Force fields for atomistic molecular dynamics

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Abstract

Computer simulations are a powerful instrument to investigate the structure and dynamics of many-body systems like biological macromolecules. In principle, all details of molecular structures and interactions can be predicted using quantum mechanical calculations. Unfortunately, the applicability of such so-called *ab initio* computations is limited due to their extremely high computational cost. Hence, these calculations are only feasible for a few particles and short time scales, which is why no dynamics can be simulated.

To enable the study of larger systems, simplified models and methods are thus needed. One method is *molecular dynamics*, which relies on Bohr's correspondence principle stating that the behavior of systems, described by the theory of quantum mechanics, reproduces classical physics in the limit of large quantum numbers. That means, for large systems and for large energies, quantum mechanical calculations must agree with classical calculations [6]. Hence, the atoms and molecules of the system can be treated as classical particles following the principles of classical physics. In this report, molecular dynamics will not be covered specifically but rather its foundation, namely the idea of classical *force fields*.

Therefor, the definition of classical force fields will be introduced in the first section. Their role in molecular dynamics will be quickly emphasized, followed by a detailed description of the functional form and the parameterization procedure of a force field.

In the second part, a general overview of classes of force fields and their applications will be given first. To emphasize the importance of the choice of force field parameters and the physical model, a closer look will be taken at different water models differing from each other by the choice of interaction parameters as well as by the treatment of the electrostatic interaction between water molecules. Since the so far discussed force field models rely on classical physics, they encounter difficulties with the treatment of chemical reactions. Hence, recently developed QM/MM hybrid models will be quickly introduced with which these obstacles can be overcome.

Last but not least, a summary of the strengths and weaknesses of force fields in general will be provided.

1 Force fields and molecular dynamics

Although quantum mechanical calculation methods allow an accurate treatment of the microscopic interactions between the system's particles and may also provide the entire information about the electronic states of the system, they are accompanied by a few but important limitations. One of them is the high computational cost which, in case of the simplest models, scales as $\mathcal{O}(N^3)$ where N is the number of atoms in the system [3].

In contrast to these methods, molecular dynamics relies on classical physics to describe the interactions between atoms and molecules in the simulated system. Consider therefor a system containing two atoms. All the microscopic quantum mechanical interactions in that exemplary system, i.e. electron-electon, nucleus-nucleus and electron-nucleus interactions, will be therefore approximated by an effective classical pair-interaction and the respective potential between the atomic centers. This approximation is based on second-order perturbation theory [13]. Note that because of the pairwise treatment of the interactions, the computational cost of molecular dynamic based simulations in principle scales as $\mathcal{O}(N^2)$. The use of clever algorithms and calculation techniques may even decrease the scaling to the order of $\mathcal{O}(N)$ [3].

The two bodies in the mentioned exemplary system can now be treated as classical particles following Newton's equation of motion

$$\boldsymbol{F}_i = m_i \frac{\mathrm{d}^2}{\mathrm{d}t^2} \boldsymbol{r}_i, \tag{1}$$

where i denotes the respective particle, m_i its (constant) mass and $\boldsymbol{r}_i$ its position while $\boldsymbol{F}_i$ describes the force acting on it.

Now as we will discuss in the next section, a force field provides the entire information about the potential energy $U(\boldsymbol{r}_1, ..., \boldsymbol{r}_N)$ of the investigated system containing N particles. The force in eq. (1) can then be calculated by using the relation

$$\boldsymbol{F}_i = -\nabla_i U(\boldsymbol{r}_1, ..., \boldsymbol{r}_N). \tag{2}$$

By integrating eq. (1) for each particle, their trajectory can be reproduced. This can be done by using known integrators with different integration schemes and methods (e.g. Euler method, Velocity-Verlet integration or Runge-Kutta method), which will not be covered in this report. It can be noticed that without a force field, the equation of motion is incomplete and thus, no molecular dynamics can be done. Force fields are therefore the foundation of molecular dynamics.

2 Theory of classical force fields

2.1 Definition of a force field

In principle, force fields underlie two important assumptions. The first one states the additivity of each single potential energy terms. It thus implies that the potential energy of the system can be written as a sum of different contributions with a simple physical interpretation (e.g. bond deformations, electrostatics or dispersion forces).

Furthermore, the idea of transferability of force fields means, that a force field can be applied to molecules with similar chemical groups of those molecules, which were used in the development of the force field [16].

In general, a force field consists of two components. The first one is an analytical expression describing the potential energy $U(\boldsymbol{r}_1, ..., \boldsymbol{r}_N)$ as a scalar function of the atomic coordinates $\boldsymbol{r}_i$. The second part of a force field is a set of definitions and parameters associated with this function for each *atom type* and not just for a chemical element. The reason for this is the unique influence of the atom's environment and bonding on the atom itself, e.g. carbons in alkyne side chains are not treated the same as carbons in a benzene ring. Hence, parameters are assigned based on the atom types involved.

Note that force fields are an empirical construction since there is no unique translation of the microscopic quantum-mechanical interactions into approximated classical pairwise interactions. In the following, these two components of a force field will be explained in more detail.

2.2 Functional form of a force field

A simple potential energy function of a force field can be written as

$$U = \underbrace{\sum_{\text{bond}} U_b(r) + \sum_{\text{angle}} U_\theta(\theta) + \sum_{\text{torsion}} U_\phi(\phi)}_{\text{bonded terms}} + \underbrace{\sum_{\text{non-bonded}} \{U_{\text{VdW}}(r) + U_{\text{Coul}}(r)\}}_{\text{non-bonded terms}}. \tag{3}$$

In general, the potential energy of each force field can be separated into two parts. The first one combines all the bonded interactions between atoms of a molecule while the second part describes the non-bonded interactions of all non-bonded molecules and atoms with each other.

Bond stretching The bond stretching between a pair of atoms is described by the first term. For small deviations from the equilibrium distance r_0 between the atom pair, the most common way to model the bonding is by attaching these two particles together via a spring representing a harmonic potential with the spring constant k_{ij}, where i and j denotes the involved atoms. The associated potential function $U_b(r_{ij})$ depends on the distance r_{ij} between the two atoms and can thus be written as

$$U_b(r_{ij}) = k_{ij}(r_{ij} - r_0)^2. \tag{4}$$

One weakness of this model is the exclusion of bond breaking since the spring force diverges for larger distances. To overcome this problem, one can use the Morse potential [17]

$$U_b(r_{ij}) = D_e \left(1 - e^{-a_{ij}(r_{ij} - r_0)}\right)^2, \tag{5}$$

where a_{ij} implies the stiffness of the bond and D_e describes the dissociation energy i.e. the depth of the potential well. Contrary to the harmonic approach, this potential function converges to D_e for larger distances. The Morse potential indeed gives a more accurate treatment of the bonding than eq. (4), since the function in (4) is part of the Taylor expansion of the function in (5), but is therefore computationally more expensive.

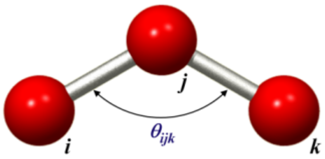

Figure 1: Illustration of the angle bending, taken from [2]. The angle θ_{ijk} is defined by the bond between atoms i, j and the bond between atom j, k.

Angle bending The second term in eq. (3) contains information about the angle bending of a three-body molecule (see figure 1). The angle included by the two bonds between atom i, j and atom j, k is defined as

$$\cos\theta_{ijk} = \frac{\boldsymbol{r}_{ij} \cdot \boldsymbol{r}_{jk}}{r_{ij}\, r_{jk}} \quad \text{with} \quad \boldsymbol{r}_{ij} = \boldsymbol{r}_i - \boldsymbol{r}_j \quad \text{and} \quad r_{ij} = |\boldsymbol{r}_{ij}|.$$

The potential for the angle bending can then again be written as a harmonic function

$$U_\theta(\theta_{ijk}) = k_{ijk}^{\mathrm{H}}(\theta_{ijk} - \theta_0)^2 \tag{6}$$

with the equilibrium bonding angle θ_0 and the stiffness k_{ijk}^{H} of the bending. However, this function becomes problematic when considering an angle of $\theta_{ijk} = 180°$ due to the factor of $1/\sin\theta_{ijk}$ in the force expression, which would lead to an infinite acceleration. Therefore, the cosine harmonic angle potential

$$U_\theta(\theta_{ijk}) = k_{ijk}^{\mathrm{CH}}(\cos\theta_{ijk} - \cos\theta_0)^2 \tag{7}$$

can be used. Note that the force constants for either the cosine harmonic or the harmonic potential differ from each other.

Torsions When it comes to a molecule involving four atoms, torsions must be considered. In figure 2, the definition of the torsional angle is illustrated. The torsional angle ϕ_{ijkl} is the angle between the plane going through the atoms i, j, k and the plane going through the atoms j, k, l. This angle can be calculated as

$$\cos\phi_{ijkl} = \frac{\boldsymbol{m}\cdot\boldsymbol{n}}{m\,n} \quad \text{with} \quad \boldsymbol{m} = \boldsymbol{r}_{ij}\times\boldsymbol{r}_{jk} \quad \text{and} \quad \boldsymbol{n} = \boldsymbol{r}_{lk}\times\boldsymbol{r}_{jk}.$$

The magnitude of the respective vectors is denoted by m and n. The dihedral potential, modeling the rotation barriers around bonds, can be expressed as

$$U_\phi(\phi_{ijkl}) = k_{ijkl}\left[1 + \cos(n_{ijkl}\phi_{ijkl} - \phi_0)\right], \tag{8}$$

where k_{ijkl} is the force constant belonging to the cosine type of potential, ϕ_0 the angle where the potential passes through its minimum value and n_{ijkl} is the multiplicity indicating the number of minima as the bond rotates through 360°.
It is important to note that these mentioned terms do not always describe the entire bonded interaction of atoms of a molecule. For complex substances, additional terms have to be taken into account. In principle, the freedom of choice, how accurate the reality should be reproduced and which functions to use, emphasizes the empirical character of a force field.

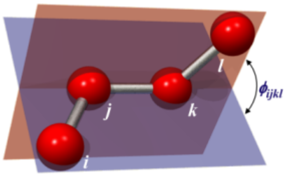

Figure 2: Illustration of the torsional angle, taken from [2]. The angle ϕ_{ijkl} is included by the plane going through the atoms i, j, k and the plane going through the atoms j, k, l.

Van der Waals interaction The fourth term in eq. (3) describes the Van der Waals interactions between two non-bonded particles. This kind of interaction generally consists of an attractive and a repulsive component.
The physical origin of the attractive term lies in the dispersion forces generated between instantaneous dipoles, which arise from fluctuations in the electronic charge distributions in all molecules. In the influence of an electric field of the strength E, a molecule with the polarizability α shows an induced moment $M = \alpha\cdot E$ and its energy is given by

$$U = -\frac{1}{2}\alpha E^2. \tag{9}$$

Assume now that molecule i produces an electric field of the strength $E \propto \mu_i/r^3$ near molecule j, where μ_i denotes the dipole moment of molecule i. As a consequence, this field polarizes molecule j and gives rise to an additional interaction energy

$$U \propto -\frac{\alpha_j}{2}\frac{\mu_i}{r^6} \tag{10}$$

according to eq. (9).

Furthermore, it is shown in [14] that the average total interaction between two particles of the same kind (i.e. same dipole moment and polarizability) is

$$U_{\text{attractive}} = -\frac{2\alpha\mu^2}{r^6}. \tag{11}$$

The repulsive term represents the Pauli exclusion principle stating that below a certain distance, the atoms repel each other, which is caused by the overlap of the electron clouds of both atoms [18]. In contrast to the attractive term, there is no analytical solution to describe the repulsion. The most commonly used potential function to model the Van der Waals interaction is the Lennard-Jones potential, which can be written as

$$U_{\text{LJ}}(r_{ij}) = 4\epsilon_{ij}\left[\left(\frac{\sigma_{ij}}{r_{ij}}\right)^{12} - \left(\frac{\sigma_{ij}}{r_{ij}}\right)^{6}\right], \tag{12}$$

with ϵ_{ij} as the depth of the potential well and σ_{ij} as the distance at which the potential energy is zero. As above-mentioned, the functional form of the attractive term has a physical justification, which does not hold for the repulsive term with the exponent 12. However, it turns out that it can be efficiently computed as the square of $1/r_{ij}^6$ [1].

Another matter of computational efficiency is the treatment of this interaction for large distances. Therefore, a cutoff radius R_{cut} is introduced, which sets the maximum distance for which the Van der Waals interaction is treated as described by eq. (12). For distances larger than R_{cut}, the potential energy is then set to zero. This approximation can be justified since the function in eq. (12) converges to zero very fast. Hence, a relatively large cutoff radius would result in errors with a neglectable order of magnitude.

Note that the parameters in eq. (12) are mostly not given for a specific pair, but as a parameter for the atom itself. To treat interactions between two different types of atoms, mixing rules are therefore needed. One possibility is given by the Lorentz-Berthelot rules [15, 5] stating that

$$\sigma_{ij} = \frac{\sigma_{ii} + \sigma_{jj}}{2} \quad \text{and} \quad \epsilon_{ij} = \sqrt{\epsilon_{ii}\epsilon_{jj}}. \tag{13}$$

These mixing rules are purely empirical and have no theoretical justification. Since there are countless and also more complicated ways to determine such pair parameters, the choice of the combination rules is also an important part of a force field.

Coulomb interaction Finally, the last term in eq. (3) contains the Coulomb interaction between the partial charges q_i and q_j of the atom i and j, respectively. Partial charges are created due to the asymmetric distribution of electrons in chemical bonds, which may arise from the difference in the electronegativity of the involved atoms. When an electrically neutral atom is bonding to another but more electronegative neutral atom, its electrons are partially drawn away. This leaves the region about that atom's nucleus with a positive partial charge and creates a negative partial charge on the atom to which it is bonded. The electrostatic potential can then be computed as

$$U_{\text{Coul}}(r_{ij}) = \frac{q_i q_j}{4\pi\epsilon(r_{ij})r_{ij}}, \tag{14}$$

where the local dielectric constant $\epsilon(r_{ij})$ can be rescaled to get a better agreement with the experimental data. Since this function only decays with $1/r_{ij}$, neglecting the potential for the treatment of long-range interactions like in the previous approach is not valid. For periodic system, a solution was proposed by Ewald [10]. In this Ewald summation method, the long-range interaction is divided into two parts: a short-range and a long-range contribution. The first mentioned is calculated in real space, whereas the long-range contribution is computed using a Fourier transform. There also exist different variants of this summation called particle-mesh methods (e.g. Particle Mesh Ewald [8]) allowing a more efficient computation of the Coloumb forces. Note that these methods calculating the electrostatic interactions between particles in a system, can achieve a scaling of the computational cost as $\mathcal{O}(N)$.

Special terms The potential energy function in eq. (3) is an example for problems, which can be sufficiently treated using simple functions. For a more accurate treatment, not only do these functions become more complicated but also special terms must be considered. These may include cross terms describing the coupling between stretching, bending and torsion and adding corrections to the bonded potential.

However, the most relevant change of the functional form in eq. (3) is the explicit inclusion of polarization effects i.e. the charge redistribution of a particle due to an electric field exerted by other particles. This can be done by using the fluctuating charge model, the Drude oscillator model or the induced point dipole model [7].

2.3 Parameterization of force fields

In the previous section, several possibilities of the functional form of a force field were discussed. All these functions have in common that they include parameters with physical meaning e.g. the equilibrium bond length or the stiffness of the binding. These parameters must be provided to the force field and can in principle be acquired by experimental measurements or *ab initio* calculations. The equilibrium bond lengths can be obtained from x-ray or neutron diffraction measurements while infrared spectroscopy can be used for the bending angle. The latter one can also be used to obtain the stiffness of the binding. Of course, these exemplary parameters can also be generated by using quantum mechanical calculations. An overview of the sources for parameter sets used by the popular AMBER, CHARMM, OPLS and GROMOS force field is provided in the supplement materials of [11].

Next, these parameters have to be optimized. It is therefore essential to specify the target properties as well as the target objects of the force field for which the experimental results have to be reproduced as best as possible, since it is impossible to achieve optimal results for all properties and every substances as we will see in the next section.

With the given initial parameters, the atomic structures can be evaluated. After generating enough sample states, the target observables can be calculated and the error against the reference data can be estimated. Optimization algorithms then provide new optimized parameter sets with which this whole procedure will be repeated until the error is sufficiently small or the maximum number of optimization steps has been reached. With the final set of parameters, the limits of the developed force field regarding its transferability must be investigated. It will therefore be applied to substances, which were not included in the parameterization process.

3 Comparison of force fields

In this section, the applicability of existing force fields will be discussed. Especially the effect of differences in parameters and physical models will be analyzed based on water models, a simple and widely used version of a force field.

As a researcher using molecular dynamics, one has to choose a force field from a pool of countless possibilities. To have a better overview, several types of force fields can be distinguished [9]. The first type are rule-based force fields using generic rules to generate parameters for a range of interactions from a small set of atomic-based parameters and having broad applicability across the periodic table. In contrast to them, class I force fields are parameterized but still kept simple by using simple harmonic functions for bonded and the Lennard-Jones potential for non-bonded interactions. This type of force field is commonly used to investigate large systems like DNA or proteins because of their computational efficiency. On the other hand, class II force fields are intended for studying small to medium molecules and materials science, since they provide a higher accuracy by adding cross-terms, cubic, or quartic expansions of stretch and bend and using exponential-type potentials for dispersion interactions. On top of that, class III force fields include polarization effects.

It is important to note that this categorization does not imply class III force fields to be in general a better choice than, for example, those of class I. This has several reasons. First, although the higher classes include more physical terms in a more accurate way, the detailed treatment of the interactions will lead to a higher computational cost than using simpler models with no complex construction of their functional form.

Moreover, the increased complexity and number of interaction terms requires more parameters. Consequently, the transferability of force field parameters will be strongly limited since such force fields are designed and parameterized for one particular problem. The transferability of a force field is an essential aspect to pay attention to, because applying a force field for other target substances than those included in the parameterization will lead to unreliable predictions.

Finally, these limitations implicate that such force fields are less developed than the simpler ones. This is because not everyone is always studying that particular substance for which the respective high class force field was made, although it undoubtedly reproduces very accurate results. On the contrary, due to their simplicity and wide applicability, class I force fields are the preferred choice for most of the researchers, which is why many people from many different research groups have contributed to the development of such force fields for many years. In short, more experience has been put into simpler force fields than into those complex, high accurate ones. An overview of popular force fields and their applicability can be found in [9].

3.1 Water as a paradigm

To exemplify the consequences of the choice in the parameters and the physical models of force field, water models will be discussed due to their simplicity, them being commonly studied and them being a version of a force field with a simple funtional form and a manageable number of parameters. The complexity of the models can be assigned to three types [20]. In the simplest model, water molecules are treated as rigid bodies i.e. the distances and angles between the atoms are fixed. The only interactions of interest are non-bonded types. on the other hand, flexible water models include bond stretching and angle bending by attaching the atoms together via springs. This allows the reproduction of vibration spectra. On top of that, polarizable models include an explicit term for polarization effects.

In the following, we assume rigid water models, where the Van der Waals interaction between two water molecules is represented by the Lennard-Jones potential between their oxygen atoms. Due to their size, the Lennard-Jones radius is large enough to include the hydrogens.

Additionally, the electrostatic interactions can be modeled in different ways by using different number of interaction sites to reproduce the electrostatic interactions. Therefore, massless dummy atoms are introduced taking the partial charge of the oxygen atom. This is illustrated in figure 3. As an example, the four-site model includes a dummy atom M near the oxygen along the bisector of the HOH angle of the three-site model. The partial charge of the oxygen is now relocated to the dummy atom, which improves the electrostatic distribution around the water molecule. In the five-site model, a pair of dummy atoms L (L stands for lone pair) is used instead and the charge of the oxygen atom will be split among these two sites. The advantage of these n-site water models is the gained flexibility in the electrostatic distribution and thus in the Coulomb interactions. Lastly, the six-site model combines the idea of the previous mentioned models. Note that the computational time differs using different models, since different number of distances and forces have to be computed. The most commonly used water models are based on this method of reproducing the electrostatic interactions between rigid water molecules.

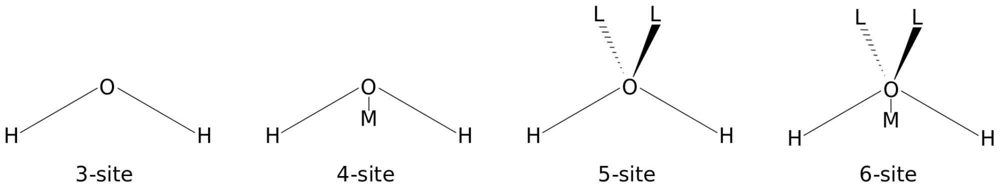

Figure 3: Overview of different site models, taken from [4]. For models with more than three sites, massless dummy atoms (denoted by M and L) can be introduced to place the charge of the oxygen atom.

Popular models and their chosen parameters are listed in table 1. It contains the bond length d_{OH} of the oxygen and hydrogen, the bending angle of the water molecule, the Lennard-Jones parameters for interactions between non-bonded oxygen atoms as well as the hydrogen charge q_{H} and the distance d_{OM} and d_{OL} between the oxygen and the dummy atoms. The charge of the oxygen or the dummy atom is not explicitly listed, since it is equal to $-2\,q_{\mathrm{H}}$. A closer look at the TIPnP water models shows that they mainly differ from each other by the choice of both the hydrogen charge and the Lennard-Jones parameters. Note that force fields are often parameterized with respect to a particular water model. That is why certain water models may only work with certain force fields, e.g. the TIP3P water model for the AMBER force field.

Table 1: An overview of commonly used water models and their parameters, taken from [19]. The parameters include the bond length d_{OH} of the oxygen and hydrogen, the bending angle, the Lennard-Jones parameters for interactions between non-bonded oxygen atoms as well as the hydrogen charge q_{H} and the distance between the oxygen and the dummy atoms d_{OM} and d_{OL}.

Model	n	d_{OH} [Å]	H-O-H [°]	σ_{OO} [Å]	$\epsilon_{\mathrm{OO}}/k_{\mathrm{B}}$ [K]	q_{H} [e]	d_{OM} [Å]	d_{OL} [Å]
SPC/E	3	1.0	109.47	3.1656	78.20	0.423	0	-
TIP3P	3	0.9572	104.52	3.1506	76.54	0.417	0	-
TIP4P	4	0.9572	104.52	3.1540	78.02	0.52	0.15	-
TIP4P/2005	4	0.9572	104.52	3.1589	93.2	0.5564	0.1546	-
TIP5P	5	0.9572	104.52	3.1200	80.51	0.241	-	0.70

An extensive comparison was done by Vega *et al.* in 2008 by comparing the quality of reproducing ten properties of water using the listed models [19]. The goal of the research was to find the water model that can reproduce water and ice as best as possible. It turns out that each water model comes with its strengths and weaknesses.
One benchmark, for example, was the melting point of ice, which is 273.15 K. Simulations based on the TIP5P reproduced a melting point of 274 K while those using TIP4P/2005 resulted in a melting point of 252 K. So if this quantity plays a significant role in our research, the obvious choice would be TIP5P. However, this situation changes if we consider the critical temperature of water, which is 647.1 K. Simulations using TIP5P resulted in 521 K while using TIP4P/2005 reproduced a critical temperature of 640 K, which is obviously in a much better agreement with the experimental data than the result from TIP5P.
Lastly, to emphasize the importance of the choice of parameters, we compare TIP4P and TIP4P/2005 which both are based on the four-site water model. As shown by Vega *et al.*, the overall performance of these two models have significant differences. While TIP4P/2005 achieved a very accurate reproduction of nine of the ten predefined properties, TIP4P could only reproduce four properties with only acceptable accuracy, although these two models differ from each other just by the choice of hydrogen charge and the potential's depth (see table 1).
This water based example demonstrates the importance of first, the chosen physical model and second, the parameter sets involved in the development of a force field.

3.2 QM/MM approaches

So far, we have discussed the idea of classical force field. Despite their computational efficiency, they encounter difficulties with simulating chemical reactions since these cannot be treated by classical physics. Therefore, hybrid QM/MM approaches were introduced.
The idea behind this concept is to use the computational efficiency of molecular dynamics and at the same time allow an accurate treatment of the relevant interactions using quantum mechanical calculations. Therefor, the system will be separated into first a small part comprising the chemically active region and where quantum mechanical calculation methods will be used. The rest of the system then will be treated classically. This separation is justified because of the local character of most chemical reactions. More information on this can be found in [12].

4 Conclusion

In this report, the foundation of molecular dynamics was introduced, namely the concept of classical force fields. With its functional form and the corresponding set of parameters, a force field provides the entire information on the potential energy of the simulated system with which the total force acting on each particle can be computed.
Since there is no unique translation of the microscopic quantum-mechanical interactions into approximated classical pairwise interactions, force fields are an empirical construction. What seems to be disadvantageous at first sight is, in fact, a strength since therefore, force fields with different levels of accuracy, transferability and computational efficiency exist. The user can thus select the force field, which is most suited for his research.
Moreover, force field based simulations provide insight into microscopic motions of atoms and molecules, which can be used to investigate the behavior of the particles in equilibrium and non-equilibrium. Thus, it is able to visualize e.g. the melting process of ice.
In addition to that, the simple toolkit structure and the additivity of the force field's functional form allow an uncomplicated and independent modification of each energy expression. The

influence of each of the energy terms on the observed behavior can hence be easily examined. The biggest advantages over *ab initio* calculations, however, is the computational cost of simulations based on force fields. As mentioned in the first section, a scaling of even $\mathcal{O}(N)$ for the computational time can be realized by using clever calculation techniques and algorithms. That is why simulations of large systems can be done.

Nevertheless, the application of classical force fields is accompanied by a few limitations. First, the gained information by using force field based simulations is limited since such simulations have difficulties with electronic transitions (photon absorption), electron transport phenomena, proton transfer (acid/base reactions) and chemical reactions. Therefore, no information about electronic, magnetic or vibrational properties can be obtained.

In addition to that, the applicability of force fields is limited only to those substances, which contain the functional groups of those molecules, which were included in the development. The transferability of a force field is also limited regarding simulating systems under different conditions than those used in the development of the force field.

Finally, the limited accuracy of force field methods has to be mentioned. This arises from approximations on which the functional form of force fields is based. One example is the pairwise treatment of non-bonded interactions. The accuracy also depends strongly on the quality of the parameterization of the force field.

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