Computational biology

Sequence-structure-function paradigm

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Statistiques pour les sciences du Vivant et de l'Homme

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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 27th 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 15th of December

Evaluation: project-based + 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.

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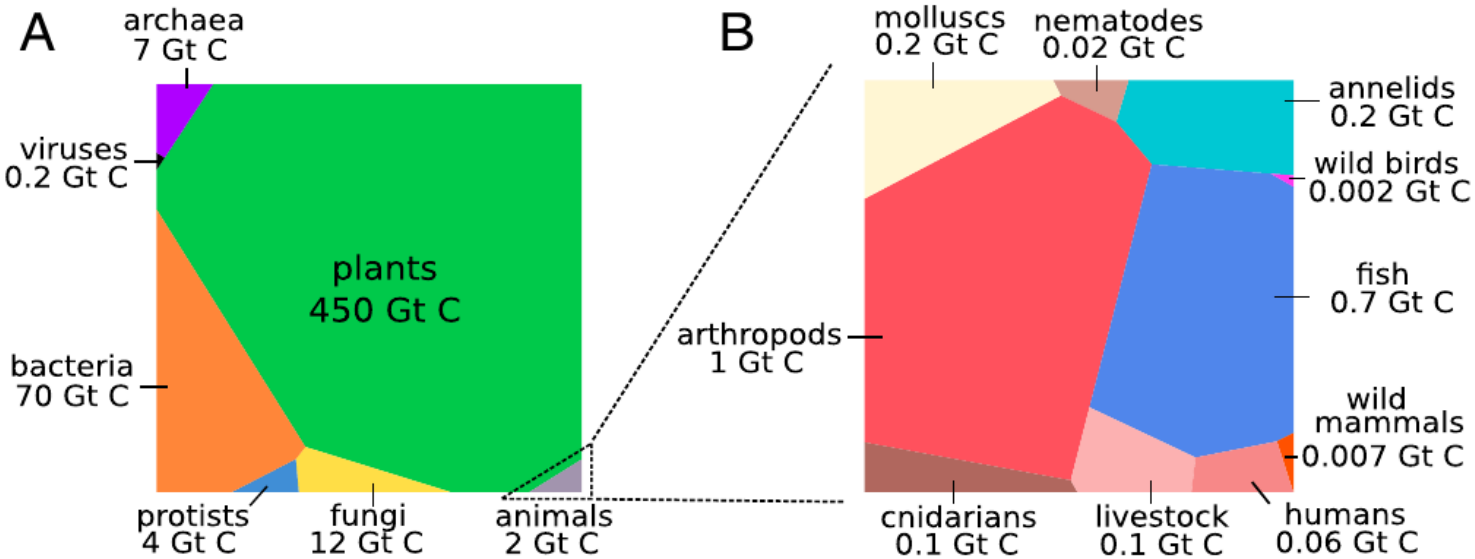

[YM Bar-On, PNAS 18]

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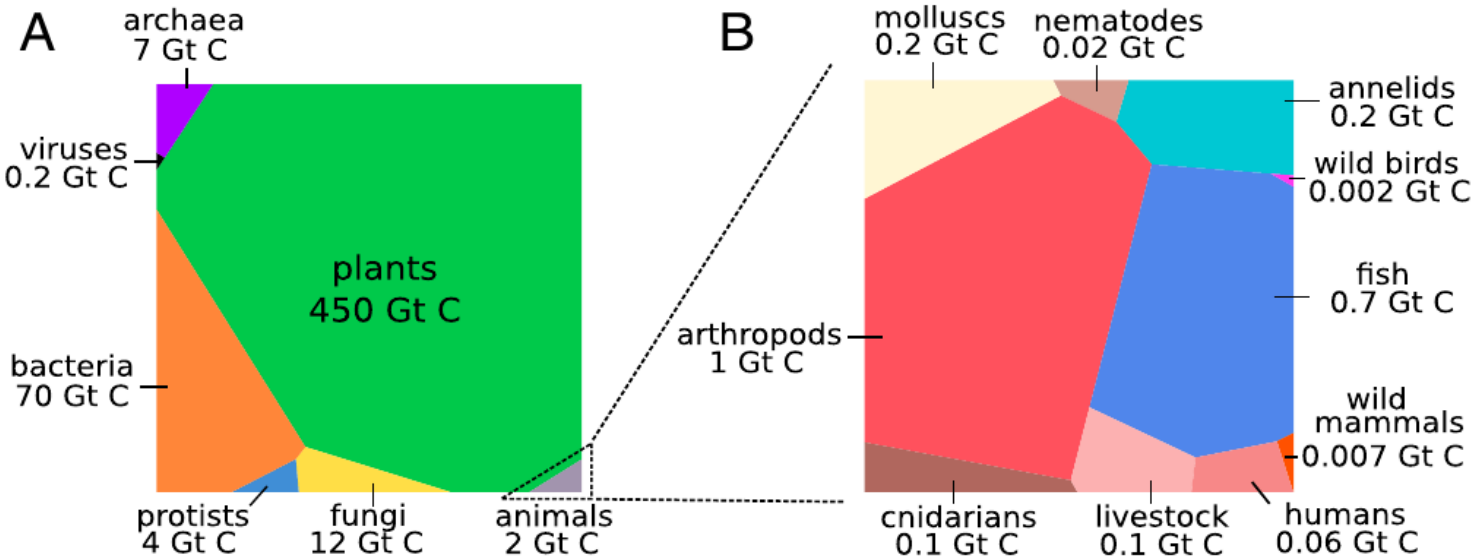

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But in term of number of entities and biodiversity, microbes are by far the winners.

Tree of life

"Nothing in biology makes sense

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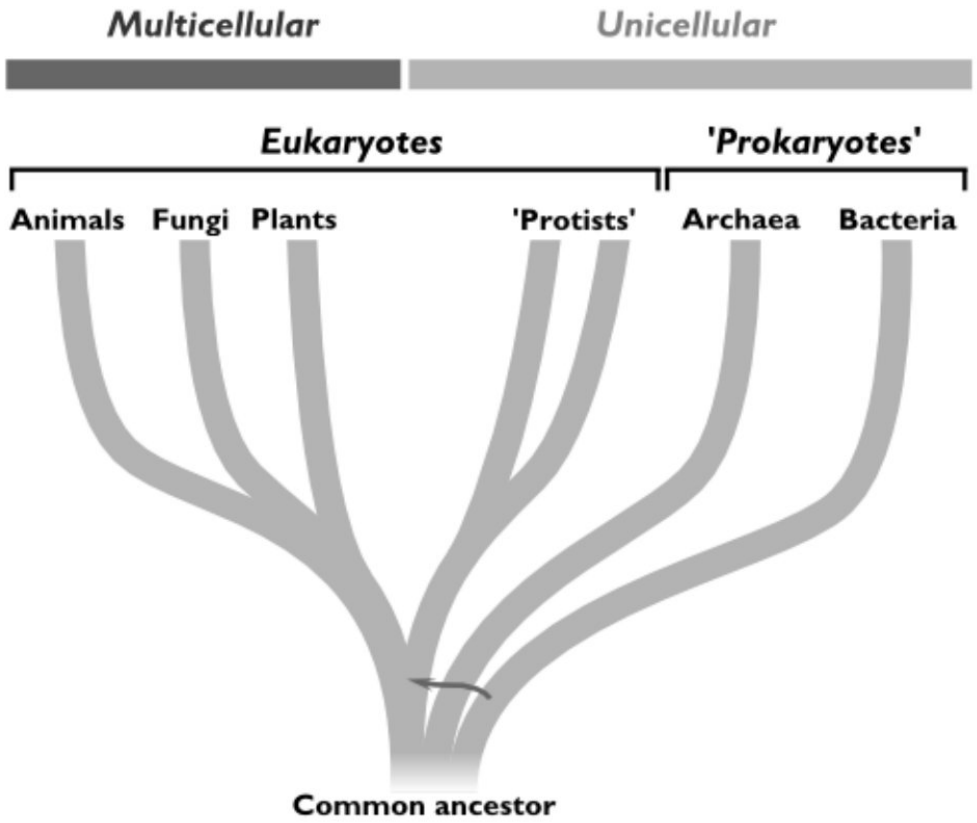

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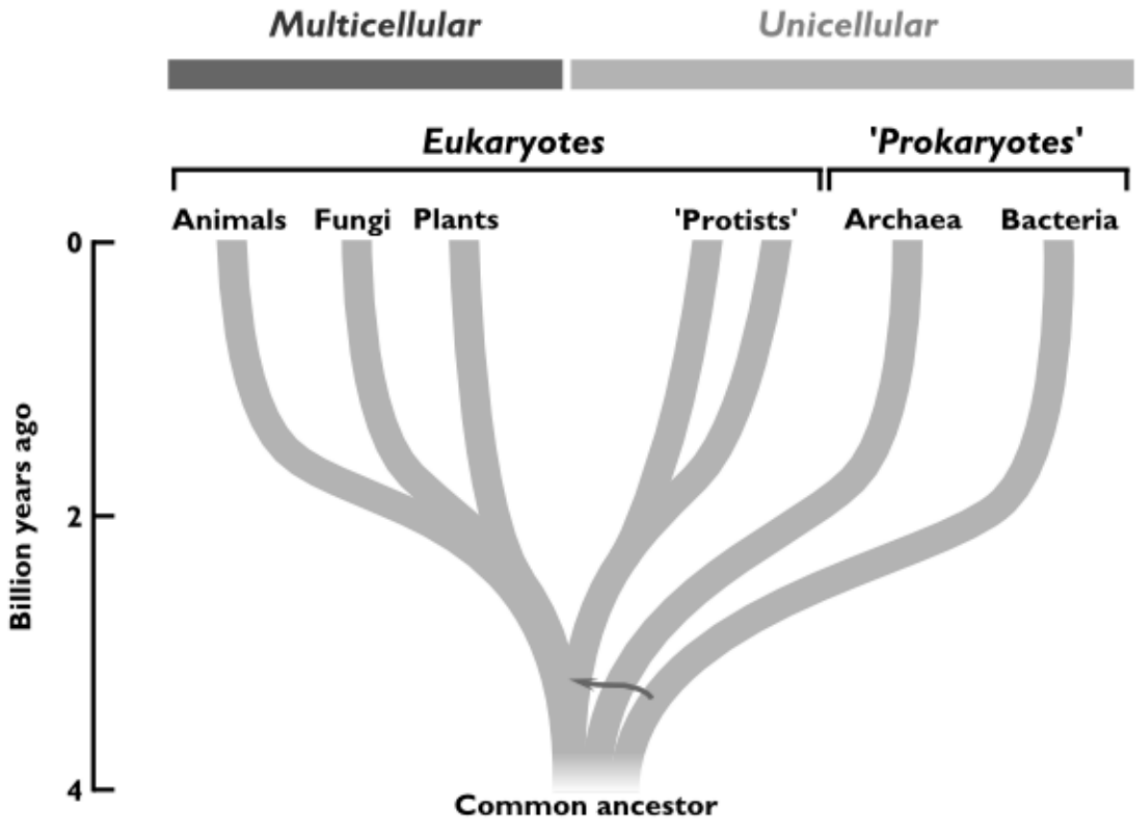

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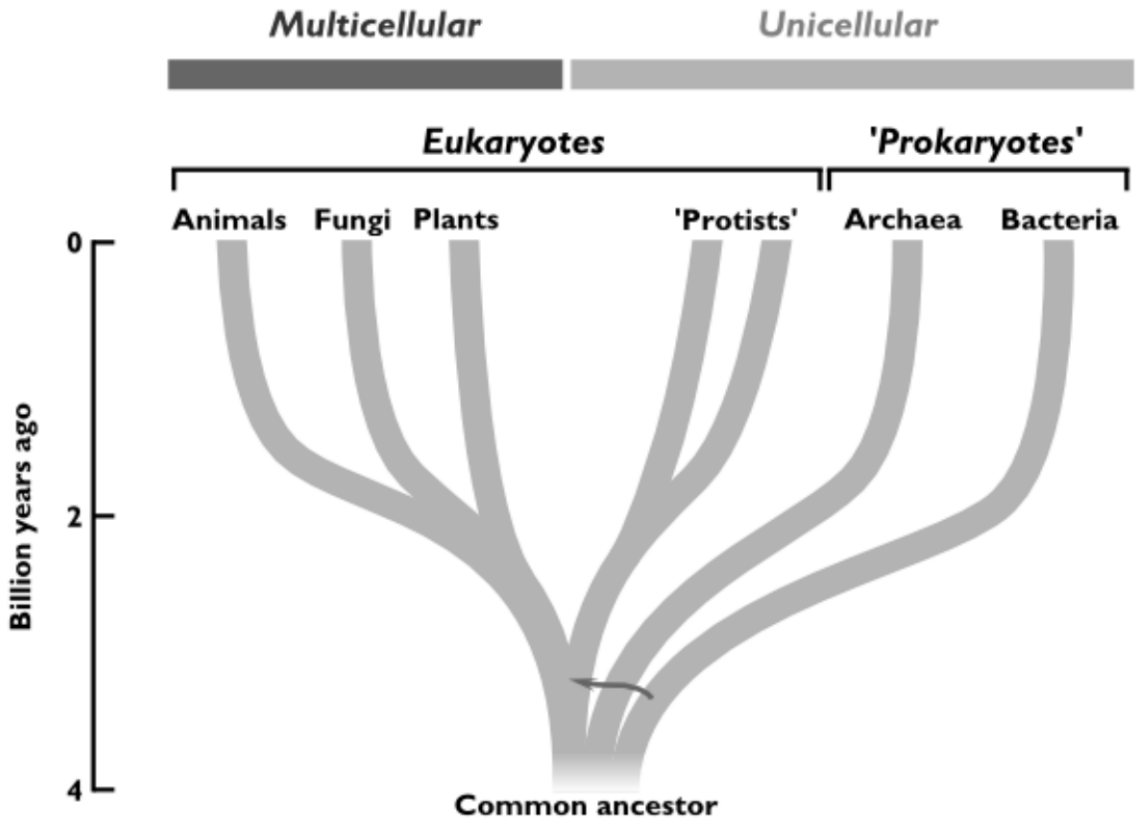

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When was the split between *Homo* and apes?

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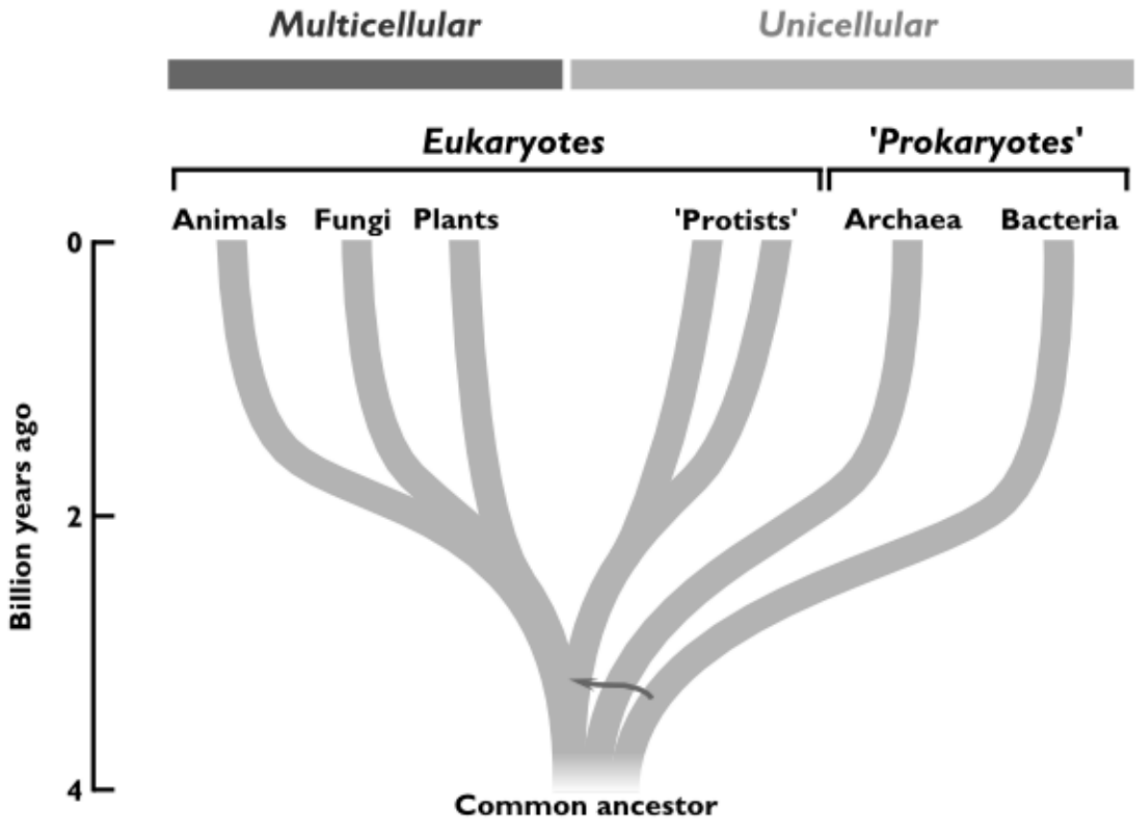

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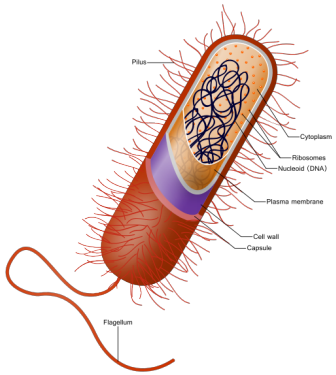
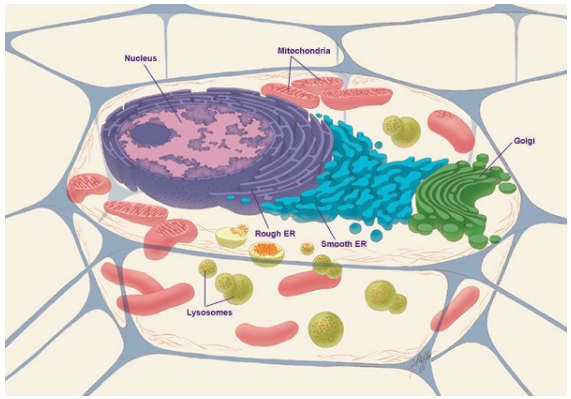
When was the split between *Homo* and apes? $\approx$ 3M y. ago.

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.

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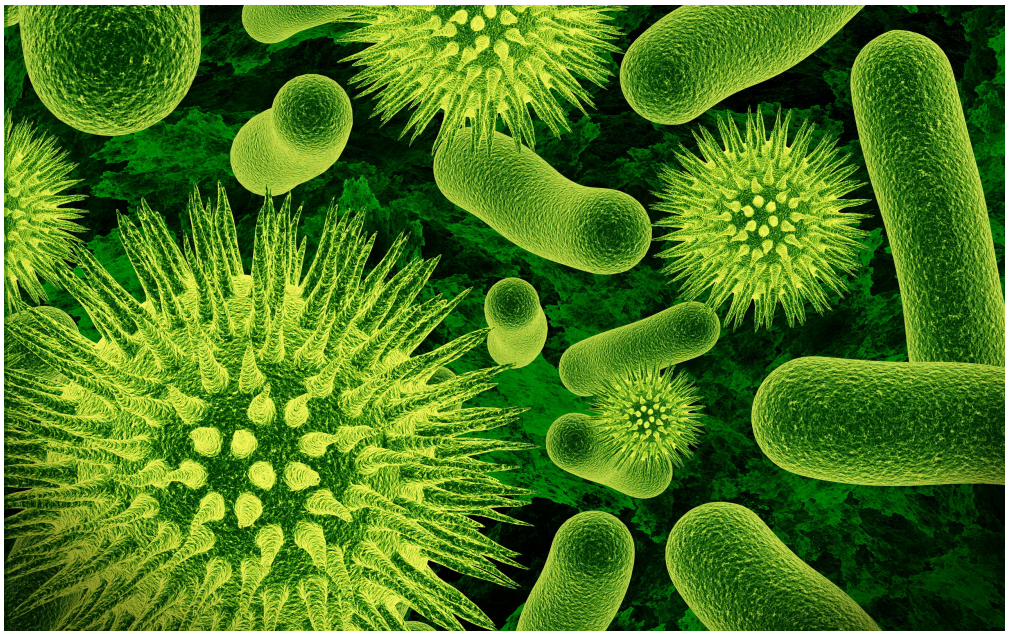
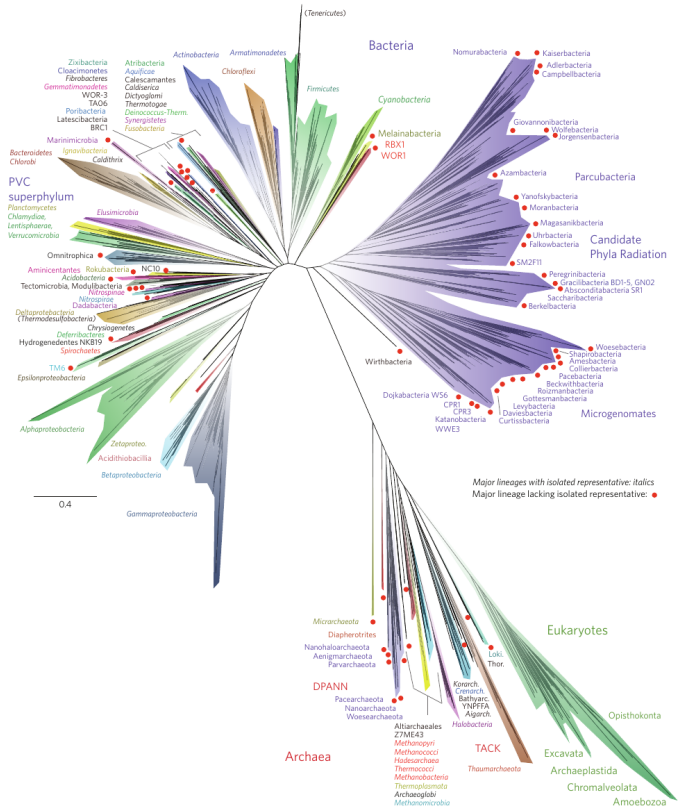


There are very diverse in terms of morphology, mechanisms, and genetics: bacteria, fungus, viruses, picoeukaryotes, etc.

Origins and evolution of micro-organisms

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



[Hug et al. 2016]

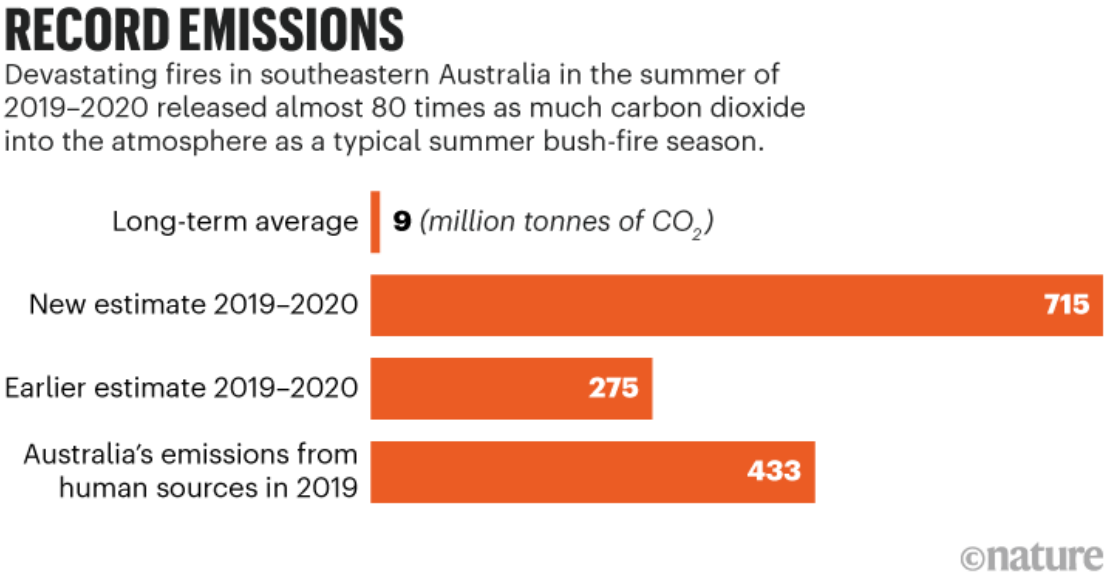
The Candidate Phyla Radiation (top right, in purple) has been discovered in 2016!

Microbiome importance in biogeochemical cycles

Nitrogen cycle [Canfield et al., Science 2010]

CO_2 turnover: viruses kill 20% of the living biomass in the ocean every day! [Suttle, Nat. Microbiol. 2007]

A recent example: Wildfires in Autralia



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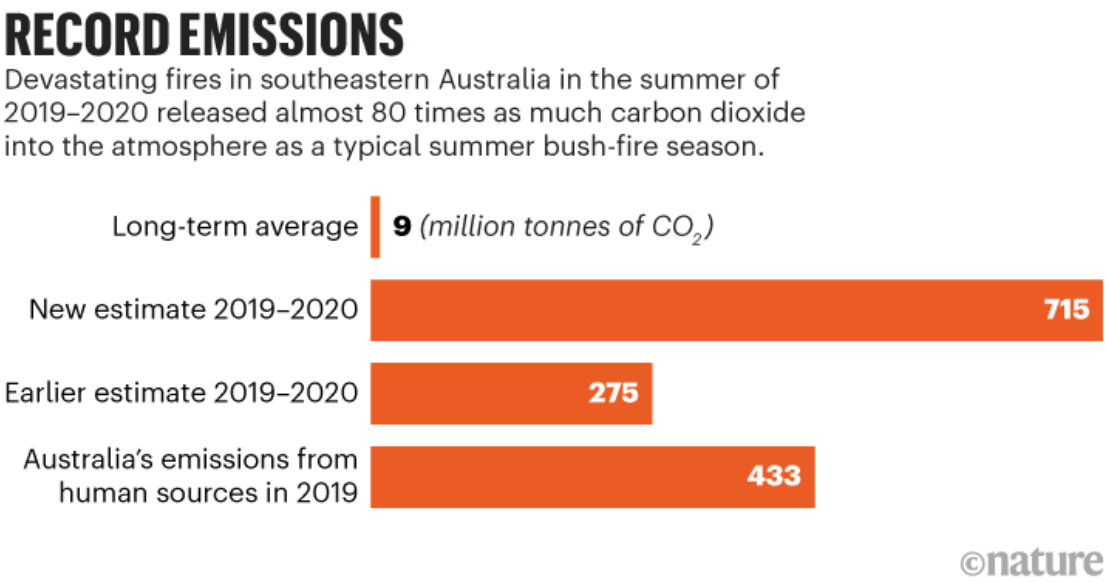


95% of emitted CO2 has been pumped down by planktonic bloom.

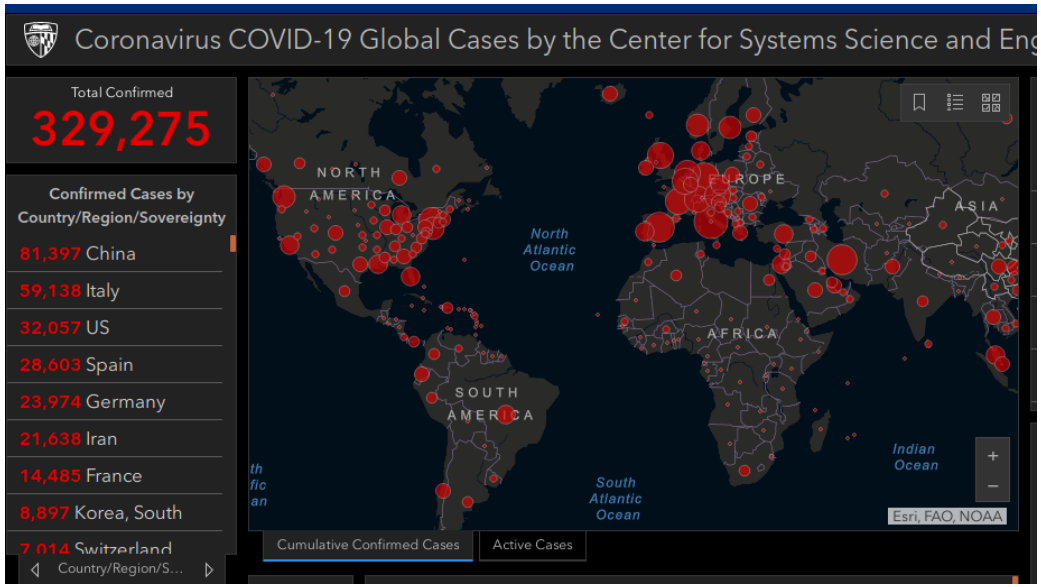
[Nature 597, 459-460 (2021), Tang et al. Nature (2021)]

Microbiome importance in human health

The bright side:

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

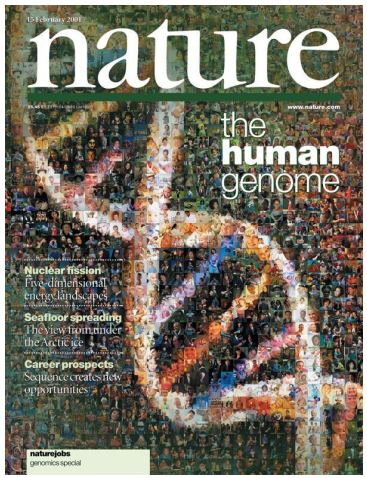
The dark side:



Covid-19

The human gut microbiome

2000's
Human genome



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$\approx$ 20k protein-coding genes

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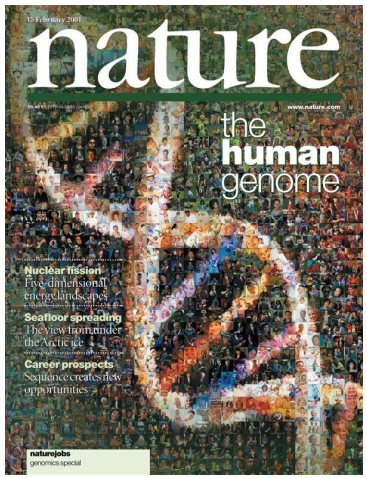

2010's
Gut metagenomes

$\approx$ 20k protein-coding genes $\xrightarrow{\times 100}$ $\approx$ 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 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 $\rightarrow$ AUC ROC 0.81)

  [Qin et al. *Nature* 2012]
- Parkinson's differential abundance of gut microbial species

  [Heintz-Buschart et al. *Mov. Disord.* 2018]

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

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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.

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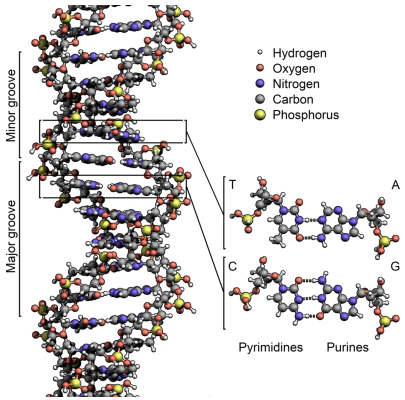
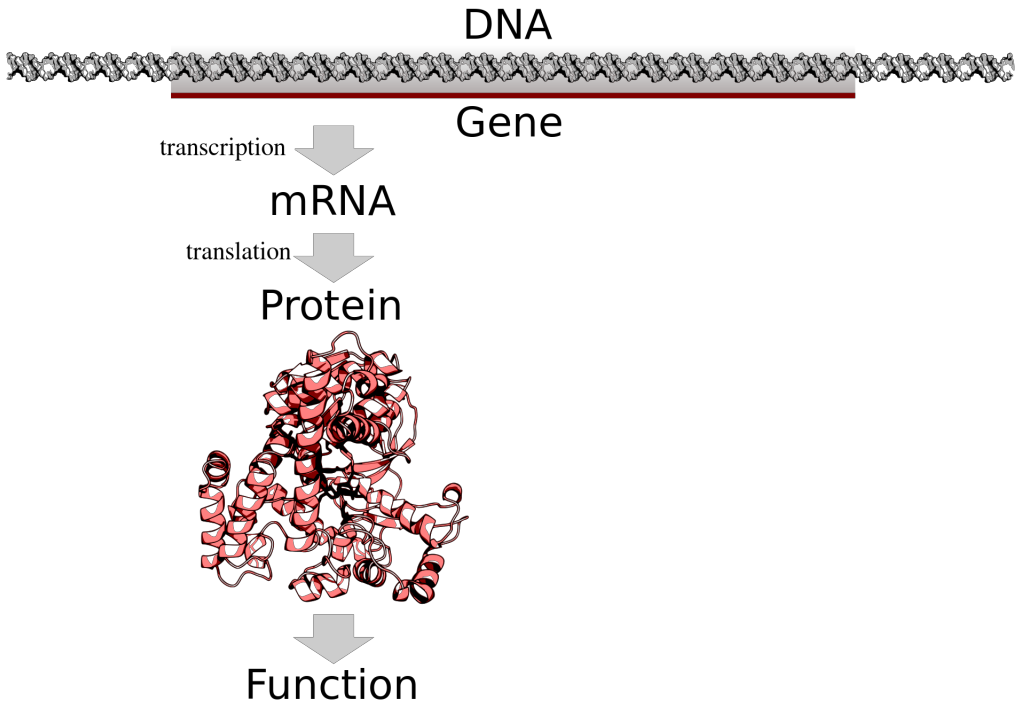
- 1952 Hershey and Chase: DNA is known to encode genetic information
- 1953 Physical structure (double-helix) of DNA is solved using X-Ray diffraction by Franklin (but that's Watson & Crick who got the awards)



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

$\rightarrow$

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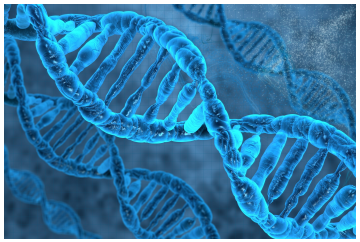

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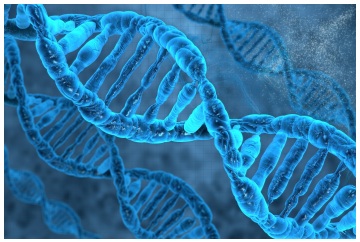

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Illumina/Nanopore

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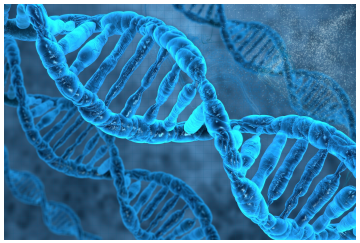

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100's bp - few kbp

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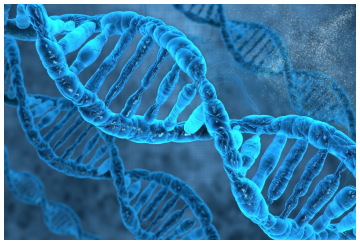

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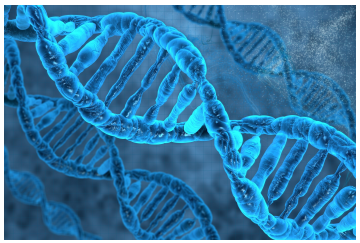

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How does it help?

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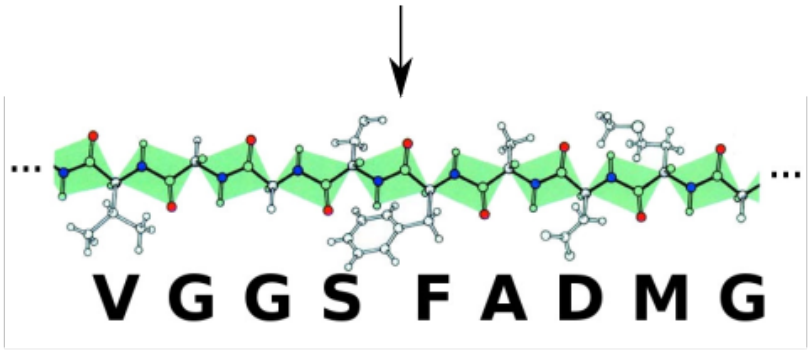

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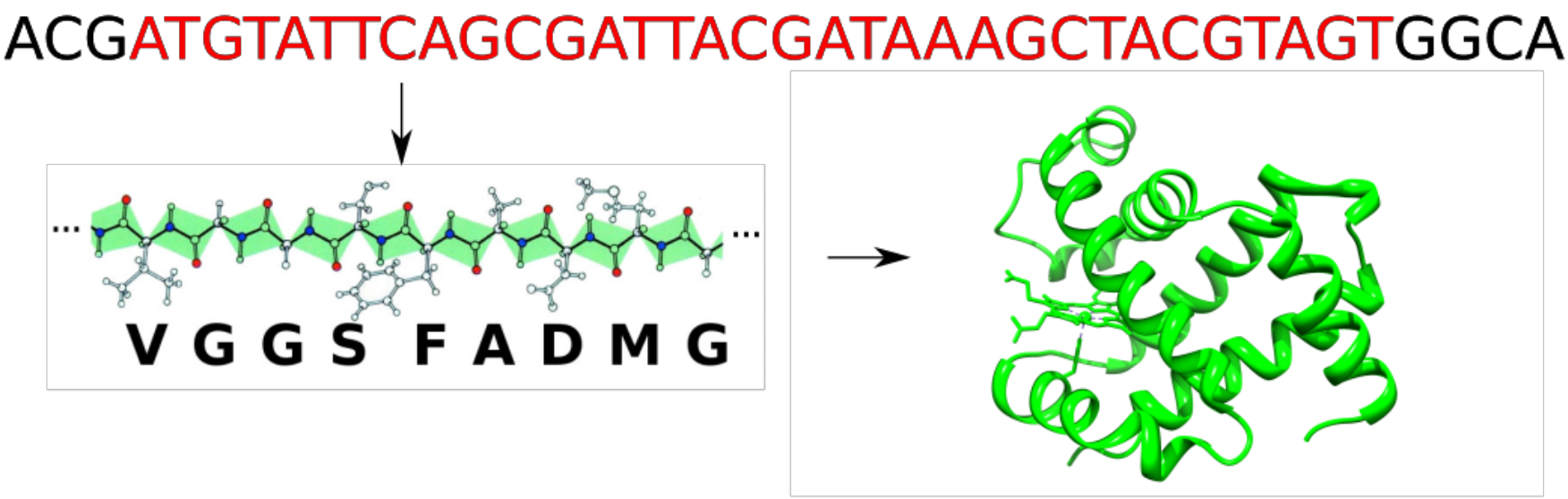

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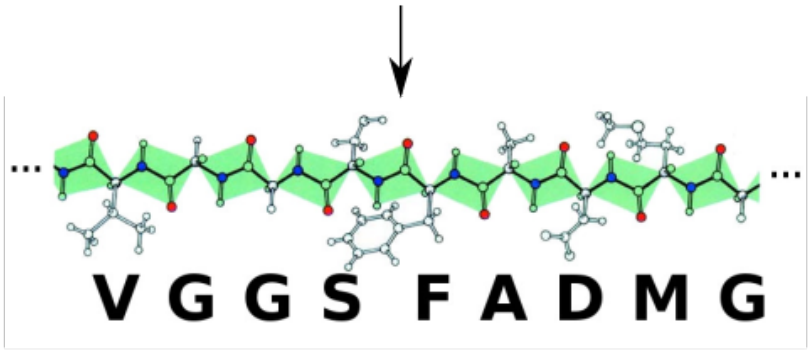
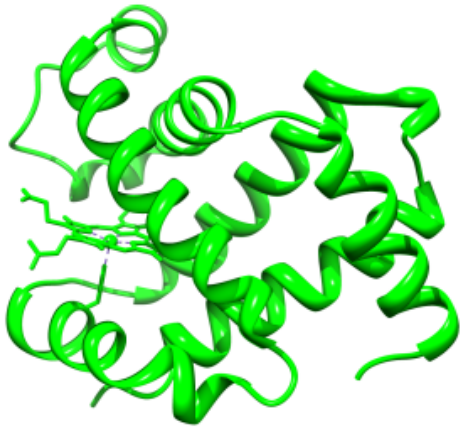
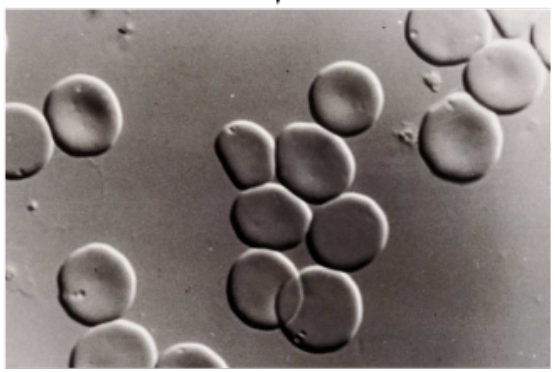


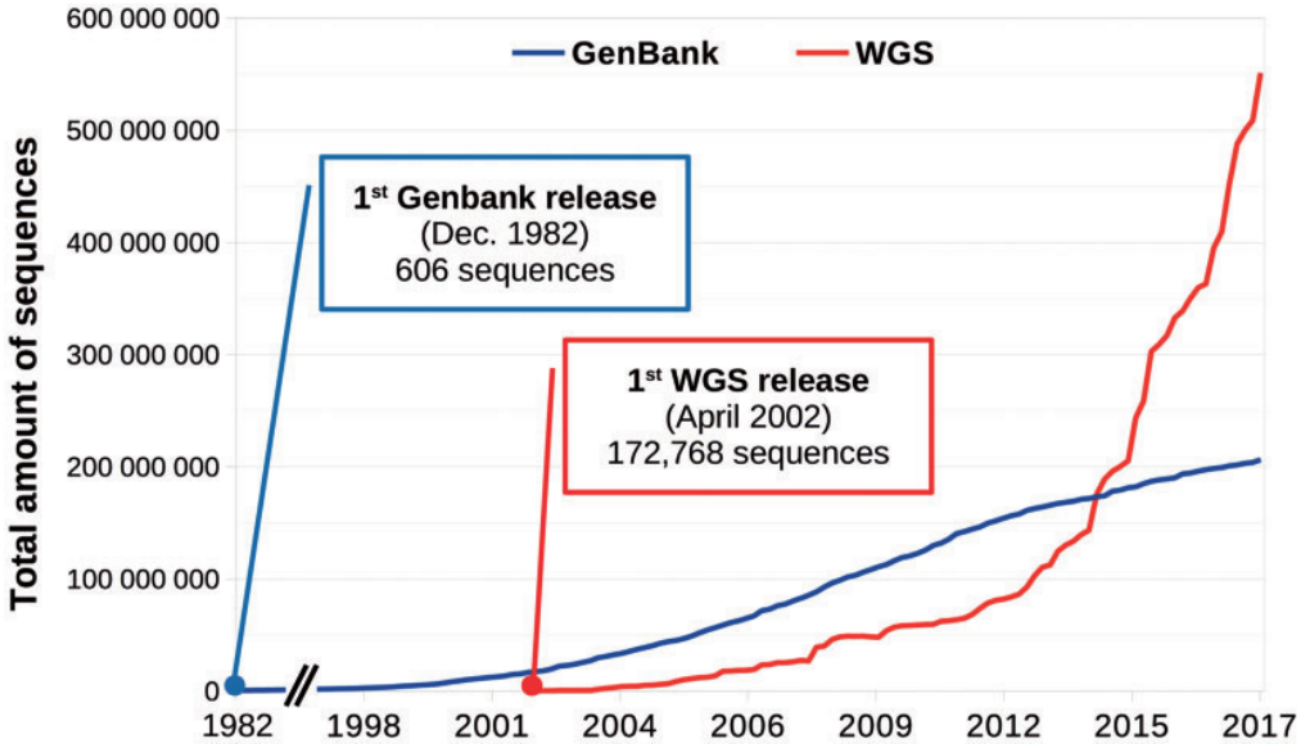




O_2 transport

Genomics, the first breakthrough

1977: first DNA sequencer.

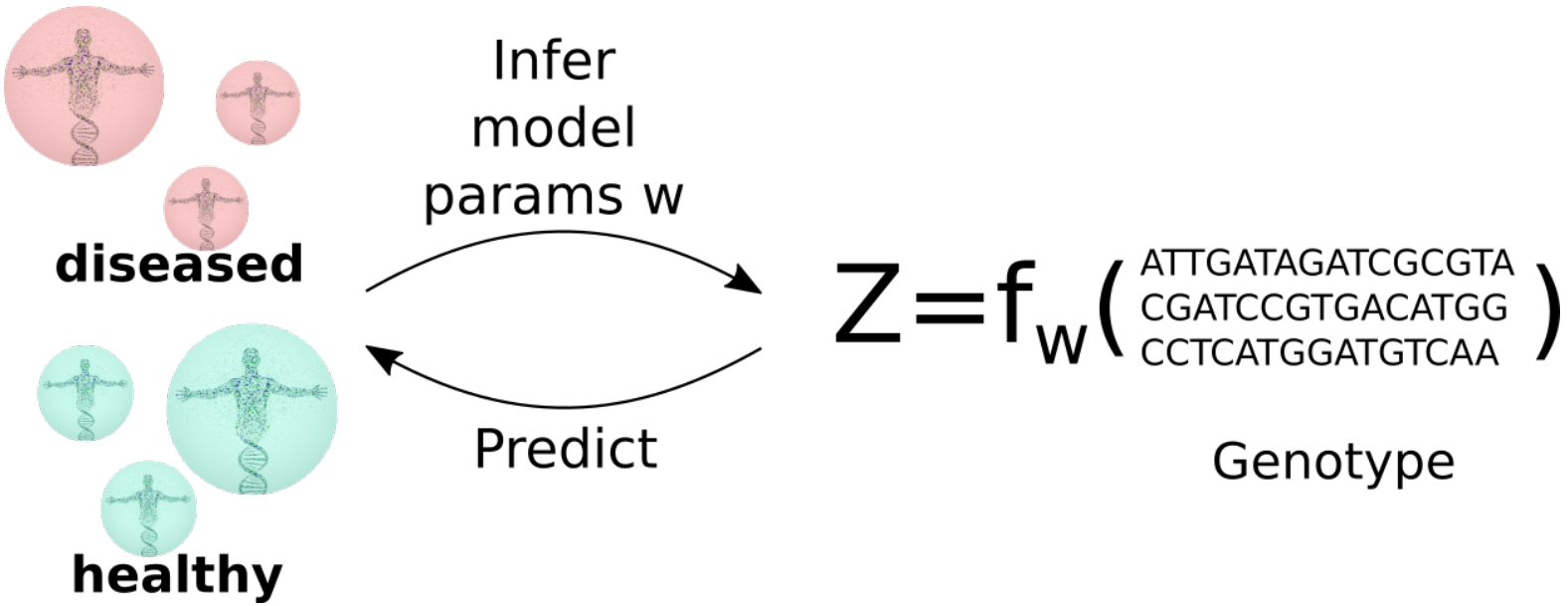


You can now sequence a human cell for less than a thousand euros.

What to do with these DNA sequences?

Example: association studies

Relates the variation of the genome to the phenotype.



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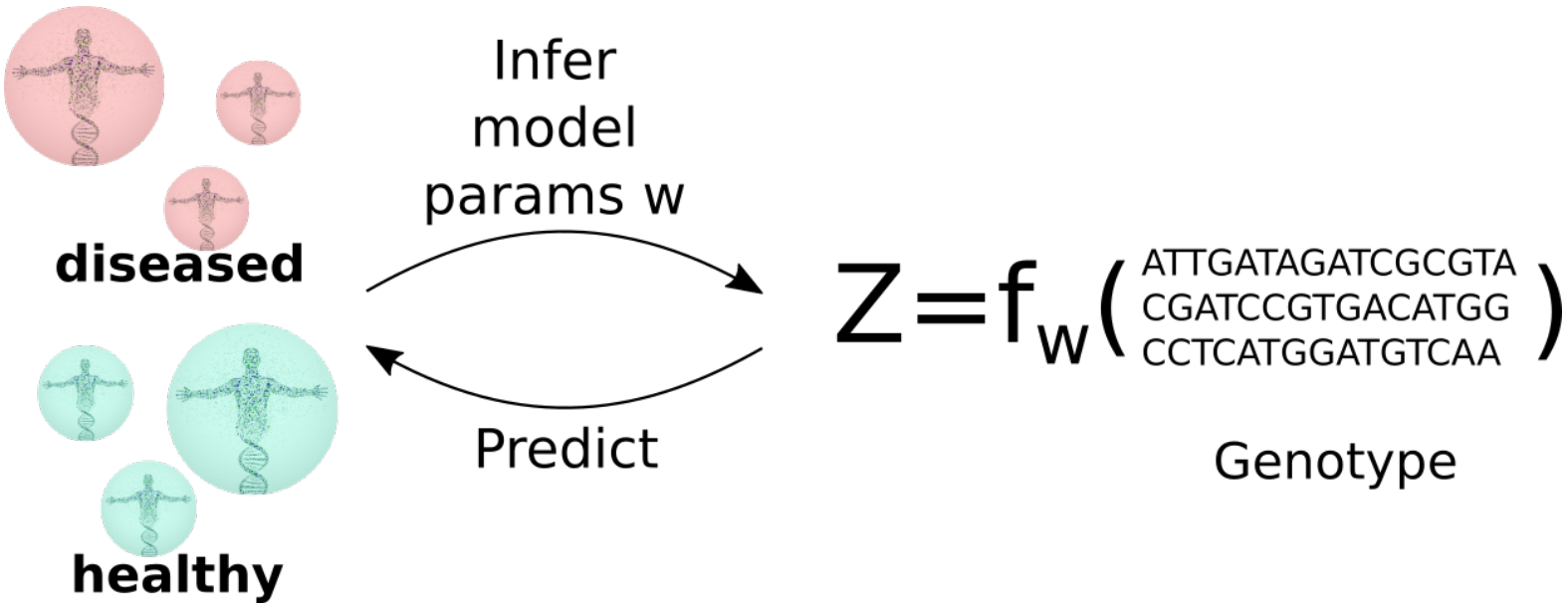

Define a predictor $f : \{A, T, C, G\}^M \to [0, 1]$ such that it minimizes a *loss* on a training set $(\vec{x}_1, z_1), ..., (\vec{x}_N, z_N)$:

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

Lots of data is not just for fun!

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

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Human genome: 3Gbp.

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In practice, one "reference genome" and "only" $\approx 88.10^6$ possible mutation places [The 1000 Genomes Project Consortium, 2015] .

Which mutation is responsible for a specific disease?

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

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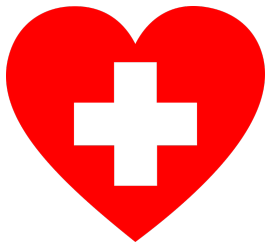
-  clinics

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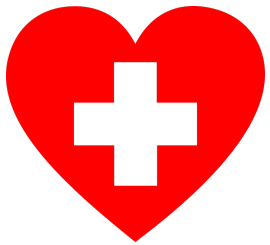
-  clinics
- ecology 

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- ecology 
-  biochemistry

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...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 see 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

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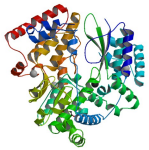
- Protein structures 
  - X-Ray or NMR structures
  - New: computationally resolved structures

Biology from the data perspective: not only DNA!

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

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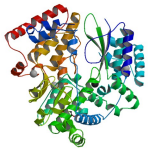
  - (Meta)Genomic: DNA sequence of one (several) organism
- Protein structures 
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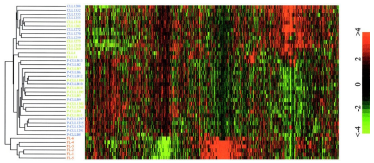
- Abundances 
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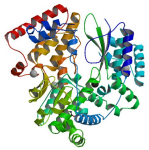
- Protein structures 
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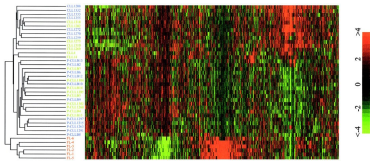
- Abundances 
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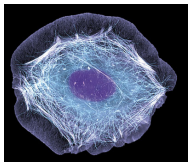
- Images 
  - Neuroimaging
  - Cell imaging
- Mass spectrometry
- ...

Two reasons pushing computational biology forward

Computational biology

Data coupled to statistical models, machine learning, data visualization.

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Computational biology

Data coupled to statistical models, machine learning, data visualization.

- Availability of data
- Computing capacities

Hands-on

Hands-on: realistic public health issue

!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.

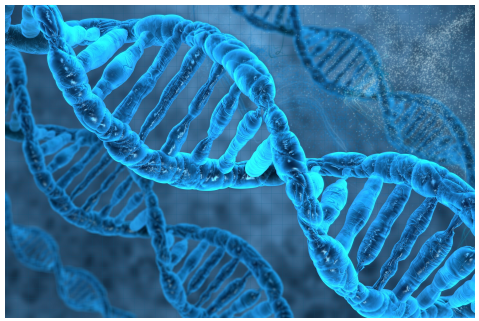
- Skim the context in the `hands-on/session1` on the git (15 min)
- Try to understand individually the work you will have to do and write down questions you have (10 min)
- Share your understanding with people in your group (10 min)
- We share together our understanding and elaborate a common strategy (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 ($\sim$ 250bp)

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

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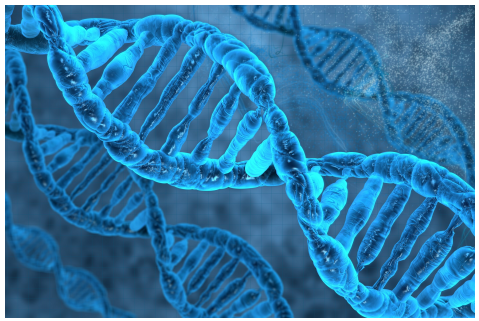

DNA

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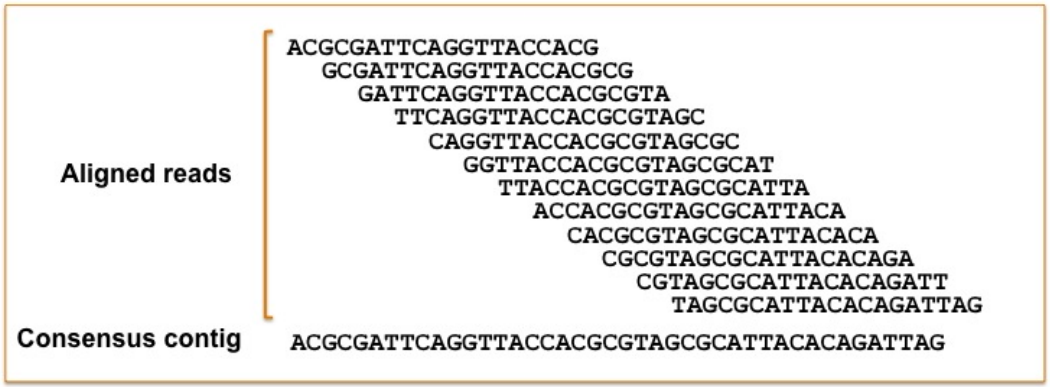
Assembly: from reads to **contigs**:



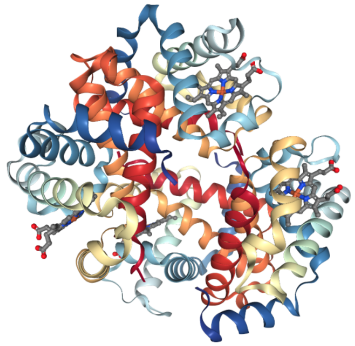
Sequencing data

Two leading technologies:

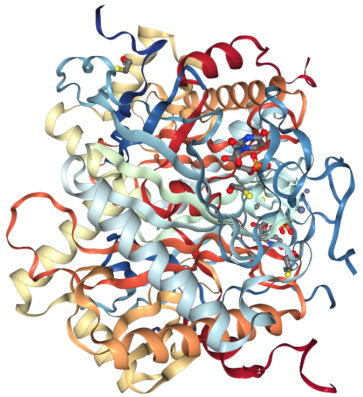
- Illumina: pieces of sequences (called **reads**, 150-250bp)
  - +: reliable, about 1% sequencing errors.
  - -: short reads, only have local view of the genome
  - Errors: rare (1 over 200 bases) almost uniformly distributed, almost all **mutations**.
- Nanopore: long reads, 10kb-100kb
  - +: long 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

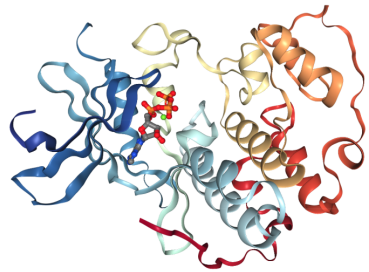
```
>1A3N:A|PDBID|CHAIN|SEQUENCE
VLSPADKTNVKAAWGKVGAHAGEYGAEALER
MFLSFPTTKTYFPHFDLSHGSAQVKGHGKKV
ADALTNAVAHVDDMPNALSALSDLHAHKLRV
DPVNFKLLSHCLLVTLAAHLPAEFTPAVHAS
LDKFLASVSTVLTSKYR
```



```
>1HXP:A|PDBID|CHAIN|SEQUENCE
MTQFNPVDHPHRRYNPLTGQWILVSPHRAKRPW
EGAQETPAKQVLPAHDPDCFLCAGNVRVTGDKN
PDYTGTYVFTNDFAALMSDTPDAPESHDPLMRC
QSARGTSRVICFSPDHSKTLPELSVAALTEIVK
TWQEQTAELGKTYPWVQVFENKGAAMGCSNPHP
HGQIWANSFLPNEAEREDRLQKEYFAEQKSPML
VDYVQRELADGSRTVVETEHWLAVVPYWAAWPF
ETLLLPKAHVLRITDLTDAQRSDLALALKKLTS
RYDNLFQCSFPYSMGWHGAPFNGEENQHWQLHA
HFYPPLLRSATVRKFMVGYEMLAETQRDLTAEQ
AAERLRAVSDIHFRESGV
```



```
>1HCK:A|PDBID|CHAIN|SEQUENCE
MENFQKVEKIGEGTYGVVYKARNKLTGEVVAL
KKIRLDTETEGVPSTAIREISLLKELNHPNIV
KLLDVIHTENKLYLVFEFLHQDLKKFMDASAL
TGIPLPLIKSYLFQLLQGLAFCHSHRVLHRDL
KPQNLLINTEGAIKLADFGLARAFGVPVRTYT
HEVVTLWYRAPEILLGCKYYSTAVDIWSLGCI
FAEMVTRRALFPGDSEIDQLFRIFRTLGTPDE
VVWPGVTSMPDYKPSFPKWARQDFSKVVPPLD
EDGRSLLSQMLHYDPNKRISAKAALAHPFFQD
VTKPVPHLRL
```



CASP competition

Blind competition. Simple principle:
- a sequence is given
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13th CASP...

... AI wins !

Google's DeepMind