A Generalized-Ensemble approach to Systematic Coarse-Graining in Molecular Simulations using Relative Entropy

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ABSTRACT: Computer simulations have become a powerful tool for studying the structure, dynamics, or other characteristics of a wide variety of physical systems. The goal of coarse-grained (CG) models is to simplify the representation of the physical system while still maintaining enough information to capture the desired properties of the system. A main challenge in the development of CG models is determining the potential energy, ECG, which often depends on a large number of unknown model parameters, λ. Different methods for determining these model parameters have been proposed, (potential of mean force, multi-scale coarse-graining), but they rely on determining quantities, such as the free energy, that are computationally difficult to calculate.

Here we develop a systematic method to determine the optimal parameters for coarse-grained models of molecular systems, using the relative entropy as a metric to compare a target ensemble to an ensemble generated from a CG model. The relative entropy depends on the free energy, and a novel approach for determining the free energy was developed and used. The free energy was obtained from a generalized ensemble Monte Carlo simulation, which allowed the model parameters to be dynamic, meaning they are allowed to change during the simulation. These simulations allow for the free energies, FCG(λ), to be obtained directly by tuning the marginal probability distribution during the simulation. Then, the relative entropy, Srel(λ), was calculated and minimized with respect to the CG model parameters in order to obtain the optimal model parameters. The systematic method was applied to a CG model for protein folding to determine the optimal model parameters that allowed a protein to fold to its native structure. Two different potential energy functions were tested, which depended on 13 or 91 unknown model parameters, and the optimal model parameters were determined. In addition, the relative entropy was calculated for two different target ensembles: the experimentally determined single native structure and an ensemble generated from an all-atom simulation.

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