582670 Algorithms for Bioinformatics

Lecture 4: Dynamic Programming and Sequence Alignment

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Sequence Similarity

Many applications of comparing and finding sequences that are similar but not identical

- Motif finding
- DNA sequencing
  - Comparing reads against other reads or reference genome(s)
- Finding similar genes/proteins (homologs)
  - Hints about function or structure
  - Estimating evolutionary distance

Measuring Sequence Similarity

- To determine how similar two sequences are, we need either a similarity measure or a distance measure
- We have seen the Hamming distance that counts mismatches

A	G	G	T	A	C	
A	C	G	T	C	C	
	1			+1		=2

- A possible similarity measure could count matches

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

What is wrong with Hamming distance?

- Only for sequences of the same length
- Does not allow insertions or deletions
- Example: Hamming distance is high

G	G	A	T	A	C	
A	G	G	A	T	C	
1	+1	+1	+1	+1		=5

but the sequences are clearly similar

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

Alignments with Indels

- Indel = insertion or deletion
- Example

-	G	G	A	T	A	C
A	G	G	-	T	C	C
I	M	M	D	M	S	M

- M = match
  S = Substitution
  I = Insertion
  D = Deletion

Scoring alignments

- Many possible alignments
- Which one is better?

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

S  M  M  S  D  M
```

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

D  M  M  D  M  I  M
```

- We need a score for alignments
- The best score over all possible alignments can be used as a similarity or distance between the strings

Longest Common Subsequence

- Subsequence of a string is a subset of the letters in the same order
- Example: GGTC is a subsequence of GGATAC and AGGTCC
- The matching letters in an alignment form a *common subsequence*

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

- The number of matches, i.e. the length of the common subsequence, can be used as a score for an alignment
- The maximum score over all alignments, i.e, the length of the *longest common subsequence* (LCS), is a string similarity
- The LCS itself can be of interest

What is wrong with LCS?

- Which one is the better alignment?

G	C	C	A	G	G	G	
G	G	G	A	T	T	G	
1			+1			+1	= 3

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

- Indels are often rare in biological sequences

Edit distance

- We can use the number of substitutions and indels as a score

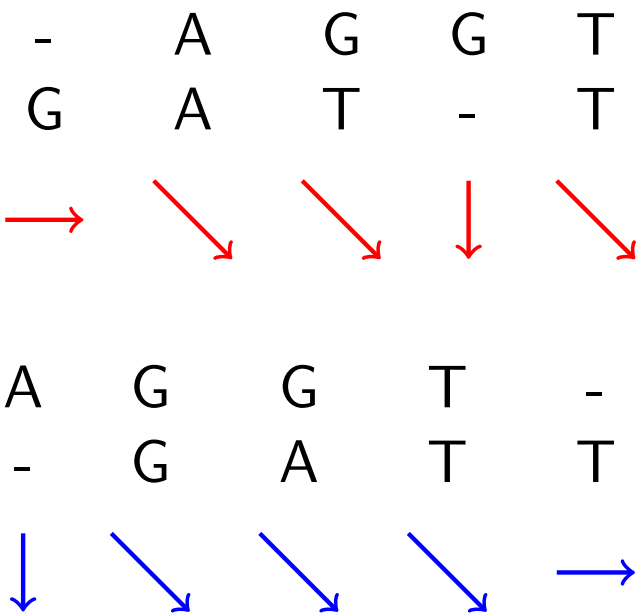
G	C	C	A	G	G	G	
G	G	G	A	T	T	G	
	1	+1		+1	+1		= 4

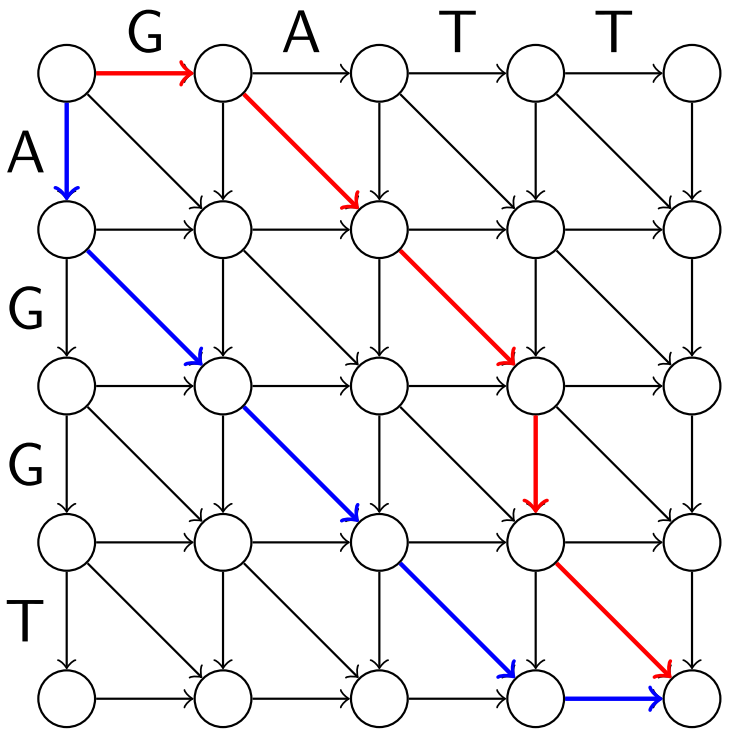
G	C	C	A	G	G	-	-	-	G
G	-	-	-	G	G	A	T	T	G
	1	+1	+1			+1	+1	+1	= 6

- The *minimum* score over all alignments is the *edit distance* of the strings
- Alternatively defined as the minimum number of edit operations (substitutions and indels) to convert one string into the other
- Also known as the Levenshtein distance

Alignment Graph

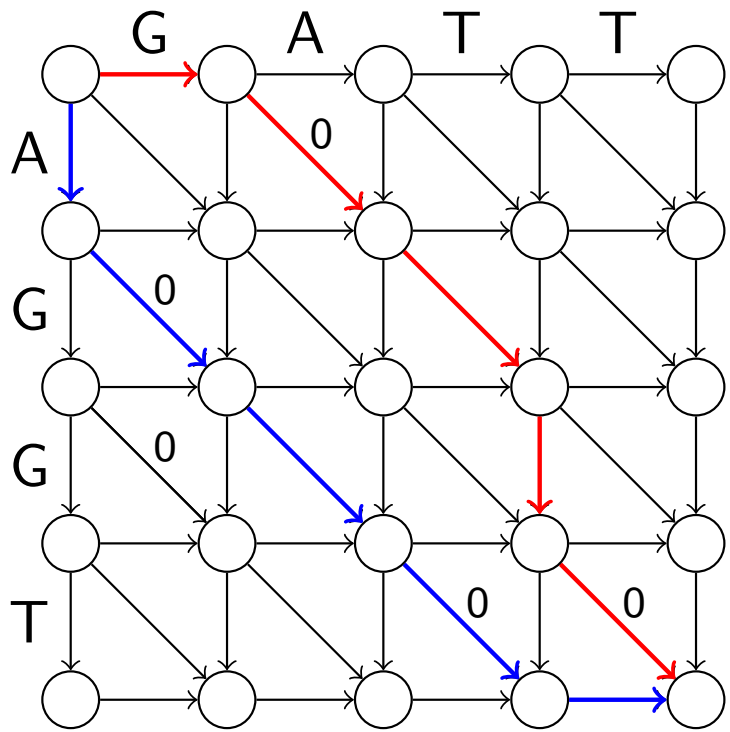
- Each alignment corresponds to a path in a rectangular graph





Edit distance as a shortest path problem

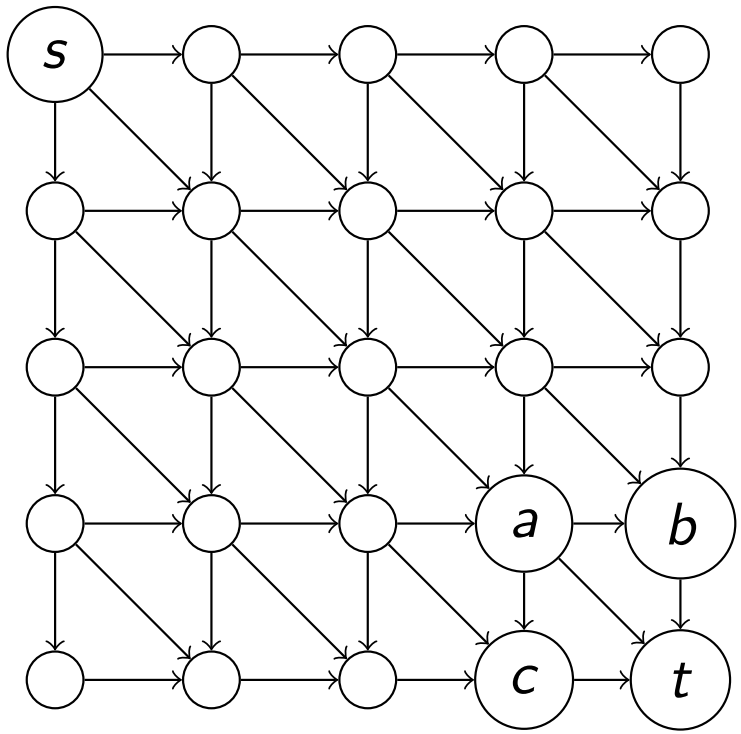
- Assign weights to the edges according to the scoring scheme
- For edit distance
  - Match edges have weight 0
  - Other edges have weight 1
  - (Only 0s shown here)
- The length/weight of a path is the sum of edge weights
  - The same as the score of the alignment
  - Example: both marked paths have length 3



- Edit distance is the length of the shortest path

Finding shortest path

- We want to compute the shortest path from the source node s to the sink node t
- Every path from s to t must go through one of the neighboring nodes a, b and c
- Basic idea: find the shortest path from s to each of the nodes a, b and c, add the weights of the edges from a, b and c to t and take the minimum.



Finding shortest path

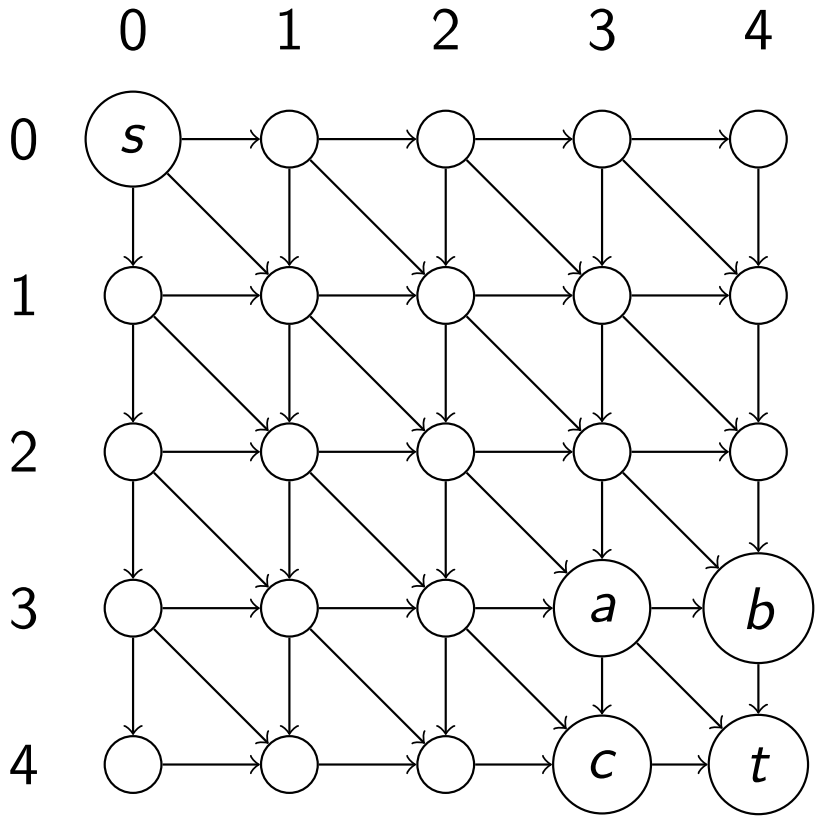
- Define
  - $w(u, v)$ = weight of the edge from node u to node v
  - $d(u, v)$ = length of shortest path from u to v
- We compute $d(s, t)$ using the formula

$$d(s,t) = \min \begin{cases} d(s,a) + w(a,t) \\ d(s,b) + w(b,t) \\ d(s,c) + w(c,t) \end{cases}$$

- The values $d(s, a)$, $d(s, b)$ $d(s, c)$ are computed similarly from their neighbors

Naming nodes by coordinates

- Take advantage of the grid structure by naming the nodes by a pair of coordinates
- $s = (0, 0)$
- $t = (m, n)$ (here $m = n = 4$)
- $a = (m - 1, n - 1)$
- $b = (m - 1, n)$
- $c = (m, n - 1)$



Shortest path length

- Let $D(i,j) = d(s,(i,j))$ be the shortest path length from s to (i,j)
- We compute $D(i,j)$ using the formula

$$D(i,j) = \min \begin{cases} D(i-1,j-1) + w((i-1,j-1),(i,j)) \\ D(i-1,j) + w((i-1,j),(i,j)) \\ D(i,j-1) + w((i,j-1),(i,j)) \end{cases}$$

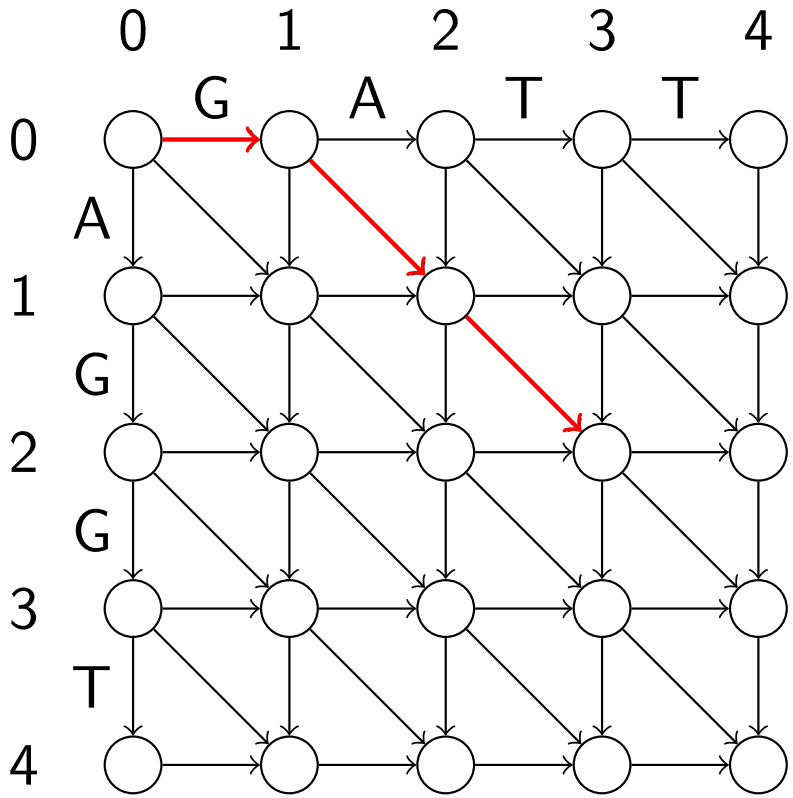
  when $i > 0$ and $j > 0$
- Separate formulas for zero coordinates

$$\begin{aligned} D(i,0) &= D(i-1,0) + w((i-1,0),(i,0)) \\ D(0,j) &= D(0,j) + w((0,j-1),(0,j)) \\ D(0,0) &= 0 \end{aligned}$$

Subpath is prefix alignment

- A (sub)path from s to (i, j) corresponds to an alignment of string prefixes of lengths i and j
- Example: alignment for path to $(2, 3)$

-	A	G
G	A	T



Edit distance computation

- Consider strings $A = a_1 a_2 \ldots a_m$ and $B = b_1 b_2 \ldots b_n$
- We want to compute the edit distance $d_L(A, B)$

- $D(i, j)$ is the length optimal path to node (i, j)
- This is the same as the score of the optimal alignment between $a_1 \ldots a_i$ and $b_1 \ldots b_j$, i.e.,

$$D(i, j) = d_L(a_1 \ldots a_i, b_1 \ldots b_j)$$

and

$$D(m, n) = d_L(A, B)$$

- We can compute the edit distance using the equations we saw earlier
  - Edge weights $w(\cdot, \cdot)$ are either 0 (match) or 1

Edit distance equations

- We want to compute $D(m, n)$
- When both $i > 0$ and $j > 0$, use

$$D(i,j) = \min \begin{cases} D(i-1, j-1) + (\text{ if } a_i = b_j \text{ then } 0 \text{ else } 1) \\ D(i-1, j) + 1 \\ D(i, j-1) + 1 \end{cases}$$

- Otherwise use

$$D(i,0) = D(i-1,0) + 1 = i$$
$$D(0,j) = D(0,j-1) + 1 = j$$
$$D(0,0) = 0$$

Recursive computation

- The main formula:

$$D(i,j) = \min \begin{cases} D(i-1,j-1) + (\text{ if } a_i = b_j \text{ then 0 else 1}) \\ D(i-1,j) + 1 \\ D(i,j-1) + 1 \end{cases}$$

- A natural way to implement this is using recursion to solve the subproblems $D(i-1,j-1)$, $D(i-1,j)$ and $D(i,j-1)$
- This is very inefficient because each recursive call generates three new calls
- Some values $D(i,j)$ are computed many times during the recursive computation
- A possible solution is to store each $D(i,j)$ value when it is computed for the first time and later use the stored value instead of using recursion
  - This is known as memoization

Dynamic Programming

- The idea of dynamic programming is similar to memoization:
  store solutions to subproblems
- The difference is how the computation is organized:
  subproblems are computed and stored *before* they are needed for the first time
- Requires finding an appropriate order for computing the subproblems
- Often leads to simple and efficient code

Example: Computing Fibonacci numbers

- Fibonacci numbers are defined by the equation:

$$F(n) = \begin{cases} 1 & \text{if } n = 1 \text{ or } n = 2 \\ F(n-1) + F(n-2) & \text{otherwise} \end{cases}$$

- Computing $F(6)$ by recursion

$$\begin{aligned} F(6) &= F(5) + F(4) \\ &= (F(4) + F(3)) + (F(3) + F(2)) \\ &= (F(3) + F(2)) + (F(2) + F(1)) + (F(2) + F(1)) + 1 \\ &= (F(2) + F(1)) + 1 + 1 + 1 + 1 + 1 + 1 \\ &= 1 + 1 + 1 + 1 + 1 + 1 + 1 + 1 \\ &= 8 \end{aligned}$$

- Each recursive call generates two new calls until the calls reach the bottom
- The call $F(3)$ is made three separate times, the call $F(2)$ five times

Example: Computing Fibonacci numbers

- Fibonacci numbers are defined by the equation:

$$F(n) = \begin{cases} 1 & \text{if } n = 1 \text{ or } n = 2 \\ F(n-1) + F(n-2) & \text{otherwise} \end{cases}$$

- Computing $F(6)$ by dynamic programming

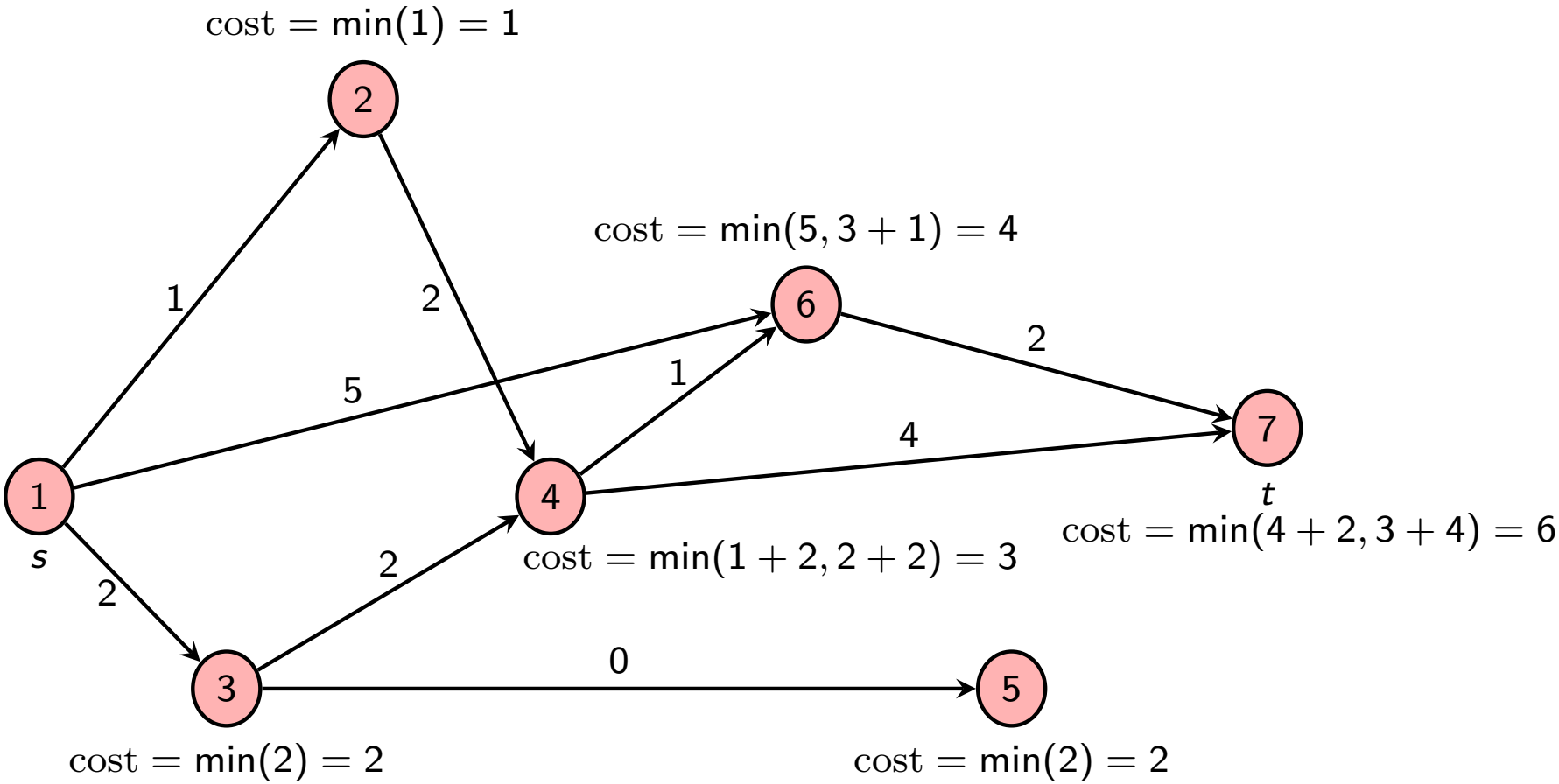
$$\begin{aligned} F[1] &= F[2] = 1 \\ F[3] &= F[2] + F[1] = 1 + 1 = 2 \\ F[4] &= F[3] + F[2] = 2 + 1 = 3 \\ F[5] &= F[4] + F[3] = 3 + 2 = 5 \\ F[6] &= F[5] + F[4] = 5 + 3 = 8 \end{aligned}$$

- The square brackets indicate that the values are stored in an array
  - In fact, only the two previous values need to be kept
- Here the ordering of the subproblems is simple

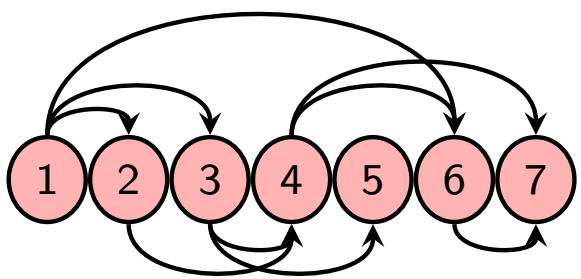
Example: Shortest path in a DAG

DAG=directed acyclic graph

Shortest path from s to t?



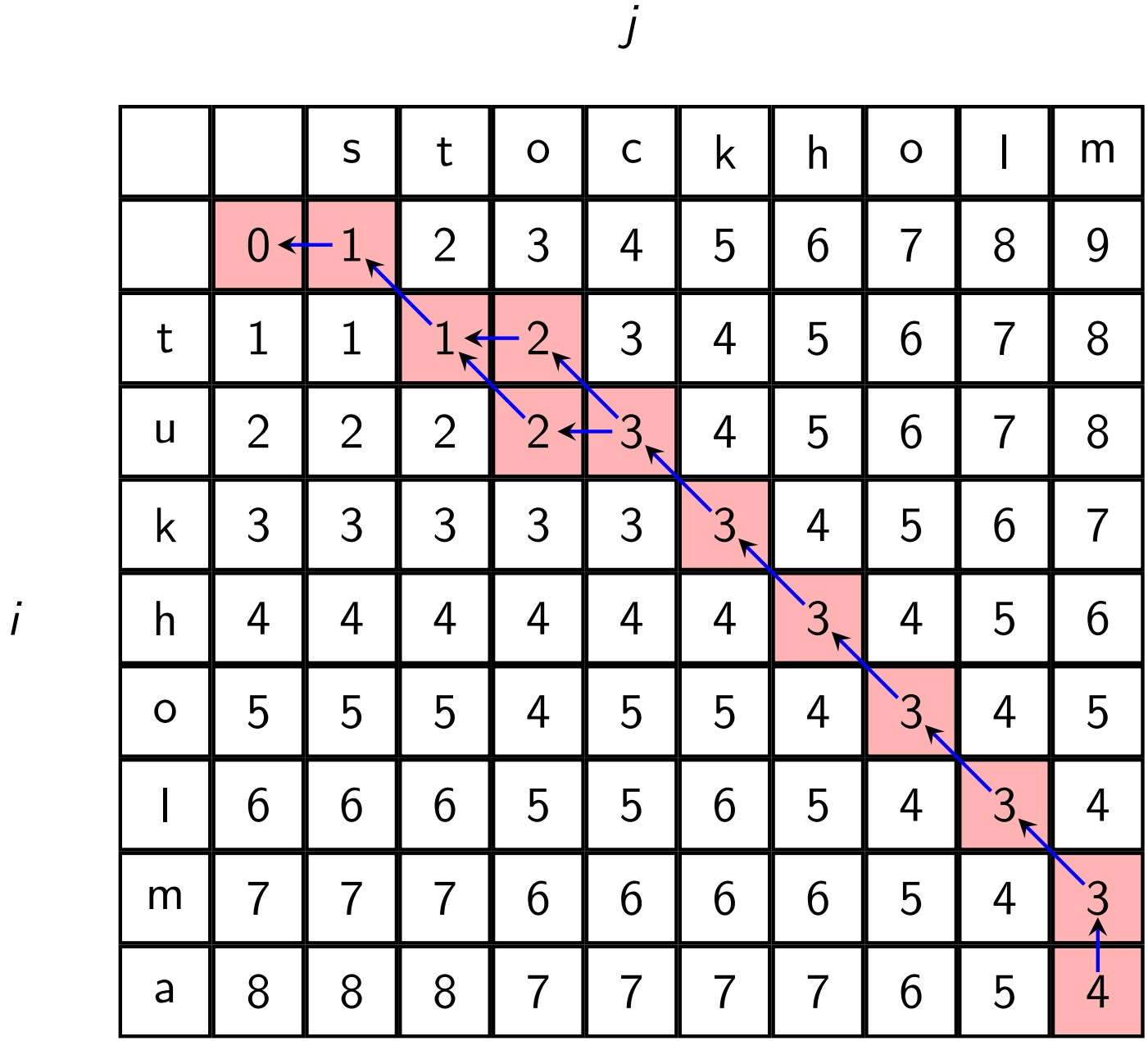
Topological sort to order subproblems:



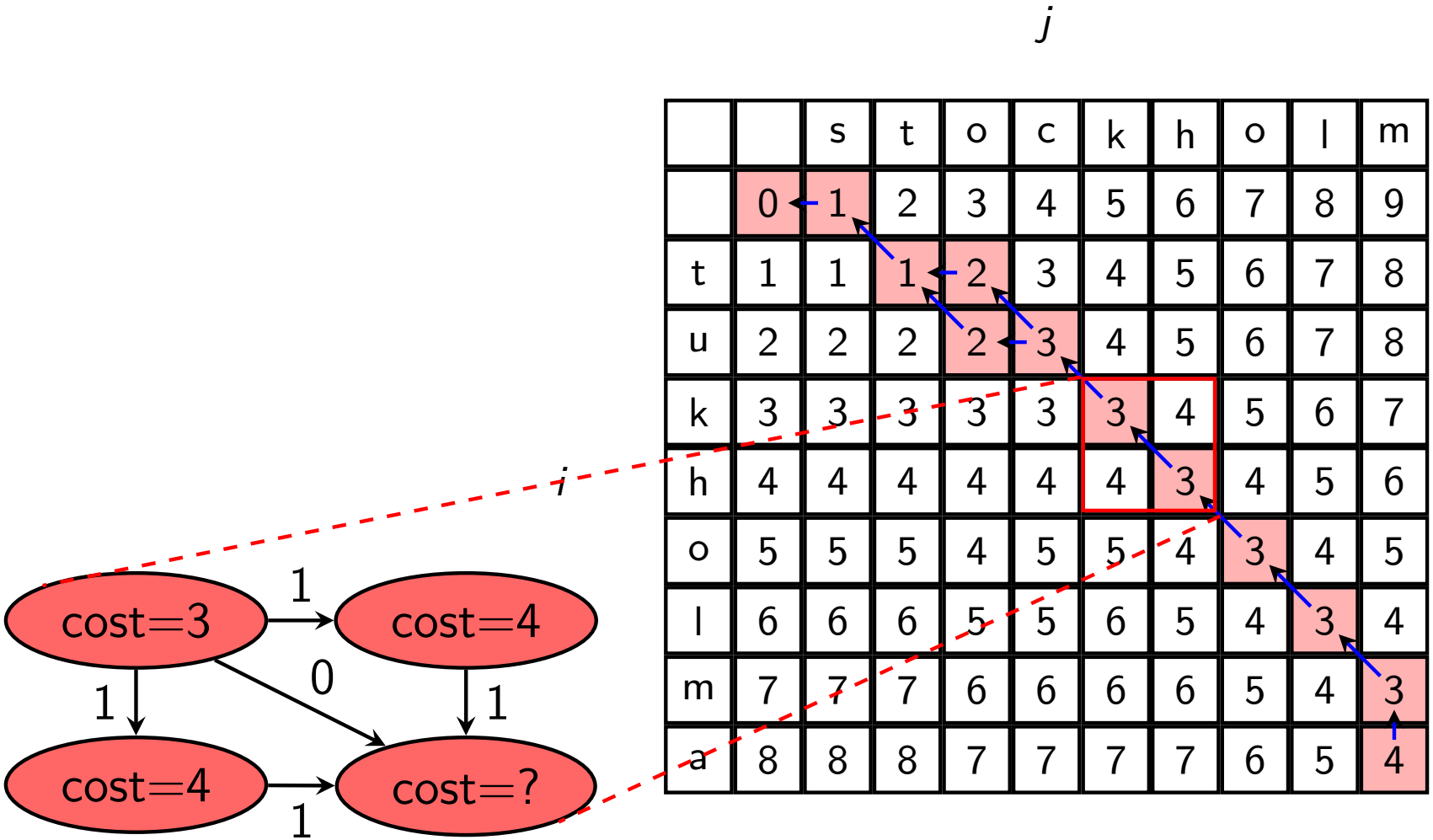
Edit distance by dynamic programming

- Compute all the values $D(i, j)$
- Start from small values of i and j and proceed to bigger values
  - For example, column-by-column or row-by-row
- Store computed values in a two-dimensional array $D[0..m, 0..n]$
  - D is often called the edit distance matrix
- No recursive calls; All subproblem values are obtained from the matrix

Edit distance matrix: example



Edit distance matrix as a graph



		s	t	o	c	k	h	o	l	m
	0	1	2	3	4	5	6	7	8	9
t	1	1	1	2	3	4	5	6	7	8
u	2	2	2	2	3	4	5	6	7	8
k	3	3	3	3	3	3	4	5	6	7
h	4	4	4	4	4	4	3	4	5	6
o	5	5	5	4	5	5	4	3	4	5
l	6	6	6	5	5	6	5	4	3	4
m	7	7	7	6	6	6	6	5	4	3
a	8	8	8	7	7	7	7	6	5	4

$$\text{cost} = \min(3 + 0, 4 + 1, 4 + 1) = 3$$

Finding optimal alignments

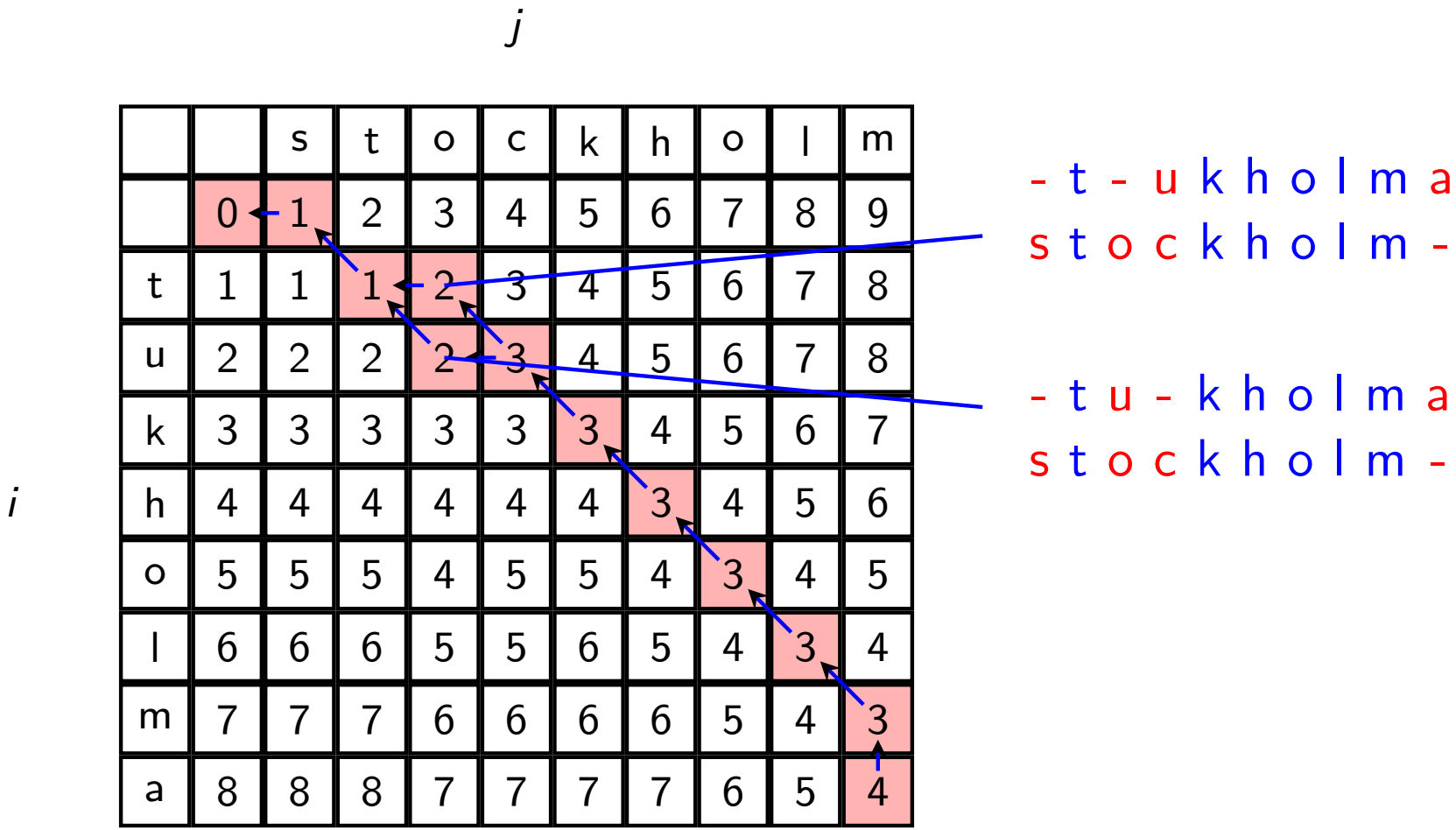
One alignment:

- Store pointer to each cell telling from which cell the minimum was obtained.
- Follow the pointers from (m, n) to $(0, 0)$.
- Reverse the list.

All alignments:

- Backtrack from (m, n) to $(0, 0)$ by checking at each cell (i, j) on the path whether the value $D[i, j]$ could have been obtained from cell $(i, j-1)$, $(i-1, j-1)$, or $(i-1, j)$.
- Explore all directions.
  - All three directions possible.
  - Exponential number of optimal paths in the worst case.

Optimal alignments: example



Variations and generalizations

- The problem we have been looking at is known as the global alignment problem
- There are other alignment problems:
  - Approximate string matching or fitting alignment
  - Overlap alignment
  - Local alignment

Global alignment

- Input: Two strings A and B
- Output: Best alignment between A and B

- Example applications
  - Compare two motifs
  - Compare two genes/proteins

Fitting alignment or approximate string matching

- Input: Two strings P and T
- Output: The substring S of T with the best alignment between P and S

- Example applications
  - Compare a read against a reference genome
  - Compare a gene against a genome to find similar genes

Overlap alignment

- Input: Two strings A and B
- Output: The suffix S of A and the prefix P of B with the best alignment between S and P

- Example application
  - Find overlaps between reads

Local alignment

- Input: Two strings S and T
- Output: The substring A of S and the substring B of T with the best alignment between A and B

- Example application
  - Find partial similarities between genes/proteins (e.g., conserved regions)

Approximate string matching

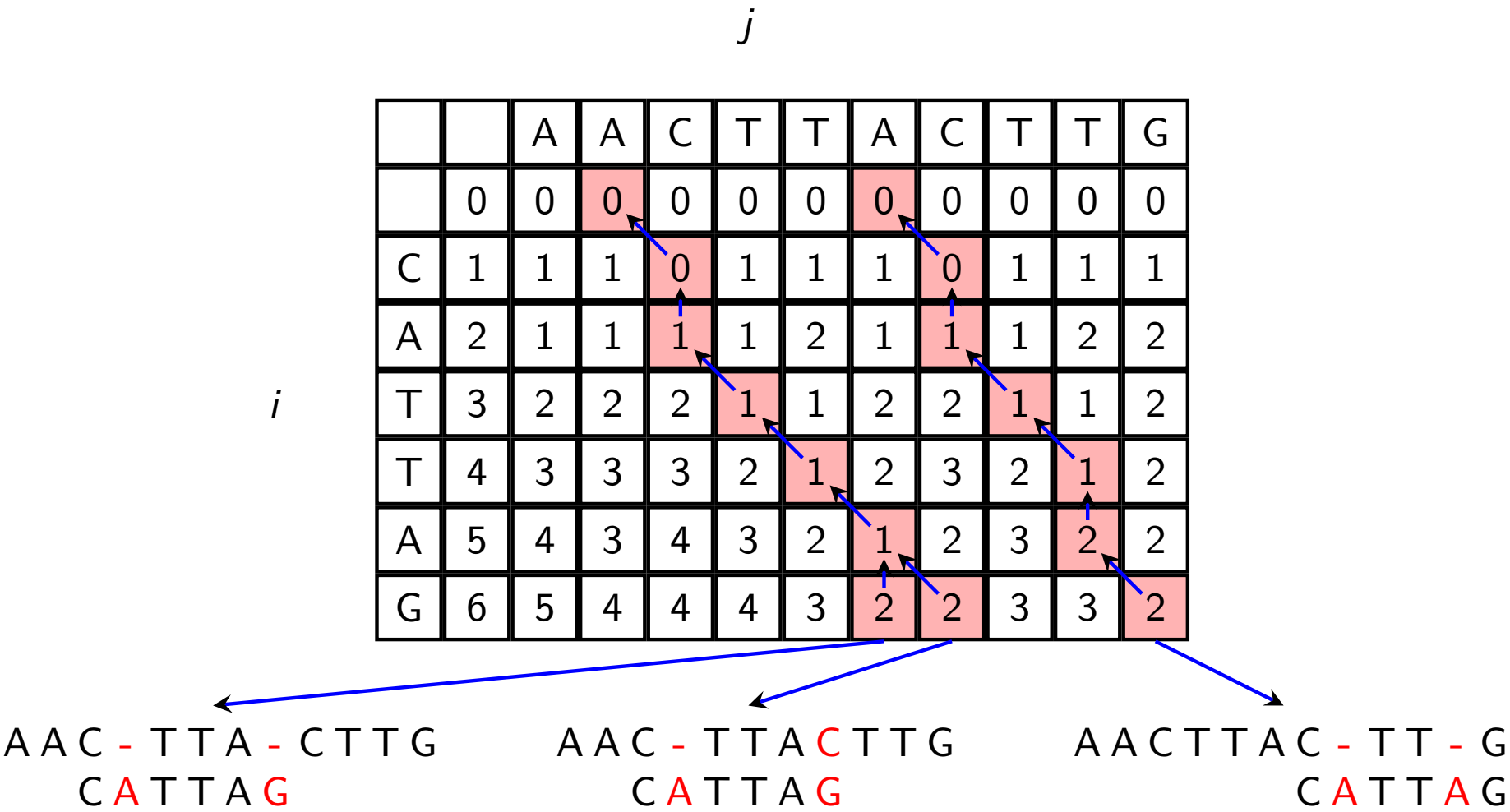
- k-errors problem
  - Input: Two strings $P[1..m]$ and $T[1..n]$ and an integer k
  - Output: Substrings S of T such that $d_L(P, S) \leq k$

- Can be solved using a "zero first row trick"
  - Compute $D[0..m, 0..n]$ as when computing the edit distance except

$$D[0, j] = 0 \text{ for all } j$$

  - $D[i, j]$ then equals the minimum number of edits to convert $P[1, i]$ into *some suffix of* $T[1, j]$.
  - If $D[m, j] = k' \leq k$ then $d_L(P, S) = k'$ for some substring S of T ending at position j in T

Approximate string matching: example



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

Problem with edit distance

- Edit distance is good scoring system for global alignment and approximate string matching but not for local alignment or overlap alignment
- Edit distance favors short overlaps

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

   1           +1        = 2
```

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

                                  = 0
```

General scoring scheme

- $\delta(a, b)$ is the score for changing symbol a into b
  - If $a = b$ this the score of a match
- $\delta(a, -)$ is the score of deleting a
- $\delta(-, b)$ is the score of inserting b

- Typically
  - $\delta(a, b) = 1$ if $a = b$
  - $\delta(a, b) = -\mu$ if $a \neq b$
  - $\delta(a, -) = \delta(-, b) = -\sigma$
- Similarity measure
  - Best alignment has maximal score
  - Find longest path in alignment graph

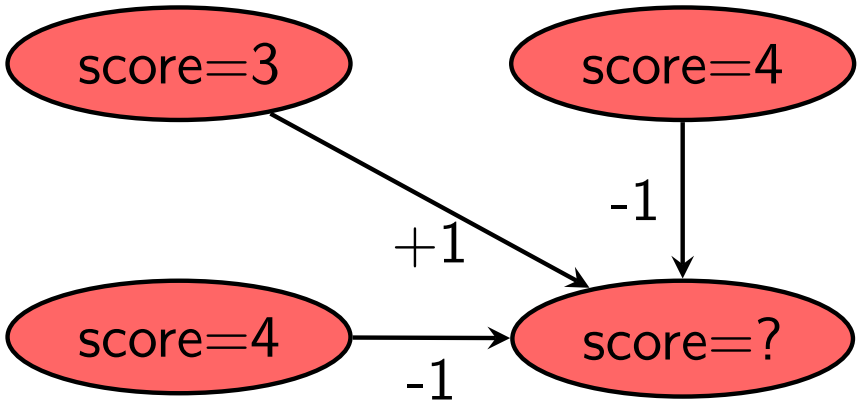
Scoring scheme for local and overlap alignment

- Positive score for good things and negative score for bad things is required in local and overlap alignment
- For example $\mu = \sigma = 1$

C	G	G	A	G	-	T		
	T	G	A	G	C	T	A	
-1	+1	+1	+1	-1	+1			$= +2$

C	G	G	A	G	T						
					T	G	A	G	C	T	A
					1						$= +1$

Global alignment



$$\text{score} = \max(3 + 1, 4 - 1, 4 - 1) = 4$$

$$S[i,j] = \max \begin{cases} S[i-1,j-1] + \delta(a_i, b_j) \\ S[i-1,j] + \delta(a_i, -) \\ S[i,j-1] + \delta(-, b_j) \end{cases}$$

Global alignment: Example

$\delta(a_i, b_j) = 1$, if $a_i = b_j$

$\delta(a_i, b_j) = -1$, otherwise

$\delta(a_i, -) = \delta(-, b_j) = -1$

j

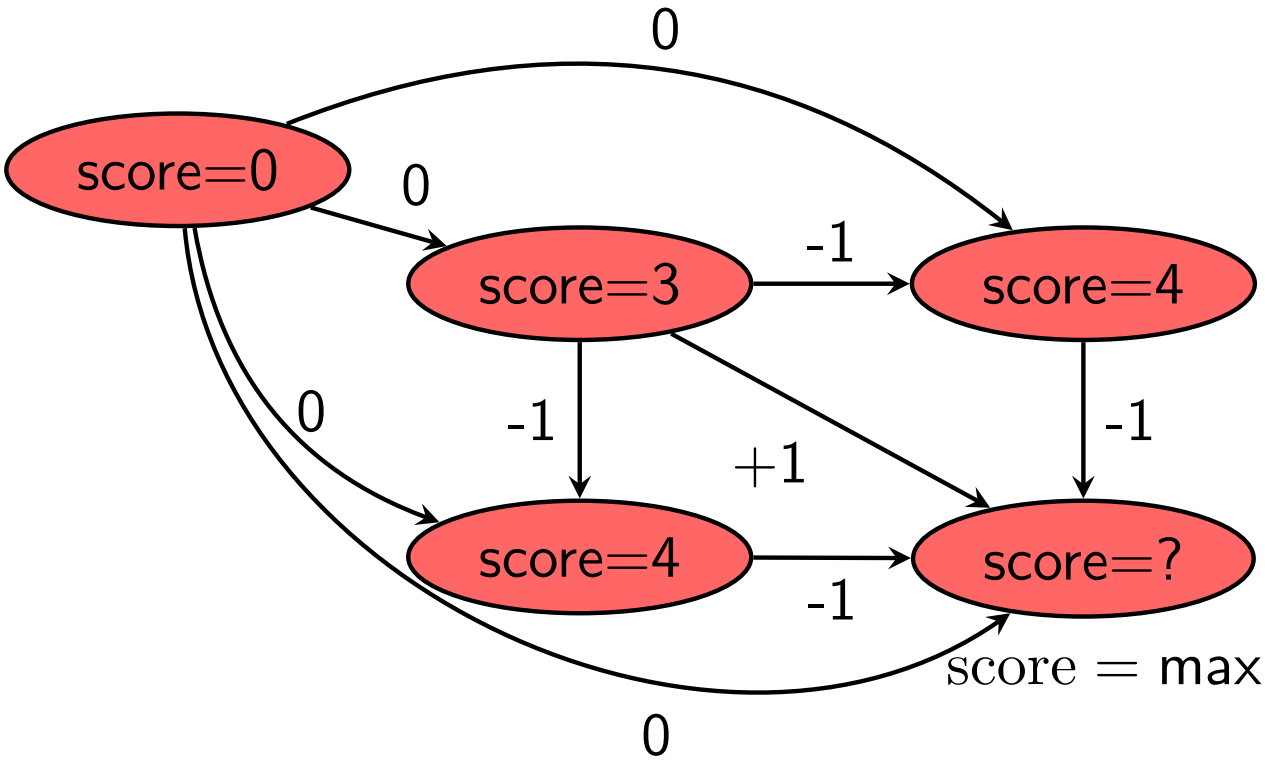
		A	A	C	T	T	A	C	T	T	G
	0	-1	-2	-3	-4	-5	-6	-7	-8	-9	-10
C	-1	-1	-2	-1	-2	-3	-4	-5	-6	-7	-8
A	-2	0	0	-1	-2	-3	-2	-3	-4	-5	-6
T	-3	-1	-1	-1	0	-1	-2	-3	-2	-3	-4
T	-4	-2	-2	-2	0	+1	0	-1	-2	-1	-2
A	-5	-3	-1	-2	-1	0	+2	+1	0	-1	-2
G	-6	-4	-2	-2	-2	-1	+1	+1	0	-1	0

i

Local alignment

- Heaviest/longest path beginning anywhere and ending anywhere
- Beginning anywhere
  - Add 0 weight edge from source node $(0, 0)$ to every other node
  - Consider all paths starting from $(0, 0)$
  - No negative heaviest path scores because we can always choose the zero weight path from the source as the maximum
- Ending anywhere
  - Find maximum score over all nodes

Local alignment



$$\text{score} = \max(0, 3+1, 4-1, 4-1) = 4$$

$$S[i,j] = \max \begin{cases} 0 \\ S[i-1,j-1] + \delta(a_i, b_j) \\ S[i-1,j] + \delta(a_i, -) \\ S[i,j-1] + \delta(-, b_j) \end{cases}$$

Local alignment: Example

$\delta(a_i, b_j) = 1$, if $a_i = b_j$

$\delta(a_i, b_j) = -1$, otherwise

$\delta(a_i, -) = \delta(-, b_j) = -1$

j

i

		A	A	C	T	T	A	C	T	T	G
	0	0	0	0	0	0	0	0	0	0	0
C	0	0	0	1	0	0	0	1	0	0	0
A	0	1	1	0	0	0	1	0	0	0	0
T	0	0	0	0	1	1	0	0	1	1	0
T	0	0	0	0	1	2	1	0	1	2	1
A	0	1	1	0	0	1	3	2	1	1	1
G	0	0	0	0	0	0	2	2	1	0	2