Space-Efficient Alignment

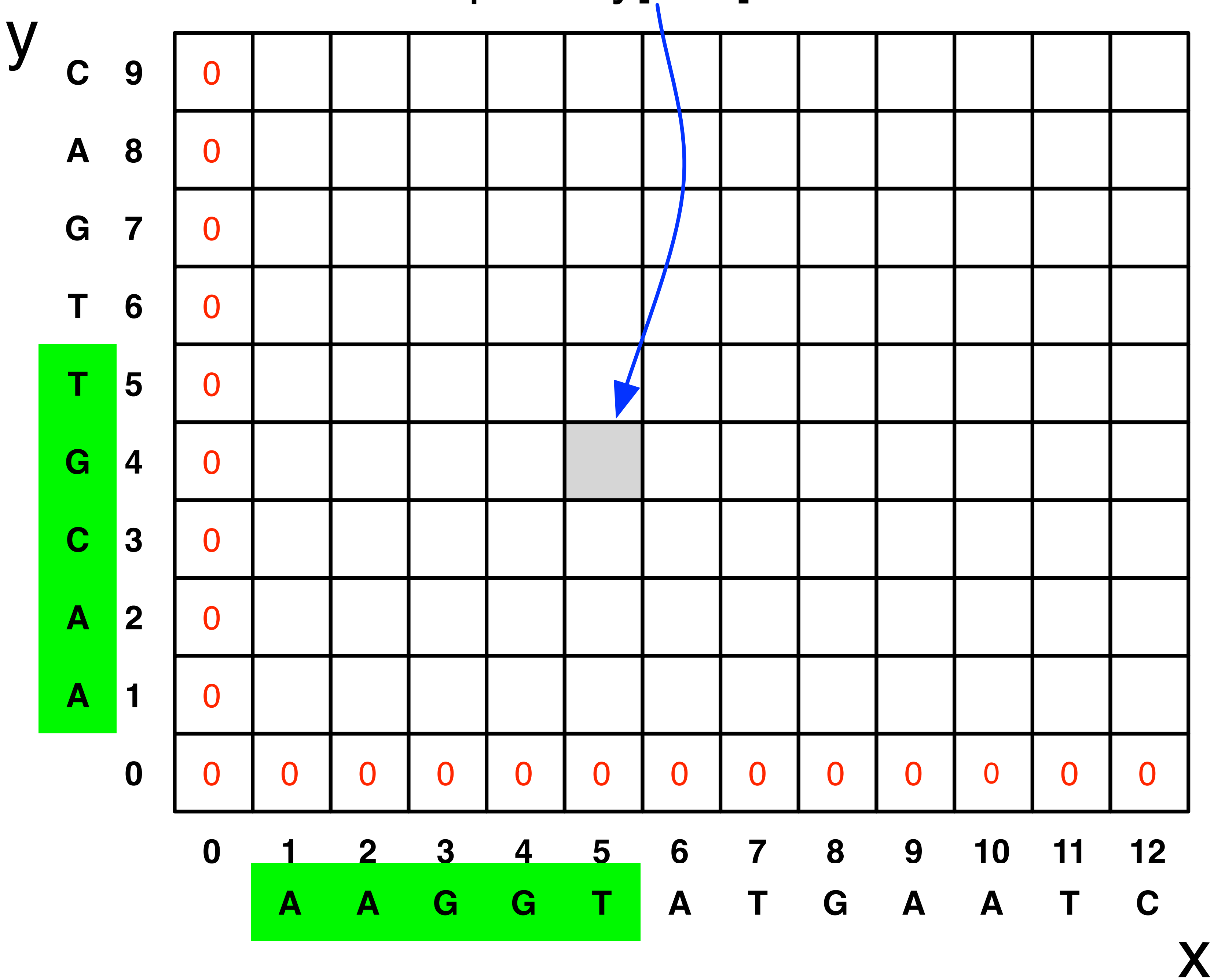
CMSC 858S

Space Usage

- $O(n^2)$ is pretty low space usage, but for a 10 Gb genome, you'd need a huge amount of memory.
- Can we use less?
    - Hirschberg's algorithm

Remember the meaning of a cell

Best alignment
between prefix x[1..5]
and prefix y[1..5]



Linear Space for Alignment **Scores**

- If you are only interested in the **cost** or **score** of an alignment, you need to use only O(n) space.
- How?

Linear Space for Alignment **Scores**

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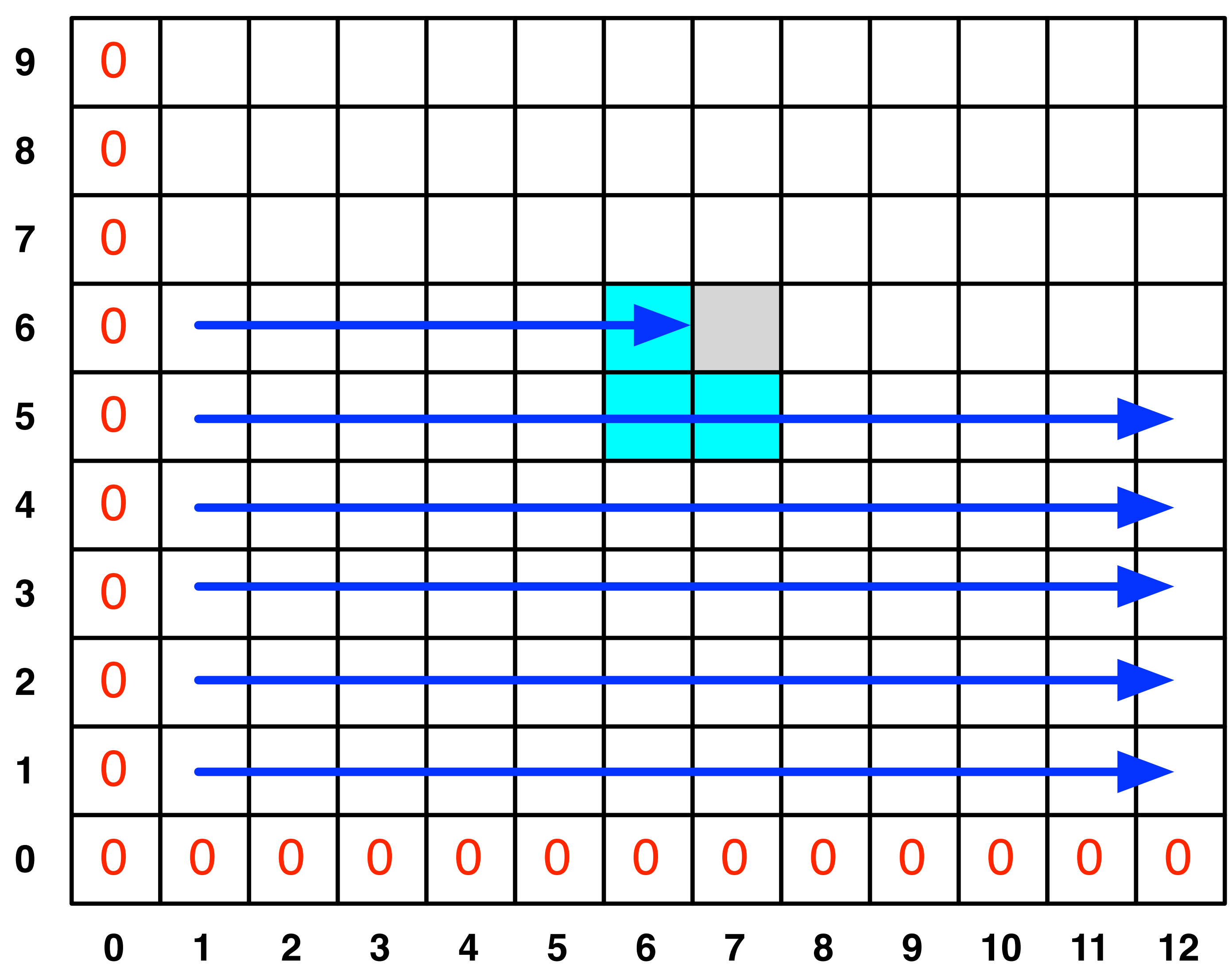
- How?



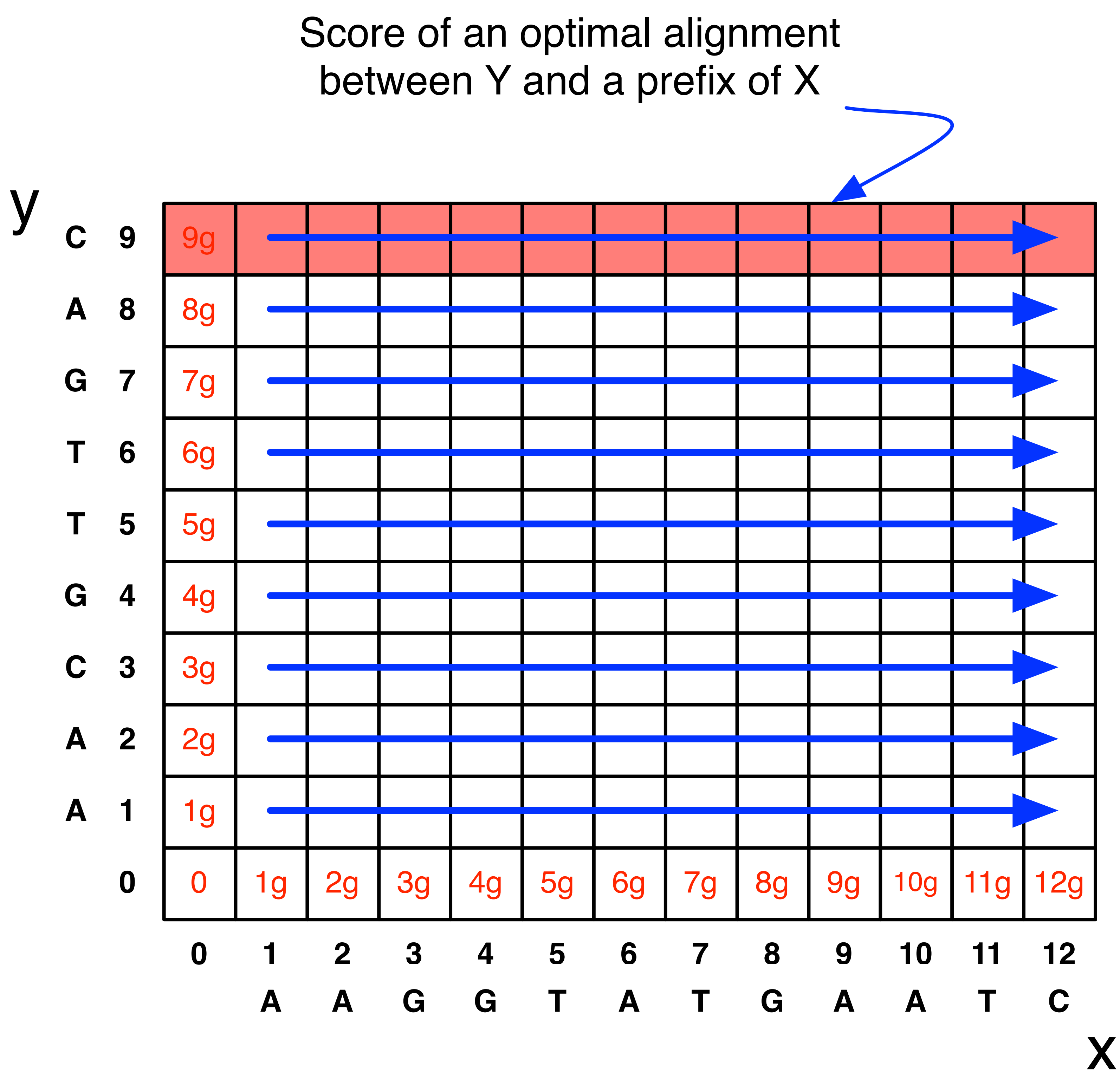
When filling in an entry (gray box) we only look at the current and previous rows.

Only need to keep those two rows in memory.

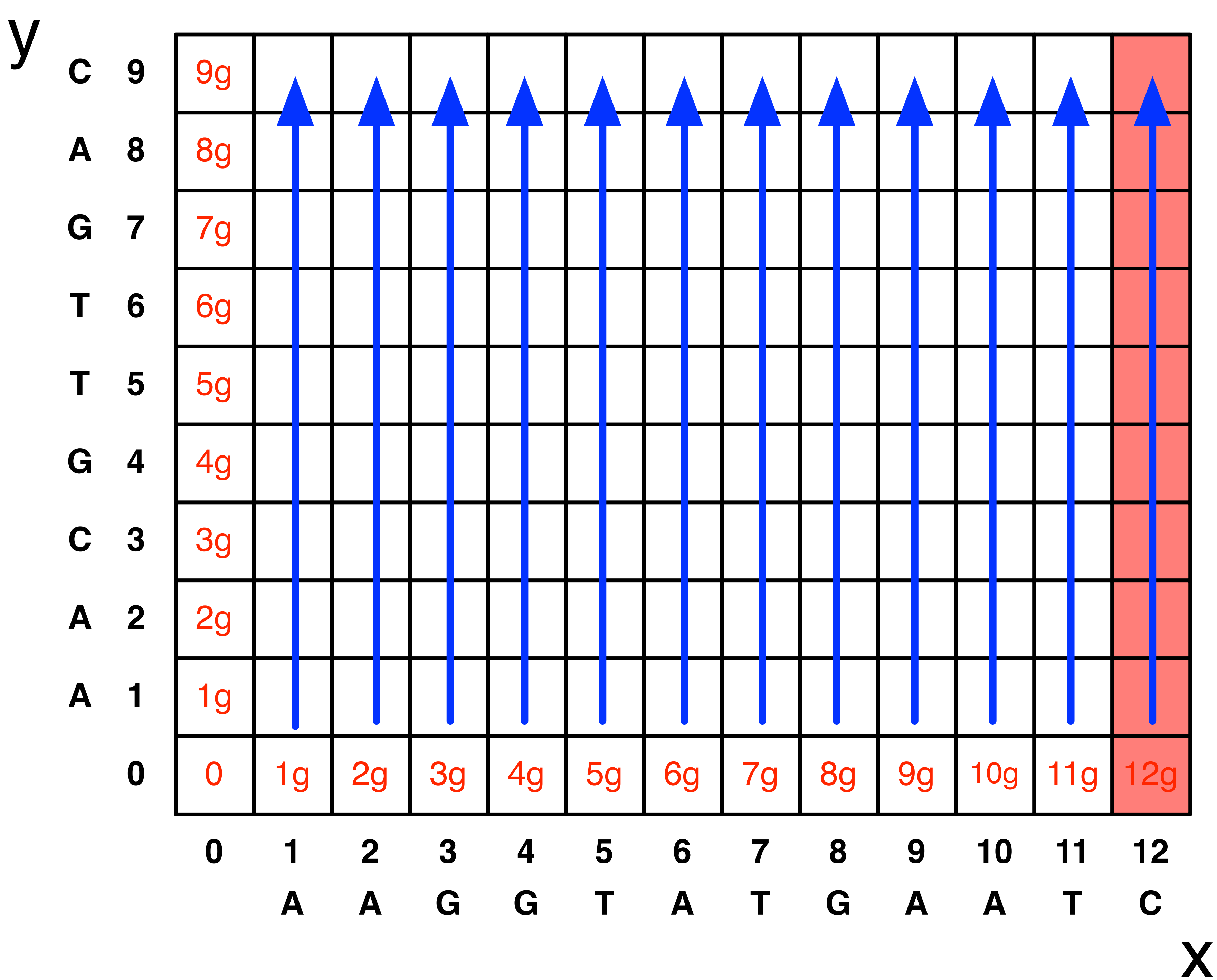
We can do more...

- Given 2 strings X and Y, we can, in linear space and O(nm) time, compute the **cost** of aligning...
  - every prefix of X with Y
  - X with every prefix of Y
  - a particular prefix of X with every prefix of Y
  - a particular suffix of X with every suffix of Y
- How can we do that?

Best Alignment Between Prefix of X and Y

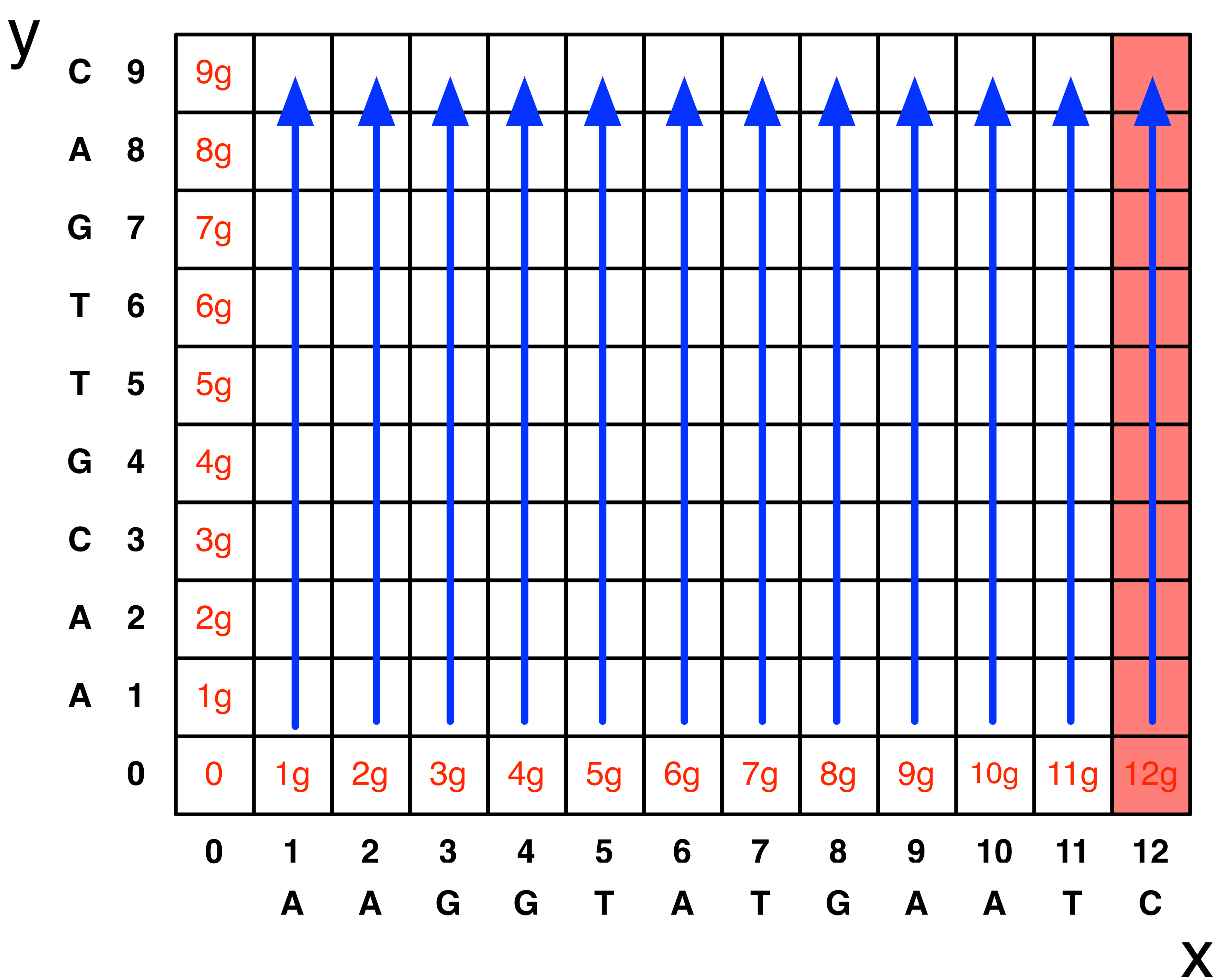


Fill in the matrix by columns...



What is this column?

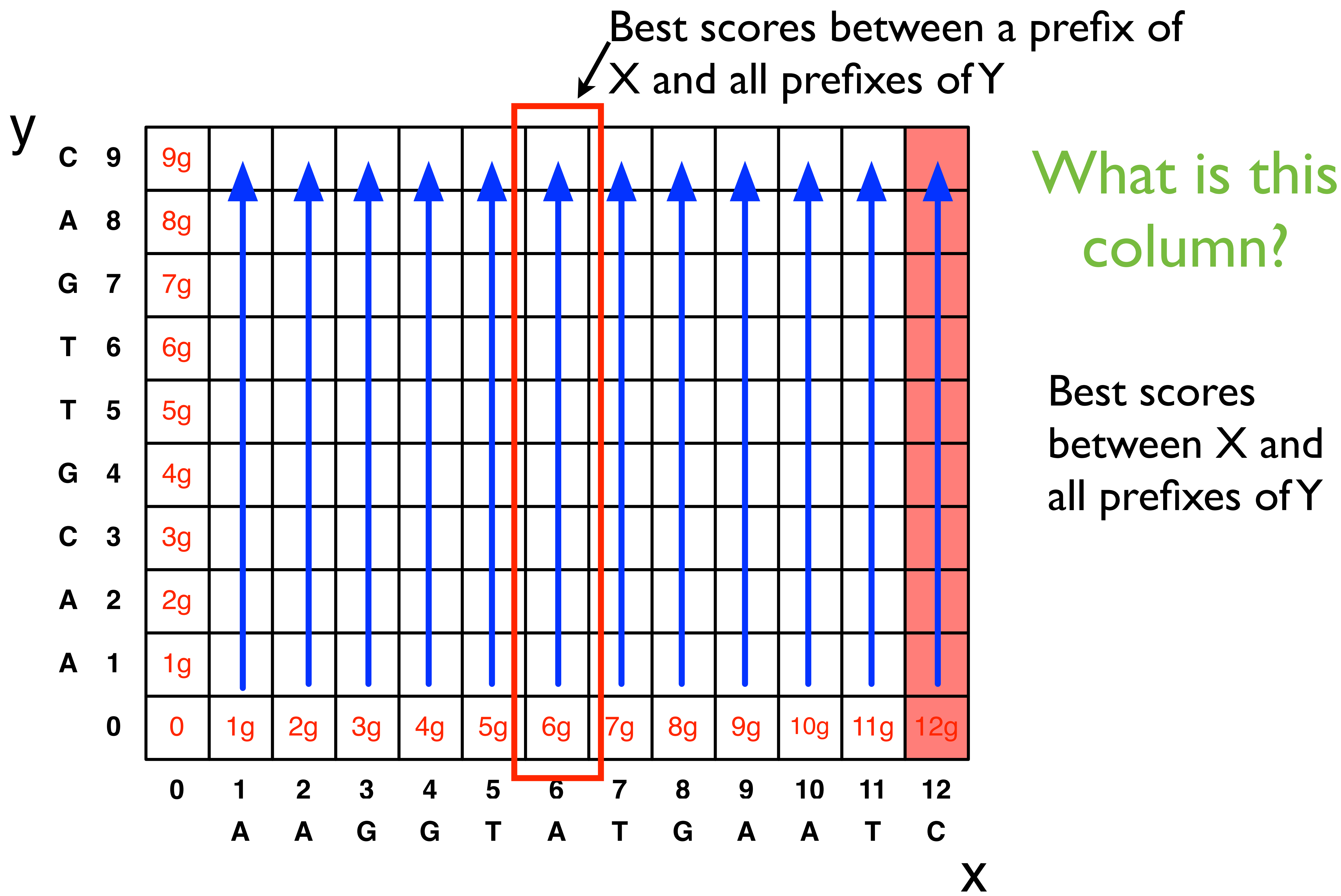
Fill in the matrix by columns...



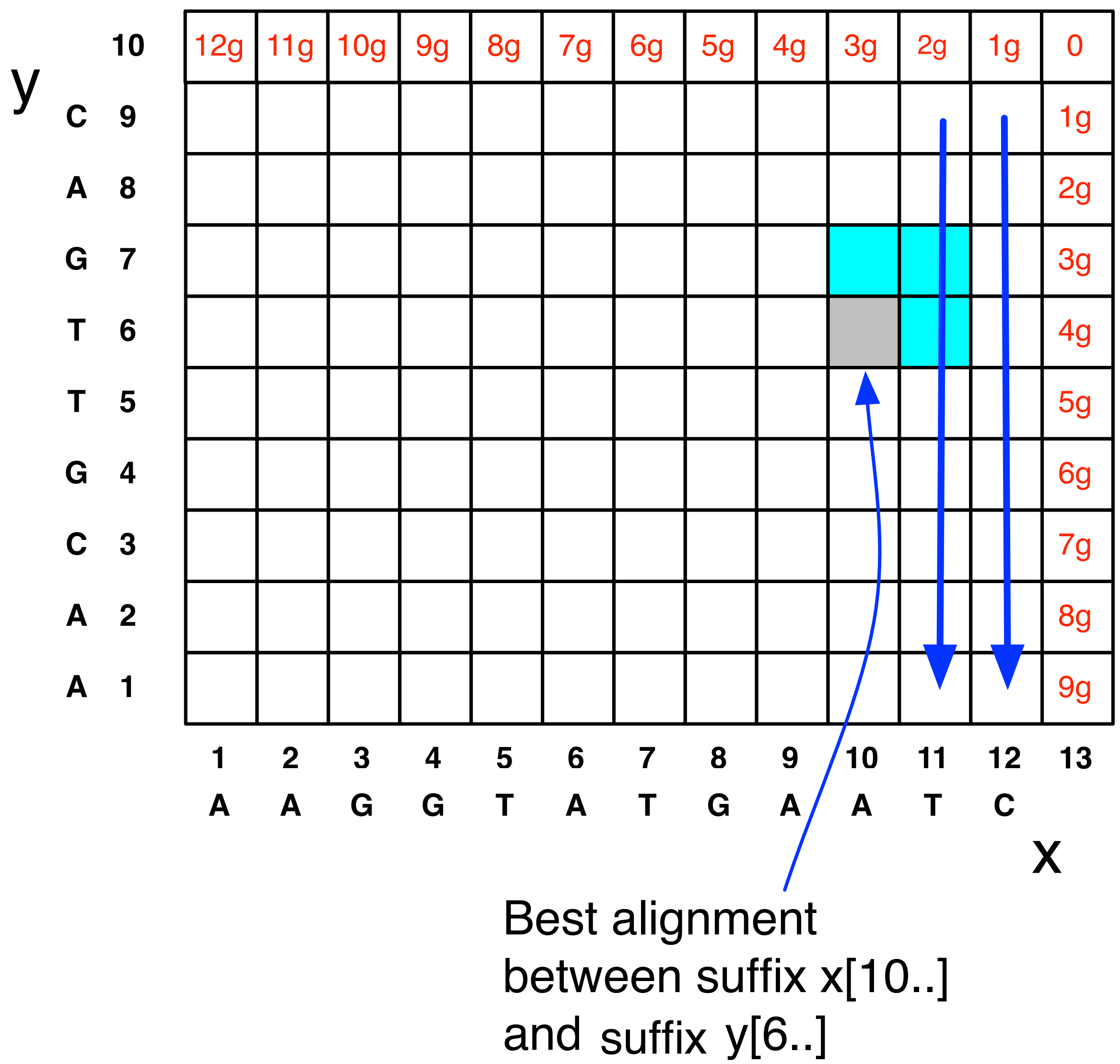
What is this column?

Best scores between X and all prefixes of Y

Fill in the matrix by columns...

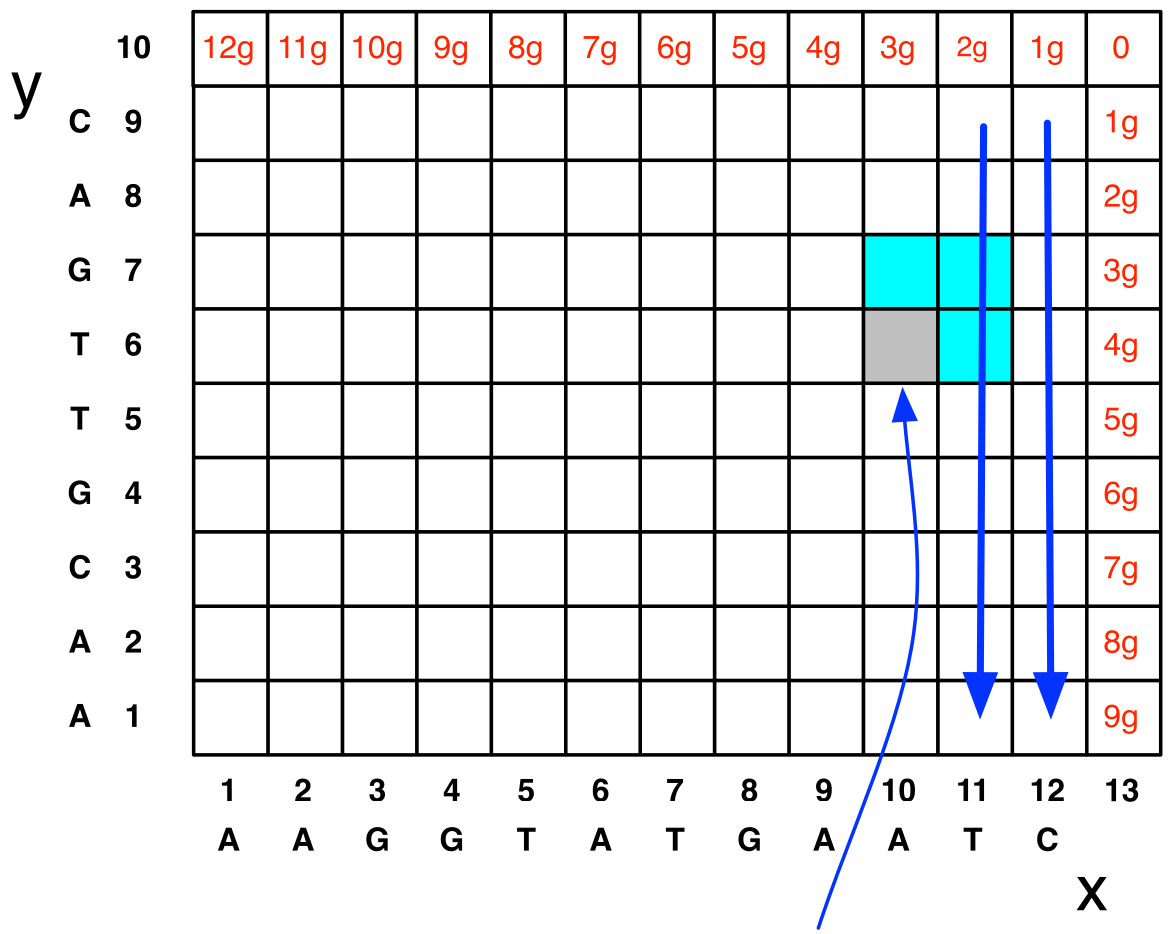


Cost of Alignment Between X and All Suffixes of Y



$$B[i,j] = \min \begin{cases} \text{cost}(x_i, y_j) + B[i+1, j+1] \\ \text{gap} + B[i, j+1] \\ \text{gap} + B[i+1, j] \end{cases}$$

Cost of Alignment Between X and All Suffixes of Y

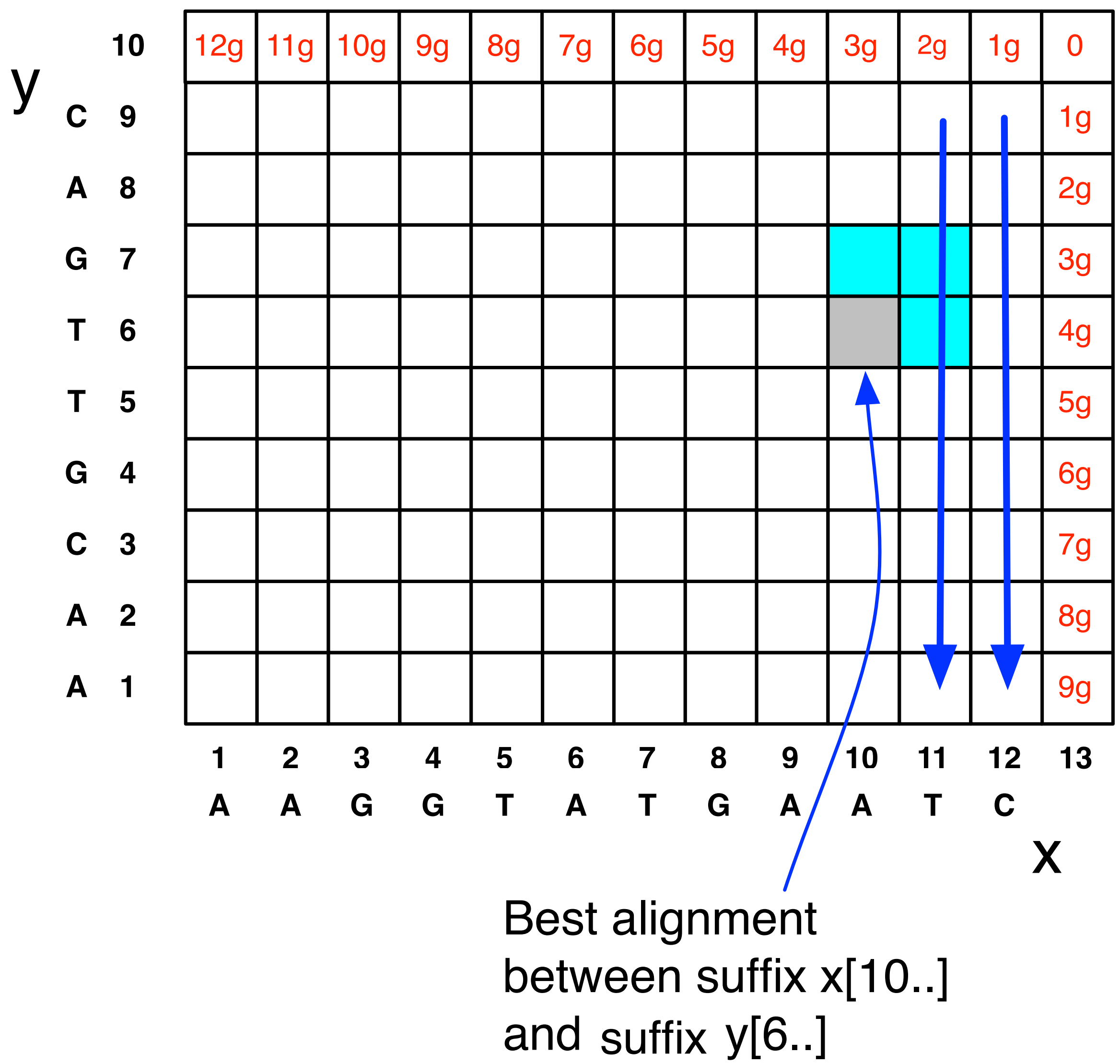


Best alignment between suffix x[10..] and suffix y[6..]

Exactly the same reasoning as doing the "forward" dynamic programming.

$$B[i,j] = \min \begin{cases} \text{cost}(x_i, y_j) + B[i+1, j+1] \\ \text{gap} + B[i, j+1] \\ \text{gap} + B[i+1, j] \end{cases}$$

Cost of Alignment Between X and All Suffixes of Y



"Backward" dynamic programming.

Exactly the same reasoning as doing the "forward" dynamic programming.

$$B[i,j] = \min \begin{cases} \text{cost}(x_i, y_j) + B[i+1, j+1] \\ \text{gap} + B[i, j+1] \\ \text{gap} + B[i+1, j] \end{cases}$$

Can We Find the Alignment in O(n) Space?

- Surprisingly, yes, we can output the optimal alignment in linear space.

- This will cost us some extra computation but only a constant factor

- for such a dramatic reduction in space, it's often worth it.

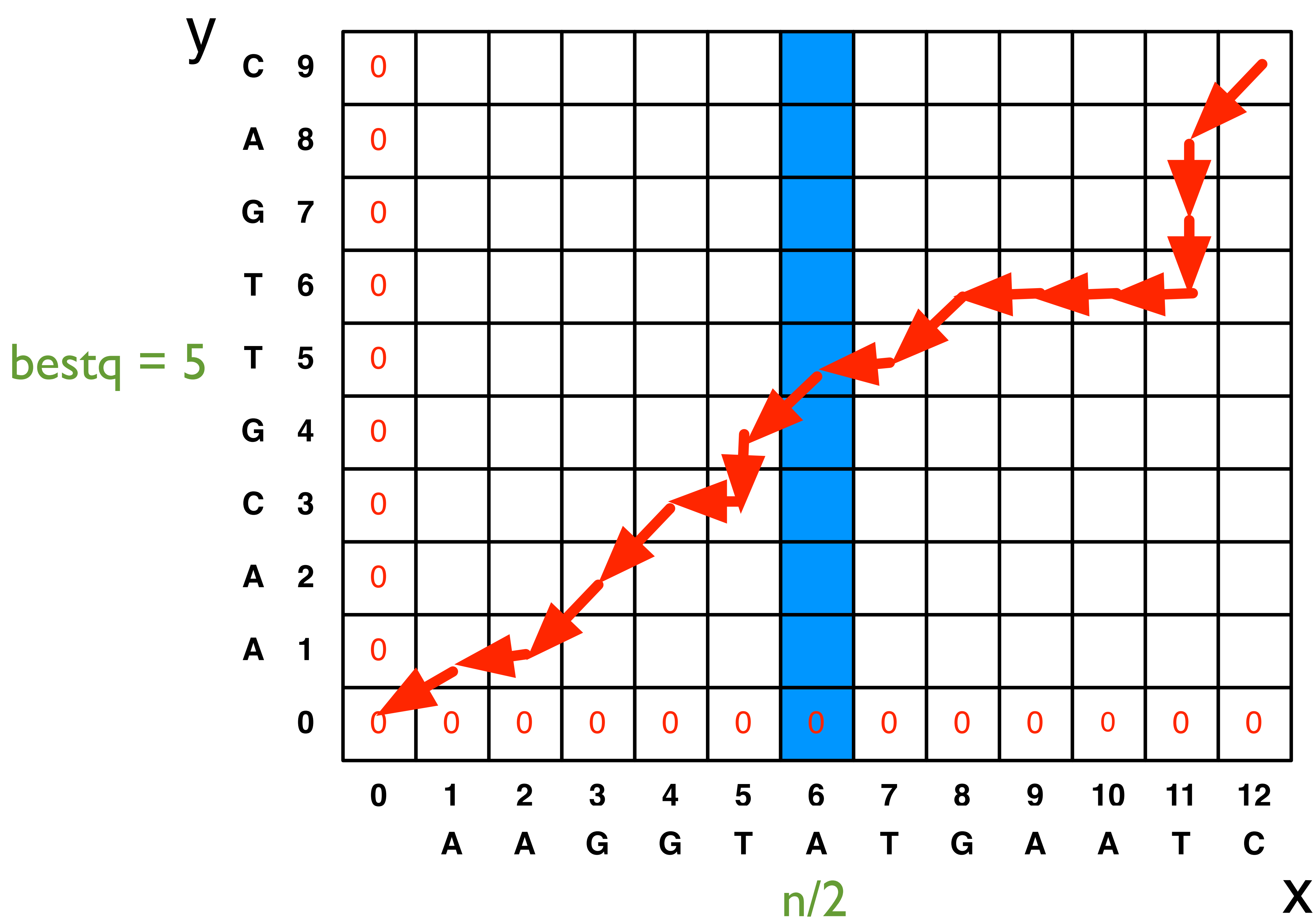
- **Idea**: a divide-and-conquer algorithm to compute half alignments.

Divide & Conquer

- General algorithmic design technique:
  - Split large problem into a few subproblems.
  - Recursively solve each subproblem.
  - Merge the resulting answers.

- You probably know such algorithms:
  - Merge sort
  - Quick sort

The Best Path Uses Some Cell in the Middle Column



Notation

- **AlignValue**(x, y) = compute the *cost* of the best alignment between x and y in O(min |x|, |y|) space.

- Finding the actual alignment is equivalent to finding all the cells that the optimal backtrace passes through.

- Call the optimal backtrace the **ArrowPath**.

First Attempt At Space Efficient Alignment

In the optimal alignment, the first n/2 characters of x are aligned with the first q characters of y for some q.

```
     12345678
x = ACGTACTG
y = A-GT-CTG
```

$$\underbrace{\texttt{A-GT-}}_{q\ =\ 3}$$

We don't know q, so we have to try *all* possible q.

```
ArrowPath := []
def Align(x, y):
  n := |x|; m := |y|
  if n or m ≤ 2: use standard alignment
  for q := 0..m:
    v1 := AlignValue(x[1..n/2], y[1..q])
    v2 := AlignValue(x[n/2+1..n], y[q+1..m])
    if v1 + v2 < best: bestq = q; best = v1 + v2

  Add (n/2, bestq) to ArrowPath
  Align(x[1..n/2], y[1..bestq])
  Align(x[n/2+1..n], y[bestq+1..m])
```

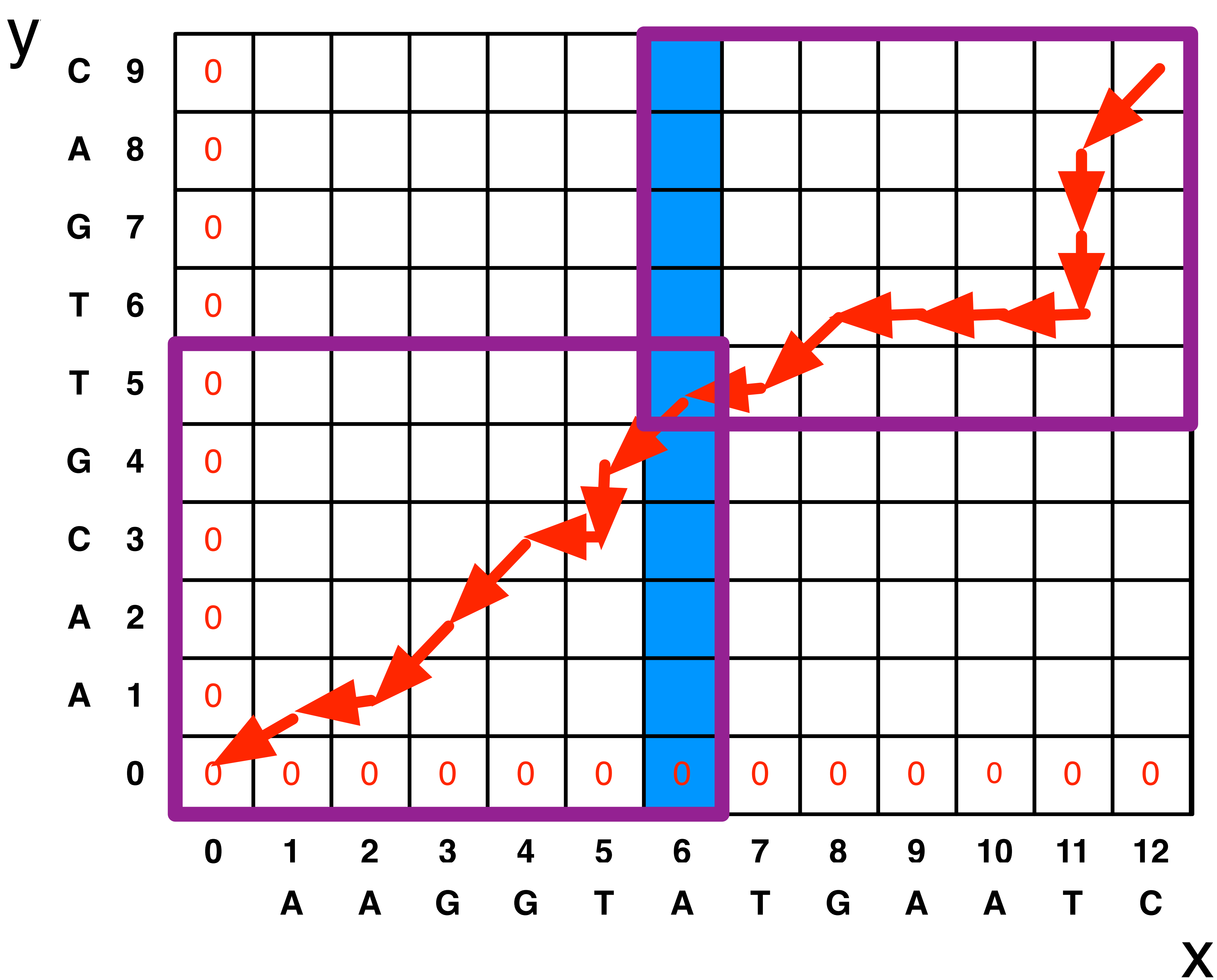
O(n) or O(m) space

O(n+m) space

O(n+m) space

find the q that minimizes the cost of the alignment

The Best Path Uses Some Cell in the Middle Column



Problem

- This works in linear space.
- BUT: not in O(nm) time.
- It's too expensive to solve all those AlignValue problems in the **for** loop.
- Define:
  - **AllYPrefixCosts**(x, i, y) = returns an array of the scores of optimal alignments between x[1..i] and all prefixes of Y.
  - **AllYSuffixCosts**(x, i, y) = returns an array of the scores of optimal alignments between x[i..n] and all suffixes of y.
  - These are implemented as described in previous slides by returning the last row or last column of the DP matrix.

Space Efficient Alignment

```
     12345678
x  = ACGTACTG
y  = A-GT-CTG
```

$\underbrace{\texttt{A-GT}}_{q\,=\,3}$

We still try all possible q, but we use the fact that we can compute the cost between a given prefix and *all* suffixes in linear space.

```
ArrowPath := []

def Align(x, y):
  n := |x|; m := |y|
  if n or m ≤ 2: use standard alignment

  YPrefix := AllYPrefixCosts(x, n/2, y)
  YSuffix := AllYSuffixCosts(x, n/2+1, y)

  for q := 0..m:
    cost = YPrefix[q] + YSuffix[q+1]
    if cost < best: bestq = q; best = cost

  Add (n/2, bestq) to ArrowPath
  Align(x[1..n/2], y[1..bestq])
  Align(x[n/2+1..n], y[bestq+1..m])
```

O(n) or O(m) space

O(n+m) space

find the q that minimizes the cost of the alignment, using the costs of aligning X to prefixes and suffixes of Y

Running Time Recurrence, I

Full recurrence:

$$
\begin{aligned}
&T(n,2) \le cn \\
&T(2,m) \le cm \\
&T(n,m) \le cmn + \underbrace{T(n/2,q)}_{\texttt{Align(x[1..n/2], y[1..bestq])}} + \overbrace{T(n/2,m-q)}^{\texttt{Align(x[n/2+1..n], y[bestq+1..m])}}
\end{aligned}
$$

Too complicated because we don't know what *q* is.

Simplify: assume both sequences have length n, and that we get a perfect split in half every time, *q*=*n*/2:

$$T(n) \le 2T(n/2) + cn^2$$

Solves as:

$$T(n) = O(n^2)$$

Running Time Recurrence, 2

$$T(n,2) \le cn$$
$$T(2,m) \le cm$$
$$T(n,m) \le cmn + T(n/2,q) + T(n/2,m-q)$$

Guess: T(n,m) ≤ kmn, for some k.

Proof, by induction:

Base cases: If k ≥ c then T(n,2) ≤ cn ≤ c2n ≤ k2n = kmn

Induction step: Assume T(**m', n'**) ≤ k**m'n'** for pairs (m',n') with a product smaller than mn:

$$\begin{aligned} T(m,n) &\le cmn + T(n/2,q) + T(n/2,m-q) \\ &\le cmn + kqn/2 + k(m-q)n/2 \quad \leftarrow \text{apply induction hypothesis} \\ &= cmn + kqn/2 + kmn/2 - kqn/2 \\ &= (c + k/2)mn \end{aligned}$$

$$k = 2c \implies T(m,n) \le 2cmn = kmn \qquad \square$$

Recap

- Can compute the cost of an alignment easily in linear space.
- Can compute the cost of a string with all suffixes of a second string in linear space.
- Divide and conquer algorithm for computing the *actual* alignment (traceback path in the DP matrix) in linear space.
- Still uses O(nm) time!