Pair HMMs

* Match state M: emission probability $p_{ab}$ for emitting an aligned pair $a:b$
* States X and Y: emission probabilities $q_a$ for emitting symbol $a$ against a gap
* Emits a pairwise alignment instead of a single sequence
Pair HMMs
Pair HMMs And Alignments

- Start in the Begin state and repeat the following two steps:
  1. Pick the next state according to the transition probabilities leaving the current state
  2. Pick a symbol pair to be added to the alignment according to the emission probabilities in the new state
Viterbi Algorithm For Pair HMMs

Initialization:

\[ v^M(0, 0) = 1, \quad V^X(0, 0) = v^Y(0, 0) = 0, \quad \text{and} \quad v^*(−1, j) = v^*(i, −1) = 0. \]

Recurrence: \( i = 0, \ldots, n, \quad j = 0, \ldots, m: \)

\[
\begin{align*}
v^M(i, j) &= p_{xy_{ij}} \max \left\{ (1 − 2\delta − \tau)v^M(i−1, j−1), (1 − \varepsilon − \tau)v^X(i−1, j−1), (1 − \varepsilon − \tau)v^Y(i−1, j−1) \right\} \\
v^X(i, j) &= q_{xt} \max \left\{ \delta v^M(i−1, j), \varepsilon v^X(i−1, j) \right\} \\
v^Y(i, j) &= q_{yt} \max \left\{ \delta v^M(i, j−1), \varepsilon v^Y(i, j−1) \right\}
\end{align*}
\]

Termination:

\[ v^E = \tau \max(v^M(n, m), v^X(n, m), v^Y(n, m)). \]
Pairwise Alignment Using HMMs

- To find the best alignment, we keep pointers and trace back as usual.
- To get the alignment itself, we keep track of which residues are emitted at each step in the path during the traceback.
We need an HMM “component” that models the “irrelevant” (low score) parts, which are not part of the local alignment.
A Pair HMM For Local Alignment
A significant advantage of HMM approaches to alignment over standard DP approaches, is that HMMs allow for calculating the probability that a given pair of sequences are related according to the HMM by any alignment.

This is achieved by summing over all alignments:

\[
P(x, y) = \sum_{\text{alignment } \pi} P(x, y, \pi)
\]
Full Probability Of The Two Sequences

- The way to calculate the sum is by using the forward algorithm
- \( f^k(i,j) \): the combined probability of all alignments up to \((i,j)\) that end in state \(k\)
Forward Algorithm For Pair HMMs

Initialization:

\[ f^M(0, 0) = 1. \quad f^X(0, 0) = f^Y(0, 0) = 0. \]

All \( f^*(i, -1), f^*(-1, j) \) are set to 0.

Recursion:

\[ f^M(i, j) = p_{x_iy_j} \left[ (1 - 2\delta - \tau)f^M(i - 1, j - 1) + (1 - \varepsilon - \tau)(f^X(i - 1, j - 1) + f^Y(i - 1, j - 1)) \right]. \]

\[ f^X(i, j) = q_{x_i} \left[ \delta f^M(i - 1, j) + \varepsilon f^X(i - 1, j) \right]. \]

\[ f^Y(i, j) = q_{y_j} \left[ \delta f^M(i, j - 1) + \varepsilon f^Y(i, j - 1) \right]. \]

Termination:

\[ f^E(n, m) = \tau \left[ f^M(n, m) + f^X(n, m) + f^Y(n, m) \right]. \]
Forward Algorithm For Pair HMMs

Initialization:

\[ f^M(0, 0) = 1, \quad f^X(0, 0) = f^Y(0, 0) = 0. \]

All \( f^*(i, -1), f^*(-1, j) \) are set to 0.

Recursion:

\[ f^M(i, j) = p_{x_iy_j} \left[ (1 - 2\delta - \tau) f^M(i - 1, j - 1) + \right. \]
\[ \left. (1 - \varepsilon - \tau)(f^X(i - 1, j - 1) + f^Y(i - 1, j - 1)) \right]. \]

\[ f^X(i, j) = q_{x_i} \left[ \delta f^M(i - 1, j) + \varepsilon f^X(i - 1, j) \right]. \]

\[ f^Y(i, j) = q_{y_j} \left[ \delta f^M(i, j - 1) + \varepsilon f^Y(i, j - 1) \right]. \]

Termination:

\[ f^E(n, m) = \tau \left[ f^M(n, m) + f^X(n, m) + f^Y(n, m) \right]. \]
**Full Probability Of The Two Sequences**

- \( P(x,y) \) gives the likelihood that \( x \) and \( y \) are related by some unspecified alignment, as opposed to being unrelated.

- If there is an unambiguous best alignment, \( P(x,y) \) will be “dominated” by the single path corresponding to that alignment.
How Correct Is The Alignment

Define a posterior distribution $P(\pi|x,y)$ over all alignments given a pair of sequences $x$ and $y$

$$P(\pi | x,y) = \frac{P(x,y,\pi)}{P(x,y)}$$

Probability that the optimal scoring alignment is correct:

$$P(\pi^* | x,y) = \frac{P(x,y,\pi^*)}{P(x,y)} = \frac{v^E(n,m)}{f^E(n,m)}$$
How Correct Is The Alignment

* Define a posterior distribution \( P(\pi | x, y) \) over all alignments given a pair of sequences \( x \) and \( y \)

\[
P(\pi | x, y) = \frac{P(x, y, \pi)}{P(x, y)}
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Probability that the optimal scoring alignment is correct:

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P(\pi^* | x, y) = \frac{P(x, y, \pi^*)}{P(x, y)} = \frac{v^E(n, m)}{f^E(n, m)}
\]
How Correct Is The Alignment

* Define a posterior distribution $P(\pi|x,y)$ over all alignments given a pair of sequences $x$ and $y$

$$P(\pi \mid x,y) = \frac{P(x,y,\pi)}{P(x,y)}$$

Probability that the optimal scoring alignment is correct:

$$P(\pi^* \mid x,y) = \frac{P(x,y,\pi^*)}{P(x,y)} = \frac{v^E(n,m)}{f^E(n,m)}$$

- Viterbi algorithm
- Forward algorithm
Usually the probability that the optimal scoring alignment is correct, is extremely small!

Reason: there are many small variants of the best alignment that have nearly the same score
The Posterior Probability That Two Residues Are Aligned

- If the probability of any single complete path being entirely correct is small, can we say something about the local accuracy of an alignment?
- It is useful to be able to give a reliability measure for each part of an alignment.
The idea is:

- calculate the probability of all the alignments that pass through a specified matched pair of residues \((x_i, y_j)\).

Compare this value with the full probability of all alignments of the pair of sequences.

- If the ratio is close to 1, then the match is highly reliable.
- If the ratio is close to 0, then the match is unreliable.
The Posterior Probability That Two Residues Are Aligned

* Notation: $x_i \diamond y_j$ denotes that $x_i$ is aligned to $y_j$

* We are interested in $P(x_i \diamond y_j | x, y)$

* We have

$$P(x_i \diamond y_j | x, y) = \frac{P(x, y, x_i \diamond y_j)}{P(x, y)}$$

* $P(x, y)$ is computed using the forward algorithm

* $P(x, y, x_i \diamond y_j)$: the first term is computed by the forward algorithm, and the second is computed by the backward algorithm ($= b^M(i, j)$ in the backward algorithm)
Backward Algorithm For Pair HMMs

Initialization:

\[ b^M(n, m) = b^X(n, m) = b^Y(n, m) = \tau. \]

All \( b^*(i, m + 1), b^*(n + 1, j) \) are set to 0.

Recursion: \( i = n, \ldots, 1, j = m, \ldots, 1 \) (except \( (n, m) \));

\[ b^M(i, j) = (1 - 2\delta - \tau)p_{x_{i+1}y_{j+1}} b^M(i + 1, j + 1) + \delta \left[ q_{x_{i+1}} b^X(i + 1, j) + q_{y_{j+1}} b^Y(i, j + 1) \right]. \]

\[ b^X(i, j) = (1 - \varepsilon - \tau)p_{x_{i+1}y_{j+1}} b^M(i + 1, j + 1) + \varepsilon q_{x_{i+1}} b^X(i + 1, j). \]

\[ b^Y(i, j) = (1 - \varepsilon - \tau)p_{x_{i+1}y_{j+1}} b^M(i + 1, j + 1) + \varepsilon q_{y_{j+1}} b^Y(i + 1, j). \]