Comment on “Can existing models quantitatively describe the mixing behavior of acetone with water” [J. Chem. Phys. 130, 124516 (2009)]

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In 2003 one of us published a relatively simple force field (KBFF) for the simulation of acetone (*a*) and water (*w*) mixtures.¹ This force field was developed in an attempt to reproduce the experimentally obtained Kirkwood–Buff (KB) integrals, representative of the molecular distributions, as a function of composition. Subsequently, this and several other force fields for acetone mixtures were tested and critically evaluated using Monte Carlo simulations.² Even though exact agreement with experiment was not observed for all the KB integrals, even for the KBFF model, it was found that only the KBFF model was miscible with water. Recently, Jedlovsky *et al.*³ have questioned that the KBFF model indeed mixes with SPC/E water below acetone mole fractions (x_a) of 0.28. This is a surprising claim considering the two previously published studies and prompted this comment.

It should be noted that immiscibility is often difficult to determine from computer simulations. In favorable cases immiscibility is obvious from examination of the atomic configurations. Unfortunately, micro immiscibility may be present which is difficult to detect visually, or by examining the distribution functions. Thermodynamically, however, the stability of the solution can be determined from the value of $D = \beta d\mu_a/d \ln x_a$ —which must be positive for mixing to occur.⁴ Jedlovsky *et al.* determined the Helmholtz free energy of acetone and water mixtures between $x_a=0$ –0.26 using thermodynamic integration (TI), which indicated solution instability (demixing) in this region and contradicts the previous studies. In our opinion, this conclusion is questionable for the following reasons.

The solution stability can be tested using the KB integrals obtained from the simulations. The KB integrals can be used to evaluate D , which is provided by $1+f_{aa}$ in the notation of Ref. 1. This involves no approximations. Jedlovsky *et al.* determined D by performing TI calculations on the mixtures to obtain the excess Helmholtz free energy. This data was then fitted using the Margules equation and the values of D obtained from the second derivative of this fitting function. In our opinion, this process, while formally correct, can be challenging in practice. In particular, computing excess free energies or chemical potentials in liquid mixtures using TI is difficult.⁵ It is much easier to integrate a set of distribution functions to give the KB integrals, and then combine these to provide D . The only issue lies in the convergence of the KB integrals. We have performed additional simulations of acetone and water mixtures ($x_a=0.10$ and 0.26) using larger simulation volumes and longer simulation times to precisely determine the KB integrals (see Table I) and eliminate system size effects and convergence issues. The values of the KB integrals and D obtained after 5 ns of simulation are essentially the same as those obtained previously in two different studies.^{1,2} For both mixtures we find positive values for D , in good agreement with experiment and our previous results (Fig. 4 of Ref. 1), but noticeably different from the result obtained by Jedlovsky *et al.*³ of -0.4 at $x_a=0.1$ and 0.0 at $x_a=0.26$. It seems clear from the previous and present results that our mixtures are thermodynamically stable.

Both of the initial studies describe a favorable enthalpy or energy of mixing for the mole fraction range of 0–0.26

TABLE I. Molecular dynamics results for acetone (*a*) and water (*w*) mixtures at 300 K. (Symbols: N_a , number of acetone molecules; L , box length (nm); ΔE_m , energy or enthalpy of mixing (kJ/mol); G_{ij} , KB integrals (cm³/mol); and P , pressure (bar). Sources for the experimental data have been described previously (Ref. 1). Simulations performed with box lengths of 3.211 and 3.564 nm correspond to the experimental densities.)

x_a	N_a	Ens	L	ΔE_m	G_{aa}	G_{ww}	G_{aw}	D	P
0.10	86	<i>NPT</i>	3.208	−0.45	102	34	−138	0.38	1
0.10	688	<i>NPT</i>	6.419	−0.44	227	57	−192	0.28	1
0.10	86	<i>NVT</i>	3.211	−0.38	73	30	−128	0.42	−73
		exp		−0.48	−14	9	−91	0.59	
0.26	225	<i>NPT</i>	3.552	−0.71	−1	192	−166	0.24	1
0.26	1800	<i>NPT</i>	7.103	−0.69	−6	185	−158	0.25	1
0.26	225	<i>NVT</i>	3.564	−0.56	9	219	−183	0.22	−53
		exp		−0.51	−9	126	−156	0.27	

(see Fig. 5 of Ref. 1 and Fig. 1 of Ref. 2), whereas the latter study describes a positive mixing energy (see Fig. 4 of Ref. 3). While the absolute potential energies can be affected by the choice of simulation conditions (cutoff, electrostatic treatment, ensemble, etc.), the energy of mixing for a model should be very reproducible. Indeed, reproducibility is observed between Refs. 1 and 2. It is unclear how a difference in mixing energy on the order of 1 kJ/mol at $x_a=0.2$ can be observed with the same model, even acknowledging some differences in the simulation details. Even if the results were affected by the simulation conditions, the choice of non-bonded cutoff and treatment of electrostatics are usually considered part of the model. Hence, a definitive conclusion concerning the behavior of KBFF model for acetone should only be made when comparing simulations performed under exactly the same conditions.

The explanation provided by Jedlovsky *et al.*³ for the absence of demixing in the previous studies involved either short simulation times on small systems and/or errors introduced by using the Wilson equation during the analysis. The original simulations involved mixtures of approximately 1500 molecules simulated for 4 ns—not particularly small or short simulations. However, we have run the larger systems

described above for over 25 ns and observed no demixing. Furthermore, while we agree that the analysis of the experimental data can be affected by the fitting equation, the simulated value of D can be obtained *directly* from the simulated KB integrals and is therefore unaffected. No fitting is required. These values are clearly positive (see Table I) and thereby indicate stable mixtures. The fitting is only performed to provide values of D and the excess Gibbs energy over the whole composition range.

In summary, the previous and present results clearly contradict the firm conclusion presented in Ref. 3 that the KBFF model for acetone is immiscible with water at low acetone mole fractions. We believe our original results are therefore correct.

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