CSI5126. Algorithms in bioinformatics

Pairwise Sequence **Alignment**

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Summary

In this lecture, we learn that molecular sequences suffer mutations. We distinguish between two kinds of similar sequences: orthologues and paralogues. We derive an algorithm to compare molecular sequences taking into account their mode of evolution.

General objective

- Describe in your own words the pairwaise sequence alignment problem and explains its asumptions.

Reading

- Bernhard Haubold and Thomas Wiehe (2006). *Introduction to computational biology: an evolutionary approach.* Birkhäuser Basel. Pages 11-15, 30-33.

Comparative sequence analysis

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Why?

Comparative sequence analysis

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*"Determining **function** for a sequence is a matter of tremendous complexity, requiring biological experiments of the highest order of creativity. Nevertheless, with only DNA sequence it is possible to execute a computer-based algorithm **comparing the sequence to a database of previously characterized genes**. In about 50% of the cases, such a mechanical comparison will indicate a sufficient degree of **similarity** to suggest a putative enzymatic or structural function that might be possessed by the unknown gene."*
*Caskey et al. (1995) Genome Digest **2**:6-9.*

Comparative sequence analysis

A **molecular sequence alignment** aims

- to identify **similar regions** between two sequences
- to determine if two sequences have a **common origin**

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- Evolution transforms the sequences: **point mutations** (insertions, deletions, substitutions), **duplications**, **inversions**, **transpositions**, etc. Consequently, making it more difficult (interesting) to find the common origins.
- Information (function, structure, etc.) that is known about a sequence can generally be **transferred to** "similar" sequences.
- Comparative sequence analysis is therefore an **essential** and **powerful tool**.

Caveat

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- The genomic content of the proto-cell (proto-organism) certainly arose by a series of events, including duplication content, from smaller sequence fragments.
- **Conclusion**: all the sequences are related one to another.
- **This is not a very productive statement.** The evolutionary relationships that are considered interesting are those that can be explained by the techniques presented here, for which there are convincing statistical evidences.

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- How to align sequences **when** $|S_1| << |S_2|$?
- How to score **substitutions**?
- How to score **insertions** and **deletions**?
- Any two sequences can be aligned, how to evaluate (the **likelihood** of) an alignment?

Requirements (continued)

Are these two sequences similar?

```
A       VLSAADKGNVKAAWGKVGGHAAEYGAEALERMFLSFPTTKTYFPHFDLSHGSAQVKG
B       SLSAAQKDNVKSSWAKASAAWGTAGPEFFMALFDAHDDVFAKFSGLFSGAAKGTVKN
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         !!!! ! !!!  ! ! !       !       !         !            !
```

14 out of 57 (25 % of) amino acids are **identical**.

Requirements (continued)

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```
A     VLSAADKGNVKAAWGKVGGHAAEYGAEALERMFLSFPTTKTYFPHFD-LSHGSAQ--VKG
B     SLSAAQKDNVKSSWAKA---SAAWGTAGPEFFMALFDAHDDVFAKFSGLFSGAAKGTVKN
         !!!! ! !!!  ! !    ! ! !   !    !     ! ! ! ! !  !!
```

Insertion/deletions, two evolutionary events, must be taken into account

21 out of 60 (35 % of) positions are identical.

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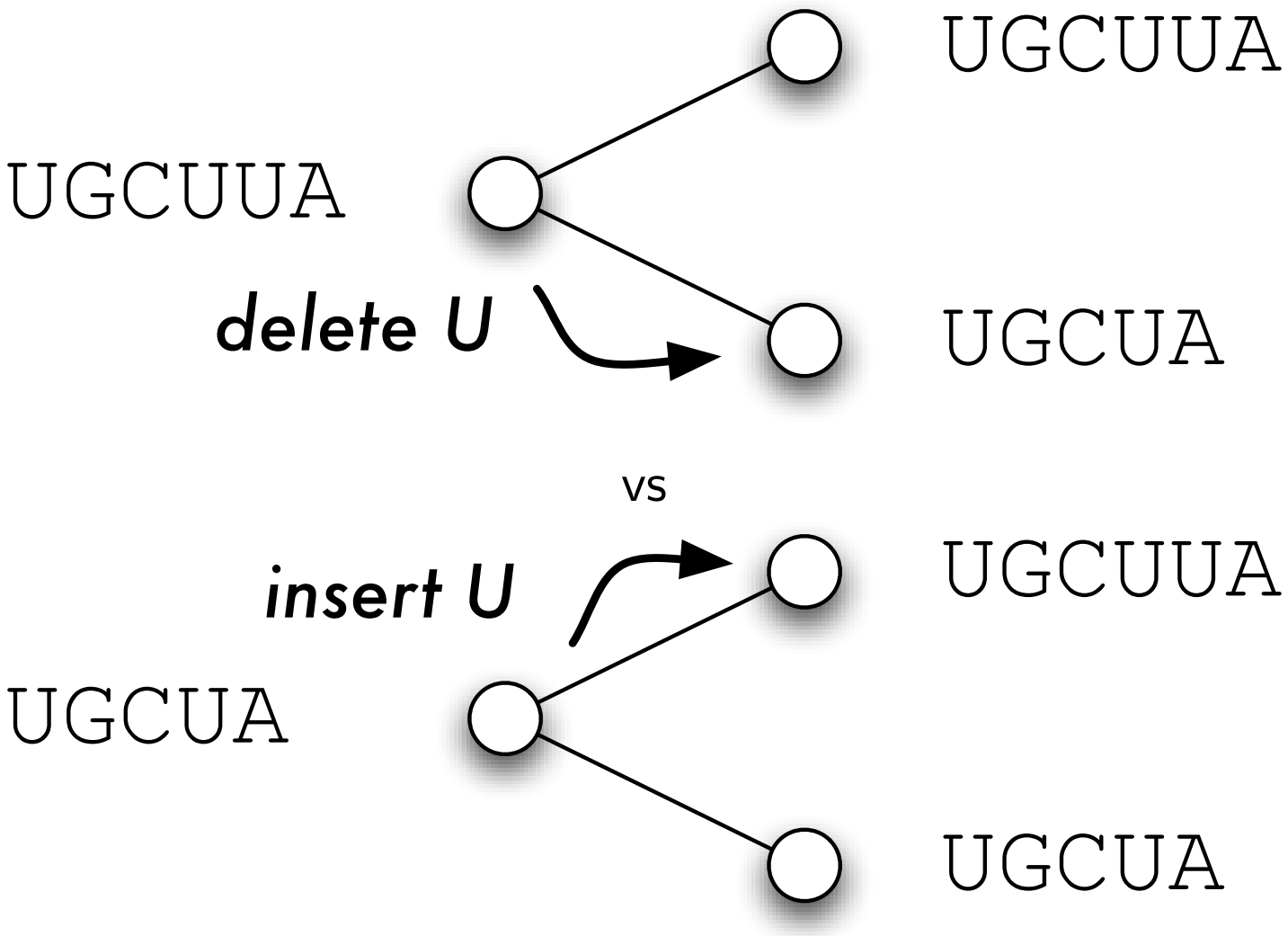
- **Indel** stands for **insertion or deletion**.
- **Given exactly two sequences, I am claiming that insertions cannot be distinguished from deletions, hence the use of the word indel.** What do I mean?
- Consider the following pairwise alignment, was the **U**, present in **S1**, deleted, to produce **S2**? Or, was is a **U** inserted into **S2** to produce **S1**?

```
S1 = UGCUUA
S2 = UGC-UA
```

What's an **indel**?



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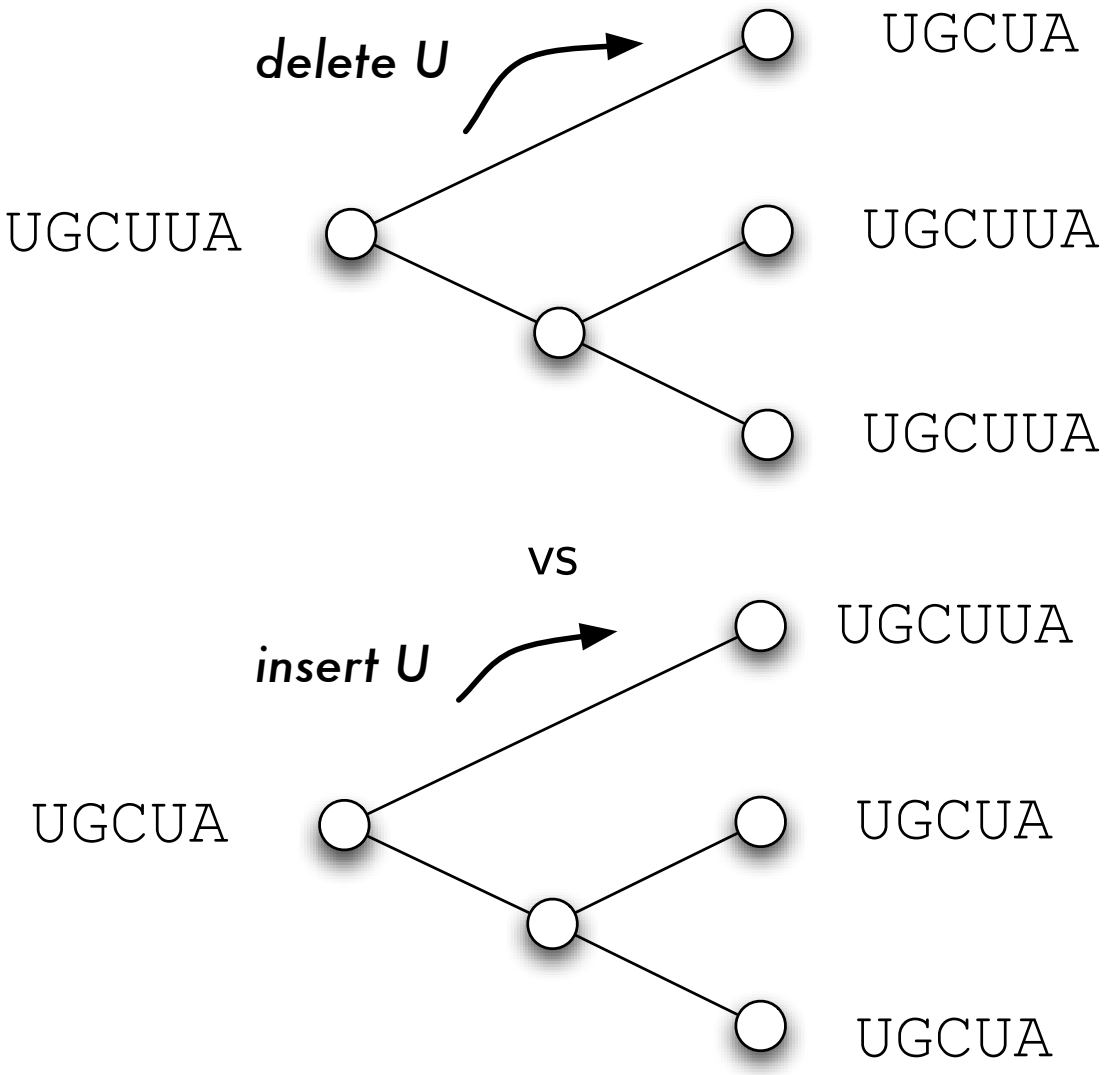

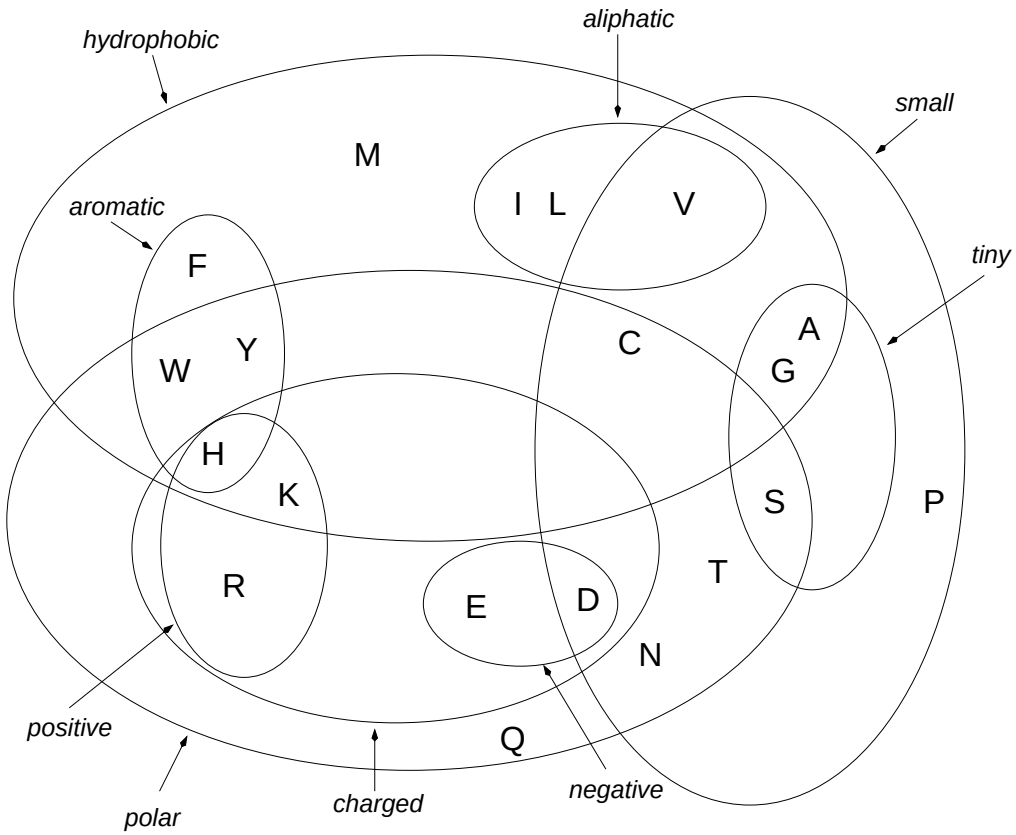

VLSAADKGNVKAAWGKVGGHAAEYGAEALERMFLSFPTTKTYFPHFD–LSHGSAQ
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! !

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  ! ! ! ! . !   ! ! ! . . ! . ! .     .!  .!.  .  !  ..   !  .      !  .!.  !   !.!.
```

38 out of 60 (63 % of) positions have the **same or similar properties**.

Requirements

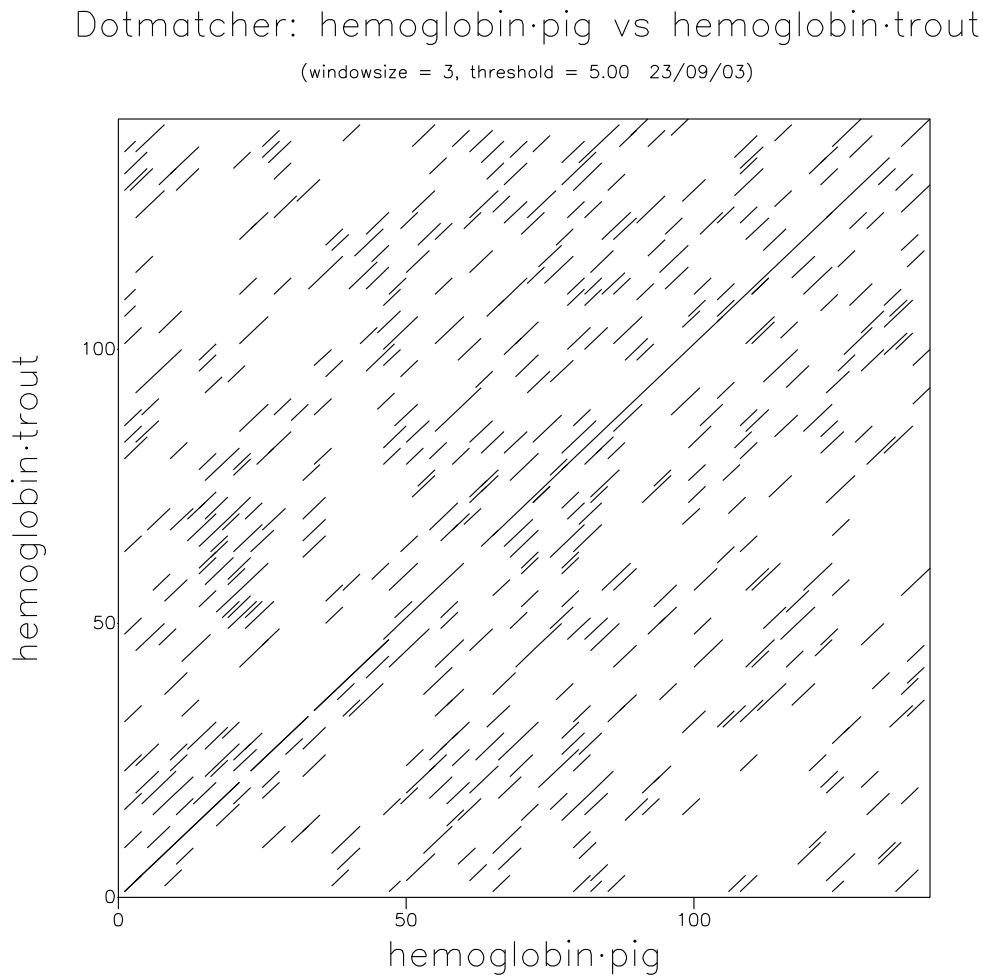
Are these two sequences **similar**? (...have similar regions?)

```
> Escherichia coli (K-12), complete genome
AGCTTTTCATTCTGACTGCAACGGGCAATATGTCTCTGTGTGGATTAAAAAAAGAGTGTC
TGATAGCAGCTTCTGAACTGGTTACCTGCCGTGAGTAAATTAAAATTTTATTGACTTAGG
TCACTAAATACTTTAACCAATATAGGCATAGCGCACAGACAGATAAAAATTACAGAGTAC
ACAACATCCATGAAACGCATTAGCACCACCATTACCACCACCATCACCATTACCACAGGT
AACGGTGCGGGCTGACGCGTACAGGAAACACAGAAAAAAGCCCGCACCTGACAGTGCGGG
CTTTTTTTTTCGACCAAAGGTAACGAGGTAACAACCATGCGAGTGTTGAAGTTCGGCGGT
ACATCAGTGGCAAATGCAGAACGTTTTCTGCGTGTTGCCGATATTCTGGAAAGCAATGCC
...(4,639,675)...
GCATGATATTGAAAAAAATATCACCAAATAAAAAACGCCTTAGTAAGTATTTTTC

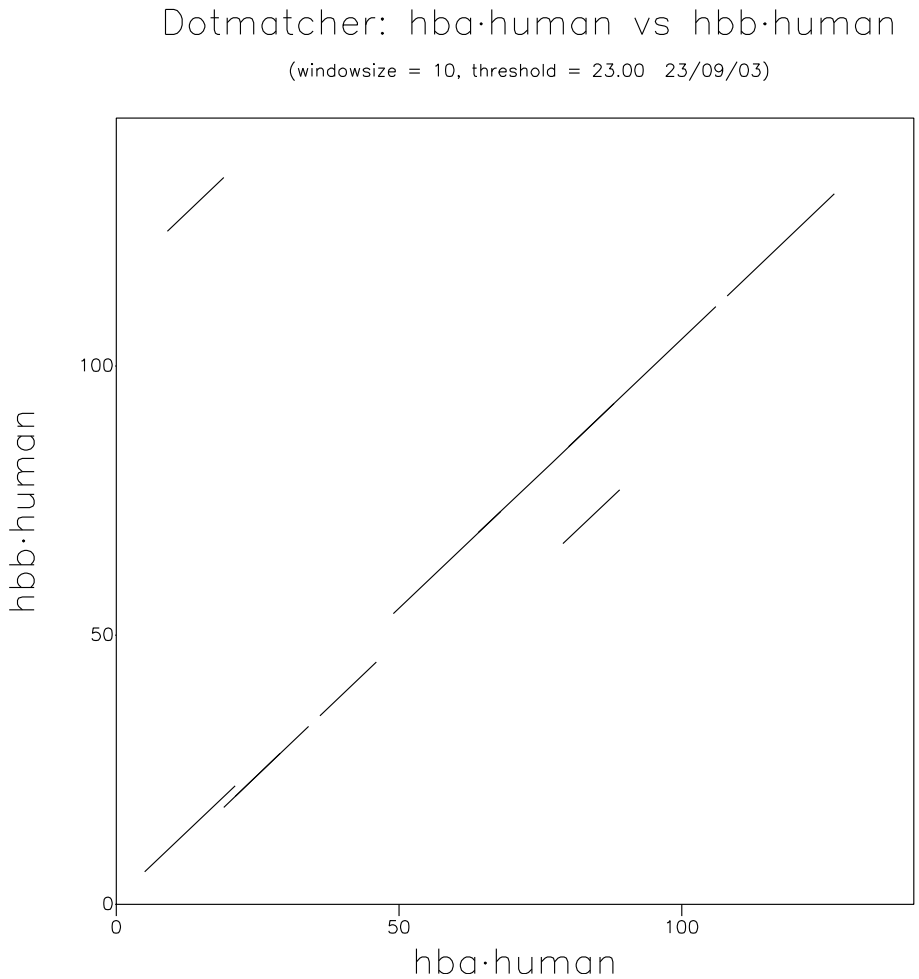
> Methanococcus vannielii SB, DNA-directed RNA polymerase
ATGGATAGATTTGATGTTCCAAAGGAAATCGGAGATATTACATTTGGATTGCTCTCTCCA
GAACAGATAAGGACAATGTCTGTTGCAAAAATCGTTACAGCAGATACTTATGATGACGAT
... (2,670) ...
ACAAAAGTCATTTCAAAATATGAAAATTAA
```

Dot plot

- A **dot plot** is a useful tool to compare two sequences.
- It consists of a **two dimensional diagram**, such that one sequence is written along one of its axes, and the other sequence along the other axis.
- In its simplest form, **a dot is plotted at position i and j if the characters i and j of the two respective strings are identical**.



The resulting diagram often contain too much noise (is too busy).



A **window-based** approach is generally used to circumvent the problem, i.e. a **dot** is plotted only if x **characters** (amino acids or nucleotides) **out** w **characters** are **identical**, where w is the window size.

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Dot plots

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- Shows **duplications**
- Identifies **local** similarity
- Shows **inverted repeats** (anti-diagonals)
- **Not suitable for automated analyses**

Finding an appropriate **metric**

When insertions and deletions are allowed, there are many possible alignments of the two input sequences.

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```
S1 A T T C G      S1 A T T C G -      S1 A T T C G - -
S2 T T C C A      S2 - T T C C A      S2 - T T C - C A
     x   x             x x x              x x x
```

- How many alignments for two input sequences of length 5?

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- Which one to choose?
- The **edit distance** is the minimum number of edit operations that are needed to transform one string into the other.
- The edit distance is sometimes referred to as **Levenshtein distance**.

Edit distance

The edit operations that are useful to model evolutionary processes are **insertions** (I), **deletions** (D) and the **substitutions** (S).

```
S1        A T T C G
S2          T T C C A
```

- The set of operations can be augmented with the **match** (M) operation, which simply rewrites a letter from the input onto the output.
- However, the match operation will not be counted when calculating the edit distance; in other words, it can be seens as having a weight of 0.

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- **Identically distributed**. The likelihood does not depend on the specific value of i, the position.
- **Is this realistic?**

Edit **transcript**

An **edit transcript** is a string over $\{I, D, S, M\}$ that summarizes the edit operations that are applied to the first string in order to produce the second one.

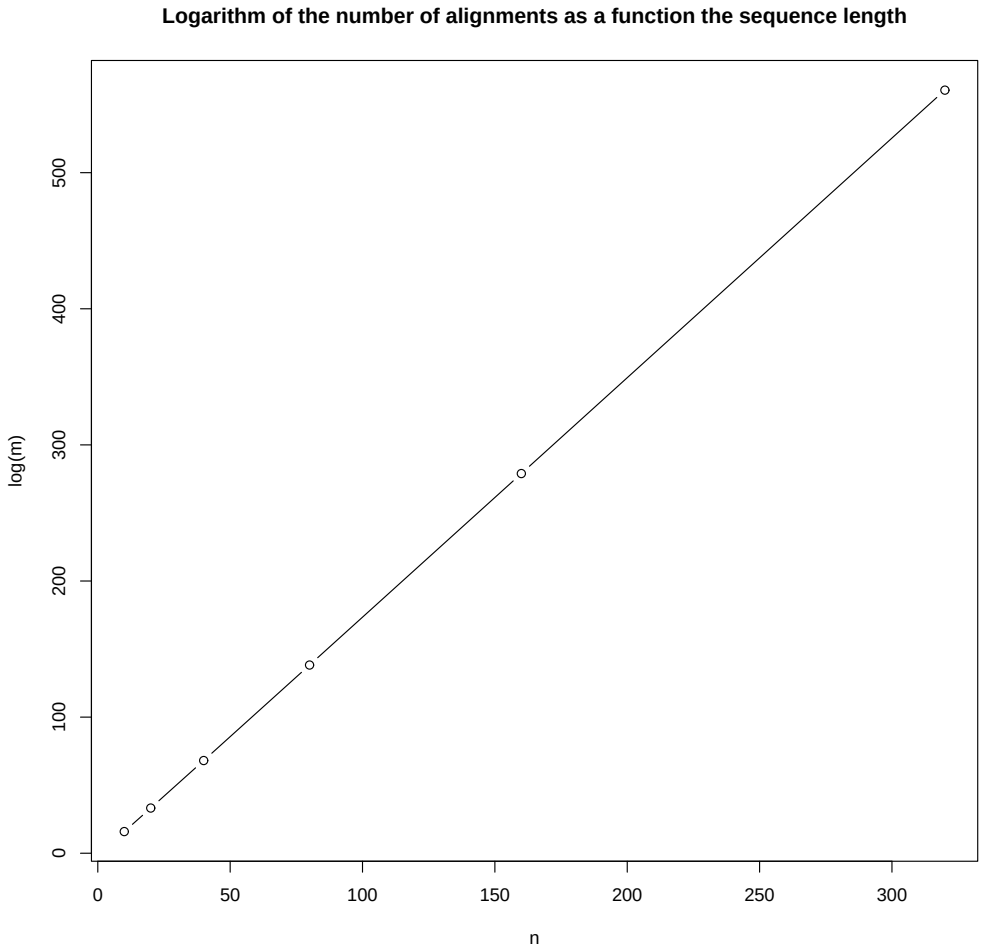
```
Transcript : D M M M S I
S1         : A T T C G -
S2         : - T T C C A
```

Pairwise alignment problem

- A **string alignment** consists of two input strings, written one on the top of the other, such that space (or dash) symbols have been added to the first, or second, string when insertions, or deletions, are seen in the edit transcript.
- The **edit distance problem** consists in finding the alignment (or equivalently the edit transcript) that minimizes the edit distance.

Size of the search space

Length	# alignments
10	8.097453e+06
20	2.605438e+14
40	3.781502e+29
80	1.121607e+60
160	1.392368e+121
320	3.031221e+243



Edit distance (continued)

- Uses of the edit distance occur **outside of the context of biological sequence comparisons**, examples are: spelling correction methods or textual database retrieval.
- The **Unix program diff** is an example of a program that is based on the notion of edit distance. It is a program that compares the content of two files.
- When ran with the argument **e** the program program produces a series of commands for the editor **ed** to transform the first file into the other.

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- The notation $S_1[i, j]$ stands for the substring of S_1 starting at position i and ending at position j, $S_1[i, j] = S_1(i)S_1(i+1)\dots S_1(j)$, e.g. $S_1 = TATAAT$, $S_1[3, 5] = TAA$.

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- I like considering the problem from the point of view of the edit transcript.

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- First, consider a transcript ending with the operation **I**.

$$\begin{array}{cc} & I \\ S_1 & - \\ S_2[1, m-1] & S_2(m) \end{array}$$

where $S_2(m)$ is the last symbol of S_2. Make sure to understand the details of above illustration. S_2 has been decomposed into a prefix and the last symbol, $S_2[1, m-1]S_2(m) = S_2$, a dash symbol has been added to the end of S_1.

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- Assuming this transcript leads to an optimal alignment, **how many edit operations are needed to transform S_1 into S_2?**

- Similarly for D (deletion),

$$\begin{array}{cc} & D \\ S_1[1, n-1] & S_1(n) \\ S_2 & - \end{array}$$

- and S (substitution),

$$\begin{array}{cc} & S \\ S_1[1, n-1] & S_1(n) \\ S_2[1, m-1] & S_2(m) \end{array}$$

- and M (match),

$$\begin{array}{cc} & M \\ S_1[1, n-1] & S_1(n) \\ S_2[1, m-1] & S_2(m) \end{array}$$

Obviously, only if $S_1(n) = S_2(m)$!

- and M (match),

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- For each case, how many edit operations are needed to transform S_1 into S_2?

$$\begin{array}{cc} & I \\ S_1 & - \\ S_2[1, m-1] & S_2(m) \end{array}$$

The number of edit operations required is?

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The number of edit operations required is?

$$D(S_1, S_2[1, m-1]) + 1$$

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The number of edit operations required is?

$$D(S_1[1, n-1], S_2) + 1$$

$$\begin{array}{cc} & S \\ S_1[1, n-1] & S_1(n) \\ S_2[1, m-1] & S_2(m) \end{array}$$

The number of edit operations required is?

$$D(S_1[1, n-1], S_2[1, m-1]) + 1$$

$$\begin{array}{cc} & M \\ S_1[1, n-1] & S_1(n) \\ S_2[1, m-1] & S_2(m) \end{array}$$

The number of edit operations required is?

$$D(S_1[1, n-1], S_2[1, m-1]) + 0$$

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- Consider $S_1 = \underline{ATT}GC$, $S_2 = \underline{A}GC$, and $D(3, 1)$, it does not mean that $S_1(3) = T$ is aligned against $S_2(1) = A$

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- Any other alignment than the one below would involve 3 or more edit operations (2 deletions and one substitution)

```
S1    ATT
      |
S2    A--
```

- Let's change the representation slightly so that $D(i, j)$ denotes the edit distance of $S_1[1, i]$ and $S_2[1, j]$
- In other words, $D(i, j)$ represents the minimum number of edit operations that are necessary to transform the first i characters of S_1 into the first j characters of S_2
- Does it mean that $S_1(i)$ and $S_2(j)$ are aligned?
- Consider $S_1 = \underline{ATT}GC$, $S_2 = \underline{A}GC$, and $D(3, 1)$, it does not mean that $S_1(3) = T$ is aligned against $S_2(1) = A$
- Any other alignment than the one below would involve 3 or more edit operations (2 deletions and one substitution)

```
S1    ATT
      |
S2    A--
```

- Here, the edit transcript of the optimal alignment is ending with a deletion (D)

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- Similarly, to transform the first j characters of S_2 into the first **zero** characters of S_1, i.e. $D(0,j)$, we have delete the first j characters of S_2,

$$D(0,j) = j$$

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- Given, two sequences S_1 and S_2 of length m and n respectively, which particular value of D solves the problem?
- $D(m, n)$ **is the value that we are looking for. It is the minimum number of edit operations that are needed to transform the first** m **characters of** S_1 **into the first** n **characters of** S_2

Recurrence equation for the edit distance problem

Base conditions,

$$D(0,0) = 0$$

$$D(i,0) = i,\ \ i \in 1 \ldots n$$

$$D(0,j) = j,\ \ j \in 1 \ldots m$$

General case,

$$D(i,j) = \min \begin{cases} D(i-1,j) + 1, \\ D(i,j-1) + 1, \\ D(i-1,j-1) + 1, \text{if } S_1(i) \neq S_2(j), \\ D(i-1,j-1) + 0, \text{if } S_1(i) = S_2(j), \end{cases}$$

Solution,

$$D(m,n)$$

Algorithm for solving the edit distance recurrence equation

Two strategies:

- Top-down
- Bottom-up

Top-down computation

- In the top-down computation, a first call is made to compute $D(m, n)$, which will force the computation of $D(m-1, n)$, $D(m, n-1)$ and $D(m-1, n-1)$

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- Many values will be re-computed several times in the top-down computation
- It is easy to see that an exponential number of operations will be performed!
- A complete 3-way tree of depth m has $\Theta(3^m)$ nodes.

Bottom-up (tabular) computation

- Hum, but there are only $(n+1) \times (m+1)$ distinct $D(i,j)$ values!

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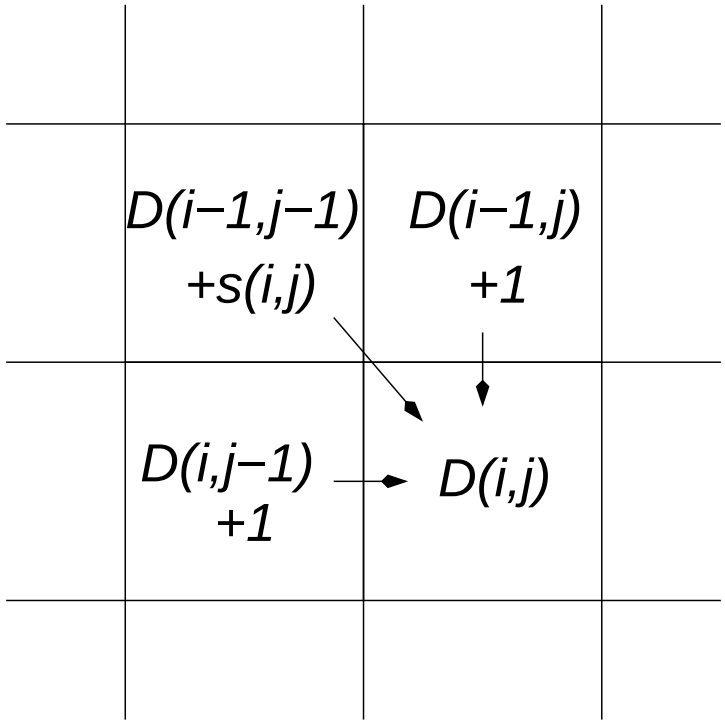
- Hum, but there are only $(n+1) \times (m+1)$ distinct $D(i,j)$ values!
- The bottom-up computation proceeds with the small values of i and j first.
- Furthermore, the algorithm memorizes (caches) the values of $D(i,j)$ so that a given $D(i,j)$ is computed only once.

Bottom-up (tabular) computation (continued)

1. This technique is known as **dynamic programming**;
2. Dynamic programming can only be applied to problems with a structure known as the **Bellman principle**.

Bottom-up computation



where $s(i,j) = 1$ if $S_1(i) \neq S_2(j)$ and 0 otherwise.

Bottom-up computation

		0	1	2	3	4	5
		–	A	T	C	G	C
0	–	0	1	2	3	4	5
1	A	1					
2	G	2					
3	G	3					
4	C	4					

$\Rightarrow$ **Base conditions**.

Bottom-up computation

		0	1	2	3	4	5
		–	A	T	C	G	C
0	–	0	1	2	3	4	5
1	A	1	0	1	2	3	4
2	G	2	1	1	2		
3	G	3					
4	C	4					

$\Rightarrow$ Notice the two **alternatives**: $D(1,2)+1 = D(2,2)+1 = 2$

Bottom-up computation

		0	1	2	3	4	5
		–	A	T	C	G	C
0	–	0	1	2	3	4	5
1	A	1	0	1	2	3	4
2	G	2	1	1	2	2	3
3	G	3	2	2	2	2	3
4	C	4	3	3	2	3	2

$\Rightarrow$ The **final result** is $D(4,5) = 2$. What does it tell us?

Bottom-up computation

		0	1	2	3	4	5
		–	A	T	C	G	C
0	–	0	1	2	3	4	5
1	A	1	0	1	2	3	4
2	G	2	1	1	2	2	3
3	G	3	2	2	2	2	3
4	C	4	3	3	2	3	2

$\Rightarrow$ We now know that **one sequence can be transformed into the other** with as little as **2 edit operations**!

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- **How** do you fill up the matrix: by **row**? by **column**? by **diagonal**? it is not important?

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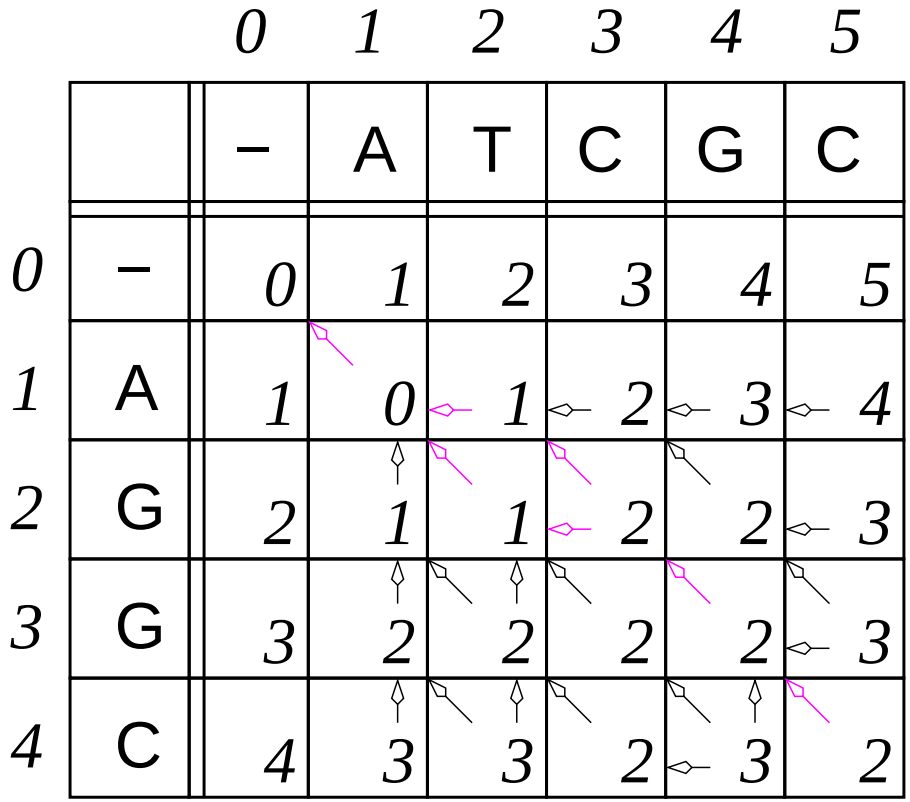
- **How** many cells can be filled simultaneously? Leading to parallel computation.
- $D(4,5) = 2$, it's possible to transform S_1 into S_2 with two edit operations, **which ones**?
- **How** to compute the actual alignment?

Dynamic Programming

		0	1	2	3	4	5
		–	A	T	C	G	C
0	–	0	1	2	3	4	5
1	A	1	0	1	2	3	4
2	G	2	1	1	2	2	3
3	G	3	2	2	2	2	3
4	C	4	3	3	2	3	2

$\Rightarrow$ **How to recover the underlying alignment?**

Traceback


0 1 2 3 4 5
– A T C G C
0 – 0 1 2 3 4 5
1 A 1 0 1 2 3 4
2 G 2 1 1 2 2 3
3 G 3 2 2 2 2 3
4 C 4 3 3 2 3 2

Traceback

In cell $D(i,j)$:

- set $\nwarrow$ if $D(i-1,j-1)+s(S_1(i),S_2(j))=D(i,j)$,
- set $\leftarrow$ if $D(i,j-1)+1=D(i,j)$,
- set $\uparrow$ if $D(i-1,j)+1=D(i,j)$.

Traceback (continued)

To recover the edit transcript, the alignment, follow a path from $D(n, m)$ to $D(0, 0)$. Interpreting each pointer as follows:

- $\leftarrow$: deletion of $S_1(j)$,
- $\uparrow$: insertion of $S_2(i)$,
- $\nwarrow$: match of $S_1(i)$ and $S_2(j)$ if $S_1(i) = S_2(j)$ and substitution otherwise.

The two optimal alignments:

```
ATCGC        ATCGC
A-GGC   or   AG-GC
```

$\Rightarrow$ It takes $\mathcal{O}(n + m)$ time to compute the traceback for one path.

Remarks

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Remarks

- There was **more than one optimal alignment**.
- Only one solution was recovered, but we could have recorded all of them.
- **How many optimal alignments are there**?
- **Can you enumerate them**?

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References

Pensez-y!

L'impression de ces notes n'est probablement pas nécessaire!