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Free Energy computation: methods to efficiently sample phase space

Molecular Dynamics is a popular tool to compute the free energy of molecular systems along a reaction coordinate, e.g. a torsion angle in a backbone or the distance between two molecules... A simple approach consists in computing the probability density function of the reaction coordinate, from which the free energy profile can be derived. However, such a simulation is often difficult to perform as the system tends to stay for very long periods of time in local energy minima, resulting in poor statistical convergence and a large computational cost. Several methods have been developed to address this issue. We will review the method of constraints, the fast growth method (FGM) of C. Jarzynski, and an original approach, the adaptive biasing force (ABF) method developed by E. Darve et al. We will present theoretical and numerical results on the efficiency and accuracy of each method. We will demonstrate in particular that FGM is not competitive with the method of constraints and with ABF for systems which are easily driven out of equilibrium.