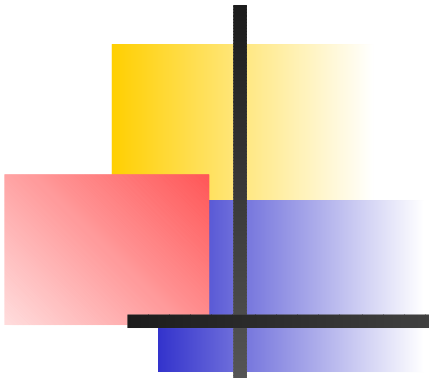

Phylogenetic Inference: Sequence Alignment

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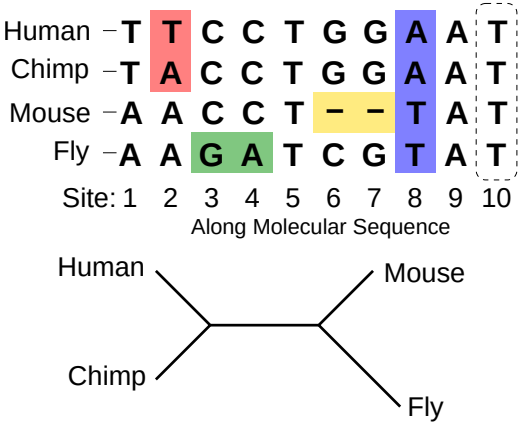
Sequence Alignments

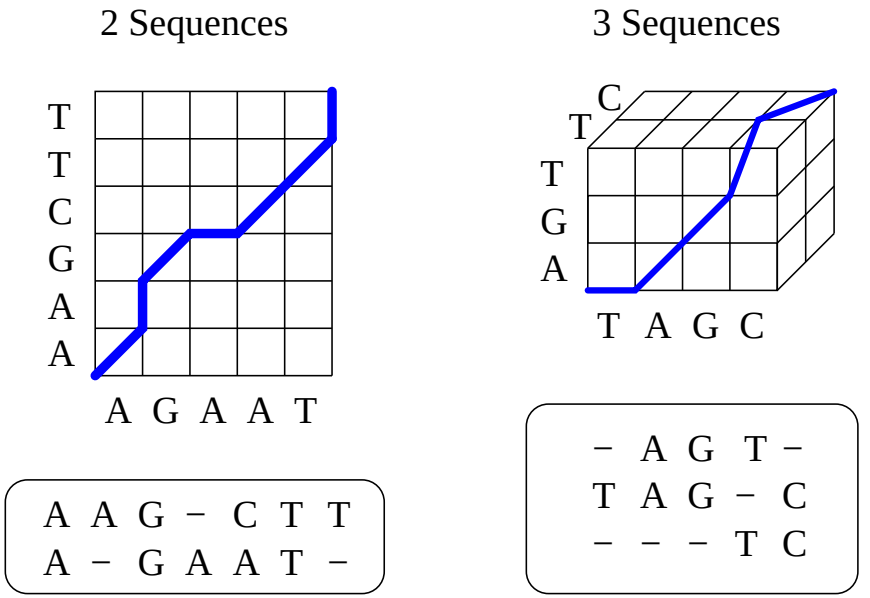
Assign homology between characters from different taxa. Two characters are **homologous** if they share a common ancestor by vertical descent.



Important:

- Homology statements allow one to find conserved (functionally important) sites
- Almost universally, phylogenetic methods condition on (**assume as fixed**) a sequence alignment. Concern: "garbage-in, garbage-out"

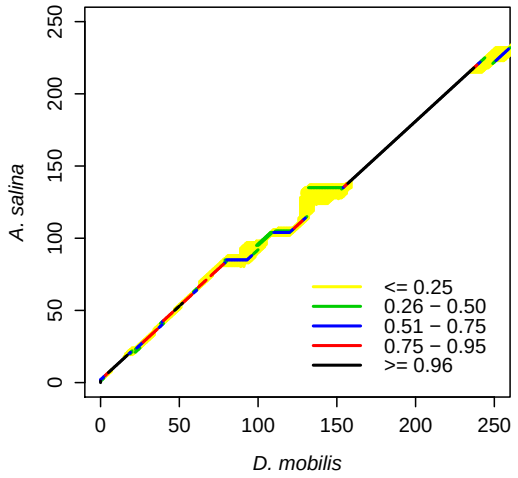
Alignment Path Graphs

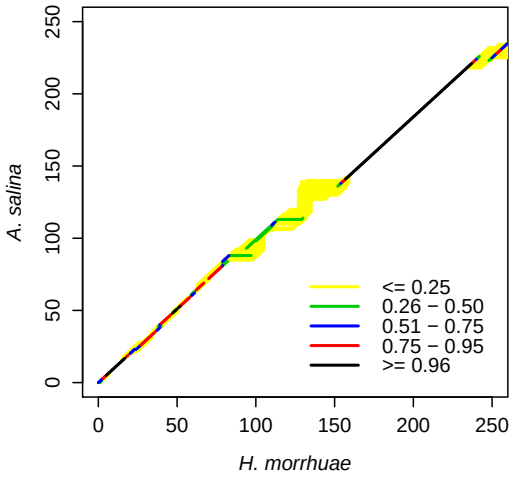


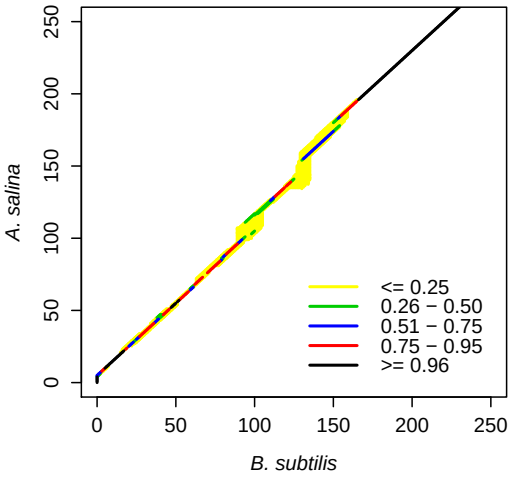
Represent a multiple alignment as an increasing **path** within a N-dimensional lattice cube:

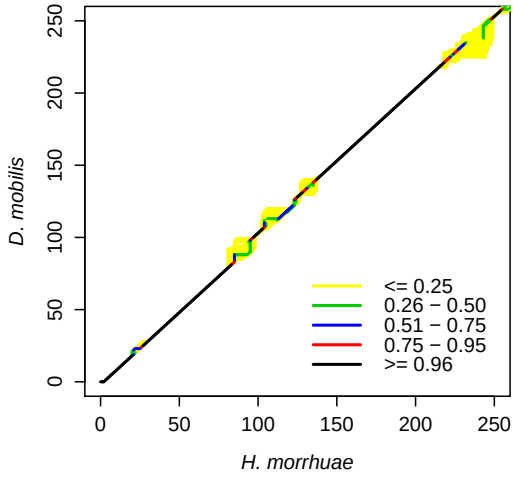
- Runs from lattice point $(0, \ldots, 0)$ to $(\ell_1, \ldots, \ell_N)$, and
- Edges (segments between points) correspond to alignment patterns.

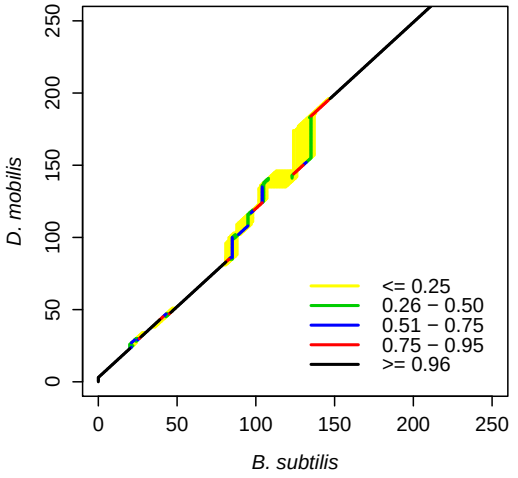
16/18S rRNA Alignment for the Tree of Life

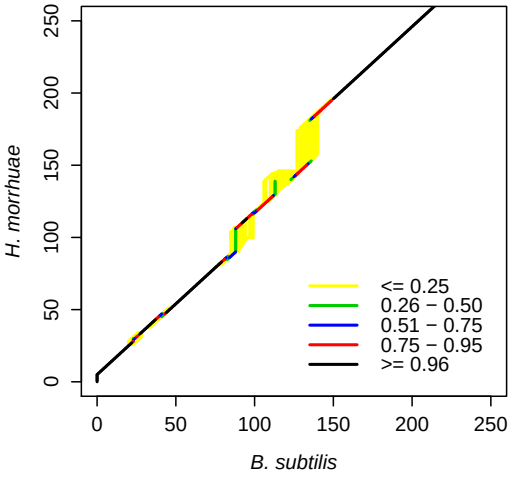






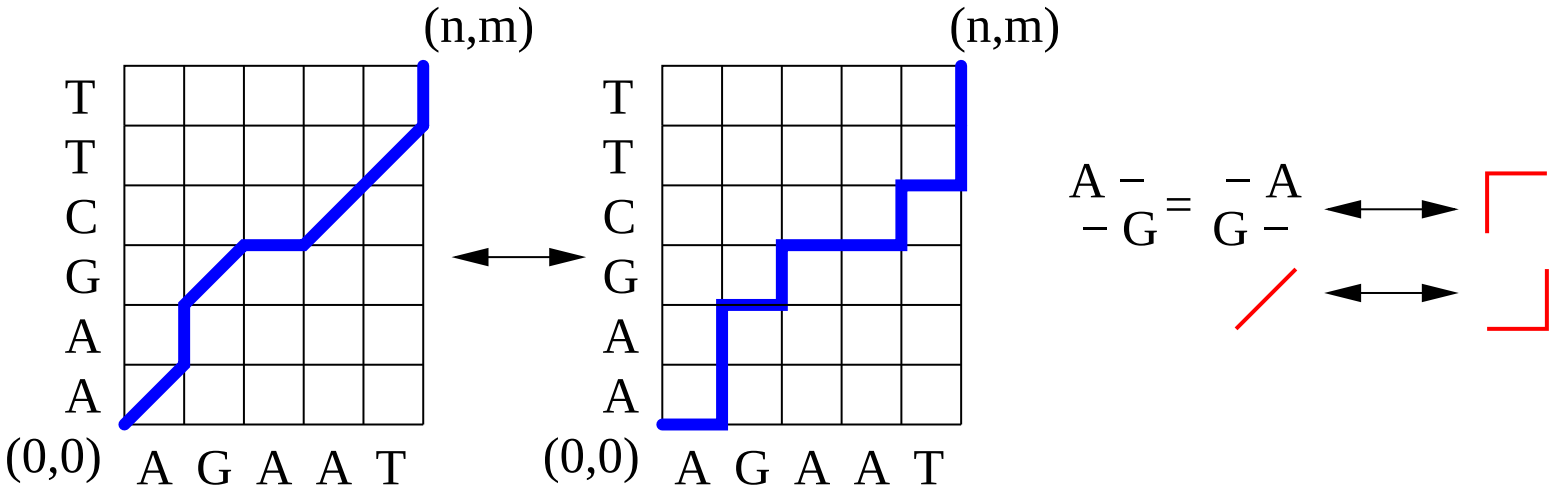






Counting Pairwise (2-Taxon) Alignments

Equivalence between alignment and lattice path graphs



Alignment Path **Lattice Path**

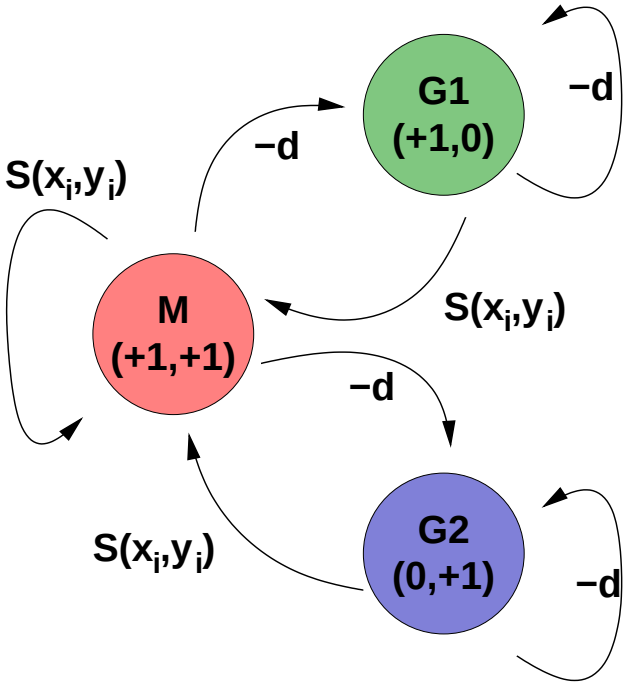
Impose a strict ordering on gaps. Then there exist $\binom{n+m}{n}$ possible lattice paths

- Justification: there are $n + m$ total steps of which n must be to the right

Modeling Pairwise Alignments

Consider a Markov chain on the following graph:

- 3 states – match (M) and gaps (G1/G2)
- characters x_i and y_i are homologous with score $S(x_i, y_i)$
- a gap scores $-d$



Extensions:

- Gap opening vs. gap elongation
- Fix (BLOSUM50/$d = 8$) or estimate scores

Finding the Optimal Path

Use dynamic programming (or forward-backward algorithm) to reduce exponential search space to polynomial $O(nm)$

Needleman-Wunsch algorithm:

- Idea: build up optimal alignment from previous solutions for smaller subsequences
- How: Construct matrix $\boldsymbol{F} = \{F(i,j)\}$, where $F(i,j)$ equals the **score** of the optimal alignment between segments $x_1 \cdots x_i$ and $y_1 \cdots y_j$
- Key: $\boldsymbol{F}$ is build recursively

	A	**G**	**C**	**T**
A	10	−1	−3	−4
G	−1	7	−5	−3
C	−3	−4	9	0
T	−4	−3	0	8

Example $S(x_i, y_j)$

Needleman-Wunsch algorithm

$F(0,0) \leftarrow 0, F(i,0) \leftarrow -id, F(0,j) \leftarrow -j \; i = 1,\ldots,N, \; j = 1,\ldots,M$ **{initialization}**

for $i = 1,\ldots,N$ **do**

  for $j = 1,\ldots,M$ **do**

    $f_{\mathsf{M}} \leftarrow F(i-1,j-1) + S(x_i, y_j)$

    $f_{\mathsf{G1}} \leftarrow F(i-1,j) - d$

    $f_{\mathsf{G2}} \leftarrow F(i,j-1) - d$

    $F(i,j) = \max\{f_{\mathsf{M}}, f_{\mathsf{G1}}, f_{\mathsf{G2}}\}$ {always chose the optimal}

    Label $F(i,j)$ with a pointer to the previous M, G1 or G2 selected cell

  end for

end for

$F(n,m)$ is the optimal score

Follow pointers from $F(n,m) \rightarrow F(0,0)$ to obtain optimal alignment **{traceback}**

Intuition: nested $\max$ statements leads to a "branch-and-bound"-like path

Model Pairwise Alignment as a Hidden Markov Model

Permits simultaneous estimation of HMM parameters θ

Work-horses:

- **Forward-backward algorithm** – computes the probability of the alignment given θ
- **Baum-Welch algorithm** – computes ML estimates (posterior modes) of θ given the alignment
- **Viterbi algorithm** – finds the most likely sequence of hidden states

More details in course if time permits