A Scalable Molecular Force Field Parameterization Method Based on Density Functional Theory and Quantum-Level Machine Learning

Raimondas Galvelis,†,§ Stefan Doerr,†,‡,§ João M. Damas,† Matt J. Harvey,† and Gianni De Fabritiis∗,†,‡,¶

†Acellera Labs, C/ Doctor Trueta 183, 08005 Barcelona, Spain
‡Computational Science Laboratory, Universitat Pompeu Fabra, PRBB, C/ Doctor Aiguader 88, 08003 Barcelona, Spain
¶Institució Catalana de Recerca i Estudis Avançats (ICREA), Passeig Lluis Companys 23, 08010 Barcelona, Spain
§Contributed equally to this work

E-mail: gianni.defabritiis@upf.edu

Abstract

Fast and accurate molecular force field (FF) parameterization is still an unsolved problem. Accurate FFs are not generally available for all molecules, like novel druglike molecules. While methods based on quantum mechanics (QM) exist to parameterize them with better accuracy, they are computationally expensive and slow, which limits applicability to a small number of molecules. Here, we present an automated FF parameterization method which can utilize either DFT calculations or approximate
QM energies produced by different neural network potentials (NNPs), to obtain improved parameters for molecules. We demonstrate that for the case of torchani-ANI-1x NNP, we can parameterize small molecules in a fraction of time compared with an equivalent parameterization using DFT QM calculations while producing more accurate parameters than FF (GAFF2). We expect our method to be of critical importance in computational structure-based drug discovery. The current version is available at PlayMolecule [www.playmolecule.org](http://www.playmolecule.org) and implemented in HTMD, allowing to parameterize molecules with different QM and NNP options.

**Introduction**

In molecular mechanics (MM), molecular interactions are represented by empirical potentials and their parameter sets. These parameter sets, called force fields (FFs), are crucial for MM’s accuracy and applicability. MM has been successfully applied in large-scale biomolecular simulations in many cases ranging from protein folding,[1] protein-protein interactions,[2] to protein-ligand binding.[3] Typically, the development of a FF is cumulative and collective effort focused on a particular subset of the chemical space. For example, the most popular biomolecular FF families AMBER[4,5] and CHARMM[6,7] have parameters for proteins, lipids, DNA, etc. If one needs parameters for a particular molecule outside that chemical space, it has to be parameterized, which is a non-trivial, time-consuming and computationally expensive process.

In this work, we focus on small biologically-active (i.e. drug-like) molecules with ~100 atoms. The accessible chemical space is estimated to span from $10^{14}$ to $10^{180}$ molecules.[8] Accessing accurate FF parameters for any of these molecules in a fast manner is critical for many fields of computational chemistry, especially computational structure-based drug discovery (SBDD).

For both AMBER and CHARMM there are general FFs (e.g. GAFF,[9] CGenFF[10]), which extend the base FFs with more chemical groups and intend to cover more molecules through
heuristic pattern matching. Unfortunately, this approach does not always provide accurate FF parameters, especially for dihedral angle parameters. In Figure 1, we highlight this problem in a molecule, where an energy profile with GAFF parameters is in disagreement with the reference quantum mechanics (QM) calculations. For example, such inaccurate parameterization will result in poor computational SBDD results, potentially failing to identify the best drug candidates.

\[ \text{Figure 1: (a) 2-methyl-3-pentene is rotated around the marked bond and (b) the energies of the rotamers are calculated using DFT (see section “Evaluation datasets” for details), GAFF and GAFF2 parameters. This highlights the limitation of the GAFF methods.} \]

Several methods (GAAMP, \textsuperscript{11} ffTK, \textsuperscript{12} and ATB \textsuperscript{13} ) have been developed to circumvent such problems. Typically, they take one of these general FFs as a base and improve the parameters of each individual molecule (mostly dihedral angle parameters, but also atomic charges) by fitting to QM results. However, due to the high computational cost of QM, this approach is only tractable for a limited number of small molecules.

Recent advances in machine learning (ML) have lead to the development of neural network potentials (NNPs), \textsuperscript{14,15} which are trained on QM data to predict the total energies of molecules at a fraction of the computational cost.\textsuperscript{16–25} For example, ANI-1x was trained on organic molecules and achieved the mean absolute error (MAE) of 1.6 kcal/mol for the energies of COMP6 benchmark,\textsuperscript{20,21} while it took less than a second per molecule. Such
speed and accuracy can be exploited for FF parameterization.

In this work, we develop a method, called Parameterize, for the FF parameterization of individual molecules. It combines a general FF and NNP: the initial FF parameters are obtained with GAFF2, then selected dihedral angles are scanned and their parameters are fitted to ANI-1x\textsuperscript{20,21} energies. This allows to improve the dihedral angle parameters, while keeping the computational cost low. The quality of FF dihedral angle parameters is important for correct molecular shape, conformation distribution, and thermodynamic properties.\textsuperscript{26} We believe that the accuracy and speed of this method makes it practical for many applications, in particular computational SBDD. Parameterize is implemented with HTMD\textsuperscript{27} and available as an application on PlayMolecule (www.playmolecule.org).\textsuperscript{28}

Methods

The parameterization method (Figure 2) consists of three main parts. First, the initial FF is constructed using GAFF2\textsuperscript{9} parameters and AM1-BCC\textsuperscript{29,30} atomic charges. Second, parameterizable dihedral angles (i.e. rotatable bonds) are selected and scanned by generating a set of rotamers. The rotamers are minimized with the initial FF and their reference energies are evaluated with ANI-1x.\textsuperscript{20,21} Finally, the dihedral angle parameters are fitted to reproduce the reference energies, resulting in an improved FF for a target molecule. The following sections provide detailed descriptions of each part.

Initial FF parameters and atomic charges

GAFF\textsuperscript{9} is a general AMBER force field for drug-like molecules based on heuristic pattern-matching. We use its second version (GAFF2), as implemented in Antechamber\textsuperscript{31} to assign atom types and initial FF parameters (bonded and Van der Waals terms) for the target molecule (Figure 2). The use of GAFF2 ensures that our parameters are compatible with AMBER\textsuperscript{31} FF and can be used for bio-molecular simulations.
GAFF2 parameters are designed to be used with either with AM1-BCC or RESP charges. We use AM1-BCC, as it is computationally cheaper than RESP, which requires QM calculations. Another problem with AM1-BCC (and RESP) is the charge dependency on the conformation of the target molecule, so the equilibrium conformation has to be used.

Also, we found out that geometry minimization of drug-like molecules with QM occasionally results in topology and local geometry changes incompatible with the initial FF. For example, a hydrogen atom moves to a different protonation state or an amine group minimizes to the pyramidal shape, while GAFF2 parameters keeps it planar.

We circumvent this issue by using intermediate Gasteiger charges, which depend on molecular topology, but not conformation. First, the target molecule is minimized with the initial GAFF2 parameters and Gasteiger charges. Then, the minimized conformation of the
molecule is used to compute AM1-BCC (Figure 2). This scheme has a double benefit: we avoid computationally expensive minimization with QM and ensure that our FF can model the minimized molecule (i.e. the topology and local geometries are consistent).

Dihedral angle selection and scanning

Our selection of the dihedral angles for parameterization is based on a four-step scheme:

1. Select all covalent bonds between non-terminal atoms, except the bonds in rings. For symmetric molecules, only one of the equivalent bonds are chosen arbitrarily. In an example (Figure 3), C1–C2, C5–C8, and C8–C9 bonds are selected.

2. Exclude the bonds in the methyl groups, i.e. the C1–C2 bond is excluded.

3. Select the dihedral angles which contain the selected bonds their centers. For the C5–C8 bond, it results in four dihedrals: C4–C5–C8–O, C4–C5–C8–C9, C6–C5–C8–O, and C6–C5–C8–C9.

4. Select the dihedral angles which follow the longest chain, i.e. C4–C5–C8–C9 and C6–C5–C8–C9 have precedence over C4–C5–C8–O and C6–C5–C8–O (C4 and C6 are equivalent, so one of these dihedrals are chosen arbitrary). Additionally, priority is given to the dihedrals with the heaviest terminals, i.e. C5–C8–C9–Cl has precedence over C5–C8–C9–H.

Each selected dihedral angle is scanned by generating 36 rotamers (every 10°) from the minimized conformation of the target molecule. The potential clashes between atom are removed with constrained minimization, where the selected dihedral angle is constrained and the remaining degrees of freedom are minimized with MM using the initial GAFF2 parameters and AM1-BCC charges.
Figure 3: An example molecule with two parameterizable dihedral angles: C4–C5–C8–C9 and C5–C8–C9–Cl. See section ‘Dihedral angle selection and scanning’ for details.

Dihedral angle parameter fitting

The reference energies of the minimized rotamers are computed with a NNP (see section ‘Neural network potentials’ for details). The high-energy rotamers (>20 kcal/mol above the minimum energy) are discarded to avoid non-physical conformations.

New atom types are created for atoms, which belong to the selected dihedral angles. This ensures that our improved FF does not conflict with the original FF. The new atom types have the same charges, bonded and non-bonded parameters, except the dihedral angles parameters.

In AMBER FF, the dihedral angle potential $E_{\text{dihed}}(\phi)$ is expressed as a sum of six Fourier terms:

$$E_{\text{dihed}}(\phi) = \sum_{n=1}^{6} k_n (1 + \cos(n\phi + \phi_n)),$$

where $\phi$ is a dihedral angle value, $k_n$ is a force constant, and $\phi_n$ is a phase angle. For each parameterizable dihedral, a separate set of 12 parameters (6 force constants and 6 phase angles) is used. The potential energy of the molecule consists of the parameterizable dihedral angle terms and other force field terms:

$$E_{\text{MM}} = E_{\text{other}} + \sum_{i=1}^{N_{\text{dihed}}} E_{\text{dihed},i},$$

where $N_{\text{dihed}}$ is the number of parameterizable dihedral angles, including their equivalents.
\( E_{\text{other}} \) includes all other force field terms (i.e. bonded terms, planar angle terms, non-parameterizable dihedral angle terms, and non-bonded terms), which are precomputed and kept constant during parameterization.

The fitting of dihedral angle parameters is performed by minimizing the RMSD of the reference energies and estimated MM energies:

\[
\mathcal{L}_{\text{RMSD}} = \sqrt{\frac{\sum_{i=1}^{N_{\text{rot}}} (E_{\text{ref},i} - E_{\text{MM},i} + C)^2}{N_{\text{rot}}}},
\]

where \( N_{\text{rot}} \) is the number of rotamers and \( C \) is an offset constant accounting for the absolute difference between the reference and MM energies. The \( \mathcal{L}_{\text{RMSD}} \) is a multi-modal function with respect to \( k_n \) and \( \phi_n \), which requires a global optimization.

For the global optimization, we use an iterative algorithm, where each iteration consists of two stages. In the first stage, the parameters of each dihedral angle are optimized individually with the naïve random search algorithm. The initial parameters are drawn from the random uniform distribution (\( k_n \in [0, 10] \) kcal/mol and \( \phi_n \in [0, 360) \)) followed by local minimization with L-BFGS. This assumes that the parameters of different dihedral angles are weakly correlated. In the second stage, we account for that correlation by optimizing all the dihedral angle parameters simultaneously with L-BFGS.

**Neural network potentials**

NNPs are classical models, which represent the energy potential of molecules with neural networks (NNs). NNs are universal function approximators, i.e. given enough parameters a NN can interpolate any sufficiently regular function. In the case of NNPs, NNs are used to predict atomic energies from atomic environments.

TorchANI is an implementation of ANI-1x with PyTorch. ANI-1x computes the total energy of a molecular configuration as the sum of atomic energies (Figure 4). The atomic energies are computed with atomic NNs. Each atomic NN is a fully-connected NN.
Figure 4: An example of applying a NNP to a water molecule, with $\vec{r}$ being the atom coordinates, $Z$ the elements, $G$ the featurization function producing the $G_n$ AEV of atom $n$, DNN the deep neural networks, $E_n$ the energy of atom $n$ and $E_T$ the total potential energy. As can be seen, the same hydrogen network is used to calculate the energies of both hydrogen atoms while the energy of the oxygen is calculated by a different oxygen network.

with three hidden layers using CELU activation functions and is trained to compute energies for a specific element. Currently, ANI-1x supports four elements (H, C, N, and O). The input to the atomic NNs are the atomic environment vectors (AEVs), which describe the local environment of each atom.

AEVs are computed with the modified Behler-Parrinello (BP) symmetry functions. The BP functions are atom-centred and translation/rotation invariant. They are truncated at a fixed radius to improve the scaling with the number of atoms and generalize over systems of arbitrary size.

ANI-1x consist of an ensemble of 8 NNPs with different number of hidden layers and trained on different subsets of the training data. The total energy is computed as a mean of the ensemble. The disagreements in the ensemble can be used an estimate of prediction error. For brevity, we refer to it as NNP.
Input and output

The input to Parameterize can be in Tripos MOL2 or MDL SDF molecular structures formats, which contain elements, topology, initial conformation, and molecular charge. Alternatively, the molecule can be entered as a SMILE string or with Kekule.js, an integrated graphical chemical structure drawer. In case, the initial conformation is not preset, it is generated with RDKit.

The output is Tripos MOL2 and AMBER force field parameter modification format (FR- CMOD) files. The former contains the atom types and the latter contains the corresponding FF parameters. The files could be used with Antechamber or HTMD to build simulation systems. Note, if more than one parameterized molecule is used in the same system, the atom type conflicts have to be resolved manually.

Evaluation datasets

The accuracy of NNP and our parameterization method is compared with QM. The QM calculations were performed at the density functional theory (DFT) level of theory using ωB97X-D exchange-correlation functional and 6-311++G** basis set (i.e. ωB97X-D/6- 311++G**) with Psi4. For brevity, we refer to it as DFT.

For evaluation, we use three datasets. The first dataset consists of 45 molecules from Sellers et al. (17 molecules were skipped because they contained elements not supported by NNP). The dataset contains drug-like fragments with various rotatable bonds.

The second dataset, called TopDrugs, consists of four molecules (Table 1 and Figure 5) selected to represent realistic application scenarios in computational SBDD. For that, we looked at recent top-selling drugs and selected them based on four criteria: small size (<110 atoms), contain only H, C, N, and O elements, have rotable bonds, and present in the Protein Data Bank (i.e. a reasonable structure is available).

The last dataset, called ZINC, consists of 1000 molecules from ZINC12 database, containing over 20 million commercially-available organic molecules. The molecules were selected
Table 1: Overview of TopDrugs

| Name         | PDB chemical ID | Number of atoms | Number of dihedral angles$^\dagger$ |
|--------------|-----------------|-----------------|-----------------------------------|
| Lenalidomide | LVY             | 32              | 2                                 |
| Apixaban     | GG2             | 59              | 6                                 |
| Imatinib     | STI             | 68              | 8                                 |
| Telaprevir   | SV6             | 104             | 20                                |

$^\dagger$ as described in section “Dihedral angle selection and scanning”

with a three-step procedure: first, molecules containing only H, C, N, and O elements were selected; second, they were grouped according to the number of parameterizable dihedral angles (as described in section “Dihedral angle selection and scanning”); finally, 100 molecules were selected randomly from each group (from 1 to 10 dihedral angles). The complete list of the molecules is available in SI (Table S1–S2).

Results

Parameterize is evaluated in three aspects. First, we measure the accuracy of NNP energies. Then, we assess the overall quality of FF parameters. Finally, we check parameterization time, reliability, and scaling.

Accuracy of NNP

The energies of NNP, GAFF, and GAFF2 are compared with the DFT results using the rotamers of Sellers et al.\textsuperscript{41} and TopDrugs (Table 1 and Figure 5) molecules. The dihedral angles were selected and rotamers were generated as described in section “Dihedral angle selection and scanning”. All energy profiles are available in SI (Figure S1–S49).

NNP is more accurate than GAFF and GAFF2 (Figure 6). In the case of Sellers et al.\textsuperscript{41} dataset, the MAE of energy is $0.55 \pm 0.38$ kcal/mol, while for GAFF and GAFF2 it is $1.62 \pm 1.37$ and $1.62 \pm 1.36$ kcal/mol, respectively. In the case of TopDrugs, the trend is the same, but the largest molecule (SV6) has larger errors: $1.63 \pm 0.89$ kcal/mol for NNP,
Figure 5: (a)–(d) structures of TopDrugs. The parameterized dihedral angles are shown in grey.

3.12 ± 2.23 kcal/mol for GAFF, and 2.93 ± 2.12 kcal/mol for GAFF2.

In terms of the dihedral angle types (Figure 7), NNP is more accurate than GAFF and GAFF2 in almost all cases. Noticeably, the accuracy of NNP is higher for C(sp$^3$)–C(cp$^3$), C(sp$^3$)–O(cp$^3$), and C(sp$^2$)–O(cp$^3$); than C(sp$^2$)–C(cp$^3$), C(sp$^2$)–C(cp$^2$), C(sp$^2$)–N(cp$^2$), and C(sp$^3$)–N(cp$^2$) dihedral angles. The latter dihedral angles (containing atoms with the sp$^2$ hybridization) represent more diverse chemical groups (e.g. aromatic and conjugated systems).
Figure 6: Comparison of GAFF, GAFF2, NNP, and Parameterize energies with respect to the DFT results using the rotamers of Sellers et al. and TopDrugs (Table 1 and Figure 5) molecules.

Figure 7: Comparison of dihedral angle types in terms of GAFF, GAFF2, NNP, and Parameterize energies with respect to the DFT results. The dihedral angles are typed according to the central atom elements and hybridizations.

Quality of FF parameters

All molecules from Sellers et al. and TopDrugs (Table 1 and Figure 5) datasets were parameterized with our method and the energies of theirs rotamers were computed with the new FF parameters. All energy profiles are available in SI (Figure S1–S49).

The accuracy of the new FF parameter is close to the NNP results (Figure 6). In the case
of Sellers et al.\textsuperscript{11} dataset, the MAE with respect to the DFT results is 0.61 ± 0.36 kcal/mol, which is comparable with the MAE of NNP itself (0.55 ± 0.38 kcal/mol). For TopDrugs molecules, the trend is the same: the new FF parameters reproduce the NNP results closely and are more accurate than GAFF2 for all the molecules except GG2. Also, for different dihedral angles types, the MAE does not exceed 0.5 kcal/mol (Figure 7).

Furthermore, we inspect the energy profiles of a few selected dihedral angles of STI (Figure 8). The dihedral angles were selected to illustrate the cases where the new FF parameters can reproduce the results of DFT and where they cannot. Note that the energy profiles include all the energy terms and not just the dihedral angle terms.

Finally, the overall quality of FF parameters (not just dihedral angle parameters) is checked by minimizing the TopDrugs molecules. The minimization is started and RMSD is computed with respect to the DFT-minimized structure. None of the molecules undergoes any significant conformation changes and RMSDs are 0.4 Å or less (Table 2), except SV6.

Table 2: Comparison of the minimized TopDrugs molecules. The RMSDs are computed with respect to the DFT-minimized structures.

| Molecule | GAFF | GAFF2 | Parameterize |
|----------|------|-------|--------------|
| LVY      | 0.305| 0.301 | 0.190        |
| GG2      | 0.292| 0.294 | 0.376        |
| STI      | 0.156| 0.156 | 0.126        |
| SV6      | 0.641| 0.620 | 0.827        |

Parameterization time and reliability

The benchmark of Parameterize is performed with the example molecule from Figure 1a (18 atoms and two parameterizable dihedral angles) on a single core of a 2.1 GHz processor (Intel Xeon E5-2620). Note that no graphical processing unit (GPU) is used.

The total parameterization time is 31 s (Table 3), where the energy calculations with NNP take just 3 s. For comparison, the same calculations with DFT take ~0.7 min per
Figure 8: Comparison of GAFF, GAFF2, NNP, and Parameterize energy profiles with respect to the DFT results using two selected dihedral angle of STI (a). The dihedral angles are shown in green (b) and purple (c).
rotamer. Thus, the parameterization time would be $\sim 50$ min ($2 \times 36$ rotamers)!

Table 3: Parameterization time (in seconds) for the molecule from Figure 1a with different reference energy methods (DFT and NNP).

| Procedure             | Reference | DFT | NNP |
|-----------------------|-----------|-----|-----|
| GAFF2 parameters      | 1         | 1   |
| AM1-BCC charges       | 2         | 2   |
| Dihedral scans        | 13        | 13  |
| Reference energies    | 3024      | 3   |
| Parameter fitting     | 7         | 7   |
| Other                 | 5         | 5   |
| **Total**             | **3052**  | **31** |

The reliability of Parameterize is checked with the ZINC molecules. Out of 1000 molecules, 949 molecules completed successful, 14 molecules had large errors (i.e. the MAE of dihedral parameter fitting was $\geq 2.0$ kcal/mol), and 37 molecules failed (Table S2). The failures occurred in the dihedral angle parameter fitting (26 molecules), the rotamer generation (7 molecules), and the initial atom types and FF parameters assignment (4 molecules). Note that due to limited computational resources, we do not compare with DFT results.

Finally, the scaling of Parameterize is measured with the groups of ZINC molecules containing different numbers (from 1 to 10) of parameterizable dihedral angles. The overall MAE of the dihedral angle parameter fitting is $0.32 \pm 0.68$ kcal/mol and it does not depend significantly on the number of dihedral angles (Figure 9a). Meanwhile, the parameterization time grows linearly with the number of dihedral angles (Figure 9b). The results of all the ZINC molecules are available in SI (Table S1–S2).

**Discussion**

We have demonstrated that NNPs can achieve better accuracy than MM with GAFF2 parameters (Figure 6 and 7). A question is why NNPs cannot be used directly in molecular dynamics (MD). Here, we argue that, despite the progress in developing NNPs, they are not
yet ready to replace MM. First, the BP symmetry functions used in ANI-1x are good at describing the chemical environment at short range (<6 Å), but they intrinsically lack long-range interactions. It can be seen that the results of the largest molecule (SV6) are the worst (Figure 6 and Table 2). Also, the training of NNPs with larger molecules is problematic due to rapidly growing computation cost of QM, which is needed to generate training data. However, the new types of chemical environment featurization, introduced by SchNet and AIMNet, may improve the long-range interactions. Second, current NNPs support limited number of elements. For example, ANI-1x and AIMNet implementations only support four (H, C, N, and O) and six (H, C, N, O, F, and S) elements, respectively. That is not sufficient for typical SBDD simulations, which may contain H, C, N, O, P, S, halogens, and metal cations. Thus, Parameterize bridges the gap between NNPs and MD. It leverages the accuracy and speed of NNPs to improve the FF parameters of individual molecules, while benefiting from remaining compatible with existing MD software and established FFs. Moreover, Parameterize allows a quick adaptation of improved NNP methods, when they will become available, or Psi4 can be used directly for QM energies, if the computational cost is acceptable.
Further, we have demonstrated that the accuracy of the FF for drug-like molecules can be improved just fitting dihedral angles parameters (Figure 6 and 8), while the rest parameters are taken from a general FF (GAFF2 in our case). This simplifies the parameterization procedure and allows a quick adaptation to other FF families. For example, Parameterize could be adapted to CHARMM using CGenFF.

In some cases, the new FF parameters cannot reproduce the DFT results (Figure 8). A part of the errors can be attributed to the accuracy of NNPs, but, in addition, we have identified at least three other components of the parameterization procedure (Figure 2), which are going to be improved in the future. The atomic charges are assigned with AM1-BCC. It would be more accurate to use the RESP charges, but it requires expensive QM calculation. This could be solved with ML-based charge assignment methods. Also, the atomic charges are conformation dependent, so it is better to average them over a representative ensemble of conformations rather than just use a single conformation. In addition, the more accurate Lennard-Jones parameters by Boulanger et al. could be used, rather than the GAFF2 parameters. Moreover, we have found that, for the dihedral angle scanning and the following parameter fitting, it is better to use MM-optimized conformations than more accurate QM-minimized ones. Partially, this can be solved by fitting more soft mode parameters (e.g. improper dihedral angles), but ultimately the accuracy is limited by the potential forms of FF. For example, AMBER family FFs do not include explicit potentials to model correlation between dihedral angles, hydrogen bonds, π–π stacking, etc.

Finally, the overall reliability of Parameterize is ~95%. The majority of failures occur in the fitting of the dihedral angles parameters, where the optimizer either fails to find good quality parameters or fails completely. Another problem is that the parameter space is non-linear and multi-modal, which requires a global optimizer. Currently, it is the main bottleneck limiting the speed of Parameterize (Table 3). Our proposed optimization algorithm is an effort to balance reliability and scaling with the size of molecules (Figure 9). However, for the larger molecules (e.g. biopharmaceuticals containing hundreds of atoms and

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tens of dihedral angles), we may need a different approach, such as an automated molecule fragmentation scheme.

**Conclusion**

We have developed an FF parameterization procedure which can utilize either QM calculations or NNP energy predictions. The quality of the Parameterize method using NNPs is evaluated using 45 druglike fragments by Sellers et al. and four real drug molecules. Our validation using ANI-1x as a NNP is promising, achieving better accuracy than GAFF2 as the MAE is reduced from $1.62 \pm 1.36$ kcal/mol to $0.55 \pm 0.38$ kcal/mol in the case of Sellers et al. fragments. Furthermore, the accuracy of the FF is improved by fitting selected dihedral angle parameters to reproduce NNP energies (MAE is $0.61 \pm 0.36$ kcal/mol in the case of Sellers et al. fragments), while the rest of the parameters are taken from GAFF2. Finally, it demonstrates that small molecules parameters can be obtained in minutes (rather than hours, if DFT had been used) with $\sim 95\%$ reliability for the randomly selected ZINC12 molecules.

The current version of Parameterize is available on the drug-discovery platform PlayMolecule [www.playmolecule.org](http://www.playmolecule.org). The current limitation of atom elements of NNPs like ANI-1x limits its applicability to benchmark molecules. Yet, once this problem is solved, Parameterize using NNPs would fill the gap between the general FF (e.g. GAFF and CGenFF), which can generate parameters in seconds but with limited accuracy and QM-based methods (e.g. GAAMP, ffTK and ATB), which provide more accurate parameters but require hours or even days of computation time.

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Conflict of Interest Disclosure

All the authors are employed by Acellera.

Supporting Information Available

The following files are available free of charge.

- Figure S1–S49: the structures of the molecules from Sellers et al. and TopDrugs datasets and their energy profiles (DFT, NNP, GAFF, GAFF2, Parameterize) of parameterized dihedral angles.

- Table S1–S2: the selected molecules from the ZINC dataset, their parameterization results, and failures.

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Graphical TOC Entry

parameterize
QM data

| DIHE      | Value | Charge | Type | SCEE | SCNB |
|-----------|-------|--------|------|------|------|
| c3-c3-c3-hc | 1     | 0.0800 | 3.0  | 1.2  | 2.0  |
| c3-c3-c3-za | 1     | 0.1000 | 3.0  | 1.2  | 2.0  |
| c3-c3-c3-zc | 1     | 0.1100 | 3.0  | 1.2  | 2.0  |
| c3-c3-c3-zc | 1     | 0.2900 | 180.0| 1.2  | 2.0  |
| c3-c3-za-zu | 1     | 0.7100 | 180.0| 1.2  | 2.0  |

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