Machine Learning Directed Optimization of Classical Molecular Modeling Force Fields

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Quantitatively accurate molecular models, called force fields, are necessary for predictive molecular simulations. However, optimizing force fields to accurately reproduce experimental properties is a challenging endeavor. Here we present a machine learning directed workflow for force field optimization. Surrogate-assisted optimization is used to evaluate millions of prospective force field parameters while requiring only a small fraction of those to be evaluated with molecular simulations. The generality of the approach is demonstrated with two distinct test cases: optimizing force fields for simulations of hydrofluorocarbon (HFC) vapor–liquid equilibrium (VLE) and an ammonium perchlorate (AP) crystal phase. Our workflow identifies parameter sets for HFC-32 and HFC-125 which reproduce six experimental VLE properties to within 1.5% and 2.5% error, respectively, which are remarkably better than existing conventional all-atom force fields. When applied to AP, our workflow identifies parameter sets that better reproduce the AP structure than the best available force field in the literature and our own hand-tuned AP force field. The force field optimization workflow is general and can be used to improve the accuracy of existing force fields and develop new force fields for specific systems.

Molecular modeling and simulation use computational methods to describe the behavior of matter at the atomistic or molecular level [1]. The 2013 Nobel Prize in Chemistry emphasized the value of molecular simulations in providing detailed insights into chemical and biological systems. However, the veracity and predictive capability of molecular simulations depend critically on the accuracy of the atomic-level interaction energies, and whether the appropriate time- and length-scales are properly sampled. On one hand are a class of techniques broadly termed as ab initio or first-principles methods, where atomic interactions are determined from highly accurate quantum chemical methods [2]. Though there are applications that necessitate these methods, ab initio energies are computationally expensive to obtain, such that quantum chemical methods are limited to relatively small systems and short time scales. On the other hand, classical molecular simulations represent the atomic interaction energies with an analytic function (a “force field”) that can be evaluated much more rapidly than ab initio energy, enabling simulations of much larger systems and longer time scales than is possible with ab initio techniques. If force fields are highly accurate, classical molecular simulations have been shown to give quantitatively accurate property predictions in several fields including protein structure refinement [3], drug discovery [4], and energy storage [5].

Developing Accurate Force Fields is Difficult

There are two fundamentally different approaches to developing and improving force fields: bottom-up approaches, wherein parameters are calibrated so the model reproduces the results (e.g., forces, energies, dipoles) of more expensive and accurate methods (i.e., quantum calculations) [6], and top-down approaches, wherein parameters are calibrated so the model matches experimental results [7]. Machine learning force fields are an emerging bottom-up approach that has shown promise for several systems [8]. However, the black-box nature of the potential energy function makes the models physically uninterpretable and severely hinders model transferability beyond the specific training conditions. Developing accurate and transferable force fields with analytical functional forms is a difficult and laborious endeavor [9]. Significant efforts spanning several decades have resulted in several “off-the-shelf” force fields that describe large swaths of condensed matter chemical space [10–13]. These are most commonly “Class I” force fields that consist of harmonic or sinusoidal intramolecular terms that describe bonded interactions, atomic partial charges that represent electrostatic interactions, and intermolecular repulsion-dispersion terms. Unfortunately, these off-the-shelf force fields can yield poor property predictions, even for relatively simple compounds, particularly when they are applied in circumstances beyond the systems and conditions for which they were parameterized [14]. However, since they are well known and the parameter sets are widely distributed, these force fields are used in many molecular simulation studies.

For decades, force field development and optimization has been an active area of research. The bonded intramolecular parameters and partial charges are relatively straightforward to derive bottom-up from quantum calculations. A number of methods and tools, commonly using gradient-based techniques, evolutionary algorithms, or even analytical solutions, have been developed for this purpose [15–22]. These methods work well because the relevant quantities can be computed to a
A Machine Learning Directed Workflow Enables Rapid Optimization of Force Fields

Our force field optimization workflow is shown schematically in Fig. 1. An overview is provided here with complete methodological details reported in the Methodology section. Our strategy in this work is to optimize Lennard-Jones (LJ) repulsion-dispersion parameters, which are among the most difficult to calculate from ab initio methods [49]. Intramolecular parameters and partial charges, which can be reliably and inexpensively determined from bottom-up ab initio-based methods, were taken from existing force fields. We stress, however, that this method can be applied to calibrate any force field parameters.

First, domain knowledge is used to specify physically reasonable bounds on the search space for the parameters that are being optimized. Next, O(10^2) initial parameter sets are generated via space-filling Latin hypercube sampling (LHS). Molecular simulations are performed with each parameter set (Box 1), and the physical properties of interest are computed from the simulations. These results are used to train surrogate models (Box 2) that predict the simulation results directly from the parameter set, and optionally, the thermodynamic state point, e.g., T, p. Additional examples of surrogate model accuracy can be found in SI Fig. S1 and Fig. S2. The surrogate
The role of machine learning is only to act as a surrogate to accurately tested with physics-based molecular simulations. All of the promising candidate parameter sets are ultimately retained. Whereas molecular simulations of these parameters, the surrogate models can do so for millions of candidate parameter sets, once again generated with LHS (Box 3). The $\mathcal{O}(10^7)$ most promising parameter sets are identified from the $\mathcal{O}(10^6)$ candidate sets evaluated with the surrogate models (Box 4). User-selected system-specific metrics including error thresholds, separation in parameter space, and non-dominated status identifies these most promising parameter sets. In multiobjective optimization, the set of non-dominated points includes all parameter sets that are not simultaneously outperformed in every dimension by any other parameter set (Fig. 1a). Finally, the most promising parameter sets are used to initialize the next iteration of molecular simulations (Box 1). The process is repeated until parameter sets are generated that provide the desired accuracy for the experimental properties of interest.

The workflow uses a combination of machine learning-based surrogate models and physics-based molecular simulations to quickly optimize force field parameters for a specific system. Physically-motivated potential energy functional forms that have proven successful over decades are retained. Whereas molecular simulations of these force fields require hours-to-days to compute experimentally measurable properties from a single set of force field parameters, the surrogate models can do so for millions of parameter sets in minutes-to-hours. This means that once the surrogate models have been trained to predict the results of the molecular simulations, they enable an exhaustive search of large parameter spaces that would require $\mathcal{O}(10^7$ to $10^9)$ CPU-hours with molecular simulations. We emphasize that although the surrogate models are used to screen millions of candidate parameter sets, all of the promising candidate parameter sets are ultimately tested with physics-based molecular simulations. The role of machine learning is only to act as a surrogate for physics-based simulations, enabling the parameter search through an otherwise intractable space. The iterative procedure allows the surrogate models to improve as additional training data is collected with each iteration. The original molecular simulations are dispersed across the entire parameter space, but subsequent iterations are focused on the smaller regions of parameter space that are predicted to yield good parameter sets, enabling the surrogate models to improve in the most important regions of parameter space.

**Case Study: Hydrofluorocarbon Force Fields**

Recent international agreements, including the 2016 Kigali Amendment to the 1987 Montreal Protocol, mandated the phaseout of high global warming potential HFC refrigerants. Accurate HFC force fields that are compatible with typical all-atom functional forms are of interest as part of a broader multi-scale engineering effort to sustainably implement this phaseout. Here, we optimize force fields for difluoromethane (HFC-32) and pentafluoroethane (HFC-125), the two components of R-410a, a common household refrigerant, to accurately predict the pure-component VLE properties. While an accurate force field for HFC-32 exists in the literature [32], the existing HFC-125 force fields are either inaccurate [12] or rely on less common functional forms [50–52], which often leads to challenges with force field transferability and simulation software compatibility. For HFC-32, we show that our strategy can develop force fields that outperform expert-created models, while for both HFC-32 and HFC-125, we demonstrate the large improvements that are possible compared against “off-the-shelf” models.

We applied a two-stage approach to improve the HFC force fields. Our workflow was first applied to optimize...
the force fields to accurately predict the liquid density (LD) at the experimental saturation pressure for five temperatures spanning an 80 K temperature range. Following four iterations (LD-1, LD-2, LD-3, LD-4), 25 parameter sets with low LD mean absolute percent error (MAPE) were used to initiate the second stage of force field optimization. In this stage, force field parameters were optimized to accurately predict VLE properties: saturated liquid density, saturated vapor density, vapor pressure, and enthalpy of vaporization. The two-stage approach has advantages: (1) the molecular dynamics (MD) simulations required to compute LD in the isothermal–isobaric ensemble are computationally less expensive than the Monte Carlo (MC) simulations required to compute VLE properties in the Gibbs ensemble, and (2) the stability of the Gibbs ensemble MC simulations is more sensitive to very poor force field parameters.

Fig. 2a shows the cumulative number of parameter sets that yield less than some value of the LD MAPE for each HFC-32 LD iteration. Analogous results for HFC-125 are reported in SI Fig. S3. The strength of the surrogate model approach is highlighted by the improvement from the initial liquid density iteration, LD-1, which evaluated 25 parameter sets generated directly from LHS, to the second liquid density iteration, LD-2, which evaluated parameter sets predicted by the surrogate models to yield low LD MAPE. In LD-1 fewer than 5 parameter sets had an LD MAPE below 10%, but LD-2 yielded more than 100 parameter sets with LD MAPE below 2.5%. Limited additional improvements are observed in LD-3 and LD-4, but additional parameter sets with low LD MAPE are nonetheless generated. Fig. 2b shows the same information for three VLE workflow iterations (VLE-1, VLE-2, VLE-3). Consistent improvements in the saturated liquid density, saturated vapor density, vapor pressure, and enthalpy of vaporization are observed from VLE-1 to VLE-3. The results for the critical temperature and critical density also show improvement even though these properties were not explicitly included in the parameter optimization workflow. Note that the saturated liquid density in VLE-1, which evaluated 25 parameter sets generated during the LD stage, performs slightly worse than the results from LD-4 for two reasons: (1) the model vapor pressure is not precisely equal to the experimental vapor pressure, and (2) a smaller system size and shorter interaction cutoff were used to minimize the computational overhead of the LD iterations. Despite the approximation errors introduced by smaller system sizes and cutoffs, the success of our two-stage optimization strategy shows that initial iterations can be performed with less computationally expensive simulations.

After completing the three(five) VLE iterations, our force field parameterization workflow yielded 26 HFC-32(45 HFC-125) non-dominated parameter sets. Fig. 3 shows our non-dominated parameter sets results compared to experiments [53] and the force fields for HFC-32 and HFC-125 found in literature. Results for vapor pressure and enthalpy of vaporization are shown in SI Fig. S4. The optimized HFC-32 and HFC-125 force fields are notably better than GAFF, and multiple optimized HFC-32 force fields give improved accuracy in all properties compared to the Raabe force field[32]. We chose an error threshold metric to select a subset of top-performing parameter sets from the non-dominated sets. This yielded 4 HFC-32 top parameter sets with MAPE of less than 1.5% and 4 HFC-125 top parameter sets with MAPE of less than 2.5% for the four properties included in the optimization workflow and the critical temperature and critical density. Comparisons of critical temperature and critical density values between experiment, the top four optimized force fields, and literature force fields for both HFCs are shown in SI Tab. S1 and Tab. S2.
Case Study: Ammonium Perchlorate Force Field

Ammonium perchlorate (AP) is a key ingredient in some solid rocket propellants. Experimental data for physical properties of AP are readily available and a Class II force field parameterized by Zhu et al. [54] has been used to predict [55] pure AP properties at temperatures up to 298 K. The Class II functional form supplements the harmonic diagonal constants found in the more common Class I force fields through the inclusion of cross terms, namely, the stretch–stretch and stretch–bend interactions. The cross terms couple internal coordinates in an effort to better reproduce the molecular energetics as well as the dynamics of a system by accounting for anharmonic and coupling interactions. However, it is of interest to develop a Class I force field for AP to use in conjunction with existing Class I force fields for the other components of conventional solid propellant, aluminum oxide [56] and the polymeric binder [57]. Here, we parameterize an AP force field with our force field optimization workflow; we previously had utilized hand-tuning methods to develop a Class I AP force field. We present a comparison between the conventional hand-tuning approach and our workflow. We selected solid AP as our second case study because it represents a very different system than the HFC VLE investigated in the first case study.

The properties to which we calibrated our Class I force field were: (1) unit cell mean distance (UCMD) at 10 K, defined as the mean of the absolute residuals of equilibrium average simulated atomic positions in reference to the experimentally observed unit cell atomic positions (low values indicate the simulation maintains the experimental AP crystal structure); (2) unit cell lattice parameter average absolute percent error at the three temperatures of interest (10, 78, and 298 K); and (3) correct hydrogen bond symmetry. Cumulative error plots for the four AP iterations can be found in Fig. S5. An observation of note regarding these cumulative error plots is that varying criteria for promoting parameter sets to the next set of simulations significantly impacts the improvement in parameter set accuracy between iterations. Less strict UCMD and lattice MAPE criteria were applied when selecting parameter sets for iterations 2 and 3, and stricter criteria were applied for when selecting parameter sets for iteration 4; iteration 4 showed much greater improvement over iteration 3 whereas iterations 2 and 3 are very similar. Our workflow generated 70 parameter sets over the four iterations which gave lower UCMD and lattice parameter errors than the hand-tuned values while maintaining the correct hydrogen bonding symmetry. We applied a Pareto filter and found two non-dominated parameter sets (SI Fig. S6). These two non-dominated parameter sets will subsequently be referred to as our top two AP parameter sets. Table I compares the AP results for these top parameter sets with the hand-tuned and Class II force field results.

| Property | Top A | Top B | HT | Class II |
|----------|-------|-------|----|----------|
| a        | -0.77 | -0.40 | -2.09 | -0.21    |
| b        | -0.88 | -0.48 | -1.87 | -2.79    |
| c        | -0.24 | 0.26  | -1.38 | -3.10    |
| d        | 1.13  | 0.61  | 1.96  | 7.00     |
| e        | 1.11  | 0.89  | 1.68  | 8.19     |
| f        | 0.63  | 0.26  | 1.16  | 8.22     |
| g        | -0.18 | -0.74 | -1.04 | 1.64     |
| h        | -0.71 | -1.10 | -1.31 | 0.46     |
| i        | 0.39  | 0.04  | -0.30 | 0.32     |
| MAPE     | 0.67  | 0.53  | 1.42  | 3.55     |
| UCMD     | 0.1142| 0.1247| 0.1560| 0.3485   |

DISCUSSION

Many Distinct Parameter Sets Yield Equally Accurate Results

The conventional wisdom in molecular modeling is that there is a single “correct” or “best” set of force field parameters, but this may be a misleading way to think about the problem of force field optimization. No force field is a perfect representation of the physical world. Therefore, depending on property priorities within a specific application, model limitations will result in trade-offs between different objectives which lead to different optimal parameter sets [59]. However, our results clearly show that multiple parameter sets can reproduce several experimental properties with very low error. For AP, we found 70 parameter sets that outperform the hand-tuned Class I and existing Class II force fields, and Fig. 4 shows that these force fields are indeed distinctly different parameterizations that all lead to similar accuracy levels for our optimization objectives. For the HFCs, our procedure yielded 26 (HFC-32) and 45 (HFC-125) non-dominated parameter sets, which are distinctly different parameterizations (SI Fig. S7) and display good performance on our optimization objectives and the critical temperature and density. We also find no correlation between similarity of the force field parameters and property error (SI Fig. S8), further suggesting that distinctly different parameterizations can result in highly accurate force fields.

These findings lead to several questions that fall beyond the scope of the current work. Among these is the apparent over-parameterization of the force field model, as depicted by the wide range of the parameter values which give similar results. Because each parameter in the force field has physical significance, reducing the number
FIG. 4. Repulsion-dispersion parameters for the final 70 AP parameter sets.  shows the training objectives. The red stars and purple circles show the performance of the Class II force field of Zhu et al. [54] and the hand-tuned Class I force field, respectively.

A further question involves how final parameter sets should be selected, given that many high-quality parameter sets are available. Our workflow is explicitly not designed to identify a single optimal set of force field parameters. Instead, it searches for and identifies high quality parameter sets with respect to all of the optimization objectives, i.e., along the non-dominated front. Further narrowing down the parameter sets requires additional post hoc criteria that depend on the desired application of the force field. Here, we have chosen non-dominated status and error thresholds for all properties. Alternative strategies include weighting the different properties according to domain knowledge, ranking force fields by their error in the various properties studied via statistical tests [46], evaluating the force field’s performance for properties not included in the optimization procedure, or selecting parameter sets based upon a measure of compatibility with the force fields being used for other components of a system. Ultimately, selecting the final force field for a given application will be systematic and application dependent and rely heavily on domain expertise.

Maintaining a Physically-Motivated Analytical Functional Form Aids Transferability to Properties Not Included as Optimization Objectives

One important question is whether the force field parameters developed with this workflow will yield accurate property predictions for properties not included in the optimization workflow. We have already shown that the HFC force fields developed during the VLE tuning stage result in accurate critical temperature and density even though these properties were not optimization objectives. However, these critical properties are largely determined by accurately capturing the temperature dependence of the saturated liquid and saturated vapor density, both of which were optimization objectives. To further investigate the transferability of force field parameters developed with our workflow to properties not included as optimization objectives, we examine the performance of the 25 parameter sets used during the VLE-1 iteration. These parameter sets were used for VLE-1 because they were identified as good at predicting the temperature dependence of the liquid density during the LD iterations. Fig. 2 shows that when applied for VLE-1, many perform quite well for VLE properties. In fact, three of the HFC-32 parameter sets used for the VLE-1 iteration had less than 2% MAPE in all six properties. Furthermore, when compared with GAFF, all 25 parameter sets selected from the LD stage yield better performance for all six properties. This is strong evidence that our force field optimization workflow can, with the correct optimization objectives, yield force fields that accurately predict properties beyond the optimization objectives.

The transferability of the LD-optimized parameters to VLE gives credence to our overall force field optimization philosophy, which maintains traditional analytical functional forms and uses machine learning as a guide to identify optimal parameters. By maintaining a physically motivated analytical functional form, good parameter sets are likely to be transferable to multiple properties. However, a priori, it is unclear that there should be such a strong correlation between the liquid density and VLE properties. For many systems, accurately predicting the liquid density is a necessary, but often quite insufficient, condition for an accurate force field. We hypothesize there is a key factor that contributes to the transferability of the parameters developed during the LD iterations to VLE: the LD simulations were performed at the saturated vapor pressure across an 80 K temperature range, up to within 30 K of the experimental critical temperature. Accurately capturing the liquid density across a wide temperature range and avoiding spontaneous vaporization as the critical temperature is approached requires capturing a careful balance of the cohesive energy and molecular size, which are closely related to the LJ repulsion-dispersion parameters that were calibrated. If the correlation between LD-optimized parameters and VLE properties proves applicable to other classes of molecules, it may offer an extremely rapid
method for developing force fields with accurate VLE properties.

Selecting Good Properties for Force Field Optimization is Challenging

When optimizing force fields for the HFC case study, we were interested in developing force fields that accurately predict HFC VLE behavior. As such, we chose to calibrate parameters to the saturated liquid and vapor densities, vapor pressure, and enthalpy of vaporization. However, these properties are expensive to compute in molecular simulations, making it difficult to evaluate a large parameter space. Therefore we used less computationally expensive LD iterations to generate good parameter sets for VLE and narrow the parameter search space. This demonstrates that a cheaper “screening” property can be used to narrow the parameter search space drastically when good parameter sets for the screening property are a superset of the good parameter sets for the final properties of interest.

The AP case study had different challenges. The MD simulations required to predict the AP properties were computationally inexpensive, so there was no need to first use a screening property. However, it was not immediately clear what experimental properties we should target. Our first implementation attempted to reproduce the temperature dependence of the crystal lattice parameters alone: this proved ineffective, and naive in hindsight, as we generated many force fields that yielded the correct crystal lattice parameters but incorrect crystal structures. To overcome this issue, we added the 10 K UCMD as an objective because it is a measure of how accurately the force field reproduces the experimental crystal structure at 10 K. The lattice MAPE was still included to capture the temperature dependence of the crystal dimensions since the experimental unit cell coordinates are only reported at 10 K.

The UCMD surrogate model has a notable difference from the others; whereas the other surrogate models predict a property (e.g., lattice $a$ or $p_{vap}$), the UCMD surrogate model is formulated as an objective function. The UCMD surrogate model predicts the mean distance of all of the unit cell atoms from their respective coordinates in the experimental unit cell. By definition, this distance is zero if the simulated structure perfectly matches experiment. There are benefits to using physical experimentally measured properties compared to an objective function within the optimization workflow, including providing a clear mapping between a surrogate model and the objective metric. However, using surrogate models to predict objective functions provides the opportunity to combine multiple pieces of information into a single number, as is the case with UCMD, which combines the distance of 40 atoms from their positions in the experimental unit cell into a single value. This strategy can drastically reduce the number of required surrogate models. In general, our experience with the AP case study emphasizes that careful thought must be given as to which experimental properties are best to target and how these should be accounted for within the workflow. Roughly 75% of our effort for the AP case study was dedicated to identifying the appropriate experimental properties to target.

Parameterizations Can Provide Insights into Model Limitations

The exhaustive search of parameter space enabled by our workflow provides opportunities to distinguish between inaccurate results from poor parameter sets and physical limits from our choice in force field functional form and unoptimized parameters. For example, although our workflow finds high-quality AP parameter sets, we encountered limitations that likely arise from parameters that were not calibrated, and possibly even the force field functional form that we selected. No parameter set predicted an overall UCMD of less than 0.1 Å. Given the exhaustive search enabled by our force field optimization workflow, this suggests that there are no parameter sets capable of yielding a crystal structure with UCMD below 0.1 Å, given the selected functional form, intramolecular parameters, and partial charges. SI Fig. S9 shows the per-element UCMD distances after iteration 4. Although the UCMD for the chlorine, oxygen, and nitrogen atoms fall between 0.1 Å and 0.15 Å for many parameter sets, the hydrogen UCMD rarely falls below 0.2 Å. Further investigation suggests that this effect is because the N—H bond stretching is insufficiently susceptible to the three unique local hydrogen-bonding chemical environments; experiments report that the N—H bond lengths range between 1.028–1.058 Å whereas in simulations the N—H bond lengths typically cover a much smaller range — between 1.025–1.033 Å — for parameter sets that well reproduce the experimental physical properties. The N—H stretching force constant was not included in our parameterization process. However, even if it was, it is not clear that it would be possible to capture the correct bond stretching behavior and match the vibrational spectra and the N—H bond lengths with a Class I functional form (see SI Methods for further discussion).

CONCLUSIONS

We have presented a machine learning directed workflow for top-down optimization of force field parameters. By harnessing surrogate-assisted optimization, our workflow drastically reduces the number of simulations necessary to find optimal force field parameters by replacing them with computationally tractable surrogate model evaluations. We synthesize GPR and SVM surrogate models and multiobjective optimization into a generic approach to optimize all-atom force fields for realistic
systems. We have applied our workflow to optimize HFC force fields to VLE properties, and an AP force field to the experimental crystal structure. These case studies show that our workflow can be applied to most molecular systems and optimization objectives, provided sufficient reference data. Surrogate models could be used to predict difficult-to-compute thermodynamic properties such as solubilities and binding energies, and transport properties such as self-diffusivity and thermal conductivity. While we have focused on calibrating repulsion-dispersion parameters in this work, this workflow could be used to calibrate any parameters within the force field in a fully top-down approach or as part of a bottom-up force field development workflow, by including ab initio data in the fitting procedure [40]. Additionally, we discussed the reasons for successes and limitations of the workflow, the potential challenges of applying this workflow to a particular system (i.e., choosing optimization objectives), and the questions about molecular modeling these results present. We highlight that this workflow is built on a foundation of domain knowledge in selecting the parameters to calibrate, the parameter bounds, and the experimental properties to ensure results are reasonable.

Finally, while we believe that our workflow will enable more efficient force field development and optimization in the future, reducing the need for laborious hand-tuning practices, quantifying the workflow’s efficiency was beyond the scope of this work. We can, however, anecdotally note for the AP case study that the hand-tuning approach utilized \( \sim 15,000 \) simulations (\( \sim 240,000 \) CPU-hours) and only found 1 optimal parameter set. This is in contrast to our presented workflow, which evaluated \( \sim 3,000,000 \) parameter sets using surrogate models, \( O(10^9) \) times as many as the hand-tuning method, but only required 3,000 simulations, to find 70 parameter sets from these regions of parameter space where \( \hat{y} \) may or may not be close to the experimental values, \( y^{\exp} \). The goal of this work is to refine \( U(r) \) by optimizing \( O(10^4) \) force field parameters, \( \zeta' \subseteq \zeta \), such that \( y^{\sim} \approx y^{\exp} \) for one or more physical properties of interest.

The functional form and most force field parameters are taken without modification from existing force fields. In both case studies presented here, the LJ parameters, \( \sigma \) and \( \varepsilon \), are optimized. Upper and lower bounds for each parameter are selected to span a wide range of physically reasonable values. The initial \( O(10^2) \) parameter sets are randomly selected from within these bounds with LHS.

**Step 1: Perform Molecular Simulations with \( O(10^2) \)**

**Physics-Based Force Fields**

Molecular simulations are performed for each parameter set with the molecular dynamics (MD) or Monte Carlo (MC) method. For each parameter set, \( y^{\sim} \) is computed from the simulation output. Simulations may be performed at multiple thermodynamic conditions (e.g., \( T, p \)) for each parameter set if the experimental data exists. Signac-flow was used to manage the setup and execution of all molecular simulations [60, 61].

**Step 2: Train Surrogate Models to Predict Simulation Results from Force Field Parameters**

Gaussian process (GP) surrogate models are trained to predict \( y^{\sim} \) as a function of the calibrated parameters \( \zeta' \). For each property, we train:

\[
\hat{y}^{\sim} = GP_i(m_i(\zeta'), \text{cov}_i(\zeta', \zeta'))
\]

where \( \hat{y}^{\sim} \) is the surrogate model prediction of \( y^{\sim} \), \( GP_i \) is the GP model for property \( i \), \( m_i \) is the mean function, and \( \text{cov}_i \) is the covariance (kernel) function. All GP models were implemented in GPFLOW 2.0.0 [62]. To improve the accuracy of the GP models in regions of parameter space where \( y^{\sim} \approx y^{\exp} \), we exclude particularly poor parameter sets from the GP training data. We then trained support vector machine (SVM) classifiers to predict if a parameter set was unphysical (e.g., simulation fails) so that parameter sets from these regions of parameter space could be excluded when the GP models were used to predict the results of trial parameter sets. All SVM classifiers were implemented in scikit-learn [63] with a radial basis function kernel.
Step 3: Evaluate Surrogate Models for $O(10^6)$ Trial Force Field Parameter Sets

After the GP and SVM models are trained, $O(10^6)$ trial parameter sets are generated with LHS. For each parameter set, the SVM and GP models are used to calculate the surrogate model estimates of $\hat{y}_{\text{sim}}$, $\tilde{y}_{\text{sim}}$.

Step 4: Select Parameter Sets that Surrogate Models Predict Will Best Reproduce Experiments

Parameter sets where the surrogate models predict good agreement with experiment, $\hat{y}_{\text{sim}} \approx y_{\text{exp}}$, are selected for the next iteration. If needed, we apply an optional distance-based search algorithm (see SI Methods) to down-select only parameter sets that are far apart in parameter space.

HFC Systems

Force fields were independently developed for HFC-32 and HFC-125. Two stages of optimization were used for each HFC. The first stage used MD simulations in the $NpT$ ensemble at: 241 K, 261 K, 281 K, 301 K, 321 K for HFC-32 and 229 K, 249 K, 269 K, 289 K, 309 K for HFC-125. For each temperature, the pressure was set to the experimental saturation pressure. The only property considered during the first stage was the liquid density ($y = \{\rho_l\}$). In the second stage of optimization, Gibbs ensemble Monte Carlo (GEMC) was performed. The property objectives were the saturated liquid density, saturated vapor density, vapor pressure, and enthalpy of vaporization, or $y = \{\rho_{\text{sat}}^l, \rho_{\text{sat}}^v, P_{\text{vap}}, \Delta H_{\text{vap}}\}$. Simulations were performed at the same temperatures used for the first stage. Four iterations of the stage 1 optimization were performed for both HFC-32 and HFC-125. Three and five iterations of stage 2 optimization were performed for HFC-32 and HFC-125, respectively.

Force Field Parameters

The functional form was taken from GAFF [12]:

$$U(r) = U_{\text{intra}}(r) + \sum_i \sum_{j>i} \frac{q_i q_j}{4\pi\varepsilon_0 r_{ij}} + \sum_i \sum_{j>i} 4\varepsilon_{ij} \left[ \left( \frac{\sigma_{ij}}{r_{ij}} \right)^{12} - \left( \frac{\sigma_{ij}}{r_{ij}} \right)^{6} \right]$$

where $U_{\text{intra}}$ contains all the intramolecular terms (see SI Methods), $r_{ij}$ is the distance between atoms $i$ and $j$, $q$ is the atomic charge, $\varepsilon_0$ is the permittivity of free space, and $\sigma_{ij}$ and $\varepsilon_{ij}$ parametrize the LJ potential that describes the repulsion-dispersion interactions between atoms $i$ and $j$. The intramolecular parameters and partial charges were taken from GAFF. The force field optimization method was used to determine $\sigma$ and $\varepsilon$ for 3 unique atom types in HFC-32 and 5 unique atom types in HFC-125, yielding a total 6 and 10 calibrated parameters for HFC-32 and HFC-125, respectively. The lower and upper bounds for each parameter were selected per-element ($\sigma$ in $\AA$, $\varepsilon/k_B$ in K): $3.0 \leq \sigma_C \leq 4.0$, $2.5 \leq \sigma_F \leq 3.5$, $1.7 \leq \sigma_H \leq 2.7$, $20 \leq \varepsilon_C/k_B \leq 60$, $15 \leq \varepsilon_F/k_B \leq 40$, $2 \leq \varepsilon_H/k_B \leq 10$. All unlike LJ interactions were computed with Lorentz–Berthelot mixing rules. See the SI Methods for details of the atom types, intramolecular parameters, and partial charges.

Classifier

An SVM classifier was trained to predict parameter sets that yielded spontaneous vaporization ($\rho' < 500$ kg/m$^3$) in MD simulations initiated at liquid density from $\zeta'$ and $T$.

GP Model

The GP models predicted the value of a physical property from $\zeta'$ and $T$. The LD iterations used one GP model that predicted $\rho'$. Parameter sets with $\rho' < 500$ kg/m$^3$ were excluded from the GP training data. The VLE iterations used one GP model for each property: $\{\rho_{\text{sat}}^l, \rho_{\text{sat}}^v, P_{\text{vap}}, \Delta H_{\text{vap}}\}$. All GP models used a radial basis function or Matérn $\nu = 5/2$ kernel and a linear mean function [64].

Selecting Parameter Sets for the Next Iteration

A new LHS with 1,000,000 (HFC-32) or 500,000 (HFC-125) parameter sets was generated for each iteration. LD iterations: Each parameter set was evaluated with the LD SVM classifier at the highest $T$. Each parameter set was evaluated with the LD GP model at each $T$, and the root mean square error (RMSE) between the GP model prediction and experimental liquid density across all five temperatures was calculated for each parameter set. The 100 lowest RMSE parameter sets that the SVM predicted would remain liquid, and the 100 lowest RMSE parameter sets that the SVM predicted would transform to vapor, were selected for the next iteration. The low-RMSE, predicted-vapor parameter sets were included because they reflect disagreement between the SVM and GP models. After four LD iterations, parameter sets for the VLE-1 iteration were selected from the 800 simulated parameter sets. A distance-based search algorithm (see SI Methods) was used to select 25 well-separated parameter sets with RMSE $\leq 10$ kg/m$^3$. VLE iterations: Each parameter set from the LHS was evaluated with the LD GP model. Parameter sets predicted to yield
LD RMSE > 25 kg/m$^3$ were discarded. This step was included to make use of the training data generated during the LD iterations, since the LD GP model is very accurate after four LD iterations. The remaining parameter sets were evaluated with the four GP models trained to predict VLE properties ($\rho_{\text{sat}}, \rho'_{\text{sat}}, P_{\text{vap}}, \Delta H_{\text{vap}}$). The RMSE difference between the GP model predictions and experimental values across all five temperatures was calculated for each property and parameter set. A four-objective Pareto filter was used to identify and discard all dominated parameter sets. A parameter set is dominated if one or more parameter set performs better than it in all of the considered objective dimensions (e.g., physical properties). The 25 parameter sets selected for the next iteration comprised the top performing parameter set for each physical property and 21 parameter sets selected from the remaining non-dominated parameter sets. A distance-based search algorithm (see SI Methods) identified parameter sets that were well-separated in parameter space.

**MD Simulations**

Simulations of 150 HFC molecules were performed in the $NpT$ ensemble at the experimental saturation pressure. Initial configurations were generated at 1000 kg/m$^3$. Following an energy minimization, systems were equilibrated for 500 ps with the Bussi thermostat [65] and Berendsen barostat [66] with $\tau_T = 0.1$ ps, $\tau_p = 0.5$ ps. The production simulations were 2.5 ns in length with the Bussi thermostat and Parrinello-Rahman barostat [67] with $\tau_T = 0.5$ ps and $\tau_p = 1.0$ ps. The final 2.0 ns of the production simulations were used to compute the average density.

The equations of motion were integrated with the leapfrog algorithm and a time step of 1.0 fs. LJ interactions and short range electrostatics were cut off at 1.0 nm. The particle mesh Ewald method was used to compute the average density.

**MC Simulations**

GEMC simulations were performed with 1000 HFC molecules. The initial liquid box (800 HFC molecules) was generated at the experimental liquid density and pre-equilibrated with a 5000 sweep $NpT$ MC simulation. The initial vapor box (200 HFC molecules) was randomly generated at the vapor density estimated from the ideal gas law. The combined system was simulated with GEMC. The systems were equilibrated for 10,000 MC sweeps followed by a production GEMC simulation was 90,000 MC sweeps.

LJ interactions and short range electrostatics were cut off at 1.2 nm in the liquid box and 2.5 nm in the vapor box. Long range electrostatics were computed with an Ewald summation with a relative accuracy of $10^{-5}$. Analytical tail corrections to the LJ interactions were applied to energy and pressure. Simulations were performed with MoSDeF Cassandra 0.1.1 [70] and Cassandra 1.2.2 [71].

**AP System**

Simulations of AP were performed at 1 atm and 10, 78, and 298 K. Two properties were considered: (1) the absolute percent error from the experimental lattice parameters averaged across all three temperatures, i.e. the mean absolute percent error (MAPE), and (2) the mean of the absolute residuals of equilibrium average simulated atomic positions in reference to the experimental unit cell at 10 K. To assess the symmetry expected in AP's Pnma space group, the difference in the $N$-$H(3) \cdot \cdot \cdot O(3)$ mirror symmetric bond lengths and angles were computed. Hydrogen bonds within 0.001 Å and angles within 0.3° were considered symmetric. Four workflow iterations were performed.

**Force Field Parameters**

The Class II force field of Zhu et al. [54] served as a basis for the development of the Class I force fields in this work. The partial charges were left unchanged [55]. The Class II intramolecular bonds and angles were recast to the Class I harmonic functional forms (see SI Methods). The force field optimization method was used to determine LJ parameters $\sigma$ and $\varepsilon$ for the 4 unique atom types in the AP model. The lower and upper bounds for each parameter were as follows ($\sigma$ in Å, $\varepsilon$ in kcal/mol): $3.5 \leq \sigma_{\text{Cl}} \leq 4.5$, $0.5 \leq \sigma_H \leq 2.0$, $2.5 \leq \sigma_N \leq 3.8$, $2.5 \leq \sigma_O \leq 3.8$, $0.1 \leq \varepsilon_{\text{Cl}} \leq 0.8$, $0.0 \leq \varepsilon_H \leq 0.02$, $0.01 \leq \varepsilon_N \leq 0.2$, $0.02 \leq \varepsilon_O \leq 0.3$. All unlike LJ interactions were calculated with geometric mixing rules.

**Classifier**

Two SVM classifiers were trained. The first classifier predicted whether a parameter set would yield an accurate 10 K unit cell with UCMD < 0.8 Å, and the second classifier predicted whether a parameter set would yield the desired hydrogen bond symmetry, as defined above.

**GP Model**

Two GP surrogate models were trained. The first GP model predicted the 10 K UCMD from $\zeta'$. Parameter
sets with UCMD $\geq 0.8$ Å were not included in the training data. The second GP model predicted the absolute percent error (APE) of the lattice parameters from $\zeta'$ and $T$. Both GP models used a Matérn $\nu = 3/2$ kernel and a linear mean function [64].

Selecting Parameter Sets for the Next Iteration

1,000,000 new parameter sets were generated using LHS for each iteration. Each parameter set was evaluated with the UCMD and symmetry classifiers. Parameter sets that did not meet the UCMD threshold were discarded. The remaining parameter sets were evaluated with the two GP models. The lattice APE GP model was evaluated three times for each parameter set, with $T = 10$ K, 78 K, and 298 K. The mean of the lattice parameter APE at each temperature was calculated and recorded as the lattice MAPE. All parameter sets that did not meet the UCMD and lattice MAPE thresholds listed in the Tab. S3 were discarded. All non-dominated parameter sets that met the thresholds were selected for the next iteration. The remaining parameter sets were selected from all that met the thresholds with an $L_1$ distance metric in scaled parameter space and the distance-based search to identify well-separated parameter sets. In an attempt to improve accuracy between iterations, when selecting parameter sets for iteration 4, we applied stricter error thresholds, evaluated the symmetry SVM and removed all parameter sets that did not meet the symmetry threshold.

MD Simulations

Simulations of orthorhombic AP were performed in the $NpT$ ensemble at 1 atm and 10, 78, and 298 K. The AP structure was taken from the 10 K data of Choi et al.[58] The simulation cell comprised 378 ($6 \times 9 \times 7$) unit cells. Initial velocities were drawn from a Gaussian distribution with the linear and angular momentum set to zero. A 1.0 fs time step was utilized with the time integration scheme derived by Tuckerman et al.[72] The equations of motions were those of Shinoda et al.[73] Nosé–Hoover style algorithms were utilized for both the thermostat and barostat with relaxation times of 0.1 ps and 1.0 ps, respectively. The $x$-, $y$-, and $z$-dimensions were allowed to fluctuate independently while maintaining an orthorhombic geometry. All simulations utilized 100 ps of equilibration followed by an additional 100 ps for generating production data. Pairwise LJ and Coulombic interactions were computed up to 1.5 nm and long-range electrostatic interactions were computed using the particle–particle particle–mesh method[74] with a relative accuracy of $10^{-5}$. No analytical tail corrections were applied to the repulsion-dispersion interactions. All bonds were fully flexible. Simulations were performed with LAMMPS, version 7 Aug 2019 [75].

| Abbreviation | Expansion                       |
|--------------|---------------------------------|
| GP           | Gaussian process                |
| GPR          | Gaussian process regression     |
| HFC          | Hydrofluorocarbon               |
| HFC-32       | Difluoromethane                 |
| HFC-125      | Pentfluoroethane                |
| VLE          | Vapor-liquid equilibrium        |
| LD           | Liquid density                  |
| APE          | Absolute percent error          |
| MAPE         | Mean absolute percent error     |
| MD           | Molecular dynamics              |
| MC           | Monte Carlo                     |
| AP           | Ammonium perchlorate            |
| UCMD         | Unit cell mean distance         |
| LJ           | Lennard-Jones                   |
| LHS          | Latin hypercube sampling        |
| SVM          | Support vector machine          |
| GEMC         | Gibbs ensemble Monte Carlo      |

TABLE II. Description of abbreviations utilized.

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Supporting Information for: Machine Learning Directed
Optimization of Classical Molecular Modeling Force Fields

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SI METHODS

HFC Case Study

The functional form of GAFF [1] given in the main text was:

\[
U(r) = U^{\text{intra}}(r) + \sum_i \sum_{j>i} \frac{q_i q_j}{4 \pi \varepsilon_0 r_{ij}} + \sum_i \sum_{j>i} 4 \varepsilon_{ij} \left[ \left( \frac{\sigma_{ij}}{r_{ij}} \right)^{12} - \left( \frac{\sigma_{ij}}{r_{ij}} \right)^6 \right]
\] (1)

where \( r_{ij} \) is the distance between atoms \( i \) and \( j \), \( q \) is the atomic charge, \( \varepsilon_0 \) is the permittivity of free space, and \( \sigma_{ij} \) and \( \varepsilon_{ij} \) parameterize the LJ potential that describes the repulsion-dispersion interactions. The intramolecular portion of the potential is:

\[
U^{\text{intra}}(r) = \sum_{\text{bonds}} k_r (r - r_{eq})^2 + \sum_{\text{angles}} k_\theta (\theta - \theta_{eq})^2 + \sum_{\text{dihedrals}} \nu_n \left[ 1 + \cos \left( n \phi - \gamma \right) \right]
\] (2)

where \( r_{eq} \) and \( \theta_{eq} \) are the nominal bond length and angle, respectively, \( k_r, k_\theta, \) and \( \nu_n \) are force constants, \( n \) is the multiplicity and \( \gamma \) is the nominal dihedral angle. The sums are over all bonds, angles, and dihedrals in the system, respectively. The bond, angle, and dihedral parameter for HFC-32 and HFC-125 were taken from GAFF [1]. The parameters are reported in Tab. S4. Partial charges were determined with RESP [2] as implemented in AmberTools 1.4 [3]. The quantum electrostatic potential was computed with Gaussian 09 [4] with B3LYP/6-311++g(d,p) [5, 6]. Partial charges for HFC-32 and HFC-125 are reported in Tab. S4.

HFC-32 has three atom types, C, F, and H. HFC-125 has five atom types: C1, C2, F1, F2, and H. C1 is the carbon bonded to one carbon atom, two fluorine atoms, and one hydrogen atom. C2 is the carbon bonded to one carbon atom and three fluorine atoms. F1 is bonded with to C1 and F2 is bonded with C2. The \( \sigma \) and \( \varepsilon \) parameters for each atom type were optimized, resulting in 6 parameters that are optimized for HFC-32 and 10 parameters that are optimized for HFC-125.

AP Case Study

For each simulated parameter set, AP was modeled at 10, 78, and 298 K. At each temperature, the average lattice parameters were compared to experimental values [7]. The mean
absolute percent error (MAPE) of the lattice parameters, taking all temperature data into account, was utilized as a single-metric quantity to assess the performance of a parameter set in reproducing experimental lattice parameters. At 10 K, the simulated unit cell was compared to the experimental unit cell by comparing atomic positions and summing the absolute residuals. In an effort to be more consistent with the refined hydrogen positions described by Choi et al.[7], the hydrogen atoms listed in their primitive cell were extended along their N—H vectors to match the N—H lengths listed in their Table V. To assess the symmetry that should be present in orthorhombic AP’s Pnma space group, the differences in the N—H(3)· · ·O(3) mirror symmetric bond lengths and angles were computed. To determine tolerances for assessing symmetry, the manually tuned force field was utilized and the frequency of saving coordinate data over the 100 ps production run was varied between 100–10,000 fs. When saving the coordinates every 100 fs, the symmetric hydrogen bond lengths were within 0.00003 Å and the angles were within 0.01° of each other. When saving the coordinates every 10,000 fs, the resolution of symmetry decreases to within 0.001 Å for bonds and 0.3° for angles. For data management reasons, the coordinates were saved every 10,000 fs and the corresponding symmetry tolerances were utilized in classifying if a given parameter set was successful in reproducing the experimentally observed symmetry in the hydrogen bonding structure of AP.

The Class II force field of Zhu et al.[8] served as a basis for the development of the Class I force fields investigated in this work. The partial charges were left unchanged, as described by Tow and Maginn [9]. The Class II intramolecular bonds and angles were recast to the harmonic functional forms typically utilized in Class I force fields; this process was ad hoc and involved qualitative matching to the experimental infrared spectrum. The most significant outcome of this procedure was that at 298 K the N—H stretching mode split into two separate peaks for the Class I force field, as opposed to the single peak observed by both experiment and the Class II force field. This is likely due to inherent limitations in the harmonic representation of the vibrational mode; in the context of our future work, this trade-off in vibrational behavior for the simplicity and transferability of the Class I AP force field is acceptable. The AP force field parameters that were not optimized are reported in Tab. S5.
Identifying parameter sets that are well-separated in parameter space

The distance between each parameter set is taken as the $L_1$ norm in scaled parameter space. Scaled parameter space is defined such that the lower bound of a parameter is equal to 0.0 and the upper bound is equal to 1.0. The following algorithm was used to select well-separated points: (1) define a distance threshold, (2) select one parameter set at random and add it to the list of those for the next iteration (3) discard all parameter sets within the distance threshold of the parameters sets selected for the next iteration, (4) return to (2) and continue iterating until no parameter sets remain, (5) check the final number of parameter sets identified for the next iteration, and if more than desired, start over and return to (1) with a larger distance threshold.
FIG. S1. The simulation result compared with the GP surrogate model prediction for the surrogate models trained during the VLE-2 iteration for HFC-32. Comparisons are shown for $\rho_{\text{sat}}^l$ (a, b), $\rho_{\text{sat}}^v$ (c, d), $P_{\text{vap}}$ (e, f), $\Delta H_{\text{vap}}$ (g, h). Comparisons for the training data are shown in the left column (a, c, e, g) and the comparisons for the test data are shown in the right columns (b, d, f, h). Radial basis function (RBF), Matérn $\nu = 3/2$ (Matern32), and Matérn $\nu = 5/2$ (Matern52) refer to the kernel for the GP surrogate models [10]. These results are representative of the GP model accuracy for LD and VLE iterations of the HFC force field optimization.
FIG. S2. Examples of the GP surrogate model means (lines) and variances (shaded regions) for one parameter set from the VLE-2 iteration for HFC-32. Radial basis function (RBF), Matérn $\nu = 3/2$ (Matern32), and Matérn $\nu = 5/2$ (Matern52) refer to the kernel for the GP surrogate models [10]. Points shown in black were included in the training data for the GP models, whereas points in red were excluded. GP surrogate models shown for $\rho_{\text{sat}}^l$ (a), $\rho_{\text{sat}}^v$ (b), $P_{\text{vap}}$ (c), $\Delta H_{\text{vap}}$ (d). These results are representative of the GP model accuracy for LD and VLE iterations of the HFC force field optimization.
FIG. S3. Cumulative number of HFC-125 parameter sets per iteration with less than some MAPE for (a) the liquid density iterations 1–4 (LD-n) and (b) vapor–liquid equilibrium iterations 1–5 (VLE-n), where n is the iteration number. Inset in panel (a) shows the LD behavior for liquid density MAPE < 2.5%.
FIG. S4. Vapor pressure and enthalpy of vaporization for HFC-32 and HFC-125 force fields compared with literature [1, 11] and experiment [12]. The 26 (HFC-32) and 45 (HFC-125) non-dominated parameter sets are shown as lightly shaded colored circles. All the non-dominated parameter sets for both HFCs well reproduce the experimental values and are thus highly overlapped.
FIG. S5. Cumulative number of AP parameter sets per iteration with less than some value of (a) the 10 K unit cell mean distance (UCMD) and (b) the lattice MAPE. Insets have the same axis titles and focus on the improvement from iteration 3 to iteration 4. Less strict UCMD and lattice MAPE criteria were applied when selecting parameter sets for iterations 2 and 3, and stricter criteria were applied when selecting parameter sets for iteration 4. Threshold values for selection next iteration parameter sets are shown in Tab. S3.
FIG. S6. 70 AP parameter sets that yield lower UCMD and lattice parameter errors than the hand-tuned values while maintaining the correct hydrogen bonding symmetry. The red points are non-dominated and indicate our top two AP parameter sets. The blue points are dominated.
FIG. S7. Repulsion-dispersion parameters for (a) 26 HFC-32 and (b) 45 HFC-125 high quality parameter sets. $\sigma$ is reported in units of Å and $\varepsilon$ is reported in units of K/$k_B$. Each parameter set is connected by a different color line. Thick lines indicate the top 4 parameter sets for each molecule. The y-axes are scaled to show the full range investigated for each parameter. The final four y-axes show the performance for the training objectives. The gray squares and cyan triangles show the performance of GAFF [1] and the force field of Raabe [11], respectively. For HFC-32 the GAFF MAPE for $\rho_{\text{vap}}$ and $P_{\text{vap}}$ are not shown as they are 133 and 104, respectively.
FIG. S8. Distance between the best parameter set for each property ($L_1$ norm with normalized parameter values) and all other parameter sets versus the property error for HFC-32 VLE iterations. The point with an $L_1$ norm of 0.0 shows the performance of the best parameter set for a given property. One point is shown for each parameter set tested during the VLE iterations. The lack of correlation between the $L_1$ distance from the top performing parameter set and the property error emphasizes that high quality parameter sets are distributed throughout parameter space.
FIG. S9. Overall (gray line) unit cell mean distance (UCMD) compared with UCMD of the four different atom types (points) for the parameter sets tested during iteration 4 of the ammonium perchlorate force field optimization. The hydrogen bond symmetry is reported as abs(Δhbond), where Δhbond is the difference in the symmetric hydrogen bond lengths.
TABLE S1. Critical temperatures and densities predicted by GAFF [1], the force field of Raabe [11], and the top four HFC-32 parameter sets compared to experiment [12]

| Critical Property Predictions | Force Field | $T_c$ (K) | $\rho_c$ (kg/m$^3$) |
|-------------------------------|-------------|-----------|---------------------|
| GAFF                          | 315.3       | 400.1     |
| Raabe                         | 344.1       | 430.9     |
| Top A                         | 351.1       | 431.0     |
| Top B                         | 352.8       | 430.5     |
| Top C                         | 351.9       | 431.8     |
| Top D                         | 352.9       | 430.9     |
| Experiment                    | 351.4       | 429.8     |

TABLE S2. Critical temperatures and densities predicted by GAFF [1] and top four HFC-125 parameter sets compared to experiment [12]

| Critical Property Predictions | Force Field | $T_c$ (K) | $\rho_c$ (kg/m$^3$) |
|-------------------------------|-------------|-----------|---------------------|
| GAFF                          | 370.0       | 523.4     |
| Top A                         | 342.5       | 570.9     |
| Top B                         | 341.5       | 562.9     |
| Top C                         | 341.8       | 567.5     |
| Top D                         | 343.1       | 576.6     |
| Experiment                    | 339.4       | 571.9     |

TABLE S3. Screening criteria for AP iterations

| Iteration | Structure Classifier Threshold (Å) | Hydrogen Bond Symmetry Classifier Threshold (Å) | UCMD Threshold (Å) | Lattice MAPE Threshold |
|-----------|-----------------------------------|-----------------------------------------------|-------------------|-------------------------|
| 1-2       | 0.8                               | -                                             | 0.35              | 2.5                     |
| 2-3       | 0.8                               | -                                             | 0.35              | 2.5                     |
| 3-4       | 0.8                               | 0.001                                         | 0.2               | 1.5                     |
### Partial Charges

| Type | GAFF Type | $q$ (e) |
|------|-----------|---------|
| C    | c3        | 0.405467|
| F    | f         | -0.250783|
| H    | h2        | 0.0480495|
| C1   | c3        | 0.224067|
| C2   | c3        | 0.500886|
| F1   | f         | -0.167131|
| F2   | f         | -0.170758|
| H1   | h2        | 0.121583|

### Bonds

| GAFF Type | $k_r$ (kcal mol$^{-1}$ Å$^{-2}$) | $r_{eq}$ (Å) |
|-----------|---------------------------------|---------------|
| c3-f      | 356.9                           | 1.3497        |
| c3-h2     | 331.7                           | 1.0961        |
| c3-c3     | 300.9                           | 1.5375        |

### Angles

| GAFF Type | $k_\theta$ (kcal mol$^{-1}$ rad$^{-2}$) | $\theta_{eq}$ (deg) |
|-----------|---------------------------------------|---------------------|
| f-c3-f    | 70.9                                  | 107.36              |
| f-c3-h2   | 51.1                                  | 108.79              |
| c3-c3-f   | 66.1                                  | 109.24              |
| c3-c3-h2  | 46.2                                  | 110.22              |
| h2-c3-h2  | 39.0                                  | 110.20              |

### Dihedrals

| GAFF Type | $\nu_n$ (kcal mol$^{-1}$) | $n$ | $\gamma$ (deg) |
|-----------|---------------------------|----|---------------|
| f-c3-c3-f | 1.20                      | 1  | 180.0         |
| f-c3-c3-h2| 0.1556                    | 3  | 0.0           |
TABLE S5. Partial charges and intramolecular parameters for AP

| Partial Charges | q (e) |
|-----------------|-------|
| Cl              | 1.5456|
| H               | 0.387625|
| N               | -0.5505|
| O               | -0.6364|

| Bonds           | $k_r$ (kcal mol$^{-1}$ Å$^{-2}$) | $r_{eq}$ (Å) |
|-----------------|---------------------------------|---------------|
| Cl-O            | 426.42                          | 1.4523        |
| H-N             | 413.55                          | 1.0300        |

| Angles          | $k_\theta$ (kcal mol$^{-1}$ rad$^{-2}$) | $\theta_{eq}$ (deg) |
|-----------------|----------------------------------------|---------------------|
| H-N-H           | 33.45                                  | 109.5               |
| O-Cl-O          | 107.60                                 | 109.5               |
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