

Smith & Waterman Algorithm for Pairwise Local Alignment

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Lecture Outline

- 1 Sequence Alignment
- 2 Sequence Edits
- 3 Dynamic Programming
- 4 Local Sequence Alignment
- 5 Smith & Waterman Algorithm
- 6 Example

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Sequence Alignment

- Why do we need to align sequence?
- Evolutionary Relationships

Why do we need to align sequence?

- Comparing DNA/protein sequences for
 - Similarity
 - Homology
- Prediction of function
- Construction of phylogeny Shotgun assembly
 - End-space-free alignment / overlap alignment
- Finding motifs

Sequence Alignment

- Procedure of comparing to (Pairwise) or more (Multiple) sequences by searching for a series of individual characters that are in the same order in the sequence.

G	C	T	A	G	T	C	A	G	A	T	C	T	G	A	C	G	C	T	A
		T	G	G	T	C	A	C	A	T	C	T	G	C	C	G	C		

- **Definition**

Given two strings $x = x_1 x_2 \dots x_m$ and $y = y_1 y_2 \dots y_n$, an alignment is an assignment of gaps to positions $0 \dots M$ in x and $0 \dots N$ in y , so as to line up each letter in one sequence with either a letter or a gap in the other sequence.

A Simple Alignment

- Let us try to align two short nucleotide sequences:
-AATCTATA and AAGATA
- Without considering any gaps (insertions/deletions) there are 3 possible ways to align these sequences

A A T C T A T A
A A G A T A

A A T C T A T A
A A G A T A

A A T C T A T A
A A G A T A

- Which one is better?

What is a Good Alignment

A G G C T A G T T , A G C G A A G T T

A G G C T A G T T -
A G C G A A G T T T

Matches = 6
Mismatches = 3
Gap = 1

A G G C T A - G T T -
A G - C G A A G T T T

Matches = 7
Mismatches = 1
Gaps = 3

A G G C - T - G T T -
A G - C G - A A G T T

Matches = 7
Mismatches = 0
Gaps = 5

Scoring the Alignments

- We need to have a scoring mechanism to evaluate alignments
 - match score
 - mismatch score
- We can have the total score as:

$$\sum_{i=1}^n \text{match or mismatch score at position } i$$

- For the simple example, assume a match score of 1 and a mismatch score of 0:

A A T C T A T A
A A G A T A

4

A A T C T A T A
A A G A T A

1

A A T C T A T A
A A G A T A

3

Simple Alignment with Gaps

- Considering gapped alignments vastly increases the number of possible alignments:

A	A	T	C	T	A	T	A
A	A	G	-	A	T	-	A

1

A	A	T	C	T	A	T	A
A	A	-	G	-	A	T	A

3

A	A	T	C	T	A	T	A
A	A	-	-	G	A	T	A

3

- If gap penalty is -1, what will be the new scores?

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Sequence Edits

Lets do some sequence edits and view scores

Sequence Edits

Three types of sequence edits

- 1 Mutations
- 2 Insertions
- 3 Deletions

Mutations

A	G	G	C	C	T	C
A	G	G	A	C	T	C

Insertions

A	G	G	C	C	T	C	
A	G	G	G	C	C	T	C

Deletions

A	G	G	C	C	T	C
A	G	G	.	C	T	C

Scoring Function

Match: +m

Mismatch: -s

Gap: -d

Score $F = (\# \text{ matches}) \times m - (\# \text{ mismatches}) \times s - (\# \text{ gaps}) \times d$

Score Matrix

- Assign scores to each pair of symbol
 - Higher score means more similarity.

Score Matrix

- DNA
 - Match = +1
 - Mismatch = -3
 - Gap penalty = -5
 - Gap extension penalty = -2
- Protein sequences
 - Blossum62 matrix
 - Gap open penalty = -11
 - Gap extension penalty = -1

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- How do we compute the best alignment?

Alignment is Additive

- Observation:

The score of aligning $x_1 \dots x_M$ and $y_1 \dots y_N$ is additive

Say that $x_1 \dots x_i$ $x_{i+1} \dots x_M$
aligns to $y_1 \dots y_j$ $y_{j+1} \dots y_N$

The two scores add up:

$$F(x[1 : M], y[1 : N]) = F(x[1 : i], y[1 : j]) + F(x[i + 1 : M], y[j + 1 : N])$$

Types of Alignment

- Global
 - Strings of similar size
 - Genes with a similar structure
 - Larger regions with a preserved order (syntenic regions)
- Local
 - Finding similar regions among:
 - Dissimilar regions
 - Sequences of different lengths

Dynamic Programming

- Instead of evaluating every possible alignment, we can create a table of partial scores by breaking the alignment problem into subproblems.
- Consider two sequences CACGA and CGA
 - we have three possibilities for the first position of the alignment

First Position	Score	Remaining seqs
C C	+1	ACGA GA
- C	-1	CACGA GA
C -	-1	ACGA CGA

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Local Sequence Alignment

- Suppose we have a long DNA sequence (eg 4000 bp) and we want to compare it with the complete yeast genome (12.5Mbp)
- What if only a portion of our query, say 200 bp length, has strong similarity to a gene in yeast.

Local Sequence Alignment Problem

- Given two strings

$$x = x_1 \dots x_M$$

$$y = y_1 \dots y_N$$

Find substring y' , x' whose similarity (optimal global alignment value) is maximum.

$x = \text{aaaaccccccggggta}$

$y = \text{ttcccggggaaccaacc}$

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Smith & Waterman Algorithm

- $F(i, j)$ = optimal local similarity among suffixes $A(1 : i)$ and $B(1 : j)$
- Recurrence relation
 - $F(i, 0) = 0$
 - $F(0, j) = 0$
 - $F(i, j) = \max[0, F(i, j - 1) + s(-, B(j)), F(i - 1, j) + s(A(i), -), F(i - 1, j - 1) + s(A(i), B(j))]$

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Example

Q = E Q L L K A L E F K L P = K V L E F G Y

Linear gap model

Gap= -1

Match= 4

Mismatch= -2

	-	E	Q	L	L	K	A	L	E	F	K	L
-												
K												
V												
L												
E												
F												
G												
Y												

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Algorithm

$F(i,0) = 0$

$F(0,j) = 0$

	-	E	Q	L	L	K	A	L	E	F	K	L
-	0	0	0	0	0	0	0	0	0	0	0	0
K	0											
V	0											
L	0											
E	0											
F	0											
G	0											
Y	0											

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$$F(i, j) = \max [0, F(i, j-1) + s(-, Q(j)), F(i-1, j) + s(P(i), -), F(i-1, j-1) + s(P(i), Q(j))]$$

	-	E	Q	L	L	K	A	L	E	F	K	L
-	0	0	0	0	0	0	0	0	0	0	0	0
K	0	0										
V	0											
L	0											
E	0											
F	0											
G	0											
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	-	E	Q	L	L	K	A	L	E	F	K	L
-	0	0	0	0	0	0	0	0	0	0	0	0
K	0	0	0									
V	0											
L	0											
E	0											
F	0											
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	-	E	Q	L	L	K	A	L	E	F	K	L
-	0	0	0	0	0	0	0	0	0	0	0	0
K	0	0	0	0								
V	0											
L	0											
E	0											
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G	0											
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	-	E	Q	L	L	K	A	L	E	F	K	L
-	0	0	0	0	0	0	0	0	0	0	0	0
K	0	0	0	0	0							
V	0											
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	-	E	Q	L	L	K	A	L	E	F	K	L
-	0	0	0	0	0	0	0	0	0	0	0	0
K	0	0	0	0	0	4						
V	0											
L	0											
E	0											
F	0											
G	0											
Y	0											

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	-	E	Q	L	L	K	A	L	E	F	K	L
-	0	0	0	0	0	0	0	0	0	0	0	0
K	0	0	0	0	0	4	3	2	1	0	4	3
V	0											
L	0											
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	-	E	Q	L	L	K	A	L	E	F	K	L
-	0	0	0	0	0	0	0	0	0	0	0	0
K	0	0	0	0	0	4	3	2	1	0	4	3
V	0	0	0	0	0	3	2	1	0	0	3	2
L	0	0	0	4	4	3	2	6	5	4	3	7
E	0	4	3	3	3	2	1	5	10	9	8	7
F	0	3	2	2	2	1	0	4	9	14	13	12
G	0	2	1	1	1	0	0	3	8	13	12	11
Y	0	1	0	0	0	0	0	2	7	12	11	10

Example

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Alignment

Q: F

P: F

	-	E	Q	L	L	K	A	L	E	F	K	L
-	0	0	0	0	0	0	0	0	0	0	0	0
K	0	0	0	0	0	4	3	2	1	0	4	3
V	0	0	0	0	0	3	2	1	0	0	3	2
L	0	0	0	4	4	3	2	6	5	4	3	7
E	0	4	3	3	3	2	1	5	10	9	8	7
F	0	3	2	2	2	1	0	4	9	14	13	12
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Alignment

Q: E F

P: E F

	-	E	Q	L	L	K	A	L	E	F	K	L
-	0	0	0	0	0	0	0	0	0	0	0	0
K	0	0	0	0	0	4	3	2	1	0	4	3
V	0	0	0	0	0	3	2	1	0	0	3	2
L	0	0	0	4	4	3	2	6	5	4	3	7
E	0	4	3	3	3	2	1	5	10	9	8	7
F	0	3	2	2	2	1	0	4	9	14	13	12
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Q = E Q L L K A L E F K L P = K V L E F G Y

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Match= 4

Mismatch= -2

Alignment

Q: . . . L E F

P: . . . L E F

	-	E	Q	L	L	K	A	L	E	F	K	L
-	0	0	0	0	0	0	0	0	0	0	0	0
K	0	0	0	0	0	4	3	2	1	0	4	3
V	0	0	0	0	0	3	2	1	0	0	3	2
L	0	0	0	4	4	3	2	6	5	4	3	7
E	0	4	3	3	3	2	1	5	10	9	8	7
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Q: . . - L E F

P: . . V L E F

	-	E	Q	L	L	K	A	L	E	F	K	L
-	0	0	0	0	0	0	0	0	0	0	0	0
K	0	0	0	0	0	4	3	2	1	0	4	3
V	0	0	0	0	0	3	2	1	0	0	3	2
L	0	0	0	4	4	3	2	6	5	4	3	7
E	0	4	3	3	3	2	1	5	10	9	8	7
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Q: . A - L E F

P: . - V L E F

	-	E	Q	L	L	K	A	L	E	F	K	L
-	0	0	0	0	0	0	0	0	0	0	0	0
K	0	0	0	0	0	4	3	2	1	0	4	3
V	0	0	0	0	0	3	2	1	0	0	3	2
L	0	0	0	4	4	3	2	6	5	4	3	7
E	0	4	3	3	3	2	1	5	10	9	8	7
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Q: K A - L E F

P: K - V L E F

	-	E	Q	L	L	K	A	L	E	F	K	L
-	0	0	0	0	0	0	0	0	0	0	0	0
K	0	0	0	0	0	4	3	2	1	0	4	3
V	0	0	0	0	0	3	2	1	0	0	3	2
L	0	0	0	4	4	3	2	6	5	4	3	7
E	0	4	3	3	3	2	1	5	10	9	8	7
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Q: K A - L E F

P: K - V L E F

	-	E	Q	L	L	K	A	L	E	F	K	L
-	0	0	0	0	0	0	0	0	0	0	0	0
K	0	0	0	0	0	4	3	2	1	0	4	3
V	0	0	0	0	0	3	2	1	0	0	3	2
L	0	0	0	4	4	3	2	6	5	4	3	7
E	0	4	3	3	3	2	1	5	10	9	8	7
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Alignment

Q: K - A L E F

P: K V - L E F

	-	E	Q	L	L	K	A	L	E	F	K	L
-	0	0	0	0	0	0	0	0	0	0	0	0
K	0	0	0	0	0	4	3	2	1	0	4	3
V	0	0	0	0	0	3	2	1	0	0	3	2
L	0	0	0	4	4	3	2	6	5	4	3	7
E	0	4	3	3	3	2	1	5	10	9	8	7
F	0	3	2	2	2	1	0	4	9	14	13	12
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Q: K A L E F

P: K V L E F

	-	E	Q	L	L	K	A	L	E	F	K	L
-	0	0	0	0	0	0	0	0	0	0	0	0
K	0	0	0	0	0	4	3	2	1	0	4	3
V	0	0	0	0	0	3	2	1	0	0	3	2
L	0	0	0	4	4	3	2	6	5	4	3	7
E	0	4	3	3	3	2	1	5	10	9	8	7
F	0	3	2	2	2	1	0	4	9	14	13	12
G	0	2	1	1	1	0	0	3	8	13	12	11
Y	0	1	0	0	0	0	0	2	7	12	11	10

Thank you

Stay Home, Stay Safe