Scientific Background on the Nobel Prize in Chemistry 2013

DEVELOPMENT OF MULTISCALE MODELS FOR COMPLEX CHEMICAL SYSTEMS

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The Royal Swedish Academy of Science has decided to award the 2013 Nobel Prize in Chemistry to

Martin Karplus, Harvard U., Cambridge, MA, USA
Michael Levitt, Stanford U., Stanford, CA, USA
and
Arieh Warshel, U. Southern Ca., Los Angeles, CA, USA

For

"Development of Multiscale Models for Complex Chemical Systems"

Multiscale models for Complex Chemical Systems

The Nobel Prize in Chemistry 2013 has been awarded to Martin Karplus, Michael Levitt and Arieh Warshel for development of multiscale models of complex chemical systems.

Background

Chemistry and Biochemistry have developed very rapidly during the last 50 years. This applies to all parts of the fields, but the development of Biochemistry is perhaps the most striking one. In the first half of these 50 years the determination of protein structure was perhaps the field where the largest efforts were spent and the largest progress was made. The standard methods to analyse the structure of proteins are X-ray crystallography of crystals or analysing the spin – spin couplings obtained from NMR-spectroscopy. What is perhaps less well known is that in the computer programs that are used to analyse the diffraction pattern from an X-ray investigation or the spin-spin couplings obtained from a NMR experiment there is hidden a computer code that calculates the energy of the considered structure based on empirically and theoretically obtained potentials describing the interaction between the atoms in the system. The reason for this is that there is not enough experimental information to uniquely determine the structure of the studied system. This is just one of the aspects of how computers and theoretical models have become essential tools for the experimental chemist.

Today the focus of chemical research is much more on function than on structure. Chemists ask questions like "How does this happen?" rather than "What does this look like?" . Questions about function are generally difficult to answer using experimental techniques. Isotope labelling and femtosecond spectroscopy can give clues, but rarely produce conclusive evidence for a given mechanism in systems with the complexity characterizing many catalytic chemical processes and almost all biochemical processes. This makes theoretical modelling an important tool as a complement to the experimental techniques. Chemical processes are characterized by a transition state, a configuration with the lowest possible (free) energy that links the product(s) with the reactant(s). This state is normally not experimentally accessible, but there are theoretical methods to search for such structures. Consequently theory is a necessary complement to experiment.

The work awarded this year´s Nobel Prize in Chemistry focuses on the development of methods using both classical and quantum mechanical theory which are used to model large complex chemical systems and reactions. In the quantum chemical model the electrons and the atomic nuclei are the particles of interest. In the classical models atoms or groups of atoms are the particles that are described. The classical models contain much fewer degrees of freedom and they are consequently evaluated much faster on a computer. Furthermore, the physics that is

used to describe the classical particles is much simpler and this also contributes to speeding up the modelling on a computer. This year´s laureates have shown methods to develop models that describe part of a system using first principle, quantum chemical models for a central part of the system and how to link this part to a surrounding, which is modelled using classical particles (atoms or group of atoms). The key accomplishment was to show how the two regions in the modelled system can be made to interact in a physically meaningful way. Frequently the entire molecular system is embedded in a dielectric continuum. A cartoon of a typical system is shown in Figure 1.
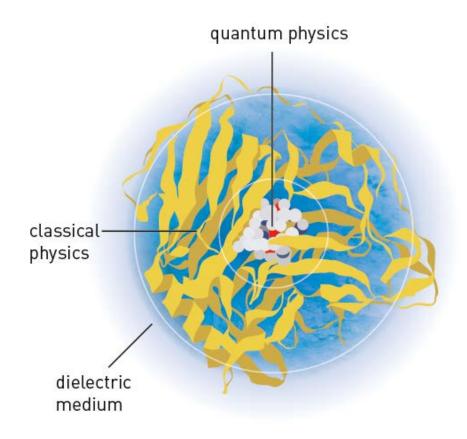

Figure 1

Figure 1 Multi-copper-oxidase embedded in water [1].

Historical perspective

Theoretical modelling as described above rests on basically four different types of development. The central region in the system, the spacefilling atoms (red and gray), is described using a Quantum Chemical method [2]. Walter Kohn and John Pople were awarded the Nobel Prize in Chemistry 1998 for the development of such methods. The development of Quantum

Mechanics[3], which the Quantum Chemistry rests on is almost 75 years older and was the basis for five different Nobel Prizes in Physics from 1918 – 1933. The laureates were M. Planck in 1918, N. Bohr in 1922, Prince de Broglie in 1929, W. Heisenberg in 1932, and E. Schrödinger and P. Dirac in 1933.

The theory used for the modelling of the surrounding molecular system consists of several pieces. First of all a model is needed to describe the intramolecular potential for these molecules. The model that is used today originates from 1946, when three groups[4-6] independently suggested such a model, based on Coulomb and van der Waals (van der Waals was awarded the Nobel Prize in Physics 1910) interactions. F.H. Westheimers group soon became leading in this field. In those days computers did not exist. N. Allinger developed computer code and used computers to optimize the structure of molecules using such classical, empirical potentials in a set of molecular mechanics methods[7] called MM1, MM2 and so on. In these methods the energy of the system was minimized to obtain the structure of the studied system. The MM-methods were primarily used for systems built from organic molecules.

In a parallel line of development G. Némety and H. Scheraga[8] used the ideas of Westheimer and Allinger and developed simplified versions of their potentials for the use in statistical mechanics simulations and for energy minimisation of protein structures. Roughly at this time quantum chemical methods started be used for the construction of inter- and intramolecular potentials for complex systems. Leading persons in this field were S. Lifson and A. Warshel with the development of the Consistent Force Field (CFF) method[9]. M. Levitt and S. Lifson were the first to use such potentials to minimize the energy of a protein[10]. Another well-known example of a theoretically constructed potential was the so-called MCY[11] potential for the water – water interaction. This potential was based entirely on quantum chemical calculations that were used to create a classical potential with terms describing electrostatic and van der Waals interactions.

The advantage of the classical potential-based methods is that the energy can easily be evaluated and large systems can be studied. The drawback is that they can only be used for structures where the interacting molecules are weakly perturbed. Consequently they cannot be used for the study of chemical reactions where new molecules are formed from the reactants.

Conversely, quantum chemical methods can be used for the study of chemical reactions where molecules are formed and destroyed, but they are very demanding with respect to computer time and storage and only smaller systems can be handled.

Given that the problem with the potential functions describing the surrounding is solved, the problem of deciding the proper conformation(s) for the surrounding remains. There are two different approaches to this problem, the one used by Allinger in his MMX methods, to

minimize the energy of the system and generate one characteristic conformation, and that used by Némety and Scheraga, to use statistical mechanics methods, like Molecular Dynamics (MD) [12] or Monte Carlo (MC) [12] and generate many configurations with a correct (in principle) statistic weight.

The importance of the work of the laureates is independent of what strategy is used for the choice of the studied configuration(s). The prize focuses on how to evaluate the variation in the energy of the real system in a accurate and efficient way for systems where relatively large geometry changes or changes in electronic configuration in a smaller part of the studied system is strongly coupled to a surrounding that is only weakly perturbed. One way to address this problem is to develop an efficient computer code based on the Schrödinger equation that makes it possible to handle systems of the size that is required. The Car – Parrinello approach [13] is the leading strategy along this line. It is however still too demanding with respect to computer resources to be able to handle the large systems necessary for biomolecular modelling or extended supra-molecular systems with the required accuracy. The solution to the problem is instead to combine classical modelling of the larger surrounding, along the line suggested by Westheimer [4], Allinger [7], Némety and Scheraga [8], with quantum chemical modelling of the core region, where the chemically interesting action takes place.

The contributions of the three laureates

The first step in the development of multiscale modelling was taken when Arieh Warshel came to visit Martin Karplus at Harvard in the beginning of the 70'ies. Warshel had a background in inter- and intramolecular potentials and Karplus had the necessary quantum chemical experience. The goal was to study molecules similar to retinal. This chromophore, responsible for animal vision, had attracted Karplus attention[14]. Partly based on the ideas presented by Honig and Karplus[14], Karplus and Warshel constructed a computer program that could calculate the π-electron spectra and the vibration spectra of a number of planar molecules with excellent results[15]. The basis for this approach was that the effects of the σ-electrons and the nuclei were modelled using a classical approach and that the π-electrons were modelled using a PPP[16] (Pariser – Parr – Pople) quantum chemical approach corrected for nearest overlap. Figure 2 shows a typical molecule studied in that work.
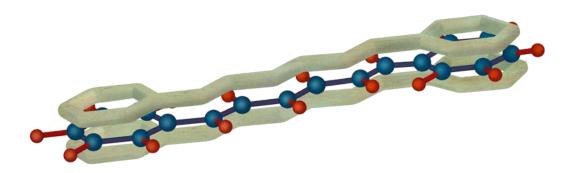
Figure 2. The mirror symmetric molecule 1,6-Diphenyl-1,3,5-hexatriene studied by Martin Karplus and Arieh Warshel[15]

This was the first work to show that it is possible to construct hybrid methods that combine the advantages of classical and quantum methods to describe complex chemical systems. This particular method is restricted to planar systems where symmetry makes a natural separation between the π-electrons that were quantum chemically described and the σ-electrons that were handled by the classical model, but this is not a principal limitation, as was shown a few years later, in 1976. Then Arieh Warshel and Michael Levitt showed that it is possible to construct a general scheme for a partitioning between electrons that are included in the classical modelling and electrons that are explicitly described by a quantum chemical model. This was made in their study of the "Dielectric, Electrostatic and Steric Stabilisation of the Carbonium Ion in the Reaction of Lysosyme"[17]. Several fundamental problems needed to be solved in order for such a procedure to work. Energetic coupling terms that model the interaction between the classical and the quantum system must be constructed, as well as couplings between the classical and quantum parts of the system with the dielectric surrounding. The studied system is shown in Figure 3.
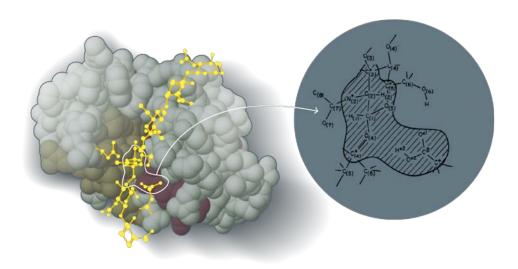
Figure 3. To understand how lysozyme cleaves a glycoside chain, it is necessary to model only the relevant parts of the system using quantum chemistry, while most of the surrounding may be treated using molecular mechanics or a continuum model. The figure is adapted from[17]

In the time between the publishing of the two publications referred to above (1975), another important step, which made it possible to study even larger systems, was taken by Michael Levitt and Arieh Warshel in their study of the folding of the protein Bovine Pancreas Trypsin Inhibitor (BPTI)[18]. The type of simplifications of the studied system used in that study is illustrated in Figure 4.
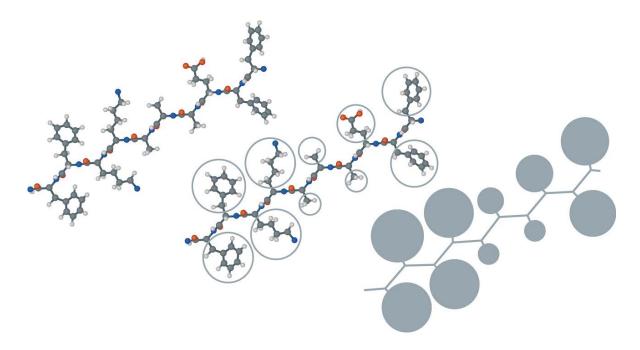
Figure 4. The detailed structure of a polypeptide chain (top) is simplified by assigning each amino acid residue with an interaction volume (middle) and the resulting string-of-pearls like structure (bottom) is used for the simulation.

In this work, the folding of the protein from an open conformation to a folded conformation was studied, and it was shown that it is possible to group atoms in a classical system into rigid units and to treat these as classical pseudoatoms. Obviously, this approach further speeds up the modelling of a system.

Multiscale modelling today

The work behind this year's Nobel Prize has been the starting point for both further theoretical developments of more accurate models and applied studies. Important contributions have been given not only by this year's laureates[19-22] but also by many others including J. Gao [23], F. Maseras and K. Morokuma [24], U.C. Sing and P. Kollman [25] and H. M. Senn and W. Thiel [26]. The methodology has been used to study not only complex processes in organic chemistry and biochemistry, but also for heterogeneous catalysis and theoretical calculation of the spectrum of molecules dissolved in a liquid. But most importantly, it has opened up a fruitful cooperation between theory and experiment that has made many otherwise unsolvable problems solvable.

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1. Figure 1 was kindly provided by Professor Ulf Ryde

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