

Preface

The aim of this book is to provide a comprehensible introduction to diffraction- and image-based methods for finding the structures of complex biological macromolecules. The reader is presumed to be a biologist or biochemist, interested in how these methods have revealed the extraordinary sub-cellular world of molecular machines, yet lacking the physical and (especially) the mathematical background to follow the primary literature. Fortunately, this common obstacle of higher mathematics can be circumvented, in the case of Fourier transform theory. For there exists an *intuitive* version of the theory, in which symbolism and calculation are replaced by pictures and pictorial rules, and yet sound conclusions can be drawn. This theory, covered in Part I, provides the key to understanding the applications of Fourier transforms described in later parts. It also forms the basis for keeping all the mathematics in this book (outside Part V) at the level of simple algebra, despite presenting some highly mathematical topics.

The applications of Fourier transforms include Part II (light- and electron-optics and diffraction theory), and (in Part IV) the more 'crystallographic' methods of image processing, used in X-ray crystallography and the analysis of electron micrographs of (especially) crystalline sheets and helices. However, structural analysis also uses other methods. *Symmetry theory* is needed to understand the organization of natural aggregates of identical subunits (relevant to viruses and muscle) and also those artificial aggregates, like protein crystals, constructed to facilitate structural analysis. *Matrix methods* are also needed for data-analysis (especially by 'single particle' methods). All these extra techniques are explained in Part III, which also discusses the general problem of turning 2D images into 3D structures.

All detailed structural analyses fall into different classes through the specimen's inherent symmetry (crystals, helices, polyhedral viruses and asymmetrical particles). These alternatives are covered in Part IV, which deals with those classes in declining order of symmetry-order. Naturally, the methods required to analyze highly symmetrical crystals (Chapters 13 and 14) differ from those appropriate for isolated, randomly-oriented, asymmetrical particles (Chapter 17). Thus two different kinds of method are in use. 'Crystallographic' methods, based on Fourier transforms, are suitable for structures with translational symmetry (crystals and helices) whereas 'single particles' need correlation and statistical techniques.

To accommodate newcomers, Parts I–IV (inclusive) are a (higher) mathematics-free zone. However, some readers may eventually develop an interest in the native mathematical ‘language’ of structure research; so an elementary introduction is provided for them in Part V. But this isn’t required for understanding other chapters, though it would be required to understand most other books or papers on the subject.

There is a wide range of structural techniques, and a comprehensive coverage would produce an encyclopedic tome whose contents would also lack overall coherence. Therefore the topics chosen here have been restricted to molecular structure determination and to image-based methods. The main topic is high-resolution electron microscopy, but the framework also includes X-ray crystallography, which also produces images. However, NMR is excluded, despite its importance, because it is a very different kind of method, and a proper account of it must include quantum-mechanical spin-operators. Another important exclusion is electron cryo-tomography, a major new bridge between light microscopy and molecular structures. However, it lies rather more on the non-molecular side of this gap. Nevertheless, its promise and its use of three-dimensional reconstruction techniques makes this omission a matter of regret, justified mostly by practical considerations. Yet another regretted omission is the reconstruction of sections of thick crystals (applied most notably to muscle), a topic included in the long review article (Moody, 1990, Image analysis of electron micrographs, pp. 145–287. In: *Biophysical Electron Microscopy* (P.W. Hawkes & U. Valdrè, eds.). London: Academic Press.) on which this book was originally based.

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