

## 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:

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

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

1a)

```

x: AGCGG----
   :::
y: --ACAGGGG
  
```

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

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

$Prob(path, O) = Prob(O|path) \times Prob(path)$

**Solution**  $Prob(path = I_x I_x M M M I_y I_y I_y) = 0.2 \cdot 0.79 \cdot 0.21 \cdot 0.96^2 \cdot 0.02 \cdot 0.79^3 = 0.000301452... \approx 3.0 \cdot 10^{-4}$

$Prob(O|path) = 0.3 \cdot 0.2 \cdot \frac{3}{80} \cdot \frac{3}{40} \cdot \frac{1}{80} \cdot 0.2^4 = 3.375 \cdot 10^{-9} \approx 3.4 \cdot 10^{-9}$

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

1b)

```
x: -AGCGG-
   :::||
y: ACAGGGG
```

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

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

$Prob(path, O) = Prob(O|path) \times Prob(path)$

**Solution**  $Prob(path = I_y M M M M M I_y) = 0.2 \cdot 0.21 \cdot 0.96^4 \cdot 0.02 = 0.0007134... \approx 7.1 \cdot 10^{-4}$

$Prob(O|path) = 0.3 \cdot \frac{3}{80} \cdot \frac{1}{80} \cdot \frac{3}{40} \cdot \frac{1}{8}^2 \cdot 0.2 \approx 3.3 \cdot 10^{-8}$

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

1c)

```
x: AGCGG-----
   :
y: ----ACAGGGG
```

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**Formulae**  $Prob(path = I_x I_x I_x I_x M I_y I_y I_y I_y) = \pi(I_x) \cdot \epsilon^3 \cdot (1 - \epsilon) \cdot \delta \cdot \epsilon^5$

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

$Prob(path, O) = Prob(O|path) \times Prob(path)$

**Solution**  $Prob(path = I_x I_x I_x M I_y I_y I_y I_y I_y) = 0.2 \cdot 0.79^3 \cdot 0.21 \cdot 0.02 \cdot 0.79^5 = 0.0000127... \approx 1.3 \cdot 10^{-4}$   
 $Prob(O|path) = 0.3 \cdot 0.2^3 \cdot \frac{1}{80} \cdot 0.2 \cdot 0.3 \cdot 0.2^4 = 2.88 \cdot 10^{-9} \approx 2.9 \cdot 10^{-9}$   
 $Prob(path, O) \approx 3.7 \cdot 10^{-13}$

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## 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.

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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  $I_y$ .

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## 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  $\eta$  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

