Lecture 10

Sequence Alignments

Part 1: Alignments Between Sequences

Machine Learning for Structured Data
Vlad Niculae · LTL, UvA · `https://vene.ro/mlsd`

Sequence Alignments

Alignments Between Sequences

We have two related sequences of possibly different lengths.

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biology:

DNA, RNA, or protein
sequences:

align `CAAT` and `ATTACA`:

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find the best sequence of edits between strings

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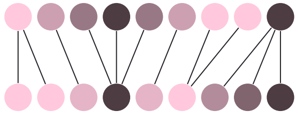
signal processing:

stretch or compress signals (e.g., audio) to match.



Alignment Are Structures

Alignments are structured objects: many possible alignments between same strings.

```
--CA-AT   -CAAT-    CAAT--    CAAT------   CAAT-----
ATTACA-   ATTACA   ATTACA     ----ATTACA   ---ATTACA  . . .
```

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We need to figure out:

1. How to score an alignment
2. How to compute argmax over alignments
3. How to compute logsumexp over alignments

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```

We need to figure out:

0. How to represent alignments

1. How to score an alignment

2. How to compute argmax over alignments

3. How to compute logsumexp over alignments

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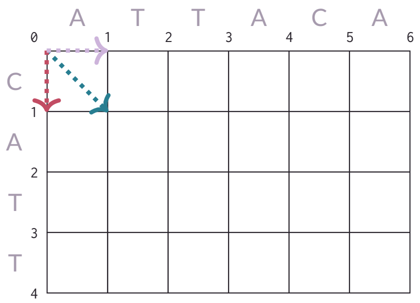
Sequence Alignments

Alignment Tables



At point (i, j) in the grid we either:

- **M**: match tokens i in `seq1` to j in `seq2`,
- **I**: skip token i in `seq1`,
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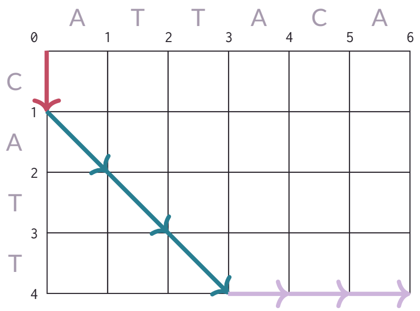
Some alignments and corresponding trajectories:

Alignment Tables



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- `IMMMDDD`:
  ```
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  -ATTACA
  ```

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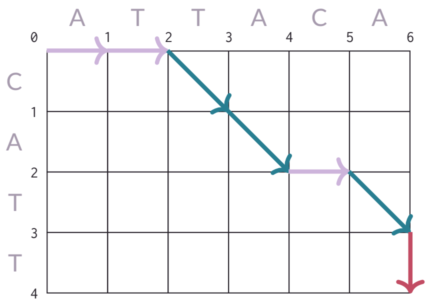

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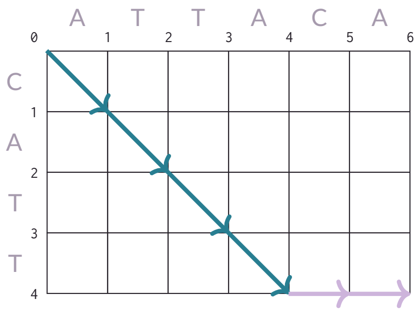

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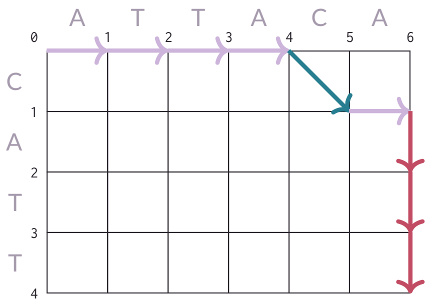

At point (i, j) in the grid we either:

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- `DDDDMDIII`:
  ```
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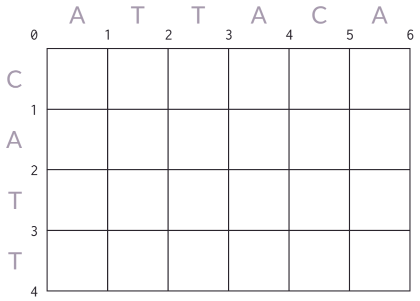

DAG representation:

Nodes at grid points
$V = \{(i,j) : 0 \leq i \leq n, 0 \leq j \leq m\}$

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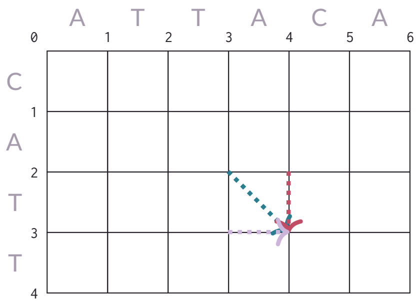

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Three incoming edges for each node.

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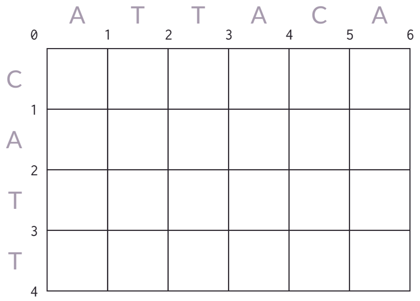

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Three incoming edges for each node.

Number of paths from $(0, 0)$ to (n, m):
$D(n, m) = \sum_{k=0}^{\min(n,m)} \binom{m}{k}\binom{n}{k} 2^k$ (Delannoy numbers)

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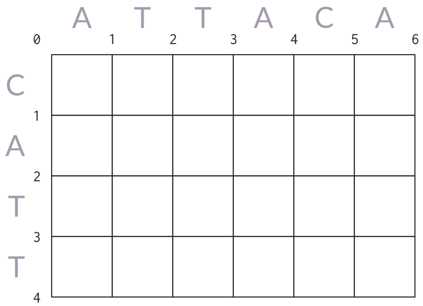
Scoring an alignment



A “default” scoring strategy:

- Get a score of 1 for matching identical characters.
  i.e., if action `M` taken at grid position (i, j) and `seq1[i] == seq2[j]`, add 1 to the score.
- Get a score of -1 for any insertion or deletion.

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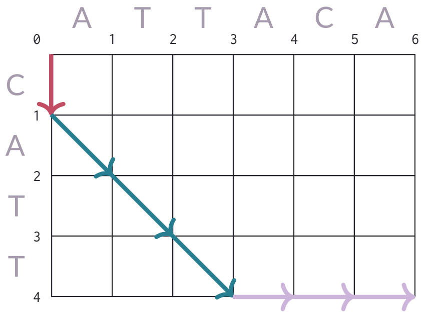

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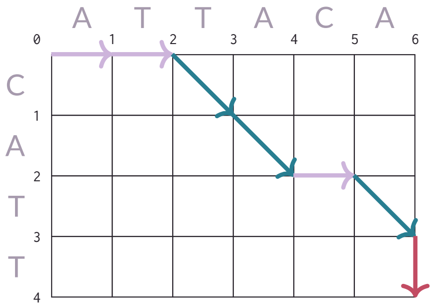

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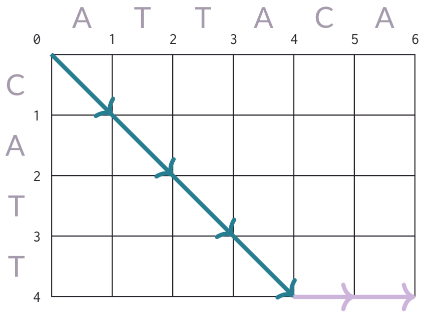

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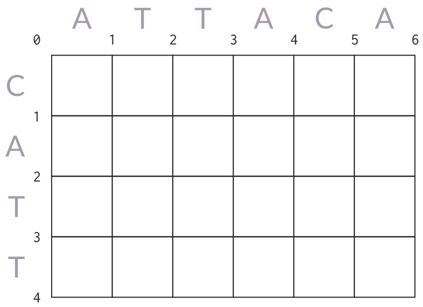

let $\boldsymbol{A}$ a score array of shape $(n+1, m+1, 3)$:

- $a_{i,j,0}$ is the score for Matching token i in `seq1` with token j in `seq2`.
- $a_{i,j,1}$ is the score for an Insertion at (i, j): skipping token i in `seq1` when the cursor is at j in `seq2`.
- $a_{i,j,2}$ is the score for a Deletion at (i, j): skipping token j in `seq2` when the cursor is at i in `seq2`.

note: in these slides, we use zero-indexing into $\boldsymbol{A}$, but one-indexing into the sequences.

We can set the specific values of $\boldsymbol{A}$ to replicate the default scoring from before.

But this parametrized version lets us learn how to score alignments.

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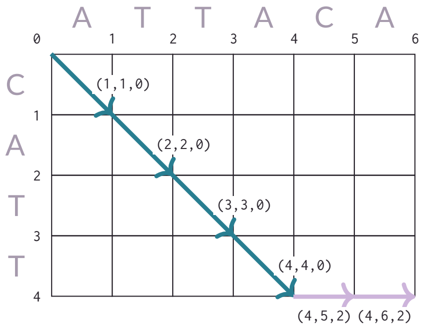

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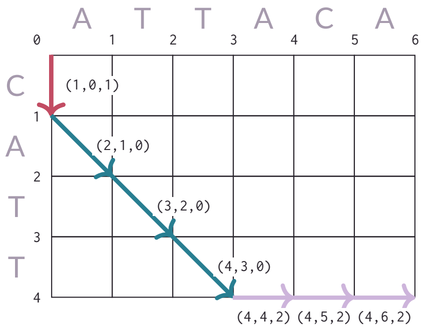

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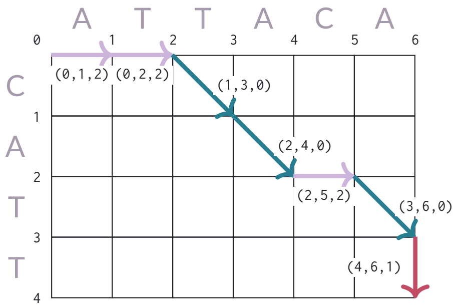

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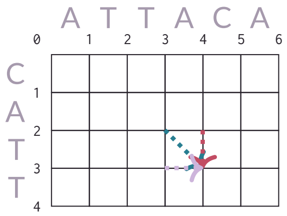
Sequence Alignments

Dynamic Programming for Alignments



Alignments = paths in DAG from $(0, 0)$ to (n, m).

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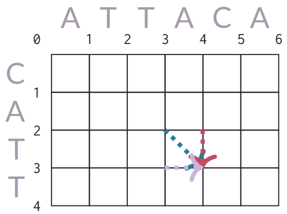

F=

0						

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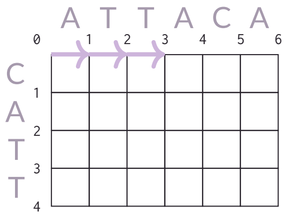
Computing the max score:
Fill in a table $\boldsymbol{M}$, size $(1 + n, 1 + m)$,
s.t. m_{ij} = the max score up to (i, j).

$$m_{ij} = \begin{cases} m_{i-1,j-1} + a_{i,j,0} \\ m_{i-1,j} + a_{i,j,1} \\ m_{i,j-1} + a_{i,j,2} \end{cases} \quad \text{for any } i > 0, j > 0.$$

What is a topological order?

Dynamic Programming for Alignments



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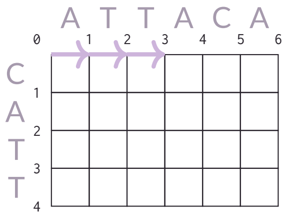

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0	a_{012}	a_{012} $+a_{022}$	$\cdots$			

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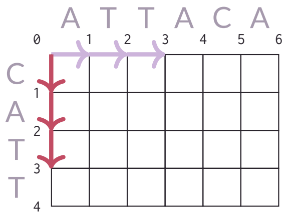

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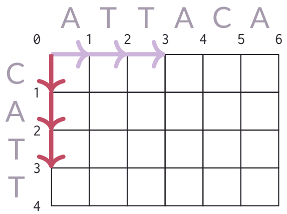

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a_{101}						
a_{101} $+a_{201}$						
$\cdots$						

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History of DP Alignments

Small variants of this algorithm are known by many names and were reinvented many times:

- in biology: Needleman-Wunsch, and (with a small change) Smith-Waterman.
- in compling / information retrieval, Levenshtein / Edit Distance / Wagner-Fischer
- in time series / signal processing: Dynamic Time Warping (DTW)

As far as we know, the first inventor is actually Ukrainian mathematician Taras Vintsiuk, for speech applications.

Viterbi for alignments

```
input: Scores $\boldsymbol{A}$ ($n+1 \times m+1 \times 3$ array), zero-indexed
initialize $\boldsymbol{F}$, same shape as $\boldsymbol{A}$,
$M_{00} = 0, \quad M_{i0} = \sum_{k=1}^{i} a_{k,0,1}, \quad M_{0j} = \sum_{k=1}^{j} a_{0,k,2}.$

*Forward*: compute max. scores recursively
for $i = 1$ to $n$ do
    for $j = 1$ to $m$ do
        $M_{ij} = \max \begin{cases} M_{i-1,j-1} + a_{i,j,0} \\ M_{i-1,j} + a_{i,j,1} \\ M_{i,j-1} + a_{i,j,2} \end{cases} ; \qquad \pi_{ij} = \arg\max \begin{cases} M_{i-1,j-1} + a_{i,j,0} \\ M_{i-1,j} + a_{i,j,1} \\ M_{i,j-1} + a_{i,j,2} \end{cases} ;$
$f^\star = M_{n,m}$

*Backward*: follow backpointers
$i = n, j = m, \boldsymbol{y}^\star = ()$
while $(i,j) \neq (0,0)$ do
    insert $\pi_{ij}$ at the front of $\boldsymbol{y}^\star$,
    decrease $i$, $j$, or both, depending on $\pi_{ij}$

output: The highest-scoring alignment path $\boldsymbol{y}^\star$, and its total score $f^\star$.
```

Forward algorithm for alignments

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*Forward*: compute scores recursively
for $i = 1$ to $n$ do
    for $j = 1$ to $m$ do
        $M_{ij} = \log \sum \exp \begin{cases} M_{i-1,j-1} + a_{i,j,0} \\ M_{i-1,j} + a_{i,j,1} \\ M_{i,j-1} + a_{i,j,2} \end{cases} ;$
return $M_{n,m}$
```

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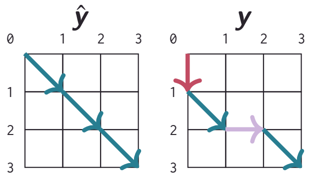
Evaluating Alignments

So far we are representing alignments as sequences of "moves" on a grid.

How to evaluate if we predict $\hat{\boldsymbol{y}}$ = `MMM` when the correct label is $\boldsymbol{y}$ = `IMDM`?

Alignment-level accuracy always an option.
Finer-grained eval?



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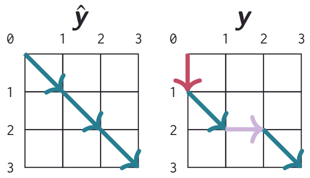
Alignment-level accuracy always an option.
Finer-grained eval?

In protein alignment, we care most about getting the aligned indices (i, j) right.

(getting the M–edges right!)

- precision: n. correct M–edges / n. predicted M–edges
- recall: n. correct M–edges / n. true M–edges
- F-score: harmonic average of P and R.



$$\text{indices}(\hat{\boldsymbol{y}}) = \{(1,1),(2,2),(3,3)\},$$
$$\text{indices}(\boldsymbol{y}) = \{(2,1),(3,3)\}.$$

Summary

- Monotonic alignments between two sequences.
- Once again, dynamic programming gives us polynomial-time complexity.
- Algorithm rediscovered many times across many different fields under different names.