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**A Comparison Between Adaptive Integration and Path-Sampling
Methods for Calculating Free Energy Differences in Molecular Systems**

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ROBERT H. SWENDSEN, Carnegie Mellon University — The calculation of free energy differences (ΔF) is essential for the understanding of protein-ligand binding, the conformational stability of proteins and many molecular processes, yet it remains one of the most challenging tasks in computational biophysics. Here we present a study of two recently developed free energy methods, both applied to molecular systems for the first time. The first approach is an adaptive integration Monte Carlo procedure which continually updates the free energy profile connecting the two states of interest. The second method is a path-sampling implementation of the Jarzynski relation which uses a Monte Carlo procedure to generate an ensemble of non-equilibrium paths connecting the two states of interest. Both techniques are compared to the standard methods of thermodynamic integration and use of the Jarzynski relation, by calculating ΔF values for growing and for charging a simple ion in explicit SPC water. Adaptive integration is found to have the highest precision and accuracy for long simulation times. However, if very rapid ΔF estimates are the goal, the path-sampling approach is found to be the most efficient.

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