

Estimating Thermodynamic Differences

Huafeng Xu

(Dated: November 12, 2007)

Monte Carlo (MC), and kindred in spirit, molecular dynamics (MD), simulations are now widely used in many disciplines of science. They estimate statistical averages of physical observables, $O(x)$, by generating configurations, $x_i, i = 1, 2, \dots, N$, with the desired probability distribution, $\rho(x)$. The statistical average

$$\langle O \rangle \equiv \int dx \rho(x) O(x) \quad (1)$$

is obtained from these sampled configurations by

$$\bar{O} = \frac{1}{N} \sum_{i=1}^N O(x_i) \quad (2)$$

In the limit of infinite samples ($N \rightarrow \infty$), the estimate \bar{O} approaches the true average $\langle O \rangle$.

Often, we are not interested in the average itself, but in its difference between two systems of distinct probability functions, ρ_A and ρ_B . For example, we may want to compute the enthalpic difference between a system at two temperatures, or the difference in the solvation thermodynamics of two different ions, or the change in magnetization of a material in different external fields.

The difference in an average quantity between two probability distribution, ρ_A and ρ_B , is given by

$$\begin{aligned} \Delta \bar{O} &= \langle O_B \rangle_B - \langle O_A \rangle_A \\ &= \sum_s \rho_B(s) O_B(s) - \sum_{s'} \rho_A(s') O_A(s') \end{aligned} \quad (3)$$

where s iterates over all microscopic state of the system. $\rho(s)$ is the thermodynamic distribution density of state s ; for instance, $\rho(s) = Z^{-1} \exp(-\beta H(s))$ in a canonical ensemble.

Given two set of states, $\{s\}_A$ and $\{s\}_B$, each sampled according to its corresponding thermodynamic distribution density, the difference in Eq. 3 can be calculated by taking the average of the observables in both sets, and then subtract the first from the second: $\Delta \bar{O} \approx (\sum_{s \in \{s\}_B} O_B(s))/n_B - (\sum_{s \in \{s\}_A} O_A(s))/n_A$. This approach, however, is troubled by large statistical error. The variance in the estimated difference is

$$\begin{aligned} \sigma_{\Delta \bar{O}}^2 &= \sigma_{O_B}^2 + \sigma_{O_A}^2 \\ &= \langle O_B^2 \rangle_B - \langle O_B \rangle_B^2 + \langle O_A^2 \rangle_A - \langle O_A \rangle_A^2 \end{aligned} \quad (4)$$

Thus the statistical uncertainty is proportional to the fluctuations in the observable.

I suggest an improved estimator for thermodynamic differences. The following identity holds for an arbitrary function of $\psi(s)$,

$$\langle \psi \frac{\rho_A}{\rho_B} \rangle_B = \langle \psi \rangle_B \quad (5)$$

Therefore, the thermodynamic difference is also

$$\Delta \bar{O} = \langle O_B - \psi \frac{\rho_A}{\rho_B} \rangle_B - \langle O_A - \psi \rangle_A \quad (6)$$

The quantity $K = \rho_A/\rho_B$ involves ratio of the partition functions of A and B , which is usually not known *a priori*, but can be estimated from well established techniques in free energy calculations, such as the Bennett acceptance ratio method.

The variance in $\Delta \bar{O}$ from Eq. 6 is

$$\begin{aligned} \sigma_{\Delta \bar{O}}^{*2} &= \sigma_{O_B}^2 + \sigma_{O_A}^2 \\ &+ \langle \psi^2 K^2 \rangle_B - \langle \psi K \rangle_B^2 + 2(\langle O_B \rangle_B \langle \psi K \rangle_B - \langle O_B \psi K \rangle_B) \\ &+ \langle \psi^2 \rangle_A - \langle \psi \rangle_A^2 + 2(\langle O_A \rangle_A \langle \psi \rangle_A - \langle O_A \psi \rangle_A) \end{aligned} \quad (7)$$

I now minimize $\sigma_{\Delta\bar{O}}^2$ with respect to $\psi(s)$. This leads to

$$\begin{aligned} 0 &= \frac{1}{2} \frac{\delta \sigma_{\Delta\bar{O}}^{*2}}{\delta \psi} \\ &= \psi K^2 \rho_B - \langle \psi K \rangle_B K \rho_B + \langle O_B \rangle_B K \rho_B - O_B K \rho_B \\ &\quad + \psi \rho_A - \langle \psi \rangle_A \rho_A + \langle O_A \rangle_A \rho_A - O_A \rho_A \end{aligned} \quad (8)$$

Therefore the optimal choice of ψ is

$$\begin{aligned} \psi &= \frac{1}{K+1} (O_B + O_A - \langle O_B \rangle_B - \langle O_A \rangle_A + \langle \psi K \rangle_B + \langle \psi \rangle_A) \\ &= \frac{1}{K+1} (O_B + O_A + C) \end{aligned} \quad (9)$$

where in the second line $C = \langle \psi K \rangle_B + \langle \psi \rangle_A - \langle O_B \rangle_B - \langle O_A \rangle_A$ is a constant, and is determined by substituting its expression back in Eq. 9. The result is

$$C = \left(\left\langle \frac{1}{K+1} \right\rangle_B - \left\langle \frac{1}{K+1} \right\rangle_A \right)^{-1} \left(\left\langle \frac{K O_A - O_B}{K+1} \right\rangle_B - \left\langle \frac{K O_A - O_B}{K+1} \right\rangle_A \right) \quad (10)$$

The variance in $\Delta\bar{O}$, using the optimal ψ , is

$$\begin{aligned} \sigma_{\Delta\bar{O}}^{*2} &= \sigma_{O_B}^2 + \sigma_{O_A}^2 \\ &\quad - (\langle \psi^2 K^2 \rangle_B - \langle \psi K \rangle_B^2 + \langle \psi^2 \rangle_A - \langle \psi \rangle_A^2) \\ &= \sigma_{O_B}^2 + \sigma_{O_A}^2 - (\sigma_{\psi K|B}^2 + \sigma_{\psi|A}^2) \\ &< \sigma_{\Delta\bar{O}}^2 \end{aligned} \quad (11)$$

Therefore the estimator always reduces the statistical variance. The larger the fluctuation in ψK and ψ , the larger the reduction in $\sigma_{\Delta\bar{O}}^2$.

The benefit of the estimator is manifest by considering the following mock problem of calculating zero: from two independent simulations of the same thermodynamic state, estimate the difference in a thermodynamic average. The correct answer, of course, is zero, as both simulations are of the same thermodynamic state. Taking the straightforward difference of the two averages, however, will not yield zero: the result is subject to fluctuations of the quantity. In contrast, the estimator proposed here will always answer zero. This is because: 1) Bennett acceptance ratio method yields $K = \rho_A/\rho_B$ to be exactly 1; 2) the estimator then takes $\psi = O + C/2$, where C is now an arbitrary constant; 3) the estimated $\Delta\bar{O}$ is then $\Delta\bar{O} = \langle O - O - C/2 \rangle_A - \langle O - O - C/2 \rangle_B = 0$. There is no uncertainty in the estimate!

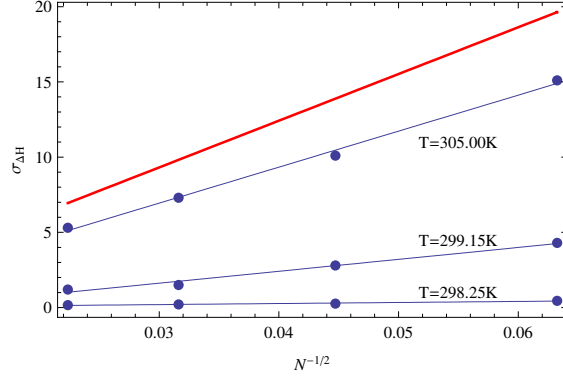
As a realistic example to illustrate the power of the estimator, I consider the computation of the enthalpy difference of water at two close temperatures. 768 SPC water molecules are simulated by molecular dynamics under 1 atmospheric pressure, at four different temperatures: 298.15K, 298.25K, 299.15K and 305K. The ratio of two partition functions at different temperatures is computed by the temperature version of Bennett acceptance ratio method, solving the following equation for $\Delta\beta F \equiv \beta_2 F_2 - \beta_1 F_1 = \ln(Z_1/Z_2)$:

$$\sum_{i=1}^{n_1} \frac{1}{n_1/n_2 \exp((\beta_2 - \beta_1)E_i - \Delta\beta F) + 1} - \sum_{i=1}^{n_2} \frac{1}{n_2/n_1 \exp((\beta_1 - \beta_2)E_i + \Delta\beta F) + 1} = 0 \quad (12)$$

where n_1, n_2 are the numbers of sample points in the simulations at temperatures T_1, T_2 , E_i is the energy of the i th point, $\beta_1 = 1/(kT_1)$ and $\beta_2 = 1/(kT_2)$. With $\Delta\beta F$ obtained from eqn. 12, we can plug in $K(s) = \rho_{T_1}(s)/\rho_{T_2}(s) = \exp(-\Delta\beta F) \exp((\beta_2 - \beta_1)E(s))$ in eqn. 6 to obtain the optimal estimate of the thermodynamic difference.

Table I lists the enthalpy differences between various temperatures and reference temperature 298.15K. The differences are estimated by the estimator and by naive difference, both using 2000 configurations sampled from the simulations. The variance for the estimator is calculated from 5 independent estimates of enthalpy difference using different 2000 random sample points. The variance for the naive difference is calculated by $\sqrt{(\langle (H - \bar{H})_{T_2}^2 \rangle + \langle (H - \bar{H})_{T_1}^2 \rangle) / 2000}$. As expected, the estimator consistently outperforms naive difference in precision. Its superiority is most evident at small temperature differences: computing the enthalpy difference between 298.15K and 298.25K, the estimator is $(6.9/0.16)^2 \approx 1850$ times more efficient than naive difference. The advantage of the estimator diminishes as the temperature difference increases, but at a difference of $305 - 298.15 = 6.85K$, it is

FIG. 1: The variance of the estimator decreases linearly with the $N^{1/2}$, N being the number of uncorrelated sampling points. The red thick line represents the variance by naive difference.



T(K)	$\sigma_{\Delta H}$ (kJ/mol)		ΔH (kJ/mol)	
	estimator	naive difference	estimator	naive difference
298.15	0.0	6.9	0.0	0.1
298.25	0.16	6.9	6.5	1.9
299.15	1.2	6.9	64.4	64.1
305.00	5.3	7.0	436.4	435.6

TABLE I: The enthalpy difference of 768 SPC water molecule at different temperatures from the reference temperature 298.15K.

still $(7.0/5.3)^2 = 1.7$ times more efficient than naive difference. Fig. 1 shows how the variance decreases linearly with $N^{1/2}$, N being the number of uncorrelated sampling points.

With the ability to compute the enthalpy difference at such high precision, I can compute the heat capacity by

$$C_p = \frac{dH}{dT} \approx \frac{H(298.25K) - H(298.15K)}{298.25K - 298.15K} = 65.0 \pm 1.6 \text{ kJ/mol/K} \quad (13)$$

This agrees with the heat capacity computed by $C_p = (\langle H^2 \rangle - \langle H \rangle^2)/(kT^2) = 64.9 \pm 1.3 \text{ kJ/mol/K}$, and with the literature value of $84.6 \pm 2.5 \text{ J/mol/K} \times 768 = 65 \pm 1.9 \text{ kJ/mol/K}$ (Jorgensen *et al.* Journal of Computational Chemistry, **19**, 1179-1186 (1998)).

As a second example, I compute the difference in the enthalpy and partial molar volume of the solvation of K^+ and Na^+ ions. CHARMM parameters are used for ions and CHARMM version of TIP3P parameters for water. Eqn. 6 can be used with

$$K(s) = \frac{\rho_{K^+}(s)}{\rho_{Na^+}(s)} = \frac{Z_{Na^+}}{Z_{K^+}} \exp(-\beta(U_{K^+}(s) - U_{Na^+}(s))) \quad (14)$$

But in practice, this approach fails because the configurations in Na^+ and K^+ simulations do not overlap, and most $K(s)$ is either close to zero or enormous. Therefore, I introduce a one-to-one mapping between the configurations in Na^+ and K^+ simulations: from each configuration sampled in the simulation of Na^+ , a NVE simulation of time τ is carried out with a time-dependent Hamiltonian such that $U_{Na^+ \rightarrow K^+}(t=0) = U_{Na^+}$ and $U_{Na^+ \rightarrow K^+}(t=\tau) = U_{K^+}$; inversely, each configuration in the simulation of K^+ is taken by a NVE simulation under Hamiltonian $U_{K^+ \rightarrow Na^+}(t) = U_{Na^+ \rightarrow K^+}(\tau - t)$. This mapping is unitary, and can be compactly expressed as

$$s' = e^{\int_0^\tau dt iL(t)t} s \quad (15)$$

where $iL(t)$ is the Liouville operator corresponding to the time-dependent Hamiltonian.

With this mapping, eqn. 6 can be modified to

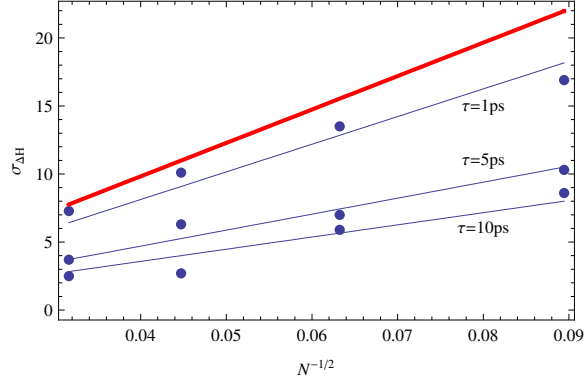
$$\Delta \bar{O} = \langle O_B(s) - \psi(s', s) \frac{\rho_A(s')}{\rho_B(s)} \rangle_B - \langle O_A(s') - \psi(s, s') \rangle_A \quad (16)$$

where the function $\psi(s', s)$ is symmetric in s and s' and can be determined by similar procedures.

$\tau(ps)$	ΔH (kJ/mol)	$\sigma_{\Delta H}$ (kJ/mol)	ΔV (nm ³ /mol)	$\sigma_{\Delta V}$ (nm ³ /mol)
10.	97.7	2.5	0.017	0.002
5.	103.0	3.7	0.017	0.002
1.	100.1	7.3	0.019	0.005
naive difference	105.8	8.8	0.018	0.007

TABLE II: The difference in enthalpy and partial molar volume of solvation of Na⁺ and K⁺. CHARMM parameters are used for ions: $\sigma_{\text{Na}^+} = 2.43\text{\AA}$, $\epsilon_{\text{Na}^+} = 0.0469\text{kJ/mol}$; $\sigma_{\text{K}^+} = 3.14\text{\AA}$, $\epsilon_{\text{K}^+} = 0.087\text{kJ/mol}$.

FIG. 2: The variance of ΔH between Na⁺ and K⁺ solvation, which decreases linearly with the $N^{1/2}$, N being the number of uncorrelated sampling points. The red thick line represents the variance by naive difference.



The results, taken from 5 independent sets of 1000 sampling points each, are given in Table. II. The advantage of the estimator is quite clear. Fig. 2 shows that the variance of the estimator decreases with $N^{-1/2}$ of the number of uncorrelated sampling points.