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Molecular replacement and its relatives

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The Collaborative Computational Project in macromolecular crystallography (CCP4) is much more than a collection of free programs to academics. The project endeavours to promote and disseminate in a neutral way advances in computational aspects of protein crystallography. The study weekend embodies this tradition by inviting leaders in their field and young scientists (whether or not they contribute to CCP4) to discuss their ideas and to teach the next generation of protein crystallographers. CCP4 survives by the quality of its software. For this to keep up to date, it relies on the academic and industrial laboratories that contribute programs, time and resources to it. Please keep involved and get involved with CCP4.

The collection of articles in this issue form the proceedings of the 2001 CCP4 Study Weekend on molecular replacement and its relatives. The purpose of this study weekend was to present a complete overview of molecular replacement with emphasis on both the fundamentals and the details of existing methods as well as some of the more recent innovations. In particular we placed a great deal of emphasis on the teaching aspect of this meeting and all the talks should have been accessible to students with little previous training.

Molecular replacement was last covered in the 1992 CCP4 Study Weekend and its not surprising that many of the speakers and topics covered in 1992 also played a big role in this study weekend. The paper by P. Evans gives a general introduction to the method and the nomenclature, which is then followed by a paper with a historical overview of the principle underlying the technique given by M. Rossmann.

J. Navaza followed up his introduction to the *AMoRe* package given in the 1992 proceedings with a paper on the current implementation of the now widely used program. The paper by R. Read describes the use of maximum-likelihood methods in molecular replacement as implemented in the package *Beast*. He describes how in some instances difficult molecular replacement problems may be solved more easily by using a multi-variate likelihood function with multiple search models. G. Bricogne described insights into the use maximum likelihood in molecular replacement but no paper describing this talk was submitted.

The locked rotation and translation functions are a powerful way of taking advantage of the presence of non-crystallographic symmetry and this approach has been implemented in the *GLRF* program (L. Tong). R. W. Grosse-Kunstleve gave an overview of the principles and use of Patterson correlation methods that are used in the molecular replacement procedures of *CNS*.

Trial models for molecular replacement can come from a variety of sources. NMR structures are becoming increasingly more widespread and R. Pauptit presented a case study of their use. E. Dodson reviewed the steps required and the pitfalls encountered when exploiting electron-microscopy images as models for molecular replacement. One possibility for an initial model is to use a predetermined envelope available from sources such as solution scattering. Q. Hao described how the program *FSEARCH* exploited such envelopes for molecular replacement solution. J. Naismith's paper describes a case where the structure solution relied on the placement of experimental density into a new crystal form.

J. Thornton discussed the increasing rate of protein structure determination in particular from structural genomics projects. Unfortunately, Thornton was unable, owing to time pressure, to supply a manuscript for this presentation. As more structures become available the chance of determining an unknown structure by molecular replacement becomes more likely. However, it is already possible to solve an unknown structure using only structure features attained from data mining the PDB as the starting model (T. Oldfield). Another technique that utilizes the vast structural data already deposited at

preface

the PDB is structure prediction methods and threading in particular. D. Jones evaluates the potential for structure-determination techniques in molecular replacement and outlines how a successful and reliable technique would represent a significant advance in protein structure determination.

Unless there is a very high structural and sequence homology between the trial model and the sample structure, finding a solution for a molecular replacement problem is often only the first hurdle. Determining structures within the initial map can be a lengthy process, although more automated ways of deriving structures are now available. The fast Fourier feature recognition algorithm as implemented in the program *FFFear* (K. Cowtan) is one such procedure. The program *MOLREP* (A. Vagin) also extends the molecular replacement method to locate macromolecular fragments in an electron-density map by using a spherically averaged phased translation and phased rotation function. The paper by A. Perrakis presents the capabilities of the *ARP/wARP* software for refining and automatically building protein models, starting from molecular replacement solutions. This paper also suggests useful protocols and suggestions based on worked examples.

One session of the study weekend was dedicated to new approaches within molecular replacement. An overview of the use of NMR models to solve crystal structures is presented here in a paper by Y. Chen. The paper describes a protocol developed recently that places particular emphasis on the preparation of search models and has been found to offer

good results. The paper by N. Glykos describes a molecular replacement method that simultaneously determines the rotational and translational parameters of all copies of a search model in the asymmetric unit of a target crystal structure. A pitfall associated with multidimensional searches is that they are frequently time consuming. A rapid six-dimensional molecular replacement search can be carried out using an evolutionary optimization algorithm. The performance of this algorithm and its dependence on search model quality and target function is discussed in a paper by C. Kissinger. The last paper by C. Yang discusses how peaks from S atoms and other anomalous scatterers in anomalous difference Fourier maps can confirm the tracing of the peptide chain and provide an independent, unbiased confirmation of molecular replacement results.

The scientific organisers would like to thank all the speakers who contributed to the study weekend, as well as the reviewers of the papers who helped to ensure the high quality of the proceedings.

The organisation of this meeting would not have been possible without the efforts of David Brown, Pat Broadhurst, W. Silversides (Daresbury Laboratory), and the assistance of the staff at the University of York conference office. The preparation of these proceedings was greatly aided by David Brown, Maeri Howard Eales (Daresbury Laboratory) and Louise Jones (IUCr, Chester). David Brown has retired and we will miss him greatly. We noted sadly the departure of Sue Bailey who had become for many the face of CCP4. As an organisation, CCP4 wishes Sue well in her new job.