Phylogenetic trees

Likelihood computations and inference

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Outline

Tree Notation

Notation and model: let...

x_n	be (actual) state of node n
y_n	be (observed) character at leaf node n
$X = \{x_n\}$	be the set of all node states
$Y = \{y_n\}$	be the set of all observed characters at leaf nodes
Y_n	be the set of all y_m descended from node n
$\overline{Y_n} = Y \setminus Y_n$	be the set of all remaining y_m
t_{mn}	be evolutionary "distance" (time) from m to n

Root node is node 1.
For convenience, number nodes in preorder (parents < kids)

Conditional & Prior Probabilities

Parent x_p, child x_c:

$$P(x_c|x_p) = M(t_{pc})_{x_p x_c} = \exp(\mathbf{R} t_{pc})_{x_p x_c}$$

Leaf node c:

$$P(y_c|x_c) = \delta_{x_c y_c}$$

i.e. observation y_c fully specifies state x_c. We can drop the x_c:

$$P(y_c|x_p) = \sum_{x_c} P(x_c|x_p) P(y_c|x_c) = M(t_{pc})_{x_p y_c}$$

Assumption: Ur-ancestor was in evolutionary equilibrium

$$P(x_1) = \pi_{x_1}$$

(Root node is always node 1)

Felsenstein's Algorithm: Two Taxa

- Felsenstein's pruning algorithm: our first DP
  - Consider tree T_1: $\begin{tikzcd}[column sep=tiny, row sep=small] & 1 \arrow[dl, no head] \arrow[dr, no head] & \\ 2 & & 3 \end{tikzcd}$ with the following dependencies between state variables X and observations Y:

$$\begin{tikzcd}[column sep=tiny] & x_1 \arrow[dl, no head] \arrow[dr, no head] & \\ x_2 \arrow[d, no head] & & x_3 \arrow[d, no head] \\ y_2 & & y_3 \end{tikzcd}$$

  - Joint likelihood of all nodes:

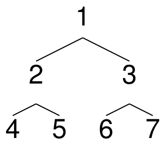
$$P(X,Y) = P(x_1)P(x_2|x_1)P(x_3|x_1)P(y_2|x_2)P(y_3|x_3)$$

  - Marginal likelihood of leaves:

$$\begin{aligned} P(Y) &= \sum_X P(X,Y) \\ &= \sum_{x_1} P(x_1)P(y_2|x_1)P(y_3|x_1) \end{aligned}$$

Felsenstein's Algorithm: Four Taxa

Now consider tree T_2:

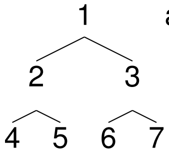


Joint likelihood of all nodes:

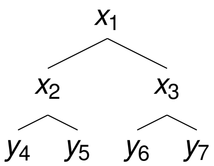
$$\begin{aligned} & P(X, Y) \\ = \quad & P(x_1)P(x_2|x_1)P(x_3|x_1)P(x_4|x_2)P(x_5|x_2)P(x_6|x_3)P(x_7|x_3)\prod_{n=4}^{7} P(y_n|x_n) \end{aligned}$$

Felsenstein's Algorithm: Rearranging Terms

Tree T_2:



and model



Marginal likelihood of leaves:

$$P(Y) = \sum_X P(X, Y)$$

$$= \sum_{x_1} \sum_{x_2} \sum_{x_3} P(x_1)P(x_2|x_1)P(x_3|x_1)P(y_4|x_2)P(y_5|x_2)P(y_6|x_3)P(y_7|x_3)$$

$$= \sum_{x_1} P(x_1)\left[\left(\sum_{x_2} P(x_2|x_1)[P(y_4|x_2)P(y_5|x_2)]\right)\left(\sum_{x_3} P(x_3|x_1)[P(y_6|x_3)P(y_7|x_3)]\right)\right]$$

Terms in square brackets have the form:

$$F_n(x_n) = P(\{y_i : i \text{ descended from } n\}|x_n) = P(Y_n|x_n)$$

Felsenstein's Algorithm: Generalization

- Let C_n be the set of immediate children of n (so e.g. $C_1 = \{2, 3\}$)
- Rule to compute F_n is then

$$
\begin{aligned}
F_n(x_n) &= \begin{cases} \prod_{c \in C_n} \left(\sum_{x_c} P(x_c|x_n) F_c(x_c) \right) & \text{if } n \text{ is internal} \\ P(y_n|x_n) & \text{if } n \text{ is a leaf} \end{cases} \\
P(Y) &= \sum_{x_1} P(x_1) F_1(x_1)
\end{aligned}
$$

- This is the pruning algorithm (Felsenstein, 1981).

Felsenstein's Algorithm: Recursion

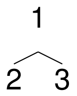
$$F_n(x_n) = \begin{cases} \prod_{c \in C_n} \left(\sum_{x_c} P(x_c|x_n) F_c(x_c) \right) & \text{if } n \text{ is internal} \\ P(y_n|x_n) & \text{if } n \text{ is a leaf} \end{cases}$$

$$P(Y) = \sum_{x_1} P(x_1) F_1(x_1)$$

- Term after "$\prod$" sign in F_n can be written $E_c(x_p) = P(Y_c|x_p) = \sum_{x_c} P(x_c|x_p) F_c(x_c)$ where p is parent of c
- An instance of the sum-product algorithm on a factor graph

Pulley Principle

- “Pulley principle” for reversible models.



  - Using $\pi_i M(t)_{ij} = \pi_j M(t)_{ji}$ and $\mathbf{M}(t)\mathbf{M}(t') = \mathbf{M}(t+t')$

$$\begin{aligned} P(y_2, y_3) &= \sum_{x_1} \pi_{x_1} M(t_{12})_{x_1 y_2} M(t_{13})_{x_1 y_3} \\ &= \sum_{x_1} \pi_{x_2} M(t_{12})_{y_2 x_1} M(t_{13})_{x_1 y_3} \\ &= \pi_{y_2} M(t_{12} + t_{23})_{y_2 y_3} \\ &= \pi_{y_3} M(t_{12} + t_{23})_{y_3 y_2} \end{aligned}$$

  - $P(y_2, y_3)$ depends only on $t_{12} + t_{23}$
  - Can slide root node (like a pulley) w/out affecting likelihood
  - Corollorary: can re-root tree at any node, including any leaf

Alignment Probability

- So far we have looked at $P(C|T)$, the probability of an individual alignment column, conditioned on a tree
- Probability of an entire alignment conditioned on tree, $P(A|T)$, is product of column probabilities:

$$P(A|T) = \prod_{C \in A} P(C|T)$$

  - Denote maximum likelihood tree by $T_{\text{ML}} = \text{argmax}_T P(A|T)$
- Note that so far we have neglected the indel history that is also (partially) specified by the alignment

Ancestral State Reconstruction on a Phylogeny

- Motivation:
  - Probability distribution of ancestral state, $P(x_n|Y)$
  - Probability distribution of $p \rightarrow c$ branch, $P(x_p, x_c|Y)$
- Recall tree notation:
  - $Y = \{y_i\}$ is the set of all leaf states
  - Y_n contains all y_i descended from node n
  - $\overline{Y_n}$ contains all y_i not descended from node n
    - Note $Y_1 \equiv Y$, since node 1 is the root node.

Probabilities of Ancestral States

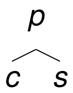
- Felsenstein's pruning algorithm computes $F_n(x_n) = P(Y_n|x_n)$
  - and thus $P(Y) = \sum_{x_1} \pi(x_1) F_1(x_1)$
- We will now give recursions for $G_n(x_n) = P(x_n, \overline{Y_n})$.
- With these we can easily get posterior probabilities for...
  - State of ancestral node
  - State of ancestral branch

State of Ancestral Node

$$
\begin{aligned}
F_n(x_n) &= P(Y_n|x_n) \\
G_n(x_n) &= P(x_n, \overline{Y_n}) \\
P(x_n|Y) &= \frac{P(x_n, Y)}{P(Y)} \\
&= \frac{1}{P(Y)} P(x_n, \overline{Y_n}) P(Y_n|x_n) \\
&= \frac{1}{P(Y)} G_n(x_n) F_n(x_n)
\end{aligned}
$$

State of Ancestral Branch

- Joint state of ancestral branch



$$\begin{aligned} P(x_p, x_c | Y) &= \frac{P(x_p, x_c, Y)}{P(Y)} \\ &= \frac{1}{P(Y)} P(x_p, \overline{Y_p}) P(x_c | x_p) P(Y_c | x_c) P(Y_s | x_p) \\ &= \frac{1}{P(Y)} G_p(x_p) P(x_c | x_p) F_c(x_c) E_s(x_p) \end{aligned}$$

where $E_s(x_p) = \sum_{x_c} P(x_c | x_p) F_s(x_s)$ as before

Peeling Recursion

- Recursion for $G_c(x_c) = P(x_c, \overline{Y_c})$

$$G_c(x_c) = \begin{cases} \sum_{x_p} G_p(x_p) P(x_c|x_p) E_s(x_p) & \text{if } c > 1 \text{ (not root)} \\ P(x_c) & \text{if } c = 1 \text{ (root)} \end{cases}$$

  - aka Elston-Stewart peeling algorithm

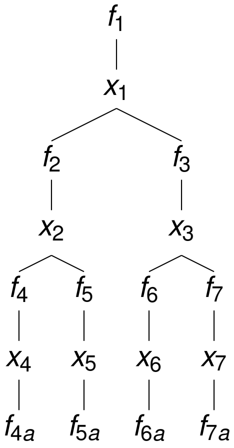
Degenerate characters

IUPAC ambiguity code	Possibilities
R	A G
Y	C T
M	A C
K	G T
S	C G
W	A T
H	A C T
B	C G T
V	A C G
D	A G T
N or X	A C G T

- Recall the hidden state x_i behind observation y_i
- $P(y_i|x_i) = A_{x_i y_i}$ reflects ambiguous y_i
- Can be extended to read quality scores, etc.
- $P(X, Y)$ is product of π_i's, M_{ij}'s and A_{ij}'s

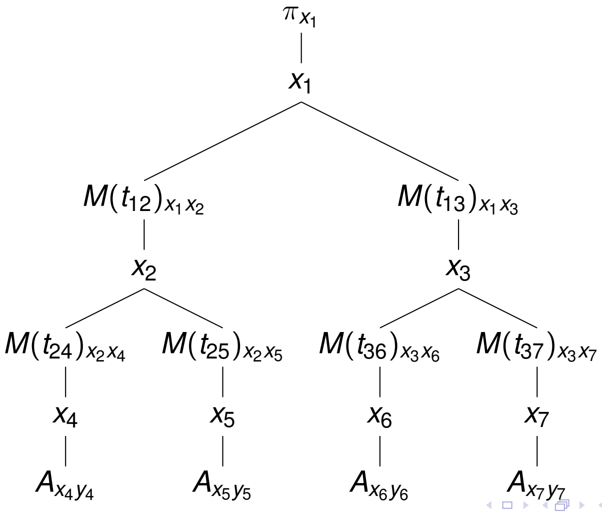
Bigraph representation of $P(X, Y)$

2-coloring: variables $X = \{x_i\}$, functions $\mathcal{F} = \{f_n\}$

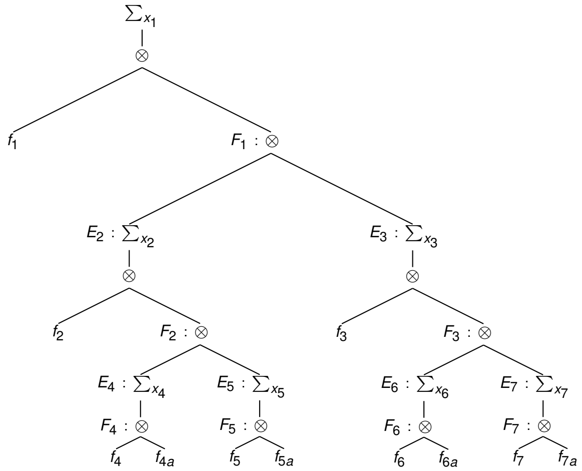


$$
\begin{aligned}
f_1(x_1) &= \pi_{x_1} \\
f_2(x_1, x_2) &= M(t_{12})_{x_1 x_2} \\
f_3(x_1, x_3) &= M(t_{13})_{x_1 x_3} \\
f_4(x_2, x_4) &= M(t_{24})_{x_2 x_4} \\
f_5(x_2, x_5) &= M(t_{25})_{x_2 x_5} \\
f_6(x_3, x_6) &= M(t_{36})_{x_3 x_6} \\
f_7(x_3, x_7) &= M(t_{37})_{x_3 x_7} \\
f_{4a}(x_4) &= A_{x_4 y_4} \\
f_{5a}(x_5) &= A_{x_5 y_5} \\
f_{6a}(x_6) &= A_{x_6 y_6} \\
f_{7a}(x_7) &= A_{x_7 y_7} \\
P(x_1 \ldots x_7; y_4 \ldots y_7) &= f_1(x_1) f_2(x_1, x_2) f_3(x_1, x_3) \\
&\quad \times f_4(x_2, x_4) f_5(x_2, x_5) f_6(x_3, x_6) f_7(x_3, x_7) \\
&\quad \times f_{4a}(x_4) f_{5a}(x_5) f_{6a}(x_6) f_{7a}(x_7)
\end{aligned}
$$

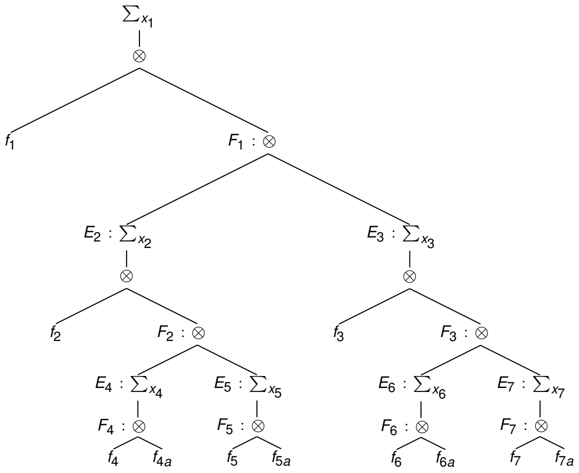
Bigraph representation of $P(X, Y)$ showing functions

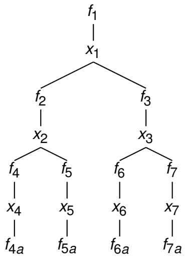


Expression tree of $P(Y)$



Expression tree of $P(Y)$ and factor graph of $P(X, Y)$





Factor Graphs

- The idea of computing marginals and posteriors on a graphical network of variables has been generalized
    - "Factor graphs", "Graphical models", "Bayesian networks", "Markov random fields"
    - "Sum-product algorithm", "Message-passing", "Belief propagation"
- Here we use the Factor Graph variant of the formalism
    - Kschichang, Frey & Loeliger, IEEE 47:2, February 2001.

The summary operator

- The "summary" or "not-sum" operator, $\sum_{\sim\{\}} f(\cdot)$
  - Suppose $V \subseteq W \subseteq X$.
  - The summary of $f(W)$ w.r.t. V is obtained by summing $f(W)$ over all $x_i \notin V$. The result is a function of V.
    - For example...

$$\sum_{\sim\{x_3,x_4\}} f(x_2,x_3,x_4,x_5,x_6) = \sum_{x_2}\sum_{x_5}\sum_{x_6} f(x_2,x_3,x_4,x_5,x_6)$$

  - Define the summary of f w.r.t. its own arguments as f itself:

$$\sum_{\sim\{W\}} f(W) \equiv f(W)$$

  - The summaries of a joint likelihood are the marginals: If $g(X) = P(X)$, then $\sum_{\sim\{V\}} g(V) = P(V)$

Message-passing

- Factor graphs contain
  - function nodes (f_i)
  - variable nodes (x_i)
  - An edge f_i—x_j indicates x_j is a parameter of f_i
- Computation proceeds by message-passing
- A “message” is actually a pre-computed function over some subset of the variables in the graph
- The message from node *a* to node *b* is written $\mu_{a \to b}$

Message-passing

- Message from f_i to x_j:

$$\mu_{f_i \to x_j} = \sum_{\sim\{x_j\}} f_i \prod_{k \neq j} \mu_{x_k \to f_i}$$

  where $\{\mu_{x_k \to f_i}\}$ are the incoming messages to f_i
- Message from x_i to f_j:

$$\mu_{x_i \to f_j} = \prod_{k \neq j} \mu_{f_k \to x_i}$$

  where $\{\mu_{f_k \to x_i}\}$ are the incoming messages to x_i

Message-passing

$$\begin{aligned}\mu_{f_i \to x_j} &= \sum_{\sim\{x_j\}} f_i \prod_{k \neq j} \mu_{x_k \to f_i} \\ \mu_{x_i \to f_j} &= \prod_{k \neq j} \mu_{f_k \to x_i}\end{aligned}$$

The message sent from a node *n* on an edge *e* is...

- the product of:
  1. the local function at *n* (or the unit function, $x_n \to 1$, if *n* is a variable node);
  2. all messages received at *n* on edges *other* than *e*,
- summarized for the variable associated with *e*.

Phylogenetic message-passing

For a phylogenetic tree, the messages are as follows ($c - p - s$ denoting child—parent—sibling)

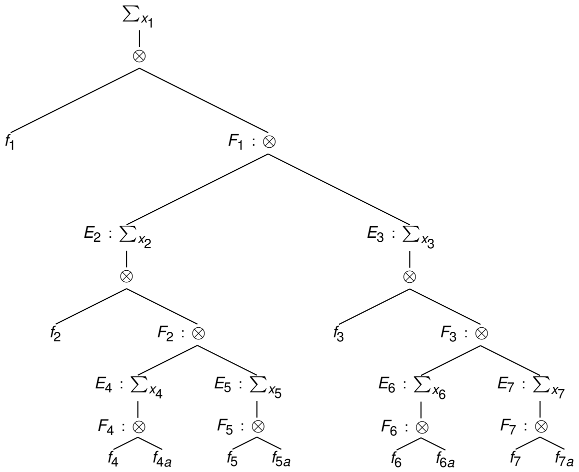
- Leaves-to-root:

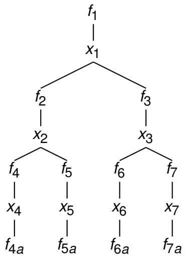
$$\begin{aligned} \mu_{f_{na} \to x_n} &= f_{na}(x_n) \\ \mu_{x_n \to f_n} &= F_n(x_n) \\ \mu_{f_c \to x_p} &= E_c(x_p) \end{aligned}$$

- Root-to-leaves:

$$\begin{aligned} \mu_{f_n \to x_n} &= G_n(x_n) \\ \mu_{x_p \to f_c} &= G_p(x_p) E_s(x_p) \end{aligned}$$

Expression tree of $P(Y)$ and factor graph of $P(X, Y)$





Factor Graphs

- Many applications in biology...
  - Markov models
  - Phylogenetic trees
  - Hidden Markov models
  - Inference on ontologies
  - Markov random fields (images, gene networks, ...)
- ...and beyond...
  - Error-correcting codes

Changing the Operators

- The “sum” and “product” operators in the sum-product algorithm are arbitrary
  - The sum-product algorithm works by factorising terms like

$$\sum_{x_1}\sum_{x_2} f(x_1)f(x_2) = \left(\sum_{x_1} f(x_1)\right)\left(\sum_{x_2} f(x_2)\right)$$

  - This in turn relies on the distributive law,

$$a \times (b + c) = a \times b + a \times c$$

and can be applied to any semiring with operators $(\otimes, \oplus)$

Changing the Operators: ML inference

- For example, consider

$$\begin{aligned} a \oplus b &\equiv \max(a, b) \\ a \otimes b &\equiv ab \end{aligned}$$

- The pruning algorithm now calculates $\max_X P(X, Y)$
- It is straightforward to recover $\mathrm{argmax}_X P(X, Y)$
  - i.e. the MAP (Maximum *A Posteriori*) ancestral state history
  - note that $\mathrm{argmax}_X P(X, Y) = \mathrm{argmax}_X P(X|Y)$
  - this may not give the same results as $\mathrm{argmax}_{x_i} P(x_i|Y)$

Changing the Operators: Parsimony

- Another example: consider

$$\begin{aligned} a \oplus b &\equiv \min(a, b) \\ a \otimes b &\equiv a + b \end{aligned}$$

and set $M(t)_{ij} = A_{ij} = 1 - \delta_{ij}$ and $\pi_i = 0$

  - Then M counts the number of substitutions, and pruning returns the most parsimonious imputation of $\{x_i\}$
- A number of neat results for parsimony exist
  - e.g. a branch-and-bound algorithm to find the most parsimonious tree
- but parsimony is v restrictive “model”; strong assumptions:
  - all substitutions equally likely, no back-substitutions...
  - parsimony not really compatible w/ probabilistic methods

Summary

- Message-passing on phylogenetic trees
  - Felsenstein’s pruning algorithm
  - Elston-Stewart peeling algorithm
- Pulley principle & reversibility