Protein phase structure study within gauge field theory model

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Motivations

Frenet Frames protein geometry and gauge symmetries

Integrable model of protein: Soliton solutions

Soliton structure of myoglobin

Folding and unfolding: Temperature

Conclusion

Motivations:

- Theoretical: Structural and dynamical properties of proteins are strongly correlated with their function and the understanding of this relation is of fundamental importance for deciphering the molecular mechanisms of life.
- Fundamental: We do not know how at specific physical conditions the tertiary and quaternary structure of the protein can be deduced from the DNA sequence. Since the biological function of the protein is closely related to its form, the problem of protein folding is one of the most important unsolved problems in science.
- Practical: Misfolding tertiary and quaternary structure of certain proteins causes a variety of neurodegenerative diseases such as Alzheimers, Parkinsons and Creutzfeldt-Jakobs diseases, type 2 diabetes, and many cancers.

Existing approaches:

- Molecular dynamics: mimic protein structure and dynamics on the atomic level. Much progress in understanding protein function.
  However: MD is limited concerning both the system size and the attainable time scales. Computing power by 5-6 orders of magnitude greater than is technically achievable in nearest future is needed for a molecular dynamics realistic simulations of the tertiary and quaternary structures on large spatial and temporal scales.
- Coarse grain modelling: Can successfully describe protein structure in terms of effective building blocks without huge computing power needed.
  However: Fundamental ground for the basic structures is needed

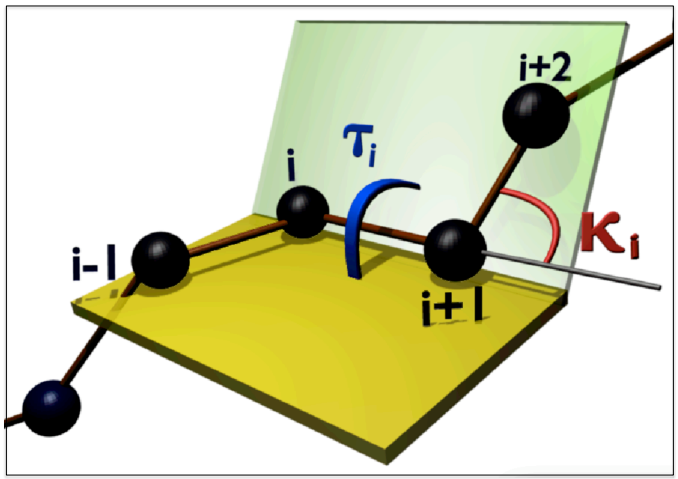


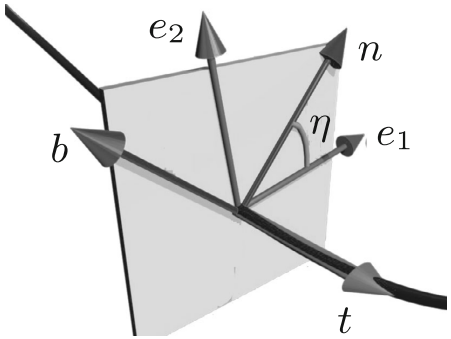
Figure: Definition of C_α backbone bond (κ) and torsion (τ) angles

Protein is described as a one-dimensional manifold in three dimensional space. Variables:

- l - coordinate of a point from the begining of line (i - number of an amino-acid in the discreet case)
- $\kappa(l)$ - bending angle at the point l (κ_i in the discreet case)
- $\tau(l)$ - torsion angle at the point l (τ_i in the discreet case)

The geometry of the string is defined by the Frenet equations:

$$\begin{cases} \frac{d\mathbf{t}}{ds} = \kappa\mathbf{n} \\ \frac{d\mathbf{n}}{ds} = -\kappa\mathbf{t} + \tau\mathbf{b} \\ \frac{d\mathbf{b}}{ds} = -\tau\mathbf{n} \end{cases}$$



where

$$\mathbf{t} = \frac{d\mathbf{r}}{ds}, \quad \mathbf{n} = \frac{d^2\mathbf{r}}{ds^2} \quad \mathbf{b} = [\mathbf{t} \times \mathbf{n}]$$

First equation does not contain **b** and **n** explicitly, thus the string remains unchanged upon rotation around direction of **t**.
For the ideal free chain the frame rotation exhibits local SU(2) symmetry dynamical properties of the amino acids brakes the SU(2) symmetry to the U(1) - Abelian Higgs model

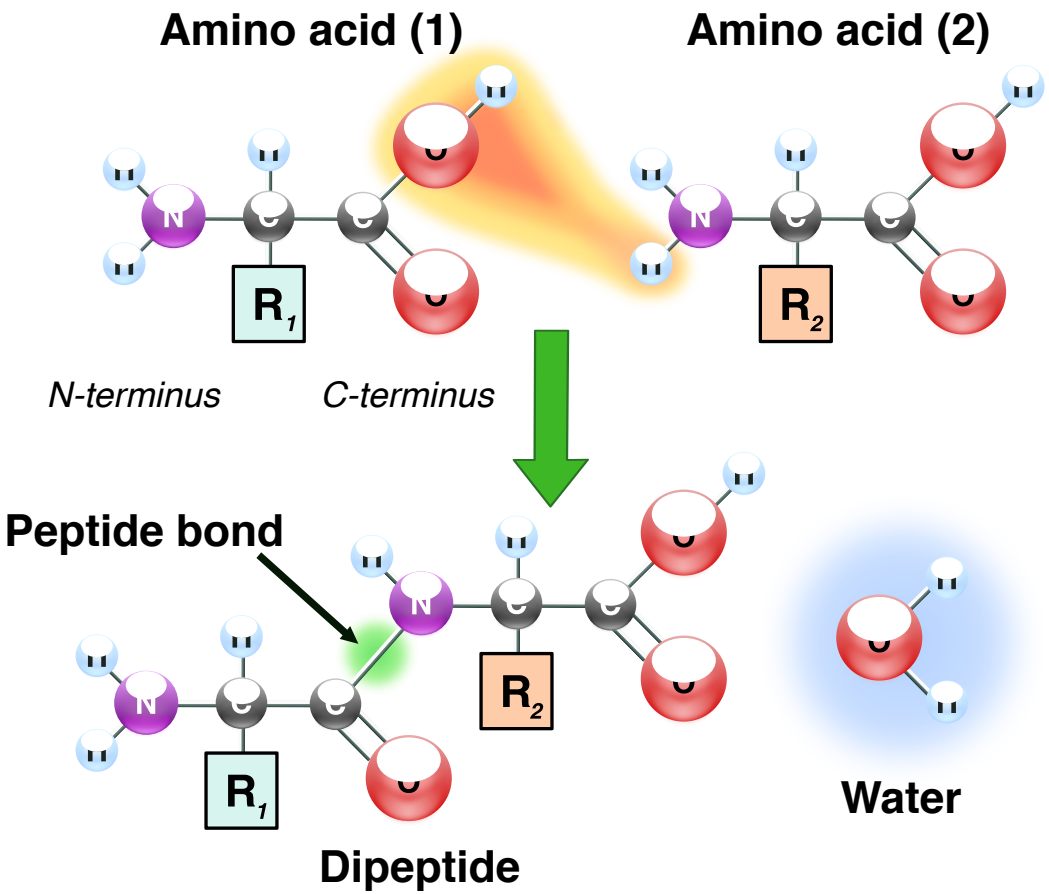


Figure: Peptide bond formation

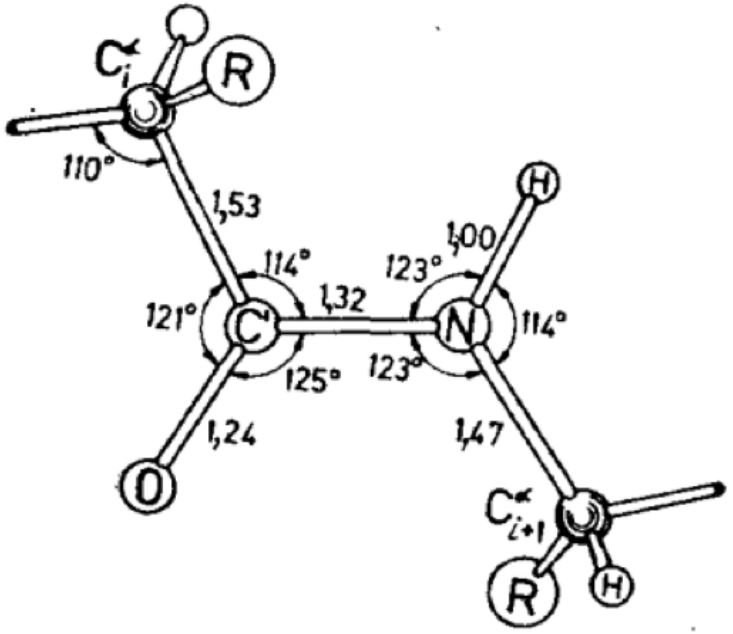


Figure: Bending is defined by the amino group angles

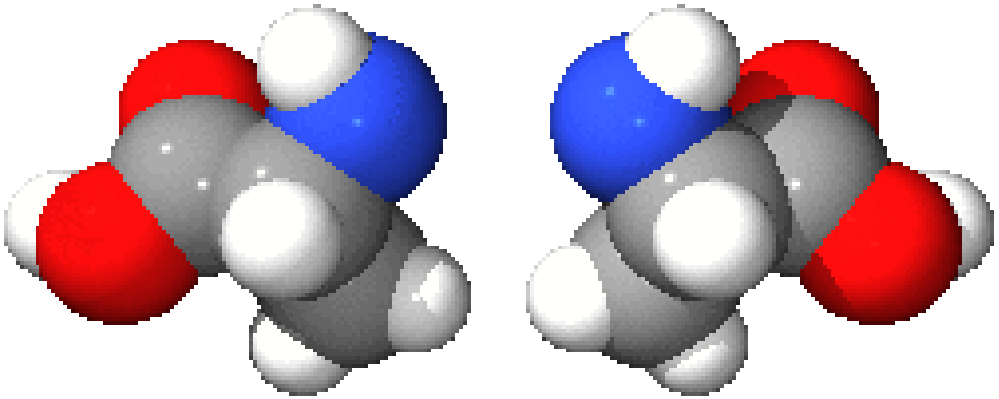


Figure: D and L Alanine

Protein chiral symmetry locally broken by 3D structure of amino-acids. Famous example - left handed amino-acids are poisonous for right handed organisms due to protein misfolding.

The analogy between the the U(1) symmetry and the Frenet Frame rotation:

$$\frac{d}{ds}\begin{pmatrix}\mathbf{e}_1\\ \mathbf{e}_2\\ \mathbf{t}\end{pmatrix} = \begin{bmatrix}0 & (\tau+\eta_s) & -\kappa cos(\eta)\\ (\tau+\eta_s) & 0 & \kappa sin(\eta)\\ \kappa cos(\eta) & -\kappa sin(\eta) & 0\end{bmatrix} \times \begin{pmatrix}\mathbf{e}_1\\ \mathbf{e}_2\\ \mathbf{t}\end{pmatrix}$$

This symmetry transformation can be written as gauge U(1) transformation of the gauge and Higgs field:

$$\kappa \sim \phi \rightarrow \kappa e^{-i\eta} \equiv \phi e^{-i\eta}$$

$$\tau \sim A_i \rightarrow \tau + \eta_s \equiv A_i + \eta_s$$

The SU(2) theory with the local gauge and chiral symmetry intrinsically broken by the structure of an amino acid

Thus, the Abelian Higgs Model Hamiltonian takes the form:

$$H = \int_0^L ds(|(\partial_s + ie\tau)\kappa|^2 + \lambda(|\kappa|^2 - m^2)^2 + a\tau)$$

term $a\tau$ is the Chern-Simons term ensuring chirality breaking - domination of the right hand alpha-helices.
It allow us to use full power of the field theory approach to study protein structure and dynamics in terms of the collective degrees of freedom

Topological sectors of the vacuum (structures in the protein):

α-helices (broken chiral symmetry, negative parity):

$$\begin{cases} \kappa \simeq \frac{\pi}{2} \\ \tau \simeq 1 \end{cases}$$

β-strands (restored chiral symmetry, positive parity):

$$\begin{cases} \kappa \simeq 1 \\ \tau \simeq \pi \end{cases}$$

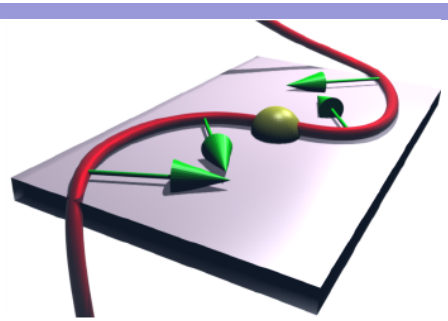


Figure: Inflection point: curve flattening

It is impossible to determine bending and torsion in a such point

Z_2 symmetry

:

$$\kappa \rightarrow -\kappa$$

$$\tau \rightarrow \tau + \pi$$

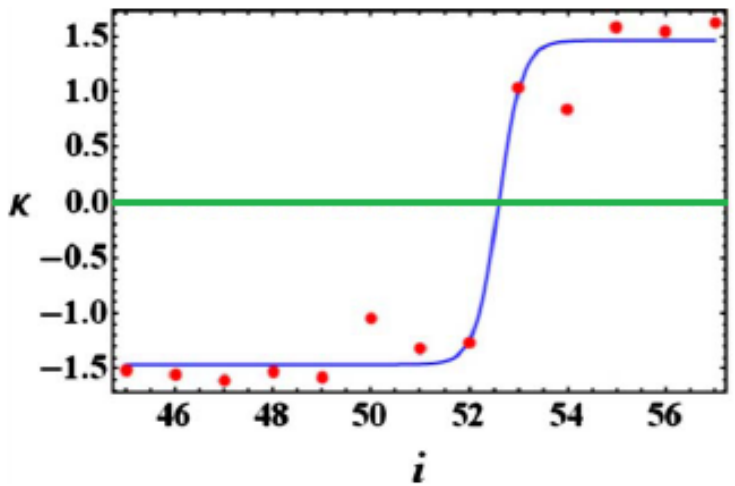


Figure: One-dimensional structure (vortex at 1+1 space-time) at the inflection point

Real part of the Abelian Higgs Model Hamiltonian:

$$H_\kappa = \int_{-\infty}^{\infty} ds(\kappa_s^2 + \lambda(\kappa^2 - m^2)^2)$$

contains soliton solutions:

$$\kappa(s) = m tanh(m\sqrt{\lambda}(s - s_0))$$

energy of the kink:

$$E = \int ds(\kappa_s^2 + \lambda(\kappa^2 - m^2)^2 - a\tau - b\kappa^2\tau + \frac{c}{2}\tau^2 + \frac{d}{2}\kappa^2\tau^2)$$

Simple example:

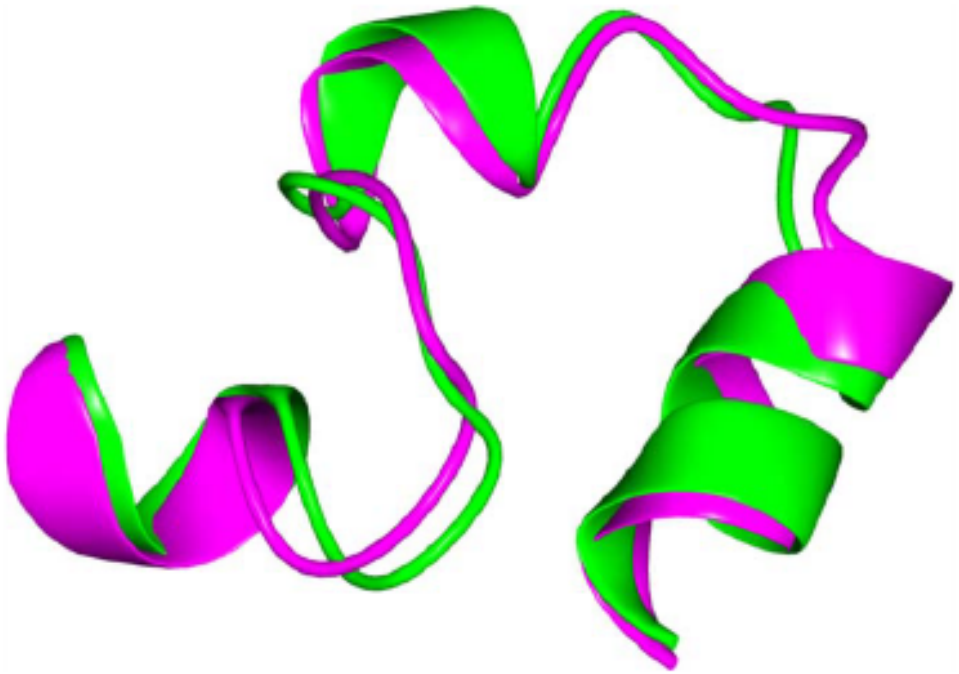


Figure: Willin described by two solitons. Green - PDB data, pink - two-soliton configuration (Chernodub M., Hu S., Niemi A.J., Phys. Rev. E82 011916 (2010))

Myoglobin structure:

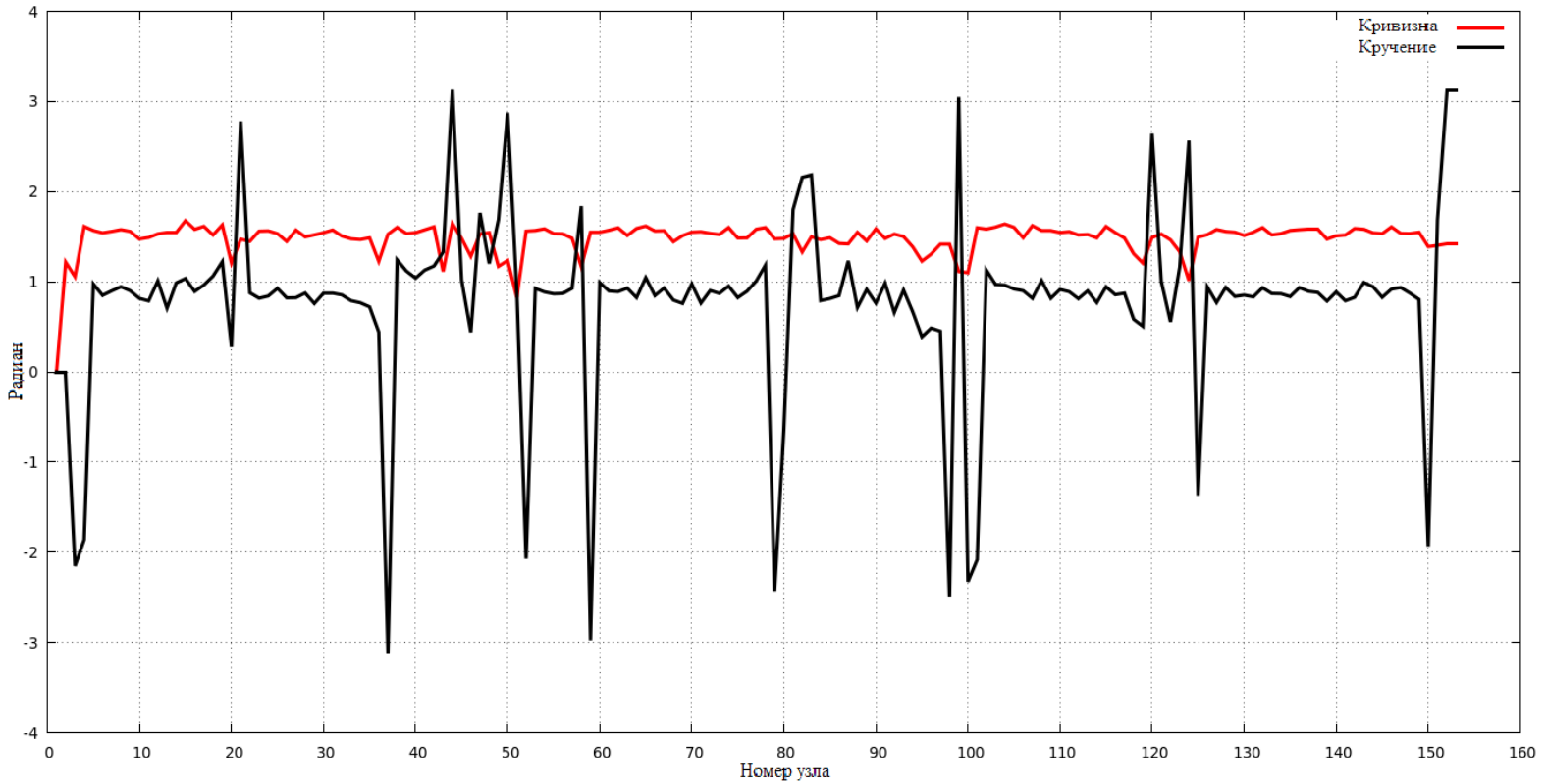


Figure: Bending and torsion of myoglobin molecule

α-helix criteria:

- Bending fluctuates around $\frac{\pi}{2}$
- Torsion does not has fluctuations larger than $\frac{\pi}{2}$

β-strand criteria:

- Bending fluctuates around 1
- Torsion has absolute value π with sign changing.

Soliton center criteria:

- Bending has sharp local minimum
- Torsion changes more than $\frac{3\pi}{4}$

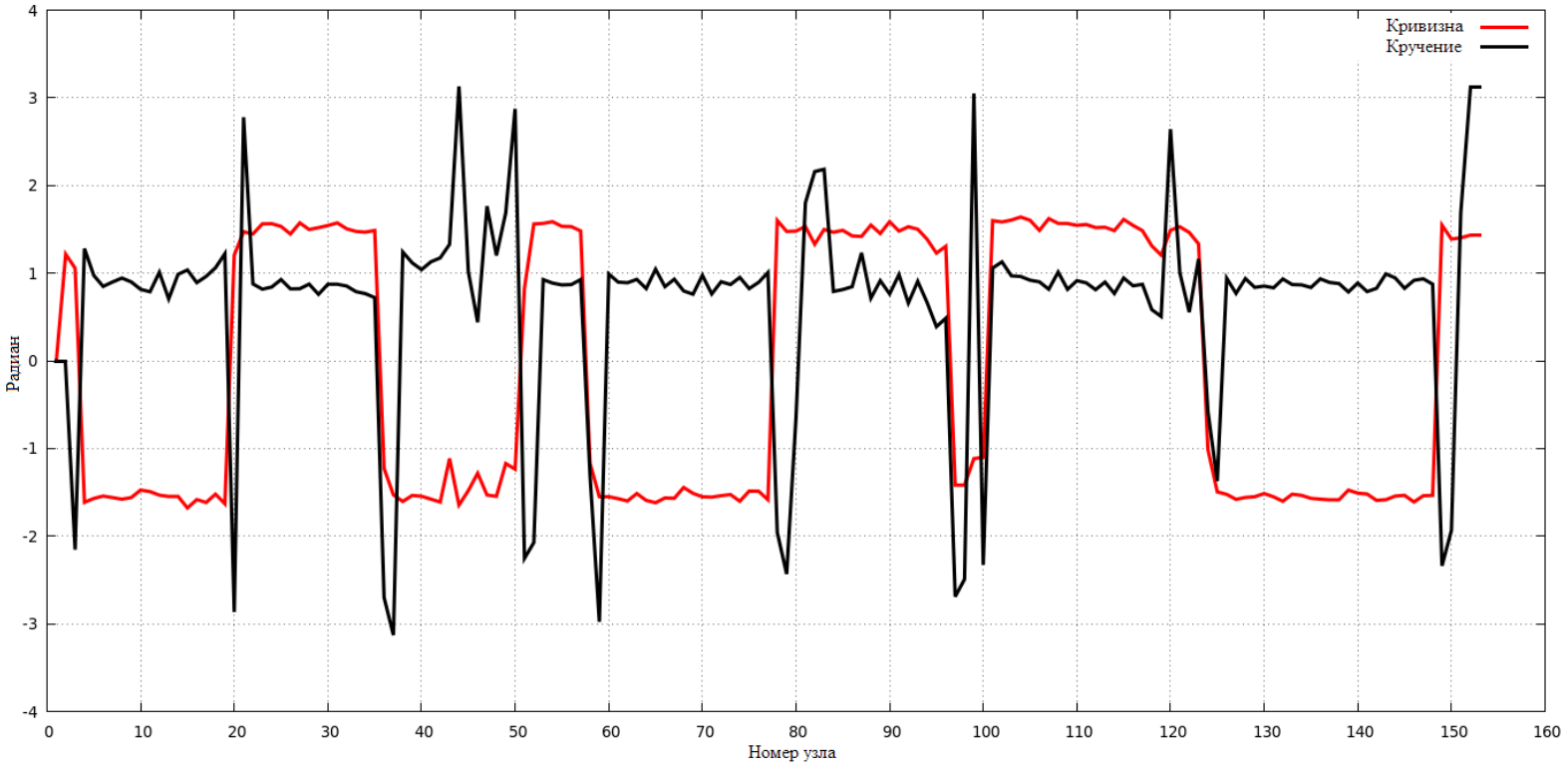


Figure: Bending and torsion of myoglobin molecule with soliton structure defined

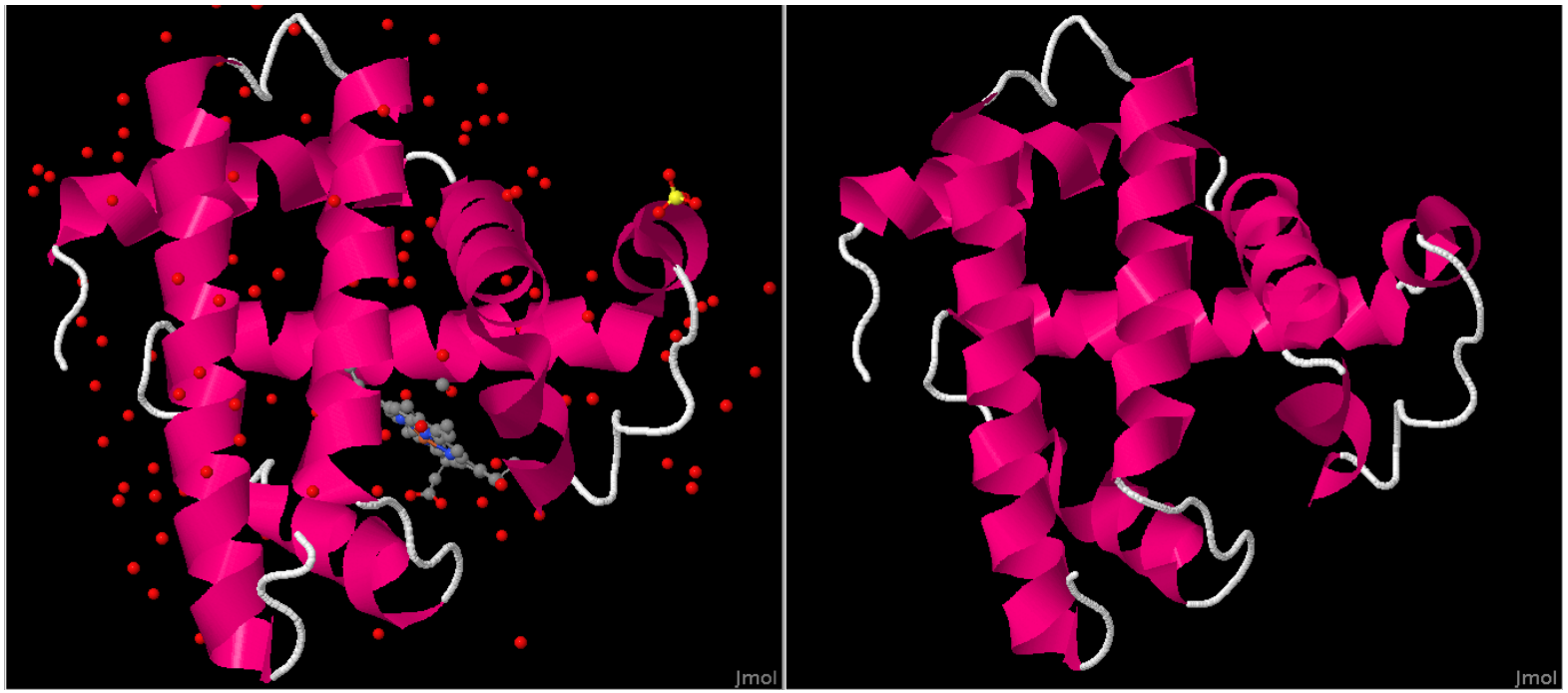


Figure: Structure of myoglobin described by solitons.Left - original PDB structure, right - soliton structure

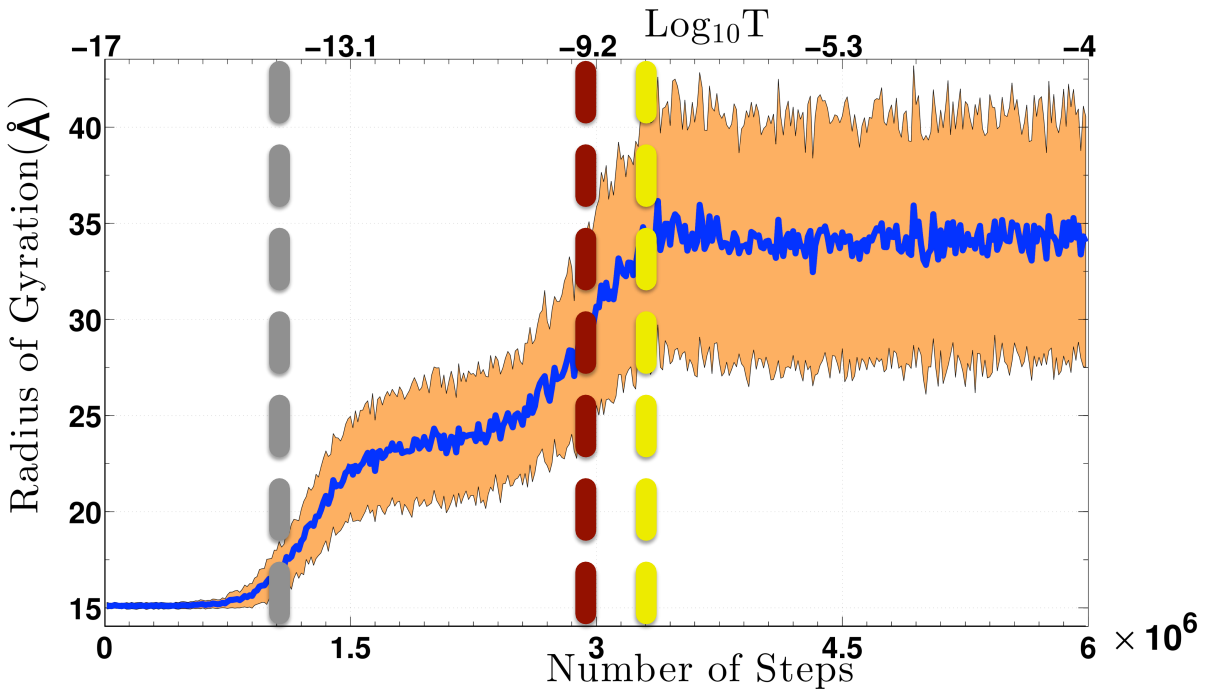


Figure: The dependence of radius of gyration as a function of Glauber temperature factor. The blue line is average value and the orange band denotes the one standard deviations fluctuation distance. The dashed grey line estimates 25°C, the dashed red line estimates 75°C and the dashed yellow line estimates 90°C (A. Niemi at al.)

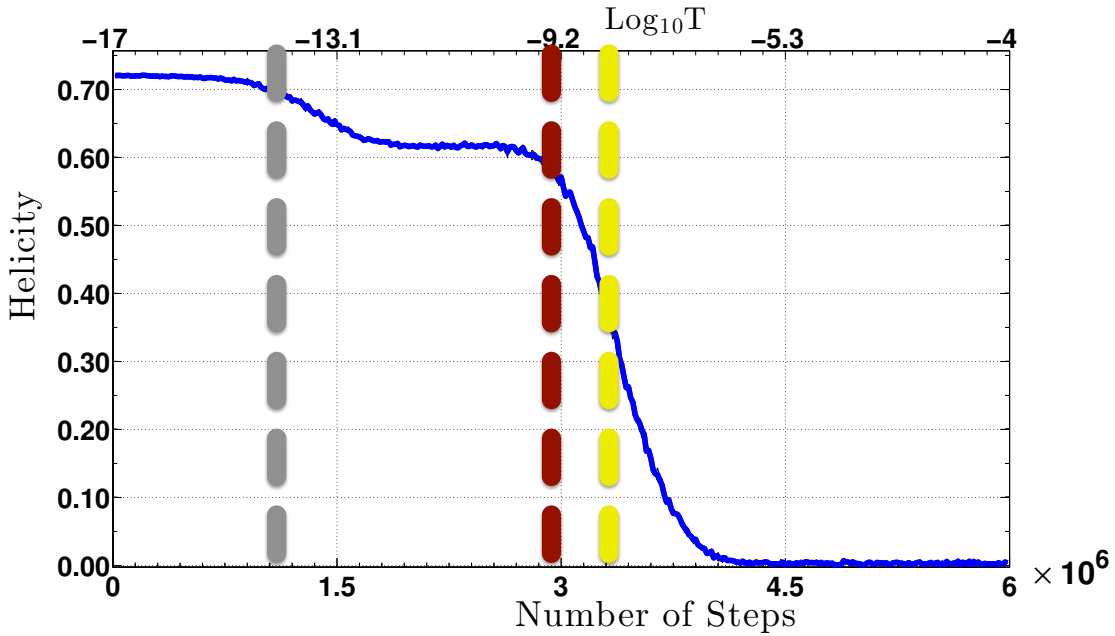


Figure: Simulated -helical content (in %) as a function of Glauber temperature T: The dashed grey line estimates 25°C, the dashed red line estimates 75°C and the dashed yellow line estimates 90°C (A.Niemi at al.)

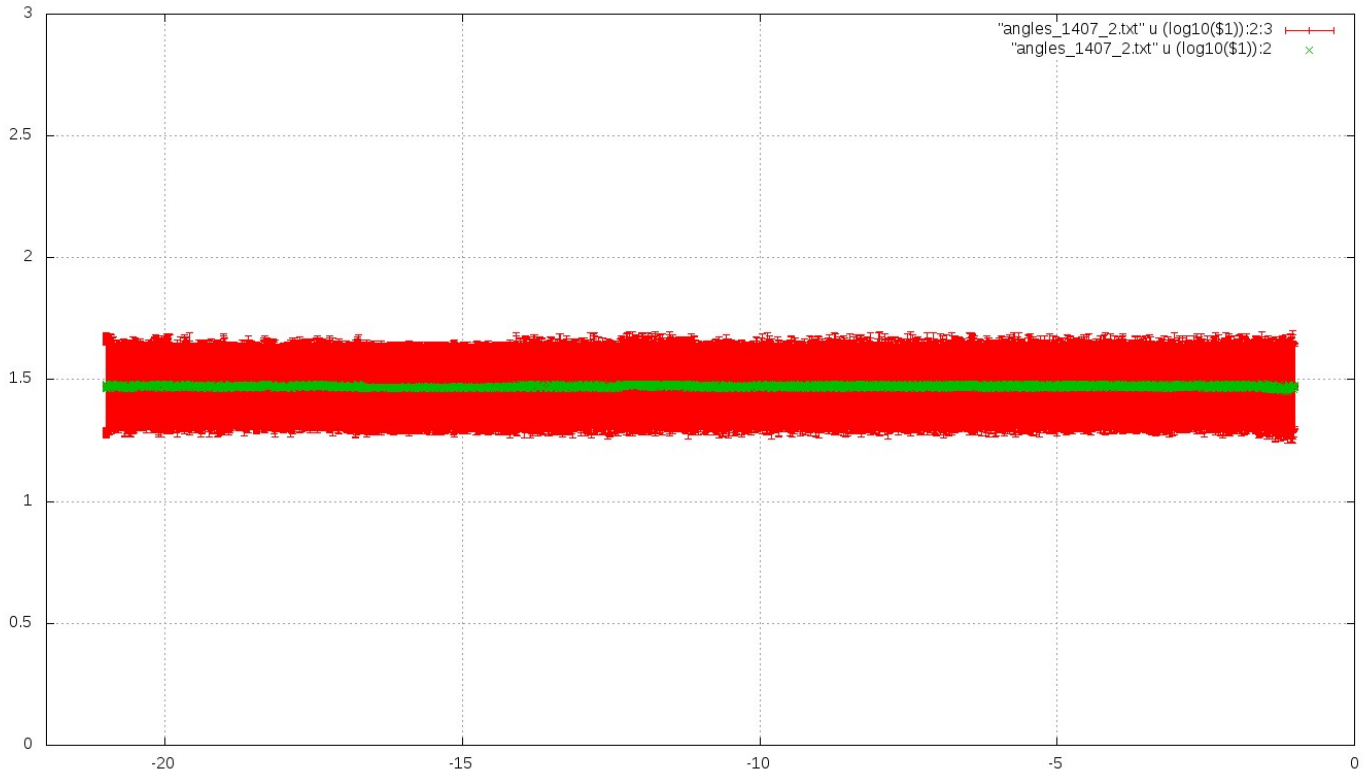


Figure: Dependence of mean value of bending κ as a function of Glauber temperature factor

Temperature dependence exhibits two crossovers: native state - molten globule, molten globule - self avoiding random walk with constant bending

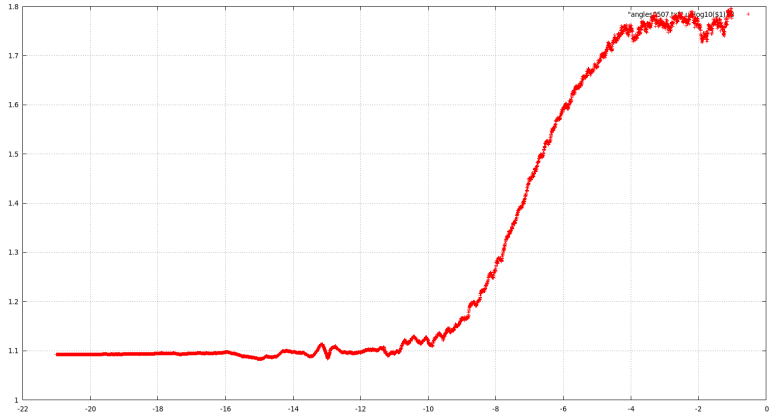


Figure: Absolute value of twisting angle τ as a function of Glauber temperature factor

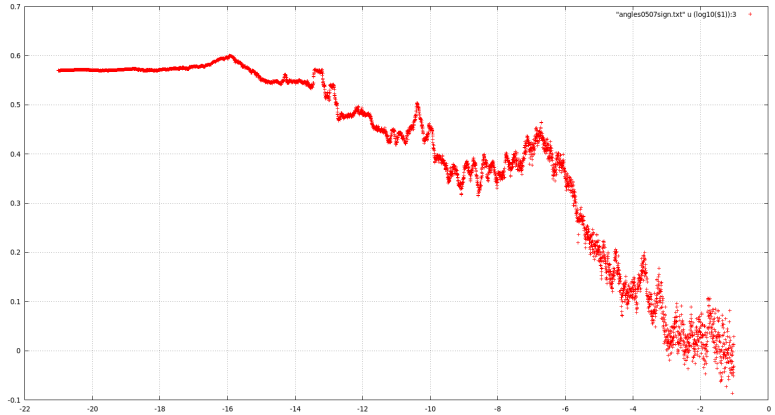


Figure: Mean value of twisting angle τ as a function of Glauber temperature factor

Self avoiding random walk with constant bending exhibits chiral symmetry restoration at high temperature

Conclusions:

- Local amino-acids structure leads to gauge and chiral symmetry breaking in proteins that defines its secondary and tertiary structure
- The protein structure can be reproduced in terms of topological solutions superposition
- Temperature dependence exhibits two crossovers: native state - molten globule, molten globule - self avoiding random walk with constant bending