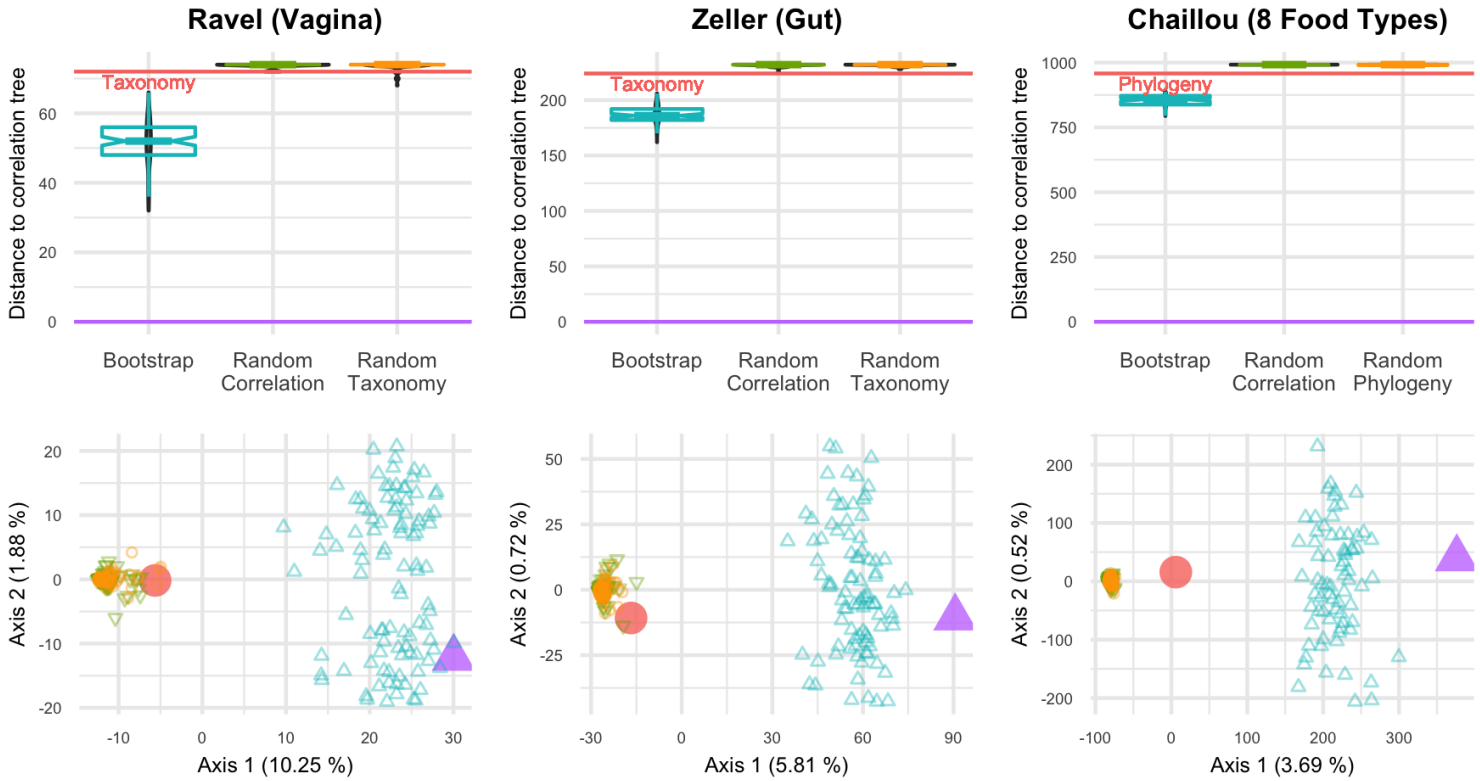
Hierarchical clustering on $1 - C$



Convergence to the correlation tree



With Robinson-Foulds distance



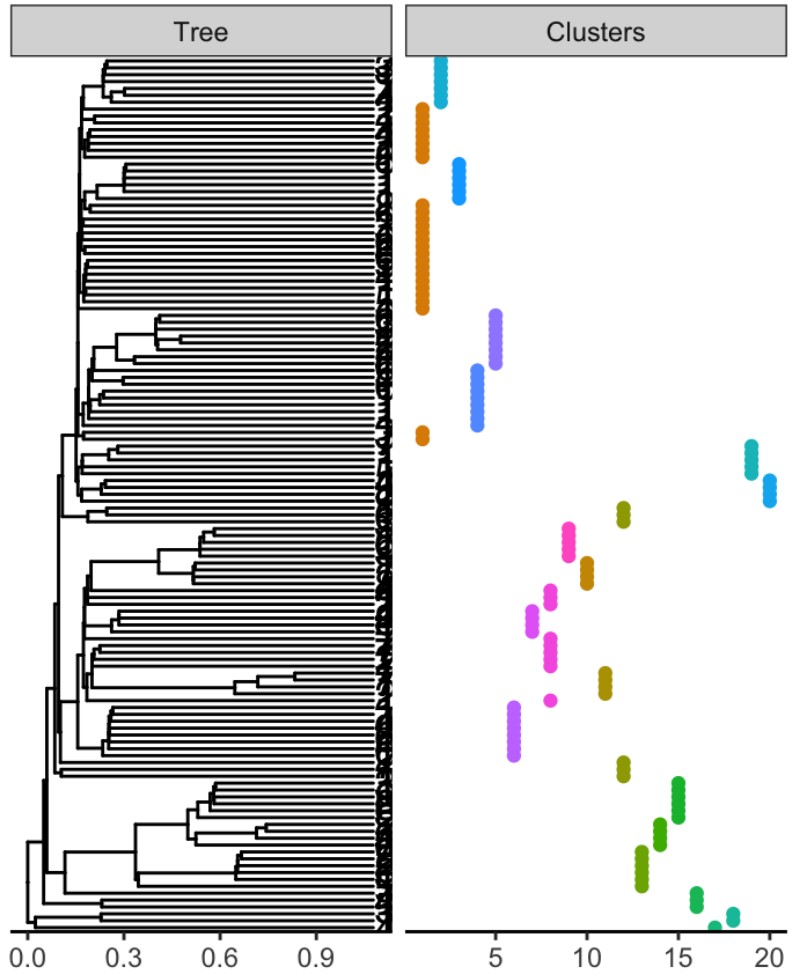
Robinson and Foulds [RF81]

Hierarchically consistent taxa

> The choice of differentially abundant taxa is done in a hierarchically consistent manner.

A partitioning around medoids (PAM) algorithm on the patristic distances matrix $\left(d_{i,j}\right)_{i,j}$ is use for this purpose.

1 to 5 clusters among 20 are selected to be differentially abundant.

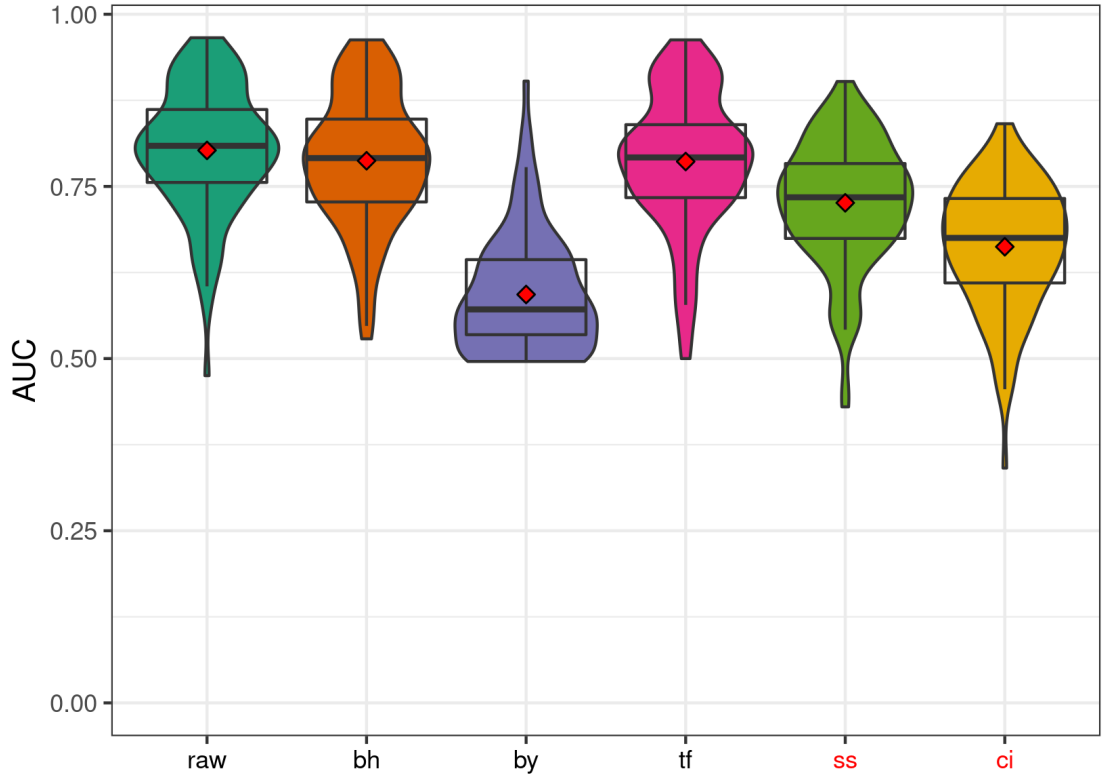


Quantitative results about FDP

(in %)	FDR			P(FDP > 5%)		
method	fc = 3	fc = 5	fc = 10	fc = 3	fc = 5	fc = 10
bh	2.69	2.46	3.23	4.40	7.20	12.20
by	0.40	0.36	0.85	0.40	0.60	2.20
tf	4.75	5.96	4.90	8.72	14.58	18.06
ss	8.17	5.26	3.99	12.40	8.40	8.80
ci	9.41	5.98	5.63	14.80	12.60	18.60

Negative simulations

When differentially abundant taxa are chosen uniformly.



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université PARIS-SACLAY

Discovering multi-scale metagenomic signatures through hierarchical organization of species

PhD defense

Antoine BICHAT
LaMME – Enterome
December 9, 2020

C. Ambroise

M. Mariadassou

J. Plassais

F. Strozzi

université PARIS-SACLAY

Laboratoire de Mathématiques et Modélisation d'Évry LaMME

MaIAGE

enterome

Context

Microbiota

Ecological community of microorganisms that reside in an environmental niche.

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Ecological community of microorganisms that reside in an environmental niche.

For human gut

- 10^{14} bacterial cells in one gut...
- ... weighting $2\ kg$.
- More than 1500 different species.
- More than 10 millions unique genes.
- Helpful for nutrient absorption and anti inflammatory properties.

Ley Peterson, et al. [LPG06]; Flint Scott, et al. [Fli+12]; Canani Di Costanzo, et al. [Can+11]

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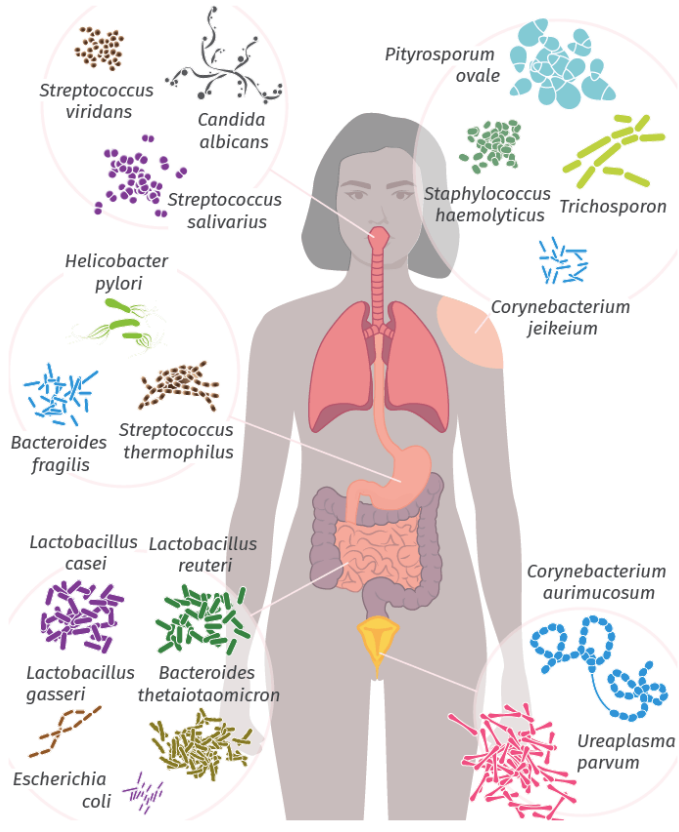

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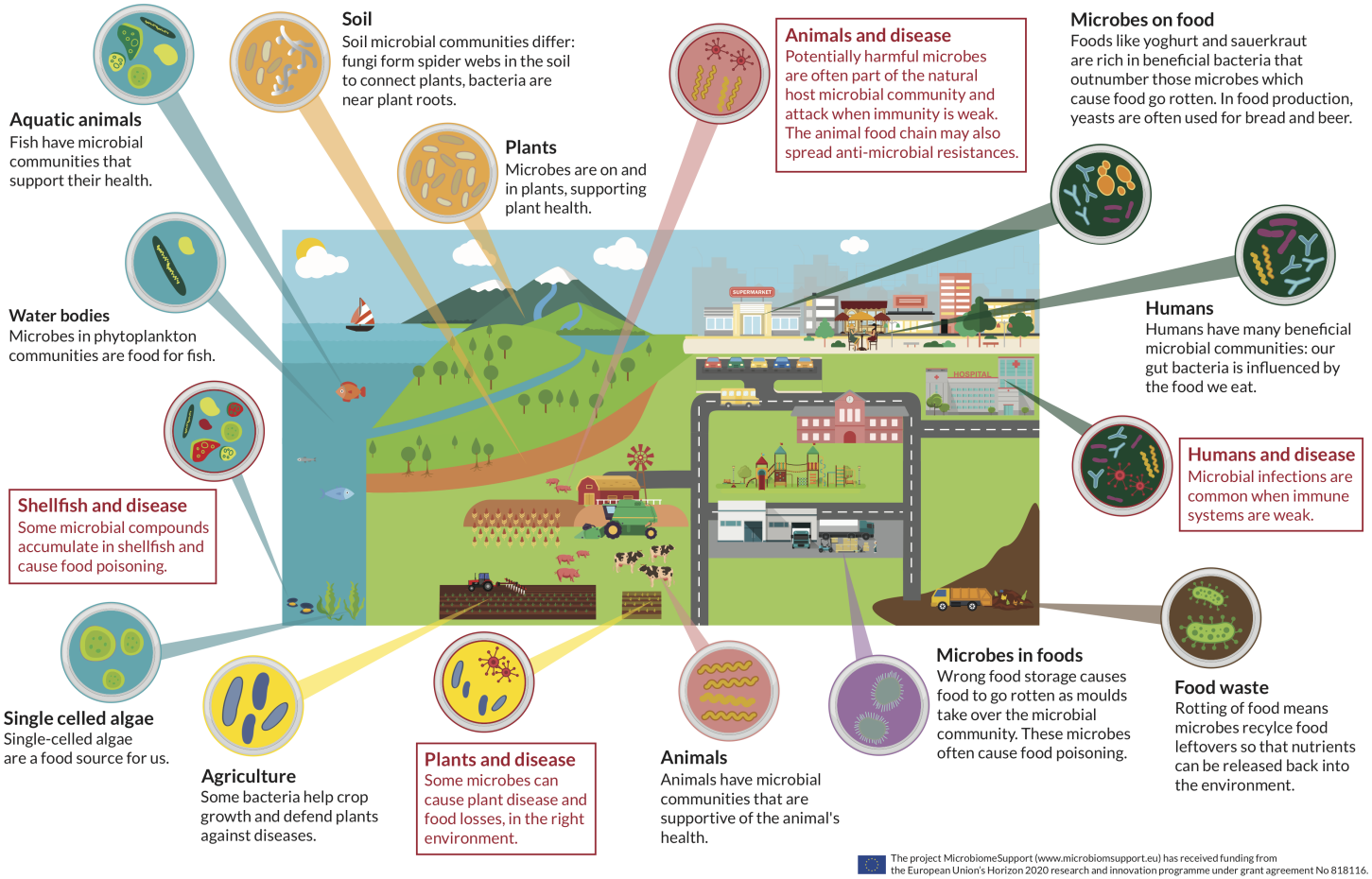
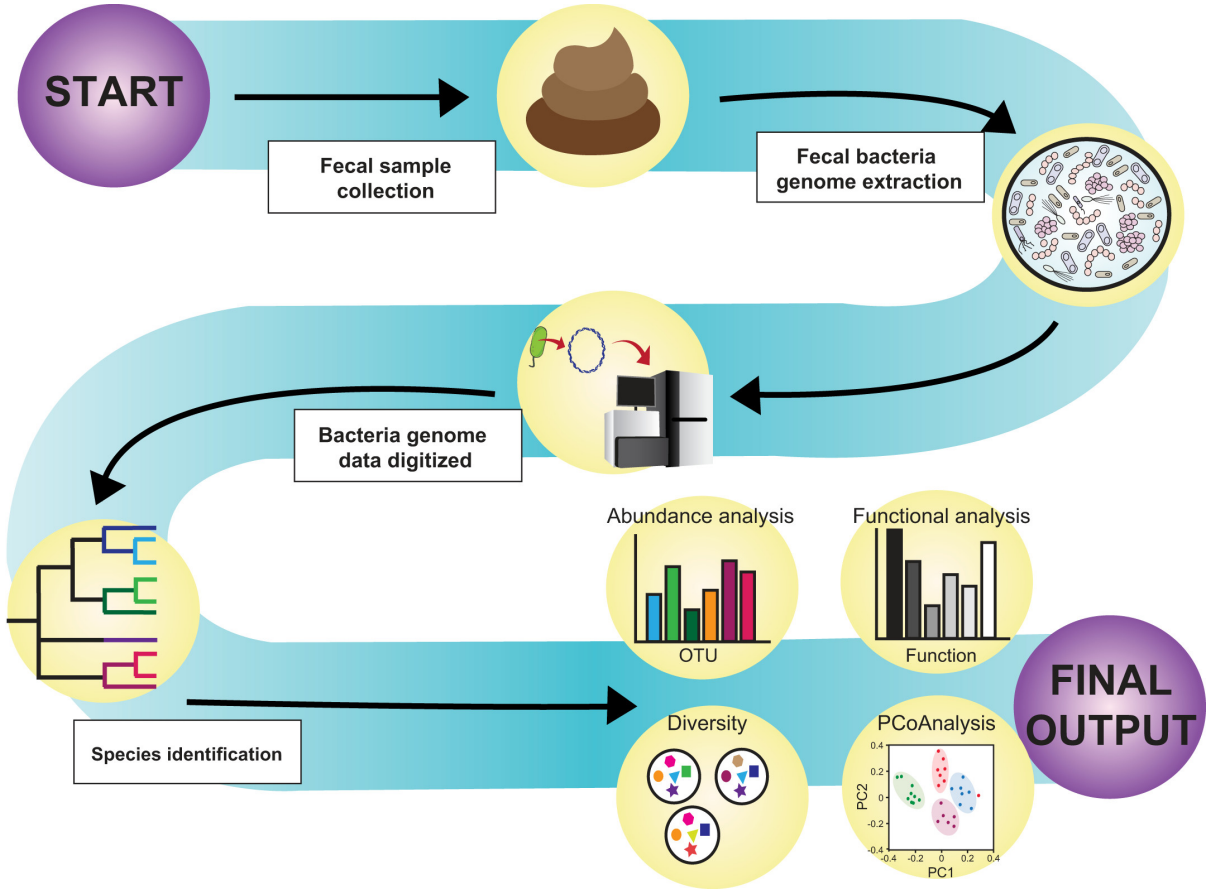
Microbiota everywhere



The project MicrobiomeSupport (www.microbiomsupport.eu) has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 818116.

Sequencing



Cryan O'Riordan, et al. [Cry+19]

Abundance table

- Matrix with m taxa and p samples.
- Count or compositional data, with inflation in zero.
- Correlation between abundances.

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Bacteroides dorei	89893	2567192	648639	0	0	8498
Bifidobacterium longum	376119	0	30671	0	1292193	1830318
Enterobacter cloacae	756064	12234	142652	2186	238175	535786
Escherichia coli	256424	5551041	9905179	76052	70234	79805
Klebsiella pneumoniae	1057187	0	515407	0	887678	1620535
Megamonas hypermegale	0	0	0	0	0	27317
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Brito Yilmaz, et al. [Bri+16]

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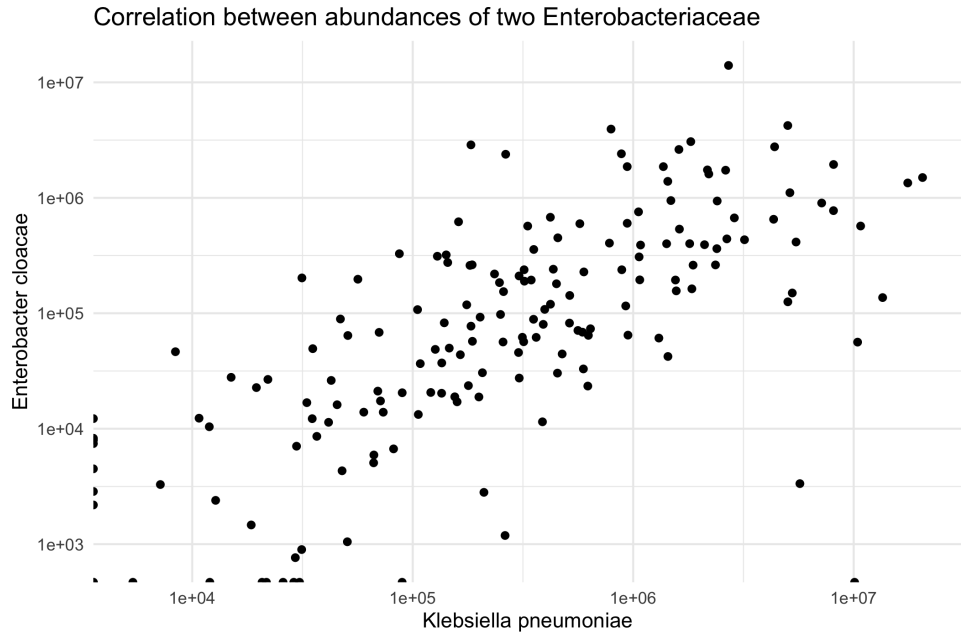

Brito Yilmaz, et al. [Bri+16]

Phylogeny

- Tree with m leaves which describes the evolutionary history of the taxa.

Brito Yilmaz, et al. [Bri+16]

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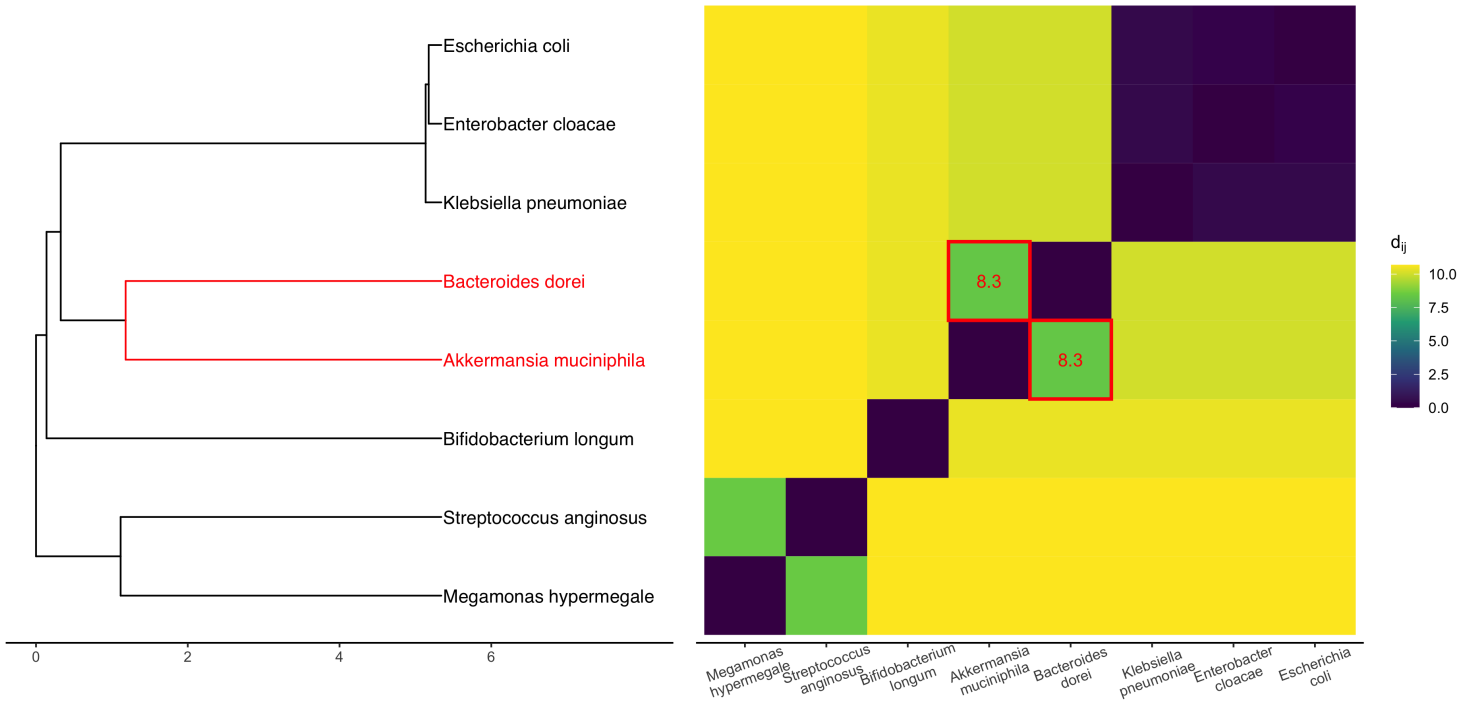
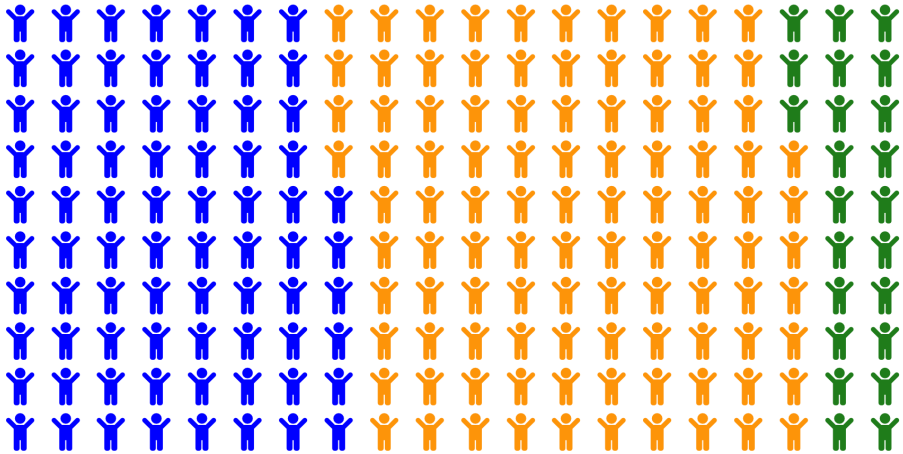


Brito Yilmaz, et al. [Bri+16]

Differential abundance studies



Used to find **associations** between microbiota and

- diet [Dav+14],
- birth mode [Bok+16],
- age [Yat+12],
- pet owning [Kat+20],
- tobacco [Ops+16],
- antibiotics [Pal+18],
- Crohn's disease [Mor+12],
- cirrhosis [Qin+14]
- schizophrenia [Zhe+19]...

Classical approach

Vector $\mathfrak{p} \in [0, 1]^m$ of p-values, computed on each taxa independently.

Wilcoxon and Kruskal-Wallis non-parametric tests can be used.

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Each taxon fall into one class of the confusion matrix:

		True condition	
		Positive	Negative
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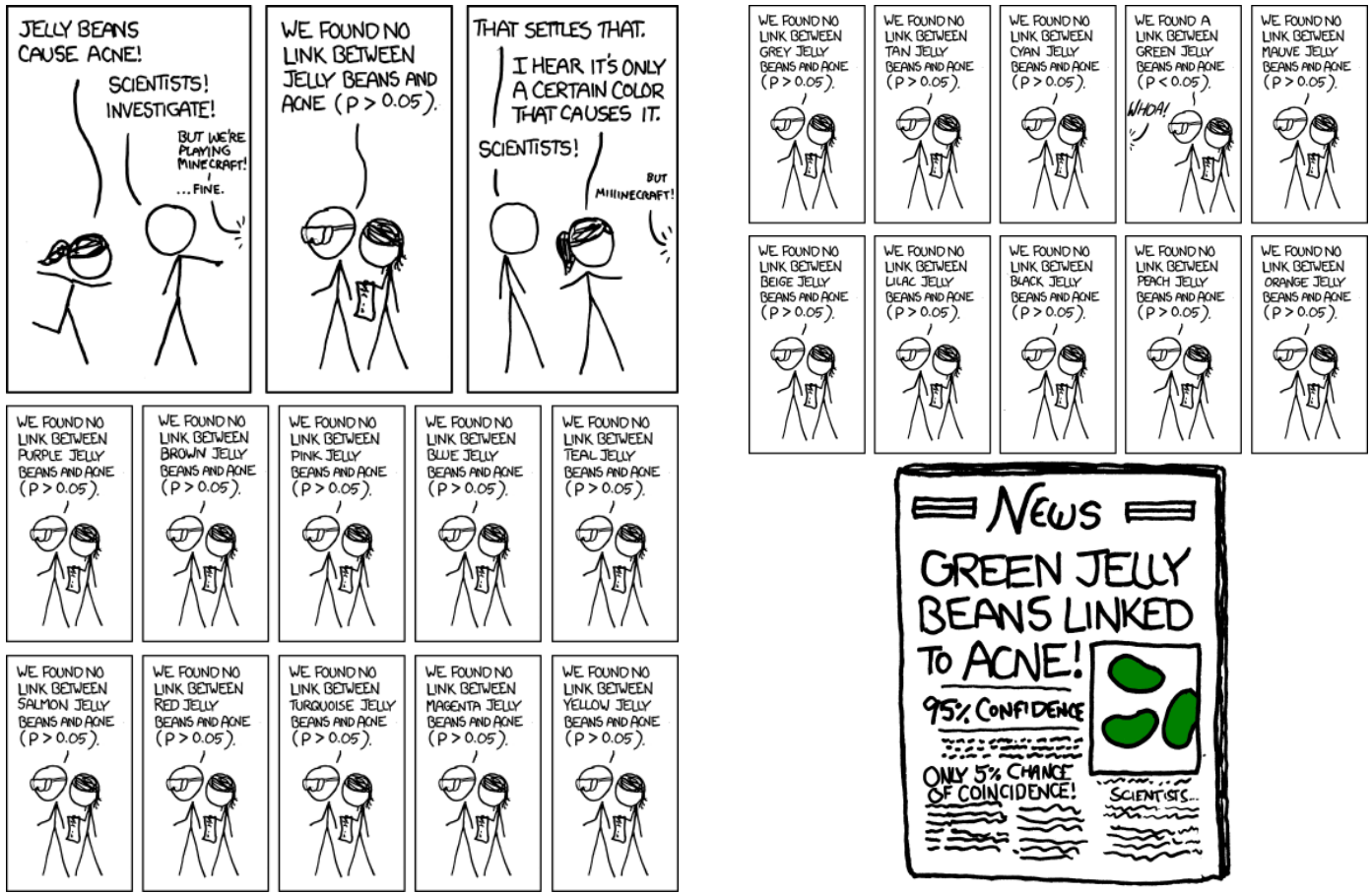
Under $\mathbb{H}_0$, $\mathfrak{p}_i \sim \mathcal{U}([0,1])$.

Multiple testing problem



XKCD

TPR and FDR

		True condition: Positive	True condition: Negative
Detection	Positive	TP	FP
	Negative	FN	TN

True Positive Rate:

$$\mathrm{TPR} = \frac{\mathrm{TP}}{\mathrm{TP} + \mathrm{FN}}.$$

False Discovery Rate:

$$\mathrm{FDP} = \frac{\mathrm{FP}}{\mathrm{TP} + \mathrm{FP}}, \mathrm{FDR} = \mathbb{E}[\mathrm{FDP}].$$

Multiple testing problem correction

Correction with Benjamini-Hochberg procedure to respect an *a priori* FDR : q^{bh}.

Benjamini and Hochberg [BH95]

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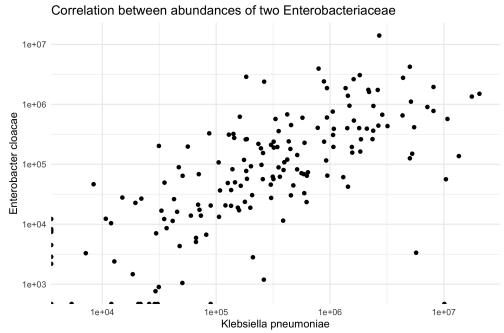

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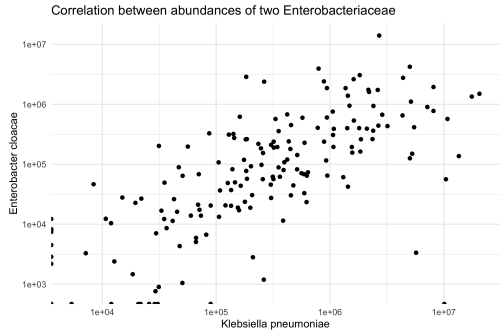


One can use Benjamini-Yekutieli correction which does not make any assumption about dependence between taxa but

- it's too conservative,
- we want to correct explicitly for correlation between taxa.

Benjamini and Hochberg [BH95]; Benjamini and Yekutieli [BY01]

Incorporation of hierarchical information

Goal

- Correct explicitly for correlation between taxa.

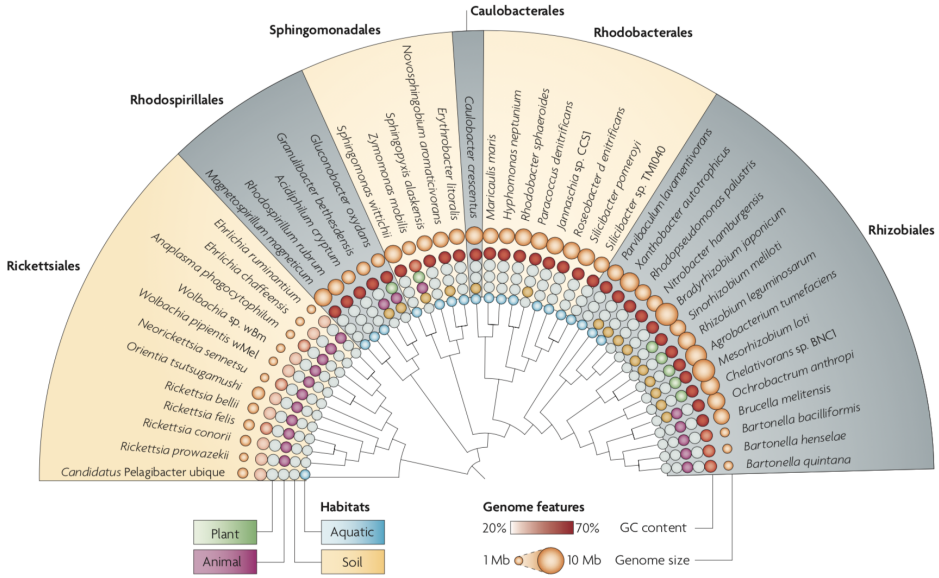
Goal

- Correct explicitly for correlation between taxa.
- Increase power.

Goal

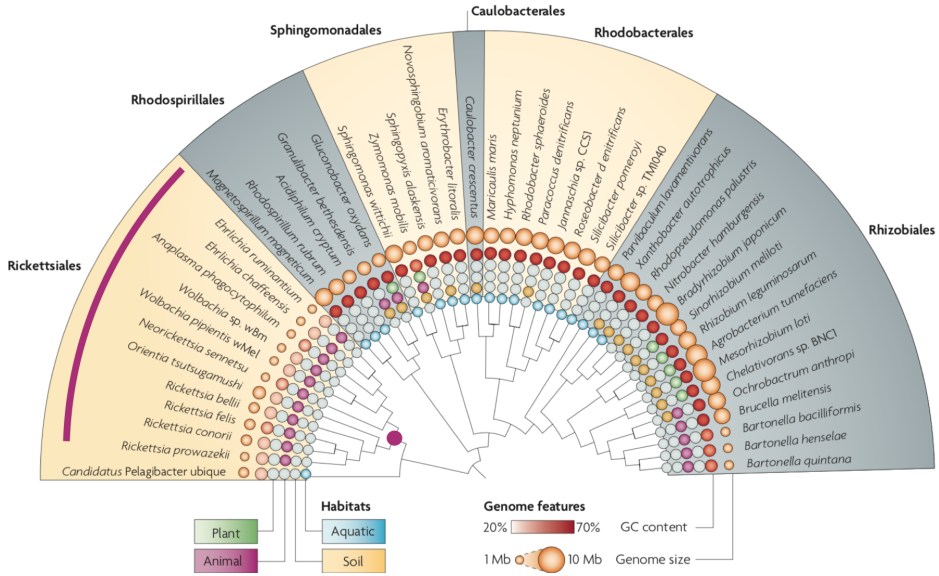
- Correct explicitly for correlation between taxa.
- Increase power.
- Keep FDR under a desired level.

Rationale



Philippot Andersson, et al. [Phi+10]

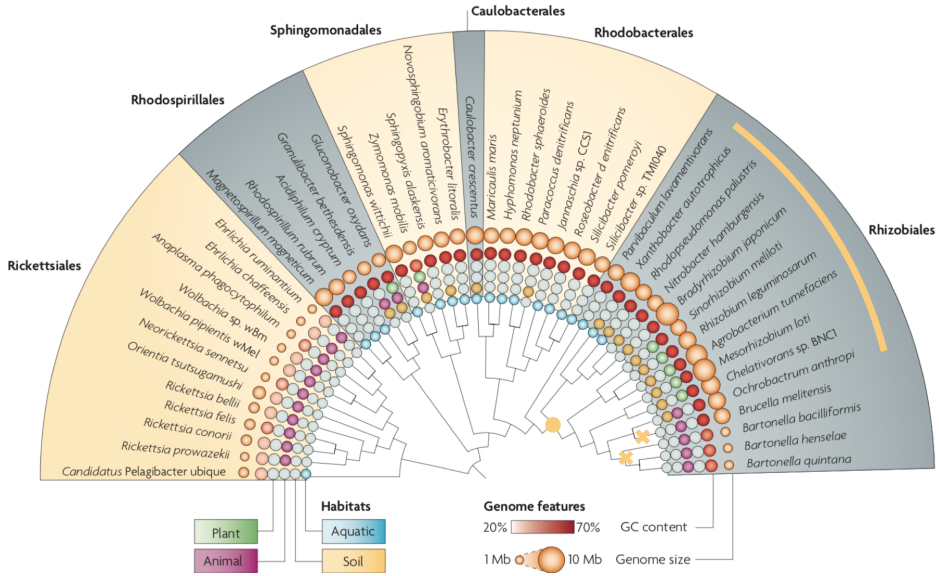
Rationale



These species are associated with animals.

Philippot Andersson, et al. [Phi+10]

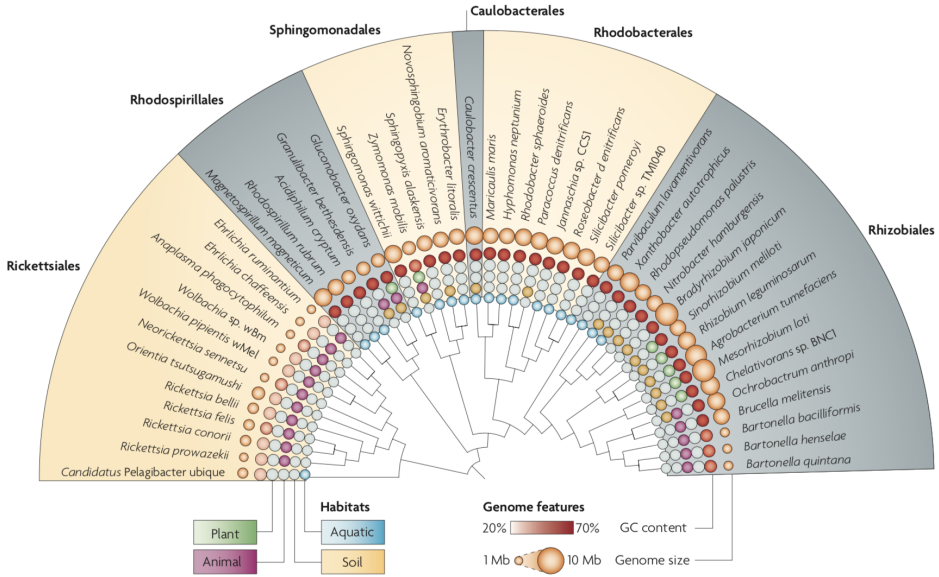
Rationale



These species are associated with soil.

Philippot Andersson, et al. [Phi+10]

Rationale



Already used in

- Hierarchical FDR [Yek08; SH14],
- **TreeFDR [XCC17]**.

Philippot Andersson, et al. [Phi+10]

z-scores smoothing with TreeFDR

$\mathfrak{z} = \Phi^{-1}(\mathfrak{p})$ is the vector of observed z-scores and μ the vector of "true" z-scores.

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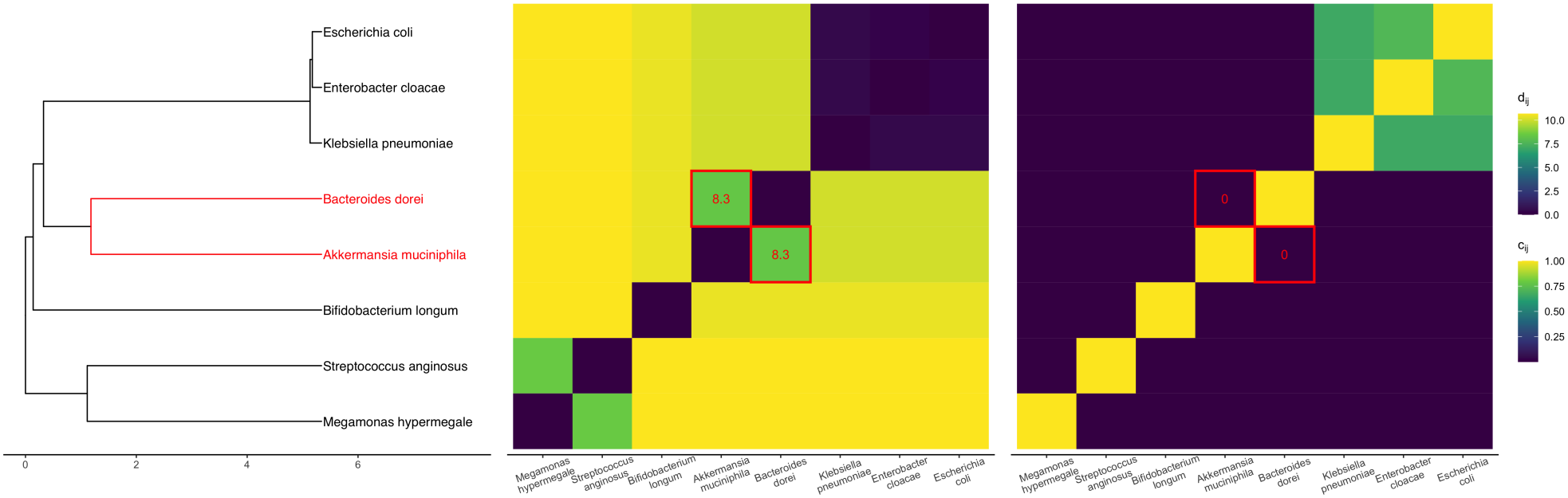
Assume a hierarchical model: $\mathfrak{z} \mid \mu \sim \mathcal{N}_m(\mu, \sigma^2 \mathbf{I}_m)$ and $\mu \sim \mathcal{N}_m(\gamma \mathbf{1}_m, \tau^2 C_\rho)$ with $C_\rho = \left(\exp\left(-2\rho d_{i,j}\right)\right)_{i,j}$.



z-scores smoothing with TreeFDR

Then $\mathcal{Z} \sim \mathcal{N}_m\left(\gamma \mathbf{1}_m, \tau^2 C_\rho + \sigma^2 \mathbf{I}_m\right)$ by Bayes formula and the maximum a posteriori gives

$$\mu^* = \left(\mathbf{I}_m + k^2 C_\rho^{-1}\right)\left(k^2 C_\rho^{-1} \gamma \mathbf{1}_m + \mathcal{Z}\right),$$

with $k = \frac{\sigma}{\tau}$ and ρ_0 hyperparameters to optimize.

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with $k = \frac{\sigma}{\tau}$ and ρ_0 hyperparameters to optimize.

At the end, a multiple testing correction by resampling is done on smoothed values.

Which tree?

- Phylogeny? Taxonomy?

😀 Proxy for correlations at high-level niches.

☹ Not so much for low-level niches?

☹ Not available every time.

Which tree?

- Phylogeny? Taxonomy?

😀 Proxy for correlations at high-level niches.

☹ Not so much for low-level niches?

☹ Not available every time.

- Correlation tree?

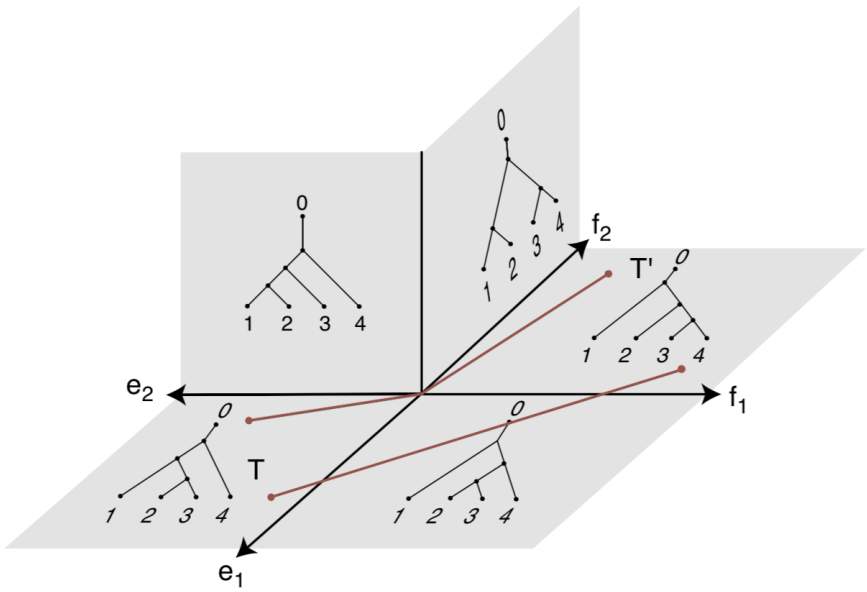
😀 Actual correlation between taxa.

😀 Always available.

☹ Risk of overfitting.

Bichat Plassais, et al. [Bic+20]

Billera-Holmes-Vogtmann distance



- Each tree is mapped into a space composed by merged orthants.
- An orthant corresponds to a topology.
- The BHV distance is the length of the unique shortest path between the trees on treespace.
- It can be computed with a $O\left(m^4\right)$ algorithm.

Billera Holmes, et al. [BHV01]

Quantifying distance between trees

- Trees of primary interest:
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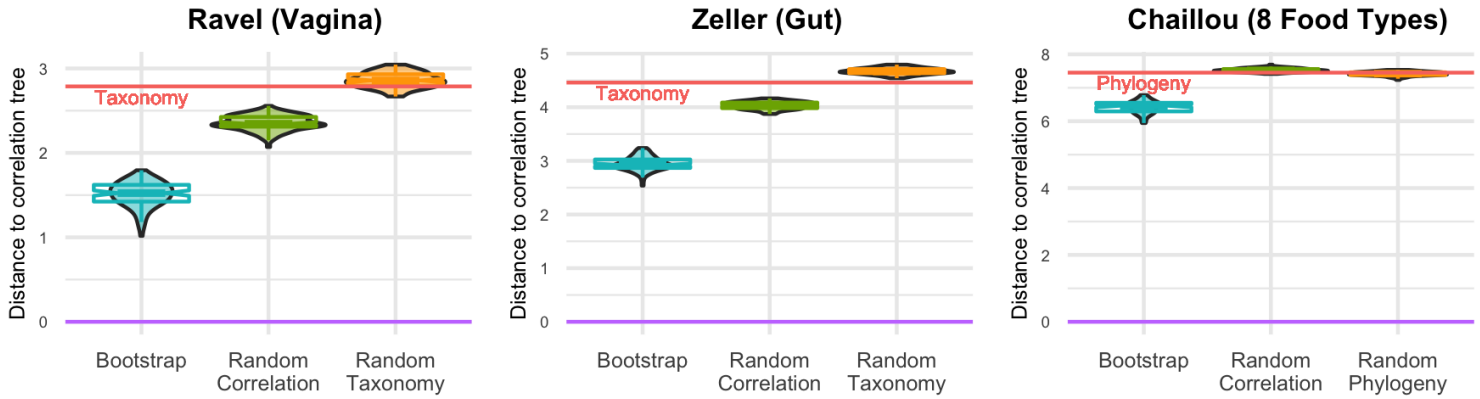
We compute all pairwise distances between these trees.

Comparisons between trees

Neither phylogeny nor taxonomy is in the confident region of the correlation tree.



[Bic+20; Rav+11; Zel+14; Cha+15]

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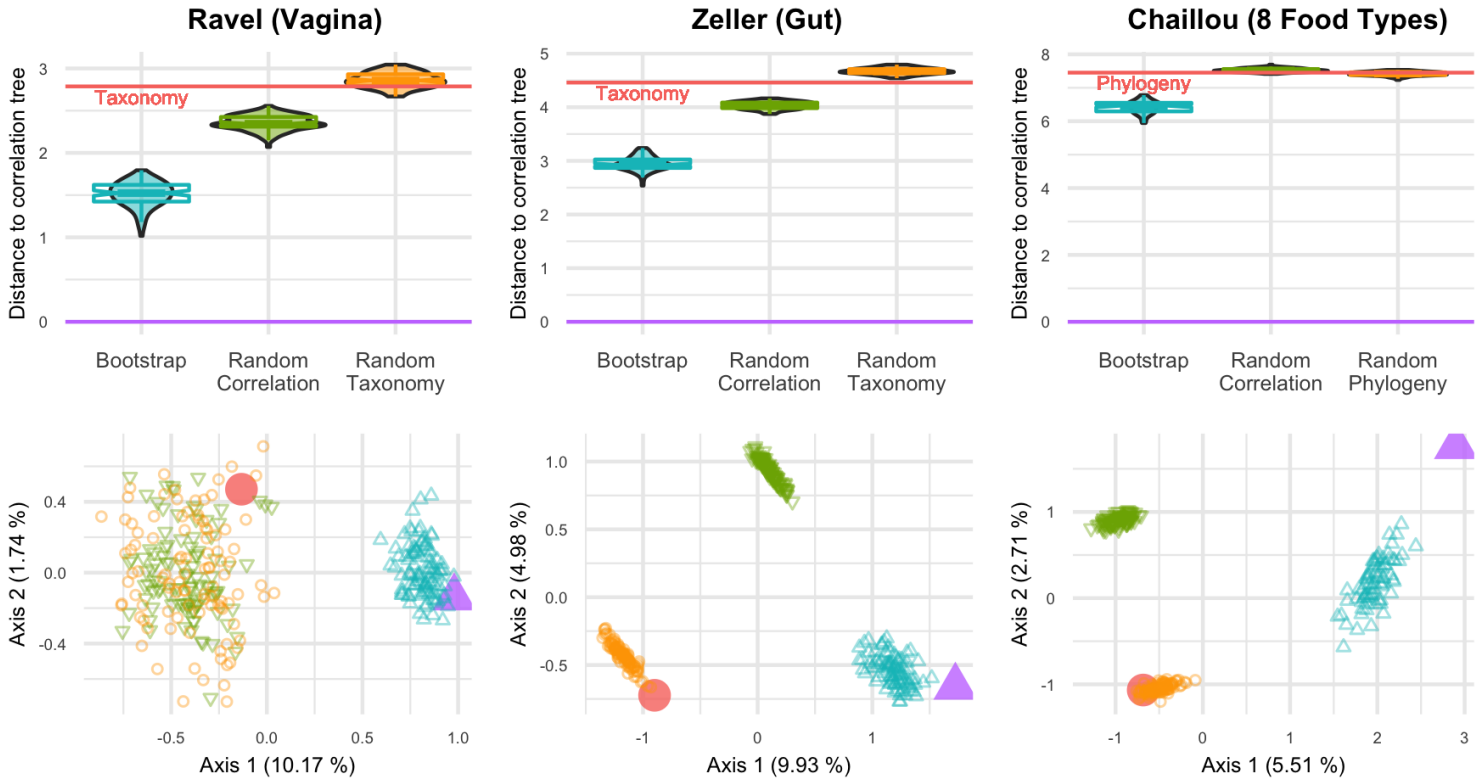
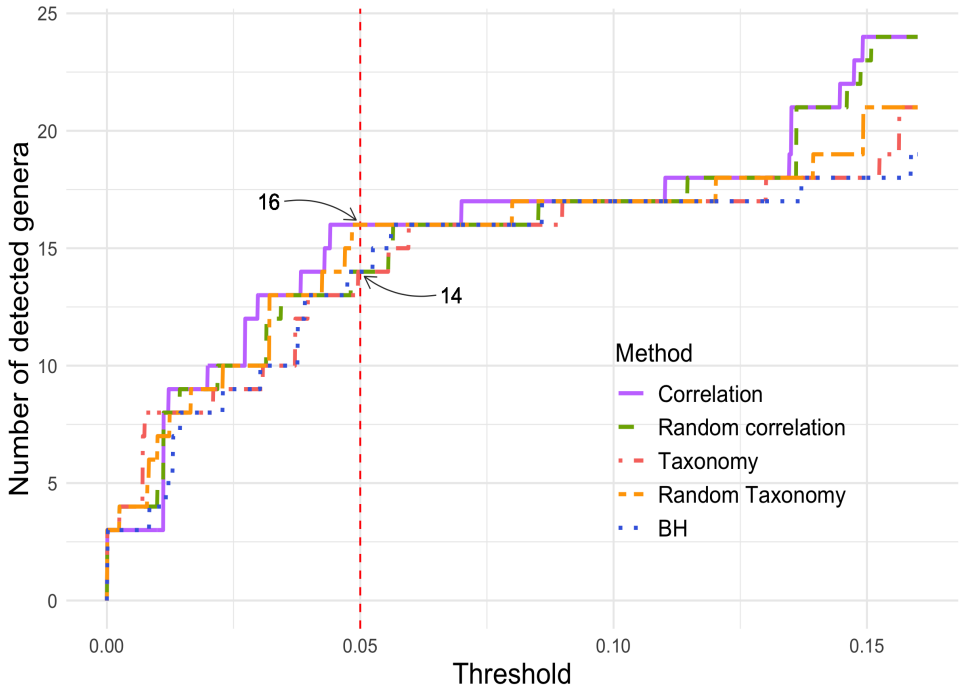


[Bic+20; Rav+11; Zel+14; Cha+15]

Impact of the tree with Zeller dataset

All hierarchies give highly similar results.



- 119 genera
- 199 patients
  - 66 healthy
  - 42 adenoma
  - 91 colorectal cancer

Bichat Plassais, et al. [Bic+20]; Zeller Tap, et al. [Zel+14]

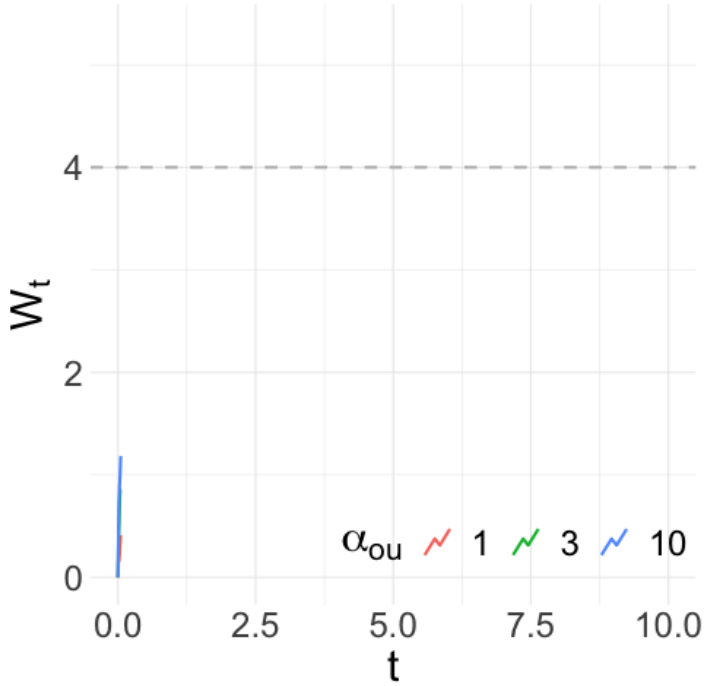
zazou

Z-scores AZ Ornstein-Uhlenbeck

Ornstein-Uhlenbeck process

An Ornstein-Uhlenbeck (OU) process with an optimal value of β_{ou} and a strength of selection $\alpha_{\text{ou}} > 0$ is a Gaussian process that satisfies the SDE

$$\mathrm{d}W_t = -\alpha_{\text{ou}}(W_t - \beta_{\text{ou}})\mathrm{d}t + \sigma_{\text{ou}}\mathrm{d}B_t.$$



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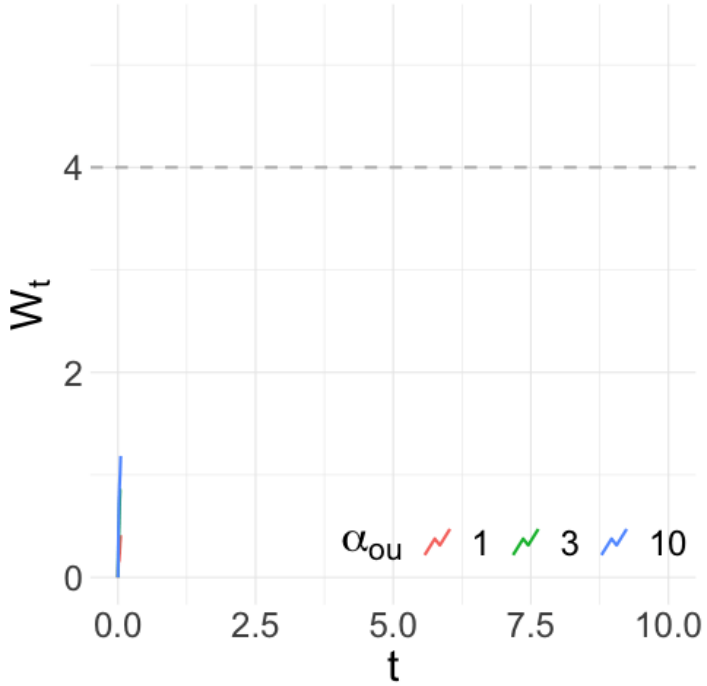
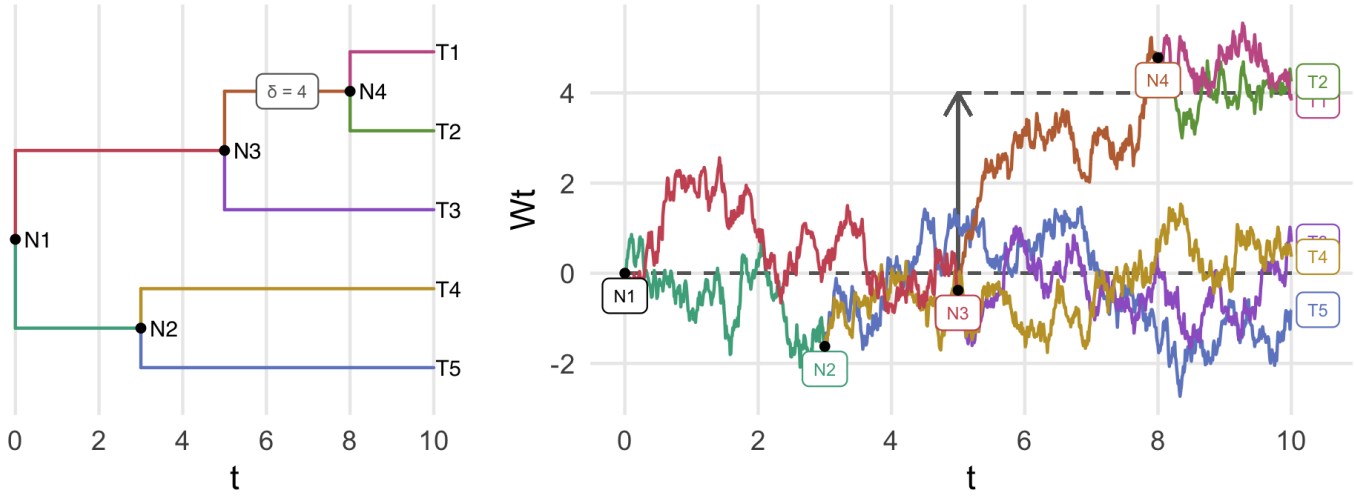


W_t is Gaussian with bounded variance and

$$W_t \xrightarrow[t\to\infty]{} \mathcal{N}\left(\beta_{\text{ou}}, \frac{\sigma_{\text{ou}}^2}{2\alpha_{\text{ou}}}\right).$$

OU process on a tree with shifts δ



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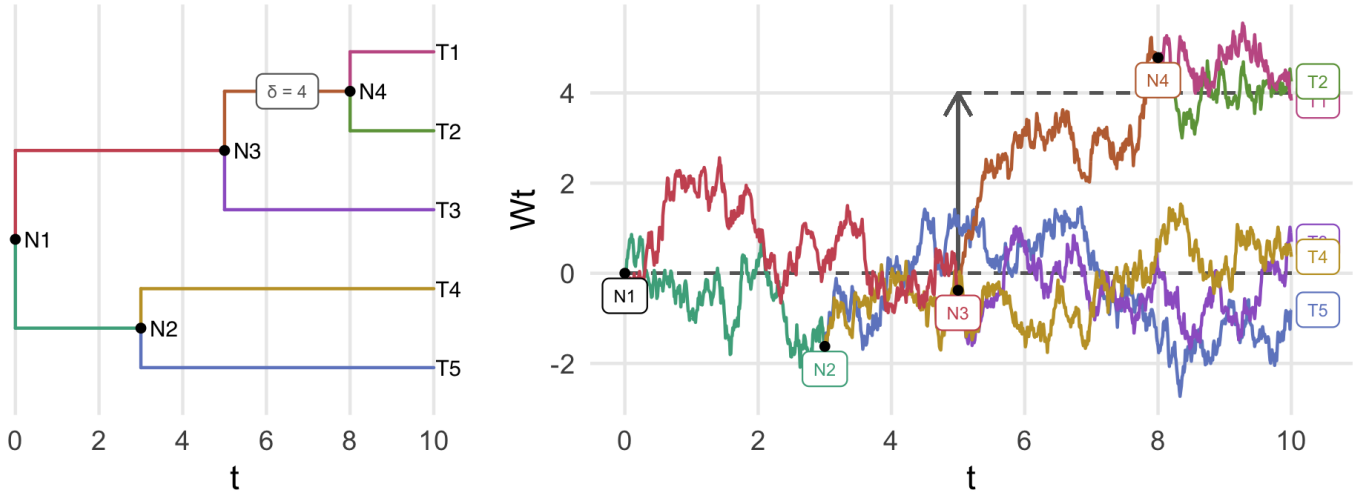

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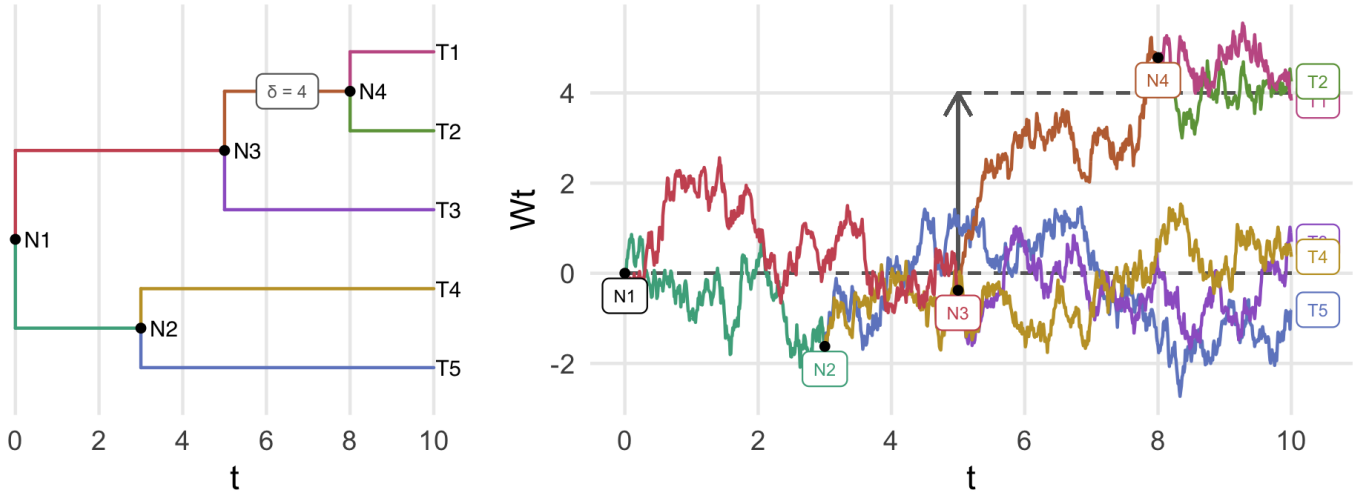

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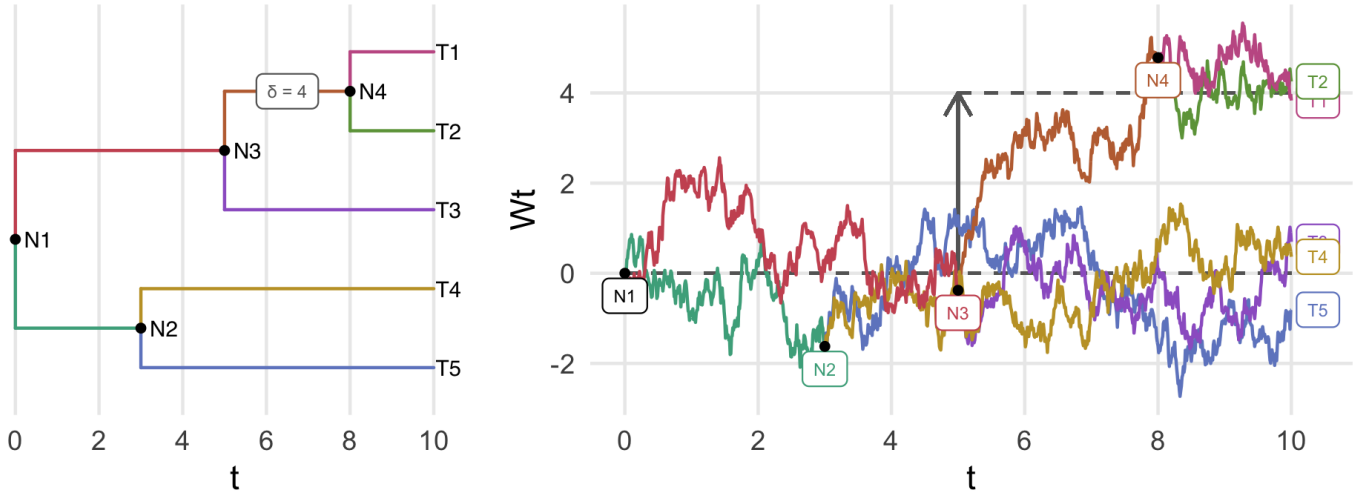

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- At each node, the process splits into two independent processes with the same initial value.
- The optimal value can shift at a node.

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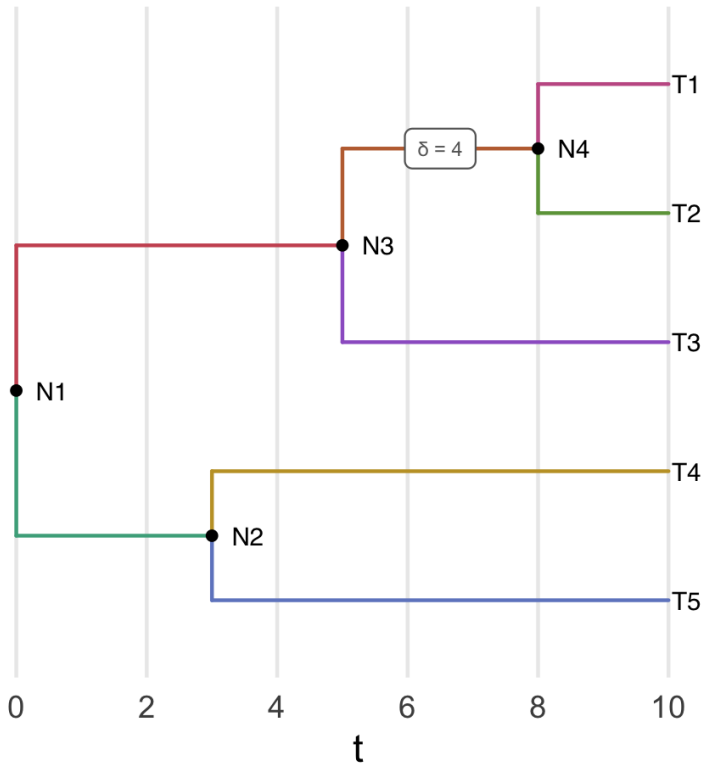
Incidence matrix and vector of shifts



$T = (\mathbb{1}_{\{i \in \mathrm{desc}(j)\}})_{ij} \in \{0,1\}^{m \times n}$ is the incidence matrix of the tree:

$$\begin{bmatrix} 1 & 0 & 1 & 1 & 1 & 0 & 0 & 0 & 0 \\ 1 & 0 & 1 & 1 & 0 & 1 & 0 & 0 & 0 \\ 1 & 0 & 1 & 0 & 0 & 0 & 1 & 0 & 0 \\ 1 & 1 & 0 & 0 & 0 & 0 & 0 & 1 & 0 \\ 1 & 1 & 0 & 0 & 0 & 0 & 0 & 0 & 1 \end{bmatrix}$$

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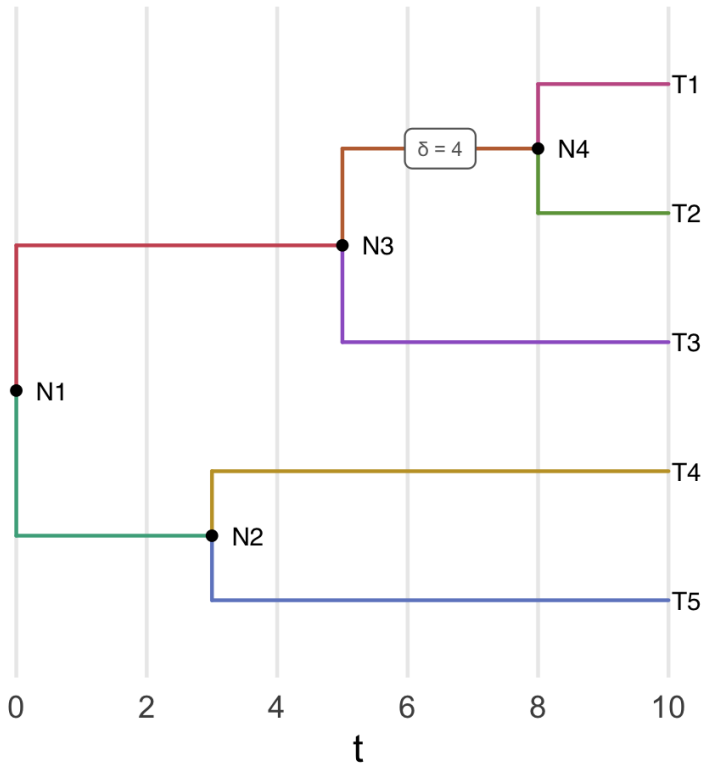

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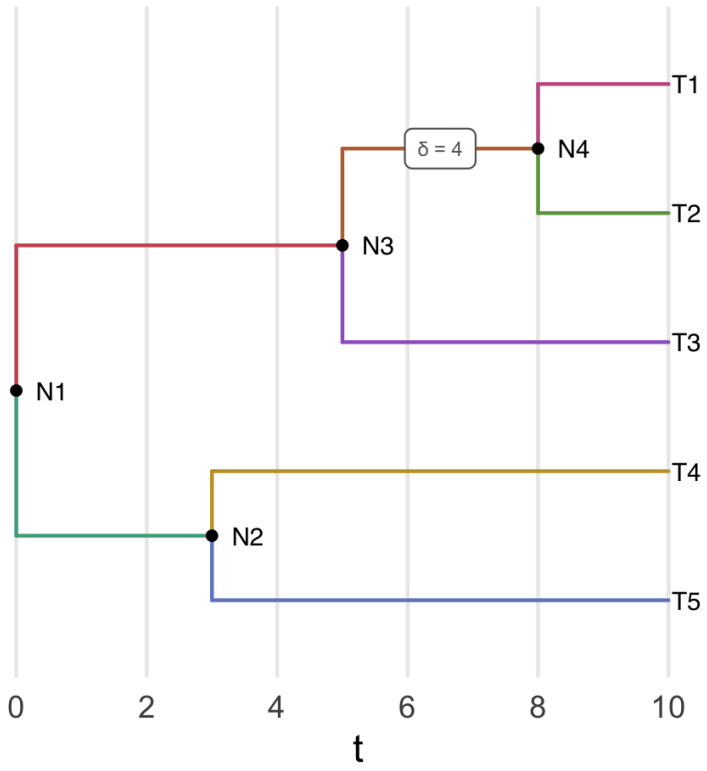

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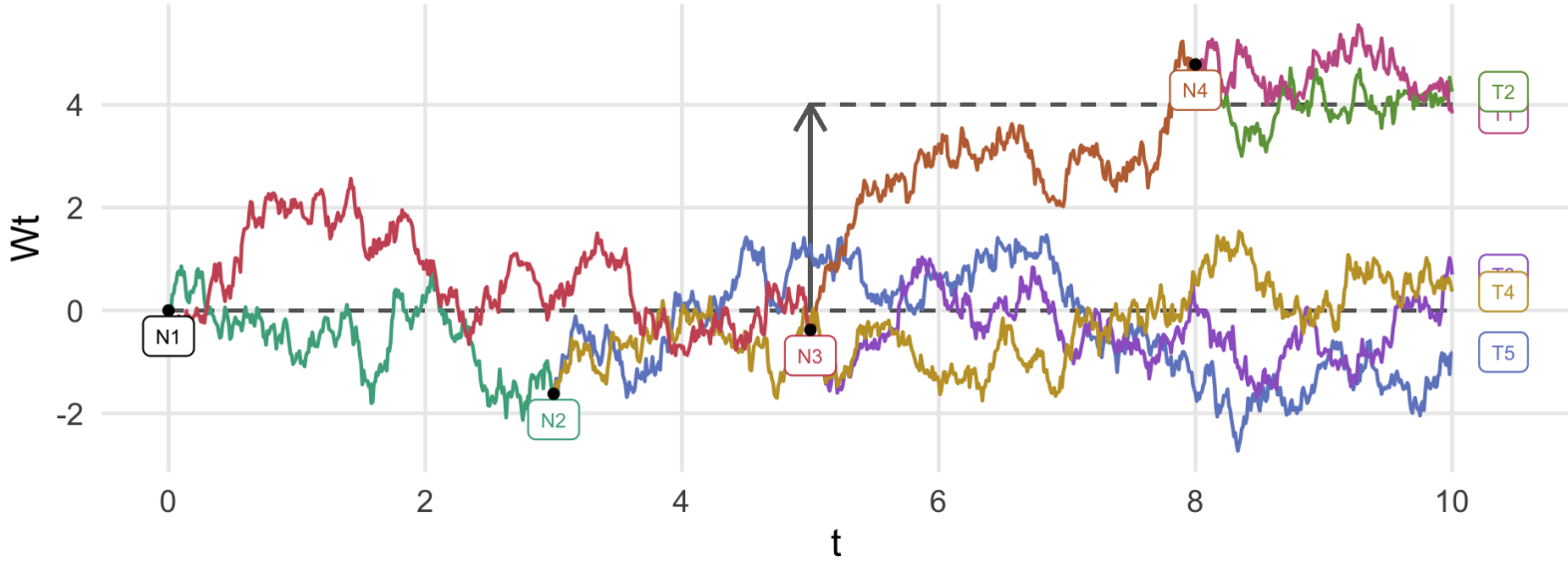
The product $T\delta$ is the vector of optimal values on leaves.

Random variables on leaves



The random variables on leaves are jointly Gaussian $\mathcal{N}_m(T\delta, \Sigma)$ with

$$\Sigma_{i,j} = \frac{\sigma^2_{\text{ou}}}{2\alpha_{\text{ou}}}\left(1 - e^{-2\alpha_{\text{ou}} t_{i,j}}\right) \times e^{-\alpha_{\text{ou}} d_{i,j}}.$$

First assumption

z is the realization of an OU on a tree with shifts δ.

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$\mathfrak{z}$ is the realization of an OU on a tree with shifts δ.

Then,

$$\mathfrak{z} \sim \mathcal{N}_m(\mu, \Sigma)$$

with $\mu = T\delta$ and Σ depends on α_{ou} and σ_{ou} by

$$\Sigma_{i,j} = \frac{\sigma_{\text{ou}}^2}{2\alpha_{\text{ou}}}\left(e^{-\alpha_{\text{ou}} d_{i,j}} - e^{-2\alpha_{\text{ou}} h}\right)$$

for a tree with total height h.

Second assumption

For a taxa i,

- if $\mathcal{H}_i \in \mathbb{H}_0$, $\mathfrak{p}_i \sim \mathcal{U}([0,1])$ so $\mathfrak{z}_i \sim \mathcal{N}(0,1)$,
- if $\mathcal{H}_i \notin \mathbb{H}_0$, $\mathfrak{p}_i \preccurlyeq \mathcal{U}([0,1])$ so $\mathfrak{z}_i \sim \mathcal{N}(\mu_i, 1)$ with $\mu_i < 0$.

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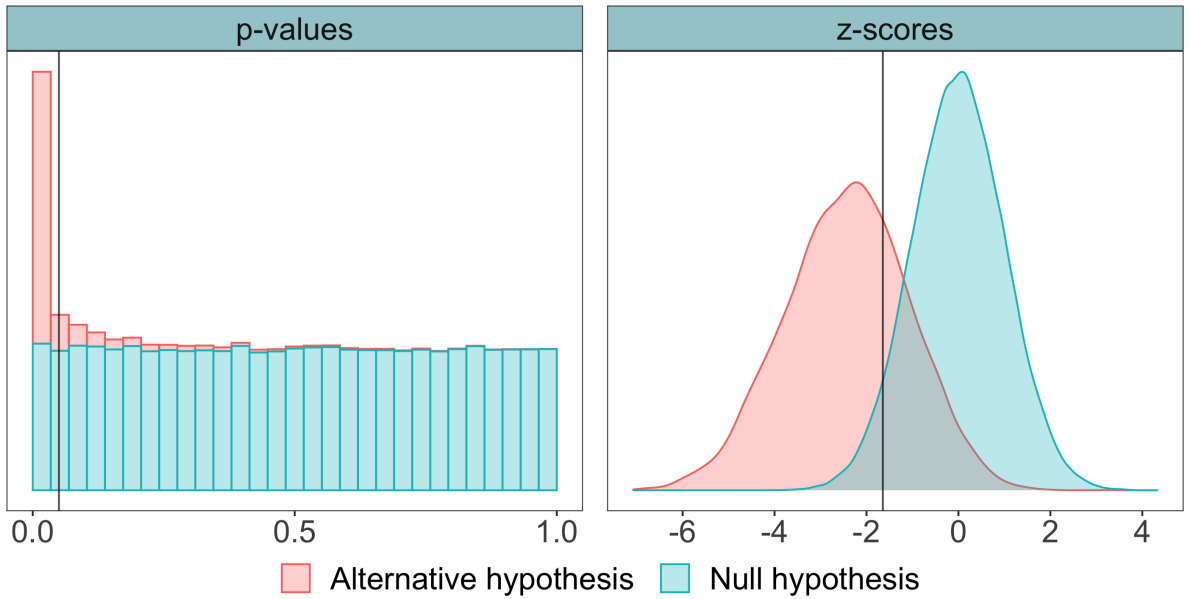

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Then,

$$\mathfrak{z} \sim \mathcal{N}_m\left(\mu \in \mathbb{R}_-^m, \Sigma\right).$$

One will find **differentially abundant** taxa by finding the **non-zero elements** of μ.

This impose $\Sigma_{i,i} = 1$ so $\sigma_{\text{ou}} = \frac{2\alpha_{\text{ou}}}{1-e^{-2\alpha_{\text{ou}}h}}$.

McLachlan and Peel [MP04]

Estimation of μ

With Σ known, a naive ML estimator gives

$$\hat{\mu} = \underset{\mu \in \mathbb{R}^m_-}{\operatorname{argmin}} \|\mathfrak{z} - \mu\|^2_{\Sigma^{-1},2}.$$

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To add hierarchically coherent sparsity in our estimate

$$\hat{\delta} = \underset{\delta \in \mathbb{R}^n / T\delta \in \mathbb{R}^m_-}{\operatorname{argmin}} \|\mathfrak{z} - T\delta\|^2_{\Sigma^{-1},2} + \lambda\|\delta\|_1.$$

Estimation of μ (bis)

By Cholesky decomposition, $\Sigma^{-1} = R^T R$

$$\begin{aligned}
\|\mathfrak{z} - T\delta\|^2_{\Sigma^{-1},2} &= (\mathfrak{z} - T\delta)^T \Sigma^{-1} (\mathfrak{z} - T\delta) \\
&= (\mathfrak{z} - T\delta)^T R^T R (\mathfrak{z} - T\delta) \\
&= (R\mathfrak{z} - RT\delta)^T (R\mathfrak{z} - RT\delta) \\
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with $y = R\mathfrak{z}$ and $X = RT$.

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with $y = R\mathfrak{z}$ and $X = RT$.

Finally, we fall back to a constrained lasso problem:

$$\hat{\delta} = \underset{\delta \in \mathbb{R}^n / T\delta \in \mathbb{R}^m_-}{\operatorname{argmin}} \|y - X\delta\|_2^2 + \lambda \|\delta\|_1.$$

Numerical resolution

The previous problem could be numerically solved by the shooting algorithm, **iterating unidirectional updates** form the associated problem:

$$\begin{cases} \underset{\theta \in \mathbb{R}}{\operatorname{argmin}}\, h(\theta) = \dfrac{1}{2}\|y - z - x\theta\|_2^2 + \lambda|\theta| \\ \text{s.t. } u + v\theta \leq 0. \end{cases}$$

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But Σ and λ are not yet known.

Fu [98]

Estimation of Σ and choice of λ

$\widehat{\Sigma} = \left(\frac{e^{-\hat{\alpha}_{\text{ou}} d_{ij}} - e^{-2\hat{\alpha}_{\text{ou}} h}}{1 - e^{-2\hat{\alpha}_{\text{ou}} h}} \right)_{i,j}$ is determined by $\hat{\alpha}_{\text{ou}}$.

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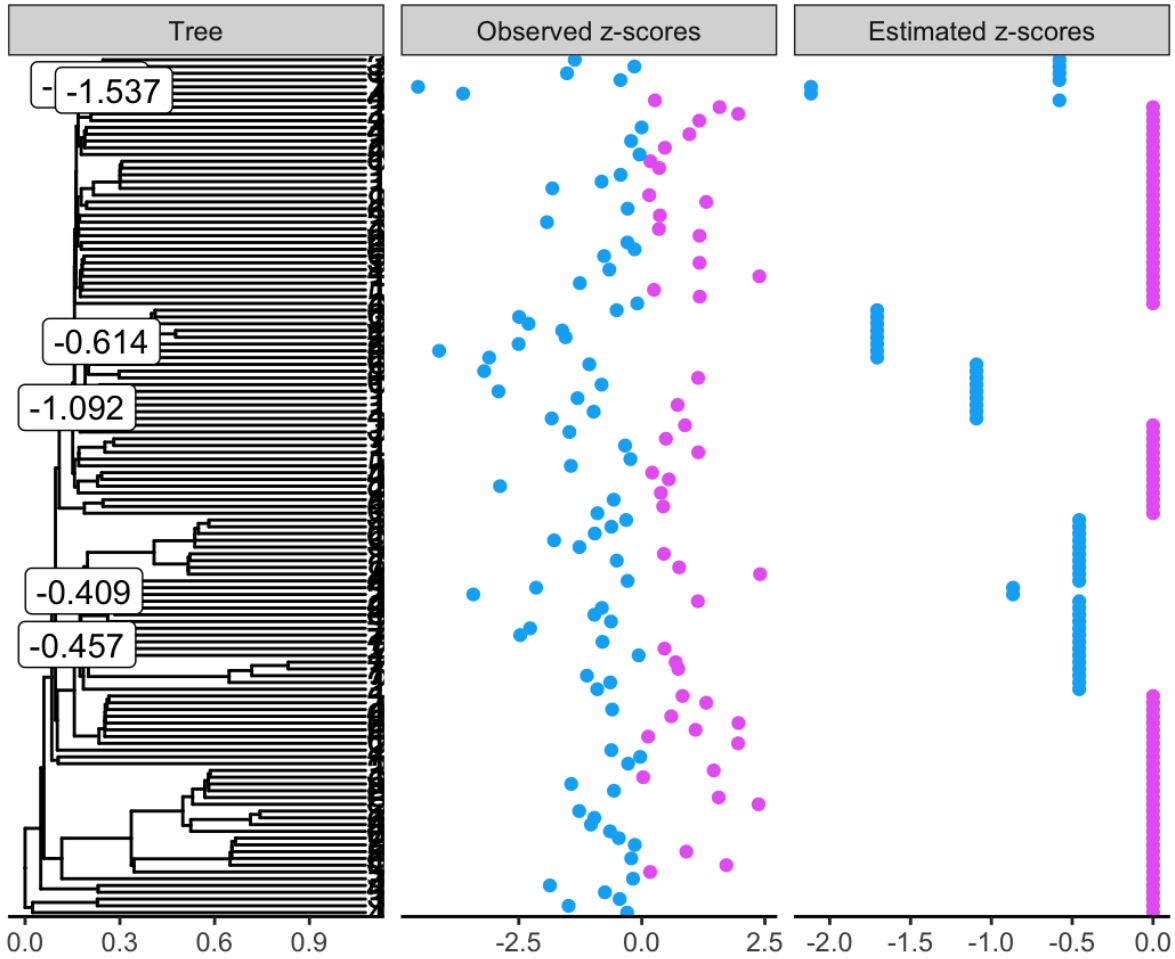
The optimal $(\alpha_{\text{ou}}, \lambda)$, is chosen on a bidimensional grid as the argmin of the BIC

$$\|\mathfrak{z} - T\delta_{\alpha_{\text{ou}},\lambda}\|^2_{\Sigma(\alpha_{\text{ou}})^{-1},2} + \log|\Sigma(\alpha_{\text{ou}})| + \|\delta_{\alpha_{\text{ou}},\lambda}\|_0 \log m.$$

Effect of hierarchical smoothing



Find non zero values

Estimation from lasso provides biased estimators without confidence intervals.

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Use of a debiasing procedure

- **score system (ss) [ZZ14],**
- column-wise inverse (ci) [JM13; JM14].

Scaled lasso

The debiasing procedure requires a **initial joint estimator** of $\delta^{(\text{init})}$ and its associated standard error σ.

This can be done with a scaled lasso

$$\left(\hat{\delta}^{(\text{init})}, \hat{\sigma}\right) = \underset{\delta,\sigma}{\operatorname{argmin}} \frac{\|y - X\delta\|_2^2}{2\sigma n} + \frac{\sigma}{2} + \lambda\|\delta\|_1.$$

Sun and Zhang [SZ12]

Score system

The **score system** $S \in \mathbb{R}^{n \times p}$ associated with X and y where s_j is the residual of the (classical) lasso regression of y against X_{-j}:

$$s_j = y - \delta_{\text{lasso}}^{-j} X_{-j}.$$

S is as **weak orthogonalisation** of X.

Debiasing procedure

From the initial estimator $\hat{\delta}_j^{(\text{init})}$ of the scaled lasso, one can do a **one-step correction**

$$\hat{\delta}_j = \hat{\delta}_j^{(\text{init})} + \frac{\langle s_j, y - X\hat{\delta}^{(\text{init})} \rangle}{\langle s_j, x_j \rangle}.$$

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Asymptotically, $\hat{\delta} \sim \mathcal{N}_n(\delta, V)$ with

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$$v_{i,j} = \hat{\sigma} \frac{\langle s_i, s_j \rangle}{\langle s_i, x_i \rangle \langle s_j, x_j \rangle}.$$

Then the **bilateral confidence interval** for a shift $\hat{\delta}_j$ is

$$\left[\hat{\delta}_j \pm \phi^{-1}\left(1 - \frac{\alpha}{2}\right) \sqrt{v_{j,j}} \right].$$

Smoothed p-values

To have the **unilateral hierarchically smoothed p-values** $\mathfrak{p}^{\mathrm{h}}$, we need to propagate the shifts with the incidence matrix T

$$\mathfrak{p}_i^{\mathrm{h}} = \Phi\left(\frac{t_{i.}^T \hat{\delta}}{\left(t_{i.}^T V t_{i.}\right)^{1/2}}\right)$$

with $t_{i.}$ the i^{th} row of T.

Multiple testing correction

Let $\mathrm{t}_i = \frac{t_{i.}^T \hat{\delta}}{\left(t_{i.}^T V t_{i.}\right)^{1/2}}$ be the t-scores, $t_{\max} = \sqrt{2\log m - 2\log\log m}$ and

$$t^\star = \inf\left\{0 \leq t \leq t_{\max} : \underbrace{\frac{2m(1-\Phi(t))}{R(t) \vee 1}}_{\widehat{\mathrm{FDR}}(t)} \leq \alpha\right\}$$

with $R(t) = \sum_{i=1}^m \mathbb{1}_{\{\mathrm{t}_i \leq -t\}}$.

Javanmard Javadi, et al. [JJ19]

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One reject if $\mathrm{t}_i \leq -t^\star$ and the associated **hierarchical q-values** are

$$\mathrm{q}_i^{\mathrm{h}} = \frac{\mathrm{p}_i^{\mathrm{h}} \alpha}{\Phi(-t^\star)}.$$

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- a modeling of z-scores by an Ornstein-Uhlenbeck process on a tree with shifts,
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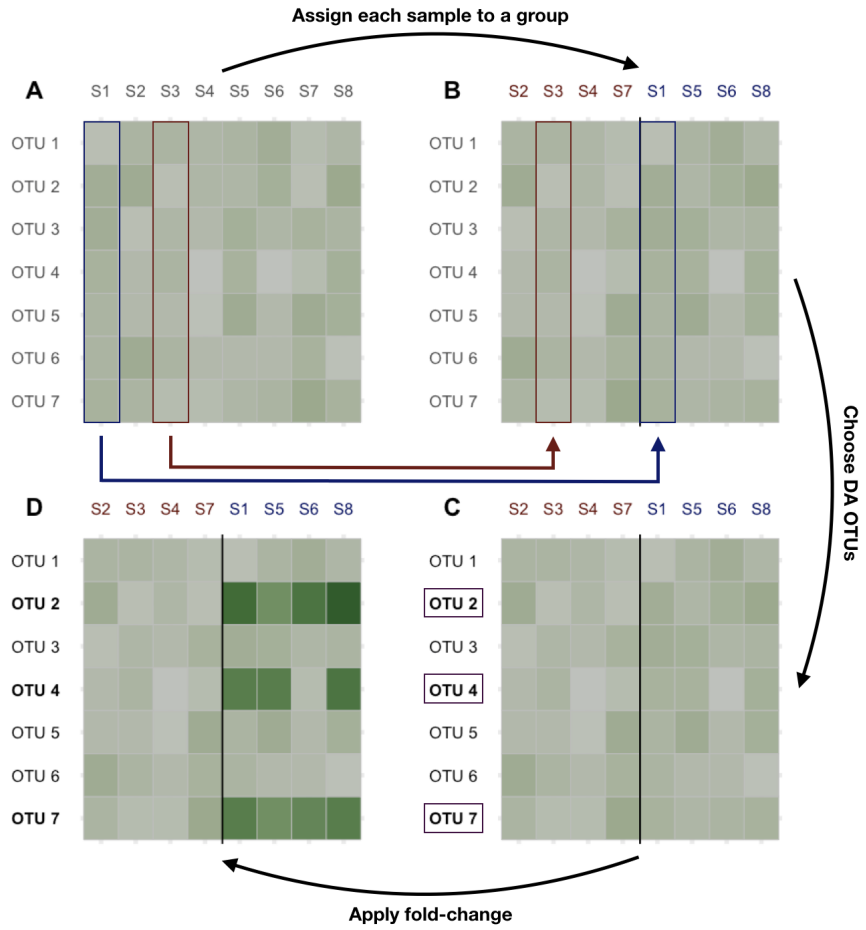
- a debiased lasso designed multiple testing procedure.

Evaluation of zazou

Simulations



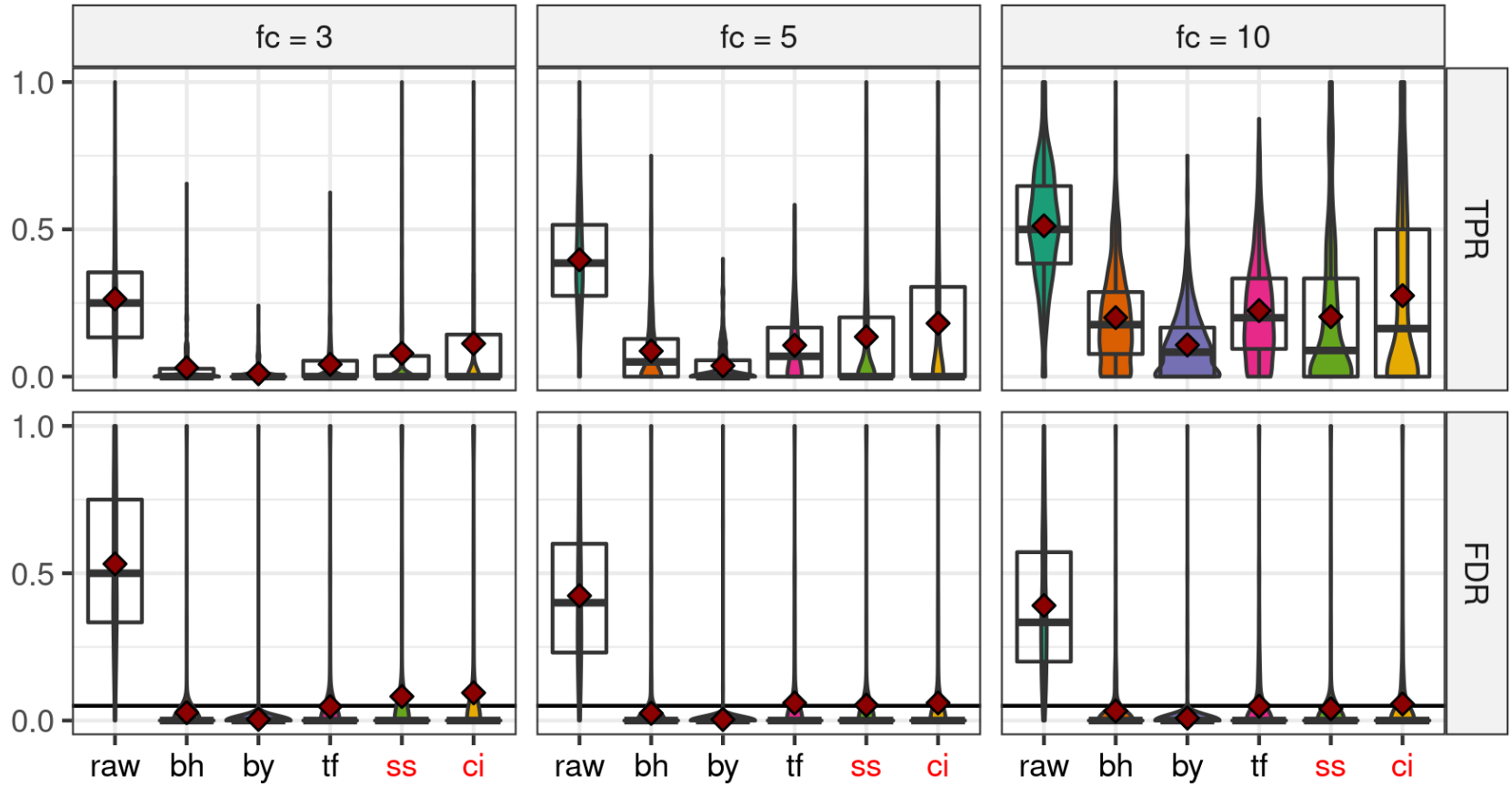
The choice of differentially abundant taxa is done in a hierarchically consistent manner.

- $m = 127, p = 49$ split into two groups.
- Fold-changes of 3, 5 and 10.
- 5 estimated proportions of π_1.
- 100 replicates for each parameters.

Bichat Plassais, et al. [Bic+20]

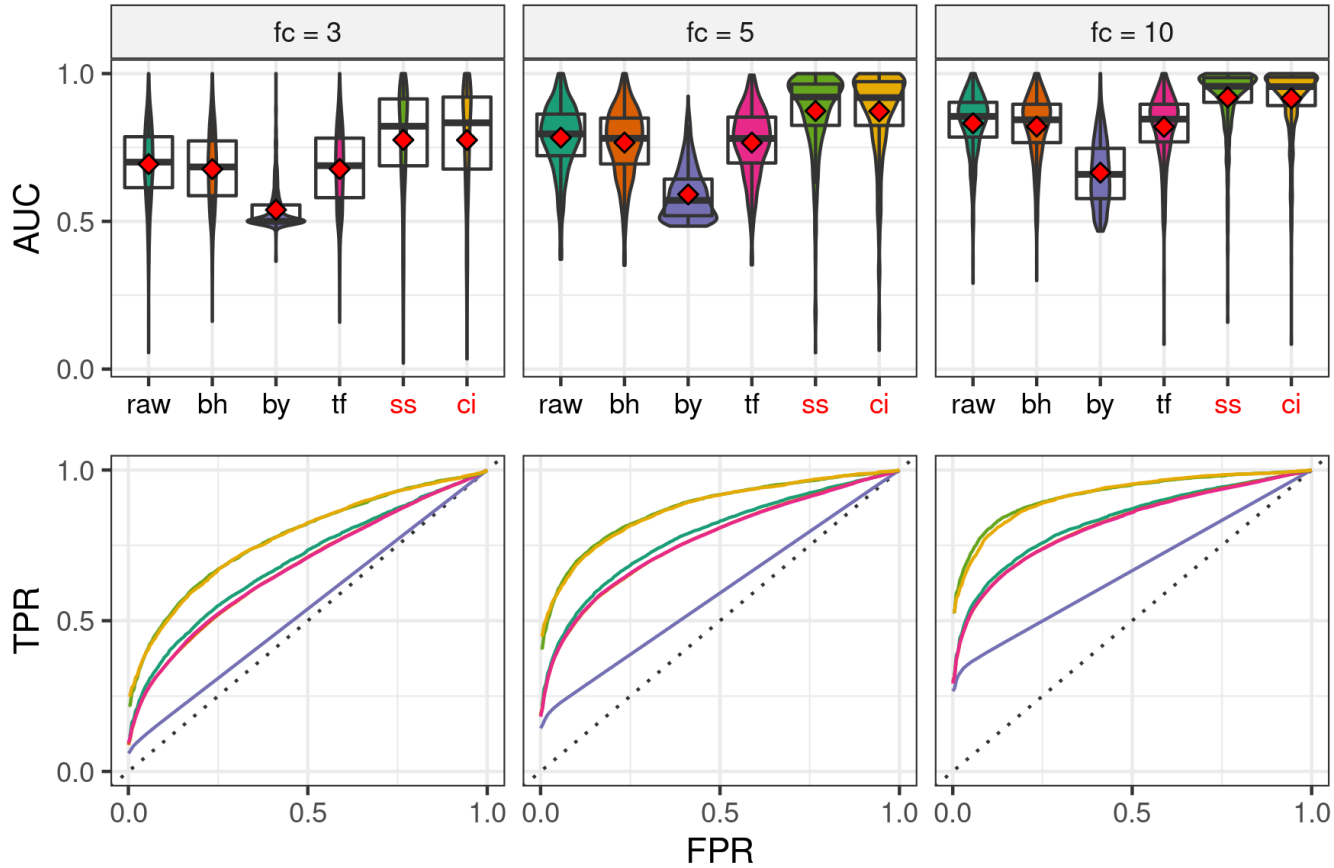
Results

zazou increases the TPR but does not always control the FDR.



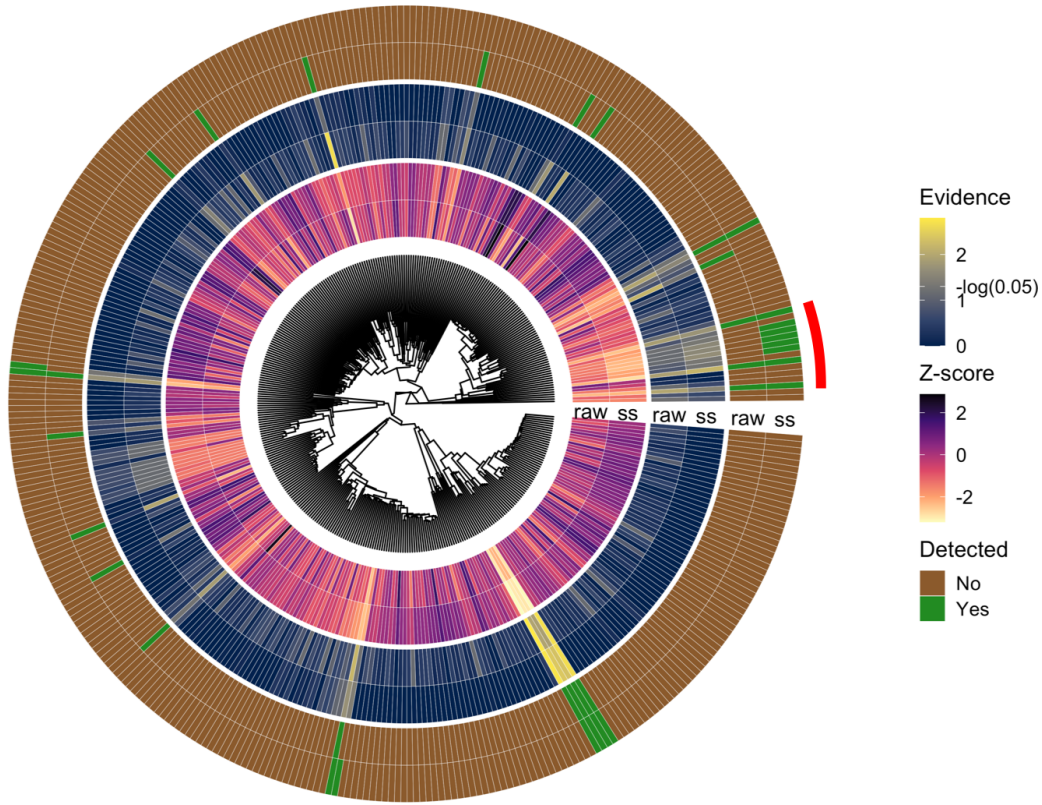
Results

zazou has better AUC and ROC curves.



Association with age

zazou identifies phylogenetically coherent taxa.



Brito Yilmaz, et al. [Bri+16]

Conclusions

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- Articles published in Frontiers in Microbiology and submitted in Statistics and Computing.

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- Use hierarchical information during testing step, and not only correction step.
- Use the framework of prediction instead of association.

Thanks!

Manuscript

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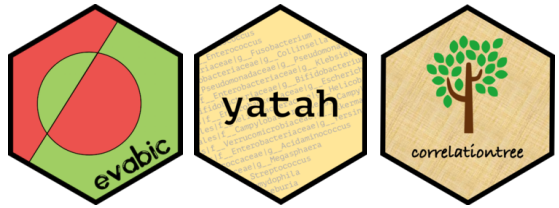
R packages



evabic evaluates the performance of binary classifiers. It can compute compute 19 different measures with tidy outputs.

yatah provides functions to manage taxonomy when lineages are described like `k__Bacteria|p__Proteobacteria|c__Gammaproteobacteria`.

correlationtree computes correlation trees.

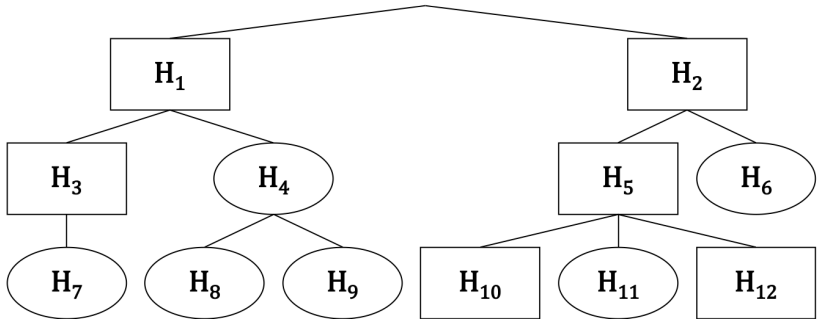
zazou implements the zazou procedure.

hadamardown contains the Université Paris-Saclay PhD manuscript template for bookdown.

Hierarchical FDR

This procedure inscreases statistical power by lessening the number of test to do with a descending method:

- test the family $\mathcal{T}_0$,
- if node t is rejected, test $\mathcal{T}_t = \{H_i \mid \mathrm{Par}(i) = t\}$ with a BH procedure at level α.



Yekutieli [Yek08]; Sankaran and Holmes [SH14]

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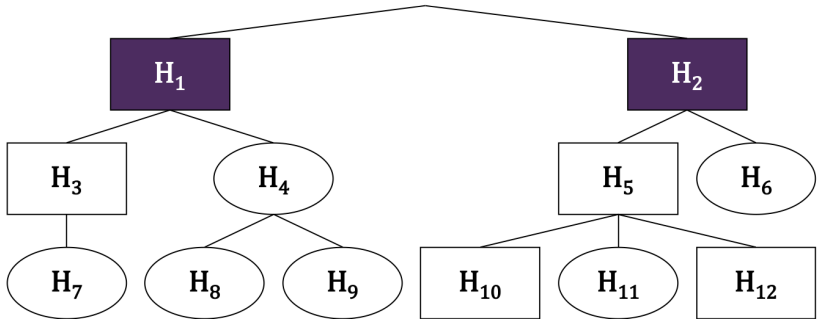

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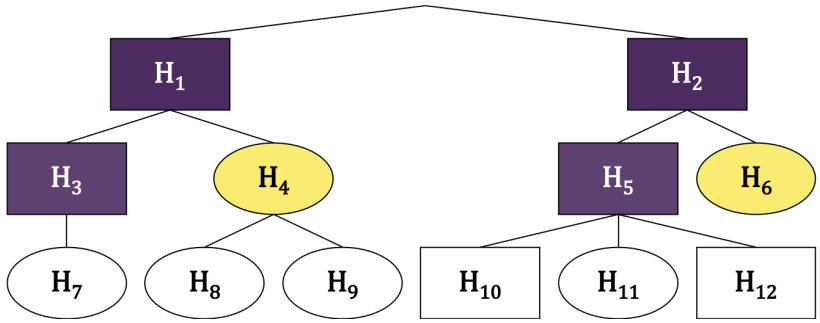

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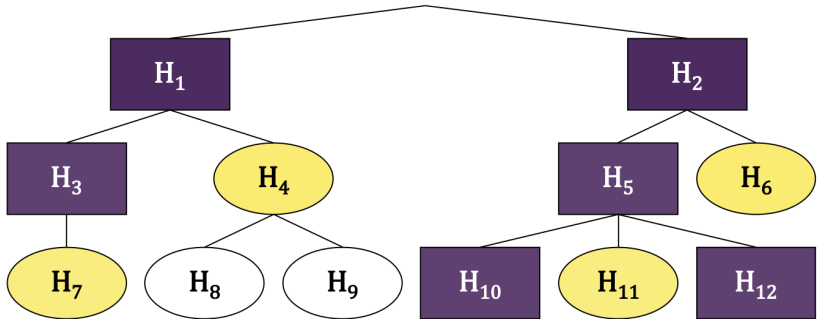

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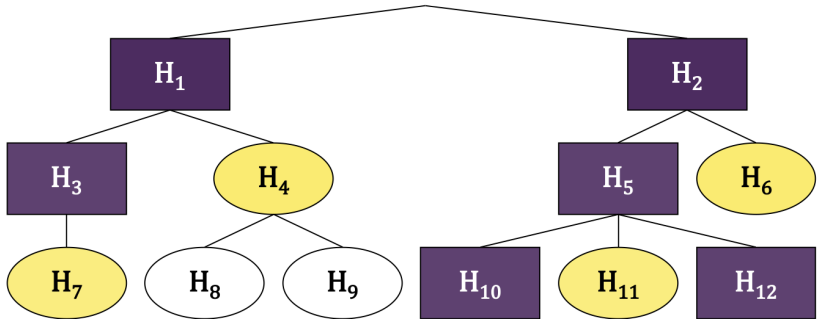
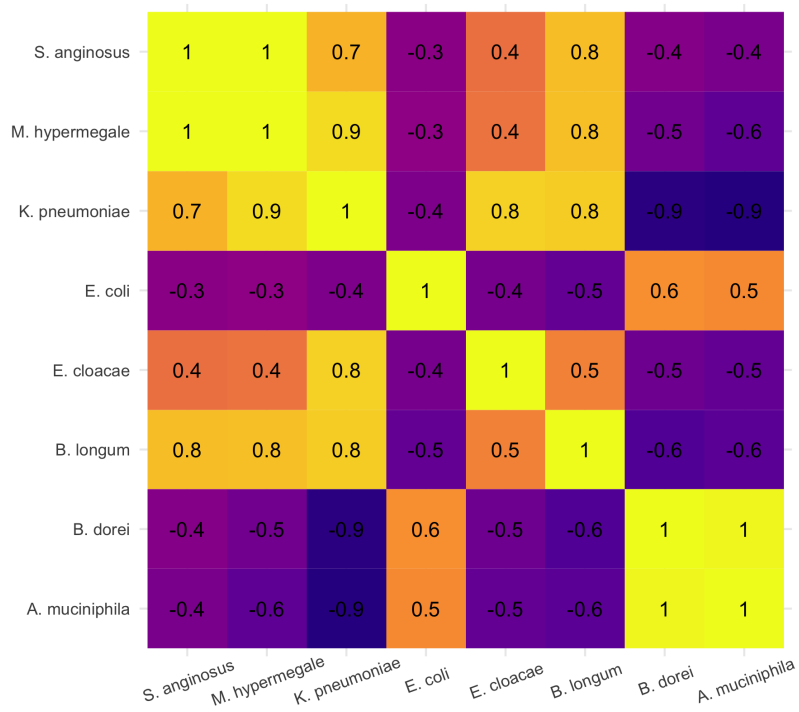


The FDR is controlled at level $\alpha' = 1.44 \times \alpha \times \frac{\#\text{discoveries} + \#\text{families tested}}{\#\text{discoveries} + 1}$.

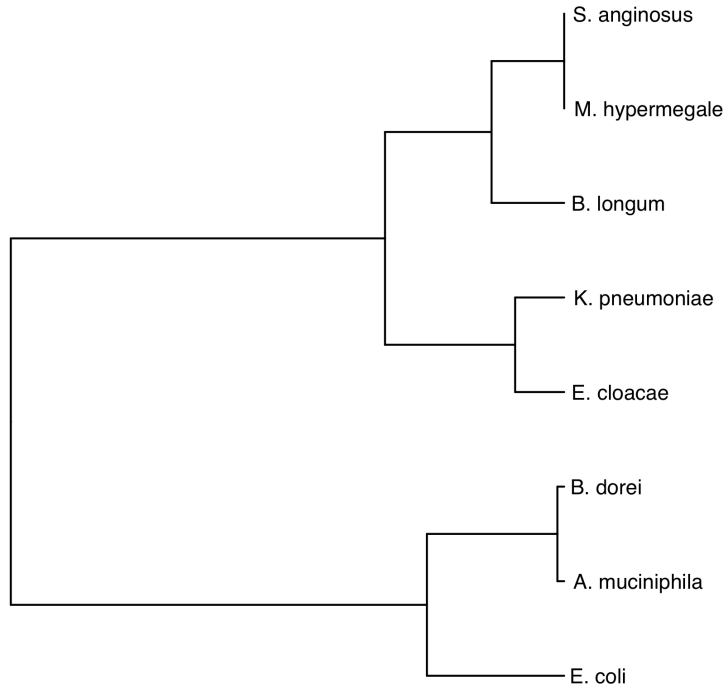
Yekutieli [Yek08]; Sankaran and Holmes [SH14]

Correlation tree

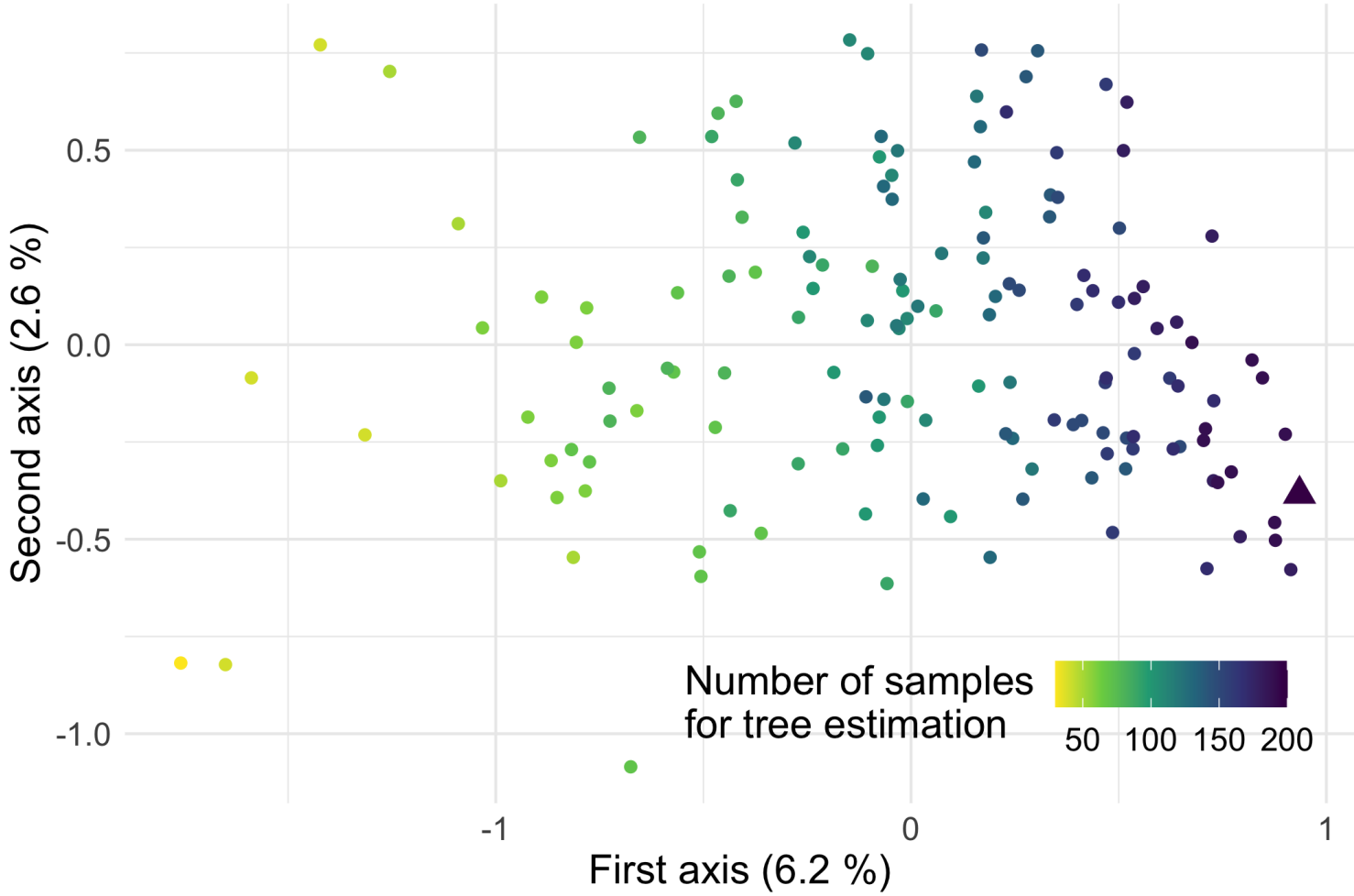
Matrix of pairwise correlation C



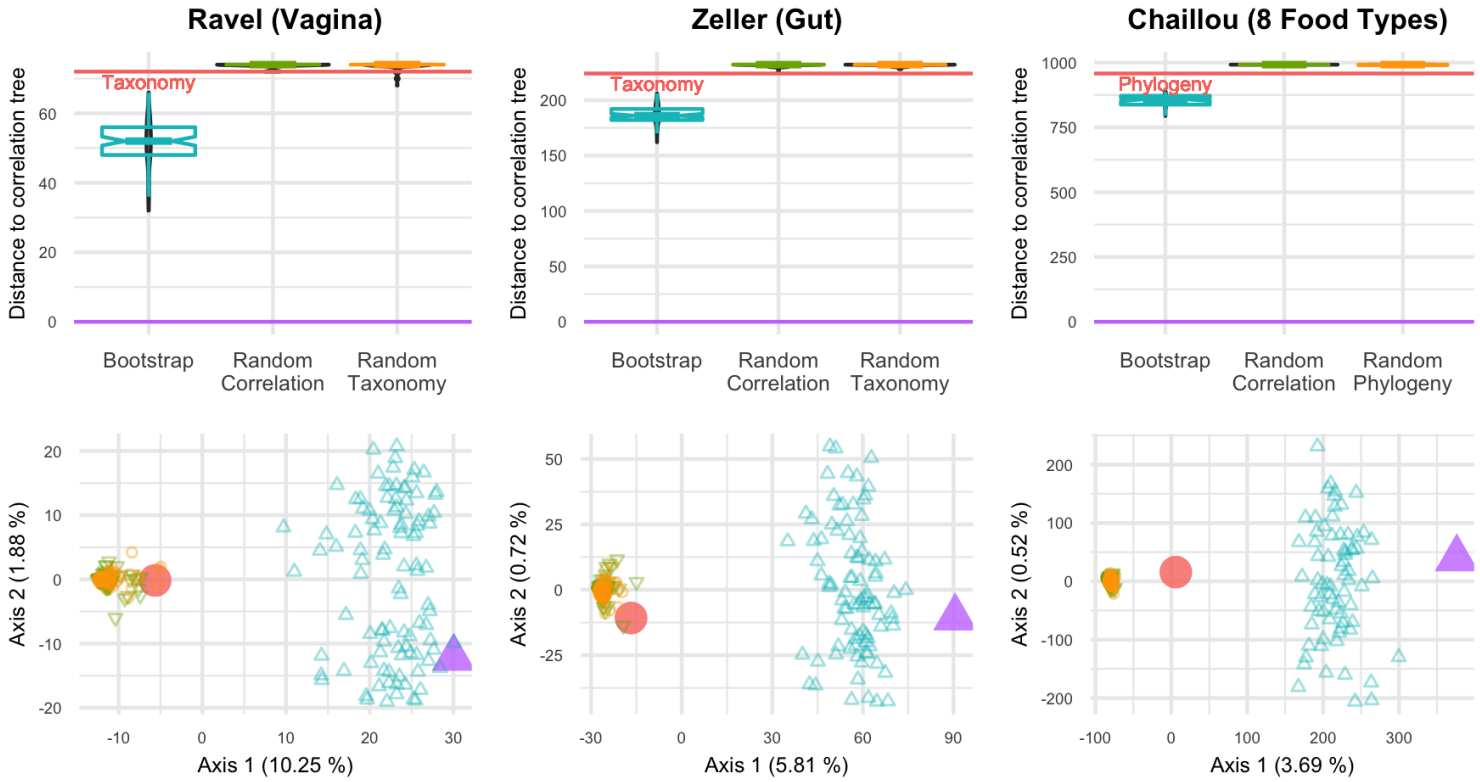
Hierarchical clustering on $1 - C$



Convergence to the correlation tree



With Robinson-Foulds distance



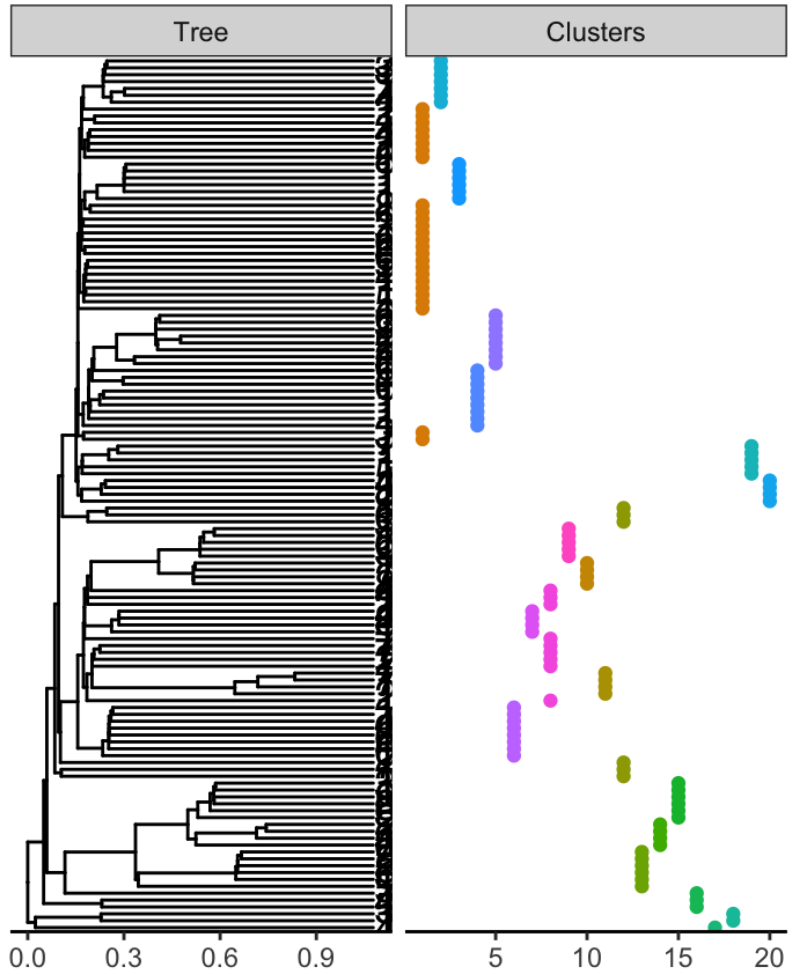
Robinson and Foulds [RF81]

Hierarchically consistent taxa

> The choice of differentially abundant taxa is done in a hierarchically consistent manner.

A partitioning around medoids (PAM) algorithm on the patristic distances matrix $\left(d_{i,j}\right)_{i,j}$ is use for this purpose.

1 to 5 clusters among 20 are selected to be differentially abundant.

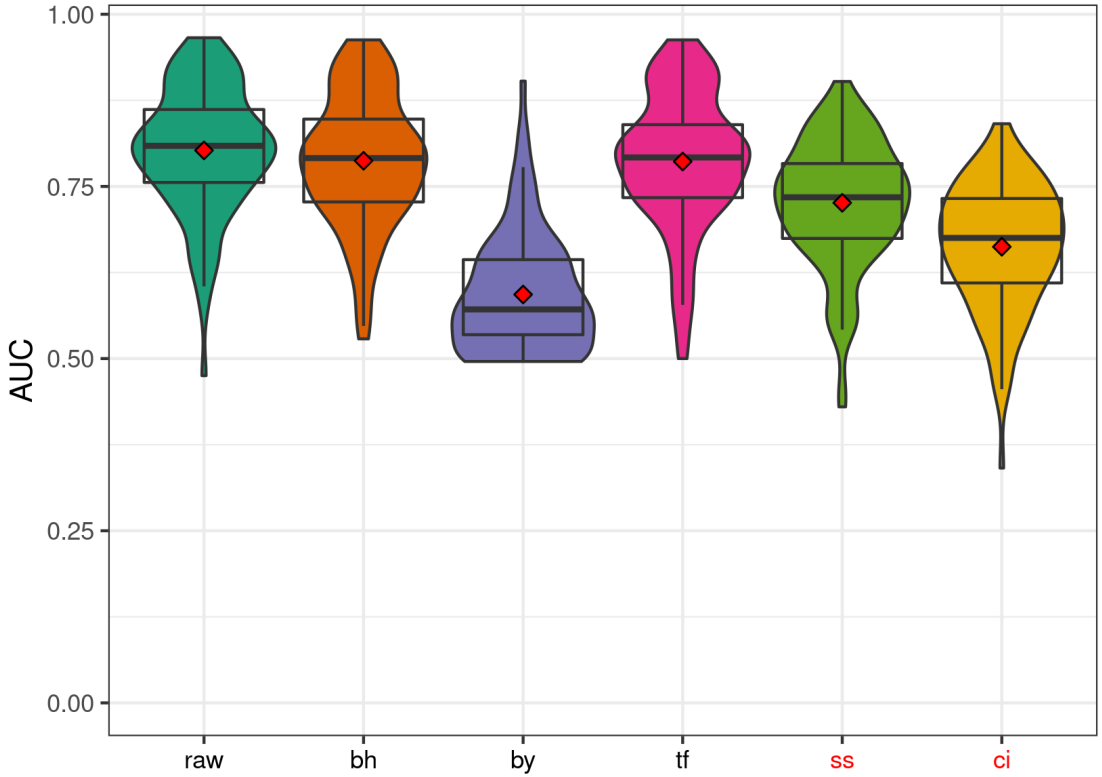


Quantitative results about FDP

(in %)	FDR			P(FDP > 5%)		
method	fc = 3	fc = 5	fc = 10	fc = 3	fc = 5	fc = 10
bh	2.69	2.46	3.23	4.40	7.20	12.20
by	0.40	0.36	0.85	0.40	0.60	2.20
tf	4.75	5.96	4.90	8.72	14.58	18.06
ss	8.17	5.26	3.99	12.40	8.40	8.80
ci	9.41	5.98	5.63	14.80	12.60	18.60

Negative simulations

When differentially abundant taxa are chosen uniformly.



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