

Multistate Bennett Acceptance Ratio replaces histogram reweighting for vapor-liquid coexistence calculations

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Abstract

1 Introduction

A key advancement in molecular simulation is the ability to accurately and efficiently estimate vapor-liquid coexistence properties, i.e., saturated liquid density ($\rho_{\text{liq}}^{\text{sat}}$), saturated vapor density ($\rho_{\text{vap}}^{\text{sat}}$), saturated vapor pressures ($P_{\text{vap}}^{\text{sat}}$), and enthalpy of vaporization (ΔH_v). The accuracy of coexistence estimates depends on the underlying molecular model (a.k.a., force field, potential model, or Hamiltonian) while the computational efficiency depends primarily on the simulation methods. Due to the abundance of experimental vapor-liquid coexistence data and the sensitivity of such properties to both short- and long-range non-bonded interactions, numerous force fields have been parameterized using $\rho_{\text{liq}}^{\text{sat}}$, $P_{\text{vap}}^{\text{sat}}$, and ΔH_v . Although the development of accurate force fields has been greatly enabled by the improved efficiency of simulation methods, parameterization of non-bonded interactions with vapor-liquid coexistence calculations remains an arduous and time-consuming task.¹⁻³

Several methods exist for computing vapor-liquid coexistence properties, e.g., Gibbs Ensemble Monte Carlo (GEMC), two phase molecular dynamics (2 ϕ MD), isothermal-isochoric integration (ITIC), and Grand Canonical Monte Carlo coupled with histogram reweighting (GCMC-HR). Advantages and disadvantages exist for each method. For example, GEMC and GCMC require insertion moves that are computationally inefficient for complex molecular structures with high density liquid phases. Several advanced simulation techniques are available to overcome this challenge,⁴ which has enabled GEMC and GCMC-HR to be the primary methods of choice for vapor-liquid coexistence calculations.

Some clear advantages and disadvantages exist for GCMC-HR compared with GEMC. For example, one advantage of GCMC-HR is the higher precision.⁵ Furthermore, coexis-

tence properties can be computed at temperatures that are not simulated directly. However, GEMC is arguably more straightforward in that simulations are performed only at the desired saturation temperatures (T^{sat}). By contrast, GCMC-HR requires a series of GCMC simulations for a single T^{sat} . This set includes a near-critical simulation that “bridges” the vapor and liquid phases. Obtaining the appropriate chemical potential (μ) for this bridge simulation is a cumbersome and, typically, iterative process (although more advanced methods exist to obtain a good initial estimate for μ ⁶).

Another disadvantage of GCMC-HR compared to GEMC is that GCMC-HR requires more post-processing (i.e., histogram reweighting), while simple block averaging is typically sufficient for GEMC. Histogram reweighting (and more generally, configuration reweighting) is an important tool in many fields of molecular simulation. In fact, it has long since been known that it is possible to estimate properties for state “j” by reweighting configurations that were sampled with state “i.”^{7–10} For example, umbrella sampling simulations are often processed using the weighted histogram analysis method (WHAM) to compute free energy differences between states. A popular alternative to WHAM is the Multistate Bennett Acceptance Ratio (MBAR),^{11,12} which is readily available in the *pymbar* package.

In this study, we substitute HR with MBAR for the GCMC-HR approach of computing vapor-liquid coexistence properties. Section 2.3 demonstrates that MBAR and HR are mathematically equivalent (in the limit of zero bin width) while Section 3 shows that they are also numerically equivalent (to within statistical uncertainties). Note that, as Boulougouris et al. demonstrate how to combine HR with GEMC (GEMC-HR) to estimate saturation properties at non-simulated temperatures,¹³ MBAR could alternatively be applied to GEMC simulations.

Substituting the standard HR approach with MBAR is not the primary purpose of this study. Rather, we demonstrate how GCMC-MBAR can also estimate coexistence proper-

ties for non-simulated parameter sets, which can greatly accelerate force field parameterization. In a similar study, Messerly et al. demonstrate how to combine MBAR with ITIC (MBAR-ITIC) to optimize Mie λ -6 (generalized Lennard-Jones) potentials.^{14,15} For MBAR-ITIC, a series of NVT simulations along an isotherm and isochores are performed with a “reference” force field (θ_{ref}). MBAR computes the internal energy (U) and pressure (P) (or compressibility factor, Z) for each $T - \rho$ state point with a non-simulated (“rerun”) force field (θ_{rr}). ITIC then converts the U and P values into vapor-liquid coexistence properties.^{16,17}

The results from Messerly et al. demonstrate that MBAR-ITIC is most reliable in the local domain, i.e., for parameter sets near the “reference” parameter set from which configurations are sampled.¹⁴ Furthermore, MBAR-ITIC performs best for changes in the non-bonded well-depth parameter (ϵ) while it performs significantly worse for large changes in the non-bonded size and repulsive parameters (σ and λ , respectively). This is typically referred to as poor “overlap” and can be quantified by the “number of effective samples” (N_{eff}). Poor overlap (low N_{eff}) is especially problematic for ITIC as a large number of snapshots is needed to obtain precise estimates of P in the liquid phase, which are essential to obtain reasonable values of $\rho_{\text{liq}}^{\text{sat}}$.

Our hypothesis is that GCMC-MBAR should have better overlap over the non-bonded parameter space than what was observed for GCMC-ITIC. There are two main reasons for this hypothesis/aspiration. First, the fluctuating densities of GCMC simulations, as opposed to the fixed density NVT simulations, accommodate a wider range of configurations and energies. Second, ITIC requires accurate calculations of U and P in the vapor phase, which necessitate larger box sizes (and, thereby, more molecules) than those typically utilized with GCMC. By utilizing fewer molecules, GCMC simulations experience larger energy fluctuations (on a percent basis) which improves the overlap between states. We also hypothesize that the impact of poor overlap is less severe compared to

ITIC, where poor overlap leads to sporadic coexistence estimates.

Note that the method outlined in this study is similar in spirit to “Hamiltonian scaling” (HS), which has been applied to both GEMC and GCMC simulations. The HS approach samples from multiple force fields (Hamiltonians) in a single simulation according to a weighted sampling probability. Vapor-liquid coexistence curves for each force field are estimated post-simulation by reweighting the configurations accordingly. For the Grand Canonical Monte Carlo implementation of Hamiltonian scaling (HS-GCMC), μ and T are not stationary during the simulation, rather the current value of μ and T depends on which force field is being sampled. Despite HS-GCMC proving to be a powerful tool to optimize force field parameters,^{10,18–20} it has yet to gain widespread popularity. This is likely due to the added complexity of both the simulation protocol and the histogram post-processing. Also, HS requires that a decision be made *a priori* regarding which force fields are to be tested. By contrast, MBAR does not require any modification of the simulation procedure, the post-processing is essentially unchanged, and the non-bonded parameter sets need not be selected prior to the simulations.

Recently, Weidler and Gross proposed “individualized,” i.e., compound-specific, parameter sets for compounds which contain large amounts of experimental data.²¹ To avoid overfitting, a one-dimensional optimization is employed which scales ϵ for all united-atom sites while not adjusting σ or λ . MBAR is ideally suited for this “ ϵ -scaling” approach for at least two reasons. First, as mentioned previously, MBAR is most reliable when extrapolating in ϵ rather than σ and/or λ . Second, the rate-limiting step for MBAR is recomputing the configurational energies for a different force field. Furthermore, storing millions of configuration “snapshots” is highly memory intensive. While basis functions (see Section 2.4) alleviate the additional computational cost and reduce the memory load, ϵ -scaling does not require storing/recomputing configurations or basis functions. Instead, the energies for each snapshot are simply multiplied by the ϵ -scaling parameter.

The outline for this study is the following. Section 2 provides details regarding the force fields, simulation set-up, and post-simulation analysis with MBAR. Section 3 provides a comparison of GCMC-MBAR and GCMC-HR as well as various applications of GCMC-MBAR for force field parameterization. Section 4 discusses some limitations and provides recommendations for future work. Section 5 presents the primary conclusions.

2 Methods

2.1 Force fields

The force fields utilized in this study are Transferable Potentials for Phase Equilibria (TraPPE-UA, also referred to simply as TraPPE^{1,22,23}), Potoff,^{3,24} and Nath, Escobedo, and de Pablo revised (NERD). Each force field adopts a united-atom (UA) representation, where non-polar hydrogens are not modeled explicitly. The non-bonded potential is of the generalized Lennard-Jones (Mie λ -6) form.

The bond lengths for the TraPPE, Potoff, and NERD force fields are 0.154 nm for all compounds studied. The same angle and dihedral potentials are used for each force field. Angular bending interactions are evaluated using a harmonic potential:

$$u^{\text{bend}} = \frac{k_{\theta}}{2} (\theta - \theta_0)^2 \quad (1)$$

where u^{bend} is the bending energy, θ is the instantaneous bond angle, θ_0 is the equilibrium bond angle (see Table 1), and k_{θ} is the harmonic force constant with $k_{\theta}/k_{\text{B}} = 62500 \text{ K/rad}^2$ for all bonding angles, where k_{B} is the Boltzmann constant.

Dihedral torsional interactions are determined using a cosine series:

$$u^{\text{tors}} = c_0 + c_1[1 + \cos \phi] + c_2[1 - \cos 2\phi] + c_3[1 + \cos 3\phi] \quad (2)$$

Table 1: Equilibrium bond angles (θ_0).²² CH_i and CH_j represent CH_3 , CH_2 , CH , or C sites.

Bending sites	θ_0 (degrees)
$\text{CH}_i\text{-CH}_2\text{-CH}_j$	114.0
$\text{CH}_i\text{-CH-CH}_j$	112.0
$\text{CH}_i\text{-C-CH}_j$	109.5

where u^{tors} is the torsional energy, ϕ is the dihedral angle and c_n are the Fourier constants listed in Table 2.

Table 2: Fourier constants (c_n/k_B) in units of K.²² CH_i and CH_j represent CH_3 , CH_2 , CH , or C sites.

Torsion sites	c_0/k_B	c_1/k_B	c_2/k_B	c_3/k_B
$\text{CH}_i\text{-CH}_2\text{-CH}_2\text{-CH}_j$	0.0	355.03	-68.19	791.32
$\text{CH}_i\text{-CH}_2\text{-CH-CH}_j$	-251.06	428.73	-111.85	441.27
$\text{CH}_i\text{-CH}_2\text{-C-CH}_j$	0.0	0.0	0.0	461.29
$\text{CH}_i\text{-CH-CH-CH}_j$	-251.06	428.73	-111.85	441.27

Non-bonded interactions between sites located in two different molecules or separated by more than three bonds within the same molecule are calculated using a Mie λ -6 potential (of which the Lennard-Jones, LJ, 12-6 is a subclass):

$$u^{\text{nb}}(\epsilon, \sigma, \lambda; r) = \left(\frac{\lambda}{\lambda - 6} \right) \left(\frac{\lambda}{6} \right)^{\frac{6}{\lambda - 6}} \epsilon \left[\left(\frac{\sigma}{r} \right)^\lambda - \left(\frac{\sigma}{r} \right)^6 \right] \quad (3)$$

where u^{nb} is the van der Waals interaction, σ is the distance (r) where $u^{\text{nb}} = 0$, $-\epsilon$ is the energy of the potential at the minimum (i.e., $u^{\text{nb}} = -\epsilon$ and $\frac{\partial u^{\text{nb}}}{\partial r} = 0$ for $r = r_{\text{min}}$), and λ is the repulsive exponent.

The non-bonded Mie λ -6 force field parameters for TraPPE, Potoff, and NERD are provided in Table 3. Potoff reports a “generalized” and “short/long” (S/L) CH and C parameter set. The “short” and “long” parameters are implemented when the number of

carbons in the backbone is ≤ 4 and > 4 , respectively. Also note that the NERD force field has several different parameter sets for CH_3 sites.

Table 3: Non-bonded (intermolecular) parameters for TraPPE,^{1,22} Potoff,^{3,24} and NERD.²⁵ The “short/long” Potoff CH and C parameters are included in parentheses.

United-atom	ϵ/k_B (K)	σ (nm)	λ	ϵ/k_B (K)	σ (nm)	λ
	TraPPE			Potoff (S/L)		
CH_3	98 (134.5)	0.375 (0.352)	12	121.25	0.3783	16
CH_2	46	0.395	12	61	0.399	16
CH	10	0.468	12	15 (15/14)	0.46 (0.47/0.47)	16
C	0.5	0.640	12	1.2 (1.45/1.2)	0.61 (0.61/0.62)	16
	NERD					
CH_3	104.00	0.3910	12	—	—	—
CH_3 (2-methylpropane)	78.23	0.3880	12	—	—	—
CH_3 (2,2-dimethylpropane)	74.50	0.3910	12	—	—	—
CH_3	104.00	0.3910	12	—	—	—
CH_2	45.80	0.3930	12	—	—	—
CH	39.70	0.3850	12	—	—	—
C	17.00	0.3910	12	—	—	—

Non-bonded parameters between two different site types (i.e., cross-interactions) are determined using Lorentz-Berthelot combining rules²⁶ for ϵ and σ and an arithmetic mean for the repulsive exponent λ (as recommended in Reference 3):

$$\epsilon_{ij} = \sqrt{\epsilon_{ii}\epsilon_{jj}} \quad (4)$$

$$\sigma_{ij} = \frac{\sigma_{ii} + \sigma_{jj}}{2} \quad (5)$$

$$\lambda_{ij} = \frac{\lambda_{ii} + \lambda_{jj}}{2} \quad (6)$$

where the ij subscript refers to cross-interactions and the subscripts ii and jj refer to same-site interactions.

2.2 Simulation set-up

The majority of results presented in Section 3 are obtained by reprocessing simulation output that were analyzed in previous studies utilizing histogram reweighting.^{24,27} New simulation results are provided for *n*-hexane, 2-methylpropane, 2,2-dimethylpropane, 2,2,4-trimethylhexane, 2,3-dimethylbutane, 2,3,4-trimethylpentane, 2,2,3,3-tetramethylbutane, and cyclohexane. All simulations are performed using GPU optimized Monte Carlo (GOMC) with Grand Canonical Monte Carlo (GCMC), where the chemical potential (μ), volume (V), and temperature (T) are constant.

A series of nine simulations are performed, two in the vapor phase, six in the liquid phase, and one near critical which acts as the “bridge” between the vapor and liquid phases. A low-density (less than twenty molecules) initial configuration is utilized for the vapor phase simulations, while the bridge and liquid phase simulations are initialized with a high-density (around 200 molecules) configuration. The system volume is the same for each simulation, but varies somewhat between compounds. The prescribed chemical potentials and temperatures for the branched alkanes are the same as those utilized in Mick et al.²⁴ The $\mu - T$ values for *n*-hexane and cyclohexane are determined in this study. All state points are reported in Supporting Information.

The equilibration stage for each GCMC simulation consists of 2×10^7 Monte Carlo steps (MCS). The production stage is 4×10^7 MCS for vapor simulations and 2.5×10^7 MCS for the liquid and “bridge” simulations. Snapshots (i.e., number of molecules, internal energy, and optionally the xyz coordinates) are stored every 200 MCS to reduce the correlation between sequential configurations. Thus, the total number of snapshots (N_{snaps}) is 2×10^5 for vapor simulations and 1.25×10^5 for liquid and “bridge” simulations. The type of Monte Carlo move implemented for each step is selected randomly with a 20%, 10%, and 70% probability of performing a displacement, rotation, and particle swap move, respectively. The move probabilities are slightly different for cyclohexane, namely,

30%, 10%, 40%, and 20% for displacement, rotation, particle swap, and crank-shaft moves, respectively.

Four different applications for MBAR are demonstrated in this study, where slightly different types of simulation output are required. First, we demonstrate how MBAR yields consistent results to those previously reported using histogram reweighting. The standard simulation output is used in this application, namely, a $2 \times N_{\text{snaps}}$ array containing the number of molecules and the internal energy for all N_{snaps} snapshots. Second, we demonstrate how these same data can be used with MBAR to predict VLE properties when performing ϵ -scaling. Third, we investigate how well MBAR can predict VLE for force field “j” from sampled states of force field “i.” In this case, a $3 \times N_{\text{snaps}}$ array is required, where the additional column is the internal energy computed with force field “j” for the configurations sampled with force field “i.” Fourth, we demonstrate how storing basis functions is a computationally efficient method for predicting VLE for multiple force fields that are unknown at runtime.

2.3 Multistate Bennett Acceptance Ratio

1. Traditionally, histogram reweighting (HR) has been applied with GCMC to calculate vapor-liquid coexistence properties
2. Present histogram reweighting equations
3. Discuss how to compute phase equilibria by equating pressures
4. Discuss how to compute heat of vaporization
5. In this study, we demonstrate how to compute VLE using MBAR-GCMC
6. Procedure is identical to that utilized for HR but using the MBAR equations

7. Present MBAR equations
8. MBAR for $\theta = \theta_{\text{ref}}$ is mathematically equivalent to histogram reweighting in the limit of zero bin width
9. MBAR-GCMC allows for prediction of multiple force fields from single simulation without modifying force fields mid-simulation (i.e., Hamiltonian scaling approach)
10. MBAR uncertainties are computed using bootstrap resampling

2.4 Basis functions

1. When applying MBAR to different parameter sets, $\theta \neq \theta_{\text{ref}}$, it is necessary to recompute energies
2. Basis functions accelerate the recompute energy step by storing the repulsive and attractive contributions that can be scaled by ϵ and σ
3. Basis functions are computed from GOMC using the recompute feature for different ϵ and σ and solving system of equations

3 Results

1. We validate that MBAR and HR are indistinguishable by re-analyzing the simulation results of Mick et al. and Barhaghi et al. utilizing MBAR
2. Epsilon scaling for all the compounds that Mohammad has U and N values for (branched alkanes and alkynes) and which have good experimental data
3. We estimate Potoff generalized and NERD VLE from TraPPE simulations, Potoff S/L from Potoff generalized, and TraPPE from Potoff generalized

4. For $\lambda_{\text{ref}} = 12$ and $\lambda_{\text{rr}} = 16$, MBAR-GCMC predicts vapor density, vapor pressure, and heat of vaporization more accurately than liquid density
5. For $\lambda_{\text{ref}} = 12$ and $\lambda_{\text{rr}} = 12$, i.e., computing NERD from TraPPE simulations, MBAR-GCMC predicts all four properties accurately
6. We present how basis functions allow for rapid computation of wide range of parameter sets:
 - (a) *n*-hexane
 - (b) 2-methylpropane
 - (c) 2,2-dimethylpropane
 - (d) cyclopentane or cyclohexane
7. We provide supporting information with basis functions for several branched alkanes with TraPPE and Potoff force fields

3.1 Figures

1. Percent deviation between MBAR and HR results for ρ_{holiq} , ρ_{hovap} , P_{sat} , and ΔH_v
2. Comparison between MBAR bootstrapping and analytical uncertainties and HR uncertainties
3. Scaling of epsilon post-simulation for branched alkanes and alkynes
4. Prediction of VLE for $\lambda_{\text{ref}} \neq \lambda_{\text{rr}}$
5. Prediction of VLE for $\lambda_{\text{ref}} = \lambda_{\text{rr}} = 12$
6. Prediction of VLE for $\lambda_{\text{ref}} = \lambda_{\text{rr}} = 16$

7. Two-D scans of scoring functions for $\epsilon - \sigma$ of CH3 (a) and CH2 (b) for *n*-hexane
8. Two-D scans of scoring functions for $\epsilon - \sigma$ of CH3 (a) and CH (b) for 2-methylpropane
9. Two-D scans of scoring functions for $\epsilon - \sigma$ of CH3 (a) and C (b) for 2,2-dimethylpropane
10. Two-D scans of scoring functions for $\epsilon - \sigma$ of CH2 for cyclopentane or cyclohexane (reference is TraPPE)

4 Discussion/Limitations/Future work

As ITIC is more reliable at near-triple-point conditions, MBAR-ITIC and MBAR-GCMC can be combined to cover most temperatures that span the vapor-liquid coexistence curve.

1. We recommend that future GCMC-VLE studies report the snapshots of N and U and/or basis functions to recompute U as this allows for future force field optimization
2. Improvements are possible with multiple θ or simulating a range of μ values

5 Conclusions

6 Acknowledgments

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7 Supporting Information

7.1 MBAR VLE estimates

Provide tables of MBAR estimates

7.2 Basis functions

1. Validation that basis functions give accurate energies

7.3 Raw data

1. Comparison of 2-D histograms for TraPPE and Potoff. MBAR overlap, possible?
Probably not without rerunning the simulations.