Computational biology

Homology and sequence alignment

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Today's outline: from gene sequence to protein structure

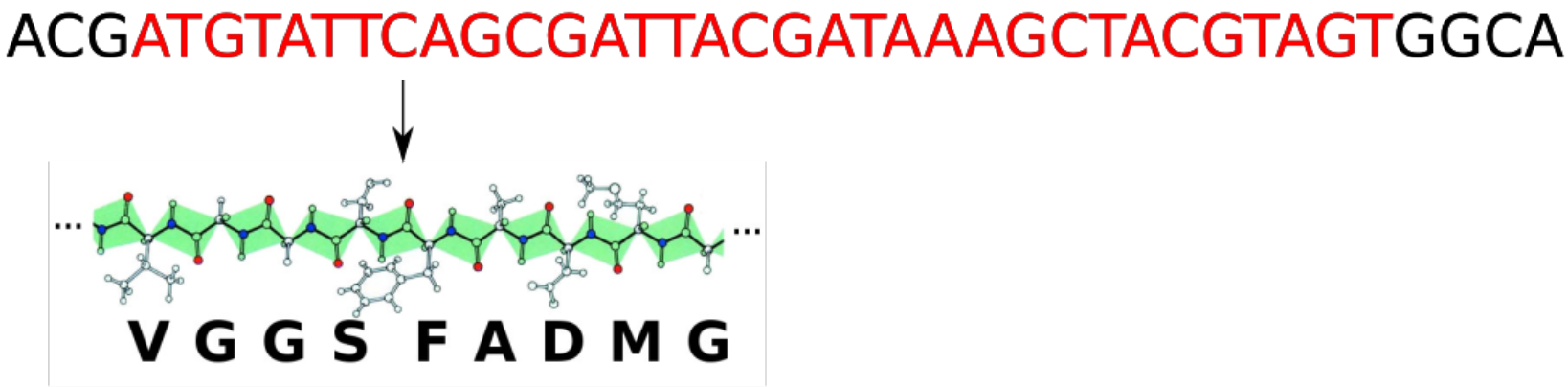
- Sequence-structure-function paradigm
  - Genomes, genes, proteins
  - Databases
- Evolution
  - Selection
  - Sequence homology
  - Multiple sequence alignment

From genome to function, the very big picture

ACGATGTATTCAGCGATTACGATAAAGCTACGTAGTGGCA

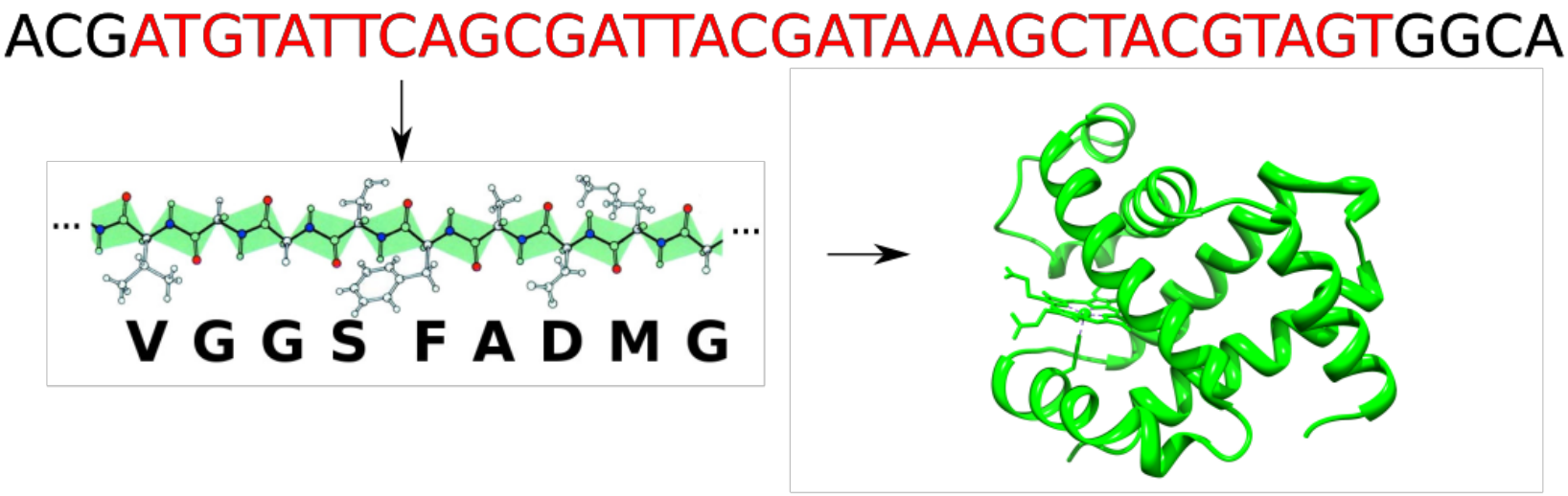
On a genome (∼5Mbp), specific motifs define begining and end of a gene

From genome to function, the very big picture



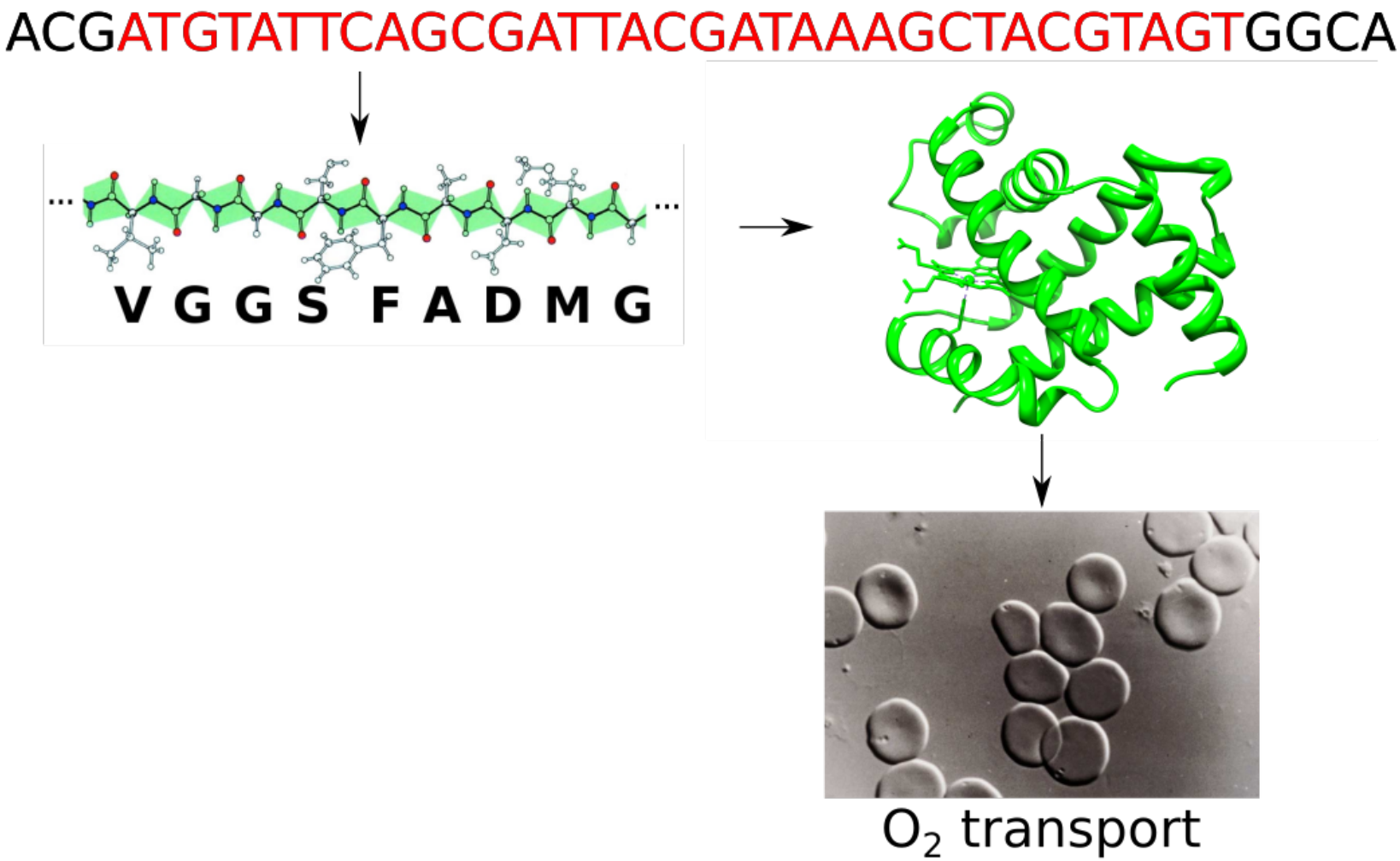
Transcription + *translation*, to form a chain of amino acids (∼300-3000AA)

From genome to function, the very big picture



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

From genome to function, the very big picture

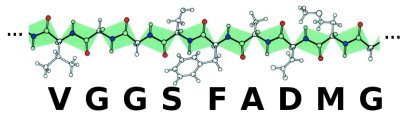


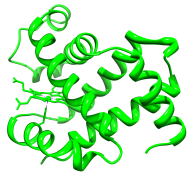
Protein endowed with a function (biochemical reactions, transport, etc.)

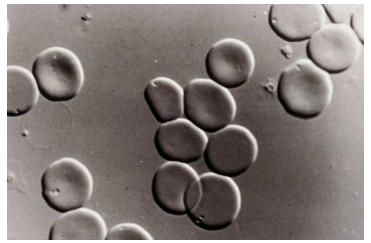
Data at every steps

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

..ATTGTCGATGAC..







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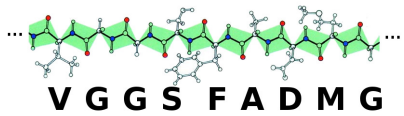
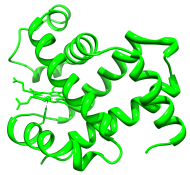
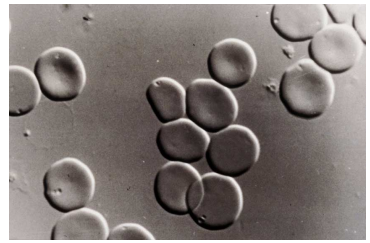
..ATTGTCGATGAC..			
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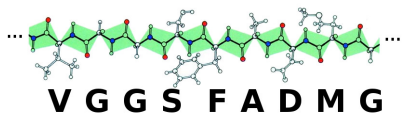
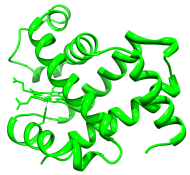
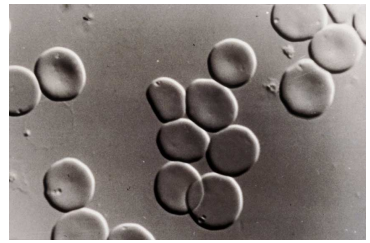
..ATTGTCGATGAC..			
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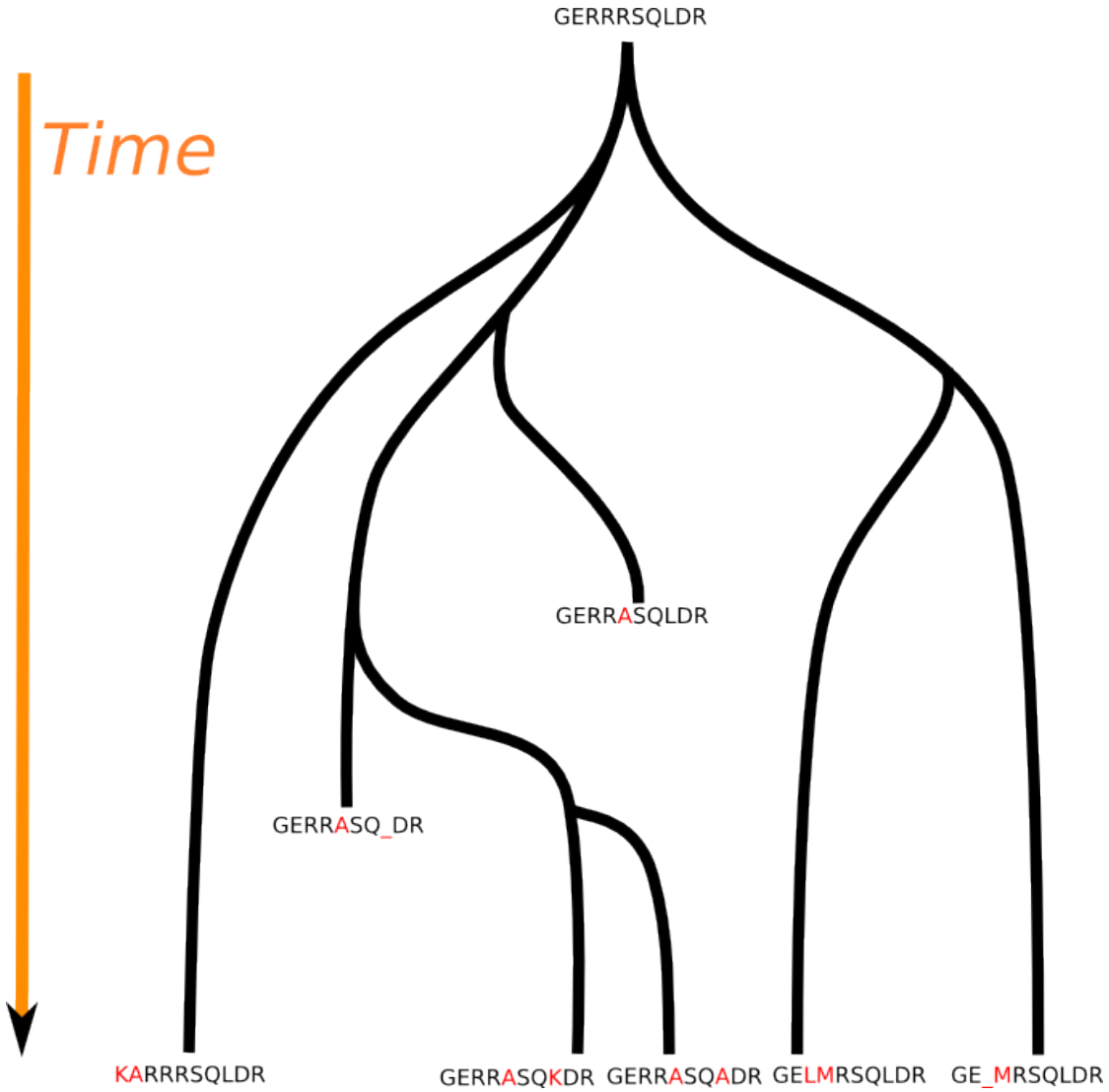
How do we predict the function from the sequence?

Protein evolution through mutations

We arrange sequences in a phylogenetic tree:



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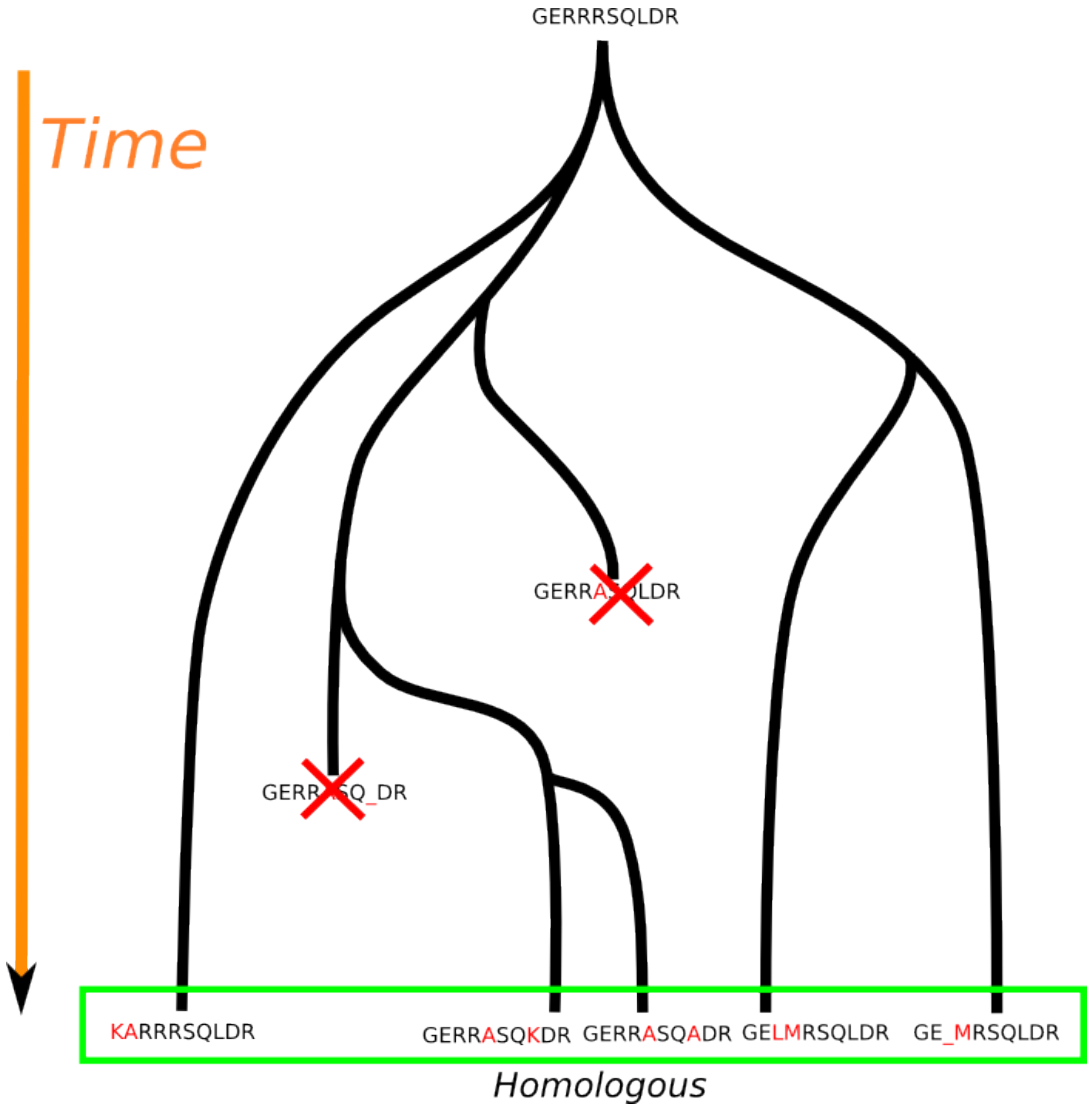

Sequence alignement: algorithm and p-value

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

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QEAIGNAMGSNI
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Algorithm (sketch):

- given a 20×20 matrix of scores between amino-acids, set gap penalties
- find the alignment maximizing the total score.

Can be solved by **dynamic programming** in $\mathcal{O}(L^2)$ (see *Smith-Waterman algorithm*).

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Can be solved by **dynamic programming** in $\mathcal{O}(L^2)$ (see *Smith-Waterman algorithm*). An approximate **p-value** can be derived to assess the significance of the alignment.

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

Big data: need for heuristic

Uniprot (amino acid db) have more than 200M sequences.

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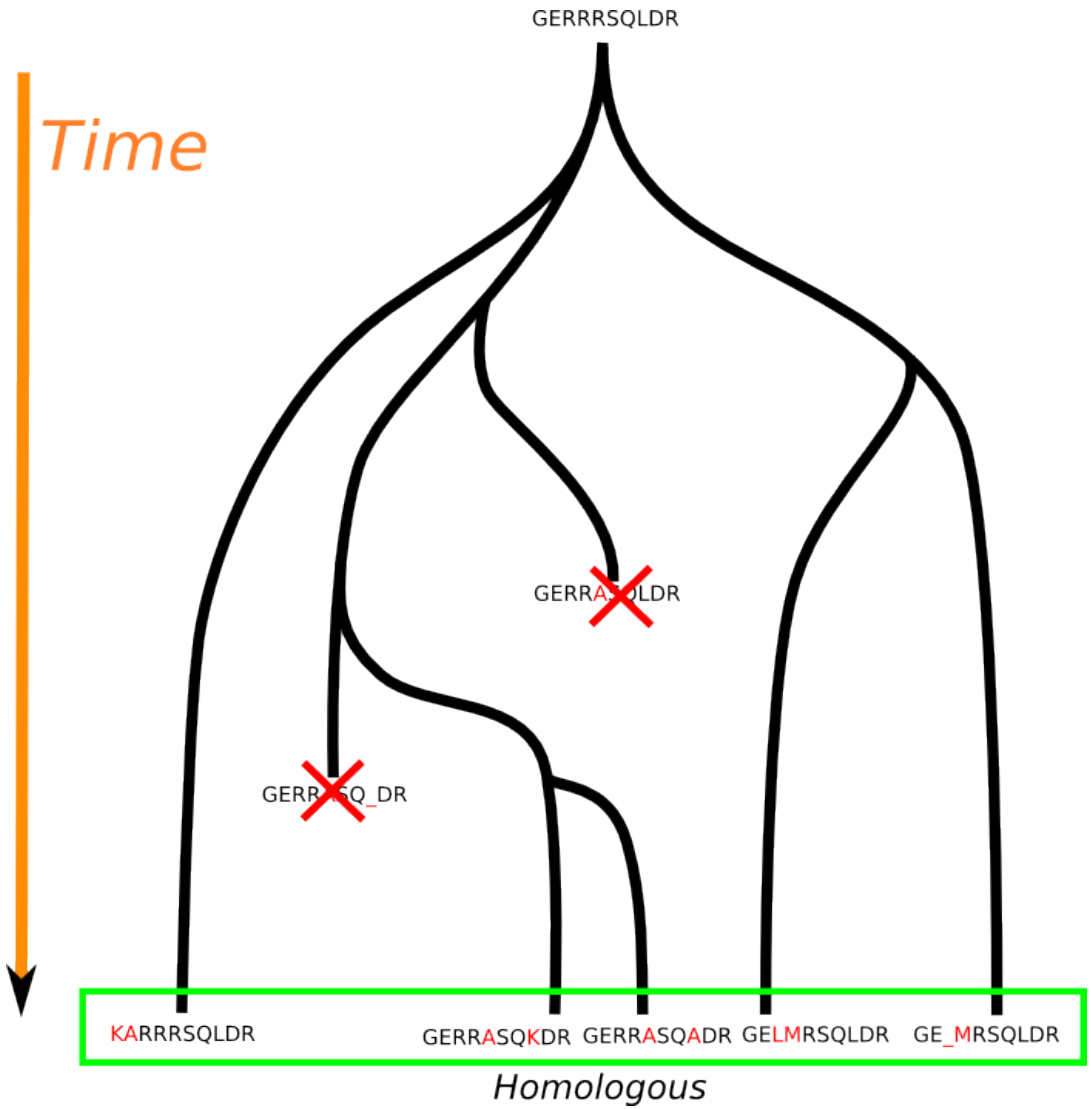
Tools have developed heuristics to filter down the possible target sequences:

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

Heuristics are mostly based on efficient pre-filtering (often using similar k-mers, with constant time looks up in hash tables).

Sequence conservation



Sequence conservation

Aligning the sequences (MSA, multiple sequence alignment):

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

Structure is determined by amino acid interactions

From sequence alignment to profile alignments

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/`

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)

Projects

Remember that your project should be like professional answers to the call:

- Clarity
- Fulfilment of the call
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You should send:

- a $\approx$ 5-page report, including:
  - description of the strategy
  - approximations and choices
  - application to the project data (what gene is impacted by the SNP)
- your code
- a step-by-step guide to reproduce the results of the report

The TATFAR
waits for
interesting answers to its call!