We would like to clarify the MBAR-ITIC procedure.

While MBAR-ITIC is simply a tool that was the focus of a previous publ

We also

We would like to note that MBAR-ITIC is simply a means to an end, and is not the true focus of the present manuscript. However, we would like to clarify two points. First, ITIC

MBAR-ITIC is a surrogate model for predicting VLE for different force field parameters than those used in the simulation. By contrast, the fundamental EOS in Reference [5] are generated for a single force field. So this procedure cannot “replace” our surrogate model.

Report on manuscript A18.05.0077:

"Uncertainty quantification confirms unreliable extrapolation toward high pressures for united-

atom Mie λ-6 force field" by Messerly, Shirts and Kazakov.

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 λ=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.

Some general comments

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.

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.

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). I may have missed it but I cannot see a hint

why no results for branched hydrocarbons are shown (supplement?). Figure and table captions

should include references and substances.

Some random specific comments

Page 2, 2nd paragraph: “...most studies...” implies a wealth of studies using hybrid data set. In

fact, such a methodology is very rare.

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

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

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

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

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

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

Page 9, 3rd paragraph: “...have a displacement in the interaction...”, “...anisotropic shift...” Are

those the same?

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

for given ρ”?

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

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

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

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

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

expand.

Page 20, 2nd paragraph: “The advantage of this assumption...” Is the assumption the uniform

prior?

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

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?

Page 21, 3rd paragraph: “The joint distribution...provide an estimate of the uncertainty...”

Expand on the statement.

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.

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

samples”?

Page 23, 2nd paragraph: The use of “departure” energy for residual energy is very unusual. This

is actually corrected on page 35, 3rd paragraph.

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

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?

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

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

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

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

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.

References: There appear to be inconsistencies in reference styles.

Summary:

Much of the work on transferable interaction potentials is published in Chemistry and Physics

journals including the Journal of Chemical Physics. I find dissemination of the authors’ findings

about those potentials in the Journal of Chemical Physics adequate. Subject to consideration of

above comments, I recommend publication.