New Developments in Force Fields for Biomolecular Simulations

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Abstract

Biomolecular force field development has been instrumental in improving the predictive power of molecular simulations over the past four decades. More recently, the era of large quantitative experimental datasets and ubiquitous high performance computing power has enabled rapid progress in the field. In this review we summarize recent developments in all-atom protein, nucleic acid, and small molecule force fields, paying specific attention to developments in parameterization methods and improvements in the representations of nonbonded interactions that are critical for solving the challenging biophysical problems of the present. We also sketch out new avenues for force field development and grand challenge applications for the near future.

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Introduction

Molecular dynamics (MD) simulations have become a powerful and ubiquitous technique for understanding the detailed structure and thermodynamics of biomolecular systems [1]. The quality –and therefore predictive and explanatory power – of these simulations has steadily improved due to parallel advancements in increasing the timescales for statistical sampling of the most relevant conformations using accelerated sampling techniques [2–4], disruptive computer hardware such as massively multicore CPUs, GPUs, and specialized hardware [5–7], and improving the accuracy of the potential energy functions (i.e., force fields) used to drive these simulations [1]. In this review we highlight recent and promising developments in force fields, paying particular attention to all-atom, fixed-charge force fields that are the workhorses of present-day biomolecular simulations. Where applicable we also discuss polarizable force fields [8–10], which can offer greater physical accuracy and transferability, and for which new algorithms are diminishing their computational cost [11–16]. We focus on force fields that have been developed for primarily small molecule ligands, proteins, and nucleic acids and bypass detailed discussions of force fields tailored for carbohydrates and lipids. For readers interested in understanding the progress and challenges in the emerging area of lipid force fields and cell membrane simulations, however, we recommend reviews [17] and [18].

Protein force fields

Modern all-atom, fixed-charge protein force fields, based on a simple pairwise additive approximation [19], owe a great deal to their progenitors such as AMBER ff94 [20], CHARMM 22 [21], and OPLS-AA [22]. These force fields have often been quite successful in simulations of globular proteins and short peptides [23] and are mature enough that protein folding simulations of small single domain proteins (~100 amino acids) are entirely feasible [24]. More recently, however, detailed experimental data have revealed that these force fields have deficiencies in simulating intrinsically disordered proteins [25–27], protein folding equilibria and their dependence on temperature [28,29], and correctly identifying protein folding pathways/intermediates [30].

One common avenue for improving protein force fields has been the torsion potentials governing the behavior of both backbone and sidechain dihedral angles. These potentials are an obvious target for improvement because they sit at the length scale where force fields transition from being dominated by bonding chemistry to being governed by nonbonded interactions. In some sense these potentials provide the major correction for deficiencies in the nonbonded interactions for atoms separated by three bonds and may even implicitly capture many-body effects. The approaches used for deriving these potentials have ranged from fitting to only *ab initio* quantum chemistry data, e.g., AMBER ff99SB-ildn [31,32], ff14SBsconly [33], or FB-15 [34] or OPLS-AA/M [35], to matching only experimental NMR or structural database data as in the developments of AMBER ff99sb*/ff03*/ff03w [36,37] and ff99sbnmr [38], while AMBER ff14SB [33] and CHARMM 36 [39,40] have used a mixture of both types of data.

An interesting alternative approach to this problem is embodied by RSFF2 [41], which is based on the AMBER force field, but uses random coil libraries and modifications to 1-5 and 1-6 van der Waals parameters to improve accuracy for the torsional degrees of freedom. A variety of these revised torsion potentials have been developed with the explicit goal of improving the accuracy of IDP simulations. In addition to AMBER ff03w mentioned above, Huang et al. modified the CMAP backbone potential of CHARMM 36 to create CHARMM 36m (intended for simulations of both folded proteins and IDPs) [42] and Song et al. generated residue-specific backbone potentials to create AMBER ff14IDPSFF [43]. While purely empirical approaches for fitting torsion potentials to experiment somewhat unsurprisingly yield improved agreement with other experimental observables, it is interesting that torsion potentials fitted to gas phase quantum chemistry data appear to be equivalently accurate when validated against the same experimental data [34]. This is evident in the AMBER FB-15 fit to high quality RI-MP2 data, where the key development is new torsion parameters that significantly lower the potential in regions away from the energy minima [34]. This allows the force field to remain accurate in simulating folded states, as well as multi-temperature simulations that agree well with protein folding equilibrium experiments [34].

While the development of more advanced torsion potentials has improved simulations of protein folding and intrinsically disordered proteins, several studies have pointed to significant deficiencies in simulations of proteins that are unlikely to be remedied by torsion potentials

alone. Most notably, nearly all force fields predict ensembles of disordered proteins and unfolded states of proteins that are far too compact [25,27,28,37]. Likewise, the solvation free energies of many amino acid analogues in water are more unfavorable than experimental values [44,45]. Together these observations suggest that most current protein force fields are generally too hydrophobic and also that the relative strengths of protein-water vs. protein-protein interactions are incorrect. Several solutions have been proposed to address this behavior and we review the main approaches here.

One approach, utilized by both Nerenberg et al. and Best et al., has been to modify the protein-water van der Waals interactions within AMBER force fields to effectively increase the strength of these interactions [44,45]. A second approach, has been to develop a new water model, TIP4P-D, with significantly strengthened dispersion interactions (i.e., both water-water and protein-water dispersion interactions) [46], and CHARMM 36m uses a modified TIP3P model for simulations of IDPs as well (although its developers suggest that further validation studies are necessary) [42]. All of these approaches yield improved agreement with experimental data, especially with respect to solvation free energies of amino acid analogues and the dimensions of disordered proteins characterized by SAXS [44–47]. These developments, however, still have known inaccuracies, including local unfolding of folded proteins [44,46] (although an additional intra-protein hydrogen bonding potential can correct this problem [44]), a lack of cooperativity in protein folding [45], and inaccurate protein folding thermodynamics [46,48,49].

A related approach pursued independently by Yoo and Aksimentiev [49,50] and Miller et al. [51] (for multiple different force fields), has been to reduce the strength of protein-protein interactions via reparameterization of van der Waals parameters, using osmotic coefficients of amino acids as target and/or validation data. Interestingly, Miller et al. showed that the protein van der Waals modifications introduced for the AMBER force field [44,52] yield good agreement with osmotic coefficient data despite not using these data in the parameterization process [51]. While these modifications have not yet been extensively tested for folded proteins or IDPs, the application of similar ideas to the AMBER ff99SB-ildn-phi force field [31,32,53] has yielded improved simulations of protein folding and unfolded state ensembles that are less compact and in better agreement with experimental data [49].

Some of the modifications to fixed-charge protein force fields and accompanying water models have been made with explicit goal of more accurately simulating the free monomeric form of IDPs. Such proteins (or regions of proteins), however, exist in a diverse array of chemical environments: interacting with folded proteins [54], undergoing disorder-to-order transitions in peptides [55], and comprising intrinsically disordered regions within folded proteins [56]. Therefore a truly transferable protein force field must be able to function accurately in many different environments. Recent work by Wu et al. aims to tackle these issues by combining RSFF2 together with TIP4P-D and an additional Lennard-Jones potential that stabilizes i to i+4 peptide backbone hydrogen bonds [48]. The combination of improved torsion potentials, a water model with stronger dispersion interactions, and strengthened intra-protein

hydrogen bonds yields significantly more accurate protein folding thermodynamics for a diverse set of peptides than previous force fields [48]. Similarly, CHARMM 36m [42] and the recent a99SB-*disp* force field from Robustelli et al. [57] have built on previous work [40,46] to more accurately simulate both folded proteins and IDPs.

Polarizable force fields for proteins [58–60], which advance upon standard fixed-charge force fields by more faithfully representing the many-body nature of molecular electrostatic response, are hypothesized to be more accurate in simulating both folded proteins as well as IDPs since they are responsive to diverse chemical environments. Recently we have tested the polarizable AMOEBA force field [59], as well as unmodified (AMBER ff99SB-ildn and TIP3P) and modified fixed-charge force fields for IDPs (AMBER ff03ws and TIP4P/2005; AMBER ff99SB-ildn and TIP4P-D), to simulate the conformational ensemble of the 24-residue disordered histatin 5 (Hst 5) peptide [61]. Experimental circular dichroism (CD) [62,63] and NMR [62,64] studies have found that in aqueous solutions Hst 5 does not display any helical conformations, and recent SAXS data determined a structural ensemble that is dominated by extended conformations, with a measured radius of gyration, $\langle R_g \rangle = 1.38$ nm [65].

As shown in Figure 1, the standard pairwise additive force field ff99SB-ildn/TIP3P is more collapsed when compared against experiment, while the two IDP-specific force fields yield $\langle R_g \rangle \approx 1.3$ nm and diminish the helical content relative to the standard model, demonstrating the ability of targeted parameter modifications to improve the ability of a fixed-charge force field to model IDPs. Nonetheless, the structural ensemble for Hst 5 generated using the AMOEBA polarizable model also exhibits good agreement with the experimental $\langle R_g \rangle$ [65] and secondary structure data [62–64]. Since this involved no changes in AMOEBA parameters, it suggests that protein-protein and protein-water interactions are better balanced and more transferable using a polarizable force field.

Method and Model	**$\langle R_g \rangle$ (nm)**
Experimental	1.38
MD, ff99SB-ildn + TIP3P	1.00 ± 0.15
MD, ff03ws + TIP4P/2005	1.30 ± 0.20
MD, ff99SB-ildn + TIP4P-D	1.32 ± 0.20
TCW, AMOEBA	1.40 ± 0.22

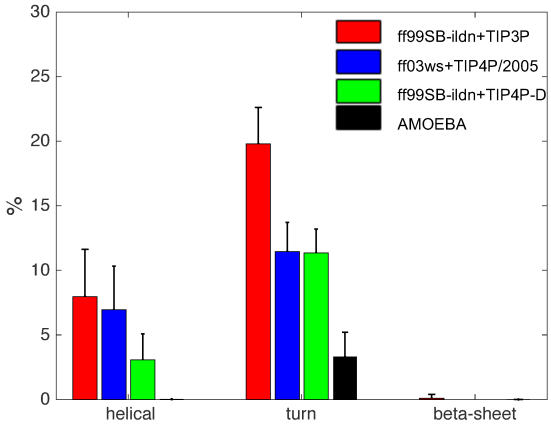

Figure 1: Histatin 5 radius of gyration and secondary structure population for different force fields. (a) Estimates for the ensemble average radius of gyration. (b) Average percentages of different secondary structural features. The data for the fixed-charge force fields was obtained from Henriques *et al.* [25,47], who used multiple μs MD simulations. Data obtained from temperature cool-walking (TCW) simulations using the AMOEBA model – with no modifications – shows improved quantitative agreement with SAXS and NMR data ($\langle R_g \rangle = 1.38$ nm and an extended conformation with no helical content).

A somewhat different approach to protein force field development – and specifically the issue of polarization in fixed-charge force fields – is AMBER ff15ipq [66]. Although it re-uses some parameters from the existing AMBER ff94 family of force fields, ff15ipq deploys unique strategies for the parameterization of angle and torsion potentials and – most notably – partial atomic charges. The overarching philosophy of ff15ipq is to fit all of the bonded potentials in the gas phase, using partial atomic charges for the MM calculations that have been derived from gas phase electrostatic potentials (ESPs) generated using the MP2/cc-pVTZ method and basis set [66,67]. This eliminates some of the ambiguity in the parameterization of other force fields in which ESPs are calculated using HF/6-31G*, which is known to yield overpolarized charge distributions for the gas phase relative to more accurate quantum chemistry methods [68]. For condensed phase simulation, however, an alternative charge set is used that represents a "halfway point" between gas phase and aqueous environments [69]. Specifically, aqueous environment charges are derived using ESP calculations with a solvent reaction field of explicit water molecules included [69]. The final charges used in simulation, however, are scaled to be halfway between the gas phase charges and aqueous environment charges [69]. This choice may implicitly capture the missing polarization cost inherent in fixed-charge force fields and echoes empirical observations of the dipole moments of various fixed-charge water models [69,70]. Moreover, the pre-polarization of these charges is likely more consistent across various moieties than the ad hoc overpolarization of charges based on ESP calculations using HF/6-31G*. Although encouraging, more experimental validation and cross-comparisons against other force fields, especially for simulations of IDPs and protein folding equilibria, are required to fully adopt the ff15ipq model.

Nucleic acid force fields

MD simulations of nucleic acids have been one of the greatest beneficiaries of increased computational power [71,72]. In part this is because many of the enhanced sampling methods that have worked well for proteins have not been nearly as successful when applied to nucleic acid systems [72]. Nevertheless, the extension of nucleic acid simulations from the ~100 ns time scale to the multi-μs time scale exposed many previously unnoticed shortcomings in these force fields.

As with protein force fields, a great deal of effort has been put into the improvement of torsion potentials, most notably for those that describe the nucleic acid backbone dihedral angles (e.g., α, β, γ, ε, and ζ), as well as the glycosidic dihedral angle, χ, and sugar pucker. For the CHARMM force field, this work is encapsulated by Denning et al. (for RNA) [73] and Hart et al. (for DNA) [74]. For the AMBER force field, two different groups have worked independently to generate parmbsc1 [75] and OL15 [76–78] for DNA. Likewise, several groups have aimed to improve the AMBER force field for simulations of RNA [79–83]. In contrast to the development of protein force fields, both parmbsc1 and OL15 explicitly include solvent effects in the derivation of the torsion potentials (e.g., by aiming to minimize the relative differences

between QM/PCM with MM/PBSA as in [84]). This is particularly interesting in light of the fact that both of these force fields use the α and γ potentials from the earlier parmbsc0 force field, which were derived in gas phase [85]. Extensive comparisons suggest that all of these force fields are able to reasonably reproduce the properties of double-stranded DNA [86,87]. RNA folding, however, remains a challenge even for the newest nucleic acid force fields [80,88,89].

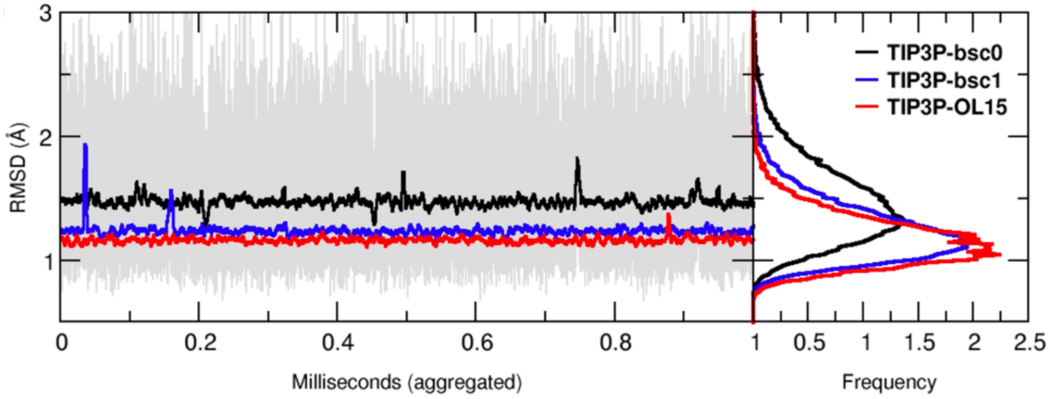

Figure 2: Root-mean-square deviations for MD simulations of the Dickerson Dodecamer (1NAJ) over 1 ms of aggregate simulation time. The 1 μs running averages of the RMSD are shown in solid-colored lines, while data from individual frames (every 2 ns) are shown in gray for all systems. RMSD probability densities are also shown. Figure adapted from ref. [86].

Relatively little effort has been expended in developing new nonbonded parameters for nucleic acid force fields, although certain interactions (e.g., base pair stacking) are known to be represented inaccurately [90,91]. At present only a few moieties have been targeted for such improvements and no one has undertaken a comprehensive reparameterization approach akin to AMBER ff15ipq (or FB-15). That said, a considerable amount of attention has been directed toward improving the fixed-charge models of ions (particularly multivalent ions), which are generally more important for accurately simulating nucleic acids. Yoo and Aksimentiev group developed parameters for water-bound Mg^{2+} (as well as monovalent ions) for the CHARMM force field [92], while Li and Merz developed the so-called 12-6-4 model for ion interactions [93], which includes a $1/r^4$ term that is meant to represent favorable ion-induced dipole interactions. Including these interactions – or some other modification of the nonbonded potentials – is necessary for fixed-charge force fields to accurately model water oxygen-ion radial distribution functions and solvation free energies (i.e., structure and thermodynamics) for multivalent ions simultaneously [93]. It should be noted that these additional parameters have required pair-specific fine-tuning to achieve a satisfactory balance between water-ion and nucleic acid-ion interactions [94].

The most extensive polarizable force field work on nucleic acids has been done with the CHARMM Drude polarizable force field [95,96]. While thus far this force field has been used primarily for simulations of DNA, it has already demonstrated that explicit polarizability yields

qualitatively and quantitatively different results for base flipping [97] and ion-groove interactions [98]. Accurately simulating multivalent ions and their interactions with nucleic acids, however, are still a challenge for this force field [99], although improvements are to be expected in future iterations.

Small molecule force fields

Small molecule force fields have played a vital role in being able to simulate ligands of natural and synthetic origin. Moreover, they have been used extensively to simulate non-aqueous solvents and mixtures for biomolecular simulations. These force fields are also often testing grounds for new paradigms in force field development that eventually make their way into the force fields for proteins, nucleic acids, and lipids. At present there are four widely used small molecule force fields: CGenFF (compatible with CHARMM biomolecular force fields) [100], GAFF/GAFF2 (designed for use with AMBER biomolecular force fields, but used more broadly) [101], OPLS [22,102], and GROMOS [103,104]. These force fields are under near-constant revision of at least an incremental nature, and our specific focus in this review will be recent developments in the representation and parameterization of nonbonded interactions, both of which may have a significant impact on the larger enterprise of biomolecular force fields.

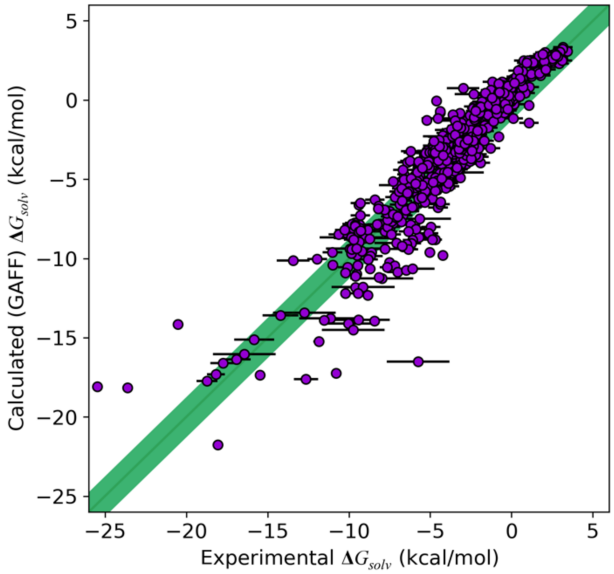

Figure 3: Calculated and experimental aqueous solvation free energies of 642 small molecules from the FreeSolv database v0.51 [105]**.** The calculated solvation free energies are generated using MD simulations with the combination of GAFF and TIP3P water. The green shaded region indicates a range of ±1.2 kcal/mol (~2 k_BT at 298 K) from perfect agreement with experimental data.

One philosophy for small molecule force field development has been to improve the accuracy of the molecular electrostatic potential (ESP), which is believed to be essential for accurately computing solvation and binding free energies. OPLS3, for example, deploys extra points to remedy known physical inaccuracies in representing ESPs of σ-holes or lone pairs in

compounds with halogen bonds, aryl nitrogens, and/or sulfur [102,106]. This parallels work indicating that similar extra points improve accuracy for solvation free energies of halogen-containing compounds with GAFF [107]. (It is worth noting that the developers of ff15ipq aim to include extra points in the next version of that force field [66].) Studies with both OPLS and GAFF have also found issues with polarization of hydroxyls which have been addressed to various degrees [108–110].

The choice of charge model is also an ongoing topic of investigation [69,109,110], and to some extent the charge derivation procedure for each force field is a matter of philosophy. GAFF, for example, can be used with two different charge models (with two different underlying derivation procedures) interchangeably: RESP HF/6-31G* and AM1-BCC [68,111,112]. IPolQ is another more recent option [69], and other charge models have been tested [107]. (We note that GAFF has recently undergone a comprehensive reparameterization of both bonded and Lennard-Jones parameters to yield GAFF2, which has been available since the AmberTools 16 distribution but not yet described in print.) CGenFF, on the other hand, has a moiety-specific charge derivation protocol [100]. OPLS3's default charge model, CM1A-BCC, is somewhat similar to AM1-BCC in GAFF (although unlike GAFF, experimental hydration free energy data are used to parameterize the charge corrections), but its developers have been actively investigating new charge derivation procedures [109,110]. The charge model of GROMOS, however, is considerably different from these other force fields. In the most recent version of GROMOS (2016H66), the charges and van der Waals parameters are derived simultaneously by fitting liquid densities, enthalpies of vaporization, and solvation free energies in both water and cyclohexane [104].

Despite these apparent differences in philosophy, the overarching goal of small molecule force field developers has been to arrive at a set of pre-polarized charges (and van der Waals parameters) that are broadly applicable for condensed phase simulation. Conversely, polarizable force fields arrive at such charge distributions automatically due to their response to the surrounding chemical environment. To that end, the AMOEBA force field has demonstrated good agreement with experimental solvation and binding free energies [8,113] and in principle should be able to accurately simulate the diverse chemical environments encountered during protein-ligand (or nucleic acid-ligand) binding, although it is likely that further development is necessary to exceed the accuracy of the best fixed-charge force fields [113].

Future directions and challenges

Although the force field case studies we have explored in this review are seemingly disparate, a few clear trends emerge for future directions, especially concerning parameterization. For example, almost all force field development to this point has assumed that there is a single optimal solution for any given parameter. This is probably not actually the case, and therefore Bayesian methods are increasingly being employed in deriving the parameters [114–117]. Bayesian methods can of course generate a single "best" estimate for any given parameter, but more interestingly they can provide information on the uncertainty/variability of that parameter

given all of the other assumptions incorporated into the parameterization process. Moreover, Bayesian methods can be used to determine if additional complexity in a given force field (e.g., using additional parameters or functional forms to describe certain interactions) provides a useful benefit in terms of increased accuracy or alternatively if having less complexity might be equally accurate.

Another fundamental aspect of force field parameterization is chemical perception, the process by which molecular simulation software recognizes the chemistry of a molecule with the ultimate goal of assigning appropriate force field parameters for that molecule. Up until now this has been done indirectly by first assigning pre-defined atom types to the molecule and then using these atom types to assign parameters. An alternative route is the use of direct chemical perception that automatically recognizes the entirety – or at least a large fragment – of the molecule and assigns parameters accordingly. Such an approach could substantially reduce the number of unique atom types and parameters necessary for biomolecular simulations, especially those involving small molecule ligands. Currently this approach is being pursued by Mobley et al. in the new SMIRNOFF format [118], which uses the SMIRKS chemical query language to define molecular structure and topology. The use of a chemical query language enables the parameterization engine to identify molecular substructures and assign parameters directly to them, thereby rendering large numbers of pre-defined atom types unnecessary.

Looking further ahead, force fields may undergo a more radical transformation, moving away from certain privileged functional forms selected based on physical motivations. Machine learning opens up the possibility of simulating interaction energies and forces without any sort of explicit functional form, or at least of automatically selecting functional forms. Machine learning-derived potentials have already been used to compute interaction energies between molecules with accuracy equivalent to the quantum chemistry methods they were trained with [119,120]. Likewise, these potentials have already been successfully used in MD simulations of relatively simple systems [120,121]. There are many open questions in this nascent subfield, including how transferable such models are to "novel" situations or how such models take into account long-range interactions that are important for complex biomolecules.

Several grand challenges face force fields for the next few years. One set of challenges involves the accurate estimation of thermodynamic quantities of interest. In particular, today's force fields are not able to compute the free energies and enthalpies of binding in relatively simple host-guest systems with acceptable accuracy [122], and this probably also holds true for biomolecular binding interactions where such calculations are more difficult [123]. Likewise, present-day force fields – including polarizable force fields – have to this point had only mixed success at accurately estimating partition/distribution coefficients (e.g., in water-octanol or water-cyclohexane) [124].

A related set of challenges is the ability of a single pairwise additive force field to accurately simulate the native states of folded proteins, intermediate states along protein folding pathways, and the conformational ensembles of IDPs. An analogous problem in the field of nucleic acids is the accurate folding of RNAs, which has thus far proven to be a major challenge

for fixed-charge force fields. In principle, polarizable force fields should provide the flexibility necessary to capture the subtle energy landscapes of folded proteins, IDPs, and protein folding intermediates. Nonetheless, improvements in sampling are necessary to validate this claim for the more expensive force fields such as AMOEBA, although long time scale MD simulations of ~0.5 μs are starting to be realized for simpler Drude polarization models [60]. However, the recent developments that we have described in this review point to encouraging and rapid progress in both pairwise additive and many-body potentials for biomolecular simulation, but whose long term predictive value will need to be assessed in future simulation studies.

Acknowledgments. THG thanks the National Science Foundation for support under Grant No CHE-1665315. We thank Sukanya Sasmal and James Lincoff for their calculations on polarizable force fields on Hst 5, David Mobley for helpful discussions on small molecule force fields and parameterization, and John Chodera and Lee-Ping Wang for helpful discussions on Bayesian force field parameterization.

Conflict of interest. The authors declare that they have no conflict of interest.

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•• of outstanding interest

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