This book develops a statistical mechanical analysis of the stability of biological macromolecules. The author's approach is valid both for the long time scale needed for DNA bond disruption, and also for highly cooperative transitions needed to explain helix melting.

The author develops a new theoretical approach for executing macromolecule calculations. In particular he devises a method for describing chemical bond disruption in these large systems, which are then used to determine when the helix melts and how drugs can dissociate from the helix. Melting temperatures and width of transitions are found to be in excellent agreement with experimental observations without the need to employ 'parameters fitted to melting'. Methods are developed to incorporate the effects of varying salt concentration, hydrostatic pressure and structural water on the melting of the helix. The author then develops methods of performing calculations on specific structures embedded in a large helix and on the dynamic effects of enzyme attachments. The role of energy in biological dynamics is studied from an analysis of the role of ATP hydrolysis in advancing a replicating fork.

The book will be of interest to research workers in the field of biomolecular dynamics, especially graduate students and researchers in biological physics, theoretical chemistry and molecular biology.

STATISTICAL MECHANICS AND STABILITY OF MACROMOLECULES

Application to Bond Disruption, Base Pair Separation, Melting, and Drug Dissociation of the DNA Double Helix

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Contents

Preface

Significant understanding of biological processes has been made by studying the dynamics of macromolecules at the microscopic level. The bulk of the researchers interested in the results are biochemists, chemists, pharmacists, and biologists. The MSPA approach developed in this book is based on methods used in condensed matter physics which are not familiar outside that discipline. The method is useful in solving long time scale problems in molecular biology that should be of interest to the biochemists etc. working in the field. This book is therefore aimed at presenting both a coherent development of the MSPA methodology and some of the background needed to understand it by persons not coming from a physics background. Biophysicists may find the results and the physics background of interest. To increase the usefulness of the book to the different readers I have, to the extent possible, concentrated on concepts and description in the main text and kept the mathematical formalism in appendices. On the other hand physicists may be interested in the way that physics methodologies have to be altered to be applied to be useful in this new situation. The complexity of biological systems is greater than that usually dealt with in condensed matter investigation and changes in approach are necessary. Physicists may also be interested in the development of a new approach to cooperative transitions that seems to work very well, particularly in large complex systems. The book is an attempt, probably a foolish one, to try to be useful to different audiences with different backgrounds and interests.

The methods developed represent a particular and personal view of the best way to attack the very difficult problem presented by complex biological systems which undergo physical processes on long time scales, long enough so that simulation is not a viable approach to use. A lot of opinion about why it should be done the way it is, is included. The practice of science requires opinions, and it has been my experience that many who have objected to elements of the work described here have done so only because they hold different opinions. In particular I have encountered a very negative reaction to the use of harmonic methods that seem to exemplify the saying 'that a little bit of knowledge is a dangerous thing'. There seems to be just enough knowledge to understand the limitations of the simple harmonic approximations but with no knowledge of the development of renormalization and selfconsistency extensions of the theory which allow it to overcome the simple harmonic limitations. Much of Chapters 3 and 4 is an attempt to explain and motivate a rationale for the use of selfconsistent harmonic approaches.

There also seems to be a lot of misunderstanding about phase transitions as applied to calculations which seem to be simply calculations of dissociation of a macromolecule. Some criticism has centred on where the second phase comes into the calculation as a result of the mistaken belief that a transition always requires the simultaneous existence of two phases. This is true for first order systems but a higher order transition can be formulated as a breakdown of a single phase. Repeat sequence DNA undergoes a second order melting transition and that is the reason that theories of dissociation give good agreement with observations on melting. Not all melting transitions can be analyzed in terms of the crossover of two free energy curves as this approach is only appropriate for first order transitions.

All of the work described in this book has been carried out in collaboration with a number of Graduate Research Assistants and Post Doctoral Research Associates. In every case the original refereed journal publications are listed in the references and the contributions of each collaborator to each section of the work should be clear. In particular the book deals extensively with the work of Dr Y.Z. Chen, who was a Research Associate, and Drs R. Beger, M. Techera, and W. Zhuang who were Research Assistants. I had helpful conversations on the validity of self-consistent phonon theory with Prof. P. Muzikar. I want to thank Profs J.W. Powell and S.A. Lee for critical reading of the entire text and making helpful suggestions.

The reference to the 'spherical cow' model used in Chapter 2 refers to a joke that I have been told by biologists, who thought it very funny. It is about a physicist who, while addressing a group of Dairymen, opens his talk with the statement 'Assume a spherical cow'.

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