Avant-garde Materials Simulation SARL, 30b, rue du vieil Abreuvoir, St-Germain-en-Laye, Ile-de-France, 78100, France, E-mail：marcus.neumann@avmatsim.eu

A comprehensive computational strategy for the prediction of crystal structures is presented that has scored an unprecedented 4 in 4 success rate at the 2007 CCDC blind test on crystal structure prediction [1]. Key components of the new approach, implemented in the GRACE software package, are a hybrid method for the accurate calculation of lattice energies, a robust procedure for the parameterization of tailor-made force fields and a novel approach for crystal structure generation. The hybrid method combines DFT calculations by means of the VASP program with an empirical van der Waals correction. It is used for the final lattice energy ranking and acts as a reference standard for force field parameterization. A tailor-made force field is derived for each molecule to be considered and used for crystal structure generation as well as for the preparation of second derivative matrices for the final lattice energy optimization with the hybrid method. Based on the known statistical deviation between the tailor-made force field and the hybrid method, a shortlist of crystal structures from a small energy window is selected for the final lattice energy optimization and ranking. In addition to the blind test results, validation studies for 15 organic molecules are presented, including ethane, ethylene, acetylene, methanol, urea, acetic acid, cyclohexane-1,4-dione, paracetamol, CCDC blind test molecules I to VI and a pharmaceutical compound for which crystal structures have been predicted in a blind test fashion. 17 out of the 18 experimentally observed crystal forms of these molecules are found among the first two most stable predicted crystal structures.
[1] Neumann, M. A., Leusen, F. J. J., Kendrick, J., Angew. Chem. Int. Ed, 2008, 47, 2427-2430

Keywords: crystal structure prediction, computer modelling solids, polymorphism

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Structure prediction of flexible small molecules - A case study

Daniel M. Toebbens, Doris Braun, Volker Kahlenberg
University of Innsbruck, Institute of Mineralogy and Petrography, Innrain 52, Innsbruck, Tirole, A-6020, Austria, E-mail：daniel.toebbens@uibk.ac.at

Predicting the crystal structures of small molecules from energy calculations is of considerable interest for a number of scientific and industrial purposes. However, in the field of polymorph-forming pharmaceuticals two main problems arise. One is the high degree of internal flexibility of many of the molecules of interest and the consequential large number of possible conformations. The resulting multitude of packing possibilities can overwhelm even fast computers. The other problem is that many of these structures have similar energies. Exact energy modeling is thus necessary to identify the real structures. We checked possible strategies using aripripazole as a test case. For this compound, a number of polymorphs and various solvates are known, as are their respective crystal structures. By comparing the experimental structures with the calculations on all stages, a number of helpful results were established: 1) Quantum-mechanical (QM) energy calculations on the isolated molecule reduce the number of possible conformations drastically. For aripripazole, seven torsional degrees of freedom allow 2916 minimum conformations. Of these, only 296 remain, once correlation of neighboring torsions is considered. Further reduction is possible, if the influence of hydrogen bonds is considered. 2) The molecule has five potential hydrogen bond acceptor sites, but QM calculations reveal that only one of these is realizable. The corresponding hydrogen bonds are realized in all experimental structures. 3) The experimental structures account for all the lowest energies found. Thus, any problem in finding the correct structures is not due to the energy model, but is a matter of the search algorithm and processor time. The treatment of the hydrogen bonds was found to be crucial in this.

Keywords: structural prediction, pharmaceutical organic molecules, energy calculations

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Increasing the effectiveness of evolutionary crystal structure prediction using fingerprint-function

Andriy O. Lyakhov[1], Artem Oganov[1], Mario Valle[2]
[1]Swiss Federal Institute of Technology Zurich (ETHZ), Department of Materials, HCI G 512, Wolfgang-Pauli-Str. 10, Zurich, Zurich, 8093, Switzerland, [2]Swiss National Supercomputing Centre (CSCS), Manno, Switzerland, E-mail：andriy.lyakhov@mat.ethz.ch

Evolutionary algorithm approach to crystal structure prediction problems has proven its effectiveness in various applications. Algorithm USPEX (Universal Structure Predictor: Evolutionary Xtallography) allows one to predict the most stable crystal structure for a given compound without requiring any experimental input. This is especially attractive for simulation of materials under extreme conditions. However, the inability to determine the degree of similarity between different structures limits the effectiveness of the algorithm and increases the probability of trapping in a particular basin of the energy surface. To solve this problem we derived a family of specially constructed fingerprint-functions. Fingerprint-function is a function, that is independent of lattice vectors choice and uniquely determines the structure of the crystal. Another important property of these functions is that the degree of correlation between functions calculated for two structures can be used as a good measure for degree of similarity between those structures. We have shown, that after modifying selection and variation operators with the help of fingerprint-functions, the effectiveness of USPEX algorithm was increased. This method also simplifies the search for metastable states by evolutionary algorithms.

Keywords: crystal structure prediction, *ab-initio structure* determination, computer algorithms

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Inverse multislice calculations: A new method for solving complex structures

Helen ML Faulkner
Monash University, Physics, Faculty of Science, Building 19,, Clayton, Victoria, 3800, Australia, E-mail：helen.faulkner@sci.monash.edu.au

The multislice approach has been used for 50 years to find the result of a wave passing through a thick sample. One problem with multislice is that it is difficult to reverse the calculation and find the structure of a sample given measurements of the exit wave. This limits the use of multislice techniques in experimental microscopy, as in general the sample structure is unknown and the aim is to find it. Iterative algorithms for microscopy have been studied since the

1970s. In recent years significant results have been achieved with their use. However iterative algorithms to date can only retrieve the complex transmission function of a thin sample. Thicker samples, where dynamical diffraction and propagation are important, can not be examined with these techniques. A recent innovation combines the ptychographical iterative engine technique of phase retrieval, with the multislice method. The result is an iterative approach that uses measured intensities of the exit wave to find the transmission functions of the slices that represent the sample structure. This generalisation of the iterative technique allows the retrieval of depth information in the sample. Much thicker structures can be analysed than was previously possible with such approaches. It is potentially possible to use the technique to solve a structure that is periodic or aperiodic in any direction. The technique is experimentally simple, requiring only a series of intensities recorded at different positions of the incident beam plus known information about that beam. The applications of this approach include any experimental situation where intensities can be measured and a thick, periodic or aperiodic sample is analysed. This includes a huge number of possibilities in crystallography and many other fields.

Keywords: inverse problem, computational methods, structure determination

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Rapid and routine determination of hydrogen positions in inorganic and organometallic compounds

Valeska P Ting[1], Mark T Weller[1], Chick C Wilson[2], Paul F Henry[3]
[1]School of Chemistry, University of Southampton, Southampton, SOUTHAMPTON, SO17 1BJ, UK, [2]Department of Chemistry, University of Glasgow, Glasgow, G12 8QQ, UK, [3]Institut Laue-Langevin, 6 Rue Jules Horowitz, BP156 38042, Grenoble CEDEX 9, France, E-mail：V.P.Ting@soton.ac.uk

Hydrogen is a fundamentally important element in many key areas of inorganic materials design, including development of technological materials (e.g. hydrogen storage media and proton-conductor fuel cell components), functional framework materials (e.g. zeolites), catalysts, organometallic co-ordination complexes and inorganic hydrates. Due to weak X-ray scattering by light elements, and hydrogen's large incoherent neutron background, determination of hydrogen positions in inorganic materials traditionally necessitates costly sample deuteration or painstaking synthesis of large single crystals for neutron diffraction. This limitation is now being addressed via development of experimental and data refinement methodologies utilising high flux neutron powder diffractometers such as D20 at ILL. We present a selection of results demonstrating application of this new methodology to technologically important inorganic material systems with significant hydrogen content. These include in-situ studies of functional zeolites (e.g. industrial catalysts ZSM-5 and mordenite, having adsorbed hydrogenous molecules) and metal ammoniates such as $Ni(NH_3)_6Cl_2$ (candidate hydrogen storage materials). Further examples include organometallic compounds such as Zeise's salt and complexes requiring exact determination of hydrogen position (e.g. those with potential agostic hydrogens). The full structures of some heavy metal salt hydrates are also presented, confirming that hydrogen positions can be accurately determined alongside metals as heavy as uranium and bismuth. As well as highlighting the applicability and potential impact of these new methods, this work is aimed at establishing these methodologies as a valuable tool for routine study of hydrogenous materials across all inorganic fields.

Keywords: characterization methods, hydrogen, neutron and X-ray diffractometry

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Development of polarizable force field for the prediction of molecular crystal structures

Naofumi Nakayama[1], Shigeaki Obata[2], Kazuo Ohta[1], Hitoshi Goto[1,2]
[1]Conflex corporation, 2-15-19, Kami-Osaki,, Shinagawa-ku, Tokyo, 141-0021, Japan, [2]Laboratory of Computational Chemistry, Department of Knowledge-based Information Engineering, Toyohashi University of Technology, 1-1 Hibarigaoka, Tempaku-cho, Toyohashi, Aichi 441-8580, Japan, E-mail：nakayama@cochem2.tutkie.tut.ac.jp

Prediction of crystal structures for organic molecules has great importance in many industries like pharmaceuticals, pigments, dyes, and so forth, because many of the macroscopic properties of their products are highly dependent on their crystal structures. The accuracies of predictions for lattice constants and molecular geometries in crystal depend on the performance of intermolecular potential which is normally described as the electrostatic and van der Waals terms in empirical force fields. Although electrostatic parameters of partial atomic charges are generally unchanged in a potential energy calculation during geometry optimization and dynamics simulation, the charge distribution of a molecule should vary depending on conformational transformations and induced interactions with other molecules. To estimate the charge distribution according to their changes, the charge equilibration (QEq) approach [1] is proposed and can provide appropriate partial atomic charges for sufficient representation of the electrostatic interactions. Recently, we proposed new framework of QEq, named NQEq [2], that the empirical formula of Coulomb interaction is employed and that the parameter set is divided into each atom types based on Merck Molecular Force Field (MMFF) [3]. In this presentation, we introduce our extension of NQEq to molecular crystal calculations. This attempt can be obtained the appropriate charge distributions polarized by periodic environment. We will also show the results of lattice constants optimization for some organic molecular crystals using its NQEq and MMFF.

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Keywords: force field development, application development, intermolecular interactions

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Drug virtual screen by GA/GP: Docking studies with tubulin inhibitors as anticancer agents

Kuo-Long Lou, Po-Tsang Huang
National Taiwan University/College of Medicine, Biochemistry/Oral Biology, #1, Chang-Te Street, Taipei, Taiwan, 10042, Taiwan, E-mail：kllou@ntu.edu.tw

It is expected to shorten the required research time spent in the early stage of development of drug design through computer calculation. Computer Aided Drug Design is one of the most powerful concepts applied to satisfy such demand. Upon docking simulations, it is allowed to find out the binding sites and orientations between target