

Chem 860. Homework 6. Due: Apr. 8

Free energy simulations

March 29, 2009

1 Pencil exercises

1. With a linear interpolation between two states, $U(\lambda) = (1 - \lambda)U_A + \lambda U_B$, show that the 2nd derivative of the free energy difference with respect to the coupling parameter λ is negative semi-definite (i.e., $\partial^2 F(\lambda)/\partial \lambda^2 \leq 0$).
2. Show that the free energy perturbation formula of Zwanzig can be cast into an one-dimensional integral over the energy gap between the two end states and involves the distribution of the energy gap. In the context of solvation free energy simulations, use the result to discuss whether “insertion” or “deletion (annihilation)” simulation tends to be statistically more precise; i.e., whether it’s better to sample a high entropy state and perturb to a low entropy state, or the reverse. *Hint: you can find useful discussions here: <http://www.eng.buffalo.edu/~kofke/ce530/Lectures/Lecture19/>.*

2 Computational exercises

The CHARMM scripts are in: hw6_09.

Use *free_energy_ti.inp* to estimate the free energy difference associated with an “alchemy” mutation: converting ethane to methanol in water (ΔF_{aq}). [Although this value itself doesn’t have real physical meaning, the difference between ΔF_{aq} and the free energy associated with the same mutation in another media (e.g., gas phase, ΔF_{gas}) is the solvation free energy difference between ethan and methanol in these two media.] Plot the free energy derivative as a function of time during the simulation, comment on the convergence behavior. Here the example only uses a single λ value (0.5), which is unlikely sufficient for an accurate estimate of the free energy change. Can you modify the input to calculate the free energy derivative for other λ values and therefore a more accurate free energy change? **Bonus:** Can you figure out how to use BAR with CHARMM and show that BAR works better than regular TI?