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

1a)

Compute the Boltzmann-weighted score for the following alignments:

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

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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

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

Solution

$$\begin{array}{ll} \text{(a)} & e^6 = 403.43 \\ \text{(b)} & e^{-4.5} = 0.011 \end{array}$$

Exercise 2

2a)

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

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Solution

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

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.

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Hint 1: Formulae Initialization:

$$Z_{i,0}^{M} = Z_{0,j}^{M} = 0, Z_{0,0}^{M} = 1$$
$$Z_{i,0}^{I} = 0$$
$$Z_{0,j}^{D} = 0$$

Recursion:

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

Solution

Z^{M}	-	A	C
-	1	0.00	0.00
A	0	7.39	0.17
C	0	0.17	57.90

Z^{M}	-	A	C
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 $x^* = CCA$ and $y^* = CA$ is given in the matrix Z^*:

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

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'?

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

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

Z^{*}	-	C	A
-	(0,0)	(0,1)	(0,2)
C	(1,0)	(1,1)	(1,2)
C	(2,0)	(2,1)	(2,2)
A	(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)

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.

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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:

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

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 $(3,2)$:

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