The last days of crystallography

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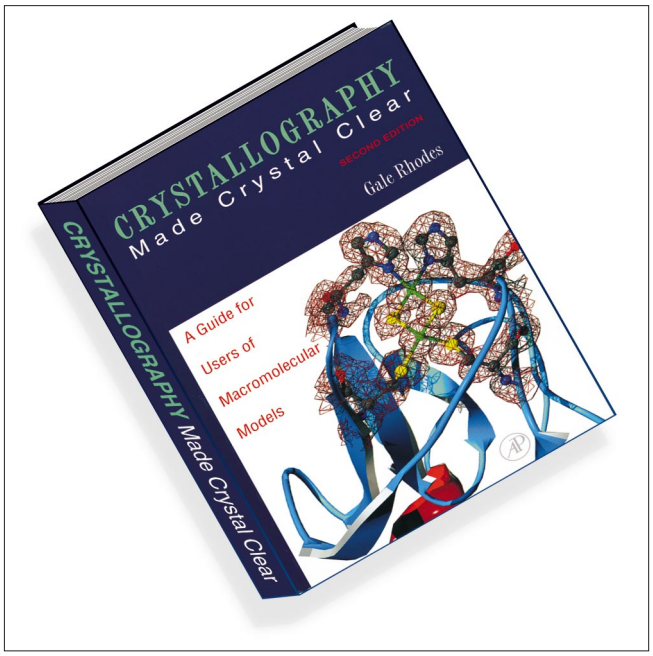
Crystallography Made Crystal Clear, 2nd edition, by Gale Rhodes, Academic Press, $44.95 paperback (ISBN 0125870728).



Biological crystallography has become a field where records are constantly broken. It was not always this way. Crystallography started like an amble in the Lake District. Investigation was as simple and as pleasurable as putting one foot in front of the other and describing the principles of structure and function evident along the way. But the ineffable beauty of myoglobin and lysozyme and the technical sweep of hemoglobin and chymotrypsin sparked changes.

Today, the action has moved to the track. Crystallographers outdo themselves (and each other) almost weekly. The -ins, -ases, -somes, channels, domains and abbreviated factors are being revealed in powerful, unprecedented detail. Just when every eye is on membrane proteins, a new record is set in kinetics. Just when it seems that the triple jump of gene–structure–drug has a powerful new champion, a new height is cleared in transcription. Like scientific Carl Lewises, crystallographers are jumping farther and running faster. And as if to turn nature on her ear, some of the toughest records are set in the masters division. How do today's crystallographers do it? Clearly, they just put one foot in front of the other.

This simple assertion is the central fiction of the elegant book by Gale Rhodes, *Crystallography Made Crystal Clear*. It is also the book's central triumph. Who could argue that crystals are grown by gently precipitating proteins from concentrated solutions (chapter 3)? Surely, Bragg's law (chapter 4) is as basic and incontrovertible a compass as ever crafted. Even phasing, the problem with a capital P, can be attacked with powerful experimental and computational methods (chapters 6 and 7). The wonderful thing about all this sure-footed simplicity is that it is true. How does Rhodes achieve this remarkable matter-of-factness?

The answer to this question lies in the plan and the style of his book. The organization is deconstructive. Rhodes summarizes the crystallographic process at the outset and marches through each step. The treatment is brief and thoughtful, with introductory and summary sections that guide the reader. With a brisk pace, Rhodes outlines crystallization, diffraction, data collection, Fourier transforms, phasing methods, model building and refinement. The discussion of Fourier methods, for example, is a particularly good introduction to the basic mathematical tools used in crystallography. One can quibble only with emphasis, such as the puzzling initial treatment of phase as an implicit quantity. Likewise, the book misses the opportunity to discuss directly one of the most confusing issues raised perennially by students — the distinction between the X-ray wavelength and the wavelengths of Fourier terms. The annotation of two crystallographic papers is particularly useful. Although not at the level of critical analysis, the discussion helps define basic criteria to judge the quality of published work. The effect is to reduce the 'Presto factor', the impression given by a number of general textbooks that a crystal structure is like a rabbit pulled out of a hat by a magician. The last chapter on using coordinates introduces useful web-based tools and emphasizes the representational character of molecular models. This idea, that models are not molecules, urges the reader on towards deeper insights derived using structural methods as one of many means of perception.

Beyond content, the effortless writing style and the introductory, consumer-oriented treatment contribute to the book's remarkable clarity. *Crystal Clear* is quite different from *Protein Crystallography* by Blundell and Johnson. This

ancient book contains 'The Word', discovered partly on stone tablets and parchments that can be read and reread without ever grasping their deepest truths. The copies of *Protein Crystallography* in my laboratory have broken bindings. In contrast, *Crystal Clear* is like a story of determining crystal structures. The style is comprehensible, nonjudgmental, even breezy — excellent to inspire students. The reader is just as likely to gain the confidence to solve structures or to become a regular reader of this journal (or both). The miracle in *Crystal Clear* is the absence of the crushing, unwritten sense that there is much more to be known, even though, of course, there is much more to be known. Each sentence encourages the reader to comprehend the next and to join the race for discovery.

Here is where the second edition of *Crystal Clear* unexpectedly stumbles. The revisions at best hint of powerful changes in the field. Only two pages, for example, are devoted to phasing by multiwavelength anomalous diffraction (MAD), a technique that has increased the pace and scope of crystallography. The description of the initial electron-density map as crude or uninterpretable misrepresents clear experimental electron-density maps that are increasingly commonplace. Where is the discussion of newer phasing methods (e.g., SHARP) and methods of automated model building and refinement (e.g., wARP)? The impact of the free R factor is dramatically underemphasized, as is the use of structural databases in model building. These and other advances are hidden by the decision to retain the annotation of papers from the early 90's. Some of the techniques used in those papers do not prepare the reader to fully understand a modern paper. Surely, annotation of recent structures that have established new functional paradigms would afford a more modern vision.

The second edition of *Crystal Clear* also contains new sections on fiber diffraction, electron diffraction, neutron diffraction, homology modeling and nuclear magnetic resonance (NMR) spectroscopy. One consequence is to make the book more suitable as a supplementary textbook. However, the effect is unbalanced. The discussion of NMR and homology modeling in a single chapter gives the mistaken impression that these techniques are equally informative. Does it take eight chapters to understand crystallographic models and half a chapter to appreciate models derived from NMR? The mismatched levels of sophistication are evident, for example, in the statement, "The end result of analyzing NMR spectra is a list of distance restraints… This is really about all that we learn about the protein from NMR." This oversimplification challenges the sense of humor of even the generous reader. These criticisms are not meant to minimize the many strengths of the second edition of *Crystal Clear*, which is a superb first book for anyone seeking a deeper understanding of X-ray methods and structural discoveries.

What, it may be asked, are crystallographers poised to discover? A leading practitioner once divided biological crystallographers into two schools: analytical rationalists exemplified by Leonardo daVinci and descriptive explorers exemplified by Christopher Columbus. A thousand ships are now at sea, and the blank spaces in the cell are filling up fast. Just as the millennium will forever be associated with sequencing the first human genome, current structural work will be a lasting touchstone for future scientists concerned with the engines of physiology. Biologists will refer back to today's structures of DNA, RNA, enzymes, membrane proteins and giant machines such as the nucleosome, the ribosome and RNA polymerase. Surely, there are many more such descriptive discoveries to be made. Just as certainly, technical innovations on the horizon will make it much easier to put one crystallographic foot in front of the other.

Palpable changes define the crystallographic frontiers that include understanding larger complexes, new classes of molecules, and new principles of design and function. The challenge of mapping the bounded protein landscape is being taken up by the push into structural genomics. The numbers are too big even for the fastest Carl Lewises. Automation is required. Surprisingly, the major crystallographic hurdles have been cleared already. Synchrotron beamlines will meet the demand for multiwavelength data. Expert systems have automated and optimized every computational step from data processing to map calculation. With an accurate, high-resolution map, available programs can build and refine a model with little human intervention. In favorable cases, new structures already can be completed in a few hours. Routine structures will soon be solved automatically at centers, like small-molecule structures today. *Crystal Clear* offers little inkling of these changes.

Instead, *Crystal Clear* confidently describes crystallography at the end of the era of handcrafted structures. Once '10,000 structures' are produced through structural genomics, however, the infrastructure will be in place to tackle new problems. 'A thousand kinases' will yield principles of recognition and specificity. A complete structural survey of a viral genome will become a doctoral thesis project. New questions will be posed: how does a cancer cell differ from its normal progenitor? and how does a cell change with age? The answers to such questions may be revealed by comparative analysis of 100–500 new structures. New tools to express and purify proteins by the score will facilitate studies of multicomponent machines. Crystallographers will focus increasingly on crystallization and on experiments with crystals to derive mechanistic principles. By providing a clear exposition of basic methods, *Crystal Clear* is a guide to this new world. Read the book and you will be introduced lucidly and enthusiastically to structure determination and molecular models. Hurry, though. The protein crystallography described in *Crystal Clear* is nearing the end of its run.