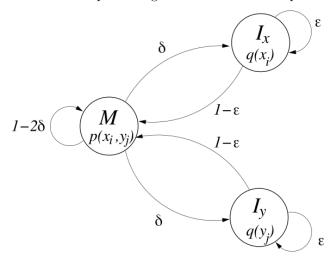
Exercise sheet 4: Pair-HMM

Exercise 1

You are given the basic pair-HMM for sequence alignment between two sequences:



Let $\delta = 0.02$ and $\epsilon = 0.79$. The initial probability distribution of the states is given by $\pi(M) = 0.6$, $\pi(I_x) = 0.2$ and $\pi(I_y) = 0.2$. Furthermore, let all $p(x_i, y_j)$ and $q(x_i)$ (and $q(y_j)$) be given in matrix p and vector q, respectively:

$$p = \begin{pmatrix} A & C & G & T \\ A & \frac{1}{8} & \frac{3}{80} & \frac{1}{80} & \frac{3}{40} \\ C & \frac{3}{80} & \frac{1}{8} & \frac{3}{40} & \frac{1}{80} \\ G & \frac{1}{80} & \frac{3}{40} & \frac{1}{8} & \frac{3}{80} \\ T & \frac{3}{40} & \frac{1}{80} & \frac{3}{80} & \frac{1}{8} \end{pmatrix} \qquad q = \begin{pmatrix} A & 0.3 \\ C & 0.2 \\ 0.2 \\ 0.3 \end{pmatrix}$$

Identify the probabilities of the following alignments between sequences x=AGCGG and y=ACAGGGG.

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Formulae
$$Prob(path = I_x I_x MMM I_y I_y I_y I_y) = \pi(I_x) \cdot \epsilon \cdot (1 - \epsilon) \cdot (1 - 2\delta)^2 \cdot \delta \cdot \epsilon^3$$

 $Prob(O|path) = q(A) \cdot q(G) \cdot p(C, A) \cdot p(G, C) \cdot p(G, A) \cdot q(G)^4$
 $Prob(path, O) = Prob(O|path) \times Prob(path)$

Solution
$$Prob(path = I_x I_x MMM I_y I_y I_y I_y) \approx 3.0 \cdot 10^{-4}$$

 $Prob(O|path) \approx 3.4 \cdot 10^{-9}$
 $Prob(path, O) \approx 1.0 \cdot 10^{-12}$

1b)

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Formulae
$$Prob(path = I_y MMMMMI_y) = \pi(I_y) \cdot (1 - \epsilon) \cdot (1 - 2\delta)^4 \cdot \delta$$

 $Prob(O|path) = q(A) \cdot p(A, C) \cdot p(G, A) \cdot p(C, G) \cdot p(G, G) \cdot p(G, G) \cdot q(G)$
 $Prob(path, O) = Prob(O|path) \times Prob(path)$

Solution
$$Prob(path = I_y MMMMMI_y) \approx 3.4 \cdot 10^{-4}$$

 $Prob(O|path) = \approx 3.3 \cdot 10^{-8}$
 $Prob(path, O) \approx 2.4 \cdot 10^{-11}$ \$

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$$\begin{aligned} \textbf{Formulae} \quad & Prob(path = I_x I_x I_x M I_y I_y I_y I_y I_y I_y I_y) = \pi(I_x) \cdot \epsilon^3 \cdot (1 - \epsilon) \cdot \delta \cdot \epsilon^5 \\ & Prob(O|path) = q(A) \cdot q(G) \cdot q(C) \cdot q(G) \cdot p(G,A) \cdot q(C) \cdot q(A) \cdot q(G) \cdot q(G) \cdot q(G) \\ & Prob(path,O) = Prob(O|path) \times Prob(path) \end{aligned}$$

$$\begin{split} \textbf{Solution} \quad & Prob(path = I_x I_x I_x I_x M I_y I_y I_y I_y I_y I_y) \approx 1.2 \cdot 10^{-4} \\ & Prob(O|path) \approx 2.9 \cdot 10^{-9} \\ & Prob(path, O) \approx 3.5 \cdot 10^{-13} \end{split}$$

Exercise 2

The following alignment of sequences a=AACTT and b=AACAT is not included in the set of alignments represented by the pair-HMM of exercise 1.

a: AACT-T
||| |
b: AAC-AT

2a)

Could you explain why?

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Solution Because the probability of moving from I_x to I_y is zero, there is no edge between I_x and I_y .

Exercise 3

As you have seen, the given pair-HMM, which emits alignments of two sequences, gives us probabilities which are quite small for any particular alignment. These probabilities are often compared to other probabilities generated by a random model.

3a)

Design a HMM which generates two random sequences with the frequencies of q_i given in exercise 1. Use the parameters η and $1 - \eta$ to describe the transition probabilities.

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Hint The proposed solution includes two main states, which in turn emits two sequences, independently of each other. Each has a loop back onto itself with probability $(1-\eta)$. As well as Begin and End states, the proposed solution includes a silent state in between X and Y, used to gather inputs from both the X and Begin states.

Solution

