Phylogeny Stability: Influence of Sites and Species

M. Mariadassou
Joint work with A. Bar-Hen and H. Kishino

Laboratoire MAP5
Université Paris Descartes

October 08
AgroParisTech-Paris5-select

Outline

Phylogeny Goal

Basic Assumption:

Evolution process can be thought of as a Tree where:

→ Populations within species accumulate differences...

→ ... and transforms into new species (=branches).

Main Objectives:

- Holy Grail: reconstruct the "Tree of Life";
- Pragmatically: reconstruct the evolutionary history of a group of species;
- Useful for gene annotation, functional genomics, gene network evolution study,...
- Different from coalescence, species are not identical.

Phylogeny Goal

Basic Assumption:

Evolution process can be thought of as a Tree where:

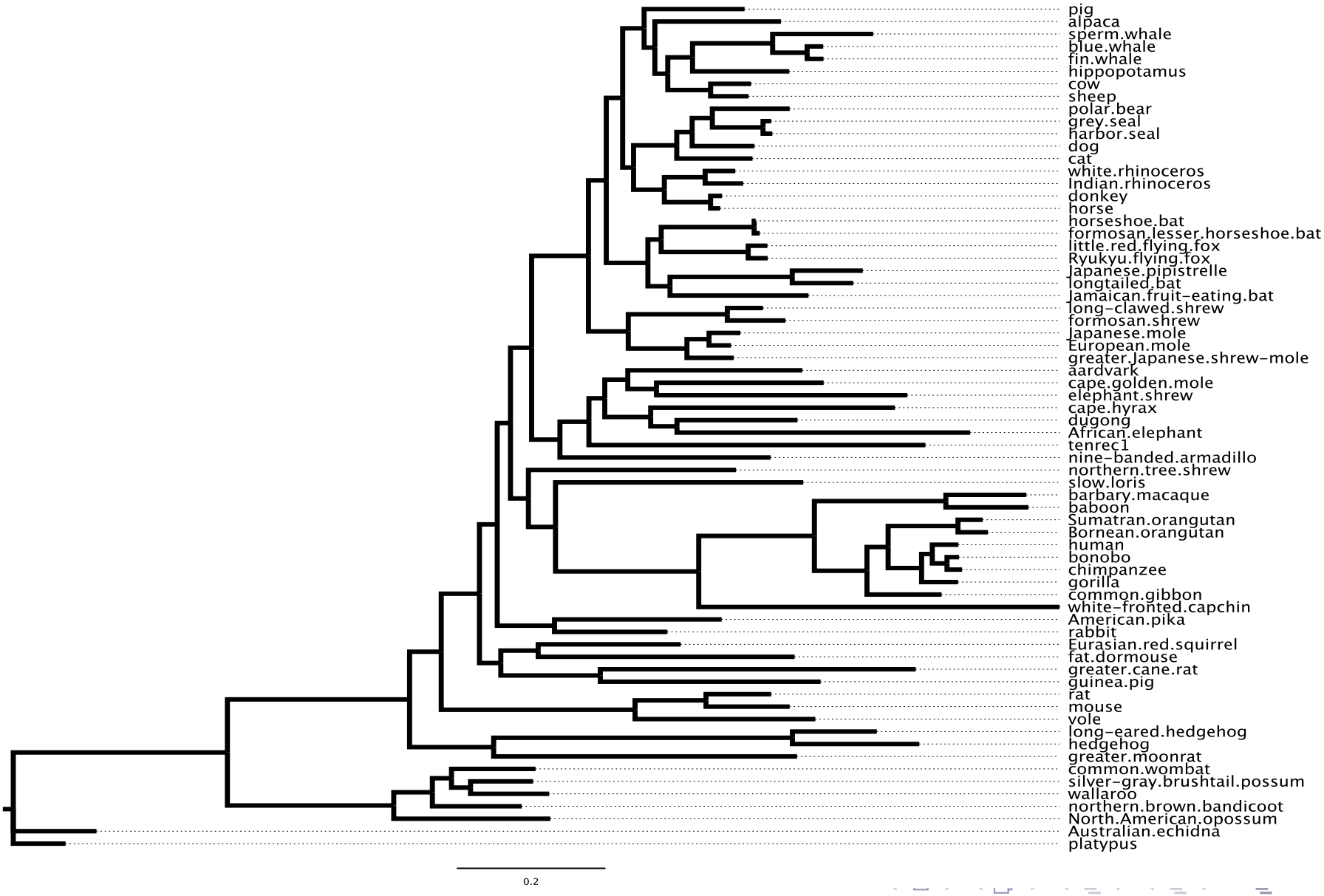
→ Populations within species accumulate differences...

→ ... and transforms into new species (=branches).

Main Objectives:

- Holy Grail: reconstruct the "Tree of Life";
- Pragmatically: reconstruct the evolutionary history of a group of species;
- Useful for gene annotation, functional genomics, gene network evolution study,...
- Different from coalescence, species are not identical.

Example of Mammal Phylogeny



Reconstruction Goals and Problems

Two levels of reconstruction

- Reconstruct the phylogeny:
  - Topology;
  - Branchs lengths.
- Reconstrut states nodes (at internal nodes).

Problems

- Genetic information available only for extant species, fossil records are unreliable;
- Reconstruction is a hard problem: the inferred tree might not be the true one.

A Wide Variety of Methods

Three Families of Methods:

- Distance-based:
  - Agglomerative approachs: (U/W)PGMA, Neighbor-Joining;
  - Iterative topology search and tree building;
- Parsimony-based: (un)corrected Maximum Parsimony;
- Likelihood-based:
  - Maximum Likelihood (ML);
  - Bayesian Methods.

But recent focus on the last one:

Consensus for likelihood-based methods:

- More computation-intensive but...
- Outperform other methods.

A Wide Variety of Methods

Three Families of Methods:

- Distance-based:
  - Agglomerative approachs: (U/W)PGMA, Neighbor-Joining;
  - Iterative topology search and tree building;
- Parsimony-based: (un)corrected Maximum Parsimony;
- Likelihood-based:
  - Maximum Likelihood (ML);
  - Bayesian Methods.

But recent focus on the last one:

Consensus for likelihood-based methods:

- More computation-intensive but...
- Outperform other methods.

A Wide Variety of Methods

Three Families of Methods:

- Distance-based:
  - Agglomerative approachs: (U/W)PGMA, Neighbor-Joining;
  - Iterative topology search and tree building;
- Parsimony-based: (un)corrected Maximum Parsimony;
- Likelihood-based:
  - Maximum Likelihood (ML);
  - Bayesian Methods.

But recent focus on the last one:

Consensus for likelihood-based methods:

- More computation-intensive but...
- Outperform other methods.

A Wide Variety of Methods

Three Families of Methods:

- Distance-based:
  - Agglomerative approachs: (U/W)PGMA, Neighbor-Joining;
  - Iterative topology search and tree building;
- Parsimony-based: (un)corrected Maximum Parsimony;
- Likelihood-based:
  - Maximum Likelihood (ML);
  - Bayesian Methods.

But recent focus on the last one:

Consensus for likelihood-based methods:

- More computation-intensive but...
- Outperform other methods.

Data at Hand and Goal

Alignment Data

- Alignment $\mathcal{X} = (X_{ij})$ of size $s \times n$ (number of species $\times$ sites);
- X_{ij} nucleotide j in taxon i valued in $\mathcal{A} = \{A, C, G, T\}$;
- $\mathbf{X}^{(j)}$ j-th line of $\mathcal{X}$, vector of size n;
- $\mathbf{X}^{(j)}$ sequence of taxon j;
- $\mathbf{X}_i$ i-th column of $\mathcal{X}$, vector of size s;
- $\mathbf{X}_i$ nucleotide pattern of site i.

Goal

- **Goal :** Find the binary tree with s leaves (one for each species) which represents the best explanation (=most probable) of the data, the maximum-likelihood tree.

Data at Hand and Goal

Alignment Data

- Alignment $\mathcal{X} = (X_{ij})$ of size $s \times n$ (number of species $\times$ sites);
- X_{ij} nucleotide j in taxon i valued in $\mathcal{A} = \{A, C, G, T\}$;
- $\mathbf{X}^{(j)}$ j-th line of $\mathcal{X}$, vector of size n;
- $\mathbf{X}^{(j)}$ sequence of taxon j;
- $\mathbf{X}_i$ i-th column of $\mathcal{X}$, vector of size s;
- $\mathbf{X}_i$ nucleotide pattern of site i.

Goal

- **Goal :** Find the binary tree with s leaves (one for each species) which represents the best explanation (=most probable) of the data, the maximum-likelihood tree.

Data Structure: An Example

Alignment example

Fin Whale	M	N	E	**N**	L	F	A	P	F	M
Harbor Seal	M	N	E	**N**	L	F	A	S	F	A
Blue Whale	M	N	E	**N**	L	F	A	P	F	M
Grey Seal	M	N	E	**N**	L	F	A	S	F	T
Horse	M	N	E	**N**	L	F	A	S	F	A
Chimpanzee	M	N	E	**N**	L	F	A	S	F	A
Bonobo	M	N	E	**N**	L	F	A	S	F	A
Gorilla	M	N	E	**N**	L	F	A	S	F	I
Bornean Orangutan	M	N	E	**D**	L	F	T	P	F	T

- $s = 9, n = 10$
- $\mathcal{X}_{24} =$ **N**;
- 4th site: $\mathbf{X}_4 =$ (**NNNNNNNND**)$'$;
- 2^{nd} taxon (Harbor Seal): $\mathbf{X}^{(2)} = MNENLFASFA$.

Inference of the ML Tree

Data modelling:

- Assume $(\mathbf{X}_i)_{i=1}^n$ *i.i.d.* (simplifying but essential assumption);
- Choose generating evolution model $M(T, \theta_T)$;
- Discrete topology T and continuous model parameter θ_T.

Likelihood Maximization

- Compute likelihood: $L_M(T, \theta_T) = \mathbb{P}((\mathbf{X}_i); M, T, \theta_T)$;
- For a given T, compute and store $\hat{\theta}_T$ maximizing $L(T, \theta_T)$;
- Repeat for all T and retrieve $(\hat{T}, \hat{\theta}_{\hat{T}})$.

Inference of the ML Tree

Data modelling:

- Assume $(\mathbf{X}_i)_{i=1}^n$ *i.i.d.* (simplifying but essential assumption);
- Choose generating evolution model $M(T, \theta_T)$;
- Discrete topology T and continuous model parameter θ_T.

Likelihood Maximization

- Compute likelihood: $L_M(T, \theta_T) = \mathbb{P}((\mathbf{X}_i); M, T, \theta_T)$;
- For a given T, compute and store $\hat{\theta}_T$ maximizing $L(T, \theta_T)$;
- Repeat for all T and retrieve $(\hat{T}, \hat{\theta}_{\hat{T}})$.

Evolution Model

Discrete space continuous time Markov chain

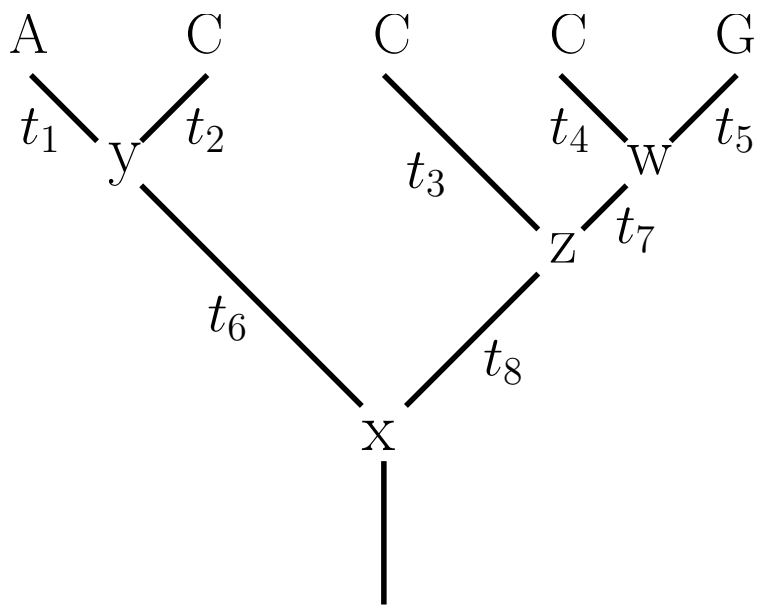
- State space: $\mathcal{A} = \{A, C, G, T\}$ (or $\mathcal{E} = \{\text{amino-acids}\}$);
- Generator (instantaneous rate matrix): $R = \Pi Q$ with

$$Q = \begin{pmatrix} * & \alpha_{AC} & \alpha_{AG} & \alpha_{AT} \\ - & * & \alpha_{CG} & \alpha_{CT} \\ - & - & * & \alpha_{GT} \\ - & - & - & * \end{pmatrix} \quad \Pi = \begin{pmatrix} \pi_A & 0 & 0 & 0 \\ 0 & \pi_C & 0 & 0 \\ 0 & 0 & \pi_G & 0 \\ 0 & 0 & 0 & \pi_T \end{pmatrix}$$

Computation of the likelihood on an example 1

For the following tree, for the given column:

$$\mathbb{P}(\mathbf{X}_i|T) = \sum_x \sum_y \sum_z \sum_w \mathbb{P}(A, C, C, C, G, x, y, z, w|T)$$



$$L = \prod_{i=1}^{n} \mathbb{P}(X_{1i}, \ldots, X_{si}|T) = \prod_{i=1}^{n} \mathbb{P}(\mathbf{X}_i|T)$$

▸ Example ?

The uncertainty issue

Inferred topology might not be the "true" topology;

Possible cause of uncertainties

- Small sequence lengths (data sampling);
- Low phylogenetic signal among the sites;
- Incomplete taxa sampling;
- Model misspecification;
- "Aberrant" species;
- Etc.

Notations

- $\mathbf{X}_i$ $i.i.d.$ with shared distribution Q;
- Empirical distribution $Q_n = \sum_i \delta_{\mathbf{X}_i}$ of the nucleotides;
- Support of Q made of all patterns with positive probability:

$$\mathcal{N}_s \subset \mathcal{A}^s \quad \text{Card}(\mathcal{N}_s) \leq 4^s$$

- True and empirical mean log-likelihood of T:

$$\ell^T = \mathbb{E}_Q[\log \mathbb{P}(\mathbf{X}; T)] = \sum_{x \in \mathcal{N}_s} Q(x) \log \mathbb{P}(x; T)$$

$$\ell_n^T = \mathbb{E}_{Q_n}[\log \mathbb{P}(\mathbf{X}; T)] = \frac{1}{n} \sum_i \log \mathbb{P}(\mathbf{X}_i; T)$$

where $\mathbb{P}(x; T)$ is the probability of pattern x under model T;

Notations

- $\mathbf{X}_i$ $i.i.d.$ with shared distribution Q;
- Empirical distribution $Q_n = \sum_i \delta_{\mathbf{X}_i}$ of the nucleotides;
- Support of Q made of all patterns with positive probability:

$$\mathcal{N}_s \subset \mathcal{A}^s \quad \text{Card}(\mathcal{N}_s) \leq 4^s$$

- True and empirical mean log-likelihood of T:

$$\begin{aligned} \ell^T &= \mathbb{E}_Q[\log \mathbb{P}(\mathbf{X}; T)] = \sum_{x \in \mathcal{N}_s} Q(x) \log \mathbb{P}(x; T) \\ \ell_n^T &= \mathbb{E}_{Q_n}[\log \mathbb{P}(\mathbf{X}; T)] = \frac{1}{n} \sum_i \log \mathbb{P}(\mathbf{X}_i; T) \end{aligned}$$

where $\mathbb{P}(x; T)$ is the probability of pattern x under model T;

ℓ^T as a scalar product

- Replace Q and Q_n, true and empirical pattern distribution, with:

$$\begin{aligned} \theta^x &= \mathbb{P}_Q(\mathbf{X} = x) \\ \theta_n^x &= \mathbb{P}_{Q_n}(\mathbf{X} = x) = \frac{1}{n}\sum_{i=1}^{n} \mathbb{1}_{\{\mathbf{X}_i = x\}} \end{aligned}$$

  $\boldsymbol{\theta} = (\theta^x)_{x \in \mathcal{N}_s}$ and $\boldsymbol{\theta}_n = (\theta_n^x)_{x \in \mathcal{N}_s}$;

- Then, with $\log P^T = (\log \mathbb{P}(x, T))_{x \in \mathcal{N}_s}$.

$$\begin{aligned} \ell^T &= \mathbb{E}_Q[\log \mathbb{P}(\mathbf{X}; T)] = \boldsymbol{\theta}.\log P^T \\ \ell_n^T &= \mathbb{E}_{Q_n}[\log \mathbb{P}(\mathbf{X}; T)] = \boldsymbol{\theta}_n.\log P^T \end{aligned}$$

- $\ell^T - \ell_n^T = (\boldsymbol{\theta} - \boldsymbol{\theta}_n).\log P^T$

ℓ^T as a scalar product

- Replace Q and Q_n, true and empirical pattern distribution, with:

$$\begin{aligned} \theta^x &= \mathbb{P}_Q(\mathbf{X} = x) \\ \theta_n^x &= \mathbb{P}_{Q_n}(\mathbf{X} = x) = \frac{1}{n}\sum_{i=1}^{n} \mathbb{1}_{\{\mathbf{X}_i = x\}} \end{aligned}$$

  $\boldsymbol{\theta} = (\theta^x)_{x \in \mathcal{N}_s}$ and $\boldsymbol{\theta}_n = (\theta_n^x)_{x \in \mathcal{N}_s}$;

- Then, with $\log P^T = (\log \mathbb{P}(x, T))_{x \in \mathcal{N}_s}$.

$$\begin{aligned} \ell^T &= \mathbb{E}_Q[\log \mathbb{P}(\mathbf{X}; T)] = \boldsymbol{\theta}.\log P^T \\ \ell_n^T &= \mathbb{E}_{Q_n}[\log \mathbb{P}(\mathbf{X}; T)] = \boldsymbol{\theta}_n.\log P^T \end{aligned}$$

- $\ell^T - \ell_n^T = (\boldsymbol{\theta} - \boldsymbol{\theta}_n).\log P^T$

Large Deviations I

- $\ell^T - \ell_n^T = (\boldsymbol{\theta} - \boldsymbol{\theta}_n).\log P^T$
- To control $\ell^T - \ell_n^T$, we need to control $\boldsymbol{\theta} - \boldsymbol{\theta}_n$, the difference between the true and the empirical pattern distribution;
- Probability of $\{\|\boldsymbol{\theta} - \boldsymbol{\theta}_n\| > \epsilon\}$ decreases exponentially towards 0;
- At what rate?

Using large deviation tools, we obtain:

$$\frac{\log \mathbb{P}(\|\boldsymbol{\theta} - \boldsymbol{\theta}_n\| > \varepsilon)}{n} \leq \frac{\log |\mathcal{N}_s|}{n} + \frac{\log 2}{n} + \max_{x \in \mathcal{N}_s} \frac{-\varepsilon^2}{\theta^x(1 - \theta^x + \varepsilon)}$$

Large Deviations II

This leads to:

$$\frac{\log \mathbb{P}\left(|\ell^T - \ell_n^T| \geq \varepsilon\right)}{n} \leq \frac{\log |\mathcal{N}_s|}{n} + \frac{\log 2}{n} + \max_{x \in \mathcal{N}_s} \frac{-\tilde{\varepsilon}^2}{\theta^x(1-\theta^x+\tilde{\varepsilon})}$$

Where $\tilde{\varepsilon} = \dfrac{\varepsilon}{|\mathcal{N}_s| \| \log P^T \|}$.

Remarks:

- For a given confidence level, we know how n evolves with s;
- Sharp bound for small $\mathcal{N}_s \Rightarrow$ accurate estimation of $|\mathcal{N}_s|$ is crucial;
- For simple models (JC69,K2P), patterns (*e.g.* $YYRR$) can be merged $\Rightarrow$ smaller $\mathcal{N}_s$.

Large Deviations II

This leads to:

$$\frac{\log \mathbb{P}\left(|\ell^T - \ell_n^T| \geq \varepsilon\right)}{n} \leq \frac{\log |\mathcal{N}_s|}{n} + \frac{\log 2}{n} + \max_{x \in \mathcal{N}_s} \frac{-\tilde{\varepsilon}^2}{\theta^x(1-\theta^x+\tilde{\varepsilon})}$$

Where $\tilde{\varepsilon} = \dfrac{\varepsilon}{|\mathcal{N}_s| \| \log P^T \|}$.

Remarks:

- For a given confidence level, we know how n evolves with s;
- Sharp bound for small $\mathcal{N}_s \Rightarrow$ accurate estimation of $|\mathcal{N}_s|$ is crucial;
- For simple models (JC69,K2P), patterns (*e.g.* $YYRR$) can be merged $\Rightarrow$ smaller $\mathcal{N}_s$.

Inversions events

- ML methods based on the model ranking induced by their likelihood score;
- But inference done on ranking induced by empirical likelihood score;
- Inversion events between models T and T' can happen;
- When comparing two models T and T', the true ranking may be different from the empirical one;
- How often does such an event happens?
- How does its probability $\mathbb{P}(\ell_n^T - \ell_n^{T'} < 0 | \ell^T - \ell^{T'} > 0)$ decreases when available information increases?

Inversions events

- ML methods based on the model ranking induced by their likelihood score;
- But inference done on ranking induced by empirical likelihood score;
- Inversion events between models T and T' can happen;
- When comparing two models T and T', the true ranking may be different from the empirical one;
- How often does such an event happens?
- How does its probability $\mathbb{P}(\ell_n^T - \ell_n^{T'} < 0 | \ell^T - \ell^{T'} > 0)$ decreases when available information increases?

Inversions events

- ML methods based on the model ranking induced by their likelihood score;
- But inference done on ranking induced by empirical likelihood score;
- Inversion events between models T and T' can happen;
- When comparing two models T and T', the true ranking may be different from the empirical one;
- How often does such an event happens?
- How does its probability $\mathbb{P}(\ell_n^T - \ell_n^{T'} < 0 | \ell^T - \ell^{T'} > 0)$ decreases when available information increases?

Concentration results

Still using large deviation tools, we obtain:

Proposition

Assume that model T is better than model T' ($\ell^T > \ell^{T'}$), then the probability that T' is better than T for our sample is such that:

$$\frac{\log \mathbb{P}(\ell_n^T - \ell_n^{T'} < 0)}{n} \leq \frac{\log |\mathcal{N}_s|}{n} + \max_{x \in \mathcal{N}_s} \frac{-\varepsilon^2}{\theta^x(1 - \theta^x + \varepsilon)}$$

where $\varepsilon = \frac{\ell^T - \ell^{T'}}{|\mathcal{N}_s| \| \log P^T - \log P^{T'} \|}$ *and* $\boldsymbol{\theta} = (\mathbb{P}_Q(\mathbf{X} = x))_{x \in \mathcal{N}_s}$.

Remarks:

- Expected result: inversion probability decreases with $\ell^T - \ell^{T'}$;
- Patterns with same likelihood under T and T' can be removed from $\mathcal{N}_s$.

Motivation and Goal

Motivation: Filter Data

Sites source of errors:

- Sequencing errors;
- Alignment errors;
- Presence of an atypical DNA segment;
- . . .

Goal

- Quantify the influence of each site on the tree;
- Detect outlier sites;
- Infer a robust tree.

Motivation and Goal

Motivation: Filter Data

Sites source of errors:

- Sequencing errors;
- Alignment errors;
- Presence of an atypical DNA segment;
- . . .

Goal

- Quantify the influence of each site on the tree;
- Detect outlier sites;
- Infer a robust tree.

About the Influence Function

Influence Function: Definition

Let $X_1, \ldots, X_n$ be *i.i.d.* with common d.f. F on $\mathcal{R}^d$ and $S(F)$ a functional of F. The influence function:

$$IF_{S,F}(x) = \lim_{\varepsilon \to 0} \frac{S[(1-\varepsilon)F + \varepsilon\delta_x] - S[F]}{\varepsilon}$$

measure the influence of a perturbation in direction x.

Empirical Version

For unknown S and finite size sample, $F \to F_n = \frac{1}{n}\sum_{j=1}^{n} \delta_{X_j}$, $\varepsilon \to -1/(n-1)$:

$$\begin{aligned} IF_{S,F_n}(X_i) &= \lim_{\varepsilon \to 0} \frac{S[(1-\varepsilon)F_n + \varepsilon\delta_{X_i}] - S[F_n]}{\varepsilon} \\ &= (n-1)\big(S(F_n) - S(F_{n,-i})\big) \end{aligned}$$

where $F_{n,-i}$ is the empirical distribution on all sites but i.

About the Influence Function

Influence Function: Definition

Let $X_1, \ldots, X_n$ be *i.i.d.* with common d.f. F on $\mathcal{R}^d$ and $S(F)$ a functional of F. The influence function:

$$IF_{S,F}(x) = \lim_{\varepsilon \to 0} \frac{S[(1-\varepsilon)F + \varepsilon\delta_x] - S[F]}{\varepsilon}$$

measure the influence of a perturbation in direction x.

Empirical Version

For unknown S and finite size sample, $F \to F_n = \frac{1}{n}\sum_{j=1}^{n} \delta_{X_j}$, $\varepsilon \to -1/(n-1)$:

$$\begin{aligned} IF_{S,F_n}(X_i) &= \lim_{\varepsilon \to 0} \frac{S[(1-\varepsilon)F_n + \varepsilon\delta_{X_i}] - S[F_n]}{\varepsilon} \\ &= (n-1)\big(S(F_n) - S(F_{n,-i})\big) \end{aligned}$$

where $F_{n,-i}$ is the empirical distribution on all sites but i.

And for Phylogenies...

Definition

Let:

- $\mathbf{X} = (\mathbf{X}_1, \ldots, \mathbf{X}_n)$ be the complete alignment,
- $\mathbf{X}_{-i} = \mathbf{X} \backslash \mathbf{X}_i$ all the sites but site i,
- $(\hat{T}, \hat{\theta}_{\hat{T}})$ the ML tree and associated parameters for $\mathbf{X}$,
- $(\widehat{T_{-i}}, \hat{\theta}_{\widehat{T_{-i}}})$ the ML tree and associated parameters for $\mathbf{X}_{-i}$,
- The statistic be:

$$l_{\hat{T}}(\hat{\theta}_{\hat{T}}|\mathbf{X}) = \frac{1}{n}\sum_{i=1}^{n} \log \mathbb{P}(\mathbf{X}_i|\hat{T}, \hat{\theta}_{\hat{T}})$$

The influence value of $\mathbf{X}_i$ is then:

$$IF_{S,F_n}(\mathbf{X}_i) = (n-1)\left(l_{\hat{T}}(\hat{\theta}_{\hat{T}}|\mathbf{X}) - l_{\widehat{T_{-i}}}(\hat{\theta}_{\widehat{T_{-i}}}|\mathbf{X}_{-i})\right)$$

And for Phylogenies...

Definition

Let:

- $\mathbf{X} = (\mathbf{X}_1, \ldots, \mathbf{X}_n)$ be the complete alignment,
- $\mathbf{X}_{-i} = \mathbf{X} \backslash \mathbf{X}_i$ all the sites but site i,
- $(\hat{T}, \hat{\theta}_{\hat{T}})$ the ML tree and associated parameters for $\mathbf{X}$,
- $(\widehat{T_{-i}}, \hat{\theta}_{\widehat{T_{-i}}})$ the ML tree and associated parameters for $\mathbf{X}_{-i}$,
- The statistic be:

$$l_{\hat{T}}(\hat{\theta}_{\hat{T}}|\mathbf{X}) = \frac{1}{n}\sum_{i=1}^{n} \log \mathbb{P}(\mathbf{X}_i|\hat{T}, \hat{\theta}_{\hat{T}})$$

The influence value of $\mathbf{X}_i$ is then:

$$IF_{S,F_n}(\mathbf{X}_i) = (n-1)\left(l_{\hat{T}}(\hat{\theta}_{\hat{T}}|\mathbf{X}) - l_{\widehat{T_{-i}}}(\hat{\theta}_{\widehat{T_{-i}}}|\mathbf{X}_{-i})\right)$$

Influence Values

Interpretation

- Positive value: enhanced support for the ML tree;
- Negative value: weakened support for the ML tree;
- Absolute value: strength of the support/disagreement;
- Many sites with small positive values and a few sites with large negative values.

Strategy towards greater stability

- Focus on outliers: sites with $IF(\mathbf{X}_i) < 0$;
- Rank them in increasing $IF(\mathbf{X}_i)$;
- Remove them one at the time until a stable tree is found.

Influence Values

Interpretation

- Positive value: enhanced support for the ML tree;
- Negative value: weakened support for the ML tree;
- Absolute value: strength of the support/disagreement;
- Many sites with small positive values and a few sites with large negative values.

Strategy towards greater stability

- Focus on outliers: sites with $IF(\mathbf{X}_i) < 0$;
- Rank them in increasing $IF(\mathbf{X}_i)$;
- Remove them one at the time until a stable tree is found.

Influence Values

Interpretation

- Positive value: enhanced support for the ML tree;
- Negative value: weakened support for the ML tree;
- Absolute value: strength of the support/disagreement;
- Many sites with small positive values and a few sites with large negative values.

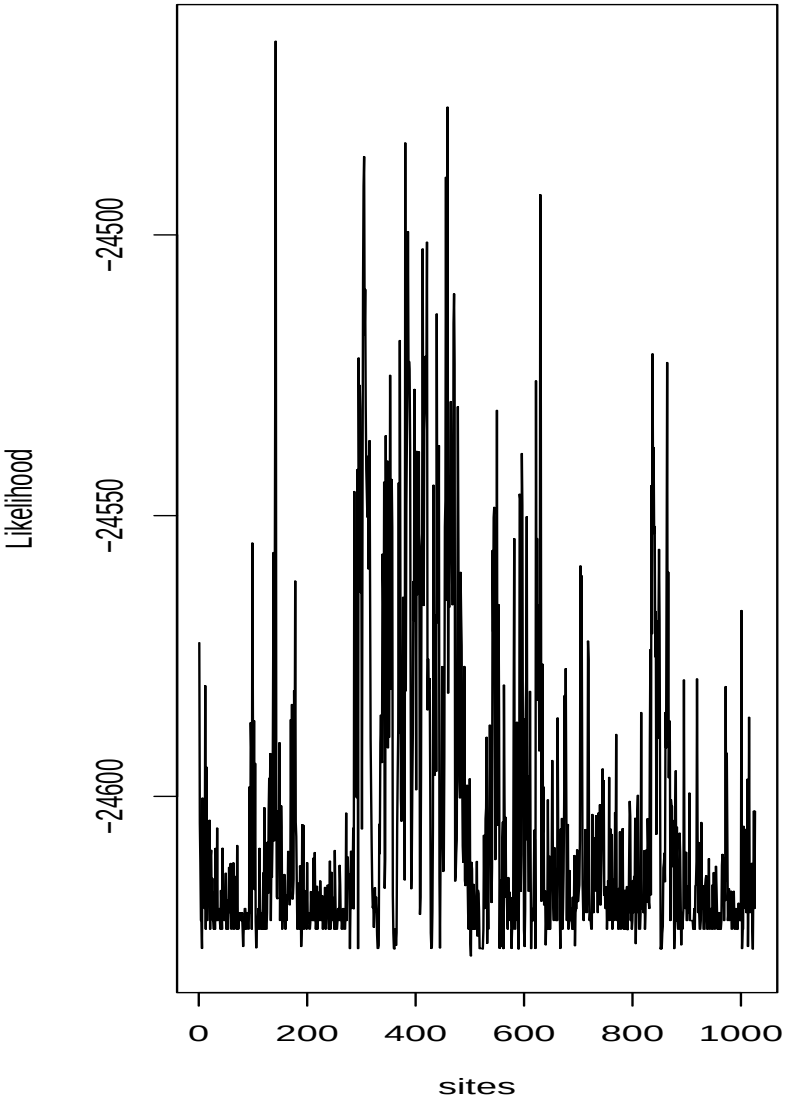
Strategy towards greater stability

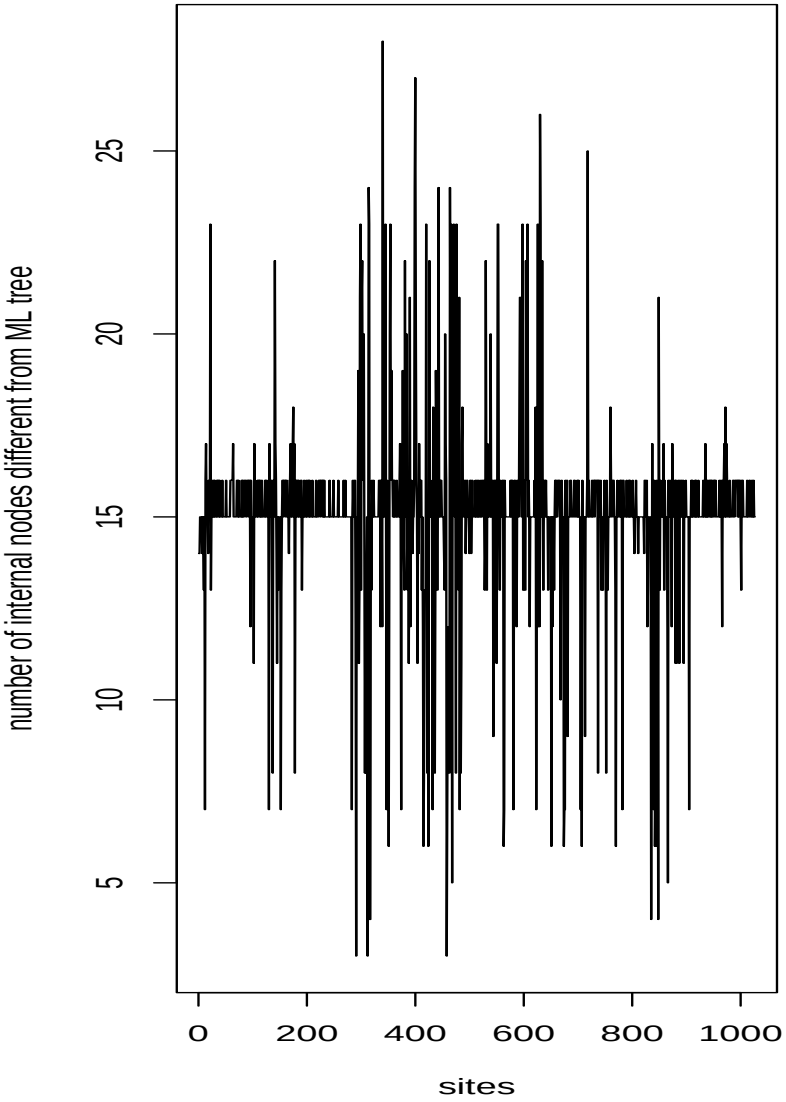
- Focus on outliers: sites with $IF(\mathbf{X}_i) < 0$;
- Rank them in increasing $IF(\mathbf{X}_i)$;
- Remove them one at the time until a stable tree is found.

Data: Zygomycetes & Chytridiomycetes

- "Lower mushrooms"
- Biology: widely unknown!
- Strong enough phylogenetic signal to correctly resolve the topology.
- 1026 sites, 158 OTUs, GTR model

Information about sites





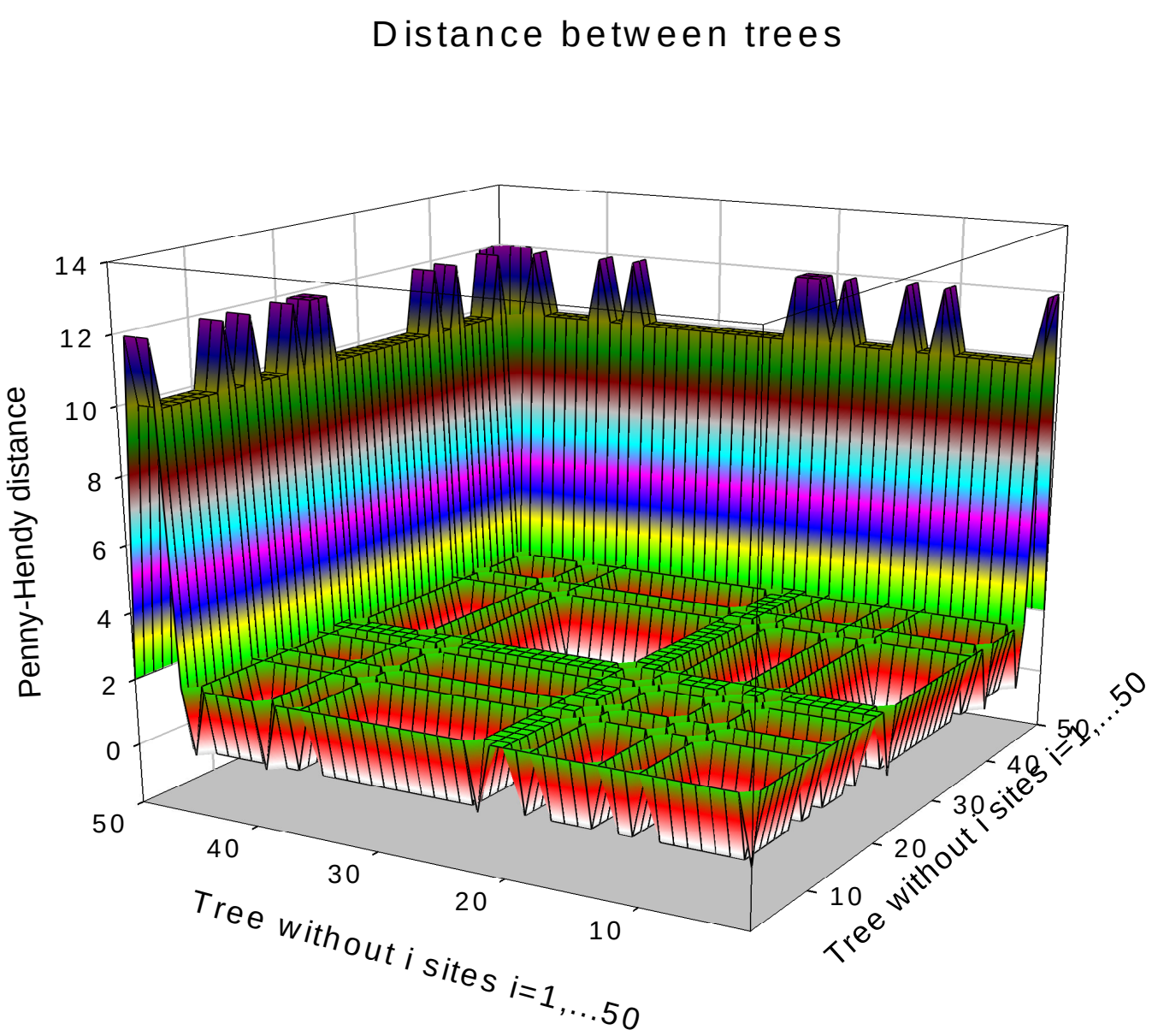
Distance between trees

0	20	18	18	18	18	18	18	18	20
20	0	2	2	2	2	2	2	2	2
18	2	0	0	0	0	0	0	0	2
18	2	0	0	0	0	0	0	0	2
18	2	0	0	0	0	0	0	0	2
18	2	0	0	0	0	0	0	0	2
18	2	0	0	0	0	0	0	0	2
18	2	0	0	0	0	0	0	0	2
18	2	0	0	0	0	0	0	0	2
20	2	2	2	2	2	2	2	2	0

T_i: trees constructed without the i most influent sites.

D_{ij}: Robinson-Foulds distance between T_i and T_j

Distance Between Trees



Motivation and Goal

Motivation: Filter Data

Species source of error:

- Poor taxon sampling;
- Sequencing errors in a species;
- Model misspecification;
- Aberrant species, etc.

Goal

- Quantify the influence of each species on the tree;
- Detect rogue species;
- Identify weak nodes.

Motivation and Goal

Motivation: Filter Data

Species source of error:

- Poor taxon sampling;
- Sequencing errors in a species;
- Model misspecification;
- Aberrant species, etc.

Goal

- Quantify the influence of each species on the tree;
- Detect rogue species;
- Identify weak nodes.

Species Leverage Index (SLI)

Definition

Let:

- $\mathbf{X} = \left(\mathbf{X}^{(1)}, \ldots, \mathbf{X}^{(s)}\right)'$ be the complete alignment,
- $\mathbf{X}^{(-i)} = \mathbf{X} \backslash \mathbf{X}^{(i)}$ all the species but species i,
- $\widehat{T}$ the ML tree and associated parameters for $\mathbf{X}$,
- $\widehat{T}^{(-i)}$ the tree $\widehat{T}$ after pruning species i,
- $\widehat{T^{(-i)}}$ the ML tree and associated

The Species Leverage Index (SLI) of species i is:

$$SLI(i) = d(\widehat{T}^{(-i)}, \widehat{T^{(-i)}})$$

where d is any adapted distance .

Species Leverage Index (SLI)

Definition

Let:

- $\mathbf{X} = \left(\mathbf{X}^{(1)}, \ldots, \mathbf{X}^{(s)}\right)'$ be the complete alignment,
- $\mathbf{X}^{(-i)} = \mathbf{X} \backslash \mathbf{X}^{(i)}$ all the species but species i,
- $\widehat{T}$ the ML tree and associated parameters for $\mathbf{X}$,
- $\widehat{T}^{(-i)}$ the tree $\widehat{T}$ after pruning species i,
- $\widehat{T^{(-i)}}$ the ML tree and associated

The Species Leverage Index (SLI) of species i is:

$$SLI(i) = d(\widehat{T}^{(-i)}, \widehat{T^{(-i)}})$$

where d is any adapted distance .

Nodes Leverage Index (NLI)

Definition

Let:

- $\mathbf{X}$, $\mathbf{X}^{(-i)}$, $\widehat{T}$, $\widehat{T}^{(-i)}$, $\widehat{T^{(-i)}}$ defined as before,
- A an internal node of $\widehat{T}$,

The Nodes Leverage Index (NLI) of A is:

$$NLI(A) = \sum_{i=1}^{n} \mathbb{1}_{\widehat{T^{(-i)}}}(A)$$

with $\mathbb{1}_{\widehat{T^{(-i)}}}(A)$ being 1 if A is present in $\widehat{T^{(-i)}}$ and 0 otherwise.

Nodes Leverage Index (NLI)

Definition

Let:

- $\mathbf{X}$, $\mathbf{X}^{(-i)}$, $\widehat{T}$, $\widehat{T}^{(-i)}$, $\widehat{T^{(-i)}}$ defined as before,
- A an internal node of $\widehat{T}$,

The Nodes Leverage Index (NLI) of A is:

$$NLI(A) = \sum_{i=1}^{n} \mathbb{1}_{\widehat{T^{(-i)}}}(A)$$

with $\mathbb{1}_{\widehat{T^{(-i)}}}(A)$ being 1 if A is present in $\widehat{T^{(-i)}}$ and 0 otherwise.

NLIs and SLIs

Interpretation

SLI:
- Low value: adding/removing the species from the dataset has (almost) impact on the tree;
- High value: “rogue” species, adding/removing it greatly affects the tree.

NLI:
- High value: stable nodes, highly resilient to taxon sampling;
- Low value: weak nodes, highly sensitive to taxon sampling.

Strategy towards greater stability

- Focus on rogues species: species with high SLI;
- Rank them in increasing SLI;
- Remove them one at the time until a stable tree is found.

NLIs and SLIs

Interpretation

SLI:
- Low value: adding/removing the species from the dataset has (almost) impact on the tree;
- High value: “rogue” species, adding/removing it greatly affects the tree.

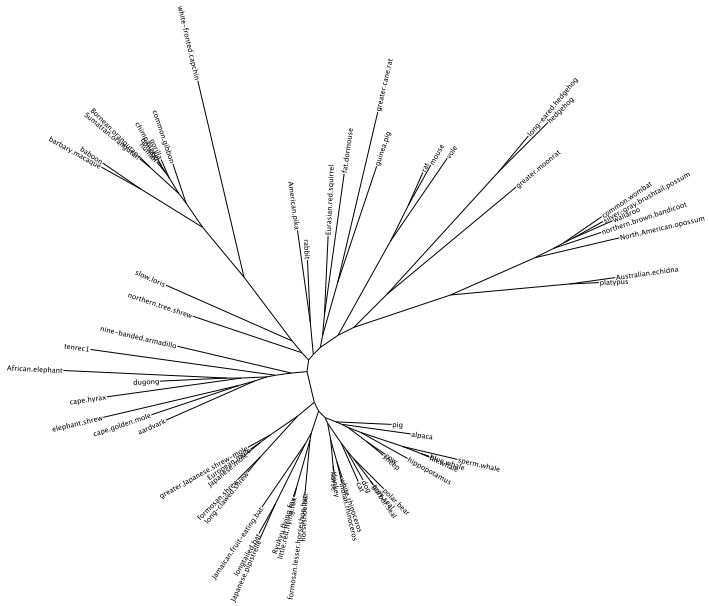
NLI:
- High value: stable nodes, highly resilient to taxon sampling;
- Low value: weak nodes, highly sensitive to taxon sampling.

Strategy towards greater stability

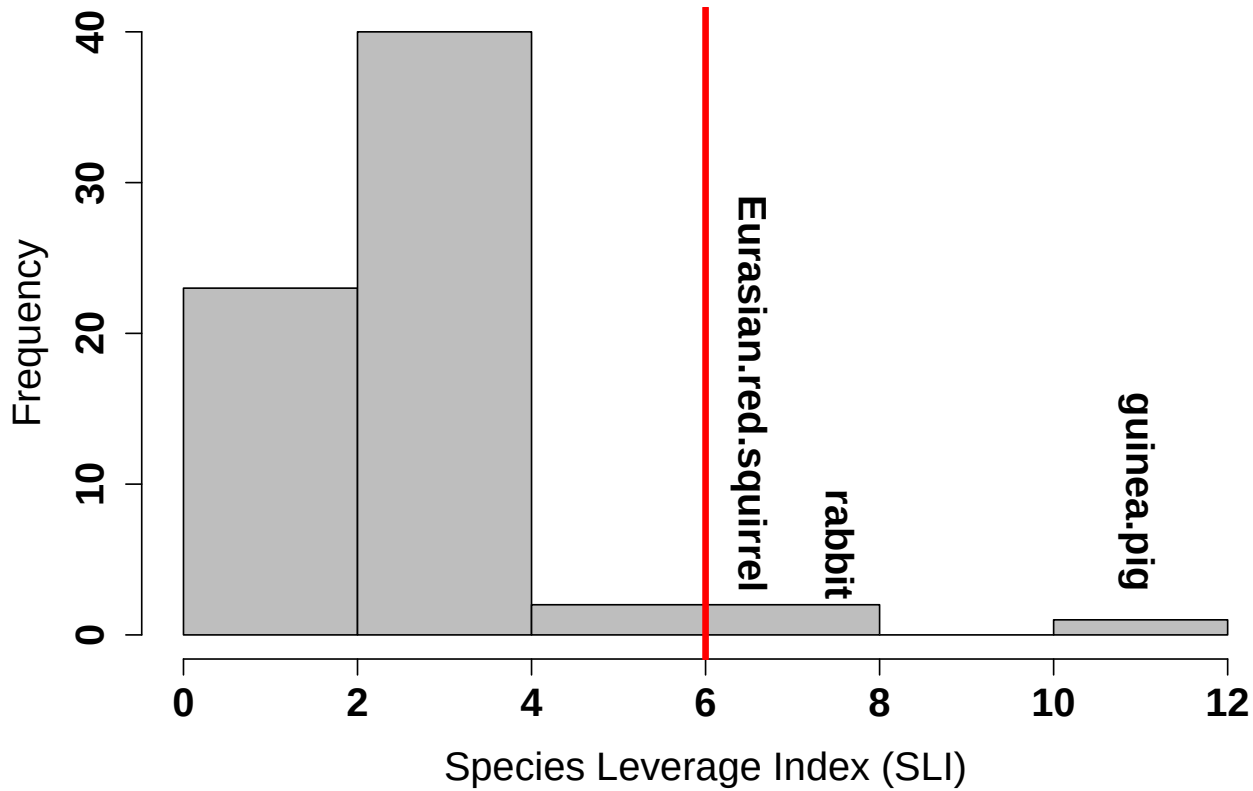
- Focus on rogues species: species with high SLI;
- Rank them in increasing SLI;
- Remove them one at the time until a stable tree is found.

Data: Placental Mammal Phylogeny

- Mitochondrial genome of 68 mammals;
- Amino Acids sequences;
- Sequences are 3658 sites long;
- Phylogeny published in Nikaido *et al.* in 2003.



SLI


Frequency
0
10
20
30
40
0
2
4
6
8
10
12
Species Leverage Index (SLI)
Eurasian.red.squirrel
rabbit
guinea.pig

Guinea Pig

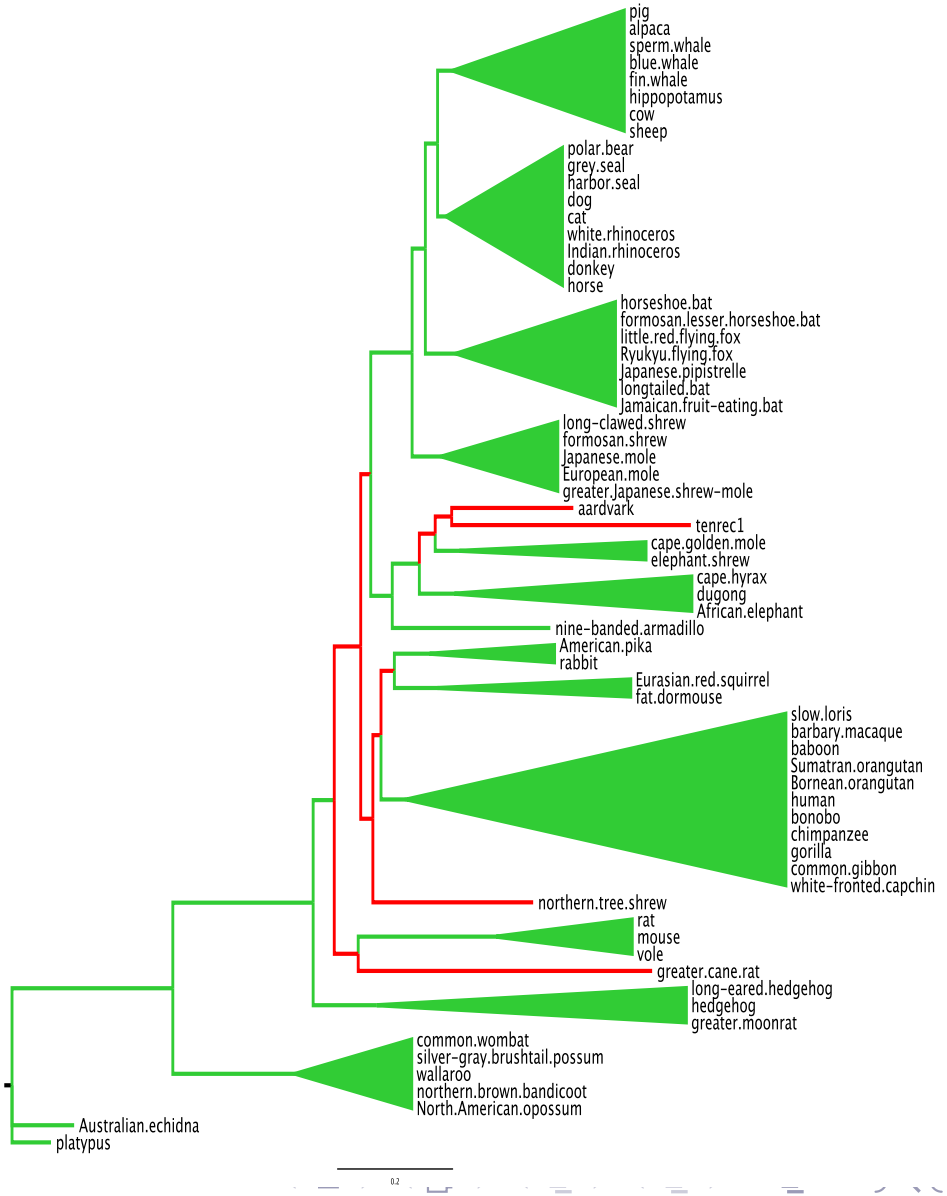
With guinea pig

Without guinea pig

Guinea Pig

With guinea pig

Without guinea pig



Summary

Three sources of uncertainties

- Data sampling;
- Outlier sites;
- Rogue species.

Three tools to detect them

- How many sites to compute the likelihood;
- Influence functions;
- Species Leverage.

Summary

Three sources of uncertainties

- Data sampling;
- Outlier sites;
- Rogue species.

Three tools to detect them

- How many sites to compute the likelihood;
- Influence functions;
- Species Leverage.

Perspectives

- Impact of the evolution model;
- Bootstrap: global measure of uncertainty;
- IF,SLI,NLI are local ones to pinpoint the sources of uncertainties;
- Decompose the “black box” of bootstrap values;
- Anything else I can think about.

Computation of the likelihood on an example 2

Markovian properties give:

$$\begin{aligned}\mathbb{P}(A,C,C,C,G,x,y,z,w|T) = \\ \mathbb{P}(x)\mathbb{P}(y|x,t_6)\mathbb{P}(A|y,t_1)\mathbb{P}(C|y,t_2) \\ \mathbb{P}(z|x,t_8)\mathbb{P}(C|z,t_3) \\ \mathbb{P}(w|z,t_7)\mathbb{P}(C|w,t_4)\mathbb{P}(G|w,t_5)\end{aligned}$$

which can be rewritten:

$$\begin{aligned}\mathbb{P}(\mathbf{X}_i|T) = \\ \sum_x \mathbb{P}(x)\left(\sum_y \mathbb{P}(y|x,t_6)\mathbb{P}(A|y,t_1)\mathbb{P}(C|y,t_2)\right) \\ \times\left(\sum_z \mathbb{P}(z|x,t_8)\mathbb{P}(C|z,t_3)\right. \\ \left.(\sum_w \mathbb{P}(w|z,t_7)\mathbb{P}(C|w,t_4)\mathbb{P}(G|w,t_5))\right)\end{aligned}$$

Computation of the likelihood on an example 3

- The factorization structure mimics the tree (A,C)(C,(C,G)) of interest.
- Felsenstein (1989) developed a recursive pruning algorithm to quickly compute the likelihood a phylogeny, from the leaves to the root.

▸ End of the example

Rooted trees and exhaustive search

The GTR model is reversible:

$$\mathbb{P}(x)\mathbb{P}(y|x,t_6) = \mathbb{P}(y)\mathbb{P}(x|y,t_6)$$

No flow of time:we infer an unrooted tree.

But there still exists $3 \times 5 \times 7 \times \cdots \times (2s-5)$ unrooted trees. Except for very small dataset, exhaustive search is impossible.