MODELING CONDENSED-PHASE CHEMISTRY THROUGH MOLECULAR DYNAMICS SIMULATION

The challenges and problems involved in simulating condensed-phase dynamics, particularly for systems involving cleavage and formation of chemical bonds, are substantial. The authors describe two methods for simulating protonated liquid water and condensed-phase reaction dynamics, in which the commonly used multi-atom empirical force fields are inadequate.

Advances in computational power have greatly facilitated the successful implementation of large-scale computer simulations of biological assemblies and complex condensed phases. Researchers have developed numerous simulation techniques, but many of these share, at their core, the so-called molecular dynamics (MD) paradigm to simulate such systems. (See the "Molecular Dynamics in a Nutshell" sidebar for more specifics.)

This article does not go into the details involving viable system sizes and allowable magnitudes of the time step in MD simulations. Suffice it to say that to model complex condensed phases using MD simulation requires approximately 1,000 to one million molecules examined over the course of multiple nanoseconds with a time step on the order of 0.001 to 0.002 picoseconds. This situation is already computationally daunting. Regardless, one goal is to extend the boundaries of accessible systems to include chemical reactions within the MD simulations. Unfortunately, this apparently logical extension to the MD method turns out to involve almost a complete restructuring of the method; in the instance that we let particles create and destroy chemical bonds, a new approach is necessary to simulate the systems.

To perform an MD simulation of a reactive system, we require an atomistic model potential energy surface (PES), or force field. The PES will contain the information required for molecules to move, rotate, and translate as well as react with one another to form new species. This article describes methods for simulating protonated liquid water and condensed-phase reaction dynamics, in which the commonly used multi-atom empirical force fields are inadequate. We discuss two approaches that generate a specific PES that we can use in an MD simulation. The first is the multistate empirical valence bond (MS-EVB) approach to study the dynamics of excess protons in condensed media, including water and biological systems. The second is the ab initio-based atom-centered density matrix propagation (ADMP) method.

Proton Diffusion Case Study

Diffusion of a molecule through a liquid can be characterized using the statistics of random-walk processes where the square of the total distance traveled is proportional to the total time taken, with the diffusion constant being the constant of proportionality between the two quantities. The

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Molecular Dynamics in a Nutshell

The idea with MD is intuitive: a complex system is modeled in time by following the dynamics of individual molecules using Newton's classical equations of motion. We obtain the motion, or trajectory, of each particle in the system by calculating the total force acting on it, due to surrounding particles and even external fields. The simulation moves forward in time as a sequence of snapshots, where each snapshot contains all the molecular information required to propagate to the next snapshot. A small time increment, known as the *time step*, coarse-grains the system evolution in time so that we can solve dynamics iteratively.
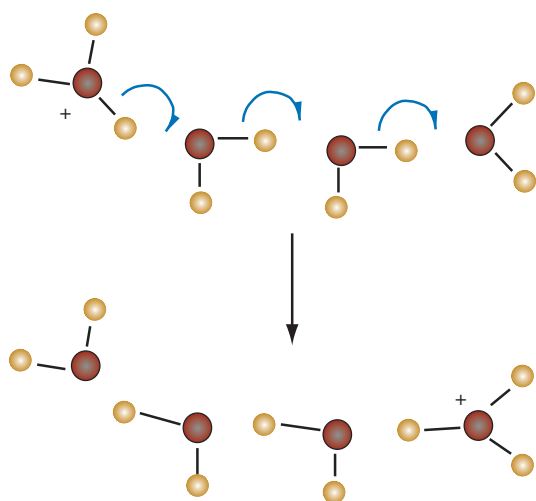

Figure 1. The discontinuous jumping of an excess proton by the Grotthuss mechanism.

diffusion constant reflects a particular molecule's rate of diffusion through a liquid. The system of an excess proton in water provides an interesting case study of the interplay between chemical and diffusional motion. The excess proton can bond to a water molecule to produce a hydronium ion (H_3O^+), which can then give up one of its three protons to another water molecule. However, the proton it donates is not necessarily the same one that was accepted.[1] Thus, there is no single excess proton in the system, which we can label and follow. Instead, a defect moves through the liquid, jumping discontinuously from molecule to molecule (see Figure 1). The diffusion constant of the excess proton is, thus, due to two factors:

- the hopping rate of protons from hydronium ions to water molecules, and
- the period between the hops, where actual diffusion of hydronium ions occurs.

Modeling such a process using an MD simulation presents a clear example of the challenge we face to include chemical reactions in the MD simulation machinery.

EVB Approach

Traditional empirical energy surfaces do not include the functionality to describe bond breaking and formation, required to model the proton shuttling process. The empirical valence bond (EVB) methodology Robert Mulliken[2] proposed and Arieh Warshel and Robert M. Weiss[3] significantly developed is one approach that lets us calculate a PES for chemical reactions in a computationally efficient manner.

The MS-EVB implementation developed by Gregory Voth and his coworkers[4–6] significantly extends these ideas to describe possible protonation states in liquid water. As an example, Figure 2 schematically indicates how we would use the MS-EVB method to study the so-called Eigen cation ($H_9O_4^+$) in the gas phase. This chemical topology requires four states for the energy calculation, each containing one hydronium ion and three waters. In the bulk liquid, many more states are needed, routinely 30 or more, to include additional solvation shells of the hydronium ion. We then calculate the energy separately for each state and from these values derive a total potential energy function.

Simulation results corroborated by experimental evidence[7] suggest that the excess proton in the liquid state also spends a large amount of time between oxygen pairs, forming a $H_5O_2^+$ Zundel state. We reproduce this in the MS-EVB model by paramaterizing the off-diagonal terms, which govern the resonance between pairs of states dictating the degree to which a pair of states couple to each other. Research in our group has shown that there is an electrostatic contribution to the off-diagonal elements, which is long range and gives a significant contribution to the stabilization of the Zundel ion in the bulk. We have found a correct description of these subtle electrostatic effects to be especially important in simulating the condensed phases, when compared against experimental observables (for example, the proton diffusion constant).[6]

The MS-EVB approach is not limited to bulk water, and we have applied it to various important biological processes.[8] The movement of protons into and out of cells through ion channels is one such example. We have also used MS-EVB to study water clusters and liquid-vapor interfaces that yield insight into important atmospheric

processes. Using our MS-EVB implementation has let researchers study diverse problems such as proton transport dynamics through water filled carbon nanotubes.

Ab Initio Molecular Dynamics

Actual chemical bonding characteristics are completely determined by the quantum mechanics of electrons. Therefore, to simulate a reactive system, an approach based on solving the quantum mechanical equations of motion is a necessity. Unfortunately, this can only be exactly solved for small systems. Larger systems require approximate methods, and perhaps the most common and computationally efficient approach available today is the density functional theory (DFT). However, even here, treating complex condensed-phase reactive systems is impossible, unless we enforce a change in paradigm.

Some important properties that a good computational method should have to efficiently treat condensed-phase reactions include

- $O(N)$ scaling (or better) of computation time with system size, where N is the number of electrons in the simulation;
- accurate treatment of long-range interactions present in condensed systems (such as water); and
- a quantum mechanical basis to treat chemical reactions, charge transfer, and time-dependent polarization effects.

One powerful and popular approach to ab initio MD is the Car-Parrinello (CP) method,[9] which relies on an on-the-fly solution of the electronic structure problem (via DFT) while time-propagating the nuclear degrees of freedom. As pioneering as the CP approach was, it is significantly limited by two important factors. The poor, $O(N^3)$, scaling of the method with system size, which can be traced to using delocalized plane-waves as basis sets to represent the system's electronic structure wavefunction in DFT, is the first. The second limiting factor is that the CP approach is generally viable only for relatively less accurate forms of DFT (local density approximation or simple gradient-corrected DFT). To model large condensed systems accurately requires that we overcome these limitations.

Recently, researchers have developed a novel ab initio MD method called the atom-centered density matrix propagation (ADMP) approach,[10–12] where the computation time scales as $O(N)$ with system size and more accurate im-
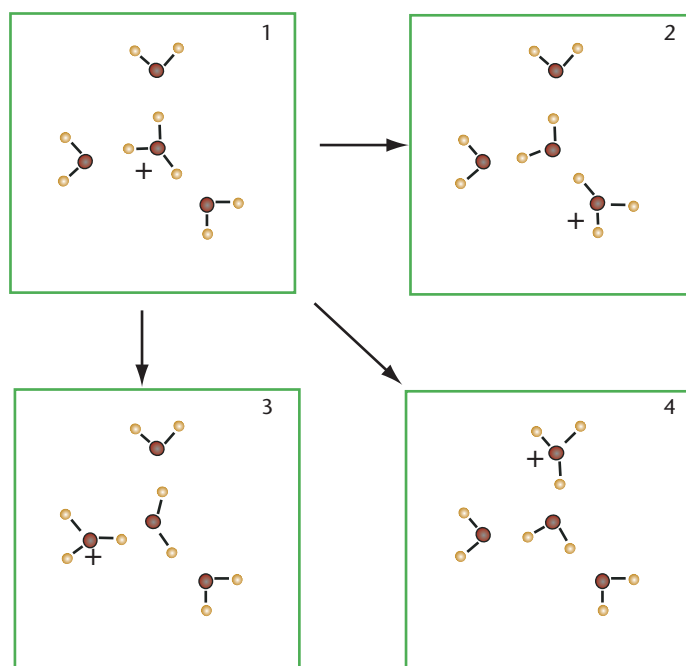

Figure 2. A four-state empirical valence bond (EVB) description for the chemical topology of an Eigen cation.

plementations of DFT are routinely applicable. These advantages make ADMP a reliable alternative in performing ab initio molecular dynamics of chemically reactive condensed-phase and interfacial dynamical processes. Challenging applications such as proton solvation in water clusters[13] and proton transport through ion channels have more recently been studied by N. Rega, Srinivasan S. Iyengar, and Gregory A. Voth using ADMP. Figure 3 is a representative configuration of one such biological ion-channel simulation. A portion of the channel (shaded, QM) is treated with ADMP while the remaining channel, water, and lipids are treated with a classical molecular mechanics (MM) force field.

To briefly outline, ADMP involves an approximate propagation of the quantum mechanical system represented by the Cartesian coordinates of the nuclei in the system and the electronic states representing the bonding characteristics of the system.[10–12] This approach has been shown to be a computationally efficient and accurate for treating reactive systems.[12] With ADMP, current state-of-the-art computer capabilities allow for direct modeling of molecular polarizability, electronic fluxes, reactive species in the condensed phase, dynamics problems at interfaces, and QM/MM treatment of biological systems
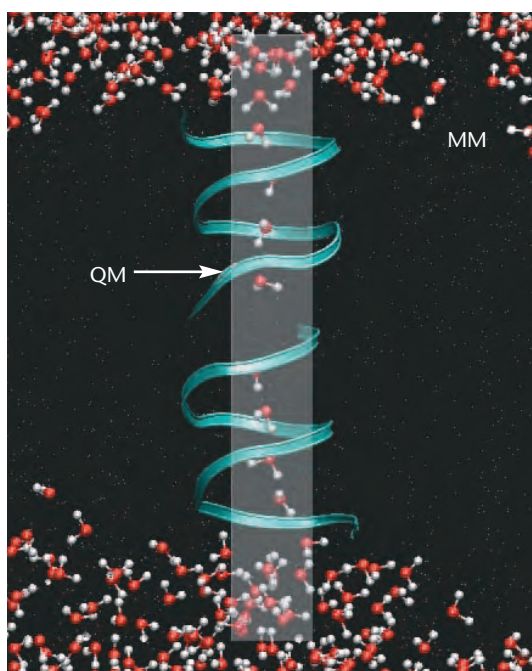
Figure 3. A representative snapshot from a quantum mechanics/molecular mechanics (QM/MM) simulation of the biological ion-channel gramicidin A. The figure shows the QM and MM zones in the simulation.

Simulating the condensed phase remains a significant intellectual and computational challenge. Over the last few decades, work has concentrated on fairly homogeneous molecular or atomic systems. Even this has been far from easy, as evidenced by the large number of papers each year describing different approaches to generating an accurate PES for pure water. We do not claim that such problems have been completely solved, but the focus is now shifting to less homogeneous and more complex systems. The simulation community is being called on, for example, to provide molecular-level descriptions to assist with interpreting biologically relevant systems, which span both large spatial and temporal domains. We also need more accurate descriptions of chemical processes in the atmosphere and in material science.

We have highlighted two paths capable of simulating chemical reactive dynamics in the condensed phase. The MS-EVB approach can successfully model proton transport in aqueous and bimolecular systems. The MS-EVB methodology is a complementary approach to electronic-structure methods. It gives us a comparatively simple and physical way to build on and extend existing PES models to simulate chemical reactions, thus, significantly increasing the domain of MD simulations. The trade-off involved when compared against ab initio simulations is that MS-EVB methods require extensive parameterization, but the resulting models are orders of magnitude faster.

The ADMP methodology, on the other hand, is proving to be a powerful computational tool for attacking problems that would be difficult, if not nearly impossible, to simulate accurately using a more empirical force-field approach. Even though empirical forces usually have the edge on ab initio methods in the CPU demands required, it can typically take months if not years of development time to construct a trustworthy and realistic PES.

Chemical problems require us to consider a combinatorial number of ways in which different atoms can bond and otherwise interact with each other. Thus, we find that every time a new molecule or species is introduced into a simulation that we have to consider yet more parameters in our model. Clearly, an advantage of ab initio based methods is that they are (nearly) parameter free and it is, thus, much easier to extend these simulations to an arbitrary number of species–species interaction types. It may be that one can overcome the parameterization explosion in empirical force fields by developing more algorithmic "cranking the handle" approaches to parameterization (as opposed to the current trial-and-error approach). This is likely to be a topic of future research.

For the future, we can hope for a greater integration of the various complementary methods we detail here. Electronic structure and ab initio dynamics methods can help us construct empirical PESs. In turn, we expect that PESs can be used as a probe of the long-time dynamics of large-scale systems that would not be feasible through direct ab initio simulations. We can also look forward to an era of multiscale simulations in which continuum approaches are bridged to MD simulations using empirical PESs, which are in turn parameterized from electronic structure calculations and ab initio dynamics.

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