Computational Challenges from the Tree of Life

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- Summary and Conclusions

Phylogenies: What?

A phylogeny is a reconstruction of the evolutionary history of a collection of organisms.

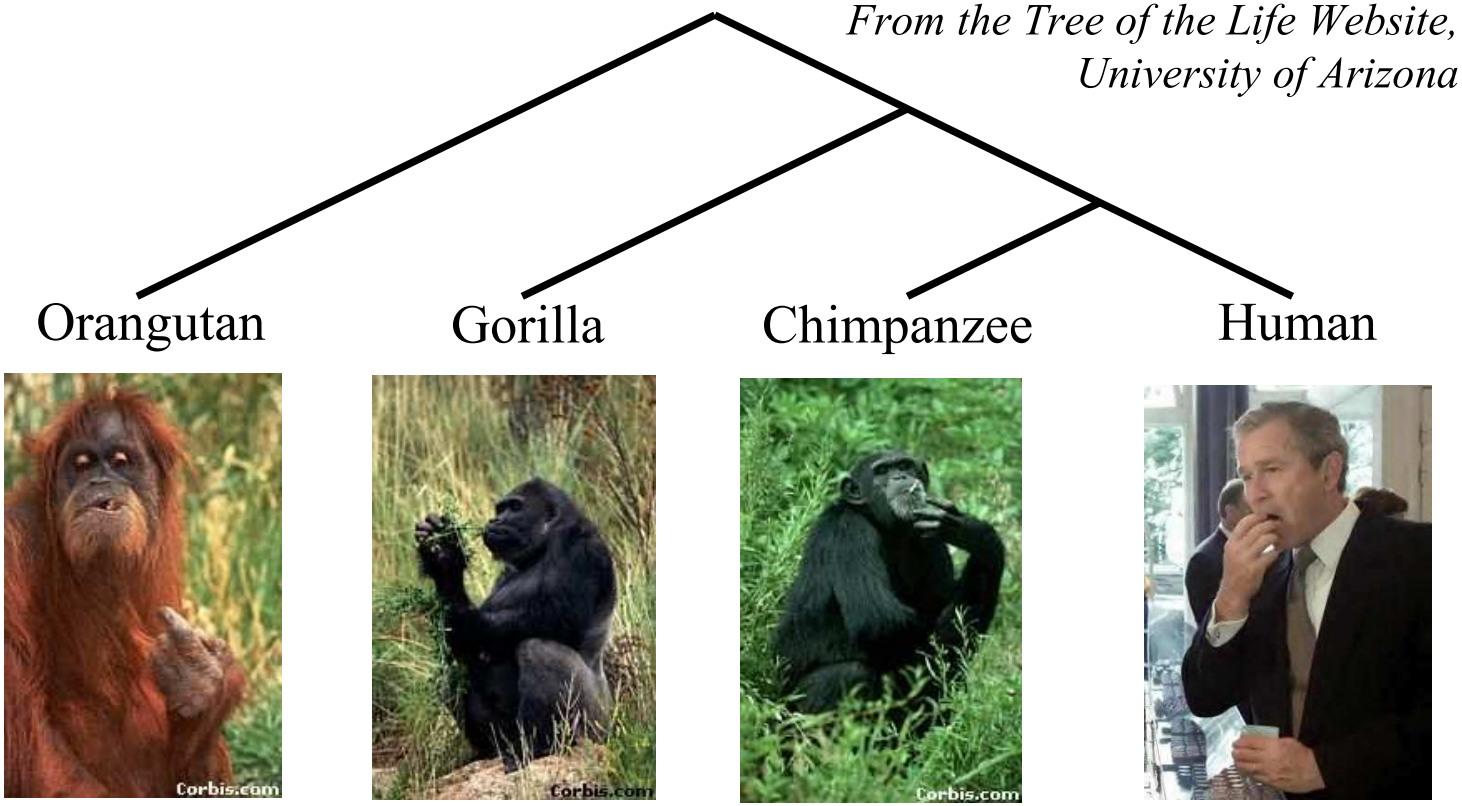
It usually takes the form of a tree.

- Modern organisms are placed at the leaves.
- Edges denote evolutionary relationships.
- “Species” correspond to edge-disjoint paths.

The Great Apes

Phylogeny

From the Tree of the Life Website, University of Arizona



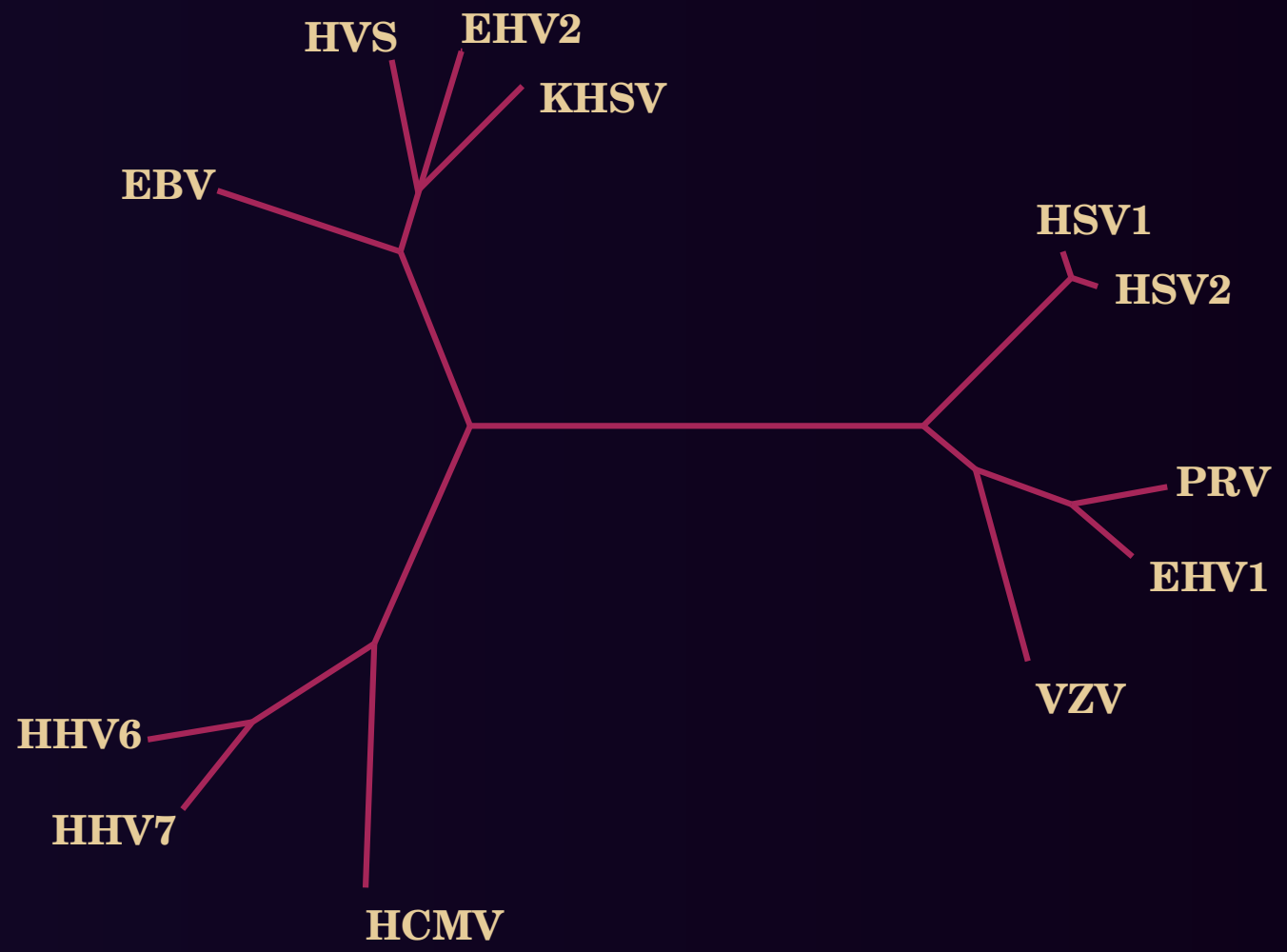
Phylogenies: Why?

Phylogenies provide the framework around which to organize all biological and biomedical knowledge.

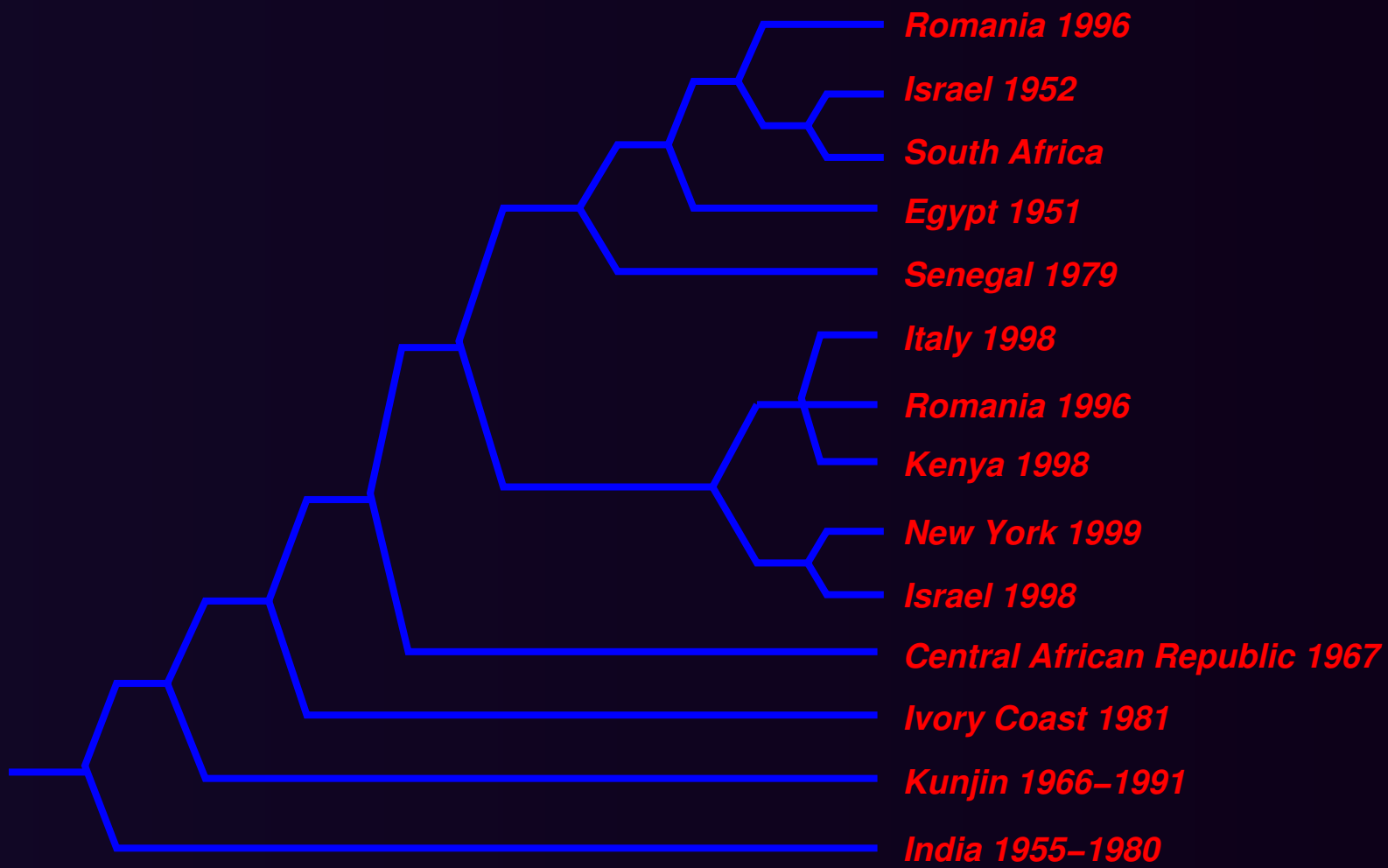
They help us understand and predict:

- functions of and interactions between genes
- relationship between genotype and phenotype
- host/parasite co-evolution
- origins and spread of disease
- drug and vaccine development
- origins and migrations of humans

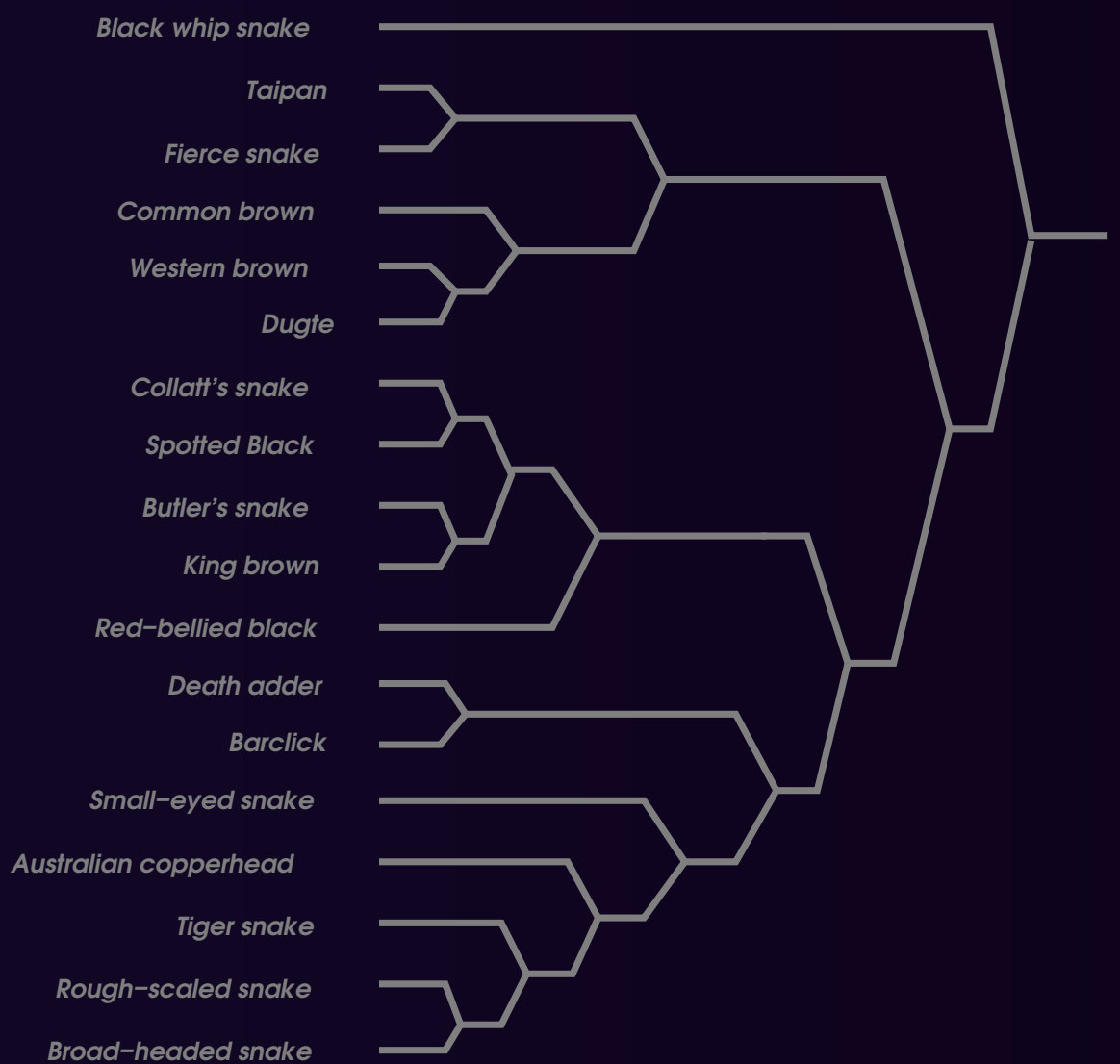
Herpes Viruses that Affect Humans



Epidemiology of West Nile Virus



Drug Design: Antivenins



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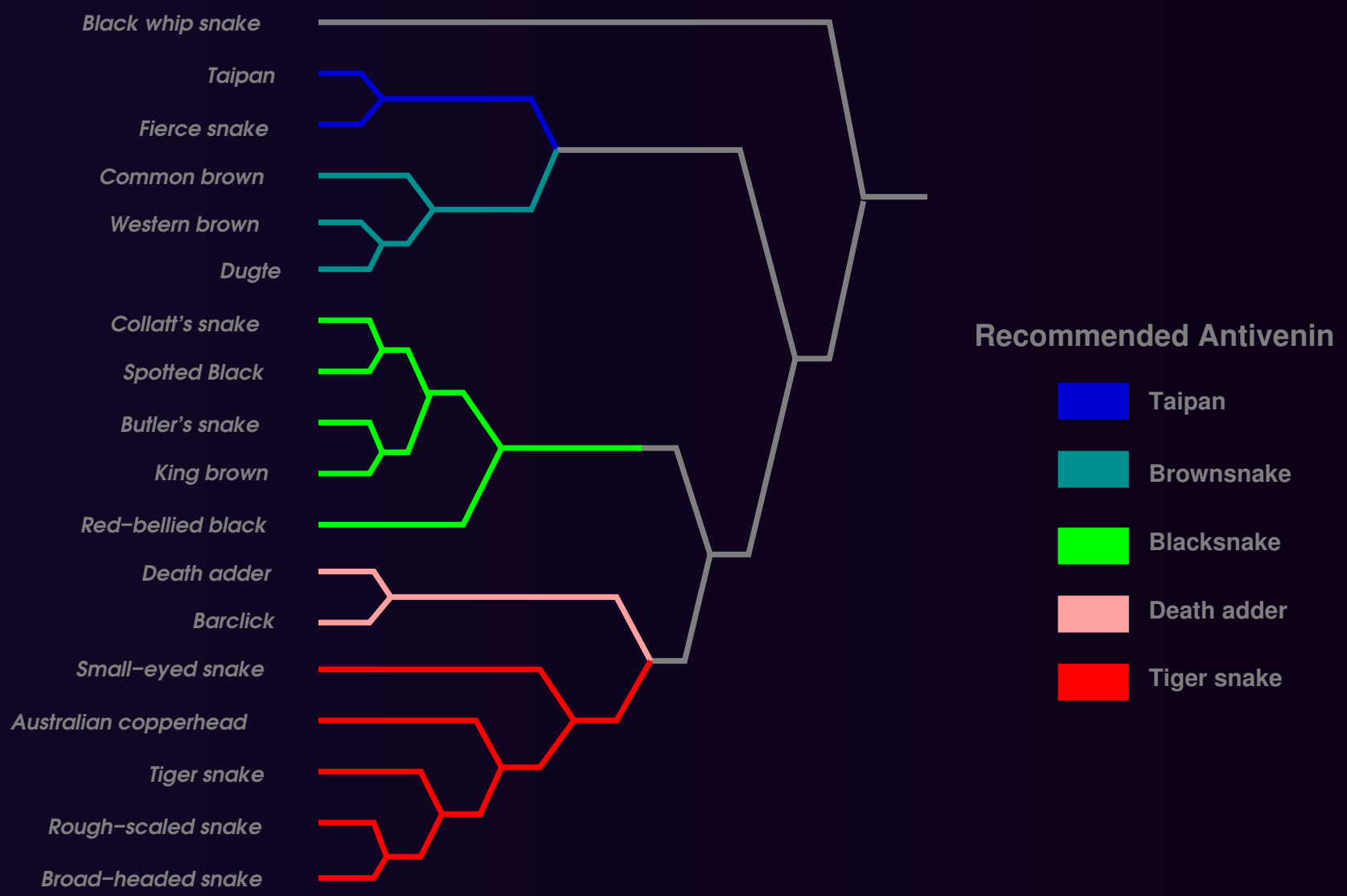
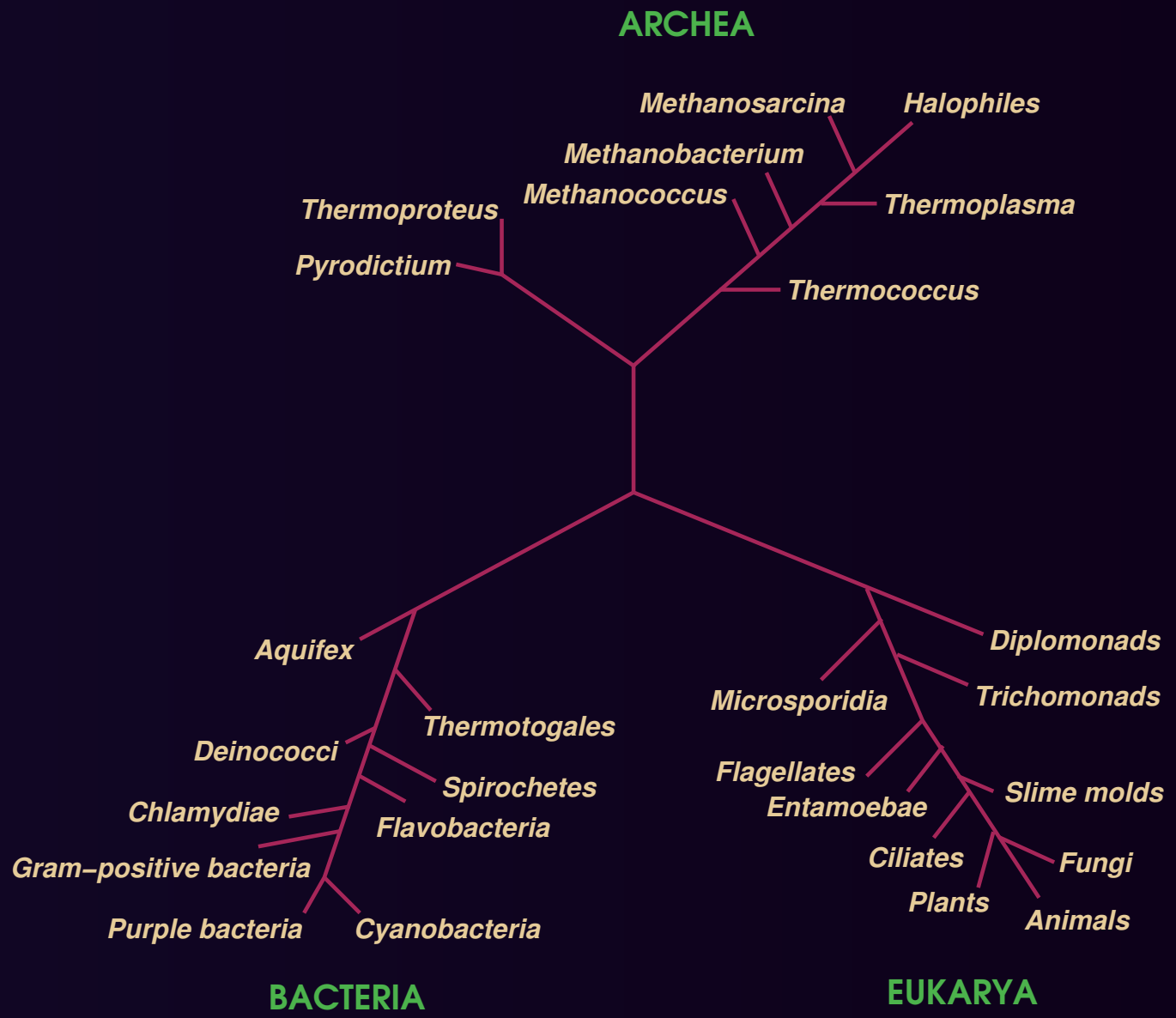


Grand Challenge: The Tree of Life



Scale of The Tree of Life

- 20 fully sequenced eukaryotic (plants, animals, protists) genomes
- 600 fully sequenced bacterial genomes
- Several sequenced genes for perhaps 50,000 species
- 1,5 million described species
- Estimates for existing species vary from 10 million to 200 million.
- Genome-based tools can handle 20–50organisms.
- Gene-based tools can handle 200–500 organisms.
- Both sets of tools scale exponentially with the amount of data.

Phylogenetic Reconstruction

- **Data:**
  behavioral, morphological, metabolic, molecular, etc.
  Main data today are DNA sequence data.
- **Models:**
  models of speciation, of population evolution, of molecular character evolution, etc.
- **Algorithms:**
  clustering, optimization, estimation of distributions, and heuristics.

Molecular Data

Typically the DNA sequence of a few genes.

Characters are individual positions in the string and can assume 4 states (nucleotides) or 20 states (codons).

Evolve through point mutations, insertions (incl. duplications), and deletions.

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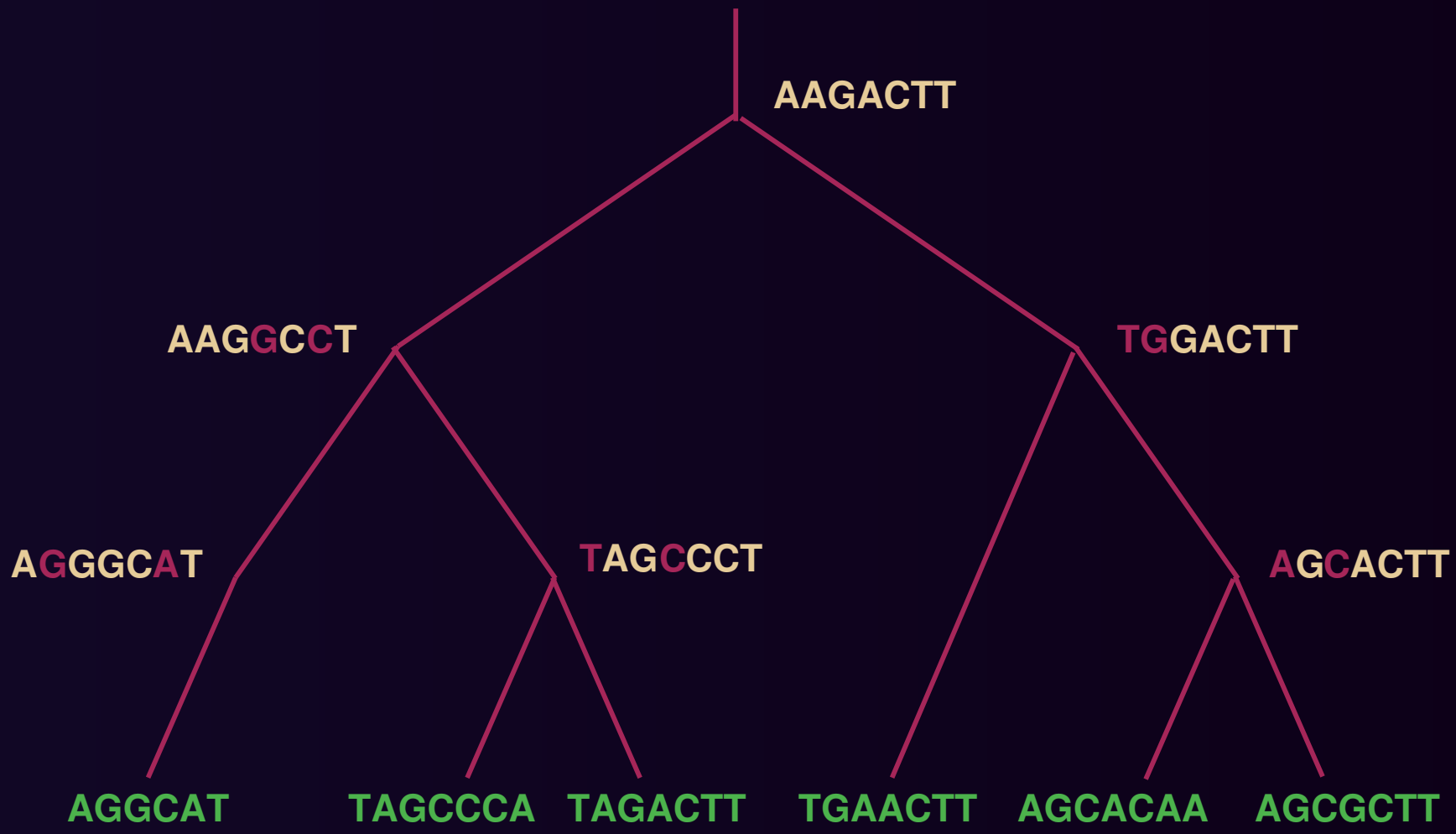
- Find homologous genes across all organisms.
- Align gene sequences for the entire set (to identify gaps—insertions and deletions—and point mutations).
- Decide whether to use a single gene for each analysis or to combine the data.
- Lengths limited by size of genes (typically several hundred base pairs)

Sequence Data: Illustration



Sequence Data: Attributes

- **Advantages:**
  - Large amounts of data available.
  - Accepted models of sequence evolution.
  - Models and objective functions provide a reasonable computational framework.
- **Problems:**
  - Fast evolution restricts use to a few million years.
  - Gene evolution need not be identical to organism evolution.
  - Multiple alignments are not well solved.

Gene-Order Data

The ordered sequence of genes on one or more chromosomes.

Entire gene-order is a single character, which can assume a huge number of states.

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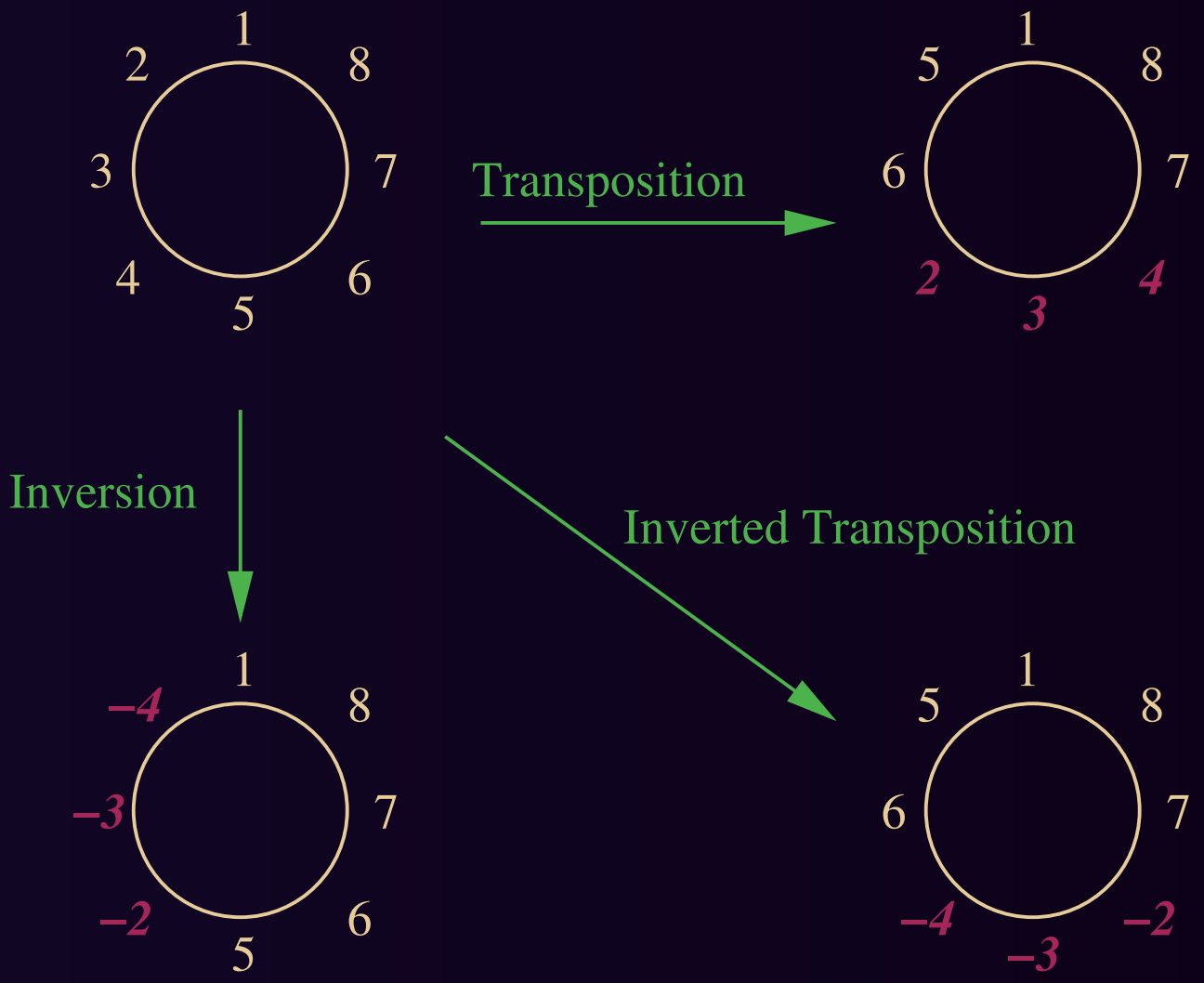
- Identify homologous genes, including duplications.
- Refine rearrangement model for given collection of organisms (e.g., handle bacterial operons or eukaryotic exons explicitly).

Gene-Order Data: Rearrangements



Gene-Order Data: Attributes

- **Advantages:**
  - No need for multiple alignments.
  - No gene tree/species tree problem.
  - Rare evolutionary events and unlikely to cause “silent" changes—so can go back hundreds of millions years.
- **Problems:**
  - Mathematics *much more complex* than for sequence data.
  - Models of evolution not well characterized.
  - Very limited data (mostly organelles).

Other Data

- **protein folds**
  remarkably conserved, but give rise to very complex models
- **metabolic pathways**
  highly specific, but insufficient for large datasets
- **morphological characters**
  not as clearly inherited and inherently fuzzy
- **etc.!**

Models

Good models emerge from collaborations among biologists, mathematicians, and computer scientists; they are:

- **biologically plausible:** they produce credible data and possess explanatory power.
- **mathematically sound:** it is possible to prove desirable properties (convergence, consistency, etc.).
- **computationally tractable:** producing data is easy and reversing the model is possible.

Speciation Models

Usually based on a birth-death process: in any time interval, there are given probabilities for extinction or speciation; also known as the coalescent or Yule-Harding model.

But need more data and refinements:

- *inheritance of tendency to speciate*
- *punctuated equilibrium*
- *connection to population genetics*

Molecular Evolution Models

From large amounts of data, models build transition matrices (4×4 for nucleotides, 20×20 for aminoacids).

- *Widely used to estimate evolutionary rates and well supported by data.*
- *Still assume independence among sites (e.g., each nucleotide or codon evolves indepedently of the others).*
- *Remain unconnected to speciation model.*

Algorithms

Algorithms

Two main categories of methods:

- Distance-based methods (UPGMA, neighbor-joining) work from a matrix of pairwise distances.
- Criterion-based methods (Minimum Evolution, Maximum Parsimony, and Maximum Likelihood) rely on an underlying model and attempt to infer or reconstruct additional data.

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In addition:

- Meta-methods (quartet-based methods, disk-covering method) decompose the data into smaller subsets, construct trees on those subsets, and use the resulting trees to build a tree for the entire dataset.

Evolutionary Distances

- **True evolutionary distance:**
  the actual number of permitted evolutionary events that took place to transform one datum into the other.
- **Edit distance:**
  the minimum number of permitted evolutionary events that can transform one datum into the other.
- **Expected true evolutionary distance:**
  obtained from the edit distance by correcting for the known (model or experiments) statistical relationship between true and edit distances.

Distance-Based Methods

- Use edit or expected true evolutionary distances.
- Usually run in *low polynomial time*.
- Reconstruct *only topologies*: no ancestral data.
- Prototype is Neighbor-Joining (NJ).
- NJ is optimal on *additive* distances (where the distance along a path in the true tree equals the pairwise distance in the matrix).
- NJ is *statistically consistent* (produces the true tree with probability 1 as the sequence length goes to infinity).

Parsimony-Based Methods

- Aim to minimize (weighted) total *number of character changes*.
- Assume that characters are *independent*.
- Reconstruct *ancestral data*.
- Known not to be statistically consistent with sequence data.
- Finding most parsimonious tree is NP-hard.
- Optimal solutions limited to about 30; heuristics appear fairly good to about 500.

Likelihood-Based Methods

- Based on a specific model of evolution and *estimate all model parameters*.
- Produce a *likelihood estimate* (prior or posterior conditional) for each tree.
- Statistically consistent.
- Reconstruct *only topologies*.
- Prone to numerical problems:
  likelihood of typical trees is infinitesimal.
- Presumably NP-hard; even scoring one tree is very expensive.
- Optimal solutions limited to 4; heuristic solutions appear fairly good to about 100.

Meta-Methods

General Principle:

decompose the dataset into smaller, overlapping subsets, reconstruct trees for the subsets (by some base method), and combine the results into a tree for the entire dataset.

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- Quartet-based methods:
  use all possible smallest subsets (quartet: set of 4 genomes); best-known is Tree-Puzzle.

  Slow and *inherently inaccurate* for any base method.
- Disk-covering method (DCM):
  set up graph from distance matrix, find overlapping triangulated subgraphs, use them for decomposition.

  High-powered machinery *succeeds* very well, especially when tree is imbalanced.

Limitations and Challenges

- **Accuracy**
  not a matter of optimization, but of *scientific truth*!
  how does it scale? how do we evaluate it?
- **Computational Demands**
  all criterion-based optimizations are NP-hard
  the more accurate the model, the worse the problem
- **Data Integration**
  a single type of data cannot answer all questions
  but integration is beyond our reach
- **Database Design**
  database “search" is often a linear search: complex objects give rise to difficult queries

Limitations on Accuracy

- **True distances cannot be computed**
- **Insufficient sequence length**
- **Primitive or erroneous models**
- **Algorithmic idiosyncrasies**
  (NJ suffers with high diameter, MP suffers from long branch attraction, ML cannot be optimized)
- **Gene evolution is not species evolution**
- **Not a tree, but a directed acyclic graph**
  (due to hybridization, lateral gene transfer, etc.)

Evaluating Accuracy

- There is only one instance!
- We want the truth,
  but it cannot be known or measured
- Optimization is done on surrogate criteria
- Simulation studies are only as good as models
- Parameter space is ridiculously large
- What matters: tree structure? edge lengths? data at internal nodes?

Database Challenges

A simple query such as

> what is the percentage of trees in the DB in which organisms $x_1, \ldots, x_m$ and organisms $y_1, \ldots, y_n$ occur in distinct subtrees?

requires a linear search through the DB!

The famous BLAST algorithm was designed to speed up a similar linear search.

How can we preprocess and store the data so as to avoid linear searches?

Research in my Laboratory

- *Scaling up methods through algorithm design, algorithm engineering, and high-performance computing.*
- *Whole-genome rearrangements in phylogenetic analysis and comparative genomics.*
- *Reticulate (non-tree) evolution and its reconstruction.*
- *Computing directly from databases (rather than in-core).*

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DCM Methods

Three varieties so far:

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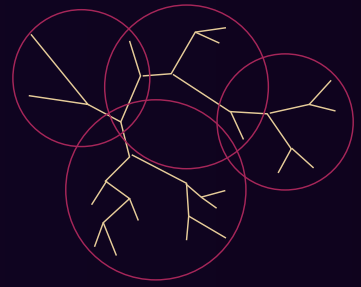
- DCM-1: Disks are cliques, to minimize diameter.



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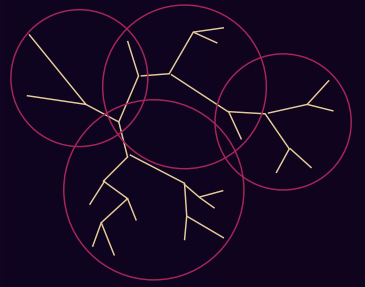
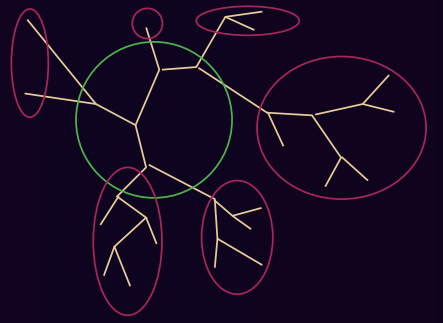


- DCM-2: Disks are made of a graph separator plus a component, so all disks share same subset.



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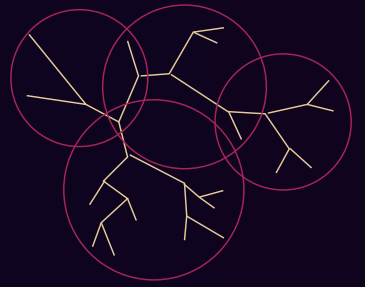

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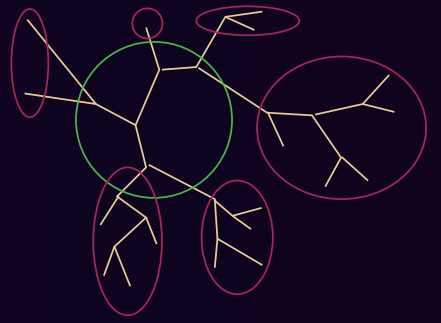


- Rec-I-DCM-3: Uses recursion and iteration, the latter controlled through a *guide tree*.

DCM-Boosted Methods

- DCM-1-NJ (with an MP last step) beats NJ and greedy MP on sequence data and is robust against size, rate, and other model variations.
- DCM-1-GRAPPA scales gracefully from the limit of 15 genomes for GRAPPA to at least 1,000 genomes.
- Rec-I-DCM-3 with MP does better than any other method on large real datasets and scales to at least 15,000 taxa..

Direct Approaches: BPAnalysis

(due to Sankoff and Blanchette)

- **Initially label all internal nodes with gene orders**
- **Repeat**
  - **For each internal node *v*, with neighbors *A*, *B*, and *C*, do**
    - **Solve the *MPB* on *A, B, C* to yield label *m***
    - **If relabelling *v* with *m* improves the tree score, then do it**
- **until no internal node can be relabelled**

GRAPPA

Genome **R**earrangements **A**nalysis under
Parsimony & other **P**hylogenetic **A**lgorithms

GRAPPA

Genome Rearrangements Analysis under Parsimony & other Phylogenetic Algorithms

- Began as a reimplementation of **`BPAnalysis`**.
- Current version runs up to one billion times faster than **`BPAnalysis`**, thanks to *algorithmic engineering*. (Fast code, better bounding, caching results, ordering computations, etc.)
- Limit: every added taxon multiplies the running time by twice the number of taxa.
  So 13 taxa take 20 mins, 15 taxa two weeks, 16 taxa a year, 20 taxa over 2 million years, and . . .

DCM-GRAPPA

Our extension to GRAPPA to scale it to large datasets (Tang and Moret).

- Scales gracefully to at least 1,000 genomes (less than 2 days of computation).
- Retains accuracy of GRAPPA: error rates on 1,000-genome datasets are consistently below 3%.
- Uses the DCM-1 approach—may do even better with forthcoming DCM-3.

DCM-GRAPPA: Details

- **Compute pairwise distances**
- **Check all possible threshold values**
- **For each threshold value**
  - Discard values above threshold
  - Create graph from reduced distance matrix
  - Triangulate the graph
  - Find maximum cliques (disks) in the graph
  - Run GRAPPA (or recursive DCM-GRAPPA) on the disks
  - Merge the resulting trees

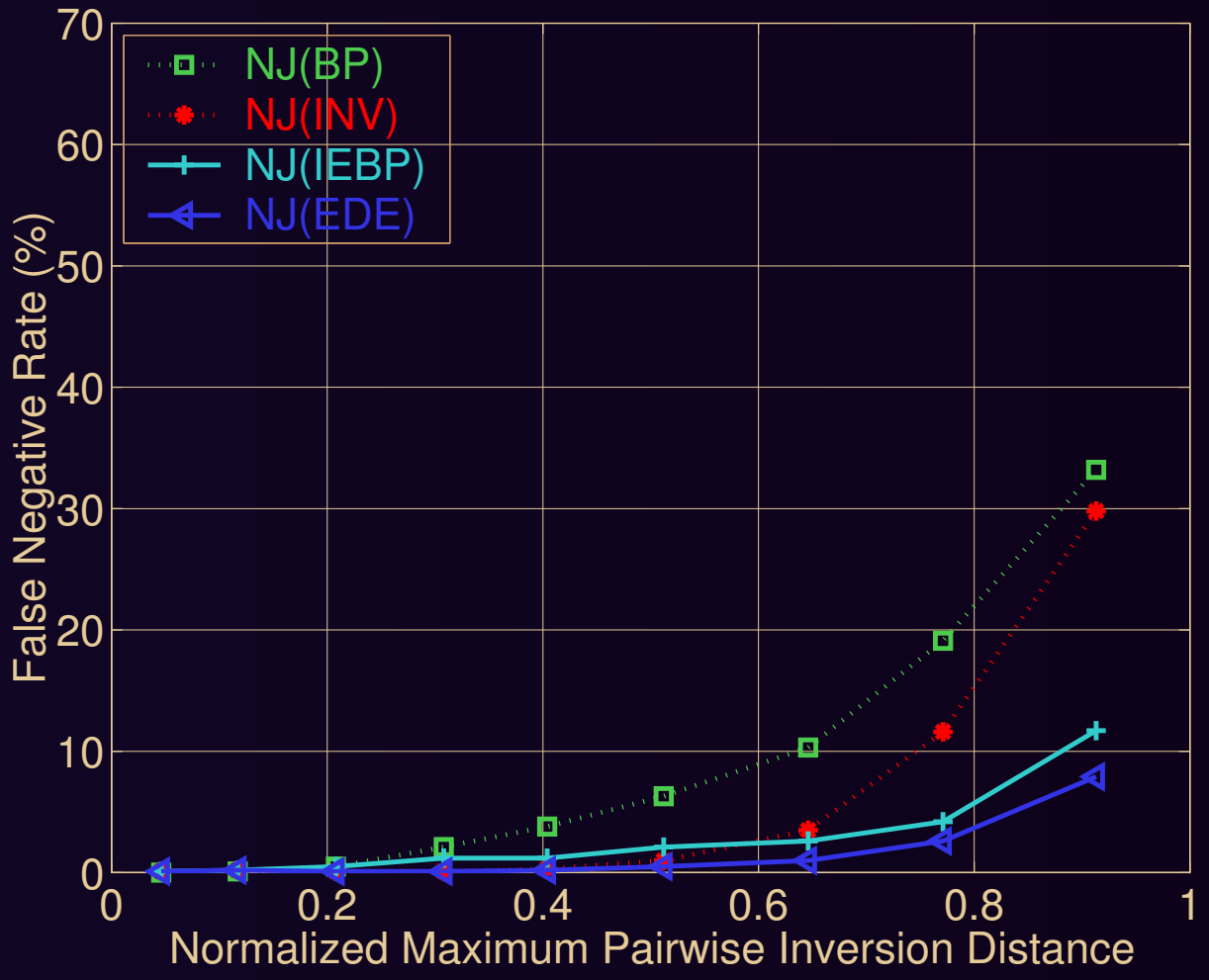
Testing Algorithms

How to choose test sets?

- Biological datasets test performance where it matters, but can be used only for ranking, are too few to permit quantitative evaluations, and are often hard ot obtain.
  Good for anecdotal reports and “reality checks."
- Simulated datasets enable absolute evaluations of solution quality and can be generated in arbitrarily large numbers.
  Only way to obtain valid characterizations.

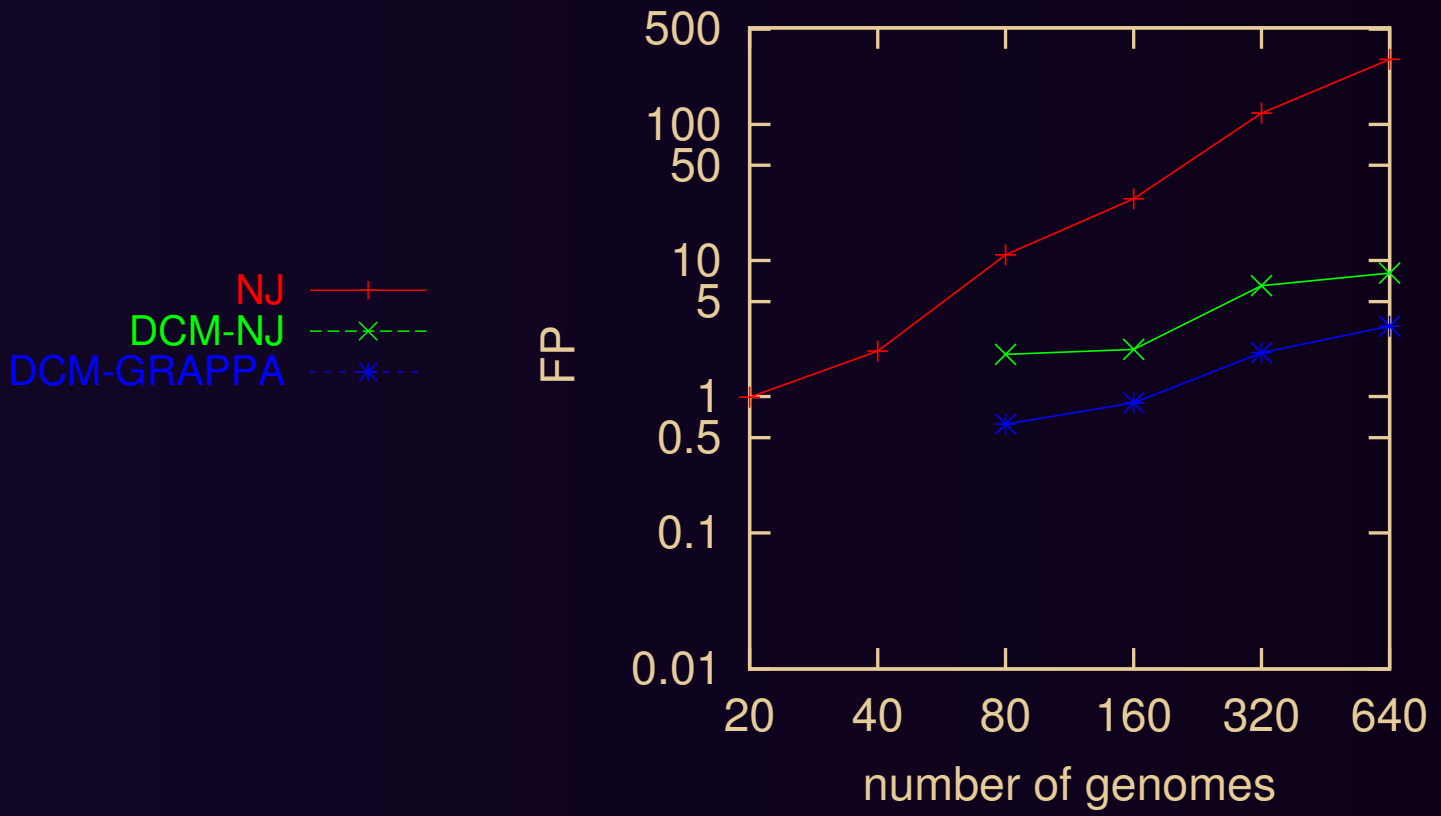
Results: Distance Methods

inversion/transposition/inverted transposition: 1:1:1 ratio
120 genes per genome, 10-20-40-80-160 genomes



Results: DCM-GRAPPA

inversion-only evolution, expected edge length 4
100 genes per genome, 20-40-80-160-320-640 genomes

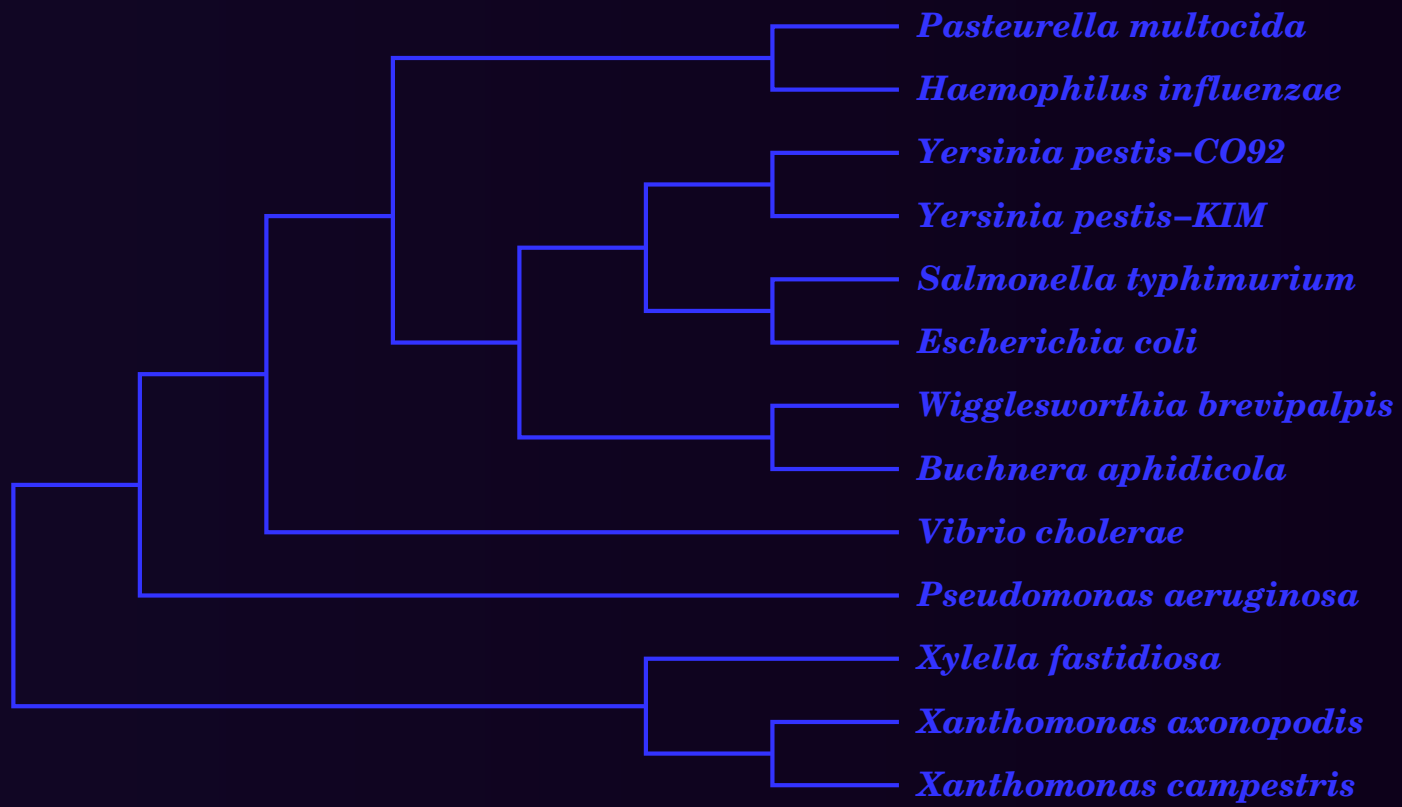


Shown is total number of edges in error (log/log scale)

Results: Unequal Gene Content (1)

Fresh off the Press: Bacterial Distances

13 gamma-proteobacteria:
from 500 genes for *B. aphidicola* (obligate endosymbiont)
to $5,000$ genes for *P. aeruginosa*



Results: Unequal Gene Content (2)

$3,430$ gene families after dropping singletons.
We concatenated the 2 chromosomes of *V. cholerae*.

Baphi	0	302	339	343	330	299	317	277	343	343	341	297	306
Ecoli	461	0	1141	1710	1175	465	1332	530	1484	1484	1040	981	991
Hinfl	484	809	0	889	574	815	827	520	829	825	745	824	823
Paer	492	1634	1050	0	1126	1624	1363	530	1574	1586	1006	1546	1577
Pmult	497	871	643	987	0	873	895	519	894	891	784	880	890
Styphi	451	458	1152	1725	1190	0	1350	520	1501	1505	1048	991	1035
Vchol	467	1115	1017	1245	1063	1120	0	511	1202	1184	929	1082	1105
Wigg	294	338	378	377	363	337	354	0	401	400	391	334	341
Xaxo	457	1379	932	1475	986	1395	1225	533	0	174	727	1281	1298
Xcamp	460	1385	934	1472	984	1403	1206	530	176	0	736	1275	1279
Xfast	454	916	780	902	806	915	865	503	553	555	0	888	895
Y_CO92	459	913	1110	1575	1147	923	1210	505	1340	1332	991	0	163
Y_KIM	468	940	1114	1609	1170	967	1250	514	1346	1335	996	166	0

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- **Notes:**
  - **We used the reference phylogeny to compute gene content and to assign loss vs. gain—hence the asymmetry.**
  - **Some pairwise distances are enormous: up to $1,600$ events!**
    On some paths, each edge has at least 400 events on it.

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  - **Some pairwise distances are enormous: up to $1,600$ events!**
    On some paths, each edge has at least 400 events on it.
- **NJ Reconstruction**
  ***Only one edge* is in error: the edge leading to *V. cholerae*, due to our handling of its two chromosomes.**

Conclusions

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- Current approaches remain unable to handle unequal gene content with duplications, but major progress has been made over the last 5 years.
- Data availability is increasing rapidly for organellar genomes, slowly for nuclear genomes, and remains very limited compared to sequence data.

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Laboratory for
High-Performance Algorithm Engineering
and Computational Molecular Biology

Includes all publications by our lab, GRAPPA source files, email addresses, and links to our main collaborators.