Atomistic Simulations for Reactions and Spectroscopy in the Era of Machine Learning

- Quo Vadis?

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Abstract

Atomistic simulations using accurate energy functions can provide molecular-level insight into functional motions of molecules in the gas- and in the condensed phase. Together with recently developed and currently pursued efforts in integrating and combining this with machine learning techniques provides a unique opportunity to bring such dynamics simulations closer to reality. This perspective delineates the present status of the field from efforts of others in the field and some of your own work and discusses open questions and future prospects.

Introduction

“Atomistic Simulations” provide molecular-level information into chemical and biological phenomena. This is largely due to the possibility to explicitly follow the dynamics of molecular systems with the full information about observables contained in the time series of
positions and velocities. The “translation” between the output from a molecular dynamics (MD) simulation (positions and velocities as a function of time) is accomplished by virtue of statistical mechanics, in particular the correlation function formalism introduced in the 1960s by Zwanzig\textsuperscript{1} and Gordon.\textsuperscript{2}

The nuclear dynamics - whether described at a classical or at a quantum level - is primarily governed by the underlying energy function \(V(\vec{x})\) where \(\vec{x}\) encompasses all \(3N\) coordinates of an \(N\)-particle system. Most rigorous for such studies will be to use an exact or near-exact solution of the electronic Schrödinger equation together with corresponding forces for each configuration \(\vec{x}\). Doing this “on the fly” is typically not possible except for systems with a small number of electrons, and not on extended time scales. Hence, such \textit{ab initio} MD (AIMD) methods often use approximations at the density functional theory (DFT) or semiempirical level of theory and typically within a mixed quantum mechanics/molecular mechanics (QM/MM) framework.\textsuperscript{3,4}

Since about 10 years the field of computational and theoretical chemistry has seen a profound change in how we think about inter- and intra-molecular interactions. One milestone has been the realization that with a sufficient number of samples the explicit solution of the electronic Schrödinger equation can be replaced by a data-driven approach based on machine learning (ML).\textsuperscript{5} This approach consistently applies principles rooted in statistical learning theory.\textsuperscript{6} A recent series of reviews delineates the present state of the art of ML-based methods for force fields,\textsuperscript{7} for small molecules,\textsuperscript{8} and for chemical reactions.\textsuperscript{9} It is of interest to mention that for intermolecular interactions such ML-based methods have been used for a considerably longer time,\textsuperscript{10,11} especially for triatomics,\textsuperscript{12} based on early work by Aronszajn on reproducing kernel Hilbert spaces (RKHS).\textsuperscript{13}

One of the particular benefits of atomistic simulations in the context of experiments is the
possibility to relate observables with particular structural features of a system. A topical example concerns infrared (IR) spectroscopy for gas- or condensed-phase systems. At ambient conditions even small peptides sample different conformations each of which exhibits potentially conformer-specific IR spectra. This applies to both, experiments in the gas phase and in solution. The question thus arises to what conformational substate a particular set of spectral lines belongs and whether a unique correspondence between structure and spectroscopy can be obtained. However, assigning the spectroscopic features to a particular conformational substate remains a challenge. One possibility to address this problem consists in carrying out extensive electronic structure calculations which, however, are time consuming and usually only applicable to gas-phase systems. Alternatively, MD simulations with improved force fields can be used to determine the underlying structural features by comparing computed and experimentally measured IR spectra.

Similarly, a beneficial interplay between experiment and computation has clarified the relationship between structure and spectroscopy for protonated water clusters. Often, such experiments are carried out in a supersonic jet combined with mass selection of particular cluster sizes which generates an ensemble of structures that is probed by light. As there is a distribution of cluster geometries that is frozen in the expansion, the spectroscopic signatures are those of a number of - typically - low-energy isomers and not of one single conformer. What spectral features belong to one particular conformation can be clarified by using hole-burning experiments and conformer-specific spectra are then determined from electronic structure calculations. Such an approach has proven very powerful, in particular for small protonated water clusters. Very recently, the infrared spectroscopy of $\text{H}^+(\text{H}_2\text{O})_{21}$ was assigned to particular structural features using Second-order Vibrational Quasi-Degenerate Perturbation Theory (VQDPT2). Based on the agreement between experiment and simulations particular features in the experimental spectra in the high-frequency (OH-stretch) region could be assigned to specific bonding patterns in the protonated water cluster.
Combining computational and experimental approaches is also valuable for chemical reactions in the gas and in the condensed phase. Typical question arising in this context are A) whether reactions proceed stepwise or concerted, e.g. for phosphate transfer\textsuperscript{25-27} Menshutkin-type,\textsuperscript{28-33} or Diels-Alder reactions,\textsuperscript{34-37} or B) for unimolecular reactions whether I) decomposition involves one or several competing routes, II) a potential barrier is involved, III) it simply progresses by stretching a chemical bond until it breaks, or IV) a combination of II) and III) is at play which was coined “roaming”.\textsuperscript{38} Also, competing pathways can occur and have been found from atomistic simulations.\textsuperscript{39-41}

In what follows an account of the status and future prospects of atomistic simulations with a particular focus on classical MD simulations in the context of experiments is given. Findings and relevant advances from recent studies in our group and others in the field are highlighted and open questions that require and spur future developments are formulated and discussed.

**Vibrational Spectroscopy**

Optical spectroscopy is a versatile and powerful method to interrogate and characterize the structural dynamics of systems in the gas\textsuperscript{42,43} and in the condensed phase.\textsuperscript{44-49} It has been proposed (for a cyano-substituted ligand bound to WT and mutant human aldose reductase)\textsuperscript{50} and explicitly demonstrated by simulations (for cyano-benzene bound to lysozyme)\textsuperscript{51} that IR spectroscopy can be used to infer ligand binding in particular protein pockets. The possibility to relate changes in the infrared spectroscopy with changes in intermolecular binding modes and/or interaction strengths is an exciting prospect for functional studies of biomolecules under realistic conditions, including solvent and ions.

One application of vibrational spectroscopy is positionally resolved infrared spectroscopy to
relate structural features and local/global dynamics with spectroscopic responses. For this, suitable spectroscopic probes are required. One such label is azidohomoalanine (AHA) for which experiments demonstrated that it can be used for site-specific information on the recognition site between the PDZ2 domain and its binding partner. AHA absorbs at around $\sim 2100 \text{ cm}^{-1}$ with a substantial extinction coefficient ($\sim 400 \text{ M}^{-1}\text{cm}^{-1}$). Attaching $-\text{N}_3$ to alanine (to give AlaN$_3$) or AHA and incorporation at almost any position of a protein has been demonstrated following known expression techniques. Furthermore, attachment of an $-\text{N}_3$ probe is a spatially small modification and the chemical perturbations induced are expected to be small. This makes AlaN$_3$ and AHA worthwhile modifications to probe local protein dynamics.

Exhaustive labeling of all 14 alanine residues in WT human Lysozyme provided dynamical information in a position-resolved manner. These simulations were carried out with a conventional protein force field but the energetics of the spectroscopic reporter ($\text{N}_3$) was a reproducing kernel Hilbert space based on high-level PNO-LCCSD(T)-F12 calculations together with the aug-cc-pVTZ basis set. This is akin to a mixed quantum mechanics/molecular mechanics (QM/MM) procedure with the advantage that a) evaluating the RKHS is computationally similarly efficient as computing energies and forces for an empirical force field which allows to carry out multi-nanosecond simulations for such a system and b) the quality of the RKHS is that of the underlying quantum chemical method.

Using the same force field for the azide probe attached to every alanine residue in Lysozyme leads to frequency maxima covering a range of $\sim 15 \text{ cm}^{-1}$. This compares favourably with an experimentally reported frequency span of $\sim 10 \text{ cm}^{-1}$ for replacements of Val, Ala, or Glu by AHA in the PDZ2 domain. The frequency fluctuation correlation functions (FFCFs) for the $\text{N}_3$ asymmetric stretch mode decay on two time scales. One is in the sub-picosecond regime and quite universal at $\tau_1 \sim 0.1 \text{ ps}$ whereas the longer decay time ranges from $\sim 1$
to \( \sim 10 \) ps depending on the position of the label. Experimentally, correlation times of 3 ps have been measured for AHA. Another relevant experimental observable is the inhomogeneous contribution which arises from dynamics that relaxes on time scales longer than \( \tau_2 \). Interestingly, the magnitude of the static component was found to correlate qualitatively with the degree of hydration of the spectroscopic probe.

Another application of simulation and experimental approaches for vibrational spectroscopy is the characterization of the conformational ensemble sampled by peptides and proteins. A widely studied model system in this context is trialanine \((\text{Ala}_3)\). The conformational ensemble from most of the investigations is dominated by the poly-proline II (ppII) structure, often followed by a \( \beta \)-sheet conformation and more rarely some right-handed \( \alpha \)-helical structure. In a notable combined experimental and simulation study the infrared spectroscopy in the amide-I region was used to refine the conformational ensemble. This was done by Bayesian ensemble refinement of the conformational ensemble such as to best reproduce the experimentally measure IR spectra. The refinement effectively reweights a reference distribution with associated basin-specific IR spectra to better describe the experimentally observed spectra. Interestingly, comparable changes in the conformational ensemble were found when going from a conventional point charge force field to a multipolar representation of the amide group although the ppII structure is probably overstabilized in these simulations.

Such studies lay the foundation for more functionally relevant studies of biomolecules such as the A\( \beta \) amyloids or insulin. 1d- and 2d-infrared spectroscopy have been used to probe structural features and the dynamics of different amyloids. One distinguishing feature of the 1-dimensional spectra is a narrow, intense absorption between 1615 and 1630 cm\(^{-1} \) which is shifted to the red of the typical \( \beta \)-sheet amide-I bands. Heavy atom labeling of individual \(-\text{CO}\) groups allows to assign the spectroscopic response to particular parts of the protein.
Using isotope labeling together with 2d-IR spectroscopy and computed spectra from MD simulations allowed to distinguish between a $\beta$–arch and a $\beta$–turn configuration of polyQ fiber segments.\textsuperscript{71}

Infrared spectroscopy is also potentially useful for following protein assembly and disassembly. Insulin, which is key for the glucose cycle, binds to the insulin receptor in its monomeric form. However, in the body the hormone is stored as zinc-bound hexamers each of which consists of three homodimers. For human WT insulin the stabilization of the dimer with respect to two separated monomers has been determined experimentally ($\Delta G = -7.2$ kcal/mol)\textsuperscript{72} and all-atom simulations in explicit solvent confirm these measurements ($\Delta G$ ranging from $-8.4$ to $-11.9$ kcal/mol from free energy simulations and $-12.4$ kcal/mol along the minimum energy path).\textsuperscript{73–75} However, for pharmaceutical applications modified insulins have been used and are being designed for which dimerization free energies are not available.

Experimental studies have provided insights about parts of the dissociation pathway between the dimer and the separated monomer. Two-dimensional IR studies in the amide-I region coupled with $T$–jump for the dimer indicate that monomers within the dimer rearrange on the 5 to 150 $\mu$s time scale.\textsuperscript{76,77} Between 250 and 1000 $\mu$s the $\beta$–sheet structure at the dimer interface is lost. Complementary to this, time-resolved X-ray scattering studies reported the population of two intermediate dimer states, $D_1$ and $D_2$, on the 310 ns and 900 ns time scale.\textsuperscript{78} Although these studies are valuable from a spectroscopic perspective, they only provide limited structural information.

Computational infrared spectroscopy based on MD simulations provides a means to link structural dynamics and spectroscopy. For insulin monomer and dimer, MD simulations using validated multipolar force fields have shown that amide-I spectroscopy at the dimerization interface - involving residues PheB24, PheB25, and TyrB26 - depends on the aggregation
Figure 1: Structural dynamics involving the PheB25 residue in monomeric and dimeric insulin. Left panel: The structure of the insulin dimer with residues PheB25 and PheD25 as highlighted by the blue spheres and the -CO group as van der Waals spheres. Upper right panel: the frequency fluctuation correlation function for PheB25 in the monomer (green), and for PheB25 and PheD25 in the dimer (red and blue). Lower right panel: the hydration of the -CO group for PheB25 in the monomer (green solid line), and for PheB25 and PheD25 in the dimer (red and blue solid lines) together with the total number of water molecules $N(r)$ as dashed lines with the same color code.
state. See Figure 1 for Phe25 as an example. In other words, the IR response of the -CO reporters for residues B24 to B26 from the isolated monomer in solution differs from that of the two monomers in the dimer. In addition, the position of the maxima in the IR absorption and the dynamics of the symmetry-equivalent residues [B24,D24], [B25,D25], and [B26,D26] is not identical. This suggests that the two monomers in the dimer are dynamically not identical on the time scale of the simulations. Figure 1 demonstrates that the FFCF for PheB25 in the monomer differs from that of PheB25 and PheD25 that also differ from one another in the dimer. These findings are also consistent with X-ray experiments which found the two monomers to be not exactly symmetric. In this context it is of interest to note that “...the ability of the insulin molecule to adopt different conformations may be an important factor in the expression of its biological activity.” Hence, the dynamical asymmetry found in the present work for WT and mutant insulin dimers may have functional implications. Overall, these findings also support the conclusions from recent MD simulations which report that early along the pathways between insulin dimer and two separate monomers the two monomers behave asymmetrically.

The spectroscopy and reaction dynamics of photodissociated CO and NO in Myoglobin (Mb) has been investigated intensely over the past ~50 years. For the present discussion, the infrared spectroscopy and rebinding dynamics (see next section) is of primary interest. Experimentally, the IR spectrum of the photodissociated CO ligand was found to exhibit a split spectrum with two peaks separated by ~10 cm$^{-1}$ which was associated with two conformational substates. Despite some early efforts, the assignment of these two states was unclear until simulations with sufficiently detailed electrostatic models for the free ligand were used. Together with subsequent mutation studies the more re-shifted peak was associated with the Fe–OC orientation whereas the less red-shifted peak corresponds to the Fe–CO state. Figure 2 shows the overall IR spectrum of the free CO ligand (red dashed line) together with spectra for the two suspected conformational substates (Fe–CO in green;
Figure 2: The infrared spectroscopy of photodissociated CO in myoglobin (Mb). Upper left panel: Structure of the protein with heme and CO as van der Waals spheres and the heme-Fe as a green sphere. Upper right panel the infrared spectrum from a 2 ns simulation using a multipolar representation for the CO molecule. The dashed line is for the full trajectory whereas the blue and green solid lines are for the parts of the trajectory during which the Fe–OC and Fe–CO are sampled predominantly. Lower left panel: the free energy profile for the rotation between Fe–CO ($\theta = 0$) and Fe–OC ($\theta = 180^\circ$) from the simulation with multipoles on the CO. Lower right panel: free energy profile along $\theta$ with a point charge model for CO. Black trace is the raw data and red trace a running average.
Fe–OC in blue). Firstly, the total spectrum agrees favourable with the experimentally reported spectrum. Secondly, the state-specific spectra suggest that although they provide an identification of the two states, while sampling one substate, e.g. Fe–CO, the spectroscopy is still sensitive to the presence of the second state, i.e. Fe–OC. The reason for this is the low isomerization barrier between the two states which is reported in the lower left panel in Figure 2. The Fe–CO state \((\theta = 0)\) is somewhat more stable than the Fe–OC orientation \((\theta = 180^\circ)\) and the two states are separated by a barrier of \(\sim 0.7\) kcal/mol, compared with the experimentally reported barrier of 0.5 kcal/mol.\(^8\)\(^9\) The lower right panel in Figure 2 shows the free energy profile along the CO rotation angle when using a point charge model and demonstrates the superiority of a more refined interaction model based on atomic multipoles.

### Reaction Dynamics

Following chemical reactions by way of computer simulations is a challenging undertaking. Although in principle \textit{ab initio} MD (AIMD) simulations provide an obvious route, computational feasibility and accuracy often preclude such an approach. Routine applications of full AIMD simulations for reactions are typically limited to tens or hundreds of trajectories covering 10s to 100s of picoseconds of simulation time at the semiempirical or density functional theory (DFT) level.\(^90\)\(^92\)

For tri- or tetra-atomic systems the investigation of reaction dynamics at the classical or quantum nuclear dynamics level has an extensive history, dating back at least to the earliest \(\text{H}+\text{H}_2\) hydrogen exchange simulations\(^93\) based on a reactive London-Eyring-Polanyi-Sato (LEPS) surface.\(^94\)\(^95\) One surprising finding was that such quasi-classical trajectory (QCT) simulations agree quite well with rigorous quantum simulations\(^97\) despite the fact that the \(\text{H}+\text{H}_2\) system is particularly susceptible to quantum effects including zero point motion and
tunneling.

With the advent of efficient, high-level electronic structure calculations the configurational space of small systems could be covered adequately by computing energies for many geometries. As a consequence, empirical PESs were largely superseded and the problem shifted to representing the computed points such that the total potential energy can be evaluated with comparable accuracy as the underlying quantum chemical calculations. Fitting full-dimensional PESs even for triatomic systems is still a formidable task and with increasing number of dimensions becomes progressively more difficult. One difficulty that is encountered and detrimental to the dynamics of the system is the presence of “holes” in the PES. Holes may even develop in non-parametric, machine-learned energy functions. On the other hand kernel-based representations with physically meaningful asymptotic decay for large separations are less prone for developing irregular features.

Recent studies of gas-phase reaction dynamics have used machine-learned PESs based on permutationally invariant polynomials (PIPs), PIPs using neural networks (NNs), Gaussian Processes, reproducing kernel Hilbert space (RKHS) representations, or deep NNs such as PhysNet or DeePMD. A topical application of a PIP-fitted PES to high-level electronic structure calculations (MRCI, CCSD(T), and CCSD(T)-F12) concerned the characterization of rotational resonances in the H$_2$CO roaming reaction. The particular interest in this study was to provide an explanation for the origin of the experimentally observed bimodal distribution of the CO fragments following the decay of the excited H$_2$CO reactant according to $[\text{H}_2\text{CO}]^\ast\rightarrow[\text{H}+\text{HCO}]^\ast\rightarrow[\text{H}_2]^\ast+[\text{CO}]^\ast$. In the second step roaming of the H-atom eventually leads to abstraction of the hydrogen from HCO to form the products. Although the QCT simulations did not quantitatively reproduce the experimentally measured rotational distributions $P(j)$, their bimodal structure was correctly captured. Analysis of the trajectories revealed that the low-$j$ portion of $P(j)$ passes through a cis-like OCH···H
geometry whereas the high-\textit{j} trajectories rather sample a trans-like OCH\cdots H geometry. This provides a detailed understanding for the relationship between the topography of the PES, the dynamics supported by it, and how this is reflected in the experimental observables.

Another area where ML-based PESs have been extensively used is in the field of high-energy reactions such as in combustion and in hypersonics. The DeePMD NN-based PES was used to understand the combustion of methane.\footnote{\textsuperscript{111}} From a 1 ns long simulation almost 800 reactions were recorded. In addition, the simulations discovered previously unknown reaction pathways and products. For example, cyclopropene was formed in a sequence of reactions involving CH\textsubscript{2}CO+CH\textsubscript{3} to form cycloprop-2-en-1-one which, after colliding with another CH\textsubscript{3}, formed CH\textsubscript{3}CCH\textsubscript{2} and finally stabilized as cyclopropene after further hydrogen loss. This also highlights that atomistic simulations based on machine learned PESs can be used to discover new reactions, provided that the statistical model covers chemical space sufficiently well and provides realistic reaction energetics.

The investigation of hypersonic re-entry is a challenging endeavour on multiple length and time scales. Hypersonic flight is characterized by shock waves with temperatures up to 20000 K. The chemistry is dominated by atom+diatom reactions with the reactant molecules often in highly excited ro-vibrational states. Because the flow contains species such as N, O, NO, N\textsubscript{2}, O\textsubscript{2}, CO, or CN, reaction networks are required to describe the chemical evolution of the flow. This is often based on thermal rates \(k(T)\) which can, however, not be determined experimentally for the entire temperature range required. Instead, rates can be determined from high-level PESs and corresponding QCT simulations.

This has been done for the [NOO],\footnote{\textsuperscript{112}} [NNO],\footnote{\textsuperscript{113}} [CNO],\footnote{\textsuperscript{114}} and [COO] systems based on full-dimensional, reactive RKHS PESs and QCT simulations. In all cases thermal reaction and vibrational relaxation rates are in good agreement with existing experiments for temper-
atures up to $T \sim 5000$ K which allows extrapolation to higher temperatures. As an example of the additional information atomistic simulations can provide the example of non-reactive and reactive vibrational relaxation of CO in collisions with atomic oxygen is considered. For the non-reactive case, non-relaxing trajectories $O+CO(v=1) \rightarrow O+CO(v'=1)$ collide predominantly in a T-shaped geometry and do not enter the strongly interacting region of the collision complex, see Figure 3A. This differs for vibrationally relaxing trajectories $O+CO(v=1) \rightarrow O+CO(v'=0)$ for which all collide in a nearly-linear geometry $O\cdots CO$ and enter the strongly interaction part of the PES in panel B. Similar to the bimodal product state distribution of CO following the decay of $\text{H}_2\text{CO}$, particular reaction channels can be associated with sampling of specific parts of the PES.

Finally, reactive PESs have also been used for applications in atmospheric chemistry. One early example is the investigation of vibrationally induced reactivity in sulfuric acid which has been proposed based on experiments and demonstrated in a series of atomistic simula-
tions using AIMD\textsuperscript{117} or reactive MD techniques,\textsuperscript{118,119} More recently, the Criegee intermediate and its decomposition to CH$_2$COH+OH has raised considerable interest due to both, its relevance in atmospheric processes, in particular in ozonolysis,\textsuperscript{121,122} and the availability of a wealth of experimental data.\textsuperscript{123,124} A first study was based on a PES fit to PIPs and used in quasiclassical trajectory (QCT) calculations. This PES was fit to $\sim 157000$ electronic energies (a mixture of CCSD(T) and CASPT2) and covered $syn$-CH$_3$CHOO, the transition state (TS) to vinyl hydroxyperoxide (VHP), several exit channel wells and the OH+vinoxy products. The QCT calculations were initiated at the TS separating the $syn$-CH$_3$CHOO and VHP wells instead of the syn minimum. This was done owing to the long lifetime of the energized $syn$-CH$_3$CHOO and the large computational effort needed to propagate the trajectories.

In a more recent exploration\textsuperscript{129} of the full reaction pathway between $syn$-CH$_3$CHOO and the CH$_2$COH+OH product a MS-ARMD-based PES surface was fit to several thousand reference energies and a PhysNet-PES was generated for $\sim 100000$ energies, both at the MP2 level of theory. Next, an aggregate of $\sim 10^5$ classical trajectory calculations from thermal ensembles at different temperatures of the $syn$-CH$_3$CHOO reactant state were carried out to follow the reactive dynamics after vibrational excitation of the CH stretch with two vibrational quanta. The energy dependence of the experimentally measured rates for OH-elimination were realistically described from such a computational approach.

Reactive dynamics simulations can also been carried out in solution. One example is the F + CD$_3$CN abstraction reaction to form DF+CD$_2$CN in CD$_3$CN which was treated with a multi-state empirical valence bond (EVB) approach.\textsuperscript{130} This work reproduced the experimentally observed solvatochromic shift of the DF product in CD$_3$CN and reported that the DF product contains a significant amount of vibrational energy ($v = 2 - 3$). EVB-based approaches have also been employed extensively in biomolecular simulations.\textsuperscript{132,133} From
a ML perspective, RKHS-represented PESs have been used akin to QM/MM simulations for ligand rebinding reactions of ligands to proteins, in particular CO and NO to heme-containing proteins.\textsuperscript{137,139}

Concluding Remarks and Prospects

So far the focus has been on carrying out atomistic simulations with input from machine learning at the level of the energy function, its parametrization and its representation.\textsuperscript{7,140} While this aspect will gain in relevance in the time to come, analysis of MD-generated trajectory is an equally important aspect. After all, the analysis of such trajectories provides the information to generate observables that can be compared with experiments. This comparison is the necessary step for validation of the computations with the laboratory experiments or from observations.

An early procedure for extracting progression coordinates from MD was based on a neural network and was applied to alanine dipeptide.\textsuperscript{141} This work employed a genetic neural network to extract a minimal set of internal degrees of freedom to describe the C$_{\text{eq}}$→\(\alpha\) transition for the solvated dipeptide. For this, the committor probability was used as the target function to be optimized. For the transition in the gas phase two descriptors (two dihedral angles) were sufficient whereas for the transition in solution three coordinates were required (one dihedral, one intramolecular separation and the torque around one C-N bond). More recently, a generalization of this framework based on artificial NNs was presented.\textsuperscript{142}

Machine learning was also used to determine essential internal coordinates from extended protein MD simulations.\textsuperscript{143} The decision tree-based method (XGBoost)\textsuperscript{144} was used to characterize metastable states of heat shock protein-35 and transitions between them and to the
open/closed transition in Lysozyme. Because the ML-based approach directly operates on a pool of candidate features (typically atom distances, valence angles, dihedral angles) the analysis provides an importance score for each of the features for a transition between two states. This differs from the more widely used principle component analysis (PCA) which only yields the linear combination of such variables. For Lysozyme analysis by XGBoost clarified that the distance $d_{4,60}$ between residues Phe4 and Lys60 is involved in the open-to-closed transition and that the more obvious separation between residues Thr21 and Thr142 is not a suitable progression coordinate. Importantly, PCA did not find the relevance of $d_{4,60}$ which suggests that ML-based methods can be profitably used to uncover mechanistic aspects of functional protein motions.

For chemical reactions ML-based methods were recently used to study determinants in the reaction well that do or do not lead to chemically productive (i.e. reactive) trajectories. This study confirmed that results from machine learning confirm earlier proposals concerning the importance of electrostatic preorganization, or enzyme-stabilized “near-attack” conformations as relevant for enzymatic activity. As MD simulations provide both, coordinate and velocity trajectories it is of interest to query whether one or the other is more suitable to predict relevant degrees of freedom. It was found that both types of information can distinguish reactive from almost-reactive trajectories and that their combination performs even slightly better. It is of interest to juxtapose the insight that while still sampling the reactant well it is possible to predict whether or not a particular trajectory is likely to react with explicit sampling of reactive vs. non-reactive initial conditions. Analysis of the minimum dynamical path for reactions in the gas phase showed that specific combinations of initial position and momenta in the reactant state lead to reactive trajectories whereas initial conditions outside this manifold do not react. Another application of ML methods to chemical reactions is the prediction of reaction rates.
This has been done directly for rates from a library of ~ 40 bimolecular reactions for which
$T-$dependent rates from transition state theory (TST), the Eckart correction to TST, and a
set of tabulated “accurate rates” from 2-dimensional calculations at 8 temperatures is avail-
able. This data was used to learn a correction to the product of the TST-rate and the
Eckart correction by using Gaussian process regression. The results for reactions not used in
the learning procedure indicate that it is possible to obtain thermal rates close to those from
explicit quantum simulations (using MCTDH) or trajectory-based quantum calculations
(ring polymer MD).

An alternative procedure was followed from determining state-to-state (STS) reaction prob-
abilities for bimolecular reactions and computing the thermal rates from the final state
distributions. From quasiclassical trajectory (QCT) simulations for the N($^4\text{S}$)+NO($^2\Pi$) → O($^3\text{P}$)+N$_2$($X^1\Sigma_g^+$) reaction the state-to-state cross sections $\sigma_{v,j\rightarrow v',j'}(E_t)$ as a function of
the translational energy $E_t$ were explicitly determined for 1232 initial states which amounted
to ~ $10^8$ QCT trajectories in total compared with an estimated $10^{15}$ QCT trajectories re-
quired for brute-force sampling of the problem. This information was used as input to train
a NN together with features such as the internal energy, the vibrational and rotation en-
ergy of the diatoms, or the turning points of the diatoms. From the NN-predicted STS
cross sections the thermal rate is obtained from integrating over all $v-$ and $j-$ states and
$E_t$ using Monte Carlo integration. Comparison with rates directly determined from QCT
simulations shows that the trained NN reaches accuracies better than 99 % over a wide
temperature range (1000 $\leq T \leq$ 20000) K. A very recent generalization was concerned with
learning entire product state distributions for specific reactant states (state-to-distribution
model; STD). The performance of this model is equally good as the STS model but at
considerably reduced computational cost. At the most coarse-grained level, NNs can also
be used to learn product state distributions from distributions of initial reactant states from
which again thermal rates can be determined.
It is also possible to apply machine learning methods to spectroscopy. One recent application is to learn spectroscopic maps that are used for 1- and 2-dimensional infrared spectroscopy.\textsuperscript{153} Gaussian regression was used for a $\Delta$-learning-based approach to improve an initial set of transition frequencies and dipole derivatives for the water-OH stretch. Compared with a conventional, parametrized spectroscopic map the machine learned model reduced the errors for the transition frequencies and the dipole derivatives by a factor of $\sim 2$. The additional computational overhead of the ML-based model compared with a conventional spectroscopic map is a factor of $\sim 10^4$.

Exploration of reaction mechanisms is another future application of ML-based techniques. This has, for example, been noted when investigating the combustion of methane.\textsuperscript{111} Atmospheric and interstellar chemistry are further fields for which this can become relevant. For example, considering the $\text{O}^1\text{D} + \text{CO}^1\Sigma^+$ reaction on amorphous solid water (ASW).\textsuperscript{154,155} Using a RKHS-based reactive PES for the recombination reaction it was not only demonstrated that CO$_2$ can form and stabilize on ASW. Consistent with earlier experiments\textsuperscript{156} the simulations also show that the COO isomer can form and stabilize, see Figure 4. Other recent applications of ML-based energy functions to interstellar chemistry concern the diffusion of atomic oxygen\textsuperscript{157} and nitrogen\textsuperscript{158} and the formation of O$_2$ on ASW.\textsuperscript{159,160}

Atomistic simulations will continue to benefit from synergies with machine learning technology. This includes both, the implementation and technical advances of ML. From a computational perspective it is desirable to fully integrate ML PESs into existing MD codes for efficiency reasons and not to use a ML PES as an external energy function akin to QM/MM calculations. From a technological perspective, rigorous application of transfer- or $\Delta$-learning approaches offer much scope to go beyond DFT-based PESs in an efficient manner. First steps in this direction have been undertaken.\textsuperscript{161,162}
Figure 4: CO+O recombination on amorphous solid water. The ground state PES supports both, the global OCO and the local COO minimum energy structure. Both are formed and stabilized from reactive MD simulations using the RKHS interpolated MRCI+Q/aug-cc-pVTZ reference energies.
Another imminent improvement is the realistic description of long range interactions. Most machine-learned PES are restricted to exploration of the energetics around well-defined reference (minimum energy) structures or for small reference systems using local representations. However, for chemical reactions or systems in the condensed phase the long range part of the intermolecular interaction is essential and determining reference structures for input into ML-based models becomes increasingly costly. This was recently addressed within the DeepMD framework by using Wannier functions centered on the atoms. Alternatively, it may also be possible to combine a short-ranged ML-PES with explicit long range representations based on multipoles as has been done for ionic complexes. On the other hand, with a suitable high-level implementation machine learned PESs from reference calculations in the gas phase may already be used in a QM/MM fashion in MD simulations. Such ML/MM MD simulations provide considerable speedup compared with conventional QM/MM simulations for sufficiently high levels of the QM reference. Combined with transfer learning techniques this will allow treatment of the solute at the correlated level of theory (such as MP2 or even CCSD(T)). Here it is important to stress that the computational cost for evaluating an ML PES is always the same, irrespective of the level of theory it was trained on. The computational cost for the different levels of theory used for the reference calculations arises for the reference calculations which, however, can be alleviated due to a) the massively parallel fashion in which this step can be carried out and b) the fact that TL can considerably reduce the number of high-level calculations that needs to be carried out.

In conclusion, with the ever increased computer power available, atomistic simulations combined with tools from ML have a bright and exciting future for exploring functional aspects of chemical systems. This concerns in particular, but not exclusively, systems for which state-of-the art experiments are available and can be carried out. An MD/ML-based approach can also be used for prediction of spectroscopic responses - e.g. upon protein mutation -
or reaction pathway and product exploration. This requires computationally efficient implementations and reference calculations at sufficiently high level of theory, both of which are becoming available.

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Author Biography

Markus Meuwly studied Physics at the University of Basel and completed his PhD in Physical Chemistry working with Prof. J. P. Maier. After postdocs with Prof. J. Hutson (Durham) and Prof. M. Karplus (Strasbourg and Harvard) as a Swiss National Science Foundation Postdoctoral Scholar he started as a Förderprofessor at the University of Basel in 2002 where he is Full Professor of Physical and Computational Chemistry. He also holds a visiting professorship at Brown University, Providence, RI. His scientific interests range from accurate intermolecular interactions based on multipolar, kernel- and neural network-based representations to applications of quantitative molecular simulations for cold (interstellar) and hot (hypersonics) environments and the investigation of the spectroscopy and reactive dynamics in proteins and in the condensed phase.
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