

Keywords: refinement, high-resolution, subatomic

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Macromolecular model-building and validation using Coot

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Coot [1] is a molecular graphics application for macromolecular model building against X-ray data. Coot provides a modern interface drawing from usability paradigms of popular desktop applications. In so doing, it has become increasingly popular [2], particularly in the UK and parts of Europe. Coot provides several tools which can be used to build, refine and protein structures and other models. In the last year, there has been more focus on developments to better handle lower resolution data, these include the fitting of alpha helices and beta strands for model building and the addition of extra restraints and modification of restraints when refining. Also to be discussed are the tools for validation for the detection of model-building errors and feature outliers.

[1] Emsley & Cowtan (2004) "Coot: Model-Building Tools for Molecular Graphics", *Acta Cryst D* 60, 2126-2132.

[2] But not close to the popularity of a more established application.

Keywords: map fitting, molecular graphics, model building

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Advances in automatic model building and structure completion in the context of ARP/wARP

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Automated protein model building procedures are becoming better and better in building partial initial models with minimum user intervention. Manual interactive building is in many cases needed only in the final stages of model building. A natural trend for automatic building developments, is thus to spend more effort towards providing a more complete model. The ARP/wARP software suite is build around the concept of a hybrid model, a partial protein model supplemented by unrestrained atoms used to model the rest of the ordered electron density. The model is iteratively build by recycling the information contained in the restraints of the partial model to obtain better phases estimates through model refinement. Here we present three types of improvement to the automated model building procedure in ARP/wARP:

Improved procedures that allow sequence assignment to the main chain in a more effective manner, using pattern classification algorithms that use the free atoms and rotamer fit to the electron density;

Algorithms to assign conditional restraints to the free atoms (the ones that do not have chemical identity yet). The goal is to enhance further

model refinement by providing additional observation in the form of restraints and improve the derived electron density. This approach enables ARP/wARP to reach a more complete model faster;

A program that uses both statistical knowledge of protein main chain structure and electron density, to build missing loops connecting main chain fragments already docked in sequence. This algorithm uses hierarchical filtering and only considers local electron density as a loose selection criterion. That allows both for speed and makes the procedure relatively unaffected by partial disorder of the residues to build.

Keywords: model building, loop building, protein crystallography

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MAIN 2008: Real space model fitting - as good as it gets

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After an initial model of a macromolecular crystal structure has been generated it goes through cycles of refinement and manual corrections until the structure is done. In order to speed up this process cycling through visual inspection and manual manipulation of the model needs to be efficient and swift. When finalizing the MAIN 2008 release the combined use of automated model rebuilding tools and the user guidance were in focus. The conjugate gradient minimizer has been rewritten. Energy minimization in combination with rotational searches of side chain and main chain conformations, fragmented rigid body minimizations can now rebuild molecular models to correspond to electron density map to the level of an expert user and better, thus as good as it gets. The role of the user is to inspect the model (guided by validation tools or own choice) and trigger appropriate functions on appropriate model parts either using mouse clicks or keyboard shortcuts. With this the manual guidance of atoms and residues into desired positions during model rebuilding became essentially obsolete. It used to be that after model building step R-value increases, however, with the new MAIN real space fitting and minimization procedures, the R-value decreases after each model rebuilding cycle. Clearly the quality of the electron density maps defines the success of real space minimization, nevertheless properly configured procedures can be used at any resolution range at any stage of model building including the very initial stages. The current limitation of the toolbox is that it does not work with multiple conformations, but only chooses the "best" one at a certain density contour level. (See "http://www-bmb.ijs.si").

Keywords: automated model rebuilding, real space refinement, density fitting

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Beyond crystallographic refinement: Broader application of TLSMD to model protein dynamics

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TLS (Translation/Libration/Screw) models provide a useful

formalism for describing rigid-body vibrational motions of arbitrary objects. Multi-group TLS models are broadly applicable to describe inter-domain and other internal vibrational modes of proteins. The web-based analysis tool TLSMD (<http://skuld/bmsc/washington.edu/~tlsmd>) generates experimentally based multi-group TLS models from a refined protein structural model and associated atomic displacement parameters. These may be used to analyze the presence and physical significance of TLS motion in existing structures, to guide additional crystallographic refinement, or to generate target models of protein flexibility for use in computational protein-protein or protein-ligand docking. The utility of TLSMD in refinement, particularly at low resolution, is now solidly established. I will present examples of applying TLSMD in other contexts to extract information on protein dynamics, domain structure, hinge locations, and binding site flexibility.

Keywords: crystallographic refinement, docking computation, dynamic properties

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Supramolecular stabilization of well-ordered water clusters

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Water may play an important role in the stabilization of molecular crystals and coordination polymers. Our view has been that information of biological significance may be obtained by a thorough study of water in such environments. We have previously published a number of articles in which trimers, octamers, and decamers have been discussed. Also of importance in supramolecular assemblies are water dimers and even monomers. The essential question is which stabilizes which? Do the water clusters stabilize the supramolecular architecture or does the supramolecular architecture stabilize the water clusters? These questions are not really philosophical, as the discussion will demonstrate. The discussion will also point out the use of metal coordination and hydrogen bonding forces to effect stabilization. However, exciting new results on the importance of weaker interactions will be revealed.

Keywords: supramolecular, water clusters, weak interactions

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Hydration structure changes around proteins at work

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Proteins fold and function in water known as a complex liquid displaying unusual physicochemical properties caused by hydrogen bonds between water molecules. To understand why water is necessary for structures and functions of proteins and biological macromolecules, interfacial structures between water and

biomolecules, so-called hydration structures must be investigated. X-ray crystallography has been contributing to visualize the hydration structures of proteins (Nakasako (1999) *J. Mol. Biol.* 289, 547.; Nakasako (2004) *Phil. Trans. B. Roy. Soc. Lond.* 359, 1191.), it is, however, still difficult to observe directly the reorganization accompanying protein motion to understand the physical mechanism underlying the reorganization. In the present study, I would like to discuss how the reorganization of hydration structures occur to accommodate to the domain motions of a multi-domain enzyme, glutamate dehydrogenase composed of six identical subunits with two separate domains. X-ray crystal structure analyses suggest the possibility that a set of hydration water molecules adsorbing on the depth of the active site cleft regulate the domain movements. A large-scale molecular dynamics simulation for the enzyme demonstrates that the domain movements are rare events and occur very short period within 50 psec. In addition to the simulation, the frequencies of the domain movements are measured by atomic force microscopy for the surface of the enzyme crystals. The results provide probabilities of the domain movement of the enzyme. To understand totally the results from the three different types of experiments, it is plausible that hydration water molecules inhibit the molecular motions of the enzyme in solution.

Keywords: hydration structure, cryogenic X-ray crystallography, molecular dynamics simulation

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Water embedded in metal-polycarboxylate crystal host

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Because water plays an indispensable role in life-sustaining processes, investigations on its structure, properties and functions have received more scientific attention than any other substance. The study of the possible structures of water clusters in different surroundings is important to understand the nature of water-water interactions in the bulk water or ice,[1] as well as in many biological, chemical, and physical processes. This realization has led to theoretical and experimental explorations of several small water clusters in the solid state. In the course of our research interest on the preparation of polycarboxylate coordination polymers and their magnetic properties, several water motifs have been obtained and characterized showing the contribution of water to the stability of the host, and the cooperative association of the water clusters and crystal host in the formation of the water clusters. Because it is impossible for water clusters in solution and in the solid state to be discrete, the precise structural data and the cooperative association of the water clusters and crystal host may be helpful in improving our understanding of the contribution of water clusters to the stability and function of the biological assemblies, as well as anomalous properties of water.

[1]S. W. Benson, E. D. Siebert, *J. Am. Chem. Soc.*, 1992, 114, 4269.