

3.2 Anatomical Imaging

3.2.1 Magnetic Resonance Imaging Contrast Agents

3.2.1.1 Nuclear Magnetic Resonance

MRI is a form of computed tomography based on a measurement technique familiar to chemists and known as Nuclear Magnetic Resonance or NMR. This exploits the effect of a strong magnetic field on the nuclei of atoms, in the case of MRI on the nuclei of hydrogen atoms in the water molecules within the body. In order to create an MRI image the subject is placed within a large cylindrical chamber so that a strong magnetic field can be applied to the region of interest (Figure 1). Once the magnetic field is applied the subject is investigated using pulses of radiofrequency radiation. These induce radiofrequency emissions (echo signals) from the subject which can be detected externally. The frequencies of the echo signals can be analysed and the results converted into a 3-dimensional image of the distribution of water within subject. Image contrast arises from the differing water contents of fat, muscle and bone as well as from other more subtle effects. The technology involved in MRI imaging is both elegant and complex but some appreciation of the underlying principles is necessary in order to better understand the role of coordination chemistry in MRI imaging applications. To this end a very much simplified account of the MRI measurement follows to explain how introducing paramagnetic metal compounds into the subject can improve the contrast in MRI scans.

The nuclei of hydrogen atoms are protons and these possess a magnetic moment rather like a simple bar magnet. In a strong magnetic field these magnetic moments precess about the magnetic field direction and, for a proton, quantum mechanics allows only two possible energy states to exist. In simple terms the protons must align with the magnetic field or against it. To attain

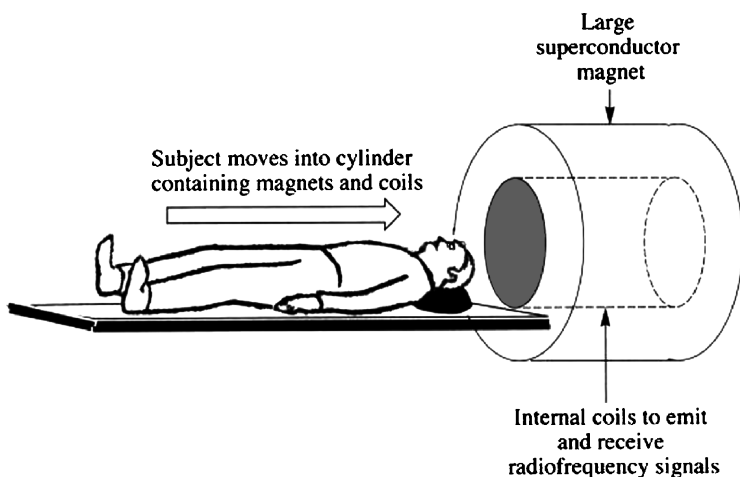


Figure 1 The physical arrangements for performing an MRI scan

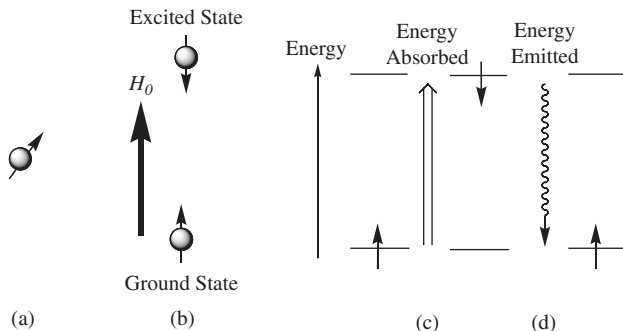


Figure 2 (a) A representation of a proton with an arrow showing the orientation of the magnetic moment. (b) The ground and excited state orientations of a proton in an applied magnetic field H_0 . (c) An energy level diagram showing the excitation of a proton through the absorption of radiofrequency radiation. (d) An energy level diagram showing the emission of radiofrequency radiation through the radiative transition of a proton from an excited state to its ground state

their lowest energy, or ground state, configuration the protons align their magnetic moments with the field direction. The other possible arrangement has the magnetic moments oriented in opposition to the magnetic field, but this is a higher energy, or excited, state (Figure 2). If radiation of the energy needed to excite the proton from the ground state to the excited state is absorbed, the proton may be promoted into the higher energy state (Figure 2c). The frequency of the energy required to do this is usually referred to as the Larmor precession frequency. The proton can subsequently relax back into its ground state by emitting radiation of an energy equivalent to the energy difference between the ground and excited states (Figure 2d), or through losing energy to its surroundings. The energy difference between the ground and excited states depends upon the magnetic field, H_0 , experienced by the proton. This field is made up from the local magnetic field within the water molecule and any externally applied magnetic field. The energy differences attainable using practicable magnetic fields are small and correspond with the radiofrequency region of the electromagnetic spectrum. At room temperature both the ground and excited states of the hydrogen nuclei are populated but there is a very small excess of protons in the ground as compared to the excited state. Thus if radiofrequency radiation of the correct energy is supplied some is absorbed, inverting the relative populations of the ground and excited states. If the radiofrequency energy source is removed the nuclei relax back to their ground states, in some cases emitting the absorbed radiofrequency radiation.

If an object containing water is placed in a magnetic field gradient, the value of H_0 , experienced by the protons in the water will vary with position (Figure 3). Thus when the a proton relaxes back to the ground state the energy, and so the frequency, of any radiation emitted will correspond with the position of the proton in the field gradient. If a patient is placed in a strong magnetic field with gradients in three directions, and exposed to a broad spectrum pulse of

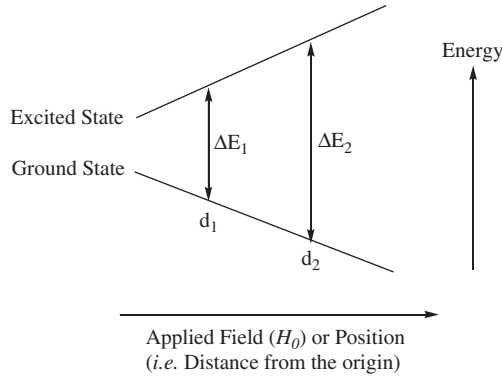


Figure 3 In a field gradient different energies, ΔE_1 and ΔE_2 , for emitted photons correspond with different respective distances d_1 or d_2 from the origin

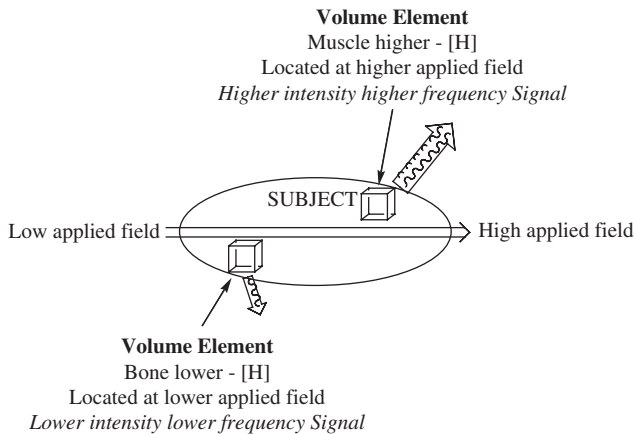


Figure 4 A schematic representation of the basis for an MRI measurement in which $[H]$ represents the local concentration of water H atoms in the tissue

radiofrequency radiation, protons in the water within the body are promoted to their excited states. When these protons subsequently relax down to their ground states and emit radiation, this will be at frequencies characteristic of their location. Measurement of the emitted radiation coupled with computed tomography, then allows a 3-dimensional image of the distribution of water within the subject to be constructed. In practice the subject is divided into a number of volume elements and the signal intensity from each is determined. An image of the human head might, for example, be made up from over 65,000 volume elements each 1 mm by 1 mm by 5 mm in size. A sequence of operator defined excitation pulses is applied, each with a duration of about a micro-second, and the emitted radiation is measured during an operator specified time period between consecutive pulses. Resolutions of down to about 1 mm can be achieved in this way (Figure 4).

The contrast in an MRI image arises from the differing signal intensities (SI) arising from the different volume elements. These SI are related to the concentrations of water protons, $[H]$, in the different tissues in the body so that muscle, fat and bone, for example, might produce signals of differing intensities. However, signal intensity is not only dependent on the concentration of water, it also depends upon the rate at which the protons concerned relax from the excited state to the ground state as a result of interactions with their surroundings and with other protons. A ‘longitudinal’ relaxation time, T_1 , is associated with the transfer of energy from the excited protons to their surroundings and a ‘transverse’ relaxation time, T_2 , is associated with the exchange of energy between ground state and excited state protons. The reciprocals of these times are the relaxation rates for the two processes. One further complication in the measurement is the need to allow for the movement of water into or out of the volume element during the time the measurement is being made. This is expressed in a parameter H_v . The MRI machine operator can optimise the image produced by varying two operator defined parameters. These are PR and SE , which respectively represent the applied radiofrequency pulse repetition time and the time during which the emitted radiation is detected, *i.e.* the spin echo time. Taking these various parameters into account an approximate expression for the signal intensity from a given volume element is given by Equation (1).

$$SI = [H]H_v[\exp(-SE/T_2)\{1-(-PR/T_1)\}] \quad (1)$$

Signal intensity tends to increase with increasing $1/T_1$ and decrease with increasing $1/T_2$ but, for most tissues, the average T_2 values are only a fraction of the corresponding T_1 values. As an example values of 747 ms for T_1 and 71 ms for T_2 were found in Putamen tissue in the brain. In a magnetic field of 1.4 T (corresponding with a frequency of 60 MHz) values for T_1 typically lie in the range 200–500 ms for different tissue types. The operator can select radiofrequency pulse sequences to emphasise the effect of changes in $1/T_1$ compared to $1/T_2$ (T_1 weighted) or, conversely, to emphasise $1/T_2$ compared to $1/T_1$ (T_2 weighted).

3.2.1.2 Contrast Agents for Magnetic Resonance Imaging

In clinical applications of MRI it is often useful if the contrast between regions in the image can be altered beyond that possible using adjustments of the scanning equipment. A simple way to do this would be to change the relative signal intensity by changing the concentration of water in one region compared to another. As an example, attempts to displace liquid containing water from the GI tract using $C_8F_{17}Br$ (Imagent[®]), an inert liquid free of water protons, showed the procedure to be possible. However, the approach was impracticable because of the cost and side effects of the treatment. Similarly replacement of water by deuterium oxide (heavy water) is precluded by the toxicity and quantity of heavy water required. Fortunately there is another way in which image contrast might be manipulated. The magnitude of SI depends, not only upon $[H]$, but also upon T_1 and T_2 so that compounds capable of modifying