CSE 421
Introduction to Algorithms

Lecture 13: Dynamic Programming
RNA folding, Sequence Alignment

Dynamic Programming for Optimization

1. Formulate the *(optimum) value* as a recurrence relation or recursive algorithm

2. Figure out the possible values of parameters in the recursive calls.
   - This should be "small", i.e., bounded by a low-degree polynomial
   - Can use memoization to store a cache of previously computing values

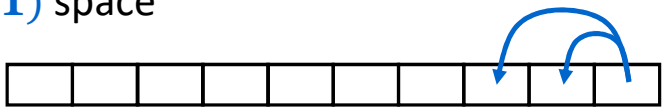
3. Specify an order of evaluation for the recurrence so that you already have the partial results stored in memory when you need them.
   - Produces iterative code
   - Store extra information to be able to reconstruct *optimal solution* and add reconstruction code

Once you have an iterative DP solution: see if you can save space.

Dynamic Programming Patterns so far

Fibonacci pattern:

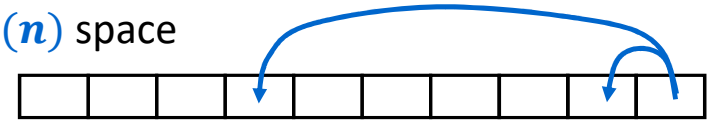
- 1-D, $O(1)$ immediately prior
- $O(1)$ space



$O(n)$

Weighted interval scheduling pattern:

- 1-D, $O(1)$ arbitrary prior
- $O(n)$ space

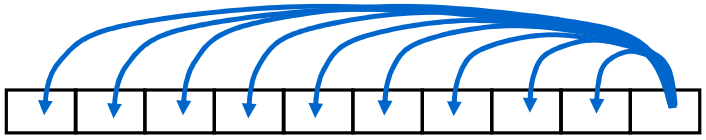


$O(n)$

Longest increasing subsequence pattern:

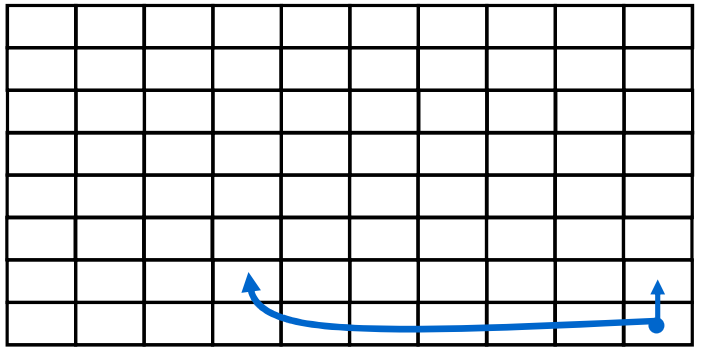
- 1-D, all $n-1$ prior
- $O(n)$ space

$O(n^2)$



Knapsack pattern:

- 2-D, O(1) elements in previous row, above and arbitrary far to the left
- $O(nW)$ space



$O(nW)$

- $O(W)$ space if only optimum value needed
  - Maintain current and previous rows

Dynamic Programming over Intervals

In this different class of problems from ones we have seen before, there are

- 1-dimensional inputs
- A notion of optimization over intervals in that 1 dimension

A number of important problems fit this paradigm

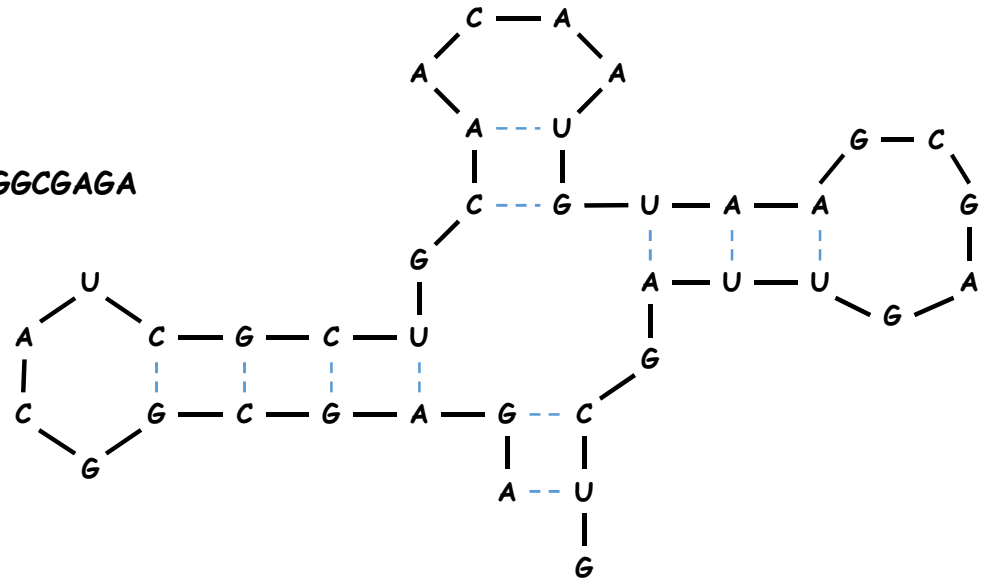
- We focus on a version of one these: RNA Secondary Structure

RNA Secondary Structure

RNA (ribonucleic acid): String $\boldsymbol{B = b_1 b_2 \cdots b_n}$ of *bases* over alphabet
{**A**, **C**, **G**, **U**} standing for adenine, cytosine, guanine, and uracil.

RNA Secondary Structure: RNA is single-stranded and tends to loop back and form bonds between pairs of its bases "base-pairs". This structure is essential for understanding behavior of the molecule.

Ex: **GUCGAUUGAGCGAAUGUAACAACGUGGCUACGGCGAGA**



complementary base pairs: *A-U, C-G*

RNA Secondary Structure

Defn: A *secondary structure* for an RNA sequence $B = b_1 b_2 \cdots b_n$ is a set of pairs $S = \{ (b_i, b_j) \}$ that satisfy:

- [Watson-Crick condition] 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 bends] The ends of each pair are separated by at least 4 intervening bases. That is, 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, then we cannot have $i < k < j < \ell$.

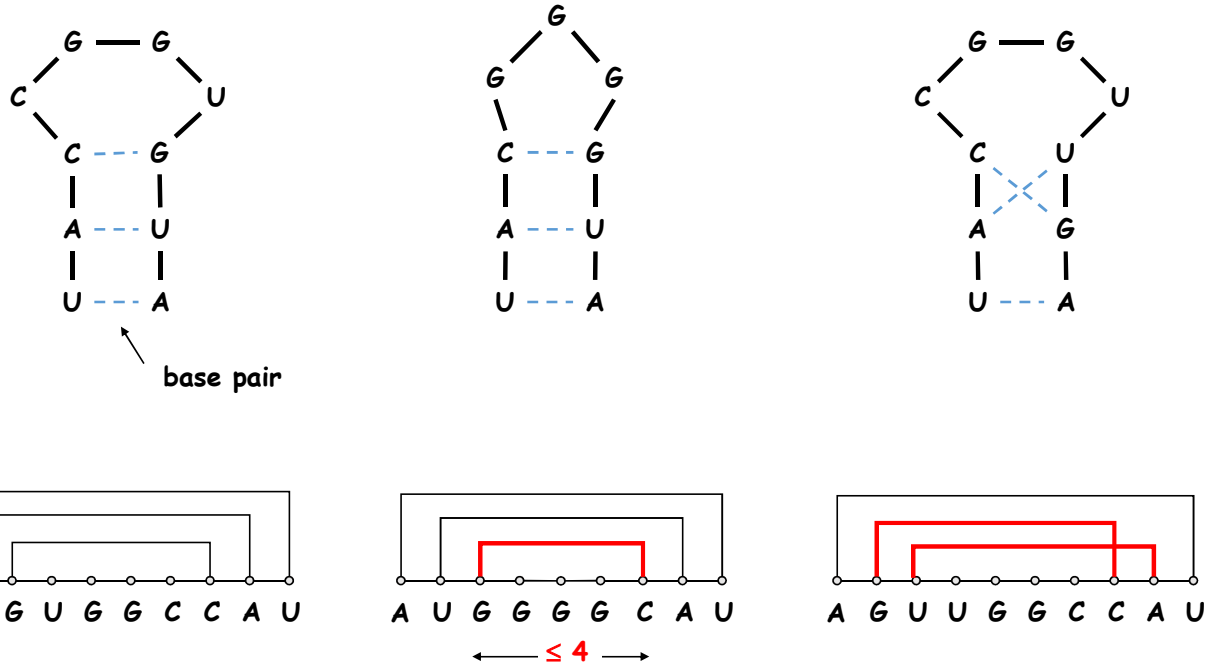
Optimizing energy: The usual hypothesis is that an RNA molecule will form a secondary structure that optimizes the total free energy. Maximizing the # of base pairs in S roughly maximizes free energy.

Given: an RNA molecule $B = b_1 b_2 \cdots b_n$,

Find: a secondary structure S for B maximizing the number of base pairs in S.

RNA Secondary Structure: Examples

Examples.



RNA Secondary Structure: False Start

As usual we consider two cases based on the status of the last base in an optimal secondary structure

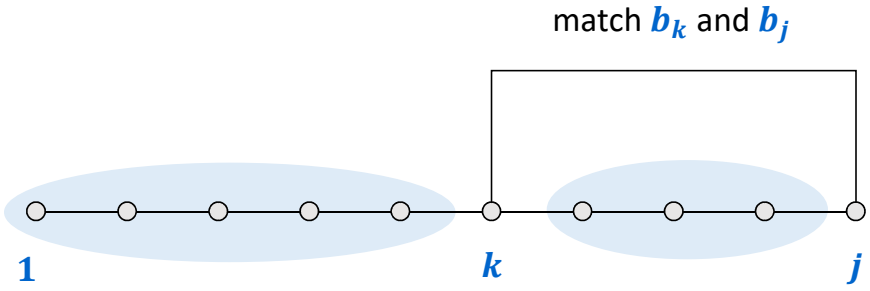
First attempt: Define **OPT(j)** = maximum # of base pairs in a secondary structure of the substring $b_1 b_2 \cdots b_j$.

Case 1: **OPT** does not match base b_j. Value is **OPT($j-1$)**.

Case 2: **OPT** contains some base pair (b_k, b_j).

Two independent* subproblems:

- One on $b_1 b_2 \cdots b_{k-1}$ with value **OPT($k-1$)**
- One on $b_{k+1} b_2 \cdots b_{j-1}$
  - Not of the same type: Need to allow starting index $\neq 1$



* Independence guaranteed by non-crossing property

RNA Secondary Structure: DP over Intervals

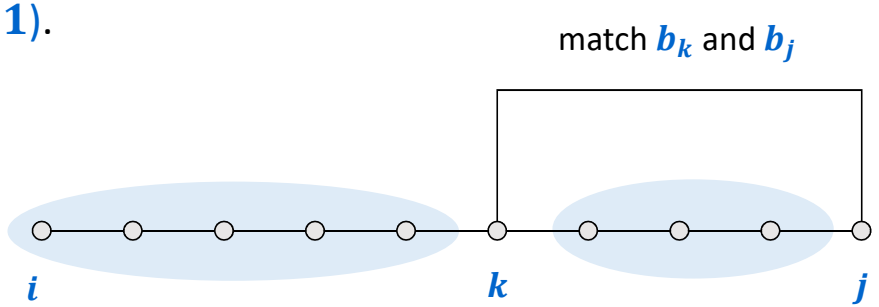
Defn: Define **OPT**(i, j) = maximum # of base pairs in a secondary structure of the substring $b_i b_2 \cdots b_j$.

Case 1: **OPT** does not match base b_j. Value is **OPT**$(i, j-1)$.

Case 2: **OPT** contains some base pair (b_k, b_j).

Two independent subproblems:

- One on $b_i b_2 \cdots b_{k-1}$ with value **OPT**$(i, k-1)$
- One on $b_{k+1} b_2 \cdots b_{j-1}$ with value **OPT**$(k+1, j-1)$



Intervals for recursive calls are shorter

$$\textbf{OPT}(i,j) = \begin{cases} 0 & \text{if } j \le i+4 \\ \max\{\textbf{OPT}(i,j-1), \max\{1+\textbf{OPT}(i,k-1)+\textbf{OPT}(k+1,j-1) : \ j > k+4,\ b_k \sim b_j\}\} & \text{if } j > i+4 \end{cases}$$

where we write $b \sim b'$ iff they are Watson-Crick complement pairs *A*-U, U-*A*,*C*-*G*, or *G*-*C*

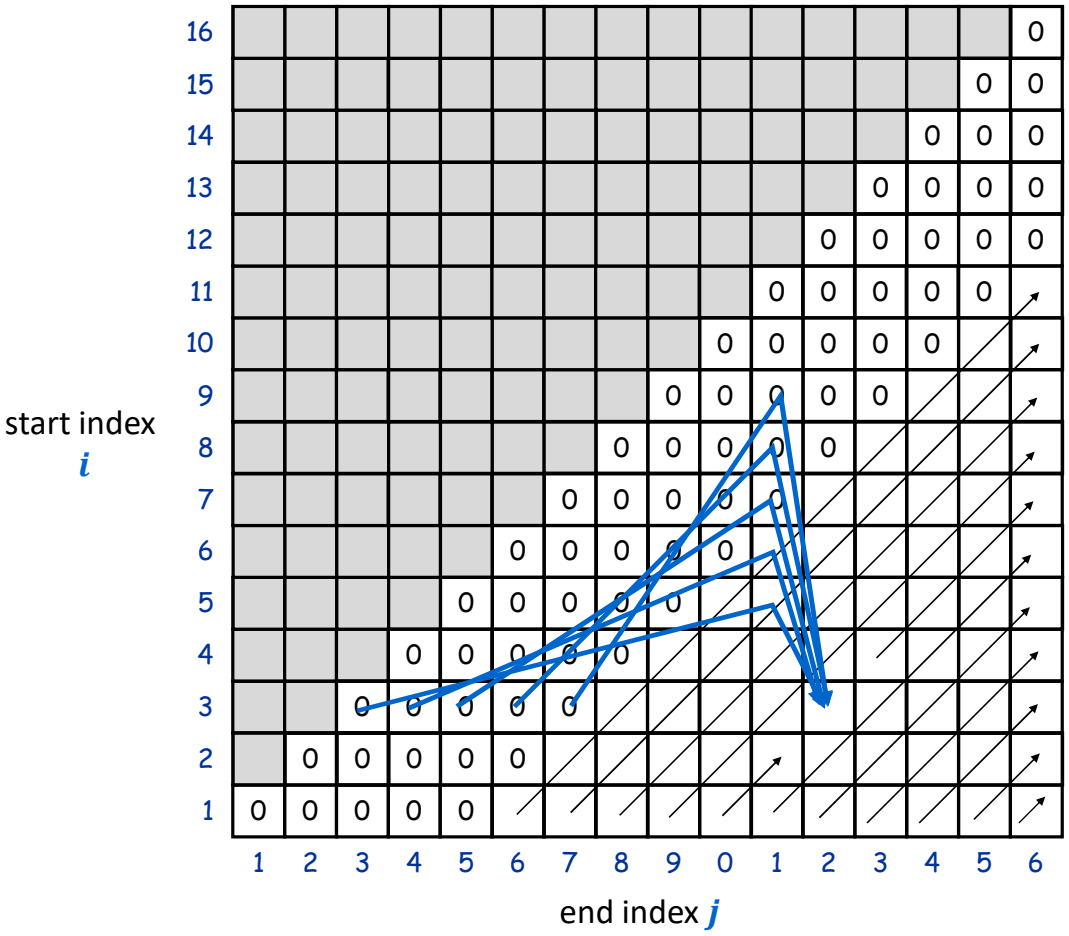
Dynamic Programming Over Intervals: Iterative Solution

Evaluate in order of increasing interval length

```
RNA(b_1,…,b_n) {
   for m = 0 to n-1        // interval length     O(n) iterations
      for i = 1 to n-m     // interval start      O(n) iterations
         j = i + m
         if m < 5
            OPT[i, j] = 0
         else {
            OPT[i, j] = OPT[i, j-1]
            for k = i to j-5     // split point    O(n) iterations
               if WatsonCrick(b_k,b_j)
                  if 1+OPT[i, k-1] + OPT[k+1, j-1] > OPT[i, j] {
                     OPT[i, j] = 1 + OPT[i, k-1] + OPT[k+1, j-1]
                  }
         }
   return OPT[1, n]
}
```

$O(n^3)$

Dynamic Programming Over Intervals: Iterative Solution



DP over intervals pattern

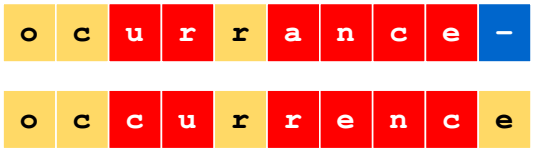
- 2-D lower triangular portion
- Fill sub-diagonals in order of distance from the diagonal
- Each of the $O(n^2)$ entries uses $O(n)$ pairs of entries in
  - a fixed row to the left and
  - a column above
- Time $O(n^3)$, space $O(n^2)$

Sequence Alignment

String Similarity

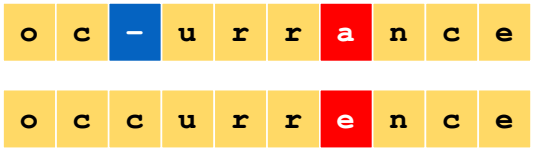
How similar are two strings?

- `ocurrance`
- `occurrence`



6 mismatches, 1 gap

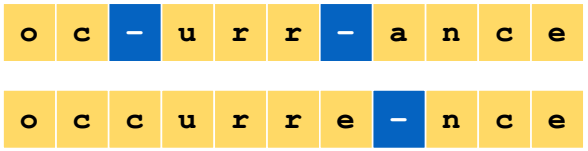
Clearly a better matching



1 mismatch, 1 gap

Maybe a better matching

- depends on cost of gaps vs mismatches



0 mismatches, 3 gaps

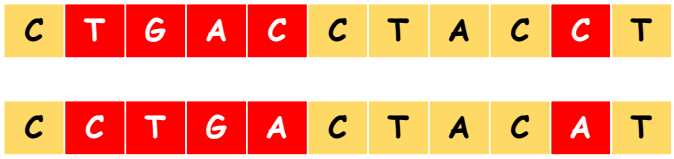
Edit Distance

Applications:

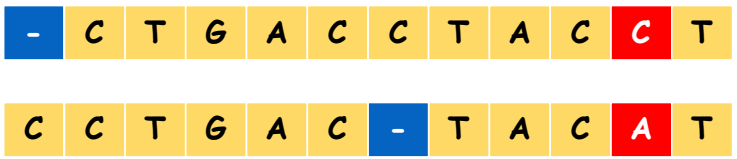
- Basis for Unix **`diff`**.
- Speech recognition.
- Computational biology.

Edit distance: [Levenshtein 1966, Needleman-Wunsch 1970]

- Gap penalty δ; mismatch penalty α_{pq} if symbol p is replaced by symbol q.
- **Cost** = gap penalties + mismatch penalties.



$\alpha_{TC} + \alpha_{GT} + \alpha_{AG} + 2\alpha_{CA}$



$2\delta + \alpha_{CA}$

Sequence Alignment

Sequence Alignment:

Given: Two strings $X = x_1 x_2 \ldots x_m$ and $Y = y_1 y_2 \ldots y_n$

Find: "Alignment" of X and Y of minimum edit cost.

Defn: An alignment M of X and Y is a set of ordered pairs x_i-y_j s.t. each symbol of X and Y occurs in at most one pair with no "crossing pairs".

The pairs x_i-y_j and $x_{i'}$-$y_{j'}$ cross iff $i < i'$ but $j > j'$.

$$\text{cost}(M) = \underbrace{\sum_{(x_i, y_j) \in M} \alpha_{x_i y_j}}_{\text{mismatch}} + \underbrace{\sum_{i:\, x_i \text{ unmatched}} \delta + \sum_{j:\, y_j \text{ unmatched}} \delta}_{\text{gap}}$$

Note: if $x_i = y_j$ then $\alpha_{x_i y_j} = 0$

Example:

CTACCG vs TACATG

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	

$M = \{x_2$-y_1, x_3-y_2, x_4-y_3, x_5-y_4, x_6-$y_6\}$

Sequence Alignment: Problem Structure

Defn: $\mathbf{OPT}(i, j)$ = min cost of aligning strings $x_1 x_2 \ldots x_i$ and $y_1 y_2 \ldots y_j$.

Case 1: OPT matches x_i-y_j.

- Pay mismatch cost $\alpha_{x_i y_j}$ for x_i-y_j + min cost of aligning strings $x_1 x_2 \ldots x_{i-1}$ and $y_1 y_2 \ldots y_{j-1}$

  Note: if $x_i = y_j$ then $\alpha_{x_i y_j} = 0$

Case 2a: OPT leaves x_i unmatched.

- Pay gap cost δ for x_i + min cost of aligning $x_1 x_2 \ldots x_{i-1}$ and $y_1 y_2 \ldots y_j$

Case 2b: OPT leaves y_j unmatched.

- Pay gap cost δ for y_j + min cost of aligning $x_1 x_2 \ldots x_i$ and $y_1 y_2 \ldots y_{j-1}$

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

Sequence Alignment: Algorithm

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

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

$O(mn)$

Example run with *AGACATTG* and *GAGTTA*: $\delta = \alpha_{\text{mis}} = 1$

		A	G	A	C	A	T	T	G
	0	1	2	3	4	5	6	7	8
G	1								
A	2								
G	3								
T	4								
T	5								
A	6								

Example run with *AGACATTG* and *GAGTTA*: $\delta = \alpha_{\text{mis}} = 1$

		A	G	A	C	A	T	T	G
	0	1	2	3	4	5	6	7	8
G	1	1	1	2	3	4	5	6	7
A	2								
G	3								
T	4								
T	5								
A	6								

Example run with *AGACATTG* and *GAGTTA*: $\delta = \alpha_{\text{mis}} = 1$

		A	G	A	C	A	T	T	G
	0	1	2	3	4	5	6	7	8
G	1	1	1	2	3	4	5	6	7
A	2	1	2	1					
G	3								
T	4								
T	5								
A	6								

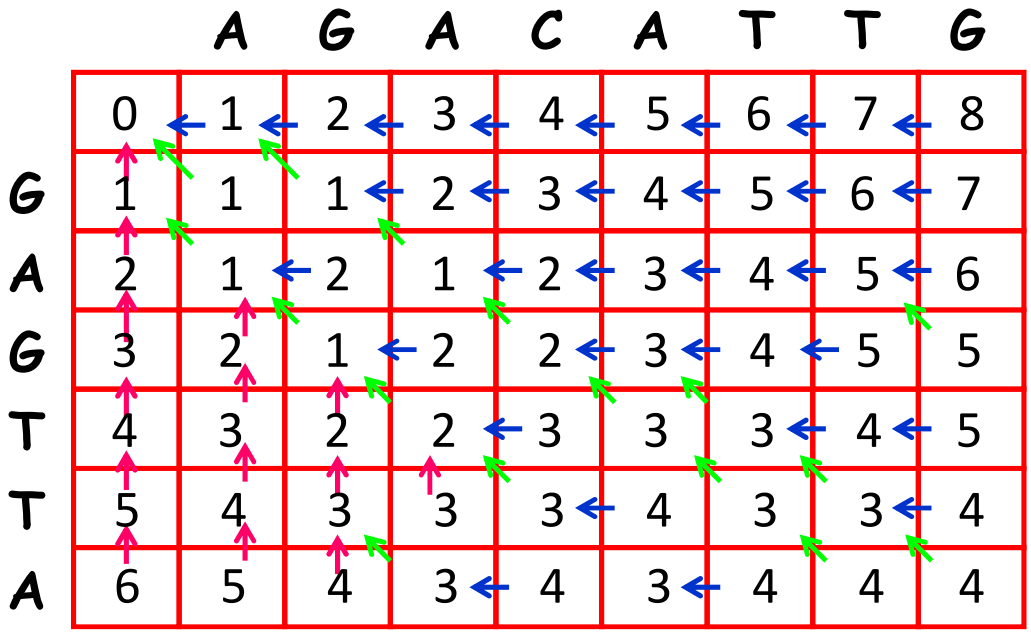
Example run with *AGACATTG* and *GAGTTA*: $\delta = \alpha_{\text{mis}} = 1$

		A	G	A	C	A	T	T	G
	0	1	2	3	4	5	6	7	8
G	1	1	1	2	3	4	5	6	7
A	2	1	2	1	2	3	4	5	6
G	3	2	1	2	2	3	4	5	5
T	4								
T	5								
A	6								

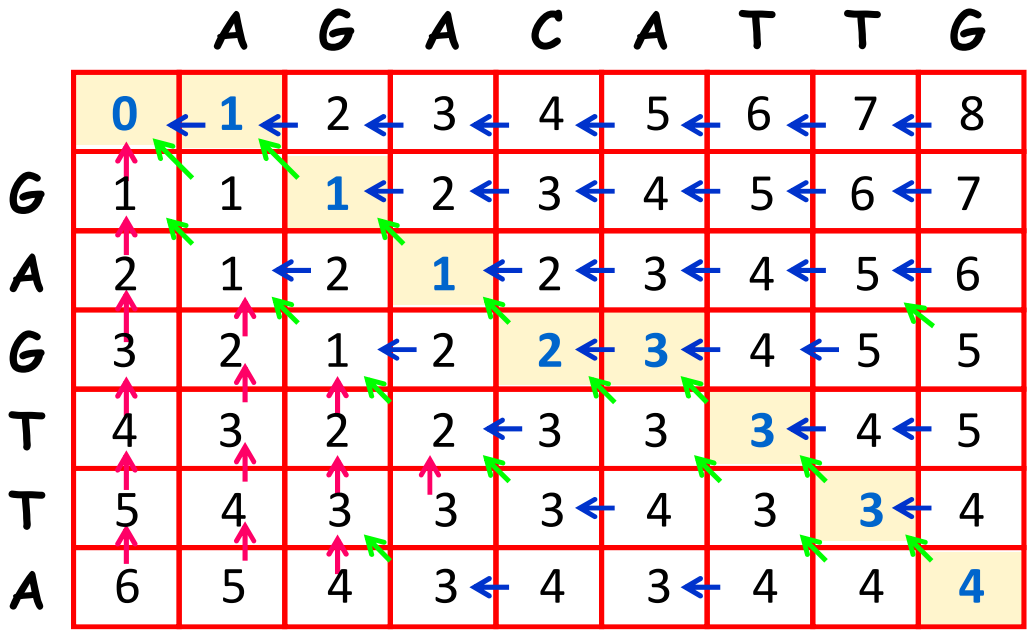
Example run with *AGACATTG* and *GAGTTA*: $\delta = \alpha_{\text{mis}} = 1$

		A	G	A	C	A	T	T	G
	0	1	2	3	4	5	6	7	8
G	1	1	1	2	3	4	5	6	7
A	2	1	2	1	2	3	4	5	6
G	3	2	1	2	2	3	4	5	5
T	4	3	2	2	3	3	3	4	5
T	5	4	3	3	3	4	3	3	4
A	6	5	4	3	4	3	4	4	4

Example run with *AGACATTG* and *GAGTTA*: $\delta = \alpha_{\text{mis}} = 1$



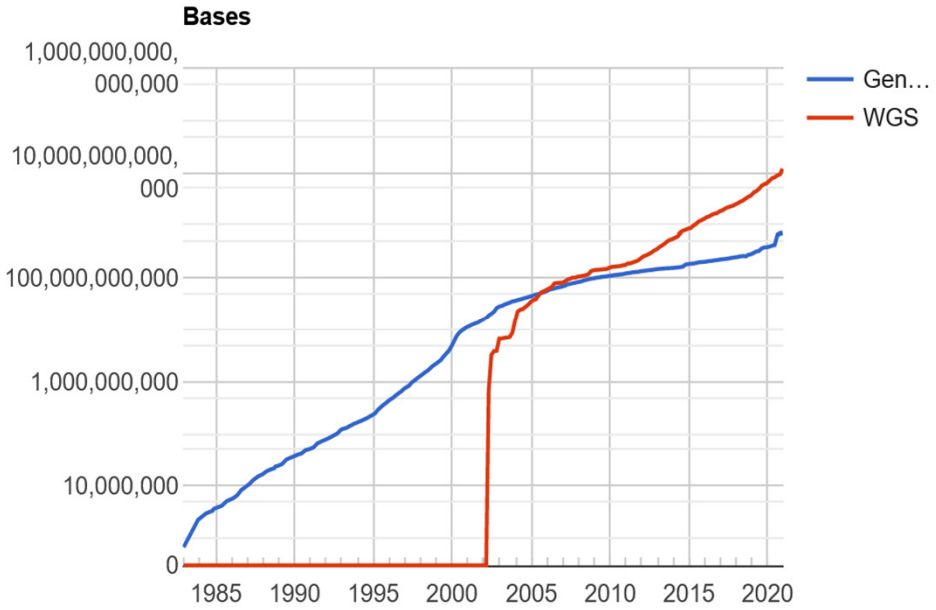
Example run with *AGACATTG* and *GAGTTA*: $\delta = \alpha_{\text{mis}} = 1$

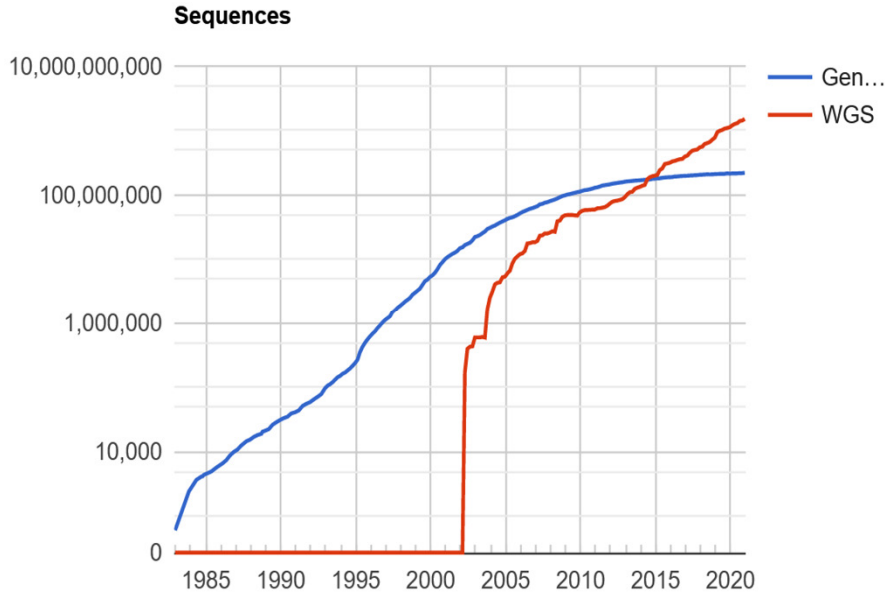


Optimal Alignment

A G A C A T T G
_ G A G _ T T A

Genbank and WGS Statistics





Sequence Alignment: Linear Space

- Lines of code for `diff`: m, n at most in 1000's
- Computational biology: m, n may be in 100,000's.

  10 billions ops OK, but 10GB array?

Q: Can we avoid using quadratic space?

Easy: Optimal value in $O(m + n)$ space and $O(mn)$ time.

- Compute **OPT**$(i, \bullet)$ from **OPT**$(i - 1, \bullet)$.
- No longer a simple way to recover alignment itself.

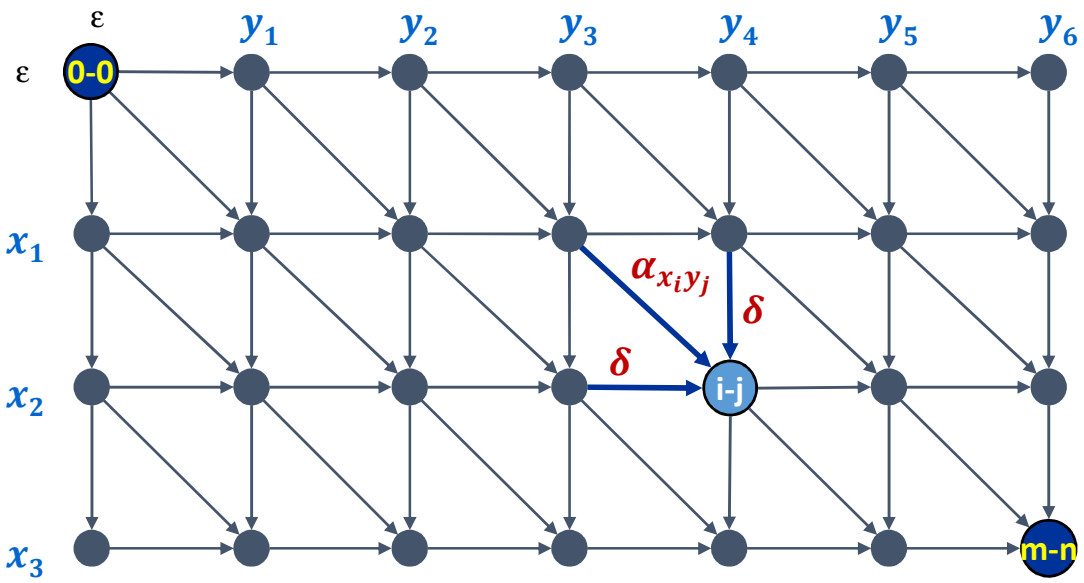
Theorem: [Hirschberg 1975] Optimal alignment in $O(m + n)$ space and $O(mn)$ time.

- Clever combination of divide-and-conquer and dynamic programming.
- Inspired by idea of Savitch from complexity theory.

Sequence Alignment: Linear Space

Edit distance graph: Horizontal & vertical edges weight δ

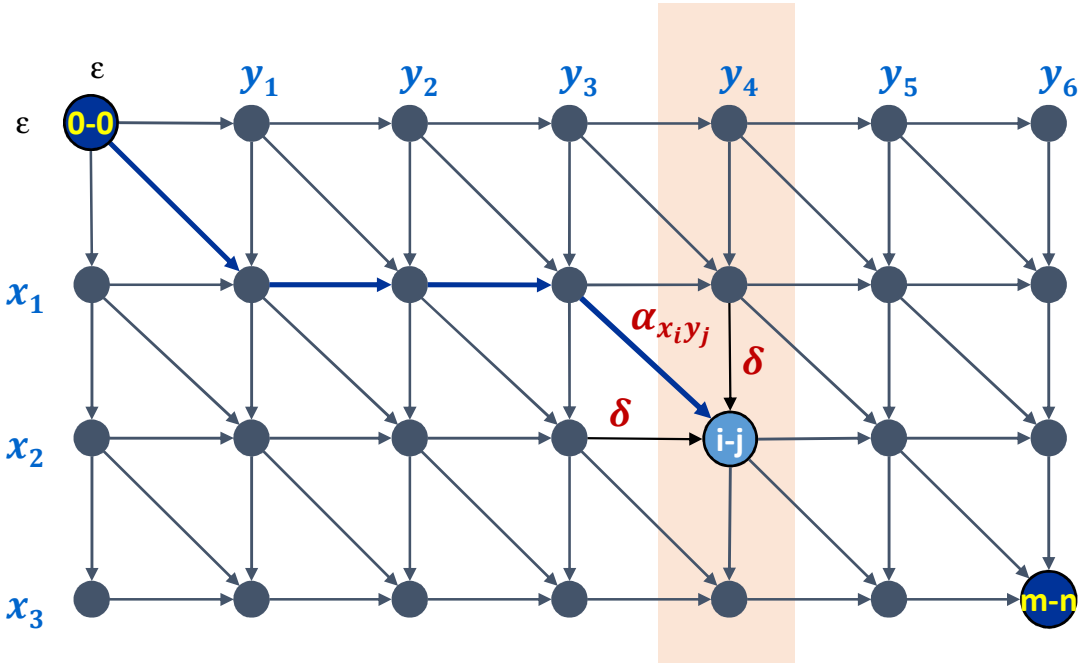
Diagonal edge into each node (i, j) weight $\alpha_{x_i y_j}$



Sequence Alignment: Linear Space

Edit distance graph: Horizontal & vertical edges weight δ

Diagonal edge into each node (i, j) weight $\alpha_{x_i y_j}$



Let $d_{\text{start}}(i, j)$ = length of shortest path from $(0, 0)$ to (i, j)

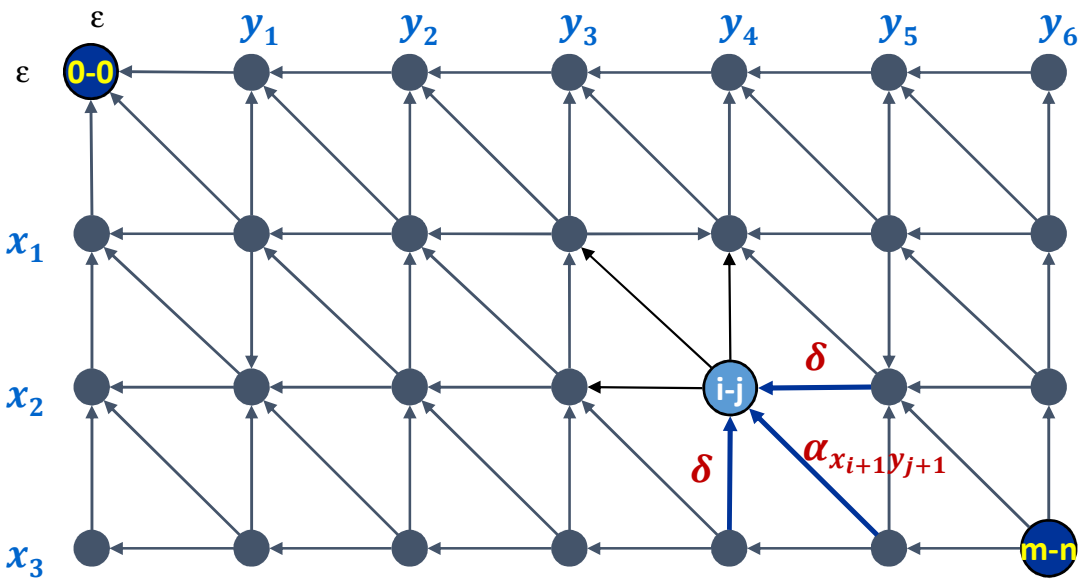
Then $\text{OPT}(i, j) = d_{\text{start}}(i, j)$.

For any fixed j can compute all $d_{\text{start}}(\cdot, j)$ in $O(n + m)$ space $O(nm)$ time

Sequence Alignment: Linear Space

Reversed edit distance graph: Horizontal & vertical edges weight δ

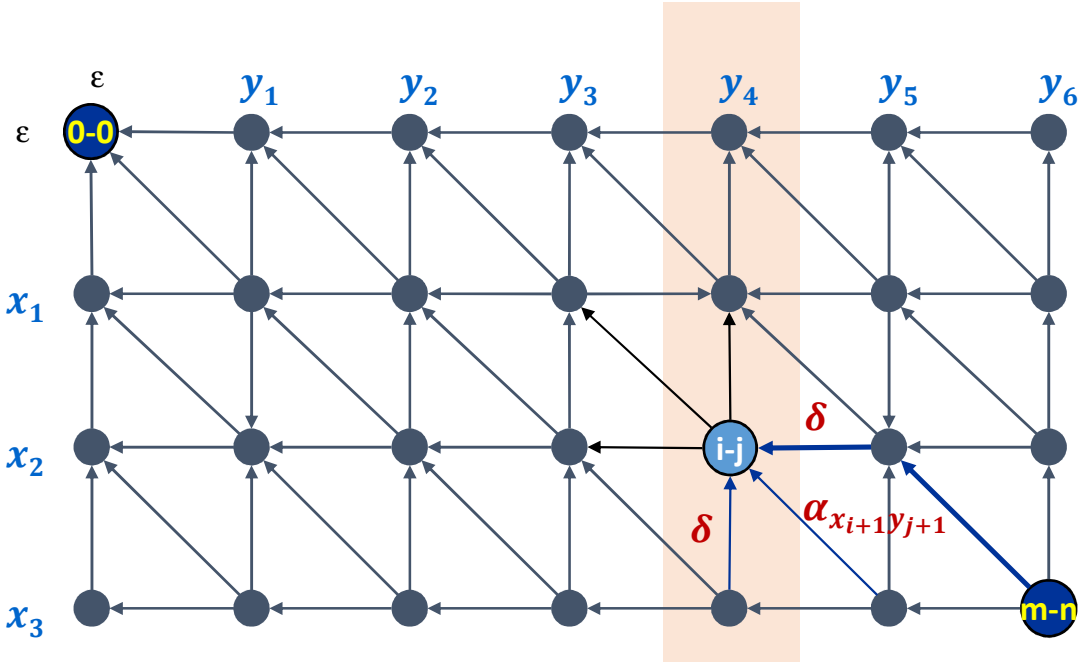
Diagonal edge into each node (i, j) weight $\alpha_{x_{i+1}y_{j+1}}$



Sequence Alignment: Linear Space

Reversed edit distance graph: Horizontal & vertical edges weight δ

Diagonal edge into each node (i, j) weight $\alpha_{x_{i+1}y_{j+1}}$



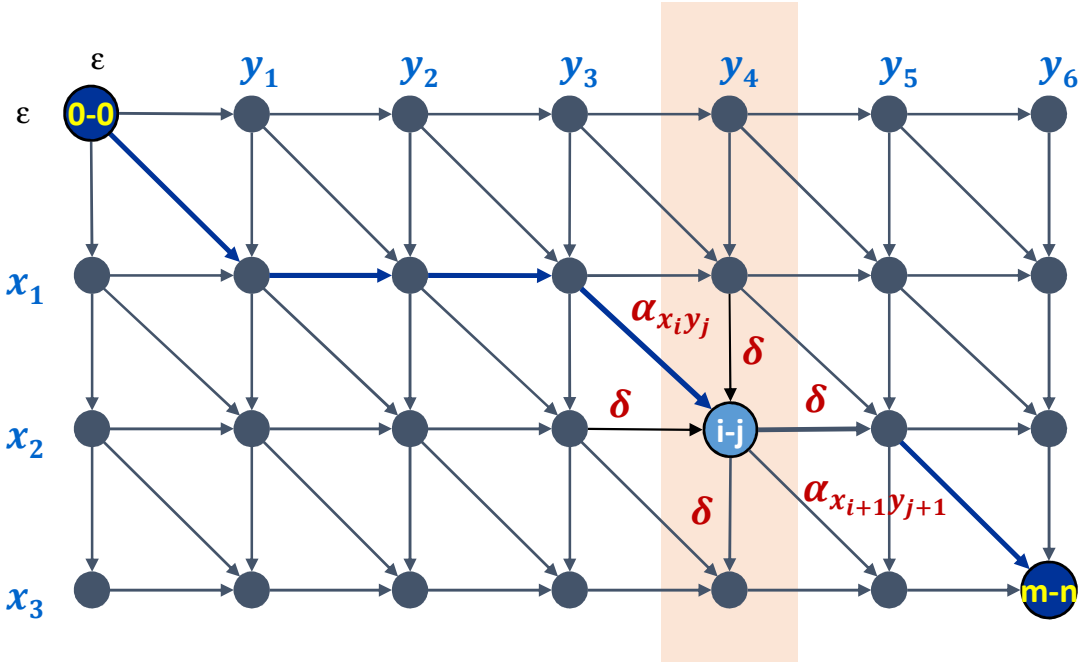
Let $d_{\text{end}}(i, j)$ = length of shortest path from (m, n) to (i, j)

For any fixed j can compute all $d_{\text{end}}(\cdot, j)$ in $O(n + m)$ space $O(nm)$ time

Sequence Alignment: Linear Space

Edit distance graph: Horizontal & vertical edges weight δ

Diagonal edge into each node (i, j) weight $\alpha_{x_i y_j}$



Optimal alignment includes exactly one node (i, j) in column j

That node minimizes

$$d_{\text{start}}(i, j) + d_{\text{end}}(i, j)$$

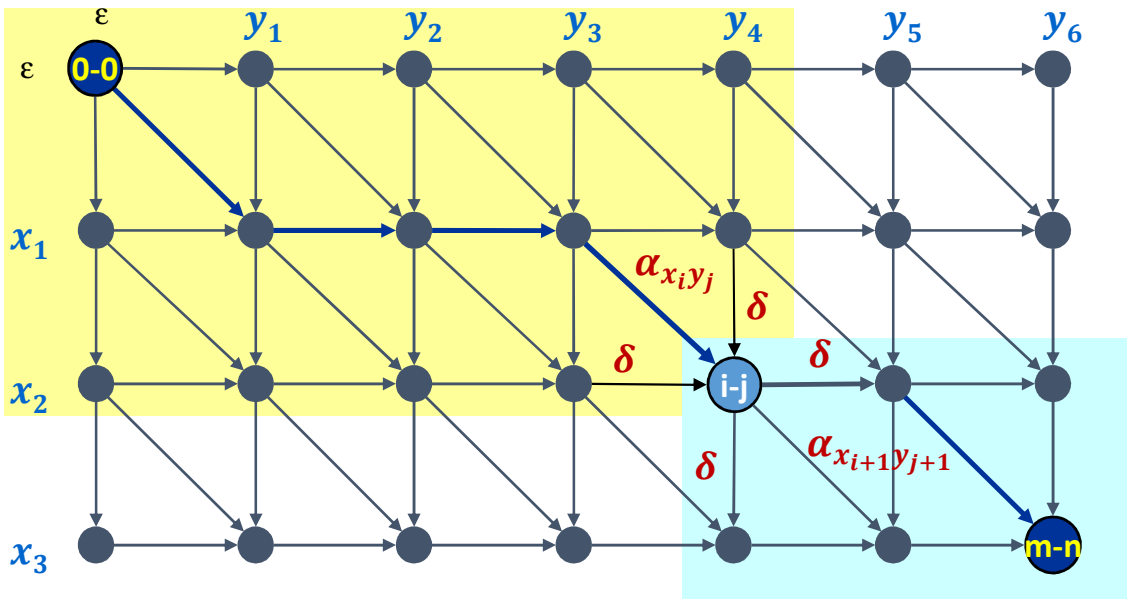
which equals **OPT**(m, n)

Divide & conquer:
Find this for $j = n/2$ and recurse

Sequence Alignment: Linear Space

Edit distance graph: Horizontal & vertical edges weight δ

Diagonal edge into each node (i, j) weight $\alpha_{x_i y_j}$



Optimal alignment includes exactly one node (i, j) in column j

That node minimizes

$$d_{\text{start}}(i, j) + d_{\text{end}}(i, j)$$

which equals $\textbf{OPT}(m, n)$

Divide & Conquer:
Find this for $j = n/2$ and recurse
Re-use space for second call.

Analytical details

Write $\boldsymbol{T(m,n)}$ for the time cost.

- Recurrence $\boldsymbol{T(m,n) = T(i,n/2) + T(m-i,n/2) + O(mn)}$

$$\boldsymbol{T(1,n) = O(n)},\ \boldsymbol{T(m,1) = O(m)}$$

- Solution $\boldsymbol{T(m,n) = O(mn)}$.
  - Not only is the value of $\boldsymbol{n}$ halved for the two subproblems, but the lengths of the first strings still only sum to $\boldsymbol{m}$.
  - Proof via induction (Exercise).

Another side of practice

In practice the algorithm is usually run on smaller chunks of a large string, e.g. m and n are lengths of genes so a few thousand characters

- Researchers want all alignments that are close to optimal not just the optimal solution
- Basic algorithm is run with
  - 2 rows/columns for values as in the space-saving solution, but
  - all mn pointers since the whole table of pointers (2 bits each) will fit in RAM