REQUIREMENTS AND DEVELOPMENTS IN NUCLEAR MAGNETIC RESONANCE INSTRUMENTATION

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Nuclear magnetic resonance (NMR) differs from other forms of spectroscopy, not only by the frequency involved (0 to 100 Mcps), but also by the fact that the energy levels of interest are not built into the molecule but, rather, are established by an applied magnetic field. This fact affords a natural separation of the problems of magnetic resonance into two major classifications, namely, those in which the width of the energy levels is determined by the inhomogeneities of the magnetic field, and those in which the internal interactions play the dominant role. The latter is known as "broad-line NMR" and the former as "high-resolution NMR." In discussing the requirements of each of these forms of spectrometry it is necessary not only to define the phenomenon of interest, but also to describe the information available and the manner of its interpretation. In general, these factors are different for the two categories and, in the case of broad-line NMR, they are difficult to enumerate by reason of the diversity of problems to be treated. In the field of high-resolution NMR, the applications are readily catalogued in regard to instrumentation requirements; as a result, the ideal instrument can be more readily defined. It is clear, however, that in this form of spectrometry one must not only specify the characteristics of the spectrometer, but must also critically analyze the magnet. This magnet is the "optical system" of the spectrometer and is the plague of all instrument makers in the field. That the achieved resolving power is as high as it is must be regarded as a marvel. In this paper, a critical examination is made of existing instrumentation, and the degree of success in reaching the ideal is emphasized; the goals in those fields in which the instrumentation falls short are elucidated.

The initial experiments that were successful in observing nuclear magnetic resonance were two, one on the east coast at Harvard University, Cambridge, Mass.,[1] and one on the west coast at Stanford University, Stanford, Calif.[2] It is interesting to note that these two experiments were quite different physically, although fundamentally related. The different approaches to the instrumentation problem have established an east-west difference that prevails even at the commercial level. In particular, one may cite the development of the marginal oscillator as contrasted with the cross-coil system.

The nature of these systems can best be seen by considering a collection of similar nuclei having angular momenta and magnetic moments. Each nucleus precesses with its characteristic Larmor frequency,[3, 4] but with a completely random phase with respect to its neighbors. Therefore, the presence of this precession cannot be detected, since no bulk property of the system changes at the Larmor frequency. However, if a rotating radio-frequency (R.F.) field is applied, two interrelated effects are produced: the one induces transitions between the energy levels of the system and the other furnishes a

phase reference for all of the nuclei in the system. The first effect may be observed by detecting the energy absorbed from the R.F. field and the second by the presence of a tuned R.F. circuit designed to pick up the induced R.F. voltage produced by the precessing bulk magnetic moment. The former effect is easily detected by inserting the sample in the tank circuit of a marginal oscillator and monitoring the oscillation level and, hence, the Q of the resonant circuit. The latter is perhaps best detected by employing a receiver coil perpendicular to the transmitter coil furnishing the rotating R.F. magnetic field. As may be obvious, there are several ways of measuring the variables involved and each method has its advantages as well as its drawbacks.

The simplest of all systems was that employed by Rollin,[5] who inserted the sample in a single-tuned coil immersed in the magnetic field and fed the coil from a constant-current signal generator while monitoring the R.F. voltage across the coil. During resonance the Q of the coil was reduced and thus the parallel impedance of the tuned circuit decreased, resulting in a drop in the R.F. voltage across it. This change in voltage was amplified and detected. The magnetic field was modulated at 25 cps by means of auxiliary modulation coils and the resultant audio signal was displayed on an oscilloscope whose time base ran in synchronism with the modulation. Such a system measures only the imaginary part of the susceptibility. A second system, that of Bloembergen *et al.*,[6] employs the sample coil as one arm of an impedance bridge, and has the advantage that either real or imaginary components of the susceptibility may be measured. Its disadvantages are the added complexity of the bridge circuit and its critical balance characteristics. The tendency toward drift and admixture of the two susceptibility components affords a margin for error. A much simpler system is that formed by employing the sample coil and a condenser as a parallel-tuned grid circuit for an R.F. oscillator. If the feedback in the oscillator circuit is kept at a minimum so as to maximize the sensitivity of the oscillator to changes of Q in the resonance circuit, such a system is quite sensitive and serves as an excellent tool for searching for unknown lines or for work not requiring extreme stability. In general, these marginal oscillators perform best at very low R.F. power levels where the sensitivity is the greatest. This is frequently a decided disadvantage in regard to signal-to-noise ratio. In the region in which such a system is applicable, the signal-to-noise ratio is approximately the same as for the bridge method.

Perhaps the most famous of these marginal oscillator circuits is that of Pound and Knight.[7] For pure quadrupole resonance where the relaxation time is generally short, large R.F. fields may be applied without producing saturation. In this case an oscillator employing super-regenerative characteristics is of great use. Such an oscillator is characterized by the repeated build-up and decay of its oscillations; these grow exponentially from the level of the signal voltage induced in the circuit. If the repetition rate is not long in comparison with the relaxation time T_2, then the coherent precession of the nuclei will not be destroyed by the time the next cycle begins. There is then a signal voltage above noise from which oscillations build up, raising to a higher level the integrated pulse energy. The original work along this line

was done by Roberts.[8] The complexity caused by the side bands renders this method undesirable in many instances.

In addition to these single-coil methods there is a double-coil method employing orthogonal transmitter and receiver coils. This system was developed by Bloch et al.[2] It has the added complexity that the balance condition is achieved by means of paddles in the R.F. region, which couple R.F. from the transmitter to the receiver coil in variable amounts and phase. Its advantage is that bridge balance is achieved geometrically and is, hence, more stable. A wide range of R.F. power may be employed with optimum sensitivity. From such a system as this, one may obtain the sign of the nuclear magnetic moment as well as its magnitude; both the real and imaginary parts of this susceptibility may be measured, as with the single-coil bridge circuits.

As has already been noted, the present purpose of NMR is to employ the magnetic properties of nuclei as sensitive probes of their chemical environments. It is sufficient, then, to demonstrate the manner in which the magnetic states of nuclei may be affected by their surroundings. If tumbling motions are sufficiently rapid to average out nearly all interactions external to a particular molecule containing the nuclei in question, then one may consider only those intramolecular interactions affecting the magnetic states of the nuclei. Many of these interactions are quite small and are the goal of high-resolution NMR, that is, chemical shifts and $I \cdot I$ couplings.

The resolving power of this form of spectroscopy, which is of extreme importance, sets the requirements on both the spectrometer and the magnet system. There are several nuclei of interest in this respect: hydrogen, carbon 13, nitrogen 15, fluorine 19, silicon 29, and phosphorus 31. The test case in this form of spectroscopy has arisen from requirements on the proton signals. At this point it becomes very difficult to enumerate the exact requirements of such a spectrometer system—the physicist wants the ultimate in resolution, whereas the chemist prefers simplicity and reproducibility at the expense of supreme resolution.

Let us first try to satisfy the physicist, who wishes to remove from high-resolution NMR the limitation of magnetic field inhomogeneities. The present resolution is limited by the magnet system and at the moment is one part in one hundred million. Although this resolving power is already phenomenal it is, in a sense, misleading, since the stability of the system falls short of this figure. Electronic techniques will eliminate short-term drifts, but it is virtually impossible to eliminate long-term drifts on an absolute basis. It is physically impossible to regulate all the variables involved to this accuracy; for example, most magnets will drift one gauss per degree centigrade change in temperature, and to regulate this to one tenth of a millidegree is impossible. Even the problem of deriving a frequency that is stable to one part in 10^8 against long-term drifts is no simple task. Fortunately this degree of absolute stability is not required; instead, the ratio of frequency to field is what must be kept constant in this amount. The solution, then, is to derive the R.F. field from an oscillator locked accurately to the applied field in question.[9] Such a system has been built and appears to meet the stability requirements. It should be emphasized at this point, however, that in the main the long-term

drifts fall into the nuisance category and do not detract markedly from the usefulness of the instrument. For this reason expensive steps to improve present stabilities are not justified.

One further aspect of the magnet should be discussed, namely, the magnitude of the magnetic field desired in high-resolution NMR. From the standpoint of a clear resolution of chemical shifts, the higher the applied field the better; however, at the present time the technology of magnets is not sufficiently advanced to make it possible to obtain the required homogeneity at fields much in excess of 14,000 gauss. Moreover, the fine structure diminishes as the chemical shift is increased and, even if the present resolving power were maintained at the higher field, detail would be lost in the $I \cdot I$ interactions— a point that may not be adequately appreciated. In regard to the R.F. portion of the spectrometer, the simultaneous presence of dispersion and absorption, as exemplified in the Kronig-Kramers relations,[10, 11] requires the use of an impedance bridge or double-coil system rather than a marginal oscillator in high-resolution NMR. Halbach[12] has suggested the possibility of employing the side bands generated by large magnetic field modulation and a marginal oscillator, but the stability problem still remains. The cross-coil system developed at Stanford University[13, 14] has had particularly good success in this field.*

As emphasized by P. C. Lauterbur elsewhere in this monograph, the ability to study the dispersive mode at high-power levels and rapid passage makes possible the observation of many nuclei, which would otherwise be impossible. This fact pertains, not only to high-resolution, but also to broad-line NMR. For optimum versatility, then, the R.F. field should be variable from microgauss to gauss.

Another innovation in high-resolution NMR has been the time separation single-coil spectrometer. This system,† which is due to Arnold,[15] has a decided advantage over the two-coil induction methods in that microphonics are virtually eliminated. Here a single coil is used alternately as a transmitter and a receiver coil at a cycling rate that is rapid compared to the relaxation times. By employing an R.F. phase-sensitive detector one may observe either the real or imaginary components of the susceptibility. Narrow bands widths may be obtained in the over-all system with excellent signal-to-noise ratio.

There are three notable accessories to high-resolution NMR: (1) the employment of a galvanometer amplifier to minimize magnetic field fluctuations,[16] (2) the use of a spinning sample to average over magnetic field inhomogeneities,[17, 18] which includes recent work on the washing machine principle, and (3) the use of double irradiation at nuclear frequencies as a spin decoupling mechanism to wash out $I \cdot I$ interactions and simplify spectra interpretation.‡

Space does not permit a detailed discussion of the numerous problems aris-

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* For several years a cross-coil system has been available commercially from Varian Associates, Palo Alto, Calif.

† An instrument of this type has been in operation at Stanford University for more than one year.

‡ Such a system, an NMR spin decoupler, is available commercially from Varian Associates, Palo Alto, Calif.

ing in high-resolution NMR and of their ultimate solutions. Examples can be found in the literature,[19] and several of the papers in this monograph also deal with one or more of them.

In the field of broad-line NMR considerable instrumentation has been developed for the solution of specific problems. In general there is little choice between the single- and double-coil systems for observing NMR under broad-line conditions. In practice the choice is often determined by local tradition, which has resulted in marking the investigator's geographic location as east or west. The single-coil methods have the advantage that the geometry of the sample container is simple and lends itself readily to adaptation to a particular application, for example, work at very high and very low temperatures. The super-regenerative oscillator is particularly useful in pure quadrupole resonance. In broad-line NMR the problem is largely that of sensitivity and versatility; again, the cross-coil system comes out ahead, at the expense of simplicity of sample probe design and construction.

No discussion of broad-line NMR instrumentation is complete without the inclusion of pulse techniques. High R.F. power levels and short pulses are employed. Transient nuclear induction signals are obtained both during and after a pulse. Examination of this transient behavior facilitates measurement of the two relaxation times T_1 and T_2 already mentioned. In this method the magnetic field remains fixed and the R.F. pulses are obtained either by direct-pulse frequency modulation of an R.F. oscillator or by gating the output of a fixed R.F. generator. In Hahn's experiments[20] the single coil acted as a transmitter during the pulse and as a receiver during the time that the pulse was turned off.

Finally, with respect to the methods of narrow banding to improve signal-to-noise ratios, it should be pointed out that there have been several innovations, including oscillating audio detectors, multiple photographic exposure using oscillographic presentation, magnetic tape integration, and phase-sensitive detection methods. The latter have come into common usage.[21] Such systems are mechanical or electronic switches run in synchronism with the modulation frequency and generally feeding alternate sides of a condenser. The resulting voltage across the condenser is averaged over several cycles and displayed on recording millivoltmeters or other monitoring instruments. Mechanical switches are limited to frequencies below 800 cps and above one half cps in most instances.

In conclusion, NMR instrumentation for both high-resolution and broad-line applications has progressed markedly, pushing theoretical limits in many cases and falling short in only a few. As to the latter, much effort is being expended to achieve perfection, and success is hoped for in the near future. It will be a long time, however, before commercial instruments approach the ideal, because the problems of engineering are many. Nevertheless, it must be emphasized that present instrumentation is not a fundamental limitation in the application of NMR; in fact, the degree of perfection presently available can be credited with making NMR a powerful spectroscopic tool in chemistry, physics, and biology.

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