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GUEST EDITORIAL

Nobel Prize in Chemistry 2013: Chemistry in cyberspace

Three scientists, Martin Karplus, Harvard University, USA (also at the University of Strasbourg, France), Michael Levitt, Stanford University, USA and Arieh Warshel, University of Southern California, USA, have been awarded the 2013 Nobel Prize in Chemistry 'for the development of multiscale models for complex chemical systems'. The field itself has received the recognition through its giant leaders, and thereby, the importance of the role played by theory, modelling and computation in experimental chemistry has been re-established.

The journey of the trio to this wonderland started about 40 years ago, when Karplus, in collaboration with his postdoc Warshel at Harvard, and later Warshel in collaboration with Levitt, paved the way for the development of a new modelling approach, where the relevant part of the system of interest (say, a small molecule in a surrounding solvent, or even the most active part of a bigger molecule) is treated using quantum mechanics (QM), while the remaining part is treated classically, using the so-called molecular mechanics (MM). The interfacial region here provides a meeting ground of the two approaches, thus leading to the QM/MM approach, representing a hand shake between the Schrödinger (quantum) description and the Newtonian (classical) framework. The journey has been fuelled by the availability of computing power, which has undergone tremendous development over the years.

The structure ('why are things the way they are'), function ('How do things happen') and dynamics ('from being to becoming') of complex chemical and biological systems have always attracted intriguing questions and created immense interest from time to time. The Prize winning work is concerned with the development of methodology, tractable enough for practical implementation through computation. The systems of interest here concern many-electron molecules and materials, both of which can be viewed as a collection of atoms (nuclei of atoms) held together by the electron glue. In this picture, any process, be it chemical, biological or physical, involves a rearrangement of these atoms in space, usually driven by forces arising from different sets of atoms or molecules coming within the proximity of interaction or external forces or even mere thermal fluctuations. Thus, in general, chemical reactions are associated with redistribution of the electron density in synchronization with atomic movements.

In principle, QM can be used to describe or model any system or process, irrespective of its size or complexity, as had been stated by Dirac, one of the founders of QM, in 1929 itself: 'The underlying physical laws necessary for the mathematical theory of a large part of physics and the whole of chemistry are thus completely known, and the difficulty is only that the exact application of these laws leads to equations much too complicated to be soluble. 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 atomic systems without too much computation' (*Proc. R. Soc. London, Ser. A*, 1929, **123**, 714). The next 40 years following this statement witnessed the development of a number of approximate methods in QM, with the applicability still limited to small molecules only. It has been further realized that it is almost impossible, in practice, to use QM directly, even with approximations, on larger systems such as biomolecules and this has prompted the development of methods where classical mechanics is also brought in, to have its share in the description. This challenging task has been conceived, executed and pursued vigorously by the three laureates of this year (2013).

Since a chemical description is possible only using QM and the systems are too large to be tackled by QM, the optimal solution is what the laureates have discovered. Their hybrid QM/MM approach prescribes QM only for the key region where bond making and bond breaking (real chemistry) takes place, while leaving the rest of the system in the hands of a classical atomistic description. The individual atoms in this outer region are assumed to move classically obeying Newton's laws of classical mechanics, involving a force field, which although can be separately calculated using QM, is usually modelled. In a typical drug–protein interaction, for example, the relevant atoms of the drug and the protein undergoing direct chemical interaction are the customers for QM, while the

remaining portions of the large protein molecule (and often the drug) are treated classically by MM. The novelty and success of this newly devised QM/MM approach lies in its ability to judiciously partition the system and make use of the best of both the worlds, through a proper prescription for coupling of the quantum and classical descriptions resulting into suitable bridging of the two regions so that the outcome represents meaningful and accurate results. The QM/MM approach is thus the first to provide a multi-scale method that bridges the microscopic (domain of QM) and atomistic or mesoscopic (domain of classical mechanics) length scales. The whole system can in turn be embedded in a larger macroscopic continuum medium representing the solvent, with again a proper bridging mechanism, resulting in a truly multi-scale approach encompassing the microscopic, mesoscopic and macroscopic length scales.

In the course of development, the initial paper of Karplus and Warshel (1972) was followed by the landmark contributions of Levitt and Warshel (1975, 1976), which aimed at understanding protein folding, structure–function relationship in proteins, and catalysis by enzymes through the QM/MM approach. The dream of Warshel to understand the role of enzymes in catalysing a reaction was, in fact, born as early as 1963, when he was still an undergraduate student at Technion, Haifa, Israel. And today half a century later, he is considered to be the founder of computational enzymology. Over the years, the QM/MM method, in the hands of Karplus and his team, has given birth to a versatile software, CHARMM (Chemistry at HARvard Macromolecular Mechanics), which is used worldwide.

Different variants of the theory have resulted from different approximations and approaches used for the QM description of the inner core region, typical examples being the wave function-based *ab initio* Hartree–Fock methods and beyond, semi-empirical Pariser–Parr–Pople method and beyond, electron density-based density functional theory, etc. It may be noted that the contribution to electronic structure theory received recognition through the 1998 Nobel Prize in Chemistry to Walter Kohn and John Pople. Analogously, there are variants of the MM description as well with different model potentials, inclusion of *n*-body interaction terms, etc. The importance of the work is however independent of these variants of methodology within a particular length scale. The QM/MM approach has become a state-of-the-art method for computational investigation of biomolecular systems. It has enabled one to overcome the size restriction for practical application of QM and study the properties and functions of large, complex biomolecular systems, including those involved in photosynthesis, protein folding, enzymetic catalysis and human vision.

The QM/MM methodology has undergone various newer modifications within the same broad framework. Within the QM region itself, the inner part is studied using a more sophisticated *ab initio* approach, while for the outer part less accurate semi-empirical approach is used resulting into the so-called ONIOM method. Analogously, although the classical MM was originally used in the atomistic length scale for geometry optimization through energy minimization, subsequently the usual classical molecular dynamics (MD) simulation has also been brought in to incorporate the dynamical aspects. The classical MD has also been supplemented later with an *ab initio* MD, where the use of empirical model potentials is replaced by the generation of *in situ* potential from QM directly in the course of the simulation.

The Prize-winning fundamental work is a novel example that shows how the concepts of chemistry can meet with those of physics and biology, and provide the infrastructure for building a new theoretical platform and simulation strategy to obtain an understanding of nature by unravelling its secrets, crossing the traditional subject boundaries. It is also a clear evidence of the triumph of collaborative efforts, where the expertise of Karplus in QM (already well known for the Karplus equation) has had a successful wedding with the expertise of classical mechanics-based computer modelling of Levitt and Warshel and the fruits are shared by all.

One interesting aspect of this year's chemistry Nobel laureates lies in their Israel connection. All the three scientists have become US citizens. Karplus holds both US and Austrian citizenship and splits his time between the University of Strasbourg and Harvard University, while Levitt holds American, British and Israeli citizenship and spends half of the year in Israel, where his wife and children live. Warshel, was born in Israel and holds US and Israeli citizenship. Karplus spent a semester in Weizmann Institute, Israel. According to Levitt, Israel had two profound influences on his life, the first being that he met his wife in Israel and the second being that it was Israel where he initiated his research path that ultimately led to the coveted prize. It may also be mentioned that Warshel and Levitt mark Israel's fifth and sixth winners of the chemistry Nobel Prize in a decade, joining the group of other chemistry Nobel laureate Israeli scientists, Avram Hershko and Aaron Ciechanover (2004), Ada Yonath (2006), and Daniel Shechtman (2011).

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