

CS 466

Introduction to Bioinformatics

Lecture 5

Mohammed El-Kebir

September 11, 2019



Course Announcements

Instructor:

- Mohammed El-Kebir (melkebir)
- Office hours: Wednesdays, 3:15-4:15pm

TA:

- Aswhin Ramesh (aramesh7)
- Office hours: Fridays, 11:00-11:59am in SC 3405

Homework 1: Due on Sept. 18 (11:59pm)

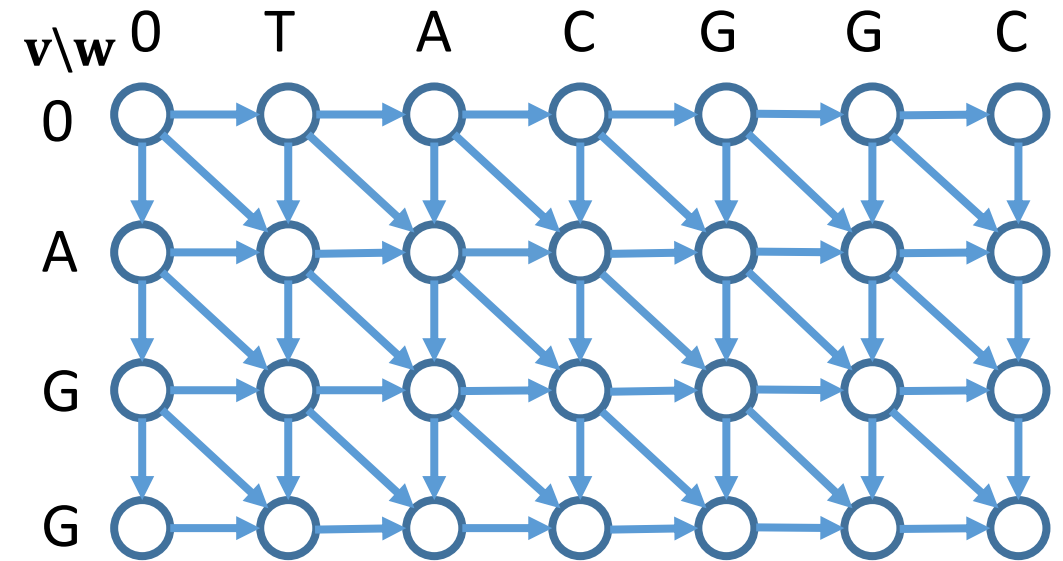
Midterm: 10/4, 11-1pm @Transportation Building 103
(conflict: 10/7, 7-9pm @Siebel 1302 -- to sign up email me)

Global, Fitting and Local Alignment

Global Alignment problem: Given strings $\mathbf{v} \in \Sigma^m$ and $\mathbf{w} \in \Sigma^n$ and scoring function δ , find alignment of \mathbf{v} and \mathbf{w} with maximum score.
[Needleman-Wunsch algorithm]

Fitting Alignment problem: Given strings $\mathbf{v} \in \Sigma^m$ and $\mathbf{w} \in \Sigma^n$ and scoring function δ , find an alignment of \mathbf{v} and a substring of \mathbf{w} with maximum global alignment score s^* among *all* global alignments of \mathbf{v} and *all* substrings of \mathbf{w}

Local Alignment problem: Given strings $\mathbf{v} \in \Sigma^m$ and $\mathbf{w} \in \Sigma^n$ and scoring function δ , find a substring of \mathbf{v} and a substring of \mathbf{w} whose alignment has maximum global alignment score s^* among *all* global alignments of *all* substrings of \mathbf{v} and \mathbf{w}
[Smith-Waterman algorithm]



Question: How to assess resulting algorithms?

Time Complexity

		A T C G				
A T G T	$\begin{matrix} \text{V} & \text{W} \\ \text{V} & \end{matrix}$	0	1	2	3	$n = 4$
	0	0	→ 0	→ 0	→ 0	→ 0
	1	↓ 0	↘ 0	↓ 0	↘ 0	↓ 0
	2	↓ 0	↘ 0	↓ 0	↘ 0	↓ 0
	3	↓ 0	↘ 0	↓ 0	↘ 0	↓ 0
	$m = 4$	↓ 0	↘ 0	↓ 0	↘ 0	↓ 0

Edit graph is a weighed, directed grid graph $G = (V, E)$ with source vertex $(0, 0)$ and target vertex (m, n) . Each edge $((i, j), (k, l))$ has weight depending on direction.

Alignment is a path from source $(0, 0)$ to target (m, n) in edit graph

Running time is $O(mn)$
[quadratic time]

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Alignment is a path from source $(0, 0)$ to target (m, n) in edit graph

Running time is $O(mn)$
[quadratic time]

Question: Compute alignment faster than $O(mn)$ time? [subquadratic time]

Space Complexity

		A T C G				
A T G T	v \ w	0	1	2	3	$n = 4$
	0					
	1					
	2					
	3					
	$m = 4$					

Size of DP table is $(m + 1) \times (n + 1)$

Thus, space complexity is $O(mn)$
[quadratic space]

Example:

To align a short read ($m = 100$) to human genome ($n = 3 \cdot 10^9$), we need 300 GB memory.

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Question: How long is an alignment?

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[quadratic space]

Example:

To align a short read ($m = 100$) to human genome ($n = 3 \cdot 10^9$), we need 300 GB memory.

Question: How long is an alignment?

Question: Compute alignment in $O(m)$ space? [linear space]

Outline

1. Recap of global, fitting, local and gapped alignment
2. Space-efficient alignment
3. Subquadratic time alignment

Reading:

- Jones and Pevzner. Chapters 7.1-7.4
- Lecture notes

Space Efficient Alignment

Computing $s[i, j]$ requires access to:
 $s[i - 1, j]$, $s[i, j - 1]$ and $s[i - 1, j - 1]$

$$s[i, j] = \max \begin{cases} 0, & \text{if } i = 0 \text{ and } j = 0, \\ s[i - 1, j] + \delta(v_i, -), & \text{if } i > 0, \\ s[i, j - 1] + \delta(-, w_j), & \text{if } j > 0, \\ s[i - 1, j - 1] + \delta(v_i, w_j), & \text{if } i > 0 \text{ and } j > 0. \end{cases}$$

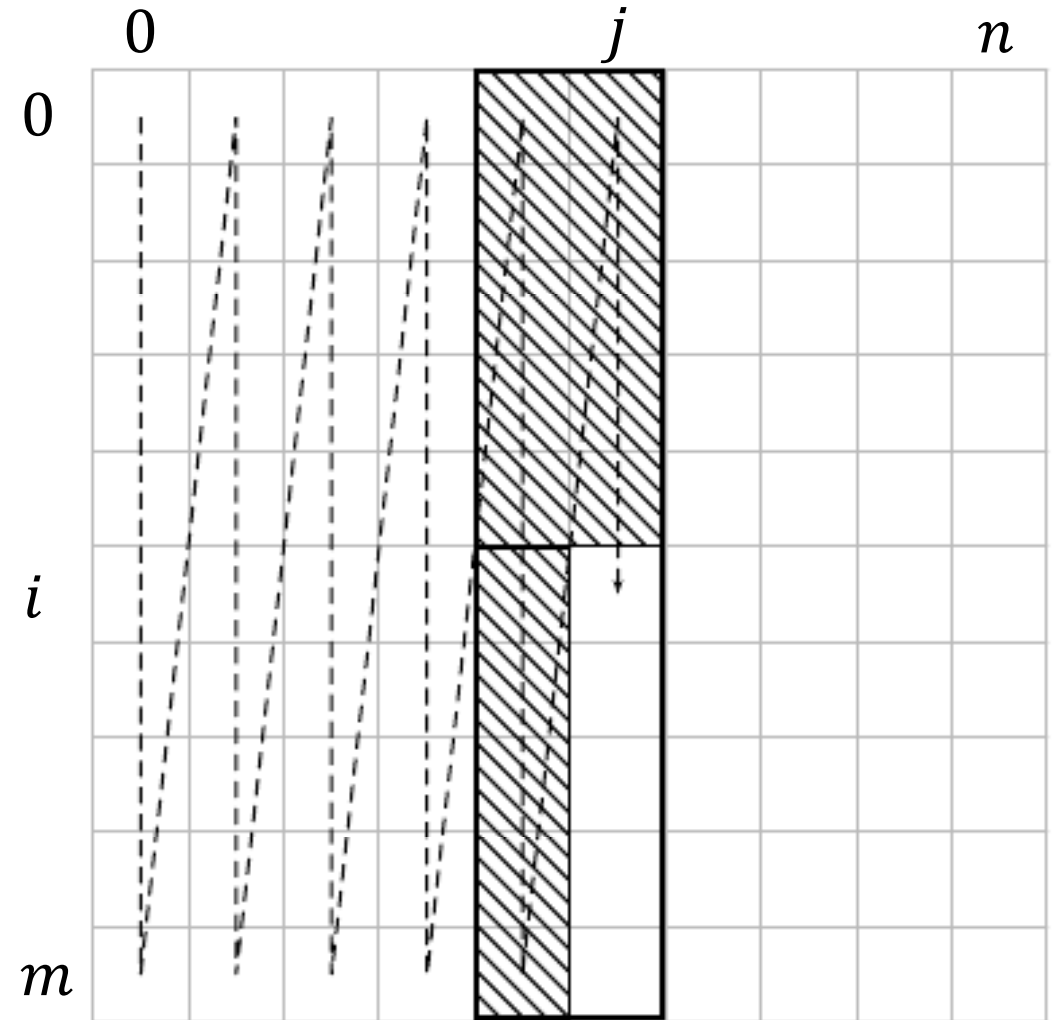


Figure 7.2 Calculating an alignment score requires no more than $2n$ space for an $n \times n$ alignment problem. Computing the alignment scores in each column requires only the scores in the preceding column. We show here the dynamic programming array—the data structure that holds the score at each vertex—instead of the graph.

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Thus it suffices to store only two columns to compute optimal alignment score $s[m, n]$,
i.e., $2(m + 1) = O(m)$ space.

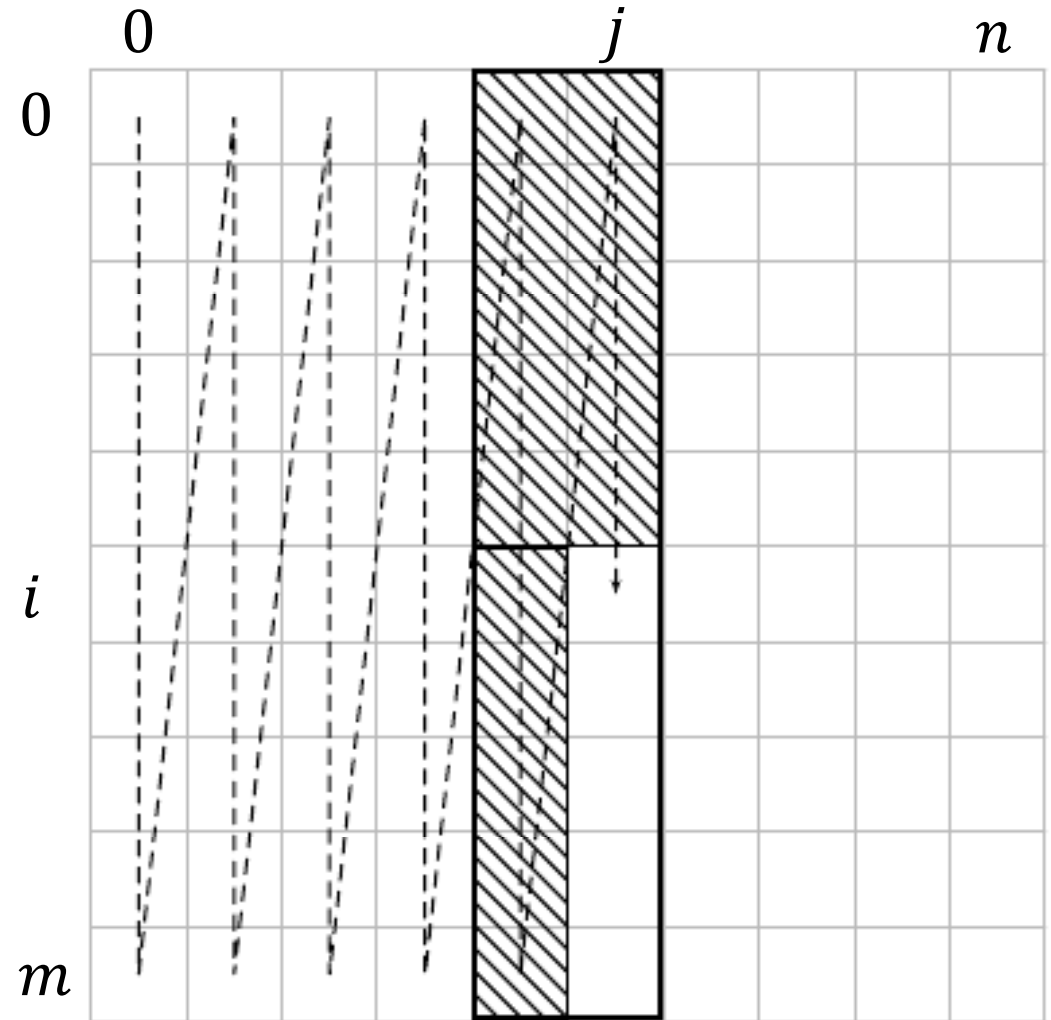


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Question: What if we want alignment itself?

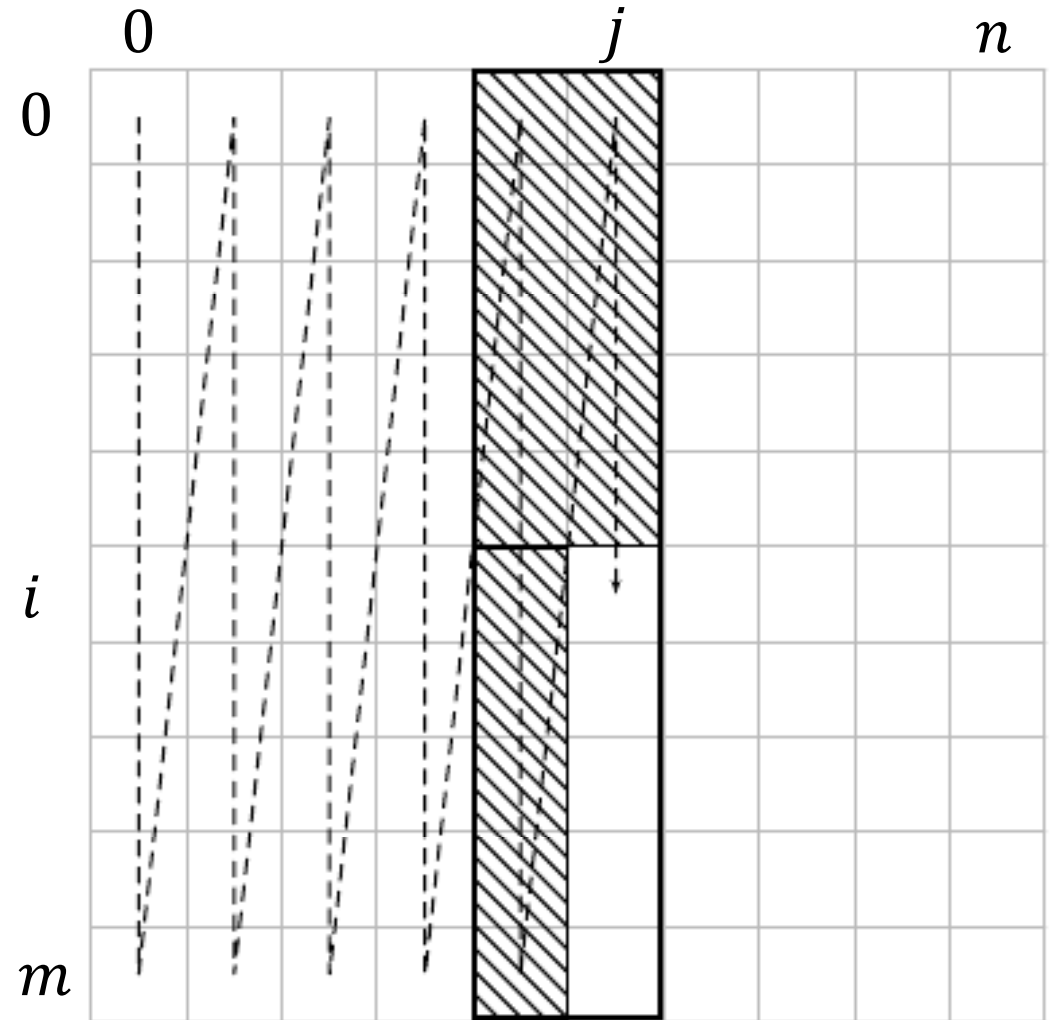
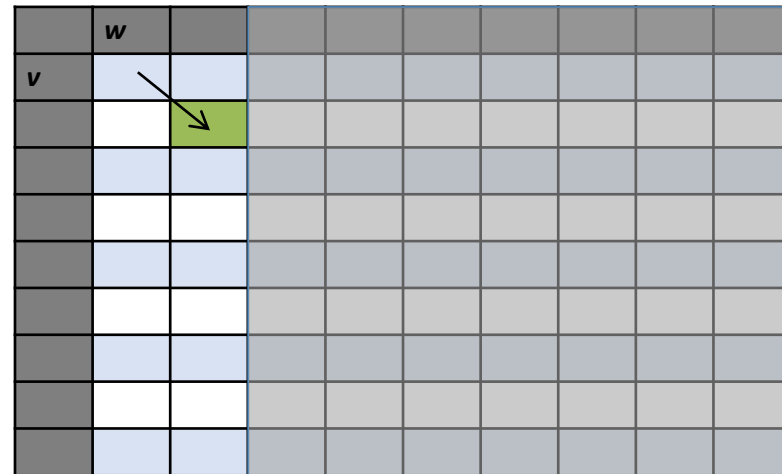
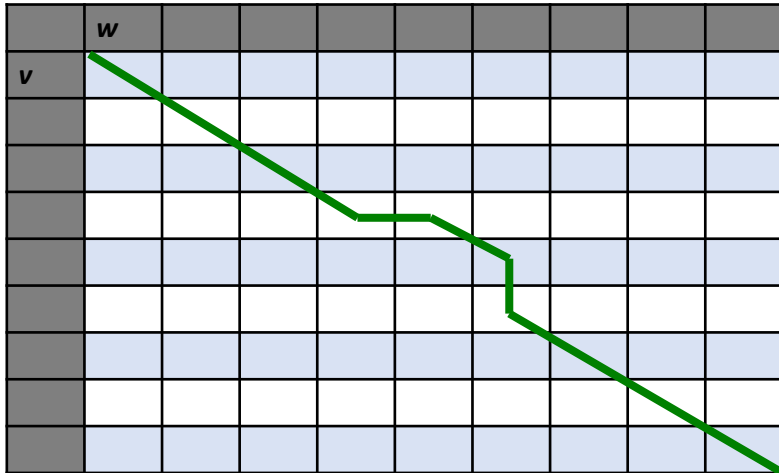


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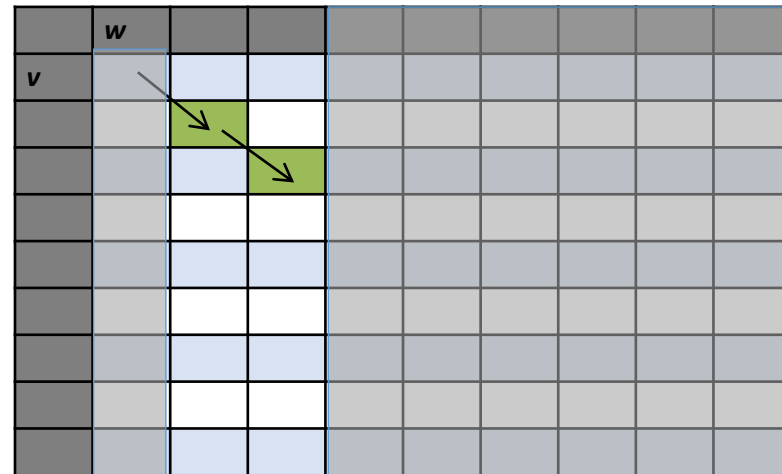
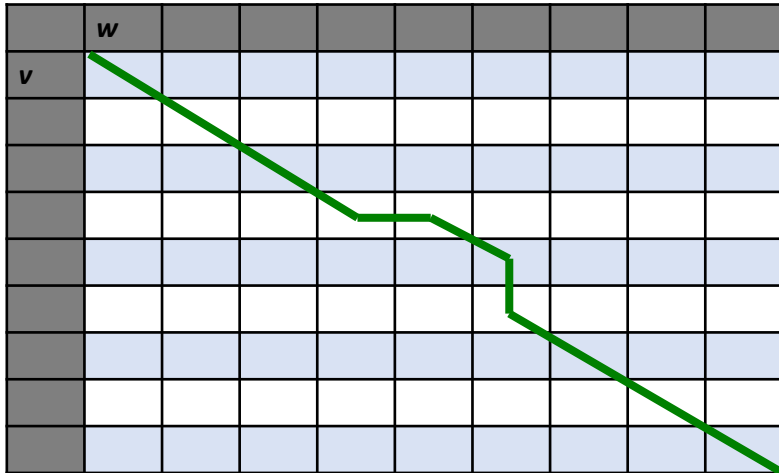
Space Efficient Alignment – First Attempt

- What if also want optimal alignment?
- **Easy**: keep best pointers as fill in table.
- **No!** Do not know which path to keep until computing recurrence at each step.



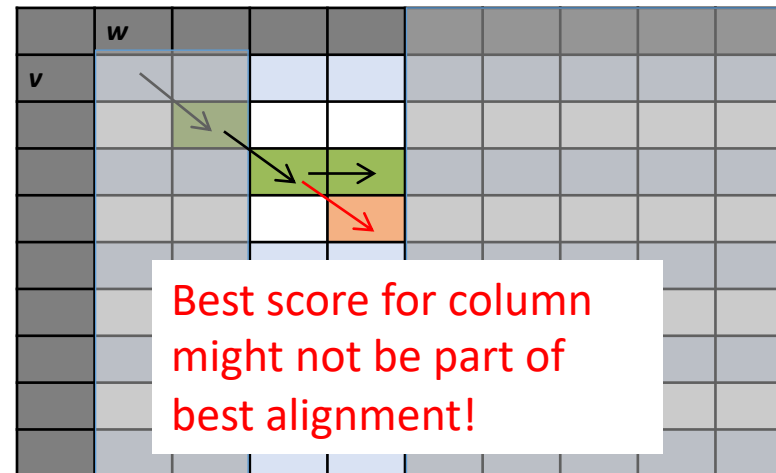
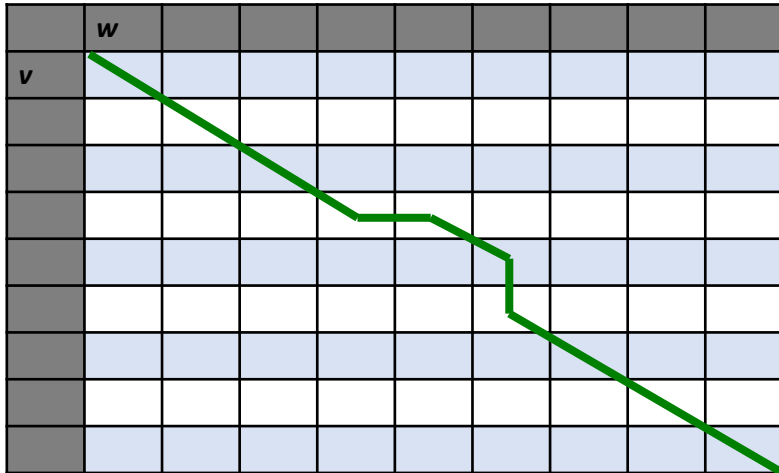
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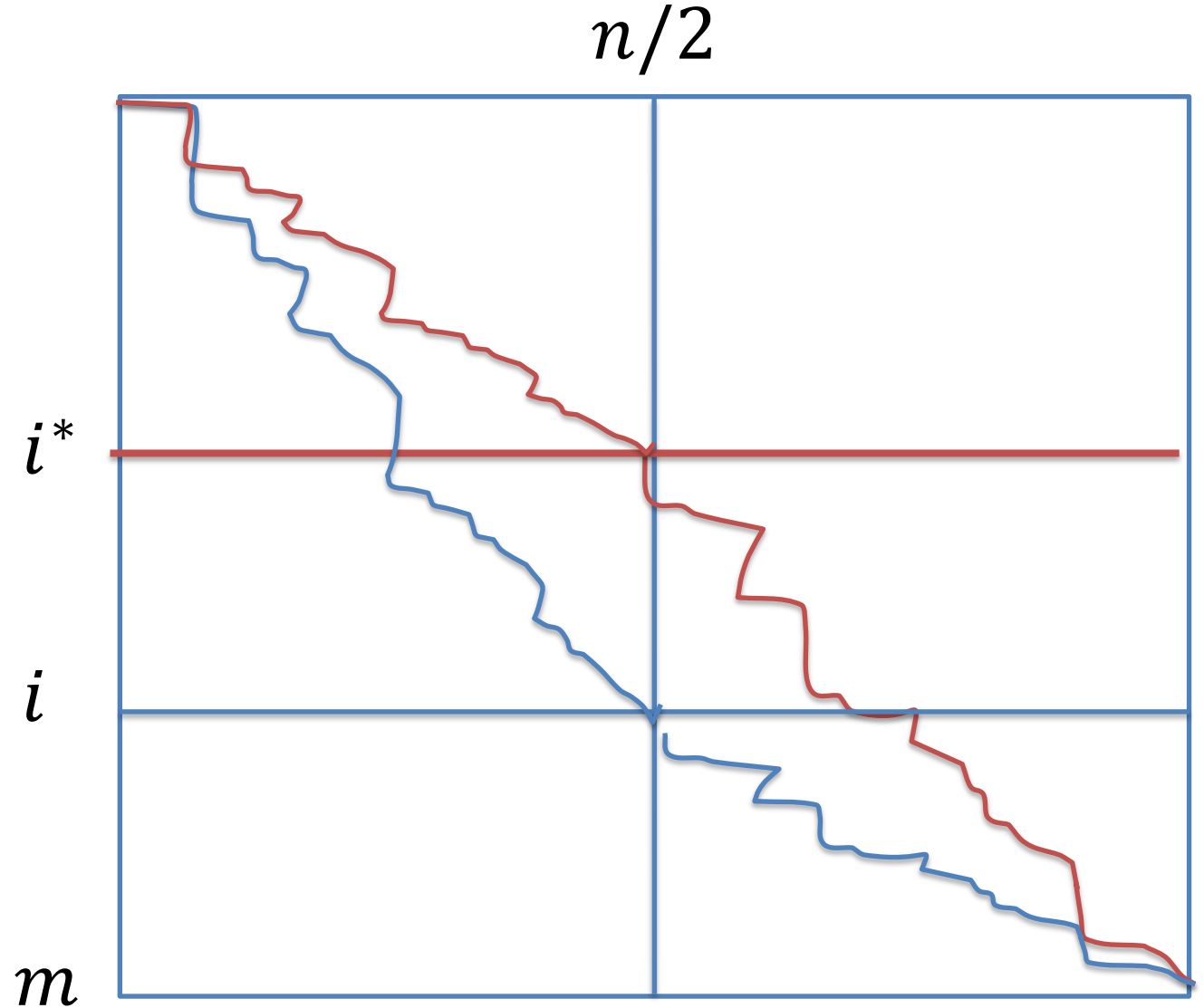


Space Efficient Alignment – Second Attempt

Alignment is a path from source $(0, 0)$ to target (m, n) in edit graph

Maximum weight path from $(0, 0)$ to (m, n) passes through $(i^*, n/2)$

Question: What is i^* ?



Linear-Space Sequence Alignment

The figure consists of six sub-diagrams arranged in a 3x2 grid, illustrating the divide-and-conquer approach to sequence alignment.

- Top-left:** A square representing the alignment space with axes from $(0,0)$ to (n,m) . A diagonal line represents the alignment path. A horizontal line at i and a vertical line at $m/2$ divide the space. The intersection on the diagonal is labeled "middle".
- Top-right:** The same square with the region to the left of $m/2$ shaded gray and the region to the right shaded black.
- Middle-left:** The square is further divided by a horizontal line at $i/2$ and a vertical line at $m/4$. The intersection on the diagonal is labeled "middle".
- Middle-right:** The square is divided into four quadrants. The top-left quadrant is shaded gray, and the bottom-right quadrant is shaded black.
- Bottom-left:** The square is further divided into smaller sub-squares. The intersection on the diagonal is labeled "middle".
- Bottom-right:** The square is divided into four quadrants. The top-left quadrant is shaded gray, and the bottom-right quadrant is shaded black.

1. if $j' - j > 1$

$$2. \quad i^* \leftarrow \arg \max_{i \leq i'' \leq i'} \text{wt}(i'')$$

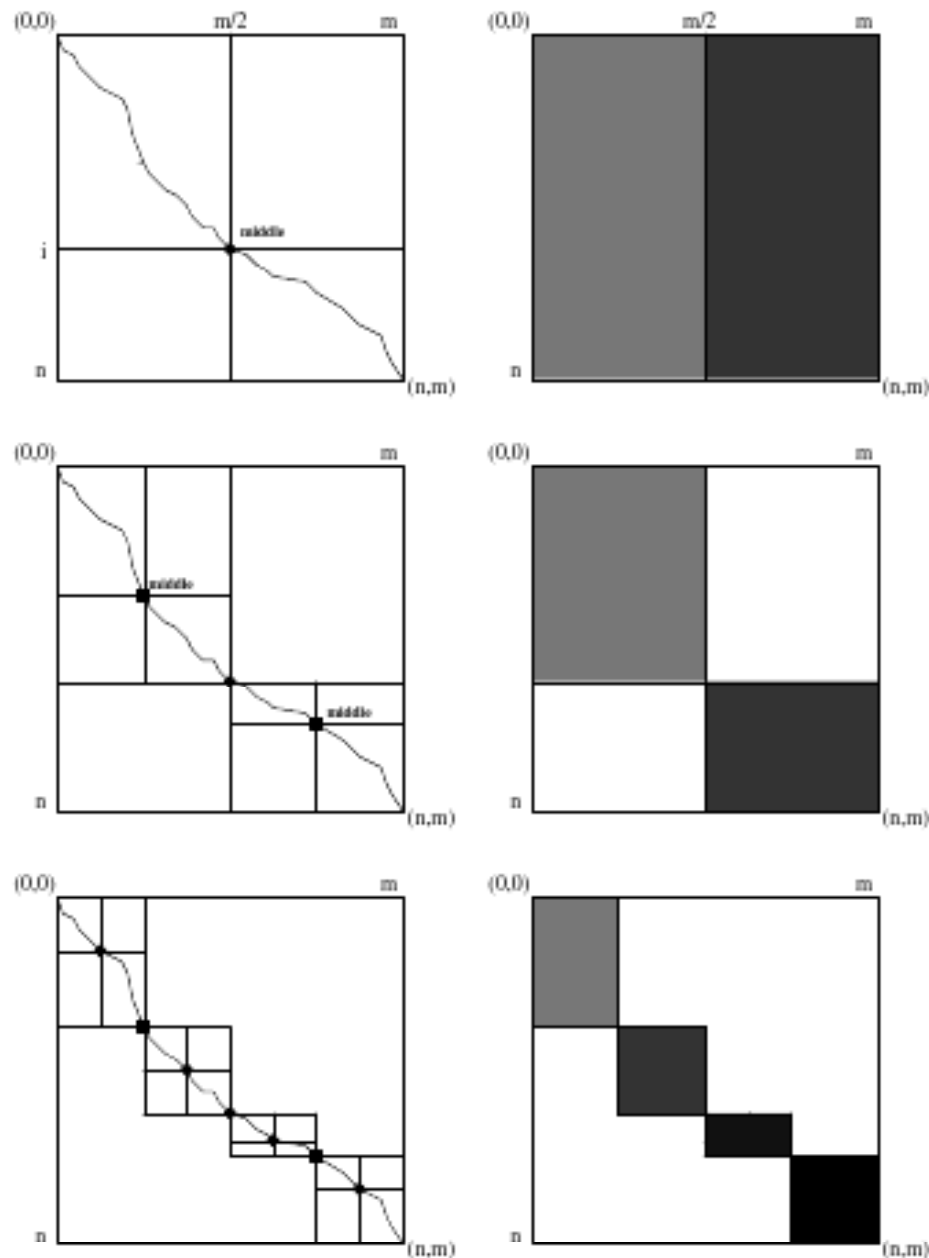
3. Report $(i^*, j + \frac{j' - j}{2})$

4. $\text{Hirschberg}(i, j, i^*, j + \frac{j' - j}{2})$

5. $\text{Hirschberg}(i^*, j + \frac{j' - j}{2}, i', j')$

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Linear-Space Sequence Alignment



Hirschberg(i, j, i', j')

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2. $i^* \leftarrow \arg \max_{i \leq i'' \leq i'} \text{wt}(i'')$
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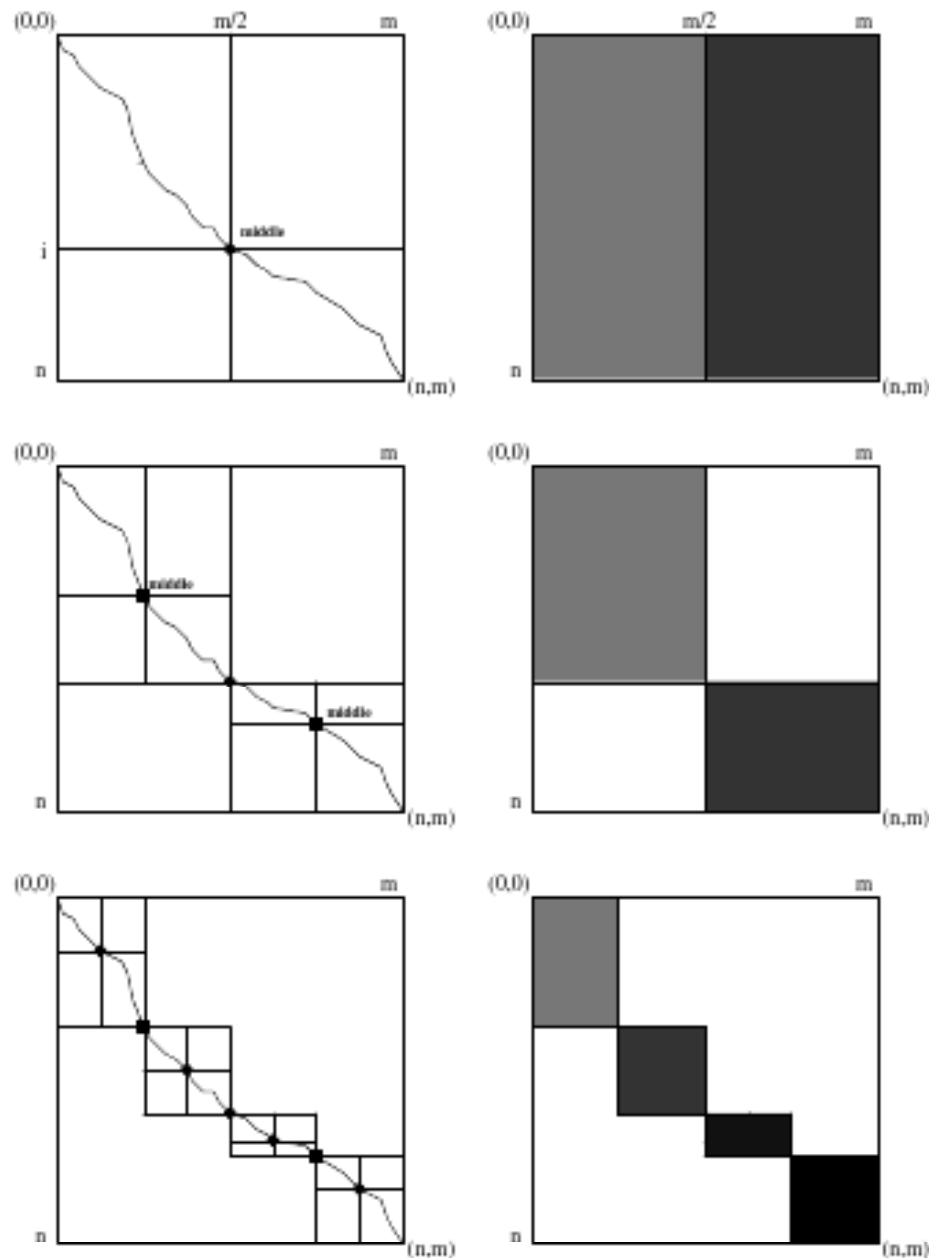
Time:

$$\begin{aligned}
 & \text{area} + \text{area}/2 + \text{area}/4 + \dots \\
 & = \text{area} (1 + 1/2 + 1/4 + 1/8 + \dots) \\
 & \leq 2 \times \text{area} = O(mn)
 \end{aligned}$$

Space: $O(m)$

Figure 7.3 Space-efficient sequence alignment. The computational time (i.e., the area of the solid rectangles) decreases by a factor of 2 at every iteration.

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Time:

$$\begin{aligned} & \text{area} + \text{area}/2 + \text{area}/4 + \dots \\ &= \text{area} (1 + 1/2 + 1/4 + 1/8 + \dots) \\ &\leq 2 \times \text{area} = O(mn) \end{aligned}$$

Space: $O(m)$

Question: How to reconstruct alignment from reported vertices?

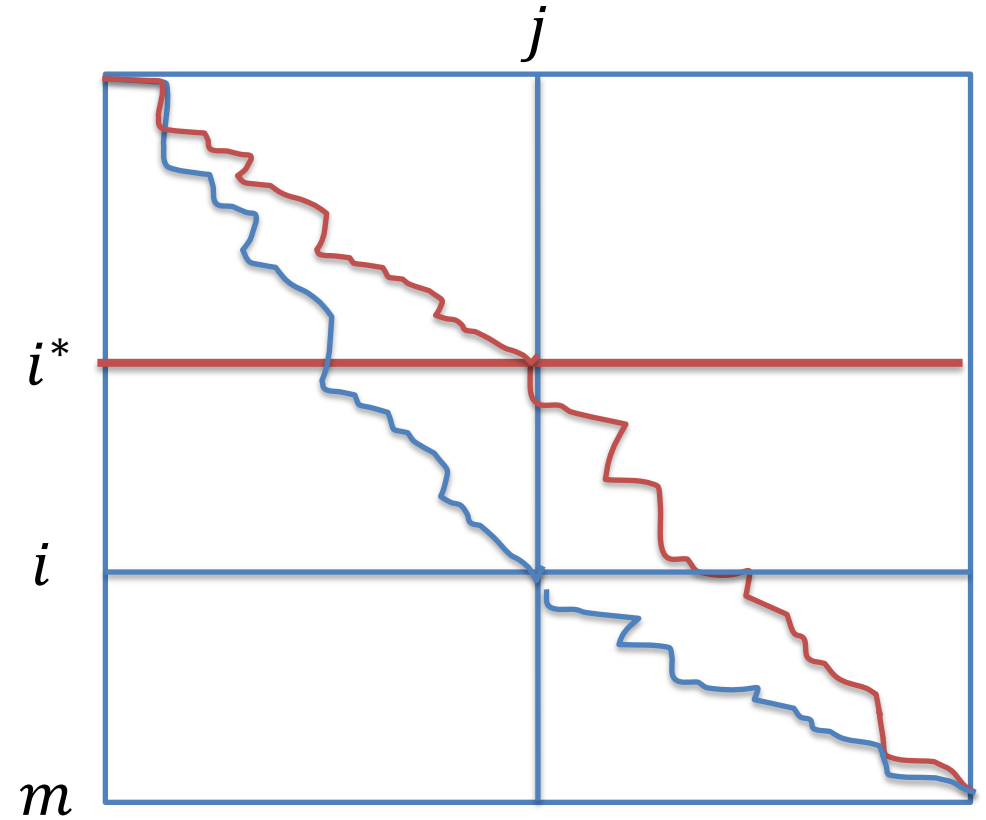
Figure 7.3 Space-efficient sequence alignment. The computational time (i.e., the area of the solid rectangles) decreases by a factor of 2 at every iteration.

Hirschberg Algorithm: Reversing Edges Necessary?

Max weight path from $(0,0)$ to (m,n) through $(i^*, n/2)$

$$i^* = \arg \max_{0 \leq i \leq m} \{ \text{prefix}(i) + \text{suffix}(i) \}$$

Compute $\{\text{prefix}(i) \mid 0 \leq i \leq m\}$ in $O(mj)$ time and $O(m)$ space, by starting from $(0,0)$ to (m,j) keeping only two columns in memory. [**single-source multiple destinations**]



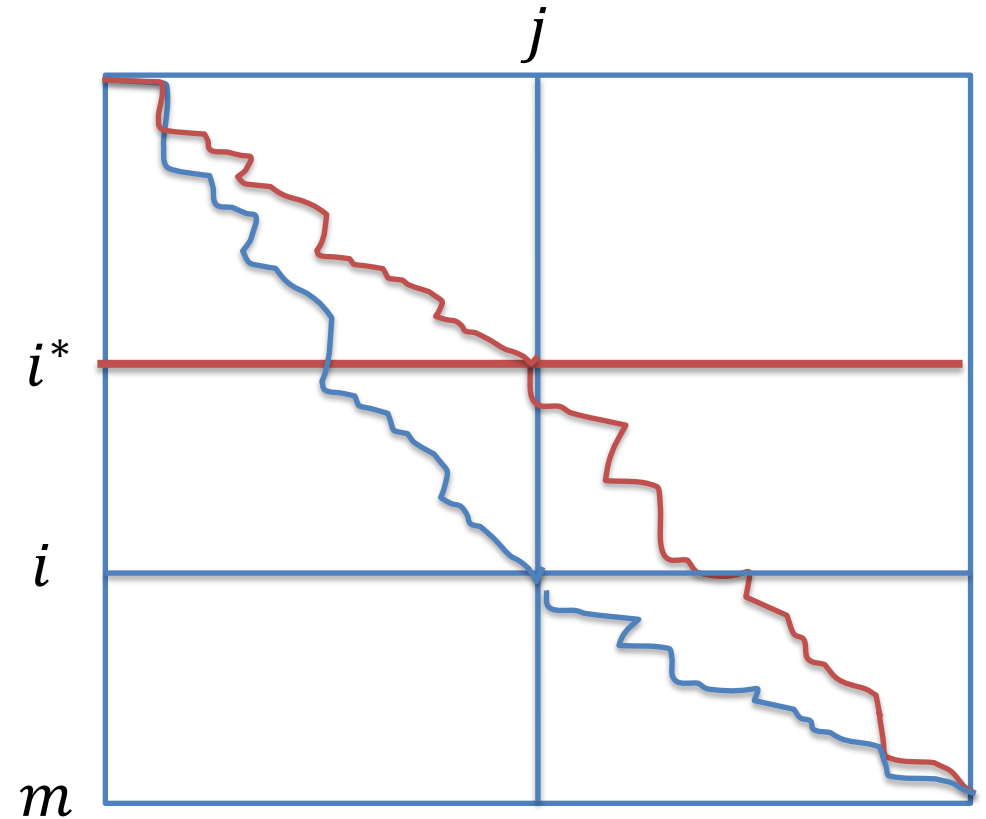
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Want: Compute $\{\text{suffix}(i) \mid 0 \leq i \leq m\}$ in $O(mj)$ time and $O(m)$ space



Doing a longest path from each (i,j) to (m,n) (for all $0 \leq i \leq m$) will not achieve desired running time!

Reversing edges enables single-source multiple destination computation in desired time and space bound!

Hirschberg Algorithm: Reconstructing Alignment

		A	T	C	G	C	
A T G T C	W v	0	1	2	3	4	5
	0	0	-1	-2	-3	-4	-5
	1	-1	1	0	-1	-2	-3
	2	-2	0	2	1	0	-1
	3	-3	-1	1	1	2	1
	4	-4	-2	0	0	1	1
	5	-5	-3	-1	1	0	2

A	T	-	G	T	C
A	T	C	G	-	C

Hirschberg(i, j, i', j')

1. if $j' - j > 1$
2. $i^* \leftarrow \arg \max_{0 \leq i \leq m} \text{wt}(i)$
3. Report $(i^*, j + \frac{j' - j}{2})$
4. Hirschberg($i, j, i^*, j + \frac{j' - j}{2}$)
5. Hirschberg($i^*, j + \frac{j' - j}{2}, i', j'$)

Problem: Given reported vertices and scores $\{(i_0, 0, s_0), \dots, (i_n, n, s_n)\}$, find intermediary vertices.

Transposing matrix does not help, because gaps could occur in both input sequences

Linear Space Alignment – The Hirschberg Algorithm

Programming
Techniques

G. Manacher
Editor

A Linear Space Algorithm for Computing Maximal Common Subsequences

D.S. Hirschberg
Princeton University



Dan Hirschberg

Professor of Computer Science & EECS
UC Irvine Senate Parliamentarian

Outline

1. Recap of global, fitting, local and gapped alignment
2. Space-efficient alignment
3. Subquadratic time alignment

Reading:

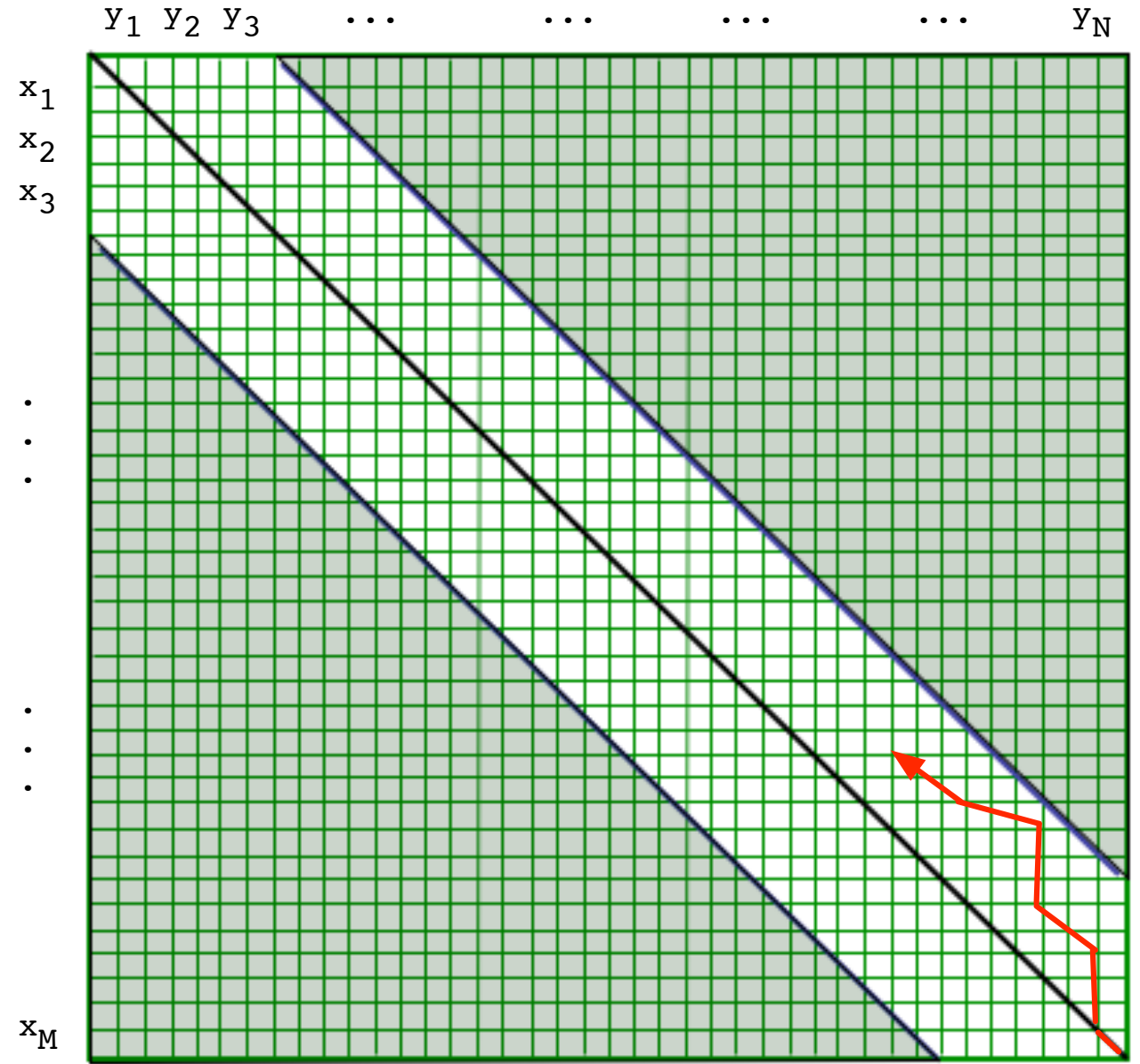
- Jones and Pevzner. Chapters 7.1-7.4
- Lecture notes

Banded Alignment

Constraint path to band of width k around diagonal

Running time: $O(nk)$

Gives a good approximation of highly identical sequences



Constrain traceback to band of DP matrix (penalize big gaps)

Figure source: http://jinome.stanford.edu/stat366/pdfs/stat366_win0607_lecture04.pdf

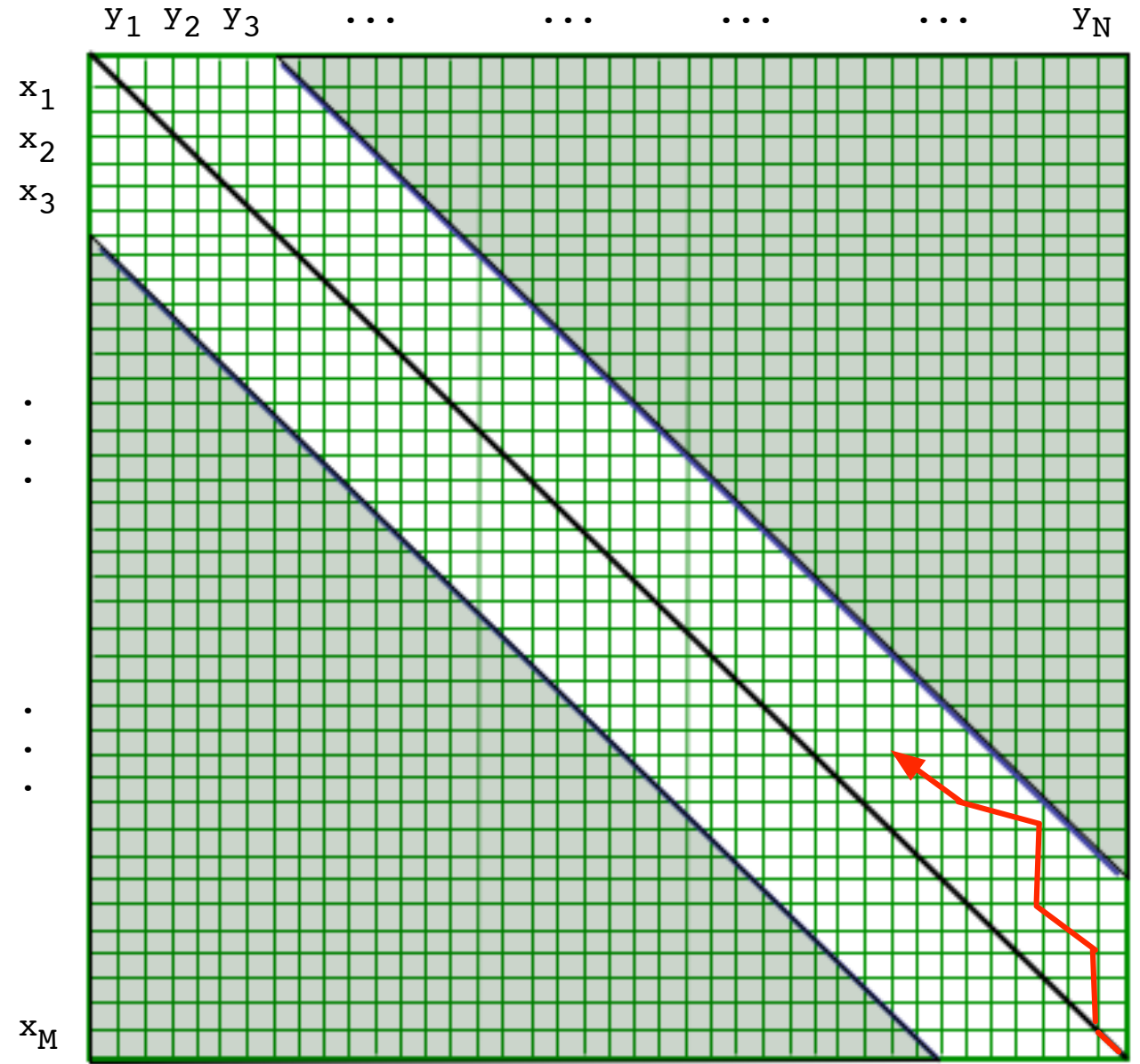
Banded Alignment

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Running time: $O(nk)$

Gives a good approximation of highly identical sequences

Question: How to change recurrence to accomplish this?



Constrain traceback to band of DP matrix (penalize big gaps)

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Block Alignment

Divide input sequences into blocks of length t

v_1, \dots, v_t

v_{t+1}, \dots, v_{2t}

...

v_{m-t+1}, \dots, v_m

w_1, \dots, w_t

w_{t+1}, \dots, w_{2t}

...

w_{n-t+1}, \dots, w_n

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W_1, \dots, W_t

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W_{n-t+1}, \dots, W_n

Require that paths in edit graph pass through **corners** of blocks

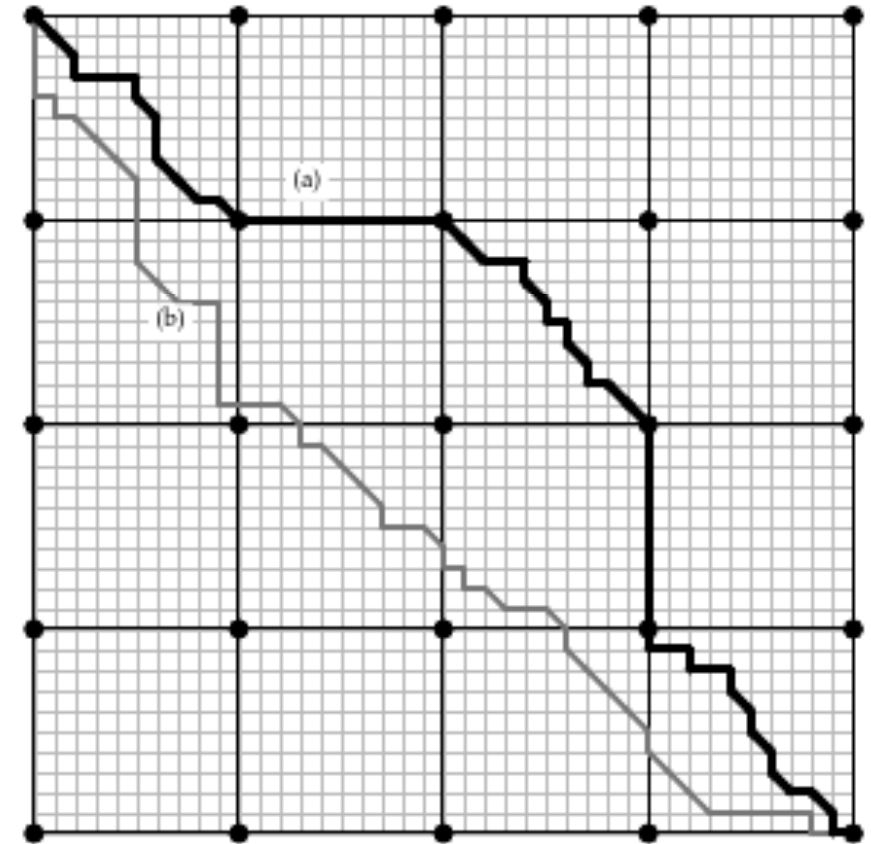


Figure 7.4 Two paths in a 40×40 grid partitioned into 16 subgrids of size 10×10 . The black path (a) is a block path, while the gray path (b) is not.

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-------------------	--------------------------	-----	-------------------------

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Require that paths in edit graph pass through **corners** of blocks

$$s[i, j] = \max \begin{cases} 0, & \text{if } i = 0 \text{ and } j = 0, \\ s[i - 1, j] - \sigma, & \text{if } i > 0, \\ s[i, j - 1] - \sigma, & \text{if } j > 0, \\ s[i - 1, j - 1] + \beta(i, j), & \text{if } i > 0 \text{ and } j > 0. \end{cases}$$

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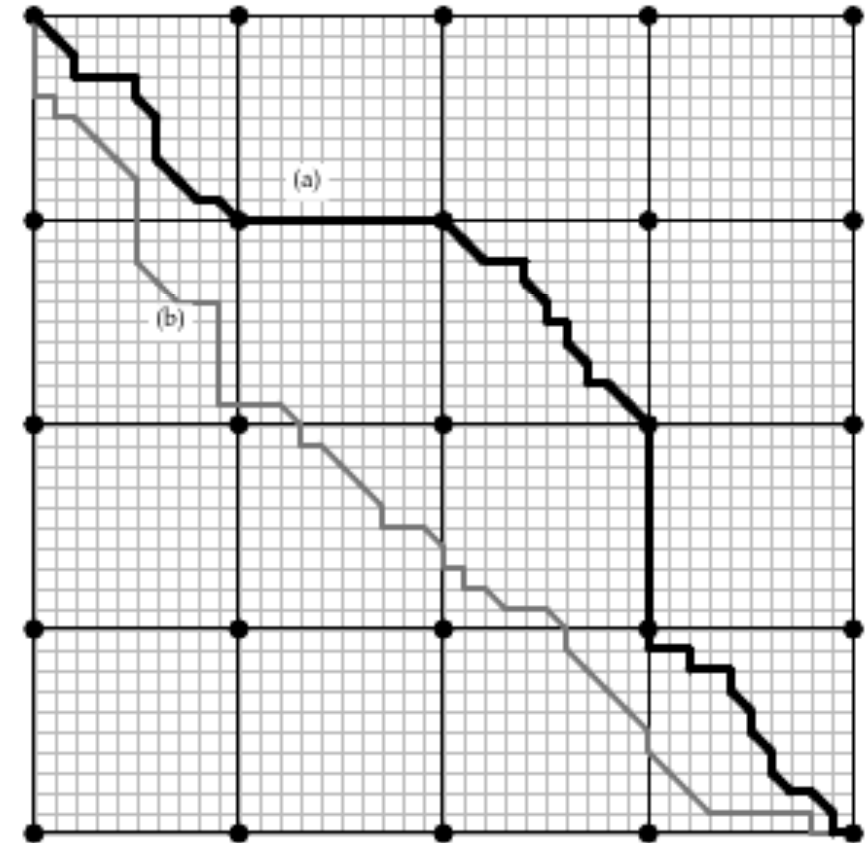
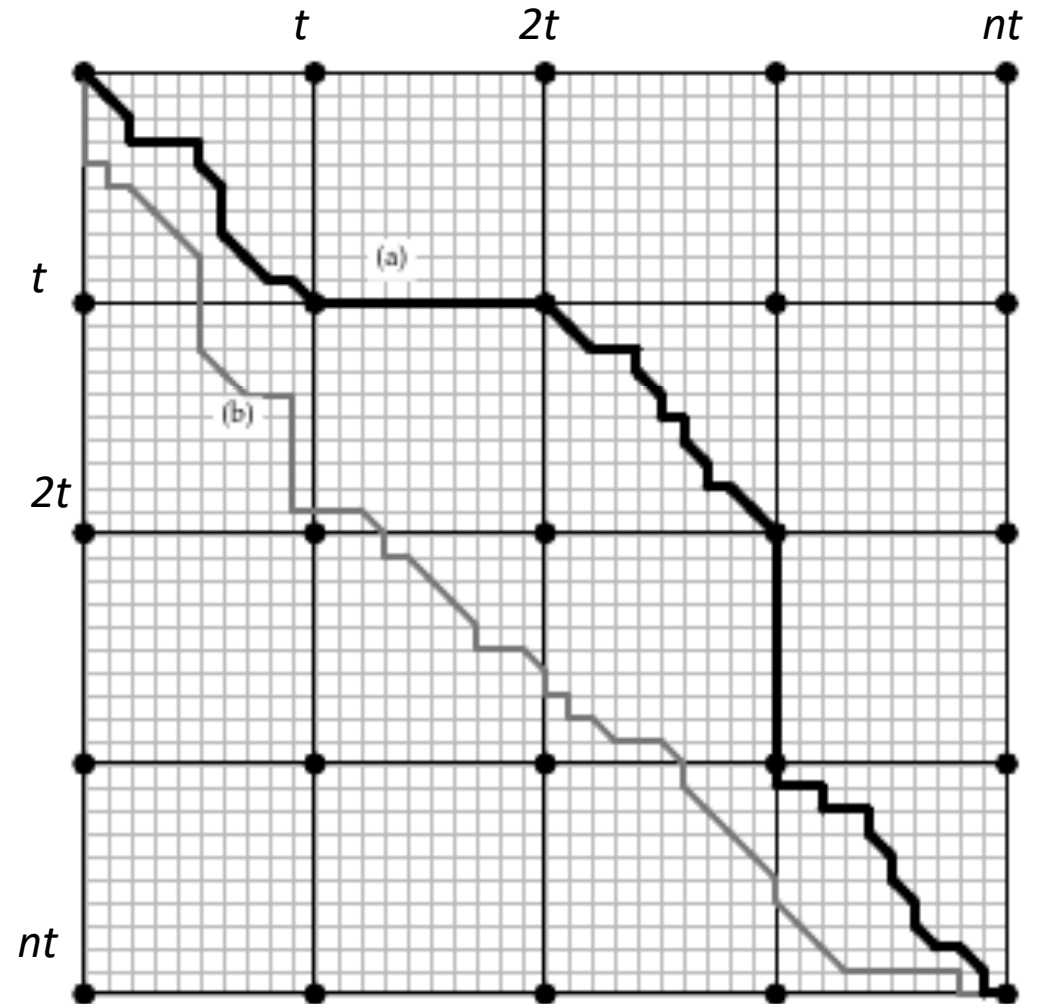


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Block Alignment – First Attempt: Pre-compute $\beta(i, j)$

$0 \leq i, j \leq n/t$ and $\beta(i, j)$ is max score alignment between block i of \mathbf{v} and block j of \mathbf{w}

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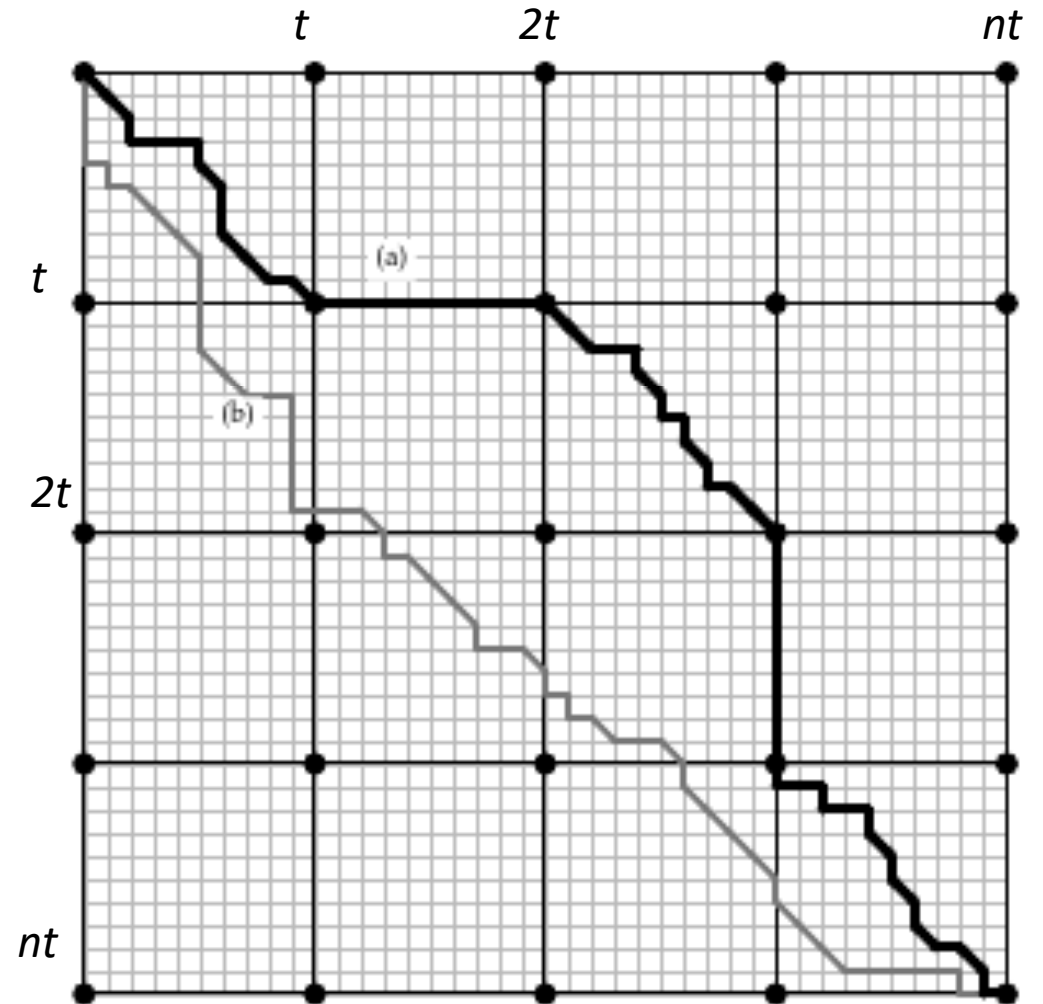
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Question:

How much time to compute all $\beta(i, j)$?



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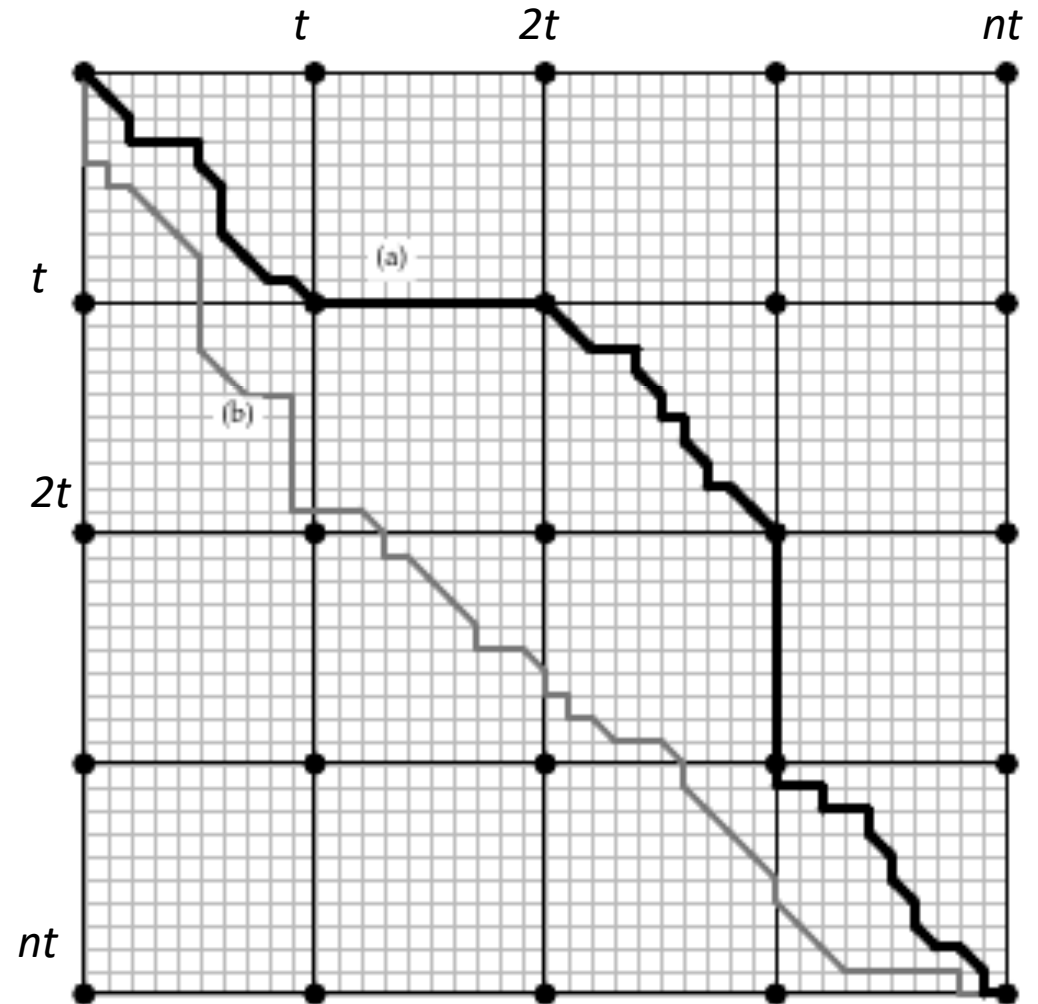
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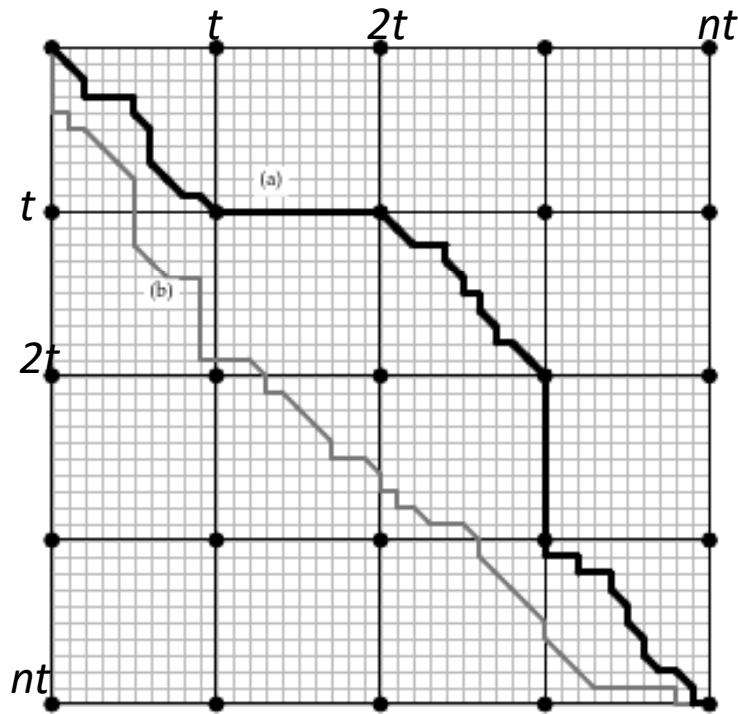
Computing $\beta(i, j)$ takes $O(t^2)$ time

There are $n/t \times n/t$ values $\beta(i, j)$

Total: $O\left(\frac{n}{t} \times \frac{n}{t} \times t^2\right) = O(n^2)$ time



Block Alignment – Four Russians Technique



~~Pre-compute and store all β_{ij}~~

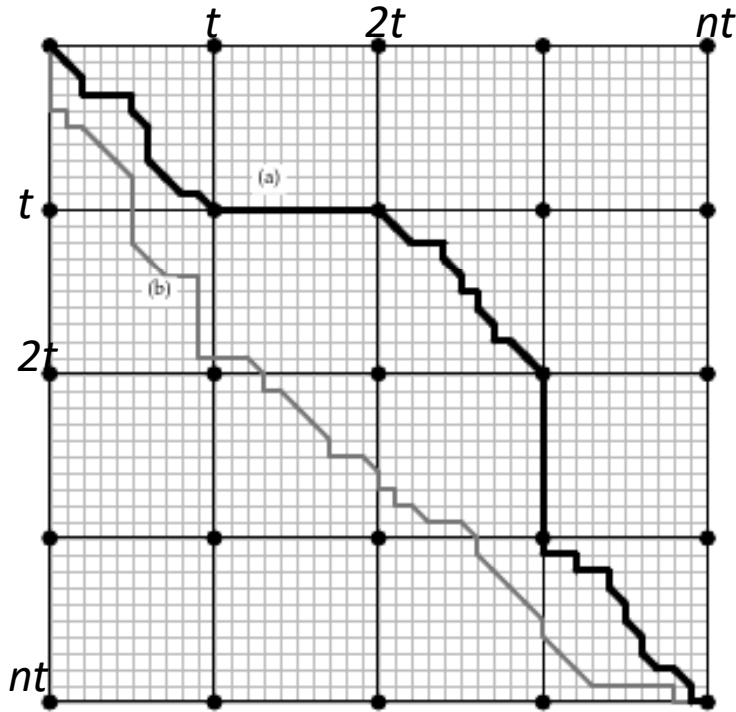
Pre-compute and store **all** max weight alignments $S[\mathbf{v}', \mathbf{w}']$ of **all** pairs $(\mathbf{v}', \mathbf{w}')$ of length t strings

Algorithm:

1. Precompute $S[\mathbf{v}', \mathbf{w}']$ where $\mathbf{v}', \mathbf{w}' \in \Sigma^t$
2. Compute block alignment between \mathbf{v} and \mathbf{w} using S

$$s[i, j] = \max \begin{cases} 0, & \text{if } i = 0 \text{ and } j = 0, \\ s[i - 1, j] - \sigma, & \text{if } i > 0, \\ s[i, j - 1] - \sigma, & \text{if } j > 0, \\ s[i - 1, j - 1] + S[v(i), w(j)], & \text{if } i > 0 \text{ and } j > 0. \end{cases}$$

Block Alignment – Four Russians Technique



~~Pre-compute and store all β_{ij}~~

Pre-compute and store **all** max weight alignments $S[\mathbf{v}', \mathbf{w}']$ of **all** pairs $(\mathbf{v}', \mathbf{w}')$ of length t strings

Question: How to choose t for DNA?

Algorithm:

1. Precompute $S[\mathbf{v}', \mathbf{w}']$ where $\mathbf{v}', \mathbf{w}' \in \Sigma^t$
2. Compute block alignment between \mathbf{v} and \mathbf{w} using S

$$s[i, j] = \max \begin{cases} 0, & \text{if } i = 0 \text{ and } j = 0, \\ s[i - 1, j] - \sigma, & \text{if } i > 0, \\ s[i, j - 1] - \sigma, & \text{if } j > 0, \\ s[i - 1, j - 1] + S[v(i), w(j)], & \text{if } i > 0 \text{ and } j > 0. \end{cases}$$

Fastest Subquadratic Alignment* Algorithm

JOURNAL OF COMPUTER AND SYSTEM SCIENCES 20, 18-31 (1980)

A Faster Algorithm Computing String Edit Distances*

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Received September 25, 1978; revised August 6, 1979

Edit distance in
 $O(n^2 / \log n)$ time

Barely subquadratic!

Want: $O(n^{2-\varepsilon})$ time
where $\varepsilon > 0$

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Barely subquadratic!

Want: $O(n^{2-\varepsilon})$ time
where $\varepsilon > 0$

Question: Is $n^{2-\varepsilon}$ in $O(n^2 / \log n)$ for any $\varepsilon > 0$?

Hardness Result for Edit Distance [STOC 2015]

Edit Distance Cannot Be Computed
in Strongly Subquadratic Time
(unless SETH is false)

← $O(n^{2-\epsilon})$ time where $\epsilon > 0$

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MIT

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Abstract

The edit distance (a.k.a. the Levenshtein distance) between two strings is defined as the minimum number of insertions, deletions or substitutions of symbols needed to transform one string into another. The problem of computing the edit distance between two strings is a classical computational task, with a well-known algorithm based on dynamic programming. Unfortunately, all known algorithms for this problem run in nearly quadratic time.

In this paper we provide evidence that the near-quadratic running time bounds known for the problem of computing edit distance might be tight. Specifically, we show that, if the edit distance can be computed in time $O(n^{2-\delta})$ for some constant $\delta > 0$, then the satisfiability of conjunctive normal form formulas with N variables and M clauses can be solved in time $M^{O(1)}2^{(1-\epsilon)N}$ for a constant $\epsilon > 0$. The latter result would violate the *Strong Exponential Time Hypothesis*, which postulates that such algorithms do not exist.

For 40 years, computer scientists looked for a solution that doesn't exist [1]



SHUTTERSTOCK

By Kevin Hartnett | GLOBE CORRESPONDENT AUGUST 10, 2015

For 40 years, computer scientists have tried in vain to find a faster way to do an important calculation known as “[edit distance](#).” Thanks to [groundbreaking work](#) from two researchers at MIT, they now know the reason they’ve continually failed is because a faster method is actually impossible to create.

In biology n does not go to infinity [2]

August 14, 2015 in reviews | Tags: complexity theory, edit distance, Needleman-Wunsch algorithm, strong exponential time hypothesis

I recently read a “*brainiac*” column in the Boston Globe titled “[For 40 years, computer scientists looked for a solution that doesn’t exist](#)” that caused me to facepalm so violently I now have pain in my right knee.



- [1] [Boston Globe](#), Aug 10, 2015
- [2] [Bits of DNA Blog](#), Lior Pachter

Take Home Messages

1. Global alignment in $O(mn)$ time and $O(m)$ space
 - Hirschberg algorithm
2. Block alignment can be done in subquadratic time
 - Four Russians Technique: $O(n^2 / \log n)$ time
3. Global alignment cannot be done in $O(n^{2-\epsilon})$ time under SETH

Reading:

- Jones and Pevzner. Chapters 7.1-7.4
- Lecture notes