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 $\sigma(x_i, y_j)$:

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

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

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

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 $Z^I_{i,j}$. Allow insertions after deletions and vice versa.

Solution

$$Z^I_{i,j} = Z^I_{i,j-1} \times e^{\frac{\beta}{T}} + Z^M_{i,j-1} \times e^{\frac{g(1)}{T}} + Z^D_{i,j-1} \times e^{\frac{g(1)}{T}}$$

Question 2B Compute the partition function Z(T) by dynamic programming for the sequences `x=ACC` and `y=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:

$$\begin{aligned} &Z^M_{i,0} = Z^M_{0,j} = 0, Z^M_{0,0} = 1 \\ &Z^I_{i,0} = 0 \\ &Z^D_{0,j} = 0 \end{aligned}$$

Recursion:

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

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^{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^{*}	-	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 $x_j ... x_{|x|}$ with $y_i ... y_{|y|}$.

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

$$j = |x| - l + 1 \Leftrightarrow l = |x| - j + 1$$
$$i = |y| - k + 1 \Leftrightarrow k = |y| - i + 1$$

Z^{*}	-	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^{'}	-	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

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

Hint 2 Mapped positions:

$$Z'_{2,2} \iff Z^*_{2,1}$$
$$Z'_{3,3} \iff Z^*_{1,0}$$
$$Z'_{4,2} \iff Z^*_{0,1}$$
$$Z'_{4,3} \iff Z^*_{0,0}$$

Solution Alignment edge $(1,1)$:

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

Alignment edge $(2,2)$:

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

Alignment edge $(3,1)$:

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

Alignment edge $(3,2)$:

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