

210D: Computing free energies of solvation for a LJ fluid using
Thermodynamic Integration (T.I.) and Bennett Acceptance
Ratio (BAR) techniques

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12/11/2019

1 Abstract

In this work I compute the Helmholtz free energy of solvating a LJ particle in a LJ fluid using Thermodynamic Integration (TI) [1] and Bennett Acceptance Ratio (BAR) [2] techniques. The free energies are computed at a reduced density (ρ^*) and reduced temperature (T^*) of 0.8 and 3.0, respectively. The simulations were performed using 240,480,960, and 1920 LJ particles ($\epsilon = 1$, $\sigma = 1$) in order to study the system size effects. The reduced free energies computed (for $N=480$) from TI and BAR are 12.11 ± 0.03 (12.11 ± 0.03 , using bootstrapping) and 12.170 ± 0.01 (bootstrapped statistics), respectively. Accounting for finite size effects too the true free energy of solvation is 12.11 ± 0.03 .

2 Solvation Free Energy

Solvation free energy is the free energy change associated with transferring a solute molecule from an ideal gas phase to a solution phase at a given temperature, pressure, and solute concentration in solution as shown in Figure 1. Solvation free energy computations play an important role in computing solubilities, partition coefficients, activity coefficients and Henrys law constants.

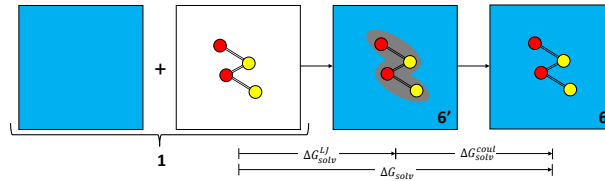


Figure 1: The Physical Reaction of Solvation

2.1 Force Field

I choose a LJ system for ease of implementation and focus on the algorithms to compute the free energies. The force field used is a LJ/cut/shift force field given by equation 2 with ϵ and σ set to 1 in equation 1. A soft core LJ potential given by equation is used to turn on the interaction (by varying the λ parameter) between the solute and its environment. The LJ potential is cut at $r_c=2.5$.

$$U_{LJ}(r) = 4\epsilon \left[\left(\frac{\sigma}{r} \right)^{12} - \left(\frac{\sigma}{r} \right)^6 \right] \quad (1)$$

$$U(r) = U_{LJ}(r) - U_{LJ}(r_c) \quad (2)$$

$$U_{LJ-Soft}(r; \lambda) = 4\lambda \left(\frac{1}{(\alpha(1-\lambda)^2 + r^6)^2} - \frac{1}{\alpha(1-\lambda)^2 + r^6} \right) \quad (3)$$

$$U_{LJ-Soft}(r; \lambda) = U_{LJ-Soft}(r; \lambda) - U_{LJ-Soft}(r_c; \lambda) \quad (4)$$

2.2 Simulations

I perform Monte Carlo simulations in the NVT ensemble to compute the Helmholtz free energies with maximum displacements between 0.11 and 0.15 giving acceptance ratios between 45-55%. A equilibrium period of 50000 MC sweeps (conservatively high) and a production period of 250000 MC sweeps data collecting frequency of 15 MC sweeps (based on autocorrelation time studies as shown in Appendix B) is used.

TI

The free energy of solvation using thermodynamic integration (TI) is given by equation 5

$$\Delta F = \int_0^1 \left\langle \frac{dU}{d\lambda} \right\rangle_{\lambda} d\lambda \quad (5)$$

In the MC code I hardwire $\langle dU/d\lambda \rangle$. I use the Gauss Quadrature method (45 points, see Table 1 for sensitivity analysis with # of Gauss points) to compute the integral in equation 5. In order to test my framework I compute the TI plot using MC simulations and using LAMMPS at the 45 Gauss points. Figure 2 shows the comparison. As seen the TI plots are in excellent agreement. The reduced Helmholtz free energy computed using TI is **12.01 ± 0.03** (see Appendix A for error analysis).

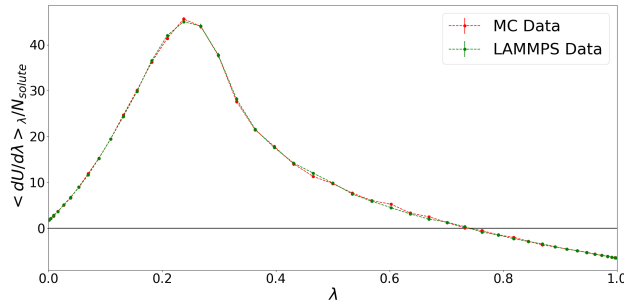


Figure 2: TI plots comparison, N=240

Table 1: Free energy variation with number of points used for integration

# of Gauss points	ΔA
15	12.03 ± 0.05
45	12.01 ± 0.03

Finite Size Effects

In order to check the system size dependence of the solvation free energy, I compute the free energies for N=240, 480, 960, and 1920 LJ particles. Figure 3 shows a plot of the free energy vs inverse of simulation box length. As seen for N=480,960 and 1920, the solvation free energy is independent of system size.

Table 2: Free energy variation with size of simulation box

N	ΔA
240	12.01 ± 0.03
480	12.11 ± 0.03
960	12.13 ± 0.03
1920	12.11 ± 0.03

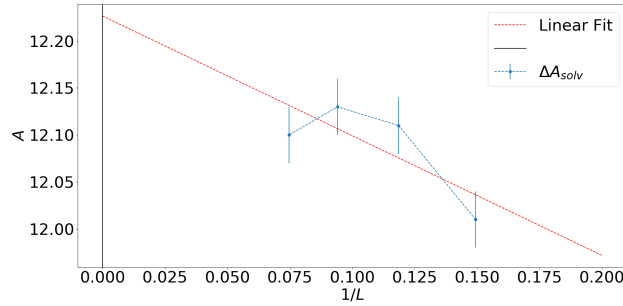


Figure 3: ΔA_{solv} vs $1/L$

BAR

The free energy difference between two states using BAR is computed by solving equation 6

$$\sum_{i=1}^{n_i} \frac{1}{1 + \exp(\ln(n_i/n_j) + \beta\Delta U_{ij} - \beta\Delta A)} - \sum_{j=1}^{n_j} \frac{1}{1 + \exp(\ln(n_j/n_i) - \beta\Delta U_{ji} + \beta\Delta A)} = 0 \quad (6)$$

where:

1. i, j are the two states
2. ΔU_{ij} is the potential energy of a frame sampled in the i^{th} state evaluated using the potential energy function of the j^{th} state
3. n_i, n_j are the number of independent samples in state i and j , respectively
4. ΔA is the Helmholtz free energy difference between the two states

I use the same Gauss points and add the end states to compute the free energy of solvation using BAR. Figure 4 shows the ΔA s for between successive states. Summing these free energy differences gives the solvation free energy which amounts to 12.00 ± 0.01 which is within error of the free energy estimate computed using TI. I have used bootstrapping for computing error bars for the BAR results.

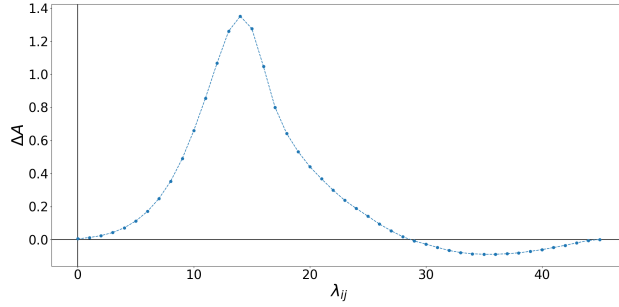


Figure 4: ΔA s between successive states computed using BAR, $N=240$

3 Results and Conclusion

Table 3 summarizes the free energy of solvation results. In order to compare the error bars I bootstrap the TI results too in order to make a reasonable comparison.

Table 3: Free energy variation with size of simulation box

N	ΔA				
	T.I.	T.I. (w/ bootstrap)		BAR (w/ bootstrap)	
		30 samples	200 samples	30 samples	200 samples
240	12.01 ± 0.03	12.01 ± 0.03	12.02 ± 0.03	12.00 ± 0.02	12.00 ± 0.01
480	12.11 ± 0.03	12.11 ± 0.03	12.11 ± 0.04	12.17 ± 0.02	12.17 ± 0.01

Thus I have successfully computed the reduced Helmholtz free energy of solvation of a LJ particle in a LJ fluid accounting for finite size effects using TI. I have also computed the same using BAR (with a bootstrapped error analysis). As seen BAR performs marginally better than TI (by comparing bootstrapped errors).

4 Caption for the movie

A fully coupled LJ particle (red) solvated in a LJ fluid (grey)

Appendix A

Error Analysis

This appendix explains how I compute my error bars on the values that I report. Let X be the property whose average I need to compute. Then \bar{X} is an estimate of $\langle X \rangle$,

$$\bar{X} = \frac{1}{n} \sum_{i=1}^n X_i \quad (\text{A.1})$$

and n is the number of independent samples.

The standard error of the mean ($\sigma_{\bar{X}}$) is given by

$$\sigma_{\bar{X}}^2 = \frac{\sigma_X^2}{n} \quad (\text{A.2})$$

where, σ_X^2 is the variance in X .

In the thermodynamic integrations that I perform, I compute the integral (I) using a Gauss Quadrature approach. For k Gauss points $(\lambda_1, \lambda_2, \dots, \lambda_k)$,

$$I = \sum_{i=1}^k w_i \cdot f_i \quad (\text{A.3})$$

where w_i are the weights given by the Gauss quadrature framework, and f_i is $\langle \frac{dU}{d\lambda} \rangle_{\lambda_i}$. Therefore,

$$\bar{I} = \sum_{i=1}^k w_i \cdot \bar{f}_i \quad (\text{A.4})$$

and,

$$\sigma_{\bar{I}}^2 = w_i^2 \cdot \sigma_{\bar{f}_i}^2 \quad (\text{A.5})$$

Appendix B

Autocorrelation Time

This appendix explains how I compute my autocorrelation times. Let A be the property whose autocorrelation time I need to compute. The slope of σ_A^2 plotted as a function of σ_A^2/t_{tot} where:

1. $\sigma_A^2 = \text{variance of the } \overline{A}_i$
 $\overline{A}_i = \text{average } A \text{ of each block } i$
2. $t_{tot} = \text{length of each block } i$
3. $\sigma_A^2 = \text{variance of } A \text{ over entire simulation trajectory}$

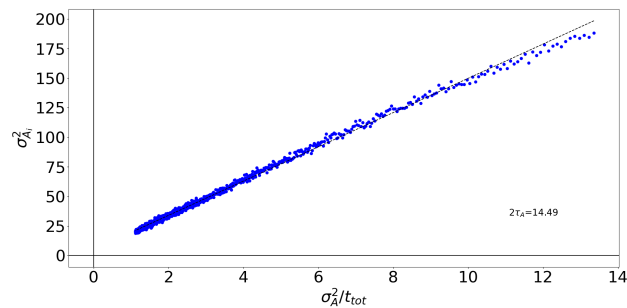


Figure B.1: Property (A) is U , i.e., potential energy

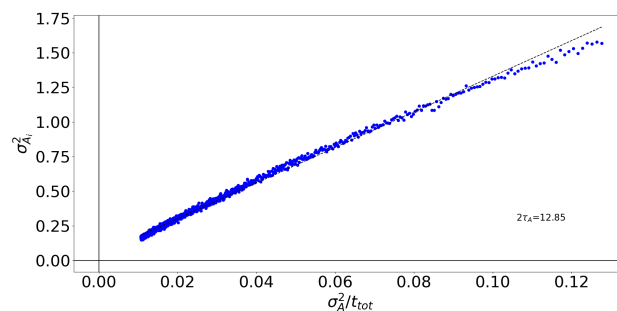


Figure B.2: Property (A) is $dU/d\lambda$

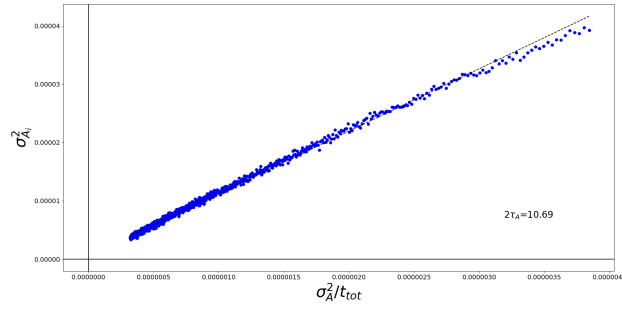


Figure B.3: Property (A) is ΔU_{ij}

Bibliography

- [1] John G Kirkwood. *The Journal of Chemical Physics*, 3(5):300–313, 1935.
- [2] Charles H Bennett. Efficient estimation of free energy differences from monte carlo data. *Journal of Computational Physics*, 22(2):245–268, 1976.