Profile HMM for multiple sequences

Pair HMM

HMM for pairwise sequence alignment, which incorporates affine gap scores.

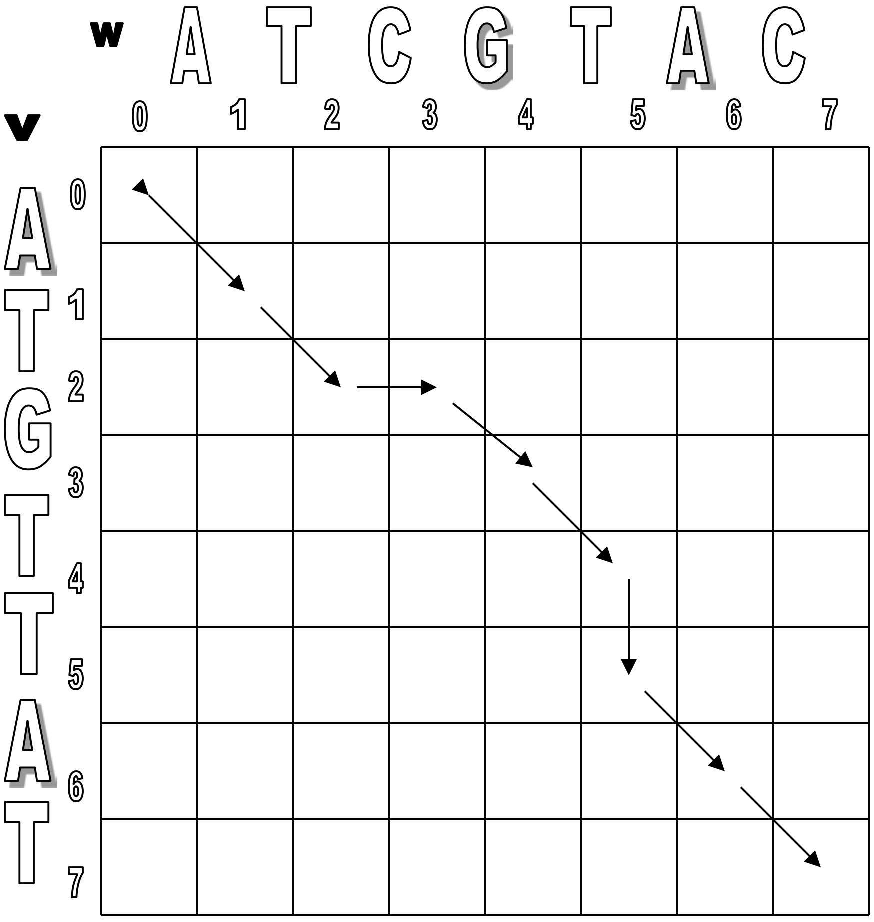
“Hidden” States

- Match (M)
- Insertion in *x* (X)
- insertion in *y* (Y)

Observation Symbols

- Match (M): {(*a*,*b*)| *a*,*b* in ∑ }.
- Insertion in *x* (X): {(*a*,-)| *a* in ∑ }.
- Insertion in *y* (Y): {(-,*a*)| *a* in ∑ }.

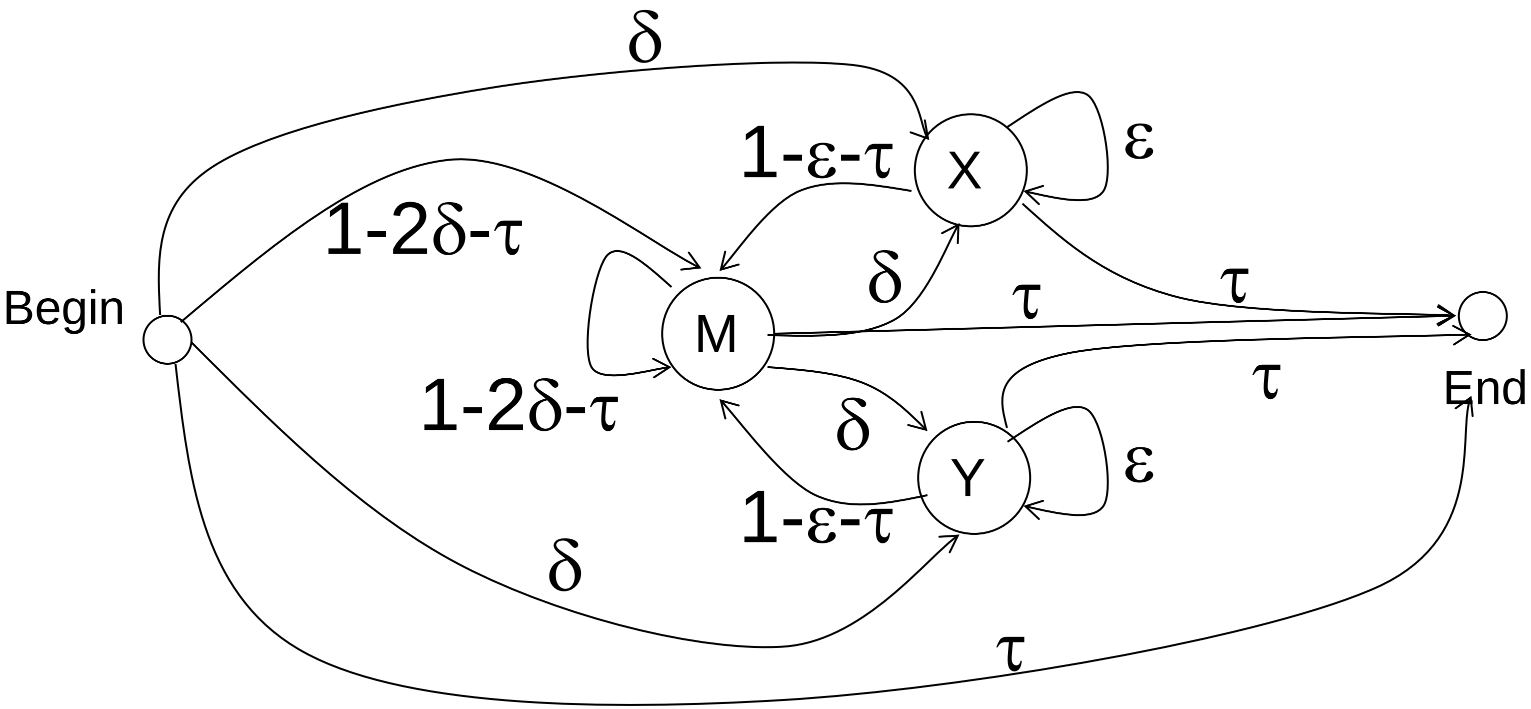
Alignment: a path → a hidden state sequence



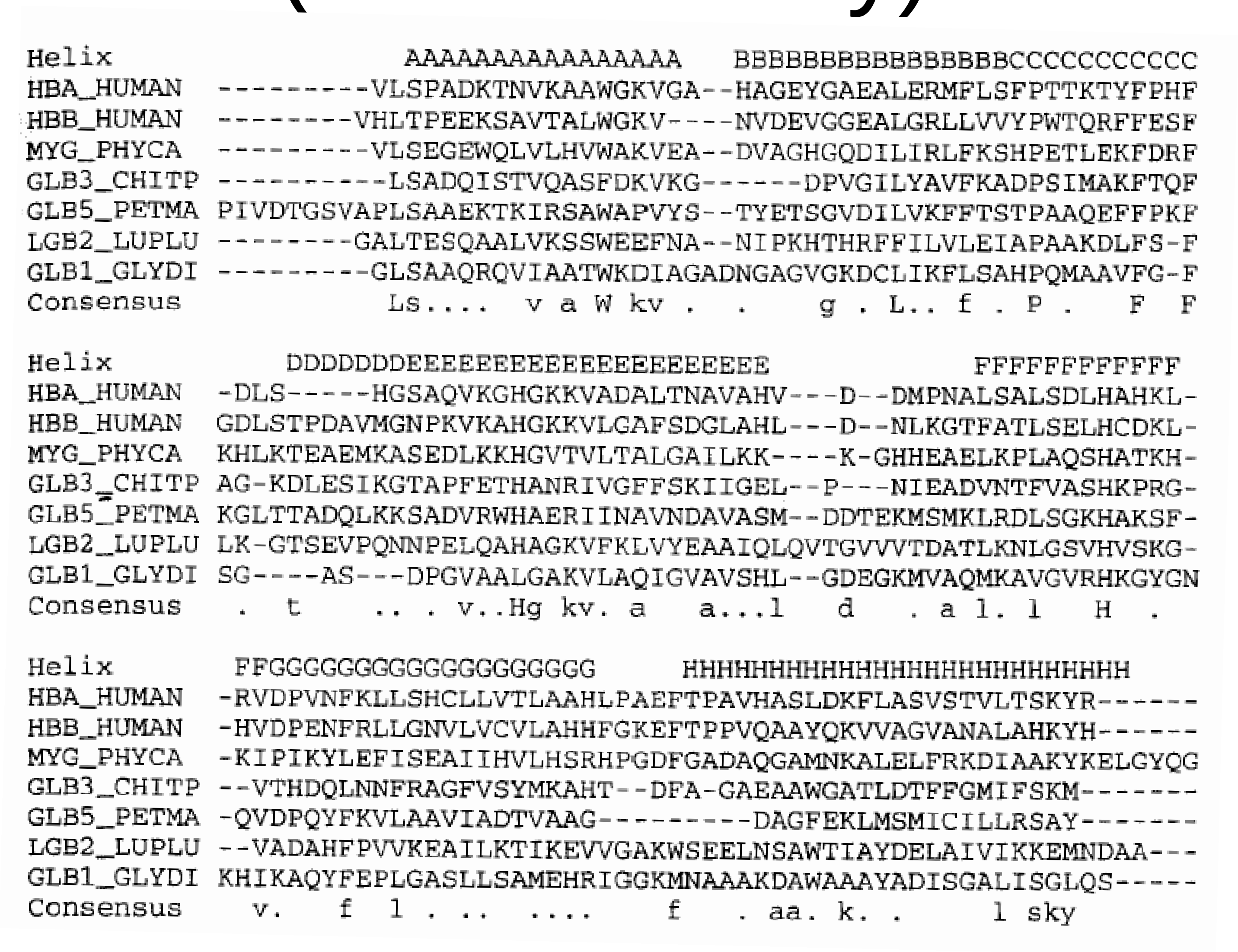
```
A T - G T T A T
A T C G T - A C

M M Y M M X M M
```

Pair HMMs



Multiple sequence alignment (Globin family)



```
Helix                 AAAAAAAAAAAAAAAA   BBBBBBBBBBBBBBBCCCCCCCCCCCC
HBA_HUMAN  ---------VLSPADKTNVKAAWGKVGA--HAGEYGAEALERMFLSFPTTKTYFPHF
HBB_HUMAN  --------VHLTPEEKSAVTALWGKV----NVDEVGGEALGRLLVVYPWTQRFFESF
MYG_PHYCA  ---------VLSEGEWQLVLHVWAKVEA--DVAGHGQDILIRLFKSHPETLEKFDRF
GLB3_CHITP ----------LSADQISTVQASFDKVKG------DPVGILYAVFKADPSIMAKFTQF
GLB5_PETMA PIVDTGSVAPLSAAEKTKIRSAWAPVYS--TYETSGVDILVKFFTSTPAAQEFFPKF
LGB2_LUPLU --------GALTESQAALVKSSWEEFNA--NIPKHTHRFFILVLEIAPAAKDLFS-F
GLB1_GLYDI ---------GLSAAQRQVIAATWKDIAGADNGAGVGKDCLIKFLSAHPQMAAVFG-F
Consensus            Ls....  v a W kv .  .    g . L.. f . P .   F  F

Helix          DDDDDDDEEEEEEEEEEEEEEEEEEEEE            FFFFFFFFFFFF
HBA_HUMAN  -DLS-----HGSAQVKGHGKKVADALTNAVAHV---D--DMPNALSALSDLHAHKL-
HBB_HUMAN  GDLSTPDAVMGNPKVKAHGKKVLGAFSDGLAHL---D--NLKGTFATLSELHCDKL-
MYG_PHYCA  KHLKTEAEMKASEDLKKHGVTVLTALGAILKK----K-GHHEAELKPLAQSHATKH-
GLB3_CHITP AG-KDLESIKGTAPFETHANRIVGFFSKIIGEL--P---NIEADVNTFVASHKPRG-
GLB5_PETMA KGLTTADQLKKSADVRWHAERIINAVNDAVASM--DDTEKMSMKLRDLSGKHAKSF-
LGB2_LUPLU LK-GTSEVPQNNPELQAHAGKVFKLVYEAAIQLQVTGVVVTDATLKNLGSVHVSKG-
GLB1_GLYDI SG----AS---DPGVAALGAKVLAQIGVAVSHL--GDEGKMVAQMKAVGVRHKGYGN
Consensus   .  t    .. . v..Hg kv. a   a...l   d   . a l. l   H  .

Helix       FFGGGGGGGGGGGGGGGGGGG     HHHHHHHHHHHHHHHHHHHHHHHHHH
HBA_HUMAN  -RVDPVNFKLLSHCLLVTLAAHLPAEFTPAVHASLDKFLASVSTVLTSKYR------
HBB_HUMAN  -HVDPENFRLLGNVLVCVLAHHFGKEFTPPVQAAYQKVVAGVANALAHKYH------
MYG_PHYCA  -KIPIKYLEFISEAIIHVLHSRHPGDFGADAQGAMNKALELFRKDIAAKYKELGYQG
GLB3_CHITP --VTHDQLNNFRAGFVSYMKAHT--DFA-GAEAAWGATLDTFFGMIFSKM-------
GLB5_PETMA -QVDPQYFKVLAAVIADTVAAG---------DAGFEKLMSMICILLRSAY-------
LGB2_LUPLU --VADAHFPVVKEAILKTIKEVVGAKWSEELNSAWTIAYDELAIVIKKEMNDAA---
GLB1_GLYDI KHIKAQYFEPLGASLLSAMEHRIGGKMNAAAKDAWAAAYADISGALISGLQS-----
Consensus    v.   f  l . ..  ....    f   . aa. k. .     l sky
```

Profile model (PSSM)

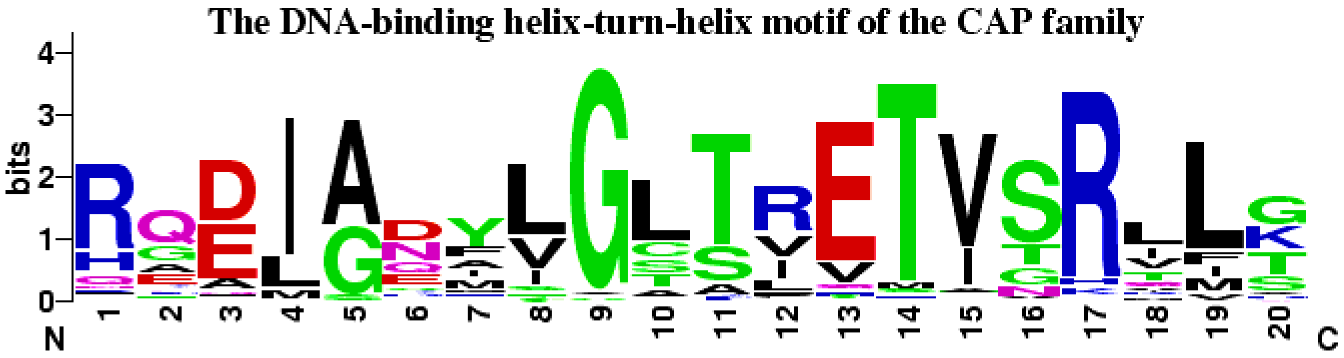
- A natural probabilistic model for a conserved region would be to specify independent probabilities $e_i(a)$ of observing nucleotide (amino acid) *a* in position *i*
- The probability of a new sequence x according to this model is

$$P(x \mid M) = \prod_{i=1}^{L} e_i(x_i)$$

Profile / PSSM

- DNA / proteins Segments of the same length L;
- Often represented as Positional frequency matrix;

```
LTMTRGDIGNYLGLTVETISRLLGRFQKSGML
LTMTRGDIGNYLGLTIETISRLLGRFQKSGMI
LTMTRGDIGNYLGLTVETISRLLGRFQKSEIL
LTMTRGDIGNYLGLTVETISRLLGRLQKMGIL
LAMSRNEIGNYLGLAVETVSRVFSRFQQNELI
LAMSRNEIGNYLGLAVETVSRVFTRFQQNGLI
LPMSRNEIGNYLGLAVETVSRVFTRFQQNGLL
VRMSREEIGNYLGLTLETVSRLFSRFGREGLI
LRMSREEIGSYLGLKLETVSRTLSKFHQEGLI
LPMCRRDIGDYLGLTLETVSRALSQLHTQGIL
LPMSRRDIADYLGLTVETVSRAVSQLHTDGVL
LPMSRQDIADYLGLTIETVSRTFTKLERHGAI
```



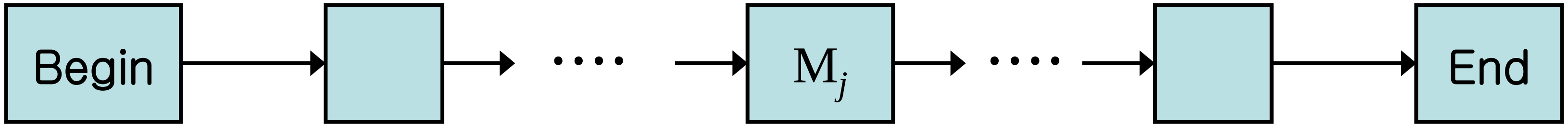
Searching profiles: inference

- Give a sequence S of length L, compute the likelihood ratio of being generated from this profile vs. from background model:
  - R(S|P)= $\prod_{i=1}^{L} \frac{e_i(x_i)}{b_s}$
  - Searching motifs in a sequence: sliding window approach

Match states for profile HMMs

- Match states
  - Emission probabilities

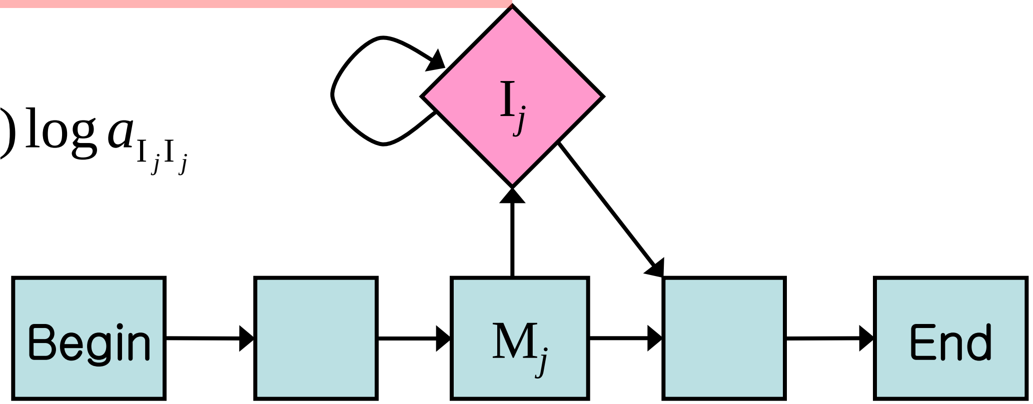
$$e_{M_i}(a)$$



Components of profile HMMs

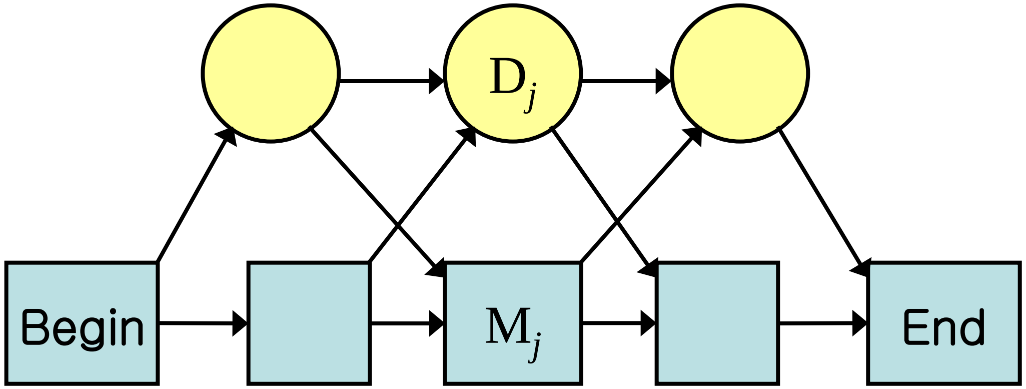
- Insert states $e_{\mathrm{I}_i}(a)$
  - Emission prob.
    - Usually back ground distribution q_a.
  - Transition prob.
    - M_i to I_i, I_i to itself, I_i to M_{i+1}
  - Log-odds score for a gap of length k (no log-odds from emission)

$$\log a_{\mathrm{M}_j\mathrm{I}_j} + \log a_{\mathrm{I}_j\mathrm{M}_{j+1}} + (k-1)\log a_{\mathrm{I}_j\mathrm{I}_j}$$

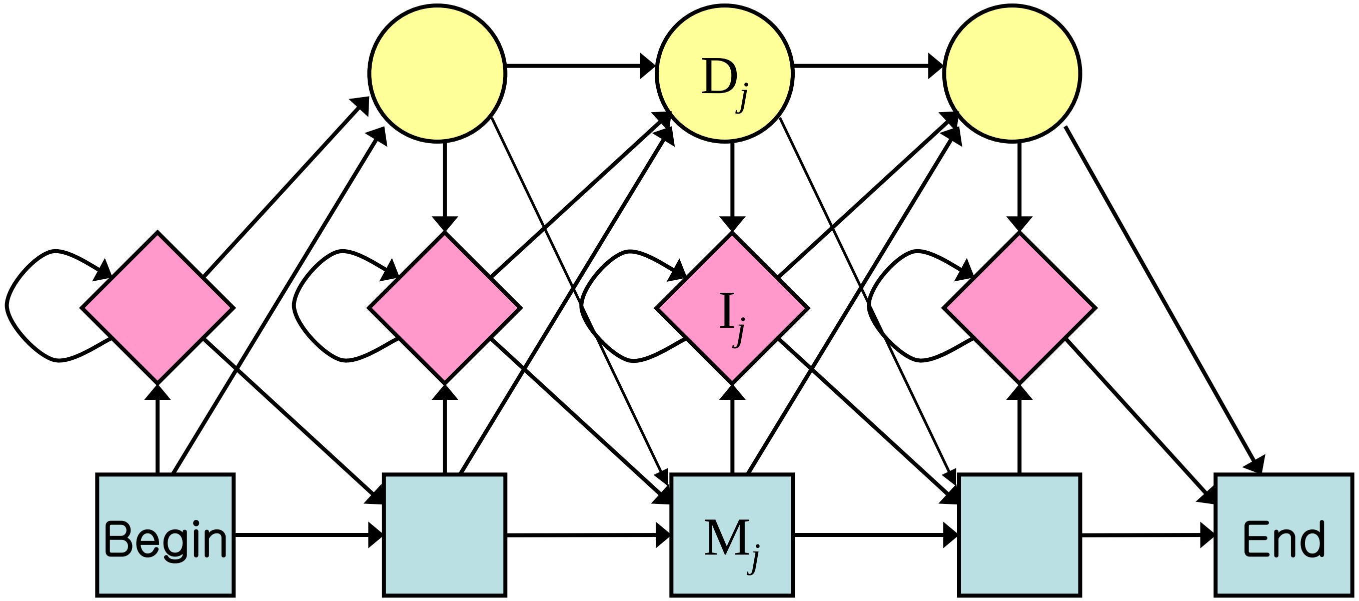


Components of profile HMMs

- Delete states
  - No emission prob.
  - Cost of a deletion
    - M→D, D→D, D→M
    - Each D→D might be different



Full structure of profile HMMs



Deriving HMMs from multiple alignments

- Key idea behind profile HMMs
  - Model representing the consensus for the alignment of sequence from the same family
  - Not the sequence of any particular member

```
HBA_HUMAN   ...VGA--HAGEY...
HBB_HUMAN   ...V----NVDEV...
MYG_PHYCA   ...VEA--DVAGH...
GLB3_CHITP  ...VKG------D...
GLB5_PETMA  ...VYS--TYETS...
LGB2_LUPLU  ...FNA--NIPKH...
GLB1_GLYDI  ...IAGADNGAGV...
               ***  *****
```

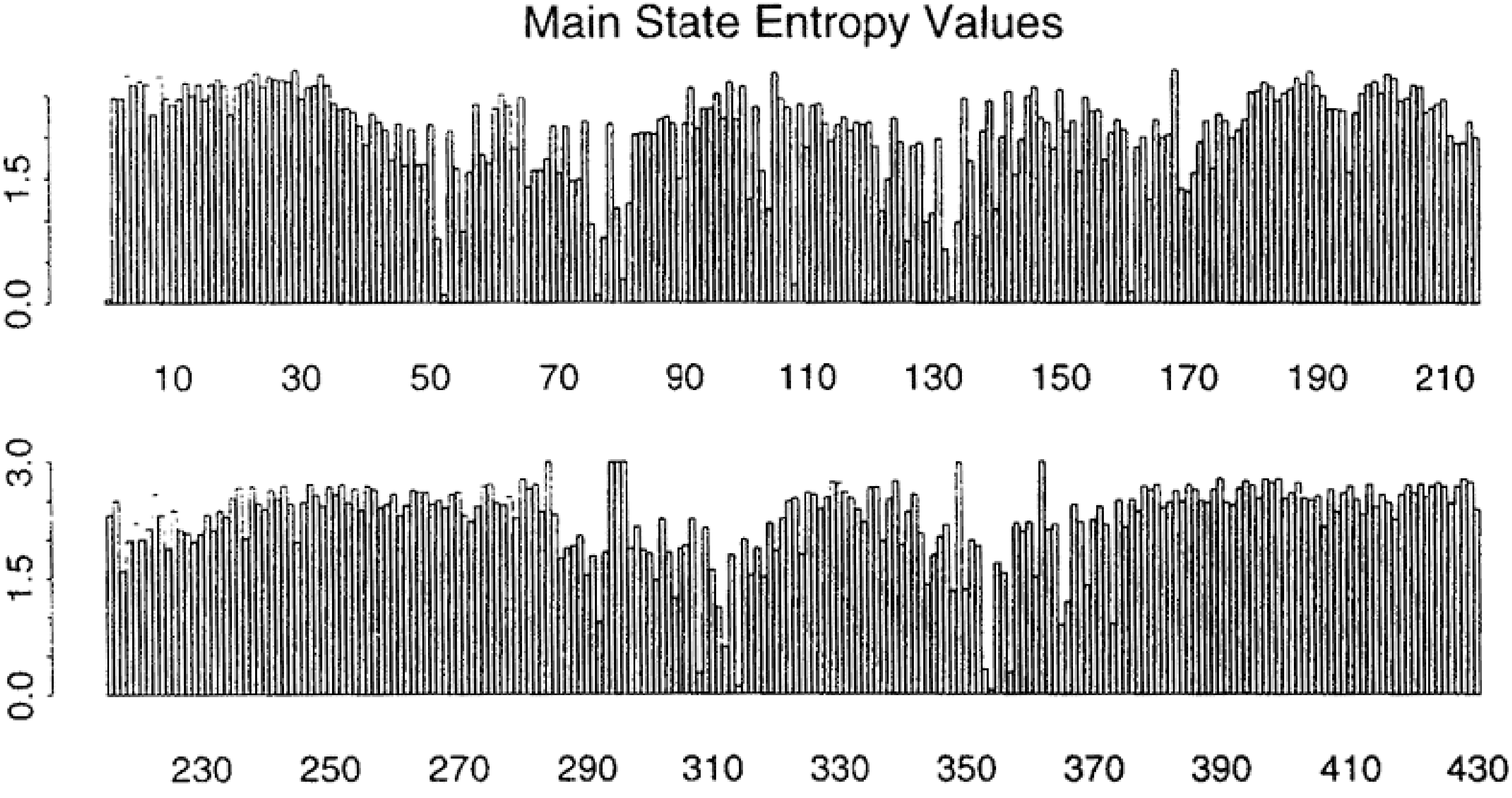
Deriving HMMs from multiple alignments

- Basic profile HMM parameterization
  - Aim: making the higher probability for sequences from the family
- Parameters
  - the probabilities values : trivial if many of independent alignment sequences are given.

$$a_{kl} = \frac{A_{kl}}{\sum_{l'} A_{kl'}} \qquad e_k(a) = \frac{E_k(a)}{\sum_{a'} E_k(a')}$$

  - length of the model: heuristics or systematic way

Sequence conservation: entropy profile of the emission probability distributions



Searching with profile HMMs

- Main usage of profile HMMs
  - – Detecting potential sequences in a family
  - – Matching a sequence to the profile HMMs
    - Viterbi algorithm or forward algorithm
  - – Comparing the resulting probability with random model

$$P(x \mid R) = \prod_i q_{x_i}$$

Searching with profile HMMs

- Viterbi algorithm (optimal log-odd alignment)

$$V_j^{\mathrm{M}}(i) = \log \frac{e_{\mathrm{M}_j}(x_i)}{q_{x_i}} + \max \begin{cases} V_{j-1}^{\mathrm{M}}(i-1) + \log a_{\mathrm{M}_{j-1}\mathrm{M}_j}, \\ V_{j-1}^{\mathrm{I}}(i-1) + \log a_{\mathrm{I}_{j-1}\mathrm{M}_j}, \\ V_{j-1}^{\mathrm{D}}(i-1) + \log a_{\mathrm{D}_{j-1}\mathrm{M}_j}; \end{cases}$$

$$V_j^{\mathrm{I}}(i) = \log \frac{e_{\mathrm{I}_j}(x_i)}{q_{x_i}} + \max \begin{cases} V_j^{\mathrm{M}}(i-1) + \log a_{\mathrm{M}_j\mathrm{I}_j}, \\ V_j^{\mathrm{I}}(i-1) + \log a_{\mathrm{I}_j\mathrm{I}_j}, \\ V_j^{\mathrm{D}}(i-1) + \log a_{\mathrm{D}_j\mathrm{I}_j}; \end{cases}$$

$$V_j^{\mathrm{D}}(i) = \max \begin{cases} V_{j-1}^{\mathrm{M}}(i) + \log a_{\mathrm{M}_{j-1}\mathrm{D}_j}, \\ V_{j-1}^{\mathrm{I}}(i) + \log a_{\mathrm{I}_{j-1}\mathrm{D}_j}, \\ V_{j-1}^{\mathrm{D}}(i) + \log a_{\mathrm{D}_{j-1}\mathrm{D}_j}; \end{cases}$$

Searching with profile HMMs

- Forward algorithm: summing over all potent alignments

$$F_j^{\mathrm{M}}(i) = \log\frac{e_{\mathrm{M}_j}(x_i)}{q_{x_i}} + \log[a_{\mathrm{M}_{j-1}\mathrm{M}_j}\exp(F_{j-1}^{\mathrm{M}}(i-1))$$

$$+ a_{\mathrm{I}_{j-1}\mathrm{M}_j}\exp(F_{j-1}^{\mathrm{I}}(i-1)) + a_{\mathrm{D}_{j-1}\mathrm{M}_j}\exp(F_{j-1}^{\mathrm{D}}(i-1))];$$

$$F_j^{\mathrm{I}}(i) = \log\frac{e_{\mathrm{I}_j}(x_i)}{q_{x_i}} + \log[a_{\mathrm{M}_j\mathrm{I}_j}\exp(F_j^{\mathrm{M}}(i-1))$$

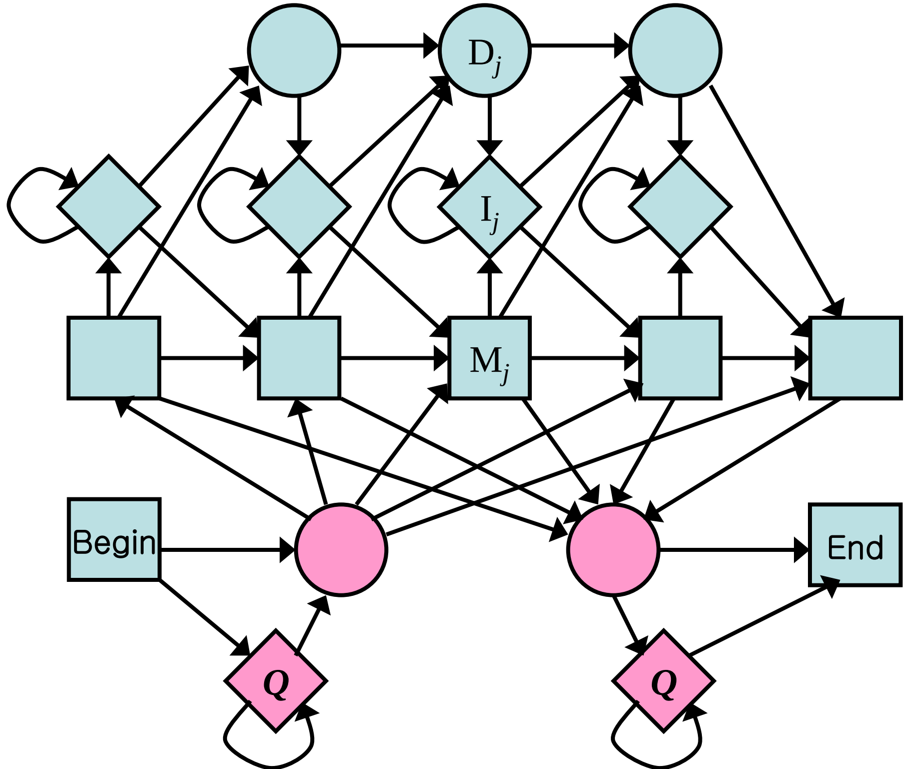
$$+ a_{\mathrm{I}_j\mathrm{I}_j}\exp(F_j^{\mathrm{I}}(i-1)) + a_{\mathrm{D}_j\mathrm{I}_j}\exp(F_j^{\mathrm{D}}(i-1))];$$

$$F_j^{\mathrm{D}}(i) = \log[a_{\mathrm{M}_{j-1}\mathrm{D}_j}\exp(F_{j-1}^{\mathrm{M}}(i)) + a_{\mathrm{I}_{j-1}\mathrm{D}_j}\exp(F_{j-1}^{\mathrm{I}}(i))$$

$$+ a_{\mathrm{D}_{j-1}\mathrm{D}_j}\exp(F_{j-1}^{\mathrm{D}}(i))];$$

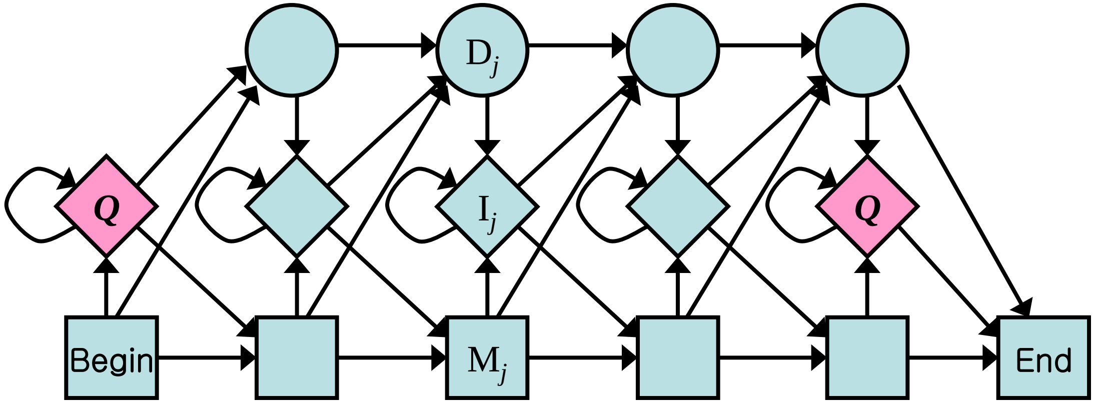
Variants for non-global alignments

- Local alignments (flanking model)
  - Emission prob. in flanking states use background values q_a.
  - Looping prob. close to 1, e.g. (1- η) for some small η.



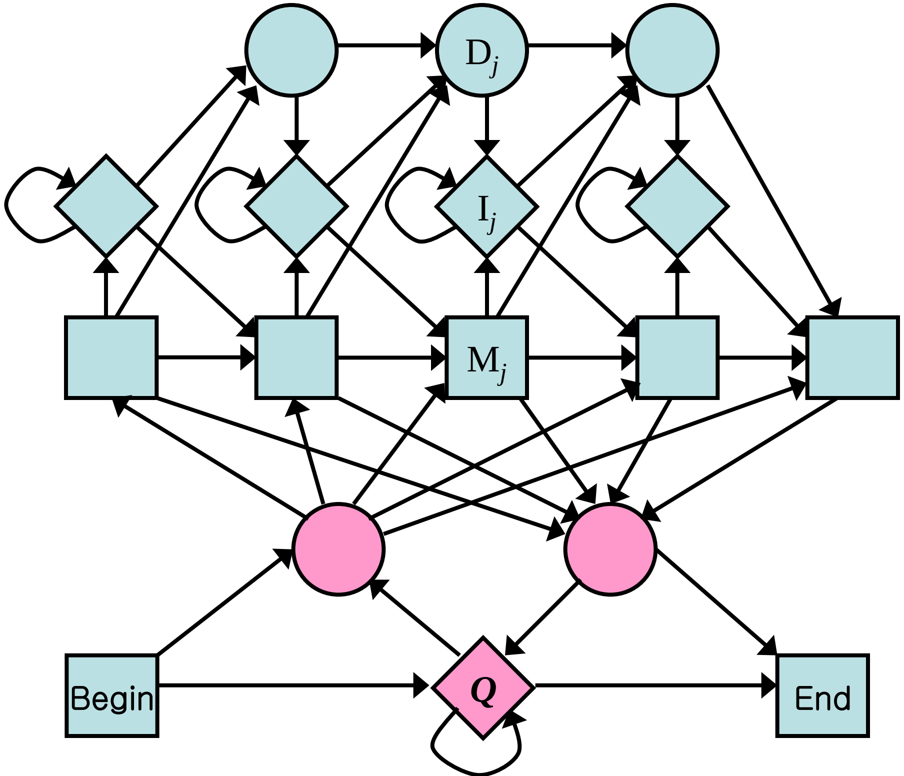
Variants for non-global alignments

- Overlap alignments
  - Only transitions to the first model state are allowed.
  - When expecting to find either present as a whole or absent
  - Transition to first delete state allows missing first residue



Variants for non-global alignments

- Repeat alignments
  - Transition from right flanking state back to random model
  - Can find multiple matching segments in query string



Estimation of prob.

- Maximum likelihood (ML) estimation
  - given observed freq. c_{ja} of residue a in position j.

$$e_{\mathrm{M}_j}(a) = \frac{c_{ja}}{\sum_{a'} c_{ja'}}$$

- Simple pseudocounts
  - q_a: background distribution
  - A: weight factor

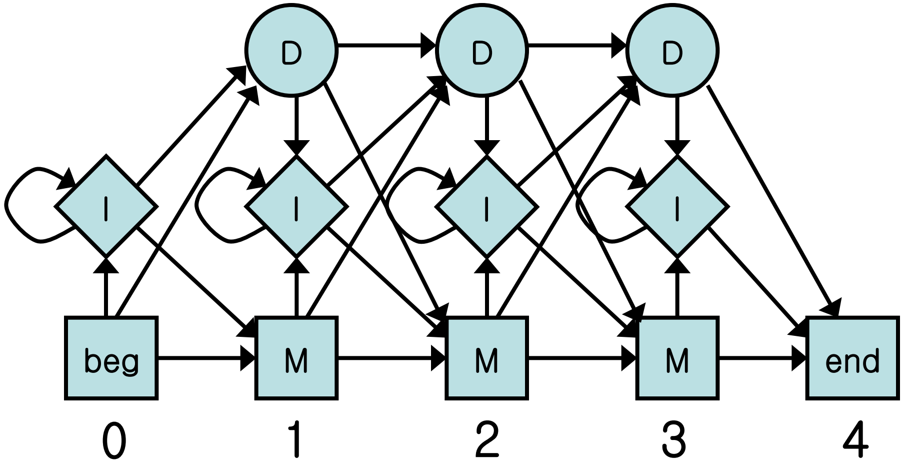
$$e_{\mathrm{M}_j}(a) = \frac{c_{ja} + Aq_a}{A + \sum_{a'} c_{ja'}}$$

Optimal model construction: mark columns

(a) Multiple alignment:

```
       x x . . . x
bat    A G - - - C
rat    A - A G - C
cat    A G - A A -
gnat   - - A A A C
goat   A G - - - C
       1 2 . . . 3
```

(b) Profile-HMM architecture:



(c) Observed emission/transition counts

		0	1	2	3
match emissions	A	-	4	0	0
	C	-	0	0	4
	G	-	0	3	0
	T	-	0	0	0
insert emissions	A	0	0	6	0
	C	0	0	0	0
	G	0	0	1	0
	T	0	0	0	0
state transitions	M-M	4	3	2	4
	M-D	1	1	0	0
	M-I	0	0	1	0
	I-M	0	0	2	0
	I-D	0	0	1	0
	I-I	0	0	4	0
	D-M	-	0	0	1
	D-D	-	1	0	0
	D-I	-	0	2	0

Optimal model construction

- MAP (match-insert assignment)
  - Recursive calculation of a number S$_j$
    - S_j: log prob. of the optimal model for alignment up to and including column j, assuming j is marked.
    - S_j is calculated from S_i and summed log prob. between i and j.
    - T_{ij}: summed log prob. of all the state transitions between marked i and j.

$$T_{ij} = \sum_{x,y \in \mathrm{M,D,I}} c_{xy} \log a_{xy}$$

  - c_{xy} are obtained from partial state paths implied by marking i and j.

Optimal model construction

- Algorithm: MAP model construction
  - Initialization:
    - $S_0 = 0$, $M_{L+1} = 0$.
  - Recurrence: for $j = 1,\ldots, L+1$:

$$S_j = \max_{0 \le i < j} S_i + T_{ij} + M_j + I_{i+1,j-1} + \lambda;$$

$$\sigma_j = \arg\max_{0 \le i < j} S_i + T_{ij} + M_j + I_{i+1,j-1} + \lambda;$$

  - Traceback: from $j = \sigma_{L+1}$, while $\sigma_j > 0$:
    - Mark column j as a match column
    - $j = \sigma_j$.

Weighting training sequences

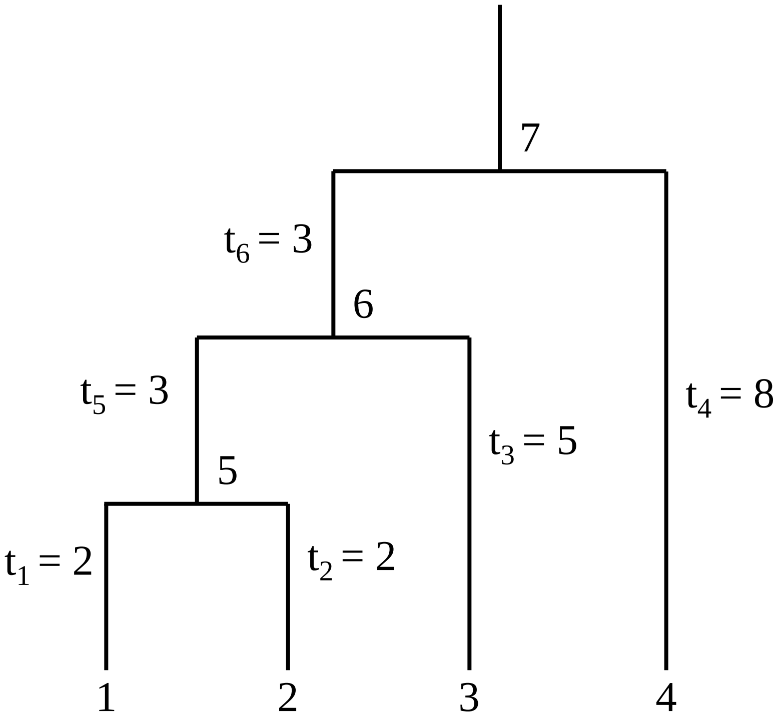
- Input sequences are random?
- “Assumption: all examples are independent samples” might be incorrect
- Solutions
  - Weight sequences based on similarity

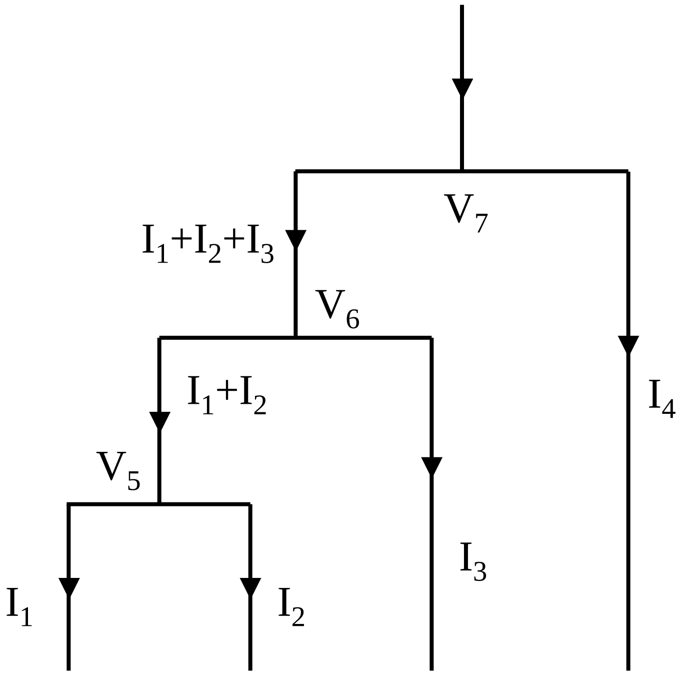
Weighting training sequences

- Simple weighting schemes derived from a tree
  - – Phylogenetic tree is given.
  - – [Thompson, Higgins & Gibson 1994b]
  - – [Gerstein, Sonnhammer & Chothia 1994]

$$\Delta w_i = t_n \frac{w_i}{\sum_{\text{leaves } k \text{ below } n} w_k}$$

Weighting training sequences





$w_1:w_2:w_3:w_4$ = 35:35:50:64

$I_1:I_2:I_3:I_4$ = 20:20:32:47

Multiple alignment by training profile HMM

- Sequence profiles could be represented as probabilistic models like profile HMMs.
  - – Profile HMMs could simply be used in place of standard profiles in progressive or iterative alignment methods.
  - – ML methods for building (training) profile HMM (described previously) are based on multiple sequence alignment.
  - – Profile HMMs can also be trained from initially unaligned sequences using the Baum-Welch (EM) algorithm

Multiple alignment by profile HMM training- Multiple alignment with a known profile HMM

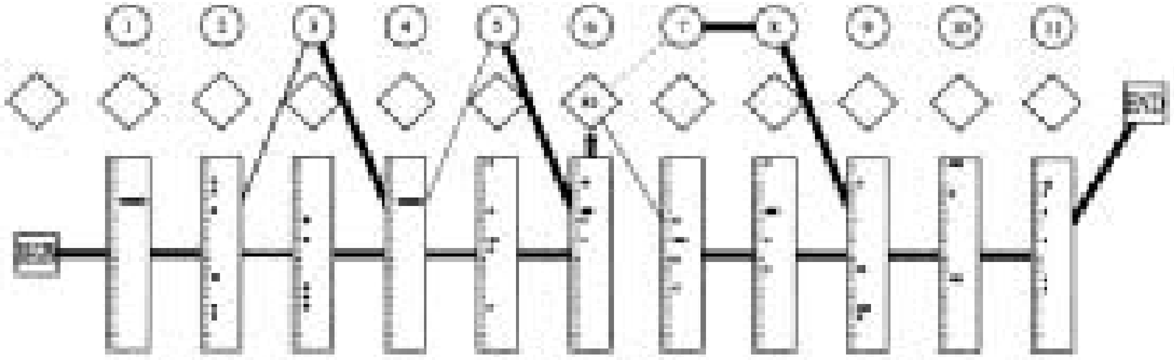
- Before we estimate a model and a multiple alignment simultaneously, we consider as simpler problem: derive a multiple alignment from a known profile HMM model.
  - This can be applied to align a large member of sequences from the same family based on the HMM model built from the (seed) multiple alignment of a small representative set of sequences in the family.

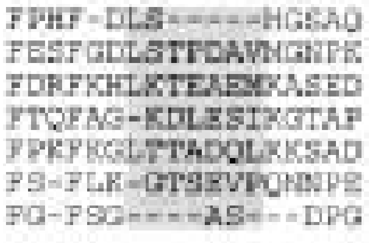
Multiple alignment with a known profile HMM

- Align a sequence to a profile HMM→Viterbi algorithm
- Construction a multiple alignment just requires calculating a Viterbi alignment for each individual sequence.
  - – Residues aligned to the same match state in the profile HMM should be aligned in the same columns.

Multiple alignment with a known profile HMM

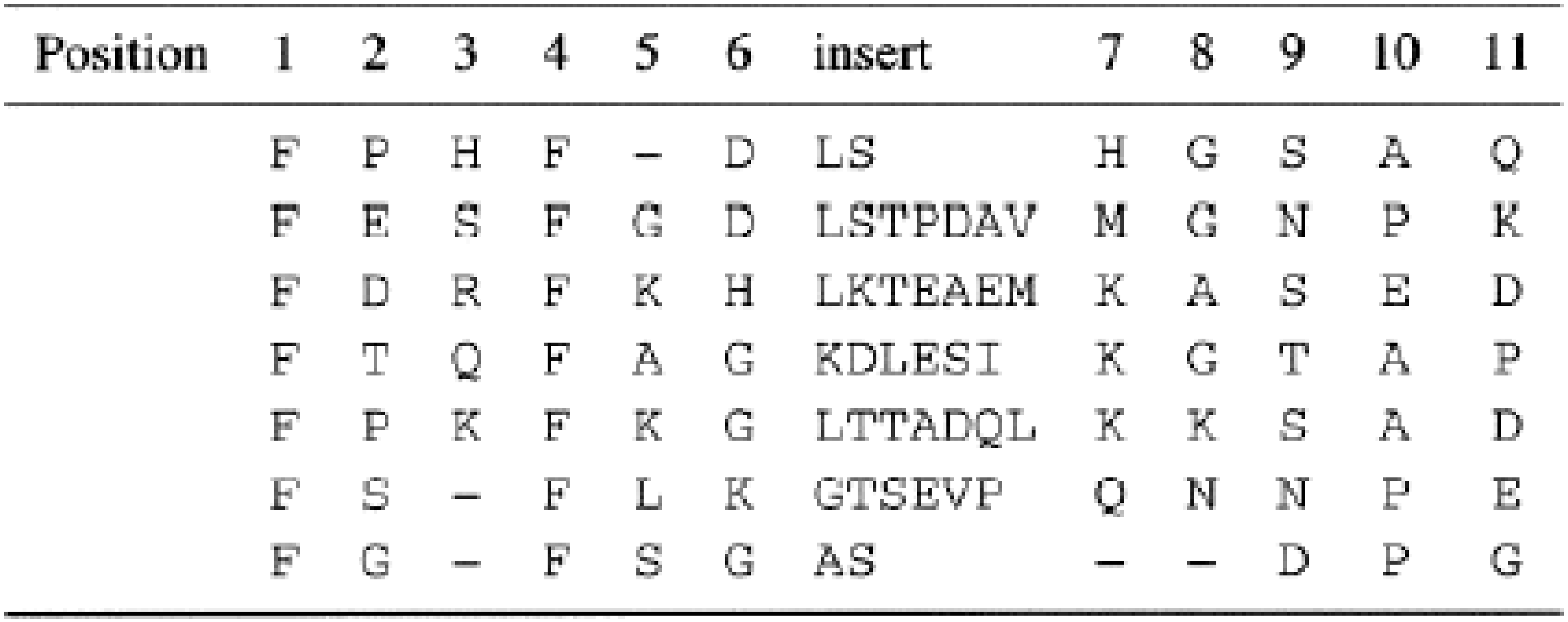
- Given a preliminary alignment, HMM can align additional sequences.





```
FPHF-DLS-----HGSAQ
FESFGDLSTPDAVMGNPK
FDRFKHLKTEAEMKASED
FTQFAG-KDLESIKGTAP
FPKFKGLTTADQLKKSAD
FS-FLK-GTSEVPQNNPE
FG-FSG----AS---DPG
```

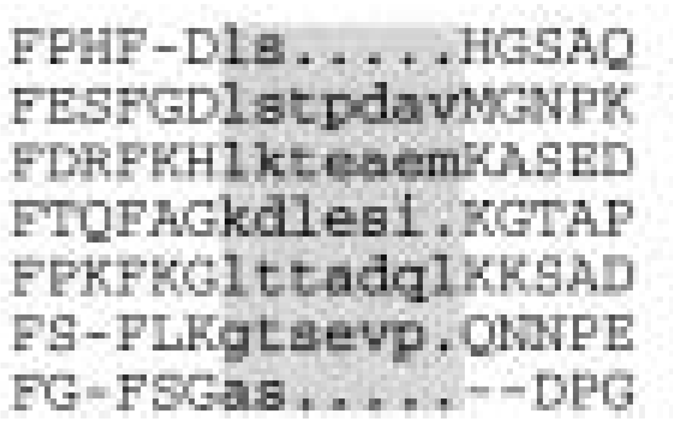
Multiple alignment with a known profile HMM

- 

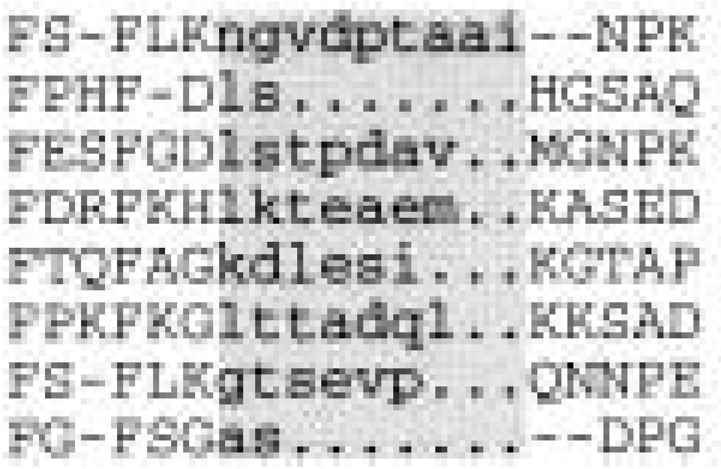
Position	1	2	3	4	5	6	insert	7	8	9	10	11
	F	P	H	F	–	D	LS	H	G	S	A	Q
	F	E	S	F	G	D	LSTPDAV	M	G	N	P	K
	F	D	R	F	K	H	LKTEAEM	K	A	S	E	D
	F	T	Q	F	A	G	KDLESI	K	G	T	A	P
	F	P	K	F	K	G	LTTADQL	K	K	S	A	D
	F	S	–	F	L	K	GTSEVP	Q	N	N	P	E
	F	G	–	F	S	G	AS	–	–	D	P	G

Multiple alignment with a known profile HMM

- Important difference with other MSA programs
  - Viterbi path through HMM identifies inserts
  - Profile HMM does not align inserts
  - Other multiple alignment algorithms align the whole sequences.



```
FPHF-Dls.....HGSAQ
FESFGDlstpdavMGNPK
FDRFKHlkteaemKASED
FTQFAGkdlesi.KGTAP
FPKFKGlttadqlKKSAD
FS-FLKgtsevp.QNNPE
FG-FSGas.....--DPG
```



```
FS-FLKngvdptaai--NPK
FPHF-Dls.......HGSAQ
FESFGDlstpdav..MGNPK
FDRFKHlkteaem..KASED
FTQFAGkdlesi...KGTAP
FPKFKGlttadql..KKSAD
FS-FLKgtsevp...QNNPE
FG-FSGas.......--DPG
```

Profile HMM training from unaligned sequences

- Harder problem
  - estimating both a model and a multiple alignment from initially unaligned sequences.
  - Initialization: Choose the length of the profile HMM and initialize parameters.
  - Training: estimate the model using the Baum-Welch algorithm (iteratively).
  - Multiple Alignment: Align all sequences to the final model using the Viterbi algorithm and build a multiple alignment as described in the previous section.

Profile HMM training from unaligned sequences

- Initial Model
  - The only decision that must be made in choosing an initial structure for Baum-Welch estimation is the length of the model M.
  - A commonly used rule is to set M be the average length of the training sequence.
  - We need some randomness in initial parameters to avoid local maxima.

Multiple alignment by profile HMM training

- Avoiding Local maxima
  - Baum-Welch algorithm is guaranteed to find a LOCAL maxima.
    - Models are usually quite long and there are many opportunities to get stuck in a wrong solution.
  - Solution
    - Start many times from different initial models.
    - Use some form of stochastic search algorithm, e.g. simulated annealing.

Multiple alignment by profile HMM - similar to Gibbs sampling

- The ‘Gibbs sampler’ algorithm described by Lawrence et al.[1993] has substantial similarities.
  - The problem was to simultaneously find the motif positions and to estimate the parameters for a consensus statistical model of them.
  - The statistical model used is essentially a profile HMM with no insert or delete states.

Multiple alignment by profile HMM training-Model surgery

- We can modify the model after (or during) training a model by manually checking the alignment produced from the model.
  - Some of the match states are redundant
  - Some insert states absorb too many sequences
- Model surgery
  - If a match state is used by less than ½ of training sequences, delete its module (match-insert-delete states)
  - If more than ½ of training sequences use a certain insert state, expand it into *n* new modules, where *n* is the average length of insertions
  - ad hoc, but works well

Phylo-HMMs: model multiple alignments of syntenic sequences

- A phylo-HMM is a probabilistic machine that generates a multiple alignment, column by column, such that each column is defined by a phylogenetic model
- Unlike single-sequence HMMs, the emission probabilities of phylo-HMMs are complex distributions defined by phylogenetic models

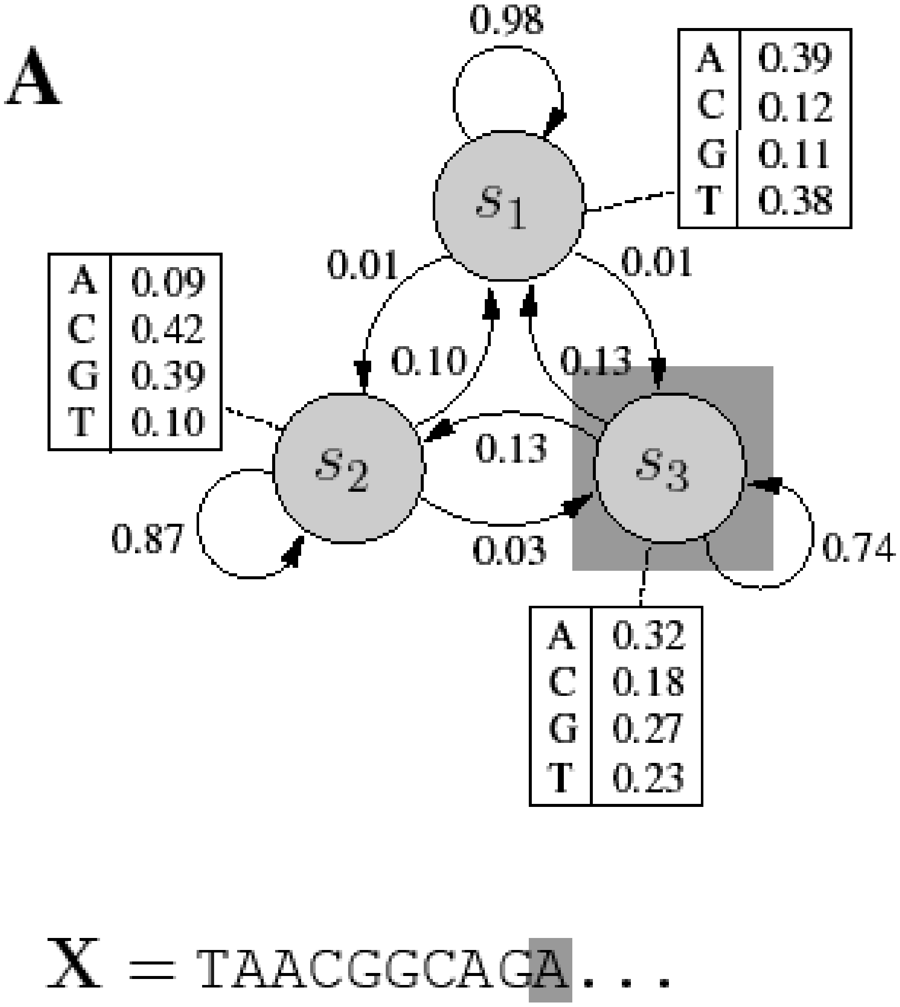
Applications of Phylo-HMMs

- Improving phylogenetic modeling that allow for variation among sites in the rate of substitution (Felsenstein & Churchill, 1996; Yang, 1995)
- Protein secondary structure prediction (Goldman et al., 1996; Thorne et al., 1996)
- Detection of recombination from DNA multiple alignments (Husmeier & Wright, 2001)
- Recently, comparative genomics (Siepel, et. al. Haussler, 2005)

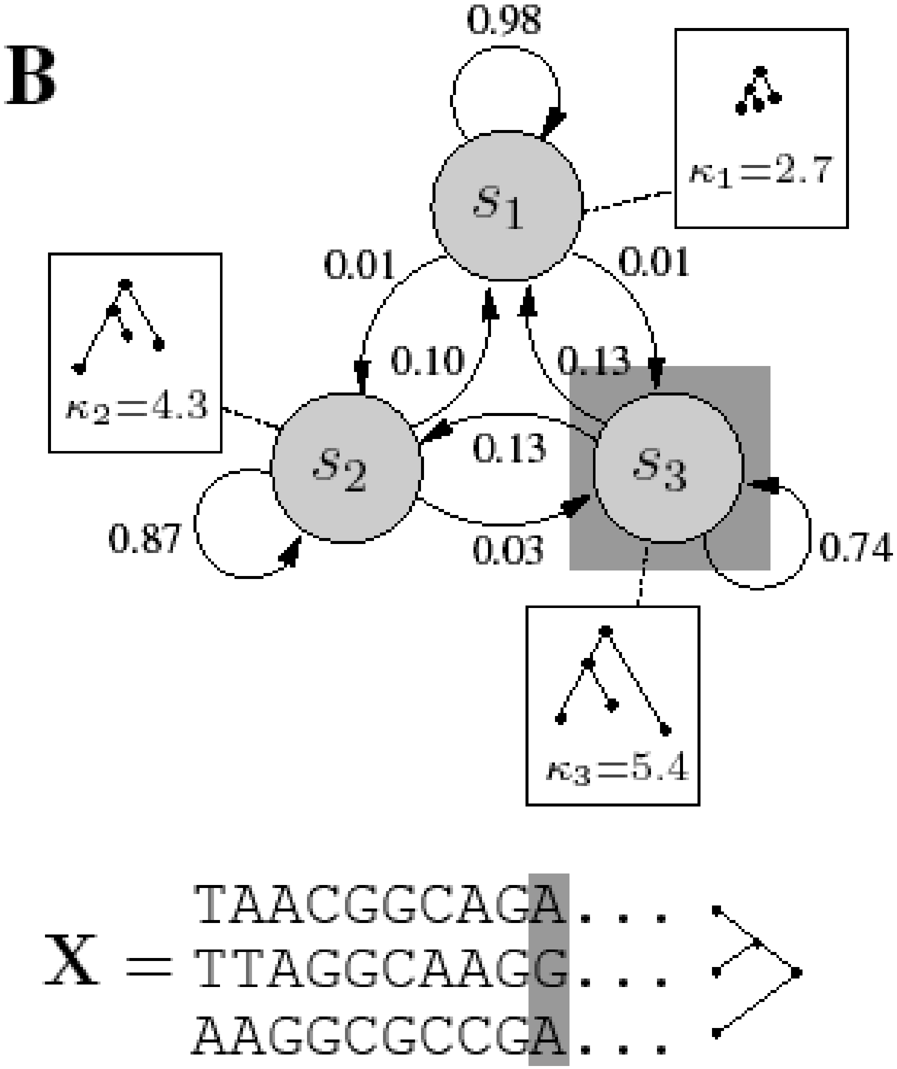
Phylo-HMMs: combining phylogeny and HMMs

- Molecular evolution can be viewed as a combination of two Markov processes
  - One that operates in the dimension of space (along a genome)
  - One that operates in the dimension of time (along the branches of a phylogenetic tree)
- Phylo-HMMs model this combination

Single-sequence HMM



Phylo-HMM



Phylogenetic models

- Stochastic process of substitution that operates independently at each site in a genome
- A character is first drawn at random from the background distribution and assigned to the root of the tree; character substitutions then occur randomly along the tree branches, from root to leaves
- The characters at the leaves define an alignment column

Phylogenetic Models

- The different phylogenetic models associated with the states of a phylo-HMM may reflect different overall rates of substitution (e.g. in conserved and non-conserved regions), different patterns of substitution or background distributions, or even different tree topologies (as with recombination)

Phylo-HMMs: Formal Definition

- A phylo-HMM is a 4-tuple $\theta = (S, \psi, A, b)$:
  - $S = \{s_1, \square, s_M\}$: set of hidden states
  - $\psi = \{\psi_1, \square \psi_M\}$: set of associated phylogenetic models
  - $A = \{a_{j,k}\} \quad (1 \leq j, k \leq M)$: transition probabilities
  - $b = (b_1, \square, b_M)$: initial probabilities

The Phylogenetic Model

- $\psi_j = (Q_j, \pi_j, \tau_j, \beta_j)$:
  - Q_j : substitution rate matrix
  - π_j : background frequencies
  - τ_j : binary tree
  - β_j : branch lengths

The Phylogenetic Model

- The model is defined with respect to an alphabet Σ whose size is denoted *d*
- The substitution rate matrix has dimension *dxd*
- The background frequencies vector has dimension *d*
- The tree has *n* leaves, corresponding to *n* extant taxa
- The branch lengths are associated with the tree

Probability of the Data

- Let X be an alignment consisting of L columns and n rows, with the i^{th} column denoted X_i
- The probability that column X_i is emitted by state s_j is simply the probability of X_i under the corresponding phylogenetic model, $P(X_i \mid \psi_j)$
- This is the likelihood of the column given the tree, which can be computed efficiently using Felsenstein’s “pruning” algorithm (which we will describe in later lectures)

Substitution Probabilities

- Felsenstein’s algorithm requires the conditional probabilities of substitution for all bases a,b$\in\Sigma$ and branch lengths t$\in\beta_j$
- The probability of substitution of a base *b* for a base *a* along a branch of length *t*, denoted $P(b\,|\,a,t,\psi_j)$ is based on a continuous-time Markov model of substitution, defined by the rate matrix Q_j

Substitution Probabilities

- In particular, for any given non-negative value *t*, the conditional probabilities $P(b\,|\,a,t,\psi_j)$ for all a,b$\in\Sigma$ are given the *dxd* matrix $P_j(t)=\exp(Q_j t)$, where

$$\exp(Q_j t)=\sum_{k=0}^{\infty}\frac{(Q_j t)^k}{k!}$$

Example: HKY model

$$\mathbf{Q}_j = \begin{pmatrix} - & \pi_{\mathrm{C},j} & \kappa_j \pi_{\mathrm{G},j} & \pi_{\mathrm{T},j} \\ \pi_{\mathrm{A},j} & - & \pi_{\mathrm{G},j} & \kappa_j \pi_{\mathrm{T},j} \\ \kappa_j \pi_{\mathrm{A},j} & \pi_{\mathrm{C},j} & - & \pi_{\mathrm{T},j} \\ \pi_{\mathrm{A},j} & \kappa_j \pi_{\mathrm{C},j} & \pi_{\mathrm{G},j} & - \end{pmatrix}$$

$$\pi_j = (\pi_{A,j}, \pi_{C,j}, \pi_{G,j}, \pi_{T,j})$$

κ_j represents the transition/transversion rate ratio for ψ_j

‘-’s indicate quantities required to normalize each row.

State sequences in Phylo-HMMs

- A state sequence through the phylo-HMM is a sequence $\phi = (\phi_1,\square,\phi_L)$ such that $\phi_i \in S \; \forall 1 \le i \le L$
- The joint probability of a path and and alignment is

$$P(\phi, X \mid \theta) = \beta_{\phi_1} P(X_1 \mid \psi_{\phi_1}) \prod_{i=2}^{L} a_{\phi_{i-1}\phi_i} P(X_i \mid \psi_{\phi_i})$$

Phylo-HMMs

- The likelihood is given by the sum over all paths (forward algorithm)

$$P(X \mid \theta) = \sum_{\phi} P(\phi, X \mid \theta)$$

- The maximum-likelihood path is (Vertebi’s)

$$\hat{\phi} = \arg\max_{\phi} P(\phi, X \mid \theta)$$

Computing the Probabilities

- The likelihood can be computed efficiently using the forward algorithm
- The maximum-likelihood path can be computed efficiently using the Viterbi algorithm
- The forward and backward algorithms can be combined to compute the posterior probability

$$P(\phi_i = j \mid X, \theta)$$

Higher-order Markov Models for Emissions

- It is common with gene-finding HMMs to condition the emission probability of each observation on the observations that immediately precede it in the sequence
- For example, in a 3-rd-codon-position state, the emission of a base x_i=“A” might have a fairly high probability if the previous two bases are x_{i-2}=“G” and x_{i-1}=“A” (GAA=Glu), but should have zero probability if the previous two bases are x_{i-2}=“T” and x_{i-1}=“A” (TAA=stop)

Higher-order Markov Models for Emission

- Considering the *N* observations preceding each x_i corresponds to using an N^{th} order Markov model for emissions
- An N^{th} order model for emissions is typically parameterized in terms of (*N*+1)-tuples of observations, and conditional probabilities are computed as

$$P(x_i|x_{i-N},\ldots,x_{i-1}) = \frac{P(x_{i-N},\ldots,x_{i-1},x_i)}{\sum_y P(x_{i-N},\ldots,x_{i-1},y)}$$

Nth Order Phylo-HMMs

Probability of the *N*-tuple

$$P(\mathbf{X}_i|\mathbf{X}_{i-N+1},\ldots,\mathbf{X}_{i-1}) = \frac{P(\mathbf{X}_{i-N+1},\ldots,\mathbf{X}_{i-1},\mathbf{X}_i)}{\sum_{\mathbf{Y}} P(\mathbf{X}_{i-N+1},\ldots,\mathbf{X}_{i-1},\mathbf{Y})}$$

Sum over all possible alignment columns Y
(can be calculated efficiently by a slight modification of Felsenstein’s “pruning” algorithm)