Methods in Enzymology
Volume 277

Methods in Enzymology

Volume 277

Macromolecular Crystallography

Part B

EDITED BY

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Part B

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Preface

Macromolecular crystallography is an indispensable component of enzymology. Structural biology, with macromolecular crystallography as its central technique, makes fundamental contributions to enzymology: one can pose few enzymological questions without first checking to see what relevant structures may be in the Protein Data Bank. Only then can one go on to learn what it implies about the mechanism, what suggestions it makes for genetic variation, and so on. We present these volumes to provide both a reference for practitioners of macromolecular crystallography and as a portal to the field for those who want to learn.

Methods in Enzymology Volumes 114 and 115, edited by Wyckoff, Hirs, and Timasheff, were timely. They provided the basic outlines and many details of macromolecular crystallography to several scientific generations of structural biologists, and many chapters remain primary resources. Since the publication of these volumes in 1985, macromolecular crystallography has evolved from an immature science, when practitioners needed to evaluate and possibly redesign each step in the process, to a set of procedures that are increasingly likely to succeed. This trend toward automation had characterized small molecule crystallography during the previous two decades, and had begun for macromolecular crystallography at the time of the publication of the two Wyckoff *et al.* volumes. The trend has accelerated and doubtless will spawn a growth industry in "service" macromolecular crystallography. This is evidenced by the growing population of practitioners whose primary interest rests not with structure determination itself, but with what can be derived from subsequent analysis. Systematic studies and comparison of mutants, ligand complexes, and different structural polymorphs depend on the rapid determination of structures.

At the same time, fundamental experimental, theoretical, and computational underpinnings of the field have experienced a parallel explosion. These include improved crystal growth and handling to provide higher resolution data, synchrotron X-ray sources, better detectors, improved methods for solving the phase problem, fragment library-based algorithms for the interpretation of electron density maps, and new refinement methods that, on the one hand, increase the radius of convergence for marginal models and, on the other, provide sophisticated models to exploit high-resolution data. We are becoming more sensitive to the importance of avoiding errors in interpretation and in understanding the limitations placed on refined parameters by the data.

A consequence of these changes is that our volumes differ from the preceding set not only in content that has arisen 10 years later, but also in emphasis. We perceive that the original practitioners of the crystallographic art were physicists, who handed the tool to chemists. Many of those now solving macromolecular crystal structures have biology as their primary training and interest. The core personnel responsible for the continued development of the field have been diluted both by the dispersion into a broad variety of departments, professional disciplines, and industrial laboratories and by the increasing numbers of relatively naive "users." Moreover, the multitude of techniques available offer multiple solutions to most of the rate-limiting steps. Often the choice of which approach to take depends more on personal experience and taste than on respect for the underlying principles. Therefore, while emphasizing experimental methods, we have included many chapters that describe the fundamentals of recent advances that may spark further transformation of the field.

The chapters in these volumes present expert witness to the state-of-the-art for many individual aspects of the field. The two volumes provide the logical train of objectives necessary to solve, refine, and analyze a macromolecular crystal structure. Although these volumes may not serve as a simple textbook to introduce the field, individual chapters should provide a comprehensive background for each topic. Students and teachers alike will benefit from a careful reading of each chapter as it becomes relevant in the course of research.

Part A (Volume 276) deals with the three requisites for structure solution: crystals, data, and phases. The first section covers aspects of the theory and practice of growing high-quality crystals. Since exploiting intrinsic information from a crystal to its full extent depends on measuring the highest quality data, the second section provides information about radiation sources, instrumentation for recording, and software for processing these data. Finding the phases represents the final rate-limiting step in the solving of a structure. Therefore the third section includes a penetrating analysis of the statistical foundations of the phase problem and covers a broad range of experimental sources of phase information and the techniques for using them effectively. It ends with several "horizon" methods that may help transform phase determination in the coming decade.

Part B (Volume 277) continues the section on horizon methods for phase determination. It follows with various ways in which structures are built, refined, and analyzed. An important development since 1985 is in model-independent, real-space refinement. Construction of atomic models is the crucial step in converting electron density maps into structures. Chapters are included that present the increasing trend toward computer-assisted and/or automated map interpretation. Fragment libraries representing how

proteins fold are already integral parts of some of the software described previously. Use of simulated annealing in model refinement has increased the radius of convergence; it has become integrated *de facto* into the process of solving structures. New tools for refinement of models to fit high-resolution data, when they can be measured, now permit the exploration of more detailed models. Procedures for cross-verification and *post hoc* analysis provide tools to help avoid unnecessary errors and possibly incorrect structures.

A long-term goal in structural biology is "molecular cinematography." The molecules we study undergo some kind of internal motion in carrying out its function. Some of these motions can be inferred experimentally by the analysis of the static diffraction patterns. Others require the use of multiple diffraction patterns recorded as a function of time. These topics are covered in the next section on dynamic properties.

The final sections sample widely used accessory software for manipulating, archiving, analyzing, and presenting structures. Databases, with tools for accessing specific information contained therein, are essential resources for those who study macromolecular structures, and even for those involved in crystal growth. Finally, we have documented some of the integrated packages of software which contain most of the tools needed for structure solution.

The ferocious march of technology places burdens on everyone concerned with the production of such a collection, and we are sincerely grateful to the authors for their cooperation and patience. The staff of Academic Press provided continuous and valuable support, which we both appreciate.

CHARLES W. CARTER, JR.
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