2.1 Nuclear Magnetic Resonance (NMR)

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Introduction

Nuclear Magnetism was detected in solid hydrogen by Lazarew and Schubnikow in 1937. The first observations in bulk material were reported independently by Bloch and by Purcell in 1946. This provided insight into the properties of nuclei, with different nuclei having characteristic resonant behaviour. The first in vivo observation of an NMR signal occurred shortly afterwards, when a strong hydrogen signal was observed from Bloch’s finger. While remaining an important means of probing nuclear structure, it was soon found that NMR spectra contained characteristic information on molecular conformation, and a major role for NMR developed in chemical analysis and in the study of molecular binding. In the 1970’s, development of larger superconducting magnets allowed these techniques to be extended to the non-invasive investigation of tissue biochemistry.

The potential of using NMR for imaging hydrogen atoms was first proposed by Lauterbur, based on spatially localising signals by adding small magnetic field gradients, that changed strength linearly with spatial displacement, to the homogeneous main magnetic field. Images could be reconstructed from sets of projections, in much the same way as images were reconstructed in X-ray computerised tomography. This approach was used in the first commercial MR system using a superconducting magnet. In parallel, Mansfield developed imaging approaches from a background of solid state physics, where techniques based on crystallographic principles could be applied to spatially sample signals. This approach led to the development of echo planar imaging (EPI) allowing a full image to be acquired in a single excitation. Further developments, particularly in research groups at the Universities of Nottingham and Aberdeen, saw development of a wide range of imaging methods, which eventually culminated in the modification of Kumar’s Fourier Zeugmatography technique by Edelstein to provide the Spin Warp imaging technique which is now almost universally used. As well as progressive development of imaging methods, there has been a continuing development in magnet design, with superconducting magnet designs providing considerable stability and allowing increases in field strength up to a current maximum of 8T for whole body systems. Recently a range of electromagnet and permanent magnets has been developed to address growing low field requirements. In clinical applications, NMR imaging is commonly referred to as magnetic resonance imaging (MRI).

In the 1980’s the first clinical NMR spectroscopy instruments were developed, using high field (1.5T or greater) magnets with specialised hardware. As clinical MRI systems at 1.5T became widespread, magnetic resonance spectroscopy (MRS) used similar techniques to MRI for spatial localisation and was incorporated in to some commercial MR systems, requiring broad band capability to allow $^{31}$P, $^1$H, $^{19}$F and $^{13}$C MRS studies. Recent developments have involved integrated studies combining imaging and spectroscopy, often using specialised radiofrequency coils and acquisition methods. Either single voxel acquisitions, or 2D or 3D spectroscopic imaging methods, where an MR spectrum is obtained in each of an array of spatially localised voxels, are employed.
Applications of Magnetic Resonance Imaging and Spectroscopy

MRI has rapidly developed to provide measurement methods that can address a wide range of clinical problems in diagnosis. The scope of these methods, and the continued rate of development, has been unprecedented in clinical imaging. MRI measures the distribution of hydrogen atoms in the body, with the signal (or image contrast) being affected by the freedom of molecules to rotate or move (relaxation times) or by the way in which the signal is manipulated by the MR pulse sequences.

These control rf pulses, magnetic field gradient switching, and signal detection. Cross sectional images can be obtained directly in any orientation through the body, aiding detection and coverage of specific anatomy. Usually a series of 2D images are acquired, but complete 3D volume images can also be obtained, allowing retrospective reconstruction of any plane, or indeed non-planar surfaces that follow a particular structure.

While a set of images usually take a few seconds or minutes to acquire, images can be obtained in 50 ms using fast imaging techniques. MRI provides unrivalled soft tissue contrast, allowing pathology to be identified, and normal anatomy to be displayed with excellent definition of tissue structures. Bone is not seen directly, as hydrogen atoms in hydroxyapatite are bound too tightly to give a signal detectable on
clinical apparatus. Flowing blood provides a signal that can be manipulated to allow MR angiography – images specifically showing vascular structures. In addition to the measurement of the intrinsic signal from tissues, a range of MR contrast agents is under development. These are compounds with intrinsic magnetic properties that affect the relaxation properties of hydrogen atoms. Gadolinium, with seven unpaired electrons, has a very strong electronic magnetic moment, and is used in the form of a chelate such as DTPA. In the form of Gd DTPA, the contrast agent has a major use in identifying areas where the brain blood brain barrier, which protects neuronal cells from blood borne toxins, is broken down. This is a common feature of lesions in the brain. Tumours elsewhere in the body also exhibit high contrast uptake. Other contrast agents utilise ferromagnetic or superparamagnetic properties, and a range of new applications is developing, including imaging gene function.

The first major application of MRI was in imaging brain disease, where the soft tissue contrast rapidly eclipsed CT. Figure 1 shows examples of brain images, showing how contrast can be altered by changing the measurement sequence. More recently angiography studies allow identification of arteriovenous malformations, carotid artery stenosis, and increasingly stroke. MRI can measure the self–diffusion of water, and the restricted diffusion coefficient is a sensitive measure of the early impact of stroke, and is being used to evaluate protective interventions. Brain perfusion can also be assessed by a range of specialised quantitative imaging techniques. Related methods can be used to measure the rate of transport of contrast agents through the vascular endothelium, providing information on delivery and permeability. A major advance was the discovery that some magnetic resonance imaging sequences were sensitive to brain activation – the changes in blood oxygenation and local perfusion that results from the increased energy demands of neurological activity. This is a powerful tool in neurological and psychiatric research, providing high resolution maps of activity that can be superimposed on excellent images of brain structure. $^1$H MRS

![Figure 2. T1 weighted images of a Ewing’s sarcoma in the tibia of a 10 year old patient. Normal marrow is white and the tumour can be seen replacing normal marrow and extending across the epiphysial plate and outside of the tibia.](attachment:figure2.png)

(b) axial view through the tumour, showing extension beyond the bone.
can be used to characterise different types of brain cancer, promising a non-invasive means of diagnosis and staging. $^{31}$P MRS has been of value in the evaluation of neonates, allowing identification of brain asphyxia. MRI is also the method of choice for investigating spinal cord disease, where excellent contrast between nerve and cerebrospinal fluid can be obtained without the invasive procedures associated with X-ray myelography.

Figure 3. A coronal section through the chest, showing the heart, liver and lung cavity. The image is T2 weighted (Turbo Spin Echo) and is obtained during a breath hold to avoid respiratory motion.

Orthopaedic applications are another major area of development. Here 3D imaging techniques provide excellent high resolution images of joints and the associated soft tissues and synovial fluid, allowing investigation of meniscal tears, cartilage injuries, degenerative disease and sports injuries. A new generation of low field open magnets, allowing imaging of movement, has increased the availability of these approaches. Peripheral angiography allows whole body surveys of vascular patency. Recently, methods for surveying whole body marrow status, allowing identification of metastatic disease from cancer, have been demonstrated. Figure 2 shows an example of a coronal slice through the tibia of a 10yr old patient, showing an Ewing’s sarcoma in the marrow cavity, extending outside of the bone.

Figure 4. A sagittal T2 weighted turbo spin echo through the abdomen of a patient with a cervical tumour. The tumour is the large dark area between the sacrum (shown by the relatively bright marrow in the vertebral bodies) and the cervix (above the very bright bladder).

Cardiac measurements have been the focus of considerable attention, leading to the development of techniques for imaging coronary arteries, heart valve function, cardiac muscle perfusion and metabolism (using $^{31}$P spectroscopy), cardiac ejection rate and cardiac wall motion. This combination of high resolution imaging and cardiac function measurement provides an exceptionally powerful tool. Figure 3 shows a coronal image through the chest, showing the heart. Figure 4 provides an example of body imaging in the abdomen, showing a sagittal view through a cervical tumour. Lung measurements have until recently been a major limitation of MRI. Rapid imaging is now overcoming the loss of signal due to air tissue interfaces, allowing measurement of lung perfusion and the identification of pulmonary emboli. A new development has been the application of hyperpolarised gases ($^3$He and $^{129}$Xe), where the spin population of the gases can be pumped to give
very high polarisations, allowing the gas to be imaged in lung spaces, with applications in chronic obstructive lung disease and in asthma.

In some cases in vivo MRS can be used to directly monitor drug pharmacokinetics and metabolism in tumour and tissues. In these cases the primary drug is identified due to the inclusion of an NMR sensitive atom, such as $^{19}$F (for example 5 fluorouracil) or $^{31}$P (ifosfamide or cyclophosphamide). Figure 5 shows an example of a set of localised $^{19}$F spectra from a patient receiving 5-fluorouracil, superimposed on a proton image of the liver. The localised spectra showed that the signal was all concentrated in the gall bladder (bright on the proton image), and the frequency of the observed peak showed that the compound observed was a bile acid conjugate of fluoro-beta-alanine, a catabolite of 5 fluorouracil. In other cases an isotopically enriched label such as $^{13}$C can be substituted for a non-NMR sensitive high abundance atom ($^{12}$C). The major advantage of MRS is that the chemical form of the parent compound can be observed, and in many cases the metabolism of the drug to active or non-active compounds can be simultaneously identified in real time. This is a unique advantage of MRS compared with other imaging methods such as PET. Figure 6 shows an example of a proton decoupled $^{31}$P MRS spectrum from a sarcoma, showing a characteristic tumour spectrum, and the separation of the characteristic phosphomonoester (PME) signal into phosphocholine and phosphoethanolamine signals. A proton localisation image is also shown, with the superimposed chemical shift imaging spectra. Measuring the metabolites in the PME peak gives information on tumour prognosis and response.

MRI measurements can also provide information about the properties of the blood supply to tumours. By employing contrast agents and using rapid imaging techniques, images can be obtained where the contrast is either affected by the rapid magnetic susceptibility changes arising from the first pass of the concentrated bolus of contrast through the vasculature – providing information on blood volume and perfusion; or by the change in signal due to contrast leaking out of the vascular space into the extracellular space - providing information on contrast delivery and vascular permeability. These measurements are, for example, allowing the effects of new therapies directed at manipulating vascular function to be assessed, and they are also relevant to assessing drug delivery.

Figure 5. An array of $^{19}$F spectra obtained using 2D chemical shift imaging from a patient receiving 5 fluorouracil chemotherapy. Significant signal is only found in one voxel, centred over the gall bladder (bright on the underlying proton image through the liver). The chemical shift of the peak identified it as the bile acid conjugated form of fluoro-beta-alanine, confirming hepatobiliary recirculation of this catabolite. (Reproduced with permission from Dzik-Jurasz et al, Magn Reson Med (2000) 44: 516-520)
$^1$H decoupled $^{31}$P MRS examination of human abdominal sarcoma.

A 3D $^{31}$P chemical shift imaging examination of a patient receiving treatment for a sarcoma. A plane of the spectral data is shown superimposed on a proton image of the same tissue slice. The spectrum from the voxel indicated is enlarged to show the characteristic tumour spectrum. PME: phosphomonoester, PE: phosphoethanolamine, PC: phosphocholine, Pi: inorganic phosphate, PCr: phosphocholine, NTP: nucleotide tri-phosphate.

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