Rich’s comments

Comments to the authors :

===================

The comments below address the points listed in the previous report.

**1. Introduction**

1.1 A fair account of earlier work on integration methods should mention that various integration methods have allowed to extend VLE simulations much below the normal boiling point (references 8, 10, 52, 60, 62). The answer appears insufficient.

This is not really what their original comment 1.1 stated. Previously they just pointed out that we need to be able to go to the triple point (which could be Tr = 0.3). The VLE simulation literature was never even mentioned, neither was the normal boiling point.

That being said, we need to respond to this new concern somehow.

1.2 Coexistence properties from Gibbs Duhem integration : OK with the answer

1.3 Comparison with earlier VLE prediction on n-dodecane : the revised version is changed but it does not comment the similar performance of GDI and ITIC in terms of accessible temperature range for this compound. The answer is acceptable but can be improved.

This is a valid point and it might help answer comment 1.1 as well. I think we need to point out (either in the introduction or the results section) that the GDI literature values are available over a similar temperature range.

**2. Theory**

2.1 Figure 1 does not show the case when saturation temperature is unknown. The revised version is indicating that the Figure 1 relates to the specific case of known saturation temperature (or accurate estimate). Adding the case of a “rare aromatic molecule” (i.e. 1-napthalenyl, 4 phenanthrenyl butane) is fine, but the initialization has benefited from earlier GEMC results from ref 62. Neither precise values of Tsat estimated nor result tables are provided for this compound. The answer is acceptable but can be improved.

Should we modify Figure 1 so that it reads “Estimated two-phase region?” If so, we would want to move points 11, 13, 15, 17, and 19 back onto the black line. Alternatively, could we show that these points have uncertainty (error bars)? We would want to remove the blue lines so that we can see clearly the error bars.

The point about our initialization benefiting from earlier GEMC results from ref 62 is NOT true. From my understanding, ref 62 just provided the force field parameters. I think the reviewer is confusing our GEMC results with literature values. We need to clarify in the manuscript and to the reviewer that the GEMC results in Figure 12 were obtained in this study for comparison with our ITIC values.

The reviewer makes a valid point that we need to report the ITIC results for the rare aromatic molecule.

2.2 Ambiguity of equation 8 . Using the same notations Adep(T,V) = (A(T,V)-AIG(T,V))/RT and Udep(T,V) = (U(T,V)-UIG(T,V))/RT as in the manuscript, equation (8) should be written :

𝐴𝑑𝑒𝑝(𝑇𝑠𝑎𝑡,𝑉)/𝑇𝑠𝑎𝑡−𝐴𝑑𝑒𝑝(𝑇𝐼𝑇,𝑉)/𝑇𝐼𝑇=∫𝑈𝑑𝑒𝑝 (𝑇,𝑉) 𝑑(1/𝑇)𝑇𝑠𝑎𝑡𝑇𝐼𝑇 (8, corrected)

The authors seem to confuse the dummy variable *T* with the end points (𝑇𝐼𝐶,𝑇𝑠𝑎𝑡) of the interval over which integration proceeds. The ambiguity may explain the error in equation (17) mentioned in point 2.3 below. The answer is clearly insufficient.

The reviewer’s concern is valid in that our notation is unclear. We need to improve our derivation.

2.3 Uncorrected error in equation (17)

The constant volume V will be dropped for simplicity in the next equations of this review:

The true mathematical integration of equation (8, corrected) at constant volume yields :

𝐴𝑛𝑒𝑤𝑑𝑒𝑝𝑇𝑛𝑒𝑤𝑠𝑎𝑡⁄−𝐴𝑜𝑙𝑑𝑑𝑒𝑝𝑇𝑜𝑙𝑑𝑠𝑎𝑡⁄=∫𝑈𝑑𝑒𝑝 (𝑇) 𝑑(1𝑇⁄)𝑇𝑛𝑒𝑤𝑠𝑎𝑡𝑇𝑜𝑙𝑑𝑠𝑎𝑡

For small variations of *Tsat* we may consider as a first order approximation that the derivative as constant, thus we get : 𝐴𝑛𝑒𝑤𝑑𝑒𝑝𝑇𝑛𝑒𝑤𝑠𝑎𝑡⁄−𝐴𝑜𝑙𝑑𝑑𝑒𝑝𝑇𝑜𝑙𝑑𝑠𝑎𝑡⁄≈𝑈𝑜𝑙𝑑𝑑𝑒𝑝 (1𝑇𝑛𝑒𝑤𝑠𝑎𝑡⁄−1𝑇𝑜𝑙𝑑𝑠𝑎𝑡⁄)

Or 𝐴𝑛𝑒𝑤𝑑𝑒𝑝= 𝐴𝑜𝑙𝑑𝑑𝑒𝑝 𝑇𝑛𝑒𝑤𝑠𝑎𝑡𝑇𝑜𝑙𝑑𝑠𝑎𝑡⁄ + 𝑈𝑜𝑙𝑑𝑑𝑒𝑝 (1−𝑇𝑛𝑒𝑤𝑠𝑎𝑡𝑇𝑜𝑙𝑑𝑠𝑎𝑡⁄)

Comparing with equation (17) of the original text (unchanged in the revised version), it seems that the authors have omitted the factor 𝑇𝑛𝑒𝑤𝑠𝑎𝑡/𝑇𝑜𝑙𝑑𝑠𝑎𝑡 of 𝐴𝑜𝑙𝑑𝑑𝑒𝑝 in the right hand side of this equation. This is a serious flaw that may explains that the convergence of the ITIC method as presented in this article is decreasing when initializing Tsat far away (Figure 8).

In explaining how they obtained equation (17) the authors refer to the linear dependence of TUdep as varying linearly with 1/T.. They do not discuss specifically this point in the main text, but let us take it for granted, as it may be a better approximation than considering Udep constant. The linear dependence of TUdep vs 1/T implies that there are two constants a and b such that :

TUdep= a + b/T

or equivalently

Udep=b/T + a/T2

Then, using the equation (8,corrected) we get through exact integration : ∫𝑈𝑑𝑒𝑝 (𝑇) 𝑑(1𝑇⁄)𝑇𝑛𝑒𝑤𝑇𝑜𝑙𝑑=∫(𝑎𝑇+𝑏/𝑇2) ( 𝑑(1𝑇⁄))𝑇𝑛𝑒𝑤𝑇𝑜𝑙𝑑

∫𝑈𝑑𝑒𝑝 (𝑇) 𝑑(1𝑇⁄)𝑇𝑛𝑒𝑤𝑇𝑜𝑙𝑑=𝑎2(1(𝑇𝑛𝑒𝑤𝑠𝑎𝑡)2⁄−1(𝑇𝑜𝑙𝑑𝑠𝑎𝑡)2⁄)+𝑏3(1(𝑇𝑛𝑒𝑤𝑠𝑎𝑡)3⁄−1(𝑇𝑜𝑙𝑑𝑠𝑎𝑡)3⁄)

This expression does not match the proposed equation (17), and the problem of having dropped the factor 𝑇𝑛𝑒𝑤𝑠𝑎𝑡/𝑇𝑜𝑙𝑑𝑠𝑎𝑡 of 𝐴𝑜𝑙𝑑𝑑𝑒𝑝 remains unsolved. It is likely that the confusion between dummy variables and interval end points in equation (8) has caused some errors in deriving equation (17) in the initial ITIC method. The answer of the authors (no changes except a short additional sentence in text) appears insufficient.

Again, the reviewer’s concerns are valid. We need to improve our derivation.

2.4 (blank item, the referee apologizes for this numbering error in previous report)

2.5 Correlation of saturation pressure and acentric factor : the revised version makes use of Antoine’s law to correlate vapor pressure (equation 27) , and it does no more refer to Lee Kesler’s method to evaluate the acentric factor. This improves the consistency of the ITIC method. The answer is OK.

**3. ITIC validation**

3.1 provide initial estimates used for Tsat for dodecane in Tables : OK with the answer

3.2 Sensitivity of VLE results to the virial coefficients : I understand from the reply and added text that the sensitivity to virial coefficients is low. The answer appears OK

3.3 Show the influence of initializing Tsat far away from the final solution : the graph showing the successive iterations for dodecane in Supplementary material in a modified figure 3b is OK. Good point. Answer is OK.

3.4 In Figure 6, how is it possible that round Tsat values are imposed ? The proposed modification of figure 6 with added explanation appears reasonable. Answer is OK

3.5 In Figure 7 the final Psat obtained by ITIC depends on the initialization. It is OK that the errors are low, but if the iterative method is well designed the deviations should not increase when initializing far away from the final solution. The example selected here, n-dodecane, is a well-known compound for which REFPROP is reliable, but small convergence issues might have larger impact on more complex molecules. Answer is acceptable, but can be improved.

I think the reviewer is again confusing the different iterative steps. Figure 7 does not iteratively improve the Tsat\_est values by computing Z at the new Tsat value (i.e., no new “simulations” are performed). So it is completely normal that the deviations will increase when the initial Tsat\_est is far away from the final value. We need to clarify that the only iterations are for solving the ITIC equations.

3.6 Accuracy limited to 0.1% : mentioned in section 2.3. OK with the answer.

**4. Simulation details**

4.1 It is surprising to read that “the MC method with fixed bond lengths is favored due to lower fluctuations at low density”. In the revised manuscript “fluctuations” is replaced by “uncertainties” which is more correct. However this is applies also to MC with variable bond lengths, as the TraPPE-UA extension of reference 62. Answer acceptable, but can be improved.

I have no idea what the reviewer is trying to convey with “this applies also to MC with variable bond lengths…” Any ideas? Although ref 62 does use variable bond lengths, I think we used fixed bonds for any compound that we simulated with the TraPPE-UA extension. Is that correct?

4.2 is it possible to apply the ITIC method at imposed Tsat = 0.65, 0.75 and 0.85 in reduced units ? The sentence has been reformulated. Answer is OK.

I think we still need to modify the sentence to say “approximately,” i.e., the sentence should read, “compared with the ITIC coexistence points obtained at liquid densities corresponding to reduced temperatures of approximately 0.65, 0.75, and 0.85.”

4.3 …computation time required by successive iterations on saturation temperature in ITIC. Explanation provided in section 2.3 of the revised version. Answer is OK.

4.4 misleading statement “for reduced temperatures of 0.45 and 0.55 … GEMC is not feasible for n-dodecane” . The revised version includes a statement that GEMC + GDI is also able to provide low temperature VLE data. However this referee maintains that it would be fair to compare ITIC, which is basically an integration method, with other state-of the art integration methods. Among the references cited by the authors, there are at least five articles applying integration methods to VLE properties or to forcefield parametrization at low reduced temperatures (references 8, 10, 52, 60, 62). Answer is acceptable, but can be improved.

Although the reviewer is letting this pass, are we satisfied? Do we need to do a better job representing the literature integration methods and how they have been applied?

4.5 Initialization of NVT simulations of the liquid phase . The revised version is pointing to Packmol when GOMC or LAMMPS is used and to Cassandra and GROMACS internal initialization features. This referee regrets that no detail is given on these features (e.g. how to avoid internetted cycles, applicability at low reduced temperature). Answer is acceptable, but can be improved.

I do not think we need to worry about all these details. Basically, if you can build the box you can run ITIC. There are lots of well-known tricks for building boxes at high densities for complex structures, we do not need to reinvent the wheel here.

**5 Calculation of virial coefficients**

**6. Finite size effects**

6.1 Figure 9 , divergence of the pressure determination in the zero density limit when the molecule has internal degrees of freedom. The revised version explains that in MD, intermolecular collisions may not be sufficiently frequent to equilibrate all degrees of freedom, and provides an additional figure in Supplementary material. Section title is changed, which is a good point. Answer is OK.

I think we should actually make Section 6 a subsection for Section 5, i.e., change Section 6 to Section 5.1 (or 5.2 if we change what is currently in Section 5 into Section 5.1). The reason being that both Sections 5 and 6 are about calculating virial coefficients. Section 5 focuses on the approach and derivation, while Section 6 focuses on obtaining good simulation results at low densities in order to obtain good virials.

6.2 Finite size effects on the compressibility factor Z and on the internal energy U for dense (liquid) phases. The revised version mentions finite size effects for ethane and acknowledges the need for further investigation. Answer is OK.

**Section VII Example simulations**

7.1 : Figures 10 and 11 : mention Tsat initialization of ITIC for methane, ethane, isobutane , isohexane, dodecane and TIP4P/2005 examples. The revised version indicates that initialization is performed with DIPPR data (reference 46). Answer is OK.

7.2 Figure 11 : compare with dodecane results GEMC + TI using TraPPE-UA [ Ungerer et al. , JCP, 112, (2000), 5499] . In the revised version these results are added in Figure 11. Answer is OK.

**Section 8. Conclusions**

8.1 application range of GEMC + TI versus ITIC methods in terms of reduced temperatures. In the revised version the computational load of ITIC is compared to GEMC or with GEMC + TI, which is fine. However the question raised by this referee in pint 8.1 was rather about the application range : is ITIC able to predict VLE down to Tr=0.3, as required for applications ? This point should be addressed in the conclusion. Answer is acceptable, but can be improved.

To finally put this whole Tr=0.3 thing to bed, can we just apply ITIC to a compound where the triple point is around 0.3? For example, ethane has a reduced triple point temperature of 0.296. Of course, we might run into the challenge that the triple point for the force field is considerably higher than the triple point for the real compound, such that we are in the solid phase at these low temperatures.

Is there a simpler way to prove that we can use ITIC at 0.3? For example, by using the REFPROP data instead of simulations. Unfortunately, the example compound for REFPROP (n-dodecane) has a reduced triple point temperature of 0.4, so it is not a satisfactory candidate. But would it be sufficient to analyze ethane using REFPROP data?

I think that simulating TraPPE-C2 near the triple point (90 K) would satisfy the reviewer. We would then need include this in Figures 10 and 11 and also point it out in the results discussion.

8.2 The authors may insist on ITIC advantage = it avoids the implementation of transfer moves in GEMC or GCMC. The revised text refers to the low acceptance of these moves. Answer is OK.

Reviewer #3: The authors have made revisions to address some of the  
concerns raised in my first review, but several of the issues remain  
unresolved and my second look through the manuscript has revealed  
additional issues that need to be fixed before publishing.  
  
Comment #6  
Please also note that the derivation seems to switch back and forth  
between k\_B (Boltzmann's contant, please include subscript B) in eq.  
4, 5, 6 and 7 and R in eq. 2, 3, 8 and following.  Please choose one  
or the other.

This is a valid point. Since we primarily focus on molar quantities, I think we should use R. Plus I think we defined U, A as molar quantities, so Equation 4-7 should not use k to begin with.  
  
The RHS of equation 8 is now a definite integral (great), but it's  
still wrong because the temperature of the LHS is not indicated.  In  
fact, the LHS is a difference in free energy between T^sat and T^IT.  
  
Even with the "single molecule" handling of the ideal gas energy, I'm  
still concerned that the derivation is incorrect.  The errors are  
masked by the confusing approach taken and sloppiness like the LHS of  
eq. 8.  This is repeated in Eq. 10 and 12.  Eq. 10 does not yield  
beta(A\_liq-A\_ig), but rather  
  
beta Aex(rho\_liq,T^sat) - beta Aex(rho=0,T^IT))  
  
Eq. 12 does not yield beta(A\_vap-A\_ig), but rather  
  
beta Aex(rho\_vap,T^sat) - beta Aex(rho=0,T^sat))  
  
Given that the reference free energies are for different temperatures,  
they will not cancel when substituted into eq. 3.

Both reviewers express this concern regarding the derivation.  
  
Please do a proper derivation.  The derivation would be simpler (and  
less confusing and prone to error) if absolute free energies are  
obtained and used in eq. 1.  I suspect that in the end, no measurement  
of ideal gas potential energy will be needed.  
  
If the ideal gas potential energy is still needed, then complexity of  
the single molecule method seems to be overstated.  First, the authors  
do not state what is so bad about using Nose-Hoover for a  
single-molecule simulation.  Second, most molecular dynamics implement  
thermostats beyond Nose-Hoover (is a Nose-Hoover chains thermostat  
sufficient?).  The Langevin thermostat is a common choice and is  
specifically implemented in LAMMPS.

We don’t really need to state why Nose-Hoover is not good for a single molecule, since we are citing the literature. But I will make this a little more clear.

The reviewer is correct that Nose-Hoover chains would solve this problem and are quite common.

I intended for “stochastic dynamics” to include Langevin dynamics, but I will make this more explicit. Essentially, we just want to clarify that single molecule MD can yield bad results if you are not careful.   
  
Comment #7  
Concerning solving eq. 14, I don't see how you can solve eq. 14 by  
itself because it has more than one unknown -- vapor density and Tsat  
(which determine Zliq, B2 and B3).  These are handled by using 14-17,  
but as it is described in section 2.2, eq 14 (and 15) can be solved  
directly.

Again, we need to make it very clear that Eq 14 is solved for rhovap at a given Tsat. After the values of Tsat are updated then Eq 14 is solved again.  
  
To add to the confusion, in section 2.3, the manuscript states "First,  
rho\_vap and Z\_liq are set to an initial near-zero value."  Is this an  
explanation of how to solve eq. 14?  Why is it in section 2.3?

Is the reviewer correct? The initial near-zero value is used as an initial guess to solve eq 14, but it is also used as an initial guess for Tsat (by interpolating Z vs 1/T), correct?   
  
Comment #16  
I'm not sure how the authors' comments address the point.  The source  
of the dashed line is irrelevant.  The error bars on the symbols in  
figure 8a are too large.

Try to point out that the reviewer’s original comment stated that “the fitted lines go right through most of the points.” Our response was that these lines are actually not fitted to the data, so they are not evidence for the error bars being too large since the error bars are computed independently.

That being said, the reviewer might have a point that the error bars are too large. For example, shouldn’t the error bars for Tr=1.2 in Figure 8a be of a similar magnitude to those in Figure 9c? Aren’t they computed using similar methods?

If we determine that the Figure 8a error bars are correct, we just need to satisfy the reviewer by stating that we verified that our calculations were correct. And then we should provide some explanation for why they are so large (maybe we only had a few replicates so the 95% confidence interval is quite large).   
  
Comment #17  
I don't see how the modifications in section 6 resolves the original  
issue. The manuscript still indicates that larger systems yield  
smaller uncertainties ("we need 3200 ethane molecules to achieve low  
enough uncertainties").

True, I also thought we modified this sentence to make it more clear that this statement only applies to MD rigid?  
  
Furthermore, I must express additional confusion about the N=1600 data  
in Fig 9a, which was previously the least precise (despite being the  
next-to-largest system size) and now have smaller error bars, but are  
still much less precise than any other system size.  Why is the N=1600  
data so imprecise?

This is quite bizarre. Any explanation?  
  
Comment #18  
It is good that the authors ran longer simulations and determined that  
issues in Fig 9b are not due to equilibration, but, sadly enough, the  
manuscript still blames equilibration:  
  
"due to the small number of intermolecular collisions at low density  
relative to the large number of intramolecular collisions, inhibiting  
the equilibration of the various components of momentum."  
  
Did the longer simulations give any indications that equilibration was  
an issue or not?  If not, then the manuscript cannot continue to say  
that it was.

Did we not mean “equilibration”, but rather “equipartition” or maybe “proper sampling?” The reviewer really doesn’t want us to use the term equilibration, since this suggests that our simulations were simply not long enough or not equilibrated. But I think what we are saying is that the simulation is actually equilibrated but the production output is still not reliable.   
  
I am even more confused as to why the compressibility factor (based on  
the total virial) reported in Fig 15 of the Supplementary Material  
goes to 0 (and not 1) and why the bonded contributions go to -1.  Is  
this Z-1 and not Z?

True, this is strange that we say Z goes to -1. Are we actually plotting the virials, such that the virials going to -1 would be a Z going to 1? We need to figure this out and modify the plot, if necessary.  
  
Comment #20  
If the error bars can't be added to figure 10, then some description  
of how big they would still be helpful.  Are they smaller than the  
symbol size (it looks like they might be in many cases)?  Where they  
disagree with GEMC/GCMC, is it due to uncertainty or systematic  
deviation?

Could we include the larger error bars? Would most be smaller than the symbol size?

I think we should make the y-range for Figure 10b from -3 to 3 (the y-region of 3 to 6 is not very useful since only one data point is found there).

As a side note, why don’t we ever compare enthalpy of vaporization? We could make Figure 10 a 2x2 plot with the fourth panel for DeltaHv. I am fine not including it in Figure 11 (since these are in the supporting information), but I think people might want to see the comparison with the literature DeltaHv values.   
  
If the conclusions are referring to using REFPROP as input, then it  
should say so.  "In the absence of simulation uncertainty" is an  
inadequate indication of this.

I don’t think all of the conclusions are referring to REFPROP values. We just need to make it clear when we are referring to REFPROP as input. I think it would be helpful to include a statement like, “The REFPROP validation provides a lower bound for the expected uncertainty in the ITIC estimates with molecular simulation.”