Chapter 5

Molecular Dynamics Simulations (2)

5.1 Ensembles and Time Averages

The classical equations of motions (in the Lagrangian (Eq. (4.1)), or in the Newtonian formulation (Eq. (4.3))) describe the dynamic evolution of a system in form of a discrete time trajectory over the potential energy surface. Equivalents to macroscopic properties such as for instance, temperature T and pressure P, can be defined on the microscopic level, e.g. as we have seen in Eq. (4.36), the temperature of the system can be related to the average kinetic energy per particle. If you perform an MD simulation of a finite size system, you will notice that the temperature fluctuates. In fact, the observed temperature fluctuations $\Delta\mathrm{T}$ will be indirectly proportional to the square root of the number of particles N, $\Delta\mathrm{T} \sim 1/(\mathrm{N}^{1/2})$.

The pressure can be defined using the (molecular or atomic) virial given in Eq. (4.37) as

$$PV = Nk_BT + \frac{1}{3}\langle\sum_{i=1}^{N}\boldsymbol{r}_i \cdot \boldsymbol{F}_i\rangle \qquad (5.1)$$

This establishes connections between macroscopic observables of ensembles containing of the order of Avogadro’s number of particles and the microscopic time-dependent properties of a single molecule. Any given point that has been visited during the time evolution of the system is characterized not only by the set of nuclear coordinates but also by the velocities (momenta) of each particle. The space that is spanned by all the position and momenta coordinates of the system is called ***phase space***. By creating MD trajectories, we thus sample different configurations in phase space.

Lets assume we follow the system for an infinite time and all parts of phase space are accessible to us that should be reachable at this temperature (***ergodic system***). Then we sample all possible configurations during our time trajectory and furthermore, we visit all of them with the proper statistical weight. Under these circumstances the average of a given property along our time trajectory becomes equivalent to its macroscopic ensemble average. This link to statistical mechanics is a very powerful one because it enables the calculation of dynamic as well as thermodynamic properties as direct excerpts from an MD trajectory. Typical examples of properties that can be calculated in this way are for instance, diffusion coefficients, characteristic relaxation times, dielectric constants, and viscosities. We also gain access to a variety of space and time correlation functions such as e.g. radial distribution functions in liquids or Fourier Transforms of the velocity-velocity autocorrelation functions as fingerprints for vibrational spectra. The probably most important feature that becomes available in this way is the possibility of determining relative free energy differences.

This is terrific! However, the accuracy of all the derived properties depends crucially on the quality of the underlying potential energy surface. Most of the time, the potential energy surface is described in terms of empirically parameterized interaction potentials (“force fields”) and the development of reliable force fields is therefore of crucial importance for the predictive power of molecular dynamics simulations.

5.2 Force Fields

In principle, we know how to determine the underlying potential energy surface: we have to solve the time-independent Schrödinger equation on a dense enough mesh of points in configuration space $\{\mathbf{R}\}$. Subsequently, we can fit the set of numerical values to an appropriate analytical form. However, it is easy to see that a procedure that attempts a full determination of the potential energy surface is impractical for most systems of more than a few atoms. Suppose that we discretize every internal degree of freedom with M points. Hence, we will have to perform of the order of $M^{(3N-6)}$ solutions of the Schrödinger equation. If we take e.g. $M \sim 100$, even for a system as small as a triatomic, we need of the order of a million quantum chemical calculations! Clearly, an evaluation of the entire potential energy surface is only feasible for very small molecules in the gas phase whereas we are also interested in extended systems in condensed phase. Unfortunately, it looks like we have to give up on the dream of an *ab initio* force field determined directly from quantum mechanics!

In Chapter 6, we will see however that there is still a possibility to work with an interaction potential that is fully based on first-principles. In so-called *ab initio* or Car-Parrinello molecular dynamics simulations, all the interactions are calculated on the fly directly from a quantum mechanical method. In this way, instead of calculating the full 3N dimensional surface, the potential energy surface is only determined where it is needed, i.e. at the points where the system actually passes through.

Most of the molecular dynamics simulations are however based on empirically parameterized potential energy surfaces (empirical “force fields”). For such a parameterization, the essential physics of the interactions has to be captured and condensed into a simple analytic form that then can be adjusted using experimental or quantum mechanical data. The art of designing smart force fields that are able to reproduce the intrinsic properties of a system is far from trivial. A comprehensive discussion of the various forms of existing force fields would go far beyond the scope of this course, only few examples of the most widely used types of force fields, those used to describe water and biological macromolecules will be discussed here.

5.2.1 Water Force Fields

Water is the most commonly used solvent and a variety of force field models exist for H_2O. In the majority of water force fields, the single water molecules are treated as rigid units, i.e. the O-H bond lengths and the HOH bond angle are fixed. This eliminates the high frequency motions due to the OH stretching, and HOH bending vibrations, which in turn enables the use of a larger time step. The rigid geometry is imposed using constraints on the OH and HH distances as described in Chapter 4.3.

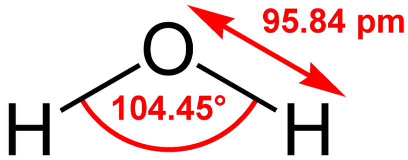


Fig.5.1 Geometry of a water molecule. (picture taken from wikipedia).

The force field contains only non-bonded van der Waals and Coulomb terms as in Eq.(5.4). Furthermore, most water models only include van der Waals interactions of the oxygen atoms, neglecting the much smaller contributions from the hydrogen atoms. The van der Waals parameters are often chosen in such a way that the denisty of liquid water at ambient conditions is reproduced. The electrostatic interactions are modelled via effective point charges q_i located at nuclear positions (e.g. 3-site water models such as TIP3P and SPC) and sometimes on additional off-atomic sites mimicking e.g. the effect of the negative charge density due to lone pair orbitals). Water models of the latter typ are TIP4P (4 interaction sites), TIP5P and TIP6P.

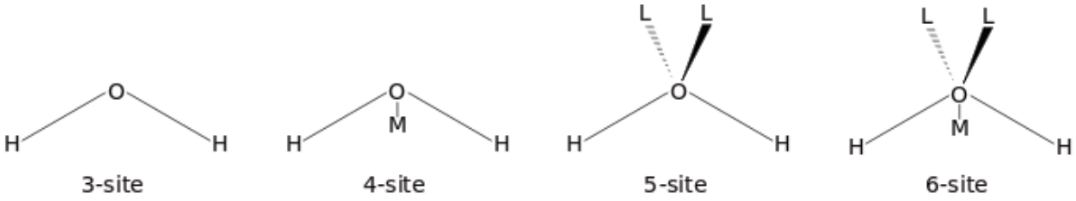
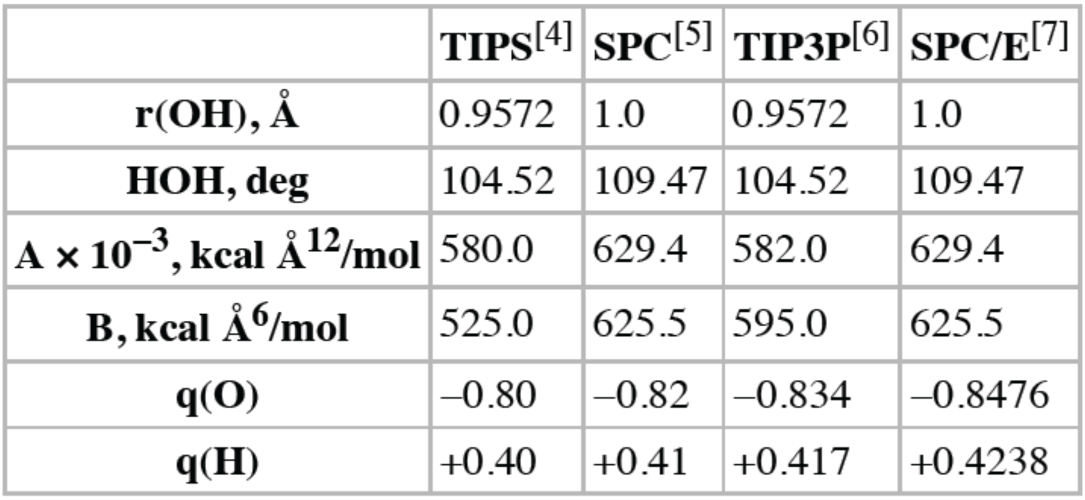


Figure 5.2 3-6 site water models (picture form wikipedia).

The atomic point charges could be chosen in such a way that the dipole moment of an isolated water molecule in gas phase (1.85 Debeye) is described correctly. However, such a choice would severly underestimate the significant increase in dipole moment in the liquid phase (~ 3 Debye). Since water models are almost exclusively used to model the liquid state, the effective point charges are chosen in such a way to account for this additional polarization. The force field parameters of the most popular 3-site water models are given in Table 5.1



	TIPS[4]	SPC[5]	TIP3P[6]	SPC/E[7]
r(OH), Å	0.9572	1.0	0.9572	1.0
HOH, deg	104.52	109.47	104.52	109.47
A × 10^{-3}, kcal $Å^{12}$/mol	580.0	629.4	582.0	629.4
B, kcal $Å^{6}$/mol	525.0	625.5	595.0	625.5
q(O)	–0.80	–0.82	–0.834	–0.8476
q(H)	+0.40	+0.41	+0.417	+0.4238

Table 5.1 Parameters of commonly used water models (from wikipedia).

The SPC/E model is an extension to the SPC water model that takes an average polarization correction to the interaction energy into account and results in a sligthly better density and self-diffusion constant.

5.2.2 Force Fields for Biological Macromolecules

Because of the large size of biological systems such as proteins, nucleic acids or lipid membranes, force fields for these systems are in wide use. They usually divide the interactions into so-called *bonded* terms (terms between interaction sites that are linked via chemical bonds) and *non-bonded* terms (interactions between particles that do not form direct chemcial bonds with each other).

$$H_{MM} = H_{MM}^{bonded} + H_{MM}^{non-bonded} \tag{5.2}$$

$$H_{MM}^{bonded} = \sum_{b} \frac{1}{2} k_b (r_{ij} - b_0)^2 + \sum_{\theta} \frac{1}{2} k_\theta (\theta_{ijk} - \theta_0)^2 + \sum_{\varphi} \sum_{n} k_n \left[1 + \cos(n\varphi_{ijkl} - \varphi_0 \right] \tag{5.3}$$

$$H_{MM}^{non-bonded} = \sum_{lm} \frac{q_l q_m}{4\pi\varepsilon_0 r_{lm}} + \sum_{op} 4\varepsilon_{op} \left(\left(\frac{\sigma_{op}}{r_{op}} \right)^{12} - \left(\frac{\sigma_{op}}{r_{op}} \right)^{6} \right) \tag{5.4}$$

where k_b, and k_θ are harmonic force constants for bond stretching and angle bending potentials, r_{ij} and θ_{ijk} refer to the instantaneous values of bonds and angles, and b_o and θ_0 are the corresponding equilibrium values. The third term in Eq. (5.3) defines a torsional potential for twisting two adjacent planes of atoms against each other. The terms in Eq. (5.4) describe non-bonded interactions including electrostatic and van der Waals forces. Eqs. (5.2-4) are a generic form and many variations are possible. For instance, anharmonic terms might be included in the bond and angle potentials. Furthermore, different forms of the torsional potentials are in use and the van der Waals potential can be diverse, e.g. an exponential form instead of the r^{-12} dependence for the repulsive part. Different force fields also use varying exclusion rules that define how the non-bonded interactions are handled for sites that already interact via bonded terms. Moreover, explicit interaction sites can be included on all the atoms (all atom force fields) or only on suitably defined pseudo atoms (e.g. a single interaction sites representing nonpolar –CH, -CH_2 or -CH_3 groups, so-called *united atom* force fields). In recent years, *coarse-grain* force fields such as the MARTINI force field, in which groups of atoms (usually containing ~4 atoms) are described by one coarse-grain interaction site. Some popular force fields of the type described in Eqs. (5.2-4) are the AMBER, CHARMM, GROMOS, or OPLS-AA force fields. They are used in combination with available water models such as SPC, SPC/E and TIPnP.

All the force fields mentioned so far are based on pair potentials, in which many-body terms in the nonbonded interactions are incorporated only in an implicit way. Force fields with explicit higher order terms such as three-body or many-body potentials have also been developed for specific systems.

Most of the current force fields are *non-polarizable*, i.e. charges that have been initially assigned to the system remain constant throughout the simulation at variance with the fact that the instantaneous chemical surrounding may change. The development of more sophisticated *polarizable* models, in which the point charges can fluctuate and adapt to changes in the environment is presently an active field of research. Several polarizable force fields have been published in the literature for water as well as for biological macromolecules.

Molecular dynamics simulations based on empirical force fields have been remarkably successful in providing a microscopic picture of complex biomolecular systems. This simple approach has however its limits. As we have seen, the underlying electronic structure enters the construction of appropriate interaction potentials only in an implicit way, and hence parameters that have been determined for a specific chemical environment are often not transferable to largely differing bonding conditions. Typical cases in which the transferability of empirical force fields usually breaks down are situations in which the electronic structure of the system experiences drastic changes, such as e.g. during a chemical reaction. Most empirical potentials are therefore not suitable to simulate directly the forming and breaking of chemical bonds. Another notoriously difficult issue is the development of reliable force fields for transition metals. For these tough cases, often the only possibility for an accurate description is an explicit treatment of the electronic structure as employed in first-principles molecular dynamics simulations (Chapter 6).

5.3 Few Tricks of the Trade

Modern molecular dynamics simulations have evolved over the years to a sophisticated technique and there are many subtle ‘tricks of the trade’ of how to setup the system and how to run and analyze the simulations.

5.3.1 Choice of Boundary Conditions

A first decision that has to be made when setting up a system for an MD simulation, is the choice of appropriate boundary conditions. The natural choice for the simulation of crystalline solids is the use of periodic boundary conditions that are chosen in such a way as to impose the infinite periodicity of the lattice. A similar selection can be adopted for the simulation of an ‘infinite’ liquid for which the system is put into a (rectangular) box and particles that go out of the box on one side automatically re-enter the system again on the opposite side (as illustrated in Fig.4.1 in the previous Chapter). However, in reality, a liquid is not a periodic system and the introduction of such circular boundaries can introduce artificial periodicity effects. The characteristic interaction length that can be described is restricted to half of the box edge.

An alternative choice is to truncate explicit interparticle interactions beyond a given spherical cutoff radius and to describe the longer-range interactions with a dielectric continuum (reaction field) model. Also in this case, the results might depend on the actual choice of the cutoff radius and dielectric constant for the surrounding medium.

An even cruder description is provided by the introduction of spherical droplets in which the solvent molecules on the surface are kept from evaporating into the vacuum by a suitably chosen restraining potential. Naturally, if not handled carefully, such a choice of boundary conditions can lead to strong spurious surface effects.

5.3.2 Treatment of Long-Range Forces

The treatment of the non-bonded interactions, and in particular the long-range electrostatic interactions are usually the computationally most demanding part of a classical MD simulation. The way in which these interactions are treated contributes in an important way to the overall quality of the simulation protocol. Several different strategies with widely varying accuracy are currently in use. The simplest (and crudest) way of treating the electrostatic interactions is the straightforward introduction of a spherical cutoff radius beyond which no interactions are taken into account. Another popular *ad hoc* solution is the introduction of a high or distance-dependent dielectric constant. A recent more rigorous approach replaces the electrostatic interactions outside a given cavity with a dielectric continuum (reaction field) representation.

The correct treatment of the long-range electrostatic interaction in systems with periodic boundary conditions is more involved as an exact calculation of the total electrostatic energy implies an infinite sum over all possible pairs among periodic replicas. A rigorous method to treat this problem has been introduced in the form of the Ewald method. The full electrostatic interactions can be separated into a short-range part that is easily calculated in real space and a smooth long-range part that is conveniently determined in reciprocal space through the application of discrete Fourier Transforms. Modifications of the original Ewald scheme that expand the charge density of the system on a real space mesh and make use of Fast Fourier Transform algorithms such as particle-mesh Ewald (PME) have also been introduced in the last years. Alternatively, schemes have been developed that are based on (hierarchical) fast multipole expansions.

5.3.2 Constant NVT and NPT Ensembles

The equations of motion in Eqs.(4.1 and 4.3) are Hamiltonian, i.e. they have the characteristic property that the total energy of the system is conserved during the time evolution. This special feature also offers a stringent test for new implementations, as inconsistencies between the calculated energy and forces affect the energy conservation in a sensitive way. Due to this property, time-averages over this type of trajectories can be related to ensemble averages of the microcanonical ensemble. Unfortunately, the microcanonical ensemble is not a very common ensemble for the measurement of macroscopic properties. In order to make direct contact with experimental data, it would be more desirable to perform simulations in a canonical (NVT) or even in a constant NPT-ensemble. A straightforward way to obtain averages in the canonical ensemble would be to perform a 'macroscopic' (i.e. very large) number of independent Boltzmann-distributed microcanonical simulations. Such an approach is quite impractical and molecular dynamics schemes have been introduced to achieve the same goal within a single simulation. Most of these schemes, couple the system to a thermal bath (thermostat) through which additional 'friction' forces are introduced that are determined in such a way as to keep the average kinetic energy of the system in accordance with the chosen temperature. One of the most popular ***constant-temperature MD*** algorithms is due to Nosé and Hoover. For some applications, it is also useful to thermostat the thermostats themselves as in the so-called Nose-Hoover chain algorithm. It can be shown that the Nose-Hoover(-chain) method generates averages in the canonical ensemble. This is an important feature that is not valid for more simplistic approaches such as a straightforward scaling of the velocities or the use of a Berendsen-thermostat. Similar extended system methods, in which the system is coupled to a heat and a pressure bath are also available. A special form of ***constant pressure MD***, that is especially powerful for the investigation of phase transitions in the solid state, is the ***Parrinello-Rahman*** method. In this elegant approach, the simulation cell itself is a dynamic variable that can change shape and size during the simulation.

Chapter 6

Advanced Molecular Dynamics Techniques

6.1 First-Principles MD Simulations with the Car-Parrinello Method

In first-principles or Car-Parrinello molecular dynamics simulations the underlying interaction potential is calculated directly via a quantum mechanical electronic structure method. This combination can in principle be achieved in a straightforward way. For every set of nuclear coordinates, the electronic structure problem is solved and the nuclear forces are calculated via the Hellman-Feynman theorem. The nuclei are then moved to the next position according to the laws of classical mechanics and the new forces are again calculated from a full electronic structure calculation. This type of *ab initio* molecular dynamics is often referred to as '*Born-Oppenheimer dynamics*'.
In 1985, Car and Parrinello have introduced an elegant alternative to this approach in which the electronic degrees of freedom, as described by e.g. one-electron wavefunctions $|\varphi_i\rangle$, are also treated as fictitious classical variables. The system is described in terms of the extended classical Lagrangian L_{ex}

$$L_{ex} = K_N + K_e - E_{pot} \tag{6.1}$$

where K_N is the kinetic energy of the nuclei, K_e is the analogous term for the electronic degrees of freedom and E_{pot} is the potential energy which depends on both, nuclear positions $\{\vec{R}_I\}$ and electronic variables $|\varphi_i\rangle$. L_{ex} can be written as:

$$L_{ex} = \sum_I \frac{1}{2} M_I \dot{\vec{R}}_I{}^2 + \sum_i \mu |\dot{\varphi}_i|^2 - \langle \Psi_0 | H | \Psi_0 \rangle + \sum_{i,j} \Lambda_{ij} \left[\left\{ \int \varphi_i{}^*(\vec{r}) \varphi_j(\vec{r}) d\vec{r} \right\} - \delta_{ij} \right] \tag{6.2}$$

where the Λ_{ij} are Lagrange multipliers that ensure orthonormality of the one-electron wavefunctions $|\varphi_i\rangle$, μ is a fictitious mass associated with the electronic degrees of freedom and the potential energy is given by the expectation value of the total (ground state) energy of the system $E = \langle \Psi_0 | H | \Psi_0 \rangle$. The Lagrangian in Eq. (6.2) determines the time evolution of a fictitious classical system in which nuclear positions as well as electronic degrees of freedom are treated as dynamic variables. The classical equations of motion are given by the Euler-Lagrange equations:

$$\frac{d}{dt}\left(\frac{\delta L}{\delta \dot{q}_i{}^*} \right) = \frac{\delta L}{\delta q_i{}^*} \tag{6.3}$$

where q_i corresponds to a set of generalized coordinates. With the Lagrangian of Eq. (6.2), the equations of motion for the nuclear degrees of freedom become

$$M_I \ddot{\vec{R}}_I = -\frac{\delta E}{\delta \vec{R}_I} \tag{6.4}$$

and for the electronic ones

$$\mu\ddot{\varphi}_i = -H\varphi_i + \sum_j \Lambda_{ij}\varphi_j \qquad (6.5)$$

where the term with the Lagrange multipliers Λ_{ij} describes the constraint forces that are needed to keep the wavefunctions orthonormal during the dynamics. The parameter μ is a purely fictitious variable and can be assigned an arbitrary value. In full analogy to the nuclear degrees of freedom, μ determines the rate at which the electronic variables evolve in time. In particular, the ratio of M_I to μ characterizes the relative speed in which the electronic variables propagate with respect to the nuclear positions. For $\mu << M_I$, the electronic degrees of freedom adjust instantaneously to changes in the nuclear coordinates and the resulting dynamics is adiabatic. Under this condition $K_e << K_N$ and the extended Lagrangian in Eq. (6.2) becomes identical to the physical Lagrangian L of the system

$$L = K_N - E_{pot} \qquad (6.6)$$

For finite values of μ, the system moves within a limited width, given by the fictitious electronic kinetic energy, above the Born-Oppenheimer surface. Adiabaticity is ensured if the highest frequency of the nuclear motion ω_I^{max} is well separated from the lowest frequency associated with the fictitious motion of the electronic degrees of freedom ω_e^{min}. It can be shown that ω_e^{min} is proportional to the gap E_g, i.e. the difference between highest occupied and lowest unoccupied energy levels

$$\omega_e \alpha \sqrt{\frac{E_g}{\mu}} \qquad (6.7)$$

For systems with a finite E_g, the parameter μ can be used to shift the electronic frequency spectrum so that $\omega_e^{min} >> \omega_I^{max}$ and no energy transfer between nuclear and electronic subsystem takes place. For metallic systems, special variations of the original method have to be adopted. In practice, it is easy to check if adiabatic conditions are fulfilled by monitoring the energy conservation of the physical Lagrangian in Eq. (6.6).

Eqs. (6.4) and (6.5) can be integrated simultaneously with one of the standard MD integration algorithm mentioned in Chapter 4. In this way, one can generate classical nuclear trajectories on a quantum mechanical potential energy surface.

The Car-Parrinello method is similar in spirit to the extended system methods for constant temperature or constant pressure dynamics. Extensions of the original scheme to the canonical NVT-ensemble, the NPT-ensemble or to variable cell constant pressure dynamics are hence in principle straightforward. The treatment of quantum effects on the ionic motion is also easily included in the framework of a path-integral formalism.

Most of the current implementations use the original Car-Parrinello scheme based on density functional theory as the underlying electronic structure method. The system is treated within periodic boundary conditions and the Kohn-Sham (KS) one-electron orbitals $|\varphi_i\rangle$ are expanded in a basis set of plane waves (with wave vectors $\vec{G}_m$)

$$\varphi_i(\vec{r}) = \frac{1}{\sqrt{V_{cell}}} \sum_m c_{im} e^{i\vec{G}_m \bullet \vec{r}} \tag{6.8}$$

up to a given kinetic energy cutoff E_{cut}. Substituting Eq. (6.8) into the extended Lagrangian of Eq. (6.2) gives

$$L_{ex} = \sum_I \frac{1}{2} M_I \dot{\vec{R}}_I^{\,2} + \mu \sum_i \sum_m \left|\dot{c}_{im}\right|^2 - E_{KS} + \sum_{i,j} \Lambda_{ij} \left[\sum_m c^*_{im} c_{jm} - \delta_{ij} \right] \tag{6.9}$$

and the equation of motion for the electronic degrees of freedom in Eq. (6.5) is replaced by analogous classical equations for the plane wave coefficients c_{im}

$$\mu \ddot{c}_{im} = -\frac{\delta E}{\delta c^*_{im}} + \sum_j \Lambda_{ij} c_{jm} \tag{6.10}$$

Typical plane wave expansions include impressive numbers of 10,000-100,000 plane wave coefficients. All of these have to be optimized or propagated simultaneously using Eq. (6.10), which makes first-principles MD approaches highly memory intensive.

Besides the traditional scheme, *ab inito* MD methods using semiempirical, Hartree-Fock, generalized valence bond (GVB), complete active space (CASSCF), and configuration interaction (CI) electronic structure methods have been realized. The Car-Parrinello scheme has also been extended into a mixed quantum/ classical QM/MM approach.

6.2 Mixed Quantum Mechanical/Molecular Mechanical (QM/MM) Simulations

An ideal simulation method just employs the computational effort that is needed to describe a given problem with a desired accuracy. For many systems, it is advantageous to apply a fast classical MD description based on empirically determined interaction potentials whenever possible and a computationally more demanding first-principles treatment where necessary. In combined quantum/classical QM/MM methods the reactive part of the system (e.g. the active site of an enzyme) is treated with a quantum chemical method while the effects of the surrounding are taken into account within a classical force field description.

This is an appealing idea but the quality of these techniques crucially depends on a rigorous treatment of the interface between quantum and classical part of the system. Significant progress has been made during the last years to develop reliable ways of coupling both semiempirical and first-principles quantum mechanical methods with a classical environment. This approach has thus become a promising and powerful option to study extended systems in which the crucial interactions are described at an advanced level.