Responses to Reviewer Comments for Manuscript ID: A18.05.0077
Uncertainty quantification confirms unreliable extrapolation toward high pressures for united-atom Mie λ-6 force field
by
Richard A. Messerly, Michael R. Shirts, and Andrei F. Kazakov

Overview

We are grateful for the feedback we received from both reviewers. Specifically, we are encouraged that Reviewer #1 feels that the manuscript is ready for publication. We also appreciate the suggestions and insight provided by Reviewer #2. We have included a response for each of the comments and recommendations that Reviewer #1 and #2 provided. We believe that the review process has strengthened this manuscript and that it is ready to be published. We appreciate your consideration of the revised manuscript for publication in the *Journal of Chemical Physics*.

Itemized List of Changes to Manuscript (Page numbers refer to revised manuscript.)

Response to Reviewer 1, Comment 1: None
Response to Reviewer 1, Comment 2: p 22, Equation 18
Response to Reviewer 2, General Comment: pp 22, 27, Tables I, II, III, V, Figures 1, 2, 4-10, 12
Response to Reviewer 2, Comment 1: p 2
Response to Reviewer 2, Comment 2: p 3
Response to Reviewer 2, Comment 3: p 4
Response to Reviewer 2, Comment 4: p 6
Response to Reviewer 2, Comment 5: p 6
Response to Reviewer 2, Comment 6: p 7
Response to Reviewer 2, Comment 7: p 8
Response to Reviewer 2, Comment 8: pp 9-10
Response to Reviewer 2, Comment 9: p 14
Response to Reviewer 2, Comment 10: p 17
Response to Reviewer 2, Comment 11: p 18
Response to Reviewer 2, Comment 12: p 18
Response to Reviewer 2, Comment 13: p 18
Response to Reviewer 2, Comment 14: p 20
Response to Reviewer 2, Comment 15: p 20
Response to Reviewer 2, Comment 16: pp 20-21, Equations 14 and 15
Response to Reviewer 2, Comment 17: p 21
Response to Reviewer 2, Comment 18: p 22
Response to Reviewer 2, Comment 19: p 22, Equation 18
Response to Reviewer 2, Comment 20: p 23
Response to Reviewer 2, Comment 21: pp 23, 11
Response to Reviewer 2, Comment 22: p 23, Equation 19

Reviewer #1

Recommendation: Optional revisions

General:

The authors present an in-depth study on the capabilities of interaction potential functions to concurrently describe vapor-liquid equilibria (VLE) and supercritical states (SCS). This assessment is laid out in full detail for ethane, for which a particularly accurate fundamental equation of state is available. Seven additional alkanes up to octane are considered in that sense as well.

It is shown that a wide range of force field parameterizations from the literature cannot simultaneously cover VLE and SCS with a high accuracy. More importantly, the authors studied whether any other parameterizations of the generalized λ-6 Mie potential may fulfill this task. Therein, λ stands for the varying (integer) exponent of the repulsive interaction polynomial. For that purpose, the Bayesian inference method was employed, which is a rather new and interesting approach in this field. Based on convincing arguments, it is found that united atom Mie λ-6 potential functions are not sufficient. Instead, other even more general potential functions are required to cover the considered thermodynamic properties in a highly accurate manner.

The paper is also written well and definitively merits publication.

Response

We are pleased that the first reviewer finds our manuscript ready for publication.

Comment #1

On pages 19, 20 and 22, the probability distribution function "Pr( )" is alternatively expressed as "L( )", which makes reading more difficult than necessary.

Response #1

The use of "L()" for likelihood is more common in the literature than "Pr()". One key reason for use of L() is because the various Pr() terms are easily confused (note that the only difference between the posterior and the likelihood is the order of the terms inside the parentheses). For this reason, we did not implement this recommendation.

Comment #2

Because Bayesian inference is rather new in this field, it would be beneficial for the reader when the according section "A. Bayesian Inference" would be extended such that the equations are written down even more explicitly.

Response #2

In accordance with this comment and comment #19 of Reviewer 2, we explicitly express how the likelihood function is computed in Equation 18 on page 22.

Reviewer #2

Recommendation: Revisions

This manuscript considers so-called transferable united atom intermolecular potentials suggested by others in the literature. Such potentials are usually adjusted to vapor-liquid equilibrium (VLE) data. Competing functional forms exist and are in wide use for hydrocarbons. The authors focus on one particularly promising Lennard-Jones type variant with repulsion exponents other than the usual $\lambda=12$ (Mie λ-6 potential).

The authors rightly note that potentials adjusted to VLE data are rarely tested at remote conditions. They also rightly note that molecular simulation has evolved to a point of direct involvement in equation of state (EOS) development, where inclusion of remote conditions are crucial. It is in this context that the unpleasant (for the inventors and proponents of Mie λ-6 transferable potentials) conclusions of this work are important and should be disseminated. The problem at hand is clearly stated. Strategies for solutions appear to be sophisticated. The amount of work committed to reach clear outcomes is large. Existing literature appears to be adequately researched. I do, though, have some comments the authors may wish to consider.

General:

The manuscript is very long. Sections I (Introduction), II (Molecular Dynamics), and III (Case Study) are written in the style of a thesis and can be shortened by tightening the text.

Response:

Although the manuscript is long, in our experience, more complete descriptions of concepts and procedures help the majority of readers better understand the concepts presented. We understand that other people may have different opinions, but we are electing to keep the length approximately the same.

On the contrary, section IV (Uncertainty Quantification) is too brief and confusing for a non-expert in Bayesian inference to grasp the essentials. The text does not flow right. The projected audience of this work is most likely not familiar with the underlying statistics. It would be helpful to stay closer to the problem at hand with more information on what to do with the equations.

Response:

We have attempted to clarify some points in Section IV. See response to comment #19. Also, we have provided more detail regarding the implementation of Bayesian inference (MCMC) than is typical in the literature. Thus, although we do not discuss the theory behind Bayesian inference and MCMC in great detail, we believe our discussion is actually quite helpful for those interested in implementing this methodology.

It appears to me that the authors' "surrogate model" in part B, awkwardly abbreviated "MBAR-ITIC" procedure, results from straightforward application of standard thermodynamic relations. It is not mentioned how the equality of chemical potentials for VLE calculations is incorporated. I also noted that their reference [5] claims that complete fundamental EOS including VLE and critical points can be reliably obtained from not much more molecular simulations than the authors used in this work (around 20). Such a procedure could replace their "surrogate model" altogether for future work. With section V the thesis style returns (see above).

Response:

ITIC is simply a method for predicting VLE; other methods could have been used (though would have required additional development). MBAR-ITIC is the use of MBAR to calculate the properties of ITIC,at different force field parameters than those used in the simulation, thus serving as a "surrogate model" for direct simulation (regardless of whether those simulation use Gibbs Ensemble Monte Carlo, ITIC, or some other VLE method). By contrast, the fundamental EOS in Reference [5] are generated for a single force field. So this procedure cannot be used in replace of our surrogate model. It is more appropriate to refer to the details and derivation of MBAR and ITIC as sufficiently described in the literature because MBAR-ITIC is not the focus of the present manuscript and, as the reviewer has noted, the paper is already somewhat long.

I may have missed it but I cannot see a hint why no results for branched hydrocarbons are shown (supplement?).

Response:

We do not perform a Bayesian analysis for branched hydrocarbons because it was not necessary considering the results for n-alkanes. Specifically, recall that in Figure 5 the force fields were much less accurate for branched alkanes than normal alkanes. Since the Mie potential cannot adequately reproduce VLE and Z for n-alkanes, agreement will only be worse for branched alkanes.

We have included the following on page 27, "As the simulation results of branched alkanes are significantly less accurate than those of n-alkanes for both VLE and high pressure properties (cf. Figures 4 and 5), we do not investigate the uncertainties of CH and C interaction sites."

Figure and table captions should include references and substances.

Response:

We have included references in the captions for Tables I, II, III, and V as well as for Figures 1, 2, 4, 5, 6, 7, 8, 9, and 12. We have also included substances in the captions for Figures 1, 8, 10, and 12.

Comment #1

Page 2, 2nd paragraph: "...most studies..." implies a wealth of studies using hybrid data set. In fact, such a methodology is very rare.

Response #1

We have changed this to "several recent studies."

Comment #2

Page 3, 3rd paragraph: "Note that..., so that..." The sentence is confusing.

Response #2

We agree that this sentence is confusing. Upon review, the meaning is clear without this sentence, so it has been removed.

Comment #3

Page 4, 1st paragraph: "...global minimum..." In what?

Response #3

The global minimum in the objective function used to optimize the force field parameters. We have reworded this sentence to read, "Although an AA force field should, in principle, be able to yield more accurate VLE

results, it is much easier to locate the ``true'' optimal parameter set for UA and AUA force fields since fewer (highly correlated) parameters are optimized simultaneously."

Comment #4

Page 6, 2nd paragraph: What is "...effective size...", "...true λ..."?

Response #4

To clarify this discussion, we have modified these sentences significantly by removing "effective size" and "true λ". They now read, "Instead, only the region that is most sensitive to the target experimental data will be adequately represented. For example, high pressure properties are sensitive to extremely close-range interactions ($r < 0.8\sigma$), while such distances are rarely sampled with VLE simulations and, thereby, do not impact VLE properties. Furthermore, the ``optimal'' $\lambda$ is an ``effective optimal'' as it accounts for numerous model assumptions,"

Comment #5

Page 6, 3rd paragraph: "...difficult to know..." What does that mean?

Response #5

The purpose of this statement is that theoretical results for noble gases and all-atom models may not apply to united-atom alkanes. To clarify this, we have modified this sentence to read, "Although the theoretical results discussed previously for noble gases and all-atom n-alkane models are not necessarily applicable to UA models for normal and branched alkanes…"

Comment #6

Page 7, 4th paragraph: What is "...time constant of 1 ps...", "...LINCS..."?

Response #6

For completeness, we have modified this to read, "thermostat time constant…" and have defined LINCS as "LINear Constraint Solver (LINCS)." We have also included the references for the thermostat and LINCS, in addition to the GROMACS manual reference.

Comment #7

Page 8, 2nd paragraph: "Nine densities..." The sentence is confusing.

Response #7

To make this less confusing, we have rewritten these sentences as, "Nine densities are simulated along the supercritical isotherm (T^{IT}). Three temperatures are simulated along each isochore, namely, T^{IT}, the REFPROP saturation temperature (T^{sat}), and $2/(1/T^{IT} + 1/T^{sat})$. Since five of the isotherm densities correspond to the five different ρ^{IC} values, a total of 19 simulations are performed for each compound and force field."

Comment #8

Page 9, 3rd paragraph: "...have a displacement in the interaction...", "...anisotropic shift..." Are those the same?

Response #8

Yes these are the same thing. The text now consistently uses the term "displacement" throughout.

Comment #9

Page 14, 2nd paragraph: "...(given for ρ)..." Does this mean "uncertainty in ρ" or "uncertainty for given ρ"?

Response #9

Uncertainty in ρ. This now reads, "REFPROP uncertainty for ρ is …"

Comment #10

Page 17, 4th paragraph: "...It seems logical..." The sentence is pure speculation.

Response #10

The reviewer is correct, and we have removed this sentence altogether.

Comment #11

Page 17, 5th paragraph: "...anisotropic displacement..." Be consistent, see page 9.

Response #11

See Response #8.

Comment #12

Page 18, 1st paragraph: "...could demonstrate the proper trend..." The sentence is confusing.

Response #12

We have removed the parenthetical clause that we assume was the source of confusion.

Comment #13

Page 18, 4th paragraph: "...rigorous approach...adequate..." That does not belong together.

Response #13

This sentence now reads, "Bayesian inference is a rigorous approach to determine all feasible $\epsilon, \sigma,$ and λ parameter sets."

Comment #14

Page 20, 1st paragraph: "...should each be interpreted as an array..." The sentence is confusing, expand.

Response #14

Changed to "are arrays of…"

Comment #15

Page 20, 2nd paragraph: "The advantage of this assumption..." Is the assumption the uniform prior?

Response #15

Yes. This now reads, "One advantage of using a uniform prior is that …"

Comment #16

Page 20, equations (14) and (15): Partial differentials are incorrect (typo).

Response #16

We have replaced partial differentials with total differentials.

Comment #17

Page 21, equation (16): Is the "proposal function" Q an arbitrary trial distribution? The acceptance rate is said to be "tuned" by parameters of this distribution. I would think that the acceptance rate is adjusted by some sized Δε and Δσ. Why am I wrong?

Response #17

The tuning parameters are the standard deviations (or variance, s_ϵ^2 and s_σ^2) in the proposal function, which determines the random displacements, $\Delta\epsilon$ and $\Delta\sigma$. To clarify this point, this section now reads, "the amount to which ϵ and σ is varied for each MCMC step (the difference between ϵ_{i+1} and ϵ_i or between σ_{i+1} and σ_i) depends on Q, specifically, on s_ϵ^2 and s_σ^2. These parameters (s_ϵ^2 and s_σ^2) are tuned such that approximately 1/3 of the moves are accepted, i.e. s_ϵ^2 and s_σ^2 are decreased if the acceptance rate of MCMC moves is less than 1/3, and vice versa."

Comment #18

Page 21, 3rd paragraph: "The joint distribution...provide an estimate of the uncertainty..." Expand on the statement.

Response #18

The original wording was likely unclear, because the joint distribution IS the estimate of uncertainty as it provides the range of feasible epsilon and sigma parameters. We have reworded this slightly as, "The joint distribution… quantifies the uncertainty…"

Comment #19

Page 22, 2nd paragraph: "The likelihood...is calculated from a normal distribution..." Do you mean L=exp(...)? If so, present the equation and remind the reader how sD,SM is to be computed.

Response #19

We have included Equation 18 on page 22 to explicitly state how the likelihood is computed, along with more details regarding how to compute $s^2_{D,SM}$.

Comment #20

Page 23, 1st paragraph: "Ensemble average..." What is the ensemble? What are "...effective samples"?

Response #20

The NVT ensemble. We have included "NVT" before "ensemble average."

Effective samples are the number of configurations that have a non-zero (or, at least, not near zero) weight. The point is that MBAR is exact when used within a certain region of parameter space, which is characterized by the number of effective samples. However, since we never discuss effective samples in this study, we have reworded this to read, "MBAR is a nearly exact surrogate model when a sufficient number of configurations

sampled by θ_{ref} are similar to those that would be sampled with direct simulation of θ, which can be easily verified by statistical measures (see discussion on number of effective samples in Reference [44])."

Comment #21

Page 23, 2nd paragraph: The use of "departure" energy for residual energy is very unusual. This is actually corrected on page 35, 3rd paragraph.

Response #21

No change was made with the terminology because "departure function" is a standard term in thermodynamics (compare https://en.wikipedia.org/wiki/Departure_function and https://en.wikipedia.org/wiki/Residual_property_(physics)). We use "departure" to be consistent with our other ITIC publications. As "residual" is used in the hybrid data set studies, we adopt the "residual" term briefly on page 35. Also, to avoid confusion, we have defined departure energy more clearly on page 23.

Comment #22

Page 23, equation (18): Partial differentials are incorrect (typo).

Response #22

We have replaced partial differentials with total differentials (now Equation 19).

Comment #23

Page 24, 2nd paragraph: "...is linear with respect to r-6 ...implement basis functions..." I do not understand the sentence. Is reference made to conformal interactions?

Response #23

We removed the first half of this sentence that discusses "linear with respect to…" since this is superfluous. Also, as we do not discuss "basis functions" anywhere else in the text, we have described this process in more detail. This sentence on page 25 now reads, "The non-bonded energies and forces, which are required for MBAR and ITIC, are rapidly recomputed post-simulation with θ_{MCMC} for each reference configuration (for details on so-called ``basis functions'' see Reference…).

Comment #24

Page 25, 1st paragraph: "...inter-laboratory comparison..." The sentence is confusing.

Response #24

We have attempted to clarify what dark uncertainty means by adding the following explanation, "…s^2_{SM} accounts for ``dark uncertainty'', i.e., uncertainties that arise from unknown sources which can lead to unresolvable discrepancies between research groups." (see page 26)

Comment #25

Page 25, 2nd paragraph: "...experimental uncertainty (uD).." Is uD different from sD?

Response #25

The difference is that u_D is the uncertainty at the 95% confidence level, so it is approximately 2 times s_D. This is now explained with, "(u_D, at the 95% confidence level)" on page 26.

Comment #26

Page 29, 2nd paragraph: "...4 and 40 factors larger..." Maybe "4 and 40 times larger" is better.

Response #26

Change made (now on page 30).

Comment #27

Page 31, 2nd paragraph: Rewrite the strange fraction.

Response #27

We list all four possible fractions explicitly (now on page 32).

Comment #28

Page 35, equation (24): The use of variables x,y for orders of derivatives is disturbing. I suggest common practice to use integers i to n. See also remark on page 23.

Response #28

The choice of x,y and partial differentials is to be consistent with the terminology in the cited hybrid data set studies. To avoid confusion, we have clearly defined on page 36 that "x and y are integer values and the derivative is of order x+y." We have also modified the indices in Tables II and III on page 11 from CH_x and CH_y to CH_i and CH_j.

Comment #29

References: There appear to be inconsistencies in reference styles.

Response #29

We found two main inconsistencies. First, some references included the month of publication. We have removed all months of publication. Second, some authors have their full name listed while others have only their initials. We tried to remedy this by utilizing \bibliographystyle{abbrv} and \bilbiographystyle{ieeetr}, but each of these introduced additional undesirable issues. We will work with the JCP proofs editor to resolve this at the galley stage.