# CSCE 471/871 Lecture 4: Profile Hidden Markov Models

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## Introduction

- Designed to model (profile) a multiple alignment of a protein family (e.g. p. 102)
- Gives a probabilistic model of the proteins in the family
- Useful for searching databases for more homologues and for aligning strings to the family



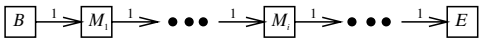
## Outline

- Organization of a profile HMM
  - Ungapped regions
  - Insert and delete states
- Building a model
- Searching with HMMs



## Organization of a Profile HMM

- Start with a trivial HMM $M$ (not really hidden at this point)




- Each match state has its own set of emission probs, so we can compute prob of a new sequence $x$ being part of this family:

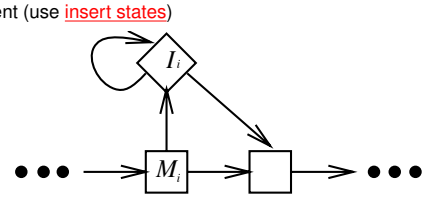
$$P(x \mid M) = \prod_{i=1}^{L} e_i(x_i)$$

- Can, as usual, convert probabilities to log-odds score



## Organization of a Profile HMM
(cont'd)

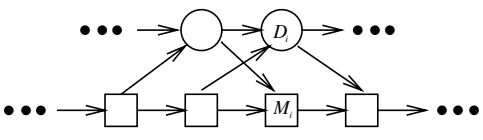
- But this assumes ungapped alignments!
- To handle gaps, consider insertions and deletions
  - Insertion: part of $x$ that doesn't match anything in multiple alignment (use insert states)



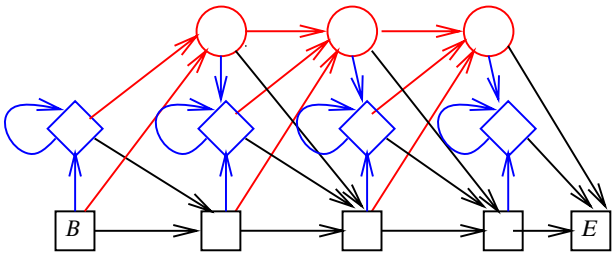



## Organization of a Profile HMM
(cont'd)

- Deletion: parts of multiple alignment not matched by any residue in $x$ (use silent delete states)



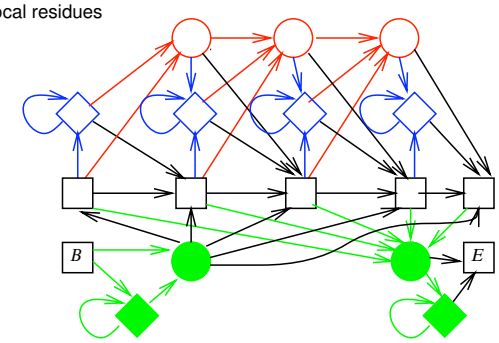
## General Profile HMM Structure






## Handling non-Global Alignments

- Original profile HMMs model entire sequence
- Add flanking model states (or free insertion modules) to generate non-local residues






## Outline

- Organization of a profile HMM
- Building a model
  - Structure
  - Estimating probabilities
- Searching with HMMs



## Building a Model

- Given a multiple alignment, how to build an HMM?
  - General structure defined, but how many match states?

```
... V G A - - H A G E Y ...
... V - - - - N V D E V ...
... V E A - - D V A G H ...
... V K G - - - - - - D ...
... V Y S - - T Y E T S ...
... F N A - - N I P K H ...
... I A G A D N G A G V ...
```



## Building a Model
(cont'd)

- Given a multiple alignment, how to build an HMM?
  - General structure defined, but how many match states?
  - Heuristic: if more than half of characters in a column are non-gaps, include a match state for that column

```
... V G A - - H A G E Y ...
... V - - - - N V D E V ...
... V E A - - D V A G H ...
... V K G - - - - - - D ...
... V Y S - - T Y E T S ...
... F N A - - N I P K H ...
... I A G A D N G A G V ...
```



## Building a Model
(cont'd)

- Now, find parameters
- Multiple alignment + HMM structure → state sequence

```
   M1  D3 I3
... V G A - - H A G E Y ...
... V - - - - N V D E V ...
... V E A - - D V A G H ...
... V K G - - - - - - D ...
... V Y S - - T Y E T S ...
... F N A - - N I P K H ...
... I A G A D N G A G V ...
```

Non-gap in match column -> match state

Gap in match column -> delete state

Non-gap in insert column -> insert state

Gap in insert column -> ignore

Durbin Fig 5.4, p. 109

## Building a Model
(cont'd)

- Count number of transitions and emissions and compute:

$$a_{kl} = \frac{A_{kl}}{\sum_{l'} A_{kl'}}$$

$$e_k(b) = \frac{E_k(b)}{\sum_{b'} E_k(b')}$$

- Still need to beware of some counts $= 0$



## Weighted Pseudocounts

- Let $c_{ja}$ = observed count of residue $a$ in position $j$ of multiple alignment

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

- $q_a$ = background probability of $a$, $A$ = weight placed on pseudocounts (sometimes use $A \approx 20$)

- Background probabilities also called a prior distribution



## Dirichlet Mixtures

- Can be thought of as a mixture of pseudocounts

- The mixture has different components, each representing a different context of a protein sequence

  – E.g. in parts of a sequence folded near protein's surface, more weight (higher $q_a$) can be given to hydrophilic residues

  – But in other regions, may want to give more weight to hydrophobic residues

- Will find a different mixture for each position of the alignment based on the distribution of residues in that column



## Dirichlet Mixtures
(cont'd)

- Each component $k$ consists of a vector of pseudocounts $\vec{\alpha}^k$ (so $\alpha_a^k$ corresponds to $Aq_a$) and a mixture coefficient ($m_k$, for now) that is the probability that component $k$ is selected

- Pseudocount model $k$ is the "correct" one with probability $m_k$

- We'll set the mixture coefficients for each column based on which vectors best fit the residues in that column

  – E.g. first column of alignment on slide 10 is dominated by V, so any vector $\vec{\alpha}^k$ that favors V will get a higher $m_k$



## Dirichlet Mixtures
(cont'd)

- Let $\vec{c}_j$ be vector of counts in column $j$

$$e_{M_j}(a) = \sum_k P\left(k \mid \vec{c}_j\right) \frac{c_{ja} + \alpha_a^k}{\sum_{a'} \left(c_{ja'} + \alpha_{a'}^k\right)}$$

- $P\left(k \mid \vec{c}_j\right)$ are the posterior mixture coefficients, which are easily computed [Sjölander et al. 1996], yielding:

$$e_{M_j}(a) = \frac{X_a}{\sum_{a'} X_{a'}} \ ,$$

where

$$X_a = \sum_k m_{k0} \exp\left(\ln B\left(\vec{\alpha}^k + \vec{c}_j\right) - \ln B\left(\vec{\alpha}^k\right)\right) \frac{c_{ja} + \vec{\alpha}_a^k}{\sum_{a'} \left(c_{ja'} + \alpha_{a'}^k\right)} \ ,$$

$$\ln B(\vec{x}) = \sum_i \ln \Gamma(x_i) - \ln \Gamma\left(\sum_i x_i\right)$$



## Dirichlet Mixtures
(cont'd)

- $\Gamma$ is gamma function, and $\ln \Gamma$ is computed via `lgamma` and related functions in C

- $m_{k0}$ is prior probability of component $k$ ($= q$ in Sjölander Table 1):

Parameters of Dirichlet mixture prior Blocks9

| | Comp. 1 | Comp. 2 | Comp. 3 | Comp. 4 | Comp. 5 | Comp. 6 | Comp. 7 | Comp. 8 | Comp. 9 |
|---|---|---|---|---|---|---|---|---|---|
| $q$ | 0.1829 | 0.0576 | 0.0898 | 0.0792 | 0.0831 | 0.0911 | 0.1159 | 0.0660 | 0.2340 |
| $\vec{\alpha}$ | 1.1806 | 1.3558 | 6.6643 | 2.0814 | 2.0810 | 2.5681 | 1.7660 | 4.9876 | 0.0995 |
| A | 0.2706 | 0.0214 | 0.5614 | 0.0701 | 0.0411 | 0.1156 | 0.0934 | 0.4521 | 0.0051 |
| C | 0.0398 | 0.0103 | 0.0454 | 0.0111 | 0.0147 | 0.0373 | 0.0047 | 0.1146 | 0.0040 |
| D | 0.0175 | 0.0117 | 0.4383 | 0.0194 | 0.0056 | 0.0124 | 0.3872 | 0.0624 | 0.0067 |
| E | 0.0164 | 0.0108 | 0.7641 | 0.0946 | 0.0102 | 0.0181 | 0.3478 | 0.1157 | 0.0061 |
| F | 0.0142 | 0.3856 | 0.0873 | 0.0131 | 0.1536 | 0.0517 | 0.0108 | 0.2842 | 0.0034 |
| G | 0.1319 | 0.0164 | 0.2591 | 0.0480 | 0.0077 | 0.0172 | 0.1058 | 0.1402 | 0.0169 |
| H | 0.0123 | 0.0761 | 0.2149 | 0.0770 | 0.0071 | 0.0049 | 0.0497 | 0.1003 | 0.0036 |
| I | 0.0225 | 0.0353 | 0.1459 | 0.0329 | 0.2996 | 0.7968 | 0.0149 | 0.5502 | 0.0021 |
| K | 0.0203 | 0.0139 | 0.7622 | 0.5766 | 0.0108 | 0.0170 | 0.0942 | 0.1439 | 0.0050 |
| L | 0.0307 | 0.0935 | 0.2473 | 0.0722 | 0.9994 | 0.2858 | 0.0277 | 0.7006 | 0.0059 |

## Outline

- Organization of a profile HMM
- Building a model
- Searching with HMMs



## Searching for Homologues

- Score a candidate match $x$ by using log-odds:
  - $P(x, \pi^* \mid M)$ is probability that $x$ came from model $M$ via most likely path $\pi^*$
    $\Rightarrow$ Find using Viterbi
  - $Pr(x \mid M)$ is probability that $x$ came from model $M$ summed over all possible paths
    $\Rightarrow$ Find using forward algorithm
  - $score(x) = \log(P(x \mid M)/P(x \mid \phi))$
    - $\phi$ is a "null model", which is often the distribution of amino acids in the training set or AA distribution over each individual column
    - If $x$ matches $M$ much better than $\phi$, then score is large and positive



## Viterbi Equations

- $V_j^M(i)$ = log-odds score of best path matching $x_{1\ldots i}$ to the model, where $x_i$ emitted by state $M_j$ (similarly define $V_j^I(i)$ and $V_j^D(i)$)
- Rename $B$ as $M_0$, $V_0^M(0) = 0$, rename $E$ as $M_{L+1}$ ($V_{L+1}^M$ = final)

$$V_j^M(i) = \log\left(\frac{e_{M_j}(x_i)}{q_{x_i}}\right) + \max\begin{cases} V_{j-1}^M(i-1) + \log a_{M_{j-1}M_j} \\ V_{j-1}^I(i-1) + \log a_{I_{j-1}M_j} \\ V_{j-1}^D(i-1) + \log a_{D_{j-1}M_j} \end{cases}$$

$$V_j^I(i) = \log\left(\frac{e_{I_j}(x_i)}{q_{x_i}}\right) + \max\begin{cases} V_j^M(i-1) + \log a_{M_jI_j} \\ V_j^I(i-1) + \log a_{I_jI_j} \\ V_j^D(i-1) + \log a_{D_jI_j} \end{cases}$$

$$V_j^D(i) = \max\begin{cases} V_{j-1}^M(i) + \log a_{M_{j-1}D_j} \\ V_{j-1}^I(i) + \log a_{I_{j-1}D_j} \\ V_{j-1}^D(i) + \log a_{D_{j-1}D_j} \end{cases}$$

- Similar to Chapter 2's gapped alignment, but with position-specific scoring scheme



## Forward Equations

$$F_j^M(i) = \log\left(\frac{e_{M_j}(x_i)}{q_{x_i}}\right) + \log\left[a_{M_{j-1}M_j}\exp\left(F_{j-1}^M(i-1)\right) + a_{I_{j-1}M_j}\exp\left(F_{j-1}^I(i-1)\right) + a_{D_{j-1}M_j}\exp\left(F_{j-1}^D(i-1)\right)\right]$$

$$F_j^I(i) = \log\left(\frac{e_{I_j}(x_i)}{q_{x_i}}\right) + \log\left[a_{M_jI_j}\exp\left(F_j^M(i-1)\right) + a_{I_jI_j}\exp\left(F_j^I(i-1)\right) + a_{D_jI_j}\exp\left(F_j^D(i-1)\right)\right]$$

$$F_j^D(i) = \log\left[a_{M_{j-1}D_j}\exp\left(F_{j-1}^M(i)\right) + a_{I_{j-1}D_j}\exp\left(F_{j-1}^I(i)\right) + a_{D_{j-1}D_j}\exp\left(F_{j-1}^D(i)\right)\right]$$

- $\exp(\cdot)$ needed to use sums and logs (can still be fast; see p. 78)



## Aligning a Sequence with a Model (Multiple Alignment)

- Given a string $x$, use Viterbi to find most likely path $\pi^*$ and use the state sequence as the alignment
- More detail in Durbin, Section 6.5
  - Also discusses building an initial multiple alignment and HMM simultaneously via Baum-Welch



Topic summary due in 1 week!