A method for redesigning molecular dynamics force field parameterization by use of a Bayesian statistical framework

Bryce C. Manubay

University of Colorado - Department of Chemical and Biological Engineering

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I. Objectives

Molecular dynamics (MD) simulation is fast becoming a more useful tool in many scientific studies. However, some limitations remain in the ability of MD force fields to accurately and transferably describe molecular environments. Many popular and currently used force fields were parameterized with fixed functional forms which, often, have poor physical motivation. The chemical intuition of experts is also often required to manually correct parameters, leading to a more suitable product. Additionally, the creation of a transferable method to update existing force fields based on new experimental data is limited due to lack of understanding and lack of consistency in how the original parameterizations were done.

A possible solution to these problems is by recasting the force field parameterization process as a bayesian inference problem. The objective of this paper is introduce a framework for using high quality experimental data in order to automatically generate families of MD force fields consistent with the data used. In this paper I will generally describe the overall parameterization framework and my roles in the project thus far. First, collecting and curating large amounts of high quality experimental thermochemical data and, currently, investigating use of the Multistate Bennett Acceptance Ratio (MBAR) as a means to improve parameterization throughput by reducing computational expense while making updates to the posterior distribution of parameter sets consistent with experimental evidence.

II. Significance

A broad variety of research from drug discovery to metallurgy has been greatly impacted by the advent and improvement of MD simulation tools. Observing physical phenomena such as protein folding dynamics and ligand docking at a molecular scale is widely studied using MD tools.[1;2] Drug discovery and deisgn of new pharmaceutical leads has also been made more efficient.[3] The fundamental part in molecular simulation for describing the energetic interactions of a system is referred to as a force field. Hence, the development of force fields which are readily transferable between dissimilar physical systems and are quantitatively accurate is imperative for the use of molecular simulation tools to continue to proliferate.

Transferability of MD force fields, and particularly sets of force field parameters, is an extremely popular topic (and current limitation) in the molecular simulation field.[4;5;6;7] Transferability of force fields encourages use by providing convenience for scientists with wide arrays of research interests and by making parameter space less complex through generalization by chemical similarity. Inaccurate and poorly parameterized force fields have been shown to grossly misrepresent molecular systems.[8;9;10]

A few notable attempts, such as GAAMP and ForceBalance, have been made in recent years towards the development of more automated and systematic force field parameterization methods.[11;12;13;14] Each made important contributions to automated force field parameterization through clever use of objective function optimization, exploiting a variety of fitting data and allowing exploration of functional forms. However, none provided the ability for the computer to automatically and systematically explore choices of fitting data, optimization algorithm and functional forms in order to objectively find families of force fields consistent with fitting data and reward those with the least model complexity. The bayesian inference scheme described in this paper will provide a workflow for discovering families of force field parameters consistent with experimental data and a variety of functional forms.

III. Background and related literature

Molecular dynamics force fields define how to construct the potential energy functions (and thereby the forces) of an atomistic system under study. The potential is constructed such that it is a function of solely the atomic coordinates and a set of parameters associated with the force field. Transferable force fields generally have three major parts: **(1)**The **functional forms** of the potential, i.e. the mathematical equations for the energy. A classic example of

a non-bonded interaction form is the 12-6 Lennard-Jones (LJ) potential; **(2) Atom types** which describe similar chemical environments such that one can assign different atoms identical parameters; **(3) Parameters** that are associated with one or many atom types which determine the magnitude of the interactions in the system. Rolled into functional forms, **combining rules** are also sometimes considered. **Combining rules** describe how to combine parameters when an interaction contains multiple atom types.

There are severe limitations in current methods for force field parameterization. Until very recently, force fields have primarily been made manually, guided by experimental and quantum chemical simulation data as well as the intuition of expert computational chemists.[15;16;17;18;19] Some functional forms used in modern force fields, like the 12-6 LJ potential, have poor physical basis. While the attractive term of the LJ potential has physical basis on the true behavior of dispersion forces, the repulsive term loosely approximates Pauli repulsion and is used for computational convenience. Despite attempts at improvement, many of the functional forms and parameters of popular force fields remain mostly unchanged due to the lack of clear, systematic methods for updating them.[20]

Parameterization methods have slowly become more sophisticated over the last decade and a half with advances in computational power and to accommodate modeling increasingly more complex systems. Many early force fields were parameterized manually for narrow classes of molecules with large redundant parameter spaces.[21] Force fields like AMBER *parm94* showed intuitive departure by shrinking parameter space with clever atom typing defined by expert computational chemists.[22] The parameterization of GAFF used a semi-automated genetic algorithm approach to select parameters.[19] Even more sophisticated optimization approaches such as least-squares optimization of an objective function have been utilized in the creation of the TIP4P-Ew water model[23] and in the ForceBalance parameterization scheme[12;13;14]. Even with these more sophisticated optimization schemes there are still issues in needing for the user to assign weights to different kinds of data (i.e. different properties) when they are included in the same objective function. Molecular systems aren't necessarily uniquely defined by a single parameter set. There are possibilities of multiple optima in parameter space (i.e. different sets of parameters that all are consistent with data used during parameterization) and least-squares optimization does not discriminate the global optima from the other possibilities.

Bayesian inference provides a robust statistical framework for force field parameterization. It has been shown that bayesian approaches can be applied to a wide variety of data driven sciences. It's been used for balancing data to help minimize influence of oversampled populations and generate more robust predictive models[24] to recalibrating initial force estimates in coarse grained MD models to target atomistic MD and experimental data[25]. Baye's theorem clearly provides a framework for the problem at hand thusly:

$$P\left(\theta|D\right) \propto P\left(D|\theta\right)P\left(\theta\right) \tag{1}$$

In **Equation (1)**, consider a model M (including functional forms and atom types) with some unknown set of parameters which produced data D. θ is a choice of parameters consistent with data D. What **equation (1)** states is that the probability of θ given D (the *posterior*) can be determined from the probability of observing D given θ (the *likelihood function*) and the probability of θ (the *prior*). The *prior* is imposed by physical constraint or by the previous round of inference. Note that in iterative bayesian inference, the posterior of the previous round becomes the prior in the new iteration. This bayesian inference produces not just a single parameter set, but an entire posterior distribution of parameters given data. This is advantageous given that many different parameter sets can be consistent with the data used and the distribution of these consistent sets of parameters can inform what new data could help narrow the distribution and improve the parameter estimates.

IV. Methods

A. Data mining and curation of thermochemical data in ThermoML

The experimental thermochemical data to be used for the parameterization process was collected from the NIST ThermoML database managed by the Thermodynamics Research Center (TRC) at the NIST Boulder campus. In order to explore the composition of the data in ThermoML I used the *ThermoPyL* Python tool developed by the Chodera lab at the Memorial Sloan Kettering Cancer Center (MSKCC).[26] The *ThermoPyL* tool parses the standard ThermoML XML format into a Pandas dataframe format. Further filters can be applied to the dataframes to filter by chemical composition, properties of thermodynamic state such as temperature or pressure, as well as thermochemical properties available.

The first planned novel use of the bayesian parameterization procedure is to parameterize a general force field for simulating small organic liquids and their mixtures. Other than being a concrete test case with readily available experimental data, this choice is motivated by shortcomings of current force fields to accurately describe organic liquid mixtures (and particularly excess properties).[27] Given this apparent problem the properties selected to be used in the pool of potential evidence were chosen for the purpose of more fully constraining parameter space with the goal of being able to accurately simulate properties of organic liquid mixtures. The properties chosen from neat liquid data were mass density, isobaric heat capacity, speed of sound and static dielectric constant. The properties chosen from the binary mixture data were mass density, speed of sound, static dielectric constant, excess molar volume, excess molar isobaric heat capacity, excess molar enthalpy and infinite dilution activity coefficients. To consider how these properties might affect the constraint of parameter space one must simply think intuitively about the physics. First, consider mass density. Ultimately, the value of mass density for a bulk liquid is determined by the volume of the system and therefore the space between molecules. Therefore, the most important parameters for this simulated quantity would be for those describing the non-bonded interactions between molecules. As a counterexample consider the static dielectric constant, which is a function of the system dipole moment or more generally electrostatics. Clearly, accurately simulating this property would require constraints placed on electrostatic interaction parameters or bonded parameters given dipoles are also affected by bond distance. Heat of vaporization was collected, but it was decided not to be included as evidence in the initial test. While heat of vaporization is a common property to parameterize to it was decided that because we are parameterizing a purely liquid force field, phase change properties might only serve to complicate the process. This data will be kept to check the accuracy of the force field in simulating this property for a wide array of chemistries.

The data filtering process is started by organizing a locally stored version of the ThermoML database into a Pandas dataframe. First, a filter is applied to discard journal articles with known erroneous data. Next, we filter all data if it doesn't fall within our previous properties of interest list. Filters for chemical composition and bond order are next applied, specifically it was decided that for initial testing to only look at organics containing C, O and/or H atoms with single or aromatic bonding. Additionally, the molecules had another filter such that they must appear in a diverse list of alkanes, ethers and alcohols (coined AlkEthOH) that was constructed by Chris Bayly of OpenEye Software. AlkEthOH represents a limited test set to validate the machinery for parameterization. Finally, only data with temperatures 250 - 400 K and pressures 1 - 1000 atm, in the liquid phase, are kept. The data is then saved in an easily machine-readable format such as JSON or PKL. Additionally, potential data for use as evidence was sent to the the TRC for validation of quality. The likelihood function described earlier will be a function of uncertainties associated with the evidence, thus accurate estimates are imperative. The TRC checks internally kept uncertainty estimates against what authors published and notes any outliers.

B. Exploring the use of multistate reweighting to reduce computational expense

During each update of iterative bayesian inference, evaluation of the likelihood function will require new simulated evidence given a perturbed parameter set. However, with sufficient phase space overlap, new evidence at adjacent states can be estimated using multistate reweighting tools such as MBAR.[28] MBAR has a much higher computational efficiency than fully simulating a new state, thus this could greatly accelerate full construction of a posterior distribution of parameters. **Equation (2)** shown below is the formulation that allows for reduced free energies to be found at other states using a simulated state as reference, i.e. it allows for the solution of free energy differences.

$$\hat{f}_i = \sum_{j=1}^{k} \sum_{n=1}^{N_j} \frac{\exp\left[-u_i\left(x_{jn}\right)\right]}{\sum_{k=1}^{K} N_k \exp\left[\hat{f}_k - u_k\left(x_{jn}\right)\right]} \tag{2}$$

Where u is a reduced potential energy, x is a configuration, K is the number of states and N is the number of configurations from the state. These free energy calculations also allow for estimating expectation values of observables at the other thermodynamic states for which relative free energies were calculated. This is done by calculating relative weights of the unsampled states to the sampled states using the formulations shown below in **equations (3),(4) and (5)**.

$$W_{na} = \hat{c}_a^{-1} \frac{\exp\left[-u\left(x_n\right)\right]}{\sum_{k=1}^{K} N_k \exp\left[\hat{f}_k - u_k\left(x_n\right)\right]} \tag{3}$$

$$\hat{c}_a = \sum_{n=1}^{N} \frac{\exp\left[-u\left(x_n\right)\right]}{\sum_{k=1}^{K} N_k \exp\left[\hat{f}_k - u_k\left(x_n\right)\right]} \tag{4}$$

$$\hat{A} = \sum_{n=1}^{N} W_{na} A\left(x_n\right) \tag{5}$$

Where $A(x)$ is some mechanical observable, W_{na} is a weight and $\hat{A}$ is the estimated expectation of $A(x)$. The goal of this exercise is to see how large of parameter perturbations can be made and still make accurate estimates of some observable at that new perturbed state. For this testing phase we use a toy problem of with single molecule simulation observables, such as bond lengths and angles, as the evidence for verifying the validity of the bayesian inference process in the least computationally expensive manner. For testing the safe extent of parameter perturbation I have devised a simple scheme for comparison of reweighted observable estimates to a true sampled value. I created a reweighting script using the Python implementation of MBAR called *pymbar* in order to make estimates of observables at new parameter states. I decided on two criteria for assessing the accuracy of a reweighted estimate: (1) the estimated uncertainty of the estimated expectation of an observable must be within 20% of a bootstraped uncertainty estimate with 100 samples and (2) the estimated value of the observable being calculated must be within 2 standard deviations of the true sampled value. These success criteria are motivated for the fact that: (1) the MBAR estimate and bootstrapped uncertainties should converge with sufficient phase space overlap and (2) the simulated distributions of bond lengths and angles are Gaussian.

Since one of my criteria for accurate reweighting is the estimated observable being within a certain number of standard deviations from the true sampled value, many simulations with perturbed force field parameters had to be run. Using ten selected molecules from the AlkEthOH set, I have run 2900 single molecule simulations for use as evidence. Simulations were carried out using the OpenMM simulation suite. Each simulation was carried out at $300K$ for a total of $200ps$ each in an NVT ensemble. The system was integrated with Langevin dynamics and 100 snapshots were recorded during every simulation.

V. Progress

A. Data mining and curation of thermochemical data in ThermoML

Upon first inspections of the ThermoML database it became immediately clear that the data was extremely concentrated in certain properties for both neat liquid properties and binary mixture properties.

As shown in **figure 1** the data is most concentrated in mass density. The amount of data per property exponentially decays until there is as little as a few dozen data points in certain properties. Initially, the OpenFF team (including myself, Michael Shirts, the Mobley lab at UCI and the Chodera lab at MSKCC) thought that this could severely limit our ability to constrain parameters beyond those associated with non-bonded interactions. However, after consultation with Chris Bayly we hypothesize that despite the lack of data in certain properties the chemical diversity in the data will allow us to fully constrain a large swath of parameter space.

Considering the three chemical classes (or environments) of the AlkEthOH set (alkanes, ethers and alcohols) the number of unique molecules per chemical class is quite balanced across both neat liquid and binary mixture properties of interest. Additionally, it was determined that although the total amount of available data per chemical class is unbalanced, it is still quite ample (especially when considering the binary mixture property data). **Figure 2(a) and 2(b)** illustrate these points, respectively.

A point of interest that came up during this search of the ThermoML database is that although the AlkEthOH set is useful in the beginning stages of verifying the bayesian parameterization process by shrinking the parameter space, it extremely limits the chemical diversity and amount of data that is available. One of the other searches that I did was on the full amount and diversity of data available for most conceivable organic species. For this search I expanded the atom filter in *ThermoPyL* to allow other common organic atoms (such as S, N, B, P, F, Cl, Br and I) to pass, removed the bond order restrictions and kept the liquid phase filter. The results showed an extremely large and diverse set of data available when compared to the results of the AlkEthOH filter. Statistics are shown in **3(a)**. Additionally, another statistic I considered was the number of molecules with at least certain numbers of pure
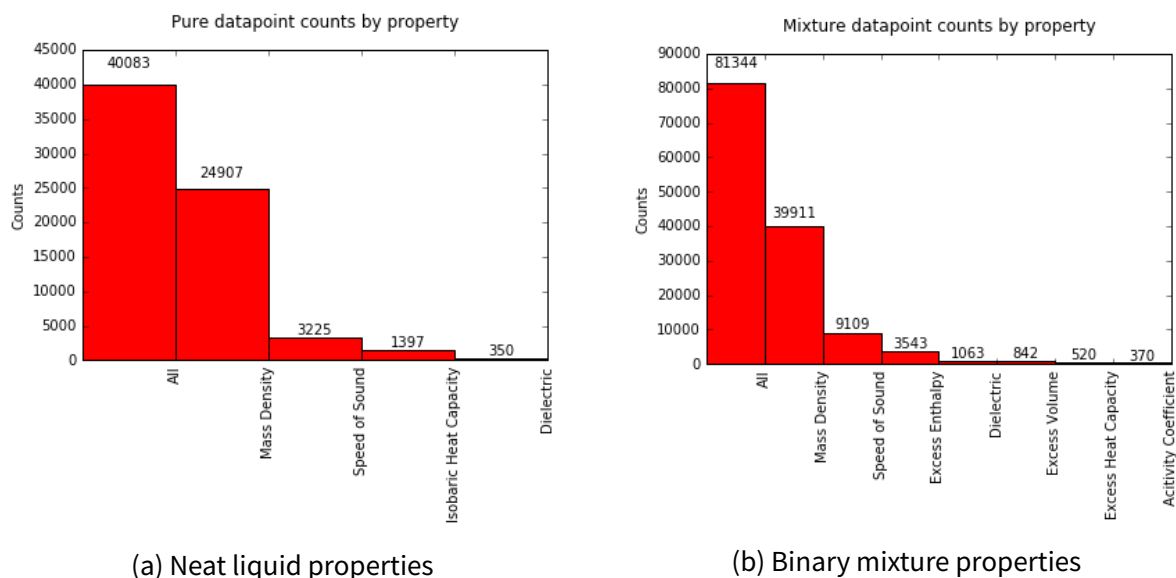
(a) Neat liquid properties

(b) Binary mixture properties

FIG. 1: The distributions of data amongst neat liquid and binary mixture properties of interest

(a) Chemical diversity per class
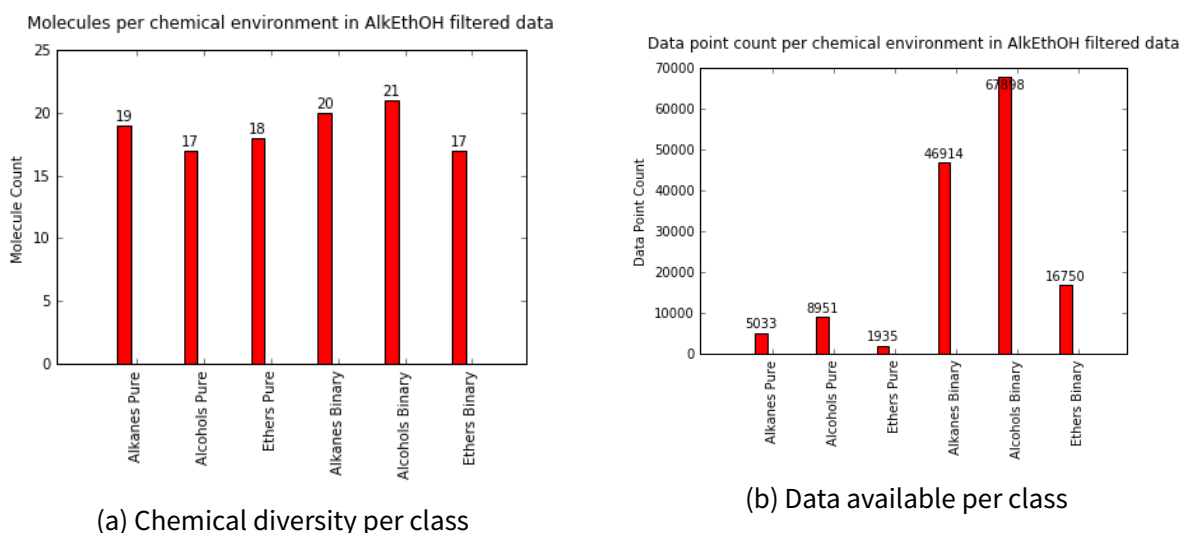
(b) Data available per class

FIG. 2: The two figures show that the chemical diversity per class in the AlkEthOH set is relatively balanced and that the amount of data available in each class is large

solvent **and** binary mixture properties available. The statistics are shown in **figure 3(b)**. Given this statistic there may be a limiting amount of data available to constrain parameter space across the full chemical diversity of the AlkEthOH set, however it should be much less of an issue when considering a larger chemical space. The issue then becomes dealing with a much larger and more complex parameter space.

B. Exploring the use of multistate reweighting to reduce computational expense

Despite the amount of time spent exploring the safe magnitude of parameter changes that result in accurate reweighted estimates of bond length and angle observables, results are still inconclusive. It was originally hypothesized that the allowable percent changes in bond or angle force constants were propotional to the percent of the molecule that was affected by the parameter change (i.e. how many instances of the atom type changed occur in

(a) Unique molecules per property
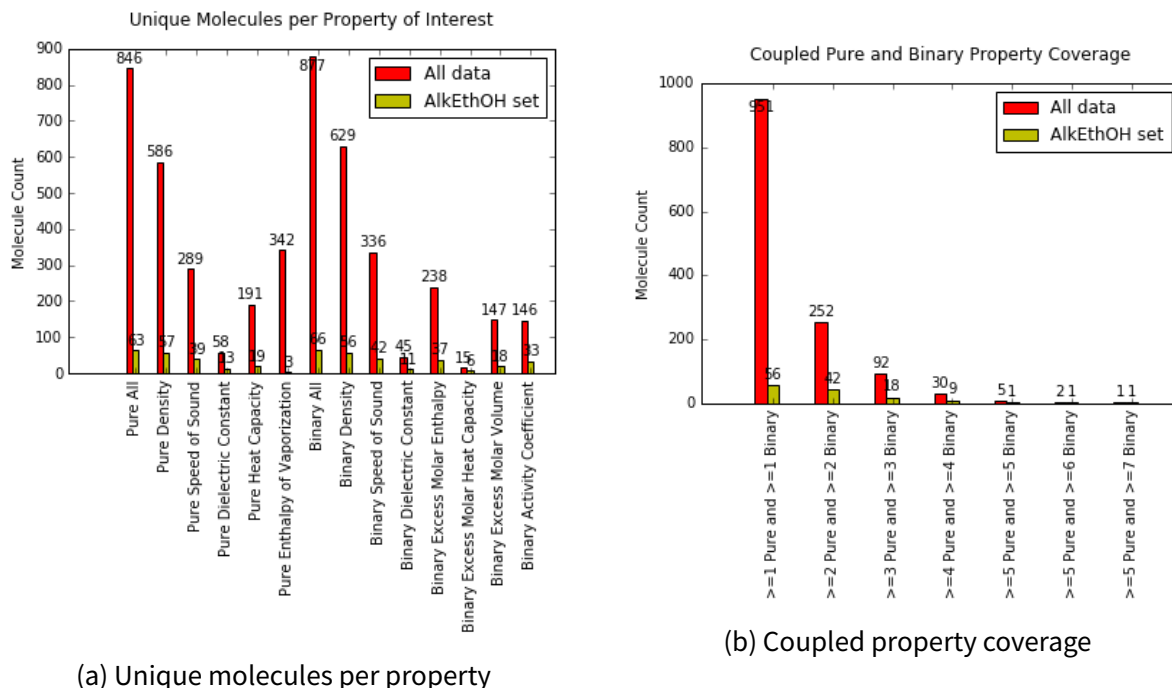
(b) Coupled property coverage

FIG. 3: The two figures show that there is an extreme diversity of molecular coverage available in the total ThermoML database and that the full organic liquid data availavle has a much better chance of well constraining parameter space when compared to the AlkEthOH set

the molecule). However, while this is true of many of the molecules tested, it is not true for all of them. I will have to continue expanding the atom types being investigated in order to get a more conclusive result of how the percent change in parameter and proportion of the molecule affected by the change relate. Additionally, I hypothesize that the allowed changes in geometric parameters such as minimum bond length and equilibrium angle will not be percents, but will be bounded by constraints of molecular geometry. This has yet to be tested though.

VI. Research plan

Short-term the trajectory of the research plan is quite clear. The first thing to be done is to finish developing general guidelines for the allowed magnitude of parameter changes that will result in accurate reweighted estimates of bond length and angle observables. Once the guidelines are clear they are to be used in testing the bayesian inference machinery using single molecule observables as evidence. The concept for the test is as follows: **(1)** Simulate distributions of bond lengths and angles using a correct original force field. This will be our evidence; **(2)** Perturb the force field to have clearly wrong or unphysical parameters; **(3)** Using the bayesian updating scheme, attempt to iteratively determine a set of parameters which reproduces the original evidence. Currently the bayesian sampling machinery is being developed my members of the Mobley lab at UCI and the Chodera lab at MSKCC. Depending on the results of the guidline development for allowable parameter changes, it may be necessary to explore configurational mapping as a means to accurately calculate free energy differences between non-overlapping states.[29] The goal is to have this toy project finished by the end of the Fall 2016 semester.

Long-term we would like to implement the bayesian inference parameterization procedure using the experimental thermochemical data I curated as evidence. Currently the property calculation API, which will both implement calculation of expectation values of mechanical observables from simulation data and handle how the experimental data and uncertainties are used, is being developed by John Chodera at MSKCC. As part of my work thus far I have compiled a review document summarizing various methods for calculating thermochemical properties of interest from simulation data. The document summarizes numerical and analytical techniques for calculating observables, characterization of uncertainty as well as recommendations on corrections to be included in some calculations and when it is most appropriate to use them. Once the skeleton of the API is finished, I will be adding

many of these calculation methods and testing them in order to publish an article on benchmarking different calculation methods for a varied set of thermochemical observables. Ultimately, one of the main goals of this project is to develop software to allow other scientists to easily parameterize high quality MD force fields from avavilable experimental data. The goal of this benchmarking project is to create guidelines to be put in the API recommending options for calculation methods and corrections to be added that will guide other scientists should they use the parameterization software. The goal is to have this mostly complete by my first committee meeting next year.

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