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Folding and Aggregation of Proteins with Monte Carlo Simulations

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An implicit water all-atom model is used to study folding, aggregation of small proteins. Physically reasonable results obtained for a variety of applications indicate healthy global properties of the interaction potential.

1 Introduction

The prevailing picture of the process of protein folding is that proteins fold into their native 3D structures because those states have the minimum free energy among all conformations the protein chain can take, and hence are thermodynamically most probable. However, it has proven to be a considerably greater challenge to explicitly formulate an effective interaction potential, such that for every given protein, the minimum free energy structure calculated from the force field corresponds to the correct experimental structure. Different potentials give very different relative weights to the α-helix and β-strand regions of the protein conformation space. A potential that successfully folds α-helical peptides often has problems with β-sheet peptides, and *vice versa*. Also, proteins fold and unfold at physiologically relevant temperatures, and most potentials need further callibration in order to give more realistic temperature dependence of observable quantities.

In this article, folding[1,2] and aggregation[3] studies with one particular model for protein folding will be summarized. The protein molecules are represented in full atomistic detail, whereas the solvent molecules are left out to reduce the number of degrees of freedom of the system. The potential used was developed through repeated folding simulations of small peptides. It does not use any information about the known experimental structures of the peptides, and spontaneous folding from random initial conformations, and not the description of properties of the folded state through simulations of small perturbations around it, has been the chief objective.

2 Model and Methods

The model discussed here includes all atoms of the polypeptide chains, including all hydrogen atoms. It assumes fixed bond lengths, bond angles and peptide torsion angles (180°), so that each amino acid only has the Ramachandran torsion angles ϕ, ψ and a number of side-chain torsion angles as its degrees of freedom.

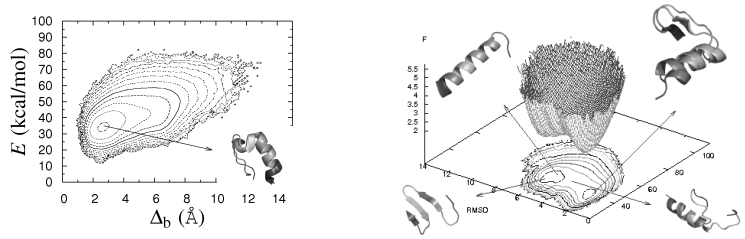

Figure 1. Free-energy estimated from the probability of occurence of different states in high statistics Monte Carlo simulations plotted as a function of energy and backbone RMSD Δ_b for, (a) For a helical protein 1RIJ where is one dominating minimum corresponding to the native state. Inset: optimal superimposition of simulation structure on the experimental structure. (b) For a protein with more complex native conformation, the free-energy surface may show many competing minima. The overlap of the global free-energy minimum with the PDB structure, as well as the 3D shape of some other minima are also shown

The force field consists of four terms, representing an $1/r^{12}$ excluded volume repulsion between every pair of atoms, a weak local electrostatics term along the protein backbone, an orientation dependent hydrogen bond term, and an effective hydrophobic attraction between non-polar side chains. For a detailed description of the model and the force field, the reader is referred to[1]. The rugged energy landscape of proteins was sampled using simulated tempering and parallel tempering Monte Carlo methods. Both single angle and a semi-local multiple-angle updates were employed on protein conformations. In aggregation studies, rigid body translations and rotations of molecules were used additionally. All simulations start with random initial conditions of the molecules. The simulations were done using the program package PROFASI[4], a C++ implementation of the model.

3 Results

We studied the folding behaviour of several small proteins of helical (Trp-cage, Fs, 1RIJ), β-sheet (GB1p, GB1m2, GB1m3, betanova, LLM, beta3s) and mixed secondary structure elements (BBA5). Unbiased simulations in the model, starting from random initial conformations are able to identify the native states of each of these proteins with one and the same choice of parameters for the energy function. The free-energy surfaces obtained in the model are found to be of different characters, depending on the eventual native fold of the protein[2]. Small proteins like Trp-cage and 1RIJ, with simple helical secondary structures have simple free-energy landscapes with one dominating minimum corresponding to the native state, as for example, in Fig. 1 (a). β–sheet proteins as well as proteins with mixed secondary structures show much more complex landscapes with several minima with significant free-energy barriers between them. One example of such a surface is shown in Fig. 1 (b). Estimates of the folding populations at experimental temperatures as well as the change of stability of peptides due to mutations agrees well with experiments.

We have also studied multiple chain systems of the Aβ_{16-22} peptide, a segment of the Alzheimer's β-amyloid peptide, that is experimentally known to form amyloid fibrils with an in-register anti-parallel cross-β organization of the strands. In simulated tempering

Figure 2. Oligomers of Aβ_{16-22} from 9 chain simulations. Many stable oligomeric forms are found, even a 9 chain barrel form (bottom right). In simulations, small oligomers show a weak preference towards ordered, anti-parallel β-strand organization. But such preference is seen to grow for the larger oligomeric species.

simulations of systems of 1, 3, 6 and 9 chains of Aβ_{16-22} peptides, the Aβ_{16-22} peptides self-assemble into β–sheet rich oligomers[3]. The isolated Aβ_{16-22} peptide is found to be unstructured, while multi-chain systems develop into a variety of different oligomeric species with a marked increase in β–sheet content, cf. Fig. 2. Of particular interest is the spontaneous formation of a 9 stranded β-barrel as one of the oligomeric species. A study of the population of parallel vs anti-parallel pairs of strands shows that larger oligomers tend to contain less defects.

4 Concluding Remarks

The simple and physically well motivated form of the interaction potential given in[1] appears to result in good global properties of the protein energy landscape. If simulations are interpreted carefully, keeping in mind the known weaknesses of the model, they could be used to extract meaningful physical predictions about the molecules in a wide variety of applications.

Acknowledgments

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