Computational biology

Co-evolution to predict protein structures

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Today's outline: from gene sequence to protein structure

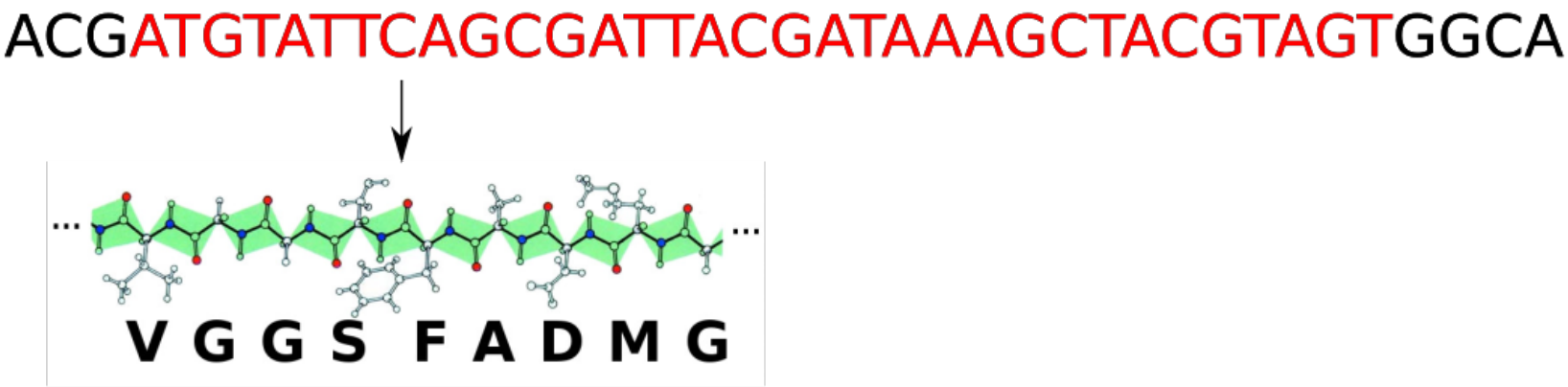
- Sequence-structure-function paradigm
  - Genomes, genes, proteins
  - Databases
- Evolution
  - Selective pressure
  - Multiple sequence alignment
  - Co-evolution

From genome to function, the very big picture

ACGATGTATTCAGCGATTACGATAAAGCTACGTAGTGGCA

On a genome (∼5Mbp), specific motifs define begining and end of a gene

From genome to function, the very big picture



Transcription + *translation*, to form a chain of amino acids (∼300-3000AA)

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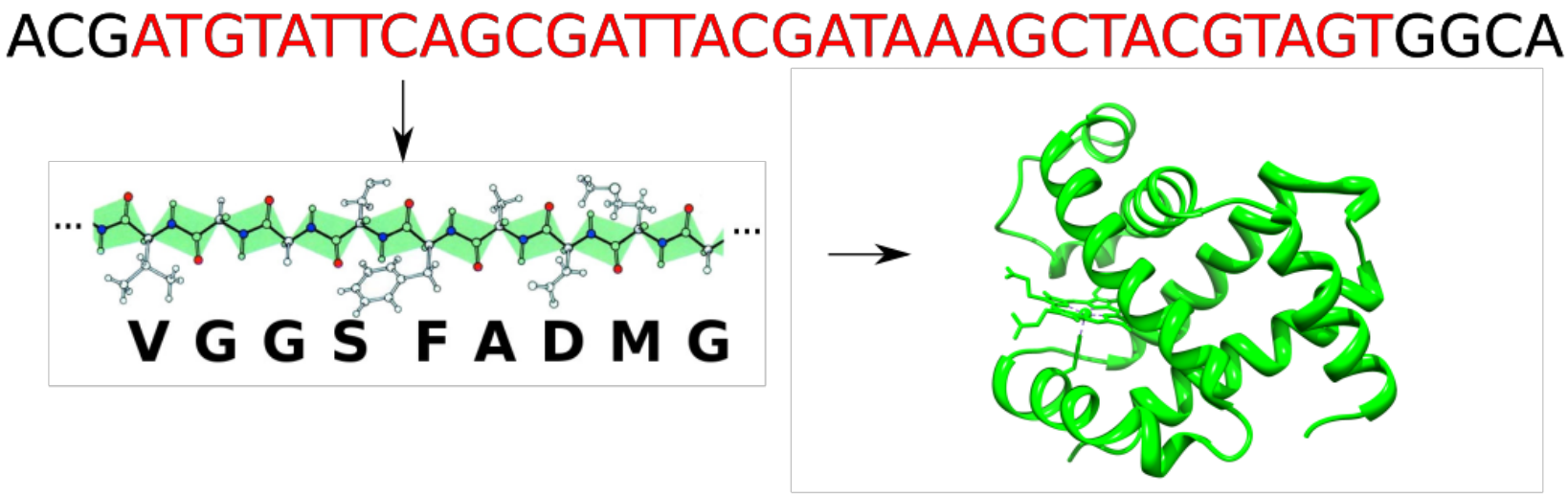
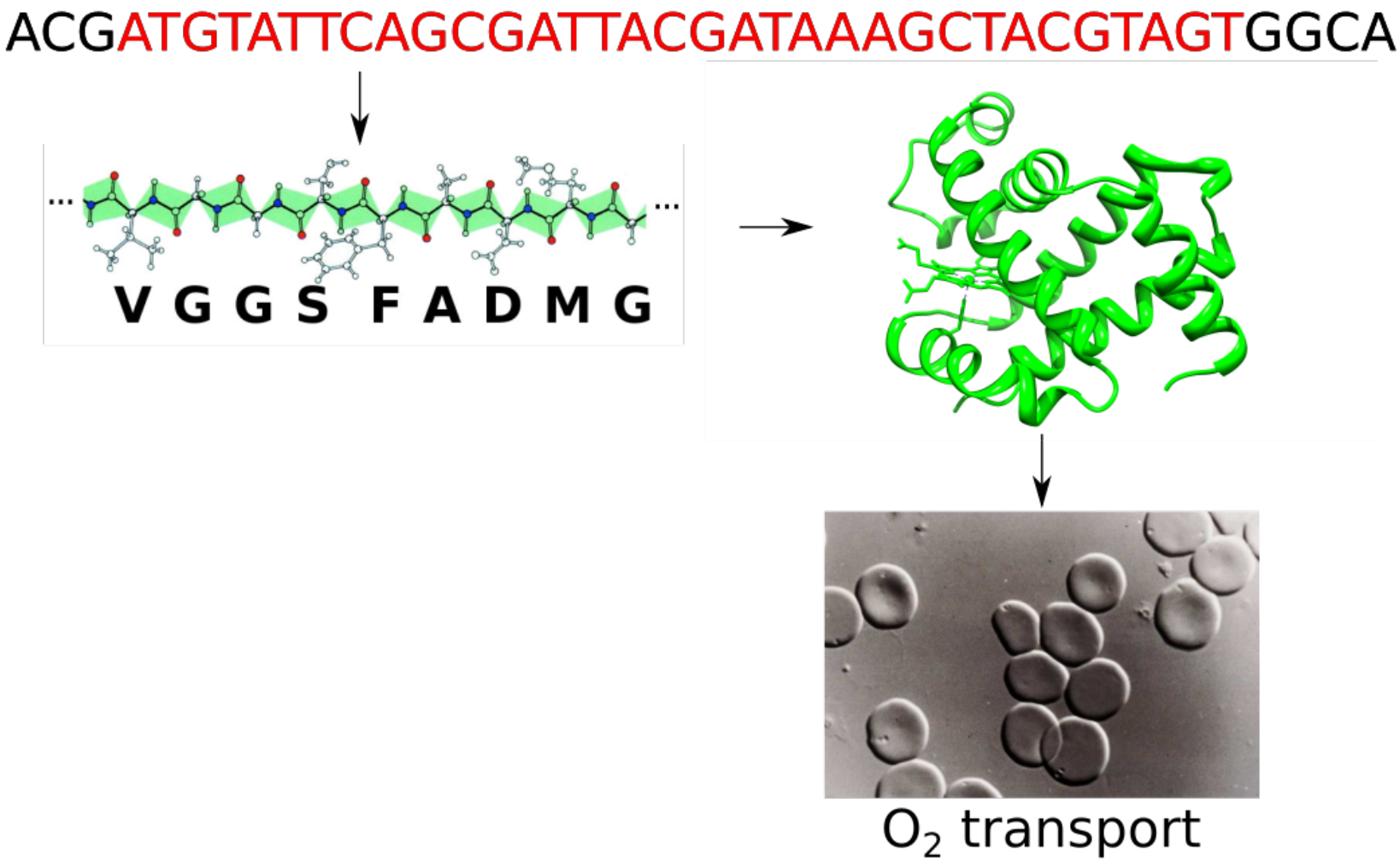


Protein folding under pysico-chemical interactions, diameter $\sim$ few nanometers

From genome to function, the very big picture

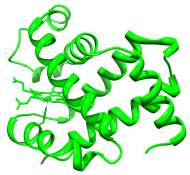


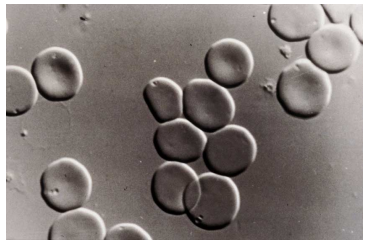
Protein endowed with a function (biochemical reactions, transport, etc.)

Data at every steps

Nucleic seq. | Amino acid seq. | Protein | Function

..ATTGTCGATGAC..





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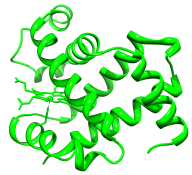
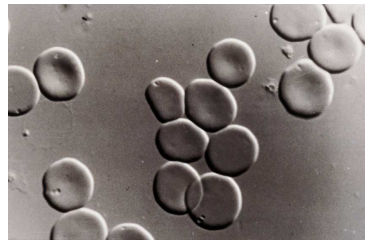
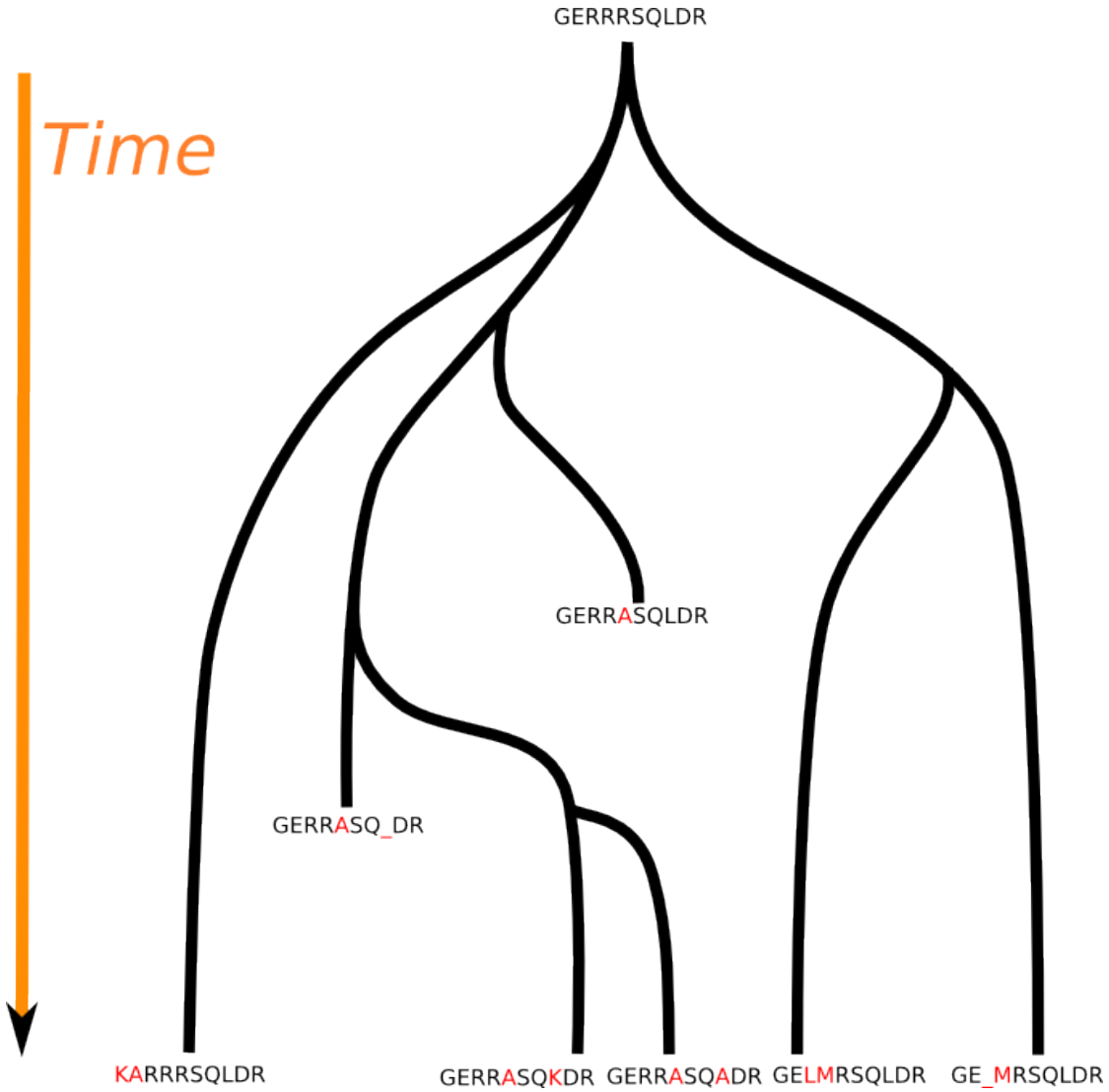
..ATTGTCGATGAC..			
NCBI	UniProt	RCSB PDB PROTEIN DATA BANK	-
`ncbi.nlm.nih.gov`	`uniprot.org`	`rcsb.org`	-

Protein evolution through mutations

We arrange sequences in a phylogenetic tree:



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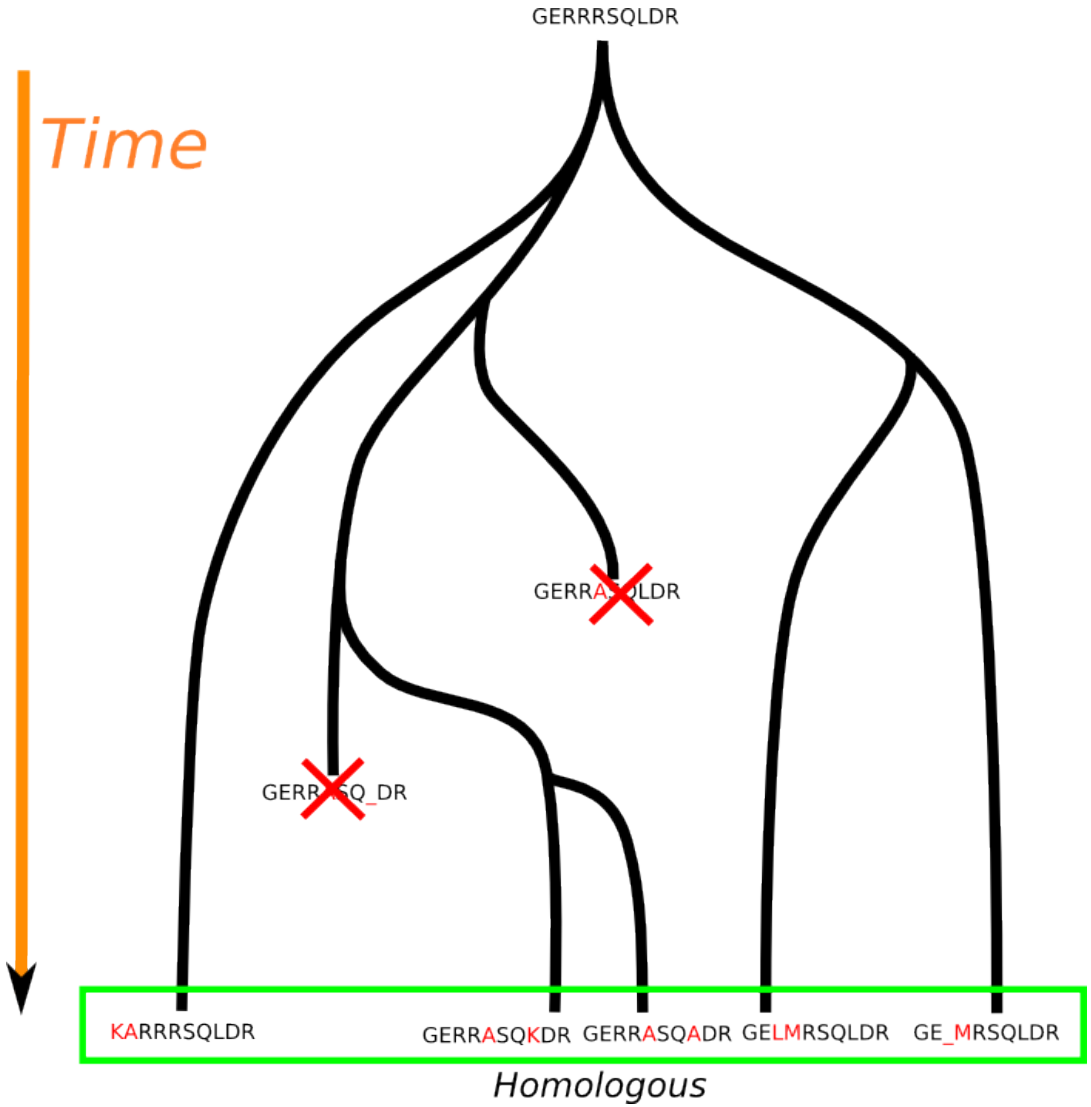

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How to compare sequences?

Sequence alignement: algorithm and p-value

Find the best alignment between your query sequence S_Q and a reference sequence S_R:

```
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Algorithm (sketch):

- given a 20×20 matrix of scores between amino-acids, set gap penalties
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Can be solved by **dynamic programming** in $\mathcal{O}(L^2)$ (see *Smith-Waterman algorithm*).

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Under a given p-value threshold we estimate the function to be similar.

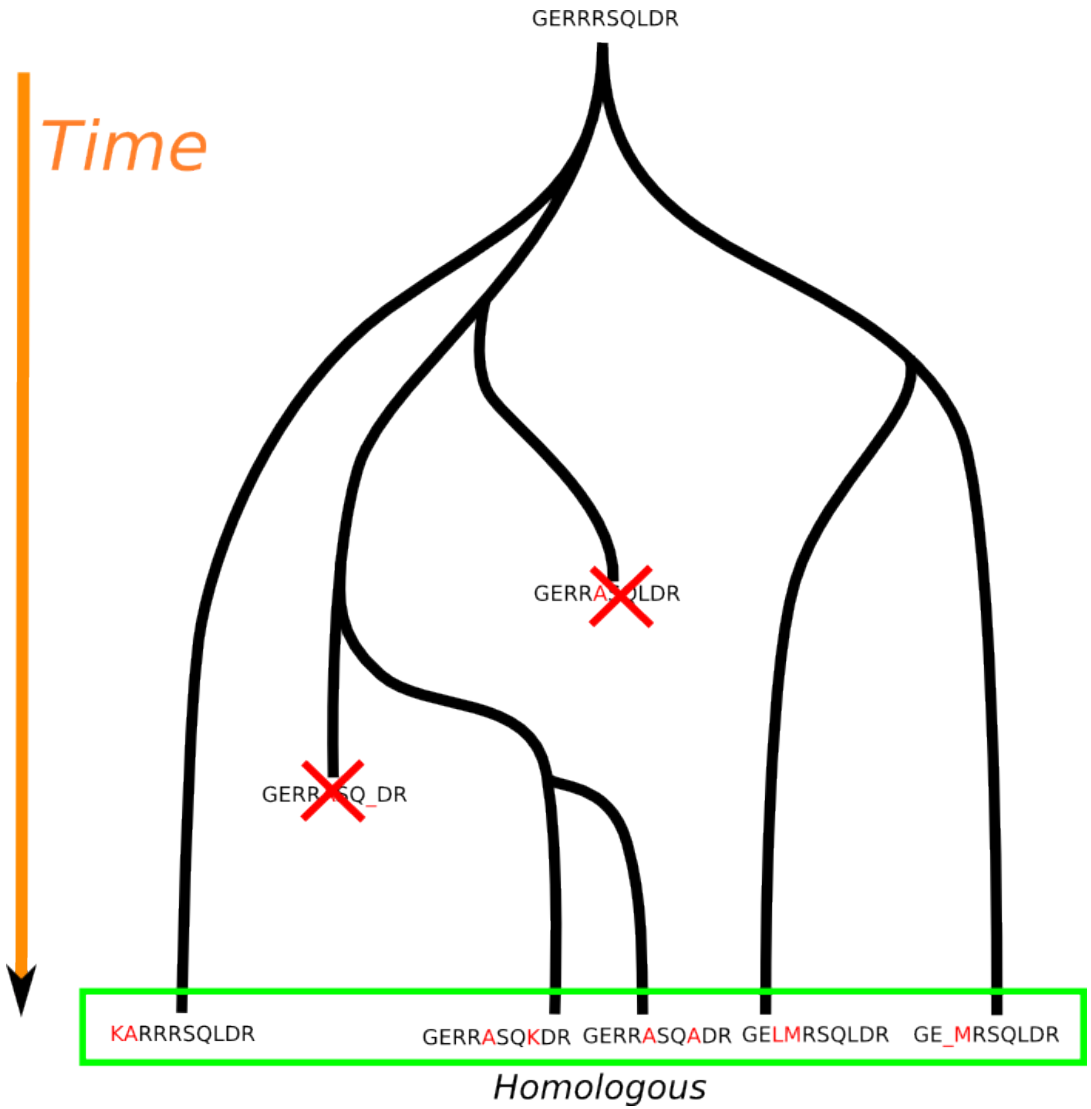
Big data: need for heuristic

Even with optimized versions of Smith-Waterman, it is still too heavy to compare sequences to all know sequences.
Tools have developed heuristics to filter down the possible target sequences:

- Blast (the historical tool)
- Diamond
- MMseqs2
- ...

Heuristics are mostly based on similar k-mers, and efficiently filtering through hash tables.

Sequence conservation



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Aligning the sequences (MSA, multiple sequence alignment):

Tools	Database
ClustalW [Larkin et al. 07]	Pfam `pfam.xfam.org`

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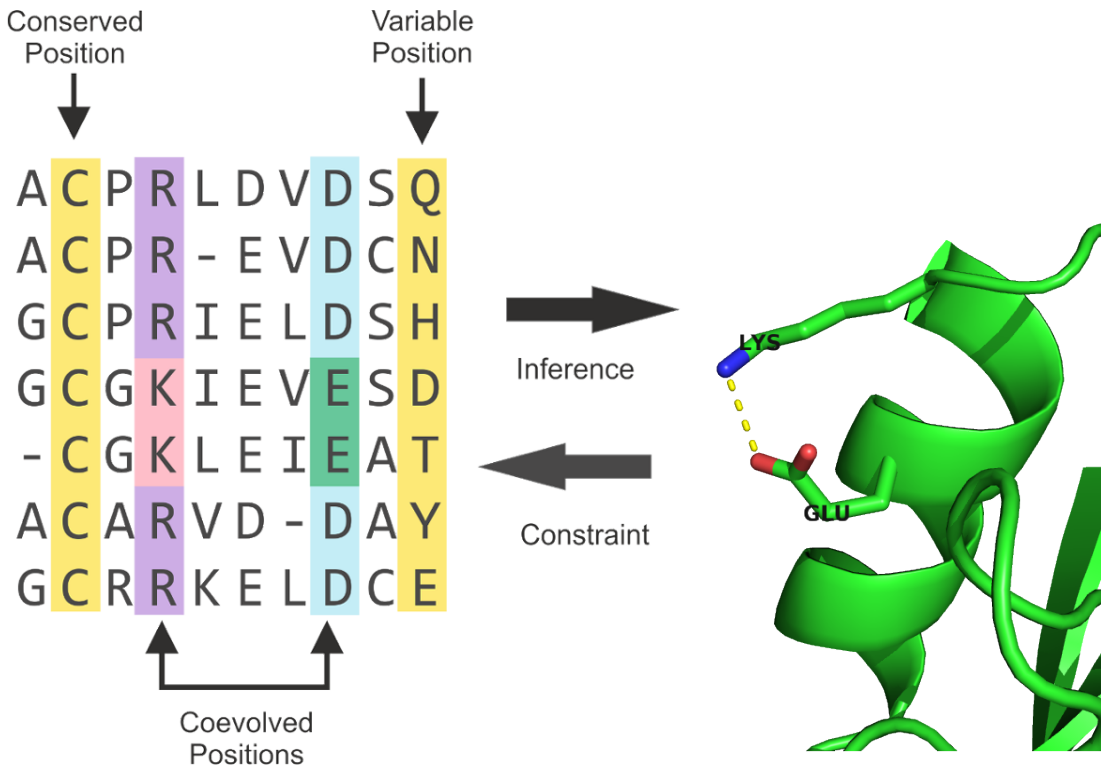
Why some positions are conserved, some other aren't?

Structure is determined by amino acid interactions

Preserving the function: coevolution of residues

As protein function is vital, **evolution selects mutations preserving structures**.
Leading to **compensatory** mutations:

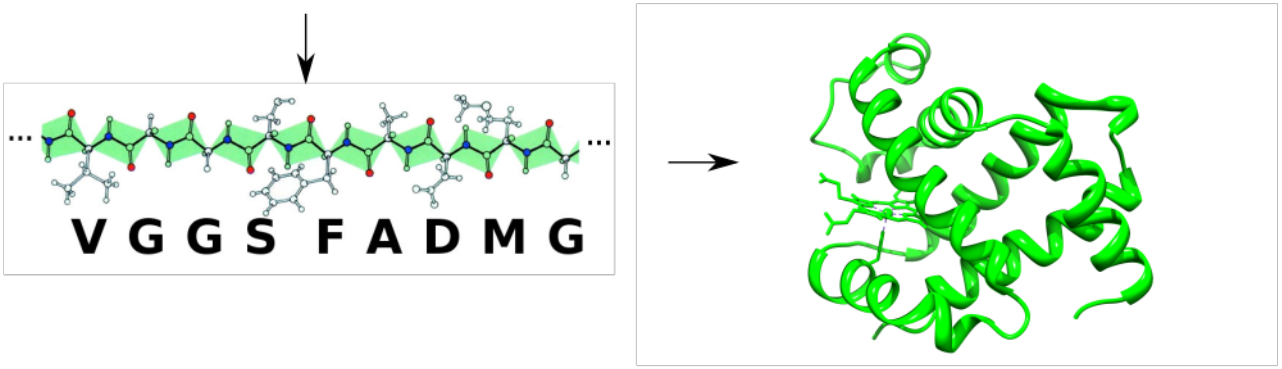


Computers and protein structure prediction

(cheap)

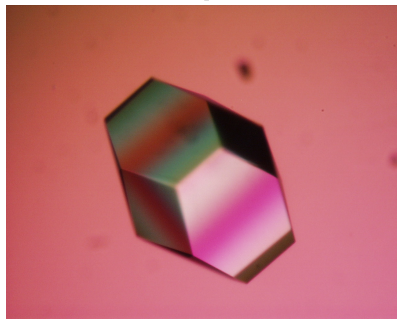
↓

ACGATGTATTCAGCGATTACGATAAAGCTACGTAGTGGCA

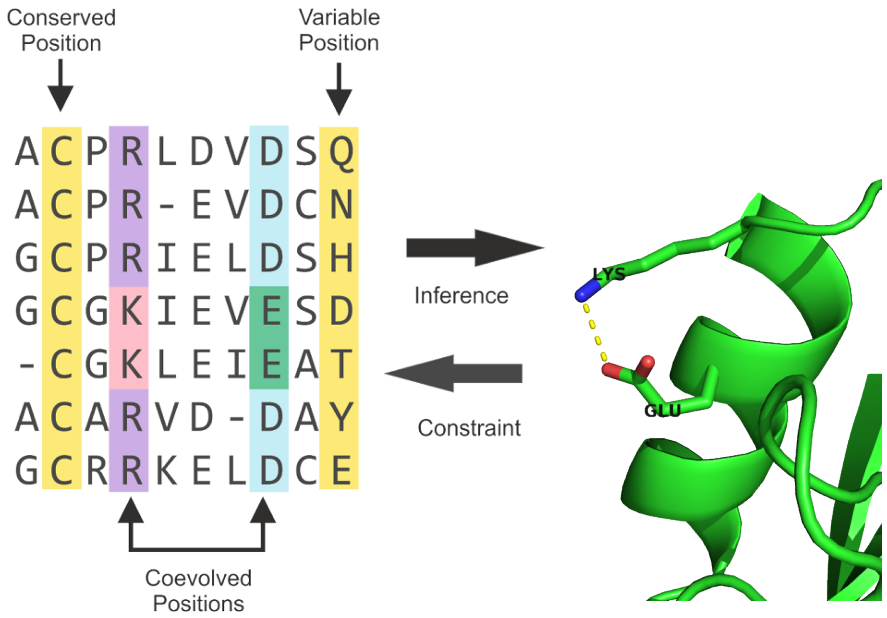


← (expensive)

Structure determined by X-Rays through a cristal of proteins



A simple approach for protein structure prediction



- Build or get multiple manio acid sequence alignments (**e.g.** in Pfam database)
- Infer what are the position in contact using machine learning

We'll check that in another module (January 2022)

On-line tools and databases

- Blastn Nucl-Nucl comparison
  `https://blast.ncbi.nlm.nih.gov/Blast.cgi?PROGRAM=blastn`
- Blastx Nucl-Prot comparison
  `https://blast.ncbi.nlm.nih.gov/Blast.cgi?PROGRAM=blastx`
- Pfam Prot-Prot comparison
  `http://pfam.xfam.org/search/sequence`
- Protein structure PDB `https://www.rcsb.org/`
- Covid-19 sequences `https://www.covid19dataportal.org`

Summary

Check what you've learn:

- What is a genome, a gene, a protein, its structure
- How real sequencing data look like
- What is a SNP, what can be the impact
- Main tools and databases in computational biology
- Potential application of computational biology for public health studies

The project involved basic skills from different area:

- biology
- statistics (Poisson distribution)
- algorithmics (linear time algorithms required)

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Bonus: download closely related SARS-Cov2 sequencing data, and run your tool on it for recovering the SNPs (procedure to be explained in the report).

The TATFAR
waits for
interesting answers to its call!