NMR Data Handbook for Biomedical Applications

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PERGAMON PRESS

New York • Oxford • Toronto • Sydney • Paris • Frankfurt

Pergamon Press Offices:

U.S.A.	Pergamon Press Inc., Maxwell House, Fairview Park, Elmsford, New York 10523, U.S.A.		
U.K.	Pergamon Press Ltd., Headington Hill Hall, Oxford OX3 0BW, England		
CANADA	Pergamon Press Canada Ltd., Suite 104, 150 Consumers Road, Willowdale, Ontario M2J 1P9, Canada		
AUSTRALIA	Pergamon Press (Aust.) Pty. Ltd., P.O. Box 544, Potts Point, NSW 2011, Australia		
FRANCE	Pergamon Press SARL, 24 rue des Ecoles, 75240 Paris, Cedex 05, France		
FEDERAL REPUBLIC OF GERMANY	Pergamon Press GmbH, Hammerweg 6, D-6242 Kronberg-Taunus, Federal Republic of Germany		

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Library of Congress Cataloging in Publication Data Beall, Paula T.

NMR data handbook for biomedical applications.

includes index.

1. Nuclear magnetic resonance spectroscopy-Handbooks, manuals, etc. 2. Nuclear magnetic-resonance--Diagnostic use-Handbooks, manuals, etc. 3. Nuclear Magnetic resonance spectroscopy--Tables. 4. Medicine--Research--Handbooks, manuals, etc. 5. Biology--Research--Handbooks, manuals, etc. 1. Amtey, Sharad R. II. Kasturi, Sitapati R. III. Title, IV. Title: N.M.R. data handbook for biomedical applications. V. Series. QP519.9.N83B43 1984 610.28 83-25660 ISBN 0-08-030774-4 ISBN 0-08-030775-2 (pbk.)

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Printed in the United States of America

PREFACE

In the decade of the 1970s, nuclear magnetic resonance (NMR) spectroscopy came into its own as a new and exciting tool in biological research. Many scientists and physicians were introduced to the power and diversity of NMR as a diagnostic method through the use of whole body NMR scanners. As these complex and expensive instruments become more common in research and medicine in the 1980s, a new generation of investigators is entering what has been until very recently the narrow and specialized field of biological NMR. This book was written for students, clinicians, and scientists seeking a clearly written simplified text as an introduction to the biological applications of NMR.

The text is divided into 10 chapters, each of which covers a specific block of material and has its own references. The volume is meant to serve as a laboratory handbook and a desk reference, containing basic NMR theory, useful formulae and physical constants, and compiled data from the NMR literature. Chapters 1 and 2 cover the basic theory of NMR and imaging by NMR techniques. The practical applications of multinuclear NMR and the actual methods of measuring NMR parameters are discussed in Chapters 3 and 4. Chapter 5 is a detailed practical guide to the handling of biological samples for in vitro studies. Examples of protocols for tissue biopsies, cultured cells, and blood experiments are given to aid in the reduction of biological variation in NMR studies. In Chapter 6 the dependence of NMR relaxation times on physical variables such as frequency, temperature, and water content is discussed, and tables of experimental data are presented. Problems and solutions to the statistical handling of NMR data are illustrated using a detailed example in Chapter 7. Chapter 8 contains 30 tables of useful physical data, formulae, and constants used in NMR. Chapter 9 contains a series of 26 tables compiled from NMR data in the literature on invertebrate, mammalian, and human systems. It covers the majority of T_1 , T_2 , and D measurements on organisms, tissues, cells, cell organelles, and body fluids in vitro. This heavily referenced section provides background material for those just becoming interested in the field. Many European and eastern European sources are included. In the last section, glossaries of both physical terms for biologists and clinicians and biomedical terms for physical scientists are included to aid in the understanding of this interdisciplinary area of research.

The volume attempts to cover the development of biological NMR through several decades of *in vitro* experiments that have laid the groundwork for and pointed to profitable areas of investigation for new *in vivo* techniques. After gaining an understanding of these basic principles and some historical perspective, the reader will be better prepared to delve into highly specialized volumes on NMR imaging techniques.

The authors wish to acknowledge the assistance of Ms. Jane Lester, Ms. Ann Thompson, Ms. Anita Harris, and Ms. Marina Evagelatos in the preparation of the manuscript. The aid and support of colleagues who contributed to the completion of the book are gratefully acknowledged. Special thanks to Dr. Carlton F. Hazlewood of the Baylor College of Medicine and to Dr. R. Vijayaraghavan of the Tata Institute of Fundamental Research, India, for their constant support and encouragement. The support of our friends and families during the preparation of the book contributed greatly to its completion. Dr. Kasturi wishes to thank his wife, Lakshmi, his daughter, Niraja, and his son, Vikas, for their patience in granting him a year's leave from family responsibilities to do research in the United States.

The authors of this book were partially supported by the following grants and contracts during the writing of the manuscript: Robert Welch Foundation Q-390and the Office of Naval Research contracts N00014-76-C-0100 and N00014-81-K-0167.

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INTRODUCTION

HISTORICAL BACKGROUND OF BIOLOGICAL NMR

Demonstrations of the nuclear magnetic resonance (NMR) phenomenon for hydrogen protons were independently published by Bloch, Hansen, and Packard¹ and Purcell, Torrey, and Pound² in 1946. For this work, Bloch and Purcell shared the Nobel Prize. In their experiments, atomic nuclei of odd spins (in this case hydrogen protons in water or paraffin) in a magnetic field were shown to absorb energy at a characteristic resonance frequency. The first NMR signal was produced from the hydrogen nuclei of water molecules, but little thought was given at that time to the future biomedical application of NMR in wet living systems. In the 1950s physicists utilized NMR to expand our knowledge of the structure and motion of simple molecules. Chemists began to exploit the phenomenon or chemical shift in NMR to collect characteristic absorption spectra of organic molecules that would allow their identification and structural analysis.

In the early 1950s, only a few individuals had begun to explore the potential biological and biomedical applications of NMR. T. M. Shaw and co-workers³⁻⁵ began to use the proton signal intensity from NMR measurements to estimate the water content of plant and animal foodstuffs. The technique has since become an important tool in the food industry for determining the optimum moisture contents for storage and the conditions for freezing meat to prevent rigor or toughness.⁶ However, the man who first published studies describing the use of NMR in the testing of biomedical hypotheses was Dr. Erik Odeblad of Sweden. In 1953, while at the Karolinska Institute in Stockholm, Odeblad, a young gynecologist with a strong interest in physics (Ph.D. in 1966), teamed up with Dr. Gunnar Lindstrom at the Nobel Institute of Physics. Using the first NMR spectrometer in Sweden they began investigations on biological systems which were published in 1955 under the title of "Some Preliminary Observations on the PMR [Proton Magnetic Resonance] in Biological Samples" in Acta Radiologica.⁷ Their initial survey included human and rabbit blood fractions, yeast cells, rabbit liver, muscle, and fat, rat liver, muscle, and fat, calf cartilage, human Achilles tendon, and D₂O. In 1956 they used NMR methods to study

the rapid exchange between D_2O and H_2O in human red blood cells.⁸ Over the next three decades, Odeblad's research team contributed more than 40 papers to the literature on biological NMR research, including studies on human cervical mucus during the menstrual cycle,⁹ tissues and fluids of the eye,¹⁰ human vaginal cells,¹¹ human milk,¹² human gingival tissue,¹³ human saliva,¹⁴ human and animal uterine myometrium,¹⁵ and tongue cells.¹⁶ Of special significance was their discovery of cyclical hormone-controlled changes in the viscosity of cervical mucus that could be related to ovulation and have become the basis of a worldwide birth control effort.¹⁷ Today, Dr. Odeblad is a professor at the University of Umeä, Sweden, and continues to work toward furthering our understanding of the biophysics of water in living systems. His unique contribution, as a physician and a physicist, was that he was a leader in recognizing not just the potential of NMR in biological research, but also its potential as a diagnostic tool in medicine. As early as 1961 he was advocating the inclusion of NMR spectrometers in medical research departments.18

Another entirely different, early biomedical application of proton NMR was its use for measuring blood flow. In 1959 J. R. Singer¹⁹ first demonstrated a method of relating the amplitude of an NMR proton signal in the tail of a live mouse to blood flow through the tail vascular system. In a later design, the difference in signal amplitude between a transmitter coil and a receiver coil, spaced some distance apart over a flowing stream of liquid, could be related to volume flow per minute.²⁰ In 1970, Morse and Singer²¹ demonstrated NMR blood flow measurements in living human subjects, one of whom was Singer's daughter, whose arm was thin enough to fit between the poles of their electromagnet. This approach is now being coupled with NMR imaging to measure blood flow in large arteries and veins with better accuracy than any other method.22

In the late 1950s and into the 1960s, numerous investigators began to realize the potential of NMR to test basic hypotheses about the role of water in biological systems. Because tissues contain 70-90% water and because of the high sensitivity of the hydrogen nucleus, it is possible to look at high-resolution NMR spectra in

the proton region to thereby gain some insight into the behavior of water from these spectra. Bratton, Hopkins, and Weinberg²³ observed a broadening of the proton line width in frog gastrocnemius muscle in a homemade spectrometer in 1965. When the muscle was stimulated to tetanic isometric contraction, the proton signal was distinctly narrowed by $20 \pm 5\%$. In seeking to understand the line broadening, these investigators utilized pulsed NMR techniques to measure T_1 and T_2 relaxation times for the protons in the muscle. Their article was probably the first to incorporate the recognition that an explanation of the NMR findings would require a model of water in the cell which would include at least a small fraction with altered physical properties relative to pure water. Upon the physiological change of contraction, they proposed that a release of a portion of water from this "bound" fraction occurred near macromolecular surfaces.

Sussman and Chin²⁴ confirmed the fact that muscles undergoing physiological changes could be evaluated by NMR methods. Codfish muscle, monitored from 10 min to 6 h after death, showed a proton line width narrowing consistent with the hypothesis that a loss of macromolecular structure and an increase in water mobility would occur.

From the start, biological NMR application was an international effort. Beginning in Sweden and then later in the United States, the field rapidly gained adherents in France, Russia, Mexico, and Japan. In 1966, Rybak et al.25 coupled an electrocardiograph and an NMR spectrometer to measure proton spectra in a beating turtle heart. The turtle heart was removed from the animal, but, as is the case with this organ in the turtle, it continued to beat for hours. Under the conditions of these experiments, a broad line for proton resonance was detectable with each contraction of the ventricle. In Russia, Bruskov also published reports on the use of NMR in biological studies in 1966.26 Cerbon, in Mexico, proposed that water could be restricted in its motion by interactions with lipid-rich membrane systems.^{27,28} Using the Nocardia asteroides microorganism, he was able to correlate changes in water proton and lipid proton absorption peaks in cells treated with Ca2+ salts. In Japan, Koga et al.²⁹ became interested in using NMR to study water in partially dried yeast. The period of 1964-1966 produced the first international burst of interest in biological applications of proton NMR.

During the 1960s and into the 1970s, the relatively small sample chambers and high costs of NMR machines designed for the chemical industry restricted the application of NMR in biology to *in vitro* studies on model systems, cells, and excised tissues. Most of these experiments are summarized in the biological data tables in this volume. So far, all the findings of proton *in vitro* studies, which have been tested, have been confirmed *in vivo*.

These publications provide a firm foundation for the interpretation of NMR imaging data and point toward many new avenues for *in vivo* investigations (see Tables 9.2–9.26 in Chapter 9).

Some investigators also began to consider the use of NMR in studying nuclei other than hydrogen protons in living systems. The greatly reduced sensitivity of other nuclei and their low concentrations in living cells made these experiments difficult. But by using isotope enrichment and signal averaging techniques, some pioneering experiments were accomplished. While Odeblad et al.⁸ had first used D₂O to observe exchange in red blood cells, Freeman Cope first used D₂O in 1969³⁰ to examine the structure of water in muscle and brain. His findings suggested that multinuclear studies using ¹H, ²D, and ¹⁷O NMR in the same system would aid in the interpretation of NMR water data (see Table 9.2 in Chapter 9). In 1965 Cope³¹ also published the first ²³Na NMR studies on biological tissues, which he interpreted as evidence for the complexing of Na⁺ to cellular proteins in muscle, brain, and kidney. However ²³Na NMR data interpretations were and still remain somewhat controversial (see Table 9.22 in Chapter 9). Biological ¹⁷O NMR studies of water were reported by Glasel³² as early as 1966 (see Table 9.23 in Chapter 9). In 1970, Cope and Damadian³³ extended their studies to the NMR of the ³⁹K nucleus in bacteria. They concluded that cellular potassium could not be considered to be in a free solution. In 1979, they were able to measure ³⁹K NMR in live newborn mice³⁴ (see Table 9.21 in Chapter 9). The use of other exotic nuclei in biological NMR was explored somewhat later.

In 1973, Moon and Richards³⁵ were able to accumulate sufficient ³¹P signals over 5.5 h to prepare a phosphorous spectrum from rabbit blood. The primary component of the spectrum was 2,3-diphosphoglycerate, from the red cells. They also originated the idea of measuring intracellular pH from the chemical shift between inorganic phosphate in the cell and the extracellular compartment (where the pH is known). This is probably the most accurate method ever invented to measure intracellular pH. In 1974 Hoult et al. demonstrated that quantitative metabolic spectra could be obtained from rabbit muscle in approximately 400 s with improved instrumentation.³⁶ Their work first showed the alternations in ATP and its metabolic products, ADP, AMP, and P_i, as a function of time in an excised rat leg muscle. ³¹P NMR has continued to yield information about metabolite levels, turnover,

interactions, and compartmentation in both normal and diseased tissues. Today, *in vivo* ³ P NMR is an exciting adjunct to whole body proton imaging techniques^{37,38} (see Tables 9.24, 9.25, and 9.26 in Chapter 9).

In 1977 Fung, using ¹³C spectra of natural and dehydrated mouse muscle, proposed that a significant amount of mobile organic molecules existed in these cells.³⁹ Enriched and natural abundance ¹³C spectra from many types of tissues are now used in characterizing physiological states and disease processes^{40,41} (see Table 9.19 in Chapter 9).

While some investigators were exploring the possibilities of multinuclear NMR experiments using biological samples, there were a few individuals who began to look into the future of NMR as a biomedical tool. They primarily concentrated on the development of *in vivo* methods to study parts of whole living organisms. The altimate medical usefulness of NMR would depend on their contributions, which led to whole body spectra and NMR imaging in humans.

One of the most interesting references in the area of in vivo NMR is the master's thesis of Thomas Richard Ligon, published in 1967 at Oklahoma State University.⁴² Ligon stated that, after reading the study by Bratton, Hopkins, and Weinberg²³ on proton NMR of an isolated frog muscle, he saw no reason why this could not be done in vivo in human arms. As a graduate student in the Department of Physics at Oklahoma State, under Dr. V. L. Pollack, he began work on a coil design for low-field NMR experiments which could be used on a human arm at frequencies of 4.26 KHz to 1.66 MHz, surprisingly close to current imaging frequencies. Recruiting fellow students as subjects and using a number of wide-gap electromagnets on the campus, he proceeded to measure proton signal, T_1 , and T_2 of the human arm. He made the fundamental discoveries that T_1 and T_2 data in vivo were not exactly exponential, that relaxed and contracted muscle could be differentiated, that prepuberty males had muscle values different from those of postpuberty males, that values for male and female arm differed, and that the fat content of the tissue was a problem in interpreting the data.

More mature scientists had also begun to think seriously about using NMR in living animals. In 1968, J. A. Jackson published two articles^{43,44} describing the design and construction of a solenoid large enough to hold a whole rat. The proton spectra he published included that of a whole chicken egg and the body of a whole live rat. These experiments certainly qualify as early *in vivo* studies, although they were not very sophisticated.

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Among those scientists still examining the diagnos-

tic potential of NMR in *in vitro* excised tissues was Raymond Damadian. In 1971, he published data supporting the possibility that NMR could distinguish normal from cancerous tissues.⁴⁵ He must also have been thinking about the future application of NMR technology in the human body because in March of 1972 he filed a United States patent application⁴⁶ entitled, "Apparatus and Method for Detecting Cancer in Tissue" (patent no. 3789832), which dealt with this idea. Weisman et al., who were familiar with the work of Damadian, published in the same year a short paper in Science showing how NMR signals from a tumor implanted in the tail of a live rat could be monitored from day to day by NMR methods.⁴⁷

However, these investigators were certainly not the only ones thinking and working on the adaptation of NMR to living animals and humans. At this point, the history of the development of NMR imaging and in vivo applications becomes much more complex. Some individuals made theoretical contributions toward the techniques that led to imaging by NMR. Some contributed in vitro data which pointed the way for future use of NMR in vivo. Others engineered and built the large magnets and specialized coils for the first attempts, and then there were those who did the first experimental work. Every case demonstrates the tremendous teamwork among physicists, engineers, and biologists that was necessary for the accomplishment of the first image of the human body in 1977.48 The following paragraphs mention only a few of the leaders of research teams that made significant early contributions.

Damadian's research group at Downstate Medical Center in New York City was dedicated to making a reality out of the possibility of localized NMR scanning in living organisms. In a recent book, he stated that he came up with the idea while making ³⁹K NMR measurements on pellets of bacteria in 1969. After the experiment in 1971⁴⁵ that showed differences in T_1 relaxation times between normal and cancerous rat tissue in vitro, his group began to work on a method for locating tumors in a living animal. The method was called "field focusing nuclear magnetic resonance" (FONAR) and used the concept of moving the sample (or body) through a point (saddle point) in a static magnetic field. Collection of data after many such movements allowed the formation of a compiled image. This technique was used to produce the first image of a live animal in 1976.49 A similar technique was proposed in the application for a patent by Abe and Tanaka in 1973.50

It had been known for some time that there was another method for the spatial localization of NMR information in simple glass and liquid constructs. The imposition of a linear magnetic field gradient on the homogeneous laboratory magnetic field would produce a one-dimensional (1D) profile or projection of proton density along the direction of the gradient.^{51,52} This 1D method would be used by Mansfield and Grannell in 1973⁵³ to investigate periodic structures by an NMR diffraction method.

However, in 1973, Lauterbur⁵⁴ conceived of an improvement in this method for the production of NMR images. His technique consisted of coupling the resonant NMR electromagnetic field with a spatially defining inhomogeneous field or static field gradient. A two-dimensional (2D) image could be made by combining several projections taken either as the object was rotated around the gradient or as the gradient was rotated about the object. Using this method he was able to produce a 2D image of two capillaries filled with water and separated by approximately 4 mm. He suggested that the term "zeugmatography," from the Greek word zeugma (that which joins together), be used for this process. The technique has now been extended to three-dimensional (3D) imaging produced by the adjustment of the currents in three sets of gradient coils. Information over a large spherical volume can be collected relatively rapidly, but requires complex computer processing.55

Some other research groups which also made significant contributions to the development of early NMR imaging techniques are mentioned below.

Hutchison and co-workers at Aberdeen began work on (ESR) spectra in biological tissues in the 1960s. They were able to transfer their knowledge to NMR, and, in 1974, Hutchison et al.⁵⁶ published a projection reconstruction image of a dead mouse that looked like a mouse and indicated differences in T_1 values among the organs of the animal. This group also has made contributions in producing pure T_1 images⁵⁷ and in a methodology called "spin-warp" imaging.⁵⁸ Mansfield and Grannell,⁵³ having had previous

Mansfield and Grannell,⁵³ having had previous experience with 1D NMR diffraction, expanded their method to measure and reconstruct an image of a live human finger in 1977 by selective irradiative line scanning.⁵⁹ Hinshaw et al.^{60,61} developed a sensitive point and a multiple sensitive point method for imaging, using one static and two oscillating field gradients. In this technique, a sensitive line was created through the sample and more data could be collected in a shorter period of time. They were able to publish an image of the live human wrist in 1977.⁶²

Other individuals and groups certainly made many contributions to theoretical and experimental improvement of NMR imaging techniques during this period. And the historical reality of this work is that it was done with little funding and despite much criticism by a few who warned that NMR imaging would never be practical. In the midst of controversy and doubt as to whether NMR imaging with good resolution would ever be achievable, Damadian et al., in 1977, published the first NMR image of a human thorax.⁴⁸ With dedication and determination, they had succeeded in demonstrating that a large enough magnet could be built and that many of the doubts about the feasibility of whole body NMR could be overcome.

From that point on, the growth of NMR imaging was phenomenal. Commercial development of whole body scanners made their use practical in medical diagnosis. Two scientific societies and a number of specialized journals are operational. The number of published articles relating to biological uses of NMR has increased from less than half a column in *Index Medicus* in 1973 to a page and a half in 1983. Hundreds of clinicians, students, and health professionals are finding that "NMR imaging" is a term they must add to their vocabularies. And research scientists, even those who were acquainted with NMR, are discovering a whole new field of specialized applications.

This volume was written to bring together the basic information and decades worth of biological data for use by those seeking an introduction to biological NMR. After reading this book, a reader will be better able to understand specialized books on NMR imaging or state of the art clinical reports. It is the authors' hope that this book will become a convenient desk reference for their colleagues in NMR.

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CHAPTER 1

STATES OF WATER IN BIOLOGY*

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1.1. INTRODUCTION

The role of water in biological processes has been under investigation since the times of the ancient Greeks. Those scientific philosophers divided matter into "earth, fire, and water." Classical investigations dealt with the determination of the water content of plants and animals by desiccation, but could go no further until more sophisticated chemical and physical techniques became available to biologists in the 20th century.

In the first half of this century biologists and biochemists were able to define some of the functions of water in cells. Water serves as the primary biological solvent in which all other cellular components and solutes diffuse in interacting with one another. In many biochemical reactions water serves as the donor of hydrogen ions, and the dissociation of water contributes to the regulation of cellular pH. Because of its high heat capacity, water stores metabolic energy and helps to regulate an organism's temperature. Through hydrophobic and hydrophilic interactions water contributes to the stabilization of three-dimensional macromolecular structure, and even stabilizes giant cellular constructs such as lipid bilayer membranes and microtubules. Water is the lubricant of the tissues and, in combination with polysaccharides, can provide low-friction films on surfaces. The end products of the metabolic pathways are carbon dioxide and water, so cells not only use water, they also synthesize it. Therefore, a great deal of biological function pertains to the consumption, regulation, and excretion of water. But what is this water like when it is inside cells? Since about 1950, techniques from physics have been borrowed by biologists to examine the physical state and mechanical properties of water in biological systems. In this chapter, some of these findings and their significance will be discussed.

6

There are three possible physical states of water in cells-gas, liquid, and solid states. In the temperature and pressure ranges of terrestrial life, we see water vapor present in the external environment or in the lungs, but rarely is the gaseous phase of water considered to be important inside the cell. Therefore, investigations of the liquid and solid states of water in biology are most commonly undertaken. Cryobiology is the study of the process of conversion of biological water to crystalline solid ice or, upon occasion, the peculiar biochemistry of organisms which prevents crystalline solid formation and substitutes other solvent forms at very low temperatures. Here, discussion will be concentrated on what has been learned about water in functioning metabolizing cells in their normal viable temperature range. Such water exists in a state somewhere between the solid state of crystalline ice and the liquid, hydrogen-bonded lattice of pure water (Fig. 1.1).

*Chapter 1 is a revision of an article entitled "States of Water in Biological Systems" that originally appeared in

Cryobiology 20:324-334, 1983. By permission of Academic Press, Inc.



ICE-----BULK

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Fig. 1.1. States of water in biological systems.

1.2. BEHAVIOR OF PURE WATER

Excellent reviews concerning the physical findings on pure water and on water in dilute solutions of salts and polymers are available.¹⁻⁵ They point out that attempts to define the physical nature of pure liquid water have not been totally successful; therefore, it seems unlikely that we will be able to define the state of water in biological systems with any great accuracy. What we can do is make comparisons between the measurements of water in living systems and those taken on pure liquid water or ice by the same techniques.⁶⁻⁹

Numerous biophysical techniques have now been applied to living systems. Some of these are shown in Fig. 1.2 in relation to the time over which a measurement of the physical properties of water can be made. A critical number on this time scale is τ_{DHO} at 10^{-11} s. The $\tau_{\rm DH,O}$ is the diffusional correlation time or the time between jumps in position for water molecules in the system. In ice, τ_D is slow at ~10⁻⁵ s, while in pure liquid water, τ_D is ~10⁻¹¹ s, or 1 million times faster. Many of the physical properties of water can be theoretically related to τ_D , and the derivations of equations for biophysical techniques often include this parameter. Consequently, the ability of a biophysical technique to yield information about the physical state of water depends on how quickly a measurement can be made. On the left side of Figure 1.2 the type of structure that a technique can probe is related to the time scale. Methods such as infrared and Raman spectroscopy and inelastic neutron scattering yield information about intramolecular factors such as H-O bond lengths and hydrogen bond angles (geometric factors, Fig. 1.3). Techniques that require measurement times greater than the diffusional correlation time, however, will always yield an average over all molecules in the population, with a kinetic contribution from diffusion. They will more generally yield information about interactions between water molecules, and between



TIME SCALE OF BIOPHYSICAL MEASUREMENTS

Fig. 1.2. Time scale of biophysical measurements. τ_D , correlation time for water motion.