475c Improving Free Energy Calculations: Staging Sampling and Fail-Safe Bias Detection

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The calculation of free energies is an important capability required of molecular simulation, because knowledge of the free energy is necessary to understand a wide range of thermophysical behaviors. However free-energy calculations may be subject to inaccuracy or inefficiency depending on different phase-space overlap relations of the systems of interest. Here we present staging methods that are designed with consideration of these overlap relations, such that single- or multi-stage perturbations are appropriately formulated to achieve the desired accuracy while retaining efficiency. The design of staging methods requires knowledge of phase-space overlap, and we present several metrics to characterize this. One of these measures, the relative entropy, is used to scale the amount of sampling to obtain a universal bias curve. This result leads to the development of a simple heuristic which can be applied to determine whether a work-based free-energy measurement is accurate.

Finally we demonstrate that this bias-detection measure is effective in identifying inaccuracy in single- as well as multi-stage calculations. Thus the effectiveness of staging sampling methods can be easily tested with this bias-detection measure. Examples used include the free-energy calculation of a multi-harmonic model, the chemical potential calculation for a Lennard-Jones liquid, model water, and a process of ionic hydration.