String Comparison

02-713

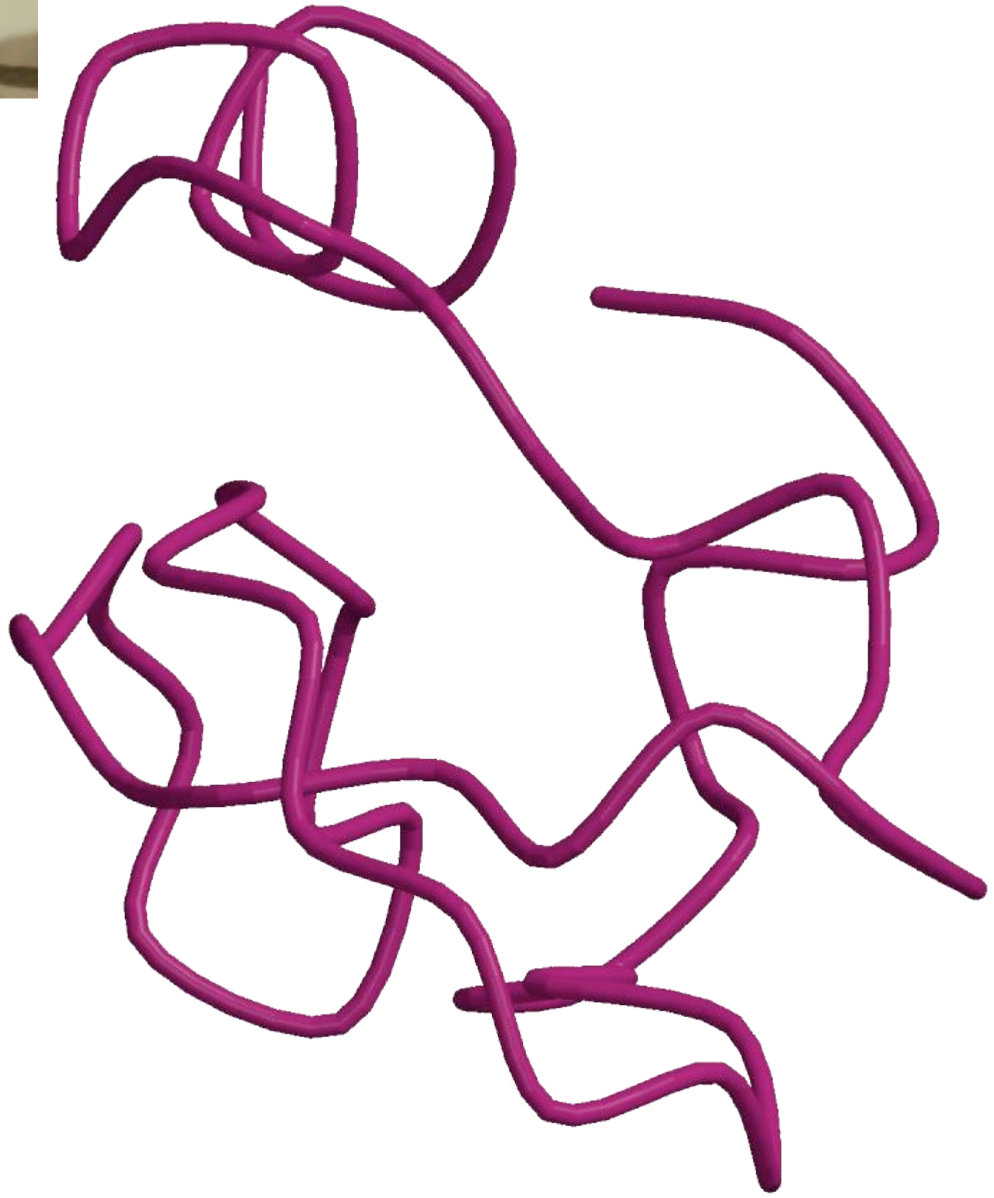
Why compare DNA or protein sequences?

Partial CTCF protein sequence in 8 organisms:

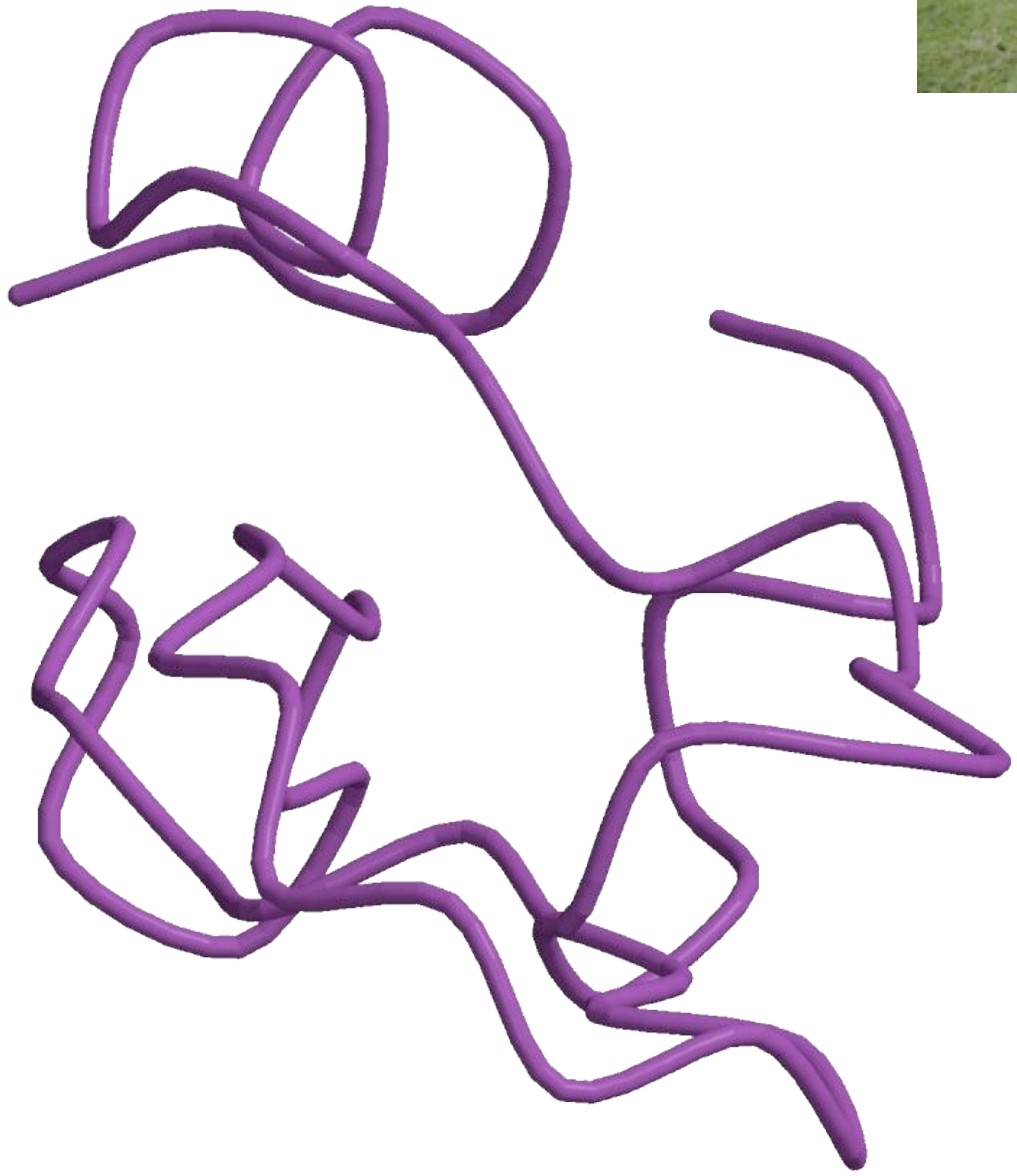
```
H. sapiens       -EDSSDS-ENAEPDLDDNEDEEEPAVEIEPEPE----------PQPVTPA
P. troglodytes   -EDSSDS-ENAEPDLDDNEDEEEPAVEIEPEPE----------PQPVTPA
C. lupus         -EDSSDS-ENAEPDLDDNEDEEEPAVEIEPEPE----------PQPVTPA
B. taurus        -EDSSDS-ENAEPDLDDNEDEEEPAVEIEPEPE----------PQPVTPA
M. musculus      -EDSSDSEENAEPDLDDNEEEEEPAVEIEPEPE--PQPQPPPPPQPVAPA
R. norvegicus    -EDSSDS-ENAEPDLDDNEEEEEPAVEIEPEPEPQPQPQPQPQPQPVAPA
G. gallus        -EDSSDSEENAEPDLDDNEDEEETAVEIEAEPE----------VSAEAPA
D. rerio         DDDDDDSDEHGEPDLDDIDEEDEDDL-LDEDQMGLLDQAPPSVPIP-APA
```

- Identify important sequences by finding conserved regions.
- Find genes similar to known genes.
- Understand evolutionary relationships and distances (D. rerio aka zebrafish is farther from humans than G. gallus aka chicken).
- Interface to databases of genetic sequences.
- As a step in genome assembly, and other sequence analysis tasks.
- Provide hints about protein structure and function (next slide).

Sequence can reveal structure



(a) 1dtk



(b) 5pti

1dtk   XAKY**C**KL**P**LRI**GPCK**RK**I**PSFY**Y**KW**KA**KQ**C**LP**F**D**Y**S**GC**GGNA**N**R**FK**TI**E**E**C**R**RTC**V**G**-

5pti   RPDF**C**LE**P**PYT**GPCK**AR**I**IRYF**Y**NA**KA**GL**C**QT**F**V**Y**G**GC**RAKR**N**N**FK**SA**E**D**C**M**RTC**G**G**A

The Simplest String Comparison Problem

Given: Two strings

$$a = a_1a_2a_3a_4\ldots a_m$$
$$b = b_1b_2b_3b_4\ldots b_n$$

where a_i, b_i are letters from some alphabet like {A,C,G,T}.

Compute how similar the two strings are.

What do we mean by "similar"?

Edit distance between strings *a* and *b* = the smallest number of the following operations that are needed to transform *a* into *b*:

- mutate (replace) a character
- delete a character
- insert a character

$$\text{riddle} \xrightarrow{\text{delete}} \text{ridle} \xrightarrow{\text{mutate}} \text{riple} \xrightarrow{\text{insert}} \text{triple}$$

Representing edits as alignments

```
prin-ciple
|||| |||xx
prinncipal
(1 gap, 2 mm)
```

```
prin-cip-le
|||| ||| |
prinncipal-
(3 gaps, 0 mm)
```

```
misspell
||| ||||
mis-pell
(1 gap)
```

```
prehistoric
   ||||||||
---historic
(3 gaps)
```

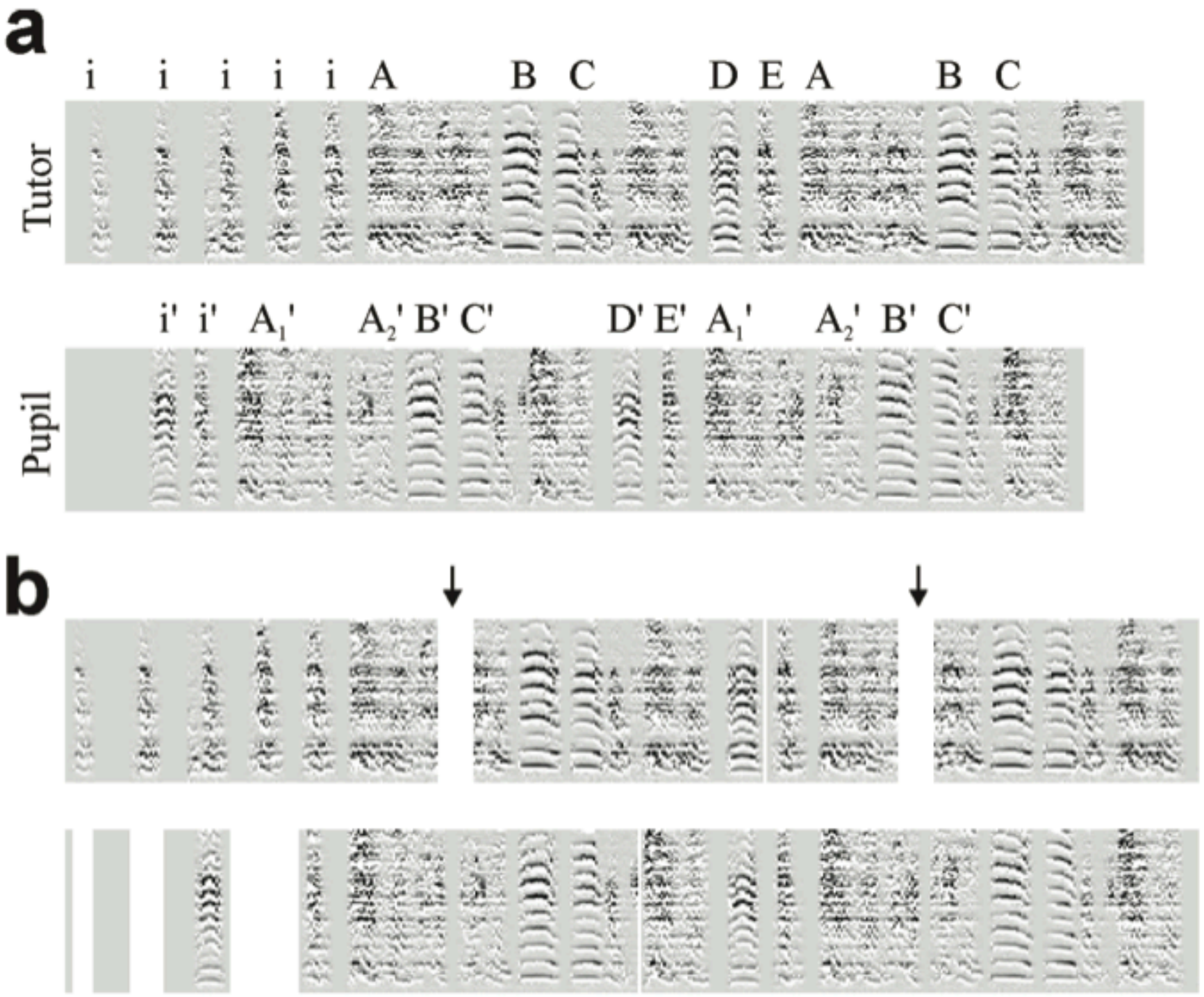
```
aa-bb-ccaabb
|x || | | |
ababbbc-a-b-
(5 gaps, 1 mm)
```

```
al-go-rithm-
|| xx ||x |
alKhwariz-mi
(4 gaps, 3 mm)
```

NCBI BLAST DNA Alignment

```
>gb|AC115706.7| Mus musculus chromosome 8, clone RP23-382B3, complete sequence

Query  1650   gtgtgtgtgggtgcacatttgtgtgtgtgtgcgcctgtgtgtgtgggtgcctgtgtgtgt  1709
              ||||||||||  |    ||  | ||||||||| | ||||||||    ||| ||  |||||
Sbjct  56838  GTGTGTGTGGAAGTGAGTTCATCTGTGTGTGCACATGTGTGTGCA--TGCATGCATGTGT  56895

Query  1710   gtg-gggcacatttgtgtgtgtgtgtgcctgtgtgtgggtgcacatttgtgtgtgtgc  1768
              ||  |||||      ||  ||| ||||||| |||||||| |||  |||  ||||| || |
Sbjct  56896  GTCCGGGCA------TGCATGTCTGTGTGCATGTGTGTGTGTGCAT--GTGTGAGTAC  56947

Query  1769   ctgtgtgtgtgtgcctgtgtgtgggggtgcacatttgtgtgtgtgtgtgcctgtgtgtgg  1828
              |||||||||| ||| ||| |||| | |||  ||| |||||  ||||||   |||||  |
Sbjct  56948  CTGTGTGTGTATGCTTGTATGTGTGTGTGTGCATGTGTGTAGGTGTGTATATGTGTAAGT  57007

Query  1829   gggtgcacatttgtgtgtgtgtgtgcctgtgtgtgtgggtgcacatttgtgtgtgtgtgt  1888
                     ||| ||||||| ||||||  |||| | |||  ||||    |||||||||| ||
Sbjct  57008  T------CATCTGTGTGTATGTGTG--TGTGAGAGTGCATGCA----TGTGTGTGTGAGT  57055

Query  1889   gcctgtgtgt--gtgggtgcacatttgtgtgtgtgtgcctgtg--tgtgt--gggtgcac  1942
               | | |||||  |||  |||  ||  || |   | |  |||||  |||||  | |||  |
Sbjct  57056  TCATCTGTGTCAGTGTATGCTTATGGGTATAACT-TAACTGTGCATGTGTAAGTGTGTTC  57114

Query  1943   atttgtgtgtgtgtgtgcctgtgtgtgtgggtgcacatttgtgtgtgtgcctgtgtgtgg  2002
              || ||||| ||||||||  |||||| ||  || ||    | ||||||||   |||||||
Sbjct  57115  ATCTGTGTATGTGTGTG--TGTGTGAGTTAGTTCA----TCTGTGTGTGAGAGTGTGTGA  57168

Query  2003   gtgcacatttgtgtgtgtgtgcctgtgtgtgtgtgcctgtgtgtgtgggtgcacatttgt  2062
              |  | ||| |||||||| || | | ||| || |||  ||||| |||| ||| |||  ||
Sbjct  57169  G--CTCATCTGTGTGTGAGTTCATCTGTATGAGTG--TGTGTATGTGTGTGTACAAATGA  57224

Query  2063   gtgtgtgtgtgcctgtgtgtgtgggtgcacatttgtgtgtgtgtgtgcctgtgtgtgt  2122
              ||   | ||||| ||||||||||        |||  ||||||   | ||  |||| ||||
Sbjct  57225  GTTCATCTGTGCATGTGTGTGTG--------TTTAAGTGTGTTCATCTG--TGTGCGTGT  57274
```

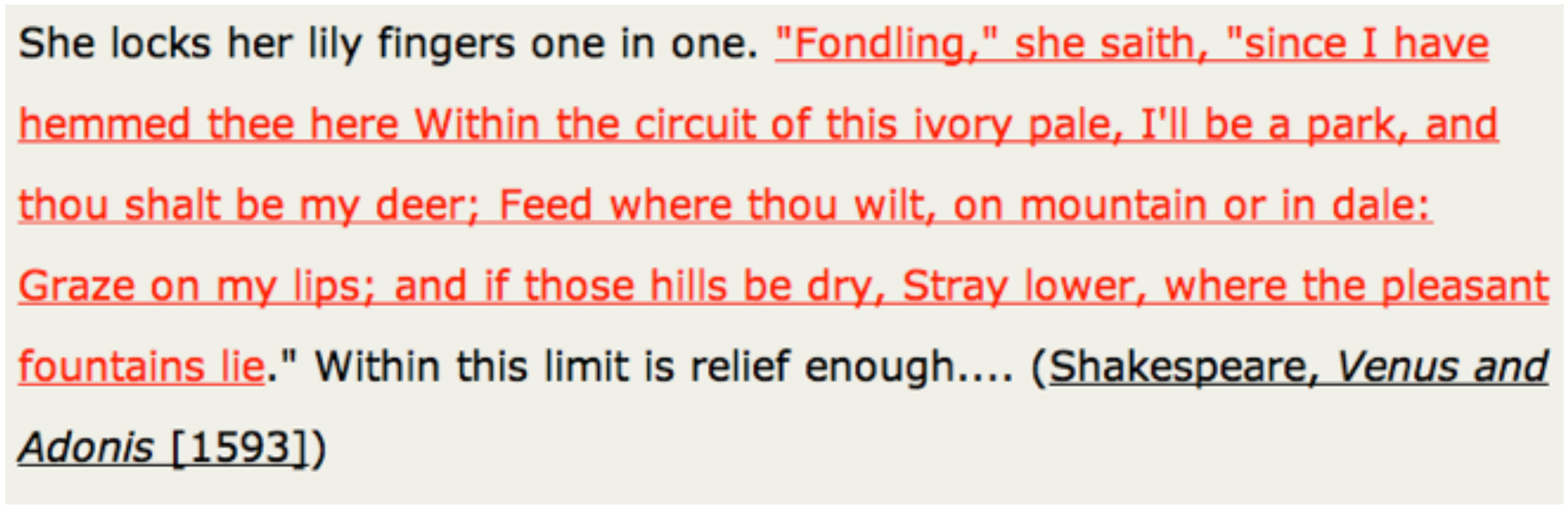
Comparing Bird Songs



Florian et al. Hidden Markov Models in the Neurosciences

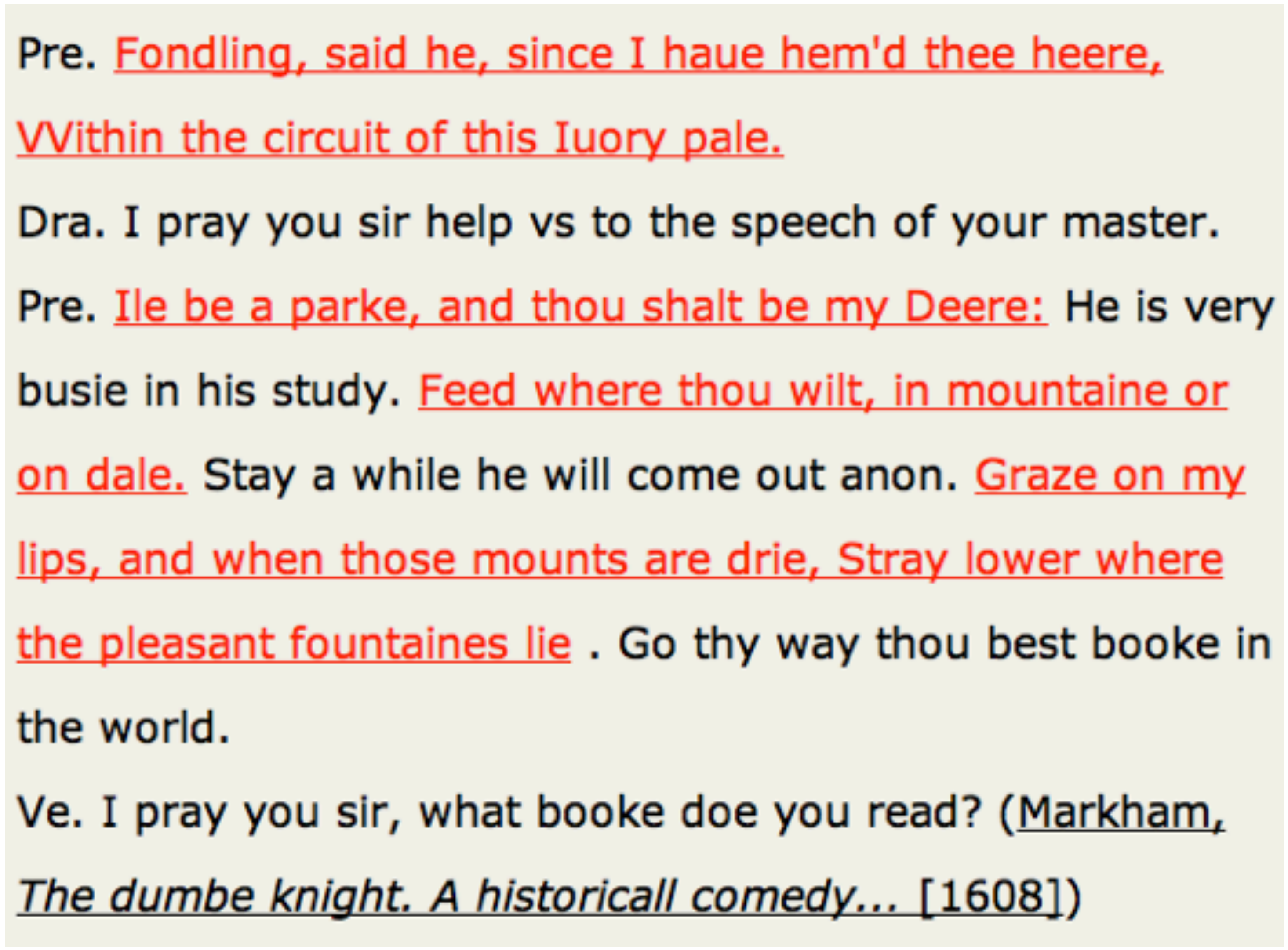
Tracing Textual Influences

Example from Horton, Olsen, Roe, Digital Studies / Le champ numérique, Vol 2, No 1 (2010)



She locks her lily fingers one in one. "Fondling," she saith, "since I have hemmed thee here Within the circuit of this ivory pale, I'll be a park, and thou shalt be my deer; Feed where thou wilt, on mountain or in dale: Graze on my lips; and if those hills be dry, Stray lower, where the pleasant fountains lie." Within this limit is relief enough.... (Shakespeare, *Venus and Adonis* [1593])

This later play by Markham references Shakespeare's poem.



Pre. Fondling, said he, since I haue hem'd thee heere, VVithin the circuit of this Iuory pale.

Dra. I pray you sir help vs to the speech of your master.

Pre. Ile be a parke, and thou shalt be my Deere: He is very busie in his study. Feed where thou wilt, in mountaine or on dale. Stay a while he will come out anon. Graze on my lips, and when those mounts are drie, Stray lower where the pleasant fountaines lie . Go thy way thou best booke in the world.

Ve. I pray you sir, what booke doe you read? (Markham, *The dumbe knight. A historicall comedy...* [1608])

Common passages identified by sequence alignment algorithms.

The String Alignment Problem

Parameters:

- "*gap*" is the cost of inserting a "-" character, representing an insertion or deletion

- *cost*(x,y) is the cost of aligning character x with character y.
  In the simplest case, *cost*(x,x) = 0 and *cost*(x,y) = mismatch penalty.

Goal:

- Can compute the edit distance by finding the **lowest cost alignment**.

- Cost of an alignment is: sum of the *cost*(x,y) for the pairs of characters that are aligned + *gap* × number of - characters inserted.

Dynamic Programming

The sequence alignment / edit distance algorithm is an example of dynamic programming.

Main idea of dynamic programming: solve the subproblems in an order so that when you need an answer, it's ready.

Requirements for DP to apply:

1. Optimal value of the original problem can be computed from some similar subproblems.

2. There are only a polynomial # of subproblems

3. There is a "natural" ordering of subproblems, so that you can solve a subproblem by only looking at **smaller** subproblems.

Dynamic Programming Design Strategy

1. Write definitions for subproblems that generalize the problem you are trying to solve in some way
   - Only worry about computing the *value* of the optimal solution.
   - Don’t worry too much in this step about how you would solve the subproblem.

2. Write the solution to every subproblem in terms of the solutions to smaller problems.

3. Give an ordering to solve the subproblems so that when trying to solve a subproblem, you have already solved the subproblems it depends on.

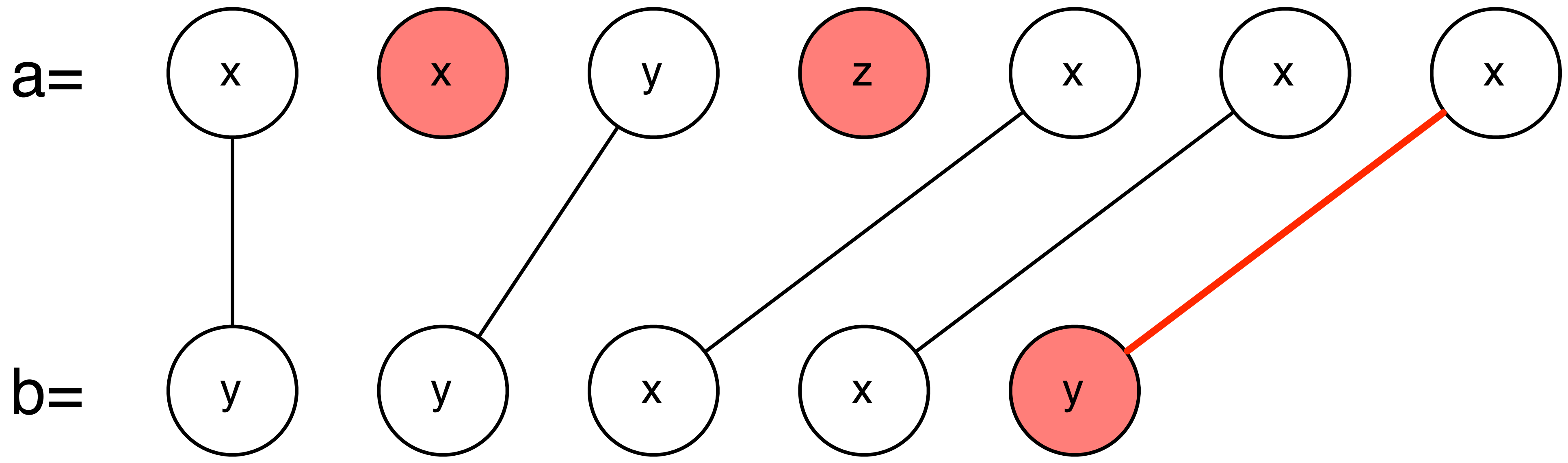
4. Show that there are are only a polynomial number of subproblems and that solving each takes a small amount of time.

5. Describe how following traceback arrows will give the actual solution.

Another View: Alignment as a Matching

Each string is a set of nodes, one for each character.

Looking for a low-cost matching (pairing) between the sequences.



Cost of a matching is:

$$\text{gap} \times \#\textit{unmatched} + \sum_{(a_i, b_j)} \textit{cost}(a_i, b_j)$$

Edges are not allowed to cross!

Algorithm for Computing Edit Distance

Consider the last characters of each string:

$$a = a_1 a_2 a_3 a_4 \ldots a_m$$
$$b = b_1 b_2 b_3 b_4 \ldots b_n$$

One of these possibilities must hold:

1. (a_m, b_n) are matched to each other
2. a_m is not matched at all
3. b_n is not matched at all
4. a_m is matched to some b_j $(j \neq n)$ and b_n is matched to some a_k $(k \neq m)$.

Algorithm for Computing Edit Distance

Consider the last characters of each string:

$$a = a_1a_2a_3a_4\ldots a_m$$
$$b = b_1b_2b_3b_4\ldots b_n$$

One of these possibilities must hold:

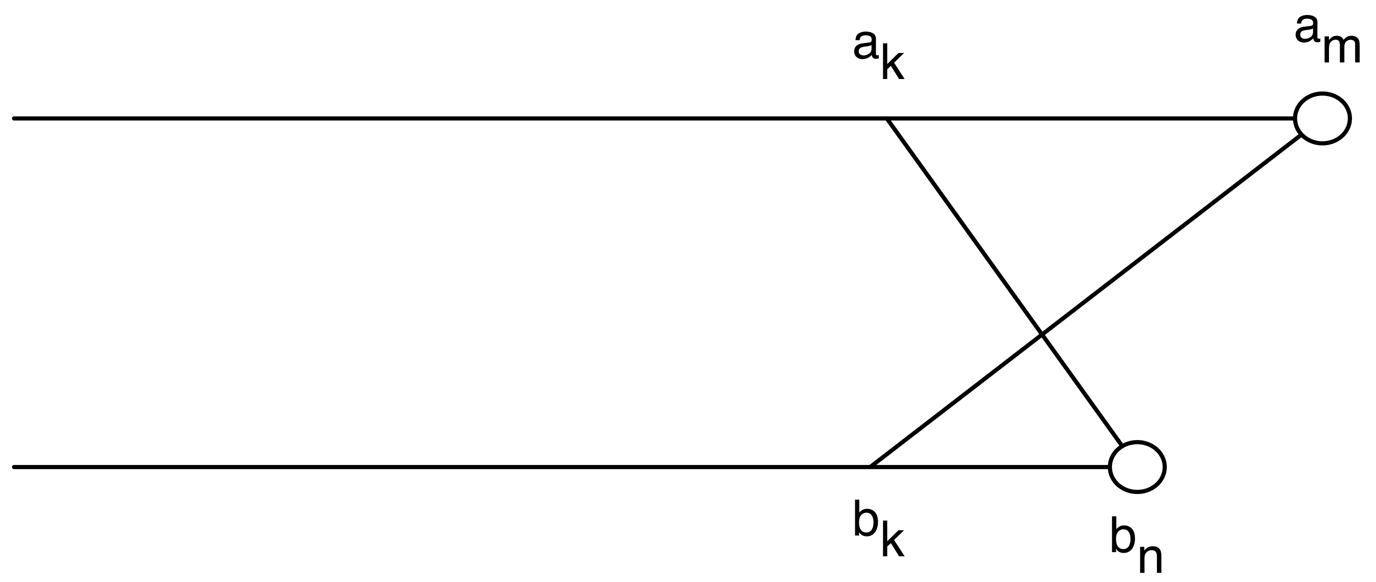
1. (a_m, b_n) are matched to each other
2. a_m is not matched at all
3. b_n is not matched at all
4. a_m is matched to some b_j $(j \neq n)$ and b_n is matched to some a_k $(k \neq m)$.

$\uparrow$

#4 can't happen! Why?

No Crossing Rule Forbids #4

4. a_m is matched to some b_j ($j \neq n$) and b_n is matched to some a_k ($k \neq m$).



So, the only possibilities for what happens to the last characters are:

1. (a_m, b_n) are matched to each other

2. a_m is not matched at all

3. b_n is not matched at all

Recursive Solution

Turn the 3 possibilities into 3 cases of a recurrence:

$$OPT(i,j) = \min \begin{cases} \text{cost}(a_i, b_j) + OPT(i-1, j-1) & \text{match } a_i, b_j \\ \text{gap} + OPT(i-1, j) & a_i \text{ is not matched} \\ \text{gap} + OPT(i, j-1) & b_j \text{ is not matched} \end{cases}$$

Cost of the optimal alignment between $a_1 \dots a_i$ and $b_1 \dots b_j$

Written in terms of the costs of smaller problems

Key: we don't know which of the 3 possibilities is the right one, so we try them all.

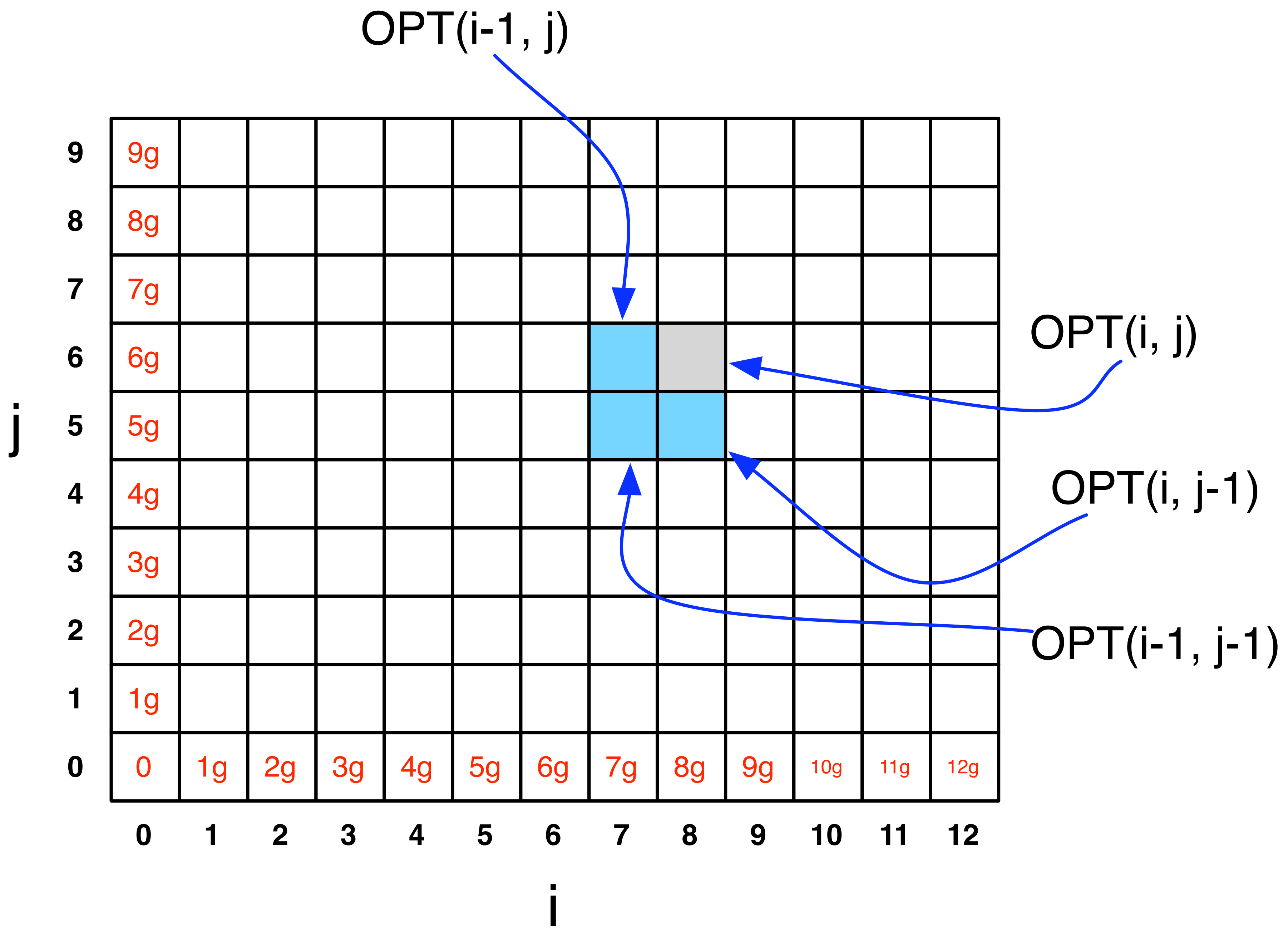
Base case: $OPT(i,0) = i \times \text{gap}$ and $OPT(0,j) = j \times \text{gap}$

(Aligning *i* characters to 0 characters must use *i* gaps.)

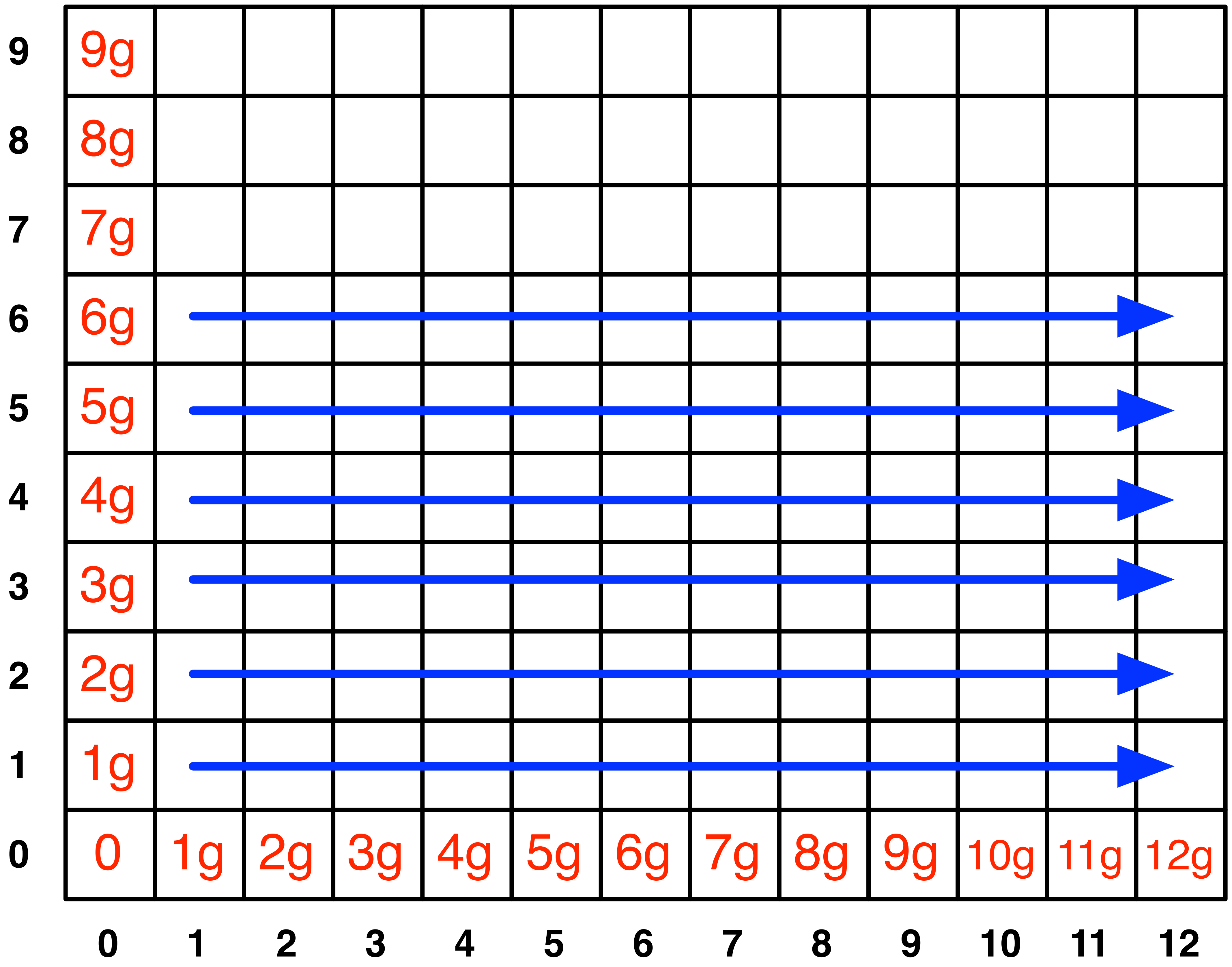
Computing OPT(i,j) Efficiently

We’re ultimately interested in $OPT(n,m)$, but we will compute all other $OPT(i,j)$ ($i \le n$, $j \le m$) on the way to computing $OPT(n,m)$.

Store those values in a 2D array:



Filling in the 2D Array



Edit Distance Computation

```
EditDistance(X,Y):
    For i = 1,...,m: A[i,0] = i*gap
    For j = 1,...,n: A[0,j] = j*gap

    For i = 1,...,m:
        For j = 1,...,n:
            A[i,j] = min(
                cost(a[i],b[j]) + A[i-1,j-1],
                gap + A[i-1,j],
                gap + A[i,j-1]
            )
        EndFor
    EndFor
    Return A[m,n]
```

Where's the answer?

OPT(n,m) contains the edit distance between the two strings.

Why? By induction: EVERY cell contains the optimal edit distance between some prefix of string 1 with some prefix of string 2.

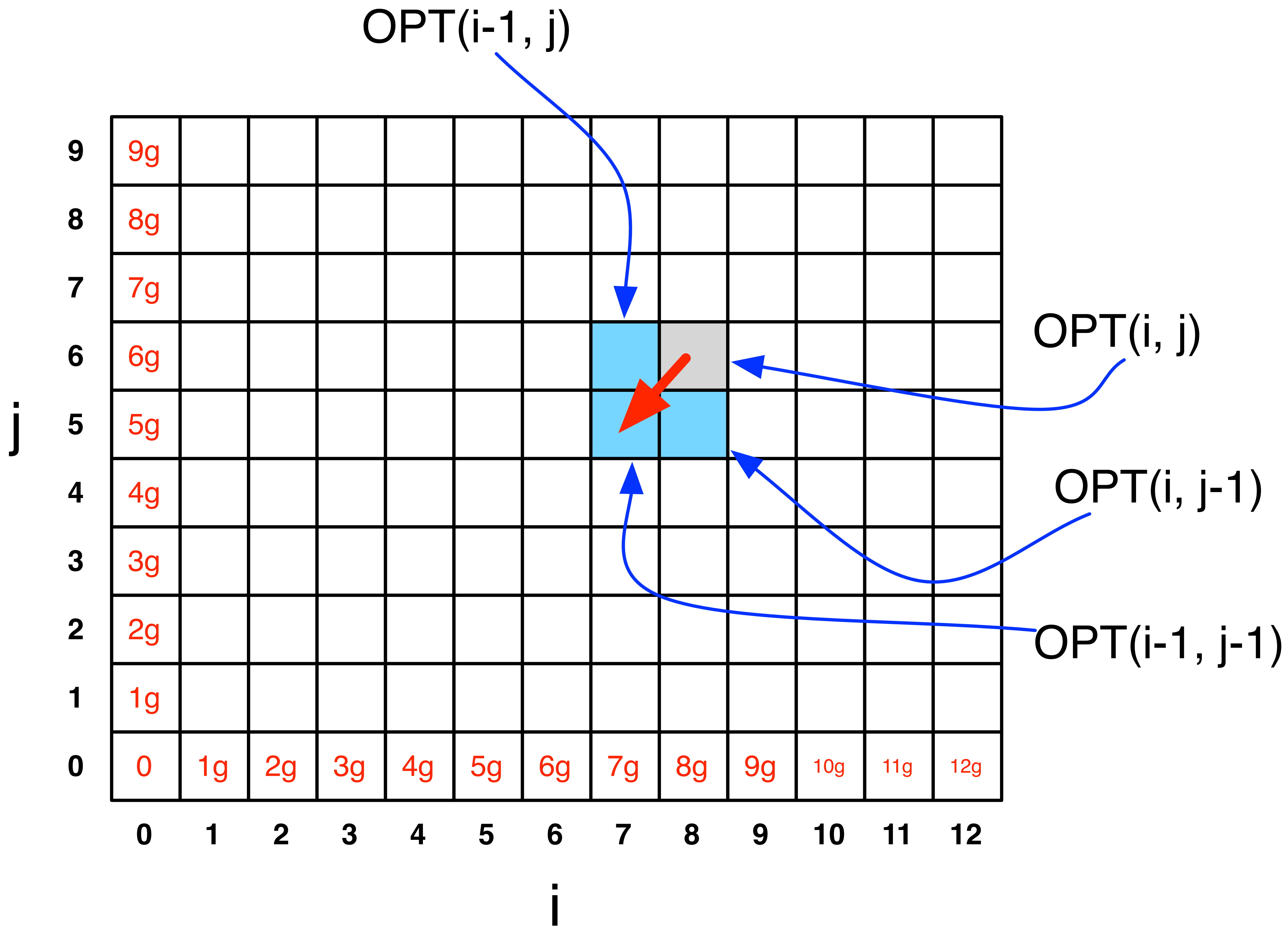
Running Time

Number of entries in array = O($m \times n$), where m and n are the lengths of the 2 strings.

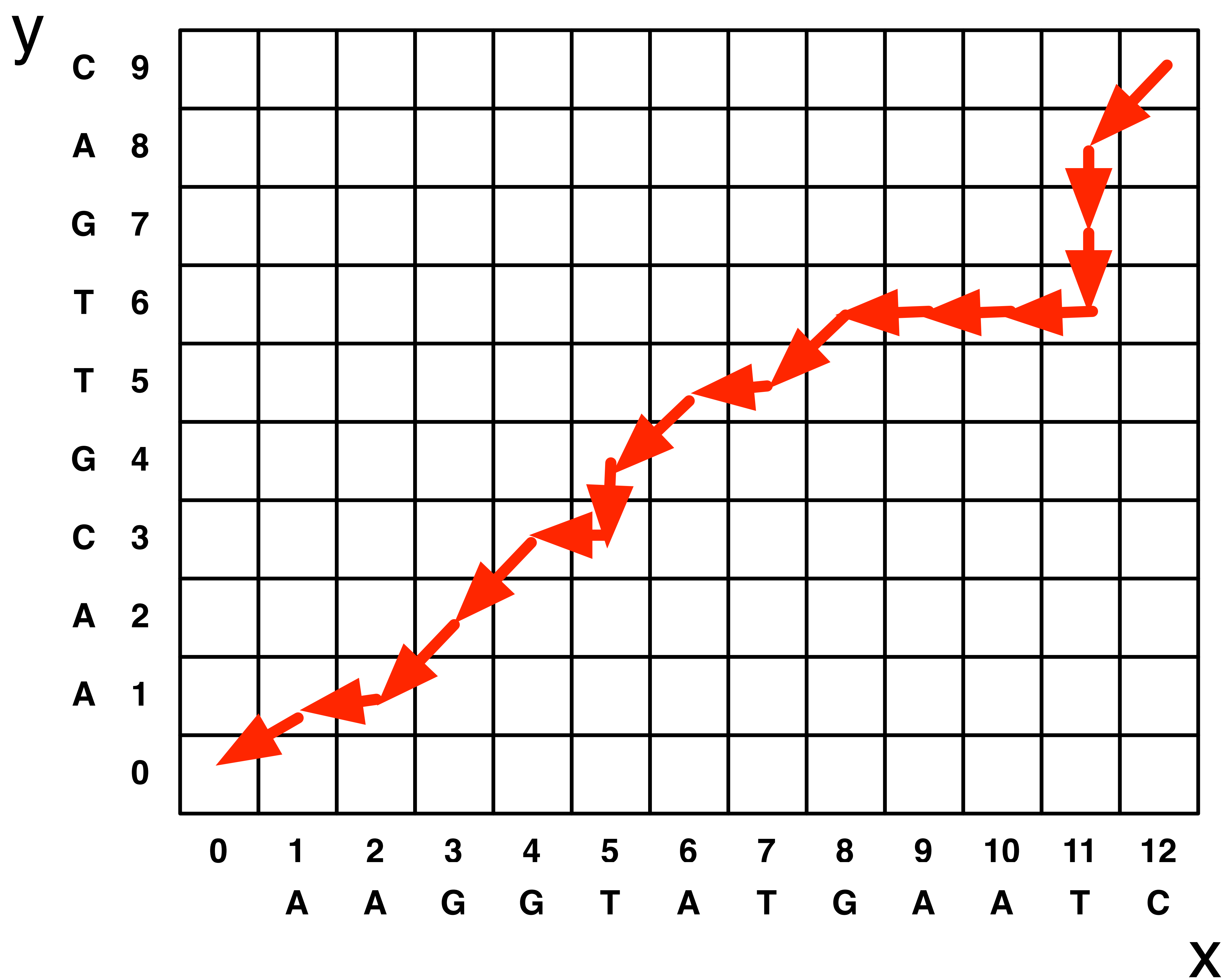
Filling in each entry takes constant O(1) time.

Total running time is O(mn).

Finding the actual alignment



Trace the arrows all the way back



Outputting the Alignment

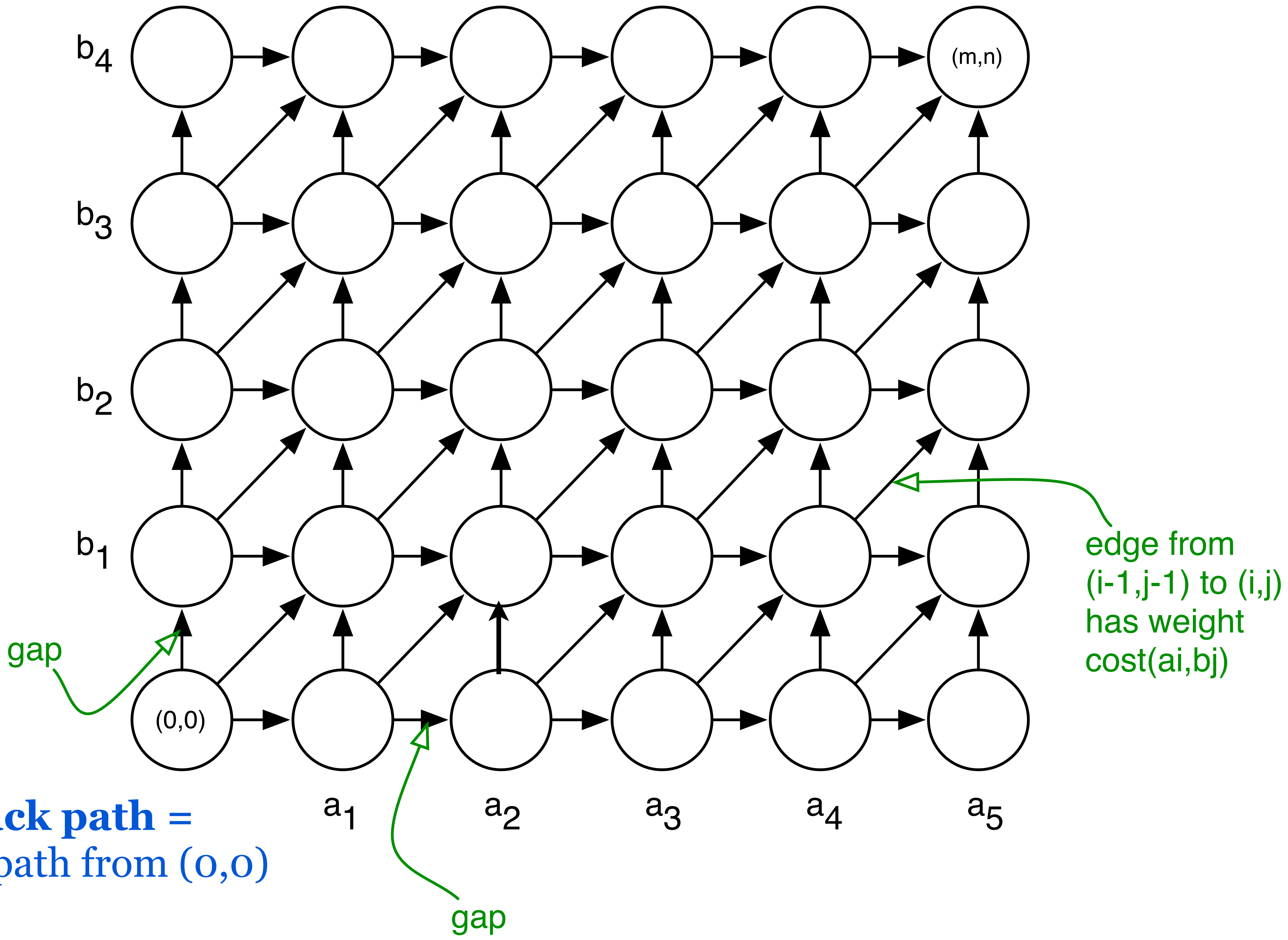
Build the alignment from right to left.

```
ACGT
A-GA
```

Follow the backtrack pointers starting from entry (n,m).

- If you follow a diagonal pointer, add both characters to the alignment,
- If you follow a left pointer, add a gap to the y-axis string and add the x-axis character
- If you follow a down pointer, add the y-axis character and add a gap to the x-axis string.

Another View: Recasting as a Graph



Traceback path =
shortest path from (0,0) to (m,n)