

# 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 ( $\rho_{rmlq}^{\text{sat}}$ ), saturated vapor density ( $\rho_{rmvap}^{\text{sat}}$ ), saturated vapor pressures ( $P_{rmvap}^{\text{sat}}$ ), and enthalpy of vaporization ( $\Delta H_{rmv}$ ). 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 simulation methods. Due to the abundance of experimental  $\rho_{\text{liq}}^{\text{sat}}$  and  $P_{\text{vap}}^{\text{sat}}$  data and the sensitivity of such properties to both short- and long-range non-bonded interactions, numerous force fields have been parameterized using vapor-liquid coexistence data.

Several methods exist for computing vapor-liquid coexistence properties, e.g., Gibbs Ensemble Monte Carlo (GEMC), two phase molecular dynamics (2 $\phi$ 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, which has enabled GEMC and GCMC to be the primary methods of choice for vapor-liquid coexistence calculations.

Although GCMC-HR has a higher precision than GEMC, GEMC remains a more popular method amongst simulation practitioners. There are at least two potential reasons why GEMC has grown in popularity relative to GCMC-HR. First, GEMC is more straightforward in that, GEMC simulations are performed directly at the desired saturation temperature ( $T^{\text{sat}}$ ). By contrast, GCMC-HR requires a series of GCMC simulations for a sin-

gle  $T^{\text{sat}}$  (although this is also an advantage of GCMC-HR as estimates can be obtained at any  $T^{\text{sat}}$  value without additional simulations). This set includes a near-critical simulation that “bridges” the vapor and liquid phases. Obtaining an initial guess for the chemical potential ( $\mu$ ) of this bridge simulation is a cumbersome and, typically, iterative process, although more advanced methods do exist to obtain a good initial estimate for  $\mu$  (e.g., Hemmen et al.). A likely second reason is that GCMC-HR requires a great deal of 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.” For example, umbrella sampling simulations are often processed using the weighted histogram analysis method (WHAM) to compute free energy differences between states. In addition, Boulougouris et al. demonstrated how histogram reweighting can be applied to GEMC output to estimate saturation properties at non-simulated temperatures (analogous to GCMC-HR).

Although the development of accurate force fields has been greatly enabled by the efficiency of the aforementioned simulation methods (e.g., GEMC, GCMC-HR), parameterization of non-bonded interactions with vapor-liquid coexistence calculations remains an arduous and time-consuming task. Recently, Messerly et al. demonstrated how MBAR coupled with ITIC (MBAR-ITIC) enables rapid force field parameterization by estimating coexistence properties for non-simulated parameter sets.

ITIC requires the internal energy ( $U$ ) and pressure ( $P$ ) (or compressibility factor,  $Z$ ) at numerous temperatures and densities. For MBAR-ITIC, these values are estimated by performing  $NVT$  simulations and reweighting the configurations with MBAR. The results from Messerly et al. demonstrate that MBAR is most reliable in the local domain,

i.e., for parameter sets near the “reference” parameter set from which configurations are sampled. Furthermore, MBAR performs best for changes in the non-bonded well-depth parameter ( $\epsilon$ ) while it performs significantly worse for large changes in the non-bonded size and repulsive parameters ( $\sigma$  and  $\lambda$ , respectively). This is typically referred to as poor “overlap.”

Our hypothesis is that GCMC simulation have better overlap between force field parameter spaces than what was observed for the *NVT* simulations utilized with MBAR-ITIC. There are two main reasons for this hypothesis/aspiration. First, a fixed density (*NVT*) leads to large energy differences for small changes in  $\sigma$  and  $\lambda$ . The fluctuating densities of GCMC simulations should accommodate greater changes in short-range interactions. Second, ITIC requires larger box sizes (and, thereby, more molecules) than those typically utilized with GCMC. By utilizing fewer molecules, GCMC simulations experience larger fluctuations which improves the overlap between states.

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 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),  $\mu$  and  $T$  are not stationary during the simulation, rather the current value of  $\mu$  and  $T$  depends on which force field is being sampled. Despite HS-GCMC proving to be a powerful tool to optimize force field parameters, 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 Hamiltonians need not

be selected prior to the simulations.

Recently, Gross et al. proposed individualized parameter sets for compounds which contain large amounts of experimental data. To avoid overfitting, Gross et al. performed a one-dimensional optimization to scale  $\epsilon$  while not adjusting  $\sigma$  or  $\lambda$ . MBAR is ideally suited for this “ $\epsilon$ -scaling” approach for at least two reasons. First, as mentioned previously, MBAR is most reliable when extrapolating in  $\epsilon$  rather than  $\sigma$  and/or  $\lambda$ . 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,  $\epsilon$ -scaling does not require storing/recomputing configurations or basis functions. Instead, the energies for each snapshot are simply multiplied by the  $\epsilon$ -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.

## 2 Methods

### 2.1 Force fields

1. Simulations are performed for united-atom generalized Lennard-Jones (a.k.a., Mie  $\lambda$ -6) force fields
2. We investigate the TraPPE, Potoff-generalized, Potoff (S/L), and NERD force fields
3. Details of force fields

## 2.2 Simulation set-up

1. Simulations performed by Mick et al. are reanalyzed using MBAR
2. Additional simulations are performed in GCMC ensemble using GPU optimized Monte Carlo (GOMC)
3. Simulation specifications, i.e., box size, number of steps, type of moves, etc.
4. State points (chemical potentials and temperatures) simulated are same as those utilized in Mick et al.

## 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  $\epsilon$  and  $\sigma$
3. Basis functions are computed from GOMC using the recompute feature for different  $\epsilon$  and  $\sigma$  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  $\rho_{\text{holiq}}$ ,  $\rho_{\text{hovap}}$ ,  $P_{\text{sat}}$ , and  $\Delta H_v$
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  $\theta$  or simulating a range of  $\mu$  values

## 5 Conclusions

## 6 Acknowledgments

Mostafa and J. Richard Elliott provided valuable insights.

## 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.