

CS 466

Introduction to Bioinformatics

Lecture 2

Mohammed El-Kebir

August 28, 2020



Course Announcements

Instructor:

- Mohammed El-Kebir (melkebir)
- Office hours: Wednesdays, 3:15-4:15pm

Zoom:

- <https://illinois.zoom.us/j/93763998549>

TA:

- Sarah Christensen (sac2), office hours: Mondays, 3-4pm via Zoom
- Wesley Wei Qian (weiqian3), office hours: Fridays, 9-10am via Zoom

Piazza: (please sign up)

- <https://piazza.com/illinois/fall2020/cs466>

Outline

1. Change problem
2. Review of running time analysis
3. Edit distance
4. Review elementary graph theory
5. Manhattan Tourist problem
6. Longest/shortest paths in DAGs

Reading:

- Jones and Pevzner. Chapters 2.7-2.9 and 6.1-6.4
- Lecture notes

The Change Problem

Change Problem: Given amount $M \in \mathbb{N} \setminus \{0\}$ and coins $\mathbf{c} = (c_1, \dots, c_n) \in \mathbb{N}^n$
s.t. $c_n = 1$ and $c_i \geq c_{i+1}$ for all $i \in [n-1] = \{1, \dots, n-1\}$,
find $\mathbf{d} = (d_1, \dots, d_n) \in \mathbb{N}^n$ s.t. (i) $M = \sum_{i=1}^n c_i d_i$ and (ii) $\sum_{i=1}^n d_i$ is minimum

- Suppose we have $n = 3$ coins:

$$\mathbf{c} = (\text{7 cent}, \text{3 cent}, \text{1 cent})$$

- What is the minimum number of coins needed to make change for $M = 9$ cents?
- Answer: $(d_1, \dots, d_n) = (1, 0, 2)$ thus $1 + 0 + 2 = 3$ coins.

The Change Problem – Four Algorithms

GreedyChange($M, c_1, \dots, c_n$)

1. **for** $i \leftarrow 1$ **to** n
2. $d_i \leftarrow \lfloor M/c_i \rfloor$
3. $M \leftarrow M - d_i c_i$

ExhaustiveChange($M, c_1, \dots, c_n$)

1. **for** $(d_1, \dots, d_n) \in \{0, \dots, \lfloor M/c_1 \rfloor\} \times \dots \times \{0, \dots, \lfloor M/c_n \rfloor\}$
2. **if** $\sum_{i=1}^n c_i d_i = M$
3. **return** $(d_1, \dots, d_n)$

RecursiveChange($M, c_1, \dots, c_n$)

1. **if** $M = 0$
2. **return** 0
3. $\text{bestNumCoins} \leftarrow \infty$
4. **for** $i \leftarrow 1$ **to** n
5. **if** $M \geq c_i$
6. $\text{numCoins} \leftarrow \text{RecursiveChange}(M - c_i, c_1, \dots, c_n)$
7. **if** $\text{numCoins} + 1 < \text{bestNumCoins}$
8. $\text{bestNumCoins} \leftarrow \text{numCoins} + 1$
9. **return** bestNumCoins

DPChange($M, c_1, \dots, c_n$)

1. **for** $m \leftarrow 1$ **to** M
2. $\text{minNumCoins}[m] \leftarrow \infty$
3. **for** $i \leftarrow 1$ **to** n
4. $\text{minNumCoins}[c_i] \leftarrow 1$
5. **for** $m \leftarrow 1$ **to** M
6. **for** $i \leftarrow 1$ **to** n
7. **if** $m > c_i$
8. $\text{minNumCoins}[m] \leftarrow \min(1 + \text{minNumCoins}[m - c_i], \text{minNumCoins}[m])$
9. **return** $\text{minNumCoins}[M]$

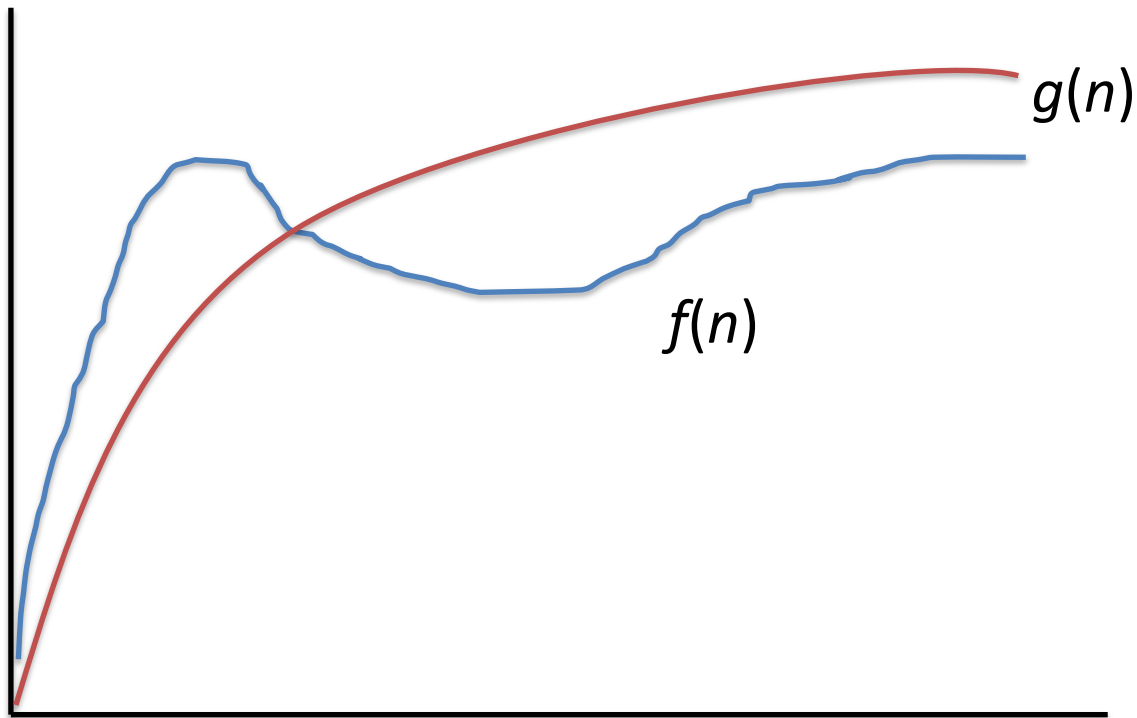
Four Different Algorithms

Technique	Correct?	Efficient?
Greedy algorithm [GreedyChange]	no	yes
Exhaustive enumeration [ExhaustiveChange]	yes	no
Recursive algorithm [RecursiveChange]	yes	no
Dynamic programming [DPChange]	yes	yes

Question: How to assess efficiency?

Running Time Analysis

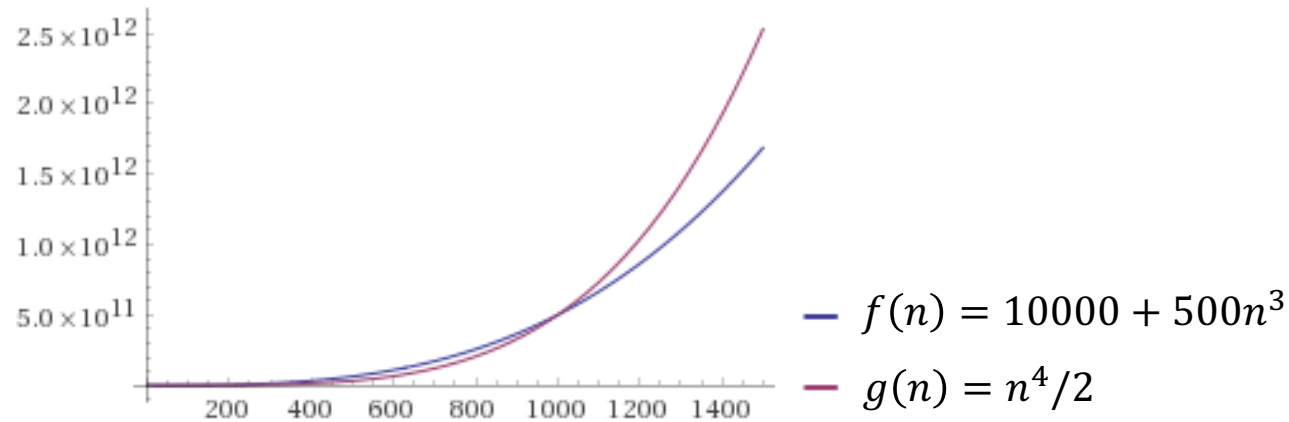
- The **running time** of an algorithm A for problem Π is the maximum number of steps that A will take on any instance of size $n = |X|$
- **Asymptotic running time** ignores constant factors using Big O notation



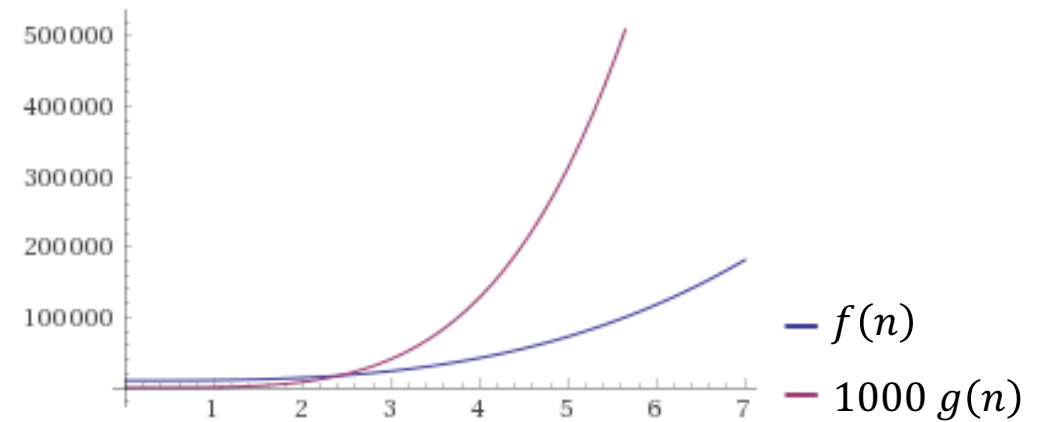
$f(n)$ is $O(g(n))$ provided there exists $c > 0$ and $n_0 \geq 0$ such that $f(n) \leq c g(n)$ for all $n \geq n_0$

Running Time Analysis – Example

$f(n)$ is $O(g(n))$ provided there exists $c > 0$ and $n_0 \geq 0$ such that
 $f(n) \leq c g(n)$ for all $n \geq n_0$



Computed by Wolfram|Alpha



Computed by Wolfram|Alpha

Pick $c = 1000$ and $n_0 = 3$. Then, $f(n) \leq cg(n)$ for all $n \geq n_0$.

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Number of operations:

- Line 2: $3 = O(1)$
- Line 3: $3 = O(1)$
- Total: $6n = O(n)$

Number of operations:

- Lines 1-2: $O(M)$
- Lines 3-4: $O(n)$
- Lines 5-8: $O(Mn)$
- Total: $O(M) + O(n) + O(Mn) = O(Mn)$

Running Time Analysis – Guidelines

- $O(n^a) \subset O(n^b)$ for any positive constants $a < b$
- For any constants $a, b > 0$ and $c > 1$,
 $O(a) \subset O(\log n) \subset O(n^b) \subset O(c^n)$
- We can multiply to learn about other functions. For any constants $a, b > 0$ and $c > 1$,
 $O(an) = O(n) \subset O(n \log n) \subset O(n n^b) = O(n^{b+1}) \subset O(nc^n)$
- Base of the logarithm is a constant and can be ignored. For any constants $a, b > 1$,
 $O(\log_a n) = O(\log_b n / \log_b a) = O(1/(\log_b a) \log_b n) = O(\log_b n)$

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Big Oh	Name
$O(1)$	Constant
$O(\log n)$	Logarithmic
$O(n)$	Linear
$O(n^2)$	Quadratic
$O(n^c) = O(\text{poly}(n))$	Polynomial
$O(2^{\text{poly}(n)})$	Exponential

Running Time Analysis – More Examples

Question: What is $O\left(\binom{n}{k}\right)$?

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- Recall that $n! = \prod_{i=1}^n i$

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Question: What is $O(n!)$?

Stirling's approximation: $n! \approx \sqrt{2\pi n} \left(\frac{n}{e}\right)^n = \sqrt{2\pi} \frac{\sqrt{n}}{\exp(n)} n^n = O(n^n) = O(2^{n \log n})$
(*) : $\sqrt{n} / \exp(n) < 1$ for all $n > 0$ (*)

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Question: Is $n^n = O(n!)$?

Question: What is $O(\log(n!))$?

Course Topic #1: Sequence Alignment

Molecular evolution of *FOXP2*, a gene involved in speech and language

Wolfgang Enard*, Molly Przeworski*, Simon E. Fisher†, Cecilia S. L. Lai†, Victor Wiebe*, Takashi Kitano*, Anthony P. Monaco† & Svante Pääbo*

* Max Planck Institute for Evolutionary Anthropology, Inselstrasse 22, D-04103 Leipzig, Germany
† Wellcome Trust Centre for Human Genetics, University of Oxford, Roosevelt Drive, Oxford OX3 7BN, UK

Nature (2002)

“Thus, although the FOXP2 protein is extremely conserved among mammals, it acquired **two amino-acid changes** on the human lineage, at least one of which may have functional consequences. This is an intriguing finding, because FOXP2 is the first gene known to be involved in the development of speech and language.”

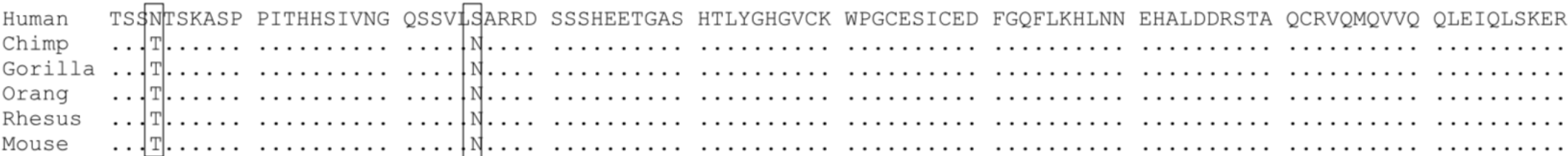


Figure 1 Alignment of the amino-acid sequences inferred from the *FOXP2* cDNA sequences. The polyglutamine stretches and the forkhead domain are shaded. Sites that differ from the human sequence are boxed.

Question: How do we **align** sequences to identify similarities/differences?

Alignment

An **alignment** between two strings **v** (of m characters) and **w** (of n characters) is a two row matrix where the first row contains the characters of **v** in order, the second row contains the characters of **w** in order, and spaces may be interspersed throughout each.

Input

v: KITTEN ($m = 6$)

w: SITTING ($n = 7$)

Output

v:	K	–	I	T	T	E	N	–
w:	S	I	–	T	T	I	N	G

Question: Is this a good alignment?

Answer: Count the number of insertion, deletions, substitutions.

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Edit Distance [Levenshtein, 1966]



Elementary operations: insertion, deletions and substitutions of single characters

Edit Distance problem: Given strings $\mathbf{v} \in \Sigma^m$ and $\mathbf{w} \in \Sigma^n$, compute the minimum number $d(\mathbf{v}, \mathbf{w})$ of elementary operations to transform $\mathbf{v}$ into $\mathbf{w}$.

$$d(\mathbf{cat}, \mathbf{car}) = 1 \quad d(\mathbf{cat}, \mathbf{ate}) = 2 \quad d(\mathbf{cat}, \mathbf{are}) = 3$$

Computing Edit Distance

Edit Distance problem: Given strings $\mathbf{v} \in \Sigma^m$ and $\mathbf{w} \in \Sigma^n$, compute the minimum number $d(\mathbf{v}, \mathbf{w})$ of elementary operations to transform $\mathbf{v}$ into $\mathbf{w}$.

$\mathbf{v}$: ATGTTAT...

$\mathbf{w}$: AGCGTAC...



prefix of $\mathbf{v}$ of length i	$\mathbf{v}_i$:	A	T	-	G	T	T	T
prefix of $\mathbf{w}$ of length j	$\mathbf{w}_j$:	A	G	C	G	T	-	C
							$j-1$	j

Optimal substructure:

Edit distance obtained from edit distance of prefix of string.

Computing Edit Distance – Optimal Substructure

$d[i, j]$ is the edit distance of $\mathbf{v}_i$ and $\mathbf{w}_j$,
where $\mathbf{v}_i$ is prefix of $\mathbf{v}$ of length i and $\mathbf{w}_j$ is prefix of $\mathbf{w}$ of length j

Deletion: $d[i, j] = d[i - 1, j] + 1$
Extend by a character in $\mathbf{v}$

...	$\mathbf{v}_i$
...	—

Insertion: $d[i, j] = d[i, j - 1] + 1$
Extend by a character in $\mathbf{w}$

...	—
...	$\mathbf{w}_j$

Mismatch: $d[i, j] = d[i - 1, j - 1] + 1$
Extend by a character in $\mathbf{v}$ and $\mathbf{w}$

...	$\mathbf{v}_i$
...	$\mathbf{w}_j$

Match: $d[i, j] = d[i - 1, j - 1]$
Extend by a character in $\mathbf{v}$ and $\mathbf{w}$

...	$\mathbf{v}_i$
...	$\mathbf{w}_j$

Computing Edit Distance – Recurrence

$d[i, j]$ is the edit distance of $\mathbf{v}_i$ and $\mathbf{w}_j$,
where $\mathbf{v}_i$ is prefix of $\mathbf{v}$ of length i and $\mathbf{w}_j$ is prefix of $\mathbf{w}$ of length j

$$d[i, j] = \min \begin{cases} d[i - 1, j] + 1, \\ d[i, j - 1] + 1, \\ d[i - 1, j - 1] + 1, & \text{if } v_i \neq w_j, \\ d[i - 1, j - 1], & \text{if } v_i = w_j. \end{cases}$$

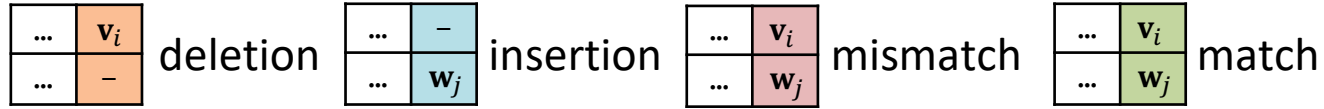
...	$\mathbf{v}_i$
...	—
...	—
...	$\mathbf{w}_j$
...	$\mathbf{v}_i$
...	$\mathbf{w}_j$
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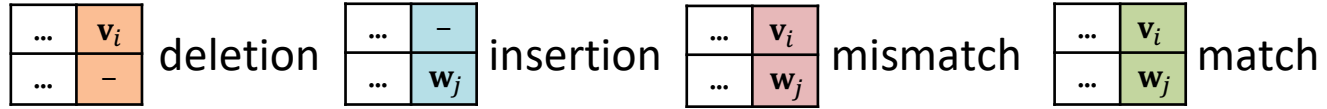
Computing Edit Distance – Dynamic Programming



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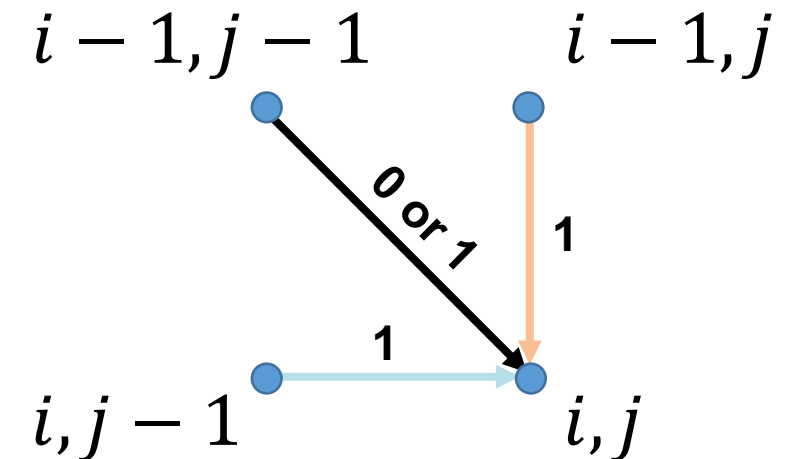
		W	A	T	C	G
V		0	1	2	3	4
	0					
A	1					
T	2					
G	3					
T	4					

Computing Edit Distance – Dynamic Programming

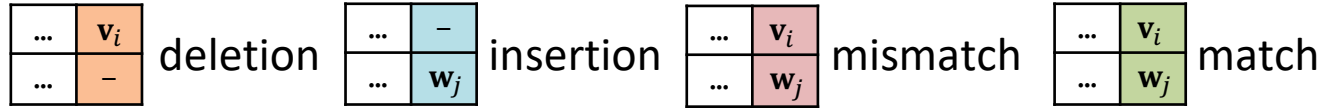


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		W	A	T	C	G
V		0	1	2	3	4
	0	0				
A	1					
T	2					
G	3					
T	4					

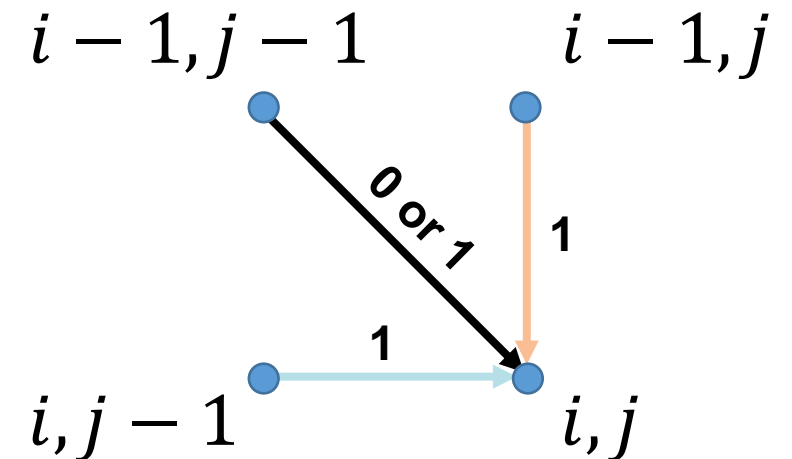


Computing Edit Distance – Dynamic Programming

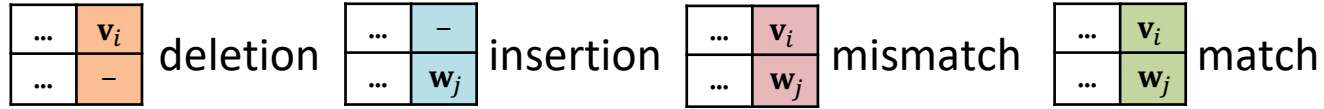


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A	1	1				
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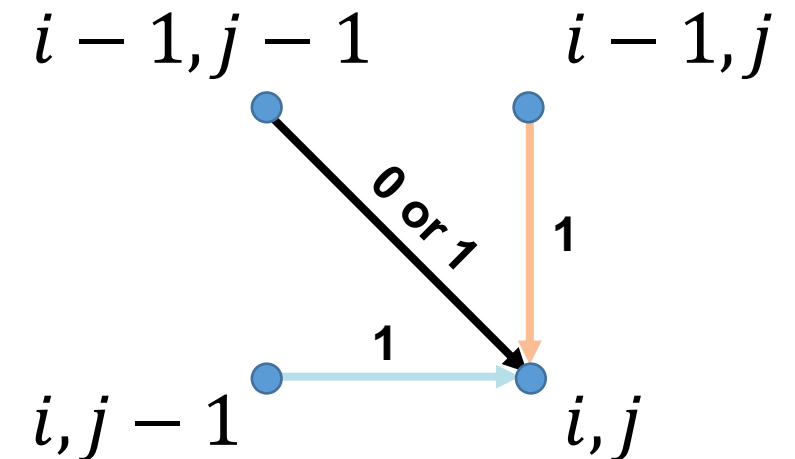


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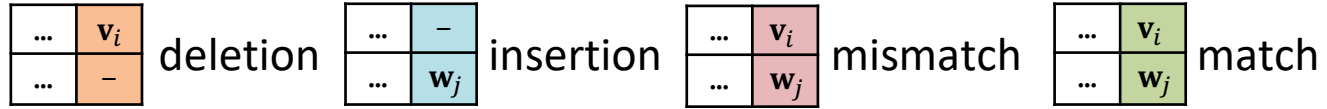


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		W	A	T	C	G
V		0	1	2	3	4
	0	0	1	2	3	4
	1	1	?			
	2	2				
	3	3				
	4	4				
A						
T						
G						
T						

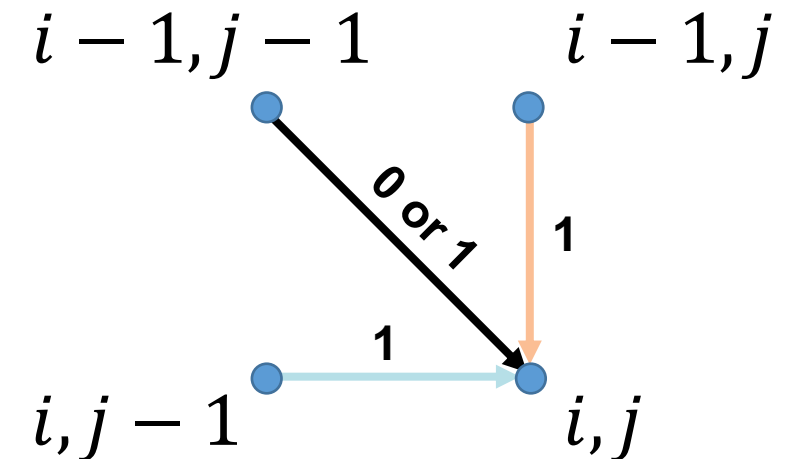


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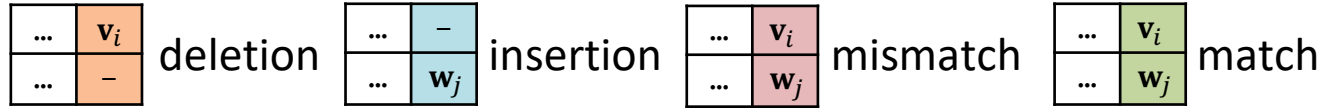


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G						
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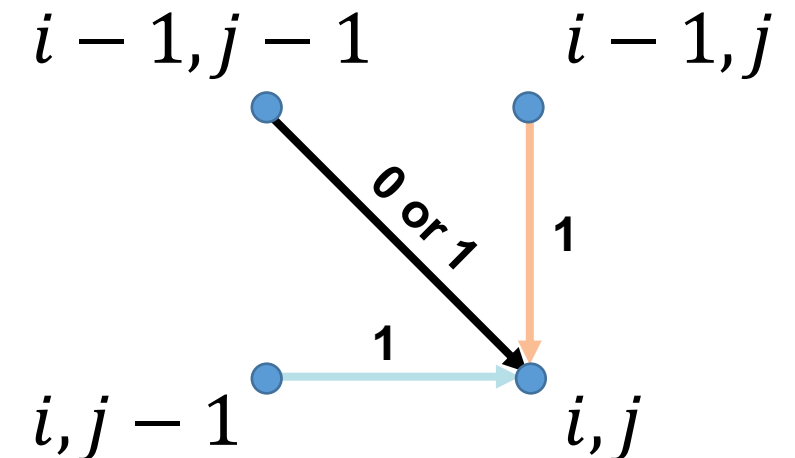


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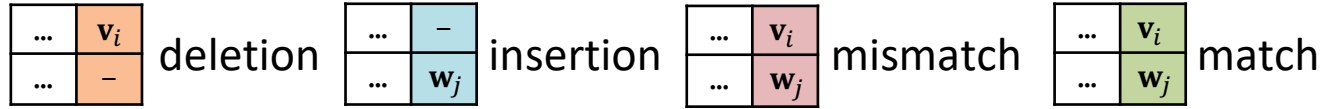


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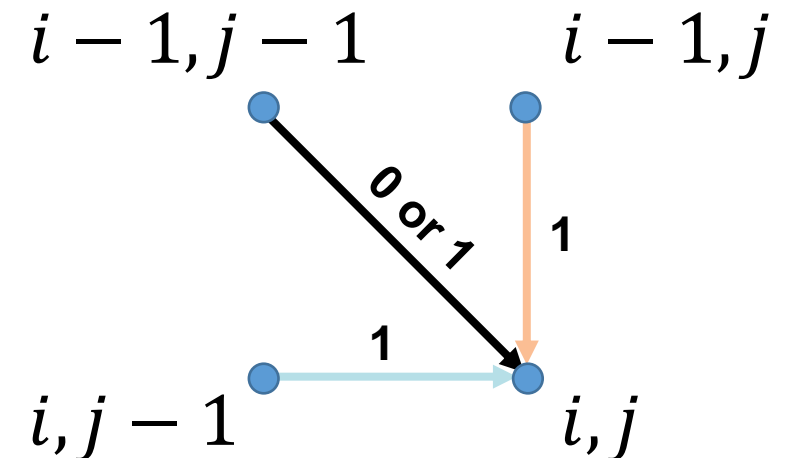


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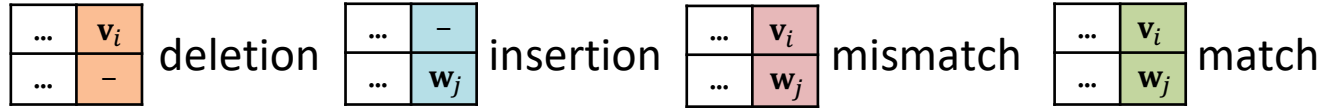


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	2	2	1			
	3	3				
	4	4				
		A	T	G	T	



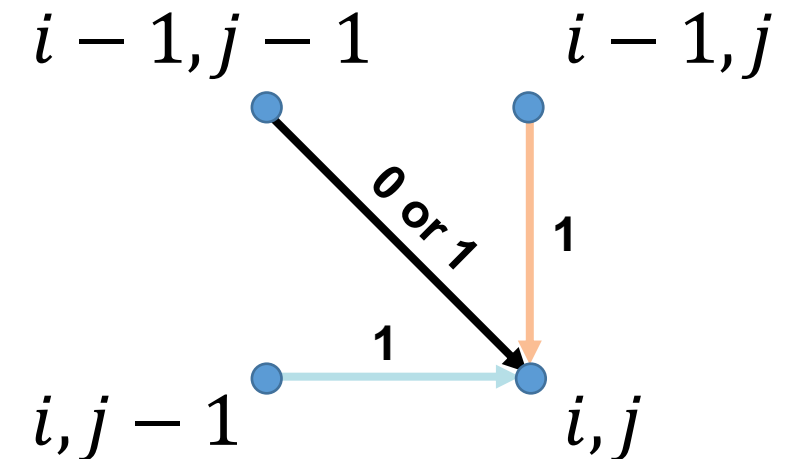
Computing Edit Distance – Dynamic Programming



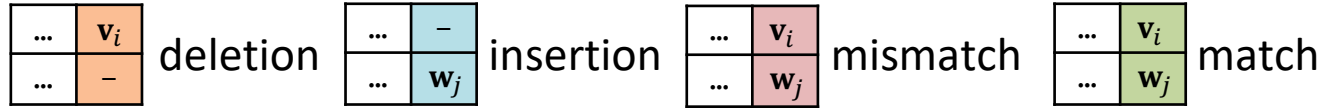
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		W	A	T	C	G
V		0	1	2	3	4
0		0	1	2	3	4
A	1	1				
T	2	2				
G	3	3				
T	4	4				

The table shows edit distances between sequence V (rows) and sequence W (columns).
 Blue arrows indicate the path from (0,0) to (0,4).
 Red arrows indicate the path from (0,4) to (4,4), showing matches (solid red) and mismatches (dashed red).

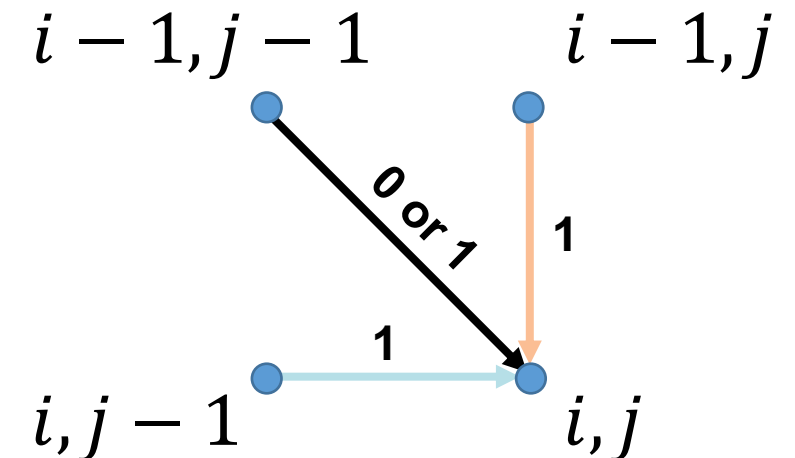


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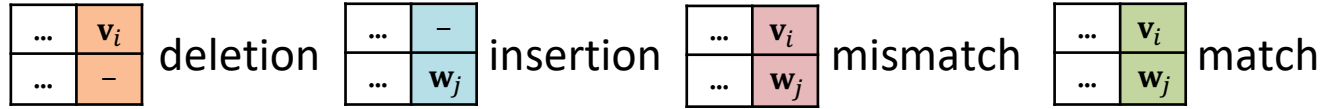


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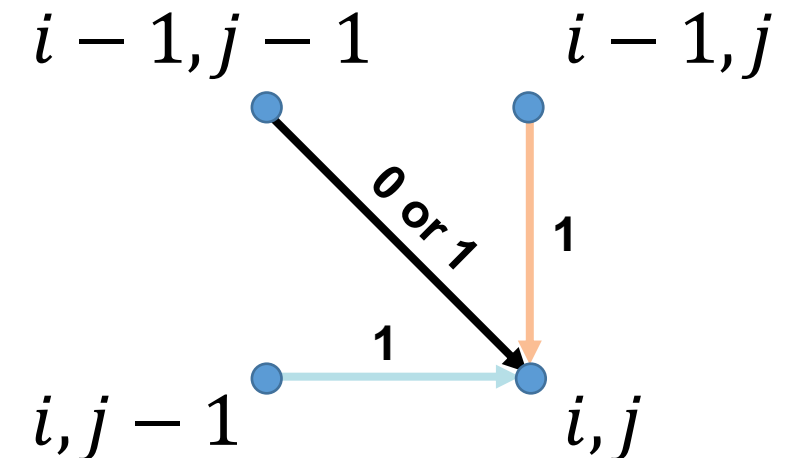


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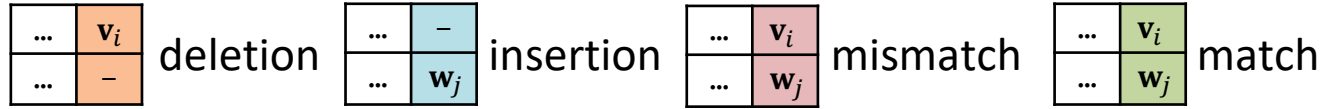


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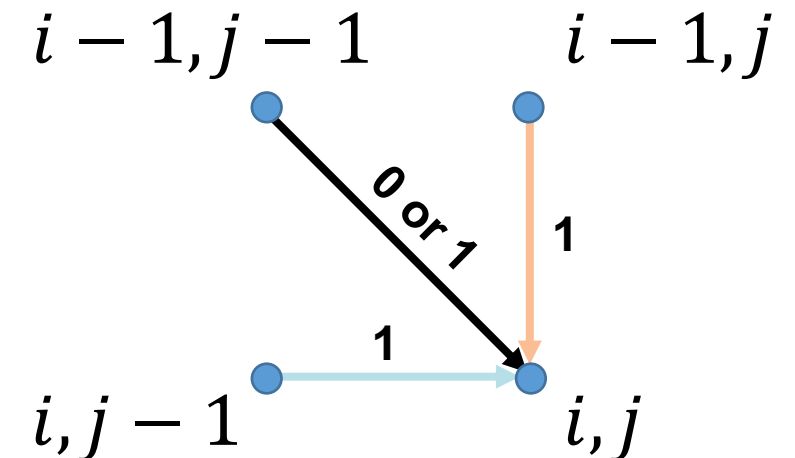


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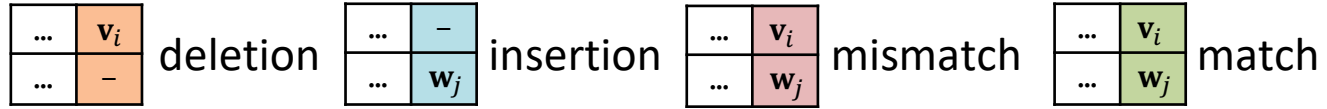


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		W A T C G				
V		0	1	2	3	4
	0	0	1	2	3	4
	1	1	0	1	2	3
	2	2	1	0	1	2
	3	3	2	1	1	1
	4	4	3	2	2	2
		A	T	G	T	

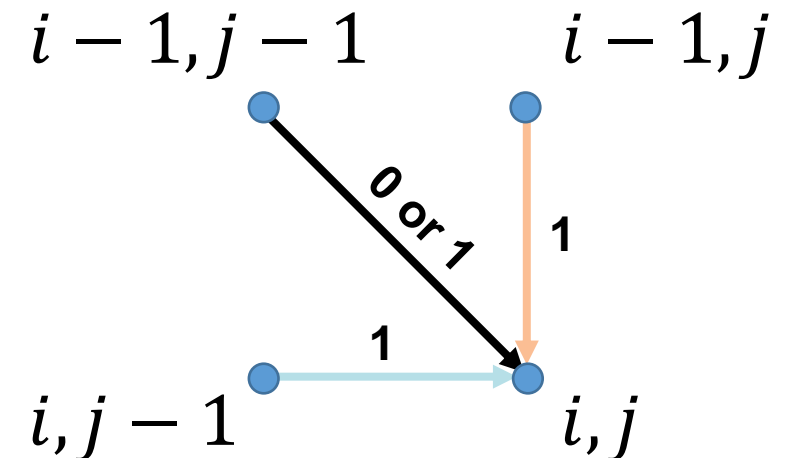


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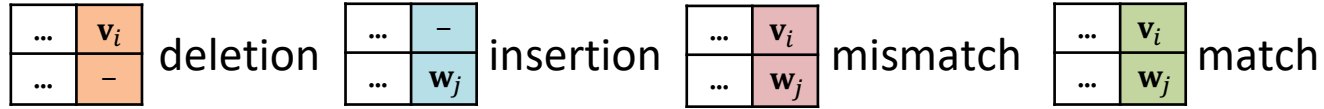


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T	3	3	2	1	1	1
	4	4	3	2	2	2



Computing Edit Distance – Dynamic Programming



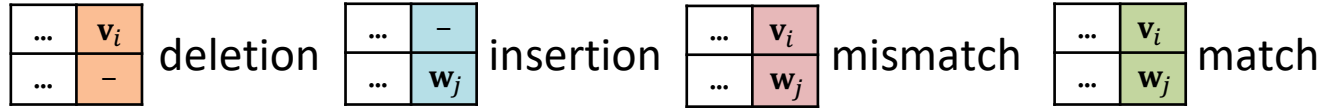
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A	T	-	G	T
A	T	C	G	-

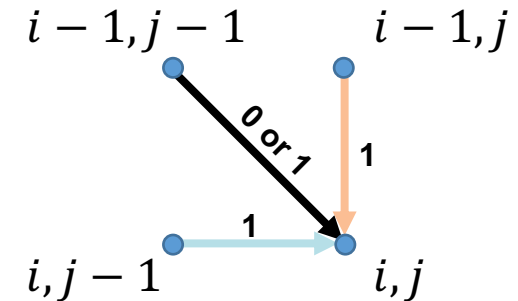
A	T	G	T
A	T	C	G

Computing Edit Distance – Running Time



$$d[i, j] = \min \begin{cases} 0, & \text{if } i = 0 \text{ and } j = 0, \\ d[i - 1, j] + 1, & \text{if } i > 0, \\ d[i, j - 1] + 1, & \text{if } j > 0, \\ d[i - 1, j - 1] + 1, & \text{if } i > 0, j > 0 \text{ and } v_i \neq w_j, \\ d[i - 1, j - 1], & \text{if } i > 0, j > 0 \text{ and } v_i = w_j. \end{cases}$$

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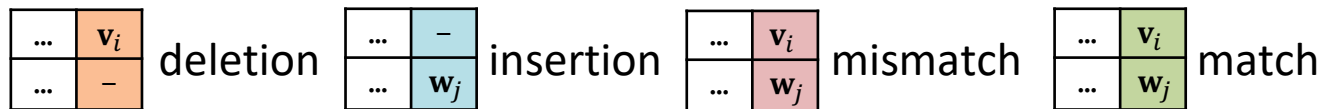


For each $(m + 1) \times (n + 1)$ entry:

- 3 addition operations
- 1 comparison operation
- 1 minimum operation

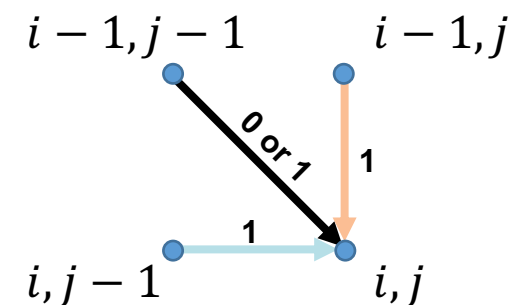
Running time: $O(mn)$ time

Computing Edit Distance – Running Time



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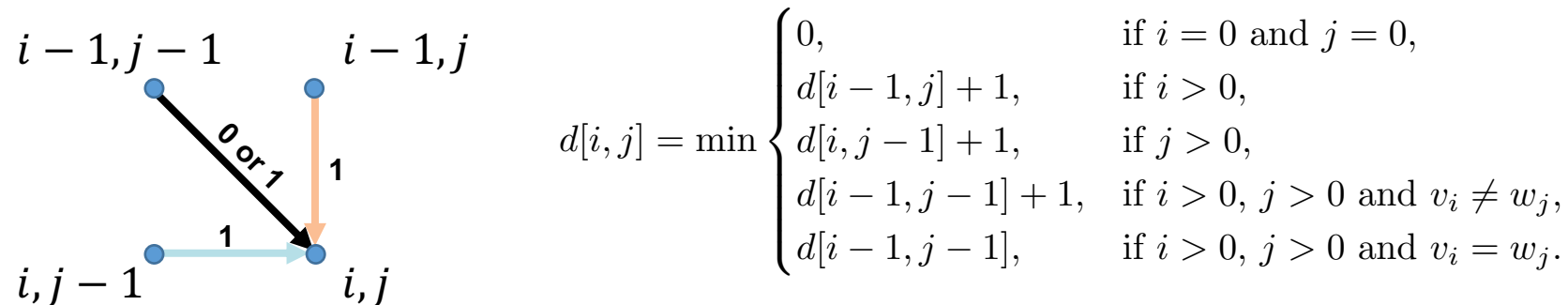
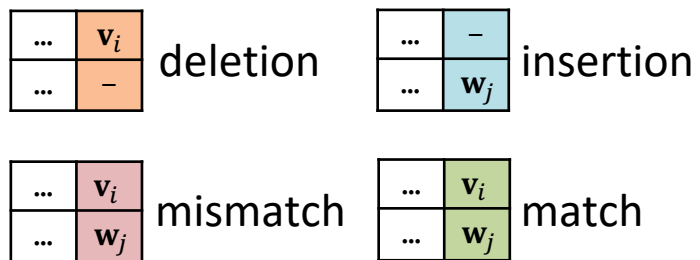


For each $(m + 1) \times (n + 1)$ entry:

- 3 addition operations
- 1 comparison operation
- 1 minimum operation

Running time: $O(mn)$ time

Computing Edit Distance – Your turn!



	W	C	A	R
V				
C				
A				
T				

	W	A	T	E
V				
C				
A				
T				

	W	A	R	E
V				
C				
A				
T				

$d(\text{cat}, \text{car}) =$

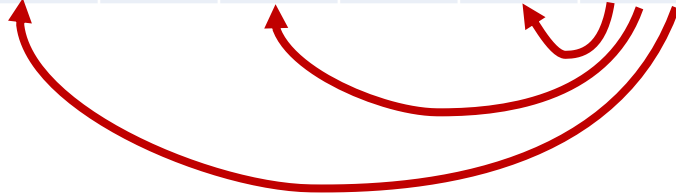
$d(\text{cat}, \text{ate}) =$

$d(\text{cat}, \text{are}) =$

Change Problem and Edit distance

Make M cents using minimum number of 1, 3 and 5 cent coins.

Value	1	2	3	4	5	6	7
Min # coins	1	2	1	2	1	2	3

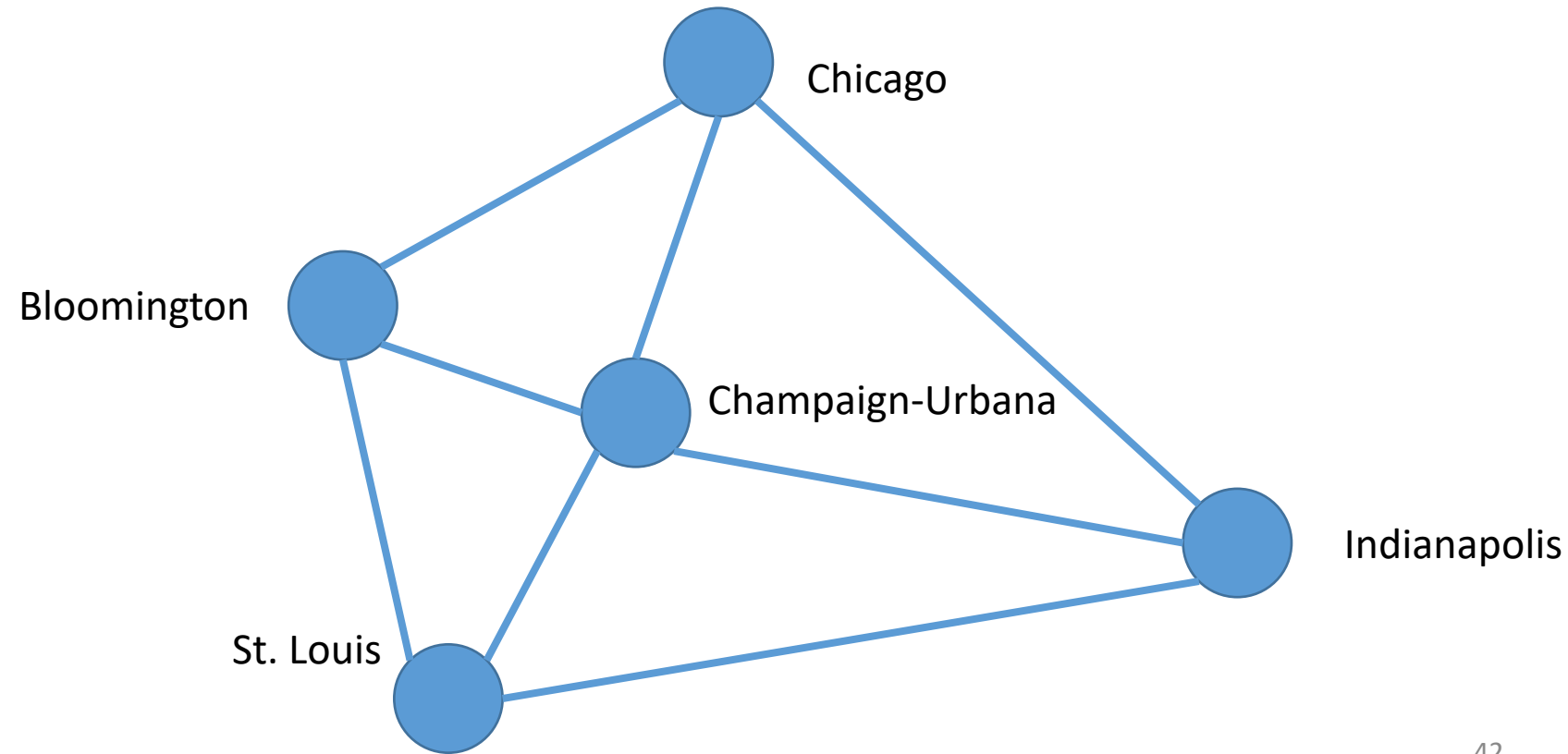


	W	A	T	C	G	
V		0	1	2	3	4
0	0	0	1	2	3	4
A	1	1	0	1	2	3
T	2	2	1	0	1	2
G	3	3	2	1	1	1
T	4	4	3	2	2	2

- Both have optimal substructure and can be solved using dynamic programming
 - These are examples of a more general problem!

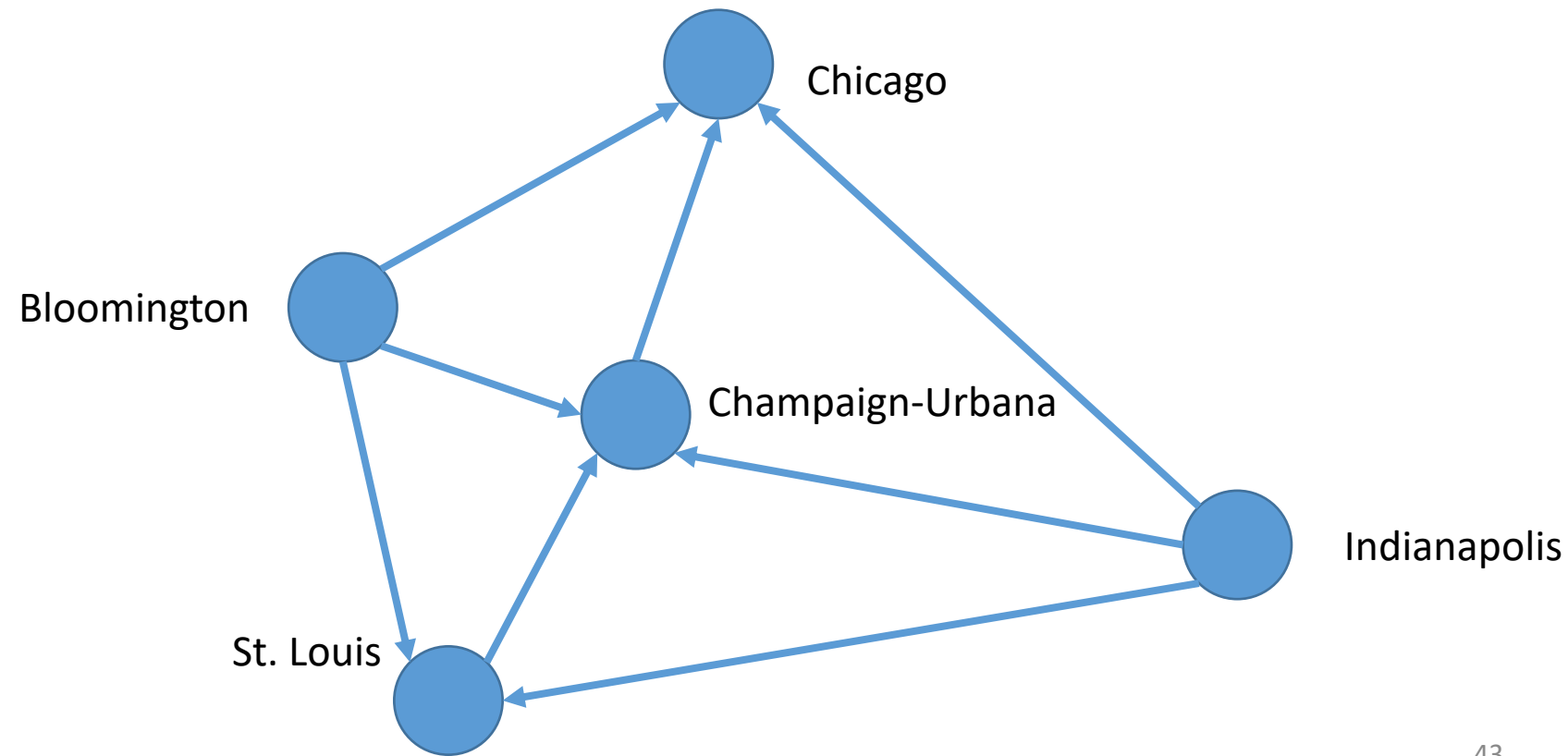
Review of Graph Theory

- Graph $G = (V, E)$
- Vertices $V = \{v_1, \dots, v_n\}$
- Edges $E = \{(v_i, v_j), \dots\}$



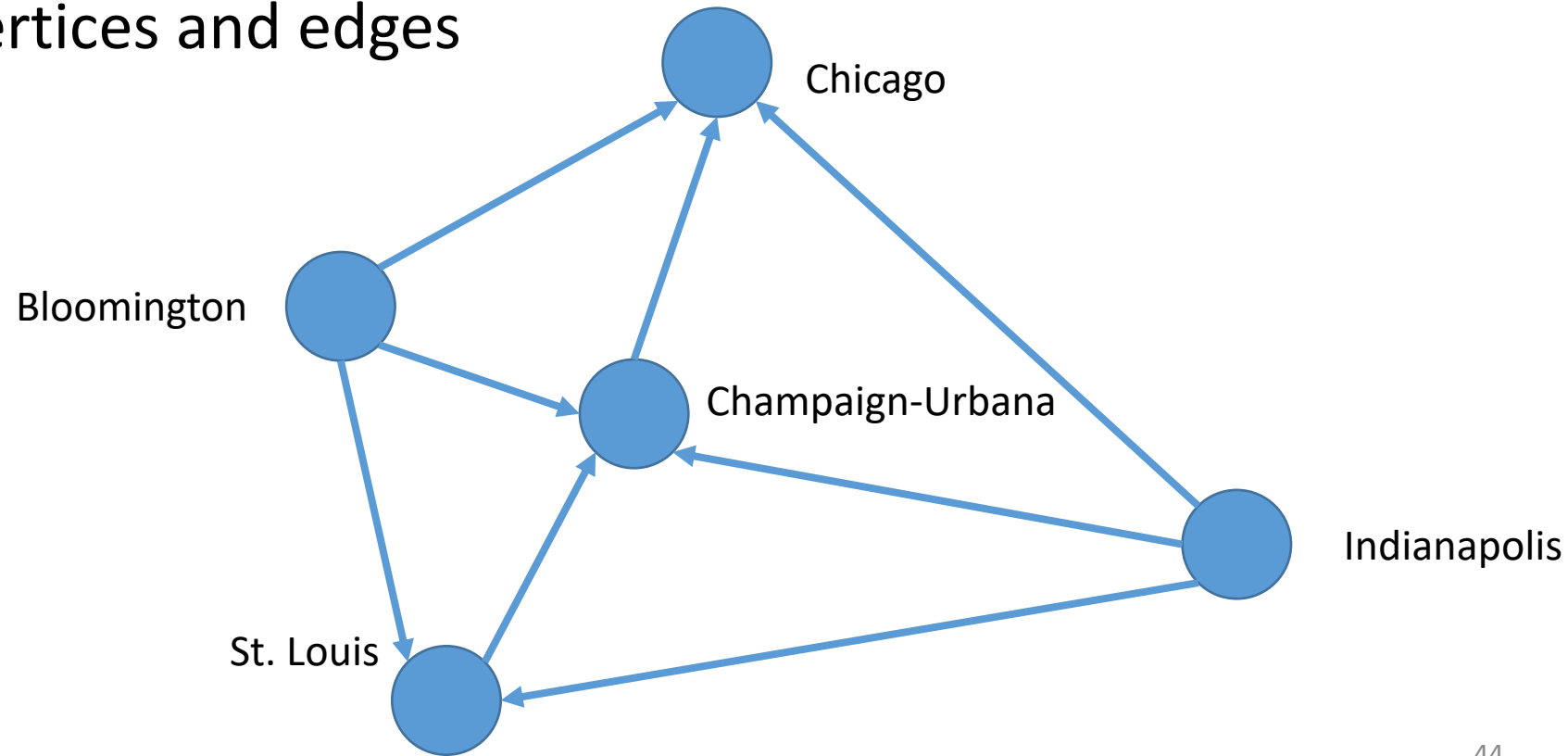
Review of Graph Theory

- Directed Graph $G = (V, E)$
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- Directed edges $E = \{(v_i, v_j), \dots\}$



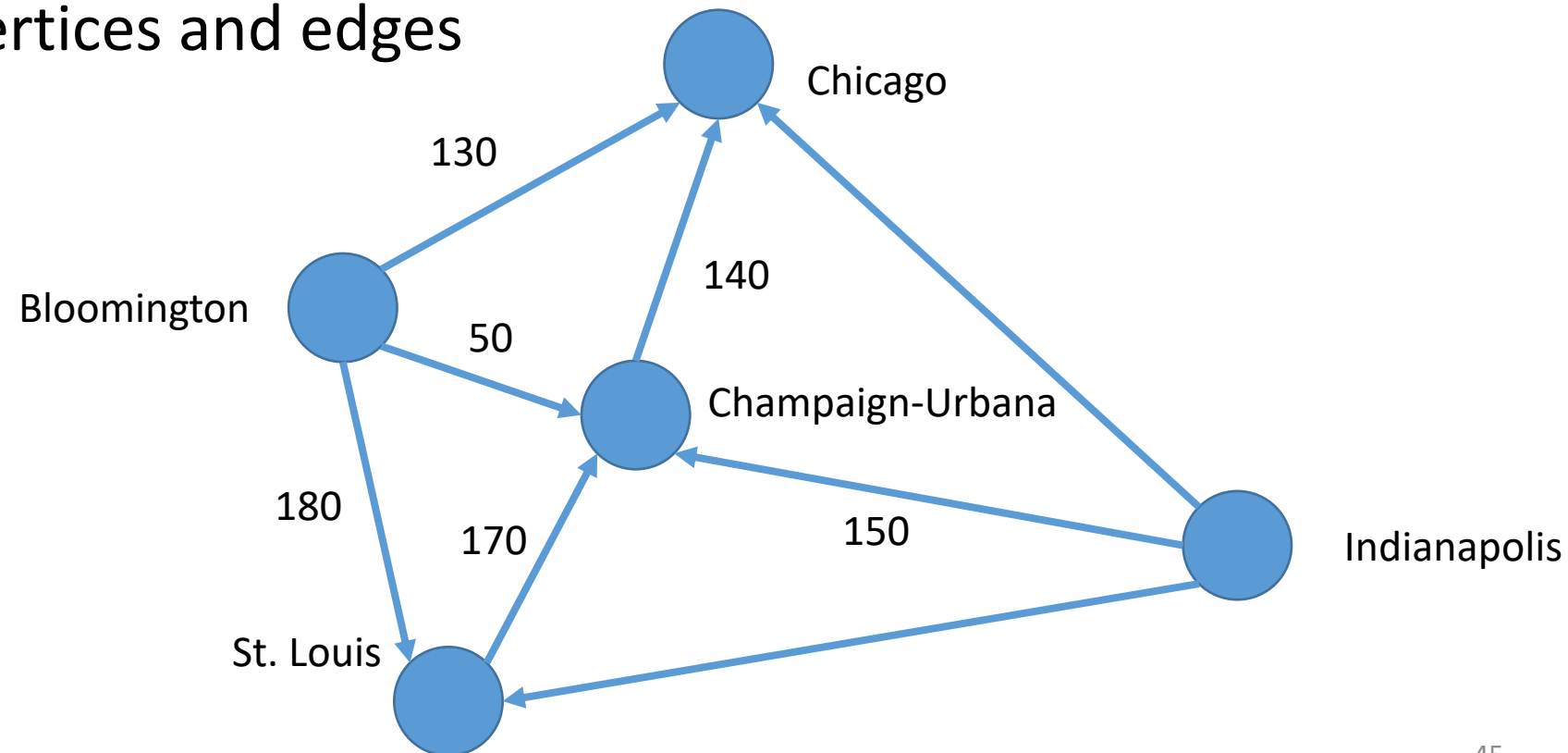
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- Directed Graph $G = (V, E)$
- Vertices $V = \{v_1, \dots, v_n\}$
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- Path is a sequence of vertices and edges that connect them



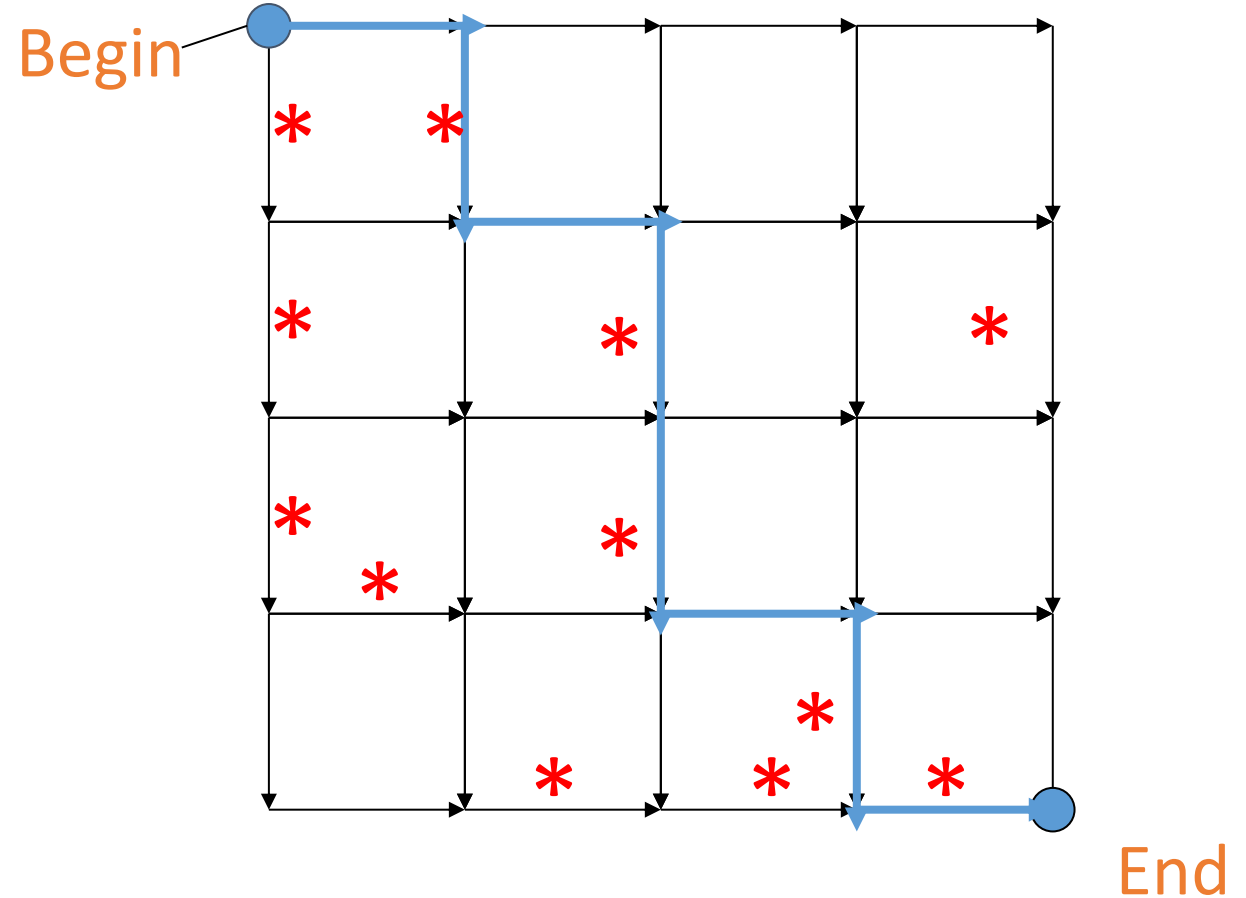
Review of Graph Theory

- Directed Graph $G = (V, E)$
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- Path is a sequence of vertices and edges that connect them
- Edges can be weighted



Manhattan Tourist Problem

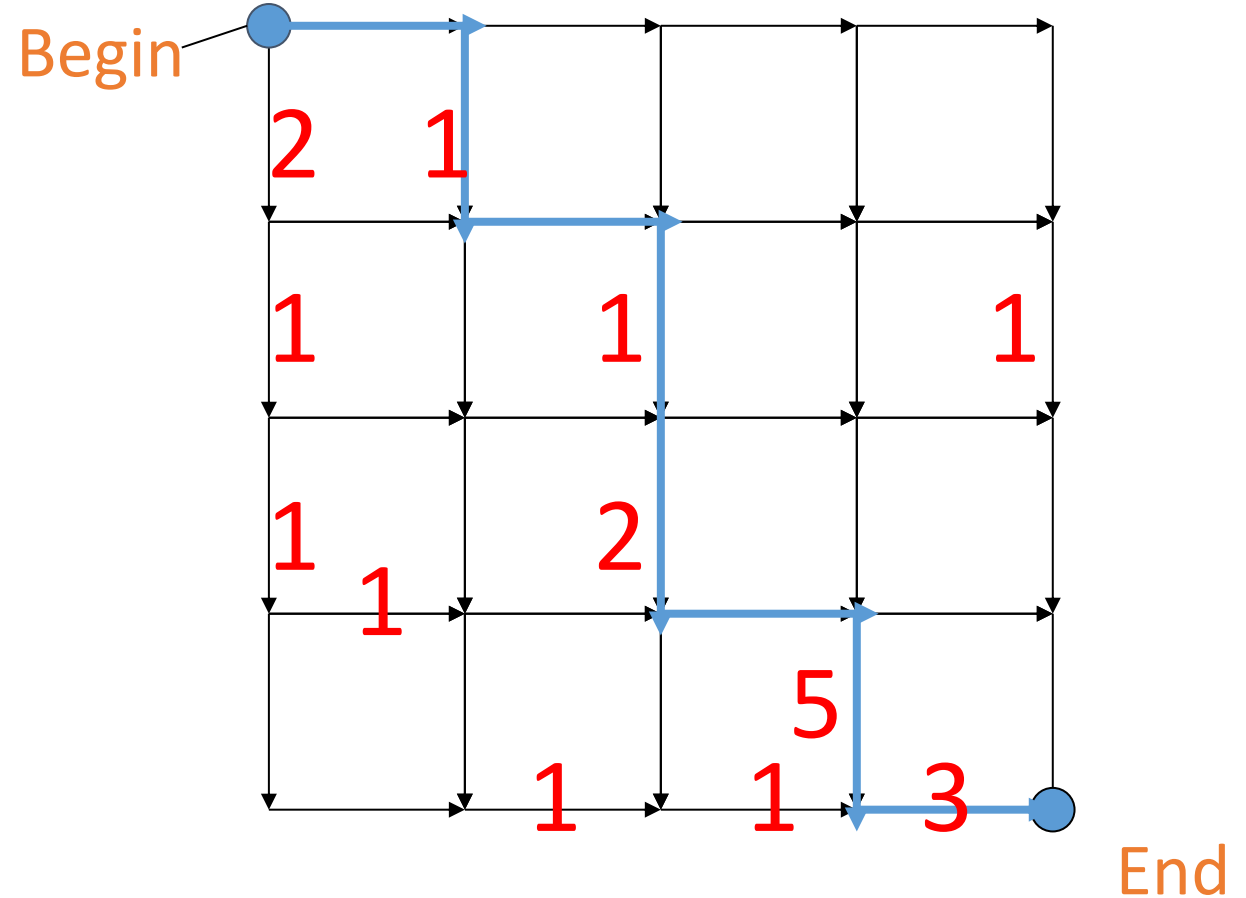
A tourist in Manhattan wants to visit the maximum number of attractions (*) by traveling on a path (only eastward and southward) from start to end



Manhattan Tourist Problem

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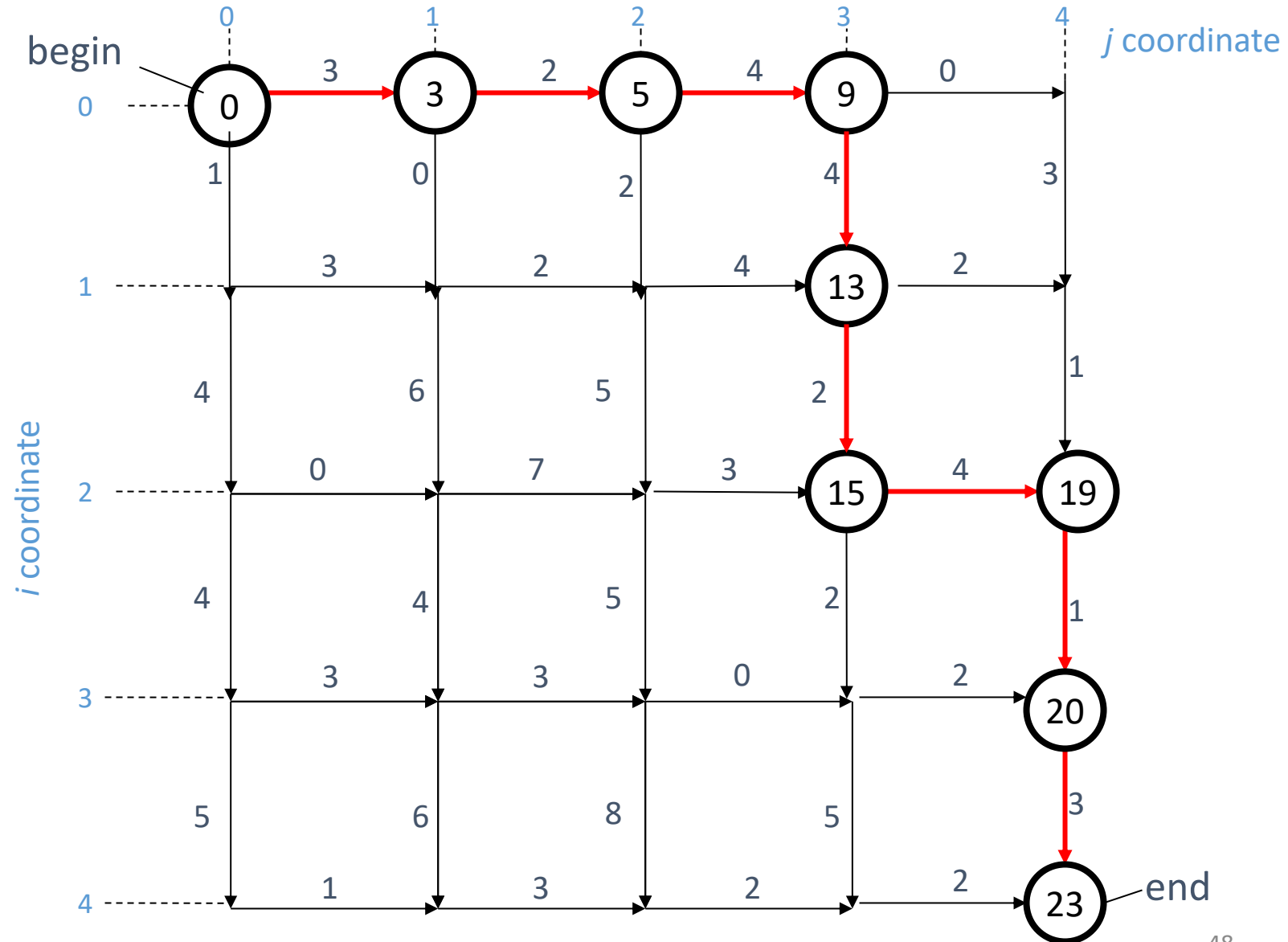
May be more than 1 attraction on a street.
Add weights!



Manhattan Tourist Problem

Manhattan Tourist Problem (MTP):

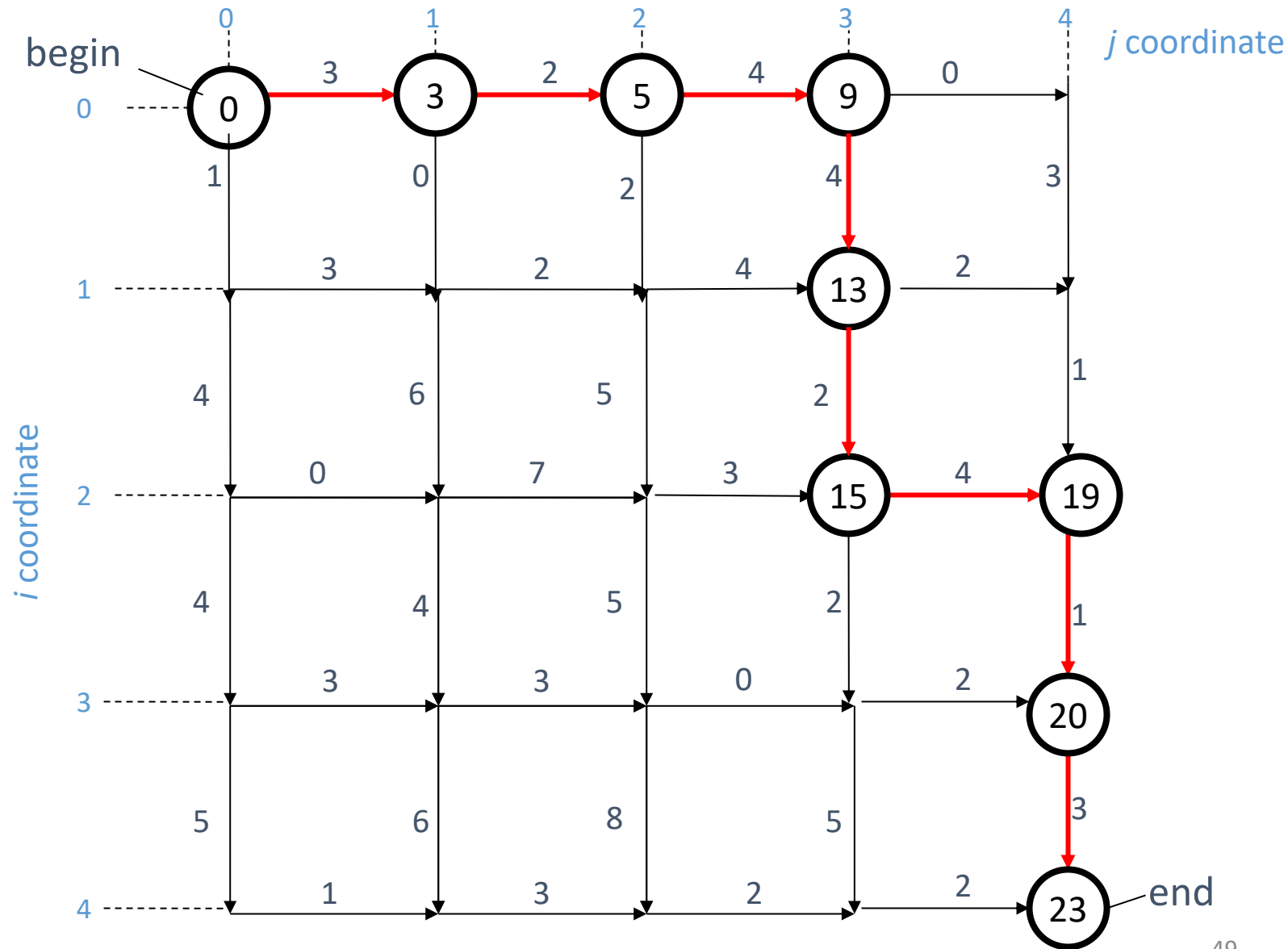
Given a weighted, directed grid graph G with two vertices “begin” and “end”, find the maximum weight path in G from “begin” to “end”.



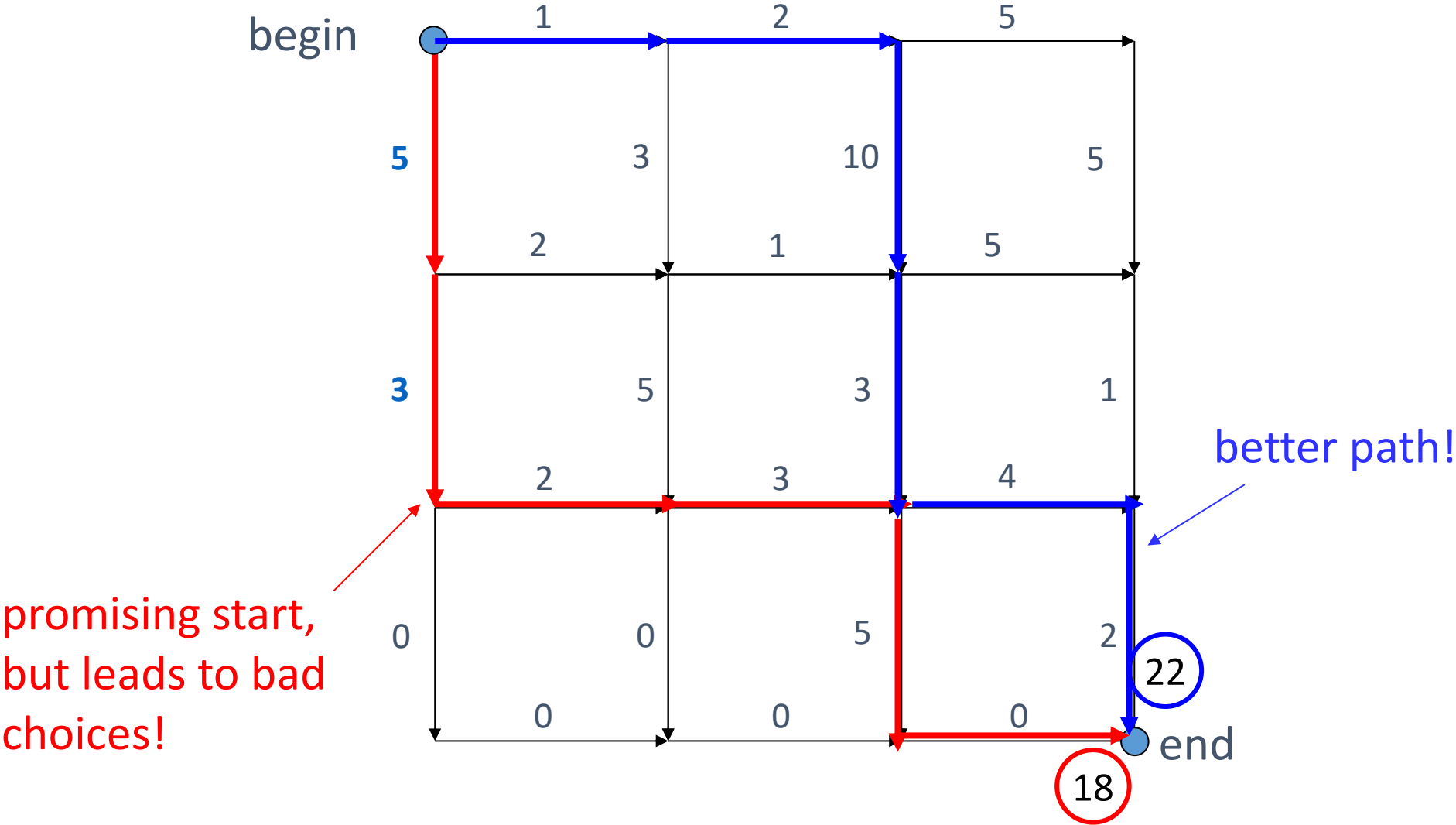
Manhattan Tourist Problem – Exhaustive Algorithm

Check all paths

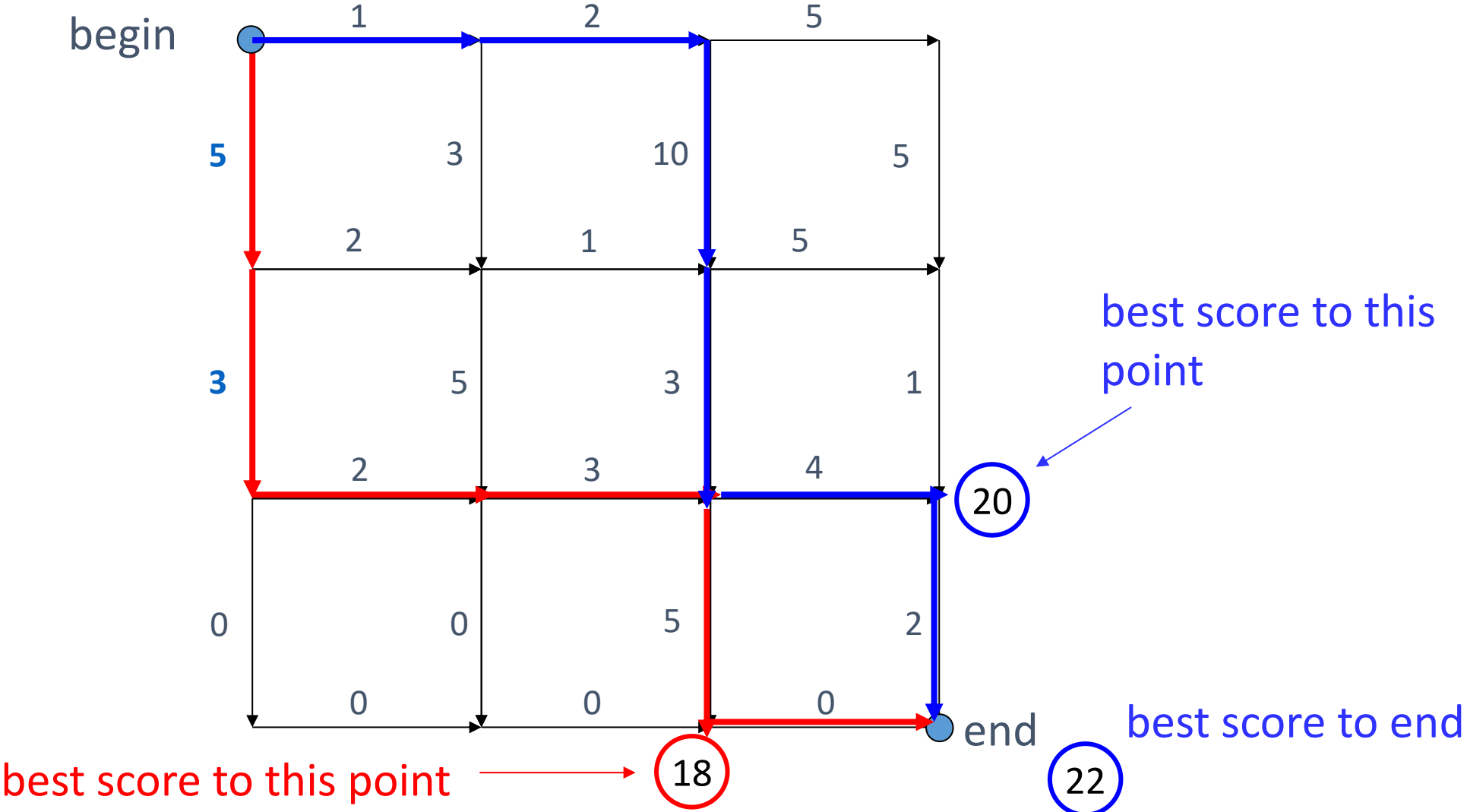
Question:
How many paths?



Manhattan Tourist Problem – Greedy Algorithm



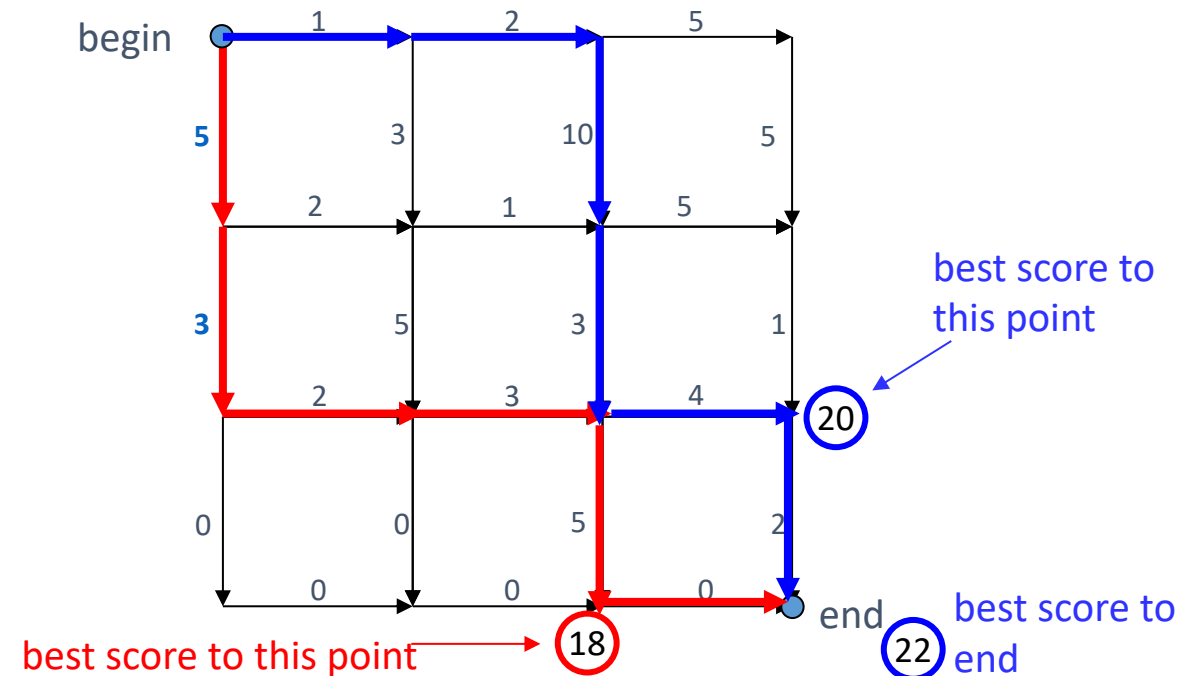
Manhattan Tourist Problem – Optimal Substructure



Manhattan Tourist Problem – Optimal Substructure

$s[i, j]$ is the best score for path to coordinate (i, j)

Question: What is the recurrence?

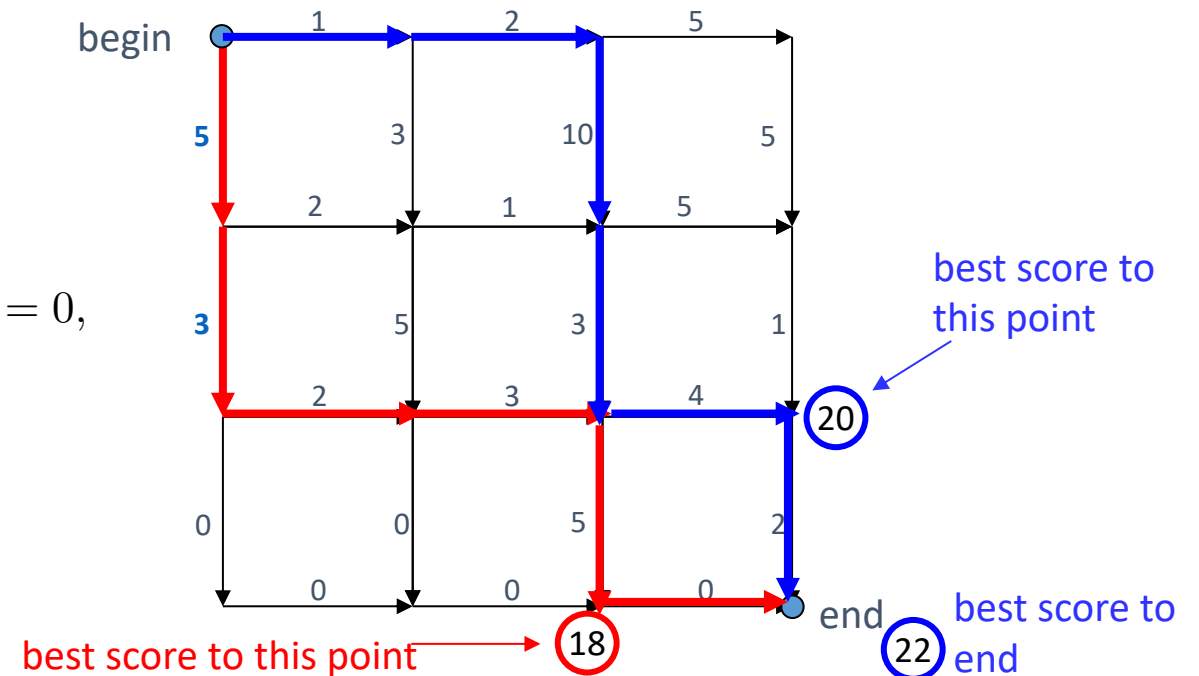


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Manhattan Tourist Problem – Optimal Substructure

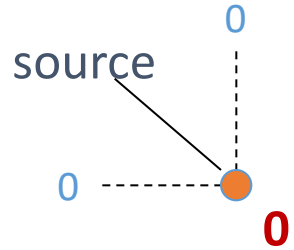
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MTP – Solving Recurrence using Dynamic Programming

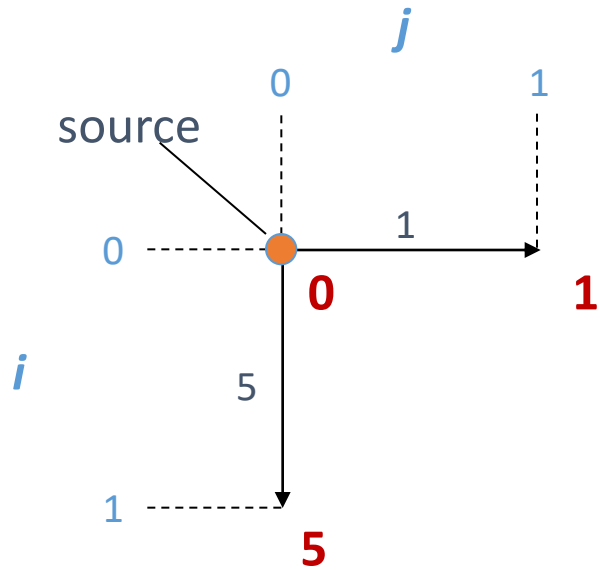


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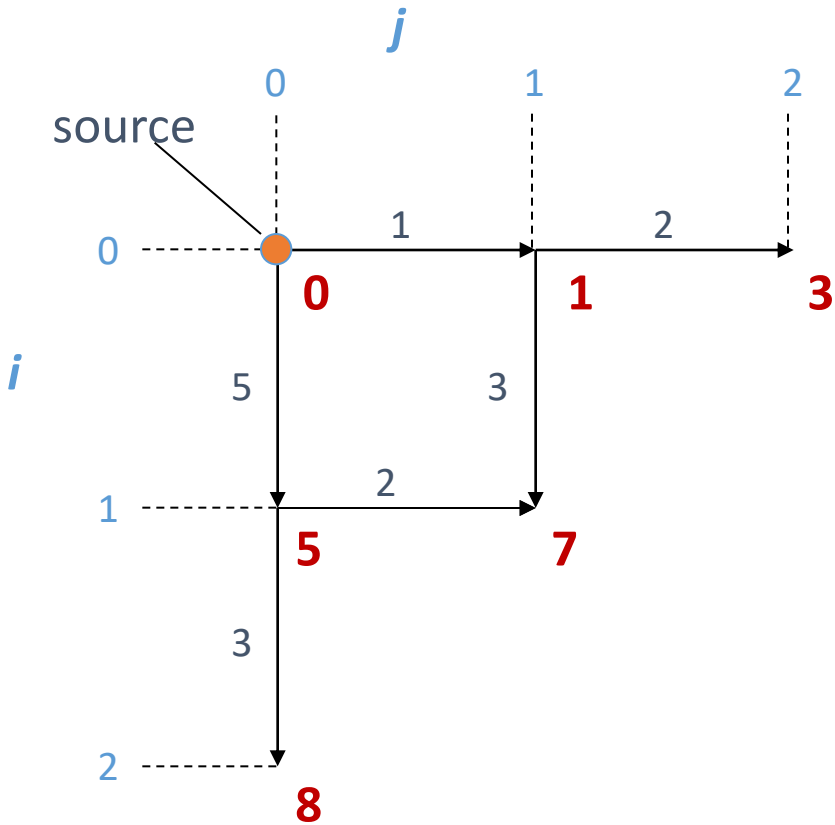


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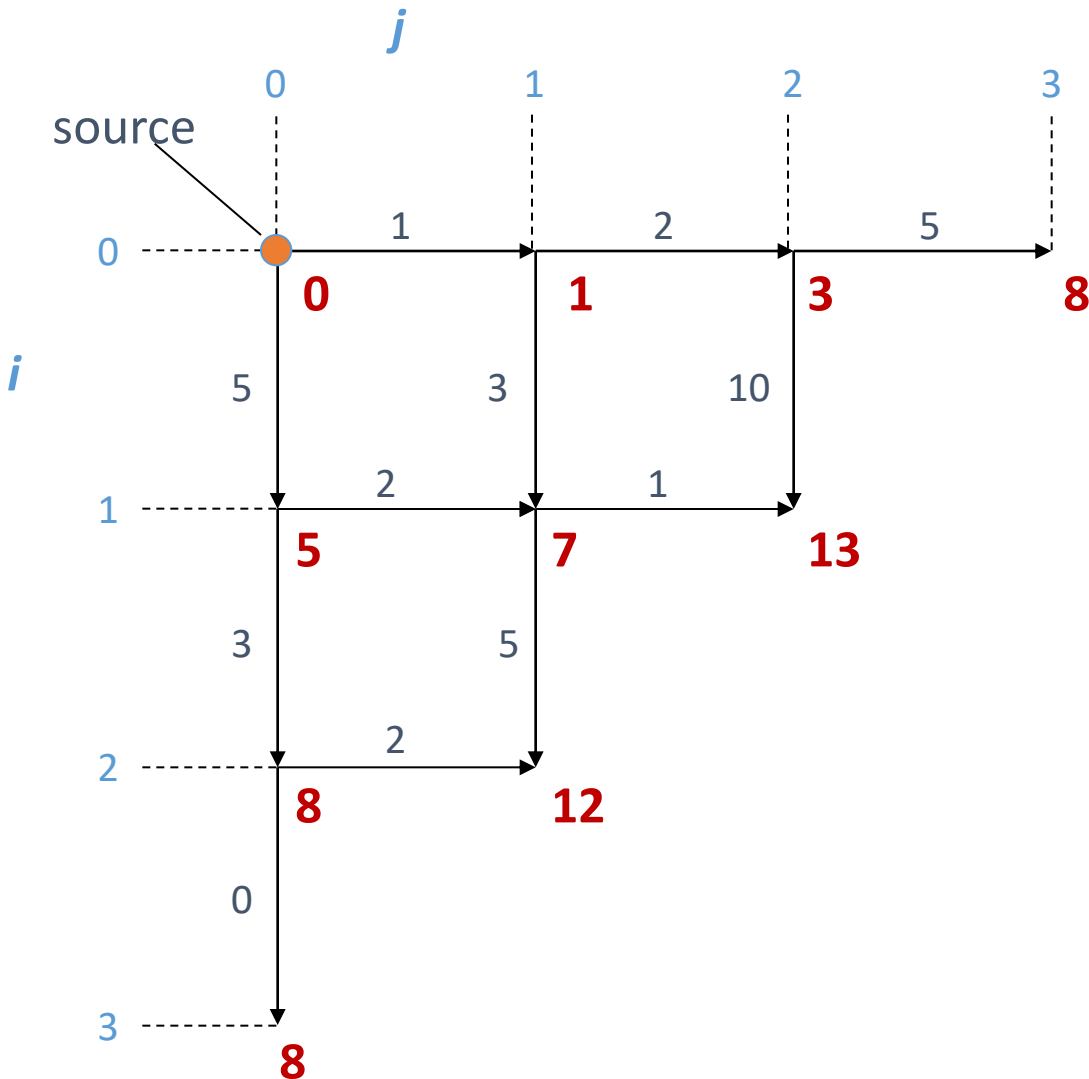


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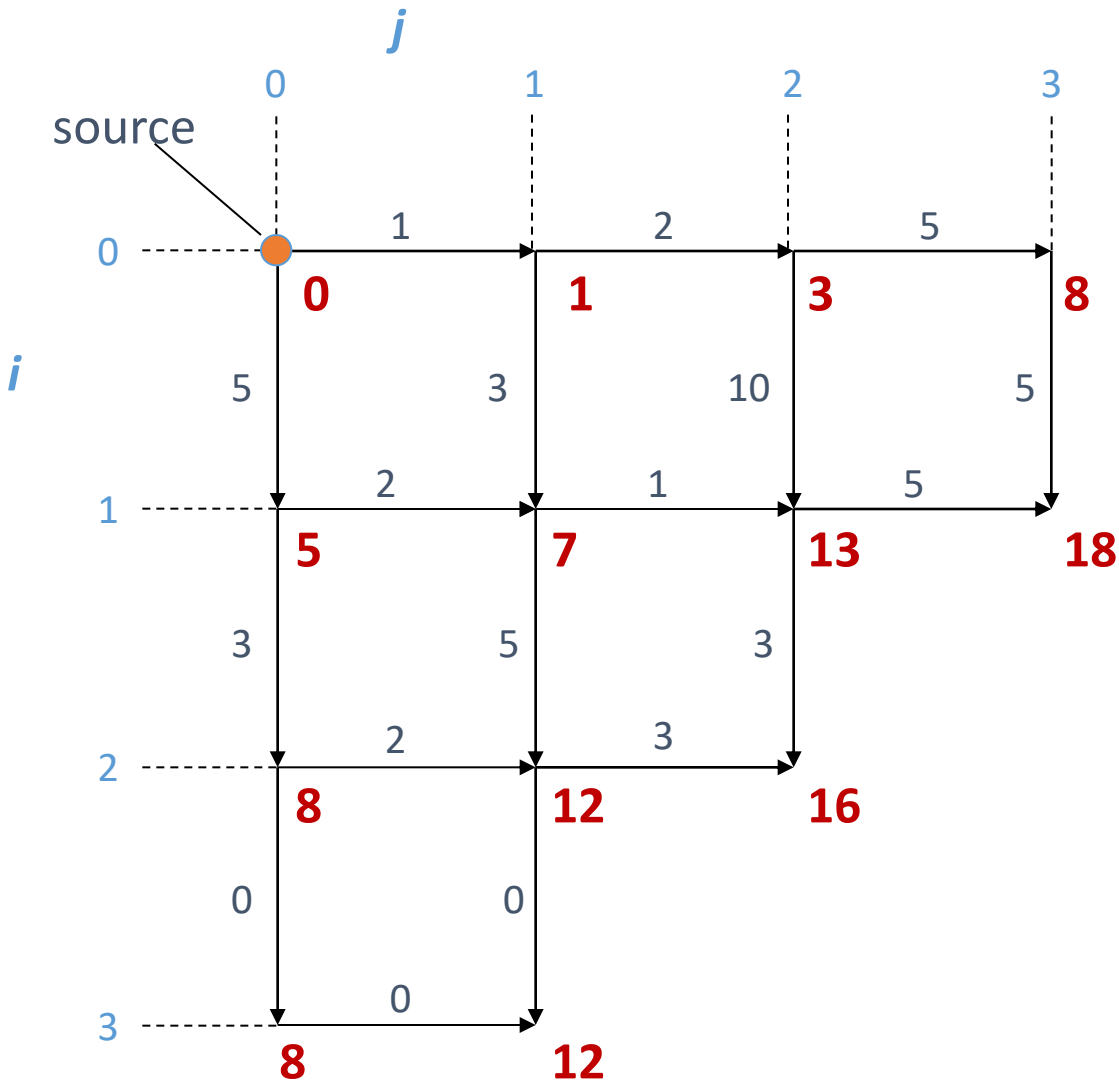


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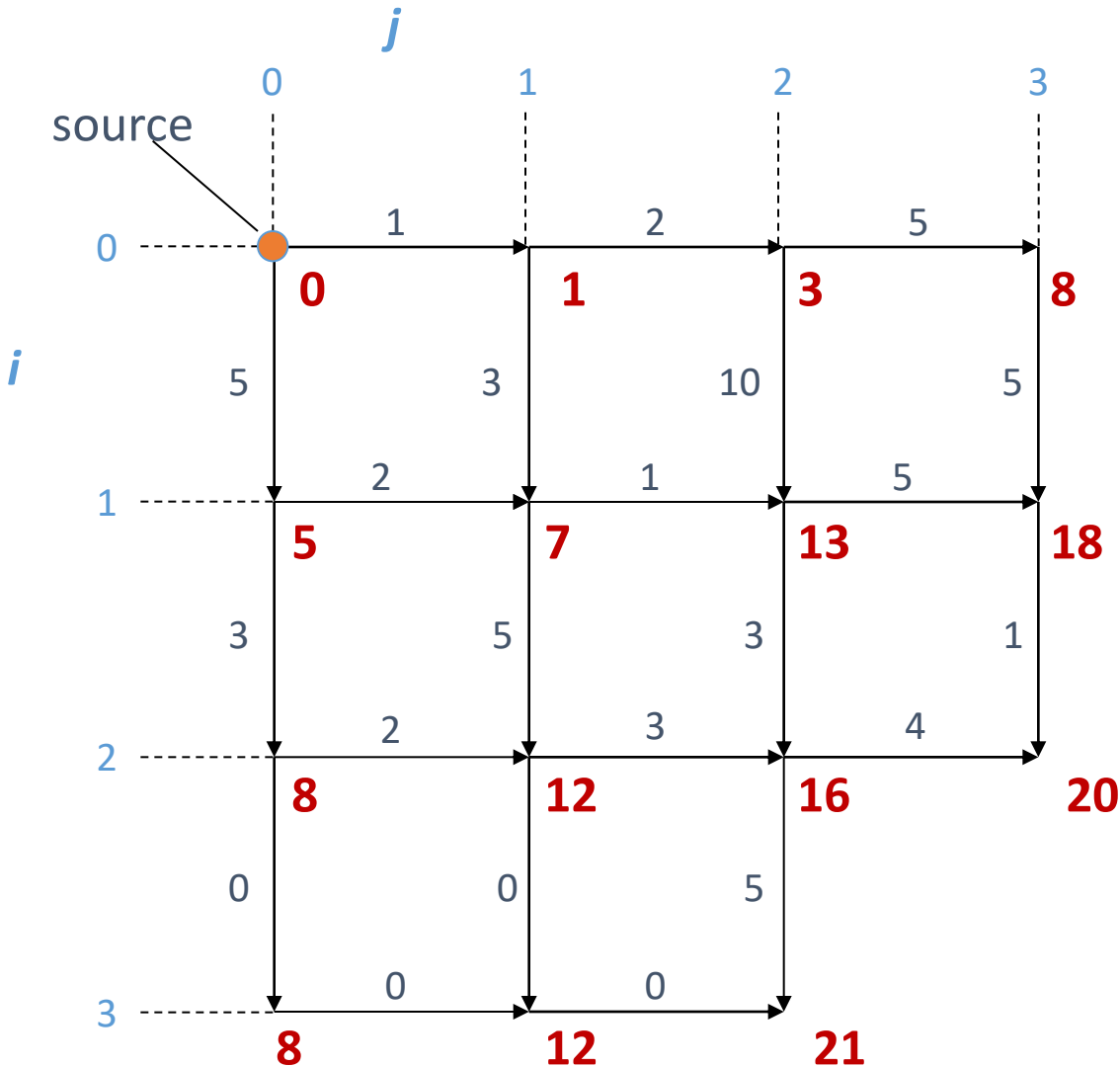


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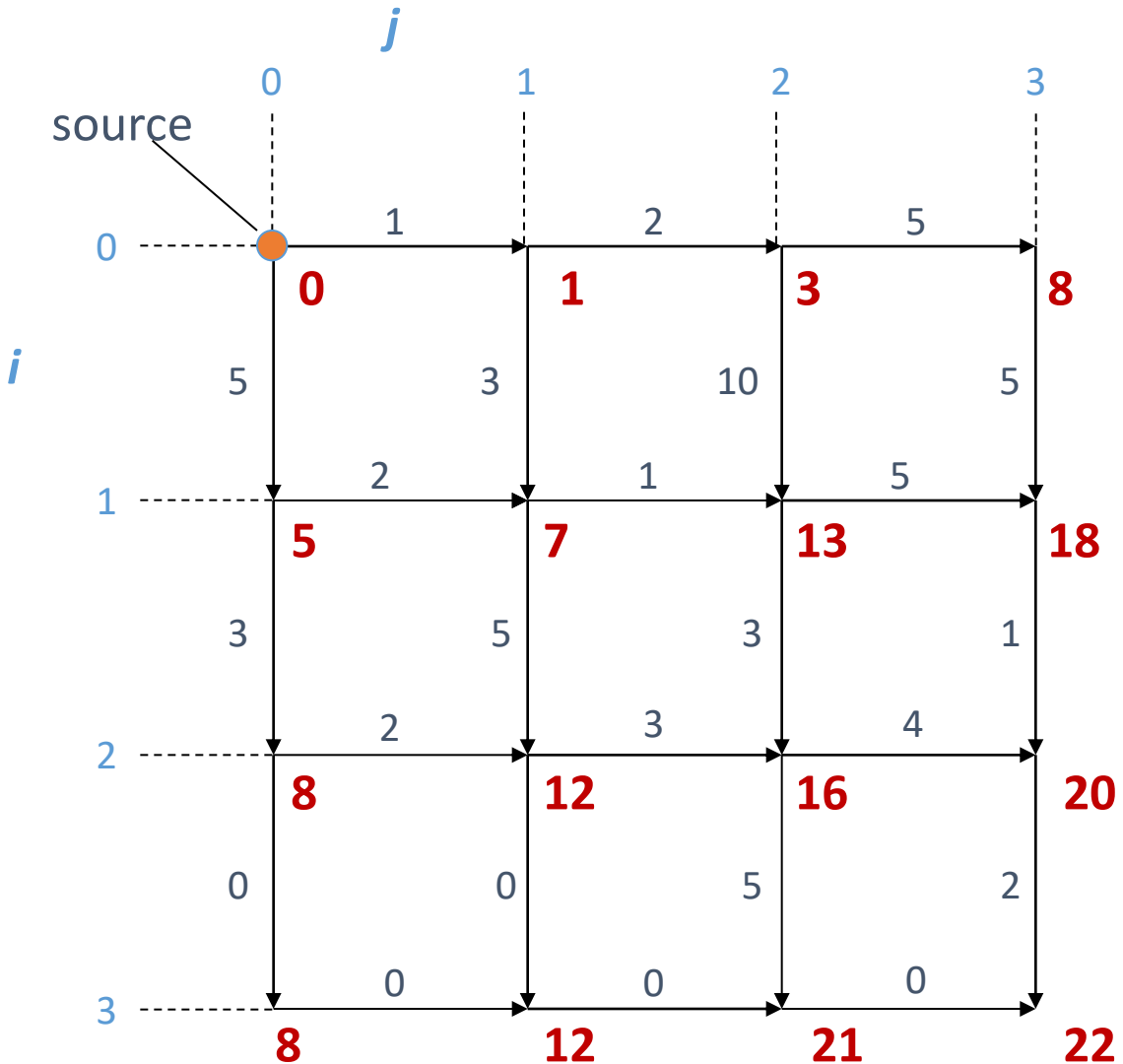


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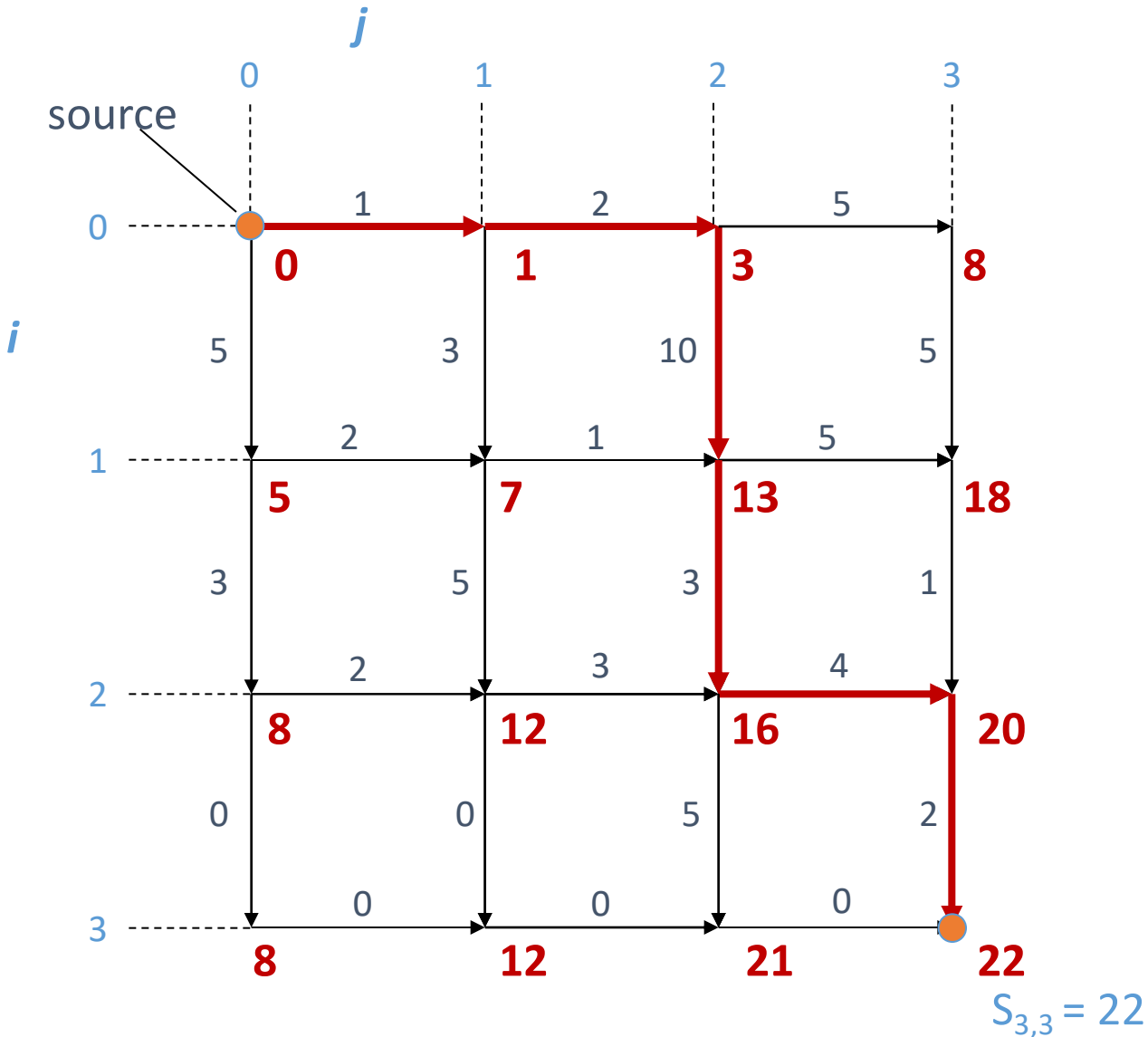


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$s[i, j]$ is the best score for path to coordinate (i, j)

$$s[i, j] = \max \begin{cases} 0, & \text{if } i = 0 \text{ and } j = 0, \\ s[i - 1, j] + w[(i - 1, j), (i, j)] & \text{if } i > 0, \\ s[i, j - 1] + w[(i, j - 1), (i, j)] & \text{if } j > 0. \end{cases}$$

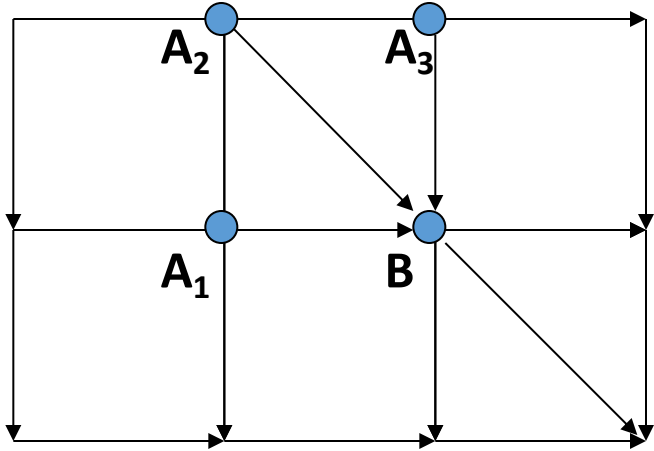
- $w[(i - 1, j), (i, j)]$ weight of street between $(i - 1, j)$ and (i, j)
- $w[(i, j - 1), (i, j)]$ weight of street between $(i, j - 1)$ and (i, j)

Let m be the number of rows and n be the number of columns.

Running time: $O(mn)$

Question: Implementation?

Manhattan Is Not a Perfect Grid

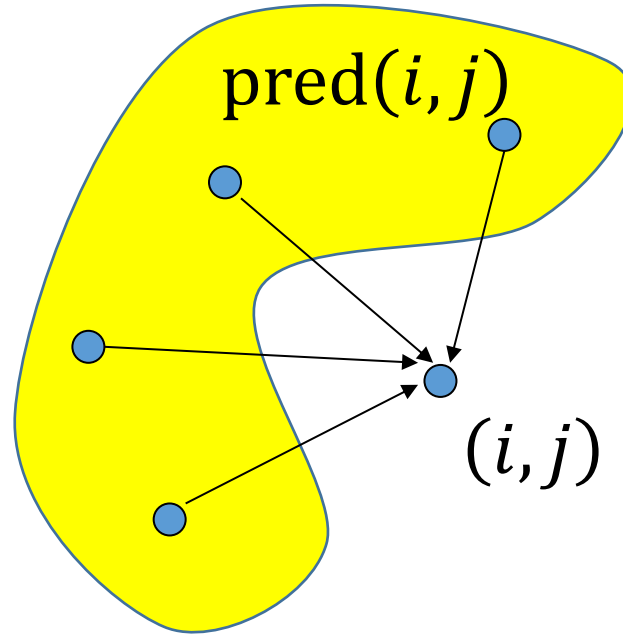


What about diagonals?

$$s[B] = \max \begin{cases} s[A_1] + w[A_1, B], \\ s[A_2] + w[A_2, B], \\ s[A_3] + w[A_3, B]. \end{cases}$$

Manhattan Is Not a Perfect Grid, It's a Directed Graph

$G = (V, E)$ is a directed acyclic graph (DAG) with nonnegative edges weights $w : E \rightarrow \mathbb{R}^+$



Each edge is evaluated once: $O(|E|)$ time

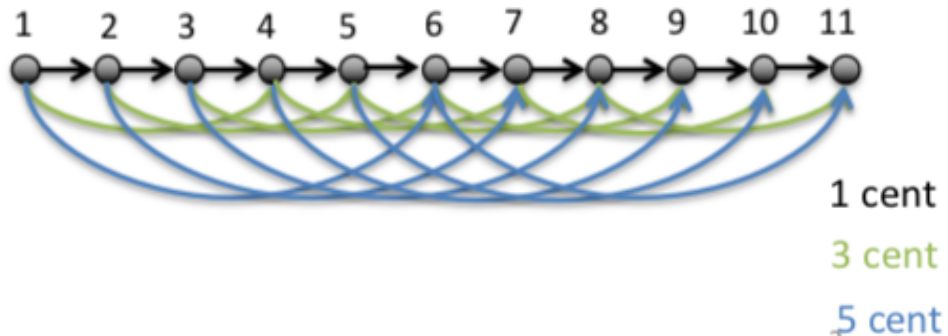
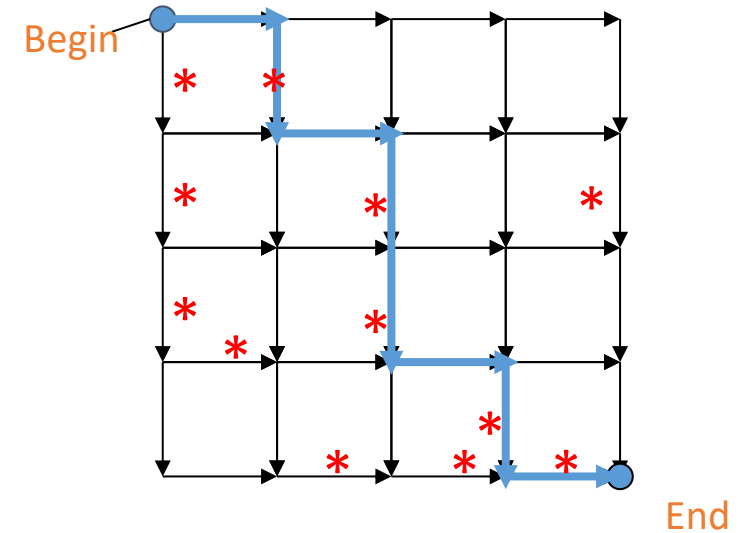
$$s[0, 0] = 0$$

$$s[i, j] = \max_{(i', j') \in \text{pred}(i, j)} \{s[i', j'] + w[(i', j'), (i, j)]\}$$

Dynamic Programming as a Graph Problem

Manhattan Tourist Problem:

Every path in directed graph is a possible tourist path. Find **maximum weight path**.
Running time: $O(mn) = O(|E|)$

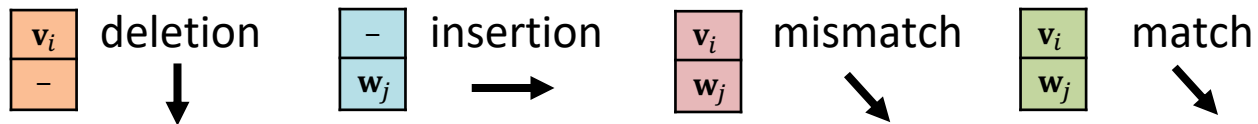


Change Problem: Make M cents using minimum number of coins $\mathbf{c} = (1, 3, 5)$. Every path in directed graph is a possible change. Find **shortest path**.
Running time: $O(Mn) = O(|E|)$

What About the Edit Distance Problem?

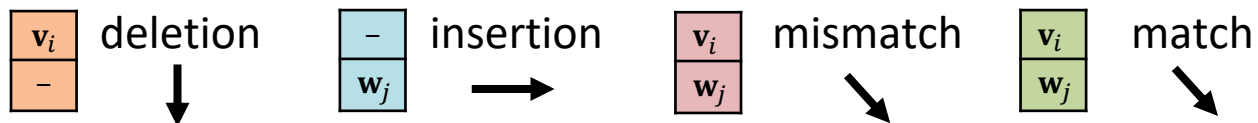
	W	A	T	C	G	
V		0	1	2	3	4
A	0					
T	1					
G	2					
T	3					
T	4					

Edit Distance problem: Given strings $\mathbf{v} \in \Sigma^m$ and $\mathbf{w} \in \Sigma^n$, compute the minimum number $d(\mathbf{v}, \mathbf{w})$ of elementary operations to transform $\mathbf{v}$ into $\mathbf{w}$.



What About the Edit Distance Problem?

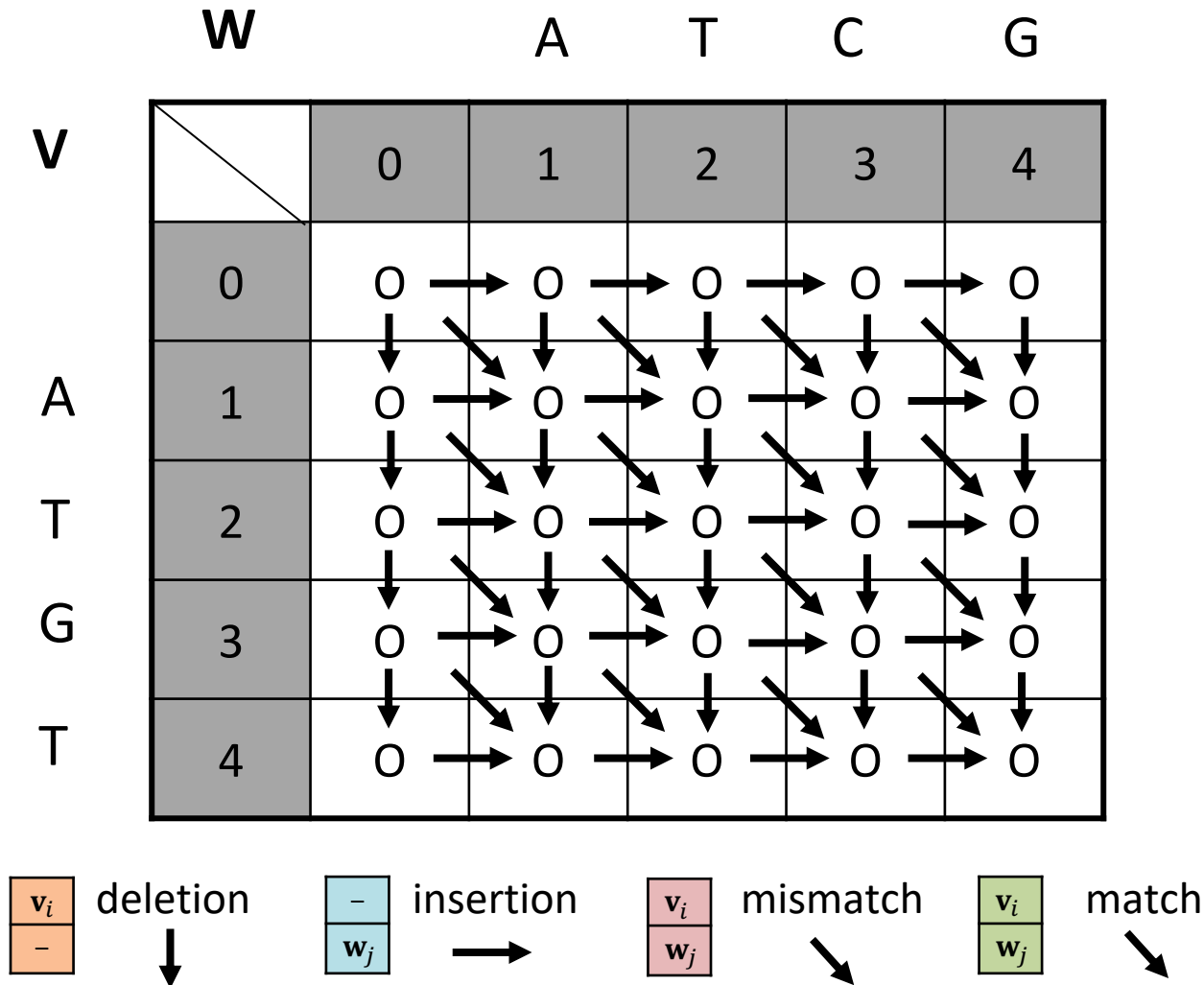
	W	A	T	C	G	
V		0	1	2	3	4
A T G T	0	0 → 0 → 0 → 0 → 0				
	1	0 → 0 → 0 → 0 → 0				
	2	0 → 0 → 0 → 0 → 0				
	3	0 → 0 → 0 → 0 → 0				
	4	0 → 0 → 0 → 0 → 0				



Edit Distance problem: Given strings $\mathbf{v} \in \Sigma^m$ and $\mathbf{w} \in \Sigma^n$, compute the minimum number $d(\mathbf{v}, \mathbf{w})$ of elementary operations to transform $\mathbf{v}$ into $\mathbf{w}$.

Edit graph is a weighed, directed grid graph $G = (V, E)$ with source vertex $(0, 0)$ and target vertex (m, n) . Each edge (i, j) has weight $[i, j]$ corresponding to edit cost: deletion (1), insertion (1), mismatch (1) and match (0).

What About the Edit Distance Problem?

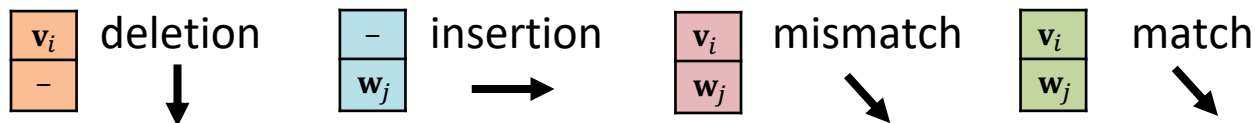


Alignment is a path from $(0, 0)$ to (m, n)

Edit graph is a weighed, directed grid graph $G = (V, E)$ with source vertex $(0, 0)$ and target vertex (m, n) . Each edge (i, j) has weight $[i, j]$ corresponding to edit cost: deletion (1), insertion (1), mismatch (1) and match (0).

What About the Edit Distance Problem?

	W	A		T		C		G		
V		0	1	2	3	4				
A T G T	0	O	→	O	→	O	→	O	→	O
	1	O	→	O	→	O	→	O	→	O
	2	O	→	O	→	O	→	O	→	O
	3	O	→	O	→	O	→	O	→	O
	4	O	→	O	→	O	→	O	→	O



Edit Distance problem: Given edit graph $G = (V, E)$, with edge weights $c : E \rightarrow \{0, 1\}$. Find shortest path from $(0, 0)$ to (m, n) .

Alignment is a path from $(0, 0)$ to (m, n)

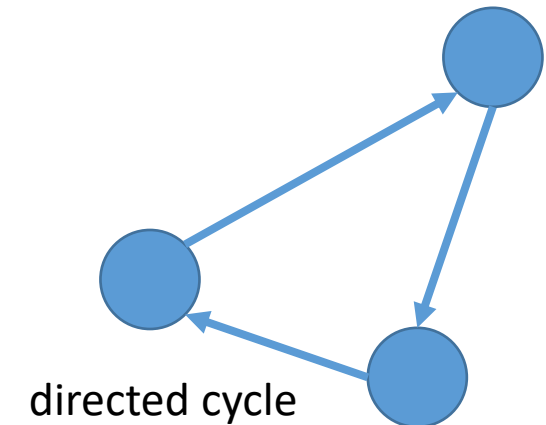
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Shortest Path vs Longest Path

- Change graph, edit graph and the MTP grid are **directed graphs G** .
- Change problem and Edit Distance problem are **minimization** problems.
- Find **shortest path** in **G** from source to sink.
- Manhattan Tourist problem is a **maximization** problem.
- Find **longest path** in **G** from source to sink.

Shortest Path vs Longest Path

- Shortest path in directed graphs can be found efficiently (Dijkstra, Bellman-Ford, Floyd-Warshall algorithms)
- Longest path in direct graphs *cannot* be found efficiently (NP-hard).
- Change graph, edit graph and MTP grid graph are **directed acyclic graphs (DAGs)**.
- No directed cycles.
- Longest path problem in a DAG can be solved efficiently by dynamic programming



Question: What's the relation between absence of directed cycles and optimal substructure?

Weighted Edit Distance

$d[i, j]$ is the edit distance of $\mathbf{v}_i$ and $\mathbf{w}_j$,
where $\mathbf{v}_i$ is prefix of $\mathbf{v}$ of length i and $\mathbf{w}_j$ is prefix of $\mathbf{w}$ of length j

$$d[i, j] = \min \begin{cases} d[i-1, j] + 1, & \text{deletion} \\ d[i, j-1] + 1, & \text{insertion} \\ d[i-1, j-1] + 1, & \text{mismatch} \\ d[i-1, j-1], & \text{if } v_i = w_j. \end{cases}$$

deletion

insertion

mismatch

...	$\mathbf{v}_i$
...	—
...	—
...	$\mathbf{w}_j$
...	$\mathbf{v}_i$
...	$\mathbf{w}_j$
...	$\mathbf{v}_i$
...	$\mathbf{w}_j$

Replace +1 with different penalties for different types of edits.

Summary

1. Change problem
2. Review of running time analysis
3. Edit distance
4. Review elementary graph theory
5. Manhattan Tourist problem
6. Longest/shortest paths in DAGs

Reading:

- Jones and Pevzner. Chapters 2.7-2.9 and 6.1-6.4
- Lecture notes

Sources

- CS 362 by Layla Oesper (Carleton College)
- CS 1810 by Ben Raphael (Brown/Princeton University)
- An Introduction to Bioinformatics Algorithms book (Jones and Pevzner)
- <http://bioalgorithms.info/>