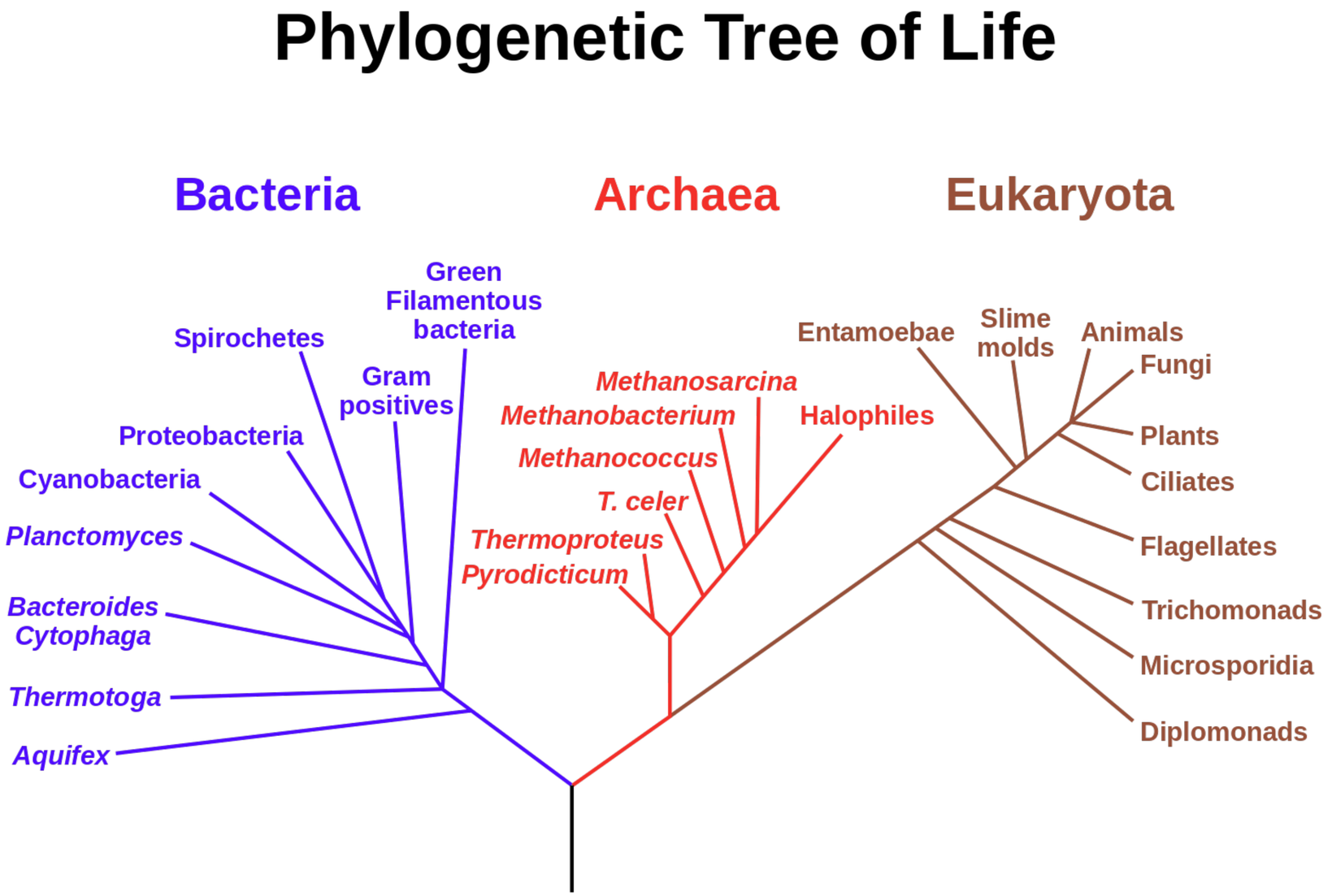
Sequence similarity and global alignment

UNIVERSITY OF MARYLAND

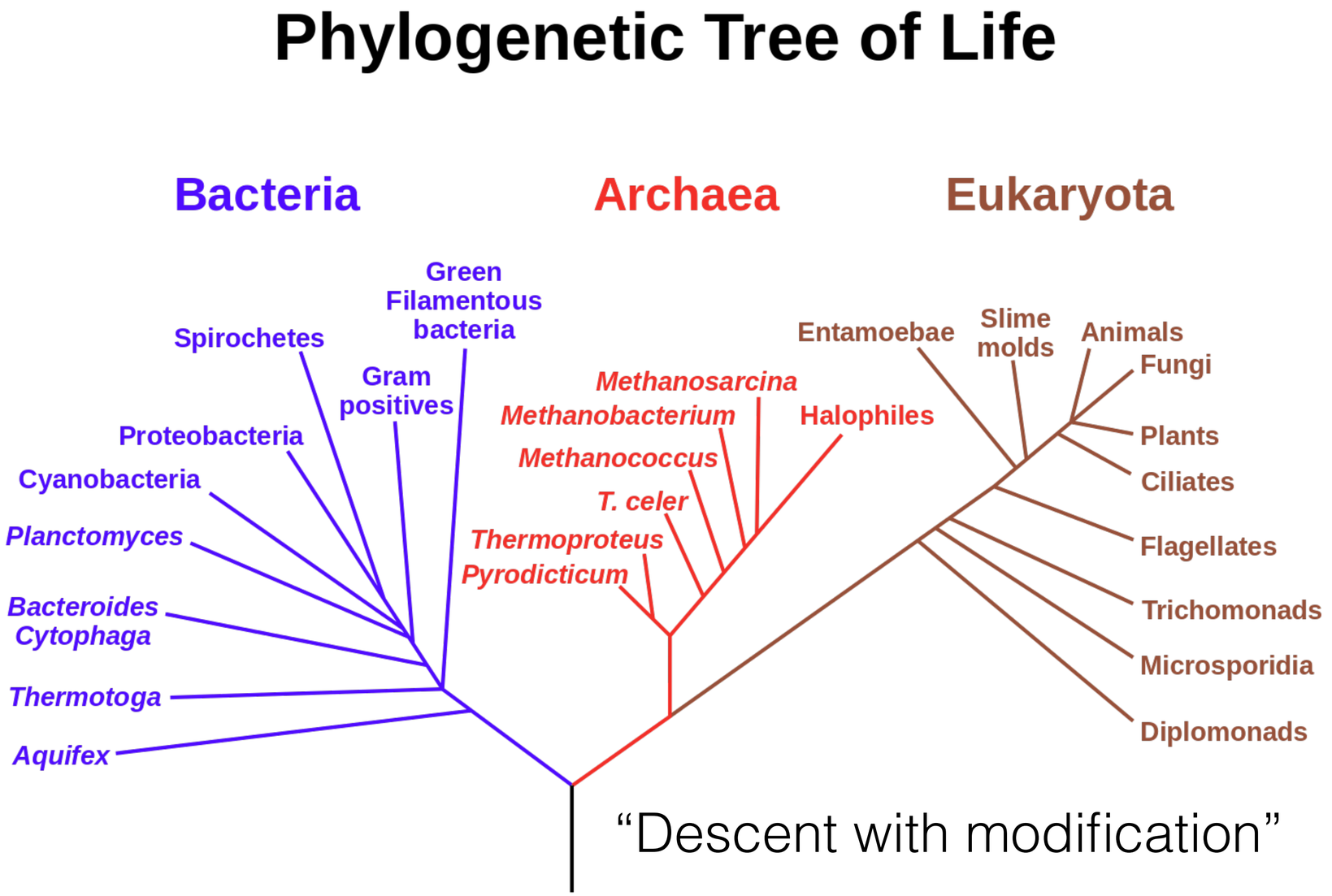
slides (w/*) courtesy of Carl Kingsford

Relatedness of Biological Sequence



https://en.wikipedia.org/wiki/Phylogenetic_tree

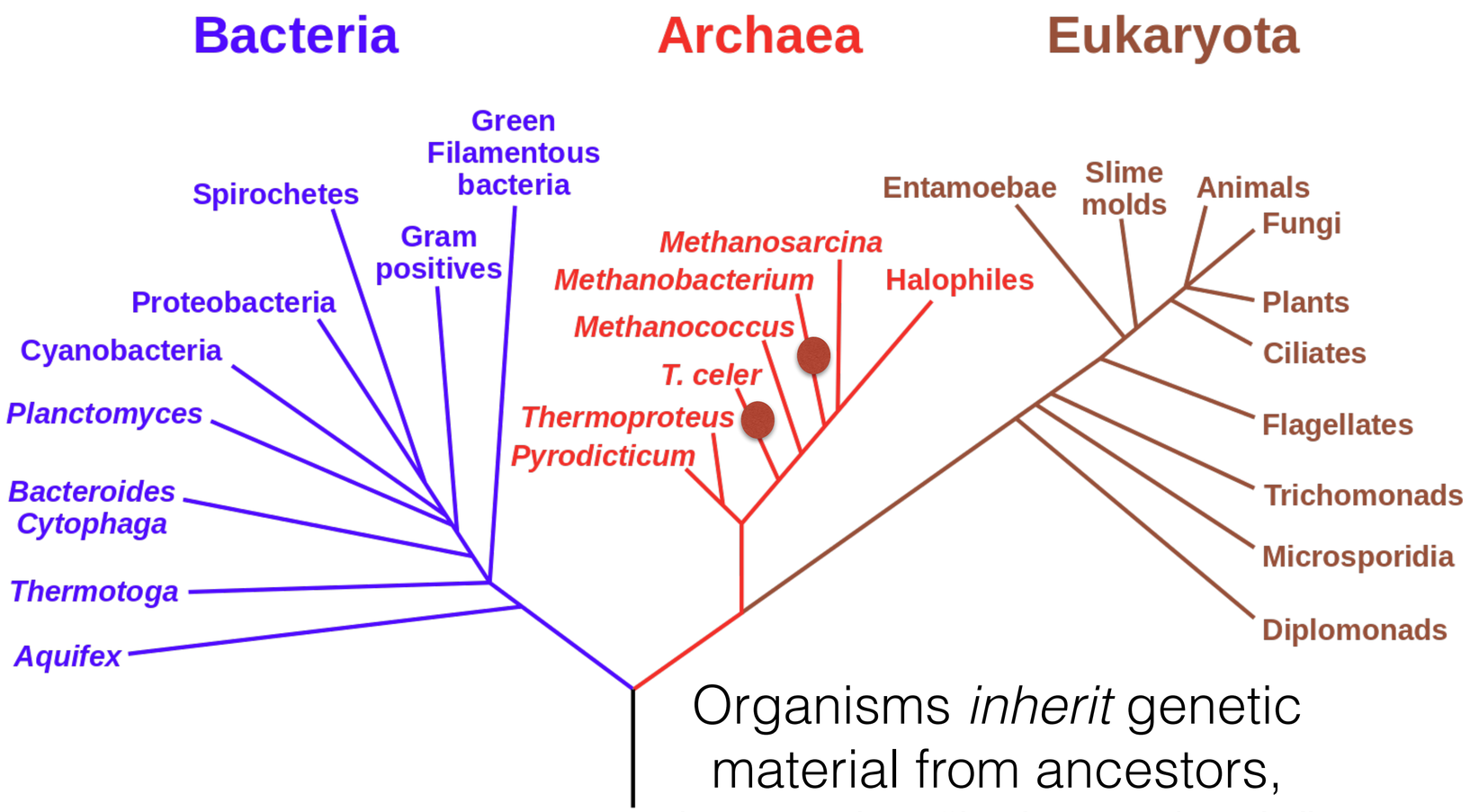
Relatedness of Biological Sequence



"Descent with modification"

https://en.wikipedia.org/wiki/Phylogenetic_tree

Relatedness of Biological Sequence

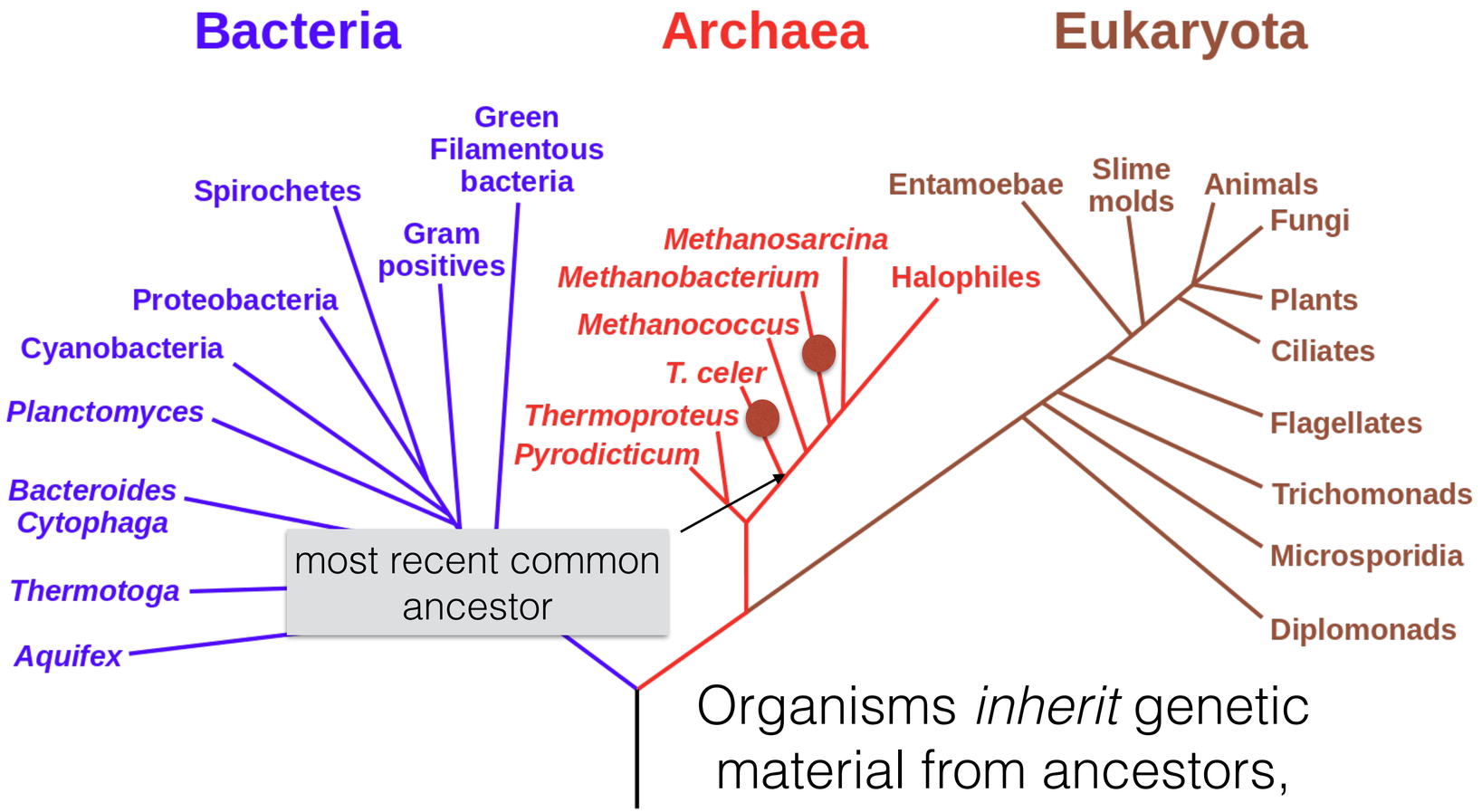


Organisms *inherit* genetic material from ancestors, but evolve "independently"

https://en.wikipedia.org/wiki/Phylogenetic_tree

Relatedness of Biological Sequence

Phylogenetic Tree of Life



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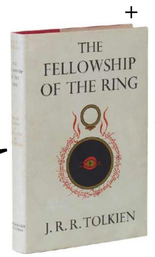
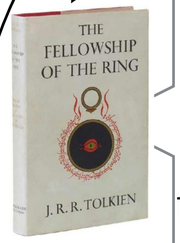
Consider an analogy



"When Mr. Bilbo Baggins of Bag End announced that he would shortly be celebrating his eleventy-first birthday with a party of special magnificence, there was much talk and excitement in Hobbiton"



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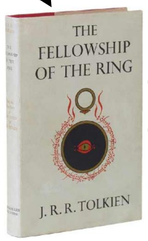


"When Mr. Bilbo Baggins of Bag End announced that he would shortly be celebrating his eleventh-first birthday with a party of special magnificence, there was much talk and excitement in **Hobbit-town**"

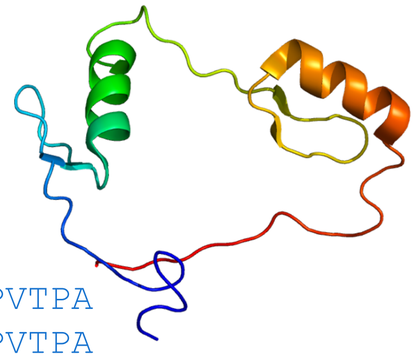
"When **Mrs**. Bilbo Baggins of Bag End announced that **she** would shortly be celebrating his eleventh-first birthday with a party of special magnificence, there was much talk and excitement in **Hobbit-town**"

+:https://en.wikipedia.org/wiki/The_Fellowship_of_the_Ring

Sequence tells a story

- If two sequences are *similar*, this provides evidence of descent from a common ancestor
- Sequences are *conserved* at different rates
- Very similar sequence can indicate a very *recent common ancestor*, or a *highly conserved function*

Why compare DNA or protein sequences?



Partial CTCF protein sequence in 8 organisms:

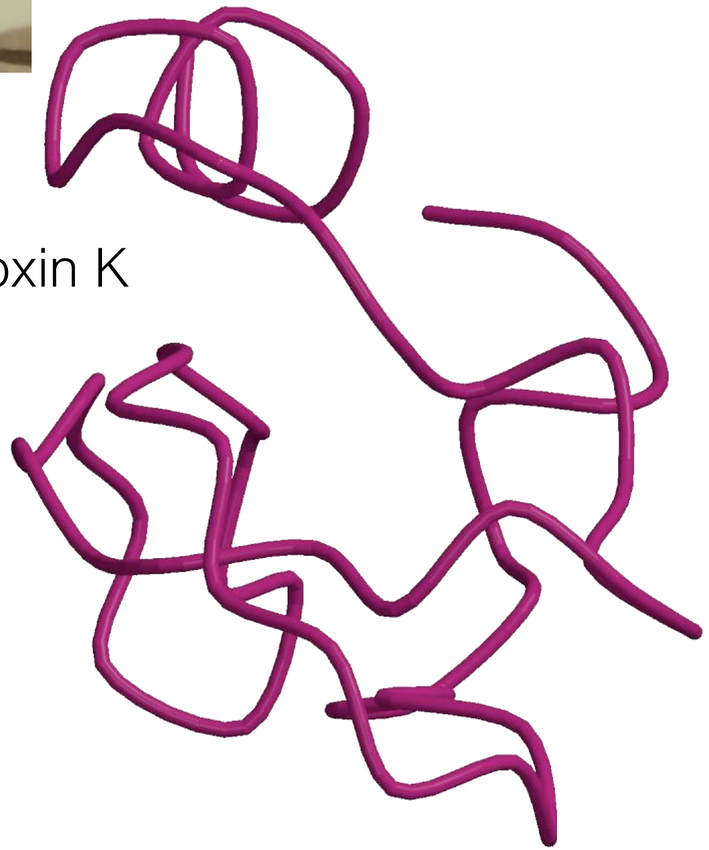
```
H. sapiens        -EDSSDS-ENAEPDLDDNEDEEEPAVEIEPEPE----------PQPVTPA
P. troglodytes    -EDSSDS-ENAEPDLDDNEDEEEPAVEIEPEPE----------PQPVTPA
C. lupus          -EDSSDS-ENAEPDLDDNEDEEEPAVEIEPEPE----------PQPVTPA
B. taurus         -EDSSDS-ENAEPDLDDNEDEEEPAVEIEPEPE----------PQPVTPA
M. musculus       -EDSSDSEENAEPDLDDNEEEEPAVEIEPEPE--PQPQPPPPPQPVAPA
R. norvegicus     -EDSSDS-ENAEPDLDDNEEEEPAVEIEPEPEPQPQPQPQPQPQPVAPA
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 slides).

*

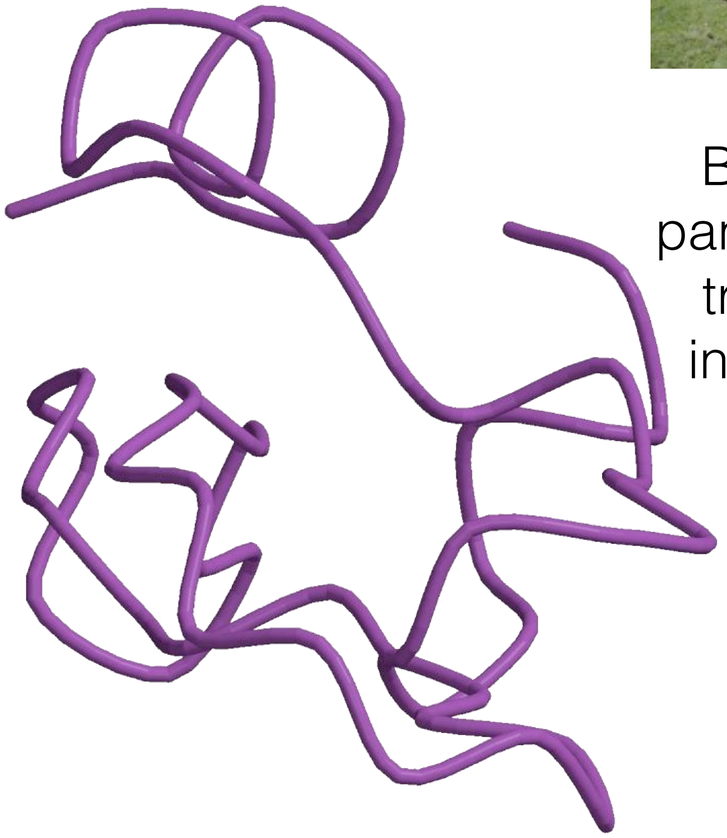
Sequence can reveal structure

dendrotoxin K



(a) 1dtk

Bovine pancreatic trypsin inhibitor



(b) 5pti

```
1dtk   XAKYCKLPLRIGPCKRKIPSFYYKWKAKQCLPFDYSGCGGNANRFKTIEECRRTCVG-
5pti   RPDFCLEPPYTGPCKARIIRYFYNAKAGLCQTFVYGGCRAKRNNFKSAEDCMRTCGGA
```

*

Why Not Exact Matching?

Suffix tree / array and BWT / FM-index are powerful tools for finding exact patterns in a large text, but exact matching is insufficient. Reads have **errors** and there is **true genomic variation** between a reference and a sample.

Typical strategy (many variants):

- Find all places where a substring of the query matches the reference exactly (seeds)
- Filter out regions with insufficient exact matches to warrant further investigation
- Perform a “constrained” alignment that includes these exact matching “seeds”

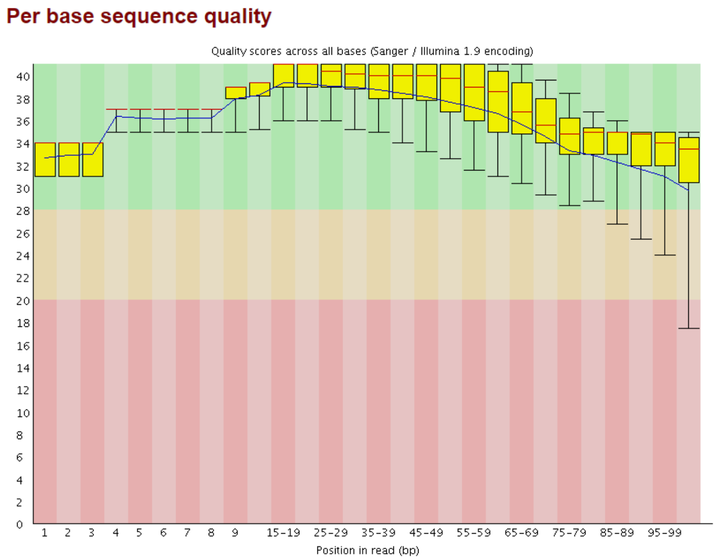
Requires efficient exact search

Here is where we use our alignment DPs

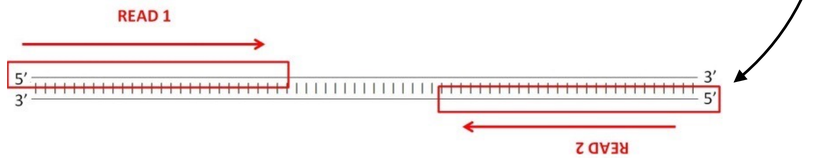
Why Is This Possible?

This is (*usually*) a **heuristic** (doesn't guarantee you find all alignment locations within the budget for a read).

But, due to the error profiles of reads, this often works well.



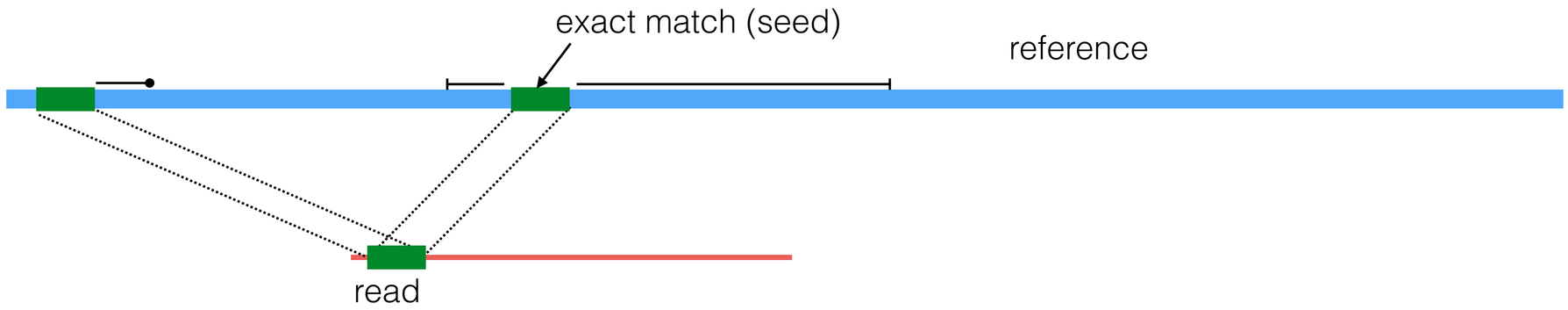
	error type	error rate	read length
Illumina	subst.	~0.1%	50-300
Nanopore	indel	10-30%	5-10kb
Pac Bio	indel	10-15%	10-15kb



2nd generation reads are often "paired-end"

Typical Strategy

Seed & Extend:



The Language of Strings

A string **s** is a finite sequence of characters

|**s**| denotes the length of the string — the number of characters in the sequence.

A string is defined *over* an alphabet, Σ

Σ_{DNA} = {A,T,C,G}
Σ_{RNA} = {A,U,C,G}
$\Sigma_{AminoAcid}$ = {A, R, N, D, C, E, Q, G, H, I, L, K, M, F, P, S, T, W, Y, V}

The empty string is denoted ϵ — |ϵ| = 0

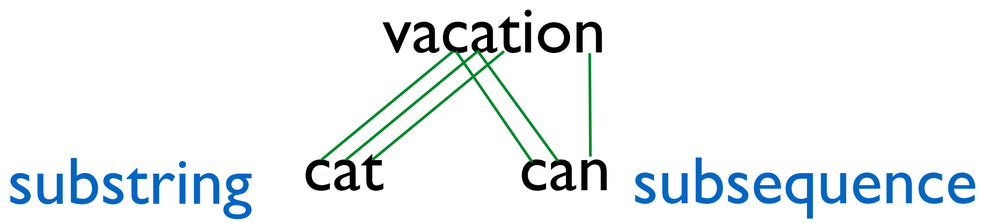
adapted from a slide by Ben Langmead

The Language of Strings

Given two strings **s,t** over the same alphabet Σ, we denote the concatenation as **st** — this is the sequence of **s** followed by the sequence of **t**

String **s** is a substring of **t** if there exist two (potentially empty) strings **u** and **v** such that **t = usv**

String **s** is a subsequence of **t** if the characters of **s** appear in order (but not nece consecutively) in **t**



String **s** is a prefix/suffix of **t** if **t** = **su/us** — if neither **s** nor **u** are ϵ, then **s** is a prefix/suffix of **t**

adapted from a slide by Ben Langmead

The Simplest String Comparison Problem

Given: Two strings

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

where a_i, b_i are letters from some alphabet, Σ, 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

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

*

The String Alignment Problem

Parameters:

- "*gap*" is the cost of inserting a "-" character, representing an insertion or deletion (insertion/deletion are dual operations depending on the string)

- *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**. (often phrased as finding **highest scoring 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.

e.g. *gap* = 3, *cost('D', 'P')* = 1

- RIDDLE
TRIP - LE

Total cost = 3+0+0+1+3+0+0 = 7

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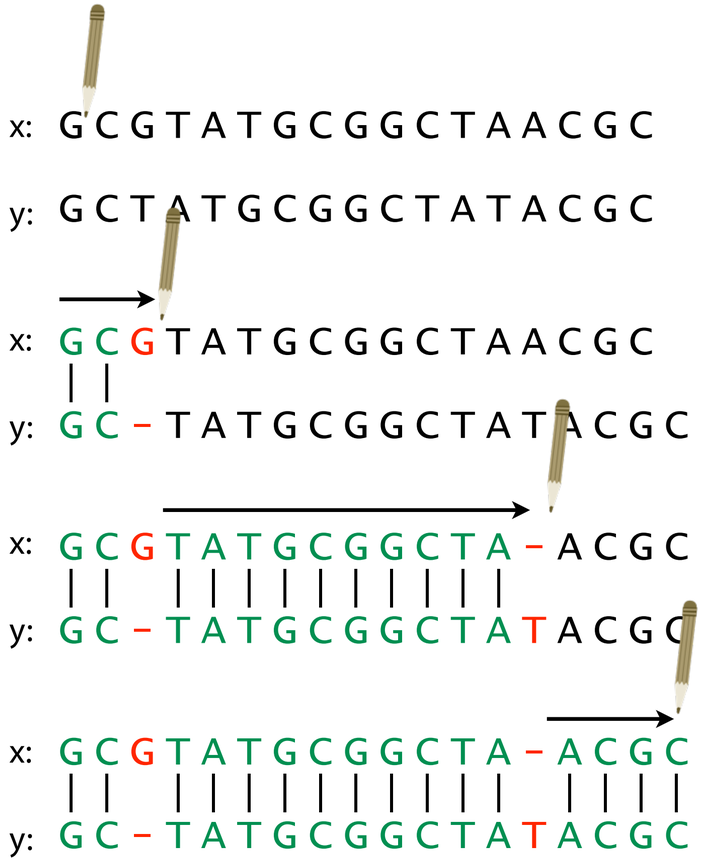
Representing alignments as edit transcripts

Can think of edits as being introduced by an *optimal editor* working left-to-right.
Edit transcript describes how editor turns *x* into *y*.



Operations:
M = match, **R** = replace,
I = insert into *x*, **D** = delete from *x*

MMD

MMDMMMMMMMMMMI

MMDMMMMMMMMMMIMMMM

Slide courtesy of Ben Langmead

Representing edits as alignments

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

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

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

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

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

```
al-go-rithm-
|| XX ||X |
alKhwariz-mi
(4 gaps, 3 mm)
MMIRRIMMRDMI
```

*

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------TGCATGTCTGTGTGCATGTGTGTGTGTGTGCAT--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   gtgtgtgtgtgcctgtgtgtgtgggtgcacatttgtgtgtgtgtgtgtgcctgtgtgtgt  2122
              ||   | ||||| ||||||||||        |||  ||||||   | ||  |||| ||||
Sbjct  57225  GTTCATCTGTGCATGTGTGTGTG--------TTTAAGTGTGTTCATCTG--TGTGCGTGT  57274
```

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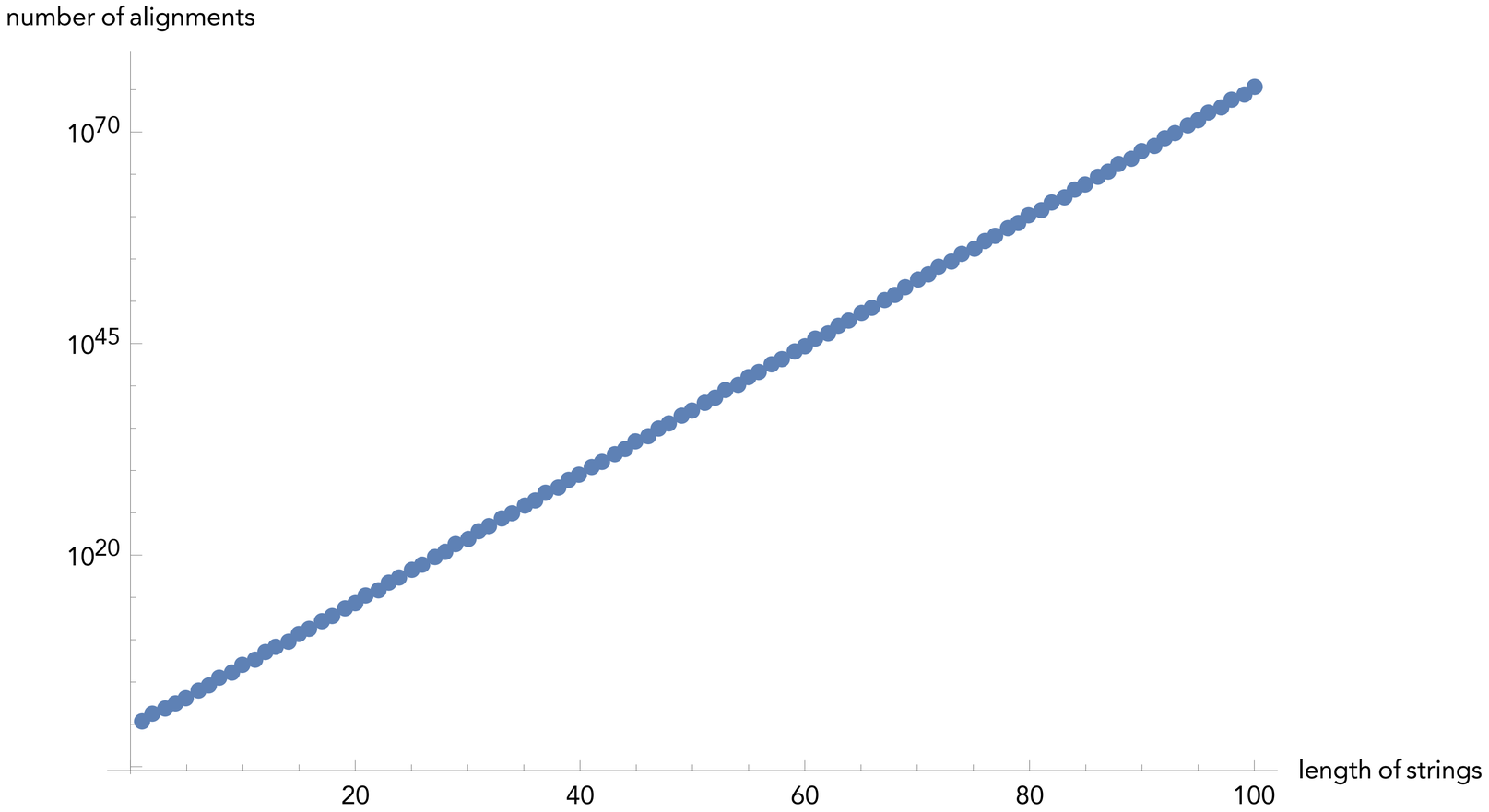
How many alignments are there?



$$f(n,m) = \sum_{k=0}^{\min(m,n)} 2^k \binom{m}{k} \binom{n}{k}$$

Andrade, Helena, et al. "The number of reduced alignments between two DNA sequences." BMC bioinformatics 15.1 (2014): 94.

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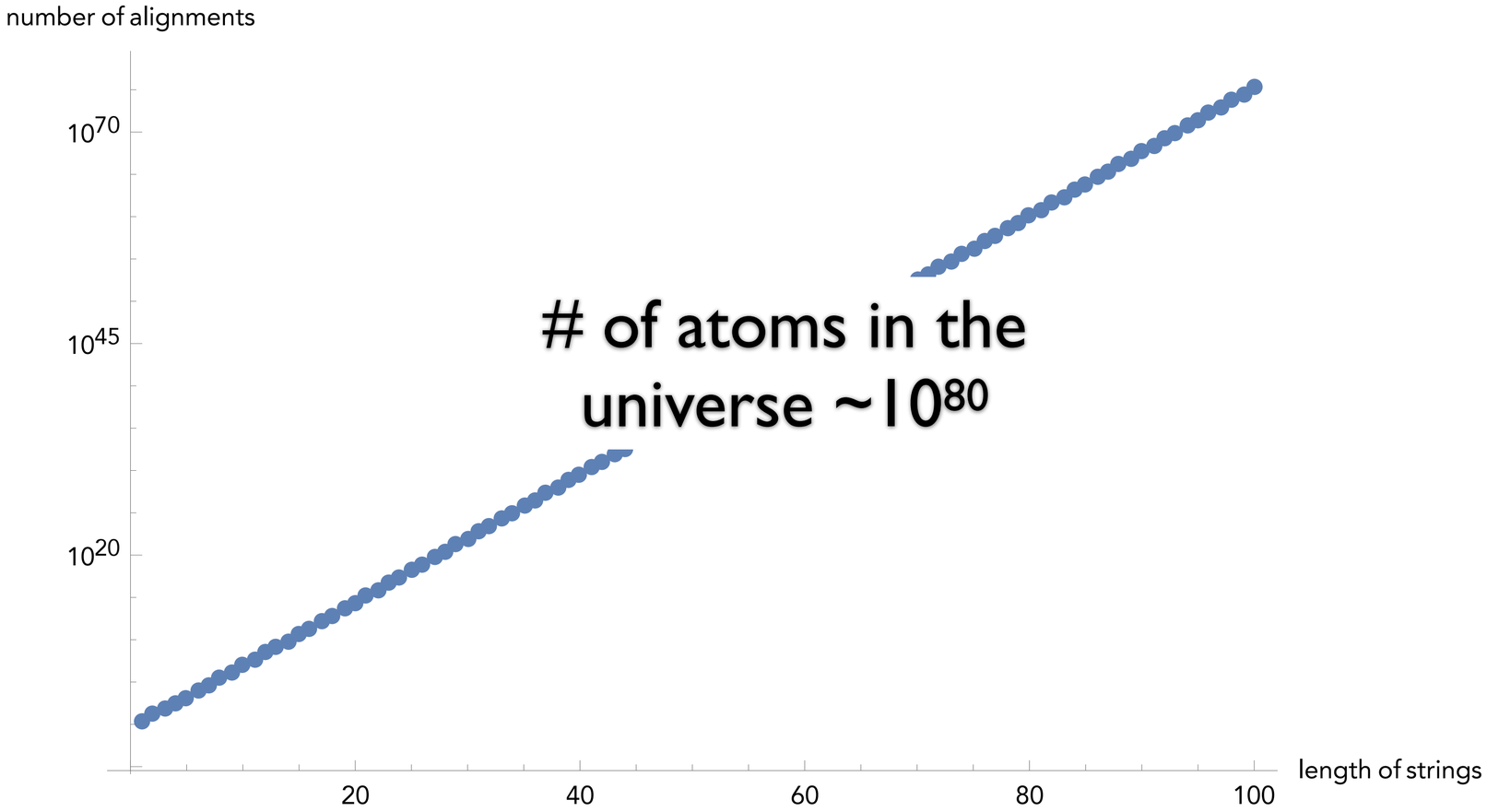

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Interlude: Dynamic Programming

General and powerful *algorithm design* technique

“Programming” in the mathematical sense — nothing to do with e.g. code

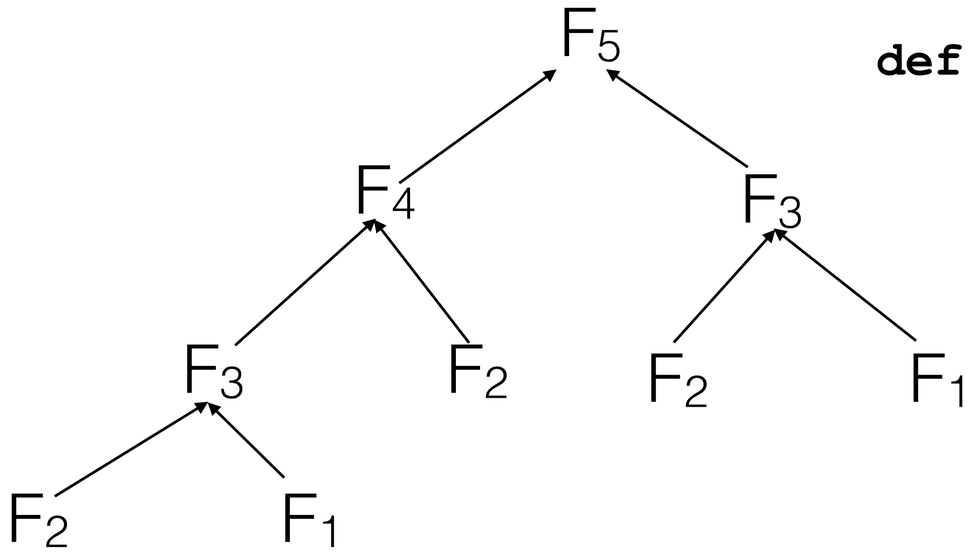
To apply DP, we need optimal substructure and overlapping subproblems

optimal substructure — can combine solutions to “smaller” problems to generate solutions to “larger” problems.

overlapping subproblems — solutions to subproblems can be “re-used” in multiple contexts (to solve multiple) larger problems

Example 1: Fibonacci Sequence

$F_n = F_{n-1} + F_{n-2}$ with $F_1 = F_2 = 1$




```
def fib(n):
    if n == 1 or n == 2:
        return 1
    else:
        return fib(n-1) + fib(n-2)
```

This recursive way of computing fib(n) is **very** inefficient!

What is the runtime of this approach (i.e. fib(n) = O(?))

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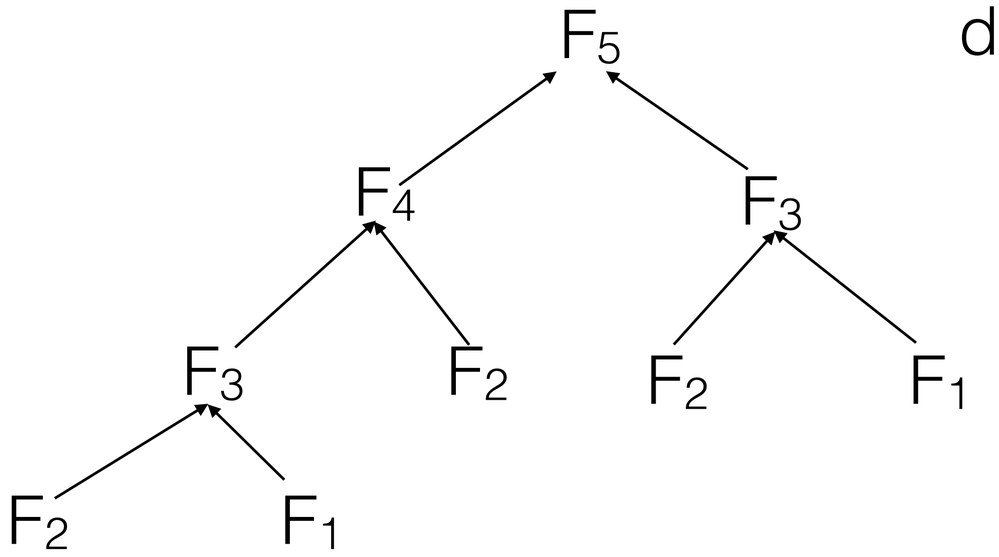


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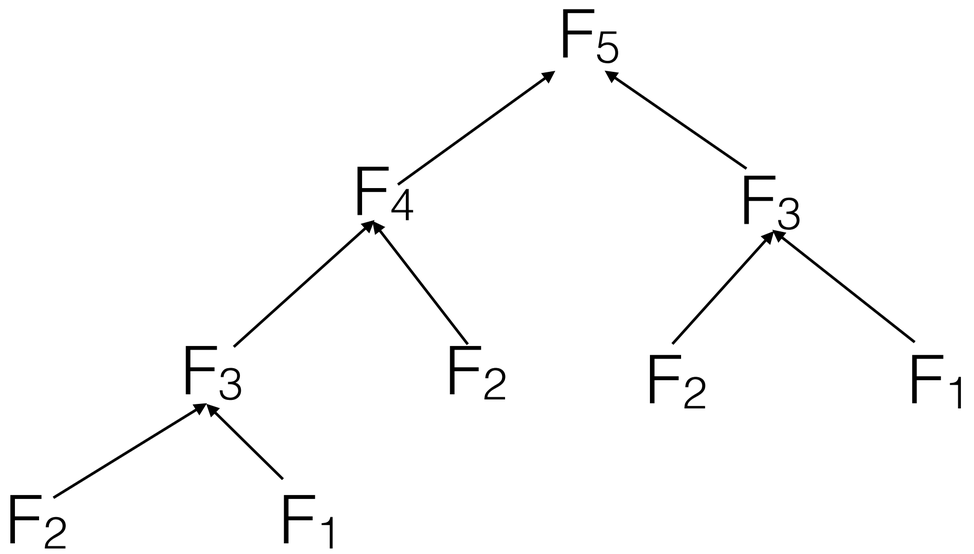
Runtime of this approach is fib(n) = $O(\phi^n)$ =$O(2^n)$

golden ratio

Example 1: Fibonacci Sequence

$F_n = F_{n-1} + F_{n-2}$ with $F_1 = F_2 = 1$

How do we do better than $O(\phi^n)$?



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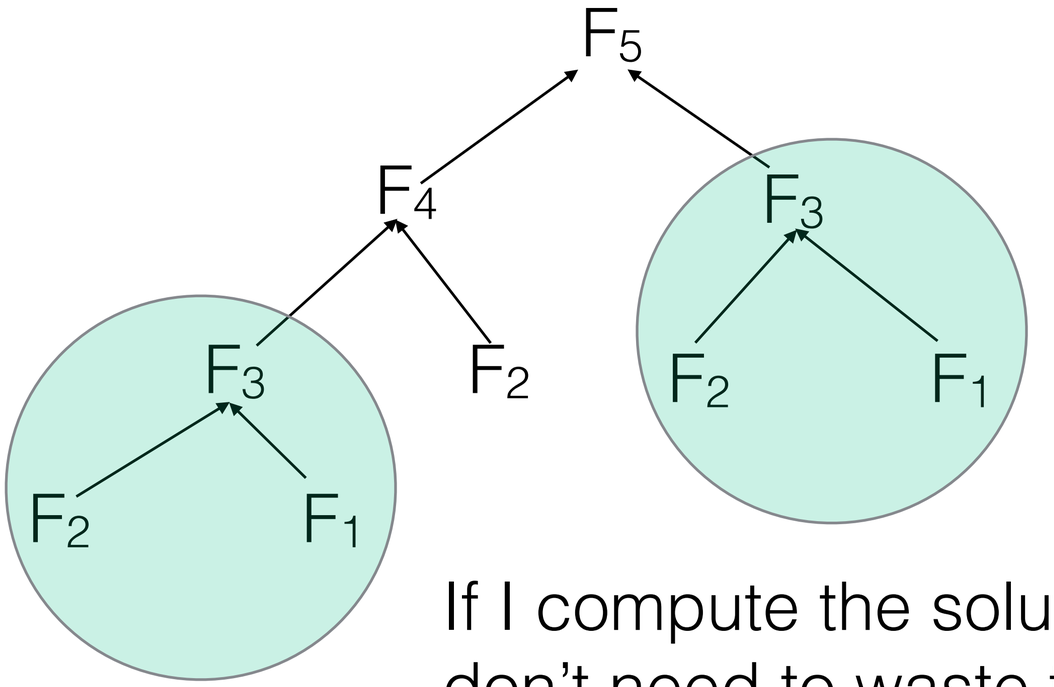

If I compute the solutions in the “right order”, I don’t need to waste time re-computing the same values.

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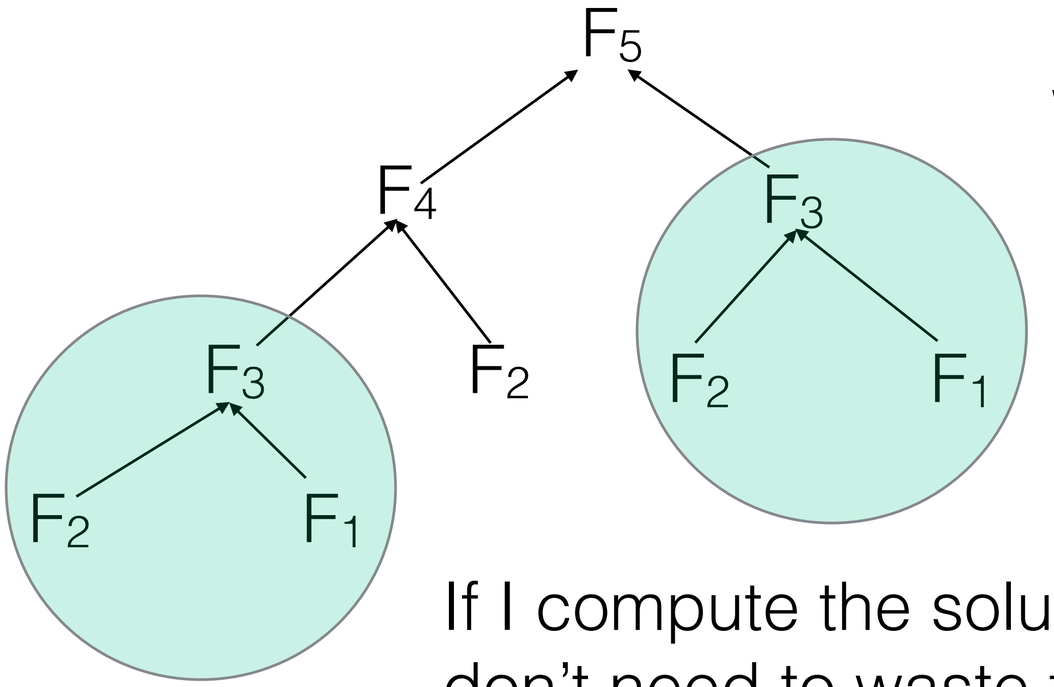

What is the “right order”?

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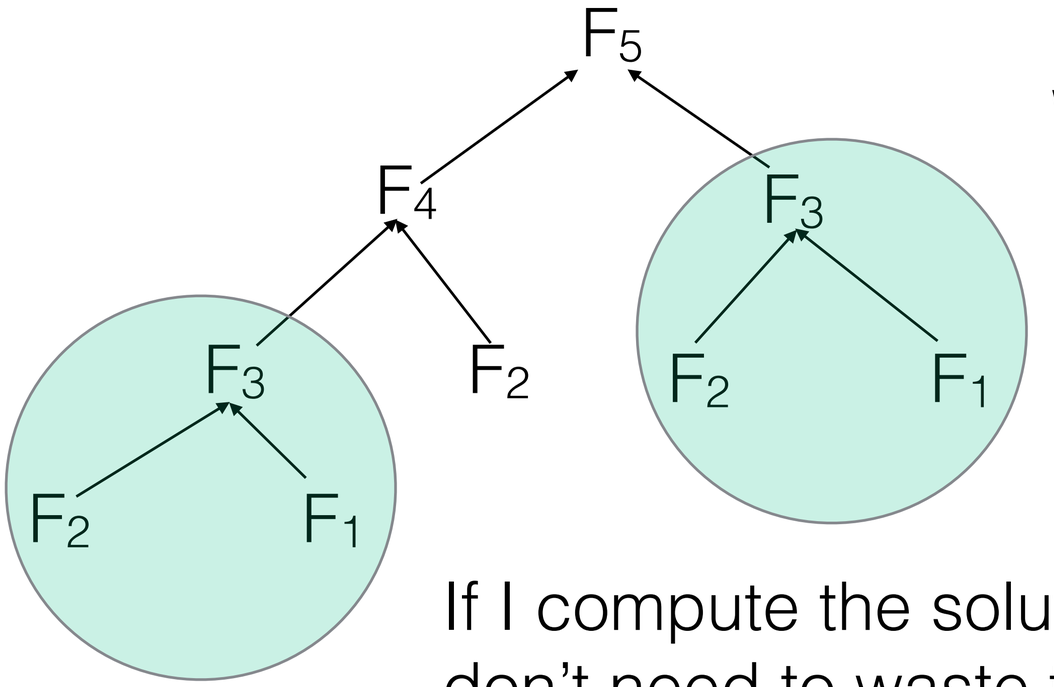


What is the “right order”?

$F_1 \rightarrow F_2 \rightarrow F_3 \rightarrow F_4 \rightarrow F_5 \ldots$

If I compute the solutions in the “right order”, I don’t need to waste time re-computing the same values.

Example 1: Fibonacci Sequence

$F_n = F_{n-1} + F_{n-2}$ with $F_1 = F_2 = 1$

How do we do better than $O(\phi^n)$?

Take 2:

```
def fib(n):
  if n == 1 or n == 2:
    return 1
  fm2, fm1 = 1, 1
  for i in xrange(2, n):
      fm2, fm1 = fm1, fm2 + fm1
  return fm1
```

We loop up to n, and perform an addition in each iteration —> O(n); **much better!** Note: O(n) assumes addition is constant, not true for large enough n.

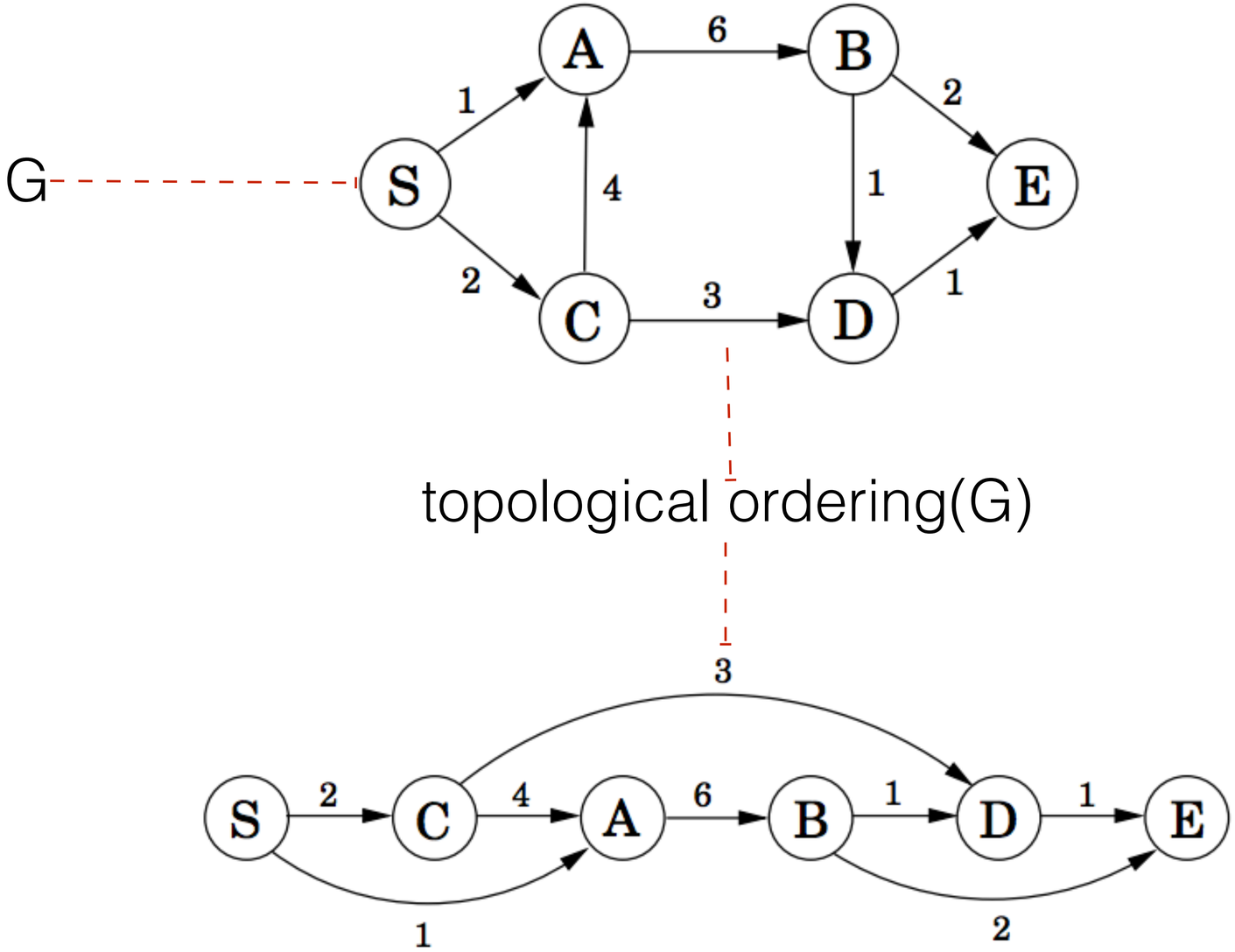
Example 2: Shortest Path in a DAG

Let G = (V,E) be a **d**irected **a**cyclic **g**raph (DAG) with vertex set V and edge set E.

Since G directed and free of cycles, there exists a (at least one) **topological order** of G — an ordering $p(v_1)$, $p(v_2)$, …, $p(v_n)$ such that for all $e = (v_i, v_j)$ in E, $p(v_i) < p(v_j)$

In other words, we can label the nodes of G such that all edges point from a vertex with a smaller label to a vertex with a larger label.

Example 2: Shortest Path in a DAG



Dasgupta, Sanjoy, Christos H. Papadimitriou, and Umesh Vazirani. Algorithms. McGraw-Hill, Inc., 2006.

Obtaining a topological ordering

Kahn's algorithm

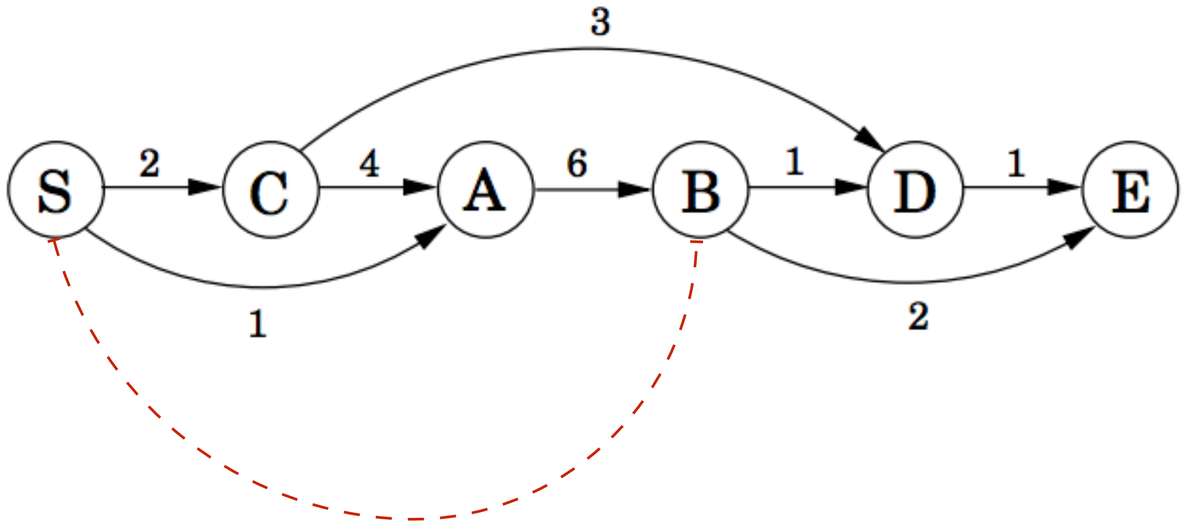
Builds up a valid topo order node-by-node

```
L ← Empty list that will contain the sorted elements
S ← Set of all nodes with no incoming edges
while S is non-empty do
    remove a node n from S
    add n to tail of L
    for each node m with an edge e from n to m do
        remove edge e from the graph
        if m has no other incoming edges then
            insert m into S
if graph has edges then
    return error (graph has at least one cycle)
else
    return L (a topologically sorted order)
```

O(|V| + |E|); why?

https://en.wikipedia.org/wiki/Topological_sorting

Example 2: Shortest Path in a DAG

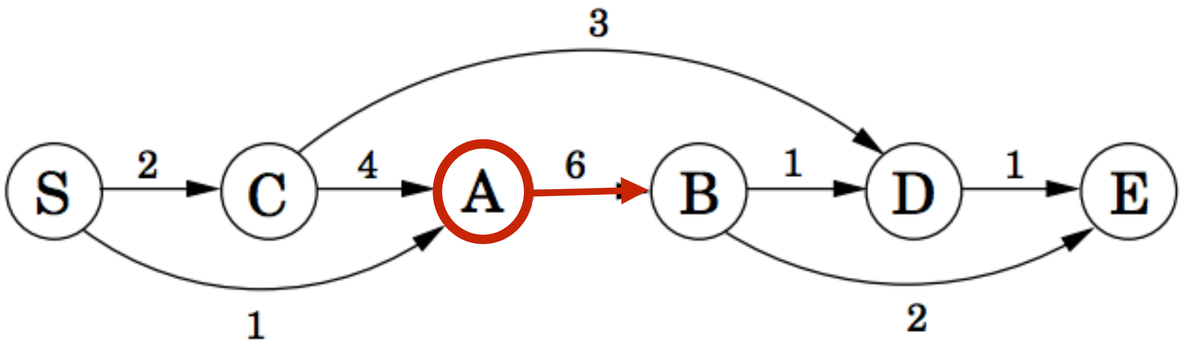


What's the distance from S to B — d(S,B) ?

Dasgupta, Sanjoy, Christos H. Papadimitriou, and Umesh Vazirani. Algorithms. McGraw-Hill, Inc., 2006.

Example 2: Shortest Path in a DAG

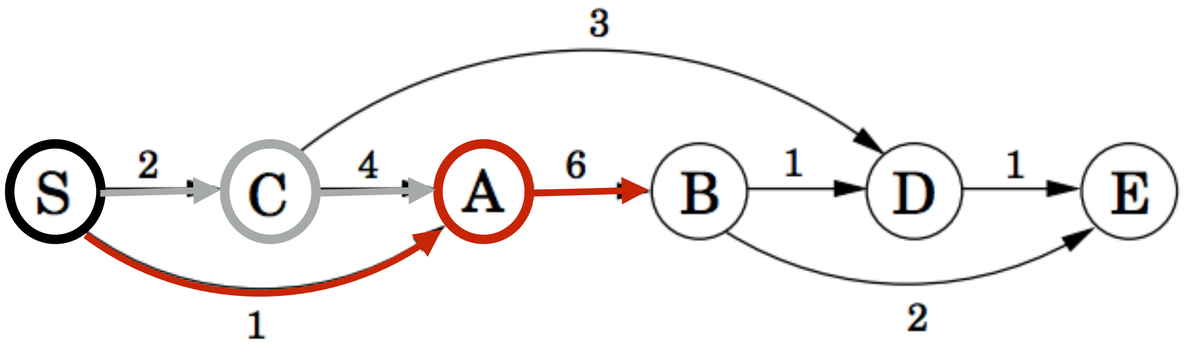
First, I **must** go through A, so it's at least d(S,A) + 6



Dasgupta, Sanjoy, Christos H. Papadimitriou, and Umesh Vazirani. Algorithms. McGraw-Hill, Inc., 2006.

Example 2: Shortest Path in a DAG

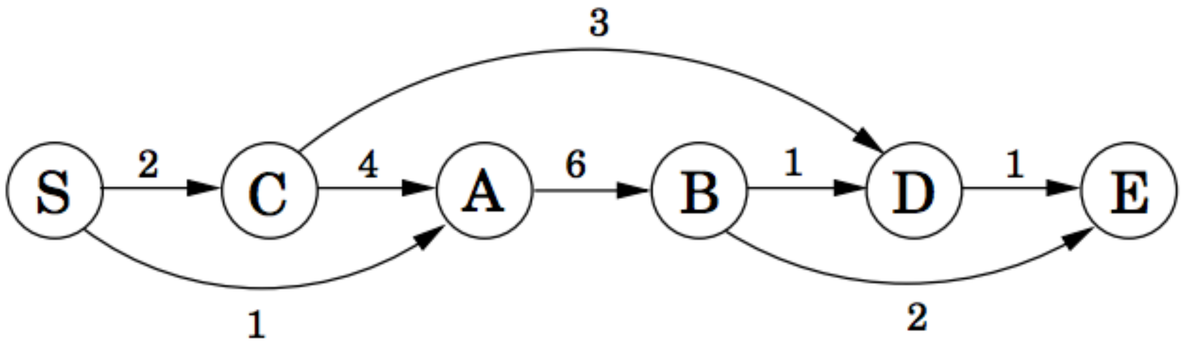
Then, there are 2 ways of getting to A — we choose the shortest.



Dasgupta, Sanjoy, Christos H. Papadimitriou, and Umesh Vazirani. Algorithms. McGraw-Hill, Inc., 2006.

Example 2: Shortest Path in a DAG

In general, d(S,X) is the
minimum value of d(S,Y) + d(Y,X) for all Y that precede X
and are connected by an edge



$$d(S,X) = \min_{Y \mid (Y,X) \in E} \{d(S,Y) + d(Y,X)\}$$

This becomes the DP recurrence for our problem

Dasgupta, Sanjoy, Christos H. Papadimitriou, and Umesh Vazirani. Algorithms. McGraw-Hill, Inc., 2006.

Example 2: Shortest Path in a DAG

The problem is solved efficiently by the following algorithm

initialize all $\text{dist}(\cdot)$ values to ∞
$\text{dist}(s) = 0$
for each $v \in V \backslash \{s\}$, in linearized order:
    $\text{dist}(v) = \min_{(u,v) \in E} \{\text{dist}(u) + l(u, v)\}$

Dasgupta, Sanjoy, Christos H. Papadimitriou, and Umesh Vazirani. Algorithms. McGraw-Hill, Inc., 2006.

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 ($k \neq m$).

*

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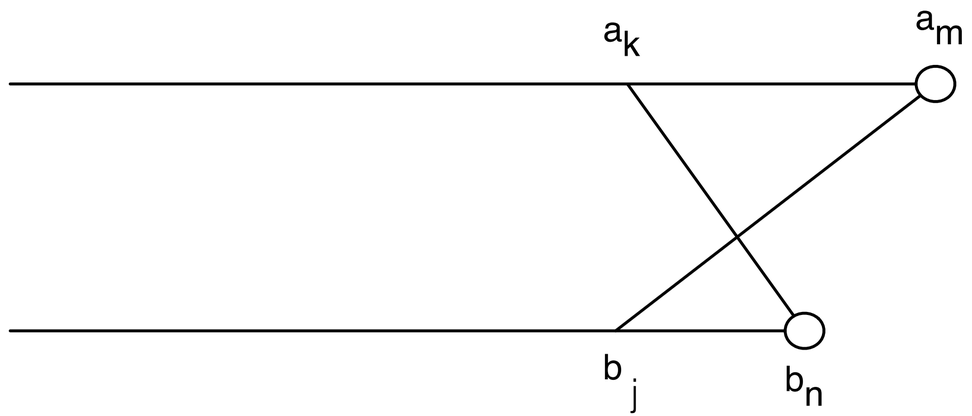
#4 can't happen! Why?

*

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:

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

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

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

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

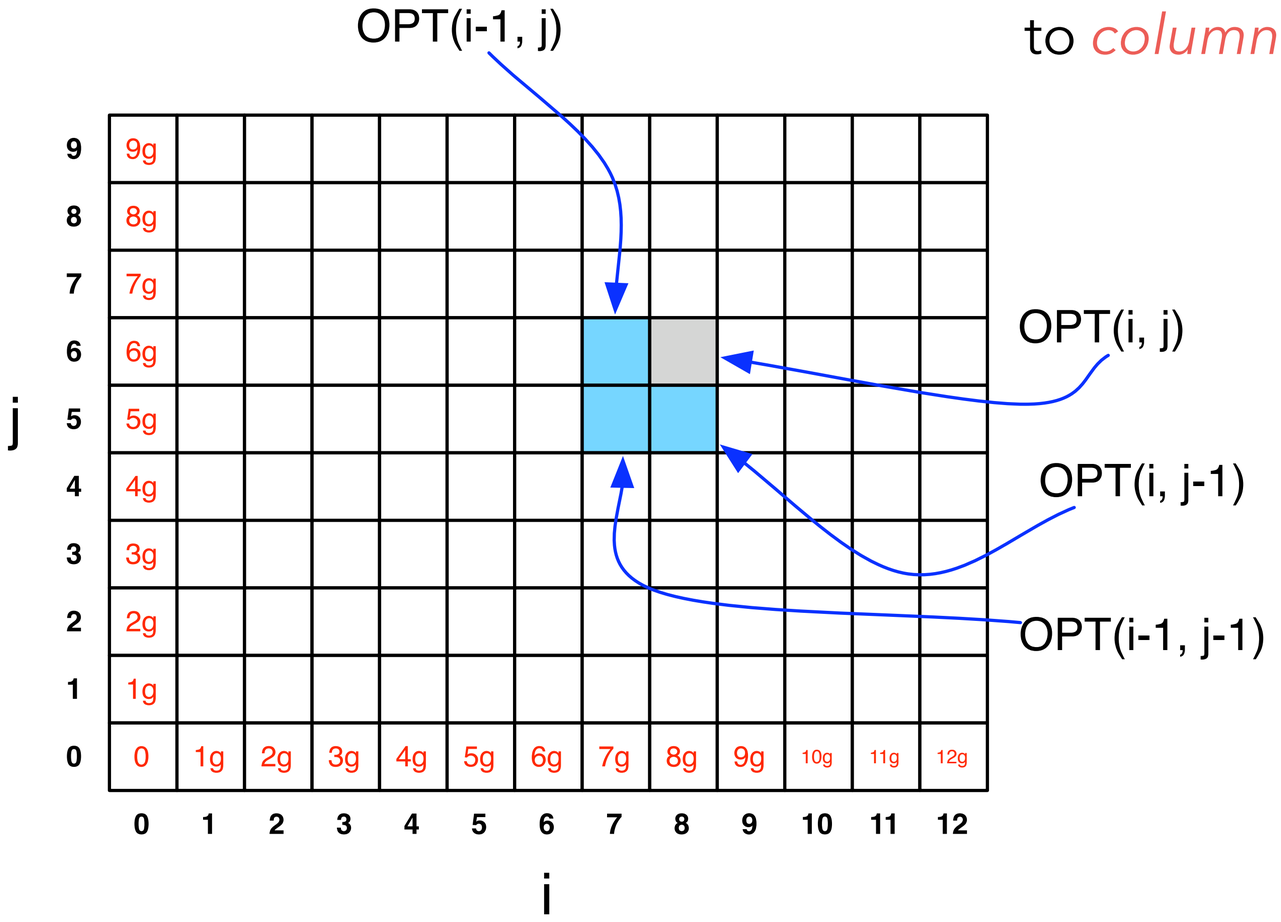
*

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 $OPT(n,m)$.

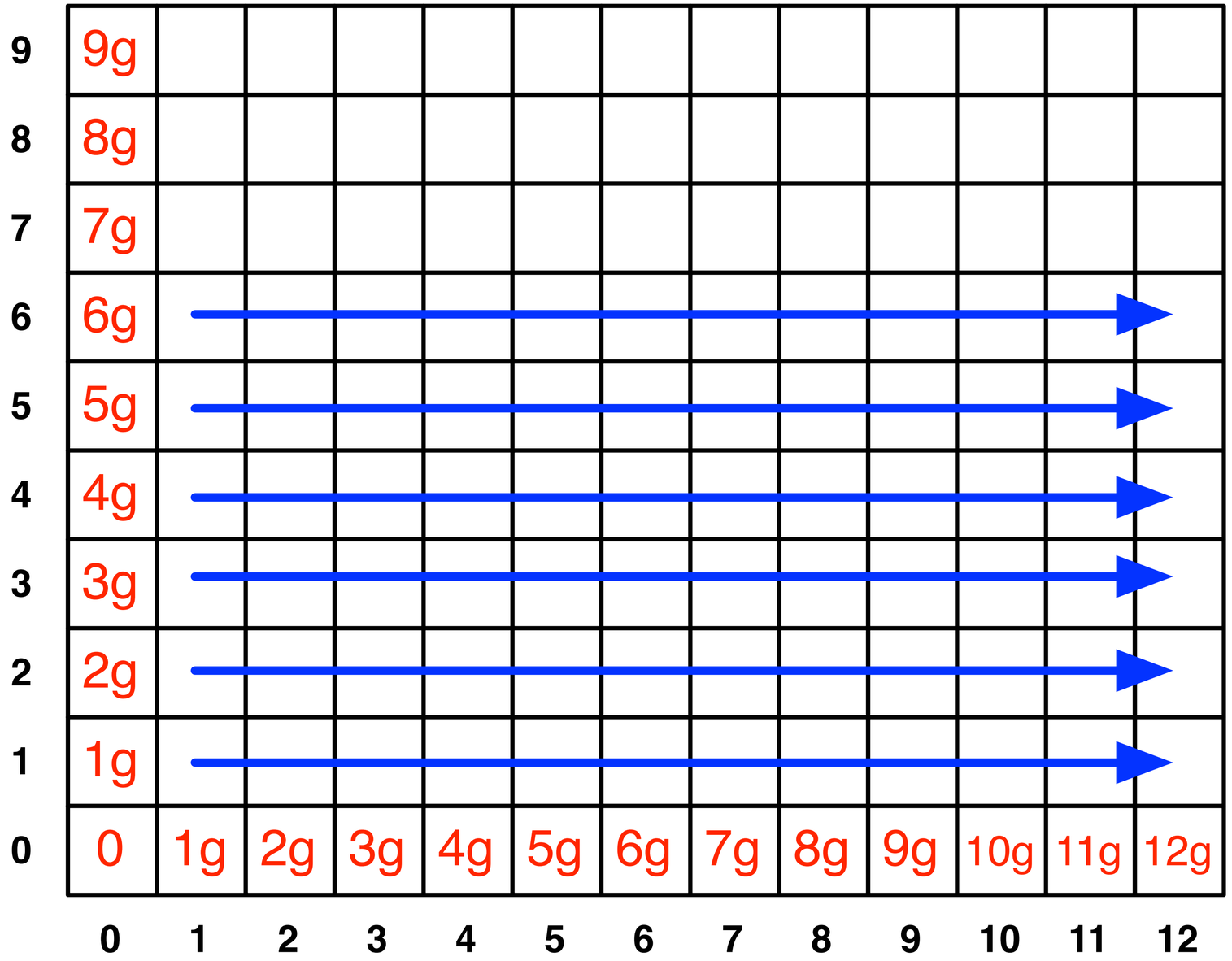
Store those values in a 2D array:

NOTE: observe the non-standard notation here; OPT(**i**,**j**) is referring to *column* i, *row* j of the matrix.



*

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

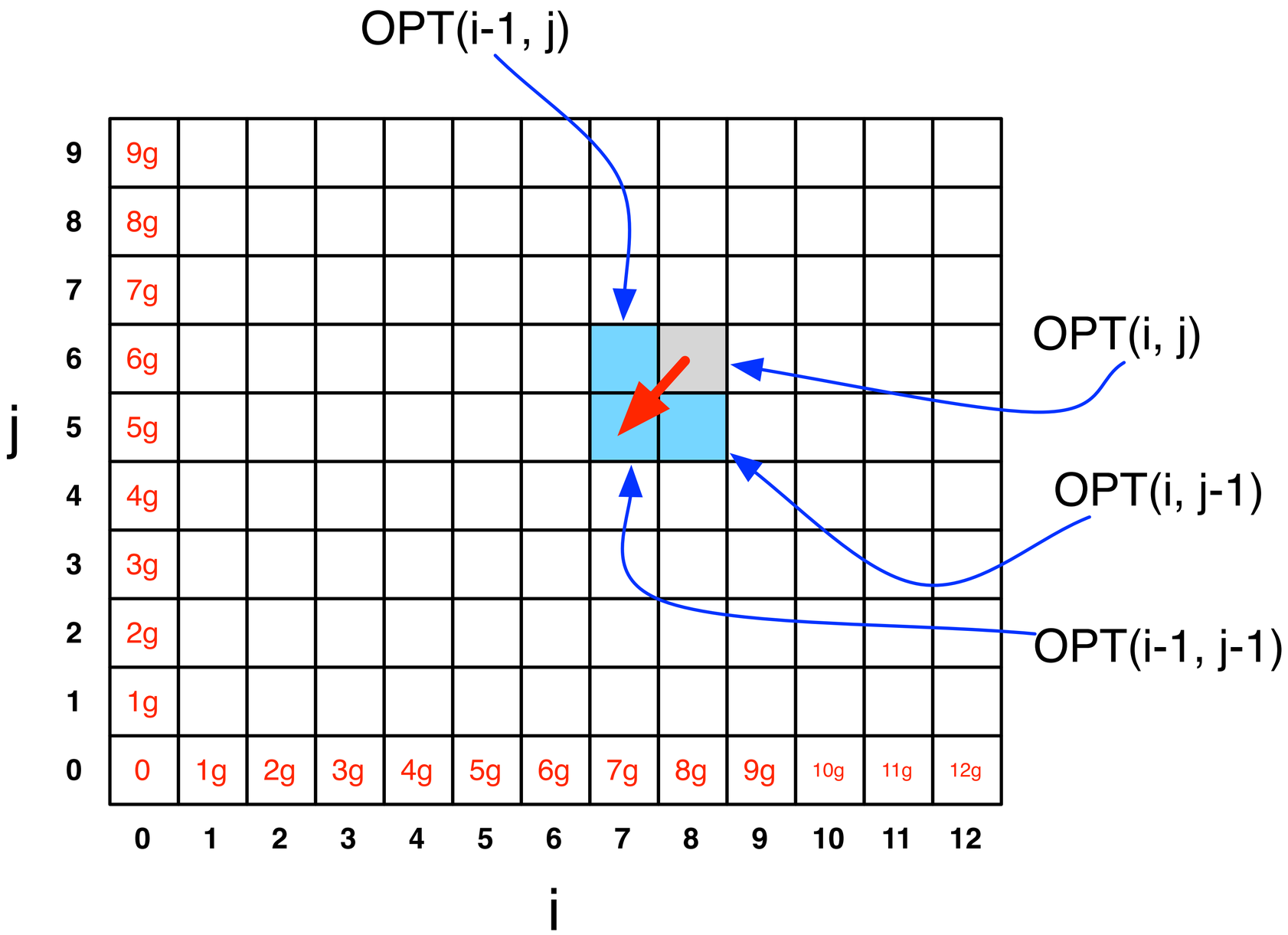
Number of entries in array = O($m \times n$), where m and n are the lengths of the 2 strings.

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

Total running time is O(mn).

*

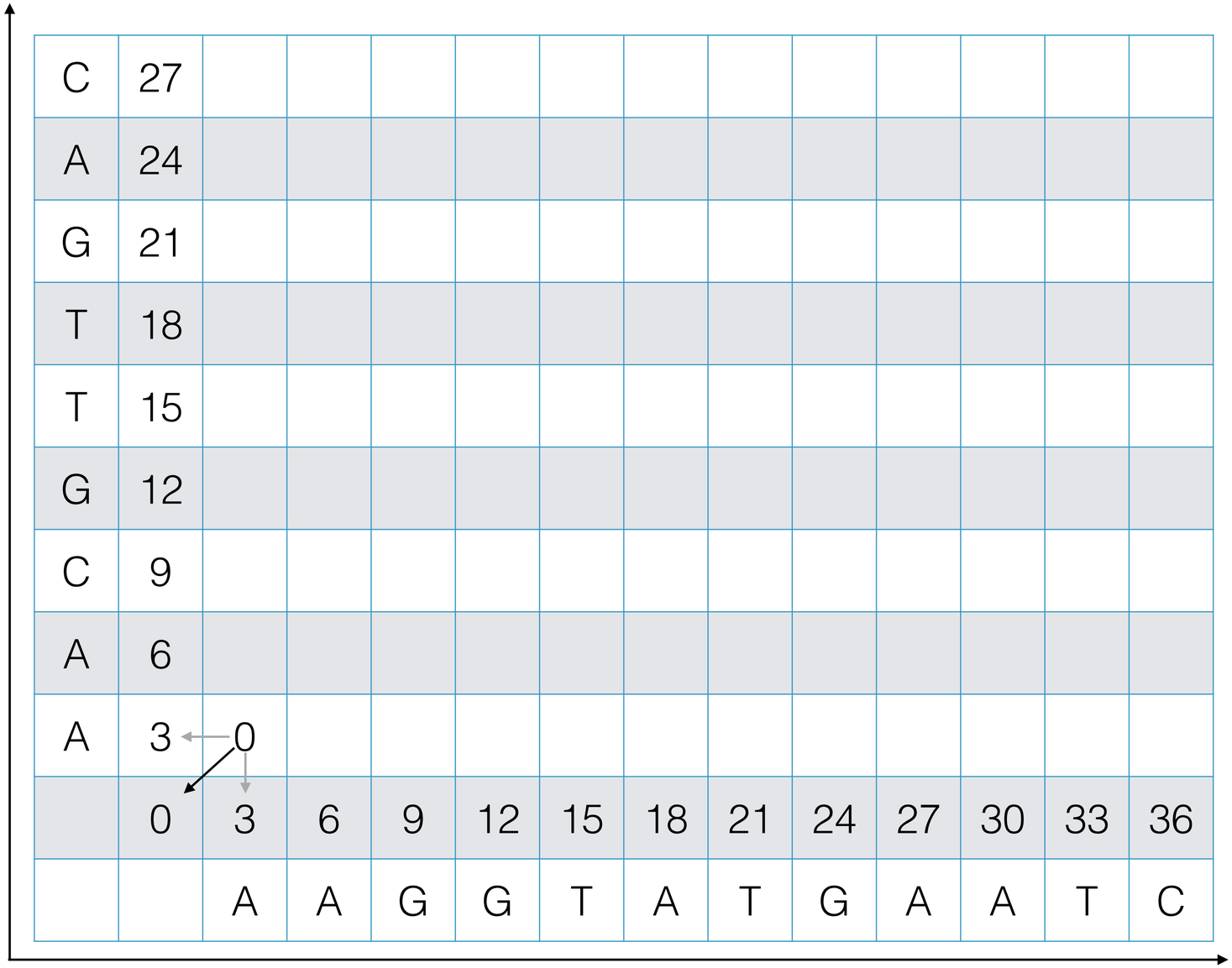
Finding the actual alignment



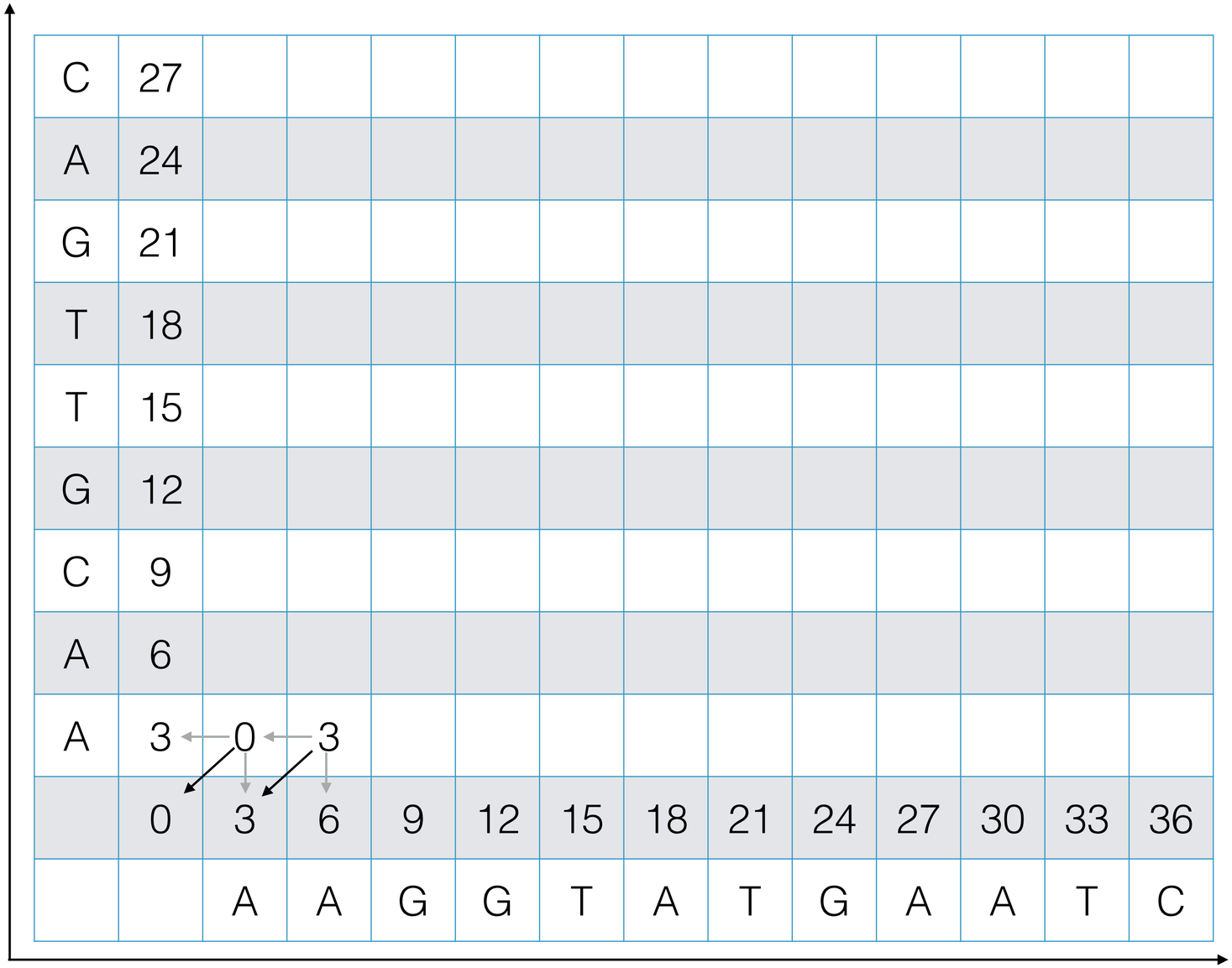
*

gap cost = 3
mismatch cost = 1

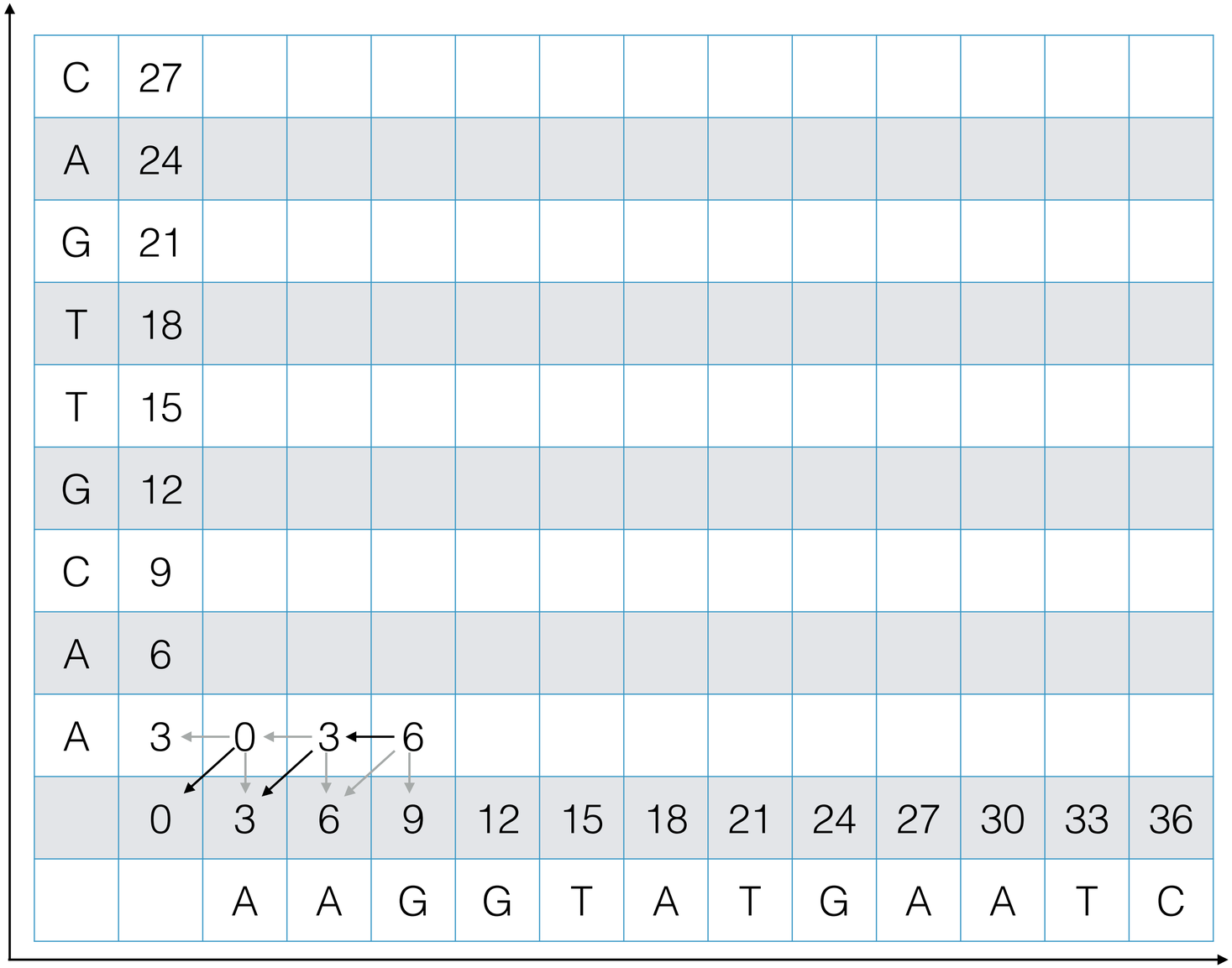
Example



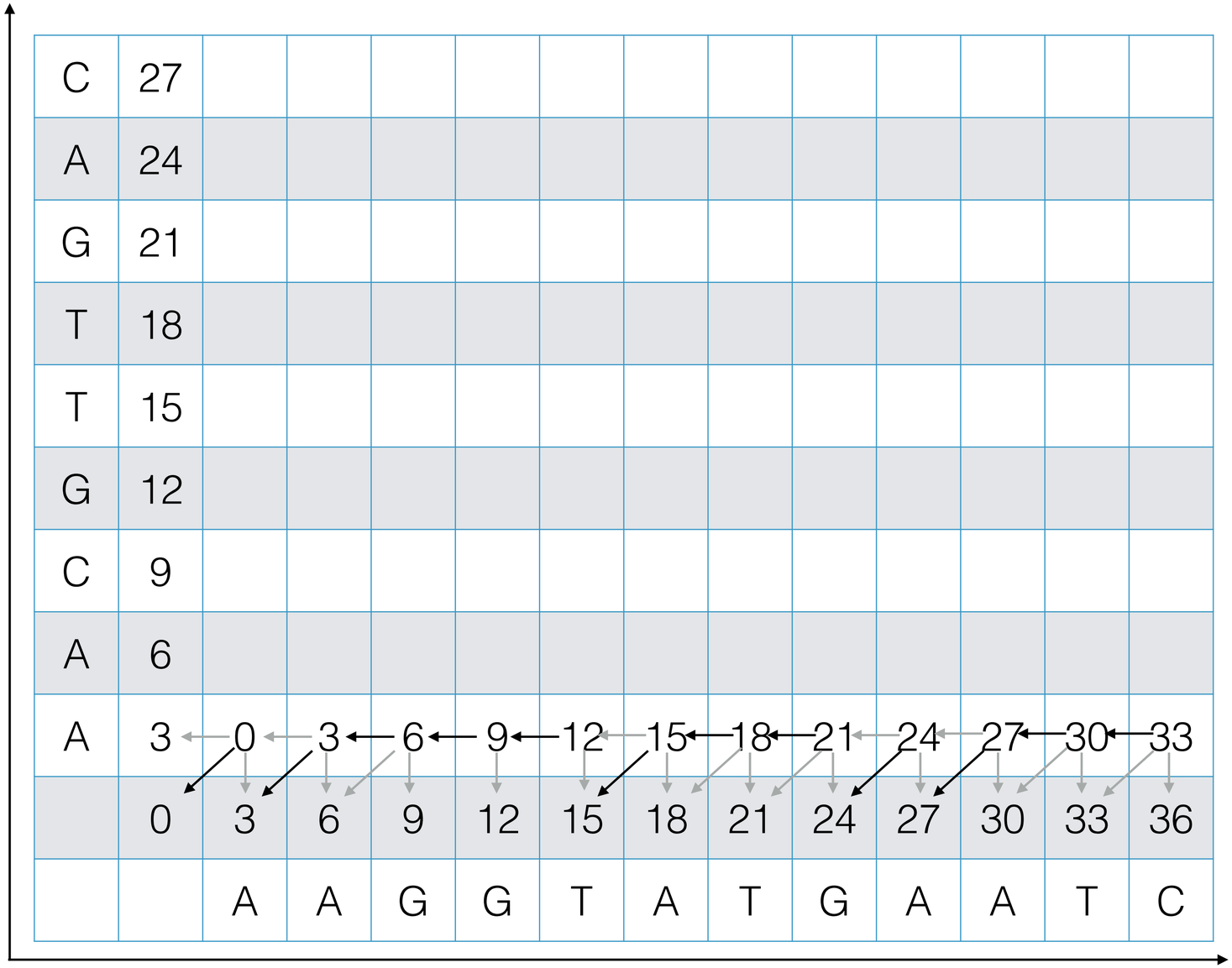
Example


C 27
A 24
G 21
T 18
T 15
G 12
C 9
A 6
A 3 0 3
0 3 6 9 12 15 18 21 24 27 30 33 36
A A G G T A T G A A T C

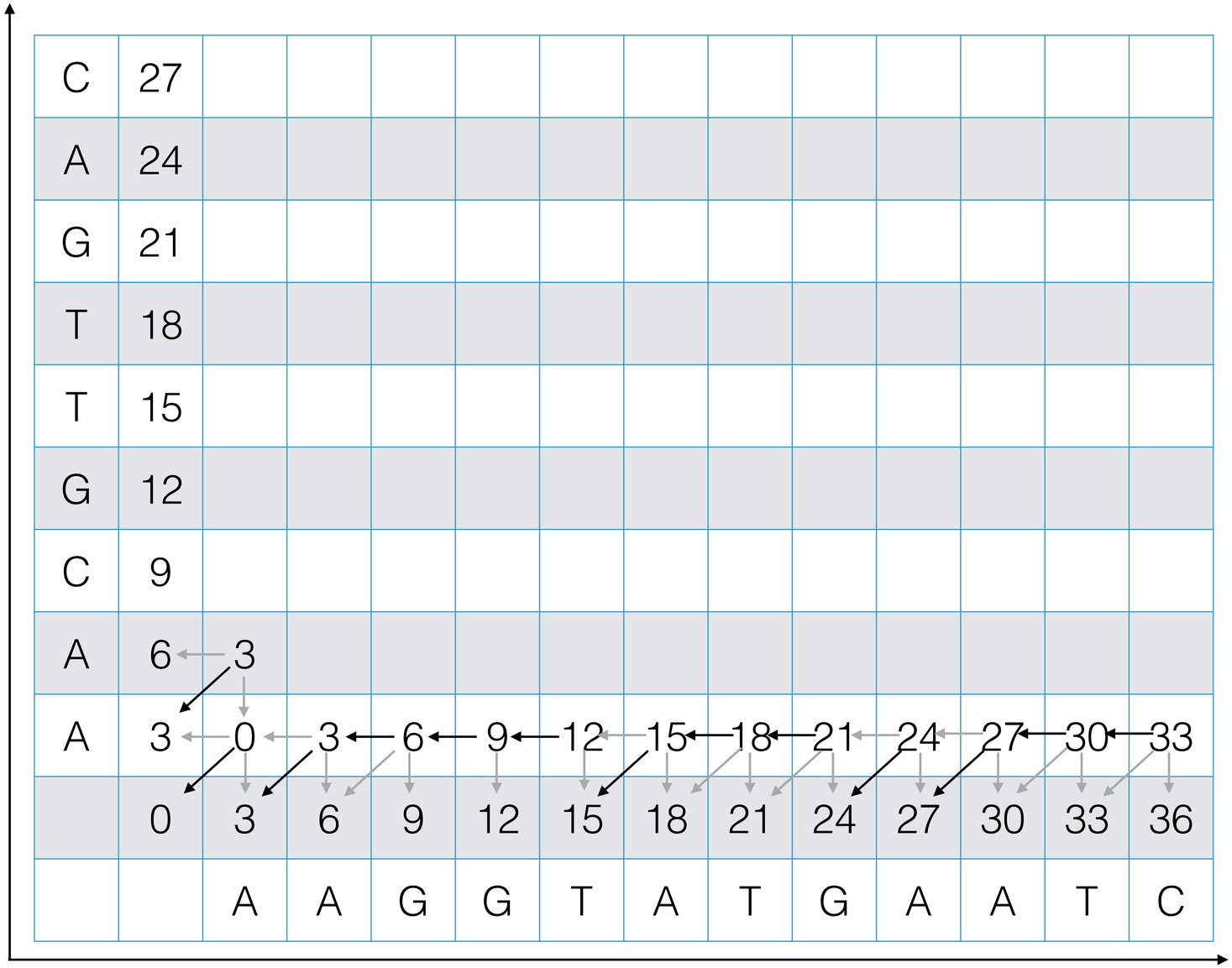
Example


C 27
A 24
G 21
T 18
T 15
G 12
C 9
A 6
A 3 0 3 6
0 3 6 9 12 15 18 21 24 27 30 33 36
A A G G T A T G A A T C

Example


C 27
A 24
G 21
T 18
T 15
G 12
C 9
A 6
A 3 0 3 6 9 12 15 18 21 24 27 30 33
0 3 6 9 12 15 18 21 24 27 30 33 36
A A G G T A T G A A T C

Example


C 27
A 24
G 21
T 18
T 15
G 12
C 9
A 6 3
A 3 0 3 6 9 12 15 18 21 24 27 30 33
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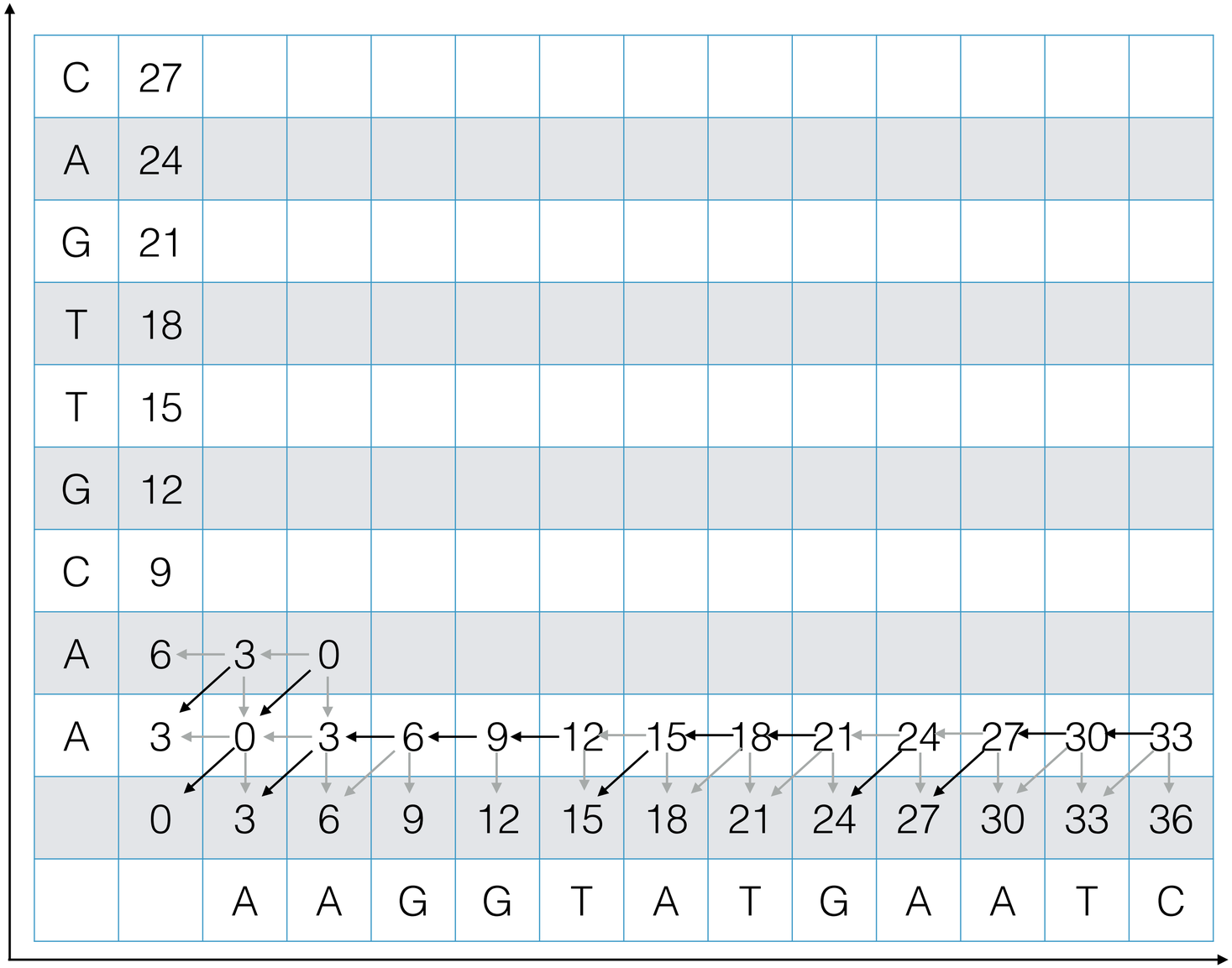
A A G G T A T G A A T C

Example


C 27
A 24
G 21
T 18
T 15
G 12
C 9
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A 3 0 3 6 9 12 15 18 21 24 27 30 33
0 3 6 9 12 15 18 21 24 27 30 33 36
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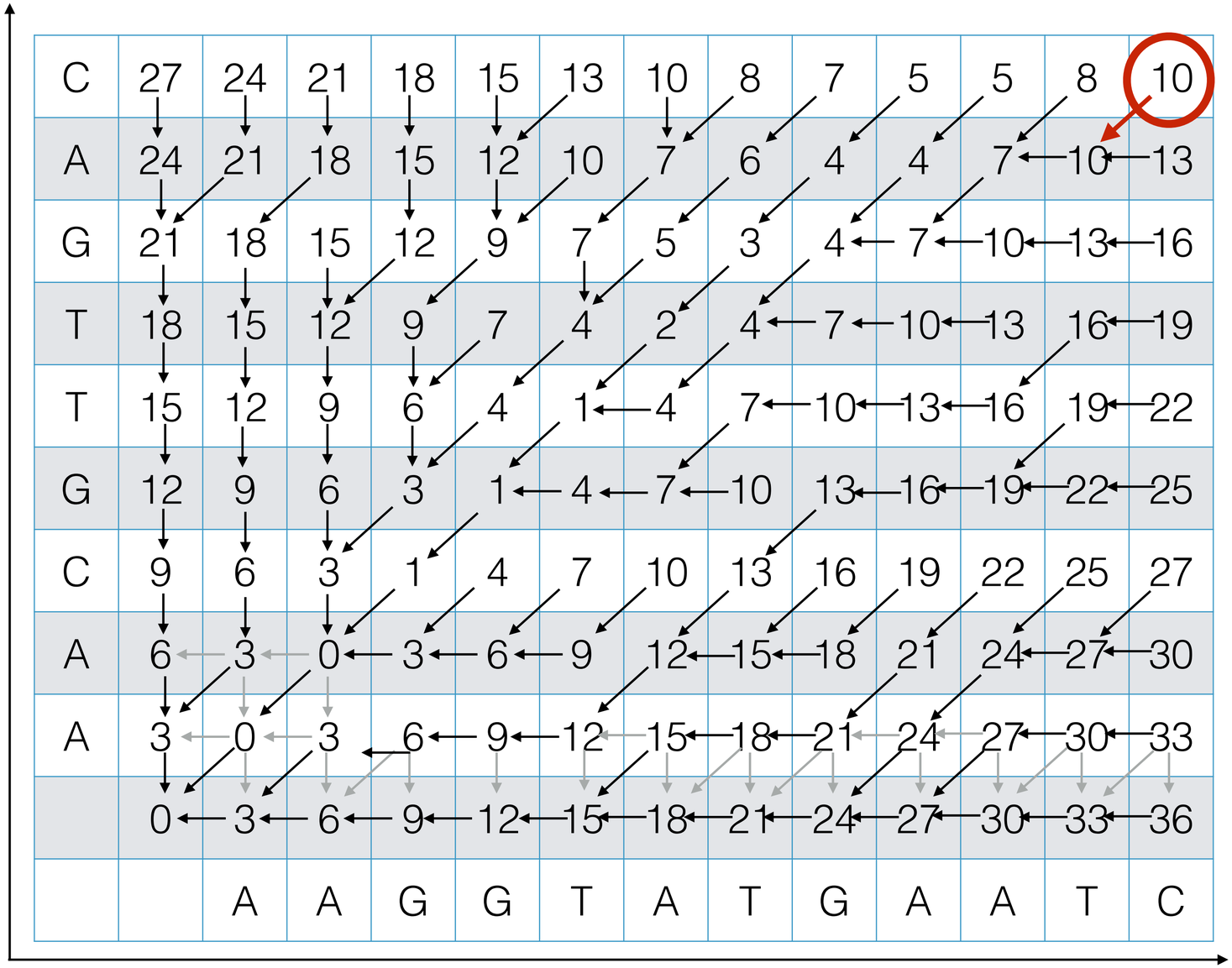
Example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A 24 21 18 15 12 10 7 6 4 4 7 10 13
G 21 18 15 12 9 7 5 3 4 7 10 13 16
T 18 15 12 9 7 4 2 4 7 10 13 16 19
T 15 12 9 6 4 1 4 7 10 13 16 19 22
G 12 9 6 3 1 4 7 10 13 16 19 22 25
C 9 6 3 1 4 7 10 13 16 19 22 25 27
A 6 3 0 3 6 9 12 15 18 21 24 27 30
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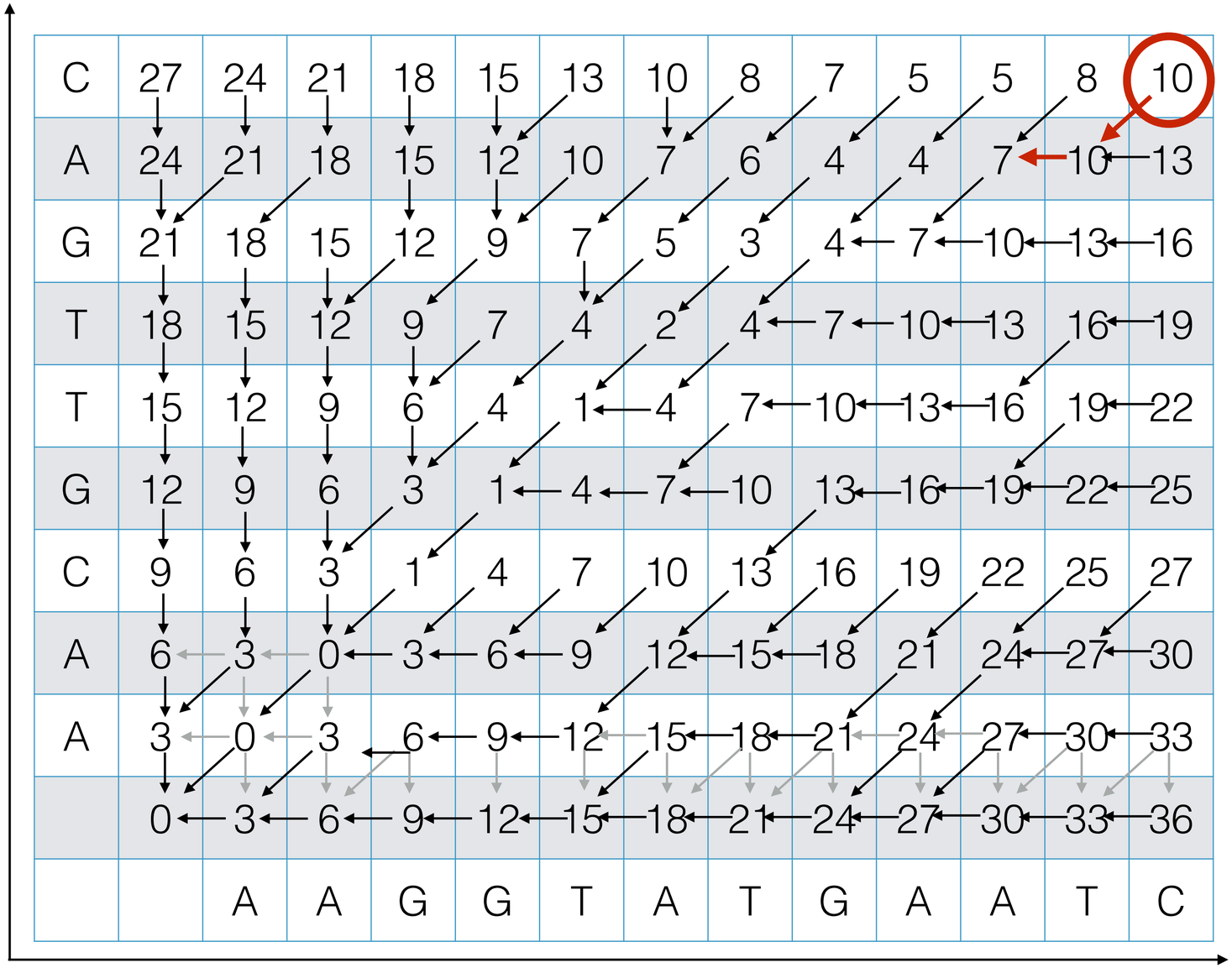
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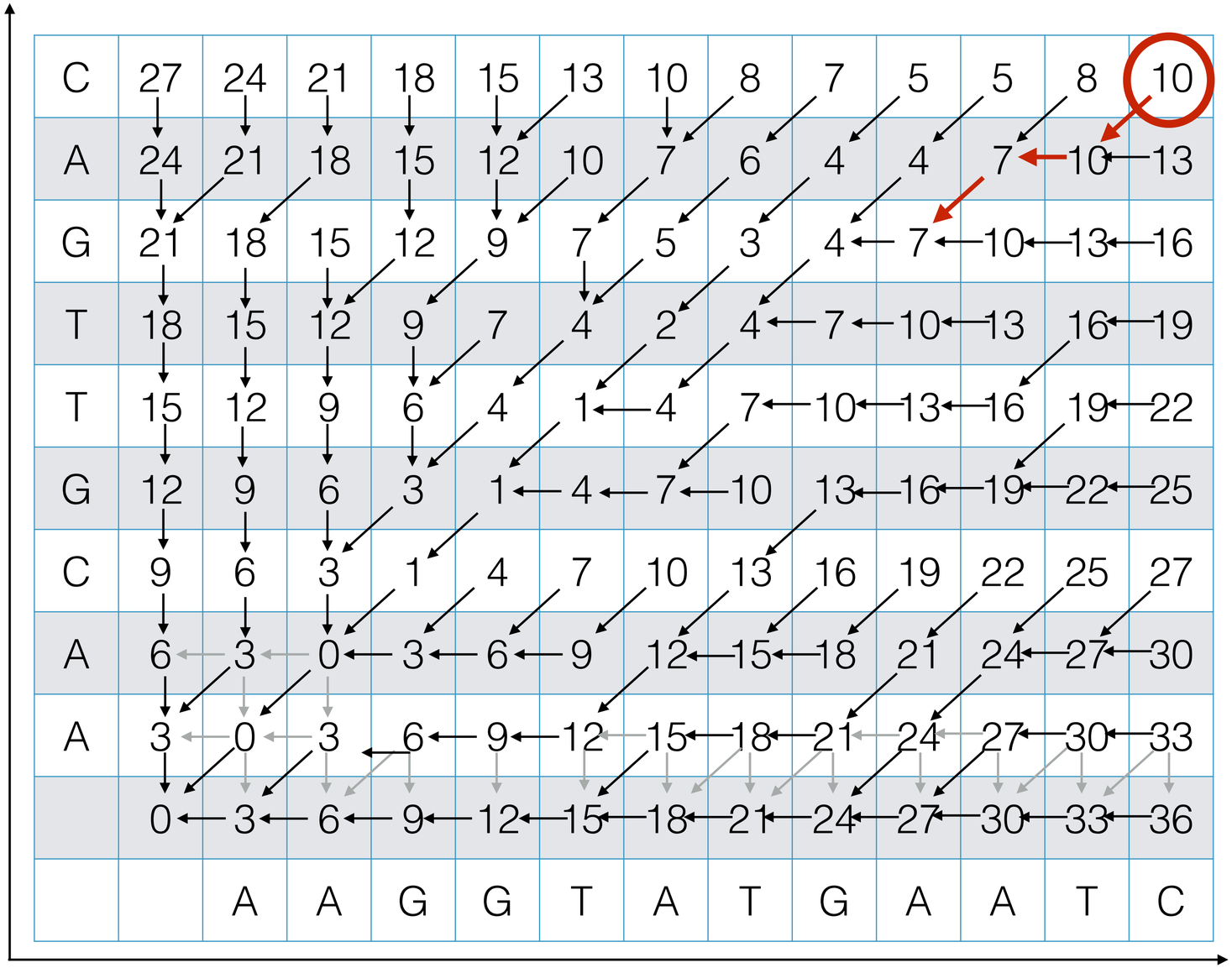
C 27 24 21 18 15 13 10 8 7 5 5 8 10
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G 21 18 15 12 9 7 5 3 4 7 10 13 16
T 18 15 12 9 7 4 2 4 7 10 13 16 19
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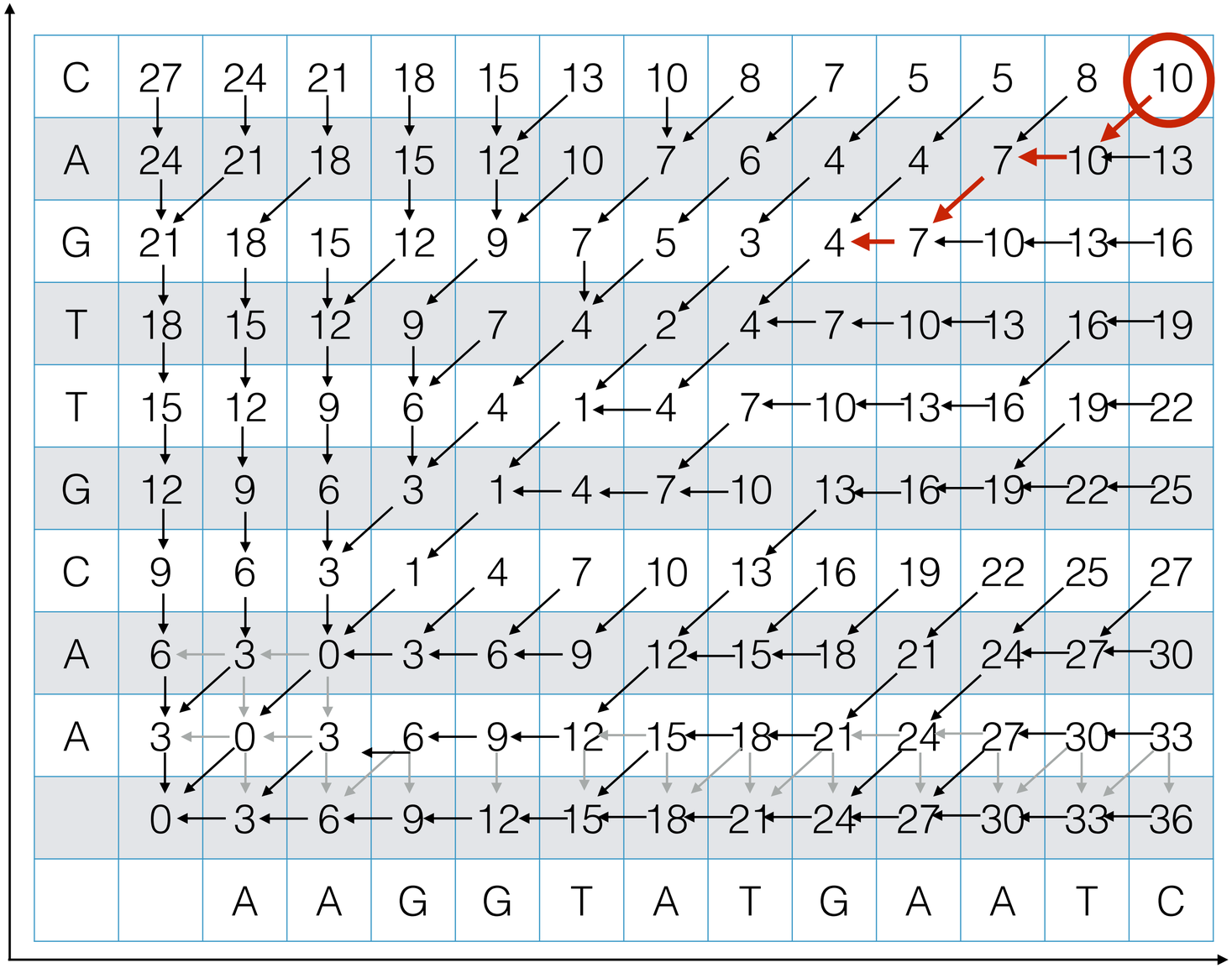
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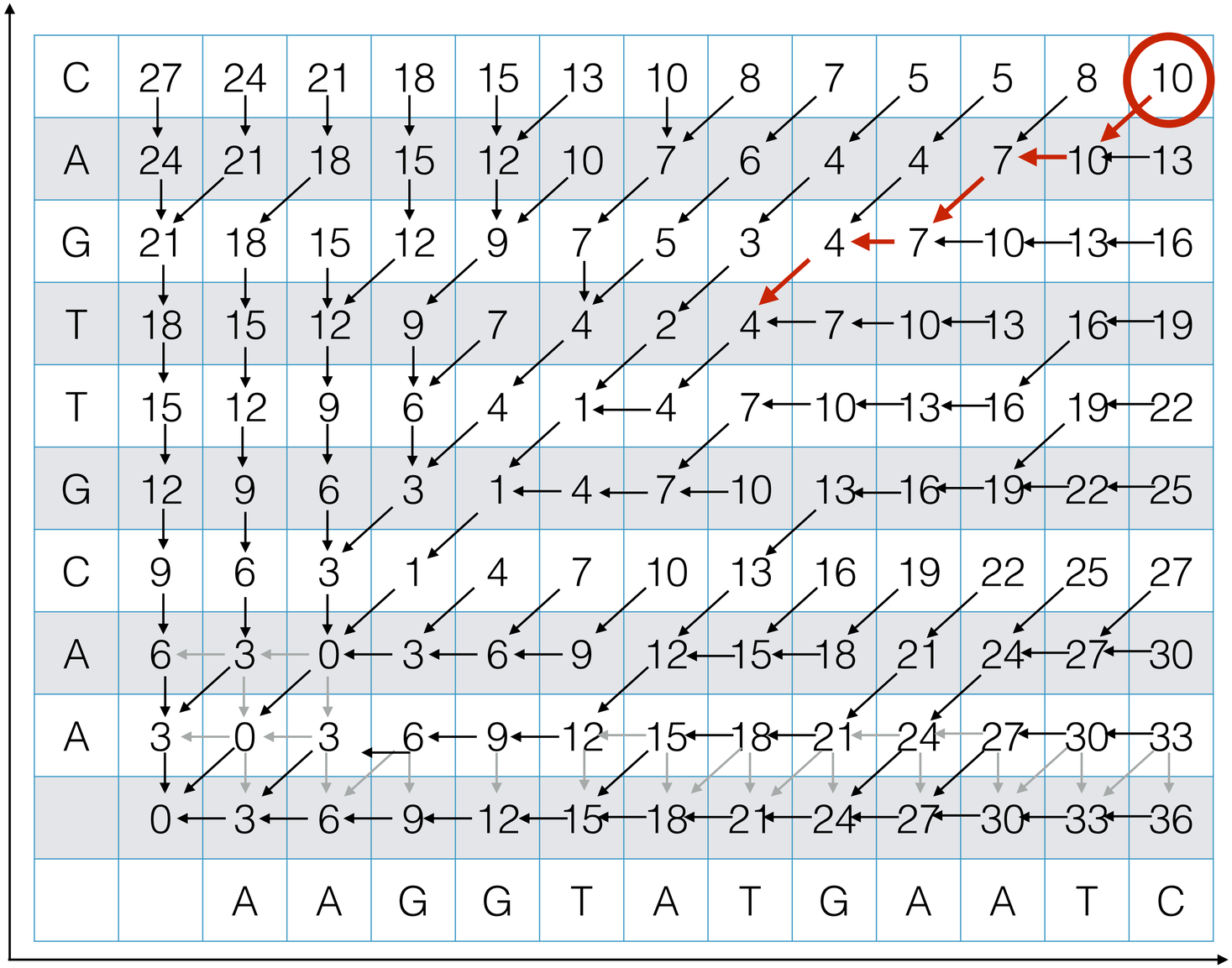
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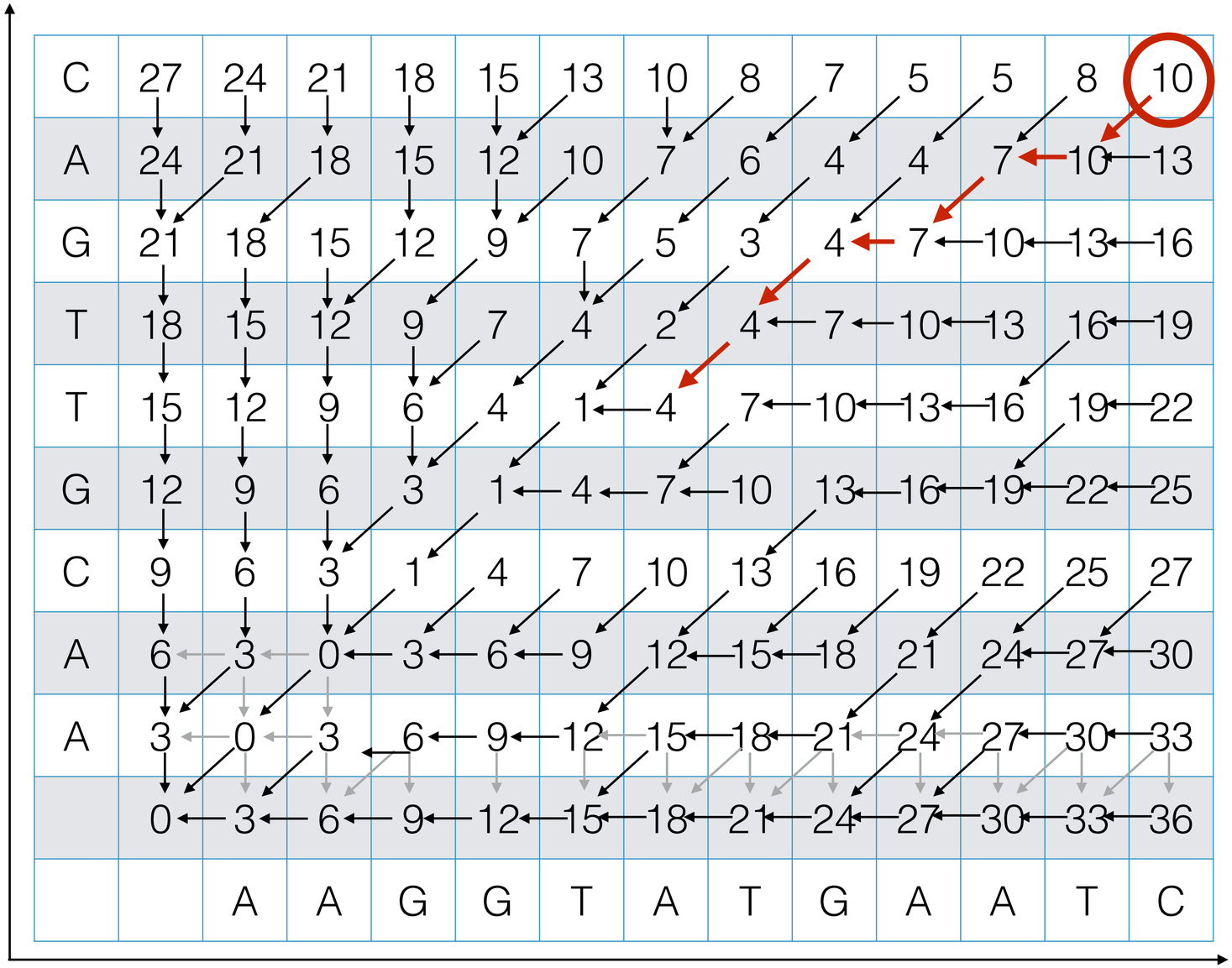
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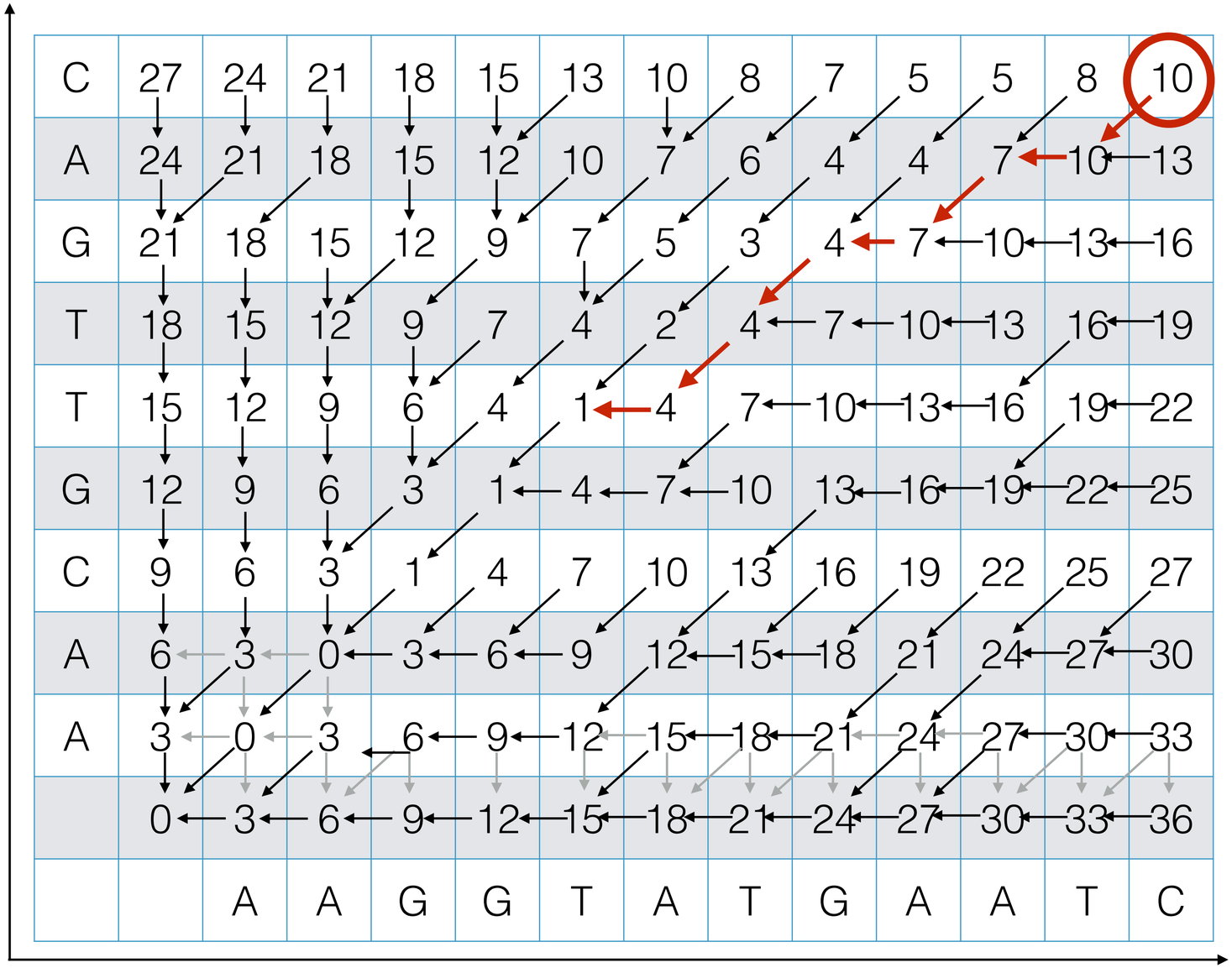
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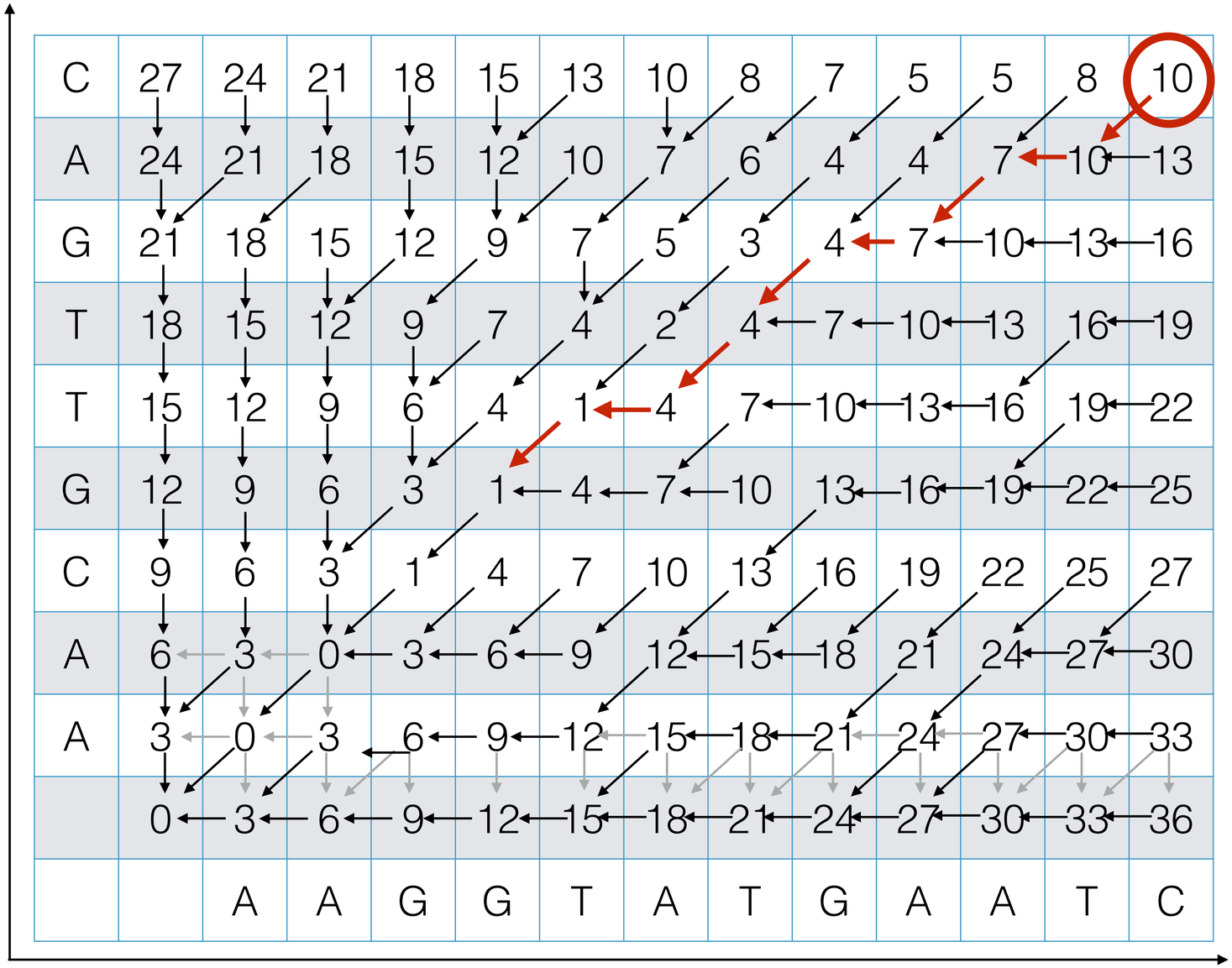
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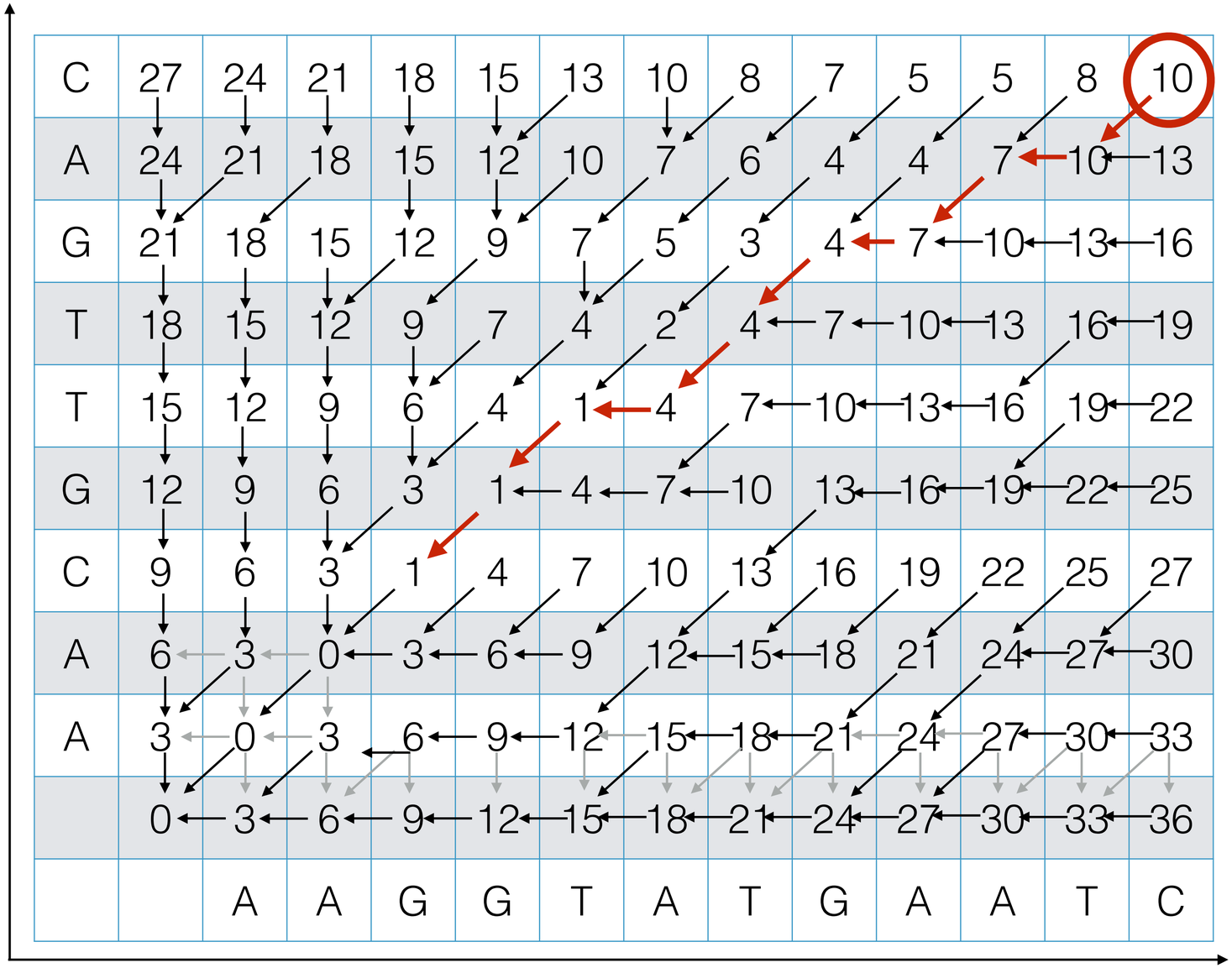
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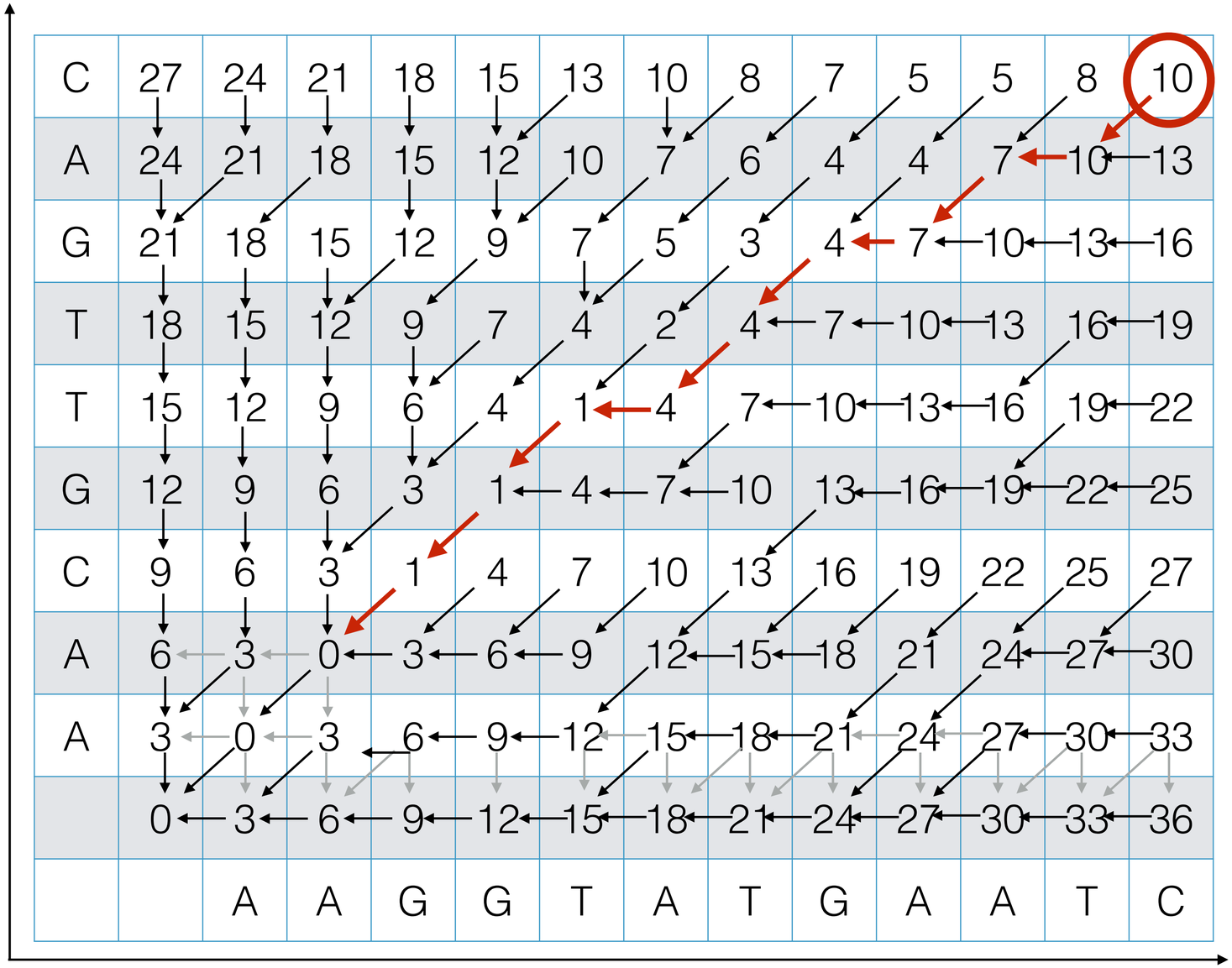
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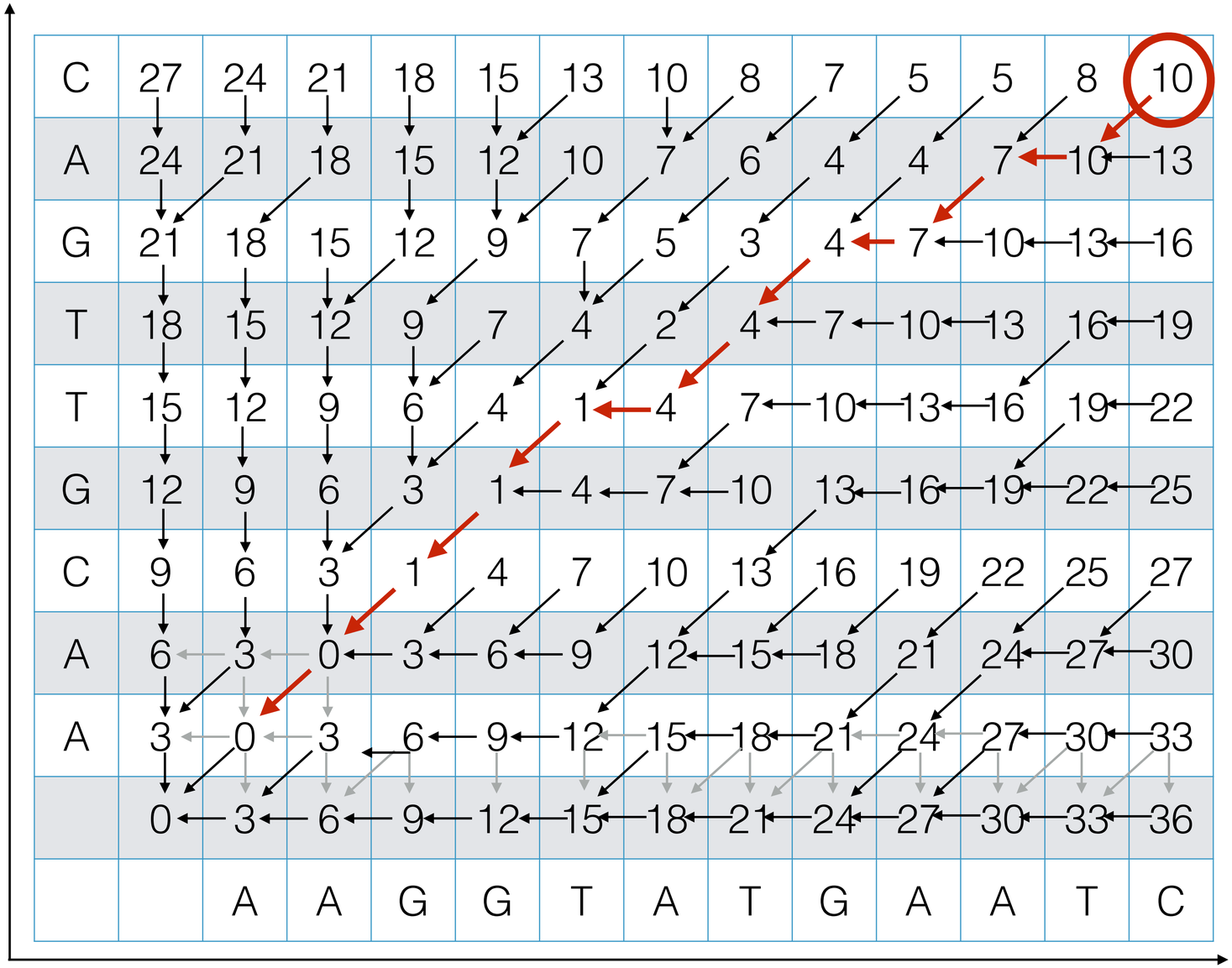
Example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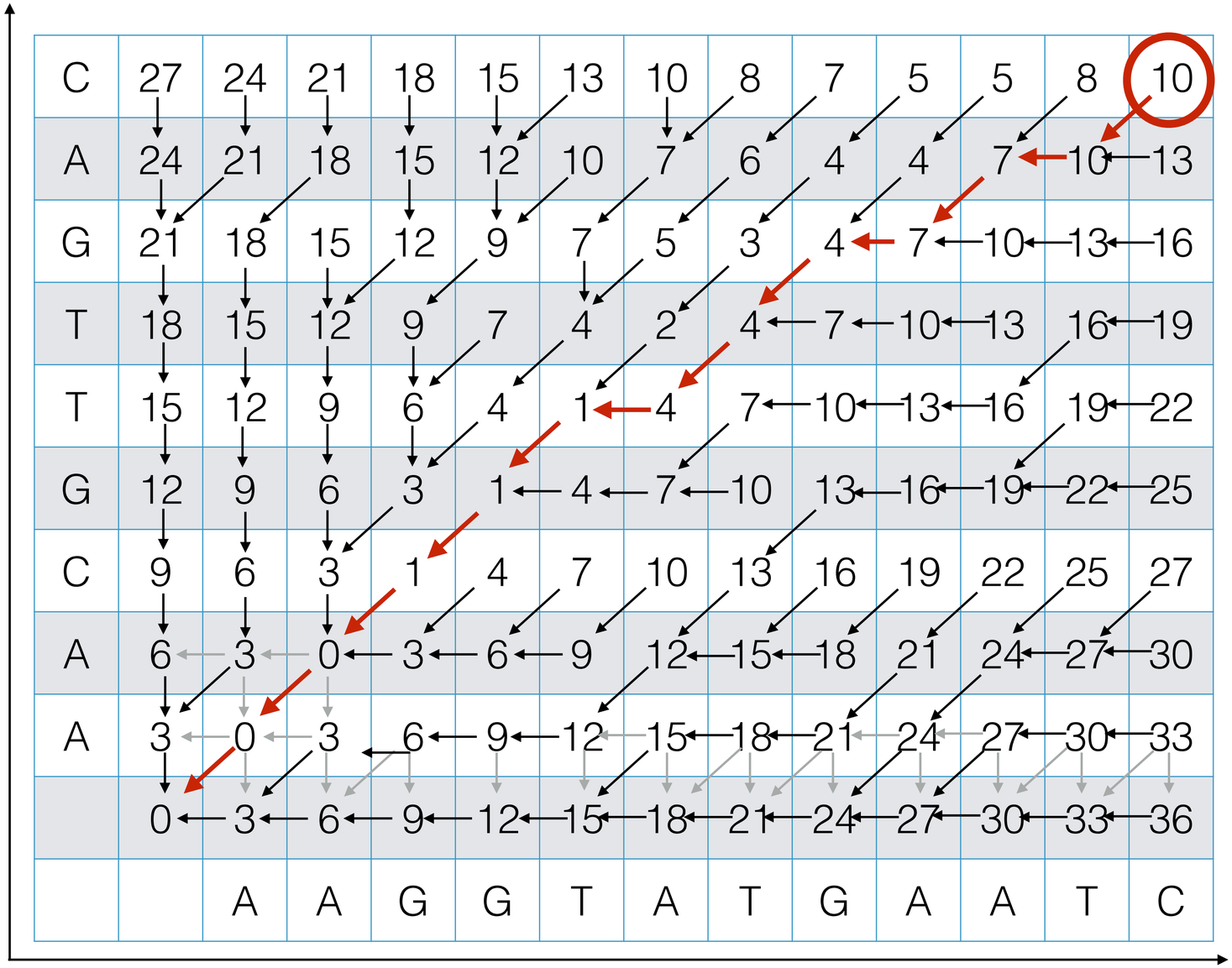
A 24 21 18 15 12 10 7 6 4 4 7 10 13
G 21 18 15 12 9 7 5 3 4 7 10 13 16
T 18 15 12 9 7 4 2 4 7 10 13 16 19
T 15 12 9 6 4 1 4 7 10 13 16 19 22
G 12 9 6 3 1 4 7 10 13 16 19 22 25
C 9 6 3 1 4 7 10 13 16 19 22 25 27
A 6 3 0 3 6 9 12 15 18 21 24 27 30
A 3 0 3 6 9 12 15 18 21 24 27 30 33
0 3 6 9 12 15 18 21 24 27 30 33 36
A A G G T A T G A A T C

Example


C 27 24 21 18 15 13 10 8 7 5 5 8 10
A 24 21 18 15 12 10 7 6 4 4 7 10 13
G 21 18 15 12 9 7 5 3 4 7 10 13 16
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A 6 3 0 3 6 9 12 15 18 21 24 27 30
A 3 0 3 6 9 12 15 18 21 24 27 30 33
0 3 6 9 12 15 18 21 24 27 30 33 36
A A G G T A T G A A T C

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.

*

Recap: Dynamic Programming

The previous 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.

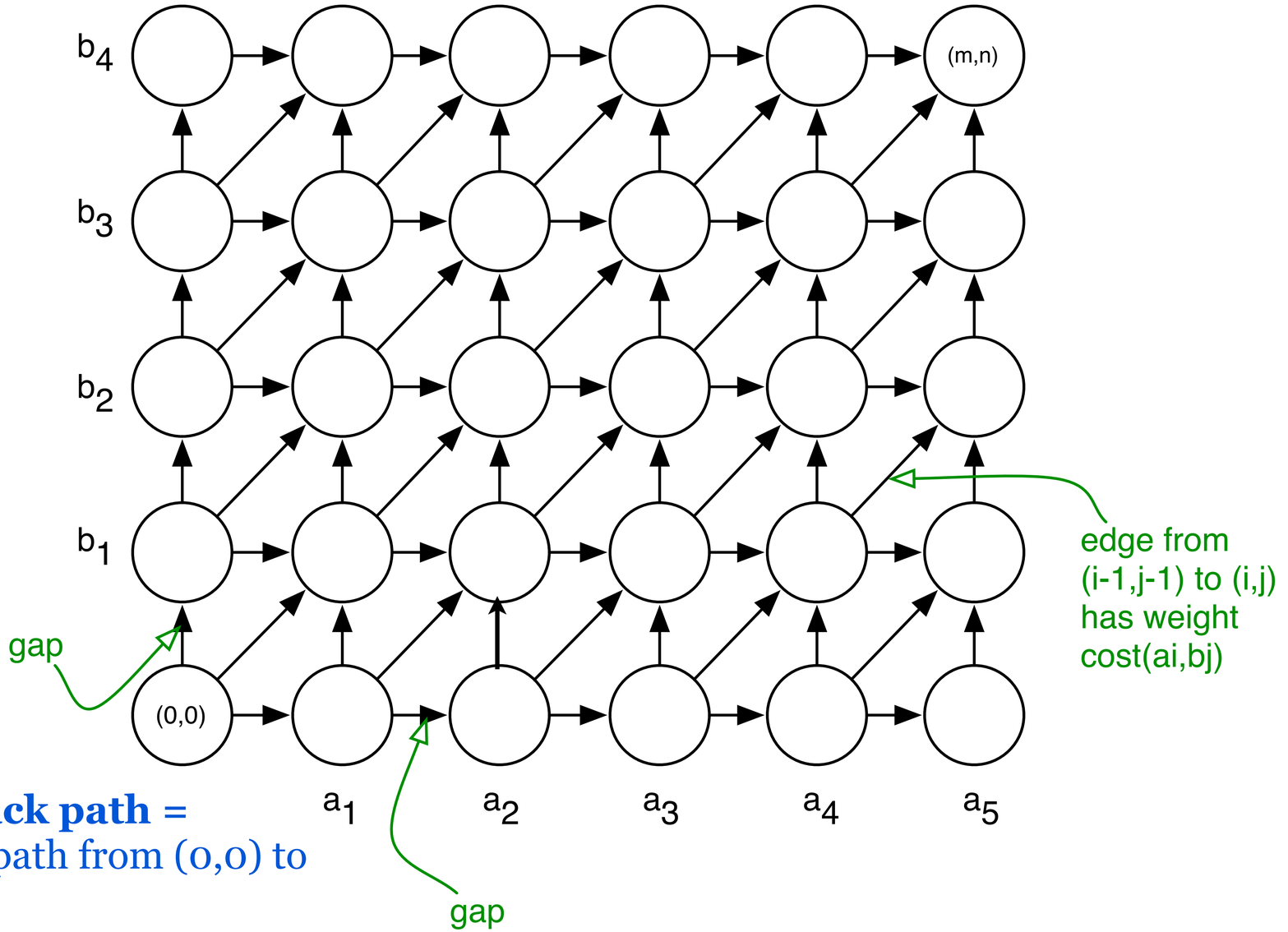
Requirements for DP to apply:

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.

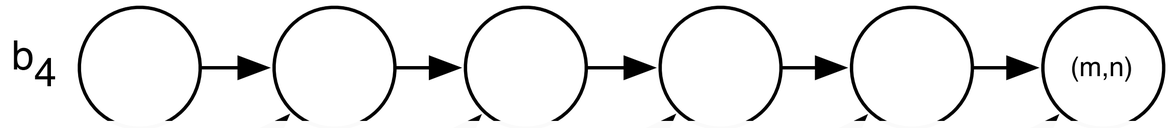
Another View: Recasting as a Graph



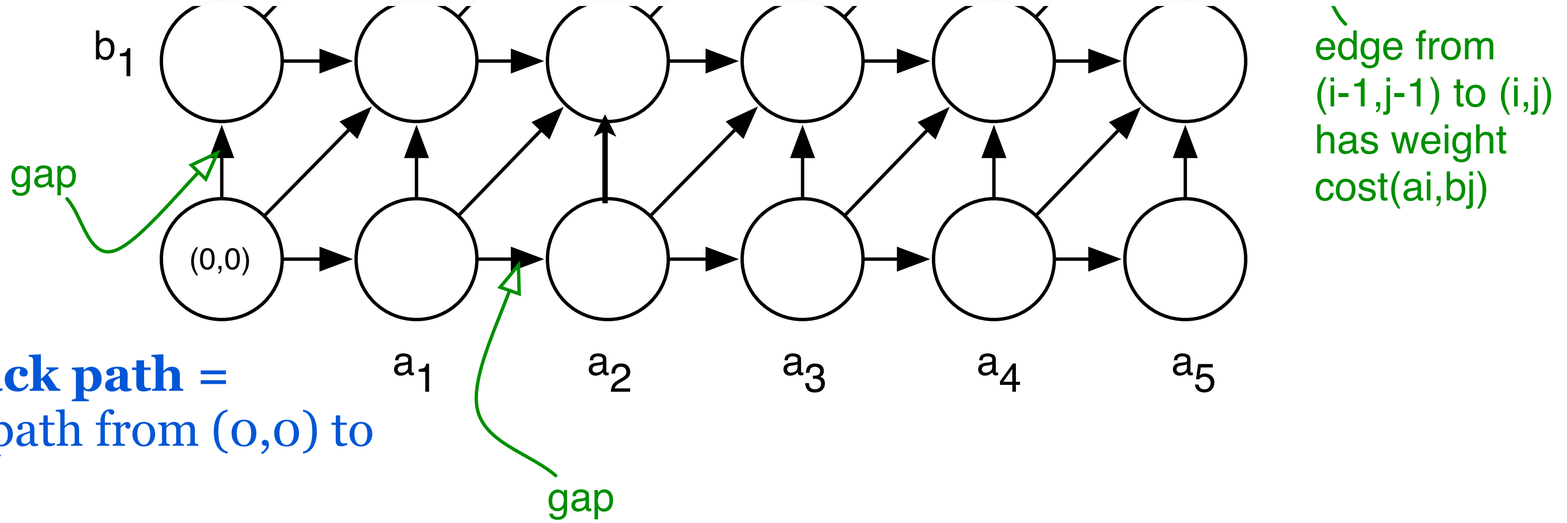
Traceback path =
shortest path from (0,0) to (m,n)

*

Another View: Recasting as a Graph



How would you find a shortest path in this graph *efficiently?*



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

*