

# Exercise sheet 5: Probalign

For the following exercises on Probalign, we use an affine gap penalty with  $g(k) = \alpha + \beta k = -0.5 - 0.25k$ , there temperature  $T = 1$  and the similarity function  $\sigma(x_i, y_j)$ :

$$\sigma(x_i, y_j) = \begin{matrix} & \begin{matrix} A & C & G & T \end{matrix} \\ \begin{matrix} A \\ C \\ G \\ T \end{matrix} & \begin{pmatrix} 2 & -1 & -1 & -1 \\ -1 & 2 & -1 & -1 \\ -1 & -1 & 2 & -1 \\ -1 & -1 & -1 & 2 \end{pmatrix} \end{matrix}$$

## Exercise 1

**Question 1A** Compute the Boltzmann-weighted score for the following alignments:

- |                |                   |
|----------------|-------------------|
| (a) x: --AGCGG | (b) x: AGCGG----- |
| :              | :                 |
| y: ACAGGGG     | y: -----ACAGGGG   |

**Hint 1 : Formulae**

$$S(a) = \sum_{x_i \sim y_j \in a} \sigma(x_i, y_j) + \sum \text{gap penalties} e^{\frac{S(a)}{T}} = \left( \prod_{x_i \sim y_j \in a} e^{\frac{\sigma(x_i, y_j)}{T}} \right) \times e^{\frac{\sum \text{gap penalties}}{T}}$$

**Hint 2** For each alignment you only need to calculate  $e^x$  once.

**Hint 3: Calculations**

- |     |  |   |
|-----|--|---|
| (a) | $e^{\sigma(A,A)} \times e^{3\sigma(G,G)} \times e^{\sigma(C,G)} \times e^{g(2)}$ | $= e^2 \times e^6 \times e^{-1} \times e^{-0.5+(-0.25 \times 2)} = e^6$               |
| (b) | $e^{\sigma(G,A)} \times e^{g(4)} \times e^{g(6)}$                                | $= e^{-1} \times e^{0.5+(-0.25 \times 4)} \times e^{0.5+(-0.25 \times 6)} = e^{-4.5}$ |

**Solution**

- |     |                    |
|-----|--------------------|
| (a) | $e^6 = 403.43$     |
| (b) | $e^{-4.5} = 0.011$ |

## Exercise 2

**Question 2A** Derive the recursion formula for  $Z_{i,j}^I$ . Allow insertions after deletions and vice versa.

**Solution**

$$Z_{i,j}^I = Z_{i,j-1}^I \times e^{\frac{\beta}{T}} + Z_{i,j-1}^M \times e^{\frac{g(1)}{T}} + Z_{i,j-1}^D \times e^{\frac{g(1)}{T}}$$


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**Question 2B** Compute the partition function  $Z(T)$  by dynamic programming for the sequences  $\mathbf{x}=\text{ACC}$  and  $\mathbf{y}=\text{AC}$ . Allow insertions after deletions and vice versa. In order to simplify the computations, you can round to two digits after the decimal point.

**Hint 1: Formulae** Initialization:

$$\begin{aligned} Z_{i,0}^M &= Z_{0,j}^M = 0, Z_{0,0}^M = 1 \\ Z_{i,0}^I &= 0 \\ Z_{0,j}^D &= 0 \end{aligned}$$

Recursion:

$$\begin{aligned} Z_{i,j}^M &= Z_{i-1,j-1} \times e^{\frac{\sigma(x_i, y_j)}{T}} \\ Z_{i,j}^I &= Z_{i,j-1}^I \times e^{\frac{\beta}{T}} + Z_{i,j-1}^M \times e^{\frac{g(1)}{T}} + Z_{i,j-1}^D \times e^{\frac{g(1)}{T}} \\ Z_{i,j}^D &= Z_{i-1,j}^D \times e^{\frac{\beta}{T}} + Z_{i-1,j}^M \times e^{\frac{g(1)}{T}} + Z_{i-1,j}^I \times e^{\frac{g(1)}{T}} \\ Z_{i,j} &= Z_{i,j}^M + Z_{i,j}^I + Z_{i,j}^D \end{aligned}$$

**Solution**

$Z^{\{M\}}$	-	A	C
-	1	0.00	0.00
A	0	7.39	0.17
C	0	0.17	57.90
C	0	0.14	30.42

$Z^{\{I\}}$	-	A	C
-	0	0.47	0.37
A	0	0.22	3.77
C	0	0.17	2.00
C	0	0.14	1.63

$Z^{\wedge}\{D\}$	-	A	C
-	0.00	0.00	0.00
A	0.47	0.22	0.17
C	0.37	3.68	2.00
C	0.29	3.10	29.85

Z	-	A	C
-	1.00	0.47	0.37
A	0.47	7.84	4.12
C	0.37	4.12	61.89
C	0.29	3.37	61.90

### Exercise 3

The partition function of the reverse sequences  $x^* = CA$  and  $y^* = CCA$  is given in the matrix  $Z^*$ :

$Z^{\wedge}\{*\}$	-	A	C
-	1.00	0.47	0.37
A	0.47	7.84	4.12
C	0.37	7.43	8.45
C	0.29	4.94	61.90

**Question 3A** Find a mapping from matrix  $Z_{k,l}^*$  to  $Z'_{i,j}$ . Which position in matrix  $Z^*$  corresponds to which position in matrix  $Z'$ ?

**Solution**  $Z'_{i,j}$  is the partition function of the alignment  $x_j \dots x_{|x|}$  with  $y_i \dots y_{|y|}$ .

$Z_{k,l}^*$  is the partition function of the alignment  $x_{|x|} \dots x_{|x|-k+1}$  with  $y_{|y|} \dots y_{|y|-l+1}$ .

$$j = |x| - l + 1 \Leftrightarrow l = |x| - j + 1$$

$$i = |y| - k + 1 \Leftrightarrow k = |y| - i + 1$$

$Z^{\wedge}\{*\}$	-	C	A
-	(0,0)	(0,1)	(0,2)
A	(1,0)	(1,1)	(1,2)
C	(2,0)	(2,1)	(2,2)
C	(3,0)	(3,1)	(3,2)

$Z \setminus \{ \}$	-	A	C	-1
-	(0,0)	(0,1)	(0,2)	(0,3)
A	(1,0)	(1,1)	(1,2)	(1,3)
C	(2,0)	(2,1)	(2,2)	(2,3)
C	(3,0)	(3,1)	(3,2)	(3,3)
-	(4,0)	(4,1)	(4,2)	(4,3)

**Question 3B** Use  $Z, Z^*$  and the mapping from  $Z^*$  to  $Z'$  to compute the probability of the alignment edges (1, 1), (2, 2), (3, 1) and (3, 2) between  $x$  and  $y$ .

**Hint 1: Formulae**

$$P(x_i \sim y_j | x, y) = \frac{Z_{i-1, j-1} \times e^{\frac{\sigma(x_i, y_j)}{T}} \times Z'_{i+1, j+1}}{Z(T)} Z_{i, j}^M = Z_{i-1, j-1} \times e^{\frac{\sigma(x_i, y_j)}{T}}$$

**Hint 2** Mapped positions:

$$\begin{aligned} Z'_{2,2} &\iff Z_{2,1}^* \\ Z'_{3,3} &\iff Z_{1,0}^* \\ Z'_{4,2} &\iff Z_{0,1}^* \\ Z'_{4,3} &\iff Z_{0,0}^* \end{aligned}$$

**Solution** Alignment edge (1, 1):

$$P(x_1 \sim y_1 | x, y) = \frac{Z_{0,0} \times e^{\frac{\sigma(x_1, y_1)}{T}} \times Z'_{2,2}}{Z(T)} = \frac{Z_{0,0} \times e^{\frac{\sigma(x_1, y_1)}{T}} \times Z_{2,1}^*}{Z(T)} = \frac{Z_{1,1}^M \times Z_{2,1}^*}{Z(T)} = \frac{7.39 \times 7.43}{61.90} = 0.89$$

Alignment edge (2, 2):

$$P(x_2 \sim y_2 | x, y) = \frac{Z_{1,1} \times e^{\frac{\sigma(x_2, y_2)}{T}} \times Z'_{3,3}}{Z(T)} = \frac{Z_{1,1} \times e^{\frac{\sigma(x_2, y_2)}{T}} \times Z_{1,0}^*}{Z(T)} = \frac{Z_{2,2}^M \times Z_{1,0}^*}{Z(T)} = \frac{57.90 \times 0.47}{61.90} = 0.44$$

Alignment edge (3, 1):

$$P(x_3 \sim y_1 | x, y) = \frac{Z_{3,1}^M \times Z'_{4,2}}{Z(T)} = \frac{Z_{3,1}^M \times Z_{0,1}^*}{Z(T)} = \frac{0.14 \times 0.47}{61.90} = 0.001$$

Alignment edge (3, 2):

$$P(x_3 \sim y_2 | x, y) = \frac{Z_{3,2}^M \times Z'_{4,3}}{Z(T)} = \frac{Z_{3,1}^M \times Z_{0,0}^*}{Z(T)} = \frac{30.42 \times 1}{61.90} = 0.49$$