Phylogeny Reconstruction

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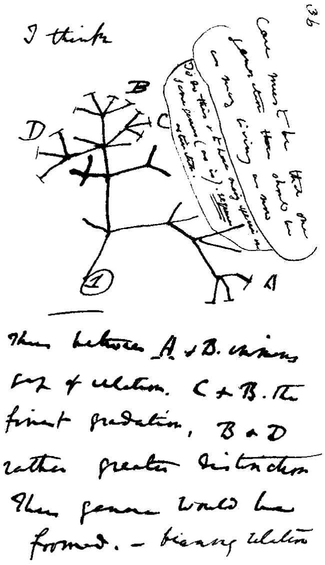
Notes

Charles Darwin: Evolutionary Relationships



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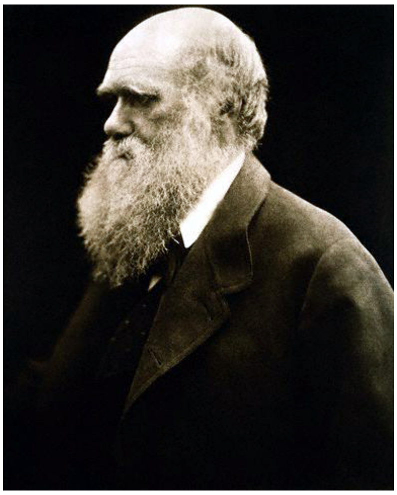
I think

Case must be that one generation then should be as many living as now. To do this & to have many species in same genus (as is) requires extinction.

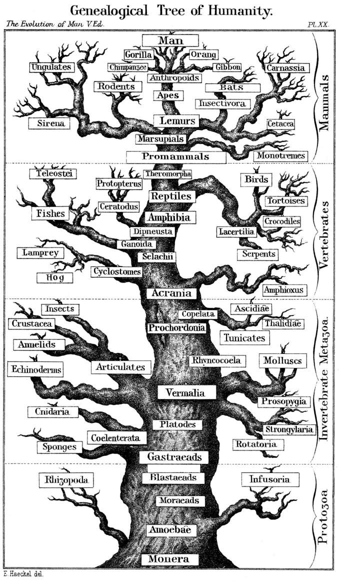
Thus between A & B immense gap of relation. C & B the finest gradation, B & D rather greater distinction. Thus genera would be formed. — bearing relation

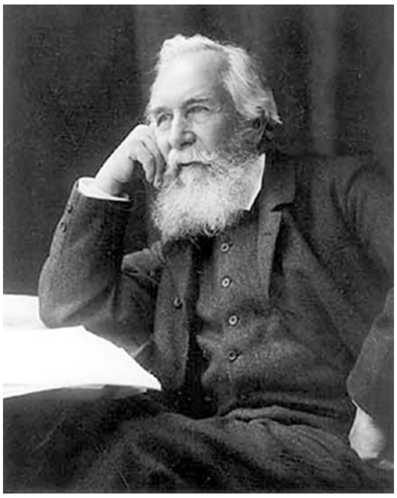


Charles Darwin (1809-1882)

Notes

Ernst Haeckel: Evolutionary Trees





Ernst Haeckel (1834-1919)

Notes

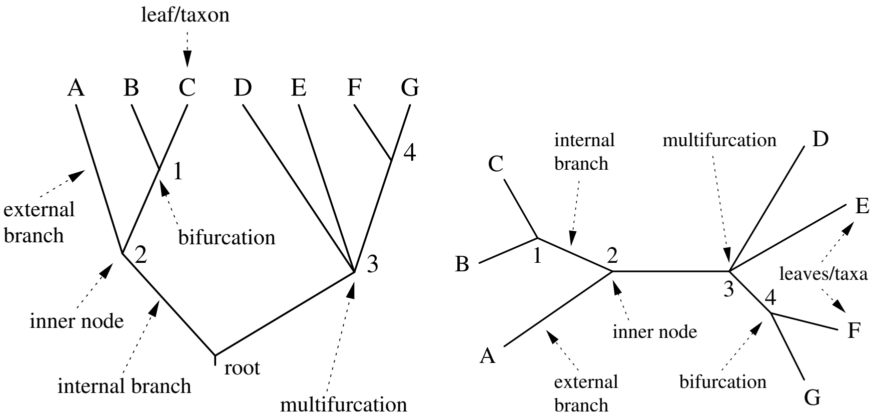
Theodosius Dobzhansky: The Light of Evolutionary

Theodosius Dobzhansky (1900-1975)

Nothing in Biology Makes Sense Except in the Light of Evolution.
Dobzhansky, 1973

Notes

Some Notation



Note: branch = edge = split, external node = leaf = taxon are used interchangebly.

Notes

Main Types of Phylogenetic Methods

Data	Method	Evaluation Criterion
Characters (Alignment)	**Maximum Parsimony**	Parsimony
	Statistical Approaches: Likelihood, Bayesian	Evolutionary Models
Distances	**Distance Methods**	

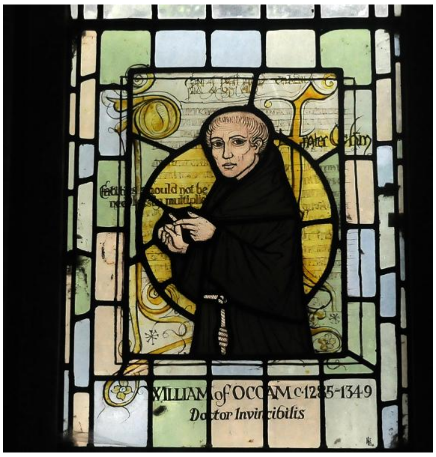
Notes

William of Ockham: The Law of Parsimony

Occam's Razor (law of parsimony) states:

> *Pluralitas non est ponenda sine necessitate.*
>
> *Plurality should not be posited without necessity.*

The principle gives precedence to simplicity; of two competing theories, the simplest explanation of an entity is to be preferred.

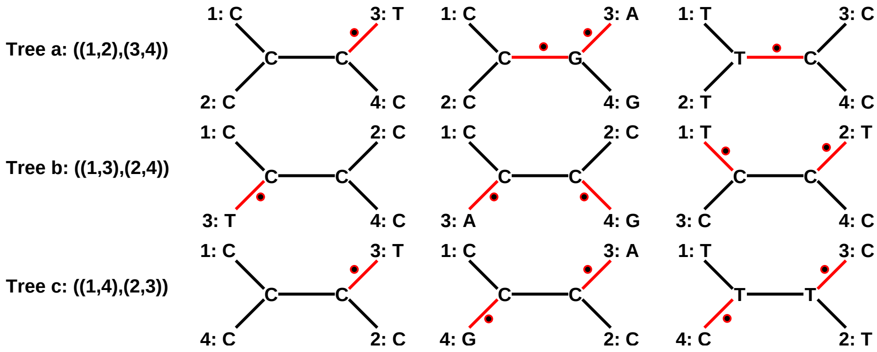


William of Ockham (1285-1347/49)

Notes

Maximum Parsimony

taxon	1	2	3	4	5	6	7	8	9
1:	C	G	C	A	C	T	G	T	T
2:	C	G	C	A	C	T	G	T	T
3:	T	G	A	A	C	T	G	C	T
4:	C	G	G	A	C	T	G	C	T
	⇑		⇑					⇑	



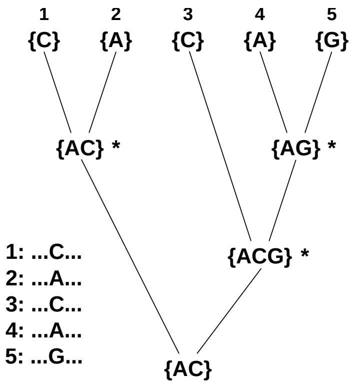
Notes

Parsimony Informative Sites

We have seen that not all variable columns are informative for the parsimony reconstruction.
To be an *informative site* for the parsimony principle the column has to contain at least two different character states, and for at least two of these states have to occur at least twice.

Notes

Maximum Parsimony: Fitch's (1970) algorithm



Note: We need 1 substitution per union in tree T (tree-length = substitutions needed).

1. Initialize state set S_k at each leaf k with the characters from the alignment.
2. Construct the state sets of all internal leaves in a post-order-traversal starting a the root.
3. Let k be the current node and i, j its decendents, then build the intersection of S_i and S_j:
   - If $S_i \cap S_j$ non-empty: set $S_k = S_i \cap S_j$,
   - if $S_i \cap S_J$ empty: set $S_k = S_i \cup S_j$ and increase the tree-length by 1.
4. Continue with the traversal until you have reconstructed the state set S_{root} of the root of T. If we have a sequence for the root, repeat Step 3 for the its character and S_{root}.

Notes

Maximum Parsimony: Objective Function

Aim: Find the tree T that minimizes the following function:

$$\mathrm{MP}(T) = \sum_{k=1}^{B} \sum_{j=1}^{L} w_j \cdot \mathrm{diff}(x_{k'j}, x_{k''j}).$$

diff: Scoring matrix for substitutions (often 1 for changes, 0 otherwise)

w_j: alignment-specific weight (often 1)

L: alignment length

B: number of edges in T

k' and k'': endnodes of edge k.

Notes

Maximum Parsimony: Better Substitution Costs

diff with substitution cost 1 and more elaborate costs:

	A	G	C	T
A	-	1	1	1
G	1	-	1	1
C	1	1	-	1
T	1	1	1	-

	A	G	C	T
A	-	1	5	5
G	1	-	5	5
C	5	5	-	1
T	5	5	1	-

Notes

How to find the Most Parsimonious Tree?

Ideally we would evaluate all trees and take the one(s) with the lowest tree-length.
However, there are too many trees. This problem affects almost every method that aims to find trees with optimal score.
So we need other strategies (which we will see later).

Notes

Problems with Parsimony

- Parsimony is often considered model-free. This is not entirely correct.
- One has no choice of a model, but nevertheless the algorithm assumes a very simple model.
- Parsimony assumes that substitutions are rare and that back-mutations do not occur.
- Although this was often true for morphological data, it is certainly not true for distantly related DNA sequences which only have four character states.

Notes

Distance-based methods

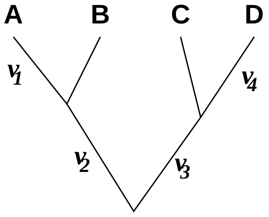
seq 1	A	G	C	T	T	A	C	C	T	G	T	T	A	C	T
seq 2	C	G	T	A	A	A	T	T	T	C	C	C	G	A	T
seq 3	C	G	C	A	A	G	T	T	T	C	C	C	G	A	T
seq 4	C	A	C	T	T	A	T	T	A	G	T	C	A	A	C

$$\Downarrow (d_{ij})_{i,j=1,\dots,4}$$

	seq 1	seq 2	seq 3	seq 4
seq 1	0	11	11	8
seq 2	11	0	2	10
seq 3	11	2	0	9
seq 4	8	10	9	0

Notes

Distance Methods: Aim



Aim: Find branch lengths v_b such that the sum of the branch lengths connecting any two leaves gets close to the measured distances between all pairs of leaves. That is, for instance

$$d^{measured}_{A,D} = v_1 + v_2 + v_3 + v_4$$

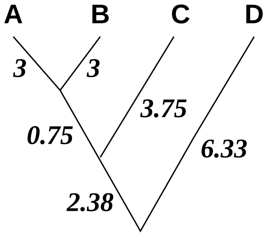
Notes

Distance Methods: UPGMA

One possibility are clustering methods like UPGMA = Unweighted Pair Group Methods using Arithmetic means.

	A	B	C	D
A	0	6	7	13
B	6	0	8	14
C	7	8	0	11
D	13	14	11	0

⇒



Notes

Distance Methods: Clustering Methods

- Clustering methods well, if sequences evolve according to a molecular clock
- or equivalently: if the ultrametric inequality

  $$D_{AB} \leq \max D_{AC}, D_{BC}$$

  holds for each triple (A, B, C).
- Then the data is ultrametric, that means according to a molecular clock.

Notes

Distance Methods: Four-point Condition

- On the other hand, a distance matrix D can only be presented as a tree, if and only if the Four-Point-Condition

$$d_{uv} + d_{xz} \leq max(d_{ux} + d_{vz}, d_{uz} + d_{vx})$$

holds for all orderings of four taxa u, v, x, z.

- Or equivalently:
- For all sets of four taxa there exists a labelling of the elements, say A, B, C, D such that

$$d_{AB} + d_{CD} \leq d_{AC} + d_{BD} = d_{AD} + d_{BC}).$$

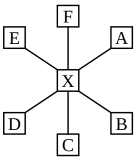
- This means, that the distance matrix is additive, i.e. it fits fits one tree.

Notes

Distance Methods: Neighbor Joining (NJ)

A widely used distance method is Neighbor-Joining:

1 begin with a start tree:



2 compute for each pair 1, 2 the net-divergence

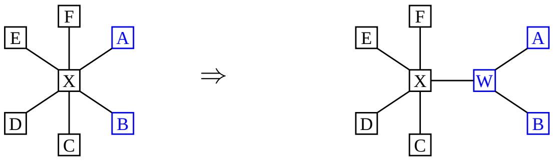
$$\frac{1}{2(N-2)} \sum_{k=3}^{N} (D_{1k} + D_{2k}) + \frac{1}{2} D_{12} + \frac{1}{N-2} \sum_{3 \leq i < j} D_{ij}.$$

3 Choose the pair (A, B) that minimizes this equation.

Notes

Distance Methods: Neighbor Joining (NJ)

4 cluster (A,B) and define an interior node W:



5 compute the branch lengths for the external edges:

$$\begin{aligned} v_{AW} &= \frac{1}{2}\left(D_{AB} + \frac{1}{m-2} \sum_{k=1}^{m} (D_{Ak} - D_{Bk})\right) \\ v_{BW} &= \frac{D_{AB}}{2} - v_{AW}. \end{aligned}$$

Notes

Distance Methods: Neighbor Joining (NJ)

6 compute distance W to the remaining m-2 leaves:

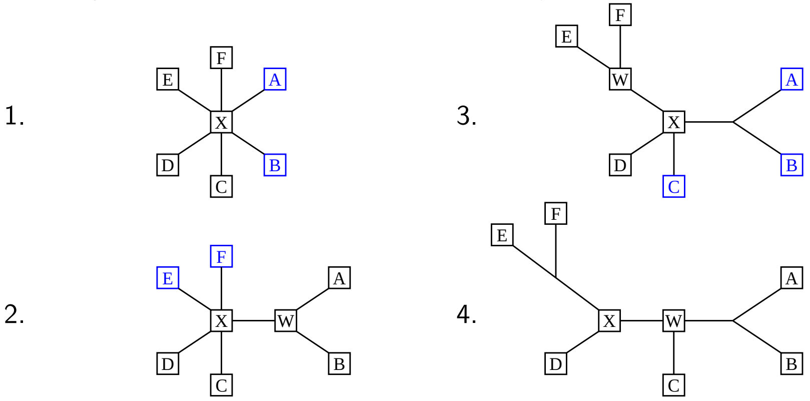
$$D_{Wk} = \frac{1}{2}\left(d_{Ak} + D_{Bk} - D_{AB}\right))$$

7 continue with the reduced set of leaves

Notes

Distance Methods: The NJ Tree Step-by-step

The algorithm is repeated until the tree is fuly resolved:



Notes

How to get distances?

Distances can be computed in various way...
Usually via Maximum Likelihood.

Notes

Introduction: ML on Coin Tossing

Given a box with 3 coins of different fairness $(\frac{1}{3}, \frac{1}{2}, \frac{2}{3}$ heads$)$

We take out one coin an toss 20 times:

$$H, T, T, H, H, T, T, T, T, H, T, T, H, T, H, T, T, H, T, T$$

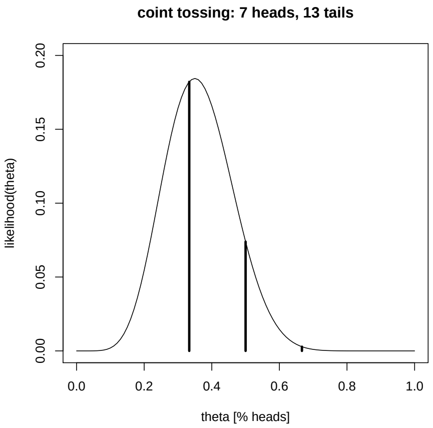
$$\begin{array}{rcl} \textbf{Probability} & & \textbf{Likelihood} \\ p(k \text{ heads in } n \text{ tosses}|\theta) & \equiv & L(\theta|k \text{ heads in } n \text{ tosses}) \\ & = & \binom{n}{k}\theta^k(1-\theta)^{n-k} \\ & & \text{(here binomial distribution)} \end{array}$$

Aim: The ML approach seaches for that parameter set θ for the generating process which maximizes the probability of our given data.

Hence, *"likelihood flips the probability around."*

Notes

Introduction: ML on Coin Tossing (Estimate)



Three coin case

$$L(\theta|7 \text{ heads in } 20) = \binom{20}{7}\theta^7(1-\theta)^{13}$$

for each coin $\theta \in \{\frac{1}{3}, \frac{1}{2}, \frac{2}{3}\}$

For infinitely many coins
$\theta = (0...1)$

ML estimate: $L(\hat{\theta}) = 0.1844$ where coin shows $\hat{\theta} = 0.35$ heads

Notes

From Coins to Phylogenies?

While the coin tossing example might look easy, in phylogenetic analysis, the parameter (set) θ comprises:

- evolutionary model
- its parameters
- tree topology
- its branch lengths

That means, a high dimensional optimization problem.
Hence, some parameters are often estimated/set separately.

Notes

Modeling Evolution

- Evolution is usually modeled as a

  stationary, time-reversible Markov process.

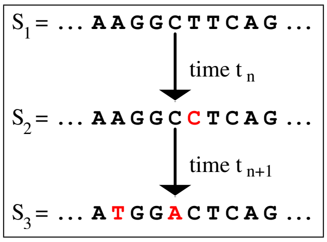
- What does that mean?

Notes

Assumptions on Evolution

Markov Process

The (evolutionary) process evolves without memory, i.e. sequence S_2 mutates to S_3 during time t_{n+1} independent of state of S_1.



S_1 = … AAGGCTTCAG …

time t $_n$

S_2 = … AAGGCCTCAG …

time t $_{n+1}$

S_3 = … ATGGACTCAG …

Notes

Assumptions on Evolution

Stationary:
The overall character frequencies π_j of the nucleotides or amino acids are in an equilibrium and remain constant.

Time-Reversible:
Mutations in either direction are equally likely

$$\pi_i \cdot P_{ij}(t) = P_{ji}(t) \cdot \pi_j$$

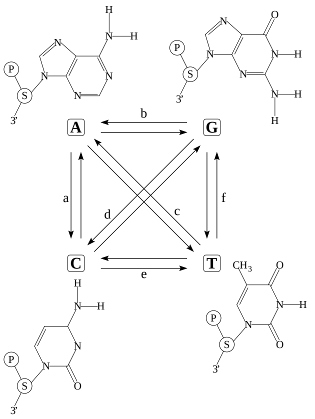
This means a mutation is as likely as its back mutation.

$$P(i \rightarrow j) = P(i \leftarrow j) \qquad \text{(JC69)}$$

Notes

Substitution Models

Evolutionary models are often described using a substitution rate matrix R and character frequencies Π. Here, 4 × 4 matrix for DNA models:



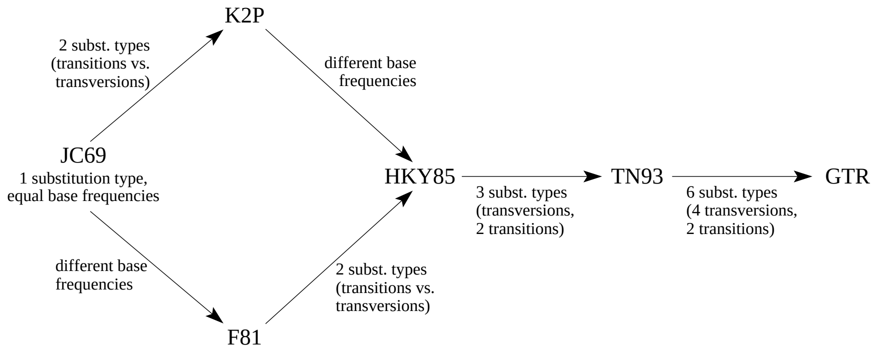
$$R = \left(\begin{array}{cccc} A & C & G & T \\ - & a & b & c \\ a & - & d & e \\ b & d & - & f \\ c & e & f & - \end{array}\right)$$

$$\Pi = (\pi_A, \pi_C, \pi_G, \pi_T)$$

From R and Π we reconstruct a substitution probability matrix P, where $P_{ij}(t)$ is the probability of changing $i \rightarrow j$ in time t.

Notes

Relations between DNA models



K2P

2 subst. types (transitions vs. transversions)

different base frequencies

JC69
1 substitution type,
equal base frequencies

HKY85

3 subst. types (transversions, 2 transitions)

TN93

6 subst. types (4 transversions, 2 transitions)

GTR

different base frequencies

2 subst. types (transitions vs. transversions)

F81

Further modification:
rate heterogeneity: invariant sites, Γ-distributed rates, mixed.

Notes

Protein Models

Generally this is the same for protein sequences, but with 20 × 20 matrices. Some protein models are:

- Poisson model ("JC69" for proteins, rarely used)
- Dayhoff (Dayhoff *et al.*, 1978, general matrix)
- JTT (Jones *et al.*, 1992, general matrix)
- WAG (Whelan & Goldman, 2000, more distant sequences)
- VT (Müller & Vingron, 2000, distant sequences)
- mtREV (Adachi & Hasegawa, 1996, mitochondrial sequences)
- cpREV (Adachi *et al.*, 2000, cloroplast sequences)
- mtMAM (Yang *et al.*, 1998, Mammalian mitochondria)
- mtART (Abascal *et al.*, 2007, Arthropod mitochondria)
- rtREV (Dimmic *et al.*, 2002, reverse transcriptases)
- . . .
- ~~BLOSUM 62 (Henikoff & Henikoff, 1992)~~ → for database searching

Notes

Computing ML Distances Using $\mathbf{P_{ij}(t)}$

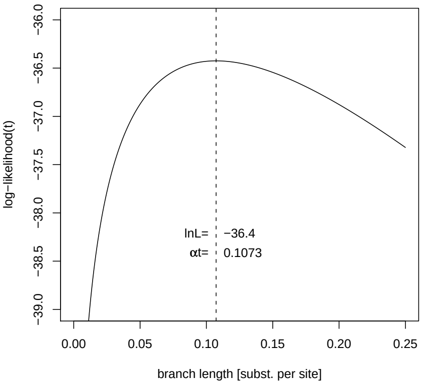
The Likelihood of sequence s evolving to s' in time t:

$$L(t|s \rightarrow s') = \prod_{i=1}^{m} \left(\Pi(s_i) \cdot P_{s_i s'_i}(t) \right)$$

Likelihood surface for two sequences under JC69:

GATCCTGAGAGAAATAAAC $= s'$
GGTCCTGACAGAAATAAAC $= s$

Note: we do not compute the probability of the distance t but that of the data $D = \{s, s'\}$.



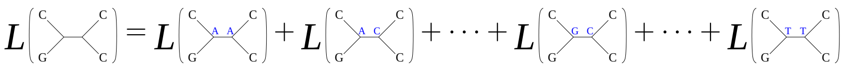
Notes

Computing Likelihood Values for Trees

Given a tree with branch lengths and sequences for all nodes, the computation of likelihood values for trees is straight forward.

Unfortunately, we usually have no sequences for the inner nodes (ancestral sequences).

Hence we have to evaluate every possible labeling at the inner nodes:

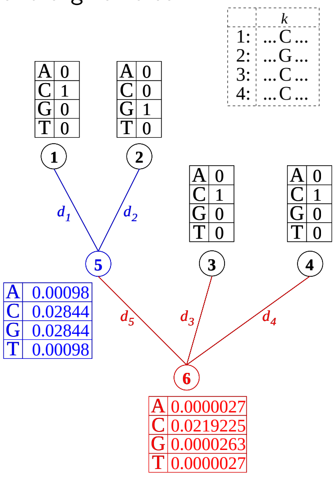


for every column in the alignment... but there is a faster algorithm.

Notes

Likelihoods of Trees (Single alignment column, given tree)

For a single alignment column and a given tree:



Likelihoods of nucleotides i at inner nodes:

$$L_5(i) = [P_{iC}(d_1) \cdot L(C)] \cdot [P_{iG}(d_2) \cdot L(G)]$$

$$L_6(i) = \prod_{v=\{2,3,4\}} \left[\sum_{j=\{ACGT\}} P_{ij}(d_v) \cdot L_v(j) \right]$$

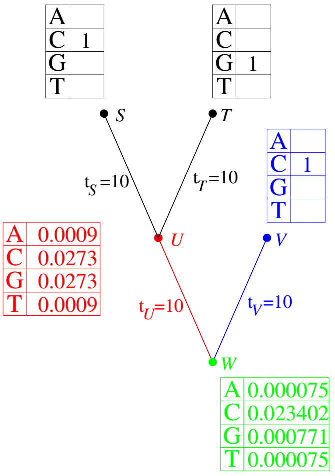
Site-Likelihood of an alignment column k:

$$L^{(k)} = \sum_{i=\{ACGT\}} \pi_i \cdot L_6(i) = 0.005489$$

with all $d_x = 0.1$ and $P_{ij}(0.1) = \begin{cases} .91 & i \neq j \\ .03 & i = j \end{cases}$ (JC)

Notes

Likelihoods of Trees (Single column $\begin{smallmatrix}C\\G\\C\end{smallmatrix}$, given tree)



Likelihoods of nucleotides at inner nodes:

$$L_U(i) = \quad [P_{iC}(10) \cdot L(C)] \cdot [P_{iG}(10) \cdot L(G)]$$

$$L_W(i) = \quad \left[\sum_{\substack{u=\\ACGT}} P_{iu}(t_U) \cdot L_U(u)\right] \cdot$$

$$\left[\sum_{\substack{v=\\ACGT}} P_{iv}(t_V) \cdot L_V(v)\right]$$

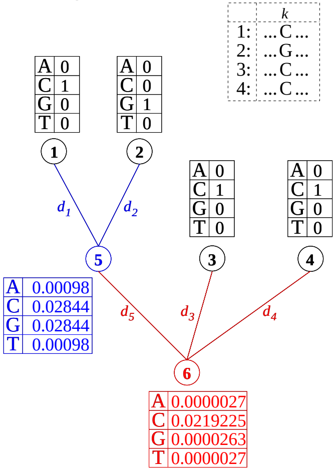
Site-Likelihood of an alignment column k:

$$L^{(k)} = \sum_{\substack{i=\\ACGT}} \pi_i \cdot L_W(i) = 0.024323$$

Notes

Likelihoods of Trees (Single alignment column, given tree)

For a single alignment column and a given tree:



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Site-Likelihood of an alignment column k:

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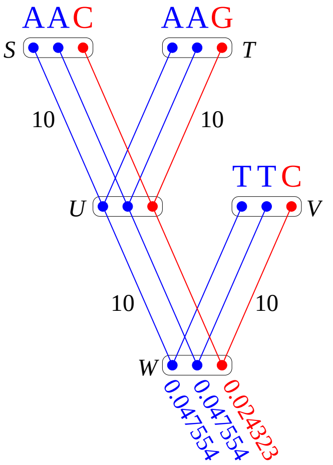
with all $d_x = 0.1$ and $P_{ij}(0.1) = \left\{ \begin{array}{ll} .91 & i \neq j \\ .03 & i = j \end{array} \right.$ (JC)

Notes

Likelihoods of Trees (multiple columns)



Considering this tree with $n = 3$ sequences of length $m = 3$ the tree likelihood of this tree is

$$\mathcal{L}(T) = \prod_{k=1}^{m} L^{(k)} \quad = \quad 0.047554^2 \cdot 0.024323$$

$$= \quad 0.000055$$

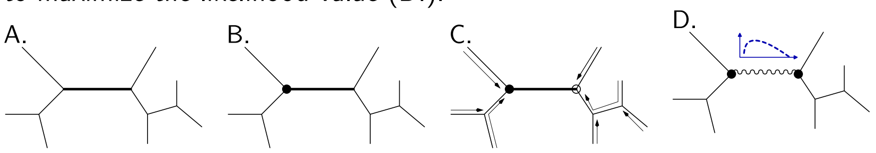
or the log-likelihood

$$\ln \mathcal{L}(T) = \sum_{k=1}^{m} \ln L^{(k)} = -9.80811$$

Notes

Adjusting Branch Lengths Step-By-Step

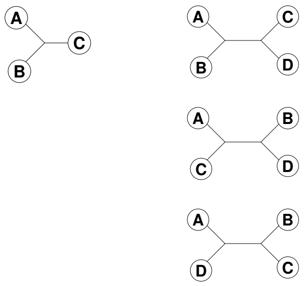
To compute optimal branch lengths do the following. Initialize the branch lengths.
Choose a branch (A.). Move the virtual root to an adjacent node (B.).
Compute all partial likelihoods recursively (C.). Adjust the branch length to maximize the likelihood value (D.).



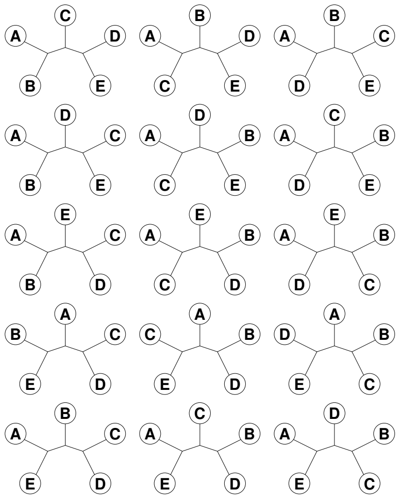
Repeat this for every branch until no better likelihood is gained.

Notes

Number of Trees to Examine. . .



$$\begin{aligned} B(n) &= \frac{(2n-5)!}{2^{n-3}(n-3)!} \\ B(10) &= 2027025 \\ B(55) &= 2.98 \cdot 10^{84} \\ B(100) &= 1.70 \cdot 10^{182} \end{aligned}$$



Notes

Finding the ML Tree

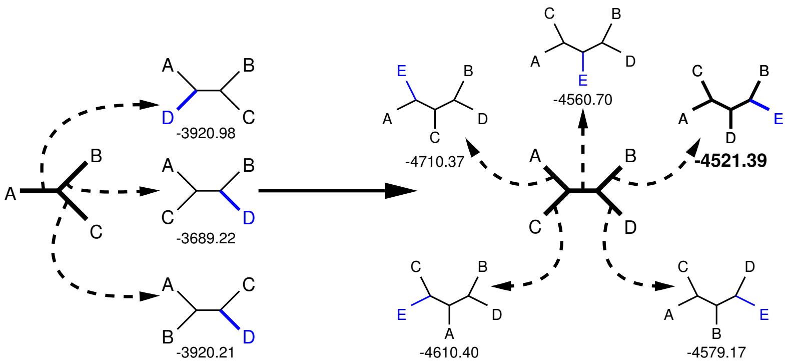
Exhaustive Search: guarantees to find the optimal tree, because all trees are evaluated, but not feasible for more than 10-12 taxa.

Branch and Bound: guarantees to find the optimal tree, without searching certain parts of the tree space – can run on more sequences, but often not for current-day datasets.

Heuristics: cannot guarantee to find the optimal tree, but are at least able to analyze large datasets.

Notes

Build up a tree: Stepwise Insertion

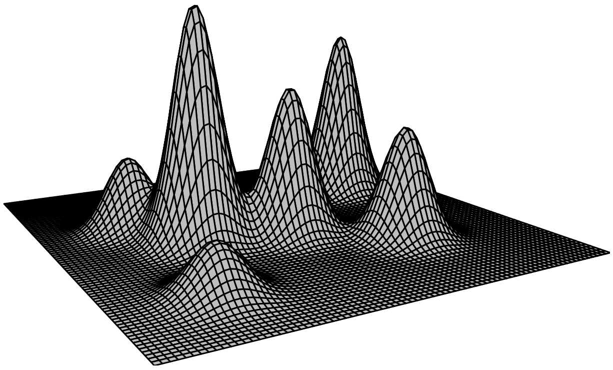


Is also used for other (non-ML) methods like parsimony.

Notes

Local Maxima

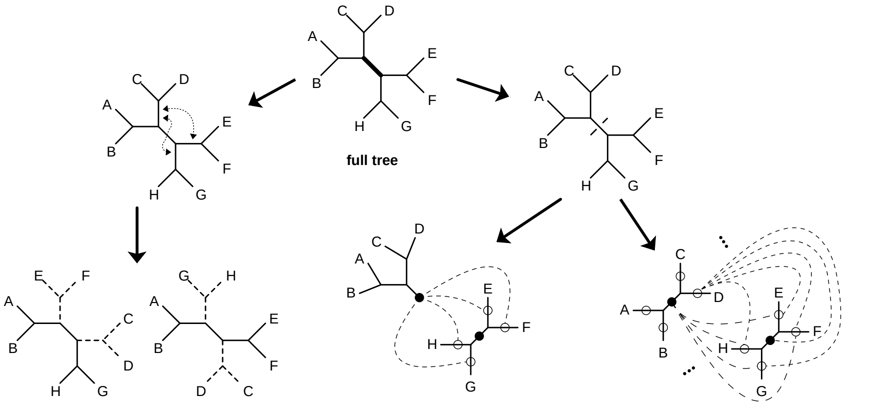
What if we have multiple maxima in the likelihood surface?



Tree rearrangements to escape local maxima.

Notes

Tree Rearrangements: Scanning a Tree's Neighborhood



Nearest Neighbor Interchange (NNI)

O(n) NNI trees

Subtree Pruning + Regrafting (SPR)

$O(n^2)$ SPR trees

Tree−Bisection + Reconnection (TBR)

$O(n^3)$ TBR trees

From a current tree construct other trees by rearranging its subtrees and evaluates all resulting trees. Repeat with the best tree found, until no better tree can be found. This also used for other (non-ML) methods, like parsimony.

Notes