1

Introduction

1.1 INTRODUCTION

This book explores the physics phenomenon that provides the foundation for and the engineering architectures that facilitate the widespread applications of nuclear magnetic resonance (NMR) spectroscopy and magnetic resonance imaging (MRI). NMR is the physics phenomenon at the basis of every MRI experiment. The first word, "*nuclear,*" refers to the core player of this phenomenon – stable atomic nuclei. The protons in a common water molecule are the most useful nuclei because of their high sensitivity and simplicity. *Please make a note that when we say* ***proton*** *in NMR and MRI literature and in this book, we mean* ***hydrogen atom****, not the nucleon*. Since these nuclei are stable, there is never any radioactivity in *NMR*. The second word, "*magnetic,*" refers to the environment that these nuclei must have – the nuclei need to be immersed in a magnetic field, which can be generated in several ways including the use of a permanent magnet. The third word, "*resonance,*" refers to a concept in physics where a system has the tendency to oscillate at the maximum amplitude at a certain frequency f (Figure 1.1). This resonance system can be mechanical (e.g., the pendulum studied by Galileo Galilei in 1602, and the collapse of several suspension bridges in Europe in the 1800s by marching soldiers), acoustic (e.g., many musical instruments), and electromagnetic (e.g., an electronic receiver in your radio and television). To receive the signal from a particular channel or station among the tens or hundreds of channels and stations available, the resonant frequency of a receiver in a radio or television set is adjusted either manually by turning a knob/dial in an analog circuit of a classical (i.e., pre-digital) radio or TV, or by scanning automatically over a range of frequencies in digital receivers. When the right frequency is met, the signal can reach the maximum.

Let us clarify the terminology of the NMR phenomenon, since it has several acronyms as well as sub-fields. NMR is the original and full name of the phenomenon, which now commonly refers to its physical principles. NMR spectroscopy is the spectroscopic application of NMR, which seeks the chemical information in the process; this term is used commonly in basic science and in particular in physics and chemistry. NMR imaging is the imaging application of NMR, which mainly seeks the spatial information in the process; this term is used mainly by the non-medical imaging community. MRI is identical in content to NMR imaging, which is the term that is commonly used in the medical community (and by everyone else who is not in basic science). Microscopic MRI (μMRI) and NMR microscopy are the high-resolution versions of MRI.

Essential Concepts in MRI: Physics, Instrumentation, Spectroscopy, and Imaging, First Edition. Yang Xia.

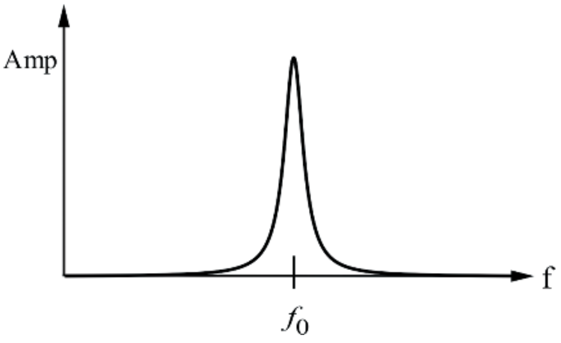
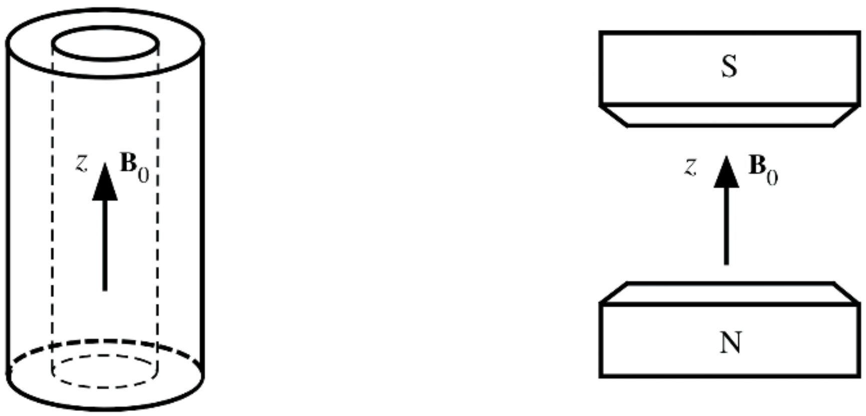


Figure 1.1 The resonance phenomenon, where the signal amplitude reaches a maximum at a particular frequency f_0.

1.2 MAJOR STEPS IN AN NMR OR MRI EXPERIMENT, AND TWO CONVENTIONS IN DIRECTION

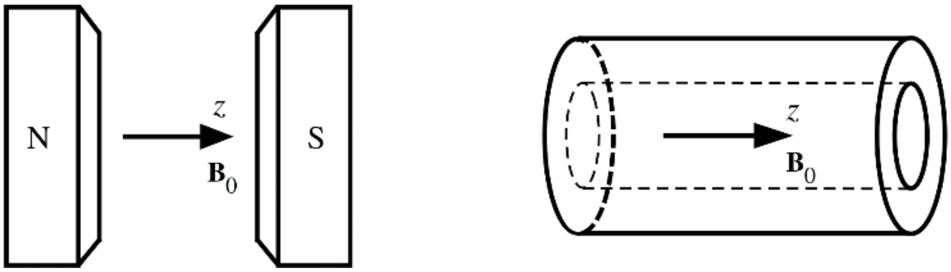
The description of NMR and MRI theory would become easier if we first briefly overview what is involved in an NMR experiment. In general, an NMR or MRI experiment consists of three sequential "stages": preparation, excitation, and detection. In the first stage, a sample is placed in an externally applied magnetic field $\boldsymbol{B}_0$, which allows the nuclear ensemble in the sample (e.g., water molecules in humans or animals or plants or test tubes) to reach the thermal equilibrium state. This preparation stage results in a net macroscopic magnetization in the sample. In the second stage, a perturbation is applied to the sample in order to force the net magnetization away from the thermal equilibrium into a non-equilibrium state. Finally, the response of the net magnetization to this perturbation is recorded via the detector, where the recording is termed as the NMR or MRI signal. Final post-acquisition signal processing generates an NMR spectrum or an MRI image. These three sequential stages in an NMR or MRI experiment are controlled by a list of individual commands, and each occurs at a different time. This list of commands is called a pulse sequence. Chapter 5, Chapter 6, and Chapter 13 will discuss the details of these instrumentational and experimental aspects.

A convention in NMR and MRI is that the externally applied magnetic field that is used to establish the net magnetization is *always* named as the $\boldsymbol{B}_0$ field, which is a vector field and has a direction *always* along the *z* axis (Figure 1.2), that is, $\boldsymbol{B}_0 = B_0\boldsymbol{k}$, where $\boldsymbol{k}$ in this expression is the usual unit vector along the *z* direction in a 3-dimensional (3D) Cartesian coordinate system. The direction of this *z* axis in Cartesian coordinates, however, can be either in the vertical direction (for vertical-bore superconducting magnets, which are common in research labs, or "open" MRI scanners, which reduce claustrophobia for some patients) or in the horizontal direction (for the electromagnets in research labs, the "vertical donut" magnet MRI, or the horizontal-bore superconducting magnets in common clinical MRI scanners).



(a) Superconducting Magnet (vertical bore)

(b) Magnet in Open MRI



(c) Electromagnet or "Vertical Donut" Magnet

(d) Superconducting Magnet (horizontal bore)

Figure 1.2 The B_0 direction in NMR and MRI. (a) Vertical-bore superconducting magnet, which is common for NMR spectrometers in science and industry laboratories. (b) “Horizontal double-donut” magnet for “open” MRI. (c) Electromagnet or magnet in “vertical double-donut” MRI. (d) Horizontal-bore superconducting magnet, which is common for whole-body imagers for humans or animals.

In addition, this book adapts the convention that the clockwise rotation is positive when one looks into the arrowhead of any axis, shown in Figure 1.3. Among the NMR and MRI literature, this convention for rotation is not consistently adapted (*i.e., some authors use the counterclockwise rotation as the positive rotation*). This inconsistency can lead to either a + or – sign in some equations that describe the motion of the macroscopic magnetization. The notation used in this book is consistent with many books; for example, those by Fukushima and Roeder [1], Callaghan [2], Canet [3], and Haacke *et al.* [4]. We will comment on this issue at several places in Chapter 2.

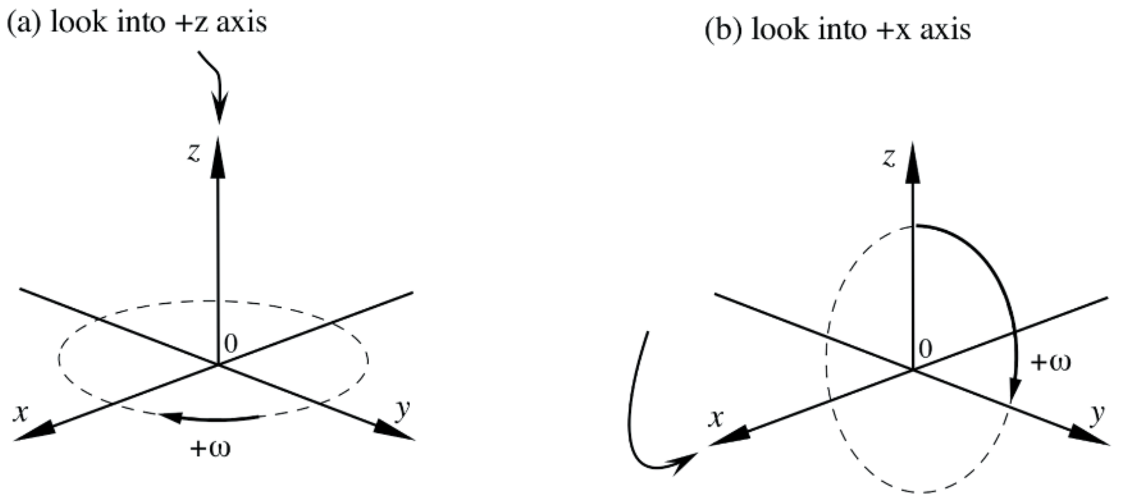


Figure 1.3 The positive directions of rotations in a 3D Cartesian coordinate system, (a) when one looks into the +*z* axis, and (b) when one looks into the +*x* axis.

1.3 MAJOR MILESTONES IN THE HISTORY OF NMR AND MRI

The physics of NMR started in 1924 when Wolfgang Pauli suggested that hydrogen nuclei might possess a magnetic moment. Pauli made this suggestion based on the observation of optical spectroscopy hyperfine splitting. The first observation of a nuclear magnetic moment was made in 1938 by Isidor I. Rabi, who used molecular-beam magnetic resonance to measure the signs of nuclear magnetic moments in individual atoms and molecules. In 1946, the phenomenon of NMR in liquids and solids was first reported simultaneously by two groups of scientists: Purcell, Torrey, and Pound at Harvard using paraffin as the specimen [5]; and Bloch, Hansen, and Packard at Stanford using water as the specimen [6]. The practical usefulness of NMR was noticed in 1950 by Proctor and Yu [7] and by Dickinson [8], who found that in ammonium nitrate and a variety of fluorine compounds, some kind of chemical effect caused the compounds to have multiple resonant lines. With the publication of the first ethanol spectrum where the three groups of protons in the same ethanol molecules resonated at three different frequencies (Figure 1.4) [9], the power of the NMR technique, being able to measure different chemical environments inside the same molecule (later termed "chemical shift"), initiated the widespread application of NMR in chemistry.

In 1950, Erwin L. Hahn developed a practical way to form a spin echo by using two radiofrequency (rf) pulses [10], which has had a long-lasting influence on NMR experiments, both spectroscopy and imaging. This was significant since once you knew how to use two (or more) pulses to manipulate the spin system, you could truly control the motion of the nuclear spins in the sample to gain insight into the molecular environment. In 1957, Irving Lowe and Richard Norberg demonstrated that the NMR spectrum in the frequency domain is mathematically equivalent to the Fourier transform (FT) of the NMR signal (called the free induction decay, FID) obtained in the time domain [11]. In 1966, Richard R. Ernst and Weston A. Anderson demonstrated the concept of FT NMR [12], which offers several orders of magnitude improvement in the signal-to-noise ratio (SNR) per unit time for a typical proton NMR spectroscopy experiment.

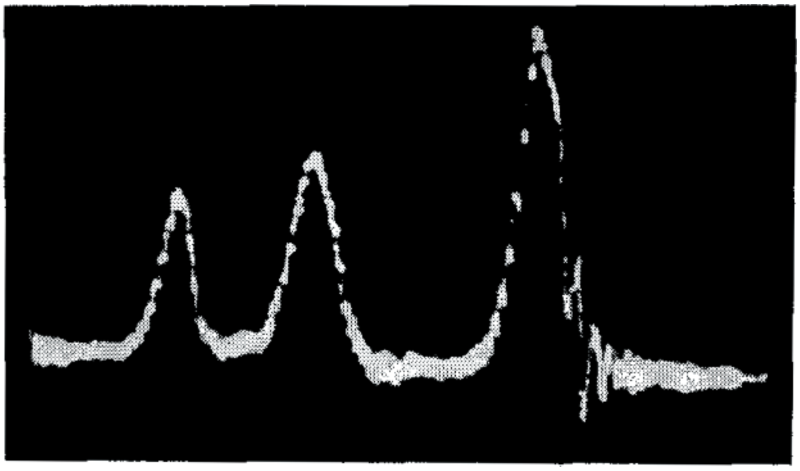


Figure 1.4 The first NMR spectrum of ethanol (CH_3CH_2OH), which demonstrated the huge potential of NMR spectroscopy by identifying three sets of non-equivalent ^1H nuclei in the same molecule. Three separate peaks corresponded to the resonant frequencies of the ^1H nuclei in the OH, CH_2, and CH_3 groups, respectively. Furthermore, the relative areas under the three peaks corresponded to the number of protons in each different chemical environment. Source: Reproduced with permission from Arnold et al. [9].

Coupled with the then-new development of personal computers and the fast Fourier transform (FFT) algorithm in the 1960s, FT NMR permits the practical use of NMR for non-experts. In 1975, Ernst demonstrated a new class of multidimensional NMR spectroscopy, now termed as 2-dimensional (2D) NMR spectroscopy (e.g., COSY, NOESY, etc.), which permits the study of specimens with a complex molecular environment or large macromolecules.

The first application of NMR to study biological samples was done in 1955 by two Swedish researchers, Erik Odeblad and Gunnar Lindström [13]. Using a primitive NMR instrument that Lindström built for his graduate research at the Nobel Institute for Physics (Stockholm, Sweden), Odeblad and Lindström studied the characteristics of NMR signals in a number of biological tissues and speculated that the signal differences between water and biological tissues could be attributed to the absorption and organization of the water molecules to the proteins in the tissue, which was remarkably accurate. A 2016 paper recounts some fascinating facts about this first biological application of NMR [14].

In 1973, Paul C. Lauterbur demonstrated the construction of 2D images using the NMR technique, which opened a completely new direction in the application of NMR (Figure 1.5) [15]. Several key developments in NMR imaging (i.e., MRI), in particular the use of a pulsed gradient approach for the slice selection by Peter Mansfield in 1974, stimulated the building of NMR scanners for humans since the late 1970s. Today, whole-body human NMR imagers, which are called whole-body MRI scanners, are the indisputable diagnostic choice for soft tissue diseases in all hospitals and clinics since MRI is completely non-invasive and totally non-destructive.

While most of the imaging community was geared toward the optimization of NMR scanners for humans, several research groups started to push the resolution of NMR imaging to the other extreme – the microscopic scale. This effort resulted in the 1986 publication of NMR images with structural features smaller than what can be recognized by the human eye (~100 microns) [16, 17]. This high-resolution imaging field has been termed as NMR microscopy (microscopic MRI, μMRI).

Figure 1.5 The first proton NMR image of two tubes of H_2O, which was produced by P.C. Lauterbur by combining four projections taken from different angles from his setup on a Varian A-60 spectrometer, which is currently on display at the State University of New York at Stony Brook. Source: Reproduced with permission from Lauterbur [15].

The latest "*history*" of this fascinating field is still being written as of today in the twenty-first century. NMR and MRI are very active and still evolving, with diverse applications in biology and medicine and various industries. There are many new and exciting developments in recent years, such as the optical pumping in NMR and MRI that improves SNR by more than 1000 times, compressed sensing that can shorten the experimental time tremendously, and exotic pulse sequences that fascinate our imagination. So far, a number of Nobel prizes have been awarded for discoveries related to NMR and MRI, including Rabi (1944) in physics, Bloch and Purcell (1952) in physics, Ernst (1991) in chemistry, Wüthrich (2002) in chemistry, and Lauterbur and Mansfield (2003) in physiology or medicine. By picking up this book, you are learning this fascinating phenomenon and joining this exciting field.

1.4 THE ORGANIZATION FOR A ONE-SEMESTER COURSE

This book is written ultimately for those who are interested in MRI. It contains the four essential components of MRI (Figure 1.6): the theory of physics that is the foundation of this fascinating phenomenon (Part I) [1, 2, 18, 19], the fundamental instrumentation and experimental techniques that facilitate the execution of this phenomenon (Part II) [1, 20], and two main applications – NMR spectroscopy (Part III) [21, 22, 23] and MRI (Part IV and Part V) [2, 4, 24]. Although each of these components could be taught in great detail in one or two semesters, the

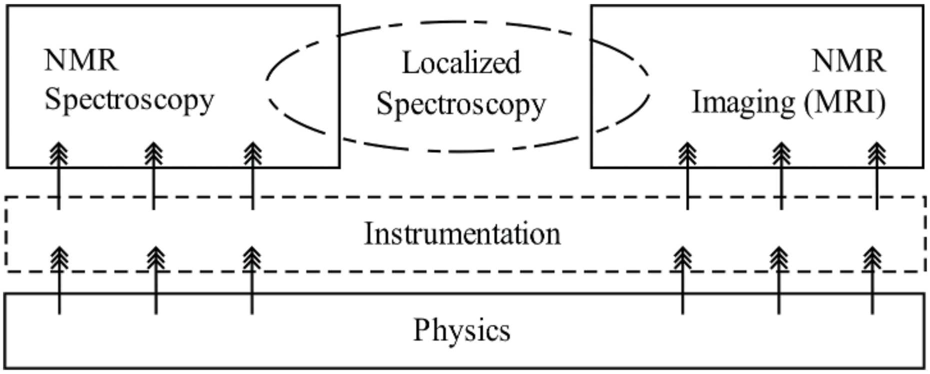


Figure 1.6 Major conceptual components of NMR and MRI.

goal of this book is to cover the essential concepts in all four components in a typical one-semester course, hence the title of the book begins with *Essential*. I trust that you would be well prepared when you need to explore any topic deeper. In addition to the numerous equations, there are about 190 figures in the book that provide the graphical descriptions for the concepts.

For the theory, I first give you the classical description of NMR, since it is easy to understand and visualize and provides a very useful first approximation. (If your goal is to do MRI on water-rich samples, the classical description is mostly sufficient.) I'll then describe NMR in a compact (i.e., abbreviated) quantum mechanical form, so that you will be at least familiar with the basic approach and terminology of the mathematical treatment.

Sandwiched between the fundamental theory and practical applications are the NMR instrumentation and experimental techniques (Part II), which facilitate the execution of this phenomenon. For these techniques, I discuss the basic unit of the NMR system. (The additional hardware in MRI is discussed in Chapter 13.) These get-your-hands-dirty discussions on hardware and experimental techniques will let you see behind the equations and behind the black box, to understand how the experiments are carried out and what are the practical issues in spectroscopy and imaging. Although the *hardware* knowledge will be described in terms of NMR and MRI, it should be useful in other modern technologies involving electronics, computer applications, signal acquisition, and imaging.

The description of NMR spectroscopy aims to supply you with basic knowledge of the topic, which is more than what you can find from any of the MRI books. I truly believe that for any MRI researchers and technical personnel, the knowledge of NMR spectroscopy is critically important. The last two parts (IV and V) cover modern practice in MRI, with an emphasis on quantitative imaging, which is at the center of modern MRI research and diagnostics.

This book can be adapted for a one-semester course in several different formats. For the students who major in science (physics, chemistry, material science, engineering), a course should include all four components of MRI (theory, instrumentation and experiment, spectroscopy, imaging). For this format, one can teach either at the undergraduate senior level or the graduate level. If the students are mainly interested in imaging, a course can be tailored toward MRI, with just a brief introduction to NMR spectroscopy. One can teach this version of the course to students in medical school. Appendix 4 has several sample syllabi for teaching.

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