Abstract

Apart from biological functions, peptides are of uttermost importance as models for unfolded, denatured or disordered state of the proteins. Similarly, miniproteins such as Trp-cage have proven their role as simple models of both experimental and theoretical studies of protein folding. Molecular dynamics and computer simulations can provide an unique insight on processes at atomic level. However, simulations of peptides and miniproteins face two cardinal problems—inaccuracy of force fields and inadequate conformation sampling. Both principal issues were tackled in this theses.

Firstly, the differences in several force field for peptides and proteins were questioned. We demonstrated the inability of the used force fields to predict consistently intrinsic conformational preferences of individual amino acids in the form of dipeptides and the source of the discrepancies was traced.

In order to shed light on the nature of conformational ensembles under various denaturing conditions, we studied host–guest AAXAA peptides. The simulations revealed that thermal and chemical denaturation by urea produces qualitatively different ensembles and shift propensities of individual amino acids to particular conformers.

The problem of insufficient conformation sampling was dealt by introducing gyration- and inertia-tensor based collective coordinates to metadynamics. We validated this newly implemented size- and shape- descriptors in simulations of alanine peptides and Trp-cage miniprotein. Such facilitated dynamics led to reproducible folding of miniprotein and extensive conformational sampling of flexible polyalanines.

A novel miniprotein were designed by idea of retro transformation of protein sequence. The resulting retro Trp-cage molecule does not fold in water but the structure emerges upon addition of a cosolvent—2,2,2-trifluoroethanol (TFE) into buffer. However, this behavior was not observed in simulations and therefore the force field model of TFE were questioned.

We further developed a novel model of TFE based on generalized amber force field by exhaustive optimization of force field parameters. The resulting model reproduces excellently the liquid state properties of pure TFE and behaves realistically in TFE/water mixtures as we investigated by means of Kirkwood–Buff theory of solutions.