# 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

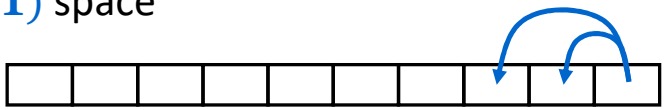
3. Specify an order of evaluation for the recurrence so that you already have the partial results stored in memory when you need them.
   - Produces iterative code
   - Store extra information to be able to reconstruct *optimal solution* and add reconstruction code

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

# Dynamic Programming Patterns so far

Fibonacci pattern:

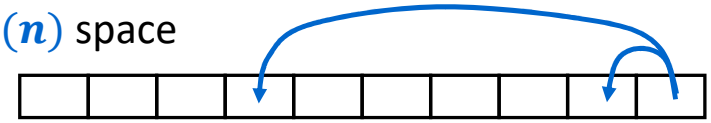
- 1-D, $O(1)$ immediately prior
- $O(1)$ space



$O(n)$

Weighted interval scheduling pattern:

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

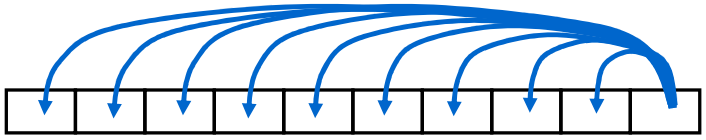


$O(n)$

Longest increasing subsequence pattern:

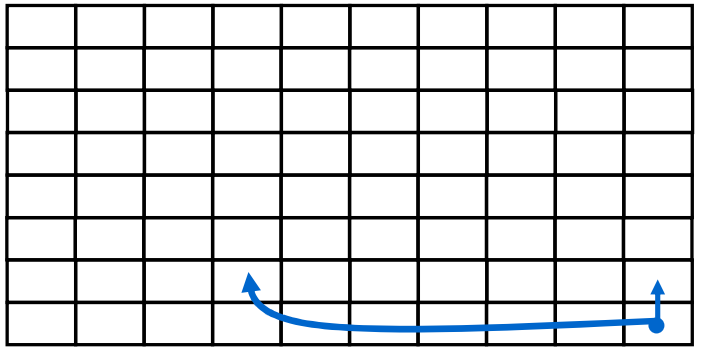
- 1-D, all $n-1$ prior
- $O(n)$ space

$O(n^2)$



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

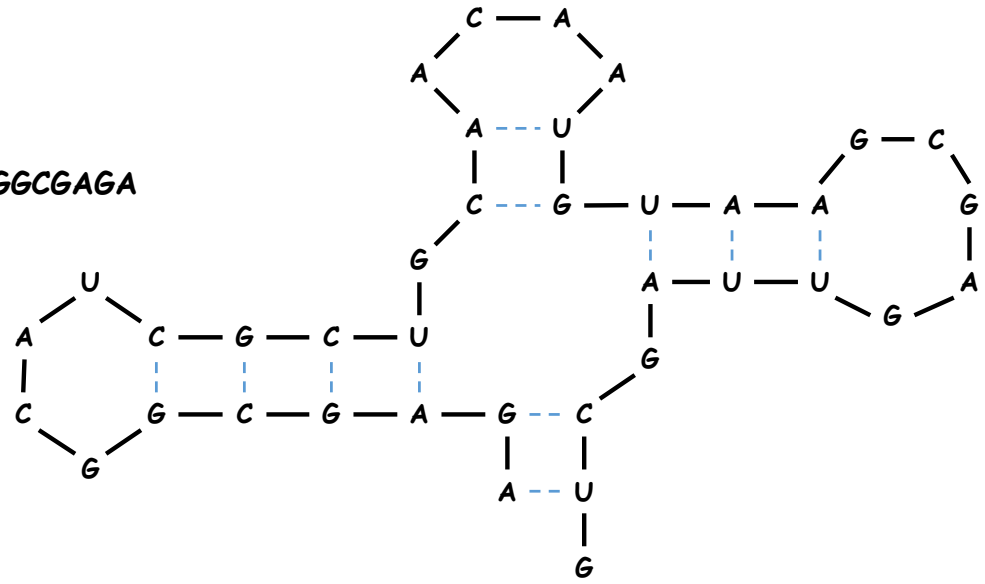
- We focus on a version of one these:  RNA Secondary Structure

# 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 $(b_k, b_\ell)$ are two pairs in $S$, then we cannot have $i < k < j < \ell$.

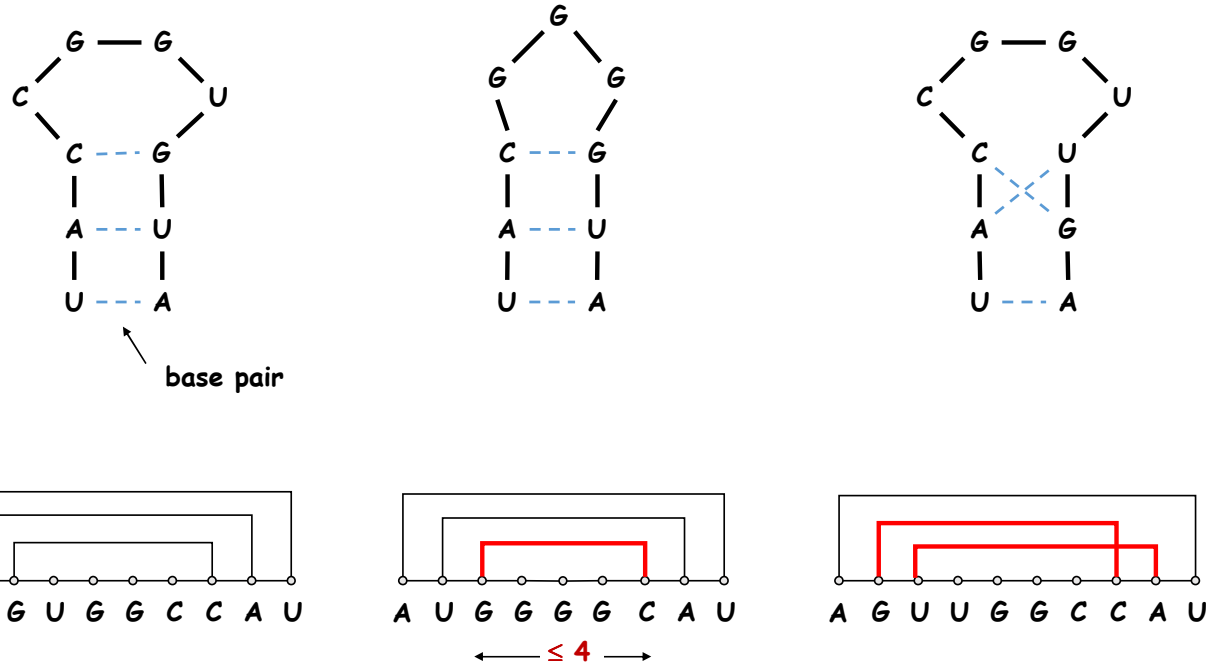
**Optimizing energy:** The usual hypothesis is that an RNA molecule will form a secondary structure that optimizes the total free energy. Maximizing the # of base pairs in $S$ roughly maximizes free energy.

**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.



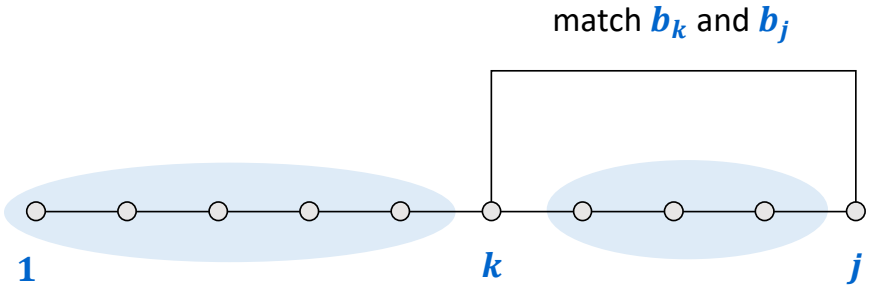
# RNA Secondary Structure: False Start

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

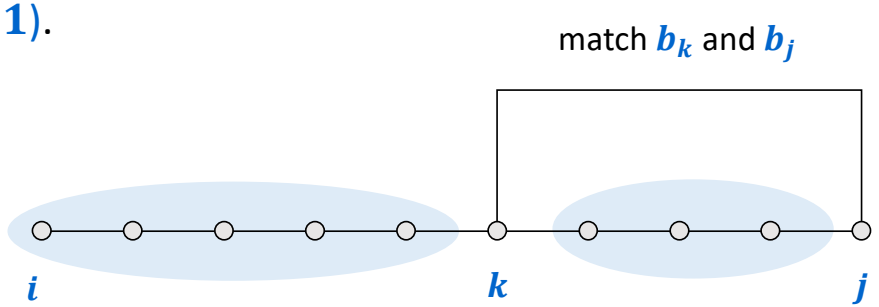
**Defn:** Define **OPT**$(i, j)$ = maximum # of base pairs in a secondary structure of the substring $b_i b_2 \cdots b_j$.

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*

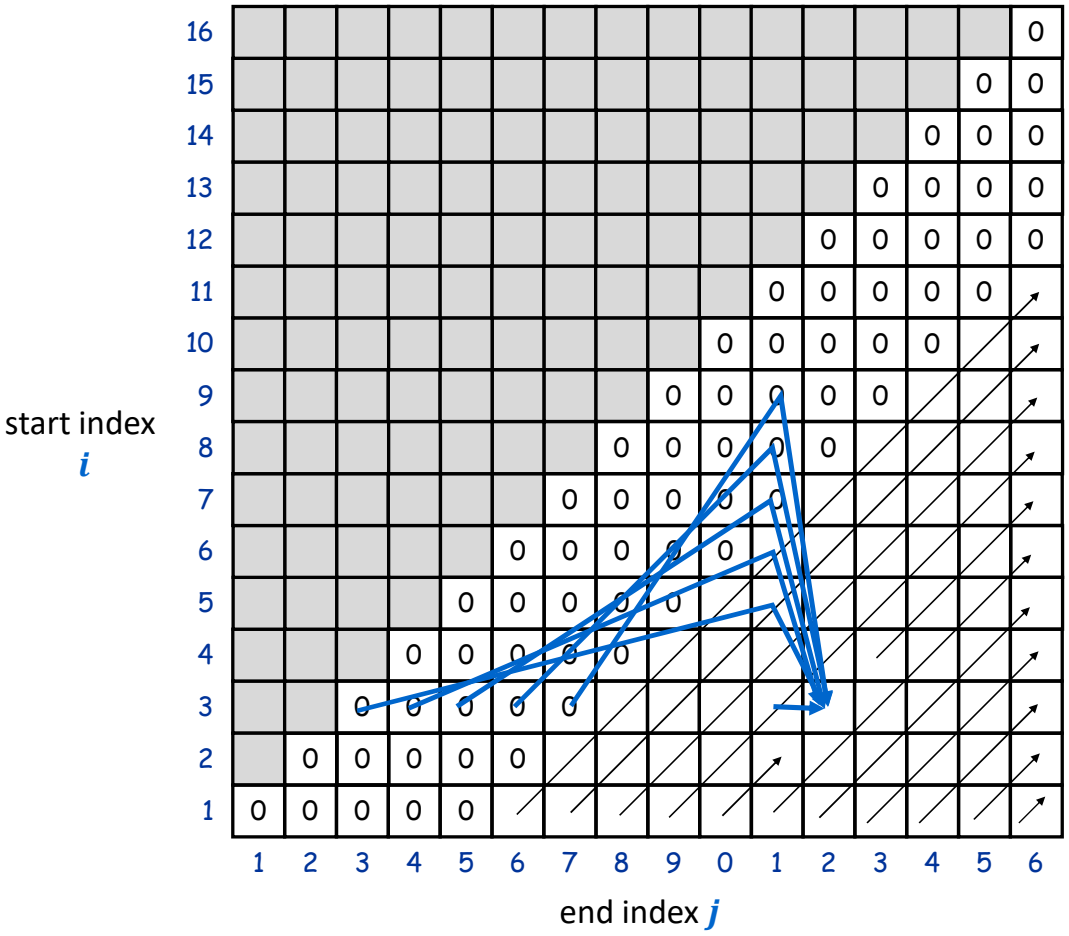
# Dynamic Programming Over Intervals: Iterative Solution

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

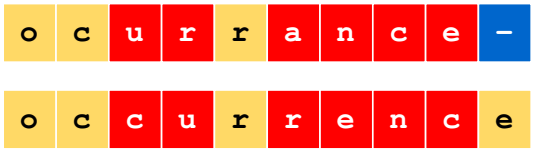
- 2-D lower triangular portion
- Fill sub-diagonals in order of distance from the diagonal
- Each of the $O(n^2)$ entries uses $O(n)$ pairs of entries in
  - a fixed row to the left and
  - a column above
- Time $O(n^3)$, space $O(n^2)$

# Sequence Alignment

# String Similarity

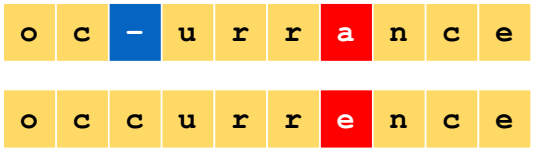
## How similar are two strings?

- `ocurrance`
- `occurrence`




6 mismatches, 1 gap

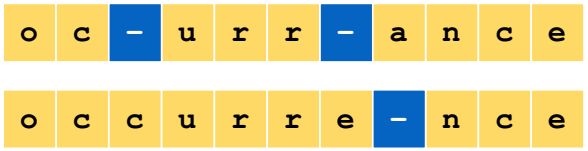
Clearly a better matching




1 mismatch, 1 gap

Maybe a better matching

- depends on cost of gaps vs mismatches




0 mismatches, 3 gaps

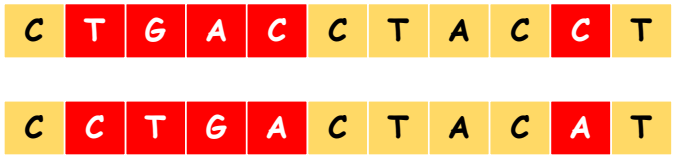
# Edit Distance

## Applications:

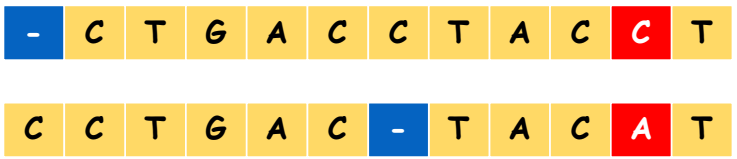
- Basis for Unix **`diff`**.
- Speech recognition.
- Computational biology.

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

- Gap penalty $\delta$; mismatch penalty $\alpha_{pq}$ 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 $X = x_1 x_2 \dots x_m$ and $Y = y_1 y_2 \dots y_n$

**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 $\delta$ 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 $\delta$ 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 | | | | | | | | |

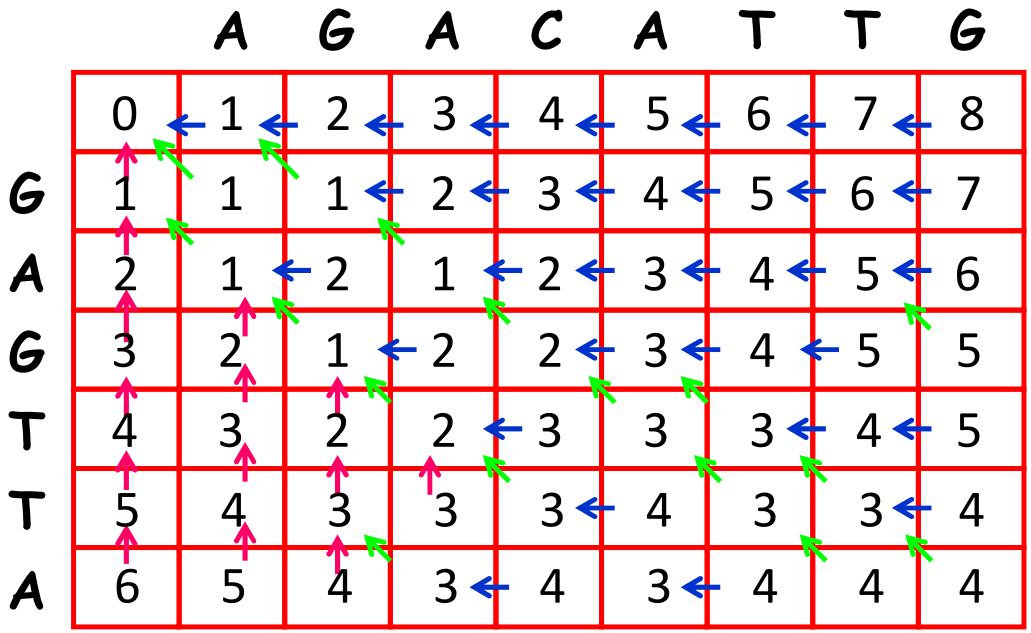
# Example run with *AGACATTG* and *GAGTTA*: $\delta = \alpha_{\text{mis}} = 1$

| | | 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 | | | | | | | | |

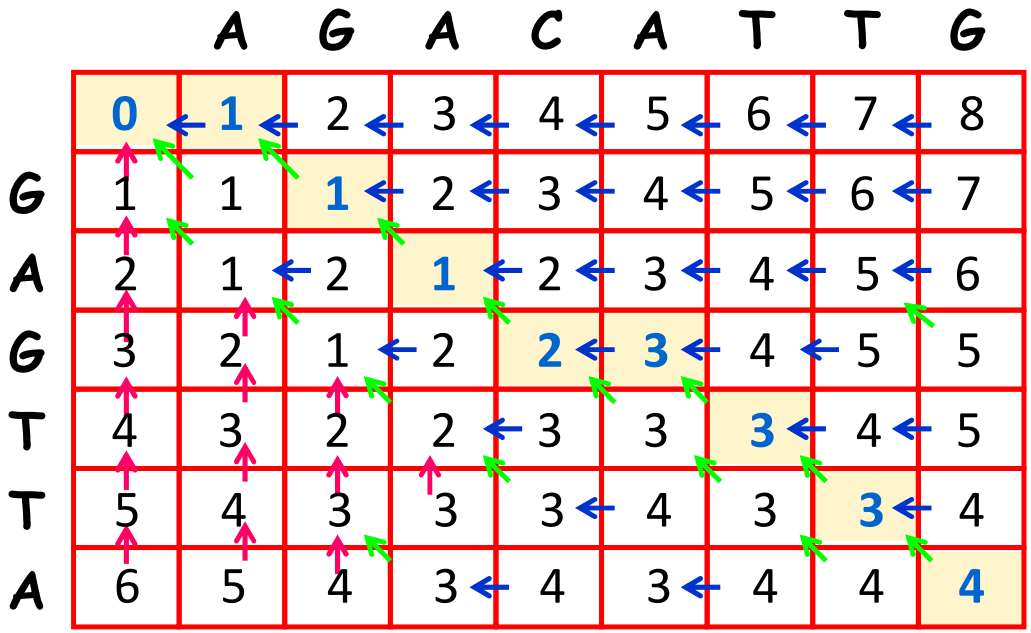
# Example run with *AGACATTG* and *GAGTTA*: $\delta = \alpha_{\text{mis}} = 1$

| | | 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*: $\delta = \alpha_{\text{mis}} = 1$



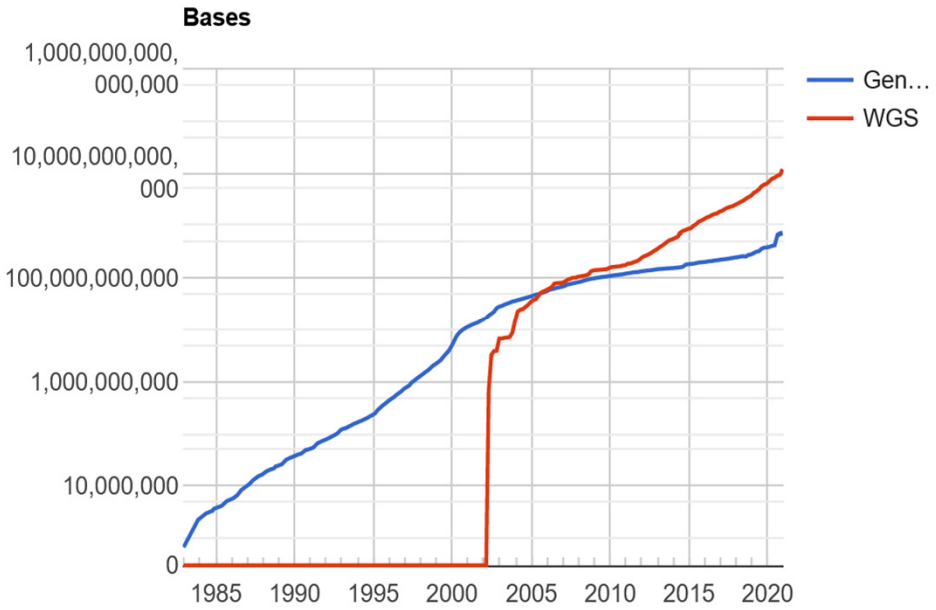
# Example run with *AGACATTG* and *GAGTTA*: $\delta = \alpha_{\text{mis}} = 1$

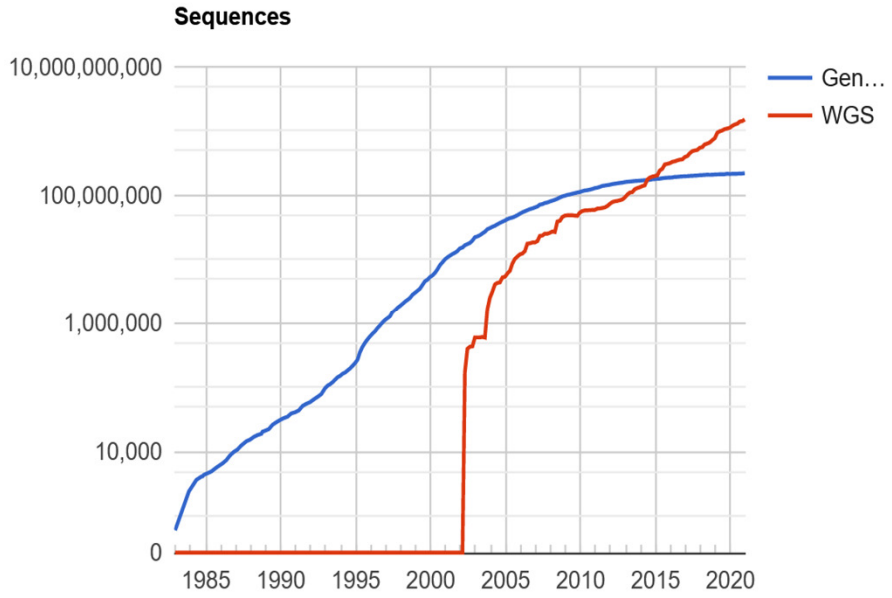



Optimal Alignment

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.

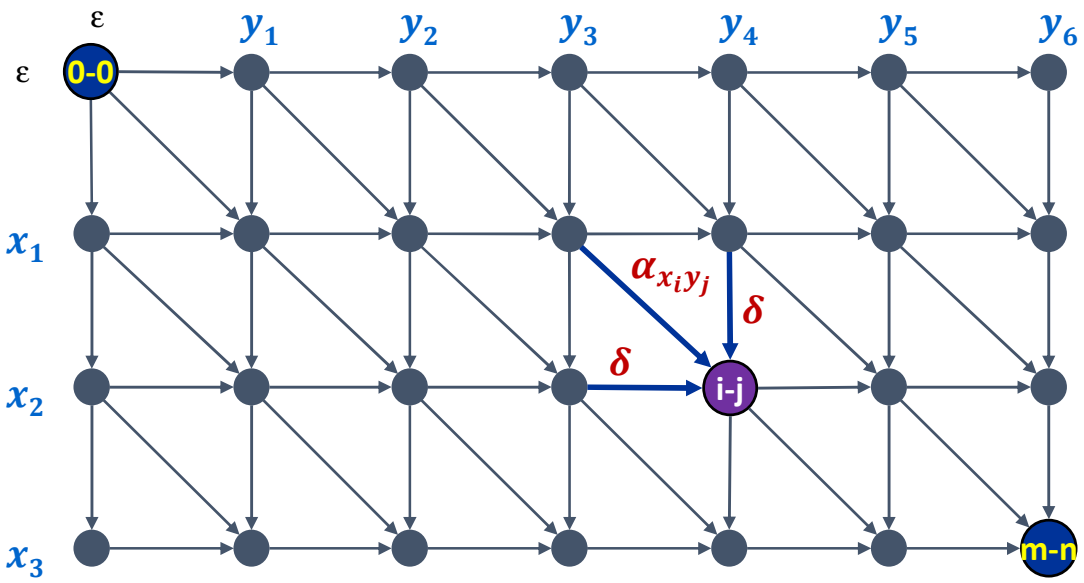
**Theorem:** [Hirschberg 1975] Optimal alignment in $O(m + n)$ space and $O(mn)$ time.

- 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 $\delta$

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



# Sequence Alignment: Linear Space

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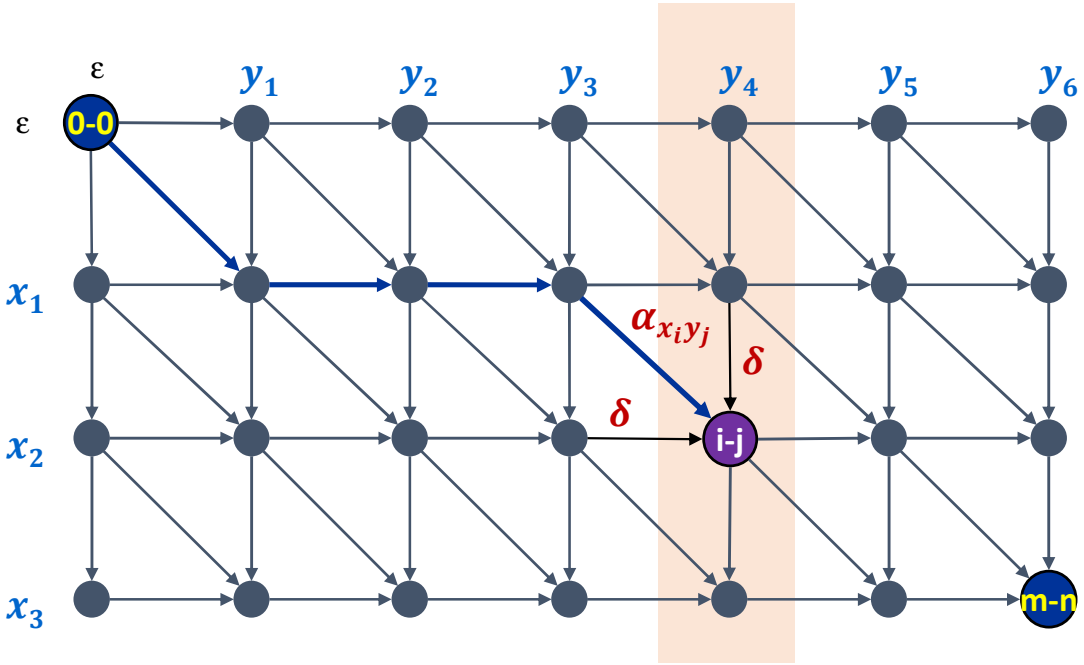
Diagonal edge into each node $(i, j)$ weight $\alpha_{x_i y_j}$




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

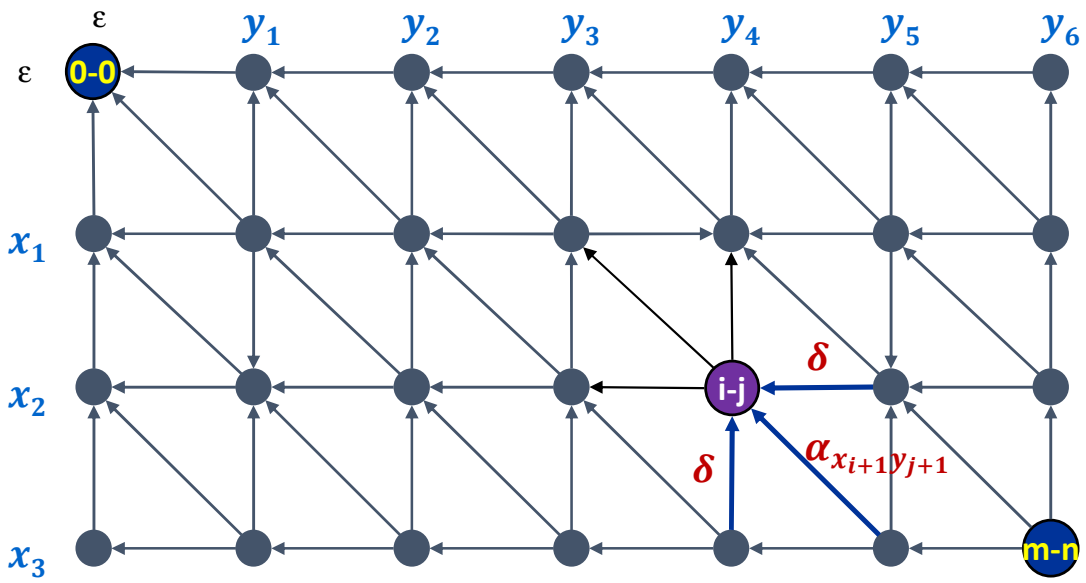
Then $\text{OPT}(i, j) = d_{\text{start}}(i, j)$.

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 $\delta$

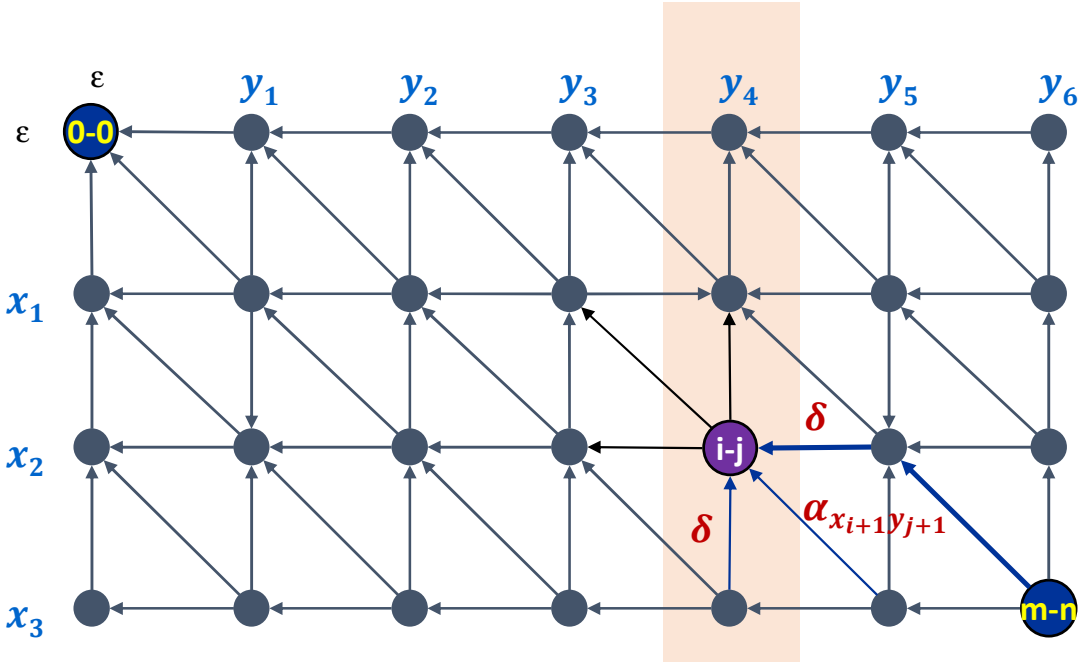
Diagonal edge into each node $(i, j)$ weight $\alpha_{x_{i+1}y_{j+1}}$



# Sequence Alignment: Linear Space

**Reversed edit distance graph:** Horizontal & vertical edges weight $\delta$

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



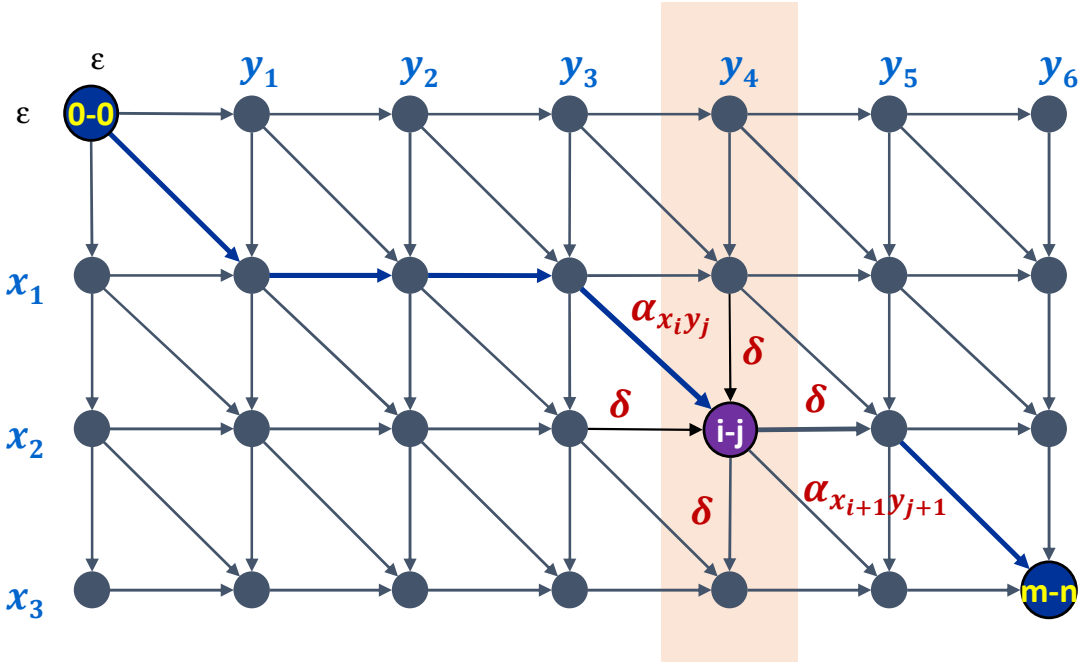

Let $d_{\text{end}}(i, j)$ = length of shortest path from $(m, n)$ to $(i, j)$

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 $\delta$

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

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

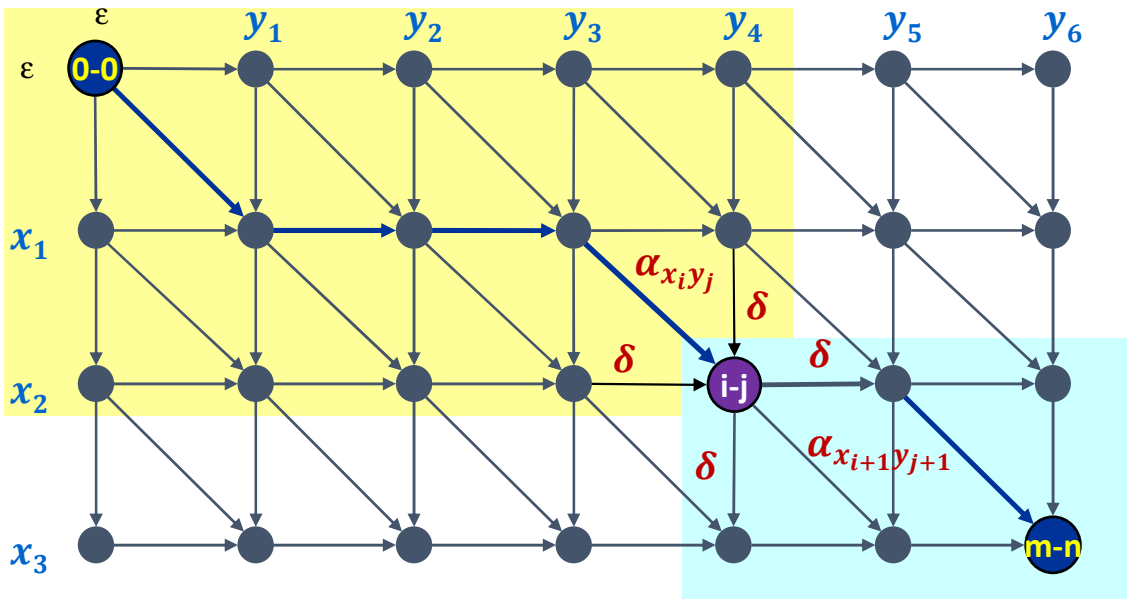
which equals **OPT**$(m, n)$

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

# Sequence Alignment: Linear Space

**Edit distance graph:** Horizontal & vertical edges weight $\delta$

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