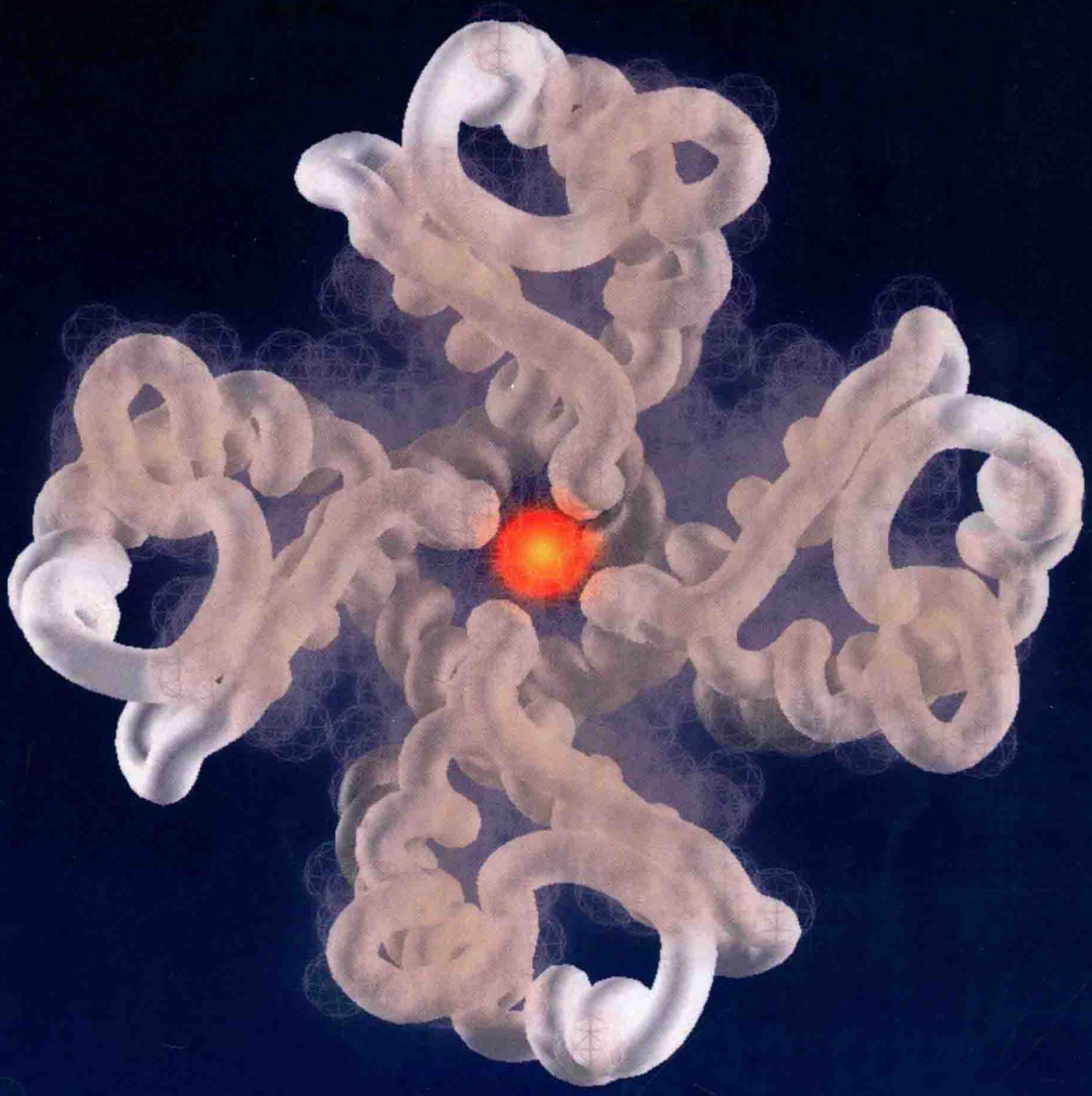
Introduction to Protein Structure

Second Edition



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Introduction to Protein Structure

Second Edition

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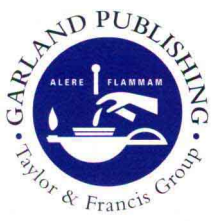

THE COVER

Front: The structure of the potassium channel from *Streptomyces lividans*, determined by Rodney MacKinnon at the Rockefeller University, New York. As discussed in Chapter 12, this structure—the first of such an ion channel—shows how the channel allows the passage of potassium ions through cell membranes with high efficiency and selectivity. The view is looking down the protein as it sits in the cell membrane, as seen from outside the cell, with a potassium ion shown in gold. This image was produced using the GRASP program (A. Nicholls and B. Honig, Columbia University) from atomic coordinates kindly provided by Rodney MacKinnon.
Back: A hand-drawn image of the potassium channel, in the same view as on the front cover, with each subunit of the tetrameric protein shown in a different color.
Cover design by Christopher Thorpe and Nigel Orme.

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Introduction to Protein Structure

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An aerial view of the European Synchrotron Radiation Facility at Grenoble, France, an advanced source of synchrotron x-ray radiation for use in the study of protein structure, as well as for use in the physical and material sciences. The synchrotron radiation is produced in the circular building in the lower left of the photograph. (Courtesy of ESRF.)

Preface

The determination of the atomic structures of proteins has seen an enormous increase in impetus since the first edition of this book was published in 1991. The number of new structures reported is close to doubling each year. Technical advances—for example the increased availability of synchrotron x-ray beams and methods for freezing crystals so as to reduce radiation damage to them, the development of multidimensional NMR and NMR machines with ever more powerful magnetic fields, and the exploitation of gene cloning, sequencing and expression systems have all contributed to the growth of protein structure determination. On the one hand, it is becoming increasingly easy to obtain relatively large amounts of naturally rare proteins, on the other hand the crystallographers can work with ever smaller crystals.

The fundamental tenet of molecular biology, namely that one cannot really understand biological reactions without understanding the structure of the participating molecules, is at last being vindicated. As the database of known protein structures rapidly expands, so does the range of biological pathways about which we can ask meaningful questions at close to atomic levels of resolution. An understanding of the principles of protein structure is becoming of ever widening significance to molecular biology.

The pharmaceutical industry has over the past decade become a major user of the protein structure databases, and a major contributor of newly determined structures. Knowledge of an enzyme's or a receptor's atomic structure is invaluable in the search for specific and strongly binding inhibitors. For example the quest for effective inhibitors of HIV protease, to be used in combination therapy for AIDS, led many pharmaceutical companies to determine the structure of that protease with bound inhibitors. Over 120 of these structure determinations have been done so far and at least two inhibitors of HIV protease are now being regularly used to treat AIDS. It seems certain that the determination of the atomic structure of target molecules will play an increasingly important role in drug design.

The commercial exploitation of our increased understanding of protein structure will not, of course, be restricted to the pharmaceutical industry. The industrial use of enzymes in the chemical industry, the development of new and more specific pesticides and herbicides, the modification of enzymes in order to change the composition of plant oils and plant carbohydrates are all examples of other commercial developments that depend, in part, on understanding the structure of particular proteins at high resolution.

As the complete genomes of more and more species are sequenced, the determination of the function of previously unidentified open reading frames is becoming an increasing and challenging problem. The possibility of

setting up centers for automated high through-put structure determinations is being seriously discussed. In the absence of any recognizable sequence homology to proteins of known function, this approach, surprising though it may seem, could become an effective way of determining function via structural homology.

The growth in the interest in high-resolution protein structure over the past decade and the reception of the first edition have encouraged us to prepare a new edition of this book. Universities are devoting more time to courses specifically on protein structure, or increasing the amount of time given to protein structure in more generally based biology and biochemistry courses. We hope that this new edition of *Introduction to Protein Structure* will prove useful both to teachers and students.

In 1988 when we began writing the first edition, about 250 protein structures had been determined to medium to high resolution and in those days a professional protein crystallographer was familiar with most of them. We were not therefore faced with a severe problem of what to leave out as we wrote. Today, the coordinates of over 6500 proteins have been deposited in the Protein Data Bank at Brookhaven, New York. Both the number of structures and the variety of biological systems to which they relate are so high that the field of protein structure is becoming more fragmented and specialized. It is becoming increasingly difficult to keep sight of the wood amongst so many trees. The question of what to include and what to omit is, for today's authors, crucially important. We have tried to resist the temptation to describe more and more proteins, adding detail but not increasing understanding of the basic concepts. This edition is inescapably a little larger than its predecessor, but to contain the increase in size we have deleted two chapters while adding four. We run the risk of disappointing not a few structural biologists whose favourite proteins are not mentioned. To them we apologize and ask for their understanding.

Acknowledgements

In preparing the second edition of this book we have again relied heavily on and benefited greatly from the advice and constructive criticism of numerous colleagues. We are particularly grateful to Ken Holmes (Max-Planck Institute, Heidelberg), Lawrence Stern (MIT), Michelle Arkin (Sunesis Pharmaceuticals), and Watson Fuller (Keele University, UK) for their contributions to, respectively, Chapters 14 and 18, Chapter 15, Chapter 17 and Chapter 18. Stephen Harrison (Harvard University) and Paul Sigler (Yale University) provided extensive help and advice on Chapters 8–10, 13 and 16, and Chapters 8–10 and 13, respectively, for which we are especially grateful.

The following, in alphabetical order, have reviewed one or more chapters, correcting our errors of fact or interpretation and helping to ensure they have the appropriate balance and emphasis: Tom Alber (University of California, Berkeley), Tom Blundell (Cambridge University, UK), Stephen Burley (Rockefeller University), Charles Craik (University of California, San Francisco), Ken Dill (University of California, San Francisco), Chris Dobson (Oxford University, UK), Anthony Fink (Unversity of California, Santa Cruz), Robert Fletterick (University of California, San Francisco), Richard Henderson (LMB, Cambridge, UK), Werner Kühlbrandt (MPI, Frankfurt), David Parry (Massey University, New Zealand), Greg Petsko (Brandeis University), and David Trentham (NIMR, London, UK).

The book depends for its accessibility upon its illustrations and we are hugely indebted to Nigel Orme, who, as with the first edition, has converted sketches into lucid figures. Keith Roberts has again advised us on how best graphically to represent chemical and structural phenomena. Jane Richardson (Duke University) has generously produced the Kinemage supplement to this edition and the book relies upon Richardson-type diagrams throughout to render the structures discussed comprehensible. We thank our publishers Garland Publishing, now part of the Taylor and Francis Group, for their support, and in particular Matthew Day for his enthusiastic editing of the complete manuscript. Miranda Robertson, in her inimitable style, has again managed the entire project.

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Part 1

Basic Structural Principles

The Building Blocks

1

Recombinant DNA techniques have provided tools for the rapid determination of DNA sequences and, by inference, the amino acid sequences of proteins from structural genes. The number of such sequences is now increasing almost exponentially, but by themselves these sequences tell little more about the biology of the system than a New York City telephone directory tells about the function and marvels of that city.

The proteins we observe in nature have evolved, through selective pressure, to perform specific functions. The functional properties of proteins depend upon their three-dimensional structures. The three-dimensional structure arises because particular sequences of amino acids in polypeptide chains fold to generate, from linear chains, compact domains with specific three-dimensional structures (Figure 1.1). The folded domains can serve as modules for building up large assemblies such as virus particles or muscle fibers, or they can provide specific catalytic or binding sites, as found in enzymes or proteins that carry oxygen or that regulate the function of DNA.

To understand the biological function of proteins we would therefore like to be able to deduce or predict the three-dimensional structure from the amino acid sequence. This we cannot do. In spite of considerable efforts over the past 25 years, this folding problem is still unsolved and remains one of the most basic intellectual challenges in molecular biology.

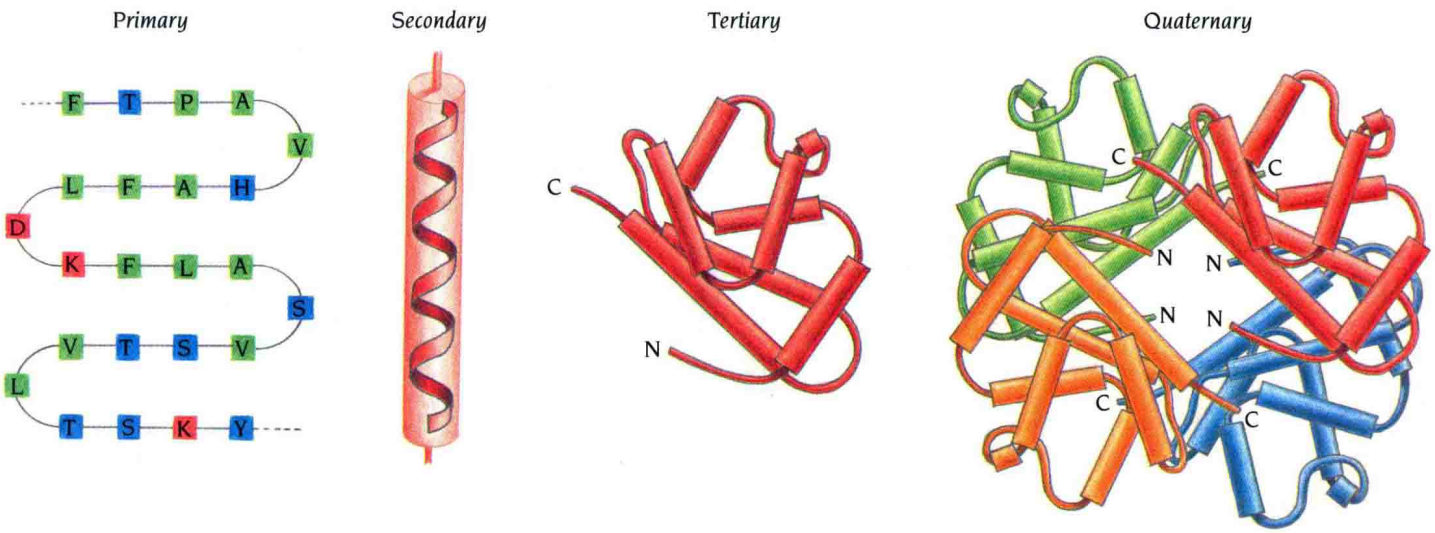

Figure 1.1 The amino acid sequence of a protein's polypeptide chain is called its **primary** structure. Different regions of the sequence form local regular **secondary** structures, such as alpha (α) helices or beta (β) strands. The **tertiary** structure is formed by packing such structural elements into one or several compact globular units called domains. The final protein may contain several polypeptide chains arranged in a **quaternary** structure. By formation of such tertiary and quaternary structure amino acids far apart in the sequence are brought close together in three dimensions to form a functional region, an **active site**.