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Regular Article

Breathing New Life into Classical Force Fields

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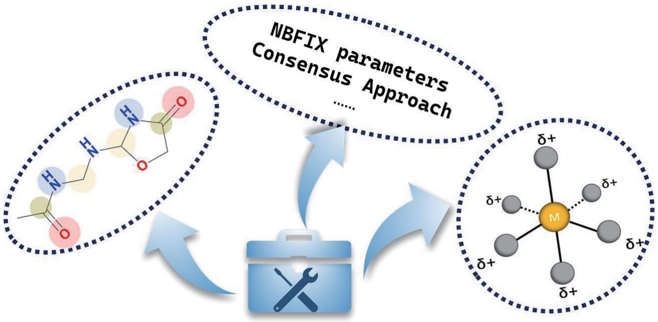
Abstract: Classical force fields form the foundation of molecular dynamics simulations. Because classical force fields are limited to pairwise-additive Lennard-Jones potentials and fixed-charge electrostatics, they cannot accurately capture explicit polarization and charge-transfer effects, metal coordination bonds, or weak, directional nonbonded interactions such as π–π stacking. Machine-learning force fields and polarizable force fields, which have been claimed to accurately characterize these types of interactions, have developed rapidly in recent years, raising an ongoing debate over whether further improvements to classical force fields are still necessary. Keeping this question in mind, we review various strategies proposed in recent years to improve the description of nonbonded interactions for classical force fields. These advances include the development of atomic charge models that accurately reflect molecular dipoles, water models that capture electrostatic screening and solvation effects, atom-pair-specific van der Waals parameters to mimic polarization, refined atom types that better represent chemical environments, and the introduction of virtual sites for accurately modeling of lone pairs. We also discuss the applicable scope of each strategy. Furthermore, by comparing classical force fields with polarizable and machine-learning-based force fields, we identify three major advantages of classical force fields: high computational efficiency, strong transferability, and ease of parameterization. Therefore, we join the ongoing debate and believe that the community will greatly benefit from further development of classical force fields. Through the improvement of the accuracy of characterizing nonbonded interactions, classical force fields can be widely applied in areas such as million-atom simulations and high-throughput screening.



“new tricks for old dogs”

Key words: force fields, polarization, charge transfer nonbonded interactions.

1. Introduction

Molecular Dynamics (MD), as a vital tool in the field of computational chemistry, fundamentally relies on the physical accuracy of force fields to ensure the reliability of simulation results [1-8]. Although mainstream classical, or fixed-charge, force fields such as AMBER [9,10], CHARMM [11,12] and OPLS [13,14] have undergone decades of parameter optimization and have achieved remarkable success in biomolecular simulations such as protein folding and drug design, [9,15-18] their accuracy in describing certain types of nonbonded interactions remains a subject of debate. It is generally believed that [15], due to the limitations of the functional form of classical force fields, phenomena such as charge transfer, polarization effects, metal coordination, and π–π interactions cannot be accurately captured [19-25]. A common viewpoint holds that the accurate description of such types of interactions requires either the introduction of new functional terms, usually the polarization term, into classical force fields or a shift toward more complex machine-learning-based models [26-36]. Therefore, models such as 12-6-4 [37,38], AMOEBA [32,34,39,40], Drude [41,42], ANI [43], Deep Potential [44] and NN PES [45] have been proposed. Despite the great success of these potentials, their application in the study of complex biochemical processes remains severely limited due to constraints in computational efficiency and software implementation, and difficulties in parameterization, especially for systems involving more than 100,000 atoms or tasks that require high-throughput simulations [20,44,46].

Recent studies have found that by employing "new tricks for old dogs", which are methods that improve the accuracy but do not change functional form of classical force fields, nonbonded interactions such as charge transfer, polarization, coordination, and π–π stacking can be accurately mimicked. Since these new techniques do not alter the functional form of classical force fields, they can serve as drop-in replacements for widely used force fields such as CHARMM [11] and AMBER [9,10] in any molecular dynamics engine, without incurring additional computational costs. As a result, these methods offer a practical way to improve the accuracy of potential energy surface descriptions in MD simulations and can be broadly applied to model a wide range of complex biochemical processes. However, because end users typically rely on default parameter files provided by MD engines, such improvements and newly developed force field parameters have not received widespread attention, adoption, or discussion.

Therefore, this paper focuses on the description of nonbonded interactions by classical force fields, reviews recent strategies proposed to improve their accuracy, and discusses their applicability. We highlight the importance of adopting these new methods and newly published parameters, and provide practical guidance for end users. By comparing classical force fields with polarizable and machine-learning-based force fields, we emphasize the continued relevance of advancing classical force field development. Furthermore, we offer perspectives on future directions for classical force fields. The outline of this review is shown in Figure 1.

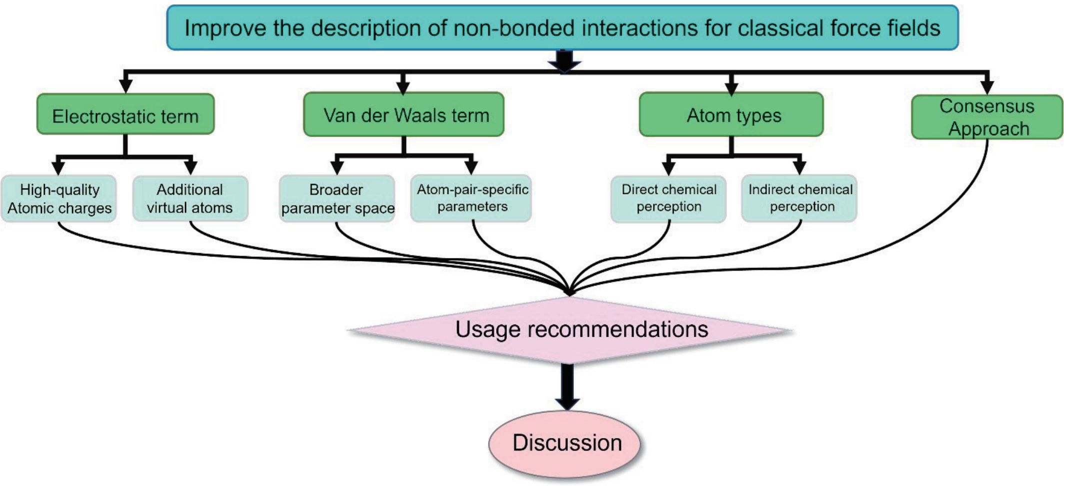


Figure 1. Outline of this review.

Functional form of classical force fields and the types of interactions they fail to describe

In classical force fields, the calculation of potential energy is decomposed into two parts: bonded and nonbonded interactions:

$$E_{\text{total}} = E_{\text{bonded}} + E_{\text{nonbonded}}$$

The functional equation for the nonbonded interaction is:

$$E_{\text{nonbonded}} = \sum_{ij} \frac{q_i q_j}{4\pi\varepsilon r_{ij}} + \sum_{ij} \varepsilon_{ij}\left[\left(\frac{\sigma_{ij}}{r_{ij}}\right)^{12} - 2\left(\frac{\sigma_{ij}}{r_{ij}}\right)^{6}\right]$$

For different atom types, the calculation of van der Waals interactions requires combination rules. For example, CHARMM and Amber force fields follow the Lorentz-Berthelot combination rule [47,48]:

$$\sigma_{ij} = (\sigma_{ii} + \sigma_{jj})/2$$
$$\varepsilon_{ij} = \sqrt{\varepsilon_i \varepsilon_j}$$

In classical force fields, Coulomb's law characterizes charge–charge, charge–dipole, and dipole–dipole interactions between molecules [49,50]. In contrast, the physical meaning of the 12-6 potential remains somewhat controversial, as it was originally proposed primarily for computational convenience [51,52]. Chipot's group and Merz's group have pointed out that the 12-6