Molecular Biology in Three Dimensions

Introduction to Protein Structure. CARL BRANDEN and JOHN TOOZE. Garland, New York, 1991. xvi, 302 pp., illus. $49.95; paper, $27.95.

The last two decades have seen an explosion in the understanding of molecular biology in three dimensions and of how the function of proteins is encoded at the molecular level. To x-ray crystallographers and structural analysts, the motivation is to understand how protein molecules mediate life's chemistry. So general principles, chemical mechanisms, and evolutionary development are at a high premium. This volume introduces some unifying themes among crystallographically determined protein structures. By focusing on some of the many families of proteins of often-related function, it serves to illustrate the diversity of protein function and the principles by which evolution has fine-tuned more specific function at the balanced cost of genetic complexity.

Part 1 of the book develops the theme of basic structural principles, with five chapters that build from descriptions of secondary structure to subdomains and the anatomy of some of the more common three-dimensional protein folds. From the outset the authors acknowledge the difficulties of representing structures in a way that communicates the three-dimensionality of the molecules; they opt for "ribbon" drawings of the kind popularized by Jane Richardson. These are beautifully colored and shaded to simplify some of the complexities apparent in the way subdomains associate in proteins. The focus is mainly anatomical, with frequent reference to evolutionary relationships that are evident from three-dimensional similarities, though some connection to function is implied by locations of binding sites in the tertiary structures. Part 1 ends with a short chapter summarizing the A-, B-, and Z-forms of DNA, which hints at mechanisms for sequence-specific recognition by enzymes.

Structure and its connection to function, probed by means of site-directed engineering, are the focus of Part 2. Chapters 7 through 9 take the reader through the topics of DNA recognition, repressor binding, the multidomain nature of transcription factors and the "zinc finger" motif, and DNA polymerase in a somewhat historical fashion and with cartoon illustrations of the general ways in which the macromolecular components associate together. The authors stop short of any of the detailed molecular interactions of side chains, hydrogen bonding, and electrostatic interactions.

Chapter 10 introduces enzymes by way of the subclass of NAD-binding dehydrogenases. The idea of a common structure preserved in evolution is illustrated without confusing the issue with discussion of the several other NAD binding sites that are not related structurally or evolutionarily. Throughout, the focus is on evolutionary ideas rather than on details of the interactions between chemical groups that help catalyze the reactions. Structural folds in the spherical viruses, antibody binding of antigen and the MHC antigen involved in T cell activation, integral membrane proteins, and the tyrosine kinase–activating receptor families are similarly introduced in the next four chapters.

Chapter 15 introduces the principle formulated in 1946 by that greatest of American chemists Linus Pauling, that enzymes catalyze chemical reactions by relatively stabilizing the energetically difficult structures found in the transition states. The serine proteases are offered as an example. This beautifully illustrates the central principles of enzyme function without going into any of the derivations of equations. Transition-state theory, covalent catalysis, and substrate specificity are illustrated by well-established examples from the trypsin family and subtilisin. Changes introduced by mutagenesis into trypsin or subtilisin are used to show some of the surprisingly unpredictable mixed effects on k_{cat} and K_m that result from side-chain replacement; no single amino acid controls a single aspect of function.

A skeptical look at today's structure-predictive methods in chapter 16 focuses on the procedures of Chou and Fasman; Garnier, Osguthorpe, and Robson; and Lim. Tryptophan synthetase provides a terrific and topical vignette of how the tertiary folded structure was predicted almost completely correctly by Kasper Kirschner. The "artificial intelligence" approach of Fred Cohen has great potential for automating predictive schemes. Protein engineering of disulfide bonds is used to highlight the interplay between conformational flexibility (an entropic factor) and strain (an enthalpic factor) introduced by the constraints on the geometry of the disulfide bridges, which governs the range of stability. Other alterations by mutation that probe helix dipole interactions, filling of cavities, charged groups, circular permutations of $\alpha\beta$ units in α/β barrel structures, and *de novo* protein design serve to demonstrate the idea that protein stability is a strongly synergistic and cooperative process.

The book illustrates many of the connections between protein structural families and the evolution of diversity within them. Especially valuable is the selection of references at the end of each chapter; these include general references to a few of the classics in each field as well as references to primary publications of specific structures that provide an excellent entry into the deeper levels of each field.

Overall Branden and Tooze bring the horizons of three-dimensional molecular biology into perspective. They show how the dazzling achievements of molecular genetics and site-specific mutagenesis over the last decade have provided new levels of wonder and sometimes confusion. Interpretations of the consequences of mutagenesis only become reasonable as the three-dimensional structures of the altered molecules and their complexes with other molecules within the cell are resolved. Today there is a resurgence of interest in protein structures, in the methods of determining them, and in how the results may be utilized. The next steps in molecular biology and its applications to human health are clearly at the level of three-dimensional structures of proteins, and the need for understanding in three dimensions is greater than ever before.

We are at the exciting start of the most dramatic revolution so far in the use of three-dimensional knowledge for design of protein therapeutics and of drugs that alter protein and cellular activity with a precision and specificity previously undreamed of. The rather modest title *Introduction to Protein Structure* draws the reader toward a profound intellectual estuary of interplay between the structure, stability, and dynamics of proteins and their function.

Introduction to Protein Structure is an up-to-date collection of recent discoveries in certain selected fields, especially where protein families have been described. It is by no means an archival collection. Sections on how proteins fold, forces in proteins, structure prediction, experimental mutagenesis,

and methods of solving protein structure clearly distinguish this volume from a biochemistry textbook. The book also provides a good overview and references for graduate courses on structure and function of macromolecules, although it does not contain details of the chemistry or stereochemistry of interactions that might be desirable for such a graduate course. It should be a very important supplementary textbook, strongly recommended for any undergraduate, premedical, or postgraduate biochemistry course.

ROBERT M. STROUD
Department of Biochemistry and Biophysics, University of California, San Francisco, CA 94143–0448

Turbulence Theory

The Physics of Fluid Turbulence. W. D. McComb. Clarendon (Oxford University Press), New York, 1990. xxiv, 572 pp., illus. $150. Oxford Engineering Science Series, 25.

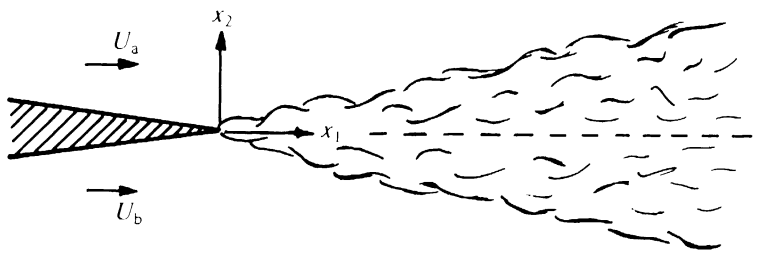
The Navier-Stokes equations are not linear, with the consequence that an equation for a given statistical moment contains the next higher moment. This "closure problem" has plagued turbulence theory since its beginning, with many suggestions made but none of them satisfactory. In 1959 Robert Kraichnan suggested borrowing from quantum field theory the renormalized perturbation methods (complete with Feynman diagrams) to close the turbulent moment hierarchy. He was followed by other pioneers (Wyld, Edwards, and Herring) and then by many more. These methods have been followed by simplified techniques (the test field model) and by the distantly related renormalization group method, also borrowed from quantum field theory.

With all these methods lumped together under a single heading, it is fair to say that they offer the only approach to turbulence that can be called a general dynamical theory (as opposed to a phenomenological one), although dynamical systems theory has recently made some progress. (Approaches like multifractals must still be regarded as statistical models.) It was thought for some time that renormalized perturbation methods were approximations that could lead to successive improvements, but it was finally realized that they were more in the nature of very sophisticated dynamical models. The approach has been conceptually very useful in understanding interactions of various wavenumbers and is actually capable of calculating a few things more or less from first principles. It has been useful in plasma physics. Nevertheless, it has not fulfilled its initial promise, primarily because, when it is applied to a shear flow at high Reynolds number, the computations are more costly than would be a direct or large-eddy numerical simulation. People are working on simplifications (such as the test field model) that would make the problem more tractable.

Approximately a third of this book is devoted to these renormalization techniques. The material is quite accessible, thorough, and complete. It is one of the few places to which a student could be referred for instruction in this subject, the others being D. C. Leslie's *Developments in the Theory of Turbulence* (Oxford University Press; paperback edition, 1989), which does not touch on renormalization group methods, and a few pages in M. Lesieur's excellent *Turbulence in Fluids* (Kluwer; 2nd edition, 1991).

McComb's great advantage over Leslie's older and rather monodisperse book is found in the other two-thirds of the volume. Here McComb gives a brief but fairly complete introduction to the semiempirical approach to turbulence and to the classical statistical approach, as well as a bit on measurement techniques, a bit on intermittency, a section on numerical simulation, a section on statistical-mechanical approaches, and a section each on coherent structures, the Lagrangian and Eulerian views of turbulent diffusion, and non-Newtonian fluid turbulence. In the sections on perturbation approaches, McComb is speaking from the heart, but on the other subjects, he is no more than an intelligent and well-informed reporter. Nevertheless, a student who actually reads this book will be moderately well informed also, which is all we can hope for. There is no question that this is a physicists' book that probably will be useful only to those who are not daunted by a great deal of formal manipulation.

JOHN L. LUMLEY
Department of Mechanical Engineering, Cornell University, Ithaca, NY 14853



"Definition sketch of a plane mixing layer between two parallel streams with different velocities U_a and U_b." [From *The Physics of Fluid Turbulence*]

Biogeochemical Cycles

Biogeochemistry. An Analysis of Global Change. WILLIAM H. SCHLESINGER. Academic Press, San Diego, CA, 1991. xii, 443 pp., illus. Paper, $39.95.

Biogeochemistry deals with the interaction between life and its chemical environment. Biogeochemical cycles, with which this book is principally concerned, describe the processes that control the composition of the environment, atmosphere, and natural waters and the processes by which the composition can change. The term "cycles" refers to the fact that much of the movement of matter is cyclical; photosynthesis, for example, transfers carbon from the atmosphere to the biota while decay transfers the carbon from the biota back to the atmosphere at an essentially equal rate. Carbon therefore cycles between atmosphere and biota. The methodology for the study of the biogeochemical aspects of global change is based largely on considerations of conservation of matter. The global environment is divided into a number of reservoirs appropriate to the problem at hand. These reservoirs might be ocean, atmosphere, and global biota, for example. The amounts of the element of interest in each of the reservoirs are established by observation, along with the rates at which material is transferred between reservoirs. Then, at least in principle, the evolution of the system can be calculated by saying that the amount of material in each reservoir changes with time at a rate equal to the difference between the rates at which material is added to the reservoir (the sources) and the rates at which material is removed from the reservoir (the sinks). This approach to the study of biogeochemical cycles is well developed in this book, with chapters devoted to the global cycles of water, carbon, nitrogen and phosphorus, and sulfur. In addition, the book sets the stage for the consideration of these global cycles with chapters on the atmosphere, lithosphere, terrestrial biosphere, biogeochemical cycling on land, in freshwater wetlands and lakes, in rivers and estuaries, and in the sea. The treatment is comprehensive and detailed. The book contains a wealth of useful information in the form of tables, diagrams, and text. There are approx-