Dynamics of proteins and nucleic acids

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J. ANDREW McCAMMON

M. D. Anderson Professor of Chemistry
University of Houston – University Park
Houston, Texas

STEPHEN C. HARVEY

Professor of Biochemistry
University of Alabama at Birmingham
Birmingham, Alabama

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Dedicated to
Anne W. McCammon and Marie A. Weaver

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PREFACE

At macroscopic levels, the dynamic character of life is dramatically self-evident. Motion is no less important at the molecular level of biology. Indeed, the marked biochemical effects of temperature changes imply that the activity of biological molecules reflects their thermal mobility. An appreciation of molecular flexibility and dynamics is essential to the understanding of the activity of naturally occurring molecules and to the design of new molecules with specified activities.

Detailed studies of the atomic motion of proteins and nucleic acids are of recent origin. Nevertheless, far more has already been done than can be adequately described in a single volume. The aim of this book is accordingly modest. We attempt to provide the reader with a self-contained introduction to the theoretical aspects of protein and nucleic acid dynamics. The level of presentation is intended to be appropriate for graduate students as well as for research workers in biophysics, physical biochemistry, and molecular biotechnology. Our principal goals are (1) to outline the theoretical methods and their capabilities, (2) to provide a sense of the nature and biological significance of biomolecular dynamics by reference to representative theoretical studies, and (3) to indicate some prospects and directions for future work. Experimental work is covered incidentally in connection with theoretical results.

The book is organized generally to progress from fundamentals to applications and from short time scales to the longer time scales characteristic of most biological activity. Proteins and nucleic acids are treated in an integrated fashion, but mostly in separate sections that can be read selectively if the reader wishes. The first four chapters provide an introduction to conceptual foundations and methodology. Chapters five through eight present the results of selected applications. There, we attempt to describe the nature of the different types of molecular motion that are found to occur in biological systems. The final chapter addresses current research and future prospects. This chapter shows that biomolecular dynamics is entering an exciting new phase, one that is concerned with the interpretation and prediction of biological activity as much as with physical properties. The fruits of this work will include useful tools for pharmacology, medicine and industry.

We hope that this book will give the reader a sense of the special challenges and rewards associated with theoretical studies of protein and nucleic acid dynamics. One of the challenges derives from the fact that these studies involve the fusion of three 'high technology' areas, namely, molecular biology, chemical physics and scientific computing. The rapid pace of development of each of these areas leads to more than the usual rate of obsolescence of research techniques. Such difficulties are, however, more than offset by the promise of aesthetic and pragmatic rewards. Among the former is the pleasure of bridging different scientific disciplines, e.g., using Newton's equations of motion to interpret basic events in biochemistry. The pragmatic rewards include the potential applicability of theoretical methods in the design of new drugs, enzymes, vaccines, etc.

The present book grew out of a review article in *Reports on Progress in Physics* (McCammon, 1984). We are grateful to the Institute of Physics for permission to use material from that article here. Some of the material on nucleic acids is drawn from another recent review article (Harvey, 1986). We also wish to acknowledge our coworkers and colleagues, who have made invaluable contributions to our own understanding of the work described herein. Several colleagues read drafts of the manuscript and made helpful suggestions; particularly valuable comments were provided by Professors P. A. Kollman and B. M. Pettitt, and by Dr T. P. Lybrand, Dr M. Prabhakaran and Dr L. J. Ransom-Wright. Special thanks are due to Denise Marshall for her skillful assistance in word processing. The authors' research in protein and nucleic acid dynamics has been supported in part by the National Science Foundation, the National Institutes of Health, the Robert A. Welch Foundation, and the Texas Advanced Technology Research Program.

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