Corso di Biofisica Sperimentale

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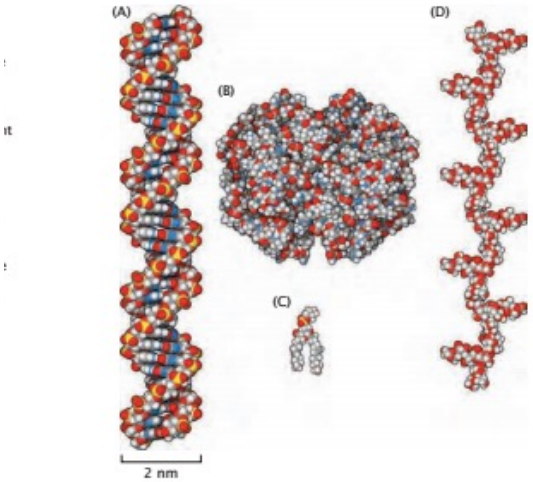
The course will be largely devoted to explore the diversity present in biological systems and its complexity by analyzing the function and physical properties associated to the organization of complex (macro)molecular systems .
The large-scale goal being of understanding how the special properties of life may emerge from fundamental physical and chemical interactions.



(A) Atomic structure of a small fragment of the **nucleic acid** DNA in the B form
(B) atomic structure of the oxygen-carrying **protein** hemoglobin (PDB 1hho)
(C) phosphatidylcholine **lipid** molecule from a cell membrane
(D) branched complex **carbohydrate**

What is biophysics?

- Physics provides the laws that govern energy, forces, and interactions.
- Biology brings complex living systems that exhibit self-organization, adaptability, and life processes.
- Biophysics merges these, aiming to explain biological phenomena in terms of physical principles.

Biophysics is the field that applies the theories and methods of physics to understand how biological systems work, i.e. the mechanisms of:

- how the molecules of life are made
- how different parts of a cell move and function
- how complex systems in our bodies—the brain, circulation, immune system, and others— work.

(ref. Biophysical Society)

Great scientific challenge not only to understand how its pieces work but also how the whole is organized internally to achieve specific functional advantages.

What is biophysics?

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Our quest to understand biology using physical laws and engineering principles is greatly aided by the rapid development of sophisticated experimental techniques that physics and technology has supplied for the use by biologists.

Biophysics Exp. techniques

- Light microscope (resolution: 400–600 nm) with various modern upgrades such as confocal, phase contrast, or cryomicroscopy.
- Electron microscope (10–100 nm)
- Neutron scattering (1–10 Å)
- X-ray crystallography (1 Å)
- Patch clamp electrophysiology
- STM, AFM, TEM
- NMR, MRI, fMRI
- Fluorescence spectroscopy
- Microwave absorption
- Laser light scattering
- Synchrotron radiation scattering
- Laser tweezers, etc.

Biophysics core fields

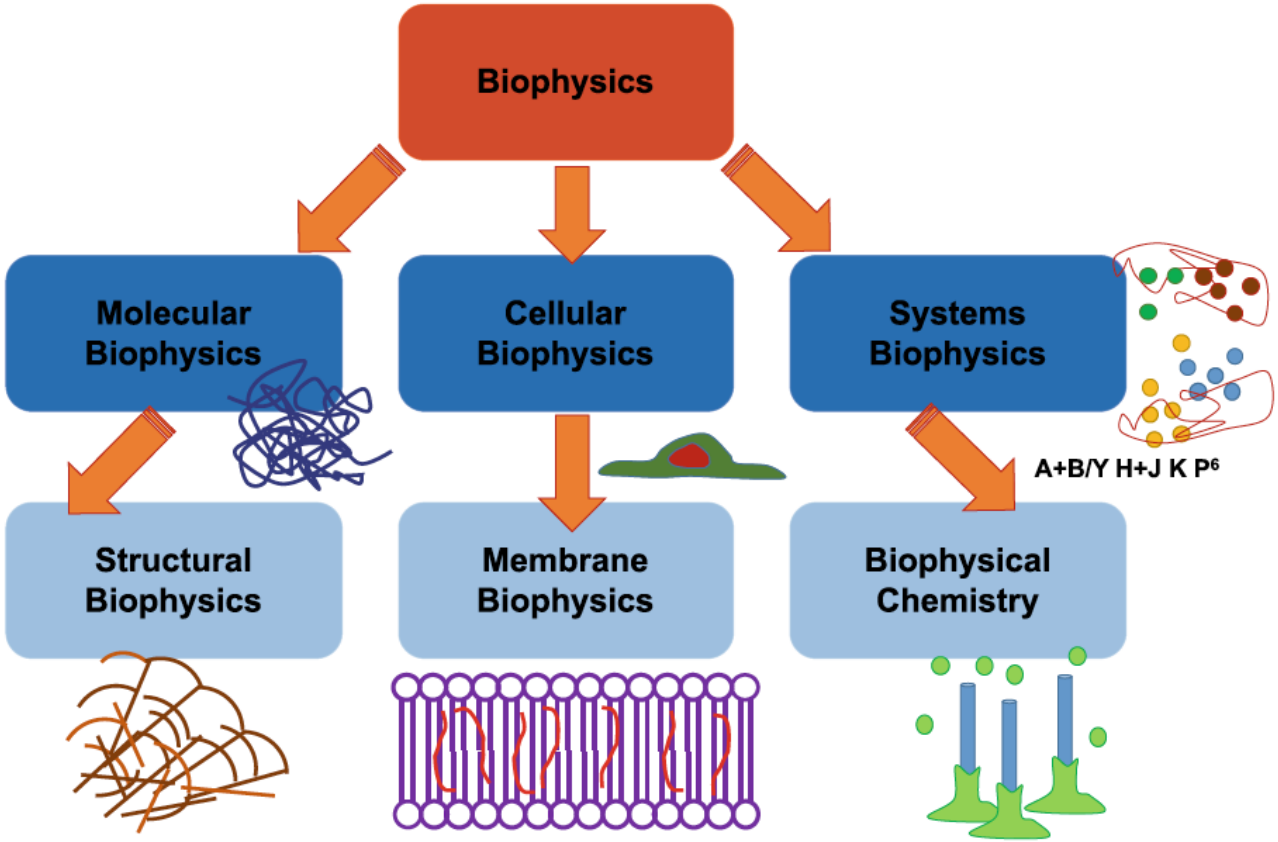


Fig. 1.5 Biophysics or biological physics is divided into at least these three main parts. These subdisciplines may be highly related and partly intertwined

Biophysics core fields

a. Molecular Biophysics (YES)

•Focus: Study of biological molecules like proteins, nucleic acids (DNA, RNA), and how they interact.

•Methods: Techniques like X-ray crystallography, NMR (Nuclear Magnetic Resonance), and cryo-electron microscopy are used to visualize molecular structures.

•Importance: Understanding how molecular machines, such as enzymes or ion channels, work inside cells.

b. Cellular Biophysics (YES)

•Focus: Understanding the physical principles behind cellular processes like membrane dynamics, energy production, and signaling.

•Methods: fluorescence microscopy, calcium imaging, AFM, cryoEM, optical tweezers, electrophysiology, etc..

•Example: The study of how the cytoskeleton provides mechanical support or the role of cell membrane in cell trafficking, or how cellular respiration occurs within mitochondria.

Biophysics core fields

c. Systems Biophysics (NO)

- Focus: Examines how biological systems work as a whole, including neural networks, muscle contractions, and the immune system's behavior.
- Techniques: Mathematical modeling and computational simulations help describe complex biological networks.

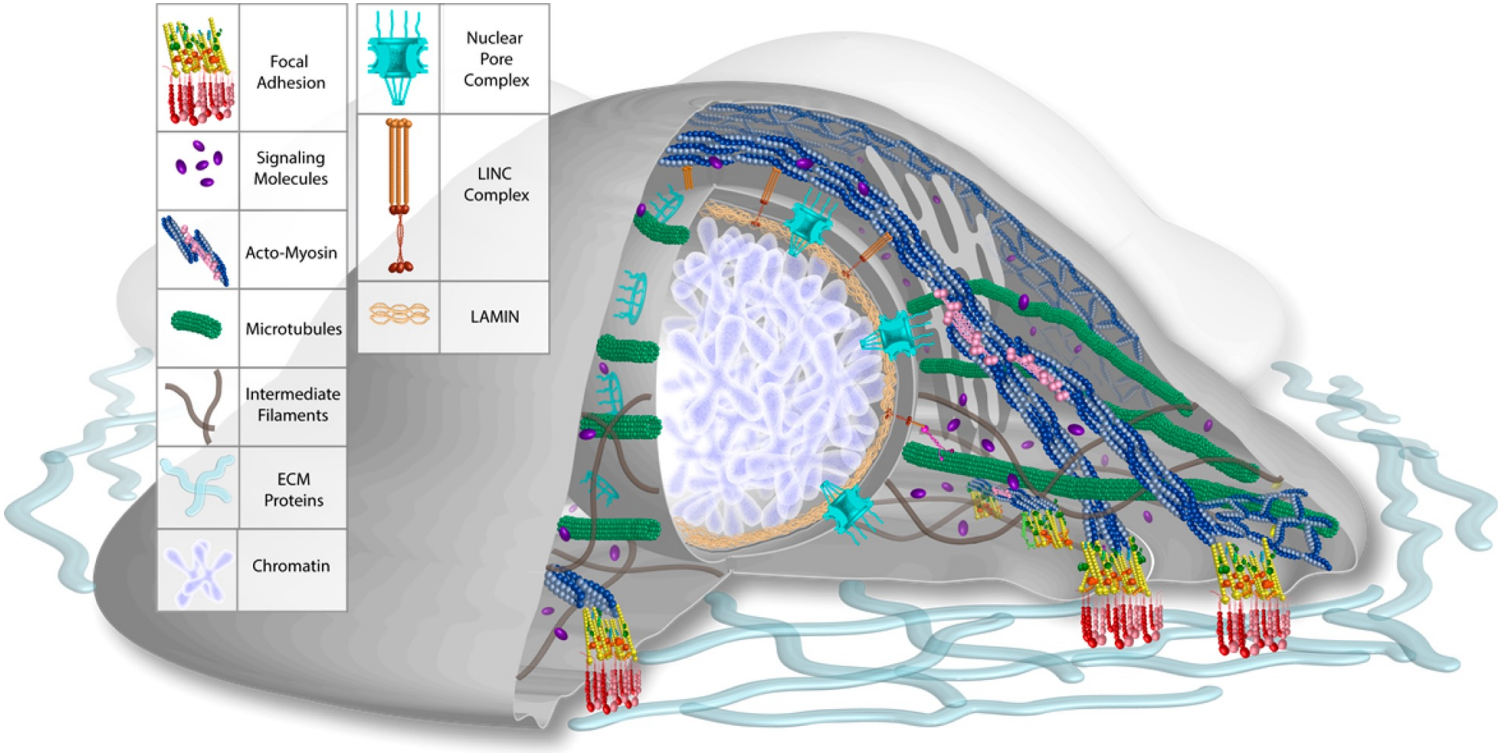
d. Medical Biophysics (NO)

- Focus: Application of biophysics to understand disease mechanisms and develop medical technologies.
- Examples: Magnetic Resonance Imaging (MRI) uses physics-based principles to image the body's internal structures non-invasively.

Il Premio Fermi 2024 (SIF) alla microscopia ottica in biologia

Il Premio Enrico Fermi della Società Italiana di Fisica per l'anno 2024 è stato assegnato congiuntamente ad Alberto Diaspro e a Francesco Saverio Pavone per le loro ricerche sperimentali nel campo della fisica applicata a sistemi biologici.

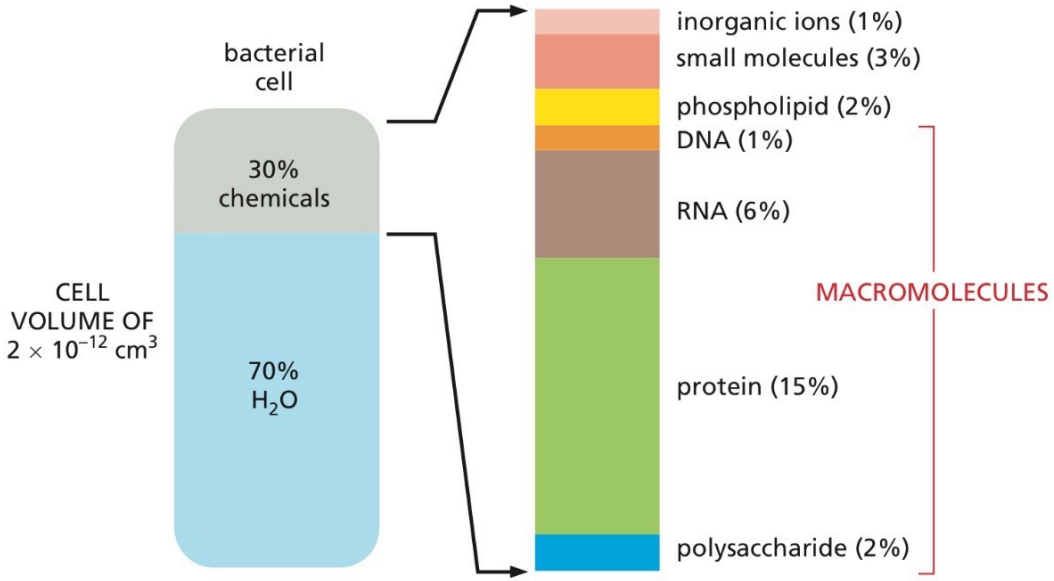
Example: mechanotransduction by cells



Cells respond to extracellular matrix (ECM) cues generating and transducing mechanical forces into biochemical signals and genomic pathways which affect cell properties. Such forces define tissue architecture and drive specific cell differentiation programs. In adults perturbation of ECM (stiffness, mutations) cause pathologies in different organs, including ageing and malignant progression.

Inside the cell: macromolecules

Many of the molecules that make up living organisms tend to be relatively large and structurally complex, and are hence called macromolecules. Living organisms also contain a large number of small, simple molecules that are critical to their function, ranging from water and metal ions to sugars such as glucose.



amount of total protein in some mammalian cells : one nanogram

Inside the cell: macromolecules

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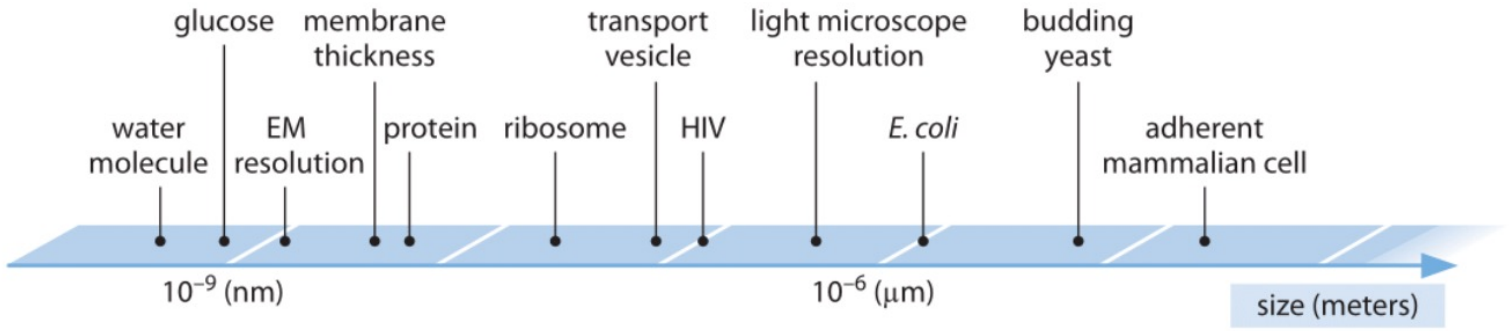
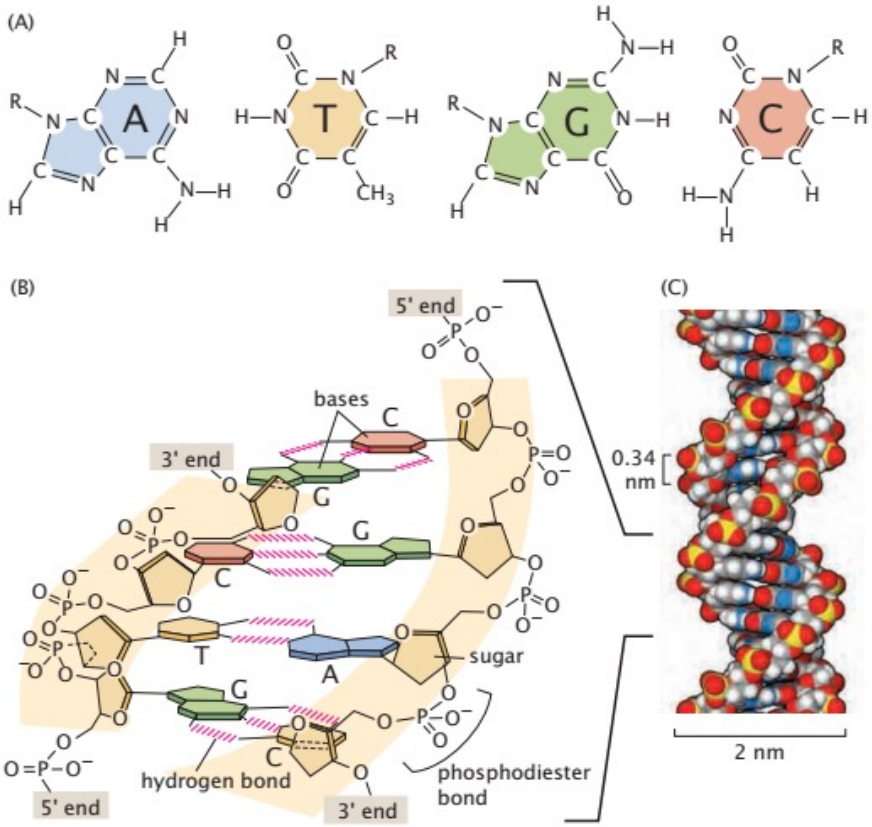


Biology spans 15 order of magnitude in length scale!



Biological Stuff Can Be Idealized Using Many Different Physical Models: DNA

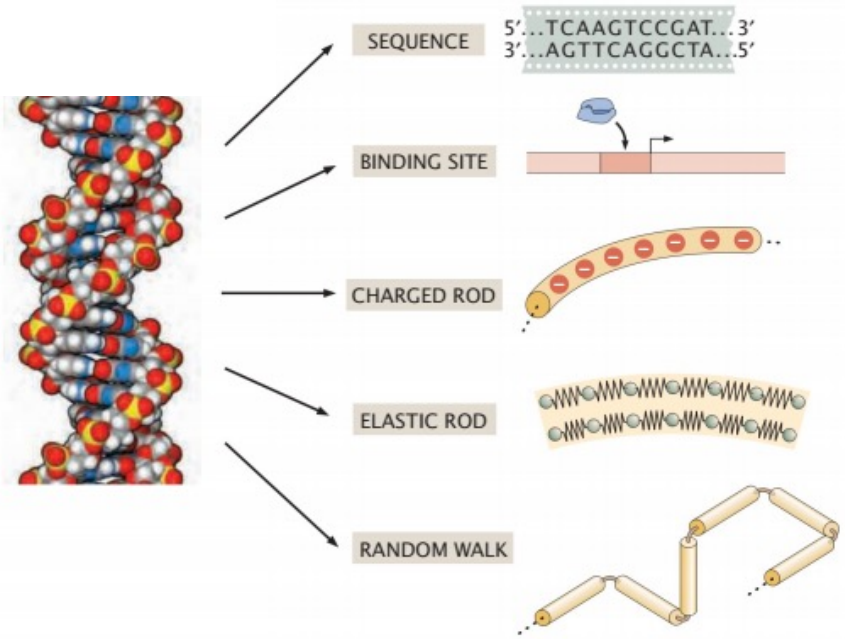


Figure 1.5: Idealizations of DNA. DNA can be thought of as a sequence of base pairs, as a series of binding sites, as a charged rod, as an elastic rod, or as a freely jointed polymer arranged in a random walk, depending upon the problem of interest.

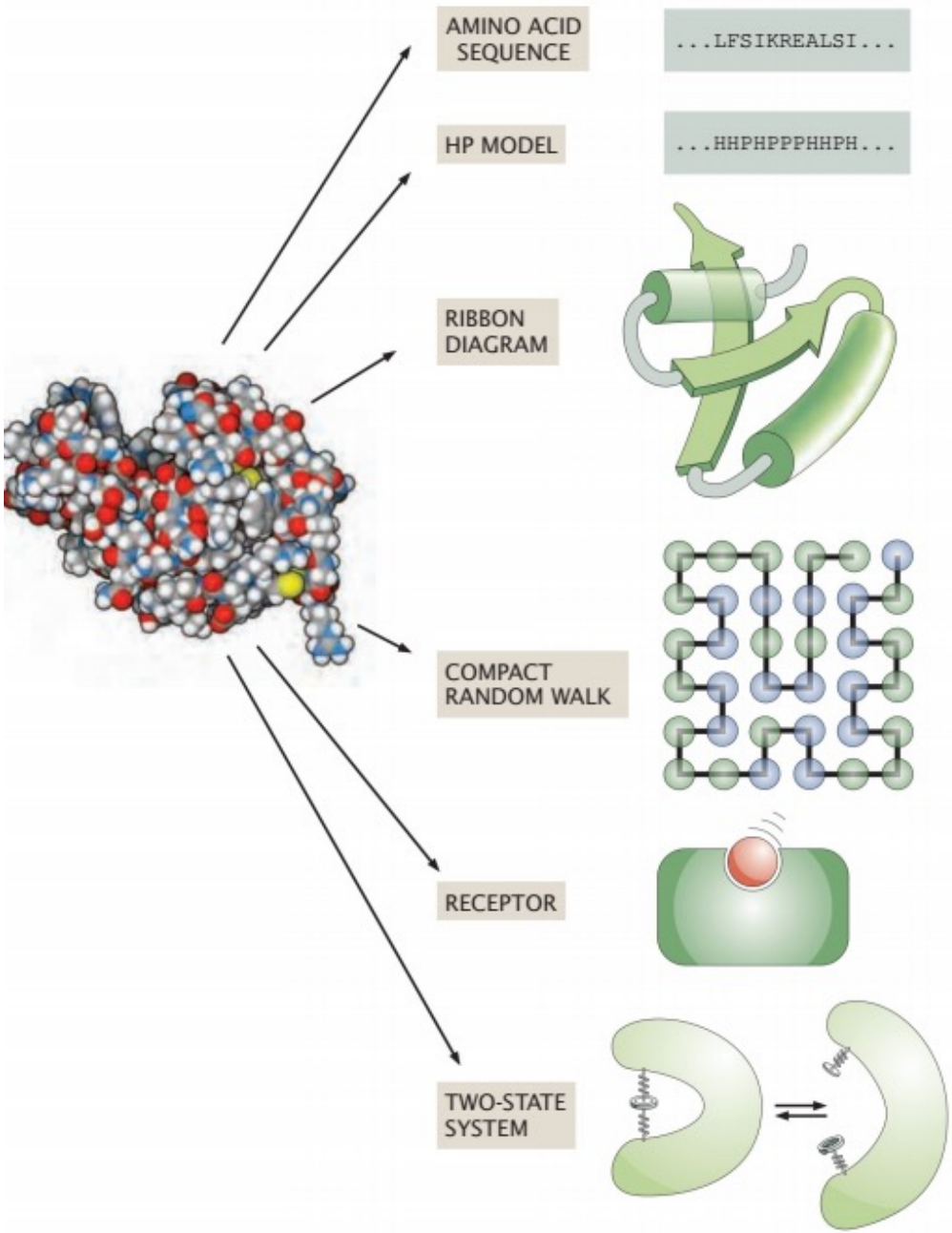
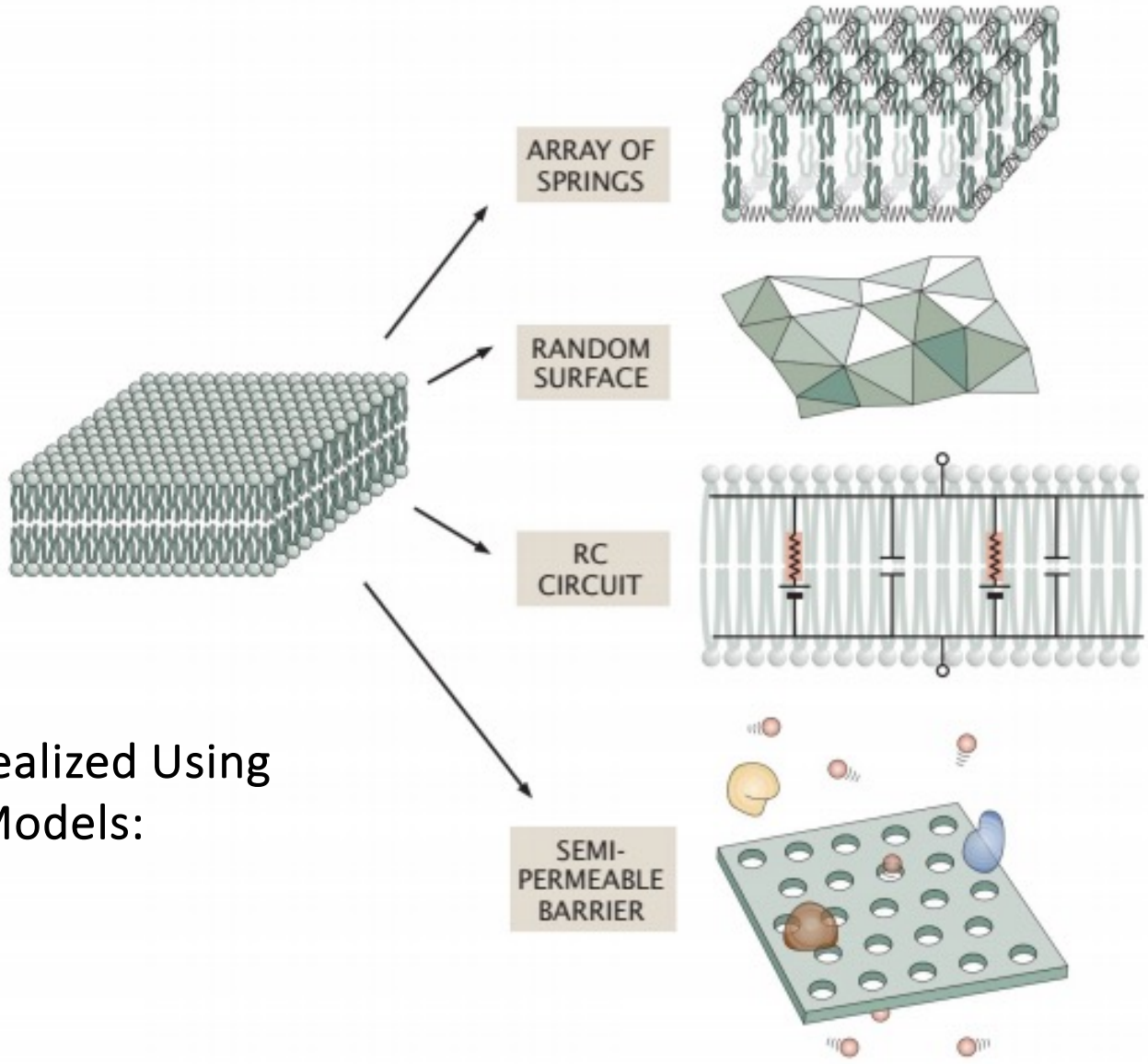


Figure 1.6: Idealizations of protein. Proteins can be thought of as a particular sequence of amino acids, as a simplified sequence reporting only the hydrophobic (H, oil-like) or polar (P, water-like) chemical character of the amino acids, as a collection of connected ribbons and cylinders, as a compact polymer on a lattice, as a binding platform for ligands, or as a two-state system capable of interconverting between different functional forms.

Biological Stuff Can Be Idealized Using Many Different Physical Models: proteins

The global conformation of a protein can be seen as a black box, without worrying about the internal machinations

Figure 1.7: Idealization of membranes. A membrane can be modeled as an elastic object that deforms in response to force, as a random surface fluctuating as a result of collisions with the molecules in the surrounding medium, as an electrical circuit element, or as a barrier with selective permeability.



Biological Stuff Can Be Idealized Using Many Different Physical Models:
Lipid membranes

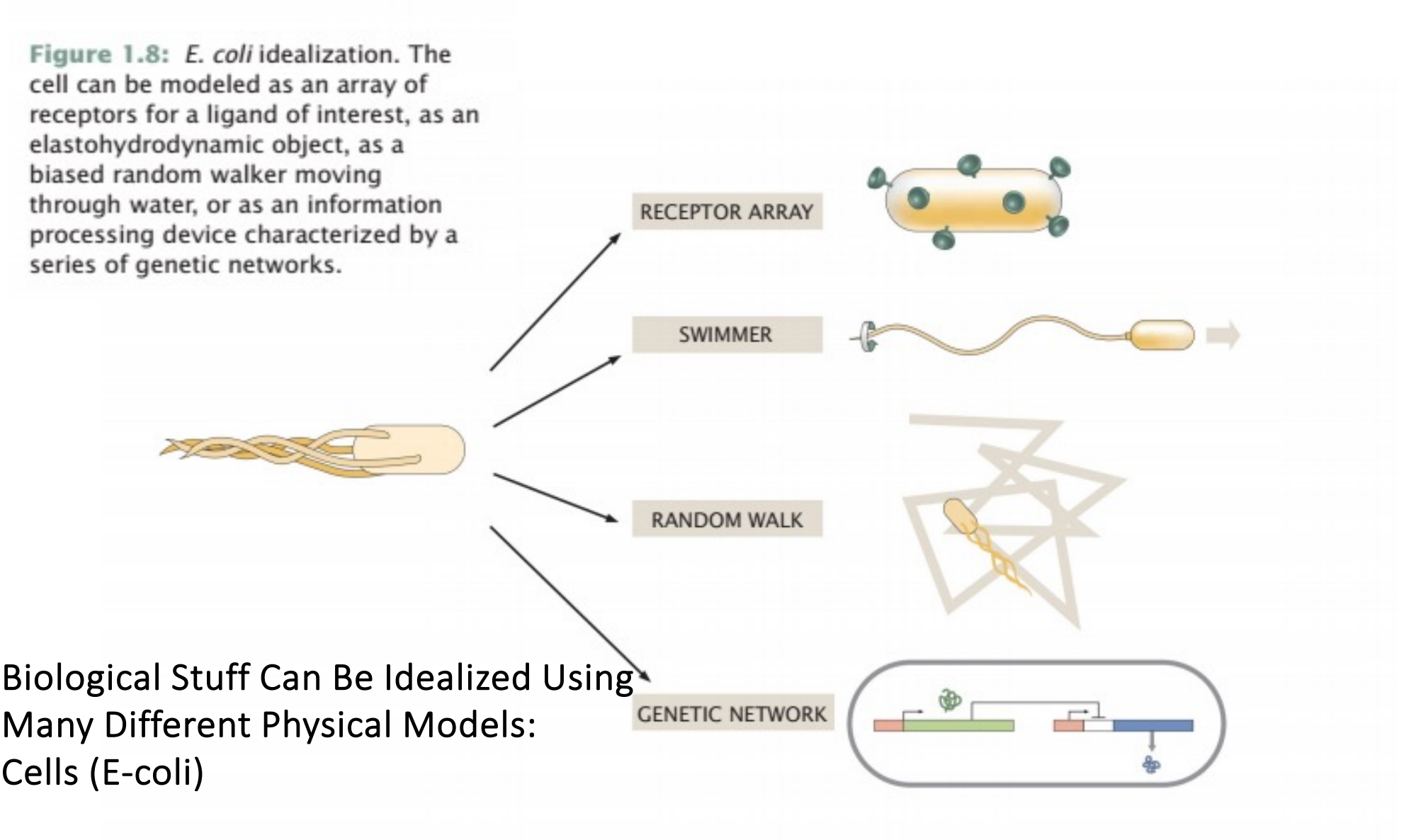
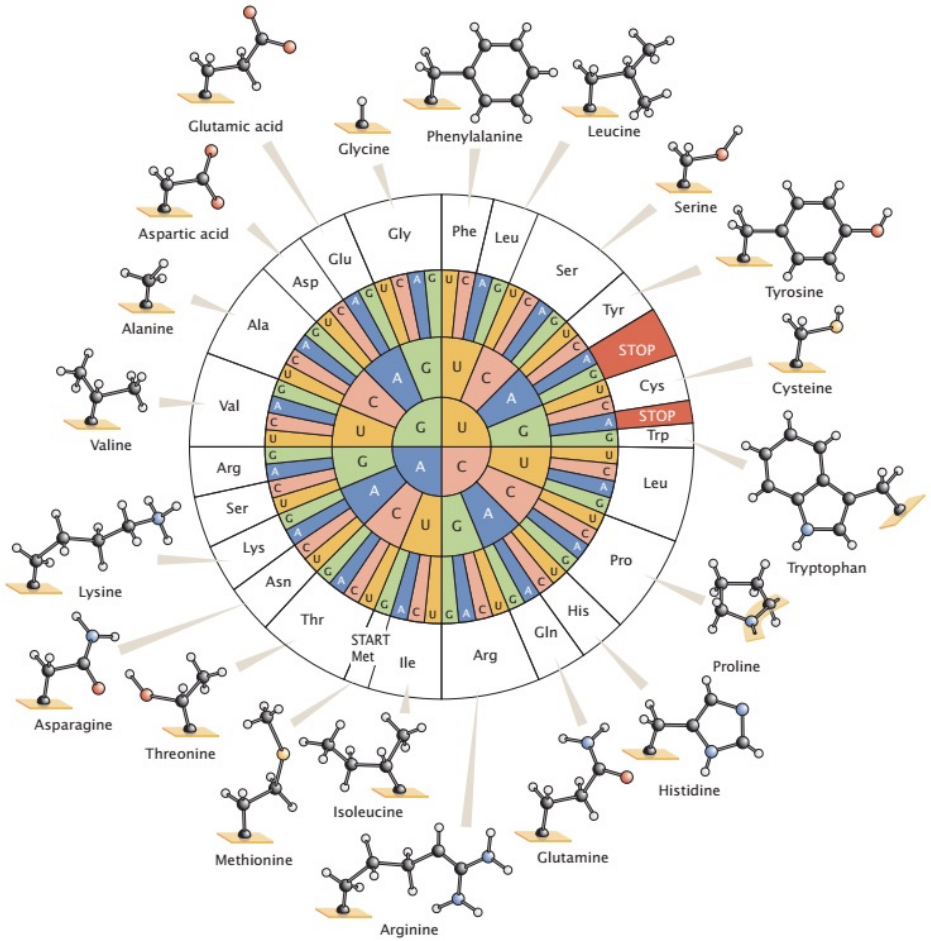


Figure 1.8: *E. coli* idealization. The cell can be modeled as an array of receptors for a ligand of interest, as an elastohydrodynamic object, as a biased random walker moving through water, or as an information processing device characterized by a series of genetic networks.

Biological Stuff Can Be Idealized Using Many Different Physical Models:
Cells (E-coli)

How can just four nucleotide bases be translated into protein sequences containing 20 different amino acids?



The sequences associated with nucleic acids and proteins are linked mechanistically (Genetic Code) through the ribosome which takes nucleic acid sequences (in the form of messenger RNA (mRNA)) and converts them into amino acid sequences (in the form of proteins).

History of Biophysics:

In 1943 Schrödinger gave a few lectures at Trinity College, Dublin, on

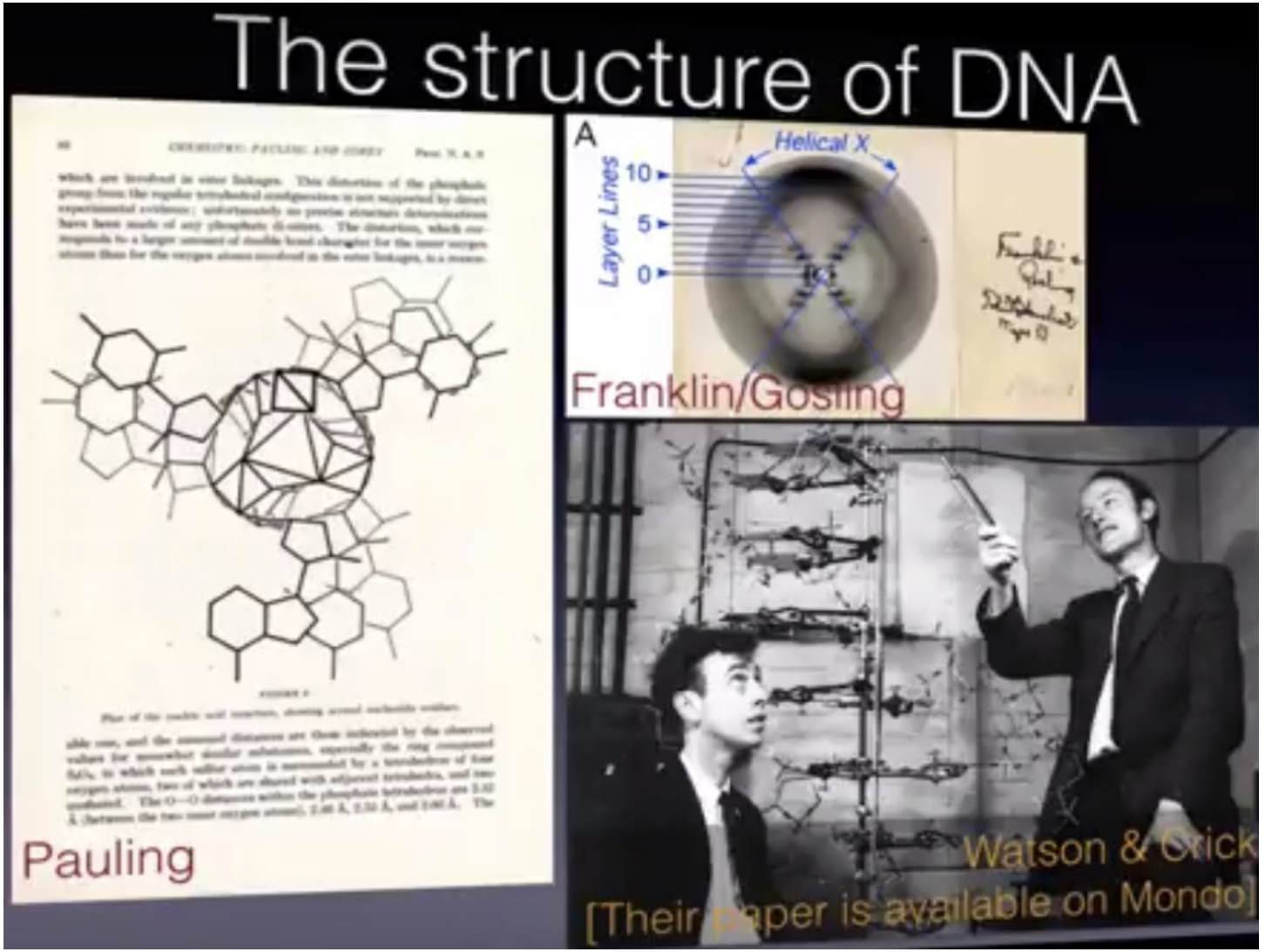
"What is life: the physical aspects of the living cell"

These lectures generated an enormous interest for biology between physicists and chemical physicists, which led to the discovery of DNA and protein structure and the development of molecular biology.

High resolution needed!

History of (Molecular) Biophysics:

Breakthrough is DNA double-helix model obtained by **J.D. Watson** (ornithologist) and **F.H.C. Crick** (physicist) following **Rosalind Franklin**, R.G. Gosling, **M.H.F. Wilkins**, A.R. Stokes, H. R. Wilson fibre diffraction/biochemical studies published on Nature in 1953



High resolution needed!

History of (Molecular) Biophysics:

•Feynman's Talk: "There's Plenty of Room at the Bottom" (1959):

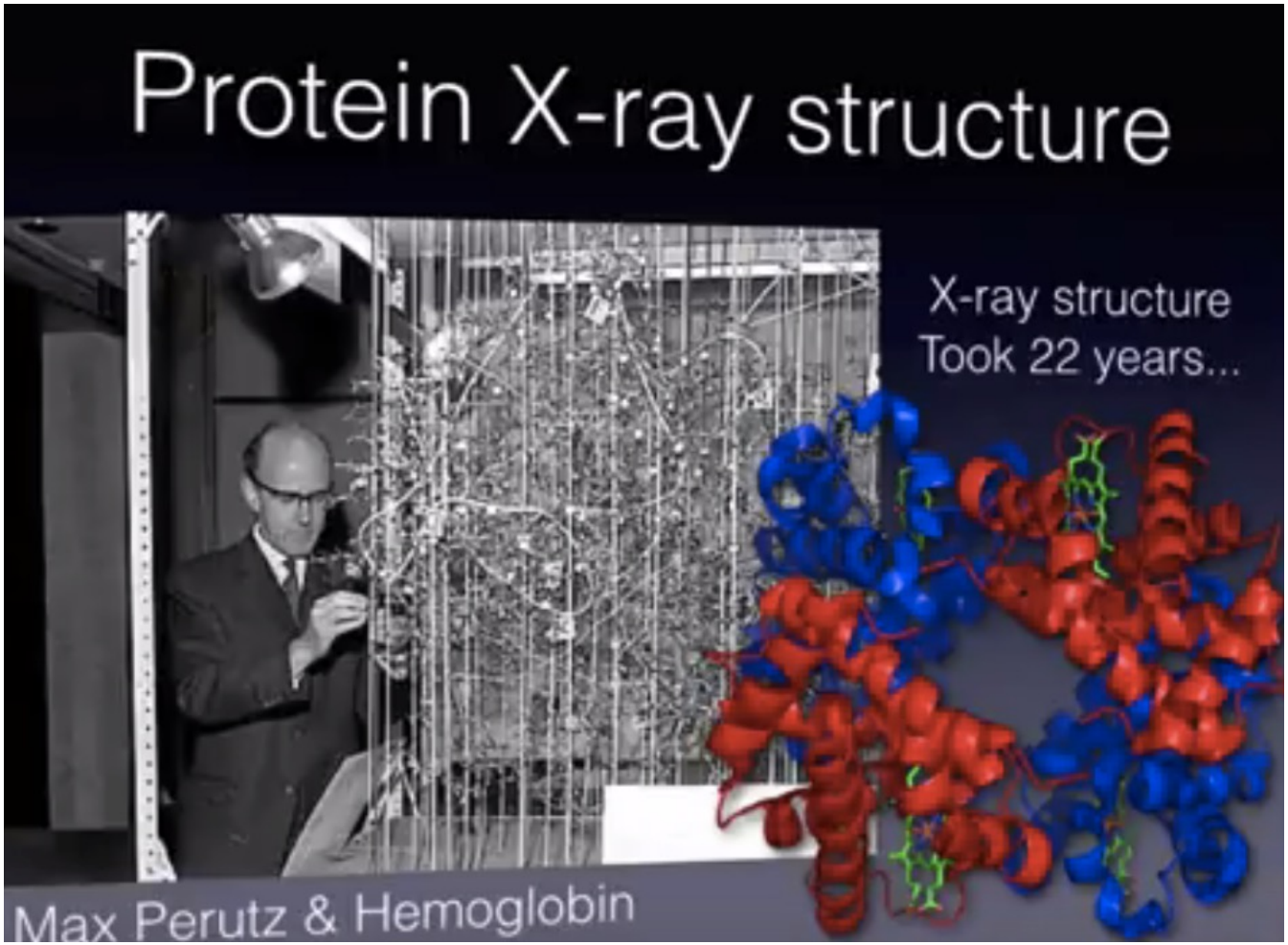
In this visionary talk, Feynman laid the foundation for what we now call **nanotechnology** and implied potential applications **for biology and medicine**. He discussed the possibility of manipulating individual atoms and molecules, long before techniques like **cryo-electron microscopy** or **molecular engineering** were available. These ideas have become instrumental in biophysics, where scientists now study biological macromolecules and develop **nanotechnology-based medical devices** and drug delivery systems.

His idea of creating machines at the molecular scale is directly relevant to biophysics, particularly in understanding biological nanomachines like **enzymes**, **motor proteins**, and other molecular structures.

History of (Molecular) Biophysics:

The first protein crystal was obtained in 1930, the first X-ray structure by **M. Perutz** and **J. Kendrew** in 1957 (myoglobin). Complex problem, needed complementary biochemical and thermodynamical tools to be solved.

Application of physical concepts and methods to biology --- biophysics!



What are the characteristics of life?

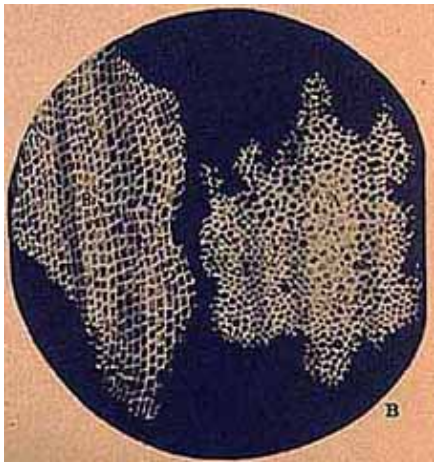
All living organisms:

- are made of highly organised and orderly structures
- have the ability to respond to stimuli
- are characterised by growth, development and reproduction
- have regulatory mechanisms that control and coordinates life functions

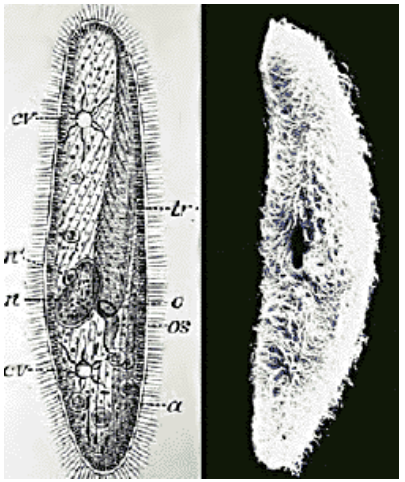
All living organisms are made of cells.

The cell: a bit of history...

Cells were first seen in the 17th century, thanks to the advances of optic and microscopy (first contribution of physics to biology!):



Robert Hook coined the term "cells" for the little structures seen in cork.



Antony van Leeuwenhoek discovered bacteria, free-living and parasitic microscopic protists, sperm cells, blood cells, microscopic nematodes and rotifers, and much more...

But only in the 19th century it was realised the central importance of cell in biology:

The Cell Theory (Schleiden & Schwann, 1839)

"each animal appears as the sum of vital units, each of which bears in itself the complete characteristic of life"

Cells, molecules and life

All living organisms are made of cells.

Some consist of single cells (unicellular), other of many cells (multicellular).

Organisms grow by the growth and division of their cells.

Cells can be taken out of an organisms and can live in the absence of the rest of the organism -> cells are truly alive.

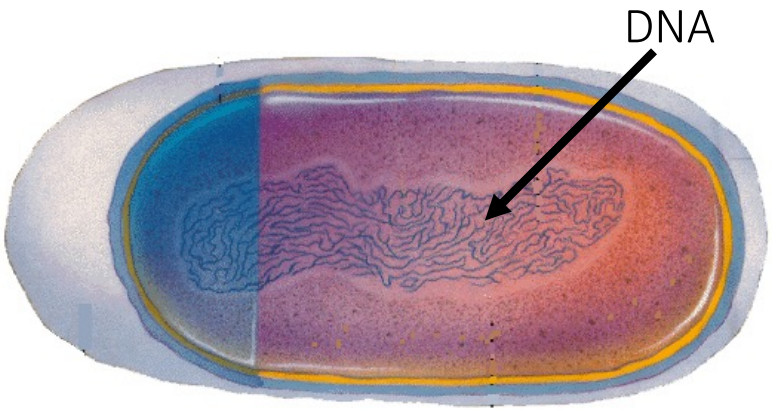
Cells are made of molecules which obey the laws of chemistry and physics, but are organised in complex systems, and are able to display complex behaviour.

The organisation of the cell

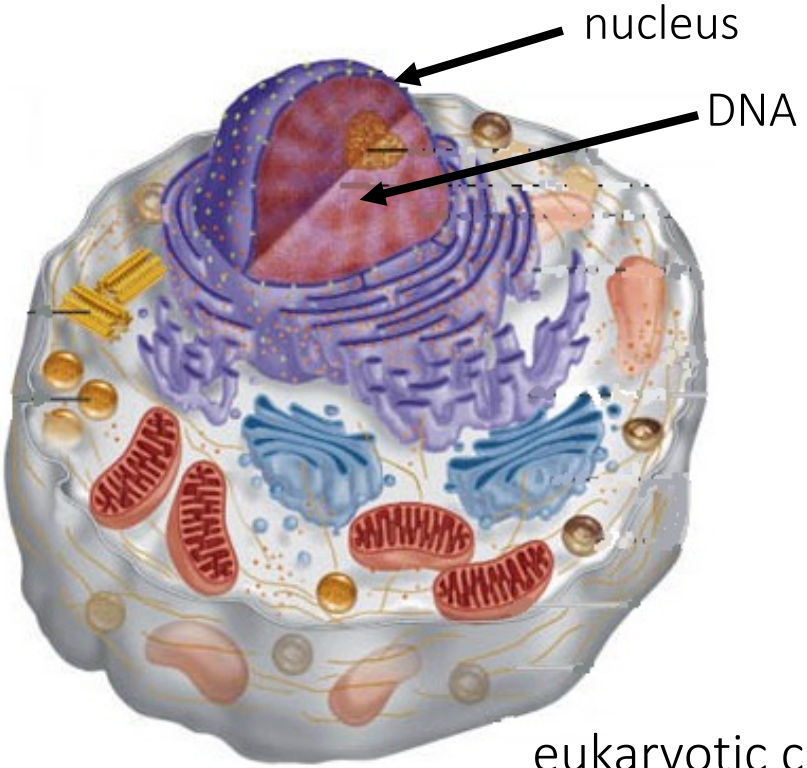
A cell membrane separates the outside from the inside of the cell; the inside is called cytoplasm and contains a high concentration of proteins, small molecules and nucleic acids (DNA and RNA).

In some cells the DNA is simply spread inside the cell, in others it is enclosed in an organelle called the nucleus.

This divides cells into two classes:
- prokaryotic cells (without nucleus)
- eukaryotic cells (with nucleus)



prokaryotic cell



eukaryotic cell

Classification of living organisms

Prokaryotes

(no nucleus, unicellular)

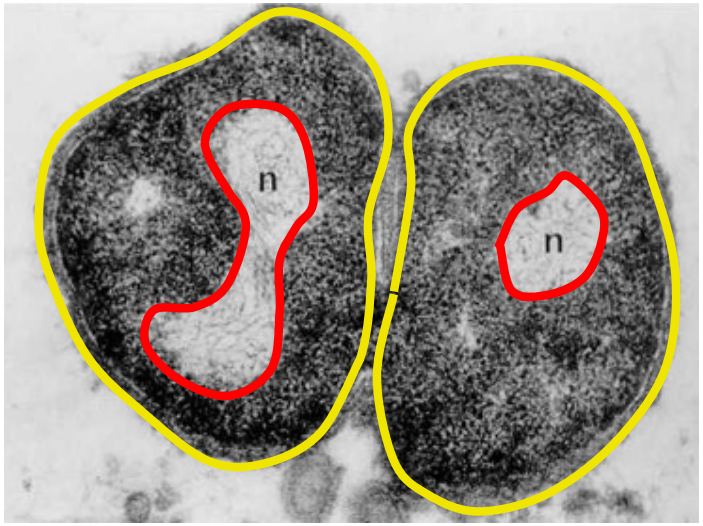
- **Archaea**
- **Bacteria** — aerobic, anaerobic, photosynthetic, etc...

Eukaryotes

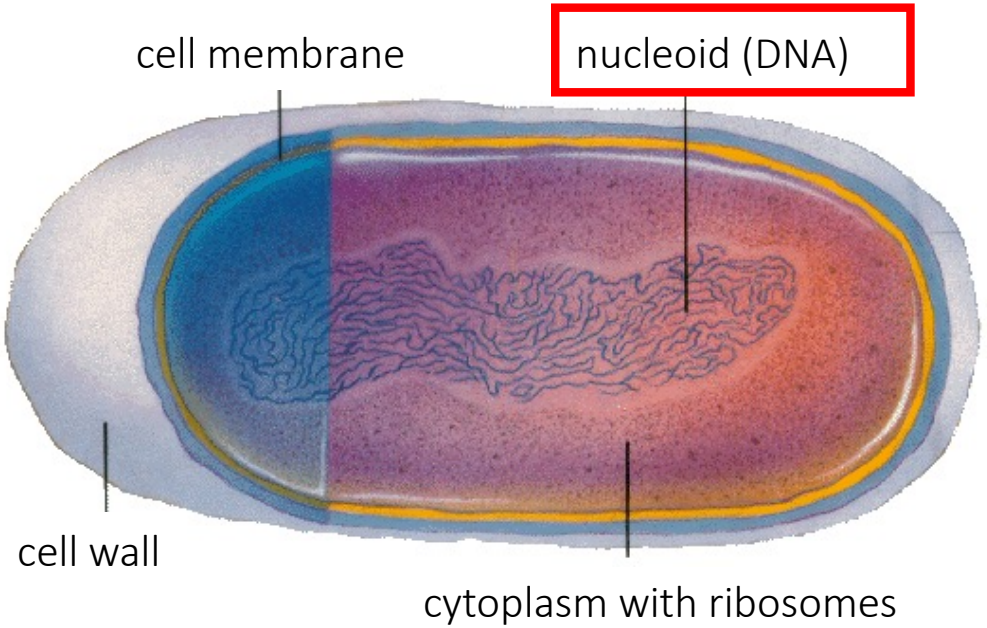
(nucleus)

- **Fungi** — unicellular/multicellular
- **Animals** — multicellular
- **Plants** — multicellular and able to carry out photosynthesis

BACTERIA



An electron micrograph of two bacteria.

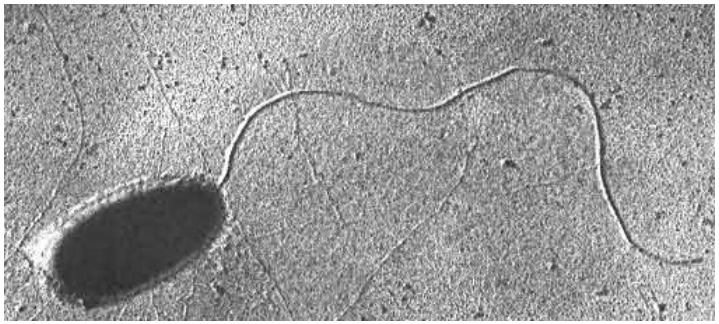


A schematic diagram of a bacterium.

Bacteria are single-cell prokaryotic organisms, ranging in size between 1-5 μm.

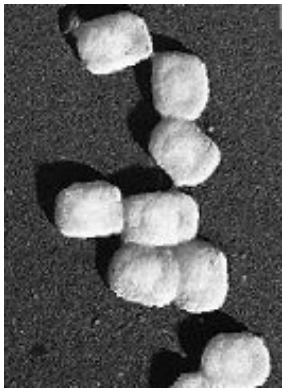
The DNA co-localises in a compact structure called the nucleoid, but there is no physical separation (i.e. no nuclear membrane) between the DNA and the rest of the cell.

Bacteria display a wide variety of shapes:



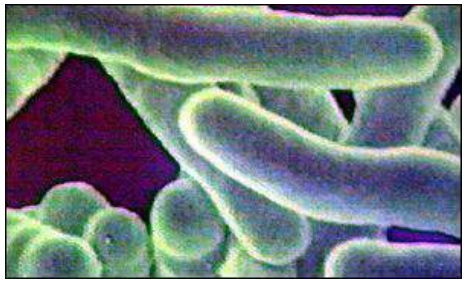
Flagellatae

Spirochete

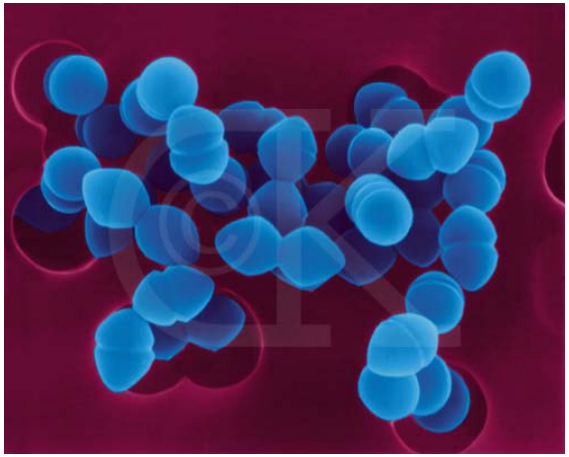


Plague bacteria

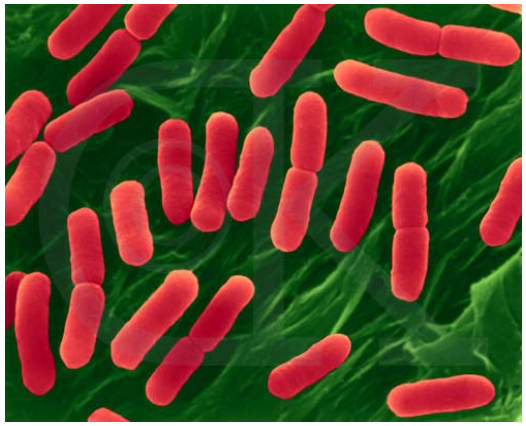
Antrax bacteria



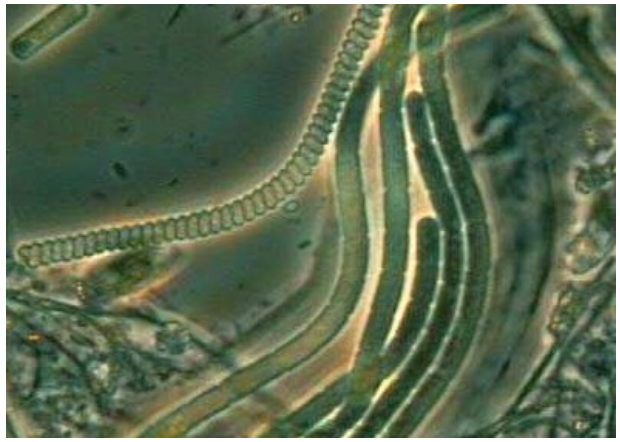
TB bacteria



Enterococcus



Escherichia coli

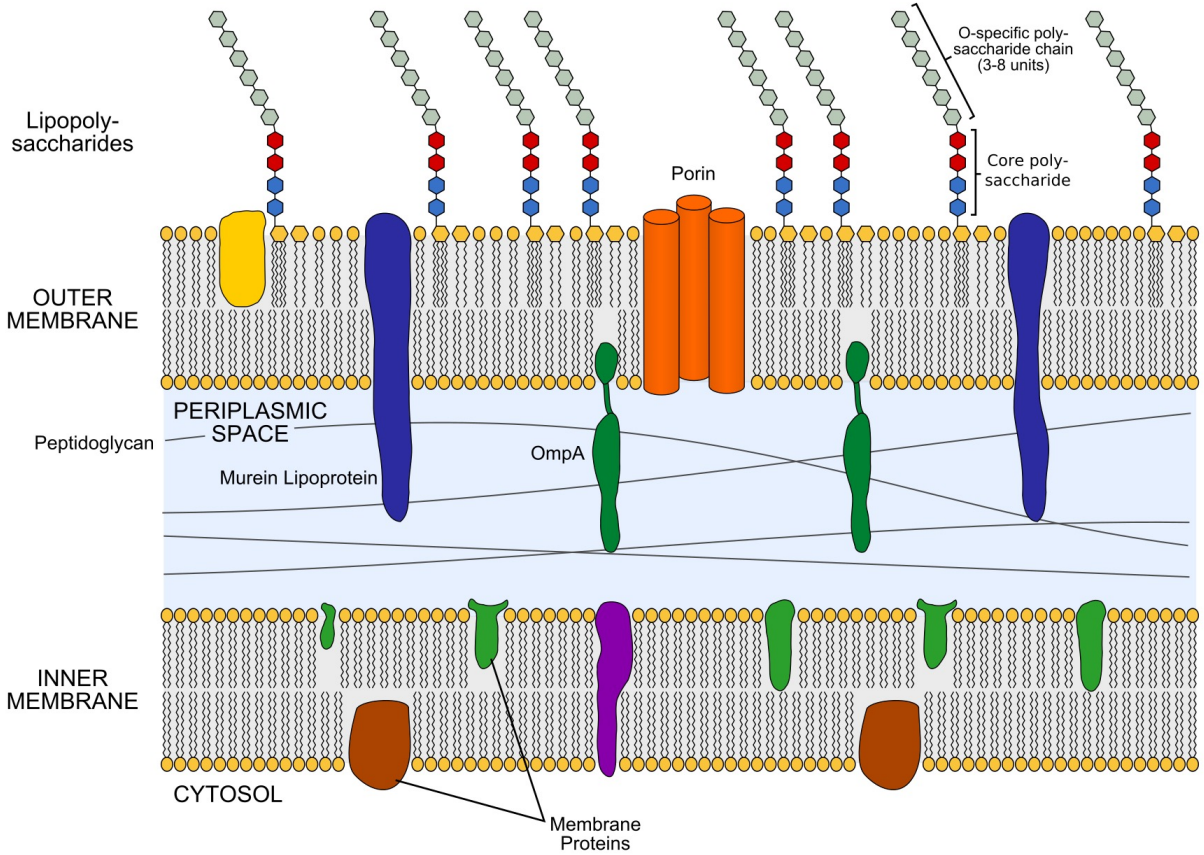


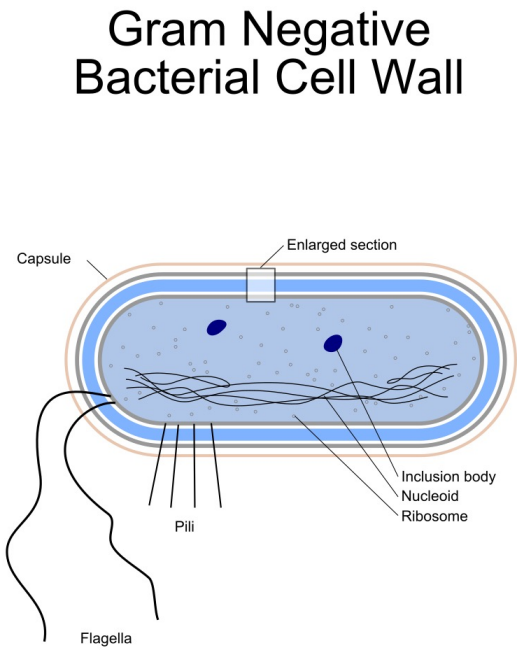
Cyanobacteria

Bacterial cell membrane

Gram positive bacteria ↦ have only one membrane impermeable to chemicals, surrounded by a cell wall made of a complex of proteins and carbohydrates

Gram negative bacteria ↦ have two membranes

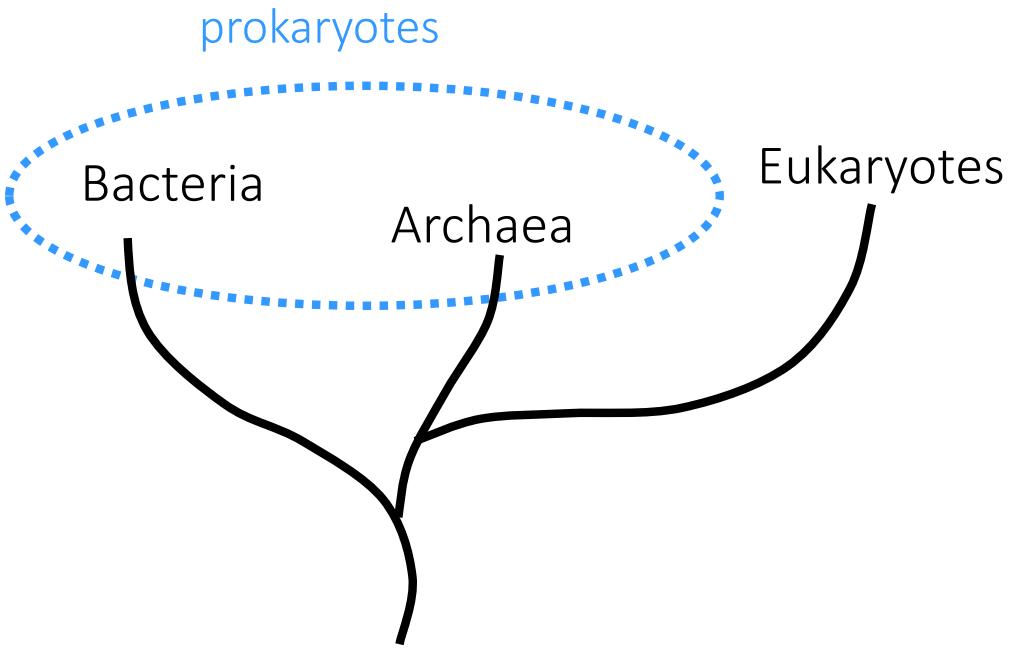




ARCHAEA

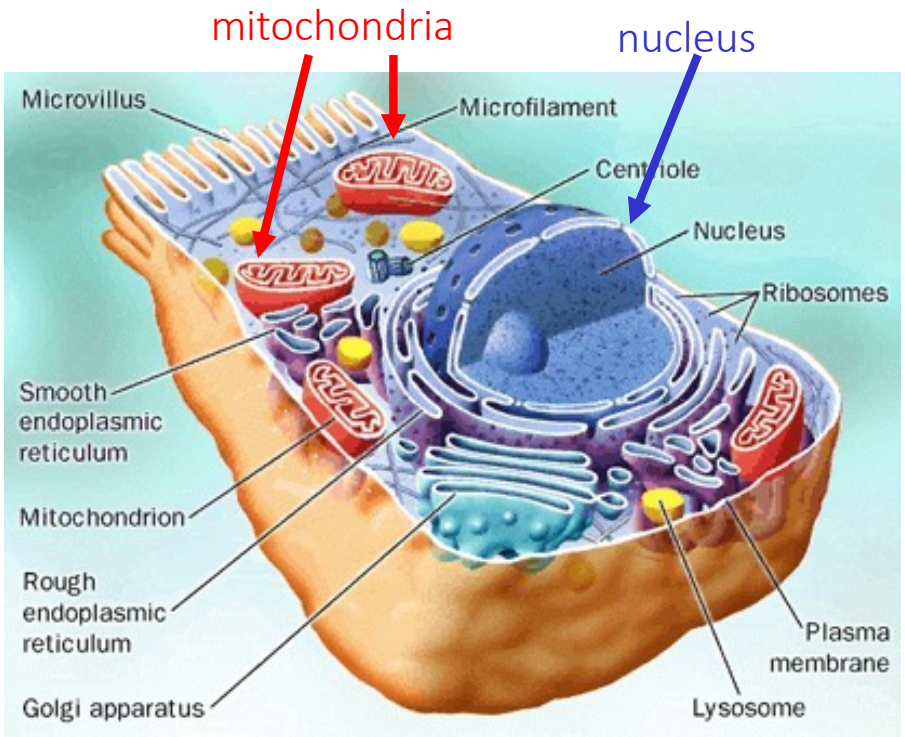
- unicellular organisms
- no nucleus (i.e. prokaryotes)
- live in very unfriendly environments (hot/sulphuric springs, the Dead Sea, deep vents in the oceans...)
- metabolic processes similar to bacteria
- but...processing of genetic information (how they copy, read, use the information written in the DNA) similar to eukaryotes!

Our current picture of the evolution of life:

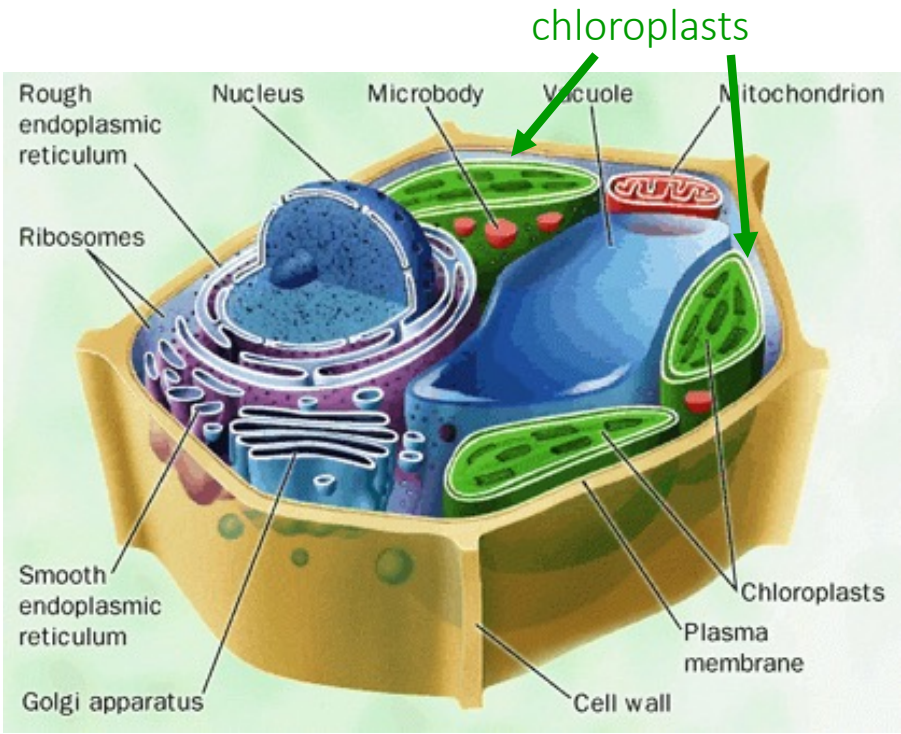


EUKARYOTES

- cell size varies between 5-50 μm
- unicellular organisms (such as yeast and protozoa)
- multicellular organisms such as animals and plants
- complex architecture, containing variety of organelles



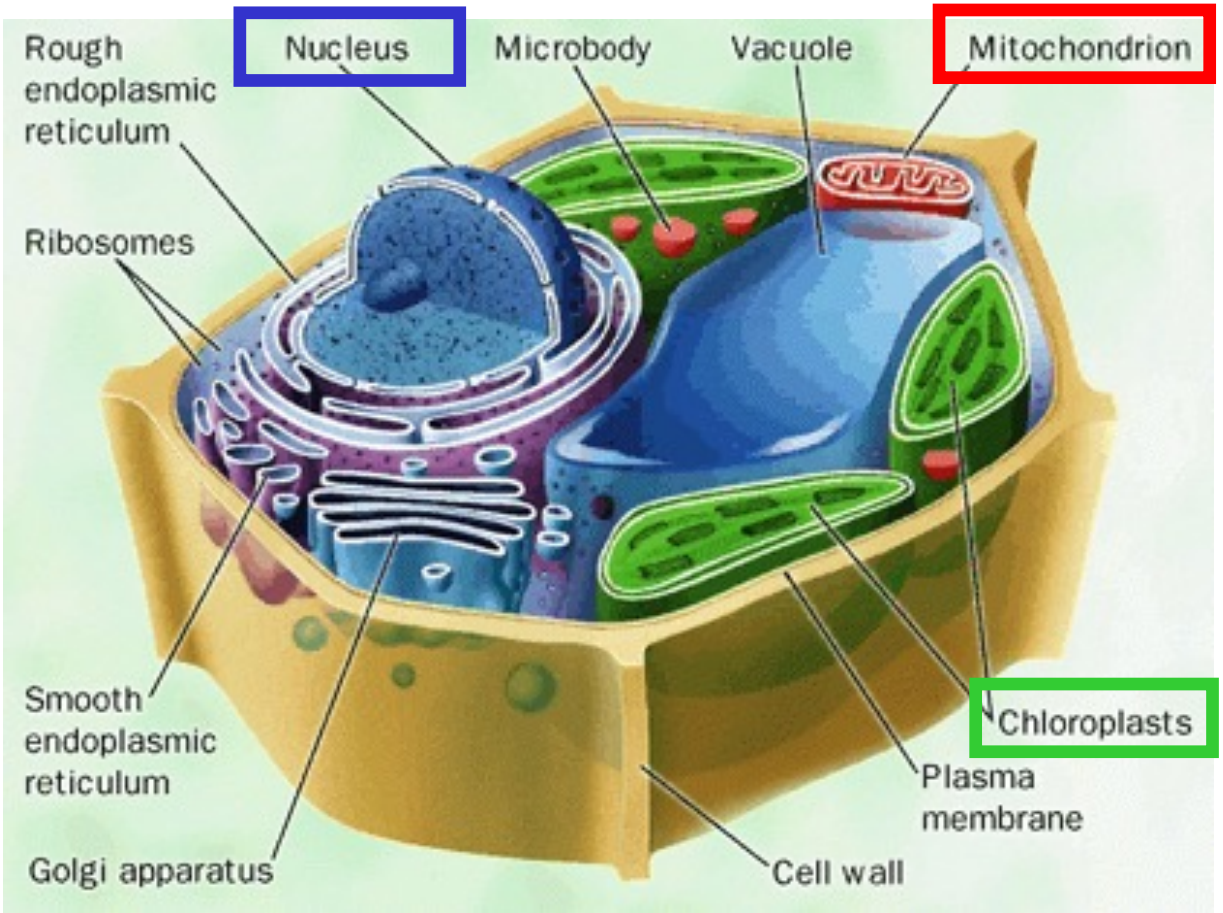
animal cell



plant cell

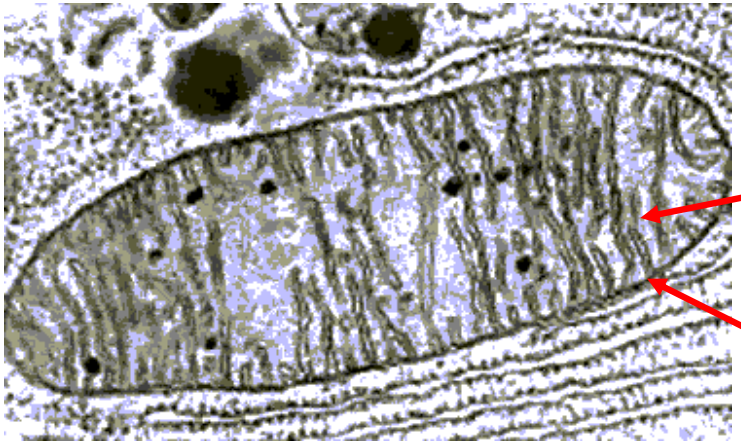
Eukaryotic organelles

- a nucleus (storing DNA)
- mitochondria (produce energy by oxidation of small molecules)
- chloroplasts (carry out photosynthesis; only in plant cells)



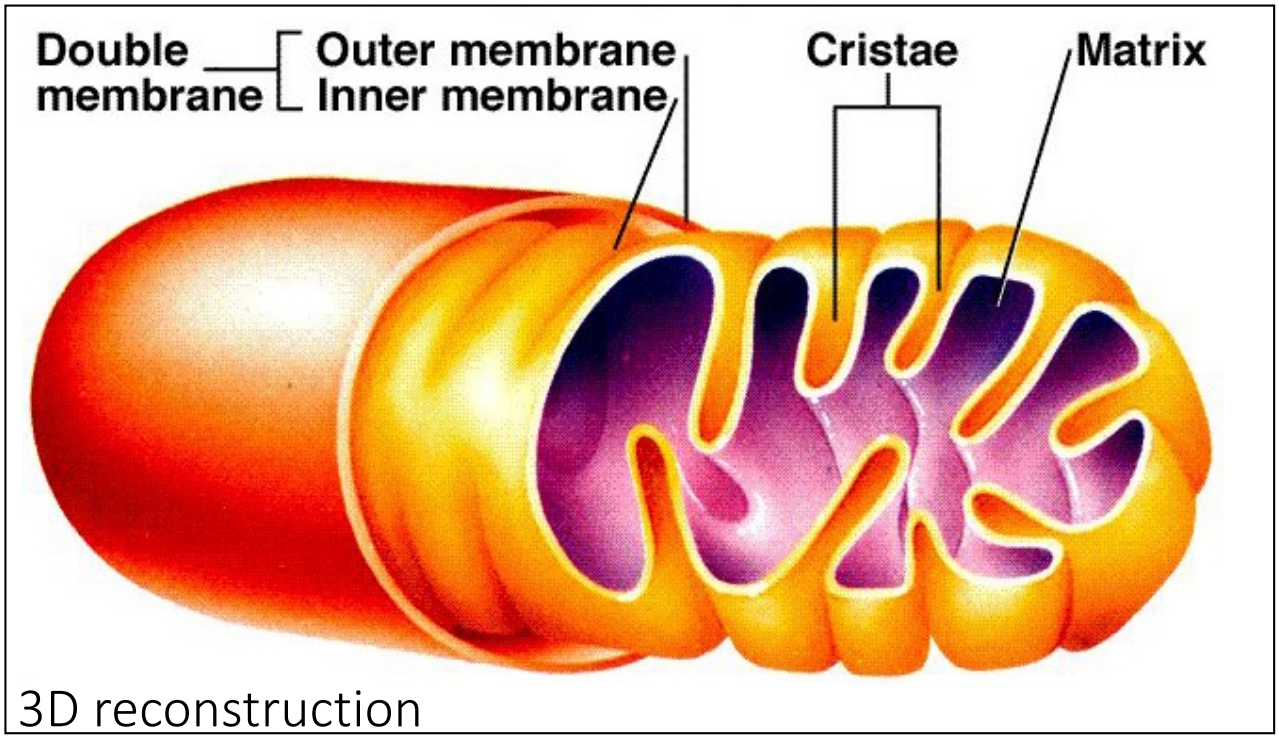
plant cell

Mitochondrion



Electron micrograph of a mitochondrion

- one external membrane
- one internal membrane forming many invaginations (cristae)



3D reconstruction

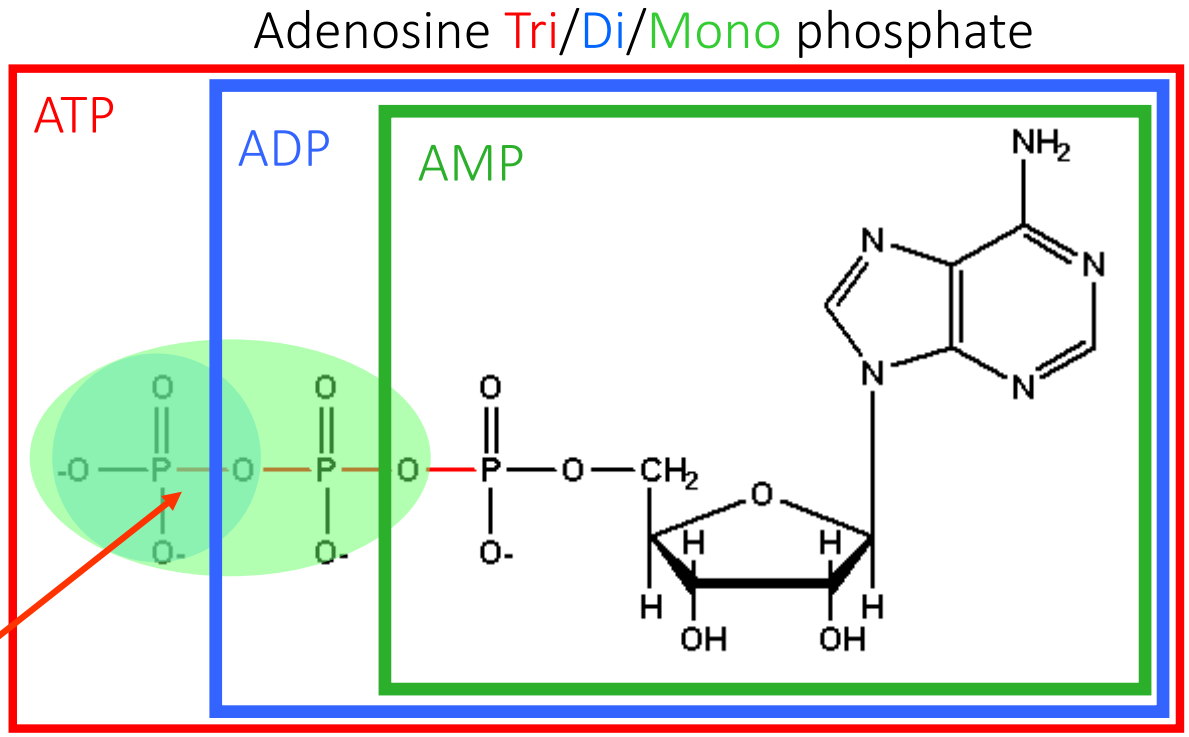
Function of mitochondria:
energy production by oxidation of small molecules (occurring in the mitochondrial matrix)

Energy in the cell: ATP

In the cell reactions that require energy are associated with ATP hydrolysis (hydrolysis= breaking down). ATP hydrolysis is an exothermic reaction, and the energy generated can be used to drive a non-spontaneous reaction.

ATP ⟼ ADP + P
(ΔH = -30 kJ/mol)

ATP ⟼ AMP + PP_i
(ΔH =-30 kJ/mol)

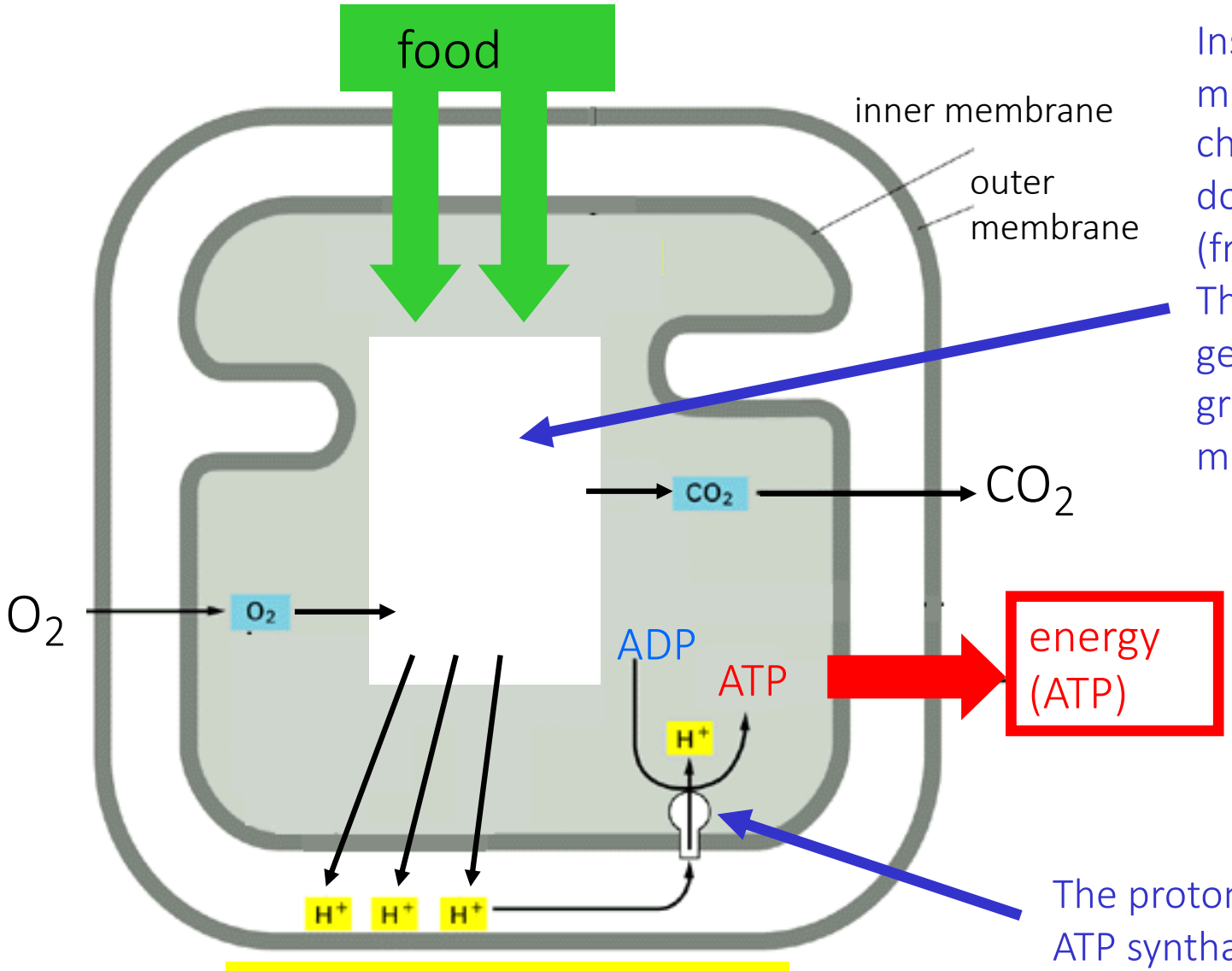


phosphodiester bonds have a large energy of hydrolysis (about 30 kJ/mol)

Energy production: accumulation of ATP

Energy consumption: breaking down (hydrolysis) of ATP ⟼ ADP or AMP

What happens in the mitochondrion?



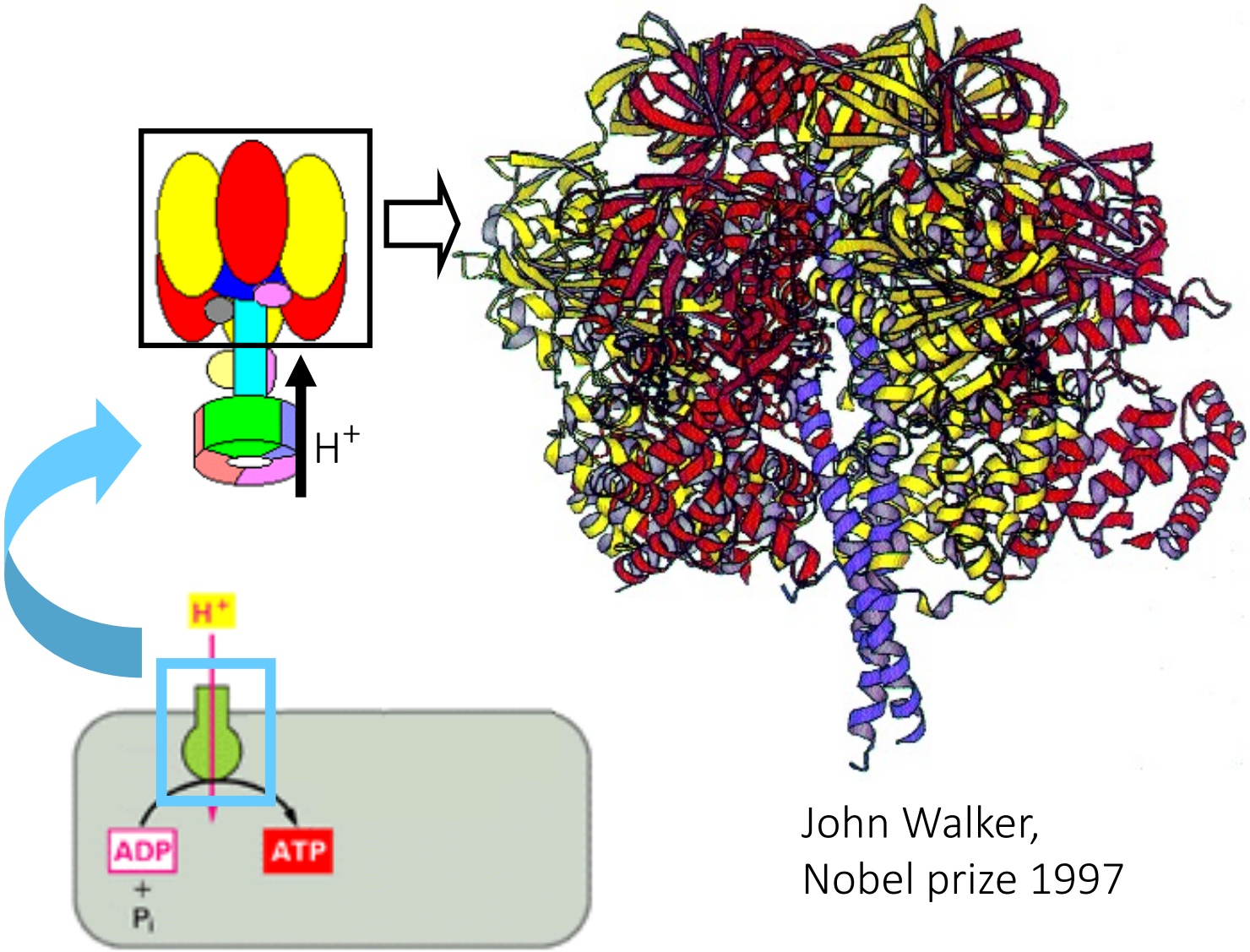
Inside the mitochondrial matrix a complex set of chemical reactions break down small molecules (from food).
This biochemical process generates a proton gradient across the inner membrane

The proton gradient drives the ATP synthase, a complex machinery that makes ATP

ATP production

The complex responsible for ATP production is called ATP synthase

The ATP synthase sits in the mitochondrial inner membrane and uses the H+ gradient to drive ATP synthesis.



John Walker,
Nobel prize 1997

Biological molecules

From a functional point of view biological molecules can be divided into:

small molecules

- made and altered by individual steps of chemical reactions
- used as substrates for making macromolecules
- used to store and distribute energy for cell processes
- broken down to extract chemical energy
- used in signalling

macromolecules

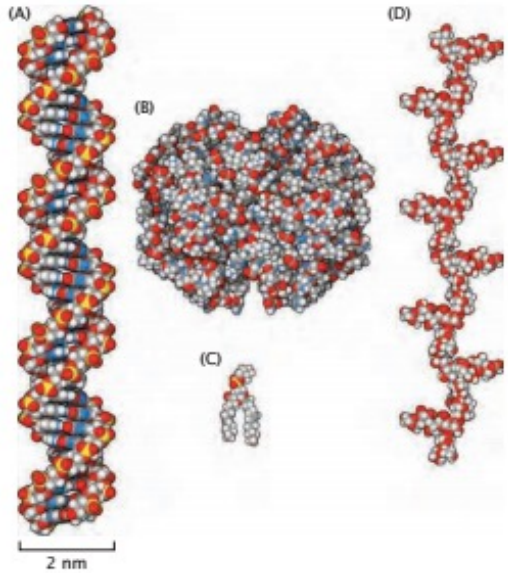
- polymers made by a linear chain of building blocks
- made by linking a defined set of small molecules (monomers) through the repetitive use of a single chemical linkage
  ↦ proteins: polymers made by a linear chain of amino acids
  ↦ nucleic acids: polymers made by a linear chain of nucleotides

EVOLUTION of LIFE = EVOLUTION OF MACROMOLECULES

Macromolecules

Macromolecules can be assembled by the cell from a small number of simpler subunit or precursor molecules. It is the combinatorial assembly of these simple subunits that gives rise to their tremendous structural diversity.

A cell needs only a few chemical reactions to be able to synthesize these sets of subunits from the food in its environment.



Atoms: O, C, N, H, sometime S, P

(A) Atomic structure of a small fragment of the nucleic acid DNA in the B form
(B) atomic structure of the oxygen-carrying protein hemoglobin (PDB 1hho)
(C) phosphatidylcholine lipid molecule from a cell membrane
(D) branched complex carbohydrate

Macromolecules

Proteins:
Structural elements that catalyze reactions fundamental to life
(TENS OF THOUSANDS OF DIFFERENT PROTEINS IN A SINGLE ORGANISM!!)

Carbohydrates:
Energy storage, surface properties on cell membranes, cell walls

Lipids:
Cell membranes, separate organelles in cells (HUNDREDS OF DIFFERENT LIPIDS EXIST)

Nucleic Acids:
Memory, operating instructions, constitute the operation mechanism to generate macromolecules

Macromolecules

Proteins:

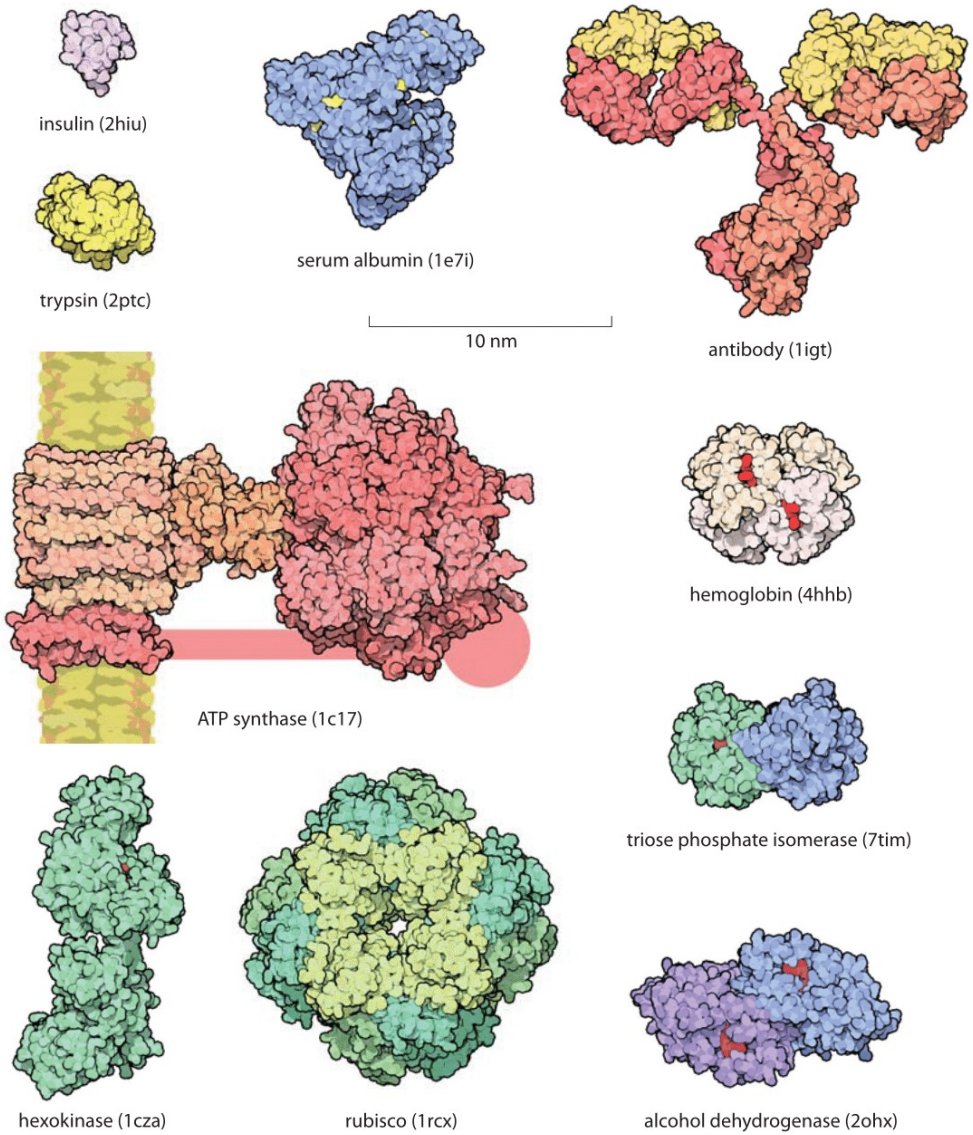
molecular machines, display a wide variety of 3D shapes and of biological functions

- catalyse small molecules synthesis and degradation
- allow cells to move and do work
- maintain cell rigidity
- control genes, switching them on/off
- direct their own synthesis
- move molecules across membranes

Nucleic acids (DNA and RNA):

- contain a coded representation of all proteins of a cell
- contain a coded set of instruction about when proteins have to be made and in which quantities

Proteins



organism	median protein length (amino acids)
H. sapiens	375
D. melanogaster	373
C. elegans	344
S. cerevisiae	379
A. thaliana	356
5 eukaryotes (above)	361
67 bacteria	267
15 archaea	247

http://book.bionumbers.org/how-big-is-the-average-protein/

Central Dogma

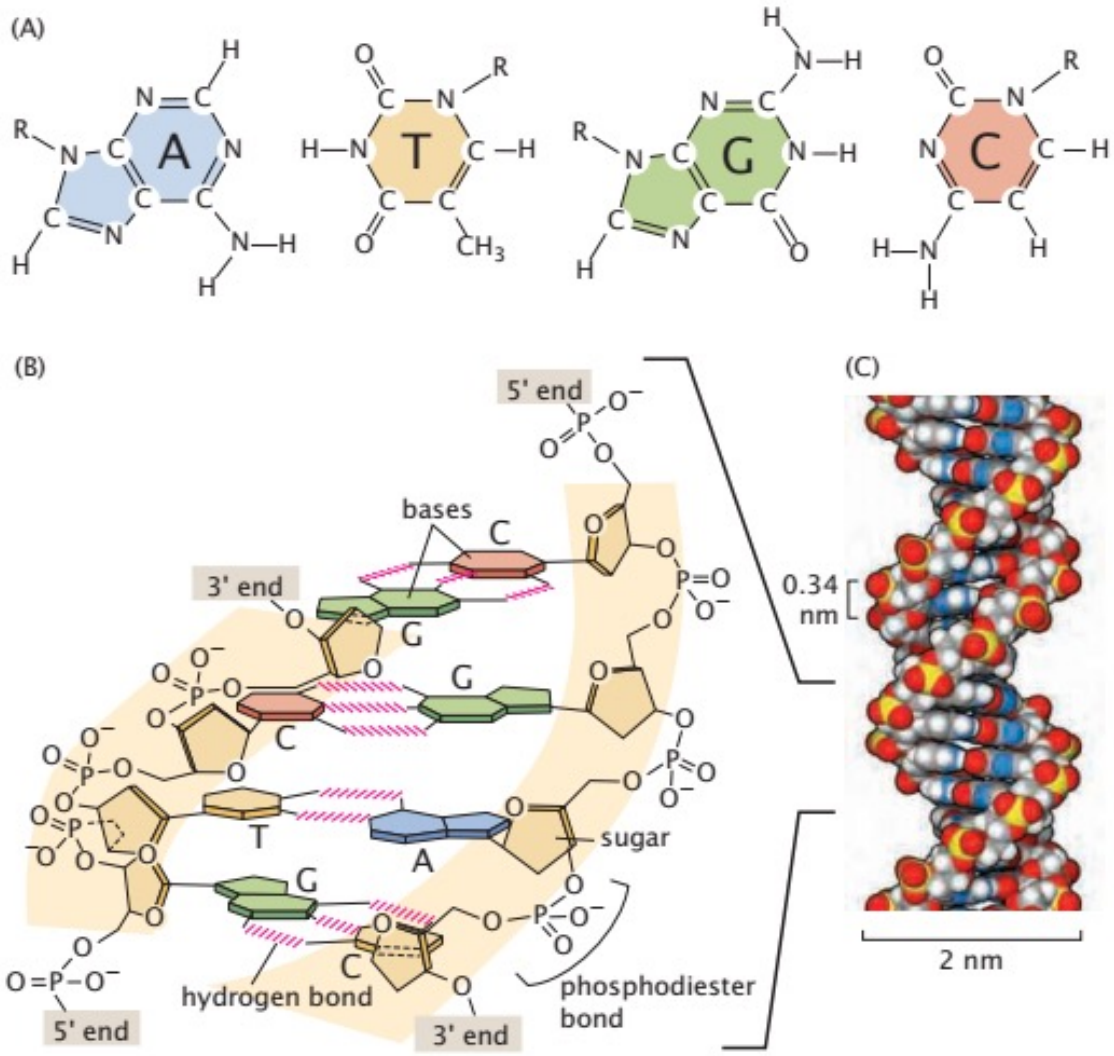
CENTRAL DOGMA OF STRUCTURAL BIOLOGY

DNA ------- PROTEIN ------FUNCTION

Also the big variety of sizes and structures in the biological world, responds to the function! The central dogma can be applied to other length scales.

Biophysics: underline macromolecules/cells structure/function/structural transition from simple principles. Explain complex processes **macromolecular structure; cell adaptation; fluctuactions.**

DNA: alphabet with 4 letters
Proteins: alphabet with 20 letters



How can just four nucleotide bases be translated into protein sequences containing 20 different amino acids?

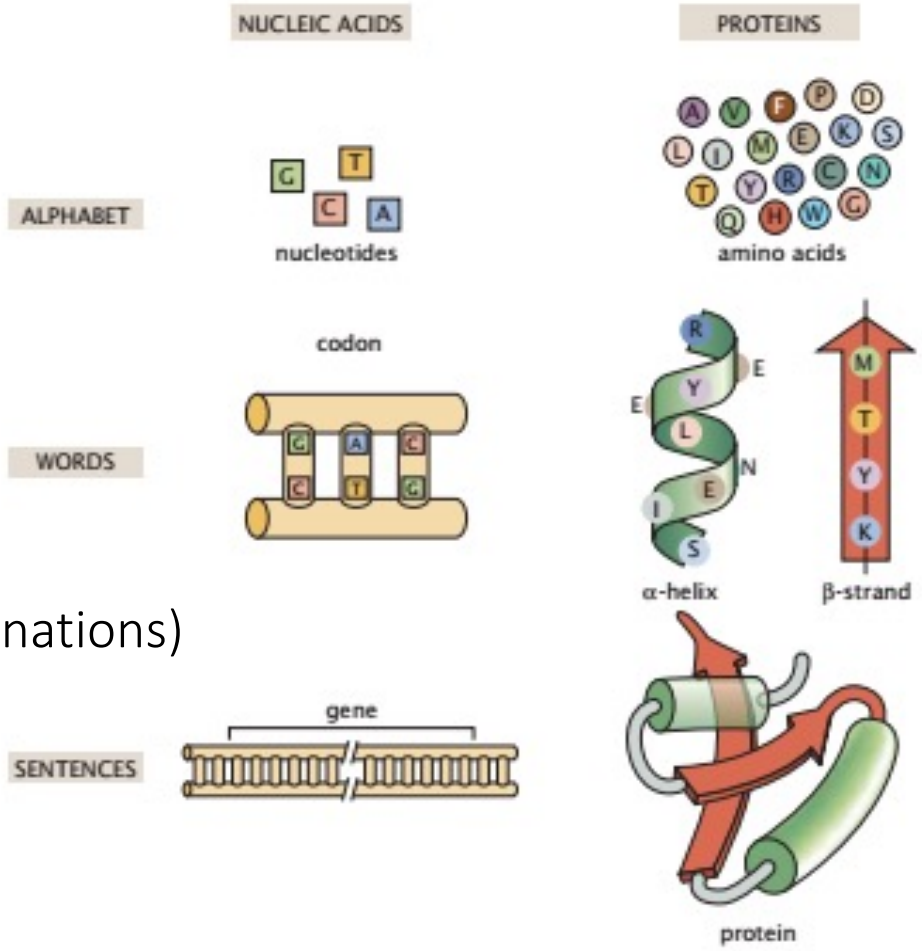


Figure 1.2: Illustration of Crick's "two great polymer languages." The left-hand column shows how nucleic acids can be thought of in terms of letters (nucleotides), words (codons), and sentences (genes). The right-hand column illustrates a similar idea for proteins, where the letters correspond to amino acids, the words to elements of secondary structure such as α helices and β strands, and the sentences to fully folded functional proteins.

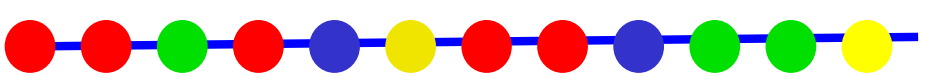
64 different codons (4^3 combinations)
For 20 aminoacids!!

The sequences associated with nucleic acids and proteins are linked mechanistically (Genetic Code) through the ribosome which takes nucleic acid sequences (in the form of messenger RNA (mRNA)) and converts them into amino acid sequences (in the form of proteins).

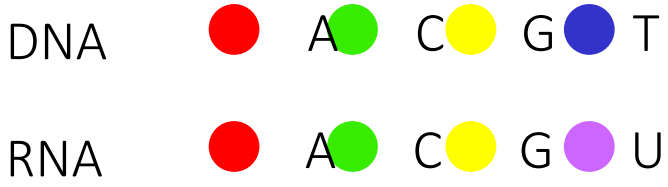
Nucleic Acids

Nucleic acids

Nucleic acids are linear chains of nucleotides.



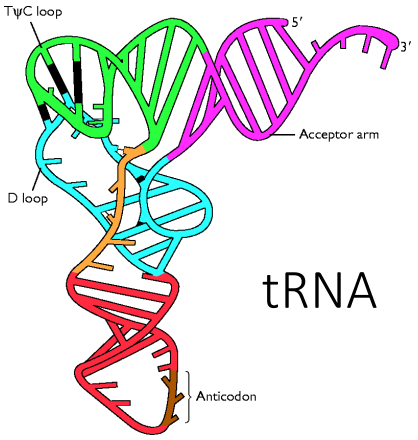
There are 5 different types of nucleotides, but either type of nucleic acid (DNA or RNA) contains only 4.



These chains fold in 3D due to the hydrogen bonds between pairs of nucleotides (A=T / A=U; C=G):

- in DNA two chains wraps around each other forming a double helix
- RNA can assume a variety of shapes

DNA



tRNA

Overview of nucleic acid architecture

1) structure and chemistry of nucleotides:

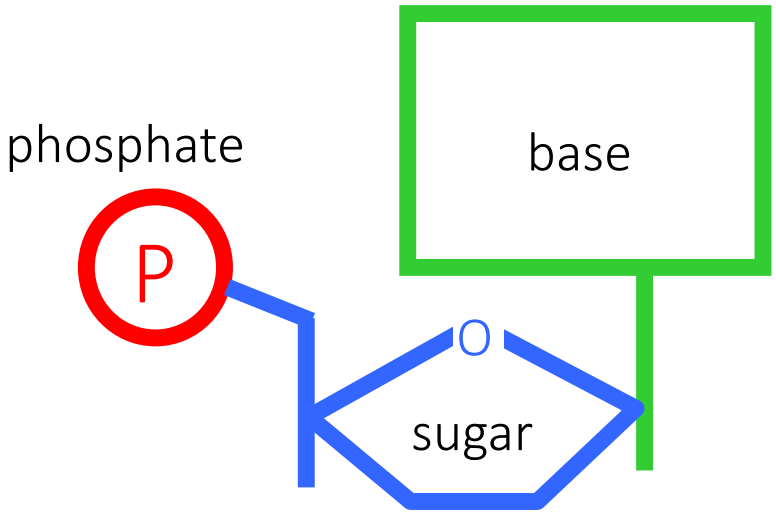
2) how nucleotides are linked together through phosphodiester bonds to form a nucleic acid chain

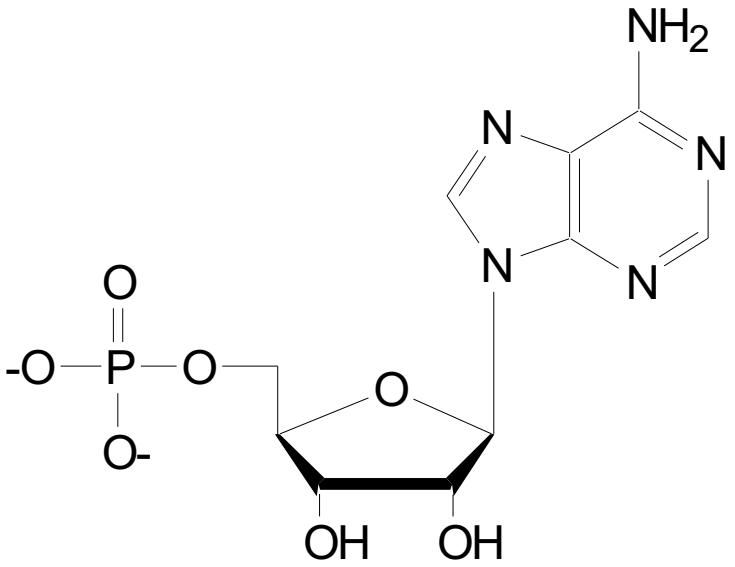
3) base pairing and the 3D structure of DNA and RNA

Structure of nucleotides

A nucleotide has 3 parts:

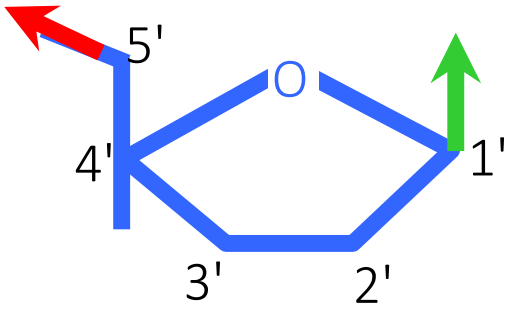
a sugar
a phosphate
a base





example: Adenosine MonoPhosphate (AMP)

Sugars: ribose or deoxyribose

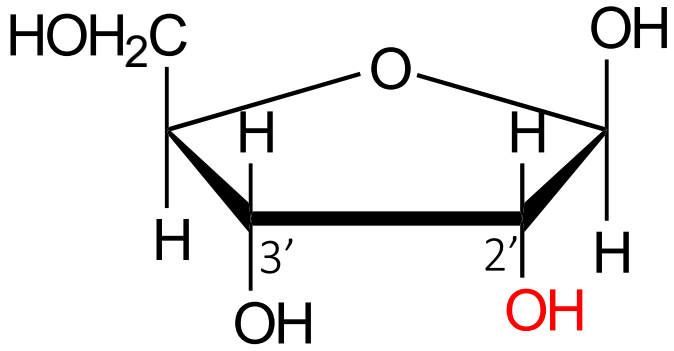


The sugar in nucleic acids is a pentose (5 C atoms numbered from 1' to 5'):

- the 1' C is linked to the base
- the 5' C is linked to the phosphate

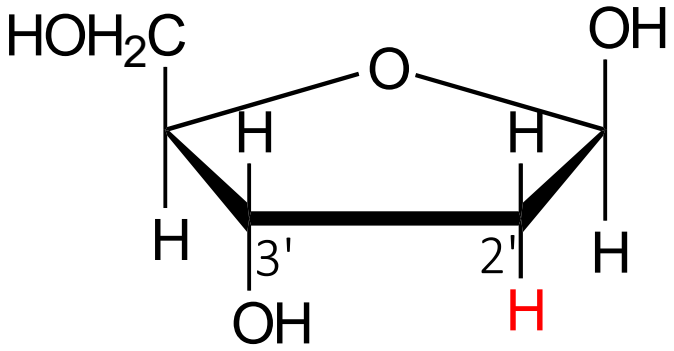
The are two sugars used in nucleic acids:

ribose, in RNA



ribose has a OH group both on the 2' and 3' C

2'-deoxyribose, in DNA

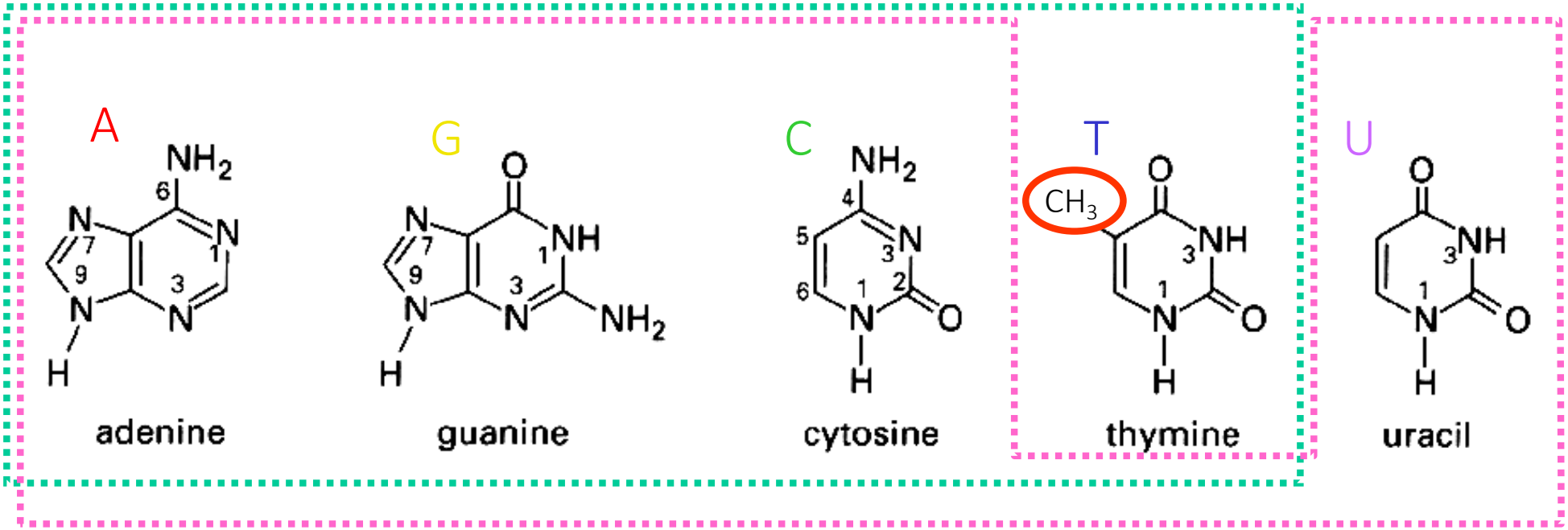


in 2'-deoxyribose the OH at 2' is substituted by an H

Bases: A, T, C, G, U

PURINES: two fused rings

PYRIMIDINES: 1 ring only



DNA contains A, T, C, G

RNA contains A, U, C, G

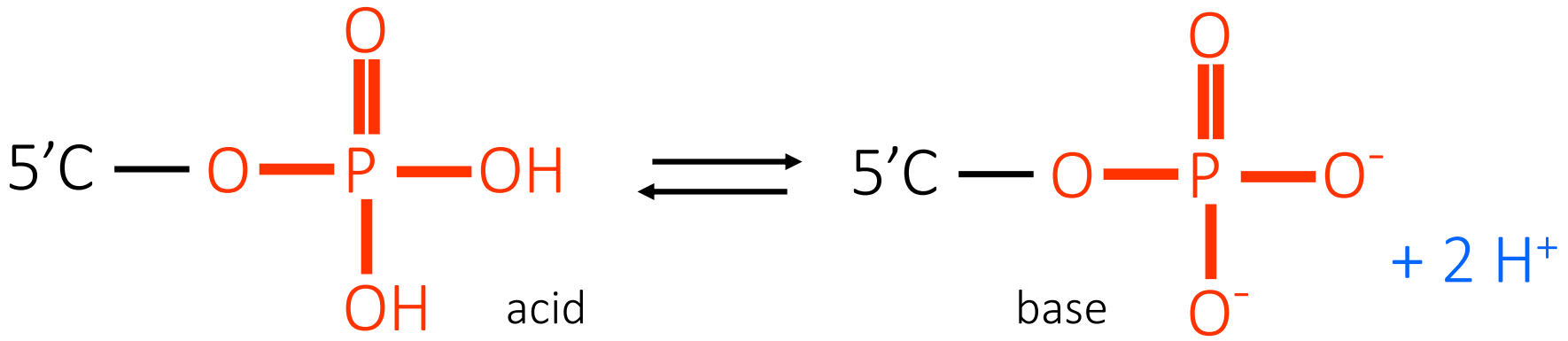
in RNA T is substituted by U
(lacks CH_3 in position 5)

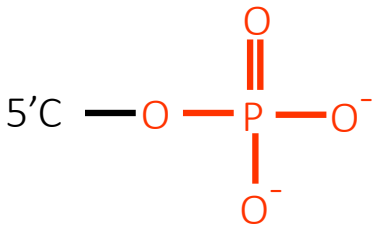
'Bases' is a misleading name: none of them is protonated at neutral pH

The phosphate group

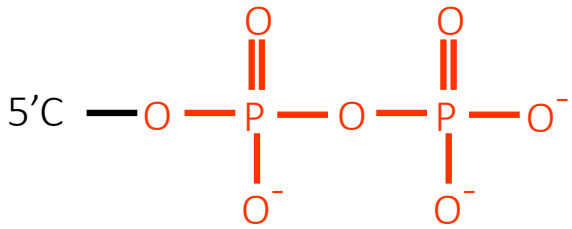
Why ‘nucleic acid’?

The acidic character is due to the presence of the phosphate group:

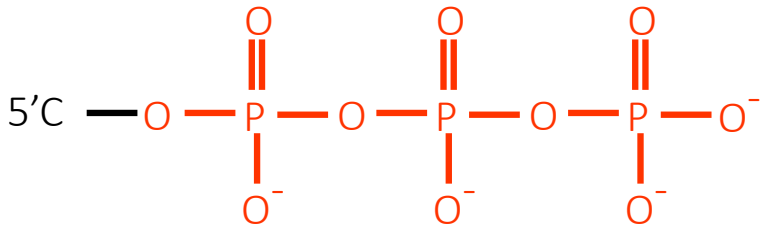




NMP=nucleotide monophosphate



NDP=nucleotide diphosphate



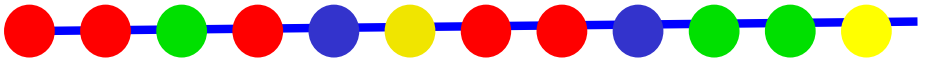
NTP=nucleotide triphosphate

where N could be A, C, G, T, U

Overview of nucleic acid architecture

1) structure and chemistry of nucleotides

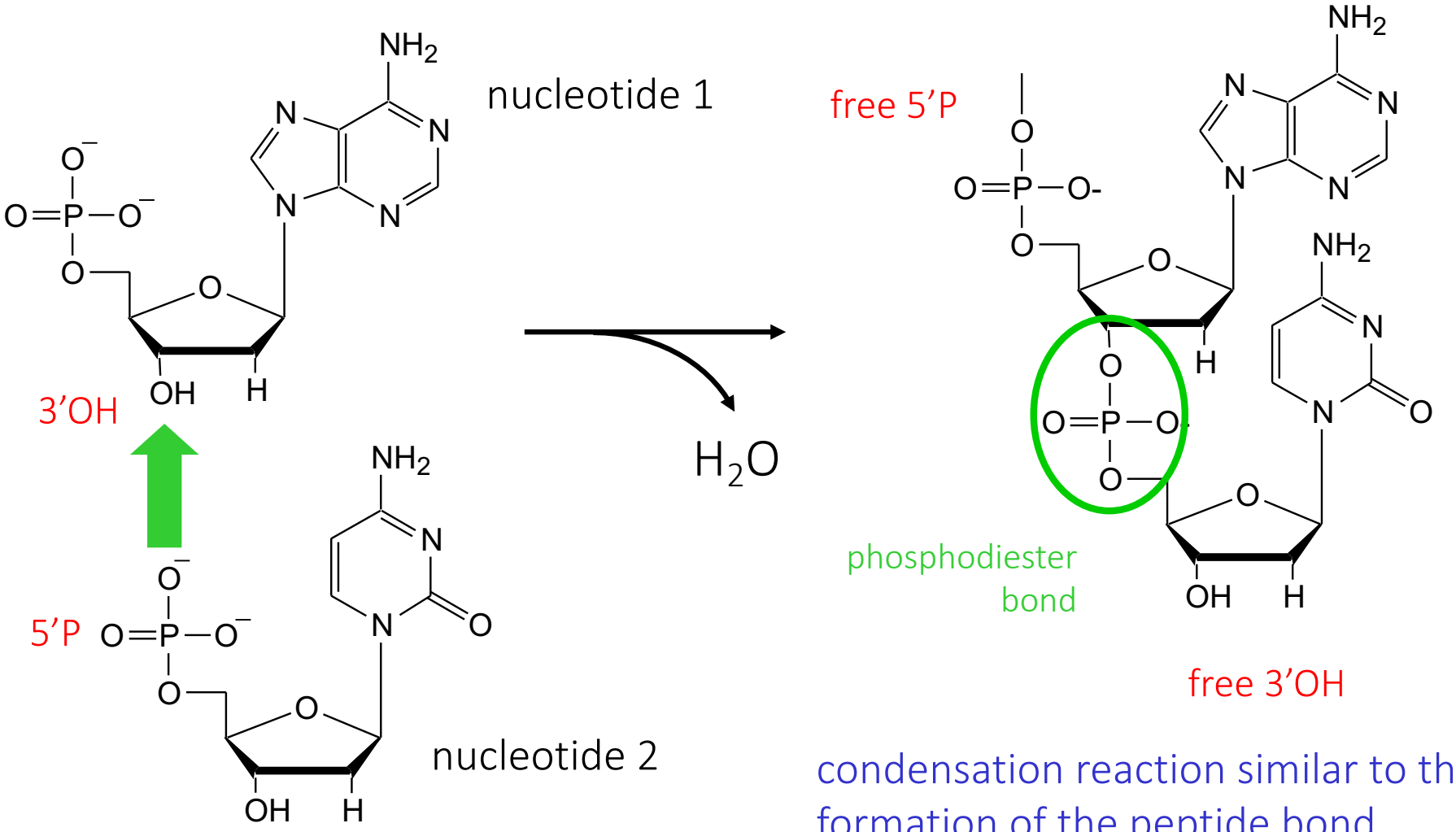
2) how nucleotides are linked together through phosphodiester bonds to form a nucleic acid chain



3) base pairing and the 3D structure of DNA and RNA

Polymerisation of nucleotides

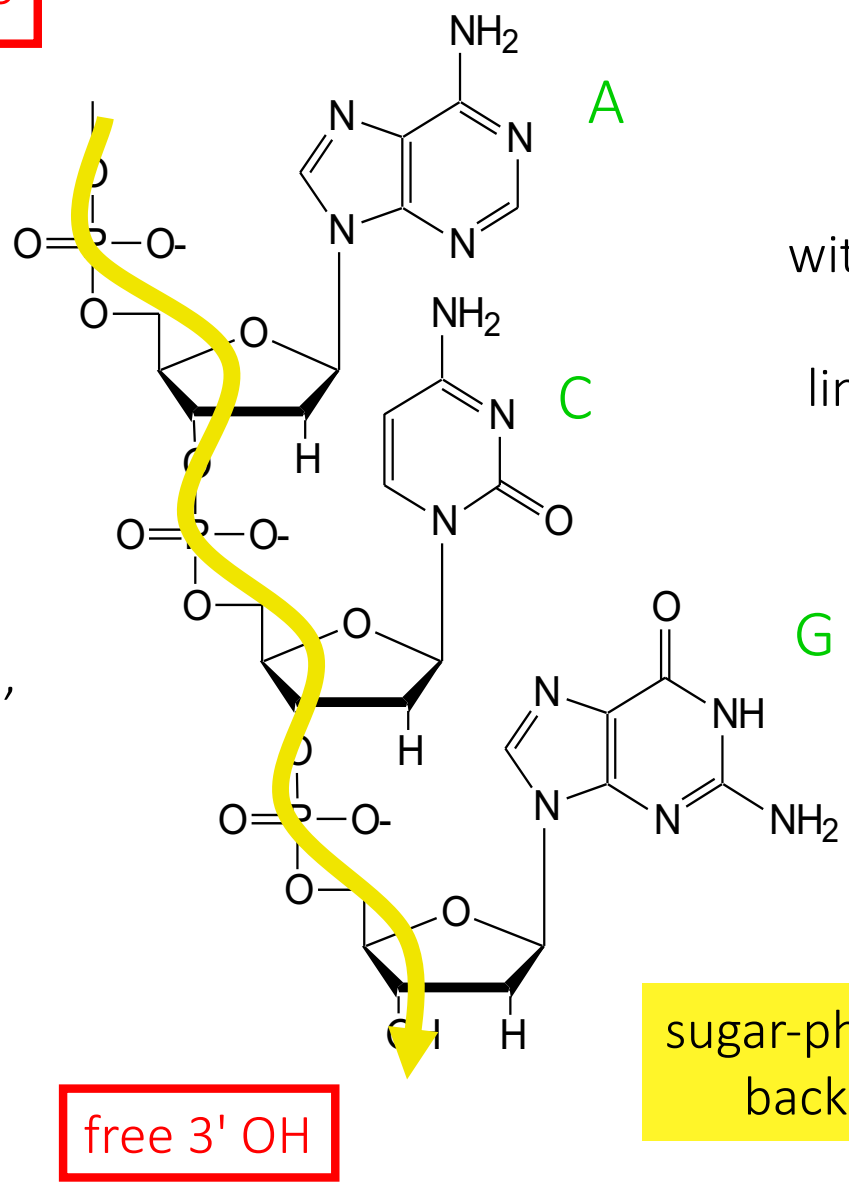
The OH on the 3' of the sugar of one nucleotide forms a bond (phosphodiester bond) with the phosphate on the 5' of another nucleotide.



condensation reaction similar to the formation of the peptide bond

Primary sequence

free 5' P



Convention:
nucleotide sequences are read in the 5' ↦ 3' direction, so that the first nucleotide has a free 5' P and the last a free 3' OH
Here: ACG...

The primary structure of a nucleotide chain is a sugar-phosphate backbone with all the bases sticking out. A chain is defined by the linear sequence of the bases.

The chain has a polarity, with one end having a free 5' P and the other end a free 3' OH.

Overview of nucleic acid architecture

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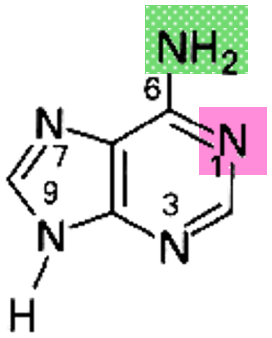
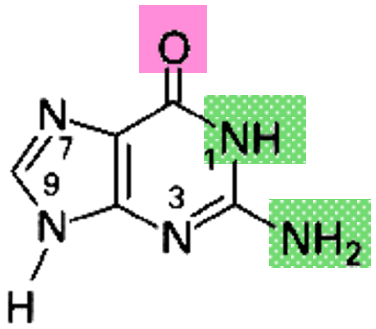
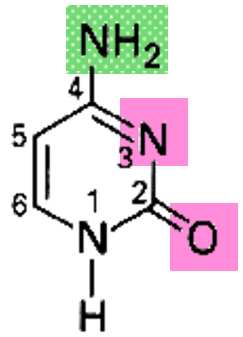
Base pairing



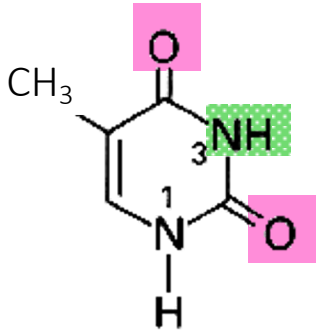
adenine



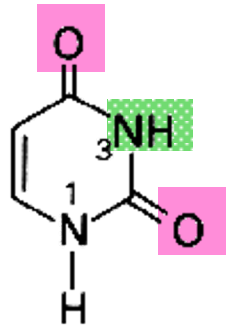
guanine



cytosine



thymine

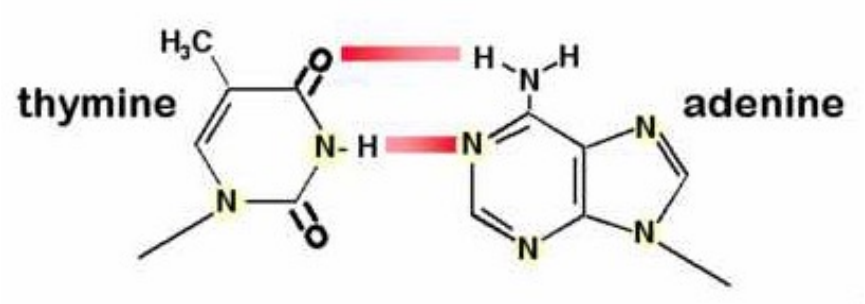


uracil

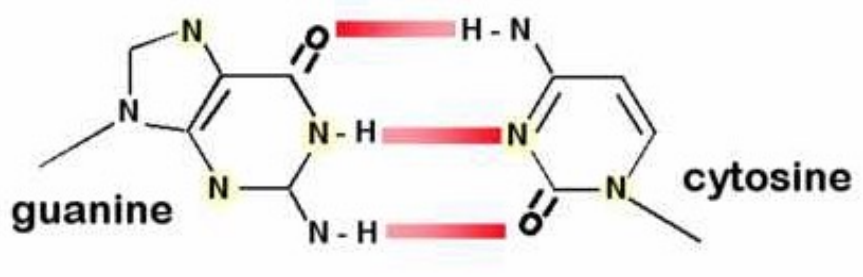
Hydrogen bond donor

Hydrogen bond acceptor

Watson-Crick base pairing:



2 hydrogen bonds



3 hydrogen bonds

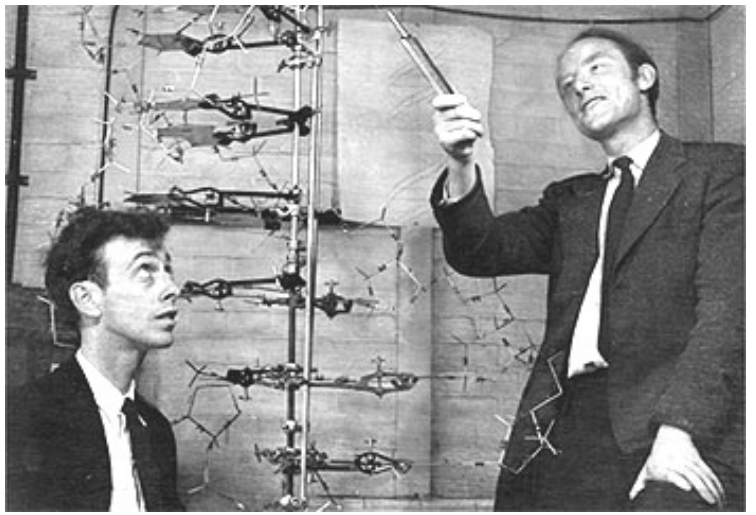
uracil has the same HB properties as thymine and can therefore make the same HB with adenine

Deoxyribonucleic acid (DNA)

DNA is the cellular library storing all the information required to build all proteins. This information is stored in units called genes: each gene is a segment of DNA containing a coded representation of a protein.

1944: DNA carries the genetic information (Avery, MacLeod, McCarthy)

1953: Double helical structure of DNA unravelled by J. Watson and F. Crick by careful analysis of the diffraction patterns from DNA fibers collected by R. Franklin and M. Wilkins.



Information available?

- DNA is made by long chains of polynucleotides
- the base composition is such that [A]=[T] and [C]=[G]
- fiber diffraction pattern indicated the presence of an helix with 10 units per turn and a characteristic spacing of 3.4 Å.

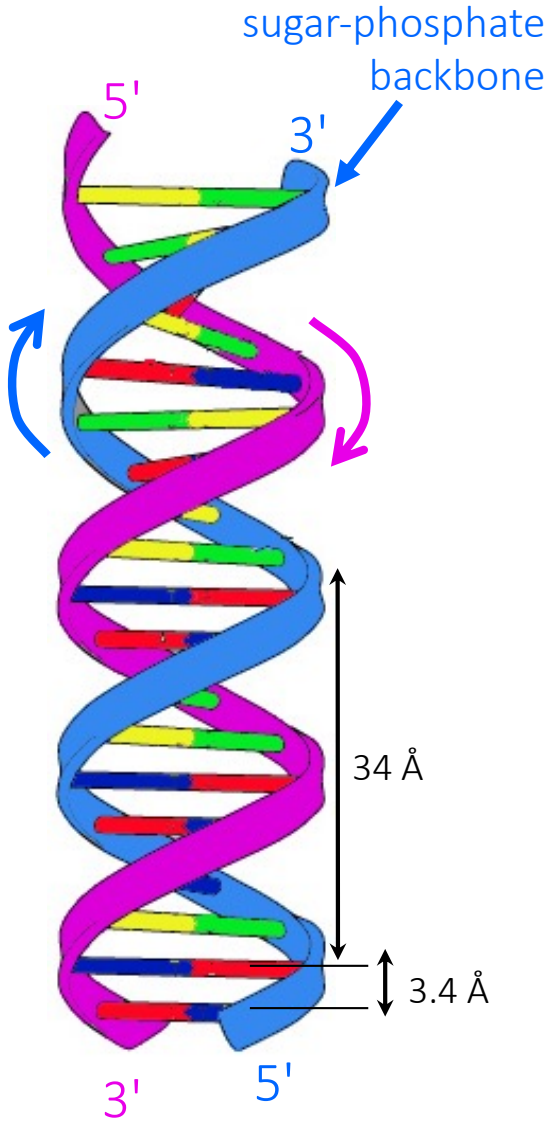
Model of DNA proposed by Watson & Crick

- DNA consists of two polynucleotide chains (strands) winding into a right-handed double helix
- the orientation of the two strands is antiparallel
- the sugar-phosphate backbone is on the outside
- the bases project into the interior
- the two strands are held together by base-pairing:

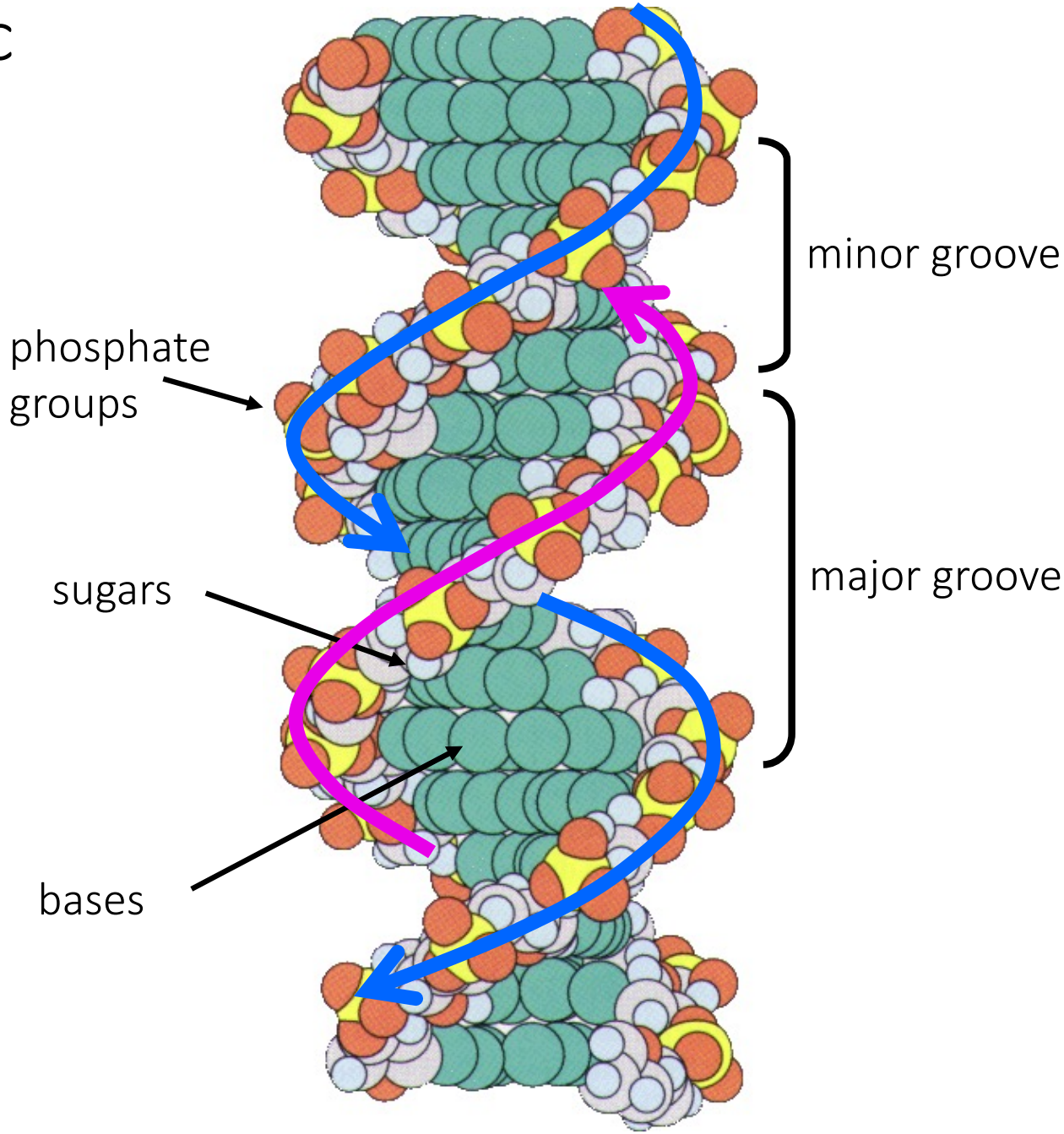
A=T (2 hydrogen bonds)
G=C (3 hydrogen bonds)

- pairs of bases are stacked on top of each other, 3.4 Å apart along the helical axis
- one helical turn is 34 Å, corresponding to 10 base pairs

The two strands are therefore held together by non covalent interactions (HB between paired bases, hydrophobic interactions between the stacked bases)



A more realistic model:

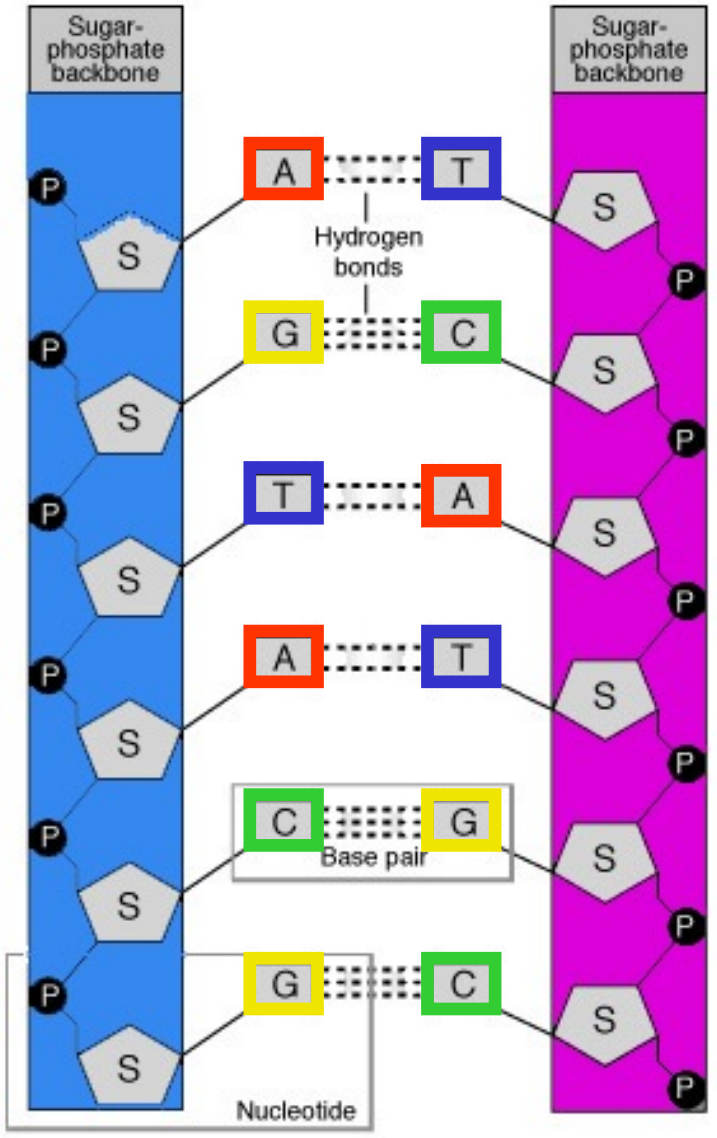


The two strands have complementary sequences

If I know the sequence of one strand I can always find the other:

```
5′ AATCGAACACCGTACCGT 3′
   ||||||||||||||||||
3′ TTAGCTTGTGGCATGGCA 5′
```

Strands can be temporarily separated by breaking the hydrogen bonds and hydrophobic interactions holding them together (for example, by increasing the temperature); the two strands can then re-anneal going back to the original structure.



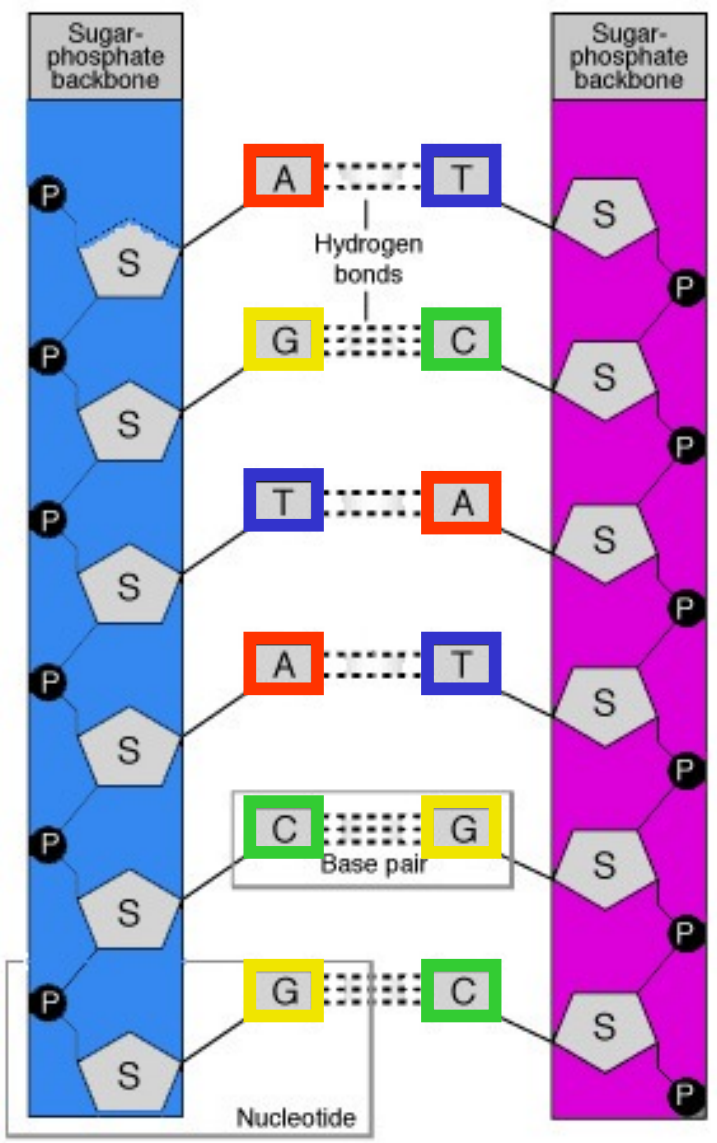
Energy Considerations for Unwinding DNA:

A-T pairs are held by two hydrogen bonds.
G-C pairs are held by three hydrogen bonds.

Base Pair Energetics:
On average, the energy required to break a hydrogen bond in DNA is approximately 1-2 kcal/mol per bond.
A-T pairs: ~2-4 kcal/mol
G-C pairs: ~3-6 kcal/mol

ATP Hydrolysis:
Helicase enzymes unwind the DNA by consuming ATP. **The hydrolysis of one molecule of ATP releases about 7.3 kcal/mol** of energy under physiological conditions.
For each base pair of DNA unwound, a helicase hydrolyzes one molecule of ATP.
(at rate of 50 to 1,000 base pairs per second!)

Boltzmann constant $k_B = 1.38 \times 10{-}23$ J/K
T=300 K
K_BT= **$4.14 \times 10{-}21$ J** or **26 meV**



Molecular forces

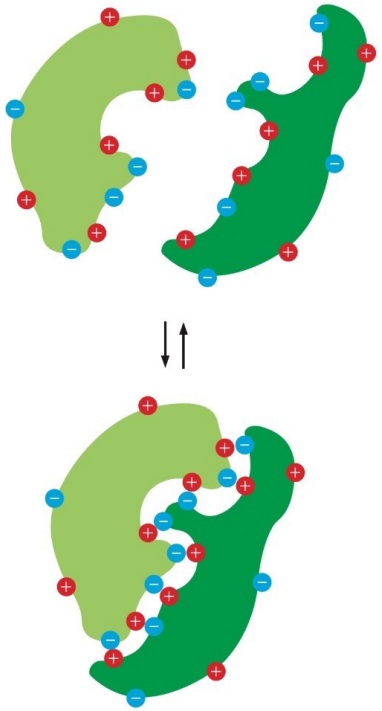
Govern how protein folds (DNA/RNA, lipid bilayer etc.) and which of its different conformations will predominate; drive ligand-macromolecules association

Covalent bonds:

- strength and direction

Non-covalent interactions:

- multipole interactions
  - ion-ion
  - ion-dipole
  - dipole-dipole ⇨ hydrogen bond
- induction interactions
- dispersion forces

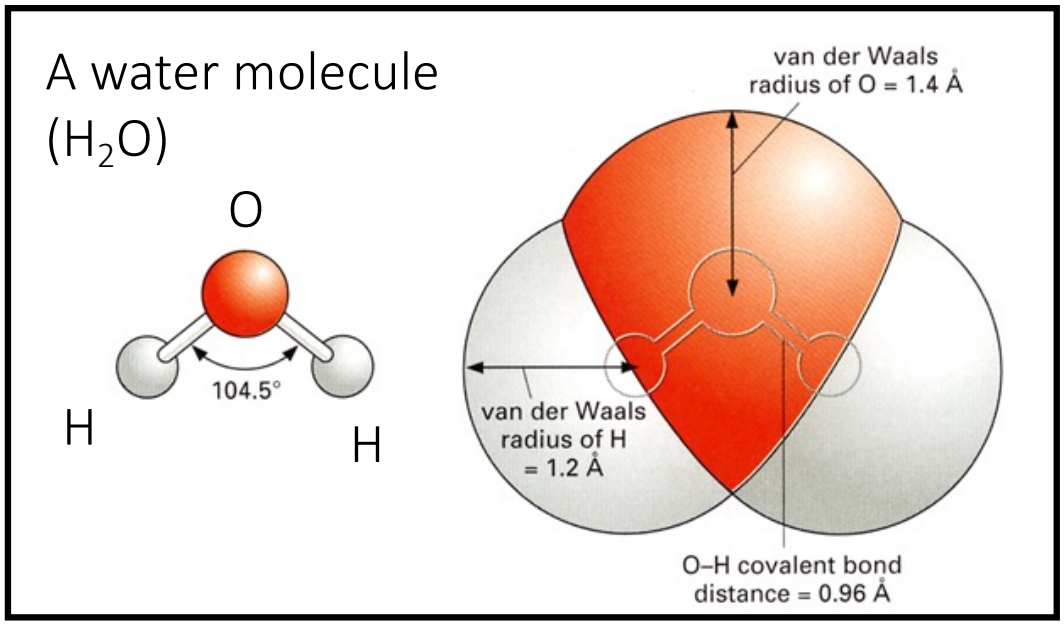


The final structure will be the result of the interplay of the different forces: complexity!

Covalent bonds

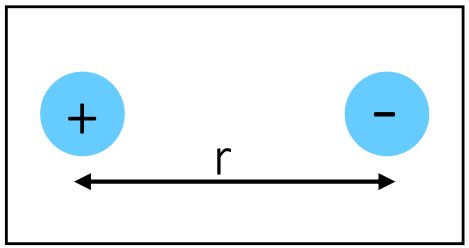
Covalent bonds are what hold “molecules” together

- strong (200-800 kJ/mol) ⇨ compare with RT~2.6 kJ/mol at 37º
- have well defined lengths
- have well defined directions



The Coulomb potential

ion-ion interactions



$$U = \frac{Q_1 Q_2}{4\pi\varepsilon_0\varepsilon_r \mathbf{r}}$$

50-350 kJ/mol

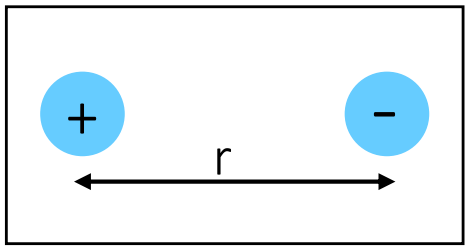
Characterizes the response of the surrounding medium to an electric field: depends on how easily the molecules are polarized

Water has a large value of ε_r (about 80). It counteracts the electric field (water mol. are highly polarizable, easily rotate)

In water ε_r is strongly T dependent decreasing by 0.46% per degree K near RT. At T= 300 K TS = -1.38 G, greater than the free energy G. Therefore, the Coulomb potential is a balance between ion-ion and ion-water molecule interaction. Ions make work on surrounding water forcing them to rotate and orient their dipoles

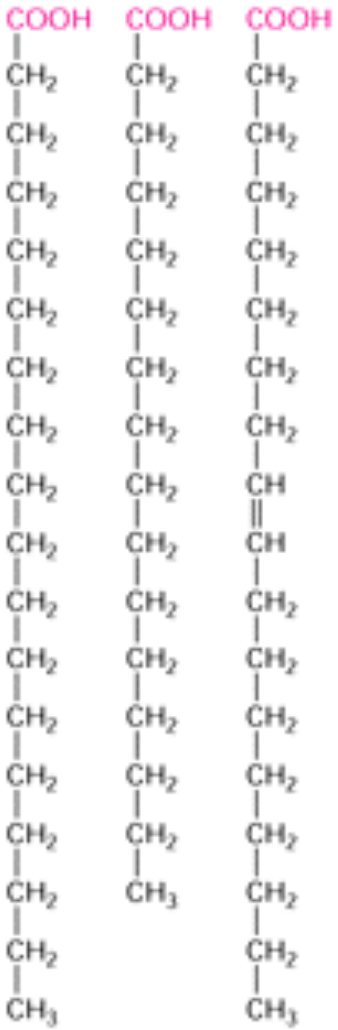
The Coulomb potential

ion-ion interactions



$$U = \frac{Q_1 Q_2}{4\pi\varepsilon_0 \varepsilon_r \mathbf{r}}$$

50-350 kJ/mol



characterizes the response of the surrounding medium to an electric field: depends on how easily the molecules are polarized

Hydrocarbons have ε_r of 2: the hydrophobic core of proteins and membranes experiences strong electrostatic interactions

1 kcal/mol = 4.2 kJ/mol = 0.043 eV

Electrostatic self-energy

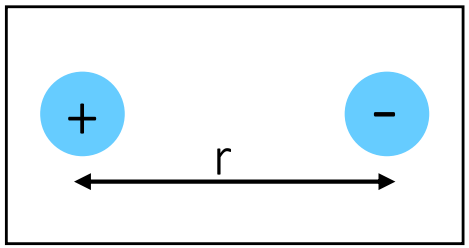
$$G = \frac{1}{\varepsilon_r r}\int_0^q q'dq' = q2/2\varepsilon_r r$$

Is the self-energy of a charge, or the energy of placing an ion in a dielectric medium (calculated from the work done to bring an increment dq' on the surface of a sphere with radius r and charge q')

For water, it is the **hydration energy**.
To transfer a Na+ ion with r = 0.95 Å from water to an hydrocarbon medium (ε goes from 80 to 2), the work necessary is of 85 kcal/mol.
In fact inorganic ions are generally insoluble in organic solvents.
It is difficult to move an ion inside a protein of a lipid bilayer!
Ions are always attracted towards the region with higher ε

Multipole interactions

ion-ion interactions

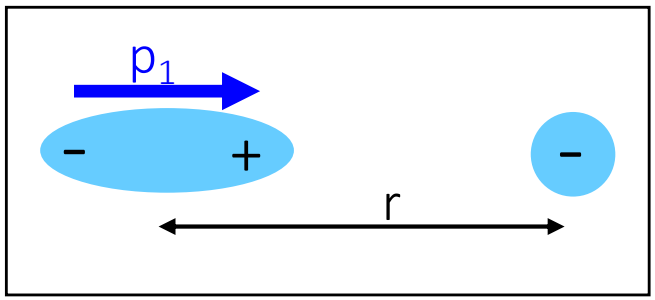


$$\frac{Q_1 Q_2}{4\pi\varepsilon_0\varepsilon_r \mathbf{r}}$$

50-350 kJ/mol

Even in neutral molecules, dipoles result from the unequal distribution of e^- due to differences in electronegativity between atoms.

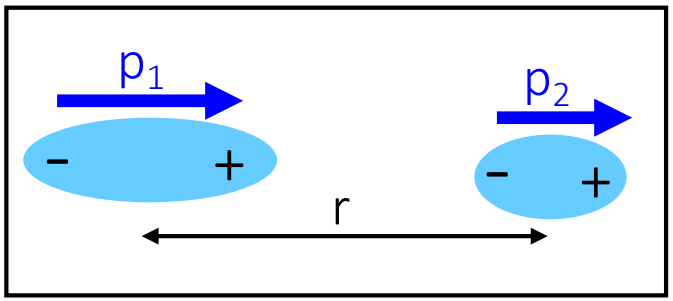
ion-dipole interactions



$$\frac{Q_1 p_1}{4\pi\varepsilon_0\varepsilon_r \mathbf{r}^2}$$

1-50 kJ/mol

dipole-dipole interactions



$$\frac{p_1 p_2}{4\pi\varepsilon_0\varepsilon_r \mathbf{r}^3}$$

0.1-10 kJ/mol

Induction forces

Ions and dipoles can polarise the electron cloud of an adjacent molecule. This causes an attractive force between the ion/permanent dipole and the induced dipole.

Interaction proportional to
- **r^{-4} for ion-induced dipole**
- **r^{-6} for permanent dipole/induced dipole interactions**

Dispersion forces

Random fluctuations of the electron clouds cause temporary dipoles even in uncharged molecules; these temporary dipoles will induce dipoles in the adjacent molecules causing a weak attractive force (He liquefies at 4K).

Van der Waals attractive forces!

0.4 kJ/mol—0.35 nm bond length
Does not change in water!!

Dispersion forces

Fluctuactions of transient dipole moments can be attractive or repulsive. The attractive configurations have a lower potential E than the repulsive ones, meaning have larger weights in Boltzmann average and therefore a net attraction.

The fluctuactions in the electronic structure responsible for the transient dipole moments are much faster than molecular rotation in liquids. Therefore such forces are not dependent on the specific medium.

Hydrophobic forces

Hydrophobic forces are very relevant in biology. They are primarily driven by an energy cost of creating hydrocarbon-water contact.
There is a reduction of entropy of water close of a hydrophobic surface: water becomes structured, even ice-like. It restricts the possible orientations close to the surface and decrease entropy.

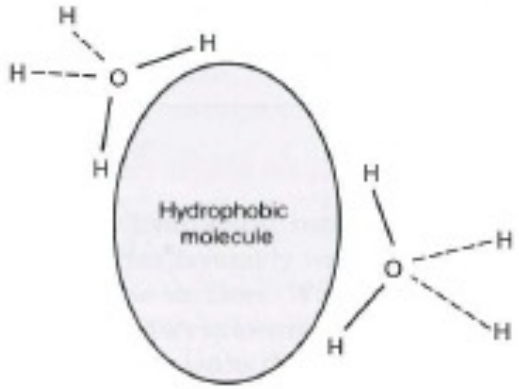
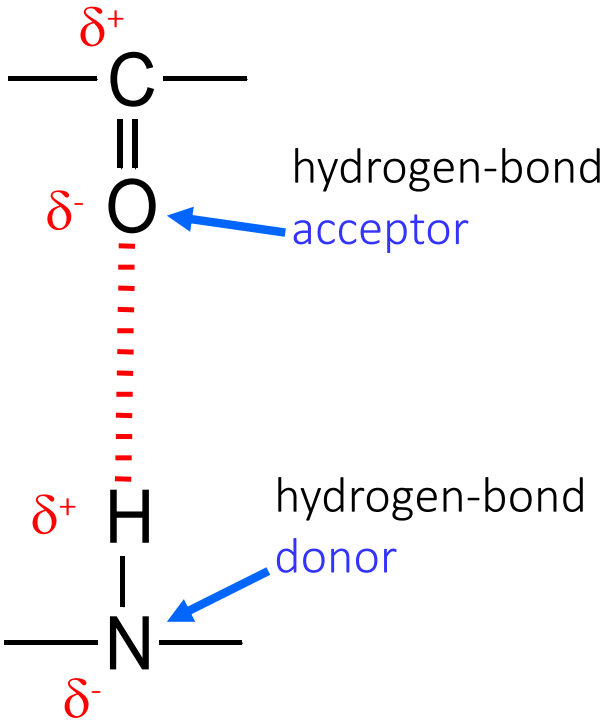


Fig. 2.7 Water molecules adjacent to a hydrophobic molecule suffer restrictions in orientation as they form hydrogen bonds with other water molecules.

Hydrogen bond

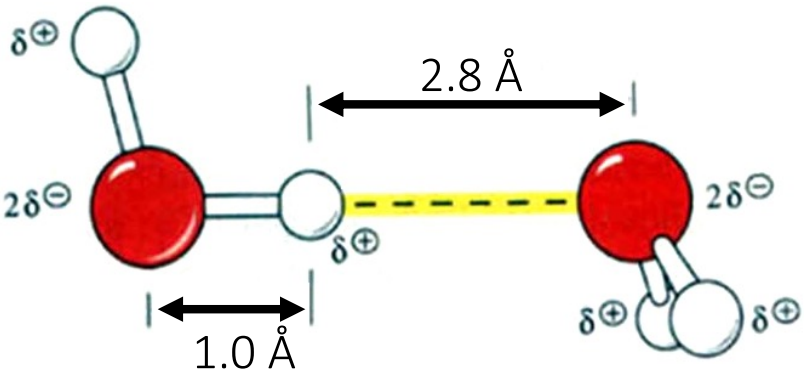
Hydrogen bonds are a particular case of a dipole-dipole interaction, unusually strong because the small size of the H atom allows the dipoles to come close to each other (~15-30 kJ/mol)

17 kJ/mol—**0.30 nm** bond length
Becomes 4.2 kJ/mol in water!!



Donors and acceptors must be electronegative atoms (O, N)

Hydrogen bonding in water:

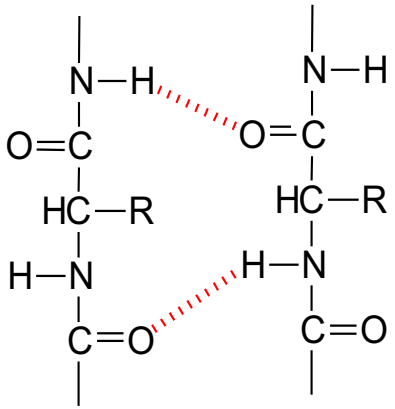


Hydrogen bonds have a defined lenght and orientation

Hydrogen bonds in biology

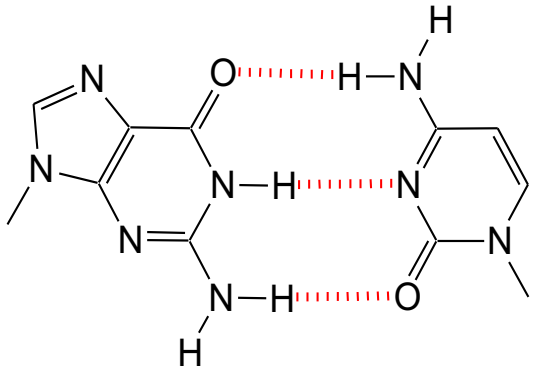
Hydrogen bonding interactions play a fundamental role in determining both the conformation of biological macromolecules and their interactions with other molecules.

The 3D structures of proteins are stabilized by hydrogen bonds between main-chain amide groups:



protein secondary structure: a β-sheet

The pairing of the bases in DNA is mediated by H-bonds:



Guanine-Cytosine base pair

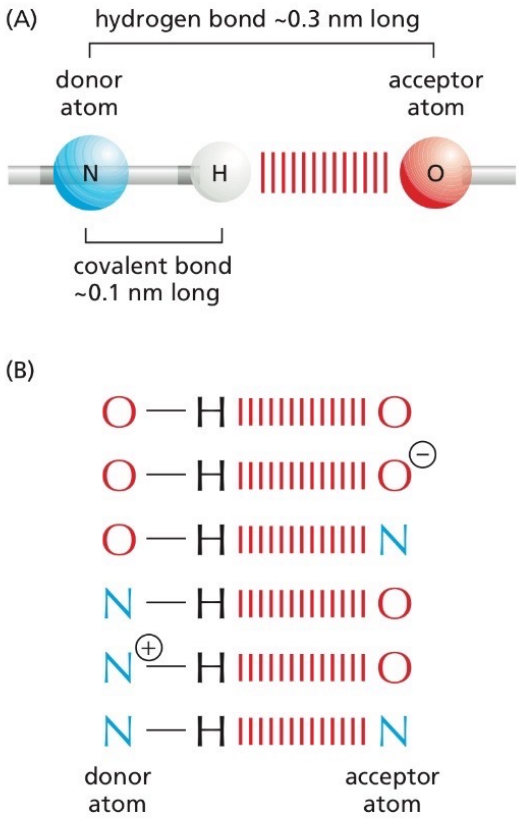


Figure 2–4 Hydrogen bonds. (A) Ball-and-stick model of a typical hydrogen bond. The distance between the hydrogen and the oxygen atom here is less than the sum of their van der Waals radii, indicating a partial sharing of electrons. (B) The most common hydrogen bonds in cells.

TABLE 2–1 Covalent and Noncovalent Chemical Bonds

Bond type		Length (nm)	Strength kJ/mole**	
			in vacuum	in water
Covalent		0.15	377 (90)	377 (90)
Noncovalent	ionic*	0.25	335 (80)	12.6 (3)
	hydrogen	0.30	16.7 (4)	4.2 (1)
	van der Waals attraction (per atom)	0.35	0.4 (0.1)	0.4 (0.1)

*An ionic bond is an electrostatic attraction between two fully charged atoms. **Values in parentheses are kcal/mole. 1 kJ = 0.239 kcal and 1 kcal = 4.18 kJ.