Formation of Biological Structures

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How Big Are They?

Figure 1.1 Physical Biology of the Cell, 2ed. (© Garland Science 2013)
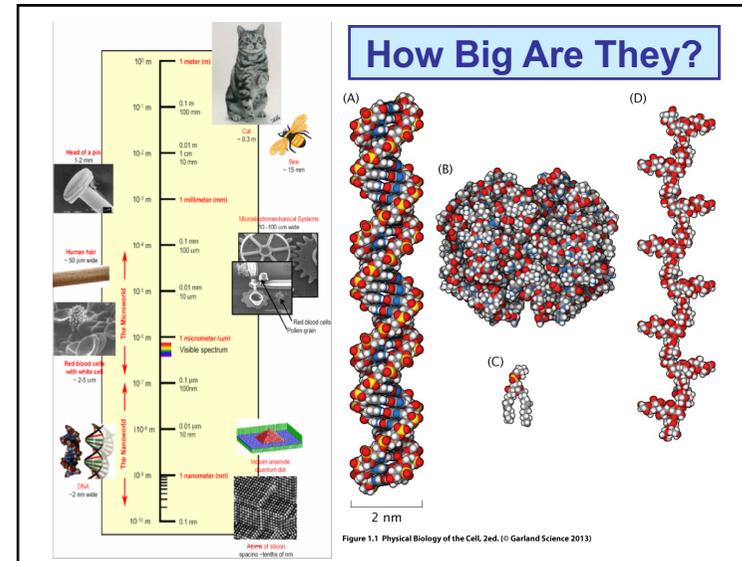
"Plenty of Room at the Bottom"

" The principles of physics, as far as I can see, do not speak against the possibility of maneuvering things atom by atom. It is not an attempt to violate any laws; it is something, in principle, that can be done; but in practice, it has not been done because we are too big."

Richard Feynman, 1959

Wave – Particle Duality

Louis De Broglie: $\lambda = h/p$
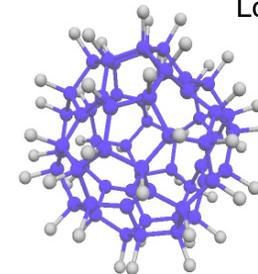

fluorofulleren
$C_{60}F_{48}$
1632 Da
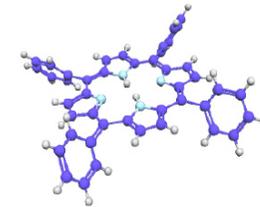
tetraphenilporfirin $C_{44}H_{30}N_4$

L Hackermuller, S Uttenthaler, K Hornberger, E Reiger, B Brezger, A Zeilinger, M Arndt;   Phys. Rev. Lett. 91 (2003) 90408

Wave – Particle Duality
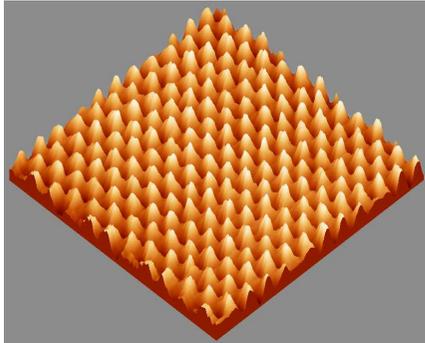

Scanning Tunneling Microscope (STM) image

The Size Range of Life Processes
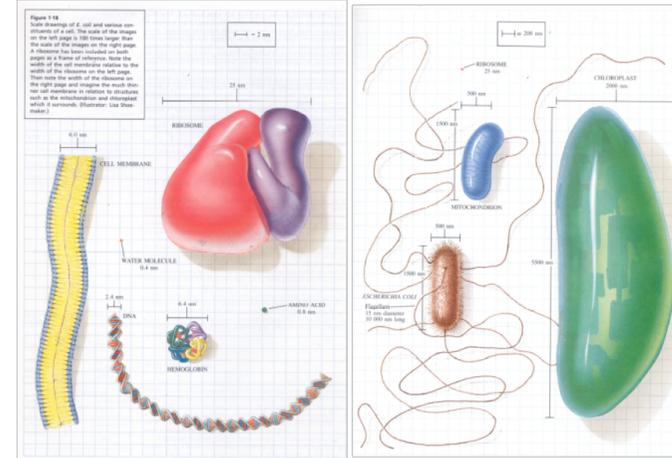

Structure – Function Relationship

From the molecular level to ecosystems, there is a strong relationship between structure and function of biological systems.

Hartmut Michel, Johann Deisenhofer, Robert Huber
1982 – 3D structure of the bacterial photosynthetic reaction center
1988 – Nobel prize
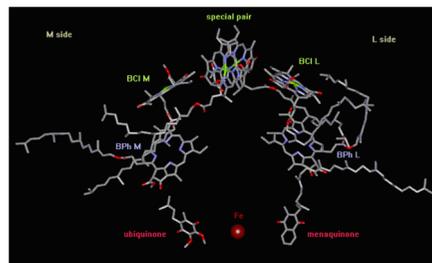
Self Assembly

Molecular recognition
(e.g. self assembly of DNA molecules into „balls").
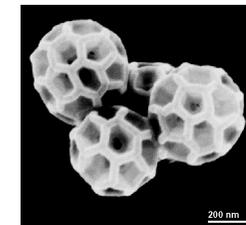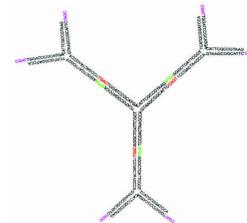
2D Order
S-layer Protein (TEM Image)
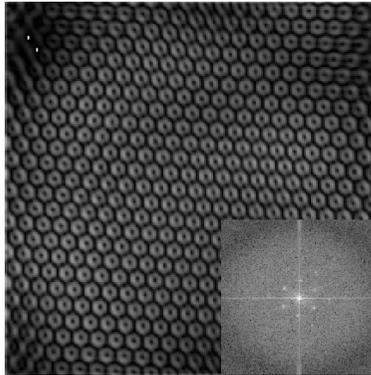
Lithography of Nanostructures
## Using S-layer Protein
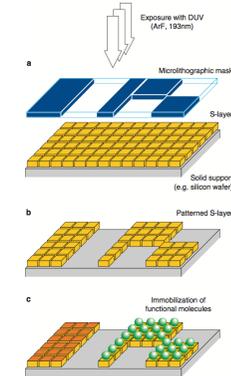
Nanotubes Built of Tubulin and
Lipids as Drug Vehicles
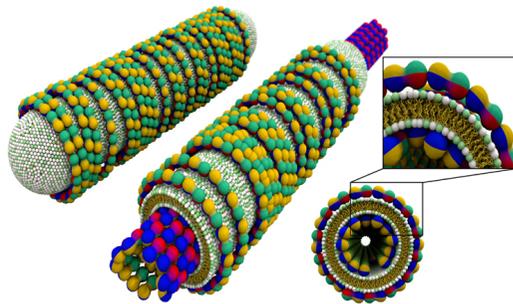
HSA Nanotubes

Nanotubes of Human Serum Albumin (HSA) grown on nanoporous polycarbonate membrane
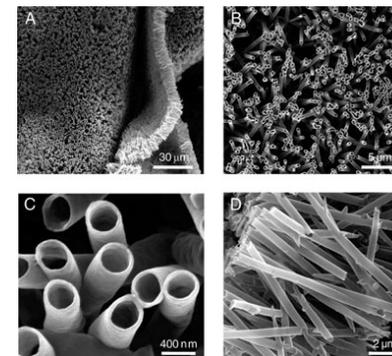
F₁-ATPase Driven Nickel Propeller
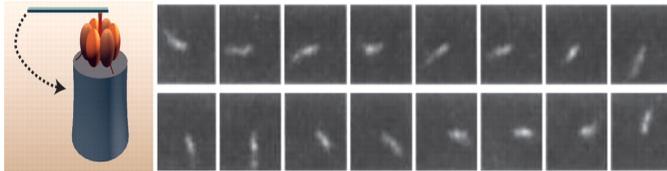
Light - Driven Swimming Structure
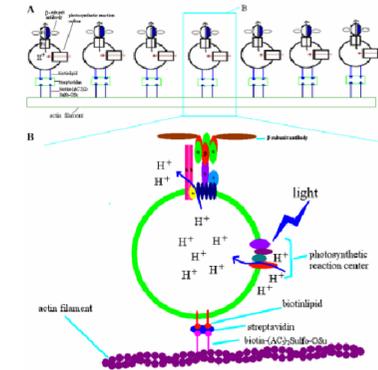
Biopolymers

reaction	$t_{1/2}$ @ 25 ºC	$t_{1/2}$ @ 100 ºC	typical number of monomeric units in a polymer molecule	number of different monomers
DNA hydrolysis	140 000 years	22 years	$3 \cdot 10^9$ (human DNA)	4
RNA hydrolysis	4 years	9 days	few dozen (tRNA)	4
protein hydrolysis	400 years	5.5 weeks	few hundred	20

Biopolymers
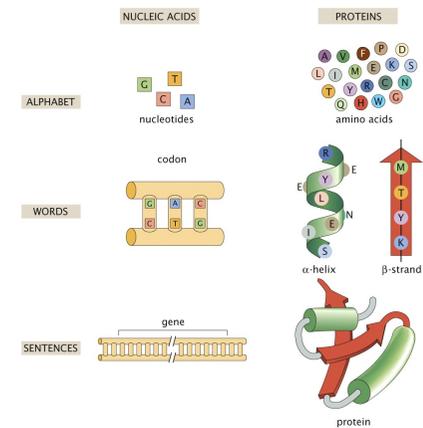
Figure 1.2 Physical Biology of the Cell, 2ed. (© Garland Science 2013)

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Role of RNA in Living Systems

- messenger (mRNS)
- ribosomal (rRNS)
- transfer (tRNS)
- regulator
- enzime (ribozim)
- switch (riboswitch)
- virus gene RNS

Ribosome Function
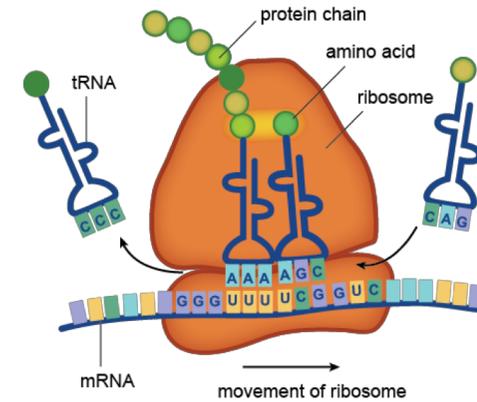

Relationship Between RNA Code and Protein Sequence
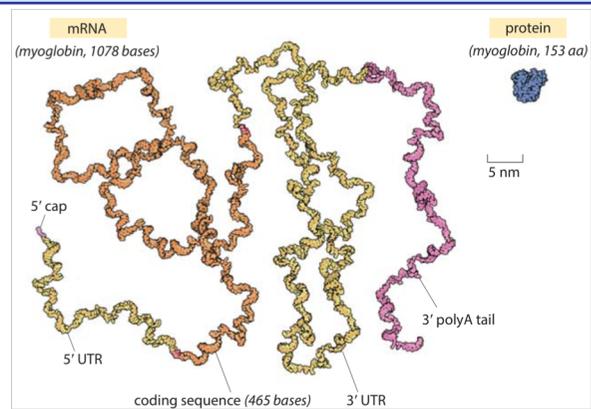
The Twenty Standard Amino Acids
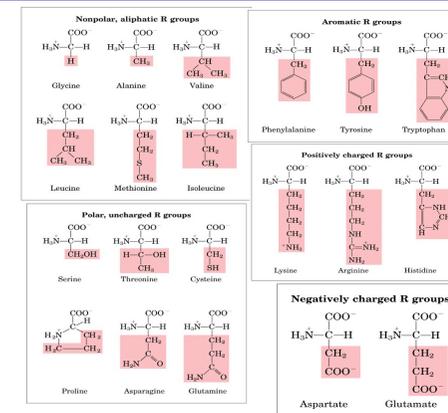
The Peptide Bond
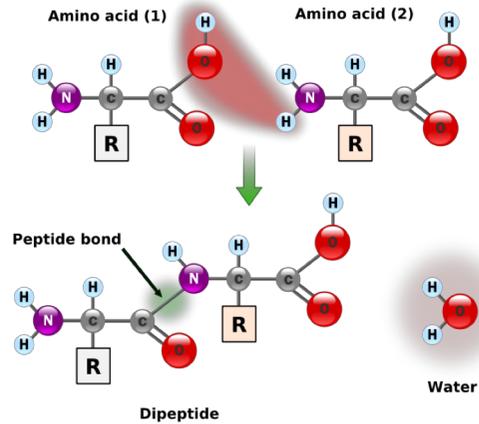
Role of Proteins in Living Systems

- chemical catalysis
- transport
- energy conversion and storage
- coordinated movement
- mechanical skeleton
- immune response
- molecular recognition
- passing information
- gene regulation
- growth and differentiation

X-ray Crystallography
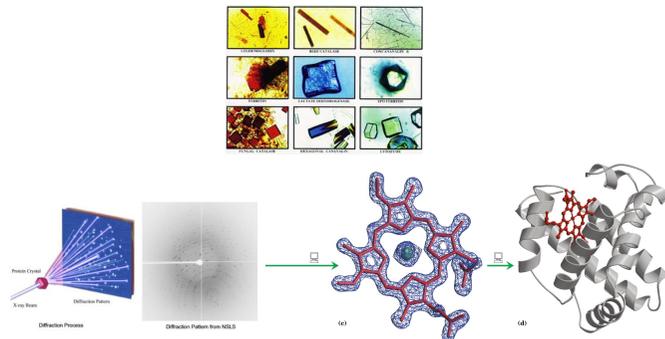
NMR Structure Determination
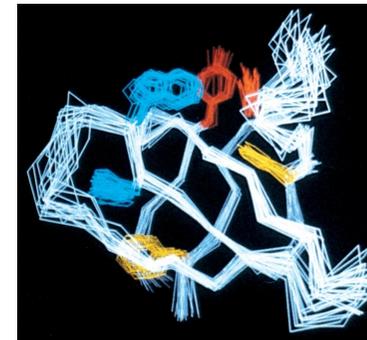
NMR structure of the 64 amino acid
SH3 domain of the Src protein

Interactions Stabilizing the Native State

short range repulsion

Van der Waals interaction

electrostatic interaction

hydrogen bonding

hydrophobic interaction

disulfide bridge

Short Range Repulsion

Due to the exchange (Pauli) interaction, at short distances there is a strong repulsion between electrons.

The potencial energy of the repulsion increases quickly with decreasing distance ($\sim 1/r^{12}$).

Atoms can be considered hard spheres with a given radius (Van der Waals radius).

Van der Waals Interaction

Occurs between any two atoms due to the interaction of induced dipole moments.

Dependence on the distance of the interaction energy: $\sim 1/r^6$

Electrostatic Interaction

Distance dependence of the interaction energy of the Coulomb force:

$$E = \frac{q \cdot Q}{4 \cdot \pi \cdot \varepsilon_0 \cdot \varepsilon_r \cdot r}$$
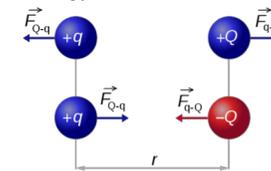
The relative dielectric constant inside the protein is approx. 4, and 80 in water.

Salt bridges between ion pairs (Lys, Arg and Glu, Asp).

There is a large hydrate shell around charges in water.

Mobile ions can strongly shield charges.

Hydrogen Bonding

Attraction force between a H atom of a more electronegative atom or group (hydrogen bond donor) and another atom bearing a lone pair of electrons (hydrogen bond acceptor).
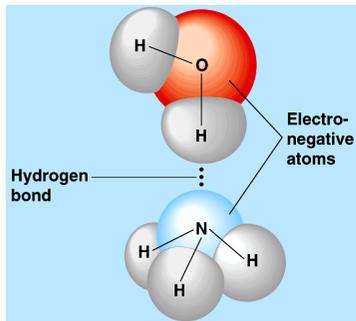
Hydrophobic Interaction

observed tendency of nonpolar surfaces to adhere in an aqueous solution and exclude water molecule

entropic effect originating from the disruption of hydrogen bonds of liquid water by the nonpolar solute
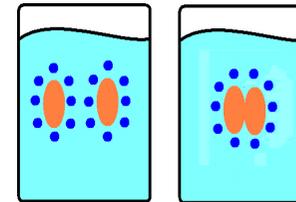
Disulfide Bridge

stabilizes the native structure
decreases the conformational entropy of the unfolded protein:

$$\Delta S = - 2.1 \ J/K - 1.5 \cdot R \cdot \ln n$$

n is the number of AAs between the two bonded AAs.

Anfinsen's Dogma
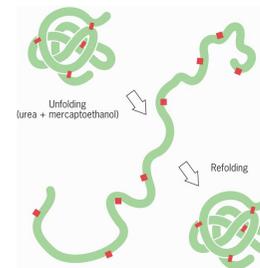
Refolding of Ribonuclease A   Christian B. Anfinsen

The information of the 3D protein structure is encoded in the 1 D AA sequence.

Importance of the Protein Folding Problem

One of the most important questions of molecular biophysics.

We sequence genomes, we build databases, but we can't predict protein structure and function based on the genetic information.

There are roughly two dozen conformational diseases:

Misfolded proteins and deposition of amyloid plaques was observed in various diseases (pl. Creutzfeld-Jakob disease, Alzheimer disease, Parkinson disease).

In vitro and *in vivo* Folding

in vitro   *in vivo*

unfolded protein

mRNA

Ribosome   Nascent polypeptide

differences:

- entire sequence / co-translational folding
- crowded intracellular environment

folded protein   folded protein

Co-Translational Folding

in vivo
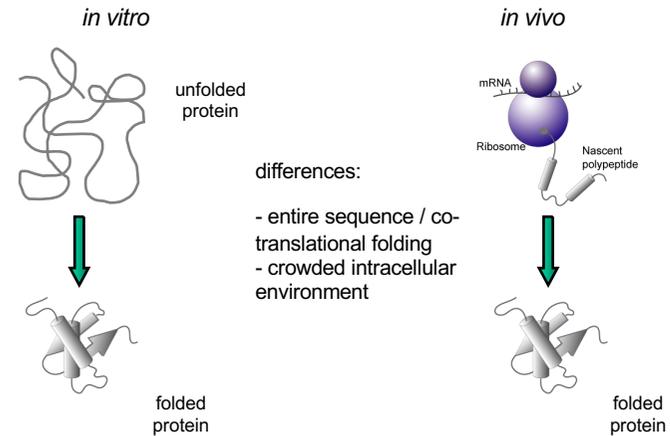
The N terminal of the nascent polypeptide chain starts to fold before completion of the translation.

20-30 AAs of the C terminal are protected within the ribosome.

mRNA

Ribosome   Nascent polypeptide

folded protein
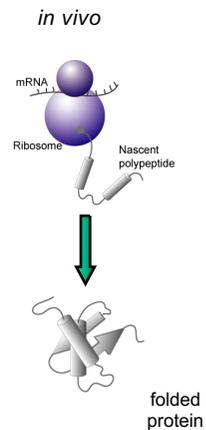
Molecular Crowding

in vitro   *E. coli* citosol

<0.1 mg/ml   **~340 mg/ml**

100 nm

ribosome
chaperon   proteins   other macromolecules
        nucleic acids
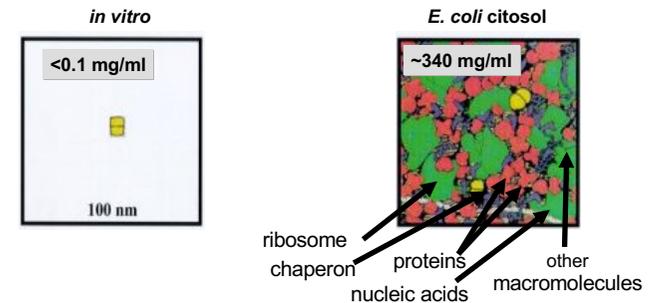
In vitro experiments
- lack of binding partner molecules
- lack of posttranslational modifications
- very different physico-chemical environment than in a cell

Effect of Molecular Crowding

Molecular crowding:
a large fraction of the volume of the cytoplasm is filled by other molecules than water.

- dissociation constants decrease
- speed of protein-protein association increases
- association of fully or partially denatured proteins speeds up

GroEL/ES Chaperon Cycle
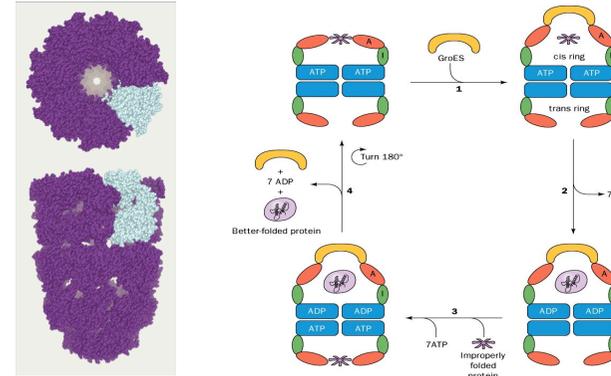

Protein Disulfide Isomerase Function
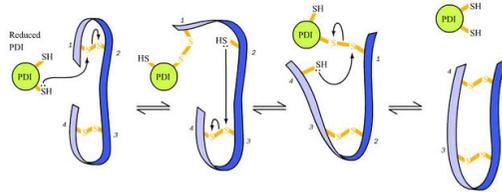
structure of the human protein disulfide isomerase
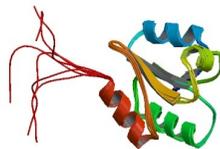
Proline Cis/Trans Isomerase

Due to the activation barrier between the cis and trans prolines, the presence of cis prolines in the native structure:
- speeds up early folding steps
- slows down the final formation of the native structure.

PPIase (peptidyl-prolyl isomerase)

PPIase structure
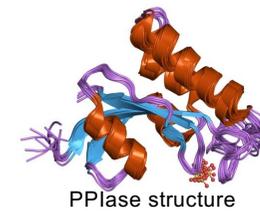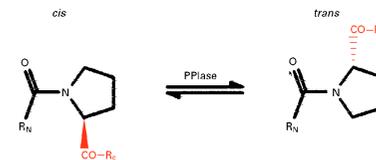
Fate of the Protein in Eukaryotic Cells

cytosol .... protein synthesis and folding,
extracellular volume .... export of folded protein
mitochondrion .... limited protein synthesis
chloroplast .... limited protein synthesis
endoplasmic reticulum .... import of unfolded protein
peroxisome .... import of folded protein
nucleus .... import of folded protein
lysosome .... import of unfolded protein

Levinthal's Paradox - Calculation

Cyrus Levinthal

Consider a protein of 151 AAs. Assume all the 150 bonds connecting them have only two possible conformations. Assume that a reorientation of the bonds happens in 10^{-13}s.

A random search through the phase space would last:
$$2^{150} * 10^{-13}\text{s} = 4.6 \cdot 10^{24}\text{years}.$$

Age of Earth: $4.6 \cdot 10^9$ years
Age of the Universe: $13.7 \cdot 10^9$ years
Proteins typically fold on the ms to s timescale.

Levinthal's Paradox - Conclusion

The phase space of a protein is way too big to find the native structure by random search.

Cyrus Levinthal
1922 - 1990