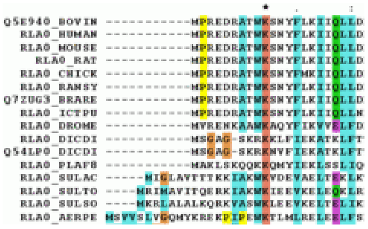
Part IV

8 Multiple sequence alignment

8.1 Multiple sequence alignment

A multiple sequence alignment is an effective tool to understand the characteristics of genes by comparing multiple sequences of different species at the same time.

Multiple Sequence Alignment (MSA) for protein sequences



```
                                 *   .    :
Q5E940_BOVIN -----------MPREDRATWKSNYFLKIIQLLD
  RLA0_HUMAN -----------MPREDRATWKSNYFLKIIQLLD
  RLA0_MOUSE -----------MPREDRATWKSNYFLKIIQLLD
    RLA0_RAT -----------MPREDRATWKSNYFLKIIQLLD
  RLA0_CHICK -----------MPREDRATWKSNYFMKIIQLLD
  RLA0_RANSY -----------MPREDRATWKSNYFLKIIQLLD
Q7ZUG3_BRARE -----------MPREDRATWKSNYFLKIIQLLD
  RLA0_ICTPU -----------MPREDRATWKSNYFLKIIQLLN
  RLA0_DROME -----------MVRENKAAWKAQYFIKVVELFD
  RLA0_DICDI -----------MSGAG-SKRKKLFIEKATKLFT
Q54LP0_DICDI -----------MSGAG-SKRKNVFIEKATKLFT
  RLA0_PLAF8 -----------MAKLSKQQKKQMYIEKLSSLIQ
  RLA0_SULAC -----MIGLAVTTTKKIAKWKVDEVAELTEKLK
  RLA0_SULTO ----MRIMAVITQERKIAKWKIEEVKELEQKLR
  RLA0_SULSO ----MKRLALALKQRKVASWKLEEVKELTELIK
  RLA0_AERPE MSVVSLVGQMYKREKPIPEWKTLMLRELEKLFS
```

Figure 8.1: An MSA of insulin proteins of seven sequences

Notation of MSA

- $\mathcal{A}$: Alignment
- m : Number of sequences in $\mathcal{A}$
- s^i_j : An amino acid or a nucleotide of sequence i and position j (without gaps)
- $\bar{s}^i_j$: An amino acid or a nucleotide of sequence i and column j (with gaps)

Example of MSA notation

```
HUMAN: TP-K
MOUSE: TLSK
RAT  : TPSK
```

- m : 3
- s^1_1 : T (1st position of HUMAN)
- s^2_2 : L (2nd position of MOUSE)
- s^3_4 : K (4th position of RAT)
- $\bar{s}^1_3$: - (3rd position of HUMAN)

Making an optimal MSA

- Insert gaps to the sequences in $\mathcal{A}$
- Maximize the score of $\mathcal{A}$

All combinations of elements per column

The number of all possible combinations of elements per column can be calculated as follows.

$$\sum_{i=0}^{m-1} \binom{m}{i} = 2^m - 1$$

Example of the number of combinations

$$\begin{array}{ccccccc}
s_1^1 & \text{-} & s_3^1 & s_4^1 & \text{-} & \text{-} & s_7^1 \\
s_1^2 & s_2^2 & \text{-} & s_4^2 & \text{-} & s_6^2 & \text{-} \\
s_1^3 & s_2^3 & s_3^3 & \text{-} & s_5^3 & \text{-} & \text{-}
\end{array}$$

- m: 3
- $2 \times 2 \times 2 - 1 = 7$

Alignment methods

- Dynamic programming with m-dimensional array (deterministic)
- Progressive alignment (heuristics)

SP score

One of the common methods to calculate the score of an alignment is using SP (sum-of-pairs) scores. SP uses pair-wise scores on all possible paired sequences to obtain the final score for the alignment. SP is defined as below.

$$S(\mathcal{A}) = \sum_{i=1}^{m-1} \sum_{j=i+1}^{m} S(\bar{s}^i, \bar{s}^j)$$

N.B. The score of $S(\bar{s}^i, \bar{s}^j)$ is 0 when both elements are gaps.

Example of SP score

Use the simple scoring scheme and calculate the SP score. Simple scoring scheme: Match: 1, Mismatch: 0, and Gap penalty: 1

```
Seq1 A-GC
Seq2 ACG-
Seq3 A-TC
```

$S(\bar{s}^1, \bar{s}^2) = 1 - 1 + 1 - 1 = 0$
$S(\bar{s}^1, \bar{s}^3) = 1 + 0 + 0 + 1 = 2$
$S(\bar{s}^2, \bar{s}^3) = 1 - 1 + 0 - 1 = -1$

$S(\mathcal{A}) = S(\bar{s}^1, \bar{s}^2) + S(\bar{s}^1, \bar{s}^3) + S(\bar{s}^2, \bar{s}^3) = 0 + 2 - 1 = 1$

Exercise 8.1

Use the simple scoring scheme and calculate the SP score.

```
Seq1 A-CC
Seq2 C-TC
Seq3 CAG-
```

8.2 Dynamic programming with m-dimensional array

Dynamic programming (DP) can be extended to handle multiple alignments.

Multi-dimensional array for dynamic programming

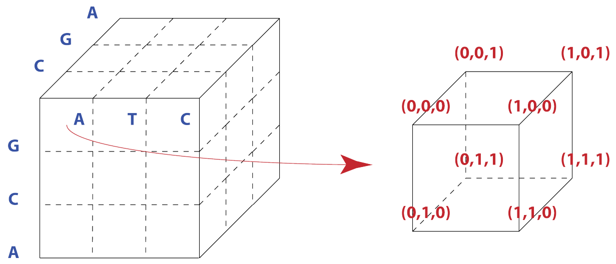


Figure 8.2: A three-dimensional DP array

Example of alignment representation

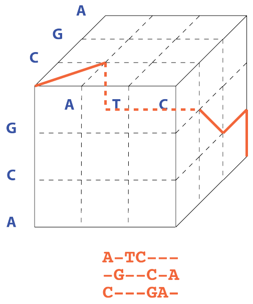


Figure 8.3: An alignment with a three-dimensional DP array

The number of candidate scores for a vertex

The number of the inbound neighboring vertices is defined as follows.

$$\sum_{i=0}^{m-1} \binom{m}{i} = 2^m - 1$$

Example of edges of 3-dimensional cell

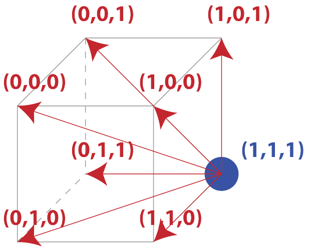


Figure 8.4: An example of seven different edges to one vertex when m = 3

A pruning method

- K : a score of an MSA (it does not need to be the optimal)
- ν : current vertex
- S_ν : best score from the start vertex to ν (by DP)
- F_ν : best score from the end vertex to ν (by non-DP)
- if $S_\nu + F_\nu < K$ then ν does not lie on the optimal path

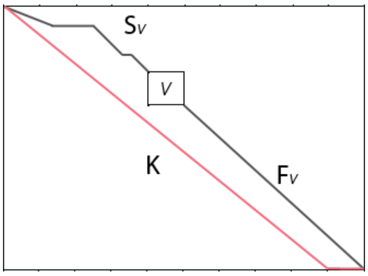


Figure 8.5: Score estimation

Forward-recursion DP for MSA

Instead of looking up inbound neighboring vertices, the forward recursion DP sends the calculated score to all outbound neighboring vertices.

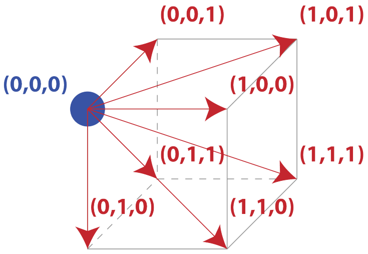


Figure 8.6: Values are forwarded to all outgoing neighbors