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Computer modellers secure chemistry Nobels

Researchers honoured for work that led to software simulations of complex biomolecules.

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The 2013 Nobel Prize in Chemistry laureates (left to right), Martin Karplus, Michael Levitt and Arieh Warshel.

Computers may one day be able to simulate exactly how enzymes, ion channels, viruses, DNA and other complex biological molecules react with each other inside a cell. And if such a software package is ever written, it will owe its development to three researchers who today won the Nobel Prize in Chemistry: Martin Karplus, of Harvard University in Cambridge, Massachusetts and the University of Strasbourg in France; Michael Levitt, of Stanford University in California; and Arieh Warshel, of the University of Southern California in Los Angeles.

Starting in the 1970s — working with computers far less powerful than today's smartphones — the three theorists made advances in computer modelling that laid the foundations for modern software used to simulate protein folding, design drugs and artificial enzymes, and understand the workings of complex catalysts.

In essence, says Sven Lidin, the chairman of the Nobel committee, they "took the chemical experiment to cyberspace". Although the researchers are not the only people to have developed simulations in this way, "they are undoubtedly three worthy winners", says Jonathan Goodman, a computational chemist at the University of Cambridge, UK.

Apart from puny computer power, the problems Levitt, Warshel and Karplus faced 40 years ago are still recognizable today. Computer programs simulate the atoms and bonds of large biomolecules as if they were balls connected by springs, obeying Newton's classical laws of motion. The springs can stretch and squeeze, so molecules can change shape. But in these simulations, bonds cannot actually break, so reactions cannot take place.

To simulate reactions in which bonds break and form over time, programmers need to model what is happening to electrons as they flit around molecules. But this is difficult, as it involves writing code to approximate the quantum mechanical equations that describe the electrons' motion, and even today's supercomputers rapidly run out of power as molecules get past a few hundred atoms. "The computer power to solve large systems using quantum mechanics isn't available, and won't be in the foreseeable future," says Goodman.

What Karplus, Levitt and Warshel realized was that to simulate how large biomolecules such as proteins wriggle and interact, most of the protein should be modelled as a 'ball-on-spring' system, but then quantum mechanics should be used to describe the parts where reactions happened — for example, the active site of an enzyme. "It's easy to say that — but how do you join the quantum part and the classical part together? How do the two scales interact?" says Goodman.

It was for developing these 'multiscale models' that the laureates — who have done other theoretical work — were honoured today. The approach "has become such a ubiquitous tool that everyone uses it, without even thinking about where it came from", says Lynn

Kamerlin, a structural biologist who was a postdoctoral researcher in Warshel's laboratory and is now at Uppsala University in Sweden.

Working with Karplus on a visit to Harvard, Warshel started with a computer program that modelled electrons buzzing around flat ring-like molecules[1]. In 1975, Levitt and Warshel announced the first simulation of protein folding[2]. The next year, the two showed how it was possible to simulate how the enzyme lysozyme cuts apart sugar-based chains[3]. This set in motion a chain of other models and applied work.

Karplus went on to develop the widely used CHARMM (Chemistry at Harvard Macromolecular Mechanics) program, still used to simulate the motion of molecules today.

As a result of the laureates' work, researchers are able to simulate increasingly complex molecules — for example, designing from scratch proteins that fold into conformations predicted by computers[4].

“The scope of the biological problems that computational chemistry can address today is completely mindblowing,” says Kamerlin. “But none of it would be possible without the Nobel work.”

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References

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