

Bioinformatics

Sequence alignment - Dinamic programming

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1 Introduction

- Objectives

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Introduction

Objectives

- Understand the importance of sequence alignment in Bioinformatics.

Introduction

Objectives

- Understand the importance of sequence alignment in Bioinformatics.
- Understand and implement the Needleman–Wunsch algorithm.

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Sequence alignment

Definition

How can we determine the similarity between two sequences?

Sequence alignment

Definition

Sequence Alignment in Biology

The purpose of a sequence alignment is to line up all residues in the inputted sequence(s) for maximal level of similarity, in the sense of their functional or evolutionary relationship.

Sequence alignment

Pairwise sequence alignment

Visit [EMBOSS](http://www.ebi.ac.uk/EMBOSS/), use the sample sequences and evaluate with BLOSUM62 matrix (no more that 62% of similarity).

Pairwise Sequence Alignment

EMBOSS Needle reads two input sequences and writes their optimal global sequence alignment to file.

STEP 1 - Enter your protein sequences

Enter a pair of
 PROTEIN

sequences. Enter or paste your first **protein** sequence in any supported format:

```
>sp|P69905|HBA_HUMAN Hemoglobin subunit alpha OS=Homo sapiens GN=HBA1 PE=1 SV=2
MVLSPADKTNVKAAWGKVGAHAGEYGAEALERMFLSFPTTKTYFPHFDLSHSAQVKGHG
KKVADALTNVAHVDDMPNALSLSLHAHLKRVDPVNFKLLSHCLLVTLAAHLPAEFTF
```

Or, upload a file: No file selected. [Use a sample sequence](#) [See more example inputs](#)

AND

Enter or paste your second **protein** sequence in any supported format:

```
>sp|P01942|HBA_MOUSE Hemoglobin subunit alpha OS=Mus musculus GN=Hba PE=1 SV=2
MVLSGEDKSNKAAWGKGGAHYGAEALERMFAFPTTKTYFPHFDVSHGSAQVKGHG
KKVAFMI ASAAGHI DDI PQAI SAI SFI HAHKI RVDVNFKI I SHCI I VTI ASHAPADFTF
```

Or, upload a file: No file selected.

STEP 2 - Set your pairwise alignment options

OUTPUT FORMAT
 pair

MATRIX	GAP OPEN	GAP EXTEND	END GAP PENALTY	END GAP OPEN	END GAP EXTEND
BLOSUM62	10	0.5	false	10	0.5

STEP 3 - Submit your job

☐ Be notified by email (Tick this box if you want to be notified by email when the results are available)

Figure: Tool for pairwise sequence alignment.

Sequence alignment

Pairwise sequence alignment

```
# Aligned sequences: 2
# 1: HBA_HUMAN
# 2: HBA_MOUSE
# Matrix: EBL0SUM62
# Gap_penalty: 10.0
# Extend_penalty: 0.5
#
# Length: 142
# Identity:      122/142 (85.9%)
# Similarity:    131/142 (92.3%)
# Gaps:          0/142 ( 0.0%)
# Score: 648.0
#
#=====
```

HBA_HUMAN	1	MVLSPADKTNVKAANGKVGAGHAGEYGAEALERMFSLFPTTKTYFPHFDLS	50
		. . : : : . .	
HBA_MOUSE	1	MVLSGEDKSNIKAANGKIGGHGAEYGAEALERMFASFPTTKTYFPHFDVS	50
HBA_HUMAN	51	HGSAQVKGHGKKVADALTNAAVAHVDDMPNALSALSDLHAHKLRVDPVNFK	100
HBA_MOUSE	51	HGSAQVKGHGKKVADALASAAGHLDDLPGALSALSDLHAHKLRVDPVNFK	100
HBA_HUMAN	101	LLSHCLLVTLAAHLPAEFTPAVHASLDKFLASVSTVLTSKYR	142
HBA_MOUSE	101	LLSHCLLVTLASHHPADFTPAVHASLDKFLASVSTVLTSKYR	142

Figure: Alignment: “|” stands for equality, “:” for similarity and “.” for non-similarity.

Pairwise Sequence Alignment

in Maths

Input data:

- Two sequences S_1 and S_2

Parameters:

- A scoring function f for **substitutions** and **gaps**.

Output:

- The optimal alignment of S_1 and S_2 , which has the maximal score.

Pairwise Sequence Alignment

in Maths

There are too many possible solution for sequence alignment.

LSPADK	L - SPADK	L - SPADK
LTPEEK	LTPEEK -	LT - PEEK
- - - - -	LSPADK	L - S - P - A - D - K -
LTPEEK - - - - -	- L - T - P - E - E - K	

$$\binom{2n}{n} = \frac{(2n)!}{(n!)^2}$$

Pairwise Sequence Alignment

in Maths

if $n = 300$

$$\binom{2n}{n} = \frac{(2n)!}{(n!)^2} = \frac{2 * 300}{(300!)^2} \approx 7 * 10^{88}$$

The visible universe is estimated to contain $10^{78} \sim 10^{80}$ atoms.

Pairwise Sequence Alignment

Dynamic Programming

Dynamic Programming

Dynamic Programming solves problems by combining the solutions to sub-problems.

- Break the problem into smaller sub-problems.
- Solve these sub-problems optimally recursively.
- Use these optimal solutions to construct an optimal solution for the original problem.

Dynamic Programming

Example

$r \backslash s$	A	G	G	ϕ
A	Best alignment between ACG and AGG	Best alignment between ACG and GG	Best alignment between ACG and G	Best alignment between ACG and ϕ
C	Best alignment between CG and AGG	Best alignment between CG and GG	Best alignment between CG and G	Best alignment between CG and ϕ
G	Best alignment between G and AGG	Best alignment between G and GG	Best alignment between G and G	Best alignment between G and ϕ
ϕ	Best alignment between ϕ and AGG	Best alignment between ϕ and GG	Best alignment between ϕ and G	Best alignment between ϕ and ϕ

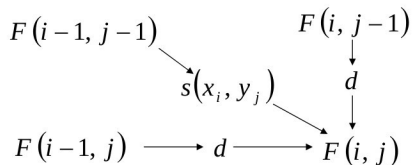
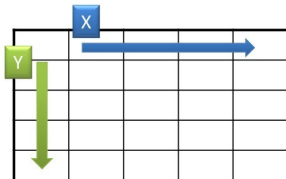
Figure: How we could divide the problem into sub-problems.

Dynamic Programming

Example

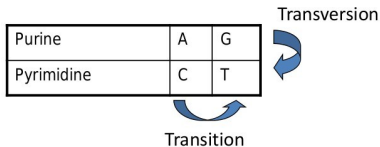
$$F(0,0) = 0$$

$$F(i, j) = \max \begin{cases} F(i-1, j-1) + s(x_i, y_j) & \mathbf{x_i \text{ aligned to } y_j} \\ F(i-1, j) + d & \mathbf{x_i \text{ aligned to a gap}} \\ F(i, j-1) + d & \mathbf{y_j \text{ aligned to a gap}} \end{cases}$$



Dynamic Programming

Example



Scoring Nucleotide

A nucleotide substitution matrix:

	A	C	G	T
A	2	-7	-5	-7
C	-7	2	-7	-5
G	-5	-7	2	-7
T	-7	-5	-7	2

Figure: Example of $s(x_i, y_j)$.

Dynamic Programming

Example

Input Sequence 1: AAG

Input Sequence 2: AGC

	A	C	G	T
A	2	-7	-5	-7
C	-7	2	-7	-5
G	-5	-7	2	-7
T	-7	-5	-7	2

For simplicity, let's set (i.e. **linear gap penalty**)

gap OPEN (d) = gap EXTEND (e) = -5

GAC - AT

C - ACAT




Diagram illustrating the alignment of the sequences GAC and C-ACAT. Arrows point from the characters of the second sequence to the first sequence, showing matches and gaps. The calculation below shows the total score: $(-7) + (-5) + (-7) + (-5) + 2 + 2 = -20$.

$$(-7) + (-5) + (-7) + (-5) + 2 + 2 = -20$$

Dynamic Programming

Example

	A	C	G	T
A	2	-7	-5	-7
C	-7	2	-7	-5
G	-5	-7	2	-7
T	-7	-5	-7	2

$$F(0,0)=0$$

$$F(i,j) = \max \begin{cases} F(i-1,j-1) + s(x_i, y_j) \\ F(i-1,j) + d \\ F(i,j-1) + d \end{cases}$$

Find the optimal alignment of AAG and AGC.

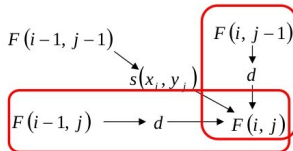
Use a linear gap penalty of $d=-5$.

		A	A	G
	0			
A				
G				
C				

Dynamic Programming

Example

	A	C	G	T
A	2	-7	-5	-7
C	-7	2	-7	-5
G	-5	-7	2	-7
T	-7	-5	-7	2



Find the optimal alignment of AAG and AGC.

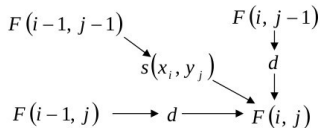
Use a linear gap penalty of $d=-5$.

		A	A	G
	0	-5	-10	-15
A	-5			
G	-10			
C	-15			

Dynamic Programming

Example

	A	C	G	T
A	2	-7	-5	-7
C	-7	2	-7	-5
G	-5	-7	2	-7
T	-7	-5	-7	2



Find the optimal alignment of AAG and AGC.
Use a linear gap penalty of $d=-5$.

		A
	0	-5
A	-5	2

$$-5 + (-5) = -10$$

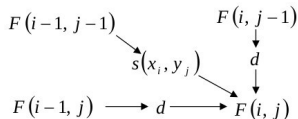
$$0 + 2 = 2$$

$$-5 + (-5) = -10$$

Dynamic Programming

Example

	A	C	G	T
A	2	-7	-5	-7
C	-7	2	-7	-5
G	-5	-7	2	-7
T	-7	-5	-7	2



Find the optimal alignment of AAG and AGC.
Use a linear gap penalty of $d=-5$.

		A	A	G
	0	-5	-10	-15
A	-5	2	-3	-8
G	-10	-3	-3	-1
C	-15	-8	-8	-6

Dynamic Programming

Example

Trace back to the upper left. Each arrow introduces one symbol at the end of each aligned sequence.

```

A  A  G  -
-  A  G  C
A  A  G  -
A  -  G  C
  
```

		A	A	G
	0	-5		
A		2	-3	
G				-1
C				-6

Questions?

