Sequence Alignment — dynamic programming - TopHat

Problem. Given two strings \( X = [x_1 \ x_2 \ldots \ x_m] \) and \( Y = [y_1 \ y_2 \ldots \ y_n] \) and costs \( \alpha, \delta \) find the minimum-cost alignment \( \text{Align}(X,Y) \).

prefix of string \( X \) with \( i \) characters \( X_i = X[:i] = x_1x_2\ldots x_i \)

Question. What are the subproblems in the DP, i.e. \( \text{OPT}(i,j) = \ldots \).

A. min cost that exactly \( r = \min\{i,j\} \) characters of \( X \) are matched to characters in \( Y \).

B. min cost that for \( r = \min\{i,j\} \) there are \textit{at most} \( r \) characters in \( X \) matched with \( r \) characters in \( Y \).

C. min cost of matching the prefix \( X_i = x_1x_2\ldots x_i \) to the prefix \( Y_j = y_1y_2\ldots y_j \)

D. min cost of matching the prefix \( X_i = x_1x_2\ldots x_i \) to the prefix \( Y_j = y_1y_2\ldots y_j \), such that \( x_i \) is assigned (matched) to \( y_j \)
Sequence Alignment — dynamic programming

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Idea: start by aligning short prefix sequences. Increase the length until you get to the full sequences.

Subproblems for sequence alignment: for all pairs \( i \) and \( j \) align the prefix strings \( X_i \) and \( Y_j \) compute the optimal cost \( \text{Align}(X_i,Y_j) \)

Optimal solution to the sequence alignment problem: \( \text{Align}(X_m,Y_n) \) such that \( \text{cost(Align}(X_m,Y_n)) \) is min

- there are \( m \times n \) subproblems
- requires two dimensional recursion
- the cost parameters \( \alpha, \delta \) are part of the input!
Sequence Alignment — dynamic programming

**DP approach:**
- make recursive calls to solving subproblems — align prefix strings of $X$ and $Y$
- in order to avoid exponential many recursive calls, “memoize” (cache) the optimal solutions for subproblems

$A = m \times n$ table
- $A[i,j] = \text{Cost}(\text{Align}(X_i, Y_j))$

Now we need to find the *recursive formula*. 
3 cases for alignment

Align($X_3$, $Y_3$): take min cost of three options. The options are based on what the last character of each sequence is matched to.

- **Case 1:**
  - Match "N" to gap
  - Recurse on $X_2$, $Y_3$

- **Case 2:**
  - Match "T" to "N"
  - Recurse on $X_2$, $Y_2$

- **Case 3:**
  - Match "T" to right gap
  - Recurse on $X_3$, $Y_2$

We don't know whether "T" is matched to the gap between "A" and "N" or to "A", that is decided in the recursive call.
Prefix sequence alignment

Idea. Start by aligning short prefix sequences, and increase the length until you get to the full sequence.

\[ A[i, j] = \text{cost}(\text{Align}(X_i, Y_j)) = \alpha \cdot \#(\text{mismatches}) + \delta \cdot \#(\text{gaps}) \]
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\[ A[i, j] = \text{cost}(\text{Align}(X_i, Y_j)) = \alpha \cdot \#(\text{mismatches}) + \delta \cdot \#(\text{gaps}) \]

Case 1. the optimal solution for \( i \) and \( j \) matches \( x_i \) with \( y_j \)

Case 2. the optimal solution for \( i \) and \( j \) leaves \( x_i \) unmatched

Case 3. the optimal solution for \( i \) and \( j \) leaves \( y_j \) unmatched

indicator of mismatch:

\[ I_{x_i \neq y_j} = \begin{cases} 
1 & x_i \neq y_j \\
0 & x_i = y_i 
\end{cases} \]
Prefix sequence alignment

**Idea.** Start by aligning short prefix sequences, and increase the length until you get to the full sequence.

\[
A[i, j] = cost(\text{Align}(X_i, Y_j)) = \alpha \cdot \#(\text{mismatches}) + \delta \cdot \#(\text{gaps})
\]

Case 1. the optimal solution for \(i\) and \(j\) matches \(x_i\) with \(y_j\)

Case 2. the optimal solution for \(i\) and \(j\) leaves \(x_i\) unmatched

Case 3. the optimal solution for \(i\) and \(j\) leaves \(y_j\) unmatched

indicator of mismatch:

\[
I_{x_i \neq y_j} = \begin{cases} 
1 & x_i \neq y_j \\
0 & x_i = y_j 
\end{cases}
\]
Prefix sequence alignment

Idea. Start by aligning short prefix sequences, and increase the length until you get to the full sequence.

\[ A[i, j] = \text{cost} \left( \text{Align}(X_i, Y_j) \right) = \alpha \cdot \# \text{(mismatches)} + \delta \cdot \# \text{(gaps)} \]

Case 1. the optimal solution for \( i \) and \( j \) matches \( x_i \) with \( y_j \)

Case 2. the optimal solution for \( i \) and \( j \) leaves \( x_i \) unmatched

Case 3. the optimal solution for \( i \) and \( j \) leaves \( y_j \) unmatched

indicator of mismatch:

\[ I_{x_i \neq y_j} = \begin{cases} 1 & x_i \neq y_i \\ 0 & x_i = y_i \end{cases} \]
Prefix sequence alignment

Idea. Start by aligning short prefix sequences, and increase the length until you get to the full sequence.

\[ A[i, j] = \text{cost}(\text{Align}(X_i, Y_j)) = \alpha \cdot \#(\text{mismatches}) + \delta \cdot \#(\text{gaps}) \]

Case 1. the optimal solution for \( i \) and \( j \) matches \( x_i \) with \( y_j \)

\[ \text{cost}_1 = \alpha I_{x_i \neq y_j} + A[i - 1, j - 1] \]

Case 2. the optimal solution for \( i \) and \( j \) leaves \( x_i \) unmatched

\[ \text{cost}_2 = \delta + A[i - 1, j] \]

Case 3. the optimal solution for \( i \) and \( j \) leaves \( y_j \) unmatched

\[ \text{cost}_3 = \delta + A[i, j - 1] \]

indicator of mismatch:

\[ I_{x_i \neq y_j} = \begin{cases} 1 & x_i \neq y_j \\ 0 & x_i = y_i \end{cases} \]

\[ A[i, j] = \min\{\text{cost}_1, \text{cost}_2, \text{cost}_3\} \]
Dynamic programming recursion

\[
A[i, j] = \begin{cases} 
\delta \cdot i & j = 0 \\
\delta \cdot j & i = 0 \\
\min \left\{ \begin{array}{l}
\alpha \cdot I_{x_i \neq y_j} + A[i - 1, j - 1] \\
\delta + A[i - 1, j] \\
\delta + A[i, j - 1]
\end{array} \right. & \text{otherwise}
\end{cases}
\]

Note that the formula above is already written wrt the memoization table A. What order can we compute the values?
### DP table for sequence alignment

<table>
<thead>
<tr>
<th></th>
<th>—</th>
<th>P</th>
<th>A</th>
<th>N</th>
<th>T</th>
<th>H</th>
<th>E</th>
<th>R</th>
</tr>
</thead>
<tbody>
<tr>
<td>—</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P</td>
<td></td>
<td>1</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td></td>
<td>2</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T</td>
<td></td>
<td></td>
<td>3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T</td>
<td></td>
<td></td>
<td>4</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>E</td>
<td></td>
<td></td>
<td></td>
<td>5</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>R</td>
<td></td>
<td></td>
<td></td>
<td>6</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>7</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The DP table is used to align the sequences A, P, A, N, T, H, E, R

- **mismatch**: $\alpha = 3$
- **gap**: $\delta = 2$

**Transition formula**:  

\[
A[i, j] = \begin{cases} 
2i & \text{if } j = 0 \\
2j & \text{if } i = 0 \\
\min \{3 \cdot I_{x_i \neq y_j} + A[i-1, j-1]; 2 + A[i-1, j]; 2 + A[i, j-1]\} & \text{otherwise}
\end{cases}
\]
Algorithm 1: SeqAlign(strings X, Y, const $\alpha, \beta$)

1. $A \leftarrow n \times m$ empty table;
2. for $i = 0 \ldots n$ do
   /* base cases */
3.     $A[i, 0] \leftarrow \delta i$;
4. for $j = 0 \ldots m$ do
5.     $A[0, j] \leftarrow \delta j$;
6. for $i = 1 \ldots n$ do
   /* recursive part */
7.     for $j = 1 \ldots m$ do
8.         $A[i, j] \leftarrow \min\{A[i - 1, j - 1] + \alpha I_{x_i \neq y_j}; A[i - 1, j] + \delta; A[i, j - 1] + \delta\}$
9. return $A[n, m]$

Running time?

The above algorithm returns the minimum value. Find an algorithm to backtrack the actual alignment.

worthy to store the “predecessor” (which of the three cases in the recursion) in a second table.
Backtracking the alignment

Input: X, Y, A, \( \alpha, \delta \)

Return: the alignment — a set of pairs of indices (i,j) to be matched

Algorithm 1: backtrackAlignment(X, Y, A, \( \alpha, \delta \))

/* X, Y are strings, A is the computed memoization table, \( \alpha \) mismatch cost, \( \delta \) gap cost */
1 \( m \leftarrow \text{len}(X), n \leftarrow \text{len}(Y); \)
2 \( \text{alignment} \leftarrow \{ \} /* \text{list containing the assignments} */ \)
3 \( i \leftarrow m, j \leftarrow n; \)
4 \textbf{while} \( i + j > 0 \) \textbf{do}
5   \textbf{if} \( i == 0 \) \textbf{then}
6     \( \text{alignment} = \text{alignment} \cup (\ast, Y_j); \)
7     \( j = j - 1; \)
8   \textbf{else if} \( j == 0 \) \textbf{then}
9     \( \text{alignment} = \text{alignment} \cup (X_i, \ast); \)
10    \( i = i - 1; \)
11  \textbf{else if} \( A[i, j] = \alpha \cdot I_{X_i \neq Y_j} + A[i - 1, j - 1] \) \textbf{then}
12    \( \text{alignment} = \text{alignment} \cup (X_i, Y_j); \)
13    \( i = i - 1, j = j - 1; \)
14  \textbf{else if} \( A[i, j] = \delta + A[i - 1, j] \) \textbf{then}
15    \( \text{alignment} = \text{alignment} \cup (X_i, \ast); \)
16    \( i = i - 1; \)
17  \textbf{else}
18    \( \text{alignment} = \text{alignment} \cup (\ast, Y_j); \)
19    \( j = j - 1; \)
20  \textbf{return} \( \text{alignment} \)

notation: \((x_i, \ast)\) indicates that character i was matched to a gap.

Exercise: backtrack the solution on the example.
Single-destination shortest paths problem

Let $G(V,E)$ be a directed graph.

We are given some weight $w(u,v)$ of each directed edge $(u,v)$.

- we call it length, weight or cost (depends on the application)
- the weight can be any numerical value

The length (weight, cost) of a path is the sum of the weights along its edges.

Problem: find the shortest weighted path from each node/source $s$ to $t$.
Shortest paths and negative edges

edge weights are non-negative
• shortest path always exists

eedge weight may be negative
• least cost path may or may not exist
Shortest paths and negative cycles

The definition of the minimum weight path is not always meaningful when negative weight edges are present. Specifically, a path of weight $-\infty$ cannot be interpreted.

**Claim.** If some path from $v$ to $t$ contains a negative cycle, then there does not exist a lowest weight path from $v$ to $t$.

**negative cycle** = a cycle along which the sum of weights is negative
What is the best way to convert USD to Euros?

- n different currencies
- exchange rates between them

represent this as a least-cost path problem:
currency exchange — application with negative edge weights

There is something funny about this example!
Design the algorithm - recursive computation

subproblems:
OPT(i,v) = minimum cost of path from a node v to t using at most i edges
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subproblems:
OPT(i,v) = minimum cost of path from a node v

Select all correct values:
A. $\text{OPT}(1,a) = 15$
B. $\text{OPT}(2,e) = \infty$
C. $\text{OPT}(4,b) = 13$
D. $\text{OPT}(4,a) = 15$
E. $\text{OPT}(4,a) = 7$
F. $\text{OPT}(3,b) = 16$
Design the algorithm - idea

Suppose the least-cost path from s to t exists.

subproblems:
OPT(i,v) = minimum cost of path from a node v to t using \textit{at most} i edges

\textbf{fact.} a simple path in a graph contains at most n-1 edges.
OPT(n-1,v) = length of the shortest (simple) path from v to t

Is it ok to limit ourselves to simple paths?
Design the algorithm - recursive computation

subproblems:
OPT(i,v) = minimum cost of path from a node v to t using \textit{at most} i edges

solve problem recursively: divide possible solutions (= paths) based on the first edge on the path from v to t.

- the path with i edges from v to t using edge (v,u) is the concatenation of the path from u to t (with i-1 edges) and edge (v,u)
Recursive formula for DP

\[ \text{OPT}(i,v) = \text{shortest path } P \text{ from } v \text{ to } t \text{ using } \textit{at most } i \text{ edges} \]

case 1: \( P \) contains at most \( i-1 \) edges

case 2: \( P \) uses exactly \( i \) edges
  - what are the possible subproblems to take the min over?

base case:
What is the recursive formula to compute the least cost from v to t using at most i edges? You may assume that the two base cases are:

\[ \text{OPT}(0,v) = 0 \text{ if } v = t \quad \text{OPT}(0,v) = +\infty \text{ if } v \neq t \]

A. \( \text{OPT}(i, v) = \min\{\text{OPT}(i, v); \min_{w \in G[v]} \text{OPT}(i - 1, w)\} \)

B. \( \text{OPT}(i, v) = \min\{\text{OPT}(i - 1, v); \min_{w \in G[v]} c(v, w) + \text{OPT}(i - 1, w)\} \)

C. \( \text{OPT}(i, v) = \min\{\text{OPT}(i, v); \min_{w \in G[v]} c(v, w) + \text{OPT}(i, w)\} \)

D. \( \text{OPT}(i, v) = \min\{\text{OPT}(i - 1, v); \min_{w \in G[v]} \text{OPT}(i - 1, w)\} \)