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A SHORT HISTORY OF NMR

Ray Freeman

Nuclear magnetic resonance (NMR) is just 50 years old, yet it has shown a remarkable growth in that short lifetime, surpassing the analytical applications of infrared spectroscopy, medical diagnostics with the x-ray scanner, and molecular structure determination by x-ray crystallography (at least for biochemical studies). This short article aims to highlight the key developments that have ensured this continued expansion; whenever NMR seemed to have reached a comfortable plateau, someone managed to discover a completely new aspect of the subject.

It all started with the independent and virtually simultaneous discoveries of NMR in bulk matter by Harvard [1] and Stanford [2] physicists in late 1945. At the time the main application appeared to be the accurate determination of the nuclear magnetic moments of all the elements in the periodic table. Very soon, discrepancies in these "constants" came to light [3, 4] and it was realized that there was a small but significant shielding effect by the extranuclear electrons – the chemical shift was born. This may have remained a mere regrettable complication for the physicists, had not a chemist (the late S. S. Dharmatti) pointed out that if the chemical shift was indeed real, then the proton NMR spectrum of ethanol should have three separate resonances. Arnold, Dharmatti, and Packard soon showed experimentally that it had [5].

No one had ever thought to build magnets with fields so homogeneous that high resolution proton spectra could be properly resolved, since this required a uniformity in space of the order of 1 part in 10^6. Undeterred by this, Arnold [6] set out to construct such a magnet, and Anderson [7] demonstrated the first truly high resolution proton spectra with linewidths as low as 0.5 Hz, using a spinning sample as proposed by Bloch [8]. Soon after this, many chemists realized the enormous potential of NMR and the race was on. New techniques seemed to spring up almost overnight – spin echoes [9], double resonance [10], time averaging [11], the Overhauser effect [12], and Hartmann–Hahn cross polarization [13].

But the technique suffered from an inherently poor sensitivity and it seemed that this could only be improved by operating at higher magnetic fields. Furthermore, higher fields meant better chemical shift dispersion, so that more complex molecules could be studied. Since the iron-cored electromagnets then in use had already reached their limit (determined by magnetic saturation) Nelson and Weaver [14] turned to superconducting solenoids where the current continued indefinitely provided that the coils were cooled to 4 K in liquid helium. First at 200 MHz, now at 750 MHz, and soon at 1000 MHz, this new generation of spectrometers gradually superseded all the iron magnets and they were hardly ever heard of again.

Soon after this, Ernst and Anderson [15] introduced Fourier transform NMR, which delivers approximately two orders of magnitude improvement in sensitivity through the multiplex advantage, by recording all the resonance lines in the spectrum at the same time. Together with the invention of noise decoupling [16] this brought the "difficult" nuclei like ^{13}C and ^{15}N within reach. Inorganic chemists and biochemists began to take a serious interest in NMR, the latter through studies of ^{31}P spectra in molecules of biological interest.

At that time, NMR spectroscopy of the solid state was rather a stagnant topic because most of the information of interest was hidden by the strong dipolar broadening (which disappears in a liquid through the rapid molecular tumbling). Then Andrew [17] showed how to circumvent this problem by rapid spinning about the "magic" angle, and Waugh [18] devised a series of intricate pulse sequences that solved the same problem in another manner. Suddenly high resolution NMR of solids was a viable proposition.

Meanwhile a Belgian physicist (Jeener) was planning to revolutionize the methodology by introducing the concept of two-dimensional Fourier spectroscopy [19, 20]. By spreading the information into a second frequency dimension, this allows all kinds of interesting correlations to be made and permits studies of normally forbidden NMR transitions. Above all, it emphasizes that the spins can be manipulated in a myriad different ways by designing the appropriate pulse sequence.

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While these exciting developments were still being digested, Lauterbur [21] showed how NMR could be applied to investigate the internal structure of an object by placing it in an intense magnetic field gradient; medical imaging was born. The interest was immediate because it had already been shown that protons in cancerous tissue tended to have a longer spin-lattice relaxation time than those in healthy organs [22]. A veritable invasion of the field by radiologists ensued, since the new method promised much clearer and more meaningful images than those obtained by x-ray scanners. The investigations now range from viewing the beating heart to "functional magnetic resonance" that pinpoints the regions of the brain that are activated by a given stimulus.

Where will it all end?

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