# Phylogenetics:
## Parsimony and Likelihood

COMP 571 - Spring 2016
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## The Problem

- Input: Multiple alignment of a set *S* of sequences
- Output: Tree *T* leaf-labeled with *S*

# Assumptions

- Characters are mutually independent
- Following a speciation event, characters continue to evolve independently

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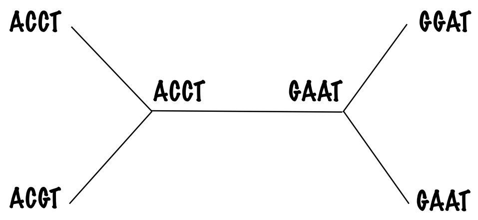
- In parsimony-based methods, the inferred tree is fully labeled.

ACCT GGAT

ACGT GAAT



# A Simple Solution: Try All Trees

- Problem:
  - (2n-3)!! rooted trees
  - (2m-5)!! unrooted trees

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# A Simple Solution: Try All Trees

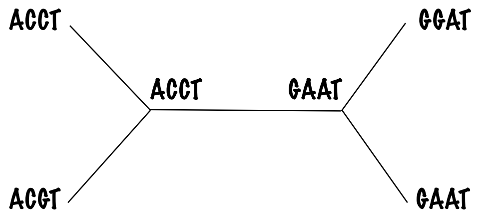
| Number of Taxa | Number of unrooted trees | Number of rooted trees |
|---:|---:|---:|
| 3 | 1 | 3 |
| 4 | 3 | 15 |
| 5 | 15 | 105 |
| 6 | 105 | 945 |
| 7 | 945 | 10395 |
| 8 | 10395 | 135135 |
| 9 | 135135 | 2027025 |
| 10 | 2027025 | 34459425 |
| 20 | 2.22E+20 | 8.20E+21 |
| 30 | 8.69E+36 | 4.95E+38 |
| 40 | 1.31E+55 | 1.01E+57 |
| 50 | 2.84E+74 | 2.75E+76 |
| 60 | 5.01E+94 | 5.86E+96 |
| 70 | 5.00E+115 | 6.85E+117 |
| 80 | 2.18E+137 | 3.43E+139 |

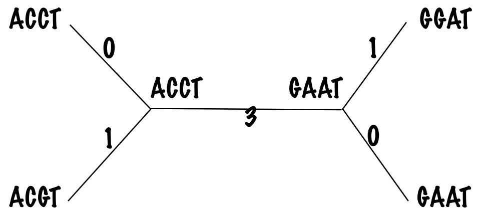
# Solution

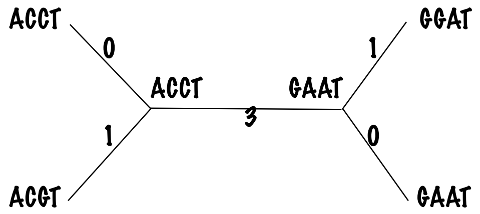
- Define an optimization criterion
- Find the tree (or, set of trees) that optimizes the criterion
- Two common criteria: parsimony and likelihood

# Parsimony

- The parsimony of a fully-labeled unrooted tree *T*, is the sum of lengths of all the edges in *T*
- Length of an edge is the Hamming distance between the sequences at its two endpoints
- PS(T)







Parsimony score = 5

# Maximum Parsimony (MP)

- Input: a multiple alignment S of n sequences
- Output: tree T with n leaves, each leaf labeled by a unique sequence from S, internal nodes labeled by sequences, and PS(T) is minimized

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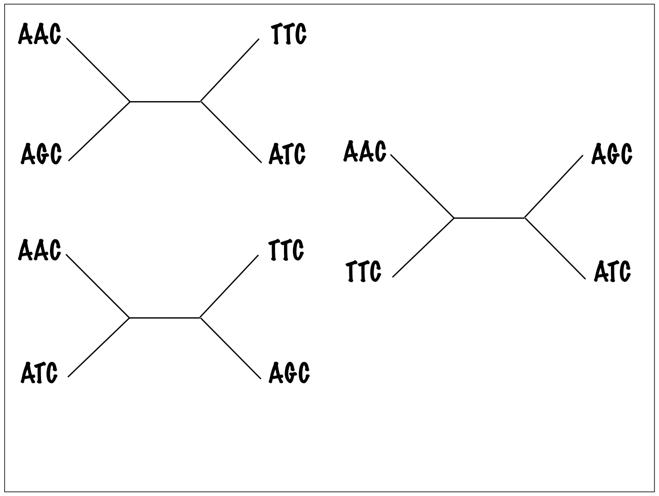
AAC AGC TTC ATC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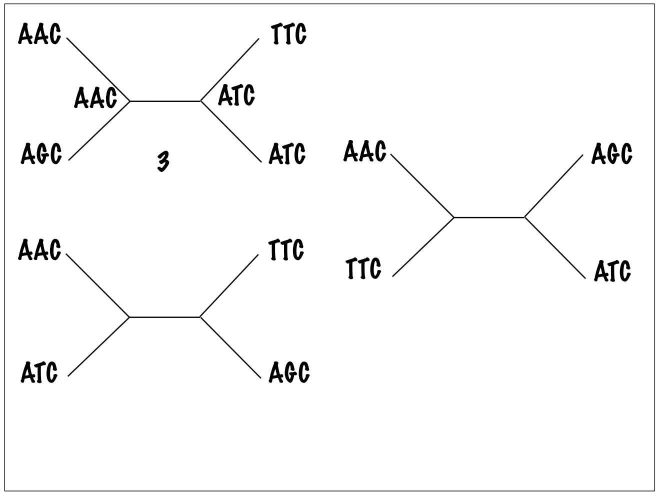
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TTC
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ATC
AGC
ATC
3
AAC
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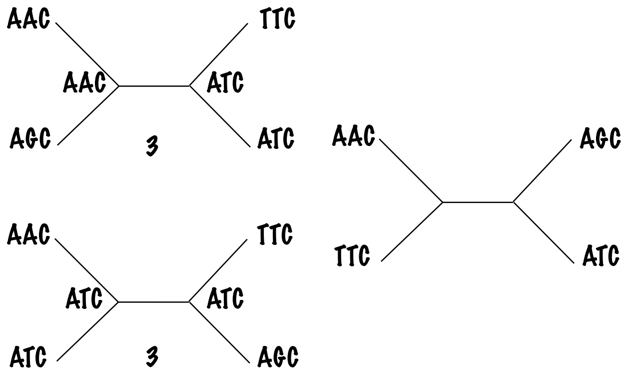
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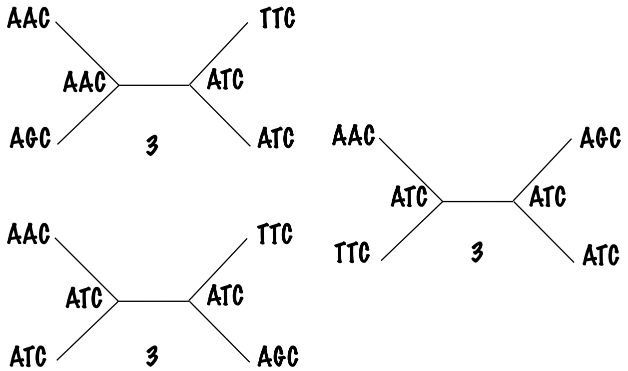
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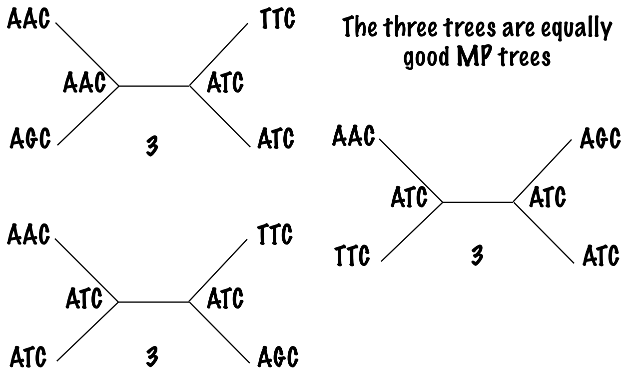

The three trees are equally good MP trees

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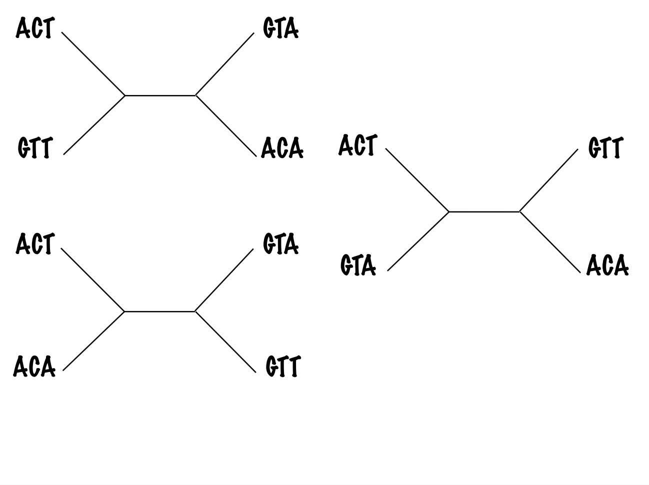
ACT GTT GTA ACA


ACT
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GTT
ACA
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GTT
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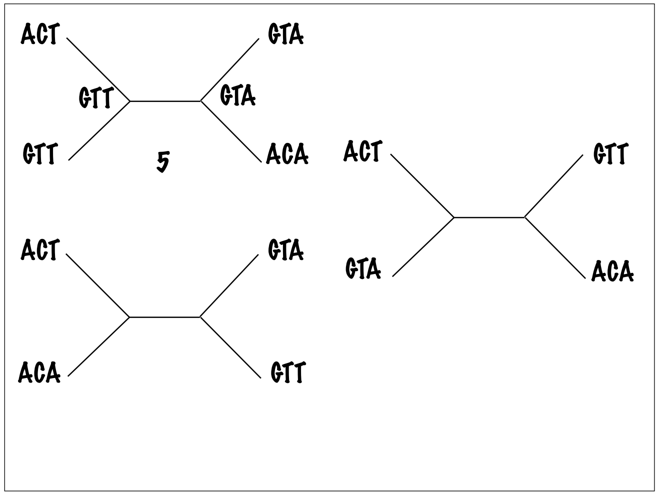
ACA
ACT
GTA
ACA
GTT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ACT
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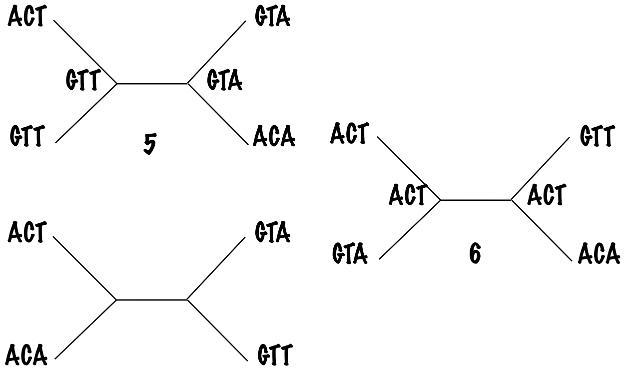
ACA
GTT


ACT
GTA
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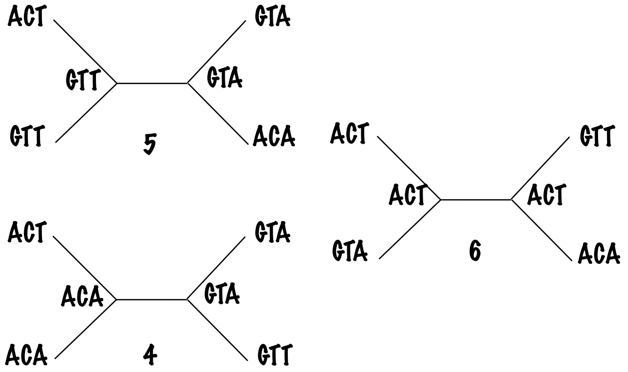
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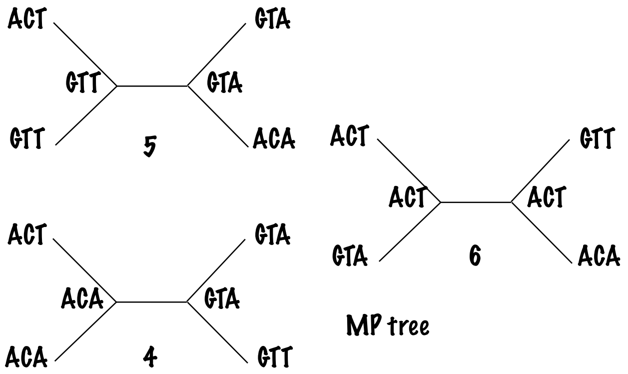

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## Weighted Parsimony

- Each transition from one character state to another is given a weight
- Each character is given a weight
- See a tree that minimizes the weighted parsimony

- Both the MP and weighted MP problems are NP-hard

# A Heuristic For Solving the MP Problem

- Starting with a random tree *T*, move through the tree space while computing the parsimony of trees, and keeping those with optimal score (among the ones encountered)
- Usually, the search time is the stopping factor

# Two Issues

- How do we move through the tree search space?
- Can we compute the parsimony of a given leaf-labeled tree efficiently?

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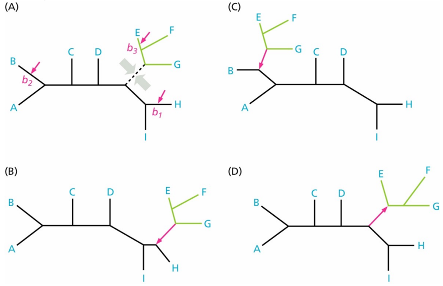
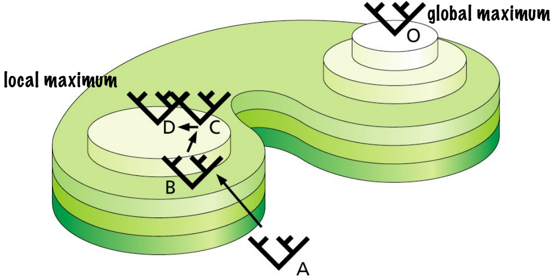
# Searching Through the Tree Space

- Use tree transformation operations (NNI, TBR, and SPR)



# Searching Through the Tree Space

- Use tree transformation operations (NNI, TBR, and SPR)



# Computing the Parsimony Length of a Given Tree

- Fitch's algorithm
- Computes the parsimony score of a given leaf-labeled rooted tree
- Polynomial time

# Fitch's Algorithm

- Alphabet Σ
- Character c takes states from Σ
- $v_c$ denotes the state of character c at node v

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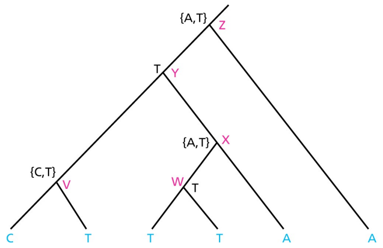
# Fitch's Algorithm

- <u>Bottom-up phase:</u>
- For each node v and each character c, compute the set $S_{c,v}$ as follows:
  - If v is a leaf, then $S_{c,v}=\{v_c\}$
  - If v is an internal node whose two children are x and y, then

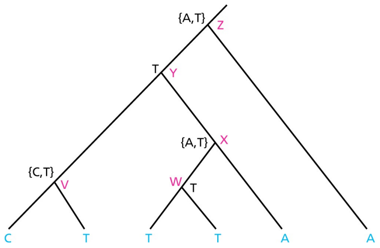
$$S_{c,v} = \begin{cases} S_{c,x} \cap S_{c,y} & S_{c,x} \cap S_{c,y} \neq \emptyset \\ S_{c,x} \cup S_{c,y} & \text{otherwise} \end{cases}$$



# Fitch's Algorithm

- Top-down phase:
- For the root r, let $r_c$=a for some arbitrary a in the set $S_{c,r}$
- For internal node v whose parent is u,

$$v_c = \begin{cases} u_c & u_c \in S_{c,v} \\ \text{arbitrary } \alpha \in S_{c,v} & \text{otherwise} \end{cases}$$


{A,T}
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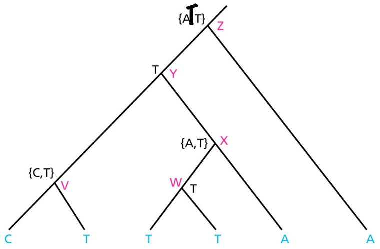
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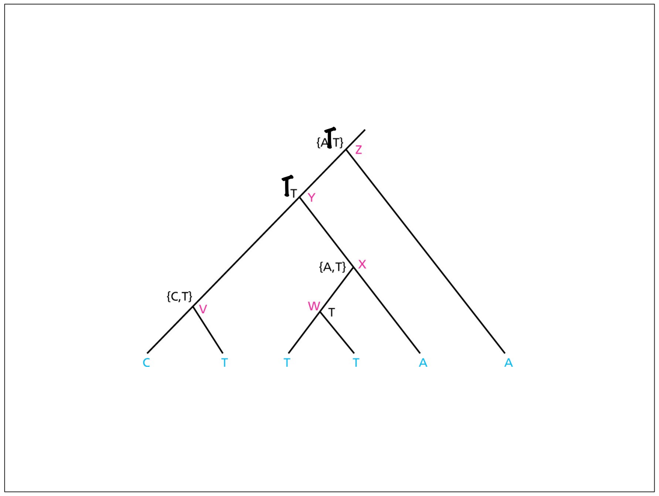
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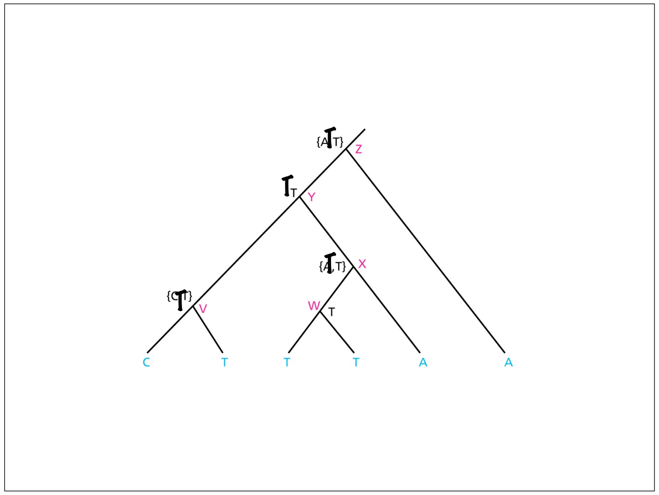
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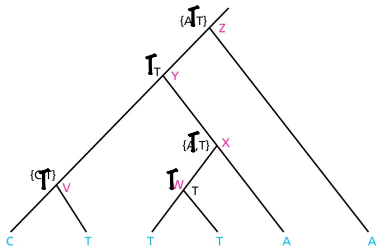

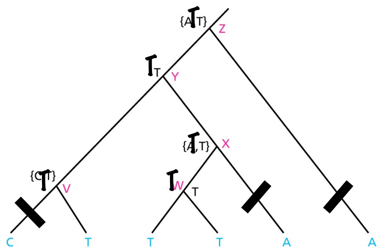

3 mutations

# Fitch's Algorithm

- Takes time O(nkm), where n is the number of leaves in the tree, m is the number of sites, and k is the maximum number of states per site (for DNA, k=4)

# Informative Sites and Homoplasy

- Invariable sites: In the search for MP trees, sites that exhibit exactly one state for all taxa are eliminated from the analysis
- Only variable sites are used

# Informative Sites and Homoplasy

- However, not all variable sites are useful for finding an MP tree topology
- Singleton sites: any nucleotide site at which only unique nucleotides (singletons) exist is not informative, because the nucleotide variation at the site can always be explained by the same number of substitutions in all topologies

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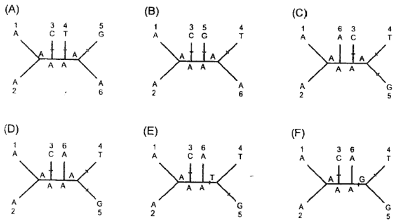

C,T,G are three singleton substitutions ⇒non-informative site

All trees have parsimony score 3

# Informative Sites and Homoplasy

- For a site to be informative for constructing an MP tree, it must exhibit at least two different states, each represented in at least two taxa
- These sites are called informative sites
- For constructing MP trees, it is sufficient to consider only informative sites

# Informative Sites and Homoplasy

- Because only informative sites contribute to finding MP trees, it is important to have many informative sites to obtain reliable MP trees
- However, when the extent of homoplasy (backward and parallel substitutions) is high, MP trees would not be reliable even if there are many informative sites available

# Measuring the Extent of Homoplasy

- The consistency index (Kluge and Farris, 1969) for a single nucleotide site (i-th site) is given by $c_i=m_i/s_i$, where
  - $m_i$ is the minimum possible number of substitutions at the site for any conceivable topology (= one fewer than the number of different kinds of nucleotides at that site, assuming that one of the observed nucleotides is ancestral)
  - $s_i$ is the minimum number of substitutions required for the topology under consideration

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# Measuring the Extent of Homoplasy

- The lower bound of the consistency index is not 0
- The consistency index varies with the topology
- Therefore, Farris (1989) proposed two more quantities: the <u>retention index</u> and the <u>rescaled consistency index</u>

# The Retention Index

- The retention index, $r_i$, is given by $(g_i-s_i)/(g_i-m_i)$, where $g_i$ is the maximum possible number of substitutions at the i-th site for any conceivable tree under the parsimony criterion and is equal to the number of substitutions required for a star topology when the most frequent nucleotide is placed at the central node

# The Retention Index

- The retention index becomes 0 when the site is least informative for MP tree construction, that is, $s_i=g_i$

# The Rescaled Consistency Index

$$rc_i = \frac{g_i - s_i}{g_i - m_i} \frac{m_i}{s_i}$$

# Ensemble Indices

- The three values are often computed for all informative sites, and the ensemble or overall consistency index (CI), overall retention index (RI), and overall rescaled index (RC) for all sites are considered

# Ensemble Indices

$$CI = \frac{\sum_i m_i}{\sum_i s_i}$$

$$RI = \frac{\sum_i g_i - \sum_i s_i}{\sum_i g_i - \sum_i m_i}$$

$$RC = CI \times RI$$

These indices should be computed only for informative sites, because for uninformative sites they are undefined

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# Homoplasy Index

- The homoplasy index is $HI = 1 - CI$
- When there are no backward or parallel substitutions, we have $HI = 0$. In this case, the topology is uniquely determined

# A Major Caveat

- Maximum parsimony is not statistically consistent!

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# Likelihood

- The likelihood of model M given data D, denoted by L(M|D), is p(D|M).
- For example, consider the following data D that result from tossing a coin 10 times:
  - HTTTTHTTTT

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- Model M1:
  - A fair coin (p(H)=p(T)=0.5)
  - $L(M1|D)=p(D|M1)=0.5^{10}$

- Model M2:
  - A biased coin (p(H)=0.8,p(T)=0.2)
  - $L(M2|D)=p(D|M2)=0.8^{2}0.2^{8}$

- Model M3:
  - A biased coin (p(H)=0.1,p(T)=0.9)
  - $L(M3|D)=p(D|M3)=0.1^{2}0.9^{8}$

- The problem of interest is to infer the model M from the (observed) data D.

- The maximum likelihood estimate, or MLE, is:

$$\hat{M} \leftarrow \mathrm{argmax}_M p(D|M)$$

- D=HTTTTHTTTT
- M1: p(H)=p(T)=0.5
- M2: p(H)=0.8, p(T)=0.2
- M3: p(H)=0.1, p(T)=0.9
- MLE (among the three models) is M3.

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- A more complex example:
  - The model M is an HMM
  - The data D is a sequence of observations
  - Baum-Welch is an algorithm for obtaining the MLE M from the data D

- The model parameters that we seek to learn can vary for the same data and model.
- For example, in the case of HMMs:
  - The parameters are the states, the transition and emission probabilities (no parameter values in the model are known)
  - The parameters are the transition and emission probabilities (the states are known)
  - The parameters are the transition probabilities (the states and emission probabilities are known)

# Back to Phylogenetic Trees

- What are the data D?
  - A multiple sequence alignment
  - (or, a matrix of taxa/characters)

# Back to Phylogenetic Trees

- What is the (generative) model M?
  - The tree topology
  - The branch lengths
  - The model of evolution (JC, ..)

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# Back to Phylogenetic Trees

- What is the (generative) model M?
  - The tree topology, $T$
  - The branch lengths, $\lambda$
  - The model of evolution (JC, ..), $E$

# Back to Phylogenetic Trees

- The likelihood is p(D|T,λ,E).
- The MLE is

$$(\hat{T}, \hat{\lambda}, \hat{E}) \leftarrow \text{argmax}_{(T,\lambda,E)} p(D|T, \lambda, E)$$

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# Back to Phylogenetic Trees

- In practice, the model of evolution is estimated from the data first, and in the phylogenetic inference it is assumed to be known.
- In this case, given D and E, the MLE is

$$(\hat{T}, \hat{\lambda}) \leftarrow \text{argmax}_{(T,\lambda)} p(D|T, \lambda)$$

# Assumptions

- Characters are independent
- Markov process: probability of a node having a given label depends only on the label of the parent node and branch length between them t

# Maximum Likelihood

- Input: a matrix D of taxa-characters
- Output: tree T leaf-labeled by the set of taxa, and with branch lengths $\lambda$ so as to maximize the likelihood $P(D|T,\lambda)$

# P(D|T,λ)

$$\begin{aligned} P(D|T,\lambda) &= \prod_{site\ j} p(D_j|T,\lambda) \\ &= \prod_{site\ j} \left(\sum_R p(D_j, R|T,\lambda)\right) \\ &= \prod_{site\ j} \left(\sum_R \left[p(root) \cdot \prod_{edge\ u\to v} p_{u\to v}(t_{uv})\right]\right) \end{aligned}$$

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- What is $p_{i\to j}(t_{uv})$ for a branch u→v in the tree, where i and j are the states of the site at nodes u and v, respectively?

- For the Jukes-Cantor model with the parameter μ (the overall substitution rate), we have

$$p_{i\to j}(t) = \begin{cases} \frac{1}{4}(1+3e^{-t\mu}) & i=j \\ \frac{1}{4}(1-e^{-t\mu}) & i\neq j \end{cases}$$

- If branch lengths are measured in expected number of mutations per site, v (for JC: v=(μ/4+μ/4+μ/4)t=(3/4)μt)

$$p_{i\to j}(\nu) = \begin{cases} \frac{1}{4}(1+3e^{-4\nu/3}) & i=j \\ \frac{1}{4}(1-e^{-4\nu/3}) & i\neq j \end{cases}$$

- The ML problem is NP-hard (that is, finding the MLE $(T,\lambda)$ is very hard computationally)
- Heuristics involve searching the tree space, while computing the likelihood of trees
- Computing the likelihood of a leaf-labeled tree T with branch lengths can be done efficiently using dynamic programming

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# $P(D|T,\lambda)$

Let $C_j(x,v) = P(\text{subtree whose root is } v \mid v_j=x)$

<u>Initialization</u>: leaf v and state x $C_j(x,v) = \begin{cases} 1 & v_j = x \\ 0 & \text{otherwise} \end{cases}$

<u>Recursion</u>: node v with children u,w

$$C_j(x,v) = \left[\sum_y C_j(y,u) \cdot P_{x\to y}(t_{vu})\right] \cdot \left[\sum_y C_j(y,w) \cdot P_{x\to y}(t_{vw})\right]$$

<u>Termination</u>:

$$L = \prod_{j=1}^{m} \left[\sum_x C_j(x, root) \cdot \mathrm{P}(x)\right]$$

## Running Time

- Takes time $O(nk^2m)$, where n is the number of leaves in the tree, m is the number of sites, and k is the maximum number of states per site (for DNA, k=4)

## Unidentifiability of the Root

- If the base substitution model is reversible (most of them are!), then rooting the same tree differently doesn't change the likelihood.

# Questions?