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Progress in n.m.r. zeugmatographic imaging

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Applications of nuclear magnetic resonance (n.m.r.) zeugmatographic imaging to medical diagnosis and to medical, physiological, and biological research require the development of appropriate imaging instrumentation and ancillary techniques, as well as an understanding of the biological significance of the imaging results. A whole body imaging system, relying primarily upon reconstruction from projections, is under development in the expectation that the reconstruction approach will be the most practical one for many purposes. In addition, injectable magnetic reagents that can selectively change tissue water relaxation times and image contrast are under development so as to increase the specificity and versatility of the measurements. If very high magnetic fields are employed, ^{31}P n.m.r. zeugmatography may be practical at very low resolution for human diagnostic studies and for experiments on perfused organs and small animals. Preliminary images, showing the spatial distributions of different phosphorus metabolites in the compartments of test objects, have been obtained at 146 MHz by reconstruction techniques.

Introduction

Nuclear magnetic resonance zeugmatographic imaging may be accomplished by a variety of techniques, all of which make use of the simple principle that each point within an object can be given a different history of exposure to the magnetic fields that are involved in generating n.m.r. signals (Andrew 1977; Lai *et al.* 1978). When the dependence of the magnetic fields on spatial coordinates changes in times short compared with n.m.r. relaxation times, innumerable methods of deducing the object from the resulting signals may be devised, these being limited only by the ingenuity of the inventor. When the fields change so slowly that the spin system retains no memory of the previous field configurations, a more limited set of possibilities exists. For each such configuration, all of the information from the resonant nuclei within the effective volume of the apparatus is converted into a one-dimensional relation between resonant frequency and the spatial coordinates. Recovery of the full three-dimensional information needed to form an image then requires a comparison of the one-dimensional signal distributions found for different field configurations. The general technique for generating such an image is known as reconstruction from projections. The mathematical manipulations may be carried out in many ways, and the theory and practical algorithms have been thoroughly studied in recent years because of the growth of useful applications in X-ray computed tomography and other fields (Ter-Pogossian *et al.* 1977).

We have chosen to emphasize the development of reconstruction techniques in our n.m.r. zeugmatographic imaging experiments because they offer several important practical advantages over alternative methods. The first of these is the possibility of obtaining simultaneously all of the signals from a three-dimensional region. Because the image quality will almost always be limited by the efficiency with which the nuclear magnetization is detected (Lauterbur 1977),

and because information about an entire volume of an object is usually desired, or even essential, techniques that limit data acquisition to a point, a line or a plane within the object will usually suffer a significant disadvantage. Three-dimensional reconstruction is not, in principle, able to take full advantage of the sensitivity associated with simultaneous data acquisition because the deconvolution required to generate the image decreases the signal: noise ratio. Fourier transform zeugmatography (Kumar *et al.* 1975) should be the optimal technique in this respect because it makes full use of both phase and amplitude information in the signals and requires less filtering to produce an acceptable point spread function in the image.

Offsetting this desirable feature is the fact that rapidly changing magnetic field gradients are required. The second advantage of the reconstruction approach is that the magnetic field configuration may be changed slowly, simplifying the instrumentation and avoiding the possibility of inducing dangerous electrical currents in the body (Budinger 1979). Of all the proposed techniques for n.m.r. zeugmatographic imaging, the reconstruction approach is likely to have the best combination of simplicity, sensitivity, reliability and safety. It does place greater demands upon digital data processing and storage devices than do some of the alternative methods, and may require greater magnetic field uniformity, but those problems seem to have relatively straightforward technical solutions.

Whole body imaging

The whole body n.m.r. zeugmatographic imaging system under development in this laboratory is similar to a somewhat smaller system that has been in use here for some time (Lai *et al.* 1978). The larger system, like the smaller one, is based upon a four-coil electromagnet wound with aluminum foil, which generates a magnetic field of 94 mT to give 4 MHz proton n.m.r. signals, but the larger magnet has an axial opening 62 cm in diameter. In our basement laboratory, the greatest deviation from the theoretical homogeneity is caused by the ferromagnetic material underneath the floor of the room. The linear component of the resulting vertical gradient can be cancelled by placing a thin sheet of iron above the magnet, and the quadratic components compensated for by a set of electrical shim coils. It is then possible to make precise adjustments of the positions of the four independently supported coils and to trim the currents with small shunts to obtain essentially the homogeneity computed from the nominal magnet design. Within an oblate region about 35 cm in diameter and 25 cm in length along the field axis, the field does not vary by more than about $\pm 1 \times 10^{-5} B_0$, or ± 1 μT. The gradient coils attached to the magnet are designed to generate x, y and z gradients of approximately 5 μT cm^{-1}, with 1% linearity over the imaging volume. True three-dimensional resolution of about 2 mm should be achievable for the head and limbs, and 3–4 mm for the torso. Relaxation times, such as the spin–lattice relaxation time, T_1, can be measured at each location within the image by the use of standard pulse sequences. The greatest uncertainties about the performance of such a system arise because of the large dynamic range required when a three-dimensional image must be recovered from one-dimensional data, the length of time required to obtain an adequate set of projections, and the effects of motion on the quality of the image. Although great demands will be placed on the computer if rapid reconstructions and useful displays of three-dimensional data are desired, it seems likely that adequate data processing and display systems will be available before n.m.r. zeugmatographic imaging comes into routine clinical use.

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Paramagmetic contrast enhancement

Although intrinsic differences in the water and fat contents of tissues and in their water proton relaxation times seem to be large enough to make possible good contrast in the imaging of normal anatomy and of many tissue abnormalities and lesions (Hutchison 1977; Lauterbur *et al.* 1976; Hinshaw *et al.* 1978; Pykett & Mansfield 1978), it is to be expected that some significant differences in the conditions of tissues will not result in large and consistent differences in their n.m.r. signals. Just as substances with high average atomic number may be injected or ingested to increase the contrast in X-ray imaging, it is possible to artificially increase the contrast in n.m.r. zeugmatograms. To alter the n.m.r. images, however, it is not necessary to inject enough of a substance for it to be directly detectable. Concentrations of paramagnetic ions and complexes in the micromolar to millimolar range can significantly decrease the relaxation times of tissue water (Lauterbur *et al* 1978), and the relaxation time differences can be converted into signal intensity differences. Within the limitations imposed by the toxicities of various paramagnetic metal ions and their complexes, there would seem to be almost limitless opportunities for the selective enhancement of contrast in the images. *In vitro* measurements have already demonstrated one promising application (Lauterbur *et al.* 1978). Although the relaxation time changes in ischaemic and infarcted myocardium are relatively small and variable, injections of manganous ion change the T_1 values of uninvolved regions of the myocardium much more than those of the region distal to the occlusion of a coronary artery of the dog, possibly because of differences in perfusion. The effects on the relaxation times, which can be as large as a factor of three at dosages of 1 mmol/kg, are sufficient to make possible almost complete contrast in an image. Similar applications to other organs seem likely also to be interesting.

^{31}P imaging

The direct observation of metabolically and structurally significant individual molecular species in n.m.r. zeugmatographic images would be the most desirable approach to medical diagnostic applications. Unfortunately, the low concentrations of most small molecules with well resolved high resolution n.m.r. spectra preclude their observation at the same degree of spatial resolution as can be achieved for water and, in the presence of the much higher water concentrations, their weaker proton signals are difficult to distinguish clearly. The resonances of other nuclei are intrinsically weaker, in addition to being present at low concentrations. Nevertheless, in favourable circumstances, there is hope that some such signals may be useful for special purposes (Lauterbur 1977). The most promising possibility seems to be the observation of the ^{31}P n.m.r. spectra of individual phosphorus metabolites. In tissues, the resonances are rather well separated and distinct (Chance *et al.* 1978) and the ^{31}P signals are about 40% as strong as ^{1}H signals at the same concentration and frequency. Separate images may be generated from each resonance line in a high resolution spectrum by several techniques (Lauterbur *et al.* 1975), but we have chosen to use the reconstruction approach in our preliminary experiments because of its relative ease of implementation in a standard high resolution Fourier transform spectrometer with a superconducting solenoid and because of the requirement, to make such experiments useful, for the highest possible sensitivity in three-dimensional images. The standard shim coils in a Bruker WH 360 spectrometer have been driven with a programmable gradient generator (Lai *et al.* 1979) so as to broaden the individual 146 MHz ^{31}P resonance

signals from simulated biological samples by amounts comparable to their separation in a high resolution spectrum. For any one gradient orientation, the resulting 'spectrum' contains both spectral and spatial information, and may be decomposed, in favourable circumstances, into separate projections for each molecular species. One useful feature of these mixtures of spectra and projections is that a reversal of the gradient inverts the spatial component but leaves the chemical shift component unchanged. The separated projections may be used to reconstruct images in the usual way. Our simulated samples, or phantoms, have contained creatine phosphate, ATP and inorganic phosphate in separate compartments, and these have been reasonably well resolved in two-dimensional images. It remains to be seen whether useful chemically resolved ^{31}P three-dimensional images of living organs can be achieved by this technique.

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Discussion

Dr Margaret A. Foster (*Department of Biomedical Physics, University of Aberdeen, Foresterhill, Aberdeen, U.K.*). I cannot quite see the advantage of your three-dimensional imaging method. Most visualization will be done only in two-dimensions anyway, especially if photographs are used. What particular advantages does Professor Lauterbur see in trying to obtain the 3-D image. Does this involve loss of information relative to taking a series of planes through the subject?

P. C. Lauterbur. The objective of direct three-dimensional imaging is to achieve the full multiplex advantage of observing simultaneously the signals from all nuclei within the volume of interest. Selective observation of each thin section, followed by the assembly of all such sections into a three-dimensional data array, is, in principle, less efficient. I believe that full three-dimensional diagnostic imaging is to be preferred to the use of selected slices and should be the goal toward which we are working. The problems of visualization and display are independent of whether the data are obtained directly in three dimensions or slice by slice.

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