flow in order to understand the viscoelastic properties of a polymeric solution. De Gennes's answer was that the polymers "slither" like snakes, and his model is consequently called the "reptation" model (from the Latin *repere*, meaning "to creep"). A chain does not move forward in a straight line; instead, its random local Brownian movements lead it to progress gradually along its own contorted contour. In this way the haphazard motions of parts of a chain result in a much smaller forward progress of the center of mass of the whole molecule.

De Gennes told us that his work on polymers owes a heavy debt to Sam Edwards of Cambridge University, England. In the early 1960s Edwards noted that polymers obey laws similar to quantum field theory, and he was able to solve them in the limit of high concentrations. (He collaborated in some of this work with Carl Freed of the University of Chicago.) Edwards also introduced a mean-field approach, by which one concentrates on one polymer and represents the effect of all the others on it by an average interaction. Edwards told us that de Gennes then realized that he could extend the study of polymers to dilute solutions by using scaling mechanisms.

Edwards also laid the groundwork for the reptation model by suggesting that polymers are hemmed in by all the other molecules in a polymer melt at high concentration and that each chain behaves as if it were confined to a tube with its axis curved in arbitrary arcs: The walls of the tube correspond to the restrictions imposed by the surrounding polymers. De Gennes pushed this model further to analyze the snake-like motion of the polymer as it wiggles along its tube. The polymer leaves one tube section by diffusion and creates another section as it winds its way through the solution.

De Gennes told us that over the last ten years he has been thinking less in terms of complex mathematics and more in terms of scaling laws. His education in that approach, he says, comes largely from Leo Kadanoff of the University of Chicago. Kadanoff in turn is impressed by the ingenious ways in which de Gennes has extended the ideas of scaling in unexpected directions. Kadanoff's Chicago colleague Thomas Witten notes that all de Gennes's diverse accomplishments embody a single style of reasoning: He strips away all possible formalism to explain the phenomenon at hand with maximum economy and simplicity. This style is well expressed in the elegant scaling arguments for which de Gennes is famous.

—Barbara Goss Levi

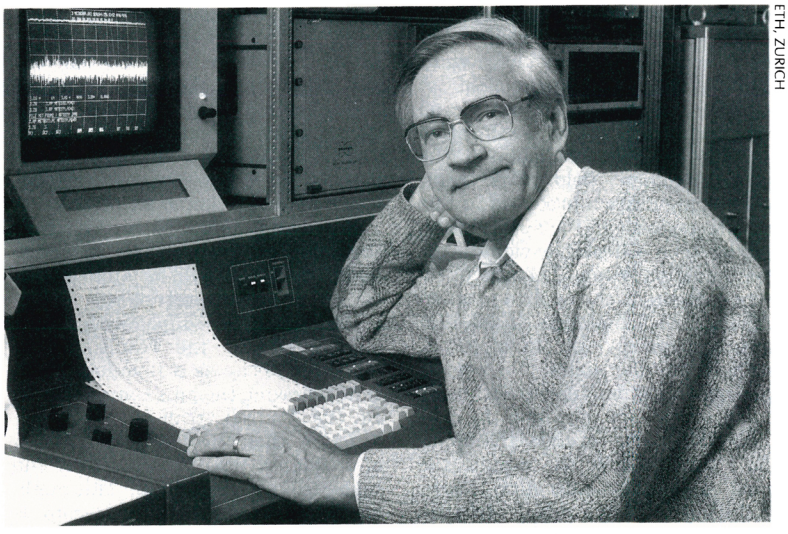
NOBEL CHEMISTRY PRIZE RECOGNIZES THE IMPORTANCE OF ERNST'S NMR WORK

Richard R. Ernst of the Swiss Federal Institute of Technology (ETH) in Zurich was reviewing research proposals on a flight from Moscow to New York, on his way to collect Columbia University's 1991 Louisa Gross Horwitz Prize, when the captain informed him he had won the 1991 Nobel Prize in Chemistry. While the news was not important enough to interrupt screening of the in-flight movie, Ernst did go forward to the cockpit to receive the radioed congratulations of the Royal Swedish Academy of Sciences, the president of Switzerland and participants in a party organized on his behalf in Zurich.

In announcing the award the academy cited Ernst's "contributions to the development of the methodology of high-resolution nuclear magnetic resonance spectroscopy." In the 46 years since the invention of nmr, a number of researchers have made highly significant advances, and consequently the first thing Ernst asked the captain was, "Who are the other two?"

"I could imagine several feasible combinations of winners where I would be only one of two or one of three," Ernst told us.

However, Ernst stands out especially because of two important developments: Fourier-transform nmr spectroscopy in the mid-1960s and two-dimensional nmr in the 1970s. He also proposed an nmr tomography method that now forms the basis of one of the most widely used magnetic resonance imaging techniques for clinical studies.



ETH, ZURICH

Richard R. Ernst in front of a spectrometer that is used to record two- and three-dimensional nmr spectra.

Early work

The first nmr experiments were carried out in 1945 by groups led by Felix Bloch at Stanford and Edward L. Purcell at Harvard. (Bloch and Purcell won the 1952 Nobel Prize in Physics for this work.) Nmr makes use of the nuclear Zeeman effect: In an applied magnetic field of the order of several tesla, different orientations of the nuclear spins have energies that differ by amounts corresponding to radio frequencies. When the nuclei are exposed to radio waves of the correct frequency, transitions between the levels can be excited. Most of the earliest experiments involved continuous-wave radio signals swept slowly through a range of frequencies; at the resonant frequencies absorption or dispersion by the sample is detected, either by the coil producing the radio waves or by a separate

receiver coil.

Pioneering studies of the use of nmr in chemistry began shortly after the discovery of nmr. In 1949 several researchers observed that an atom's chemical environment affects its nuclear resonant frequencies. Two important effects of this type are the chemical shift (caused by shielding of the applied field by the electron shells) and the scalar or J coupling between nearby nuclear spins, which is mediated by the electron pairs in bonds. Herbert S. Gutowsky (University of Illinois at Urbana–Champaign) studied these effects in extensive continuous-wave experiments and introduced the use of nmr for structural analysis in chemistry. He and Charles P. Slichter (Urbana–Champaign) developed an empirical Hamiltonian for the J coupling in the early 1950s. At the same time, Erwin L. Hahn (then at Urbana–Champaign and Stanford, now at Berkeley) independently observed the J coupling using pulse nmr techniques and deduced the same Hamiltonian.

In 1949 and 1950 Hahn performed the first free-induction-decay and spin-echo experiments. In these experiments the sample is excited by a pulse of rf that rotates the spins out of their minimum-energy alignment with the applied magnetic field. A pulse of the correct intensity and duration—a "$\pi/2$ pulse"—will rotate the spins to be perpendicular to the applied magnetic field. The transverse magnetization produced in this way precesses about the applied field, leading to a detectable signal—the free induction decay. Because of inhomogeneities in the applied magnetic field, the spins precess at different rates and quickly get out of phase, washing out the signal. In typical spin-echo experiments the $\pi/2$ pulse is followed τ seconds later by a π pulse; this pulse reverses the spins, and τ seconds after the π pulse the spins all precess back into phase, producing the "spin echo." In such experiments chemical shifts and J couplings are seen by the beating between the shifted frequencies in the detected signals.

The dependence of nmr frequencies on chemical structures suggested that nmr could have a powerful role to play in analyzing molecular structures, and by 1960 the then preferred method, continuous-wave spectroscopy, was already popular for such studies of small molecules. "Since the early 1960s every chemistry lab of any consequence has had an nmr machine to run spectra with," says Slichter. However, the continuous-wave experiments suffered from a major problem: Sensitivity was poor because of the time consumed while the frequency sweep passed through extensive frequency domains off resonance.

Fourier-transform nmr

This was the situation in 1962 when Ernst got his PhD in physical chemistry at ETH. In 1963 he moved to Palo Alto, California, where he became a research scientist at Varian Associates, working under Weston A. Anderson on methods to improve the sensitivity of nmr spectroscopy. One approach Varian was considering at the time was a multichannel spectrometer with numerous transmitters and receivers operating at different frequencies simultaneously. "Obviously this wasn't the way to go," Ernst says.

The solution was hidden in pulse experiments carried out in solid CaF_2 by Richard E. Norberg (Washington University at St. Louis) and Irving J. Lowe (then at Washington University, now at the University of Pittsburgh). In solids the dipole–dipole interaction between nuclei broadens the lines, making it extremely difficult to do the high-resolution spectroscopy that is possible with liquids. In 1957 Lowe and Norberg showed that after a $\pi/2$ pulse the resulting free induction decay (which is a function of time) could be Fourier transformed to provide a measure of the shape of the dipole-broadened absorption line (a function of frequency).

Ernst and Anderson realized that the Fourier transform of the free induction decay could be put to practical use in liquid spectroscopy. If one excited a liquid sample with a $\pi/2$ pulse, digitized the resulting free induction decay as a function of the time following the pulse, and computed the Fourier transform of that function, then the resulting function of frequency would be precisely the high-resolution spectrum. This method, Fourier-transform spectroscopy, is faster and ten to a hundred times more sensitive than the continuous-wave sweep methods because each pulse excites a range of frequencies; no time is wasted on nonresonant frequencies. "All your time is spent meaningfully listening to the voices that are speaking to you," says Slichter. Typically one repeats the experiment many times and sums the output signals from the different runs to improve the signal-to-noise ratio before doing the Fourier transformation of the output signal.

The increase in sensitivity achieved by Fourier-transform nmr revolutionized the field. Today, nearly all manufactured nmr spectrometers use the Fourier-transform technique.

In 1968 Ernst returned to ETH as a *Privatdozent* in physical chemistry and continued working on nmr techniques. (He became a full professor in 1976.) In 1971 Thomas Baumann, one of Ernst's students, heard a talk by Jean Jeener (Free University in Brussels) at the Ampère Summer School in Basko Polje, Yugoslavia, on a two-pulse technique of possible use in liquid-state spectroscopy. From Baumann's notes on Jeener's particular two-dimensional Fourier-transform nmr proposal, Ernst and his group began working on calculations that generalized and further developed Jeener's idea. In 1974 they did the first simple two-dimensional nmr experiments—"so that we would have something to present at a conference which I was organizing together with Kurt Wüthrich," Ernst jokes.

Two-dimensional nmr was another revolutionary advance in the field. It produces a spectrum that is a function of two frequency variables, which result from a two-dimensional Fourier transformation of data that depend on two time variables instead of the usual single variable of one-dimensional spectroscopy. Subjecting the sample to carefully designed sequences of radio-frequency pulses is the key to the method. Initially, during a "preparation" period, one or more such pulses excite the nuclear spin system. In many of the simplest techniques—which go by whimsical acronyms like COSY, SECSY, NOESY and ROESY—the preparation period is a single $\pi/2$ pulse that generates transverse magnetization in the sample. Following the preparation period the excited system evolves during an "evolution period" of duration t_1 before being hit by a second series of pulses in the "mixing period." For example, in a COSY experiment the mixing period consists of another $\pi/2$ pulse. Finally the signal is measured during the "detection period." This sequence of four periods is repeated with a different duration of the evolution period in each run. The measured signal is thus a function of two time variables: the duration t_1 of the evolution period and the usual time variable t_2 that parametrizes the detection period. The data are digitized and Fourier transformed with respect to both of these times, yielding a frequency spectrum in two dimensions.

Editing spectra

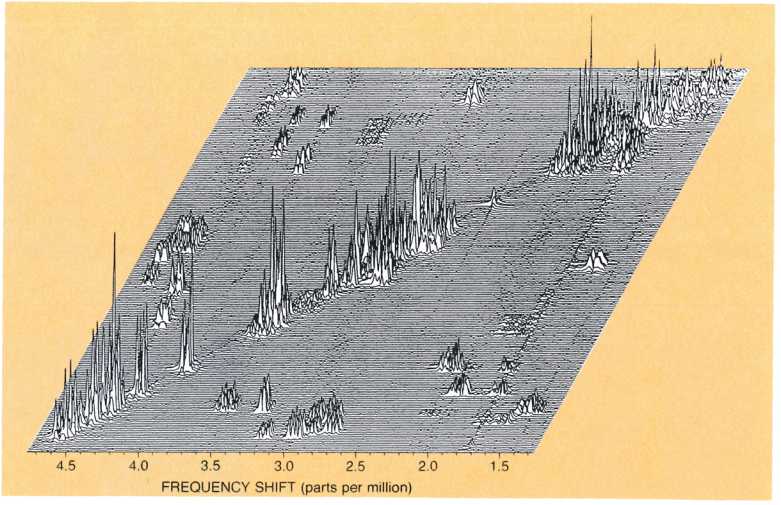
A basic advantage of this technique is that the data are distributed in two frequency dimensions. In one-dimen-

sional spectroscopy of complex molecules the many peaks overlap like a mountain range viewed from the ground. In two-dimensional Fourier-transform nmr, by contrast, the peaks are spread out like a mountain range viewed from an aircraft. (See figure at right.)

There is a more sophisticated advantage: By using cleverly designed sequences of pulses one can make the two frequency variables of the data encode specific types of information regarding the molecular environment of the nuclei. Pulse sequences can thus alter the spectrum seen—as if terms had been added to or subtracted from the Hamiltonian of the nuclear spins. (Some call this "editing" the spectrum.) "You have a sort of alchemist's power over the nature of the system," says John S. Waugh of MIT. "You can use that power to get a spectrum that is more easily interpreted than it otherwise would have been." For example, one can arrange the pulses so that one frequency corresponds to the characteristic shift of absorption frequencies of nuclei in their local electronic environment, while the other might give information on couplings such as the J coupling to nearby neighbors. A given peak in the two-dimensional frequency plane then might be readily identified as resulting from protons in a methyl group that lies near a methylene group. Groups of spins may also be manipulated collectively by means of multiple quantum spectroscopy, a technique that allows simplification and classification of the spectra.

Pioneers of such sophisticated pulse techniques include Waugh (winner of the 1983–84 Wolf Prize in Chemistry), Alexander Pines of Berkeley (who shared the 1990 Wolf Chemistry Prize with Ernst), Peter Mansfield (University of Nottingham, UK) and Ray Freeman (Cambridge University). The work of Waugh, Pines and Mansfield has been particularly important for the development of solid-state nmr in chemistry, but the techniques are also used extensively in liquid spectroscopy. It is in the use and development of elegant pulse sequences to extract detailed chemical information that Ernst has excelled. "He plays lots of music with the pulse techniques," says Hahn. "His contributions are beautiful elaborations of fundamental ideas."

As a result of the development of two-dimensional Fourier-transform nmr spectroscopy (and subsequent three- and multidimensional techniques), nmr has become an important tool in analyzing the three-dimensional structures of organic and inorganic compounds, including proteins and other large biological molecules. "Two- and multidimensional nmr has had an enormous impact, especially in biological chemistry," says Waugh. "It has made possible the relatively routine determination of the geometric structure of complicated molecules." Ernst's ETH colleague, Wüthrich (who shared this year's Louisa Gross Horwitz prize with Ernst) has been the leader in applying and further developing Ernst's techniques for this type of work. Unlike x-ray diffraction, which is the other major technique for determining structures in crystals, two-dimensional nmr can determine molecular structures in solution. This is particularly important for biological molecules, whose properties depend crucially on their secondary and tertiary structure—that is, on how they fold up in water.



Two-dimensional COSY (correlation spectroscopy) spectrum of the linear nonapeptide buserilin. Off-diagonal peaks indicate J couplings between spins of neighboring nuclei in the molecule. (Spectrum recorded by Christian Griesinger at ETH, Zurich.)

Imaging

At about the same time as his work on two-dimensional nmr, Ernst did some experiments in nmr tomography. He based his work on a method of nmr tomography proposed and developed a few years earlier by Paul Lauterbur (then at SUNY Stony Brook, now at University of Illinois at Urbana–Champaign) and Mansfield. Lauterbur's method uses an applied magnetic field that has a constant gradient. This makes the resonant frequency of a given transition vary linearly with the spatial coordinate along the field gradient and allows one to excite only a single slice of the sample. Then one images successively along different axes within the defined plane using other field gradients. The two-dimensional image is reconstructed from these one-dimensional projections much as in x-ray tomography.

Ernst's variation on the method applies the techniques of Fourier-transform nmr: One applies a field gradient in the x direction for time t_x and in the y direction for time t_y. One varies these times (or, equivalently, the field gradient) systematically, and the Fourier transform gives a two-dimensional map of the spin densities in frequency space—which now corresponds to spatial locations within the sample. Ernst's method, which has been elaborated on over the years, is now the mri technique most widely used in clinical studies.

Ernst says that at the time he did his experiments he had no idea nmr spectroscopy and mri would become the big industries that they are today. "I never believed in any idea that we were working on," he says. "I just had the feeling we were playing with these tools, and it was fun, but I did not expect that it would become as useful and practical as it has."

Ernst and his group are now working on techniques to investigate dynamic processes—how molecules change shape and interact with other molecules as a function of time. To do this requires new sequences of pulses and more quantitative work on the details of relaxation mechanisms, which are the carriers of the dynamical information.

—Graham P. Collins ■