CPSC 340:
Machine Learning and Data Mining

Sequence Mining

Fall 2015

Admin

- Assignment 5 due now.
- Assignment 6 out: due Friday of next week.
- Practice final coming next week.

Sequence Mining

- Finding patterns in data organized according to a sequence:
  - Customer purchases:
    - ‘Star Wars’ followed by ‘Empire Strikes Back’ followed by ‘Return of the Jedi’.
  - Stocks/bonds/markets:
    - Stocks going up followed by bonds going down.
  - Environmental:
    - CO_2 going up is followed by temperatures going up.
  - Website/telephone system navigation.
  - Biological sequences.
    - DNA: ATGCTTCGGCAAGACTCAAAAAATA…
    - RNA: ATGCUUCGGCAAGACUCAAAAAAUA…
    - Protein: GIVEQCCTSICSLYQLENYCN

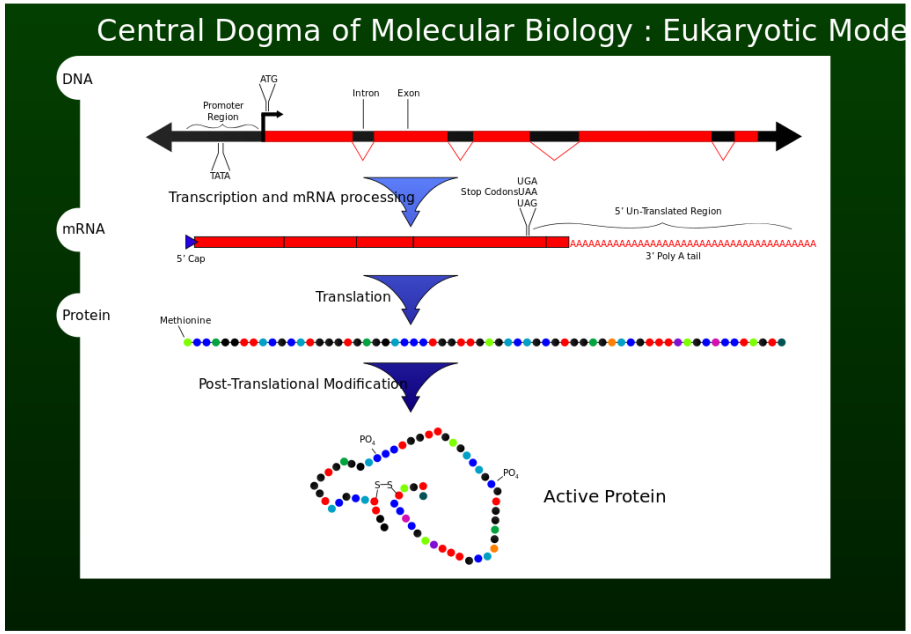
Sequential Pattern Analysis

- In data mining, called sequential pattern analysis:
  - If you buy product A, are you likely to buy product B at a later time?
- Similar to association rules, but now order matters.
  - Many issues stay the same.
- Exist sequential generalization of many association rule methods:
  - Generalized sequential pattern (GSP) algorithm is like a priori algorithm.

- We're going to instead focus on methods from bioinformatics…

Biological Sequences

- We are generated huge quantities of biological data.
- Much of it is stored as sequences.
  - DNA, RNA, and proteins.



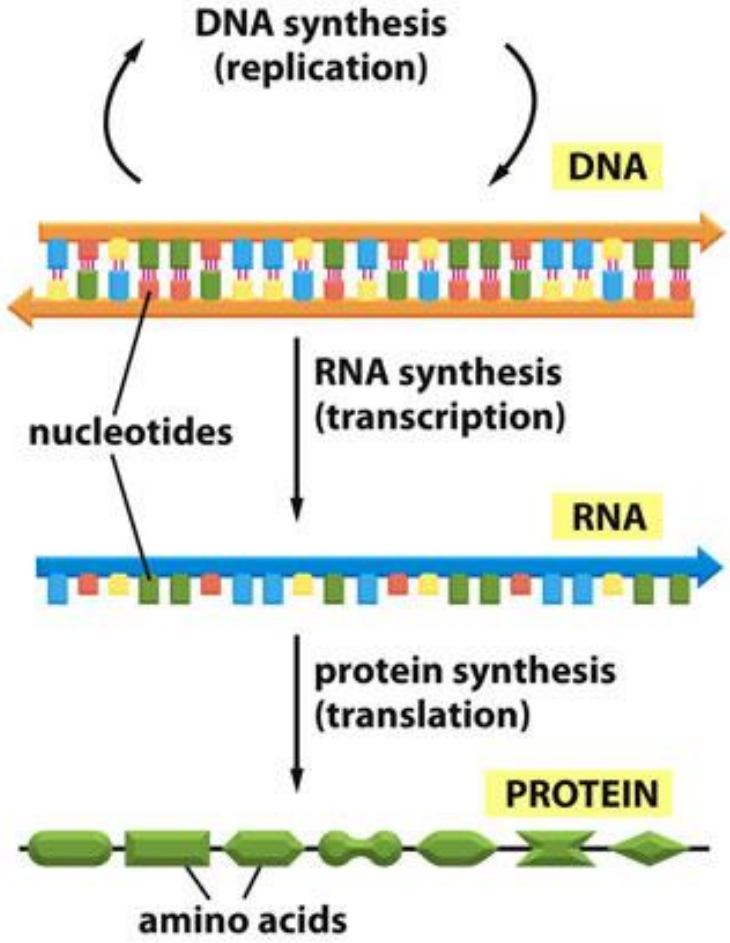
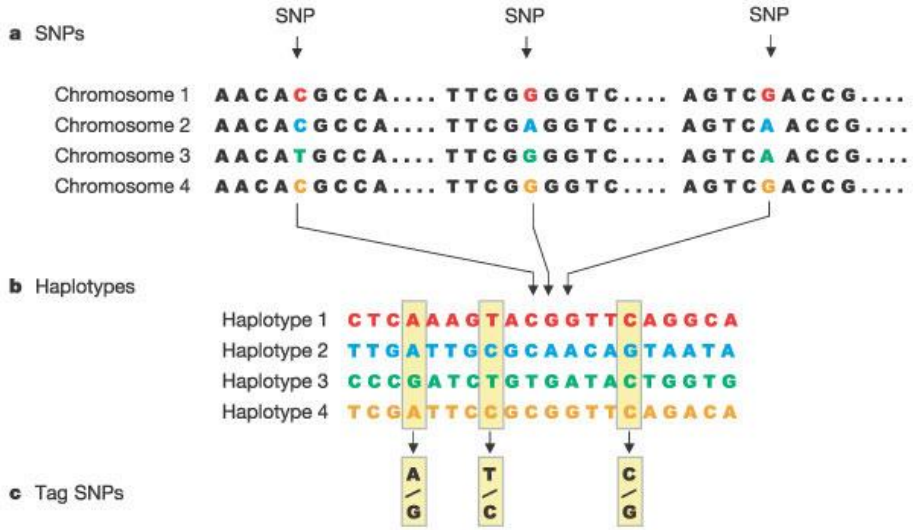


Figure 1-2 Essential Cell Biology 3/e (© Garland Science 2010)

http://trenchesofdiscovery.blogspot.ca/2012/09/the-human-machine-coding-and-uncoding.html
https://en.wikipedia.org/wiki/Central_dogma_of_molecular_biology

Whole Genome Sequencing

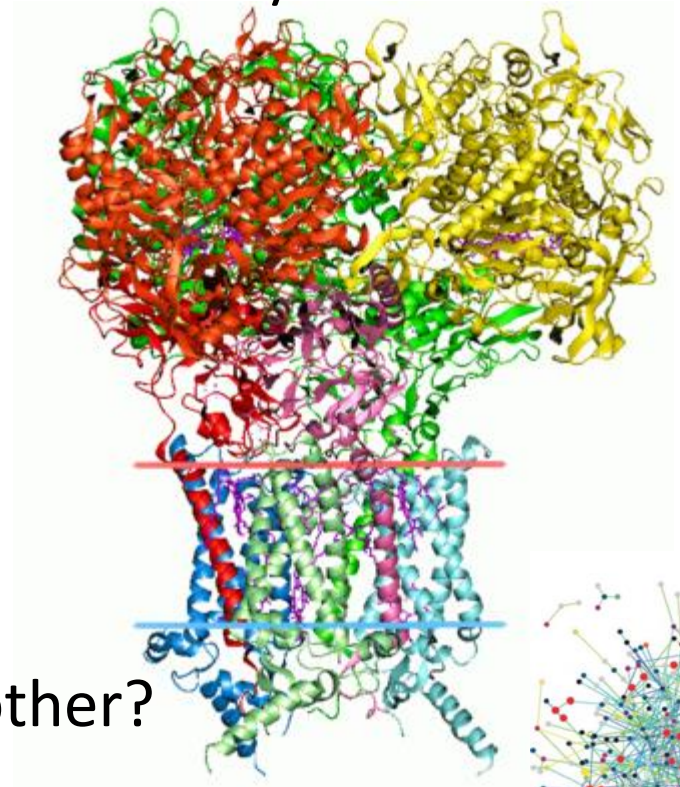
- First single-celled organisms' genomes sequenced in late 90s.
- Many animals/plants in early 2000s.
- Human genome project finished in 2003.
- Late 2000s and early 2010s:
  - Characterizing variation and function.
  - HapMap, ENCODE, 1000 genomes.
  - Potential to study infrequent variations.
  - New insights into rare diseases.
  - Promise of personalized medicine.
- Way more data than understanding:
  - One of most important scientific problems.

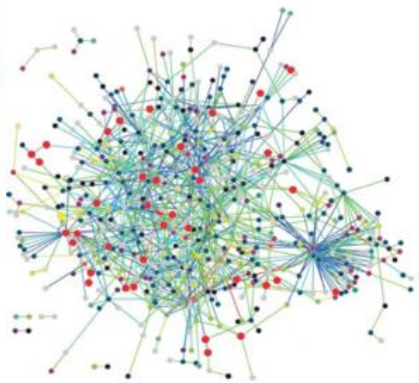


http://hapmap.ncbi.nlm.nih.gov/whatishapmap.html

Bioinformatics

- Bioinformatics: biology and databases and data analysis.
  - It's a huge area, with many interesting variations on DM/ML methods.
- Big focus on analyzing sequences.
  - We'll discuss some of the classic ideas today.
- But sequences aren't everything:
  - How do molecules 'fold' in three-dimensions?
  - Which molecules can 'fit' together?
  - What genes perform similar functions?
  - How do molecule concentrations affect each other?
  - What are signaling 'pathways'?





https://en.wikipedia.org/wiki/Bioinformatics

Finding/Testing Similar Sequences

- A classic bioinformatics problem:
  - You find an interesting part of a biological sequence.
    - E.g., this gene makes your mice live much longer or immune to a disease.
  - Do similar sequences appear elsewhere?
    - Either in the same organism, or in other organisms.
- Want to test relatedness of sequences and find related sequences.
  - Heavy use of dynamic programming.
  - Other tricks to handle huge datasets.
- We'll start from simplest case, and get more complicated.

String Search

- Simplest variant is string search:
  - We have a sequence of length ‘n’
  - We have a query of length ‘m’.
  - Does query occur in sequence?
- Example:
  - Sequence: “GIVEQCCTSICSLYQLENYCN” (insulin).
  - Query: “TSI”.
- Naïve algorithm:
  - For each of ‘n’ positions, test whether the string starts there.
  - Cost is O(nm).
- Several algorithms reduce this to O(n + m) (e.g., Knurth-Morris-Pratt).

Longest Common Substring

- What if we have multiple queries for same sequence?
  - Sequence: “GIVEQCCTSICSLYQLENYCN”.
  - Queries: “TSI”, “CCT”, “CST” (diabetes).
  - With ‘k’ queries of length <= 3, cost is O(n + km) with suffix trees.
- A related problem is longest common substring:
  - Sequence 1: “GIVEQCCTSICSLYQLENYCN” (human).
  - Sequence 2: “GIVEQCCASVCSLYQLENYCN” (cow).
  - What is longest string that occurs in both sequences?
    - In this case it’s “CSLYQLENYCN”.
- Suffix trees solve this problem in O(n + m).

Longest Common Substring vs. Subsequence

- Consider human/pig/cow insulin:
  - Sequence 1: “GIVEQCCTSICSLYQLENYCN” (human).
  - Sequence 2: “GIVEQCCASVCSLYQLENYCN” (cow).
  - Sequence 3: “GIVEQCCTSICSLYQLENYCN” (pig).
- Longest substring between human/pig is 22 (entire sequence).
- Longest substring between human/cow is 11: “CSLYQLENYCN”.
  - But have we really cut the similarity in half?
- Longest common subsequence:
  - Longest exact match by deleting characters.
  - For human/cow it’s 20: “GIVEQCCSCSLYQLENYCN” (still 22 for human/pig).

Longest Common Subsequence

- Longest common subsequence (LCS):
  - Sequence 1: “GIVEQCCTSICSLYQLENYCN” (human).
  - Sequence 2: “GIVEQCCASVCSLYQLENYCN” (cow).
  - LCS: “GIVEQCC[ ]S[]CSLYQLENYCN”.
- Finding LCS by brute force:
  - 2^n possible deletions in sequence 1.
  - 2^m possible deletions in sequence 2.
  - $O(\min(n,m)2^{n+m})$.
- Can we do better?

Longest Common Subsequence

- Suppose we have the LCS for two sequences:
  - Sequence 1: “ACE”.
  - Sequence 2:“ABCD”.
  - LCS: “AC”.
- Key idea: it’s easy to update LCS if we append one character.
  - Updated sequence 2: “ABCDE”.
  - New LCS: “ACE”.
  - Either the new character extends LCS or not: compute this in O(m).
- O(mn)-time Algorithm:
  1. Start with all of sequence 1 and empty sequence 2 (LCS = []).
  2. Sequentially append to sequence 1, tracking LCS.

Dynamic Programming

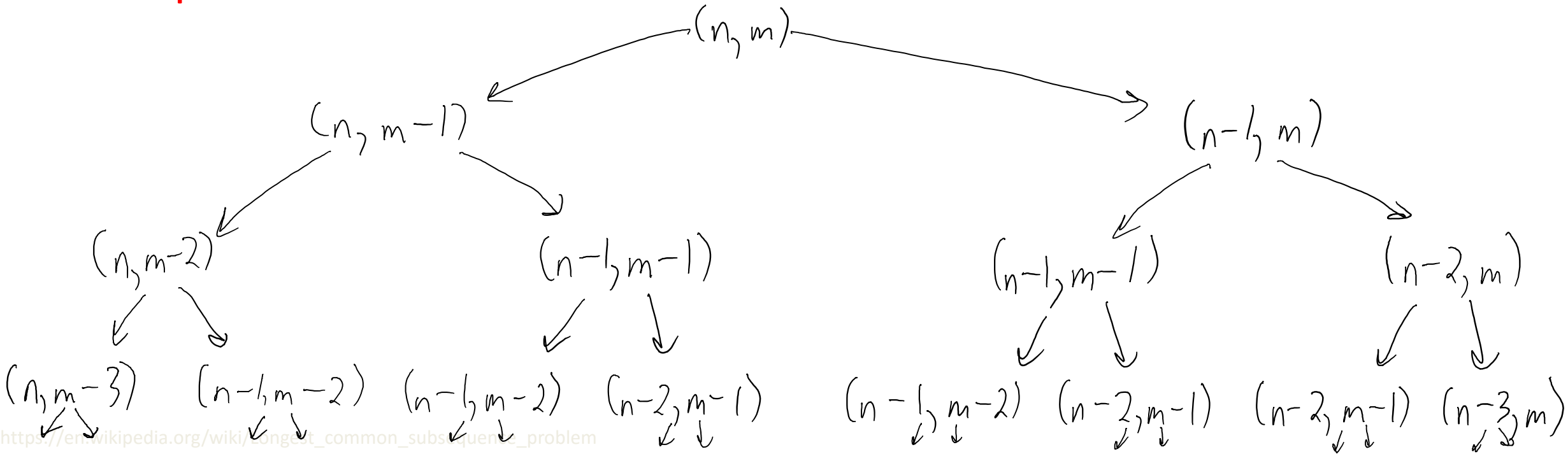
- LCS algorithm is special case of dynamic programming.
- Dynamic programming efficiency requires two ingredients:
  1. Optimal substructure:
     - Can efficiently solve the problem given solutions to 'sub-problems' (i.e. recursion).
     - For LCS: we can quickly solve problem of length 'm' given solution of length (m-1).
  2. Overlapping sub-problems:
     - Limited of *different* possible sub-problems.
     - For LCS: there are only O(mn) possible lengths for the two strings.
- Key trick: store solutions of sub-problems, instead re-computing.
  - Guarantees each sub-problem is solved at most once.

LCS with Dynamic Programming

- Let's define the LCS recursively:

$$LCS\left(X_i, Y_j\right) = \begin{cases} \emptyset & \text{if } \ i = 0 \text{ or } j = 0 \\ LCS\left(X_{i-1}, Y_{j-1}\right) \frown x_i & \text{if } x_i = y_j \\ \text{longest}\left(LCS\left(X_i, Y_{j-1}\right), LCS\left(X_{i-1}, Y_j\right)\right) & \text{if } x_i \neq y_j \end{cases}$$

- Exponential number of recursive calls in naïve method:



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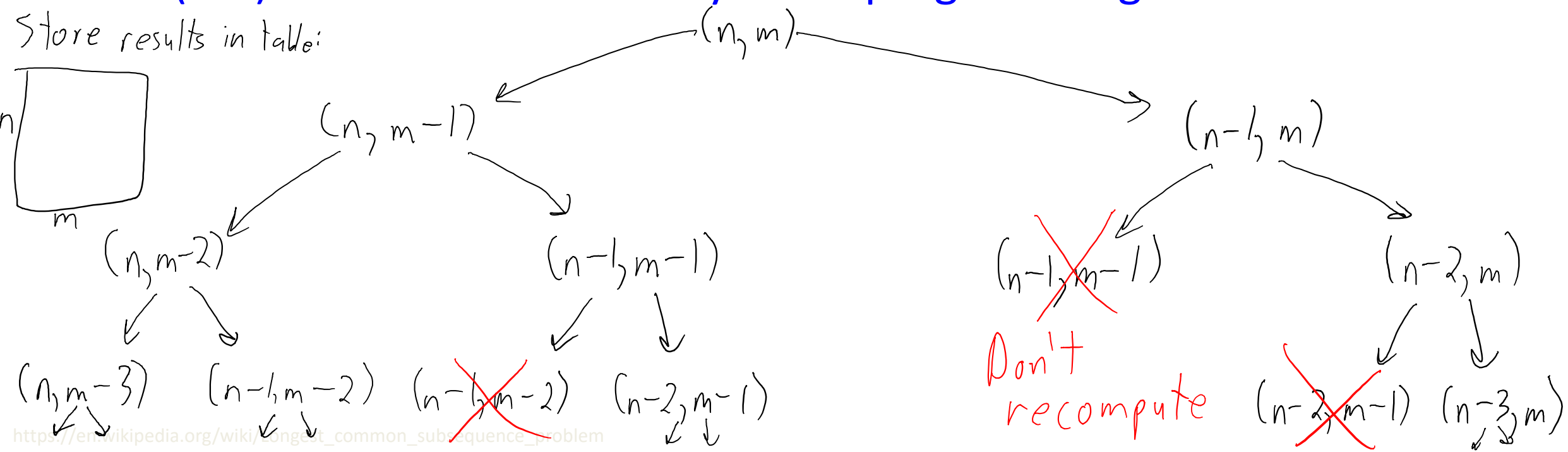
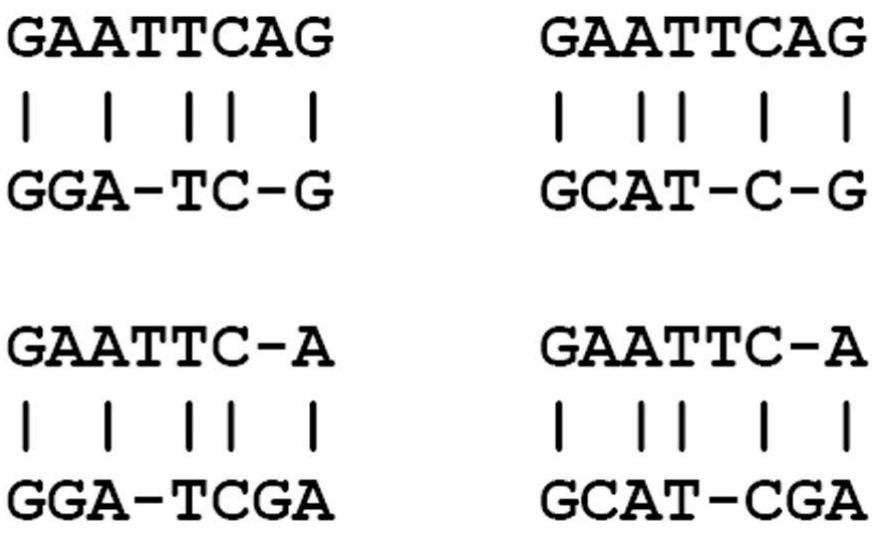
- O(mn) recursive calls with dynamic programming method:



Edit Distance



- LCS considers deletions of elements.
- We might also consider replacements:
  - Sequence 1: "GIVEQCCTSICSLYQLENYCN".
  - Sequence 2: "GIVEQCCASVCSLYQLENYCN".
  - Where different replacements have different 'costs'.
    - Some proteins can be substituted and molecule will be similar, some are disastrous.
- Edit distance:
  - Min 'cost' of turning string 1 into 2 via additions/deletions/replacements.
  - Can also be compute by dynamic programming:
    - Minimize over the 3 operations.

Edit Distance

- Edit distance between strings ‘X’ and ‘Y’ is $ED(X_m, Y_n)$ where:

$$ED(X_i, Y_j) = \begin{cases} ED(X_{i-1}, Y_{j-1}) & \text{if } X_i = Y \\ \min \begin{cases} ED(X_{i-1}, Y_j) + cost(\text{'delete } X_i\text{'}) \\ ED(X_i, Y_{j-1}) + cost(\text{'insert } Y_j\text{'}) \\ ED(X_{i-1}, Y_{j-1}) + cost(\text{'replace } X_i \text{ with } Y_j\text{'}) \end{cases} & \text{if } 1 < i \leq n \text{ and } X_i \neq Y_j \\ & \quad 1 < j \leq m \\ \sum_{k=1}^{i} cost(\text{'delete } X_k\text{'}) & \text{if } j = 0 \\ \sum_{k=1}^{j} cost(\text{'insert } Y_k\text{'}) & \text{if } i = 0 \end{cases}$$

- Cost is still O(mn), and if costs are non-negative this is a distance.

Local Edit Distance / Local Alignment

- Local alignment (Smith-Waterman):
  - Positive ‘score’ for matches, negative ‘score’ for add/delete/replace.
  - Set negative ‘d_{ij}’ values to zero, and maximize d_{ij} over ‘i’ and ‘j’.
    - Note that in bioinformatics you maximize ‘score’ rather than minimize ‘distance’.
  - Finds substrings with small edit distance:

Smith-Waterman Scoring

	D	E	-	S

		-	D	E	S	I	G	N
	-	0	0	0	0	0	0	0
	I	0	0	0	0	5	4	3
D	D	0	5	4	3	4	4	3
E	E	0	4	10	9	8	7	6
A	A	0	3	9	9	8	7	6
S	S	0	2	8	14	13	12	11

Match = +5
Mismatch = -1
Gap = -1

1: DESIGN
2: IDEAS

Aligned:
1: DE-S
2: DEAS

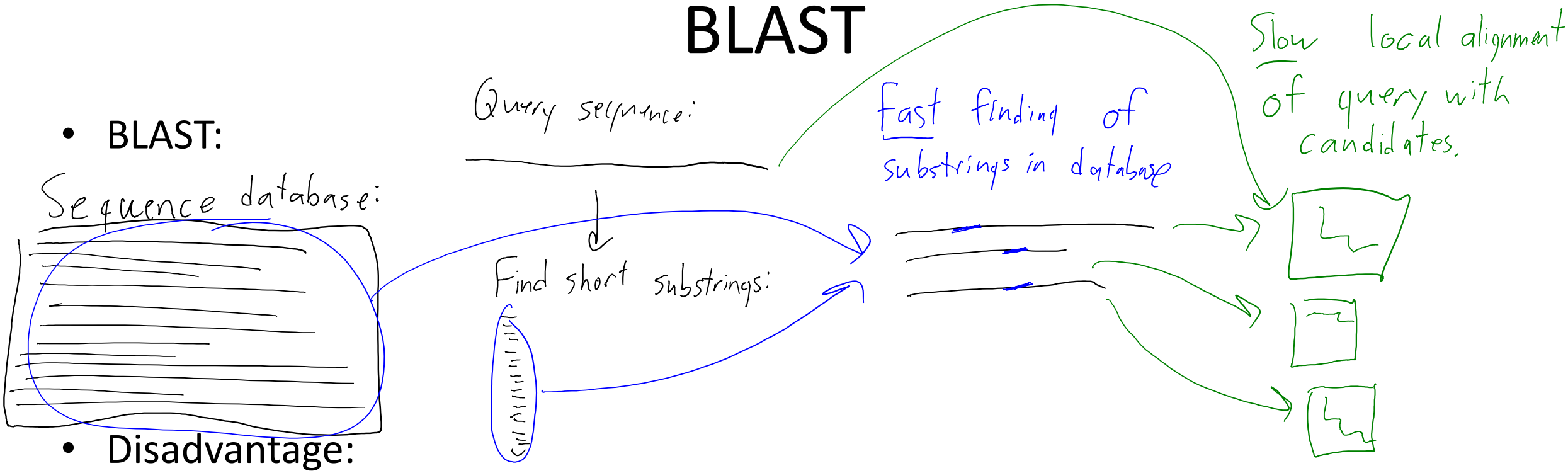
BLAST

- Basic Local Alignment Search Tool (BLAST):
  - A method for searching biological sequences.
  - Most cited paper in 1990s of all of science.
- Setup:
  - We have a huge database of sequences.
  - Individual sequences may be very long (human genome: ~3.2 billion).
  - Quickly find similar sequences to a query sequence.
- Key ideas:
  - Find interesting and short substrings in query.
  - Fast phase: Find 'candidates' that contain any substring.
  - Slow phase: apply dynamic programming on the 'candidates'.
  - Some other tricks to make it faster.

If there all 'ℓ' strings in database, finding indices of 'k' substrings of length 'm' costs $O(kmℓ)$.

No dependence on length of database sequences.

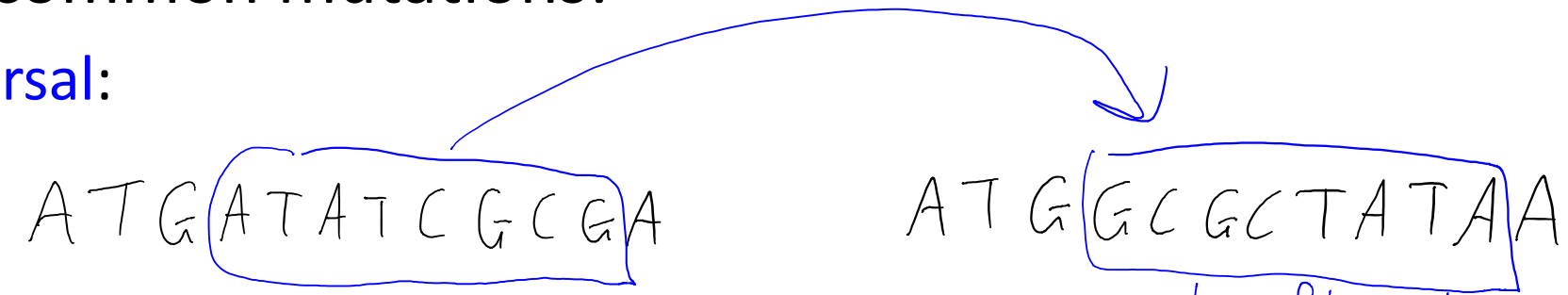
BLAST



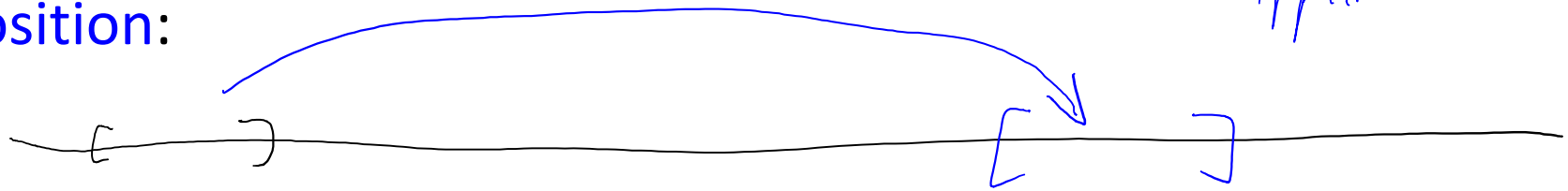
- BLAST:
- Disadvantage:
  - You could have false negatives in the first phase (you miss distantly-related sequences).
- PSI-BLAST:
  - Re-run with related sequences to find more distantly-related sequences.
- Related to hashing tricks for finding elements of a set:
  - Bloom filter: guaranteed to have no false negatives.
  - Count-min sketch: more recent probabilistic/online method.

Generalizations of Edit Distance

- We can have score based on insertion/deletion length ('gap score')
- Other common mutations:
  - Reversal:



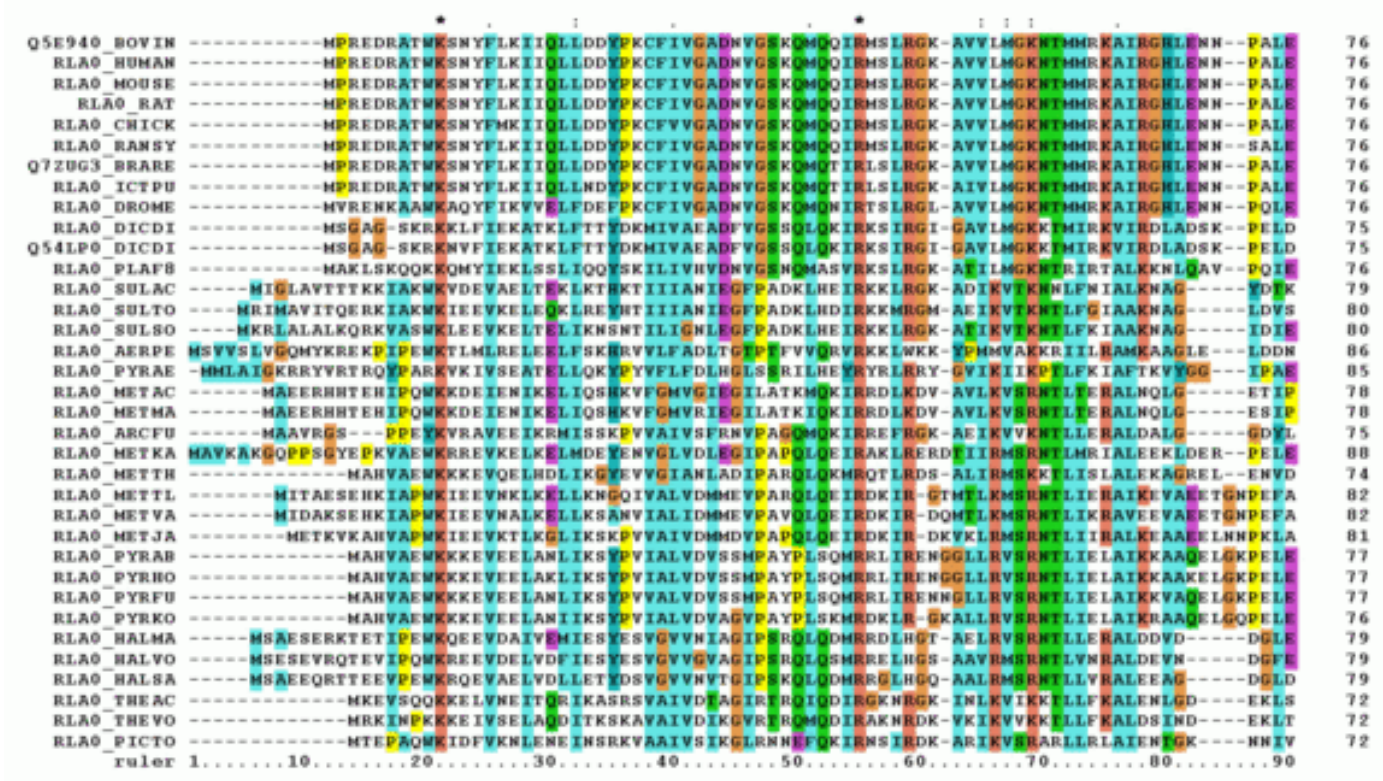
  - Transposition:



  - In general, we can't handle these efficiently: sub-problems don't overlap.
- But some special cases exist:
  - If reversals are 'contained' in each other, solve as 'context-free grammar'.

Multiple Sequence Alignment

- Multiple Sequence Alignment:
  - We have several sequences and want to jointly align them:

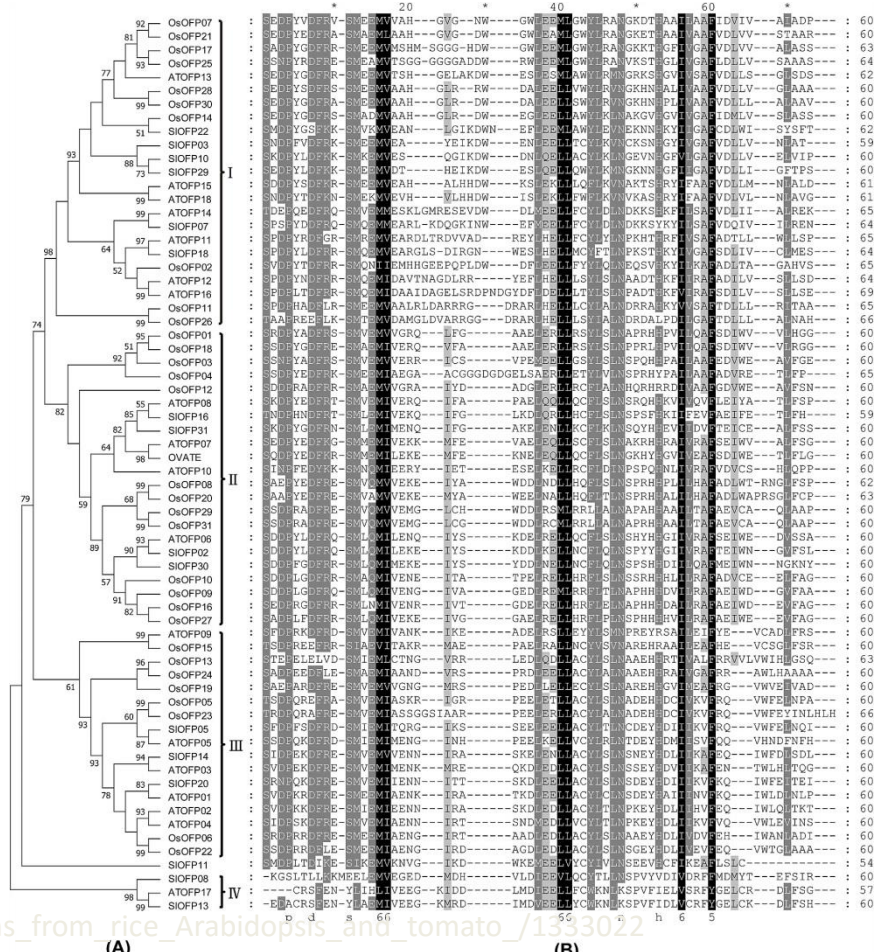


  - Dynamic programming is exponential in number of sequences.

https://en.wikipedia.org/wiki/Multiple_sequence_alignment

Multiple Sequence Alignment and Clustering

- Heuristic to avoid exponential cost of multiple sequence alignment:
  - First perform hierarchical clustering.
    - Clustering coud be interesting on its own.
  - Align sequences as we go up the tree.
- Popular method is Clustal:
  - 3 of top 15 all-time most-cited science papers:
    - BLAST, PSI-BLAST, Clustal.



http://figshare.com/articles/_Multiple_sequence_alignment_and_phylogenetic_tree_of_the_OVATE_domains_of_OFP_proteins_from_rice_Arabidopsis_and_tomato_/1333022

Summary

- Sequence data arises in applications involving time/strings.
- Sequential pattern mining: finding association rules in sequences.
- Bioinformatics: biology meets databases and data analysis.
- Common substrings can be found in linear time.
- Edit distance can be found efficiently using dynamic programming.
- BLAST combines the above two with other tricks.
- Multiple sequence alignment considers multiple sequences.

- Next time: predicting whether it will rain, when the stock market will crash, and where the verb in the sentence is.