Book Reviews

Works intended for notice in this column should be sent direct to the Book-Review Editor (R. F. Bryan, Department of Chemistry, University of Virginia, McCormick Road, Charlottesville, Virginia 22901, USA). As far as practicable, books will be reviewed in a country different from that of publication.

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Macromolecular crystallography. Part A. Methods in Enzymology, Vol. 276. Edited by Charles W. Carter Jr and Robert M. Sweet. New York: Academic Press, 1997. Pp. xxxii + 700. Price $99.00. ISBN 0-12-182177-3

By the end of 1967 there were five protein crystal structures solved by X-ray diffraction methods (myoglobin, lysozyme, chymotrypsin, carboxypeptidase and ribonuclease). Each had been the product of several years of work. By the end of 1997, the Protein Data Bank contained 6 291 protein crystal structures. Not all of these are independent structures, some represent known structures in ligand complexes or with site-directed mutations. Nevertheless, the 1000-fold increase in solved structures over the last 30 years indicates the relative ease with which some macromolecular crystal structures can be solved. The outsider might well consider that methods have become routine, as has been achieved by the highly automated and computationally efficient methods for small-molecule crystal structures. However, although some steps of macromolecular crystallography have been automated, there are many areas where the professional practitioner needs to have a thorough understanding of the methods in order to achieve results. The new volumes of *Macromolecular Crystallography* in the '*Methods in Enzymology*' series provide the basis for this understanding; they contain information at the forefront of research by some of the major practitioners in the field. The articles elaborate on the original research papers and evaluate methods in terms of successful applications. The overview sections will interest the non-professional, but the remainder of the chapters are not for the faint hearted; they are for graduate students and research workers who wish to master the fundamentals of their subject. Part *A*, reviewed here, covers crystallization, data collection, phasing and molecular replacement. Part *B*, reviewed by Professor Adman, covers map interpretation, refinement, display and validation of structures, dynamics and databases.

The recombinant DNA revolution and advances in protein purification techniques have made major contributions to the success of protein crystallography. Cloning, expression and purification methods are outside the scope of this volume and the book begins by assuming that about 1 mg of pure protein is available for crystallization trials. The material on crystallization provides both an overview and more specialist sections. The beginner could well get going by reading the overview and applying the methods of hanging-drop vapour diffusion, with the help of the Hampton Research crystal screen kit. This company supplies prepared cocktails that have proved most productive in crystallization trials with other proteins. The contributions on the use of cosolvents, understanding of physical–chemical principles, especially consideration of temporal factors in approaches to equilibrium, and the use of physical techniques to examine the state of aggregation of the protein are valuable. Sections on membrane proteins and RNA crystallization add specialist diversity. For 'desperate situations', the sections on the use of two-dimensional crystals, based on adsorption of proteins to lipid layers, and the chemical modification of proteins, such as reductive methylation that was used to obtain myosin sub-fragment 1 crystals, provide imaginative proposals. Crystallization is not yet routine. These chapters provide a good summary of the present state of the art. Reliable precise structures depend on good intensity data that in turn depend on good crystals. The chapters on data collection cover the topics that have had most impact on the ease with which crystal structures may be solved. Flash freezing of crystals to 100 K or lower alleviates radiation damage and crystals become almost immortal in the X-ray beam. Synchrotron radiation provides the brilliance needed so that even small crystals (10 μm or less) or very large unit cells may yield accurate data. These topics are covered well, together with a description of the most widely used image-plate area detectors and their likely successors, charge-coupled device based (CCD) detectors. These sections will provide the student with an understanding of the physical processes (*e.g.* the distinction between flux, brightness and brilliance of synchrotron radiation beams) and their applications. They are followed by descriptions of data-processing software (particularly *MADNES* and *DENZO*) and it is valuable to have an up-to-date account of these programs that are all too often used as 'black boxes'.

After expression and crystallization, phasing presents the next critical step in a crystal structure determination. The section describing phase determination begins with a long discussion of Bayesian methods. These are methods aimed at reconciling numerical computation and human decision making, and are based on sound probability distributions and resolution of ambiguities by systematic evaluation of multiple hypotheses about missing information. Eventually, the methods hold promise for *ab initio* phase determination but their most definite contributions to date have been to provide improved maximum-likelihood methods for heavy-atom refinement with the program *SHARP* (described in this volume) and for macromolecular refinement (described in Part *B*). I particularly enjoyed the sections on multiple isomorphous replacement, that contain a league table of successful derivatives (suitably qualified with the comment that the quality of the heavy-atom derivative is a more important criterion than the number of times a particular heavy-atom reagent has been used), and the sections on multiwavelength anomalous diffraction (MAD) methods that include the preparation of selenomethionyl proteins for phase determination. Wayne Hendrickson reports that since its first practical demonstration in 1985, the application of MAD phasing has resulted in solution of over 40 structures in the decade to 1995, nearly half of them solved in 1995. The explosion in the use of MAD methods has been made possible by cryocrystallography, by increased number of synchrotron beamlines with facilities for tuning radiation wavelength, and by the increased ease with which anomalous scatterers may be incorporated into macromolecular crystals. The application of MAD phasing is likely to make a most significant impact in the coming years.

Patterson search correlation or molecular replacement methods have proved effective for solution of structures where a similar structure is already known. As the database of protein folds increases, these methods are finding increased application. The accounts of molecular replacement methods provide a sound background and give useful advice, for example for those problems where the starting model may not be an accurate representation of the structure sought. The book ends with 'horizon' methods. There is an entertaining description of crystal structures of racemic mixtures, although the methods are restricted to those molecules that can be synthesized and crystallized in both D and L forms. The sections on *ab initio* phasing using very high resolution data and the computation of very low resolution phases, that will allow us to bridge the gap between electron microscopy and X-ray crystallography images, point the way to the future.

This is an excellent volume. It is recommended to all graduate students and postdoctoral workers in macromolecular crystallography. I shall be purchasing both volumes for my laboratory and I shall expect to refer to my copy frequently.

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Macromolecular crystallography. Part B. Advances in Enzymology, Vol. 277. Edited by CHARLES. W. CARTER JR and ROBERT M. SWEET. New York: Academic Press, 1997. Pp. xxxiii + 664. Price $99.00. ISBN 0-12-182178-1

Volumes 276 and 277 in *Methods In Enzymology* describe the tools of the trade for macromolecular crystallography, using as a template the eponymous first pair published some 12 years ago. The problems to be solved remain the same: get crystals, collect data, determine phases, interpret the map, refine the structure (taking into account the normally low data-to-parameter ratio), evaluate the quality, make a picture, and publish, roughly in that order. The tools for solving these problems have advanced as far as new technologies (faster computers, new detectors, more intense X-ray sources) permit. The chapters in Volume 277, Part *B* of the work, describe horizon methods in phasing, the various approaches to map enhancement, interpretation, and refinement, evaluation of 'correctness', tools for conveying structural information to the consumer, suites of programs currently in use for the practicing macromolecular structuralist, and databases that contain the results of these experiments. The articles are written by leaders in their respective fields; not surprisingly and very pleasantly, a fair amount of individual personality shines through the writing.

The degree of technical understanding required for individual chapters makes it likely that these volumes will be used more by practitioners than by the 'educated layman' or even by consumers of structural information. Direct methods of phasing for macromolecules are not yet in the hands of the non-experts, despite substantial strides forward in this area, but the chapters describing these efforts are rewarding. In my view the field will have been put into the hands of consumers of structural information when user-friendly programs become available, but clearly this can only be done when the theory itself has matured. Thus, in my experience, first *PROLSQ/PROTIN* made refinement a commonly used tool, and now *TNT*, *X-PLOR* and *ARP* have become industry standards, but all after the pioneering efforts of Lyle Jensen to show that refinement was possible. Lyle's article on refinement and reliability of macromolecular models is characteristically clear and unassuming, full of nuggets of wisdom, as are the articles by the authors of these last three programs. Without the graphics programs *FRODO*, and now *O*, we as a commmunity would be nowhere, and the practical wisdom in the chapter describing map fitting is priceless. The chapter entitled 'Model phases: probability and bias' by Randy Read is also exceptionally understandable (check out the figure on page 113!). The *SHELX* chapter is also very readable, and perhaps inclusion of this program signals best the connections with the small molecule world as to how to get the most out of one's data. The *CCP*4 federation of programs continues to be invaluable. Its continued responsiveness (part of the original intent of the project) to changes in the field is particularly useful. I confess to focusing on programs with which I have personal familiarity: a reviewer more familiar with *PHASES* and *CHAIN* and a different lineage of programs would, I am sure, find equal words of praise for these chapters. Unfortunately, there is not a chapter from Duncan McRee on the *XTALVIEW* system, but perhaps his own book *Practical Protein Crystallography* (Academic Press, 1993) obviated that need.

I recognize that completely automatic map interpretation (once direct phasing is a *fait accompli*) is required for the field to realize its full potential, but for me and many others such a success will be at the expense of the personal thrill of recognition in interpreting electron density and of the realization of both just how much information really is in those data and of what has to be left unmodelled! I believe that the analytical approach to map interpretation will not be successful until enough noise is removed from the maps, at which point normal interpretation is easy, albeit tedious. However, automatic map interpretation may indeed put structure determination into the hands of the biologist or enzymologist. The chapter by Fortier on this subject, that describes the renewal of efforts initiated by Carroll Johnson over a two decades ago, will perhaps be the most novel to a macromolecular crystallographer, and it points to an area that should be watched closely. The still not-quite-automatic state of the horizon phase determination methods should suggest to the consumer that s/he should still rely on experimental phases and collaborators experienced in these traditional tools. The tools described in these volumes must be understood by the practitioners, although not all by everyone. Individuals will prefer, probably, the tools with which they have grown up in their scientific career, until a problem arises their tools can't handle properly, at which point they will turn to new ones.

I think future volumes will have to include chapters from consumers. The large numbers of structures we already have, and the even larger numbers to come, demand new methods for accessing, understanding and representing them. Two of the favorite tools for producing publication quality images, *RASTER3D* and *RIBBONS*, are well described in this volume,