Pairwise alignment using HMMs - Ch.4 Durbin et al.

- Recall the Needleman-Wunsch algorithm for affine gap penalty:

$$V^M(i,j) = s(x_i, y_j) + \max \begin{cases} V^M(i-1, j-1) \\ V^X(i-1, j-1) \\ V^Y(i-1, j-1) \end{cases}$$

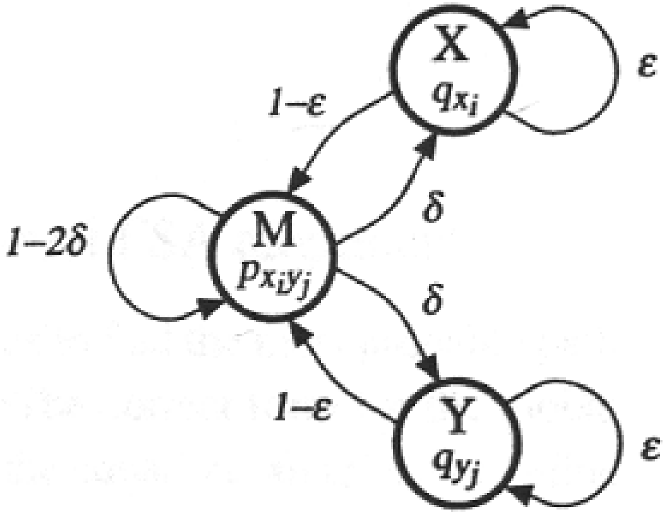
$$V^X(i,j) = \max \begin{cases} V^M(i-1, j) - d \\ V^X(i-1, j) - e \end{cases}$$

$$V^Y(i,j) = \max \begin{cases} V^M(i, j-1) - d \\ V^Y(i, j-1) - e \end{cases}$$

$$V(m,n) = \max\{V^M(m,n), V^X(m,n), V^Y(m,n)\}$$

- We can now give a probabilistic interpretation of this algorithm using a slightly generalized notion of HMM <Viterbi><ratio>

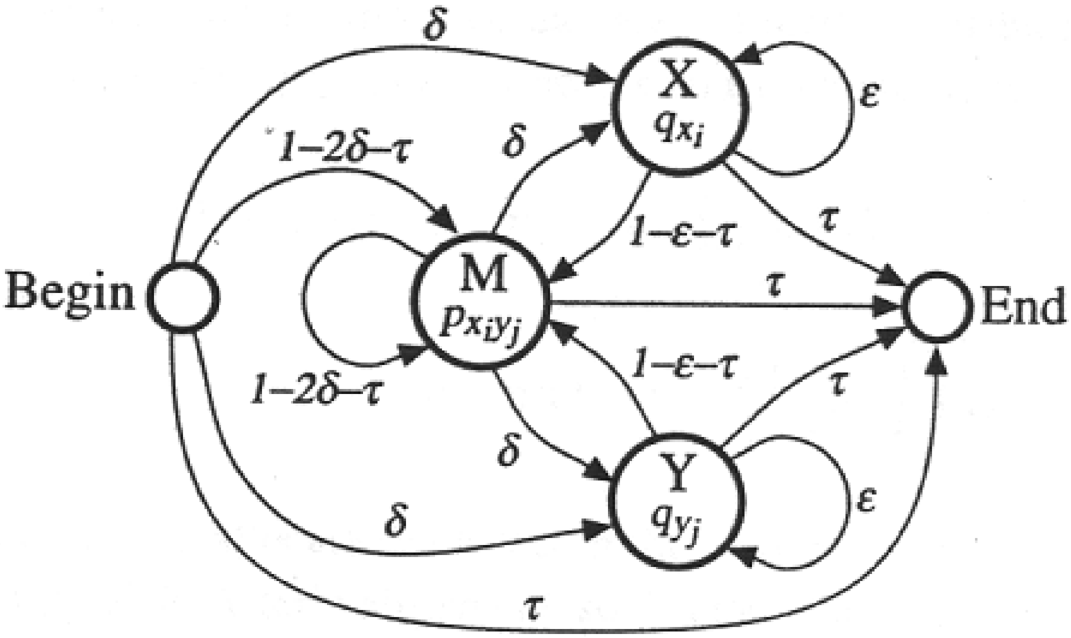
“Pair HMMs”



- A pair HMM generates an alignment by simultaneously producing two sequences of symbols
- The M (match) state emits a pair of symbols, one for each sequence: $(x_i, y_j) \sim p(x_i, y_j)$
- The X (x-insertion) state emits only an “X symbol”: $x_i \sim q(x_i)$
- The Y (y-insertion) state emits only a “Y symbol”: $y_j \sim q(y_j)$

Pair HMM - cont.

- The model above does not generate a probability distribution over all possible sequences
  - for that we need to add Begin and End states:



  - The expected length of the generated alignment is $\frac{1}{\tau}$
  - The transitions of the Markov chain are given by $p_{MM} = p_{BM} = 1 - 2\delta - \tau$, $p_{MX} = p_{MY} = \delta$, $p_{XX} = \varepsilon$, $p_{XM} = 1 - \varepsilon - \delta$, etc.

Most probable alignment

- We can only observe $\boldsymbol{x}$ and $\boldsymbol{y}$: unlike in HMMs we cannot observe the joint emission from the M state

- Let $\mathcal{S}_{ij}$ be the set of paths $\boldsymbol{s}$ *compatible* with an alignment of $\boldsymbol{x}_{1:i}$ and $\boldsymbol{y}_{1:j}$
  - i.e. the path visits states $\{M, X\}$ exatly i times and states $\{M, Y\}$ exatly j times

- Given the observed sequences $\boldsymbol{x}$ and $\boldsymbol{y}$, $\mathcal{S}_{mn}$ is in 1:1 correspondence with the set of alignments of $\boldsymbol{x}$ and $\boldsymbol{y}$

- The advantage of the pair HMM framework is now we can ask for the most probable alignment given the data
  - same as maximizing $p(\boldsymbol{x}, \boldsymbol{y}, \boldsymbol{s})$ over the path $\boldsymbol{s}$

Most probable alignment - cont.

- For $\alpha \in \{M, X, Y\}$ let

$$v^{\alpha}(i,j) = \max_{\boldsymbol{s} \in \mathcal{S}_{ij} : s(|\boldsymbol{s}|) = \alpha} p(\boldsymbol{x}_{1:i}, \boldsymbol{y}_{1:j}, \boldsymbol{s}_{1:|\boldsymbol{s}|}),$$

  where $|\boldsymbol{s}|$ is the length of the alignment of $\boldsymbol{s}$.

- Clearly,

$$\max_{\boldsymbol{s}} p(\boldsymbol{x}, \boldsymbol{y}, \boldsymbol{s}) = \max\{v^M(m,n), v^X(m,n), v^Y(m,n)\} \cdot \tau$$

  - note that the rhs is in fact $v^E(m,n)$

- The following claim shows how to recursively compute $v^{\alpha}(i,j)$

Viterbi for pair HMM

- Claim. For $m \geq i \geq 0$, $n \geq j \geq 0$ with $i + j > 0$:

$$v^M(i,j) = p(x_i, y_j) \cdot \max \begin{cases} p_{MM} \cdot v^M(i-1, j-1) \\ p_{XM} \cdot v^X(i-1, j-1) \\ p_{YM} \cdot v^Y(i-1, j-1) \end{cases}$$

$$v^X(i,j) = q(x_i) \cdot \max \begin{cases} p_{MX} \cdot v^M(i-1, j) \\ p_{XX} \cdot v^X(i-1, j) \end{cases}$$

$$v^Y(i,j) = q(y_j) \cdot \max \begin{cases} p_{MY} \cdot v^M(i, j-1) \\ p_{YY} \cdot v^Y(i, j-1) \end{cases}$$

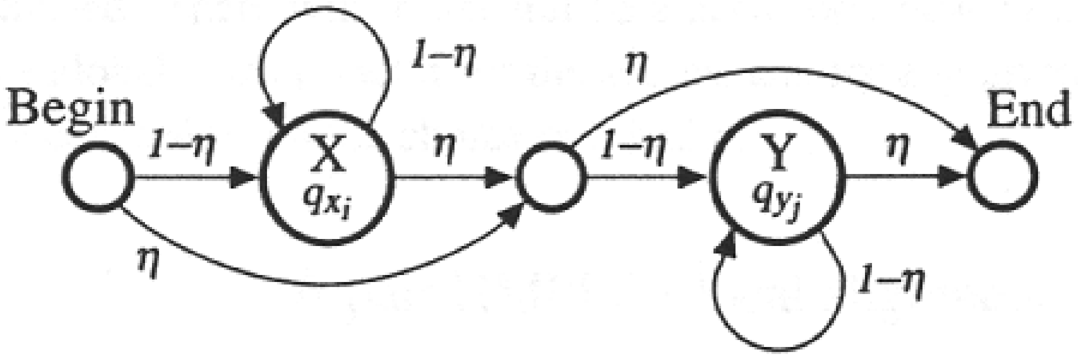
where $v^{\bullet}(i,-1) = v^{\bullet}(-1,j) = v^{[XY]}(0,0) = 0$, and $v^M(0,0) := 1$

  - $v^M(0,0)$ is in fact a surrogate for $v^B(0,0)$

<Needleman-Wunsch><ratio>

Viterbi for pair HMM - cont.

- This algorithm is similar but still differs from Needleman-Wunsch
  - logarithms should be used
  - log-odds *ratio* rather than log-odds are computed (BLOSUM/PAM)
- The following random model simply dumps the symbols of $\boldsymbol{x}$ and the $\boldsymbol{y}$ without any correlation (no match states)



$$p_R(\boldsymbol{x},\boldsymbol{y}) = \eta(1-\eta)^m \prod_{i=1}^{m} q(x_i)\eta(1-\eta)^n \prod_{j=1}^{n} q(y_j)$$

Viterbi for maximal log-odds ratio

- Look for the path $\boldsymbol{s}$ that maximizes the log-odds ratio $\log \frac{p_M(\boldsymbol{s},\boldsymbol{x},\boldsymbol{y})}{p_R(\boldsymbol{s},\boldsymbol{x},\boldsymbol{y})}$
- Let $V^{\alpha}(i,j) = \max_{\boldsymbol{s}\in\mathcal{S}_{ij}:s(|\boldsymbol{s}|)=\alpha} \log \frac{p_M(\boldsymbol{x}_{1:i},\boldsymbol{y}_{1:j},\boldsymbol{s}_{1:|\boldsymbol{s}|})}{p_R(\boldsymbol{x}_{1:i},\boldsymbol{y}_{1:j},\boldsymbol{s}_{1:|\boldsymbol{s}|})}$
- Analogously to the log-odds case we have

$$V^M(i,j) = \log \frac{p(x_i,y_j)}{q(x_i)q(y_j)} + \max \begin{cases} \log \frac{p_{MM}}{(1-\eta)^2} + V^M(i-1,j-1) \\ \log \frac{p_{XM}}{(1-\eta)^2} + V^X(i-1,j-1) \\ \log \frac{p_{YM}}{(1-\eta)^2} + V^Y(i-1,j-1) \end{cases}$$

$$V^X(i,j) = \log \frac{q(x_i)}{q(x_i)} + \max \begin{cases} \log \frac{p_{MX}}{1-\eta} + V^M(i-1,j) \\ \log \frac{p_{XX}}{1-\eta} + V^X(i-1,j) \end{cases}$$

$$V^Y(i,j) = \log \frac{q(y_j)}{q(y_j)} + \max \begin{cases} \log \frac{p_{MY}}{1-\eta} + V^M(i,j-1) \\ \log \frac{p_{YY}}{1-\eta} + V^Y(i,j-1) \end{cases}$$

<Needleman-Wunsch>

Viterbi as Needleman-Wunsch

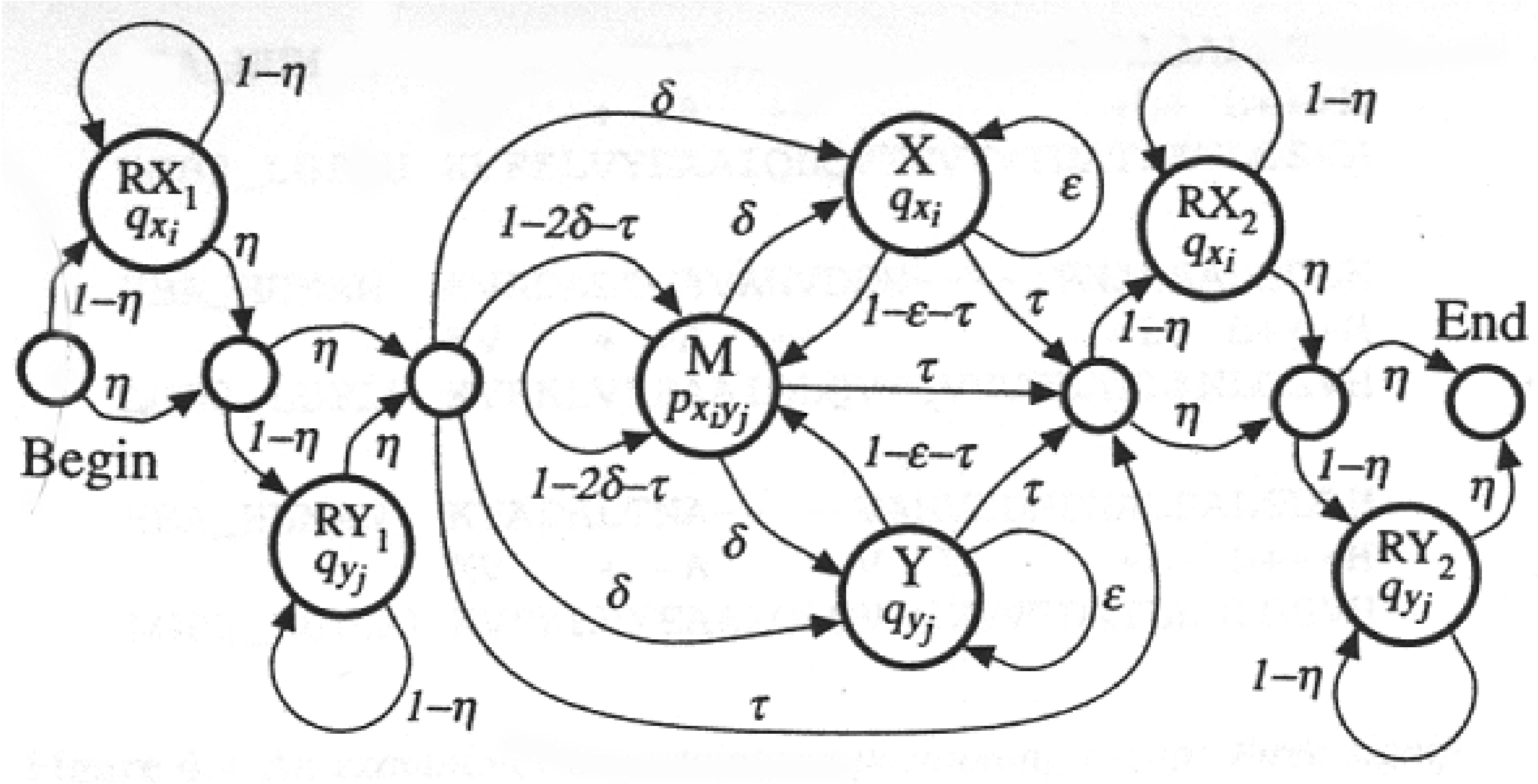
- To see the equivalence more clearly it is convenient to introduce

$$\begin{aligned} s(a,b) &= \log \frac{p(a,b)}{q(a)q(b)} + \log \frac{p_{MM}}{(1-\eta)^2} \\ -d &= \log \frac{p_{MX/Y}}{(1-\eta)} + \log \frac{p_{X/YM}}{p_{MM}} \\ -e &= \log \frac{p_{XX/YY}}{1-\eta} \end{aligned}$$

- $s(a,b)$ “assumes” we come from M
  - d “pre-corrects” that by adding $c := \log \frac{p_{X/YM}}{p_{MM}}$
- Only η^2 and the transitions from X/Y to E are left unbalanced:

$$\begin{aligned} V^M(0,0) &:= -2\log\eta \\ V^E(m,n) &:= \max\{V^M(m,n), V^X(m,n)-c, V^Y(m,n)-c\} \end{aligned}$$

pair HMM for local alignment



- As before we can look for optimal log-odds or log-odds ratio paths (the latter case will yield Smith-Waterman)

The likelihood that x and y are aligned

- While it is interesting to note that the Needleman-Wunsch algorithm can be cast in the language of HMM

- The real power of the HMM framework is that it allows us to answer questions such as
    - what is the likelihood that $\boldsymbol{x}$ and $\boldsymbol{y}$ are aligned, i.e., that they were generated by the model?

- The answer is the probability that $\boldsymbol{x}, \boldsymbol{y}$ will be generated by the model $p(\boldsymbol{x}, \boldsymbol{y}) = \sum_{\boldsymbol{s}} p(\boldsymbol{x}, \boldsymbol{y}, \boldsymbol{s})$

- An analogue of the forward algorithm computes that: let

$$f^{\alpha}(i,j) := P(\boldsymbol{X}_{1:i} = \boldsymbol{x}_{1:i}, \boldsymbol{Y}_{1:j} = \boldsymbol{y}_{1:j}, S(\tau_{ij}) = \alpha), \text{ where}$$

$$\tau_{ij} := \min\{k : \sum_{l=1}^{k} 1_{S(l)\in\{M,X\}} = i \text{ and } \sum_{l=1}^{k} 1_{S(l)\in\{M,Y\}} = j\}$$

The likelihood that x and y are aligned - cont.

- Claim. With the initial conditions

$$f^M(0,0) = 1 \qquad f^{[XY]}(0,0) = 0 \qquad f^\bullet(i,-1) = f^\bullet(-1,j) = 0,$$

for $i \geq 0$, $j \geq 0$ with $i + j > 0$:

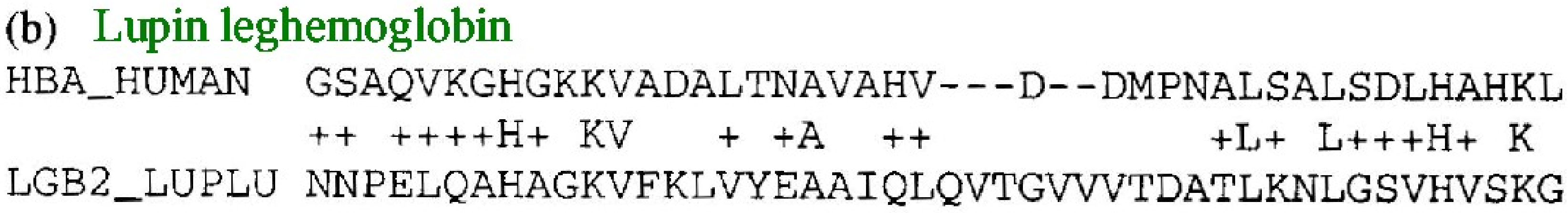
$$\begin{aligned} f^M(i,j) &= p(x_i, y_j)[p_{MM} \cdot f^M(i-1,j-1) + p_{XM} \cdot f^X(i-1,j-1) \\ &\qquad + p_{YM} \cdot f^Y(i-1,j-1)] \\ f^X(i,j) &= q(x_i)[p_{MX} \cdot f^M(i-1,j) + p_{XX} \cdot f^X(i-1,j)] \\ f^Y(i,j) &= q(y_j)[p_{MY} \cdot f^M(i,j-1) + p_{YY} \cdot f^Y(i,j-1)], \end{aligned}$$

and

$$p(\boldsymbol{x}, \boldsymbol{y}) = f^E(m,n) = \tau[f^M(m,n) + f^X(m,n) + f^Y(m,n)]$$

Posterior distribution of an alignment

- With $p(\boldsymbol{x}, \boldsymbol{y})$ we can find the posterior distribution of any particular alignment $\boldsymbol{s}$: $p(\boldsymbol{s}|\boldsymbol{x}, \boldsymbol{y}) = \frac{p(\boldsymbol{x},\boldsymbol{y},\boldsymbol{s})}{p(\boldsymbol{x},\boldsymbol{y})}$
  - In particular we can apply it for $\boldsymbol{s}^*$, the Viterbi solution
  - The answer is typically depressingly small
    - ▷ For example in the alpha globing vs. leghemoglobin case:



(b) Lupin leghemoglobin

```
HBA_HUMAN   GSAQVKGHGKKVADALTNAVAHV---D--DMPNALSALSDLHAHKL
            ++ ++++H+ KV   + +A  ++          +L+ L+++H+ K
LGB2_LUPLU  NNPELQAHAGKVFKLVYEAAIQLQVTGVVVTDATLKNLGSVHVSKG
```

    - ▷ $p(\boldsymbol{s}^*|\boldsymbol{x}, \boldsymbol{y}) = 4.6 \times 10^{-6}$

Sampling from the posterior distribution

- Given the poor posterior probability of the Viterbi alignment
  - are there parts of the alignment which we are more confident of?
  - can we estimate posterior expectation of functionals of the alignment as in posterior decoding?
- We can do that through MC sampling from the posterior distribution
  - backward sampling (using forward algorithm)
  - forward sampling (using backward algorithm)

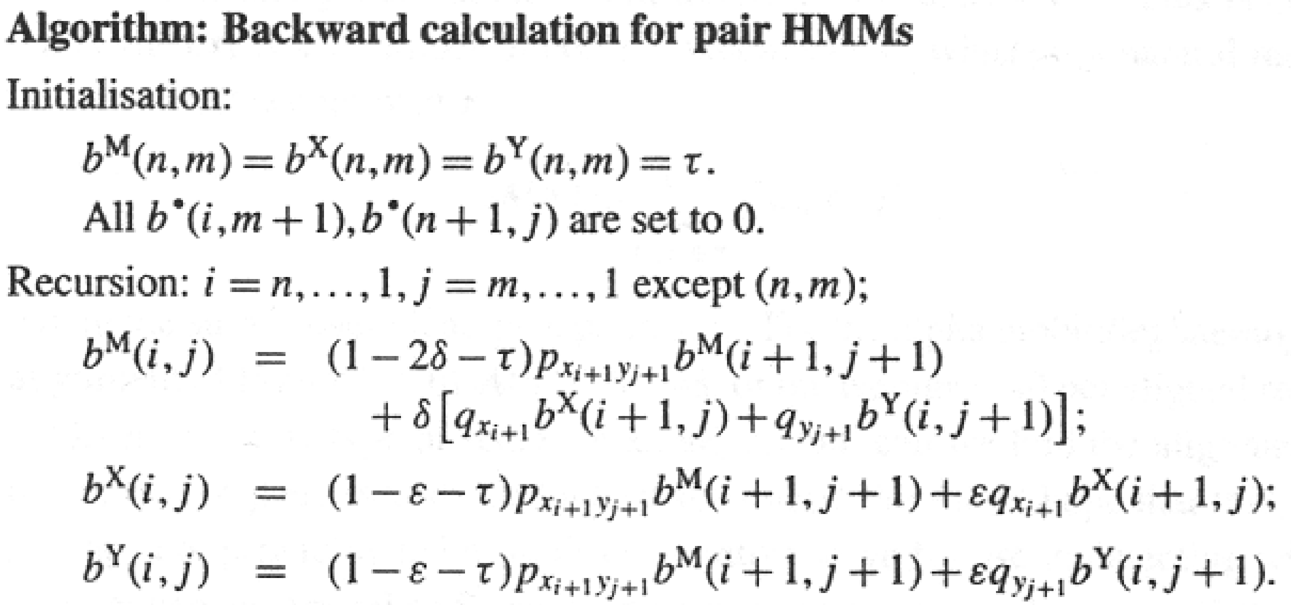
The backward algorithm

- Analogously to the backward function for HMMs we define

$$b^{\alpha}(i,j) := P(\boldsymbol{X}_{i+1:m} = \boldsymbol{x}_{i+1:m}, \boldsymbol{Y}_{j+1:n} = \boldsymbol{y}_{j+1:n}, S(\tau_{ij}) = \alpha), \text{ where}$$

$$\tau_{ij} := \min\{k : \sum_{l=1}^{k} 1_{S(l)\in\{M,X\}} = i \text{ and } \sum_{l=1}^{k} 1_{S(l)\in\{M,Y\}} = j\}$$

- Durbin et al.:



Algorithm: Backward calculation for pair HMMs

Initialisation:

$b^{\mathrm{M}}(n,m) = b^{\mathrm{X}}(n,m) = b^{\mathrm{Y}}(n,m) = \tau.$

All $b^{\bullet}(i,m+1), b^{\bullet}(n+1,j)$ are set to 0.

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

$$\begin{aligned}
b^{\mathrm{M}}(i,j) &= (1-2\delta-\tau)p_{x_{i+1}y_{j+1}}b^{\mathrm{M}}(i+1,j+1) \\
&\quad + \delta\left[q_{x_{i+1}}b^{\mathrm{X}}(i+1,j) + q_{y_{j+1}}b^{\mathrm{Y}}(i,j+1)\right]; \\
b^{\mathrm{X}}(i,j) &= (1-\varepsilon-\tau)p_{x_{i+1}y_{j+1}}b^{\mathrm{M}}(i+1,j+1) + \varepsilon q_{x_{i+1}}b^{\mathrm{X}}(i+1,j); \\
b^{\mathrm{Y}}(i,j) &= (1-\varepsilon-\tau)p_{x_{i+1}y_{j+1}}b^{\mathrm{M}}(i+1,j+1) + \varepsilon q_{y_{j+1}}b^{\mathrm{Y}}(i,j+1).
\end{aligned}$$

  - as before we can add $b^M(0,0)$ as a surrogate for $b^B(0,0)$

Forward posterior sampling (backward algorithm)

- Inductively draw from the posterior distribution as follows:
  - start at state B with $(i,j) := (0,0)$
  - while $(i,j) \neq (m,n)$:
    - ▷ given our hitherto path $\boldsymbol{s} \in \mathcal{S}(i,j)$ randomly choose our next state α according to $P[S(|\boldsymbol{s}|+1) = \alpha | \boldsymbol{x}, \boldsymbol{y}, \boldsymbol{s}]$
    - ▷ update: $\boldsymbol{s} = \boldsymbol{s} \wedge \alpha$, and $(i,j) := (i^+(\alpha), j^+(\alpha)) := (i + 1_{\alpha \in \{M,X\}}, j + 1_{\alpha \in \{M,Y\}})$
  - output the resulting $\boldsymbol{s} \in \mathcal{S}(m,n)$ (why is $\boldsymbol{s} \in \mathcal{S}(m,n)$?)
- Claim. The probability that we draw a path $\boldsymbol{s} \in \mathcal{S}(m,n)$ is $p(\boldsymbol{s}|\boldsymbol{x},\boldsymbol{y})$
- Proof. To simplify notations assume $s(0) = B$ does not count toward $|\boldsymbol{s}|$. Then

$$p(\boldsymbol{s}|\boldsymbol{x},\boldsymbol{y}) = \prod_{i=1}^{|\boldsymbol{s}|} p(s(i)|\boldsymbol{x},\boldsymbol{y},\boldsymbol{s}_{0:i-1})$$

Forward posterior sampling - cont.

- The algorithm hinges on finding

$$P[S(|\boldsymbol{s}|+1)=\alpha|\boldsymbol{x},\boldsymbol{y},\boldsymbol{s}]=\frac{p(\boldsymbol{s}\wedge\alpha,\boldsymbol{x},\boldsymbol{y})}{p(\boldsymbol{s},\boldsymbol{x},\boldsymbol{y})}$$

- Using the properties of the HMM we have:

$$\begin{aligned}p(\boldsymbol{s}\wedge\alpha,\boldsymbol{x},\boldsymbol{y})=p(\boldsymbol{x}_{1:i},\boldsymbol{y}_{1:j},\boldsymbol{s})&\\ &\times P[S(|\boldsymbol{s}|+1)=\alpha,x(i^+(\alpha)),y(j^+(\alpha))|x_i,y_j,\boldsymbol{s}]\\ &\times p[\boldsymbol{x}_{i^+(\alpha)+1:m},\boldsymbol{y}_{j^+(\alpha)+1:n}|S(|\boldsymbol{s}|+1)=\alpha]\end{aligned}$$

$$P[S(|\boldsymbol{s}|+1)=\alpha,x(i^+(\alpha)),y(j^+(\alpha))|x_i,y_j,\boldsymbol{s}]$$

$$=\begin{cases}p_{s(|\boldsymbol{s}|),M}\cdot p(x(i+1),y(j+1)) & \alpha=M\\ p_{s(|\boldsymbol{s}|),X}\cdot q(x(i+1)) & \alpha=X\\ p_{s(|\boldsymbol{s}|),Y}\cdot q(y(j+1)) & \alpha=Y\end{cases}$$

- Note that

$$p[\boldsymbol{x}_{i^+(\alpha)+1:m}, \boldsymbol{y}_{j^+(\alpha)+1:n} | S(|\boldsymbol{s}|+1) = \alpha] = b^{\alpha}(i^+(\alpha), j^+(\alpha))$$

- Finally,

$$\begin{aligned} p(\boldsymbol{s}, \boldsymbol{x}, \boldsymbol{y}) &= p(\boldsymbol{x}_{1:i}, \boldsymbol{y}_{1:j}, \boldsymbol{s}) p(\boldsymbol{x}_{i+1:m}, \boldsymbol{y}_{j+1:n} | \boldsymbol{s}) \\ &= p(\boldsymbol{x}_{1:i}, \boldsymbol{y}_{1:j}, \boldsymbol{s}) b^{\boldsymbol{s}(|\boldsymbol{s}|)}(i, j) \end{aligned}$$

Thus,

$$P[S(|\boldsymbol{s}|+1) = \alpha | \boldsymbol{x}, \boldsymbol{y}, \boldsymbol{s}] = \frac{b^{\alpha}(i^+(\alpha), j^+(\alpha))}{b^{\boldsymbol{s}(|\boldsymbol{s}|)}(i, j)}$$

$$\times \begin{cases} p_{s(|\boldsymbol{s}|),M} \cdot p(x(i+1), y(j+1)) & \alpha = M \\ p_{s(|\boldsymbol{s}|),X} \cdot q(x(i+1)) & \alpha = X \\ p_{s(|\boldsymbol{s}|),Y} \cdot q(y(j+1)) & \alpha = Y \end{cases}$$

Posterior probability that x_i is aligned to y_j

- We can estimate the posterior probability that x_i is aligned to y_j by posterior sampling of alignments
  - but we can also compute it directly
    - ▷ analogous to computing $P(S(i) = k|\boldsymbol{x})$ for HMMs
- Let $X_i \diamond Y_j$ denote the event X_i is aligned to Y_j, then

$$\begin{aligned} P(\boldsymbol{X} = \boldsymbol{x}, \boldsymbol{Y} = \boldsymbol{y}, X_i \diamond Y_j) &= P(\boldsymbol{X}_{1:i} = \boldsymbol{x}_{1:i}, \boldsymbol{Y}_{1:j} = \boldsymbol{y}_{1:j}, S(\tau_{ij}) = M) \\ &\quad \times P[\boldsymbol{X}_{i+1:m} = \boldsymbol{x}_{i+1:m}, \boldsymbol{Y}_{j+1:n} = \boldsymbol{y}_{j+1:n} | S(\tau_{ij}) = M] \\ &= f^M(i,j) b^M(i,j) \end{aligned}$$

therefore

$$P(X_i \diamond Y_j | \boldsymbol{X} = \boldsymbol{x}, \boldsymbol{Y} = \boldsymbol{y}) = \frac{f^M(i,j) b^M(i,j)}{p(\boldsymbol{x}, \boldsymbol{y})} = \frac{f^M(i,j) b^M(i,j)}{f^E(m,n)}$$

Optimizing for the “expected accuracy”

- An intuitively appealing measure of the accuracy of $\boldsymbol{s}$ is

$$A(\boldsymbol{s}) = \sum_{M_{ij} \in \boldsymbol{s}} p(x_i \diamond y_j | \boldsymbol{x}, \boldsymbol{y})$$

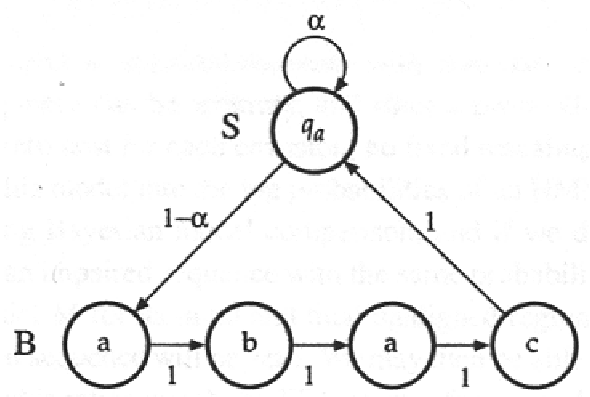
  - $A(\boldsymbol{s})$ is the expected overlap in M states between $\boldsymbol{s}$ and a random alignment drawn according to the posterior distribution

- Finding a path $\boldsymbol{s}$ which maximizes $A(\boldsymbol{s})$ is easy: let $A(i, j)$ be the optimal accuracy we can gain using only $\boldsymbol{x}_{1:i}$ and $\boldsymbol{y}_{1:j}$

$$A(i, j) = \max \begin{cases} A(i-1, j-1) + p(x_i \diamond y_j | \boldsymbol{x}, \boldsymbol{y}) \\ A(i-1, j) \\ A(i, j-1) \end{cases}$$

Viterbi failure

- Can the Viterbi algorithm discriminate between data generated by the following model vs. the random one?



- Maximizing the log-likelihood or llr is equivalent here
- If $\alpha^4 q(a)q(b)q(a)q(c) > 1 - \alpha$ then $p_S(abac) > p_B(abac)$ and the Viterbi path will never visit state B
- Since state S is random, the Viterbi path cannot discriminate between the model and random data

Viterbi failure - cont.

- However, if the data is long enough clearly the model is distinguishable from random:
  - $f_o(abac) \rightarrow p_M(abac) > p_S(abac)$
  - so simply observing the frequency of $abac$ should work for sufficiently long sequences
- Maximizing the likelihood is not always the appropriate approach
- However, comparing $p_M(\boldsymbol{x})$ and $p_R(\boldsymbol{x})$ should discriminate the two models
  - as this is the optimal test and we just saw we can discriminate
- Bonus points: figure out Figure 4.8