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Nonequilibrium Dynamics of the Helix-Coil-Transition in Polyalanine

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Introduction

The shape of a protein can influence its function or lead to a loss of function altogether, which is the cause of various diseases. While machine learning based approaches are able to accurately predict the structure of a protein based on its sequence of amino acids, we still do not comprehend the underlying mechanisms of secondary and tertiary structure formation. Specifically, the dynamics of the nonequilibrium pathways that enable proteins to fold into their native states in time scales of micro- to milliseconds is not well understood.

Since the collapse of the protein backbone is believed to play a major role in this process, numerous studies have focused on the collapse transition in polymers as a model for this process.

A quantity of significant interest in such studies of the nonequilibrium dynamics is the behavior of the collapse time τ_c as a function of the length of the polymer (typically measured by the number of monomers or residues), which usually follows a power-law scaling of the form

$$\tau \propto N^z .$$

Past studies have found z to be in the range 1-2, but a recent study found a significantly faster dynamics for the biopolymer polyglycine with $z \approx 1/2$.

In order to confirm this fast scaling and investigate the influence of secondary structure, we study the nonequilibrium dynamics of the biopolymer polyalanine, which is known to form helices.

Methods

- MD simulations of polyalanine with chain lengths $N = 25 - 300$ using OpenMM
- Simulations with Nosé-Hoover thermostat with parameters $\Delta t = 1$ fs, and $\gamma = 1$ ps^{-1}
- Equilibration at high temperature before quenching to $T = 300\ K$
- Amber14ffSB force field, generalized Born implicit solvent
- Analysis of secondary structure is performed using the DSSP algorithm
- Analysis using invariants derived from gyration tensor

$$\boldsymbol{Q} = Q_{ij} = \frac{1}{M}\sum_{m=1}^{M}(r_m^i - r_{\mathrm{CM}}^i)(r_m^j - r_{\mathrm{CM}}^j), \qquad i,j = 1,\ldots,d.$$

- Radius of gyration:

$$R_g^2 = \frac{1}{M}\sum_{m=1}^{M}(\vec{r}_m - \vec{r}_{\mathrm{CM}})^2 = \sum_{i=1}^{d} Q_{ii} = \mathrm{Tr}\,\boldsymbol{Q}.$$

- Asphericity:

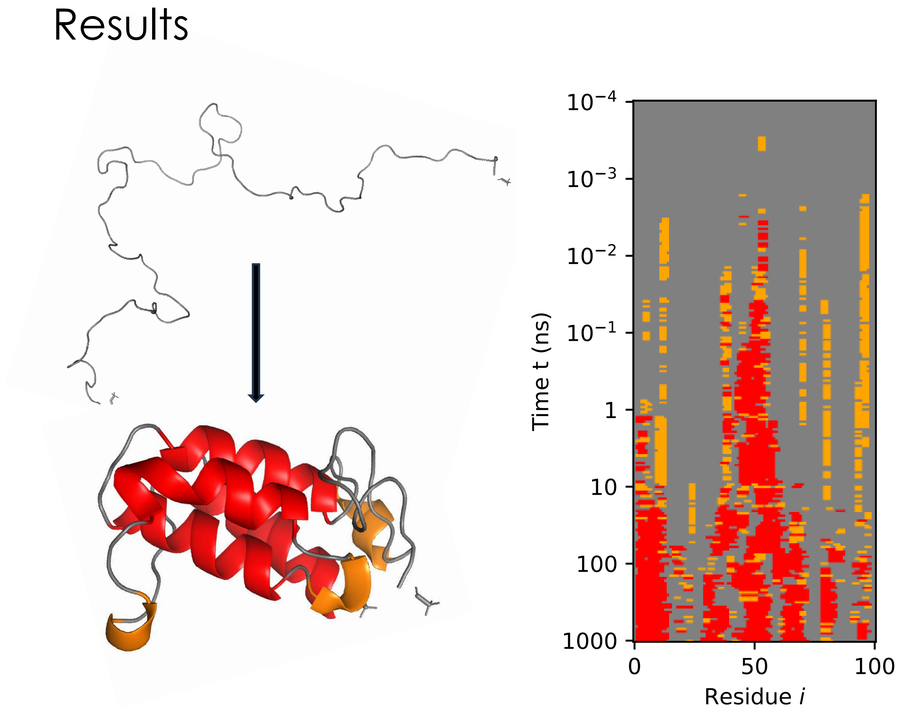
$$A = \frac{1}{6}\sum_{i=1}^{3}\frac{(\lambda_i - \bar{\lambda})^2}{\bar{\lambda}^2} = \frac{3}{2}\frac{\mathrm{Tr}\,\hat{\boldsymbol{Q}}^2}{(\mathrm{Tr}\,\boldsymbol{Q})^2},$$

- Prolateness

$$S = \frac{\prod_{i=1}^{3}(\lambda_i - \bar{\lambda})}{\bar{\lambda}^3} = 27\frac{\det\hat{\boldsymbol{Q}}}{(\mathrm{Tr}\,\boldsymbol{Q})^3}.$$

where $\hat{\boldsymbol{Q}} = \boldsymbol{Q} - \bar{\lambda}\boldsymbol{I}$ and λ the eigenvalues of the gyration tensor

Results

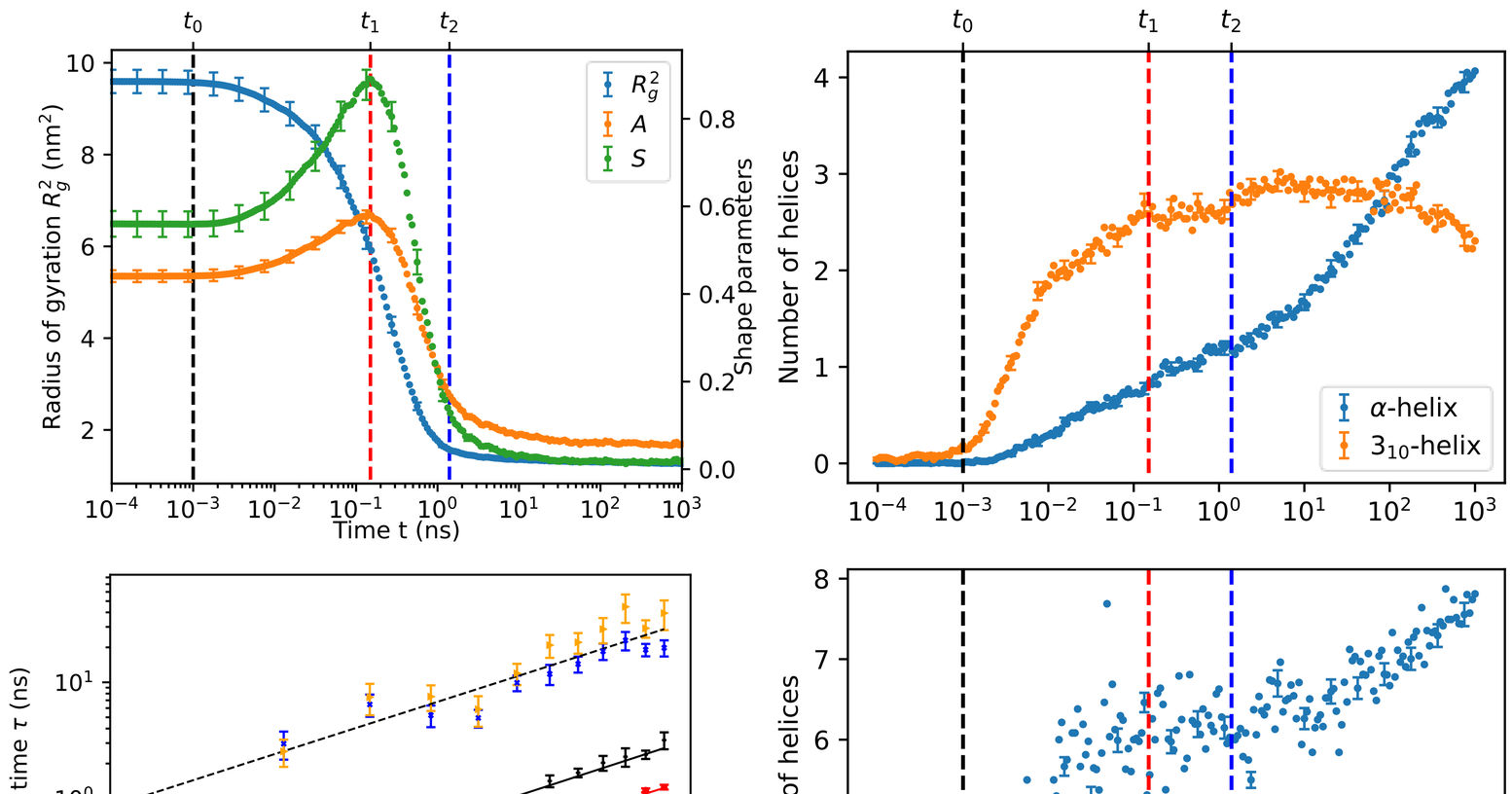


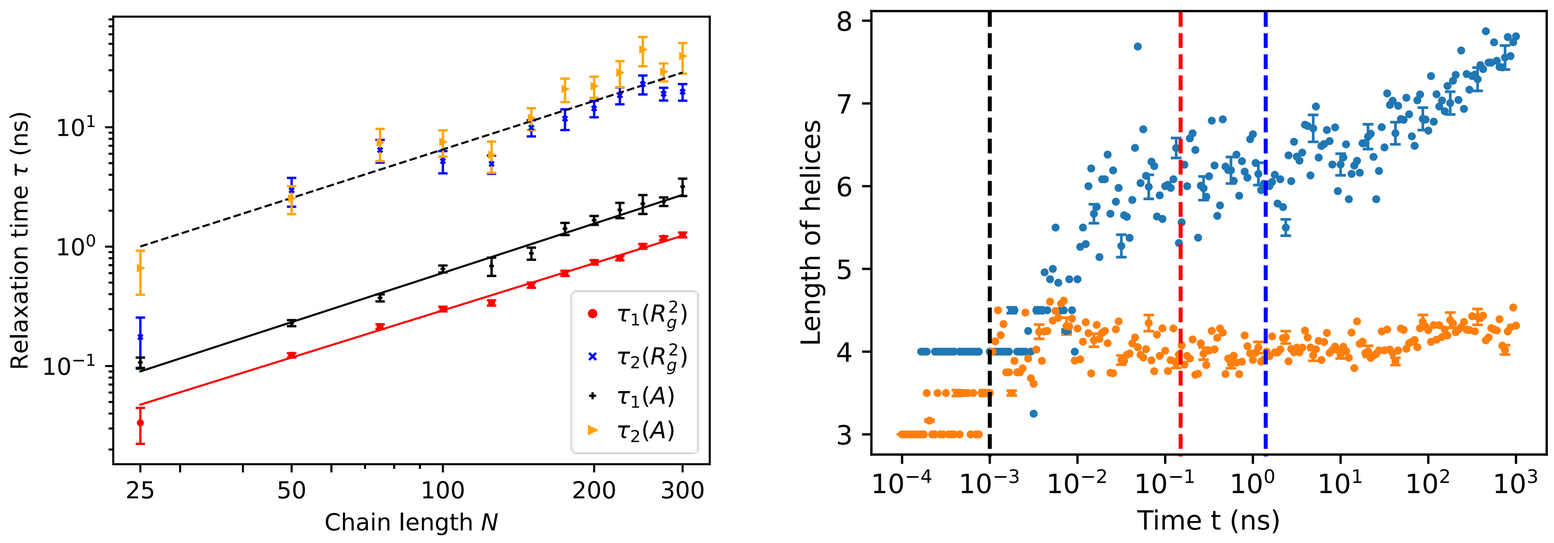
Left: Snapshots during the helix-coil transition of a single molecule. Right: Time evolution of the same molecule. α-helical residues are colored red, 3_{10}-helical residues are colored orange. Secondary structure elements are determined using DSSP.

- Polyalanine shows transition from initial random-coil state to compact helical state
- Early formation of 3_{10}-helices followed by formation of α-helices and extension of these helices
- Collapse of molecule is reflected by decrease in radius of gyration
- Asphericity A and prolateness S increase during collapse indicating formation of rod-like intermediate
- Early formation of short 3_{10}-helices until t_1, maximum in asphericty and prolateness
- Number and length of α-helices continuously increases
- Time evolution of asphericity and radius of gyration can be described by 2-exponential form

$$A(t) = ae^{-t/\tau_1} + be^{-t/\tau_2} + c$$

- Relaxation times scale with $\tau \propto N^z$ and $z \approx 1.35$





Top left: Time evolution of shape parameters for molecules of chain length N=100. Right: Average number of helices and average length of helices during the transition for molecules of length N=100. The times t_0, t_1 and t_2 mark notable events in the collapse. Bottom left: Relaxation times τ_1 and τ_2 obtained for different chain lengths N. The fitted lines correspond to $\tau \propto N^z$. The straight dotted line $\propto N^{1.35}$ through the data for τ_2 is only a guide to the eye.

Conclusion

We have investigated the helix-coil transition in polyalanine using secondary structure analysis and shape factors derived from the gyration tensor. In molecules with a chain length of $N = 100$, we observed that the transition can be split into two major stages: collapse and the subsequent transition into an equilibrium state with straight α-helices. Already during the first stage helix formation is encountered, which may be responsible for the observed straightening of the molecule halfway through the collapse. The second stage of the transition is then characterized by the formation of straight α-helices leading eventually to structures like helical bundles.

We applied a 2-exponential ansatz to the time evolutions of radius of gyration and the asphericity. For both observables we find that the smaller relaxation time τ_1 scales with an exponent of $z \approx 1.35$, similar to exponents obtained in previous studies for homopolymers.

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