Biomolecular Free Energy Profiles by a Shooting/Umbrella Sampling Protocol (`BOLAS'')

We develop an efficient technique for computing free energies corresponding to conformational transitions in complex systems by combining a Monte Carlo ensemble of trajectories generated by the shooting algorithm (based on Molecular Dynamics) with umbrella sampling. Motivated by the transition path sampling method, our scheme
`BOLAS' [1,2] (named after a cowboy's lasso) preserves microscopic reversibility and leads to the correct equilibrium distribution. This
makes possible computation of free energy profiles along complex reaction coordinates for biomolecular systems with a lower systematic
error compared to traditional, force-biased umbrella sampling protocols.

We demonstrate the validity of BOLAS by calculating the free energy profile of a particle governed by a bistable potential in one-dimension and comparing the calculated profiles to results obtained using the Jarzynski equality, as well as traditional umbrella sampling with Langevin dynamics.

We illustrate the method's scope with applications to the sugar repuckering transition in a solvated deoxyadenosine molecule, conformational transition in a solvated protein/DNA complex, both using classical force-fields, and on spontaneous hydrolysis in a solvated deoxyadenosine molecule using a mixed quantum mechanical/classical mechanical Hamiltonian.

[1] R. Radhakrishnan, T. Schlick, J. Chem. Phys., 121, 2436 (2004).

[2] R. Radhakrishnan, T. Schlick, Proc. Nat. Acad. Sci. USA, 101, 5970 (2004).