

CHAPTER 5: PAIRWISE SEQUENCE ALIGNMENT AND DATABASE SEARCHING

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Figures from: Zvelebil, M. J., & Baum, J. O. (2008). *Understanding bioinformatics*. Garland Science.

Alignment algorithms (preview)

- Needleman-Wunsch (1970) and variations:
 - for aligning two sequences
 - uses dynamic programming to "consider" all possible alignments (10^{600} for two sequences of length 1000!)
- FASTA: uses a heuristic method for efficient searches (though not guaranteed to find the optimal solution)
 - Creates dictionary of k -tuples for the query sequence which is checked against sequences in the database
 - A local alignment algorithm is used to complete the alignment
- BLAST (Basic Local Alignment Search Tool): also fast and uses a heuristic
 - Finds short matches (which do not have to be perfect)
 - Then uses local alignment to complete the alignment

Needleman and Wunsch Dynamic Programming method

- Dynamic programming method
 - A problem is broken down into smaller sub-problems that can be repeatedly (recursively) solved
- Consider the following alignment of the sequences

x = THISLINE and y = ISALIGNED

T	H	I	S	-	L	I	-	N	E	-
-	-	I	S	A	L	I	G	N	E	D

Dynamic Programming Concept

The alignment below is the optimal global alignment, with BLOSUM-62 matrix, and linear gap penalty of 4:

A key observation is that the total alignment score is the sum of partial alignment scores:

Score:	-4	-4	+4	+4	-4	+4	+4	-4	+6	+5	-4
	T	H	I	S	-	L	I	-	N	E	-
	-	-	I	S	A	L	I	G	N	E	D
Score:			0			0			7		

For any part of the alignment: The score of the global alignment from positions $1 \rightarrow L$ is the sum of the partial alignment scores from positions $1 \rightarrow u$, $u+1 \rightarrow v$, and $v+1 \rightarrow L$

Dynamic programming, key idea

The optimal alignment between sequences **x** and **y** can end in 3 possible ways (example for alignment between **x** = THIS and **y** = IS is shown):

1. An alignment between the last character of **x** and last character of **y**

Optimal alignment of
THI with I

+ S
S

2. A gap at the end of **x** aligned to the last character of **y**

Optimal alignment of
THIS with I

+ -
S

3. A gap at the end of **y** aligned to the last character of **x**


Optimal alignment of
THI with IS

+ S
-

Three possibilities for optimal alignment ending btwn THIS and IS

Optimal alignment of THI with I




THI		S
--I	+	S
-4	+	4
		
0		

This possibility has the highest score, so it is the optimal alignment between THIS and IS


Optimal alignment of THIS with I



THIS		-
--I-	+	S
-8	+	-4
		
-12		

Optimal alignment of THI with IS



THI		S
IS-	+	-
-6	+	-4
		
-10		

Dynamic Programming Algorithm

Let $S_{i,j}$ be the score of the optimal alignment of all characters up to x_i of sequence \mathbf{x} and y_j of sequence \mathbf{y} .

Then there are three possibilities for the end of this alignment

$$\begin{array}{|c|} \hline \begin{array}{cc} \cdots & x_{i-1} & x_i \\ \cdots & y_{j-1} & y_j \end{array} \\ \hline \end{array}$$

$S_{i-1,j-1}$

$$\begin{array}{|c|} \hline \begin{array}{cc} \cdots & x_i & - \\ \cdots & y_{j-1} & y_j \end{array} \\ \hline \end{array}$$

$S_{i,j-1}$

$$\begin{array}{|c|} \hline \begin{array}{cc} \cdots & x_{i-1} & x_i \\ \cdots & y_j & - \end{array} \\ \hline \end{array}$$

$S_{i-1,j}$

The optimal alignment score $S_{i,j}$ is the maximum of the following

$$S_{i-1,j-1} + s(x_i, y_j)$$

$$S_{i,j-1} + g$$

$$S_{i-1,j} + g$$

where $s(x_i, y_j)$ is the substitution (or match/mismatch score) for character x_i aligned with y_j , and g is a constant gap penalty


Example:


x = THISLINE and y = ISALIGNED


T	H	I	S	-	L	I	-	N	E	-
-	-	I	S	A	L	I	G	N	E	D

Assume a constant (linear) gap penalty $g = 4$, and $s(x_i, y_j)$ calculated using the BLOSUM-62 scoring matrix.

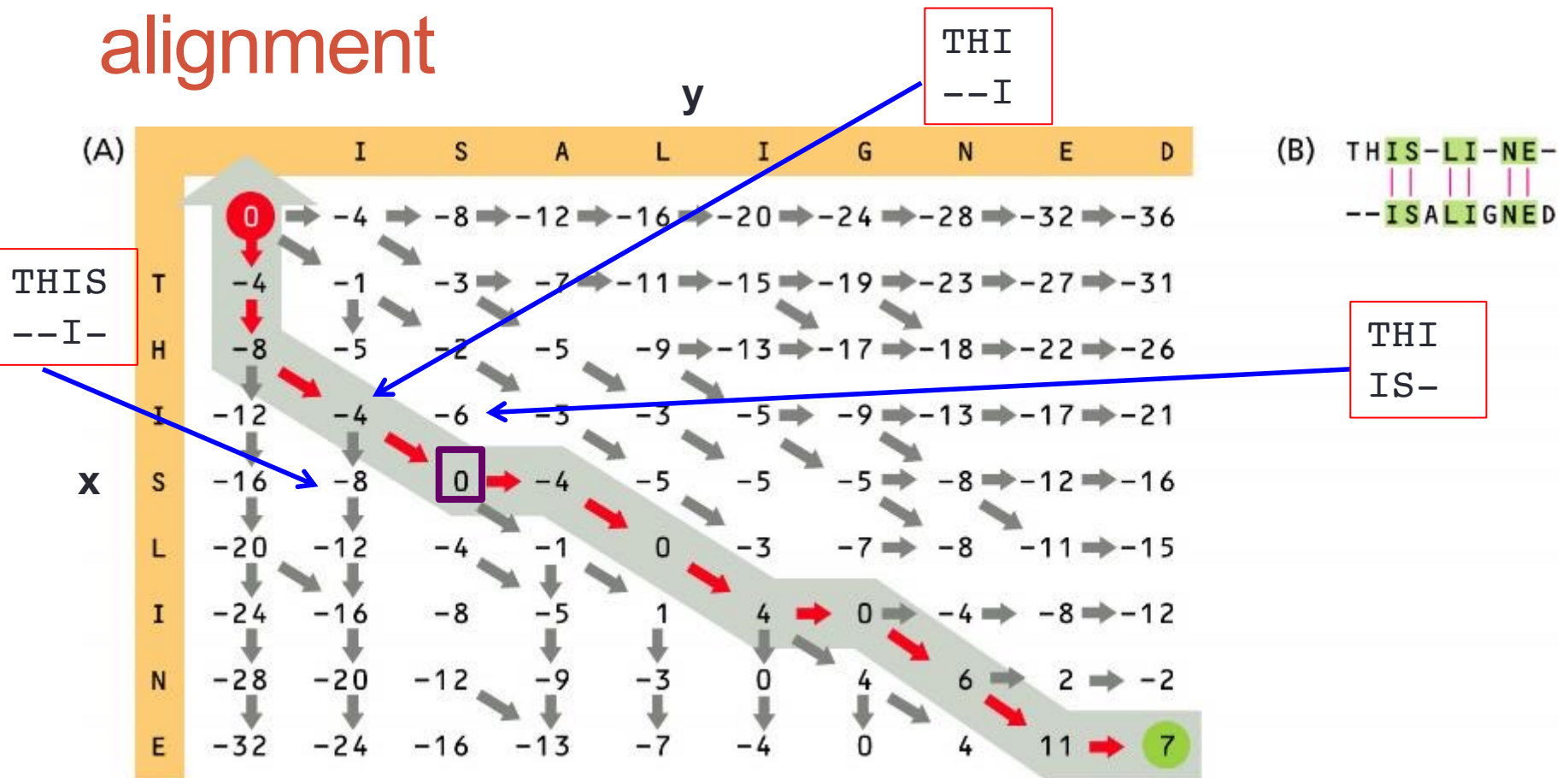
$S_{4,2}$ is the optimal score for aligning THIS with IS and is the maximum of

THI	+	S
--I	+	S
-4	+	4
		
0		

THIS	+	-
--I-	+	S
-8	+	-4
		
-12		

THI	+	S
IS-	+	-
-6	+	-4
		
-10		

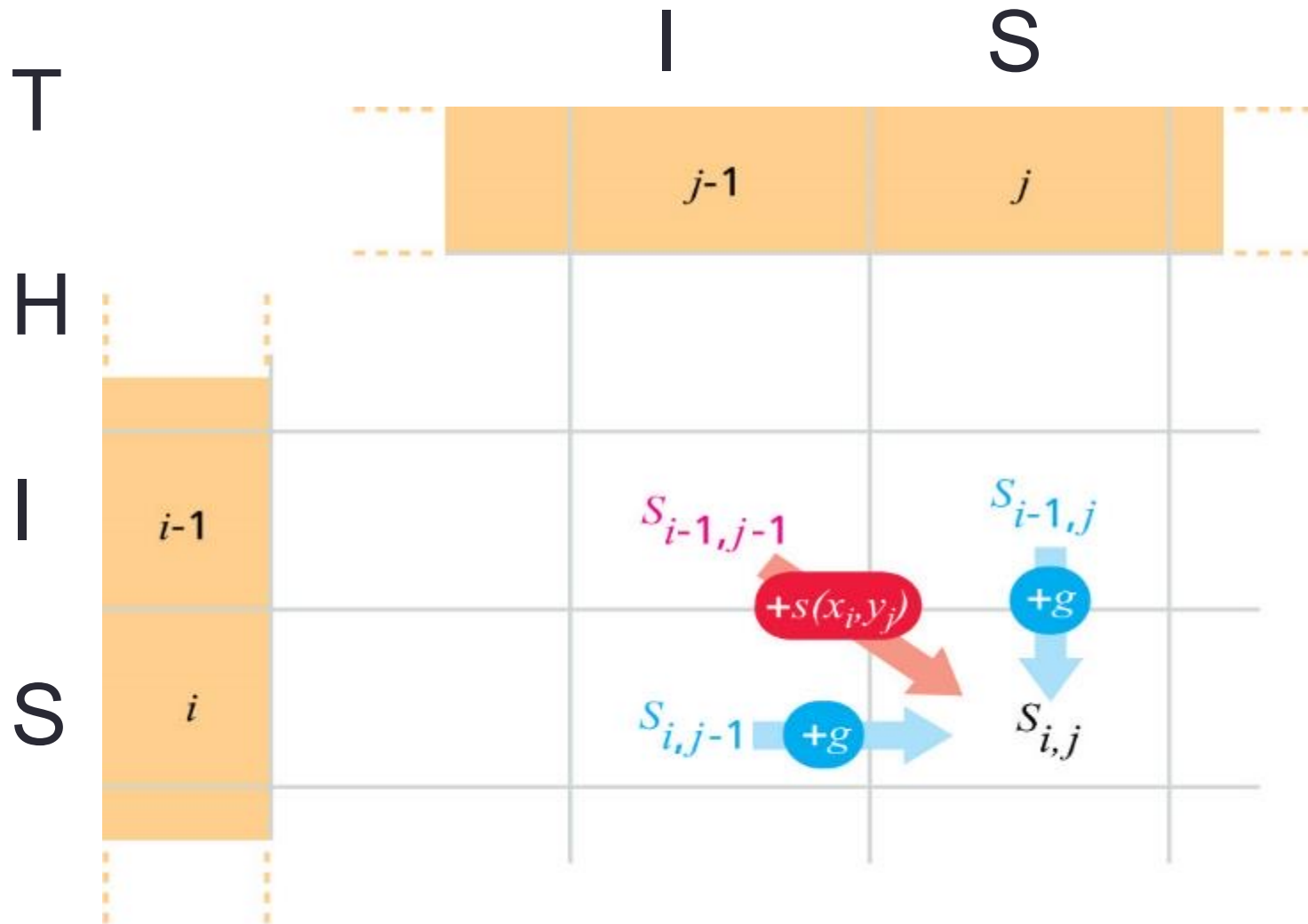
Dynamic programming matrix for global alignment



$S_{i,j}$ is the score of the optimal alignment of all characters up to x_i of sequence **x** and y_j of sequence **y**.

The score of the optimal alignment of THIS with IS is $S_{4,2} = 0$.

Dynamic programming matrix illustrating possible optimal alignments for subsequences x_1, \dots, x_i and y_1, \dots, y_j



Algorithm for finding the optimal global alignment

- For two sequences, x_1, \dots, x_m and y_1, \dots, y_n
- Construct an $(m+1)$ by $(n+1)$ matrix (starting with element $S_{0,0}$ at the top left)
- For each i , the element $S_{i,0}$ corresponds to the alignment

$$\begin{array}{cccc} x_1 & x_2 & \dots & x_i \\ - & - & \dots & - \end{array}$$

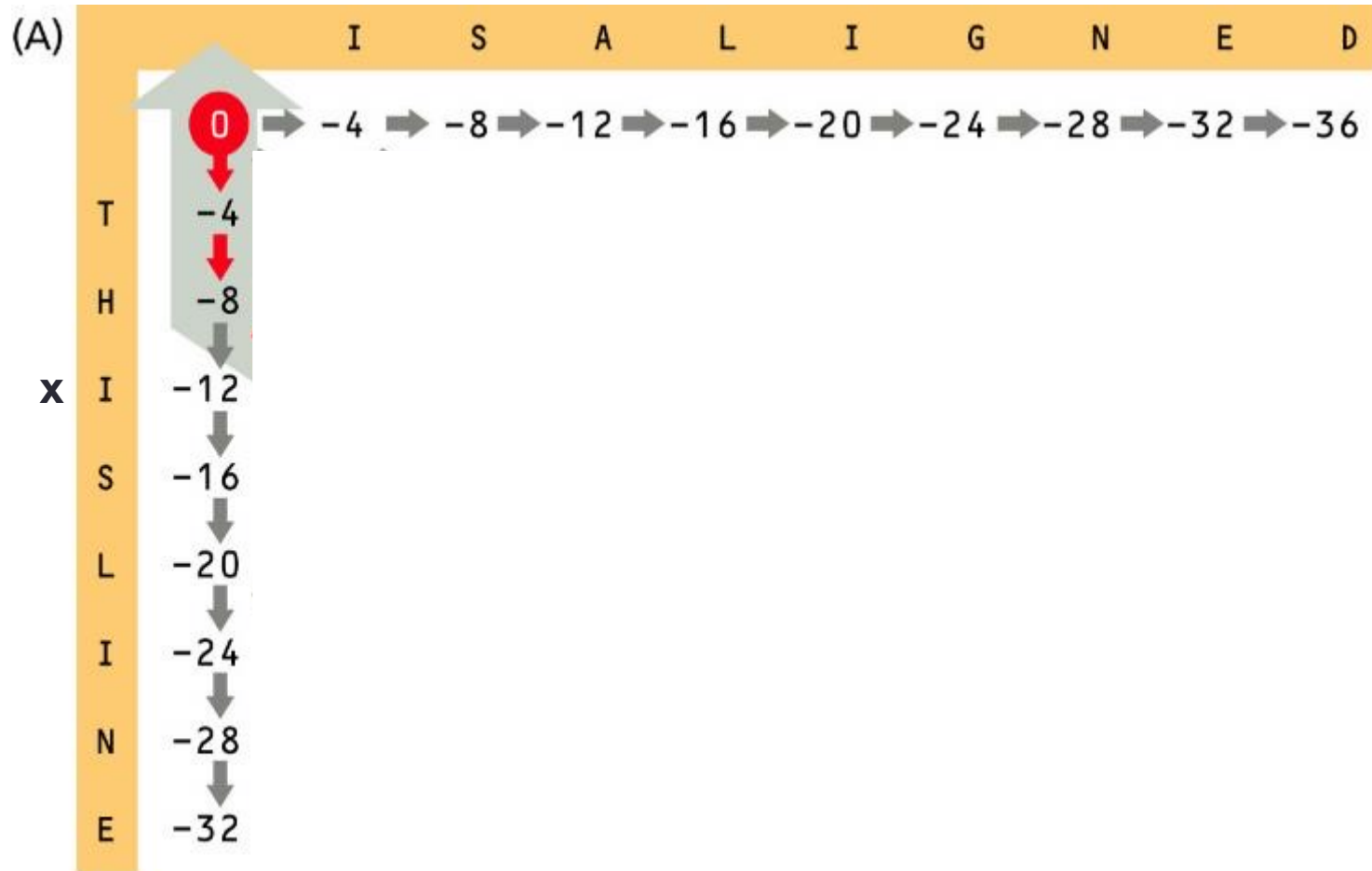
For each j , the element $S_{0,j}$ corresponds to the alignment

$$\begin{array}{cccc} - & - & \dots & - \\ y_1 & y_2 & \dots & y_i \end{array}$$

Fill in the matrix for all $S_{i,0}$ and $S_{0,j}$ appropriately

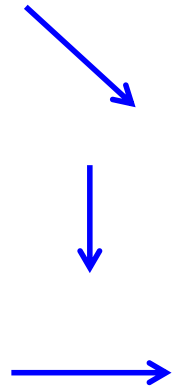
Assignment of $S_{i,0}$ and $S_{0,j}$ when a linear gap penalty of 4 is used

y



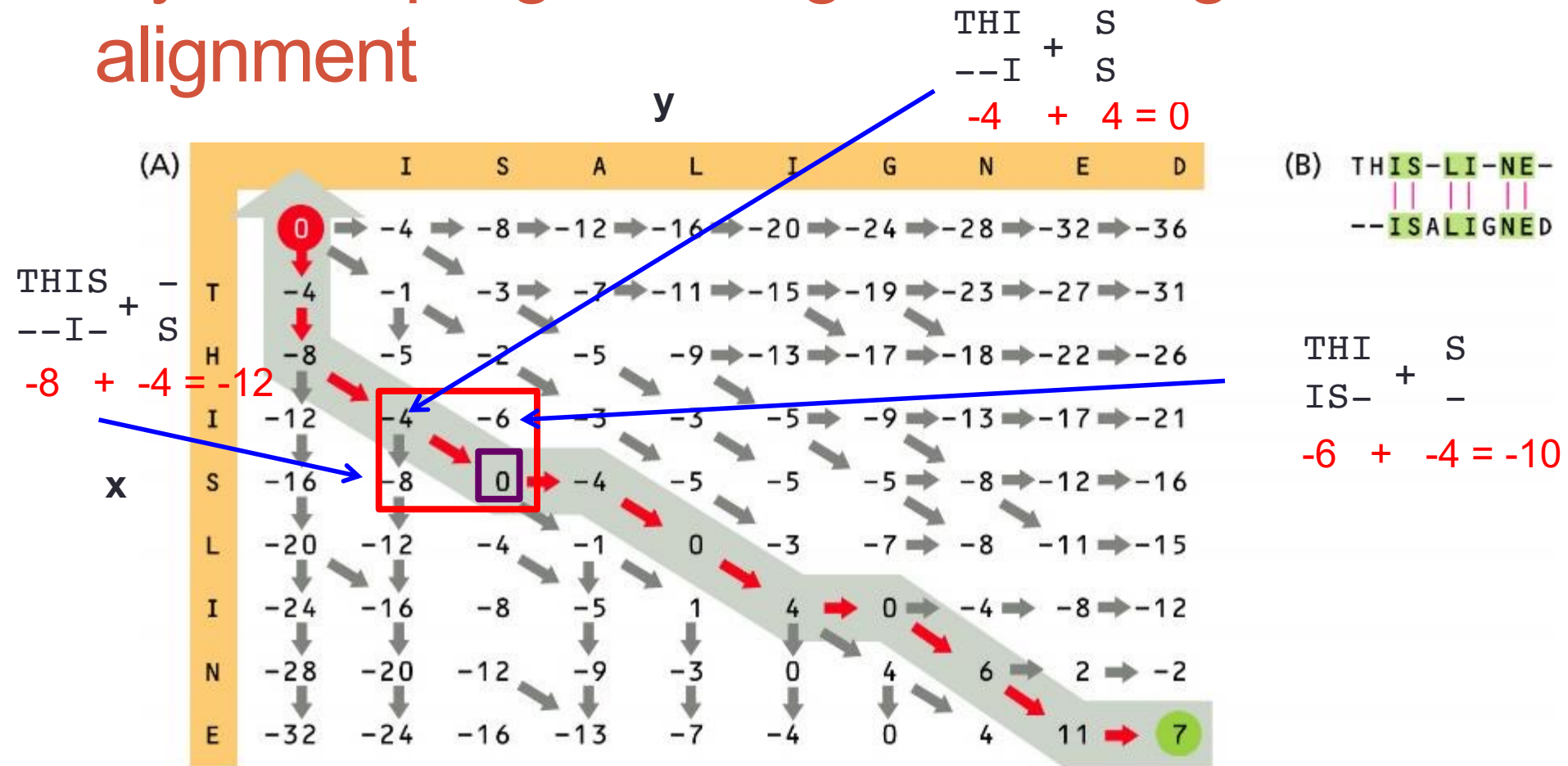
Algorithm for finding the optimal global alignment (con't)

- For $i = 1, \dots, m$ and $j = 1, \dots, n$

$$\text{set } S_{i,j} = \max \begin{cases} S_{i-1,j-1} + s(x_i, y_j) \\ S_{i-1,j} + g \\ S_{i,j-1} + g \end{cases}$$


and draw an arrow to $S_{i,j}$ from the cell where the score was derived ($S_{i-1,j-1}$, $S_{i-1,j}$, or $S_{i,j-1}$)

Dynamic programming matrix for global alignment



$S_{i,j}$ is the score of the optimal alignment of all characters up to x_i of sequence **x** and y_j of sequence **y**.

The score of the optimal alignment of **THIS** with **IS** is $S_{4,2} = 0$.

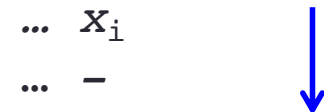
Algorithm for finding the optimal global alignment (con't)

- After the dynamic programming matrix is filled in, $S_{m,n}$ contains the score of the optimal global alignment
- A process called **traceback** is then used to recover the alignment itself, based on the path used to generate the optimal alignment score (based on the arrows), starting with $S_{m,n}$ and working backwards to $S_{0,0}$
- If the score $S_{i,j}$ was derived

- diagonally from $S_{i-1,j-1}$, then align x_i with y_j



- vertically from $S_{i-1,j}$, then align a gap with x_i



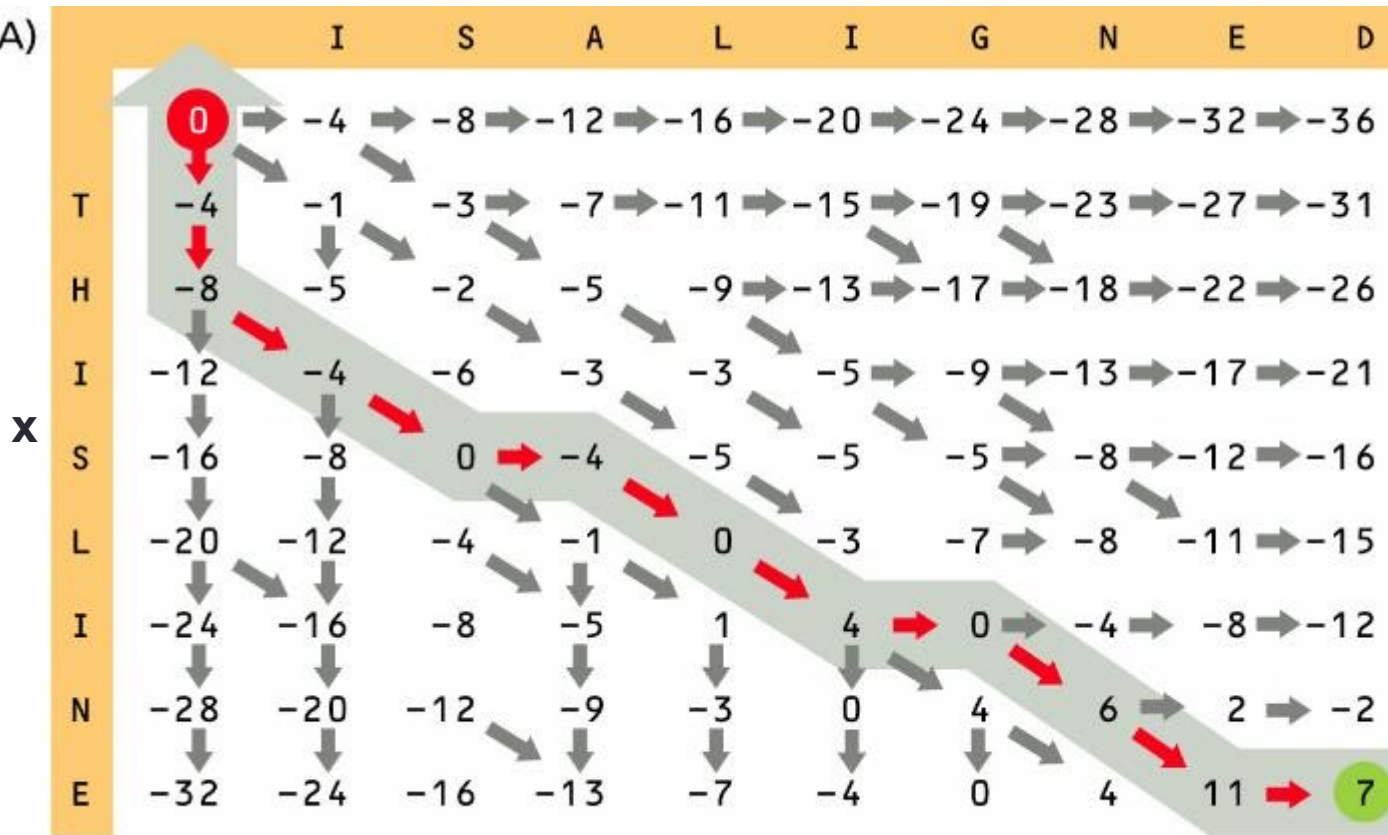
- horizontally from $S_{i,j-1}$, then align a gap with y_i



Global alignment: Dynamic programming matrix using linear gap penalty of 4

y

(A)



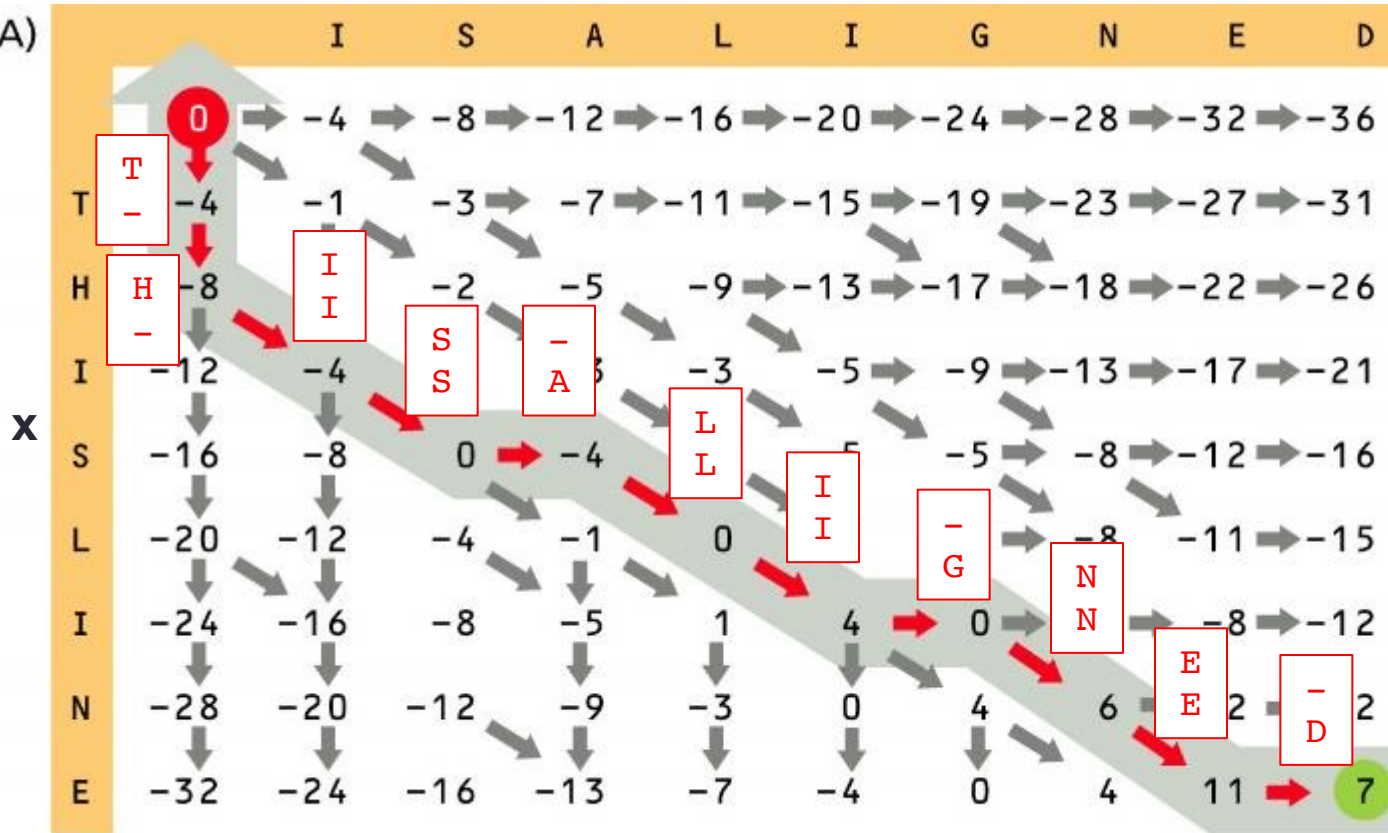
(B)

THIS-LI-NE-
--ISALIGNED

Global alignment: Dynamic programming matrix using linear gap penalty of 4

y

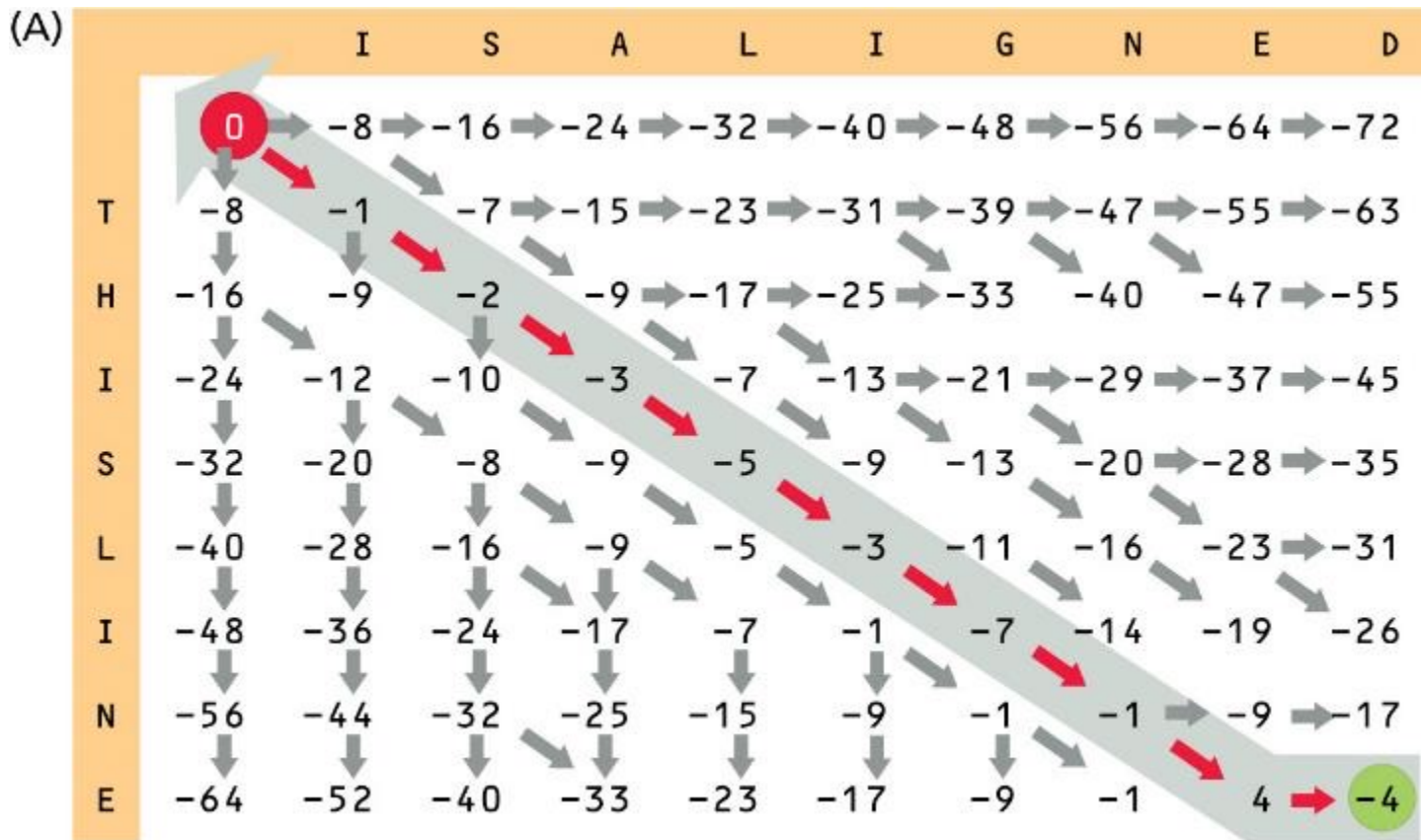
(A)



(B)

THIS-LI-NE-
--ISALIGNED

Global alignment: Dynamic Programming Matrix using linear gap penalty of 8



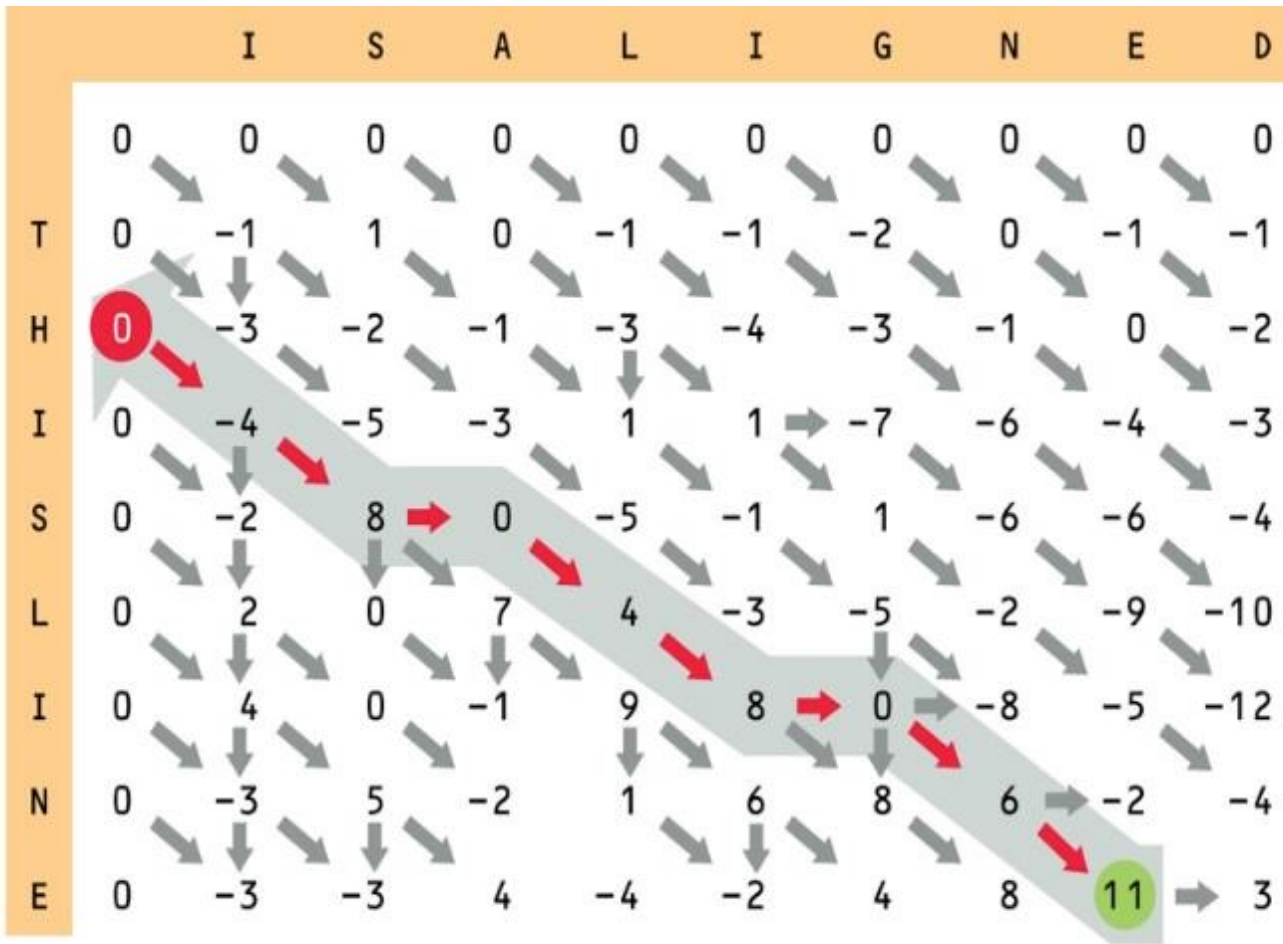
(B) THISLINE-
ISALIGNED

Modification of algorithm for semiglobal alignments

- A ***semiglobal alignment*** does not penalize gaps at the beginning or end of an alignment
- Appropriate for global alignments of sequences that are not the same length
- Modifications to algorithm for semiglobal alignment:
 - Set $S_{i,0}$ and $S_{0,j}$ to 0 for all i and j
 - Start the traceback from the highest scoring element in the bottom row or last column (but make sure to end the alignment with gaps as appropriate)

Semiglobal alignment: Dynamic Programming Matrix using a linear gap penalty of 8

(A)



(B)

THIS-LI-NE-
--ISALIGNED

Modification of algorithm for local alignments (1st proposed by Smith-Watterman)

- A **local alignment** aligns *regions* of two sequences, and will not necessarily span the length of each sequence
- Appropriate for identifying functional domains of a protein
- Modifications to algorithm for local alignment:

$$\bullet \text{ set } S_{i,j} = \max \left\{ \begin{array}{l} S_{i-1,j-1} + s(x_i, x_j) \\ S_{i-1,j} + g \\ S_{i,j-1} + g \\ 0 \end{array} \right.$$

- Assumes that the expected alignment score is negative for random sequences and is positive for similar sequences
- Traceback starts from highest scoring matrix element anywhere in the matrix and ends at 0

Local alignment: Dynamic Programming Matrix using a linear gap penalty of 8

