Systematics

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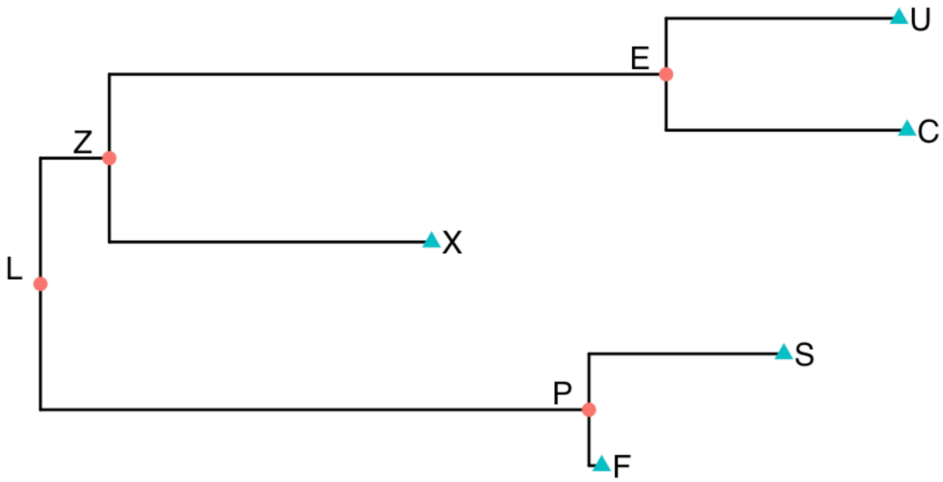
Goals

- Introduction to methods and models for phylogenetic inference
- Parameter selection
- Common language

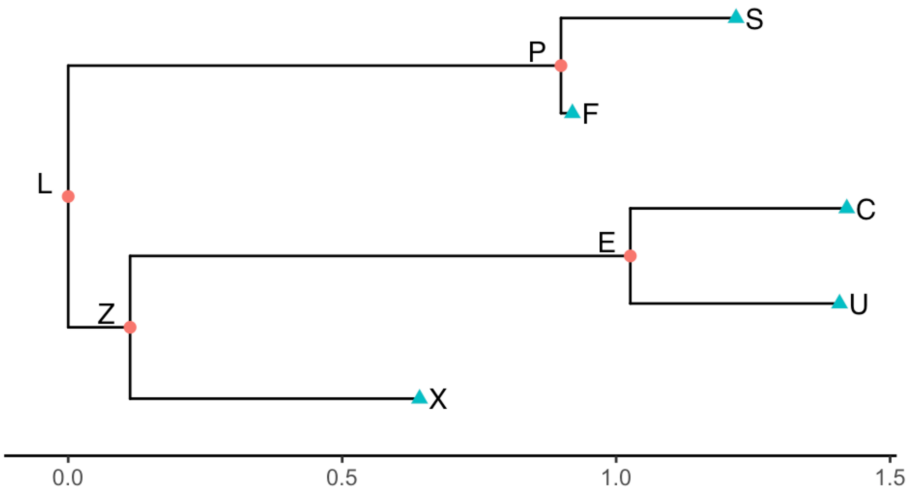
Dissecting a Tree

- Node (vertex) = divergence point
  - Internal nodes = nodes with at least one child branch
  - External nodes = nodes without child branches. Aka: “leaves”, “tips”,
- Branch (edge) = connection
  - Branch length represents the amount of distance
  - Can be external (terminating at a leaf), or internal



More on Phylogenetic Trees

- Observed (sequenced) samples are on branch tips.
- Time runs from root to tip
- The order of the leaves don't really mean anything
- Most Recent Common Ancestor (MRCA)
  - Or, Last Common Ancestor (LCA)
  - Located on internal node and Hypothetical!



Constructing Phylogenetic Trees – distance matrix-based

- **Algorithmic**

- Unweighted Pair-Group Method with Arithmetic Mean (UPGMA)
  - Branch lengths are equally split
  - Fitch-Margoliash (FM) Method modifies this to do least-squares estimate of branch length

- Neighbor-Joining (NJ) - Saitou and Nei, 1987
  - Pairwise distance matrix → overall divergence → adjusted distance matrix
  - Not a bad heuristic and useful for initial starting tree

Phylogenetic Inferences directly from sequences

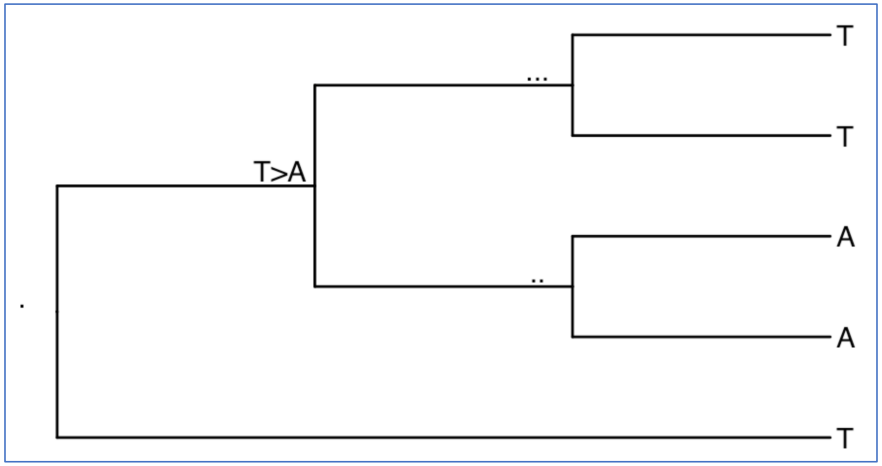
Maximum Parsimony

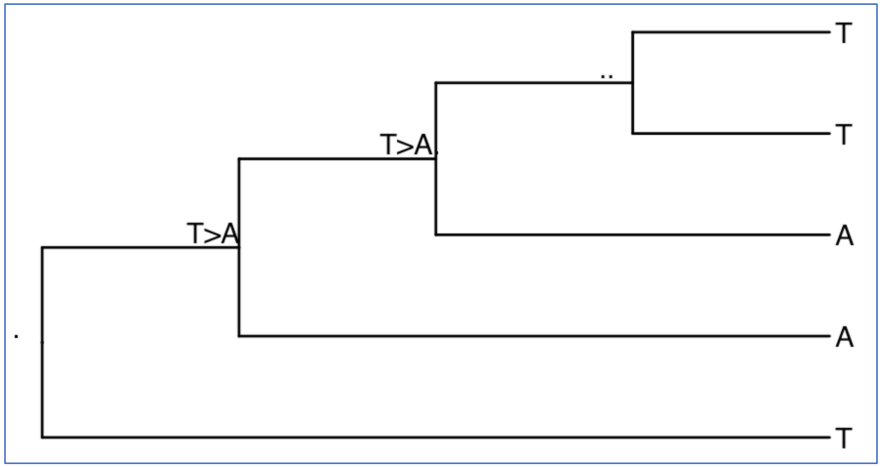
- Out of all possible trees, the best tree will have the least number of evolutionary (substitution) events
- Assumptions
  - Homologous similarity – identical alleles came from a common ancestor
  - Homoplasy (such as convergent evolution or reversal) is rare

Maximum Likelihood

- Max(Pr(data|tree)), given:
  - A sample set of sequences, and
  - A nucleotide substitution (evolutionary) model
- Assumptions
  - Evolutionary model
- Very computationally intensive!

Maximum Parsimony





Maximum Likelihood

- Topology
  - Nearest-neighbor interchange (NNI)
    - Given a topology, local arrangements are assessed for likelihood by successively deleting interior branches and testing the other possible reconstructions
    - Needs branch length (sequence distances) to compute
  - Subtree prune and regraft (SPR)
  - Tree bisection and reconnection (TBR)

- Branch length
  - Sum of log-likelihood for each nucleotide at each site (position), given a topology

Branch Support

- **Bootstrapping (Felsenstein 1985)**
  - In general, bootstrapping = random subsampling with replacement
  - Estimates the statistical error when sampling distribution is unknown

  - In phylogenetic context, estimates the reliability (consistency) of the resultant (majority-rule) consensus tree
  - The final resultant tree might not be the overall maximum-likelihood tree

Lots of models available

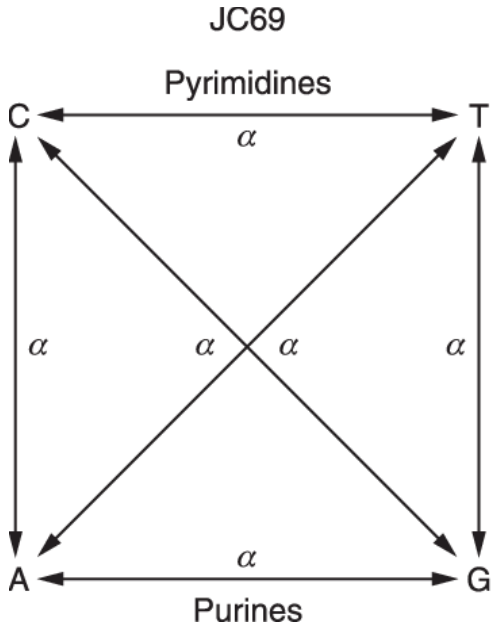
Model	df	Explanation	Code
JC or JC69	0	Equal substitution rates and equal base frequencies (Jukes and Cantor, 1969).	000000
F81	3	Equal rates but unequal base freq. (Felsenstein, 1981).	000000
K80 or K2P	1	Unequal transition/transversion rates and equal base freq. (Kimura, 1980).	010010
HKY or HKY85	4	Unequal transition/transversion rates and unequal base freq. (Hasegawa, Kishino and Yano, 1985).	010010
TN or TN93	5	Like `HKY` but unequal purine/pyrimidine rates (Tamura and Nei, 1993).	010020
TNe	2	Like `TN` but equal base freq.	010020
K81 or K3P	2	Three substitution types model and equal base freq. (Kimura, 1981).	012210
K81u	5	Like `K81` but unequal base freq.	012210
TPM2	2	AC=AT, AG=CT, CG=GT and equal base freq.	010212
TPM2u	5	Like `TPM2` but unequal base freq.	010212
TPM3	2	AC=CG, AG=CT, AT=GT and equal base freq.	012012
TPM3u	5	Like `TPM3` but unequal base freq.	012012
TIM	6	Transition model, AC=GT, AT=CG and unequal base freq.	012230
TIMe	3	Like `TIM` but equal base freq.	012230
TIM2	6	AC=AT, CG=GT and unequal base freq.	010232
TIM2e	3	Like `TIM2` but equal base freq.	010232
TIM3	6	AC=CG, AT=GT and unequal base freq.	012032
TIM3e	3	Like `TIM3` but equal base freq.	012032
TVM	7	Transversion model, AG=CT and unequal base freq.	012314
TVMe	4	Like `TVM` but equal base freq.	012314
SYM	5	Symmetric model with unequal rates but equal base freq. (Zharkikh, 1994).	012345
GTR	8	General time reversible model with unequal rates and unequal base freq. (Tavare, 1986).	012345

- Where to start…?

Basic Markov chain models for substitution

- **Jukes-Cantor (1969)**
  - Rate of nucleotide substitution is the same for all pairs

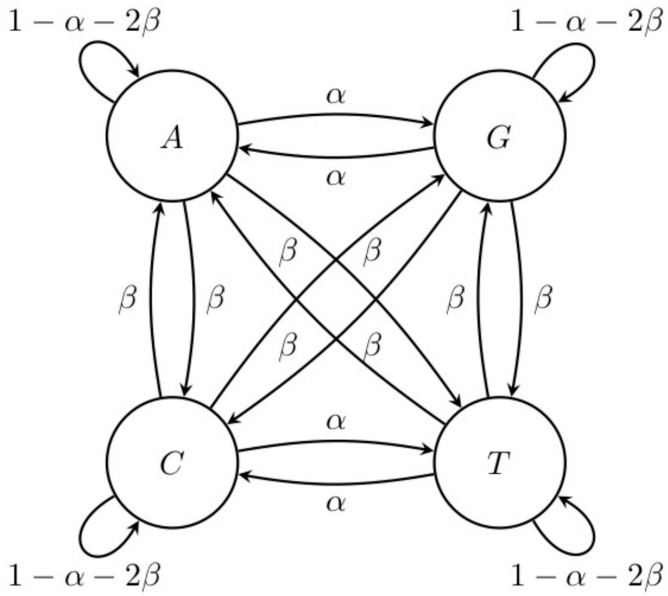
- See also: **Felsenstein (1981)**
  - Like Jukes-Cantor (equal substitution rates), but with unequal base frequency



More basic models for substitution

- **Kimura (1980)**
  - Transitions (intragroup changes) have a different rate than Transversions (intergroup changes

- See also: **Hasegawa-Kishino-Yano (1985)**
  - Like Kimura (unequal transition vs. transversion rates), but with unequal base frequency



More complex (less constrained) substitution models - GTR

- **General Time-Reversible substitution model - (Tavare 1986)**
  - Like HKY, but each possible nucleotide pair has it's own "exchangeability rate" along with unequal base frequencies
  - "Generalised time reversible (GTR) is the most general neutral, independent, finite-sites, time-reversible model possible."

$$Q = \begin{pmatrix} -(a\pi_C + b\pi_G + c\pi_T) & a\pi_C & b\pi_G & c\pi_T \\ a\pi_A & -(a\pi_A + d\pi_G + e\pi_T) & d\pi_G & e\pi_T \\ b\pi_A & d\pi_C & -(b\pi_A + d\pi_C + f\pi_T) & f\pi_T \\ c\pi_A & e\pi_C & f\pi_G & -(c\pi_A + e\pi_C + f\pi_G) \end{pmatrix}$$

Model modifications - gamma

- **+Γ (Yang 1994)**
  - Removes the assumption of per-site independence
  - Models rate heterogeneity in mutational rates across sites (ie: not all sites have equivalent nor independent mutational rates)
  - Applies gamma distribution with a shape parameter (alpha), itself usually estimated from the sample data

More complexities to address mutational heterogeneity

- Partitioning (categorization)
  - Apply specific models for a site or regions along a sequence
- Mixture models
  - Assign a model (out of a user-specified selection) on a per-site basis
- Some caution may need to be exercised to avoid over-parameterization

Why so many models and which to choose?

- Balancing between robustness and efficiency
  - ML criterion is **NP-hard**
  - Computational time, memory consumption…
- Inferential methods (ML, Bayesian) are statistically consistent
- GTR is probably the most popular model
- At least some form of rate heterogeneity modelling should be employed
- Statistical testing between models – Likelihood Ratio Tests
- Software packages and their features can help!

Bayesian Inferential Methods

- Allows for direct Pr(Tree|Data), but requires a prior probability distribution over all of the possible tree topologies…

- Uses Markov Chain Monte Carlo (MCMC) search methods
  - Metropolis coupled MCMC
  - Stochastic algorithms which should (in theory) help avoid getting trapped in sub-optimal solutions

- Can sometimes be faster than ML, but convergence is never certain

Optimizations

- Heuristics and Approximations
- Hybrids and Combinatorial approaches
  - FastTree
- Technical optimizations