

# Dynamic Programming: String Comparison

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Algorithmic Toolbox  
Data Structures and Algorithms

# Cystic Fibrosis

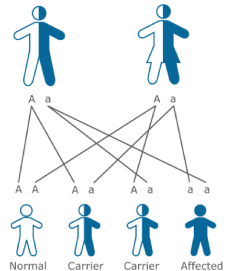
**Cystic fibrosis (CF):** An often fatal disease which affects the respiratory system and produces an abnormally large amount of mucus.

- Mucus is a slimy material that coats epithelial surfaces and is secreted into fluids such as saliva.



# Approximately 1 in 25 Humans Carry a Faulty CF Gene

- When BOTH parent carry a faulty gene, there is a 25% chance that their child will have cystic fibrosis.
- In the early 1980s biologists hypothesized that CF is caused by mutations in an unidentified gene.



# Where Is the Cystic Fibrosis Gene?

- In the late 1980s, biologists narrowed the search for the CF gene to a million nucleotide long region on chromosome 7.
- However, this regions contained many genes and it was unclear which of them was responsible for CF.



chromosome 7

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**Hint 1:** Cystic fibrosis involves sweet [secretion](#) with abnormally high sodium levels

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**Hint 1:** Cystic fibrosis involves sweat [secretion](#) with abnormally high sodium levels

**Hint 2:** By that time biologists already knew the sequences of some genes responsible for secretion, e.g., **ATP binding proteins** act as transport channels responsible for [secretion](#)

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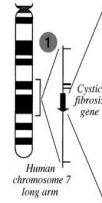
**Hint 1:** Cystic fibrosis involves sweat **secretion** with abnormally high sodium levels

**Hint 2:** By that time biologists already knew the sequences of some genes responsible for secretion, e.g., **ATP binding proteins** act as transport channels responsible for **secretion**

**Hint 3:** Should we search for genes in this region that are **similar** to known genes responsible for **secretion**?

# Identifying the Cystic Fibrosis Gene

- BINGO: One of the genes in this region was **similar** to **ATP binding proteins** that act as transport channels responsible for **secretion**.



**Hint 1:** Cystic fibrosis involves sweet **secretion** with abnormally high sodium levels

**Hint 2:** By that time biologists already knew the sequences of some genes responsible for secretion, e.g., **ATP binding proteins** act as transport channels responsible for **secretion**

**Hint 3:** Should we search for genes in this region that are **similar** to known genes responsible for **secretion**?



# Outline

- 1 The Alignment Game
- 2 Computing Edit Distance
- 3 Reconstructing an Optimal Alignment

# The Alignment Game

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

**Alignment game:** remove all symbols from two strings in such a way that the number of points is maximized:

Remove the 1st symbol from **both** strings:

1 point if the symbols match,

0 points if they don't match

Remove the 1st symbol from **one** of the strings:

0 points

# The Alignment Game

A	T	G	T	T	A	T	A
A	T	C	G	T	C	C	
+1							

# The Alignment Game

A	T	G	T	T	A	T	A
A	T	C	G	T	C	C	
+1	+1						

# The Alignment Game

A	T	-	G	T	T	A	T	A
A	T	C	G	T	C	C		
+1	+1							

# The Alignment Game

A	T	-	G	T	T	A	T	A
A	T	C	G	T	C	C		
+1	+1		+1					

# The Alignment Game

A	T	-	G	T	T	A	T	A
A	T	C	G	T	C	C		
+1	+1		+1	+1				

# The Alignment Game

A	T	-	G	T	T	A	T	A
A	T	C	G	T	-	C	C	
+1	+1		+1	+1				



# The Alignment Game

A	T	-	G	T	T	A	T	A
A	T	C	G	T	-	C	C	
+1	+1		+1	+1				

# The Alignment Game

A	T	-	G	T	T	A	T	A
A	T	C	G	T	-	C	-	C
+1	+1		+1	+1				

# The Alignment Game

A	T	-	G	T	T	A	T	A
A	T	C	G	T	-	C	-	C
+1	+1		+1	+1				

# The Alignment Game

A	T	-	G	T	T	A	T	A
A	T	C	G	T	-	C	-	C
+1	+1		+1	+1				=4

# Sequence Alignment

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

**Alignment** of two strings is a two-row matrix:  
1st row: symbols of the 1st string (in order)  
interspersed by “-”  
2nd row: symbols of the 2nd string (in order)  
interspersed by “-”

# Sequence Alignment

matches



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

# Sequence Alignment

matches

mismatches

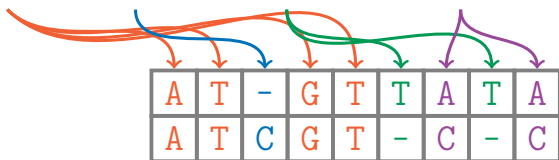


The diagram illustrates a sequence alignment between two DNA sequences. The top sequence is A T - G T T A T A and the bottom sequence is A T C G T - C - C. Arrows from the word 'matches' point to the first four columns (A-T, T-G, G-T, T-T), indicating identical base pairs. Arrows from the word 'mismatches' point to the last four columns (A-C, T-, A-, T-C), indicating differences between the sequences. The hyphen in the top sequence at the fifth column indicates a gap.

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

# Sequence Alignment

matches insertions deletions mismatches





# Alignment Score

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

Alignment score: premium for every **match** ( $+1$ ) and penalty for every **mismatch** ( $-\mu$ ), **indel** ( $-\sigma$ ).

# Alignment Score

A	T	-	G	T	T	A	T	A
A	T	C	G	T	-	C	-	C
+1	+1	-1	+1	+1	-1	+0	-1	+0

=1

Alignment score: premium for every **match** (+1) and penalty for every **mismatch** ( $-\mu$ ), **indel** ( $-\sigma$ ).

Example:  $\mu = 0$  and  $\sigma = 1$

# Alignment Score

$$\# \text{matches} - \mu \cdot \# \text{mismatches} - \sigma \cdot \# \text{indels}$$

## Optimal alignment

**Input:** Two strings, mismatch penalty  $\mu$ , and indel penalty  $\sigma$ .

**Output:** An alignment of the strings maximizing the score.

# Common Subsequence

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

Matches in an alignment of two strings  
(ATGT) form their common subsequence

# Longest common subsequence

Input: Two strings.

Output: A longest common subsequence of these strings.

# Longest common subsequence

**Input:** Two strings.

**Output:** A longest common subsequence of these strings.

Maximizing the length of a common subsequence corresponds to maximizing the score of an alignment with  $\mu = \sigma = 0$ .

# Edit distance

**Input:** Two strings.

**Output:** The minimum number of operations (insertions, deletions, and substitutions of symbols) to transform one string into another.

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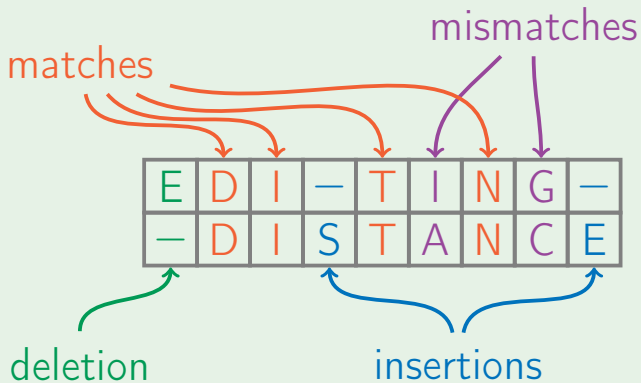
The minimum number of insertions, deletions and mismatches in an alignment of two strings (among all possible alignments).



# Example

E	D	I	-	T	I	N	G	-
-	D	I	S	T	A	N	C	E

# Example



E	D	I	-	T	I	N	G	-
-	D	I	S	T	A	N	C	E

E	D	I	-	T	I	N	G	-
-	D	I	S	T	A	N	C	E

the total number of symbols in two strings=

E	D	I	-	T	I	N	G	-
-	D	I	S	T	A	N	C	E

the total number of symbols in two strings=

+2·#matches

+2·#mismatches

+1·#insertions

+1·#deletions

E	D	I	—	T	I	N	G	—
—	D	I	S	T	A	N	C	E

the total number of symbols in two strings=

$$\begin{array}{rcl}
 & +2 \cdot \text{\#matches} & \\
 +2 \cdot \text{\#matches} & & -1 \cdot \text{\#insertions} \\
 +2 \cdot \text{\#mismatches} & = & -1 \cdot \text{\#deletions} \\
 +1 \cdot \text{\#insertions} & & +2 \cdot \text{\#mismatches} \\
 +1 \cdot \text{\#deletions} & & +2 \cdot \text{\#insertions} \\
 & & +2 \cdot \text{\#deletions}
 \end{array}$$

E	D	I	—	T	I	N	G	—
—	D	I	S	T	A	N	C	E

the total number of symbols in two strings=

$$\begin{array}{rcl}
 +2 \cdot \# \text{matches} & +2 \cdot \# \text{matches} & \\
 +2 \cdot \# \text{mismatches} & -1 \cdot \# \text{insertions} & \\
 +1 \cdot \# \text{insertions} & -1 \cdot \# \text{deletions} & \\
 +1 \cdot \# \text{deletions} & +2 \cdot \# \text{mismatches} & \\
 & +2 \cdot \# \text{insertions} & \\
 & +2 \cdot \# \text{deletions} & 
 \end{array}
 \left. \begin{array}{c} \\ \\ \\ \\ \\ \end{array} \right] \begin{array}{l} 2 \cdot \text{AlignmentScore} \\ (\mu = 0, \sigma = 1/2) \\ + \\ 2 \cdot \text{EditDistance} \end{array}$$

E	D	I	-	T	I	N	G	-
-	D	I	S	T	A	N	C	E

minimizing edit distance  
=  
maximizing alignment score



# Outline

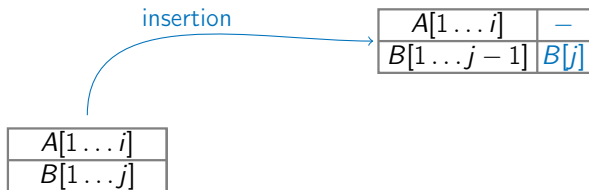
- 1 The Alignment Game
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$A[1 \dots i]$
$B[1 \dots j]$

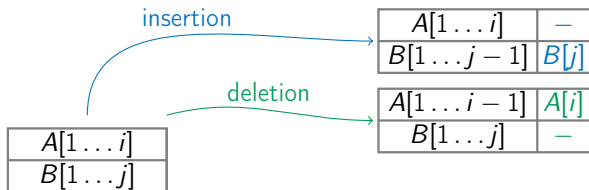
Given strings  $A[1 \dots n]$  and  $B[1 \dots m]$ , what is an optimal alignment (an alignment that results in minimum edit distance) of an  $i$ -prefix  $A[1 \dots i]$  of the first string and a  $j$ -prefix  $B[1 \dots j]$  of the second string?

$A[1 \dots i]$
$B[1 \dots j]$

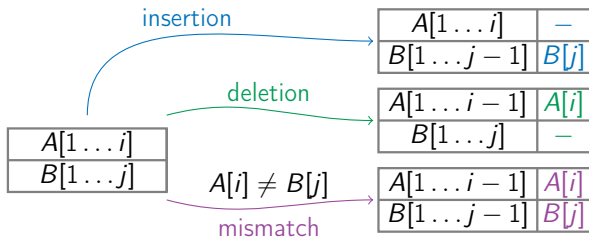
The last column of an optimal alignment is either



The last column of an optimal alignment is either  
an **insertion**,

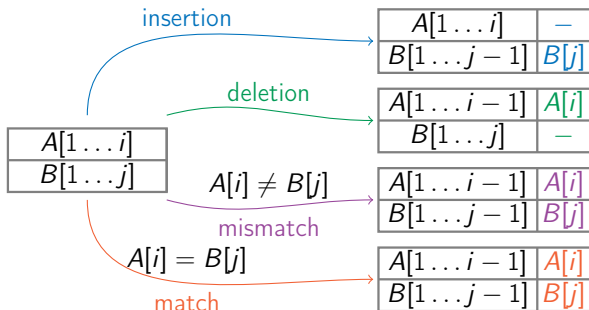


The last column of an optimal alignment is either  
an **insertion**,  
a **deletion**,



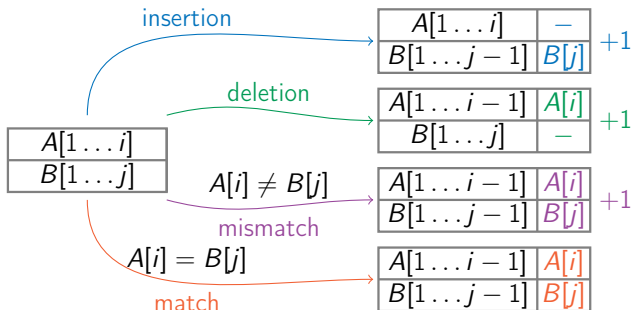
The last column of an optimal alignment is either

- an **insertion**,
- a **deletion**,
- a **mismatch**,



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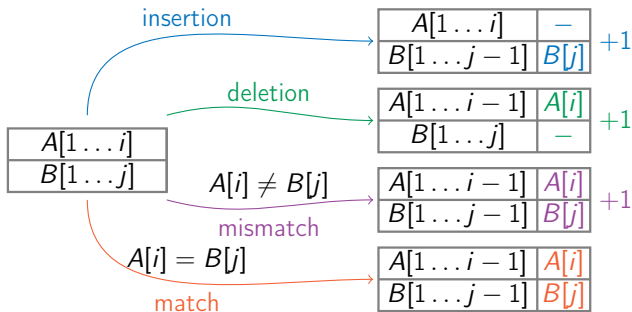
- an **insertion**,
- a **deletion**,
- a **mismatch**,
- or a **match**.



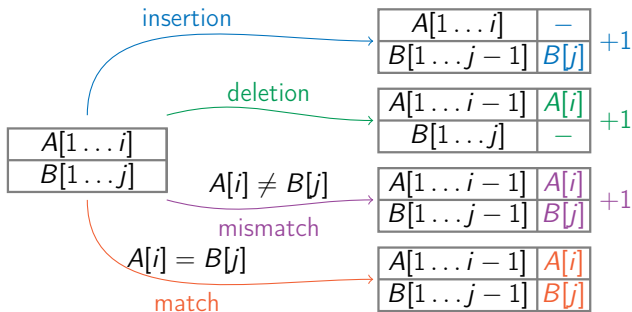
The last column of an optimal alignment is either  
an **insertion**,  
a **deletion**,  
a **mismatch**,  
or a **match**.

What is left (after the removal of the last column) is an **optimal** alignment of the corresponding two prefixes.





Let  $D(i, j)$  be the edit distance of an  $i$ -prefix  $A[1 \dots i]$  and a  $j$ -prefix  $B[1 \dots j]$ .



$$D(i, j) = \min \begin{cases} D(i, j-1) + 1 \\ D(i-1, j) + 1 \\ D(i-1, j-1) + 1 & \text{if } A[i] \neq B[j] \\ D(i-1, j-1) & \text{if } A[i] = B[j] \end{cases}$$

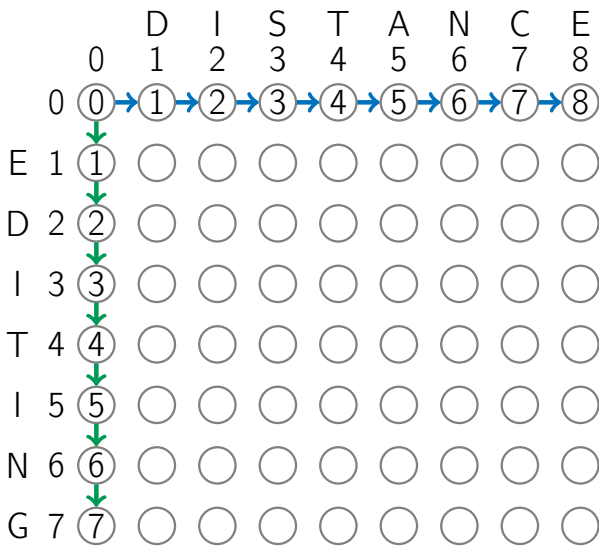
		<i>j</i>								
			D	I	S	T	A	N	C	E
		0	1	2	3	4	5	6	7	8
<i>i</i>	0	○	○	○	○	○	○	○	○	○
	E 1	○	○	○	○	○	○	○	○	○
	D 2	○	○	○	○	○	○	○	○	○
	I 3	○	○	○	○	○	○	○	○	○
	T 4	○	○	○	○	○	○	○	○	○
	I 5	○	○	○	○	○	○	○	○	○
	N 6	○	○	○	○	○	○	○	○	○
	G 7	○	○	○	○	○	○	○	○	○

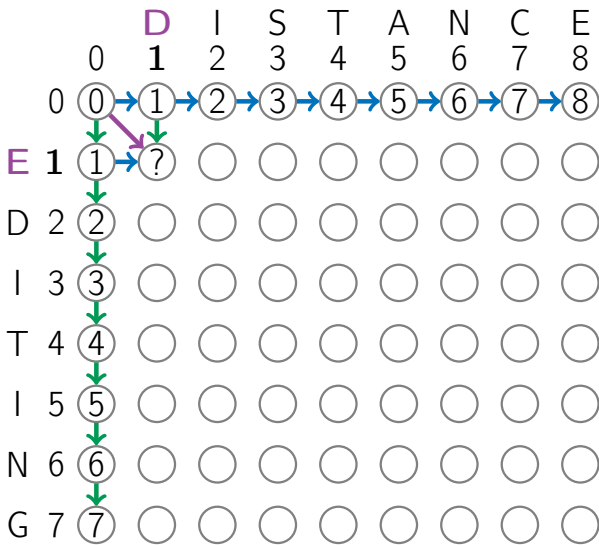
comparing  $A[1 \dots n] = \text{EDITING}$   
 and  $B[1 \dots m] = \text{DISTANCE}$

		<i>j</i>								
			D	I	S	T	A	N	C	E
		0	1	2	3	4	5	6	7	8
0		○	○	○	○	○	○	○	○	○
E	1	○	○	○	○	○	○	○	○	○
D	2	○	○	○	○	○	○	○	○	○
I	3	○	○	○	○	○	○	○	○	○
<i>i</i> T	4	○	○	○	○	● $D(i,j)$	○	○	○	○
I	5	○	○	○	○	○	○	○	○	○
N	6	○	○	○	○	○	○	○	○	○
G	7	○	○	○	○	○	○	○	○	○

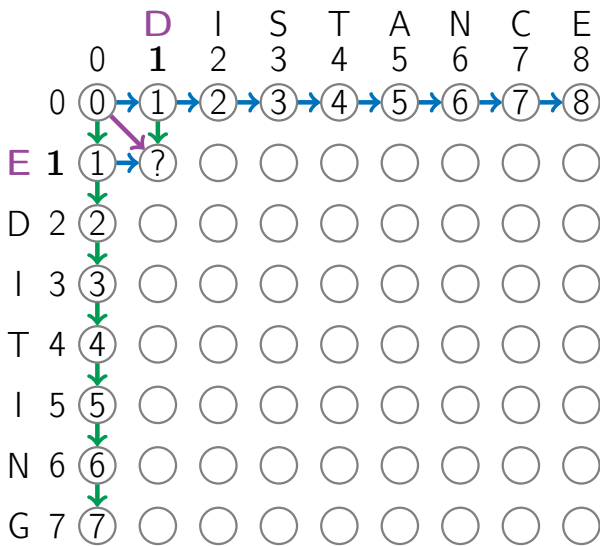
comparing  $A[1 \dots n] = \text{EDITING}$   
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		0	D 1	I 2	S 3	T 4	A 5	N 6	C 7	E 8
	0	0								
E	1	1								
D	2	2								
I	3	3								
T	4	4								
I	5	5								
N	6	6								
G	7	7								



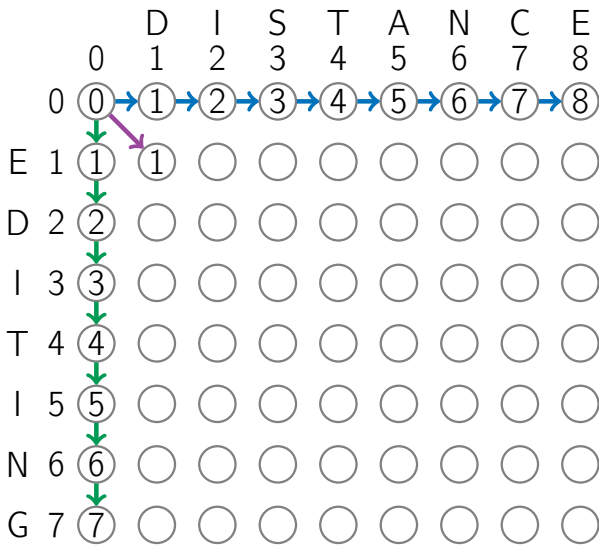


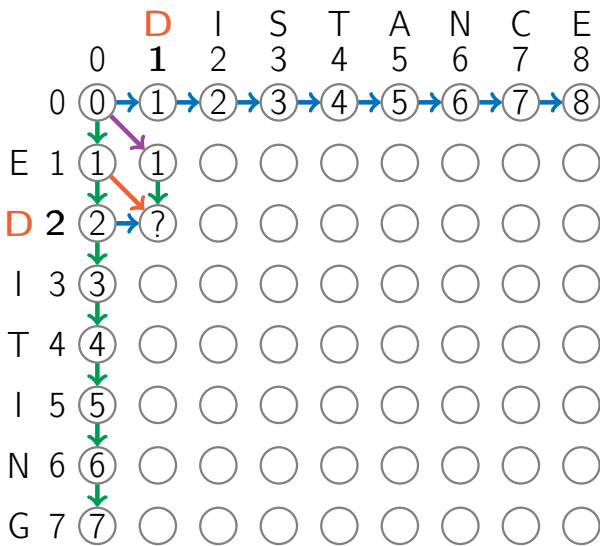
$$D(1, 1) = \min\{D(1, 0) + 1, D(0, 1) + 1, D(0, 0) + 1\}$$



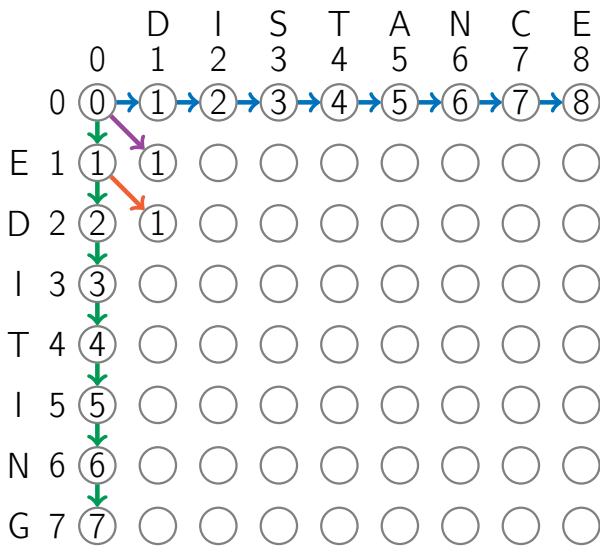
$$D(1, 1) = \min\{2, 2, 1\}$$

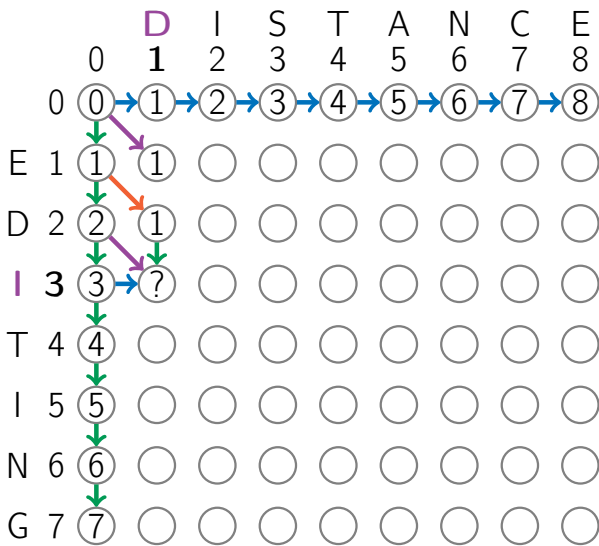




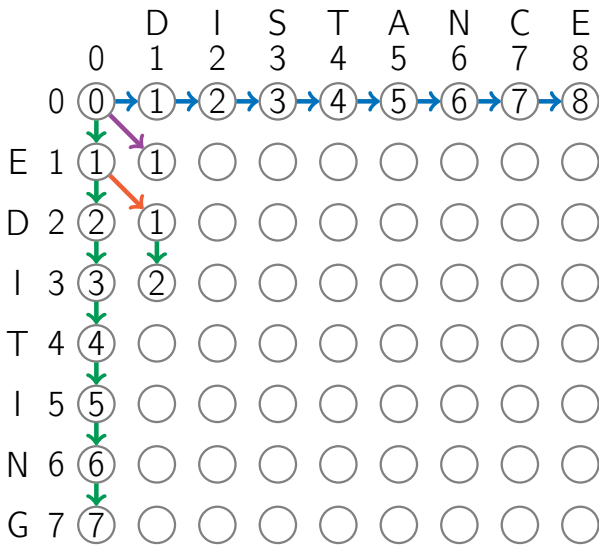


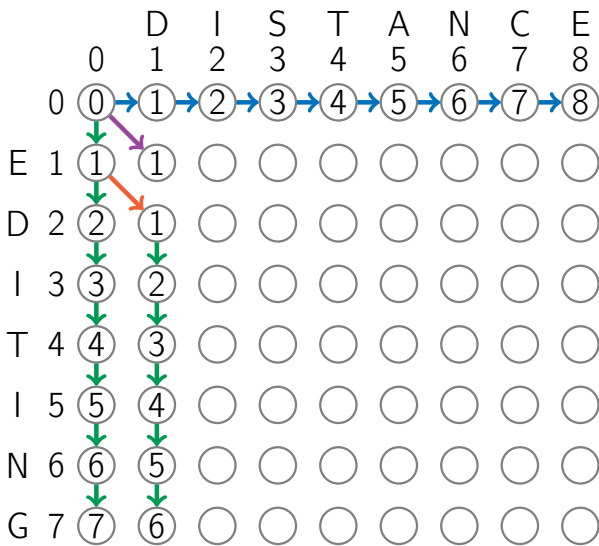
$$D(2, 1) = \min\{D(2, 0) + 1, D(1, 1) + 1, D(1, 0)\}$$

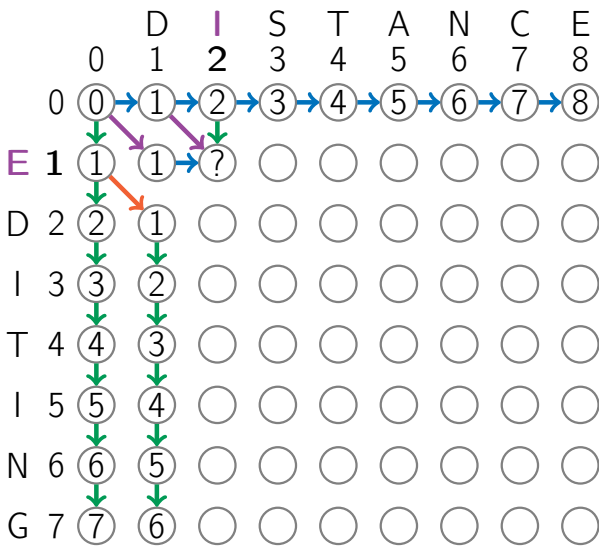




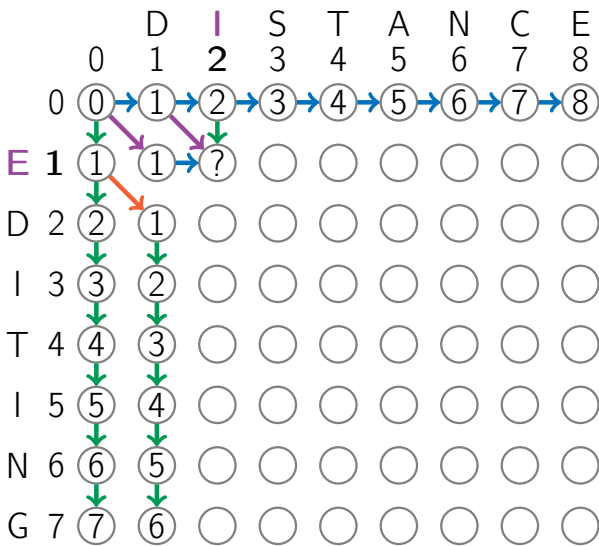
$$D(3, 1) = \min\{D(3, 0) + 1, D(2, 1) + 1, D(2, 0) + 1\}$$





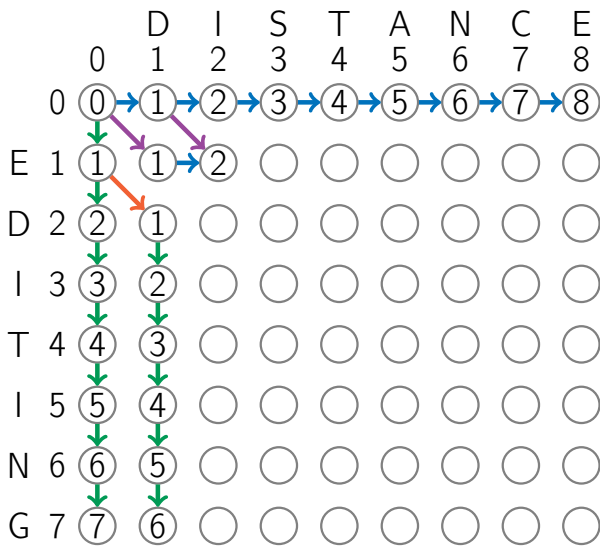


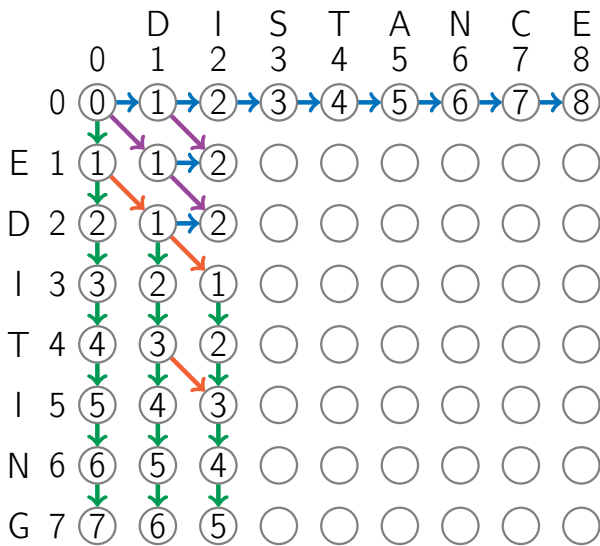
$$D(1, 2) = \min\{D(1, 1) + 1, D(0, 2) + 1, D(0, 1) + 1\}$$

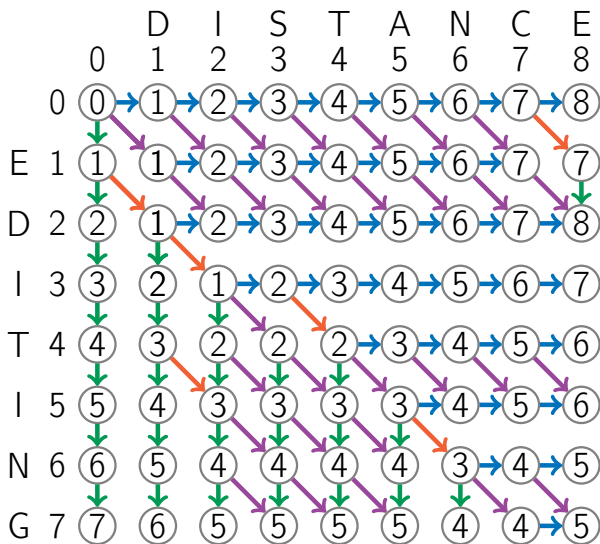


$$D(1, 1) = \min\{2, 3, 2\}$$









# EditDistance( $A[1 \dots n], B[1 \dots m]$ )

$D(i, 0) \leftarrow i$  and  $D(0, j) \leftarrow j$  for all  $i, j$

for  $j$  from 1 to  $m$ :

for  $i$  from 1 to  $n$ :

*insertion*  $\leftarrow D(i, j - 1) + 1$

*deletion*  $\leftarrow D(i - 1, j) + 1$

*match*  $\leftarrow D(i - 1, j - 1)$

*mismatch*  $\leftarrow D(i - 1, j - 1) + 1$

if  $A[i] = B[j]$ :

$D(i, j) \leftarrow \min(\textit{insertion}, \textit{deletion}, \textit{match})$

else:

$D(i, j) \leftarrow \min(\textit{insertion}, \textit{deletion}, \textit{mismatch})$

return  $D(n, m)$

# Outline

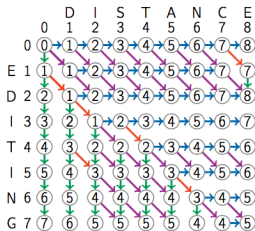
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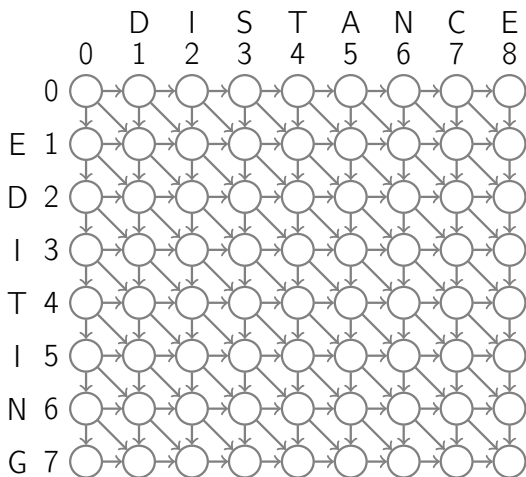
# Optimal Alignment

- We have computed the edit distance, but how can we find an optimal alignment?

# Optimal Alignment

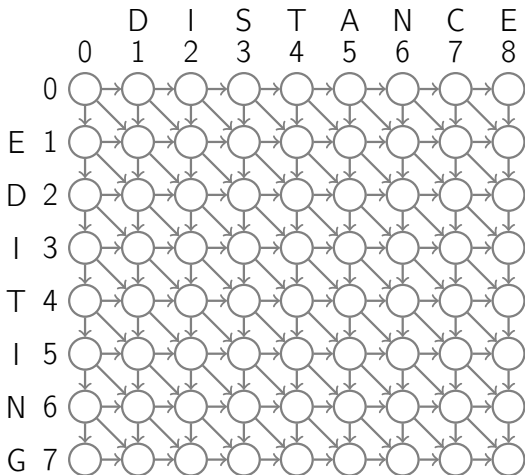
- We have computed the edit distance, but how can we find an optimal alignment?
- The backtracking pointers that we stored will help us to reconstruct an optimal alignment.



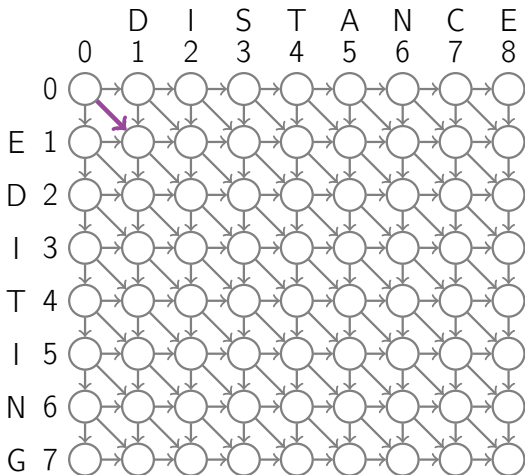




any path from  
 $(0, 0)$  to  $(i, j)$   
 spells an align-  
 ment of prefixes  
 $A[1 \dots i]$  and  
 $B[1 \dots j]$

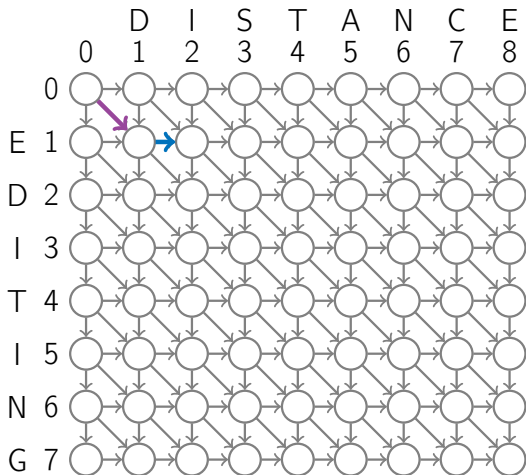


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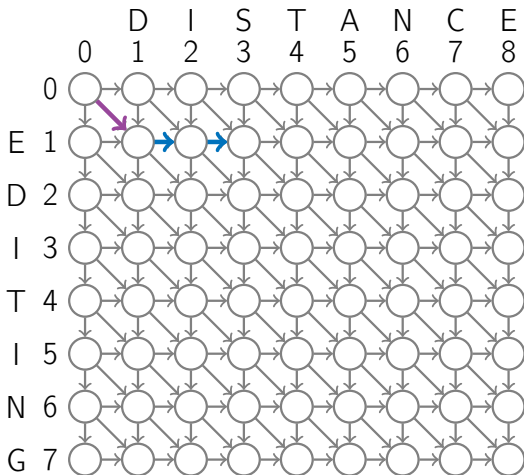


E
D

any path from  
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 $B[1 \dots j]$

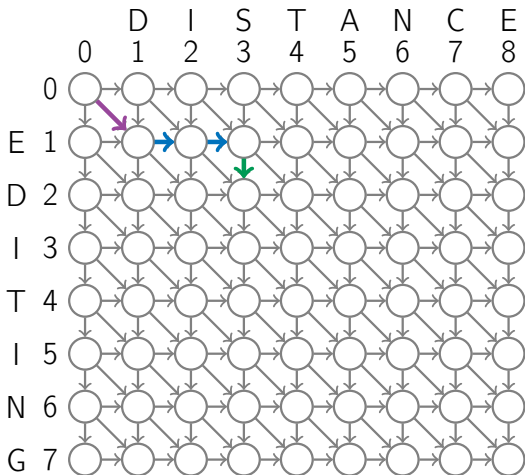


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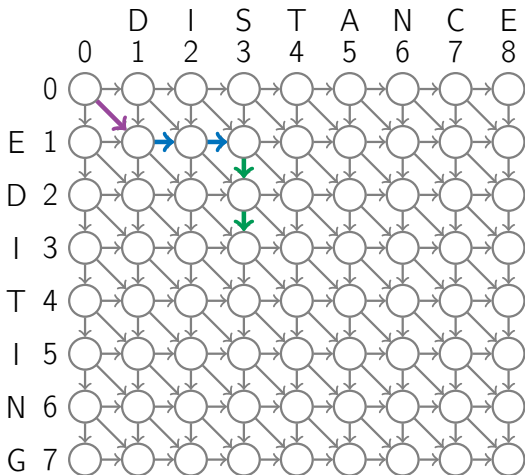
E	—	—
D	I	S

any path from  
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 ment of prefixes  
 $A[1 \dots i]$  and  
 $B[1 \dots j]$



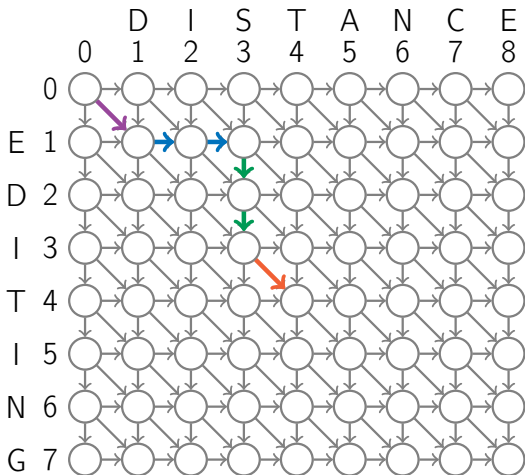
E	—	—	D
D	I	S	—

any path from  
 $(0, 0)$  to  $(i, j)$   
 spells an align-  
 ment of prefixes  
 $A[1 \dots i]$  and  
 $B[1 \dots j]$



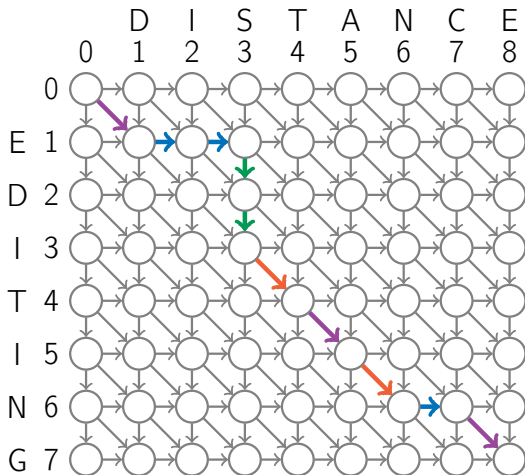
E	—	—	D	I
D	I	S	—	—

any path from  
 $(0, 0)$  to  $(i, j)$   
 spells an align-  
 ment of prefixes  
 $A[1 \dots i]$  and  
 $B[1 \dots j]$



E	—	—	D	I	T
D	I	S	—	—	T

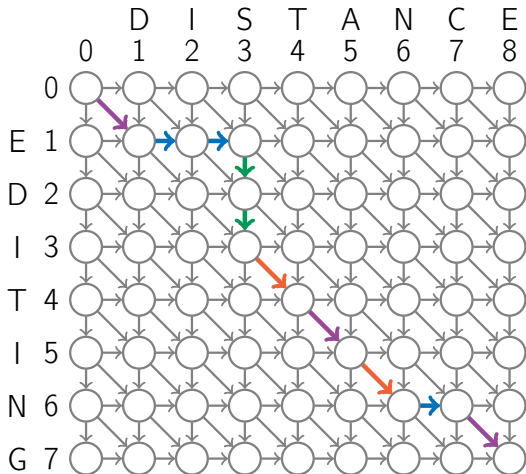
any path from  
 $(0, 0)$  to  $(i, j)$   
 spells an align-  
 ment of prefixes  
 $A[1 \dots i]$  and  
 $B[1 \dots j]$



E	—	—	D	I	T	I	N	—	G
D	I	S	—	—	T	A	N	C	E

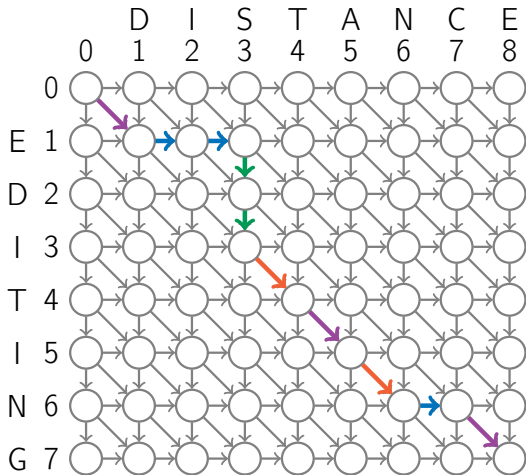


the constructed  
path corresponds  
to distance 8 and  
is not optimal  
(edit distance is 5)

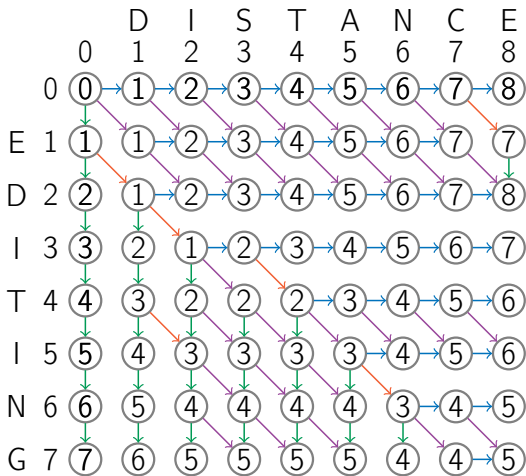


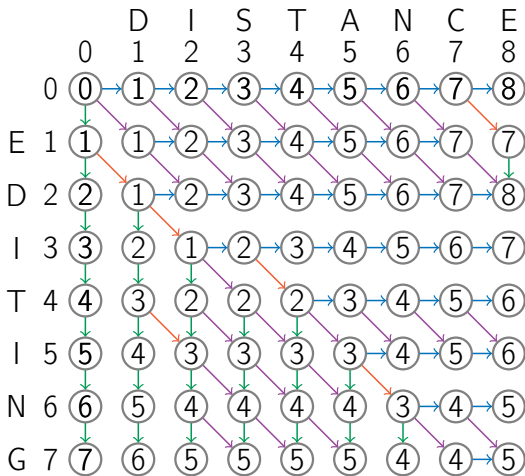
E	—	—	D	I	T	I	N	—	G
D	I	S	—	—	T	A	N	C	E

to construct an  
optimal align-  
ment we will use  
the backtracking  
pointers

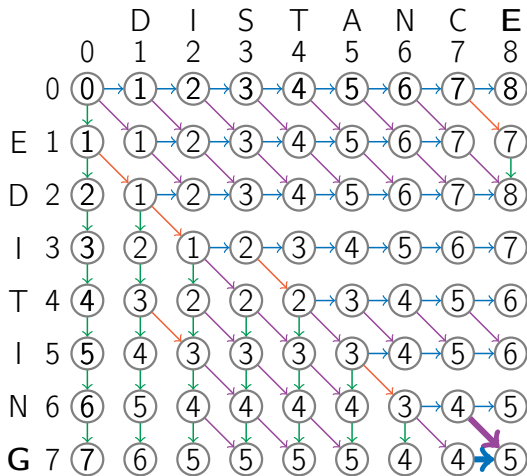


E	—	—	D	I	T	I	N	—	G
D	I	S	—	—	T	A	N	C	E

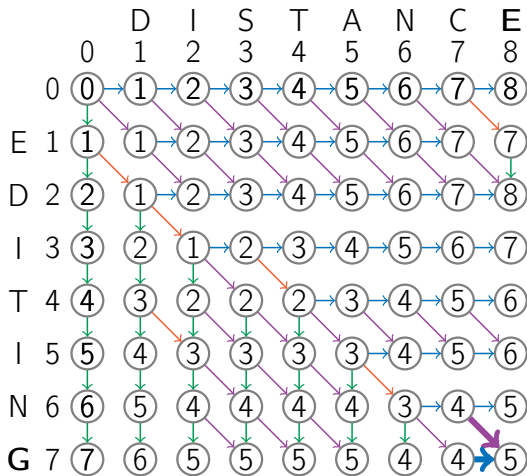




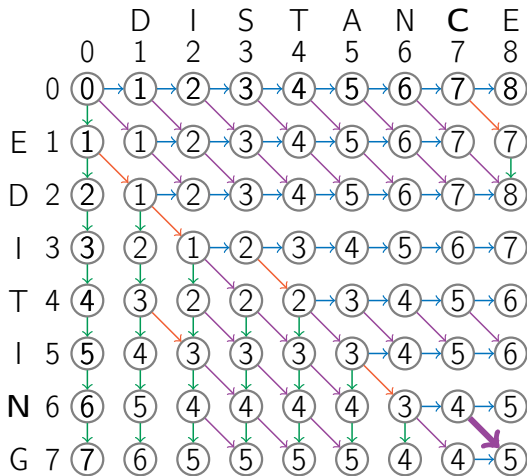
the edit distance  
is 5



we arrived to the bottom right cell by moving along the backtracking pointers shown below

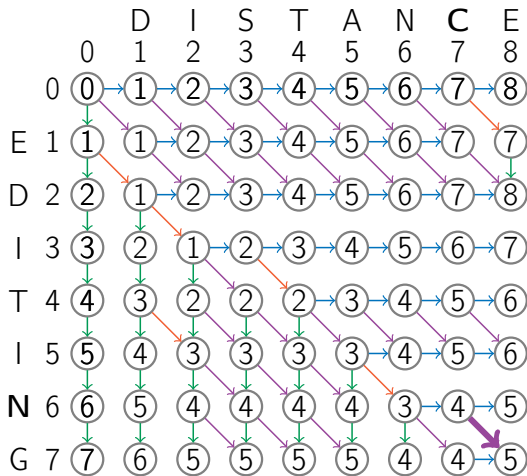


there exists an optimal alignment whose last column is a **mismatch** and an optimal alignment whose last column is an **insertion**



let's consider a  
mismatch

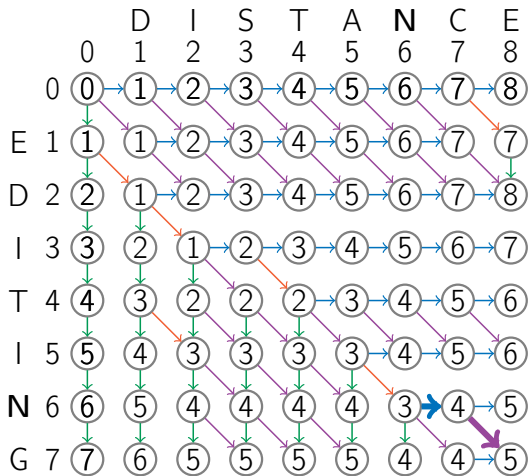
G
E



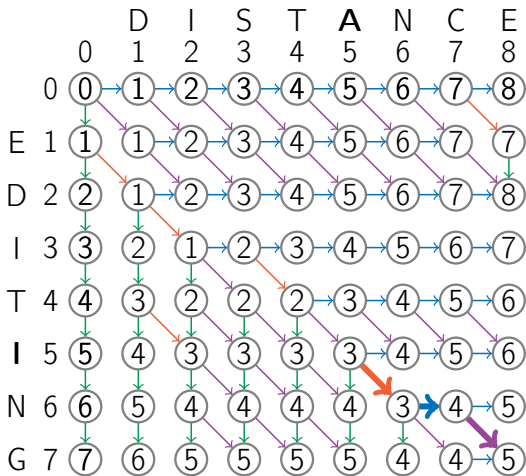
we continue in a  
similar fashion

G
E

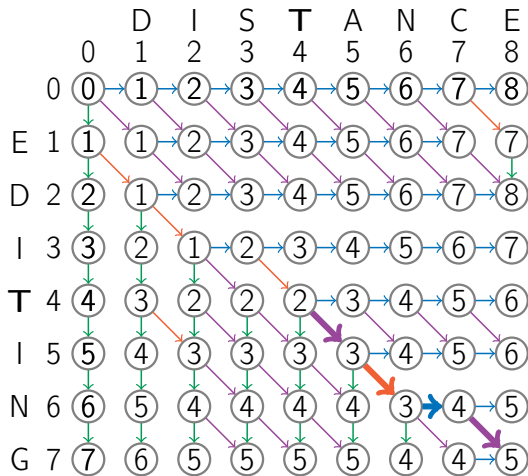




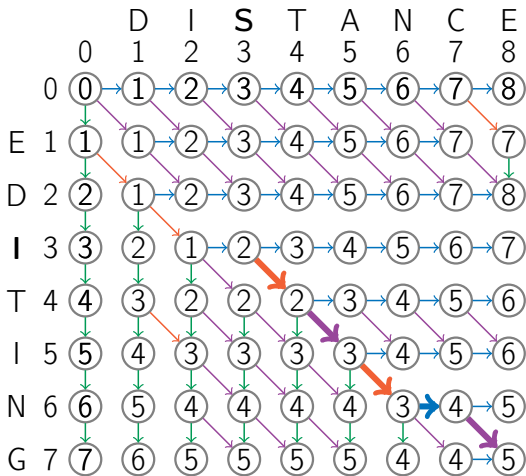
—	G
C	E



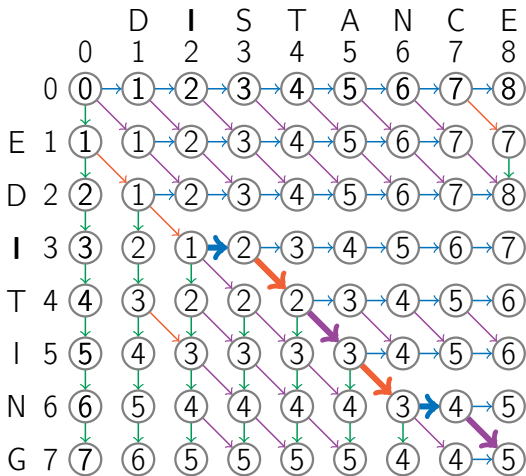
N	—	G
N	C	E



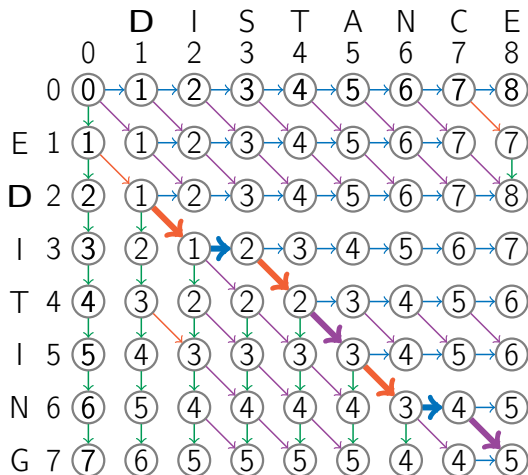
I	N	—	G
A	N	C	E



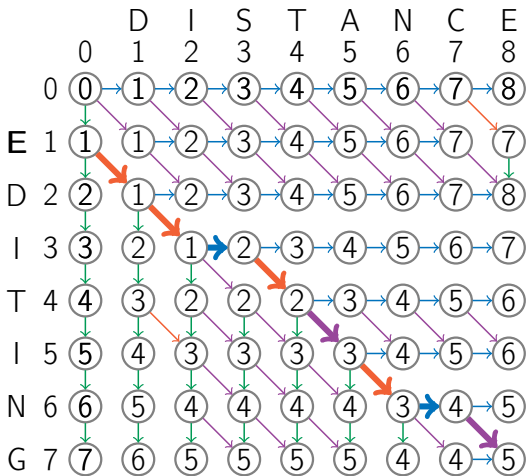
T	I	N	-	G
T	A	N	C	E



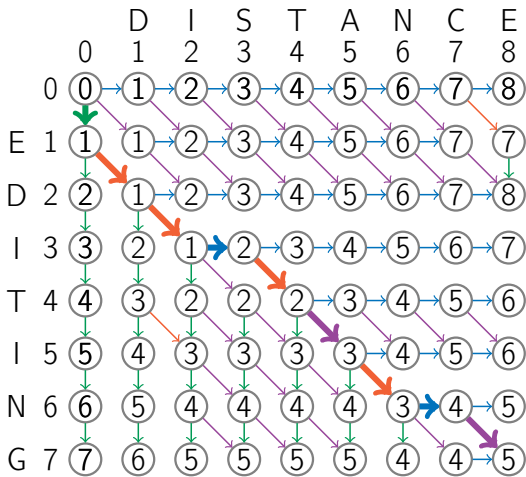
—	T	I	N	—	G
S	T	A	N	C	E



I	-	T	I	N	-	G
I	S	T	A	N	C	E



D	I	-	T	I	N	-	G
D	I	S	T	A	N	C	E



E	D	I	-	T	I	N	-	G
-	D	I	S	T	A	N	C	E



## OutputAlignment( $i, j$ )

```
if  $i = 0$  and  $j = 0$ :  
    return  
if  $\text{backtrack}(i, j) = \downarrow$ :  
    OutputAlignment( $i - 1, j$ )  
    print 

|        |
|--------|
| $A[i]$ |
| —      |

  
else if  $\text{backtrack}(i, j) = \rightarrow$ :  
    OutputAlignment( $i, j - 1$ )  
    print 

|        |
|--------|
| —      |
| $B[j]$ |

  
else:  
    OutputAlignment( $i - 1, j - 1$ )  
    print 

|        |
|--------|
| $A[i]$ |
| $B[j]$ |


```

## OutputAlignment( $i, j$ )

```
if  $i = 0$  and  $j = 0$ :  
    return  
if  $i > 0$  and  $D(i, j) = D(i - 1, j) + 1$ :  
    OutputAlignment( $i - 1, j$ )  
    print 

|        |
|--------|
| $A[i]$ |
| —      |

  
else if  $j > 0$  and  $D(i, j) = D(i, j - 1) + 1$ :  
    OutputAlignment( $i, j - 1$ )  
    print 

|        |
|--------|
| —      |
| $B[j]$ |

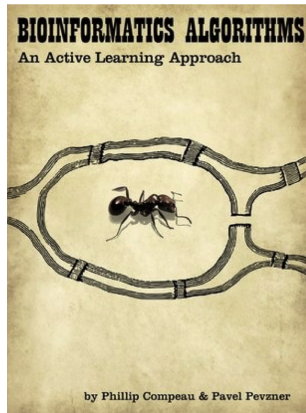
  
else:  
    OutputAlignment( $i - 1, j - 1$ )  
    print 

|        |
|--------|
| $A[i]$ |
| $B[j]$ |


```



**Comparing Genes, Proteins, and Genomes MOOC** (a part of Bioinformatics Specialization on Coursera)



Bioinformatics Algorithms textbook at [bioinformaticsalgorithms.org](http://bioinformaticsalgorithms.org) (2nd two-volume edition was published in 2015)