
CS481: Bioinformatics Algorithms

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EA224

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Outline

- DNA Sequence Comparison
 - Change Problem
 - Manhattan Tourist Problem
 - Longest Paths in Graphs
 - Sequence Alignment
 - Edit Distance
 - Longest Common Subsequence Problem
 - Dot Matrices
-

DNA sequence comparison

- Gene similarities between two genes with known and unknown function alert biologists to some possibilities
- Computing a similarity score between two genes tells how likely it is that they have similar functions
- **Dynamic programming** is a technique for revealing similarities between genes
- The ***Change Problem*** is a good problem to introduce the idea of dynamic programming

The Change Problem

Goal: Convert some amount of money M into given denominations, using the fewest possible number of coins

Input: An amount of money M , and an array of d denominations $c = (c_1, c_2, \dots, c_d)$, in a decreasing order of value ($c_1 > c_2 > \dots > c_d$)

Output: A list of d integers i_1, i_2, \dots, i_d such that

$$c_1 i_1 + c_2 i_2 + \dots + c_d i_d = M$$

and $i_1 + i_2 + \dots + i_d$ is minimal

Change Problem: Example

Given the denominations 1, 3, and 5, what is the minimum number of coins needed to make change for a given value?


Value	1	2	3	4	5	6	7	8	9	10
Min # of coins	1		1		1					

Only one coin is needed to make change for the values 1, 3, and 5

Change Problem: Example (cont'd)

Given the denominations 1, 3, and 5, what is the minimum number of coins needed to make change for a given value?

Value	1	2	3	4	5	6	7	8	9	10
Min # of coins	1	2	1	2	1	2		2		2




However, two coins are needed to make change for the values 2, 4, 6, 8, and 10.

Change Problem: Example (cont'd)

Given the denominations 1, 3, and 5, what is the minimum number of coins needed to make change for a given value?

Value	1	2	3	4	5	6	7	8	9	10
Min # of coins	1	2	1	2	1	2	3	2	3	2



Lastly, three coins are needed to make change for the values 7 and 9

Change Problem: Recurrence

This example is expressed by the following recurrence relation:

$$\text{minNumCoins}(M) = \min \text{ of } \left\{ \begin{array}{l} \text{minNumCoins}(M-1) + 1 \\ \text{minNumCoins}(M-3) + 1 \\ \text{minNumCoins}(M-5) + 1 \end{array} \right.$$

Change Problem: Recurrence (cont'd)

Given the denominations c : c_1, c_2, \dots, c_d , the recurrence relation is:

$$\text{minNumCoins}(M) = \min \text{ of } \left\{ \begin{array}{l} \text{minNumCoins}(M - c_1) + 1 \\ \text{minNumCoins}(M - c_2) + 1 \\ \dots \\ \text{minNumCoins}(M - c_d) + 1 \end{array} \right.$$

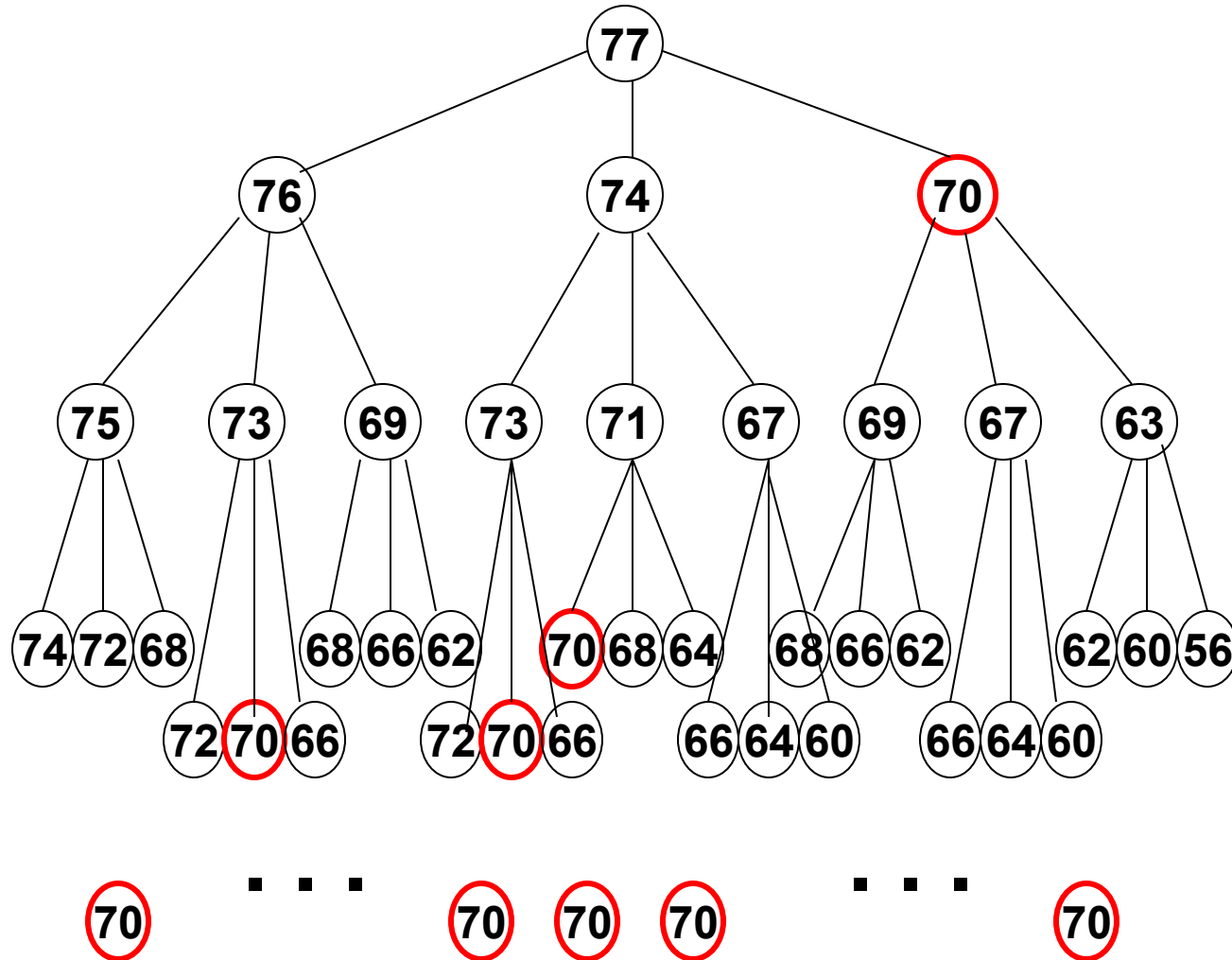
Change Problem: A Recursive Algorithm

1. RecursiveChange(*M*, *c*, *d*)
2. if $M = 0$
3. return 0
4. $bestNumCoins \leftarrow \text{infinity}$
5. for $i \leftarrow 1$ to d
6. if $M \geq c_i$
7. $numCoins \leftarrow \text{RecursiveChange}(M - c_i, c, d)$
8. if $numCoins + 1 < bestNumCoins$
9. $bestNumCoins \leftarrow numCoins + 1$
10. return $bestNumCoins$

RecursiveChange Is Not Efficient

- It recalculates the optimal coin combination for a given amount of money repeatedly
- i.e., $M = 77$, $c = (1, 3, 7)$:
 - Optimal coin combo for 70 cents is computed **9** times!

The RecursiveChange Tree



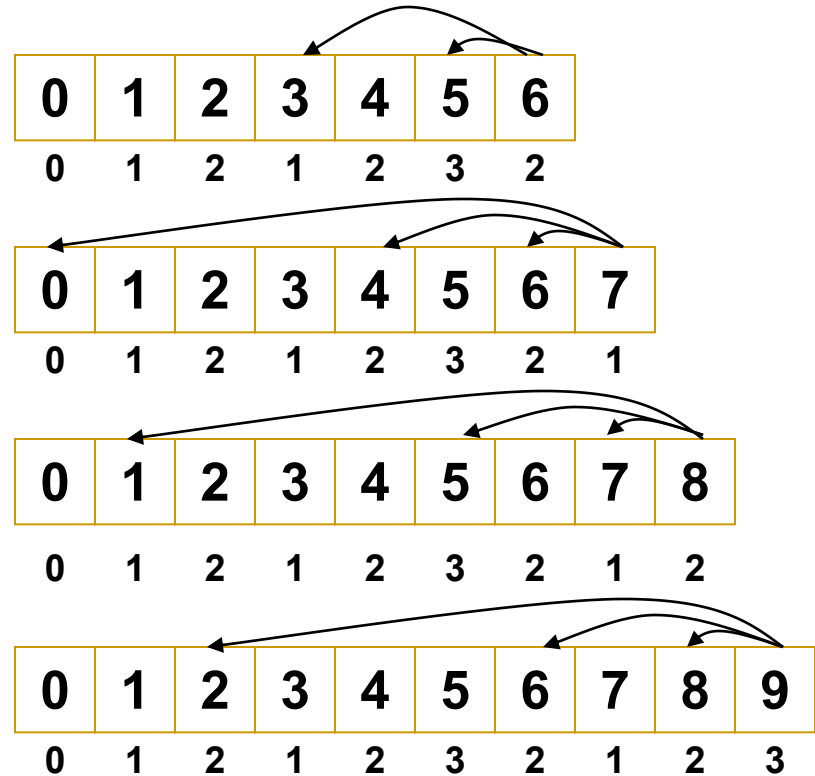
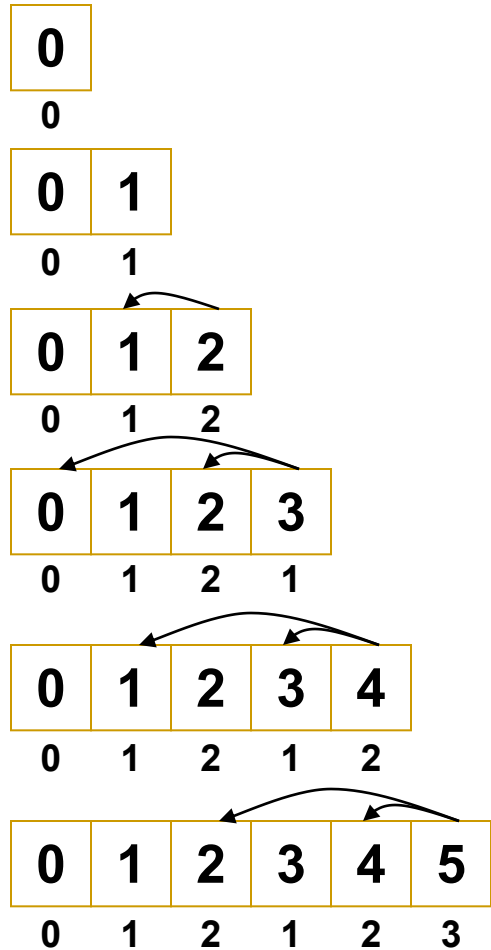
We Can Do Better

- We're re-computing values in our algorithm more than once
- Save results of each computation for 0 to M
- This way, we can do a reference call to find an already computed value, instead of re-computing each time
- Running time $M * d$, where M is the value of money and d is the number of denominations

The Change Problem: Dynamic Programming

1. DPChange(M, c, d)
2. bestNumCoins₀ \leftarrow 0
3. for m \leftarrow 1 to M
4. bestNumCoins_m \leftarrow infinity
5. for i \leftarrow 1 to d
6. if m \geq c_i
7. if bestNumCoins_{m - c_i} + 1 < bestNumCoins_m
8. bestNumCoins_m \leftarrow bestNumCoins_{m - c_i} + 1
9. return bestNumCoins_M

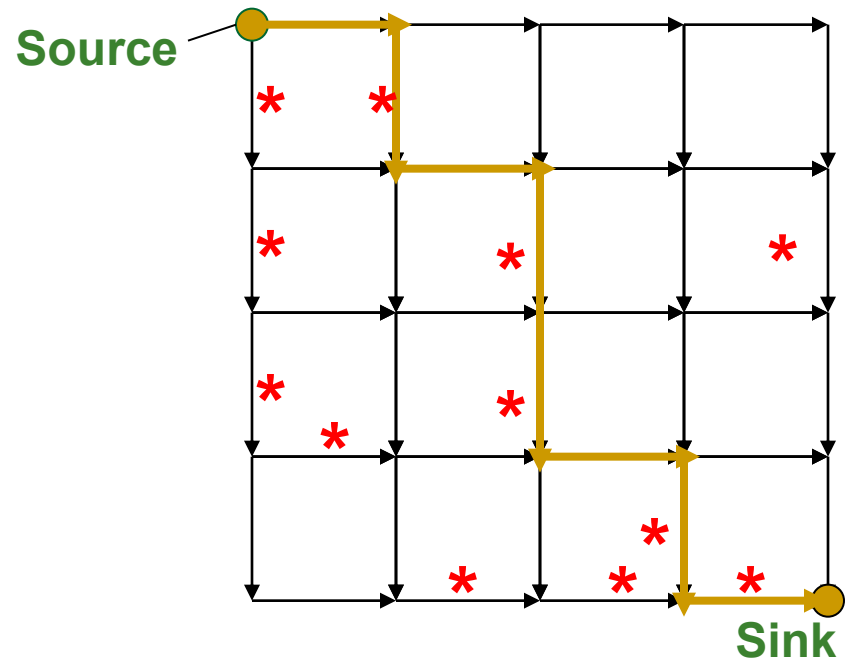
DPChange: Example



c = (1,3,7)
M = 9

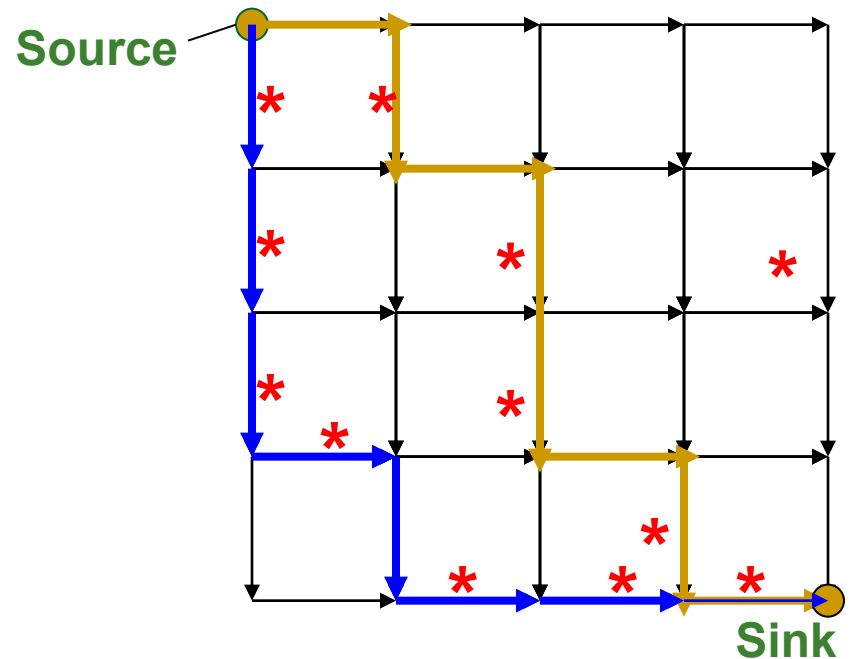
Manhattan Tourist Problem (MTP)

Imagine seeking a path (from source to sink) to travel (only eastward and southward) with the most number of attractions (*) in the Manhattan grid



Manhattan Tourist Problem (MTP)

Imagine seeking a path (from source to sink) to travel (only eastward and southward) with the most number of attractions (*) in the Manhattan grid



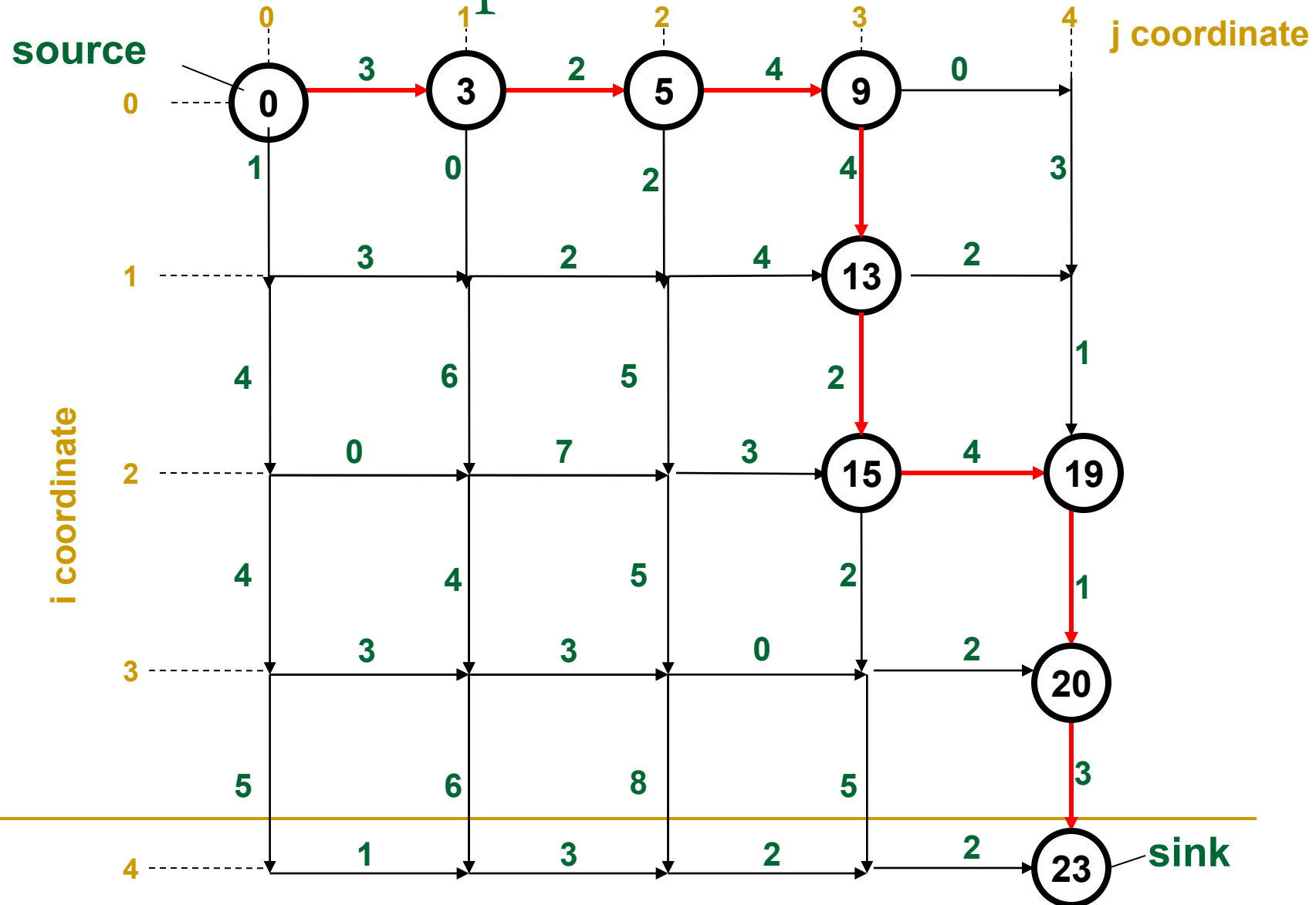
Manhattan Tourist Problem: Formulation

Goal: Find the longest path in a weighted grid.

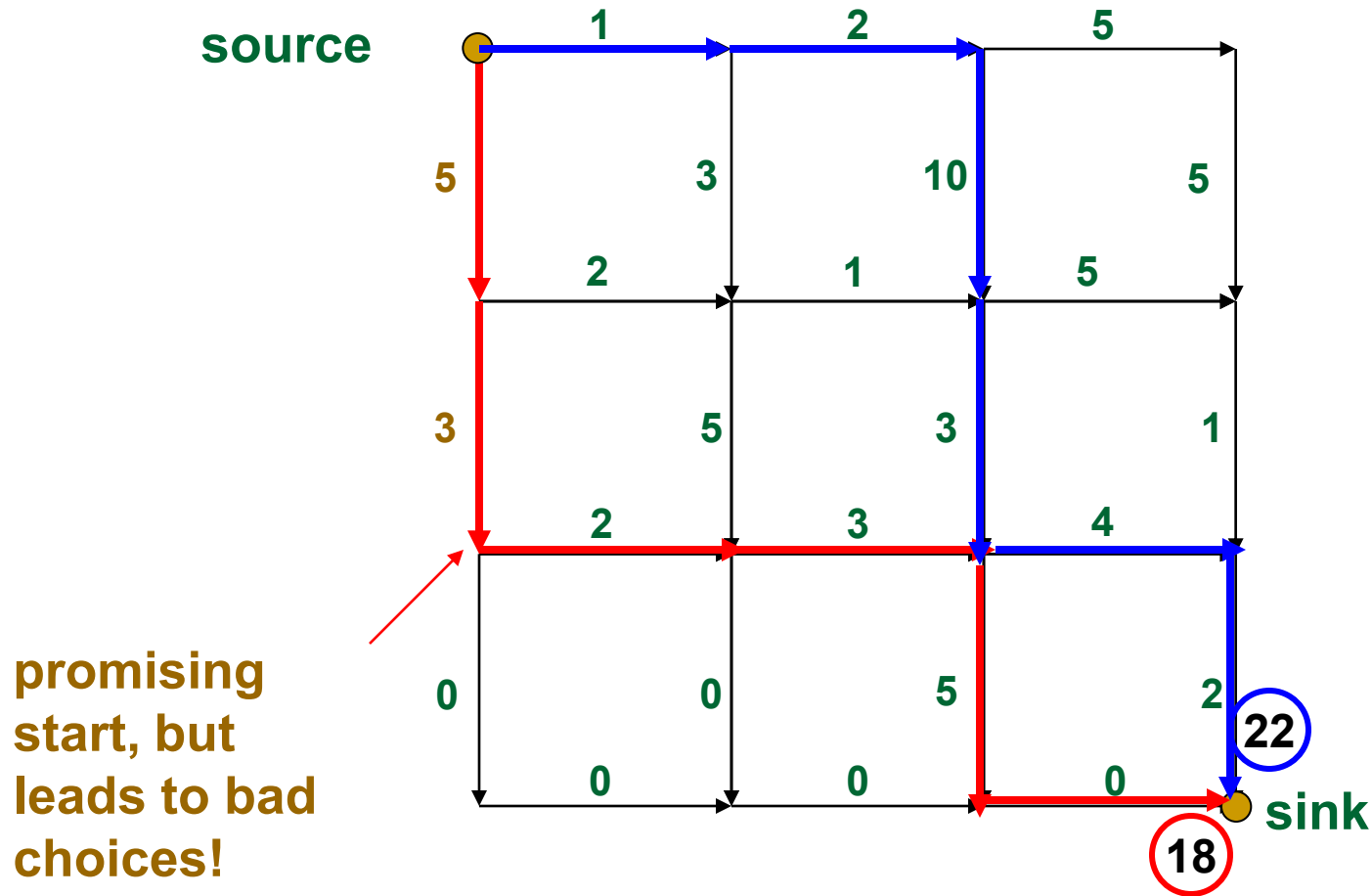
Input: A weighted grid G with two distinct vertices, one labeled “source” and the other labeled “sink”

Output: A longest path in G from “source” to “sink”

MTP: An Example



MTP: Greedy Algorithm Is Not Optimal



MTP: Simple Recursive Program

MT(n,m)

if $n=0$ or $m=0$

return MT(n,m)

$x \leftarrow \text{MT}(n-1, m) +$

length of the edge from $(n-1, m)$ to (n, m)

$y \leftarrow \text{MT}(n, m-1) +$

length of the edge from $(n, m-1)$ to (n, m)

return $\max\{x, y\}$

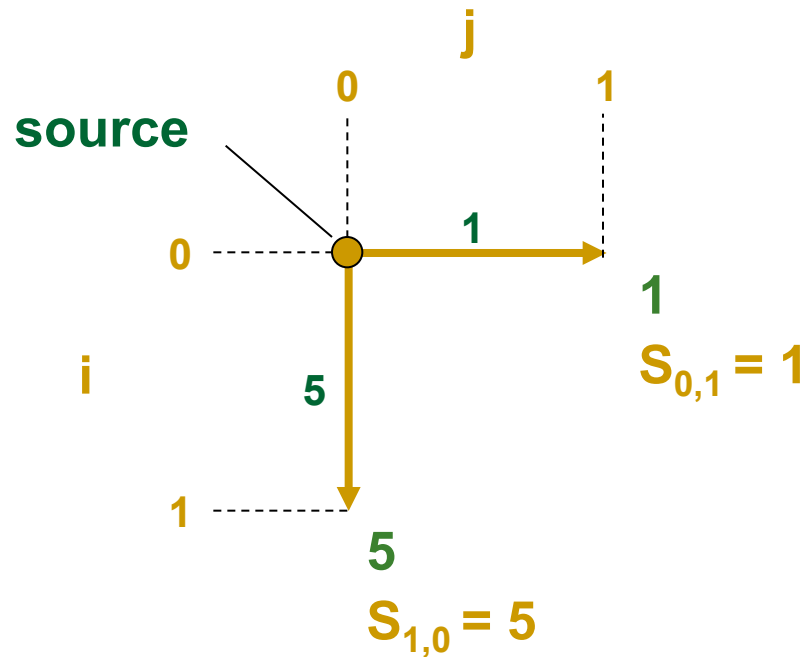
MTP: Simple Recursive Program

MT(n,m)

```
x ← MT(n-1,m)+  
    length of the edge from (n- 1,m) to (n,m)  
y ← MT(n,m-1)+  
    length of the edge from (n,m-1) to (n,m)  
return min{x,y}
```

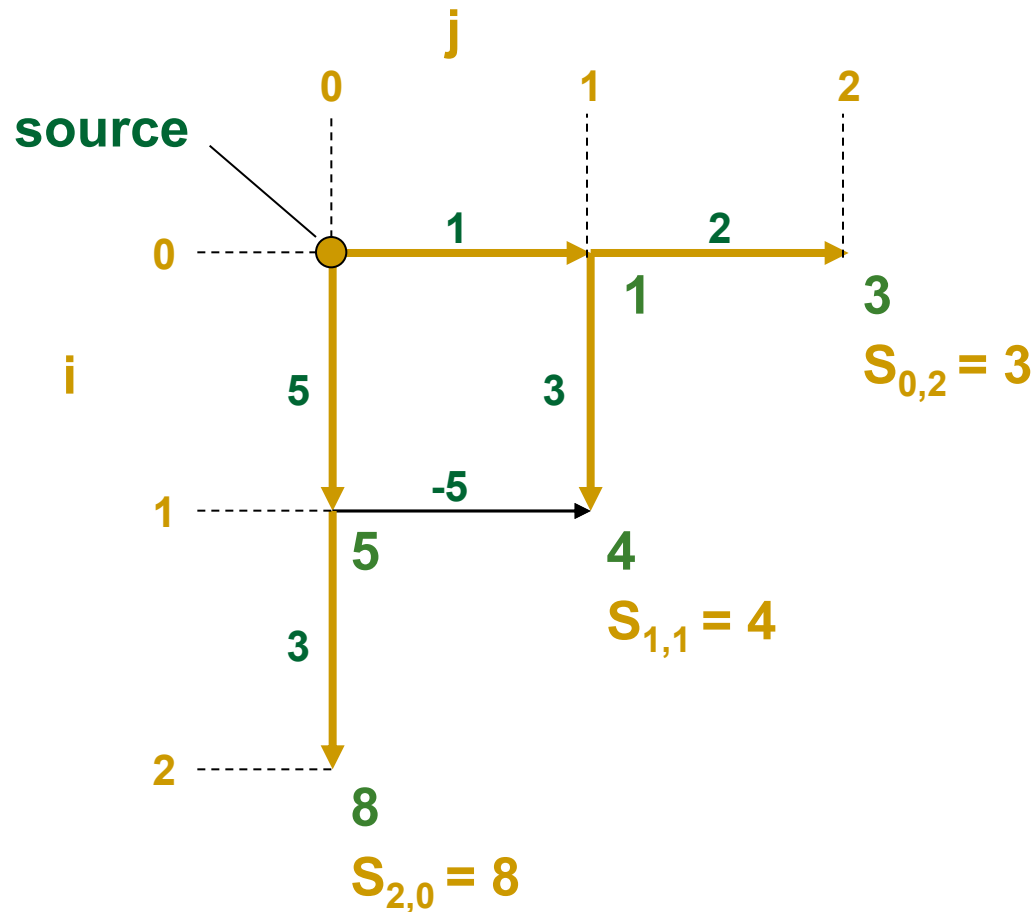
What's wrong with this approach?

MTP: Dynamic Programming

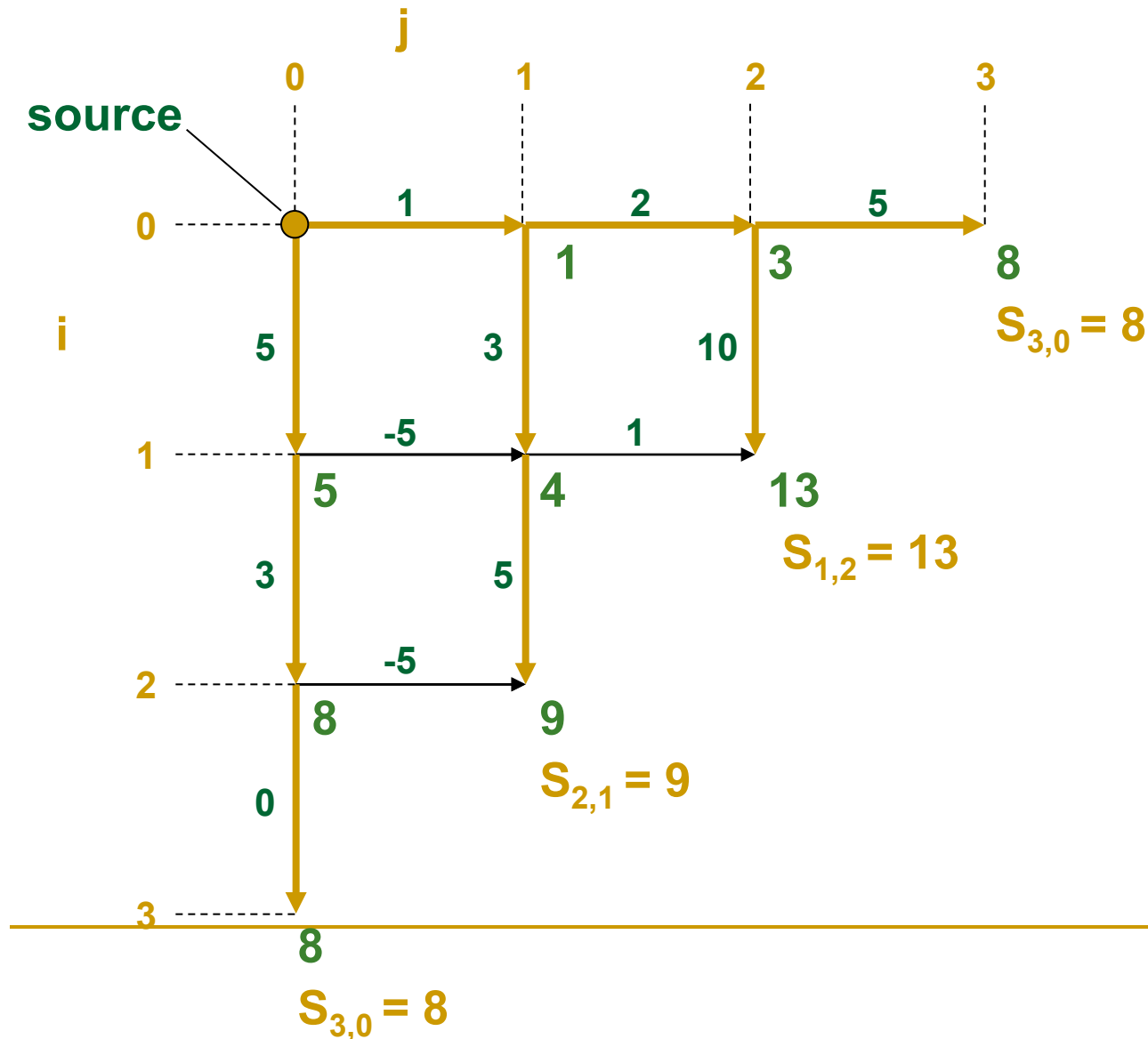


- Calculate optimal path score for each vertex in the graph
- Each vertex's score is the maximum of the prior vertices score plus the weight of the respective edge in between

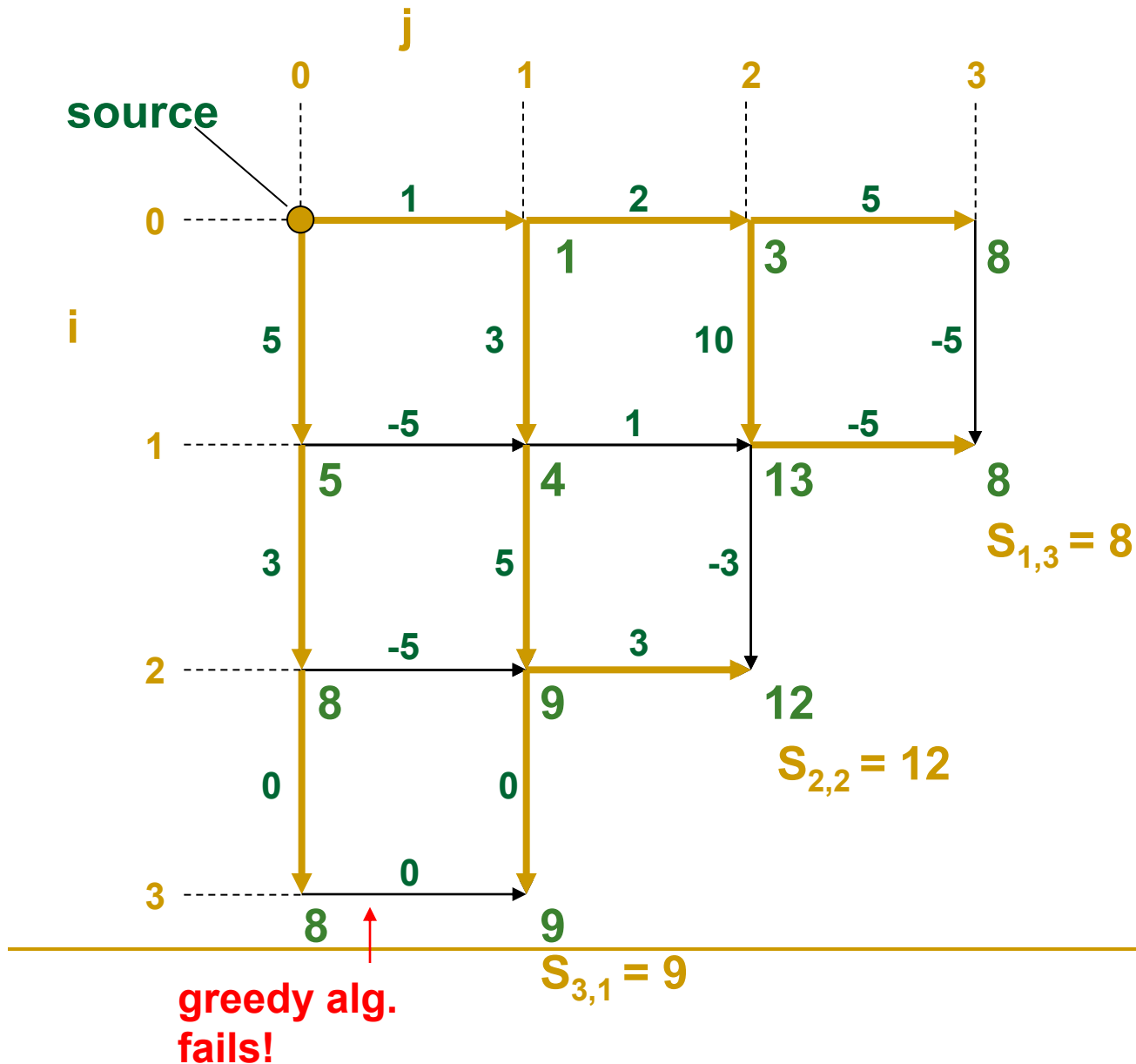
MTP: Dynamic Programming (cont'd)



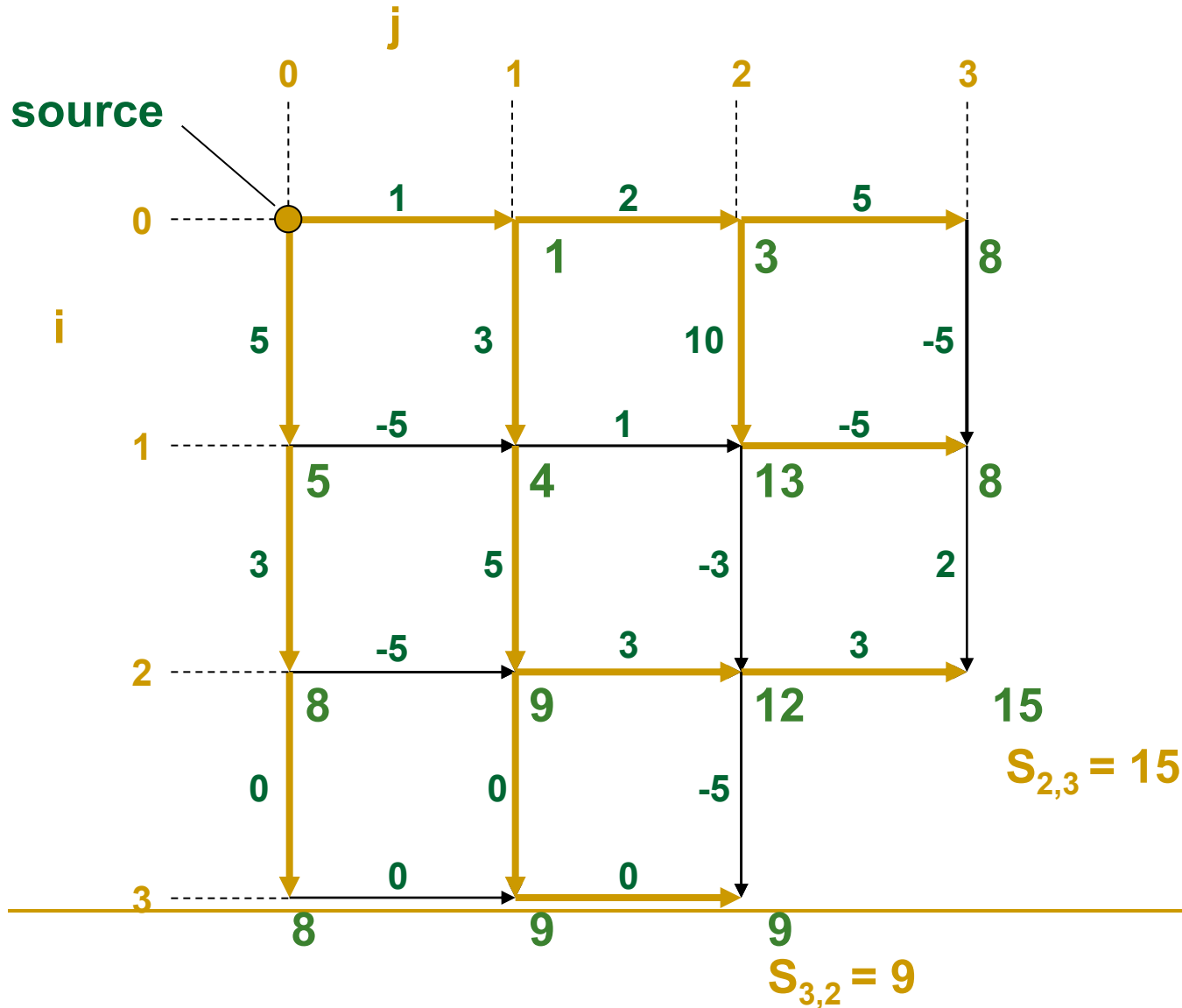
MTP: Dynamic Programming (cont'd)



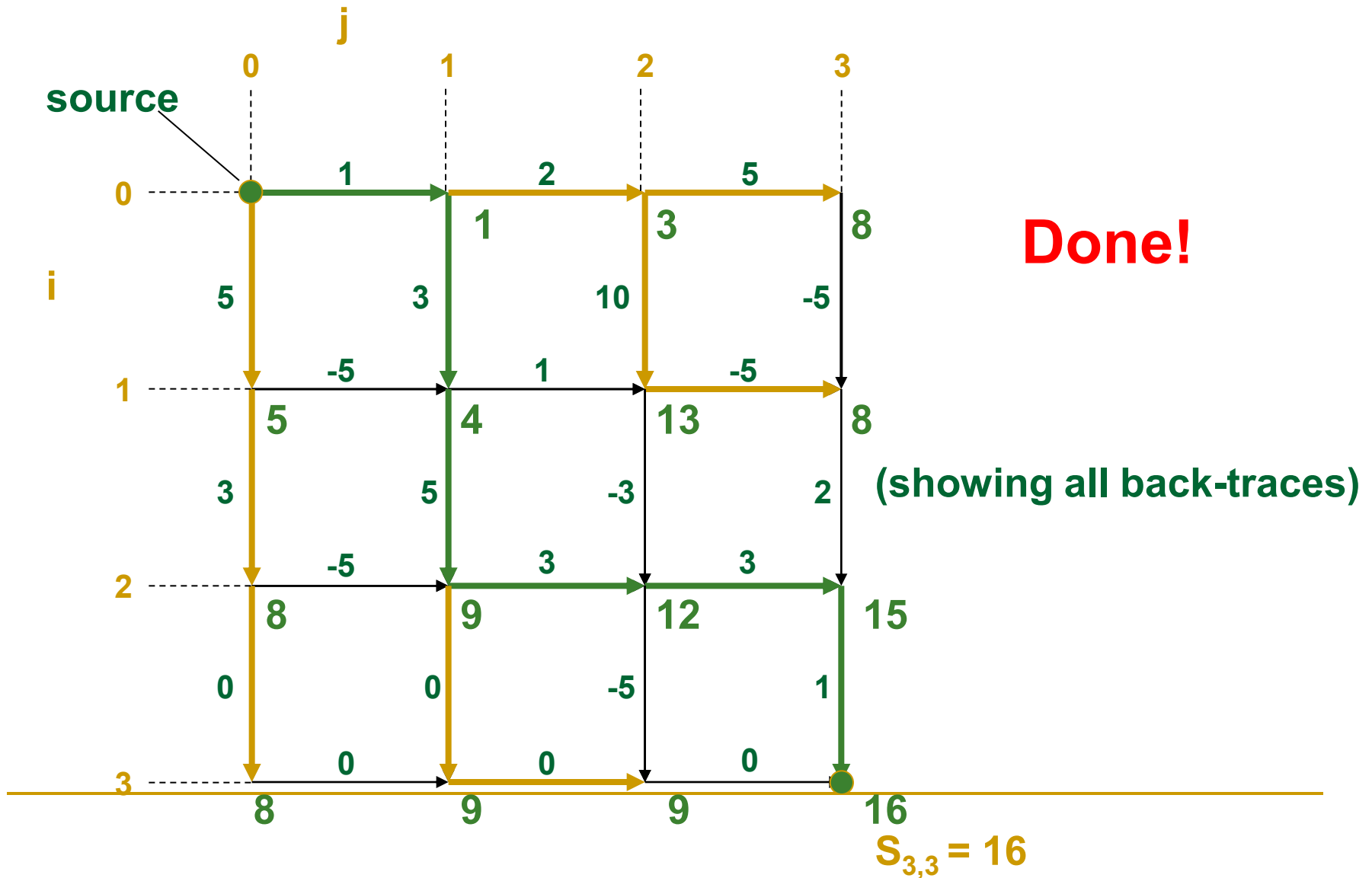
MTP: Dynamic Programming (cont'd)



MTP: Dynamic Programming (cont'd)



MTP: Dynamic Programming (cont'd)



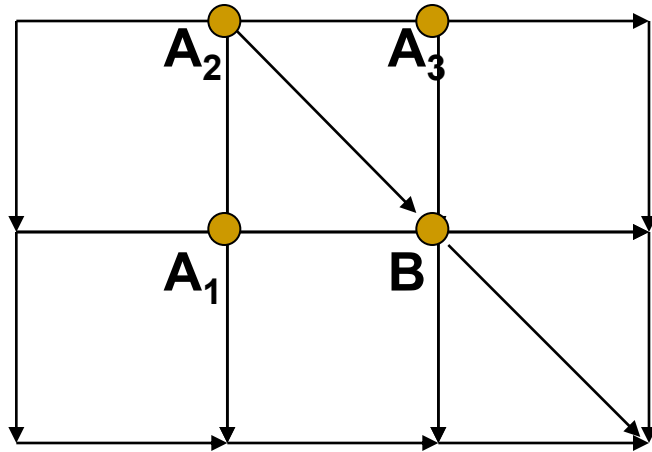
MTP: Recurrence

Computing the score for a point (i,j) by the recurrence relation:

$$s_{i,j} = \max \begin{cases} s_{i-1,j} + \text{weight of the edge between } (i-1, j) \text{ and } (i, j) \\ s_{i,j-1} + \text{weight of the edge between } (i, j-1) \text{ and } (i, j) \end{cases}$$

The running time is $n \times m$ for a n by m grid
(n = # of rows, m = # of columns)

Manhattan Is Not A Perfect Grid



What about diagonals?

- The score at point B is given by:

$$s_B = \max_{\text{of}} \begin{cases} s_{A_1} + \text{weight of the edge } (A_1, B) \\ s_{A_2} + \text{weight of the edge } (A_2, B) \\ s_{A_3} + \text{weight of the edge } (A_3, B) \end{cases}$$

Manhattan Is Not A Perfect Grid (cont'd)

Computing the score for point x is given by the recurrence relation:

$$s_x = \max_{\text{of}} \left\{ s_y + \text{weight of vertex } (y, x) \text{ where } y \in \text{Predecessors}(x) \right.$$

- Predecessors (x) – set of vertices that have edges leading to x
- The running time for a graph $G(V, E)$ (V is the set of all vertices and E is the set of all edges) is $O(E)$ since each edge is evaluated once

Traveling in the Grid

- The only hitch is that one must decide on the order in which visit the vertices
- By the time the vertex x is analyzed, the values s_y for all its predecessors y should be computed – otherwise we are in trouble.
- We need to traverse the vertices in some order
- Try to find such order for a directed cycle

DAG: Directed Acyclic Graph

- Since Manhattan is not a perfect regular grid, we represent it as a DAG

Longest Path in DAG Problem

- **Goal**: Find a longest path between two vertices in a weighted DAG
- **Input**: A weighted DAG G with source and sink vertices
- **Output**: A longest path in G from source to sink

Longest Path in DAG: Dynamic Programming

- Suppose vertex v has indegree 3 and predecessors $\{u_1, u_2, u_3\}$
- Longest path to v from source is:

$$s_v = \max_{\text{of}} \begin{cases} s_{u_1} + \text{weight of edge from } u_1 \text{ to } v \\ s_{u_2} + \text{weight of edge from } u_2 \text{ to } v \\ s_{u_3} + \text{weight of edge from } u_3 \text{ to } v \end{cases}$$

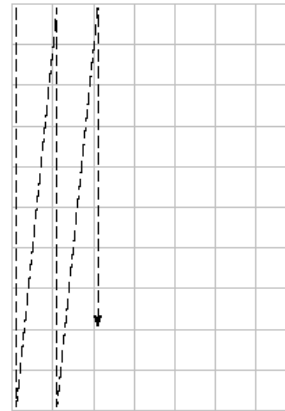
In General:

$$s_v = \max_u (s_u + \text{weight of edge from } u \text{ to } v)$$

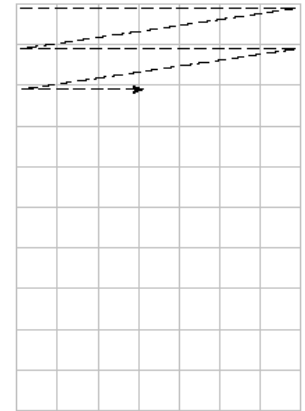
Traversing the Manhattan Grid

- **3 different strategies:**
 - **a) Column by column**
 - **b) Row by row**
 - **c) Along diagonals**

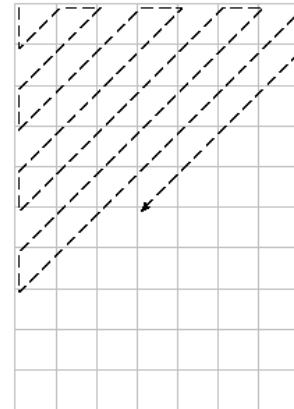
a)



b)



c)



ALIGNMENT

Alignment: 2 row representation

Given 2 DNA sequences v and w:

v : **A**T**C**T**G**A**T** m = 7
w : T**G****C**A**T**A n = 6

Alignment : 2 * k matrix (k > m, n)

letters of v	A	T	--	G	T	T	A	T	--
letters of w	A	T	C	G	T	--	A	--	C

5 matches

2 insertions

2 deletions

Aligning DNA Sequences

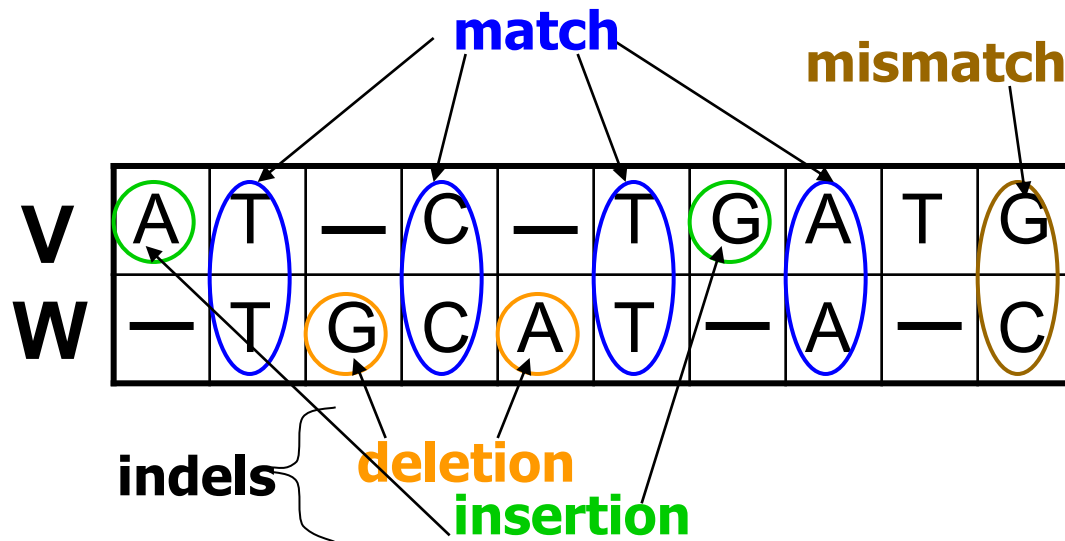
V = ATCTGATG

n = 8

W = TGCATAC

m = 7

4 matches
1 mismatch
2 insertions
2 deletions



Longest Common Subsequence (LCS) – Alignment without Mismatches

- Given two sequences

$$v = v_1 v_2 \dots v_m \text{ and } w = w_1 w_2 \dots w_n$$

- The LCS of v and w is a sequence of positions in

$$v: 1 \leq i_1 < i_2 < \dots < i_t \leq m$$

and a sequence of positions in

$$w: 1 \leq j_1 < j_2 < \dots < j_t \leq n$$

such that i_t -th letter of v equals to j_t -letter of w and t is maximal

LCS: Example

i coords:	0	1	2	2	3	3	4	5	6	7	8
elements of v	A	T	--	C	--	T	G	A	T	C	
elements of w	--	T	G	C	A	T	--	A	--	C	
j coords:	0	0	1	2	3	4	5	5	6	6	7

$(0,0) \rightarrow (1,0) \rightarrow (2,1) \rightarrow (2,2) \rightarrow (3,3) \rightarrow (3,4) \rightarrow (4,5) \rightarrow (5,5) \rightarrow (6,6) \rightarrow (7,6) \rightarrow (8,7)$

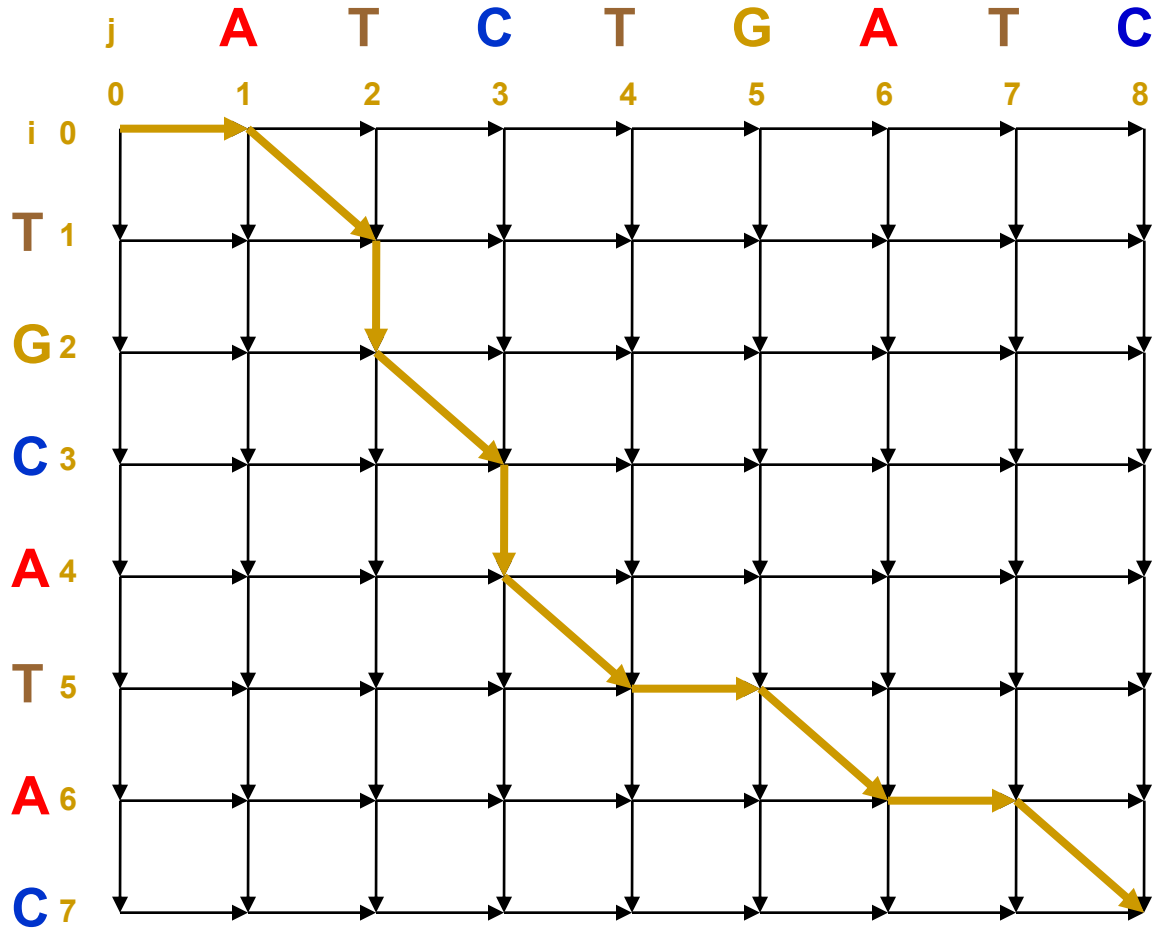
Matches shown in
red

positions in v: $2 < 3 < 4 < 6 < 8$

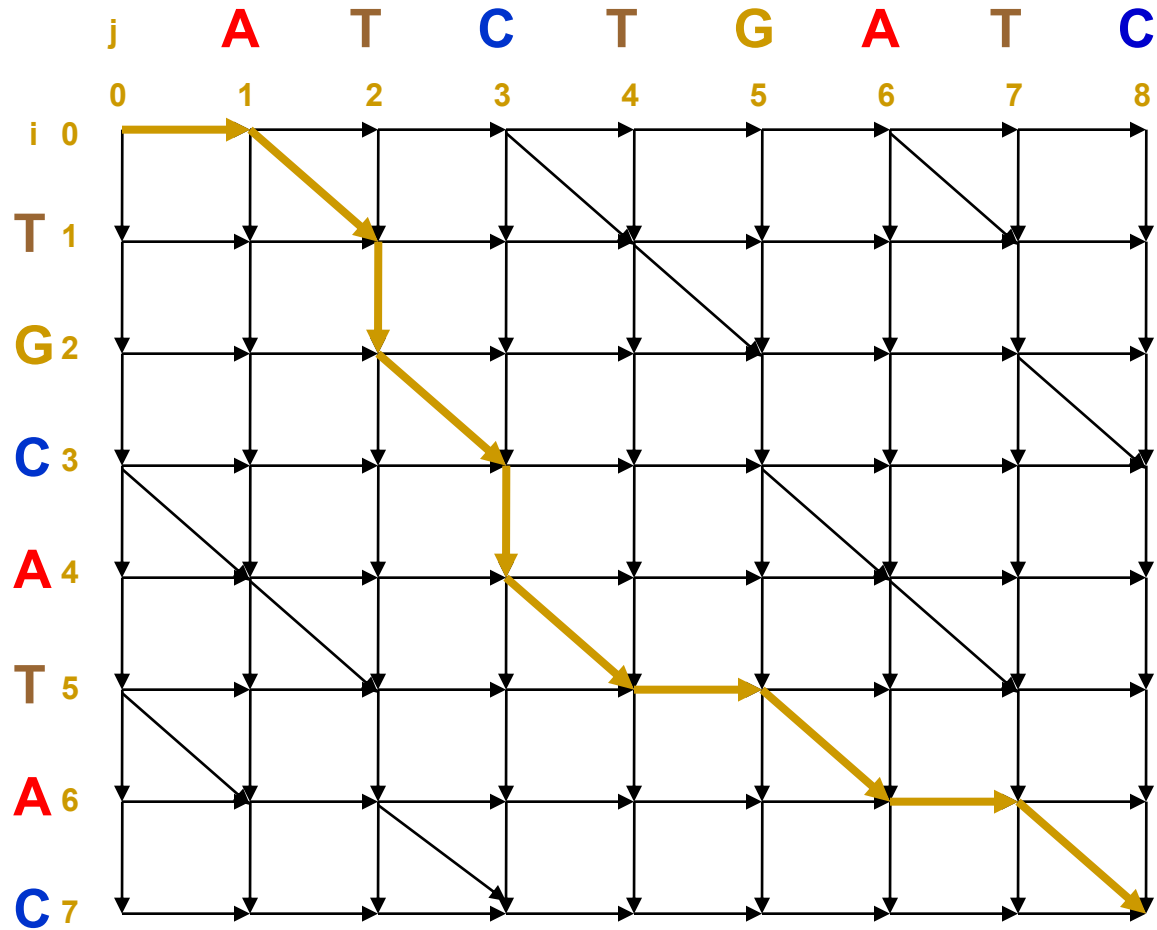
positions in w: $1 < 3 < 5 < 6 < 7$

Every common subsequence is a path in 2-D grid

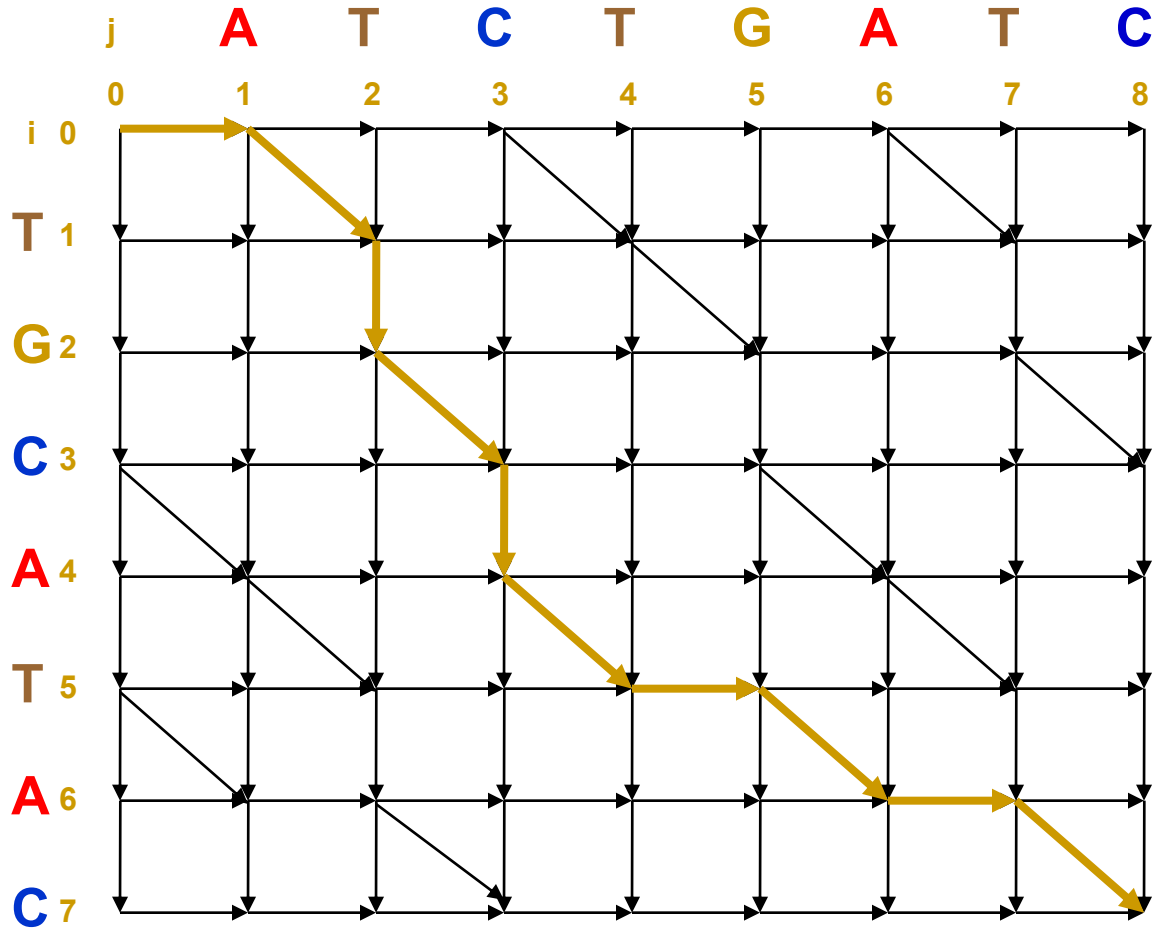
LCS Problem as Manhattan Tourist Problem



Edit Graph for LCS Problem



Edit Graph for LCS Problem



Every path is a common subsequence.

Every diagonal edge adds an extra element to common subsequence

LCS Problem:
Find a path with maximum number of diagonal edges

Computing LCS

Let v_i = prefix of v of length i : $v_1 \dots v_i$

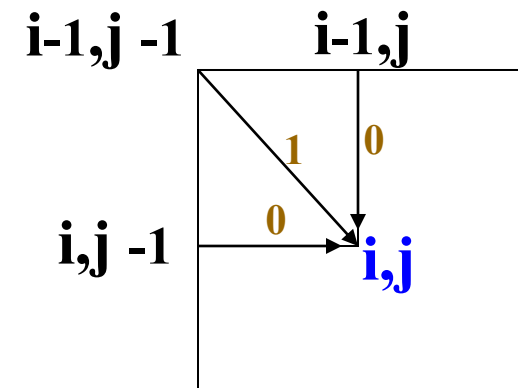
and w_j = prefix of w of length j : $w_1 \dots w_j$

The length of $\text{LCS}(v_i, w_j)$ is computed by:

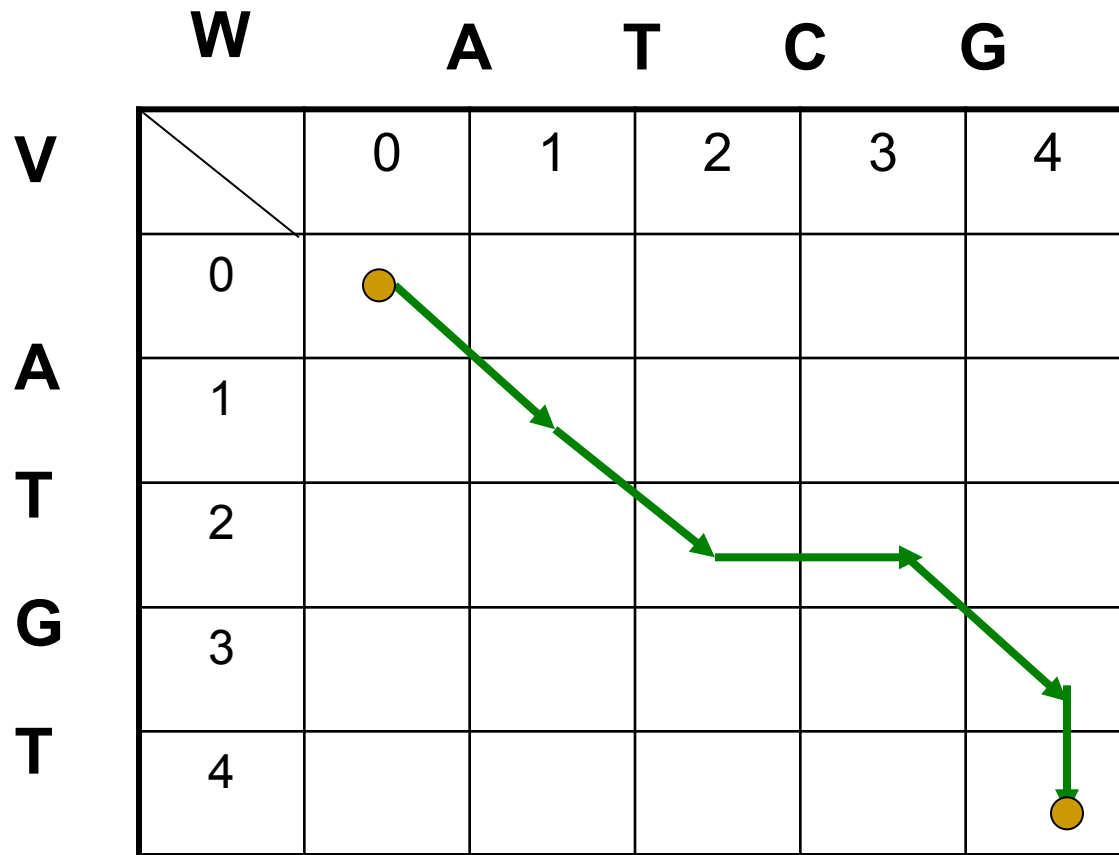
$$s_{i,j} = \max \begin{cases} s_{i-1,j} \\ s_{i,j-1} \\ s_{i-1,j-1} + 1 \text{ if } v_i = w_j \end{cases}$$

Computing LCS (cont'd)

$$s_{i,j} = \text{MAX} \begin{cases} s_{i-1,j} + 0 \\ s_{i,j-1} + 0 \\ s_{i-1,j-1} + 1, \end{cases} \quad \text{if } v_i = w_j$$



Every Path in the Grid Corresponds to an Alignment



↘ ↘ → ↘ ↓
0 1 2 2 3 4
V = A T - G T
| | |
W = A T C G -
0 1 2 3 4 4

DISTANCE BETWEEN STRINGS

Aligning Sequences without Insertions and Deletions: Hamming Distance

Given two DNA sequences v and w :

v : A T A T A T A T

w : T A T A T A T A

- **The Hamming distance: $d_H(v, w) = 8$ is large but the sequences are very similar**

Aligning Sequences with Insertions and Deletions

By shifting one sequence over one position:

v : A T A T A T --
w : -- T A T A T A

- **The edit distance: $d_H(v, w) = 2$.**
- **Hamming distance neglects insertions and deletions in DNA**

Edit Distance

Levenshtein (1966) introduced **edit distance** between two strings as the minimum number of elementary operations (insertions, deletions, and substitutions) to transform one string into the other

$d(v,w)$ = MIN number of elementary operations
to transform $v \rightarrow w$

Edit Distance vs Hamming Distance

Hamming distance

always compares

i -th letter of v with

i -th letter of w

$V = \text{ATATATAT}$

$W = \text{TATATATA}$

Hamming distance:

$$d(v, w) = 8$$

**Computing Hamming distance
is a trivial task.**

Edit Distance vs Hamming Distance

Hamming distance

always compares

i -th letter of v with

i -th letter of w

$V = \text{ATATATAT}$

$W = \text{TATATATA}$

Just one shift
Make it all line up

Hamming distance:

$$d(v, w) = 8$$

Computing Hamming distance
is a **trivial** task

Edit distance

may compare

i -th letter of v with

j -th letter of w

$V = - \text{ATATATAT}$

$W = \text{TATATATA}$

Edit distance:

$$d(v, w) = 2$$

Computing edit distance
is a **non-trivial** task

Edit Distance vs Hamming Distance

**Hamming distance
always compares**

**i -th letter of v with
 i -th letter of w**

$V = \text{ATATATAT}$
 | | | | |
 $W = \text{TATATATA}$

Hamming distance:

$$d(v, w) = 8$$

**Edit distance
may compare**

**i -th letter of v with
 j -th letter of w**

$V = -\text{ATATATAT}$
 | | | | |
 $W = \text{TATATATA}$

Edit distance:

$$d(v, w) = 2$$

(one insertion and one deletion)

How to find what j goes with what i ???

Edit Distance: Example

TGCATAT → ATCCGAT in 5 steps

TGCATAT^T → (delete last ^T)

TGCAT^A → (delete last ^A)

TGCAT → (insert ^A at front)

^AT^CCAT → (substitute ^C for 3rd ^G)

AT^CCAT → (insert ^G before last A)

ATCC^GAT (Done)

Edit Distance: Example

TGCATAT → ATCCGAT in 5 steps

TGCATAT^T → (delete last ^T)

TGCAT^A → (delete last ^A)

TGCAT → (insert ^A at front)

^AT^GCAT → (substitute ^C for 3rd ^G)

AT^CCAT → (insert ^G before last A)

ATCC^GAT (Done)

What is the edit distance? 5?

Edit Distance: Example (cont'd)

TGCATAT → ATCCGAT in 4 steps

TGCATAT → (insert **A** at front)

ATGCATAT**T** → (delete 6th **T**)

ATGC**A**TA → (substitute **G** for 5th **A**)

AT**G**CGTA → (substitute **C** for 3rd **G**)

AT**C**CGAT (Done)

Edit Distance: Example (cont'd)

TGCATAT → ATCCGAT in 4 steps

TGCATAT → (insert **A** at front)

ATGCATAT**T** → (delete 6th **T**)

ATGC**A**TA → (substitute **G** for 5th **A**)

AT**G**CGTA → (substitute **C** for 3rd **G**)

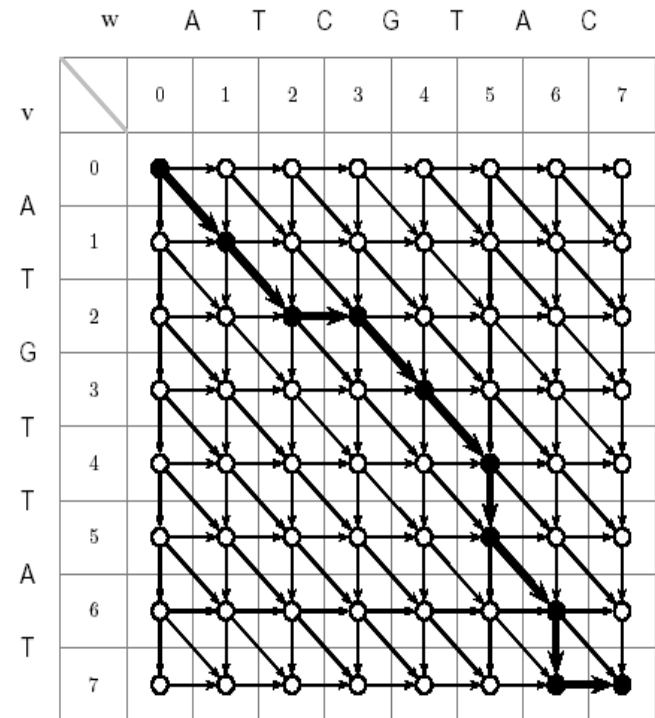
AT**C**CGAT (Done)

Can it be done in 3 steps???

The Alignment Grid

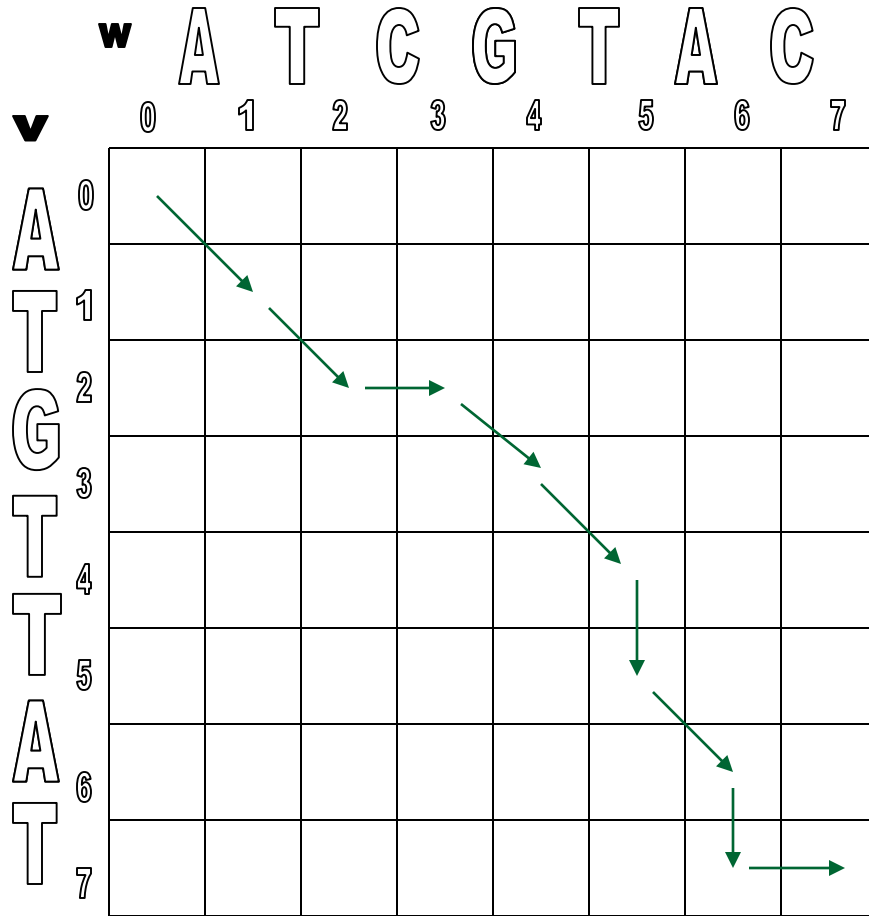
- Every alignment path is from source to sink

	0	1	2	2	3	4	5	6	7	7
v =		A	T	-	G	T	T	A	T	-
w =		A	T	C	G	T	-	A	-	C
	0	1	2	3	4	5	5	6	6	7



↘	↘	→	↘	↘	↓	↘	↓	→
A	T	-	G	T	T	A	T	-
A	T	C	G	T	-	A	-	C

Alignment as a Path in the Edit Graph

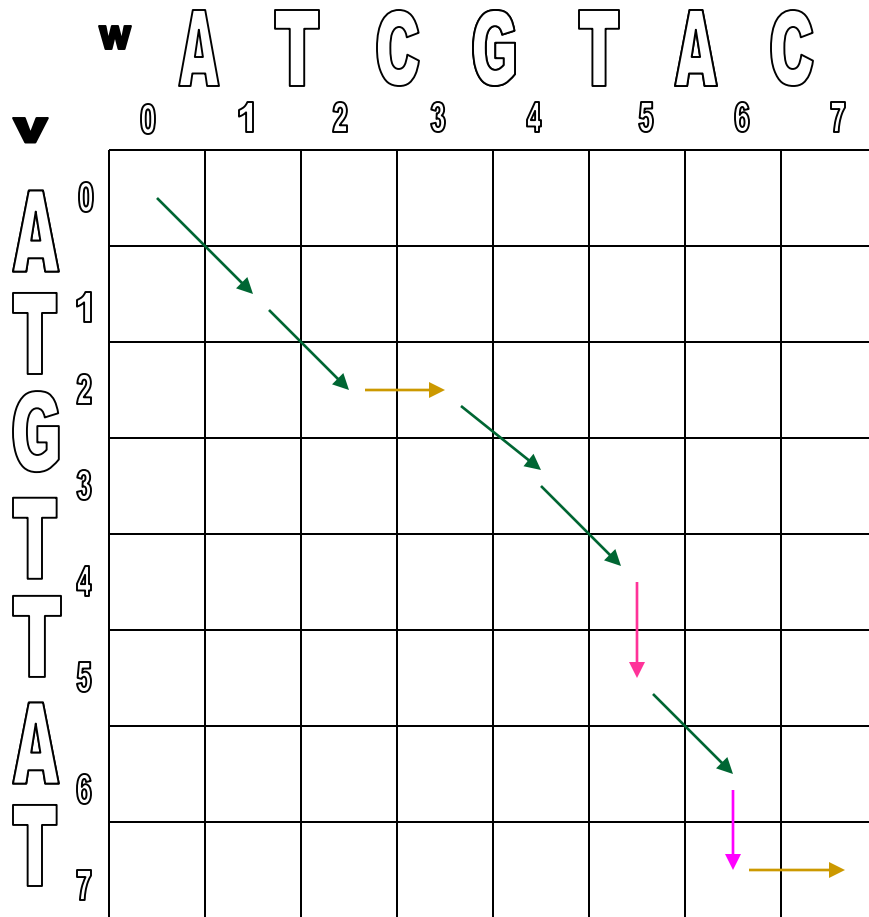


0	1	2	2	3	4	5	6	7	7
	A	T	_	G	T	T	A	T	_
	A	T	C	G	T	_	A	_	C
0	1	2	3	4	5	5	6	6	7

- Corresponding path -

(0,0) , (1,1) , (2,2), (2,3),
(3,4), (4,5), (5,5), (6,6),
(7,6), (7,7)

Alignments in Edit Graph (cont'd)

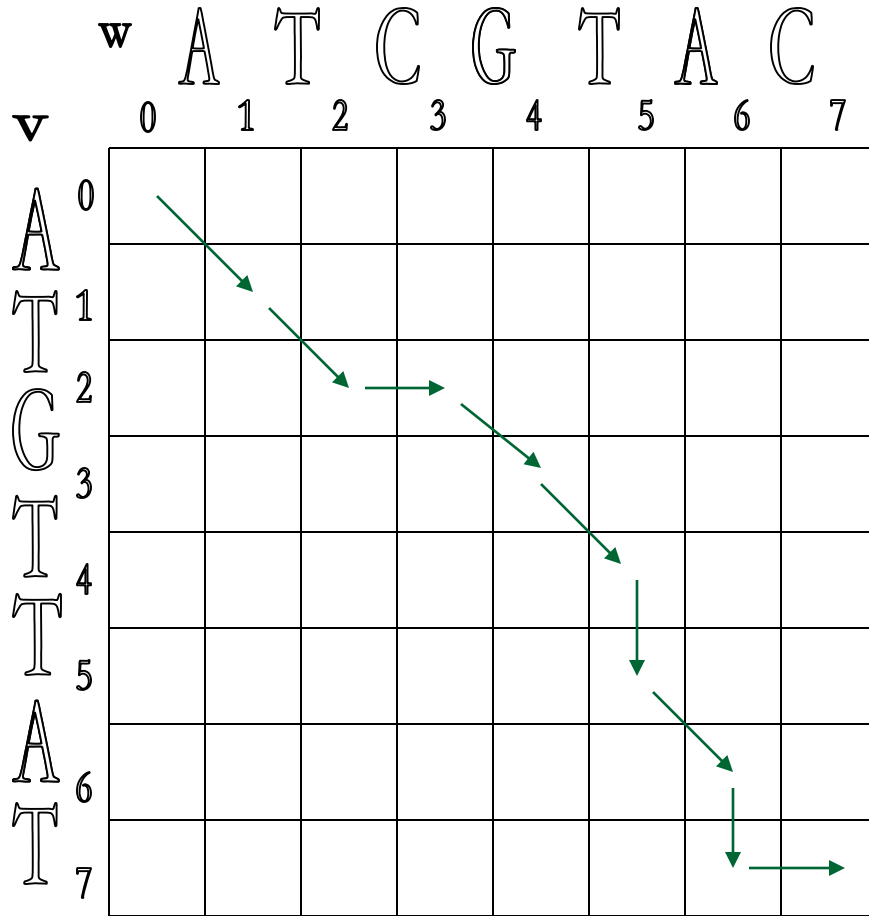


↓ and → represent indels in v and w with score 0.

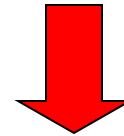
↘ represent matches with score 1.

- The score of the alignment path is 5.

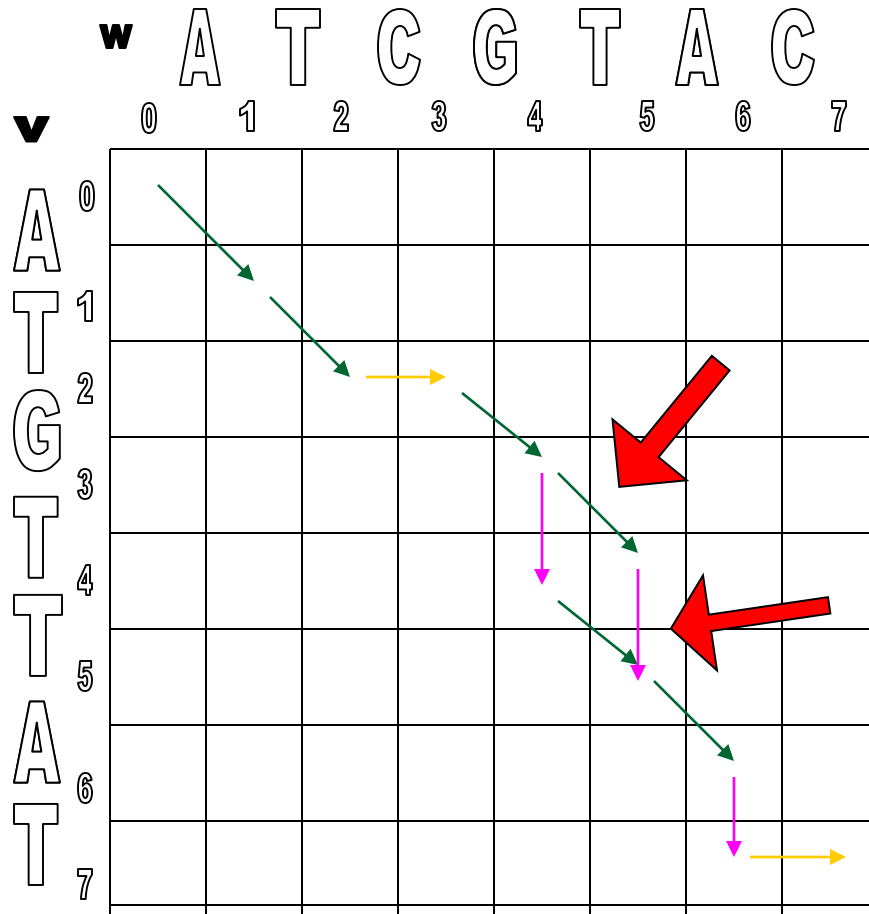
Alignment as a Path in the Edit Graph



Every path in the edit graph corresponds to an alignment:



Alignment as a Path in the Edit Graph



Old Alignment

01223**4**5677

v= AT_G**TT**AT_

w= ATCGT_**A**_C

01234**5**5667

New Alignment

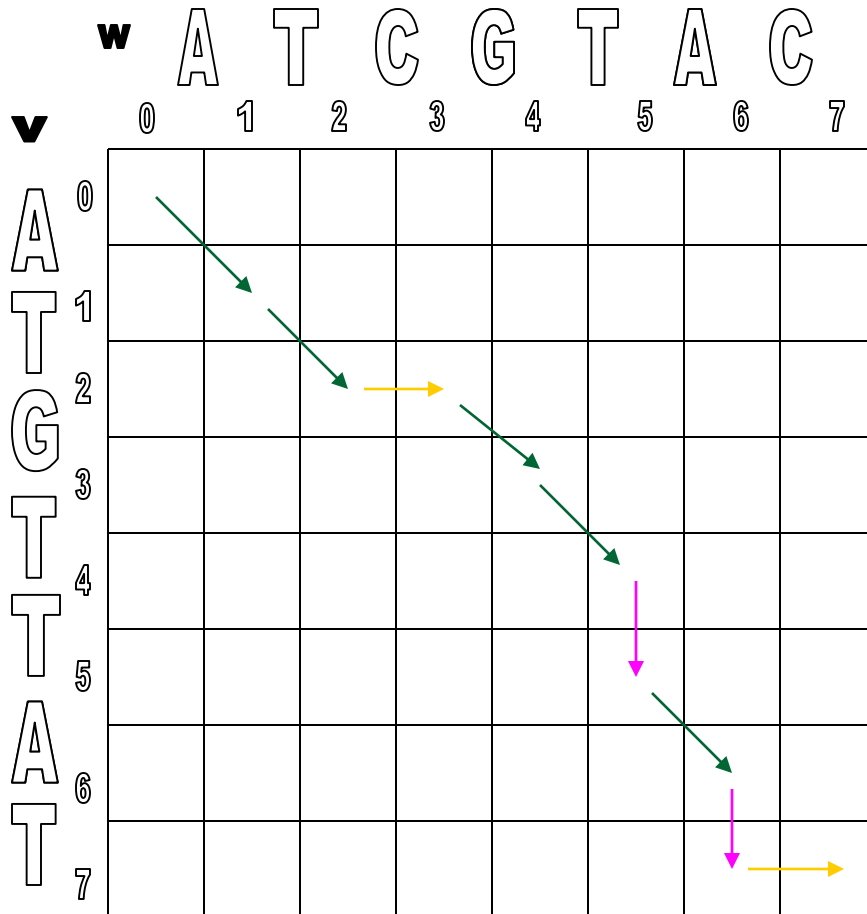
01223**4**5677

v= AT_G**TT**AT_

w= ATCG_**T**A_C

01234**4**5667

Alignment as a Path in the Edit Graph



012345677

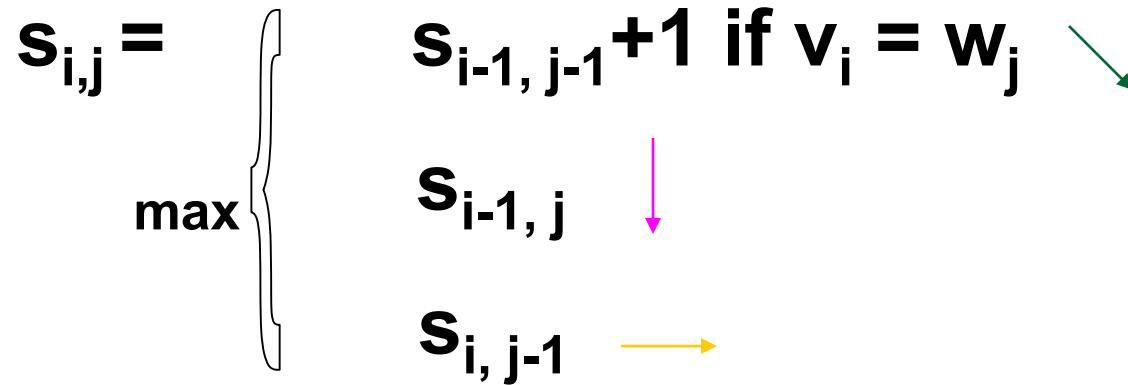
V= AT_GTTAT_

W= ATCGT_A_C

01234567

(0,0) , (1,1) , (2,2), (2,3),
(3,4), (4,5), (5,5), (6,6),
(7,6), (7,7)

Alignment: Dynamic Programming

$$s_{i,j} = \max \begin{cases} s_{i-1,j-1} + 1 & \text{if } v_i = w_j \\ s_{i-1,j} \\ s_{i,j-1} \end{cases}$$


Dynamic Programming Example

		w							
		A	T	C	G	T	A	C	
v	A	0	1	2	3	4	5	6	7
	T	0							
	G	0							
	T	0							
	T	0							
	A	0							
	A	0							
	T	0							

Initialize 1st row and 1st column to be all zeroes.

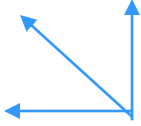
Or, to be more precise, initialize 0th row and 0th column to be all zeroes.

Dynamic Programming Example

		w							
		A	T	C	G	T	A	C	
		0	1	2	3	4	5	6	7
v	A	0	0	0	0	0	0	0	0
	T	1	0	1	1	1	1	1	1
	G	2	0	1					
	T	3	0	1					
	T	4	0	1					
	T	5	0	1					
	A	6	0	1					
	T	7	0	1					

$$S_{i,j} = \max \begin{cases} S_{i-1,j-1} & \leftarrow \text{value from NW} + 1, \text{ if } v_i = w_j \\ S_{i-1,j} & \leftarrow \text{value from North (top)} \\ S_{i,j-1} & \leftarrow \text{value from West (left)} \end{cases}$$

Alignment: Backtracking

Arrows  show where the score originated from.

 if from the top

 if from the left

 if $v_i = w_j$

Backtracking Example

		w							
		A	T	C	G	T	A	C	
		0	1	2	3	4	5	6	7
v	A	0	0	0	0	0	0	0	0
	T	1	0	1	1	1	1	1	1
	G	2	0	1	2	2	2	2	2
	T	3	0	1	2				
	T	4	0	1	2				
	T	5	0	1	2				
	A	6	0	1	2				
	T	7	0	1	2				

Find a match in row and column 2.

$i=2, j=2,5$ is a match (T).

$j=2, i=4,5,7$ is a match (T).

Since $v_i = w_j$, $s_{i,j} = s_{i-1,j-1} + 1$

$$s_{2,2} = [s_{1,1} = 1] + 1$$

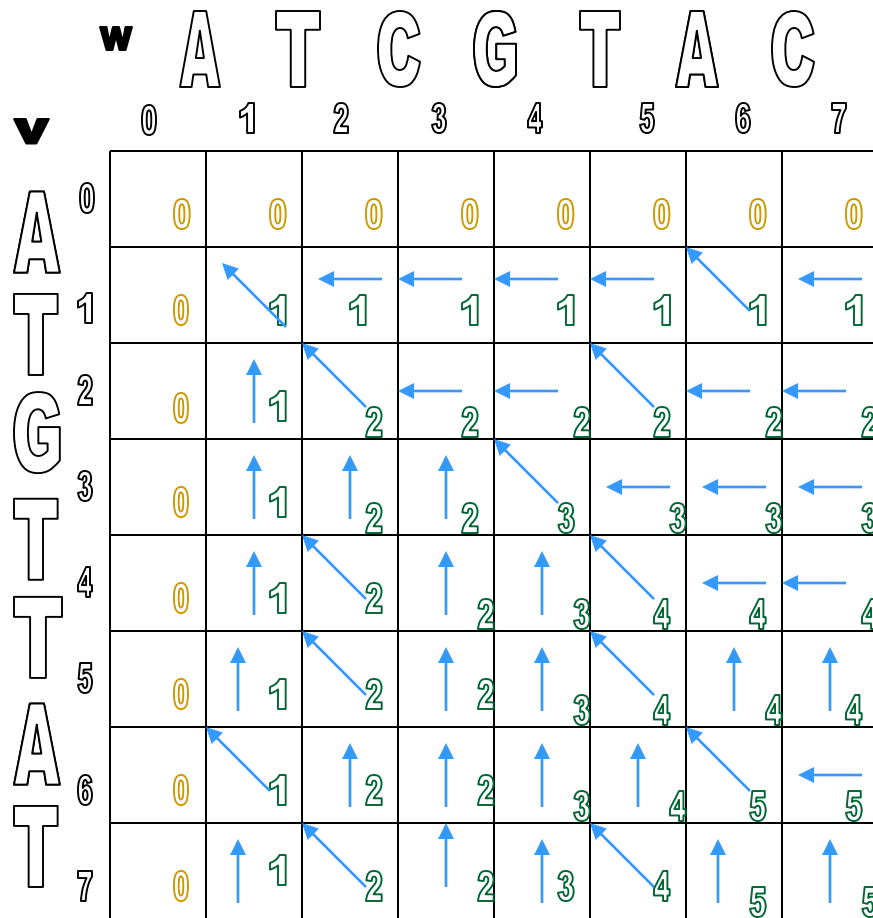
$$s_{2,5} = [s_{1,4} = 1] + 1$$

$$s_{4,2} = [s_{3,1} = 1] + 1$$

$$s_{5,2} = [s_{4,1} = 1] + 1$$

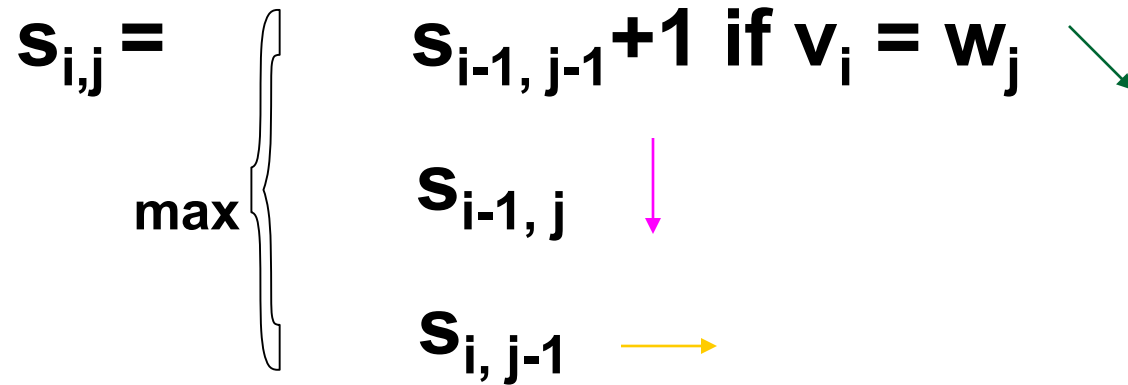
$$s_{7,2} = [s_{6,1} = 1] + 1$$

Backtracking Example



Continuing with the dynamic programming algorithm gives this result.

Alignment: Dynamic Programming

$$s_{i,j} = \max \begin{cases} s_{i-1,j-1} + 1 & \text{if } v_i = w_j \\ s_{i-1,j} \\ s_{i,j-1} \end{cases}$$


Alignment: Dynamic Programming

$$s_{i,j} = \max \begin{cases} s_{i-1,j-1} + 1 & \text{if } v_i = w_j \quad \searrow \\ s_{i-1,j} + 0 & \quad \downarrow \\ s_{i,j-1} + 0 & \quad \rightarrow \end{cases}$$

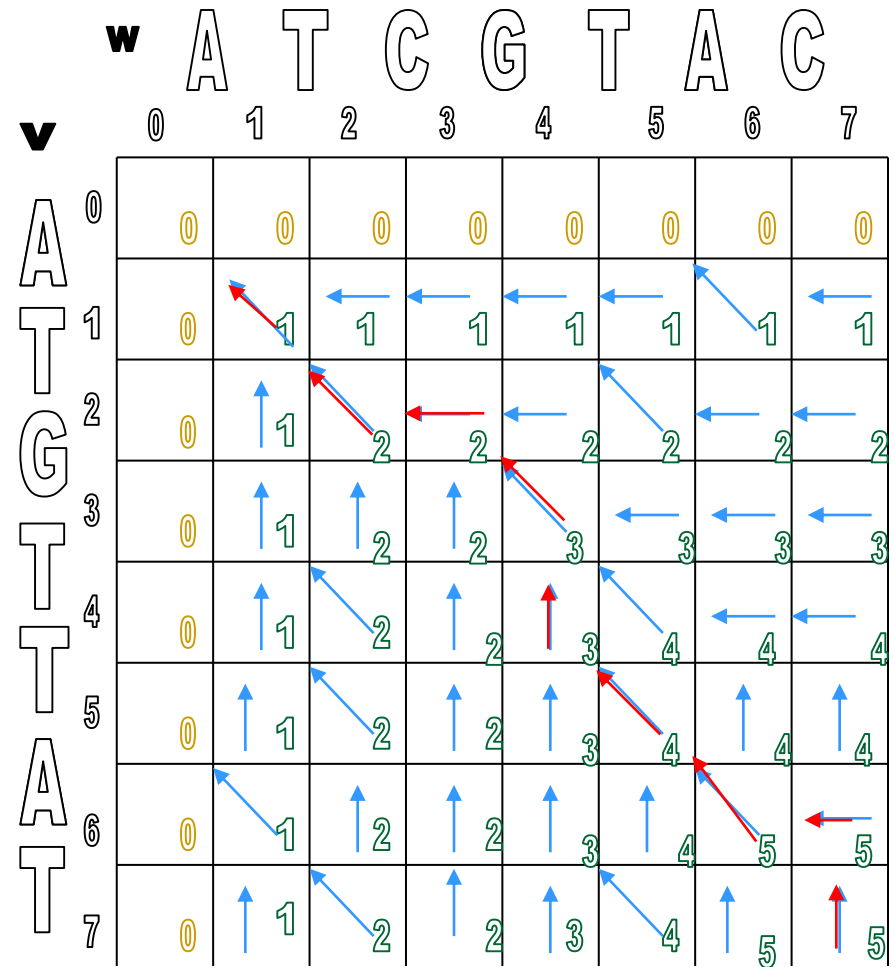
This recurrence corresponds to the Manhattan Tourist problem (three incoming edges into a vertex) with all horizontal and vertical edges weighted by zero.

LCS Algorithm

```
1. LCS(v,w)
2.   for  $i \leftarrow 1$  to  $n$ 
3.      $s_{i,0} \leftarrow 0$ 
4.   for  $j \leftarrow 1$  to  $m$ 
5.      $s_{0,j} \leftarrow 0$ 
6.   for  $i \leftarrow 1$  to  $n$ 
7.     for  $j \leftarrow 1$  to  $m$ 
8.        $s_{i,j} \leftarrow \max \begin{cases} s_{i-1,j} \\ s_{i,j-1} \\ s_{i-1,j-1} + 1, \text{ if } v_i = w_j \end{cases}$ 
9.        $b_{i,j} \leftarrow \begin{cases} \uparrow & \text{if } s_{i,j} = s_{i-1,j} \\ \leftarrow & \text{if } s_{i,j} = s_{i,j-1} \\ \swarrow & \text{if } s_{i,j} = s_{i-1,j-1} + 1 \end{cases}$ 
10.
11.
■   return  $(s_{n,m}, b)$ 
```

Now What?

- $\text{LCS}(v, w)$ created the alignment grid
- Now we need a way to read the best alignment of v and w
- Follow the arrows backwards from sink



Printing LCS: Backtracking

```
1.  PrintLCS(b,v,i,j)
2.      if  $i = 0$  or  $j = 0$ 
3.          return
4.      if  $b_{i,j} = \nwarrow$ 
5.          PrintLCS(b,v,i-1,j-1)
6.          print  $v_i$ 
7.      else
8.          if  $b_{i,j} = \uparrow$ 
9.              PrintLCS(b,v,i-1,j)
10.         else
11.             PrintLCS(b,v,i,j-1)
```

LCS Runtime

- It takes $O(nm)$ time to fill in the $n \times m$ dynamic programming matrix.

QUIZ 1

DNA mapping

$$\Delta \mathbf{X} = \{0, 1, 2, 3, 3, 5, 5, 7, 8, 8, 10, 12, 13, 13, 15, 16\}$$

Use the partial digest algorithm to find \mathbf{X}