The Nobel Prize in Chemistry 2013

The Alliance of Newton's Apple and Schrödinger's Cat

by Jean-Marie André

On Wednesday, 9 October 2013, which was the scheduled date of the official announcement of the Nobel Prize in Chemistry, the permanent secretary of the Royal Swedish Academy of Sciences, Professor Staffan Normark announced that the 2013 Nobel Prize in Chemistry was to be awarded jointly to Martin Karplus (Harvard and Strasbourg), Michael Levitt (Stanford), and Arieh Warshel (University of Southern California at Los Angeles) for the development of multiscale models for complex chemical systems.

It was a somewhat unexpected announcement, and a nice surprise, because once again the Nobel Prize in Chemistry was awarded for research of a more “theoretical” nature and joined the awards to

- William Francis GIAUQUE (University of California, Berkeley) in 1949 for his contributions in the field of chemical thermodynamics,
- Linus Carl PAULING (Caltech, Pasadena) in 1954 for his research into the nature of the chemical bond and its application to the elucidation of the structure of complex substances,
- Robert S. MULLIKEN (University of Chicago) in 1966 for his fundamental work concerning chemical bonds and the electronic structure of molecules by the molecular orbital method,
- Lars ONSAGER (Yale University, New Haven) in 1968 for the discovery of the reciprocal relations bearing his name, which are fundamental for the thermodynamics of irreversible processes,
- Ilya PRIGOGINE (Université libre de Bruxelles and University of Texas, Austin) in 1977 for his contributions to non-equilibrium thermodynamics, particularly the theory of dissipative structures,
- Kenichi FUKUI (Kyoto University) and Roald HOFFMANN (Cornell University, Ithaca) in 1981 for their theories, developed independently, concerning the course of chemical reactions,
- Rudolph MARCUS (Caltech, Pasadena) in 1992 for his contributions to the theory of electron transfer reactions in chemical systems,
- and in 1998, Walter KOHN (University of California, Santa Barbara) for his development of the density-

functional theory and John A. Pople (Northwestern University, Evanston) for his development of computational methods in quantum chemistry.

With a bit of theoretical chauvinism, we would like to add to the list the Nobel Prize to William N. Lipscomb (Harvard University, Cambridge) in 1976 for his studies on the structure of boranes illuminating problems of chemical bonding, which were discoveries issued from his investigations on electron poor bonds, and those in the mythic year 2000, which honored Alan J. Heeger (University of California, Santa Barbara), Alan G. MacDiarmid (University of Pennsylvania) and Hideki Shirakawa (University of Tsukuba) for the discovery and development of conductive polymers. The quest for the synthesis of electrically conducting polymers was a sort of chemical Holy Grail during the fifties and the golden sixties. As a beautiful symbol of this quest, the physicist Heeger was rewarded along with the inorganic chemist MacDiarmid and the organic chemist Shirakawa.

The Winners

Martin Karplus

Martin Karplus was born in Vienna in 1930 into an old Austrian Jewish family. After the Anschluss in 1938, he left his native Austria and immigrated to the United States via Switzerland and France. As a teenager, he was very interested in ornithology, which immersed him in the fascinating world of research.¹ Naturally oriented towards biology, he quickly realized that to develop a valid approach to biology at its most fundamental level, he had to acquire a strong background in chemistry, physics and mathematics. He thus decided to follow the chemistry and physics programs at Harvard. His multiple interests brought him to Caltech where he met the great masters of the time, Delbrück, Feynman, and Pauling. He obtained his PhD in 1953 under the direction of the lattermost; the topic of his research was the hydrogen bonding in the simple model HFH'. Already, it was an opportunity for him to develop a method close to the “atoms in molecules” approach, but he did not publish it. For his postdoc, he joined Charles Coulson in Oxford. This was the time of the birth of Nuclear Magnetic Resonance (NMR). He found a strong interest in this new technique and chose to

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return to the University of Illinois where Slichter and Gutowsky were developing this technique for its applications in chemistry.

The Karplus equation

$$J(\phi) = A \cos^2(\phi) + B \cos(\phi) + C$$

where A, B, and C are empirical parameters, relates the proton-proton couplings in three consecutive bonds to their dihedral angles (ϕ), which thus provides an efficient way to evaluate geometries by NMR, even if Karplus himself likes to recall its limitation.² This equation is nevertheless of paramount importance in determining the structure of organic molecules.

In 1960, after five years in Illinois, he accepted a professor position at Columbia University with the tempting opportunity to pursue research at the IBM Watson Laboratory and thus take advantage of the powerful computer resources of this period such as the IBM 650. It is here that he developed his interest in the kinetics of chemical reactions. Indeed, the IBM 650 allowed him to perform the many numerical analyses of the trajectories of the simplest chemical reactive system:

a system of three atoms and three electrons where an isolated hydrogen atom is exchanged with another one of the molecule.

In 1965, a new step for this pilgrim of the temples of science and a new home at Harvard; Karplus succeeded R. Bright Wilson as the Theodore William Richards chair, who in 1914 was the first American to win the Nobel Prize in Chemistry “in recognition of his accurate determinations of the atomic weight of a large number of chemical elements.”

This was the time to gradually turn to systems that play an important role in the living world; Karplus developed the methods and algorithms for which he was awarded the 2013 Nobel Prize. A sabbatical leave at the Weizmann Institute in 1970 gave him the opportunity to meet Ariel Warshel who followed to Harvard. The two researchers would then combine their expertise—quantum mechanics for Karplus, and classical mechanics for Warshel—to study a planar molecule, 1,6-diphenyl-1,3,5-hexatriene.³ In this paper, the π electrons of the molecule are treated quantum mechanically by the PPP (Pariser-Parr-Pople) method, while the σ electrons are considered as classical objects. It is the first model to combine quantum and classical mechanics.

It is interesting to note that the first option cho-

sen for the name of this original software had been HARMM (for HARvard Macromolecular Mechanics), but was inevitably softened to CHARMM (Chemistry at HARvard Macomolecular Mechanics).

His work on retinal will point out the difficulty of publishing theoretical results applied to biology, a problem that remains today: if the theory is in accordance with the experimental facts, it is not interesting since the results are already known; conversely, if the theoretical result is a prediction that has not yet been experimentally verified, it will be considered unpublishable since there is no indication that the prediction is correct.

It was then that Karplus' interest for hemoglobin would grow. Research on hemoglobin is a source of Nobel Prizes: in 1965, it was the proposal of the phenomenological model of allosteric control by Monod,⁴ Wyman and Changeux; in 1971, Perutz,⁵ already Nobel Laureate, published the X-ray structure of deoxyhemoglobin. Karplus approached the subject by extending the statistical methods that he was developing at that time.⁶

In 1977, Karplus was the first, with Andrew McCammon and Bruce Gelin, to publish a simulation of a protein (BPTI, Bovine Pancreatic Trypsin Inhibitor) by molecular dynamics, a paper that will serve as a reference test.⁷ These calculations were made in 1976 at the European Centre of Atomic and Molecular Computation (CECAM), established on the Orsay campus (Parix XI) and founded by the late Carl Moser.⁸

In 1996, pushed by Jean-Marie Lehn, the 1987 Nobel Prize in Chemistry winner with Donald Cram and Charles Pedersen “for their development and use of molecules with structure-specific interactions of high selectivity,” Karplus also accepted a professorship at the University of Strasbourg. For thirty years, he had spent his summer holidays near Lake Annecy.

Arieh Warshel

Ten years younger than Karplus, Arieh Warshel was born in 1940 on an Israeli kibbutz. Like many of his age, he was involved in the Six-Day War, Israel's war against Egypt, Jordan and Syria in 1967, and in the Yom Kippur War, the war waged in 1973 by Egypt and Syria against Israel, on the holiest day of the year for the Jewish people. After his degree in chemistry from the Technion in Haifa in

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1966, he received his PhD at the Weizmann Institute in Rehovot under the direction of Shneior Lifson. For him, molecules are just atoms with chemical bonds that he conventionally treats as a set of balls connected together by springs. At the Weizmann Institute, he met Levitt who was there for a visiting stay during the summer. Levitt being very familiar with scientific programming, they encoded the classical model of molecules in a way that allowed them to study proteins such as myoglobin or lysozyme.⁹ The meeting with Karplus led Warshel to Harvard where their common expertise resulted in the birth of CHARMM. Since 1972, Warshel has spent his time between Cambridge (UK) and the Weizmann Institute. The collaboration between Levitt and Warshel has been highly successful as together they developed the capabilities of the QM/MM approach (QM for Quantum Mechanics, MM for Molecular Mechanics) to study large molecular systems. To test the QM/MM feasibility, they applied it to the refolding of the Bovine Pancreatic Trypsin Inhibitor (BPTI).¹⁰ The duo is recognized for the QM/MM reference paper, i.e., their study of the formation of a carbonium ion in the active site of lysozyme.¹¹ It was in 1976 that Warshel finally emigrated to the University of Southern California (USC) Dornsife.

Michael Levitt

Michael Levitt is the youngest of the three awardees. His essential contributions to the 2013 Nobel Prize in Chemistry are noted in the above sections devoted to his co-winners, a beautiful example of creative synergy. Levitt was born in Pretoria in 1947 into a Jewish family of Lithuanian origin. He left South Africa and pursued his Bachelor of Science degree in Physics at King's College London, 1967. In 1972, he obtained his PhD at Cambridge.

Since 1968, he had been going to Israel where, like Ariel Warshel, he served in the armed forces. He made his Aliya, the act of immigration to the Holy Land by a Jew. It was also the chance to participate in an exchange program at the Weizmann Institute where the links were naturally established with Arie Warshel and Martin Karplus. It was with Warshel that Levitt developed the possibilities for the QM/MM approach to treat large molecular systems. He is known for the Jack-Levitt method that allows one to refine macromolecular structures by combining the computational approach with the direct methods of X-ray diffraction.¹²

A visiting professor at the Weizmann from 1980 to 1987, he moved to the Faculty of Medicine at Stanford University. Now, he divides his time between California and Israel. After the protein field, his interest turned to the nucleic acids. He is the first to simulate DNA in vacuo and in solution by molecular dynamics.¹³ Levitt married an Israeli sculptor and has an Israeli passport as well as his American and British passports.

The Work Awarded

The subtitle given to our paper—**The Alliance of Newton's Apple and Schrödinger's Cat**—indicates that this Nobel Prize is awarded to research that has succeeded in reconciling two very different approaches.

In chemistry, physics, or biology, chemical bonds involve particles with very low mass like protons, neutrons, and electrons. At the end of the nineteenth century, the shortcomings of classical Newtonian mechanics were becoming known. They appear if the system studied contains particles of low mass or particles moving at high speed. The very existence of these materials was difficult to understand. For example, according to the laws of electric attraction, the hydrogen atom consisting of two particles, one of positive charge and the other of negative charge, could not exist except if both particles are stuck together.

The necessary corrections to the understanding of modern phenomena were made by Einstein and his relativistic mechanics, and by the quantum mechanics of Schrödinger, Heisenberg, and the relativistic quantum mechanics of Dirac.

Two parameters allow an easy classification of these mechanics:

It is the velocity that is the important parameter for relativistic phenomena which concern us less here, even if they are essential to explaining some experimental facts such as the color of gold or the liquid state of mercury at room temperature. Either the velocity is very high (i.e., above a hundredth of the speed of light ($\approx 3.10^8 \text{ ms}^{-1}$)) or it is low (the velocity that can be reached by a macroscopic mobile, a man, a car, a plane, etc.).

The other parameter, the mass, is either macroscopic i.e., observable by traditional gravimetry (a lump of sugar, a car, an airplane, a satellite) or microscopic like the masses of subatomic particles i.e., the electron ($9.1 \times 10^{-31} \text{ kg}$), the proton or neutron ($\sim 1.67 \times 10^{-27} \text{ kg}$).

These two parameters define a table with four entries that specify the application area of the four mechanics:

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	Macroscopic masses	Microscopic masses
Slow velocity	Classical mechanics <i>Newton</i>	Quantum mechanics <i>Schrödinger, Heisenberg</i>
Rapid velocity	Relativistic mechanics <i>Einstein</i>	Relativistic quantum mechanics <i>Dirac</i>

Classical mechanics describes macroscopic objects that evolve at normal speeds. Relativistic mechanics applies to macroscopic objects imbued with a speed close to that of light. Quantum mechanics applies to elementary particles driven by a reasonable speed and it introduces the quantization of energy. While in classical mechanics, all energies are possible, in quantum mechanics, only certain energies are possible. We say that the quantum energy line spectrum is discrete while spectra are continuous in classical mechanics.

Furthermore, in classical mechanics, a system is completely determined if we know at every moment, the position and the momentum of each particle. This determinism allows us to observe in time the evolution of each component of the system and to determine its trajectory. The Heisenberg uncertainty principle is opposed to this understanding. For Heisenberg, if the position of a particle is perfectly known, we cannot specify its momentum and vice versa.

This is where the bottleneck of quantum mechanics lies. In fact, quantum mechanics replaces the notion of trajectory with that of a wave function. In its first premise, it states that although the wave function of an electron (the so-called orbital) can be used to calculate a physical property of the electron, the wave function itself has no physical meaning, but that its square corresponds to a particle density (electronic density for the electrons):

$$\rho(r) = \phi^2(r)$$

In practice, this orbital is developed into n basis functions and the computational requirement is already proportional to n^2 . The real bottleneck is that all electrons interact and that one should thus calculate repulsion terms between electron densities of the type:

$$\iint dv_1 dv_2 \frac{\rho_i(r_1)\rho_j(r_2)}{r_{12}} = \iint dv_1 dv_2 \frac{\phi_i^2(r_1)\phi_j^2(r_2)}{r_{12}}$$

whose the number increases as n^4 , which makes impossible the application to large biological systems even with the most powerful computers. Note incidentally that this proportionality happens for the simplest methods (Hartree-Fock, Density Functional Theory, DFT). More complex processes will show dependency

with respect to the number of basis functions of the order of n^7 or n^8 .

Some approximations are thus needed. The first, proposed by Born and Oppenheimer, separates the electrons and nuclei motions, because of their large mass difference ($m_H^+/m_e^- = 1836$ in the worst case, that of the atom hydrogen). Considering the nuclear mass as infinite, the approximation removes the quantification of the nuclear motions and introduces the "classical" concept of potential energy surfaces (PES). It then solves the motion of the electrons in the potential of the nuclei. The fundamental difficulty of the n^4 dependence remains. Yet it is in this type of methodology that, at the beginning of his career, Karplus studied his models of hydrogen bonding (HFH⁺) and chemical reaction ($H_2 + H$).

It is striking to recall the limitations of the computers in this period of development of quantum chemistry. Thus, in 1969, the year of the first moon landing driven by an IBM 360/91, the most powerful computer of that time, an equivalent machine that was used at IBM Research Laboratory, where Enrico Clementi developed the IBMOL ab initio program, had the following characteristics: CPU cycle time, 60 ns; memory cycle time, 780 ns; main memory, 2097152 bytes; disk storage, 360 Mbytes.

Yet it is in these primitive computational conditions that were developed the ab initio pioneering programs IBMOL, POLYATOM, GAUSSIAN that are still the basis of current software.

But the large biological systems were out of reach

$$\begin{aligned}
 U = & \sum_{\text{Bonds}} \frac{1}{2} K_b (b - b_0)^2 + \sum_{\text{Angles}} \frac{1}{2} K_\theta (\theta - \theta_0)^2 \\
 & + \sum_{\text{Torsion Angles}} K_\phi [1 - \cos(n\phi + \delta)] \\
 & + \sum_{\text{Nonbonded Pairs}} \epsilon \left[\left(\frac{r_0}{r} \right)^{12} - 2 \left(\frac{r_0}{r} \right)^6 \right] \\
 & + \sum_{\text{Partial Charges}} 332 \frac{q_i q_j}{r}
 \end{aligned}$$

Fig. 1: The total potential energy of any molecule is the sum of simple allowing for bond stretching, bond angle bending, bond twisting, van der Waals interactions and electrostatics.

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for these methods, and more reliable approximations had to be made. The most drastic, molecular mechanics (MM), models the surface elements of Born and Oppenheimer. The main potentials of the MM are described in Figure 1.¹⁴

The brilliant idea of Karplus, Warshell and Levitt was to design a hybrid model that combines the accuracy of quantum mechanics with the speed made possible by the simple classical potentials of molecular mechanics; it is the QM/MM method. This QM/MM technique partitions the system into three regions. As shown in Figure 2,¹⁵ the inner region is the one we want to study more precisely; it is the main site, the active site which is treated rigorously by quantum methods (QM region). The main site is subject to interactions with the groups of the neighboring region analyzed by classical mechanics (MM region). The challenge here was to well define how this “classical” region interacts with the “quantum” one. Finally, at a greater distance, the molecular medium is simulated by its dielectric constant.

Fig. 2: Multi-copper-oxidase embedded in water.¹⁵

In their work on BPTI¹⁰, Levitt and Warshel go even further; as illustrated in Figure 3,¹⁶ they showed that it is possible to get a considerable gain in computation time when they merge several atoms of a chemical group of the second region in a kind of pseudoatom.

Fig. 3: 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.¹⁶

Furthermore, even if they are powerful, these “static” methods are still unable to study dynamic phenomena as enzymatic reactions or conformational changes in proteins.

Such events set off from a reagent or a starting geometry to get to a reaction product or a different conformation. But if a cycling race sets off from Milano to get to San Remo by a well-marked and controlled way, the chemical species will explore all the energy space between the points of departure and arrival. The molecules do not hesitate to climb the sides of the energy mountains and sometimes, enjoying the subtleties of their quantum nature, they are able to follow paths which are rejected by common sense. Our mind were forged by equilibrium thermodynamics, but a chemical reaction is necessarily a dynamic non-equilibrium process that can exhibit rather unexpected behaviors.

As well summarized by Warshel, “an enzyme makes chemical reactions very fast. So when you know the structure of the protein, we still must know what about it makes it work so fast. One may look at a clock and see that it looks nice but that person will still not know how the clock works. You cannot figure it out experimentally because you cannot send tiny people inside to explore. At present, people don’t know how to do this. Thus we must do it by computer. So what we’ve done in the past 50 years is build models that allow us to put all of these atoms together on the computer and then to simulate how they do what they do and to understand what is responsible for each action. This field has many names, but can be classified as computer simulation of biological functions, part of computational biophysics.”¹⁷

The 2013 Nobel Prize in Chemistry rewards a kind of theoretical Varilux glass or progressive lens; we can clearly see the part of the system that is focused. That part remains influenced by its environment, but appears hazier to our eyes. If you want to see more clearly, you have to change the focus.

Let us refrain from thinking that today the computer is capable of replacing the test tube or that theory can do without the experiment. The development of the multiscale approach by Karplus, Warshel and Levitt shows, on the contrary, a close interaction to define the necessary parameters and continually refine them by the fundamental confrontation in science between theory and experiment.

The methodological approach rewarded today shows its power in different fields. Molecular biology is one of the favorite fields. Levitt even mentions the possibility of simulating a living being! The pharma-

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ceutical industry is putting a lot of effort today into computer modeling. New materials with specific properties with high added value (for instance, solar cells, LEDs, chemical or biological sensors) identify another privileged field for multiscale theoretical predictions. Catalysis and, more generally, all the petrochemical industries are major consumers of case studies that allow them to dominate the rate of chemical reactions. Computers and theoretical modeling are no longer the poor relations to sciences, purely experimental at their beginning as chemistry or biology. Today they help to find solutions to previously intractable problems.

Epilogue

This Nobel is directly in line with that of Pople and Kohn in 1998, themselves being the ones rewarded among many pioneers such as R. Parr, E. Clementi, I.G. Csizmadia, W. Hehre, R. Ahlrichs, B. Roos (†) and many others. Many researchers have contributed to the work outlined by the 2013 Nobel Prize in Chemistry. The rule is strict and the Nobel regulations limit the number of winners to three, but we cannot ignore other key figures in the field, such as S. Lifson (†), F. H. Westheimer (†), N.L. Allinger, H. Scheraga, J. Gao, P. Kollman (†), K. Morokuma, W. van Gunsteren, and W. Thiel.

The 2013 Nobel Prize rewards an association of ideas that will lead to computer programs that become essential tools in the life of any laboratory in the same way as spectrometers. But let's not close our eyes. To properly use these packages, which have increasingly become real black boxes, the full expertise and intuition of the researcher remain necessary to design the experiment, i.e., the correct simulation which will give the adequate answer to the problem.

Leave the last word to Richard Feynman in his famous Lectures on Physics:¹⁸ "Certainly no subject or field is making more progress on so many fronts at the present moment, than biology, and if we were to name the most powerful assumption of all, which leads one on and on in an attempt to understand life, it is that all things are made of atoms, and that everything that living things do can be understood in terms of the jiggings and wiggings of atoms."

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