

Proteins — *polymer molecules*,
folded in complex structures

Konstantin Popov

Department of Biochemistry and
Biophysics

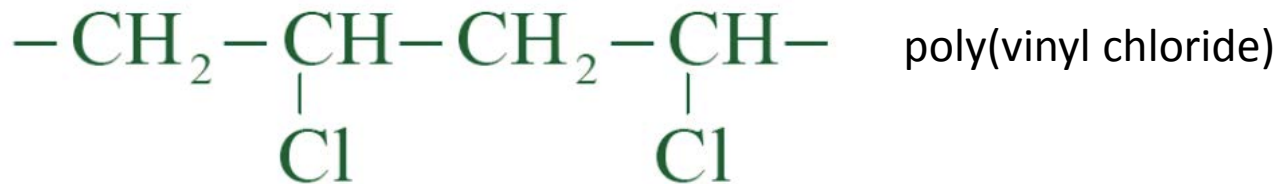
Outline

- General aspects of polymer theory
 - Size and persistent length of ideal linear polymer chain
 - Volume interactions and Coil-Globule transition
 - Electrostatic and hydrophobic interactions
- Branched polymers as a next step towards proteins
- Proteins as extremely complicated and well designed polymers

Model of ideal polymer chain

In 1920 *Hermann Staudinger* proposed existence of polymer chains — **long** chains of atoms covalently bounded one to another and called them *macromolecules*.

Examples:



Polymers are long molecules, $N \gg 1$:

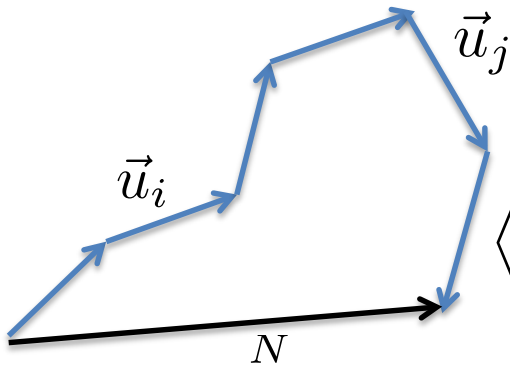
- Synthetic polymers N usually 10^2 - 10^4
- Biopolymers N up to 10^9

Model of ideal polymer chain

Ideal chain — model where monomer units do not directly interact if they are not neighbors along the chain.

Simplest example:

Freely jointed chain. No interactions, no correlations.



$$\vec{R} = \sum_{i=1}^N \vec{u}_i$$
$$|\vec{u}_j| = l$$

$$\langle \vec{R} \rangle = 0$$

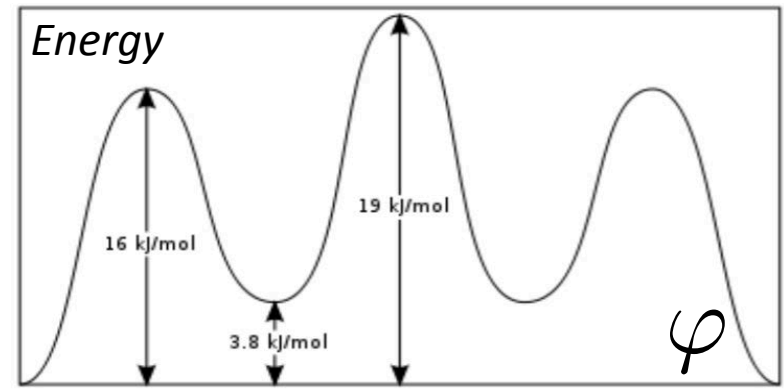
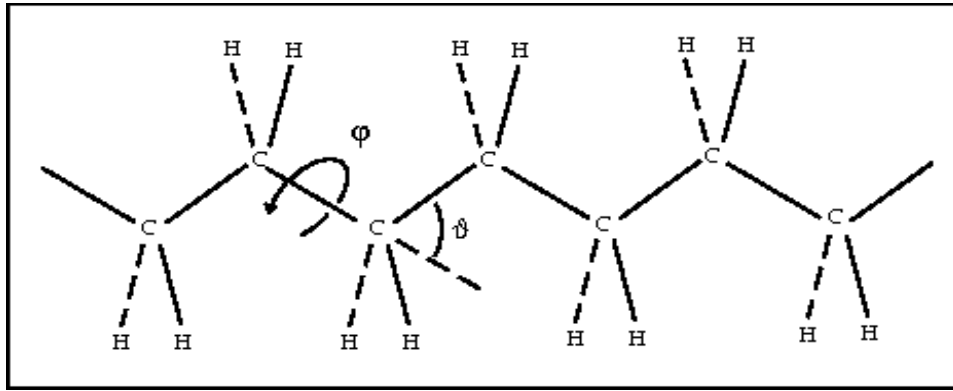
$$\langle \vec{R}^2 \rangle = \left\langle \left(\sum_{i=1}^N \vec{u}_i \right)^2 \right\rangle = \left\langle \sum_{i=1}^N \vec{u}_i^2 \right\rangle + 2 \sum_{1 \leq i < j \leq N} \langle \vec{u}_i \vec{u}_j \rangle$$

$$R = \sqrt{\langle \vec{R}^2 \rangle} = N^{1/2} l$$

$$R \ll L = Nl$$

Flexibility of ideal polymer chain

Rectilinear conformation of a poly(ethylene) chain, shown on the picture, corresponds to the minimum of the potential energy. All monomer units are in trans-position. This conformation would be an equilibrium only at $T = 0$.



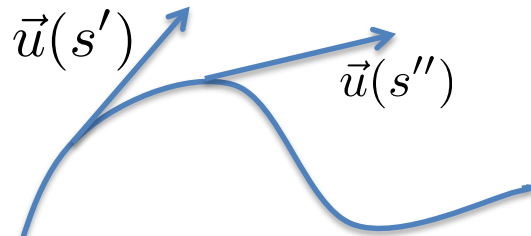
Thermal fluctuation will cause deviations from linear conformation. Probability to find particular conformation can be estimated according to Boltzmann law:

$$p(U) \sim e^{-\frac{U}{k_b T}}$$

Flexibility of ideal polymer chain

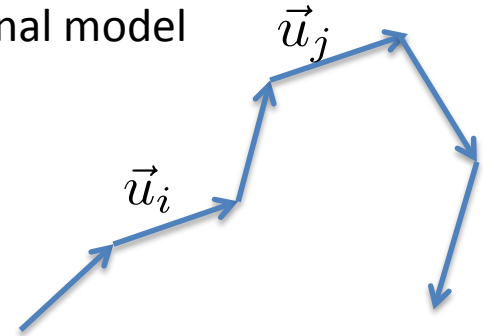
Persistent length — roughly a maximum chain section remaining straight. At greater lengths, bending fluctuations destroy the memory of the chain direction.

Persistent chain model



$$\langle \vec{u}(s') \vec{u}(s'') \rangle = \langle \cos \theta(s' + s'') \rangle$$

Internal rotational model



$$\langle \vec{u}_i \vec{u}_j \rangle = \langle \cos \theta_{ij} \rangle$$

For many polymer chains it is shown that :

$$\langle \cos \theta(s) \rangle = \exp(-s/l_p)$$



Correlations decay exponentially along the chain.

Where l_p — persistent length of the polymer.

Ideal polymer chain summary

- Monomers are connected into a chain, thus restricted in spatial movement. that makes polymer chains “poor” in entropy.
- Polymers are long chains: $N \gg 1$.
- Size of ideal polymer chain — polymer coil, is given by the universal expression that doesn't depend on selected model:

$$R = aN^{1/2}$$

Where a is monomers size and N is the number of monomer units.

- Ideal are flexible molecules. Flexibility is thermally driven. Directional correlation between two segments decay exponentially with increasing the distance separating them.

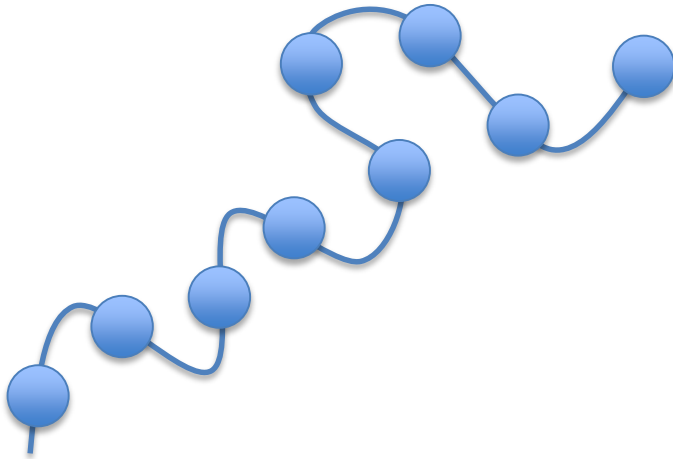
$$\langle \cos\theta(s) \rangle = \exp(-s/l_p)$$

Model of real polymer chain

Consider polymer chain with interacting monomers immersed into a solvent.

Interaction examples:

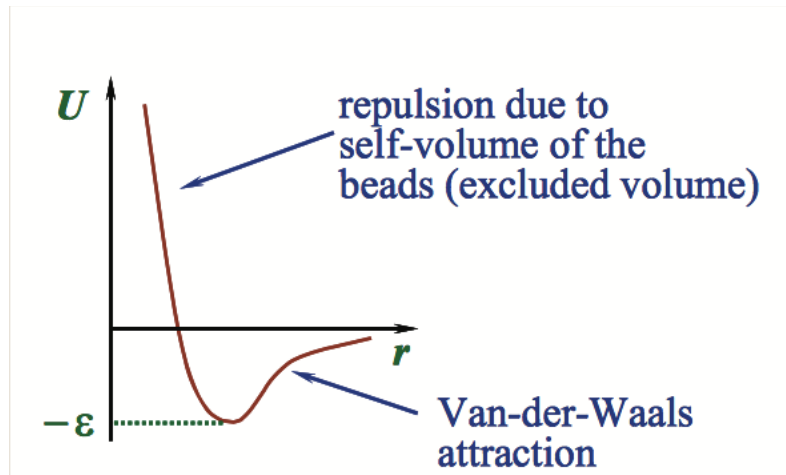
- Excluded volume interactions
- Hydrophobic/hydrophilic interactions
- Electrostatic interactions
- Hydrogen bonds



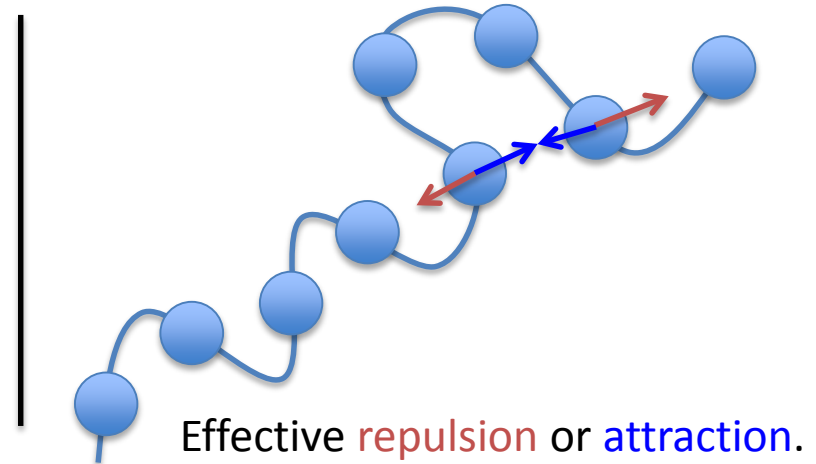
These interactions significantly change conformational behavior of macromolecules.

Solvent quality for real polymer chain

Typical potential between two monomers in the absence of solvent:



Presence of solvent can change the shape of the potential:



Solvent effect on polymer chain size: $\alpha = \frac{R}{R_{ideal}}$

- Effective repulsion will result in swelling of polymer coil $\alpha > 1$ – good solvent
- Effective attraction will result in collapse of polymer coil $\alpha < 1$ – bad solvent

Solvent quality and temperature

The *free energy* of polymer chain is a sum of energetic and entropic contribution:

$$F = U - TS$$

At $U = 0$ we have ideal chain with $R \sim N^{1/2}$

Taking into account low concentration of monomers in ideal coil we expand interaction energy in a power series of number of particles in a unit volume(virial expansion):

$$U = Nk_B T(nB + \dots), \text{ where } B(T) = \int \{1 - \exp[-u(\vec{r})/k_B T]\} d^3 r$$

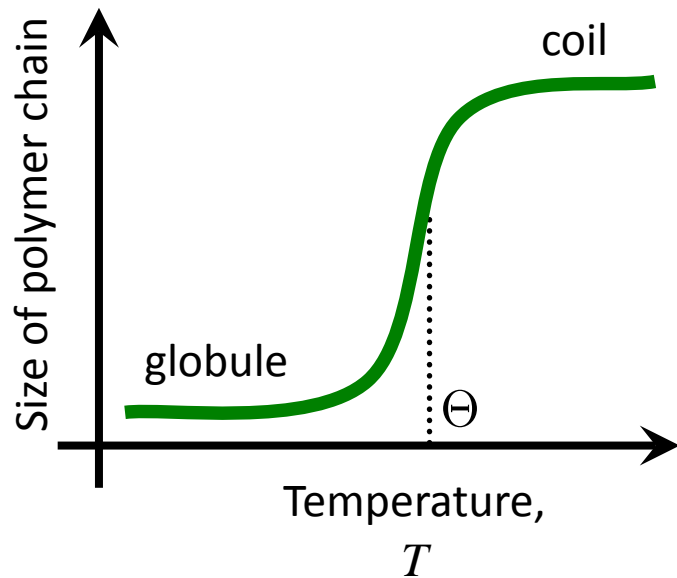
describes pair interaction between monomers.

It can be seen:

- At $T = \Theta$, $B=0$ and chain behaves as ideal
- At $T > \Theta$, $B>0$, repulsion dominate, chain swells
- At $T < \Theta$, $B<0$, attractions dominate, chain collapse

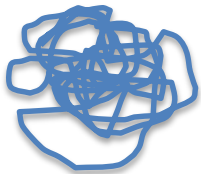
Coil-Globule transition

A globule-coil transition point lies around Theta point, and it is determined by the balance between entropy gain caused by chain extension and energy loss due to reducing attractions.

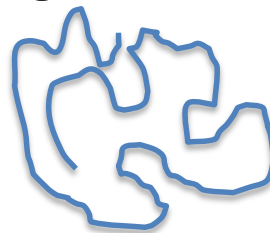


$$F = U - TS$$

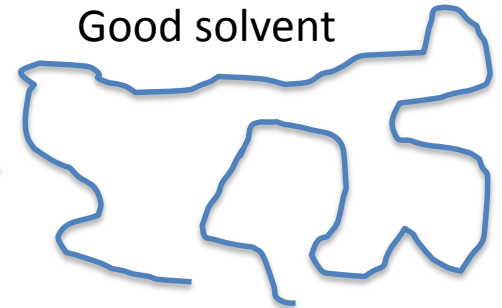
Bad solvent



Θ -solvent



Good solvent



Volume interactions summary

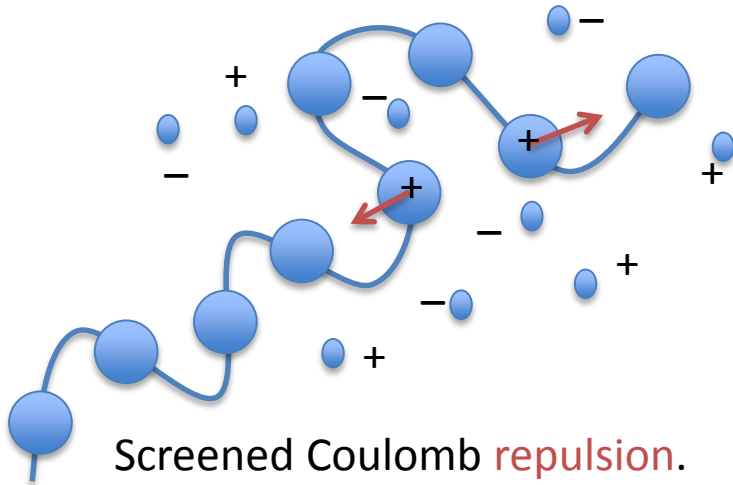
- Presence of solvent can introduce effective interaction between monomers
- Solvent quality is temperature dependent
- Size of the globule in the bad solvent is given by:
- Size of the ideal coil in the Θ solvent is given by:
- Size of the swollen coil in the bad solvent is given by:

$$R = aN^{1/3}$$

$$R = aN^{1/2}$$

$$R = aN^{3/5}$$

Electrostatic interactions



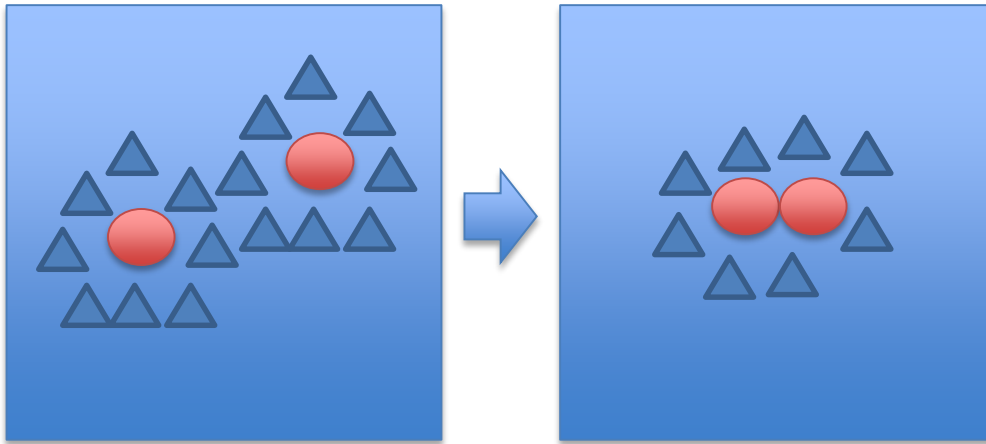
$$U(r_{ij}) = \frac{e^2}{\epsilon r_{ij}} \exp(-r_{ij}/r_D)$$

Where r_D is the screening (Debye) radius, which depends on temperature and low molecular salt concentration.

- Presence of strong electrostatic interactions increase the size of the chain
- Conformation of charged macromolecule depends mostly on fraction of charged monomers and low molecular-weight salt concentration

Hydrophobic interactions

Two non polar molecule immersed into a polar solvent (water).



Gibbs free energy:

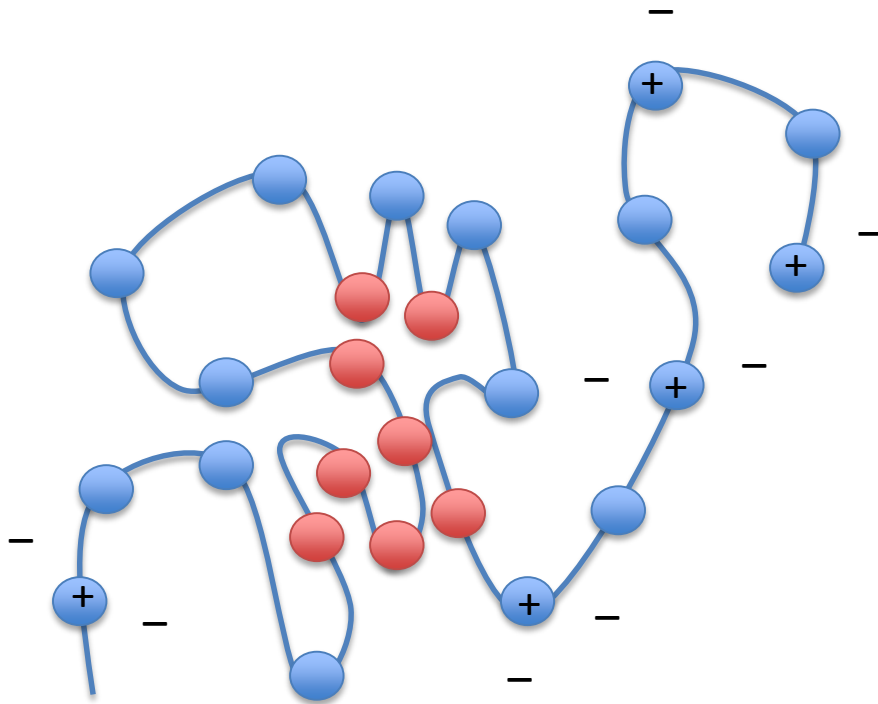
$$\Delta G = \Delta H - T\Delta S$$

ΔH – Can be either negative or positive, depending on the strength of dipole-dipole interactions

ΔS – Positive due to loss of the solvent structure

$$|T\Delta S| > |\Delta H|$$

Linear chain summary



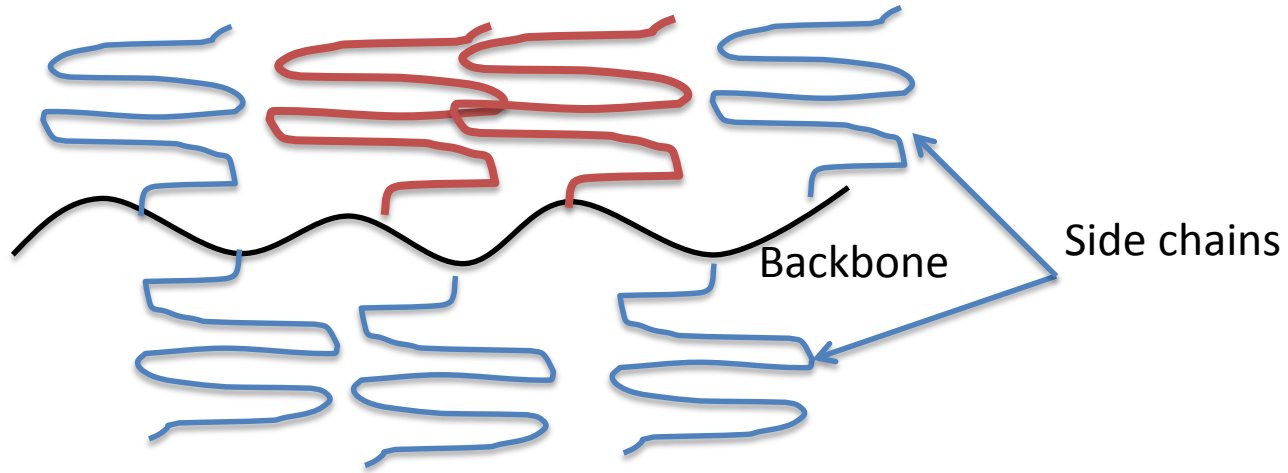
- Connectivity into the chain
- Hydrophobic core
- Stretched electrostatic part
- Swollen hydrophilic loops

All these leads to micro-phase separation phenomenon in polymer physics

Outline

- General aspects of polymer theory
 - Size and persistent length of ideal linear polymer chain
 - Volume interactions and Coil-Globule transition
 - Electrostatic and hydrophobic interactions
- Branched polymers as a next step towards proteins
- Proteins as extremely complicated and well designed polymers

Comb-like macromolecules



- Each side chain has properties of a single polymer chain, discussed above
- Chains grafted on the backbone that make entropic effects very strong
- Properties of of each grafted chain amplified on the scale of entire macromolecule

Description of such molecules is much more complicated compare to linear chains

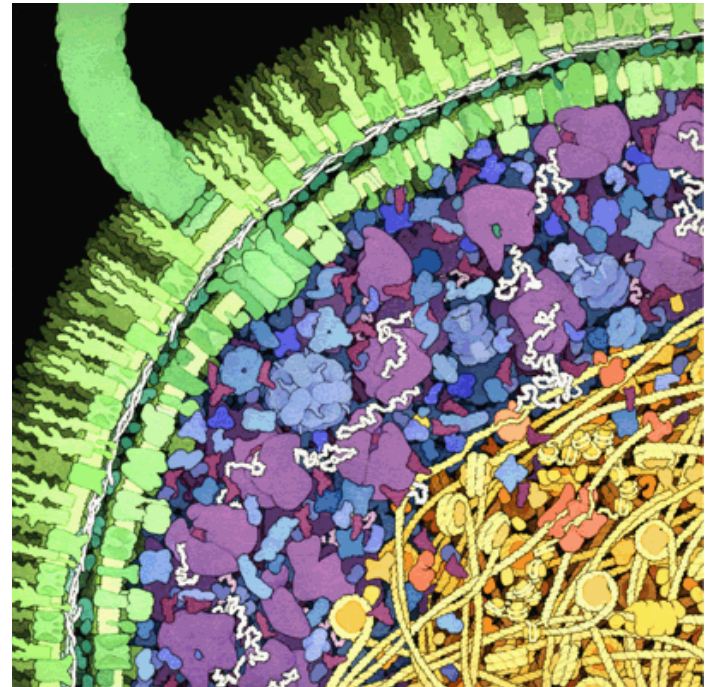
Outline

- General aspects of polymer theory
 - Size and persistent length of ideal linear polymer chain
 - Volume interactions and Coil-Globule transition
 - Electrostatic and hydrophobic interactions
- Branched polymers as a next step towards proteins
- **Proteins as extremely complicated and well designed polymers**

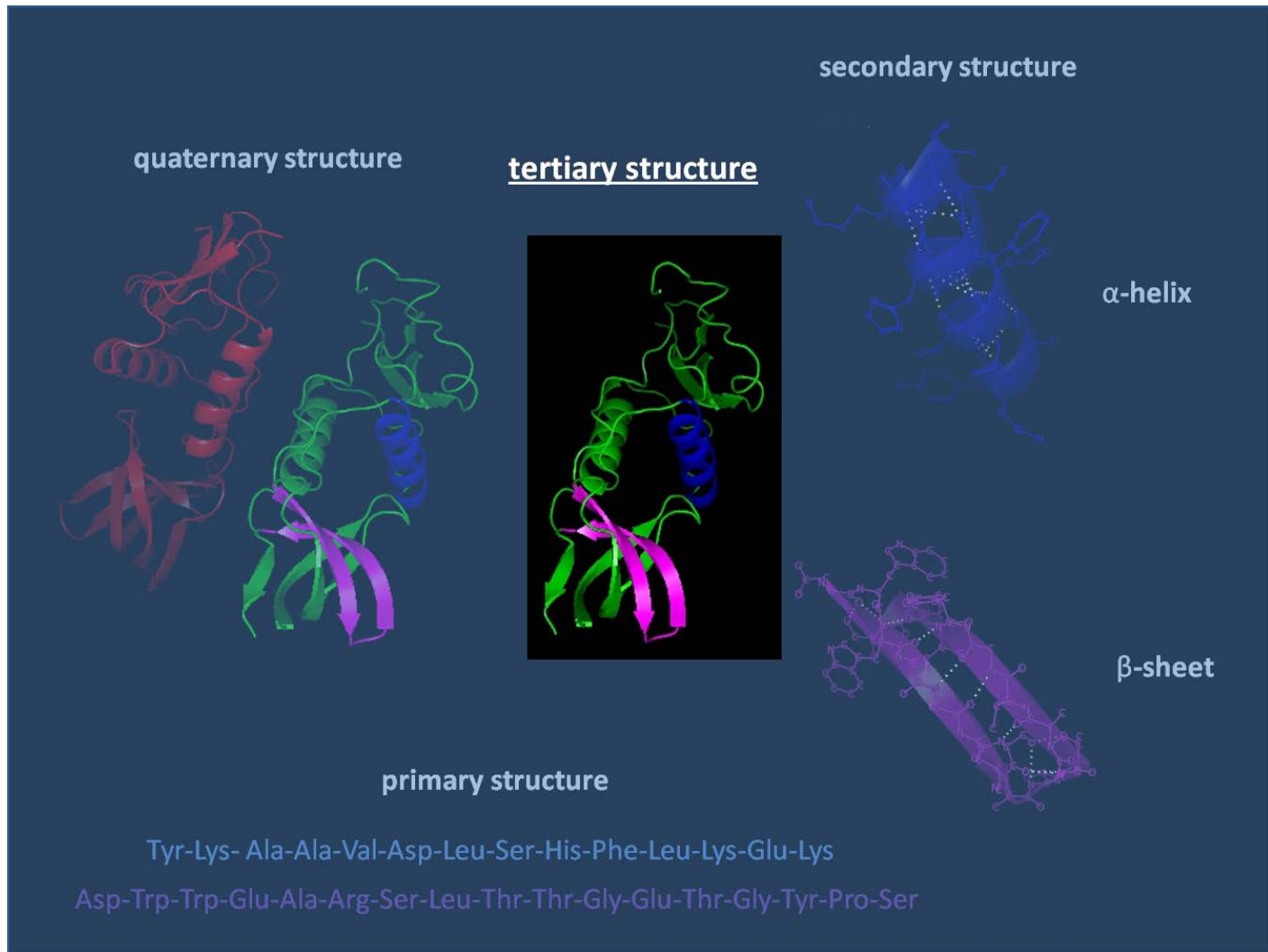
Proteins

Imagine now of branched polymer which

- Has side chains of extremely complicated nature
- Has to fold into preprogrammed structure for exact amount of time
- Has to function in a very specific biological condition
- Can not missfold
- Has to interact with other molecule in extremely crowded environment

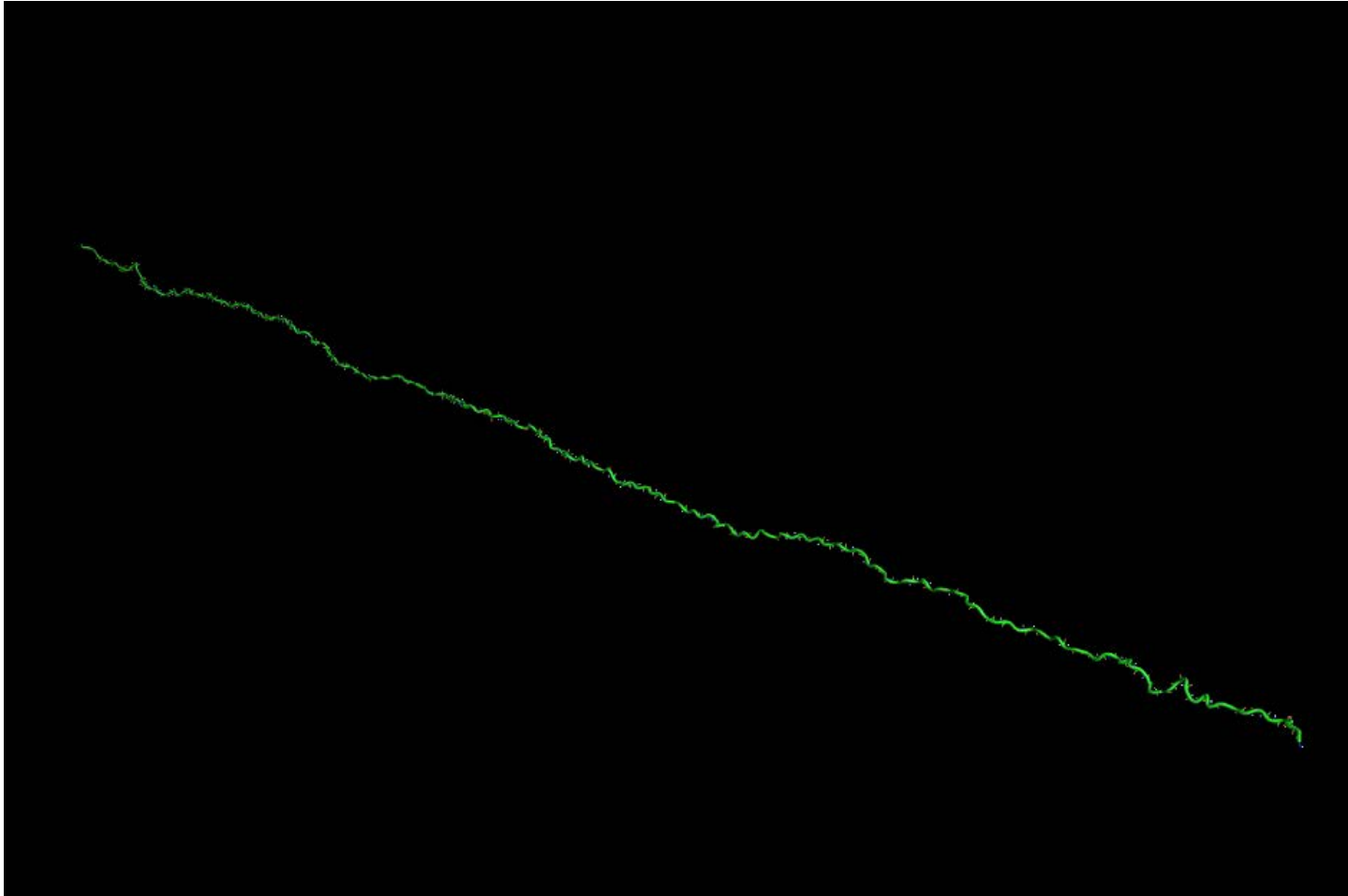
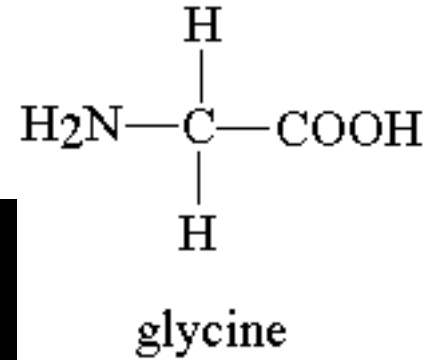


Proteins fold into specific structures



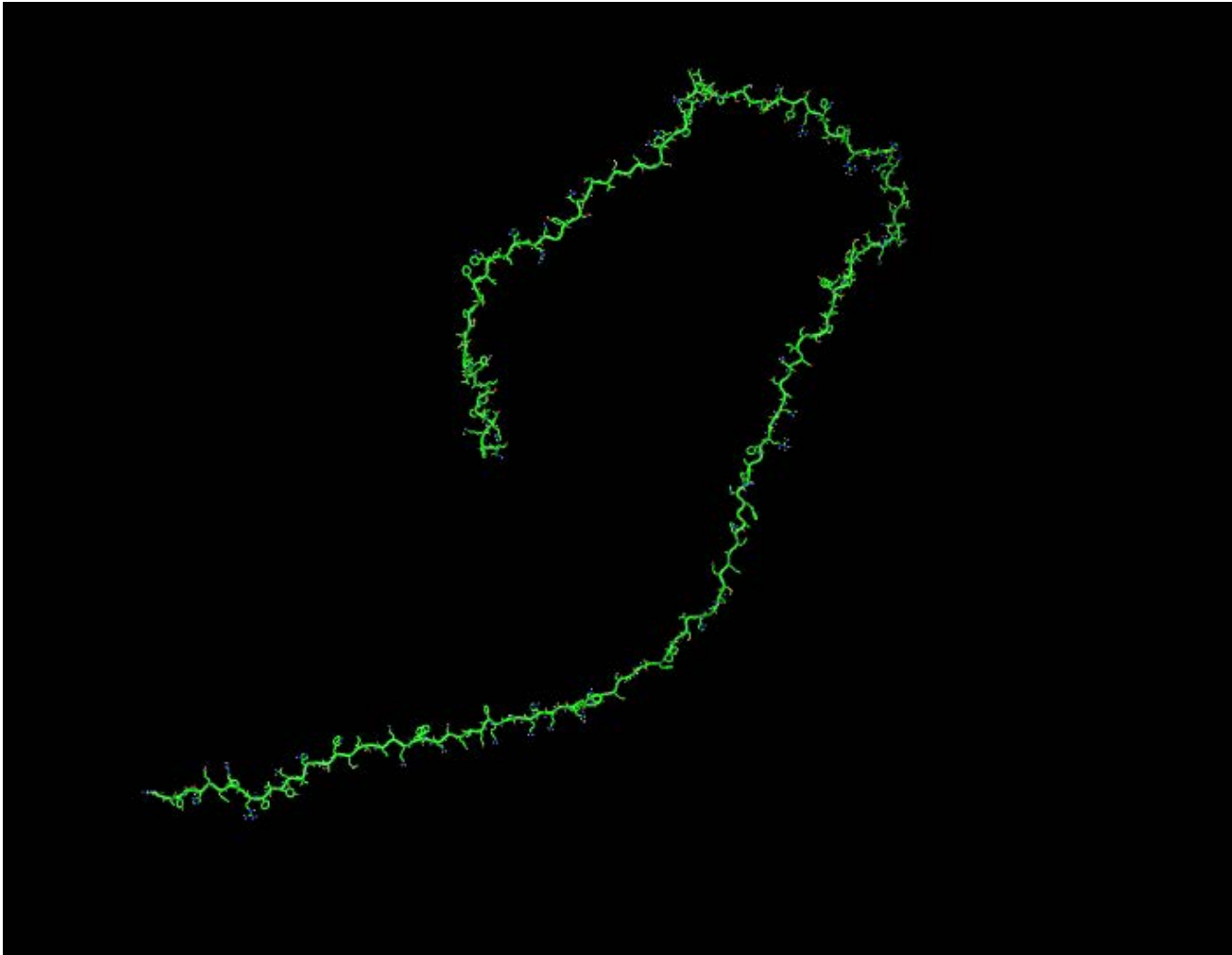
Proteins fold into specific structures

Simple homo-polymer like protein. Side chains glycine.



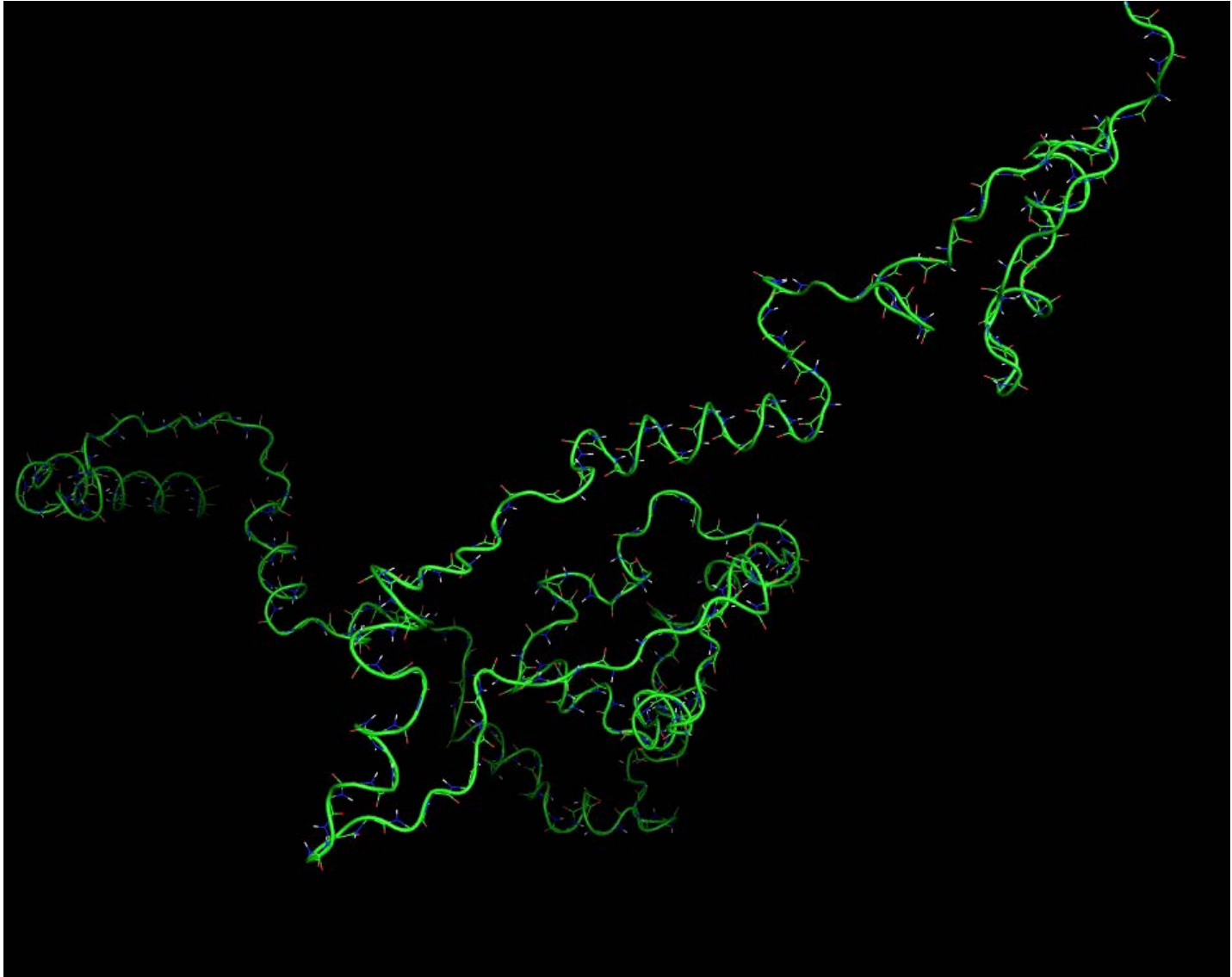
Proteins fold into specific structures

Side chains are random amino acids:

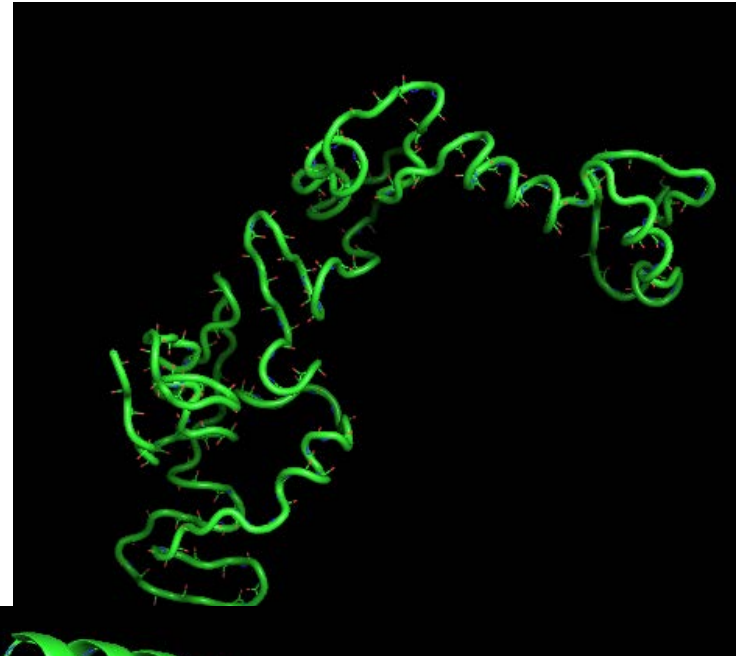
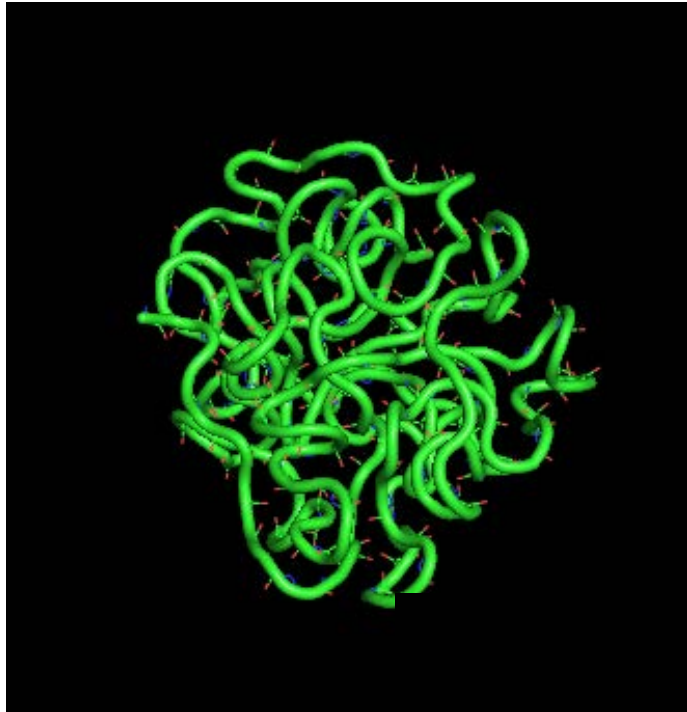


Proteins fold into specific structures

Real protein:



Proteins fold into specific structures



Thank you.