Lecture 11
Molecular phylogenetics

Course: Practical Bioinformatics (BIOL 4220)
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Lecture 11 outline

Last time: regex

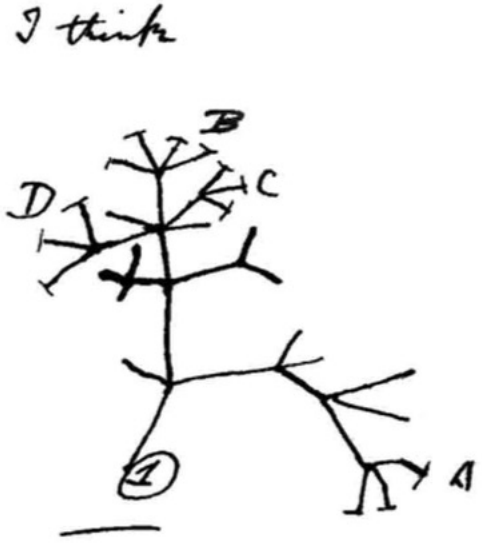
This time: phylogenetics

- interpreting trees
- tree-thinking
- inferring trees
- inference methods

Phylogenetics

Phylogenetics studies the relationships among evolutionary lineages (often called ***taxa***)

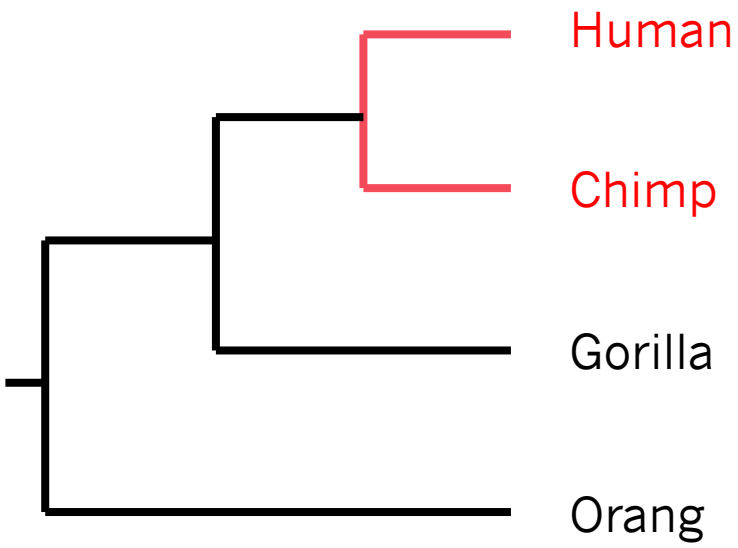
Phylogenies are useful for
- gene annotation
- tracking viral spread
- identifying zoonosis
- reconstructing tumorogenesis
- conservation biology assays
- inferring species relationships



phylogeny sketch
by Darwin

Reading a phylogeny

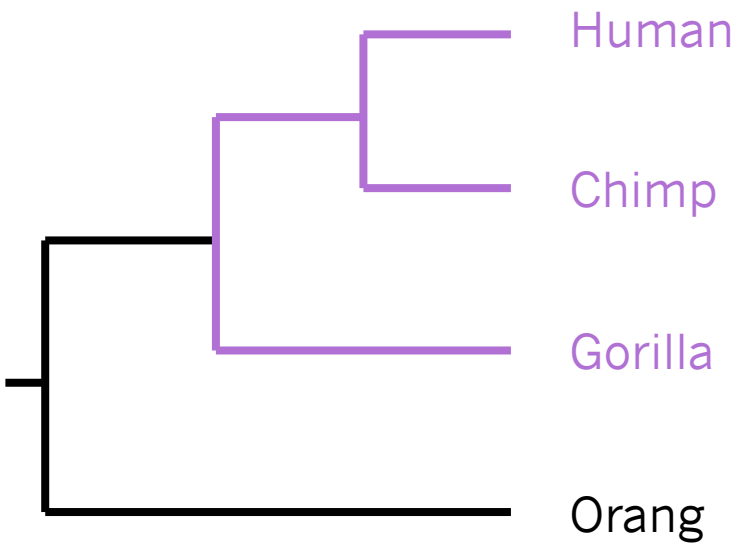
Phylogenetic relationships are hierarchical, and most often represented as bifurcating ***trees***



Human and Chimp are more closely related to each other than to Gorilla or Orang

Reading a phylogeny

Phylogenetic relationships are hierarchical, and most often represented as bifurcating ***trees***



Human, Chimp and Gorilla are more closely related to each other than to Orang

Reading a phylogeny

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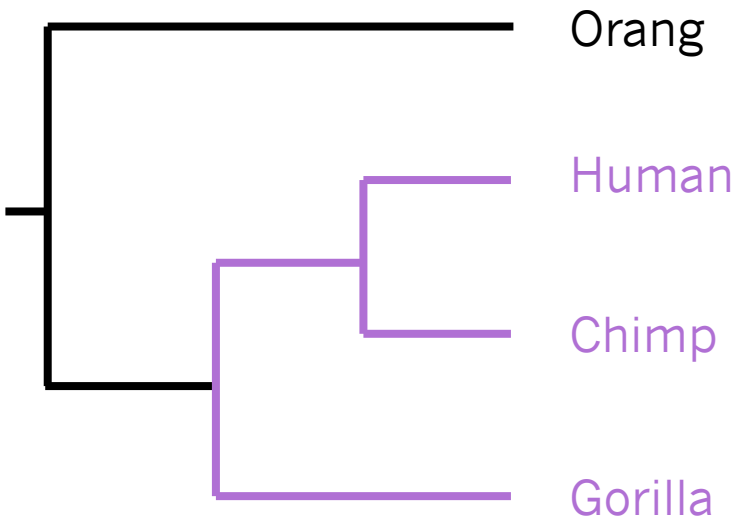
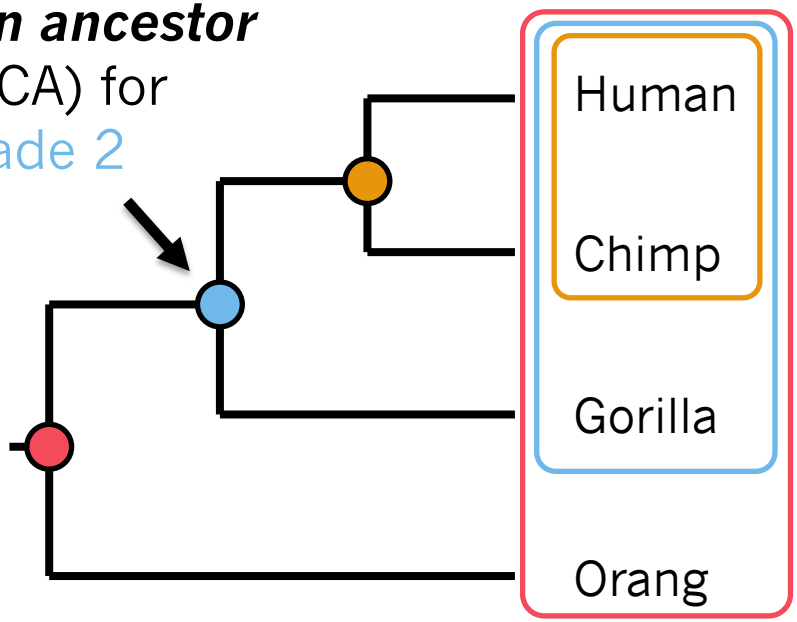


Human, Chimp and Gorilla are more closely related to each other than to Orang

Reading a phylogeny

Taxa that are more closely related to one another, over any other taxa, are called ***clades***

most recent common ancestor (MRCA) for Clade 2



Clade 1: H+C

Clade 2: H+C+G

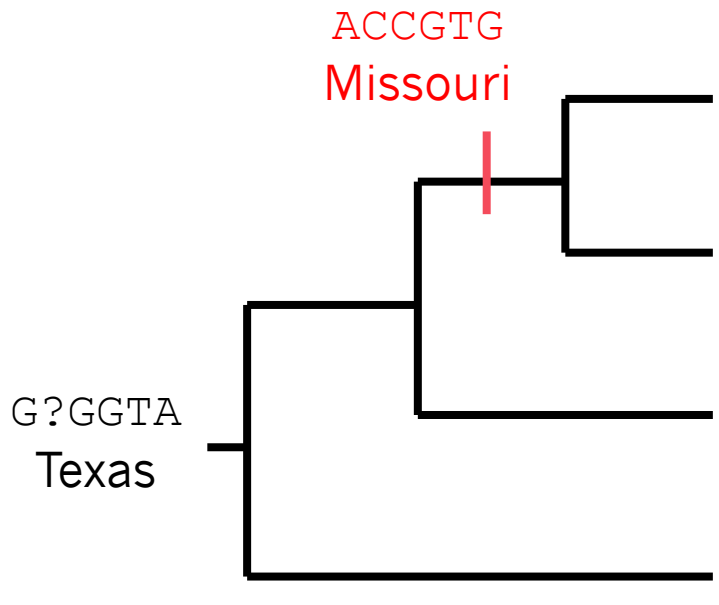
Clade 3: H+C+G+O

“Tree-thinking”

Taxon	Gene variant	Location
PT1	ACCGTG	Missouri
PT2	ACCGTG	Missouri
PT3	GAGGTA	Texas
PT4	GCGGTA	Texas

Four sequences,
but no historical context

“Tree-thinking”

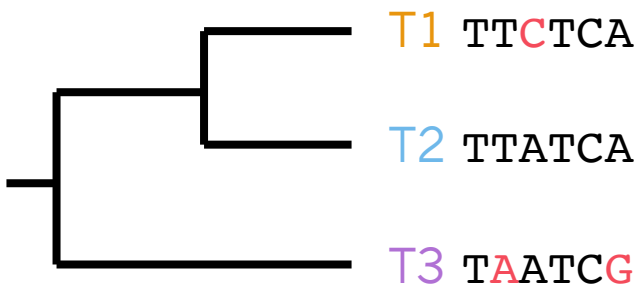


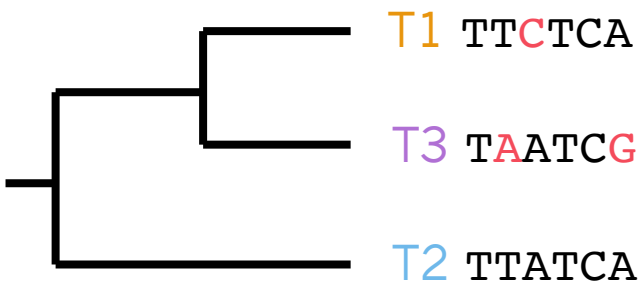
Taxon	Gene variant	Location
PT1	ACCGTG	Missouri
PT2	ACCGTG	Missouri
PT3	GAGGTA	Texas
PT4	GCGGTA	Texas

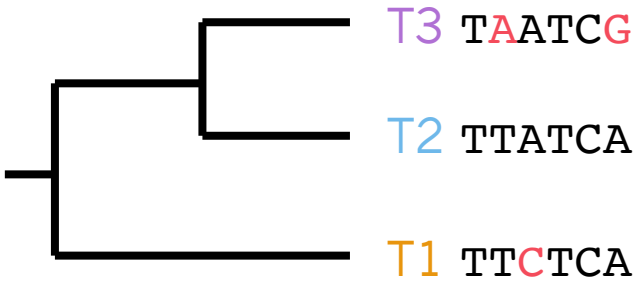
Phylogeny informs when and where variation arose, which can guide future research

Inferring phylogeny

How are taxa T1, T2, and T3 related?







Which phylogeny generated the observed pattern of molecular variation?

Inferring phylogeny

Phylogenetic inference methods take a matrix of characters (*e.g. DNA alignment*) as input

Measure how well any possible phylogenetic estimate explains the data matrix pattern by assigning a ***cost*** to each considered estimate

Methods generally ***optimize*** the cost to estimate the phylogeny with the lowest cost for the provided data matrix

Phylogenetic method types

Most methods used to infer phylogenies compute scores based on

1. pattern distances (*e.g.* ***neighbor joining***)
2. event counting (***parsimony***)
3. event probabilities (***likelihood***)

Method choice often relates to concerns regarding accuracy, speed, scalability, *etc.*

Tree-space is large

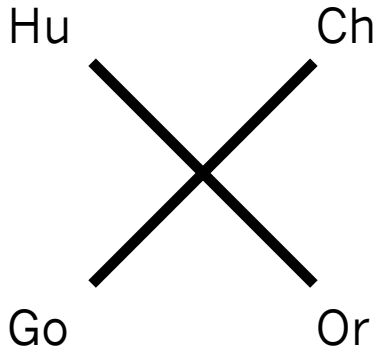
# taxa	# rooted trees
3	3
4	15
5	105
6	945
7	10395
8	135135
9	2027025
10	34459425

A major challenge: how to efficiently search for trees with optimal scores?

Neighbor-joining

	Hu	Ch	Go	Or
Hu	0	1	3	5
Ch	1	0	3	5
Go	3	3	0	2
Or	5	5	2	0

distance matrix
for sequence pairs



Select pairs of taxa with short sequence distances, and join them as neighbors

Neighbor-joining

	Hu	Ch	Go	Or
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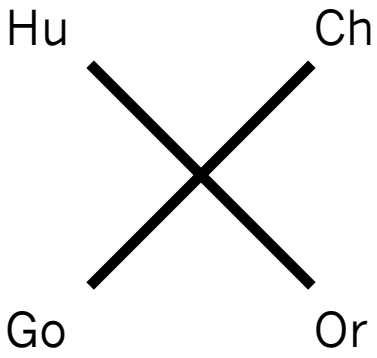
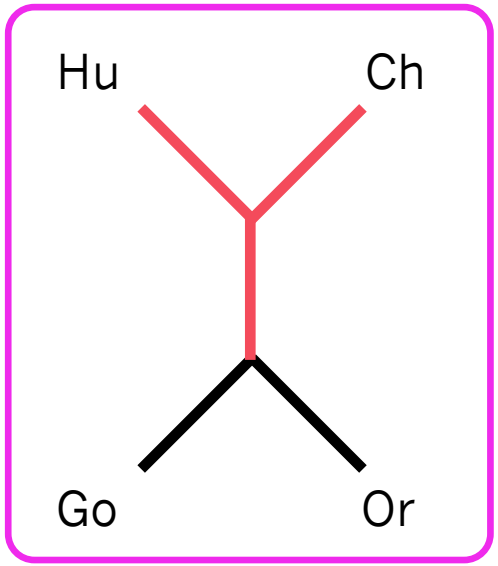
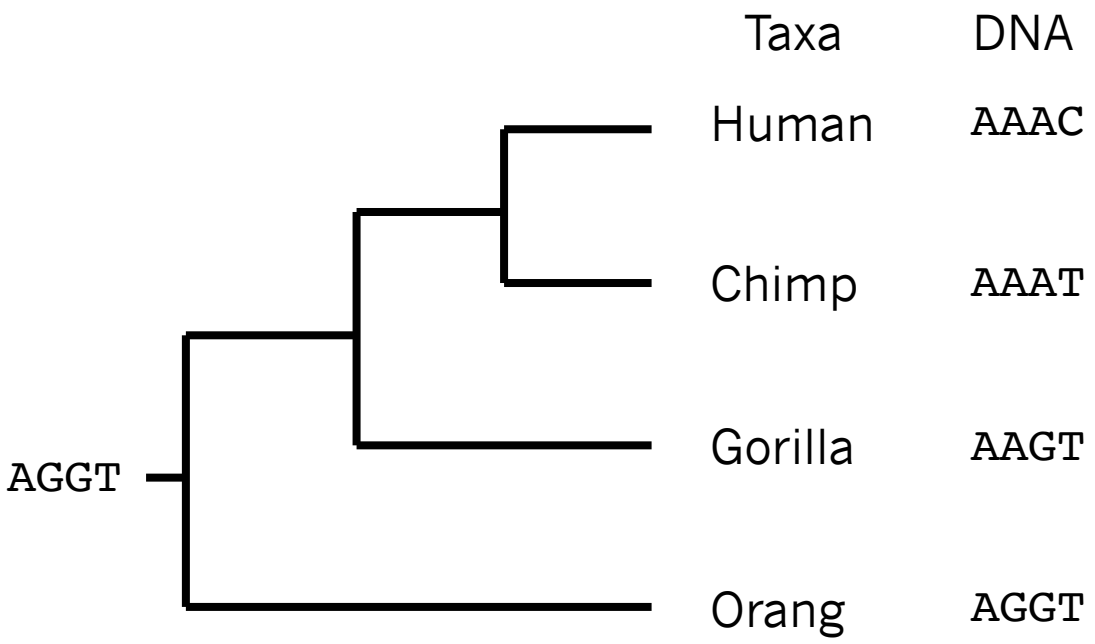


Hu and Ch
form a cluster



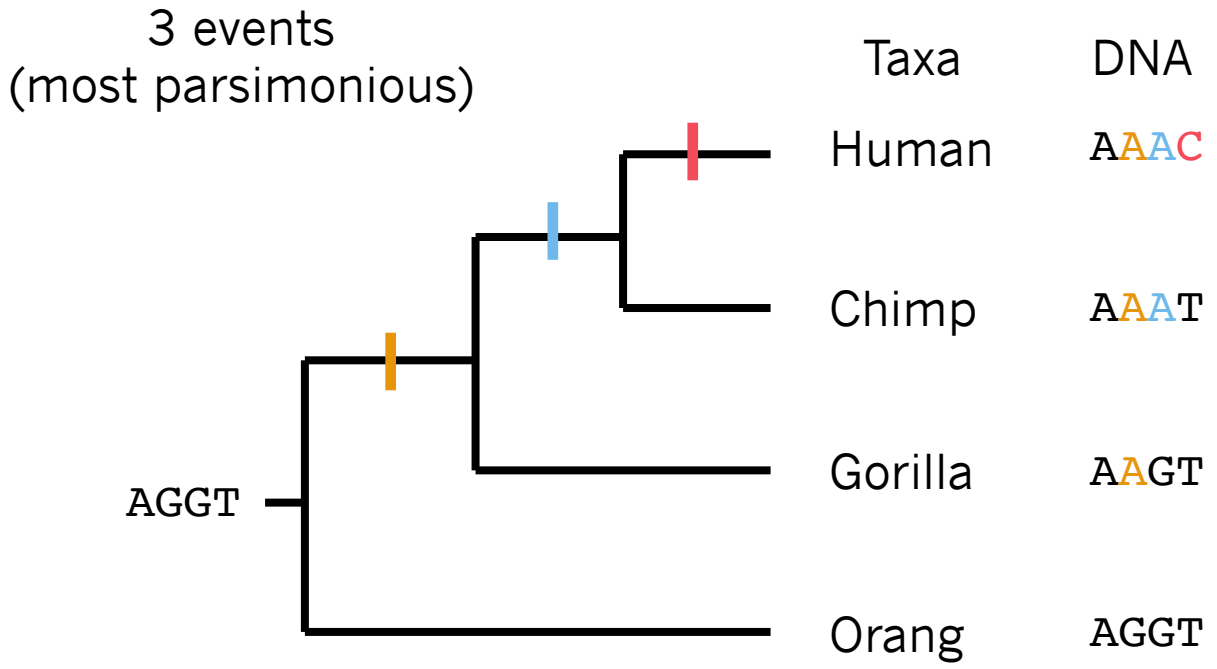
Select pairs of taxa with short sequence distances, and join them as neighbors

Parsimony



What phylogeny requires the fewest character change events?

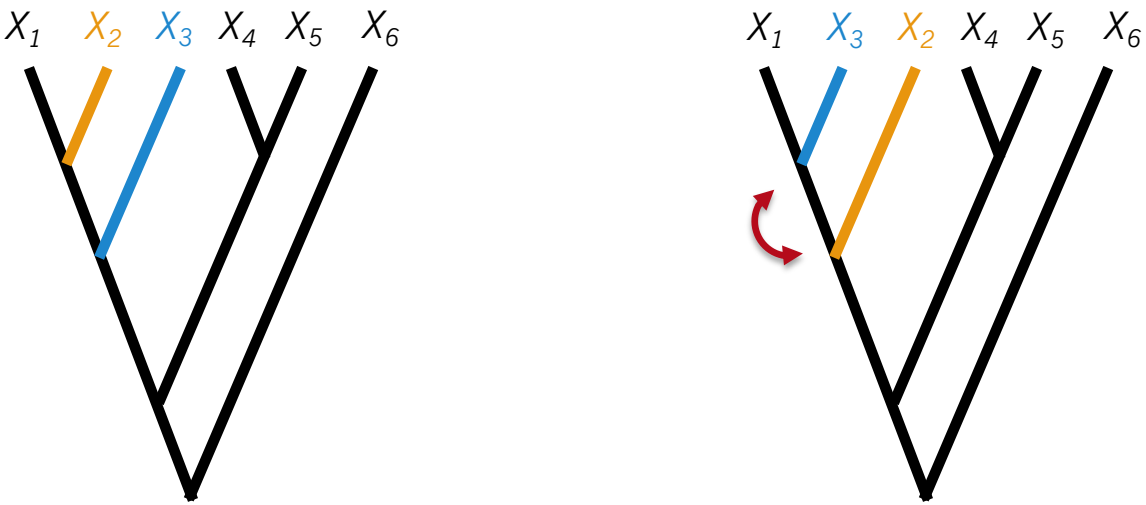
Parsimony



What phylogeny requires the fewest character change events?

Exploring tree space

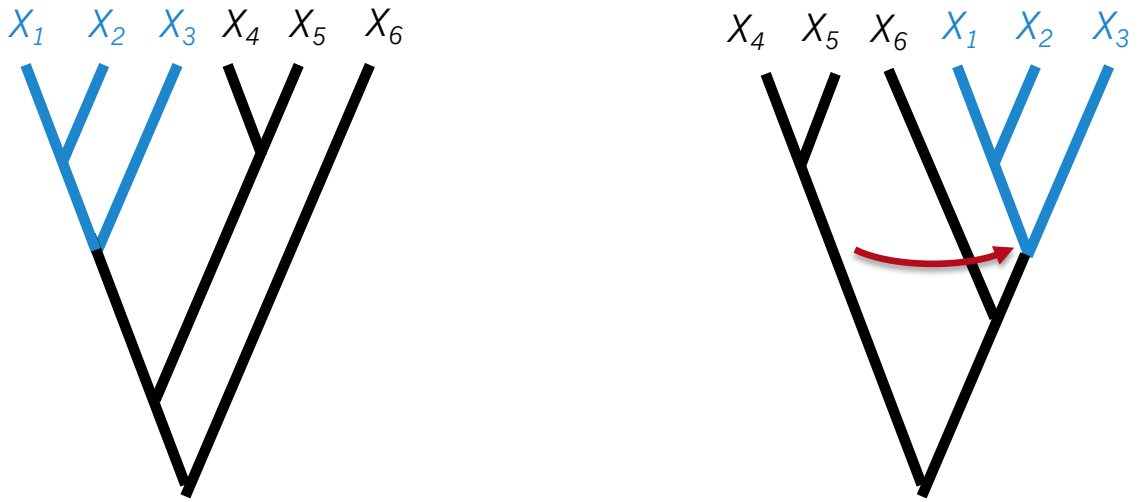
Define stochastic “moves” that modify topology, prefer moves that improve tree score



Nearest neighbor interchange (NNI)

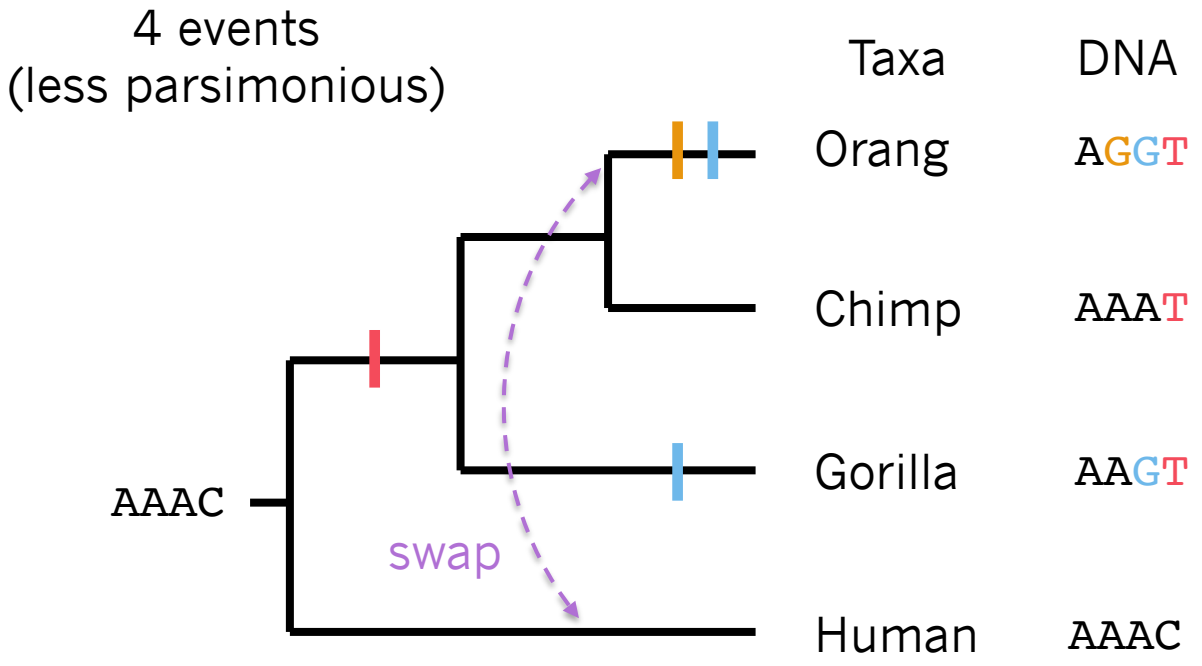
Exploring tree space

Define stochastic “moves” that modify topology, prefer moves that improve tree score



Subtree-prune-regraft (SPR)

Parsimony



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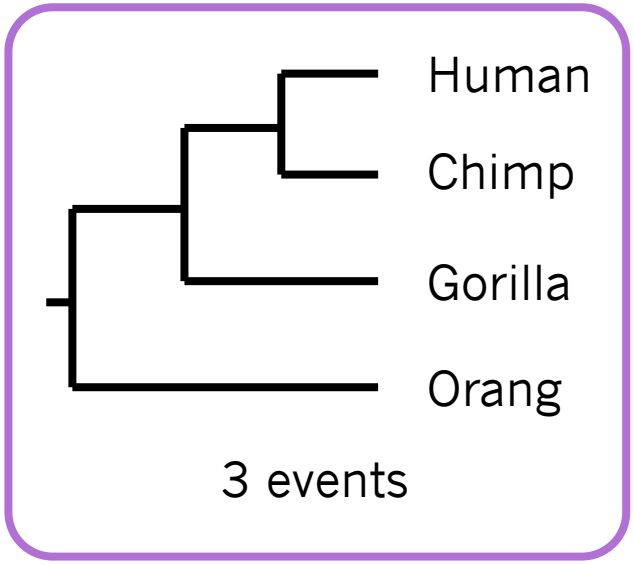
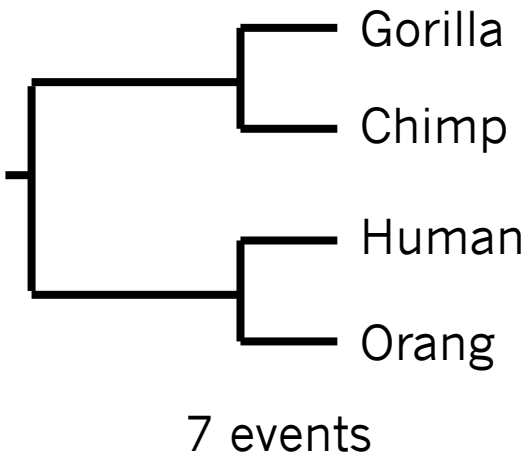
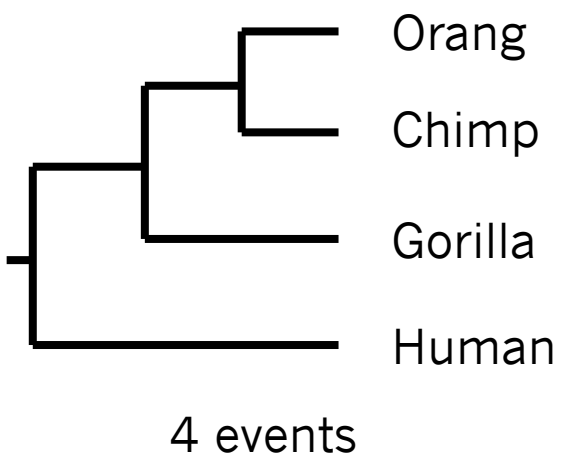
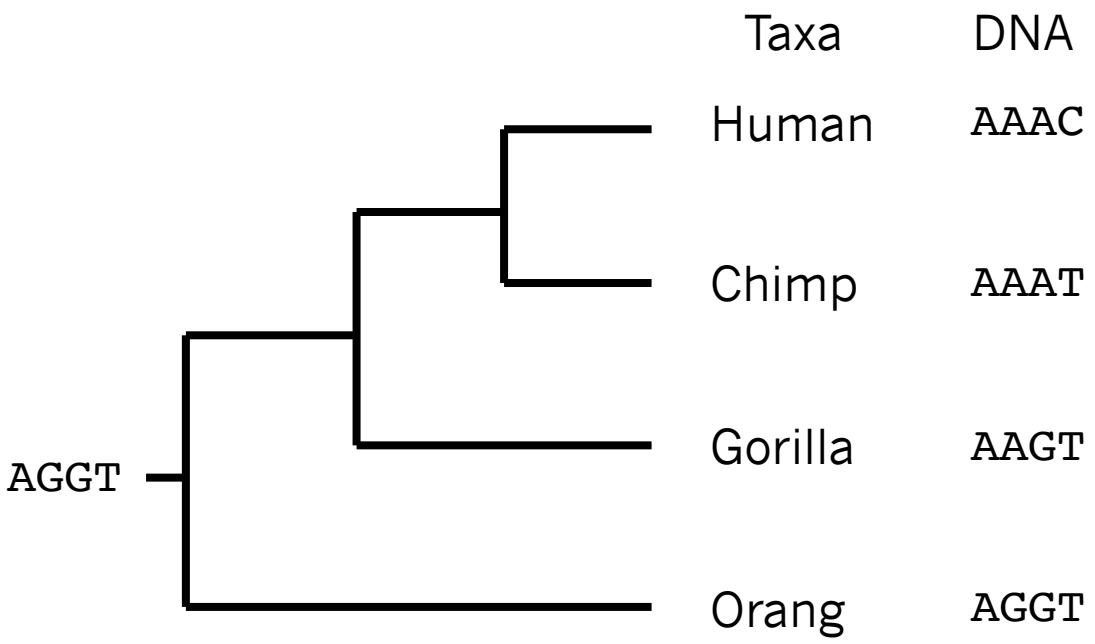






What phylogeny requires the fewest character change events?

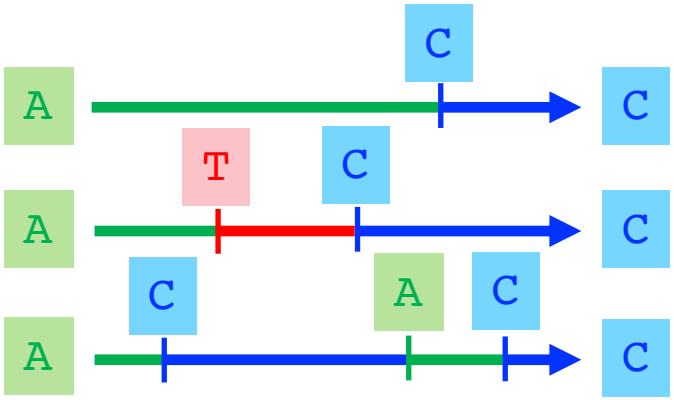
Likelihood



What phylogeny and model of evolution is *most likely* to generate the character data?

DNA evolution on branch

A single DNA site for branch *k* at time *t*
can be in one four discrete states: A, C, G, T

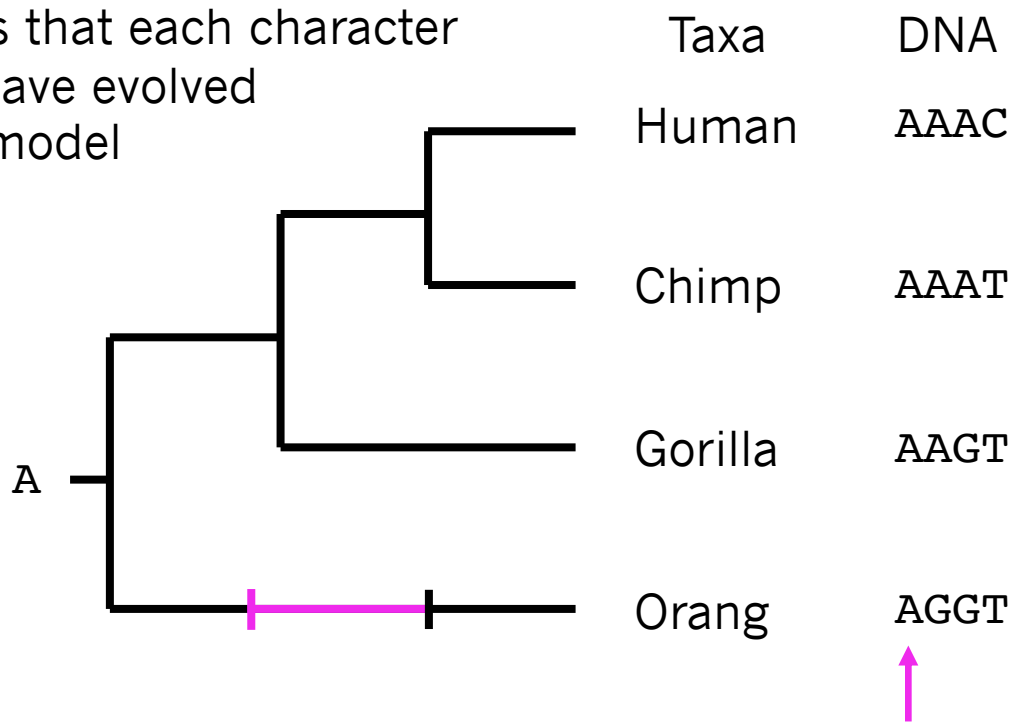


(possible evolutionary histories)

What is the probability that a DNA site in state *i*
will end in state *j* after time *t* for branch *k*?

Likelihood

Compute probability for all ways that each character could have evolved under model



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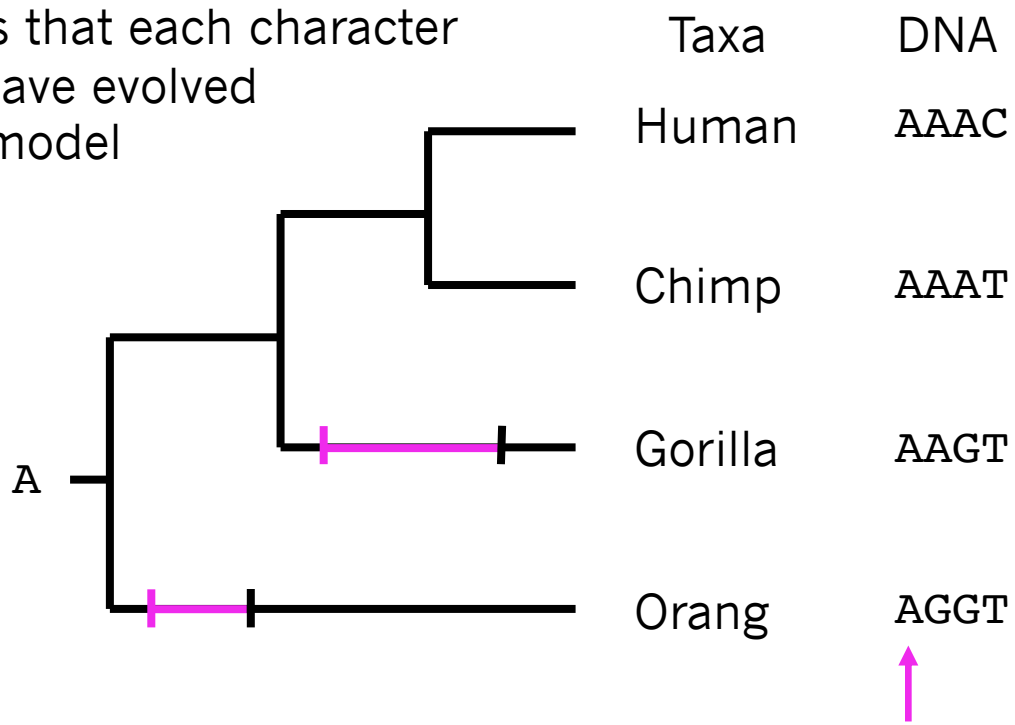

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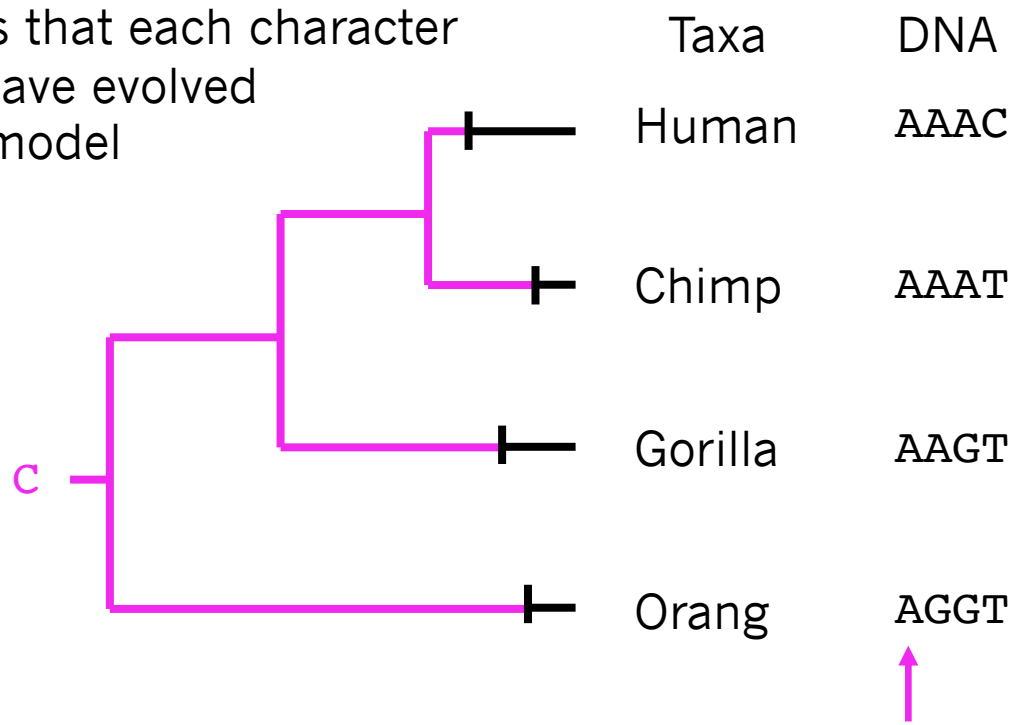

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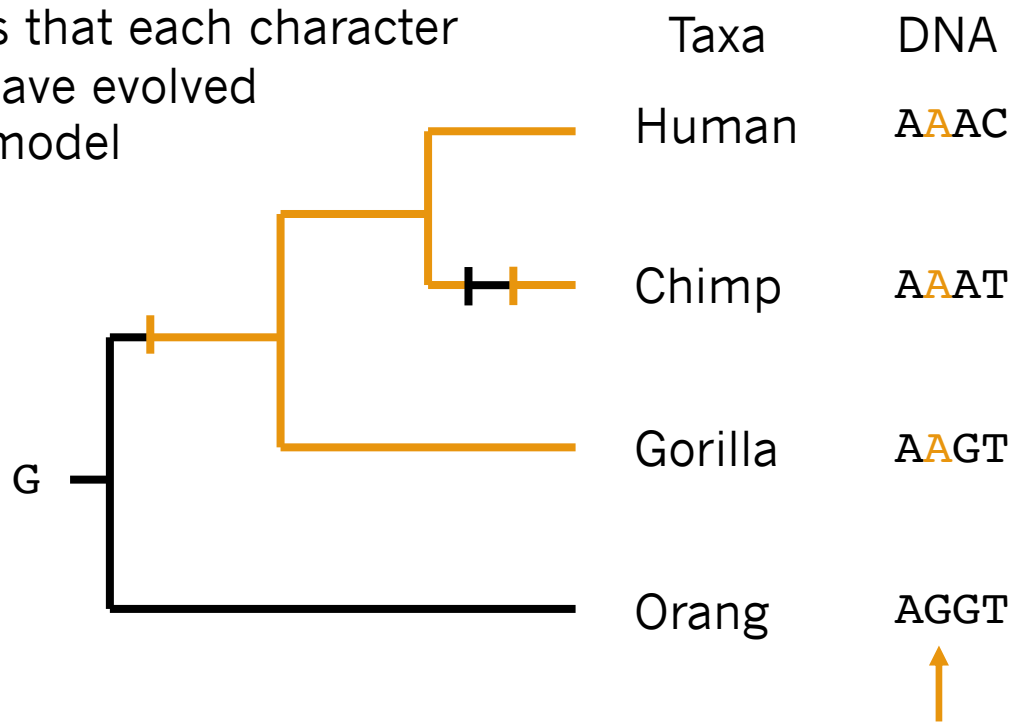

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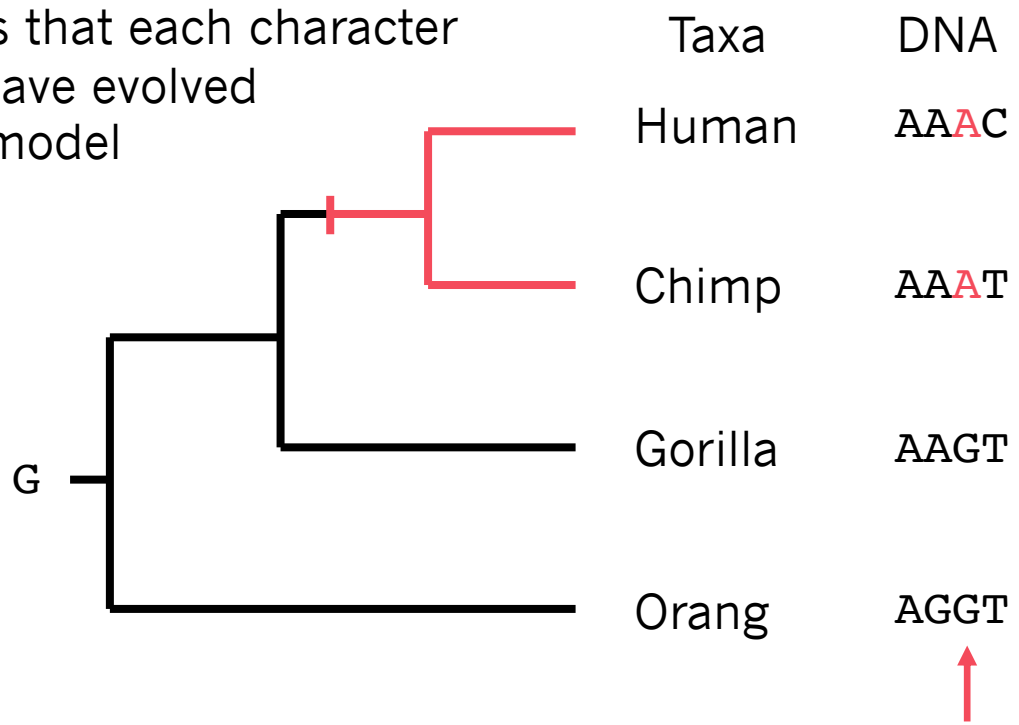

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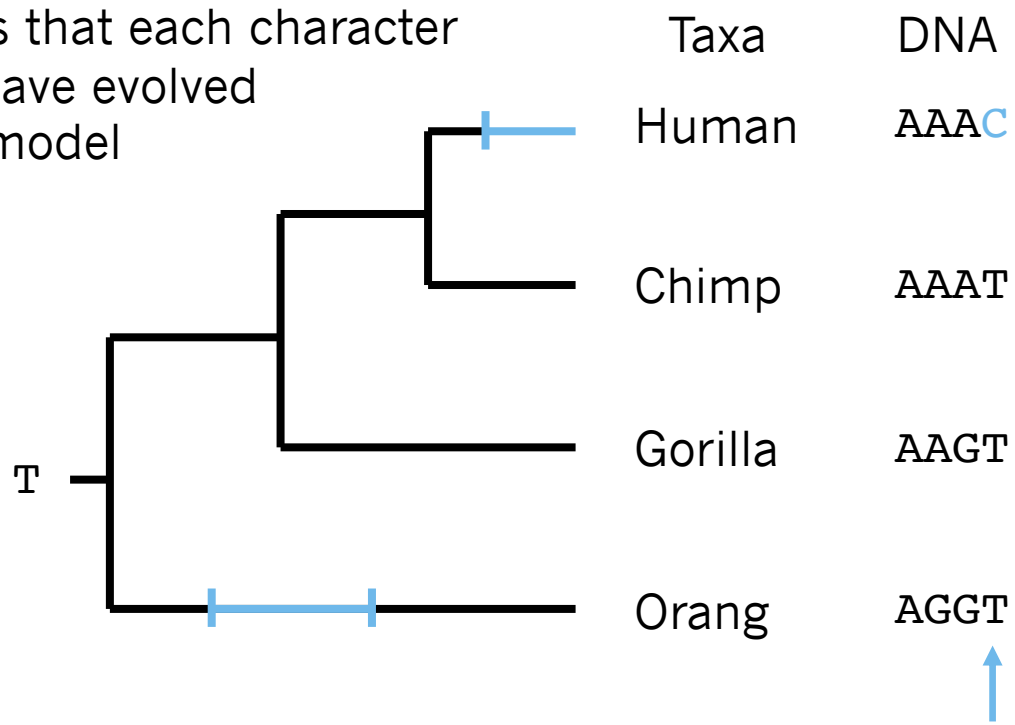
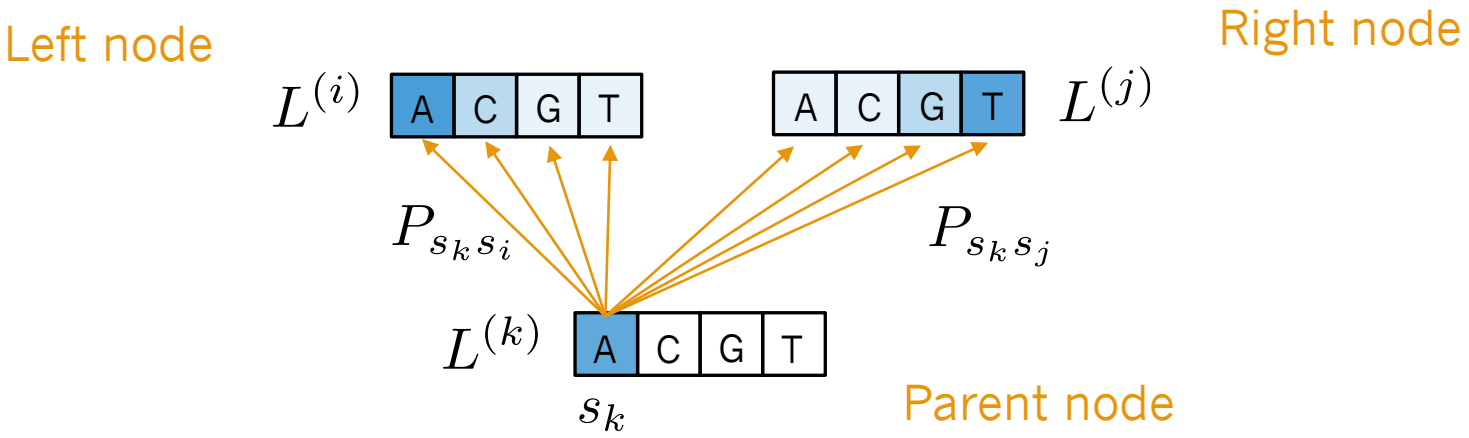


What phylogeny and model of evolution is *most likely* to generate the character data?

Phylogenetic marginalization

Compute partial likelihood ($L^{(k)}$) for each start state (s_k) against all end states (s_i, s_j)



Example for partial likelihood $L^{(k)}$ at node X_k for state s_k = A

$$L_A^{(k)} = \left(P_{AA}(t_i)L_A^{(i)} + P_{AC}(t_i)L_C^{(i)} + P_{AG}(t_i)L_G^{(i)} + P_{AT}(t_i)L_T^{(i)}\right) \times \left(P_{AA}(t_j)L_A^{(j)} + P_{AC}(t_j)L_C^{(j)} + P_{AG}(t_j)L_G^{(j)} + P_{AT}(t_j)L_T^{(j)}\right)$$

Phylogenetic marginalization

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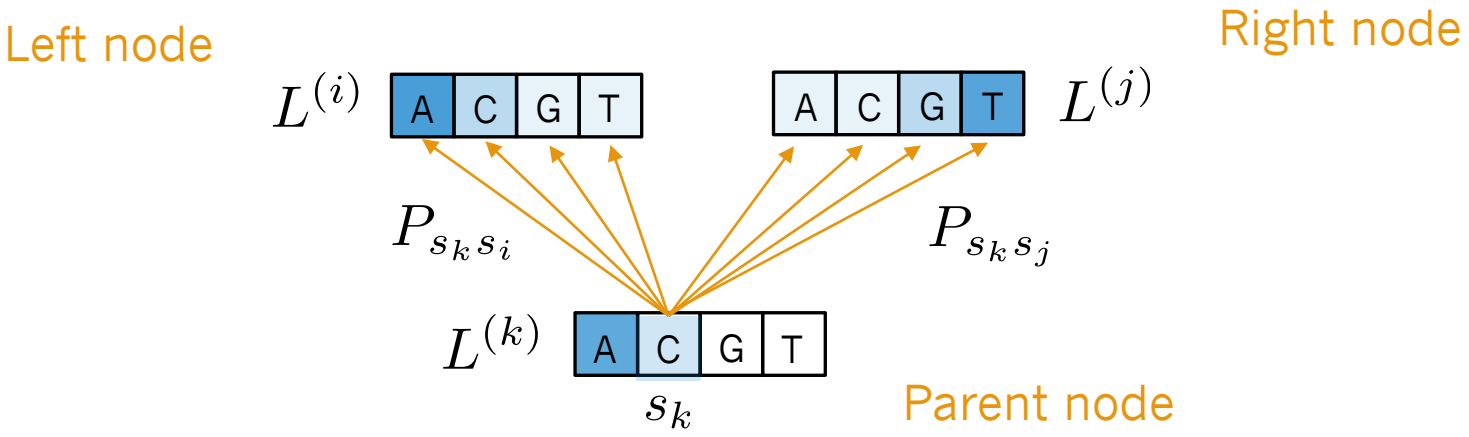
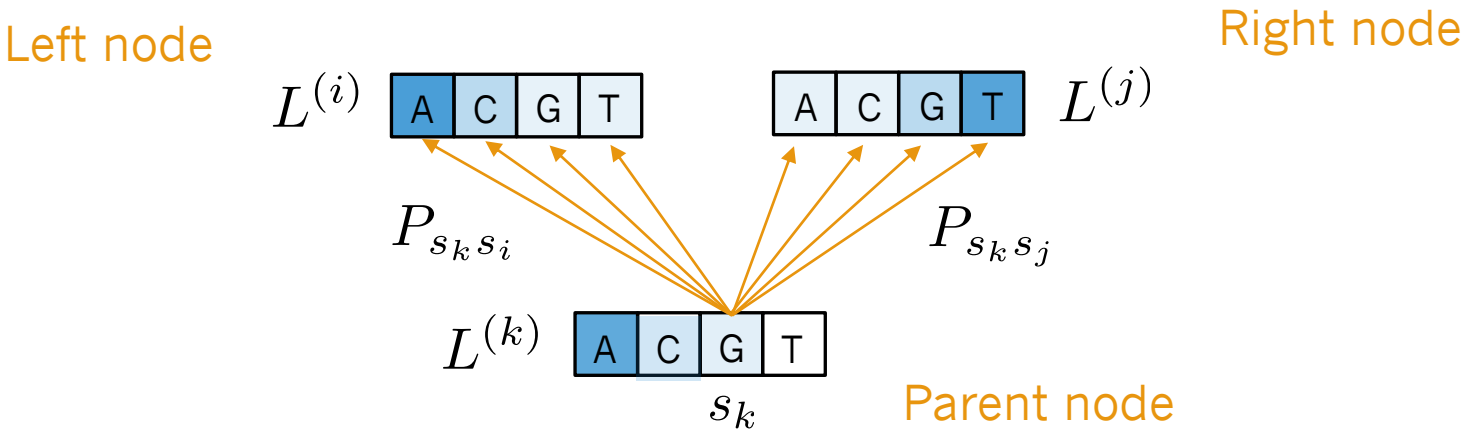


Example for partial likelihood $L^{(k)}$ at node X_k for state s_k = C

$$L_C^{(k)} = \left(P_{CA}(t_i)L_A^{(i)} + P_{CC}(t_i)L_C^{(i)} + P_{CG}(t_i)L_G^{(i)} + P_{CT}(t_i)L_T^{(i)}\right) \times \left(P_{CA}(t_j)L_A^{(j)} + P_{CC}(t_j)L_C^{(j)} + P_{CG}(t_j)L_G^{(j)} + P_{CT}(t_j)L_T^{(j)}\right)$$

Phylogenetic marginalization

Compute partial likelihood ($L^{(k)}$) for each start state (s_k) against all end states (s_i, s_j)

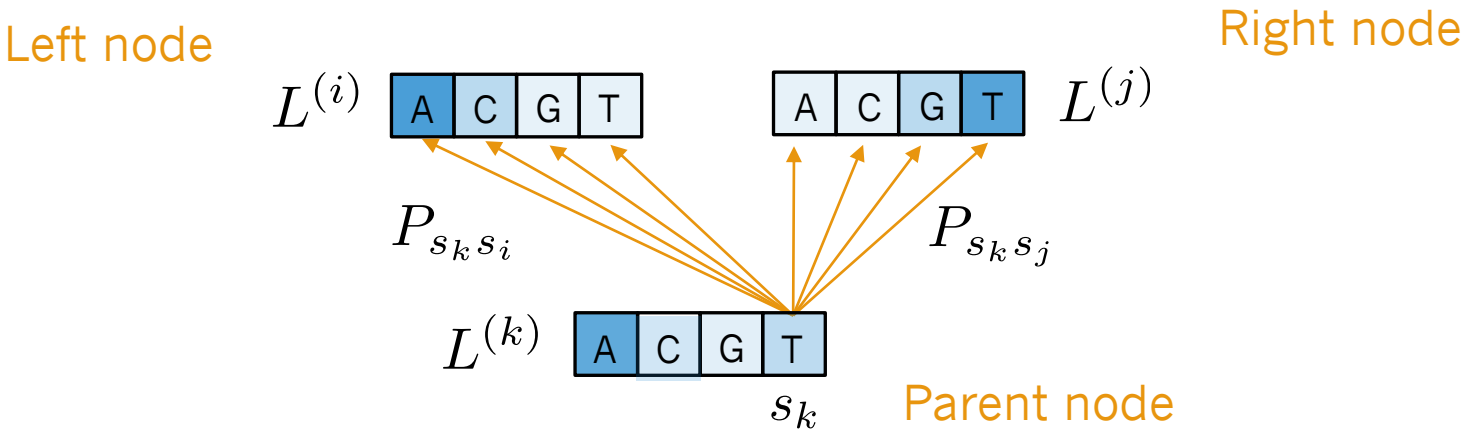


Example for partial likelihood $L^{(k)}$ at node X_k for state s_k = G

$$L_G^{(k)} = \left(P_{GA}(t_i)L_A^{(i)} + P_{GC}(t_i)L_C^{(i)} + P_{GG}(t_i)L_G^{(i)} + P_{GT}(t_i)L_T^{(i)}\right) \times \left(P_{GA}(t_j)L_A^{(j)} + P_{GC}(t_j)L_C^{(j)} + P_{GG}(t_j)L_G^{(j)} + P_{GT}(t_j)L_T^{(j)}\right)$$

Phylogenetic marginalization

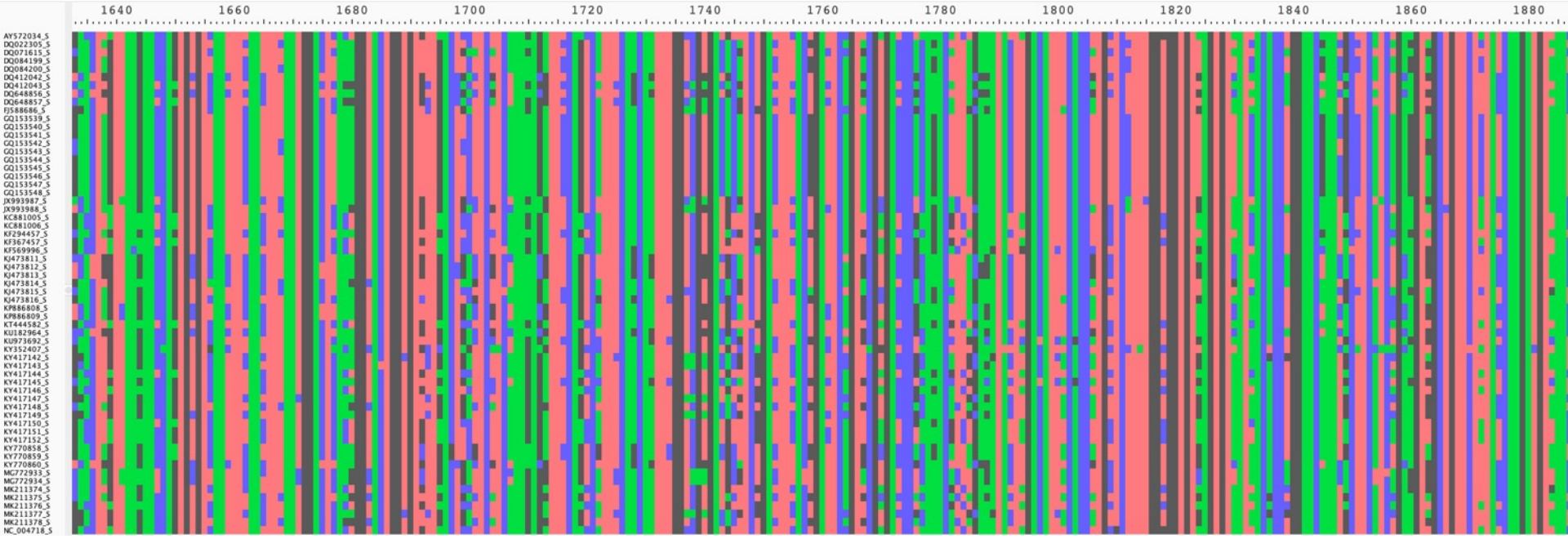
Compute partial likelihood ($L^{(k)}$) for each start state (s_k) against all end states (s_i, s_j)



Example for partial likelihood $L^{(k)}$ at node X_k for state s_k = T

$$L_T^{(k)} = \left(P_{TA}(t_i)L_A^{(i)} + P_{TC}(t_i)L_C^{(i)} + P_{TG}(t_i)L_G^{(i)} + P_{TT}(t_i)L_T^{(i)}\right) \times \left(P_{TA}(t_j)L_A^{(j)} + P_{TC}(t_j)L_C^{(j)} + P_{TG}(t_j)L_G^{(j)} + P_{TT}(t_j)L_T^{(j)}\right)$$

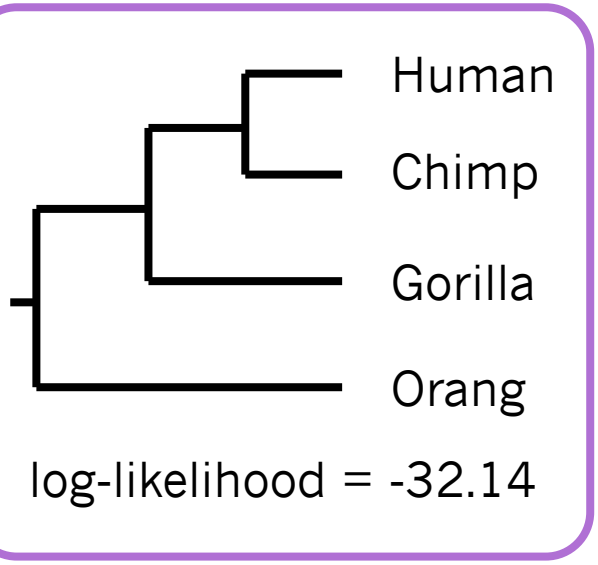
Phylogenetic likelihood



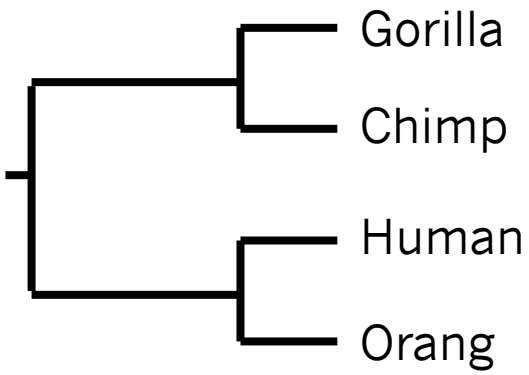
single site

Compute the total phylogenetic likelihood as the product of likelihoods across all sites

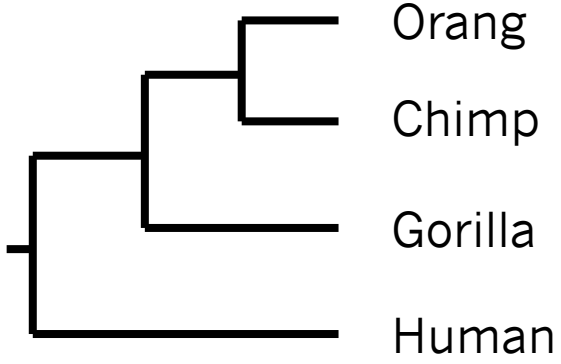
Likelihood



log-likelihood = -32.14



log-likelihood = -42.77



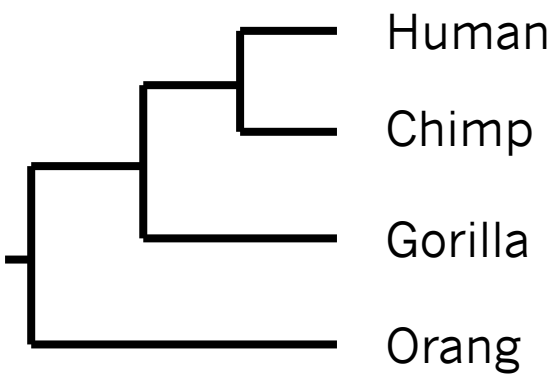
log-likelihood = -39.08

What phylogeny and model of evolution is *most likely* to generate the character data?

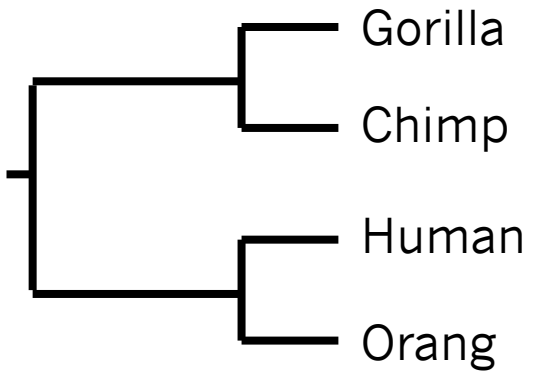
Method comparison

Method	Pros	Cons
Neighbor-joining	Extremely fast Scalable	Does not use evolutionary events to infer tree
Parsimony	Intuitive Fairly fast	Assumes change is rare; Event costs are arbitrary
Likelihood	Most accurate Most realistic Can simulate data	Slower Complex theory + algorithms

Newick strings



(((Human,Chimp),Gorilla),Orang);



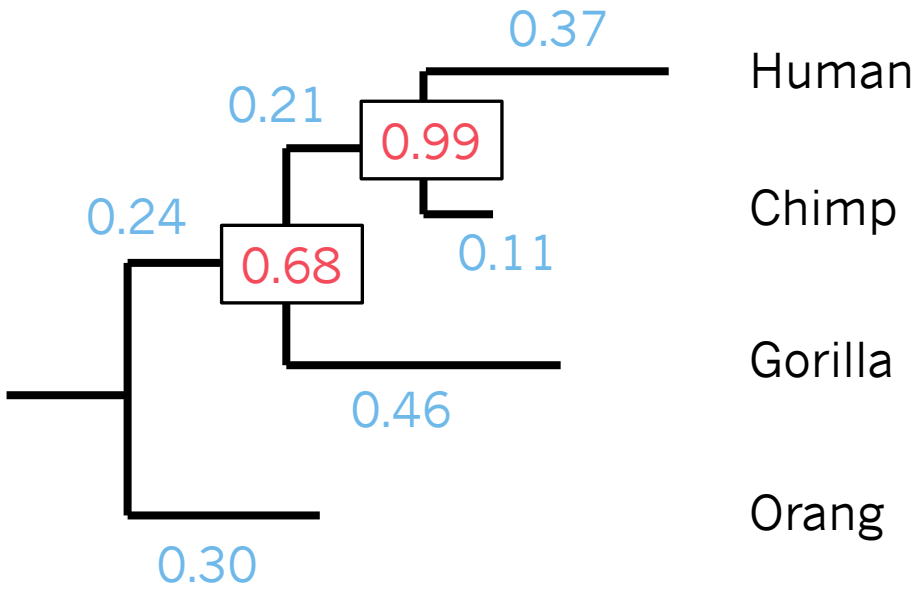
((Gorilla,Chimp),(Human,Orang));

Taxa in parentheses define clades;
commas define divergence events

Newick strings

Branch lengths measure molecular distances in expected # substitutions per site

Clade support measures reliability of clade in a tree estimate



(((Human:0.37,Chimp:0.11)0.99:0.21,
Gorilla:0.46)0.68:0.24,Orang:0.30);

Overview for Lab 11