Jay W. Pettegrew
Editor

NMR: Principles and Applications to Biomedical Research

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Jay W. Pettegrew
The Graduate School of Public Health
University of Pittsburgh
Pittsburgh, Pennsylvania 15261, USA

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Preface

Nuclear magnetic resonance (NMR) is having an enormous impact on biomedical research both at the basic science and clinical levels. In order to appreciate the elegance and power of this technology a historical perspective is in order.

In 1924 Pauli suggested that hydrogen nuclei might possess a magnetic moment. This was in fact confirmed by Rabbi in 1939 who demonstrated that a beam of hydrogen molecules in the presence of a magnetic field could be mutated by radio frequency fields resonating at the Larmor frequency.

The first successful NMR experiments in condensed matter were independently conducted in late 1945 by Purcell, Torrey and Pound and by Bloch, Hansen and Packard. The Purcell group detected proton NMR in solid paraffin and the Bloch group detected proton in liquid water. Bloch and Purcell received the Nobel Prize in physics in 1952 for these observations.

Until about 1952, studies of liquids and solids with broad resonance lines dominated the field of NMR. However, the reports of ^{31}P NMR chemical shifts in several compounds in 1949 by Knight, of ^{14}N resonances in several ions by Proctor and Yu in 1950, and of ^{19}F resonances in several compounds in 1950 by Dickinson led to the development of high resolution NMR in liquids. Since the molecular motions in liquids result in very narrow lines compared to those in

solids, much smaller chemical shifts could be detected. This resulted in high resolution NMR of liquids dominating the field for the past 30-40 years. Recently, however, there has been a significant renewed interest in the NMR of solids both in the chemical and energy industries and more recently in biomedical research. In each of these instances, solid state NMR techniques have provided insights into molecular and macromolecular structure and dynamics not available with other experimental approaches. Before NMR could develop into a more widely utilized research tool, several technological advances were necessary. In 1957 Lowe and Norberg demonstrated that the NMR spectrum in the frequency domain, as obtained by a continuous wave (cw) experiment, was the Fourier transform (FT) of the NMR free-induction decay (FID) obtained in the time domain. This important observation lead to the development of pulsed FT NMR. The increased efficiency of FT NMR over cw NMR was demonstrated in 1966 by Ernst and Anderson and FT NMR has been the predominant NMR method up to the present. However, cw NMR may find renewed application in the field of human in vivo spectroscopy in the future. Other NMR techniques were developed to remove the undesirable effect of inhomogeneity in the applied field. These were called spin-echo techniques and were first proposed by Hahn in 1950. Spin-echo techniques have been of particular importance in the measurement of spin relaxation times as described in 1954 by Carr and Purcell and further modified in 1958 by Meiboom and Gill. Another important advance was the development of high-field NMR in 1967 by Bothner-By and Dadok. These researchers are continuing the development of high field NMR and have the world's highest field NMR operating at 14.56 Tesla.

The first potential medical application of NMR was described by Damadian in 1971 for the detection of tumors and a patent for this application was awarded to Damadian in 1972. In 1973 Lauterbur

proposed and demonstrated the imaging potential of NMR. This was quickly followed by the development of several approaches to NMR imaging. In 1974 Mansfield developed the pulse gradient approach for image slice selection; in 1975 Ernst developed a phase encoding technique for imaging and in 1977 Edelstein, Hutchison, Johnson and Redpath developed the spin warp technique for imaging. The first human NMR scan was achieved by Damadian in 1977 and the first topical ^{31}P NMR spectrum was obtained by Gordon and coworkers in 1978.

Since these first demonstrations of the potential application of in vivo NMR imaging and spectroscopy to biomedical research, a great deal of progress has been made. NMR technological advances were primarily responsible for this first wave of progress. However, the next wave of advances in biomedical NMR research will come less from technological advances and more from the creative application of this powerful technique to the understanding of molecular and metabolic process operating in both normal and disease states. The purpose of this book is to review the fundamental theory and principles needed to understand selected aspects of NMR and then demonstrate the application of these principles to important unsolved biomedical research questions. It is not the intent of this book to be either encyclopedic or minutely detailed. Rather, it is hoped that the reader will sense the excitement and potential that NMR offers biomedical research and be stimulated to embark on his or her own program of continuing study. The topics chosen reflect the perceptions of the contributors as to what will be the important areas of future biomedical NMR research.

The book is presented in sections that start with one or more chapters discussing the theory and principles applicable to certain NMR topics such as high-resolution and two-dimensional NMR, NMR relaxation theory, solid state NMR and in vivo NMR spectroscopy and imaging. These chapters are immediately followed by one or more chapters that

demonstrate the application of the particular NMR method to some aspect of NMR biomedical research.

I want to thank my esteemed contributors who deserve considerable credit for all the good parts of this book. Any errors, limitations and oversights are solely of my doing. I wish to thank Kanagasbai Panchalingam and Donald Woessner for editorial assistance and Kathy Yobbi for typing the many revisions of the entire manuscript.

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Contributors

Adler, S.

Associate Dean and Professor of Medicine, University of Pittsburgh School of Medicine, M240 Scaife Hall, DeSoto and Terrace Streets, Pittsburgh, Pennsylvania 15261

Altman, R.B.

Research Associate, Stanford Magnetic Resonance Laboratory, Stanford University, Stanford, California 94305-5055.

Andreasen, N.C.

Professor of Psychiatry, Department of Psychiatry, The University of Iowa College of Medicine, 500 Newton Road, Iowa City, Iowa 52242.

Bendall, M.R.

Head, Department of Chemistry and Biochemistry, James Cook University, Townsville, Queensland, 4811, Australia

Blakley, N.R.

Systems Programmer, Department of Psychiatry, The University of Iowa College of Medicine, 500 Newton Road, Iowa City, Iowa 52242.

Bothner-By, A.

Professor Emeritus of Chemistry, Department of Chemistry, Carnegie Mellon University, 4400 Fifth Avenue, Pittsburgh, Pennsylvania 15213.

Brinkley, J.F.

Research Associate, Department of Biological Structure, SM-20, University of Washington, Seattle, Washington 98195.

Buchanan, B.

Professor of Computer Science, Department of Computer Science, University of Pittsburgh, Pittsburgh, Pennsylvania 15260.

Duncan, B.S.

Stanford Magnetic Resonance Laboratory, Stanford University, Stanford, California 94305-5055.

Ehrhardt, J.C.

Professor of Radiology, The University of Iowa College of Medicine, 500 Newton Road, Iowa City, Iowa 52242.

Farrar, T.C.

Professor of Chemistry, Department of Chemistry, University of Wisconsin, 2203 Chemistry Building, Madison, Wisconsin 53706

Frye, J.S.

Research Associate, Department of Chemistry, Colorado State University, Fort Collins, Colorado 80524.

Gasparovic, C.

Center for Non-Invasive Diagnosis, University of New Mexico, School of Medicine, Albuquerque, New Mexico 87131.

Glickson, J.D.

Professor of Radiology and Biological Chemistry, Johns Hopkins Hospital, MRI Building, Room 110, 600 North Wolfe Street, Baltimore, Maryland 21205.

Glonek T.

Associate Professor of Physiology, Chicago College of Osteopathic Medicine, Director, MR Laboratory, 5200 S. Ellis Avenue, Chicago, Illinois 60615.

Gore J.

Associate Professor, Department of Radiology, Yale University, 333 Cedar Street, New Haven, Connecticut 06510.

Greiner, J.V.

Cornea Service, Department of Ophthalmology, Harvard Medical School, The Massachusetts Eye and Ear Infirmary, Ophthalmology Service, Beth-Israel Hospital and The Eye Research Institute, Boston, Massachusetts 02114.

Griffey, R.

Assistant Professor, Department of Cell Biology, University of New Mexico School of Medicine, Albuquerque, New Mexico 87131.

Jardetzky O.

Professor of Pharmacology, Director of Stanford Magnetic Resonance Laboratory, Stanford University, Stanford, California 94305-5055.

Kyner E.

Department of Neurology and Physiology, University of New Mexico, Albuquerque, New Mexico 87131.

Lass, J.H.

Division of Ophthalmology, Case-Western Reserve University, Cleveland, Ohio 44106.

Latchaw, R.E.

Professor of Radiology and Neurological Surgery, Chief, Division of Neuroradiology, University of Pittsburgh, M-260 Scaife Hall, Pittsburgh, Pennsylvania 15261.

Li, S.J.

Assistant Professor, Department of Radiology, Milwaukee County Medical Complex, Milwaukee, Wisconsin 53226

Lowe, I.J.

Professor of Physics, Department of Physics and Astronomy, University of Pittsburgh, 0409 Allen Hall, 3941 O'Hara Street, Pittsburgh, Pennsylvania 15260.

Matwiyoff, N.A.

Professor, Department of Radiology, Director, Center for Non-Invasive Diagnosis, Chairperson, Department of Cell Biology, University of New Mexico School of Medicine. Albuquerque, New Mexico 87131.

Panchalingam, K.

Research Assistant, Professor of Psychiatry, Neurophysics Laboratory, University of Pittsburgh School of Medicine, 130 DeSoto Street, Pittsburgh, PA 15261.

Pettegrew, J.W.

Associate Professor of Psychiatry and Neurology, University of Pittsburgh School of Medicine, Director, Neurophysics Laboratory, Western Psychiatric Institute and Clinic, 130 DeSoto Street, A710 Crabtree, GSPH, Pittsburgh, Pennsylvania 15261.

Rajan, S. S.

Assistant Professor, Department of Radiology, Georgetown University School of Medicine, Washington, D.C. 20007

Rosenberg, G.A.

Professor and Chairman of the Department of Neurology and Physiology, University of New Mexico School of Medicine, Albuquerque, New Mexico 87131.

Smith, I.

Director, Division of Biological Sciences, National Research Council of Canada, Ontario, Canada K1A0R6

Steen, R.G.

Assistant Professor, Department of Radiology, University of Washington School of Medicine, Seattle, Washington 98195

Swayze, V.W. II

Assistant Professor, Department of Psychiatry, The University of Iowa College of Medicine, 500 Newton Road, Iowa City, Iowa 52242.

Wehrle, J.P.

Assistant Professor, Department of Radiology, Division of NMR Research, John Hopkins School of Medicine, Baltimore, Maryland 21205.

Welch, K.M.A.

Chairman, Department of Neurology, Henry Ford Hospital, 2799 W. Grand Blvd., Detroit, Michigan 48202.

Withers, G.

Post-Doctoral Teaching Associate, Department of Chemistry, Carnegie-Mellon University, 4400 5th Avenue, Pittsburgh, Pennsylvania 15213.

Woessner, D.E.

Senior Research Associate, Mobil Research and Development Corporation, Dallas Research Laboratory, 13777 Midway Road, Dallas, Texas 75244.

Contents

Principles of Pulse NMR Spectroscopy

T.C. Farrar

I. Introduction

A great many, if not most, of the compounds that we encounter in our daily lives are diamagnetic. These substances are not magnetic, but if we place them in a magnetic field they will develop a net magnetization. NMR spectroscopy is concerned primarily with compounds of this type. The human body is composed primarily of diamagnetic materials and because of this whole body imaging is possible. Although whole body and other imaging experiments are dramatic and exciting new ways of applying the power and versatility of NMR methods, a wide range of other applications also exit. In this introductory chapter we outline the basic principles of NMR spectroscopy and mention a few of the more important applications (Farrar 1987).

II. Relaxation and Energy Levels

It is well known from basic NMR theory [Farrar 1987] that an isolated nucleus of spin I, has 2I + 1 energy levels, equally spaced with a separation, ΔE, given by

$$\Delta E = \mu B_0 / I \qquad (1.1)$$

where B_0 is the applied magnetic field and μ, the nuclear magnetic moment, is given by

$$\mu = \gamma hI/2\pi = \gamma \hbar I \qquad (1.2)$$

where γ is the gyromagnetic ratio, a constant for a given nucleus, h is Planck's constant, and $\hbar = h/2\pi$. From the usual Bohr relation, the frequency of radiation that induces a transition between adjacent levels is

$$\nu_o = \Delta E/h = \nu B_o/(2\pi)\,\text{Hz} \tag{1.3}$$

or

$$w_o = 2\pi\nu_o = \gamma B_o(\text{rad/sec}). \tag{1.4}$$

At equilibrium, nuclei are distributed among the energy levels according to Boltzmann distribution. Following any process that disrupts this distribution, the nuclei will relax back to the equilibrium configuration. For example, if the sample is moved into or out of the magnetic field, or if the sample absorbs r.f. energy, the nuclear spin system returns to equilibrium with its surroundings, the lattice, by a first-order relaxation process characterized by a time, T_1, the spin-lattice relaxation time. We shall discuss relaxation processes in more detail later in this chapter. For the present it is sufficient to note that T_1 may vary over a wide range (approximately 10^{-4} - 10^{+6} sec). For small diamagnetic systems T_1 is typically of the order of 0.1 to about 10 sec, for a spin 1/2 nucleus.

Since a nucleus remains in a given energy level no longer than T_1 on the average, we can estimate the minimum width of the NMR line from the Heisenberg uncertainty principle:

$$\Delta E \Delta t \geq h, \tag{1.5}$$

where ΔE and Δt are the uncertainties in measurement of energy and time, respectively. For the case we are considering, with a line of full width at half-maximum (lwhm) intensity $\Delta_{1/2}$, this becomes

$$(h\Delta_{1/2})T_1 \geq h, \quad \Delta_{1/2} \geq 1/T_1 \tag{1.6}$$

Often lines are broader than indicated by equation 1.6. For example, in solids or slowly tumbling molecules in liquids, magnetic dipole-dipole interactions between nuclei lead to appreciable line broadening, sometimes several kilohertz, as compared with the width of about 1 Hz expected from equation 1.6 for T_1 = 1 sec. To account for processes that cause the nuclear spins to come to equilibrium with each other, a second time, T_2, the spin-spin relaxation time, is defined so that

$$\Delta_{1/2} = 1/T_2. \tag{1.7}$$

To agree with the more precise definition of T_2 that we shall introduce in Section 1.2, we relate T_2 to the width of a Lorenzian line by the equation

$$\Delta_{1/2} = 1/(\pi T_2). \tag{1.8}$$

In this discussion we have been referring to the natural width of the resonance line determined by molecular processes. If the magnetic field is not perfectly homogeneous, nuclei in different parts of the sample experience slightly different values of the field; hence by equation 1.3 they resonate at slightly different frequencies. This leads to a contribution to the line width due to inhomogeneity (ΔB_0) of

$$\Delta_{1/2}(\text{inhom}) = \gamma(\Delta B_0)/(2\pi). \tag{1.9}$$

By analogy to equation 1.8, we can define a time T^*_2 in terms of the observed line width as

$$\Delta_{1/2}(\text{obsvd}) = 1/(\pi T^*_2). \tag{1.10}$$

Thus T^*_2 includes contributions from both natural line width and magnetic field inhomogeneity:

$$1/T^*_2 = 1/T_2 + (\Delta B_0/2\pi) \tag{1.11}$$
$$= 1/T_2 + 1/T_2.$$

1.2 Magnetization and Demagnetization

Although many features of NMR spectra can be understood only by quantum mechanical considerations based on the energy level approach of Section 11, a number of properties are more easily visualized through a classical treatment. Most of the pulse experiments that we shall consider fall into this category. Hence we shall use the classical treatment almost exclusively. For this treatment we shall construct several simple physical pictures of the fundamental processes that take place in an NMR experiment. We shall use these simple concepts to design a number of useful experiments. The basic concepts that we shall discuss are:

1) nuclear magnetization processes

2) thermodynamic processes

3) motional processes of the magnetization vector, $\vec{M}$