Space-efficient alignment

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Space is often the limiting factor

O(nm) time is a problem, but as I've said, we **strongly believe** we can't to much better.

Can we do better in terms of *space?*

It turns out we can — at the same asymptotic time complexity!

Combining dynamic programming with the divide-and-conquer algorithm design technique.

Hirshberg's algorithm

Warmup — optimal *score* in linear space

Consider our DP matrix:

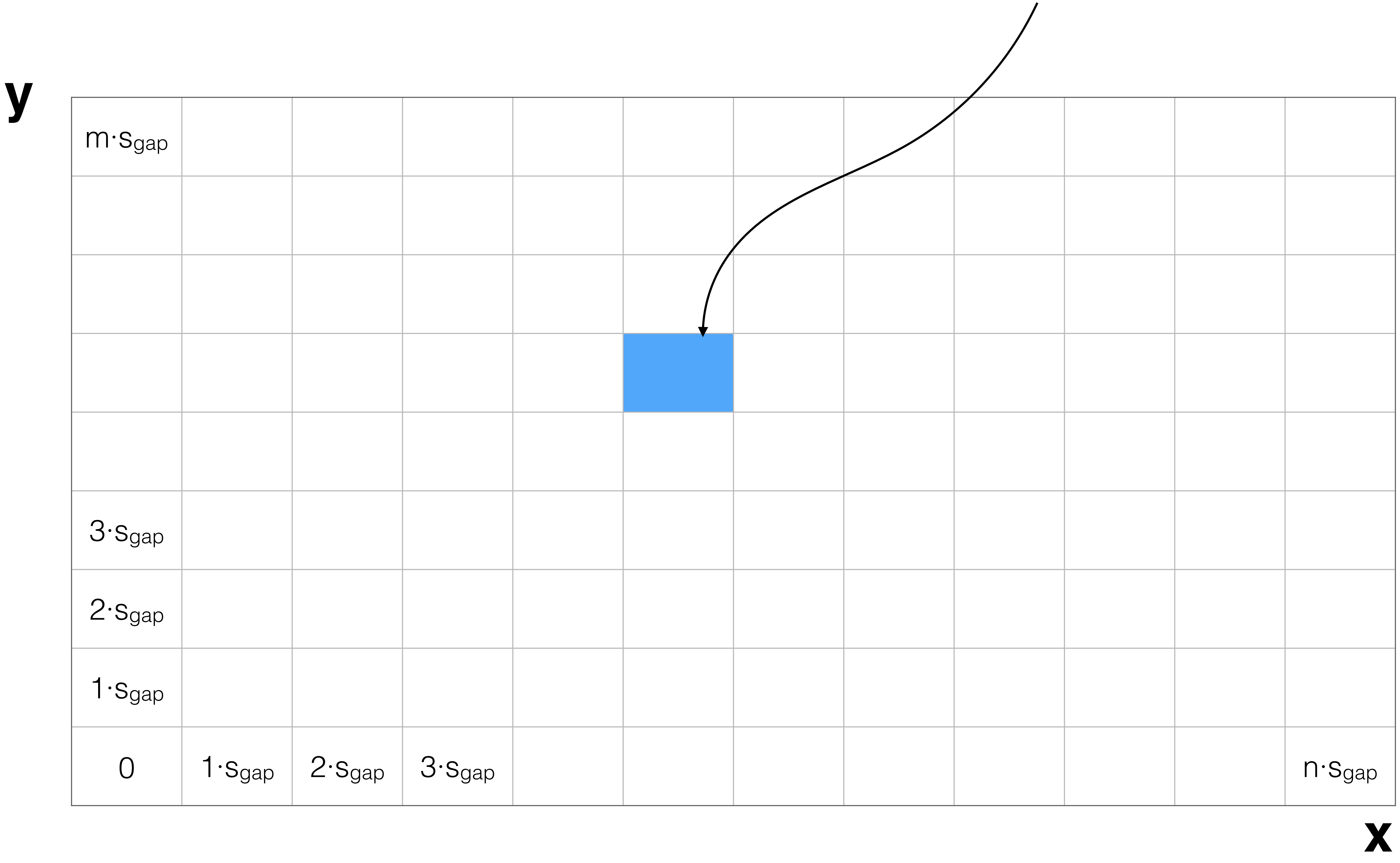
y

$m \cdot s_{gap}$											
$3 \cdot s_{gap}$											
$2 \cdot s_{gap}$											
$1 \cdot s_{gap}$											
0	$1 \cdot s_{gap}$	$2 \cdot s_{gap}$	$3 \cdot s_{gap}$								$n \cdot s_{gap}$

x

Warmup — optimal *score* in linear space

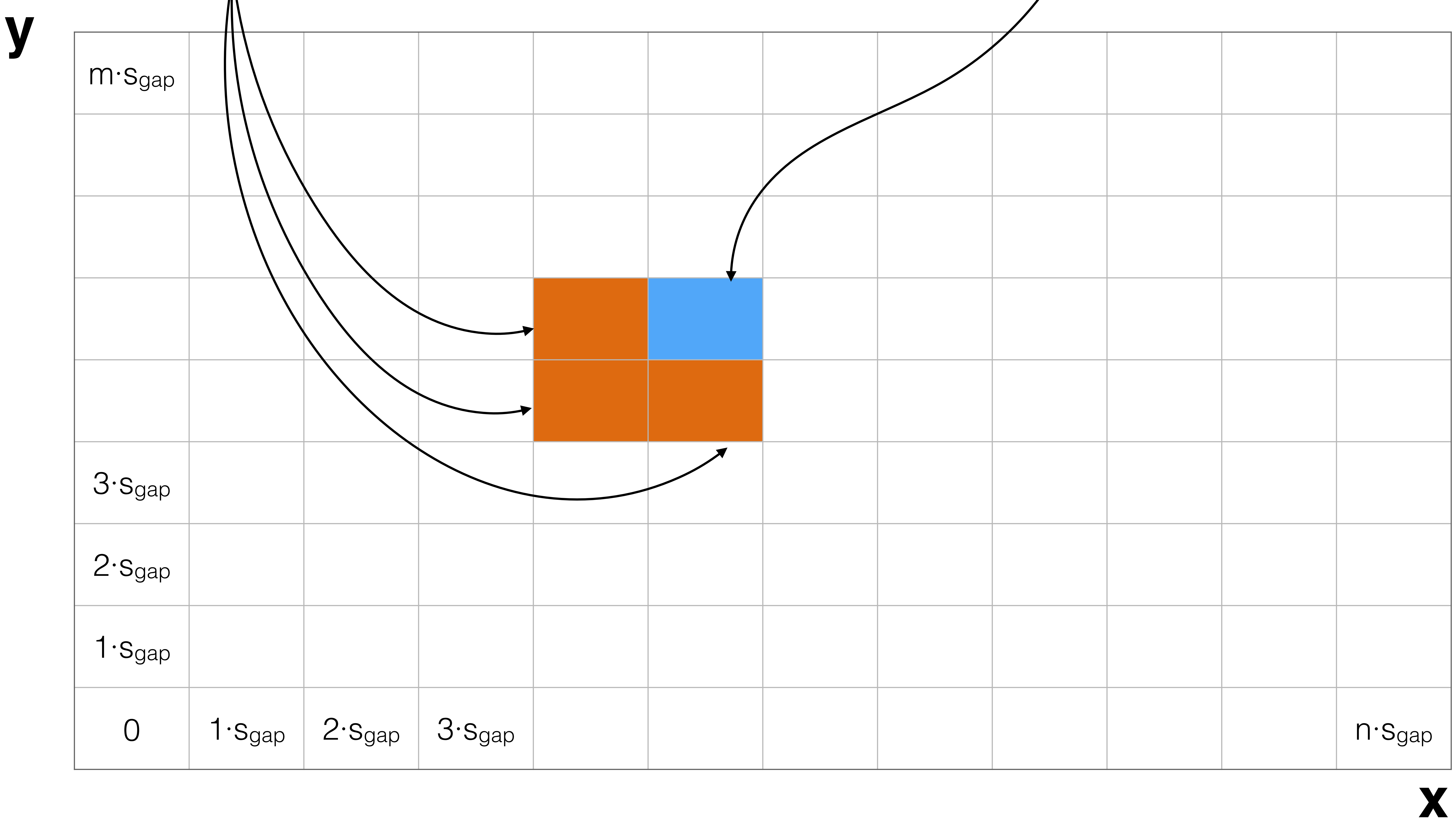
What scores to I need to know to fill in the answer here?



Warmup — optimal *score* in linear space

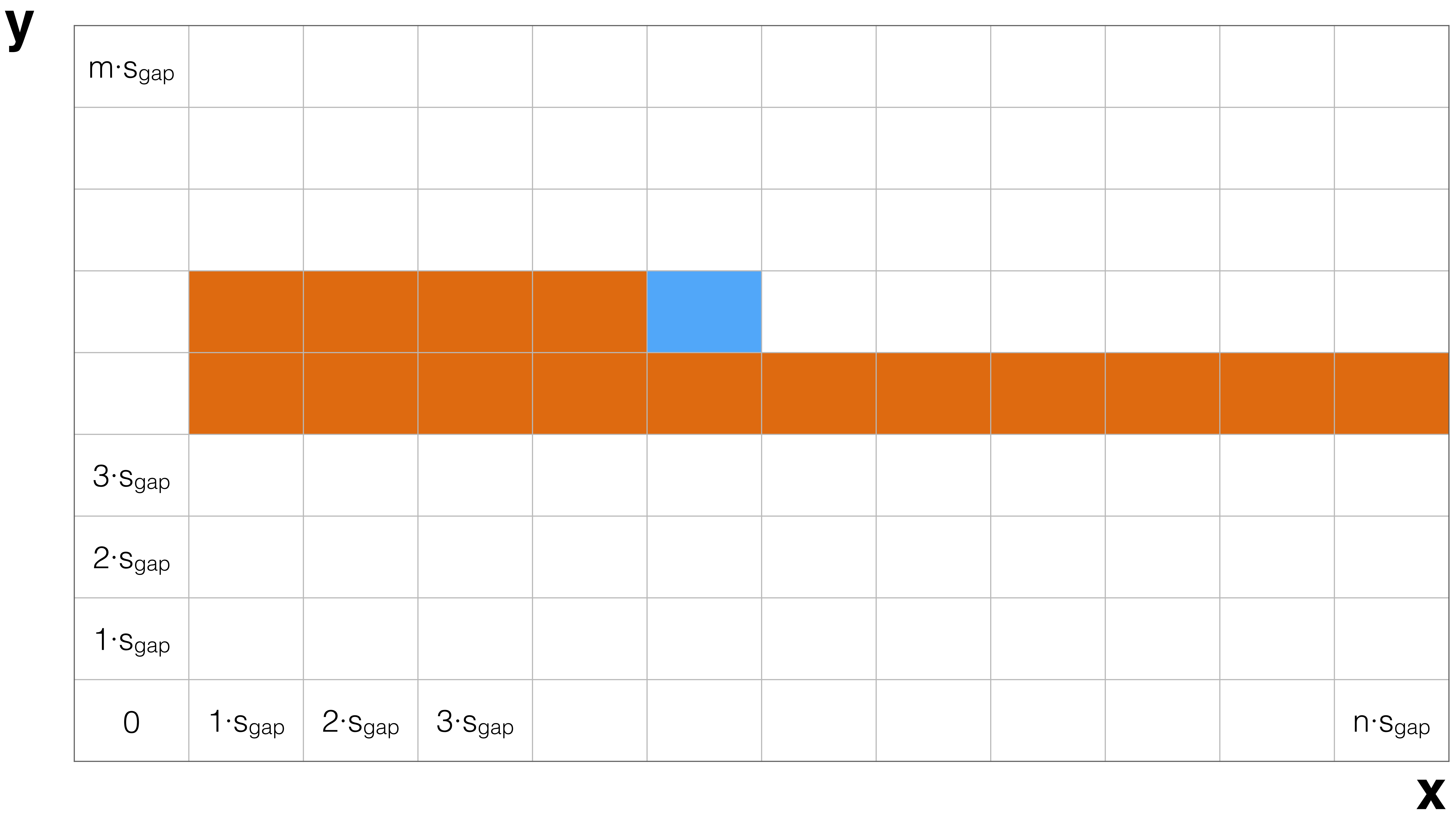
What scores to I need to know to fill in the answer here?

These



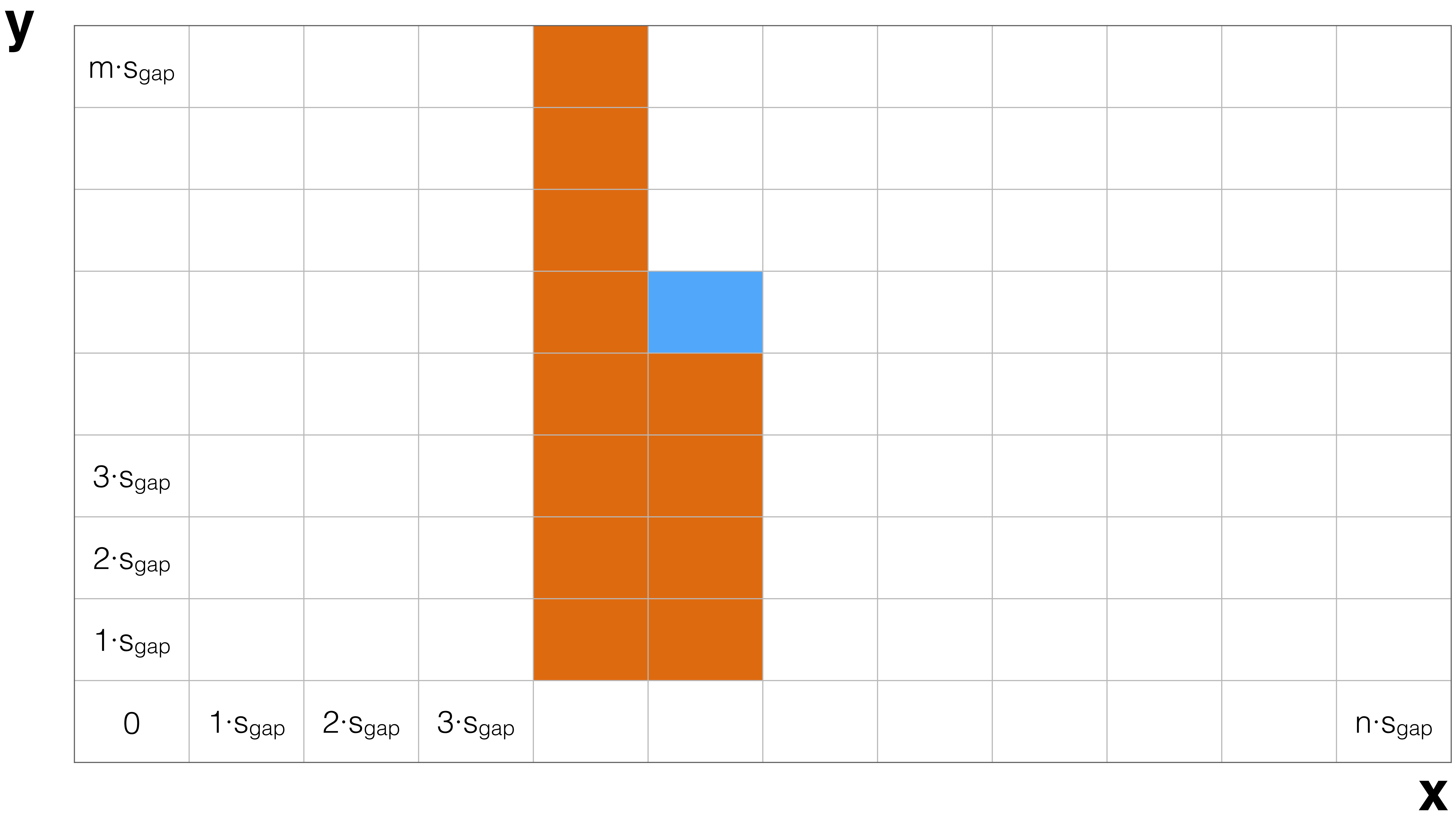
Warmup — optimal *score* in linear space

If we fill rows left - right, and bottom to top, to fill in row i, we *only* need scores from row i-1.



Warmup — optimal *score* in linear space

Columns also work; if we go left - right, and bottom to top, to fill in column i, we *only* need scores from col i-1.



Warmup — optimal *score* in linear space

If we fill rows left - right, and bottom to top, to fill in row i, we *only* need scores from row i-1.

Thus, we can compute the optimal *score,* keeping at most 2 rows / columns in memory at once.

Each row / column is *linear* in the length of one of the strings, and so we can compute the optimal *score*, in *linear space.*

How can we compute the optimal *alignment*?

This method won't work for computing the optimal alignment; we need *all* rows to be able to follow the backtracking arrows.

How can we find the optimal *alignment* in linear space?

Hirschberg's algorithm provides a solution.

Re-using subproblems

Consider, again, the meaning of the DP matrix

What is contained in the highlighted row?

y

$m \cdot s_{gap}$											
$3 \cdot s_{gap}$											
$2 \cdot s_{gap}$											
$1 \cdot s_{gap}$											
0	$1 \cdot s_{gap}$	$2 \cdot s_{gap}$	$3 \cdot s_{gap}$								$n \cdot s_{gap}$

x

Re-using subproblems

Consider, again, the meaning of the DP matrix

score of *every* prefix of **x** against *all* of **y** in this row

y

$m \cdot s_{gap}$											
$3 \cdot s_{gap}$											
$2 \cdot s_{gap}$											
$1 \cdot s_{gap}$											
0	$1 \cdot s_{gap}$	$2 \cdot s_{gap}$	$3 \cdot s_{gap}$								$n \cdot s_{gap}$

x

Re-using subproblems

Consider, again, the meaning of the DP matrix

What is contained in the highlighted column?

y

$m \cdot s_{gap}$											
$3 \cdot s_{gap}$											
$2 \cdot s_{gap}$											
$1 \cdot s_{gap}$											
0	$1 \cdot s_{gap}$	$2 \cdot s_{gap}$	$3 \cdot s_{gap}$								$n \cdot s_{gap}$

x

Re-using subproblems

Consider, again, the meaning of the DP matrix

score of *every* prefix of **y** against *all* of **x** in this column

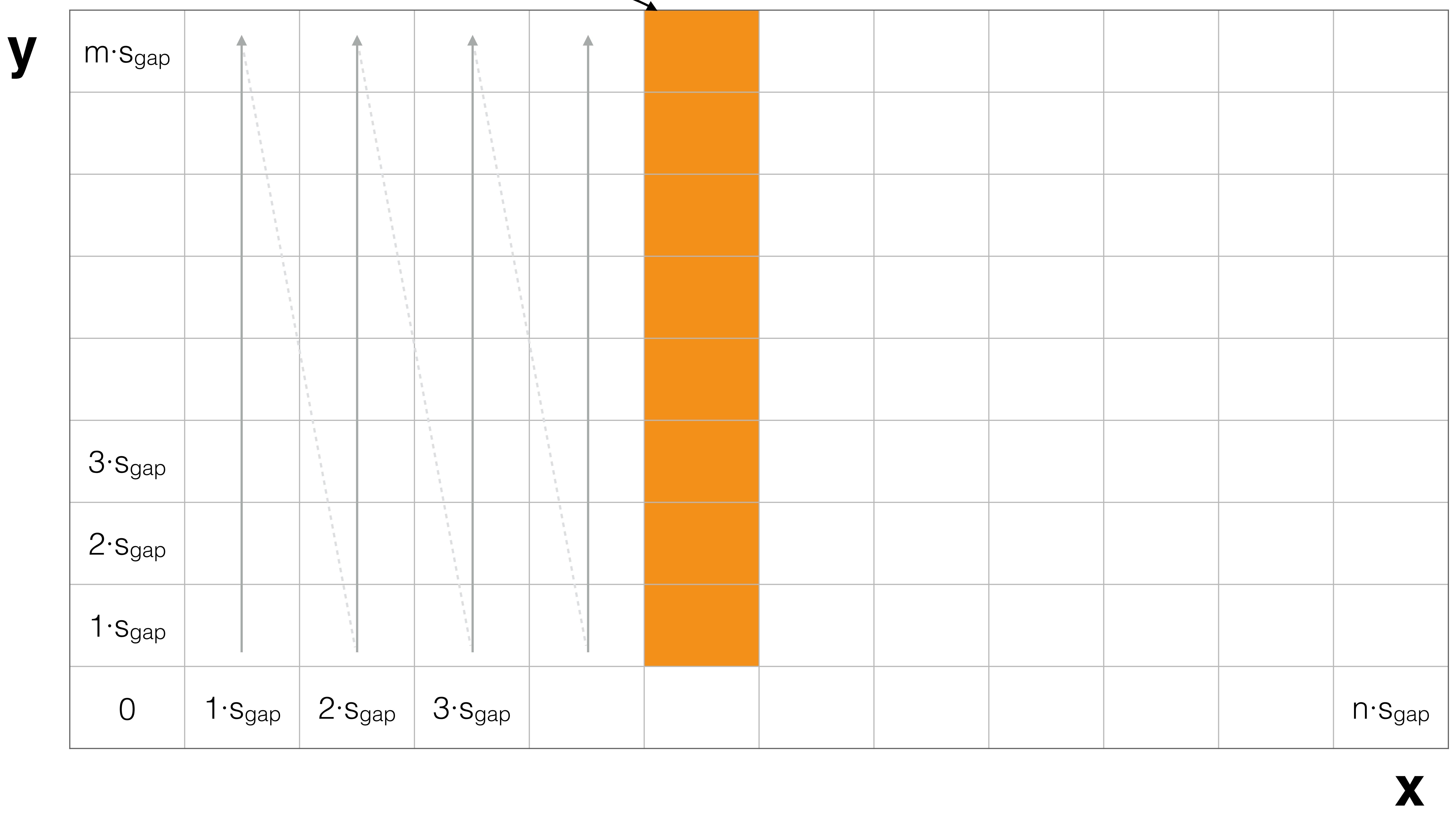
y

$m \cdot s_{gap}$											
$3 \cdot s_{gap}$											
$2 \cdot s_{gap}$											
$1 \cdot s_{gap}$											
0	$1 \cdot s_{gap}$	$2 \cdot s_{gap}$	$3 \cdot s_{gap}$								$n \cdot s_{gap}$

x

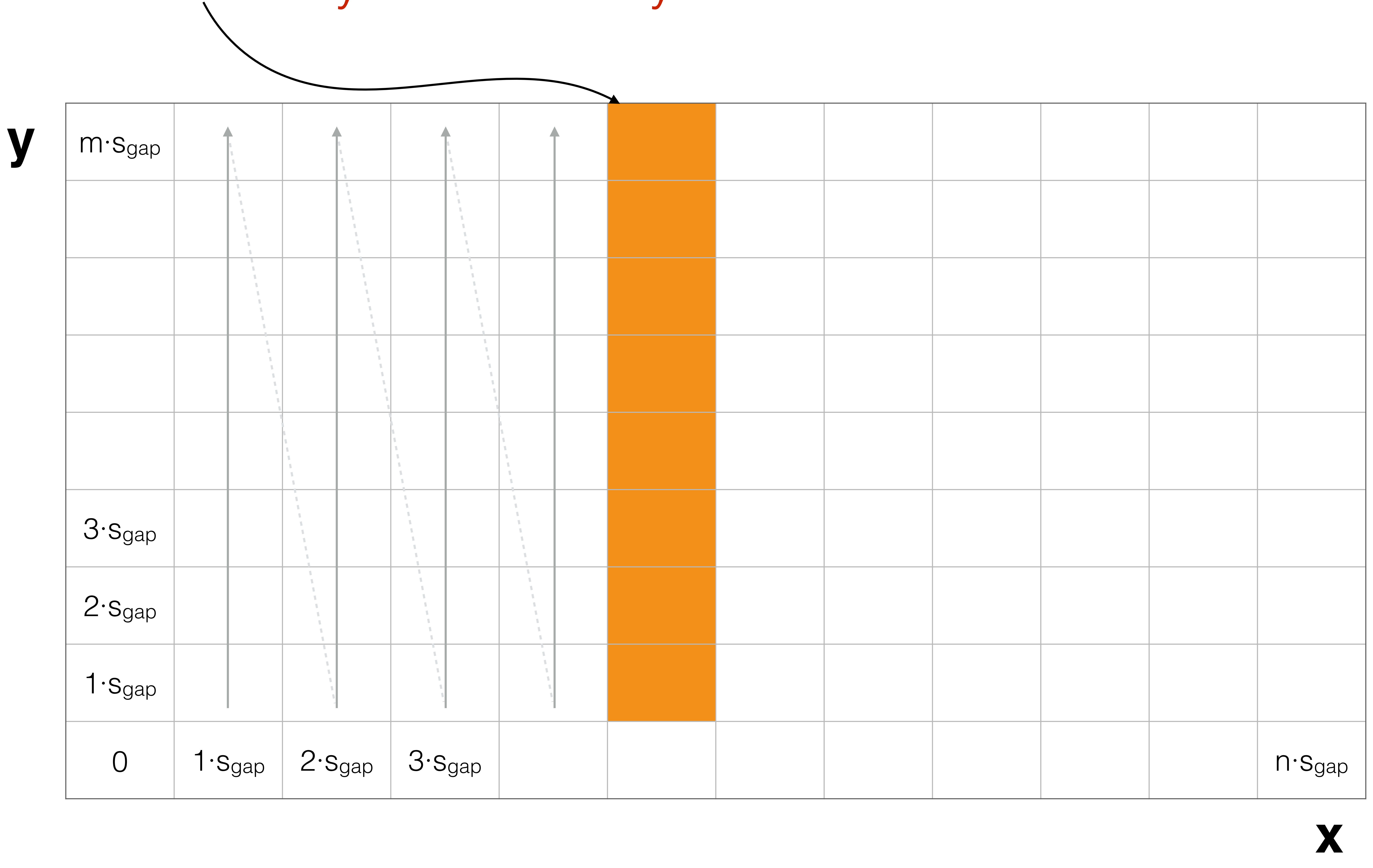
Re-using subproblems

score of *every* prefix of **y** against i^{th} prefix of **x** in the i^{th} column. How do we get these values efficiently?



Re-using subproblems

score of *every* prefix of **y** against i^{th} prefix of **x** in the i^{th} column. Easy if we fill in by columns instead of rows.



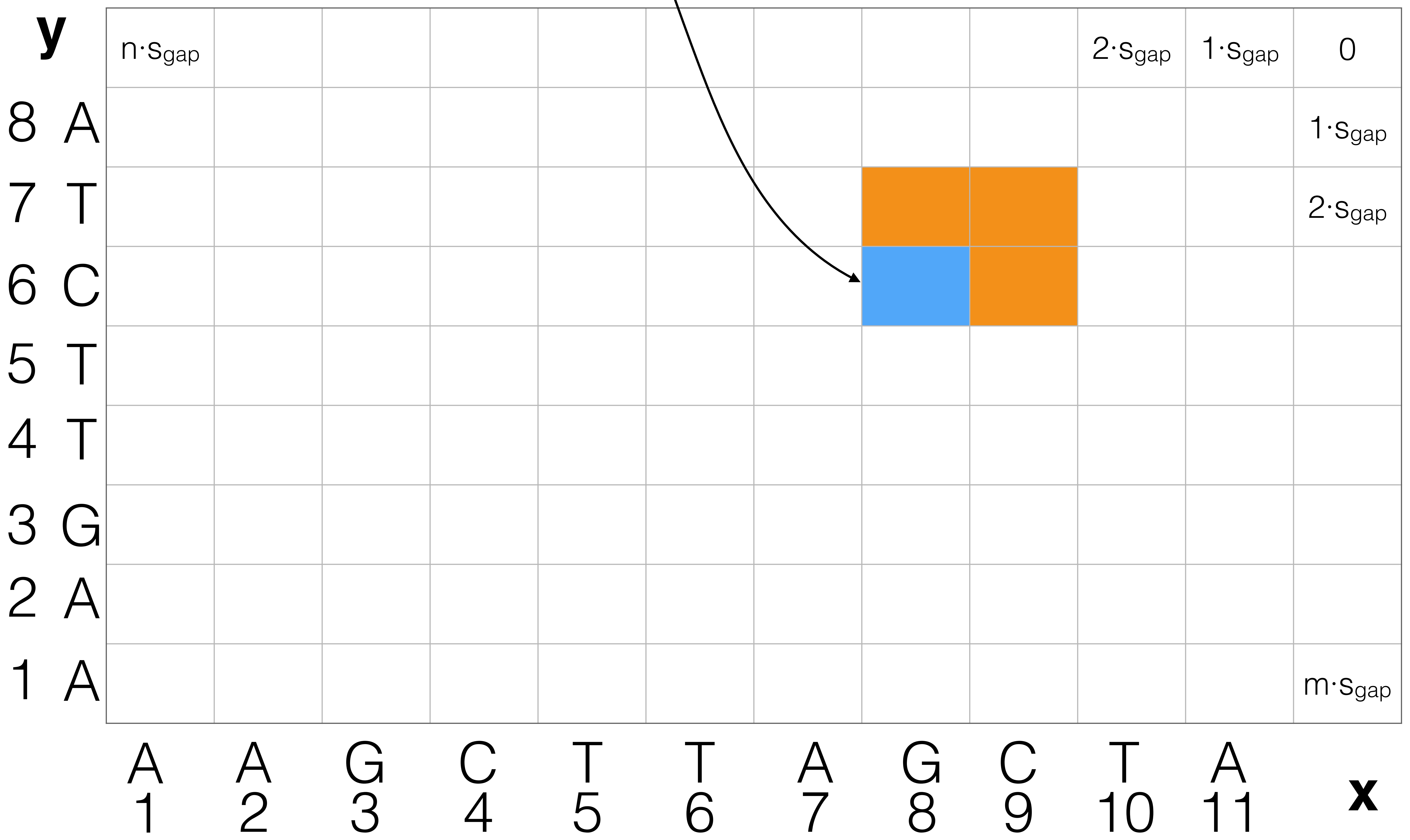
What about suffixes?

Consider filling in the DP matrix from the *opposite* direction (top right to bottom left)

y	$n \cdot s_{gap}$									$2 \cdot s_{gap}$	$1 \cdot s_{gap}$	0
8 A												$1 \cdot s_{gap}$
7 T												$2 \cdot s_{gap}$
6 C												
5 T												
4 T												
3 G												
2 A												
1 A												$m \cdot s_{gap}$
	A 1	A 2	G 3	C 4	T 5	T 6	A 7	G 8	C 9	T 10	A 11	**x**

What about suffixes?

Optimal alignment between x[8:] and y[6:]



What about suffixes?

This lets us compute optimal score between a *suffix* of **x** with *all suffixes* of **y**

y												
	$n \cdot s_{gap}$									$2 \cdot s_{gap}$	$1 \cdot s_{gap}$	0
8 A												$1 \cdot s_{gap}$
7 T												$2 \cdot s_{gap}$
6 C												
5 T												
4 T												
3 G												
2 A												
1 A												$m \cdot s_{gap}$
	A 1	A 2	G 3	C 4	T 5	T 6	A 7	G 8	C 9	T 10	A 11	**x**

What about suffixes?

Prefixes (forward):

$$\text{OPT}[i,j] = \max \begin{cases} \text{score}(x_i, y_j) + \text{OPT'}[i-1, j-1] \\ \text{gap} + \text{OPT}[i, j-1] \\ \text{gap} + \text{OPT}[i-1, j] \end{cases}$$

Suffixes (backward):

$$\text{OPT'}[i,j] = \max \begin{cases} \text{score}(x_{i+1}, y_{j+1}) + \text{OPT'}[i+1, j+1] \\ \text{gap} + \text{OPT'}[i, j+1] \\ \text{gap} + \text{OPT'}[i+1, j] \end{cases}$$

This lets us build up optimal alignments for increasing length suffixes of **x** and **y**

What about suffixes?

Prefixes (forward):

$$\text{OPT}\,[i,j] = \max \begin{cases} \text{score}\,(x_i, y_j) + \text{OPT'}\,[i-1, j-1] \\ \text{gap} + \text{OPT}\,[i, j-1] \\ \text{gap} + \text{OPT}\,[i-1, j] \end{cases}$$

Suffixes (backward):

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This lets us build up optimal alignments for increasing length suffixes of **x** and **y**

What about suffixes?

Prefixes (forward):

$$\text{OPT}\left[i,j\right] = \max \begin{cases} \text{score}\left(x_i, y_j\right) + \text{OPT'}\left[i-1, j-1\right] \\ \text{gap} + \text{OPT}\left[i, j-1\right] \\ \text{gap} + \text{OPT}\left[i-1, j\right] \end{cases}$$

Suffixes (backward):

$$\text{OPT'}\left[i,j\right] = \max \begin{cases} \text{score}\left(x_{i+1}, y_{j+1}\right) + \text{OPT'}\left[i+1, j+1\right] \\ \text{gap} + \text{OPT'}\left[i, j+1\right] \\ \text{gap} + \text{OPT'}\left[i+1, j\right] \end{cases}$$

note: the slight change in indexing here. It will make writing our solution easier.

Finding the optimal alignment

How does this help us compute the optimal alignment in linear space?

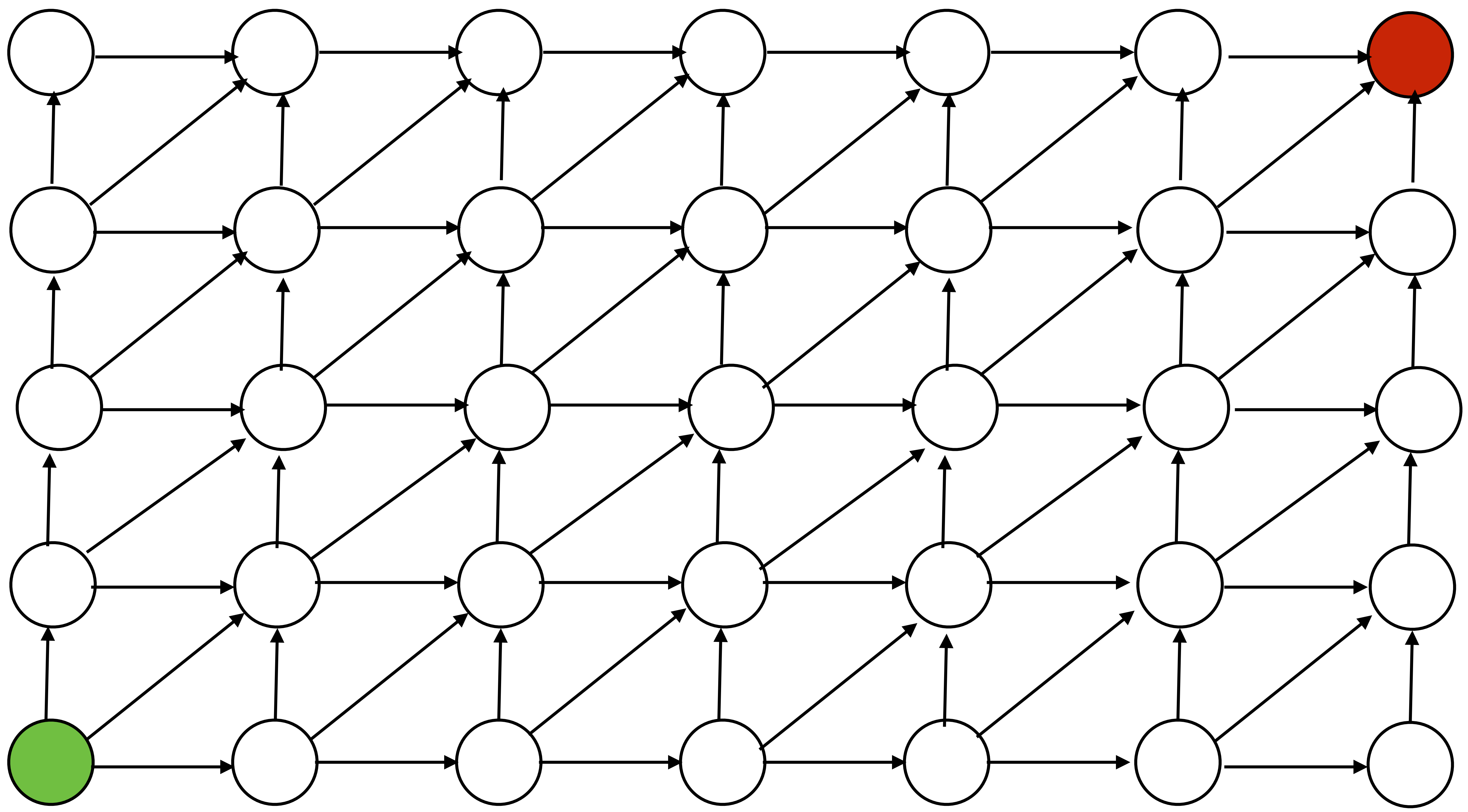
Algorithmic idea: Combine both dynamic programs using *divide-and-conquer*

Divide-and-conquer splits a problem into smaller sub-problems and combines the results (much like DP).

Examples: MergeSort & Karatsuba multiplication

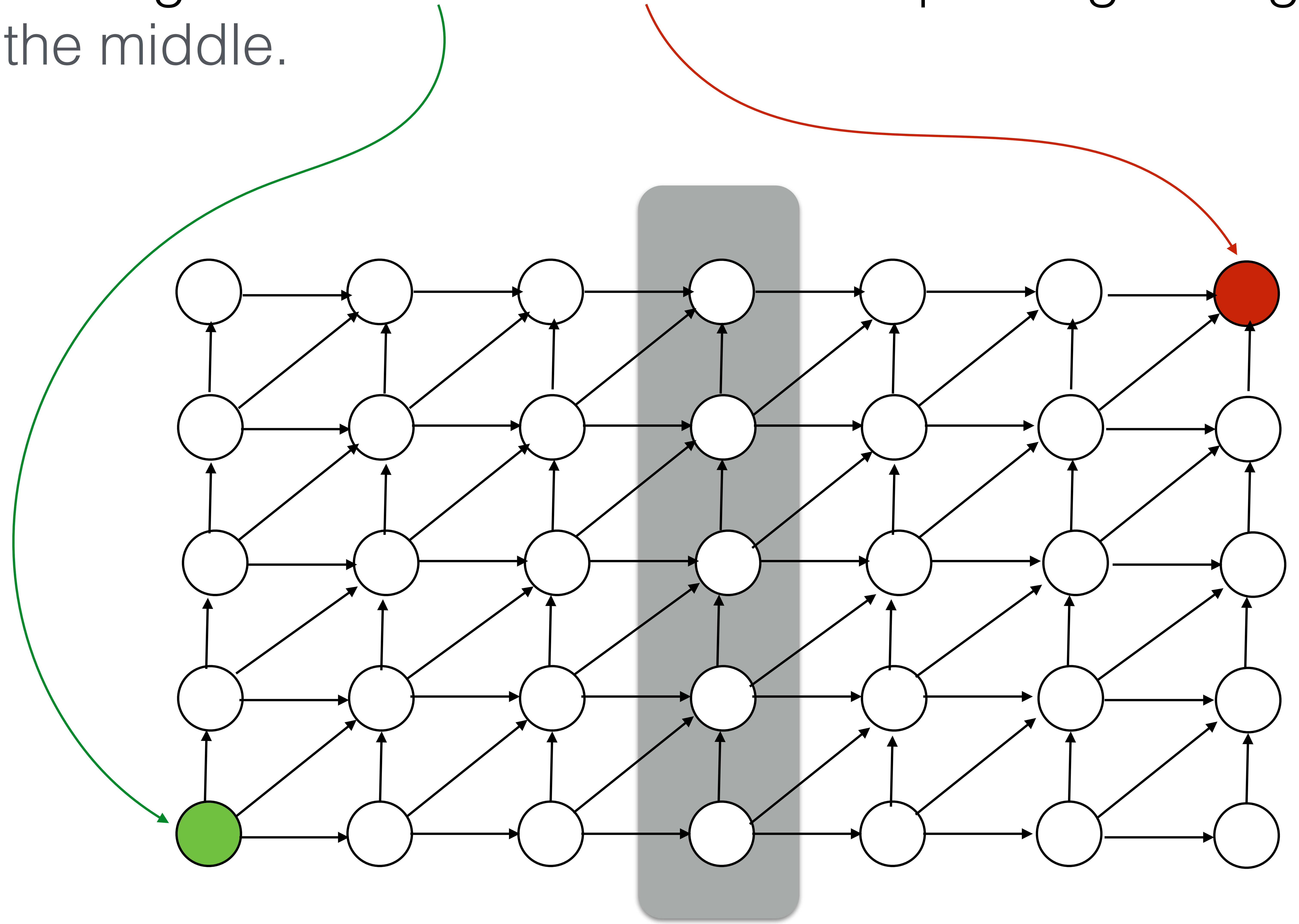
Think about this in "graph" land

What do we know about the structure of the optimal path in our "edit-DAG"?



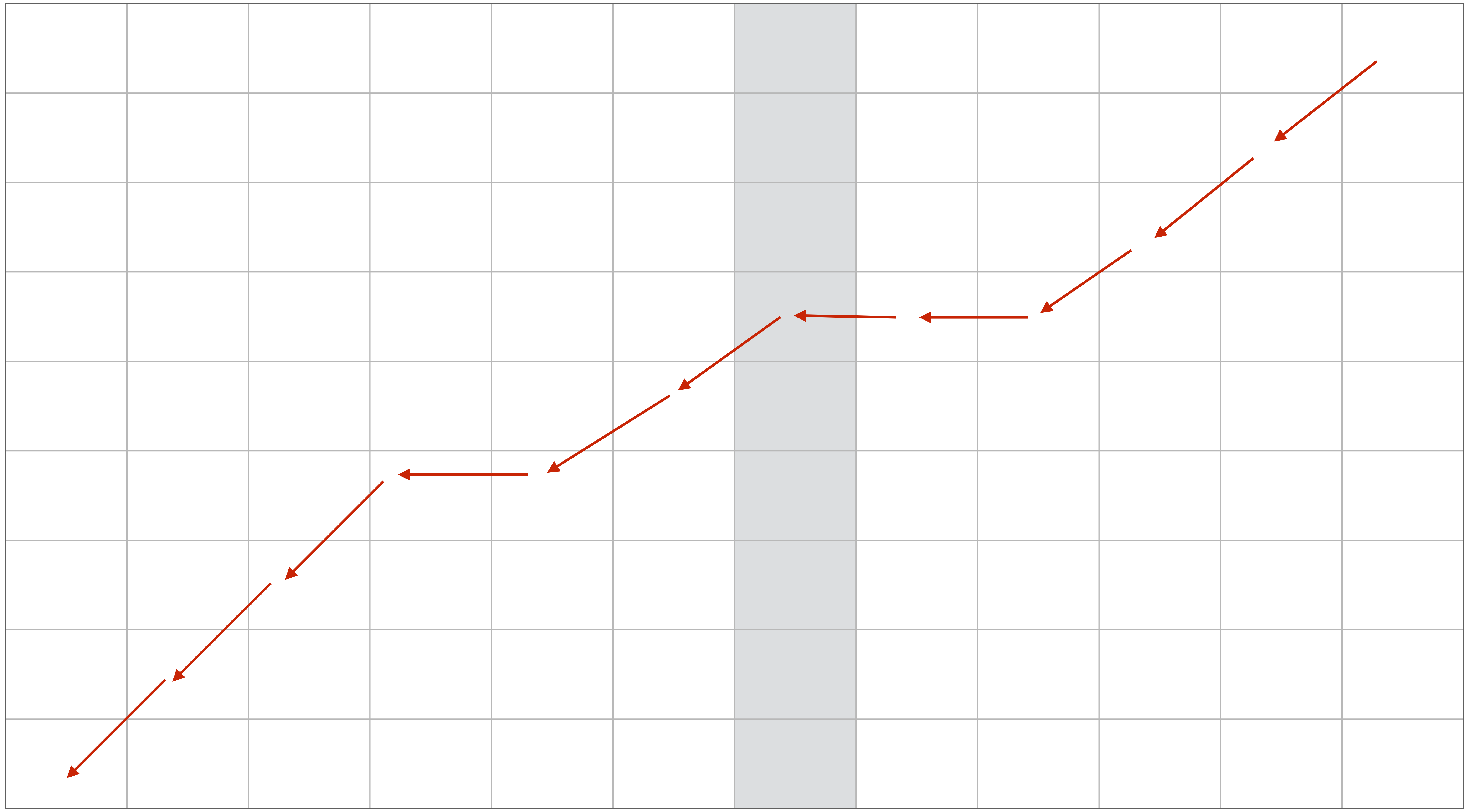
Think about this in "graph" land

Can't get from here to there without passing through the middle.



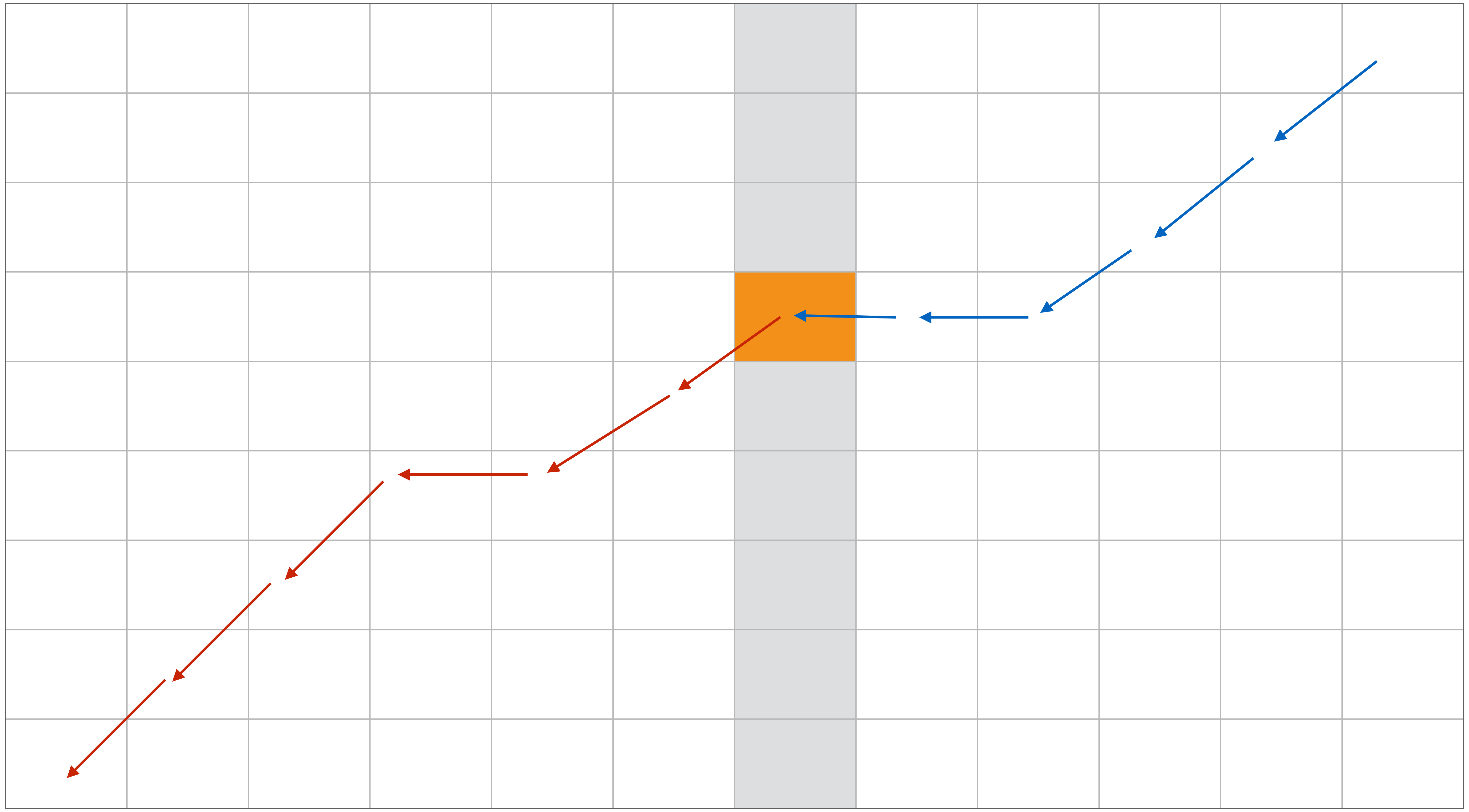
Finding the optimal alignment

Consider the middle column — we *know* that the optimal aln. must use some cell in this column; which one?



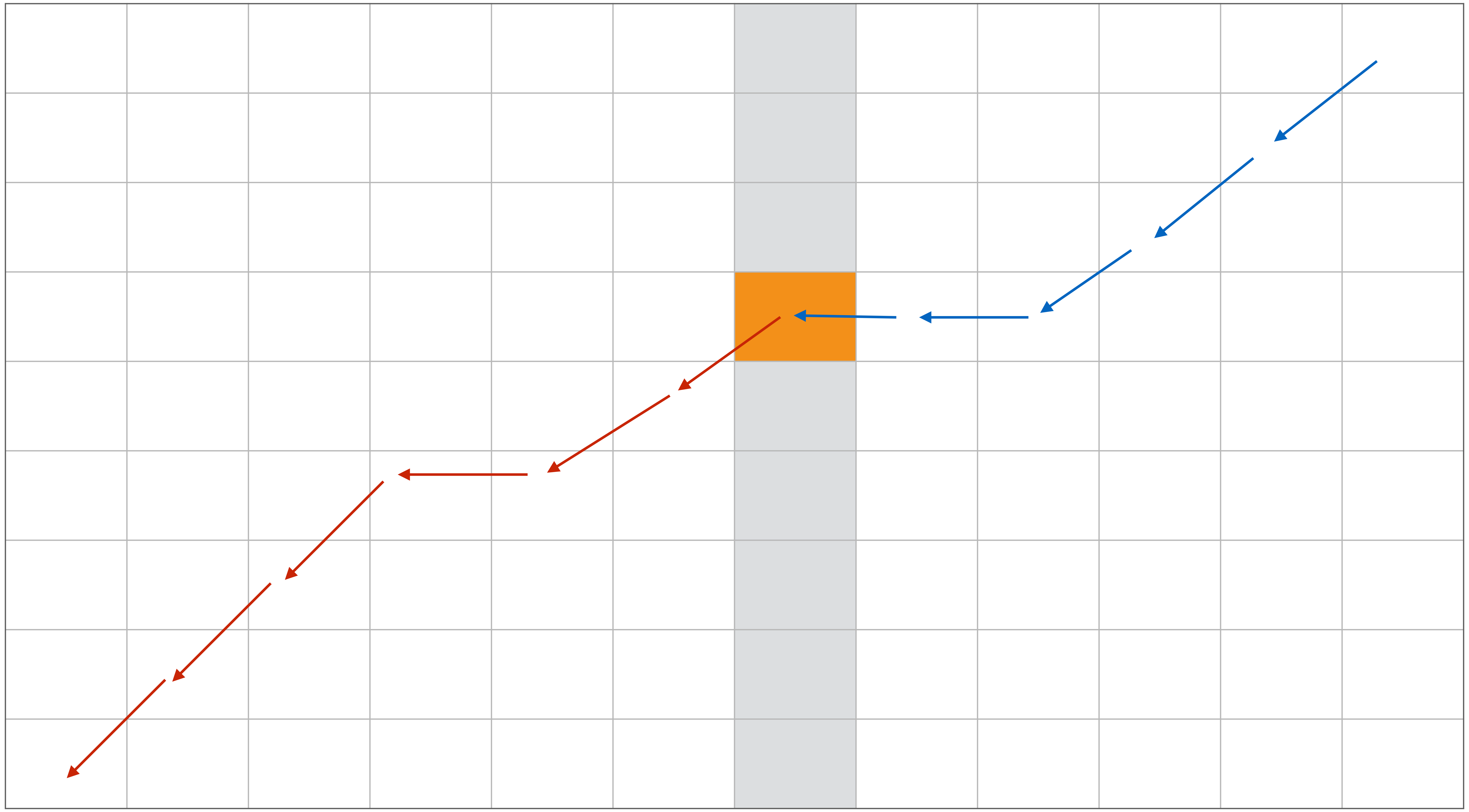
Finding the optimal alignment

It uses the cell (i,j) such that OPT[i,j] + OPT'[i,j] has the **highest score**. Equivalently, the *best path* uses some vertex *v* in the middle col. and glues together the best paths from the source *to* v and *from* v to the sink.



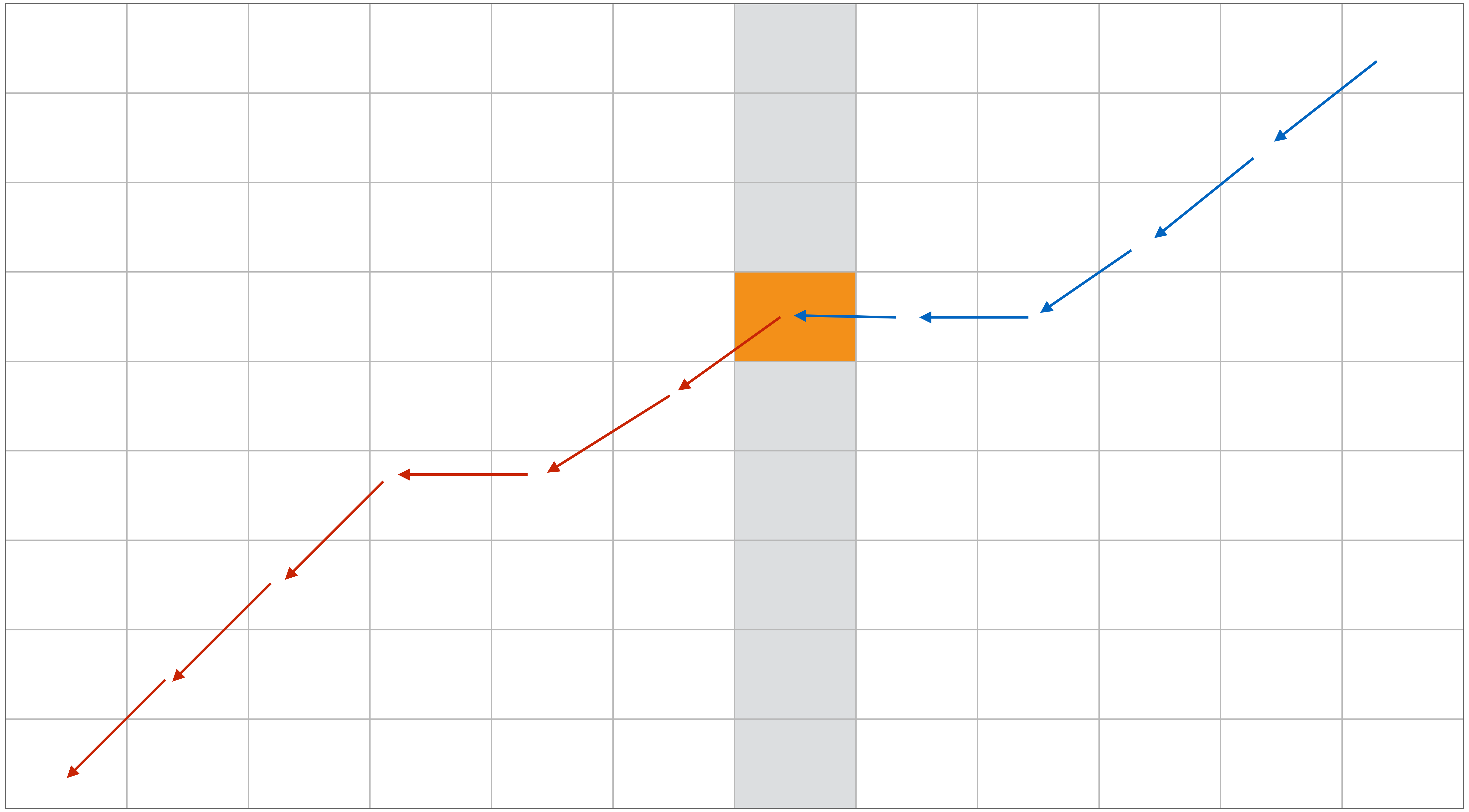
Finding the optimal alignment

Claim: OPT[i,j] and OPT’[i,j] can be computed in linear space using the trick from above for finding an optimal **score** in linear space



Algorithmic Idea

Devise a D&C algorithm that finds the optimal alignment path recursively, using the space-efficient scoring algorithm for each subproblem.



D&C Alignment

```
DCAlignment(x, y):
    n = |x|
    m = |y|
    if m <= 2 or n <= 2:
        use “normal” DP to compute OPT(x, y)
    compute space-efficient OPT(x[1:n/2], y)
    compute space-efficient OPT’(x[n/2+1:n], y)
    let q be the index maximizing OPT[n/2,q] + OPT’[n/2,q]
    add back pointer of (n/2,q) to the optimal alignment P
    DCAlignment(x[1:n/2], y[1:q])
    DCAlignment(x[n/2+1:n], y[q+1:m])
    return P
```

Adopted from “Algorithm Design” Kleinberg & Tardos (Ch. 6.7 pg 288)

D&C Alignment

How can we show that this entire process still takes quadratic time?

Let T(n,m) be the running time on strings **x** and **y** of length n and m, respectively. We have:

$$T(n,m) \leq cnm + \boxed{T(n/2,\ q)} + \boxed{T(n/2,\ m\text{-}q)}$$

`DCAlignment(x[1:n/2], y[1:q])`   `DCAlignment(x[n/2+1:n], y[q+1:m])`

with base cases:

$T(n,2) \leq cn$

$T(2,m) \leq cm$

Adopted from "Algorithm Design" Kleinberg & Tardos (Ch. 6.7 pg 289 — 290)

D&C Alignment

Base:

$T(n,2) \leq cn$

$T(2,m) \leq cm$

Inductive:

$T(n,m) \leq cnm + T(n/2, q) + T(n/2, m\text{-}q)$

Problem: we don't know what q is. First, assume both **x** and **y** have length n and q=n/2
(will remove this restriction later)

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

This recursion solves as $T(n) = O(n^2)$

Leads us to guess $T(n,m)$ grows like $O(nm)$

Adopted from "Algorithm Design" Kleinberg & Tardos (Ch. 6.7 pg 289 — 290)

Smarter Induction

Base:

$T(n,2) \leq cn$

$T(2,m) \leq cm$

Inductive:

$T(n,m) \leq knm$

Proof:

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

Thus, our proof holds if $k=2c$, and $T(n,m) = O(nm)$ QED

Adopted from "Algorithm Design" Kleinberg & Tardos (Ch. 6.7 pg 289 — 290)

Conclusion

Trivially, we can compute the *cost* of an optimal alignment in linear space

By arranging subproblems intelligently we can define a "reverse" DP that works on suffixes instead of prefixes

Combining the "forward" and "reverse" DP using a divide and conquer technique, we can compute the optimal *solution* (not just the score) in linear space.

This still only takes O(nm) time; constant factor more work than the "forward"-only algorithm.

Doing better (in time) *in practice*

Can we do better *in practice*?

What about when we know that the edit distance is small (say e << mn)?
What about when we only care about edit distances < some threshold?

Yes!

JOURNAL ARTICLE

Optimal gap-affine alignment in $O(s)$ space

Santiago Marco-Sola, Jordan M Eizenga, Andrea Guarracino, Benedict Paten, Erik Garrison, Miquel Moreto

Bioinformatics, Volume 39, Issue 2, February 2023, btad074,
https://doi.org/10.1093/bioinformatics/btad074
Published: 07 February 2023 **Article history** ▾

Exact global alignment using A* with seed heuristic and match pruning

Ragnar Groot Koerkamp [*,†] **and Pesho Ivanov** [*,†]

Department of Computer Science, ETH Zurich, Switzerland

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†These authors contributed equally to this work.

O(ns) time and O(s) space where s is the score of the *optimal alignment*!

← Practically even fewer comparisons than BiWFA

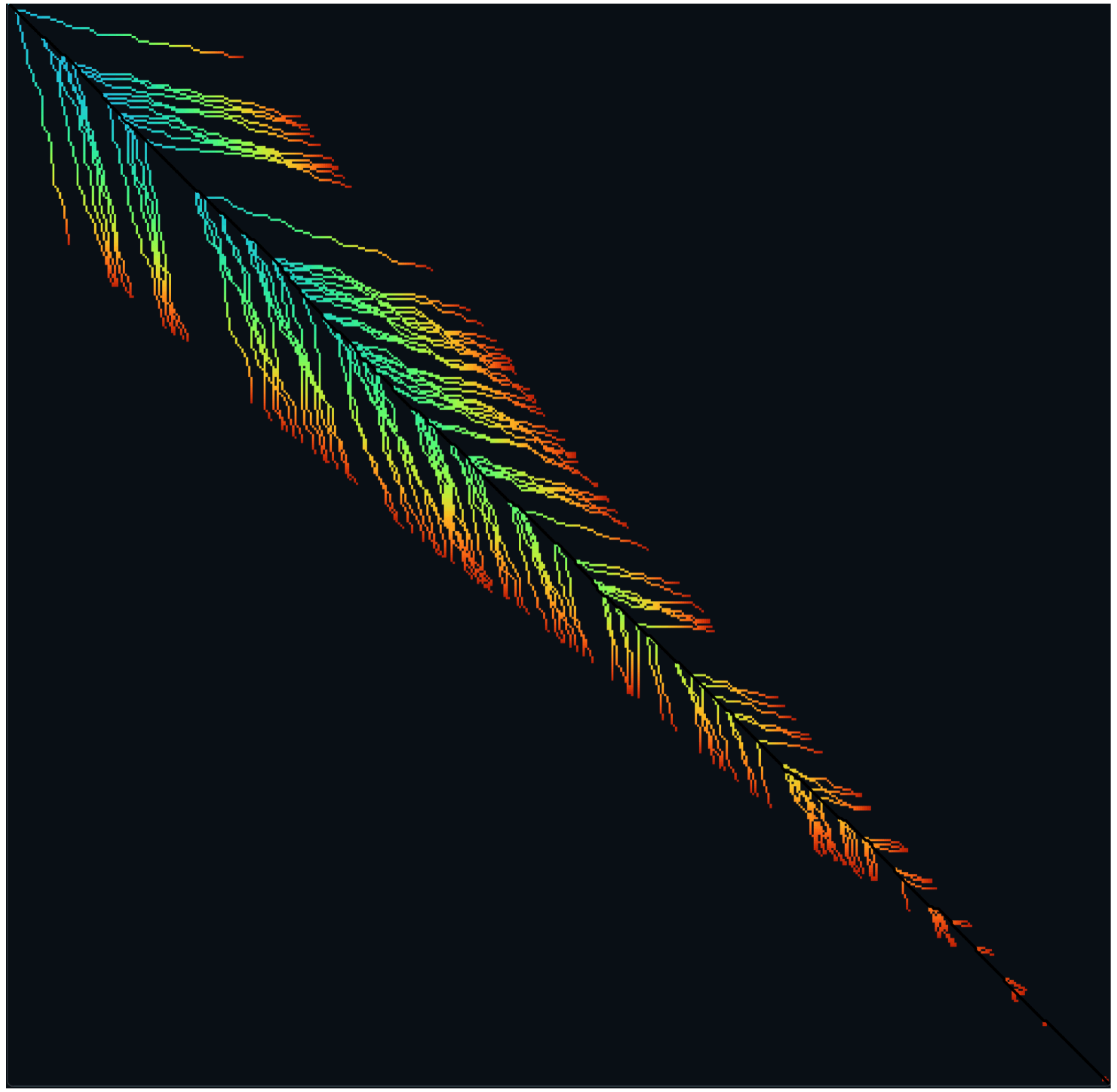
https://doi.org/10.1093/bioinformatics/btad074

https://www.biorxiv.org/content/10.1101/2022.09.19.508631v2

Doing better (in time) *in practice*

Beautiful motivation:

https://github.com/RagnarGrootKoerkamp/astar-pairwise-aligner



Diagonal transition (WFA)