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Systematic design of biomolecular force fields

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Force fields for the study of biomolecules have been developed in a predominantly organic manner by regular updates over half a century. Together with better algorithms and advances in computer technology, force fields have improved to yield more robust predictions. However, there are also indications to suggest that intramolecular energy functions have not become better and that there still is room for improvement. In this review, systematic efforts toward development of novel force fields from scratch are described. This includes an estimate of the complexity of the problem and the prerequisites in the form of data and algorithms. It is suggested that in order to make progress, an effort is needed to standardize reference data and force field validation benchmarks.

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Introduction

The use of force field methods for studies of biological molecules commenced in the 1960′s with the work of Levitt and Lifson, who stated ‘The total molecular potential energy is composed of many terms. Its exact form is unknown and the expression for potential energy used in the present calculations is a gross approximation . . . ’ [1]. It is intriguing then, or cumbersome depending on one’s perspective, that the same approximation has been used for decades, with the only ‘major’ addition being the Coulomb potential. Over the last two decades, force fields incorporating explicit polarization have become more [2•] but force fields based on Lennard-Jones interactions and point charges still dominate the field [3•].

In this review, the focus is on methods for systematic development and evaluation of force fields. Systematic design was pioneered by the Clementi group in the early 1990’s. They wrote ‘ . . . artificial intelligence and expert systems are becoming ubiquitous, especially in complex chemical systems, where correlation rather than understanding is all one can obtain.’ [4]. Although Clementi’s work to some extent was visionary rather than applicable they did produce a biomolecular force field based on *ab initio* quantum chemistry calculations [5] which, arguably, was one of the first of its kind. Incidentally, it took another two decades before artificial intelligence made a significant impact in chemistry, driven by powerful computers and development of algorithms [6,7].

The parameter space of a biomolecular force field

Most classical force fields are based on a nonbonded pair potential V_{NB} between N particles with individual charges q_i and fixed atom types:

$$V_{NB} = \sum_{i=1}^{N}\sum_{j=i+1}^{N}\frac{q_i q_j}{4\pi\varepsilon_0 r_{ij}} + 4\varepsilon_{ij}\left(\left(\frac{\sigma_{ij}}{r_{ij}}\right)^{12} - \left(\frac{\sigma_{ij}}{r_{ij}}\right)^{6}\right) \quad (1)$$

where ε_0 is the vacuum permittivity and ε_{ij} and σ_{ij} are the well depth and the Van der Waals radii corresponding to the pair of atom types and r_{ij} is the distance between atoms i and j. The ε_{ij} and σ_{ij} can be derived from the atomic ε_i and σ_i using combination rules that are beyond the scope of this review. A modern force field such as Amber ff14SB [8] has about 50 different atom types which means there are about 100 parameters that need to be determined. The nonbonded potential is not sufficiently accurate to describe intramolecular interactions, and therefore a potential V_B based on a fixed list of N_b atomic bonds b_i, a list of N_θ angles θ_i and a list of N_φ torsions φ_i is added according to:

$$V_B = \sum_{i=0}^{N_b}\frac{k_i^b}{2}\left(b_i - b_{i,0}\right)^2 + \sum_{i=0}^{N_\theta}\frac{k_i^\theta}{2}\left(\theta_i - \theta_{i,0}\right)^2 + \sum_{i=0}^{N_\varphi}\sum_{j=0}^{M}k_{i,j}^{\varphi}\cos^j(\varphi_i) \quad (2)$$

where the equilibrium bond lengths $b_{i,0}$ and angles $\theta_{i,0}$ can be derived from high-quality crystal structures of small molecules [9], although the general applicability of this approach, in particular for deriving the angles $\theta_{i,0}$ has been criticized [10]. For small molecules it is possible to derive the force constants k_i^b, k_i^θ and $k_{i,j}^\varphi$ from vibrational spectroscopy experiments. However, it is not a priori

certain that small molecule parameters are transferable to large biomolecules. With these uncertainties in mind, all force constants and geometries should be considered to be parameters in a force field. Experimental data can be used as 'initial values' in parameter optimization, however. The Amber ff14SB force field defines approximately 100 bonds, 230 angles and 180 torsions, each with 2 parameters, for a total of 1020 parameters, in addition to the 100 nonbonded parameters. Last but not least, partial charges q_i have to be determined, which usually are tabulated for proteins and nucleic acids. Assuming that the partial charges are constant in the 20 naturally occurring amino acids, there are about 210 different parameters while for nucleic acids there are about 130 different partial charges. In the above functional form, an atomistic biomolecular force field therefore contains about 1500 parameters. Polarizable force fields [2•] will typically have more than so.

Systematic design of force fields

Systematic design is defined here as a series of actions to derive a complete force field from scratch. This stands in contrast to the incremental improvements (such as Amber ff14SB [8]) that are important as well, but that should perhaps be regarded as maintenance.

The derivation of a force field corresponds, in principle, to the minimization of a cost function $\chi^2(k)$ defined based on N reference energies E^{ref} as:

$$\chi^2(k) = \sum_{n=1}^{N} \left(E_n^{ff}(k) - E_n^{ref}\right)^2 \quad (3)$$

where $E^{ff}(k) = V_{NB} + V_B$ (Eqs. (1) and (2)), with respect to the force field parameters k. For any form of the energy function and reference data set, there are many local minima, because the number of parameters in even a simple force field is large. In what follows, first data sources that can be used in force field design will be described, and then methods for parameter optimization.

Reference data for force field design

The aforementioned *ab-initio* force field due to the Clementi group was based on 30 000 hartree-Fock calculations, an unprecedented number at that time, albeit using a modest basis set only [5]. More recently, a number of larger data sets have been published with slightly different features and based on more or less accurate quantum chemistry or density functional theory (DFT) calculations.

- Hobza *et al.* did high-level quantum chemistry calculations of noncovalent complexes in the gas phase [11].
- The PubChem quantum chemistry database contains DFT calculations of 3 million compounds with a moderately small basis set [12].
- ANI-1 contains 20 million off-equilibrium structures and DFT energies for 57 000 compounds [13].
- Ramakrishnan optimized structures with DFT for 134 000 compounds, and did thermochemistry calculations for a 6000 compounds [14].
- The Alexandria library [15] contains DFT calculations with a large basis set for 2000 compounds with optimized structures and electrostatic potential grids. Thermochemistry results are provided for the same dataset [16].
- The quantum chemistry archive is maintained by the Molecular Sciences software institute [17••].
- A benchmark spectroscopy data set of over 60 000 compounds is part of the Cambridge crystallographic database [18••].

Which of the libraries above is most appropriate for biomolecular force field design is beyond the scope of this review. However, it is important that efforts be standardized to allow re-use of data. In addition to quantum chemical reference data, there are a large amount of experimental data for compounds in the gas and condensed phases that have been collected in over a century of chemistry experiments.

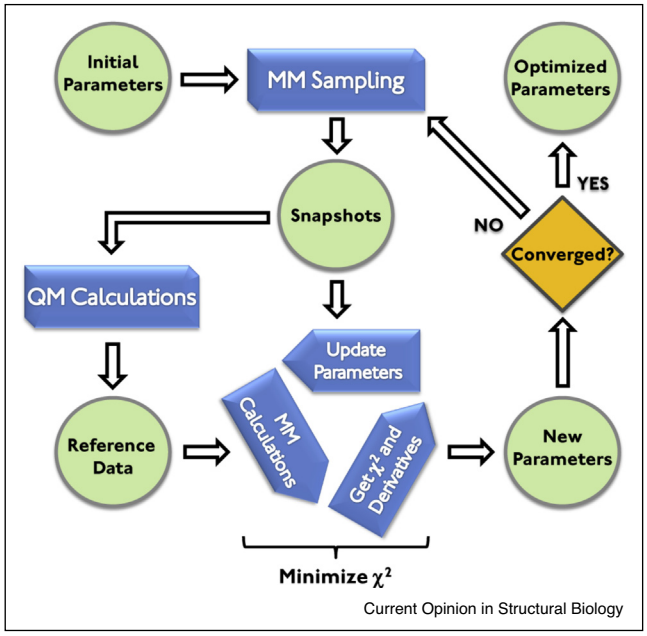
Force balance

In the force balance method, Eq. (3) is extended with a term representing the difference between atomic forces generated by the force field from reference forces from quantum chemistry [19]. In that paper, the cost function $\chi^2(k)$ is minimized iteratively using a limited memory optimizer [20] that performs molecular dynamics simulations, evaluates the cost function and updates the parameters until convergence (Figure 1). The accompanying free software has been applied to refine the Amber ff99SB model into the Amber ff15FB model [21]. For this purpose, about 30 000 quantum chemistry calculations of amino acids in many conformations were performed and energies and gradients (forces) were stored. After optimization, the new parameter set was termed Amberff15FB, and the authors reported that temperature dependence of peptide stability is improved using the new parameters [22]. In an evaluation of the hydration free energy and diffusion constants of amino acids, the Amber ff15FB model with accompanying TIP3P-FB water model [22] was found to have the same accuracy as previous models [23•]. Very recently, the first version of the Open Force Field for small molecules was released based on Force Balance [24]. The software is actively maintained and hence is a useful resource for other workers in the field.

Bayesian optimization

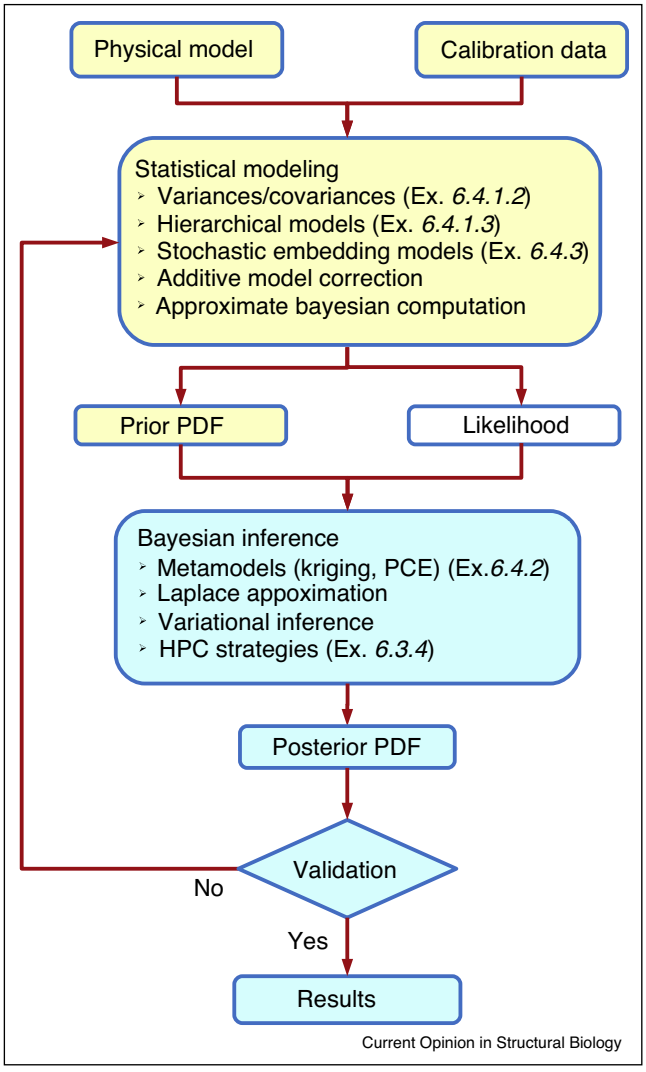
The Bayesian formalism can be used to derive force fields with well-defined uncertainties, which allows to generate predictions that also have well-defined uncertainties [25]. Starting from a physical model and a sufficient amount of

Figure 1



Force balance algorithm. Reprinted with permission from Wang *et al.* Copyright (2013) American Chemical Society, Ref. [19].

Figure 2



Flowchart of the Bayesian calibration. Reprinted with permission from Ref. [26••].

reference data, initial parameters and their uncertainties, the prior probability distribution function (PDF) of the parameters is generated and one of a series of different algorithms can be applied to improve correspondence with, for instance, a cost function, such as Eq. (3) (Figure 2). A recent review gives a detailed description of the different algorithms that can be applied [26••].

Cailliez and Pernot pioneered the Bayesian formalism in force field design by optimizing parameters for a Lennard-Jones potential for liquid Argon [25]. They showed that the posterior parameter PDFs depend on the data set used for deriving them, and that the inherent uncertainty in simulation results due to the uncertainty in the parameters is in fact larger than the statistical uncertainty. In their review, Cailliez and collaborators write that 'One of the major challenges of molecular simulation is the specification of the inter-particle interaction potentials, both in terms of the functional shape and the respective parameter values.' [26••]. This statement is depressingly similar to the one by Levitt and Lifson quoted above, from fifty years ago [1].

In response to the well-known inadequacies in the Lennard-Jones potential, Walz *et al.* used global Monte Carlo (MC) optimizations to derive parameters for alkali-halides using multiple different descriptions for the Van der Waals interactions [27••] (in the paper the optimization algorithm is called Bayesian MC but it was rather MC in parameter space with simulated annealing to minimize the cost-function). The term 'global optimization' is used here to indicate that parameters for all alkali halides were optimized at once using a single cost function. Although alkali-halides may be inorganic compounds, they provide an excellent testing ground for nonbonded potentials, since there are no intramolecular interactions. Using both gas-phase and solid-phase data, Walz *et al.* derived four different potentials, 12–6 and 8–6 Lennard-Jones potentials, a Buckingham potential and a buffered Buckingham potential [19]. Notably, the four models included explicit polarization using the shell or massless charge-on-a-spring model [28] and distributed Gaussian charges [29]. By changing the Van der Waals potential in an otherwise identical model it is possible to systematically reduce the deviation from experimental data. The normalized RMSD averaged over six properties

was 7.2 % (12–6), 4.4% (8–6), 3.4% (Buckingham) and 3.1% (Wang-Buckingham) respectively. The final model has a factor of four lower NRMSD than the next-best (non-polarizable) model due to Joung and Cheatham [30] at 12.2%. The Walz *et al.* model was subsequently applied in a number of projects, including the challenging prediction of melting points [31].

Bayesian Monte Carlo was applied for the optimization of parameters for describing distributed polarizable charges in halo-organic compounds taken from the Alexandria library [15]. Ghahremanpour *et al.* derived models for both Gaussian and Slater distributed polarizable particles [32•] to be used in conjunction with the electrostatic potential (ESP) fitting [33] for deriving atomic charges. They employed 19 atom types (based on the Generalized Amber force field [34]) and refined the 19 distribution parameters (Gaussian respectively Slater widths) with explicit uncertainties, to reproduce the electrostatic potential generated by approximately 1350 compounds [32•].

'Small' problems with small molecules

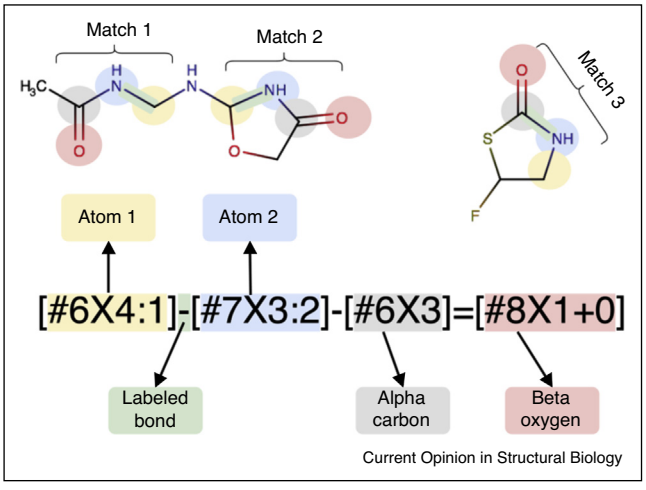
Many biological problems require modeling of small organic compounds, be they co-factors, inorganic ions or drug molecules. In addition, cells contain a plethora of different phospholipid molecules, sugars and so on [35]. The number of nucleobases and amino acids is limited and therefore their parameters can be determined once. However, in order to perform complex simulations, for instance to mimic the cytoplasmic environment, parameters for all relevant compounds must be determined [36]. In many cases, bonded potentials, as well as Lennard-Jones parameters, are taken from the force field corresponding to the biomolecule, whereas partial charges are derived from quantum chemistry by an ESP fit [33]. Determining partial charges is a topic in itself, but ESP fitting remains the state-of-the-art despite shortcomings having been known for a long time [32•,37]. Work to improve the method continues to this date [38].

Another 'small' issue in determining parameters is to define the atom types based on either a structure or another description of the compound. The complexity in building a molecular topology based on atomic coordinates should not be underestimated [39]. Most popular force fields have their own dedicated tools. For the Generalized Amber force field (GAFF) [34], the Amber tools are typically used [40] although for instance OpenBabel can be used for atom typing as well [41]. As part of the derivation of Gaussian and Slater distributed charges [32•], GAFF atom types from both Amber and OpenBabel were compared, and inconsistencies in both were found (and corrected). For the Charmm General force field (CGenFF) [42], a package called FFParam does this preprocessing [43], while for the OPLS-AA force field [44], a tool and a webserver called LigParGen is available [45] alongside non-free alternatives. Recently, Mobley *et al.* proposed an innovative method to bypass the atom-typing step (Figure 3) [46•,47]. This is advantageous, since atom types can introduce redundancy in force fields if, for instance, the parameters for a torsion potential are not dependent on the exact atom type. If redundant parameters are added, the parameter space grows and it becomes more difficult to make a parameter optimization converge.

Validation of force fields

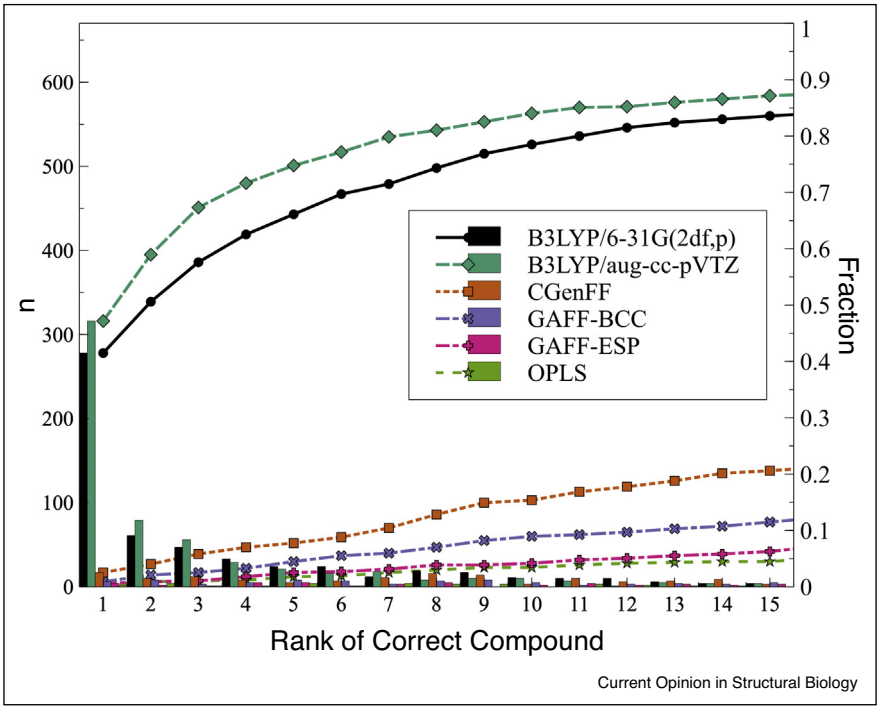
In the end, force fields old and new need to be validated by comparison to data from experiments or quantum chemistry. So-far there is no generally agreed-upon benchmark, which makes it hard to compare [48•]. A further problem is that there is limited physicochemical data on biomolecules perhaps with the exception of ligand binding energies [49••], which is why benchmarks using organic liquids and compounds are a useful proxy [50–52]. A recent benchmark of infrared spectra of compounds computed using force fields and DFT methods to experimental data shows that there is ample room for improvement of the intramolecular potentials in current non-polarizable force fields (Figure 4) [53••]. Knowing that the first force fields were geared to reproduce vibrational frequencies [3•,48•], this sadly suggests that some of the lore of days gone by has been lost. The poor reproduction of vibrational properties, that can also be noted in force field thermochemistry calculations [54], is a sign that the intramolecular potential energy surface is not accurate enough. A significant effort in force field development has been on improving ligand binding in the context of drug design [49••], and the intramolecular properties of ligands may in part cancel in free energy calculations. This might be an explanation to why this has not gained sufficient attention to address the issue.

Figure 3



The SMIRKS chemical query language enables direct chemical perception by substructure matching. Reprinted with permission from Mobley *et al.* Copyright 2018 American Chemical Society, Ref. [46•].

Figure 4



Individual and cumulative numbers and fractions of correct matches found in the first 15 ranks when experimental spectra are compared to the database of computed spectra for the short wavenumber range (550−1650 cm^{-1}). Reproduced with permission from Henschel and Van der Spoel, Copyright 2020 American Chemical Society, Ref. [53••].

Conclusion

Systematic design of force fields requires big data, some of which is now starting to appear [11–15,17••]. Some standardization of efforts is needed here, and perhaps the Quantum Chemistry archive of the Molecular Sciences software institute [17••] can provide that. To go from data to force fields, algorithms such as Force Balance [19] or Bayesian inference methods [25,26••] are needed. At this point in time, the Force Balance method seems to be more applicable [22]. However, the Bayesian framework can deliver robust uncertainties [25,32•], which will be likely required for publishing predictions in due time. Systematic design has been shown to work for small problems [25,27••], and it has been demonstrated that Van der Waals potentials can be improved systematically [27••,31]. Whether algorithms such as Force Balance or Bayesian methods will work with thousands of parameters, remains to be seen. Finally, an effort to standardize force field validation benchmarks [49••,50–52,53••,54] needs to be undertaken, such that results can be compared on an equal footing [48•], something that has been shown to advance the field over the years.

Conflict of interest statement

Nothing declared.

Credit author statement

David van der Spoel wrote the paper.

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- •• of outstanding interest

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