Probabilistic methods for phylogenetic tree reconstruction

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Downsides to parsimony methods

• Scoring function parameters (costs for substitutions) are rather arbitrary
  – The most “parsimonious” tree critically depends on these parameters

• Parsimony methods require assignments of character states to the ancestral nodes
  – Only considers score of best assignment, which may not be the true one
Alternative to parsimony: probabilistic-model based tree scoring

- Instead of cost $S(a,b)$ of a substitution occurring along a branch, we will use a probability $P(\text{child} = a \mid \text{parent} = b)$
- For a given tree, instead of finding a minimal cost assignment to the ancestral nodes, we will sum the probabilities of all possible ancestral states
- Instead of finding a tree with minimum cost will will find a tree the maximizes likelihood (probability of the data given the tree)

Probabilistic model setup

- We observe $n$ sequences, $x^1, \ldots, x^n$
- We are given a tree $T$ and want to model $P(x^1, \ldots, x^n \mid T)$
  - This is the likelihood (probability of the observed sequences given the model, the tree)
- For simplicity, we’ll just consider the case that our sequences are of length 1 (just one character)
- To generalize to longer sequences, we assume independence of each position (each column of an ungapped multiple alignment)
  - Probability of sequences = product of probability of each position/column
Probabilistic model details

- It will be easier to first consider a model in which we represent the states of the internal nodes of the tree with random variables: $X^{n+1}, \ldots, X^{2n-1}$ (assuming rooted binary tree).
- Then the probability of any particular configuration of states at all nodes in the tree will be defined as

$$P(x^1, \ldots, x^{2n-1} \mid T) = q_{x^{2n-1}} \prod_{i=1}^{2n-2} P(x^i \mid x^{\alpha(i)})$$

- $q_{x^{2n-1}}$ is the prior probability of the state of the root node.
- $\alpha(i)$ is the index of the parent node of node $i$.
- Key assumption: state of node $i$ is conditionally independent of the states of its ancestors given the state of its parent.
- For simplicity, we are ignoring branch lengths for now.

The likelihood

- We only care about the probability of the observed (extant) sequences.
- Need to marginalize (sum over possible values of ancestral states) to obtain the likelihood

$$P(x^1, \ldots, x^n \mid T) = \sum_{X^{n+1}, \ldots, X^{2n-1}} q_{X^{2n-1}} \prod_{i=1}^{2n-2} P(x^i \mid x^{\alpha(i)})$$

- But there is an exponential number of terms in this sum!
Felsenstein’s algorithm

• Dynamic programming to the rescue once again!
• Subproblem: $P(L_k | a)$: probability of the leaves below node $k$, given that the residue at $k$ is $a$
• Recurrence:

$$P(L_k | a) = \sum_{b,c} P(b | a) P(L_i | b) P(c | a) P(L_j | c)$$

$$= \sum_b P(b | a) P(L_i | b) \sum_c P(c | a) P(L_j | c)$$

• where $i$ and $j$ are the children nodes of $k$
• $b$ and $c$ represent the states of node $i$ and node $j$, respectively

Felsenstein’s algorithm

• Initialize: $k=2n-1$
• Recursion:
  – If $k$ is a leaf node,

$$P(L_k | a) = \begin{cases} 1 & \text{if } a = x^k \\ 0 & \text{otherwise} \end{cases}$$

  – Else, compute $P(L_i | a)$ and $P(L_j | a)$ for all $a$ at daughters $i$ and $j$

$$P(L_k | a) = \sum_b P(b | a) P(L_i | b) \sum_c P(c | a) P(L_j | c)$$

• Termination
  – Likelihood is equal to

$$\sum_a P(L^{2n-1} | a) q_a$$
Concluding remarks on probabilistic-model (likelihood) based approach

• Very similar to the weighted parsimony case
  – Main differences are at
    • Leaf nodes
    • Minimization versus summation for internal nodes

• Can it be used to infer ancestral states as well?
  – Instead of summing, we would maximize
  – As in the parsimony case, we would need to keep track of
    the maximizing assignment

• Substitution probabilities $P(a|b)$ can be derived from
  principled mathematical models and/or estimated
  from data

What is probability for the following set of residues

Assume the above conditional probability matrix
$P(b|a)$ for all branches
The probabilities computed for each node

<table>
<thead>
<tr>
<th></th>
<th>A</th>
<th>C</th>
<th>G</th>
<th>T</th>
</tr>
</thead>
<tbody>
<tr>
<td>$P(L_1</td>
<td>x)$</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>$P(L_2</td>
<td>x)$</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>$P(L_3</td>
<td>x)$</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>$P(L_4</td>
<td>x)$</td>
<td>0.07</td>
<td>0.01</td>
<td>0.01</td>
</tr>
<tr>
<td>$P(L_5</td>
<td>x)$</td>
<td>0.0058</td>
<td>0.0022</td>
<td>0.0154</td>
</tr>
</tbody>
</table>

Probability of sequence given tree is $0.25(0.0058+0.0022+0.0154 + 0.0058)=0.0073$