[DRAFT]: Best Practices for Thermodynamic Property Prediction from Molecular Simulations

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This document describes a collected set of best practices for computing various physical properties from molecular simulations of liquid mixtures.

Keywords: best practices; molecular dynamics simulation; physical property computation

Todo list

I. Preliminaries

Definitions

- V: Volume
- U: Total energy (including potential and kinetic, excluding external energy such as due to gravity, etc)
- S: Entopy
- N: Number of particles
- T: Temperature
- P: Pressure
- k_B: Boltzmann constant
- β: $(k_B T)^{-1}$
- M: Molar mass
- ρ: Density (M/V)
- H: Enthalpy
- G: Gibbs Free Energy (free enthalpy)
- A: Helmholtz Free Energy
- μ: Chemical potential
- D: Total dipole moment
- u: reduced energy
- f: reduced free energy

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Macroscopically, the quantities V, U, N are constants (assuming the system is not perturbed in any way), as we assume that the fluctuations are essentially zero, and any uncertainty comes from our inability to measure that constant value precisely. For a mole of compound (about 18 mL for water), the relative uncertainty in any of these quantites is about 10^{-12}, far lower than any thermodynamics experiment can actually measure.

However, in a molecular simulation, these quantites are not necessarily constant. For example, in an NVT equilibrium simulation, U is allowed to vary. For a long enough simulation (assuming ergodicity, which can pretty much always be assumed with correctly implemented simulations and simple fluids), then the ensemble average value of U = $\langle U \rangle$ will converge to a constant value, and in the limit of large simulations/long time will converge to the macroscopic value U; at least, the macroscopic value of that given model, though perhaps not the U for the real system. In an NVT simulation, clearly V is constant. In an NPT simulation, however, V is a variable, and we must estimate what the macroscopic value would be using the ensemble average $\langle V \rangle$.

The quantities T, P, and μ are typically *set* as constant during the equilibrium simulations and experiments of interest here. More precisely, the system is in contact with a thermal bath with a fixed T (or in the case of NPT simulations, in contact with a thermal and mechanical bath), and we sample from the systems in equilibrium with this bath. There are a number of quantities that can be used to ESTIMATE constants such as T and P. For example, $\langle \frac{1}{3Nk_B} \sum_i m_i |v_i|^2 \rangle$, where m is the mass of each particle and $|v_i|$ is the magnitude of the velocity of each particle, is an estimate of T (the temperature of the bath), and it's average will be equal to the T. But it is not the temperature. This quantity fluctuates, but T remains constant; otherwise the simulation could not be at constant temperature.

Ensemble averages of some quantity X ($\langle X \rangle$) are assumed to be averages over the appropriate Boltzmann weighting, i.e. in the NVT ensemble with classical statistical mechanics, they would be $\int X(\vec{x}, \vec{p}) e^{-\beta U(\vec{x},\vec{p})} d\vec{x} d\vec{p}$. We note that in the limit of very large systems, $\langle X \rangle_{NPT} = \langle X \rangle_{NVT} = \langle X \rangle_{\mu VT}$.

Ensemble averages can be computed by one of two ways. First, they can be computed directly, by running a simulation that produces samples with the desired Boltzmann distribution. In that case ensemble averages can be computed as

simple averages, $\langle V \rangle = \frac{1}{N}\sum_i V_i$, where the sum is over all observations. Uncertainties can be estimated in a number of different ways, but usually require estimating the number of uncorrelated samples. Secondly, they can be calculated as reweighted estimates from several different simulations, as $\langle V \rangle = \frac{1}{\sum_i w_i} V_i w_i$ where w_i is a reweighting factor that can be derived from importance sampling theory.

To simplify our discussion of reweighting, we use some additional notation. We define the reduced potential $u = \beta U(\vec{x})$ in the canonical (NVT) ensemble, $u = \beta U + \beta PV$ in the isobaric-isothermal (NPT) ensemble, and $u = \beta U - \beta N\mu$ in the grand canonical ensemble (similar potentials can be defined in other ensembles). We then define $f = \int e^{-u} dx$, where the integral is over all of the DOF of the system (x for NVT, x, V for NPT, and x, N for μVT. For NPT, we then have $f = \beta G$, and for NVT we have $f = \beta A$, while for μVT we have $f = -\beta \langle P \rangle V$.

To calculate expectations at one set of parameters generated with paramters that give rise to a different set of probability distributions, we start with the definition of an ensemble average given a probability distribution $p_i(x)$.

$$\langle X \rangle_i = \int X(x) p_i(x) dx \tag{1}$$

We then multiply and divide by $p_j(x)$, to get

$$\langle X \rangle_i = \int X(x) p_i(x) \frac{p_j(x)}{p_j(x)} dx = \int X(x) p_j(x) \frac{p_i(x)}{p_j(x)} dx \tag{2}$$

We then note that this last integral can be estimated by the Monte Carlo estimate

$$\langle X \rangle_i = \int X(x) p_j(x) \frac{p_i(x)}{p_j(x)} dx = \frac{1}{N} \sum_{n=1}^{N} X(x_n) \frac{p_i(x_n)}{p_j(x_n)} \tag{3}$$

Where the x_k are sampled from probability distribution $p_j(x)$

We now define the mixture distribution of K other distributions as: $p_m(x) = \frac{1}{N}\sum_{i=1}^{N} N_k p_k(x)$, where $N = \sum_k N_k$. We can construct a sample from the mixture distribution by simply pooling all the samples from k individual simulations. The formula for calculating ensemble averages in a distribution $p_i(x)$ from samples from the mixture distribution is:

$$\langle X \rangle_i = \sum_{n=1}^{N} X(x_n) \frac{p_i(x_n)}{\sum_{k=1}^{N_k} p_k(x_n)} \tag{4}$$

In the case of Boltzmann averages, then $p_i(x) = e^{f_i - u_i(x)}$, where the reduced free energy f is unknown. Reweighting from the mixture distibution becomes.

$$\langle X \rangle_i = \sum_{n=1}^{N} X(x_n) \frac{e^{f_i - u_i(x_n)}}{\sum_{k=1}^{N_k} e^{f_k - u_k(x)}} \tag{5}$$

which can be seen to be the same formula as the MBAR formula for expectations. The free energies can be obtained by setting $X = 1$, and looking at the K equations obtained by reweighting to the K different distributions.

Finite differences at different temperatures and pressures can be calculated by including states with different reduced potentials. For example, $u_j(x) = \beta_i U(x) + \beta_i (P_i + \Delta P) V$, or $u_j = \frac{1}{k_B(T_i + \Delta T)} U(x) + \frac{1}{k_B(T_i + \Delta T)} P_i V$. However, the relationship between f and G can be problematic when looking at differences in free energy with respect to temperature, because $G_2 - G_1 = \beta_2 f_2 - \beta_1 f_1$. We can in general write

$$\Delta G_{ij}(T) = k_B T \left(\Delta f_i j(T) - \Delta f_i j(T_{ref})\right) + \frac{T}{T_{ref}} \Delta G_i j(T_{ref})$$

, where $\Delta G_{ij}(T_{ref})$ is known at some temperature.

Since with MBAR, one can make the differences as small as one would like (you don't have to actually carry out a simulation at those points), we can use the simplest formulas: central difference for first derivatives:

$$\frac{dA}{dx} \approx \frac{1}{2\Delta x} \left(A(x + \Delta x) - A(x - \Delta x)\right)$$

And for 2nd deriatives:

$$\frac{d^2 A}{dx^2} \approx \frac{1}{\Delta x^2} \left(A(x + \Delta x) - 2A(x) + A(x - \Delta x)\right)$$

Thus, only properties at two additional points need to be evaluated to calculate both first and 2nd derivatives.

It may first appear that these finite difference calculations will propagate significant error as they subtract similar numbers. However, MBAR calculates the covariance matrix between $\langle A \rangle$, $A(x + \Delta x)$, and $A(x - \Delta x)$, meaning in practice the uncertainty is far lower than would be expected by standard error propagation of uncorrelated observables.

Note that if the finite differences are re-evaluated using reweighting approaches, it is important that the simulation used generates the correct Boltzmann distribution. If not, reweighted observables will be incorrect, and the results of the finite difference approach will have significant error.

The following document details calculation of various mechanical observables by both direct methods pulled from literature sources and the use of reweighting techniques. Corrections in certain observables are also summarized where suggested by previous authors.

II. Single Phase Properties

A. Pure Solvent Properties

1. Density

a. Direct calculation Starting with the equation used to calculate the density experimentally,

$$\rho = \frac{M}{V} \tag{6}$$

We replace the average with the esemble estimate (calculated either directly, or with reweighting) to obtain:

$$\rho = \frac{M}{\langle V \rangle} \tag{7}$$

b. Derivative Estimate From the differential definition of the Gibbs free energy $dG = VdP - SdT + \sum_i \mu_i dN_i$ that V can be calculated from the Gibbs free energy as:

$$V = \left(\frac{\partial G}{\partial P}\right)_{T,N} \tag{8}$$

The density can therefore be estimated from the Gibbs free energy.

$$\rho = \frac{M}{\left(\frac{\partial G}{\partial P}\right)_{T,N}} \tag{9}$$

The derivative can be estimated using a central difference numerical method utilizing Gibbs free energies reweighted to different pressures.

$$\left(\frac{\partial G}{\partial P}\right)_{T,N} \approx \frac{G_{P+\Delta P} - G_{P-\Delta P}}{2\Delta p} \tag{10}$$

The density can then finally be estimated.

$$\rho \approx \frac{M}{\frac{G_{P+\Delta P} - G_{P-\Delta P}}{2\Delta P}} \tag{11}$$

This can be calculated from the reduced free energy f if desired by simply substituting:

$$\rho \approx \frac{\beta M}{\frac{f_{P+\Delta P} - f_{P-\Delta P}}{2\Delta P}} \tag{12}$$

Intuitively, one would imagine that equation 12 would be a worse estimate of density given that the calculations involved have more room for error than direct simulations. That being said, this method should prove invaluable when estimating densities of unsampled states using MBAR.

2. Molar Enthalpy

This section is on the relation of enthalpy to Gibbs free energy (should we need it). This is not an experimental quantity, but will be helpful in calculating related properties of interest. The enthalpy, H, can be found from the Gibbs free energy, G, by the Gibbs-Helmholtz relation:

$$H = -T^2 \left(\frac{\partial \left(\frac{G}{T}\right)}{\partial T}\right)_{P,N} \tag{13}$$

Transforming the derivative in the Gibbs-Helmholtz relation to be in terms of β instead of T yields:

$$H = -T^2 \frac{\beta^2}{\beta^2} \left(\frac{\partial \left(\frac{G}{T}\right)}{\partial T} \frac{\partial T}{\partial \beta} \frac{\partial \beta}{\partial T}\right)_{P,N} \tag{14}$$

Recall that $\beta = \frac{1}{k_B T}$, therefore $\frac{\partial \beta}{\partial T} = -\frac{1}{k_B T^2}$. Substituting these values into the enthalpy equation gives:

$$\begin{aligned} H &= \frac{1}{k_B^3 T^2 \beta^2} \left(\frac{\partial \left(\frac{G}{T}\right)}{\partial \beta}\right)_{P,N} \\ &= \frac{1}{k_B} \left(\frac{\partial \left(\frac{G}{T}\right)}{\beta}\right)_{P,N} = \frac{\partial f}{\partial \beta}_{P,N} \end{aligned} \tag{15}$$

3. Heat Capacity

The definition of the isobaric heat capacity is:

$$C_P = \left(\frac{\partial H}{\partial T}\right)_{P,N} \tag{16}$$

$$C_P = \frac{\partial \left(\frac{\partial f}{\partial \beta}\right)}{\partial T}_{P,N} \tag{17}$$

$$C_P = -k_B \beta^2 \frac{\partial^2 f}{\partial \beta^2} \tag{18}$$

This could be computed by finite differences approach or analytical derivation using MBAR

The enthalpy fluctuation formula can also be used to calculate C_P[**?**].

$$C_P = \frac{\langle H^2 \rangle - \langle H \rangle^2}{N k_B \langle T \rangle^2} \tag{19}$$

The form is equivalent for isochoric heat capacity, but with derivatives at constant volume rather than pressure.

4. Isothermal Compressibility

The definition of isothermal compressibility is:

$$\kappa_T = -\frac{1}{V} \left(\frac{\partial V}{\partial P}\right)_T \tag{20}$$

a. First Derivative Thus, it can be estimated by the finite difference of $\langle V \rangle$

$$\kappa_T = -\frac{1}{2V(T,P)^2}\left(\langle V(P+\Delta P,T)\rangle - \langle V(P-\Delta P,T)\rangle\right) \tag{21}$$

Or by the finite differences evaluation of:

$$\kappa_T = -\frac{\left(\frac{\partial^2 G}{\partial P^2}\right)_{T,N}}{\left(\frac{\partial G}{\partial P}\right)_{T,N}} = -\frac{\left(\frac{\partial^2 f}{\partial P^2}\right)_{T,N}}{\left(\frac{\partial f}{\partial P}\right)_{T,N}} \tag{22}$$

κ_T can also be estimated from the ensemble average and fluctuation of volume (in the NPT ensemble) or particle number (in the μVT ensemble)[**?**]:

$$\kappa_T = \beta\frac{\langle \Delta V^2\rangle_{NTP}}{\langle V\rangle_{NTP}} = V\beta\frac{\langle \Delta N^2\rangle_{VT}}{\langle N\rangle_{VT}} \tag{23}$$

5. Speed of Sound

The definition of the speed of sound is[**?**]:

$$c^2 = \left(\frac{\partial P}{\partial \rho}\right)_S = -\frac{V^2}{M}\left(\frac{\partial P}{\partial V}\right)_S \tag{24}$$

$$c^2 = \frac{V^2}{\beta M}\left[\frac{\left(\frac{\gamma_V}{k_B}\right)^2}{\frac{C_V}{k_B}} + \frac{\beta}{V\kappa_T}\right] \tag{25}$$

Where:

$$\gamma_V = \left(\frac{\partial P}{\partial T}\right)_V \tag{26}$$

γ_V is known as the isochoric pressure coefficient. κ_T is the same isothermal compressibility from equation 20

An alternate derivation, applying the triple product rule to $\left(\frac{\partial P}{\partial V}\right)_S$ yields the following.

$$\left(\frac{\partial P}{\partial V}\right)_S = \frac{\left(\frac{\partial S}{\partial V}\right)_P}{\left(\frac{\partial S}{\partial P}\right)_V} \tag{27}$$

$$\left(\frac{\partial S}{\partial V}\right)_P = \left(\frac{\partial S}{\partial T}\right)_P\left(\frac{\partial T}{\partial V}\right)_P = \frac{C_P}{T}\left(\frac{\partial T}{\partial V}\right)_P = \frac{C_P}{TV\alpha} \tag{28}$$

Where $\alpha = \frac{1}{V}\left(\frac{\partial V}{\partial T}\right)_P = \left(\frac{\partial \ln V}{\partial T}\right)_P$ is the coefficient of thermal expansion. The second term in our triple product rule expansion, $\left(\frac{\partial S}{\partial P}\right)_V$, can be expressed as follows:

$$\left(\frac{\partial S}{\partial P}\right)_V = \left(\frac{\partial S}{\partial T}\right)_V\left(\frac{\partial T}{\partial P}\right)_V = \frac{C_V}{T}\left(\frac{\partial T}{\partial P}\right)_V = \frac{C_V}{T\gamma_V} \tag{29}$$

Thus our derivation yields:

$$\left(\frac{\partial P}{\partial V}\right)_S = \frac{C_P\gamma_V}{C_V V\alpha} \tag{30}$$

To avoid running an NVT simulation to determine C_V, the following relationship between C_P and C_V can be used:

$$C_P - C_V = TV\left(\frac{\alpha^2}{\kappa_T}\right) \tag{31}$$

This yields the following expression:

$$\left(\frac{\partial P}{\partial V}\right)_S = \left(\frac{C_P}{C_P - TV\frac{\alpha^2}{\kappa_T}}\right)\left(\frac{\gamma_V}{V\alpha}\right) \tag{32}$$

Horn et al set out several ways for calculating α[**?**]:

a. Analytical derivative of density with respect to temperature

$$\alpha = -\frac{d\ln\langle\rho\rangle}{dT} \tag{33}$$

b. Numerical derivative of density over range of T of interest The same finite differnces approach as shown for isothermal compressibility can be applied here, thus:

$$\alpha = -\frac{d\ln\langle\rho\rangle}{dT} = -\frac{1}{2\rho(T,P)}\left(\ln\langle\rho(P,T+\Delta T)\rangle - \ln\langle V(P,T-\Delta T)\rangle\right) \tag{34}$$

c. Using the enthalpy-volume fluctuation formula

$$\alpha = \frac{\langle VH\rangle - \langle V\rangle\langle H\rangle}{k_B\langle T\rangle^2\langle V\rangle} \tag{35}$$

Finite differences approximations and/or analytical derivation can also be used to calculate γ_V or by note of the relation:

$$\gamma_V = -\frac{\alpha}{\kappa_T} \tag{36}$$

Substituting Equations (24),(32), and (36), the following easily calculable expression for speed of sound is obtained:

$$c^2 = \frac{V}{M\kappa_T}\left(\frac{C_P}{C_P - TV\frac{\alpha^2}{\kappa_T}}\right) \tag{37}$$

Which can also be written in the simplified form:

$$c^2 = \frac{\gamma}{\rho\kappa_T} \tag{38}$$

Where $\gamma = \frac{C_P}{C_V}$.

6. Dielectric Constant

This equation was provided by a literature reference authored by CJ Fennell[**?**] and is the standard for calculating the dielectric constant. Below, $\epsilon(0)$ is the zero frequency dielectric constant, V is the system volume and D is the total system dipole moment.

$$\epsilon(0) = 1 + \frac{4\pi}{3k_BT\langle V\rangle}(\langle D^2\rangle - \langle D\rangle^2) \tag{39}$$

B. Binary Mixture Properties

1. Mass Density, Speed of Sound and Dielectric Constant

The methods for these calculations are the same for a multicomponent system.

2. Activity Coefficient

The definition of chemical potential in a pure substance is:

$$\mu(T,P) = \left(\frac{\partial G}{\partial N}\right)_{T,P} \tag{40}$$

which is a function of only temperaure and pressure.

Then the definition of the chemical potential μ_i of compound i in a mixture is:

$$\mu_i(T,P,\vec{N}) = \left(\frac{\partial G}{\partial N_i}\right)_{T,P,N_{j\neq i}} \tag{41}$$

N_i refers to a molecule of component i and $N_{j\neq i}$ refers to all molecules other than component i, with $\vec{N}$ the vector of all component numbers. Since μ_i is intensive, this is equivalently a function of the vector of mole fractions $\vec{x}_i$ instead of simply of N_i.

For an ideal solution, the chemical potential μ_i can be related to the pure chemical potential by

$$\mu_i(T,P,\vec{x}_i) = \mu(T,P) + k_BT\ln(\gamma_i) \tag{42}$$

By analogy to this form, we can say

$$\mu_i(T,P,\vec{x}_i) = \mu(T,P) + k_BT\ln(x_i\gamma_i) \tag{43}$$

Where γ_i is the activity coefficient of component i, and is a function of T,P,and $\vec{x}_i$. Rearrangement of the previous equation yields:

$$\gamma_i = \frac{e^{\left(\frac{\mu_i(T,P,\vec{x}_i)-\mu(T,P)}{k_BT}\right)}}{x_i} \tag{44}$$

Although chemical potentials cannot be directly calculated from simulation, chemical potential residuals can. We can calculate the difference $\mu_i(T,P,\vec{x}_i) - \mu(T,P)$ by calculating $\Delta\mu(T,P)_{liquid} - \Delta\mu(T,P)_{gas}$ using a standard alchemical simulation of the pure substance, followed by the calculation of $\mu_i(T,P,\vec{x}_i)_{liquid} - \Delta\mu(T,P,\vec{x}_i)_{gas}$, and assuming that $\Delta\mu(T,P,\vec{x}_i)_{gas} = \Delta\mu(T,P)_{gas}$. Note: there are a few subleties here relating to the $\ln x_i$ factor, but it appears that with alchemical simulations with only one particle that is allowed to change, this will cancel out (need to follow up).

Several of these alchemical simulation methods for calculating activity coefficients have been pioneered by Andrew Paluch [**?**]. A method detailing the calculation of infinite dilution activity coefficients γ_i^{inf} for binary a mixture follows directly:

$$\ln\gamma_2^{\infty}(T,P,x_2=0) = \beta\mu_2^{res,\infty}(T,P,N_1,N_2=1) + \ln\left[\frac{RT}{V_1(T,P)}\right] - \ln f_2^0(T,P) \tag{45}$$

Where $\beta\mu_2^{res,\infty}$ is the dimensionless residual chemical

potential of component 2 at inifinite dilution. The residual is defined here as the difference between the liquid and ideal gas state. $V_1\left(T,P\right)$ is the molar volume of component 1 at T and P. $\ln f_2^0\left(T,P\right)$ is the natural logarithm of the pure liquid fugacity of component 2 and is defined as:

$$\ln f_2^0\left(T,P\right) = \beta\mu_2^{res}\left(T,P\right) + \ln\left[\frac{RT}{V_2\left(T,P\right)}\right] \tag{46}$$

Paluch et al. use a multistage free energy perturbation approach utilizing MBAR in order to calculate the residual chemical potentials (recall that the chemical potential is the partial molar Gibbs free energy and dimensionless Gibbs free energy differences between multiple states are readily computed with MBAR). The idea is to connect two states of interest. In the case of a pure liquid, connecting a system of pure liquid molecules with $N-1$ interacting molecules and one fully decoupled molecule to a system of N fully interacting molecules. The coupling/decoupling process is detailed by Paluch et al [**?**], but involves a linear alchemical switching function where LJ and electronic interactions are slowly turned on for the decoupled molecule until they are fully on. The free energy of this coupling is calculated by simpling summing the free energy changes along this path.

3. Excess Molar Properties

The general definition of an excess molar property can be stated as follows:

$$y^E = y^M - \sum_i x_i y_i \tag{47}$$

Where y^E is the excess molar quantity, y^M is the mixture quantity, x_i is the mole fraction of component i in the mixture and y_i is the pure solvent quantity. In general, the simplest methods for calculating excess molar properties for binary mixtures will require three simulations. One simulation is run for each pure component and a third will be run for the specific mixture of interest. We note that only one set of pure simulations are needed to calculate excess properties at all compositions.

4. Excess Molar Heat Capacity and Volume

Excess molar heat capacities and volume will be calculated using the methods for the pure quantities in section I in combination with the general method for excess property calculation above.

5. Excess Molar Enthalpy

Excess molar enthalpy can be calculated using the general relation of molar enthalpy as it relates to Gibbs Free Energy from section I and the general method of excess molar property calculation above or by the following[**?**]:

$$H^E = \langle E^M\rangle + PV^E - \sum_i x_i\langle E_i\rangle \tag{48}$$

Where $\langle E\rangle$ denotes an ensemble average of total energy and V^E is calculated using the general method of excess molar properties.

C. Suggested Corrections

1. Heat Capacity

Horn et al suggest a number of vibrational corrections be applied to the calculation of C_P due to a number of approximations made during the simulation of the liquid [**?**]. The following terms were added as a correction.

$$\left(\frac{\partial E_{vib,l}}{\partial T}\right)_P = \left(\frac{\partial E^{QM}_{vib,l,intra}}{\partial T}\right)_P + \left(\frac{\partial E^{QM}_{vib,l,inter}}{\partial T}\right)_P - \left(\frac{\partial E^{CM}_{vib,l,inter}}{\partial T}\right)_P \tag{49}$$

Where:

$$\left(\frac{\partial E^{CM}_{vib}}{\partial T}\right)_P = k_B n_{vib} \tag{50}$$

$$\left(\frac{\partial E^{QM}_{vib}}{\partial T}\right)_P = \sum_{i=1}^{n_{vib}}\left(\frac{h^2 v_i^2 e^{\frac{hv_i}{k_B T}}}{k_B T^2\left(e^{\frac{hv_i}{k_B T}}-1\right)^2}\right) \tag{51}$$

Above, n_{vib} is the number of vibrational modes, h is Planck's constant and v_i is the vibrational frequency of mode i.

III. Properties Involving Change of Phase

A. Pure Solvent Properties

1. Enthalpy of Vaporization

The definition of the enthalpy of vaporization is[**?**]:

$$\Delta H_{vap} = H_{gas} - H_{liq} = E_{gas} - E_{liq} + P(V_{gas} - V_{liq}) \quad (52)$$

If we assume that $V_{gas} >> V_{liq}$ and that the gas is ideal (and therefore kinetic energy terms cancel):

$$\Delta H_{vap} = E_{gas,potential} - E_{liq,potential} + RT \quad (53)$$

B. Suggested Corrections

1. Enthalpy of Vaporization

An alternate, but similar, method for calculating the enthlapy of vaporization is recommended by Horn et al [**?**].

$$\Delta H_{vap} = -\frac{E_{liq,potential}}{N} + RT - PV_{liq} + C \quad (54)$$

In the above equation C is a correction factor for vibrational energies, polarizability, non-ideality of the gas and pressure. It can be calculated as follows.

$$\begin{aligned} C_{vib} &= C_{vib,intra} + C_{vib,inter} \\ &= (E_{vib,QM,gas,intra} - E_{vib,QM,liq,intra}) \\ &\quad + (E_{vib,QM,liq,inter} - E_{vib,CM,liq,inter}) \end{aligned} \quad (55)$$

The QM and CM subscripts stand for quantum and classical mechanics, resectively.

$$C_{pol} = \frac{N}{2}\frac{(d_{gas} - d_{liq})^2}{\alpha_{p,gas}} \quad (56)$$

Where d_i is the dipole moment of a molecule in phase i and $\alpha_{p,gas}$ is the mean polarizability of a molecule in the gas phase.

$$C_{ni} = P_{vap}\left(B - T\frac{dB}{dT}\right) \quad (57)$$

Where B is the second virial coefficient.

$$C_x = \int_{P_{ext}}^{P_{vap}} \left[V\left(P_{ext}\right)\left[1 - \left(P - P_{ext}\right)\kappa_T\right] - TV\alpha\right] dP \quad (58)$$

Where P_{ext} is the external pressure and $V\left(P_{ext}\right)$ is the volume at P_{ext}.

This is frequently done as a single simulation calculation by assuming the average intramolecular energy remains constant during the phase change, which is rigorously correct for something like a rigid water molecule (intramolecular energies are zero), but less true for something with structural rearrangement between gas and liquid phases.

As discussed by myself and MRS, we have decided to not initially begin the parametrization process using enthalpy of vaporization data. While force field parametrization is commonly done using said property we have ample reason to not follow classical practice. First of all, the enthalpy data is usually not collected at standard temperature and pressure, but at the saturation conditions of the liquid being vaporized [**?**]. This would require corrections to be made to get the property at STP (the process will be explained below) using fitted equations for heat capacity. Not only is this inconvenient, but it adds an unknown complexity when adjusting experimental uncertainties due to the added correction. Often times the uncertainties of these "experimental" enthalpies are unrecorded because they are estimated from fitted Antoine equation coefficients [**?**].

An additional issue is the necessity of having to use gas phase simulation data in order to validate a parametrization process meant for small organic liquids and their mixtures. Following an example of Wang et al. [**?**] we plan to instead use enthalpy of vaporization calculations as an unbiased means of testing the success of the parametrization. If the parametrization procedure is expanded to use enthalpy of vaporization, corrections can be made to the experimental data in order to get a value at STP using the following equation.

$$\Delta H_{vap}(T) = \Delta H_{vap}^{ref} + \int_{T_{ref}}^{T} \left(C_{P,gas} - C_{P,liq}\right) dT \quad (59)$$

IV. Numerical Considerations

A. Quality of Timeseries Data

With the finite computing resources that are available today, it is often necessary to make trade-offs between the uncertainty of the result and the amount of time/resources

spent. As a major assumption of Molecular Dynamics simulations is the Ergodic Hypothesis, sampling over a timeseries will only be equivalent in the limit of infinite time. In all other cases, the timeseries generated from MD will function as an *approximation* to phase space sampling. As this is the case, there is an inherent decision to be made in the collection of all timeseries data: how much effort does one need to spend to get a result with the appropriate confidence for the specific problem being addressed?

For bulk thermophysical properties, there are two major factors that consume computational resources: the length of the simulation, often measured in time units such as nanoseconds or microseconds, and the size of the system that is simulated, measured in number of molecules. Because timescales vary based on the nature of the system, a more general metric that we will use in this discussion is N, the number of uncorrelated equilibrium samples. We will denote the number of molecules as M in this discussion to distinguish the two.

1. Equilibrium Sampling

The relationship between N and uncertainty is straightforward; as one collects more samples of the same system, the standard deviation decreases as $\mathcal{O}(N^{-\frac{1}{2}})$, as would be expected for the standard formula for sample standard deviation. It is worth noting that while N follows this rule, the length of the simulation will not follow it exactly. This is because the detection of equilibration and the choice of uncorrelated equilibrium samples will vary between users and systems.

For a timeseries to satisfy the Ergodic Hypothesis and allow for calculation of equilibrium samples, the system needs to have settled into an equilibrium region, following a "burn-in" period in which the system starts at some non-equilibrium configuration and relaxes into an equilibrium configuration. This portion of a timeseries needs to be removed; the question as to how to do so is slightly trickier. For users running many simulations of similar systems, often a burn-in time is determined by inspection and then set for all subsequent simulations. However, this can backfire based on the simulation parameters being varied. For example, systems with small numbers of molecules can equilibrate much slower than larger systems, making the choice of equilibrium for one invalid for another, or discarding valuable equilibrium data. Another option is an automatic equilibration detection algorithm, like the one proposed by Chodera. In this work, this automatic equilibration algorithm is used in all analysis. It is important to note, however, that algorithms like this should not be used in a vacuum; the user should periodically check to make sure that the algorithm is functioning properly, and have a rudimentary understanding of how it works.

Another important factor in the calculation of thermophysical properties is the collection of *uncorrelated* equilibrium samples from an equilibrated timeseries. Although the system may be at equilibrium constantly after the burn-in period, samples close to each other in time are likely correlated. Two common methods for obtaining uncorrelated samples are through subsampling and block averaging. In block averaging, the timeseries is separated into "blocks" of data and observations are taken from the mean of each block. This requires for a size of block to be chosen, and as the block size increases, the variance of the observable will eventually reach a plateau where samples are uncorrelated. Another method is subsampling, where the statistical inefficiency g is estimated and then snapshots are chosen based on this parameter, without averaging. In this work, subsampling is used for all calculations.

B. System Size

For the number of molecules M, relationships with uncertainty are more complicated and vary from property to property. This can lead to unintuitive results in which a larger M may reduce uncertainty in one physical quantity, but for a *derived* property of said quantity, the same increase in M may not improve estimates.

1. Enthalpy and Heat Capacity

This is best illustrated with the example of energy and heat capacity. From Eq. 19, the *extensive* heat capacity is directly proportional to the variance in the enthalpy, which is defined as $\langle H^2 \rangle - \langle H \rangle^2$. For any extensive property, its value has a linear relationship with M; as you go from 100 molecules to 200 molecules, the total heat capacity (or enthalpy, or volume, etc.) will double.

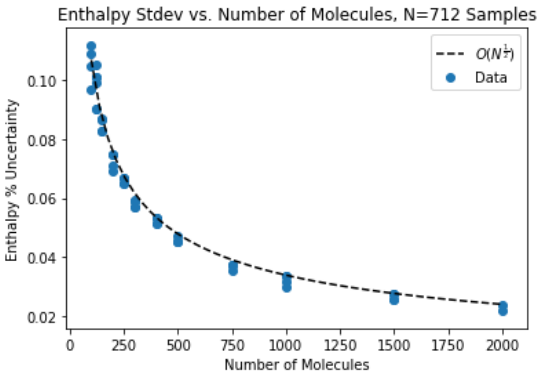
Therefore, the heat capacity goes as $C_P \sim \mathcal{O}(M)$, and subsequently, so does the variance of the enthalpy: $Var(H) \sim C_P \sim \mathcal{O}(M)$. If we wish to examine the variance of the *molar* enthalpy, an *intensive* quantity, we can make use of this standard formula for variances:

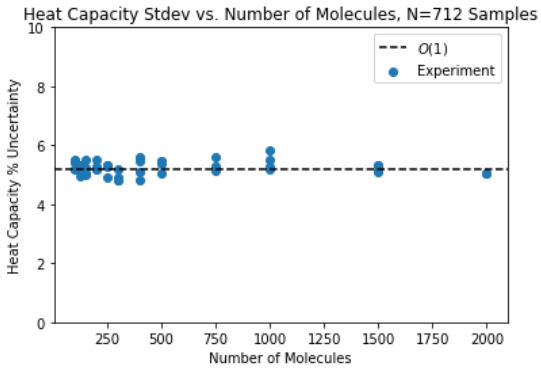
$$Var(aX) = a^2 Var(X) \tag{60}$$

Since molar enthalpy is defined as $h = \left(\frac{H}{M}\right)$, the variance of the molar enthalpy is given by:

$$Var(h) = Var\left(\frac{H}{M}\right) = \frac{1}{M^2} Var(H) \sim \frac{\mathcal{O}(M)}{M^2} \sim \mathcal{O}(1/M) \tag{61}$$

So, the standard deviation of the molar enthalpy goes as $\mathcal{O}(M^{-\frac{1}{2}})$, meaning that quadrupling the size of the system will cut the uncertainty in half, just as quadrupling N would. This relationship is shown in figure:





Now, we examine the uncertainty behavior of C_P, the extensive heat capacity. Since we know $C_P \sim Var(H)$, it follows that $Var(C_P) \sim Var(Var(H))$. For normally distributed samples, the variance of the variance is given by:

$$Var(Var(X)) \approx \frac{2(N-1)}{N^2}(Var(X))^2 \tag{62}$$

Holding N constant and applying to the enthalpy, we obtain the following:

$$Var(C_P) \sim Var(Var(H)) \sim (Var(H))^2 \sim \mathcal{O}(M^2) \tag{63}$$

As we examine the *molar* heat capacity $c_P = C_P/M$ and apply the variance formula from above, we obtain:

$$Var(c_P) = Var(\frac{C_P}{M}) = \frac{Var(C_P)}{M^2} \sim \frac{\mathcal{O}(M^2)}{M^2} \sim \mathcal{O}(1) \tag{64}$$

So, even though estimates of the molar enthalpy h improve as the size of the system increases, estimates of the molar heat capacity c_P, which is alternatively defined as the derivative of h with respect to T, do not. Note that while this derivation is for NPT systems, a similar derivation follows for NVT systems, replacing H with E and C_P with C_V.

2. *Volume and compressibility*

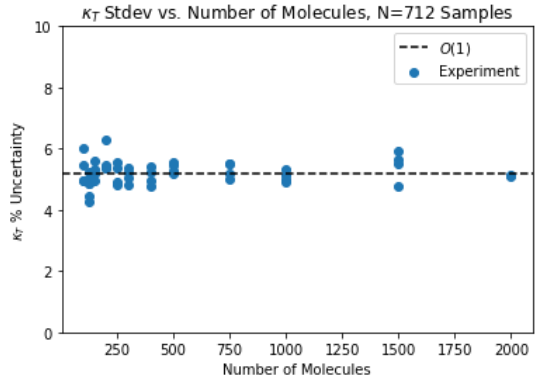
For the volume V, the standard deviation also goes as $\mathcal{O}(M^{-\frac{1}{2}})$. This follows from the information we already know about energy and enthalpy and the relationship between the two. Since they are related by $H = E + PV$, and the variance of H and E both go as $\mathcal{O}(M)$ due to their relationship with the heat capacities C_P and C_V, the variance of V must also go as $\mathcal{O}(M)$. By similiar analysis to that for the molar enthalpy h, it follows that the standard deviation of the molar volume v goes as $\mathcal{O}(M^{-\frac{1}{2}}$, and this claim is supported by experimental data in figure.

For the isothermal compressibility, the variance is easy to calculate once the variance of the volume is known. From Eq. 23, we can see that with constant temperature, the variance of κ_T is as such:

$$Var(\kappa_T) \sim Var\left(\frac{Var(V)}{V}\right) = \frac{1}{V^2}Var(Var(V)) \tag{65}$$

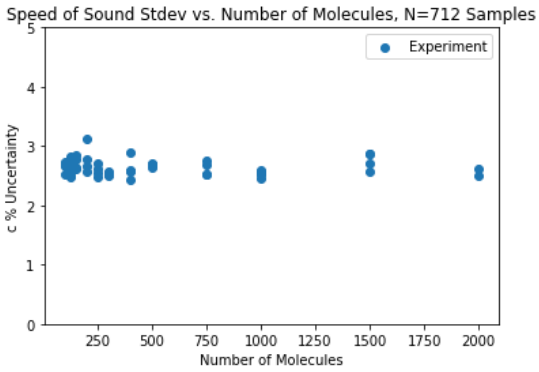
$$Var(\kappa_T) \sim \frac{1}{V^2}(Var(V))^2 \sim \frac{\mathcal{O}(M^2)}{\mathcal{O}(M^2)} \sim \mathcal{O}(1) \tag{66}$$

So, the uncertainty of the compressibility is independent of the number of molecules used to simulate the system. This claim is supported by experimental data in figure 3:



3. *Speed of Sound*

For thermophysical properties that are calculated from several other basic properties, such as speed of sound $c = \frac{\gamma}{\rho\kappa_T}$, it is important to examine the relative contributions of the error to determine the overall uncertainty behavior of the property. For example, γ and κ_T are both properties with uncertainties that do not depend on M, but ρ should have an $\mathcal{O}(N^{-\frac{1}{2}})$ uncertainty behavior, similar to molar volume. Therefore, one would expect the overall uncertainty behavior to be dependent on M, but data from experiment in Figure 4 shows no correlation.



4. Discussion

From these analyses, we can see that properties taken from direct averages of timeseries data, (V, E, H) have standard deviation that goes as $\mathcal{O}(M^{\frac{1}{2}}$. The molar versions of these properties subsequently have standard deviation that goes as $\mathcal{O}(M^{-\frac{1}{2}}$. However, this does not imply the same for properties calculated via fluctuations. Fluctuation properties can have standard deviation as $\mathcal{O}(M)$, like C_P, or with no dependence on M, like c_P or κ_T. Additionally, they can have a very weak dependence on M, such as speed of sound c. Because of these varying dependencies between quantities, and the extra computational cost of a larger system size, we recommend that additional computational resources be used to collect more equilibrium samples, which has a consistent effect on uncertainty for all properties. This recommendation comes with the caveat that systems need to be large enough to avoid finite size effects. When systems are too small, systems may not equilibrate very quickly, amongst other problems. For a more in-depth discussion of finite size effects, see. It is also important to remember when modifying the number of molecules in a system that Molecular Dynamics programs report energies in units of energy/-mole of box, rather than energy per mole of compound. For pure compounds, one must divide the "moles of box" value by the number of molecules in order to get a true molar energy.

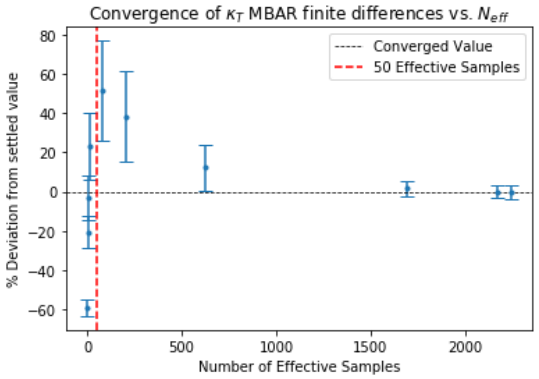
C. Comparison of Calculation Methods

For the properties discussed in this paper, the methods of calculation generally fall into one of two categories: derivatives via finite differences or calculations from fluctuation properties. Therefore, it is worth investigating whether these all methods are equivalent, or if there are differences in methods which may make them more or less attractive, depending on the situation.

1. Comparison of MBAR finite differences and direct finite differences

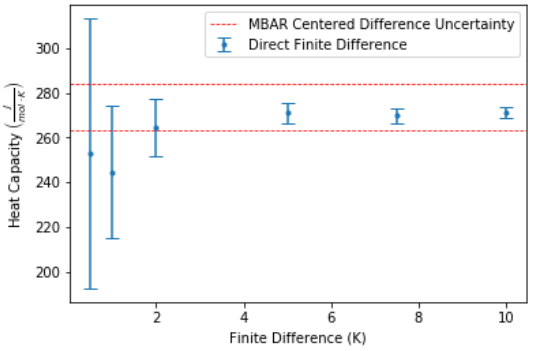
Suppose we are interested in calculating a thermodynamic property B at state X, defined as $B = \mathrm{d}A/\mathrm{d}X$. When calculating this property from timeseries data via centered finite difference (such as in Eq. 10,21), the simplest and most nature choice is to choose a finite difference ΔX, perform simulations at $X - \Delta X$ and $X + \Delta X$, take the expectations $\langle A(X - \Delta X)\rangle$ and $\langle A(X + \Delta X)\rangle$, and then calculate the finite difference from these two values ("Direct Finite Differences"). Another possibility is take a simulation at X, and use reweighting via the MBAR method [**?**] to estimate A at $X - \Delta X$ and $X + \Delta X$, then calculate the finite difference from these estimates ("MBAR Finite Differences"). The choice of finite difference is important here, as ΔX will determine the accuracy of the calculation. Theoretically, we would like the smallest finite difference possible to minimize potential bias in the calculation. For direct finite differences, however, a small ΔX will provide unreliable estimates, as timeseries data at very similar state points are highly correlated, leading to high uncertainty. As ΔX increases, the timeseries data becomes less correlated and uncertainty goes down, but there is potential for bias, which depends on the behavior of the function.

When using MBAR finite differences, the problem is opposite: MBAR estimates are inherently decorrelated, leading to decent uncertainty at small ΔX, but MBAR requires significant phase overlap between the simulated state and the desired state, so estimates become more unreliable as ΔX increases. However, since MBAR finite differences are stable over a large range of $\Delta X/X$ $((10^{-6} - 10^{-3})$ for heat capacities), this is less of an issue. However, it does make comparisons of direct finite differences and MBAR finite differences difficult, as the minimum ΔX in direct finite differences that produces uncertainties equivalent to MBAR finite differences is roughly 10^{-2} in heat capacity; MBAR estimates are already poor at this point. In order to quantify the reliability of the MBAR finite difference, the number of effective samples (N_{eff}) metric can be used. This metric quantifies how many of the samples from simulated state A could be drawn from reweighted state B. Previous use of this metric has shown that a rough minimum of $N_{eff} = 50$ is required for statistics to be stable, but for *accurate* finite differences, the percentage of effective samples $((N_{eff}/N) \times 100\%)$ is a better metric, but may depend on the property being calculated. For example, MBAR finite differences for C_P agree with fluctuations with roughly 10 % of effective samples, but is more like 75% for κ_T.



Since the number of effective samples is easily adjusted, as a best practice, we recommend a percentage of effective samples of 90 % or higher. It is also important to recognize that for properties that require reweighting in multiple variables, such as speed of sound, the number of effective samples for all variables needs to be taken into account (in the example of speed of sound, T and P). In general, comparison with fluctuation calculations is the ultimate metric for accuracy of MBAR finite differences.

To test this, we performed a 10 ns simulation of cyclohexane at 293.15 K and 1.01 bar, as well as several pairs of 5 ns cyclohexane simulations, also at 1.01 bar, but spaced at intervals of 0.5, 1, 2, 5, 7.5, and 10 K apart from 293.15 K. Heat capacity calculations from finite differences were performed via MBAR on the 10 ns simulation, and directly on the pairs of 5 ns simulations.



2. *Finite differences and fluctuations*

For properties that can be calculated via finite differences or fluctuations, such as κ_T (Eq. 21, 23), C_P (Eq. 16, 19), or α (Eq. 33,35), the two methods should be theoretically equivalent, as fluctuation formulas are derived by substituting statistical mechanical expressions for energy, enthalpy, or volume into derivative formulas and evaluating the derivative. In the limit of infinitely small finite differences and infinitely long timeseries, this will be exactly true; however, since neither condition can be met, it is important to understand if these methods are approximately equivalent under normal conditions.

Because of the large number of particles and the chaotic nature of the interactions between them, replicate timeseries are often slightly different, and will provide substantially different sets of uncorrelated equilibrium samples. Therefore, agreement between finite differences and fluctuation methods are not based on agreement to some "grand truth" but agreement between the data used to compute the derivative and the fluctuations. This point is illustrated with the following relation:

$$\frac{H(T_2) - H(T_1)}{T_2 - T_1} \approx \left(\frac{\partial H}{\partial T}\right)_P = \left(\frac{Var(H)}{RT^2}\right)_\infty \approx \left(\frac{Var(H)}{RT^2}\right) \tag{67}$$

As fluctuation calculations and finite differences are both approximations to the "grand truth" of true derivatives and true fluctuations, they will not agree unless they come from the same data source. For direct finite differences, since simulations are taken at different conditions than the simulation used for the fluctuation calculation ($X + \Delta X$ and $X - \Delta X$ instead of X), the agreement between fluctuations and finite differences is significant. In the case of MBAR finite differences, the same data can be used to calculate the finite differences and the fluctuations, so these two methods should agree, up to numerical error caused by the finite difference size chosen for MBAR. In this way, MBAR finite differences and fluctuations are a good sanity check, as they should be almost identical if implemented correctly.