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Crystallography of complexes

Tadeusz Skarzynski[a] and Airlie McCoy[b]

[a]GlaxoSmithKline, Gunnels Wood Road, Stevenage SG1 2NY, England, and [b]University of Cambridge, Department of Haematology, Cambridge Institute for Medical Research, Wellcome Trust/MRC Building, Hills Road, Cambridge CB2 2XY, England

The CCP4 Study Weekend 2006 covered a wide range of topics associated with structural studies of complexes between proteins, proteins and nucleic acids and proteins and small molecules. The programme was composed of lectures from different areas of structural biology including: preparation and characterization of complexes for structural analysis, co-crystallization and soaking techniques, molecular replacement with multiple protein components, and fitting and refinement of small-molecule ligands. However, the underlying theme of the presentations was about those aspects of macromolecular crystallography which are specific to the determination of crystal structures of molecular ensemblies, undertaken to throw light on biological processes or reveal molecular interactions between protein targets and potential drug molecules. The meeting, held at the University of Leeds, attracted the highest number of participants (over 550) in the history of these popular annual gatherings, which clearly showed that the topics presented in the lectures were seen as relevant to the research activities of a large number of structural biologists from different areas. As usual, the talks were focused on methods rather than the final results of authors' research for the benefit of a large number of students and young scientists in the audience.

The first day of the meeting was devoted to the methods and techniques specific to the studies of complexes between macromolecules. The importance of such studies for better understanding of biology at the molecular level was illustrated by excellent talks by Joël Janin and Michael Rossmann in the opening session called Biology *is* Molecular Interactions. The subsequent presentations by Tim Dafforn and John Ladbury described methods of preparation of macromolecular complexes for structure determination and techniques to study the formation of such complexes in solution, prior to crystallisation attempts, using a variety of biochemical and biophysical approaches including dynamic light scattering (DLS), ultracentrifugation and isothermal titration calorimetry (ITC). The final session of the day included talks on the application of molecular replacement methods to multi-component protein complexes (Airlie McCoy), modelling of high-resolution structures into medium-resolution electron-microscopy maps (Ruth Nussinov) and on computational analysis of surface complementarity in macromolecular complexes (Martin Noble).

Structural studies of the interactions between macromolecules and small ligands were the subject of the lectures on the second day of the meeting. First, an introduction to the geometry of small molecules, linked to their chemical properties, was presented by Phil Evans and set the scene for a number of later talks on the modelling and refinement of such molecules, bound to their protein targets. Several presentations in the first two sessions of the day, given by speakers from pharmaceutical companies, covered a wide spectrum of methodologies applied to facilitate the crystallographic analysis of protein-small molecule interactions.

Biophysical methods to detect formation of protein–small molecule ligand complexes in solution prior to co-crystallization experiments were described by Chun-wa Chung, followed by a presentation by Annie Hassell of a large number of standard and non-standard techniques and tricks used to create well diffracting crystals of complexes with potential drugs. An overview of the impact structural biology had on the design of new leukaemia drugs, presented by Sandra Jacob, convincingly illustrated the role macromolecular crystallography of complexes plays in the discovery of new medicines. The last session of the meeting included talks on the different approaches used to fit small molecules into corresponding electron density and refine them using appropriate geometrical restraints (Tom Terwilliger and Victor Lamzin). In the same session, Gerard Kleywegt once more emphasised the importance of using the right sets of geometry descriptors for the ligands in both model building and refinement.