

Nuclear Magnetic Resonance

An Early History

B D Nageswara Rao

This article summarizes the early history of nuclear magnetic resonance (NMR) during the first 25–30 years. The methodology went through vigorous growth and development during this time, laying the theoretical basis for understanding a wide array of applications. The stage was set for the breathtaking advances the technique underwent by taking advantage of technological developments in superconducting magnets, and computational and digital technologies. It has thus become the versatile investigative tool for natural phenomena that it is today, not only in physics and chemistry, but also in biology and medicine.

Principle and Discovery

Atomic nuclei with a non-zero spin angular momentum $I\hbar$ (I may be a half or full integer and $\hbar = h/2\pi$ where h is Planck's constant) possess a magnetic moment collinear with it given by $\mu = \gamma I\hbar$ where γ is the gyromagnetic ratio¹, which may be positive or negative depending on the nucleus. In a magnetic field of strength B_0 , the spin precesses about the direction of the field with an angular frequency $\omega_0 = \gamma B_0$, e.g., for protons ($I = 1/2$) with a B_0 of 1 Tesla, $\omega_0 \approx 2\pi$ (42.5 MHz), in the radio-frequency (RF) region (*Figure 1*).

Consider that a weak RF magnetic field of frequency $\omega \approx \omega_0$, and polarized in a direction orthogonal to that of B_0 , is externally imposed on an assembly of such spins. The radiation from the RF generator is coherent, and therefore induces coherent motion of the spin system in the orthogonal plane. Nuclear magnetic resonance (NMR) is the experimental observation of the resonant absorption of energy by the nuclei from the RF source. This is a classical description of the principle behind NMR.



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¹ The gyromagnetic ratio is the ratio of an object's magnetic dipole moment to its angular momentum.

Keywords

NMR, basic theory, Bloch equations, spin echoes, Overhauser effect, double resonance, polarization transfer, FTNMR, solid state NMR, line narrowing, cross polarization.



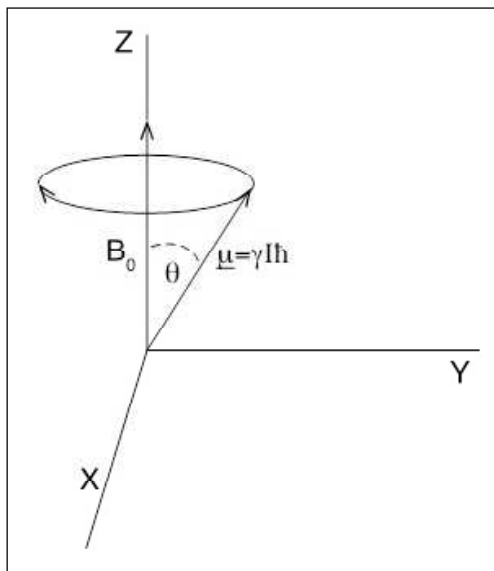


Figure 1. Precession of spins in the laboratory coordinate system.

Quantum mechanically, the Hamiltonian (in angular frequency units) for the magnetic moment μ placed in an external magnetic field consisting of a static field, \mathbf{B} along z -axis and a weak RF field, of amplitude B_1 , polarized along x -axis is given by

$$\begin{aligned} \hbar \hat{H} &= -\boldsymbol{\mu} \cdot \mathbf{B} \ , \\ \text{with } \mathbf{B} &= B_0 \mathbf{k} + 2B_1 \cos \omega t \mathbf{i} \quad (1) \\ &= B_0 \mathbf{k} + B_1 (e^{i\omega t} + e^{-i\omega t}) \mathbf{i} \ . \end{aligned}$$

Note that the oscillating field is decomposed into two counter-rotating fields in the x - y plane. Only one of these, rotating along with the precessing spin (counterclockwise, if γ is positive) will partake in resonance, and the other may be ignored.

Thus we may write,

$$\begin{aligned} \hat{H} &= \hat{H}_0 + \hat{H}_1 \ , \\ \text{with } \hat{H}_0 &= -\omega_0 I_z \ , \quad (2) \\ \text{and } \hat{H}_1 &= \gamma B_1 I_x e^{-i\omega t} \ . \end{aligned}$$

\hat{H}_0 and \hat{H}_1 may be referred to as spin and RF Hamiltonians. Each spin has $(2I+1)$ energy levels, $E_m = -m\omega_0$, labeled by the eigenvalues of I_z (from $-I$ to $+I$ in steps of one). The effect of \hat{H}_1 , treated by the time-dependent perturbation theory of quantum mechanics, yields magnetic dipole transitions with a selection rule $\Delta m = \pm 1$, and a transition probability that is maximum for $\omega = \omega_0$. This is the quantum mechanical version of the principle of the NMR experiment.

The experimental observation of NMR in bulk matter was independently accomplished, in 1946, by two research groups: one at Harvard headed by Purcell [1] and the other at Stanford headed by Bloch [2], using somewhat different, but equivalent methods. The Harvard group detected the absorption of energy from the RF source at resonance, whereas the Stanford group detected the voltage induced in an orthogonal coil, due to coherent-free precession of spins, at resonance. Purcell and Bloch shared the 1952 Nobel Prize in Physics.



Since this issue of *Resonance* observing seventy years of magnetic resonance is being published by the Indian Academy of Sciences, it may be worth noting that in India, NMR was first seen in 1949 [3], about a mile from the Academy building, by Suryan, a 25-year old lecturer at the Indian Institute of Science, Bengaluru. Suryan published two other papers: one in which he proposed improving the signal-to-noise ratio of detection by signal averaging, and demonstrated it by using a synchronous magnetic recorder [4], and another in which he utilized a flowing liquid sample to overcome RF saturation effects [5]. The signal-averaging idea was prophetic as it became a standard part of NMR spectrometers about two decades hence, and the flowing-sample idea has since been used by many around the world in specific applications of NMR. This was a truly remarkable accomplishment.

Relaxation and Bloch Equations

While the description given above accounts for the occurrence of resonance, the design and success of Purcell and Bloch in the experimental demonstration of NMR in bulk matter is due, in no small measure, to their recognition of some critical missing factors. For instance, in the quantum mechanical description, given above, considering a spin- $\frac{1}{2}$ with two energy levels, the transition probabilities for stimulated absorption and emission are equal (spontaneous emission is negligible in the RF region), and a net absorption of energy occurs only because the lower energy level has a higher population by a factor $\exp(\Delta E/kT)$ where ΔE is the energy difference, k is the Boltzmann constant and T is the temperature of the sample. In bulk matter, the spin degree of freedom is in thermal equilibrium with the other degrees of freedom (termed the ‘lattice’). The thermal capacity of the spin system is negligible compared to that of the lattice, and therefore, T is essentially the lattice temperature. Spin–lattice interactions are responsible for thermal equilibrium and the higher occupancy of the lower spin energy level. Thus, in a steady state experiment, the net absorption of energy by the spin system involves a competition between the RF field which depletes the

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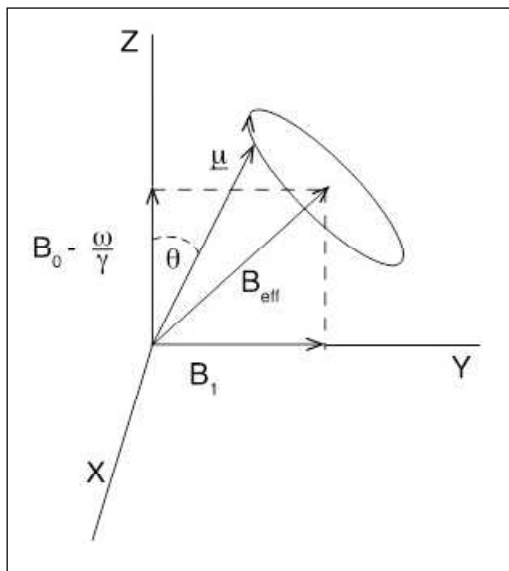


Figure 2. Precession in a coordinate frame rotating at an angular frequency, $-\omega k$.

excess population in the lower level and spin-lattice relaxation which replenishes it.

If the RF field strength is excessive, or if the relaxation processes are inefficient, the NMR signal may be unobservable. Similarly, in the classical description of the NMR experiment, given above, before the RF field is applied, the sample acquires a magnetization $M_0 = \chi_0 B_0$, where χ_0 is the bulk susceptibility, exclusively along the z-axis, with no magnetization in the transverse plane, due to spin-relaxation processes. The effect of the RF field may be visualized in a coordinate frame, rotating about the z-axis at the RF frequency ω in the same sense as the spin

precession. In this frame, the static field appears diminished to a value $(B_0 - \omega/\gamma)$, and the RF field B_1 appears static along the x-axis (Figure 2). The role of the RF field will be to tip the magnetization away from the z-axis into the x-y plane giving rise to the NMR signal in the form of an induced voltage in an orthogonal coil in this plane (as in the Bloch experiment). In this description, it may be seen that the role of relaxation processes will be to restore magnetization back to M_0 along the z-axis and reduce it back to zero in the x-y plane, thus diminishing the NMR signal in competition with RF field.

Bloch insightfully recognized that these two time variations of magnetization components, namely, the growth along the static field, and the decay in the transverse plane, occur in general at different rates (and are implicitly governed by different – but not necessarily non-overlapping – set of interactions). He proposed, on phenomenological basis, an equation of motion for the macroscopic magnetization:

$$d\mathbf{M}/dt = \gamma \mathbf{M} \times \mathbf{B} - (M_x \mathbf{i} + M_y \mathbf{j})/T_2 - (M_z - M_0) \mathbf{k}/T_1 \quad (3)$$

T_1 and T_2 are called spin-lattice (longitudinal) and spin-spin (transverse) relaxation times. This vector equation is extremely

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useful for diagrammatic analysis of the effects of a variety of NMR pulse sequences and experimental schemes. However, there are limitations. A steady-state solution of (3) yields a Lorentzian line-shape (with a full-width at half-height given by $\Delta\omega = 2/T_2$) for the resonance absorption provided, the saturation factor, given by, $\gamma^2 B_i^2 T_1 T_2 \ll 1$. This line-shape is usually obtained for simple diamagnetic liquids, but not for solids to which the Bloch equations were shown to be inapplicable. For liquids, $T_1 \approx T_2$ are typically seconds or longer, whereas solids have short T_2 's of milliseconds or longer, due to dipolar interactions, and long T_1 's of many minutes or longer.

From a basic physics perspective, the study of spin relaxation by which thermal equilibrium is attained by the spin degree of freedom within itself and with other degrees of freedom, belongs to the general problem of understanding irreversible processes. The Purcell group laid the basis for spin relaxation in liquids and gases through the spectral densities of correlations functions arising from fluctuations in spin–lattice interactions [6]. The Bloch group incorporated irreversibility into a formal density-matrix theory for the treatment of relaxation processes applicable to a wide range of experimental conditions [7, 8]. Redfield [9] elegantly recast this formalism into a tractable form, which is most commonly used, and is referred to as the ‘relaxation matrix theory’.

Transient NMR and Spin Echoes

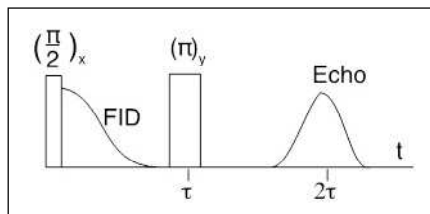
A resonant B_1 field applied for a duration Δt rotates the z-magnetization M_0 by an angle $\gamma B_1 \Delta t$ radians, about the x-axis in the rotating frame described above. By appropriately choosing B_1 and Δt , this angle may be made $\pi/2$, for example. At the end of the $\pi/2$ pulse, the magnetization will be along the negative y-axis. Following the pulse, the magnetization should exponentially decay and vanish with a time constant T_2 according to (3). This decay is called the free induction decay or FID.

In 1950, Hahn [10] made a startling discovery that, if a second

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Figure 3. Spin-echo pulse sequence.

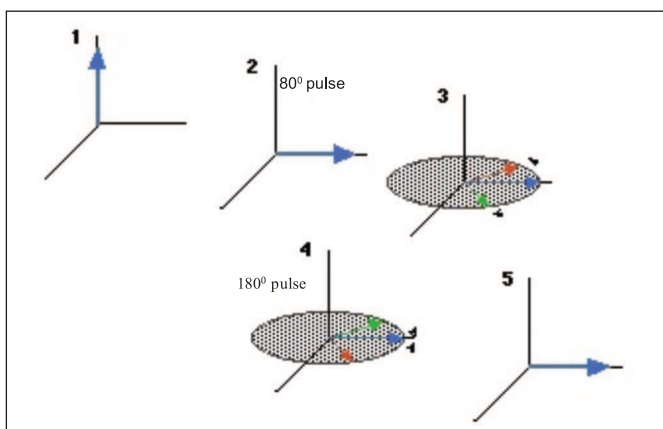


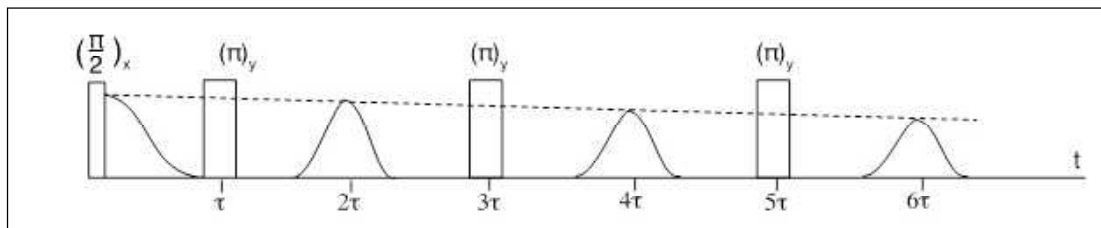
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pulse is applied at time τ after the first, a bell-shaped, time-dependent signal centered around the time 2τ is observed, which he called a 'spin-echo' (Figure 3). The explanation for the echo can be easily seen by following the magnetization vector for a $((\pi/2)_x - \tau - \pi_y - \tau)$ sequence at the end of which the echo appears.

This sequence is a variant, due to Purcell, of that used by Hahn. In his original experiment, Hahn used two $(\pi/2)_x$ pulses because reportedly, he had only one pulse generator available! If τ is short relative to T_2 , the decay following the first pulse arises primarily due to the inhomogeneity in B_0 across the sample on top of that due to T_2 , because spins at different locations precess with slightly different frequencies, about the z -axis, thereby fanning out their magnetizations in the x - y plane, leading to a vanishing sum with time. The second π_y pulse flips them around the y -axis without changing the rate or sense of precession, resulting in a refocusing of the spins along the y -axis at the time 2τ , thus giving the echo (Figure 4). The fanning out in the first interval τ , and the subsequent refocusing in the second interval occur because the spins retain the memory of their phase dispersion by virtue of

Figure 4. The Hahn spin echo. Starting from the initial magnetization in the z -direction (1), a 90° pulse brings the magnetization in the positive and negative directions in the x - y plane (2) which starts to precess (3). A 180° pulse reverses the magnetization in the x - y plane (4), which refocuses to initial position, giving an echo (5).





their location in the sample. With increasing τ , the echo diminishes in strength due to T_2 -decay, as well as due to translational diffusion in the sample causing spatial migration of the spins, which vitiates the phase memory.

Carr and Purcell [11] showed that a repetitive sequence $(\pi/2)_x - \tau - (\pi_y - 2\tau)_n$ which has echo signals in the middle of the time interval 2τ in the repeating segment, leads to an exclusive T_2 -decay of the sequence of echoes if n is large (Figure 5). Thus, both T_2 and the translational diffusion constant may be determined from these measurements.

Hahn's spin-echo experiments were a landmark event in the history of NMR. They strikingly demonstrate that the apparent loss of coherence in the spin system (following a $\pi/2$ pulse) in an inhomogeneous magnetic field is reversible, and open the possibility of manipulating and preparing the spin system in a variety of coherent states. They have also heralded the development of an extraordinary array of imaginative pulse sequences that came into vogue in later NMR studies. Furthermore, they were a forerunner of the physical experiments that became possible, by analogy, when coherent sources such as lasers, became available at high frequencies [12]. For example, in optical spectra of gases, Doppler broadening is analogous to magnetic field inhomogeneity broadening in NMR [13].

Overhauser Effect, Double Resonance, and Polarization Transfer

In 1953, Albert Overhauser [14] made a dramatic prediction that by saturating the conduction electron resonance in a metal in a magnetic field, the nuclear polarization will be enhanced by a

Figure 5. Carr–Purcell train of pulses $(\pi/2)_x - \tau - (\pi_y - 2\tau)_n$ with echoes at $2\tau, 4\tau, \dots, 2n\tau$.



factor of over a thousand. This suggestion was met with widespread skepticism from the luminaries of magnetic resonance at that time. However, the first attempt to experimentally see the effect, made by Carver and Slichter [15], on Li^7 in metallic lithium was a resounding success. Not long after this, Feher [16] performed an electron-nuclear double resonance (ENDOR) experiment, in which nuclear resonance was observed through the effect on the saturated ESR line of an electron to which the nuclei are coupled by magnetic hyperfine interaction. Roughly speaking, the polarization transfer in ENDOR is the reverse of that in the Overhauser effect experiment.

A closer examination of the Overhauser prediction reveals the generality that polarization transfers can occur between any two spins, if the interaction responsible for their relaxation couples their angular momenta. The experimental confirmation of the Overhauser effect provided a broad-based impetus for a genre of experiments that may, in general, be called double resonance techniques. In these experiments, the spin system, or part thereof, is detected with one RF field, while a second RF field of adjustable amplitude, frequency and duration perturbs the spins. It is clear that these experiments may be conducted in a variety of ways by choosing the characteristic parameters of the perturbing RF field, on the basis of the specific information sought to be gathered. Depending also on the ingenuity and inventiveness of the experimentalist, they may be either steady state or transient in nature, the second RF field may be continuous or pulsed, the observed and perturbed spins may be homonuclear or heteronuclear, or electron and nucleus as above, and so on. In general, the strong perturbing RF field produces coherence effects that are seen as spectral frequency or multiplicity changes, as well as relaxation effects which are seen as intensity changes signifying a polarization transfer. A comprehensive analysis of the results usually requires the use of the density matrix theory [32].

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During the 15–20 years following Overhauser effect and leading up to the time when the Fourier transform method became the



normal operating mode of all NMR spectrometers, double resonance studies have contributed a large body of unique and significant experimental data in physics and chemistry of NMR along with a theoretical sophistication to match. We outline some of these developments below.

High Resolution NMR in Liquids, FT NMR

As NMR data on spin- $\frac{1}{2}$ nuclei in simple diamagnetic liquids emerged, it became clear that the line-width of the observed signals was primarily due to inhomogeneity (ΔB_0) in the static magnetic field B_0 , and the natural line-width is maybe a fraction of 1 Hz, whereas the NMR operating frequency is 100 MHz or more. A desire to obtain spectra approaching natural line-width conditions, places a requirement on the fractional inhomogeneity and stability of B_0 , and on the stability of the RF circuitry used for recording the spectra, to be in the range of 1 part in 10^8 or 10^9 . Varian Associates in Palo Alto, which had on its research staff NMR stalwarts like Anderson, Ernst and Freeman, developed the instrumentation that launched high resolution NMR spectroscopy. The inhomogeneity across the sample in a well-designed magnet was cancelled (or minimized) by superposing adjustable field gradients (of opposite sign) produced from a system of coils that were configured for this purpose. Finally, the cylindrical sample was spun about its axis to further reduce the residual gradients by spatial averaging.

High-resolution NMR spectra reveal a fine structure characteristic of the molecule. For example, the ^1H spectrum of CH_3CHO shows a 1:1 doublet for CH_3 and a 1:3:3:1 quartet for CHO. A formal understanding of these spectra requires writing the spin Hamiltonian for a molecule consisting of multiple spins as:

$$\hat{H}_0 = -\sum_i \omega_i I_{zi} + \sum_{i<j} 2\pi J_{ij} \mathbf{I}_i \cdot \mathbf{I}_j \quad , \quad (4)$$

where $\omega_i = \omega_{0i} (1 - \delta_i)$, δ_i is the chemical shift, which signifies the influence of the chemical (electronic) environment on the NMR frequency of the nucleus i ; the second term is a magnetic interaction between spins i and j mediated through their electronic

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environment, J_{ij} is the indirect spin–spin coupling constant (called indirect to distinguish from direct through-space dipole–dipole interaction) in units of Hz. The first term is a sum over all the spins i in the molecule, and the second is summed over all pairs i and j . If $|\omega_i - \omega_j| \gg 2\pi J_{ij}$, the spins i and j are weakly coupled, the dot product in the second term may be replaced by $I_{zi} I_{zj}$. In such a case, the resonance of spin i will split due to this coupling into as many lines as the number of spin states of j , and vice versa for j (as in the example of CH_3CHO given above). If the condition for weak coupling is not met, the spectrum will be complex and analysis requires diagonalization of the Hamiltonian in (4). Note that the resonance frequency shift due to δ is linearly proportional to B_0 , whereas J is independent of B_0 .

Therefore, obtaining NMR spectra at higher operating frequencies is desired because it not only increases the sensitivity of detection, but also simplifies the spectra by making weak coupling a better approximation. Although initially proton spectra were extensively studied, for obvious reasons, other spin- $1/2$ nuclei like ^{13}C , ^{15}N , and ^{31}P were soon added to the list because of their ubiquity in organic chemistry and biochemistry (the first two of these nuclei usually require isotopic enrichment due to their low abundance). Nuclei with spin 1 or more possess an electric-quadrupole moment, which interacts with electric field gradients at their sites resulting in additional complexity in their spectra, and shall not be discussed here. The chemical shifts and spin–spin coupling constants have been interpreted in terms of molecular structure and conformation at various levels of incisiveness, ranging from qualitative to quantitative. More significantly, these parameters characterize an *NMR signature spectrum* for the molecule, a feature that is central to the promise of NMR as a macromolecular structural tool.

A common chemical phenomenon that is dramatically displayed in NMR is the ‘chemical exchange’ in which a moiety containing the nucleus alternates between two (or more) sites where its chemical shifts are different with resonance frequencies ω_i and ω_j . Assuming that the resonances for two equally populated sites



are simple lines, if the exchange rate $1/\tau \gg |\omega_i - \omega_j|$ (fast exchange), the two resonances move towards each other and coalesce in the middle. On the other hand, if $1/\tau \ll |\omega_i - \omega_j|$ (slow exchange), the two resonances are not shifted but their full-width at half-height is broadened by $2/\tau$, and for intermediate rates, both line-broadening and frequency-shifting result. If the resonances in the absence of exchange are multiplets due to either strong or weak spin–spin coupling, a density matrix simulation [17] is needed for the analysis of the observed spectra to extract the values of τ , ω_i and ω_j .

Nuclear spin relaxation in liquids and gases is mediated by all interactions involving the spin that rapidly fluctuates in a random fashion, due to processes such as molecular motion, such that their time-averaged (first order) effect on the resonance frequency vanishes [6]. The translational and rotational degrees of freedom of the molecule comprise the lattice. For example, intermolecular dipolar interactions are averaged by translational diffusion, whereas anisotropic parts of all intramolecular second rank tensor interactions such as dipolar, quadrupolar (spin $> 1/2$), chemical shift, and spin-rotation interactions are averaged by rotational diffusion. The non-vanishing isotropic part of any tensor interaction (given by one-third of the trace) enters the spin Hamiltonian as a scalar interaction. The two terms containing the chemical shift δ_i , and the indirect spin–spin coupling constant J_{ij} in (4), are notable examples of this. Scalar or tensor interactions with a paramagnetic ion or a quadrupolar nucleus are additionally averaged by the rapid relaxation of the latter. Each term in the spin–lattice interaction Hamiltonian is a product of a randomized lattice function and a spin operator. Relaxation occurs as a second-order effect through the spectral densities of time correlation functions of the lattice functions, at frequencies determined by the respective spin operators. Note that, when several mechanisms of relaxation are present, cross-correlation effects occur [18]. Relaxation processes in liquids and gases were extensively investigated through measurements of T_1 , T_2 and translational diffusion constant D (where appropriate) as functions of vari-

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ables such as temperature and frequency, leading to unique insights into dynamical processes operating in the molecules.

If the NMR spectrum exhibits multiplet structure due to chemical shifts and spin–spin couplings, double resonance methods need to be used to determine relaxation information [18]. However, double resonance also introduces various coherence effects such as spin decoupling, and its analysis requires density matrix formulation, which includes relaxation as a super matrix [9, 18]. For heteronuclear or weakly-coupled homonuclear spin systems, double resonance techniques offer a means of monitoring polarization transfer between nuclei mediated through intramolecular dipolar interactions, known as the nuclear Overhauser effect or NOE [19]. This effect is proportional to $1/r^6$ where r is the internuclear distance, and provides a means of deducing structural data if motional parameters are independently determinable.

While high resolution methodology provided a wealth of unique information on the structure and dynamics of small molecules in liquids, attempts to extend these methods to biological macromolecules were beset by sensitivity requirements. Concentrations (100 to 500 mM or more) typically used for small molecules are orders of magnitude larger than those feasible or appropriate for solutions of biological macromolecules. The maximum sensitivity enhancement obtainable by averaging n spectra is \sqrt{n} . The acquisition of spectral data in continuous wave (CW) mode under slow-passage conditions required 5–10 minutes per spectrum making the time required for signal-averaging excessive and impractical.

It is a well-known physical principle that a Fourier transform of the transient response of a linear system to an impulse is the frequency spectrum of the system. Lowe and Norberg [20] verified this relationship for NMR signals. Ernst and Anderson [21], working at Varian Associates, demonstrated that the Fourier transform (FT) methodology, in which the data is acquired in the time domain following a pulse (the FID), signal-averaged (and Fourier transformed to obtain the spectrum in the frequency



domain), provides enhanced sensitivity by one to two orders of magnitude over the CW-mode, for the same duration of data acquisition. This discovery was followed by notable developments in computational and digital technologies for data acquisition and processing. Moreover, the use of pulse methods opened up a variety of options for manipulating the spins so that relaxation and spectral measurements may be made on the same instrument. Thus, FT NMR became the method of choice as NMR emerged as a macromolecular structural tool in biology. The quest for higher sensitivity continued through higher spectrometer frequencies afforded by developments in superconducting magnet technology.

Solid-State NMR, Line Narrowing, Cross Polarization

The NMR signal of a solid sample shows a broad resonance pattern due to static intra and intermolecular, homonuclear and heteronuclear, dipolar interactions superposed on other interactions such as anisotropic chemical shift and indirect spin–spin interactions (these are all second order tensor interactions whose anisotropic parts are averaged to zero by molecular motion in liquid samples). In the first decade and more, NMR line shape patterns have been analyzed to derive some structural data and information on internal motions in the solids. It was then recognized [22,23] that if a cylindrical sample, oriented at an angle θ with respect to the external magnetic field, is rotated sufficiently fast about the field, the motion-averaged dipolar coupling vanishes if θ is chosen such that $(3\cos^2\theta - 1) = 0$. This value of θ ($= 54.7^\circ$) is referred to as the ‘magic angle’, and the method of line narrowing as ‘magic angle spinning’. Since the same angular factor occurs for all second rank tensor interactions, the corresponding terms in all such interactions are neutralized. The rate of rotation required for neutralizing dipolar broadening is usually larger than that for other interactions. The research groups of Waugh [24] and Mansfield [25] developed pulsed methods to exclusively neutralize homonuclear dipolar broadening caused by the secular term in the dipolar interaction, given by $(3I_{z1}I_{z2} - I_{x1}I_{x2})(3\cos^2\theta - 1)$, for a pair of like spins. These methods aim to

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neutralize the first term by flipping the spins among selected relative orientations (known as spin-flip narrowing), whereas magic angle spinning averages the second term which is common to all second-rank tensor interactions such as anisotropic chemical shift and quadrupolar interactions. Thus, high-resolution NMR of solids emerged.

Hahn and Hartman [26] developed an ingenious cross-polarization method, which is extremely useful for detecting less abundant nuclei (*S*) interacting with abundant ones (*I*), for example ^{13}C and ^1H . The method involves application of $\pi/2$ resonant RF pulse to *I* followed by a $\pi/2$ phase shift for the RF field (B_I) which will now be aligned with the *I* magnetization (this procedure is called spin-locking), and at the same time applying a second resonant RF field (B_S) to *S* such that $\gamma_I B_I = \gamma_S B_S$. Now, if *I* and *S* are viewed in their respective rotating frames, they will be precessing about their respective RF fields with identical frequencies. Thus, the magnetization of *I* will be shared by *S*, if the spins interact by either dipolar or scalar coupling. Note that this cross-polarization, which occurs through coherence matching, is distinct from that in the nuclear Overhauser effect which occurs through cross-relaxation. Cross-polarization schemes have been refined further by the Waugh group [27], and are extensively used in both solid and liquid state studies involving less abundant nuclei such as ^{13}C and ^{15}N .

Epilogue

In writing this short survey of NMR covering the period from 1946 to about 1973 or 74, some interesting topics such as NMR in oriented systems have not been included due to space limitations as well as the need to cover the topics most appropriate for introducing the reader to the articles that follow in this issue. It was a difficult choice to make.

NMR went through an impressive evolution of technological advancement coupled with theoretical sophistication during the period covered. Operating frequencies of spectrometers and sen-



sitivity of instrumentation continued to grow. The field held considerable promise to become a structural tool for biological macromolecules in solution phase in which they normally function. Nevertheless, there were limitations in its versatility compared to x-ray crystallography, and there was discernible concern whether the capabilities were reaching a plateau.

However, just around this time (1973–74), a seemingly straightforward suggestion was made by Jeener [28] about collecting NMR data as a function of time in a second domain, in addition to that in the usual detection period, and performing a double Fourier transform covering both domains. On an altogether different level, Lauterbur subjected a bell-pepper slice to a magnetic field gradient and imaged the water (proton) concentration across its cross-section [29]. He named the method ‘zeugmatography’ (the term apparently has a Greco–Sanskrit origin based on the word ‘yugma’) [30]. He followed it with an image of the body of a semi-starved mouse stuffed into a 20mm NMR tube. There was a pale spot in the center of the image, which he attributed to the ‘soul’ of the mouse! We all know now that in the next decade, the ‘2D-revolution’ in NMR emerged from the first suggestion [31], and Lauterbur initiated the field of ‘NMR imaging’ with his images. The panorama of the evolution of NMR in the last 40 years, in which four Nobel Laureates emerged in the field (Ernst, Wüthrich, Lauterbur and Mansfield) has been spectacular. The remaining articles in this issue of *Resonance* capture this excitement.

Suggested Reading

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The cross-polarization, which occurs through coherence matching, is distinct from that in the nuclear Overhauser effect which occurs through cross-relaxation.



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