Class Announcements

- Next Tuesday: Video lecture, on topic
  - Voting results: 5 to cancel, 6 to have a video, 0 for Skype
  - Within the 6 votes for the video, 4 were to be on topic
- Volunteer to set up video in class
- Free to watch from home rather than in person

Inexact String Matching

CS 4390/5390

Based on Chapter 2 of *Algorithms in Bioinformatics: A Practical Introduction* by Wing-Kin Sun

Edit Distance

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- Example: S_1 = **`baseball`** & S_2 = **`ballcap`**.
  - `  RRR DR`
    `baseball`
    `ballca p`
  - 5 operations: change `s→l`, `e→l`, `b→c`, delete `l`, `l→p`

Global Alignment Problem

- An **alignment** of two sequences is formed by inserting gap characters,'–', in arbitrary locations along the sequences so that they end up wit the same length and there are no two spaces at the same position of the two augmented strings.

```
baseball---
----ballcap
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```
baseball      baseball---      baseball
-ballcap      ----ballcap      ballca-p
```

How do we know which one of these is best?

Alignment

- In general, associate a similarity score with each pair of aligned characters:
  - for characters $x,y \in \Sigma \cup \{-\}$, let $\delta(x,y)$ be the similarity of x and y
- Let the score, Δ, of an alignment, $A = (S'_1, S'_2)$, be defined as $\Delta(A) =: \sum_{1 \leq i \leq |S'_1|} \delta(S'_1[i], S'_s[i])$
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	-	a	b	c	e	l	p	s
-		-1	-1	-1	-1	-1	-1	-1
a	-1	0	-1	-1	-1	-1	-1	-1
b	-1	-1	0	-1	-1	-1	-1	-1
c	-1	-1	-1	0	-1	-1	-1	-1
e	-1	-1	-1	-1	0	-1	-1	-1
l	-1	-1	-1	-1	-1	0	-1	-1
p	-1	-1	-1	-1	-1	-1	0	-1
s	-1	-1	-1	-1	-1	-1	-1	0

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How can we compute an alignment that optimizes Δ?

	-	a	b	c	e	l	p	s
-		0	0	0	0	0	0	0
a	0	2	-1	-1	-1	-1	-1	-1
b	0	-1	2	-1	-1	-1	-1	-1
c	0	-1	-1	2	-1	-1	-1	-1
e	0	-1	-1	-1	2	-1	-1	-1
l	0	-1	-1	-1	-1	2	-1	-1
p	0	-1	-1	-1	-1	-1	2	-1
s	0	-1	-1	-1	-1	-1	-1	2

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c	0	-1	-1	2	-1	-1	-1	-1
e	0	-1	-1	-1	2	-1	-1	-1
l	0	-1	-1	-1	-1	2	-1	-1
p	0	-1	-1	-1	-1	-1	2	-1
s	0	-1	-1	-1	-1	-1	-1	2

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Needleman-Wunsch

- brute-force, compute all possible alignments and score them, would take exponential time to compute the optimal alignment

- using dynamic programming Needleman and Wunsch [1970][1] found that the optimal alignment can be computed in *O(mn)*-time.

[1]Notice we have gone back in time, suffix trees were introduced in 1973, Ukkonen's algorithm was 1995, Suffix Arrays were 1993

Needleman-Wunsch

- Dynamic programming, generally, works by solving sub-problems, storing the results, and combining the solution to (most times) multiple sub-problems to find the answer.

- Given two strings *S[1...n]* and *T[1...m]*, find the best alignment.

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- Given two strings *S[1...n]* and *T[1...m]*, find the best alignment given the best alignments of:
  - *S[1...(n-1)]* and *T[1...m],*
  - *S[1...n]* and *T[1...(m-1)],* and
  - *S[1...(n-1)]* and *T[1...(m-1)]*

Needleman-Wunsch

- Define an *n*x*m* array *V*, the cell *V(i,j)* will hold the score of the best sub alignments of *S[1…i]* and *T[1…j]*

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- The recurrence relation (the base of any DP)

$$V(i,j) = \max \begin{cases} V(i-1,j-1) + \delta(S[i], T[i]) & \text{match/mismatch} \\ V(i-1,j) + \delta(S[i], -) & \text{delete} \\ V(i,j-1) + \delta(-, T[j]) & \text{insert} \end{cases}$$

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- The initialization is:
  $V(0,0) = 0$
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Optimal alignment score is in *V(n,m)*

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$\delta(-,x) = -1$ for $x \in \Sigma$

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$\delta(x,y) = 1$ for y = x

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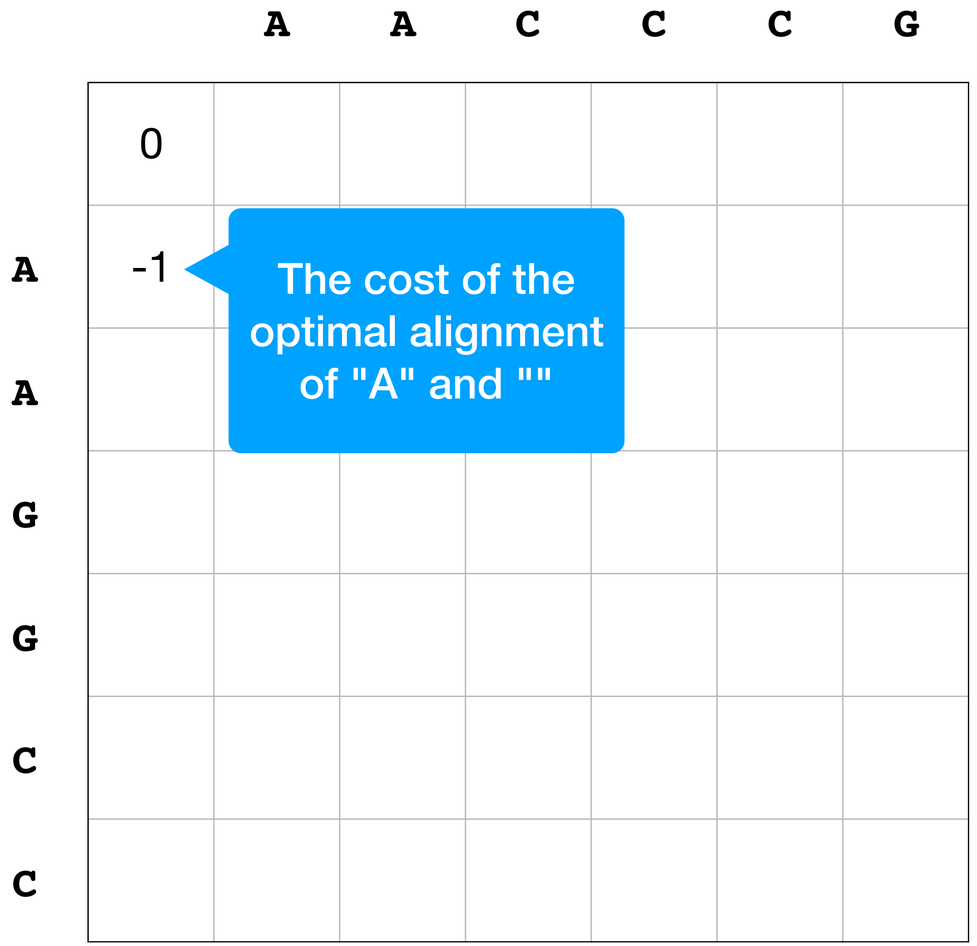

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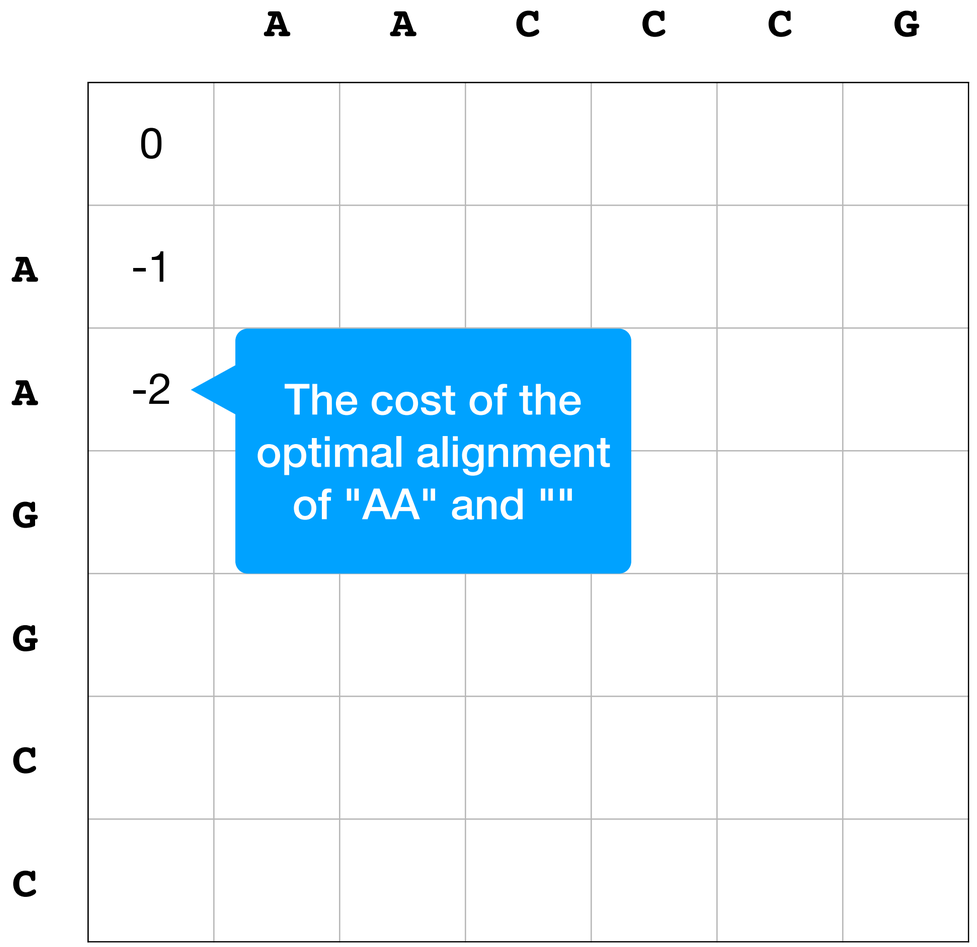

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		A	A	C	C	C	G
	0	-1					
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C	-5						
C	-6						

The cost of the optimal alignment of "" and "A"

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-

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```
A   -
-   A
```

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A **–**
– + **A**

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$$\begin{matrix} - \\ A \end{matrix} + \begin{matrix} A \\ - \end{matrix}$$

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$$\begin{matrix} A \\ - \end{matrix} + \begin{matrix} - \\ A \end{matrix}$$

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$$\begin{matrix} & \mathbf{A} \\ + & \mathbf{A} \end{matrix}$$

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A
\+ A

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\- A
A + -

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$\delta(x,y) = 1$ for y = x

$\delta(x,y) = -1$ for y ≠ x

		A	A	C	C	C	G
	0	-1	-2	-3	-4	-5	-6
A	-1	1	0				
A	-2						
G	-3						
G	-4						
C	-5						
C	-6						

Needleman-Wunch

$\delta(-,x) = -1$ for $x \in \Sigma$

$\delta(x,-) = -1$ for $x \in \Sigma$

$\delta(x,y) = 1$ for y = x

$\delta(x,y) = -1$ for y ≠ x

		A	A	C	C	C	G
	0	-1	-2	-3	-4	-5	-6
A	-1	1	0				
A	-2						
G	-3						
G	-4						
C	-5						
C	-6						

Needleman-Wunch

$\delta(-,x) = -1$ for $x \in \Sigma$

$\delta(x,-) = -1$ for $x \in \Sigma$

$\delta(x,y) = 1$ for y = x

$\delta(x,y) = -1$ for y ≠ x

		A	A	C	C	C	G
	0	-1	-2	-3	-4	-5	-6
A	-1	1	0	-1			
A	-2						
G	-3						
G	-4						
C	-5						
C	-6						

Needleman-Wunch

$\delta(-,x) = -1$ for $x \in \Sigma$

$\delta(x,-) = -1$ for $x \in \Sigma$

$\delta(x,y) = 1$ for y = x

$\delta(x,y) = -1$ for y ≠ x

		A	A	C	C	C	G
	0	-1	-2	-3	-4	-5	-6
A	-1	1	0	-1	-2	-3	-4
A	-2	0	2	1	0	-1	-2
G	-3	-1	1	1	0	-1	0
G	-4	-2	0	0	0	-1	0
C	-5	-3	-1	1	1	1	0
C	-6	-4	-2	0	2	2	1

Needleman-Wunch

$\delta(-,x) = -1$ for $x \in \Sigma$

$\delta(x,-) = -1$ for $x \in \Sigma$

$\delta(x,y) = 1$ for y = x

$\delta(x,y) = -1$ for y ≠ x

		A	A	C	C	C	G
	0	-1	-2	-3	-4	-5	-6
A	-1						
A	-2						
G	-3						
G	-4						
C	-5						
C	-6						

Needleman-Wunch

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$\delta(x,y) = 1$ for y = x

$\delta(x,y) = -1$ for y ≠ x

		A	A	C	C	C	G
	0	-1	-2	-3	-4	-5	-6
A	-1	1					
A	-2						
G	-3						
G	-4						
C	-5						
C	-6						

+δ(A,A)

+δ(-,A)

+δ(A,-)

Needleman-Wunch

$\delta(-,x) = -1$ for $x \in \Sigma$

$\delta(x,-) = -1$ for $x \in \Sigma$

$\delta(x,y) = 1$ for y = x

$\delta(x,y) = -1$ for y ≠ x

		A	A	C	C	C	G
	0	-1	-2	-3	-4	-5	-6
A	-1	1					
A	-2						
G	-3						
G	-4						
C	-5						
C	-6						

Needleman-Wunch

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$\delta(x,-) = -1$ for $x \in \Sigma$

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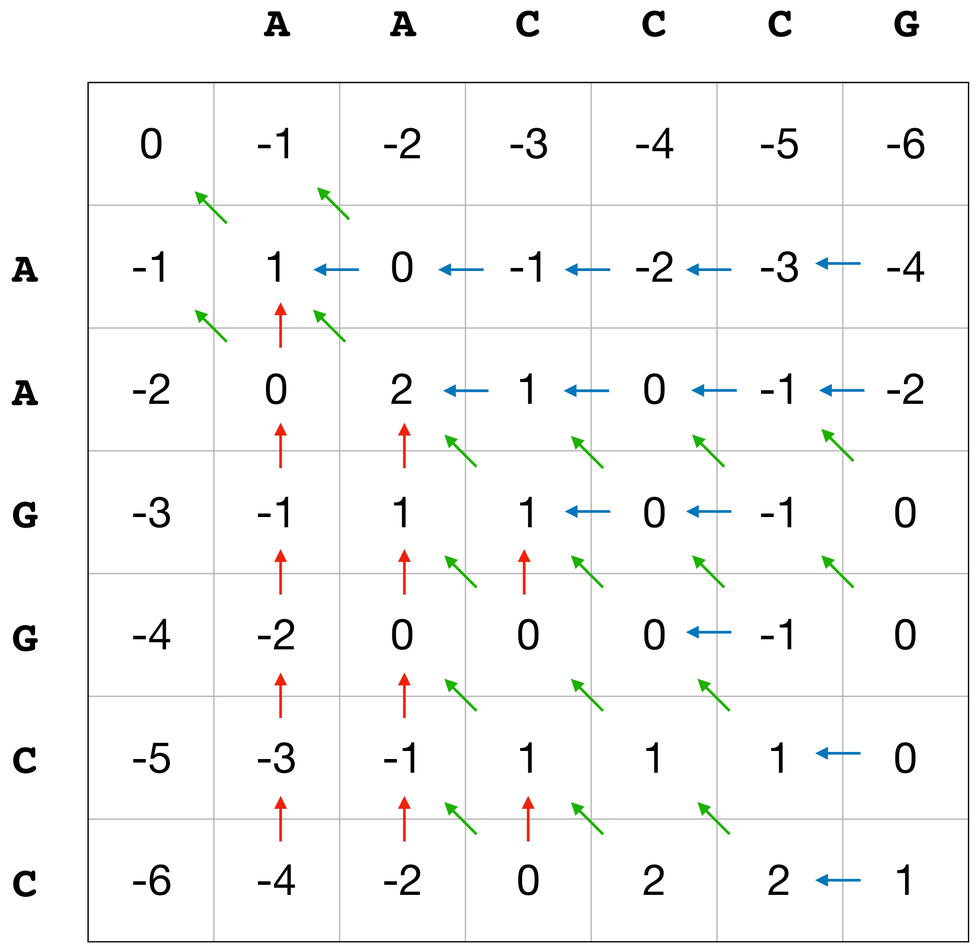


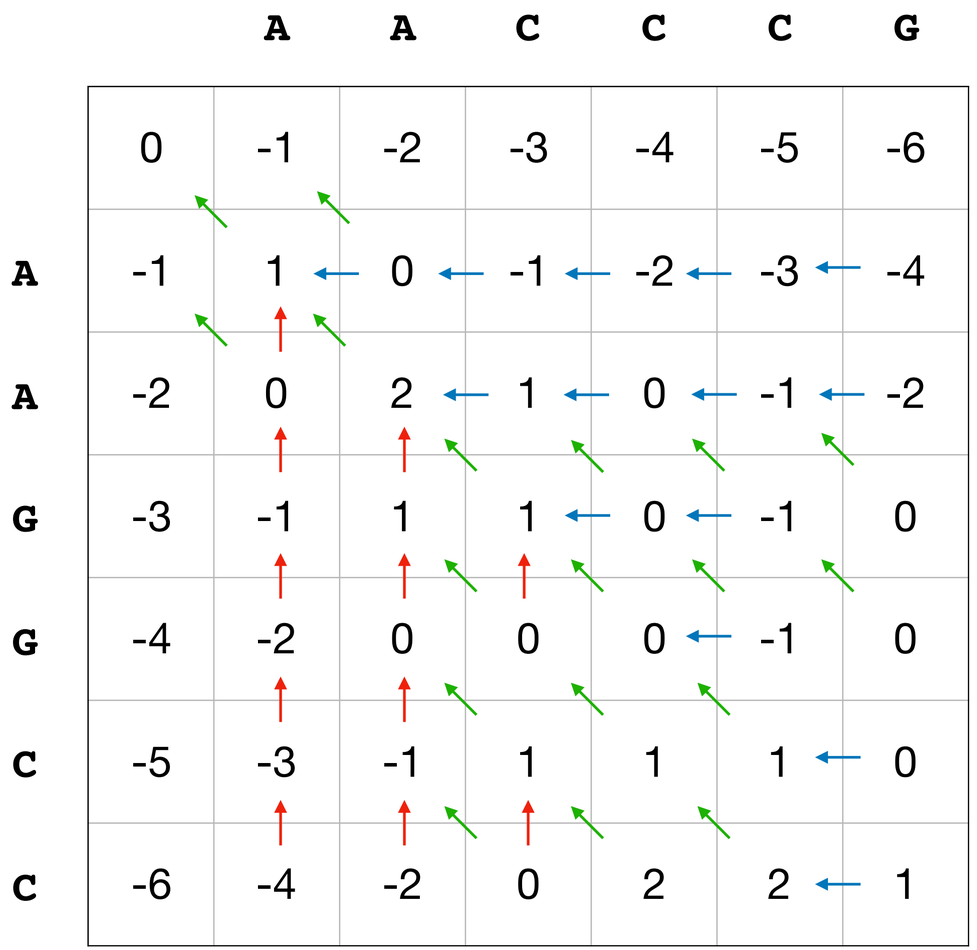
Needleman-Wunch

$\delta(-,x) = -1$ for $x \in \Sigma$

$\delta(x,-) = -1$ for $x \in \Sigma$

$\delta(x,y) = 1$ for y = x

$\delta(x,y) = -1$ for y ≠ x



Needleman-Wunch

$\delta(-,x) = -1$ for $x \in \Sigma$

$\delta(x,-) = -1$ for $x \in \Sigma$

$\delta(x,y) = 1$ for y = x

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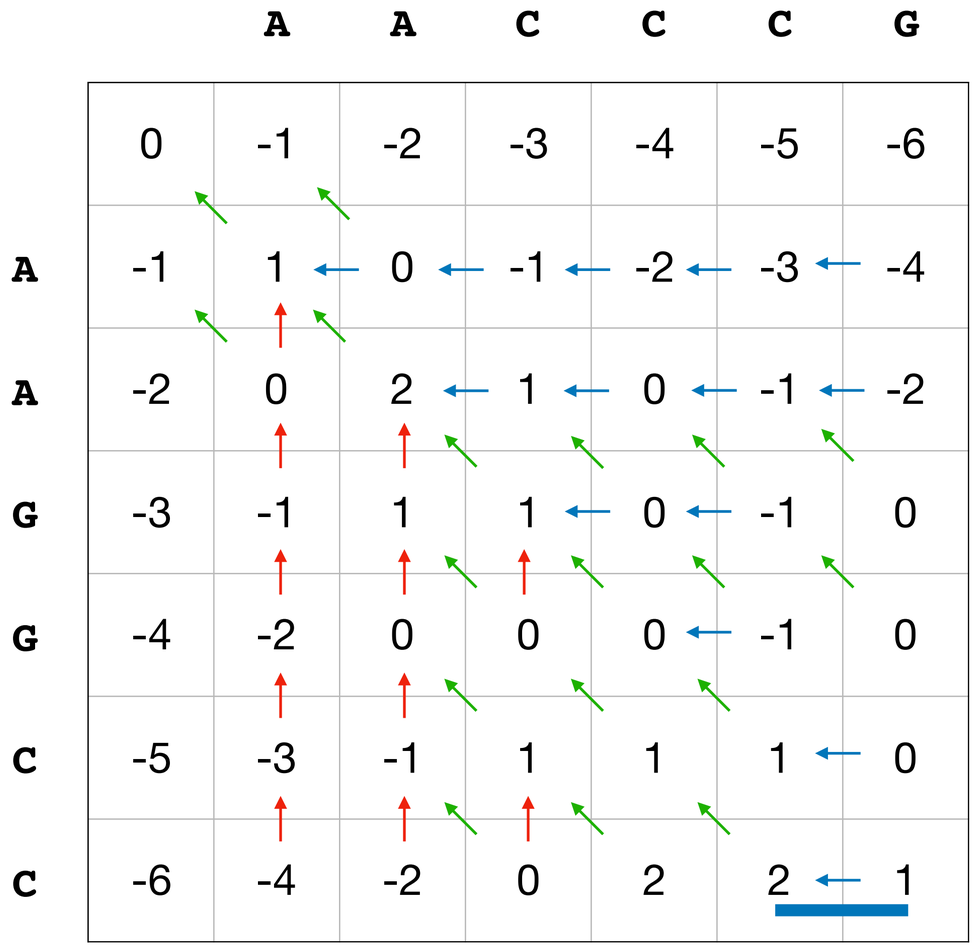


Needleman-Wunch

$\delta(-,x) = -1$ for $x \in \Sigma$

$\delta(x,-) = -1$ for $x \in \Sigma$

$\delta(x,y) = 1$ for y = x

$\delta(x,y) = -1$ for y ≠ x

		A	A	C	C	C	G
	0	-1	-2	-3	-4	-5	-6
A	-1	1	0	-1	-2	-3	-4
A	-2	0	2	1	0	-1	-2
G	-3	-1	1	1	0	-1	0
G	-4	-2	0	0	0	-1	0
C	-5	-3	-1	1	1	1	0
C	-6	-4	-2	0	2	2	1

G
-

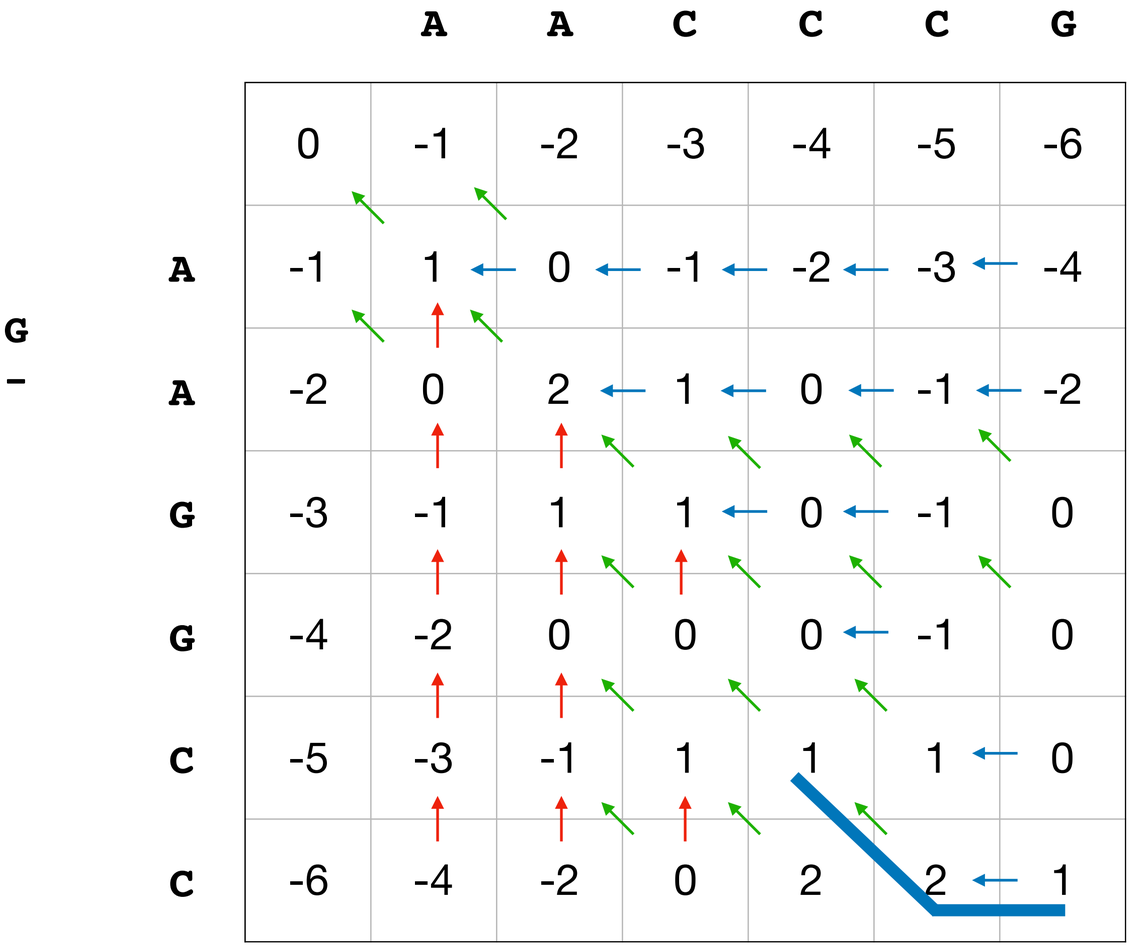
Needleman-Wunch

$\delta(-,x) = -1$ for $x \in \Sigma$

$\delta(x,-) = -1$ for $x \in \Sigma$

$\delta(x,y) = 1$ for y = x

$\delta(x,y) = -1$ for y ≠ x



Needleman-Wunch

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$\delta(x,-) = -1$ for $x \in \Sigma$

$\delta(x,y) = 1$ for y = x

$\delta(x,y) = -1$ for y ≠ x

C G
C –

		A	A	C	C	C	G
	0	-1	-2	-3	-4	-5	-6
A	-1	1	0	-1	-2	-3	-4
A	-2	0	2	1	0	-1	-2
G	-3	-1	1	1	0	-1	0
G	-4	-2	0	0	0	-1	0
C	-5	-3	-1	1	1	1	0
C	-6	-4	-2	0	2	2	1

Needleman-Wunch

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$\delta(x,y) = 1$ for y = x

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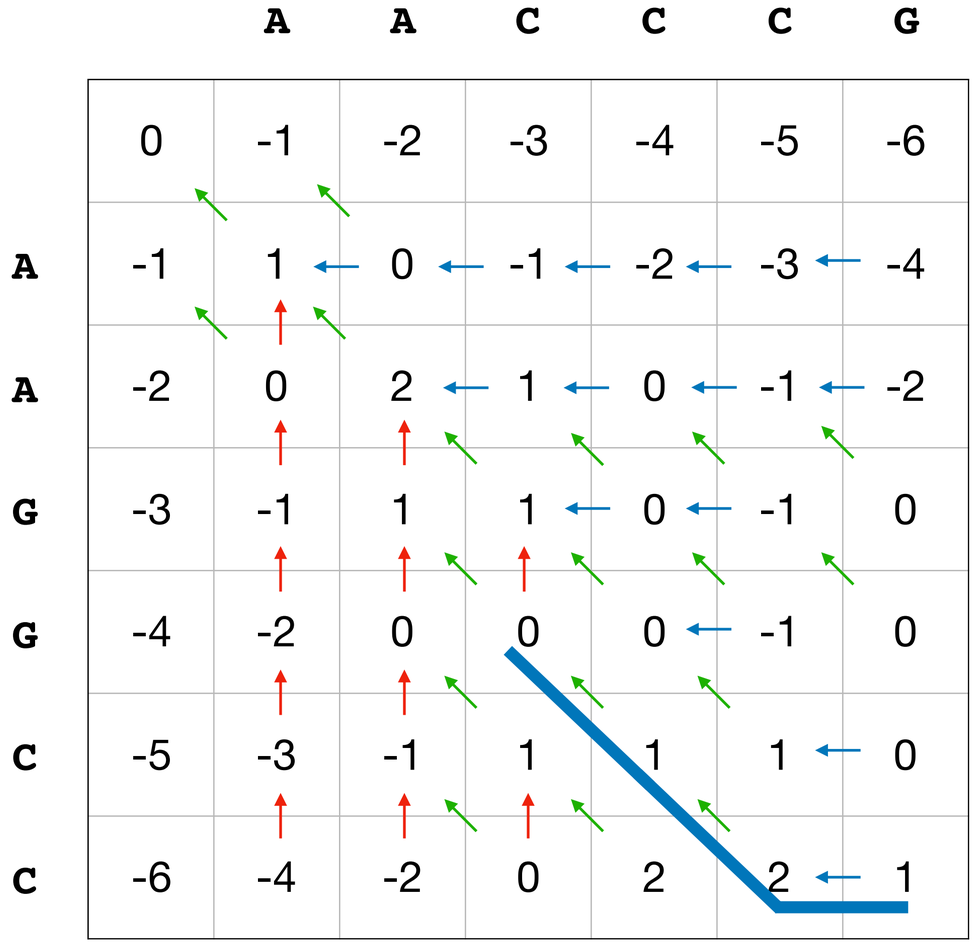
C G
C –



Needleman-Wunch

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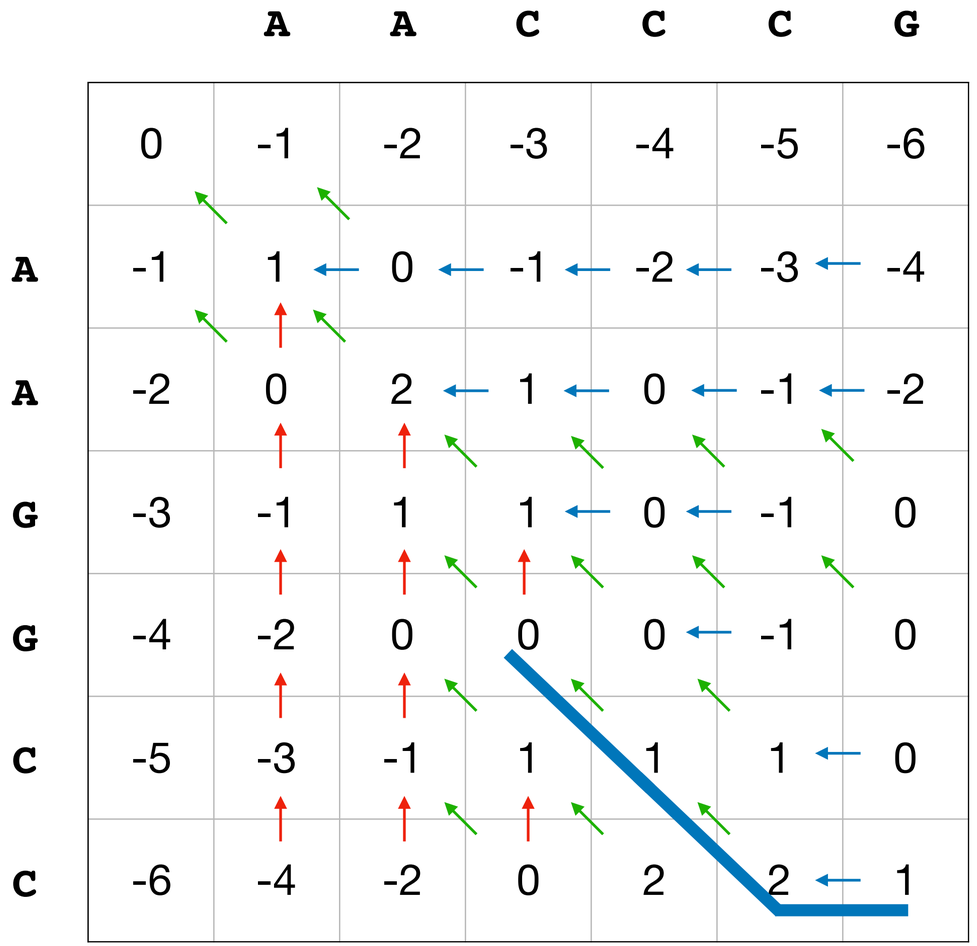
$\delta(x,-) = -1$ for $x \in \Sigma$

$\delta(x,y) = 1$ for y = x

$\delta(x,y) = -1$ for y ≠ x

C C G
C C –



Needleman-Wunch

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$\delta(x,-) = -1$ for $x \in \Sigma$

$\delta(x,y) = 1$ for y = x

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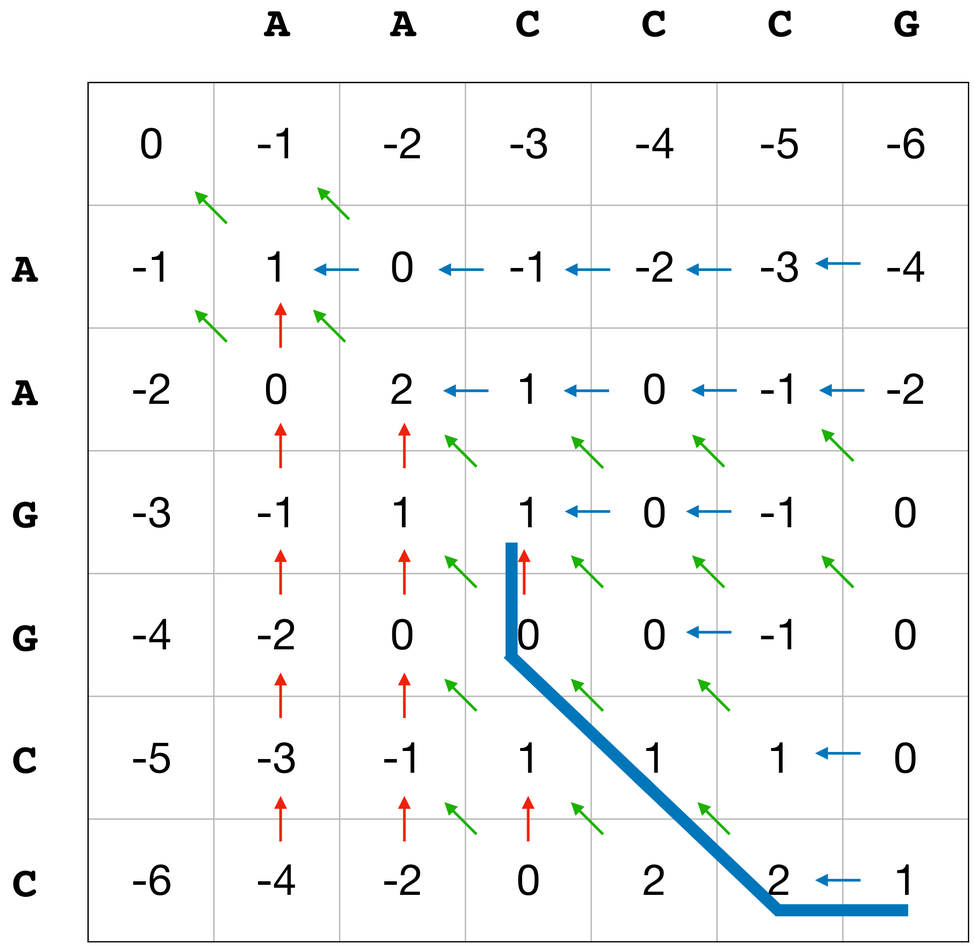
C C G
C C –



Needleman-Wunch

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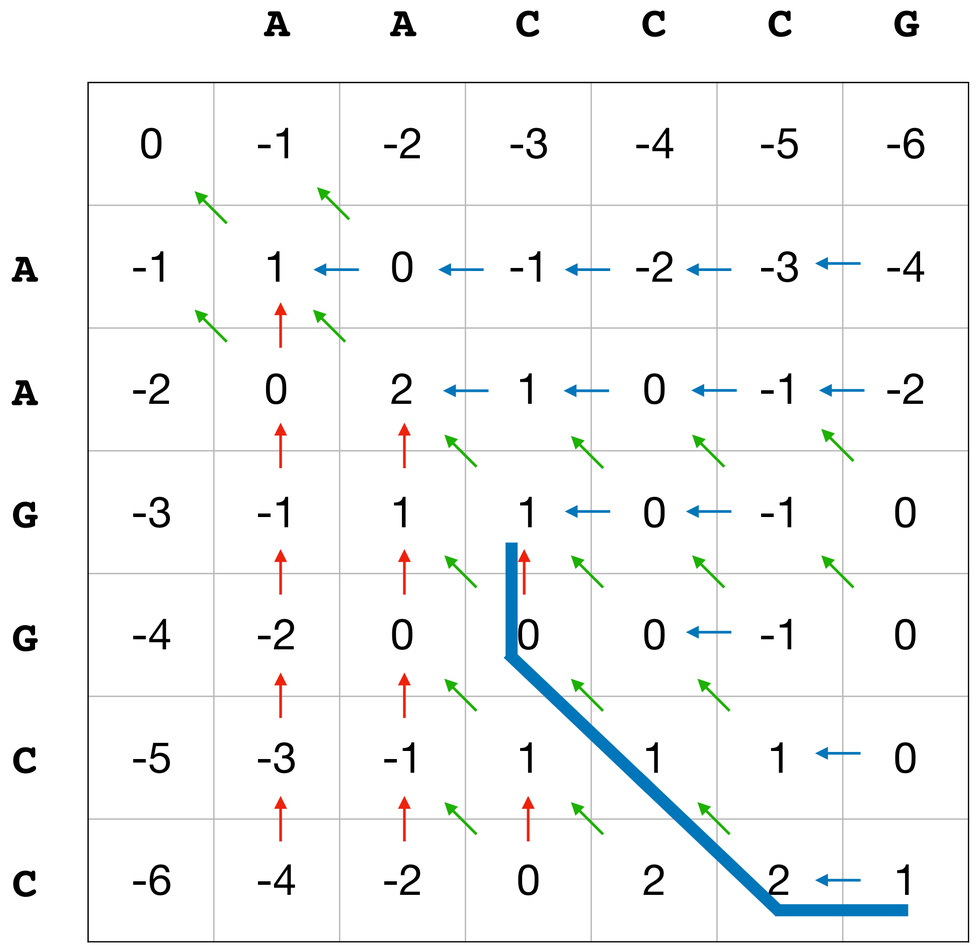
- C C G
G C C -



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$\delta(x,-) = -1$ for $x \in \Sigma$

$\delta(x,y) = 1$ for y = x

$\delta(x,y) = -1$ for y ≠ x

- C C G
G C C -

		A	**A**	**C**	**C**	**C**	**G**
	0	-1	-2	-3	-4	-5	-6
A	-1	1	0	-1	-2	-3	-4
A	-2	0	2	1	0	-1	-2
G	-3	-1	1	1	0	-1	0
G	-4	-2	0	0	0	-1	0
C	-5	-3	-1	1	1	1	0
C	-6	-4	-2	0	2	2	1

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$\delta(x,-) = -1$ for $x \in \Sigma$

$\delta(x,y) = 1$ for y = x

$\delta(x,y) = -1$ for y ≠ x

C - C C G
G G C C -

		A	A	C	C	C	G
	0	-1	-2	-3	-4	-5	-6
A	-1	1	0	-1	-2	-3	-4
A	-2	0	2	1	0	-1	-2
G	-3	-1	1	1	0	-1	0
G	-4	-2	0	0	0	-1	0
C	-5	-3	-1	1	1	1	0
C	-6	-4	-2	0	2	2	1

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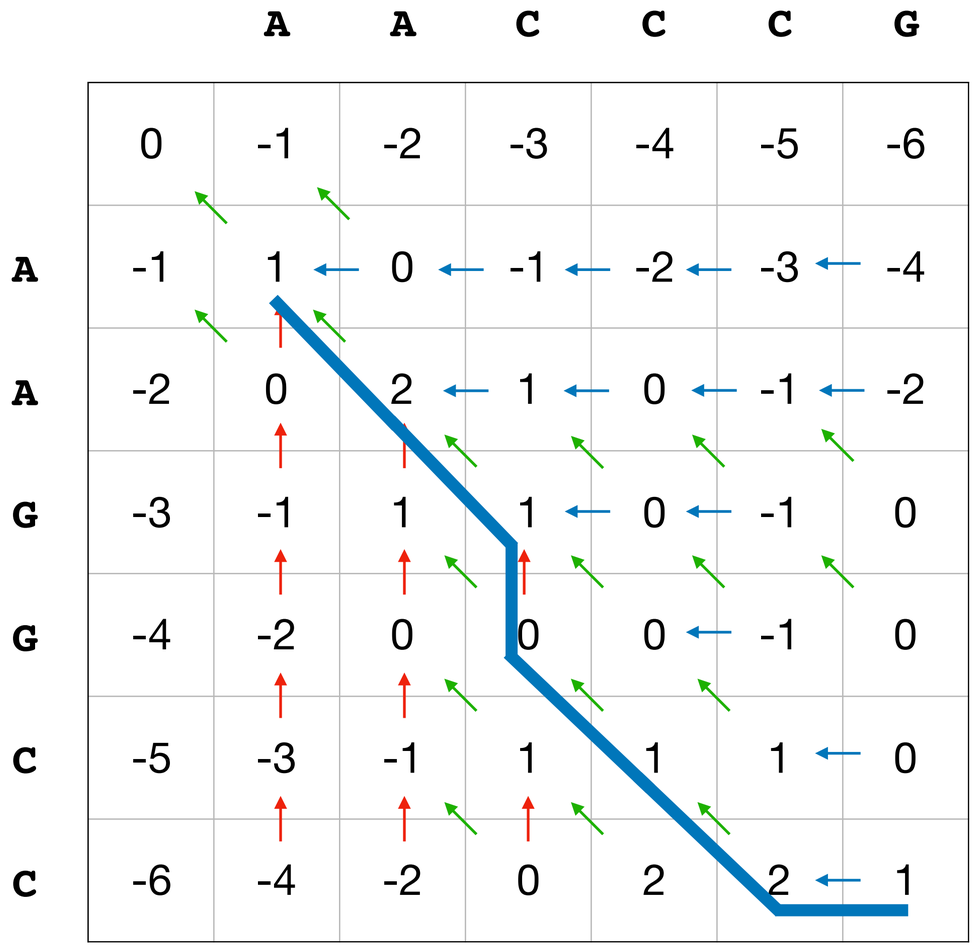
C – C C G
G G C C –



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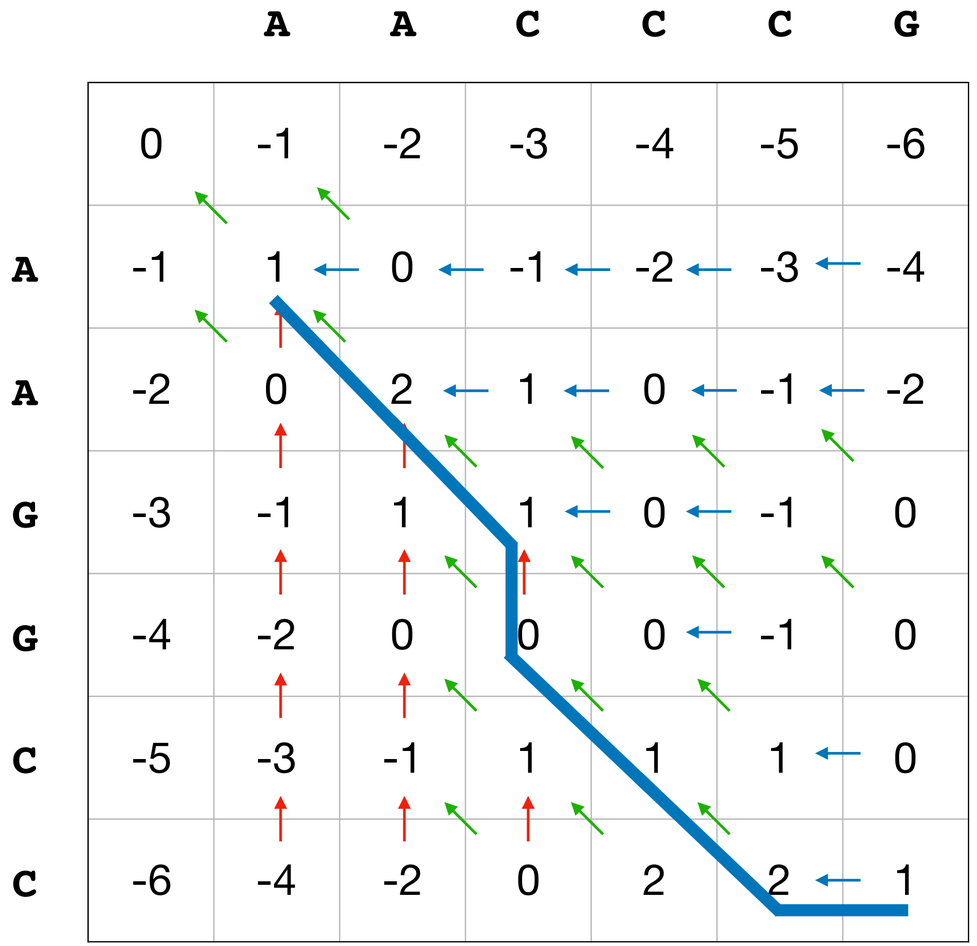
$\delta(x,-) = -1$ for $x \in \Sigma$

$\delta(x,y) = 1$ for y = x

$\delta(x,y) = -1$ for y ≠ x

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



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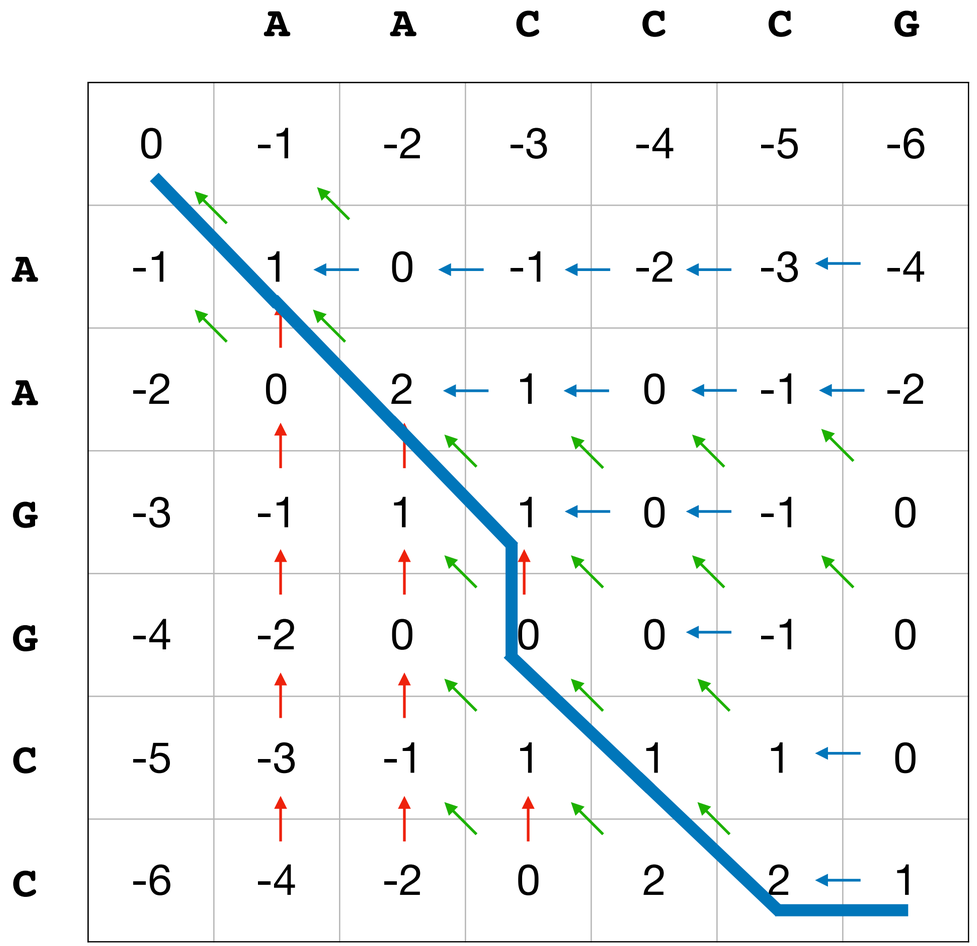
$\delta(x,-) = -1$ for $x \in \Sigma$

$\delta(x,y) = 1$ for y = x

$\delta(x,y) = -1$ for y ≠ x

A C – C C G
A G G C C –



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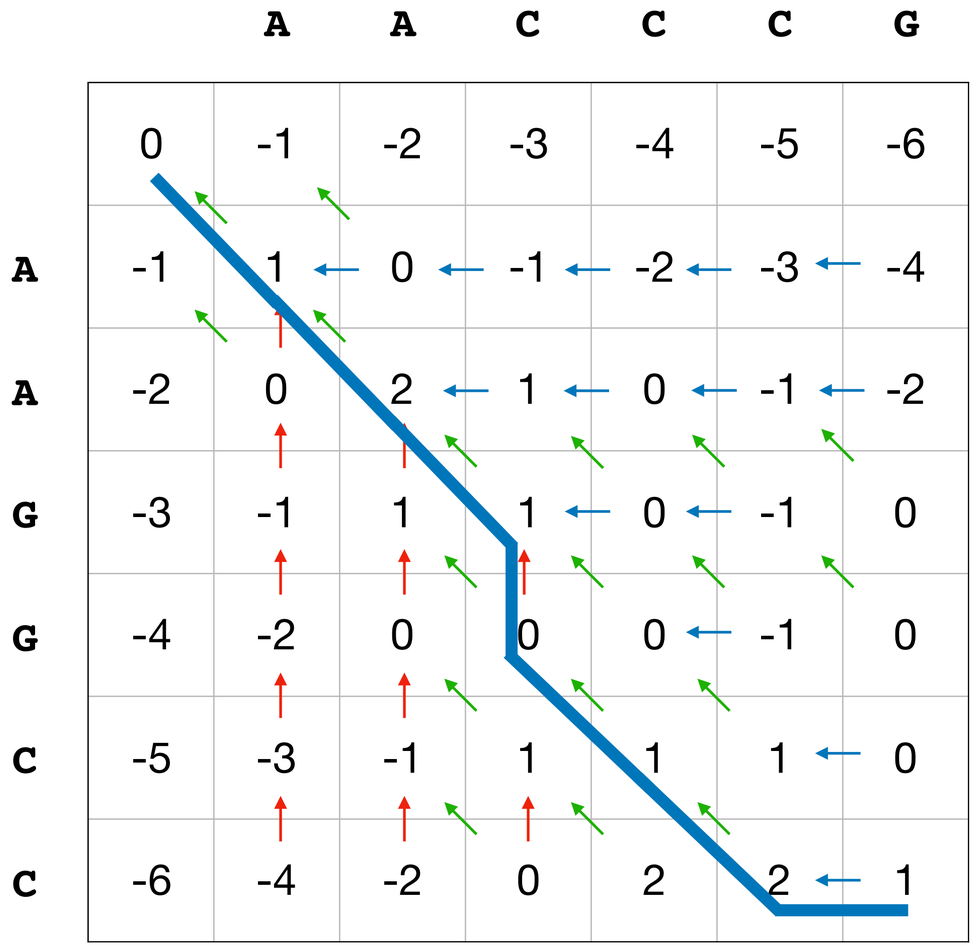
$\delta(x,y) = 1$ for y = x

$\delta(x,y) = -1$ for y ≠ x

A A C – C C G
A A G G C C –



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$\delta(x,-) = -1$ for $x \in \Sigma$

$\delta(x,y) = 1$ for y = x

$\delta(x,y) = -1$ for y ≠ x

A A C – C C G
A A G G C C –

		A	A	C	C	C	G
	0	-1	-2	-3	-4	-5	-6
A	-1	1	0	-1	-2	-3	-4
A	-2	0	2	1	0	-1	-2
G	-3	-1	1	1	0	-1	0
G	-4	-2	0	0	0	-1	0
C	-5	-3	-1	1	1	1	0
C	-6	-4	-2	0	2	2	1

Needleman-Wunch

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$\delta(x,-) = -1$ for $x \in \Sigma$

$\delta(x,y) = 1$ for y = x

$\delta(x,y) = -1$ for y ≠ x

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

		A	A	C	C	C	G
	0	-1	-2	-3	-4	-5	-6
A	-1	1	0	-1	-2	-3	-4
A	-2	0	2	1	0	-1	-2
G	-3	-1	1	1	0	-1	0
G	-4	-2	0	0	0	-1	0
C	-5	-3	-1	1	1	1	0
C	-6	-4	-2	0	2	2	1

Needleman-Wunch

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$\delta(x,-) = -1$ for $x \in \Sigma$

$\delta(x,y) = 1$ for y = x

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

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

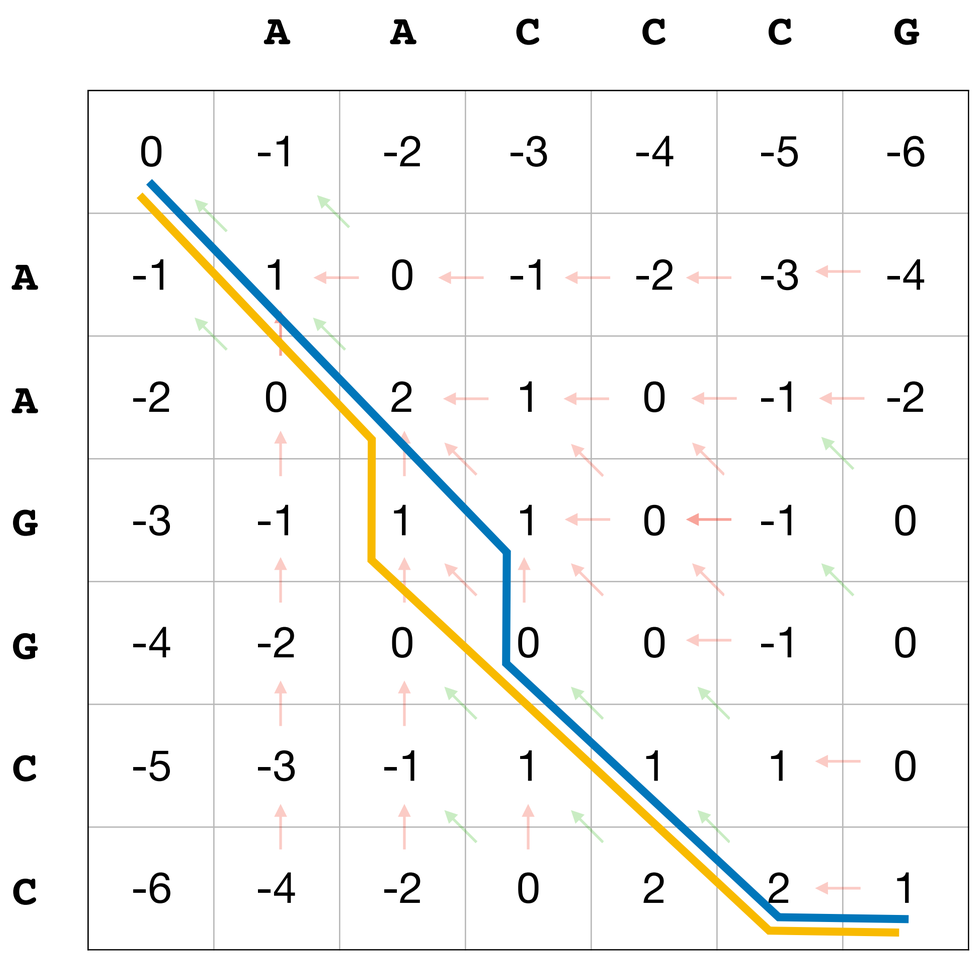
		A	A	C	C	C	G
	0	-1	-2	-3	-4	-5	-6
A	-1	1	0	-1	-2	-3	-4
A	-2	0	2	1	0	-1	-2
G	-3	-1	1	1	0	-1	0
G	-4	-2	0	0	0	-1	0
C	-5	-3	-1	1	1	1	0
C	-6	-4	-2	0	2	2	1

Needleman-Wunch

What about the running time and memory requirements?

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

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



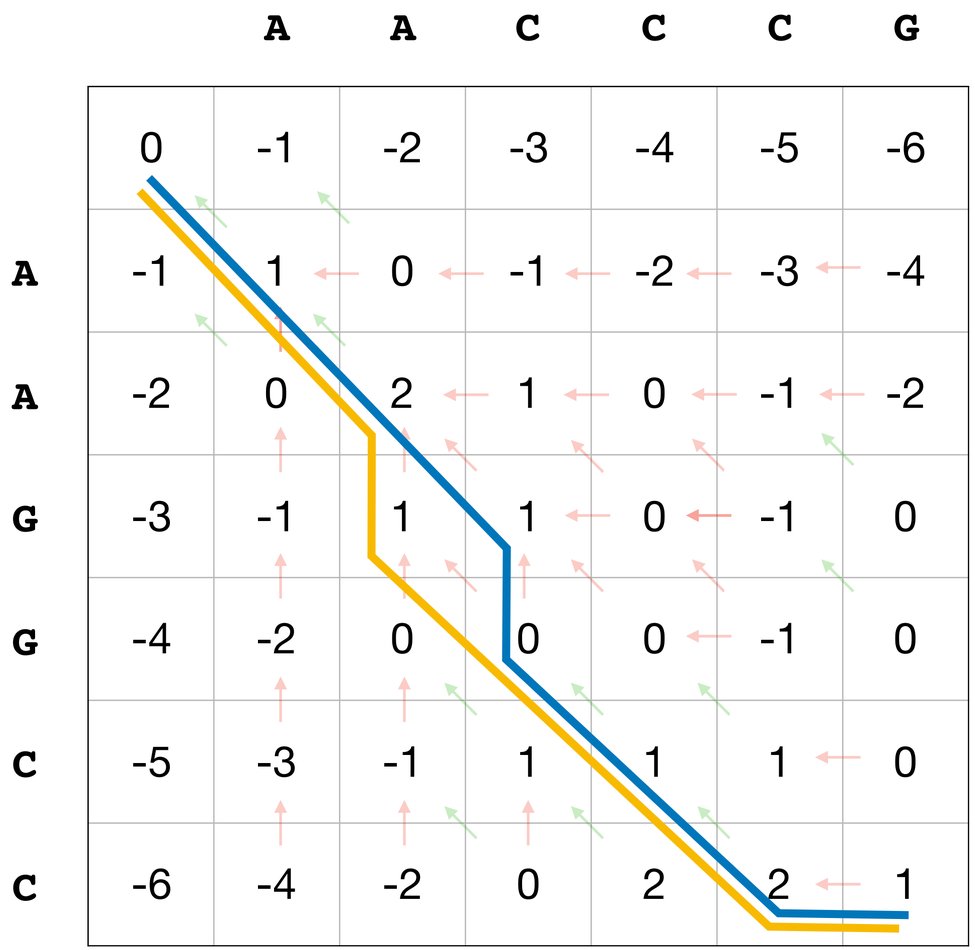
Needleman-Wunch

What about the running time and memory requirements?

- Filling in each cell of the table:

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

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



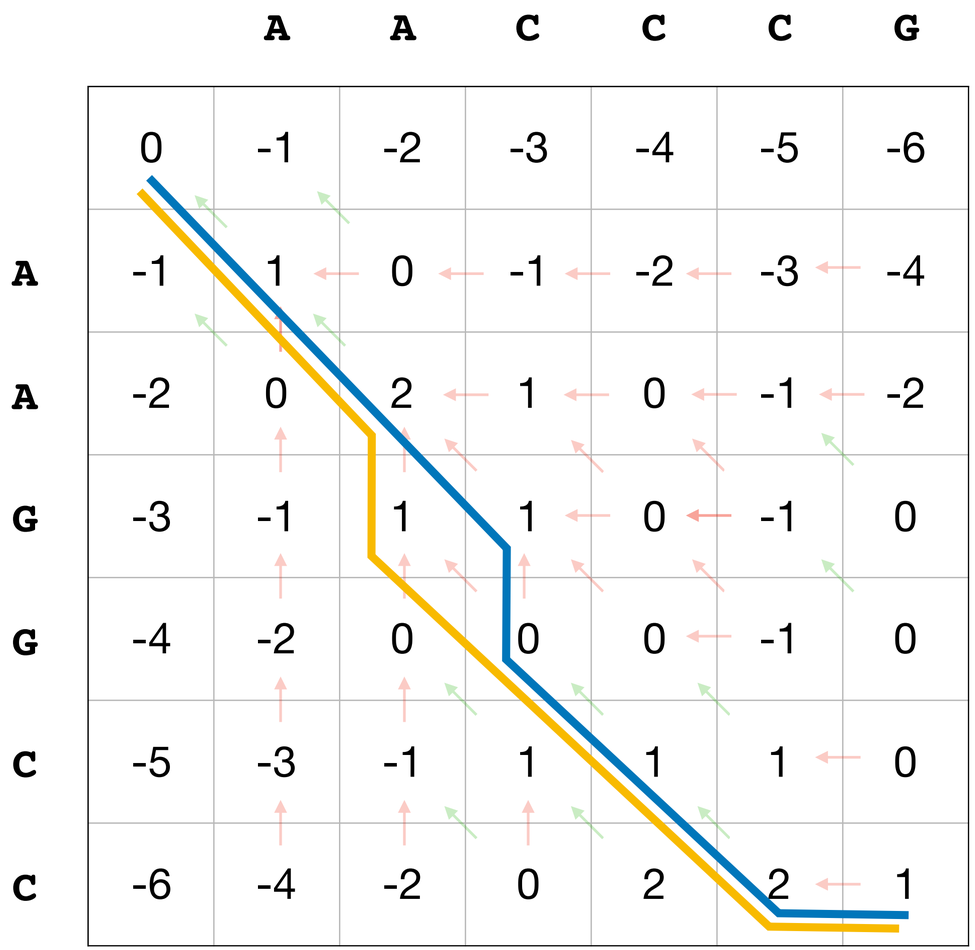
Needleman-Wunch

What about the running time and memory requirements?

- Filling in each cell of the table:
  O(1)-time, *O(1)*-space

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

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



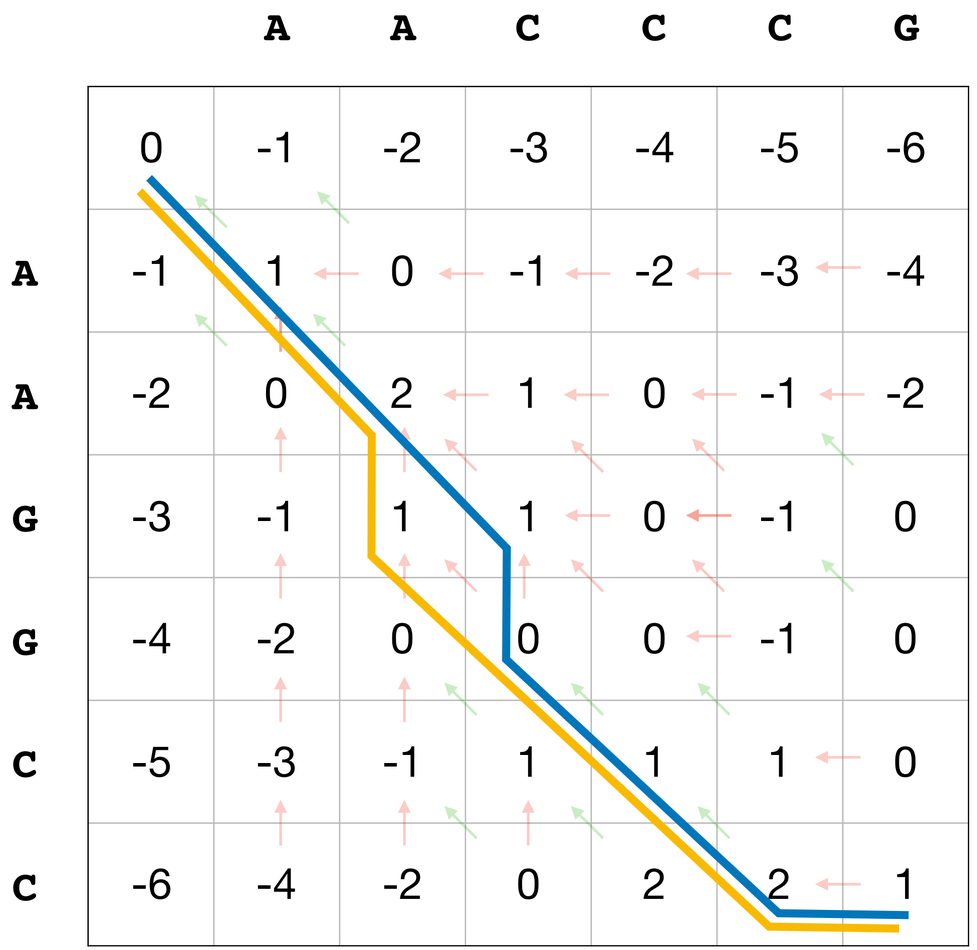
Needleman-Wunch

What about the running time and memory requirements?

- Filling in each cell of the table:
  O(1)-time, *O(1)*-space
- Table is *nxm*

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

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



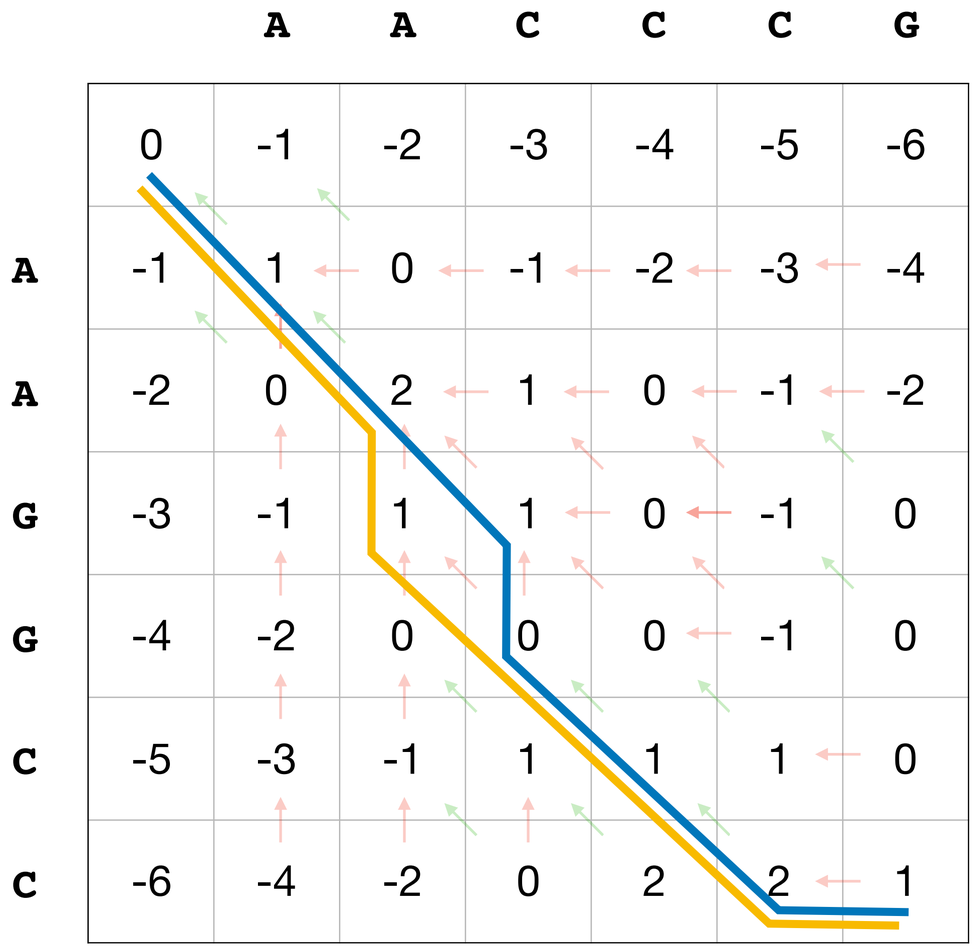
Needleman-Wunch

What about the running time and memory requirements?

- Filling in each cell of the table:
  O(1)-time, *O(1)*-space
- Table is *nxm*
- Filling in the table:

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

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



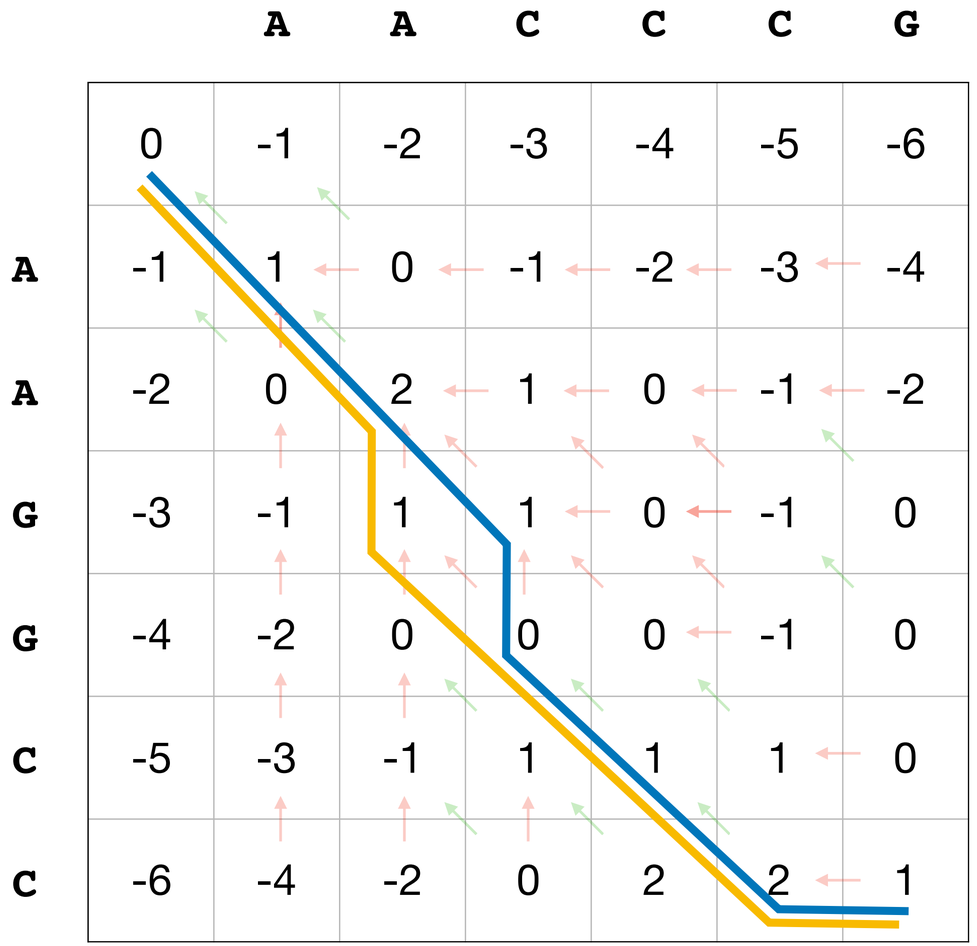
Needleman-Wunch

What about the running time and memory requirements?

- Filling in each cell of the table:
  O(1)-time, *O(1)*-space
- Table is *nxm*
- Filling in the table:
  O(mn)-time, *O(mn)*-space

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

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



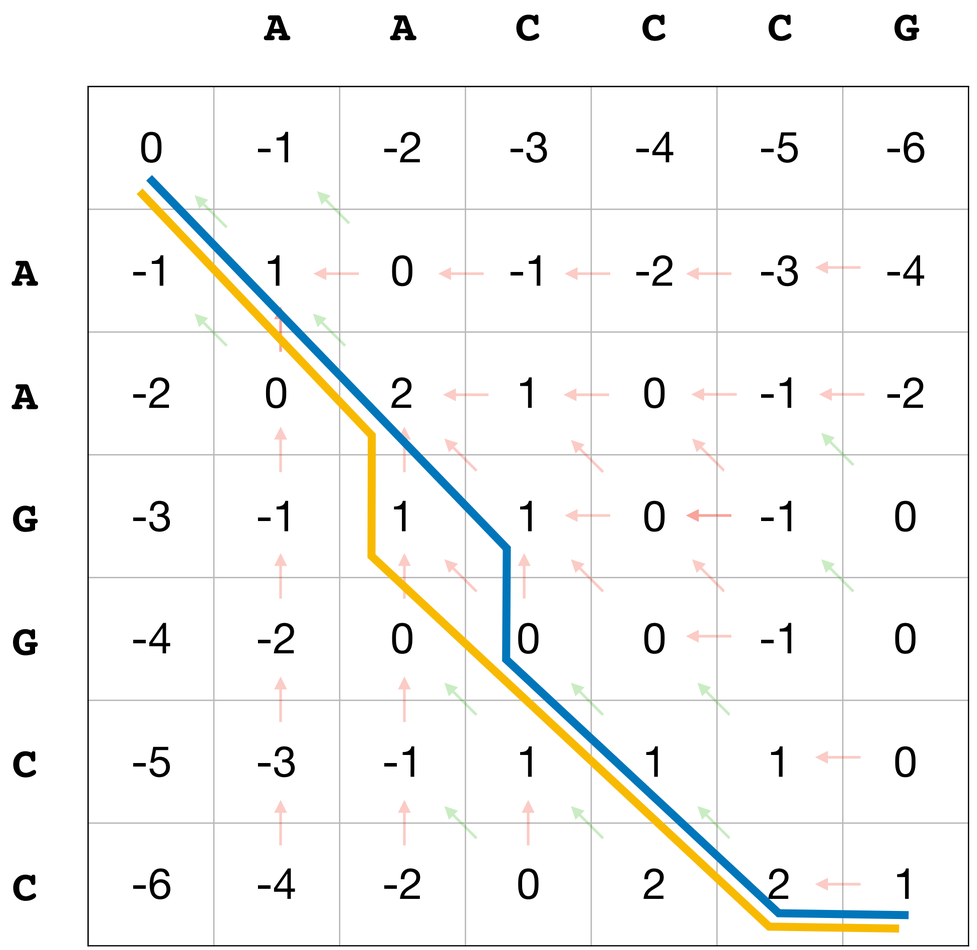
Needleman-Wunch

What about the running time and memory requirements?

- Filling in each cell of the table:
  O(1)-time, *O(1)*-space
- Table is *nxm*
- Filling in the table:
  O(mn)-time, *O(mn)*-space
- Traceback?

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

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



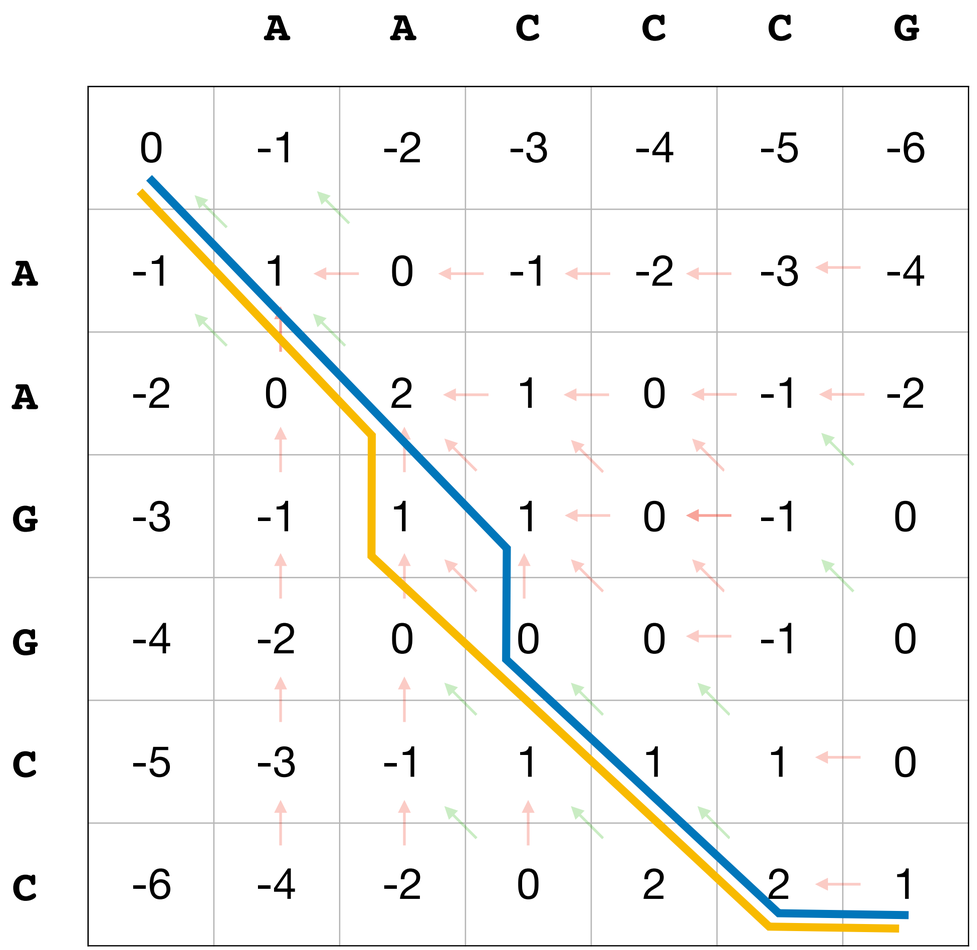
Needleman-Wunch

What about the running time and memory requirements?

- Filling in each cell of the table:
  O(1)-time, *O(1)*-space
- Table is *nxm*
- Filling in the table:
  O(mn)-time, *O(mn)*-space
- Traceback?
  - Each column of the alignment:

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

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



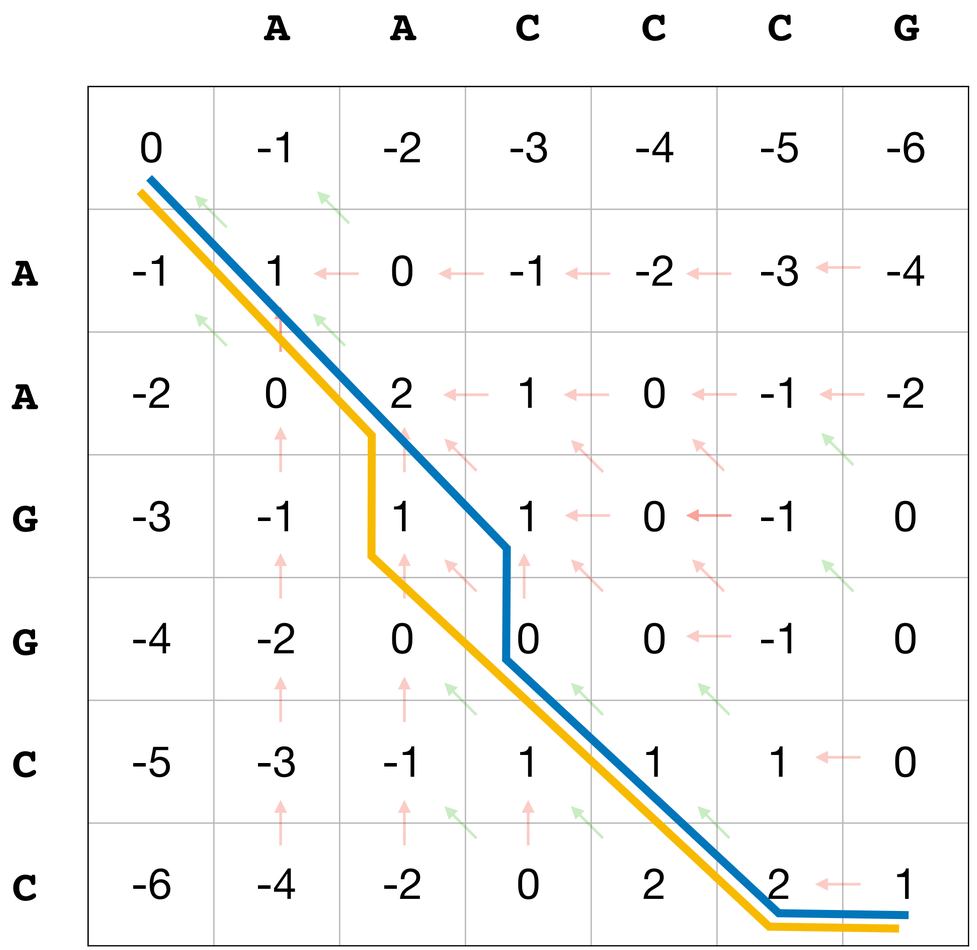
Needleman-Wunch

What about the running time and memory requirements?

- Filling in each cell of the table:
  O(1)-time, *O(1)*-space
- Table is *nxm*
- Filling in the table:
  O(mn)-time, *O(mn)*-space
- Traceback?
  - Each column of the alignment:
    O(1)-time

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

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



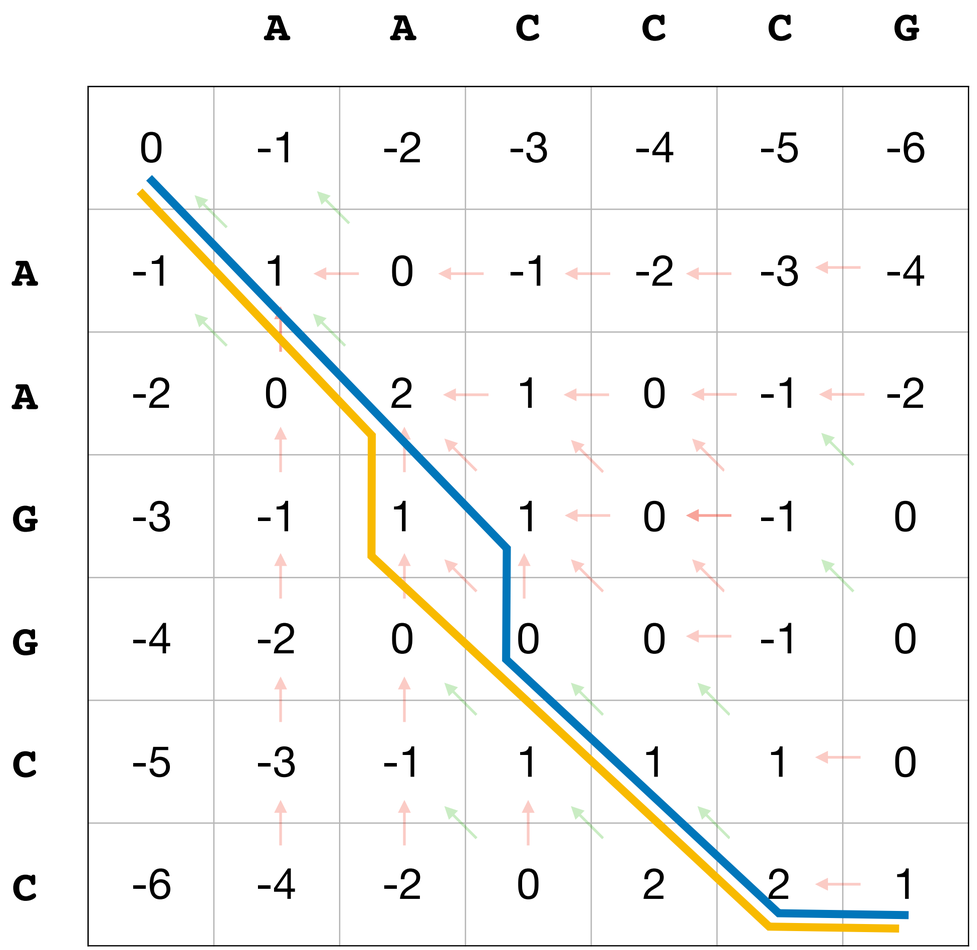
Needleman-Wunch

What about the running time and memory requirements?

- Filling in each cell of the table:
  O(1)-time, *O(1)*-space
- Table is *nxm*
- Filling in the table:
  O(mn)-time, *O(mn)*-space
- Traceback?
  - Each column of the alignment:
    O(1)-time
  - Maximum Alignment Length:

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

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



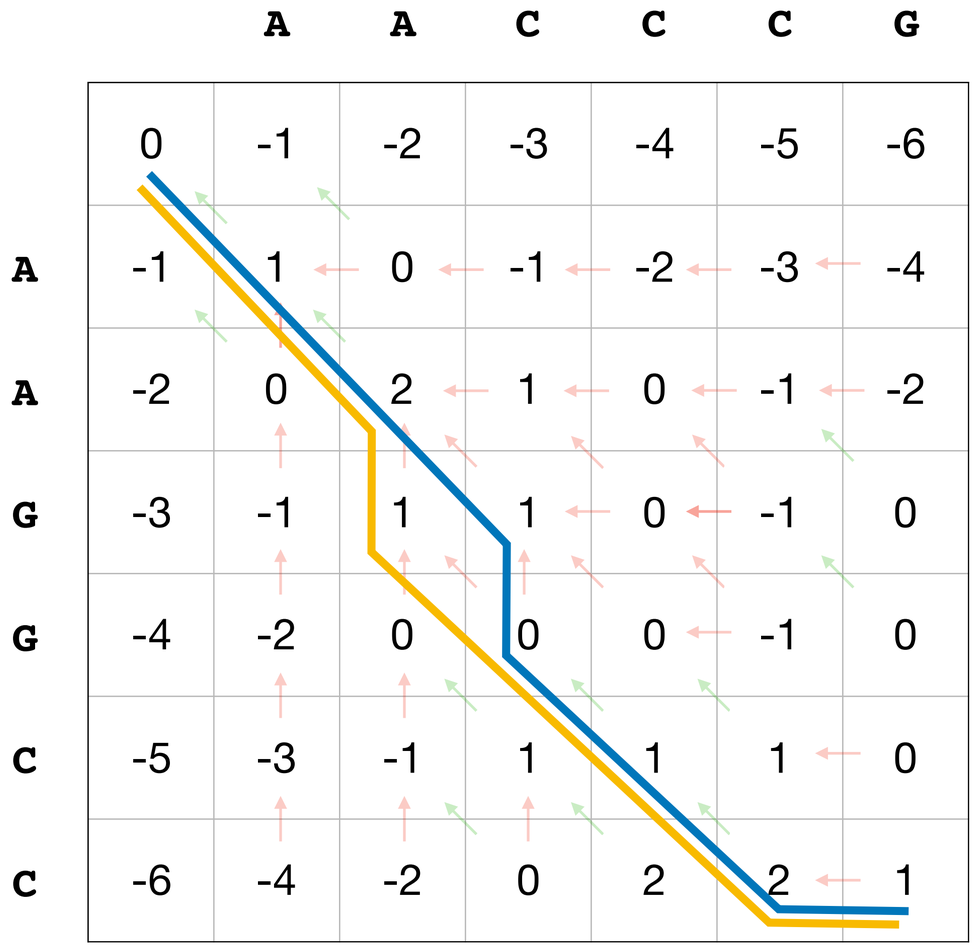
Needleman-Wunch

What about the running time and memory requirements?

- Filling in each cell of the table:
  O(1)-time, *O(1)*-space
- Table is *nxm*
- Filling in the table:
  O(mn)-time, *O(mn)*-space
- Traceback?
  - Each column of the alignment:
    O(1)-time
  - Maximum Alignment Length:
    O(m+n)

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

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



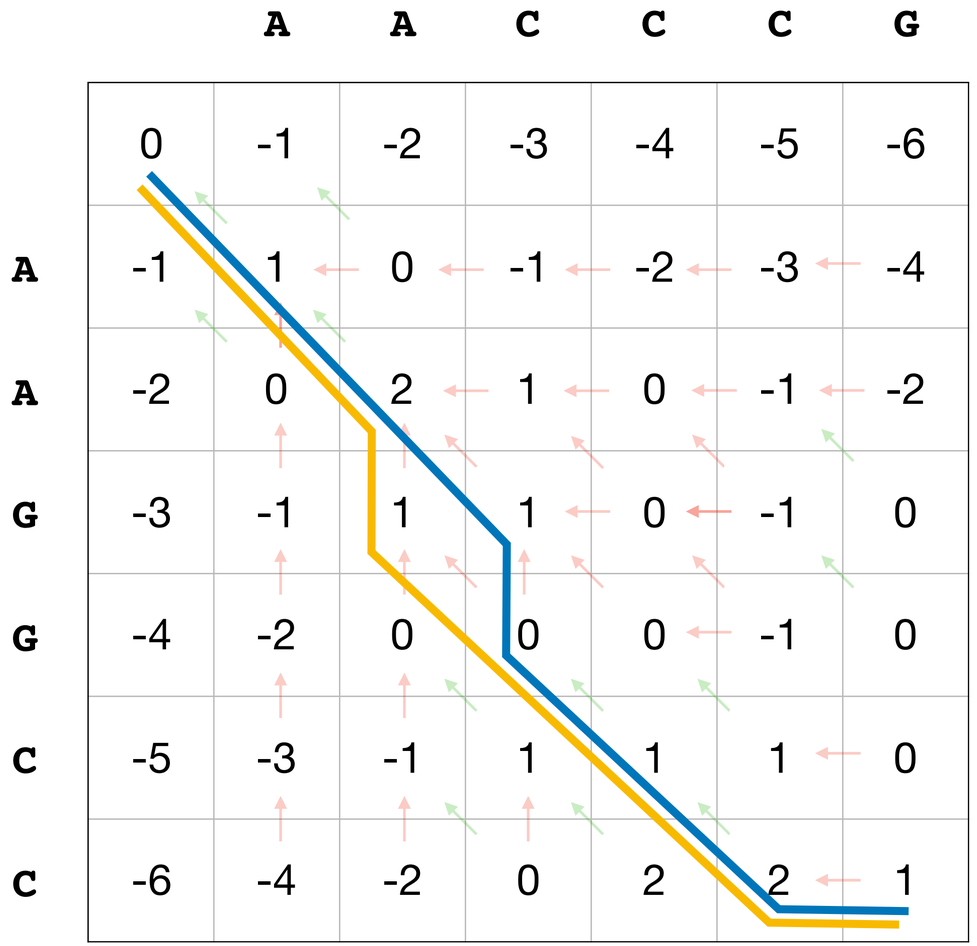
Needleman-Wunch

What about the running time and memory requirements?

- Filling in each cell of the table:
  O(1)-time, *O(1)*-space
- Table is *nxm*
- Filling in the table:
  O(mn)-time, *O(mn)*-space
- Traceback?
  - Each column of the alignment:
    O(1)-time
  - Maximum Alignment Length:
    O(m+n)
    (times the number of optimal alignments)

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

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



- The same problem from the end of Tuesday's class:
  Is pattern *P* present with at most 1 error in text *T?*

Local Alignment

- Given two strings *S* and *T*, find the two substrings, *A* of *S* and *B* of *T,* with the highest alignment score.

- Brute-force: Align all substrings of *S* with all substrings of *T.* There are $\binom{n}{2}$ substrings of *S*, and $\binom{m}{2}$ substrings of *T*. The total running time would be $O(n^3m^3)!$

- Smith and Waterman [1981] developed an algorithm, similar to Needleman-Wunch, that is able to find the optimal local alignment in $O(mn)$-time.

Smith-Waterman

- Still going to use an *n*x*m* sized matrix *V*, but:
  - each index *(i,j)* will hold the maximum global alignment score for all substrings *S[k....i]* and *T[h...j]* where *1≤k≤i* and *1≤h≤j* (the substrings could be empty).
- Then the score of the best local alignment is not necessarily in *V(i,j)*, but is $\max_{i,j} V(i,j)$

Smith-Waterman

- The recurrence relation

$$V(i,j) = \max \begin{cases} 0 & \text{align empty strings} \\ V(i-1,j-1) + \delta(S[i], T[i]) & \text{match/mismatch} \\ V(i-1,j) + \delta(S[i], -) & \text{delete} \\ V(i,j-1) + \delta(-, T[j]) & \text{insert} \end{cases}$$

- The initialization is:

  $V(0,j) = V(i,0) = 0$

Smith-Waterman

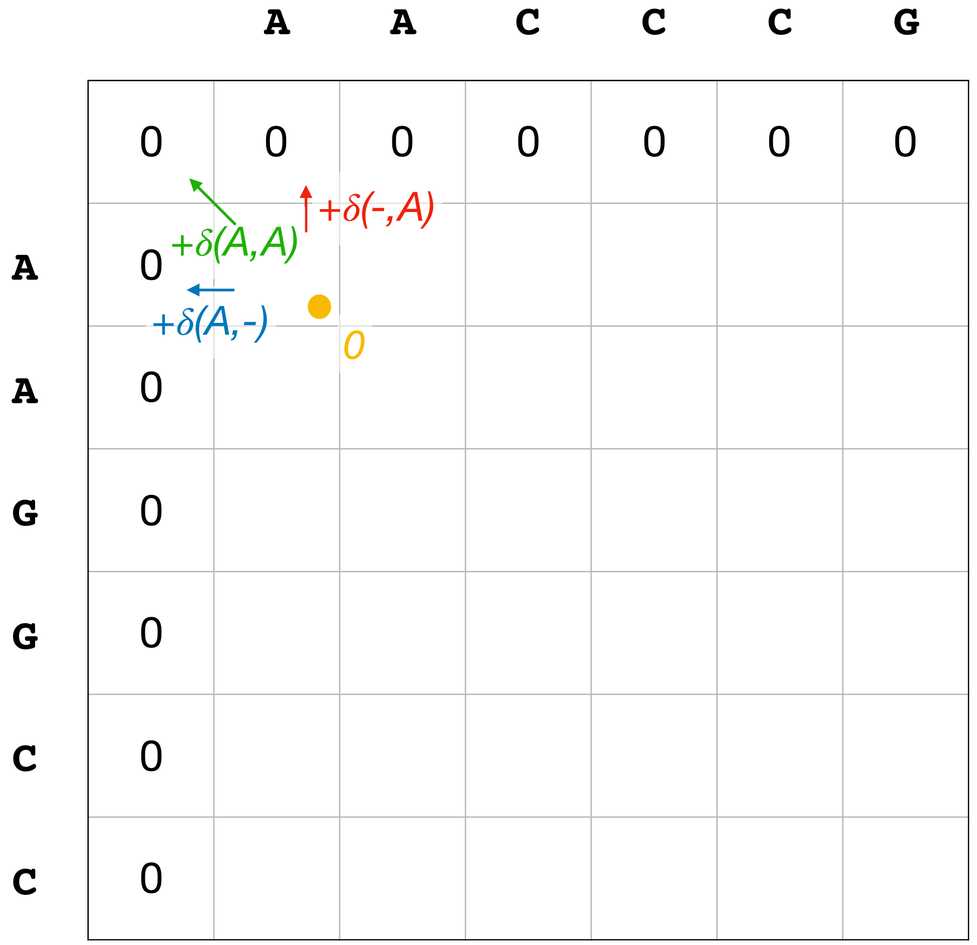
$\delta(-,x) = -1$ for $x \in \Sigma$

$\delta(x,-) = -1$ for $x \in \Sigma$

$\delta(x,y) = 1$ for y = x

$\delta(x,y) = -1$ for y ≠ x

$$V(i,j) = \max \begin{cases} 0 & \text{align empty strings} \\ V(i-1,j-1) + \delta(S[i], T[i]) & \text{match/mismatch} \\ V(i-1,j) + \delta(S[i], -) & \text{delete} \\ V(i,j-1) + \delta(-, T[j]) & \text{insert} \end{cases}$$



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		A	**A**	**C**	**C**	**C**	**G**
	0	0	0	0	0	0	0
A	0	1					
A	0						
G	0						
G	0						
C	0						
C	0						

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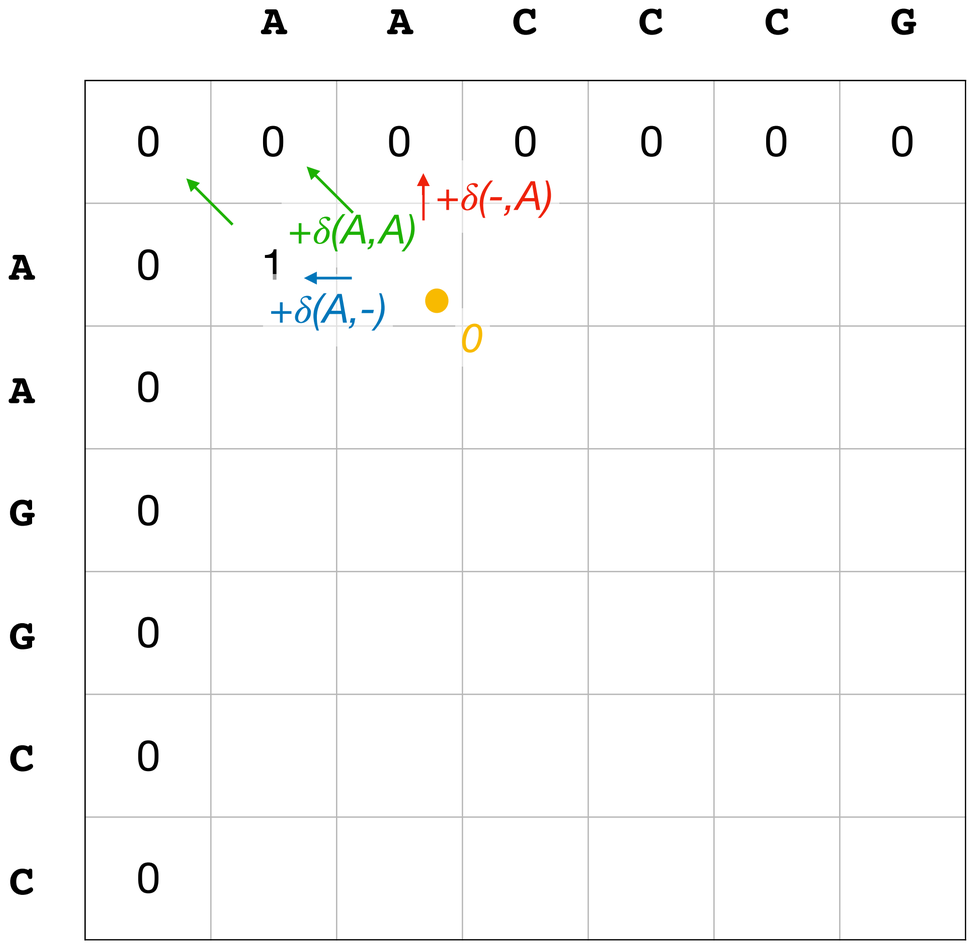

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		A	**A**	**C**	**C**	**C**	**G**
	0	0	0	0	0	0	0
A	0	1	1				
A	0						
G	0						
G	0						
C	0						
C	0						

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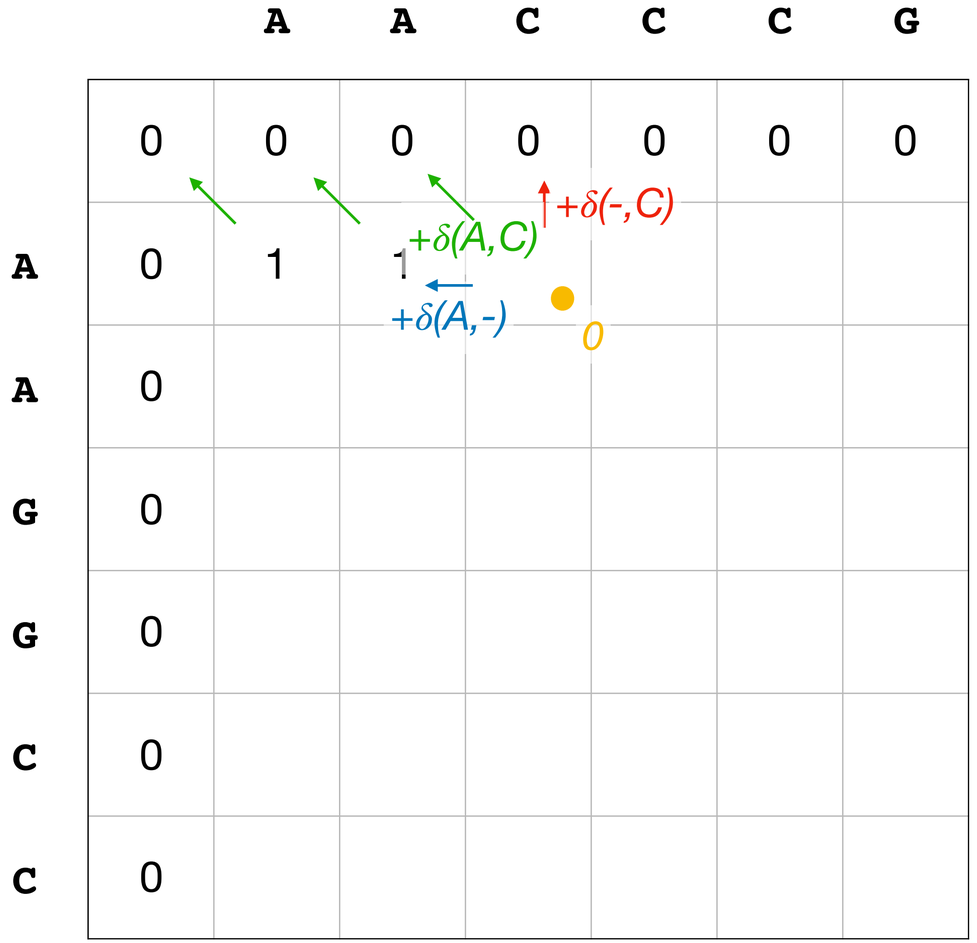

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		A	A	C	C	C	G
	0	0	0	0	0	0	0
A	0	1	1	0			
A	0						
G	0						
G	0						
C	0						
C	0						

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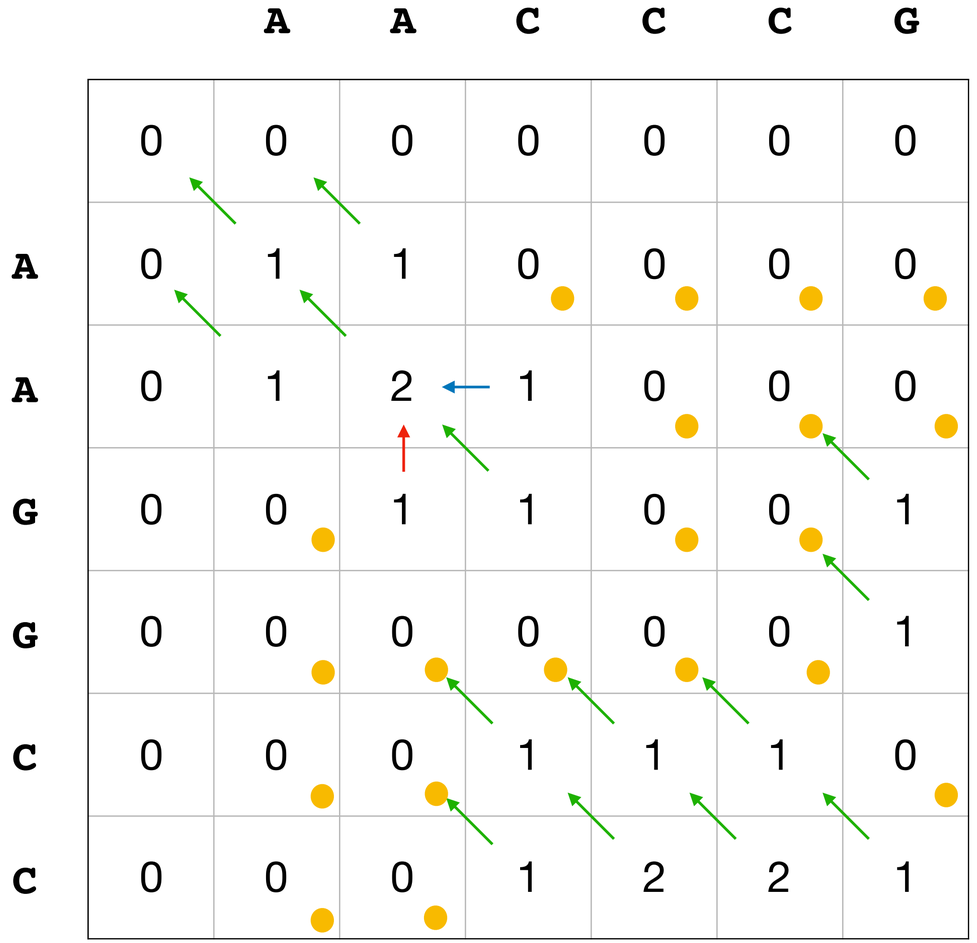

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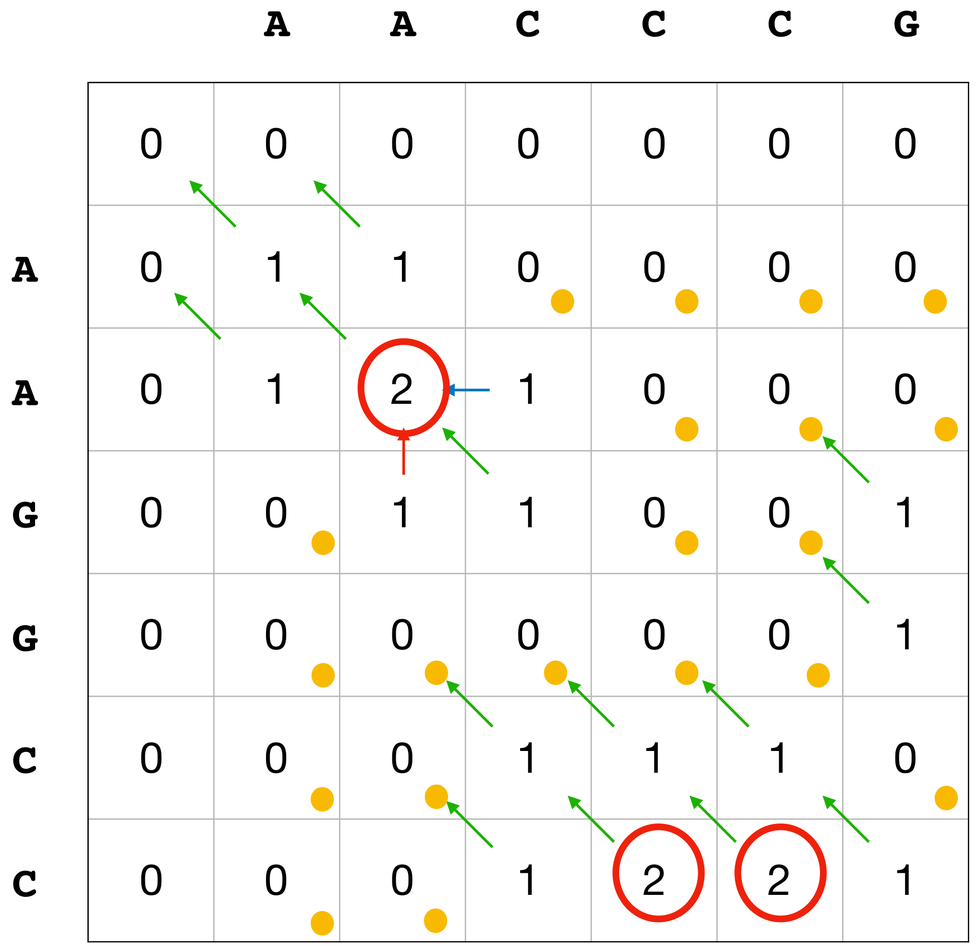

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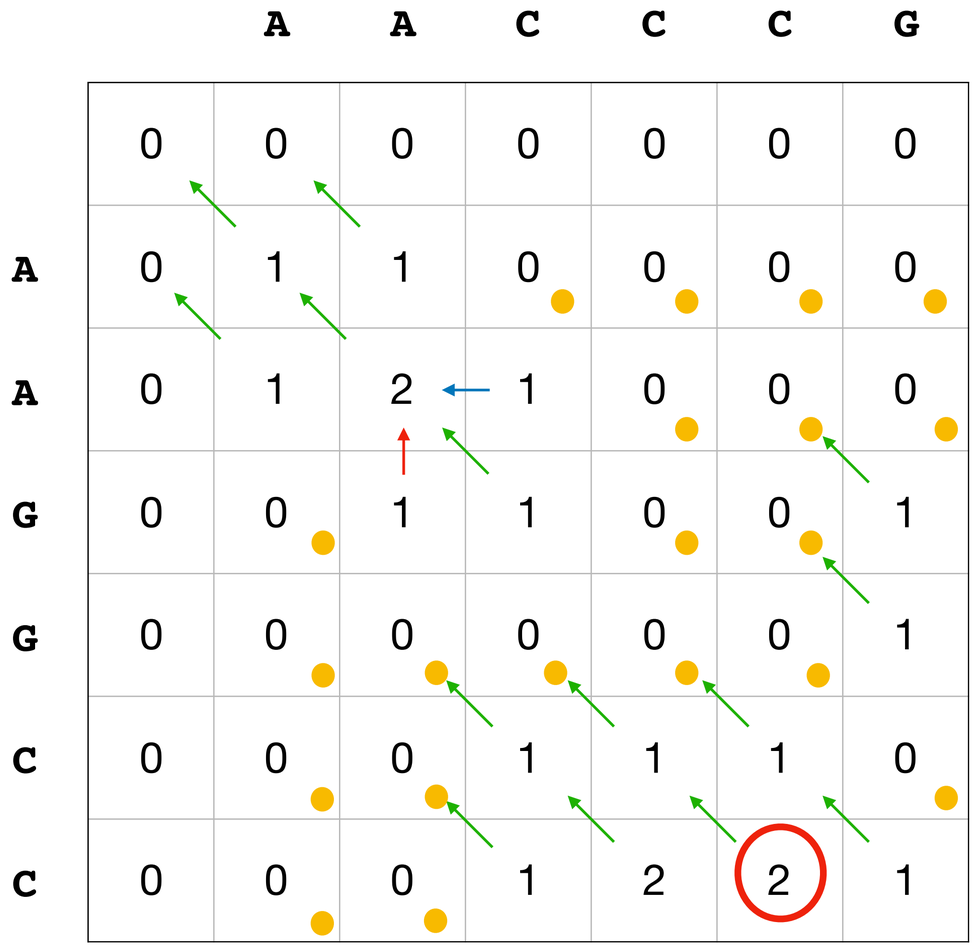

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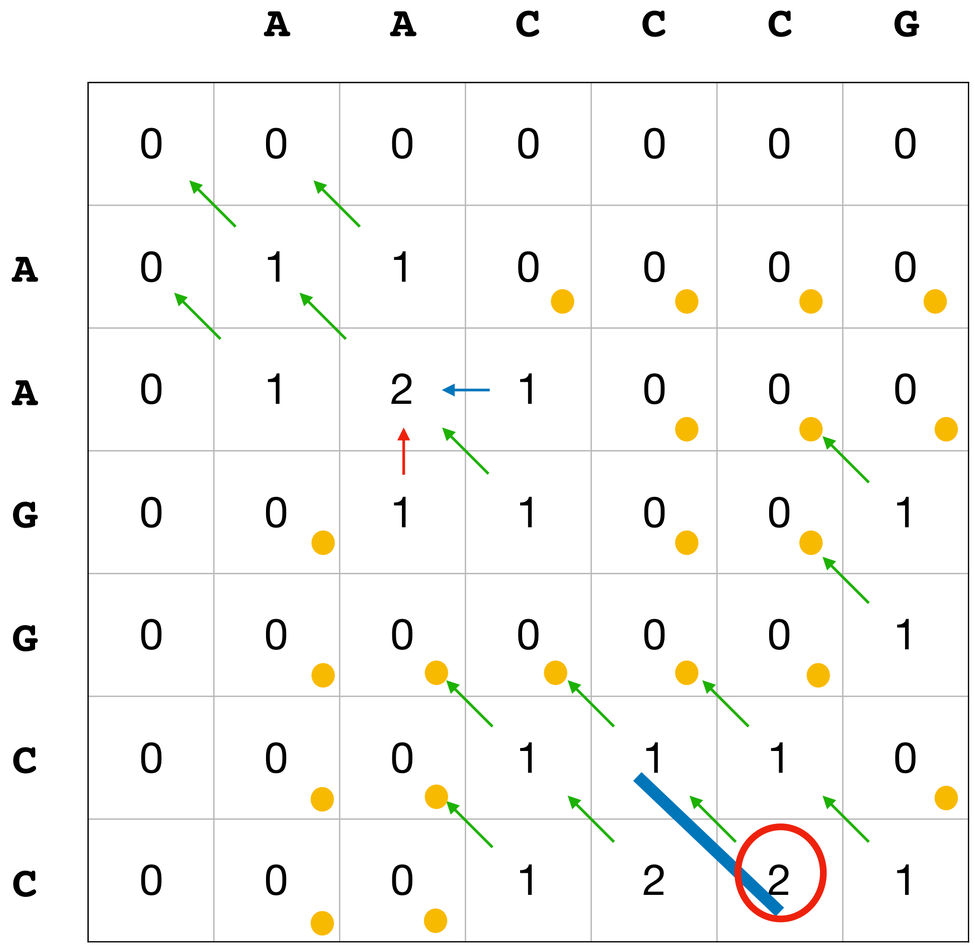

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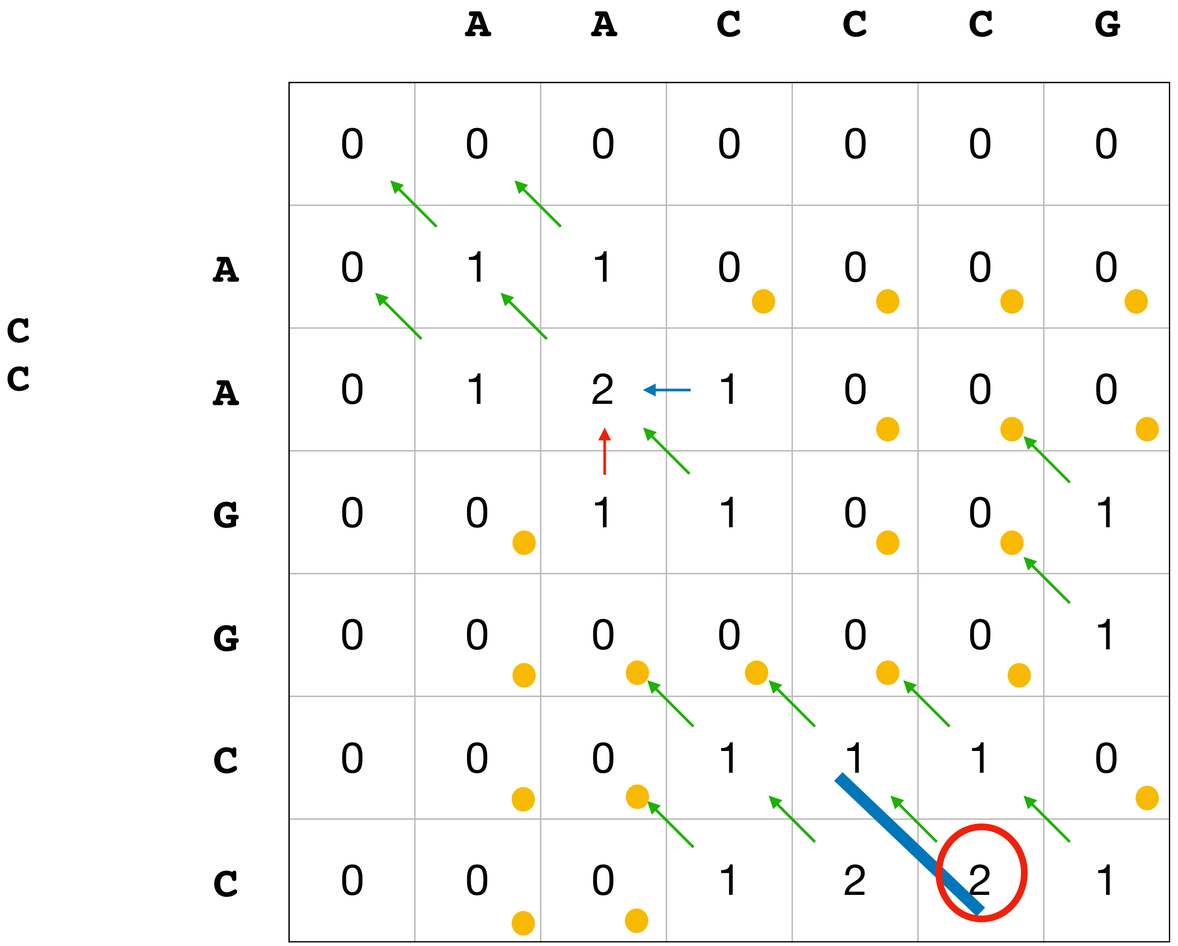

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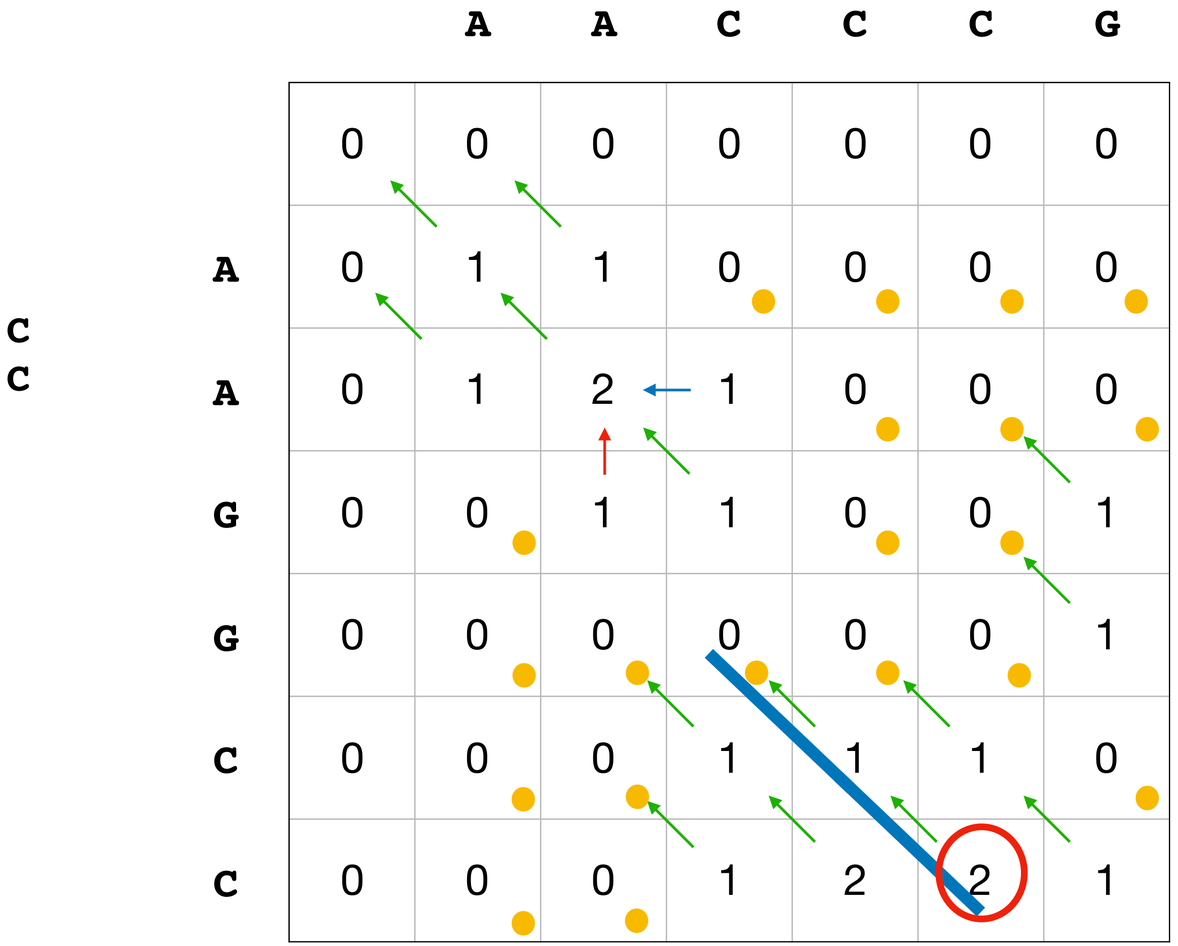

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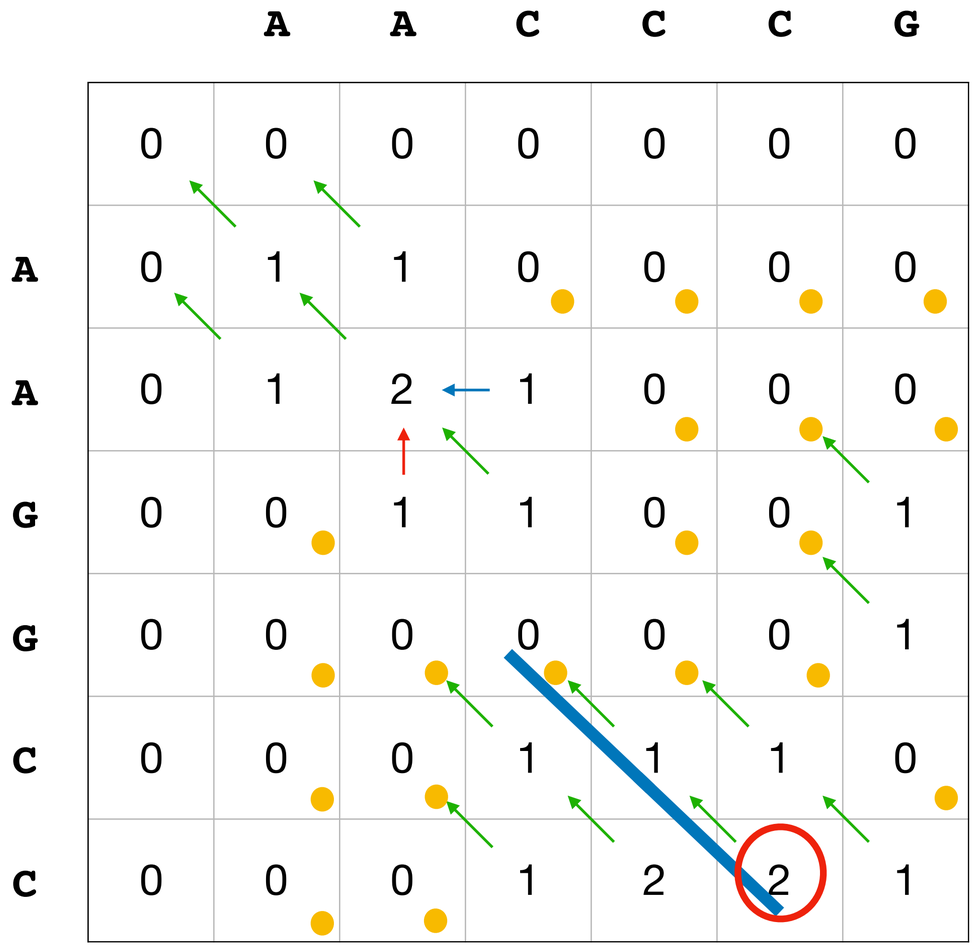
C C
C C

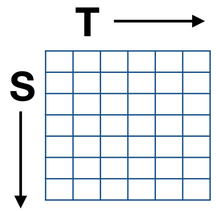


Semi-global Alignment

- In some cases one of the sequence may be smaller than the other
  - in biology, this may be due to sequencing ending early or some process in the cell
- In this case, we may want to not penalize gaps at the beginning or end of one of the sequences
- How can this be done using a slight adjustment to the Myers-Miller algorithm?

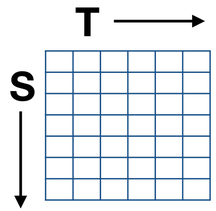
Semi-global Alignment

Ignored spaces	Modification
The beginning of S	
The end of S	
The beginning of T	
The end of T	



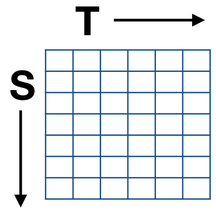
Semi-global Alignment

Ignored spaces	Modification
The beginning of S	Initialize column 0 to 0s
The end of S	
The beginning of T	
The end of T	



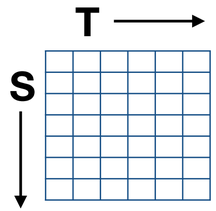
Semi-global Alignment

Ignored spaces	Modification
The beginning of S	Initialize column 0 to 0s
The end of S	Search for the maximum value in the last column
The beginning of T	
The end of T	



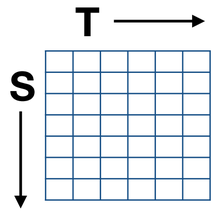
Semi-global Alignment

Ignored spaces	Modification
The beginning of S	Initialize column 0 to 0s
The end of S	Search for the maximum value in the last column
The beginning of T	Initialize row 0 to 0s
The end of T	



Semi-global Alignment

Ignored spaces	Modification
The beginning of S	Initialize column 0 to 0s
The end of S	Search for the maximum value in the last column
The beginning of T	Initialize row 0 to 0s
The end of T	Search for the maximum value in the last row



Lets talk about gaps!

- Up to now inserting a gap character (-) was always a constant cost operation
- In real life (i.e. in biology) starting an inserting 10 bases and inserting 12 bases causes close the same amount of disruption, whereas inserting 0 bases and inserting 2 is a big difference
- So we want to score alignments with this in mind
- Generally, for a gap (set of contiguous insertions or deletions) of length *k,* we want the score to be some function *f(k)* of the length

General Gap Costs

- Given that a gap of length *k* receives a score *f(k)*, in global alignment we change the recursion to the following:

$$V(i,j) = \max \begin{cases} V(i-1,j-1) + \delta(S[i], T[i]) & \text{match/mismatch} \\ \max_{0 \le h \le j-1} \left\{ V(i,h) - f(j-h) \right\} & \text{insert T[h+1...j]} \\ \max_{0 \le h \le j-1} \left\{ V(h,j) - f(i-h) \right\} & \text{delete S[h+1...i]} \end{cases}$$

- And initialization changes slightly:
  V(0,0) = 0
  V(0,j) = -f(j)
  V(i,0) = -f(i)

- This change also increases the running time. Each entry now takes *O(m+n)*-time, therefore the total running time is *O(mn(m+n))*

Affine Gap Costs

- The one everyone uses!
- Attributed to Gotoh [1982]
- Define the function $f_{a,b}(k) =: a + b * k$ where a and b are tunable parameters (if $a=0$, this is the same as before)
- Can still be solved in $O(mn)$-time and $O(mn)$-space, but we need a bit more sophistication

Gotoh's Algorithm

- Define 3 *n*x*m* matricies:
  - *G* -- the alignment score for alignments that end in a match (the last column)
  - *F* -- the alignment score for alignments that end in an insertion
  - *E* -- the alignment score for alignments that end in a deletion

Gotoh's Algorithm

Recursion

$$F(i,j) = \max \begin{cases} F(i-1,j) - b \\ G(i-1,j) - f_{a,b}(1) \end{cases}$$

$$E(i,j) = \max \begin{cases} E(i,j-1) - b \\ G(i,j-1) - f_{a,b}(1) \end{cases}$$

$$G(i,j) = \max \begin{cases} G(i-1,j-1) + \delta(S[i], T[j]) \\ E(i,j) \\ F(i,j) \end{cases}$$

Initialization

$$G(0,j) = E(0,j) = -1 f_{a,b}(j)$$
$$G(i,0) = F(i,0) = -1 f_{a,b}(i)$$
$$E(i,0) = -\infty$$
$$F(0,j) = -\infty$$

Gotoh's Algorithm

$G(0,j) = E(0,j) = -1f_{a,b}(j)$

$G(i,0) = F(i,0) = -1f_{a,b}(i)$

$E(i,0) = -\infty$

$F(0,j) = -\infty$

E

		A	**A**	**C**	**C**	**C**	**G**
	-∞	-∞	-∞	-∞	-∞	-∞	-∞
A	-4						
A	-5						
G	-6						
G	-7						
C	-8						
C	-9						

G

		A	**A**	**C**	**C**	**C**	**G**
	0	-4	-5	-6	-7	-8	-9
A	-4						
A	-5						
G	-6						
G	-7						
C	-8						
C	-9						

F

		A	**A**	**C**	**C**	**C**	**G**
	-∞	-4	-5	-6	-7	-8	-9
A	-∞						
A	-∞						
G	-∞						
G	-∞						
C	-∞						
C	-∞						

δ(x,y) = 10 for y = x

δ(x,y) = -2 for y ≠ x

$$E(i,j) = \max \begin{cases} E(i,j-1) - b \\ G(i,j-1) - f_{a,b}(1) \end{cases}$$

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$$F(i,j) = \max \begin{cases} F(i-1,j) - b \\ G(i-1,j) - f_{a,b}(1) \end{cases}$$

a = 3

b = 1

Gotoh's Algorithm

$G(0,j) = E(0,j) = -1f_{a,b}(j)$

$G(i,0) = F(i,0) = -1f_{a,b}(i)$

$E(i,0) = -\infty$

$F(0,j) = -\infty$

E

		A	**A**	**C**	**C**	**C**	**G**
	-∞	-∞ ↑ -b	-∞	-∞	-∞	-∞	-∞
A	-4						
A	-5						
G	-6						
G	-7						
C	-8						
C	-9						

G

		A	**A**	**C**	**C**	**C**	**G**
	0	-4	-5	-6	-7	-8	-9
A	-4						
A	-5						
G	-6						
G	-7						
C	-8						
C	-9						

F

		A	**A**	**C**	**C**	**C**	**G**
	-∞	-4	-5	-6	-7	-8	-9
A	-∞						
A	-∞						
G	-∞						
G	-∞						
C	-∞						
C	-∞						

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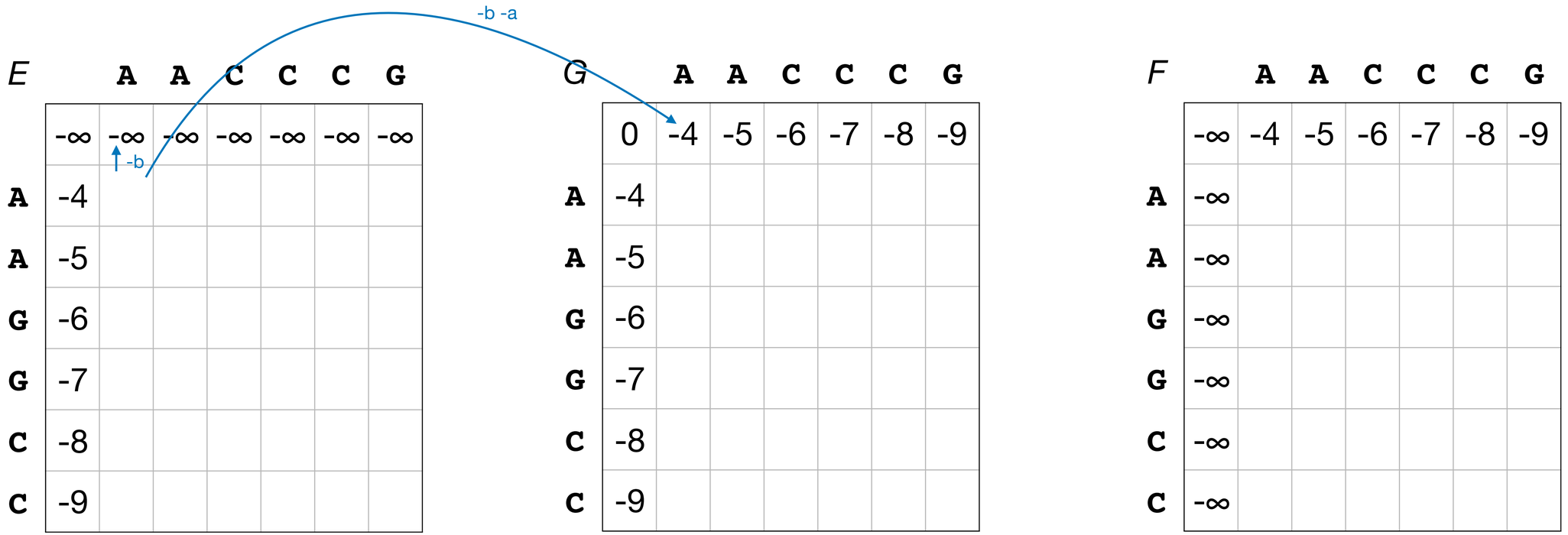

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b = 1

Gotoh's Algorithm

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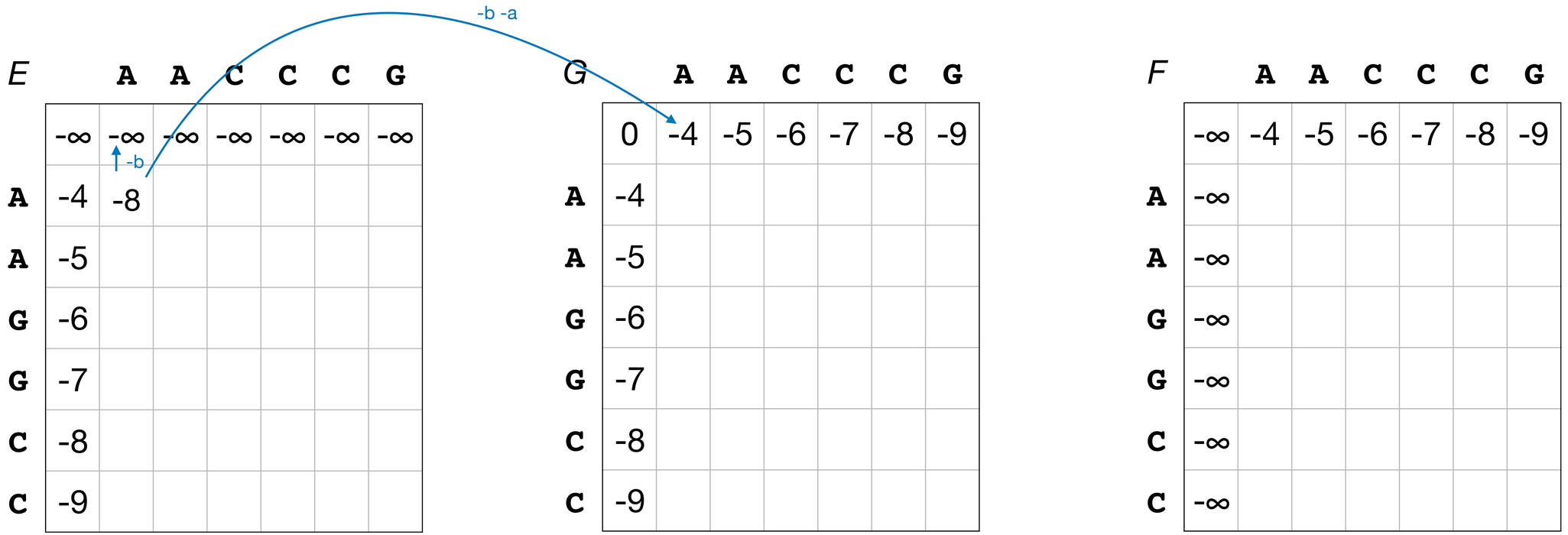

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$$F(i,j) = \max \begin{cases} F(i-1,j) - b \\ G(i-1,j) - f_{a,b}(1) \end{cases}$$

a = 3

b = 1

Gotoh's Algorithm

$G(0,j) = E(0,j) = -1f_{a,b}(j)$

$G(i,0) = F(i,0) = -1f_{a,b}(i)$

$E(i,0) = -\infty$

$F(0,j) = -\infty$

E

		A	**A**	**C**	**C**	**C**	**G**
	-∞	-∞	-∞	-∞	-∞	-∞	-∞
A	-4	-8					
A	-5						
G	-6						
G	-7						
C	-8						
C	-9						

G

		A	**A**	**C**	**C**	**C**	**G**
	0	-4	-5	-6	-7	-8	-9
A	-4						
A	-5						
G	-6						
G	-7						
C	-8						
C	-9						

F

		A	**A**	**C**	**C**	**C**	**G**
	-∞	-4	-5	-6	-7	-8	-9
A	-∞						
A	-∞						
G	-∞						
G	-∞						
C	-∞						
C	-∞						

δ(x,y) = 10 for y = x

δ(x,y) = -2 for y ≠ x

$$E(i,j) = \max \begin{cases} E(i,j-1) - b \\ G(i,j-1) - f_{a,b}(1) \end{cases}$$

$$G(i,j) = \max \begin{cases} G(i-1,j-1) + \delta(S[i], T[j]) \\ E(i,j) \\ F(i,j) \end{cases}$$

$$F(i,j) = \max \begin{cases} F(i-1,j) - b \\ G(i-1,j) - f_{a,b}(1) \end{cases}$$

a = 3

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E

		A	**A**	**C**	**C**	**C**	**G**
	-∞	-∞	-∞	-∞	-∞	-∞	-∞
A	-4	-8					
A	-5						
G	-6						
G	-7						
C	-8						
C	-9						

G

		A	**A**	**C**	**C**	**C**	**G**
	0	-4	-5	-6	-7	-8	-9
A	-4						
A	-5						
G	-6						
G	-7						
C	-8						
C	-9						

F

		A	**A**	**C**	**C**	**C**	**G**
	-∞	-4	-5	-6	-7	-8	-9
A	-∞	-b					
A	-∞						
G	-∞						
G	-∞						
C	-∞						
C	-∞						

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E

		A	**A**	**C**	**C**	**C**	**G**
	-∞	-∞	-∞	-∞	-∞	-∞	-∞
A	-4	-8					
A	-5						
G	-6						
G	-7						
C	-8						
C	-9						

G

		A	**A**	**C**	**C**	**C**	**G**
	0	-4	-5	-6	-7	-8	-9
A	-4						
A	-5						
G	-6						
G	-7						
C	-8						
C	-9						

F

-b -a

-b

		A	**A**	**C**	**C**	**C**	**G**
	-∞	-4	-5	-6	-7	-8	-9
A	-∞						
A	-∞						
G	-∞						
G	-∞						
C	-∞						
C	-∞						

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		A	**A**	**C**	**C**	**C**	**G**
	-∞	-∞	-∞	-∞	-∞	-∞	-∞
A	-4	-8					
A	-5						
G	-6						
G	-7						
C	-8						
C	-9						

G

		A	**A**	**C**	**C**	**C**	**G**
	0	-4	-5	-6	-7	-8	-9
A	-4						
A	-5						
G	-6						
G	-7						
C	-8						
C	-9						

F

-b -a

-b

		A	**A**	**C**	**C**	**C**	**G**
	-∞	-4	-5	-6	-7	-8	-9
A	-∞	-8					
A	-∞						
G	-∞						
G	-∞						
C	-∞						
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		A	**A**	**C**	**C**	**C**	**G**
	-∞	-∞	-∞	-∞	-∞	-∞	-∞
A	-4	-8					
A	-5						
G	-6						
G	-7						
C	-8						
C	-9						

G

		A	**A**	**C**	**C**	**C**	**G**
	0	-4	-5	-6	-7	-8	-9
A	-4						
A	-5						
G	-6						
G	-7						
C	-8						
C	-9						

F

		A	**A**	**C**	**C**	**C**	**G**
	-∞	-4	-5	-6	-7	-8	-9
A	-∞	-8					
A	-∞						
G	-∞						
G	-∞						
C	-∞						
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E

		A	**A**	**C**	**C**	**C**	**G**
	-∞	-∞	-∞	-∞	-∞	-∞	-∞
A	-4	-8					
A	-5						
G	-6						
G	-7						
C	-8						
C	-9						

G

		A	**A**	**C**	**C**	**C**	**G**
	0	-4	-5	-6	-7	-8	-9
A	-4						
A	-5						
G	-6						
G	-7						
C	-8						
C	-9						

F

		A	**A**	**C**	**C**	**C**	**G**
	-∞	-4	-5	-6	-7	-8	-9
A	-∞	-8					
A	-∞						
G	-∞						
G	-∞						
C	-∞						
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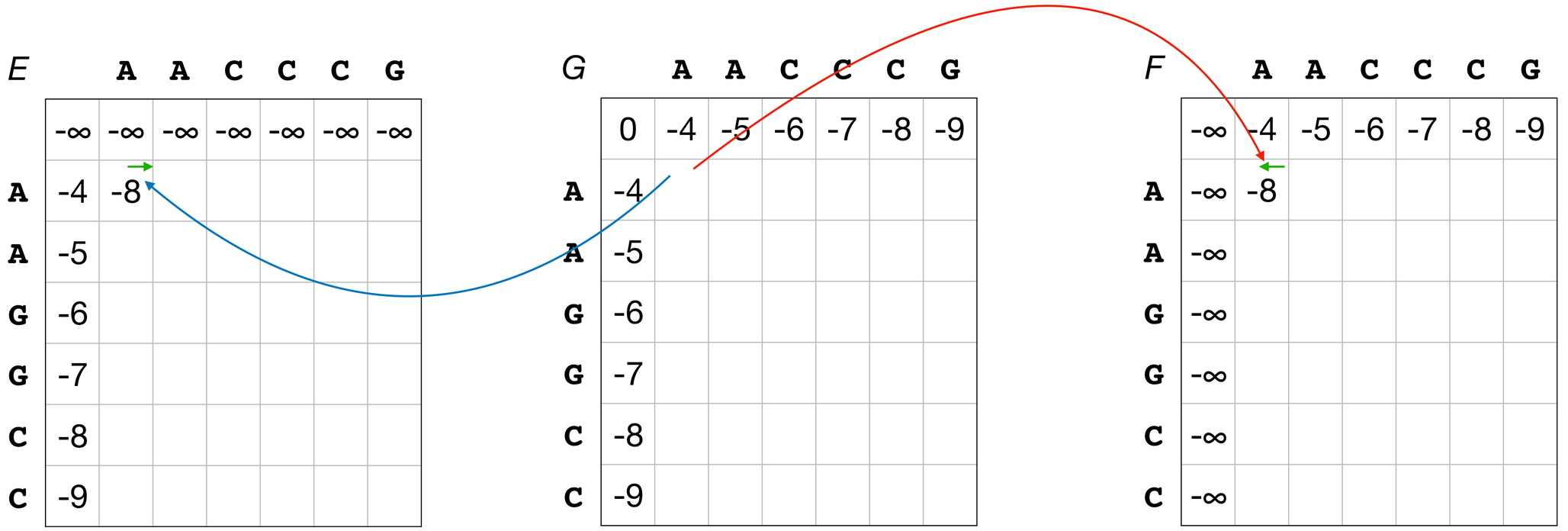

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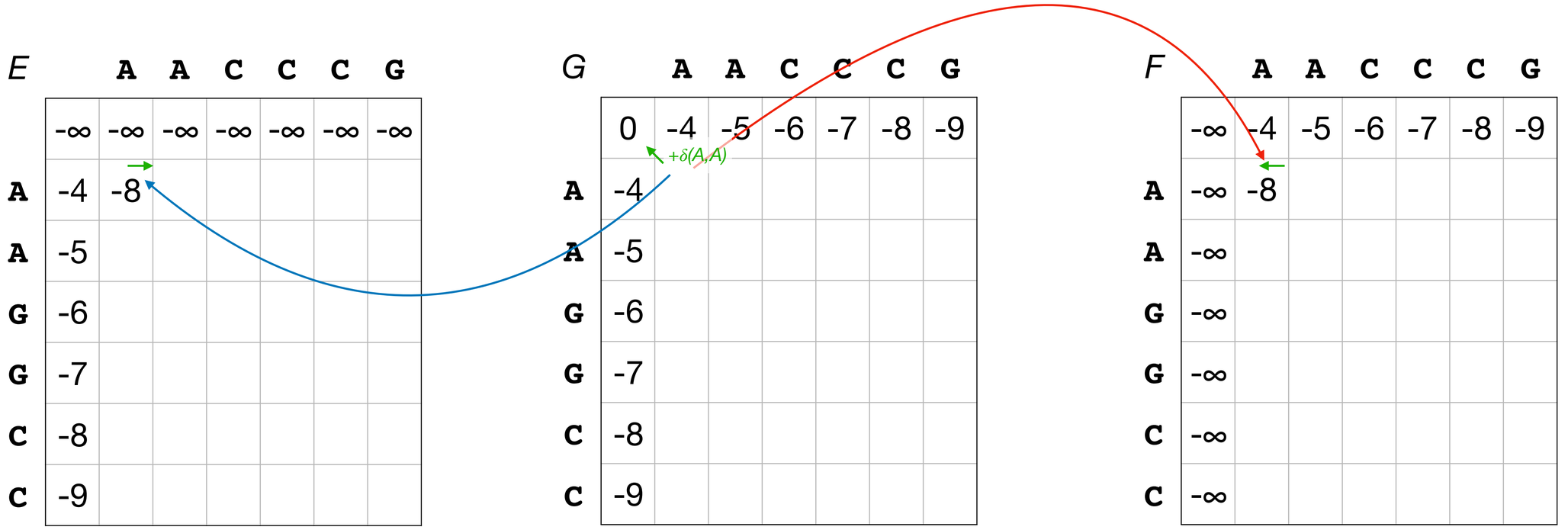

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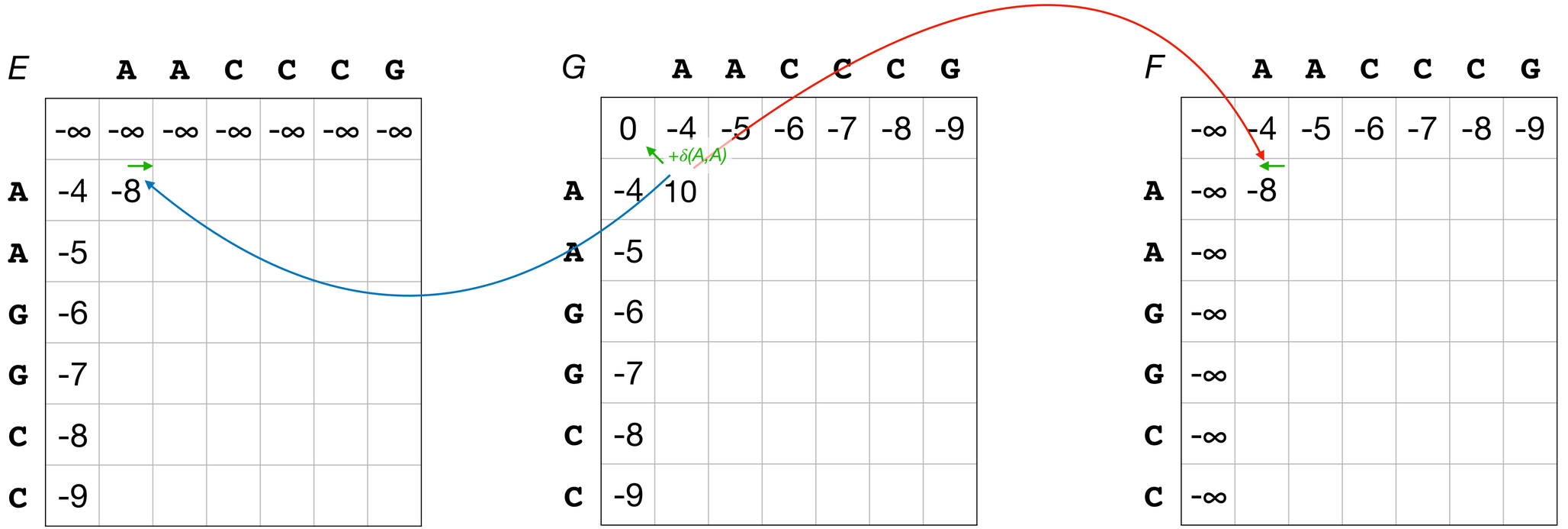

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$F(0,j) = -\infty$

E

		A	**A**	**C**	**C**	**C**	**G**
	-∞	-∞	-∞	-∞	-∞	-∞	-∞
A	-4	-8	-9	-10	-11	-12	-13
A	-5	6	2	1	0	-1	-2
G	-6	5	16	12	11	10	9
G	-7	4	15	14	10	9	20
C	-8	3	14	13	12	8	19
C	-9	2	13	21	20	22	18

G

		A	**A**	**C**	**C**	**C**	**G**
	0	-4	-5	-6	-7	-8	-9
A	-4	10	6	5	4	3	2
A	-5	6	20	16	15	14	13
G	-6	5	16	18	14	13	24
G	-7	4	15	14	16	12	23
C	-8	3	14	25	24	26	22
C	-9	2	13	24	35	34	30

F

		A	**A**	**C**	**C**	**C**	**G**
	-∞	-4	-5	-6	-7	-8	-9
A	-∞	-8	6	5	4	3	2
A	-∞	-9	2	16	15	14	13
G	-∞	-10	1	15	14	13	12
G	-∞	-11	0	11	10	12	11
C	-∞	-12	-1	10	21	20	22
C	-∞	-13	-2	8	20	31	30

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a = 3

b = 1

Gotoh's Algorithm

E

		A	**A**	**C**	**C**	**C**	**G**
	-∞	-∞	-∞	-∞	-∞	-∞	-∞
A	-4	-8	-9	-10	-11	-12	-13
A	-5	6	2	1	0	-1	-2
G	-6	5	16	12	11	10	9
G	-7	4	15	14	10	9	20
C	-8	3	14	13	12	8	19
C	-9	2	13	21	20	22	18

G

		A	**A**	**C**	**C**	**C**	**G**
	0	-4	-5	-6	-7	-8	-9
A	-4	10	6	5	4	3	2
A	-5	6	20	16	15	14	13
G	-6	5	16	18	14	13	24
G	-7	4	15	14	16	12	23
C	-8	3	14	25	24	26	22
C	-9	2	13	24	35	34	30

F

		A	**A**	**C**	**C**	**C**	**G**
	-∞	-4	-5	-6	-7	-8	-9
A	-∞	-8	6	5	4	3	2
A	-∞	-9	2	16	15	14	13
G	-∞	-10	1	15	14	13	12
G	-∞	-11	0	11	10	12	11
C	-∞	-12	-1	10	21	20	22
C	-∞	-13	-2	8	20	31	30

(6,6)

Gotoh's Algorithm

E

		A	**A**	**C**	**C**	**C**	**G**
	-∞	-∞	-∞	-∞	-∞	-∞	-∞
A	-4	-8	-9	-10	-11	-12	-13
A	-5	6	2	1	0	-1	-2
G	-6	5	16	12	11	10	9
G	-7	4	15	14	10	9	20
C	-8	3	14	13	12	8	19
C	-9	2	13	21	20	22	18

G

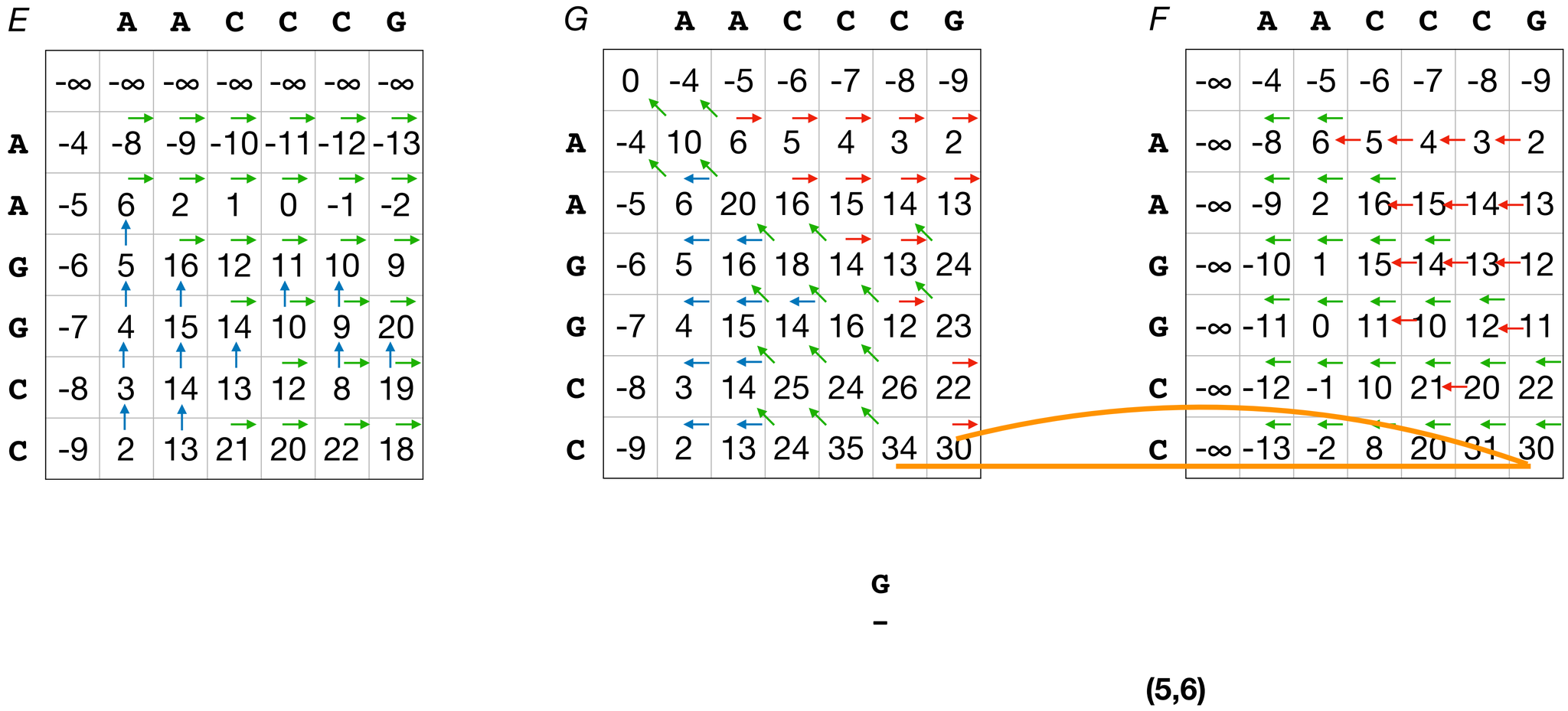
		A	**A**	**C**	**C**	**C**	**G**
	0	-4	-5	-6	-7	-8	-9
A	-4	10	6	5	4	3	2
A	-5	6	20	16	15	14	13
G	-6	5	16	18	14	13	24
G	-7	4	15	14	16	12	23
C	-8	3	14	25	24	26	22
C	-9	2	13	24	35	34	30

F

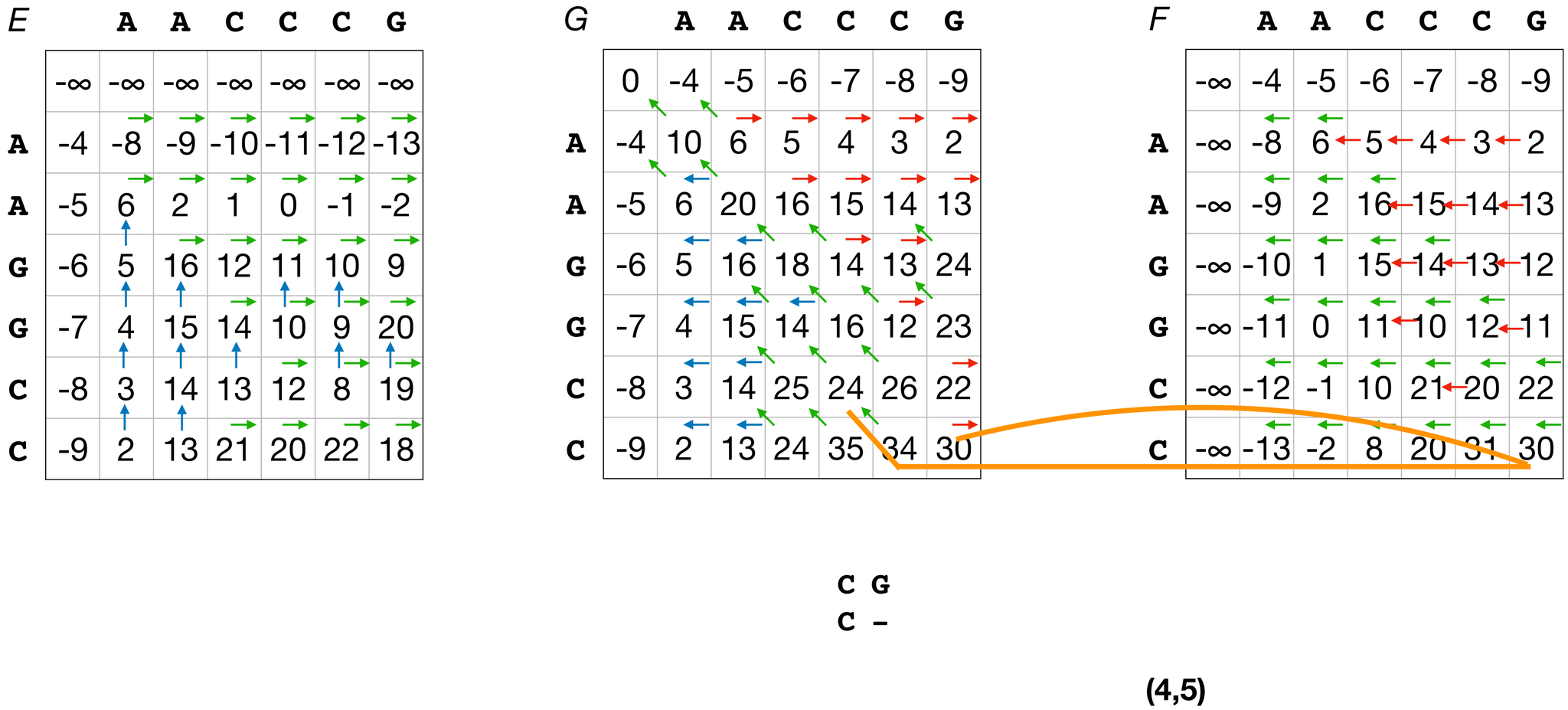
		A	**A**	**C**	**C**	**C**	**G**
	-∞	-4	-5	-6	-7	-8	-9
A	-∞	-8	6	5	4	3	2
A	-∞	-9	2	16	15	14	13
G	-∞	-10	1	15	14	13	12
G	-∞	-11	0	11	10	12	11
C	-∞	-12	-1	10	21	20	22
C	-∞	-13	-2	8	20	31	30

(6,6)

Gotoh's Algorithm



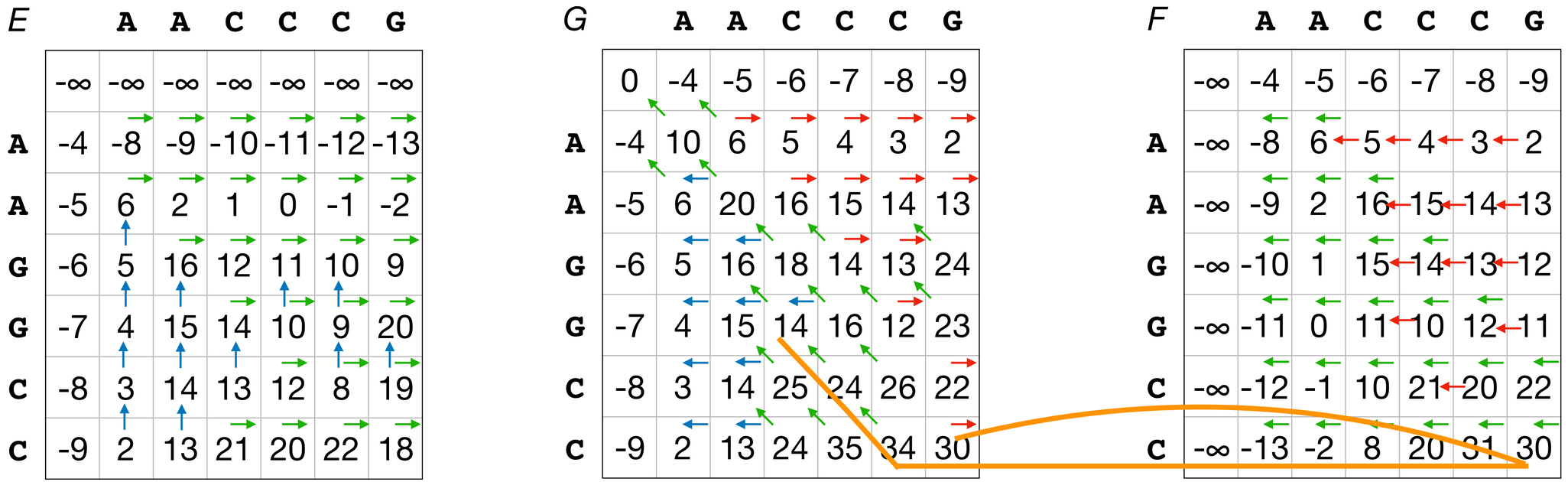
Gotoh's Algorithm



C G
C –

(4,5)

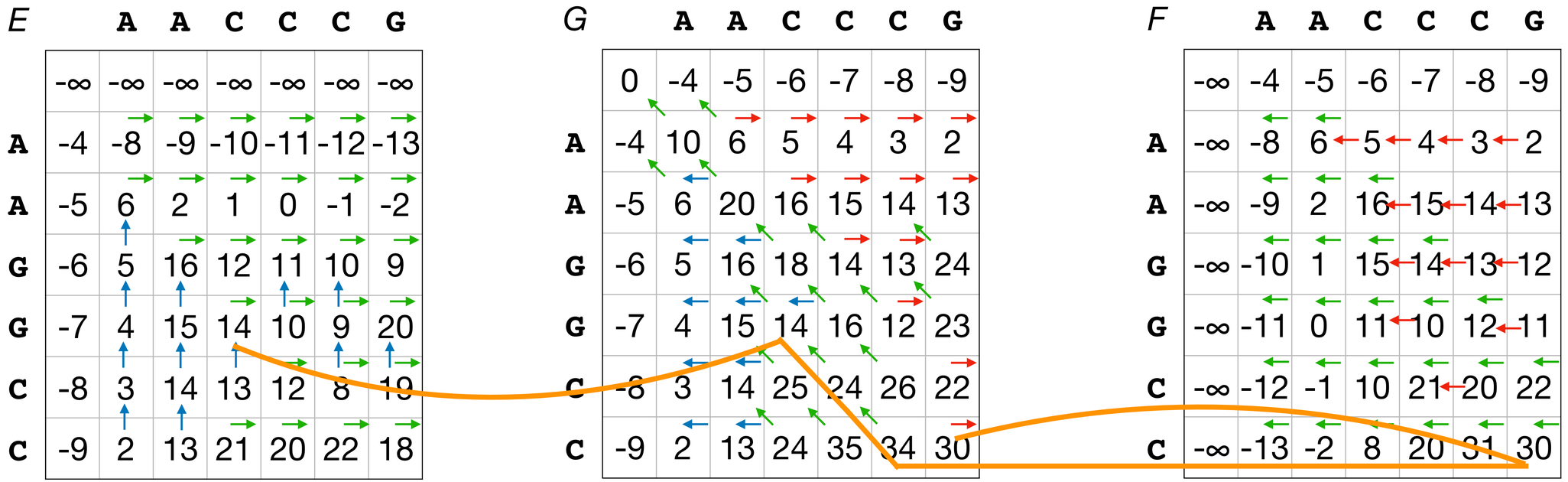
Gotoh's Algorithm



C C G
C C –

(3,4)

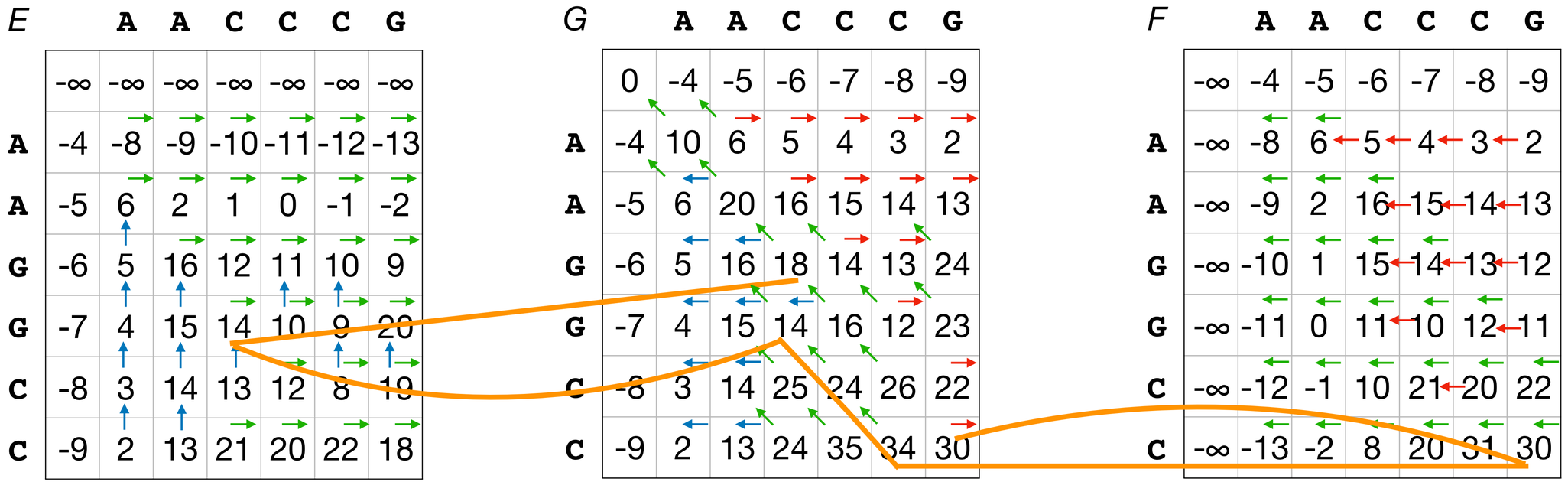
Gotoh's Algorithm



C C G
C C –

(3,4)

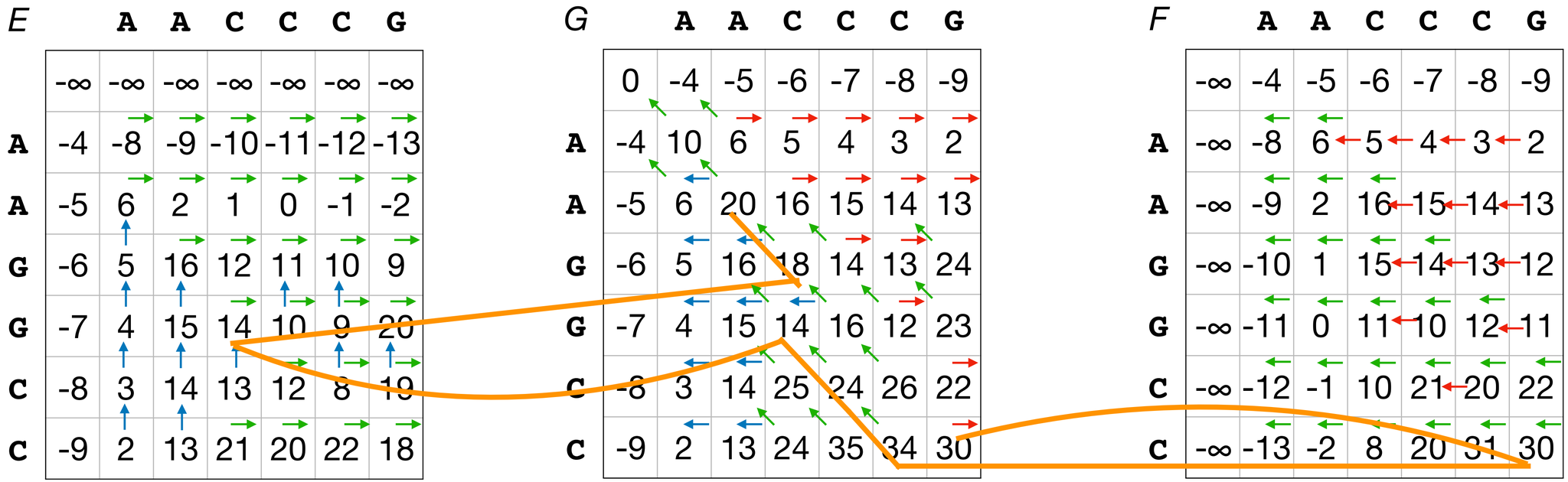
Gotoh's Algorithm



– C C G
G C C –

(3,3)

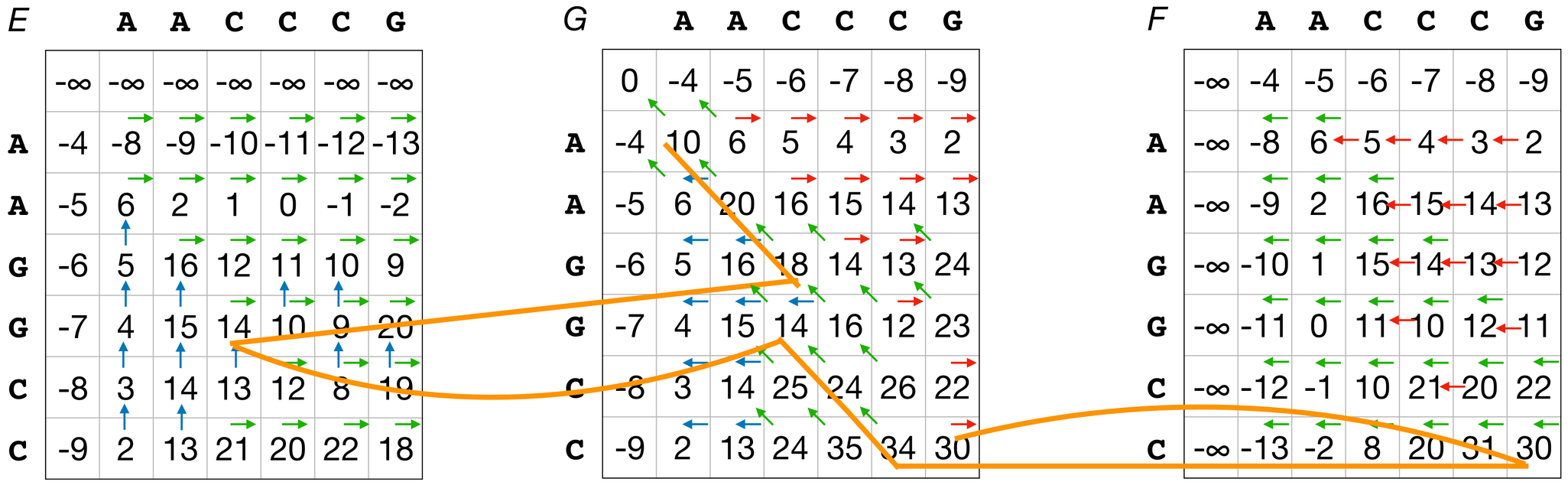
Gotoh's Algorithm



C – C C G
G G C C –

(2,2)

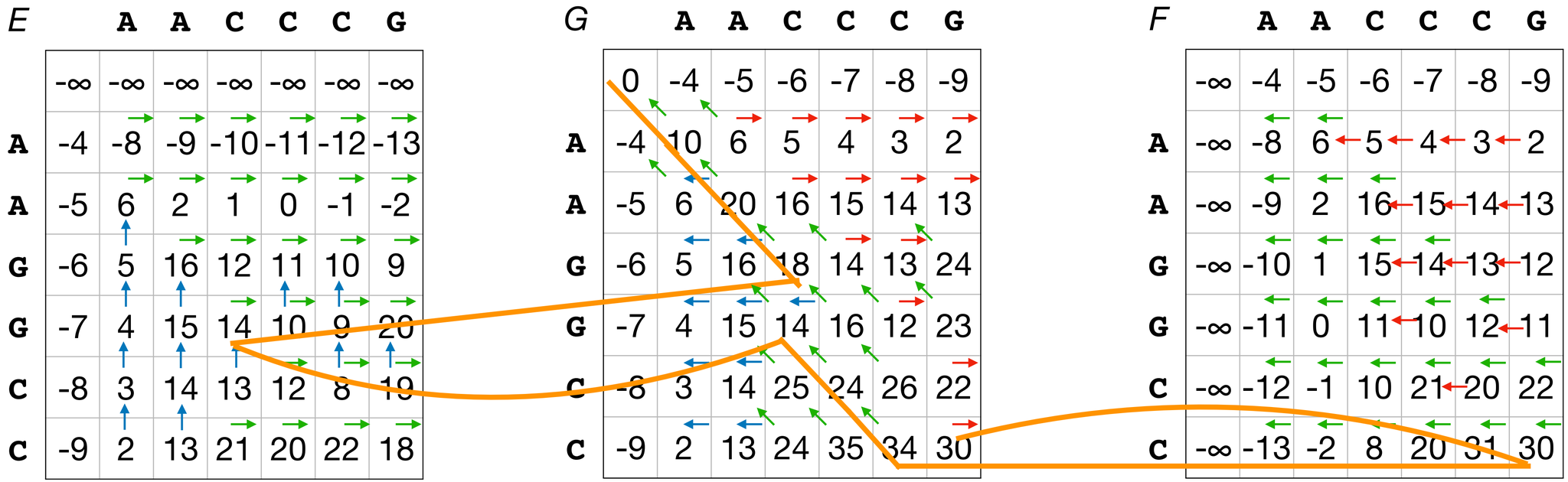
Gotoh's Algorithm



A C – C C G
A G G C C –

(1,1)

Gotoh's Algorithm



A A C – C C G
A A G G C C –

(0,0)

Computing alignments in linear space

- Up to now, global, local, and semi-global alignments using fixed, general, and affine gap costs have all taken $O(mn)$-time and $O(mn)$-space

- For long sequences we may not be able to keep the whole table in main memory, therefore if the space can be reduced it would improve the practicality of the algorithms

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- Hershberg [1975] shows that global alignment can be computed in *O(n+m)*-space[1]

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Computing alignments in linear space

- Up to now, global, local, and semi-global alignments using fixed, general, and affine gap costs have all taken *O(mn)*-time and *O(mn*)-space
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- The key is that when computing *V*, (in row-major, left to right order) the value only depends on the row above, and the current values in the same row to the left

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- The key is that when computing *V*, (in row-major, left to right order) the value only depends on the row above, and the current values in the same row to the left
- But with only that observation you can find the best alignment **score** in linear space, but not the alignment itself

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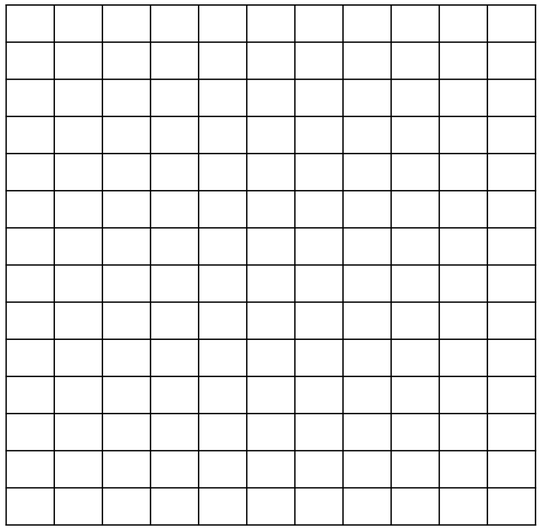
Hirschberg's Algorithm



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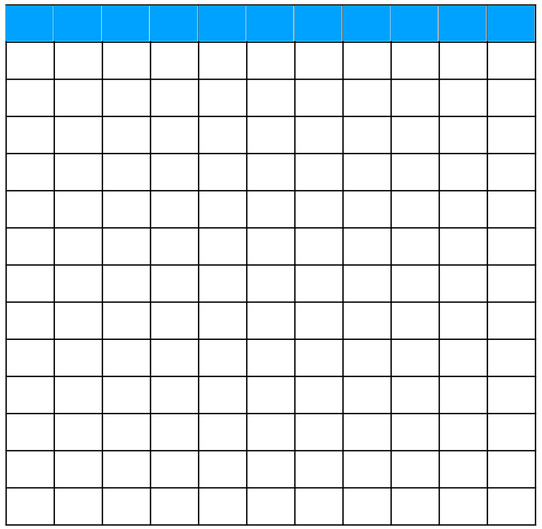

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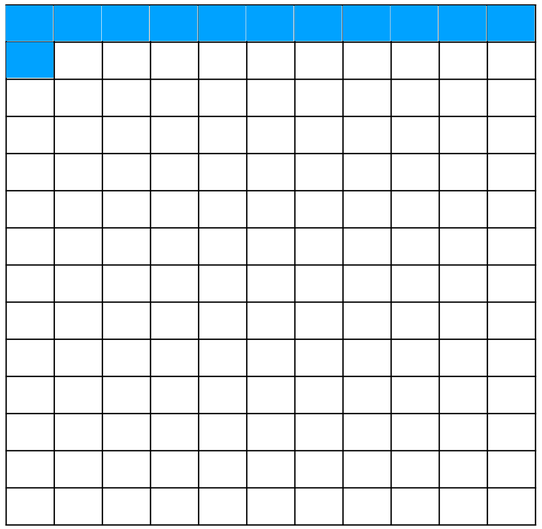

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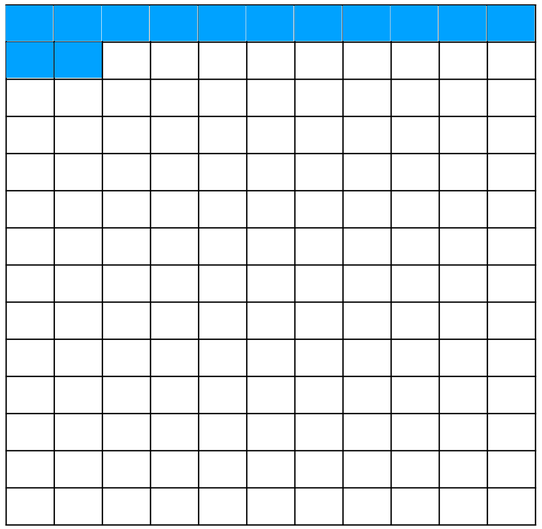

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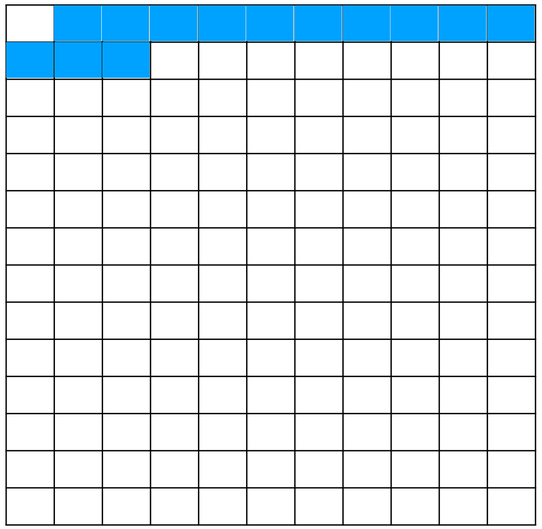

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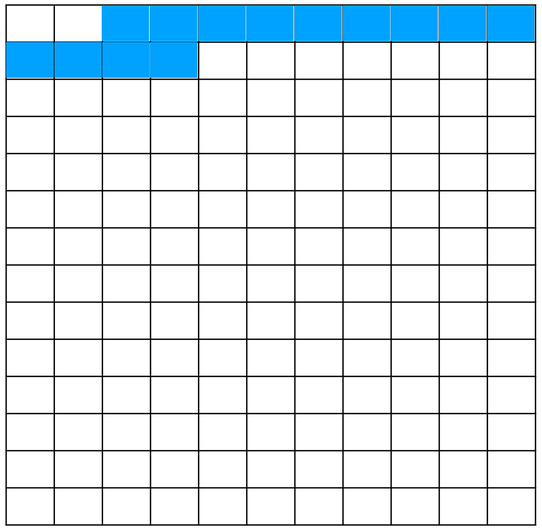

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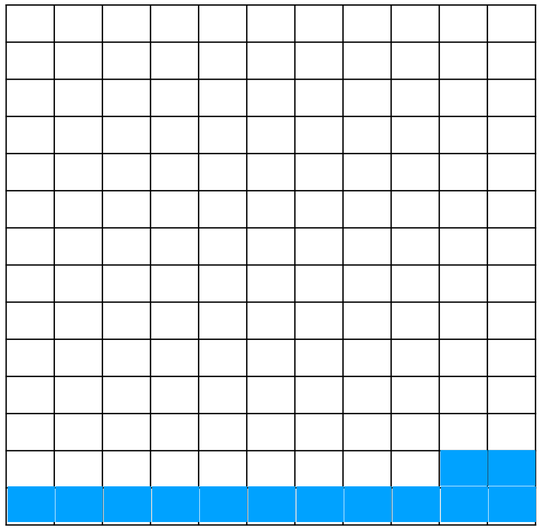

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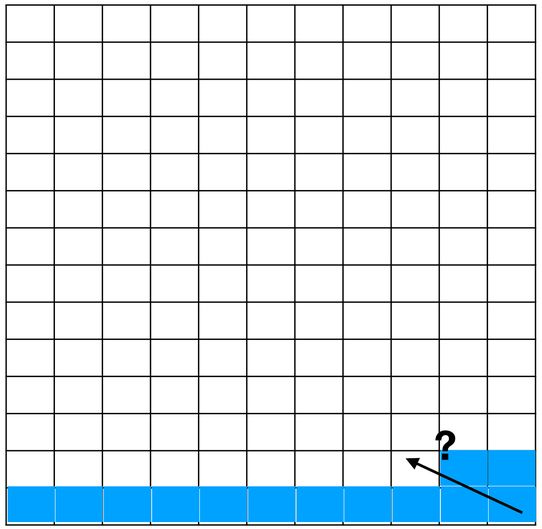

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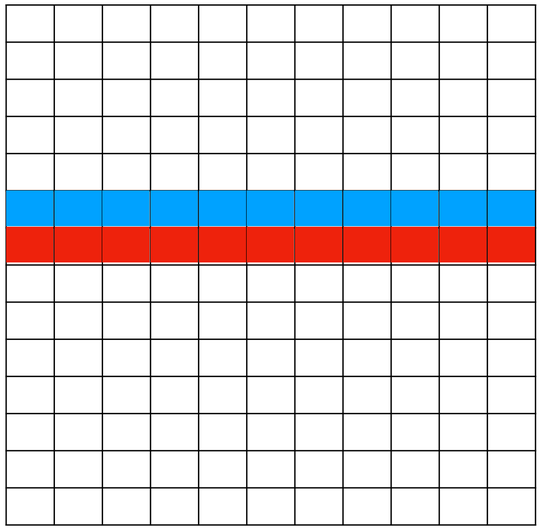

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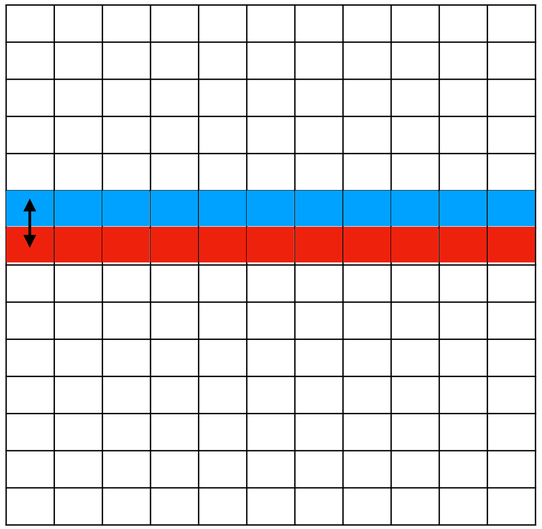

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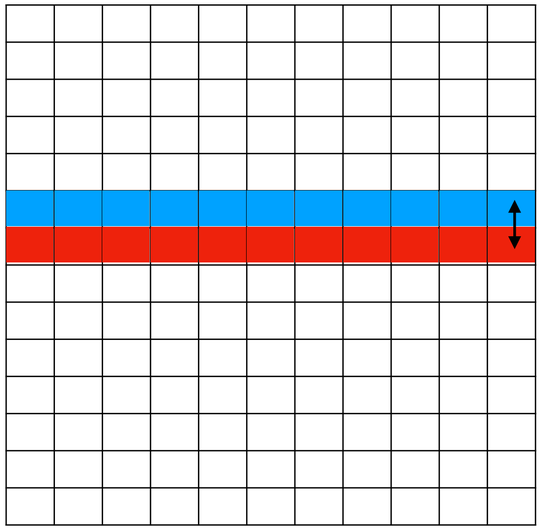

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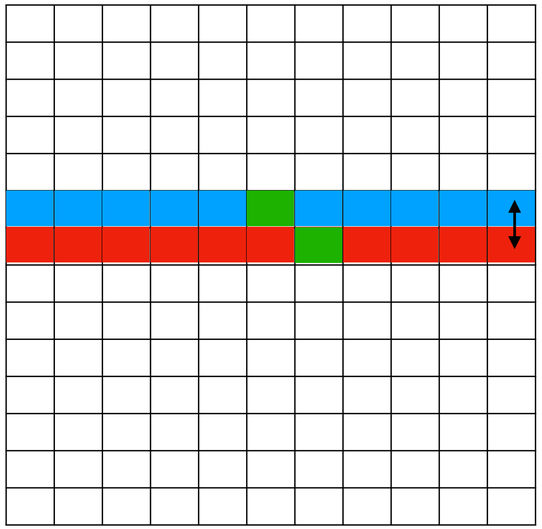

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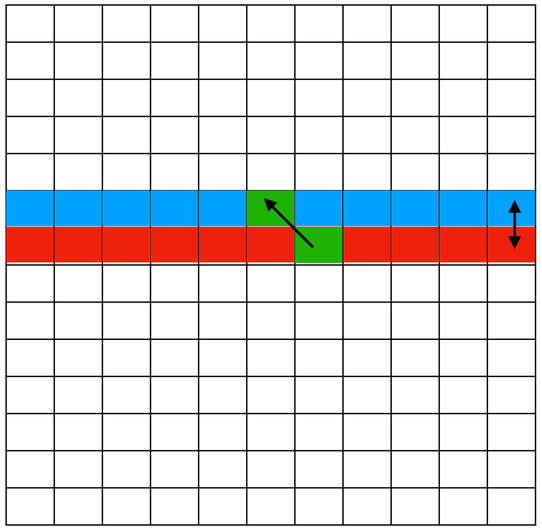

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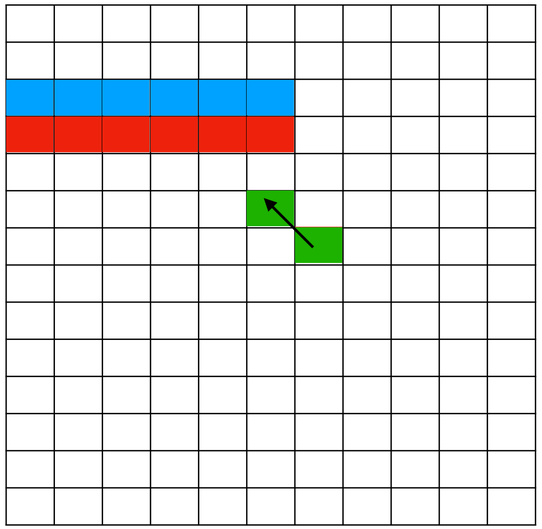

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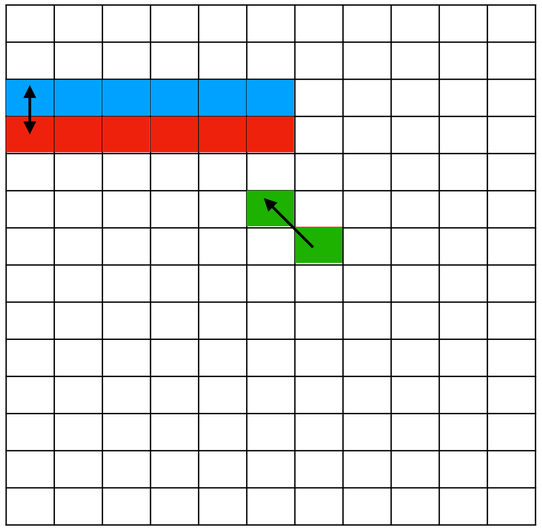

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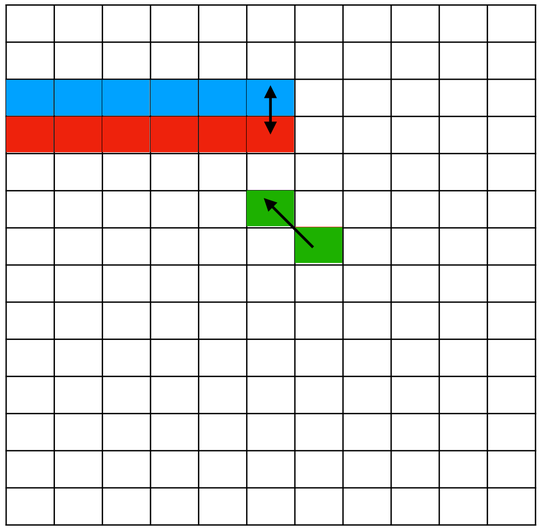

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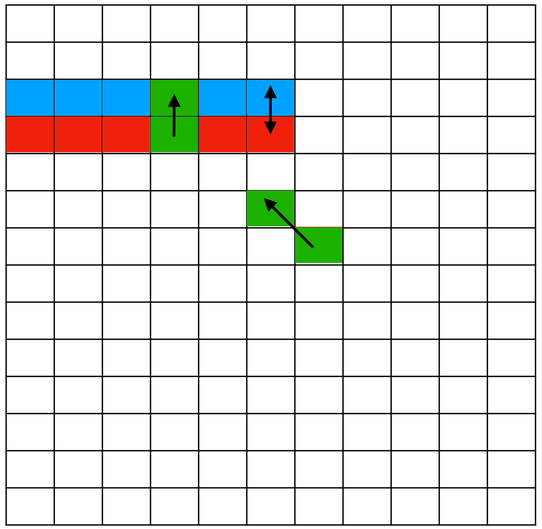

Hirschberg's Algorithm

FindMid(*S[1...n],T[1...n]):*
  F = CostOnlyNWForward(*S[1...n/2],T[1...m]*)
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  return argmax$_j \left\{ F[j] + B[j] \right\}$

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Concatenation

Hirschberg's Algorithm

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O(m)-space, freed after each call

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O(n)-space, to store the stack

Concatenation

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O(mn)-time

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Concatenation

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O(mn)-time
O(mn)-time

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O(mn)-time
O(mn)-time
O(1)-time

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O(mn)-time
O(mn)-time
O(1)-time

O(mn)-time for each call

HirschbergAlign(*S[i...j],T[x...y]*):
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Concatenation

Hirschberg's Algorithm

FindMid(*S[1...n],T[1...n]):*
  F = CostOnlyNWForward(*S[1...n/2],T[1...m]*) — *O(mn)*-time
  B = CostOnlyNWBackward(*S[n/2+1...n],T[1...m]*) — *O(mn)*-time
  return argmax$_j \{F[j] + B[j]\}$ — *O(1)*-time

O(mn)-time for each call

HirschbergAlign(*S[i...j],T[x...y]*): — *Time(n,m)*
  if *i=j* **then** compute full Needleman-Wunsch and **return** the alignment
  mid = (i+j)/2
  z = **FindMid**(*S[1...n],T[1...n]*)
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Concatenation

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O(mn)-time
O(mn)-time
O(1)-time

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Time(n,m)

O(mn)-time

Concatenation

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O(mn)-time
O(mn)-time
O(1)-time

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Time(n,m)

O(mn)-time

Time(n/2,z) + Time(n/2,m-z)

Concatenation

Hirschberg's Algorithm

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  F = CostOnlyNWForward(*S[1...n/2],T[1...m]*)
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O(mn)-time
O(mn)-time
O(1)-time

O(mn)-time for each call

HirschbergAlign(*S[i...j],T[x...y]*):
  if *i=j* **then** compute full Needleman-Wunsch and **return** the alignment
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  z = **FindMid**(*S[1...n],T[1...n]*)
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Time(n,m)

O(mn)-time

Time(n/2,z) + Time(n/2,m-z)

O(mn)-time total

Concatenation

Alignment Scores

- In all of the examples we have been given δ, *a, b,* etc. and using fixed values we are able to find the optimal alignment in *O(mn)*-time
- Since different values of those parameter induce different alignments, how do we know which parameter values are best?
- This is a problem known as *inverse parametric alignment* (or just parametric alignment) where you want to find ***all*** possible alignments of the two sequences.
- How many *optimal* alignments do you think there are? (notice that optimal is emphasized)