南方科技大学
SOUTHERN UNIVERSITY OF SCIENCE AND TECHNOLOGY

Algorithm Design and Analysis (H)

CS216

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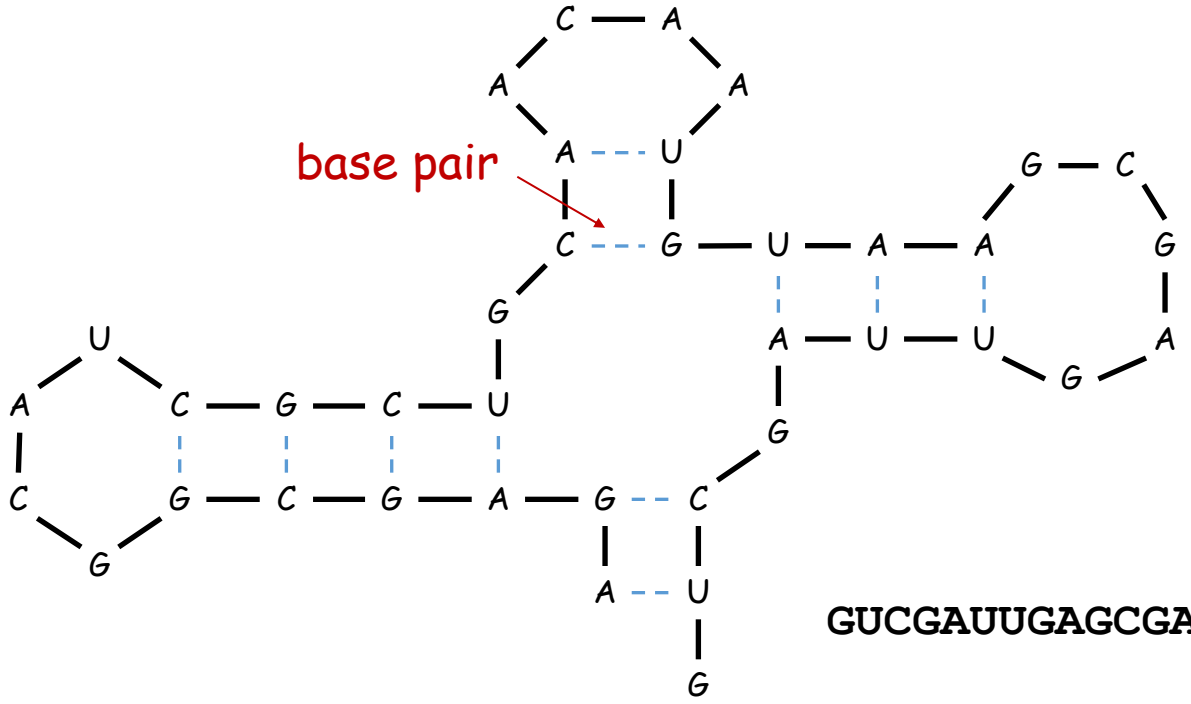
(slides edited from Prof. Shiqi Yu)

Dynamic Programming

4. RNA Secondary Structure

RNA Secondary Structure

- **RNA.** String B = $b_1 b_2 \ldots b_n$ over alphabet { A, C, G, U }.
- **Secondary structure.** RNA is single-stranded so it tends to loop back and form base pairs with itself. This structure is essential for understanding behavior of molecule.

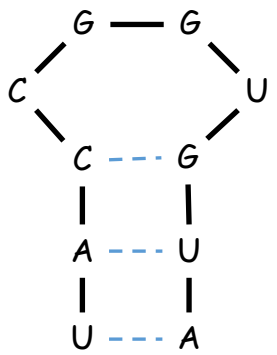


GUCGAUUGAGCGAAUGUAACAACGUGGCUACGGCGAGA

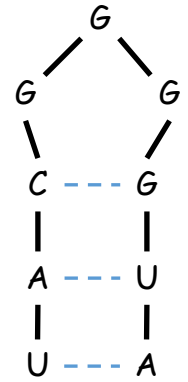
RNA Secondary Structure

- **Secondary structure.** A set of pairs $S = \{ (b_i, b_j) \}$ that satisfy:
  - [Watson-Crick] S is a matching and each pair in S is a Watson-Crick complement: A-U, U-A, C-G, or G-C.
  - [No sharp turns] The ends of each pair are separated by at least 4 intervening bases. If $(b_i, b_j) \in S$, then $i < j - 4$.
  - [Non-crossing] If (b_i, b_j) and (b_k, b_l) are two pairs in S, we cannot have $i < k < j < l$.

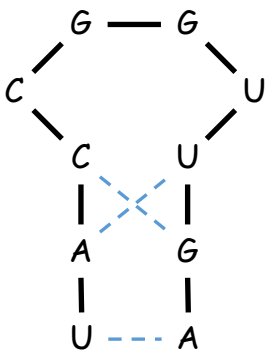
Watson-Crick complements

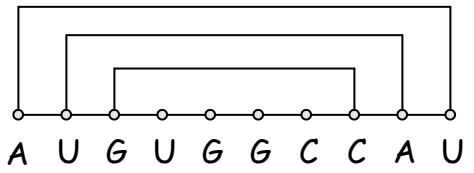


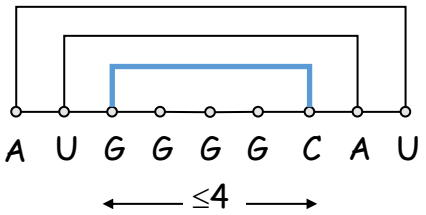
sharp turn

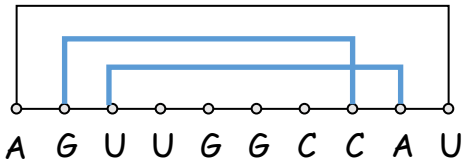


crossing









RNA Secondary Structure

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  - [Non-crossing] If (b_i, b_j) and (b_k, b_l) are two pairs in S, we cannot have $i < k < j < l$.

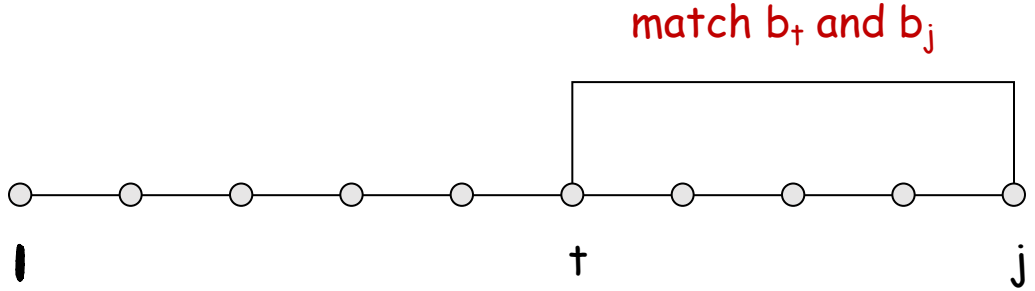
- **Free energy hypothesis.** RNA molecule will form the secondary structure with the minimum total free energy.

approximate by number of base pairs
more base pairs ⇒ lower free energy
most number base pairs.

- **Goal.** Given an RNA molecule $B = b_1 b_2 \ldots b_n$, find a secondary structure S that maximizes the number of base pairs.

RNA Secondary Structure: Subproblems

- **First attempt.** OPT(j) = maximum number of base pairs in a secondary structure of the substring $b_1 b_2 \ldots b_j$.
- **Goal.** OPT(n)

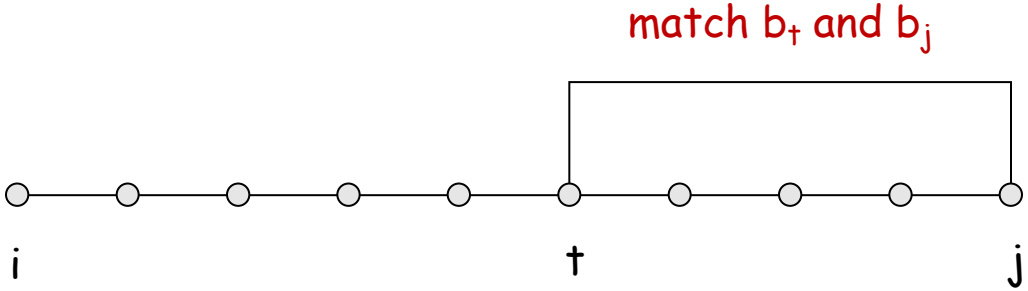


- **Difficulty.** OPT(j) results in two sub-problems (but one of wrong form).
  - Find secondary structure in: $b_1 b_2 \ldots b_{t-1}$. ← OPT(t - 1)
  - Find secondary structure in: $b_{t+1} b_{t+2} \ldots b_{j-1}$. ← need more subproblems

no crossing

Dynamic Programming over Intervals

- **Def.** OPT(i, j) = maximum number of base pairs in a secondary structure of the substring $b_i b_{i+1} \ldots b_j$.
- **Goal.** OPT(1, n)

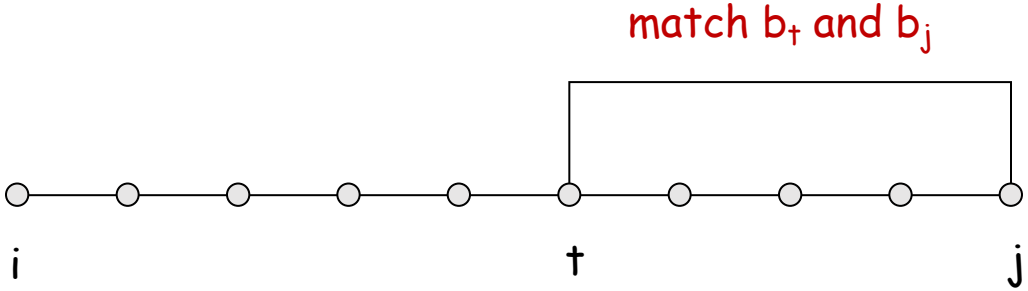


- **To compute OPT(i, j):**
  - Case 1. $i \geq j - 4$: OPT(i, j) = 0 by no-sharp-turns condition.
  - Case 2. Base b_j is not involved in a pair: OPT(i, j) = OPT(i, j – 1)
  - Case 3. Base b_j pairs with b_t for some $i \leq t < j - 4$.
    - ✓non-crossing constraint decouples resulting sub-problems
    - ✓$OPT(i, j) = 1 + \max_t \{ OPT(i, t - 1) + OPT(t + 1, j - 1) \}$

take max over t such that $i \leq t < j - 4$ and b_t and b_j are Watson-Crick complements

Dynamic Programming over Intervals

- **Def.** OPT(i, j) = maximum number of base pairs in a secondary structure of the substring $b_i b_{i+1} \ldots b_j$.
- **Goal.** OPT(1, n)



- **To compute OPT(i, j):**

compute in which order?

$$\text{OPT}(i,j) = \begin{cases} 0, & \text{if } i \geq j-4 \\ \text{OPT}(i,j-1), & b_j \text{ cannot be paired} \\ 1 + \max_t \{OPT(i,t-1) + OPT(t+1,j-1)\}, & b_j \text{ can be paired} \end{cases}$$

take max over t such that $i \leq t < j - 4$ and b_t and b_j are Watson-Crick complements

Dynamic Programming over Intervals

- **Dynamic programming algorithm (bottom-up).**

```
RNA(b1,…,bn) {
    for k = 5, 6, …, n - 1        ← shortest intervals first
        for i = 1, 2, …, n - k
            j = i + k
            Compute M[i, j] using formula

    return M[1, n]
}
```

all needed M[,] values already computed

$$\mathrm{OPT}(i,j) = \begin{cases} 0, & \text{if } i \geq j-4 \\ \mathrm{OPT}(i,j-1), & b_j \text{ cannot be paired} \\ 1 + \max_t \{OPT(i,t-1) + OPT(t+1,j-1)\}, & b_j \text{ can be paired} \end{cases}$$

- **Running time.** $O(n^3)$ **Space.** $O(n^2)$

RNA-Secondary-Structure Algorithm: Demo

RNA sequence *ACCGGUAGU*

4	0	0	0	
3	0	0		
2	0			
$i = 1$				
	$j = 6$	7	8	9

Initial values

4	0	0	0	0
3	0	0	1	
2	0	0		
$i = 1$	1			
	$j = 6$	7	8	9

Filling in the values for $k = 5$

4	0	0	0	0
3	0	0	1	1
2	0	0	1	
$i = 1$	1	1		
	$j = 6$	7	8	9

Filling in the values for $k = 6$

4	0	0	0	0
3	0	0	1	1
2	0	0	1	1
$i = 1$	1	1	1	
	$j = 6$	7	8	9

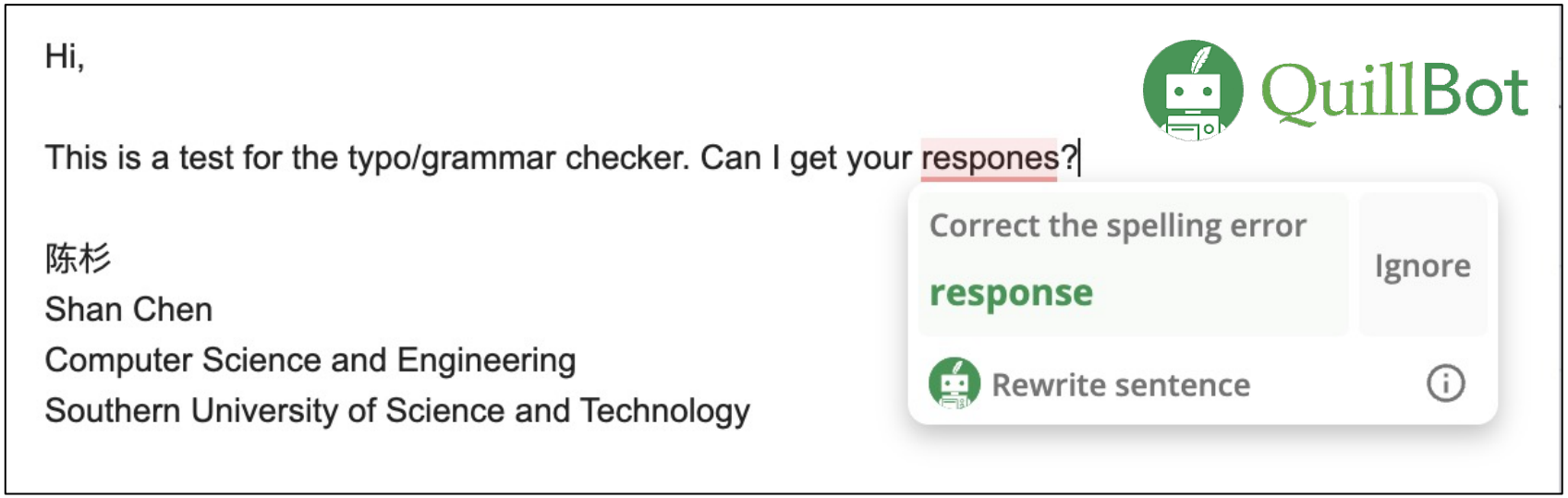
Filling in the values for $k = 7$

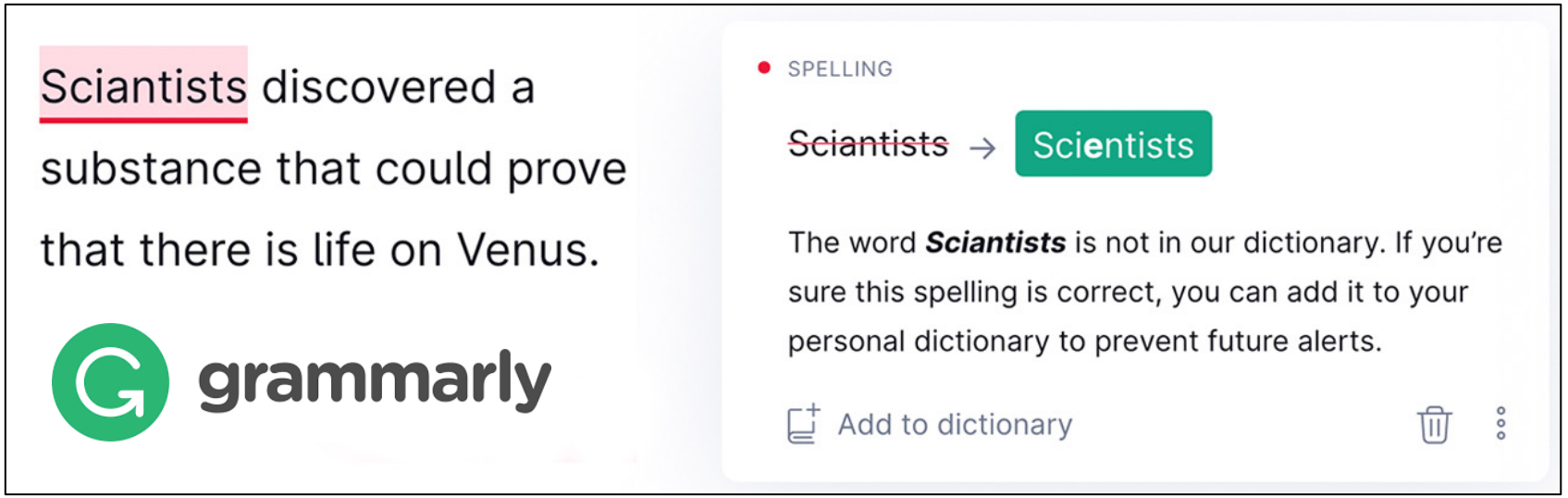
4	0	0	0	0
3	0	0	1	1
2	0	0	1	1
$i = 1$	1	1	1	2
	$j = 6$	7	8	9

Filling in the values for $k = 8$

5. Sequence Alignment

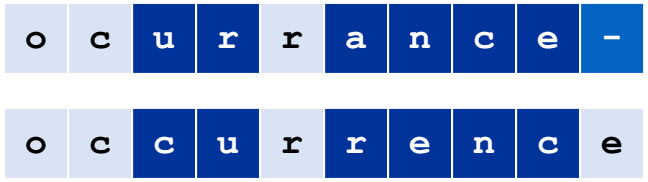
Spell Correction



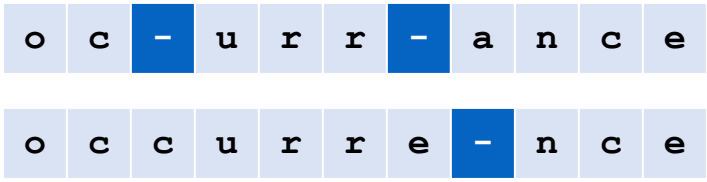


String Similarity

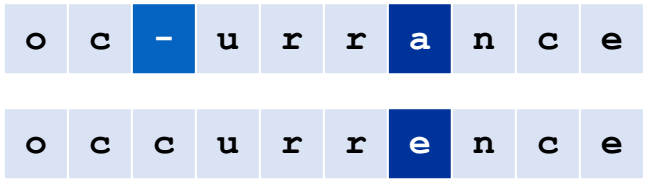
- **Q.** How similar are two strings?
- **Ex.** ocurrance and occurrence.



6 mismatches, 1 gap



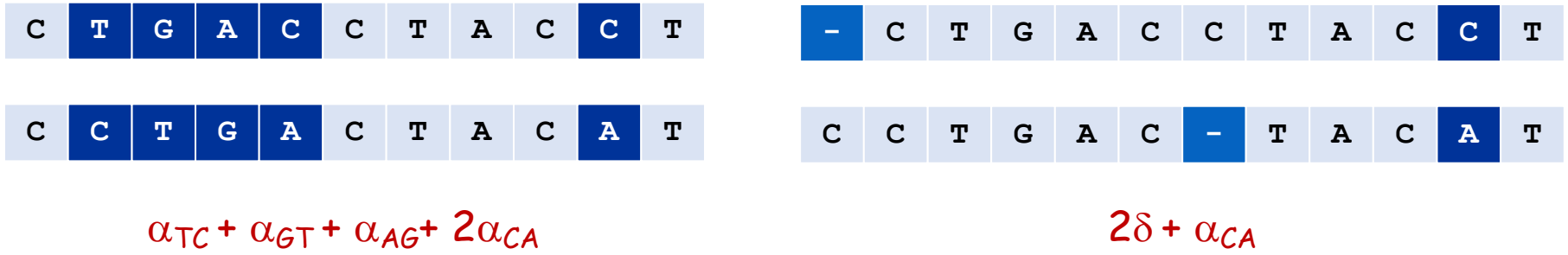
0 mismatches, 3 gaps



1 mismatch, 1 gap

Edit Distance

- **Edit distance.** [Levenshtein 1966, Needleman-Wunsch 1970]
  - Gap penalty δ; mismatch penalty α_{pq}. (Typically, $\alpha_{pp} = 0$.)
  - Cost = sum of gap and mismatch penalties.
  - Edit distance is the minimum cost.



- **Applications.** Bioinformatics, spell correction, machine translation, speech recognition, information extraction, ...

Sequence Alignment

- **Goal.** Given two strings $x_1x_2 \ldots x_m$ and $y_1y_2 \ldots y_n$ find a min-cost alignment.
- **Def.** An alignment M is a set of ordered pairs x_i-y_j such that each item occurs in at most one pair and there are no crossings.

x_i-y_j and $x_{i'}$-$y_{j'}$ cross if $i < i'$ but $j > j'$

- **Ex.** CTACCG vs. TACATG (gap penalty $\delta = 2$; mismatch penalty $\alpha_{pq} = 1$)
- Sol: M = x_2-y_1, x_3-y_2, x_4-y_3, x_5-y_4, x_6-y_6.

x_1	x_2	x_3	x_4	x_5		x_6
C	T	A	C	C	-	G

-	T	A	C	A	T	G
	y_1	y_2	y_3	y_4	y_5	y_6

Sequence Alignment: Problem Structure

- **Def.** OPT(i, j) = min cost of aligning prefix strings $x_1x_2 \dots x_i$ and $y_1y_2 \dots y_j$
- **Goal.** OPT(m, n)

- **To compute OPT(i, j):**
  - **Case 1:** OPT matches x_i-y_j.
    - ✓Pay mismatch for x_i-y_j + min cost of aligning $x_1x_2 \dots x_{i-1}$ and $y_1y_2 \dots y_{j-1}$
  - **Case 2a:** OPT leaves x_i unmatched.
    - ✓Pay gap for x_i + min cost of aligning $x_1x_2 \dots x_{i-1}$ and $y_1y_2 \dots y_j$
  - **Case 2b:** OPT leaves y_j unmatched.
    - ✓Pay gap for y_j + min cost of aligning $x_1x_2 \dots x_i$ and $y_1y_2 \dots y_{j-1}$

Sequence Alignment: Problem Structure

- **Def.** OPT(i, j) = min cost of aligning prefix strings $x_1x_2 \ldots x_i$ and $y_1y_2 \ldots y_j$.
- **Goal.** OPT(m, n)

- **Bellman equation.**

$$\mathrm{OPT}(i,j) = \begin{cases} j\delta, & \text{if } i = 0 \\ i\delta, & \text{if } j = 0 \\ \min \begin{cases} \alpha_{x_i y_j} + \mathrm{OPT}(i-1, j-1) \\ \delta + \mathrm{OPT}(i-1, j) \\ \delta + \mathrm{OPT}(i, j-1) \end{cases} & \text{otherwise} \end{cases}$$

Sequence Alignment: Algorithm

- **Dynamic programming algorithm (bottom-up).**

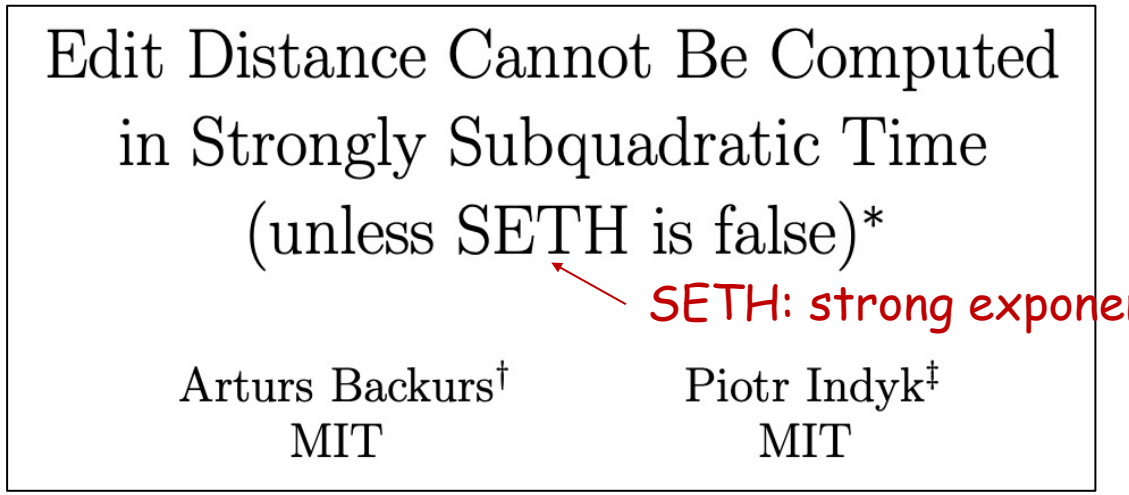
```
Sequence-Alignment(m, n, x1x2...xm, y1y2...yn, δ, α) {
   for i = 0 to m
      M[i, 0] = iδ
   for j = 0 to n
      M[0, j] = jδ

   for i = 1 to m
      for j = 1 to n
         M[i, j] = min(α[xi, yj] + M[i-1, j-1],
                       δ + M[i-1, j],
                       δ + M[i, j-1])
   return M[m, n]
}
```

all needed M[,] values already computed

- **Running time and space.** O(mn) ← m, n ≤ 10 for English words; m, n ≈ 10^5 for biology applications

Sequence Alignment: Impossibility Result

- **Theorem.** [Backurs–Indyk 2015] If can compute edit distance of two strings of length n in $O(n^{2-\varepsilon})$ time for some constant $\varepsilon > 0$, then can solve SAT with n variables and m clauses in $poly(m)2^{(1-\delta)n}$ time for some constant $\delta > 0$.



- **Takeaway.** It is very difficult (if not impossible) to improve the O(mn) running time of computing the edit distance of two strings.

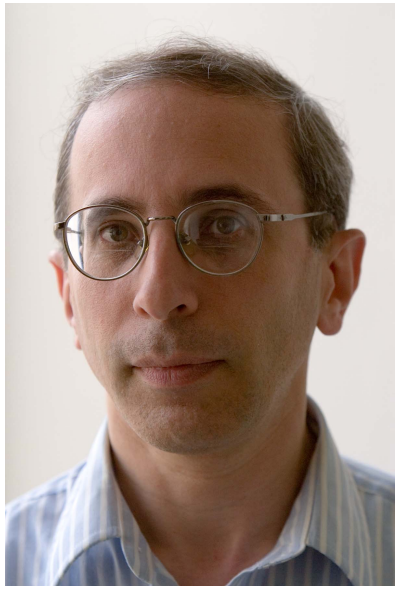
Sequence Alignment in Linear Space

- **Theorem.** [Hirschberg] There exists an algorithm to find an optimal alignment in $O(mn)$ time and $O(m + n)$ space.
  - Clever combination of divide-and-conquer and dynamic programming.
  - Inspired by idea of Savitch from complexity theory.

Programming Techniques — G. Manacher Editor

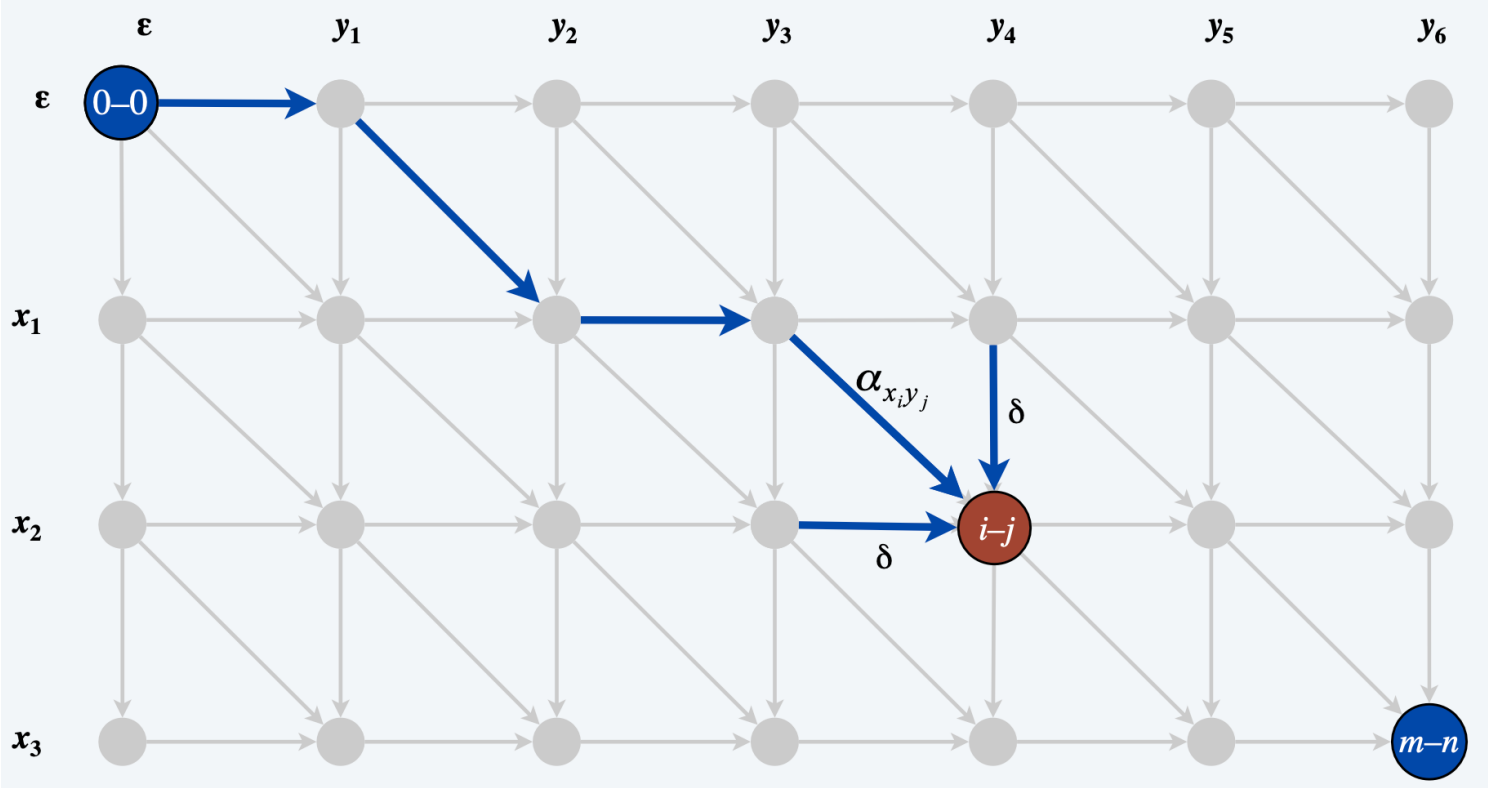
A Linear Space Algorithm for Computing Maximal Common Subsequences

D.S. Hirschberg
Princeton University



Sequence Alignment: Hirschberg's Algorithm

- **Edit distance graph.**
  - Let $f(i, j)$ denote length of shortest path from $(0, 0)$ to (i, j).
  - **Lemma:** $f(i, j) = OPT(i, j)$ for all i and j.



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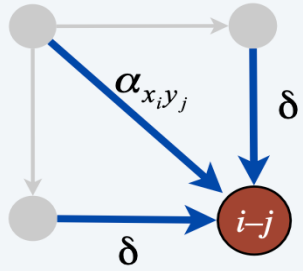
  - Let $f(i, j)$ denote length of shortest path from $(0, 0)$ to (i, j).
  - **Lemma:** $f(i, j) = OPT(i, j)$ for all i and j.
- Pf of Lemma. (by strong induction on $i + j$)
  - Base case: $f(0, 0) = OPT(0, 0) = 0$.
  - Inductive hypothesis: assume true for all (i', j') with $i' + j' < i + j$.
  - Last edge on shortest path to (i, j) is from $(i - 1, j - 1)$ or $(i - 1, j)$ or $(i, j - 1)$.

$$
\begin{aligned}
f(i,j) &= \min\{\alpha_{x_i y_j} + f(i-1,j-1),\ \delta + f(i-1,j),\ \delta + f(i,j-1)\} \\
&= \min\{\alpha_{x_i y_j} + OPT(i-1,j-1),\ \delta + OPT(i-1,j),\ \delta + OPT(i,j-1)\} \\
&= OPT(i,j) \ \blacksquare
\end{aligned}
$$

inductive hypothesis

Bellman equation



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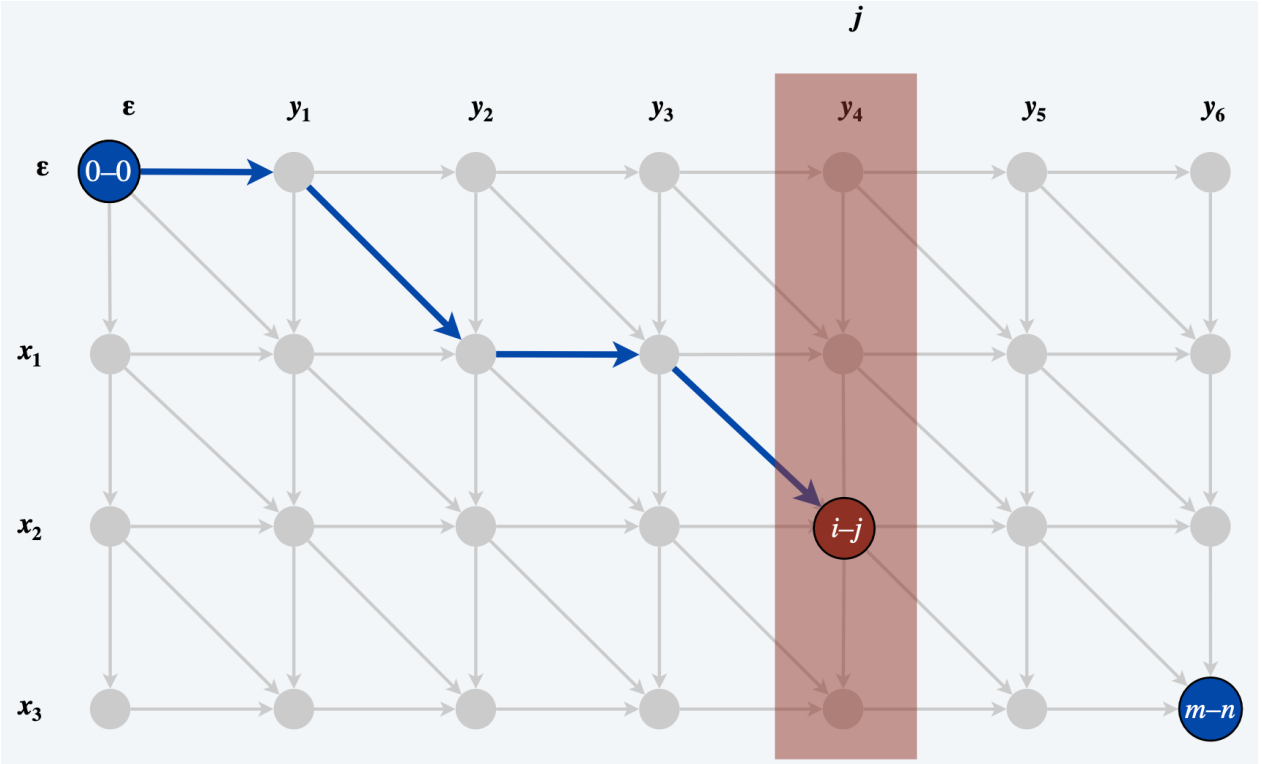
  - Can compute $f(\cdot, j)$ for any specific j in $O(mn)$ time and $O(m)$ space.

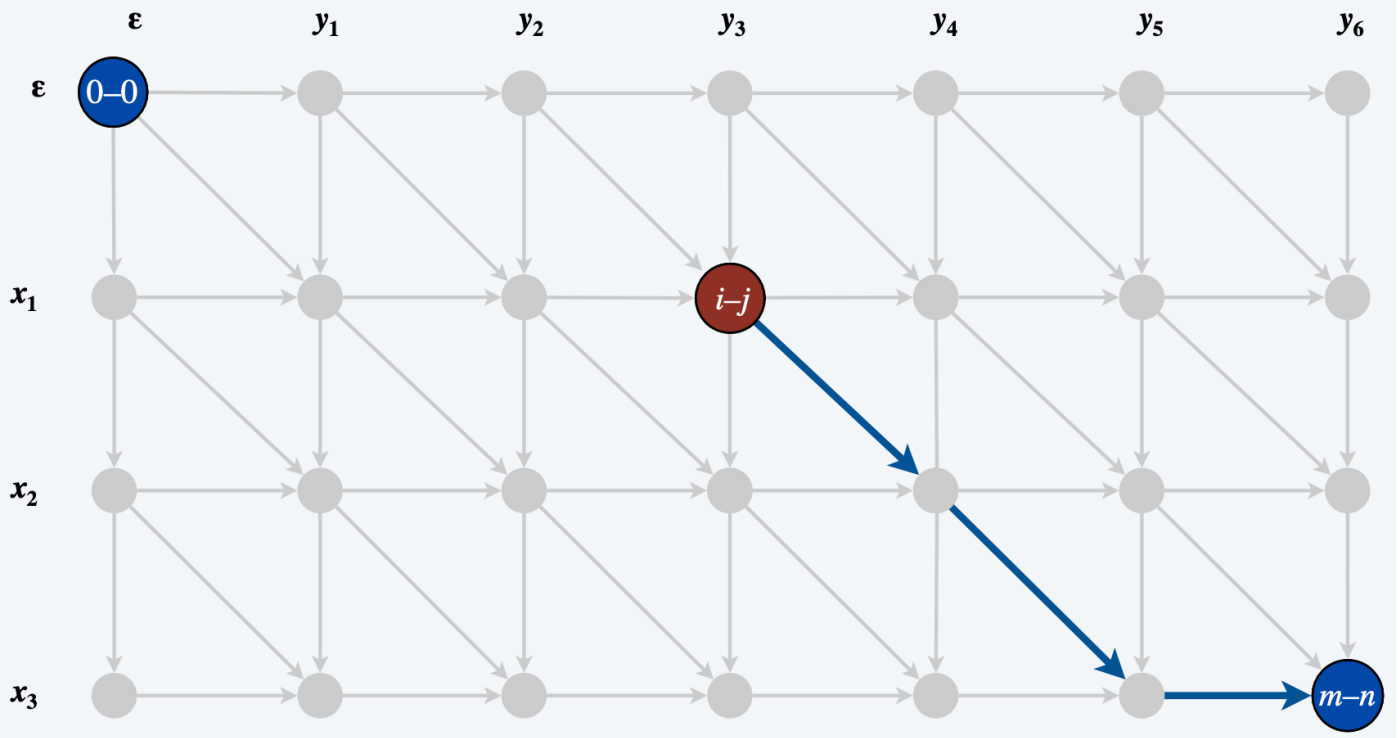


O(m) scrolling array

← f(·, j) depends only on f(·, j - 1)

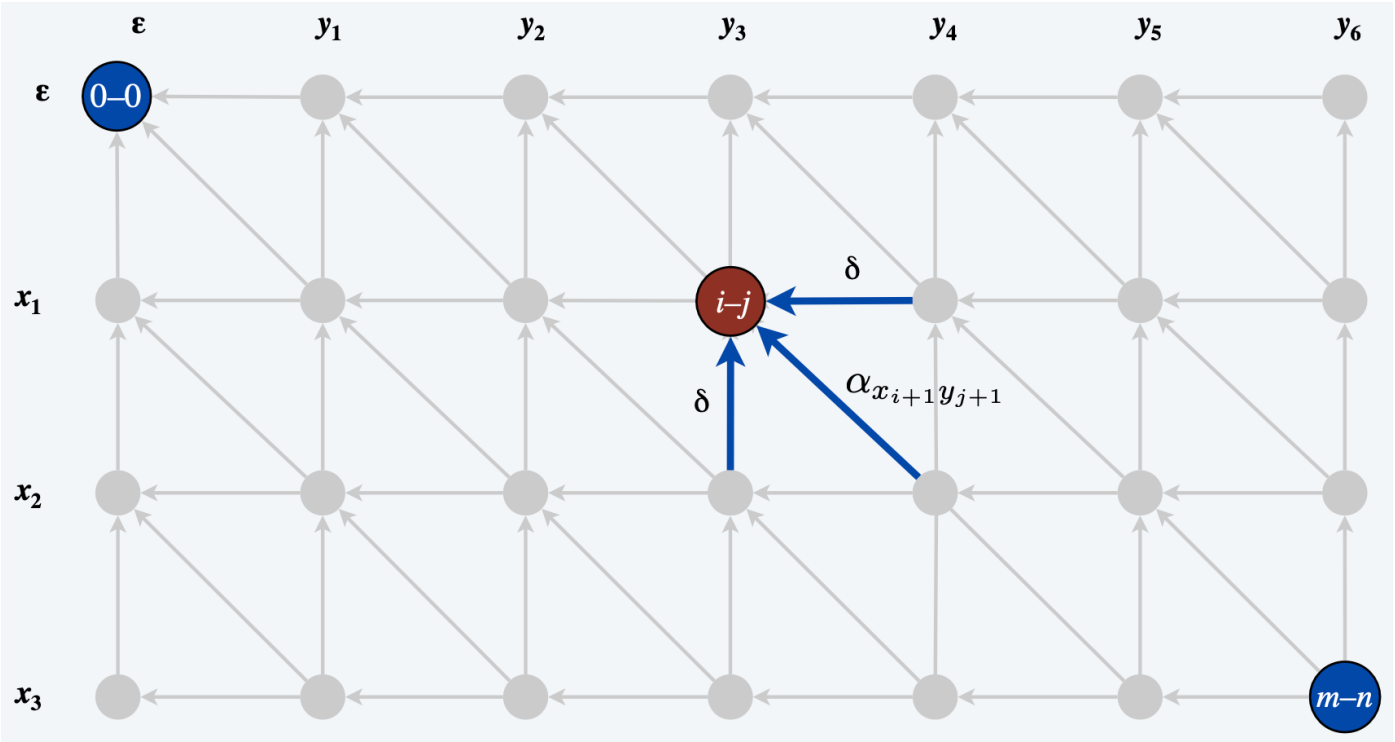
Sequence Alignment: Hirschberg's Algorithm

- **Edit distance graph.**
  - Let $g(i, j)$ denote length of shortest path from (i, j) to (m, n).



Sequence Alignment: Hirschberg's Algorithm

- **Edit distance graph.**
  - Let $g(i, j)$ denote length of shortest path from *(i, j)* to *(m, n)*.
  - Can compute $g(i, j)$ by reversing edges and the roles of (0, 0) and (m, n).



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- **Edit distance graph.**
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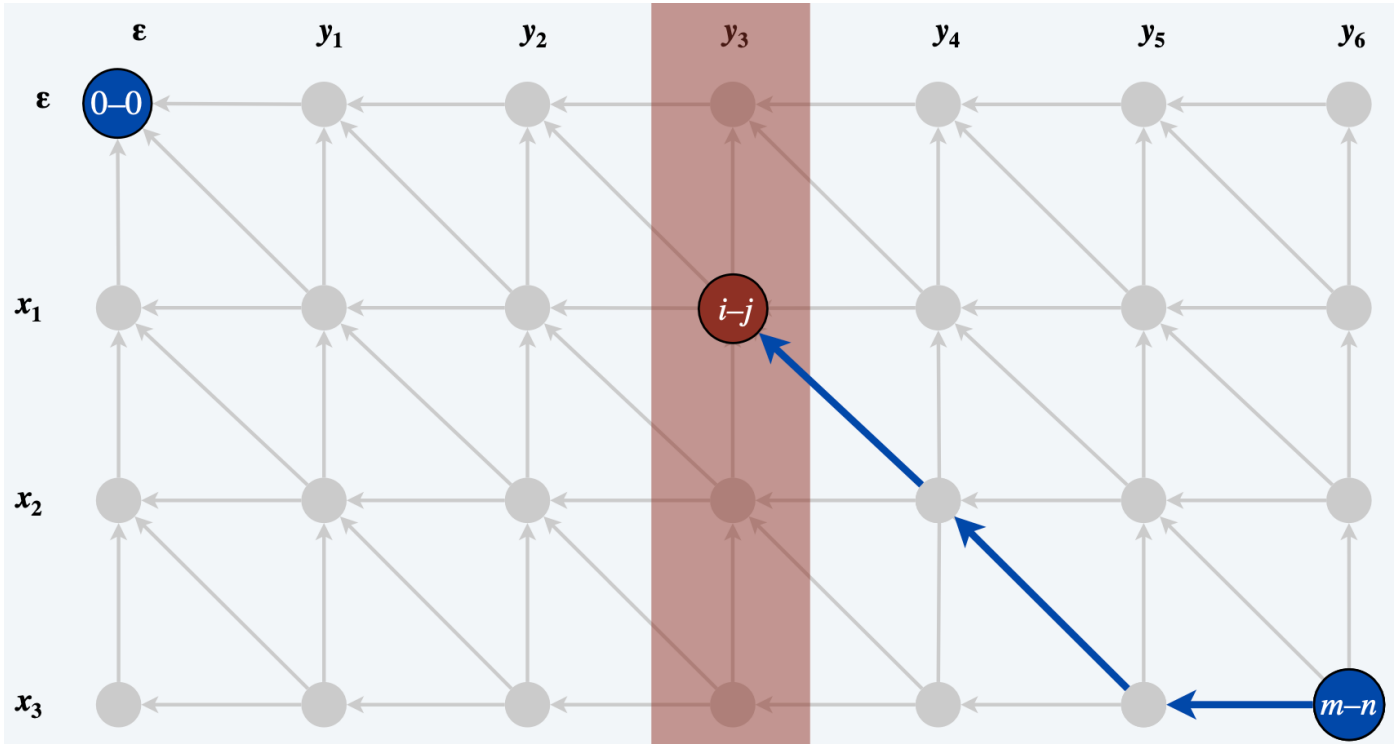
  - Can compute $g(i, j)$ by reversing edges and the roles of (0, 0) and (m, n).
  - Can compute $g(\cdot, j)$ for any specific j in $O(mn)$ time and $O(m)$ space.

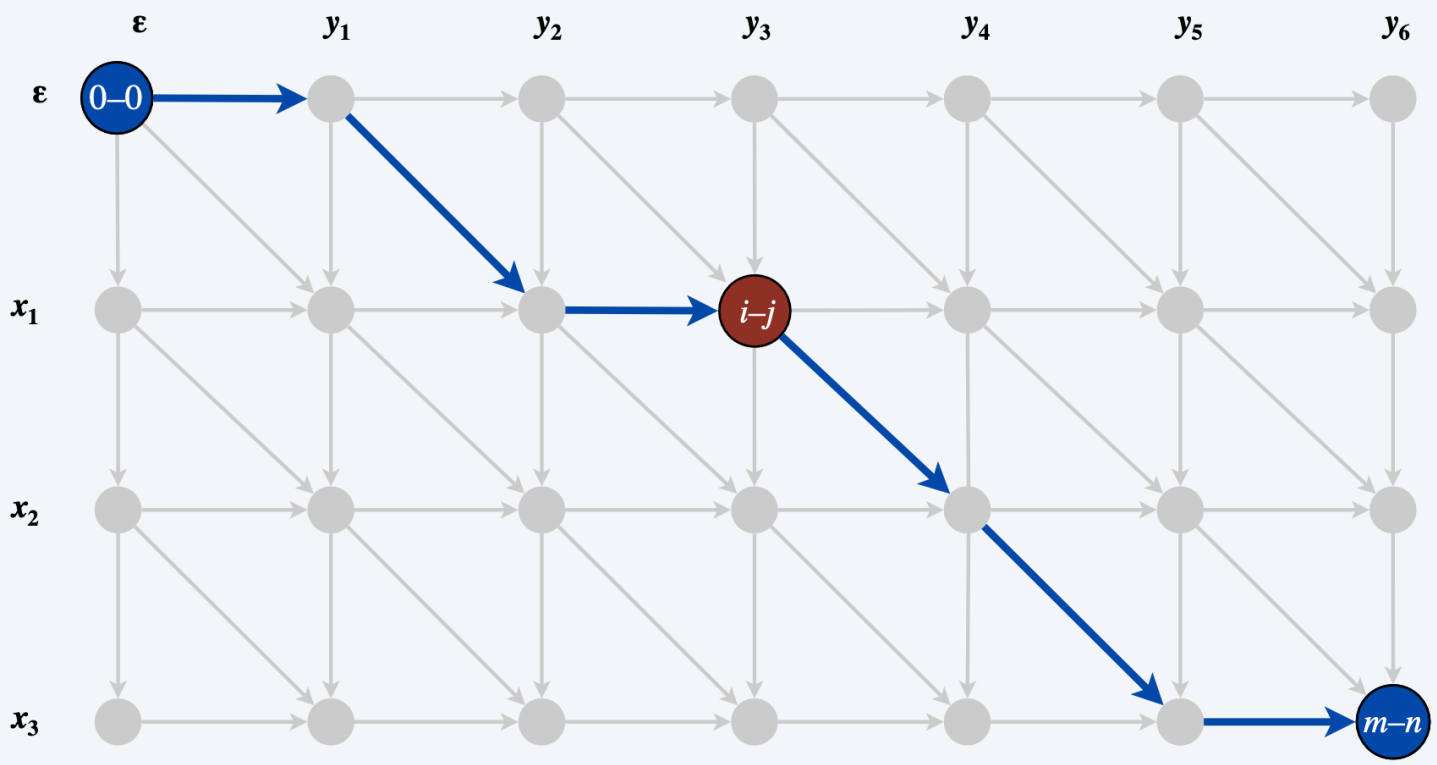


O(m) scrolling array

← g(·, j) depends only on g(·, j + 1)

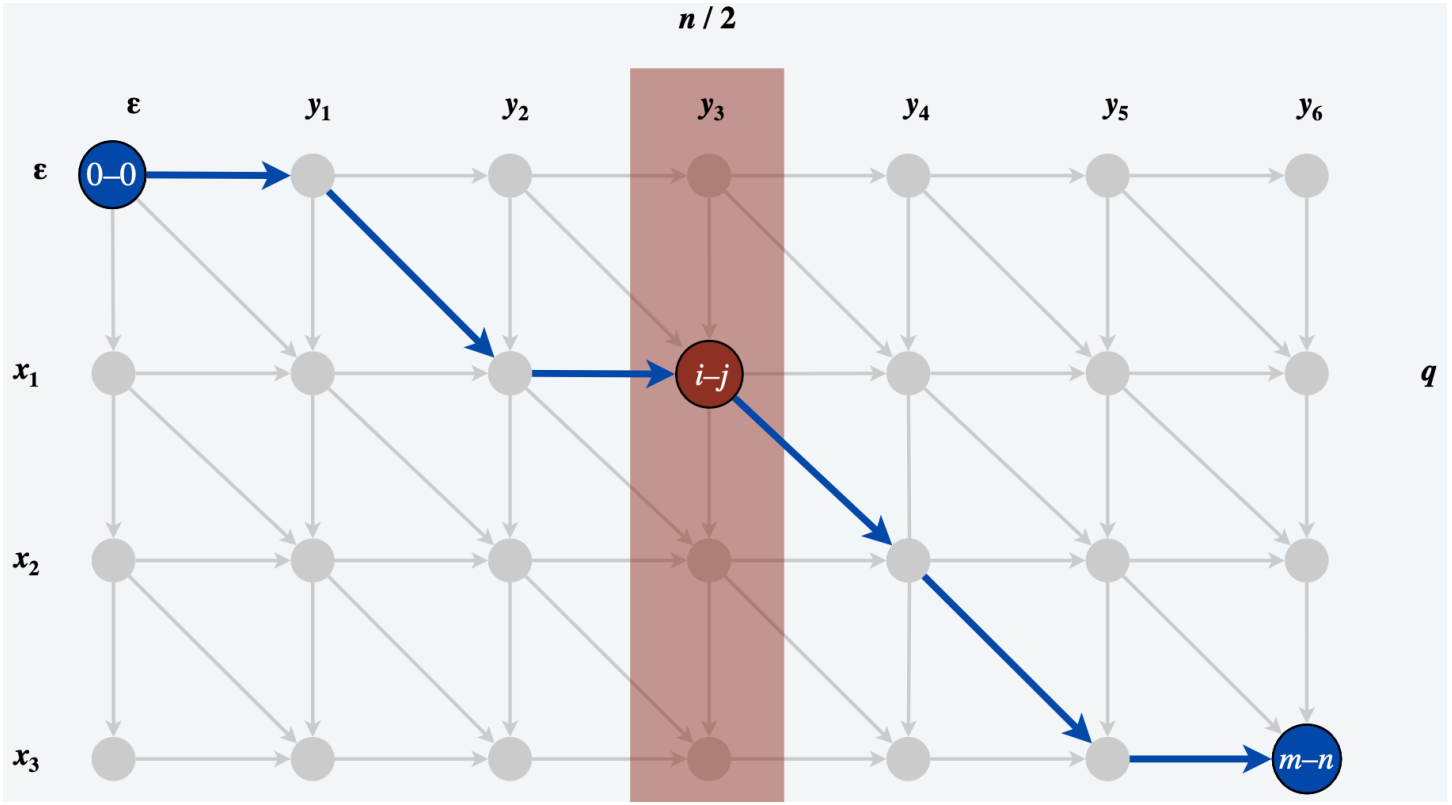
Sequence Alignment: Hirschberg's Algorithm

- **Observation.** The length of a shortest path via (i, j) is $f(i, j) + g(i, j)$.



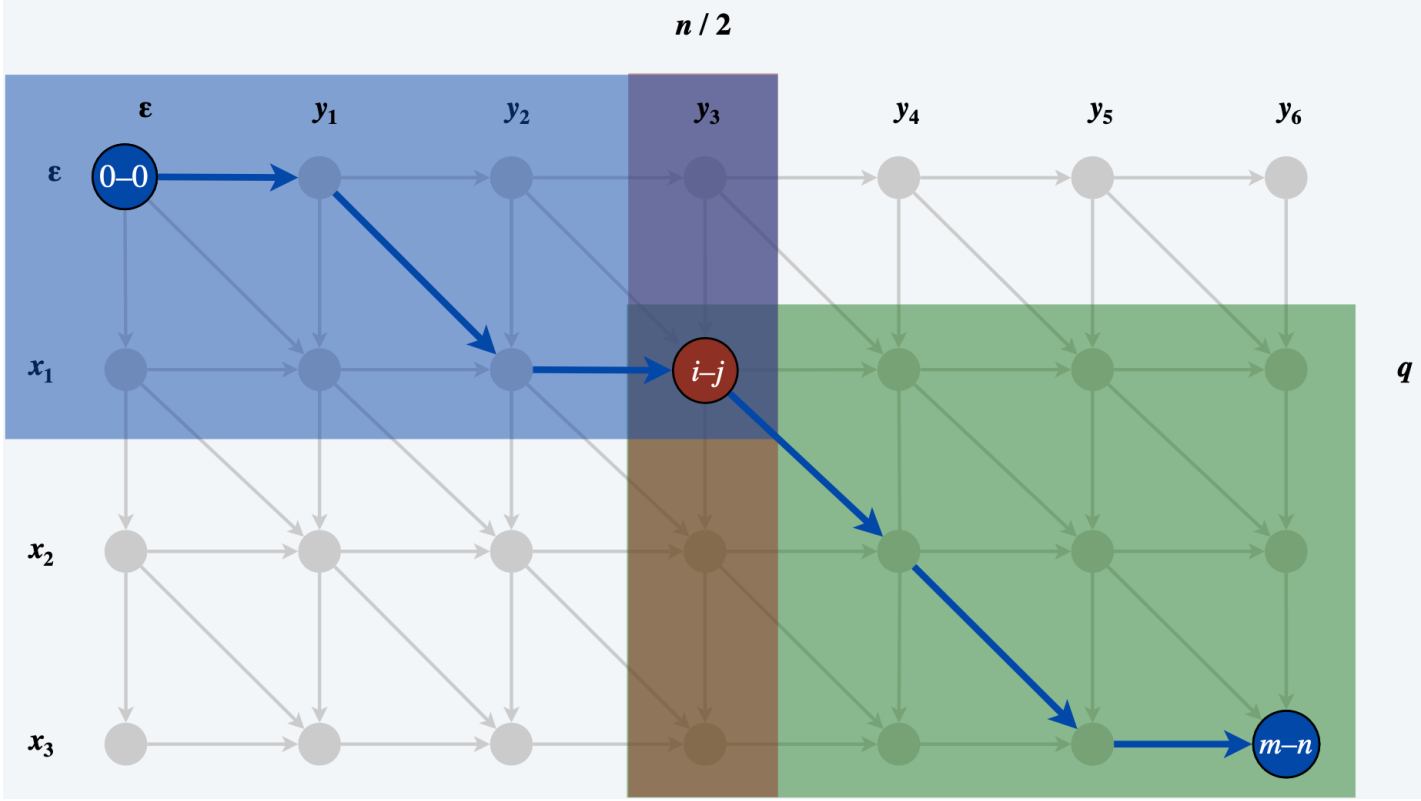
Sequence Alignment: Hirschberg's Algorithm

- **Observation.** The length of a shortest path via (i, j) is $f(i, j) + g(i, j)$.
- **Observation.** Let q be an index that minimizes $f(q, n/2) + g(q, n/2)$. Then, there exists a shortest path from $(0, 0)$ to (m, n) that uses $(q, n/2)$.



Sequence Alignment: Hirschberg's Algorithm

- **Divide.** Find index q that minimizes $f(q, n/2) + g(q, n/2)$; save this dividing node as part of solution.
- **Conquer.** Recursively compute optimal alignment in each piece.



Hirschberg's Algorithm: Analysis

- **Theorem.** Hirschberg's algorithm uses O($m + n$) space.
- Pf.
  - Each recursive call uses O(m) space to compute $f(\cdot, n/2)$ and $g(\cdot, n/2)$.
  - Only O(1) space needs to be maintained per recursive call.
  - Number of recursive calls $\leq n$. ▪

- **Q.** Does Hirschberg's algorithm also run in O(mn) time?

Hirschberg's Algorithm: Analysis

- **Theorem.** Hirschberg's algorithm runs in $O(mn)$ time.
- Pf. (by strong induction on $m + n$)
  - $O(mn)$ time to compute $f(\cdot, n/2)$ and $g(\cdot, n/2)$ and find index q.
  - $T(q, n/2) + T(m - q, n/2)$ time for two recursive calls.
  - Choose constant c so that:
    - ✓ $T(m, 1) \le cm$, $T(1, n) \le cn$, $T(m, n) \le cmn + T(q, n/2) + T(m - q, n/2)$
  - **Claim.** $T(m, n) \le 2cmn$.
    - ✓ Base cases: $m = 1$ and $n = 1$.
    - ✓ Inductive hypothesis: $T(m, n) \le 2cmn$ for all (m', n') with $m' + n' < m + n$.
    - ✓ $T(m, n) \le T(q, n/2) + T(m - q, n/2) + cmn \le 2cqn/2 + 2c(m-q)n/2 + cmn$
      $= cqn + cmn - cqn + cmn = 2cmn$ ▪

Exercise: Longest Common Subsequence

- **Problem.** Given two strings $X = x_1x_2 \ldots x_m$ and $Y = y_1y_2 \ldots y_n$, find a common subsequence that is as long as possible.
- **Alternative viewpoint.** Delete minimum number of characters from string x and string y such that the resulting strings are the same.

- **Ex.** LCS(GGCACCACG, ACGGCGGATACG) = GGCAACG
- **Applications.** Unix diff, git, bioinformatics, …

- **Q.** How to solve this problem via DP?