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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Protein structure - new approaches to disease and therapy.

By MAX PERUTZ. Pp. 326. Oxford, New York: W. H. Freeman, 1992. Price £32.95 (hardcover), £21.95 (paperback). ISBN 0-7167-7021-0 (hardcover), 0-7167-7022-9 (paperback).

The fertile and creative mind of Max Perutz has given the world yet another treasure. This copiously illustrated little book provides a fresh and compelling look at the practical benefits of our rapidly expanding knowledge of protein structures. As Perutz notes in the preface, 'The first protein structures revealed wonderful new faces of nature, but they did not help to cure anyone.' The turning point - for Perutz - was the report in 1988 that prolonged remissions had been induced in two terminally ill leukemia patients by humanized rat anti-T-cell antibodies (developed by Herman Waldmann and Gregory Winter). The successful engineering of the crucial antibodies depended, as Perutz points out, on X-ray crystallographic analysis of immunoglobulin structures. In recent years, the number of protein structures solved annually has risen exponentially and, as Perutz notes, the value to medicine of many of these structures only became apparent after their solution. In 'Protein Structure,' Perutz celebrates the coming of age of protein crystallography by describing how protein structures are determined and how these studies have revolutionized the treatment of disease.

The first chapter presents a unique nonmathematical description of X-ray crystallography and its application to protein structural determinations. Subtitled 'Diffraction Without Tears,' it is a masterful presentation of the fundamentals of crystallography. For those more comfortable with mathematics, the first appendix of the book provides a concise yet complete discussion of the requisite mathematical principles.

Chapter 2, titled 'How Proteins Recognize Each Other,' surveys some of the most interesting and timely examples of protein-protein interactions, including antigen-antibody association, recognition of the major histocompatibility complex with T-cell receptors, CD4-HIV interactions, heat-shock proteins and chaperones. This is followed by chapters on protein interactions with DNA and RNA (emphasizing the roles of proteins in transcription) and the binding of drugs to proteins and nucleic acids. Chapter 5 discusses the role of protein structure determinations in drug design, including an account of the computer-based search of the Cambridge Structural Database for compounds complementary in structure to the active site of HIV-1 protease, the resulting identification of bromoperidol and its subsequent use as a model for the synthesis of HIV-1 protease inhibitors.

Chapter 7 describes the role of gene technology in optimization of protein function. One of the examples cited here is that of insulin, which normally exists as a hexamer, but which must dissociate into monomers in order to bind to insulin receptors and thus regulate serum glucose levels. Slow dissociation of insulin hexamers is responsible for the slow action of subcutaneously injected insulin, but the Danish pharmaceutical firm Novo is presently testing a genetically engineered mutant insulin which dissociates to monomers more effectively, due to electrostatic repulsion between subunits arising from the substitution of an aspartate (for proline) at the subunit interface. As Perutz points out, knowledge of the three-dimensional structure of oligomeric insulin was instrumental in the engineering of this faster-acting insulin.

Chapter 8, on virus structure and vaccine engineering, and Chapter 9, describing cytokines, growth factors and differentiation factors, are both excellent. Historical accounts and anecdotes are deftly intertwined with Perutz's lucid descriptions of scientific discovery. One of the best of these is the story of Rita Levi-Montalcini, Stanley Cohen and the serendipitous discovery of nerve growth factor in the snake venom which they were using to try to degrade (the same) nerve growth factor in mouse tumor extracts.

Chapter 10 consists of a table of 'Some Medically Important Protein Structures Not Discussed in the Preceding Chapters.' It is clearly the book Perutz was tempted to write as a sequel to the present one, and it makes good reading by itself.

Perhaps the only fault one might find with this lovely book is a minor typesetting flaw. Some of the headings of sections within chapters are in bold type, whereas others are italicized, and there is no apparent pattern to these headings which correlates with the table of contents. It might be added that the italicized headings do not stand out well from the body of the text, and bold type might have been preferable throughout.

Protein Structure by Max Perutz is a special contribution from a very special man. Researchers, teachers and students will all find much to enjoy in this book and, for most, it will enhance and broaden their awareness of the modern impact of protein structure information. It is essential reading for anyone working in protein structure, and it is sure to inspire a generation of younger crystallographers and biochemists.

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Atlas of protein side-chain interactions. Vols. I and II.

By J. SINGH and J. M. THORNTON. Pp. 427 and 399. Oxford Univ. Press (IRL Press), 1992. Price £55.00. ISBN 0-19-963302-9.

This atlas is a two volume set describing all 400 possible pairwise interactions between the 20 different types of amino-acid side chains. It is an elaboration by the authors of the

previously published paper: '*SIRIUS*. An automated method for the analysis of the preferred packing arrangements between protein groups' [*J. Mol. Biol.* (1990), **211**, 595-615].

The raw data consist of 62 highly refined structures deposited in the Brookhaven Protein Data Bank. An interacting pair is defined simply based on distance. A reference set of atoms is given for each amino acid. This is used for the superposition of atoms in the pair and for calculations of characteristic interaction angles. Their significance is assessed by a χ^2 test against a random distribution.

About 20 pages describe the making of the atlas. Then for each of the 400 pairs, two pages of information are presented. First, the atoms defining the geometry are given along with statistical data in the form of tables and histograms. Stereo line drawings giving three orthogonal views to highlight the clustering of the distributions are presented on the second page. To avoid clutter, at most 50 representative structures of the given pair are chosen randomly.

The selection of a reference set of atoms presents problems, as a subjective judgement must be made for most side chains. The choice made by the authors is to consider the functional groups or the extremities of the side chain, rather than a definition always involving the α-C atom. There is no consideration of rotamer conformations, nor any account of peptide-side-chain interactions here. There are only about 100 observations for each pair type with a median value of 56 observations. Approximately one fifth of the interactions have highly significant interaction angles (less than 5% likelihood that they are due to chance). Many of these significant patterns, however, are hard to discern by visual inspection of the stereo plots.

The overall presentation of the atlas is well done, but it would have been helpful had 20 × 20 tables been included to summarize the statistical data. The type of information provided should be useful to crystallographers and molecular modelers, and would be most useful when used in conjunction with an interactive display system. Thus, a visual check of a proposed model against the previously observed patterns for a particular pairwise interaction could be a useful modeling tool and an assessment of the statistical likelihood of proposed interaction angles by comparison with those in the atlas could provide an unbiased check of the reasonableness of a proposed side-chain packing mode.

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