

Benchmarking Simulations against the ThermoML Database: Neat Liquid Densities and Static Dielectrics

Kyle A. Beauchamp^{*,†}, Julie M. Behr^{*,†}, Patrick B. Grinaway^{,†} Bas^{,†},
Michael R. Shirts^{,‡}, Kenneth Kroenlein,[¶] and John D. Chodera^{*,†}

*Memorial Sloan-Kettering Cancer Center, New York, NY, Department of Chemical Engineering,
University of Virginia, Charlottesville, VA, and NIST Thermodynamics Research Center,
Boulder, CO*

E-mail: jchodera@mskcc.org

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Abstract

Useful atomistic simulations require accurate depictions of solvent. Simple experimental observables, such as density and static dielectric constants, offer straightforward targets for evaluating forcefield quality. Here we examine the possibility of benchmarking atomistic models against the NIST ThermoML database of physicochemical measurements, which curates thousands of density, dielectric, and other measurements. We present a

^{*}To whom correspondence should be addressed

[†]Memorial Sloan-Kettering Cancer Center, New York, NY

[‡]Department of Chemical Engineering, University of Virginia, Charlottesville, VA

[¶]NIST Thermodynamics Research Center, Boulder, CO

detailed benchmark of the GAFF forcefield against measurements extracted from ThermoML and discuss the extent of available data for neat liquids. We show that empirical polarizability models correct systematic biases inherent in predicting dielectric constants with fixed-charged forcefields. Combining our dataset with the Virtual Chemistry benchmark set provides an extensive benchmark suite for liquid properties.

Introduction

Intro

Results

Neat Liquid Measurements in ThermoML

To assess the feasibility of benchmarking organic molecule forcefields against ThermoML, we performed a number of queries to summarize the data content of ThermoML. Our aim is to explore neat liquid data with functional groups relevant to drug-like molecules. We therefore applied the following sequence of filters: Druglike elements (H, N, C, O, S, P, F, Cl, Br), Heavy Atom Count (≤ 10), Temperature [K] ($270 \leq T \leq 330$), and Pressure [kPa] ($100 \leq P \leq 102$). After applying these filters, we also assume that all pressures within this range are one atmosphere. We also assume that temperatures can be rounded to one decimal place. These approximations are motivated by common data entry errors; for example, an experiment performed at water’s freezing point at ambient pressure might be entered as either 101.325 kPa or 100 kPa, with a temperature of either 273 K or 273.15 K.

Table 1: ThermoML Statistics

Filter	Mass Density	Static Dielectric
0. Single Component	130074	1649
1. Druglike Elements	120410	1649
2. Heavy Atoms	67897	1567
3. Temperature	36827	962
4. Pressure	13598	461
5. Aggregate T, P	3591	432
6. Density+Dielectric	245	245

Benchmarking GAFF against ThermoML: Mass Density

Mass density has been widely used as a critical ingredient for parameterizing and testing forcefields, particularly the Lennard Jones parameters. We therefore used the present ThermoML compilation as a benchmark of the Generalized Amber Force Field.

Benchmarking GAFF against ThermoML: Static Dielectric

As a measure of the electronic medium, the static dielectric constant of neat liquids provides a critical benchmark that is orthogonal to density and thermodynamic quantities. We therefore compare our GAFF simulations against the measurements in our ThermoML compilation. Overall, we find the dielectric constants to be qualitatively reasonable, but with clear deviations from experiment. In particular, the nonpolar organics show a clear discrepancy, with the MD predictions of 1.0 being substantially less polar than the measurements near 2.0. Because this deviation likely stems from the lack of electronic polarization, we added a simple empirical correction for polarization,¹ which leads to better agreement with experiment. A similar polarization correct was used in the development of the TIP4P-EW water model;² however, the need is much greater for the nonpolar organics, as the missing polarizability is the dominant contribution to the static dielectric constant. For comparison, we also applied the same empirical correction to the Virtual-Chemistry dataset and saw similarly improved agreement with experiment for both the

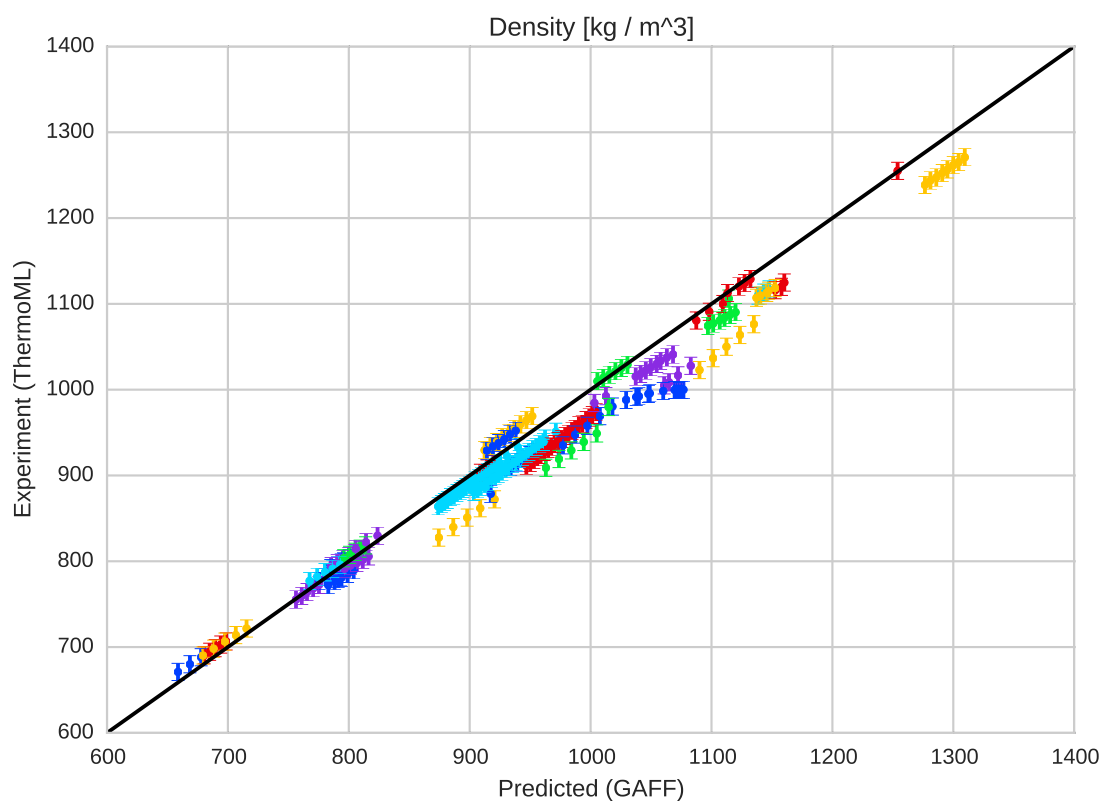
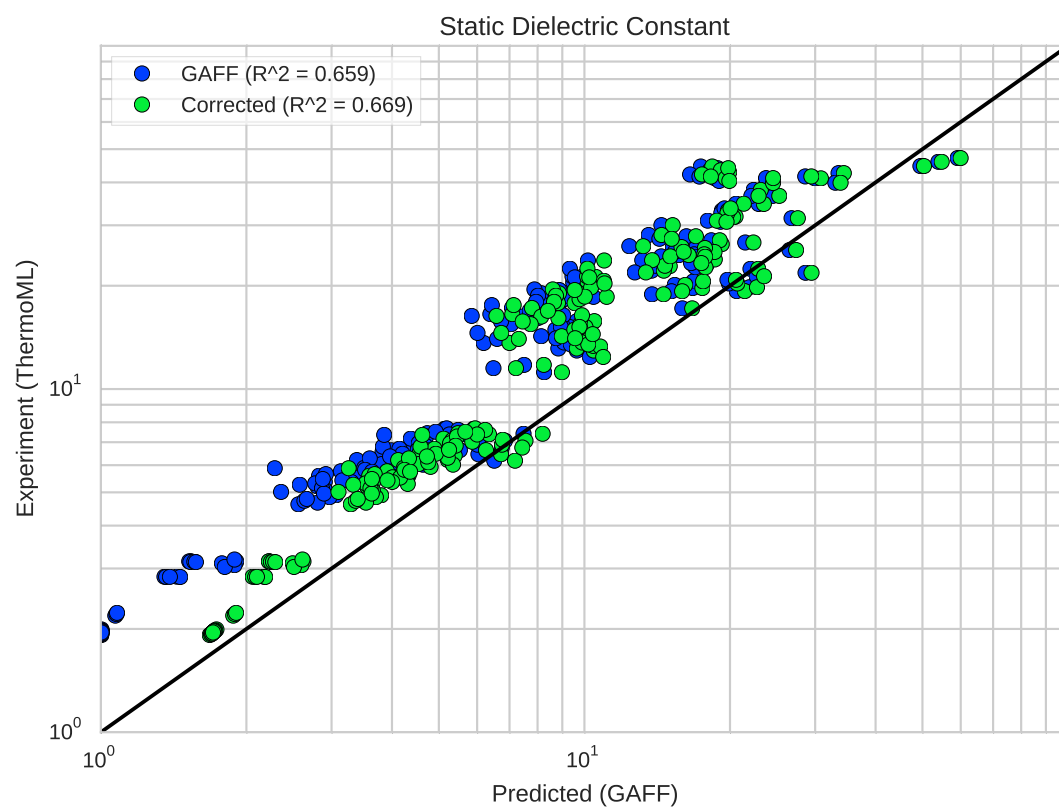
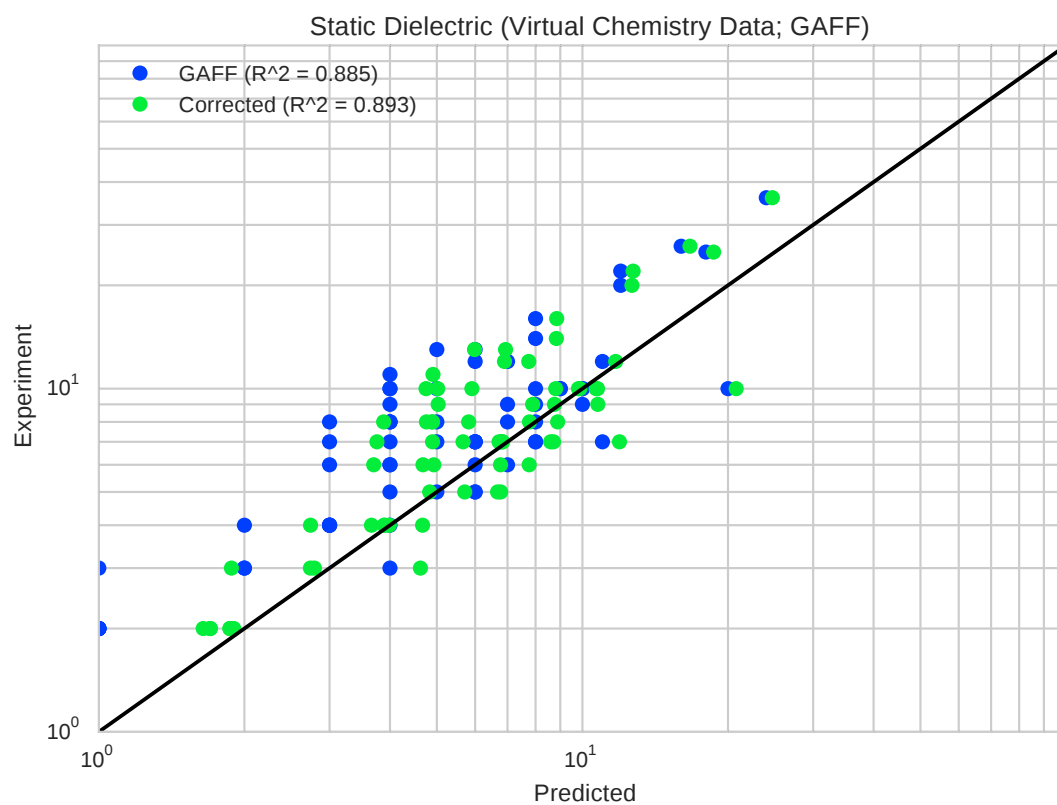
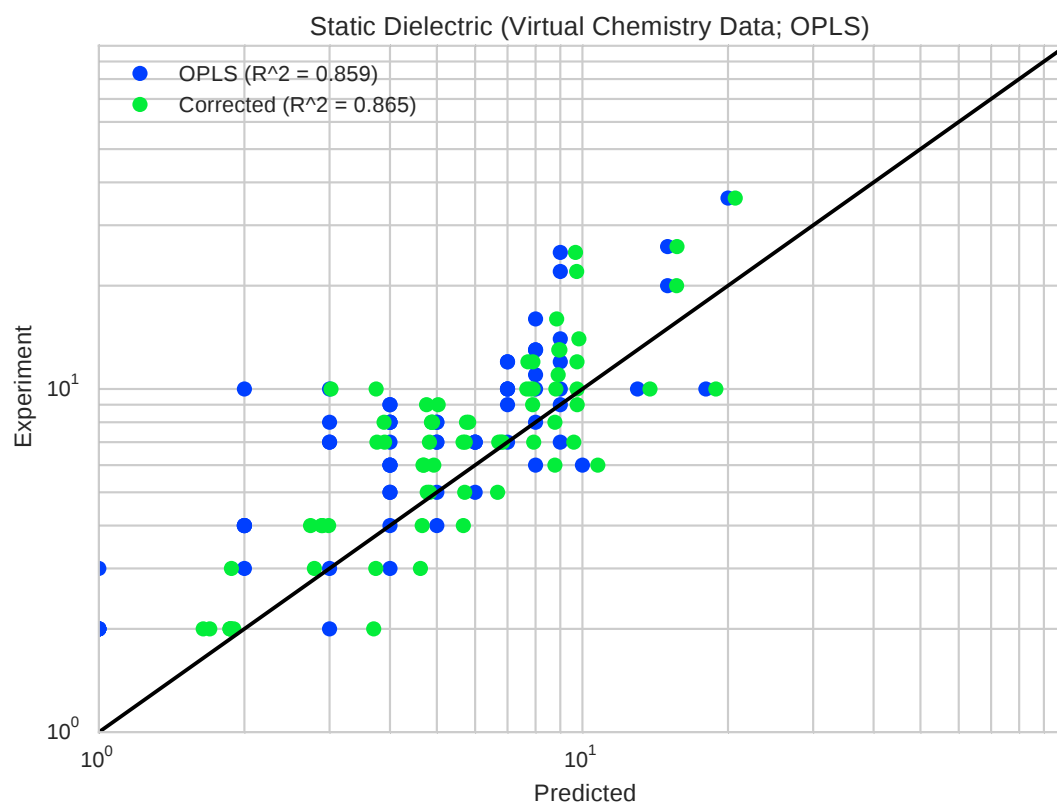


Figure 1: Measured (ThermoML) versus predicted (GAFF) densities. Color groupings represent identical chemical formulas. Simulation error bars represent one standard error of the mean, with the number of effective (uncorrelated) samples estimated using pymbar. Experimental error bars indicate SO AND SO.

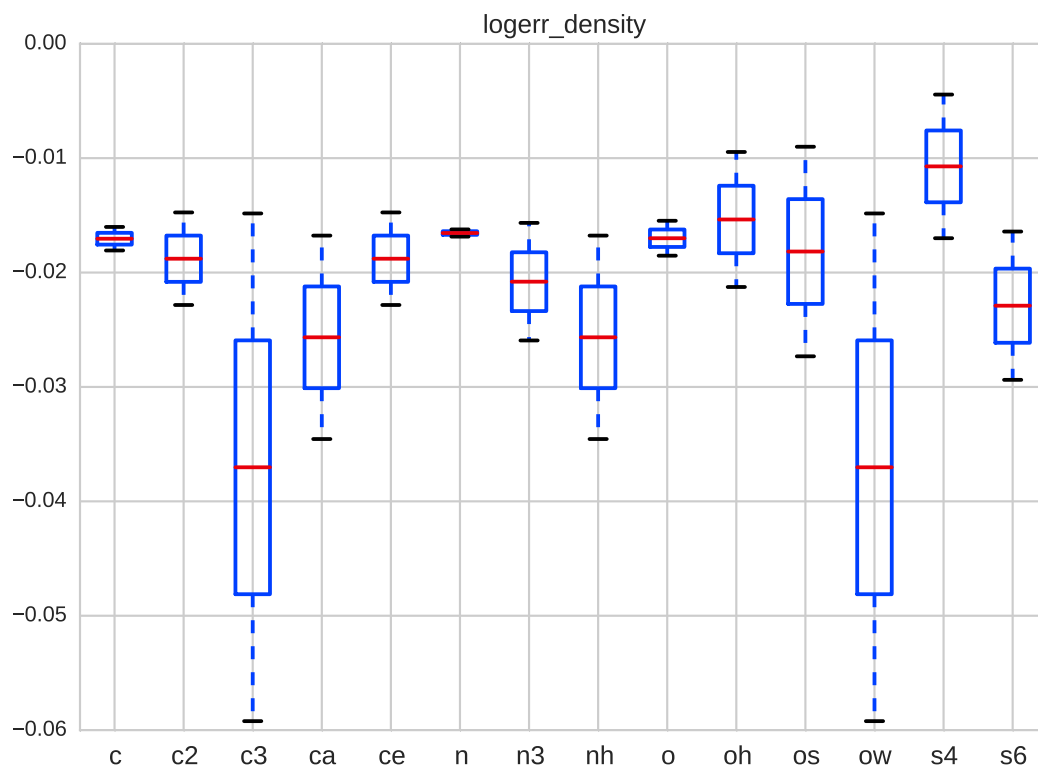
GAFF and OPLS forcefields.

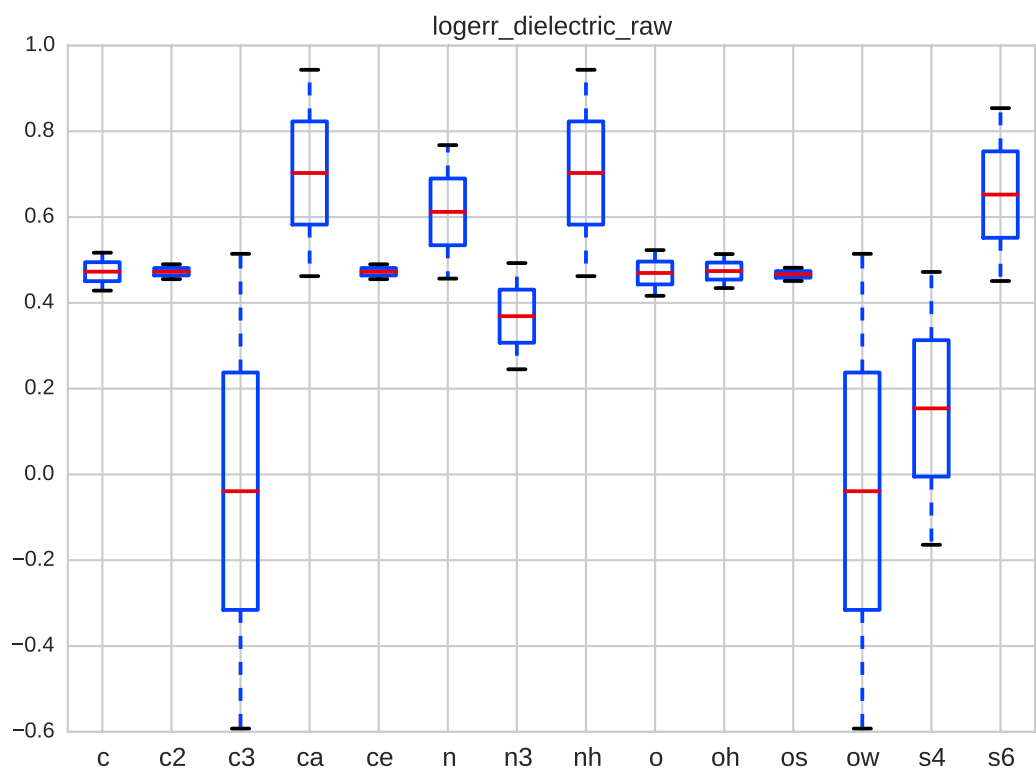
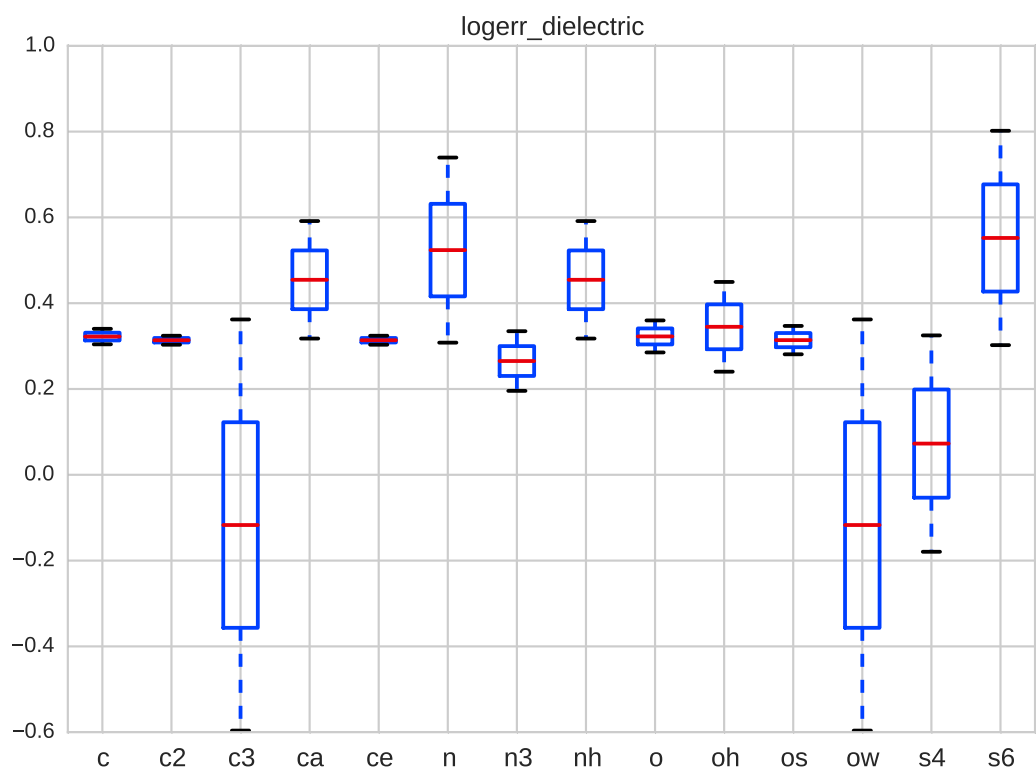




Discussion

Forcefield Accuracy Depends on Functional Group





Fitting Forcefields to Dielectric Constants

Recent forcefield development has seen a resurgence of papers fitting dielectric constants as primary data.^{3,4} However, a number of authors have pointed out potential challenges in constructing self-consistent fixed-charge force fields.^{5,6} Interestingly, a recent work by Dill⁵ pointed out that, for CCl_4 , reasonable choices of point charges are incapable of recapitulating the observed dielectric of 2.X, instead producing dielectric constants in the range of $1.0 \leq \epsilon \leq 1.05$. Suppose, for example, that one attempts to directly fit the static dielectric constants of CCl_4 , CHCl_3 , CH_2Cl_2 , CH_3Cl , CH_4 . In moving from the tetrahedrally-symmetric CCl_4 to CHCl_3 , it suddenly becomes possible to achieve the observed dielectric constant of 4.8. However, the model for CHCl_3 uses fixed point charges to account for *both* the net dipole moment and the (electronic) polarizability, whereas the CCl_4 model contains no treatment of polarizability. We hypothesize that this inconsistency in parameterization may lead to strange mismatches, where symmetric molecules (e.g. benzene, CCl_4) have qualitatively different properties than closely related asymmetric molecules (e.g. toluene, CHCl_3). As a first-order fix, we suggest using empirical polarization corrections before directly comparing measured static dielectric constants to fixed-charge models—particularly when examining low-dielectric solvents. Separating the contributions of fixed charges and polarization may also lead to the development of improved models of electrostatics that account for the missing polarization physics.

ThermoML as a Data Source

The present work has focused on the neat liquid density and dielectric measurements present in ThermoML⁷⁻⁹ as a target for molecular dynamics forcefield validation. While densities and dielectric constants have been widely in forcefield work, several aspects of ThermoML make it a unique resource for the forcefield community. First, the curation, support, and dissemination of ThermoML is supported by NIST, whose mission makes

these tasks a long-term priority. Second, ThermoML is actively growing, through partnerships with journals such as J. Chem. Thermo—new experimental measurements published in these journals are critically examined by the TRC and included in the archive. Finally, the files in ThermoML are machine readable via a formal XML schema, allowing facile access to thousands of measurements. In the future, we hope to examine additional measurement classes, including both mixture and two-phase data.

Methods

ThermoML Processing

ThermoML XML files were obtained from the the NIST TRC. To explore their content, we created a python (version 2.7.9) tool (ThermoPyl: <https://github.com/choderalab/ThermoPyl>) that munges the XML content into spreadsheet-like format accessible within the python Pandas (version 0.15.2) tool. Here we describe its operation. First, we obtained the XML schema (<http://media.iupac.org/namespaces/ThermoML/ThermoML.xsd>) defining the layout of the data. This scheme was converted into a Python object via PyXB 1.2.4 (<http://pyxb.sourceforge.net/>). Finally, the scheme was used to extract the data.

Simulation

Boxes of 1000 molecules were constructed using PackMol.¹⁰ AM1-BCC charges were generated using OpenEye toolkit 2014-6-6,¹¹ using the XYZ module with parameter ZYX. The selected conformer was then processed using antechamber in AmberTools 14. The resulting AMBER files were converted to OpenMM¹² XML files. Simulation code used libraries gaff2xml 0.1, TrustButVerify 0.1, openmm 6.2, and MDTraj¹³ 1.2.

Molecular dynamics simulations were performed using OpenMM 6.2 using a Langevin

integrator (friction 1ps^{-1}) and a 1 fs timestep; interestingly, we found that a 2 fs timestep led to insufficient accuracy in equilibrium densities (Fig. S1). Pressure coupling was achieved with a Monte Carlo barostat applied every 25 steps. Particle mesh Ewald¹⁴ was used with a long-range cutoff of 0.95 nm and an isotropic dispersion correction. Simulations were continued until density standard errors were less than 2×10^{-4} g / mL, as estimated using the equilibration detection module in pymbar 2.1.¹⁵ Trajectory analysis was performed using OpenMM¹² and MDTraj.¹³

Conclusions

1. ThermoML is a potentially useful resource for the forcefield community 2. We have curated a subset of ThermoML for neat liquids with druglike atoms, with thousands of densities and hundreds of dielectrics 3. Empirical polarization models correct a systematic bias in comparing fixed-charge forcefields to static dielectric constants

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