Space-Efficient Alignment: Hirschberg's Algorithm

02-714

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]

y														
C	9	0												
A	8	0												
G	7	0												
T	6	0												
T	5	0												
G	4	0												
C	3	0												
A	2	0												
A	1	0												
	0	0	0	0	0	0	0	0	0	0	0	0	0	0
		0	1	2	3	4	5	6	7	8	9	10	11	12
			A	A	G	G	T	A	T	G	A	A	T	C

x

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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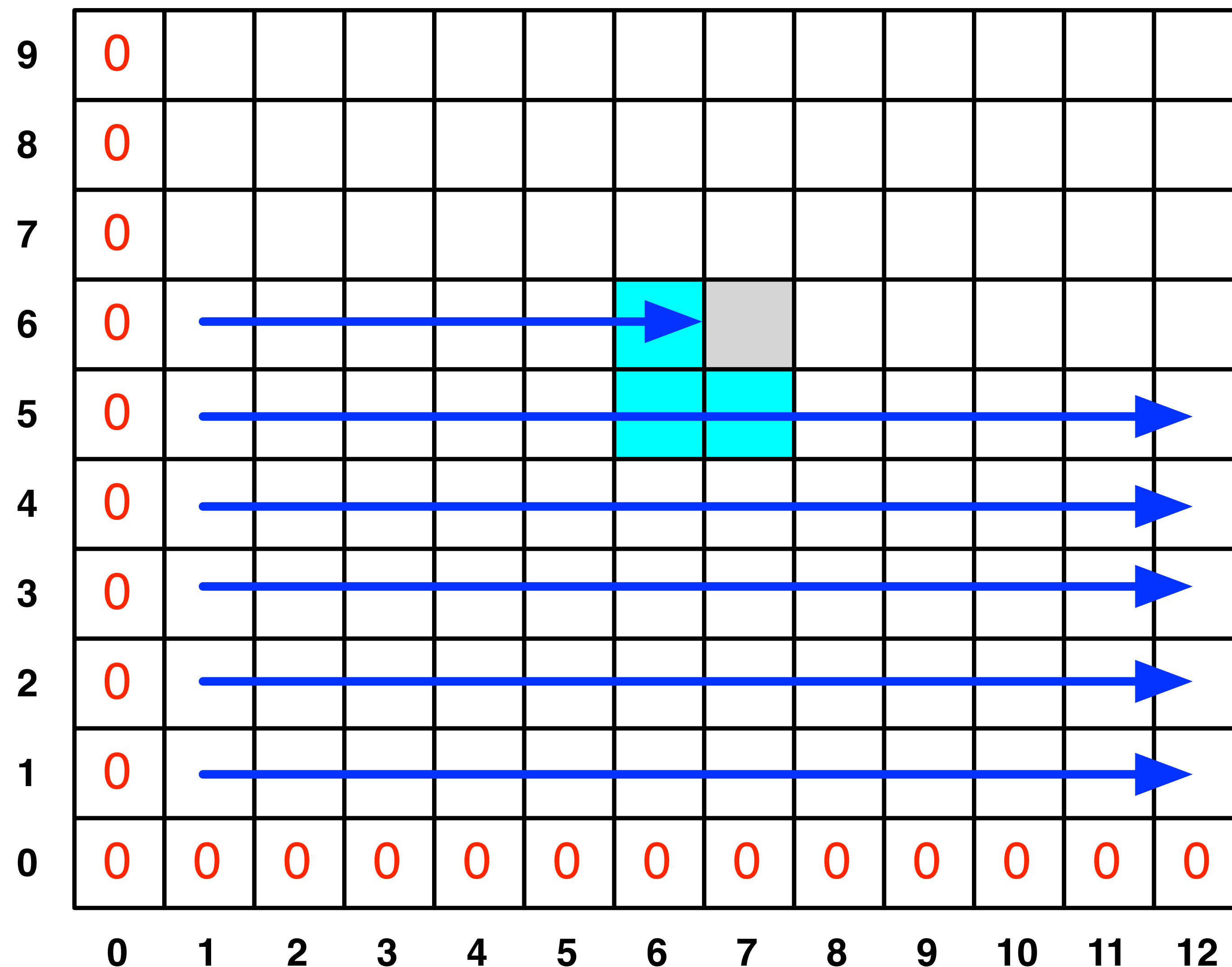
- How?



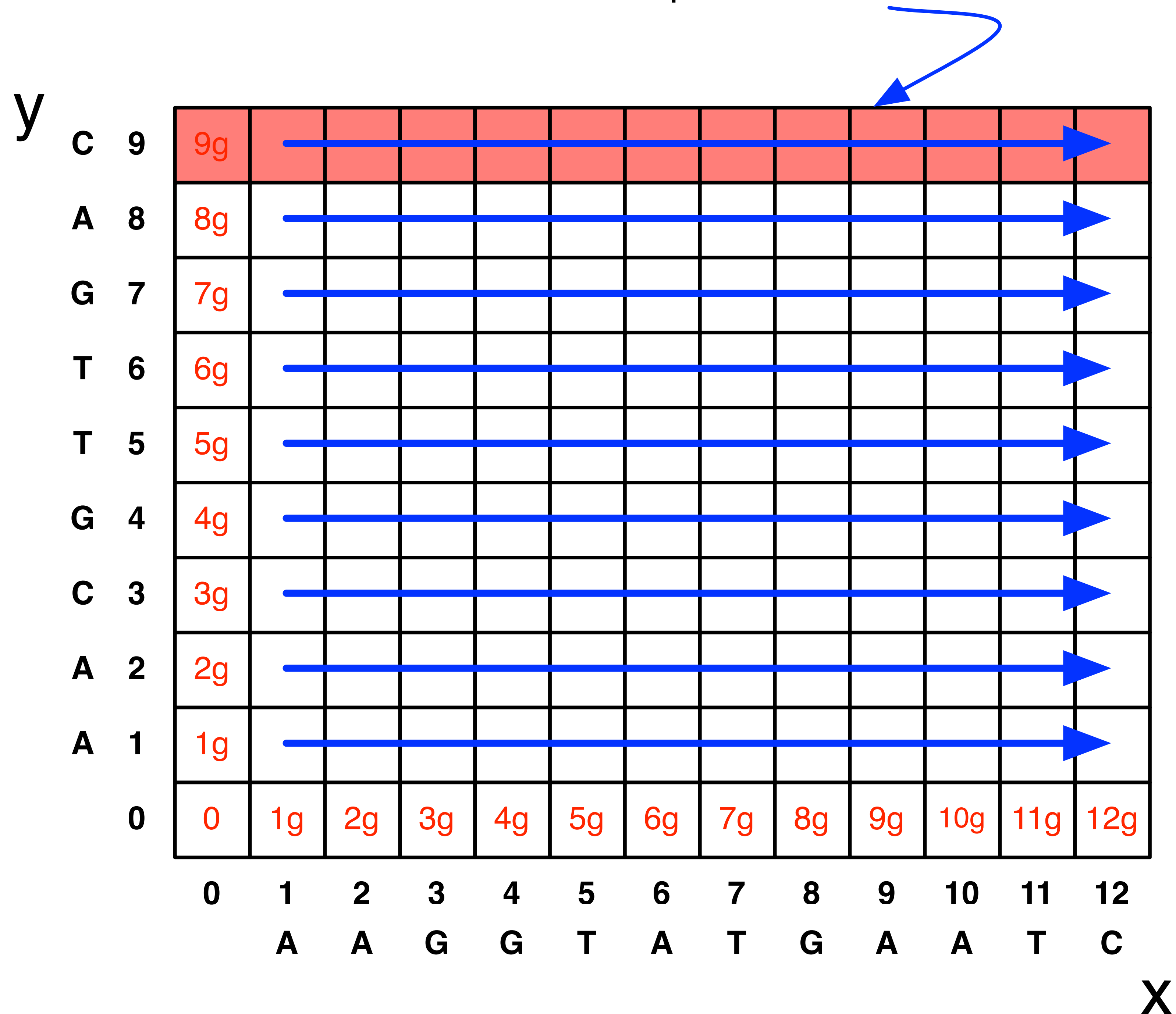
When filling in an entry (gray box) we only look at the current and previous rows.

Only need to keep those two rows in memory.

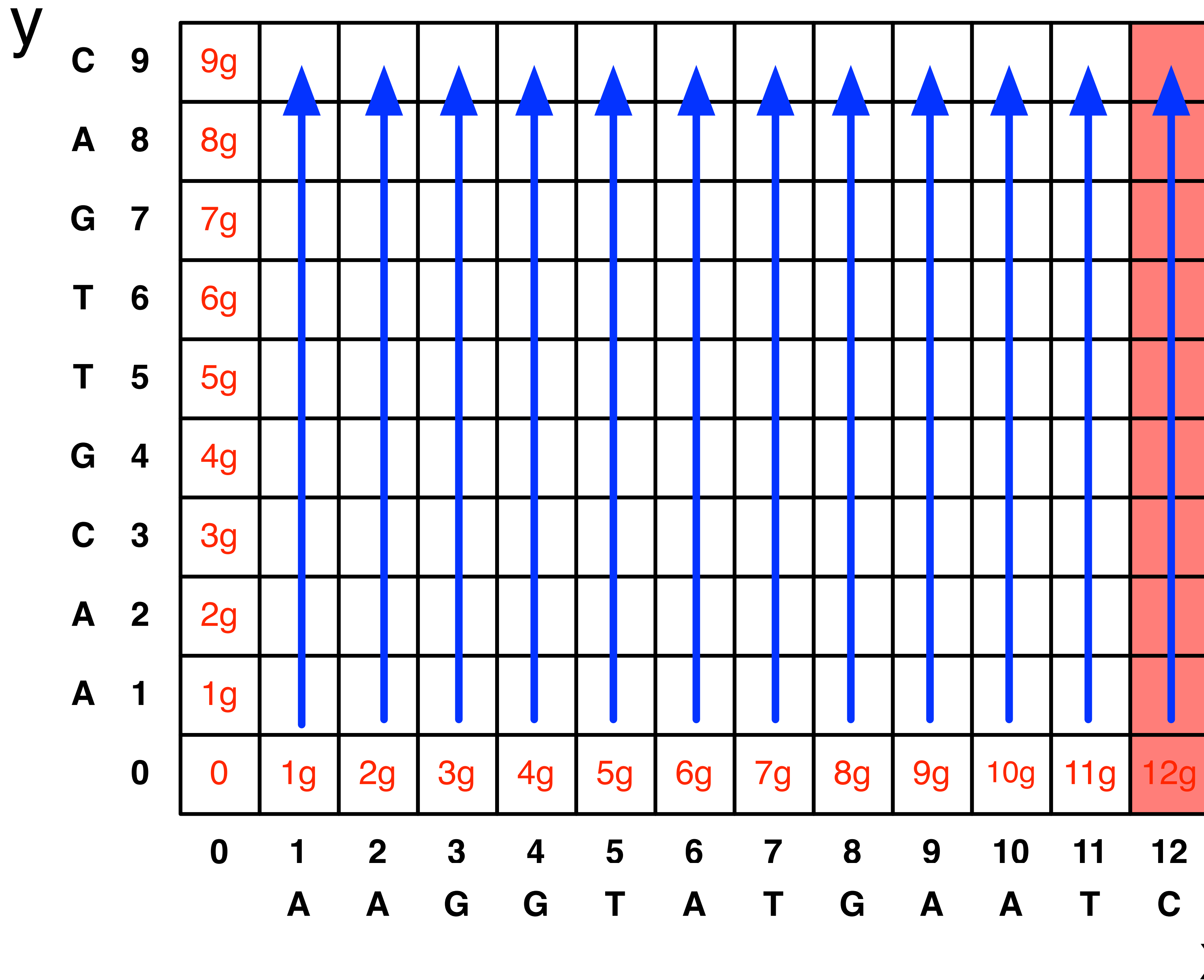
We can do more...

- 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...

y

C	9	9g												
A	8	8g												
G	7	7g												
T	6	6g												
T	5	5g												
G	4	4g												
C	3	3g												
A	2	2g												
A	1	1g												
	0	0	1g	2g	3g	4g	5g	6g	7g	8g	9g	10g	11g	12g
		0	1	2	3	4	5	6	7	8	9	10	11	12
			A	A	G	G	T	A	T	G	A	A	T	C

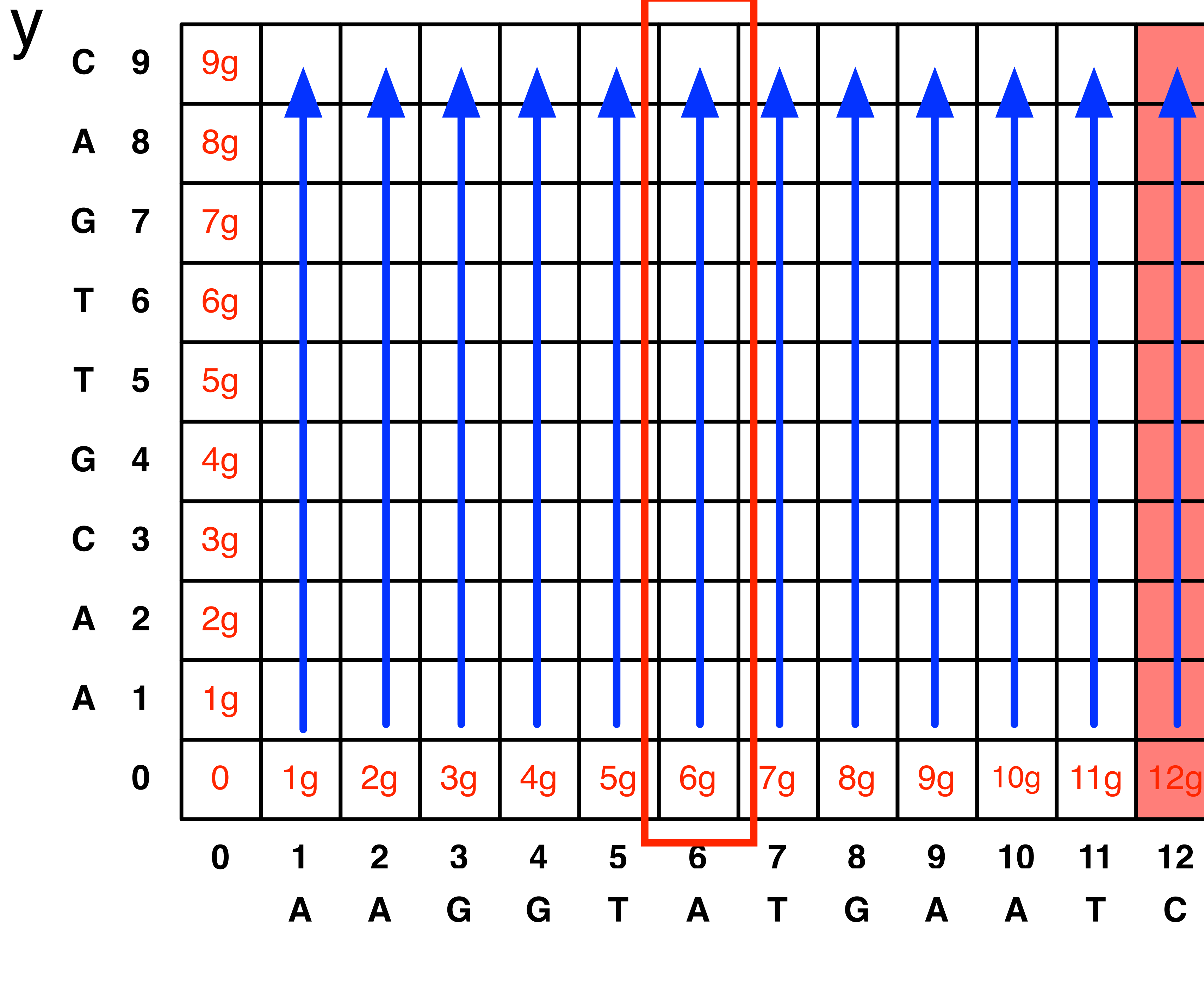
X

What is this column?

Best scores between X and all prefixes of Y

Fill in the matrix by columns...

Best scores between a prefix of X and all prefixes of Y



What is this column?

Best scores between X and all prefixes of Y

Cost of Alignment Between X and All Suffixes of Y

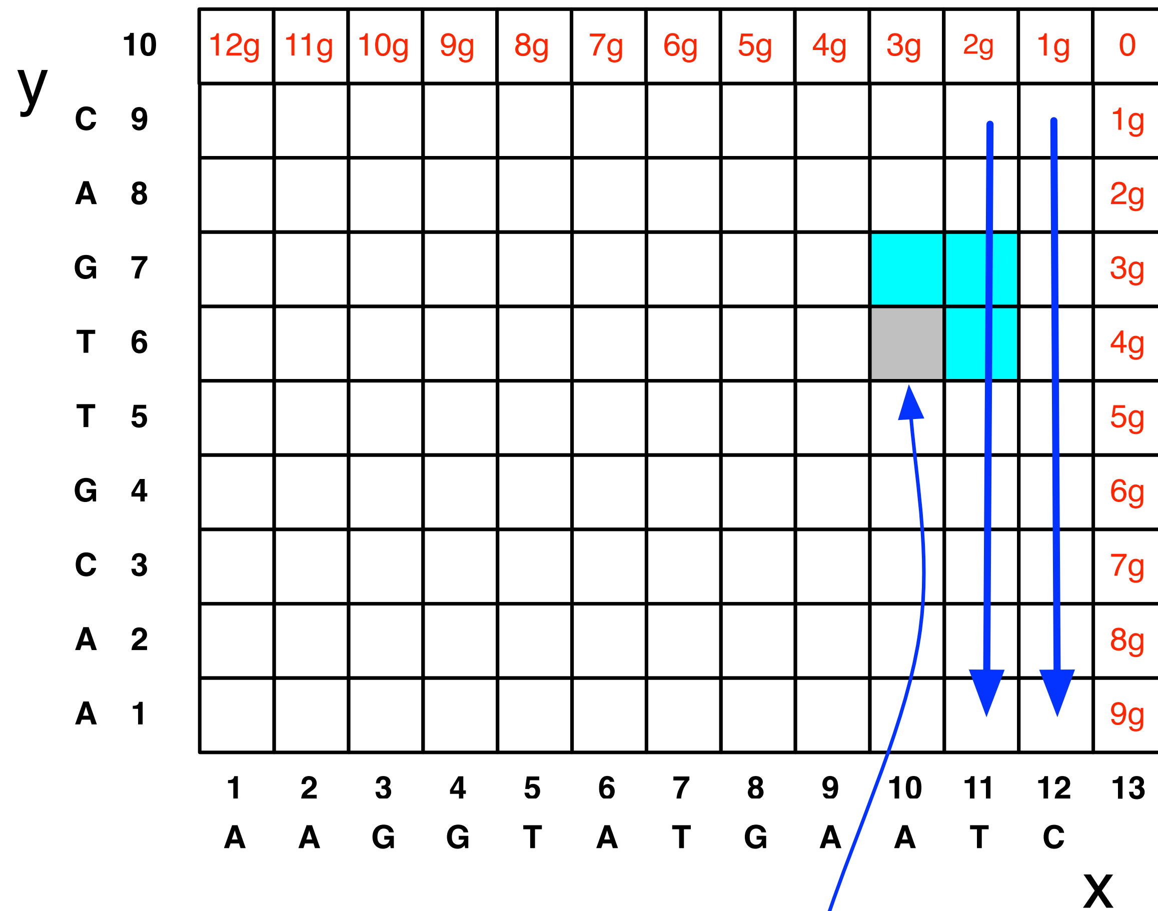
y														
	10	12g	11g	10g	9g	8g	7g	6g	5g	4g	3g	2g	1g	0
C	9													1g
A	8													2g
G	7													3g
T	6													4g
T	5													5g
G	4													6g
C	3													7g
A	2													8g
A	1													9g
		1	2	3	4	5	6	7	8	9	10	11	12	13
		A	A	G	G	T	A	T	G	A	A	T	C	

x

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

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

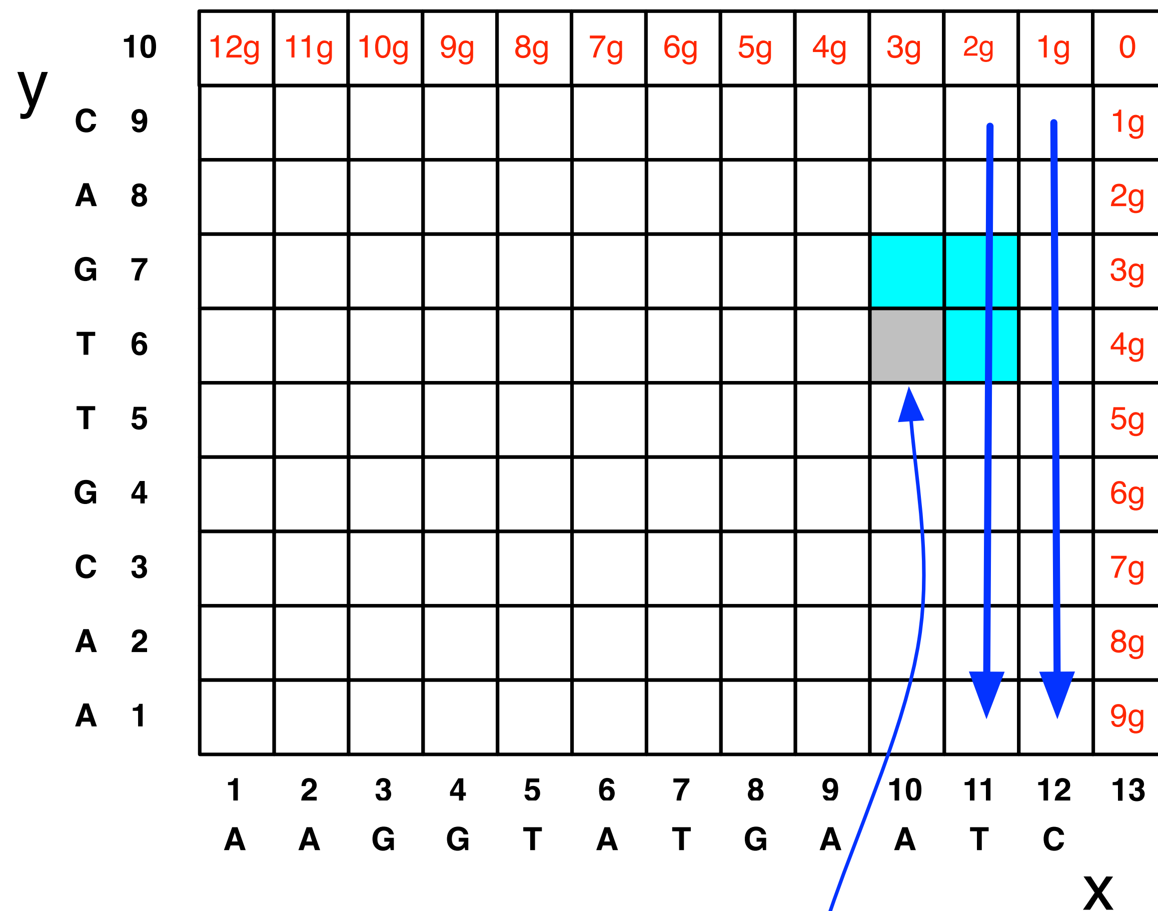
Cost of Alignment Between X and All Suffixes of Y



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

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

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

	y													
C	9	0												
A	8	0												
G	7	0												
T	6	0												
T	5	0												
G	4	0												
C	3	0												
A	2	0												
A	1	0												
	0	0	0	0	0	0	0	0	0	0	0	0	0	0
		0	1	2	3	4	5	6	7	8	9	10	11	12
			A	A	G	G	T	A	T	G	A	A	T	C

bestq = 5

n/2

x

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
```

$q = 3$

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])
```

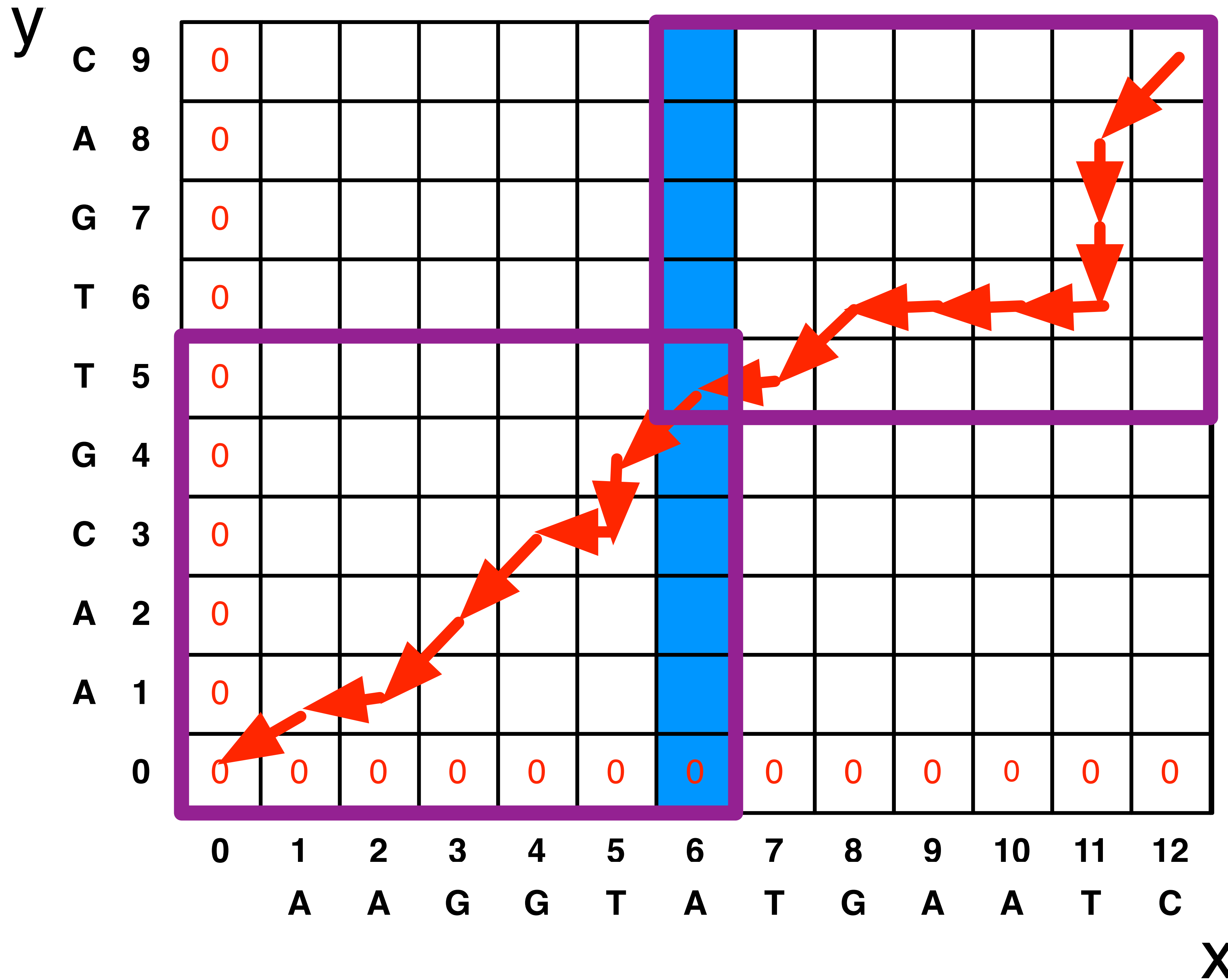
O(n) or O(m) space

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



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- This works in linear space.
- BUT: not in $O(nm)$ time. Why?
- 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
```

$q = 3$

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:

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

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:

$$T(n) = O(n^2)$$ ⇒ guess O(nm)

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:

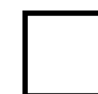
Base cases: If k ≥ c then T(n,2) ≤ cn ≤ c2n ≤ k2n = kmn

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

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

← apply induction hypothesis

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



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!