STRUCTURAL ORGANIZATION OF LIVING SYSTEMS

At all levels, from molecules to ecosystems, there is a close relationship between the structure and function of biological systems.

Both the chemical structure and the 3D conformation of the molecules are important determinants of the biological function. The structure of many proteins, nucleic acids and macromolecular complexes has been elucidated with atomic resolution. On December 6, 2011, 77709 biomolecular structures were deposited in the RCSB (Research Collaboratory for Structural Bioinformatics) Protein Data Bank (*www.pdb.org*).

Role and Structure of Water

Living organisms are comprised primarily of water. No organism can remain biologically active without water.

Living Organism	Water content (%)
Jellyfish	98
Snail	84
Shark	81
Frog	80
Human embryo	95
Human	55

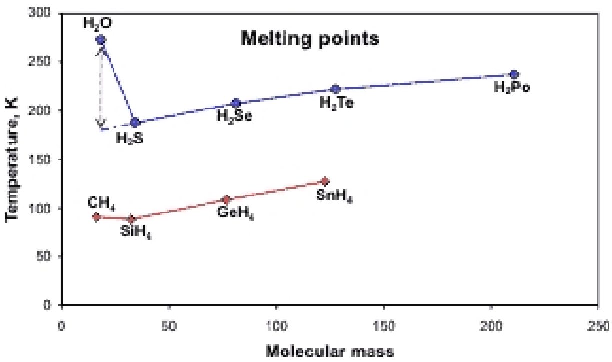
Human Tissue or Organ	Water content (%)
Lungs	83
Blood	82
Muscle	79
Brain	73
Skin	65
Fat	50
Bone	32

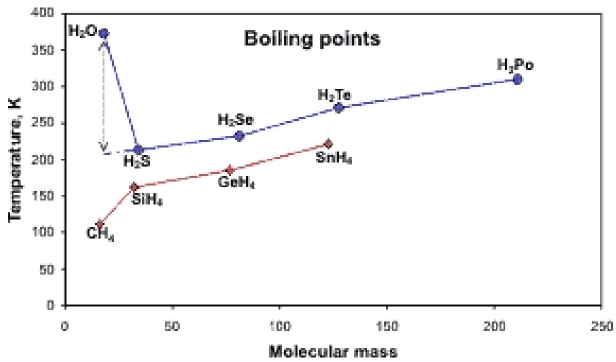
Water content of different living organisms and human organs.

Water provides a passive background for life processes (diffusion, osmosis, different transport reactions etc.), but bound water is also essential in many biomolecular structures. There is a deep connection between the extraordinary properties of water and its role in life.

Physical and chemical properties of water:

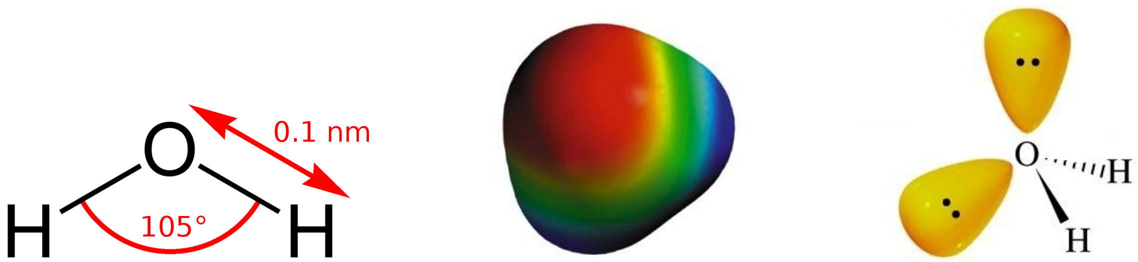
- As a gas, water is one of lightest known, as a liquid it is much denser than expected and as a solid it is lighter than its liquid form.
- Water is liquid in a wide range of temperatures at atmospheric pressure.
- Water has unusually high melting and boiling point.





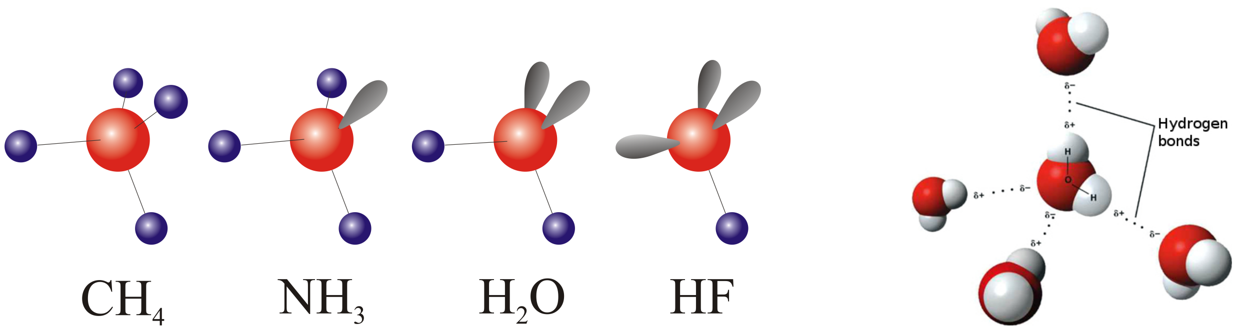
- The dielectric constant of water is high (78.4 at 25°C).
- Proton and hydroxide ion mobilities are anomalously large.
- Water ionizes and allows easy proton exchange between molecules, contributing to the richness of the ionic interactions in biology.
- Water is an excellent solvent due to its polarity, high dielectric constant and small size, particularly for polar and ionic compounds.

- Water has the second highest specific heat capacity of any known chemical (after ammonia), as well as a high heat of vaporization.
- The maximum density of water is at 3.98 °C.
- Water has high surface tension.

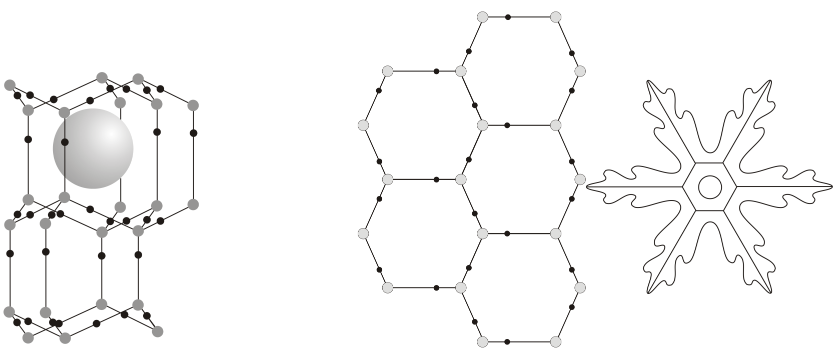


Models showing structural properties of the water molecule. Van der Waals radii of the oxygen and hydrogen atoms are 0.15 and 0.12 nm, respectively.

To explain the anomalous properties of water one needs to take into account the interactions between the water molecules as well. The most important one is hydrogen bonding. The background for understanding the hydrogen bonding of water is its electronic structure. The six electrons of the second shell ($2s^2 2p^4$) of the oxygen form a stable octet configuration together with the 1 s electrons of the hydrogen atoms.



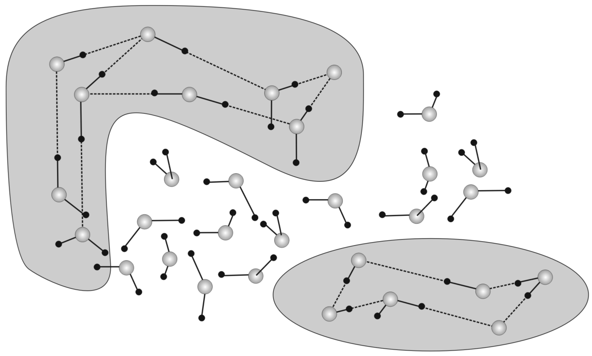
Different molecules can act as hydrogen bond donors, acceptors, or both. Water can donate two and also accept two hydrogen bonds. Because of this, it can form extended hydrogen bonded structures.



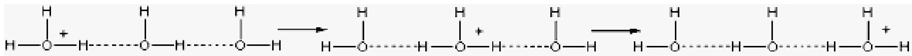
Structure of ice is a good starting point to understand hydrogen bonding in liquid water.

Water retains even at 100 ^{0}C about 60% of the number of the hydrogen bonds found in ice. Hydrogen bonds in liquid water, however, do not form static structures. Hydrogen bonds break and reform 10^{10} times every second.

Around the surface of molecules and membranes there is a layer of tightly associated water. This hydration shell around protein molecules is 0.4 - 0.5 nm thick, and its mass can reach as much as 30% of that of the mass of the protein. In the B-helix structure of DNA 10 water molecules bind to every basepair.



Volumetric mesh (lattice) structures form through hydrogen bonds in liquid water.



Proton transfer by Grotthuss mechanism.

Important Biopolymers

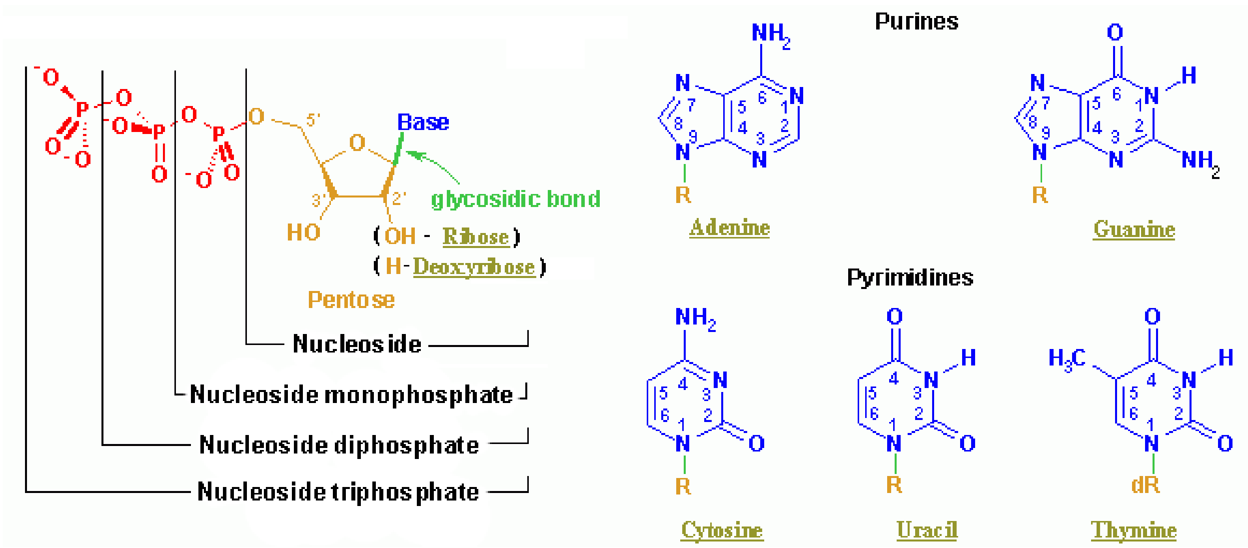
DNA, RNA and proteins are biological polymers. They have distinct chemical and structural properties, and they interact differently with other molecules. Their interactions and their chemical stability determines what they can be used for by the living cell.

reaction	$t_{1/2}$ at 25^0C	$t_{1/2}$ at 100^0C	typical no. of bonds per polymer
DNA hydrolysis	140,000 years	22 years	$3{\cdot}10^9$ (human DNA)
RNA hydrolysis	4 years	9 days	few dozen (tRNA)
protein hydrolysis	400 years	5.5 weeks	few hundred

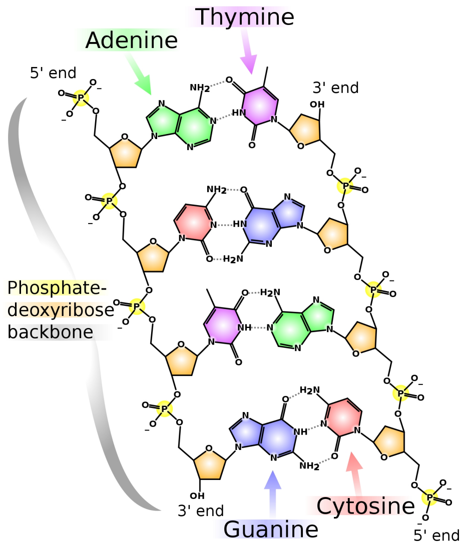
Primary structure: order of the building blocks in the polymer.
Secondary structure: general three-dimensional shape of *local segments* of the biopolymers.
Tertiary structure: three-dimensional structure of the *entire polymer chain*.
Quaternary structure: arrangement of multiple folded molecules in a multi-subunit complex.

Structure of DNA

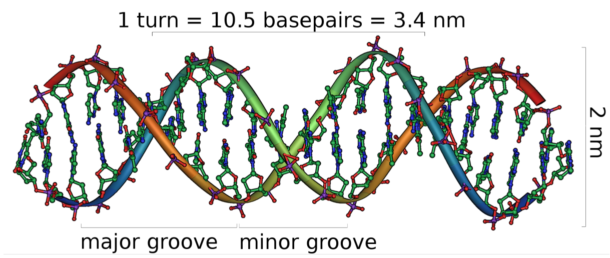
Desoxyribonucleic acid (DNA) is a linear polymer built of four different desoxyribonucleotides. It is chemically very stable, which makes it suitable for long term genetic information storage.



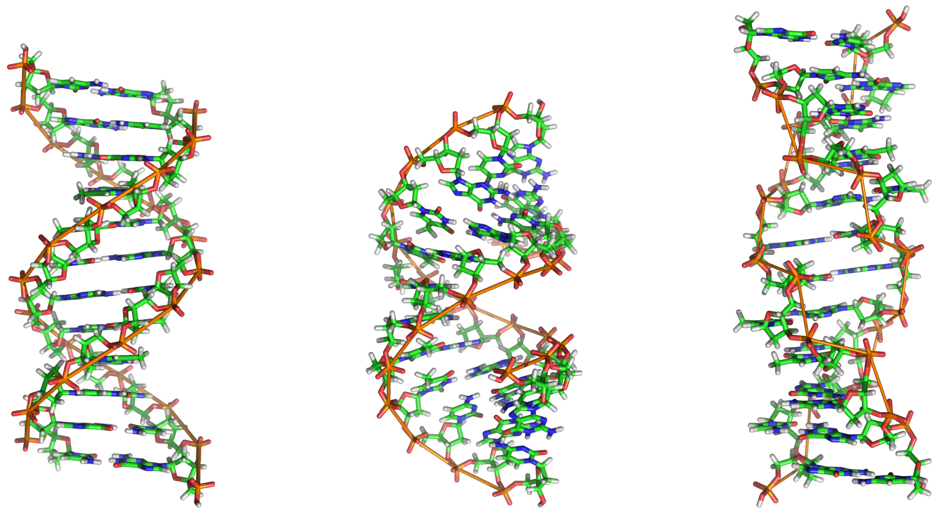
James D. Watson and Francis Crick showed that the secondary structure of DNA is a double helix. This discovery had a major impact on genetics in particular and biology in general.



Chemical structure of DNA.



The most abundant secondary structure of DNA is the B helix.



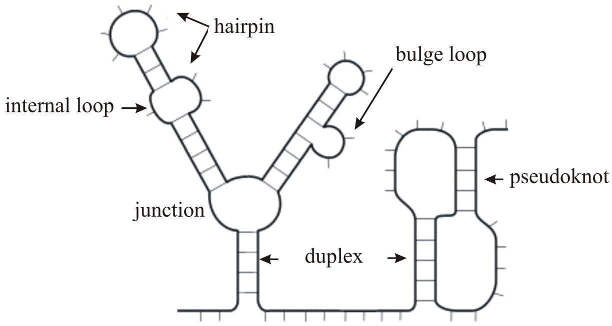
Representation of the 3D structure of the DNA B, A, and Z helices.

Parameter	B-helix	A-helix	Z-helix
helix type	right	right	left
basepairs/turn	10.4	11	12
distance between the basepairs (nm)	0.33	0.25	0.37
pitch (nm)	3.4	2.5	4.5
diameter of the helix (nm)	2	2.3	1.8
rotation per basepair	34.6^0	32.7^0	-30^0
inclination of base to helix axis	1.2^0	19^0	9^0

RNA Structure

The sugar of RNA is ribose, not desoxyribose. The 2'-hydroxil group:

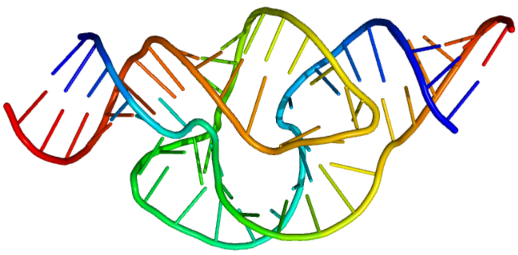
- prevents RNA molecules from forming B conformation, it usually adopts A helix when double stranded
- allows more tertiary interactions to form complex structures
- promotes chemical reactions, thus RNA is chemically less stable than DNA.



RNA secondary structural elements.

RNA molecules fulfill diverse functions:

- entire genetic material of some bacteria and viruses
- mRNA (messenger)
- tRNA (transfer)
- rRNA (ribosomal)
- snRNA (small nuclear)
- siRNA (silencing)
- riboswitch (regulate protein expression)
- ribozyme (RNA enzyme)



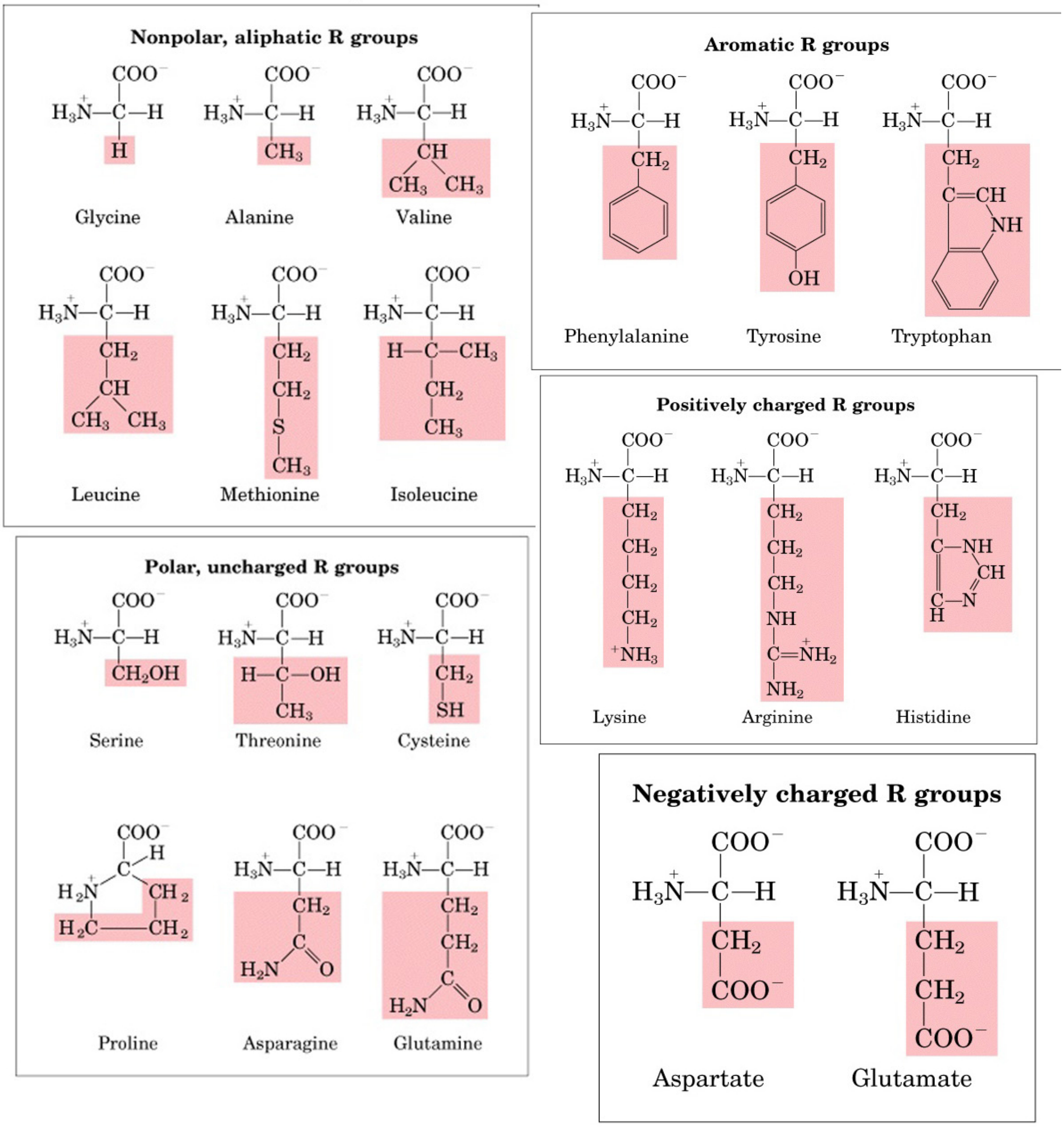
Structure of the hammerhead ribozyme.

Protein Structure

Proteins are polymers, made of twenty different amino acids. They are the chief actors within the cell, carrying out duties specified by the information encoded in the genes. The most important characteristic of proteins that allows their varied set of functions is their ability to bind other molecules specifically and tightly.

Roles fulfilled by proteins in the cell are very diverse. To list just a few:

- provide skeleton for the cell structure (structural proteins)
- catalyze reactions (enzymes)
- regulate processes (hormones)
- actively transport molecules along elements of the cytoskeleton or across membranes
- form channels for facilitated or passive diffusion

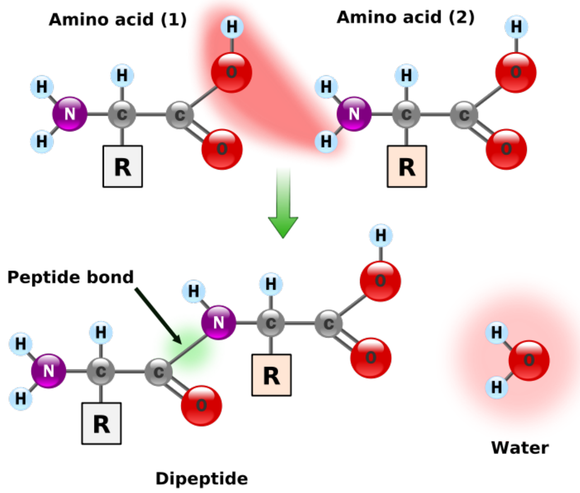


The twenty standard amino acids.

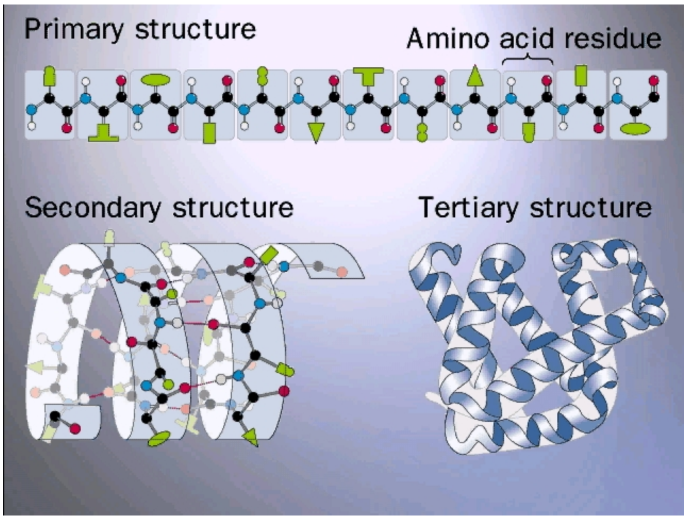
There are intrinsically disordered proteins, for which the disordered state is necessary for the function. Some disordered proteins can participate in several reactions by forming diverse structures when they interact with different partner molecules (moonlighting). Many proteins, however, form well defined structures, which is important for their biological function.

In 1968 Cyrus Levinthal noted that, because of the very large number of degrees of freedom in an unfolded polypeptide chain, the molecule has an astronomical number of possible conformations. Let us consider a protein that is built of 100 amino acid residues. If we take, that each amino acid has 2 possible conformations, the whole polypeptide chain must have 2^{100} possible conformations. If the protein tries every possible conformation during its folding, and we give 1 picosecond for each transition between the conformational states, the time required for the folding process would be 10^{18} seconds (10^{10} years), which is roughly the age of our Universe. Many small proteins fold spontaneously on a millisecond or even microsecond time scale, showing that proteins do not fold by sampling all possible conformations.

Christian Anfinsen (Nobel Prize, 1972) proved that (at least for small globular proteins), the native 3D structure is entirely determined by the protein's amino acid sequence. Interactions between the amino acid residues direct the organization of the polypeptide chain towards the biologically active "native" structure. The native structure is stabilized by non-covalent forces: hydrophobic interaction,

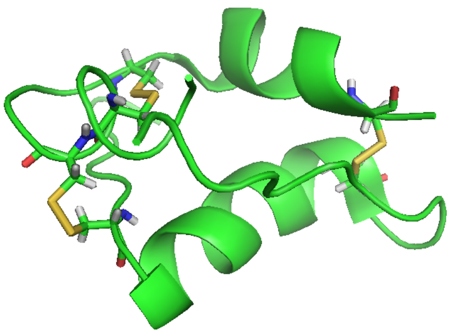


Peptide bond formation.



Hierarchical organization of the protein structure.

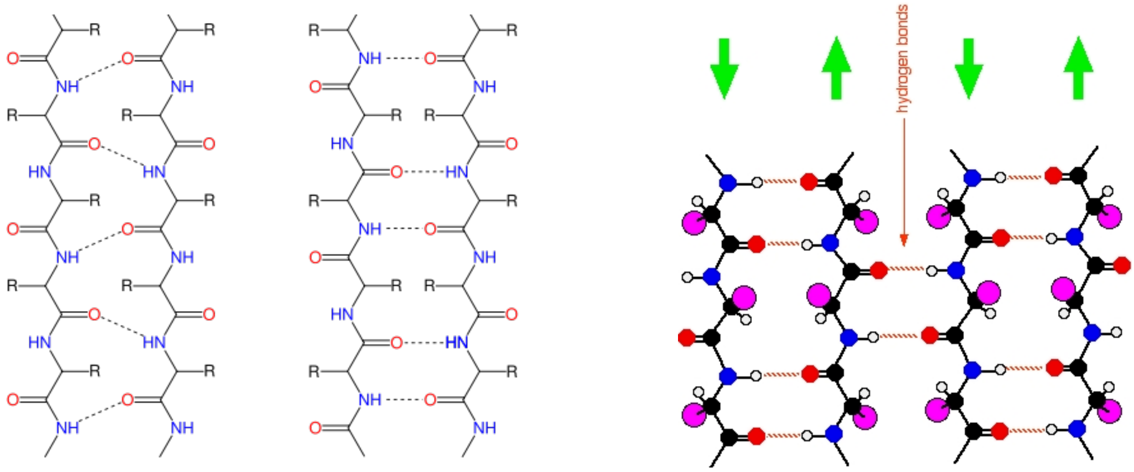
hydrogen bonds, salt bridges, Van der Vaals forces. The only covalent interaction is the formation of disulphide bonds between cysteine residues.



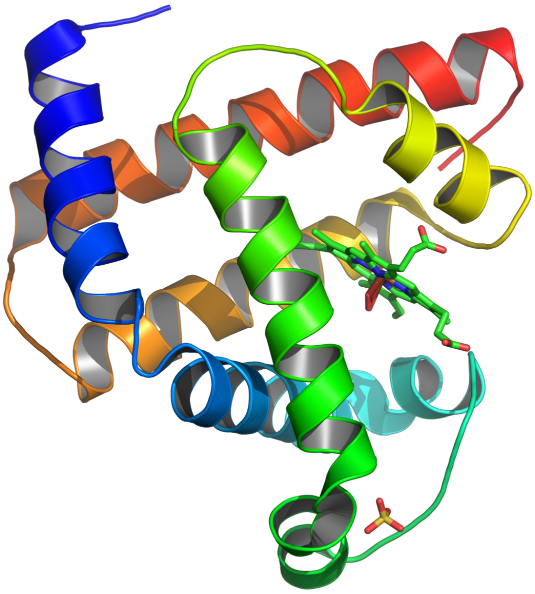
Role of disulphide bonds in the stabilization of the structure of insulin.

Domains are compact dominions of the protein structure within which elements interact more extensively, than with elements outside of it.

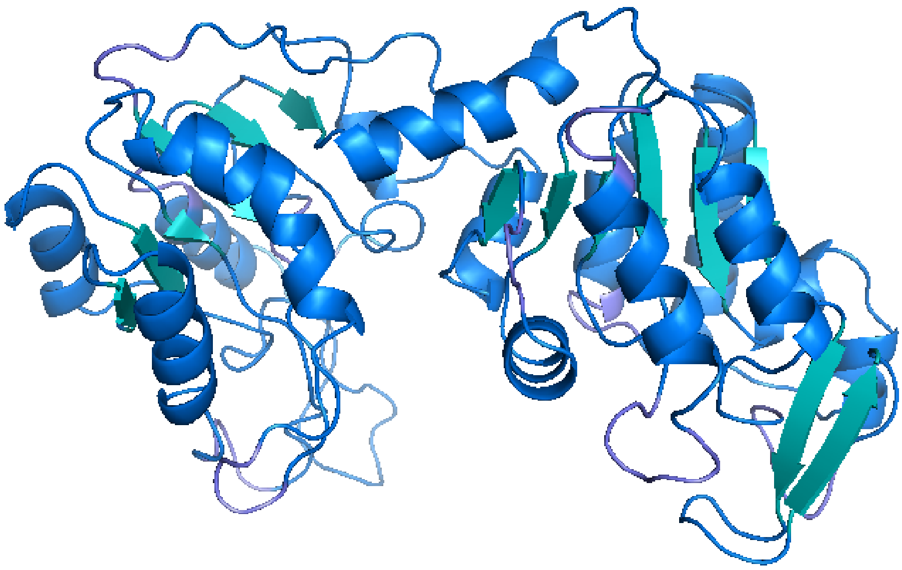
Role of hydrogen bonds in the stabilization of the structure of an α-helix.



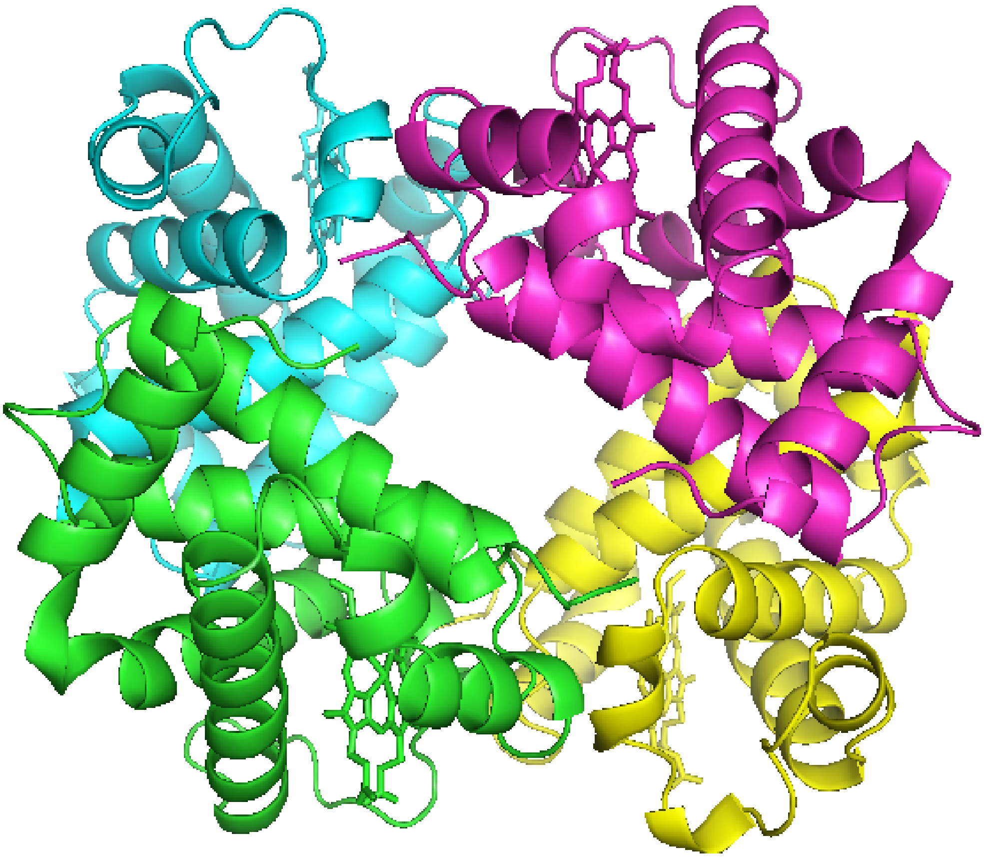
Scheme of the hydrogen bonding in the parallel and the antiparallel β-sheet, and a representation of a structural model of the antiparallel β-sheet.



Secondary and tertiary structure of a one-domain protein: myoglobin.



Secondary and tertiary structure of a two-domain protein: phosphoglycerate kinase.



Representation of the secondary, tertiary and quaternary structure of hemoglobin.