Atomistic simulations of reactive processes in the gas- and condensed-phase

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Atomistic simulations of reactive processes in the gas- and condensed-phase

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This review focuses on force-field-based approaches to investigate – through computer simulations – reactive processes in chemical and biological systems. Both, reactions in the gas-phase and in condensed-phase environments are discussed and opportunities and the potential for further developments are pointed out. Where available, results are compared with alternative methods and the advantages and drawbacks of the methods are compared. Particular applications include vibrationally and electronically induced (photo)dissociation of small molecules, proton transfer in the gas- and condensed phase and ligand un- and re-binding in proteins.

Keywords: Molecular Dynamics; Reactive MD; Force Field; Proton Transfer; Ligand Binding

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1. Introduction
Calculating the rate at which chemical reactions occur from first principles is a formidable task. The problem involves several steps, each of which poses its own challenges. Most fundamentally, one has to represent the intermolecular forces which govern the interactions between the atoms involved. Next, the dynamical problem of how the atoms move from educt to product on the potential energy surface (PES) has to be solved. Finally, a rate constant can be computed from integrating over the initial state distribution.

Fundamentally, the total interaction energy of an aggregate of atoms can be computed in two different ways: either by (approximately) solving the exact electronic Schrödinger equation or by a more or less empirical energy expression. Accurately solving the electronic Schrödinger equation has made tremendous progress since the 1960s and by now it is possible to converge total electronic energies to better than fractions of a kcal/mol for small-to medium-sized molecules (up to a few heavy atoms). On the other hand, repeated evaluation of energies as necessary for rate calculations becomes computationally prohibitive. Consequently, alternative means have been developed in parallel. They include:

- Additional simplifications to the rigorous electronic Schrödinger equation which lead to semiempirical methods, including parameterisations such as Parameterised Model 3 (PM3) or Austin Model 1 (AM1) and their variants. A more recent semiempirical theory is self-consistent charge-density functional tight binding (SCC-DFTB).
- Fully dimensional PESs which can be pre-calculated from electronic structure methods and then represented through a parameterised function. This is generally only applicable to systems with few degrees of freedom because fitting high-dimensional functions also becomes prohibitive with increasing dimensionality of the problem.
- A fully empirical energy expression.

This latter class is considered in more detail in the following.

Empirical force fields emerged in the late 1960s to study primarily conformational properties of alkanes [1,2]. They were subsequently used to refine protein structures, the first of which was myoglobin [3]. This development paved the way for the first molecular dynamics (MD) simulation of a protein on the picosecond time scale [4]. While very suitable for ground state conformational dynamics of a molecular system, force fields do not explicitly contain electronic degrees of freedom which is – strictly speaking – necessary to follow photochemical or reactive processes. Therefore, an additional layer needs to be introduced to investigate these phenomena. For reactive processes, one very promising step forward was to combine a force field description for the larger part of a system and to treat the reactive part with a quantum chemical method. Such a mixed quantum mechanics/molecular mechanics (QM/MM) ansatz has been used to study chemical reactions in larger systems. In QM/MM the system is divided into a reactive region, containing fewer atoms and described quantum mechanically (QM), and the rest of the system, containing the rest of the atoms and treated with an empirical force field (MM) [5–7]. The computationally demanding QM part is the bottleneck of the method that
dictates the accessible time scale of the simulations. Except for cases where semi-empirical methods are used for the QM-part, the nuclear dynamics and conformational sampling are typically not included in such studies. Improvements in the quality and speed of QM/MM methods, including SCC-DFTB and ‘neglect of differential overlap’ (NDDO), have been presented in recent reviews [8,9].

An alternative to study chemical reactions is to use empirical force fields with provisions to form and break bonds [10]. One approach, based on valence bond theory, is the ‘atoms in molecules’ (AIM) and the ‘diatomics in molecules’ (DIM) method, derived from it [11,12]. Originally developed to explain the electronic structure of polyatomic molecules from information about all possible diatomic and monoatomic fragments, it later matured into a technique which built globally valid PESs for molecular systems including the description of bond breaking and bond formation [13]. Related to this is empirical valence bond (EVB) [14], which has been extensively used to investigate catalytic reactions in biological systems with particular emphasis on including environmental effects. An alternative to EVB is the adiabatic reactive MD (ARMD) that has been recently proposed [15–17]. In ARMD the reactant and product are treated with individual force fields and transitions between the states occur on the basis of an energy criterion. The algorithm employs an energy criterion to decide when a crossing should occur. After a crossing is detected, the two states are mixed over a short period of time and the simulation continues on the second surface [16,17]. Such an approach allows to treat efficiently bond breaking and bond formation reactions in the framework of classical MD simulations (for some more technical details, see Section 2.2). Another promising method is ReaxFF, which is a reactive force field based on bond-order potentials [18]. Applications of ReaxFF were more focused on material science and high-energy processes including explosive materials and combustion [19,20]. Alternatively, empirical potentials consisting of Coulomb- and dispersion interactions and the Born–Meyer–repulsion, fitted to Hartree–Fock calculations on a SiO$_4$$^{2-}$ cluster, allowed to estimate structural and energetic differences between four alternative crystal structures [21]. A somewhat refined parameterisation allowed to directly study the pressure-induced phase transition between various polymorphs of silica [22]. During the transitions, bonds between atoms need to be formed and broken and hence the force field is also ‘reactive’. A more recent extension is temporal QM/MM that combines conventional FFs with semiempirical and quantum chemical methods [23]. For the nonreactive portions of a trajectory, a conventional FF is employed whereby the conformations sampled are scored with a coordinate-dependent metric. Whenever the metric suggests a reaction to take place, a semiempirical calculation is used to decide whether or not the actual structure is likely to move towards the product. If this probability is high, the simulation is continued with quantum chemical methods and potential energies are mixed over a finite time window, similar to ARMD.

Compared to most other methods, ARMD does not employ geometrical descriptors to decide whether the system samples the product or educt state. This makes ARMD quite unique because possible reaction (or progression) coordinates are not determined \textit{a priori} but rather can be extracted \textit{a posteriori} from the reactive trajectories themselves. Suitable algorithms to do this have been presented in the literature [24]. All classical dynamics-based methods are limited in that they are not rigorously applicable in cases where the quantum nature (e.g. tunnelling, non-adiabaticity, coherence) of the reaction dominates. This is most obviously the case in small systems for which other and potentially more
suitable approaches are available [25–27]. Whenever a barrier-crossing is more appropriately described by a tunnelling frequency, ARMD is not the method of choice. In cases where a reaction rate is the more appropriate picture, ARMD provides a lower bound for the rate as it does not include transitions away from the crossing seam.

2. Gas phase reactions

The use of force fields to investigate reaction dynamics for gas phase reactions is by now an established area of research. Since the pioneering work on the $\text{H} + \text{H}_2$ exchange reaction [28,29], which used a London–Eyring–Polanyi–Sato PES [30,31], many gas phase reactive processes have been studied using more or less empirical potential energy functions. Subsequently, approximations were made as to the dimensionality of the problem while retaining as much accuracy in the remaining degrees of freedom [32] or the problem was addressed in full dimensionality while sacrificing accuracy in treating details of the nuclear dynamics [33,34]. One of the largest calculations carried out so far concerns approximate diffusion Monte Carlo calculations on a parameterised, fully dimensional PES for proton transfer (PT) in malonaldehyde (MA) [35].

2.1. PT reactions with force fields

PT is fundamental for the function, structure and dynamics of chemically and biologically relevant systems. Direct investigation of PT dynamics is difficult experimentally. The most direct evidence for PT to occur are splitting of spectral features [36]. However, this is only available from high-resolution spectroscopy of small molecules in the gas phase [37–40]. Recently, high-resolution vibrational spectra have been recorded for protonated clusters. In 2003 Asmis et al. reported the vibrational spectrum of the shared proton in the protonated dimer [41]. Johnson et al. used vibrational predissociation spectroscopy to characterise the spectral signature of protonated molecular clusters [42,43]. Duncan et al. [44] reported photodissociation infrared spectra of water clusters $\text{H}_3^+ (\text{H}_2\text{O})_n (n = 2–5)$ with and without Ar tagging. Time-resolved vibrational spectroscopy [45,46] and photoelectron spectroscopy [47] are also used to study PT in bulk water. The analysis of these experimental spectra is usually accompanied by computations. The vibrational transitions associated with the intermolecular PT or ‘low-barrier’ hydrogen bonds are very sensitive to the chemical environment, and the infrared signatures exhibited are diffuse [48,49]. Such highly dynamical systems involving anharmonic vibrations makes computational simulations, especially MD simulations valuable for analysing spectra of the studied system [50–53].

During the past few years, a force field-based method – Molecular Mechanics with Proton Transfer (MMPT) – has been developed and successfully applied to a variety of chemical and biological systems [51,54–60]. MMPT has been applied to several model PT systems. Examples include intermolecular PT in protonated water dimer [51], protonated ammonia dimer [55] and 2-pyridone-2-hydroxypyridine (2PY2HP) dimer [55], as well as intramolecular PT in protonated diglyme [51], MA [57] and acetylacetone [59].

In MMPT the interaction within a general $\text{D}–\text{H}\cdots\text{A}$ motif is described by a parameterised three-dimensional PES $V(R, r, \theta)$ where $R$ is the distance between donor (D) and acceptor (A), $r$ is the distance between the D and H atom, and $\theta$ is the angle between $\vec{R}$ and $\text{D}–\text{H}$.
and \( r \) (Figure 1). To facilitate the parameterisation of MMPT potentials, the internal coordinate \( r \) is replaced by a dimensionless coordinate

\[
\rho = \frac{(r - r_{\text{min}})}{(R - 2r_{\text{min}})}
\]

where \( r_{\text{min}} = 0.8 \text{ Å} \) is in principle arbitrary but should be sufficiently small to cover the shortest possible D–H separations to avoid \( \rho \) becoming negative. Such 3D PESs \( V(R, \rho, \theta) \) are employed together with a standard force field which is CHARMM in this case [61]. To allow the breaking of the D–H and the formation of the H–A bond, bonded and non-bonded interactions on both the donor and acceptor side are explicitly evaluated, and are switched on and off depending on the position of the transferring atom (D–H \( \cdots \) A or D \( \cdots \) H–A).

MMPT PESs are available for generic proton- or hydrogen-transfer motifs including symmetric single minimum (\( \text{H}_2\text{O}–\text{H}^+ \cdots \text{OH}_2 \), Figure 1), symmetric double minimum (\( \text{H}_3\text{N}–\text{H}^+ \cdots \text{NH}_3 \)) and asymmetric double minimum (\( \text{H}_2\text{O}–\text{H}^+ \cdots \text{NH}_3 \)), calculated at the MP2/6-311++G(d,p) level of theory. The parameterised MMPT PESs \( V(R, r, \theta) \) have been fit to different functional forms. The radial dependence is always modelled by a double-Morse potential whereas for the \( \theta \)-dependence harmonic oscillators or Legendre polynomials are available. The detailed expressions and parameters are given in the literature [55,60]. These ‘generic’ or zeroth-order PESs can then be subsequently ‘morphed’ to adapt their overall shapes to topologically similar, but energetically different PESs depending on their chemical environment. In practice, morphing is achieved by modifying the MMPT parameters in a systematic way [62]. This can be a simple scaling [63] or a more general coordinate transformation depending on whether the purpose of this study and the experimental data justify such a more elaborate approach. For example, the MMPT PES of acetylacetone (AcAc, methyl-substituted MA) can be generated from that of MA [57] via the following PES morphing transformations [59]:

\[
V^{\text{AcAc}}(R, \rho, \theta) = \lambda V^{\text{MA}}(R - R_0, \rho, \theta)
\]

The morphing parameters \( \lambda = \Delta E^{\text{AcAc}}/\Delta E^{\text{MA}} = 0.796 \) and \( R_0 = R_{\text{opt}}^{\text{AcAc}} - R_{\text{opt}}^{\text{MA}} = 0.03 \text{ Å} \) are determined by comparing the PT energy barrier (\( \Delta E \)) and the equilibrium donor–acceptor distance (\( R_{\text{opt}} \)) of AcAc and MA computed by electronic structure calculations at the same level (MP2/aug-cc-PVTZ). PES morphing can also be performed to reproduce the X-ray structure [53] or even involves explicit fitting to dynamically averaged data [56,64].

Figure 1. (Colour online) Protonated water dimer \( \text{H}_2\text{O}–\text{H}^+ \cdots \text{OH}_2 \) as a prototype system for MMPT. \( R, r \) and \( \theta \) are the distance between the donor and acceptor atom, the distance between the donor and transferring proton atom and the angle between them, respectively.
Constructed along the lines described above, MMPT is effectively a mixed QM/MM method where the QM part is precalculated and not evaluated on-the-fly. It has the additional advantage that no link atoms are required to connect the quantum and the classical part [65].

It is important to validate the PESs by comparing with experimental observables or other computational methods. For the protonated water dimer (H$_2$O$_2^+$), MMPT/MD simulations find the asymmetric O–H⋯O stretching vibration at 830 cm$^{-1}$ which compares favourably with 861 cm$^{-1}$ computed from MD simulations by Bowman and co-workers on a 15-dimensional PES of H$_2$O$_2^+$ at 100 K [66,67]. In H$_2$O$_2^+$ this band strongly depends on temperature (724 cm$^{-1}$ at 5 K compared with 830 cm$^{-1}$ at 100 K) whereas in protonated diglyme the same vibration is at 870 cm$^{-1}$ with no temperature dependence [51].

One advantage of MMPT is its ability to directly investigate PT. With atomistic MD simulations, the time series of donor–acceptor and donor–proton distances can be studied in detail [55,57,59]. Over-the-barrier rates for PT reactions can be calculated from the slope of Hazard plots [55,68]. For example, the intramolecular PT rate at 300 K in MA in vacuum and water is computed to be 2.4 and 10 ns$^{-1}$, respectively. The fact that solvent enhances the rate by a factor of 5 implies a strong coupling between the transferring hydrogen atom and the solvent water [57]. For AcAc, the proton hopping rate in gas-phase is ≈0.25 ps$^{-1}$ [59], which is two orders of magnitude faster than that of MA. Other detailed information of the PT reaction, for example the fundamental role of the N–N vibration as the gating mode for PT in NH$_4^+$⋯NH$_3$, can also be captured [55]. It should be noted that with classical MD simulations only the over-the-barrier hopping rate can be determined, which should be considered as the lower limits for the PT rates. Including quantum tunnelling effects will increase the corresponding rates.

In situations where tunnelling plays a role, PT should rather be analysed in terms of a splitting than in terms of a rate constant. To estimate the tunnelling splitting, a suitable Hamiltonian for the quantum dynamics calculation is required. One suitable Hamiltonian is the harmonic bath averaged (HBA) Hamiltonian [32,57,69]:

$$H_{\text{HBA}}(p_s, s) = \frac{1}{2} \frac{p_s^2}{1 + \Delta_s} + V_0(s) + \sum_{k=1}^{3N-7} \frac{\omega_k(s)}{2} \left( 1 + \frac{\Delta_k(s)}{1 + \Delta_s} \right)$$  \hspace{1cm} (3)$$

where $s = \sqrt{\frac{m_p}{m_H}} (r_1 - r_2)$ is the hydrogen mass-weighted reaction path coordinate for PT and $p_s$ is the corresponding momentum. It is important to emphasise that, although only 2 degrees of freedom are explicitly treated in the dynamics, such a Hamiltonian takes into account the effect of all degrees of freedom of the system. Based on this Hamiltonian, the experimentally observed H*-tunnelling splitting of 21.6 cm$^{-1}$ is found if the mass of the transferring hydrogen atom H* is chosen appropriately. This, however, determines the mass of the transferring deuterium atom D* for which the tunnelling splitting has also been measured. The calculated D*-tunnelling splitting is 2.8 cm$^{-1}$, which is in very good agreement with the experiment (2.9 cm$^{-1}$). The fact that the transferring particle is associated with a different mass than its physical one reflects the kinetic coupling between its degrees of freedom and the environment [57]. Furthermore, the IR active H* and D* fundamental vibrations can be obtained which are found at 1573 cm$^{-1}$ and 1136 cm$^{-1}$, similar to recent computational results using alternative methodologies [35,70,71].
2.2. Gas phase dissociation reactions

PT reactions described above are particularly attractive because the time scales involved are short. On the other hand, quantum effects related to tunnelling and zero-point motion can become important. A different type of reaction concerns processes whereby chemical bonds between atoms are broken and new molecules are formed. Such reactions can involve one or several electronic states.

2.2.1. Vibrationally induced dissociation of sulphuric acid (H$_2$SO$_4$)

The notion that molecules in different internal states react more or less efficiently is a fascinating topic which is best studied under controlled conditions. An example for a vibrational mode-specific reaction involves CH$_4$ on a Ni(100) surface. It was found that the reactivity of methane changes depending on whether two quanta are vibrationally excited along the same CH stretch or whether one quantum is deposited in two separate CH stretching modes [72]. This insight precludes the applicability of statistical models to correctly describe the underlying reaction mechanism. Another example is the Cl$^+$CHD$_3$ → HCl + CD$_3$ reaction for which it was found that vibrational excitation of the CH-stretch in CHD$_3$ was no more effective in driving the reaction than translational energy [73]. Computationally, this process was recently investigated in much detail based on fully dimensional PESs and quasiclassical MD simulations [74]. From $2 \times 10^6$ trajectories, the cross sections for the reaction were determined as a function of the collision energy. The simulations found that compared to the vibrational ground state, vibrational excitation of stretch and bend vibrations indeed do enhance the reaction rate. However, at the same total energy $E_{\text{tot}} = E_{\text{coll}} + E_{\text{vib}}$, translational energy is more effective than the vibrational energy to drive the reaction for low $E_{\text{coll}}$.

Another process for which the reactivity of a molecule depends on its internal state is the vibrationally induced photodissociation of H$_2$SO$_4$ into water and SO$_3$. In the atmosphere, sulphur is emitted mainly as sulphur dioxide (SO$_2$), which is oxidised to SO$_3$ and subsequently hydrolysed to H$_2$SO$_4$ [75, 76]. The cycling between SO$_2$ and H$_2$SO$_4$ has been studied mainly because it plays an important role in the troposphere aerosol layer formation, which is related to global atmospheric chemistry [77, 78]. At high altitudes, SO$_2$ molecules could be generated from H$_2$SO$_4$ photolysis according to

$$\text{H}_2\text{SO}_4 \rightarrow \text{SO}_3 + \text{H}_2\text{O}$$

with subsequent rapid photolysis of SO$_3$ to produce SO$_2$ [79, 80]. However, there is no experimental observation of the electronic absorption spectrum of H$_2$SO$_4$ up to 140 nm [81]. Moreover, UV photons are absorbed at higher altitudes [82], therefore only few photons penetrate into the atmosphere with wavelengths shorter than 179 nm [83].

An alternative process was proposed whereby the dissociation of H$_2$SO$_4$ proceeds mainly from highly excited OH-stretching vibrational overtones [84, 85]. Experimentally, using cavity ring-down spectroscopy, the asymmetric OH stretching vibration $v_9$ of H$_2$SO$_4$ with $v_9 = 4$ and $v_9 = 5$ has been characterised [86]. They were found at 13,490 and 16,494 cm$^{-1}$, respectively. The barrier energy for H$_2$SO$_4$ hydrolysis is predicted to be between 32 and 40 kcal/mol [76, 87]. The amount of energy absorbed by several quanta in the OH stretching vibration $v_9$ would then be sufficient for H$_2$SO$_4$ hydrolysis.
The reaction dynamics after excitation of H$_2$SO$_4$ is still a matter of debate. Initially, the vibrational dynamics following IR-excitation was investigated using classical trajectory simulations at the PM3 level [88]. For 98 trajectories, propagated for 400 ps each, it was found that in 5% of the photodissociation cases takes place with an average reaction time of 9 ps. To characterise the statistical limit of the reaction, Rice-Ramsperger–Kassel–Marcus (RRKM) theory was used to calculate reaction constants ($k_{\text{RRKM}}$) and yields $k_{\text{RRKM}} = 1.7 \times 10^7$, $8.9 \times 10^8$ and $1.1 \times 10^9$ s for $v_9 = 4$, 5 and 6 quanta, respectively [89].

To atomistically analyse the reaction dynamics of vibrationally induced H$_2$SO$_4$ decomposition (Figure 2) from a statistically significant number of trajectories, adiabatic reactive molecular dynamics (ARMD) was used [16,17,90]. Because ARMD was developed for empirical force fields, extensive sampling of phase space is possible and several thousand trajectories can be run and analysed [91]. ARMD involves two or multiple PESs defined by individual sets of force-field parameters corresponding to reactant and product states. For macromolecular systems the number of energy terms by which the PESs differ is much smaller compared to the total number of energy terms. Thus, by providing only a controllable number of additional parameters compared to a standard MD simulation, it is possible to describe the difference between the states of the system which limits computational overhead [17]. The dynamics of the system is initiated and propagated in its initial state and the energy difference $\Delta E$ between all states is monitored at each time step. When $\Delta E$ changes sign, a crossing is detected. The trajectory is restored in the configuration at time $T_{\text{mix}}/2$ earlier and restarted on an appropriately mixed surface for a time $T_{\text{mix}}$ such that at the end of the mixing time the system smoothly approaches the target state [17]. The choice of mixing time, which is often a few tens of fs, needs to be assessed, but so far has had only a small effect on the resulting trajectories [16,17]. During crossing, the energies and forces from the newly created or broken bonded terms are added or subtracted and the corresponding nonbonded interactions are updated.

Different schemes to prepare nonequilibrium initial conditions exist [92]. For example, both positions and velocities can be scaled, which leads to modifications in the kinetic and

Figure 2. (Colour online) Photodissociation of H$_2$SO$_4$: after IR-excitation of one OH stretching vibration $v_9$ the two limiting cases (a) impulsive H-transfer and (b) partial or complete IVR followed by dissociation are illustrated. One of the important degrees of freedom in IVR are torsions which are discussed in more detail in Figure 4.
potential energy to prepare a nonequilibrium state. One possible drawback of such a procedure is the fact that after excitation a short equilibration period (a few ps) is required to avoid artefacts due to close proximity of atoms [92]. Alternatively, the instantaneous velocity vector along the normal mode direction corresponding to the mode of interest can be scaled [50]. For excitation of the asymmetric OH-stretching mode ($v_9$), the velocity vectors along the O–H bond were scaled to energies equivalent to $v_9 = 4, 5$ and 6 quanta, respectively [91]. The OH-stretch is to a good approximation a local mode.

From the large number of reactive events (several thousand) the distributions of dissociation times $p(\tau)$ for the excitation of $v_9 = 4–6$ is determined (Figure 3). The distributions $p(\tau)$ can be conveniently characterised by Gamma-distributions where the mean values for different degrees of excitation are $\tau_d = 201$ ps (for $v_9 = 5$) and $\tau_d = 40$ ps (for $v_9 = 6$) [91]. Both, $p(\tau)$ and time series for the internal coordinates support the notion of a gradual transition from fully impulsive (very short reaction times) to almost complete internal vibrational redistribution (IVR) for the decomposition reaction. For the impulsive process one of the hydroxyl H is transferred to the other OH, resulting in SO$_3$ and H$_2$O formation. This was observed by Miller and Gerber, where the process was called H-hopping [88]. Trajectories that follow this process are located at the beginning of the gamma distribution, few picoseconds after photoexcitation (Figure 3). For IVR it is necessary that the initially deposited vibrational energy rapidly redistributes over the remaining degrees of freedom before a sufficiently large amount returns into the dissociative coordinates (Figure 3) [89,91].

![Figure 3](image_url)

Figure 3. (Colour online) Normalised distribution of dissociation events $p(\tau)$ as a function of time $\tau$ for 5000 different trajectories with excitations of $v_9 = 4$, $v_9 = 5$ and $v_9 = 6$, respectively. The blue distribution (red curve) correspond to $v_9 = 4$, green (magenta) to $v_9 = 5$ and brown (black) to $v_9 = 6$. Red, magenta and black curves were determined by fitting to gamma distributions. Average dissociation times are 753, 201 and 40 ps for $v_9 = 4$, $v_9 = 5$ and $v_9 = 6$, respectively.
Figure 4 reports probability distribution functions $p(\phi)$ for the O6–S1–O4–H5 torsional angle $\phi$ from reactive trajectories at $v_0 = 6$ with different reaction times (6 (A), 244 (B) and 588 (C) ps). For each reactive trajectory (Figure 4 (red)) only one equilibrium trajectory (Figure 4 (black)) was used to compare the values for the torsional angle $\phi$. For each case the amount of data to build the distribution from equilibrium and nonequilibrium simulations was the same (e.g. if the reaction time was 6 ps as in Figure 4(A) only 6 ps from the equilibrium trajectory were used). Probability distributions for the equilibrium state (before excitation) are in black whereas those corresponding to the activated state are in red. The two equilibrium positions are at $\phi = \pm 40^\circ$. An impulsive reaction is analysed in Figure 4(A). For this case the equilibrium and nonequilibrium distribution closely match each other and the ratio $p_{\text{activated}}/p_{\text{equil}}$ is basically featureless – also because of the short simulation time (the reaction occurs after 6 ps). In particular, the transition state $\phi = 0$ is sampled equally by both trajectories. However, for longer reaction times (Figure 4B and C) the transition state is much more readily sampled from the nonequilibrium trajectories. This indicates that this particular coordinate is considerably activated through direct or indirect coupling to the vibrationally excited O–H stretching vibration. Also, a larger angular range is explored as is suggested from $p_{\text{activated}}/p_{\text{equil}}$ beyond $\pm 40^\circ$.

Approximate IVR rates can also be extracted from ARMD simulations. They are ($\tau_d = 7 \times 10^{10}, 2 \times 10^{10}$ and $4 \times 10^{11}$) which is about two orders of magnitude more rapid than those from the RRKM theory (see above). However, in view of complete IVR the simulations carried out so far have probably not reached the statistical limit and further work is required. One can expect that complete IVR takes about an order of magnitude

---

Figure 4. (Colour online) Probability distribution for one O–S–O–H torsional angle $\phi$ (see Figure 2) for equilibrated (black) and vibrationally activated (red) H$_2$SO$_4$. The angle $\phi$ describes the transition between the $C_2$ and the $C_s$ structure. Panels A, B and C report $\phi$-distributions for trajectories exhibiting different reaction times (6, 244 and 588 ps, respectively). The green curve is the ratio $p_{\text{act}}(\phi)/p_{\text{eq}}(\phi)$. For long reaction times the transition state region separating the two metastable states ($C_2$ and $C_s$) is more readily sampled.
longer which brings the RRKM and explicitly simulated decomposition times within about 1 order of magnitude.

Overall, atomistic simulations support the suggestion that vibrational excitation of \( v_B > 4 \) allows the photodissociation of \( \text{H}_2\text{SO}_4 \) into \( \text{SO}_3 + \text{H}_2\text{O} \) in the gas phase [88,91]. The reaction times for \( v_B = 4 \) to \( v_B = 6 \) are on the picosecond time scale. Two limiting mechanisms were found to be operative: impulsive H-transfer and almost complete IVR with subsequent dissociation. All intermediate scenarios are also found as is evident from the smooth reaction probability functions. It is expected that trajectory calculations along these lines can considerably improve our understanding of energy redistribution on longer time scales.

2.2.2. Final state distribution following photodissociation

Photodissociation reactions, i.e. dissociation reactions induced through the absorption of photons, have played an important role in elucidating intermolecular interactions, ground- and excited state dynamics and energy flow in small molecules [93,94]. In the gas phase such reactions are typically considered to occur in a two-step fashion. Starting from the electronic ground-state \( X \) of molecule \( \text{ABC} \), the absorption of a photon leads to an activated complex \( \text{ABC}^* \) which decays upon energy transfer between electronic and ro-vibrational degrees of freedom to \( A + \text{BC} \). In its final state, \( \text{BC} \) will again assume a wide range of internal states whose population depends on the available energy and the details of the intermolecular dynamics and energy redistribution mechanisms.

A particularly well-studied example concerns the photodissociation of \( \text{ClCN} \) [94–99]. Classical and quantum simulations were carried out and had been found to be in very good agreement [99]. Compared to the experiment, the computed rotational state distribution \( P(j) \), where \( j \) is the angular momentum of the photodissociated \( \text{CN} \) molecule, were found to be in qualitative agreement [96,97]. However, contrary to the experiments, simulations did not find a characteristic wavelength-dependence of both, the width of \( P(j) \) and the location \( j_{\text{max}} \).

Extending ARMD to electronic transitions allowed to more realistically model this process [100]. Using the original PESs [96,101], several thousand trajectories were statistically analysed and found good agreement between computed and experimentally observed \( P(j) \) was found. Based on this agreement, further adjustments of the interaction potentials could now be attempted. Because photodissociation is an intrinsically rapid process and ARMD simulations can be carried out at MD-speed, the process could also be investigated in a water-droplet. It was found that \( P(j) \) is strongly quenched due to the presence of the solvent. Furthermore, the wavelengths at which photodissociation was possible differed between the reaction gas- and solution-phase. Also, the proportion of reactive trajectories differed between the two environments. Corresponding work has also been carried out for \( \text{ICN} \) in solution and at surfaces using MD-based approaches. These simulations focused on the dissociation dynamics at fixed wavelength and included nonadiabatic effects in the excited states [102–104]. These examples illustrate that MD-based techniques with refined interaction potentials hold much promise to investigate the adiabatic and non-adiabatic dynamics in realistic gas- and solution-phase processes.
3. Condensed phase reactions

Compared to gas-phase processes, reactions in the condensed phase have an environment (solvent, surrounding protein) as an active participant. Amongst others, the environment can electrostatically shield or assist reaction partners or modify the dynamics through its viscosity and intermolecular interactions. As most biological and the majority of chemically interesting processes occur in the presence of an actual environment, taking its role into account is of great interest. Methods based on electronic structure calculations are difficult to extend to the relevant spatial scales. It is for these types of processes that methods such as EVB [14] or ARMD[17] have been developed.

3.1. PT in proteins

Recent advances in molecular biology and structural biology have highlighted the importance of PT in biological systems [105]. It serves as a rapid means to transport charge in systems including bacteriorhodopsin [106,107] and cytochrome c oxidase [108,109] PT also participates in numerous enzymatic catalysis – often as an elementary step [110] including liver alcohol dehydrogenase (LADH) [111–114] and dihydrofolate reductase [115–117]. LADH catalyses the oxidation of alcohols to aldehydes with the reduction of the coenzyme nicotinamide adenine dinucleotide (NAD$^+$ to NADH). A key step has been suggested to be the transport of one proton from the alcohol to solvent through a hydrogen-bonded network that consists of the hydroxyl group of Ser$^{48}$, NAD$^+$ and His$^{51}$ (Figure 5). This three-step PT has been studied with QM/MM simulations where the QM and MM regions are treated with SCC-DFTB [118,119] and the CHARMM22 force field [61], respectively [112]. Classical MD simulations with the MMPT force fields are currently being carried out to investigate such PT processes. For this, the enzyme is solvated in a pre-equilibrated 90.0 Å × 68.3 Å × 65.2 Å water box and periodic boundary conditions were applied. As a preliminary result, the one-dimensional potential of mean force (PMF) for the first PT step was computed using umbrella sampling [120,121], shown in Figure 5. A free energy barrier of 16 kcal/mol is found, and the structures and energies of reactant and product for this PT step compare favourably with the results by Cui et al. [112]. Extensive atomistic simulations concerning the remaining two PT steps, as well as the refinement of MMPT parameters and development of algorithms allowing continuous PT, are currently in progress.

The first atomically resolved PT reaction in a biological system was suggested to be found in ferredoxin I of *Azotobacter vinelandii* [122]. However, preliminary MD simulations [122] only found rare and quite long-distance acceptor-hydrogen distances, which make direct transfer of the proton from the protein to the buried [3Fe–4S] cluster unlikely. In detail, the reaction suggested was Asp$^{15}$–COOH + [3Fe–4S]$^0$ → Asp$^{15}$–COO$^-$ + [3Fe–4S]$^+$H$. Subsequent MD simulations suggested that water molecules can have extended lifetimes (sub-ns) between the Asp15 residue and the buried [3Fe–4S]$^0$ cluster [123,124]. Consequently, the alternative water-assisted process Asp$^{15}$–COOH + H$_2$O + [3Fe–4S]$^0$ → Asp$^{15}$–COO$^-$ + H$_2$O + [3Fe–4S]$^0$H$^+$ was studied [58]. MMPT simulations and electronic structure calculations yield a barrier of 11.7 kcal/mol for the forward reaction which is in good agreement with the experimental value (13.3 kcal/mol) [125]. These simulations also suggest that no stable intermediate hydronium ion (H$_3$O$^+$) is expected. Contrary to that, the originally proposed, water-
unassisted process is found to have a barrier of $\Delta E \approx 35 \text{ kcal/mol}$ [58] and therefore can be ruled out.

### 3.2. Ligand binding in proteins

One of the paradigm reactive processes in proteins is ligand binding and unbinding in globins – especially hemo (Hb) – and myoglobin (Mb). Small ligands including CO, NO or O$_2$ can diffuse into the protein and form more or less strongly bound ligand–Fe bonds with the heme-iron. Using flash photolysis, the kinetics of ligand rebinding to the heme-group in Mb was studied in detail across a wide range of temperatures [126–135], viscosities and in different regions of the electromagnetic spectrum. For CO, geminate rebinding occurs on the sub-microsecond time scale whereas for NO and O$_2$ this process involves only small barriers and happens on the picosecond time-scale. Experimental studies of the rebinding of CO after photodissociation at different temperatures have shown that the superficially simple rebinding reaction is surprisingly complex [126–135]. The room temperature rebinding of CO is approximately exponential (with a time constant of 100 ns), while at low temperatures the rebinding is non-exponential in time and varies in a non-Arrhenius fashion with temperature [126,129,130,132,136]. This behaviour has been attributed to a distribution of barrier heights for ligand rebinding in the effectively frozen protein [126,130,137,138]. This assumes that the relaxation of the protein at low temperatures is slow relative to the rebinding reaction so that the system is inhomogeneous with each protein molecule having a different barrier for rebinding.
Nitric oxide, on the other hand, rebinds extremely rapidly and non-exponentially at all temperatures [133]. Assuming a power law dependence for the rebinding time yields a time constant of around 33 ps while a fit to a double exponential gave time scales of 28 and 280 ps [133]. A recent time-resolved infrared spectroscopy study [139] has reproduced this non-exponential behaviour but finds that the rebinding is even quicker, with time constants of 5.3 and 133 ps. Femtosecond mid-infrared experiments [140] have found that rebinding occurs mainly from a metastable state $B_1$ with time-dependent rates, in agreement with earlier simulations [15]. In addition to $B_1$, two other populations ($B_0$ and $B_2$) were identified.

Given these widely different time scales, different computational approaches need to be considered. For CO, which will not be discussed any further, various approximations ranging from dimensional reduction [137,138] to application of MD-quenching techniques [141] based on Marcus theory and separating the actual dynamics from the energetics have been pursued in the past [142,143]. Contrary to that, the picosecond time-scale reaction of NO with heme-iron is ideally suited to be investigated with all-atom, fully dimensional MD simulations. It is for this type of processes for which ARMD was originally developed. The primary incentive is to follow chemical reactions along the time-coordinate without imposing a geometrical reaction coordinate.

Interactions of myoglobin and its mutants with NO have been studied experimentally and theoretically for almost four decades now [15,16,126,144–158]. Experiment [147,159] has shown that the rebinding of NO to Mb features non-exponential kinetics at all temperatures. Rebinding times vary from 5.3 to 34 ps and from 133 to 280 ps for the fast and slow components, respectively [139,147,160,161], with the most recent study pointing to shorter recombination times. However, the experiment itself is not able to provide an atomistically resolved mechanistic picture of the processes involved.

Several models were put forward to explain the observed non-exponential rebinding times. First, they have been attributed to distributed barriers [162] related to internal relaxation of the heme unit, second, a related multiple binding site model [163] within Mb from which a fraction of the photodissociated ligands can rebind has been proposed, and finally the relaxation model which features a time-dependent barrier that modulates ligand rebinding [133]. ARMD simulations were carried out whereby two states of the system were included: the hexacoordinate, bound MbNO conformation and the pentacoordinate, unbound Mb–NO state. The analysis of several thousand all-atom simulations in explicit solvent demonstrated that rebinding of NO indeed is nonexponential and occurs on the picosecond time scale [16]. Apart from the independently validated force fields for the two states, the only free parameter in such simulations is the asymptotic energy separation $\Delta$ between the two energy manifolds [16,164]. The free parameter is usually estimated from electronic structure calculations and a conformational-independent value is assumed which, however, is an approximation. In these simulations [16], rebinding times of 3.8 and 18.0 ps compared with 28 and 280 ps [133], 5.3 and 133 ps [139] from the experiment were found. Given the substantial differences between the reported experimental data [133,139,165], the computed results can be considered to qualitatively agree with the experimental data. More importantly, the simulations allow to analyse individual families of trajectories. It is found that the early processes after photodissociation are governed by
heme relaxation, resulting from the displacement $d$ of the iron out of the heme plane. This is reflected in the iron-out-of-plane probability distribution $p(d)$ for specific rebinding times. For rapid rebinding, $p(d)$ has a broad maximum between 0.2 and 0.3 Å whereas for slower rebinding the maximum in $p(d)$ shifts to 0.33 Å which agrees quite well with results from X-ray crystallography [166]. Furthermore, on the nanosecond time scale NO molecules are found in both the distal heme pocket and the Xe4 pocket which suggests that rebinding can occur from different sites within the protein, and thus supports the multiple site model for longer time scales.

Recent time-resolved resonance Raman experiments suggested that the photodissociated ligand can rebind to the domed, Fe-out-of-plane conformation of the heme unit [156]. This experiment found that the heme-iron motion and NO rebinding kinetics are not synchronised. Upon NO-photolysis, the transition from an in-plane to a domed-Fe conformation occurs on the subpicosecond time scale whereas the opposite process (domed to in-plane) takes ≈30 ps. On the other hand, in the infrared the rapid rebinding component occurs within 5 ps which suggests that the returning ligand can rebind to a domed-iron conformation. This has already been suggested by Ionascu et al. [159]. To shed additional light on the structural dynamics underlying this process, an extended model for the heme-NO interaction is currently being developed. Apart from the previously considered relative orientation of the NO ligand to the heme-iron [150,152,153,158,167,168], the iron-out-of-plane (doming) coordinate will be explicitly considered. Experimentally, the existence of two nitrosyl linkage isomers (FeNO and FeON) was confirmed by infrared difference spectroscopy [150,167,168].

PESs for the in-plane $d = 0$ and one of the out-of-plane $d = 0.2$ Å positions of the iron atom are reported in Figure 7. The PESs are characterised by two minima including the known Fe–NO bent minimum (Fe–N–O angle $\phi \approx 146^\circ$), and a more shallow Fe–ON ($\phi = 23^\circ$) minimum ≈ 22 kcal/mol higher than the first minimum for the Fe-in-plane ($d = 0$) conformation. Unrestrained ab initio optimisations lead to structures with $\phi = 24^\circ$ (approximately 18 kcal/mol higher than the global Fe–NO minimum) which have $\phi = 141^\circ$. The barrier for the Fe–ON $\rightarrow$ Fe–NO transition is ≈ 3 kcal/mol. For $d = 0.2$ Å (Fe-out-of-plane) the primary minimum is less stable by 10 kcal/mol than for the $d = 0$ PES. The Fe–ON minimum determined on the $d = 0.2$ Å surface located ≈ 21.5 kcal/mol above the global Fe–NO minimum, is, however, shifted toward smaller values of $\theta$ ($\approx 120^\circ$), with a geometry resembling more the metastable Fe–ηNO described previously [153]. The barrier between these minima is less than 0.5 kcal/mol. Initially, the effect of the different interaction potentials on the ligand motion in its bound state was briefly considered. Starting from geometries close to the FeON geometry, 100 trajectories were run and their relaxation into the global FeNO minimum was followed. The investigated system contained a total number of 2532 protein atoms, nitric oxide [16,153], and 178 water molecules represented by a modified TIP3P potential [169]. Classical MD simulations were performed using CHARMM [170] with the CHARMM22 force field [171] supplemented with parameters described earlier [153]. Trajectories were propagated for 10 ps with a time step of 1 fs. All simulations were performed at 300 K. A few selected trajectories are projected onto the corresponding PES and reported in Figure 7. Trajectories on the $d = 0$ PES sample the FeON minimum for up to 4 ps before isomerisation to FeNO occurs. This contrasts with the $d = 0.2$ PES where the vanishing barrier leads to almost immediate isomerisation. It is also instructive to consider the crossing geometries for the
two PESs. Both surfaces feature very wide crossing seams, which are shown in Figure 8. Although crossing occurs in both cases at almost the same distance of NO from the iron atom (see Figure 8 top), for the domed heme $\theta$ angles are shifted significantly towards larger values as shown in the middle panel of Figure 8. These characteristics along with much narrower distributions of the transition times (see bottom of Figure 8) are consistent
with the picture obtained from the projection of trajectories shown in the right panel of Figure 7 showing minor sampling of FeON geometries followed by almost immediate transition to the FeNO minimum. Simulations in the full 3D PES and including the unbound state to follow the rebinding dynamics should provide further insight into the complex dynamics following NO photodissociation from Mb.

The NO rebinding dynamics has been investigated with a range of techniques. The information about time scales of NO recombination is available from the early room temperature-induced absorption measurements in the visible light regime by Petrich et al. [133]. They reported double exponential character of the NO rebinding, with rebinding times of 28 and 280 ps for the short and the long component, respectively. Later studies [139,151,156,159] also found two time scales with quite different rebinding time scales. For example, the picosecond absorption and the time-resolved resonance Raman measurements [151,156] report short ~10 and long ~100 ps rebinding times, while the corresponding values obtained from mid-IR [139] and transient absorption [159] report 5.3 and 13.8 ps for a short and 133 and 200 ps for the long component, respectively. Time-resolved resonance Raman measurements provided structural information about process that has not been reported yet by the X-ray diffraction measurements. For example, the picosecond absorption and the time-resolved resonance Raman measurements by Martin and co-workers [151,156] provide information about the in-plane movement of ferrous heme-iron following NO rebinding after fs-photodissociation. Femtosecond transient absorption [159] experiments investigate the influence of protein environment (temperature, viscosity) on the NO-rebinding barriers whereas mid-IR absorption spectroscopy [139] probes the influence of conformational substates of the protein on the rebinding dynamics by monitoring changes in the intensity of the NO intensity stretching mode.

Figure 7. (Colour online) Projection of selected trajectories (yellow) onto two-dimensional representations of the PESs determined for the conformation corresponding to the in-plane (left) and domed (right) heme. Energies are reported in kcal/mol, \( R \) and \( \theta \) in Å and degrees, respectively.
upon photolysis. Although all these different experimental techniques find two time scales for the rebinding kinetics, no uniform picture as to the atomistic interpretation underlying the process has been obtained so far. This underlines the need for reliable computational investigations of the underlying processes.

Figure 8. (Colour online) Probability distribution function of the Fe–CoBNO ($R_{TS}$) distance (top), Fe–CoBNO–N ($\theta_{TS}$) angle (middle), and time ($t_{TS}$) (bottom) determined for the crossing geometries. Values for in-plane $d=0$ and out-of-plane $d=-0.2$ Å positions of the iron atom are shown in black and red, respectively.

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3.2.1. Denitrification in truncated hemoglobin

Truncated hemoglobin N (trHbN) (Figure 9) – a member of the truncated hemoglobin (trHb) family – is involved in efficient NO scavenging [172,173] whereby toxic NO is converted to harmless nitrate (NO$_3^-$). Due to its physiological significance the entire family has received much recent interest, both experimentally and computationally [174–186]. The conversion of O$_2$ and NO to NO$_3^-$ has been studied with a range of experimental techniques in globins from different organisms. On the basis of stopped flow kinetic measurements, it was proposed [187] that the reaction pathway for NO oxidation in Mb involves the peroxynitrite (Fe(III)–OONO) intermediate which undergoes O–O homolysis to form free nitrite radicals (NO$_2^-$). In this model NO$_2^-$ then binds to the oxo-ferryl (Fe(IV)=O) group to form the nitrato complex (Fe(III)–ONO$_2^-$), which ultimately leads to free nitrate. Alternatively, rapid-scan ultraviolet-visible (UV-vis) spectroscopy [187–191] and electron paramagnetic resonance (EPR) spectroscopy [192]. provided evidence for a Fe(III)–OONO (high-spin) intermediate in both oxy-Mb and oxy-Hb under alkaline conditions (pH=9.5). At neutral pH, the reaction proceeds without any observed intermediates [188], suggesting a rapid rearrangement of the Fe(III)–OONO intermediate to nitrate. These different processes are summarised in the following reaction equations:

$$\begin{align*}
\text{Fe(II)}-\text{O}_2 + \text{NO} &\rightarrow \text{Fe(III)}-[-\text{OONO}] \quad (I) \\
\text{Fe(III)}-[-\text{OONO}] &\rightarrow \text{Fe(IV)}=\text{O} + \text{NO}_2 \quad (II) \\
\text{Fe(IV)}=\text{O} + \text{NO}_2 &\rightarrow \text{Fe(III)}-[-\text{ONO}_2] \quad (III) \\
\text{Fe(III)}-[-\text{ONO}_2] &\rightarrow \text{Fe}^+\text{(III)} + [\text{NO}_3^-] \quad (IV)
\end{align*}$$

Figure 9. X-ray structure of truncated hemoglobin (PDB code 1s56 [179]). The backbone is represented in blue and the helices are labeled. The heme and Phe62 residues are shown in red and black sticks, respectively. The five xenon pockets found experimentally in the X-ray data are represented by yellow spheres to indicate the main docking sites. The solvent accessible surface is represented as a transparent black volume around the protein.
Stopped-flow spectroscopy yielded a second-order rate constant of $7.5 \times 10^8 \text{M}^{-1}\text{s}^{-1}$ [193]. Compared with the values obtained for vertebrate Mbs and Hbs, the reaction is 10–20 times faster in trHbN. Such rates make the NO dioxygenation reaction (Fe(II)–NO + O$_2$ → Fe$^{3+}$ (III) + [NO$_3^-$]) ideal to be studied by atomistic simulations. Irrespective of the reaction mechanism (see below), it is commonly agreed that in trHbN the diffusion-controlled migration of the ligands (NO and O$_2$) to the heme active site is the slowest process in NO detoxification and, hence, it is the rate determining step [194,195].

Experimentally, no intermediates have been found so far. This and the fact that the studies in Mb and Hb provide conflicting and inconclusive views [187,188,196,197] suggested that computational studies should be of value to clarify mechanistic aspects of the reaction. To allow bond breaking and ARMD formation, simulations were employed in order to account for fluctuations in the nuclear motion [15–17]. The necessary force fields for the different states in reactions I–IV (see above) were derived from electronic structure calculations for a model system containing the porphyrin ring, Fe atom and an imidazole ring representing the proximal histidine and the O$_2$ and NO ligands [198]. ARMD simulations allow to follow specific pathways. Earlier suggestions involved pathway A including all four steps I–IV described above [187,190,199,200], whereas pathway B involves a rearrangement reaction from Fe(III)[–ONO] to the Fe(III)[–ONO$_2$] complex [188,201]. ARMD simulations for steps I, III, and IV, along pathway A yield rate constants on the picosecond time scale [198]. However, step II was not found to be reactive. As the simulations were carried out for several nanoseconds, step II must be considerably slower than this time scale. The free-energy profile along the O1–O2 distance was calculated from umbrella sampling simulations at 300 K. It exhibits NO$_2$ dissociation barriers of 12–15 kcal/mol which precludes second-order rate constants of $7.5 \times 10^8 \text{M}^{-1}\text{s}^{-1}$ based on transition state theory.

On the other hand, ARMD simulations for the rearrangement reaction (pathway B) yield rate constants in the picosecond range [198], which readily explains the rapid overall NO dioxygenation that is associated with a second-order rate constant of $7.5 \times 10^8 \text{M}^{-1}\text{s}^{-1}$ in trHbN [193]. Moreover, Herold et al. were unable to observe any dissociated NO$_2$ which should emerge along pathway A. All these observations suggest that pathway B may be preferred [188,191]. Such a model has also been supported recently through experiments on a hexacoordinate oxy-globin model Fe(Por)(O$_2$)(NH$_3$) which was reacted with NO at $\approx$80 K [202]. FTIR and visible spectra were recorded upon warming the sample. Spectroscopic signatures characteristic of the –O$_2$ complex disappeared whereas new bands corresponding to an $\eta^1$-coordinated nitrate (–ONO$_2$) compound emerged. The barrier for the overall process was estimated to be $\approx$7 kcal/mol which favourably compares with the computations (upper limit of 8.6 kcal/mol) [198].

### 3.2.2. Fe–NO substitution reaction

One last point that deserves discussion is the fact that the NO-bound protein is more stable than the O$_2$-bound one. In group II truncated hemoglobin (trHbO) of *Mycobacterium Tuberculosis*, the rate constant for NO binding to ligand-free trHbO (0.18 μM$^{-1}\text{s}^{-1}$ (80%) and 0.95 μM$^{-1}\text{s}^{-1}$ (20%)) is slightly larger than the corresponding rate constant for O$_2$ binding (0.11 μM$^{-1}\text{s}^{-1}$ (80%) and 0.85 μM$^{-1}\text{s}^{-1}$ (20%)) [181,203]. Given this and the typically higher affinity of Fe(II) towards NO than to O$_2$, it is likely that the
reaction sequence discussed above (see Equation (4)) is preceded by a ligand exchange step (Figure 10):

\[ \text{Fe(II)} - \text{NO} + \text{O}_2 \rightarrow \text{Fe(II)} - \text{O}_2 + \text{NO} \]  

In other words, starting from the ligand-free protein, the likely sequence of elementary steps includes NO and O\(_2\) diffusion in the protein, NO-binding, replacement of NO by O\(_2\) and finally denitrification as described above. Nitric oxide migration has been analysed for O\(_2\)-bound trHbN and a network of ligand migration pathways has been found [90]. From several thousand transitions between the metastable binding sites [90,179], a ligand migration network was built and analysed with a transition network analysis which captures the essential ligand dynamics [204]. NO migration to the reactive site is about 10 times slower than the reaction time found in ARMD which supports the notion that ligand migration is the rate limiting step. More recently, we also started to investigate the network for O\(_2\)-migration in NO-bound trHbN [205]. By comparing O\(_2\) and NO as free ligands, it is found that both ligands, have their own favourable docking sites.

The ligand-exchange reaction – either SN1 (bond breaking and formation are two independent steps) or SN2 (bonds are created and broken in a concerted step) – can also be studied by means of ARMD simulations. New features in ARMD now allow to consider multiple PESs corresponding to different chemical connectivity [91]. Thus, the Fe + NO + O\(_2\) (S1), Fe–NO + O\(_2\) (S2) and Fe–O\(_2\) + NO (S3) states can be involved simultaneously. From propagation on S2, the system can proceed through two different mechanisms without choosing a priori any path (S1 for SN1 or S3 for SN2), as illustrated in Figure 11. Initial ARMD simulations suggest that the substitution reaction is an SN1 mechanism as the unbinding of NO always takes place before O\(_2\) eventual binding.
after a few tens of picoseconds of dynamics on the unbound PES (S1). These results are also supported by quantum calculations where no concerted substitution has been observed.

4. Advantages and disadvantages of various methods

In the following, advantages and disadvantages of the different approaches are briefly summarised. If entropic effects are expected to be important, use of rigorous QM/(MM) methods is precluded due to their computational demands to sample a representative number of conformations. This will be the case for most, if not all condensed-phase reactions but is not necessarily true for gas-phase – in particular PT – reactions. If one chooses to use electronic structure-based schemes, (reparameterised) semiempirical methods including AM1, PM3 or SCC-DFTB are attractive alternatives. Parameterised PESs, such as MMPT, are not only computationally efficient but also require adjusted PESs to include environmental effects. In any case, reparameterization of these methods is mandatory either to improve their performance for a given problem and/or to include environmental effects.

Fully dimensional, fitted PESs based on accurate ab initio calculations are only a viable approach for small systems for several reasons. First, the computation of the energies to be fitted has to be carried out on a grid. Assuming 10 points per internal degree of freedom (dof), 10^n points are needed for n internal dofs. In other words, for a nonlinear molecule with 6 atoms, 10^{12} single point calculations are in principle needed although the actual number of evaluations may be reduced, e.g. due to symmetry. Fitting such a PES to a global, parameterised form is the next obstacle which is not easily overcome. Finally, the utility of this parameterised PES is limited to gas phase investigations as its shape depends on the chemical environment. One possibility would then be to morph the entire PES given either reference experimental (solution) data or additional computations with an environment present.
In general, semi-empirical methods are faster than the Hartree–Fock or post-Hartree–Fock methods. The fact that such methods are parameterised can be seen as a strength or a weakness, but it is clear that this provides a large degree of flexibility. However, the reparameterisation step can be tedious and is usually no-unique. On the other hand, such methods allow to treat proteins (up to 15,000 atoms), for example, with the MOZYME algorithm, which uses localised molecular orbitals (LMO) [206]. As another example, phosphoryl transfer reactions have been studied with ab initio (MP2), DFT and several semi-empirical methods (AM1, PM3, MNDO, MNDO/d and SCC-DFTB). All methods give large errors in the proton affinity and although the phosphoryl transfer mechanism is still controversial, the re-parameterisation of SCC-DFTB for phosphor-containing systems gives improved structures and energetics compared to previous studies [207]. The disadvantage of semi-empirical methods is that the parameterisation is seldom transferable and only properties of molecules similar to those used in the parameterisation can be expected to be reproduced reliably.

Force field-based approaches now provide several ways to treat efficiently bond breaking and bond formation reactions in the framework of classical MD simulations. Their main advantage is that they allow long time scale simulations on large systems including a realistic chemical environment (solvent) or multiple (thousands) simulations for fast reactions from which a detailed picture of the inter- and intramolecular dynamics can be obtained. Moreover, the full system (reactive/non-reactive) is treated at a consistent level of accuracy. As an example, EVB treats the dynamics on a well-defined potential surface and is relatively easy to implement. Nevertheless, the parameterisation can again be tedious. This is largely because the off-diagonal terms in EVB, i.e. the coupling between the states, needs to be determined ‘empirically’ [208,209]. Usually a functional expression for the coupling term needs to be assumed a priori and the corresponding parameters are determined by fitting to ab initio calculations. These parameters are, however, usually non-transferable and also implicitly define a reaction coordinate through the functional dependence of the off-diagonal element.

This is one of the advantages of ARMD where possible reaction coordinates are not determined a priori but rather can be extracted a posteriori from the reactive trajectories themselves. This advantage, due to the absence of geometrical descriptors, is also a limitation of the technique as it makes fitting the force field for the reactive states more difficult. In particular, careful optimisation of the van der Waals ranges is necessary because they loose their meaning in the reactive region [91].

In conclusion, QM or QM/MM methods are most accurate but suffer from the computational burden they present for large-scale and long-time simulations. Often, only one or a few trajectories can be run [88], which leaves the question open of how representative the results are. On the other hand, semi-empirical and entirely force-field-based methods can be applied to a broad range of reactive processes even including a realistic environment, but they all require a level of refinement for the intermolecular interactions. This step is non-trivial and future efforts should seriously address this point. Once suitable computational tools are available for this step, such methods will find more widespread applications and acceptance in chemistry, physics and biology. Furthermore, the accuracy of force fields is still limited and may not be uniform throughout configuration space but steady progress is made in improving their performance [210,211].
5. Conclusion and outlook

The current review summarises developments to follow reactive processes at the atomic scale using parameterised methods. The distinguishing feature of ARMD over alternative methods (such as EVB or ReaxFF) is the fact that instead of geometrical reaction coordinates, time as the ‘natural’ coordinate is used as the progression variable. The majority of applications so far uses classical MD simulations. However, if the process in question requires nuclear dynamics to be followed at a quantum level, this is also possible. Future extensions of ARMD include multi-surface dynamics, which is currently being developed [91], and non-classical transitions which can be effectively included by surface hopping whereby a transition between two PESs is modelled as a stochastic process [25,26].

Multi-surface dynamics in multi-dimensional systems at the classical dynamics level has recently been used for characterising the vibrationally induced photodissociation in H2SO4. Because the parameterisation allowed two product states to be populated (SO3 + H2O and SO3 + OH + H), the dynamics involves three states. Including the correct asymptotic energetics of each of the product channels allowed to realistically populate the possible final states [91]. Provided that suitable force fields are available for each of the states involved, extensions to more PESs is straightforward.

A particularly interesting application of reactive MD simulations of any flavour are processes in solution. Recent examples include photodissociation dynamics of ICN [103,104] and ClCN [100] in explicit solvent. For solvated ICN, a combined experimental and computational study provided detailed insight into laser-induced reaction dynamics in the condensed phase [104]. We anticipate that approaches as those discussed here will be of considerable importance to understand condensed phase reactions on multiple time and spatial scales at an atomistic level and provide insights that are complementary and sometimes inaccessible to direct experimentation.

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