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# Conformational transitions of heteropolymers

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## Abstract

We study conformational transitions of simple coarse-grained models for protein-like heteropolymers on the simple cubic lattice and off-lattice, respectively, by means of multicanonical sampling algorithms. The effective hydrophobic/polar models do not require the knowledge of the native topology for a given sequence of residues as input. Therefore these models are eligible to investigate general properties of the tertiary folding behavior of such protein-like heteropolymers.

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## 1. Introduction

Proteins are prominent and important examples for heteropolymers in biological systems, where they fulfill many specific functions such as, e.g., transport of water through cell membranes, enzymatic activity, ATP synthase, DNA polymerization, etc. The specific function a protein is able to perform strongly corresponds with its geometric shape and this so-called native conformation is a consequence of the folding of the chain of different amino acid residues, linked by peptide bonds, the heteropolymer consists of. Thus the sequence of amino acids, 20 different of which

are relevant for proteins, determines the biological function of the protein. Only a few of the possible sequences (which consist of 20 to 4000 monomers) are actually of importance. The main reason is that the native fold must be unique and stable, i.e. the conformation possesses global minimal free energy and resides in a deep, funnel-like valley of the free-energy landscape. It is one of the essential questions of protein research how the folding process towards the global energy minimum conformation, which takes milliseconds to seconds, proceeds and which conformational transitions slow down the dynamics. The time scale is far too large for molecular dynamics simulations of realistic all-atom models with explicit solvent. Therefore, frequently, kinetics and thermodynamic properties are studied by means of Monte Carlo simulations of usually extremely simplified models, which are often based on contact matrices of the na-

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tive topology and, hence, knowledge-based and specific for the protein under consideration. In our studies we employ more general properties of protein-like heteropolymers. We use effective hydrophobic/polar models such as the HP model [1] on the lattice and the off-lattice AB model [2] to study the influence of different sequences of hydrophobic and polar or hydrophilic monomers on the strength of conformational transitions between random coils, intermediary globules, and hydrophobic-core conformations.

## 2. Conformational transitions

Protein structures are usually divided into four categories. The primary structure denotes the sequence of amino acid residues. Helices,  $\beta$  sheets, and hairpins are secondary structures and the global arrangement of the monomers within a single domain is tertiary. Quaternary structures are formed by macromolecules with more domains. The sequence is fixed through the genetic code and therefore single-domain proteins experience during the folding process conformational transitions into secondary and tertiary structures. Secondary structures are caused by the formation of hydrogen bonds. The associated interaction is not present in the models we studied. Our investigation is focused on the tertiary structure, which is mainly due to the hydrophobic effect, i.e. the formation of a core of the hydrophobic monomers separated from the aqueous environment by a shell of polar monomers.

### 2.1. Lattice heteropolymers

For our studies of lattice heteropolymers we used the original formulation of the HP model [1]. Two different types of monomers are distinguished: hydrophobic ( $H$ ) and polar/hydrophilic ( $P$ ) residues. In the simplest form of the model only the attractive interaction between hydrophobic monomers that are next neighbors on the lattice but nonadjacent along the chain is accounted for. We performed extensive enumeration of all possible HP sequences and conformations on the simple-cubic (s.c.) lattice for chains with up to 19 monomers and found a characteristic correspondence between the degeneracy of the lowest-energy states and the occurrence of a pronounced low-temperature peak of the energetic and conformational

fluctuations indicating a transition between globular and hydrophobic-core dominated conformations [3]. This means that lowering the temperature leads to a rearrangement of the monomers in the globules, being globally compact conformations, and the formation of a compact hydrophobic core surrounded by the polar monomers. Sequences with nondegenerate ground state (designing sequences) experience the strongest low-temperature transition, while it is much weaker or not present for the other sequences. There is also another indication for a transition between random coils and globules at higher temperature that is common to all sequences. This behavior is similar for longer sequences, where sophisticated methods must be used. We developed a multicanonical chain-growth algorithm [4] in order to sample lattice heteropolymers with up to 103 monomers precisely for all temperatures [5]. For an exemplified 42mer with only fourfold ground-state degeneracy we found the typical three-phase behavior while for ten studied 48mers, whose ground states are all high-degenerate, the low-temperature transition is rather weak.

It is known, however, that intermediary states are avoided in the folding kinetics of short realistic peptides. These miniproteins typically possess a rather smooth free-energy landscape, where only a single barrier separates folded and unfolded states [6]. Therefore, the original HP model is not sufficiently two-state cooperative, as the globular phase (“traps”) slows down the folding dynamics. Simple modifications of the original HP model towards a slightly more realistic description seem to change, however, the folding behavior significantly. A first generalization of the model is the introduction of an additional interaction between nonbonded hydrophobic and polar monomers [7] based on rules derived from the Miyazawa–Jernigan matrix of contact energies. A second modification regards the underlying lattice type. Simulations on a face-centered cubic (f.c.c.) lattice are more promising than on the s.c. lattice, where almost all simulations were performed in the past, since the influence of the underlying artificial lattice is reduced. A prominent lattice artefact of the s.c. lattice, the impossibility that the  $i$ th and the  $(i + 2)$ th monomer be next neighbors, is not present on the f.c.c. lattice. In fact, with these modifications, we observed that trapping is reduced and a single peak in the temperature

dependence of fluctuations such as the specific heat indicates two-state folding.

## 2.2. Effective off-lattice models

In order to exclude artificial lattice effects we have also performed precise multicanonical simulations of exemplified heteropolymers with 20 monomers using AB-like off-lattice models [8]. In the original formulation of the AB model (*A*: hydrophobic, *B*: polar monomers) [2], bending energy and pairwise residue-dependent Lennard–Jones interactions (*AA*, *BB* contacts are long-range attractive, *AB* overall repulsive) are considered. Although there is also a general tendency to three-phase behavior, the intermediary states are, however, only weakly stable. Modifying the model by introducing a curvature energy term accounting for torsion and making the interaction of *AB* pairs attractive at long range [9], trapping is almost completely avoided and folding proceeds in a single step.

We have also compared the folding behavior of the heteropolymers with the purely hydrophobic homopolymer. Although both exhibit a two-state kinetics, the dense folds differ significantly. As expected, the homopolymer collapses at the (finite-size!)  $\Theta$  temperature from random coils to highly compact globules. The heteropolymers, however, form a core of hydrophobic monomers and a polar shell. The global energy minimum conformation of the heteropolymers is less compact (larger mean radius of gyration), the more hydrophobic monomers are in the sequence.

## 3. Summary

We have investigated conformational transitions of protein-like heteropolymers with different simple coarse-grained lattice and off-lattice models by means of multicanonical sampling methods. Although the identification of “phases”, where certain classes of conformations dominate, is difficult due to the impos-

sibility of performing a scaling towards the thermodynamic limit, we find random coil structures at high temperatures and dense conformations with hydrophobic core at low temperatures which can be, model-dependent, separated by intermediary globular states. The main advantage of these models for tertiary folding is that no input, such as the sequence-dependent contact topology of the native fold, is required. Therefore, it is possible to study qualitatively basic principles being responsible for the cooperativity between the phases of the heteropolymer (where the sequence of different types of monomers induces some kind of disorder).

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