

Computational biology

Sequence-structure-function paradigm

Clovis Galiez



Grenoble

Statistiques pour les sciences du Vivant et de l'Homme

September 23, 2025

Goal

- Get an overview of computational biology topics
 - Topics (genomics, metagenomics, proteomics, etc.)
 - Know basic elements in biology (gene to function)
 - Know some important databases
 - Know standard tools (Blast) and libraries (BioPython)
- Have a basic culture of order of magnitude in computational biology
 - Quantity of data
 - Size of genomes
 - Size of organisms
- Toward autonomy for design and implementation of methods
 - Case study of SNP detection
 - Protein structure prediction

Lecture organization

- Part I: Genomics
 - Session I: some background in biology, starting your project
 - Session II hands-on: development, simulation
 - Session III hands-on: application: database mining, sequence searching

1st Project to be handed-out on the 17th of October.

- Part II: Structure prediction
 - Session I: history and state-of-the-art in protein structure prediction
 - Session II & III hands-on

2nd project to be handed out on the 14th of November

Evaluation: project-based + quizz + bonus for participation

Elements of biology

Why studying biology?

Why studying biology?

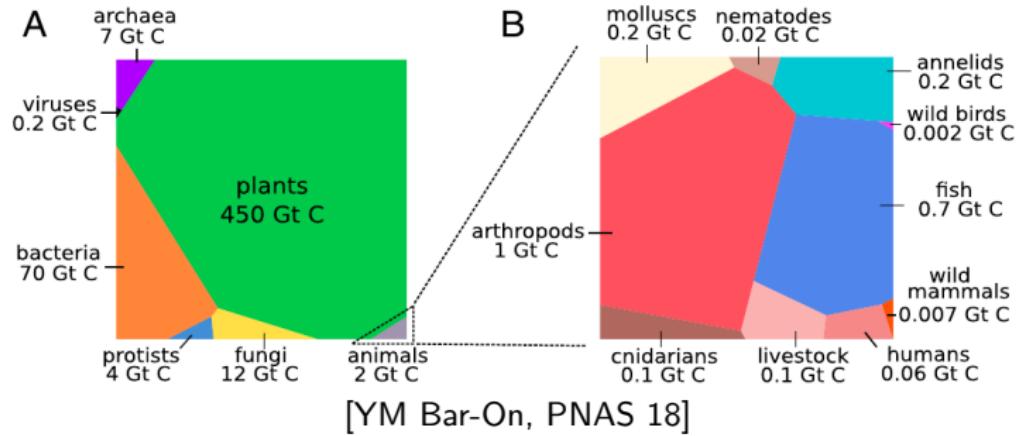
- Just as other sciences: understand the world around us
- For human health: diseases, epidemics, etc.
- For biotech production (e.g. synthesis of materials)
- But also for studying environment

Orders of magnitude: mass repartition

Biology is hardly about humans.

Orders of magnitude: mass repartition

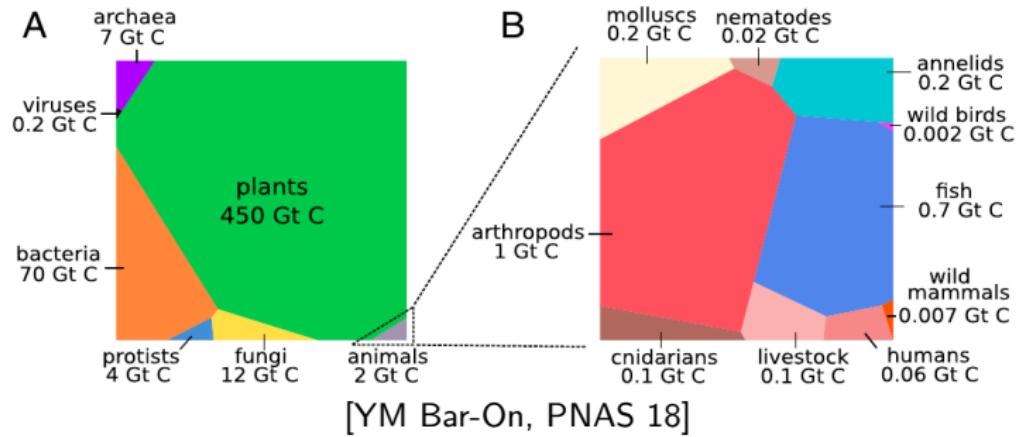
Biology is hardly about humans.



humans $\approx 0.01\%$ global living biomass.

Orders of magnitude: mass repartition

Biology is hardly about humans.



humans $\approx 0.01\%$ global living biomass.

In term of number of entities and biodiversity, microbes are by far the winners.

Tree of life

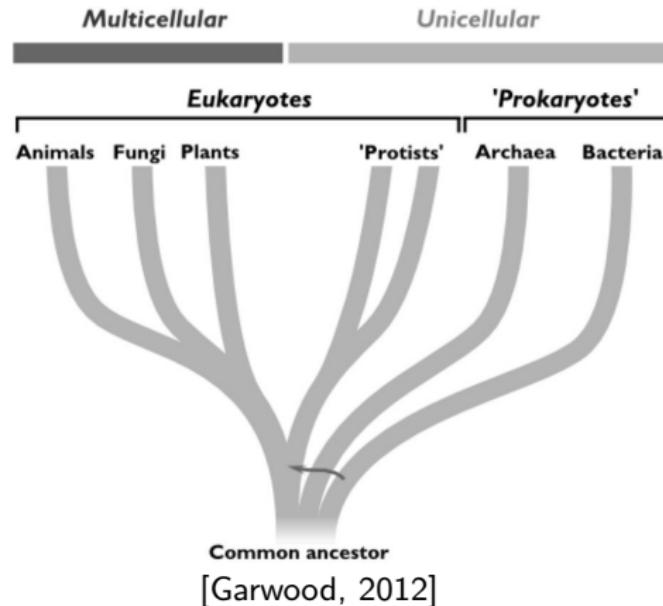
"Nothing in biology makes sense

Tree of life

"Nothing in biology makes sense except in the light of Evolution" T. Dobzhansky

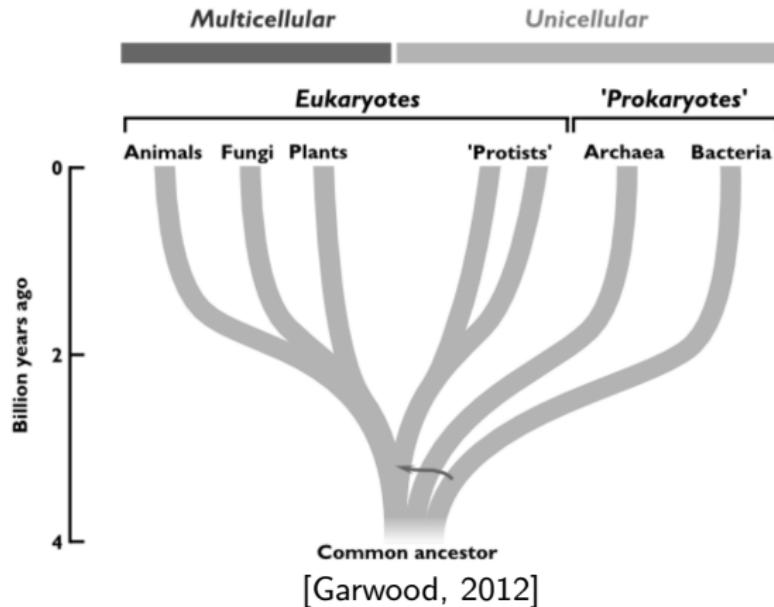
Tree of life

"Nothing in biology makes sense except in the light of Evolution" T. Dobzhansky



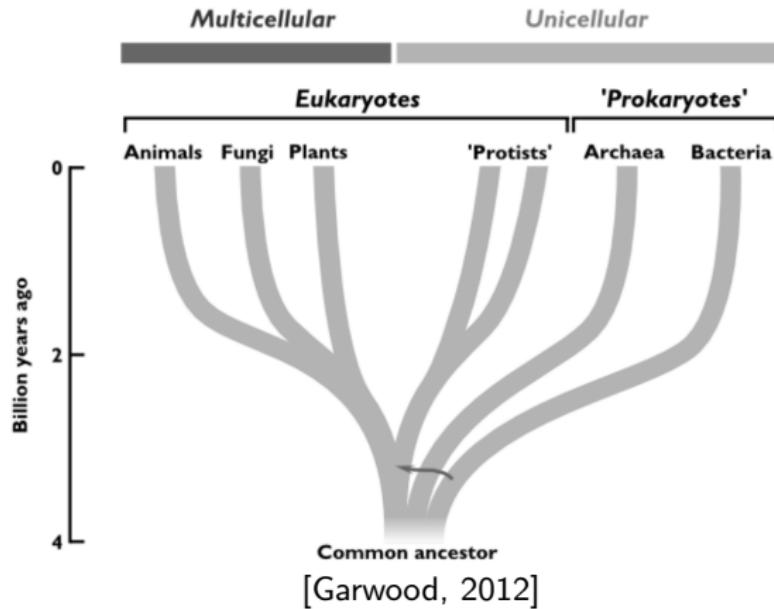
Tree of life

"Nothing in biology makes sense except in the light of Evolution" T. Dobzhansky



Tree of life

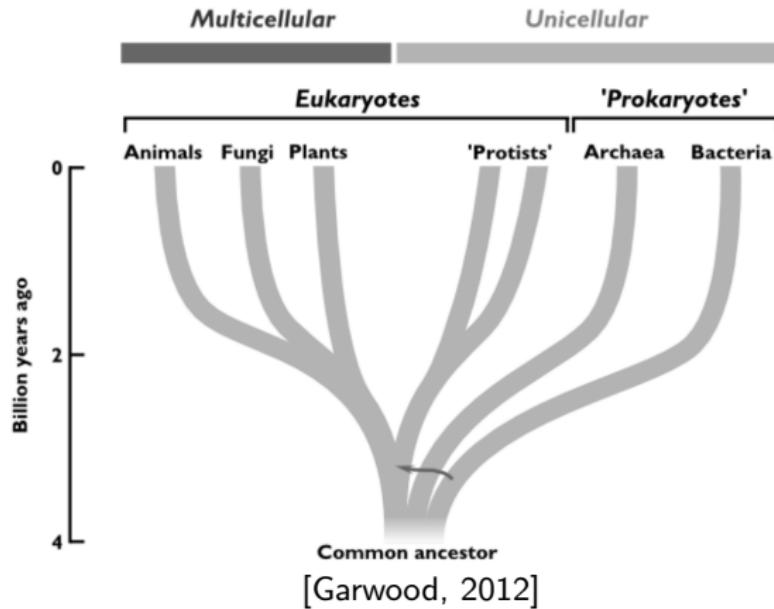
"Nothing in biology makes sense except in the light of Evolution" T. Dobzhansky



When was the split between *Homo* and apes?

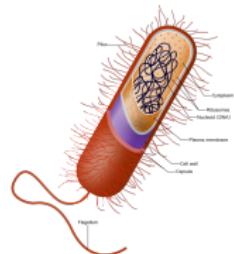
Tree of life

"Nothing in biology makes sense except in the light of Evolution" T. Dobzhansky



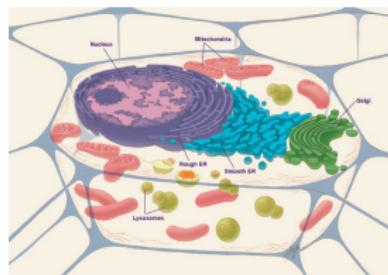
When was the split between *Homo* and apes? $\approx 3M$ y. ago.

Main split: prokaryotes and eukaryotes



Prokaryotes

"Simple", no nucleus



Eukaryotes

Advanced, nucleus

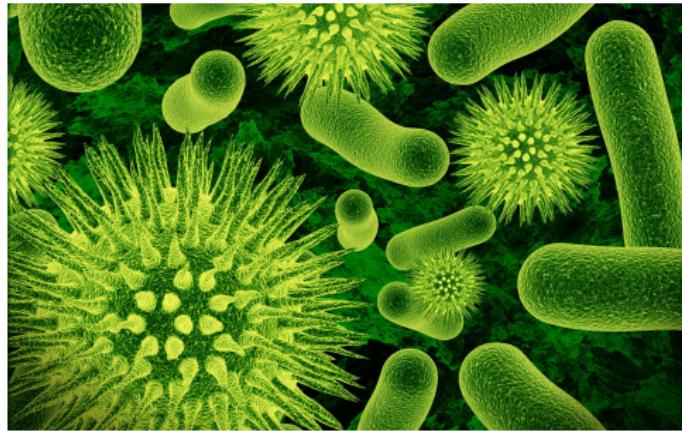
Focus on the microbial world

The microbial world

They are everywhere... they work hard 24h a day... they fight against each other... and they collaborate.

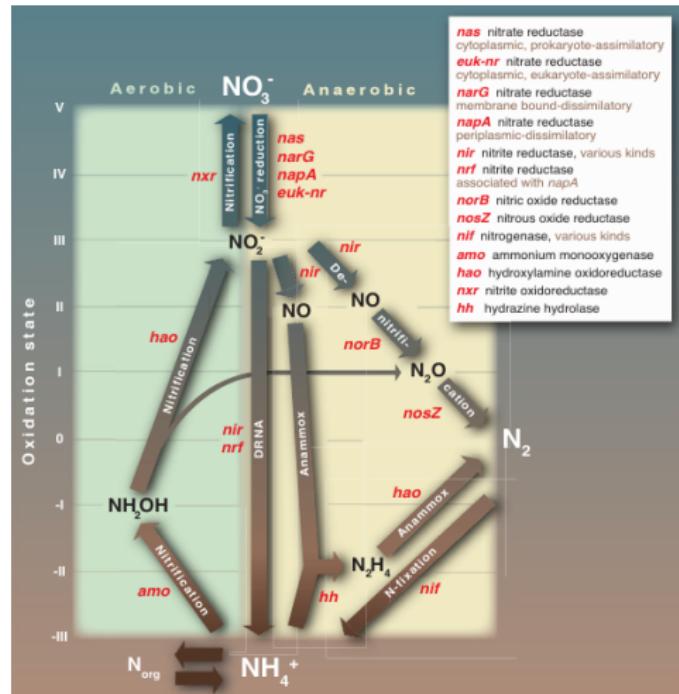
The microbial world

They are everywhere... they work hard 24h a day... they fight against each other... and they collaborate.



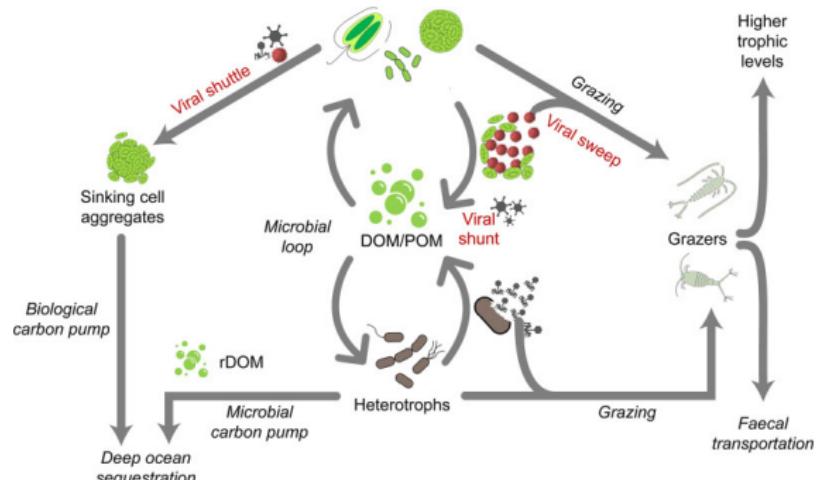
There are very diverse in terms of morphology, mechanisms, and genetics: bacteria, fungus, viruses, picoeukaryotes, etc.

Prokaryotes make nitrogen available for plants



[Canfield et al., Science 2010]

Ocean microbiome pumps CO₂



[Mayers et al., mBio 2023]

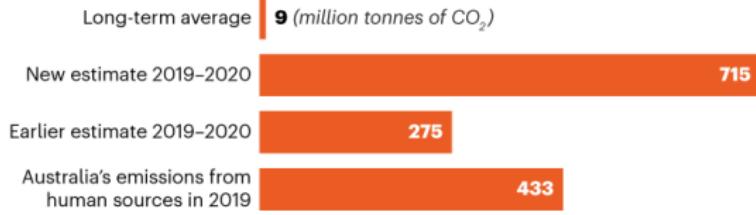
CO₂ turnover: viruses kill 20% of the living biomass in the ocean every day! [Suttle, Nat. Microbiol. 2007]

Microbiomes at swift feedbacks



RECORD EMISSIONS

Devastating fires in southeastern Australia in the summer of 2019–2020 released almost 80 times as much carbon dioxide into the atmosphere as a typical summer bush-fire season.

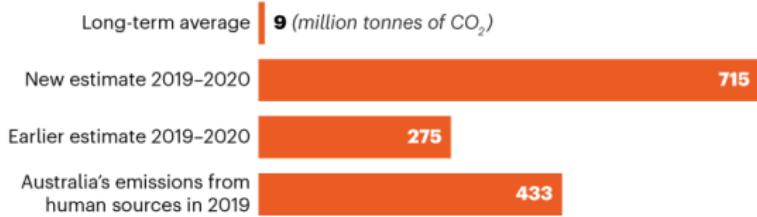


©nature

Microbiomes at swift feedbacks

RECORD EMISSIONS

Devastating fires in southeastern Australia in the summer of 2019–2020 released almost 80 times as much carbon dioxide into the atmosphere as a typical summer bush-fire season.



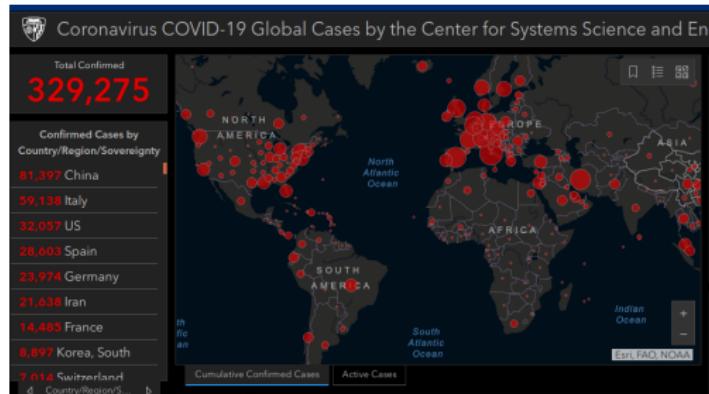
©nature

95% of emitted CO₂ has been pumped down by planktonic bloom.

[Nature 597, 459–460 (2021), Tang et al. Nature (2021)]

Microbes are strongly implied in human health

“Negative” effects:



Covid-19

“Positive” effects:

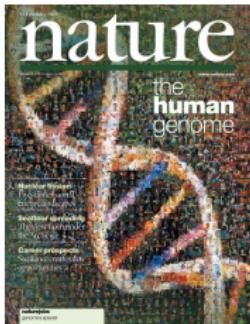


Health status highly correlated with the diversity of the gut microbiome [Valdes et al. 2018]

The human gut microbiome

2000's

Human genome



≈ 20k protein-coding genes

2010's

Gut metagenomes



The human gut microbiome

2000's

Human genome



≈ 20k protein-coding genes

$\xrightarrow{\times 100}$

2010's

Gut metagenomes



≈ 2M protein-coding genes

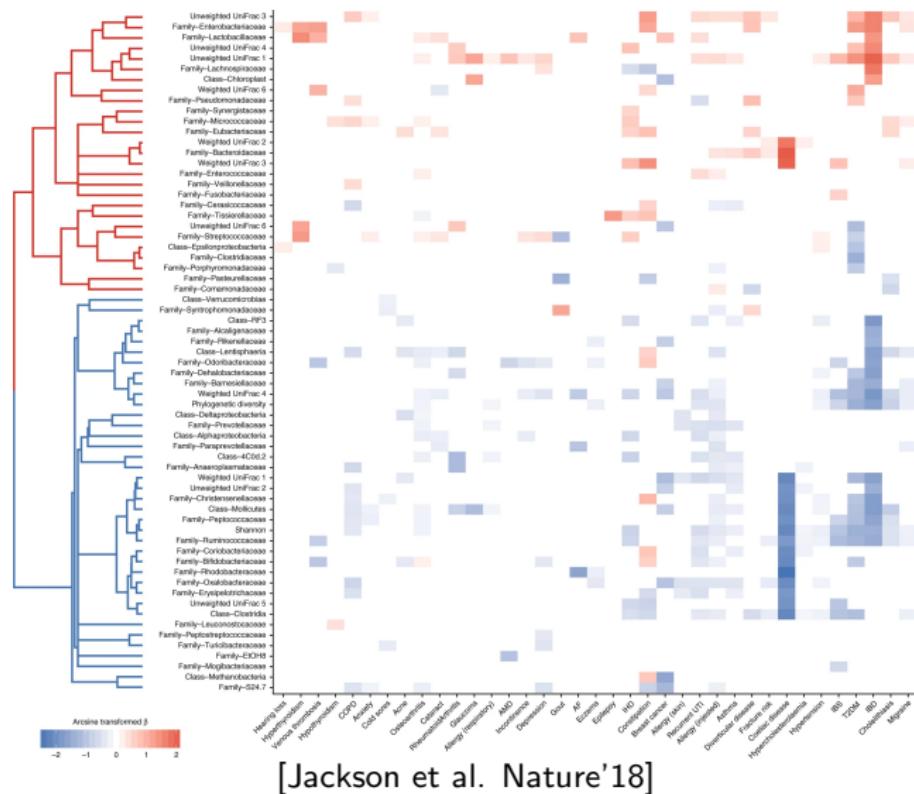
Human gut microbiome is rich! What microbes do there is absolutely necessary to keep alive!

Gut microbiota and higher order diseases: some examples

Some known associations:

- **Autism**
spectrum disorder (ASD), but the underlying mechanisms are unknown. Many studies have shown alterations in the composition of the fecal flora and metabolic products of the gut microbiome in patients with ASD. The gut microbiota influences brain development and behaviors through the neuroendocrine, neuroimmune and autonomic nervous systems. In addition, an abnormal gut microbiota is associated with several diseases, [Li et al. *Front. in Cell. Neur.* 2017]
- Type II diabetes (50 microbial genes → AUC ROC 0.81)
[Qin et al. *Nature* 2012]
- Parkinson's differential abundance of gut microbial species
[Heintz-Buschart et al. *Mov. Disord.* 2018]

Gut microbiota and higher order diseases



How to study living systems?

- A *tiny* fraction of microbes are cultivable in a lab (probably less than few percent).
- Conducting biological/medical experiments is long and costly

How to study living systems?

- A *tiny* fraction of microbes are cultivable in a lab (probably less than few percent).
- Conducting biological/medical experiments is long and costly

How to study them, without observing them in the lab? How to study jointly humans and bacteria?

DNA: a universal way of coding (rather recent knowledge!)

Universal code

All known living organisms are coded through their DNA information. This determines to a large extent their morphologies and functions.

DNA: a universal way of coding (rather recent knowledge!)

Universal code

All known living organisms are coded through their DNA information. This determines to a large extent their morphologies and functions.

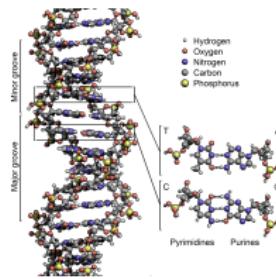
- 1952 Hershey and Chase: DNA is known to encode genetic information

DNA: a universal way of coding (rather recent knowledge!)

Universal code

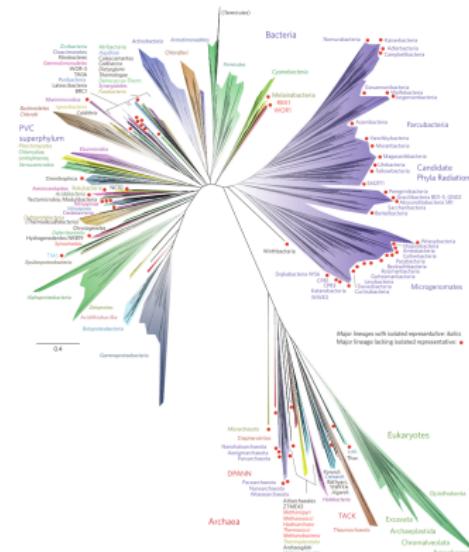
All known living organisms are coded through their DNA information. This determines to a large extent their morphologies and functions.

- 1952 Hershey and Chase: DNA is known to encode genetic information
- 1953 Physical structure (double-helix) of DNA is solved using X-Ray diffraction by Franklin (but that's Watson & Crick who got the awards)



Origins and evolution of micro-organisms

Not a fixed knowledge: **we still continue to discover new branches of life:**

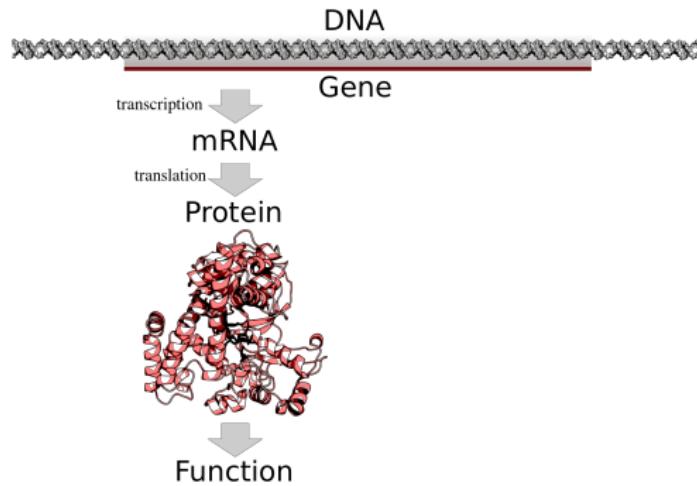


[Hug et al. 2016]

The Candidate Phyla Radiation (top right, in purple) has been discovered in 2016!

How DNA determines an organism?

The big picture (for computer scientists): see video.



Proteins are responsible for most of the biological functions in organisms (biochemical reactions (enzymes), nutrient transportation, structural proteins, etc.)

Sequence-structure-function paradigm

Studying biological function through DNA information

From an organism to its **genome**...



Organism

Studying biological function through DNA information

From an organism to its **genome**...



Organism



DNA

Studying biological function through DNA information

From an organism to its **genome**...



Organism



DNA



Illumina/Nanopore

Studying biological function through DNA information

From an organism to its **genome**...



Organism



DNA



Illumina/Nanopore



A vertical stack of several lines of text representing DNA sequence data. The text is composed of four-letter combinations (A, T, C, G) representing the four nucleotide bases. The lines are slightly offset vertically for readability.

100's bp - few kbp

Studying biological function through DNA information

From an organism to its **genome**...



Organism



DNA



Illumina/Nanopore



Genomes



few kbp - few Gbp

A grid of blue text representing DNA sequence data, showing several lines of sequence such as ATTCGA, GACTACGGCGAT, and CTTAGACTACGACGGAT.

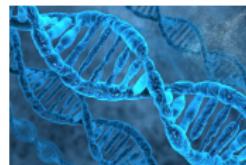
100's bp - few kbp

Studying biological function through DNA information

From an organism to its **genome**...



Organism



DNA



Illumina/Nanopore



Genomes



few kbp - few Gbp

A grid of DNA sequence data represented by a grid of colored squares (A, T, C, G) corresponding to the sequence ATTCGAACTACGGCGNAGATCTGTGCAGCTGNCTAGACTACAGACGGATACTACGGCGATCTACGATCTGTGCAGCTGATCTACGACGTTATCGT.

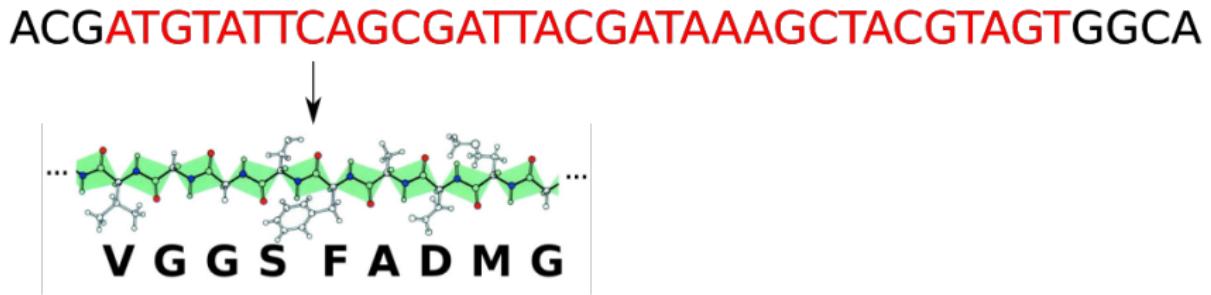
100's bp - few kbp

How does it help?

Bioinformatics: from genome to function

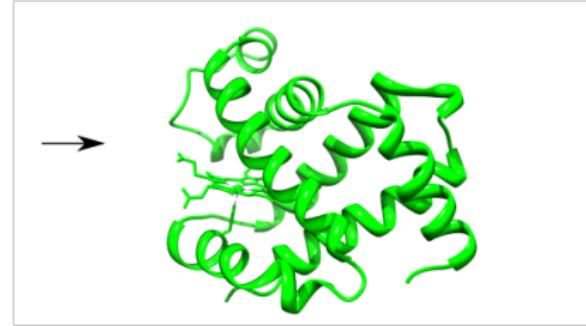
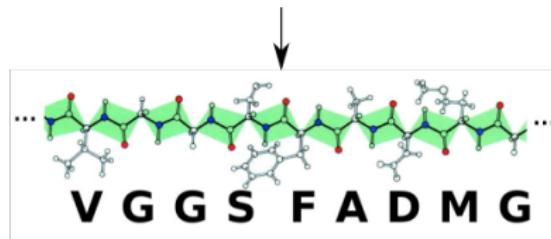
ACGATGTATTCA
GCGATTACGATAAAGCTACGTAGTGGCA

Bioinformatics: from genome to function



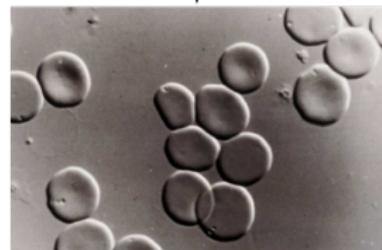
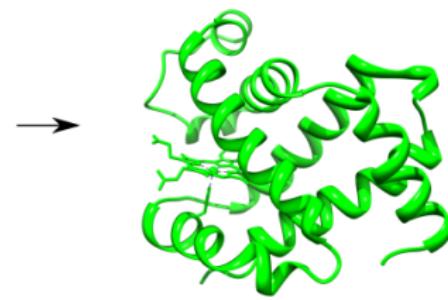
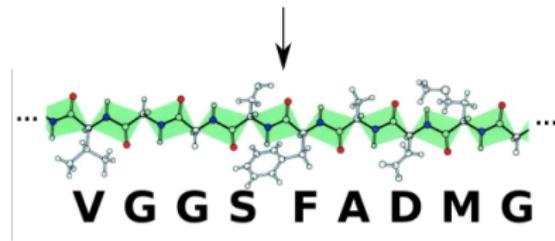
Bioinformatics: from genome to function

ACG**ATGTATT**CAGCGATTACGATAAAGCTACGTAGT**GGCA**



Bioinformatics: from genome to function

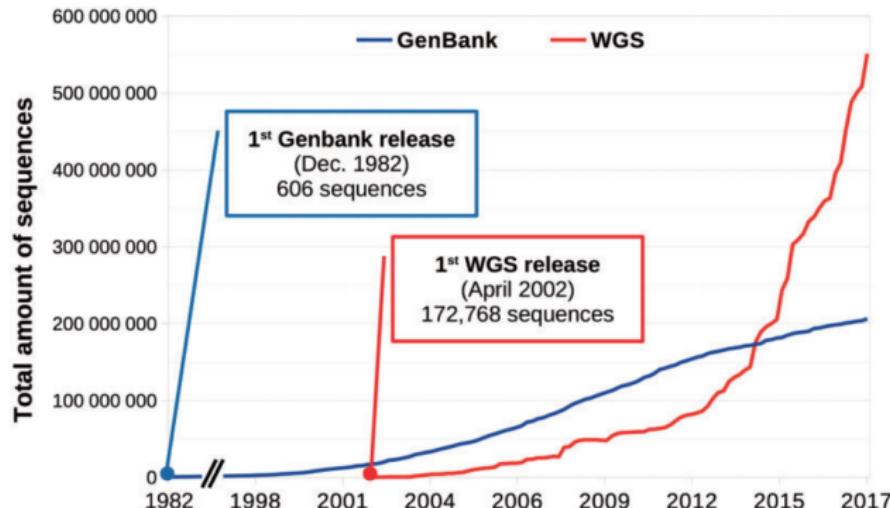
ACG**ATGTATTCA**GCAGATTACGATAAAGCTACGTAGT**GGCA**



O₂ transport

Genomics, the first breakthrough

1977: first DNA sequencer.

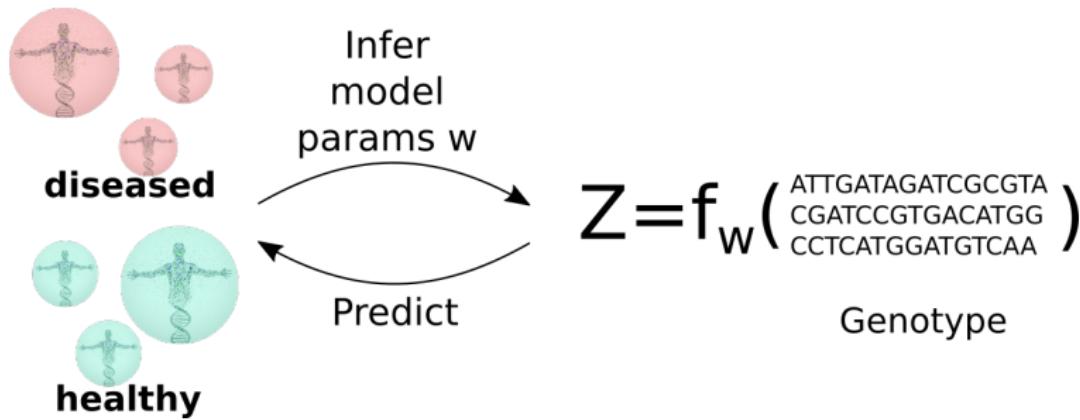


You can now sequence a human cell for less than a thousand euros.

What to do with these DNA sequences?

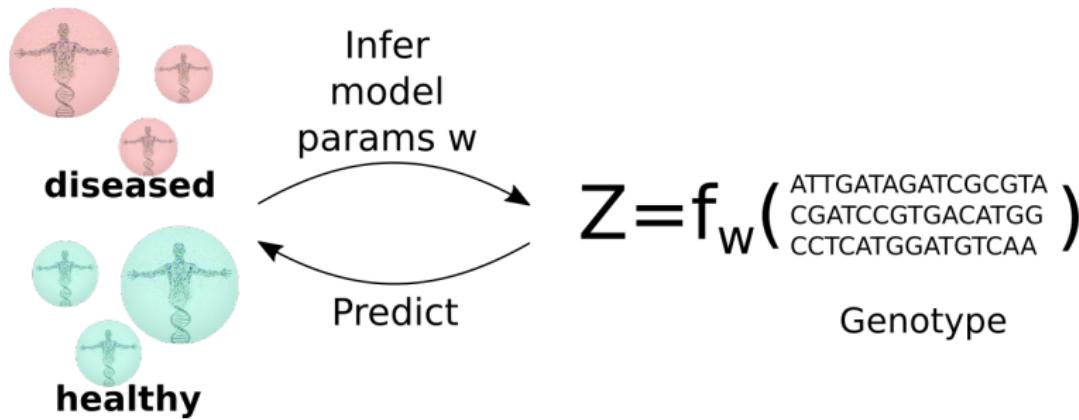
Example: association studies

Relates the variation of the genome to the phenotype. Recent review
[Uffelmann et al. 2023]



Example: association studies

Relates the variation of the genome to the phenotype. Recent review
[Uffelmann et al. 2023]



Define a predictor $f : \{A, T, C, G\}^M \rightarrow [0, 1]$ such that it minimizes a *loss* on a training set $(\vec{x}_1, z_1), \dots, (\vec{x}_N, z_N)$:

$$\min_f - \sum_{i=1}^N z_i \cdot \log f(\vec{x}_i) + (1 - z_i) \cdot \log(1 - f(\vec{x}_i))$$

Lots of data is not just for fun!

Human genome: what size? 1 Kbp? 10 Mbp?

Lots of data is not just for fun!

Human genome: 3Gbp.

Lots of data is not just for fun!

Human genome: 3Gbp.

With $f : \{A, T, C, G\}^M \rightarrow [0, 1]$, the theoretical number of input possibilities is:

Lots of data is not just for fun!

Human genome: 3Gbp.

With $f : \{A, T, C, G\}^M \rightarrow [0, 1]$, the theoretical number of input possibilities is:

$$4^{3 \cdot 10^9} =$$

Lots of data is not just for fun!

Human genome: 3Gbp.

With $f : \{A, T, C, G\}^M \rightarrow [0, 1]$, the theoretical number of input possibilities is:

$$4^{3 \cdot 10^9} = 10^{1806179974} \text{ possibilities :-/}$$

Lots of data is not just for fun!

Human genome: 3Gbp.

With $f : \{A, T, C, G\}^M \rightarrow [0, 1]$, the theoretical number of input possibilities is:

$$4^{3 \cdot 10^9} = 10^{1806179974} \text{ possibilities :-/}$$

In practice, one “reference genome” and “only” $\approx 88 \cdot 10^6$ possible mutation places [The 1000 Genomes Project Consortium, 2015] .

Which mutation is responsible for a specific disease?

Lots of data is not just for fun!

Human genome: 3Gbp.

With $f : \{A, T, C, G\}^M \rightarrow [0, 1]$, the theoretical number of input possibilities is:

$$4^{3 \cdot 10^9} = 10^{1806179974} \text{ possibilities :-/}$$

In practice, one “reference genome” and “only” $\approx 88 \cdot 10^6$ possible mutation places [The 1000 Genomes Project Consortium, 2015] .

Which mutation is responsible for a specific disease?

Better with **more** data... and fine statistics.

Scope of applications for DNA sequence data

Computationally processing DNA sequences has a huge number of applications, in particular in the fields of:

Scope of applications for DNA sequence data

Computationally processing DNA sequences has a huge number of applications, in particular in the fields of:

-  clinics

Scope of applications for DNA sequence data

Computationally processing DNA sequences has a huge number of applications, in particular in the fields of:

-  clinics
-  ecology

Scope of applications for DNA sequence data

Computationally processing DNA sequences has a huge number of applications, in particular in the fields of:

-  clinics
-  ecology
-  biochemistry

Scope of applications for DNA sequence data

Computationally processing DNA sequences has a huge number of applications, in particular in the fields of:

-  clinics
-  ecology
-  biochemistry

...and sometimes involving the three at the same time!

Artificial intelligence, second and recent breakthrough

Since 2021

Protein structure predictions (from DNA sequence) reached an accuracy equal to X-Ray crystallography using deep neural networks.

So now, using easy accessible DNA information, biologists can predict how protein interact with other compounds, and get more insight of the functions of the genes.

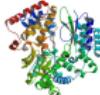
Biology from the data perspective: not only DNA!

Biology brings various types of data, to get insights on various questions:

- Sequences **ATTCAGTACAT**
 - (Meta)Genomic: DNA sequence of one (several) organism

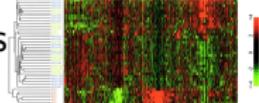
Biology from the data perspective: not only DNA!

Biology brings various types of data, to get insights on various questions:

- Sequences **ATTCAGTACAT**
 - (Meta)Genomic: DNA sequence of one (several) organism
- Protein structures 
 - X-Ray or NMR structures
 - New: computationally resolved structures

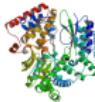
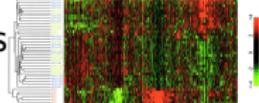
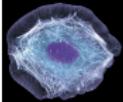
Biology from the data perspective: not only DNA!

Biology brings various types of data, to get insights on various questions:

- Sequences **ATTCAGTACAT**
 - (Meta)Genomic: DNA sequence of one (several) organism
- Protein structures 
 - X-Ray or NMR structures
 - New: computationally resolved structures
- Abundances 
 - Marker gene/species abundance
 - Expression level of genes

Biology from the data perspective: not only DNA!

Biology brings various types of data, to get insights on various questions:

- Sequences **ATTCAGTACAT**
 - (Meta)Genomic: DNA sequence of one (several) organism
- Protein structures 
 - X-Ray or NMR structures
 - New: computationally resolved structures
- Abundances 
 - Marker gene/species abundance
 - Expression level of genes
- Images 
 - Neuroimaging
 - Cell imaging
- Mass spectrometry
- ...

Two reasons pushing computational biology forward

Computational biology

Biological data coupled with
statistical models, machine learning, data visualization.

Two reasons pushing computational biology forward

Computational biology

Biological data coupled with
statistical models, machine learning, data visualization.

- Availability of data
- Computing capacities

Hands-on

!ALERT! Salmonella OUTBREAK



Breaking news

Bad infections kill many people. Antibiotics do nothing.

Hands-on in two parts, you will develop tools to:

- Identify responsible gene
- Model the 3D structure of the involved protein

Disclaimer

- **No fully guided syllabus**
- Act as a junior professional
 - Analyze provided information, think of a solution
 - Ask/discuss with your colleagues
 - Ask/discuss with your senior colleague (me)

Plan of this session

First, think and plan - 1h.

- Skim the context in the `hands-on/session1` on the git (15 min)
- Try to understand individually the work you will have to do and write down questions you have (10 min)
- Share your understanding with people in your group (10 min)
- We share together our understanding and elaborate a common strategy (20 min).

Then start developing - till the end :).

- Start developing T1, paying attention to pitfalls (noise in the data in particular)
- Build your own tests. You can make use of the data in the `hands-on/reference-data` directory

Genomics

From DNA to **reads**...



DNA



Illumina



reads ($\sim 250\text{bp}$)

$$\eta_{err} \approx 1\%$$

Genomics

From DNA to **reads**...



DNA



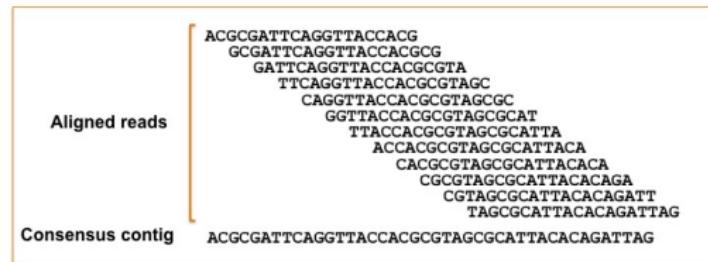
Illumina



reads ($\sim 250\text{bp}$)

$$\eta_{err} \approx 1\%$$

Assembly: from reads to **contigs**:



Sequencing data

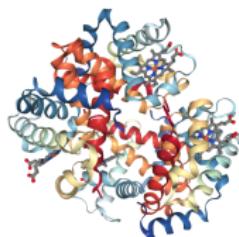
Two leading technologies:

- Illumina: pieces of sequences (called **reads**, 150-250bp)
 - +: reliable, about 1% sequencing errors.
 - -: short reads, only have local view of the genome
 - Errors: rare (1 over 200 bases) almost uniformly distributed, almost all **mutations**.
- Nanopore: long reads, 10kb-100kb
 - +: long reads, easy to assemble, cheap and portable
 - -: high error rate
 - Errors: mostly insertion-deletion, mostly homopolymers (e.g. AAAAA)

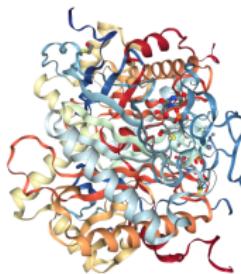


Predict the structure from sequence: the data

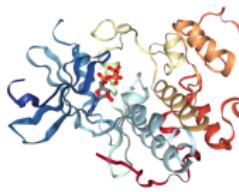
```
>1A3N:A|PDBID|CHAIN|SEQUENCE  
VLSPADTKNVKAANGKVGAAHGEYGAALER  
MPLSFPTTKTYFPHFDSLHSQAVKGHGKKV  
ADALTNAAVAHVDDMPNALSDSLHAKLRLV  
DPVNFKLLSHCLVTLA AHLPAEFTPAVHAS  
LDKFPLASVSTVLTSKYR
```



```
>1HXP:A|PDBID|CHAIN|SEQUENCE  
MTQFNPNVDPHPHRRYNPFLTQWNLIVSPHRAKRWP  
EGAQETTPAKQVLPAHDPPDCFLCAGNVVRTGDKN  
PDYTGTTFPTNDPAALMSDTPDAPESHDPLMR  
QSAROTTSRVICSPDITKTLPELSVAALTEIVK  
TWQEQTEAELGKTYPFWVQVEENKAAMGCSNPHP  
HQGIWANSFLPKNEAEREDRLQKEYFAEQKSPML  
VDYVQRELADGSRTVVETEHNLAVVPVWAAMPF  
ETLLLPPKAHVRLIRITDLTDAQRSDLALAKKLTS  
RYDNLPQCSPYNSMGWHGAPFNGEEENQHNWLQHA  
HYFPPLRLSATVTRKFMVGYEMLAETQRDLTAEQ  
AAERLRAVSDIHPRESGV
```



```
>1HCK:A|PDBID|CHAIN|SEQUENCE  
MENFOKEVKIGEGTYGVYKARNKLTGEVVAL  
KKIRLDTEKTEGPVSTAIREISLNLKELNHIPNIV  
KLLDVINTENKLYLWFEFLHQDJKKFMDSAL  
TGIPPLPLIKSYLPQLLQGLAFCHSHRVHLHRDL  
KPNQNLINTEGAIKLLADPGLARARAFGVPVRYYT  
HEVVTLYWRAPEIILGGCKYYSSTAVDIWSLGCY  
FAEMVTRRALPFGOSEIDQDLFRIFRTLGTGDE  
VWWPGVTSMPDYKPSFPKWARQDFSKVVPPLD  
EDGRSLLSQMLHYDPNKRISAKAALAHPPFFQ  
VTKPVPHRLR
```



CASP competition

Blind competition. Simple principle:

- a sequence is given
- have to predict the structure.

CASP competition

Blind competition. Simple principle:

- a sequence is given
- have to predict the structure.

13th CASP...

... AI wins !

Google's DeepMind

