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Model predicts structure of crystals

"One of the continuing scandals in the physical sciences is that it remains impossible to predict the structure of even the simplest crystalline solids from their chemical composition." So wrote the chemist and former *Nature* editor John Maddox in 1988 (see *Nature* 335, 201), who was bemoaning the lack of a computational method to predict how molecules will arrange themselves in the solid state.

At present, chemists use X-ray crystallography to determine how atoms are arranged in a molecule and how molecules pack into a crystal. It is a time-consuming method that has remained practically unchanged for almost a century, and it means that experimentalists need to produce a high-quality crystal. Software that could predict the three-dimensional structure of compounds could allow the properties of materials, or potential drug candidates, to be examined and the different possible molecular configurations to be screened in advance, before they are made experimentally.

The problem has been attacked head-on by the Cambridge Crystallographic Data Centre (CCDC) in Britain. Every three years since 1999, the centre has set a challenge for software developers to predict the structure of four molecules, the structure of which was known only to the CCDC. But nobody had been able to predict the correct structures of all four molecules.

This year saw a breakthrough. A team consisting of Frank Leusen and John Kendrick of the University of Bradford, UK, and Marcus Neumann of Avant-garde Materials Simulation in Saint-Germain-en-Laye, France, correctly predicted the structure of all four molecules. "We have made a big step forward," says Leusen.

The 15 teams performing this year's test were each given a sketch of four molecules that showed all the atoms present and some details about how they were crystallized. These were all unpublished small organic molecules, of between 8 and 33 atoms. From this starting point, the teams ran calculations about the possible positions of the atoms and molecules within a crystal.

In most branches of chemistry, it is not enough to know a molecule's formula. For

Chemists have to use time-consuming experimental processes to determine the atomic structure of a crystal.

instance, to predict a compound's solubility, colour or how it will be taken up by the body, chemists need to know how the molecules align in a crystal. Even the smallest compound may have hundreds of thousands of possible arrangements of its molecules in a solid crystal. The structure depends on the energies of the atoms both within and between the molecules; and also on the relative positions of the atoms and molecules. The structure that scientists try to predict is the one with the lowest value for these energies: the most stable configuration. "Modelling the growth of a crystal is a daunting thing," says the CCDC's Graeme Day. "The main problem is when the molecule has options for its own shape as well as for how it packs."

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Finding the most stable structure is especially important in the pharmaceutical industry. If one crystal arrangement, or polymorph, is overlooked, and it happens to be more soluble than the others, then a patient could end up taking a greater dose of a drug than is needed. And because patents are granted for a specific polymorph, companies risk being gazumped

if they don't know the entire range possible.

The winning predictive method used a new approach. "We took a route that is different from everyone else," says Neumann, who wrote the program that the team used. The team added a quantum mechanical round of calculations in between two sets of the more usual classical simulations. The first molecular-mechanics step screens the possible energies of the crystals and ranks them in order of stability. The new step then calculates a force field of the bond energies for the most stable configurations, which helps to whittle down the original list of possible structure candidates to the most likely 100 or so. "Now we can do this additional refinement that re-ranks the structures," says Leusen. Finally, this re-ranked list goes through another round of molecular-mechanical calculations based on the lattice energy and stability of the molecule.

Flexible functions

And the system worked, even for the trickiest test. Day had thrown into the test a co-crystal of two molecules, as well as a compound that was long and floppy. "In the first three tests we had no successes for flexible compounds," says Day. But in this year's test, three teams got it right.

"This is very welcome news," says David Baker, at the University of Washington in Seattle, who works on predicting the structure of proteins. But he cautions that the technique isn't necessarily applicable to larger molecules such as proteins because of the computing power needed to perform quantum calculations on large systems. Even very small proteins have hundreds of atoms — insulin, for instance, has nearly 800. And the largest proteins can have hundreds of thousands of atoms.

Neumann says that at the moment their technique will work for only 5% of the molecules that are useful for the pharmaceutical industry. The next goal is use the structure to accurately predict a crystal's properties, he says.

Maddox greeted the achievement with enthusiasm. The problem of structure prediction "stuck out like a sore thumb" 20 years ago, he says. But he isn't surprised that it has taken so long to crack. "Science doesn't necessarily move at the speed of jets."

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