HMM Lecture Notes

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1 Notation

1. N states ($S_1..S_N$)
2. M symbols in alphabet, Σ
3. parameters, λ:
    1. initial distribution of states $\pi(i)$
    2. transition probabilities $a_{ij} = P(q_t = S_i | q_{t-1} = S_j)$. Note that $\sum_{i=1}^{N} a_{ij} = 1, \ \forall j$
    3. emission probabilities $e_i(a)$ probability state i emits a
4. Sequence of symbols: $O = O_1, O_2, ..., O_T$
5. Sequence of states: $Q = q_1, q_2, ..., q_T$

2 HMM topology and Profile HMMs

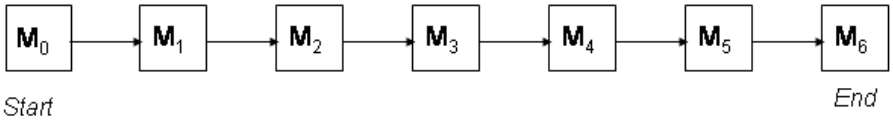
- Characteristics: number of nodes, alphabet, which edges to consider. We could just choose a fully connected graph, but this has too many parameters too estimate.
- Instead we can exploit **domain knowledge**. Choose a topology that limits the number of states and edges while still being expressive enough to represent the relationships they believe to exist.
- The choice of topology can impose a probability distribution on the length of the sequences that the HMM recognizes. For example, a simple self loop with probability p results in an exponentially decaying (geometric) distribution $P(l \text{ residues}) = (1-p)p^{l-1}$. There are topologies that assume other length distributions (see Durbin, 3.4 for more on this subject).

A basic topology:

Suppose we wish to construct an HMM for the `WEIRD` motif, based on the following alignment which has no gaps and no positional dependencies:

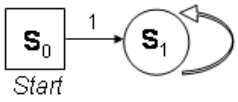
```
WEIRD
WEIRD
WEIRE
WEIQH
```

We can recognize the WEIRD motif using an HMM with this topology:



where the transitions probabilities are $a_{i,j} = 1$ if $j = i + 1$ and zero, otherwise. The emission probabilities are $e_j(\alpha) = F[\alpha, j]$, where $F[\alpha, j]$ is the same frequency matrix that we derived for the PSSM example, using pseudocounts. The Start and End states (M_0 and M_6) are silent. The above model is our alternate hypothesis, H_A.

To score a new sequence, we also need a background model (the null hypothesis, H_0):



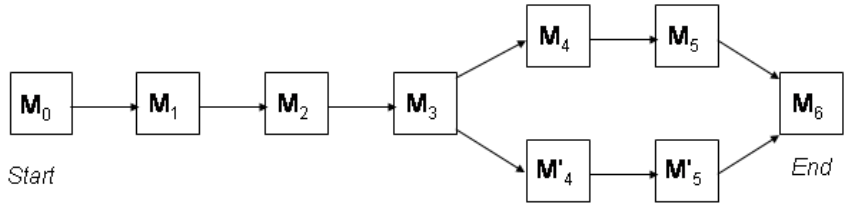
In this model, all transition probabilities are equal to one. The emission probabilities are $e_j(\alpha) = p(\alpha)$, where $p(\alpha)$ is the background frequency of residue α. We can then score a new sequence, O, by calculating $\log \frac{P(O|H_A)}{P(O|H_0)}$. We obtain a score equivalent to $\sum_{i=1}^{5} S[O_i, i]$, the score we would have obtained with the PSSM for the WEIRD motif.

Positional dependencies:

Now suppose that our motif has a positional dependency like this one, in which we see either `RD` or `QH` in the last two positions, but never `QD` or `RH`.

```
WEIRD
WEIRD
WEIQH
WEIRD
WEIQH
WEIQH
```

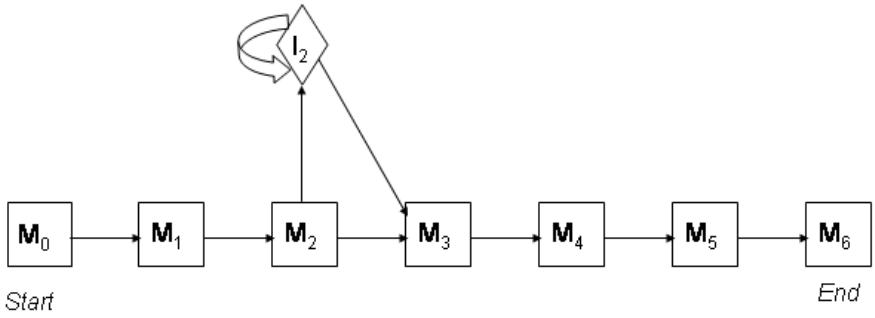
A PSSM for this motif, however, would give the sequences `WEIRD` and `WEIRH` equally good scores. So would the basic HMM above. We can construct an HMM to model this pairwise dependency like this:



where the emission probabilities are $e_{M_4}(R) = 1$, $e_{M_5}(D) = 1$, $e_{M'_4}(Q) = 1$ and $e_{M'_5}(H) = 1$.

Insertions:

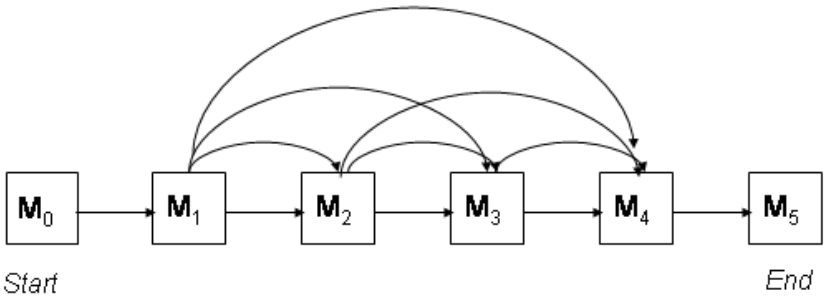
We can modify the basic HMM to recognize query sequences with insertions such as $O =$ `WECIRD`:



where the emission probabilities for the insertion states are the background frequencies.

Deletions:

Suppose our query sequences has a deletion, e.g., $O =$ `WERD`. One approach to capturing such deletions would be to add edges allowing us to jump over any set of match states:

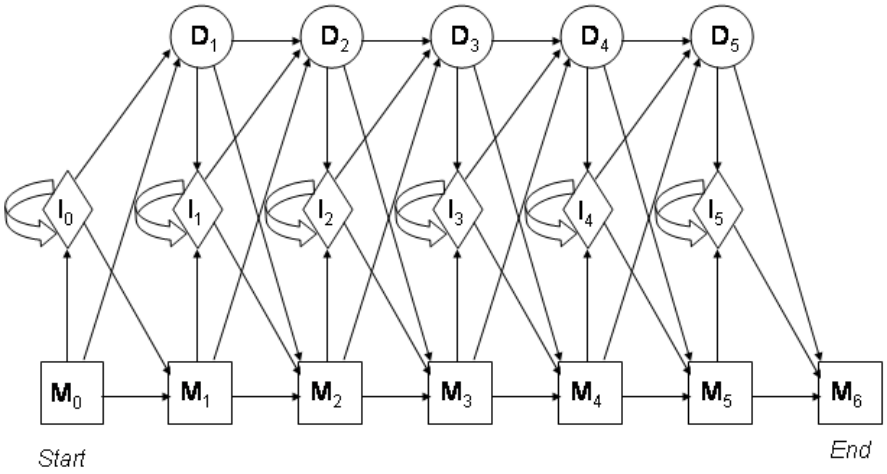


The disadvantage to this approach is that to infer the transitions, we would need a very large set of training data, one in which all deletions of all possible sizes were represented. Instead, we can model long deletions as sequences of short ones, as seen in the HMM below.

3 Profile HMMs

A *Profile HMM* is a standard topology for modeling sequence motifs. It was proposed by Krogh and Haussler in 1994.

A profile HMM of length 5



Insertion and Match states emit the 20 AA. Delete states emit "-". The emission and transition probabilities must be estimated from data.

Parameter estimation:

Given labeled training data (i.e., we are given the state path), we use maximum likelihood to estimate the parameters. In general,

$$e_k(\sigma) = \frac{E_i(\sigma) + b}{\sum_j E_j(\sigma) + 20b}$$

$$a(i,j) = \frac{A(i,j)}{\sum_l A'(i,l)}$$

where $E_i(\sigma)$ is the number of instances in the training data where symbol σ is emitted in state i and $A'(i,j)$ is the number of transitions from i to j in the training data plus a pseudocount to take transitions that are not observed into account (see page 6 for an example.

For our Profile HMM, the estimation of the emission probabilities might look like this:

$$e_{M_6}(i) = e_{M_0}(i) = 0 \forall i$$

$$e_{I_k}(i) = p_i \forall ik$$
$$e_{D_k}(i) = 0 \qquad e_{D_k}(\text{“}-\text{”}) = 1$$
$$e_{M_k}(i) = \frac{E_k(i) + b}{\sum_j E_k(j) + 20b}$$

where p_i is the background frequency of residue i.

Constructing a Profile HMM from an unlabeled data

We can use the Profile HMM formalism to model a shared pattern in biomolecular sequences. If the sequences are already aligned, then we have labeled data. In other words, we can determine from the alignment which state is associated with each symbol in each sequence. In that case, all we need to do is determine the number of match states in the Profile HMM, set up the topology, and determine the parameters from the labeled data.

Given unlabeled sequences that are known to share a pattern, we can use the Profile HMM to discover the pattern, label the data, and construce a multiple sequence alignment. We give an example of each case below.

An example: A profile HMM for a variable length motif with labeled data Profile HMM's like the one above can be used to model variable length motifs, such as this one:

```
VG--H
V---N
VE--D
IAADN
```

The length of the HMM should be the average of the length of the sequences. The above sequences are of lengths 3, 2, 3 and 5, respectively, yielding an average of 3.25. Our HMM will have a silent start state M_0, match states M_1, M_2, M_3, insertion states I_0, I_1, I_2, I_3, deletion states D_1, D_2, D_3 and a silent end state M_4.

In order to estimate the parameters, we need to assign labels to the data using the multiple alignment. Positions in the alignment that have gaps in less than 50% of the rows correspond to match states. Those with more than 50% gaps correspond to insertion states:

V	G	-	-	H
V	-	-	-	N
V	E	-	-	D
I	A	A	D	N
M_1	M_2	I_2	I_2	M_3

This yields the following labeled sequences:

V	G	H		
M_1	M_2	M_3		
V	-	H		
M_1	D_2	M_3		
V	E	D		
M_1	M_2	M_3		
I	A	A	D	N
M_1	M_2	I_2	I_2	M_3

From these labeled sequences, we can estimate the parameters. For example, using $b = 1$ as a super count, we obtain

$$e_{M_1}(V) = \frac{3+1}{4+20}$$

and

$$a_{M_2 I_2} = \frac{1+1}{(2+1)+(1+1)+(0+1)}$$

The three sums in the denominator correspond to all possible transitions out of state M_2, plus pseudocounts. Specifically, in the training sequences there are two transitions from M_2 to M_3, one one transition from M_2 to I_2 and no transitions from M_2 to D_3.

Modeling unlabeled data with a Profile HMM An example of this is given in Ewens and Grant, pp. 337 - 339.

To discover a pattern in unlabeled data requires the following steps:

1. **Estimating the length:** Given a set of unaligned sequences, where each sequence is an instance of the pattern, let L, the length of HMM (i.e., the number of match states) be the average length of sequences. An example of this type of input would be sequences ≈ 50 residues long, where each sequence corresponded to a different instance of the Ig domain. If you are given sequences that contain a pattern but are much longer than the pattern, then you need to some approach to estimating the length. An example of this type of input would

be a set of protein sequences, each several hundred residues in length, each of which contains an instance of an unknown domain. In this case, you might estimate the length of the pattern to be ≈ 100, since that is the length of a typical domain.

2. **The topology:** Construct a Profile HMM with $L+2$ match states. M_0 and M_{L+1} are silent states corresponding to the start state and the end state.

3. **Learn parameters** Guess "good" initial parameters (e.g., $a_i(M_j) >> a_i(I_j)$ *or* $a_i(D_j)$). Train model using Baum Welch.

4. **Determining the motif** Use the Viterbi algorithm ($\pi^* = argmax_j P(\pi, s_j) \forall s^j$) or posterior decoding to find path most likely to produce each sequence. The Viterbi recurrence can be greatly simplified and expressed in terms of log odds for the special case of Profile HMMs. The log odds formulation avoids underflow and to reduces length effects. This was not covered in class but yo are responsible for reading the sections on the specialized forms of both the Viterbi and Forward algorithms for Profile HMMs are given in Durbin, pp 108-110. Note the similarity to the dynamic programming algorithm for pairwise alignment.

5. **Multiple Sequence Alignment** The most paths for each sequence obtained from decoding can be used to obtain a multiple alignment of the input sequences. If O_t^d and O_u^c were emitted by same match state, then align positions t and u. See Ewens and Grant, p 337 - 339 for a discussion and example of multiple sequence alignment using Profile HMMs.

6. **Model surgery:** The topology of the model can be iteratively refined. If more than half of the sequences enter the delete state at a particular position remove that match state from the topology. If more than half of the sequences enter the insert tate at a given position, add match states (number equal to average length of the insertion).

7. **Re-estimate the parameters:** If the states change due to model surgery, you will need to re-estimate the parameters. Label the multiple alignment with the new states and calculate the transition and emission probabilities as described above for labeled data. If the number of states that are changed is a significant percentage of the entire HMM, then you may want to retrain with Baum Welch.

Compared with the exact dynamic programming algorithm for multiple sequence alignment, which runs in exponential time, this approach can align many sequences quickly. Note that this method doesn't say how to align indel sequences of different length. Correspond to unconserved portions, not meaningfully alignable. Often just left-justified and shaded.

Pattern recognition with profile HMM's Once you have constructed your Profile HMM, how do you determine whether a new, unlabeled sequence, O, contains the motif?

- Calculate $\log \frac{P(O|H_A)}{P(O|H_0)}$ using the Forward algorithm. This gives a score but doesn't tell us the location.
- Find the most likely path using the Viterbi algorithm. The location of the motif corresponds to the symbols emitted by the match states. If no symbols were emitted by match states, then the motif is not present in O. You could also use posterior decoding.

There are specialized versions of the Forward and Viterbi algorithms for profile HMM's (see Durbin, pp 109-110.)