Biasing the Sampling of Local States to Drive the Exploration of Global Conformations in Proteins

Introduction

Conformational changes associated with protein function often occur at timescales inaccessible to unbiased Molecular Dynamics (MD) simulations, consequently different approaches have been developed to accelerate their sampling. Here we investigate how the knowledge of backbone conformations preferentially adopted by protein fragments, as contained in pre-calculated libraries known as Structural Alphabets (SA)[1], can be used to explore the landscape of global protein conformations in MD simulations.

Methods

SAs were successfully used to analyze protein dynamics after simulation[2,3]. Here we define a novel SA-based Collective Variable (CVSA) to bias the sampling of backbone conformations of protein fragments towards experimentally preferred local states[4].

Results

We find that: a) Enhancing the sampling of native local states allows recovery of global folded states, both in Metadynamics and in Steered MD, when the local states are encoded by strings of SA letters derived from the native structures. b) Global folded states are still recovered when the information on the native local states is reduced by using a low-resolution SA, where the original letters are clustered into macrostates. The macrostates provide the approximate shape of the fragments, while sampling with the atomistic force field allows the structure to adopt the native conformation of the specific amino acid sequence. c) SA strings derived from collections of structural motifs can be effectively used to sample alternative conformations of pre-selected regions. These findings have potential impact on a wide range of applications, from protein model refinement to folding and design.

References

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