

MS62 ADVANCES IN COMPUTATIONAL METHODS FOR PROTEIN CRYSTALLOGRAPHY**Chairpersons:** Piet Gros, Kevin D. Cowtan**MS62.28.1***Acta Cryst.* (2005). **A61**, C81**New Likelihood-based Phasing Methods in Phaser****Randy J. Read**, Airlie J. McCoy, Laurent C. Storoni, *Department of Haematology, University of Cambridge, CIMR, Wellcome Trust/MRC Building, Hills Road, Cambridge.* E-mail: rjr27@cam.ac.uk

We have been developing a new program, *Phaser*, to apply likelihood to solving macromolecular crystal structures by molecular replacement and experimental phasing methods.

Initial experiences with molecular replacement using brute-force likelihood targets in the program *Beast* [1] showed that likelihood had greater power to discriminate correct solutions, but the brute-force approach was prohibitively slow. To address this problem we have developed likelihood-based fast rotation [2] and fast translation [3] functions. The combination of these fast targets in *Phaser* with powerful automation strategies makes it possible to solve many difficult molecular replacement problems routinely.

More recent developments in *Phaser* focus on experimental phasing. The program includes new likelihood targets for phasing by SAD [4], as well as by MAD or MIRAS (unpublished). Completion of the heavy-atom substructure is accomplished through the automated interpretation of log-likelihood-gradient maps.

Applications of *Phaser* to difficult structure solutions will be discussed, along with plans for future development.

[1] Read R.J., *Acta Cryst.*, 2001, **D57**, 1373. [2] Storoni L.C., McCoy A.J., Read R.J., *Acta Cryst.*, 2004, **D60**, 432. [3] McCoy A.J., Storoni L.C., Read R.J., *Acta Cryst.*, 2005, **D61**, in press. [4] McCoy A.J., Storoni L.C., Read R.J., *Acta Cryst.*, 2004, **D60**, 1220.

Keywords: likelihood, molecular replacement, experimental phasing**MS62.28.2***Acta Cryst.* (2005). **A61**, C81**Broken symmetries in macromolecular crystallography****Marc Schiltz**^a, Gerard Bricogne^b, *^aLaboratory of Crystallography, Ecole Polytechnique Fédérale de Lausanne (EPFL), Switzerland. ^bGlobal Phasing Ltd. Cambridge, UK.* E-mail: marc.schiltz@epfl.ch

The space-group symmetry of a crystal structure imposes a point-group symmetry on its diffraction spectrum, giving rise to so-called symmetry-equivalent reflections. This introduces a certain redundancy in diffraction data recorded with area detectors and is exploited in macromolecular X-ray crystallography to increase the accuracy of the data by averaging over the symmetry-equivalent measurements (data merging).

We will discuss two instances where the symmetry in reciprocal space is broken, *i.e.* where symmetry-related reflections are no longer equivalent. One such situation occurs in the presence of resonant (anomalous) scattering, when the resonant sites display anisotropy in their local atomic environment. The second example of a broken symmetry is when the sample suffers from site-specific radiation damage during the X-ray measurement. Both situations commonly occur in macromolecular crystallography. In such cases, the genuine intensity differences between symmetry-related reflections can actually be exploited to yield useful phase information in the structure solution process. In this approach, the usual separation of the data merging and phasing steps is abandoned. At the phasing stage, structural (*i.e.* real-space) models are refined which can account for the observed intensity differences between symmetry-related reflections, thus yielding phase information.

Keywords: resonant scattering, anomalous dispersion methods, MAD phasing**MS62.28.3***Acta Cryst.* (2005). **A61**, C81**Statistical Direct Methods of Phase Determination****Hongliang Xu**, Charles M. Weeks, Herbert A. Hauptman, *Hauptman-**Woodward Medical Research Institute, Buffalo, New York, USA.* E-mail: xu@hwi.buffalo.edu

In the minimal principle method, one of the most successful direct methods of phase determination, the phase problem is formulated as a problem in constrained global minimization. The cosine minimal function, based on probabilistic estimates of the cosines of the structure invariants, serves as the foundation of an optimization procedure called *Shake-and-Bake* [1] that automatically and repetitively alternates reciprocal-space phase refinement with a complementary real-space density modification to impose the atomicity constraints.

A new statistical minimal function and its minimal principle, based on the statistical properties of the structure invariants themselves, have recently been formulated. Favorable applications of the corresponding statistical *Shake-and-Bake* algorithm have been made to the *ab initio* phase determination of small proteins as well as Se-atom substructures, and the results have shown an overall improvement in success rate relative to traditional *Shake-and-Bake*.

Statistical *Shake-and-Bake* is being incorporated as the default optimization procedure in newly distributed versions of the *SnB* and *BnP* computer programs. This research was supported by NIH grants EB002057 and GM072023.

[1] Weeks C.M., Miller R., *J. Appl. Cryst.*, 1999, **32**, 120.**Keywords:** phase problem, direct methods, shake-and-bake**MS62.28.4***Acta Cryst.* (2005). **A61**, C81**Direct Use of SAD Phase Information in Automated Model Building and Refinement****Pavol Skubák**, Navraj S. Pannu, *Biophysical Structural Chemistry, Leiden Institute of Chemistry, Leiden University, The Netherlands.* E-mail: p.skubak@chem.leidenuniv.nl; raj@chem.leidenuniv.nl

The incorporation of prior phase information in a maximum likelihood formalism has been shown to strengthen model refinement. However, the currently available likelihood refinement target using prior phase information has shortcomings: the refinement target considers experimental phase information indirectly and statically in the form of Hendrickson-Lattman coefficients. Furthermore, the current refinement target implicitly assumes that the prior phase information is independent from the calculated model structure factor.

We have derived a multivariate likelihood function that overcomes these shortcomings and directly incorporates experimental phase information from a single-wavelength anomalous diffraction (SAD) experiment allowing for the simultaneous refinement of heavy atom and model parameters [1]. We have implemented this SAD function in the refinement program REFMAC5 [2]. The SAD function has been tested on many different real test cases yielding consistently better results than currently available functions. In some cases, the automated model building program ARP/wARP [3] can only successfully build a model when using the SAD function.

[1] Skubak P., Murshudov G.N., Pannu N.S., *Acta Cryst.*, 2004, **D60**, 2196–2201. [2] Murshudov G.N., Vagin A.A., Dodson E.J., *Acta Cryst.*, 1997, **D53**, 240–255. [3] Perrakis A., Morris R.M., Lamzin V.S., *Nature Struct. Biol.*, 1999, **6**, 458–463.**Keywords:** automated model building and refinement, macromolecular X-ray crystallography, prior phase information**MS62.28.5***Acta Cryst.* (2005). **A61**, C81–C82**Hybrid Programming in Crystallography: Phenix.refine and Phenix.hyss****Ralf W. Grosse-Kunstleve**, Pavel V. Afonine, Paul D. Adams, *Lawrence Berkeley National Laboratory, Berkeley, California, U.S.A.* E-mail: rwgrosse-kunstleve@lbl.gov

The *Phenix* project [1] is an international collaboration aimed at the development of a comprehensive, highly automated software system for the solution and refinement of macromolecular crystal structures. At Lawrence Berkeley Laboratory we have developed

algorithms for the determination of substructures (*phenix.hyss*), the refinement of macromolecular structures (*phenix.refine*), and the underlying “hybrid” open-source software framework, *cctbx*.

The *Phenix* Hybrid Substructure Solution (*phenix.hyss*) combines Patterson methods and dual-space direct methods, automatic substructure comparisons and simple substructure refinement into a highly integrated algorithm. The *Phenix* refinement tools include Cartesian dynamics simulated annealing, a novel robust bulk-solvent correction procedure including overall anisotropic scaling, maximum likelihood refinement with and without experimental phases, and isotropic and anisotropic refinement of displacement parameters.

Both *phenix.hyss* and *phenix.refine* are designed to minimize the need for tedious and error-prone manual intervention. Development of the required tools is made practical by the tight integration of a scripting language (Python) with a compiled language (C++), and maximization of source code reuse through a library-based approach.

[1] Adams P.D., Gopal K., Grosse-Kunstleve R.W., Hung L.-W., Ioerger T.R., McCoy A.J., Moriarty N.W., Pai R.K., Read R.J., Romo T.D., Sacchettini J.C., Sauter N.K., Storoni L.C., Terwilliger T.C., *J. Synchrotron Rad.*, 2004, **11**, 53-55.

Keywords: macromolecular refinement, substructure solution, cctbx

MS63 CHEMICAL INSIGHTS FROM ELECTRON DENSITY STUDIES AND WAVEFUNCTIONS

Chairpersons: Nour Eddine Ghermani, Peter Blaha

MS63.28.1

Acta Cryst. (2005). A61, C82

Quantum Mechanical Basis of Conceptual Chemistry

Richard F. W. Bader, Department of Chemistry, McMaster University, Hamilton ON, L8S 4M1 Canada. E-mail: bader@mcmaster.ca

Science is observation, experiment and theory. This is the path that led to the development of the molecular structure hypothesis - that a molecule is a collection of atoms with characteristic properties linked by a network of bonds that impart a structure – a concept forged in the crucible of nineteenth century experimental chemistry. One hundred and fifty years of *experimental* chemistry underlie the realization that the properties of some total system, molecule or crystal, are the sum of its atomic contributions. The lecture will demonstrate that this conceptual basis of chemistry is recovered in its entirety by the Quantum Theory of Atoms in Molecules, [1] a theory grounded in the quantum mechanics of an open system and given physical expression in terms of a system’s measurable [2] charge distribution.

[1] Bader R. F. W., “*Atoms in Molecules: A Quantum Theory*”, Oxford University Press, Oxford UK, 1990. [2] Coppens, P., “*X-Ray Charge Densities and Chemical Bonding*”, IUCR Texts on Crystallography.4. Oxford University Press, Oxford UK, 1997.

Keywords: atoms, electron density, quantum mechanics

MS63.28.2

Acta Cryst. (2005). A61, C82

Construction or Refinement of Approximate Reduced Density Matrices

Jean-Michel Gillet, Pierre Becker, Blandine Courcot, Sébastien Ragot, Ecole Centrale Paris, SPMS UMR CNRS 8580 1, Grande Voie des Vignes, 92295 Châtenay-Malabry, France. E-mail: gillet@spms.ecp.fr

One electron density matrices (1RDM) are useful tools since they convey information concerning charge, spin and momentum densities. Their determination from ab-initio calculations is nowadays straightforward for simple systems. However, few attempts have been made to construct a semi-empirical 1RDM from data originating from different experiments [1]. One difficulty is the lack of a generic model, generalizing the Hansen-Coppens approach for charge density refinements. Furthermore, when reaching large systems, such as those encountered in biology or pharmacology, ab-initio methods turn out to be both cumbersome and sometime “too” precise [2].

After a brief review, we will propose, for those two issues, some

suggestions and tracks that are or can be fruitfully explored.

[1] Gillet J.M., Becker P., *J.Phys. Chem Solids*, 2004, **65**, 2017. [2] Ragot S, Gillet J.M., Becker P., *Physical Review B*, 2002, **65**, 235115.

Keywords: ab-initio calculations, density matrices, refinement

MS63.28.3

Acta Cryst. (2005). A61, C82

Atomic and Bond Topological Properties of Strained Carbon Ring and Cage Systems

Peter Luger, Free University of Berlin, Institute of Chemistry/Crystallography, Germany. E-mail: luger@chemie.fu-berlin.de

The discovery of the fullerenes in the 80s brought a new class of carbon cage compounds with unusual structural properties into the scope of chemical research, similarly as happened with Cope systems in the 60s, where, for example, bullvalene with its unique property to exist in more than 1.2 million isomers [1], raised considerable attention. Not only preparative chemists, but also nature was able to generate complicated oligocyclic carbon cages, as for example, for several opioide derivatives. They all have in common to contain carbon atoms in very unusual steric arrangements and to exhibit C-C bonds of unusual lengths. Distances far beyond normal single bond lengths are then in question whether or not a covalent bond exists. We have analyzed experimental and theoretical electron densities of a number of strained carbon cages from the compound classes mentioned above. We could derive quantitative atomic and bond topological properties making use of Bader’s AIM formalism [2]. The existence/non existence of bond critical points and the analysis of the Laplacian function allowed also the characterization of bond/no bond regions in a [1.1.1]propellane and a related bicyclo [1.1.1]pentane derivative. Electron densities on bond critical points allowed bond orders to derive which were found remarkably smaller than one in several strained cages, for example in halogenated C₆₀ derivatives.

[1] Doering W.E. von, Roth W.R., *Tetrahedron*, 1963, **19**, 715. [2] Bader R.F.W., *Atoms in Molecules*, Clarendon Press, Oxford, 1990.

Keywords: electron density, topological analysis, carbon cages

MS63.28.4

Acta Cryst. (2005). A61, C82

Chemical Bonding in Hypervalent Silicon and Germanium Compounds

Alexander Korlyukov, Konstantin A. Lyssenko, Mikhail Yu. Antipin, A. N. Nesmeyanov Institute of Organoelement Compounds, Moscow, Russia. E-mail: alex@xrlab.ineos.ac.ru

On the basis of the analysis of experimental and calculated electron density distribution functions of different atranes and monochelated compounds we have investigated the nature of the chemical bonding in their axial D-M-X (D = O, N; M=Si, Ge; X = Cl, OH, OH₂) fragment.

Both in crystal and isolated molecules the hypervalent D...M bonds are characterized by the intermediate type of interatomic interaction in terms of R. F. Bader’s “Atoms in Molecules” theory. The transition of molecules of this type from crystal to isolated state leads to a noticeable decrease of electron density and potential energy density values in critical points (3, -1) of D...M hypervalent bonds that implies the weakening of this bonds. The extent of such weakening depends on the nature of D, M and X atoms.

The usage of the same theoretical background and periodic DFT calculations allow us to reveal the influence of intermolecular interactions on the geometry of M atom coordination centre.

On the basis of topological analysis and NBO population analysis we have estimated the strength of hypervalent bonds in monochelated compounds and atranes. For instance, in a number of six-membered cyclic compounds (X=Hal, OAlk) the strength of D...O bonds (1.96 ÷ 2.45 Å) varies in the range 4 - 29 kcal/mol.

Keywords: charge density distribution, topological properties of charge, theoretical crystal calculations