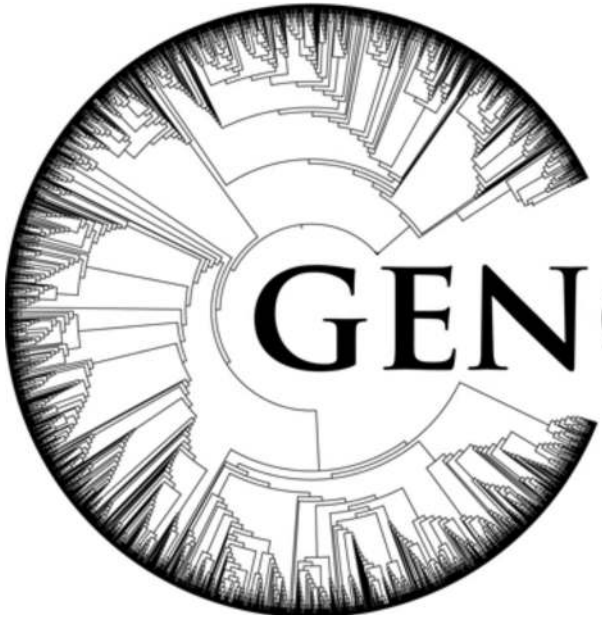
(A VERY SHORT INTRO TO)

PHYLOGENOMICS



Rosa Fernández

Institute of Evolutionary Biology (CSIC-UPF)

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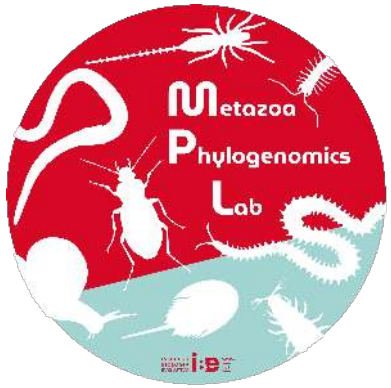
rosa.fernandez@ibe.upf-csic.es



A little bit about myself

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Madrid (PhD)

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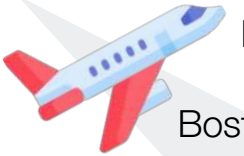

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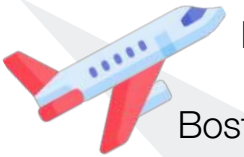

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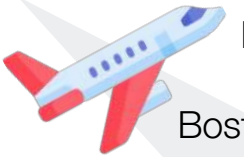

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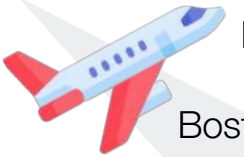

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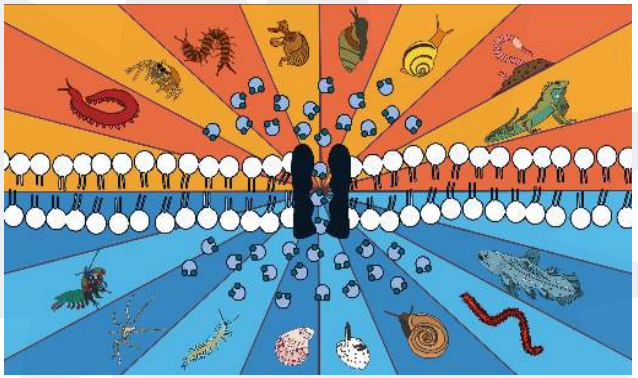

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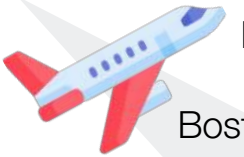

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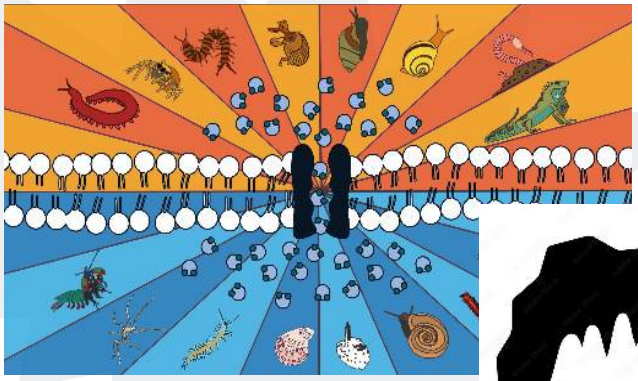

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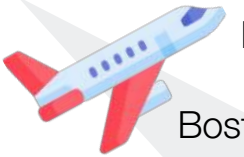

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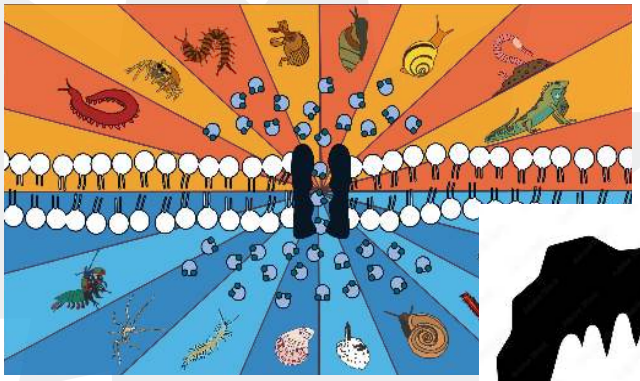

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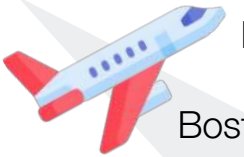

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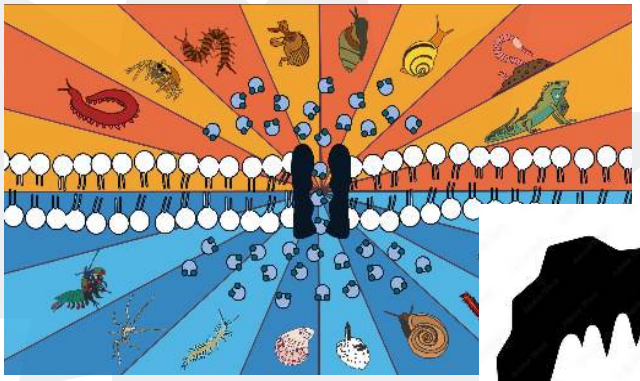

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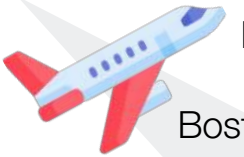

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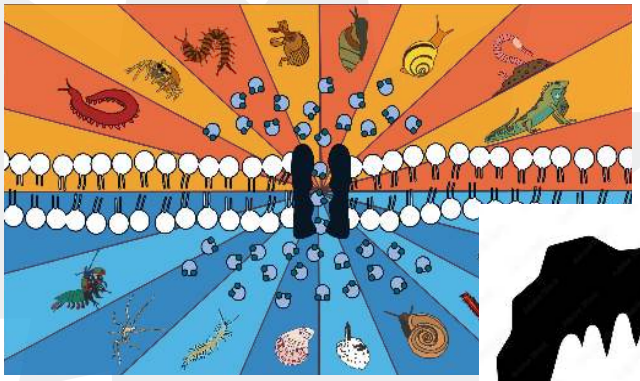

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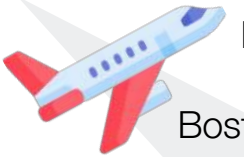

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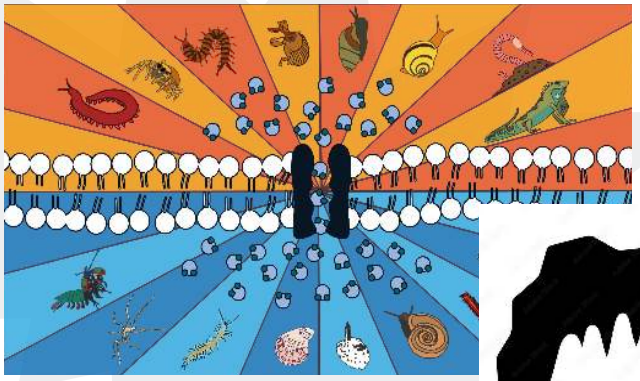

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(Workshop on Phylogenomics 2017)

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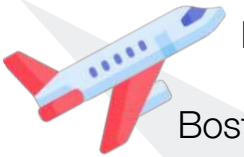

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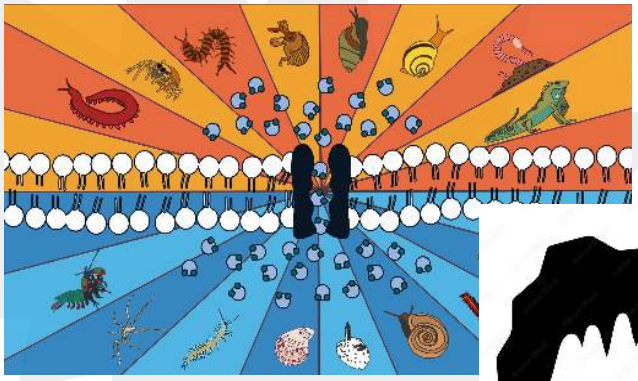

SPOILER ALERT: there will be BEARS!!

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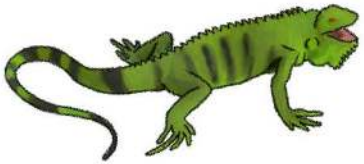
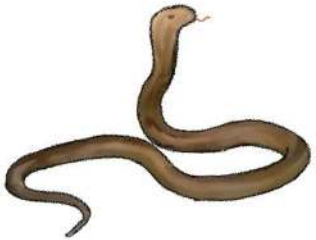
Which came first, the chicken or the egg?

Which came first, the chicken or the egg?

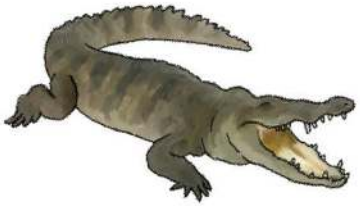
Turtles



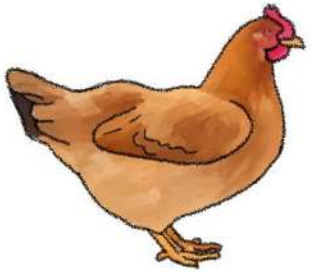
Lizards



Snakes

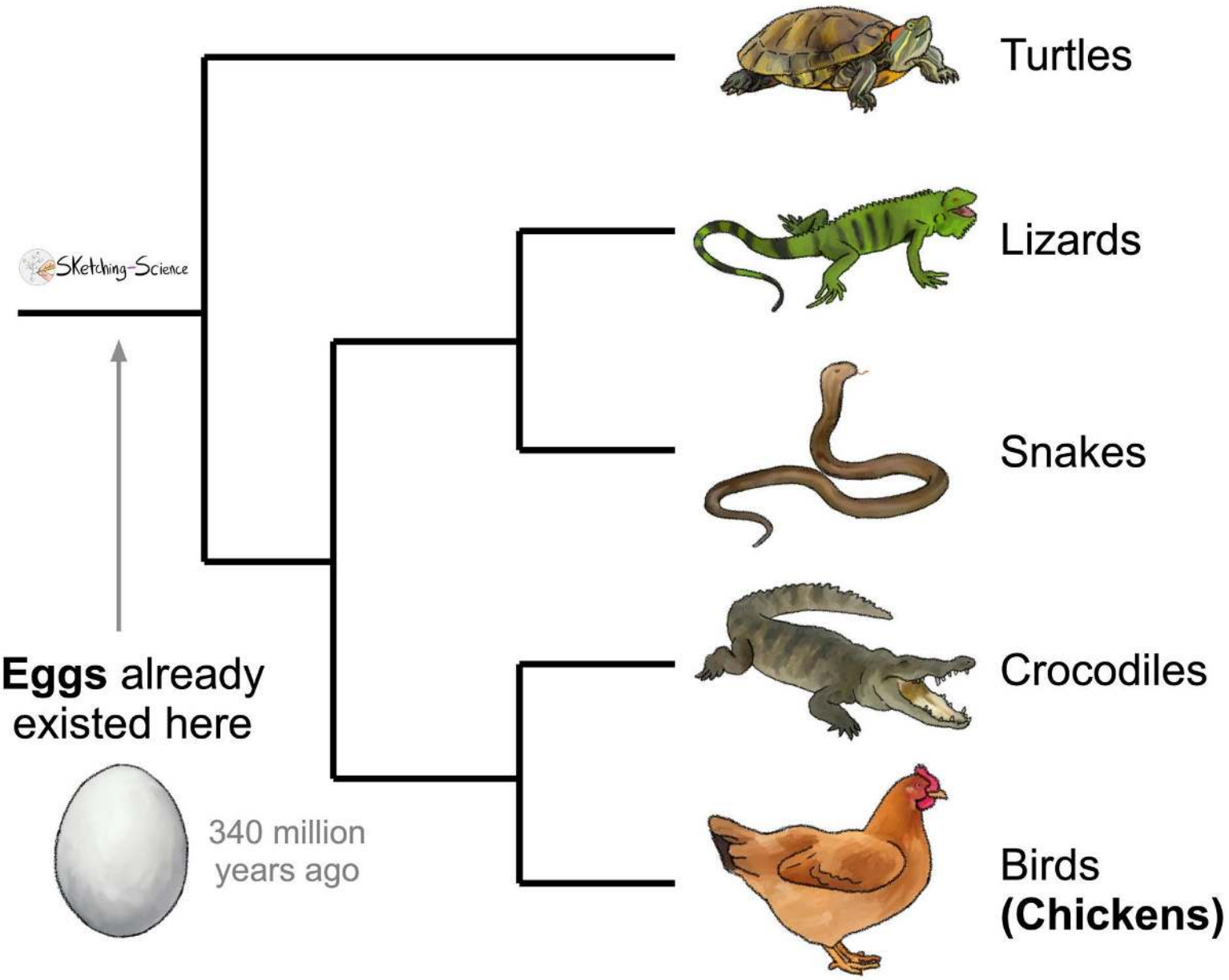


Crocodiles

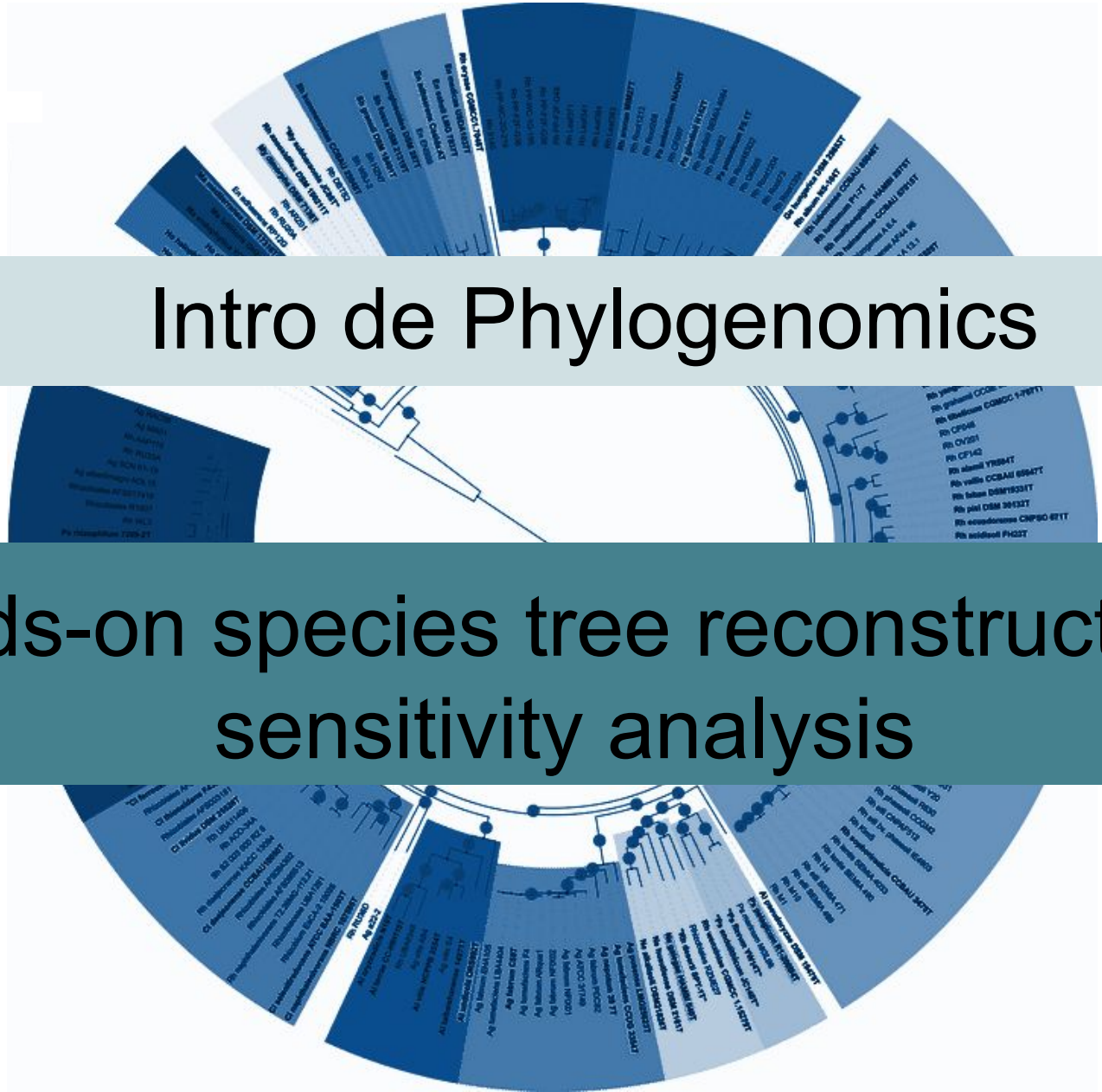


Birds
(Chickens)

Which came first, the chicken or the egg?



Content today's lecture

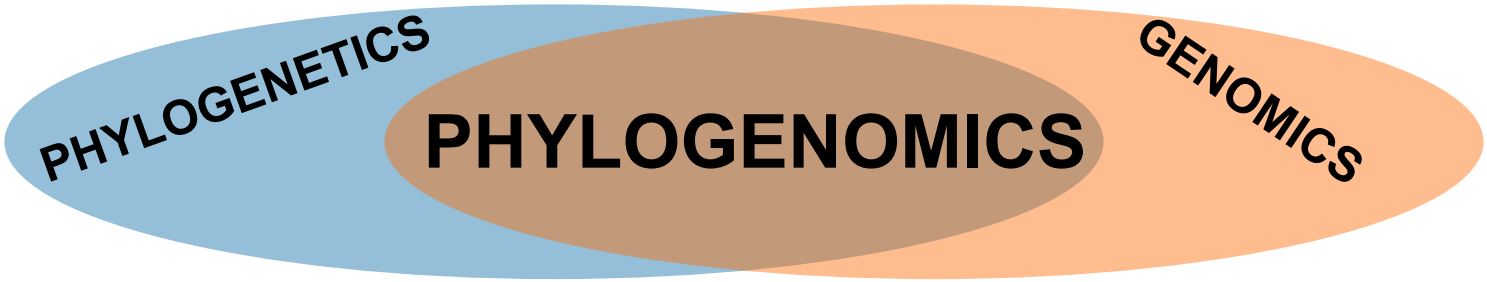


Intro de Phylogenomics

Hands-on species tree reconstruction & sensitivity analysis

Intro to Phylogenomics

Intro to Phylogenomics



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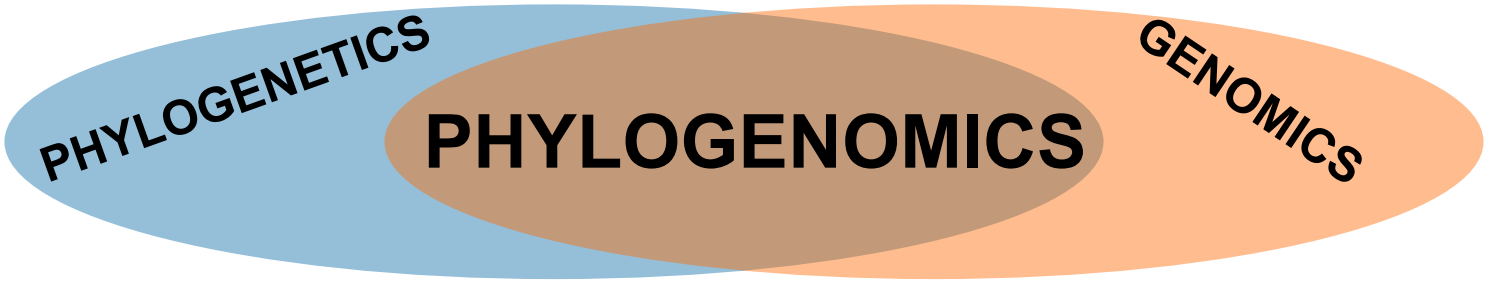

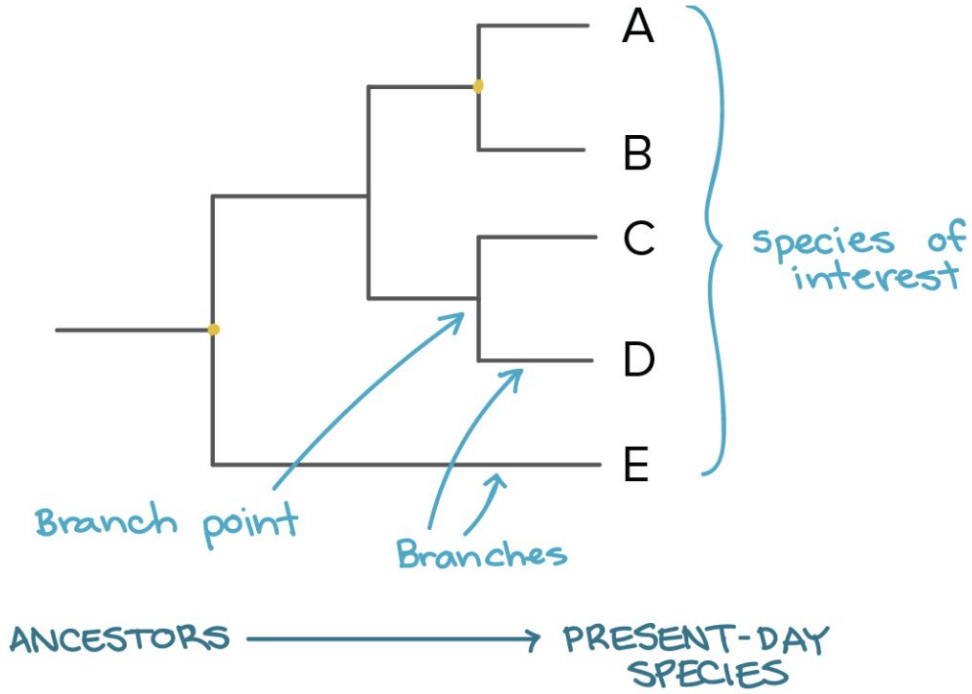

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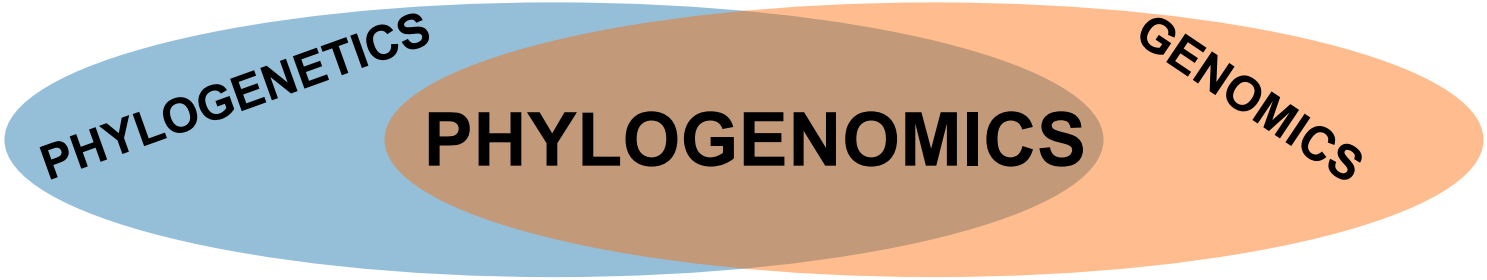
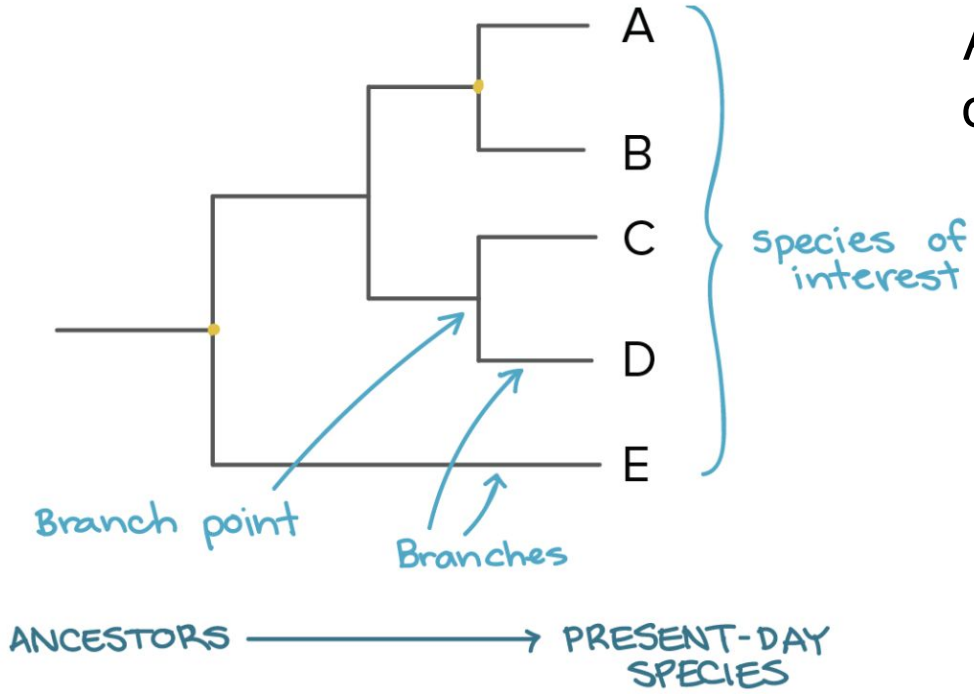
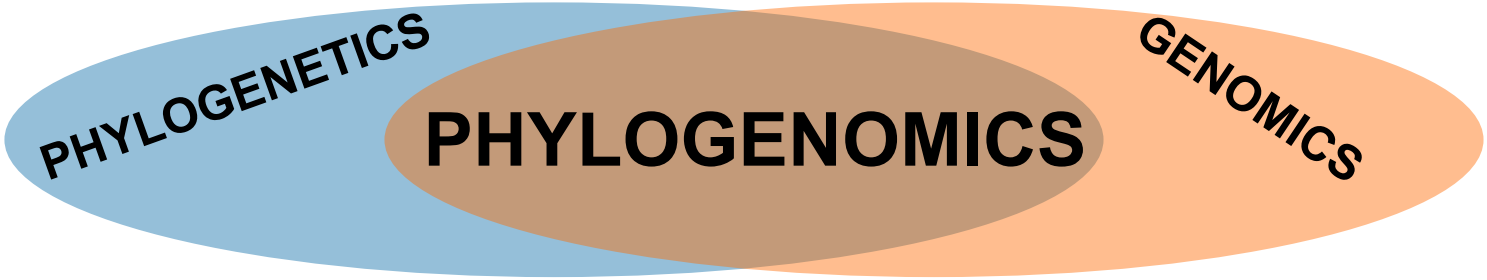
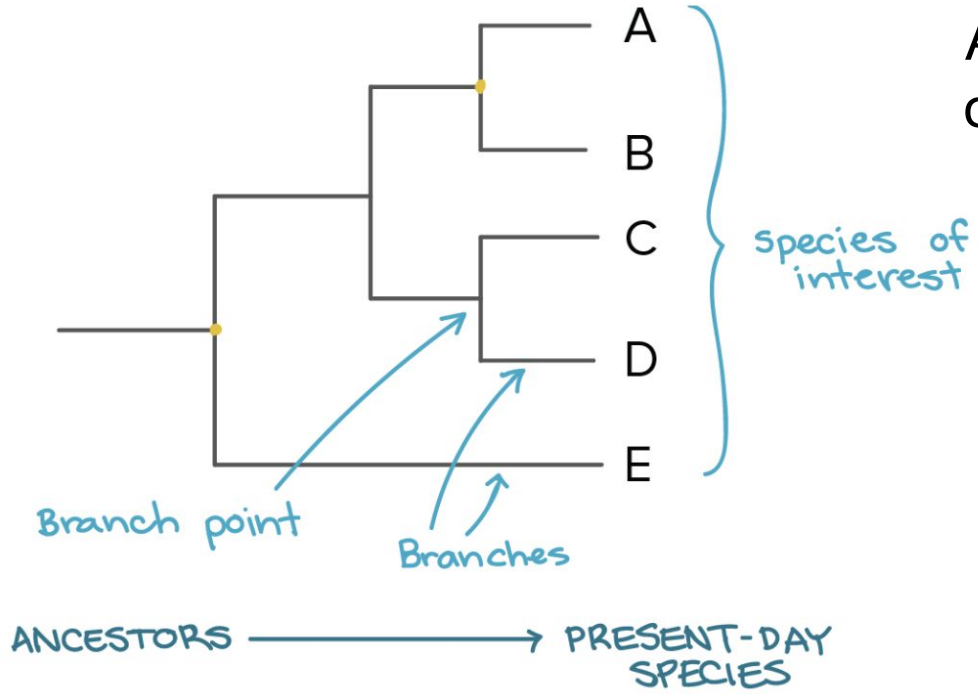




A **phylogenetic tree** is a hypothesis of how species or genes are related through evolution

Intro to Phylogenomics





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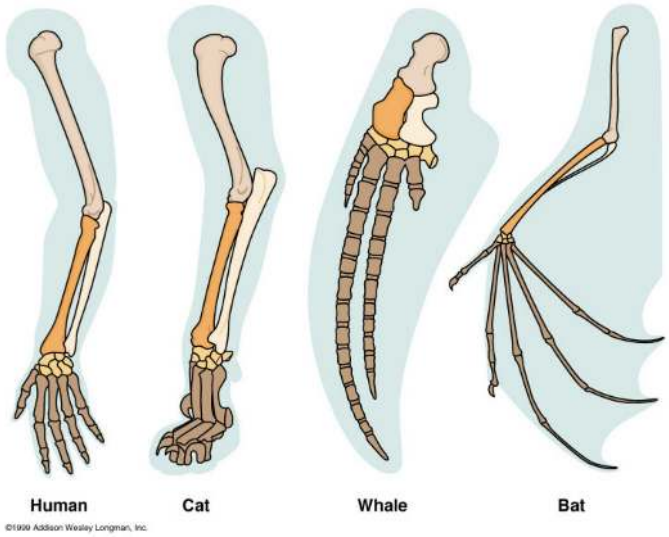

Morphological traits

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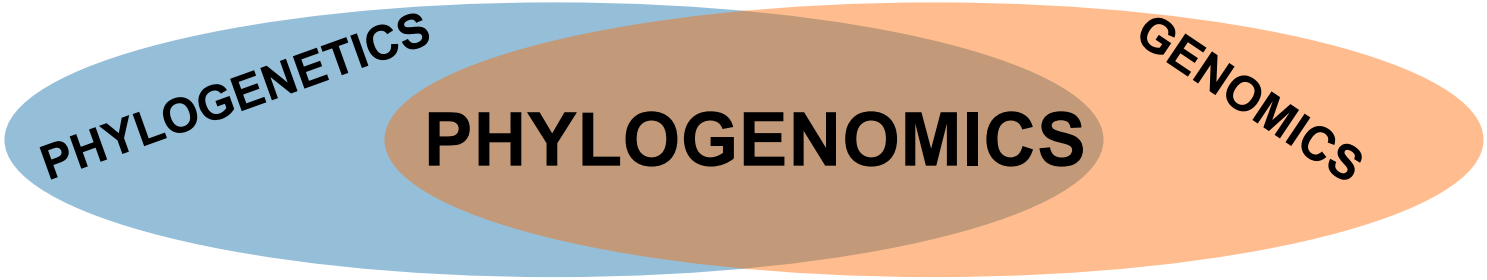

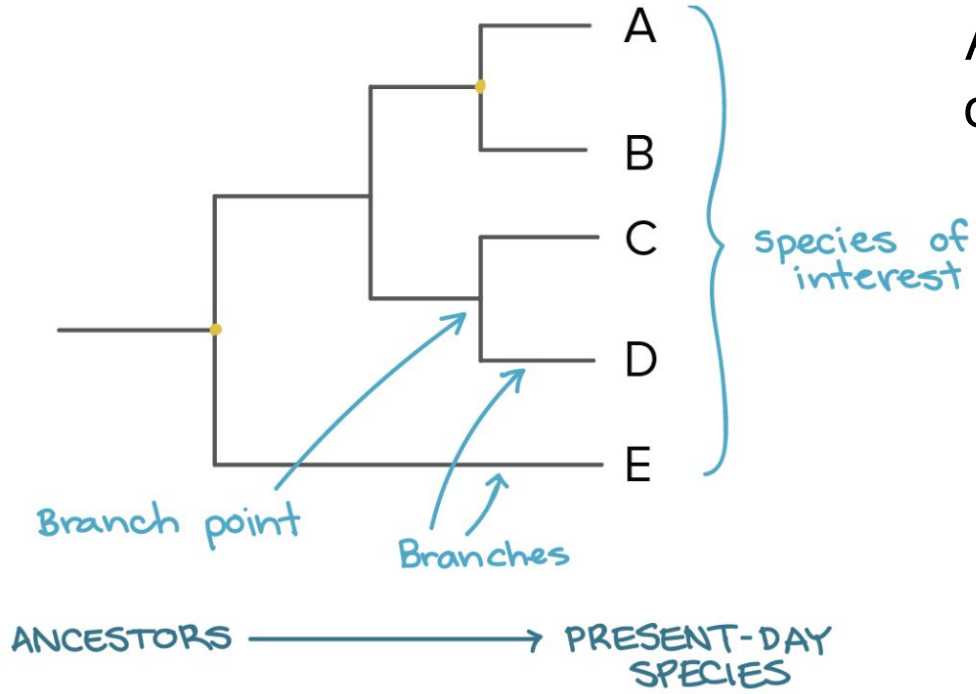

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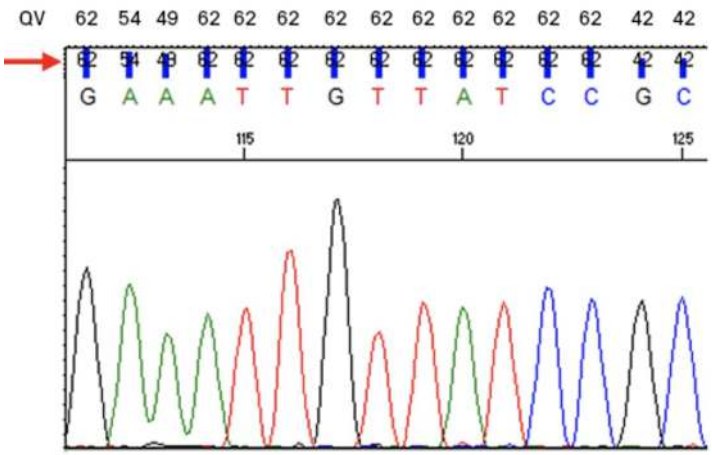
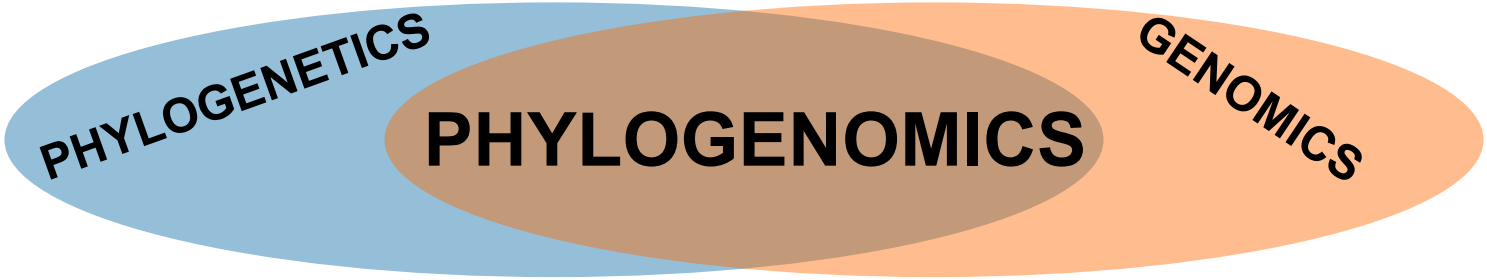
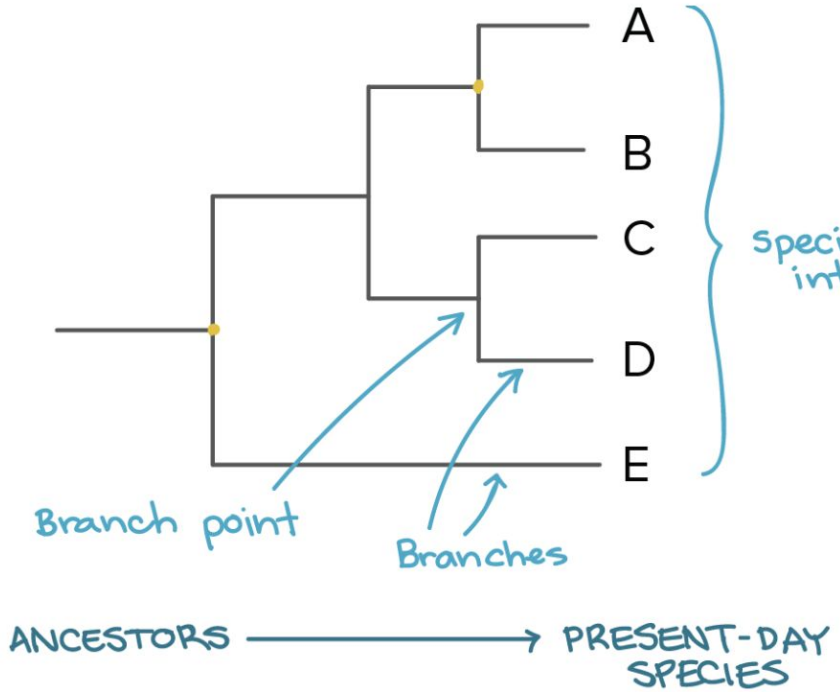


A few genes (eg, COI)

Intro to Phylogenomics





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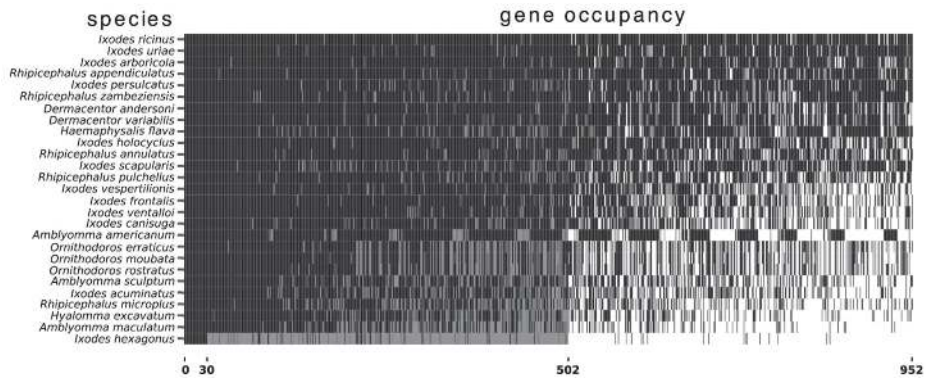

100s / 1,000s of genes

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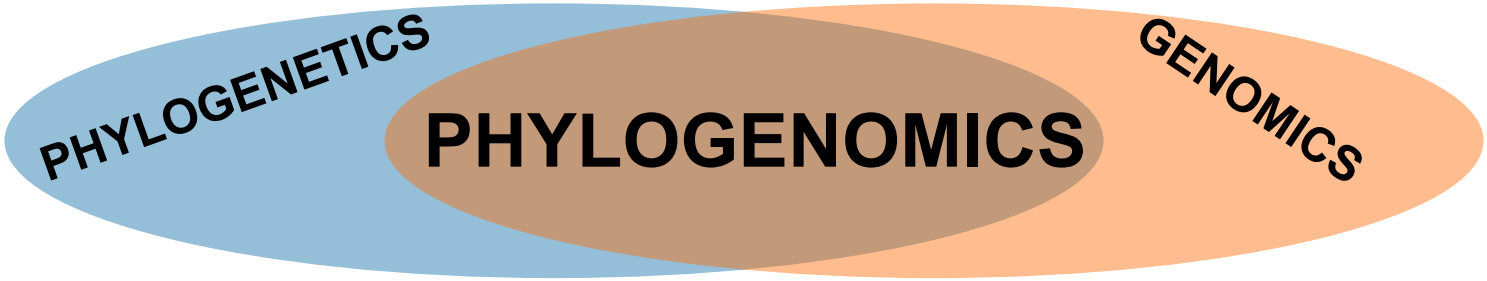

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Insight/Outlook

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

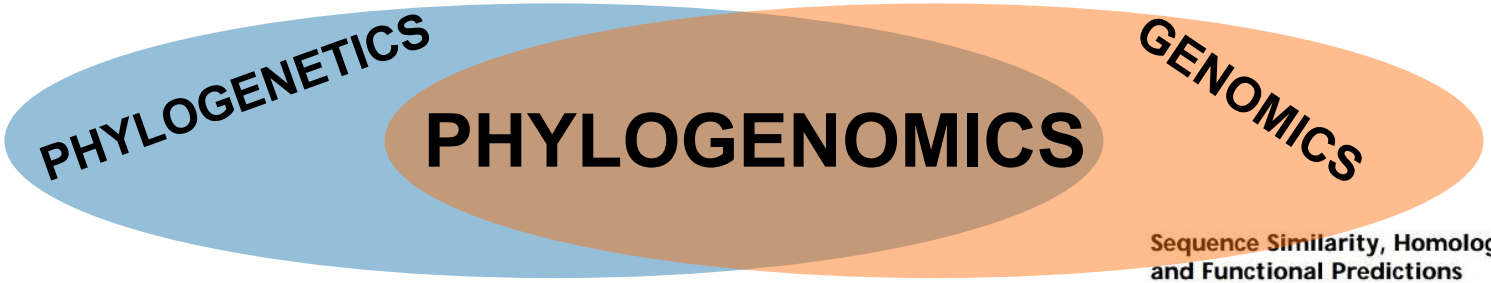
The ability to accurately predict gene function based on gene sequence is an important tool in many areas of biological research. Such predictions have become particularly important in the genomics age in which numerous gene sequences are generated with little or no accompanying experimentally determined 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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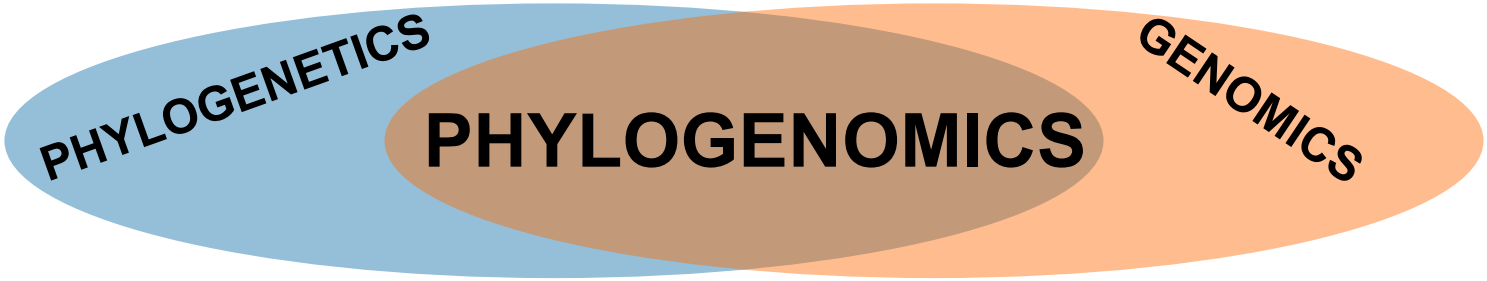
Sequence Similarity, Homology, and Functional Predictions

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

Intro to Phylogenomics



8:163–167 ©1998 by Cold Spring Harbor Laboratory Press ISSN 1054-9803/98 $5.00; www.genome.org

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

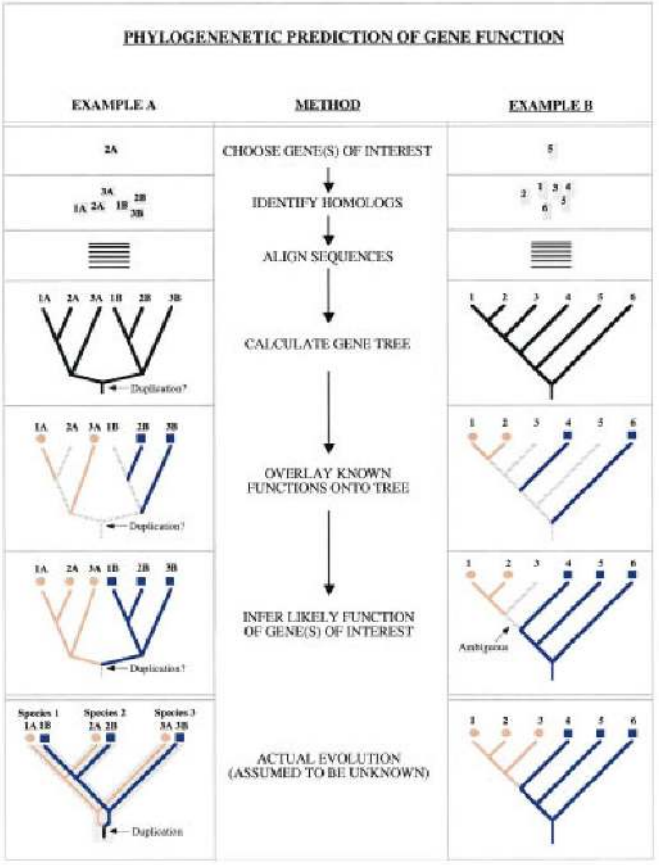
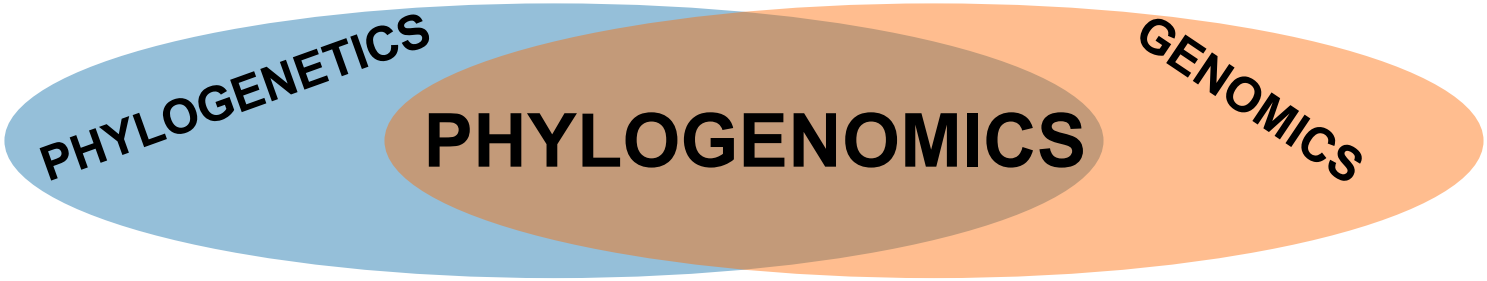


Figure 1 Outline of a phylogenomic methodology. In this method, information about the evolutionary relationships among genes is used to predict the functions of uncharacterized genes (see text for details). Two hypothetical scenarios are presented and the path of trying to

Intro to Phylogenomics



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

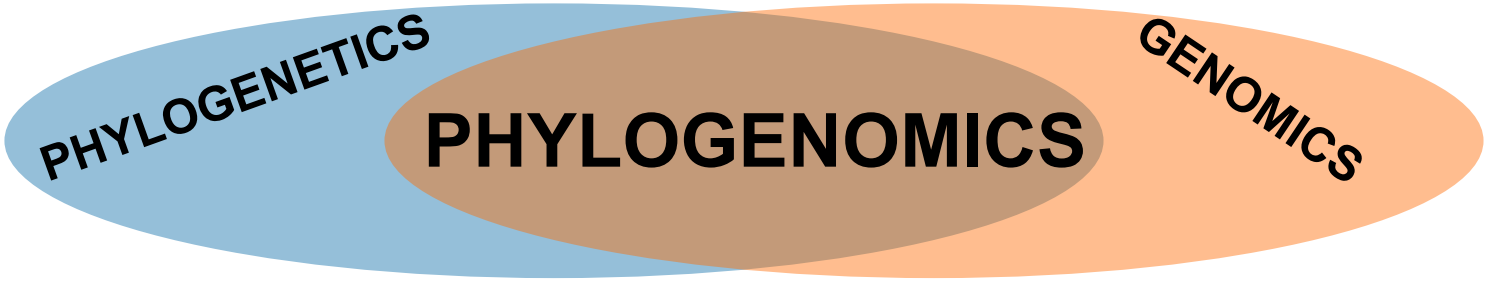
The analysis of 100 genes supports the grouping of three highly divergent amoebae: *Dictyostelium*, *Entamoeba*, and *Mastigamoeba*

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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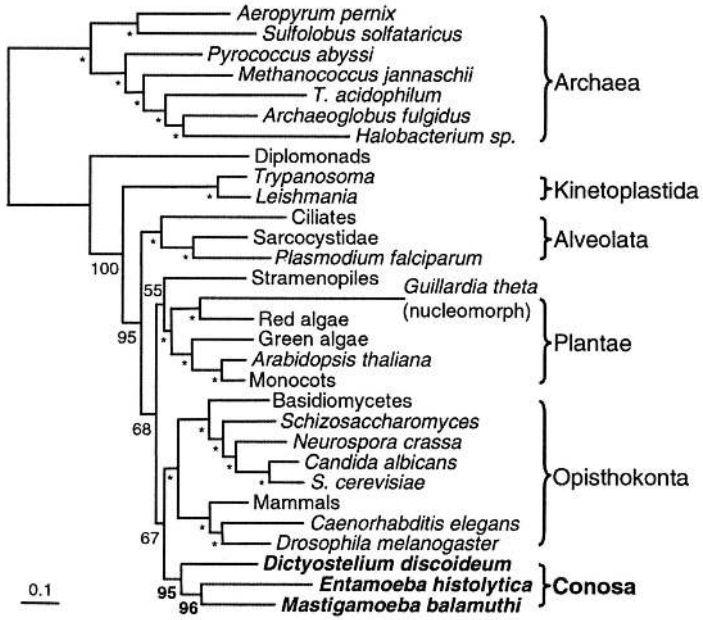
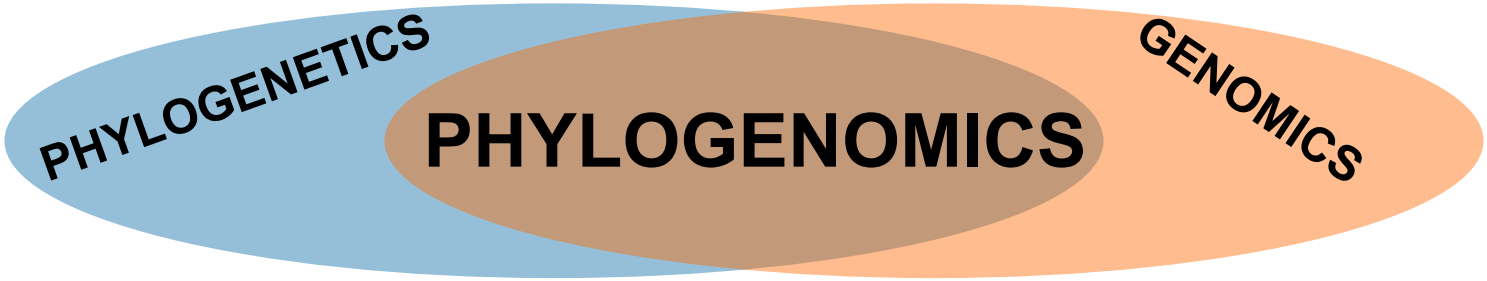
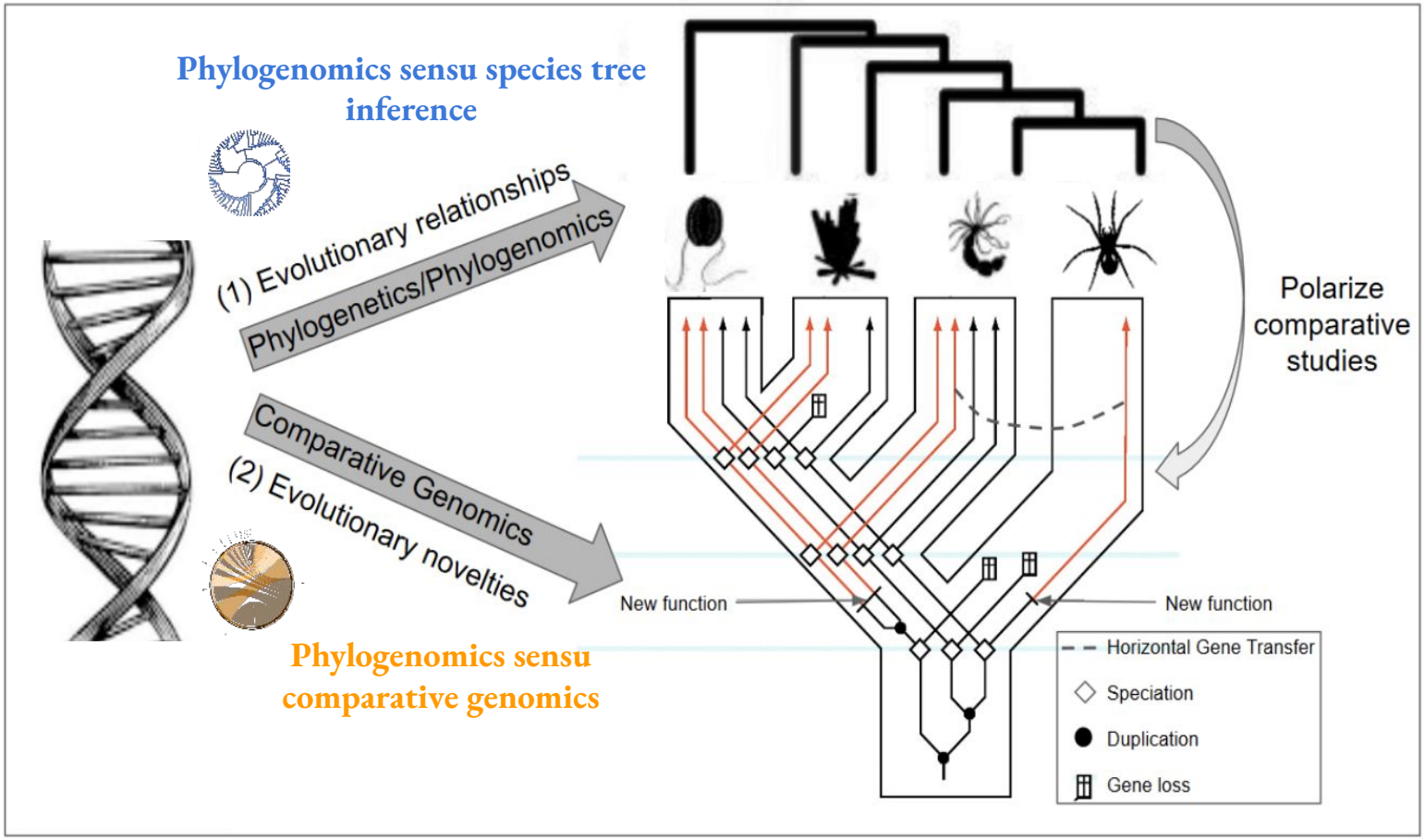


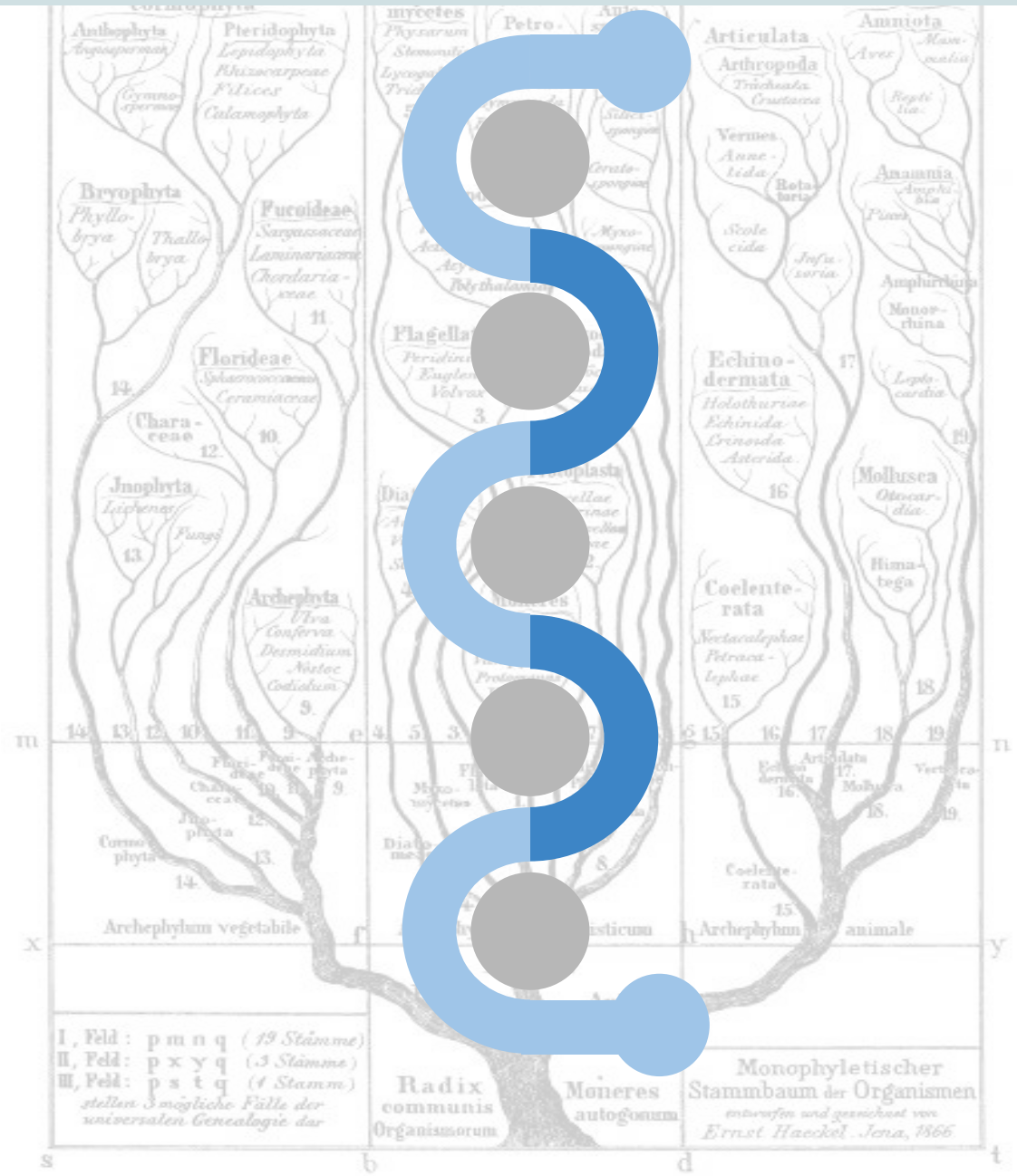
ML tree based on 25,032 aa positions. * indicates a constrained node. We used the JTT model, without taking into account among-sites rate variation. The branch lengths have been computed on the concatenated sequences. BVs were obtained by bootstrapping the 123 genes.

Intro to Phylogenomics





How to infer a species tree



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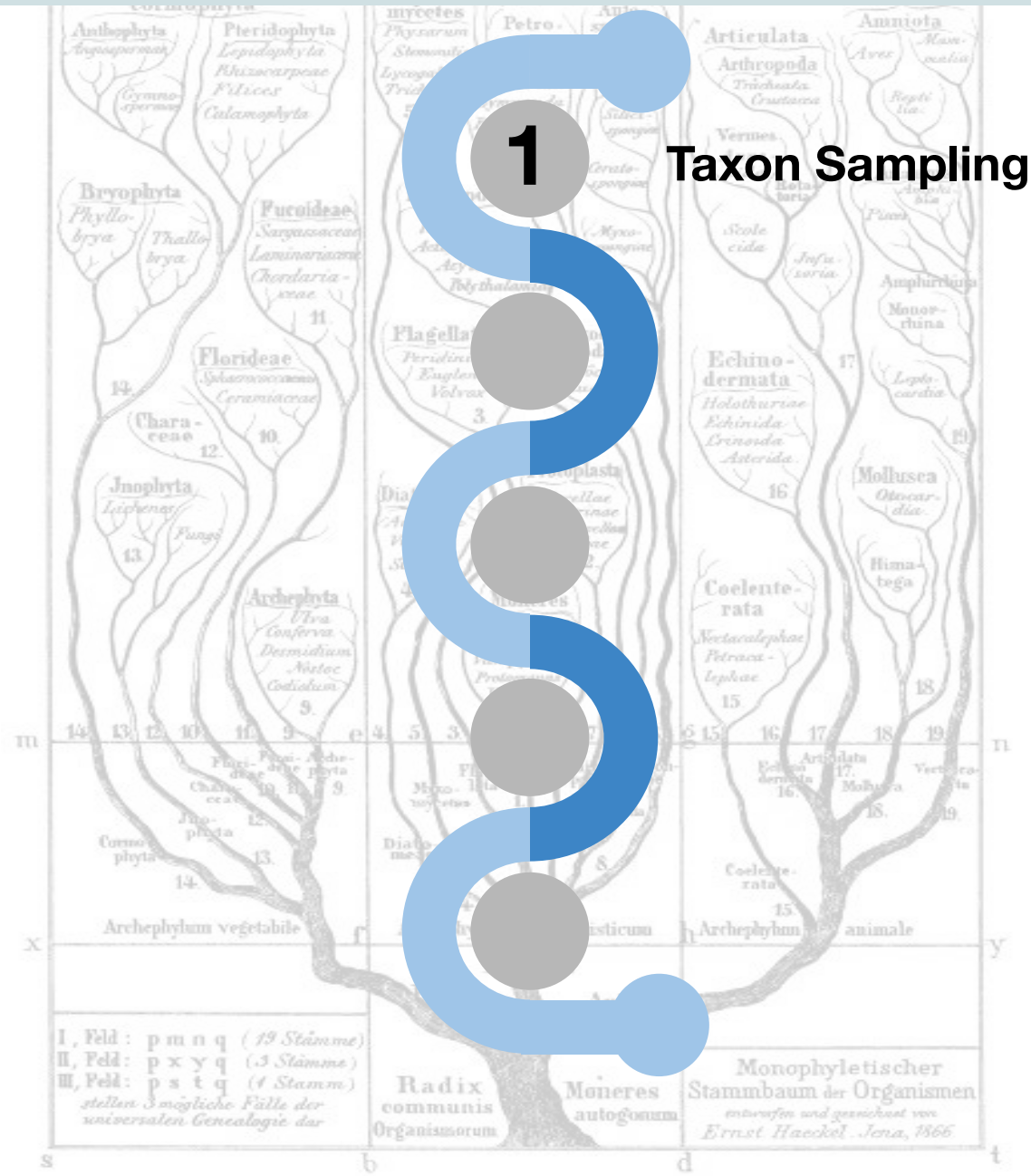

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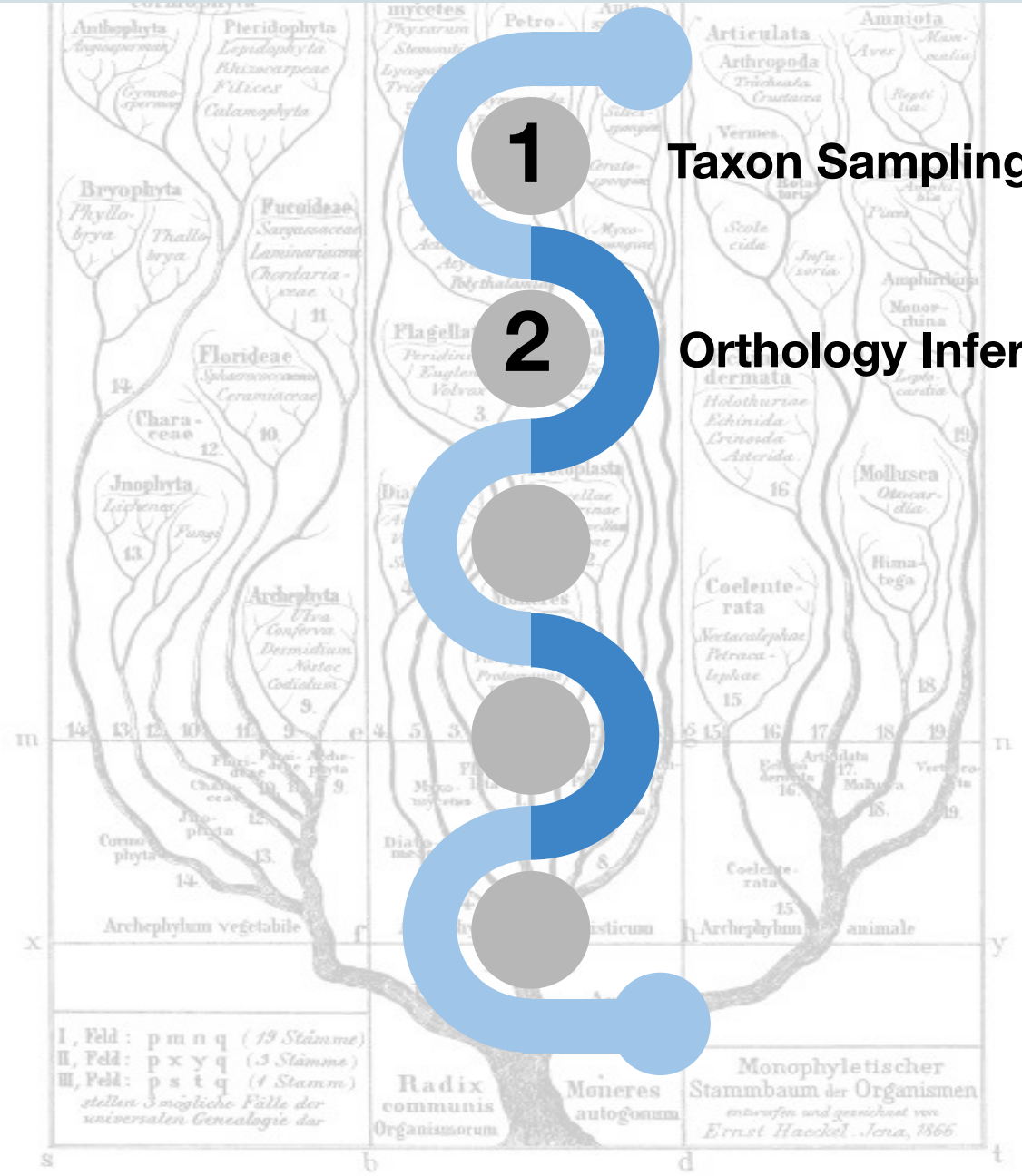

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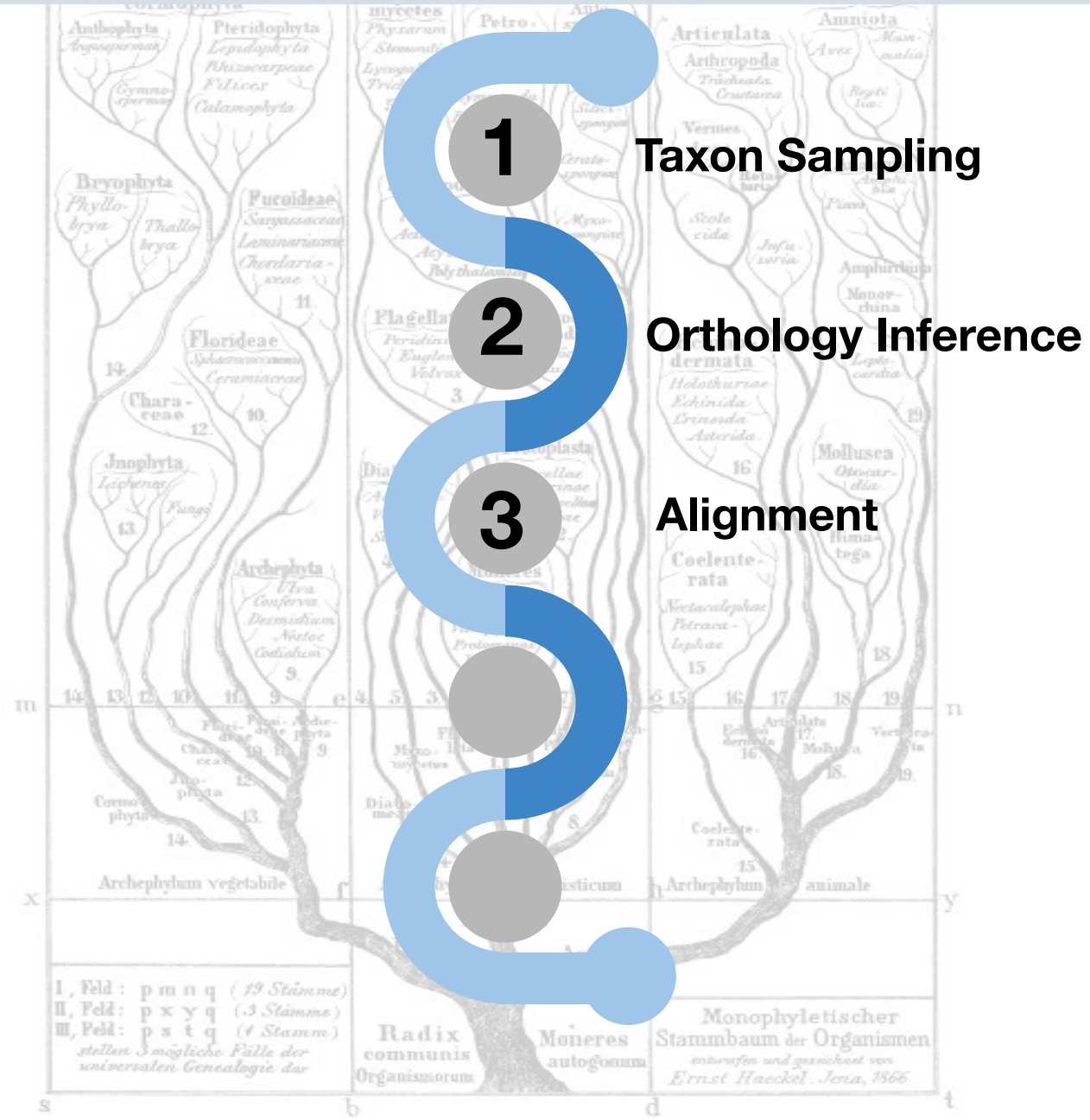

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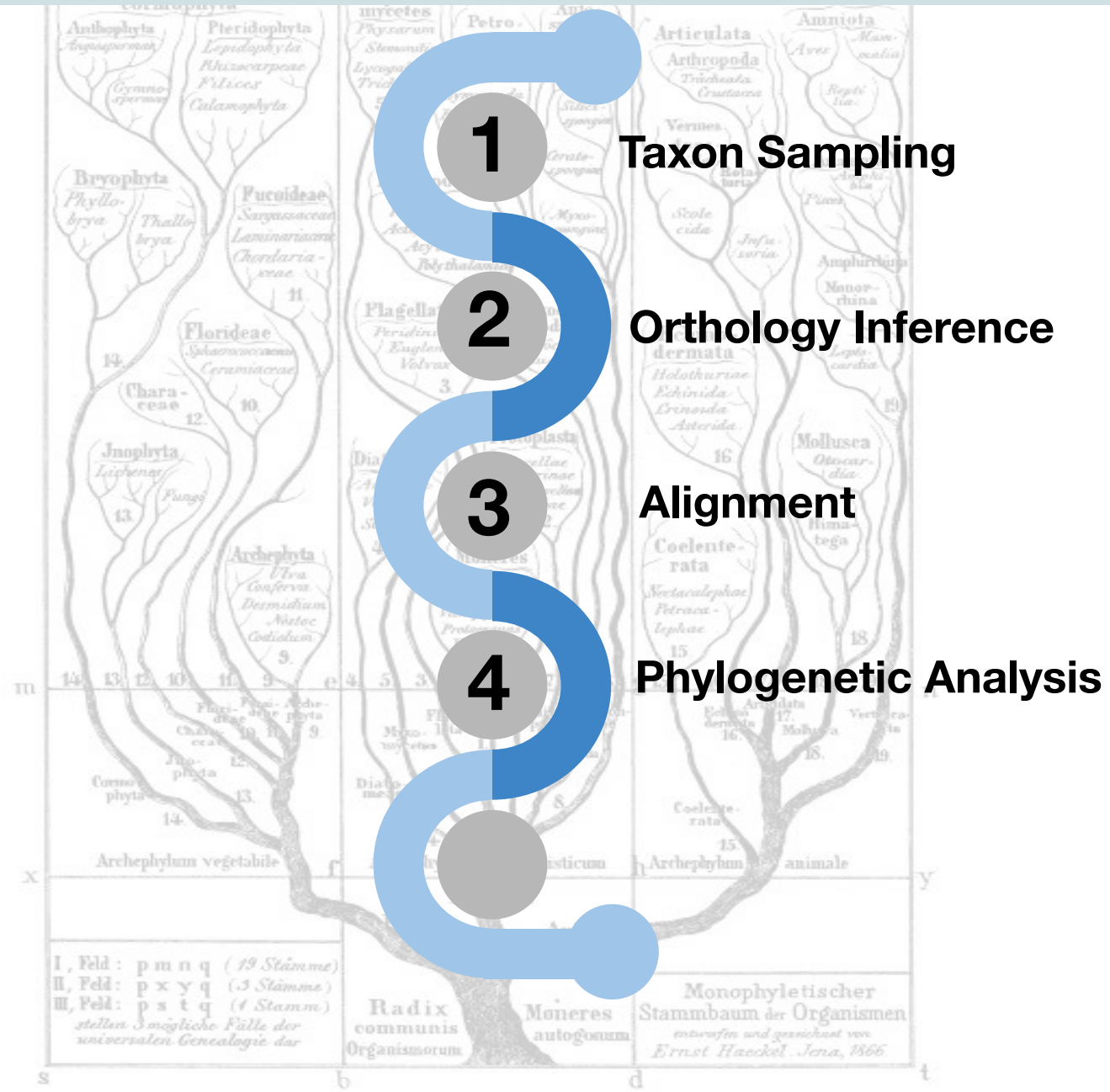

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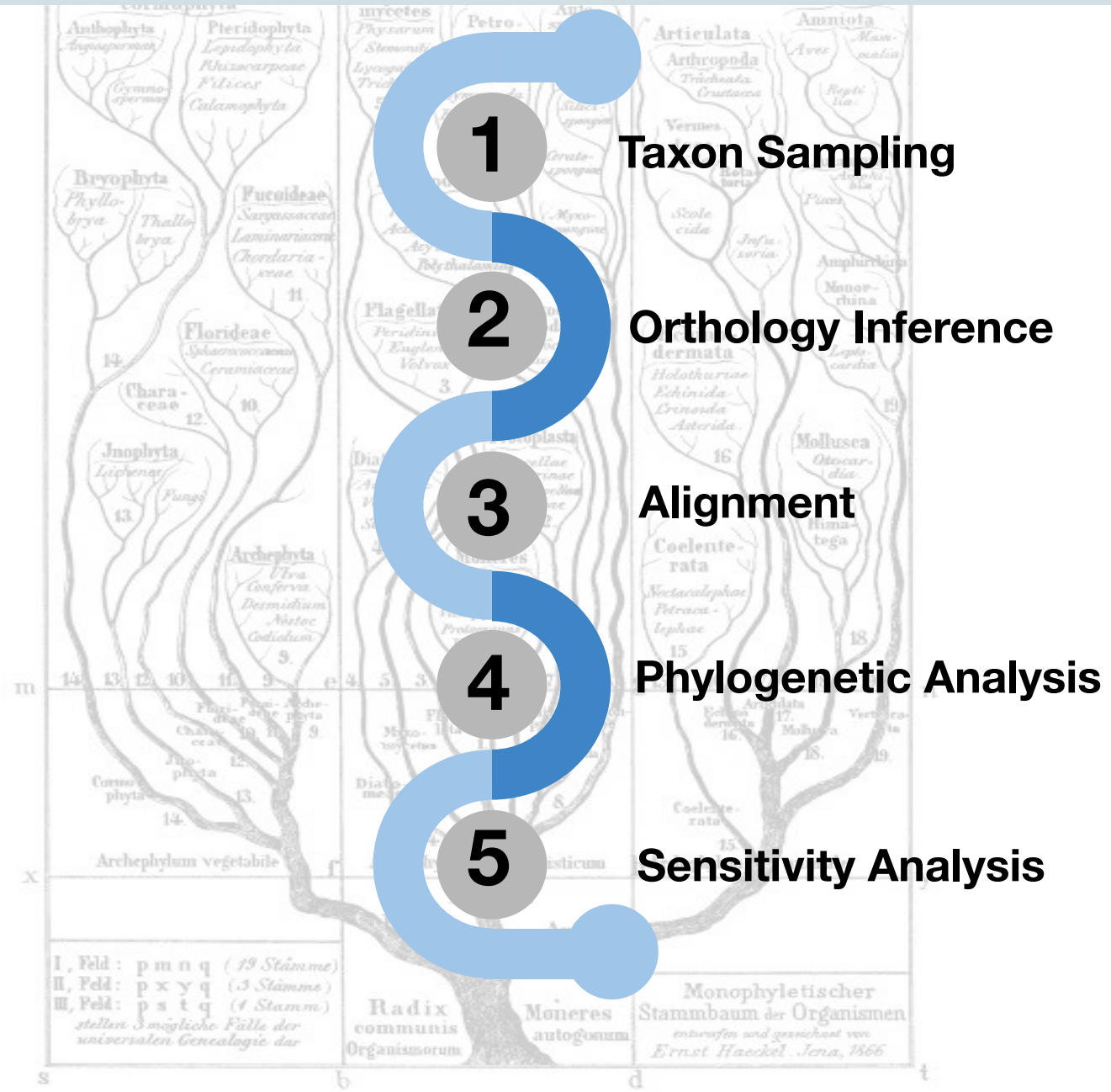

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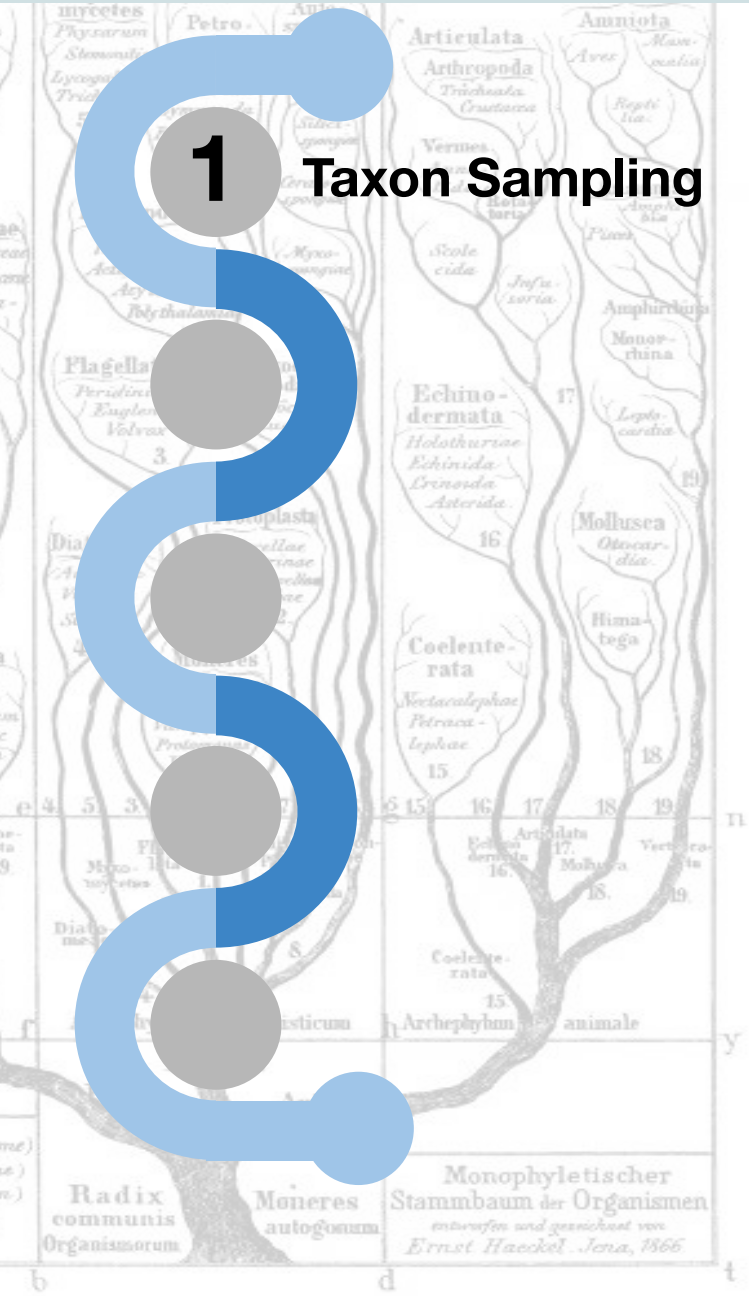

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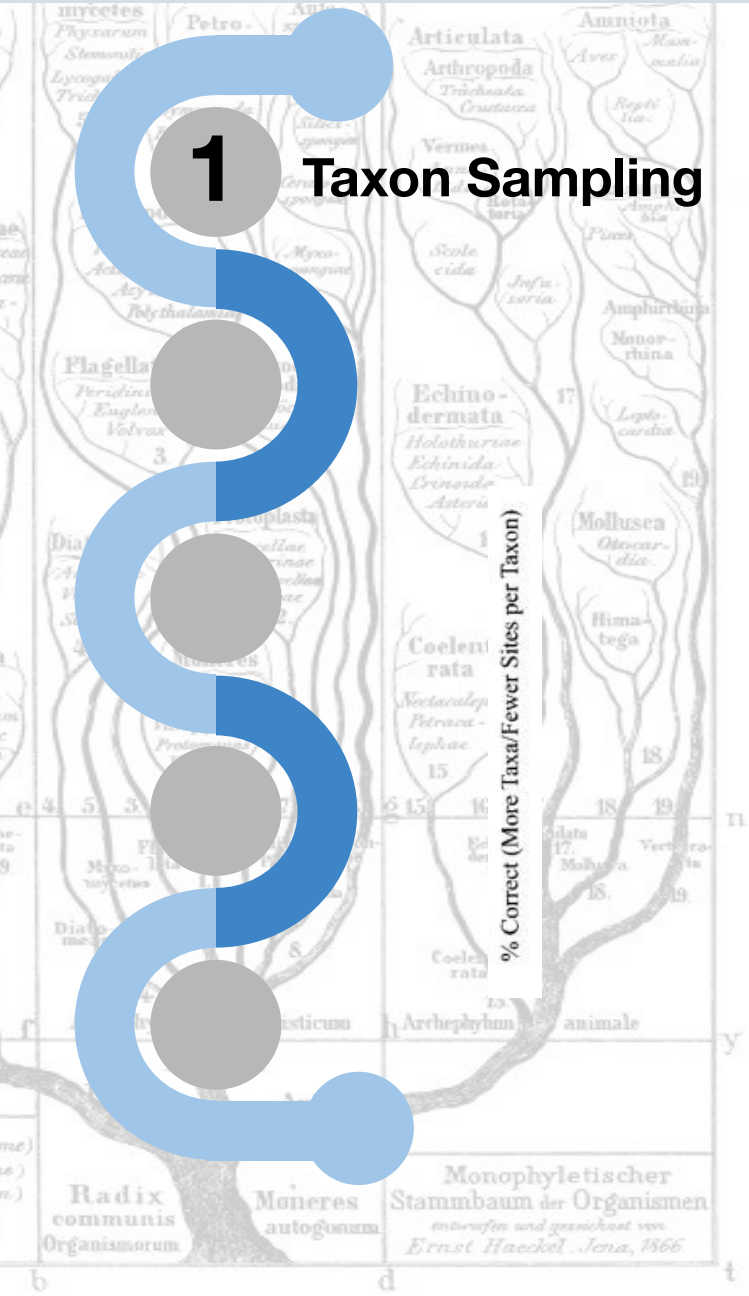

Key message: taxon sampling matters <u>a lot</u>

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

How to infer a species tree

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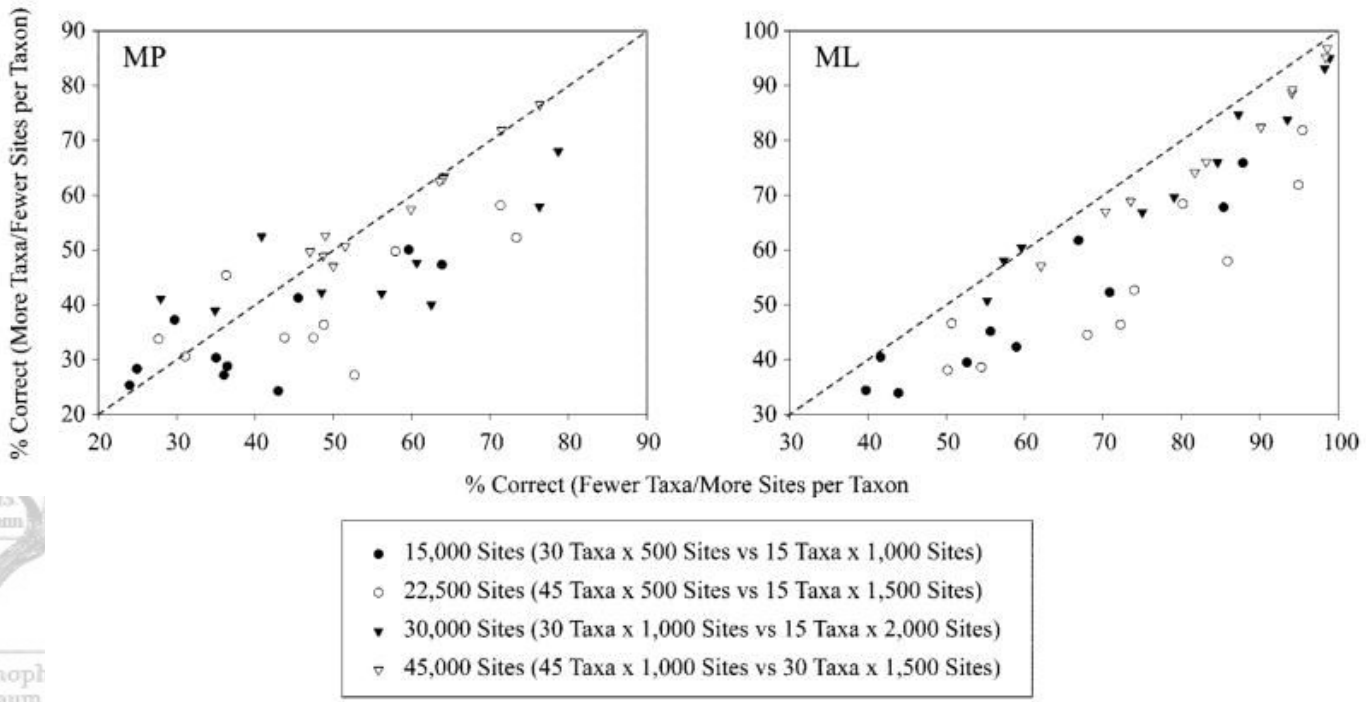

Rosenberg & Kumar 2003

How to infer a species tree

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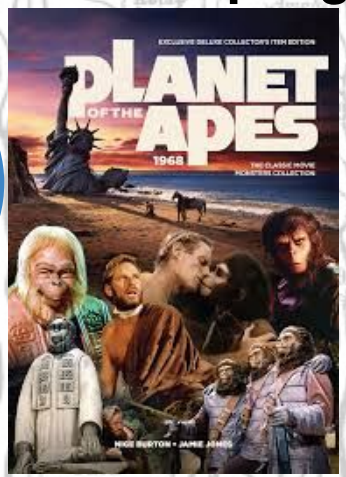

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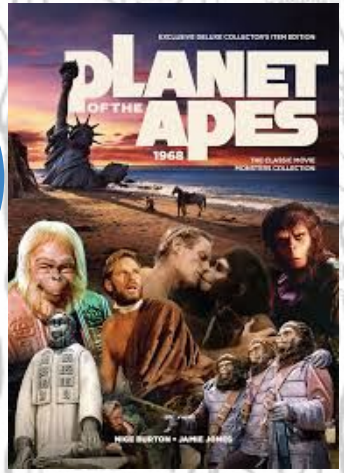

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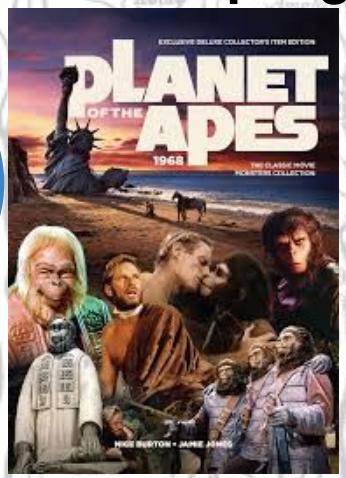

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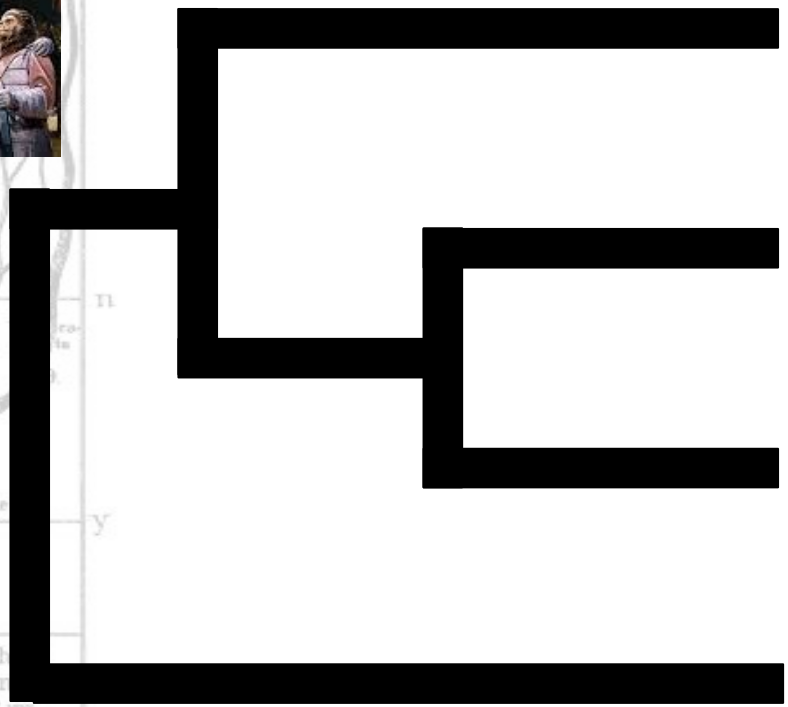

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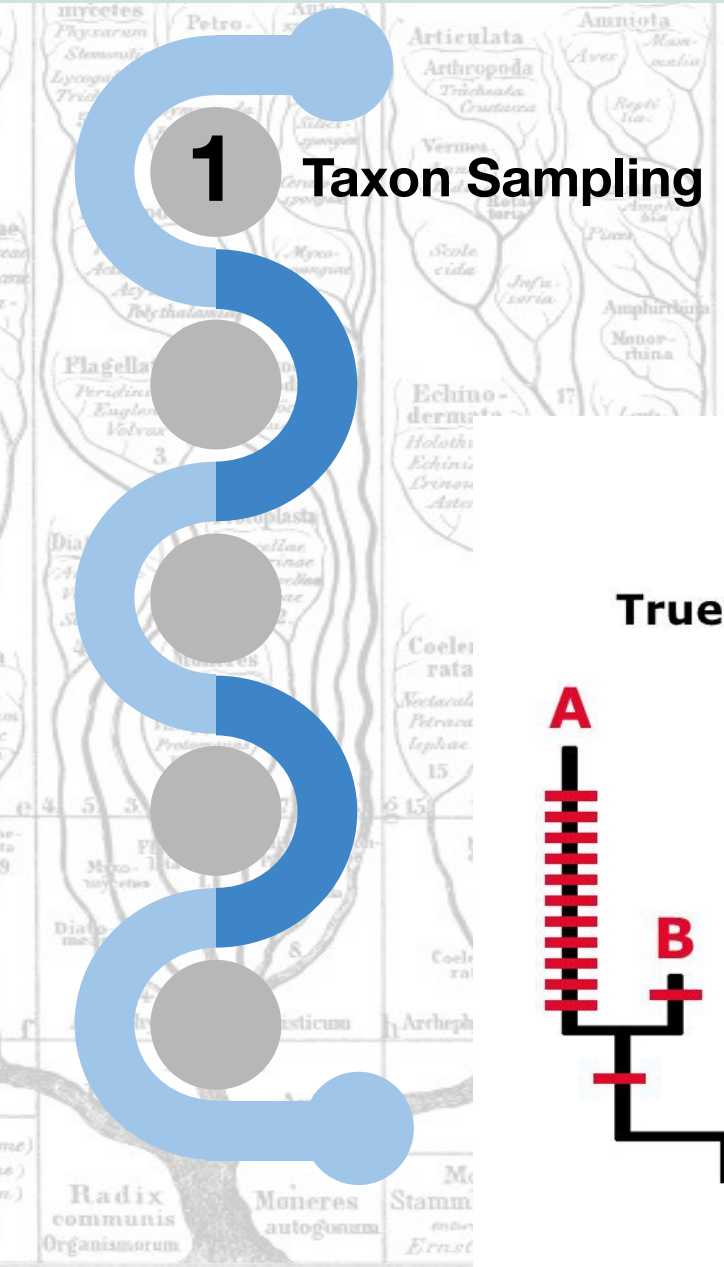

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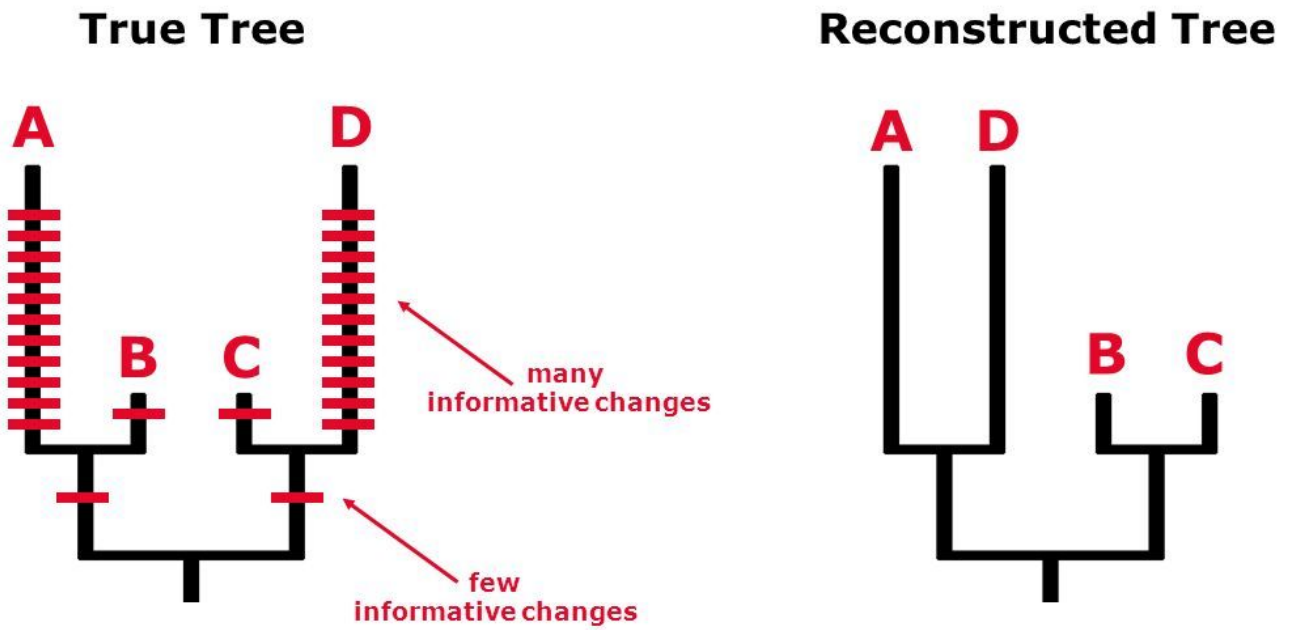
Long Branch Attraction



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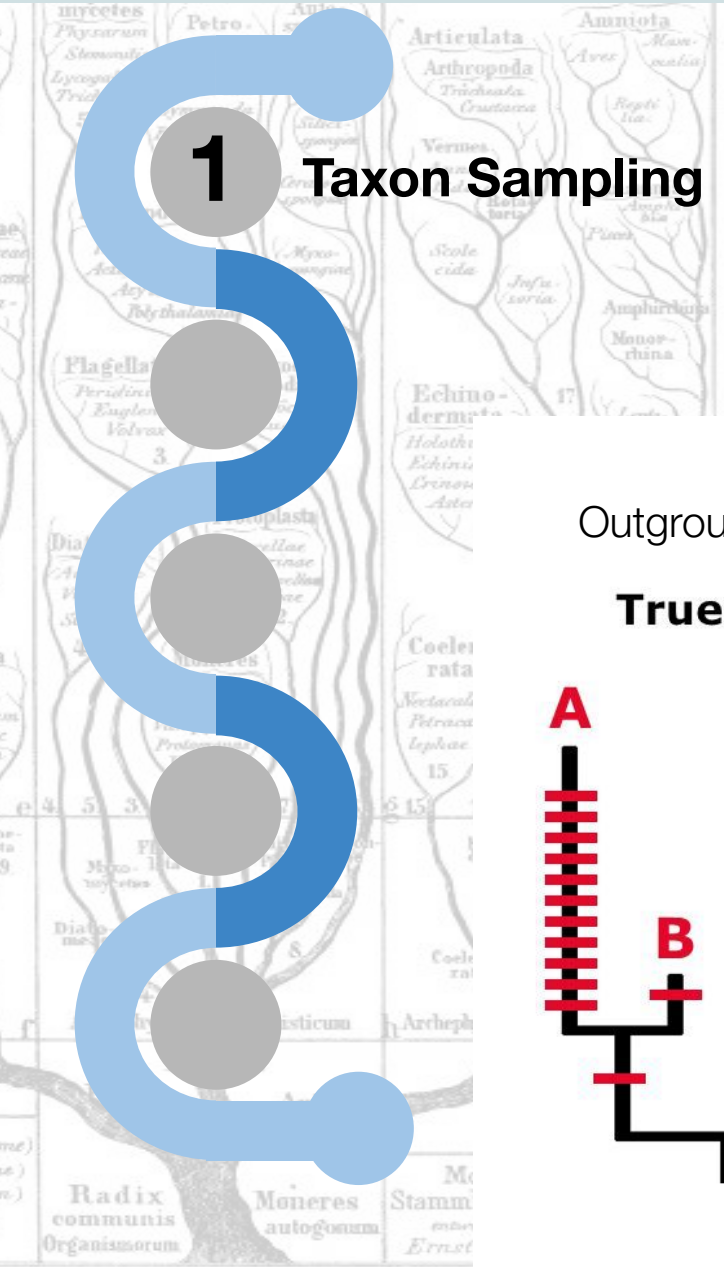

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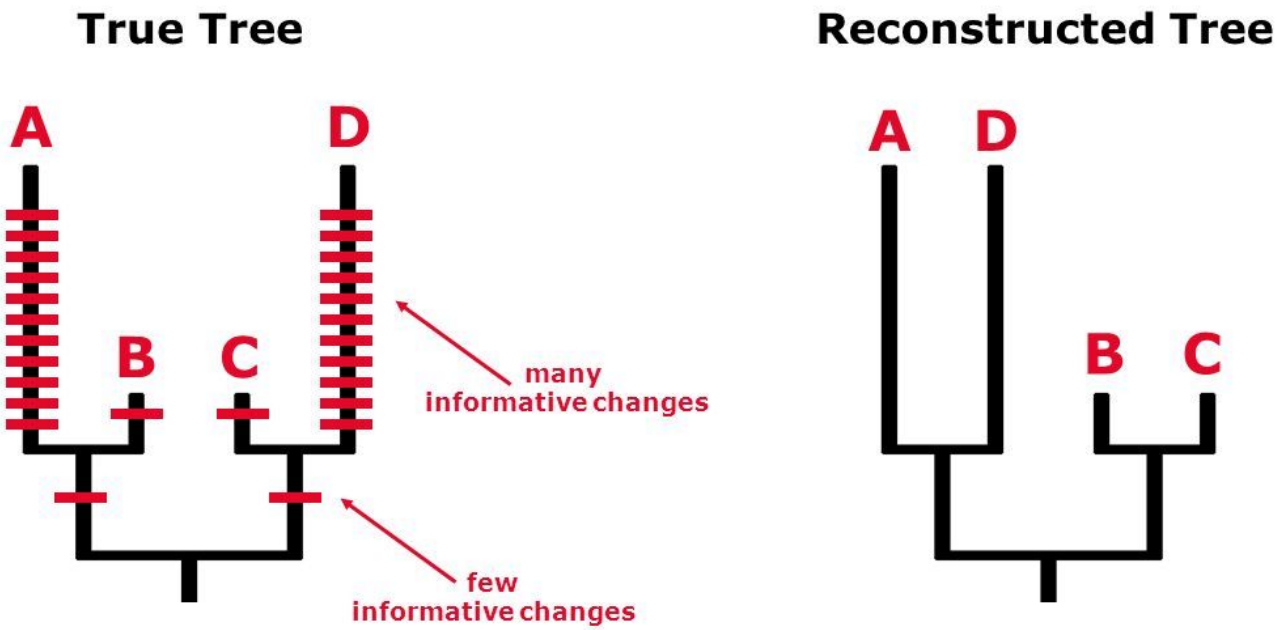
Long Branch Attraction

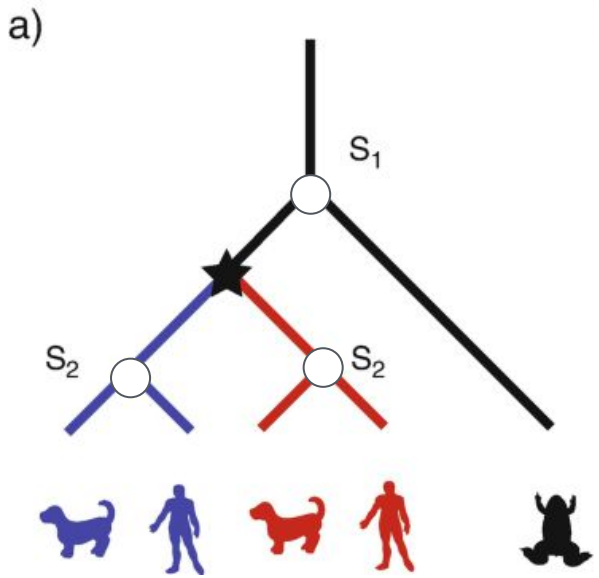
Outgroups / Fast-evolving lineages / Compositional heterogeneity



How to infer a species tree

1 Taxon Sampling

2 **Orthology Inference**



Altenhoff, Glover & Dessimoz 2019

How to infer a species tree

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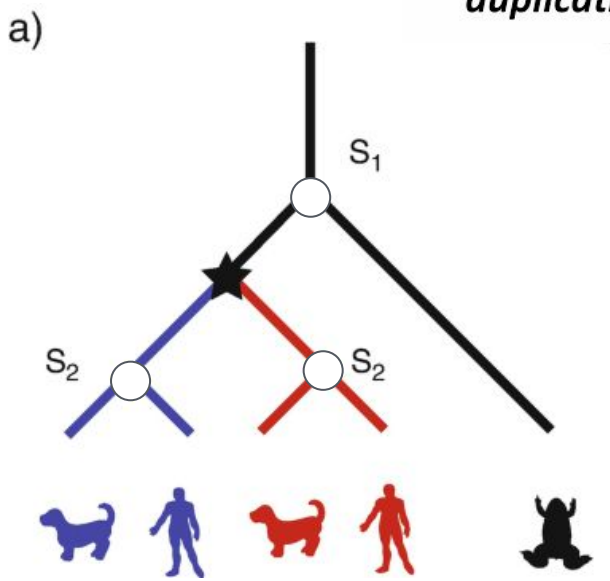
Definitions

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



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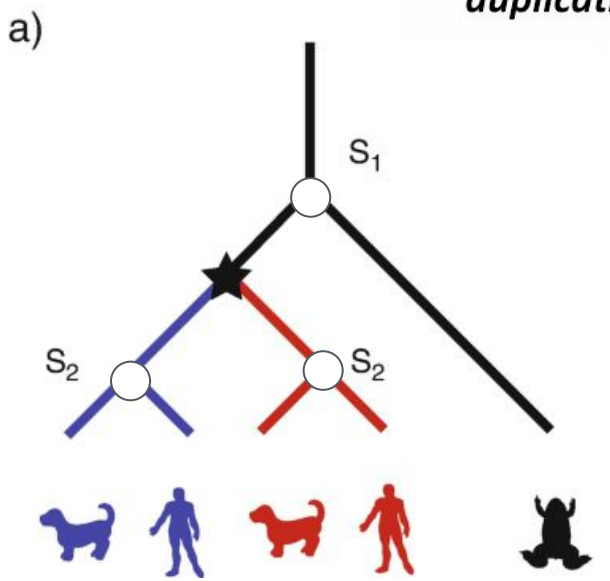

Orthology relationships are inferred pairwise

Altenhoff, Glover & Dessimoz 2019

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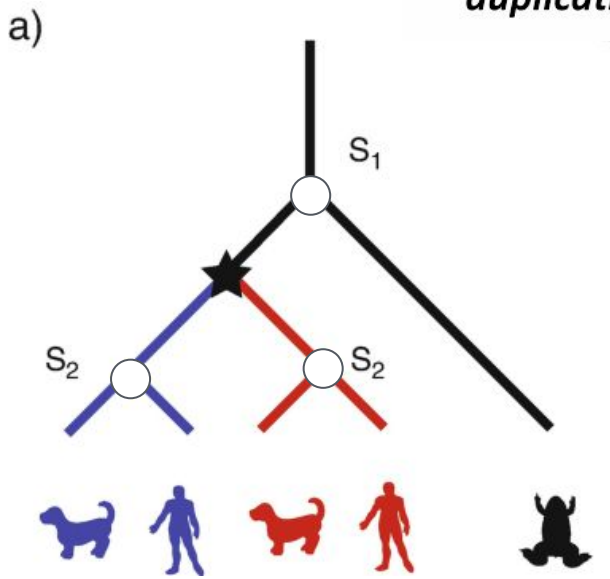

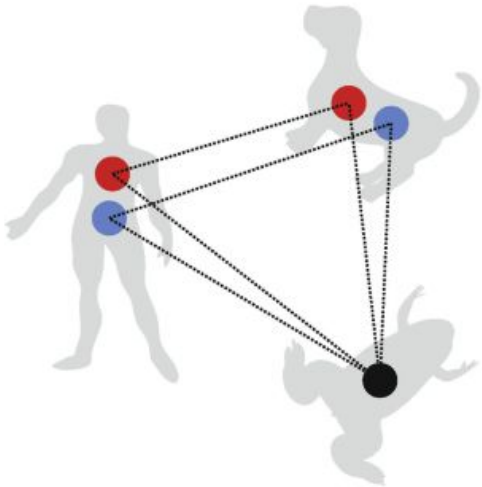

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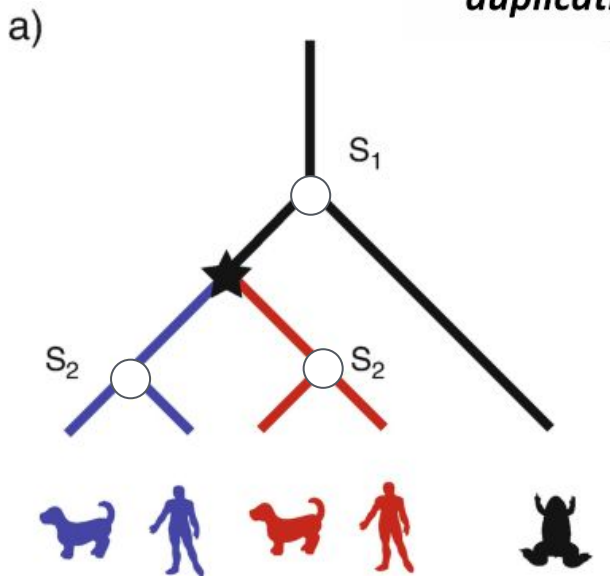

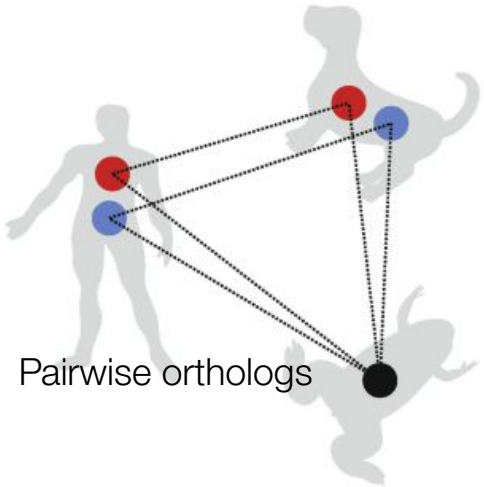

Pairwise orthologs

Orthology relationships are inferred pairwise

Altenhoff, Glover & Dessimoz 2019

How to infer a species tree

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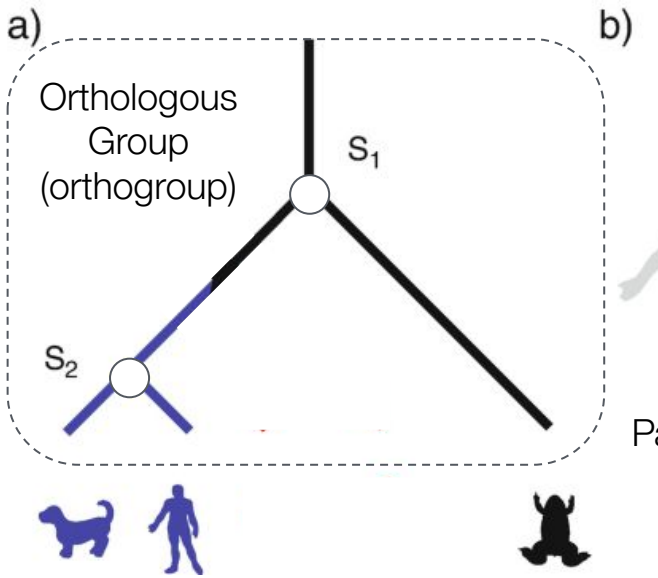
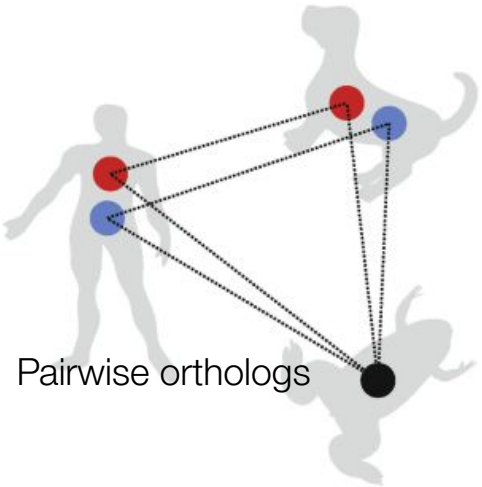
For phylogenetic inference, our starting point are the Orthologous Groups, (OGs) since they are derived from speciation events





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Altenhoff, Glover & Dessimoz 2019

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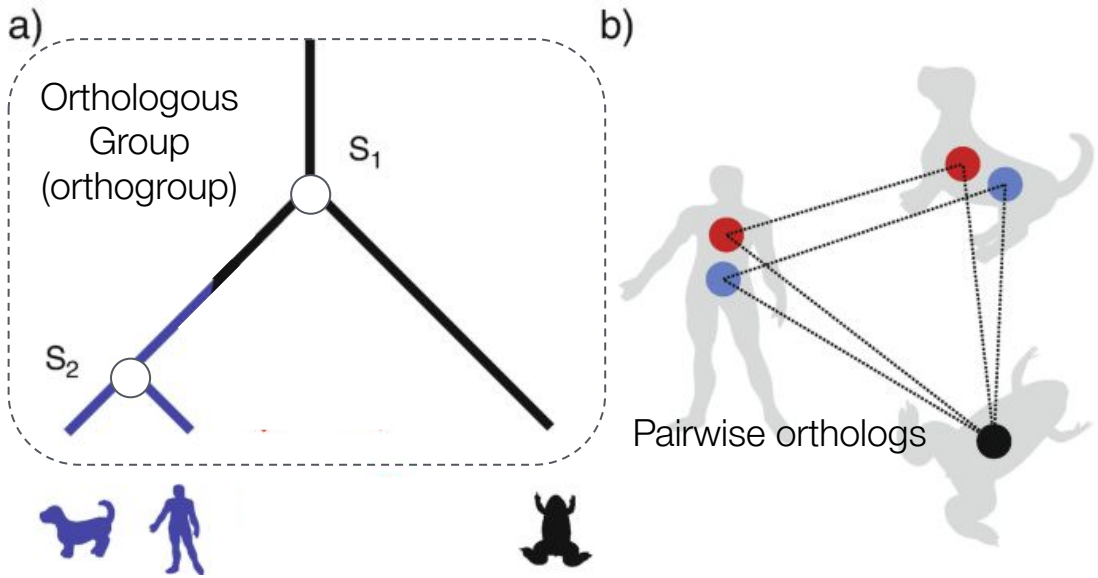

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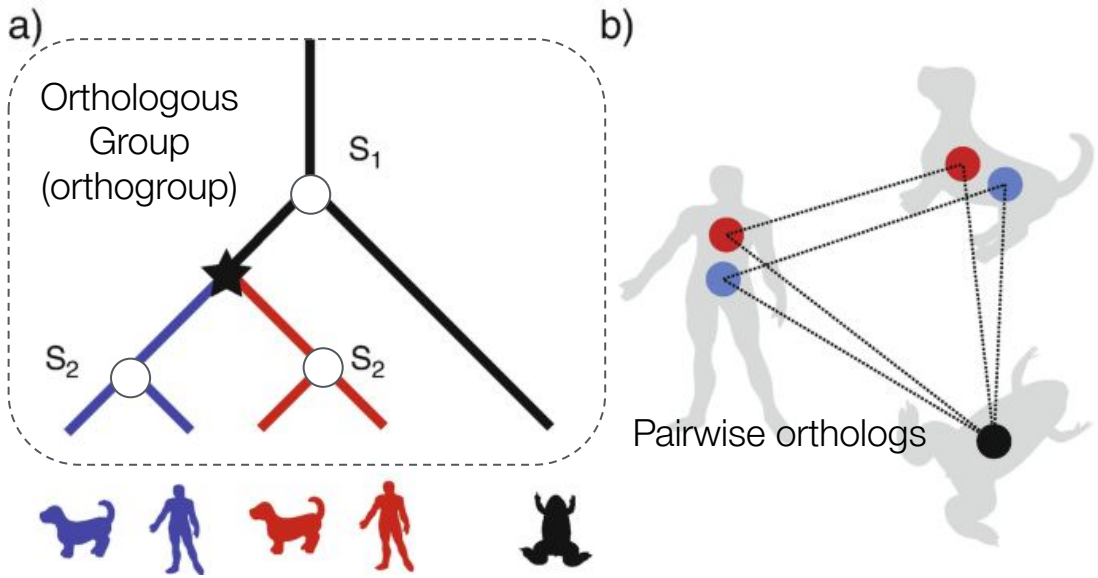

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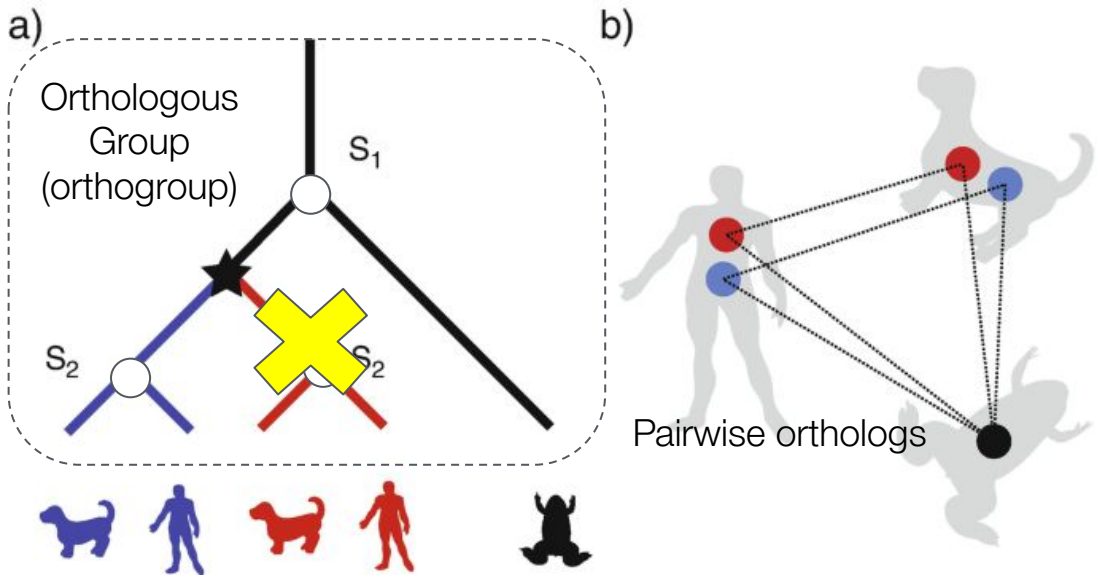

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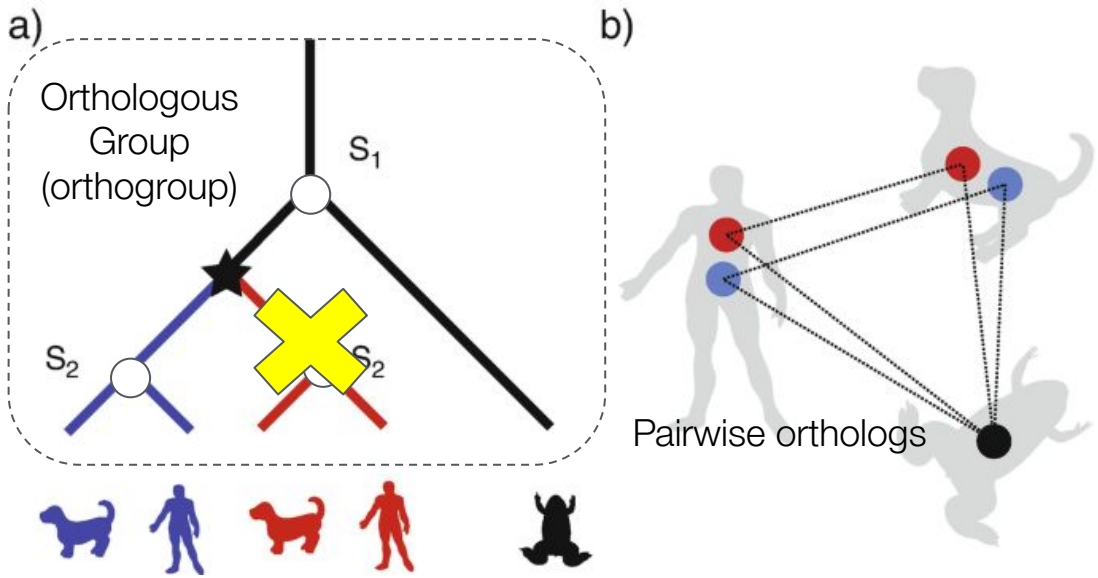
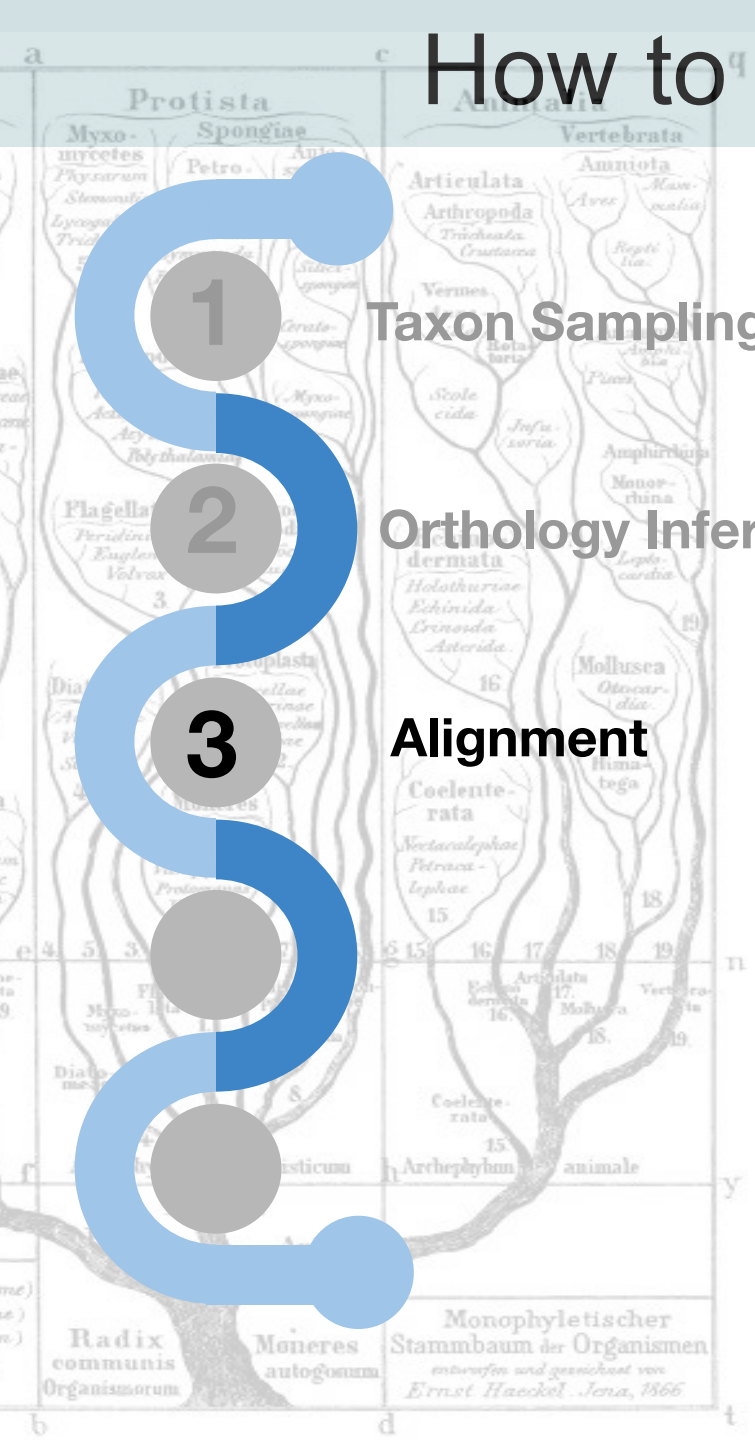


Key message: the selection of OGs for further analysis matters <u>a lot</u>

Altenhoff, Glover & Dessimoz 2019

How to infer a species tree



1 Taxon Sampling

2 Orthology Inference

3 **Alignment**

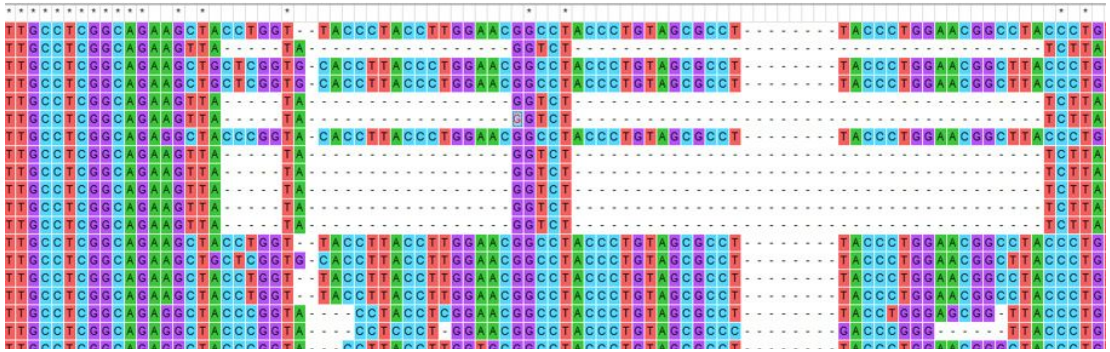
Extensively covered last week
by Mike, Rob & Francesco

How to infer a species tree

1. Taxon Sampling
2. Orthology Inference
3. **Alignment**

Extensively covered last week by Mike, Rob & Francesco

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



How to infer a species tree

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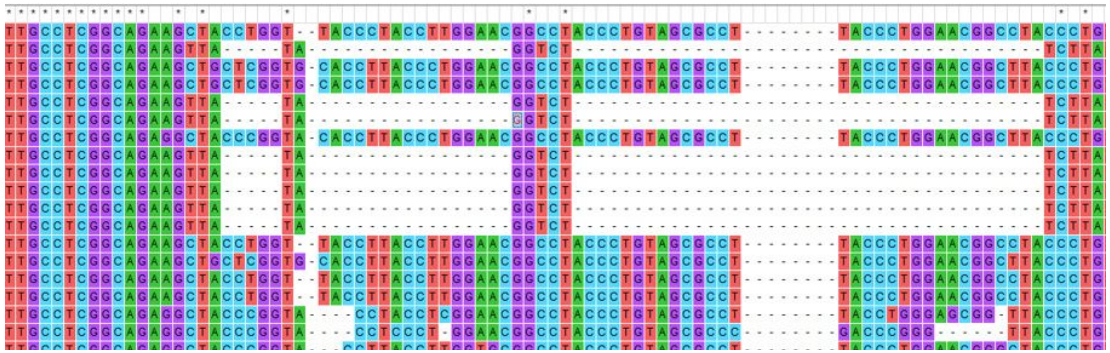
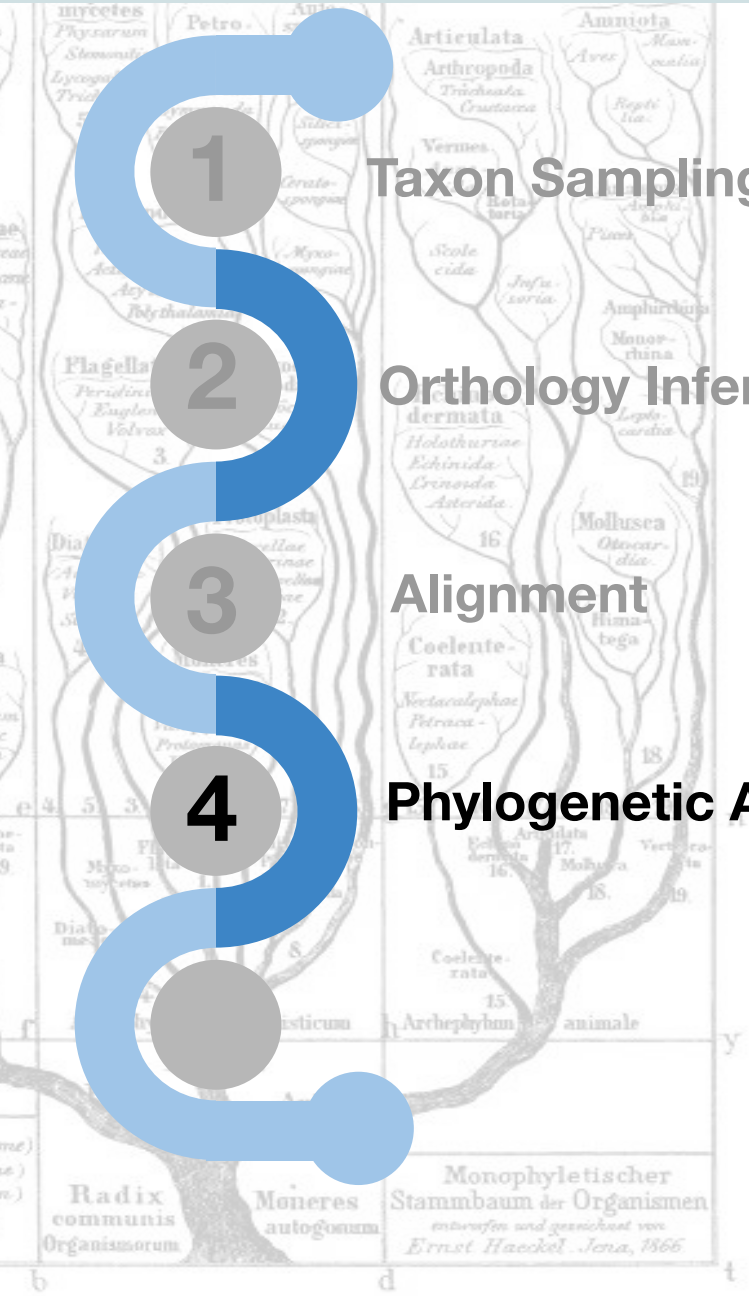
trimAl
A tool for automated alignment trimming

PREQUAL

(prealignment quality filter)



How to infer a species tree



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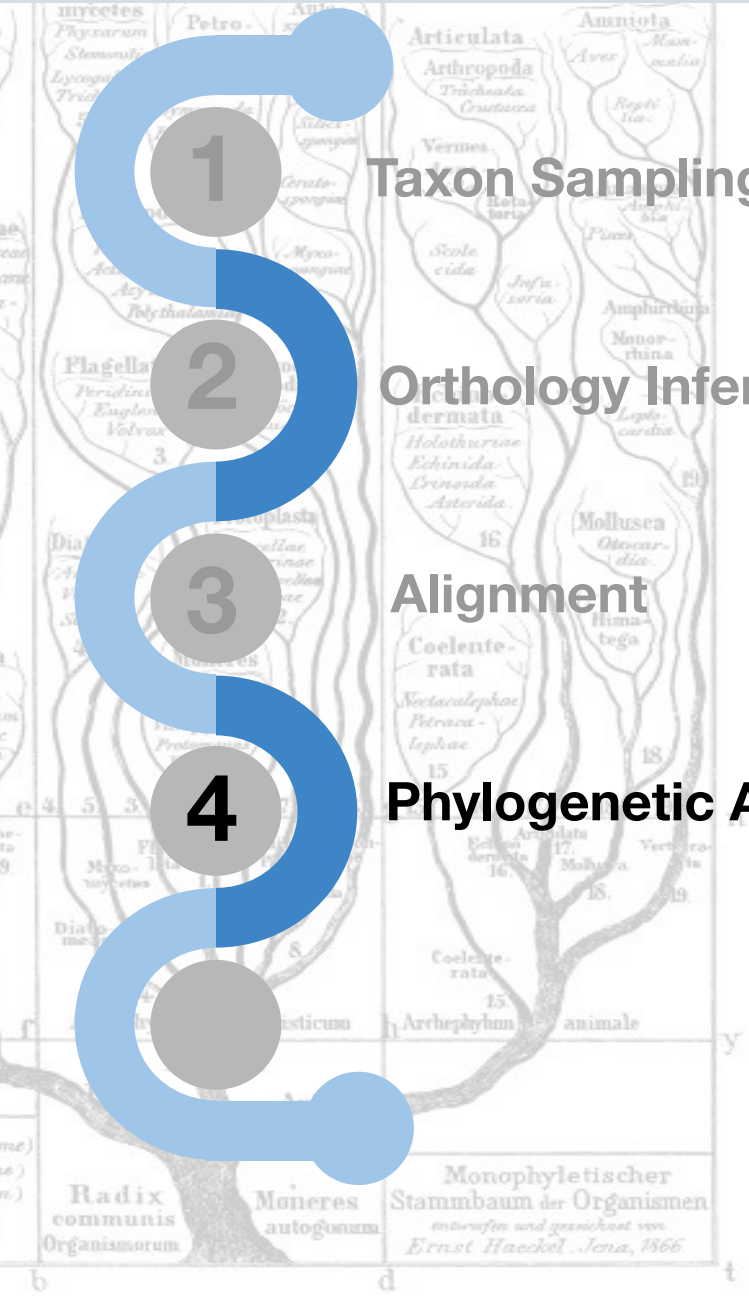

Taxon Sampling

Orthology Inference

Alignment

Phylogenetic Analysis

DATA

How to infer a species tree

1. Taxon Sampling
2. Orthology Inference
3. Alignment
4. **Phylogenetic Analysis**

DATA

+

MODEL OF EVOLUTION

describe the relative rates of different changes

How to infer a species tree

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describe the relative rates of different changes

Seq1 ATGGCA

Seq2 ACGCCG

Seq3 AGGGCC

How to infer a species tree

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3 changes

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Jukes and Cantor 1969 (JC69)

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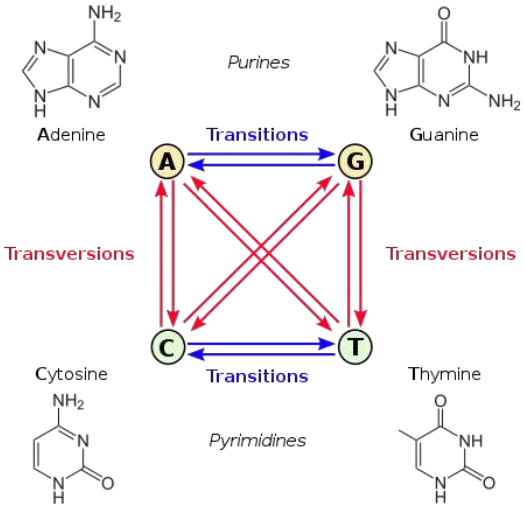
Eg, mutational biases and purifying selection favoring conservative changes are probably responsible for the relatively high rate of **transitions** compared to **transversions** in evolving sequences



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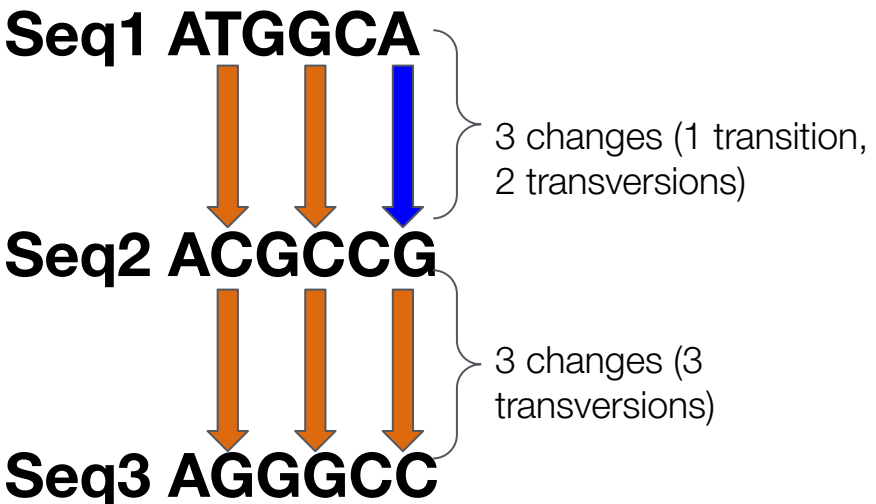

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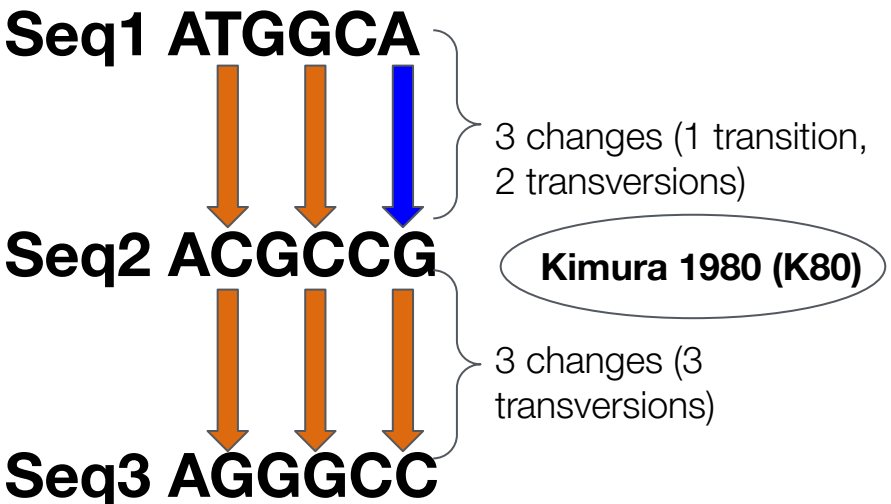

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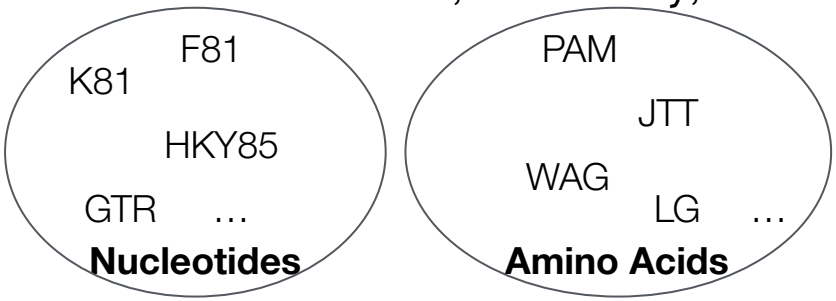
There are many models that take into account other factors that can influence the rate of changes, eg time, reversibility, etc.



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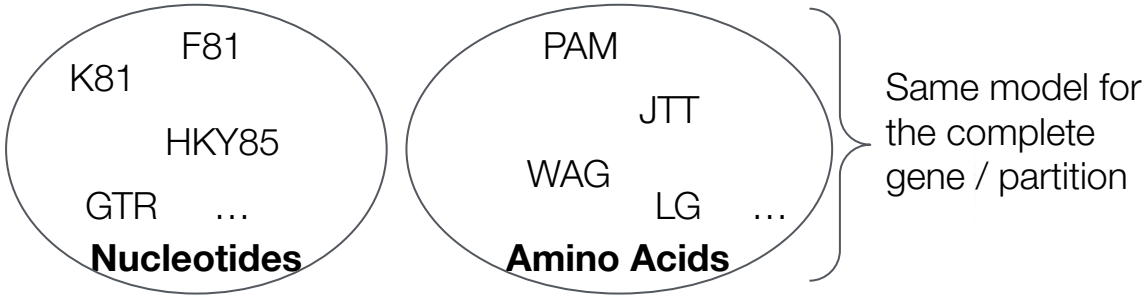

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Mixture models

C10 C20 C60 CAT

per-site variation of the model

F81 K81 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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So… how do I select a model for my data?

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

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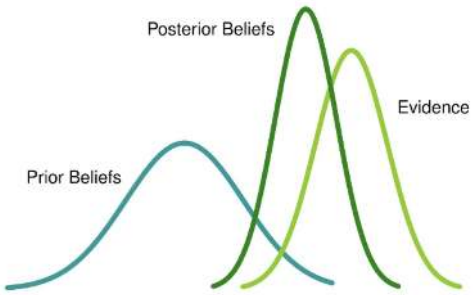
So… how do I select a model for my data?

Key message: the selection of the model matters a lot

How to infer a species tree

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



1. Taxon Sampling
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4. **Phylo. Analysis**

How to infer a species tree

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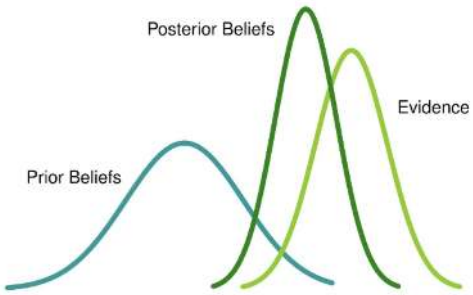

Two main methods:
Maximum Likelihood (ML) and **Bayesian Inference (BI)**

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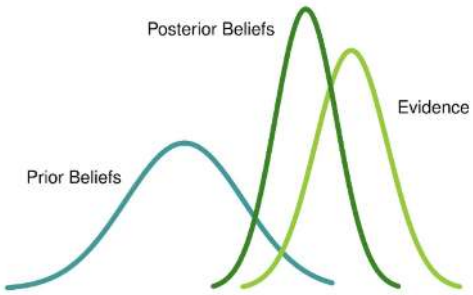

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Basic question in BI:
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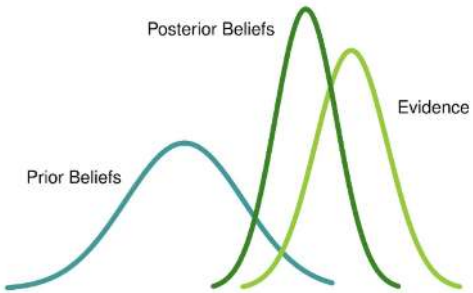

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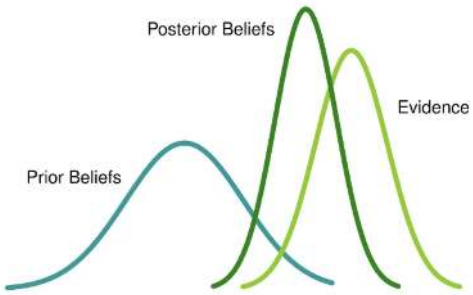

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BI seeks P(T|D), while ML maximizes P(D|T)

How to infer a species tree

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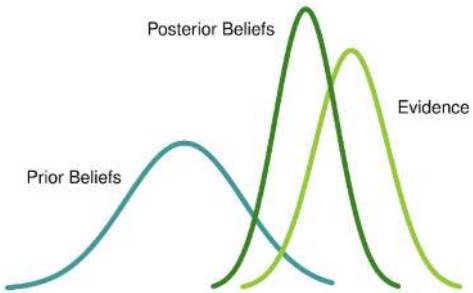

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RAxML

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

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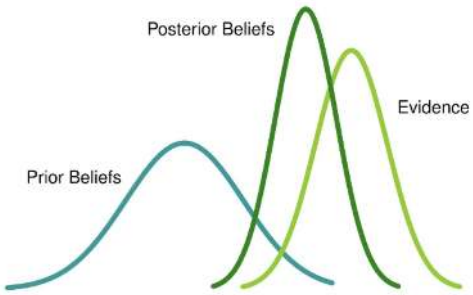
DATA + **MODEL OF EVOLUTION** + **METHOD**



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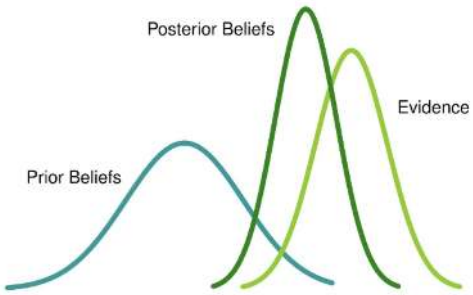

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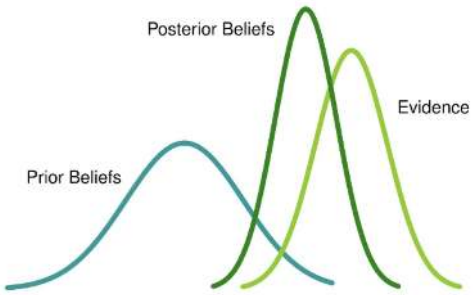

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Which one should I choose?

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

How to infer a species tree

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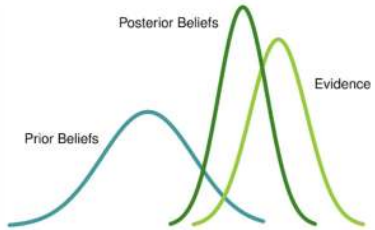
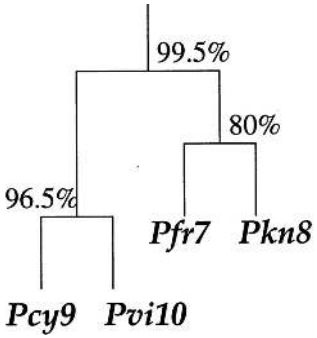
DATA + **MODEL OF EVOLUTION**



+ **METHOD** +



A WAY TO ASSESS HOW GOOD OUR HYPOTHESIS IS

How to infer a species tree

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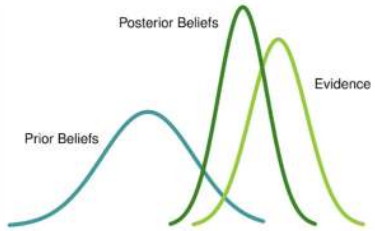

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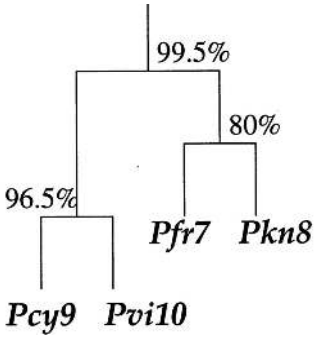

A WAY TO ASSESS HOW GOOD OUR HYPOTHESIS IS

- 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% bootstrap support and/or ultrafast bootstrap > 95% and/or approx. LRT > 80%.
- BI: posterior probability (between 0 and 1)
  - you ‘believe’ in a clade with > 0.9 pp

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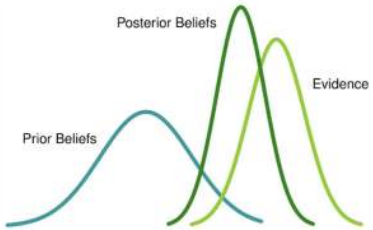

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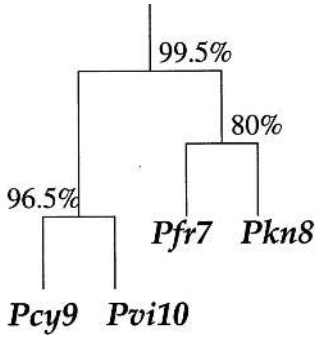


A WAY TO ASSESS HOW GOOD OUR HYPOTHESIS IS

- New metrics (highly recommended in large matrices):
  - concordance factor (IQTREE): 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

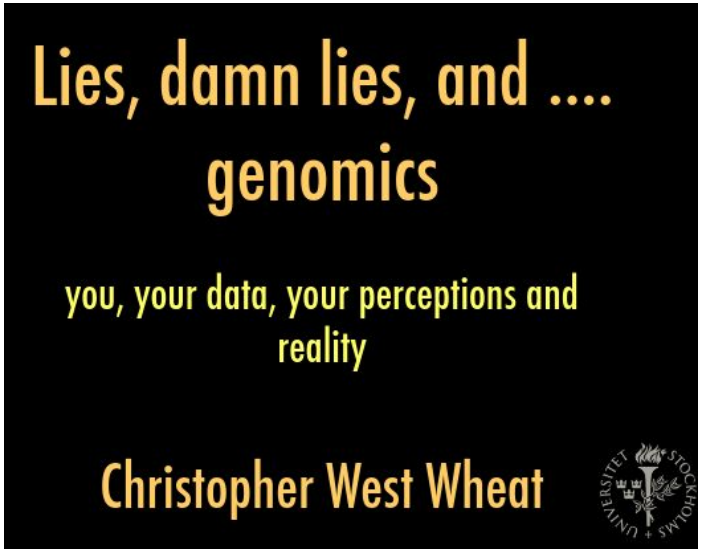
Lies, damn lies and phylogenomics

How to infer a species tree

1. Taxon Sampling
2. Orthology Inference
3. Alignment
4. Phylo. Analysis
5. **Sensitivity Analysis**

Lies, damn lies and phylogenomics

inspired by



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!!

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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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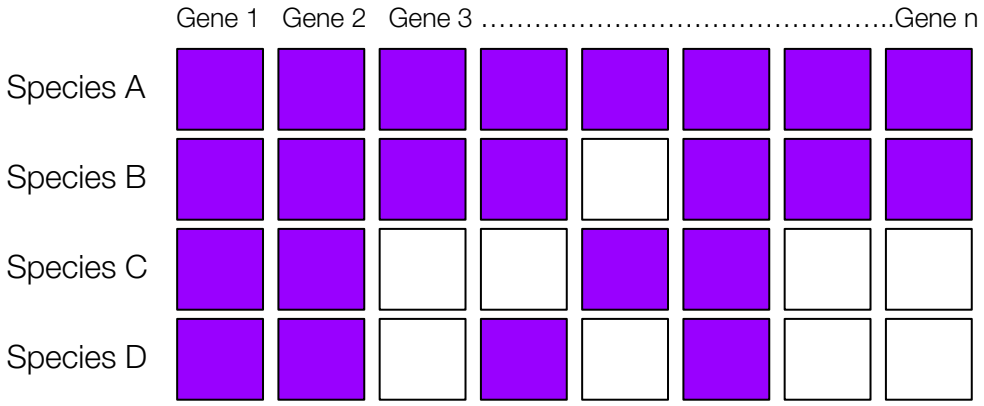

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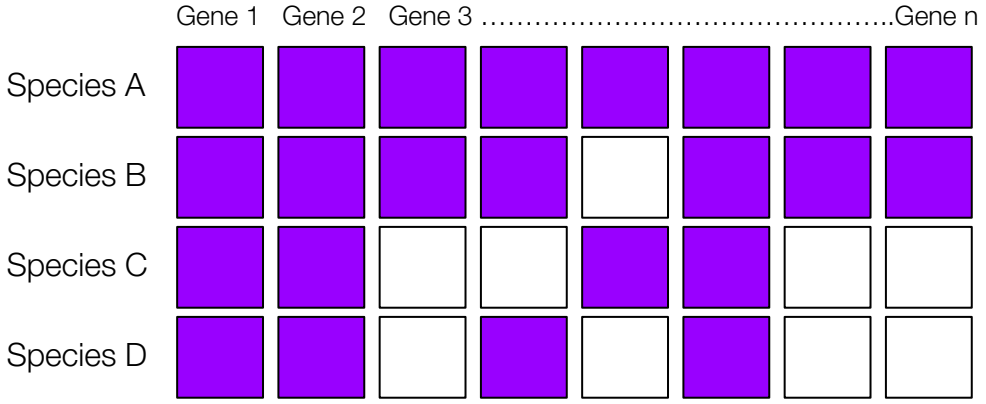

“Gruyère effect”

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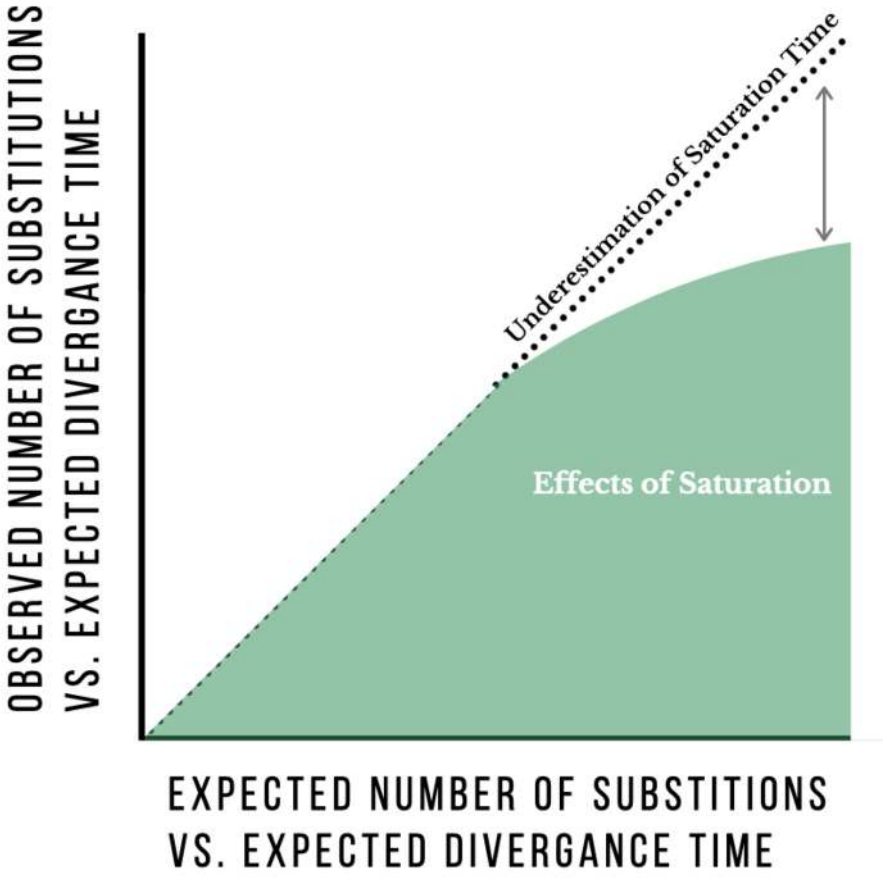

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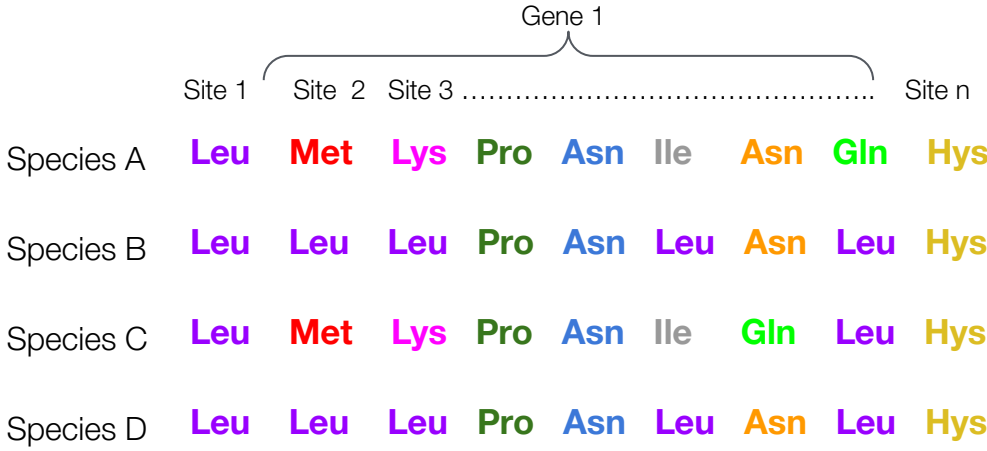
Compositional Heterogeneity



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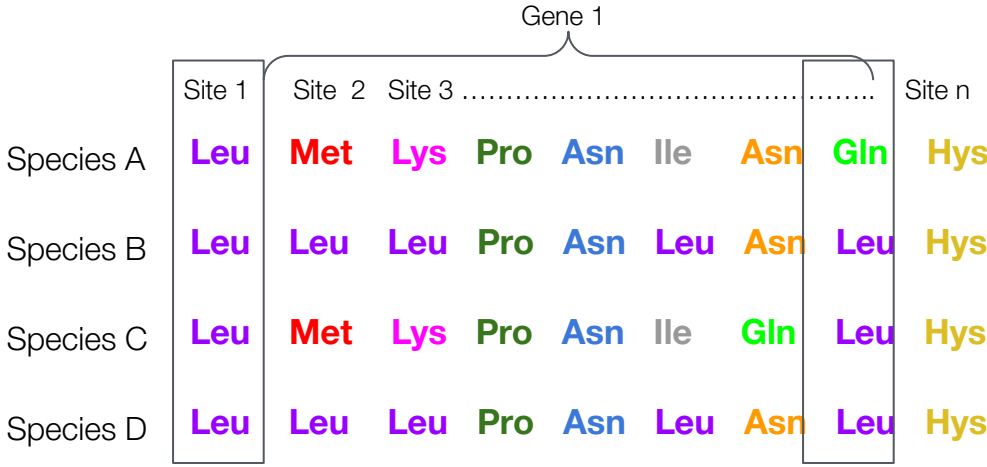

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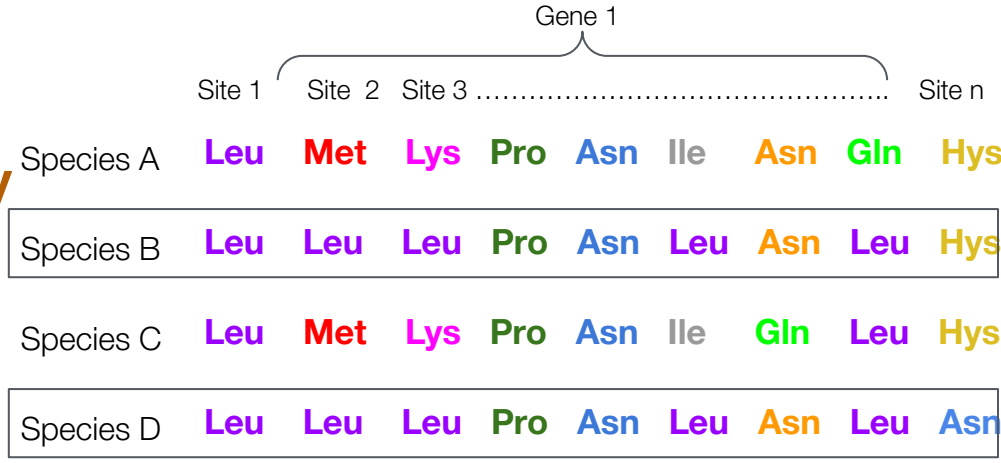

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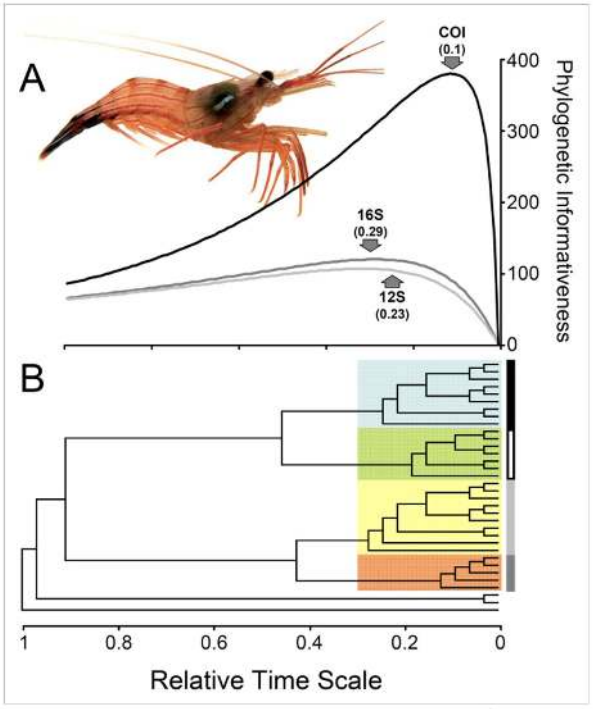
Lack of phylogenetic signal for your node of interest



Baeza & Fuentes 2013

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

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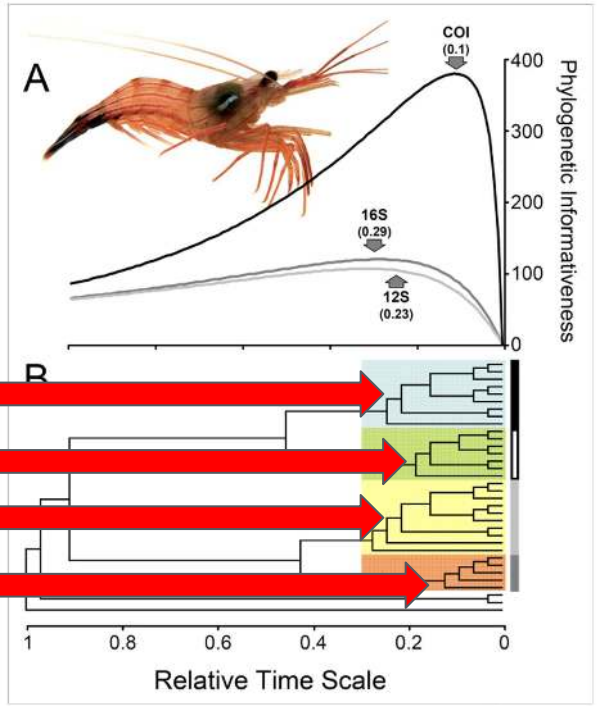
Lack of phylogenetic signal for your node of interest

Good information to resolve these nodes



Baeza & Fuentes 2013

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

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Missing data

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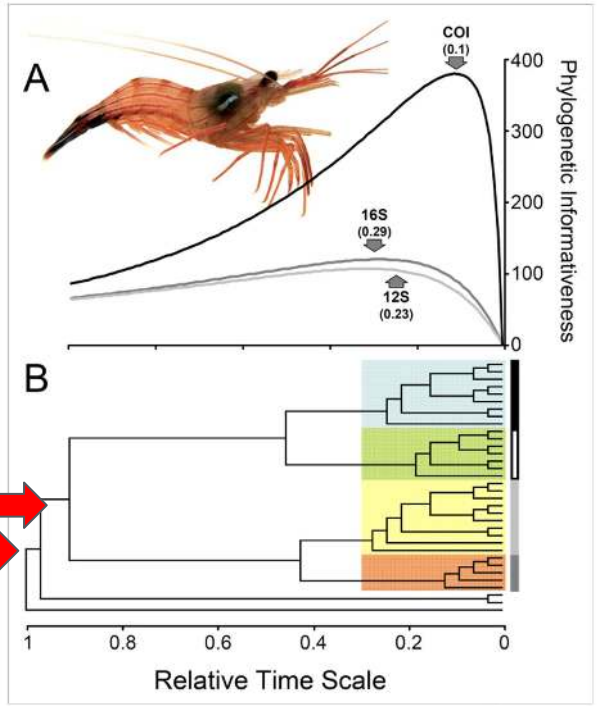
Lack of phylogenetic signal for your node of interest

<u>Not</u> enough information to resolve these nodes



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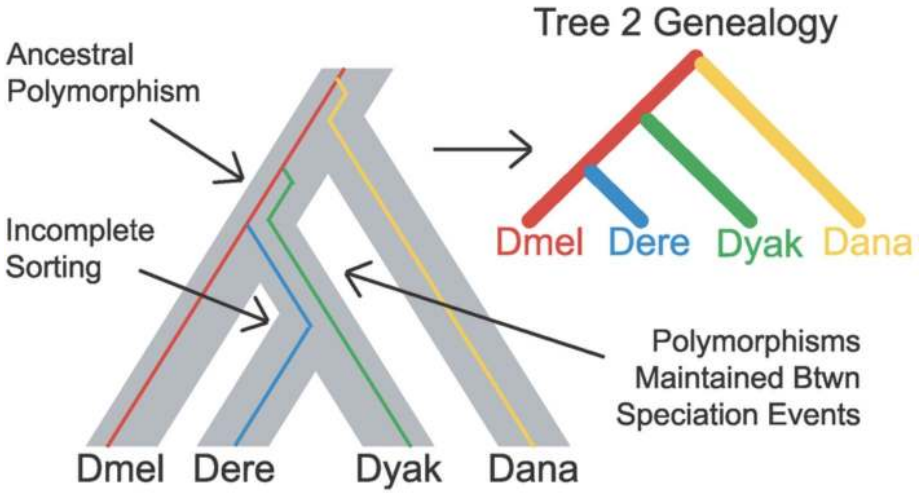

Incomplete Lineage Sorting The history of a gene (colored lines) is drawn in the context of a species tree (gray bars). New lineages arising from new polymorphisms in the gene are drawn in different colors. In this case, the two alleles in the population prior to the split of Dmel are maintained through 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

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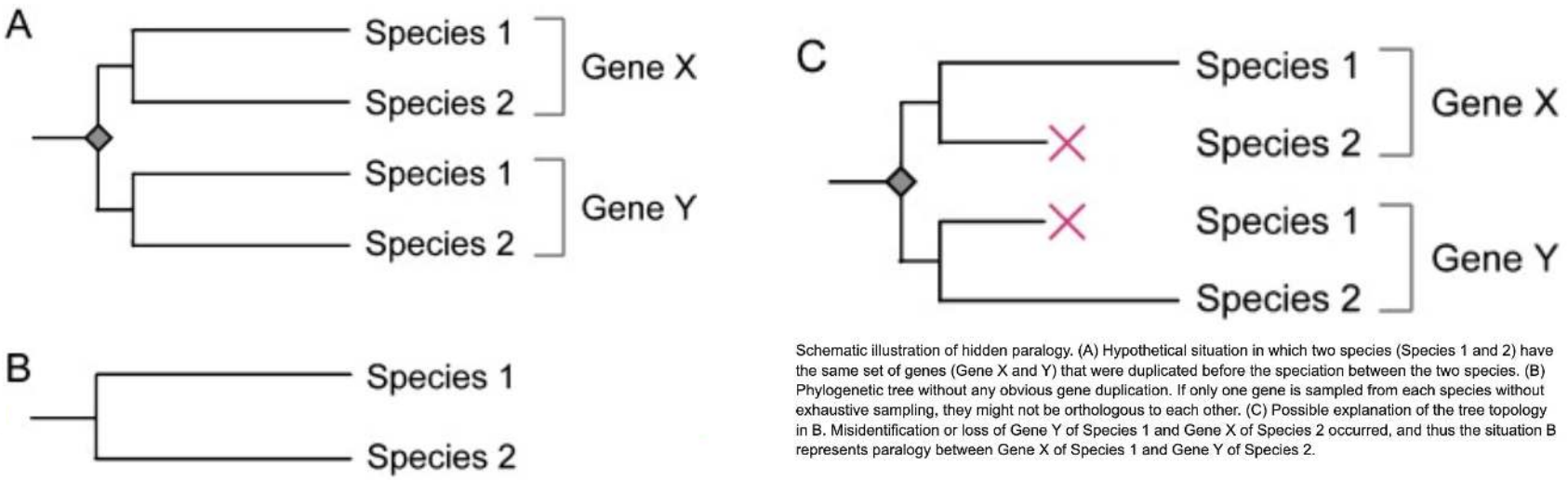

Schematic illustration of hidden paralogy. (A) Hypothetical situation in which two species (Species 1 and 2) have the same set of genes (Gene X and Y) that were duplicated before the speciation between the two species. (B) Phylogenetic tree without any obvious gene duplication. If only one gene is sampled 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

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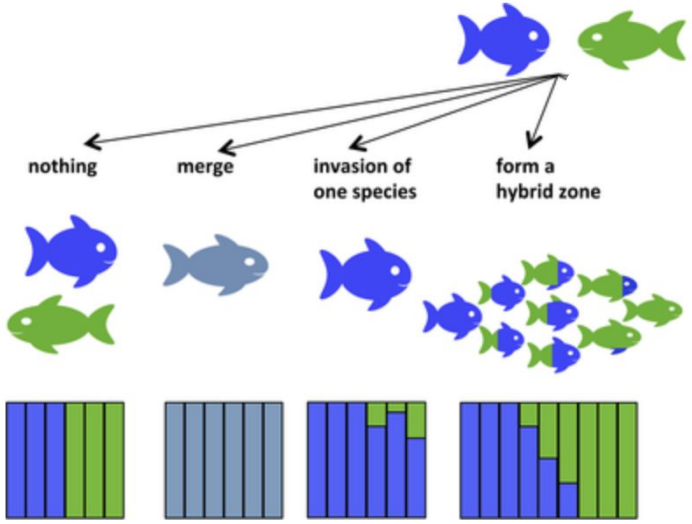

Fig 2.

Schematic representation of homoploid and allopolyploid hybrid speciation.

Runemark et al. 2019

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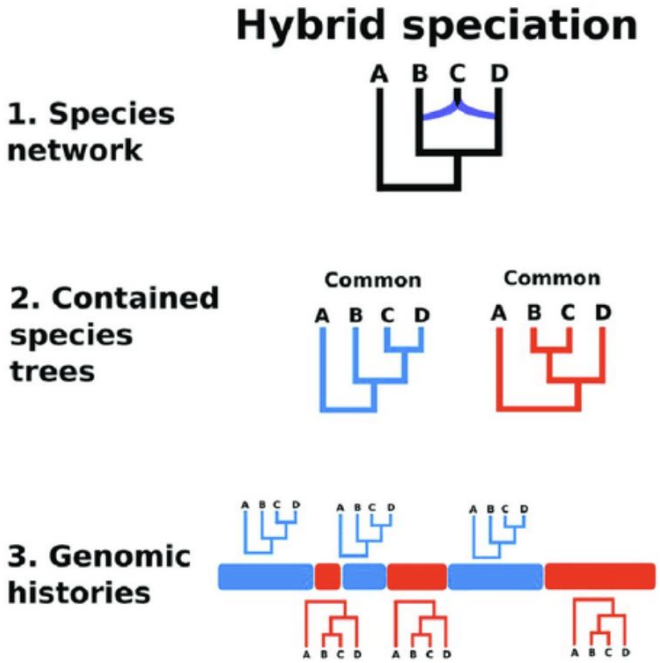

Folk et al. 2018

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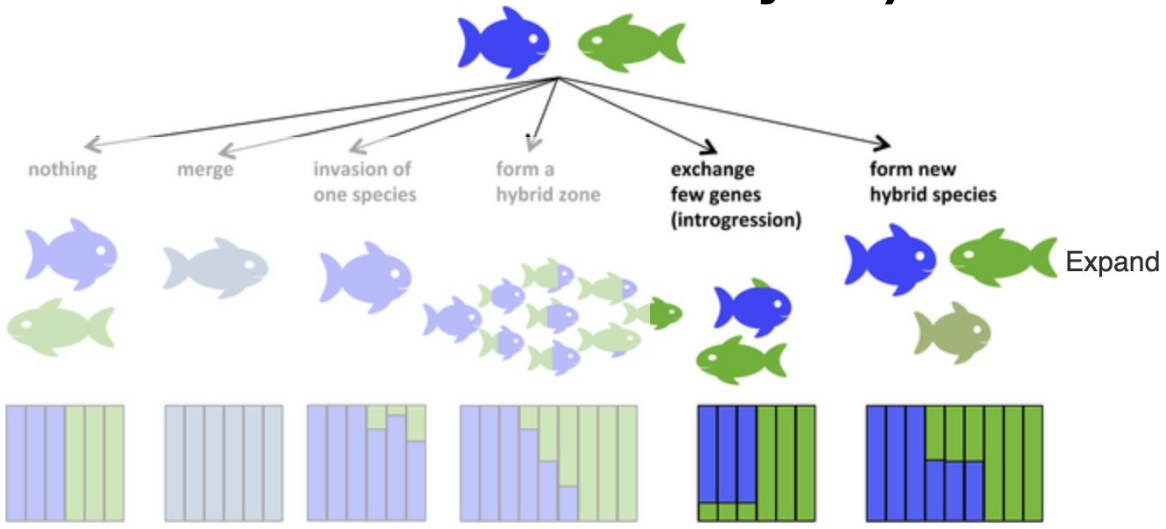

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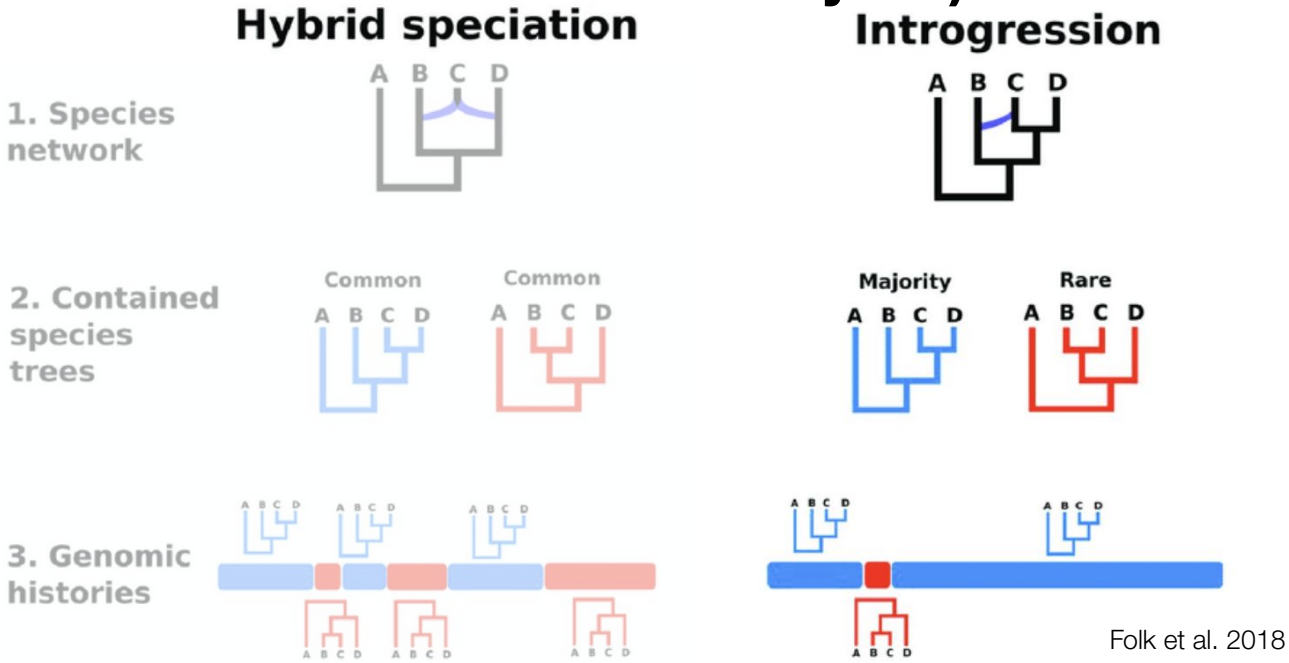

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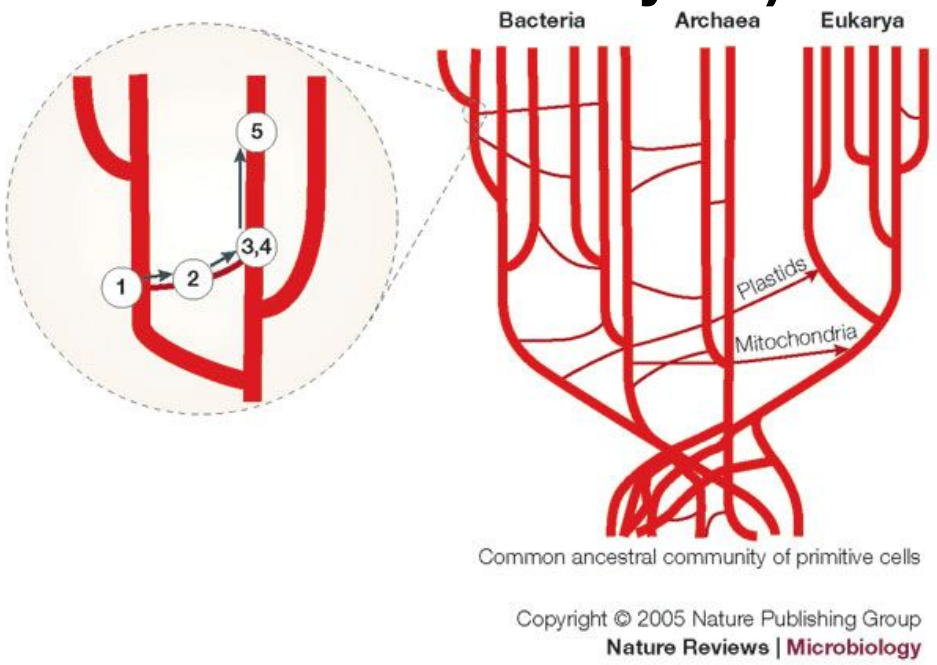

Smets and Barkay 2005

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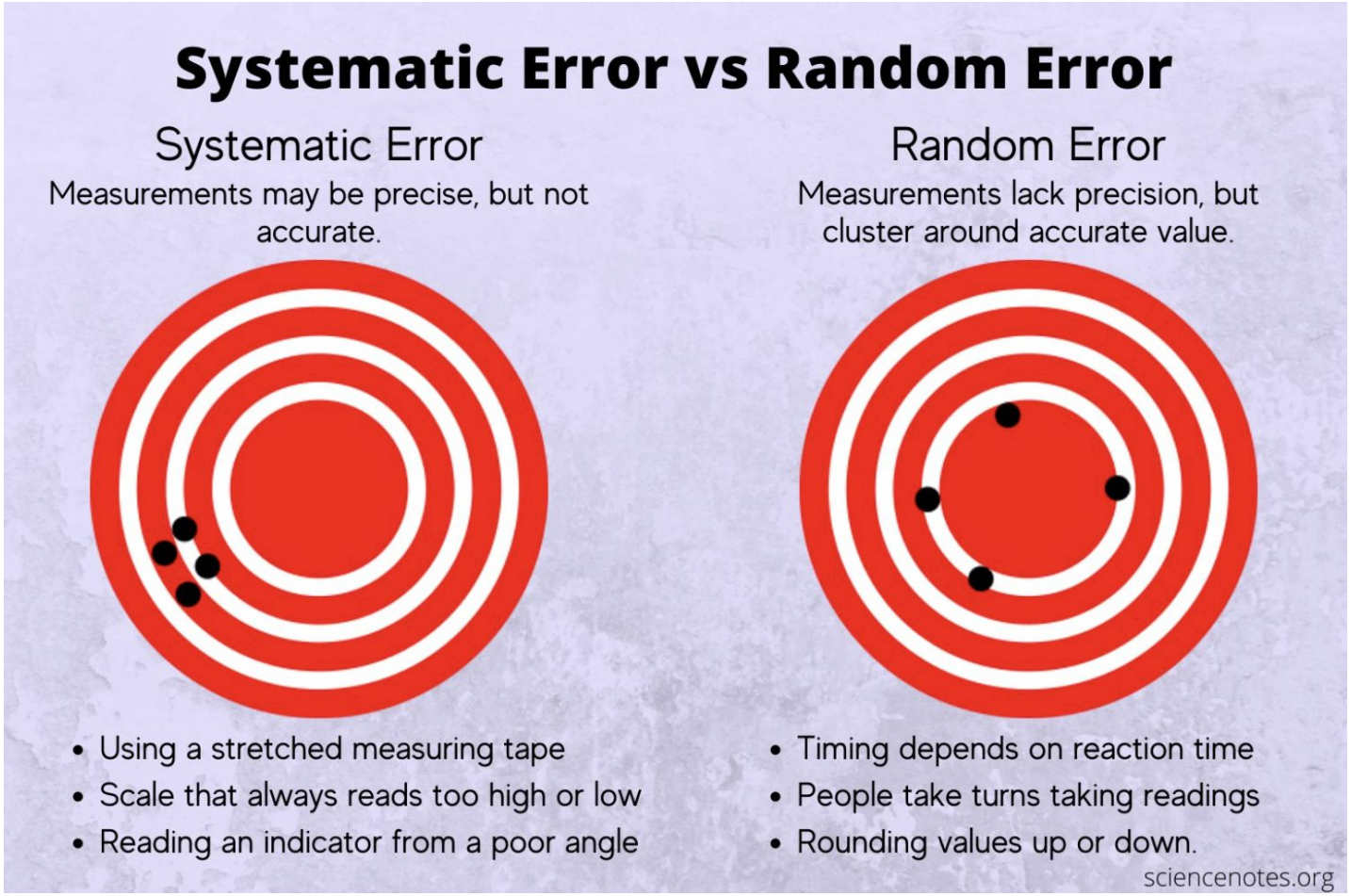

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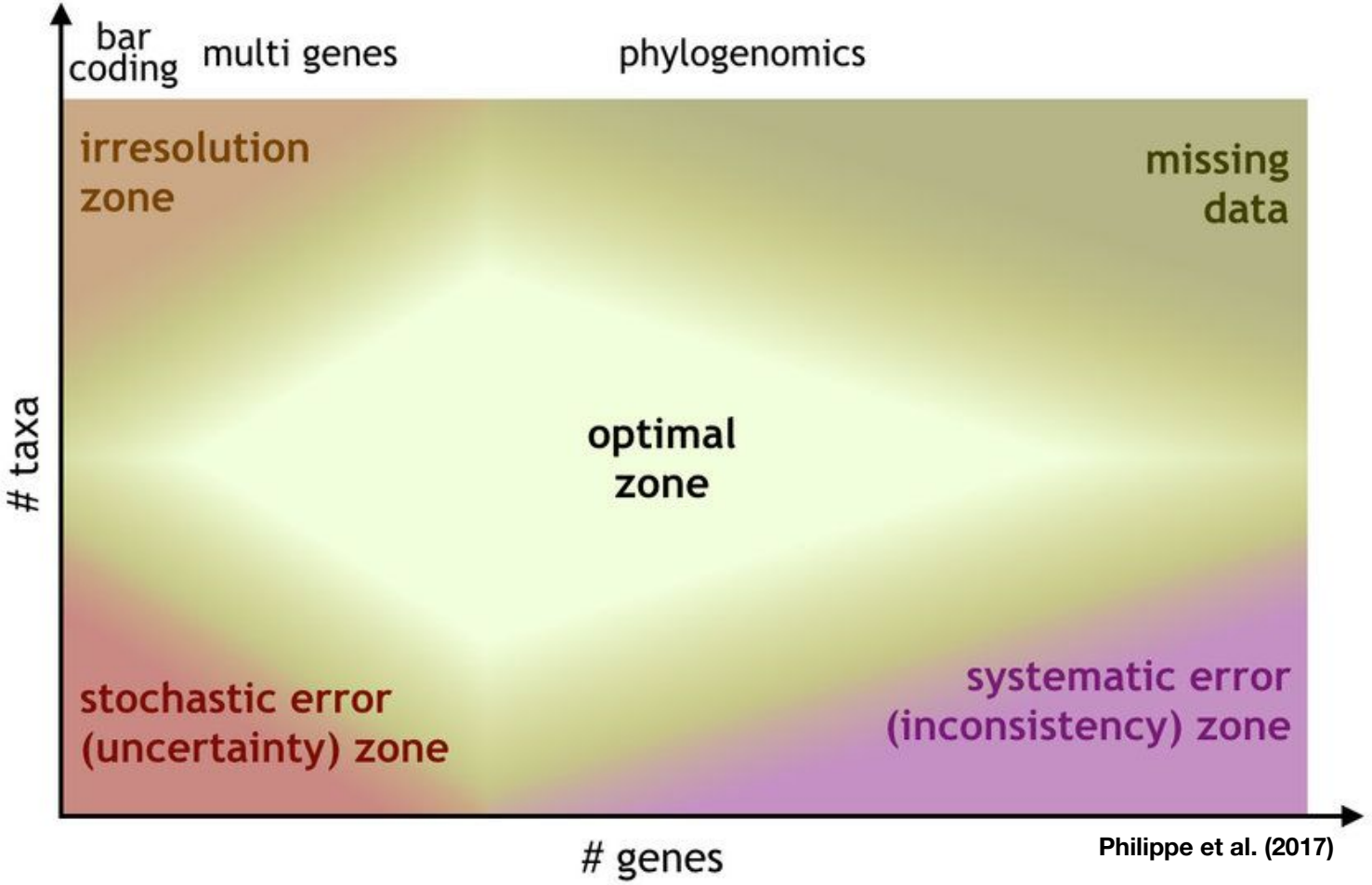

Philippe et al. (2017)

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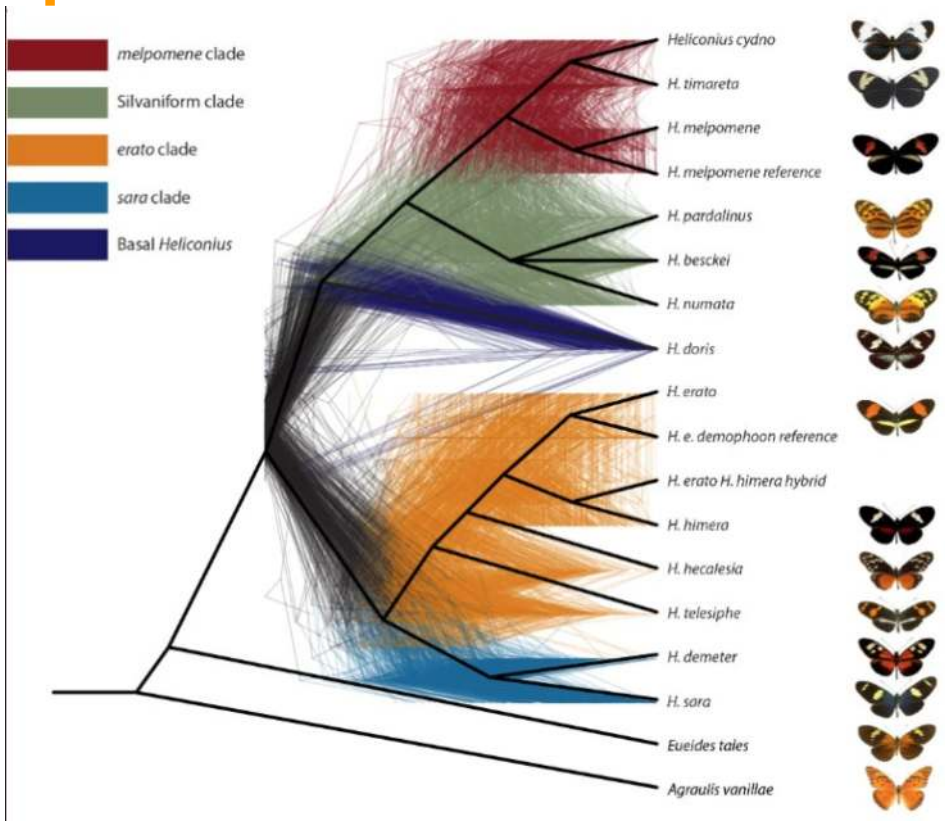

Edelman et al. 2019

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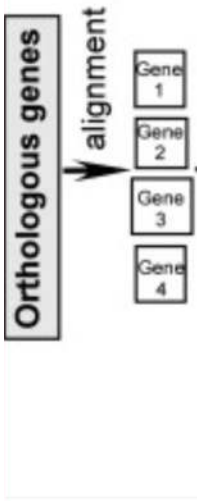

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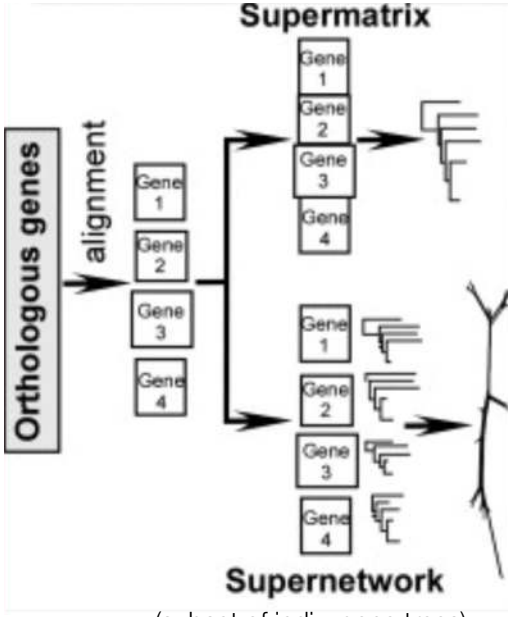

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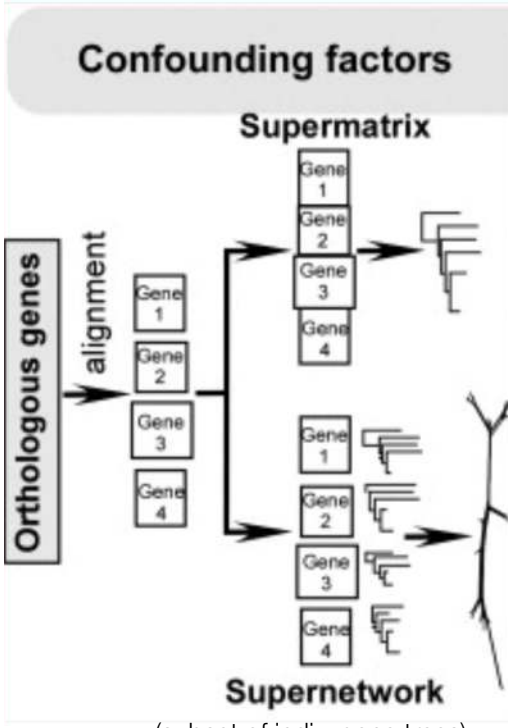

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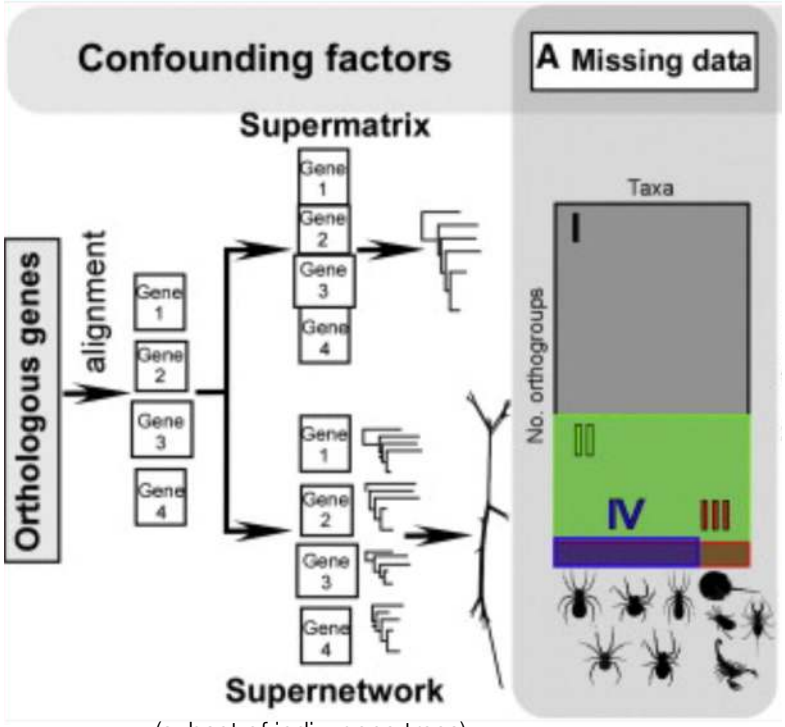

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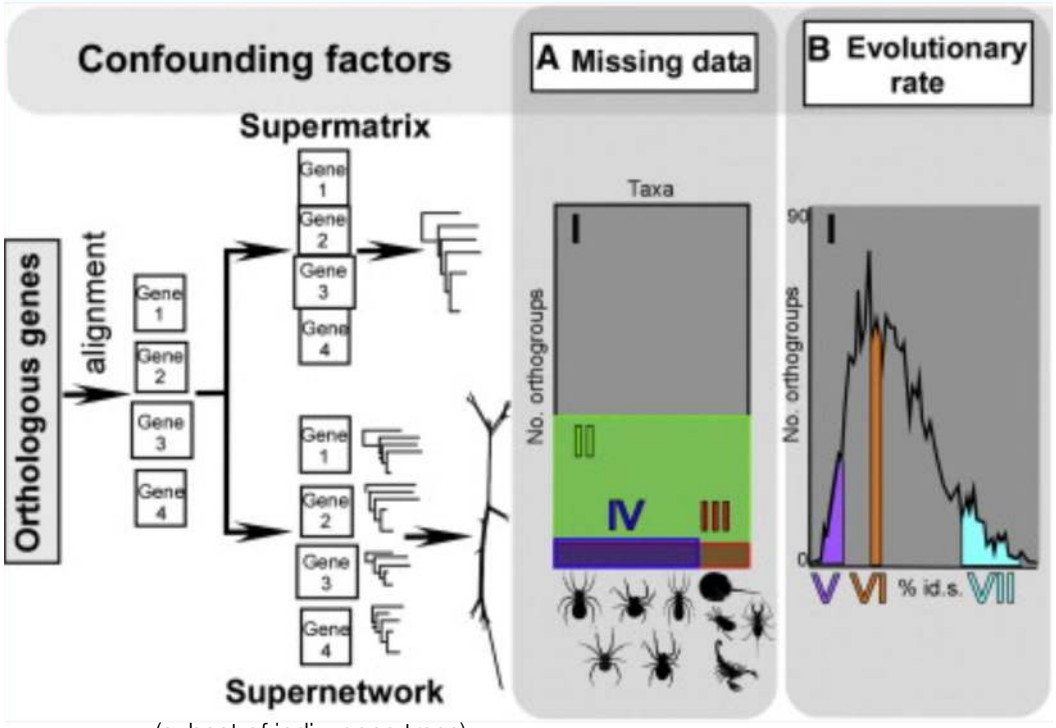

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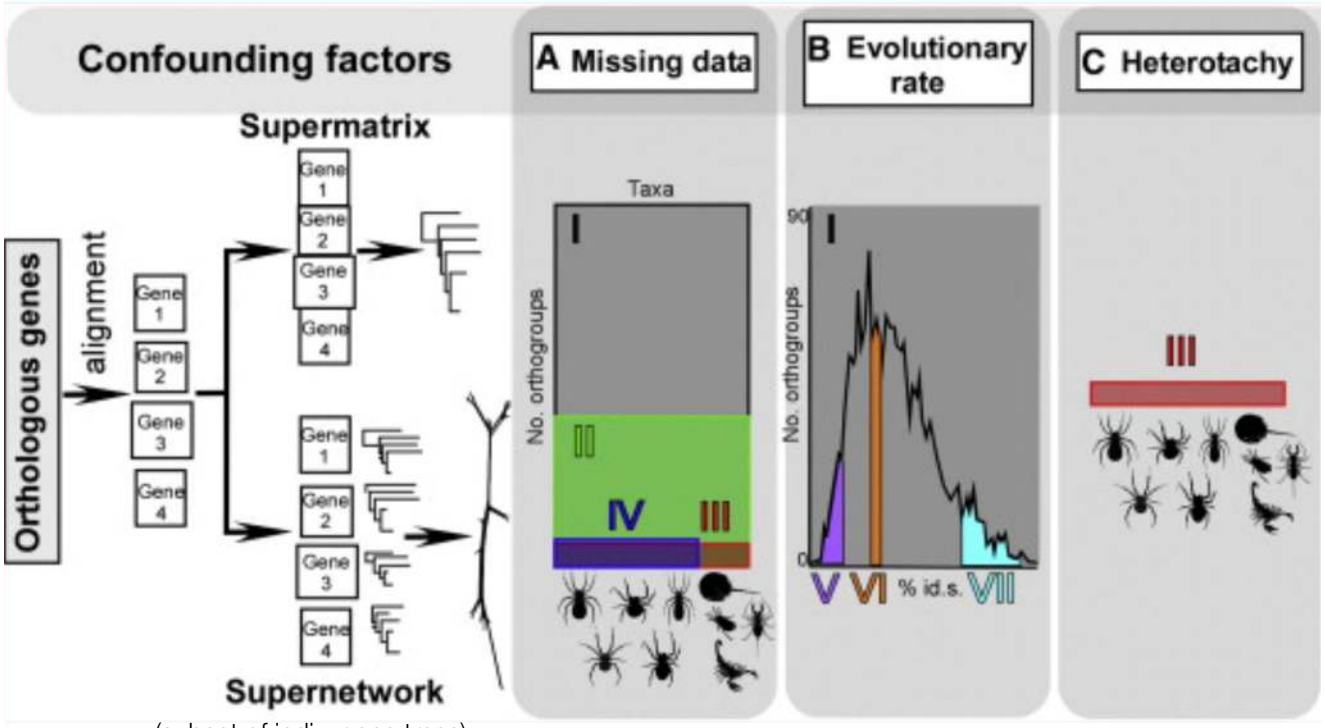

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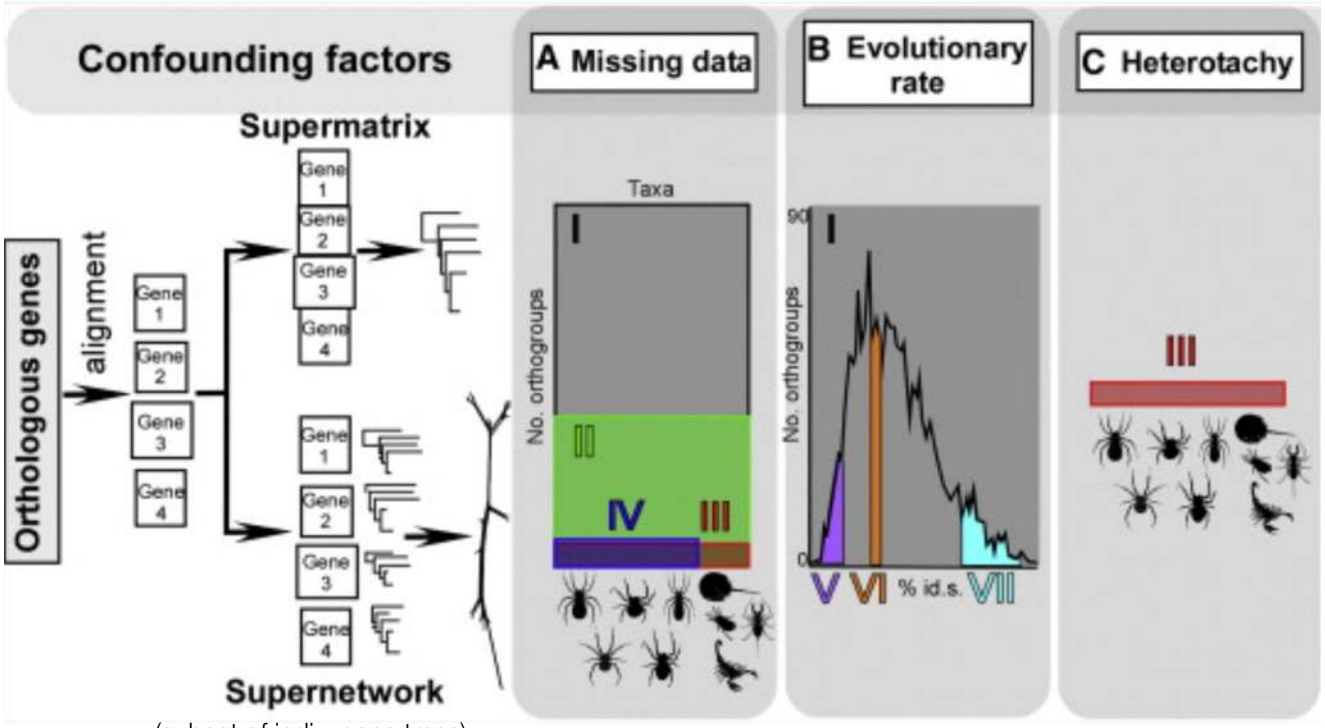

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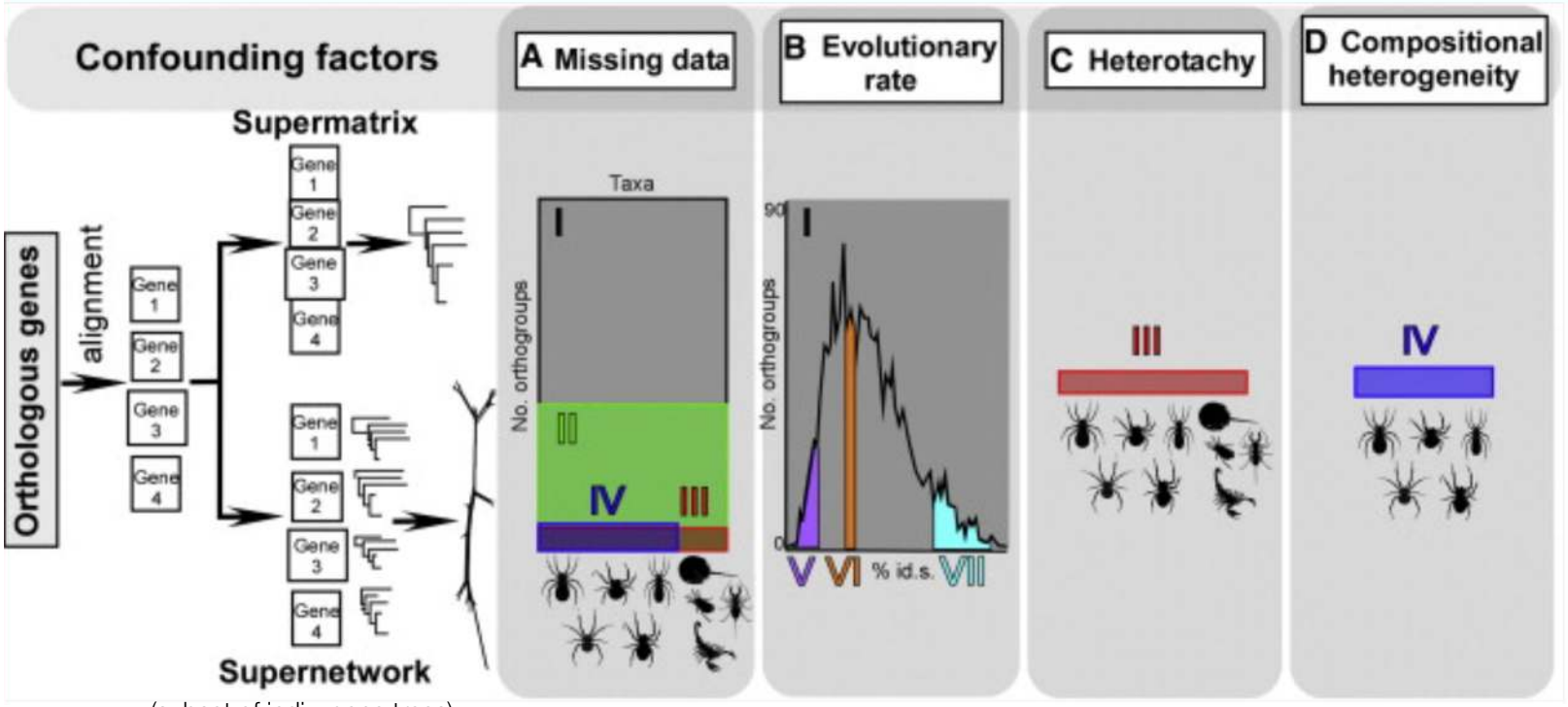

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We will be doing this today in our hands-on session

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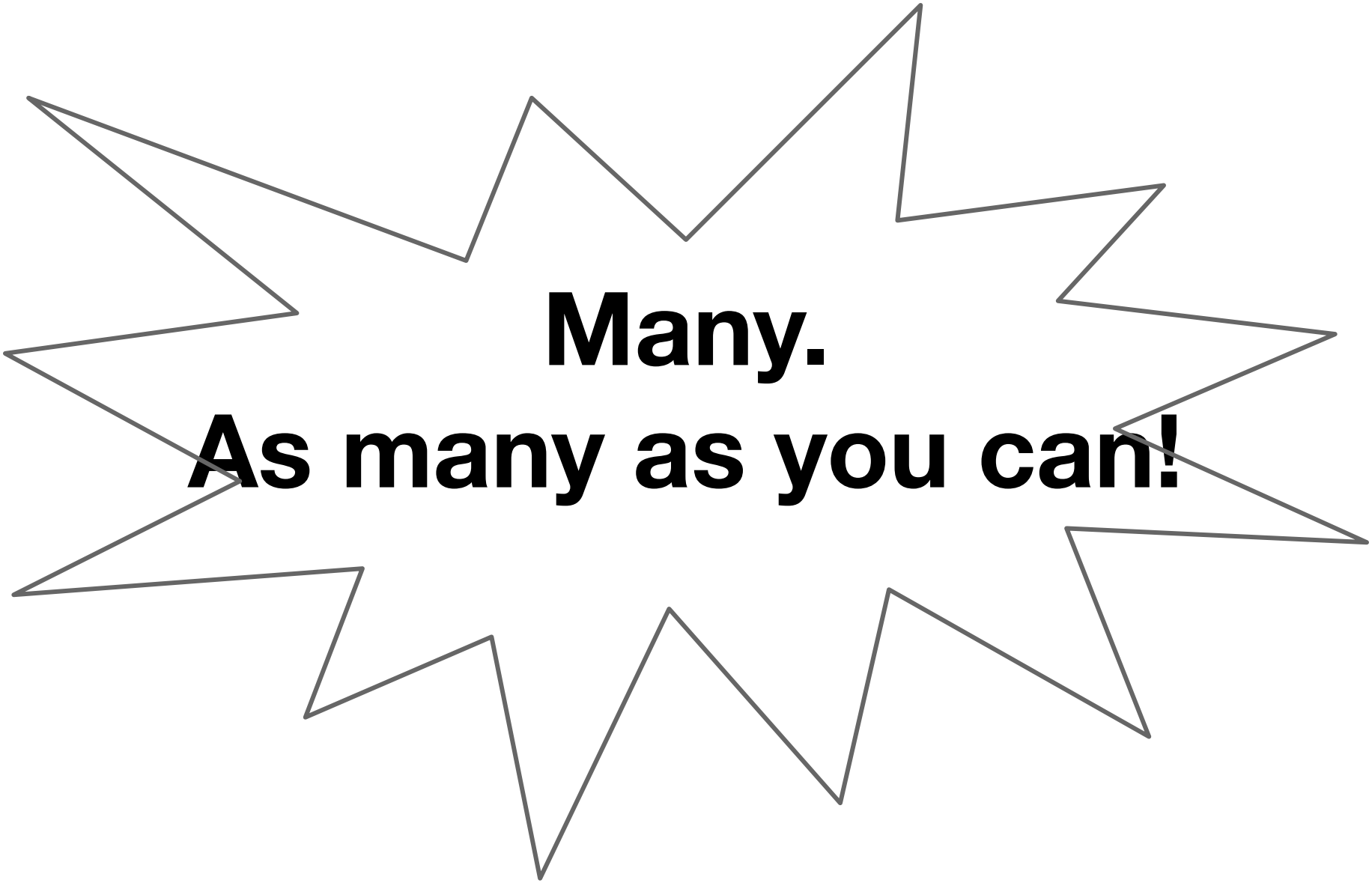

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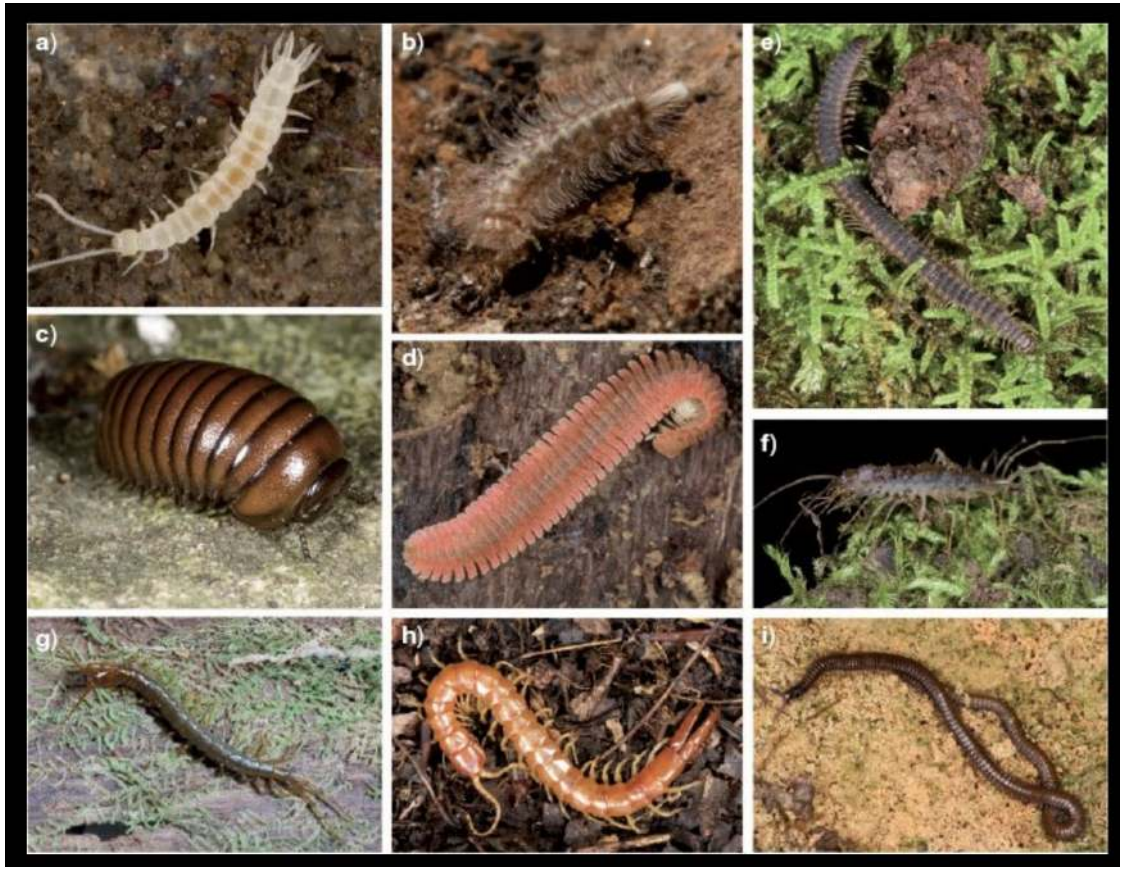

Fernández, Edgecombe & Giribet (2016) Syst Biol

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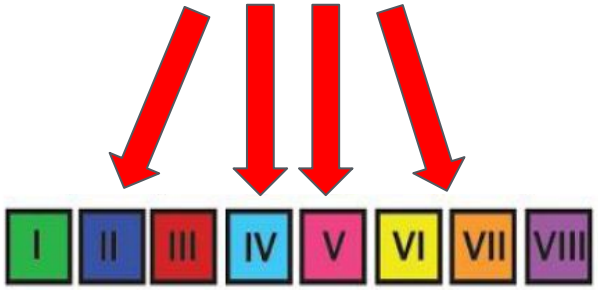

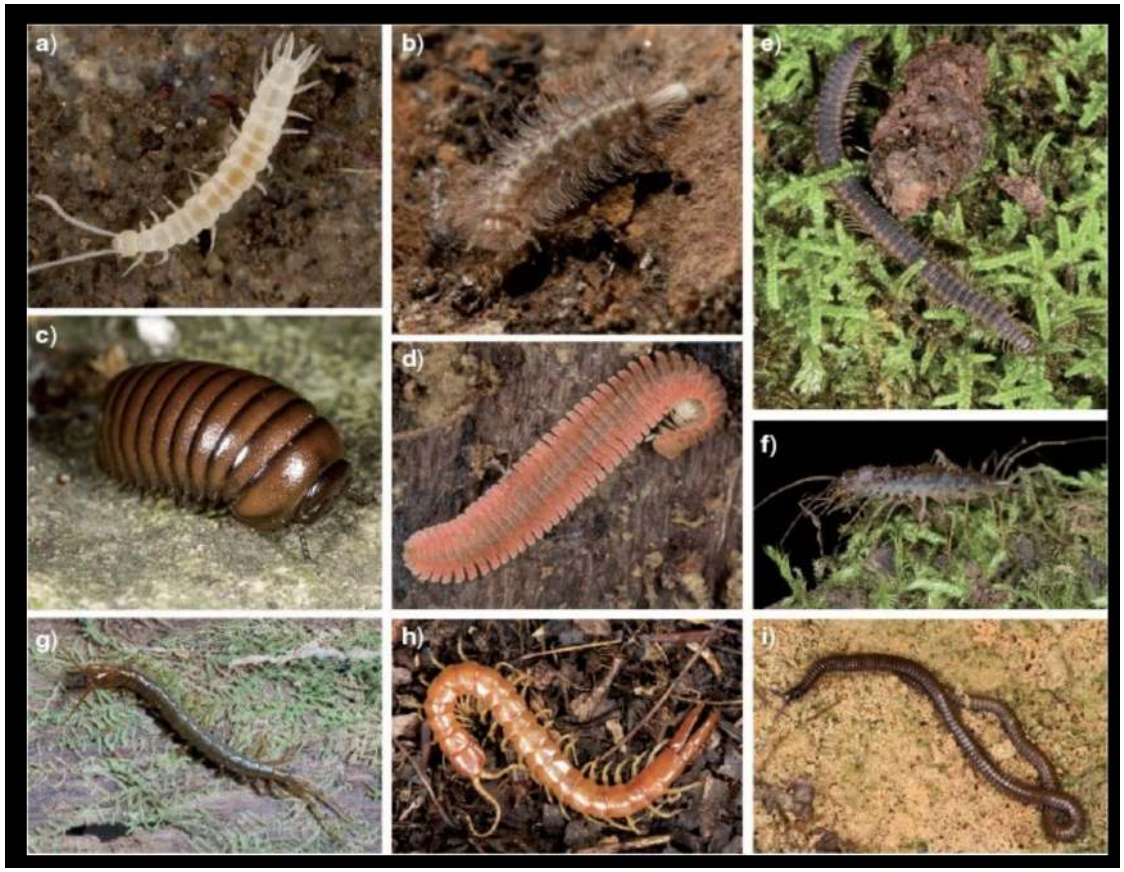

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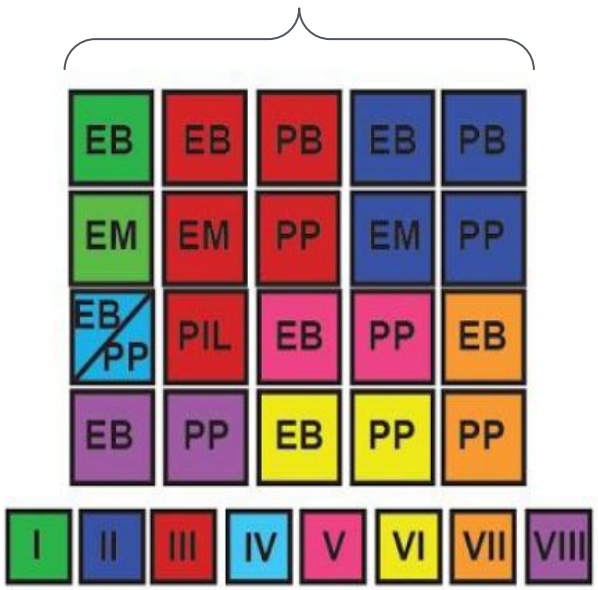

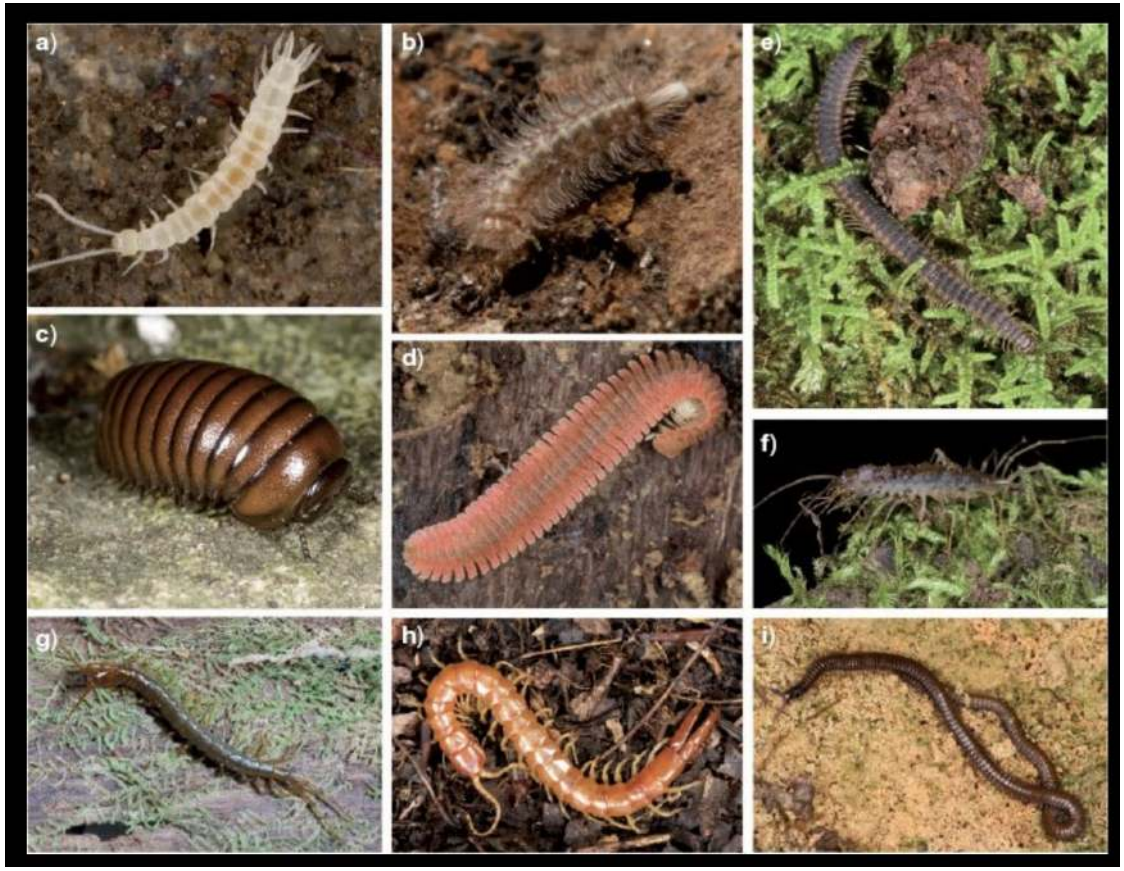

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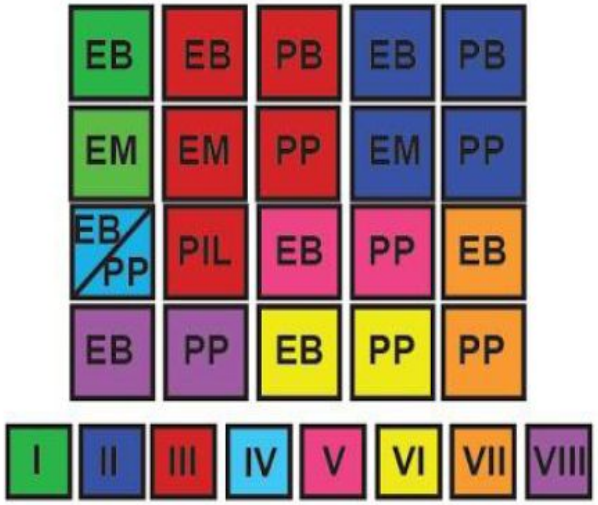

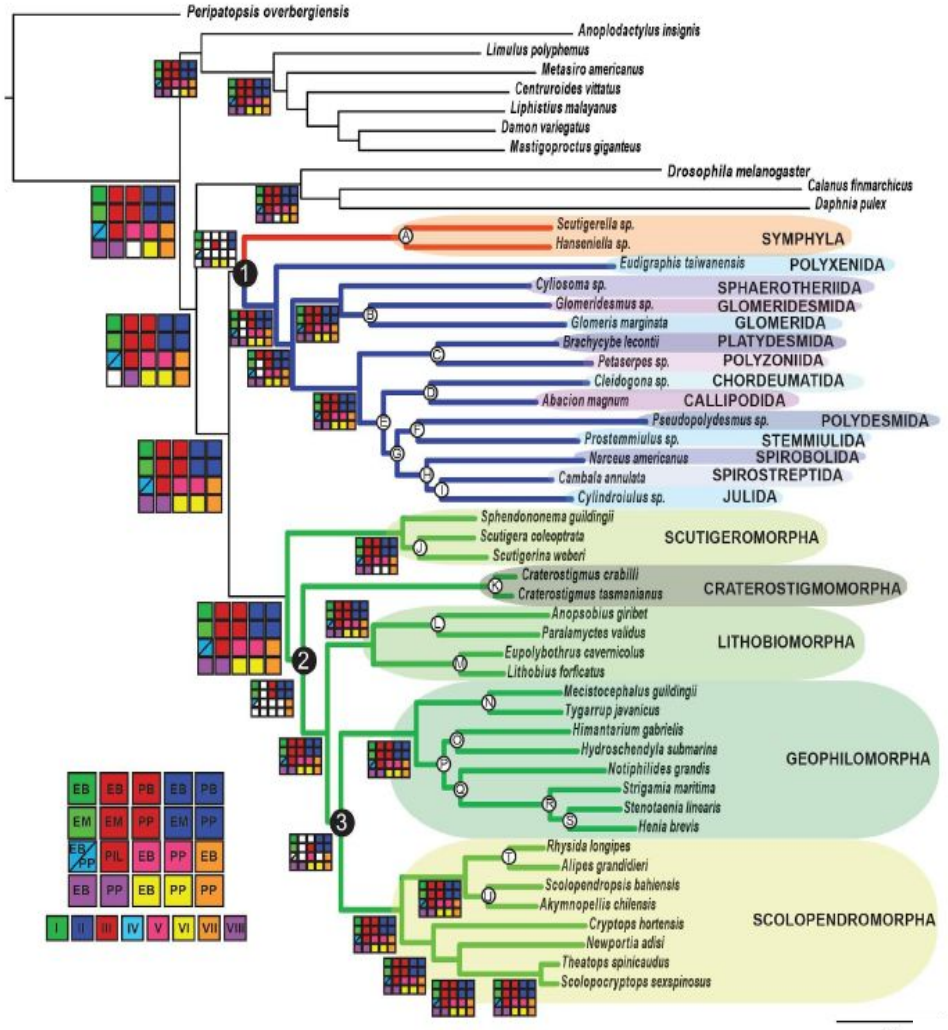

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