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Model building and refinement

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The collection of papers in this issue, form the proceedings of the CCP4 Study Weekend held in Leeds in January 2004. The meeting focused on challenges of the macromolecular structure determination process that present themselves after the determination of an initial phase set. The topics covered focused on model building (interactive or automated), but extended upstream to recent developments in density modification and downstream to model refinement, validation and analysis.

A review of computational tools that address this stage of the structure determination pipeline is particularly timely, as two developments have increased the need for rapidly moving from electron-density maps to validated and refined models. Firstly, automation and algorithmic developments have begun to have an impact on the upstream processes of crystal growth, data collection, and phase determination by experimental methods or molecular replacement. Secondly, the widespread use of crystallography both as the major method for structure determination in structural proteomics initiatives and the central tool for analysing numerous protein:ligand complexes in the pharmaceutical industry, has lead to the point where model building, refinement and validation could once again become rate limiting. Moreover, efficient approaches to extracting and communicating functional inferences have to be developed to analyse the accumulating volume of structural data and deduce structure–function relationships in novel proteins, or structure–activity relationships in series of protein:ligand complexes.

Professor Alwyn Jones, whose overview of the evolution of model building approaches was complemented by a presentation of novel approaches to map interpretation, presented the keynote lecture. Together with other talks about interactive model building, these presentations illustrated that algorithm still trails somewhat behind intuition in the interpretation of lower resolution electron-density maps. Increasingly, however, advanced computational tools – often pre-filtered on the basis of fit to electron density and stereochemical criteria – are being offered so that the role of the structural biologist is one of making decision among automatically derived options.

The interplay between model and phases was also emphasised in papers that addressed the iterative use of partial model phases in phase improvement. Increasingly, these partial models are built automatically through techniques that adopt building blocks that may be atoms, residue fragments, amino acids, or even entire secondary-structural elements. Whereas excellent results are being achieved at even moderate resolutions, the advantage of introducing larger fragments into the map interpretation process promises to extend automatic model building into the lower resolution regime. As with other processes in crystallographic computing, implementation of these approaches in a more or less rigorous maximum-likelihood framework appears to be valuable.

Model refinement, particularly taking advantage of maximum likelihood, has seen further advances. Papers which explained the theoretical background to these techniques were particularly appreciated, and will hopefully ensure that methods development will remain accessible to the crystallographic community in general.

The final session of the meeting dealt with model analysis and illustration. As the volume and pace of structure determination increases, it is very encouraging to see that methods of extracting and communicating subtle aspects of the structure–function relationship are also advancing. It is beyond question that the profile enjoyed by structural biology in recent years has relied heavily on the visual impact that our results have on the imagination and insight of the rest of the biological community. As illustration becomes ever more elaborate, expanding into the dimension of time and beyond, it is to be hoped that this impact can be maintained.