Computational biology

Homology and sequence alignment

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Today's outline: from gene sequence to protein structure

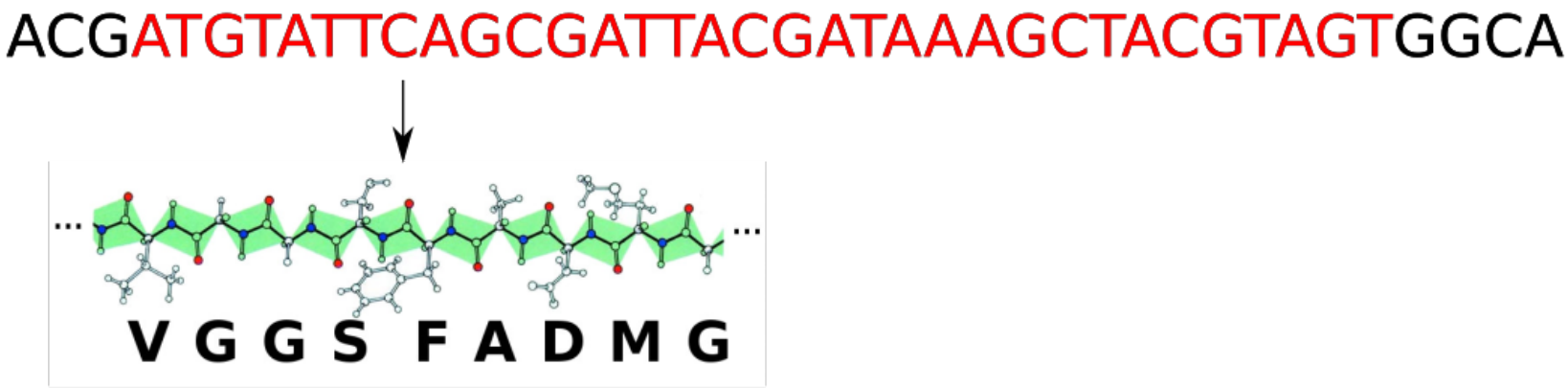
- Sequence-structure-function paradigm
  - Genomes, genes, proteins
  - Databases
- Evolution
  - Selection
  - Sequence homology
  - Multiple sequence alignment

From genome to function, the very big picture

ACGATGTATTCAGCGATTACGATAAAGCTACGTAGTGGCA

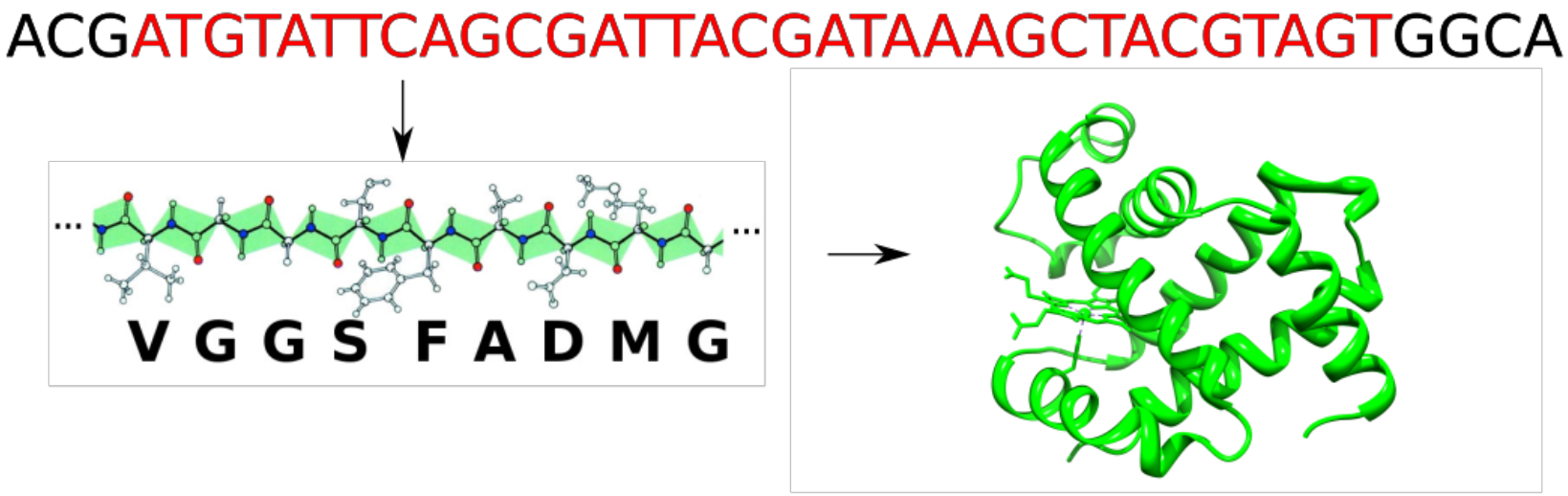
On a genome, specific motifs define begining and end of a gene

From genome to function, the very big picture



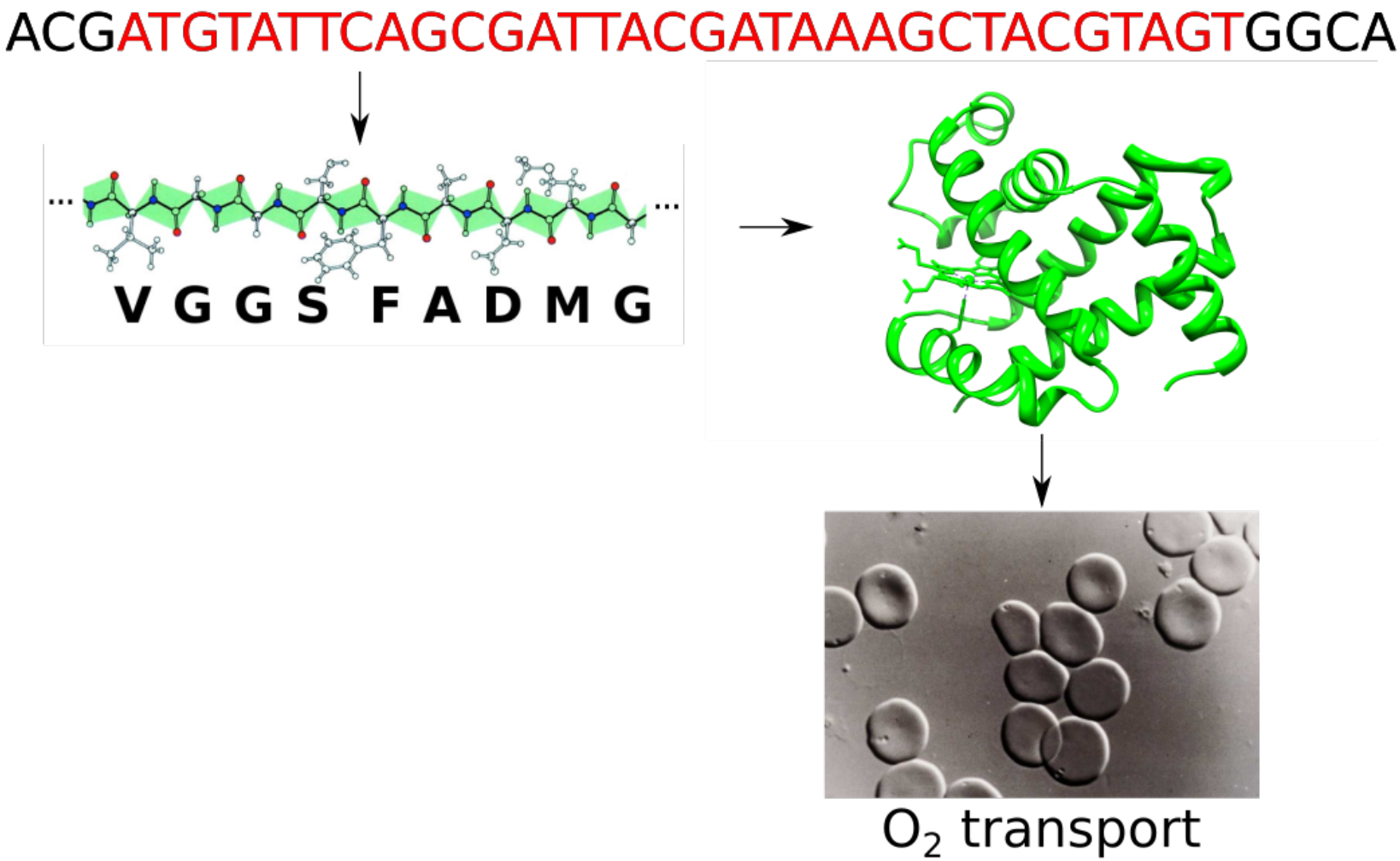
Transcription + *translation*, to form a chain of amino acids (∼300-3000AA)

From genome to function, the very big picture



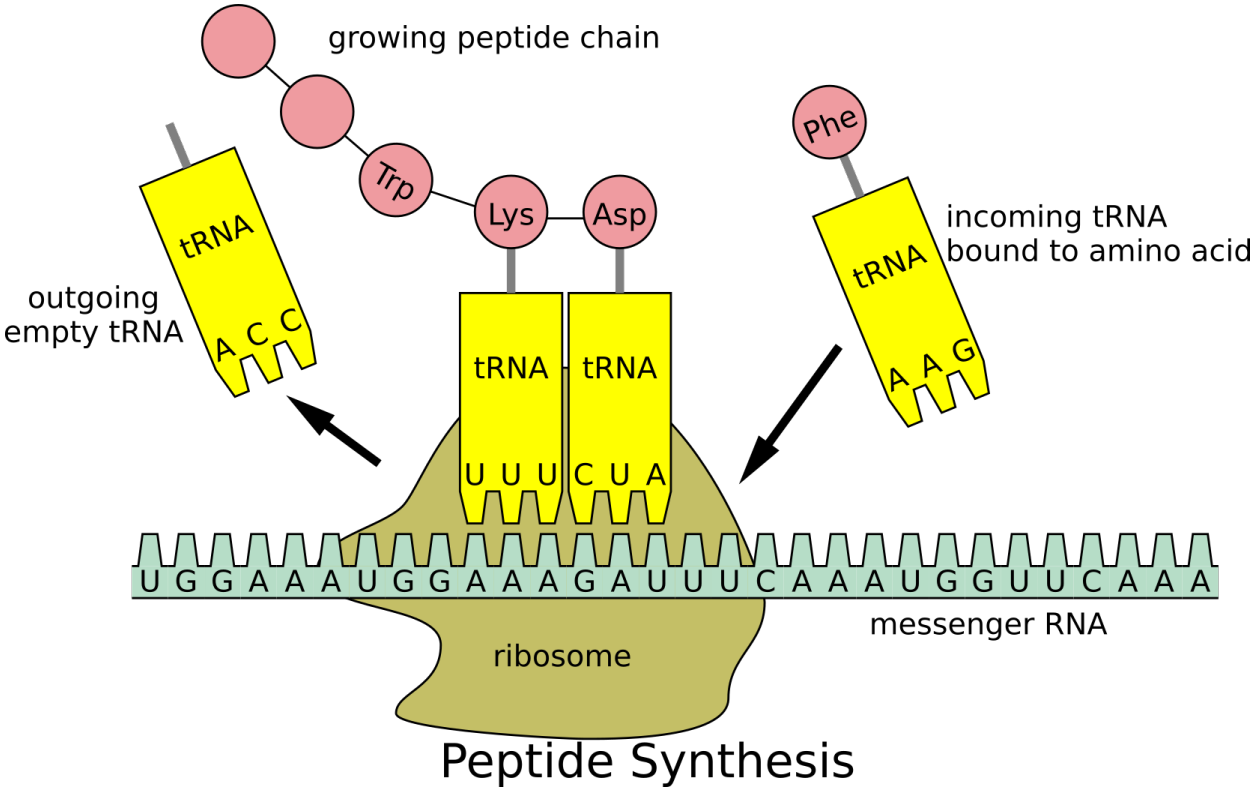
Protein folding under pysico-chemical interactions, diameter $\sim$ few nanometers

From genome to function, the very big picture



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

Zoom: genes to proteins (translation)



RNA codon table

1st position	2nd position U	2nd position C	2nd position A	2nd position G	3rd position
U	Phe	Ser	Tyr	Cys	U
	Phe	Ser	Tyr	Cys	C
	Leu	Ser	stop	stop	A
	Leu	Ser	stop	Trp	G
C	Leu	Pro	His	Arg	U
	Leu	Pro	His	Arg	C
	Leu	Pro	Gln	Arg	A
	Leu	Pro	Gln	Arg	G
A	Ile	Thr	Asn	Ser	U
	Ile	Thr	Asn	Ser	C
	Ile	Thr	Lys	Arg	A
	Met	Thr	Lys	Arg	G
G	Val	Ala	Asp	Gly	U
	Val	Ala	Asp	Gly	C
	Val	Ala	Glu	Gly	A
	Val	Ala	Glu	Gly	G

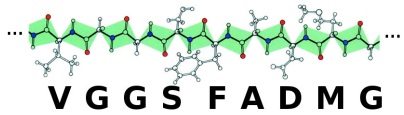
Amino Acids

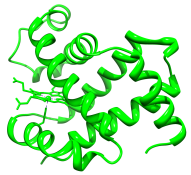
Ala: Alanine
Arg: Arginine
Asn: Asparagine
Asp:Aspartic acid
Cys:Cysteine
Gln: Glutamine
Glu: Glutamic acid
Gly: Glycine
His: Histidine
Ile: Isoleucine
Leu: Leucine
Lys: Lysine
Met: Methionine
Phe: Phenylalanine
Pro: Proline
Ser: Serine
Thr: Threonine
Trp: Tryptophane
Tyr: Tyrosisne
Val: Valine

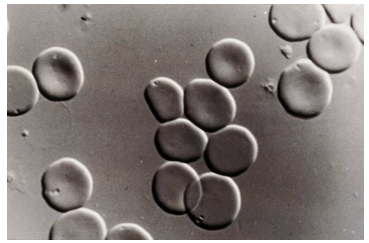
Data at every steps

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

..ATTGTCGATGAC..







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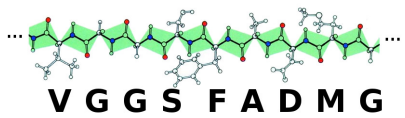
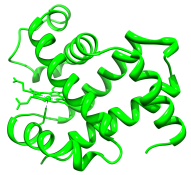
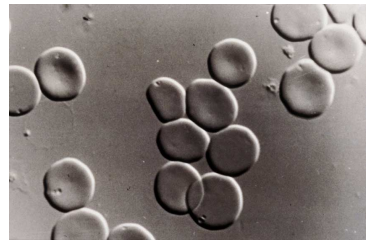
..ATTGTCGATGAC..			
ncbi.nlm.nih.gov	uniprot.org	rcsb.org	geneontology.or

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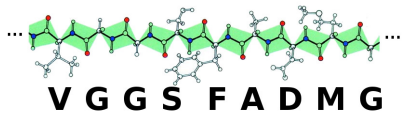
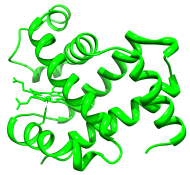
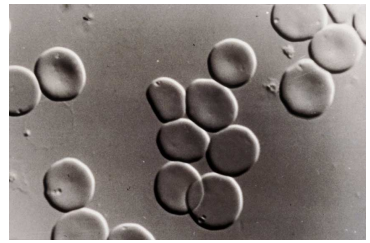
..ATTGTCGATGAC..			
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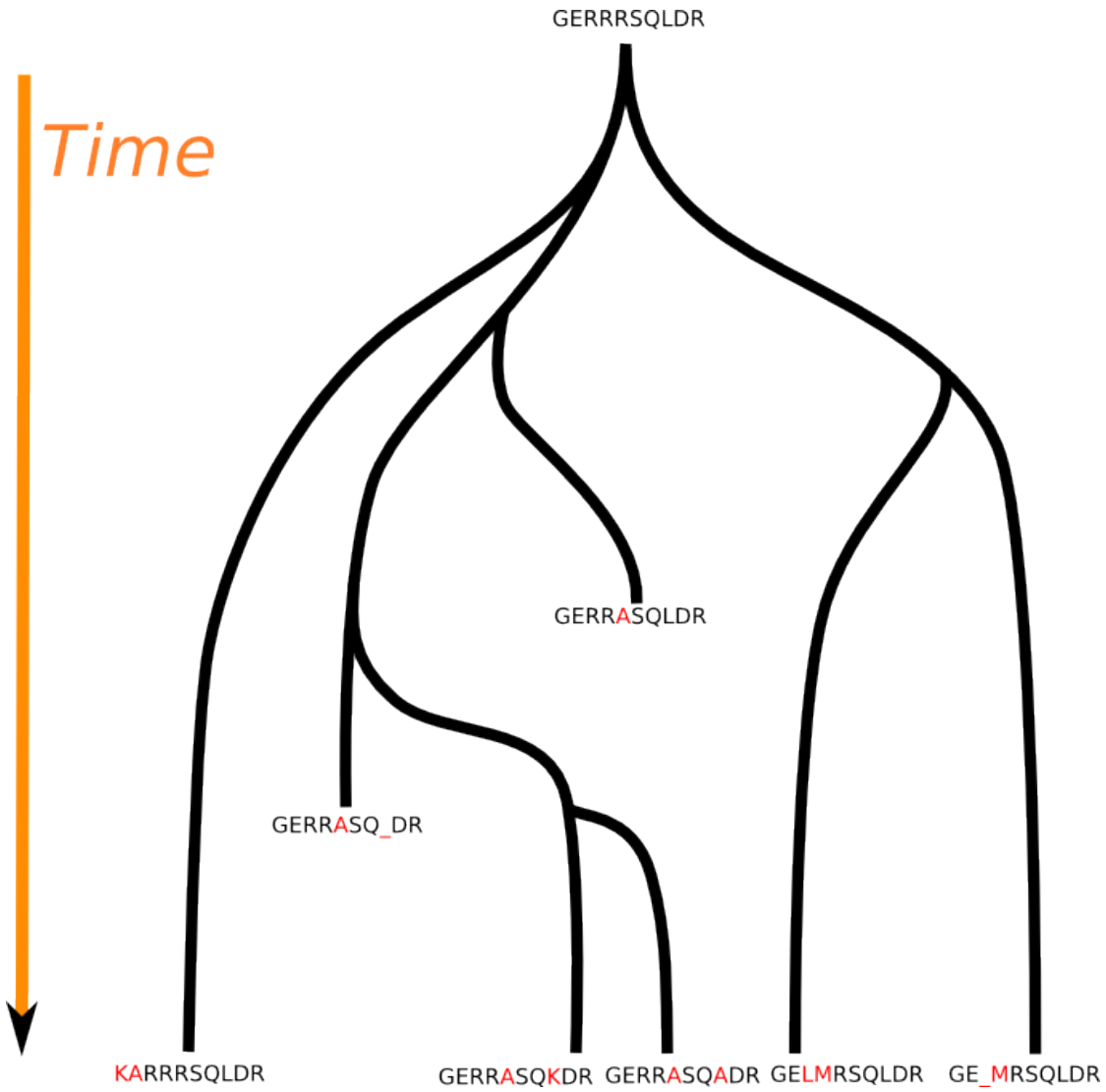
How do we predict the function from the sequence?

Protein evolution through mutations



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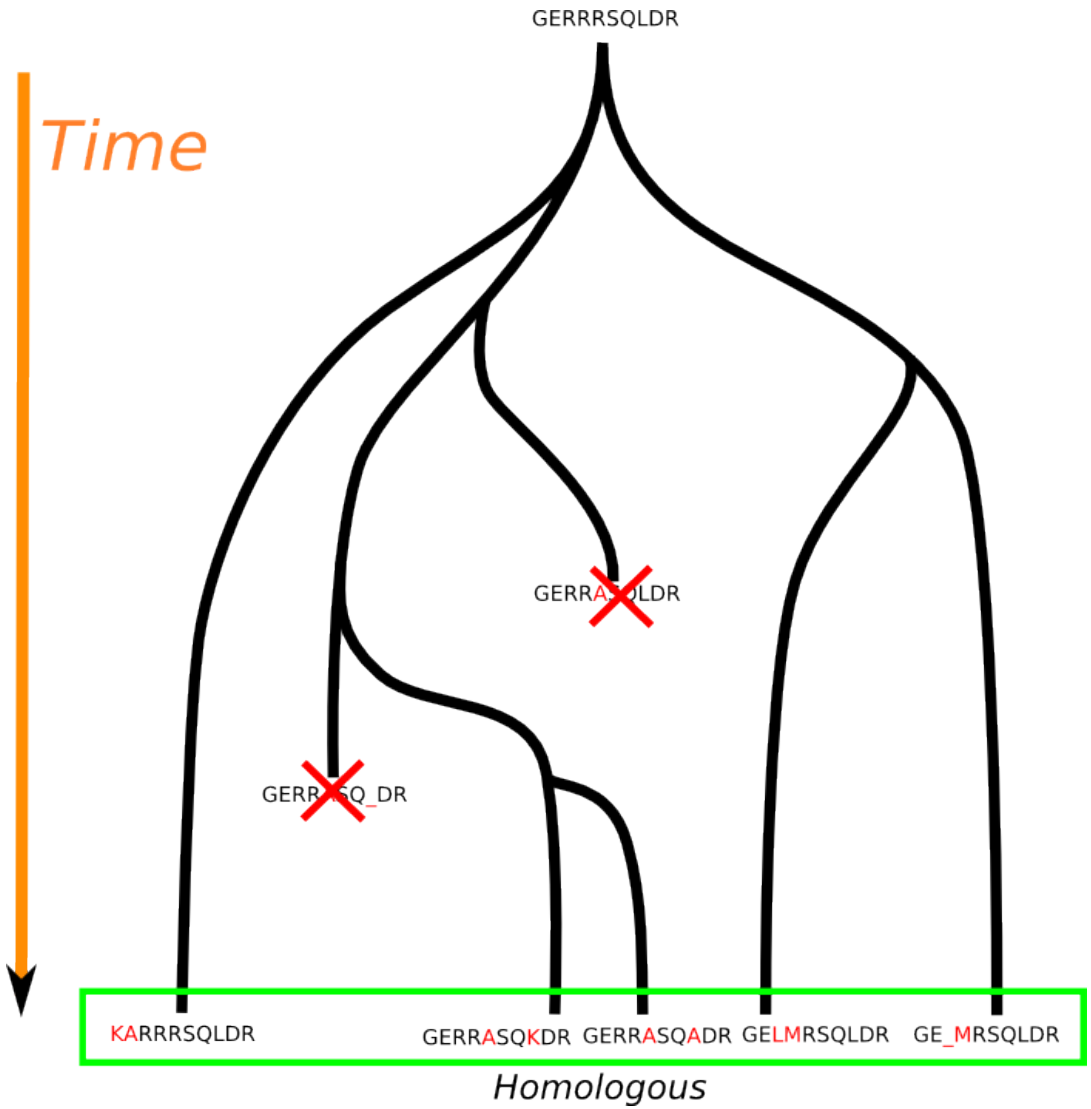

Sequence alignement: algorithm and p-value

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

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

Big data: need for heuristic

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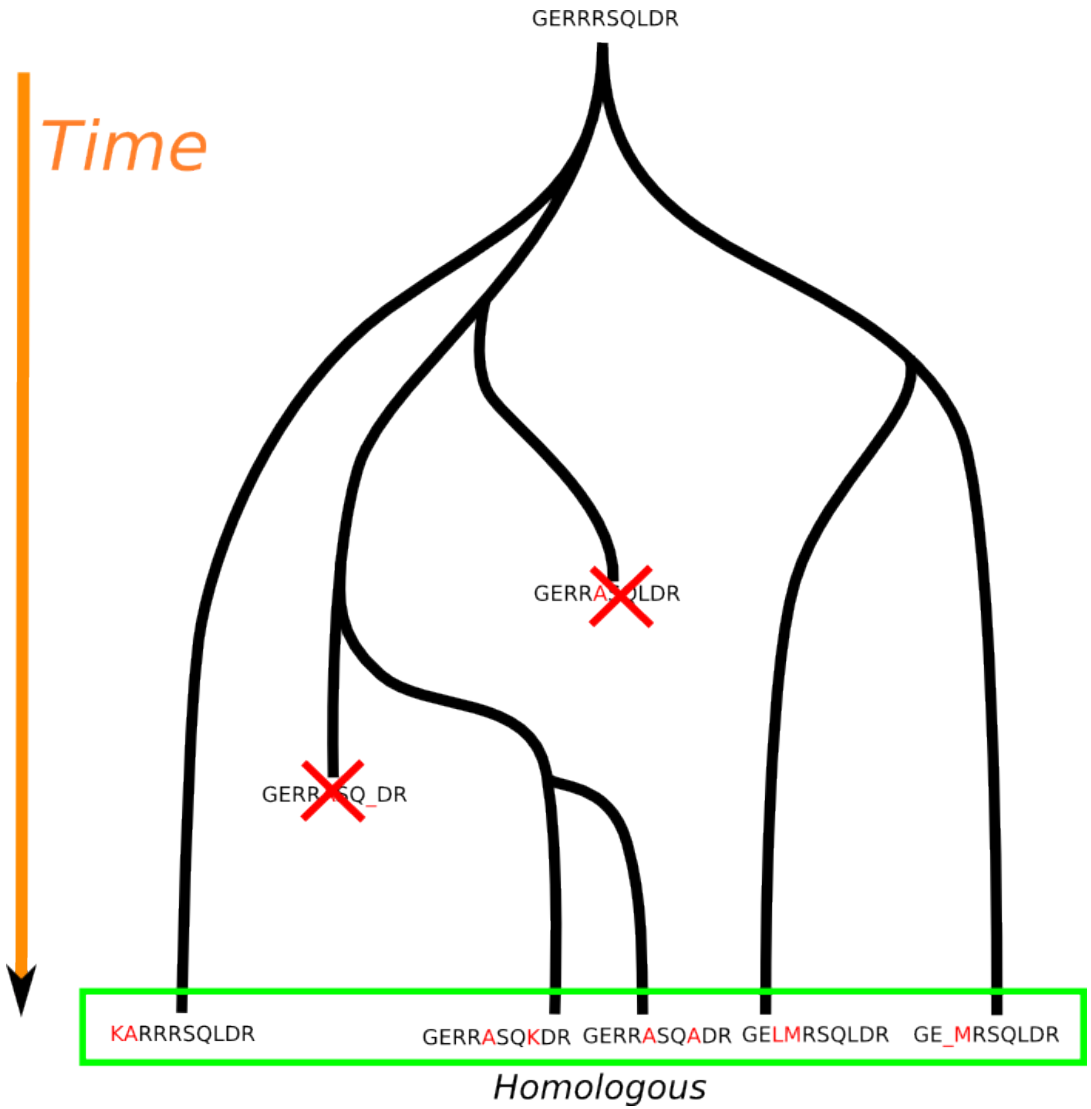
Tools have developed heuristics to filter down the possible target sequences:

- 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



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Aligning the sequences (MSA, multiple sequence alignment):

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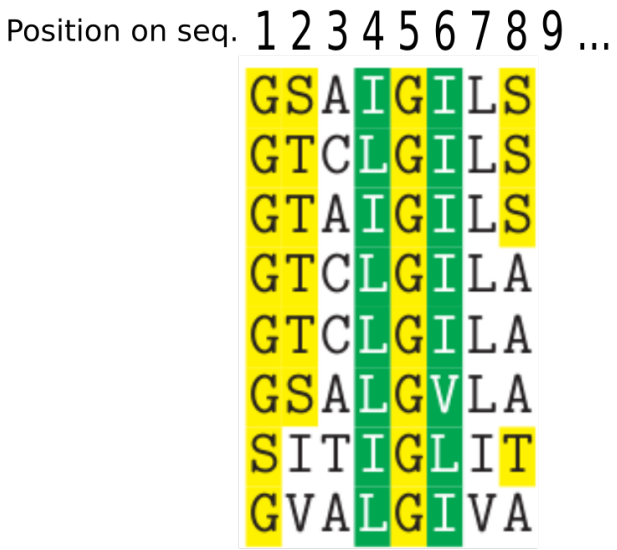
Why some positions are conserved, some other aren't?

Conserved amino acids are essential for the structure/function

From sequence alignment to profile alignments

From an MSA, we can easily build a **probabilistic model** for modelling the sequence of the protein family:



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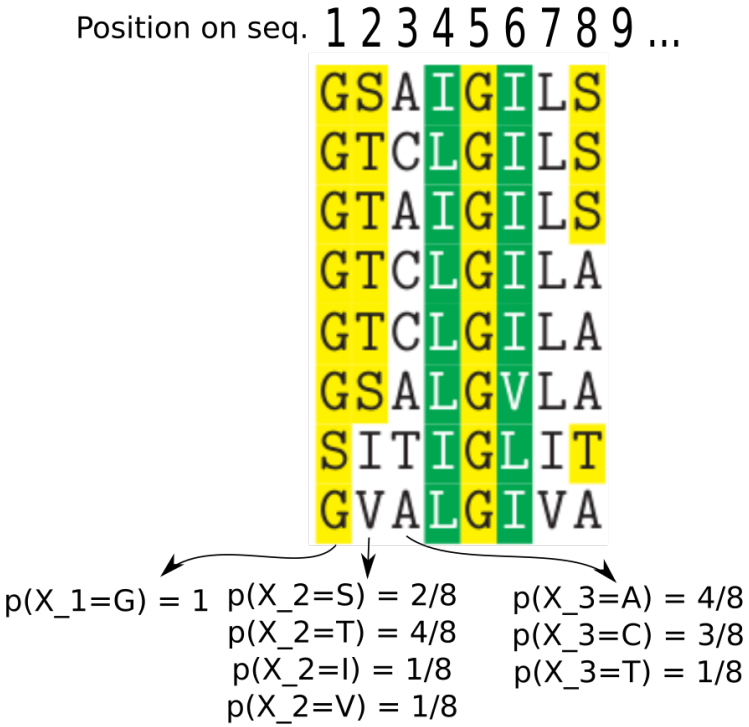

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By assuming independence of positions, one find the best alignment σ that maximizes the likelihood of a given sequence s=GICLGILA:

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This can be solved again using Smith-Waterman algorithm again.
Matching important (=conserved) positions will play an important role in the likelihood $\rightarrow$ it finds homologs with matching conserved regions.

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!