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Solving Chemical Problems with a Mixture of Quantum-Mechanical and Molecular Mechanics Calculations: Nobel Prize in Chemistry 2013**

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According to Richard Feynman, "Everything that living things do can be understood in terms of the jiggling and wiggling of atoms."[1] Unfortunately, probing these jigglings and wigglings directly is not so easy, as the required time and spatial resolutions are hard to achieve in experiment. Alternatively, Paul Dirac's statement that "the underlying physical laws necessary for the mathematical treatment of the whole of chemistry are completely known",[2] suggests that we can use computers instead. However, Dirac also realized that "the exact application of these laws leads to equations much too complicated to be soluble" and that "it therefore becomes desirable that approximate practical methods of applying quantum mechanics should be developed, which can lead to an explanation of the main features of complex atomistic systems without too much computation."[2]

Forty-five years later, Dirac's dream came true. This year's Nobel Prize in Chemistry is awarded to Martin Karplus, Michael Levitt, and Arieh Warshel in recognition for their contribution to the development of the desired "approximate practical methods". To avoid the computationally demanding evaluation of the many-electron wave function in complex biological systems, in the mid-1970s, they approximated its influence by analytical interaction functions, the molecular mechanics force field. After careful parameterization, today's force fields rival quantum chemistry in accuracy in many cases, at a fraction of the computational cost. With such force fields, the laureates were the first to observe the jiggling and wiggling of proteins on a computer.[3,4]

Their work marked the beginning of an era in which the view of proteins as static structures changed to proteins as highly dynamic molecular nanomachines. If the picture of a crystal structure already says more than thousand words, the movie created from a molecular dynamics (MD) simulation has a lot more to say about the protein's function. Karplus, Levitt, Warshel, and many other theoretical chemists have thus turned Feynman's idea into a reality that to understand life processes (protein function, for a start) not only the static structure is needed, but also its dynamics. Over the past four decades, dramatic advances in computer power, algorithmic developments, and improvements in the accuracy of the force fields have established MD simulation as an important and predictive technique, and three of its main developers have now thus received the highest scientific recognition. The level of achievement that is possible in this area today is demonstrated by work from the group of David Shaw: they recently succeeded in simulating the folding of several small soluble proteins de novo, and thus established that it is possible to predict protein structure from amino acid sequence (biological laws) and physical laws alone.[5]

Despite their success in capturing protein dynamics, force fields are not suited for processes that involve charge transfer and electronic rearrangements, such as chemical reactions, for example in enzymes. Instead, for these processes a quantum-mechanical (QM) description for the electrons remains essential. Unfortunately, the high computational effort required for computing the many-electron wave function at every step of a MD simulation is a major obstacle for using computers to understand enzymatic catalysis, the main goal of chemical biology. To overcome this limitation, the laureates have introduced a hybrid method that combines the best of both approaches (Figure 1) and treats only a small part of the system at an appropriate level of quantum mechanics, while retaining the computationally much less demanding molecular mechanics (MM) force field for the remainder.

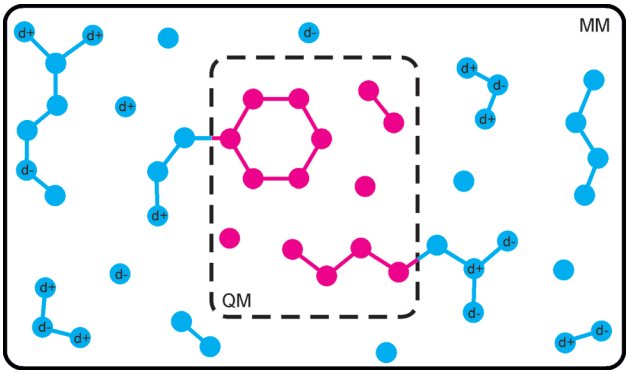

Figure 1. Illustration of the QM/MM concept. A small region in which a chemical reaction occurs is treated quantum-mechanically. The remainder of the system is modeled at the molecular-mechanics level.

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This hybrid QM/MM multi scale approach has been highly successful, mainly because of the local character of a chemical reaction. A distinction can often be made between a reaction center or active site, with atoms that are directly involved in the reaction and a surrounding, in which the atoms do not directly participate in the reaction, but are essential due to their steric, electrostatic, or entropic coupling to the active site. For example, many reactions in solution involve the reactants and the first few solvation shells, whereas the bulk solvent is hardly affected. The same is true for most enzymes, in which the chemical process is restricted to an active site.

The QM/MM Hamiltonian contains three classes of interactions: interactions between atoms inside the quantum-mechanical region, interactions between atoms inside the molecular mechanics region, and interactions between the two subsystems. Interactions within the QM region can be described at any level of ab initio, density-functional, or semi-empirical theory, while interactions between atoms within the MM region are described with a force field. The real challenge is the appropriate coupling between the two subsystems, for which Warshel and Levitt derived the necessary energy terms.[6] Although this seminal paper on the catalytic mechanism of lysozyme clearly demonstrated the full power of the QM/MM approach, it would not become a main stream method until Karplus and co-workers made it available to a broader community by implementing a semi-empirical QM/MM interface in their CHARMM molecular modeling software package.[7]

Since then, QM/MM calculations have revealed detailed mechanistic insights into a very wide variety of enzymatic reactions.[8] In contrast to mutation experiments, QM/MM based enzymology allows the effect of individual amino acids on the catalysis process, as well as alternative reaction pathways, to be investigated without perturbing the protein structure. As a consequence, QM/MM methods have contributed dramatically to our current understanding of how enzymes have evolved to mediate catalysis. The atomistic insights from such simulations have confirmed the views of Linus Pauling[9] that enzymes speed up chemistry by stabilizing the transition state in a pre-organized polar environment. Reported deviations between QM/MM results and experimentally observed kinetics often suggest a lack of sampling in the simulations rather than a deficiency of the QM/MM model itself, and illustrate the need to improve the conformational sampling, another important area of computational chemistry to which the laureates also provided seminal contributions.

Because there are no fundamental limitations on the level of quantum chemistry or the nature of the molecular mechanics force fields, QM/MM is not limited to enzymes, but can be used to investigate chemical reactions and conformational motions of any complex system. QM/MM is also not limited to the ground state, and Warshel was actually the first to explore retinal photo-isomerization in rhodopsin,[10] using a clever representation of the still unknown protein structure at that time in combination with a method that he and Karplus had developed a few years earlier for calculating electronic ground and excited states of conjugated chromophores.[11] Today, QM/MM is used extensively to compute the optical properties and excited state dynamics of biological systems, as illustrated in Figure 2. In photochemical reactions, nuclear quantum effects are important, but a suitable description of these effects for larger systems is still lacking. Therefore, the development of efficient methods that bring the nuclei back into the realm of quantum mechanics is one of the current major challenges in computational chemistry.

The award of the Nobel Prize in Chemistry 2013 to three of the leading minds of computational chemistry underscores the broad impact that computer simulations have made in fields as diverse as chemistry, biophysics, structural biology, or material science. Computer simulations are now widely used for interpreting experimental results, testing hypotheses and inspiring new experiments. This year's Nobel prizewinners in chemistry have devoted their lives to develop methods with which the foundations of biology can be studied on a computer.

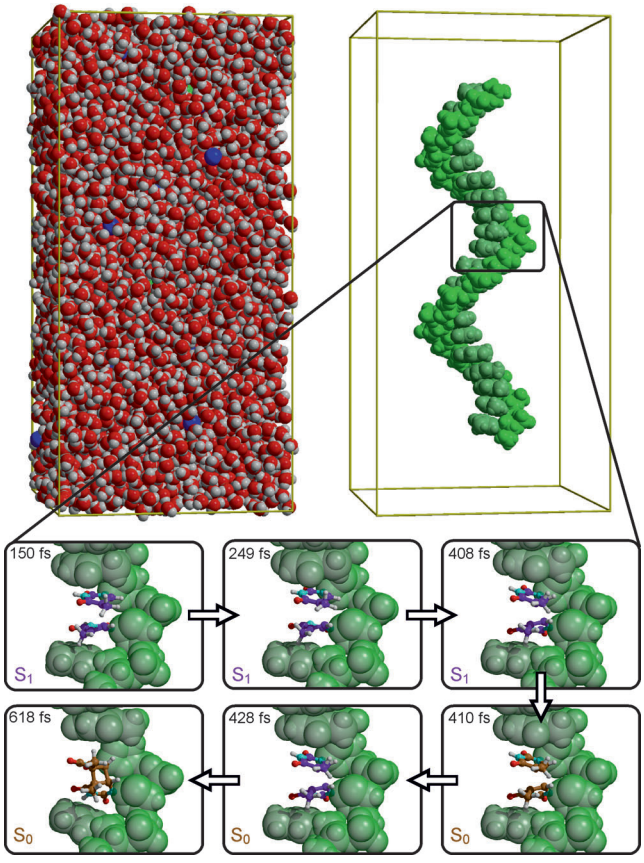

Figure 2. QM/MM simulation of a photo-excited stacked thymine pair in a dT_{20} single-strand DNA molecule solvated in water. The QM region is shown in the ball-and-stick representation, while the MM region is shown in space-filling representation. The snapshots show how the thymine residues can photo-dimerize in a matter of femtoseconds after absorption of a UV photon at $t = 0$ fs. The two thymine bases were described at the CASSCF(8,8)/6-31G level of theory. The rest of the DNA and sodium chloride ions were described with the Amber force field, and the tip3p model was used for the water. A transition from the excited (S_1) to the ground state (S_0) is triggered when the trajectory reaches the seam of conical intersection.

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