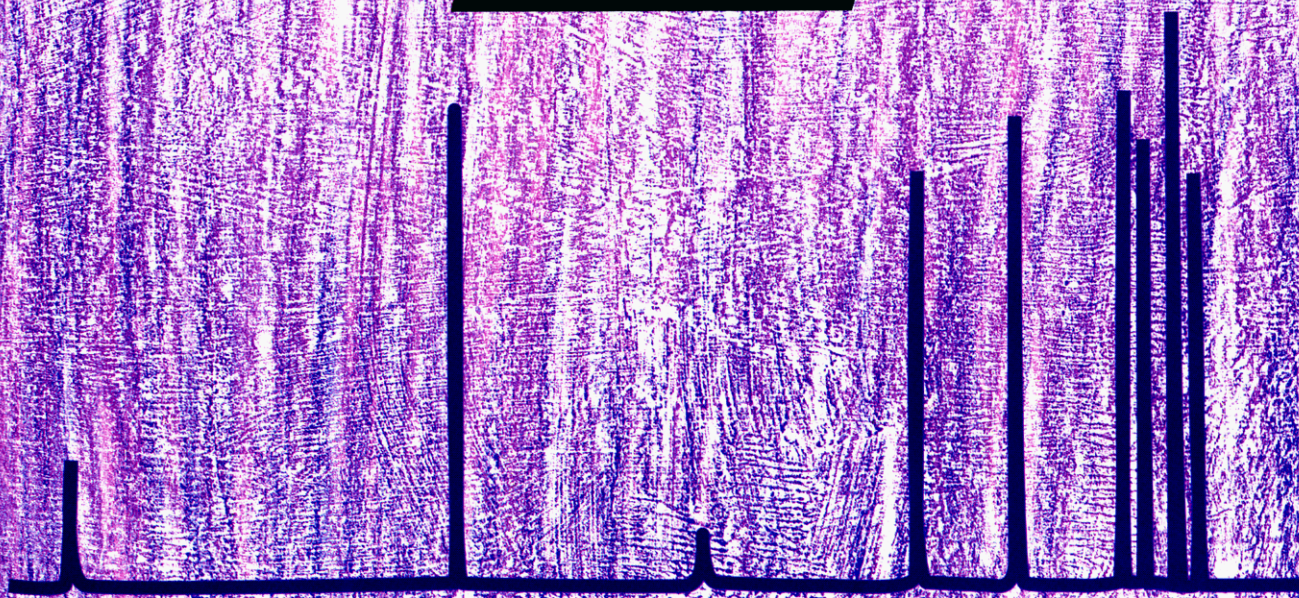# THE FOURIER TRANSFORM
REVOLUTION IN NMR SPECTROSCOPY

Ray Freeman
Department of Chemistry
Cambridge University
Lensfield Road
Cambridge CB2 1EW, England

It was in the mid-1950s that chemists began to take an interest in NMR spectroscopy after the publication of the high-resolution spectrum of ethanol obtained by Arnold, Dharmatti, and Packard (*1*), followed by the remarkable thesis work of Arnold (*2*) and Anderson (*3*), who convincingly demonstrated the enormous potential of the technique. Visionaries such as Shoolery and Gutowsky worked hard to convince the chemistry community that this strange new piece of physics could work wonders for structural chemistry. A few farsighted individuals set out to build their own high-resolution spectrometers from scratch—magnet and all—which was not an easy task in a chemistry laboratory. A California company, Varian Associates, offered a commercial machine. (Hereafter, Varian refers to Russell Varian; Varian Associates refers to the company.)

Most of these pioneering researchers found themselves banished to dusty basements over concerns that the heavy iron magnets posed a threat because of floor loading regulations. At that time it seemed quite natural to fix the radio frequency (rf) and sweep the magnetic field to scan the spectrum, because the field drifted rather rapidly.

A key item in basic NMR instruction in those days was the derivation of the steady-state solutions to the Bloch equations (*4*), which described the form of the resonance response observed under continuous-wave (CW), slow-passage conditions. The transient solutions that apply to the case of pulse excitation did not seem to be so relevant. Nevertheless, a few physicists were already thinking about the conceptually more difficult pulse excitation problem. Bloch had described several pulse experiments (*4*), and Hahn had already detailed the spin-echo phenomenon (*5*).

Varian disclosed a patent (*6*) for a spectrometer with enhanced sensitivity that "excited simultaneous resonance of a plurality of resonance lines" (Figure 1). Lowe and Norberg (*7*) pointed out that the transient free induction decay (FID) and the steady-state slow-passage spectrum form a Fourier transform (FT) pair. Thus it appeared that some type of broadband excitation could be used for high-resolution spectra and that the resulting transient signals should be Fourier transformed to give the desired frequency-domain spectrum. The idea that steady-state slow-passage spectroscopy might not be the best way to excite a high-resolution spectrum was therefore already "in the air," yet nothing constructive was done about it for almost a decade. Almost unnoticed by the NMR community, IR spectroscopists were beginning to use FT methods to improve sensitivity through what they understood as the "Fellgett advantage" (*8*).

One feature of certain chemical explosions is the existence of an induc-

tion period during which nothing seems to be happening. The Fourier revolution in NMR spectroscopy had a similar induction period while various ideas, equipment, and people came together at a crucial time. Resistance to change also played an important role in delaying the inevitable explosion.

The advantages of the pulse excitation method are greatest for high-resolution spectra that contain large numbers of narrow resonances, but physicists were not particularly interested in these applications. The need to derive the FT appeared to be a serious obstacle because it was not then evident that this should be done digitally on a computer. The organic chemist could already do so many fascinating things with proton NMR spectroscopy that he was too busy to worry about revolutionary new technology—his goose was already laying some golden eggs! The courageous few who appreciated the potential of high-resolution ^{13}C spectroscopy were seriously deterred by the low natural abundance of ^{13}C (1%) and by a widespread misconception that ^{13}C spin-lattice relaxation times were inordinately long, rendering this nucleus particularly intractable to NMR techniques.

The "prayer wheel"

Seeds of the FT concept in NMR spectroscopy can be traced to Varian's idea (6) of exciting the nuclei

with a wide band of frequencies from a noise generator to cause all the resonances to occur at once. One of his proposals was to convert the signals to audio frequencies (by heterodyne action) and to record them on magnetic tape. After the recording was complete, the magnetic tape would be made into a continuous loop that could be played back at different speeds. A fixed-frequency filter and an integrator would then select different frequency components, creating a crude Fourier analyzer. The NMR spectrum would be scanned (but not in real time) by varying the playback speed of the magnetic tape. Note the preoccupation with the difficulty of obtaining an FT.

The stochastic excitation concept has some inherent disadvantages. Individual frequencies are incoherent, and conventional phase-sensitive detection cannot be used. Furthermore, stochastic excitation introduces "systematic noise" into the NMR spectrum, which is difficult to remove.

In 1964 Anderson began to try out some ideas that circumvented these problems. Initially he set out to exploit the postulated "multiplex advantage" by the direct method of constructing a multichannel NMR spectrometer. The plan was to excite with an extensive "comb" consisting of N weak rf sources and to detect with the corresponding array of N

phase-sensitive detectors, each provided with the appropriate reference signal. No field (or frequency) sweep would be necessary; each transmitter–receiver unit would simply accumulate signals continuously from the appropriate point in the high-resolution spectrum. Theory suggested that the sensitivity should increase as the square root of N, at least as long as N is not too large. Good resolution would also require a large N, but there were obvious practical difficulties in constructing a very large number of detectors.

The requisite comb of evenly spaced frequencies was generated by an ingenious device known as the "prayer wheel," so named because of its resemblance to the Tibetan prayer wheel; however, this terminology also reflected a healthy skepticism about the entire project. Later, the device was renamed the "wheel of fortune." It was a lucite cylinder about 6 in. in diameter and 8 in. high with a strip light inside (Figure 2). The cylinder could be rotated about its axis by an electric motor. The outer surface of the cylinder was machined in about 20 small steps, giving slightly different diameters at different levels. A photographic sheet with alternating light and dark bands (a type of grating) was cut into strips that were glued to each level of the stepped cylinder in such a way that the join did not interrupt the regularity of the black and white alternation. Thus each step of the cylinder transmitted an oscillating light beam at a slightly different frequency that was detected by a common photoelectric detector.

The output of this detector contained the required comb of audio frequencies that could be used to generate modulation sidebands of the main rf transmitter. These sidebands were used to excite the NMR spectrum. Multichannel detection made use of the same prayer wheel. NMR signals from the receiver, heterodyned down to audio frequencies, were fed to another light source inside the cylinder so that they could be demodulated by the chopping effect of the alternating light and dark bands. The output from each level of the cylinder was fed to a separate photoelectric detector combined with an integrator. The voltage on each integrator increased with time as it accumulated signals from one frequency component of the NMR spectrum, increasing the signal-to-noise ratio. The system was designed to operate in real time with no delay for signal processing. One embodiment
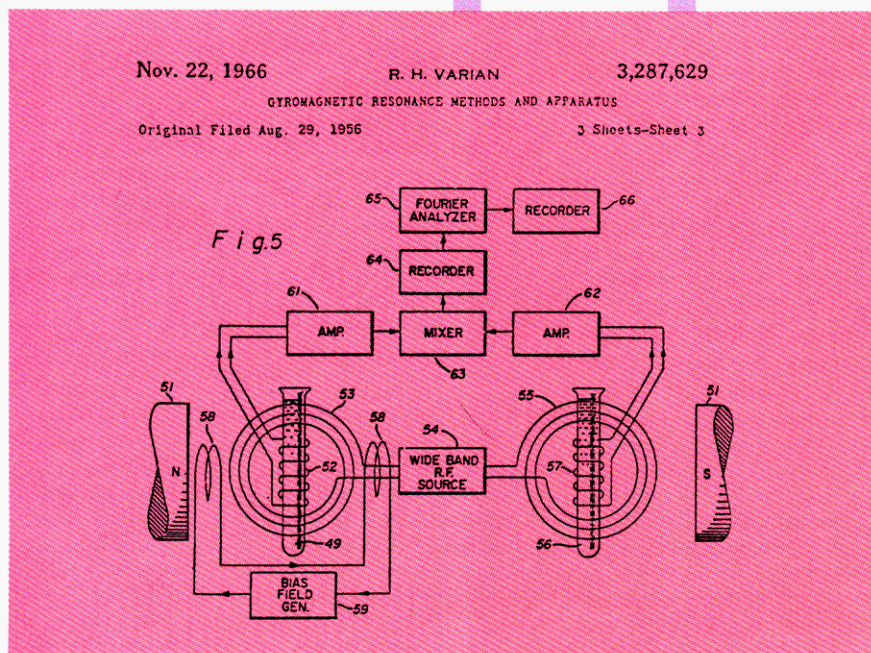

Figure 1. Front page of an early patent obtained by Russell Varian.

The apparatus includes a broadband rf source (54) and signal processing via a Fourier analyzer (65). The dual-sample field/frequency regulation scheme is incidental to the main theme.

of this idea in the form of a disk rather than a cylinder is shown in an extract from Anderson's laboratory notebook (Figure 3).

The prayer wheel was never used. Although the cylinder was constructed, the tricky part of installing the strips of photographic film in such a manner as to ensure a continuous audio frequency output was not completed. As luck would have it, a much better idea came along. Later, the prayer wheel was consigned to the Smithsonian Institution on the grounds that it had played an important role in the thought processes that led to the FT revolution.

This new approach evolved from a collaboration between Anderson and a young Swiss scientist, Richard Ernst, who had recently joined Varian Associates after completing his doctoral research with Hans Primas at the Eidgenössiche Technische Hochschule in Zürich. The ensuing cross-fertilization of ideas led to an elegant solution to the problem. The idea was to use a short pulse of rf power to excite resonances over a wide band of frequencies.

Anderson's laboratory notebook of June 3, 1964, shows a clear exposition of this concept (Figure 4). A repetitive train of coherent rf pulses is shown to be equivalent to a spectrum of discrete frequencies having an envelope resembling a sinc function. If the pulses are sufficiently narrow (on the order of microseconds), the center portion of this distribution is approximately uniform and may be used for exciting the NMR response. This development solved the wideband excitation part of the problem but left the challenge of devising a suitable multichannel detector. (Ernst was awarded the 1991 Nobel Prize in Chemistry for his contributions to modern NMR spectroscopy.)

Fourier transformation

During the 1960s Technical Measurement Corporation introduced an instrument called a computer of average transients, or CAT. This multichannel storage device was soon adopted by NMR spectroscopists to improve sensitivity by accumulating several consecutive spectra in exact frequency registration. Today this technique is commonly known as time averaging.

The original version of the CAT had only 400 channels. Anderson and Ernst appreciated the fact that this concept was essential if one wanted to exploit the advantage of pulse excitation. The free induction signal after each rf pulse, converted
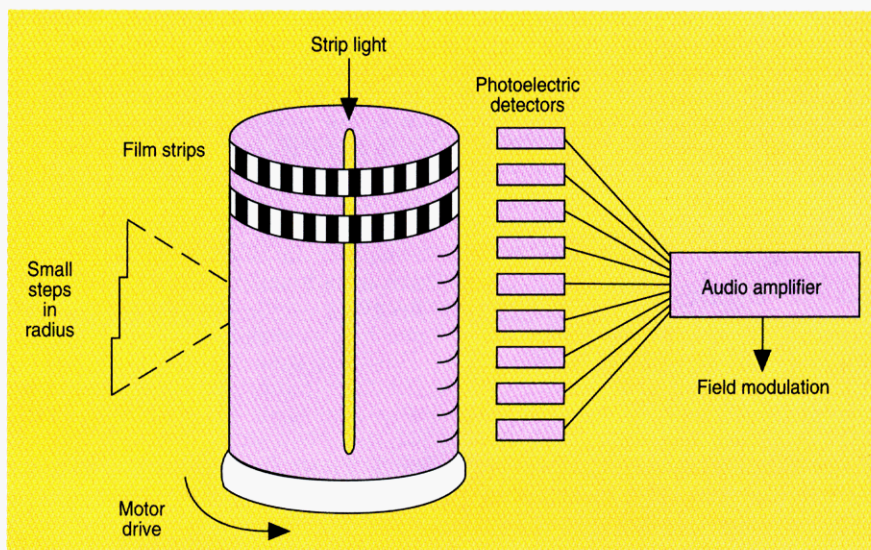

Figure 2. Prayer wheel used to generate a comb of audio frequencies for obtaining an NMR spectrum and to demodulate the resulting NMR responses.
In practice about 20 film strips and detectors were used.

to audio frequencies, could be digitized and stored in the CAT. When a large number of such transient signals had accumulated, the signal-to-noise ratio would be improved.

The key to multichannel detection was to FT this free induction signal. This idea, already being used in IR interferometers, stems from the original concept of Fourier: Any arbitrary waveform can be constructed from a superposition of a series of sine waves with suitable phases and relative intensities. The information content of the free induction signal is exactly the same as that of the frequency-domain high-resolution spectrum, its FT. Spectroscopists, however, like to have this information in the frequency domain (the spectrum) and are not equipped to study free induction "interferograms." In a similar manner, a mu-

sician prefers to play individual notes one at a time rather than to drop the instrument onto a hard concrete floor to elicit the impulse response. The FT was therefore an essential component of the new NMR revolution.

Strangely enough, it did not seem to occur to other NMR spectroscopists that the sensitivity improvement from pulse excitation would be so dramatic and well worth the extra trouble. Those who did appreciate the principle were physicists uninterested in the problems of high-resolution NMR spectroscopy; clearly it was a field for chemists. Fortunately, Anderson was working in a company in which the scientific and commercial importance of high-resolution techniques was clearly understood and Ernst had been trained as a chemist.
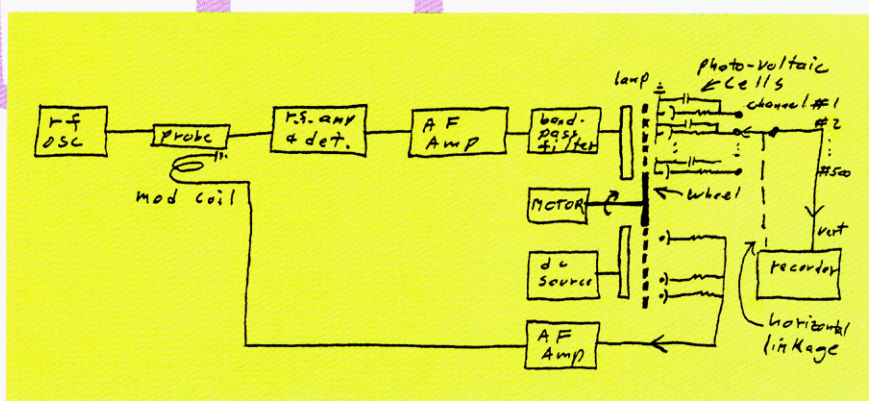

Figure 3. Extract from Anderson's laboratory notebook dated Sept. 10, 1962, describing a disk arrangement instead of a cylinder for generating a comb of audio frequencies and for demodulating the NMR response.

Considerable practical problems had to be overcome, not the least of which was the reluctance of referees to recognize a really fundamental breakthrough when it was carefully explained to them (9). Some ideas are just too revolutionary. Fortunately, the authors had faith in their new method and disclosed a patent (10) just to be on the safe side.

Multiplex advantage

It is useful to spend a moment examining how the sensitivity advantage of the FT method arises. In a CW slow-passage experiment, individual NMR lines are broadened and distorted unless the sweep rate is kept sufficiently slow. The most prominent feature is a decaying oscillation on the trailing edge of each line: the "wiggles."

Suppose we are dealing with the natural linewidth, determined by the reciprocal of the spin–spin relaxation time T_2. True slow passage (to minimize the wiggles) requires that the time taken to sweep through the line be on the order of T_2. In practice this requirement can be somewhat relaxed because the lines are broadened predominantly by instrumental effects (magnetic field inhomogeneity), usually represented by a shorter decay time constant T_2^*. Slow passage then requires the sweep rate to be slow enough that the linewidth Δ

is scanned in a time of nT_2^*, where n is a small number, about 2 or 3. If the total width of the spectrum is F Hz, the total time in seconds for a complete slow passage is nT_2^*F/Δ.

In the FT experiment the free induction signal must be sampled for a sufficiently long time that it decays to a negligible level; otherwise, the resonance lines after transformation are broadened and distorted, with decaying oscillations on each side of the line, resembling a sinc function. The decay time constant is T_2^*; hence, the free induction signal should be acquired for a time equal to mT_2^*, where m is a small number, about 2 or 3. The pulse excitation scheme may be repeated many times (N) in the time required for one complete slow-passage experiment. If these N FT signals are time-averaged, the signal-to-noise ratio increases as $N^{1/2}$, thus

$$NmT_2^* = nT_2^*F/\Delta$$

If we assume that n is approximately equal to m, then $N \approx F/\Delta$. Thus the signal-to-noise ratio increases by a factor of approximately $(F/\Delta)^{1/2}$. This number can be as high as 2 orders of magnitude for ^{13}C spectroscopy; typical values might be $F = 20$ kHz and $\Delta = 2$ Hz. It is this dramatic improvement that makes ^{13}C spectroscopy a practical proposition in spite of the low natural abundance of ^{13}C. A sen-

sitivity improvement of this magnitude renders many more chemical problems amenable to NMR spectroscopic analysis. Today we can contemplate using submicrogram quantities of sample for proton NMR spectroscopy. Every element with a gyromagnetic moment has been studied at one time or another, bringing the inorganic chemist into the fold along with the biochemist who deals with minute amounts of precious macromolecules.

20–20 Hindsight

An FT modification for an existing spectrometer was offered in late 1968, and high-resolution spectrometers designed for FT operation appeared around 1971. It soon became clear that there was little point in retaining the CW slow-passage approach that had served so well for more than a decade. The Fourier revolution was complete.

The question that arises is why this had not occurred earlier. To answer that, we have to try to put ourselves in the shoes of an NMR spectroscopist in the mid-1960s. When Ernst and Anderson started this research (9) there were no small laboratory computers available, and data storage and retrieval methods were very crude. The experimental FID, digitized initially on the CAT, had to be converted into punched paper tape and then transcribed onto IBM punch cards (one data point per card) (Figure 5). These cards were then taken to an adjacent building where the IBM 7090 computer was housed, for FT processing overnight, competing (mostly unsuccessfully) with the rival demands of Varian Associates payroll and factory inventory processing (11). If the spectrum needed to be rephased—and it almost always did—another day would be wasted before the new spectrum was obtained. Meanwhile, the chemists were running high-resolution spectra by the old-fashioned, pedestrian, slow-passage method and publishing the results.

Fortunately, small laboratory computers were becoming available. A Digital Equipment Corporation PDP-8 minicomputer with 4 KB of memory was purchased. This amount of memory seems ridiculously small, but at that time it was adequate for the task at hand. This crucial improvement meant that the FT could be performed in house with direct transfer of the data between computer and spectrometer, greatly reducing turnaround time. Moreover, the computer itself served as a time-
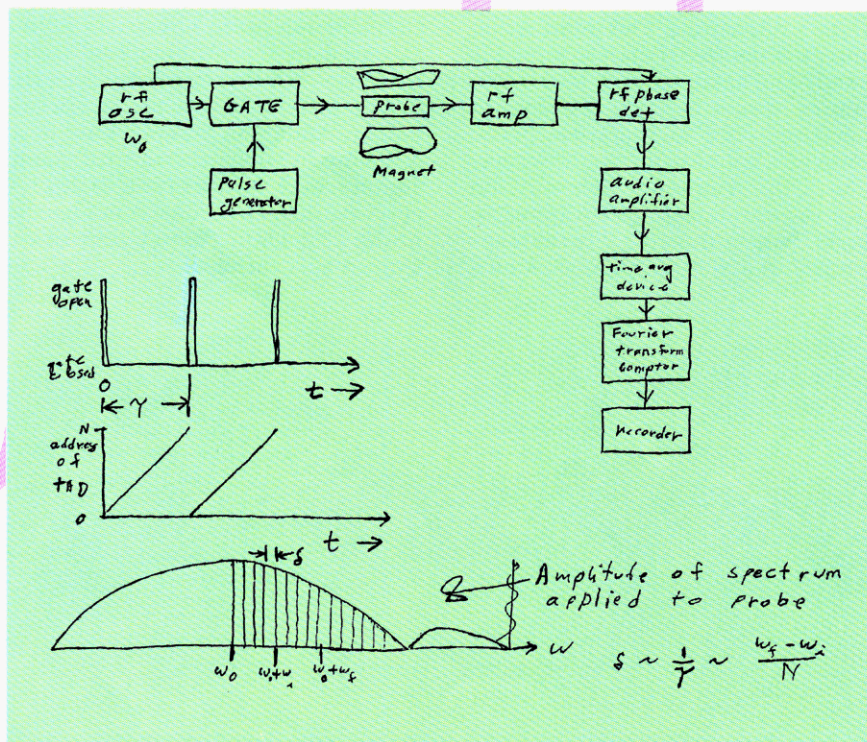

Figure 4. Extract from Anderson's laboratory notebook dated June 3, 1964, outlining the idea of pulse-excited, high-resolution NMR spectroscopy.

averaging device. (In later years it became clear that a computer would have to be part of the spectrometer itself and that it could then take on some of the control functions of the experiment.)

There was, however, a serious drawback: The transformation program used at that time required about 20 min. Imagine demonstrating this marvelous new technique to a prospective customer: "Let's go and have a coffee while the FT is being calculated." It took a great deal of faith to believe that anyone would have the patience to use the new technique.

Two gentlemen had in fact already supplied the remedy, just in time for the NMR project. Cooley and Tukey (12) realized that the standard FT algorithm then in use was far from efficient. It used too many multiplication operations, one of the slowest steps in many calculations on a digital computer. By introducing a restriction that the data set had to comprise 2^n items, where n is an integer, they showed that the problem could be factored in a manner that greatly reduced the number of multiplications. The transformation was speeded up enormously and completed in a matter of seconds rather than minutes. Finally, FT spectroscopy had become a practical proposition.

Computer speeds have increased considerably in the intervening years, and even multidimensional FT may now be contemplated with equanimity. The induction period was over, and the explosion could now begin. Soon everyone was using FT-NMR techniques.

Time-dependent experiments

Although this enormous sensitivity improvement was the crucial factor in opening up ^{13}C NMR spectroscopy and spectroscopy of the less common nuclei, the FT concept also suggested entirely new experiments, such as the study of time-dependent phenomena by NMR. It was already possible to use selective rf pulses to measure the spin–spin or spin–lattice relaxation times of individual lines of a high-resolution spectrum (13), but only one line could be measured at a time. Considerable patience and spectrometer time were required.

Fourier methods could be used to examine the entire high-resolution spectrum and follow the time development of each line in the spectrum during a spin-lattice relaxation experiment (14). There soon followed a

rash of papers on relaxation, particularly those involving the ^{13}C nucleus (15, 16).

Chemically induced nuclear polarization (17) was another obvious candidate for study by FT spectroscopy. At last it was possible to use NMR spectroscopy to take a snapshot of an evolving process without "blurring the image." It was as if the old plate camera that required the subject to sit perfectly still for a long period had been replaced by a modern high-speed camera.

2D spectroscopy

In 1971, in the midst of this popular revolution, another anarchist was plotting his own revolutionary

scheme. Jean Jeener had been contemplating an experiment that might produce data that in some way reflected the theoretical "relaxation matrix." He applied two pulses to the sample and varied their separation, the "evolution period" t_1. The signal was detected as the FID S (t_2) following the second pulse. Because it was inconvenient to gather data during t_1, the behavior of the spins during this period was deduced indirectly by FT of the detected signal as a function of both t_1 and t_2. This gave a 2D matrix of intensity as a function of two frequency parameters f_1 (the transform of t_1) and f_2 (the transform of t_2).
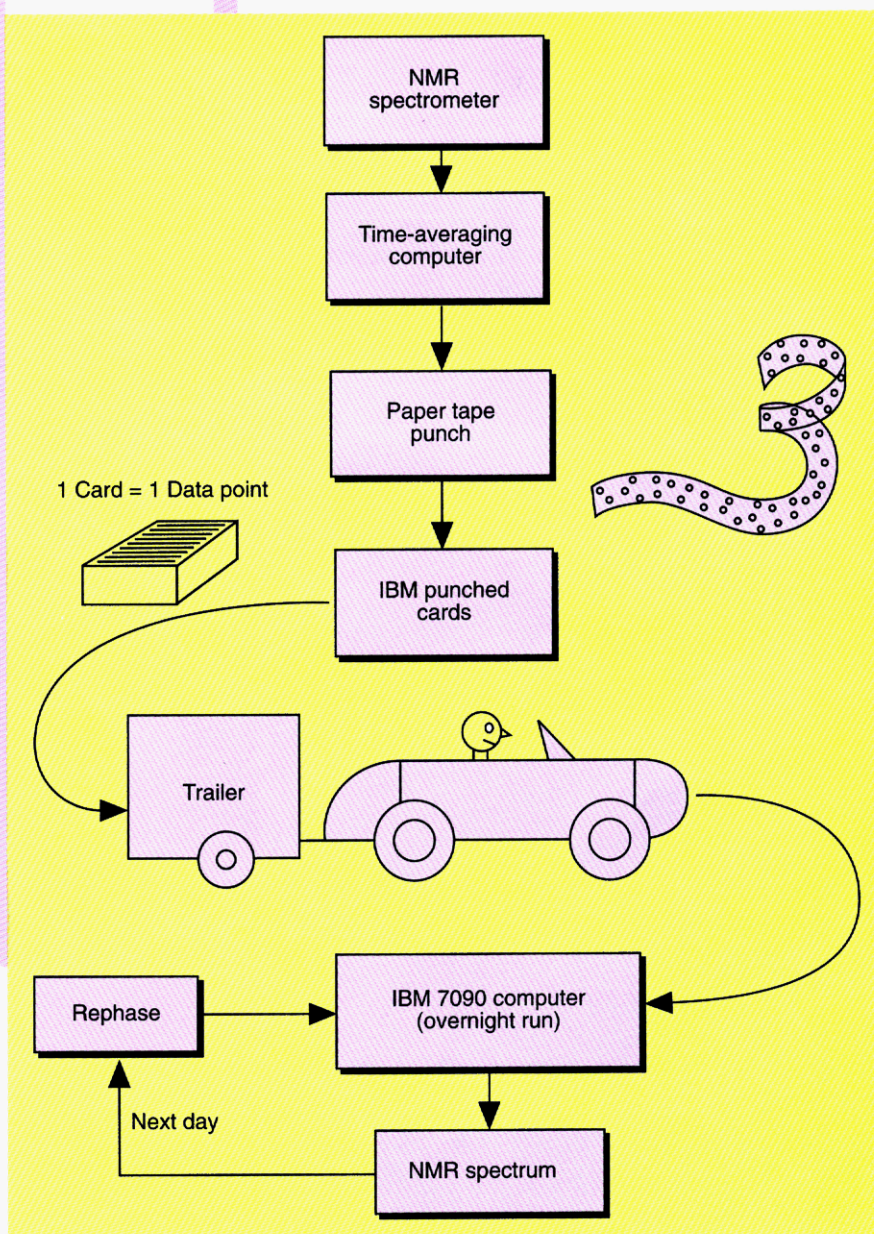
Jeener realized that this 2D spec-

Figure 5. Cartoon outlining the first FT-NMR experiments in 1965.

REPORT

trum in fact told him not the relaxation properties but the pattern of couplings between the spins. Although similar information could be obtained from a series of double-resonance experiments performed in the frequency domain, Jeener saw that the new 2D technique gave a very clear picture of the connectivities and that the sensitivity was essentially as high as a conventional 1D experiment. Unfortunately, these first 2D spectra were never published; the only reference to this work is in a set of lecture notes for a summer school (17).

This technique, which was comprehensively analyzed and put into practice by Ernst (18), became known as correlation spectroscopy (COSY). The spectrum consists of two types of response: diagonal peaks, which have the same frequency coordinates in both dimensions and reflect the conventional 1D spectrum, and cross peaks, which are responses that lie off the main diagonal and indicate which diagonal peaks are connected by spin coupling (Figure 6). This graphic representation of the network of scalar couplings has proved surprisingly useful as a general method for assigning NMR spectra. More important, as demonstrated by Ernst (18, 19), it is the prototype of an entire family of 2D experiments discovered during the past 15 years.

Of particular importance to the study of biochemical molecules is an offshoot of COSY known as nuclear Overhauser enhancement spectroscopy (NOESY) applied to 2D proton NMR. The interaction responsible for forming cross peaks is the nuclear Overhauser effect, the enhancement of the intensity of one NMR line when the resonance of a close neighbor is saturated. Only if there is a significant dipole–dipole interaction between the two spins is there an Overhauser enhancement. Because this effect falls off as the inverse sixth power of distance, it provides a sensitive criterion for proximity within the molecule. An enormous amount of work on the structure and conformation of proteins in solution hinges on this particular experiment (20).

An organic chemist concerned with the structure of small molecules might be more attracted to a third
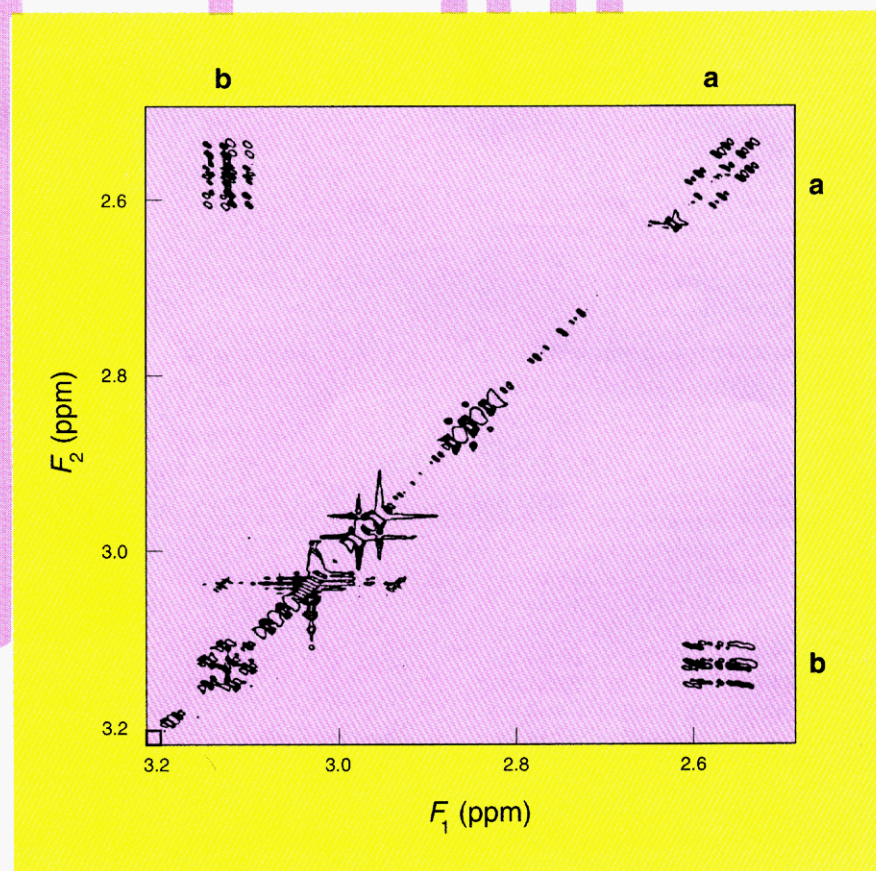
Figure 6. Part of the 2D proton correlation spectrum (COSY) of erythromycin showing a single pair of cross peaks, indicating that proton *a* is spin-coupled to proton *b*.

REPORT

slice—first in one spatial dimension and then in an orthogonal dimension—followed by 2D FT spectroscopy. This technique, initially called Fourier zeugmatography, has been widely adopted for medical imaging.

Offshoots of 2D spectroscopy

Two-dimensional spectroscopy became the catalyst for a host of new NMR techniques. Previously, high-resolution spectroscopists working with liquid samples had given little thought to the design of complex pulse sequences, although such sequences were widely used in solid-state NMR spectroscopy. Now "spin choreography" became an essential art. For example, polarization transfer techniques for enhancing the sensitivity of rare spins (24) and methods for editing ^{13}C spectra according to the number of attached protons (25) derive directly from ideas used in 2D heteronuclear correlation experiments. Forced to learn new tricks of spin gymnastics in 2D experiments, the high-resolution spectroscopist began to apply them in many other situations. Scientific curiosities, such as multiple-quantum coherence, suddenly became serious business.

One development that would prove important for conventional high-resolution work stemmed from an idea used in heteronuclear 2D COSY. In this technique, designed to relate proton and ^{13}C chemical shifts, it is convenient to remove the effects of CH coupling during the evolution period so that CH splittings are suppressed in the f_1 frequency dimension. This can be achieved by introducing a 180° pulse at the midpoint of the evolution period so that two diverging ^{13}C magnetization vectors are brought back to a focus.

At that time the accepted method for broadband decoupling was noise irradiation but, in some applications at high field, difficulties were experienced with excessive rf power deposition in the sample. A more efficient scheme was sought. One possibility was to adapt the refocusing idea, applying a rapid sequence of 180° pulses to the protons and confining the ^{13}C sampling to the focus points. Unfortunately, the use of this technique restricts the sampling rate too severely for practical ^{13}C spectroscopy. However, by using composite refocusing pulses, made up of the 90° (x), 180° (y), 90° (x) sequence, the same refocusing effect can be achieved for much lower rf power (26). Then the pulses can be applied continuously, but to avoid cumulative errors they must be made part

2D experiment that traces the carbon backbone of the molecule one link at a time. This technique (21) relies on the presence of two directly adjacent ^{13}C spins and is therefore of low sensitivity. It excites ^{13}C double-quantum coherence during the evolution period and reconverts it into observable magnetization during detection. Thus not only is each ^{13}C spin pair labeled in an unambiguous manner, but the intense and undesirable signals from isolated ^{13}C spins are suppressed. The result is a surprisingly faithful representation of the carbon–carbon connectivity in which chain branching and ring formation are clearly identified.

Magnetic resonance imaging

The concept of 2D FT spectroscopy had an important impact in a quite different field. In 1973 magnetic resonance methods were applied to derive spatial images of living objects by exciting proton resonance in intense magnetic field gradients (22). The intent was to investigate anomalies in the physiology (e.g., tumors) by obtaining maps of proton density within the body. Later, these ideas were expanded to cover angiography, organs in motion such as the beating heart, tissue differentiation through relaxation effects, and in vivo spectroscopy. The operative word for this technique is noninvasive, an approach that differs from the classical reliance on the scalpel or irradiation of the body with X-rays. Even for magnetic resonance imaging, the term noninvasive is actually a euphemism because the patient is exposed to an intense static field, rf fields, and rapidly pulsed field gradients during the investigation.

Usually the experiment starts with selection of the NMR signal from a particular "slice" through the patient. The goal is to obtain a 2D map of proton density within that slice. The observable quantity is the projection of the spin density onto the direction defined by the applied field gradient. If several measurements are taken with the gradients applied in different directions, the projected densities contain enough information to reconstruct a 2D proton density map. This data processing scheme, called projection–reconstruction, is inspired by earlier work in X-ray tomography.

Ernst showed that there is a much more efficient method (23) in which the time dependence of the NMR signal is followed while gradients are applied in the plane of the selected

of a phase-alternating cycle or supercycle (26). The ^{13}C free induction signal may be sampled at any desired rate, not necessarily in synchronism with the proton pulses. The use of this technique led to the development of the widely used broadband decoupling sequences MLEV-64 and WALTZ-16 (27).

Some 2D spectra can be projected in such a way as to create a new 1D spectrum. One of the most useful examples derives from a 2D proton J-spectrum obtained by exciting a modulated spin-echo during the evolution period (28). By using the symmetry properties of the 2D multiplets, high-resolution proton spectra can be recorded without any spin–spin splittings (29). More generally, 2D experiments can often be simplified into a 1D version by the substitution of a selective rf pulse (30, 31) or can be extended into three (32) or four (33) frequency dimensions by tacking together two or more building blocks (e.g., COSY or NOESY).

Revolutions are usually irreversible. This is certainly the case for FT spectroscopy, and the slow-passage method—once universally accepted as the norm—now seems to afford no advantage whatsoever. Multidimensional spectroscopy is common today, but it could hardly have developed without the FT concept. We owe a great debt to those who imagined this entirely new approach to NMR.

References

(1) Arnold, J. T.; Dharmatti, S. S.; Packard, M. E. *J. Chem. Phys.* **1951**, *19*, 507.
(2) Arnold, J. T. *Phys. Rev.* **1956**, *102*, 136.
(3) Anderson, W. A. *Phys. Rev.* **1956**, *102*, 151.
(4) Bloch, F. *Phys. Rev.* **1956**, *102*, 104.
(5) Hahn, E. L. *Phys. Rev.* **1950**, *80*, 580.
(6) Varian, R. H. U.S. Patent 3 287 629, 1966.
(7) Lowe, I. J.; Norberg, R. E. *Phys. Rev.* **1957**, *107*, 46.
(8) Fellgett, P., Ph.D. Thesis, Cambridge University, 1951.
(9) Ernst, R. R.; Anderson, W. A. *Rev. Sci. Instrum.* **1966**, *37*, 93.
(10) Anderson, W. A.; Ernst, R. U.S. Patent 3 475 680, 1969.
(11) Anderson, W. A. *Radiology Today* **1992**, *9*, 1.
(12) Cooley, J. W.; Tukey, J. W. *Mathematical Computation* **1965**, *19*, 297.
(13) Freeman, R.; Wittekoek, S. *J. Magn. Reson.* **1969**, *1*, 238.
(14) Vold, R. L.; Waugh, J. S.; Klein, M. P.; Phelps, D. E. *J. Chem. Phys.* **1968**, *43*, 3831.
(15) Freeman, R.; Hill, H.D.W. *J. Chem. Phys.* **1970**, *53*, 4103.
(16) Kaptein, R.; Freeman, R.; Hill, H.D.W. *Chem. Phys. Lett.* **1974**, *26*, 104.
(17) Jeener, J. Presented at Ampere International Summer School, Basko Polje, Yugoslavia, 1971.
(18) Aue, W. P.; Bartholdi, E.; Ernst, R. R. *J. Chem. Phys.* **1976**, *64*, 2229.
(19) Ernst, R. R.; Bodenhausen, G.; Wokaun, A. *Principles of Nuclear Magnetic Resonance in One and Two Dimensions*; Oxford University Press: Oxford, 1987.
(20) Wüthrich, K. *NMR Spectra of Proteins and Nucleic Acids*; John Wiley & Sons: New York, 1986.
(21) Bax, A.; Freeman, R.; Frenkiel, T. A. *J. Am. Chem. Soc.* **1981**, *103*, 2102.
(22) Lauterbur, P. C. *Nature* **1973**, *242*, 190.
(23) Kumar, A.; Welti, D.; Ernst, R. R. *Naturwissenschaften* **1975**, *62*, 34.
(24) Morris, G. A.; Freeman, R. *J. Am. Chem. Soc.* **1979**, *101*, 760.
(25) Doddrell, D. M.; Pegg, D. T.; Bendall, M. R. *J. Magn. Reson.* **1982**, *48*, 323.
(26) Levitt, M. H.; Freeman, R. *J. Magn. Reson.* **1979**, *33*, 473; **1981**, *43*, 502.
(27) Shaka, A. J.; Keeler, J.; Freeman, R. *J. Magn. Reson.* **1983**, *53*, 313.
(28) Aue, W. P.; Karhan, J.; Ernst, R. R. *J. Chem. Phys.* **1976**, *64*, 4226.
(29) Xu, P.; Wu, X. L.; Freeman, R. *J. Am. Chem. Soc.* **1991**, *113*, 3596.
(30) Kessler, H.; Oschkinat, H.; Griesinger, C.; Bermel, W. *J. Magn. Reson.* **1986**, *70*, 106.
(31) Kessler, H.; Mronga, S.; Gemmecker, G. *Magn. Reson. Chem.* **1991**, *29*, 527.
(32) Greisinger, C.; Sørensen, O. W.; Ernst, R. R. *J. Magn. Reson.* **1989**, *84*, 14.
(33) Kay, L. E.; Clore, G. M.; Bax, A.; Gronenborn, A. M. *Science* **1990**, *249*, 411.
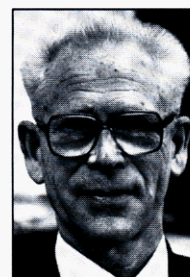
Ray Freeman received his doctorate from Oxford University with his thesis on NMR spectroscopy of Co, Ga, and Tl. After postdoctoral research in Paris, he studied double-resonance techniques at the National Physical Laboratory in Teddington, England. In 1961 he joined Varian Associates, where he developed new physical techniques in high-resolution NMR spectroscopy and constructed the first commercial FT spectrometer. He lectured in physical chemistry at Oxford University for 14 years and has held the John Humphrey Plummer chair of magnetic resonance at Cambridge University since 1987.