

## 4 Nuclear Magnetic Resonance and MRI

February 26, 2008

The technique of nuclear magnetic resonance, known as NMR for short, was developed simultaneously by Felix Bloch at Stanford and Edwin Purcell at Harvard, for which they both received the 1952 Physics Nobel Prize. Magnetic resonance methods have found wide uses in physics, chemistry, materials science, and in the life sciences.

The development of Magnetic Resonance Imaging (MRI) by Paul Lauterbur, then at SUNY Stony Brook, and Peter Mansfield, at the University of Nottingham, in the mid 1970s enabled three-dimensional images to be obtained of human tissue in which the distribution of particular chemical or physical features could be made to show up. These two physicists received the 2003 Nobel Prize for Physiology or Medicine. The use of this method depended not only on the availability of NMR techniques, but also of high speed computers to control the scanning of the resonance conditions through the material, and to analyze the convoluted data to form readable images.

Nuclear magnetic resonance depends on very different features of nuclei than nuclear power does. It depends on the fact that many nuclei have intrinsic angular momentum and magnetic moments – this is true of the ground states of all nuclei except those for which both the proton number  $Z$  and the neutron number  $N$  are even. Because the nucleus is deep inside the atom it is largely undisturbed by other nuclei in neighboring atoms, and it is mostly influenced by the applied magnetic field, and by how that is changed by the changes it induces in the surrounding atoms

The theory of magnetic resonance spectroscopy involves a delicate mixture of classical mechanics, in which the nucleus is regarded as a gyroscope with a permanent magnet aligned with the axis around which it spins, and quantum mechanics, in which a nucleus with angular momentum  $\hbar I$ , where  $I$  is an integer or half-integer, has  $2I + 1$  degenerate states in the absence of a magnetic field, which are broken into  $2I + 1$  equally spaced energy levels by the application of a magnetic field.

### 4.1 Physics of nuclear magnetic resonance

I will start by considering the behavior of a proton in a magnetic field. This is one of the simplest cases because the intrinsic angular momentum is  $\hbar/2$ ,

so there are only two states of the proton, but it is also one of the important cases, since hydrogen atoms are very common in living materials. The proton has a magnetic moment of  $\mu_p = 1.409 \times 10^{-26}$  joules per tesla, and the splitting between the two energy levels of the spin 1/2 proton due to a magnetic field of magnitude  $B$  is  $2B\mu_p$ . A transition between these two states involves the emission or absorption of a photon of twice this energy, and therefore frequency  $2B\mu_p/h$ . For a field of 1.00T this gives a frequency of 42.6 MHz, and a wavelength of 7.05 m, in the traditional radio frequency range.

The energy of a proton in a field of one tesla is  $1.02 \times 10^{-3}k_B$ , where  $k_B$  is the Boltzmann constant, so at room temperature there is very little alignment of the proton spins by any practicable magnetic fields; the fraction of aligned spins at one tesla is a few parts in a million. A big magnet in an ordinary laboratory may give 10 T, but anything much bigger than that will be in a specialized high magnetic field lab, or perhaps be a pulsed field produced by an implosion. Any detectable signal that is produced at room temperature must depend on manipulation of the few parts in a million of the protons that are aligned by a magnetic field. As in the operation of a laser, we want to get a state in which the nuclear moments are disturbed from their equilibrium configurations to form some sort of inverted population. An obvious, but impracticable, way to do this would be to let the protons come to equilibrium with the field in the  $x$  direction, and then suddenly move the magnet round so that the field is in the  $z$  direction, but the protons are left half pointing in the  $+z$  direction, and half in the  $-z$  direction. Fortunately there are cleverer ways to produce the same effect which I do not describe in detail, and a pulse of resonant radiation can be applied to turn all the proton spins through an angle of  $\pi/2$  about the  $x$  axis, to align the tiny magnetization in the  $x$  direction instead of the  $z$  direction. This is called a  $\pi/2$  pulse, and a  $\pi$  pulse lasts twice as long and reverses the polarization direction.

The magnetic moment of the aligned protons is minute. If one compares with the magnetization of iron, the magnetic moment of an individual proton is down on the magnetic moment of an electron in iron by a factor of about  $10^3$ , because of the smaller value of the nuclear magneton, and it is down by another factor of  $10^5$  or so because of the very small polarization of the protons, so there is a factor of about  $10^8$  between the two magnetic moment densities. However, just as resonance techniques can be used to produce a nonequilibrium magnetization, so also they can be used to detect this small

magnetization with high precision.

At this point I switch to using a classical, rather than a quantum, description of the motion of the spins. The spins, originally aligned in the  $\pm\hat{z}$  direction, are now aligned in the  $\pm\hat{x}$  direction, perpendicular to the magnetic field. A magnetic dipole in a uniform magnetic field has no net force on it, but there is a torque on it tending to align it with the magnetic field. The magnitude of the torque is  $B\mu_p \sin\theta$ , where  $\theta$  is the angle between the directions of the field and the magnet, and the torque acts about an axis perpendicular to these two directions. For those who like vector notation, the torque is given by the vector product of the field and the magnetic dipole moment. The result of such a torque is to give a rate of change of the angular momentum equal to the torque. Since the rate of change is always perpendicular both to the magnetic moment and the  $\hat{z}$  direction, the torque just pushes the end of the spin angular momentum vector round a circle of radius  $\sin\theta\hbar/2$  at a speed  $B\mu_p \sin\theta$ , so the frequency with which the angular momentum vector precesses round the direction of the field is

$$\nu_p = 2B\mu_p/h, \quad (1)$$

just the frequency of photons emitted in the transition between the two magnetic states of the proton.

All the polarized protons, those few which were preferentially polarized in the  $\hat{z}$  direction, started in the  $\hat{x}$  direction after the  $\pi/2$  pulse is applied, so, if the magnetic field is really constant in space and time, all will precess together, forming a coherent rotating magnet. According to Maxwell's electromagnetic theory, such a rotating magnetic dipole source will produce electromagnetic radiation of frequency  $\nu_p$ . The source is not strong, because of the weak initial magnetization, but, as we shall discuss later, it is very coherent, so the radiation can be detected by a circuit tuned to the right frequency, and this signal amplified by the usual techniques of radio reception in the megahertz range.

## 4.2 Chemical shifts

The resonance frequency of a proton in a magnetic field is 42.6 hertz per tesla of field acting on the proton. However, the chemical environment of a nucleus produces a shift of the magnetic field acting on the proton away from the value that the magnet would produce in empty space. Covalent bonding

between atoms usually produces molecules that have no free electronic spins, but magnetic fields acting on the saturated covalent bonds induce currents in the electron system, which tend to reduce the magnetic field in the material. This small negative magnetic susceptibility is known as *diamagnetism*, and this can reduce the observed resonance frequency, producing one example of what is known as a *chemical shift* of the resonance. A famous example of this is shown by liquid ethanol, with chemical formula  $(\text{CH}_3)(\text{CH}_2)\text{OH}$ , where three distinct proton resonances are observed. The intensities of these three resonances are in the ratio 3:2:1, corresponding to the three different chemical environments of the hydrogen atoms bonded to the oxygen atom, and to the two differently placed carbon atoms.

Other sorts of shifts can occur. For example, the electrons in a metal are polarized by the applied magnetic field, and these polarized electron spins produce a magnetic field acting on the nuclei, which gives a shift of the resonance line known as the *Knight shift*.

In all this discussion it should be remembered that, although we talk about line widths and line broadening, actual measurements are usually not done by changing the tuning of the receiver, but by modulating a small additional magnetic field to shift the shifted or broadened line back to the fixed resonance frequency.

### 4.3 Line broadening and narrowing

In fact there are many different reasons for the magnetic field on the nuclei to vary from one atom to another, and to vary with time. The dipolar field which is exerted on one nucleus by its neighboring nuclei can be quite large. Since the dipole-dipole potential depends on the orientation of the spins relative to the displacement of one from the other, energy can flow between from one nucleus to another, and the net polarization can also change, transferring magnetic energy to the phonon system.

The chemical inhomogeneities of the sample can lead to different precession rates for different nuclei, and this leads to the different spins polarized in the  $\hat{x}$  direction getting out of phase with one another, so that eventually the radio frequency signal disappears. If this type of phase incoherence is all that is happening, the signal can eventually be restored by applying, at time  $T$ , a  $\pi$  pulse to rotate all the spins by  $\pi$  about the  $\hat{x}$  axis. This reverses all the azimuthal angles  $\phi$ , and now all these angles retrace their path until at time  $2T$  they are all in phase again, and the magnetization and radio

frequency signal are restored. This is known as a *spin echo* experiment. In reality the signal is not completely restored, because static inhomogeneity of the magnetic field is not all that is happening, and so the rate at which the spin echo fades gives information about how important these other processes are, while the rate at which the original signal fades gives information about the field inhomogeneity.

One might expect that the more motion there is in the system, the more the resonance line will be broadened. In fact a small chemical shift can be measured in liquid ethanol, while solids may not show such shifts against a background of other line broadening effects. A molecule in a liquid has very irregular motions, translational motion, rotation, and vibration, but these occur over a much shorter time-scale than the microsecond time-scale of the nuclear precession. The precessional frequency is determined by the *average* precession rate, and if the deviations from the average occur much more rapidly than the precessional frequency, the effects of these deviations on the line-width of the resonance can be very small. This effect is known as *motional narrowing* of the resonance line.

Felix Bloch developed a set of phenomenological equations, firmly based on quantum mechanics, to describe, up to a point, nuclear magnetism. These equations have the form

$$\begin{aligned}\frac{dM_z}{dt} &= -\frac{M_z - M_0}{T_1} - \gamma(\mathbf{M} \times \mathbf{B})_z, \\ \frac{dM_{x,y}}{dt} &= -\frac{M_{x,y}}{T_2} - \gamma(\mathbf{M} \times \mathbf{B})_{x,y},\end{aligned}\tag{2}$$

where  $\mathbf{M}$  is the nuclear magnetization as a function of time, and  $M_0$  is the equilibrium magnetization in a steady and uniform field  $B_0$  in the  $z$  direction. The *longitudinal* relaxation time  $T_1$  gives the time it takes for the magnetization in the  $z$  direction to relax back to its equilibrium value  $M_0$ , while the *transverse* relaxation time  $T_2$  gives the time the azimuthal angles of the spins to get out of phase with one another, as they do in the first step of a spin-echo experiment. In a spin-echo experiment the initial rate of decay of the signal is determined by a combination of  $1/T_1, 1/T_2$ , while the rate of decay of the echo is  $1/T_1$ .

## 4.4 Imaging

Imaging techniques have been an important benefit of the computer revolution. Even in the fifties, when Cambridge University had one 250 Hz computer, much of its time was taken up by reconstructing the spatial structure of biological molecules such as insulin or icosahedral viruses from X-ray diffraction patterns, and reconstructing the distribution of radio sources in the sky from the correlations of signals received in a small array of small radio telescopes. Important diagnostic techniques such as Computer Assisted Tomography with X-rays and Magnetic Resonance Imaging with atomic nuclei are two examples of such an exploitation of large and fast computers. To get a three-dimensional image with a nuclear resonance technique (MRI) it is necessary to add to the large uniform magnetic field a small field gradient, whose direction can be adjusted by varying the currents through a set of carefully controlled coils. For any given setting of these additional fields the nuclei will only be in resonance near one particular plane. Such a scan gives the integrated density of resonant nuclei as a function of the one-dimensional position of the plane on which the resonance occurs. There are some complications due to varying chemical shifts, and varying widths of the resonance.

Without these complications a set of three different scans should be sufficient to determine the density of resonant nuclei as a function of position in three-dimensional space, but even without the complication due to chemical shifts no scientist or engineer would rely on a minimal set of measurements. It is important to reinforce the analysis with additional scanning directions. Features such as the chemical shifts and widths of the resonance in different places can give additional diagnostic information. Lauterbur's 2003 Nobel Lecture gives an interesting and readable account of how this method was developed. Mansfield's lecture gives more technical details of how the analysis is made, and there are good illustrations of apparatus and of actual scan results. Both these lectures can be found at [http://nobelprize.org/nobel\\_prizes/medicine/laureates/2003/](http://nobelprize.org/nobel_prizes/medicine/laureates/2003/) Click on Nobel Lecture in the third column, under either of their names.

I have not yet found a good general account of MRI. Let me know if you find one.