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Low-resolution structure determination and validation

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In recent years, the forefront of structural biology has moved from small proteins and enzymes to large complexes and molecular machines. These large assemblies bring new challenges, not the least of which is their tendency to form poorly ordered crystals that diffract to relatively low resolution. The CCP4 Study Weekend 2008, held at the University of Leeds, looked at the rewards that such structures can bring us, and addressed the difficulties in working with them.

The meeting opened with an introductory session, in which Wayne Hendrickson reviewed the nature of the information that can be gained from crystal-structure determinations at different resolutions, and Tom Steitz demonstrated how the determination of large structures can progress through different stages of resolution. Next, a session on 'Biological insights at low resolution' showed that fascinating questions can be answered, if you ask the right questions. Piet Gros spoke about the structures of complement components, Simon Jenni about fungal fatty acid synthase, Florian Brückner about the RNA pol II elongation complex, and Preben Morth about the sodium/potassium antiporter.

Manfred Weiss opened a session on 'Model building and refinement at low resolution' by reviewing the different ways we might choose to define 'the resolution' of a structure. Nick Furnham showed how the program *Rapper* can be used to test the consistency of various structural hypotheses with chemical knowledge, in order to interpret low-resolution data. Axel Brunger discussed the techniques that his group has developed to generate appropriate structural interpretations at low resolution.

The second day opened with a session on validation, which is important at any resolution but absolutely essential at low resolution. Gerard Kleywegt introduced the session with a general discussion of the philosophy and principles of validation. Randy Read discussed an approach to validation borrowing a case-control methodology from clinical trials. Jane Richardson closed the session with a description of new tools in the program *MolProbity* aimed at the validation of both proteins and nucleic acids. The next session focused on the other molecules that are often found in macromolecular crystal structures. Ton Spek shared the experiences of the small-molecule crystallography community in validating small organic molecules on their own. Alexander Schüttelkopf described techniques that can be used to validate ligands as parts of complexes with macromolecules. Thomas Lütteke discussed the issues associated with carbohydate modifications, where knowledge of allowed pathways and stereochemistry can help to validate the structures.

The meeting closed with a session entitled 'Looking Backwards and Forwards'. Rhiju Das described recent breakthroughs in molecular modelling and how these will influence the future practice of crystallography. Gert Vriend looked forward to a time when automated refinement methods will allow continuous improvement of the quality of the PDB, and illustrated this with a pilot study. The final two speakers provided cautionary tales on the fallout of the infamous 'pentaretraction': Chris Tate described controversies over the structure of EmrE, and Phil Jeffrey analysed where things went wrong with the ABC transporter structure determinations.