Computational Biology

Lecture 3

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Sequencing

- As before, DNA is cut into small (≈ 0.4KB) fragments and a clone library is formed.
- Biological experiments allow to read a certain number of these short fragments per experiment.
- Entire genome (≈ 4GB long) must be assembled from the knowledge of these short fragments.

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Shortest Superstring

- The simplest naive approximation of DNA sequencing, ignoring unavoidable experimental errors, is the following:
- Shortest Superstring Problem: Given a set of strings $s_1,\ldots,s_n$, find the shortest string s such that each s_i appears as a substring of s.
- This problem is NP-hard.

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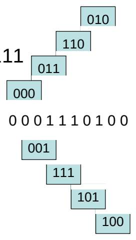
Shortest Superstring

- Set of strings:
  {000,001,010,011,100,101,011,111}
- A trivial superstring:
  000 001 010 011 100 101 011 111
- A shortest superstring:



Sequencing by Hybridization

- Although DNA sequencing is a fast and efficient procedure now, it was time consuming and hard 10 years ago.
- In 1988, 4 groups of biologist independently and simultaneously suggested a new approach called Sequencing by Hybridization (SBH).
- Build a DNA chip containing thousands of short DNA fragments (probes) working like the chip's memory.
- Each probe will reveal some information about an unknown DNA fragment.
- All the pieces of information combined would solve the DNA sequencing.
- Of course, in 1988, no one believed that such a thing could work! Now, building DNA arrays with thousands of probes has become an industry.

SBH

- Given a DNA fragment with an unknown sequence, a DNA array would provide its *l*-tuple composition, i.e. information about all substrings of length *l* contained in this fragment.
- **SBH Problem**: Reconstruct a string by its *l*-tuple decomposition.
- Although conventional DNA sequencing and SBH are different approaches, computationally they are similar. SBH is a special instance of the Shortest Superstring problem when $s_1 \ldots s_n$ represent all substrings of a fixed length.
- While the general Shortest Superstring problem in NP-hard, SBH can be solved efficiently.

Finding CG-islands

- The most infrequent dinucleotide in many genomes is CG (CG has tendency to mutate to TG).
- However, CG appears relatively frequently around genes in areas called CG-islands.
- How to define and find CG-islands in a genome?
- This is similar to the following analogy of the Casino: the dealer uses two coins: biased and unbiased. He switches coins with probability *p*. Given a sequence of coin tosses, can you find out when the biased coin was used?
- Why is that a good analogy? Because as we go along the genome, we can switch between two states: CG-island and non CG-island. Each state has different probability for the occurrence of CG. Given the genome, can you tell when you are in a CG island?

Similarity Search

- After sequencing, biologist have no idea about the function of the newly sequenced gene.
- Hoping to find a clue, they compare it with previously sequenced genes with known functionality.
- **Edit distance**: number of operations needed to transform one string into another, where operations are insertion of a symbol, deletion of a symbol, and substitution of a symbol.
- Since mutations in DNA can be represented by the above operations, the edit distance is a natural measure of similarity between DNA fragments.
- Variations to the basic edit distance above are possible and lead to alignment algorithms.

Sequence Alignment

Similar Sequences

- These two look very much alike

```
GACGGATTAG
GATCGGAATAG
```

- Aligning them one above the other

```
GA-CGGATTAG
GATCGGAATAG
```

Alignment

- <u>Alignment</u>: Insertion of gaps in arbitrary locations along the sequences so that they end up with the same size.
- No gap in one sequence should be aligned to a gap in the other.
- We want the *best* alignment, but what is best?

Simple Scoring

- Two identical characters receive a score of + *m* (match)
- Two different characters receive a score of – *s* (mismatch)
- A character and a gap receive a score of – *d* (gap)
- score = (#matches).*m* – (#mismatches).*s* – (#gaps).*d*

Example

- m = 1
- s = 1
- d = 2

```
GA-CGGATTAG
GATCGGAATAG
```

score = +1(9) -1(1) -2(1) = 6

Why do we penalize gaps more?
Insertions and Deletions are less likely than substitutions

More General Scoring

The scoring scheme can be more general

- Given two sequences x and y, aligning x_i and y_j could add a score of $s(x_i,y_j)$. Therefore, we have a scoring matrix.
- [later] Gap penalty is not linear, once you have a gap, it is likely to have another one so we should penalize the start of the gap more

Greedy Algorithm

- To obtain the best alignment, try all possible alignments and find the best one
  - Exponentially many alignments!
  - How many? (homework)
- Greedy would result in a very slow algorithm

Dynamic Programming

- Solving an instance of the problem by taking advantage of already computed solution for smaller instances of the problem.
- To find optimal alignment for sequences *x* and *y*, compute optimal alignments for prefixes of *x* and *y*.

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Alignment is Additive

- The score of aligning
  $x_1..x_m$
  $y_1..y_n$
  is additive (with our particular scoring scheme)
- If the alignment is $x_1..x_i \quad x_{i+1}..x_m$
  $y_1..y_j \quad y_{j+1}..y_n$

then the score is:

$\text{score}(x_1..x_i, y_1..y_j) + \text{score}(x_{i+1}..x_m, y_{j+1}..y_n)$

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Optimal structure

Optimal solution => optimal solution of sub-problems

```
optimal   optimal
GA-CG  |  GATTAG
GATCG  |  GAATAG
```

cut optimal alignment anywhere

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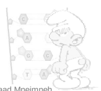
Dynamic programming

- Assume we want to align

$$x_1..x_m$$
$$y_1..y_n$$

- Let A(i,j) be the score of optimally aligning the two prefixes

$$x_1..x_i$$
$$y_1..y_j$$



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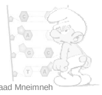
Dynamic Programming (cont.)

Three possible cases for aligning $x_1..x_i$ and $y_1..y_j$

1. $\boxed{\begin{matrix} x_1..x_{i-1} \\ y_1..y_{j-1} \end{matrix}} \begin{matrix} x_i \\ y_j \end{matrix}$ $\quad A(i,j) = A(i-1, j-1) + \begin{cases} m, \text{ if } x_i = y_j \\ -s, \text{ if not} \end{cases}$
2. $\boxed{\begin{matrix} x_1..x_{i-1} \\ y_1..y_j \end{matrix}} \begin{matrix} x_i \\ - \end{matrix}$ $\quad A(i,j) = A(i-1, j) - d$
3. $\boxed{\begin{matrix} x_1..x_i \\ y_1..y_{j-1} \end{matrix}} \begin{matrix} - \\ y_j \end{matrix}$ $\quad A(i,j) = A(i, j-1) - d$



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Dynamic Programming (cont.)

Inductive step:

$A(i, j-1)$, $A(i-1, j)$, $A(i-1, j-1)$ are correct

Then,

$$A(i, j) = \max \begin{cases} A(i-1, j-1) + s(x_i, y_j) \\ A(i-1, j) - \mathrm{d} \\ A(i, j-1) - \mathrm{d} \end{cases}$$

Where $s(x_i, y_j) =$ m, if $x_i = y_j$;
$-s$, if not

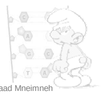

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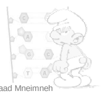
Illustration

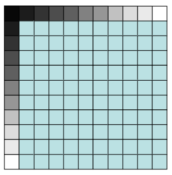
$$\begin{tikzcd} A(i-1,j-1) & A(i-1,j) \\ A(i,j-1) & A(i,j) \arrow[l] \arrow[u] \arrow[ul] \end{tikzcd}$$

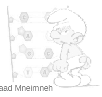
A(m,n) will be the optimal score



What Else?

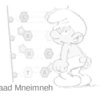
- Base case
  - *A*(0,0) = 0
  - *A*(*i*,0) = – *d.i*   *i* = 1…*m*
  - *A*(0,*j*) = – *d.j*   *j* = 1…*n*



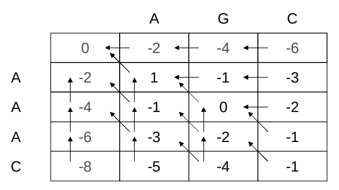


AAAC and AGC

		A	G	C
	0	-2	-4	-6
A	-2	1	-1	-3
A	-4	-1	0	-2
A	-6	-3	-2	-1
C	-8	-5	-4	-1



Obtaining Actual Alignment



		A	G	C
	0	-2	-4	-6
A	-2	1	-1	-3
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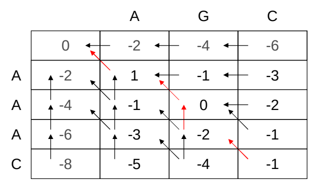
Obtaining Actual Alignment



		A	G	C
	0	-2	-4	-6
A	-2	1	-1	-3
A	-4	-1	0	-2
A	-6	-3	-2	-1
C	-8	-5	-4	-1

```
AAAC
AG-C
```

Needleman-Wunsch Algorithm

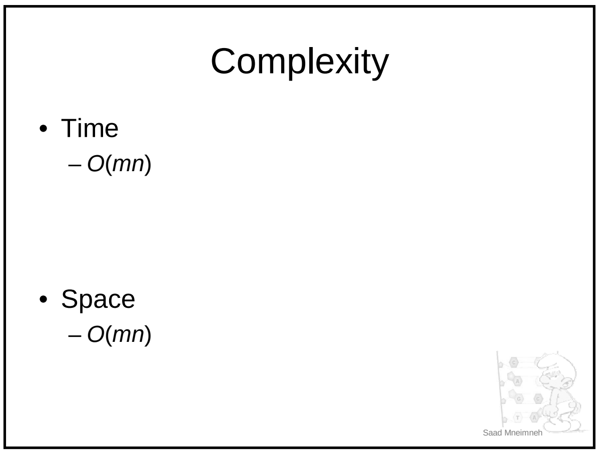
```
1.  Initialization
        A(0, 0)   = 0
        A(i, 0)   = – i.d for i = 1…m
        A(0, j)   = – j.d for j = 1…n

2.  Main Iteration (Aligning prefixes)
        for each   i = 1…m
            for each   j = 1…n
```

$$A(i,j) = \max \begin{cases} A(i-1, j-1) + s(x_i, y_j) & \text{[case 1]} \\ A(i-1, j) - d & \text{[case 2]} \\ A(i, j-1) - d & \text{[case 3]} \end{cases}$$

$$Ptr(i,j) = \begin{cases} \text{Diag} & \text{[case 1]} \\ \text{Up} & \text{[case 2]} \\ \text{Left} & \text{[case 3]} \end{cases}$$

```
3.  Termination
        A(m, n) is the optimal score, and
        from Ptr(m, n) can trace back optimal alignment.
```



Complexity

- Time
  - $O(mn)$
- Space
  - $O(mn)$

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