Structural Biology

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Practical NMR Applications

Second Edition

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Preface

The second edition of "Structural Biology: Practical NMR Applications" retains the focus of the previous edition, which is to provide readers with a systematic understanding of fundamental principles and practical aspects of NMR spectroscopy. At the beginning of each section, questions and objectives highlight key points to be learned, and homework problems are provided at the end of each chapter, except Chap. 9. One hundred multiple-choice questions with answers are provided to further aid in understanding the topics. In response to comments and suggestions from readers, and based on my own research and teaching experiences, I have made improvements and added a new chapter (Chap. 9) on metabolomics, which is an important application of NMR spectroscopy.

Over the years since NMR was first applied to solve problems in structural biology, it has undergone dramatic developments in both NMR instrument hardware and methodology. While it is established that NMR is one of the most powerful tools for understanding biological processes at the atomic level, it has become increasingly difficult for authors and instructors to make valid decisions concerning the content and level for a graduate course of NMR spectroscopy in structural biology. Because many of the details in practical NMR are not documented systematically, students entering into the field have to learn the experiments and methods through communication with other experienced students or experts. Often such a learning process is incomplete and unsystematic. This book is meant to be not only a textbook but also a handbook for those who routinely use NMR to study various biological systems. Thus, the book is organized with experimentalists in mind, whether they are instructors or students. For those who have a little or no background in NMR structural biology, it is hoped that this book will provide sufficient perspective and insight. Those who already have NMR research experience may find new information or different methods that are useful to their research.

Because understanding fundamental principles and concepts of NMR spectroscopy is essential for the application of NMR methods to research projects, the book begins with an introduction to basic NMR principles. While detailed mathematics and quantum mechanics dealing with NMR theory have been addressed in several

well-known NMR books, Chap. 1 illustrates some of the fundamental principles and concepts of NMR spectroscopy in a more descriptive and straightforward manner. Such questions as, "How is the NMR signal generated? How do nuclear spins behave during and after different radio-frequency pulses? What is the rotating frame, and why do we need it?" are addressed in Chap. 1. Next, NMR instrumentation is discussed starting with hardware components. Topics include magnetic field homogeneity and stability, signal generation and detection, probe circuits, cryogenic probes, analog-to-digital conversion, and test equipment. A typical specification for an NMR spectrometer is also included in the chapter. There is also a chapter covering NMR sample preparation, a process that is often the bottleneck for the success of the NMR project. Several routine strategies for preparing samples for macromolecules as well as complexes are dealt with in detail.

Chapter 4 discusses the practical aspects of NMR, including probe tuning, magnet shimming and locking, instrument calibrations, pulse field gradients, solvent suppression, data acquisition and processing, and homonuclear two-dimensional experiments. In Chap. 5, experiments that are routinely used in studying biological molecules are discussed. Questions to be addressed include how the experiments are setup and what kind of information we can obtain from the experiments.

The next chapter focuses on the application of NMR techniques to the study of biological molecules. The use of NMR in studying small biological molecules such as ligands, drugs, and amino acids involved in different biological pathways is covered. Then, applications in studies of macromolecules such as proteins, protein–peptide, and protein–protein complexes are discussed in Chap. 7. Chapter 8 deals with dynamics of macromolecules, important information that can be obtained uniquely by NMR methods.

Chapter 9 discusses essential principles and applications of NMR-based metabolomics. First, fundamentals of multivariate analysis are addressed in a simple and easily understood manner. The next section focuses on sample preparation, which includes detailed procedures and protocols on collecting and preparing biofluid samples, quenching cells and tissues, and extracting metabolites from cells and tissues. Practical aspects of NMR experiments routinely used in metabolomics are also discussed in detail, including experimental setup, data processing and interpretation. In the next section, a number of examples are worked out in detail to illustrate statistical analyses of NMR data and interpretation of the statistical models. Several protocols for using software packages for multivariate analysis are also provided in this section. The last four sections focus on applications of NMR-based metabolomics, including metabolomics of biofluids, cellular metabolomics, live cells, and applications to cancer research.

I would like to thank many colleagues who have used the previous edition in their teaching, and those who have contributed directly or indirectly to this book. I am particularly grateful to Dr. Jun Qin for writing sections of Chaps. 3 and 7, and for numerous discussions, and Drs. Kristen Mayer, Weidong Hu, Steve Unger, Fang Tian, John Glushka, Chalet Tan, Drew Ekman, and Timothy Collette for reviewing all or part of the text and providing corrections, valuable comments, and

encouragement. I am appreciative of the investigators and publishers who have allowed me to use their figures in this text. I am also indebted to the editors and staff at Springer Science+Business Media, especially to Editor Portia Formento, Senior Editor Andrea Macaluso, and Senior Publication Editors Patrick Carr and Felix Portnoy, who made this book happen.

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