# Pair HMMs and Pairwise Sequence Alignment

COMP 571
Luay Nakhleh, Rice University

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## 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

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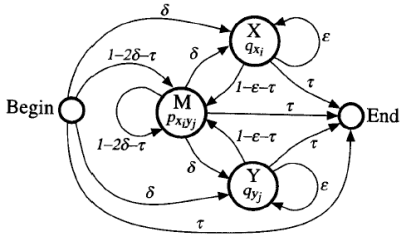
## Pair HMMs

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# Pair HMMs And Alignments

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- 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

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**Initialization:**

$v^M(0,0) = 1$. $V^X(0,0) = v^Y(0,0) = 0$, and $v^*(-1,j) = v^*(i,-1) = 0$.

**Recurrence:** $i = 0, \ldots, n$, $j = 0, \ldots, m$:

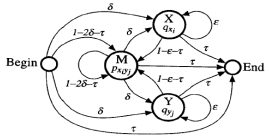
$$v^M(i,j) = p_{x_i y_j} \max \begin{cases} (1-2\delta-\tau)v^M(i-1,j-1) \\ (1-\varepsilon-\tau)v^X(i-1,j-1) \\ (1-\varepsilon-\tau)v^Y(i-1,j-1) \end{cases}$$

$$v^X(i,j) = q_{x_i} \max \begin{cases} \delta v^M(i-1,j) \\ \varepsilon v^X(i-1,j) \end{cases}$$

$$v^Y(i,j) = q_{y_j} \max \begin{cases} \delta v^M(i,j-1) \\ \varepsilon v^Y(i,j-1) \end{cases}$$

**Termination:**

$$v^E = \tau \max(v^M(n,m), v^X(n,m), v^Y(n,m)).$$




# Pairwise Alignment Using HMMs

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- 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

## A Pair HMM For Local Alignment

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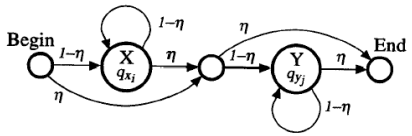


- We need an HMM "component" that models the "irrelevant" (low score) parts, which are not part of the local alignment

## A Pair HMM For Local Alignment

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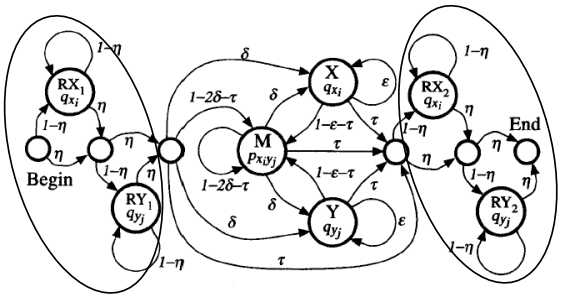


## Full Probability Of The Two Sequences

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- 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 <u>any</u> 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

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## Forward Algorithm For Pair HMMs

**Initialization:**

$f^M(0,0) = 1.\ f^X(0,0) = f^Y(0,0) = 0.$

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

**Recursion:**

$$f^M(i,j) = p_{x_i y_j}\Big[(1-2\delta-\tau)f^M(i-1,j-1) + (1-\varepsilon-\tau)(f^X(i-1,j-1) + f^Y(i-1,j-1))\Big].$$

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

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

**Termination:**

$$f^E(n,m) = \tau\Big[f^M(n,m) + f^X(n,m) + f^Y(n,m)\Big].$$

11-1

## Forward Algorithm For Pair HMMs

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

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

**Termination:**

P(x,y) → $f^E(n,m) = \tau\Big[f^M(n,m) + f^X(n,m) + f^Y(n,m)\Big].$

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## 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

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## 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:

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

13-1

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Viterbi algorithm

13-2

# How Correct Is The Alignment

13-3

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Viterbi algorithm

Forward algorithm

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- 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

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- 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 Posterior Probability That Two Residues Are Aligned

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- 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

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- Notation: $x_i \Diamond y_j$ denotes that $x_i$ is aligned to $y_j$
- We are interested in $P(x_i \Diamond y_j \mid x,y)$

$$P(x_i \Diamond y_j \mid x,y) = \frac{P(x,y,x_i \Diamond y_j)}{P(x,y)}$$

- We have

$$P(x,y,x_i \Diamond y_j) = P(x_{1\ldots i}, y_{1\ldots j}, x_i \Diamond y_j) P(x_{i+1\ldots n}, y_{j+1\ldots m} \mid x_i \Diamond y_j)$$

- 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

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**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 $(n,m)$);

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

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

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

# Questions?