Researchers have used computers to tackle one of chemistry's greatest challenges

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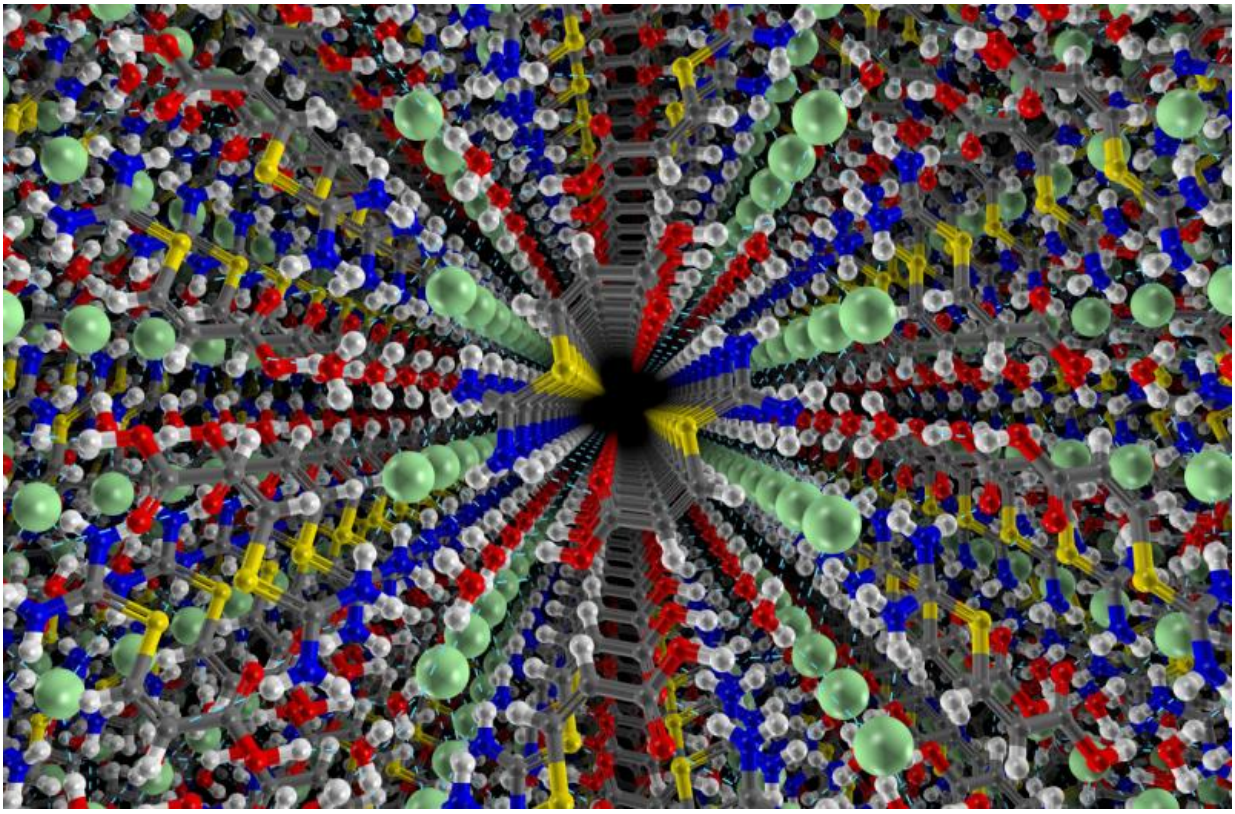

Crystal structure of the hydrated Chloride salt. Drs Neumann, Kendrick and Leusen were the only participants in the blind test to predict this challenging structure. Credit: University of Bradford

Researchers from the University of Bradford have joined forces with German high-tech company, Avant-garde Materials Simulation, to

successfully predict the crystal structures of small organic molecules by computational methods without experimental input.

These findings were revealed in the 6th blind test of crystal structure prediction, an exercise conducted by twenty five international research groups that was organised by the Cambridge Crystallographic Data Centre (CCDC).

Crystal structures describe the periodically repeating arrangement of molecules in a material and determine many of a material's properties, such as solubility, dissolution rate, hardness, colour and external shape. The ability to predict crystal structures could therefore enable the design of materials with superior properties, for example the creation of brighter pigments, more effective pharmaceuticals, or even lower calorie foodstuff.

In particular, the pharmaceutical industry would gain huge benefit from being able to reliably predict crystal structure because pharmaceutical molecules are prone to crystallise in more than one crystal structure (or polymorph), depending on the conditions under which the molecule is crystallised. The specific polymorph that goes into a formulation must be strictly controlled to ensure consistency of delivery to the patient. The ability to predict crystal structures could save pharmaceutical companies time and money by being able to quickly identify and develop polymorphs with superior properties. It would also help pharmaceutical companies with patent protection and product life cycle management.

Different approaches to the problem have been developed and these have been evaluated over the years in international exercises, known as the blind tests of crystal structure prediction. Twenty five research groups who have been developing methods for predicting crystal structures of organic molecules took part in the latest test. In this test participants were challenged to predict nine recently determined crystal

structures of five target compounds given only the chemical diagram of the molecules and conditions of crystallisation, with two sets of predictions allowed per target compound.

Only one group managed to predict nearly all targets correctly. These very successful results were obtained by Dr Marcus Neumann of Avant-garde Materials Simulation and Prof Frank Leusen and Dr John Kendrick of the University of Bradford.

Dr Marcus Neumann, author of the computer program GRACE for crystal structure prediction, which predicted eight out of nine targets correctly in this blind test and eight out of ten targets in the previous two blind tests, said: "Obviously, we are delighted with these results, in particular because unlike in earlier blind tests they have been obtained by a fully automated procedure that can be used as a black box in industrial working environments."

Dr Frank Leusen, Professor of Computational Chemistry, University of Bradford, said: "I am particularly impressed that GRACE correctly predicted the crystal structure of a hydrated chloride salt, which poses a real challenge both in terms of the size of the search problem and in terms of the required accuracy. This result will be of particular interest to the pharmaceutical industry as they often deal with this type of compound."

Dr John Kendrick, University of Bradford, added: "Recent developments within the Grace package meant that the process of predicting the crystal structures in the Blind Test was nearly automatic, very little intervention was required from the user."

Although the whole problem is not solved - the predictions cannot yet explain the influence of solvent, impurities, additives or temperature on the outcome of a crystallisation experiment - these recent results

demonstrate significant capabilities in the field.

Further Information

The results of previous blind tests, in 1999, 2001, 2004, 2007 and 2010, demonstrated that the crystal structures of small organic molecules can be predicted under favourable conditions. Success rates were low in the first three blind tests, but the fourth blind test in 2007 saw a major breakthrough with one group predicting all four target crystal structures, each as their most likely prediction. This was achieved by the same group of Drs. Neumann, Kendrick and Leusen who collaborated to predict eight out of nine targets in the latest blind test. The target compounds in the fifth blind test in 2010 became significantly more complex, but the success rate remained high, with particularly good results for a large flexible molecule which could be regarded as a prototype pharmaceutical compound.

In the current, sixth, blind test, there were five targets, including a small semi-rigid molecule, a medium sized flexible molecule with five known polymorphs, a hydrated Chloride salt, a co-crystal and a large flexible molecule.

The results were discussed at the Blind Test workshop on 27 and 28 October 2015 at the Cambridge Crystallographic Data Centre and featured in the journal *Nature*.

Provided by University of Bradford