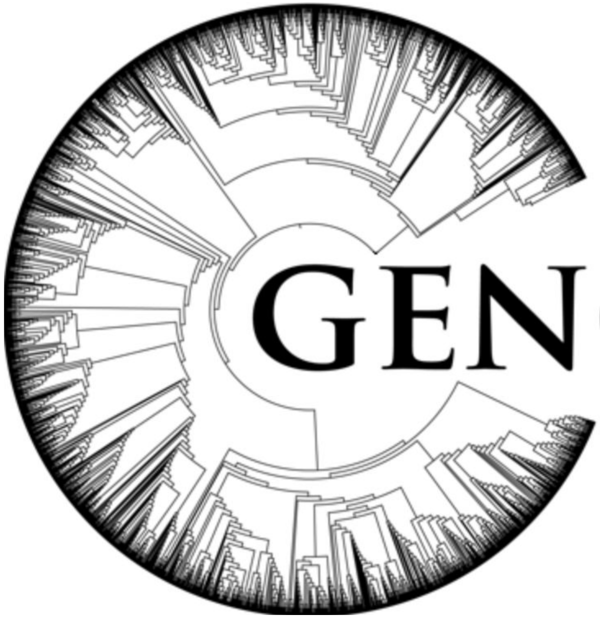
(A VERY SHORT INTRO TO)

PHYLO GENOMICS

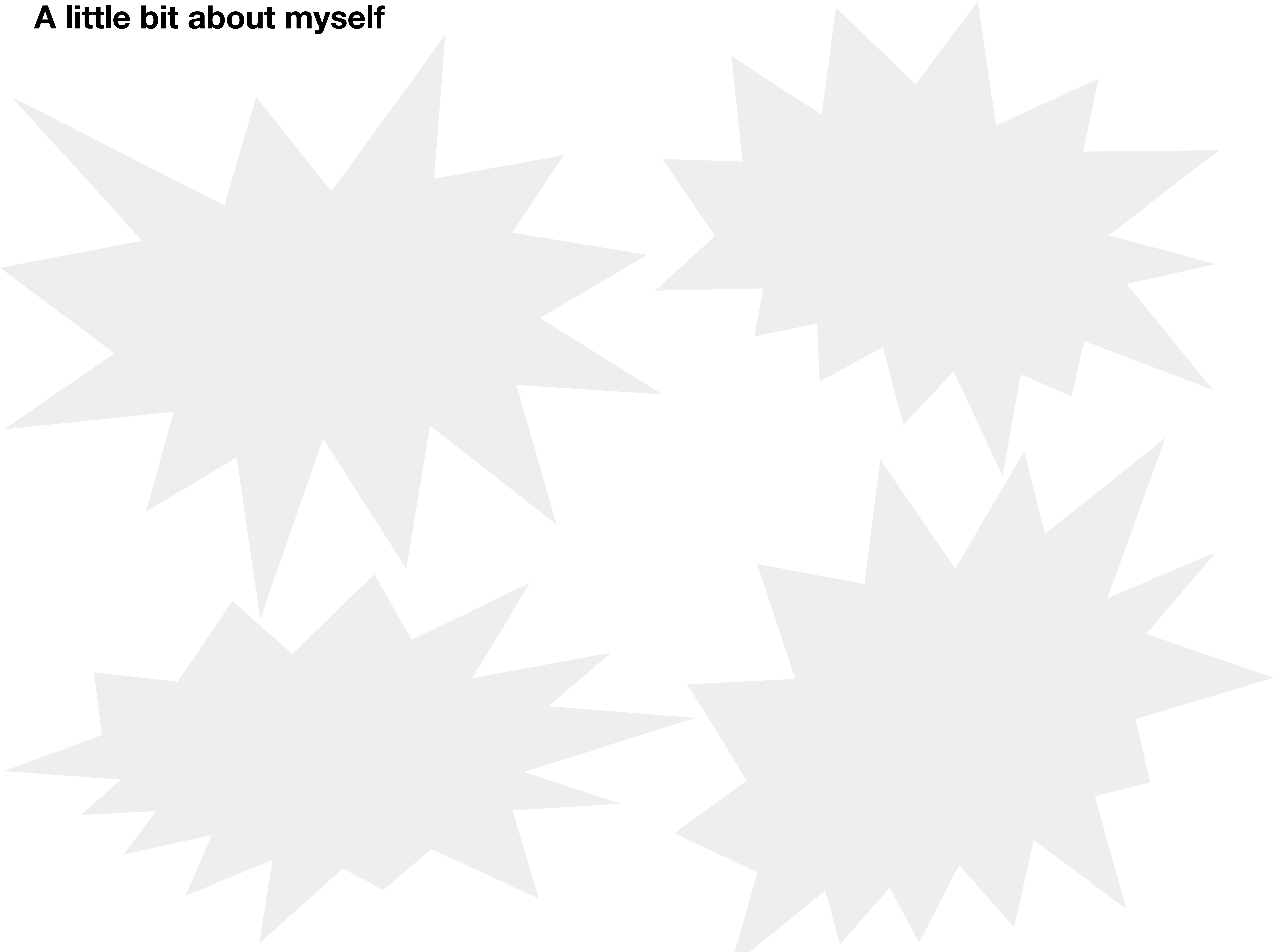


Rosa Fernández

Institute of Evolutionary Biology (CSIC-UPF)

rosa.fernandez@ibe.upf-csic.es

A little bit about myself



A little bit about myself

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⇩

Boston (1st postdoc)

HARVARD
UNIVERSITY

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www.metazomics.com

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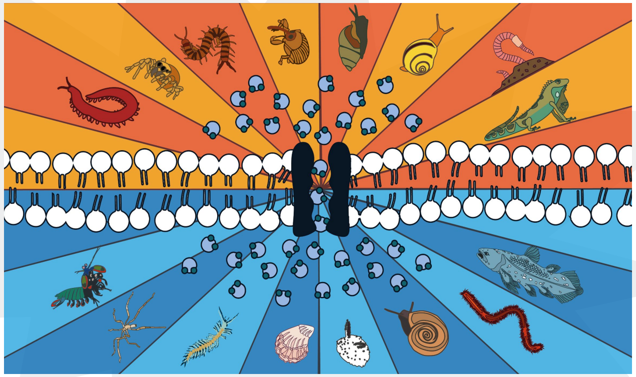

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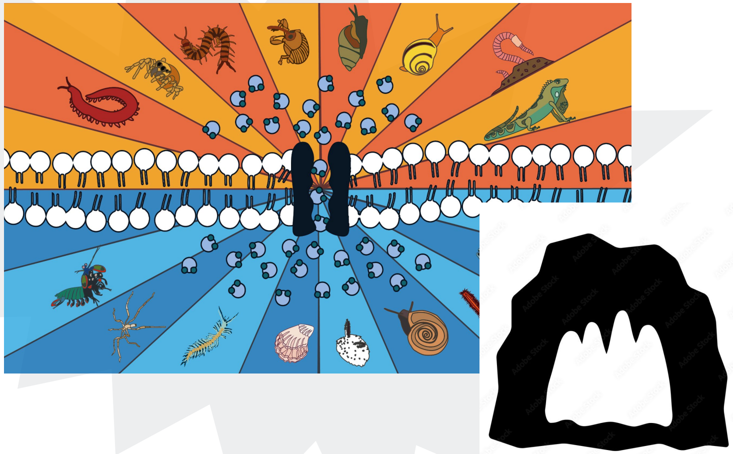

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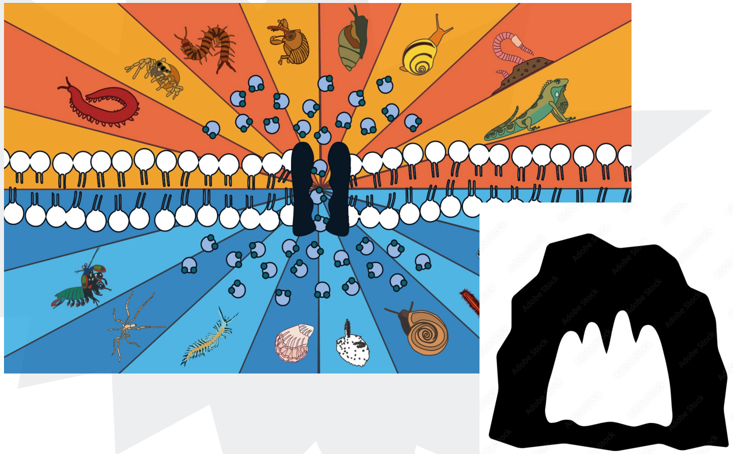

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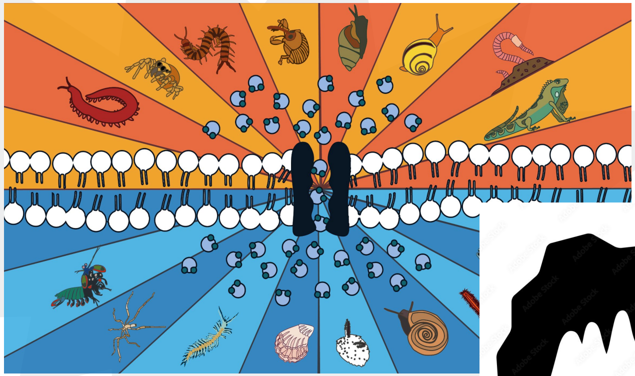

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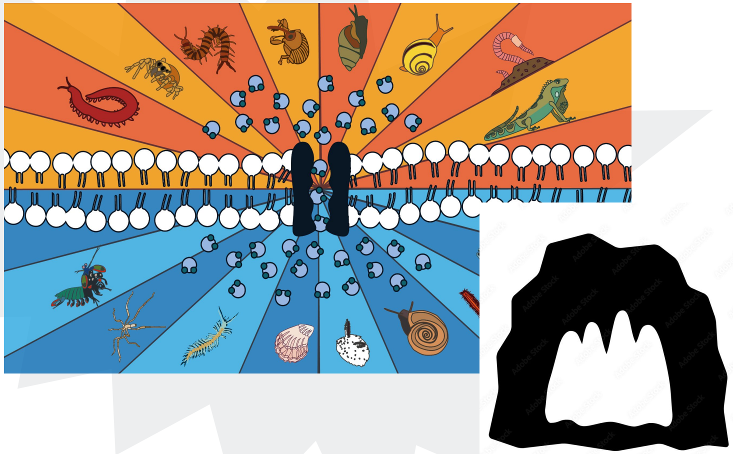

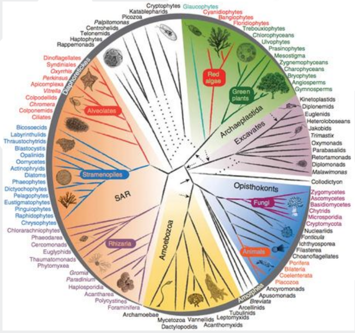

Also organizing the Workshop on Phylogenomics

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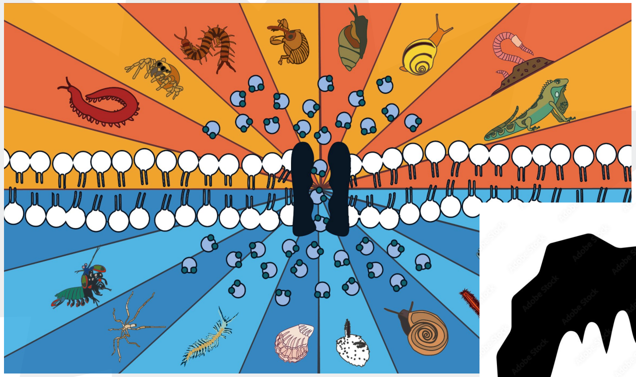

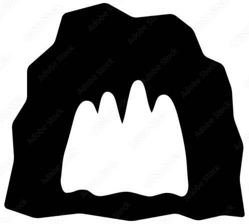

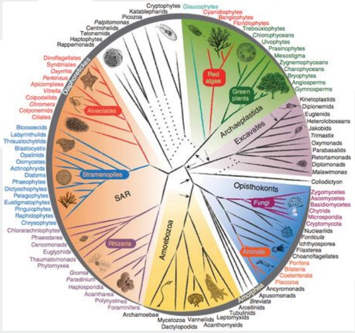

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SPOILER ALERT: there will be BEARS!!

Which came first, the chicken or the egg?

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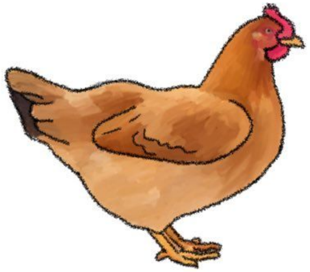
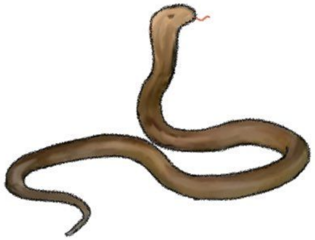


Birds
(Chickens)

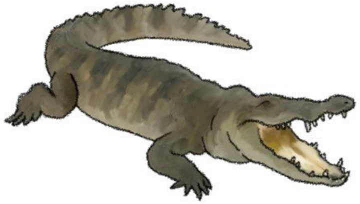
Which came first, the chicken or the egg?

Turtles

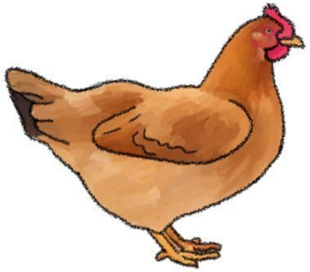
Lizards



Snakes



Crocodiles



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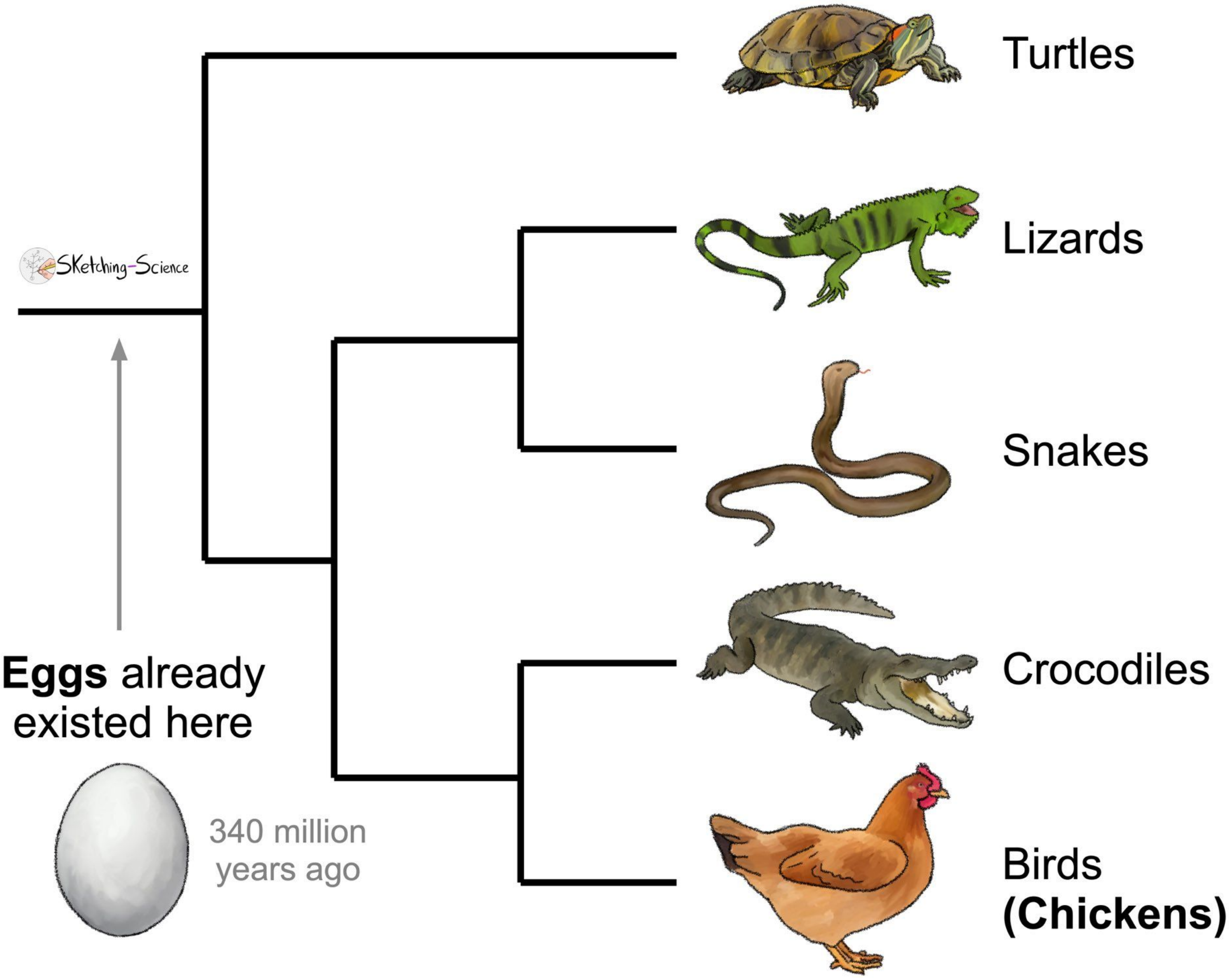


Turtles

Lizards

Snakes

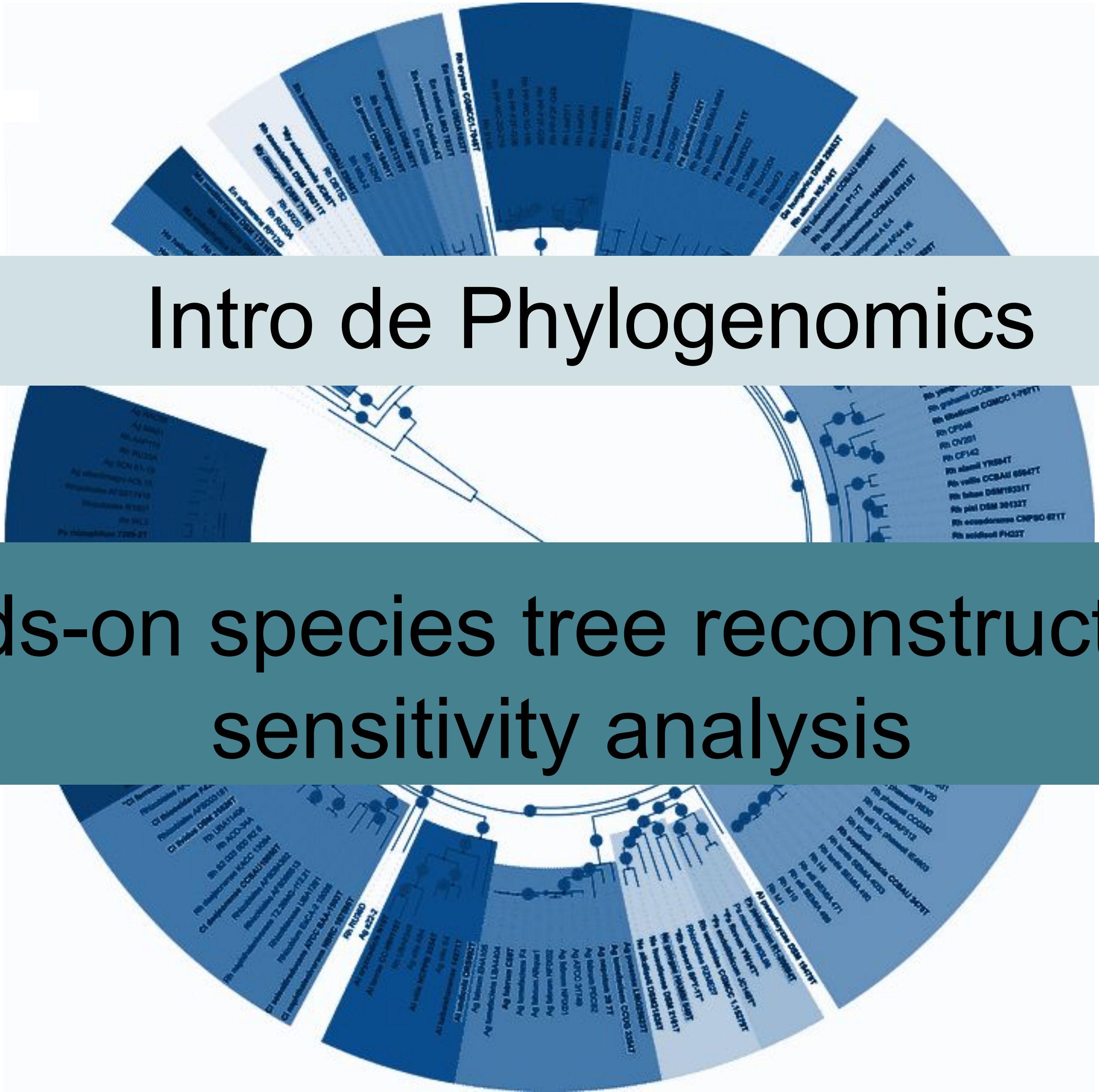
Crocodiles

Birds
(Chickens)

Eggs already
existed here

340 million
years ago

Content today's lecture

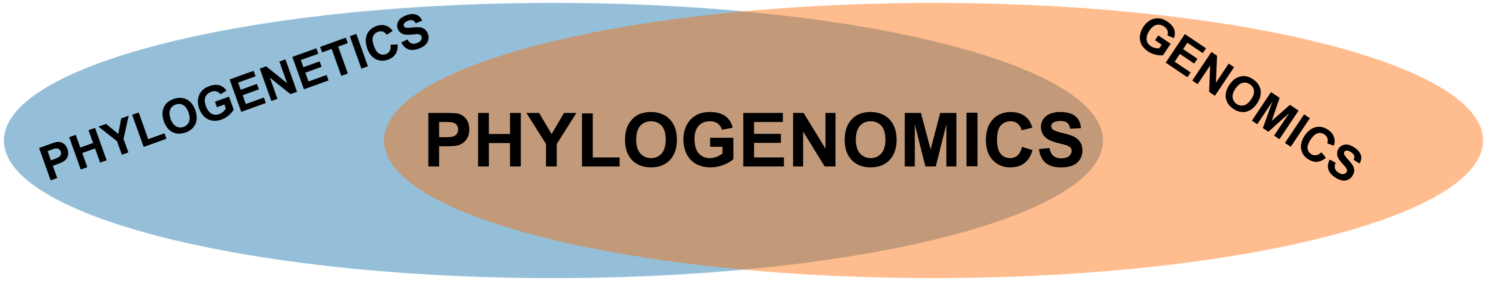


Intro de Phylogenomics

Hands-on species tree reconstruction & sensitivity analysis

Intro to Phylogenomics

Intro to Phylogenomics



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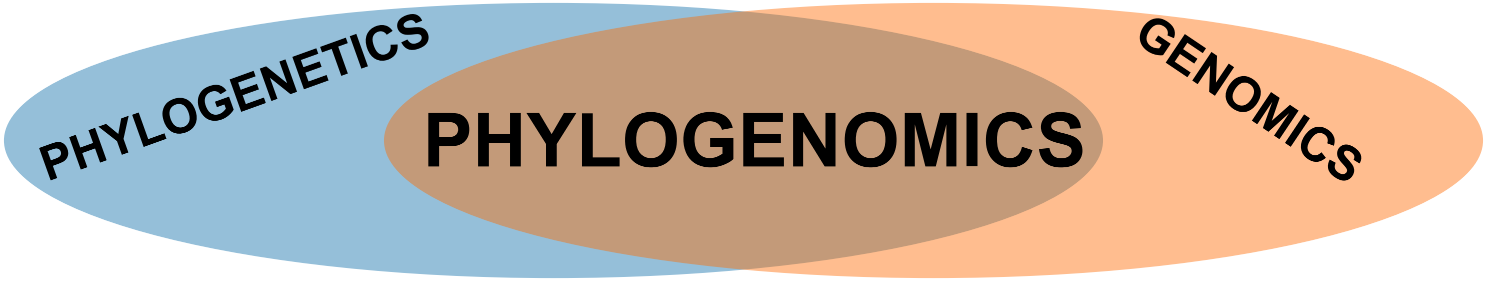

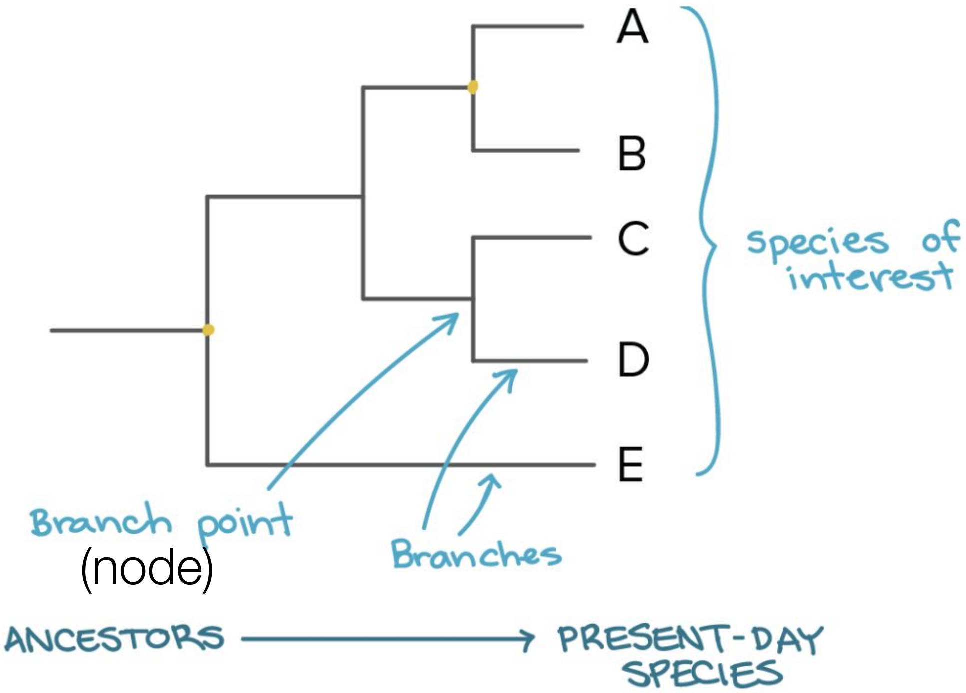

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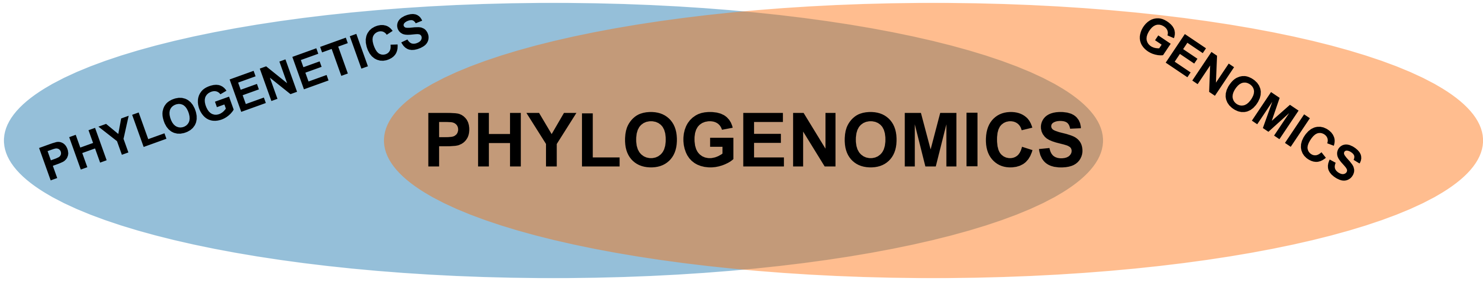

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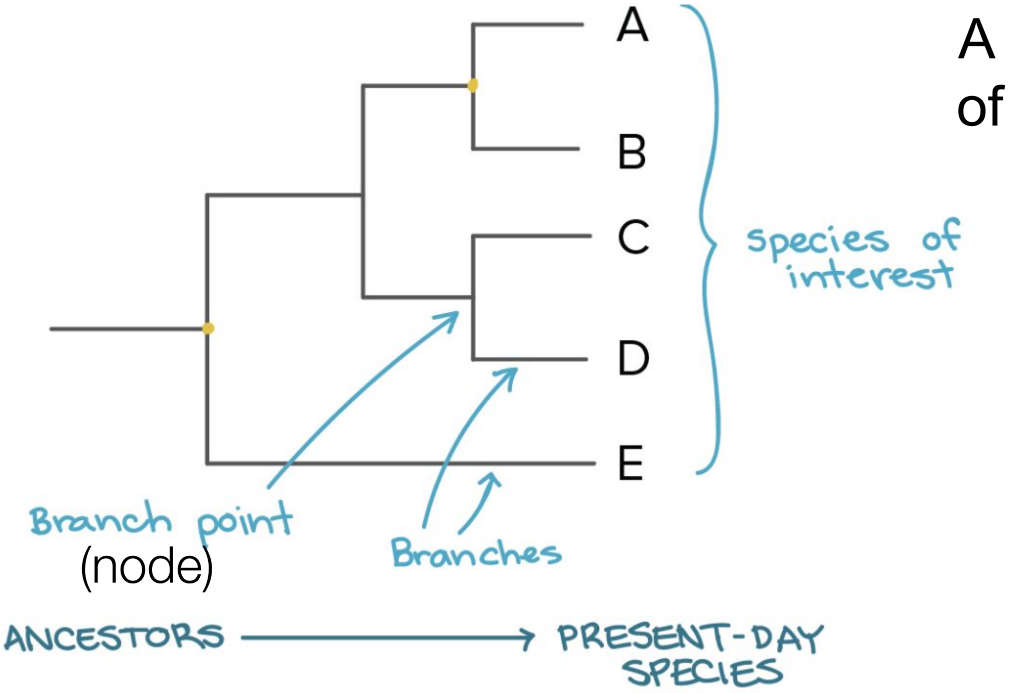
PHYLOGENOMICS

GENOMICS



A **phylogenetic tree** is a hypothesis of how species or genes are related through evolution

Image modified from *Taxonomy and phylogeny: Figure 2* by Robert Bear et al., CC BY 4.0

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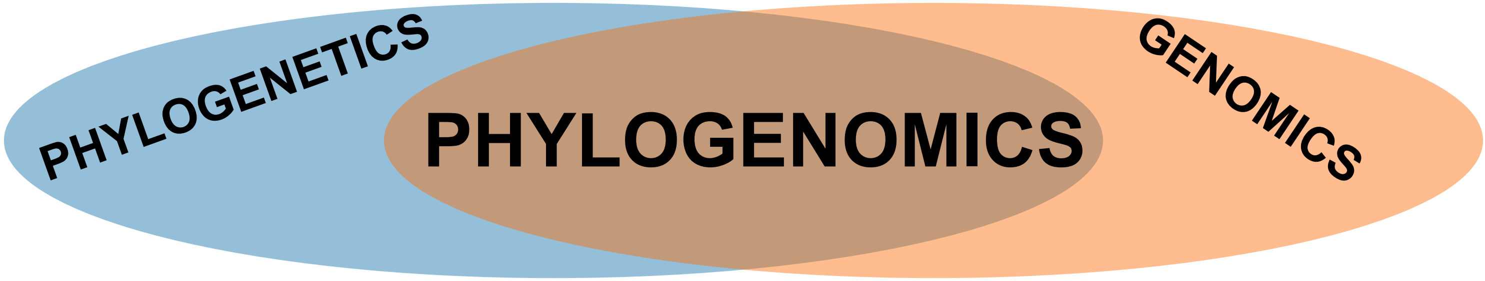

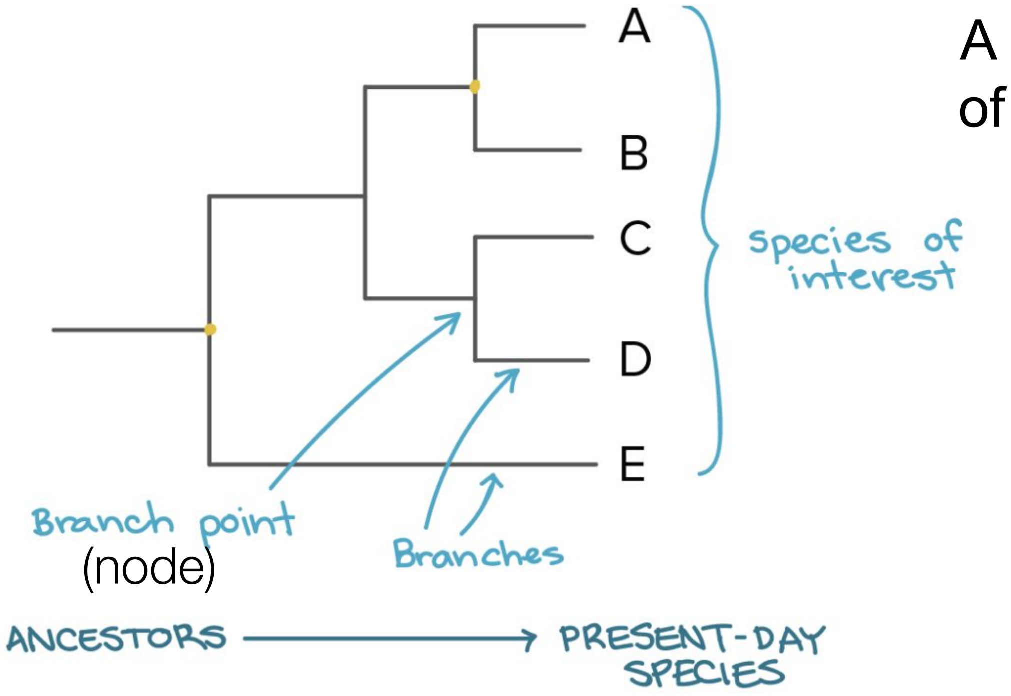

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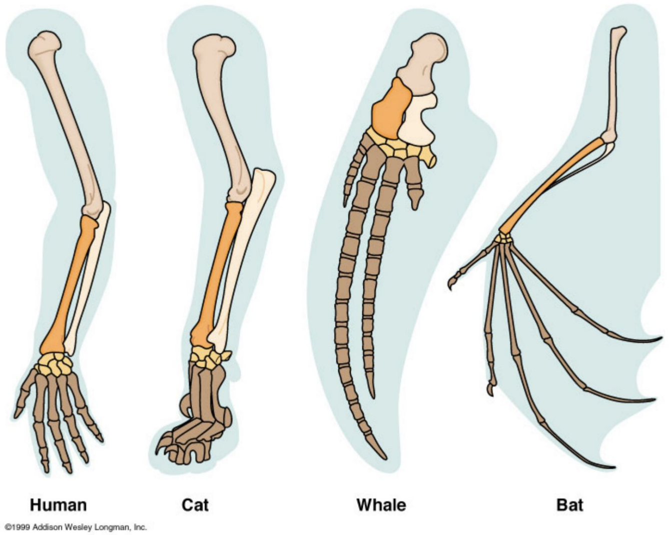

Morphological traits

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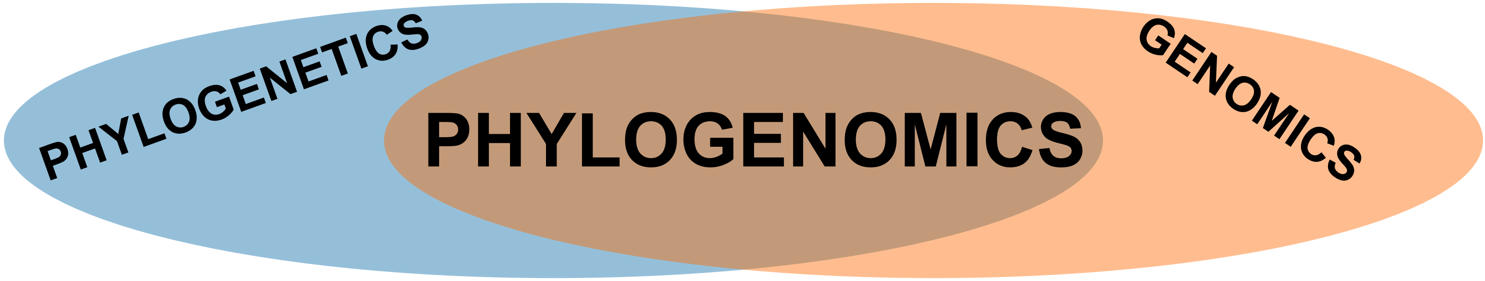

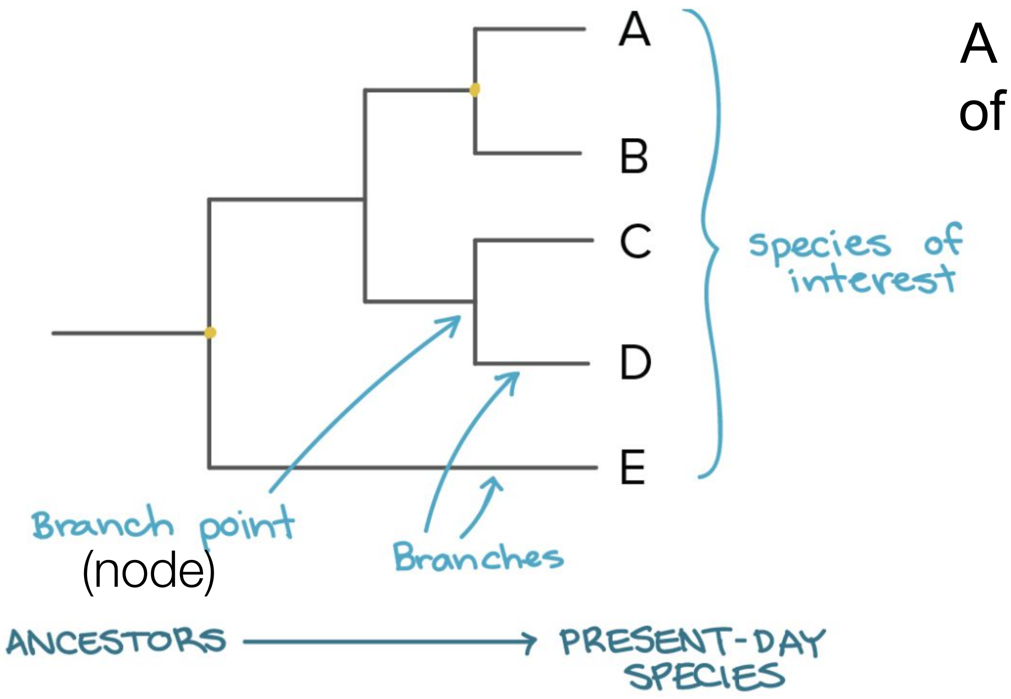

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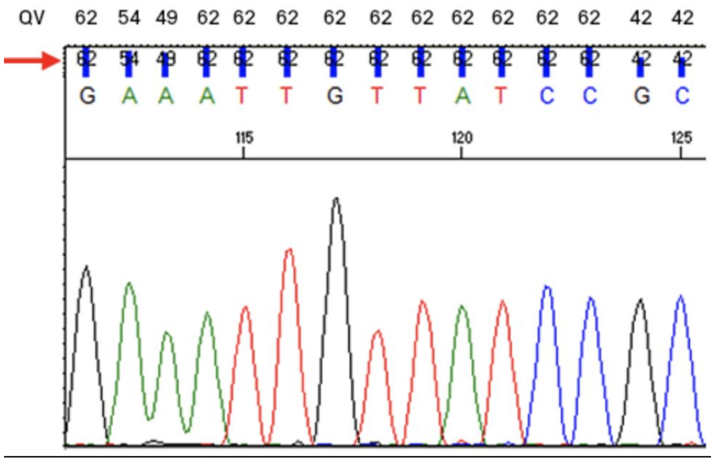

A few genes (eg, COI)

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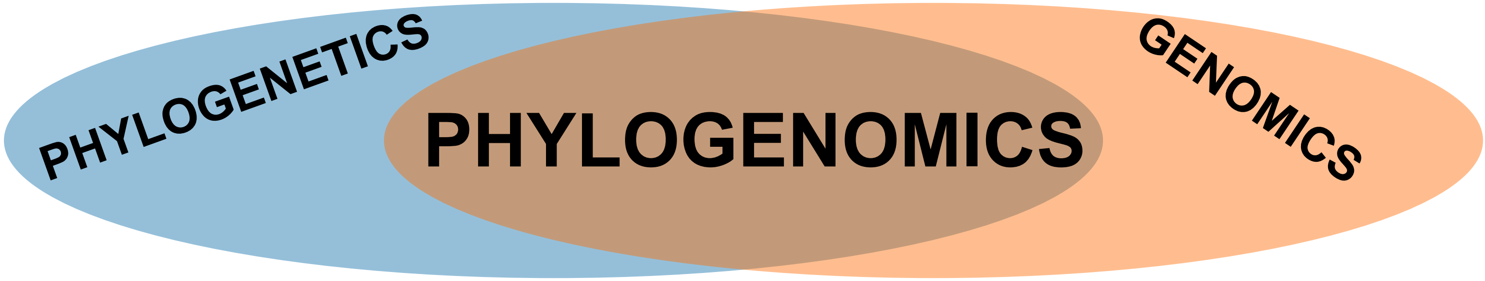

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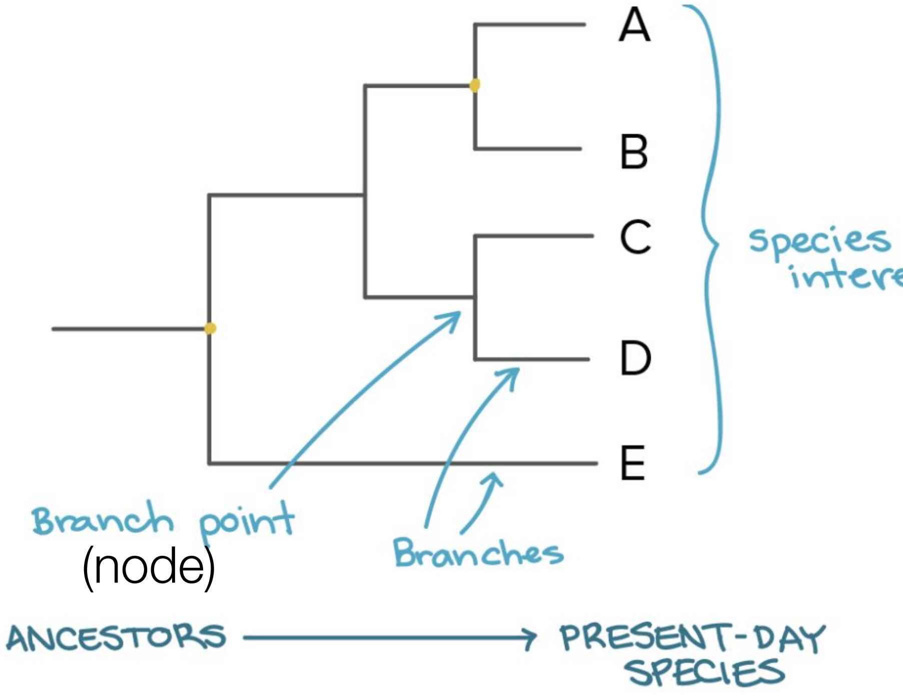

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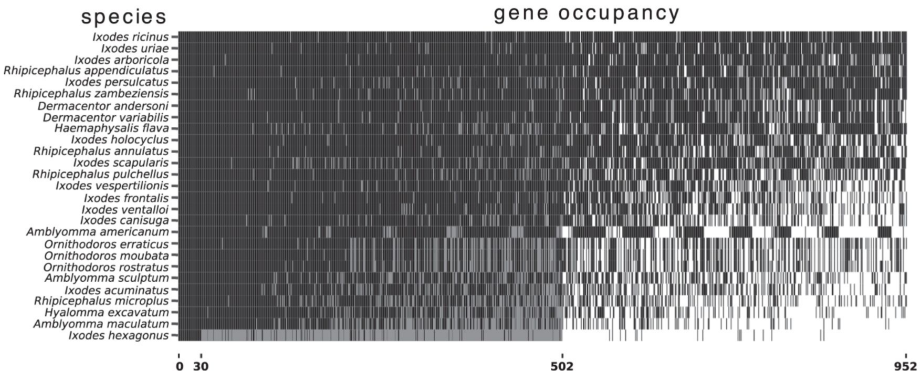

100s / 1,000s of genes

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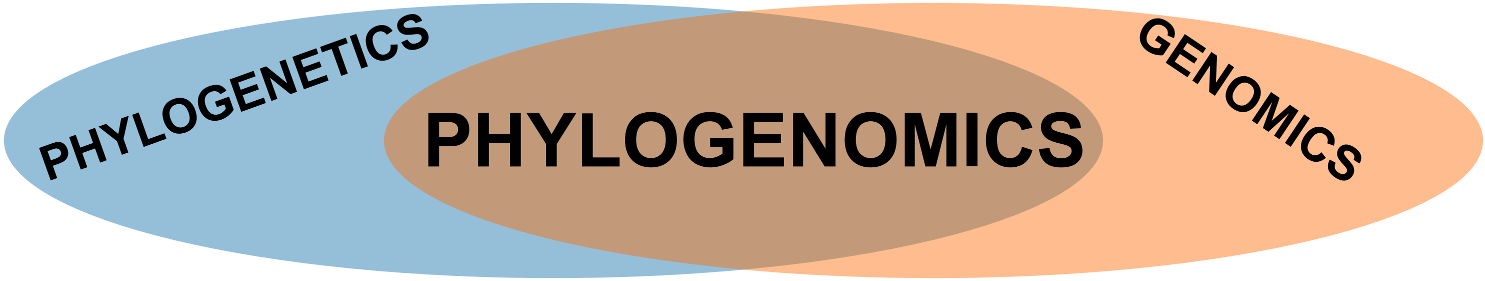

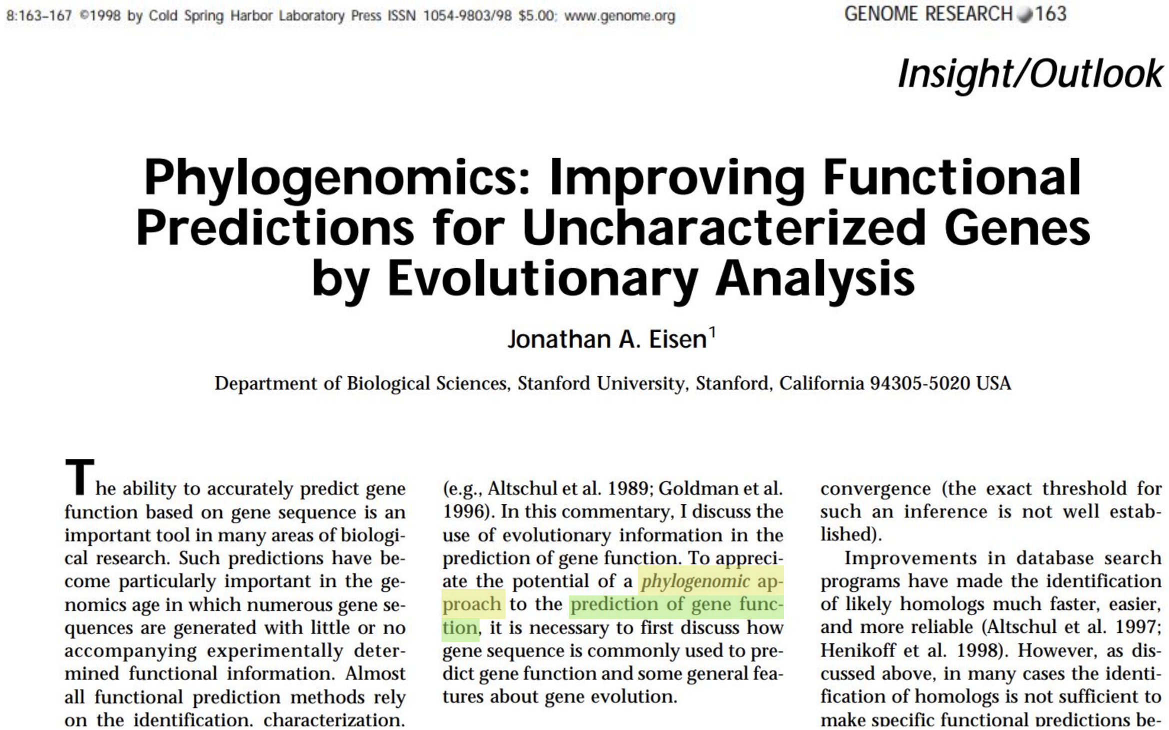

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GENOME RESEARCH 163

Insight/Outlook

Phylogenomics: Improving Functional Predictions for Uncharacterized Genes by Evolutionary Analysis

Jonathan A. Eisen[1]

Department of Biological Sciences, Stanford University, Stanford, California 94305-5020 USA

The ability to accurately predict gene function based on gene sequence is an important tool in many areas of biological research. Such predictions have become particularly important in the genomics age in which numerous gene sequences are generated with little or no accompanying experimentally determined functional information. Almost all functional prediction methods rely on the identification, characterization,

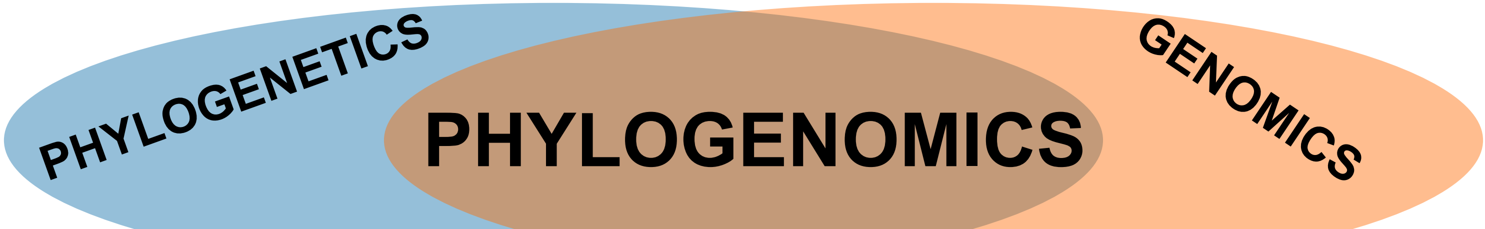
(e.g., Altschul et al. 1989; Goldman et al. 1996). In this commentary, I discuss the use of evolutionary information in the prediction of gene function. To appreciate the potential of a *phylogenomic* approach to the prediction of gene function, it is necessary to first discuss how gene sequence is commonly used to predict gene function and some general features about gene evolution.

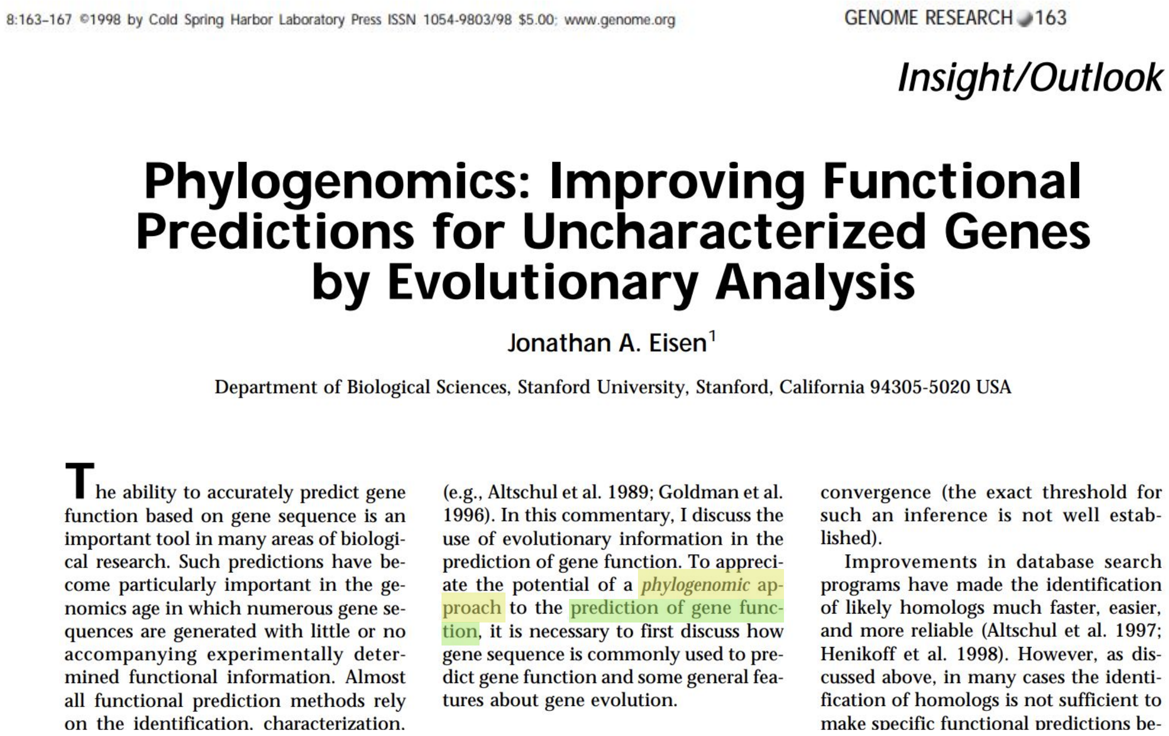
convergence (the exact threshold for such an inference is not well established).

Improvements in database search programs have made the identification of likely homologs much faster, easier, and more reliable (Altschul et al. 1997; Henikoff et al. 1998). However, as discussed above, in many cases the identification of homologs is not sufficient to make specific functional predictions be-

Phylogenomics: prediction of gene function and gene family evolution

Intro to Phylogenomics

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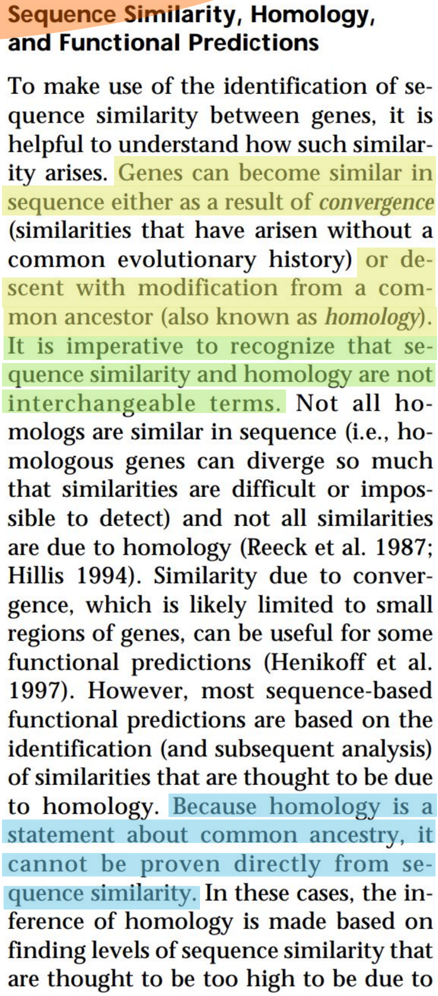
Sequence Similarity, Homology, and Functional Predictions

To make use of the identification of sequence similarity between genes, it is helpful to understand how such similarity arises. Genes can become similar in sequence either as a result of *convergence* (similarities that have arisen without a common evolutionary history) or descent with modification from a common ancestor (also known as *homology*). It is imperative to recognize that sequence similarity and homology are not interchangeable terms. Not all homologs are similar in sequence (i.e., homologous genes can diverge so much that similarities are difficult or impossible to detect) and not all similarities are due to homology (Reeck et al. 1987; Hillis 1994). Similarity due to convergence, which is likely limited to small regions of genes, can be useful for some functional predictions (Henikoff et al. 1997). However, most sequence-based functional predictions are based on the identification (and subsequent analysis) of similarities that are thought to be due to homology. Because homology is a statement about common ancestry, it cannot be proven directly from sequence similarity. In these cases, the inference of homology is made based on finding levels of sequence similarity that are thought to be too high to be due to

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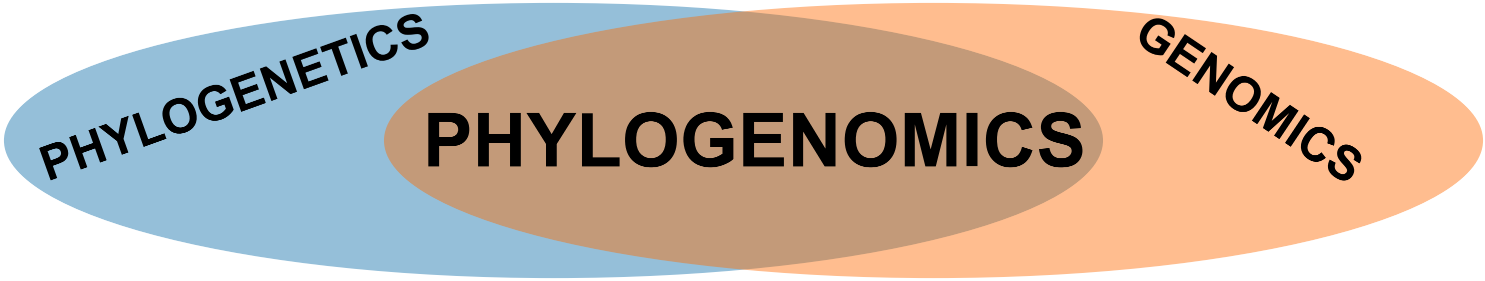

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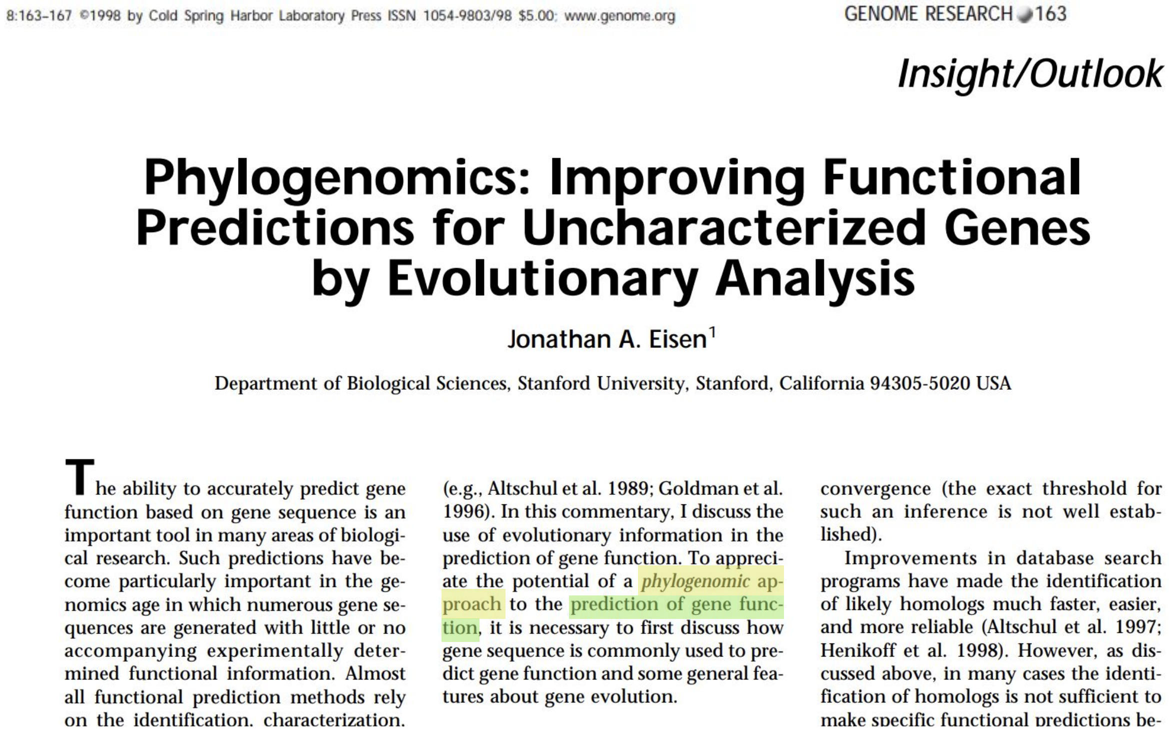

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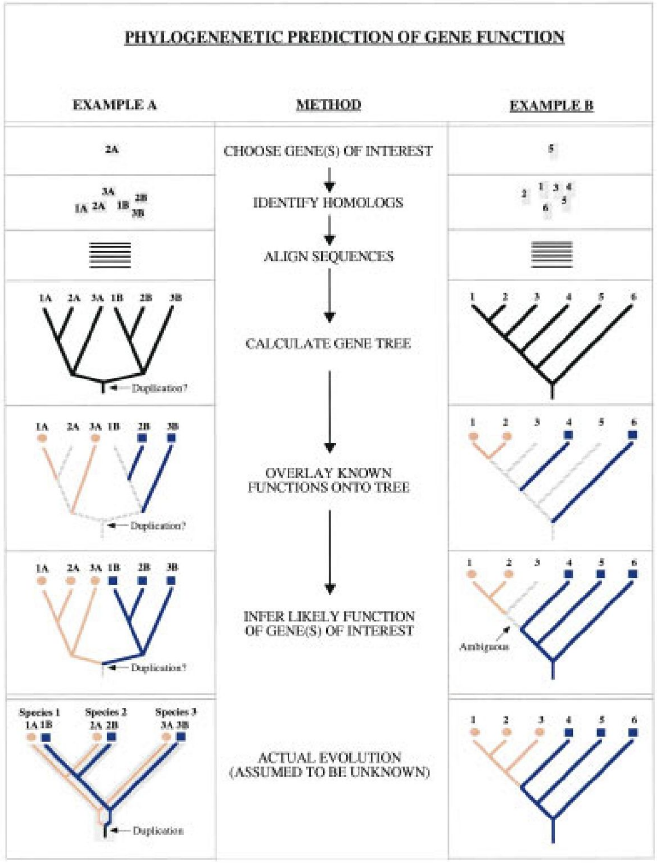
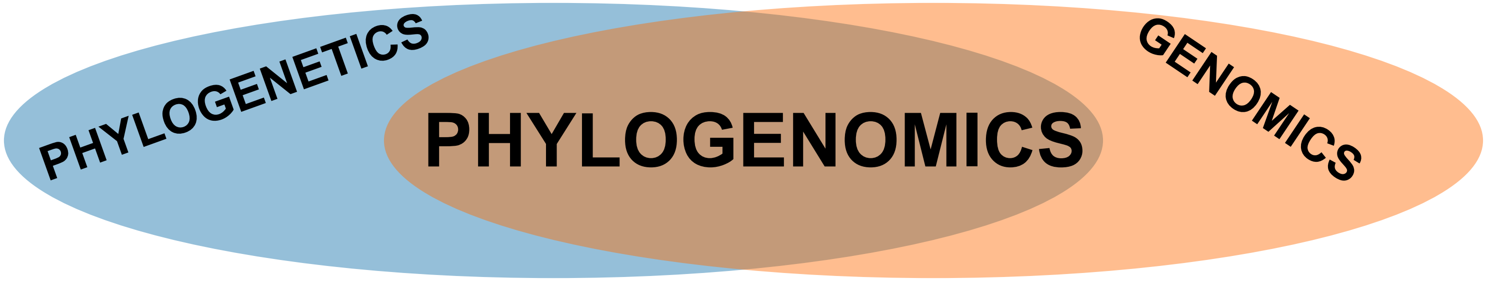


Figure 1 Outline of a phylogenomic methodology. In this method, information about the evolutionary relationships among genes is used to predict the functions of uncharacterized genes (see text for details). Two hypothetical scenarios are presented and the path of trying to infer the function of two uncharacterized genes in each case is traced. (A) A gene family has

Intro to Phylogenomics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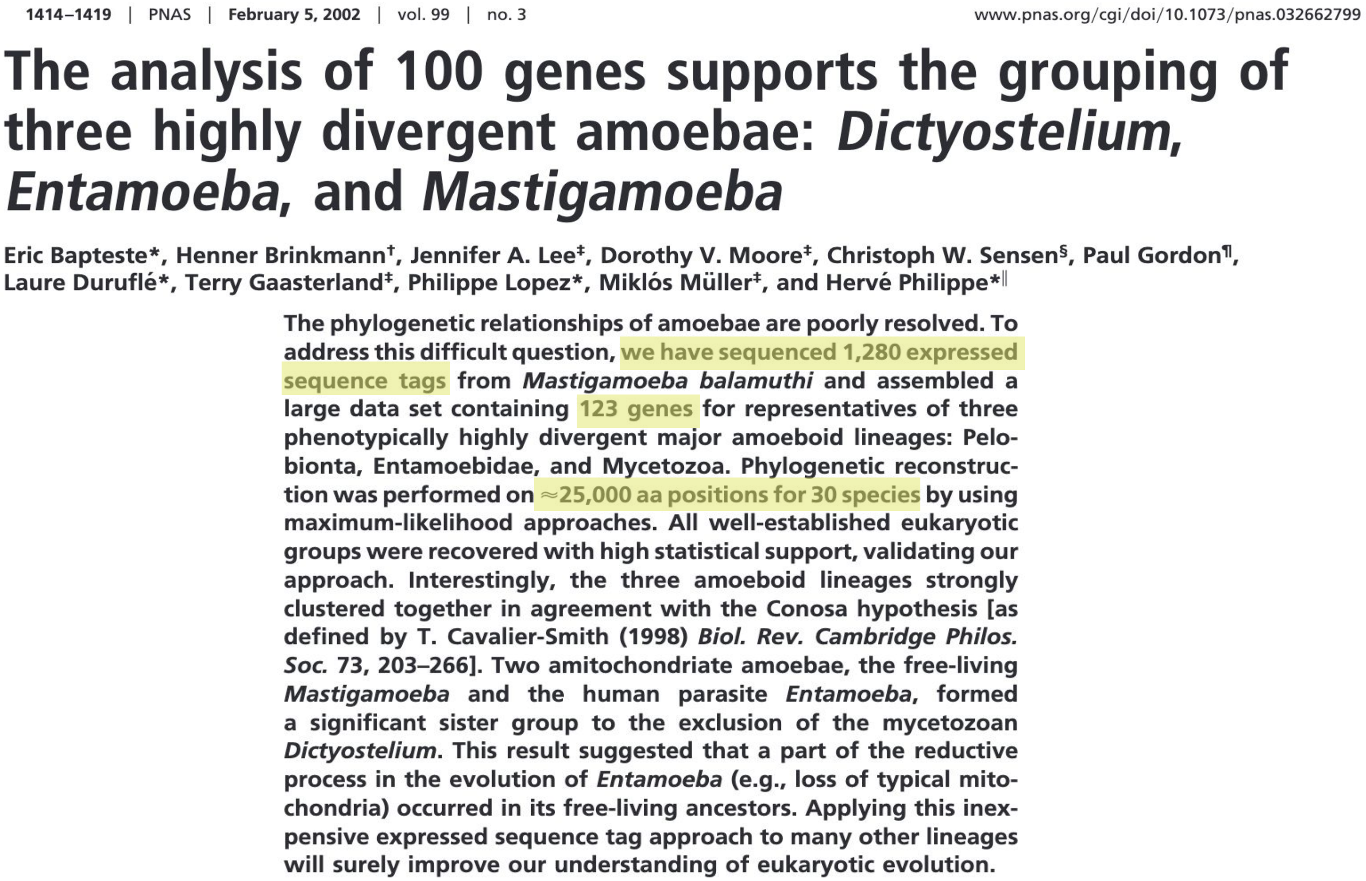

1414–1419 | PNAS | February 5, 2002 | vol. 99 | no. 3 www.pnas.org/cgi/doi/10.1073/pnas.032662799

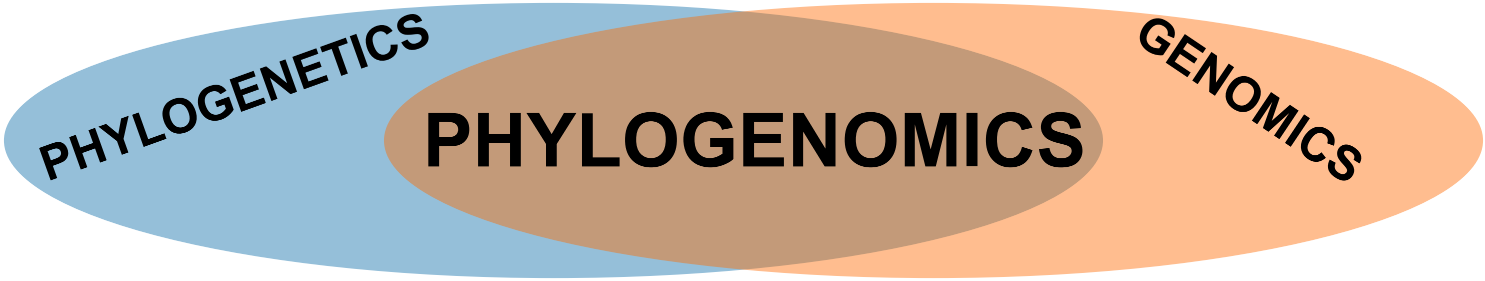
The analysis of 100 genes supports the grouping of three highly divergent amoebae: *Dictyostelium*, *Entamoeba*, and *Mastigamoeba*

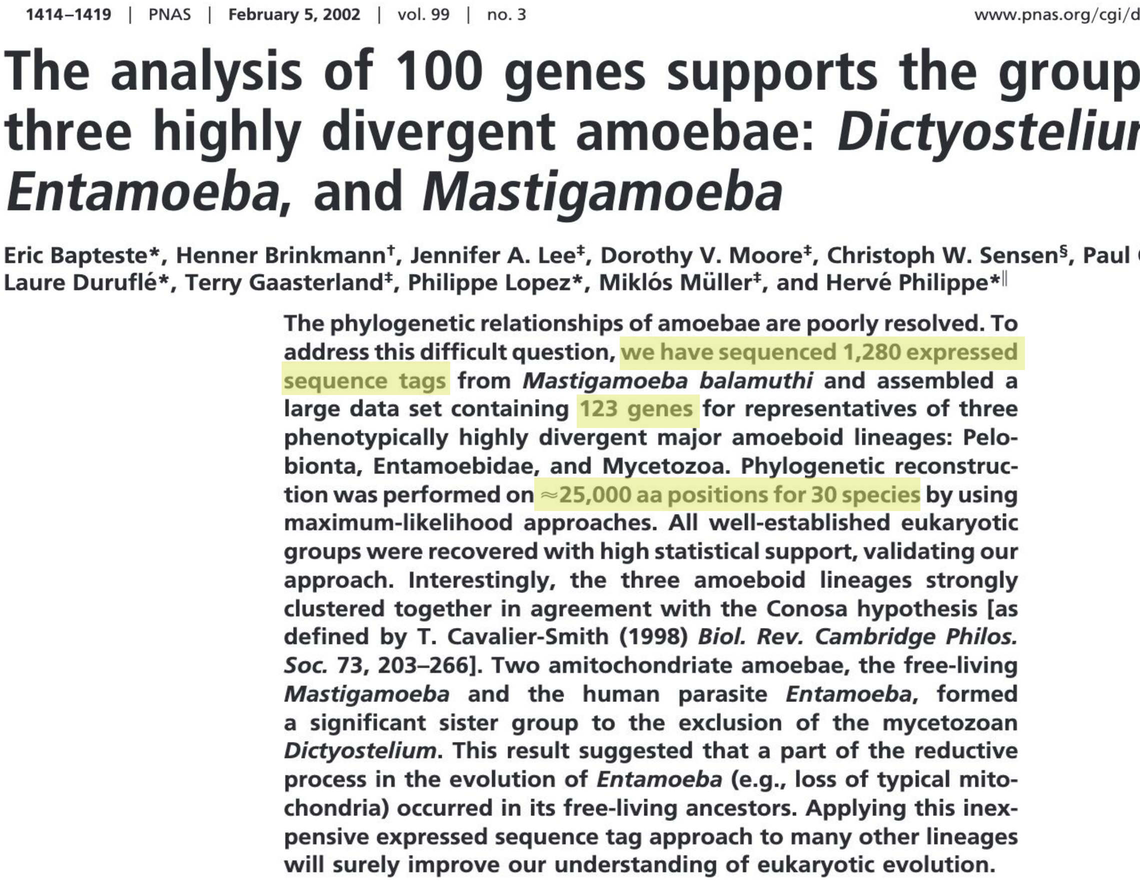
Eric Bapteste[*], Henner Brinkmann[†], Jennifer A. Lee[‡], Dorothy V. Moore[‡], Christoph W. Sensen[§], Paul Gordon[¶], Laure Duruflé[*], Terry Gaasterland[‡], Philippe Lopez[*], Miklós Müller[‡], and Hervé Philippe[*][‖]

The phylogenetic relationships of amoebae are poorly resolved. To address this difficult question, we have sequenced 1,280 expressed sequence tags from *Mastigamoeba balamuthi* and assembled a large data set containing 123 genes for representatives of three phenotypically highly divergent major amoeboid lineages: Pelobionta, Entamoebidae, and Mycetozoa. Phylogenetic reconstruction was performed on ≈25,000 aa positions for 30 species by using maximum-likelihood approaches. All well-established eukaryotic groups were recovered with high statistical support, validating our approach. Interestingly, the three amoeboid lineages strongly clustered together in agreement with the Conosa hypothesis [as defined by T. Cavalier-Smith (1998) *Biol. Rev. Cambridge Philos. Soc.* 73, 203–266]. Two amitochondriate amoebae, the free-living *Mastigamoeba* and the human parasite *Entamoeba*, formed a significant sister group to the exclusion of the mycetozoan *Dictyostelium*. This result suggested that a part of the reductive process in the evolution of *Entamoeba* (e.g., loss of typical mitochondria) occurred in its free-living ancestors. Applying this inexpensive expressed sequence tag approach to many other lineages will surely improve our understanding of eukaryotic evolution.

Phylogenomics: species tree inference

Intro to Phylogenomics





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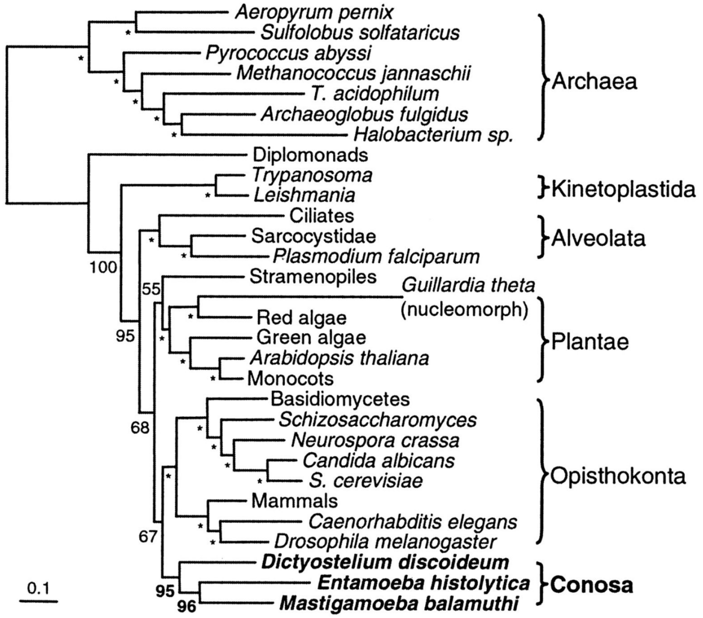
The analysis of 100 genes supports the grouping of three highly divergent amoebae: *Dictyostelium*, *Entamoeba*, and *Mastigamoeba*

Eric Bapteste*, Henner Brinkmann†, Jennifer A. Lee‡, Dorothy V. Moore‡, Christoph W. Sensen§, Paul Gordon¶, Laure Duruflé*, Terry Gaasterland‡, Philippe Lopez*, Miklós Müller‡, and Hervé Philippe*||

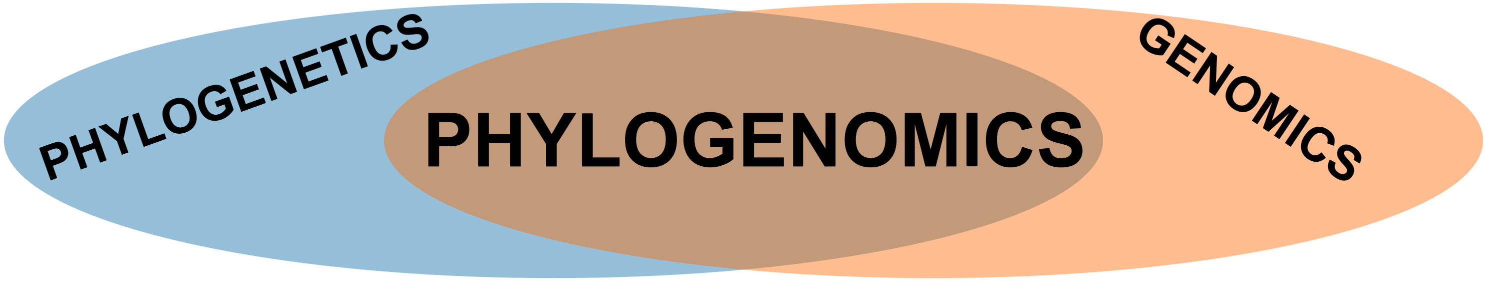
The phylogenetic relationships of amoebae are poorly resolved. To address this difficult question, we have sequenced 1,280 expressed sequence tags from *Mastigamoeba balamuthi* and assembled a large data set containing 123 genes for representatives of three phenotypically highly divergent major amoeboid lineages: Pelobionta, Entamoebidae, and Mycetozoa. Phylogenetic reconstruction was performed on ≈25,000 aa positions for 30 species by using maximum-likelihood approaches. All well-established eukaryotic groups were recovered with high statistical support, validating our approach. Interestingly, the three amoeboid lineages strongly clustered together in agreement with the Conosa hypothesis [as defined by T. Cavalier-Smith (1998) *Biol. Rev. Cambridge Philos. Soc.* 73, 203–266]. Two amitochondriate amoebae, the free-living *Mastigamoeba* and the human parasite *Entamoeba*, formed a significant sister group to the exclusion of the mycetozoan *Dictyostelium*. This result suggested that a part of the reductive process in the evolution of *Entamoeba* (e.g., loss of typical mitochondria) occurred in its free-living ancestors. Applying this inexpensive expressed sequence tag approach to many other lineages will surely improve our understanding of eukaryotic evolution.



ML tree based on 25,032 aa positions. * indicates a constrained node. We used the JTT model, without taking into account among-sites rate variation. The branch lengths have been computed on the concatenated sequences. BVs were obtained by bootstrapping the 123 genes.

Phylogenomics: species tree inference

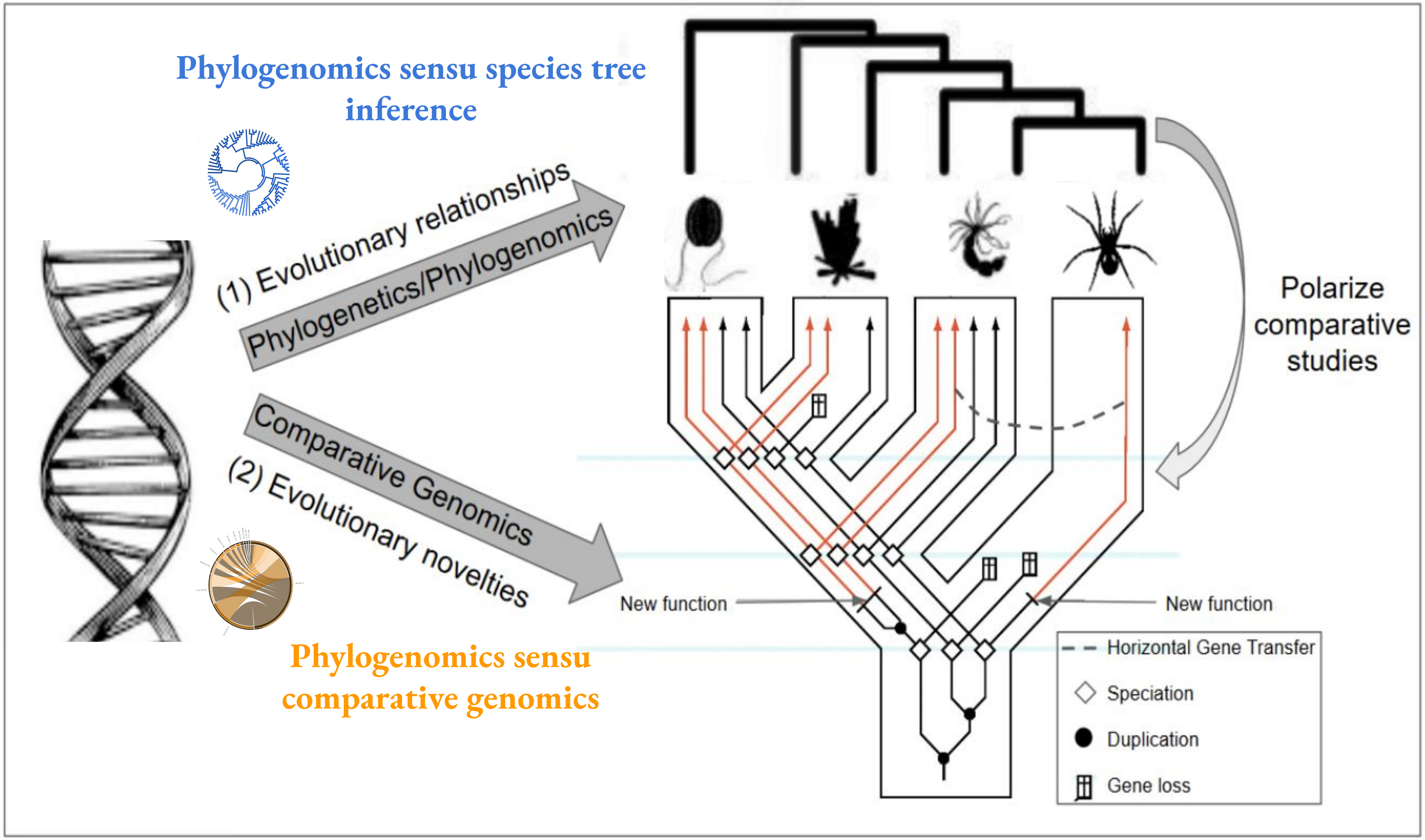
Intro to Phylogenomics



PHYLOGENETICS

PHYLOGENOMICS

GENOMICS

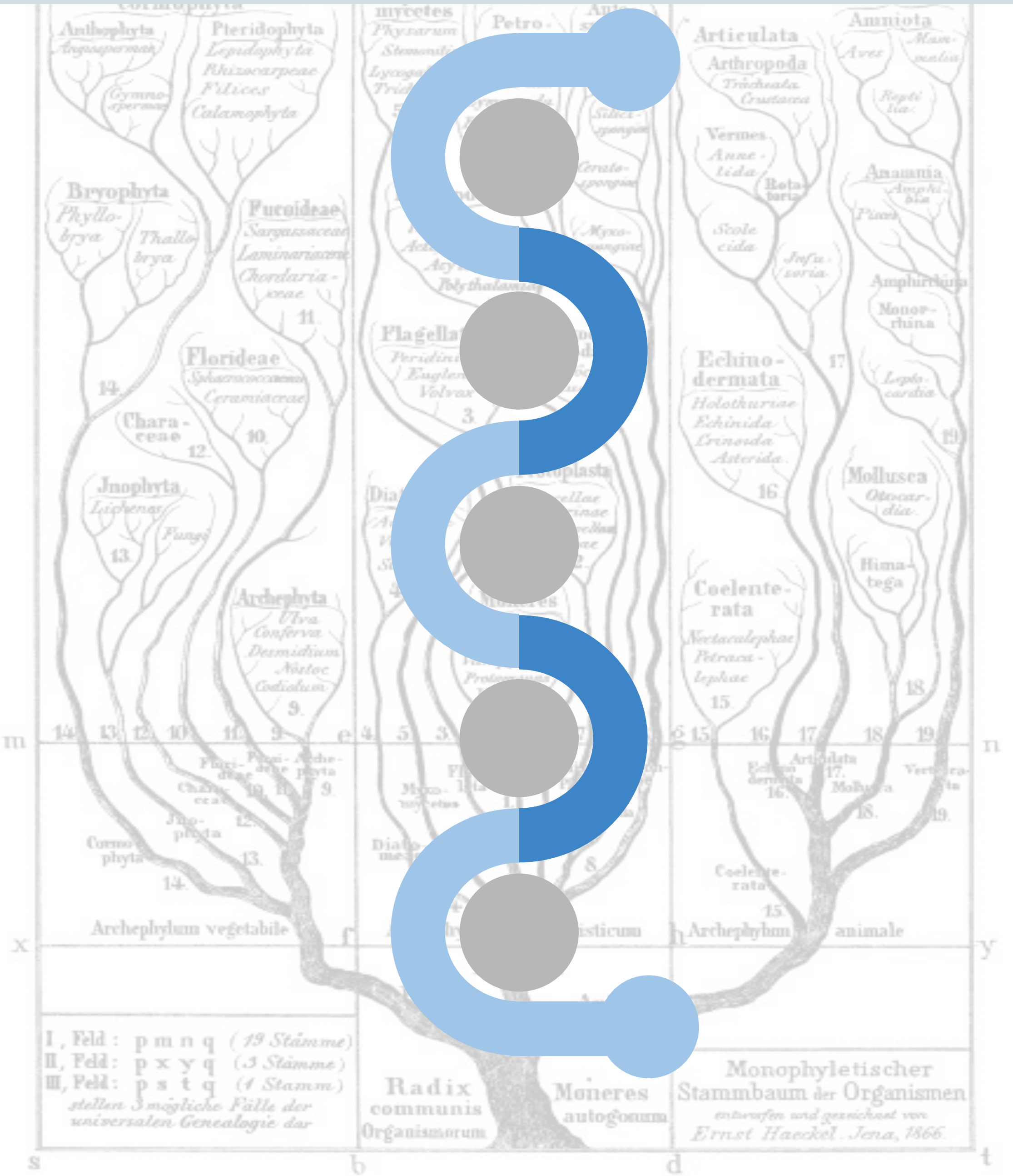


Phylogenomics sensu species tree inference

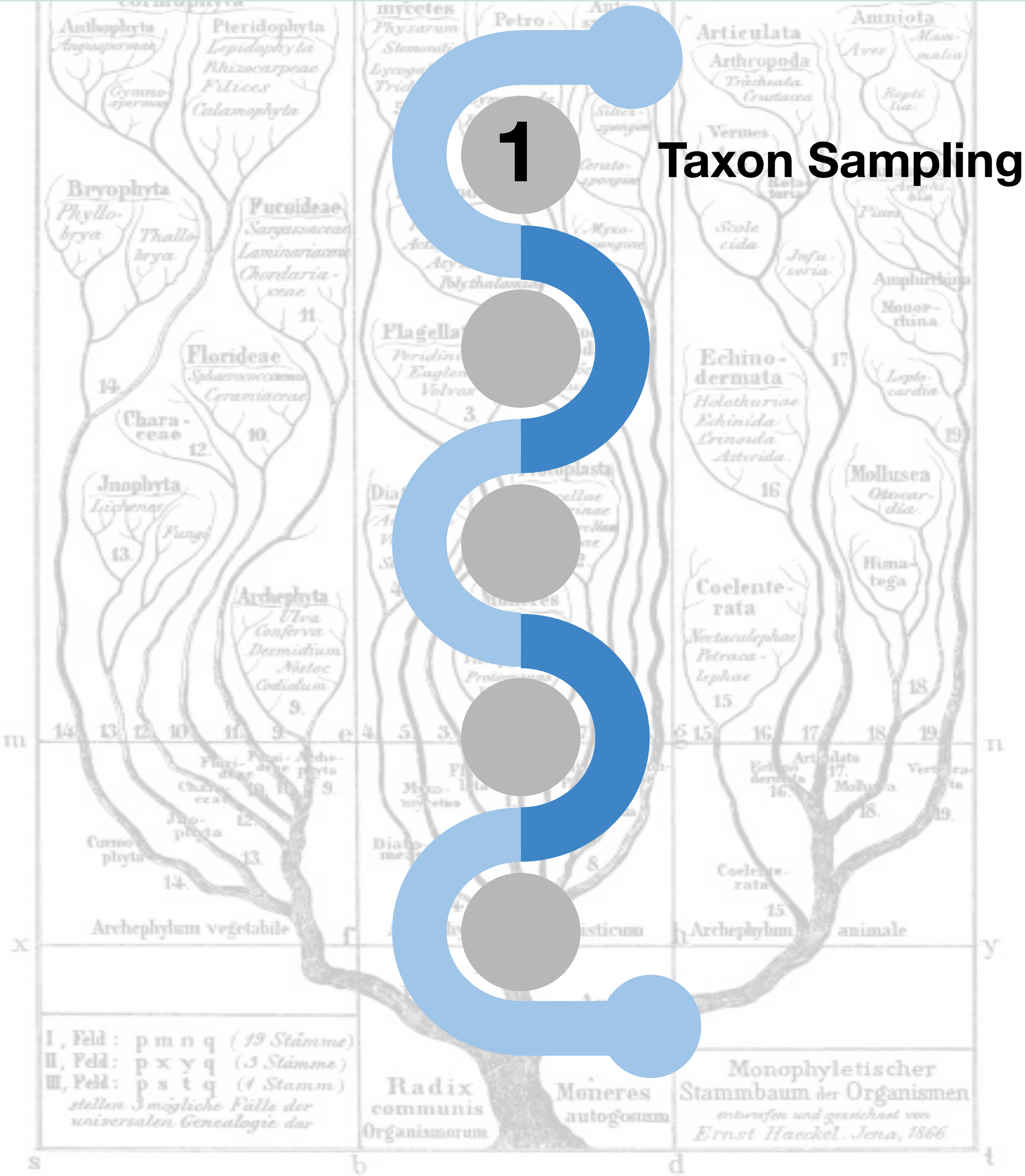
Phylogenomics sensu comparative genomics

(1) Evolutionary relationships
Phylogenetics/Phylogenomics
Comparative Genomics
(2) Evolutionary novelties
Polarize comparative studies
New function
New function
- - Horizontal Gene Transfer
◇ Speciation
● Duplication
Gene loss

How to infer a species tree

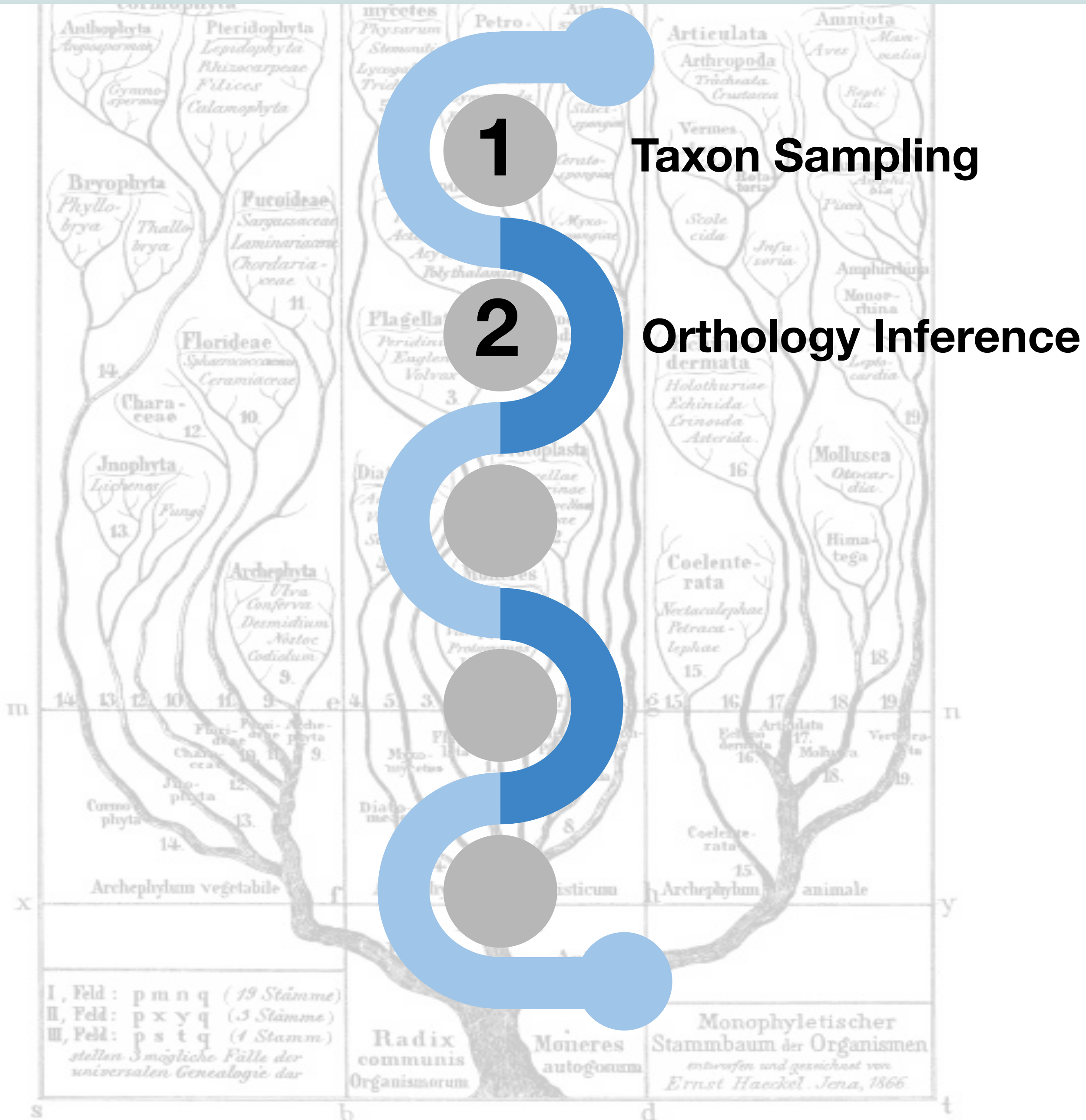

Articulata
Arthropoda
Amniota
Aves
Mammalia
Bryophyta
Pteridophyta
Fucoideae
Florideae
Chara-ceae
Jnophyta
Archephyta
Vermes
Echinodermata
Coelenterata
Mollusca
Anamnia
Amphirhina
Flagellata
Protoplasta
Moneres
Archephylum vegetabile
Archephylum animale
I, Feld: p m n q (19 Stämme)
II, Feld: p x y q (3 Stämme)
III, Feld: p s t q (1 Stamm)
stellen 3 mögliche Fälle der universalen Genealogie dar
Radix communis Organismorum
Moneres autogonum
Monophyletischer Stammbaum der Organismen
entworfen und gezeichnet von Ernst Haeckel. Jena, 1866.

How to infer a species tree



Taxon Sampling

How to infer a species tree


1
2
Monophyletischer Stammbaum der Organismen
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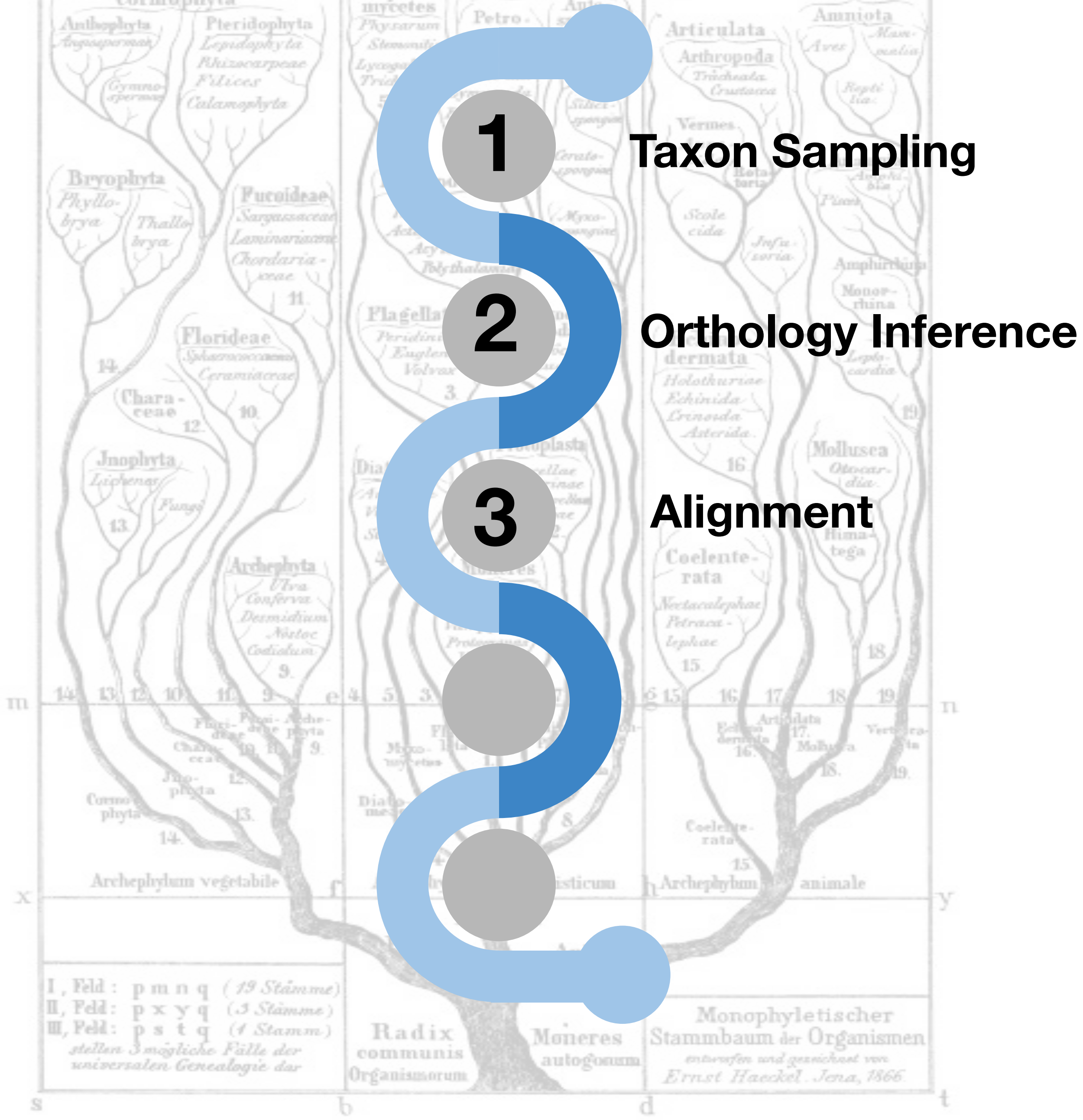
Radix communis Organismorum
Moneres autogonum
Archephylum vegetabile
Archephylum animale

1 Taxon Sampling

2 Orthology Inference

How to infer a species tree

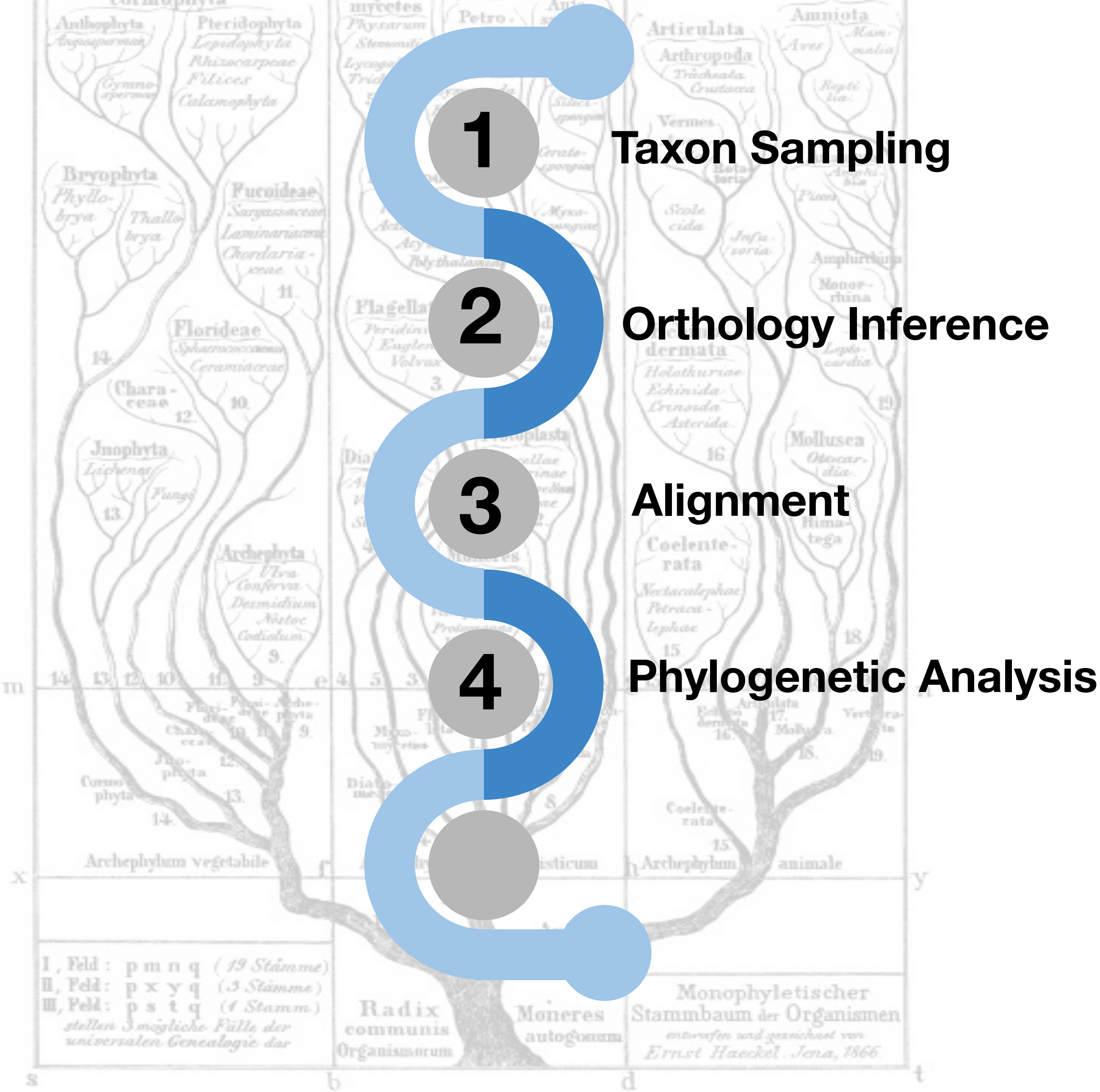


1 Taxon Sampling

2 Orthology Inference

3 Alignment

How to infer a species tree



1 Taxon Sampling

2 Orthology Inference

3 Alignment

4 Phylogenetic Analysis

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Radix communis Organismorum
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Archephylum vegetabile
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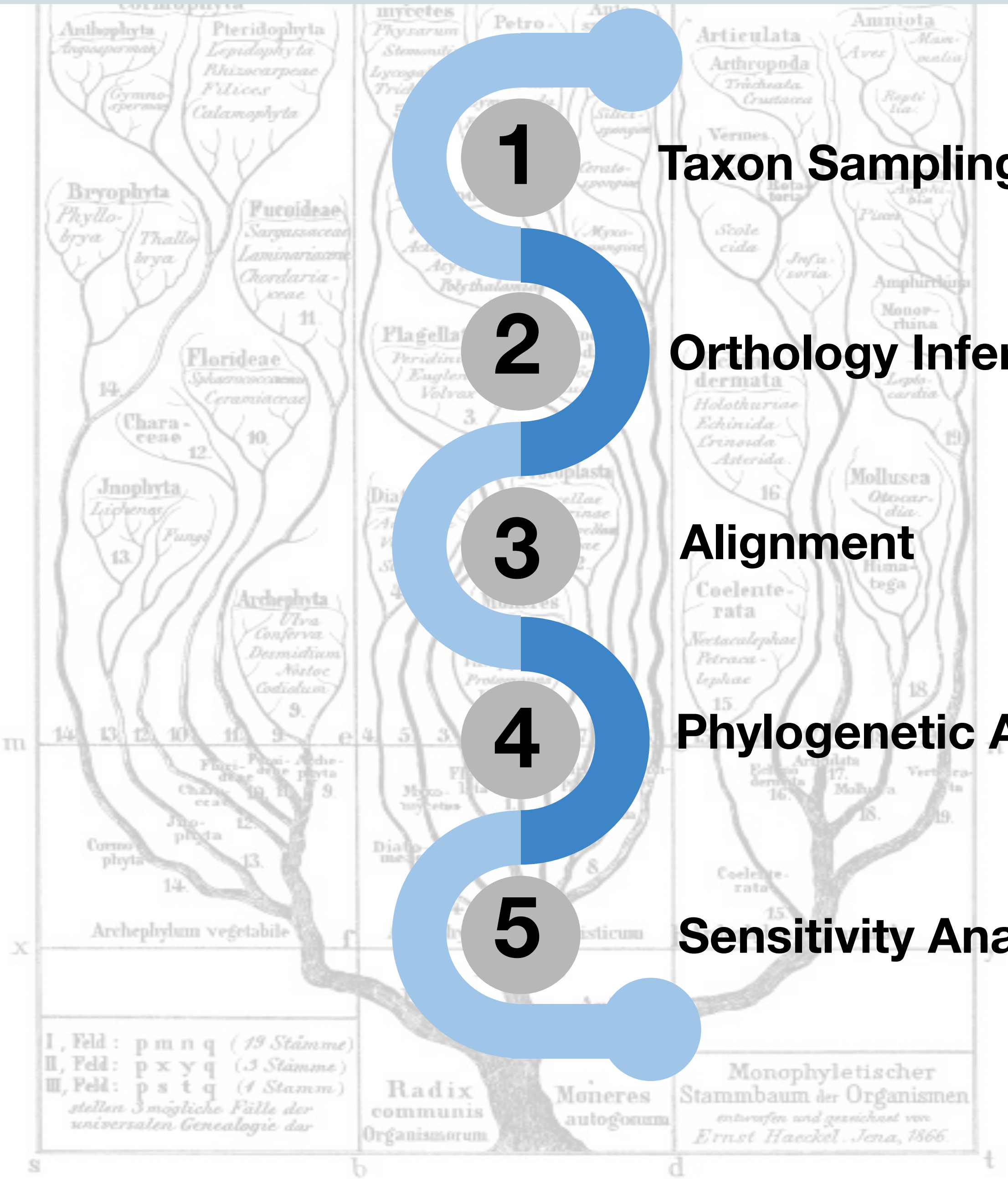
How to infer a species tree



1 Taxon Sampling

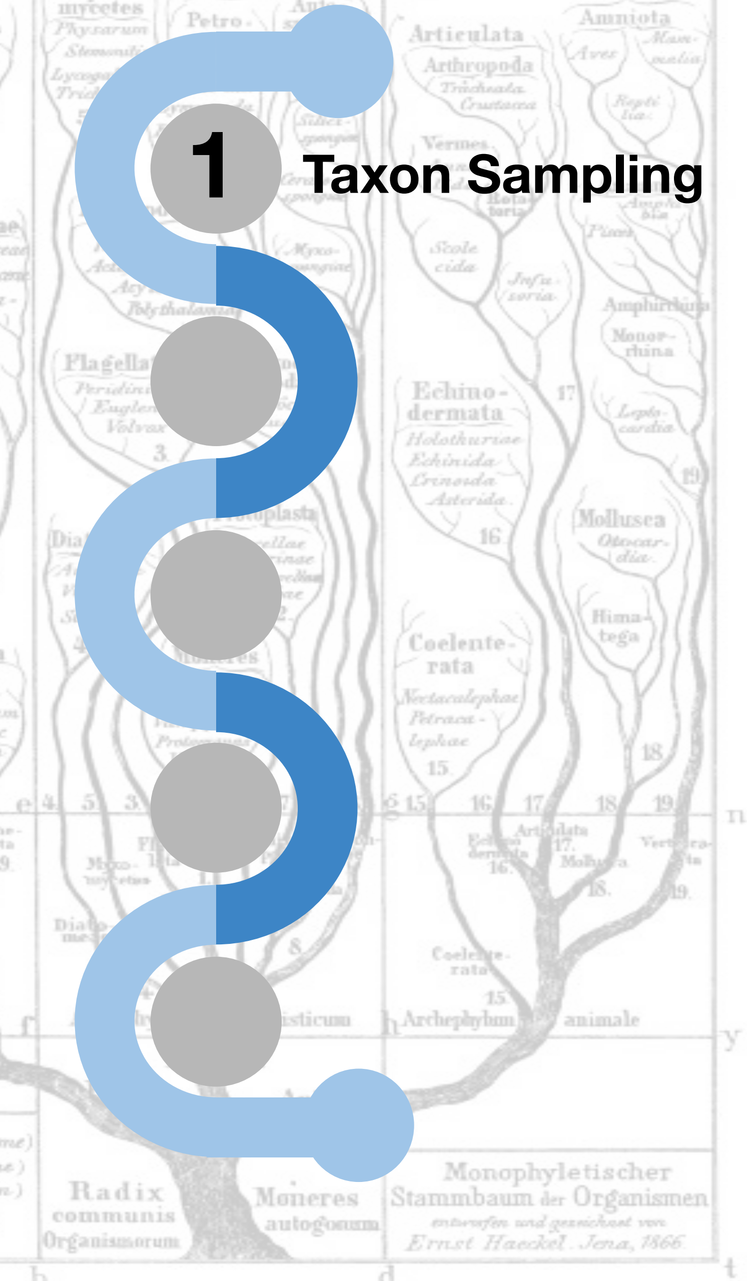
2 Orthology Inference

3 Alignment

4 Phylogenetic Analysis

5 Sensitivity Analysis

How to infer a species tree



1 **Taxon Sampling**

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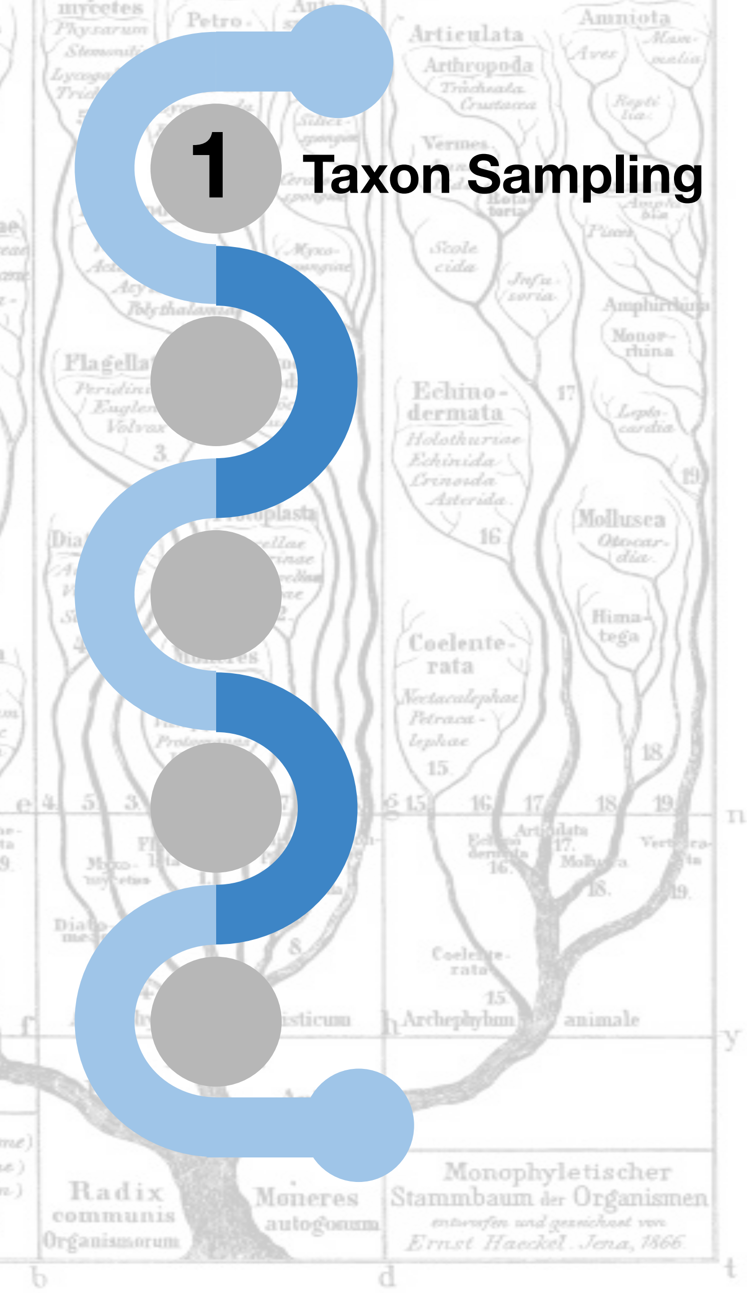
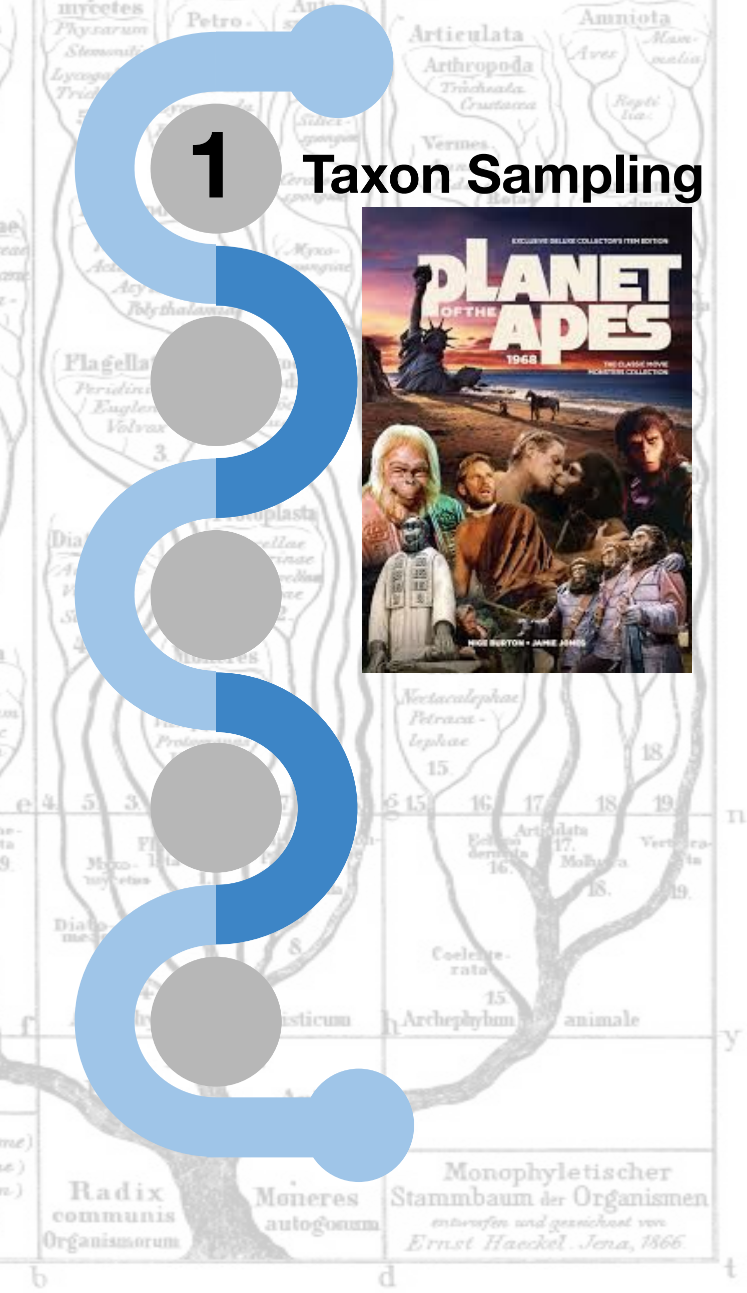


Key message: taxon sampling matters a lot

Incomplete, biased, or improper taxon sampling can lead to misleading results in reconstructing evolutionary relationships.

How to infer a species tree


1
Taxon Sampling
PLANET OF THE APES
1968
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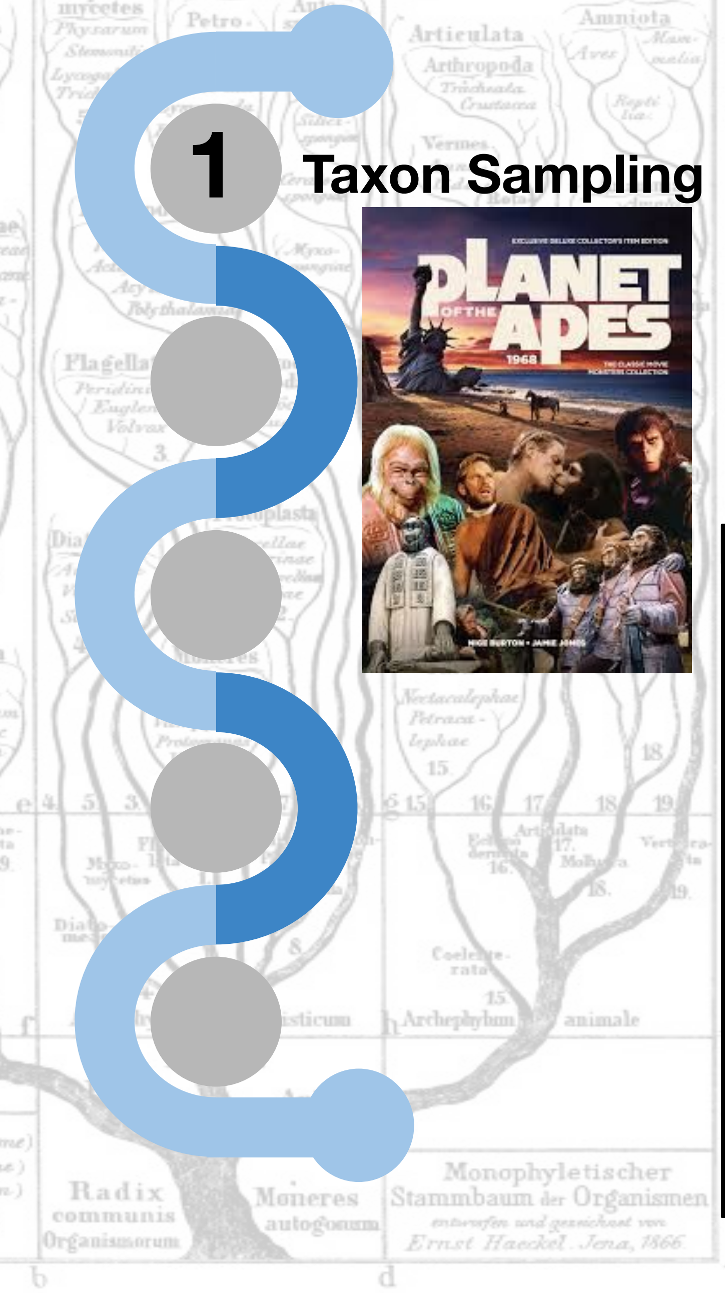
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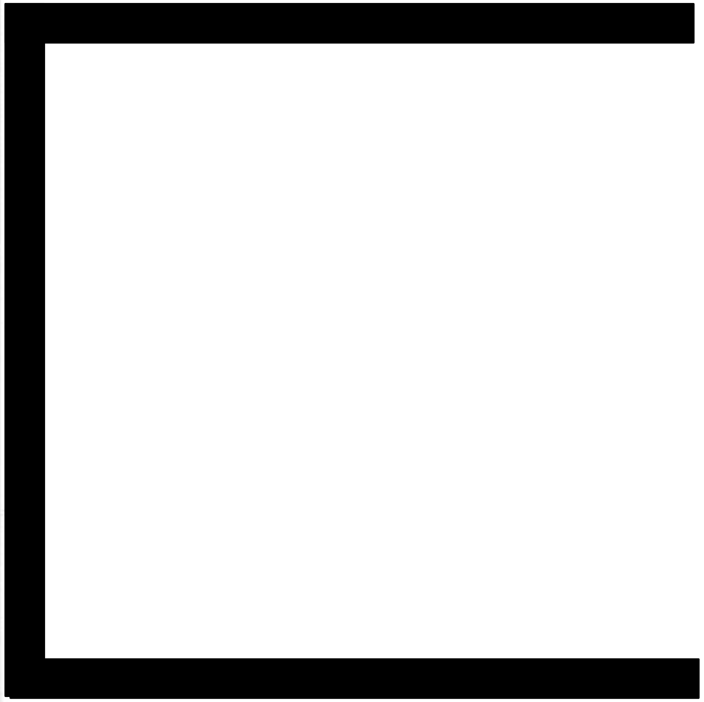
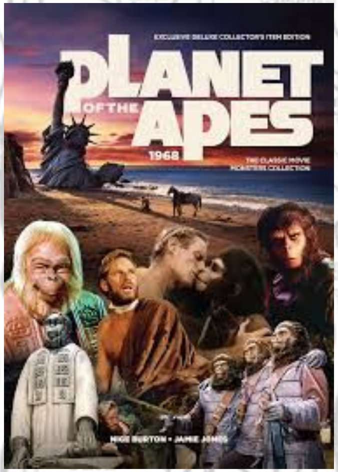


How to infer a species tree

1 Taxon Sampling



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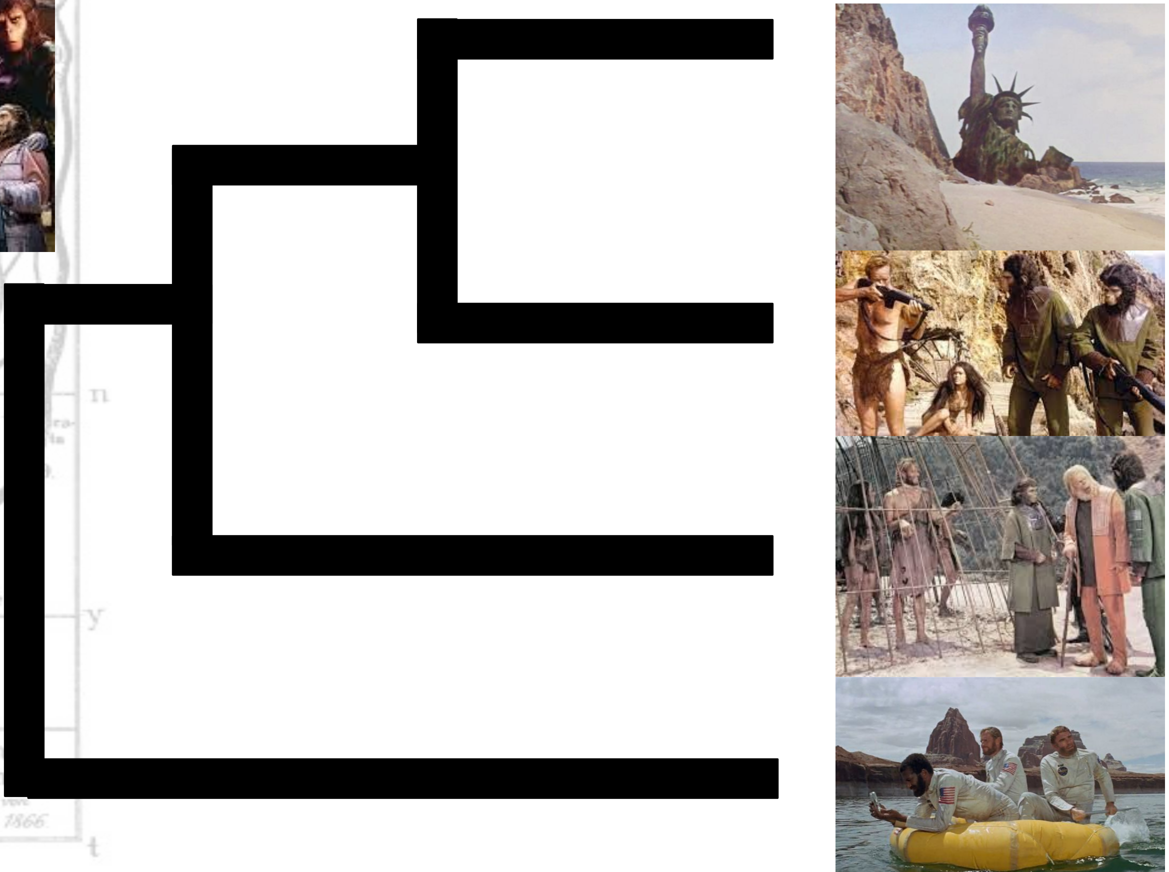

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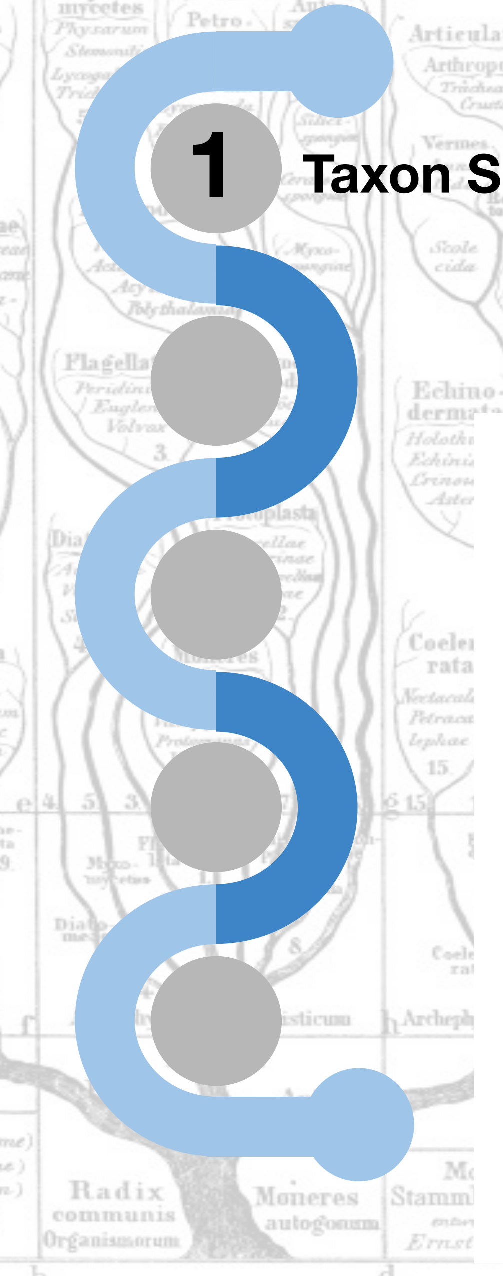

Taxon Sampling

Key message: taxon sampling matters <u>a lot</u>

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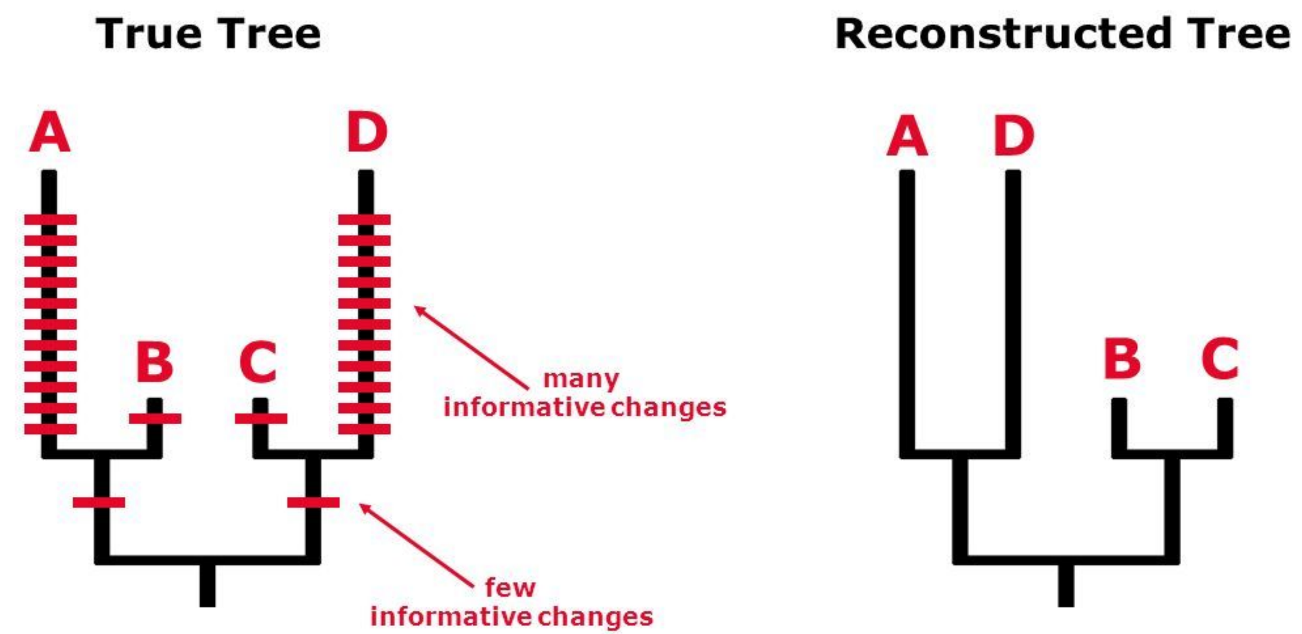
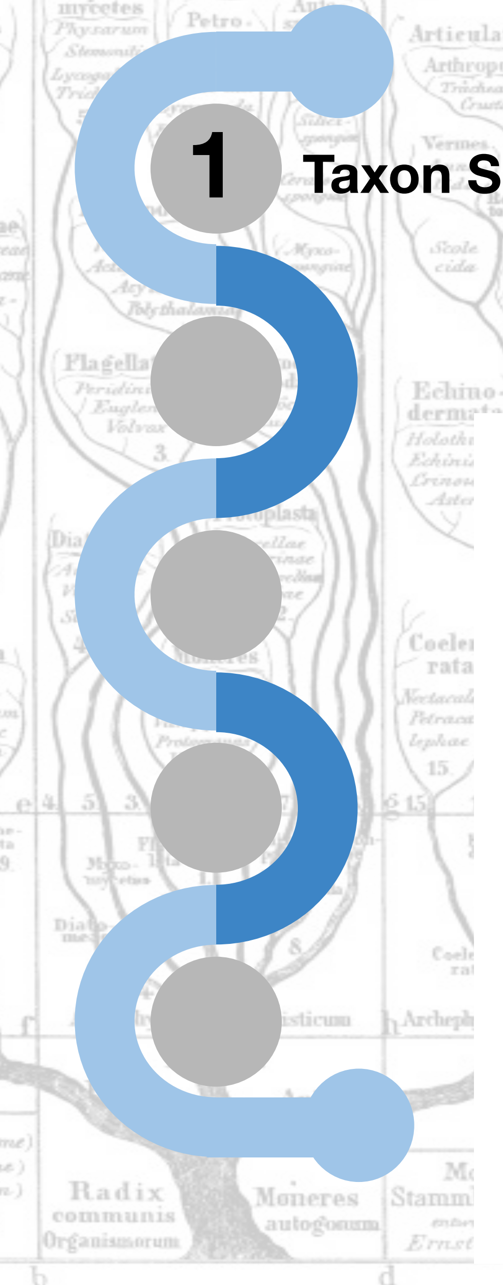
Long Branch Attraction



How to infer a species tree



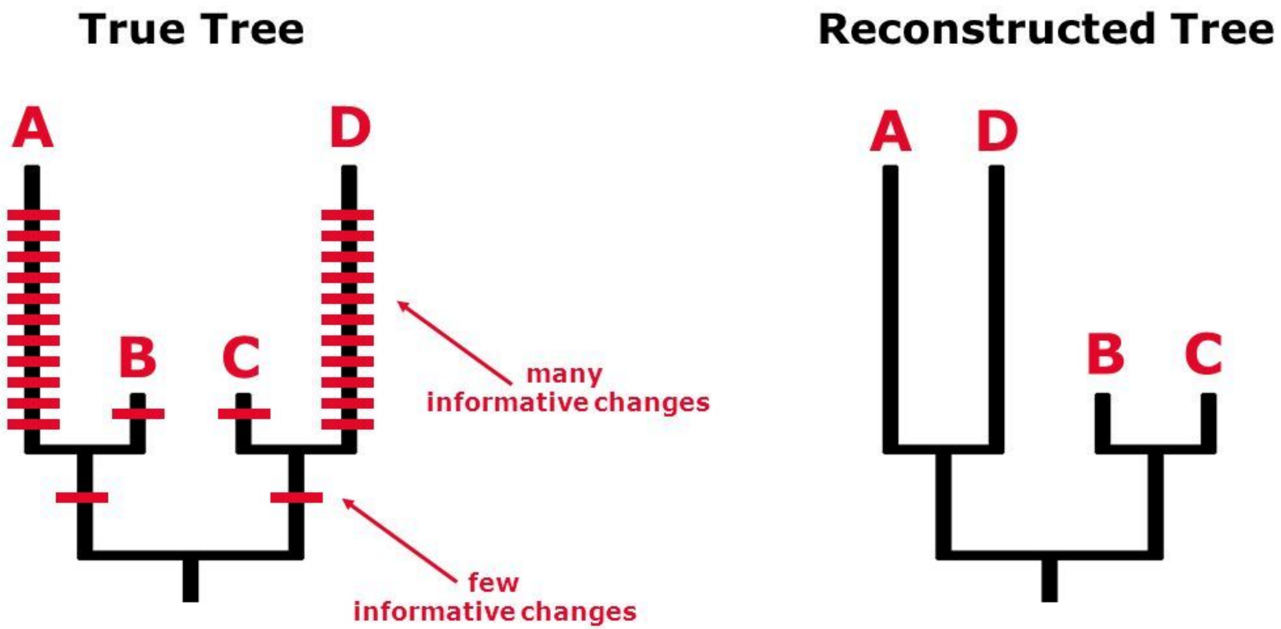
Taxon Sampling

Key message: taxon sampling matters a lot

Incomplete, biased, or improper taxon sampling can lead to misleading results in reconstructing evolutionary relationships.

Long Branch Attraction

Outgroups / Fast-evolving lineages / Compositional heterogeneity



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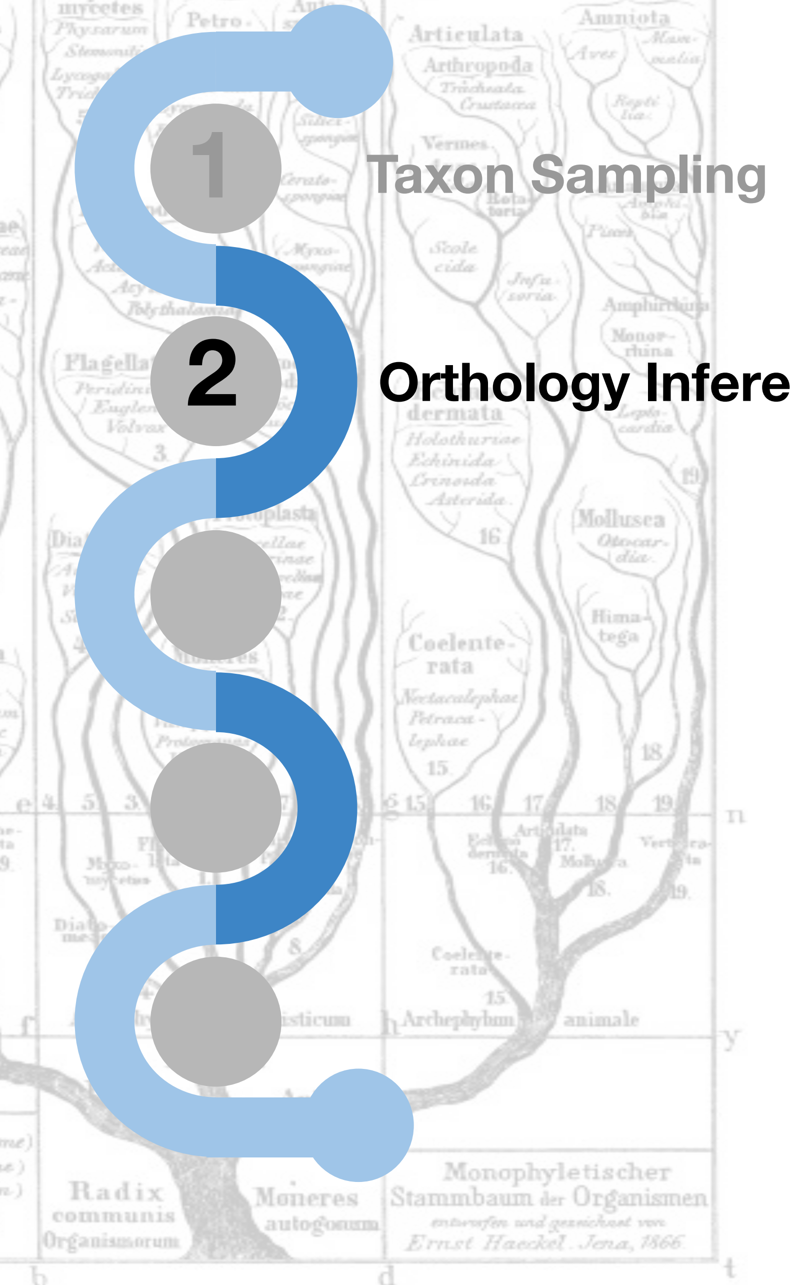
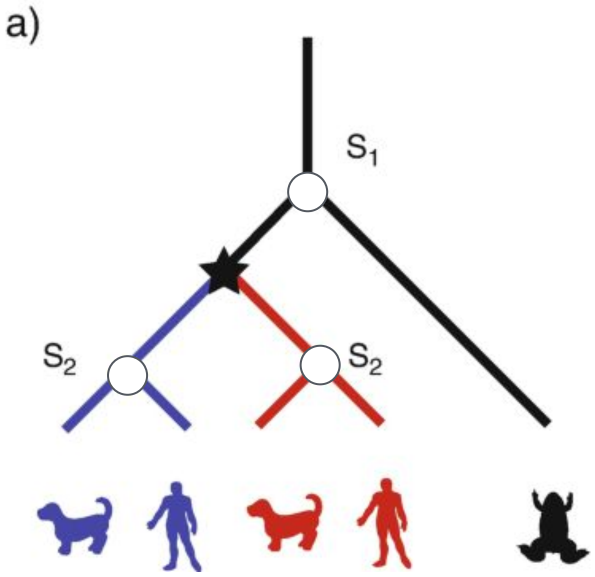


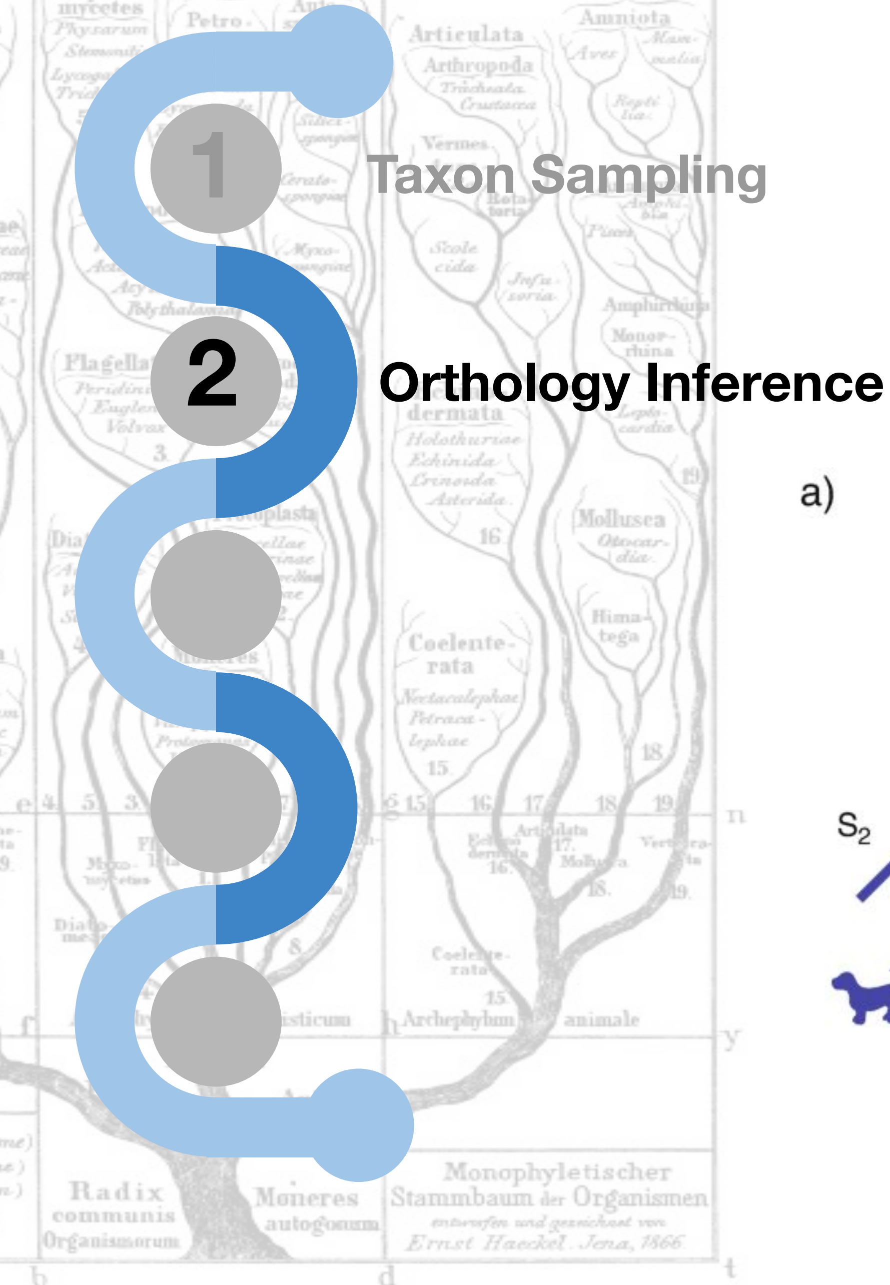
1 Taxon Sampling

2 **Orthology Inference**



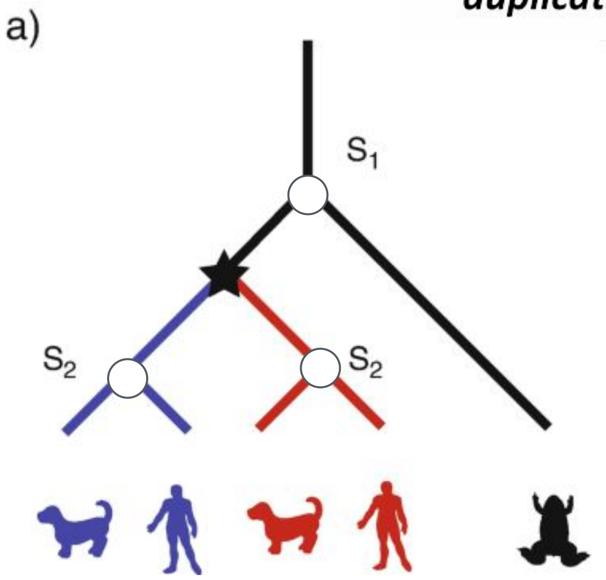
Altenhoff, Glover & Dessimoz 2019

How to infer a species tree



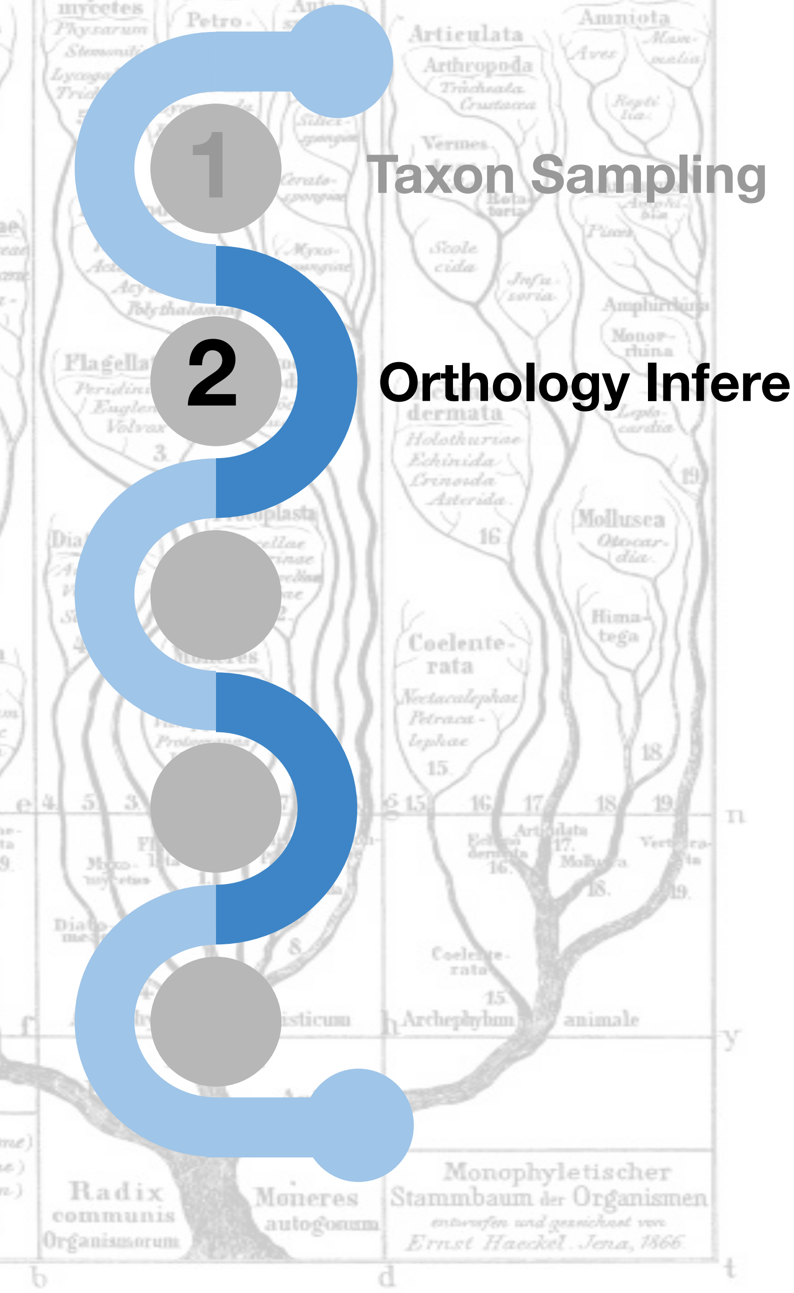
Definitions

- Two genes are **orthologs** if their MRCA is a ***speciation***: ○
- Two genes are **paralogs** if their MRCA is a ***duplication***: ★



Altenhoff, Glover & Dessimoz 2019

How to infer a species tree


1
2
Monophyletischer Stammbaum der Organismen
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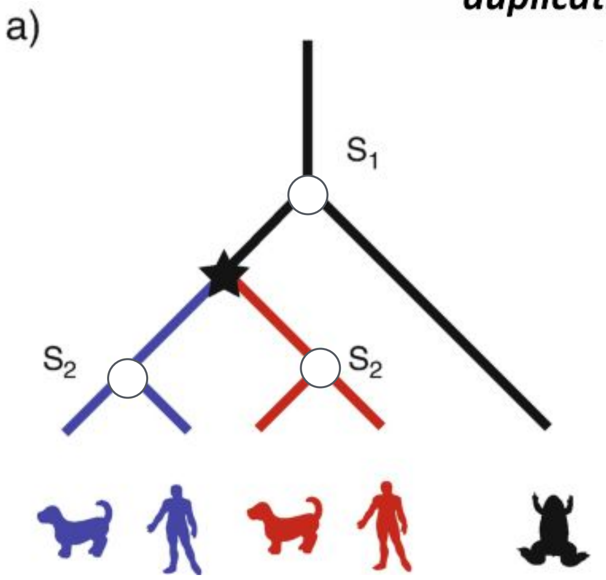
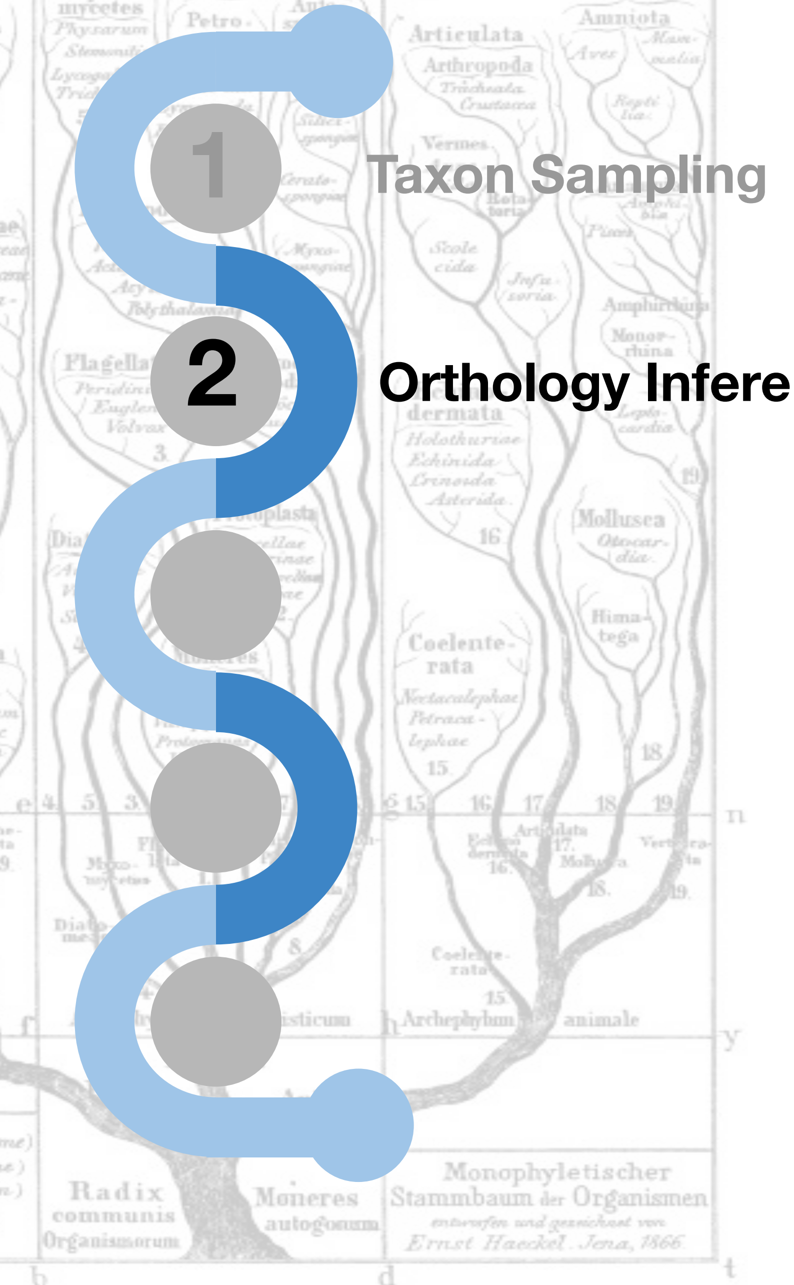


Orthology relationships are inferred pairwise

Altenhoff, Glover & Dessimoz 2019

How to infer a species tree



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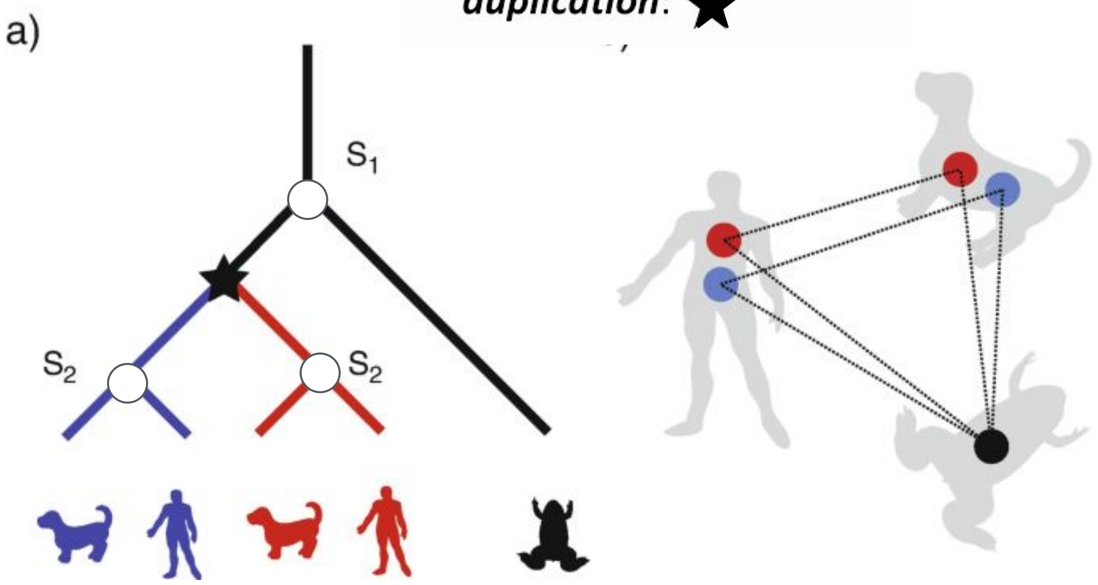

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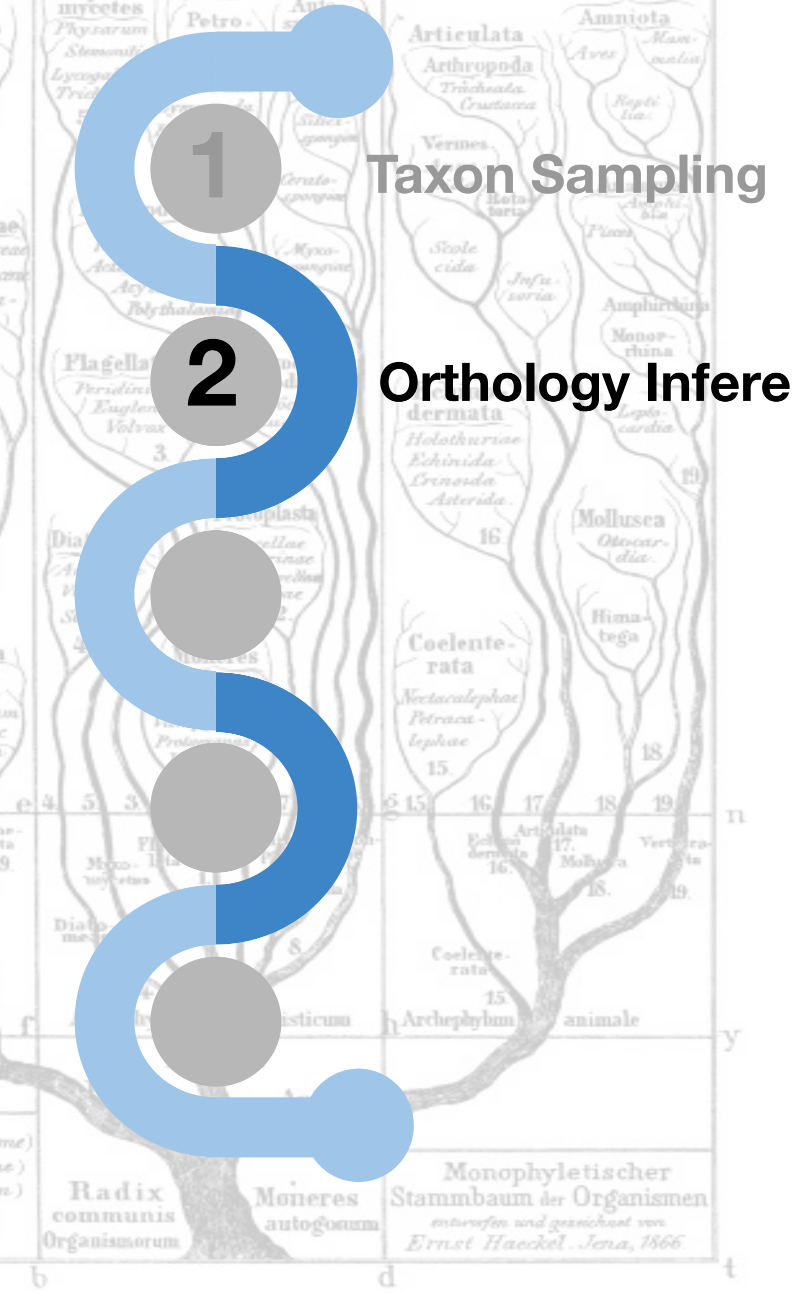
Altenhoff, Glover & Dessimoz 2019

How to infer a species tree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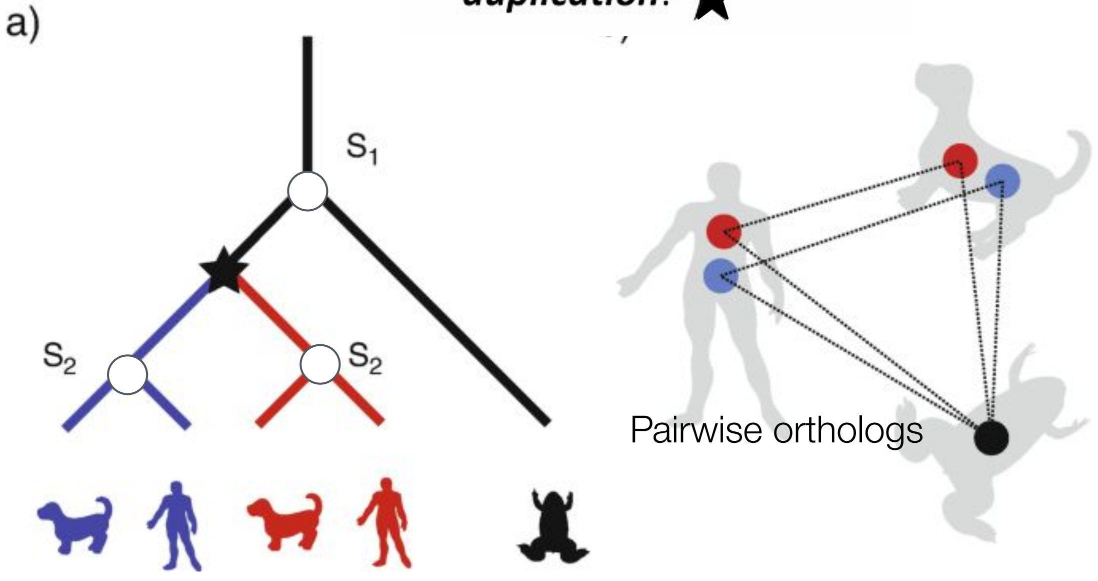

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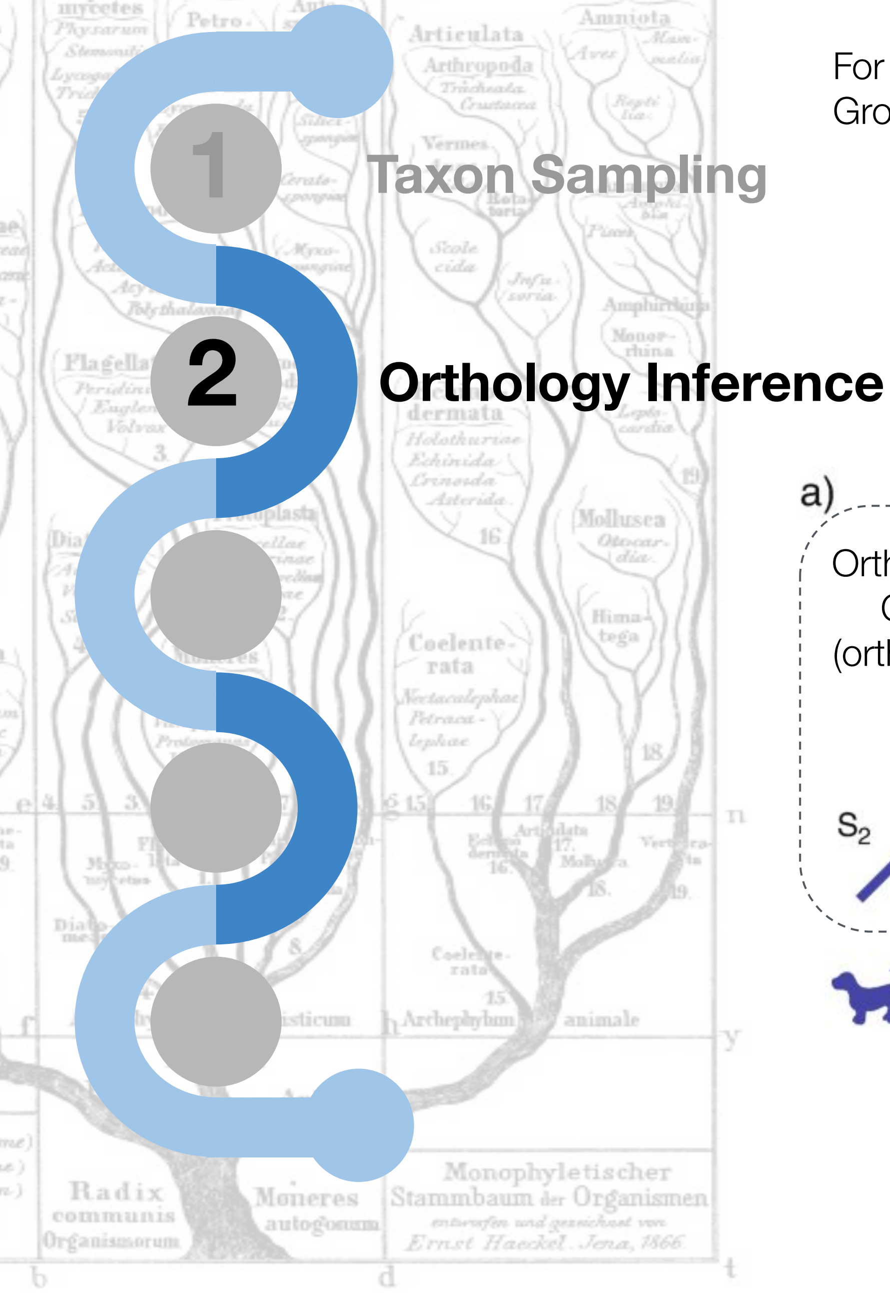
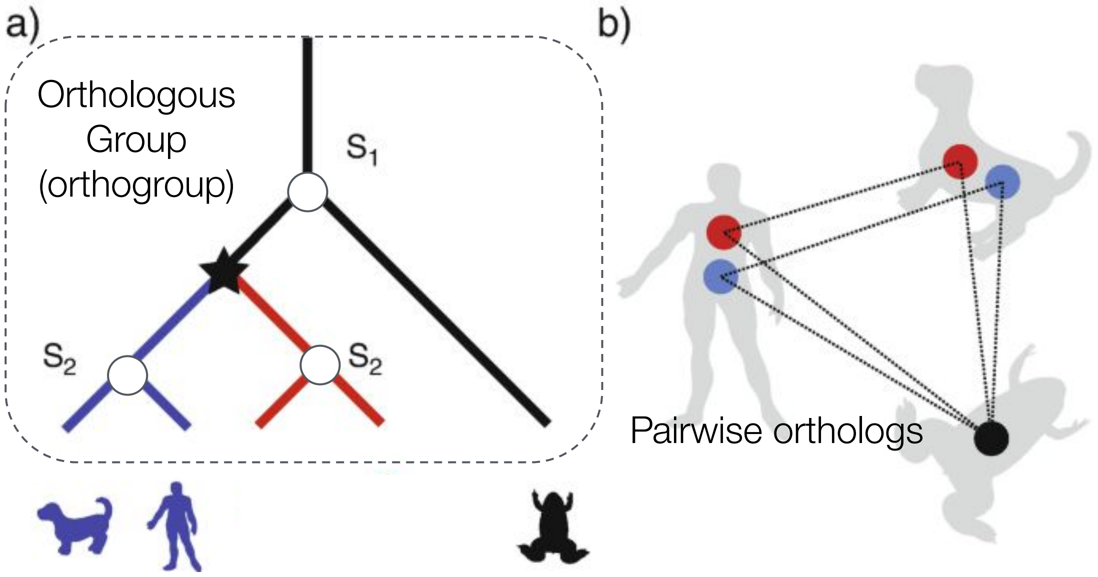
Altenhoff, Glover & Dessimoz 2019

How to infer a species tree



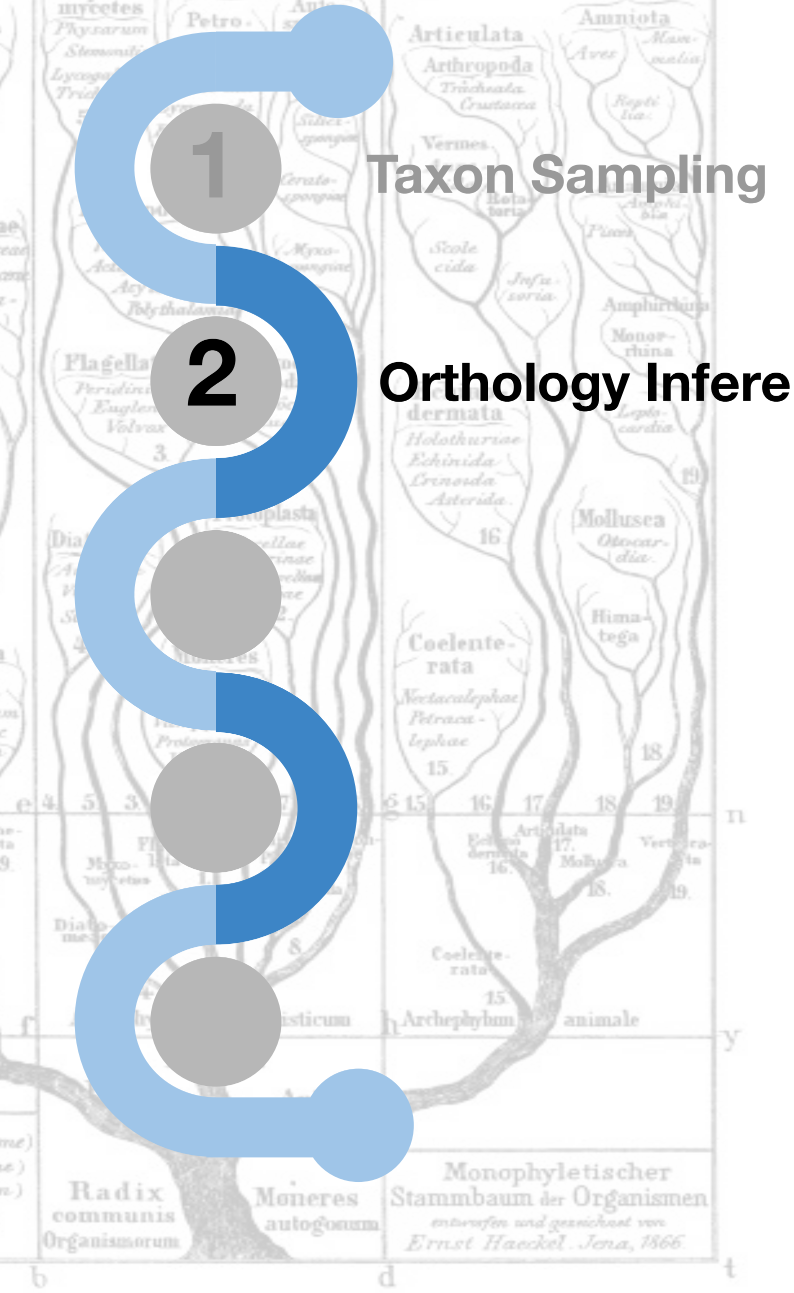
For phylogenetic inference, our starting point are the Orthologous Groups, (OGs) since they are derived from speciation events



Orthology relationships are inferred pairwise

Altenhoff, Glover & Dessimoz 2019

How to infer a species tree


1
2
Articulata
Arthropoda
Amniota
Aves
Mammalia
Vermes
Flagellata
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Coelenterata
Monophyletischer Stammbaum der Organismen
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Radix communis Organismorum
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animale

Taxon Sampling

Orthology Inference

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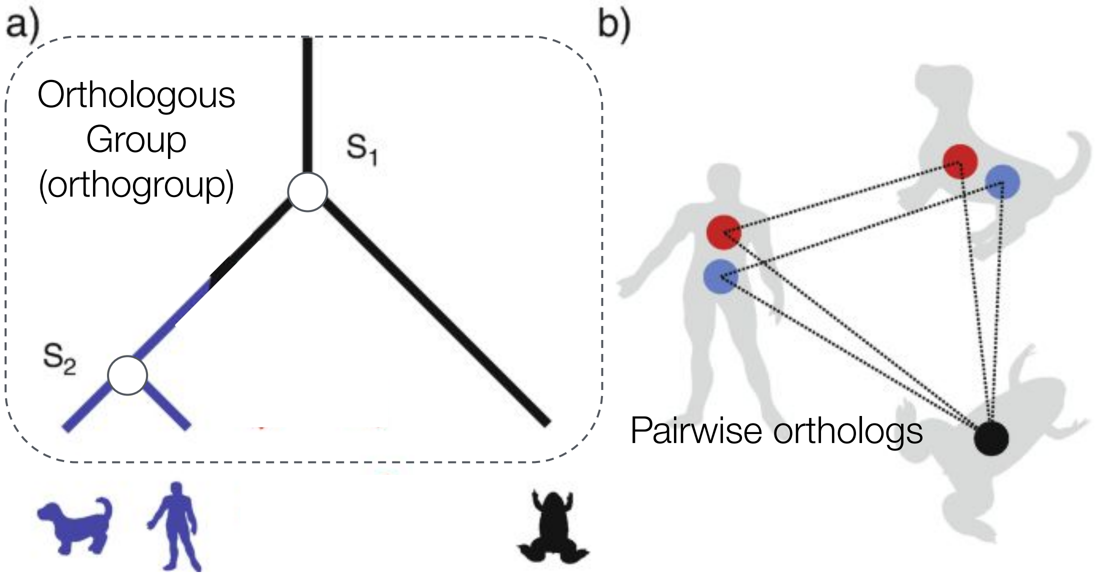
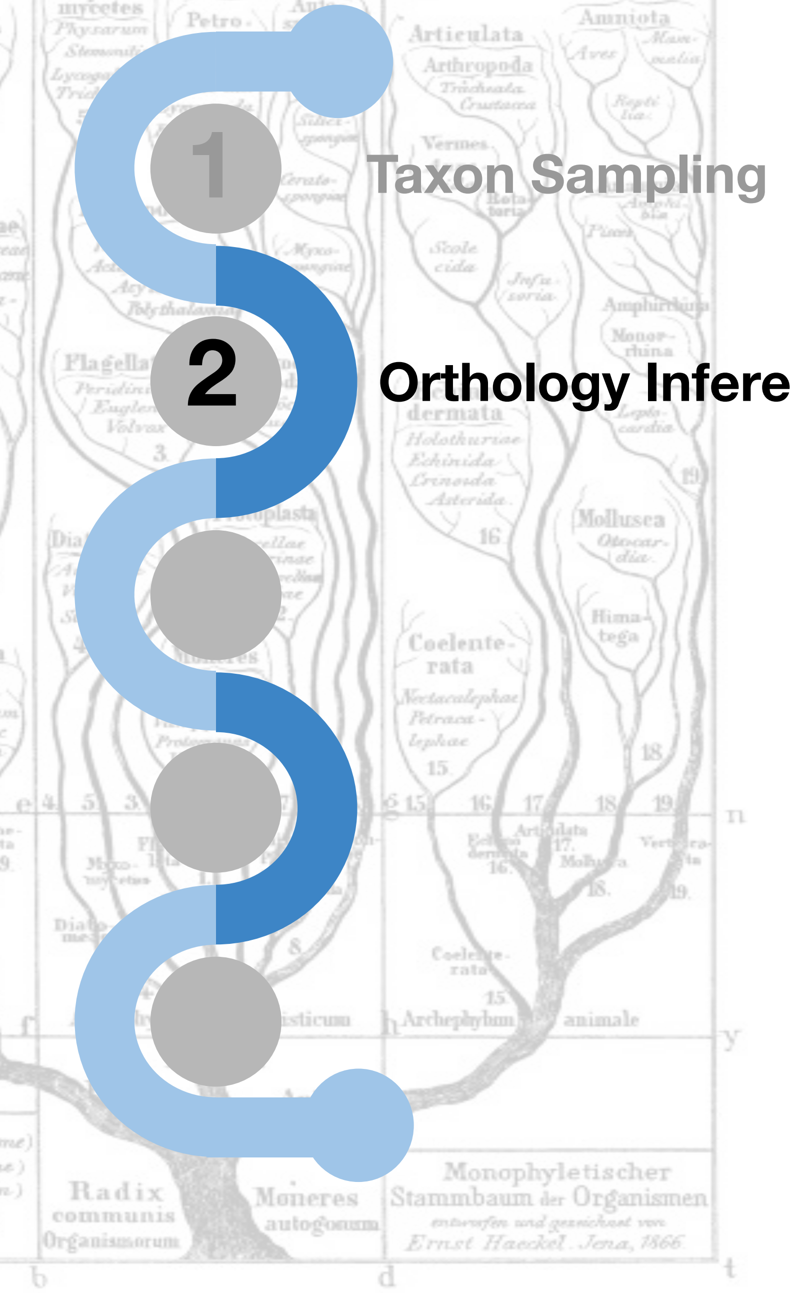


Orthology relationships are inferred pairwise

Altenhoff, Glover & Dessimoz 2019

How to infer a species tree



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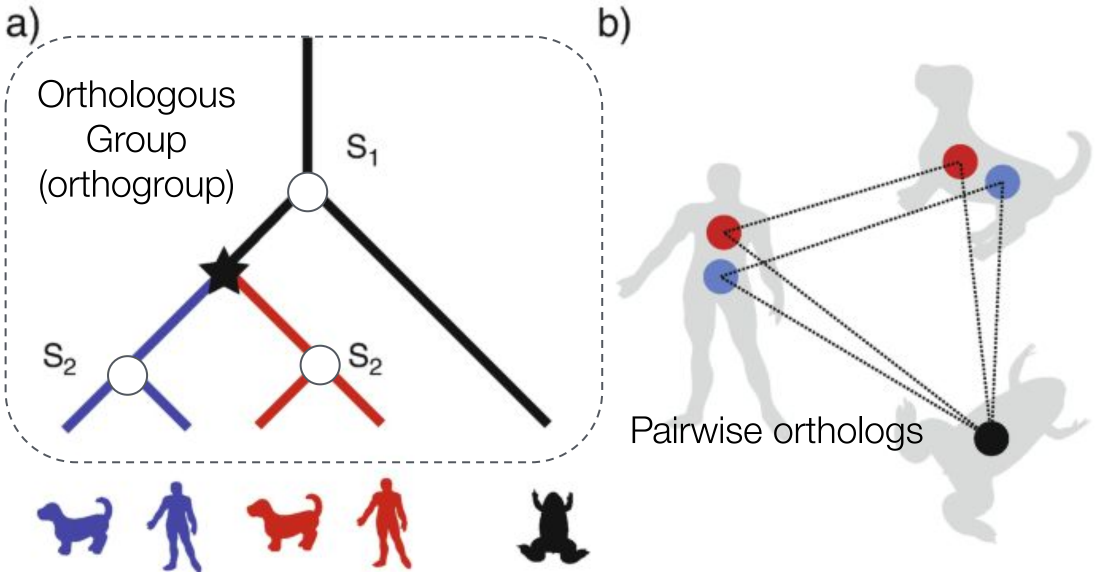
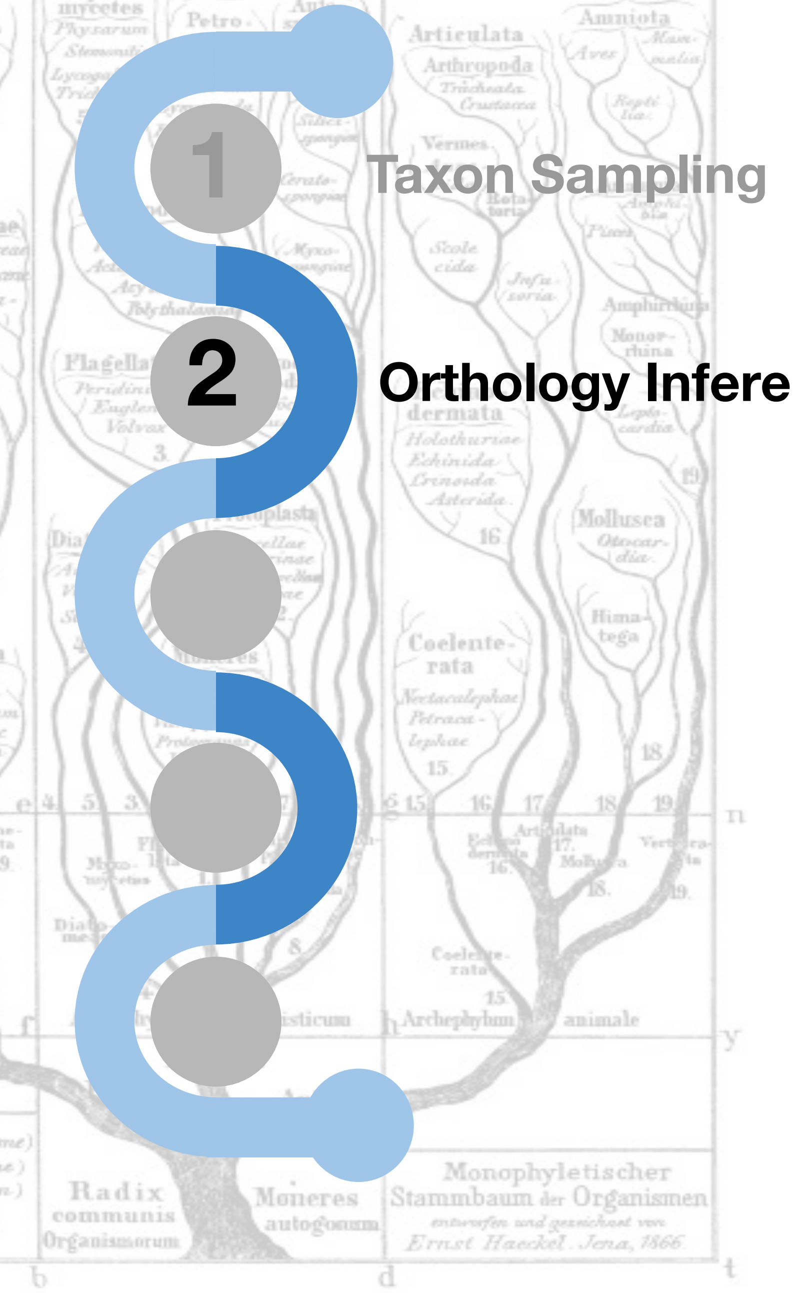


Orthology relationships are inferred pairwise

Altenhoff, Glover & Dessimoz 2019

How to infer a species tree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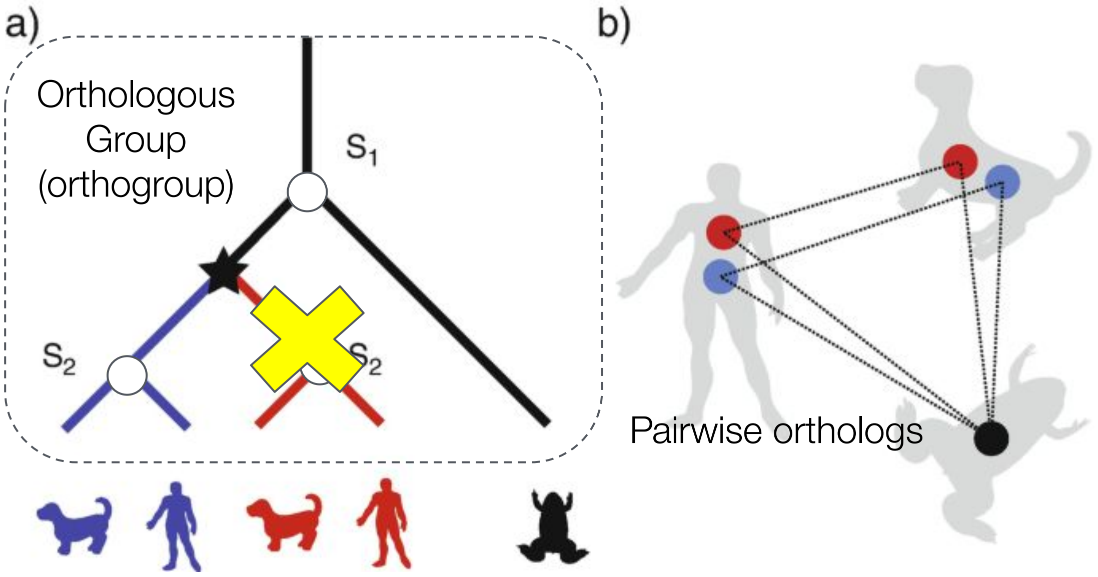
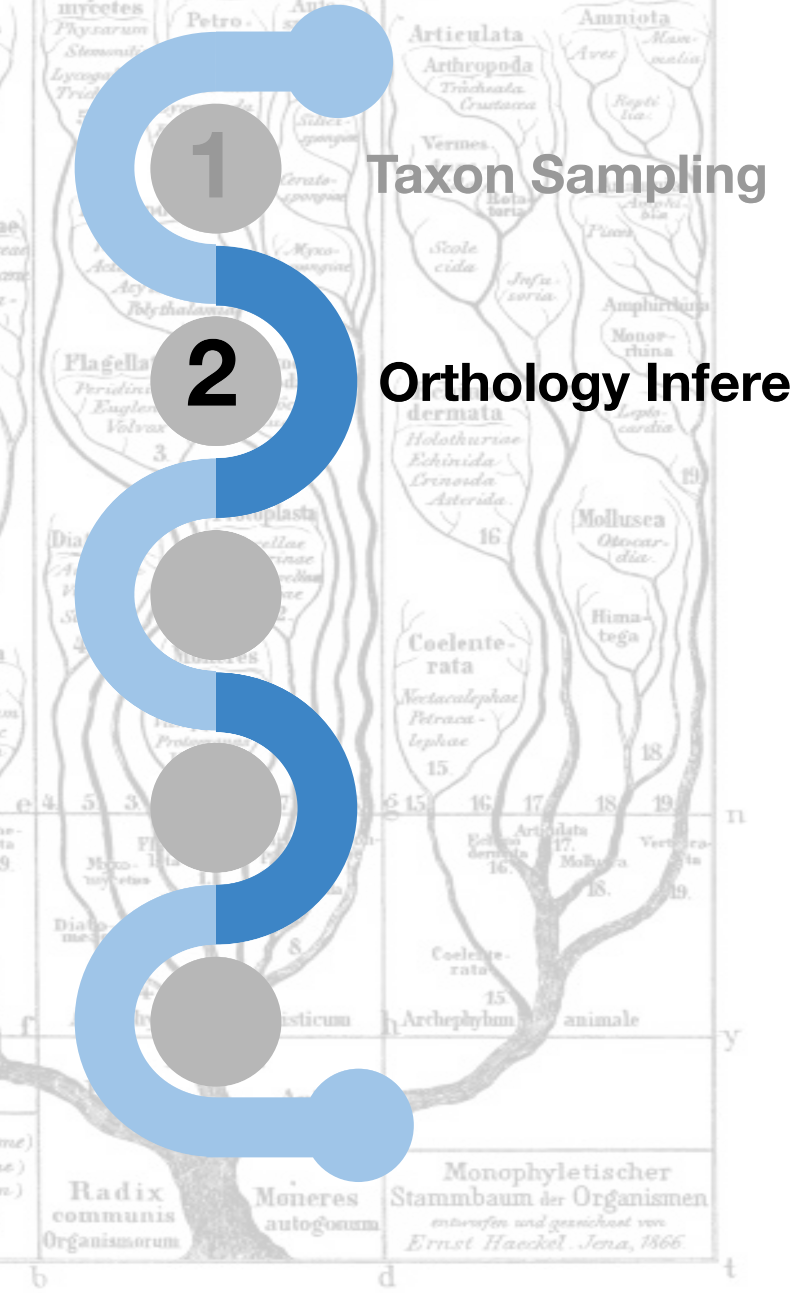


Orthology relationships are inferred pairwise

Altenhoff, Glover & Dessimoz 2019

How to infer a species tree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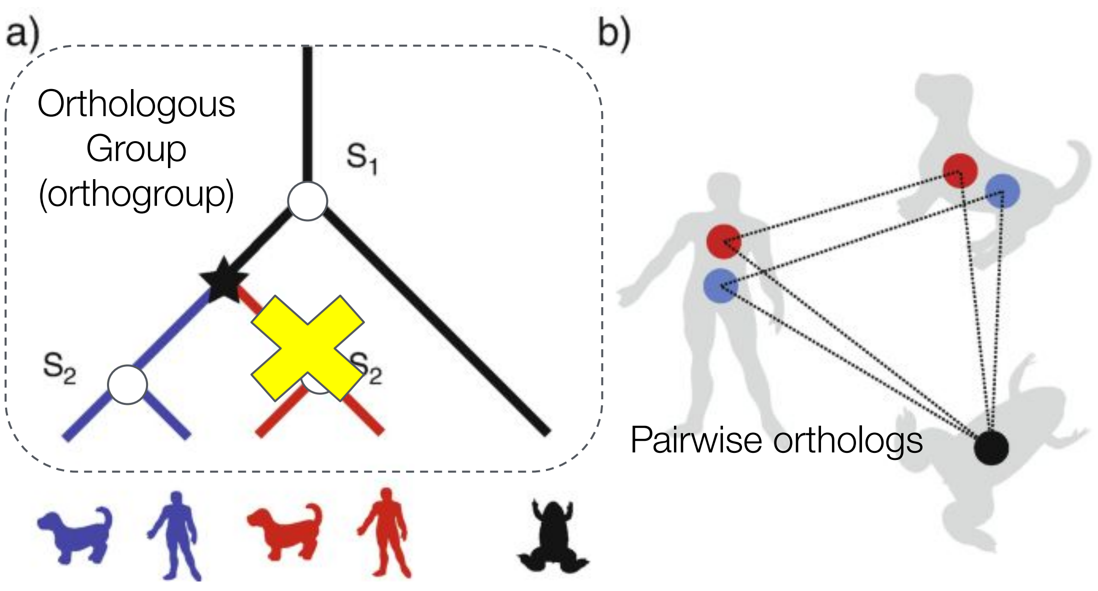
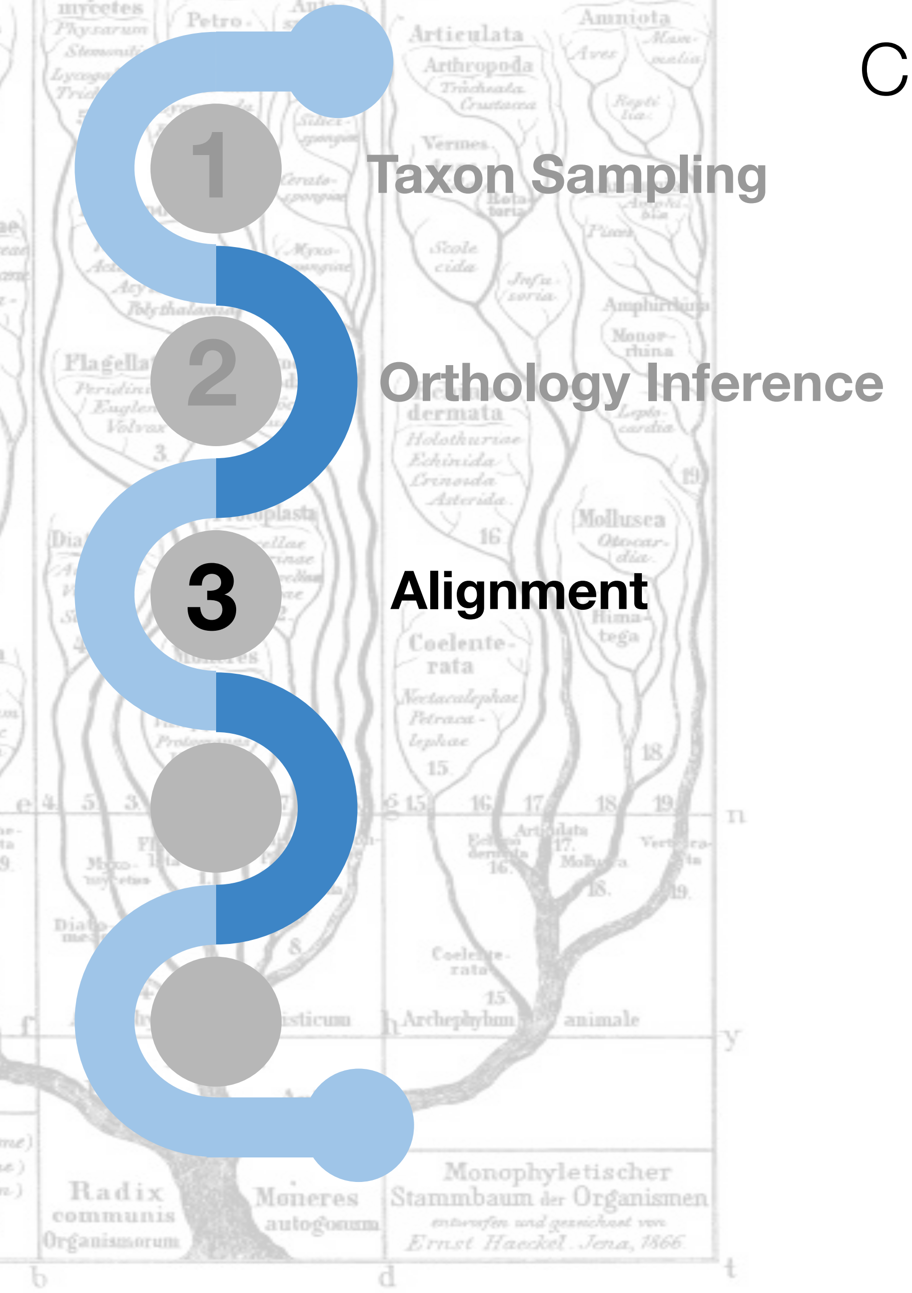


Key message: the selection of OGs for further analysis matters a lot

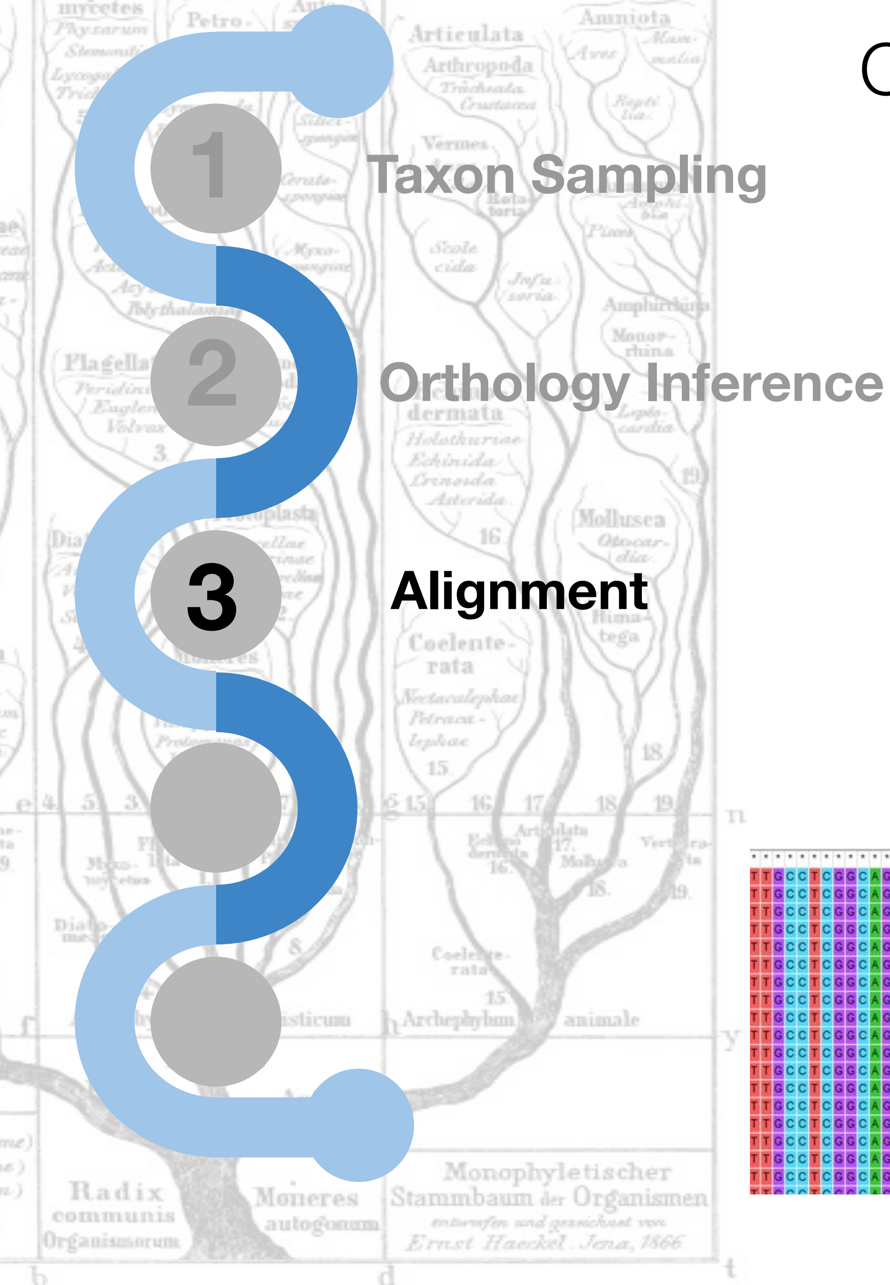
Altenhoff, Glover & Dessimoz 2019

How to infer a species tree



Covered last week by Rayan

How to infer a species tree



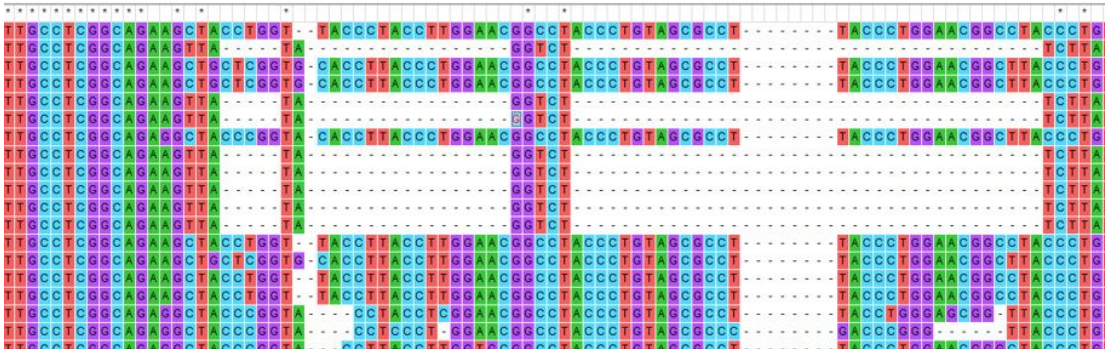
1 Taxon Sampling

2 Orthology Inference

3 Alignment

Covered last week by Rayan

If the sequences are poorly aligned, you may want to consider trimming the poorly aligned areas. There are several tools for it:



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TTGCCTCGGCAGAAGTTA-----TA-----------------GGTCT---------------------------------------TCTTA
TTGCCTCGGCAGAAGCTGCTCGGTG-CACCTTACCCTGGAACGGCCTACCCTGTAGCGCCT--------TACCCTGGAACGGCTTACCCTG
TTGCCTCGGCAGAAGCTGCTCGGTG-CACCTTACCCTGGAACGGCCTACCCTGTAGCGCCT--------TACCCTGGAACGGCTTACCCTG
TTGCCTCGGCAGAAGTTA-----TA-----------------GGTCT---------------------------------------TCTTA
TTGCCTCGGCAGAAGTTA-----TA-----------------GGTCT---------------------------------------TCTTA
TTGCCTCGGCAGAGGCTACCCGGTA-CACCTTACCCTGGAACGGCCTACCCTGTAGCGCCT--------TACCCTGGAACGGCTTACCCTG
TTGCCTCGGCAGAAGTTA-----TA-----------------GGTCT---------------------------------------TCTTA
TTGCCTCGGCAGAAGTTA-----TA-----------------GGTCT---------------------------------------TCTTA
TTGCCTCGGCAGAAGTTA-----TA-----------------GGTCT---------------------------------------TCTTA
TTGCCTCGGCAGAAGTTA-----TA-----------------GGTCT---------------------------------------TCTTA
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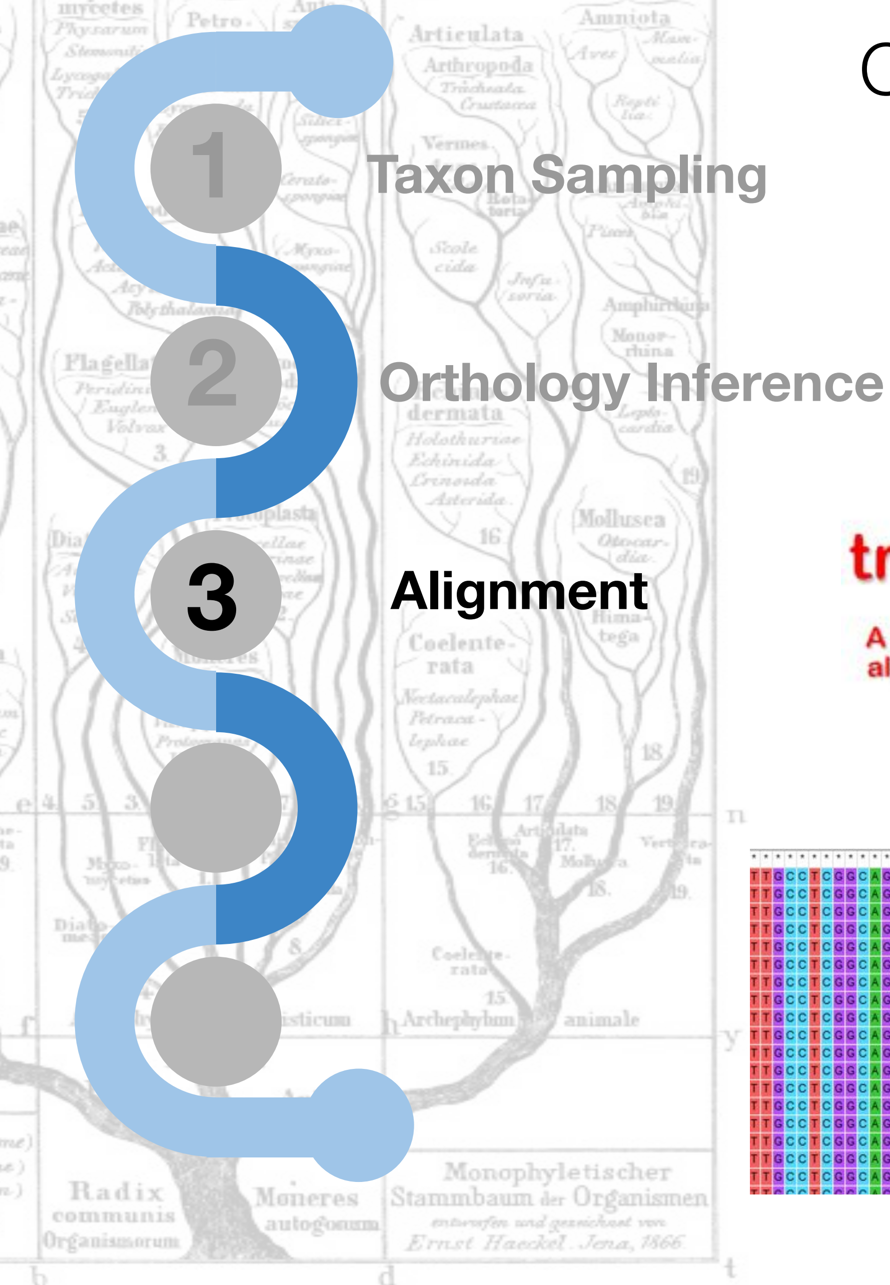
TTGCCTCGGCAGAAGCTACCTGGT--TACCTTACCTTGGAACGGCCTACCCTGTAGCGCCT--------TACCCTGGAACGGCCTACCCTG
TTGCCTCGGCAGAAGCTACCTGGT--TACCTTACCTTGGAACGGCCTACCCTGTAGCGCCT--------TACCCTGGAACGGCCTACCCTG
TTGCCTCGGCAGAGGCTACCCGGTA----CCTACCTCGGAACGGCCTACCCTGTAGCGCCT--------TACCTGGGAGCGG-TTACCCTG
TTGCCTCGGCAGAGGCTACCCGGTA----CCTCCCT-GGAACGGCCTACCCTGTAGCGCCC--------GACCCGGG------TTACCCTG
```

How to infer a species tree



1 Taxon Sampling

2 Orthology Inference

3 **Alignment**

Covered last week by Rayan

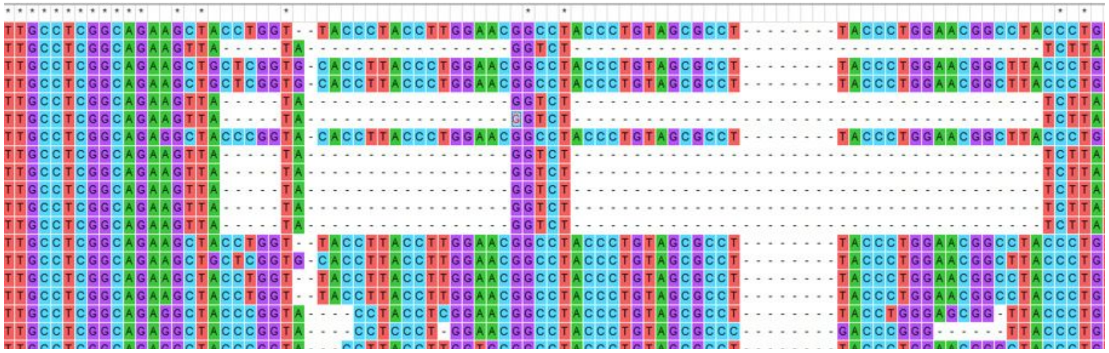
If the sequences are poorly aligned, you may want to consider trimming the poorly aligned areas. There are several tools for it:

trimAl

A tool for automated alignment trimming

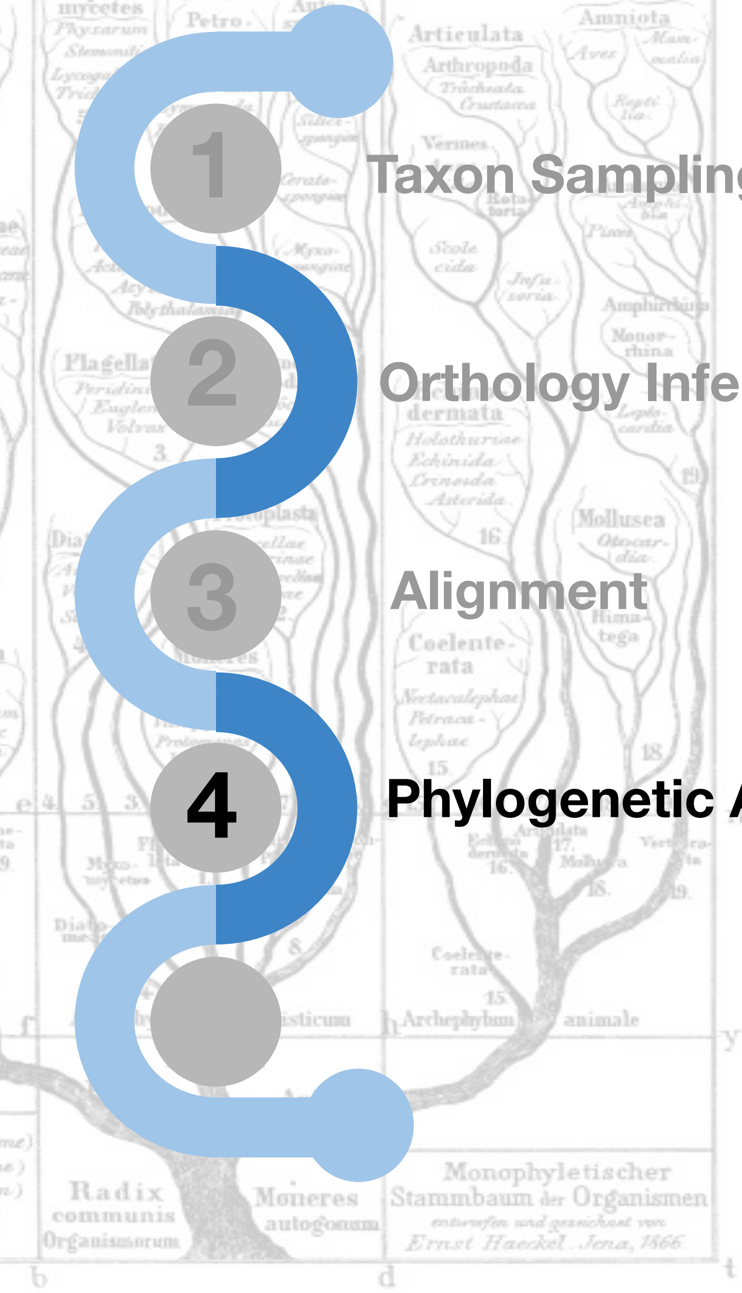
PREQUAL

(prealignment quality filter)



```
************  * *      *                   *  *                                        * *
TTGCCTCGGCAGAAGCTACCTGGT--TACCCTACCTTGGAACGGCCTACCCTGTAGCGCCT--------TACCCTGGAACGGCCTACCCTG
TTGCCTCGGCAGAAGTTA-----TA-----------------GGTCT---------------------------------------TCTTA
TTGCCTCGGCAGAAGCTGCTCGGTG-CACCTTACCCTGGAACGGCCTACCCTGTAGCGCCT--------TACCCTGGAACGGCTTACCCTG
TTGCCTCGGCAGAAGCTGCTCGGTG-CACCTTACCCTGGAACGGCCTACCCTGTAGCGCCT--------TACCCTGGAACGGCTTACCCTG
TTGCCTCGGCAGAAGTTA-----TA-----------------GGTCT---------------------------------------TCTTA
TTGCCTCGGCAGAAGTTA-----TA-----------------GGTCT---------------------------------------TCTTA
TTGCCTCGGCAGAGGCTACCCGGTA-CACCTTACCCTGGAACGGCCTACCCTGTAGCGCCT--------TACCCTGGAACGGCTTACCCTG
TTGCCTCGGCAGAAGTTA-----TA-----------------GGTCT---------------------------------------TCTTA
TTGCCTCGGCAGAAGTTA-----TA-----------------GGTCT---------------------------------------TCTTA
TTGCCTCGGCAGAAGTTA-----TA-----------------GGTCT---------------------------------------TCTTA
TTGCCTCGGCAGAAGTTA-----TA-----------------GGTCT---------------------------------------TCTTA
TTGCCTCGGCAGAAGTTA-----TA-----------------GGTCT---------------------------------------TCTTA
TTGCCTCGGCAGAAGCTACCTGGT--TACCTTACCTTGGAACGGCCTACCCTGTAGCGCCT--------TACCCTGGAACGGCCTACCCTG
TTGCCTCGGCAGAAGCTGCTCGGTG-CACCTTACCTTGGAACGGCCTACCCTGTAGCGCCT--------TACCCTGGAACGGCTTACCCTG
TTGCCTCGGCAGAAGCTACCTGGT--TACCTTACCTTGGAACGGCCTACCCTGTAGCGCCT--------TACCCTGGAACGGCCTACCCTG
TTGCCTCGGCAGAAGCTACCTGGT--TACCTTACCTTGGAACGGCCTACCCTGTAGCGCCT--------TACCCTGGAACGGCCTACCCTG
TTGCCTCGGCAGAGGCTACCCGGTA----CCTACCTCGGAACGGCCTACCCTGTAGCGCCT--------TACCTGGGAGCGG-TTACCCTG
TTGCCTCGGCAGAGGCTACCCGGTA----CCTCCCT-GGAACGGCCTACCCTGTAGCGCCC--------GACCCGGG------TTACCCTG
```

How to infer a species tree


Articulata
Arthropoda
Amniota
Mollusca
Coelenterata
Archephylum
animale
Radix communis Organismorum
Moneres autogonum
Monophyletischer Stammbaum der Organismen
entworfen und gezeichnet von Ernst Haeckel. Jena, 1866

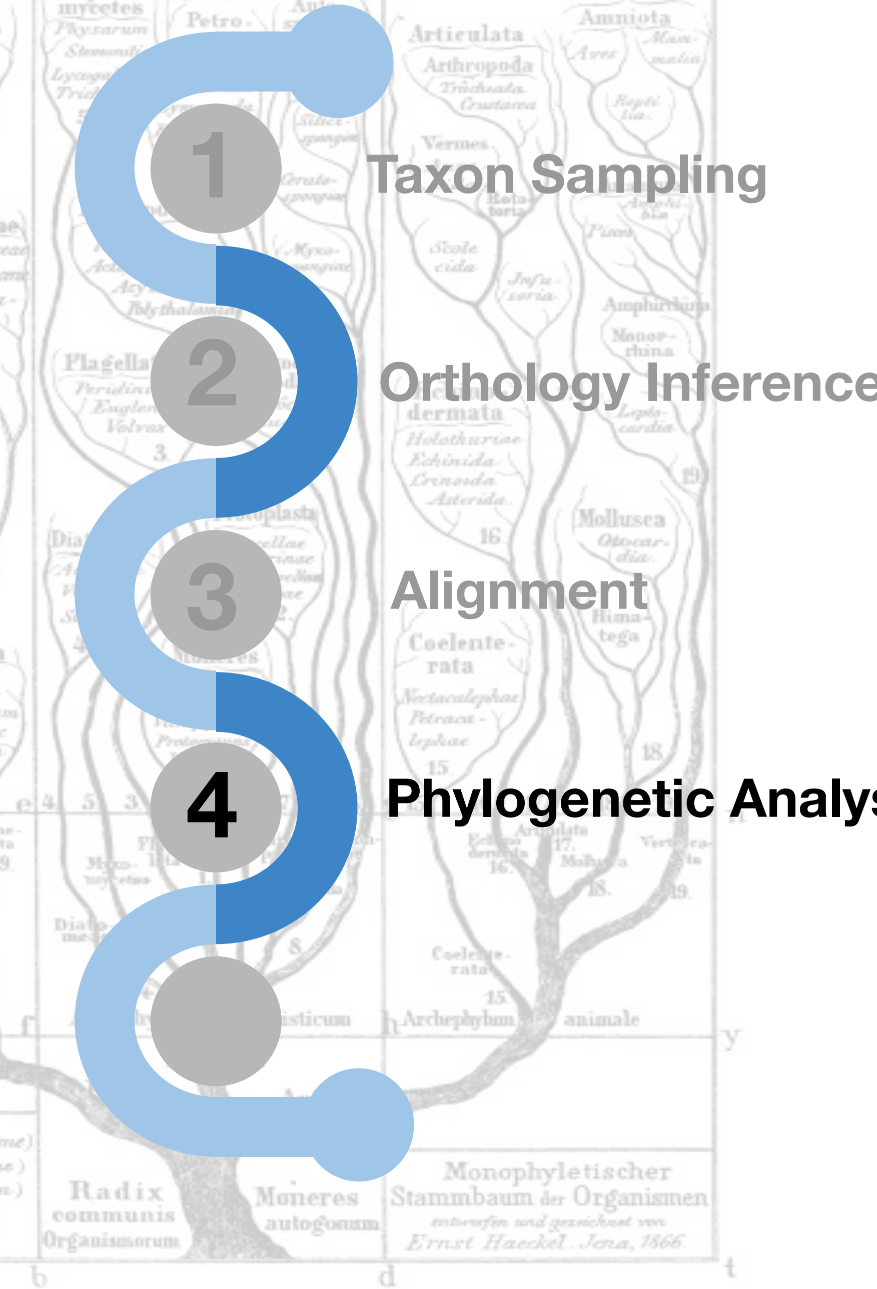
1 Taxon Sampling

2 Orthology Inference

3 Alignment

4 Phylogenetic Analysis

How to infer a species tree



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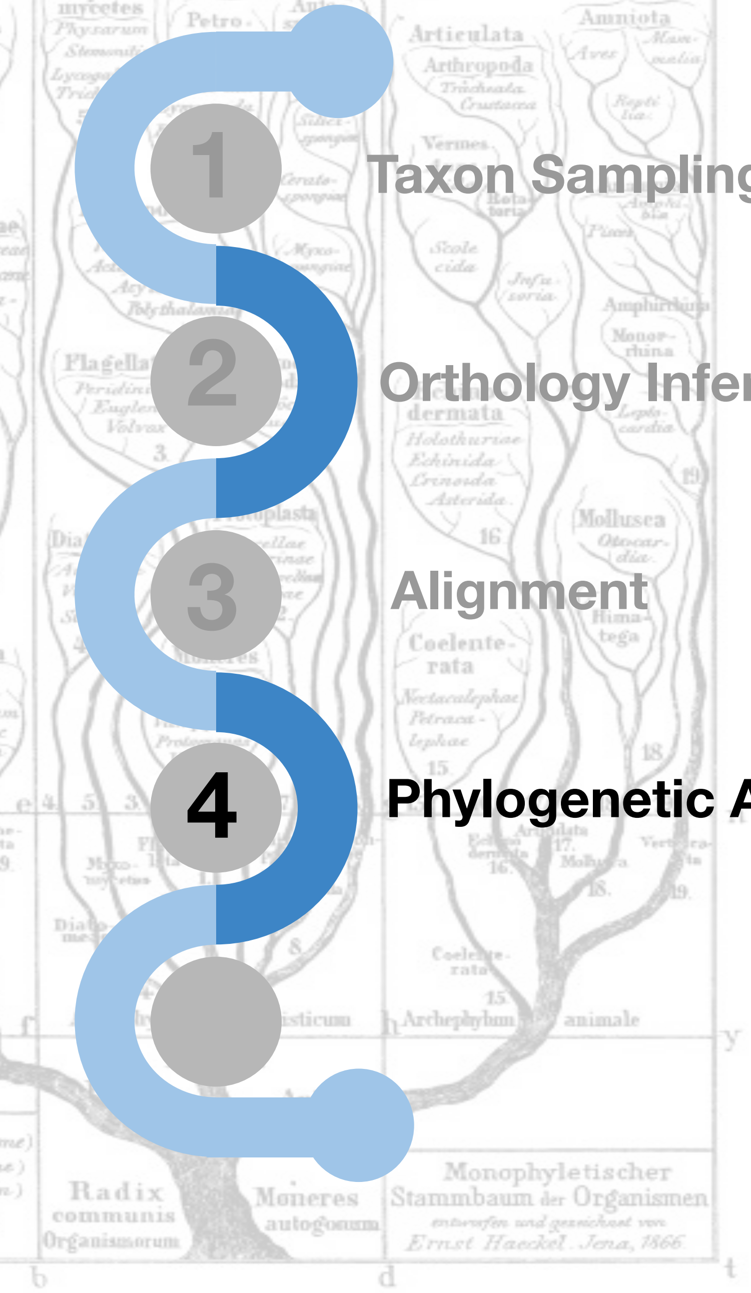
DATA

How to infer a species tree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4 **Phylogenetic Analysis**

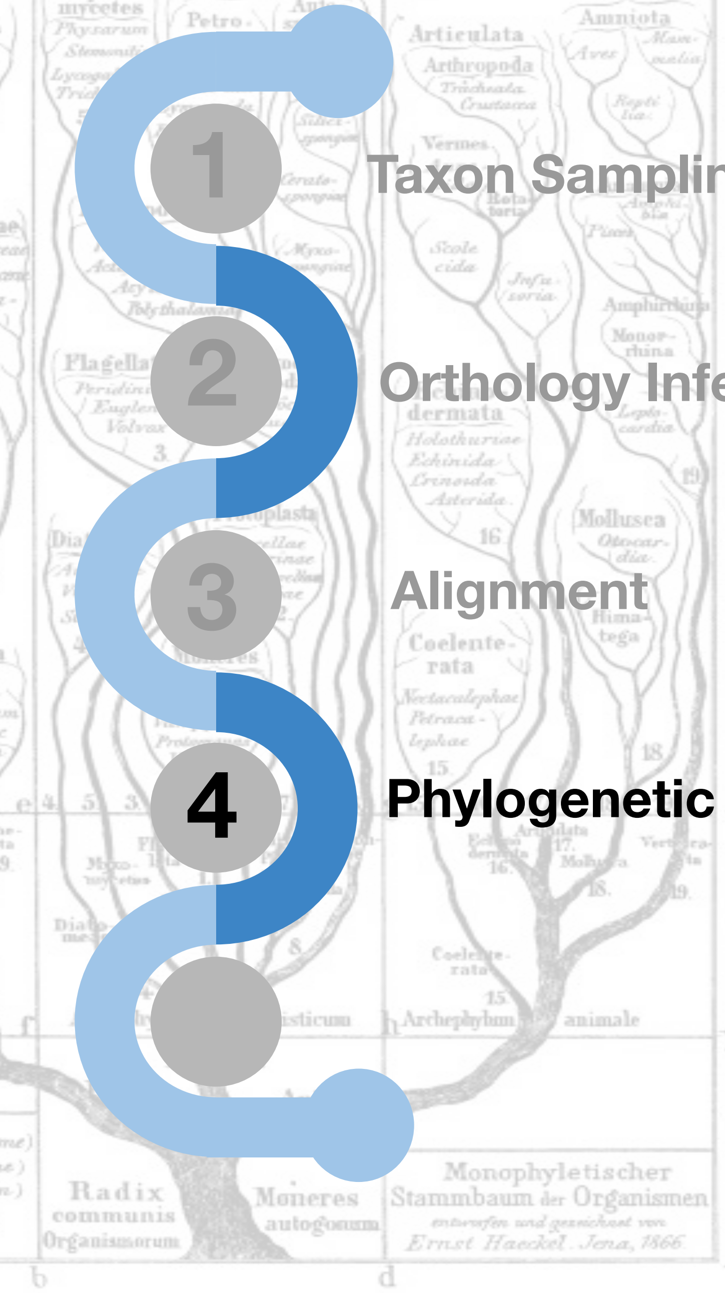
DATA

+

MODEL OF EVOLUTION

describes the relative rates of different changes

How to infer a species tree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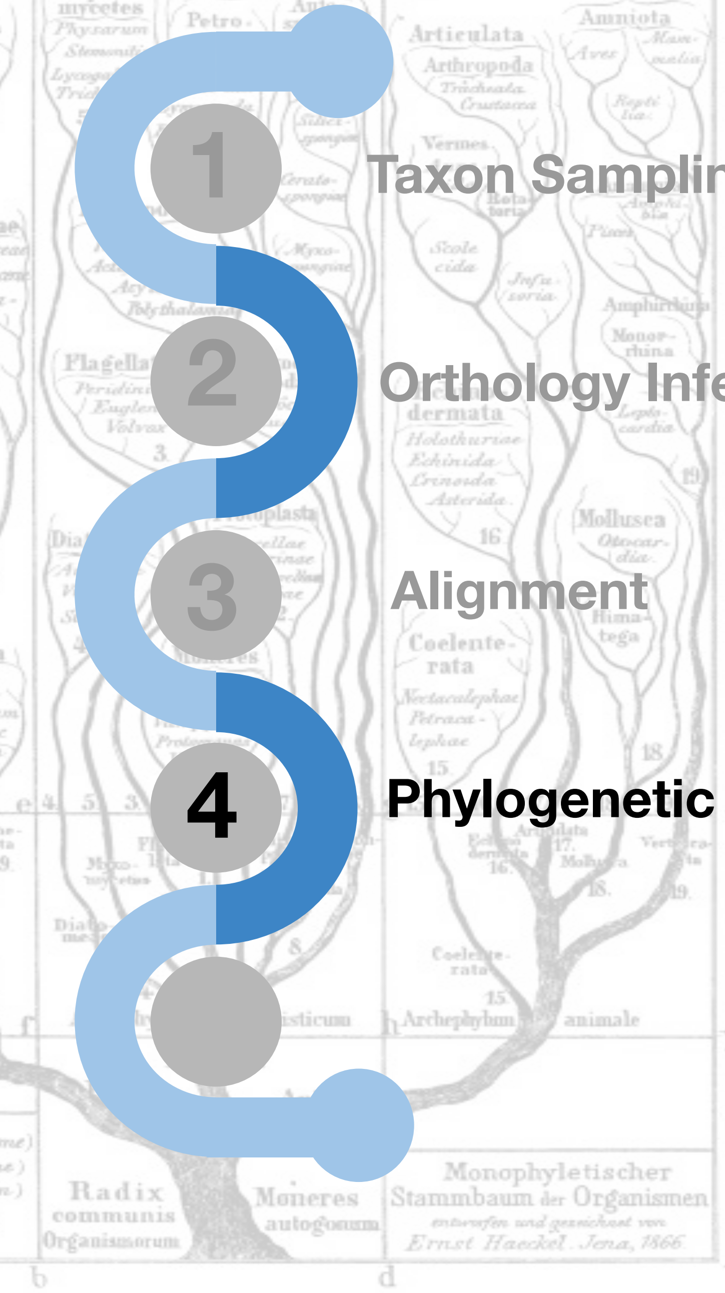
describes the relative rates of different changes

Seq1 ATGGCA

Seq2 ACGCCG

Seq3 AGGGCC

How to infer a species tree



Taxon Sampling

Orthology Inference

Alignment

Phylogenetic Analysis

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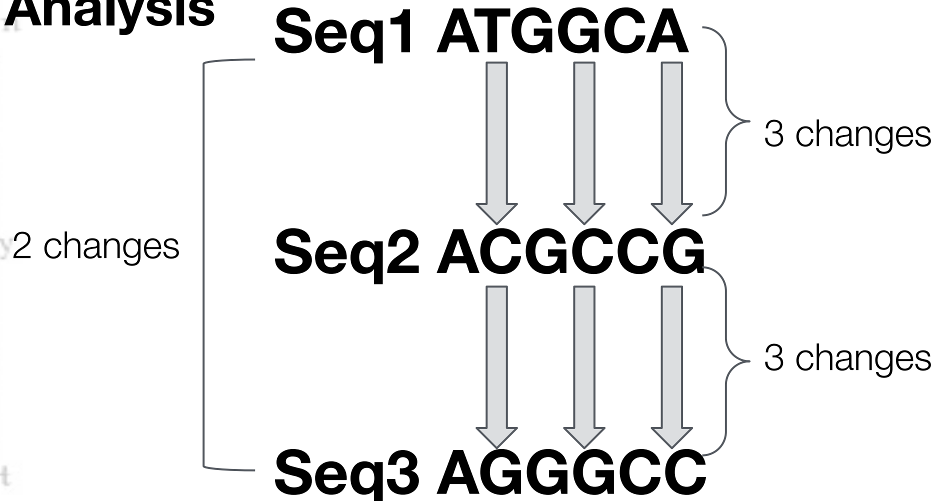

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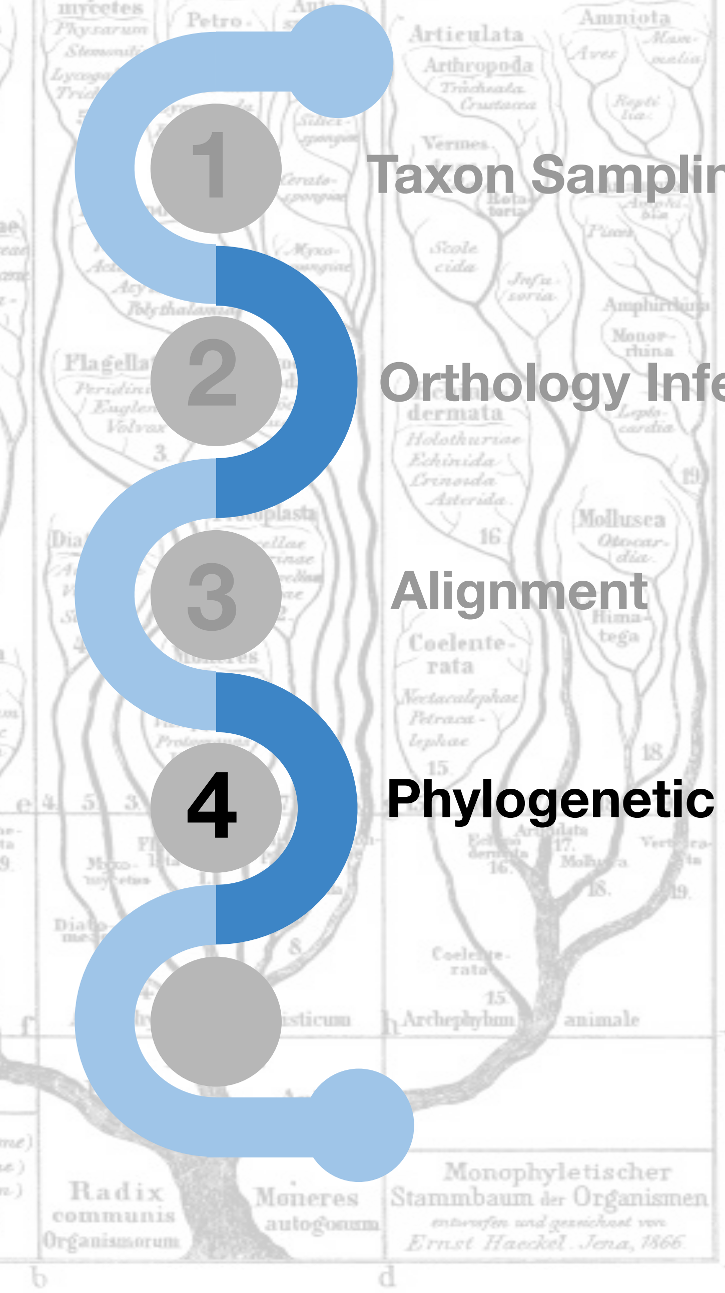

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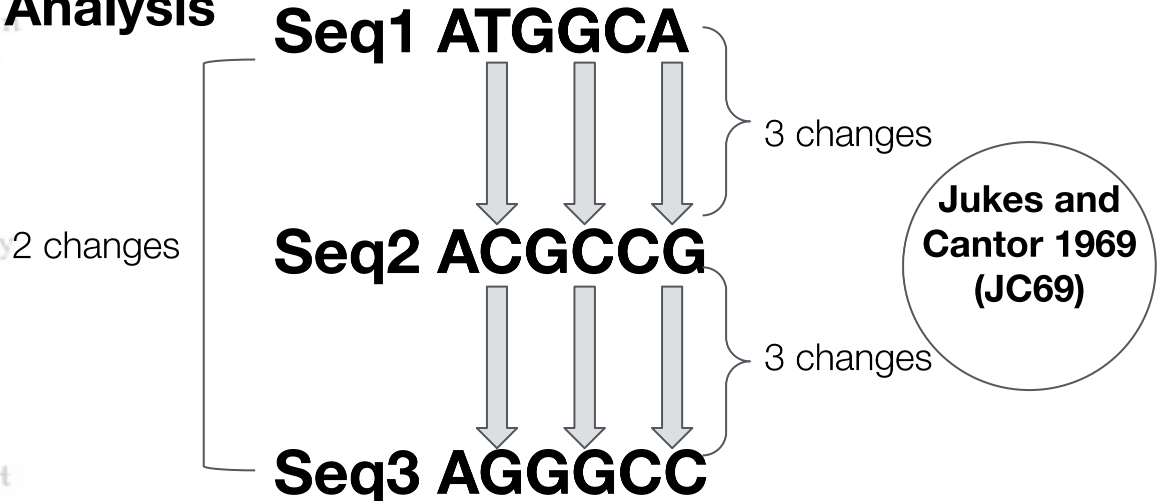

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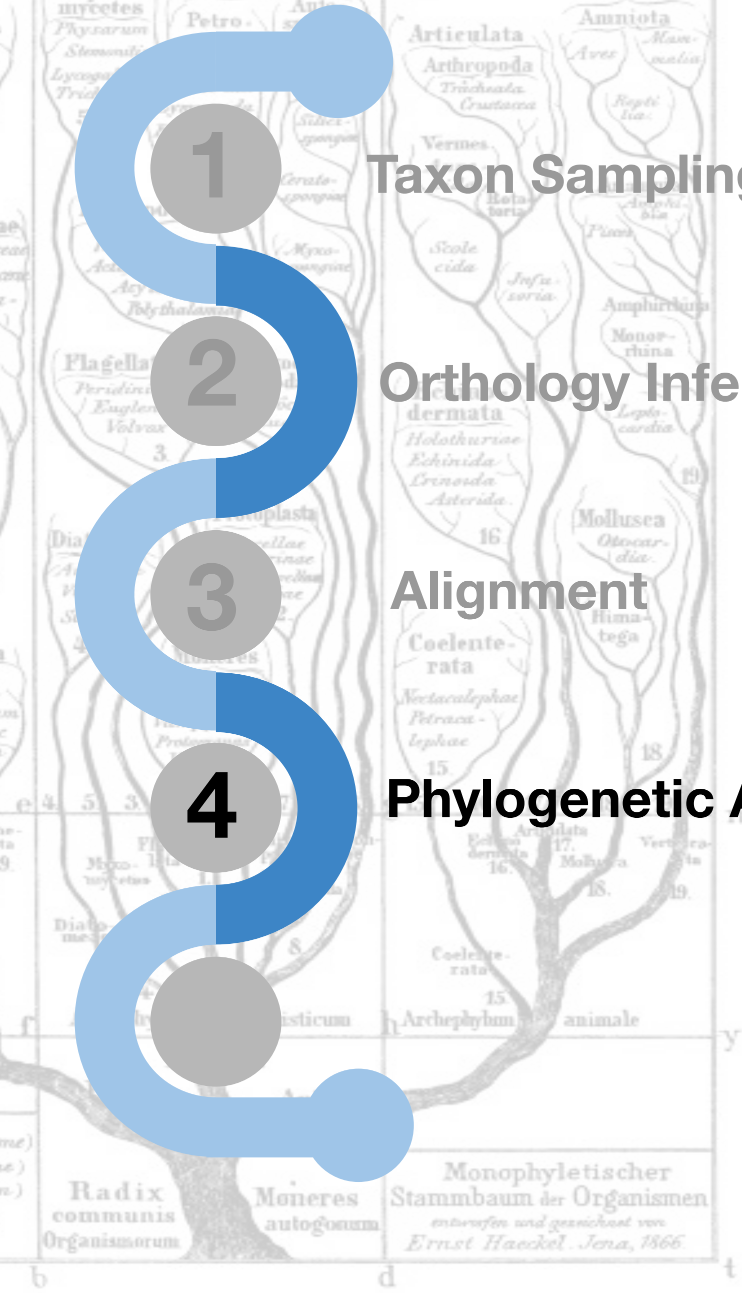
Jukes and Cantor 1969 (JC69)

How to infer a species tree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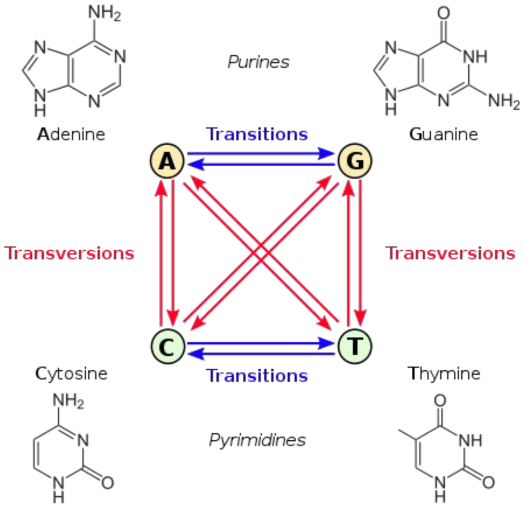
Eg, mutational biases and purifying selection favoring conservative changes are probably responsible for the relatively high rate of **transitions** compared to **transversions** in evolving sequences



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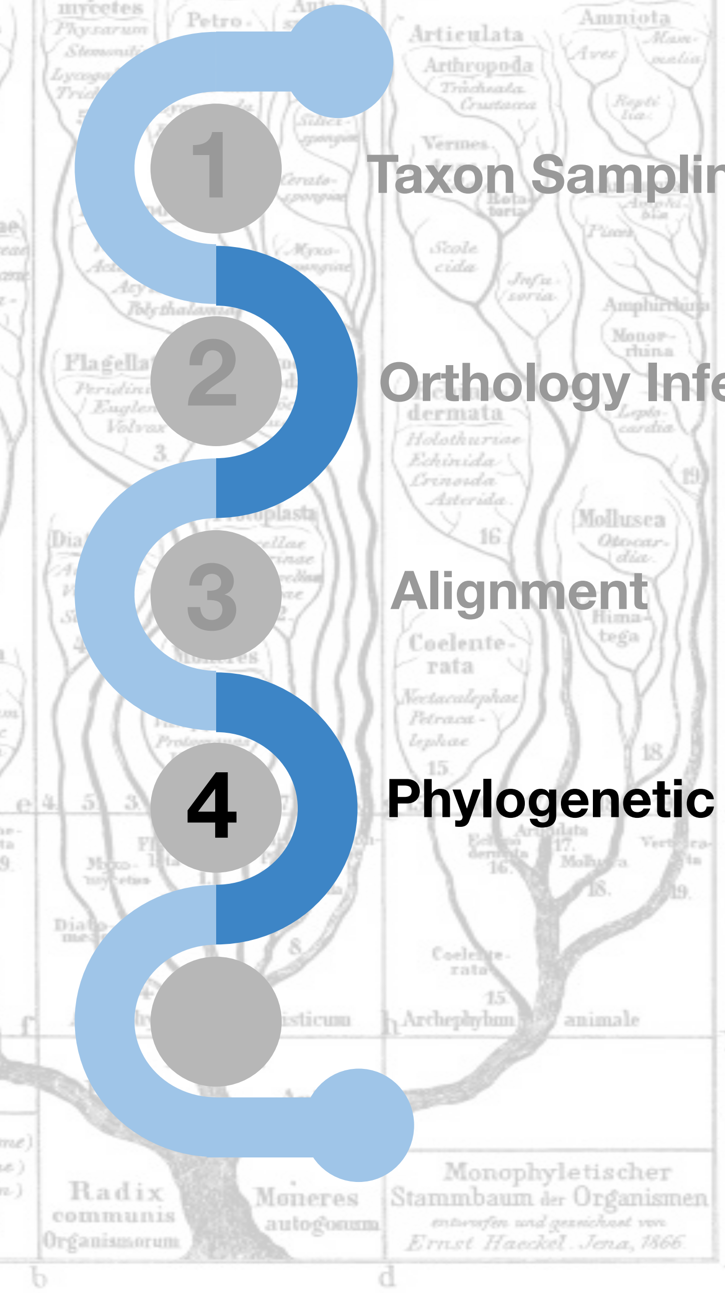

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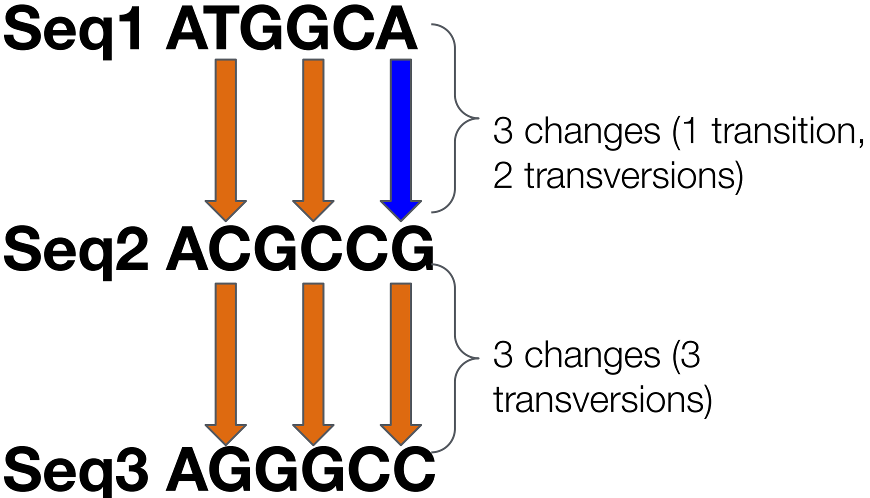


Seq1 ATGGCA

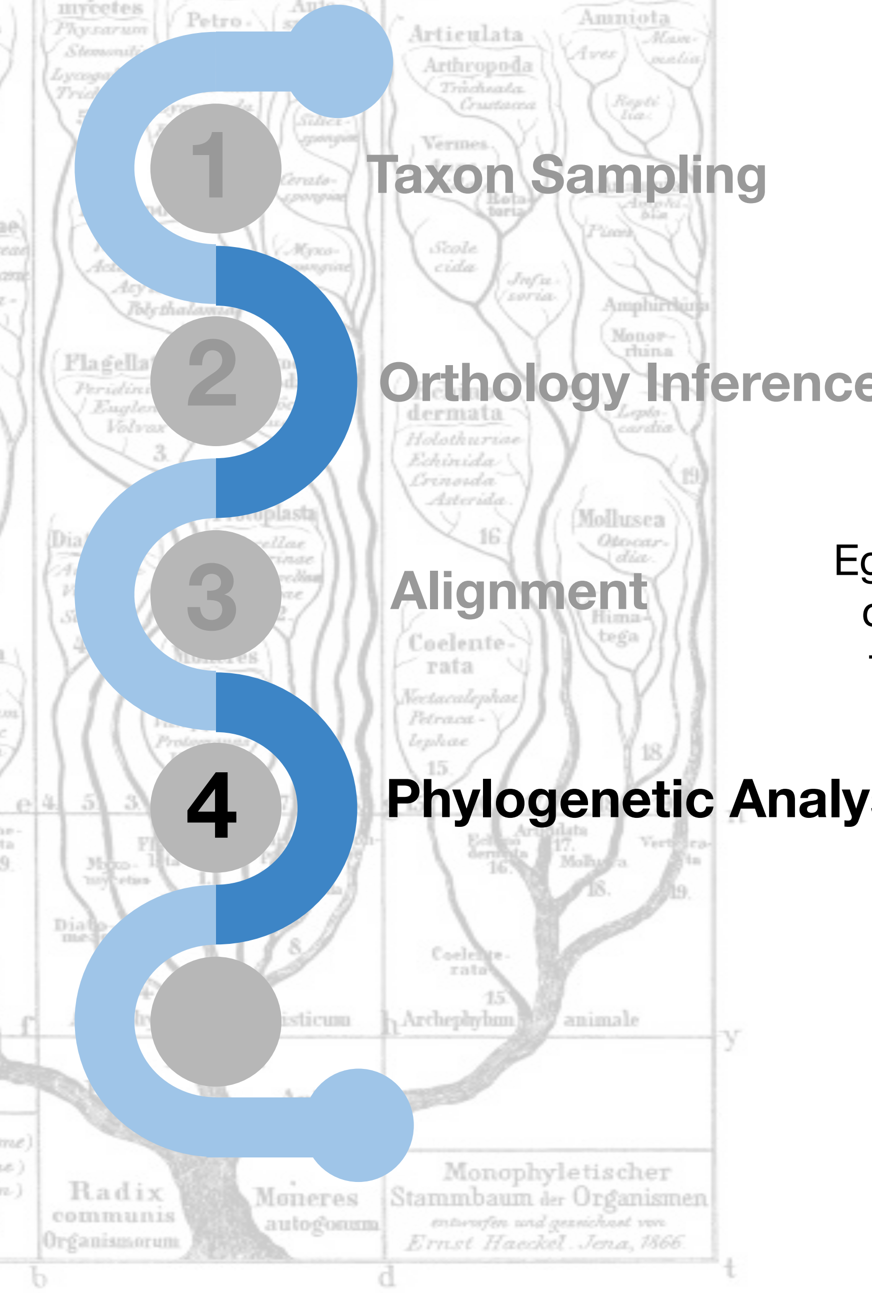
3 changes (1 transition, 2 transversions)

Seq2 ACGCCG

3 changes (3 transversions)

Seq3 AGGGCC

How to infer a species tree



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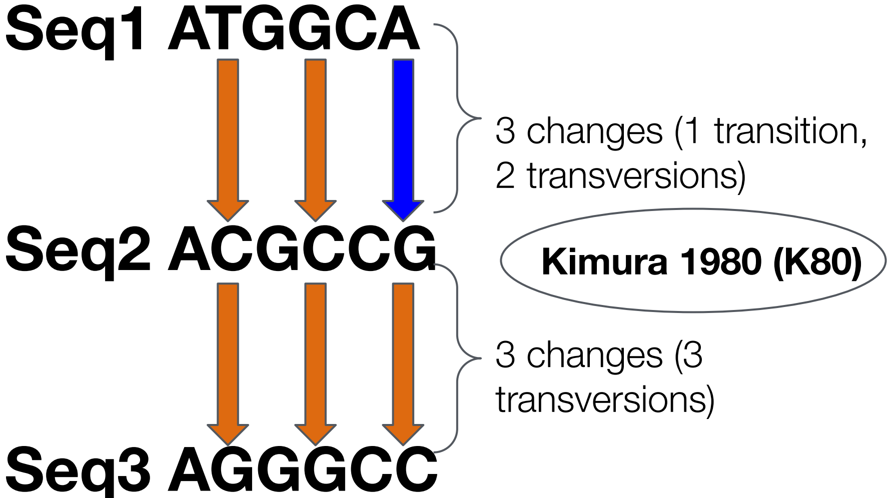

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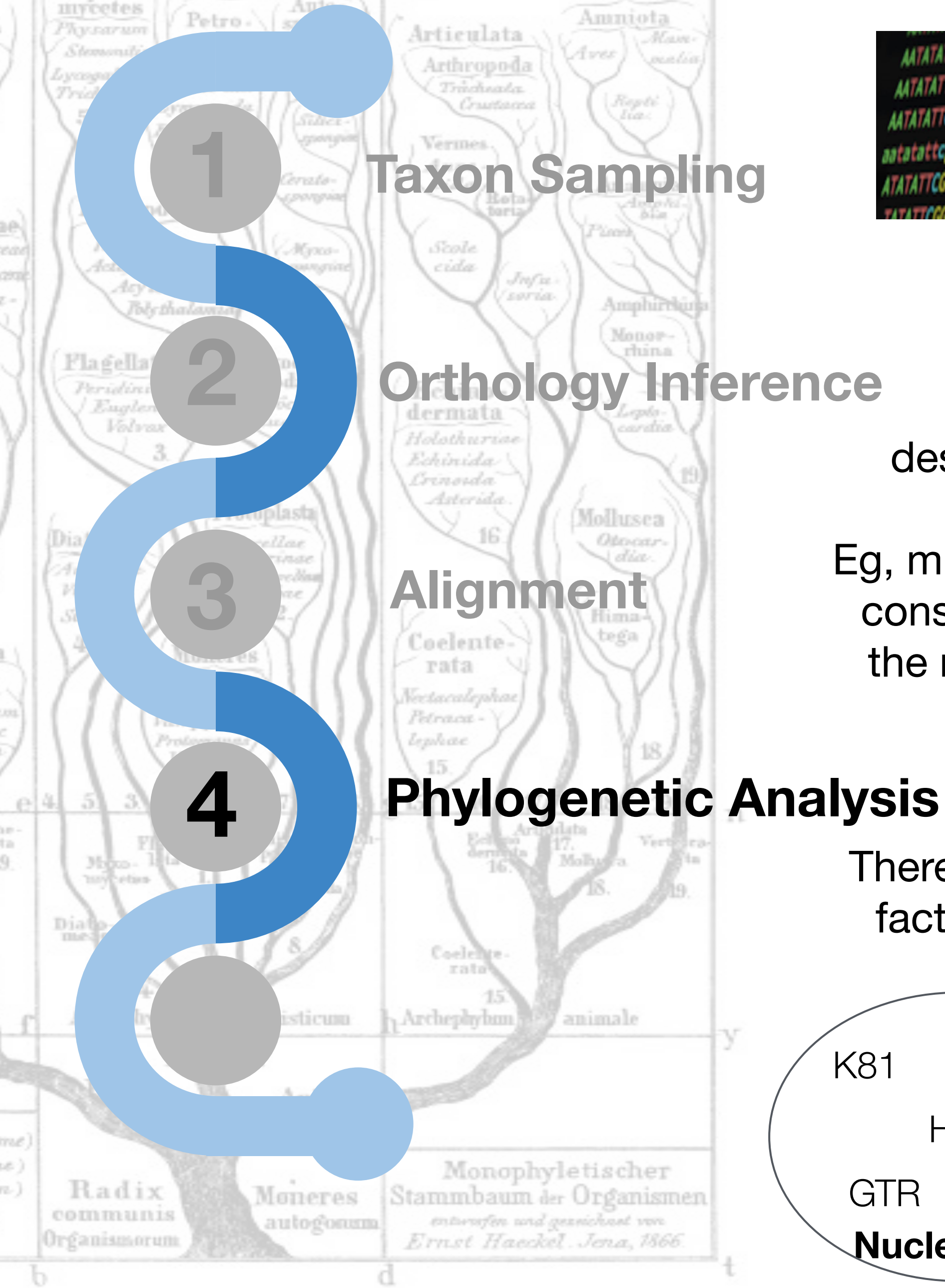
Kimura 1980 (K80)

3 changes (3 transversions)

Seq3 AGGGCC

How to infer a species tree



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Eg, mutational biases and purifying selection favoring conservative changes are probably responsible for the relatively high rate of **transitions** compared to **transversions** in evolving sequences

There are many models that take into account other factors that can influence the rate of changes, eg time, reversibility, etc.

F81

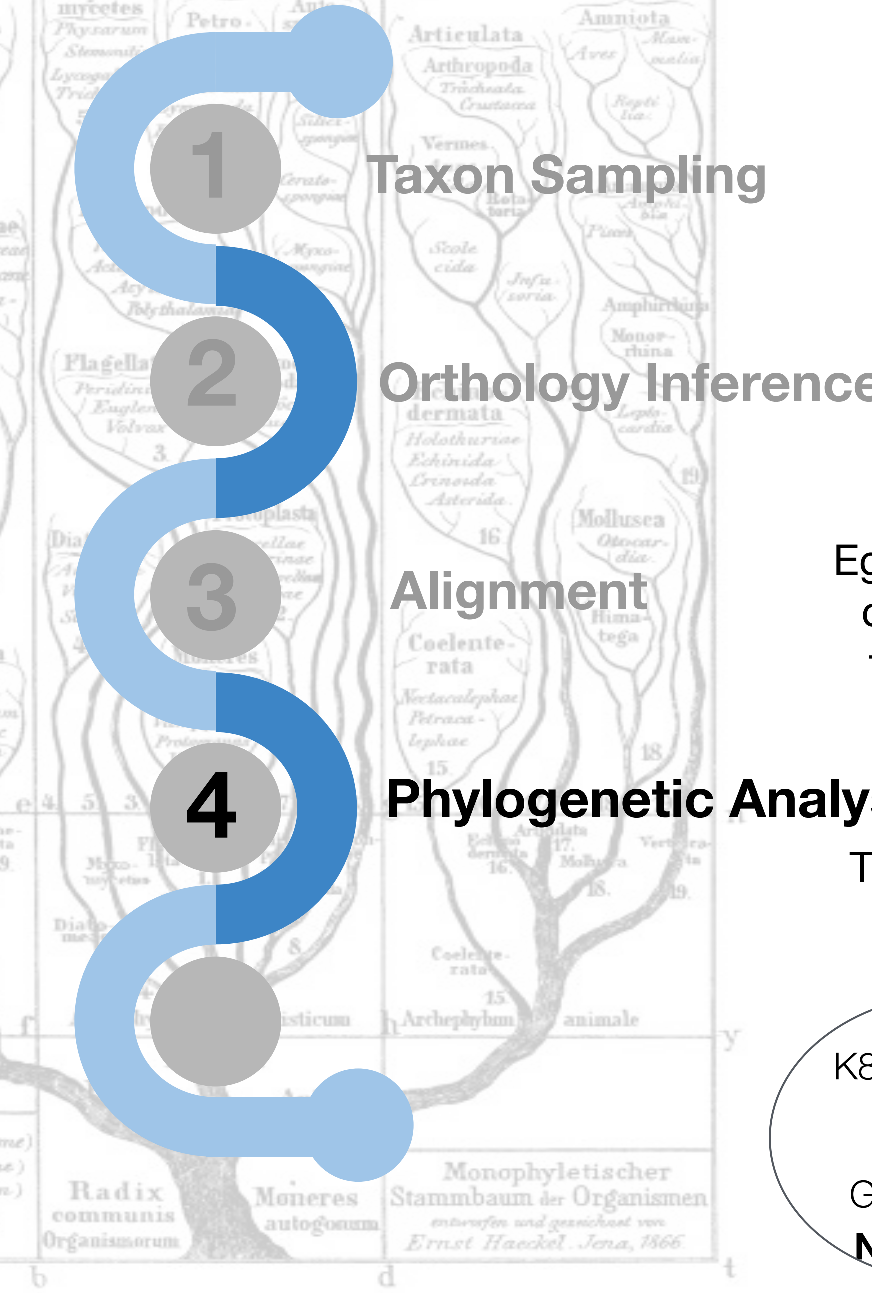
K81

HKY85

GTR …

Nucleotides

How to infer a species tree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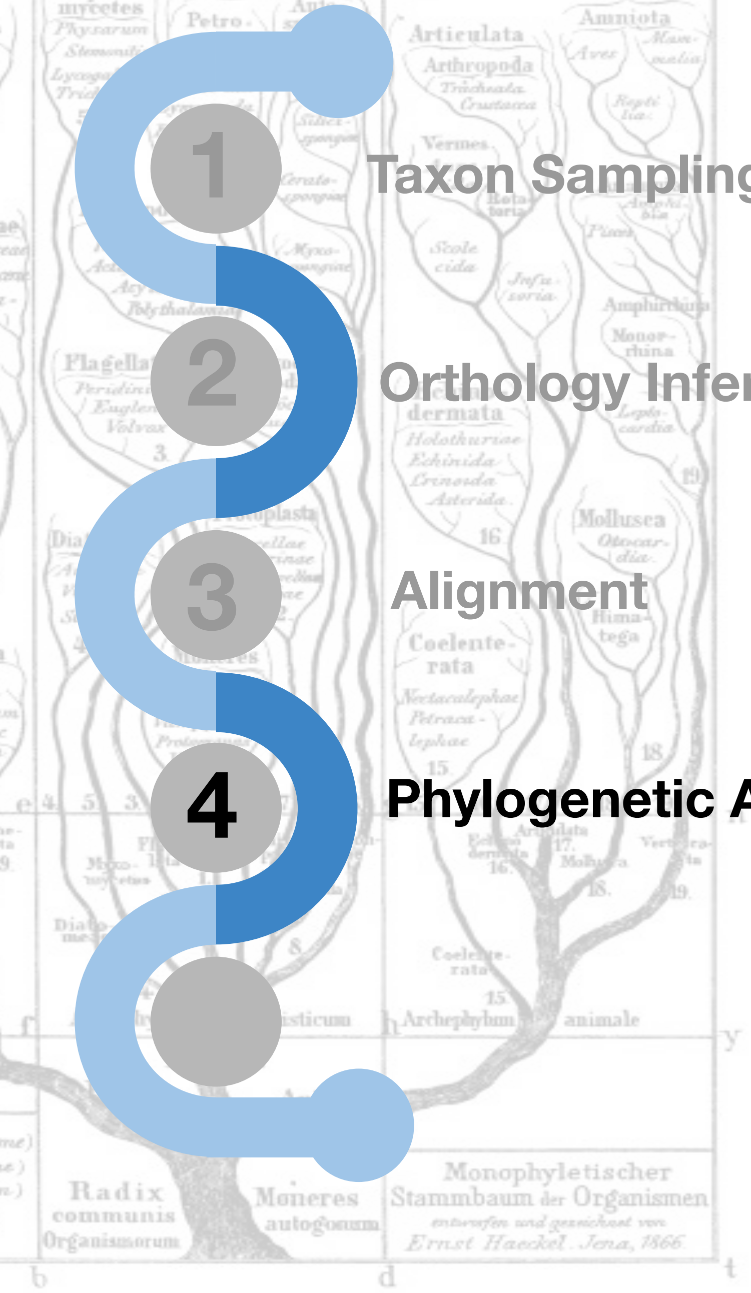
F81
K81
HKY85
GTR …
Nucleotides

PAM
JTT
WAG
LG …
Amino Acids

How to infer a species tree



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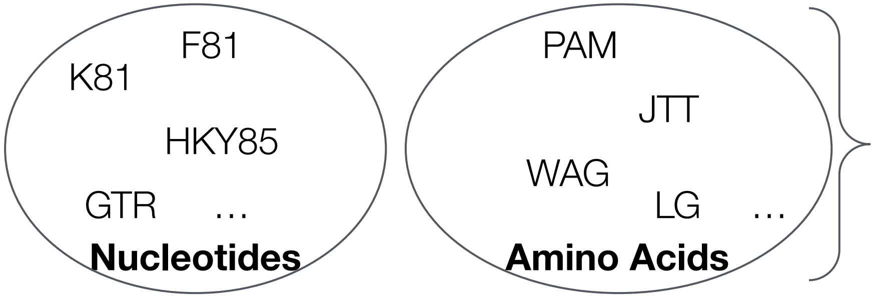


K81 F81 HKY85 GTR …

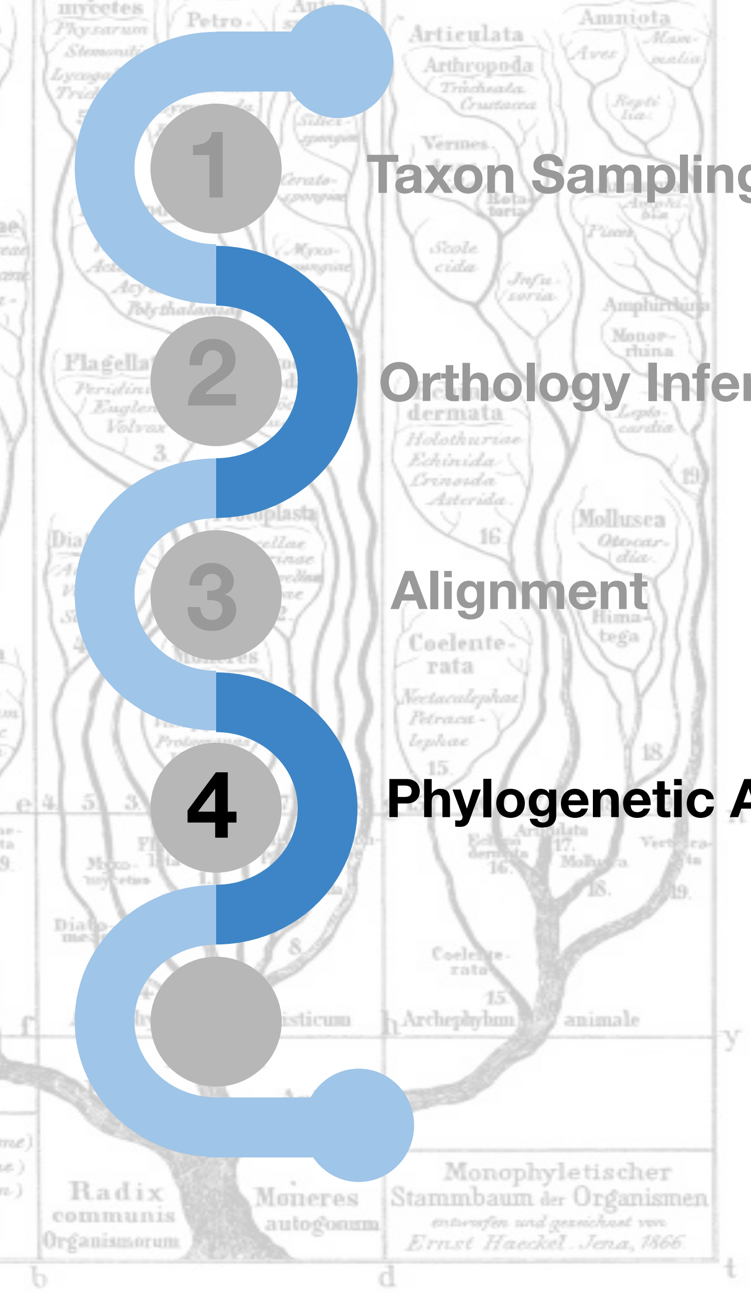
Nucleotides

PAM JTT WAG LG …

Amino Acids

Same model for the complete gene / partition

How to infer a species tree



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4 **Phylogenetic Analysis**

DATA

+

MODEL OF EVOLUTION

describe the relative rates of different changes

Eg, mutational biases and purifying selection favoring conservative changes are probably responsible for the relatively high rate of **transitions** compared to **transversions** in evolving sequences

Mixture models: C10, C20, C60, CAT

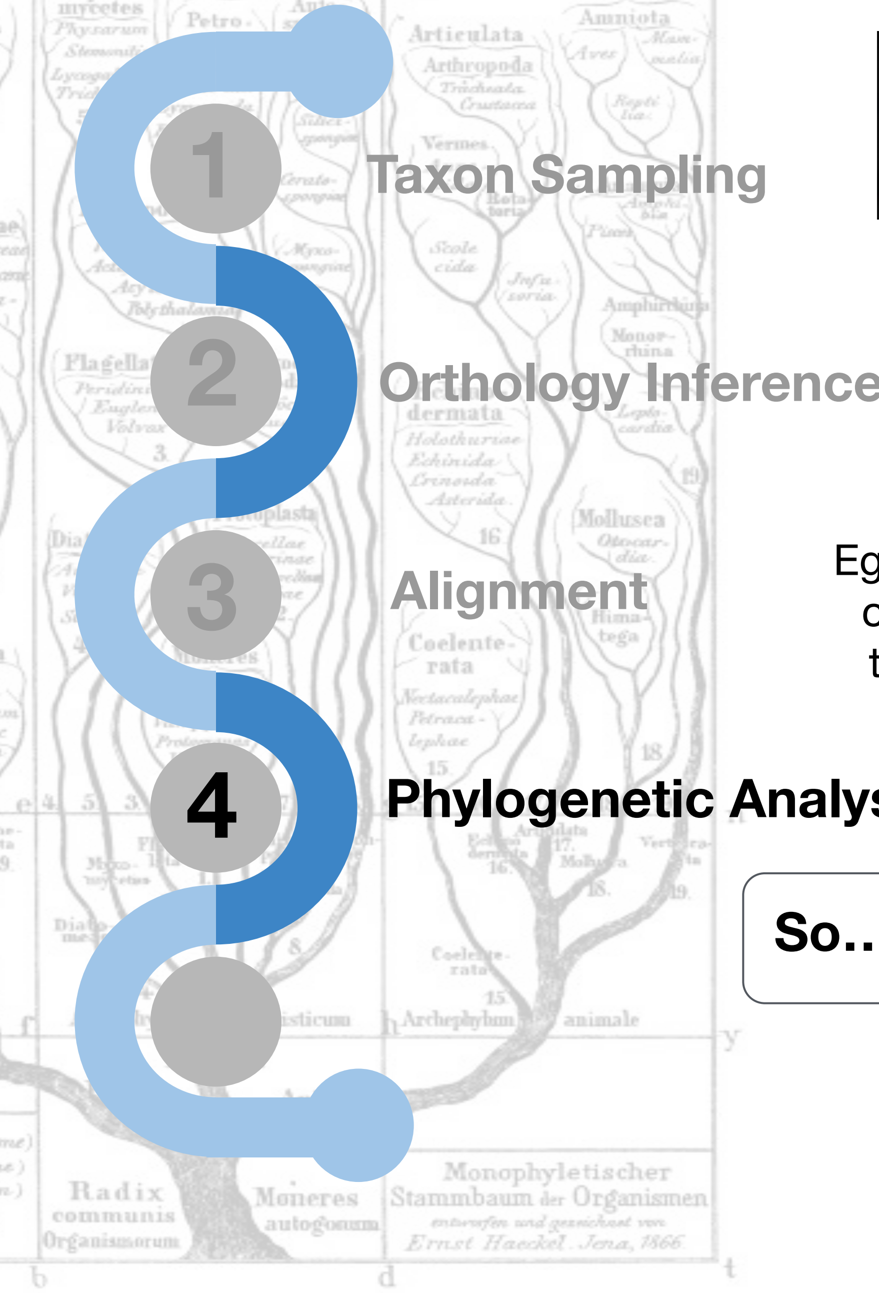
per-site variation of the model

Nucleotides: K81, F81, HKY85, GTR …

Amino Acids: PAM, JTT, WAG, LG …

Same model for the complete gene / partition

How to infer a species tree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DATA

➕

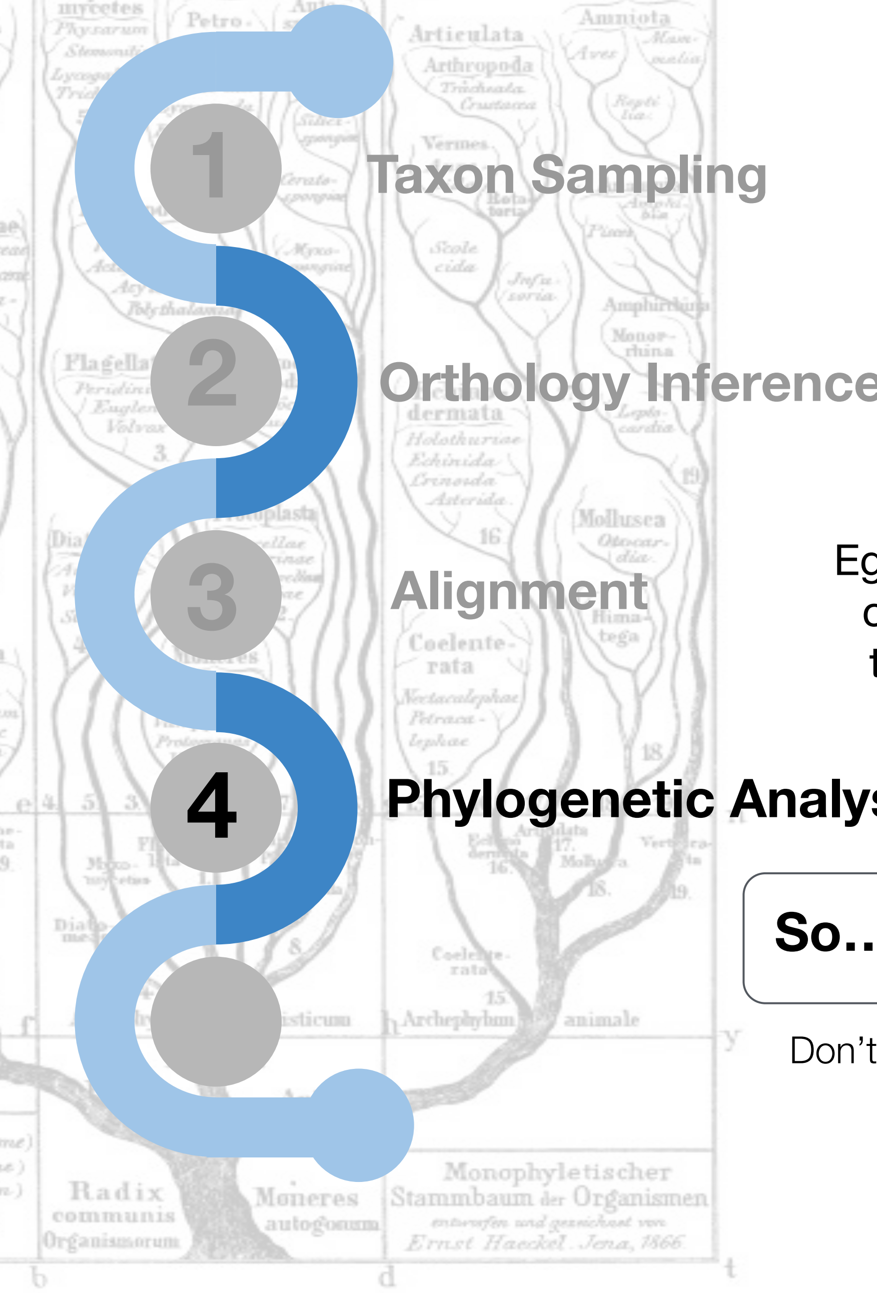
MODEL OF EVOLUTION

describe the relative rates of different changes

Eg, mutational biases and purifying selection favoring conservative changes are probably responsible for the relatively high rate of **transitions** compared to **transversions** in evolving sequences

So… how do I select a model for my data?

How to infer a species tree



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4 **Phylogenetic Analysis**

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AATATATTCGGGTAACCGAAGATGAGAACGATGAGCCCATTGAA
aatatattcgggtaaccgaagatgagaacgatgagcccattgaa

DATA

+

MODEL OF EVOLUTION

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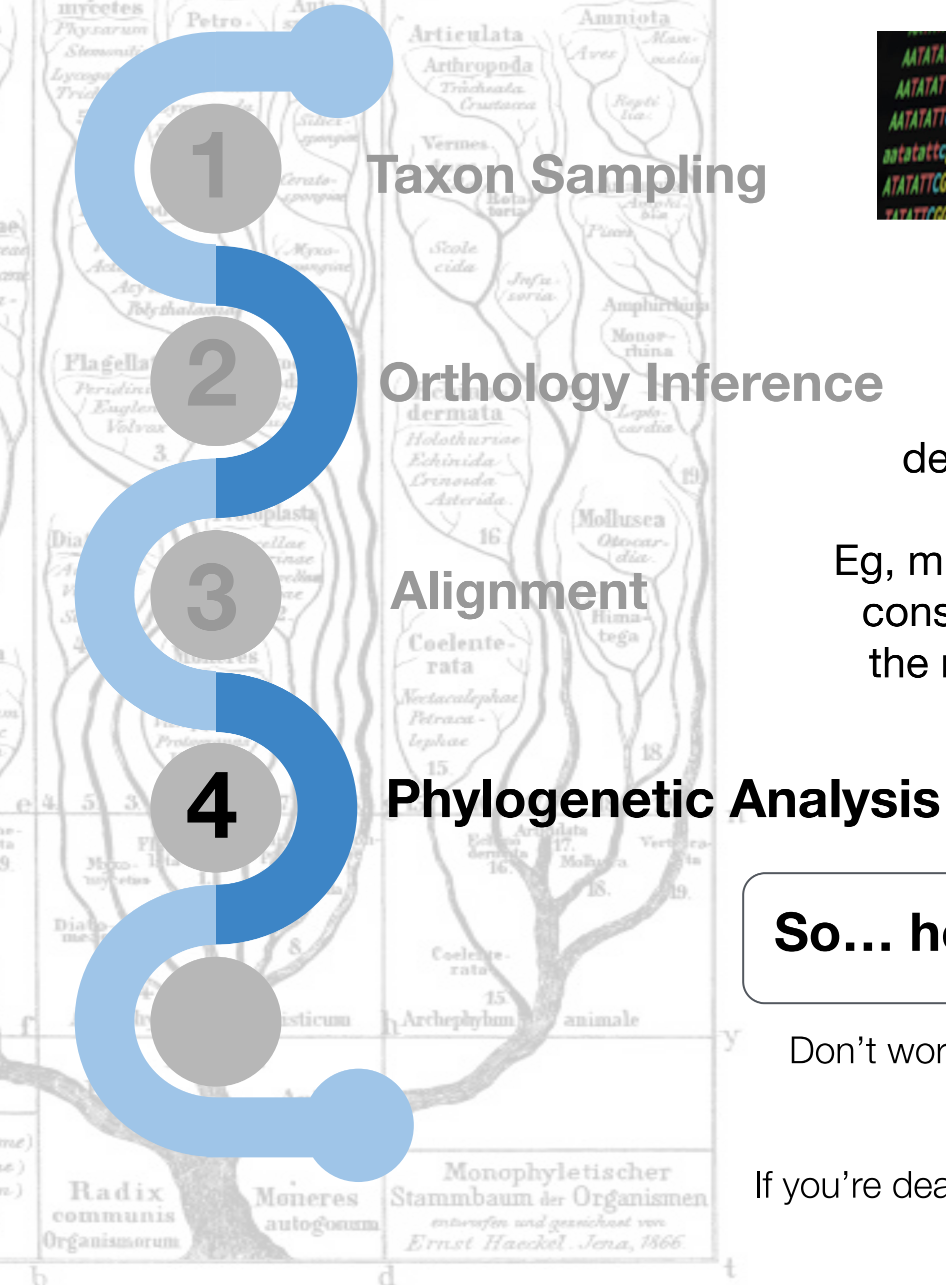
So… how do I select a model for my data?

Don’t worry, most phylogenetic programs have a tool to infer the model that better fits your data :-)

How to infer a species tree



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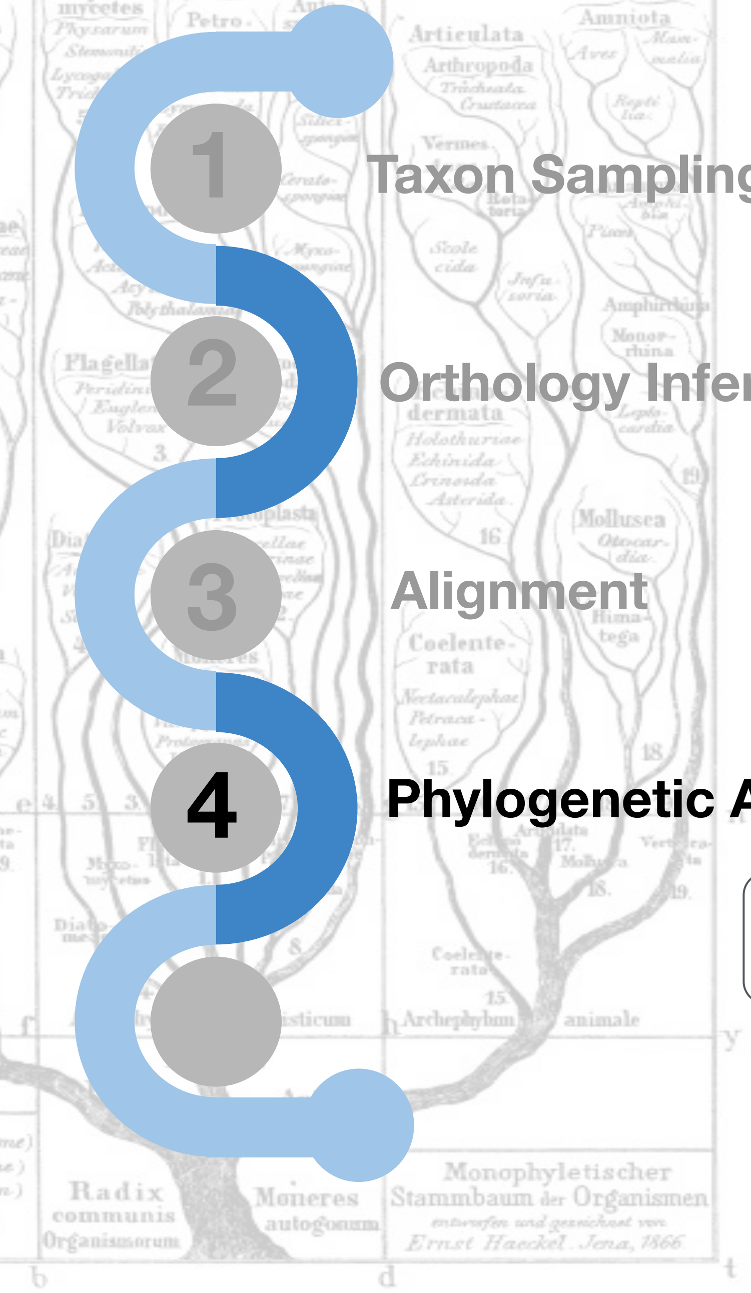
If you’re dealing with a difficult phylogenetic problem, mixture models are probably a good idea

How to infer a species tree



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MODEL OF EVOLUTION

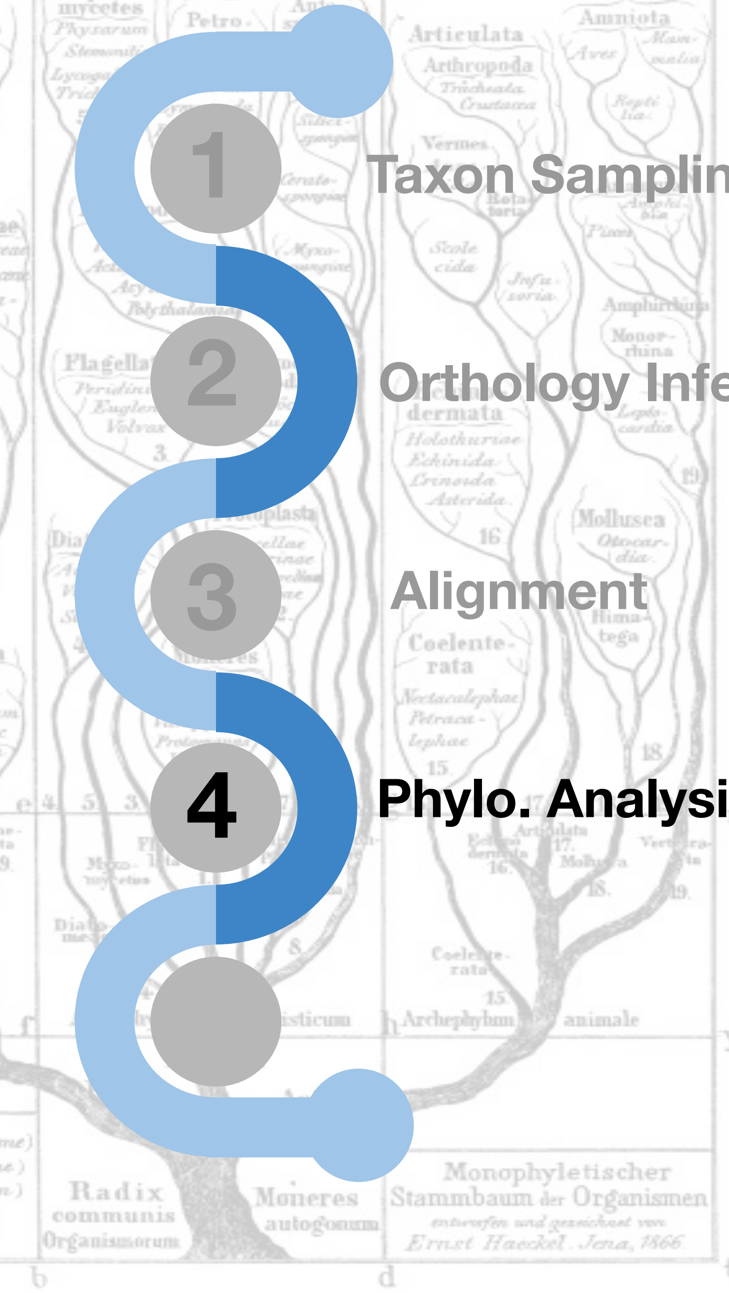
describe the relative rates of different changes

Eg, mutational biases and purifying selection favoring conservative changes are probably responsible for the relatively high rate of **transitions** compared to **transversions** in evolving sequences

So… how do I select a model for my data?

Key message: the selection of the model matters <u>a lot</u>

How to infer a species tree



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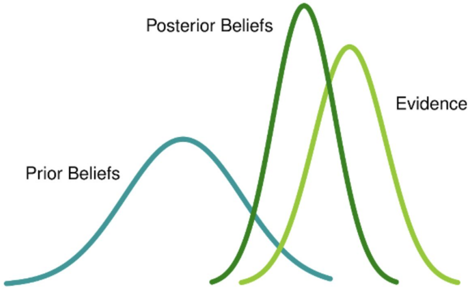
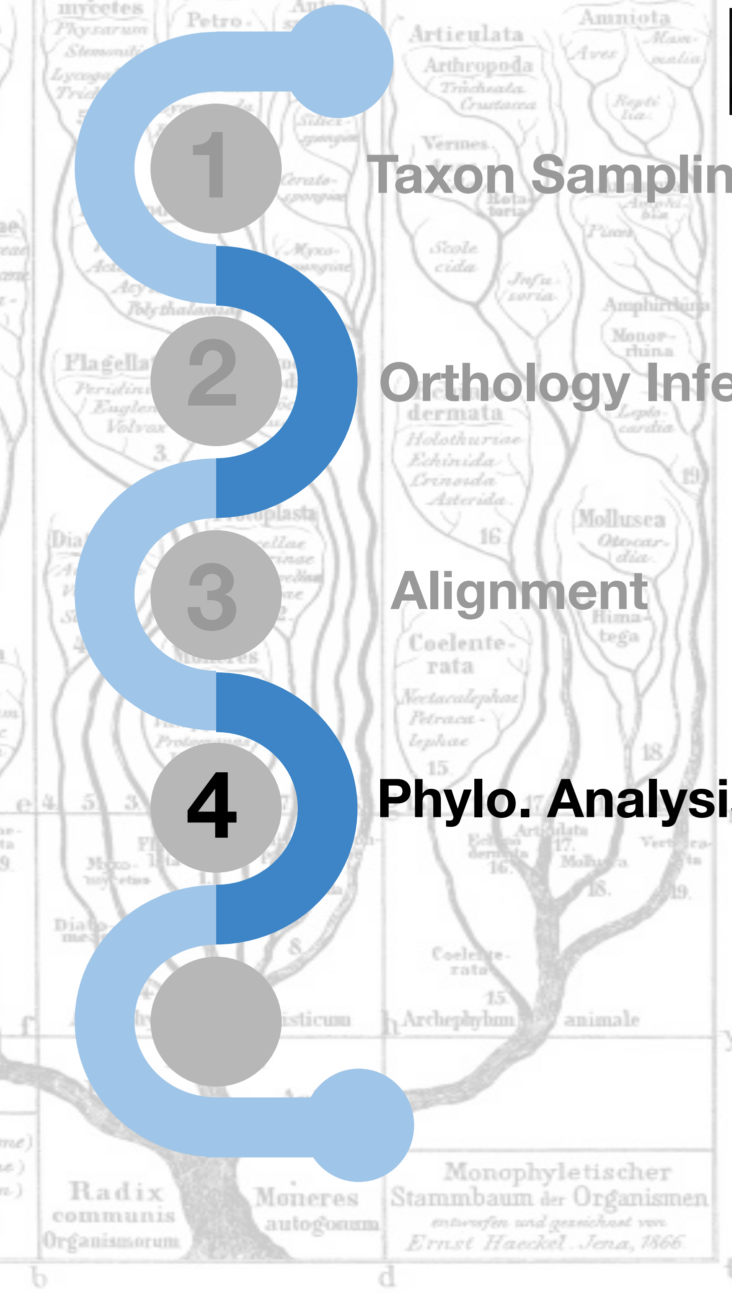
DATA + **MODEL OF EVOLUTION**



+ **METHOD**

How to infer a species tree



1 Taxon Sampling

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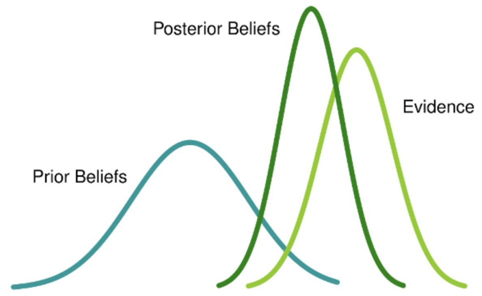
4 **Phylo. Analysis**

DATA + **MODEL OF EVOLUTION**

+

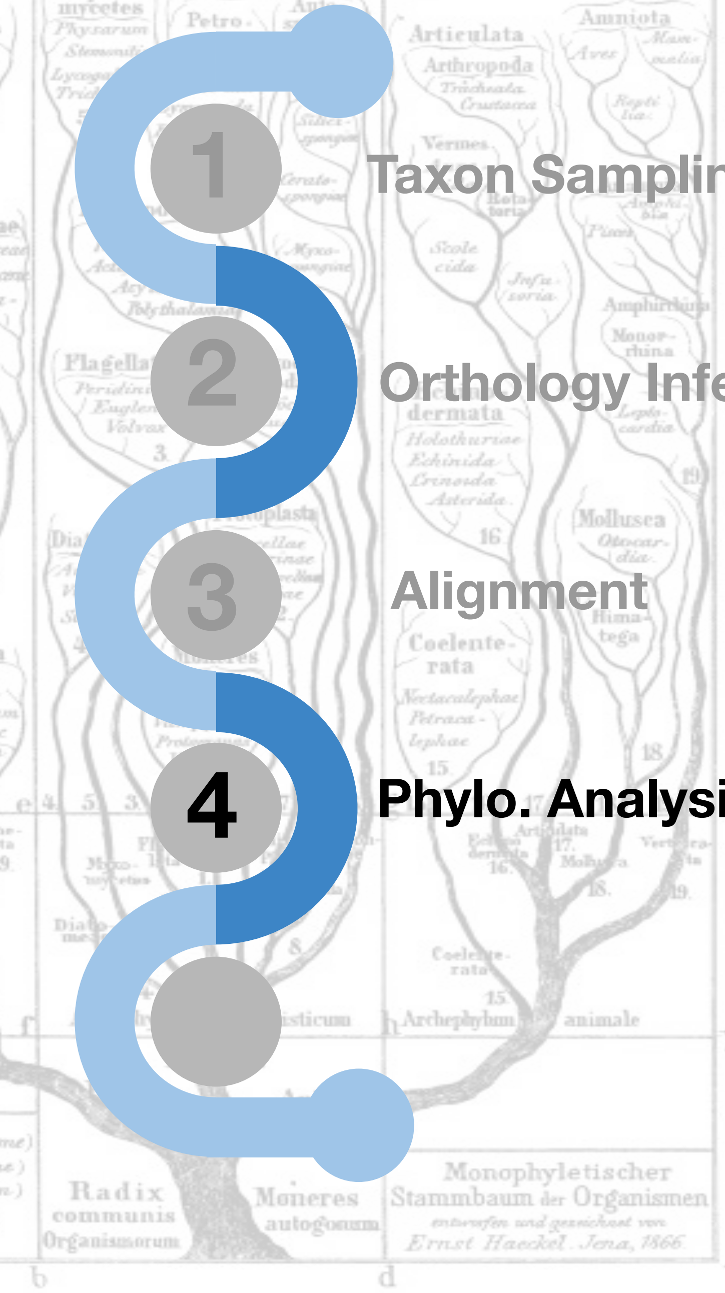
METHOD



Two main methods:

Maximum Likelihood (ML) and **Bayesian Inference (BI)**

How to infer a species tree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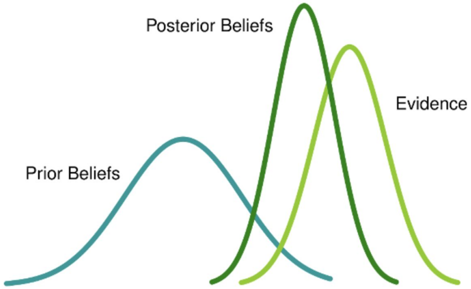
DATA + **MODEL OF EVOLUTION** + **METHOD**



Two main methods:
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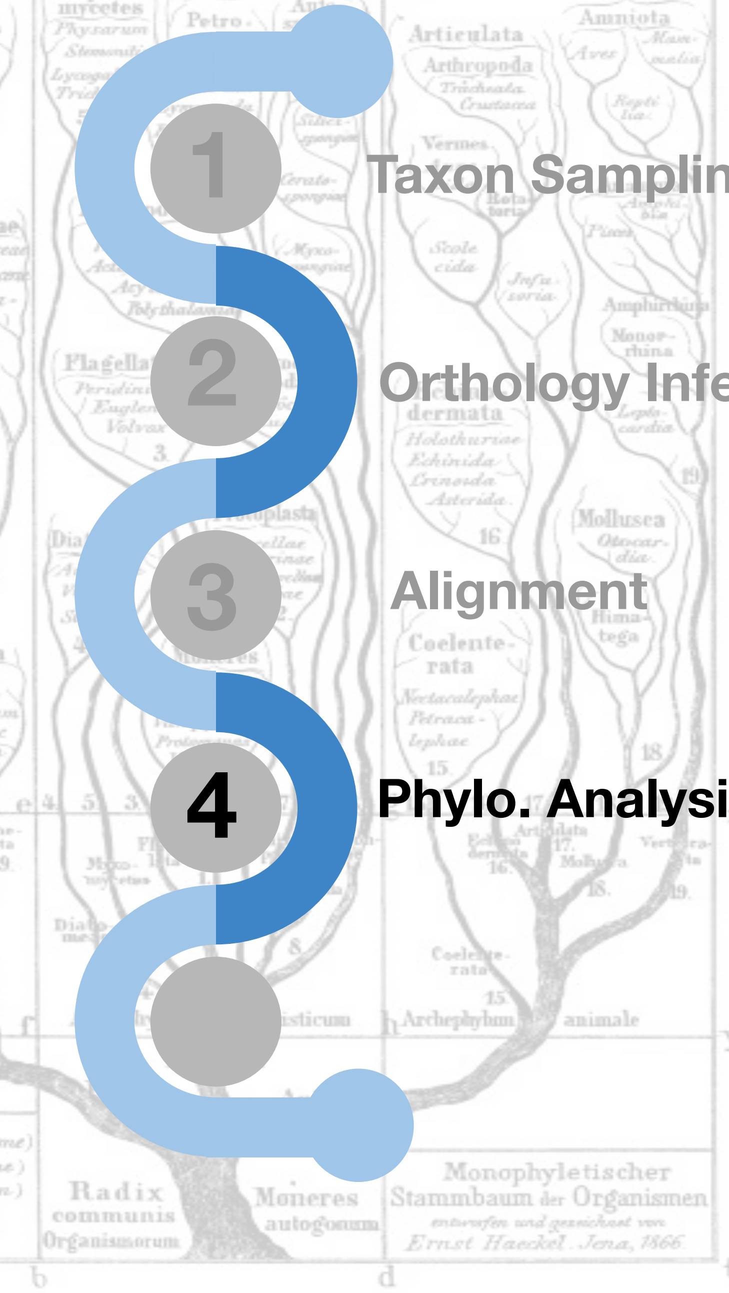
<u>Basic question in BI</u>:
'What is the probability that this model (T) is correct, given the data (D) that we have observed?'

How to infer a species tree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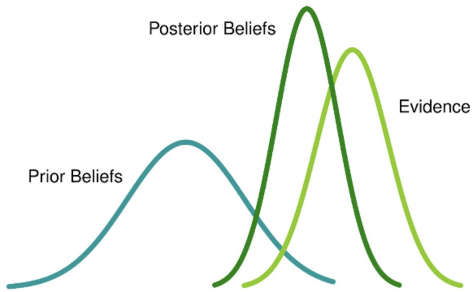
DATA + **MODEL OF EVOLUTION** + **METHOD**



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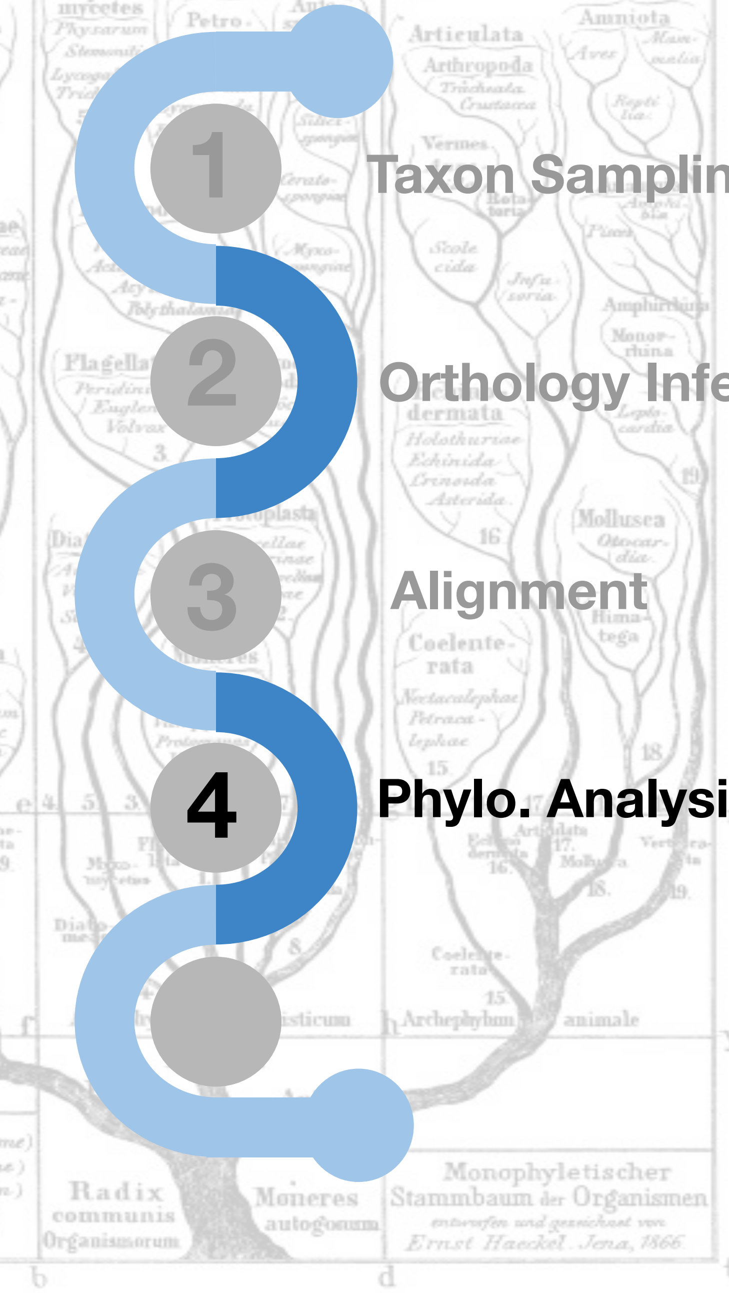
How to infer a species tree



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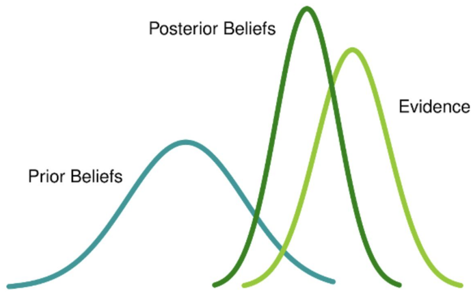
DATA + **MODEL OF EVOLUTION** + **METHOD**



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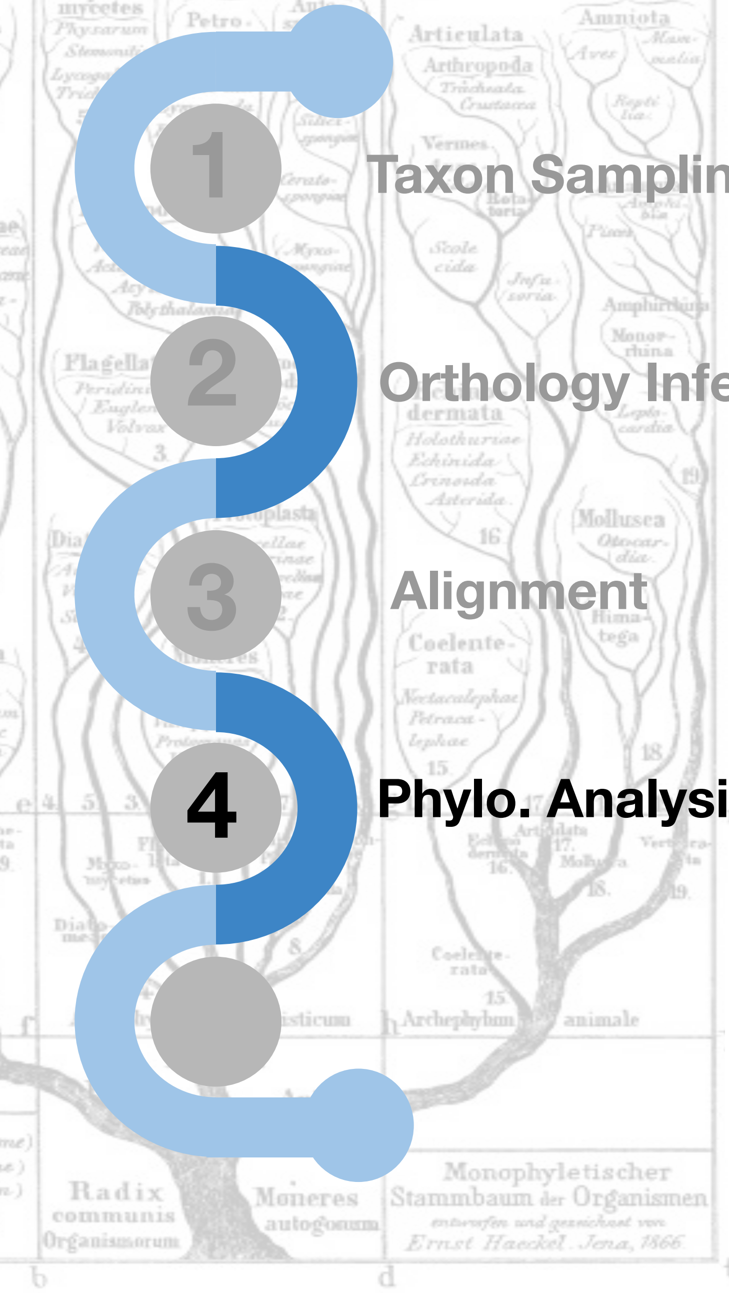
Basic question in ML:
'What is the probability of seeing the observed data (D) given that a certain model (T) is true?'

BI seeks P(T|D), while ML maximizes P(D|T)

How to infer a species tree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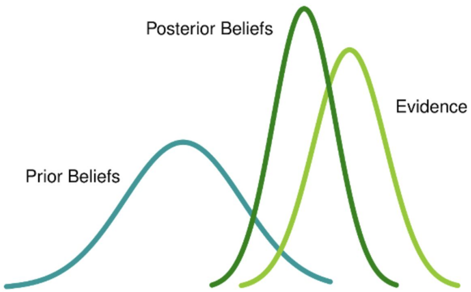
DATA + **MODEL OF EVOLUTION** + **METHOD**



Two main methods:

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RAxML

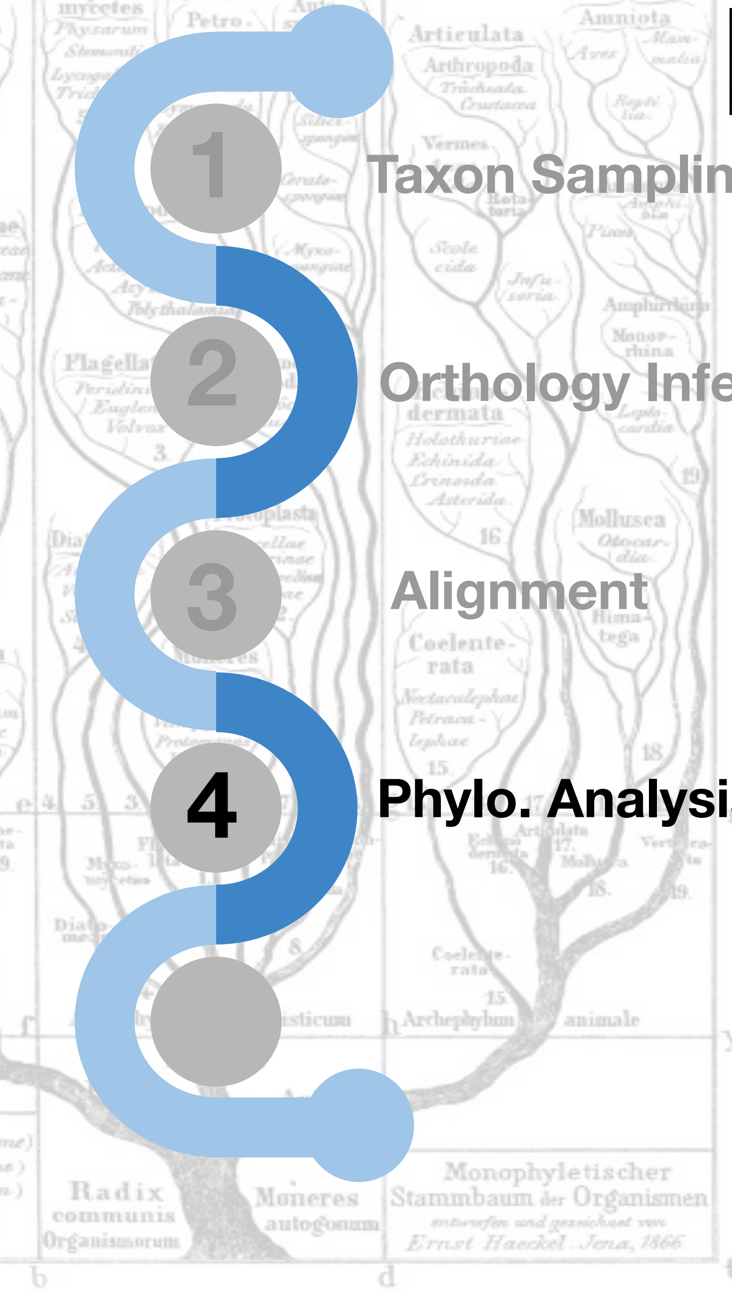
RevBayes

IQ-TREE

fasrc/**phylobayes**

A Bayesian Monte Carlo Markov Chain (MCMC) sampler for phylogenetic reconstruction and molecular dating.

How to infer a species tree



1 Taxon Sampling

2 Orthology Inference

3 Alignment

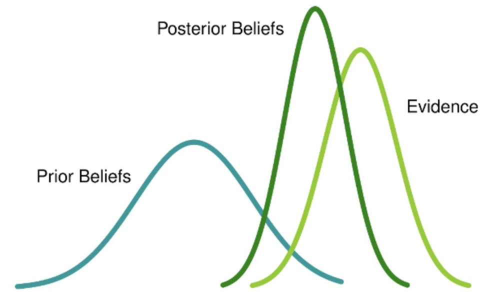
4 Phylo. Analysis

Monophyletischer Stammbaum der Organismen
entworfen und gezeichnet von Ernst Haeckel. Jena, 1866
Radix communis Organismorum
Moneres autogonum

DATA + **MODEL OF EVOLUTION**

+

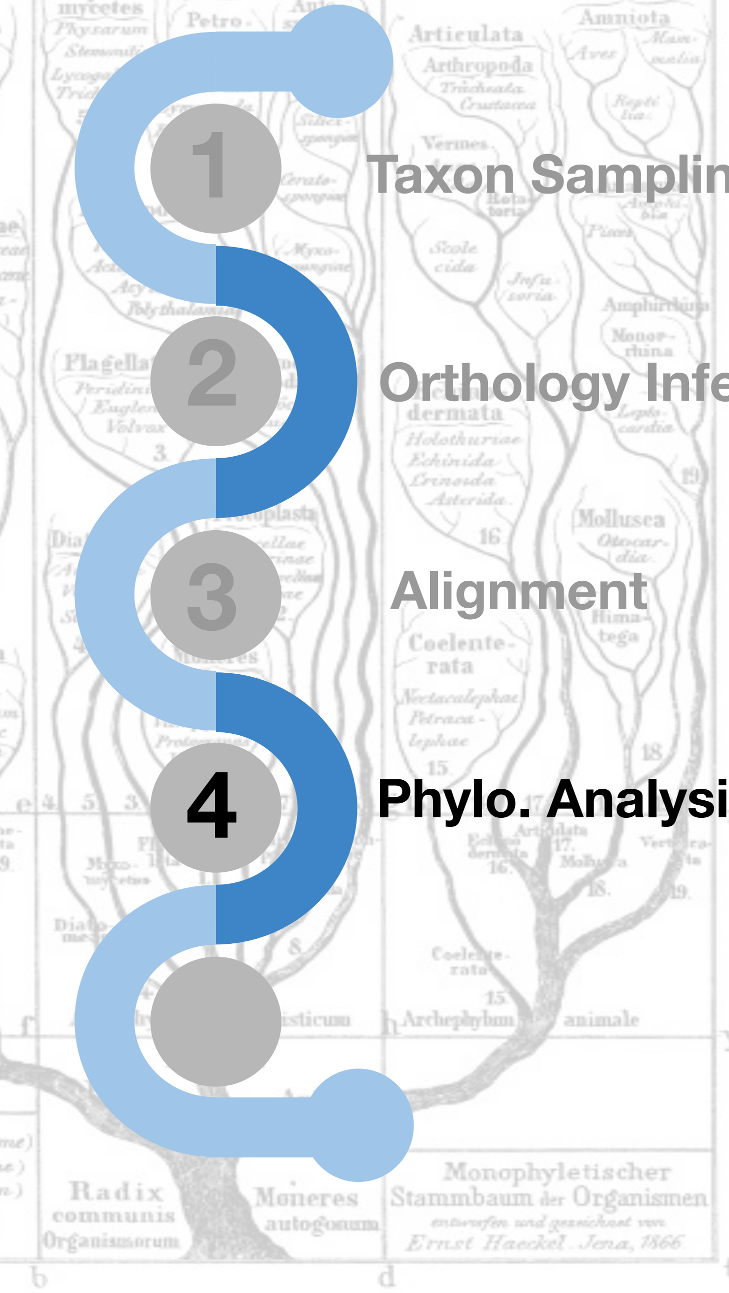
METHOD



Two main methods:
Maximum Likelihood (ML) and **Bayesian Inference (BI)**

Which one should I choose?

How to infer a species tree



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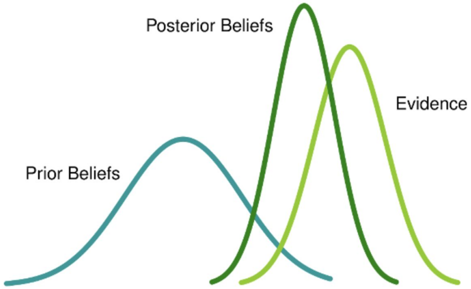

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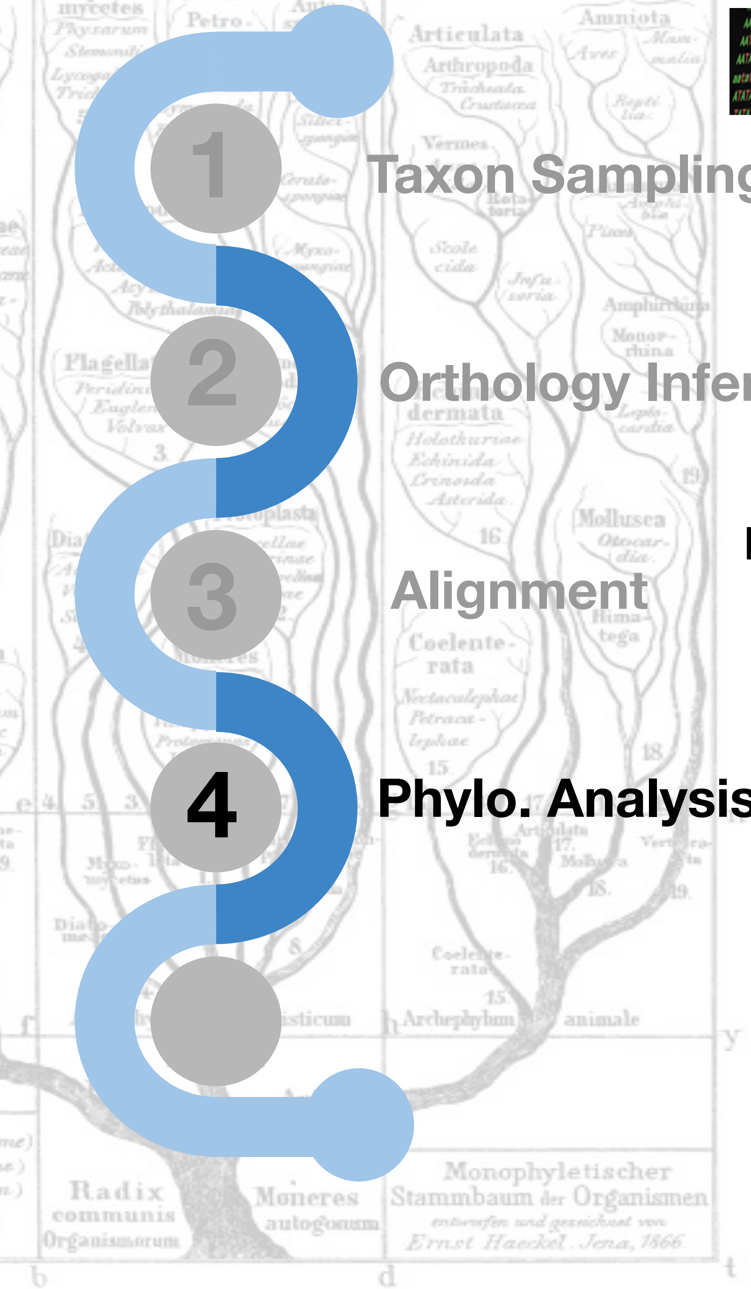
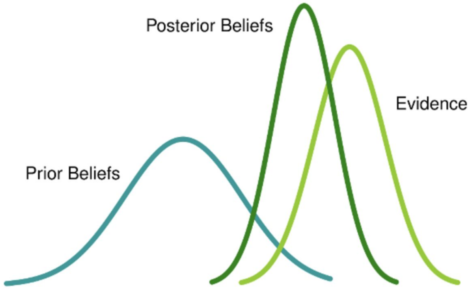


DATA ➕ **MODEL OF EVOLUTION**



➕

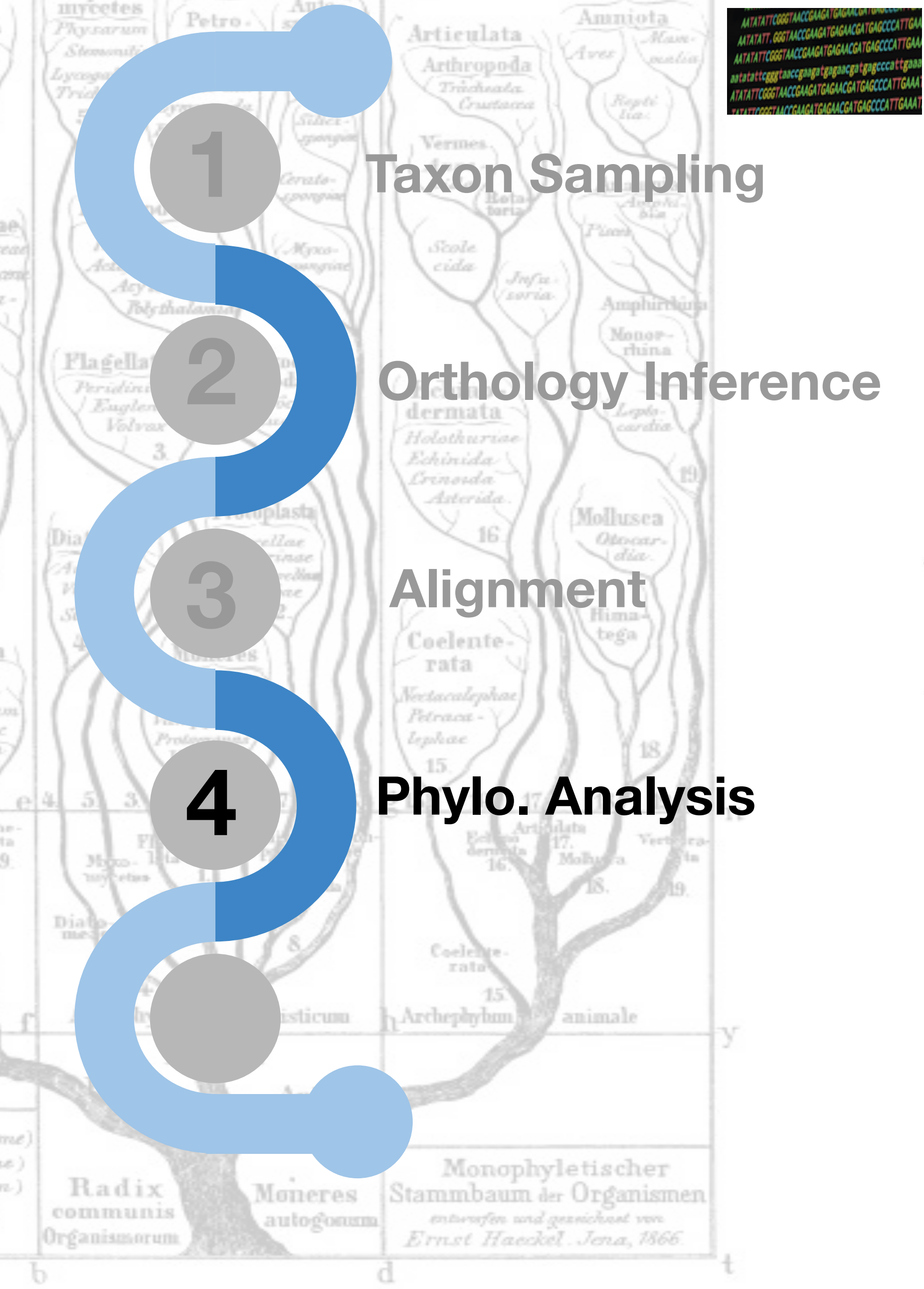
METHOD

Two main methods:
Maximum Likelihood (ML) and **Bayesian Inference (BI)**

Which one should I choose?

Factors to consider: running time, availability of ‘complex’ models, etc.

How to infer a species tree



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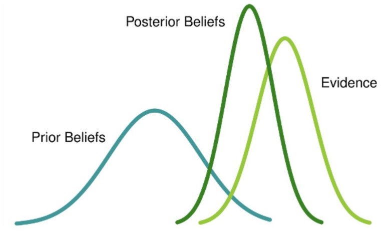
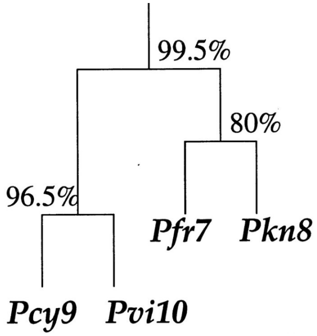
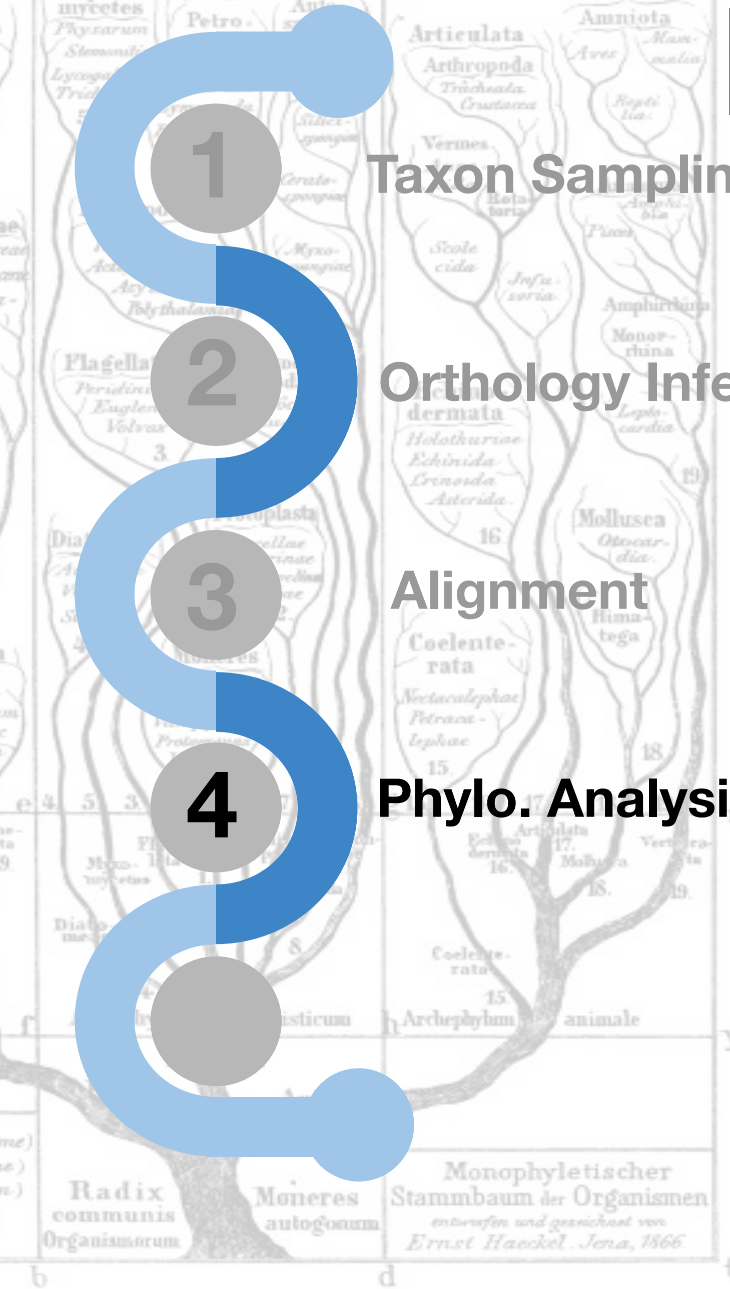


+ METHOD



+ A WAY TO ASSESS HOW GOOD OUR HYPOTHESIS IS

How to infer a species tree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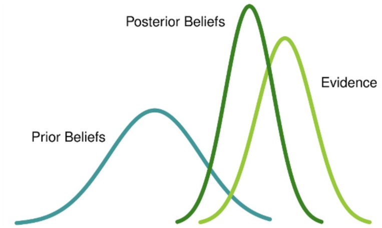
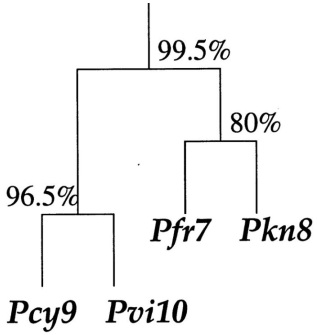


+ METHOD

+

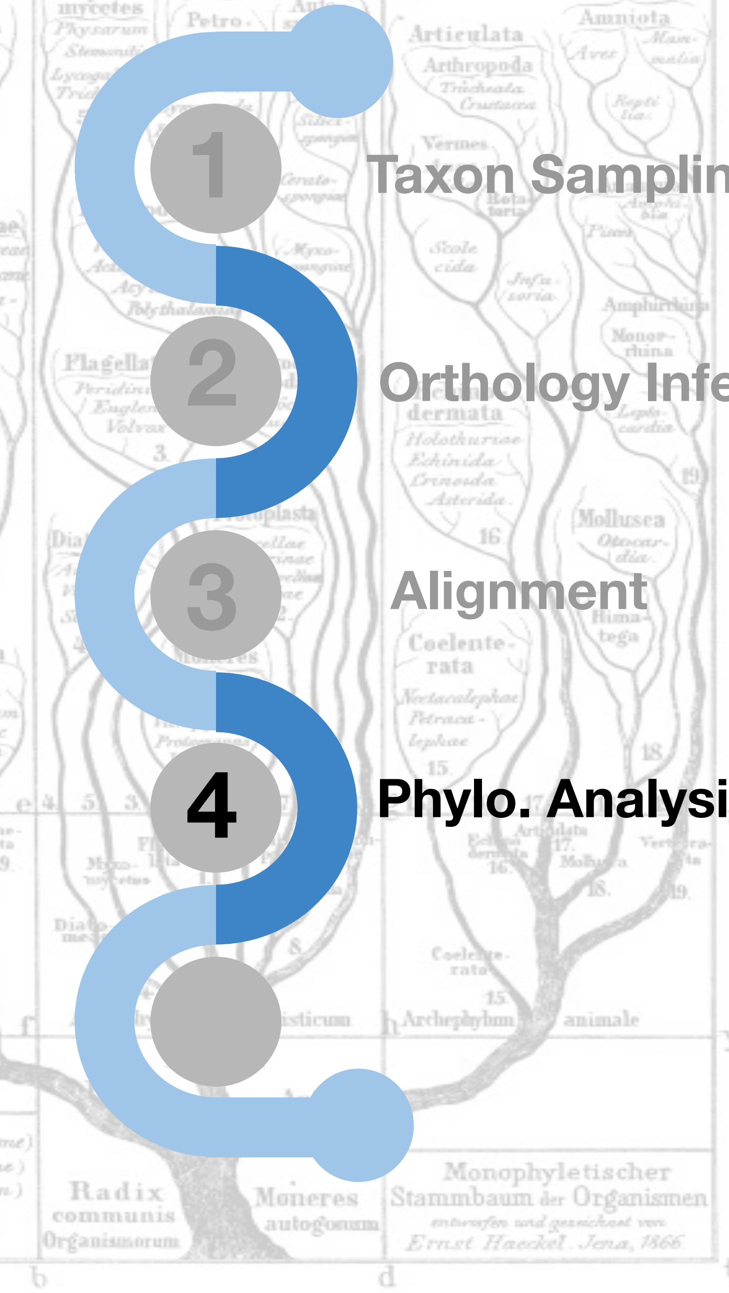


A WAY TO ASSESS HOW GOOD OUR HYPOTHESIS IS

- ML: standard nonparametric bootstrap (100 reps), approximate likelihood ratio test (1,000 reps), ultrafast bootstrap (1,000 reps)(between 1 and 100)
    - you ‘believe’ in a clade with > 80-90% bootstrap support and/or ultrafast bootstrap > 95% and/or approx. LRT > 80-90%.

- BI: posterior probability (between 0 and 1)
    - you ‘believe’ in a clade with > 0.9 pp

How to infer a species tree



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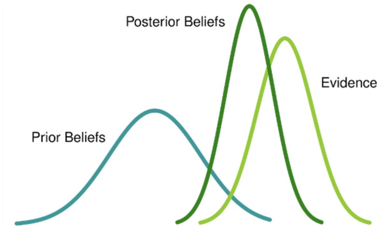
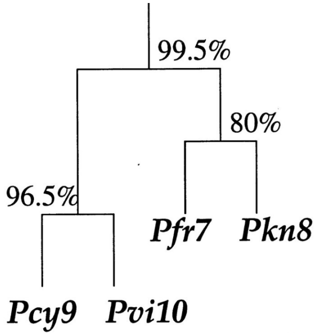
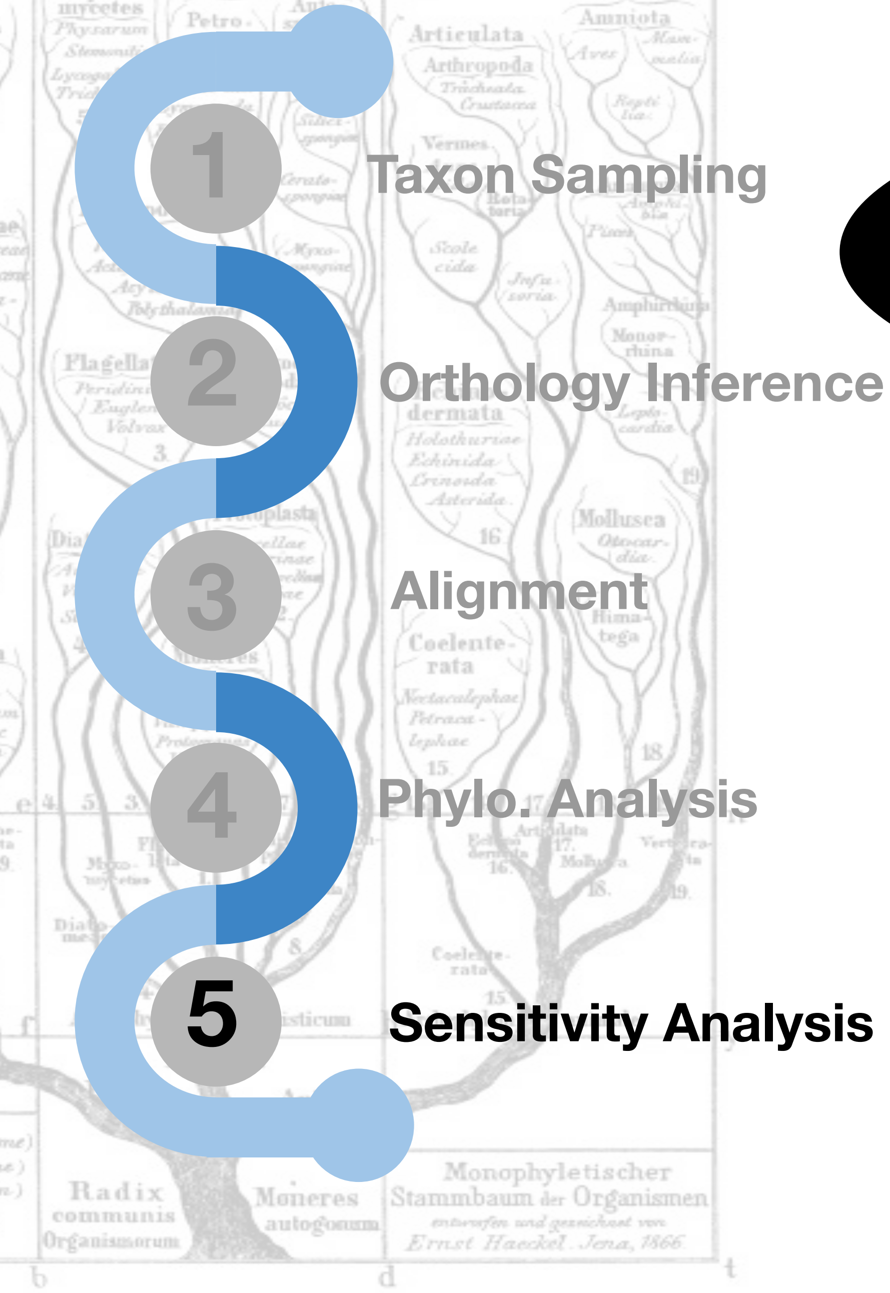
DATA + **MODEL OF EVOLUTION** + **METHOD** + **A WAY TO ASSESS HOW GOOD OUR HYPOTHESIS IS**





- New metrics (highly recommended in large matrices):
  - concordance factor (IQ-TREE): for every branch of a reference tree, the concordance factor is defined as the percentage of “decisive” gene trees containing that branch.
  - internode certainty (RAxML): a measure of the support for a given internode by considering its frequency in a given set of trees jointly with that of the most prevalent conflicting internode in the same set of trees.
  - tree certainty (RAxML): the sum of all the internode certainty across all internodes.

How to infer a species tree



1
2
3
4
5
Monophyletischer Stammbaum der Organismen
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1 Taxon Sampling

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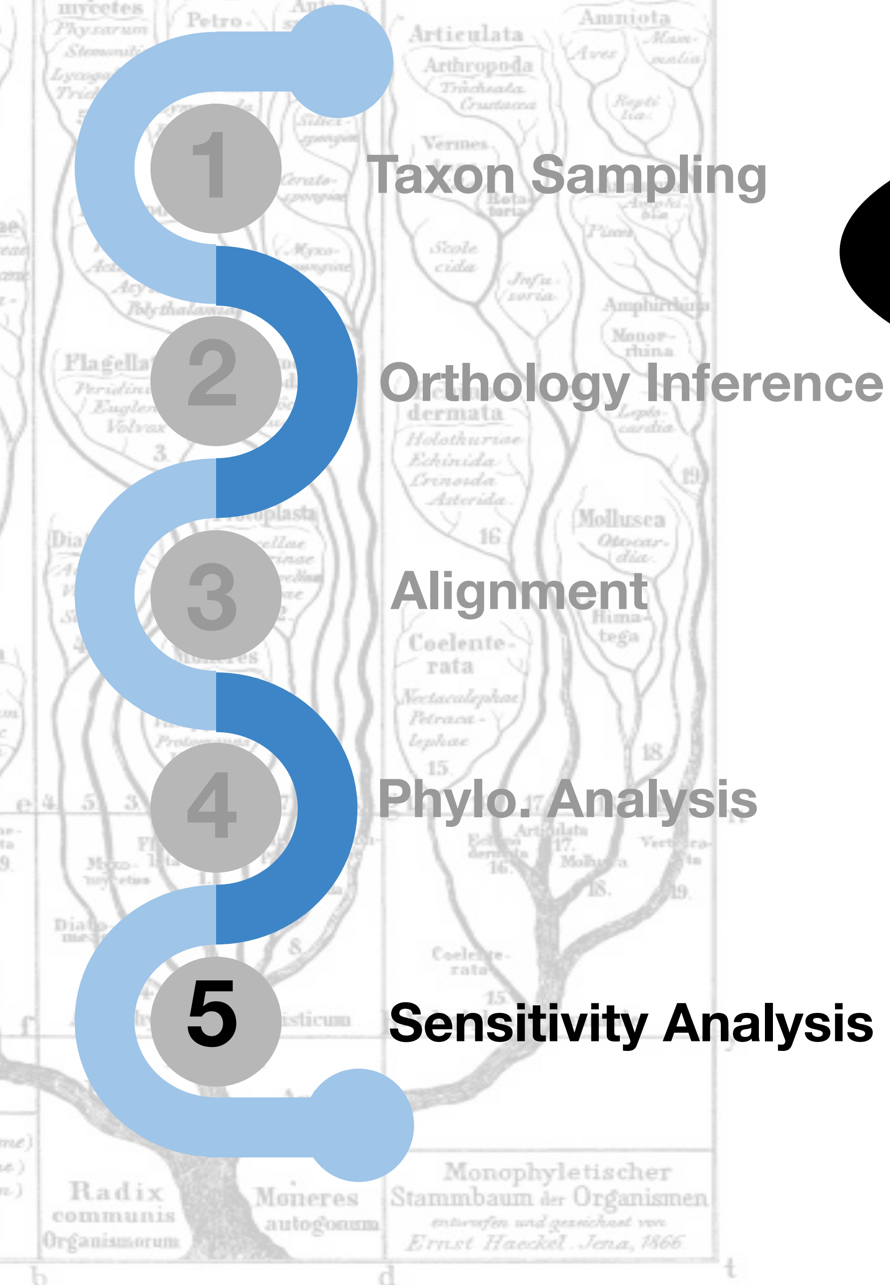
3 Alignment

4 Phylo. Analysis

5 Sensitivity Analysis

Lies, damn lies and phylogenomics

How to infer a species tree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1 Taxon Sampling

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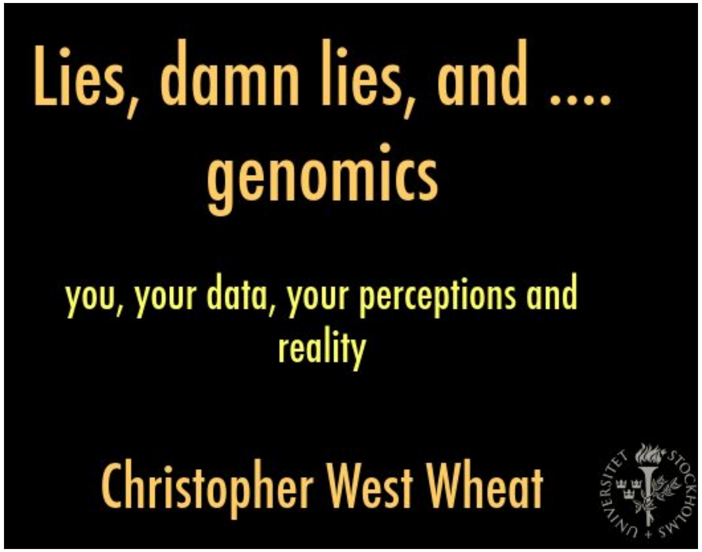
5 **Sensitivity Analysis**

Lies, damn lies and phylogenomics

inspired by



Lies, damn lies, and .... genomics

you, your data, your perceptions and reality

Christopher West Wheat

Can I trust my results (or the results of others)?

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High support in an analysis *does not* mean that you can trust your tree!!

Can I trust my results (or the results of others)?

High support in an analysis *does not* mean that you can trust your tree!!

Wait, what?? And WHY is that?

Understanding your data (and the errors it may trigger in downstream analyses)

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(1) *Intrinsic* properties

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Missing data

Understanding your data (and the errors it may trigger in downstream analyses)

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Missing data

	Gene 1	Gene 2	Gene 3	…………………………………………				..Gene n
Species A	■	■	■	■	■	■	■	■
Species B	■	■	■	■	□	■	■	■
Species C	■	■	□	□	■	■	□	□
Species D	■	■	□	■	□	■	□	□

Understanding your data (and the errors it may trigger in downstream analyses)

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	Gene 1	Gene 2	Gene 3	....				..Gene n
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Species B	■	■	■	■	□	■	■	■
Species C	■	■	□	□	■	■	□	□
Species D	■	■	□	■	□	■	□	□

“Gruyère effect”

Understanding your data (and the errors it may trigger in downstream analyses)

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Saturation

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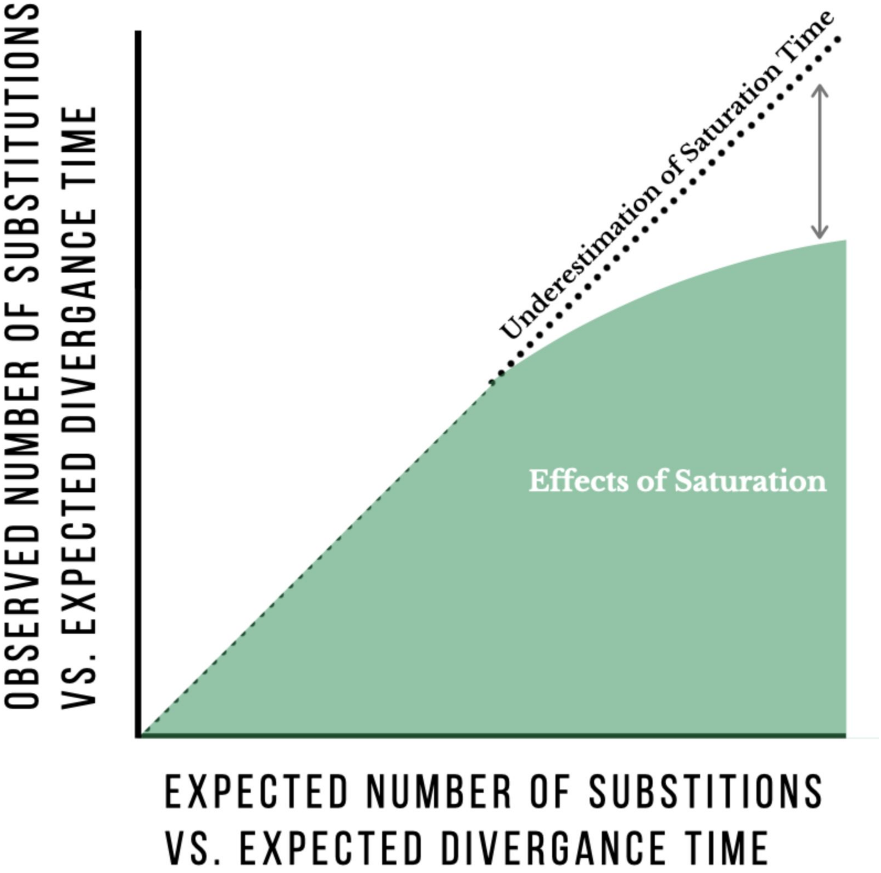

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Saturation

Compositional Heterogeneity

Gene 1

	Site 1	Site 2	Site 3						Site n
Species A	Leu	Met	Lys	Pro	Asn	Ile	Asn	Gln	Hys
Species B	Leu	Leu	Leu	Pro	Asn	Leu	Asn	Leu	Hys
Species C	Leu	Met	Lys	Pro	Asn	Ile	Gln	Leu	Hys
Species D	Leu	Leu	Leu	Pro	Asn	Leu	Asn	Leu	Hys

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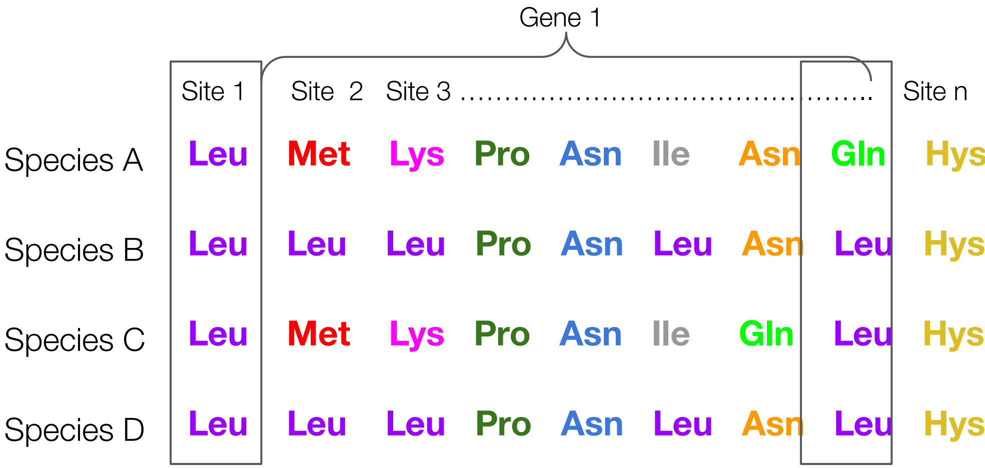

	Site 1	Site 2	Site 3	....			....	Site n
Species A	Leu	Met	Lys	Pro	Asn	Ile	Asn	Gln	Hys
Species B	Leu	Leu	Leu	Pro	Asn	Leu	Asn	Leu	Hys
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Species D	Leu	Leu	Leu	Pro	Asn	Leu	Asn	Leu	Hys

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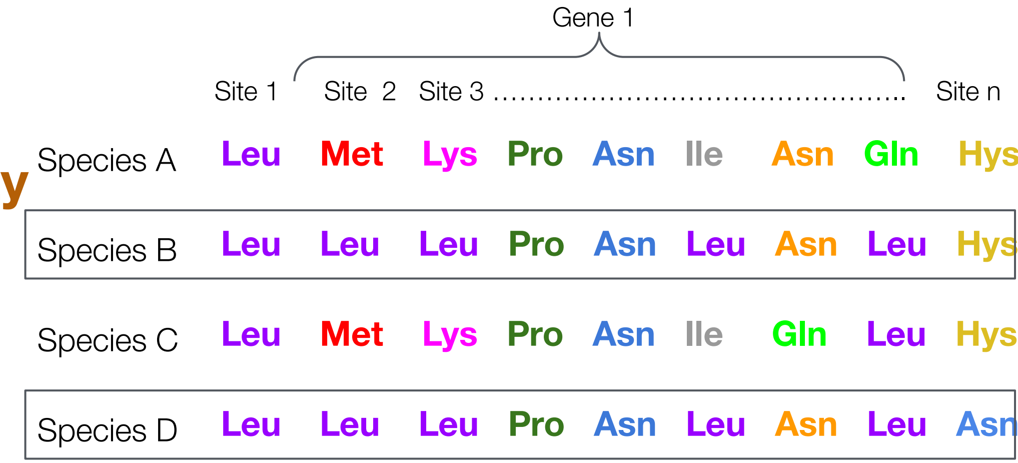

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(1) *Intrinsic* properties

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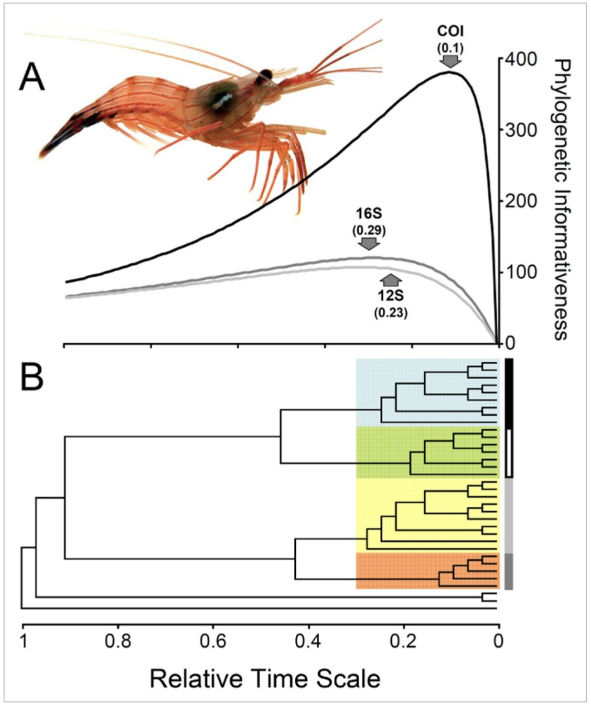
Compositional Heterogeneity

Lack of phylogenetic signal for your node of interest



Baeza & Fuentes 2013

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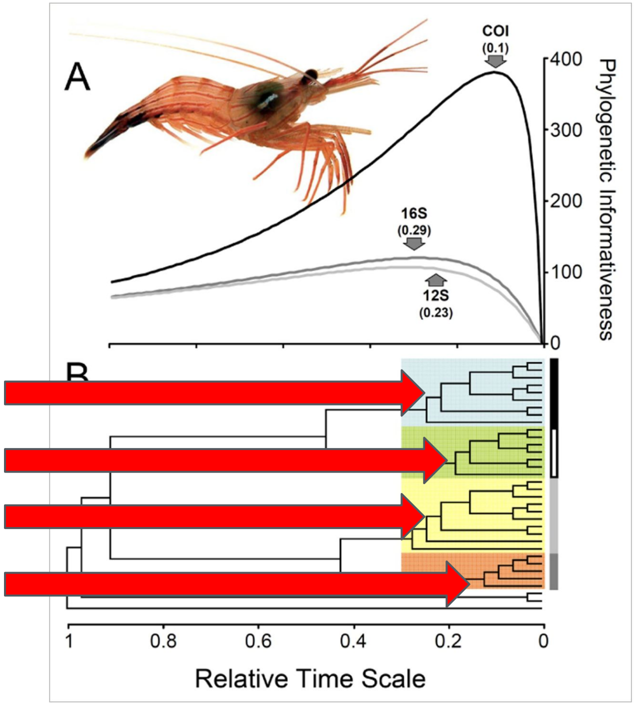

Good information to resolve these nodes

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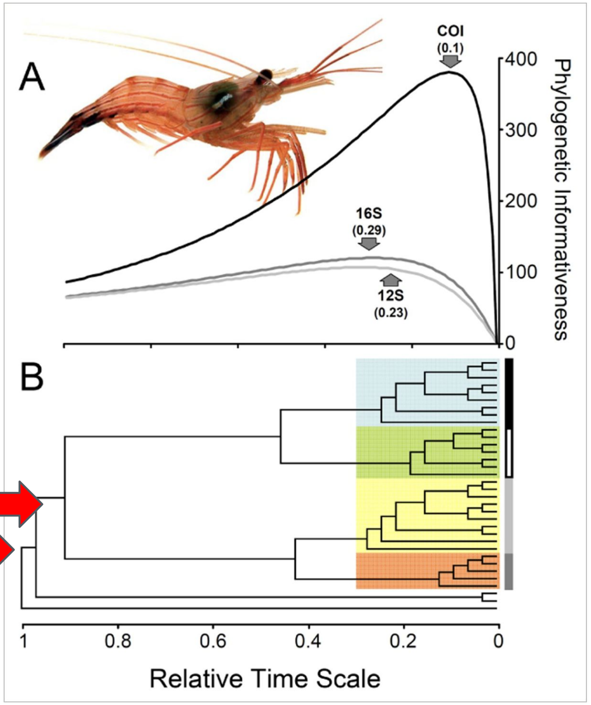

Not enough information to resolve these nodes

Baeza & Fuentes 2013

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etc.

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(2) Conflict between individual gene trees and the species tree

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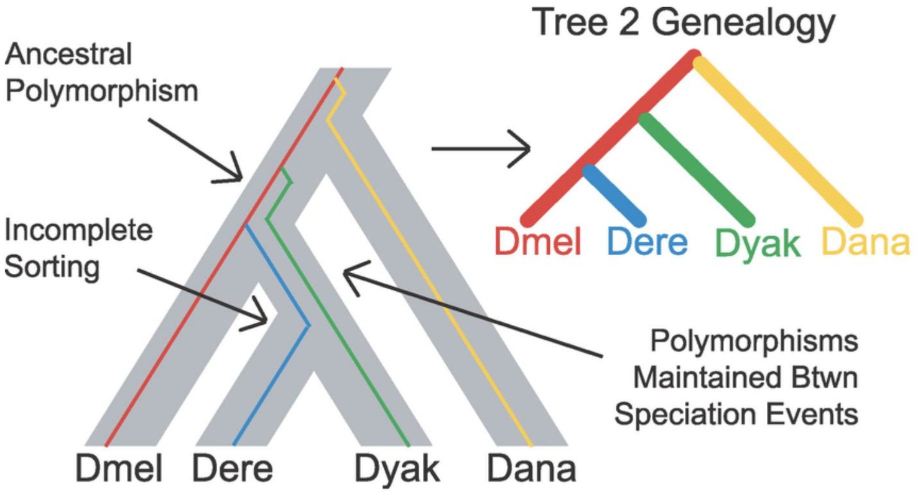
Incomplete lineage sorting

Understanding your data (and the errors it may trigger in downstream analyses)



Incomplete Lineage Sorting The history of a gene (colored lines) is drawn in the context of a species tree (gray bars). New lineages arising from new polymorphisms in the gene are drawn in different colors. In this case, the two alleles in the population prior to the split of Dmel are maintained through to the split of Dere and Dyak, leading to incomplete lineage sorting and an incongruent genealogy (tree 2). The greater the diversity in the ancestral population and the shorter the time between speciation events, the more likely nonspecies genealogies are.

Pollard et al. 2006

(2) Conflict between individual gene trees and the species tree

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Understanding your data (and the errors it may trigger in downstream analyses)

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Gene loss (eg, hidden paralogy)

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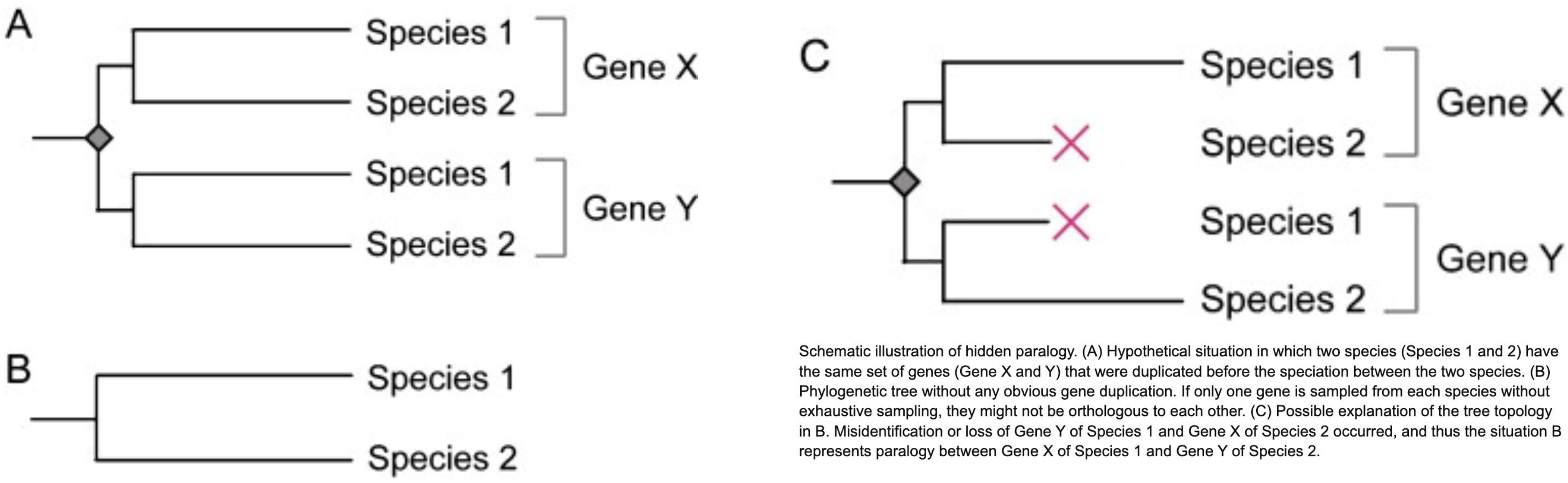

Schematic illustration of hidden paralogy. (A) Hypothetical situation in which two species (Species 1 and 2) have the same set of genes (Gene X and Y) that were duplicated before the speciation between the two species. (B) Phylogenetic tree without any obvious gene duplication. If only one gene is sampled from each species without exhaustive sampling, they might not be orthologous to each other. (C) Possible explanation of the tree topology in B. Misidentification or loss of Gene Y of Species 1 and Gene X of Species 2 occurred, and thus the situation B represents paralogy between Gene X of Species 1 and Gene Y of Species 2.

Kuraku 2013

(2) Conflict between individual gene trees and the species tree

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Hybridization

Understanding your data (and the errors it may trigger in downstream analyses)

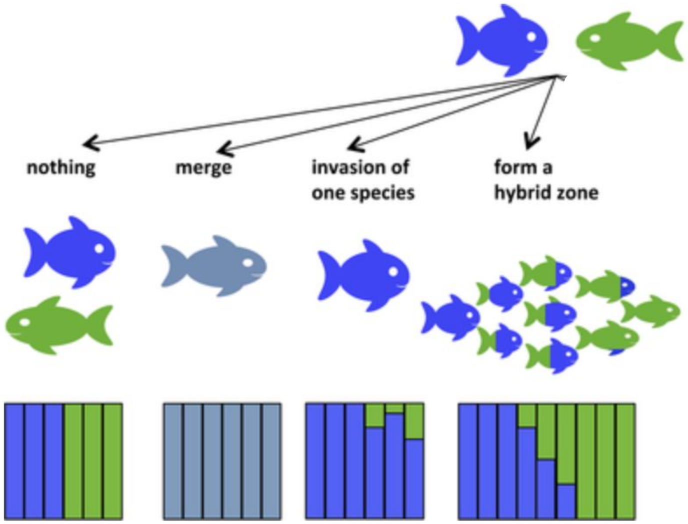

Fig 2.

Schematic representation of homoploid and allopolyploid hybrid speciation.

Runemark et al. 2019

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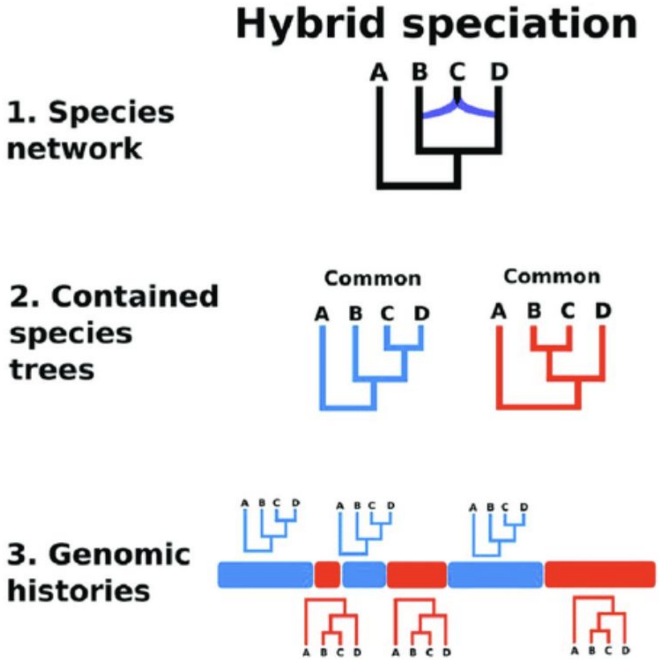

Folk et al. 2018

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Introgression

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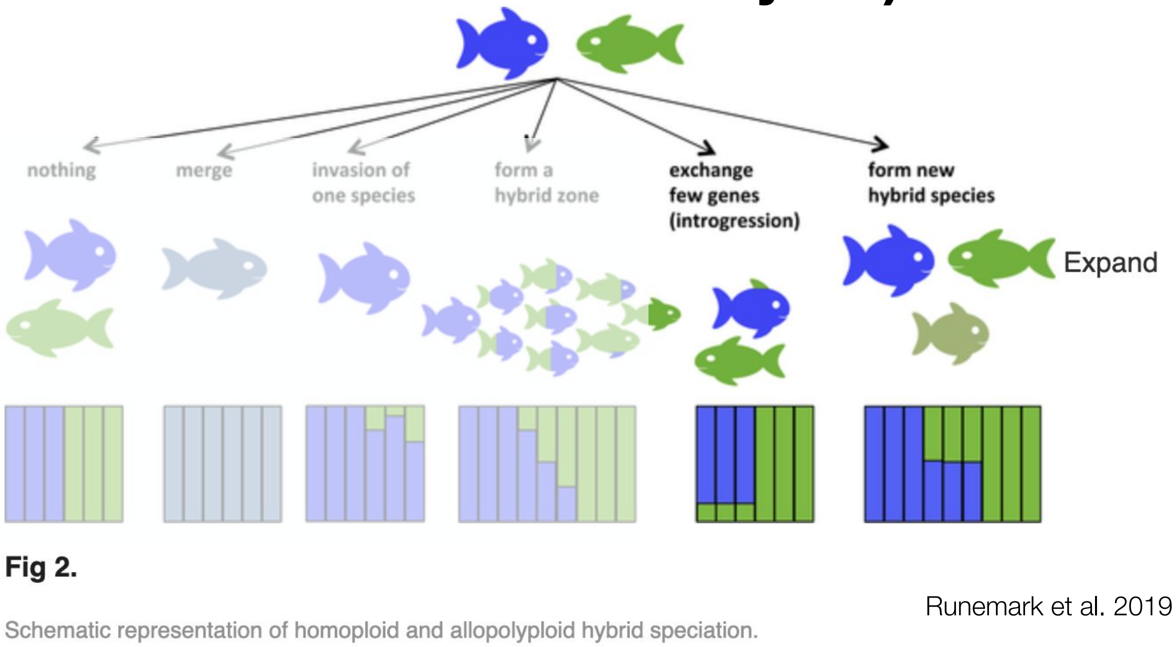

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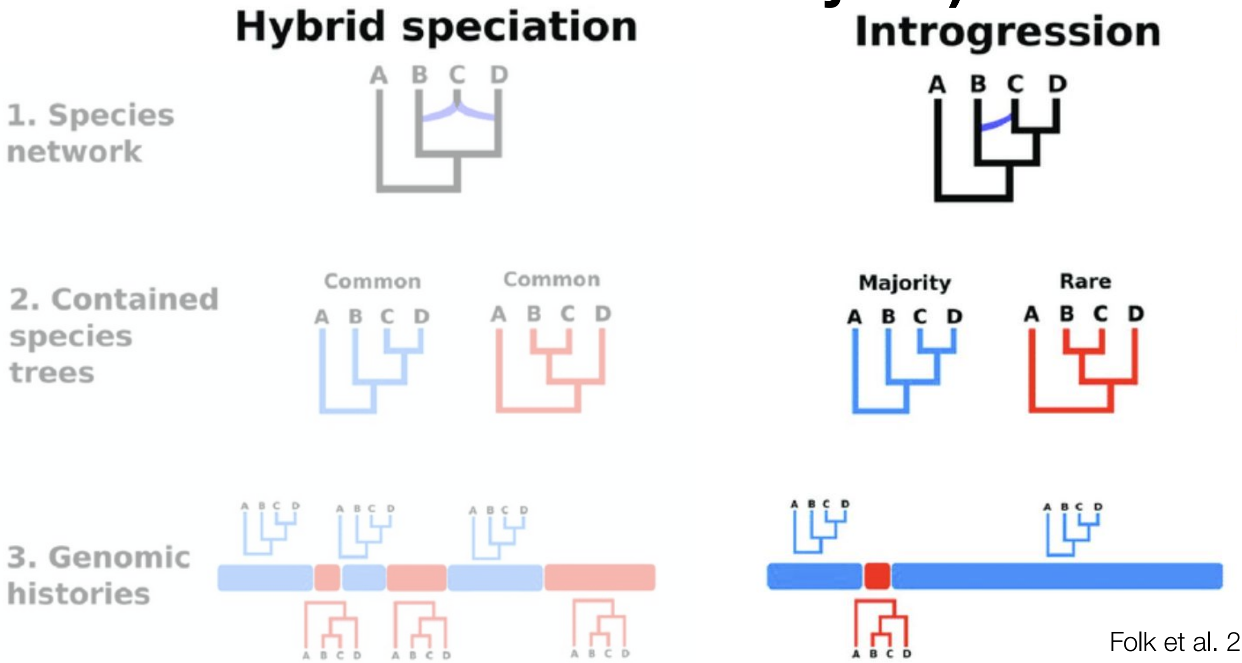

Folk et al. 2018

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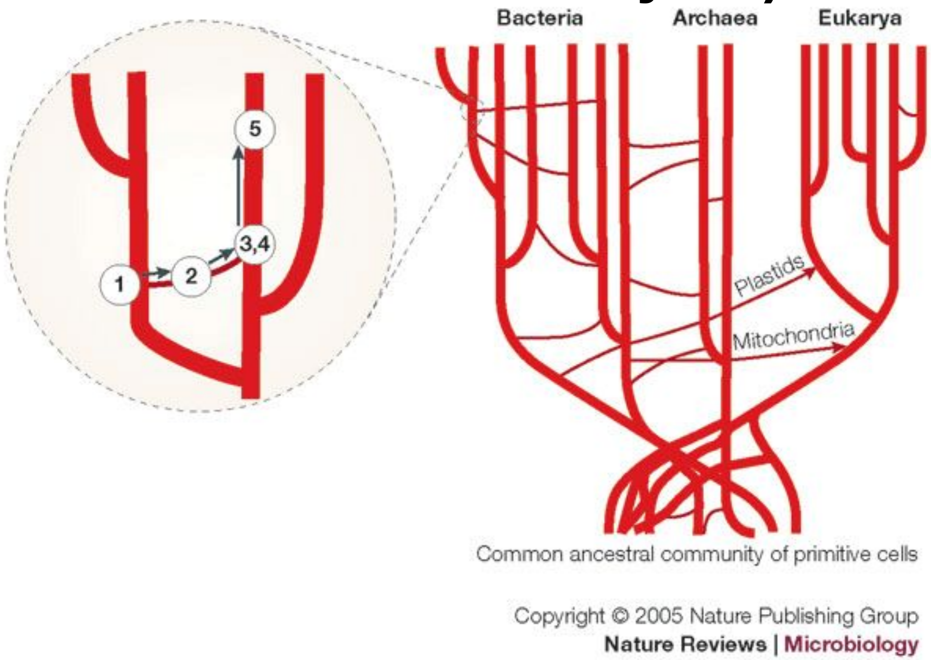
Horizontal gene transfer

Understanding your data (and the errors it may trigger in downstream analyses)


Bacteria
Archaea
Eukarya
5
3,4
2
1
Plastids
Mitochondria
Common ancestral community of primitive cells
Copyright © 2005 Nature Publishing Group
Nature Reviews | Microbiology

Smets and Barkay 2005

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Why may these properties result in a highly supported ‘wrong’ tree?

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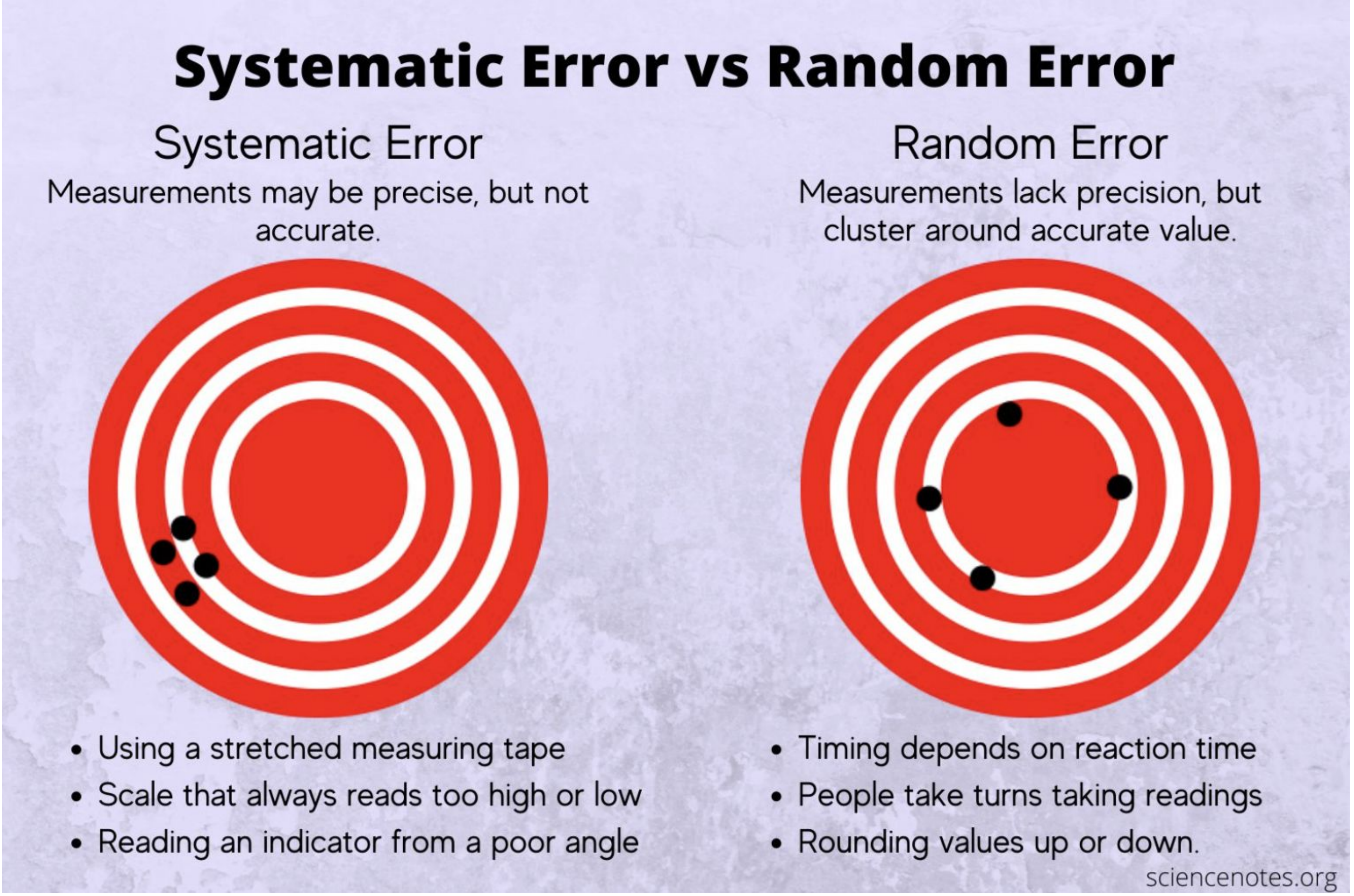

Systematic Error vs Random Error

Systematic Error

Measurements may be precise, but not accurate.

- Using a stretched measuring tape
- Scale that always reads too high or low
- Reading an indicator from a poor angle

Random Error

Measurements lack precision, but cluster around accurate value.

- Timing depends on reaction time
- People take turns taking readings
- Rounding values up or down.

sciencenotes.org

Why may these properties result in a highly supported ‘wrong’ tree?

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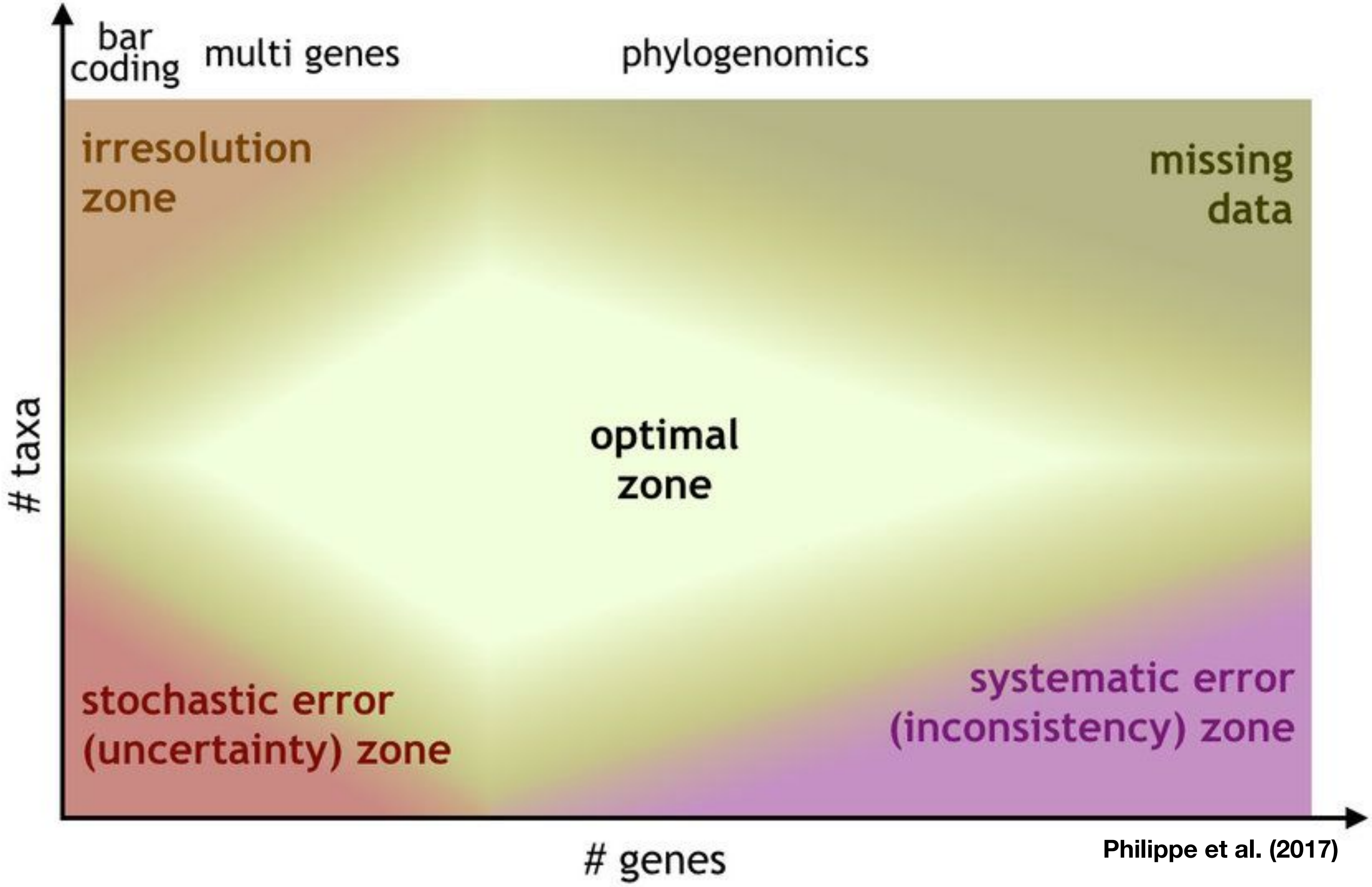
1) Systematic error



Philippe et al. (2017)

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2) **Model violation**

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Eg 3, genes evolved through duplication and not through speciation

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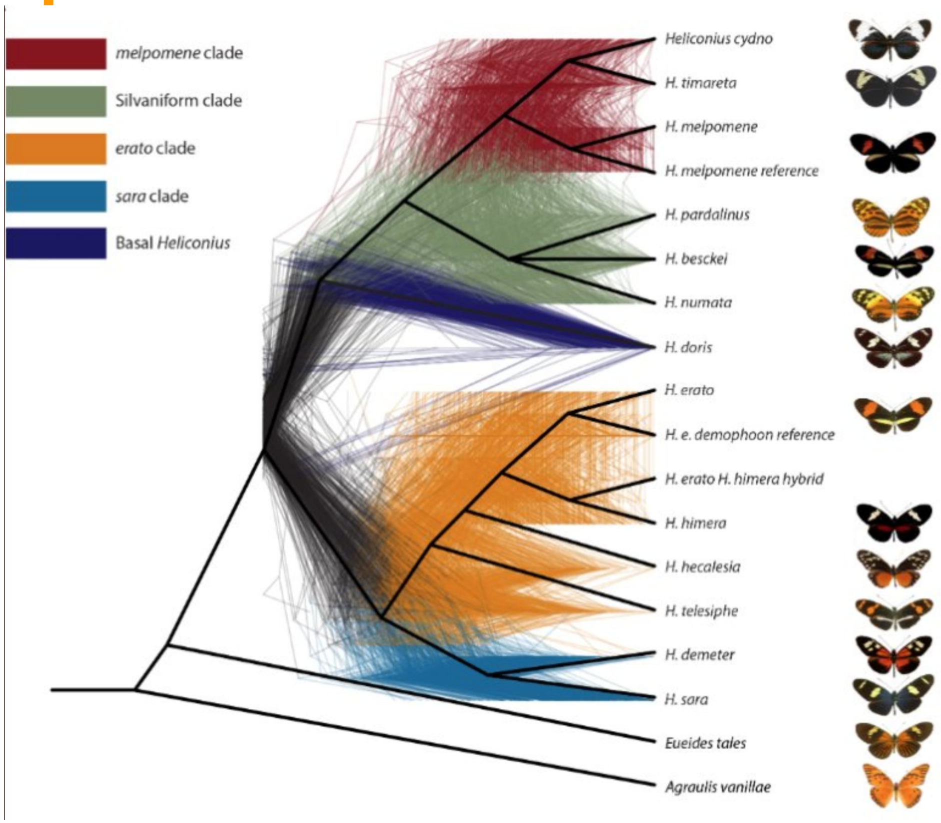
Eg 3, genes evolved through duplication and not through speciation

etc.

Why may these properties result in a highly supported ‘wrong’ tree?

Because of:

1) Systematic error
2) Model violation
3) **Gene tree/species tree discordance**



Edelman et al. 2019

So… what do we do to test the robustness of our tree?

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1) **Build different subsets of your data through a subsampling strategy selecting genes with different properties**

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So… what do we do to test the robustness of our tree?

1) Build different subsets of your data through a subsampling strategy selecting genes with different properties

2) Run different analyses that rely on different assumptions and/or apply different models

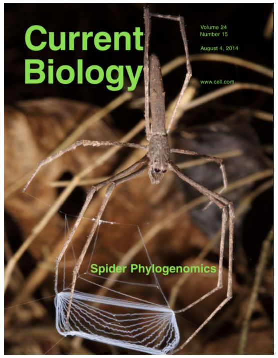
3) **Do 1) and 2) both at the level of *supermatrix* and *subset of individual gene trees***

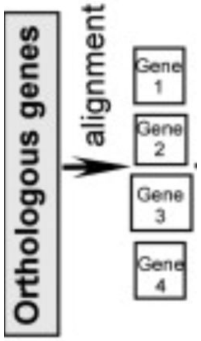
So… what do we do to test the robustness of our tree?

1) Build different subsets of your data through a subsampling strategy selecting genes with different properties

2) Run different analyses that rely on different assumptions and/or apply different models

3) Do 1) and 2) both at the level of *supermatrix* and *subset of individual gene trees*





Fernández, Hormiga and Giribet 2014

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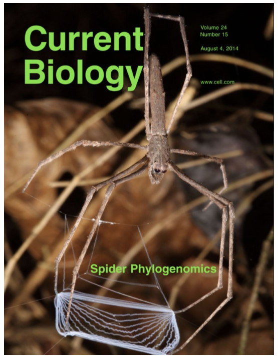

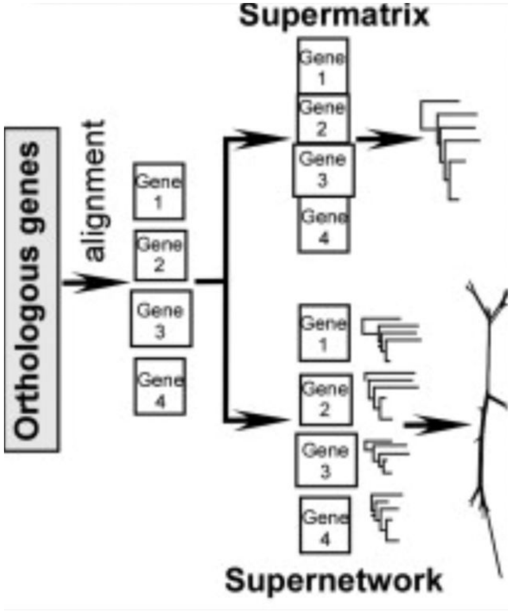

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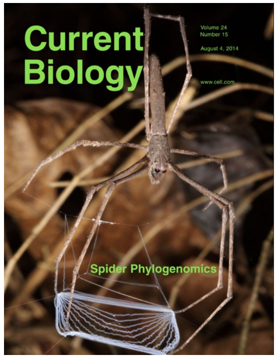

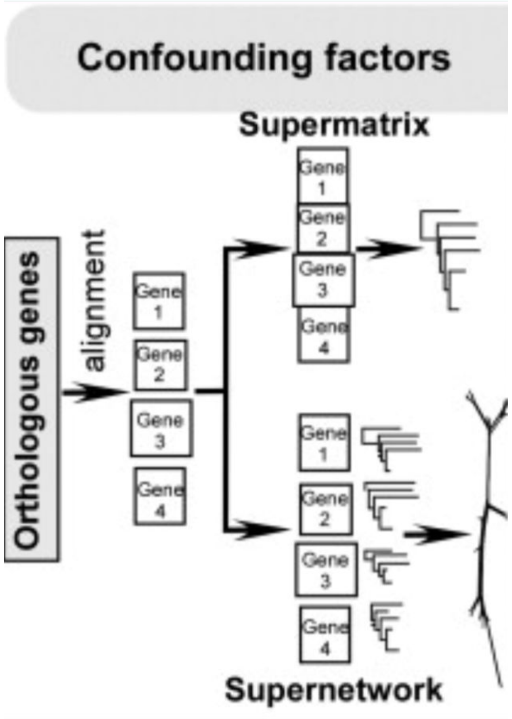

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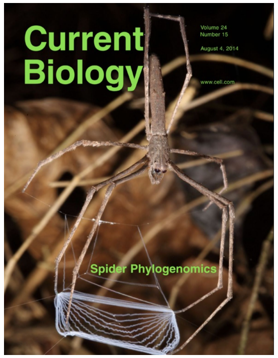

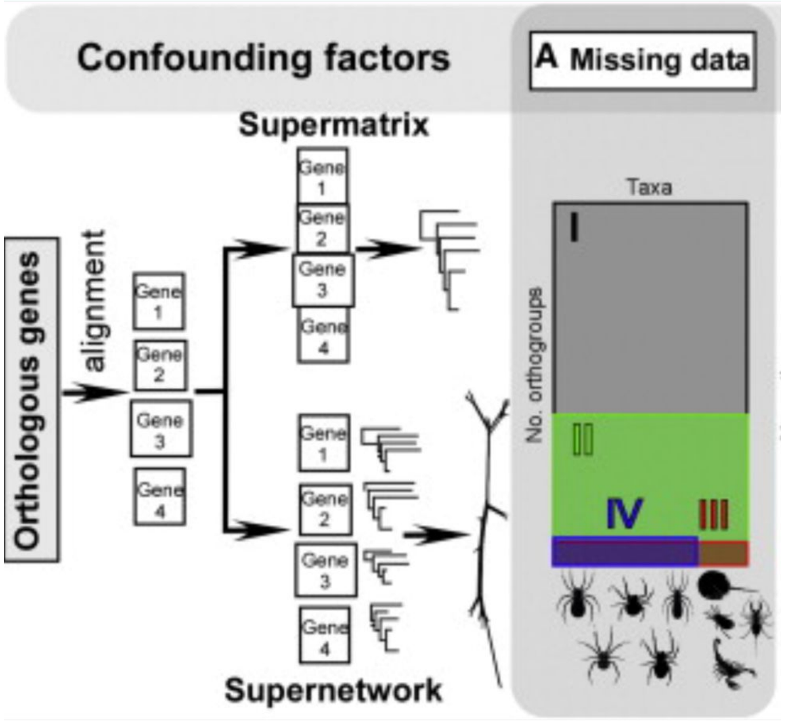

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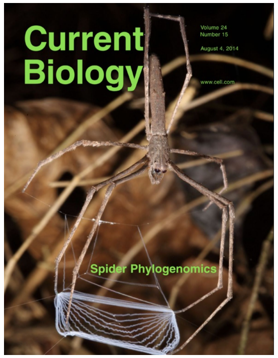

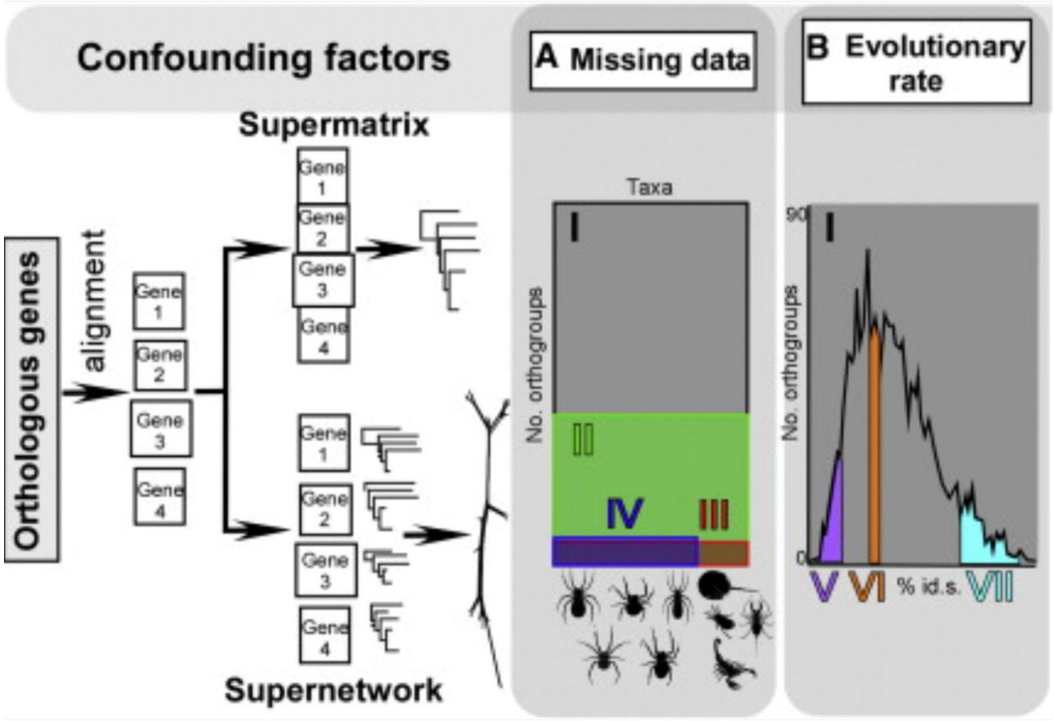

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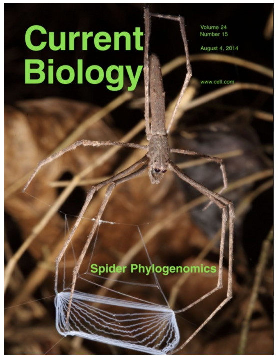

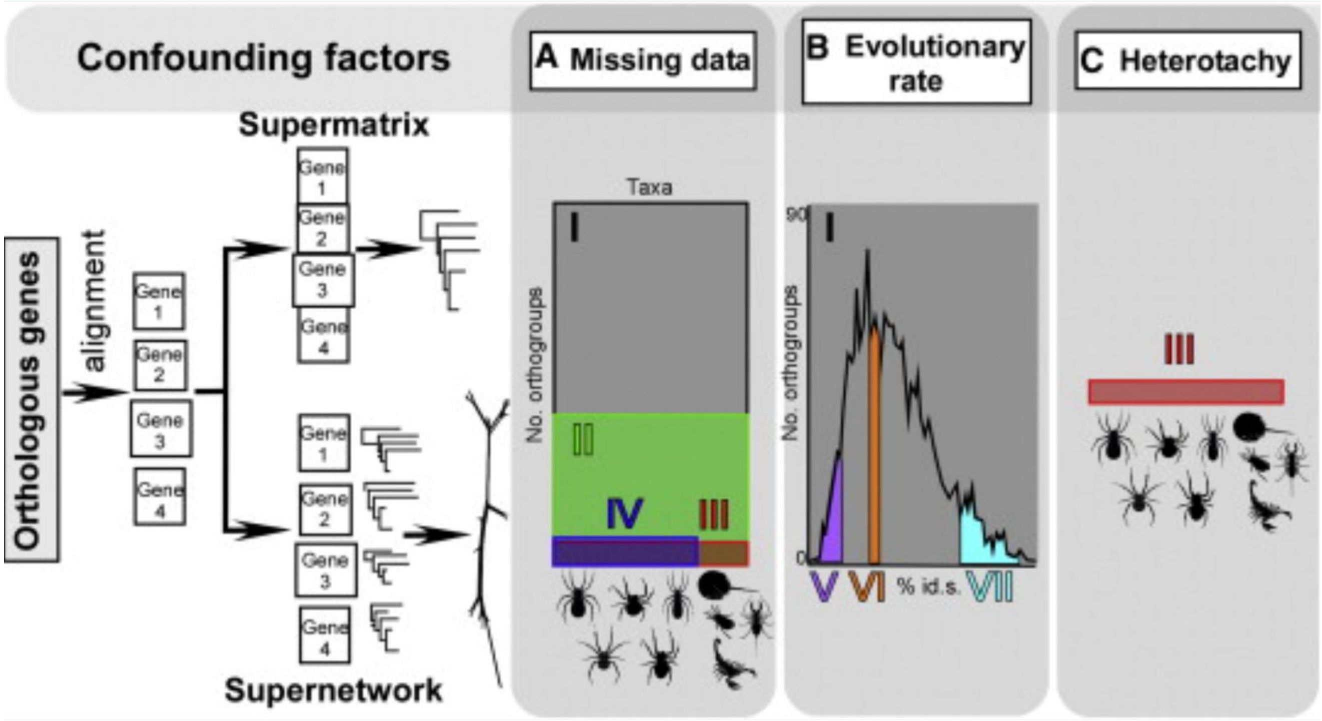

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Fernández, Hormiga and Giribet 2014

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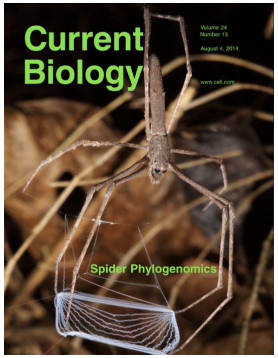
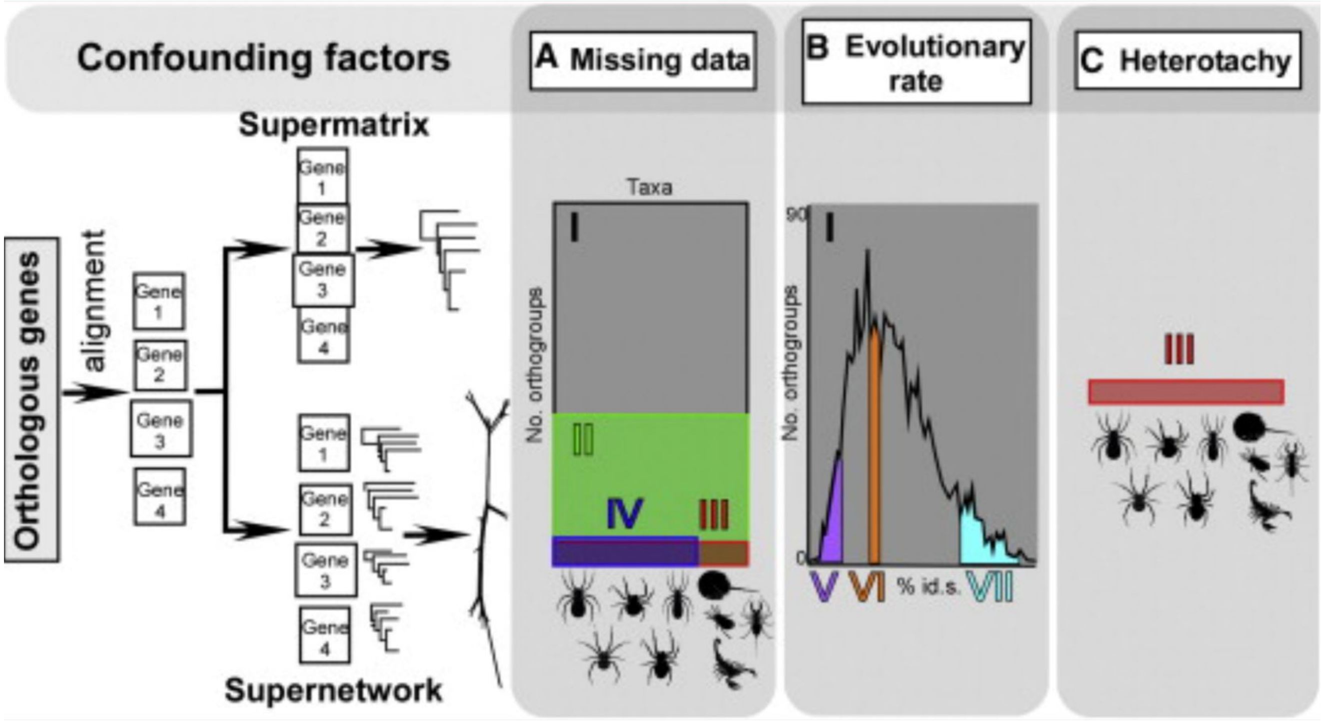
Heterotachy refers to the phenomenon of **a site in a gene-sequence changing its rate of evolution throughout the tree** (ie, sometimes evolving fast, some others evolving slow)





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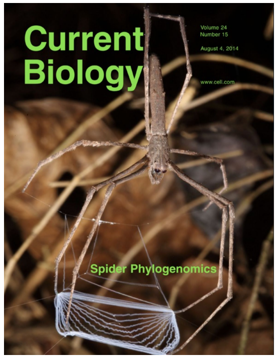

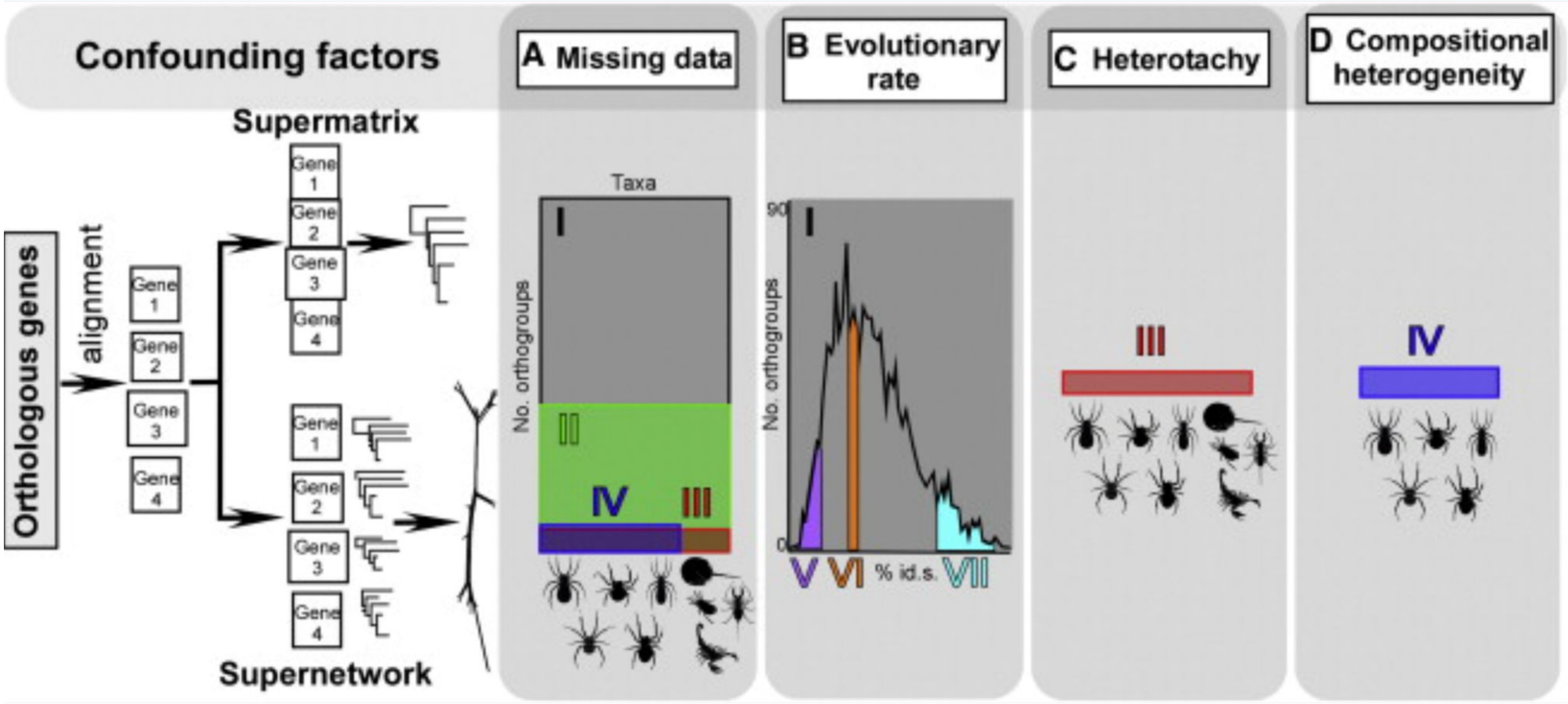

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Fernández, Hormiga and Giribet 2014

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We will be doing this today in our hands-on session

So… how many matrices/subsets/analyses should I analyze?

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Many.

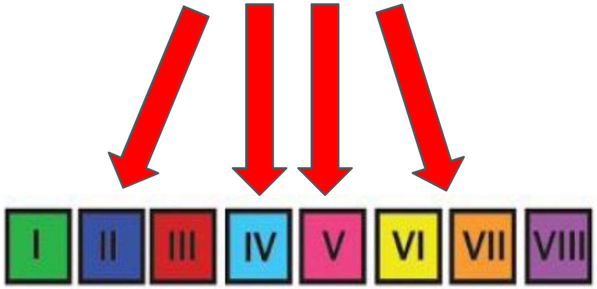
As many as you can!

So… how many matrices/subsets/analyses should I analyze?

Fernández, Edgecombe & Giribet (2016) Syst Biol

So… how many matrices/subsets/analyses should I analyze?

These are **matrices/subsets** of individual gene trees



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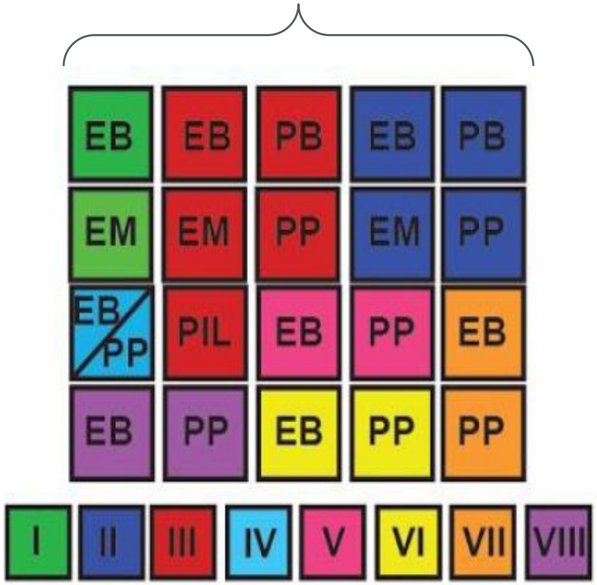
These are **analyses**



EB EB PB EB PB

EM EM PP EM PP

EB/PP PIL EB PP EB

EB PP EB PP PP

I II III IV V VI VII VIII

Fernández, Edgecombe & Giribet (2016) Syst Biol

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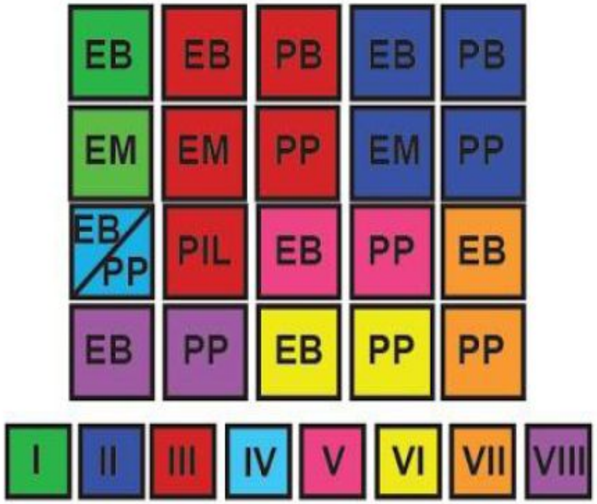
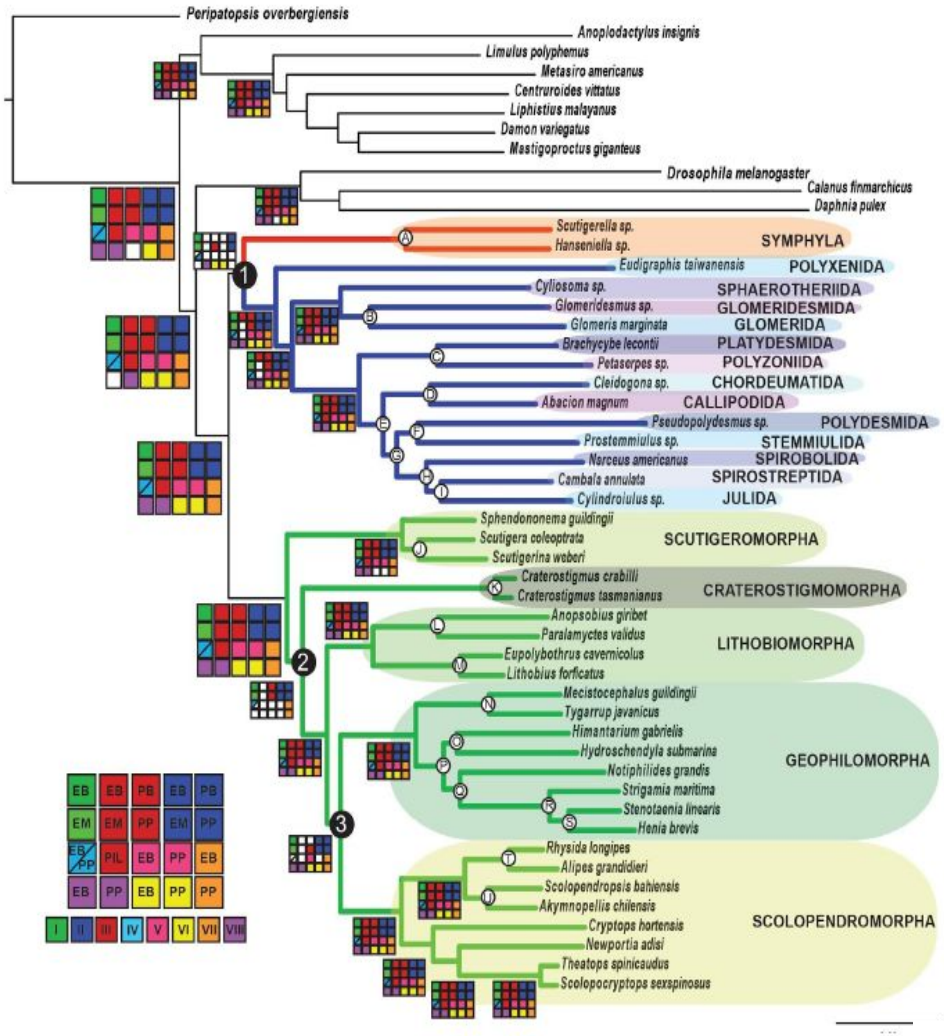


EB	EB	PB	EB	PB
EM	EM	PP	EM	PP
EB/PP	PIL	EB	PP	EB
EB	PP	EB	PP	PP

I	II	III	IV	V	VI	VII	VIII



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Generating phylogenomic data matrices: hands-on session

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The Český Krumlov town hall decides to fund a project to understand whether the brown bear is more closely related to the polar bear or the American black bear

Generating phylogenomic data matrices: hands-on session

(Important piece of information (shared by Scott): Český Krumlov locals used to refer to the workshop participants as ‘**molekulos**’)

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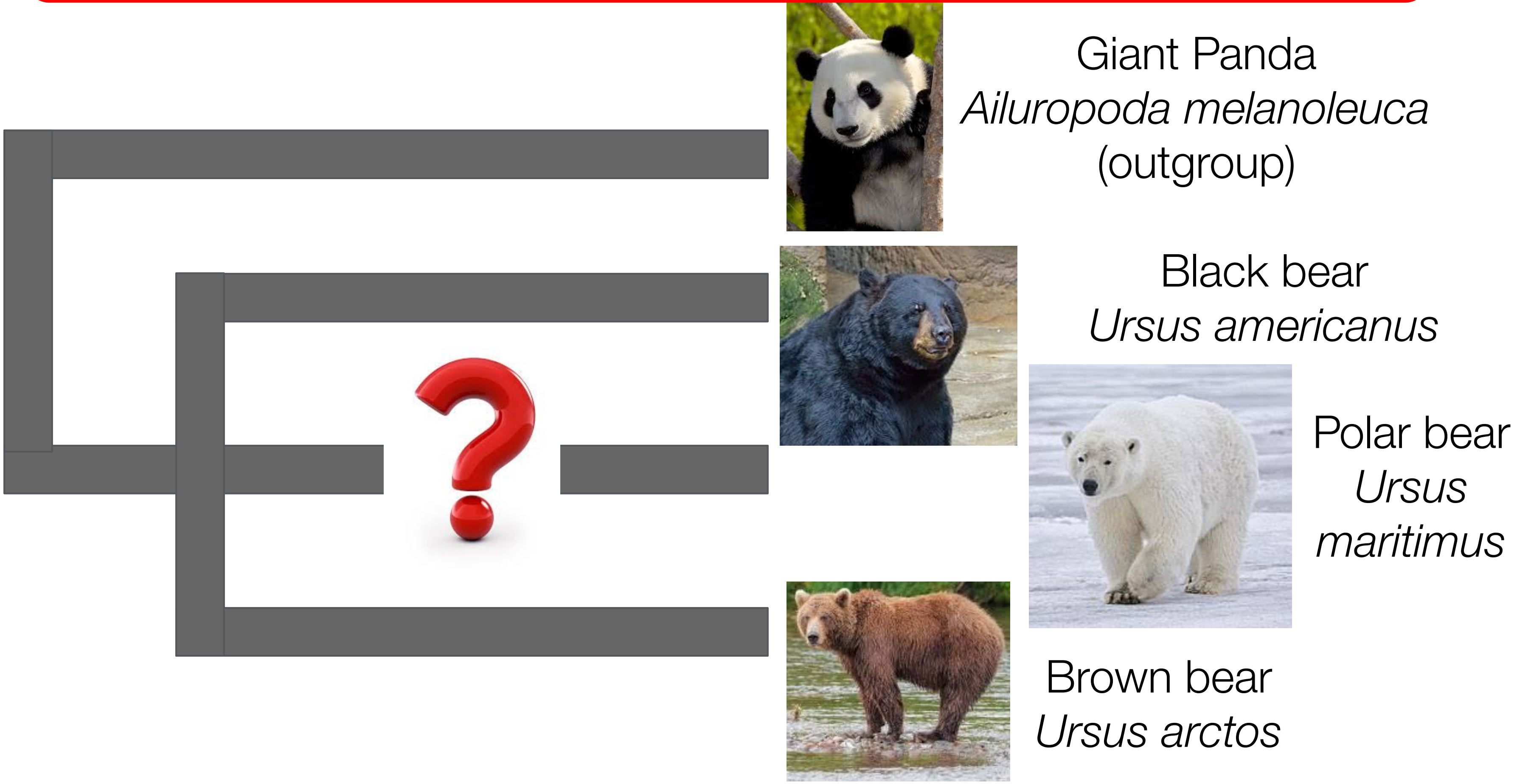
The Český Krumlov town hall decides to fund a project to understand whether the brown bear is more closely related to the polar bear or the American black bear

Let’s ask the ‘molekulos’ for help!!

Generating phylogenomic data matrices: hands-on session

Is the polar bear the sister group to the American black bear or the brown bear?



Giant Panda
Ailuropoda melanoleuca
(outgroup)

Black bear
Ursus americanus

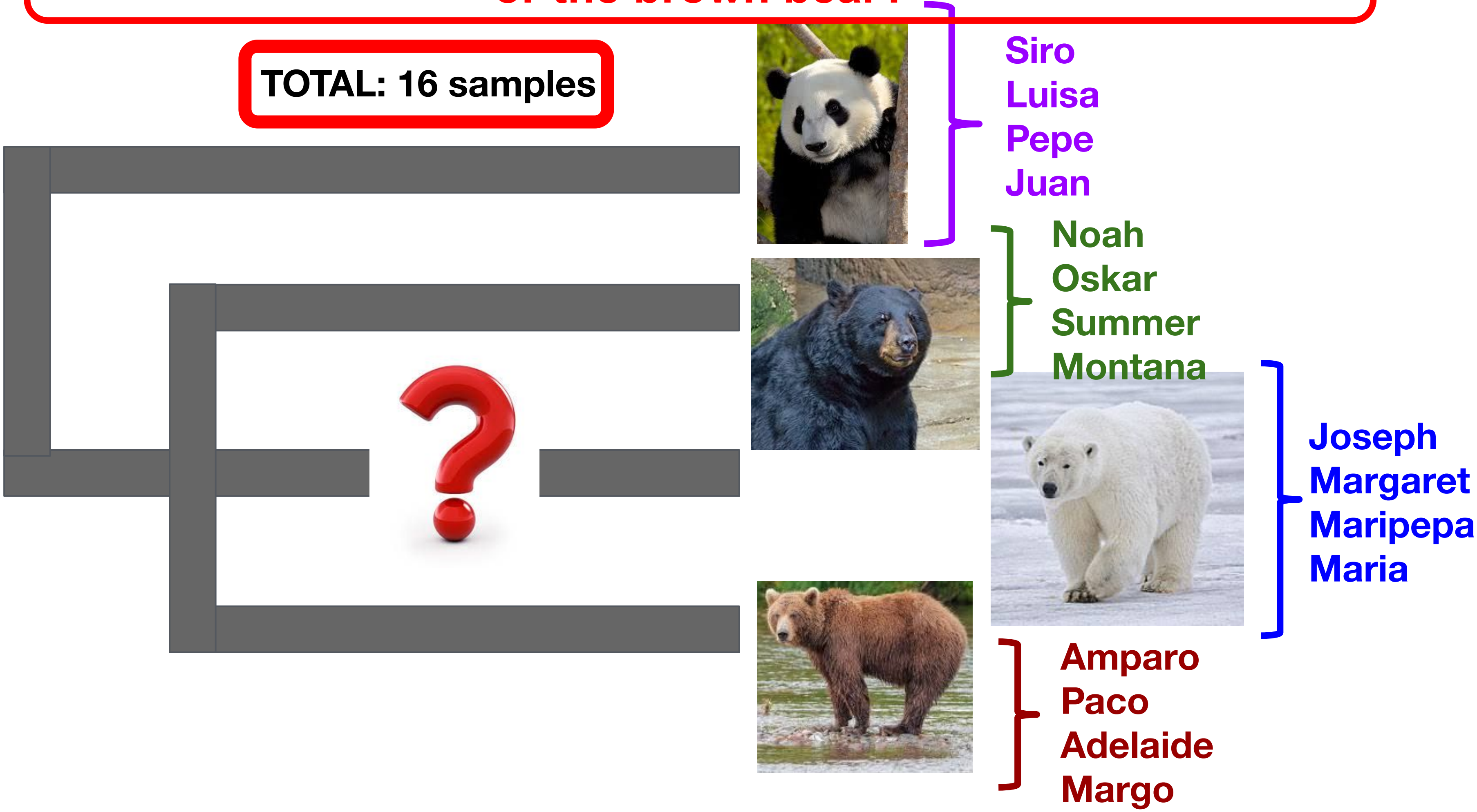
Polar bear
Ursus maritimus

Brown bear
Ursus arctos

Generating phylogenomic data matrices: hands-on session

Is the polar bear the sister group to the American black bear or the brown bear?

TOTAL: 16 samples



Siro
Luisa
Pepe
Juan

Noah
Oskar
Summer
Montana

Joseph
Margaret
Maripepa
Maria

Amparo
Paco
Adelaide
Margo

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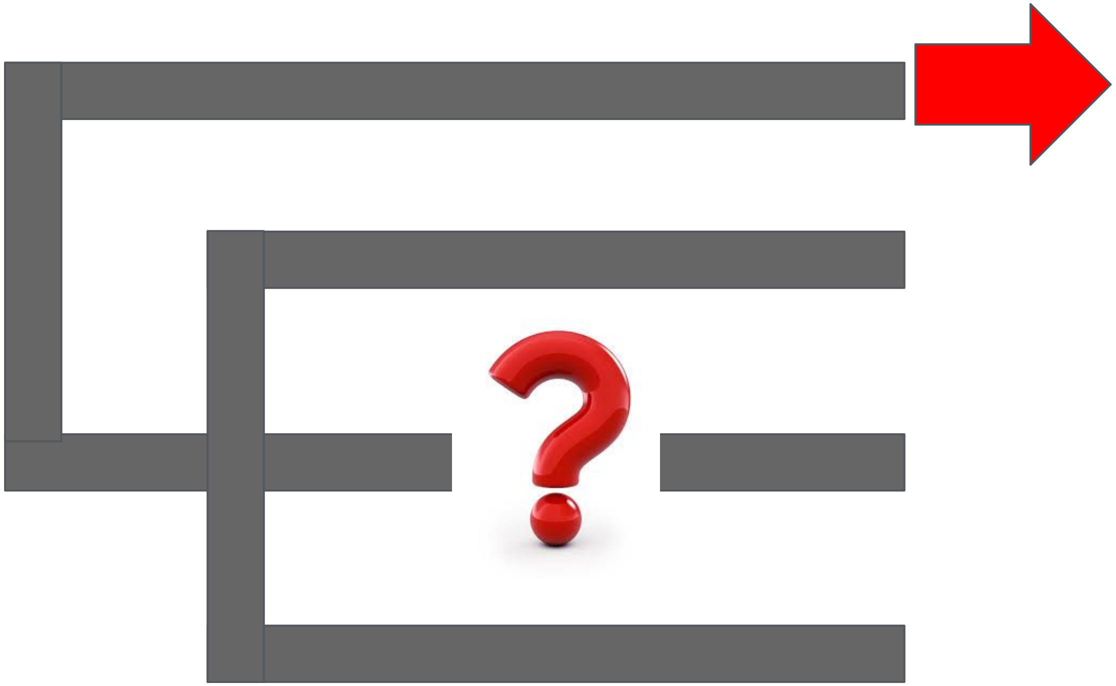
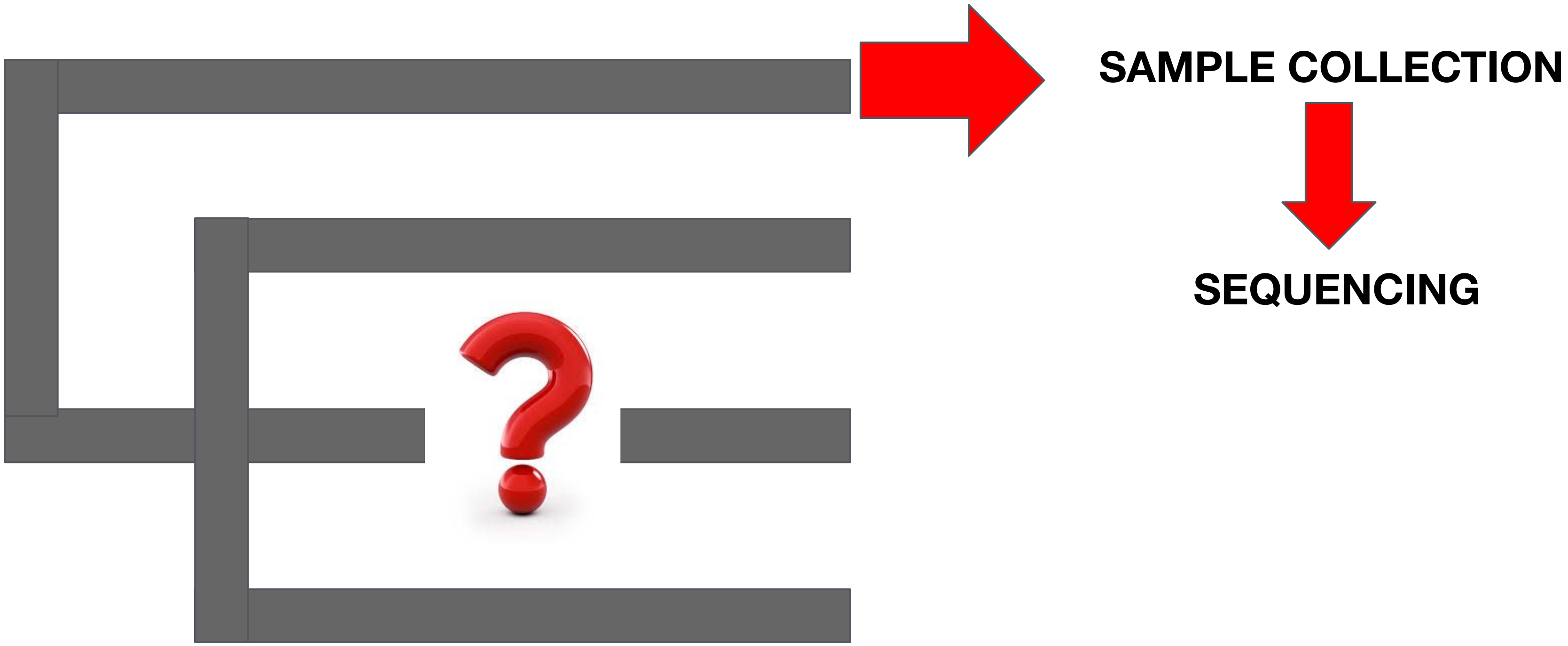


SAMPLE COLLECTION

Generating phylogenomic data matrices: hands-on session

Is the polar bear the sister group to the American black bear or the brown bear?



SAMPLE COLLECTION

SEQUENCING

Generating phylogenomic data matrices: hands-on session

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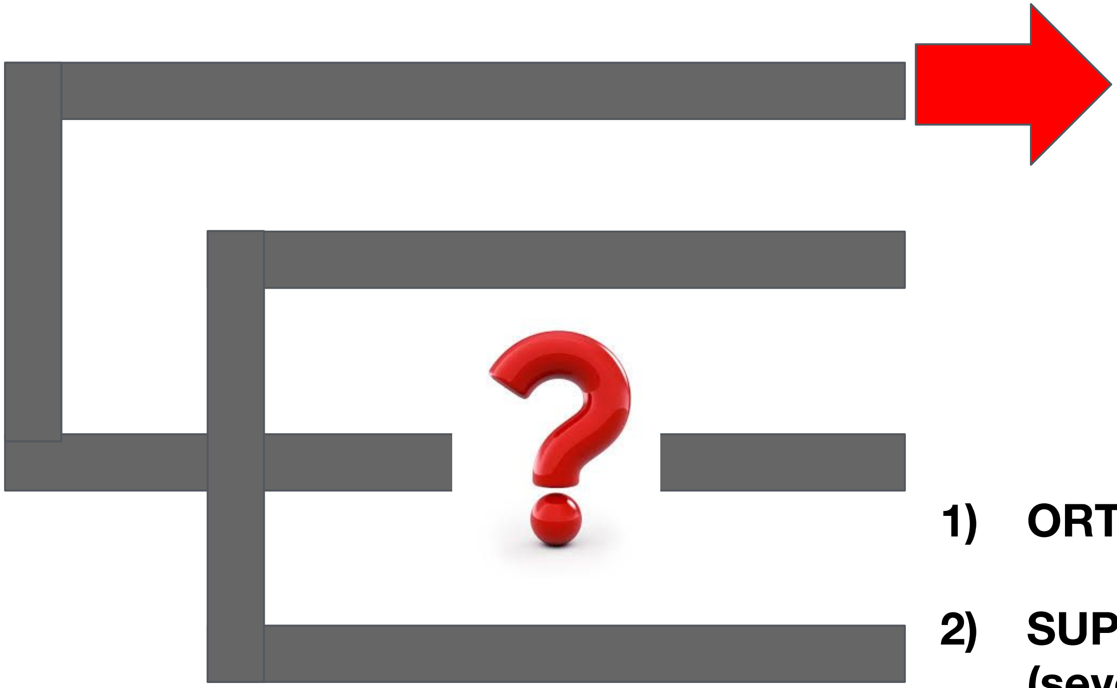


SAMPLE COLLECTION

SEQUENCING

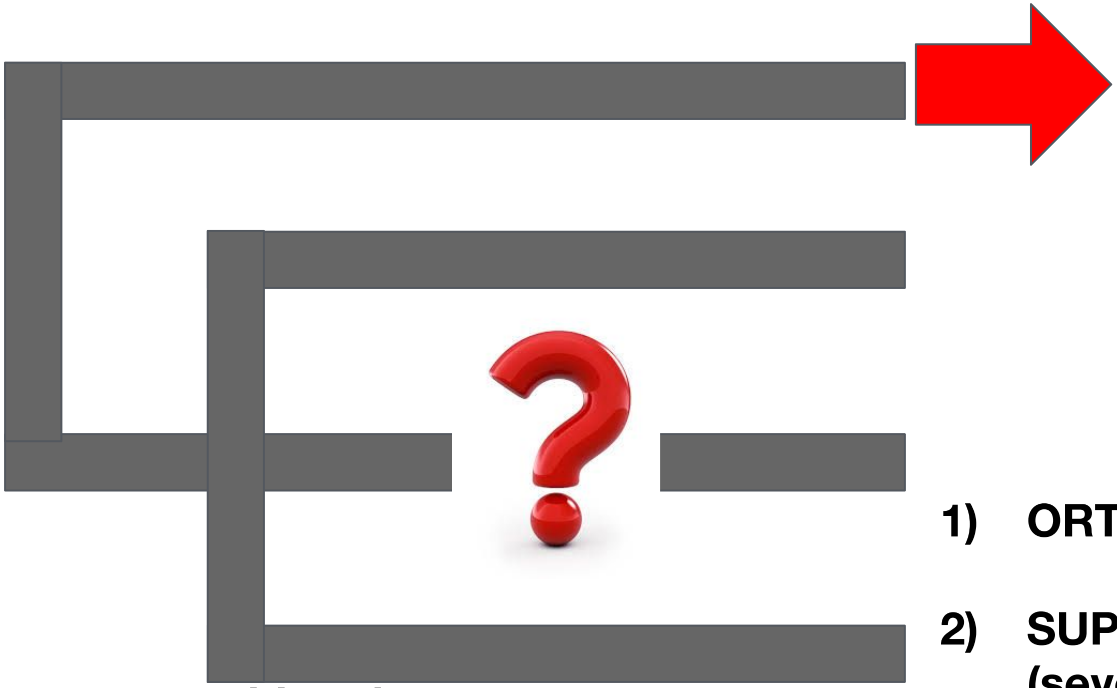
1) ORTHOLOGY INFERENCE

2) SUPERMATRIX CONSTRUCTION (several ones)

3) PHYLOGENETIC INFERENCE (MAXIMUM LIKELIHOOD)

Generating phylogenomic data matrices: hands-on session

Is the polar bear the sister group to the American black bear or the brown bear?



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(**Important considerations**:

- the genes provided come from real transcriptomic data; I have filtered them out to have only the longest isoform per gene
- we are going to work at the level of amino acid data, not nucleotide (TransDecoder)

KEEP
CALM
AND
TAKE
A
BREAK

Generating phylogenomic data matrices: hands-on session

Is the polar bear the sister group to the American black bear or the brown bear?

During the first part of the tutorial, you have…

1) Inferred orthologous groups with OrthoFinder.
2) Created a supermatrix selecting genes based on:
   a) their amount of missing data
   b) their 'decisiveness' (ie, representation among species)
   c) removing outliers accounting for a bunch of confounding factors (eg, compositional heterogeneity, saturation, etc.).
3) Inferred ML phylogenetic trees from these matrices

Which topology are your analyses supporting? Is this topology robust, or are the analyses showing any

Generating phylogenomic data matrices: hands-on session

Is the polar bear the sister group to the American black bear or the brown bear?

SCIENCE & NATURE

Phylogenomics illuminate the interrelationships of the genus *Ursus* and supports the brown bear as sister group to the polar bear

Authors: Participants of the 2023 Workshop on Genomics český Krumlov (‘molekulos’)

Generating phylogenomic data matrices: hands-on session

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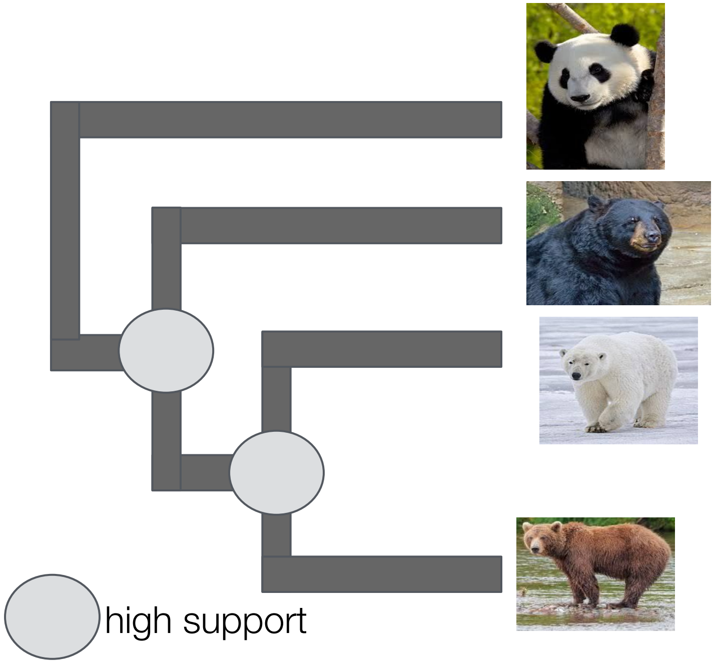

Abstract:

The interrelationships within the genus *Ursus* have been contentious based on the analysis of a limited amount of molecular markers. Here, we sequenced full genomes of 16 specimens of the American black bear, brown bear, polar bear and giant panda and explored their phylogenetic relationships through a phylogenomic spyglass. **Our results, based on the analysis of multiple supermatrices to account for the effect of missing data, compositional heterogeneity and other confounding factors, strongly support a sister relationship of the brown bear to the polar bear.** Our findings pave te road towards understanding bear evolution at a deeper level.

Generating phylogenomic data matrices: hands-on session

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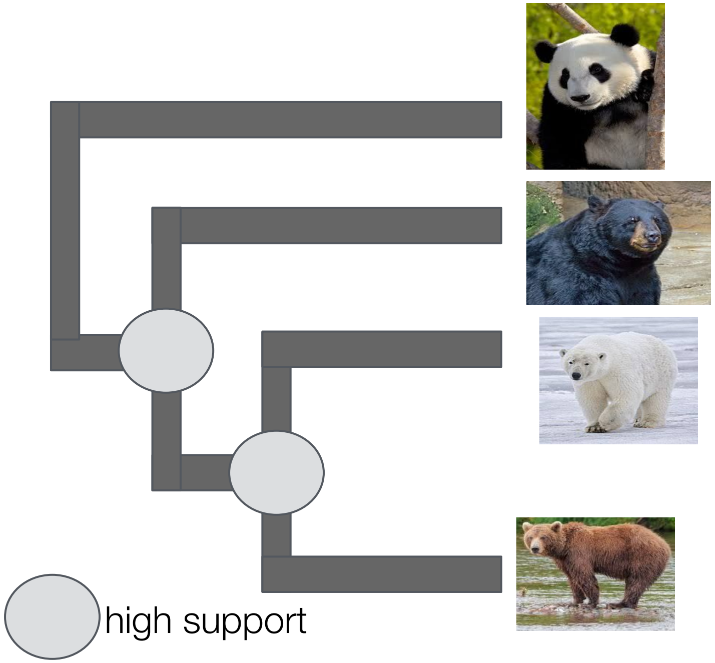

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contentious unt of
molecular m nes of 16
specimens (r, polar bear
and giant pa elationships
through a pl sed on the
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REJECTED

Generating phylogenomic data matrices: hands-on session

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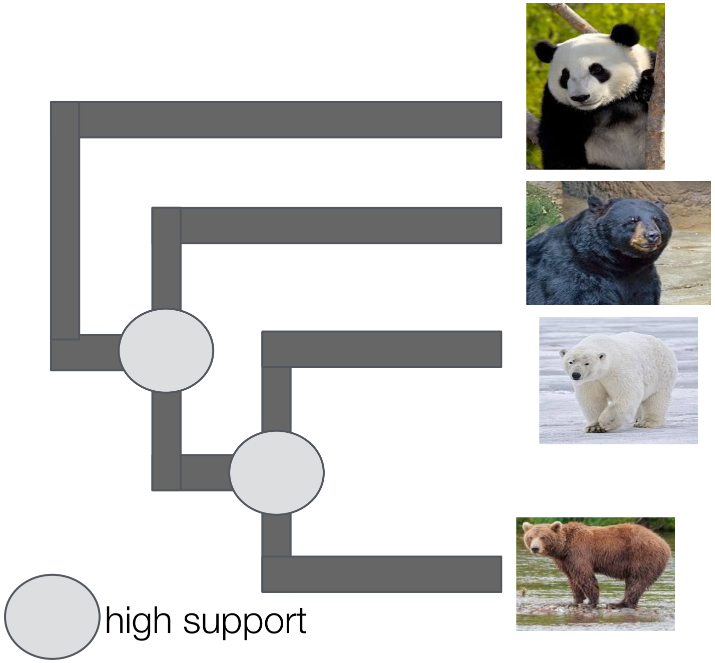

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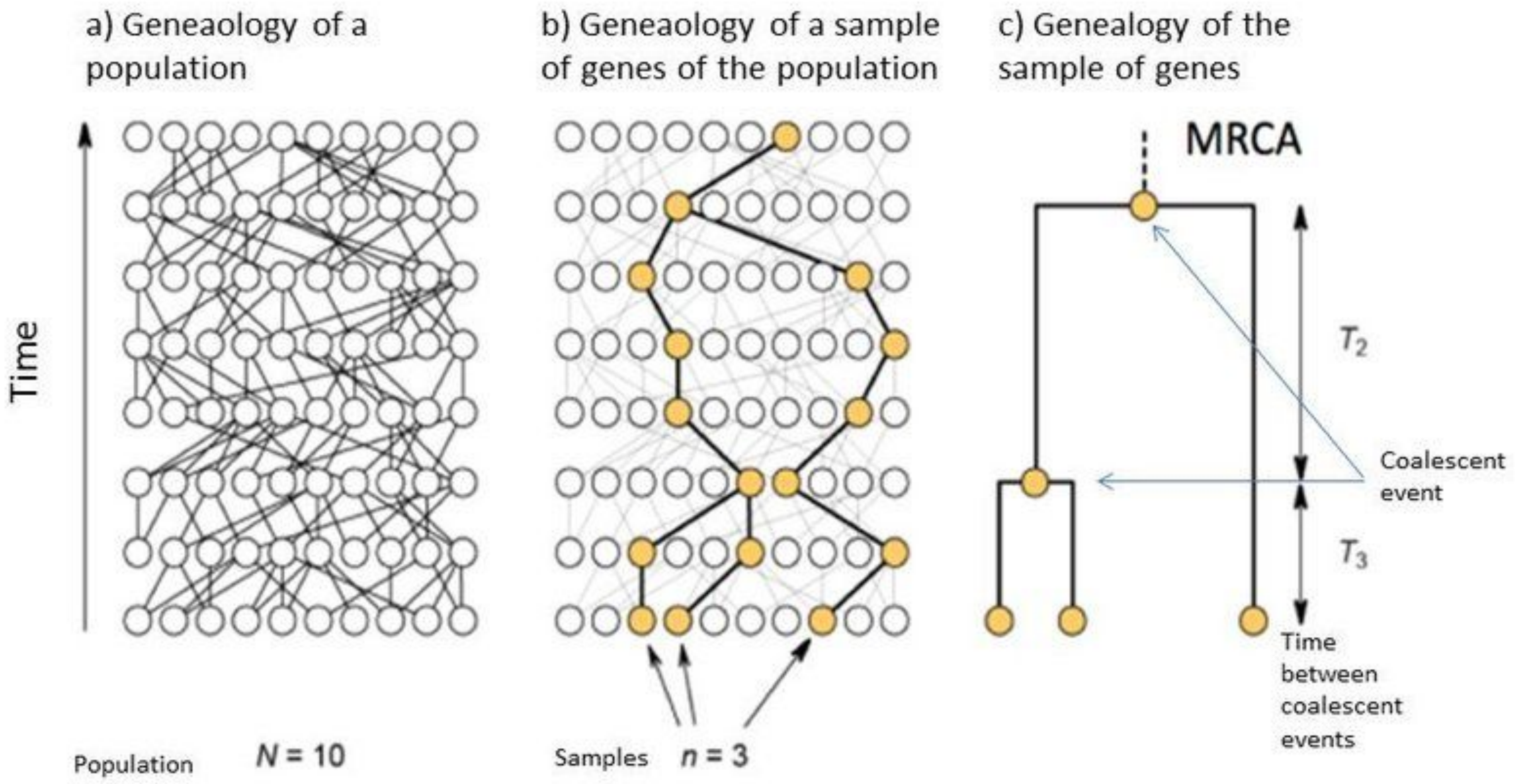
contentious unt of
molecular m nes of 16
specimens r, polar bear
and giant pa elationships
through a pl sed on the
analysis of multiple supermatrices to account for the effect of

REJECTED

Reviewer #3: although I appreciate the efforts of the authors to account for confounding factors and test the robustness of their results, they failed to test whether their hypothesis was driven by incongruence between individual gene evolutionary trajectories.

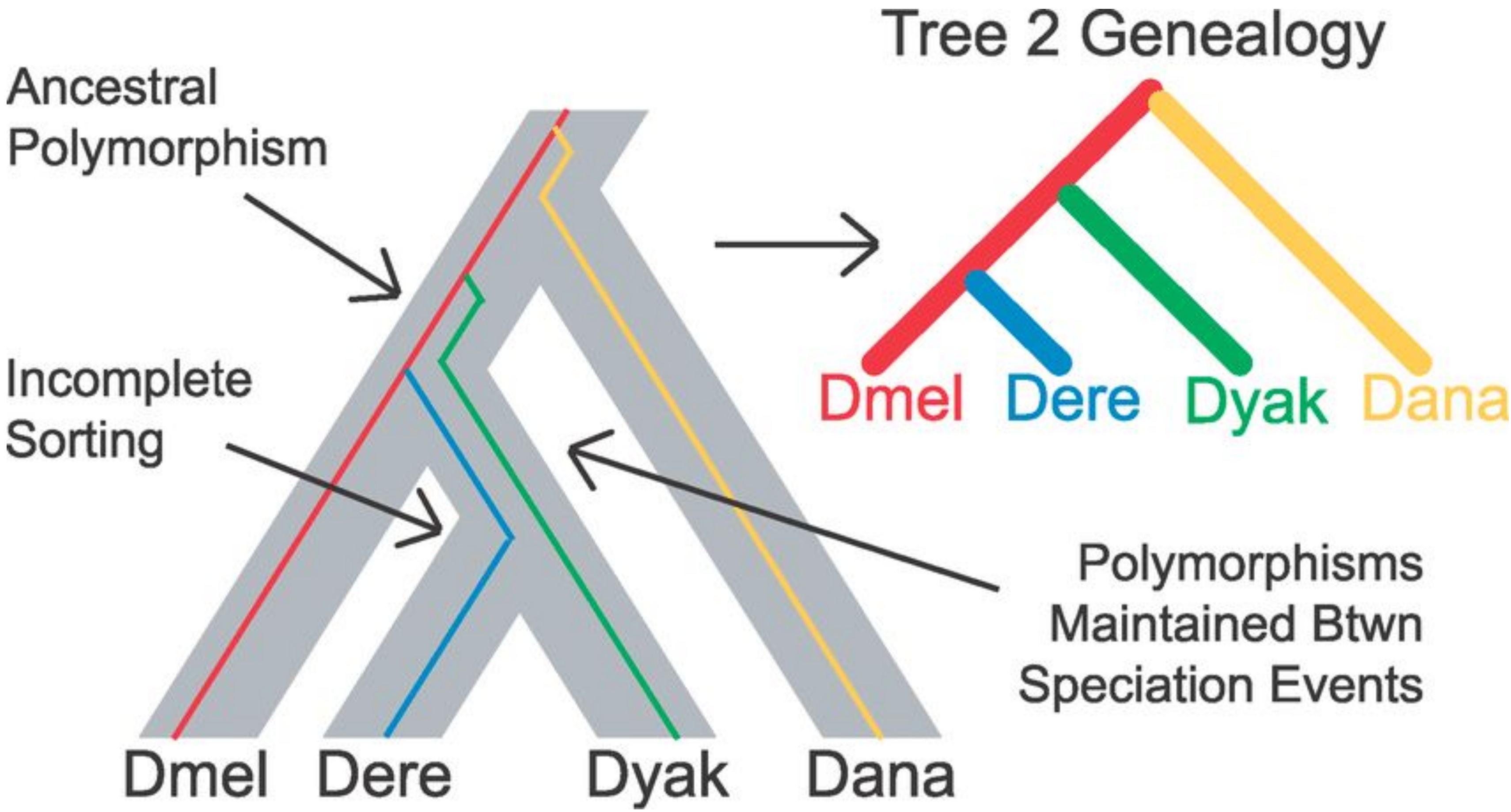
Analyzing gene tree/species tree conflict: hands-on session

Brief introduction to coalescent theory


a) Geneaology of a population
b) Geneaology of a sample of genes of the population
c) Genealogy of the sample of genes
Time
MRCA
T_2
T_3
Coalescent event
Time between coalescent events
Population
$N = 10$
Samples
$n = 3$

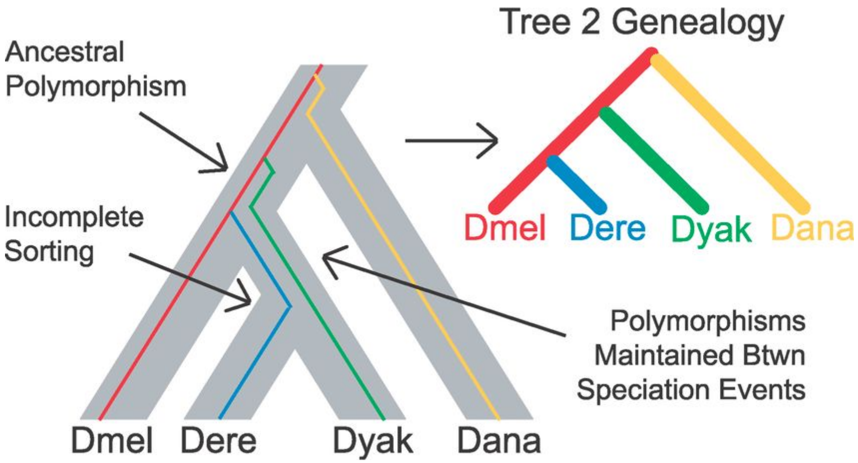
Analyzing gene tree/species tree conflict: hands-on session

Brief introduction to coalescent theory

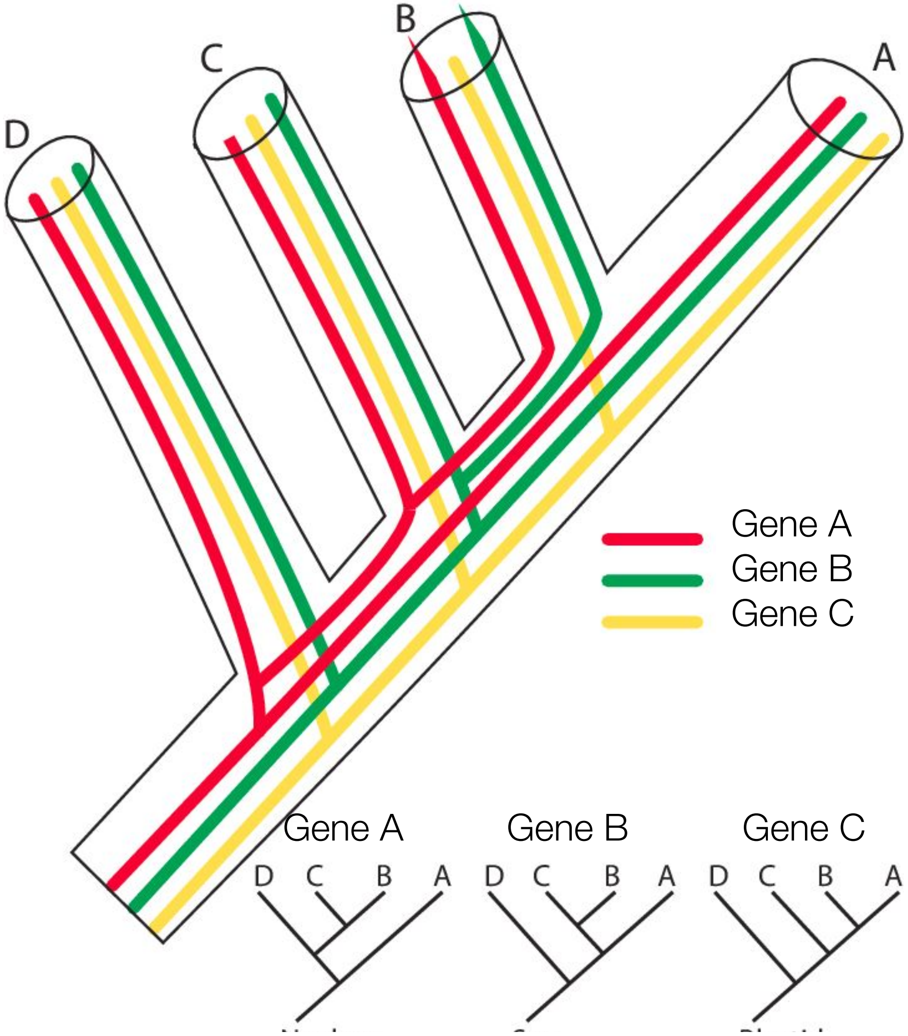


Pollard et al. 2006

Brief introduction to coalescent theory



Pollard et al. 2006



Naciri and Li 2015

Analyzing gene tree/species tree conflict: hands-on session

Is the polar bear the sister group to the American black bear or the brown bear?

ASTRAL is a tool for estimating an unrooted species tree given a set of unrooted gene trees.
ASTRAL is statistically consistent under the multi-species coalescent model (and thus is useful for handling incomplete lineage sorting, i.e., ILS).
ASTRAL finds the species tree that has the maximum number of shared induced quartet trees with the set of gene trees, subject to the constraint that the set of bipartitions in the species tree comes from a predefined set of bipartitions.

Analyzing gene tree/species tree conflict: hands-on session

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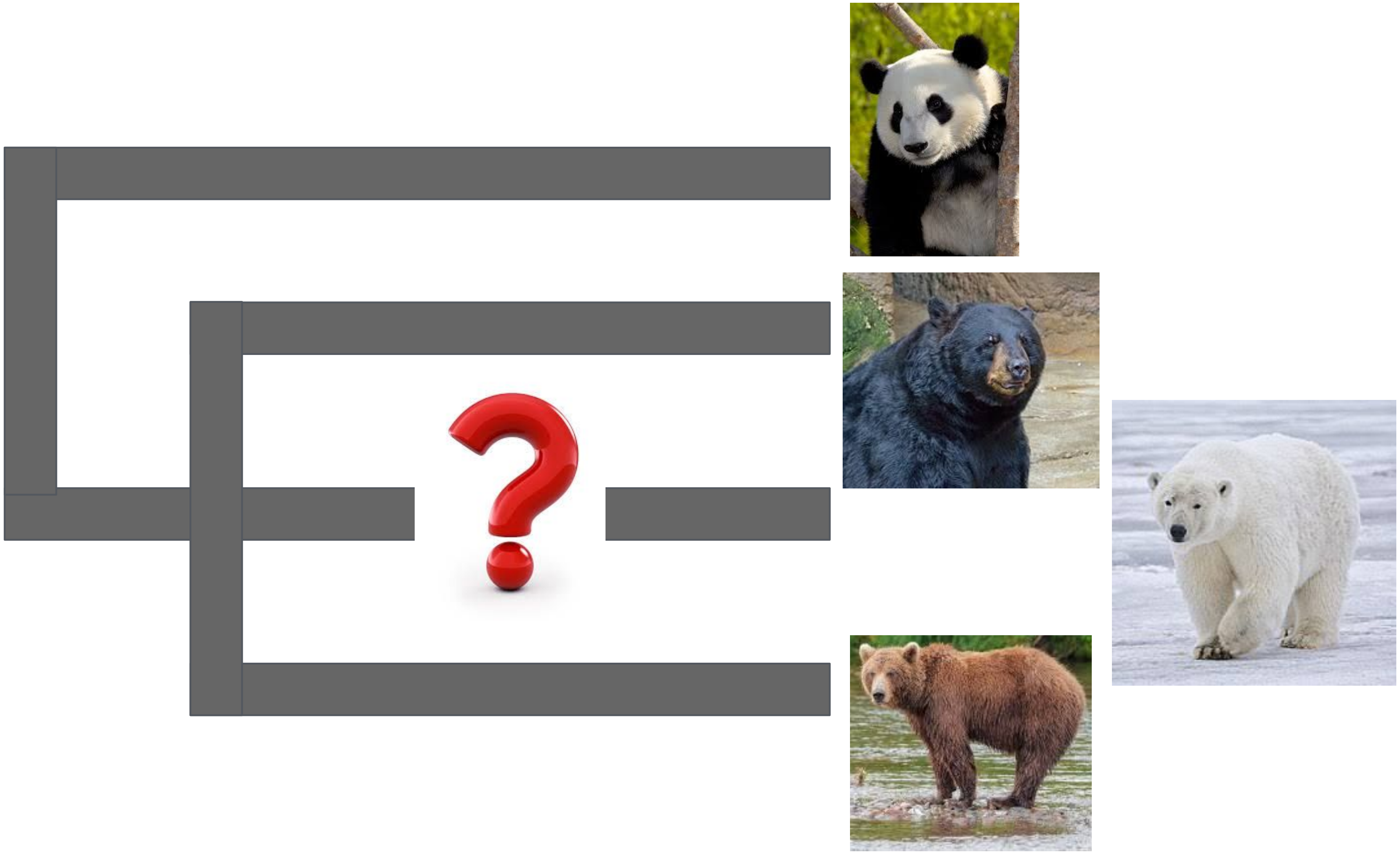
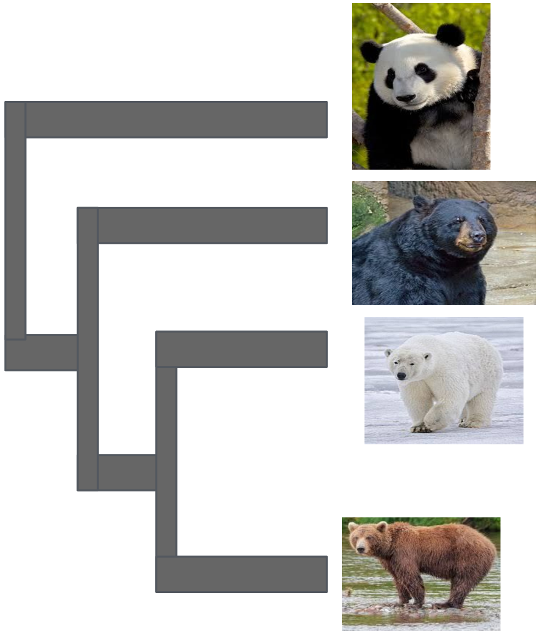


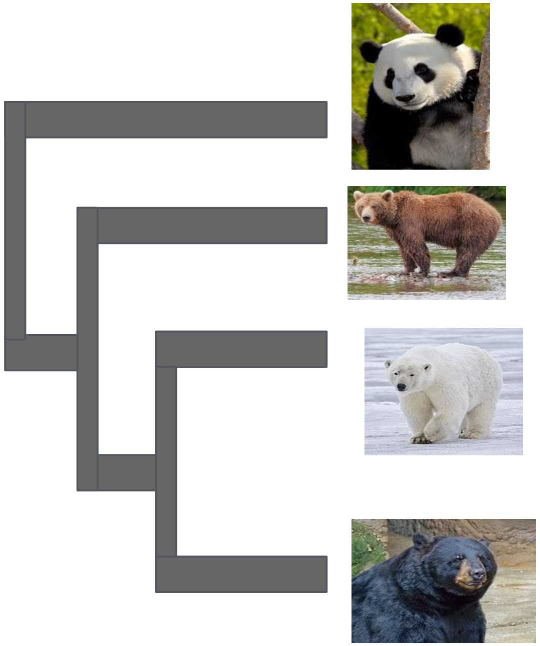
Analyzing gene tree/species tree conflict: hands-on session

Is the polar bear the sister group to the American black bear or the brown bear?

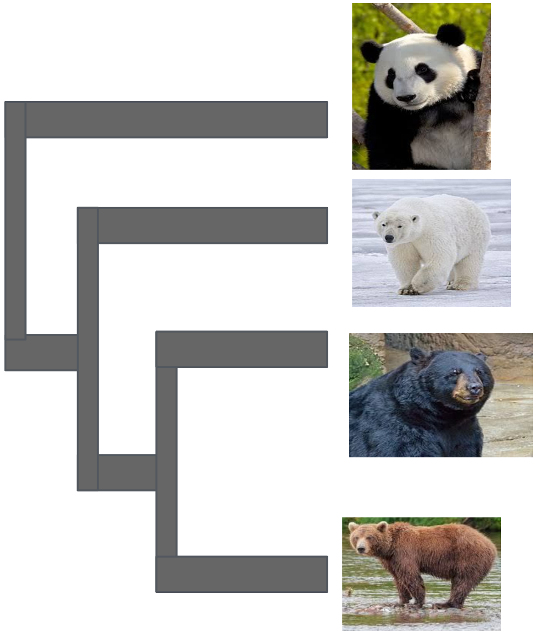
Second part of the tutorial: analyzing how the evolutionary trajectory of each individual orthogroup supports each of the three topologies.



Species Tree 1



Species Tree 2



Species Tree 3

Generating phylogenomic data matrices: hands-on session

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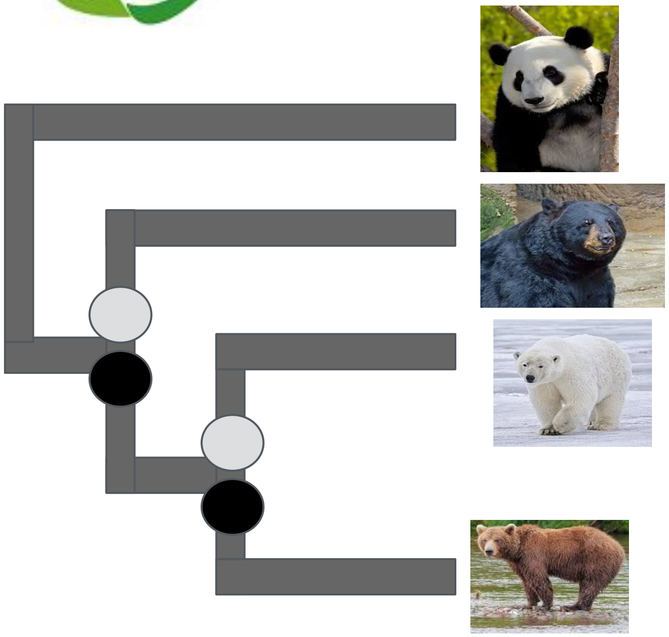


○ high support supermatrix

● high support indiv. gene trees (multispecies coalescent)

Abstract:

The interrelationships of the species within the genus *Ursus* has been contentious based on the analysis of a limited amount of molecular markers. Here, we sequenced full genomes of 16 specimens of the American black bear, brown bear, polar bear and giant panda and explored their phylogenetic relationships through a phylogenomic spyglass. Our results, based on the analysis of multiple supermatrices to account for the effect of missing data, compositional heterogeneity and other confounding factors, **as well as accounting for incongruence between individual gene trees under the multispecies coalescent model**, strongly support a sister relationship of the brown bear to the polar bear. Our findings pave te road towards understanding bear evolution at a deeper level.

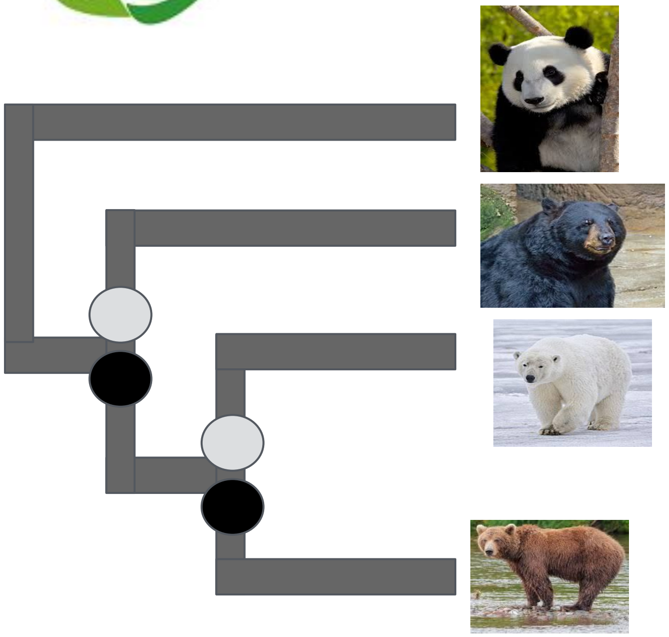
Generating phylogenomic data matrices: hands-on session

Is the polar bear the sister group to the American black bear or the brown bear?

SCIENCE & NATURE

Phylogenomics illuminate the interrelationships of the genus *Ursus* and supports the brown bear as sister group to the polar bear

Authors: Participants of the 2023 Workshop on Genomics český Krumlov ('molekulos')



○ high support supermatrix

● high support indiv. gene trees (multispecies coalescent)

Abstract:

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trees under the multispecies coalescent model, strongly support a sister relationship of the brown bear to the polar bear. Our findings pave te road towards understanding bear evolution at a deeper level.

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