ミニレビュー

Some Limitations and Requirements for *in - vivo* Spectroscopy in a Whole Body Machine

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Abstract

This paper is a very brief review of the methods of *in-vivo* spectroscopy. It begins with a glance at the basic physics then continues through methods of suppressing unwanted signals, techniques for location of regions of interest, the sensitivity of the experiment, and ends with a few results.

1 Introduction

The principles which underly the procedures of NMR spectroscopy are similar to those in imaging. Their application is however, somewhat different, and these differences may lead to the conclusion that what is an optimum machine for one function is not the best for the other. Nevertheless, the form of the two machines is very similar, so that the physical opportunity exists for combining their functions, and it is instructive, therefore, to examine where the differences in approach and emphasis are to be found.

2 Chemical Shift

The prime cause of the differences in resonance frequency of different nuclei of the same species in a molecule is the effect of the local electronic environment, which induces marginally different fields at the nuclei of each. The same basic relationship as governs all NMR processes holds:

$$\omega=\gamma B_0;\ (\omega_0+\delta\omega)=\gamma(B_0+\gamma B_0)$$

where ω is the angular frequency, γ the gyromagnetic ratio and B_0 the static field. The difference in frequency ($\delta\omega$) between two lines is proportional to B_0, and so increases with field. Since the time for which the signal may be observed (assuming a perfect machine) is proportional to T_2 (which may vary relatively little in animal tissue as the field is altered) this means that the useful phase dispersion during data acquisition increases with field—which, since resolution of two adjacent lines (by the Nyquist criterion) requires a minimum phase difference of π radians, implies that in ideal circumstances, additional line structure can be obtained.

There is a second effect that is often visible in spectra—a coupling effect between neighbouring nuclear spins within a molecule, which is a function, amongst other things, of how closely bonded they are to each other. This interaction results in single lines being split into multiplets, with the relative magnitudes and splittings of the lines in a group providing much information about the identity of the molecule.

The coupling constants (ie, frequency separations of the lines in a multiplet) are independent of the field strength, although the multiplets are only clearly evident when the coupling constant is less than the frequency separation of the two coupled spins. The clear resolution of coupled signals can therefore be a substantial inducement to working at high field.

One factor to be born in mind is that the relaxation times of the various components is still pertinent. The spin-lattice time T_1 still affects the useful repetition rates of the experiment while T_2 (assuming a good field) is important in determining the ultimate resolution that is possible. Clearly if the line is intrinsically broad (ie, with a short T_2) the chances of resolving some structure in it is reduced since the signal vanishes too quickly. The spectrum in fig. 1 of an extract

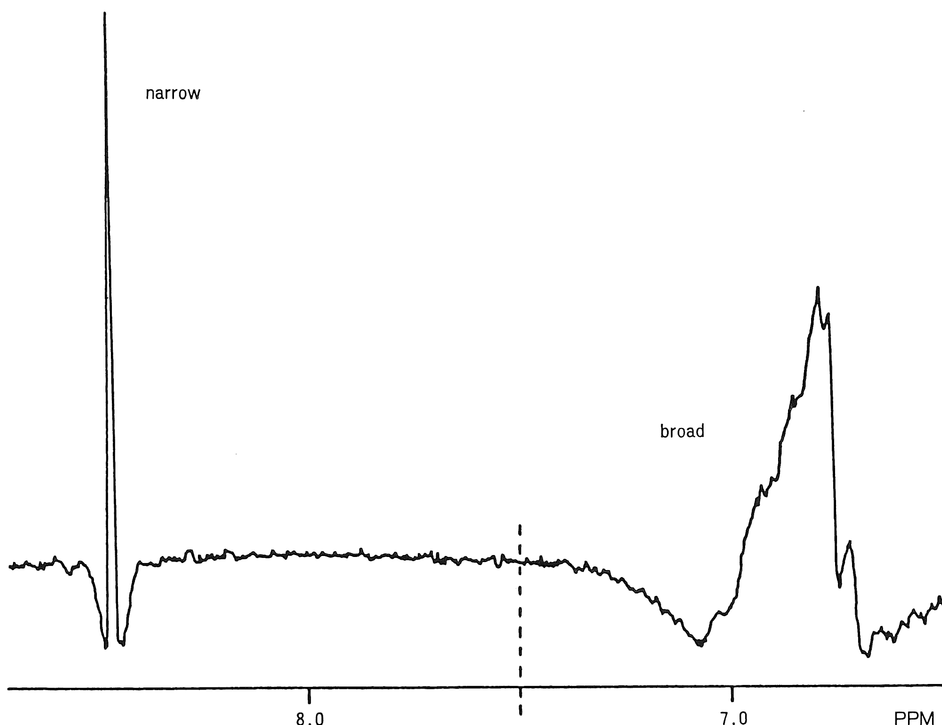


Fig. 1 Section of a proton spectrum of an extract from a tumour grown on the foot of a mouse to illustrate the difference between broad and narrow lines. The former have a short T_2 and decay very fast (Spectrum acquired at 360 MHz; repetition time 5 sec; 128 averages).

from a tumour grown on a mouse's foot illustrates the differences between broad and narrow lines. (Details are in the figure legend.)

3 Manipulation of Spectra

Techniques have been developed in traditional specroscopy for the acquisition and manipulation of spectra in very many ways. It is clearly impossible to review them in a short paper, but instead attention will be concentrated on techniques which are used, or are likely to be of use in the near future, in whole body applications.

Spectra in which all the components of interest are of approximately the same concentration are relatively easy to handle. Phosphorus, for example, can be acquired as a direct FID, and the data processed only by phase correction and convolution (to reduce the level of broad components from bone in examining the brain, for example, or for resolution enhancement by methods such

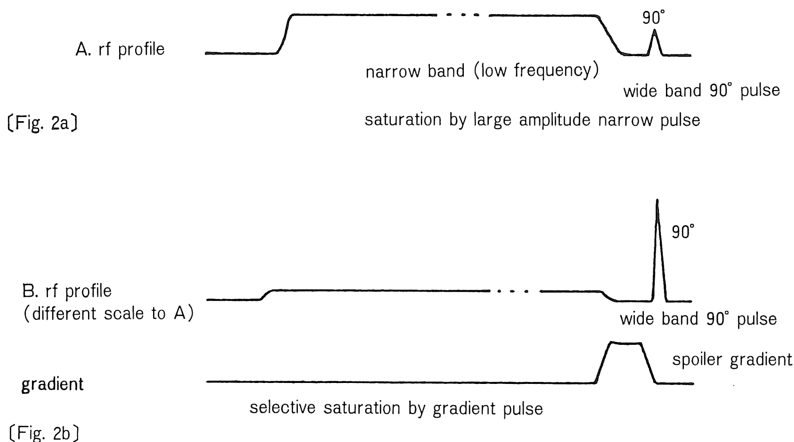


Fig. 2 Simple saturation methods for eliminating large solvent signal
Methods of suppression of large solvent signals using narrow band rf signals.
a) by high power low band width signal designed to saturate target line
b) by selective excitation of the target line, then dephasing, before wide band excitation of the whole spectrum.

as convolution differencing[1]. Fluorine 19, which only appears because of being introduced for some experimental reason, is another example of a nucleus which can be handled simply.

Carbon 13, although very attractive theoretically, because of the richness of its spectrum, presents problems in terms of enhancing its sensitivity (either by decoupling, which might require excessive rf power doses; or by increasing its abundance by giving the subject food containing it in large quantities, something which is likely to remain very expensive even if sufficient use were to reduce the price substantially[2].

Hydrogen, because of its presence in so many molecules, also has an immensely complex and interesting spectrum. However, two of the components are very much larger than the others, with the water line, in particular, being relatively immense. The protons in water have a concentration of around 90 M while those in many of the metabolites of interest may have concentrations of no more than 1–10 mM. The usual method of approaching the difficulty is to attempt to reduce the relative size of the water signal, by suppressing it.

The simplest method is to saturate the unwanted signal, by applying an rf pulse of the correct frequency to excite the line to be removed and of a bandwidth appropriate to span only the section of the spectrum which is to be eliminated. The procedure is shown in diagrammatic form in [Fig. 2a] For practical reasons, *in vivo*, it is more difficult to saturate the line properly than with small samples, but if imaging-type gradients are available, as has been shown[3], a gradient can be used to dephase a selectively excited line [Fig. 2b]. The risk in the method is that sub-

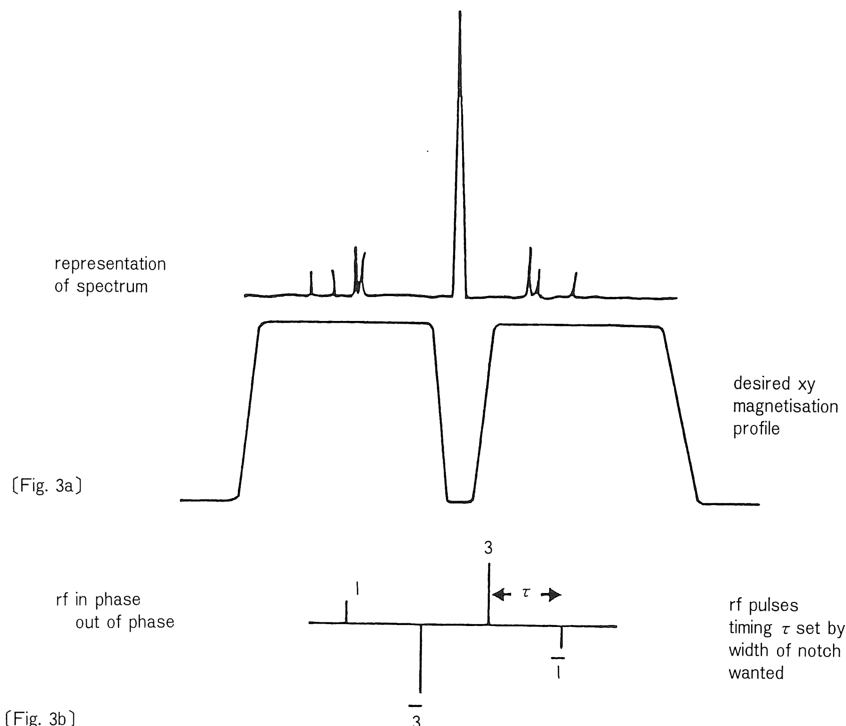


Fig. 3 Suppression of solvent peak using a composite pulse
Suppression by composite (1331) pulse-showing a diagrammatic spectrum and appropriate excitation profile (a) and the pulse pattern of which this is the approximate Fourier transform (b).

sequent excitation of a region of interest using gradients may result in some unexpected rephasing of the solvent peak.

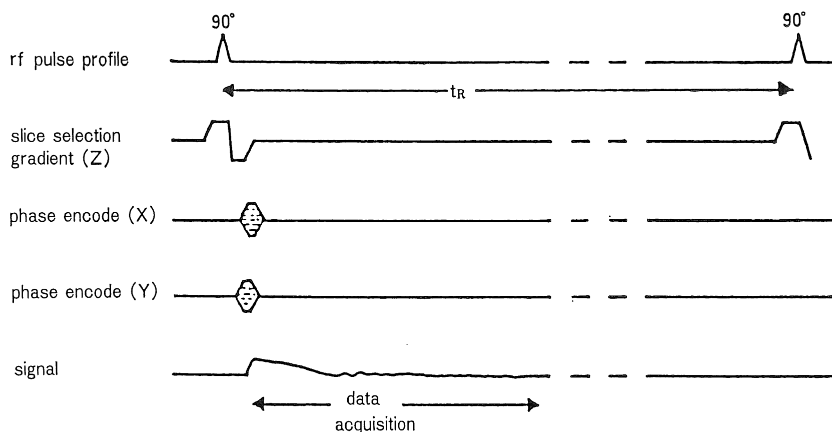
A most attractive method is the use of composite pulses—or sets of pulses separated by appropriate times. There are a number of variants which have been suggested, but there is space here only to discuss one—the 1331 pulse[4),5)] which may be thought of in terms of a Fourier transform model. 〔Fig. 3a〕 shows the kind of excitation pattern that might be intended—with no excitation at a central region where the peak to be suppressed exists, while allowing full rf amplitude elsewhere. This waveform is approximately the Fourier transform of the group of pulses shown in 〔Fig. 3b〕—hence their use. Increasing the complexity of the group does not result in much improvement as the references show.

In some circumstances where the relative T_1 value are appropriate the type of manipulation used in imaging is appropriate, eg, the elimination of lipid signals using inversion recovery as in the STIR sequence[6)] or the reduction of some signals because their T_2 is relatively short.

4 Spatial Localization

When dealing with a whole body it is clearly essential to define the region from which spectral data is acquired, particularly when an analysis of a pathological condition is intended. An early approach to the problem was the TMR method[7] which involved profiling the main field using complex gradients so as to create a single region in the magnet at which an appropriate rf frequency could excite the nuclei. While some of the earlier work on *in-vivo* spectoroscopy was done with this method, it is clumsy, because the coils and electrical powers needed to move the region are substantial, and it is much easier to move the sample relative to the field—even if this means a magnet that is larger than would be necessary otherwise. By far the most common methods at this time depend on surface coils[1], which have the advantages of sensitivity (to tissue adjacent to them), simplicity and a substantial degree of spatial selectivity, although their characteristics are non-linear and they can give misleading results from the large signals due to tissue very close to the coil plane. However, as has been shown, tissue parameters can be measured accurately[8),9] although quantifying the lines of a spectrum is more difficult if there is any uncertainty about the region from which the signals come.

The first attempt at chemical shift imaging avoided the problem[10], using the sequence illustrated in Fig. 4. This is an elegant solution, but very slow, as sufficient projections are needed



Chemical shift imaging experiment using selective slice and XY phase encoding

Fig. 4 Drawing showing a chemical shift imaging sequence in which the whole spectrum is acquired with 2-dimensional spatial resolution of a plane. Note that no solvent suppression is shown with this sequence-although some types are possible.

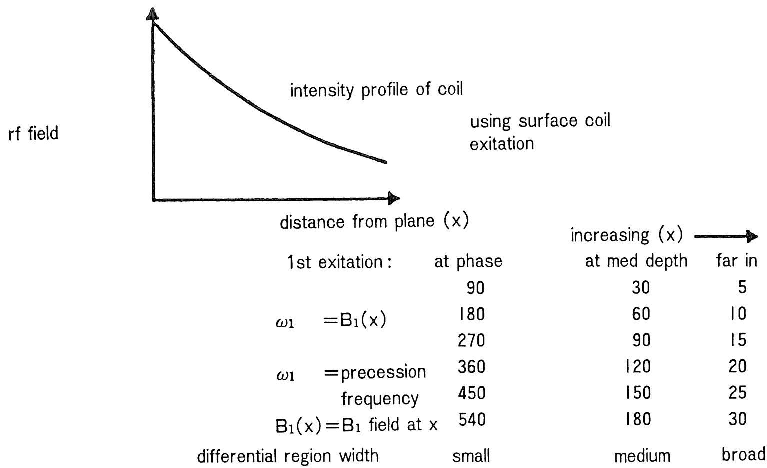


Fig. 5 Representation of rotating frame zeugmatography

Representation of spatial resolution by rotating frame zeugmatography, showing the effective rotation angles at narrow depths in different experiments. Also indicated are the differences, due to coil sensitivity changes, in the effective resolution.

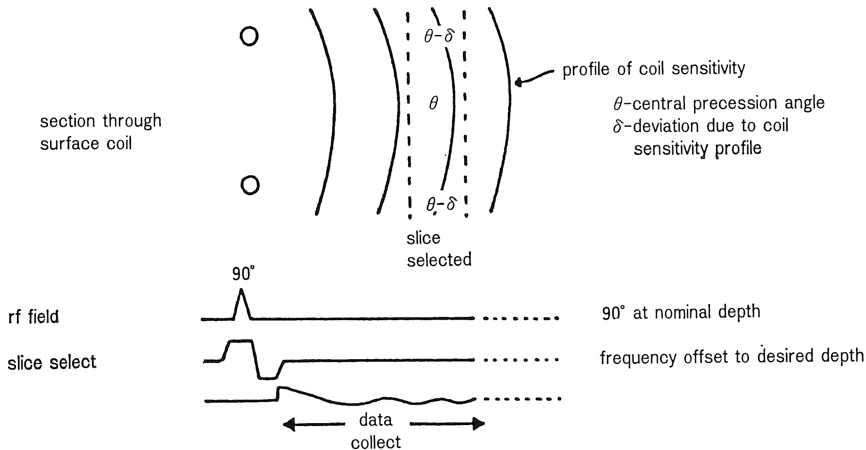


Fig. 6 Representation of selection using gradient

Figure showing spatial selection using a slice selection type gradient in conjunction with a surface coil as transmitter as well as receiver. The sequence is shown but the variation in precession angle due to the angling of rf and gradient characteristics is to be noted.

to resolve both spatial directions, so that if a resolution of n voxels in each direction is needed the number of projections required is nxn.

Thereafter, methods used have involved a reduced degree of spatial encoding in conjunction with surface coils. One technique uses rf encoding. adjusting the rf angle from one experiment to another[11] in a method directly analogous to the encoding used in rotating frame zeugmatography[12]. This method is illustrated schematically in Fig. 5, and has the advantages of avoiding the use of gradients, and of allowing early data acquisition for there is no need for rephasing. On the other hand, it does need substantial rf pulses, which may result in the experiment having to be slowed to keep power dissipation within acceptable safety levels.

The DRESS technique[13] and its variants[14] uses a "slice selection" procedure in conjunction with a surface coil to achieve its localization. This is a flexible method, with simple demands on equipment (as illustrated in Fig. 6) and can be used with solvent suppression methods with some care.

Finally, there are methods based on the ISIS approach[15] which involves forming a region of interest using a multiplicity of experiments with different gradient and rf pulse configurations, then performing simple arithmetic to extract the signal from the region of interest. This method tends to have dynamic range problems, but otherwise is capable of selecting a region anywhere in a body—without the constraints which operate to some degree with all the other methods.

5 Sensitivity

The criteria for selecting field level in spectroscopy are different from those in imaging. Whereas in imaging the basic argument is almost entirely a signal-to-noise ratio one (except in fields of very substantial inhomogeneity) in spectroscopy there is an additional requirement that the quality of the field be adequate for resolution of spectal lines. The width of a line is given by

$$\Delta=\frac{1}{T_2{}^*}=\frac{1}{T_2}+\gamma\delta B_0$$

where δB_0 is the field error (in absolute terms) throughout the region being sampled. Many metabolites have quite substantial values of T_2 so that unless δB_0 is small (less than around 3×10^{-7} T if $T_2{}^*$ is to be greater than about 50 msec.), this implies an smaller percentage error is required as the field increases. Field level also affects the resolution of fine structures as mentioned before. Reducing it results in a collapse of the fine structure, although the level at which this happens varies. On the other hand, the sensitivity argument in terms of signal-to-noise ratio is very similar to that for imaging. The gain is thus less than it would have been in the equivalent experiment with a small sample. As has been discussed extensively elsewhere[16),17] the improvement with field is at best moderate, and so it is not reasonable to expect the gains obtained with small

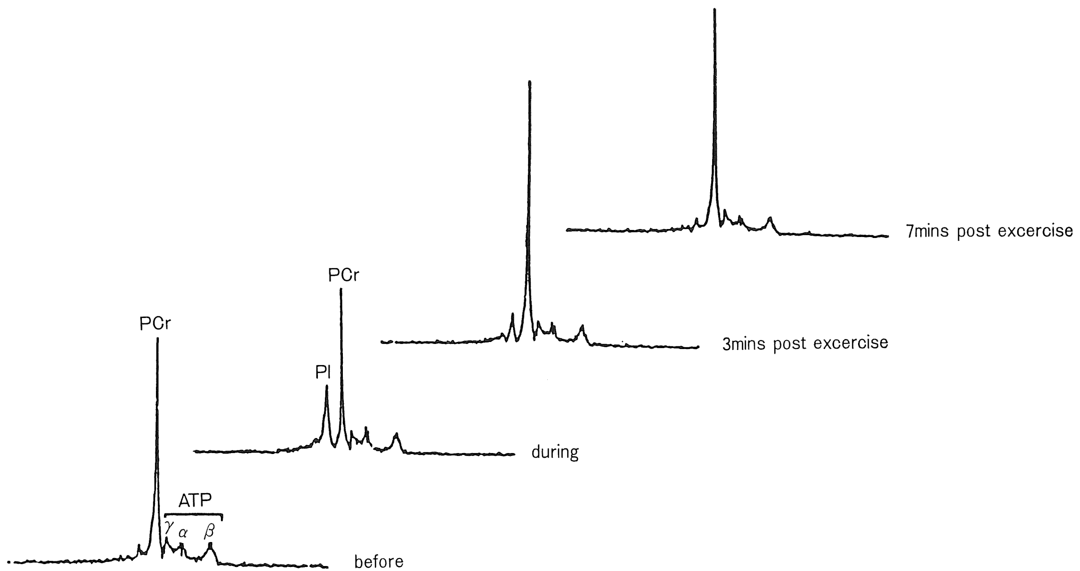


Fig. 7 Series of spectra showing the changes in the phosphorus metabolites before, during and following exercise of a volunteer's arm. The inorganic phoshorus peak develops at the expense of phospho-creatine, which then recovers (Each spectrum took 3 minutes to acquire at 27.4 MHz; 180 averages).

bore spectroscopy.

6 Results

The results of the clinical applications of spectroscopy have so far been limited. The pioneering work of the Oxford group[18] began with the sort of muscle study illustrated in Fig. 7 (which is a typical time course series following the exercise and recovery of a volunteer's arm). Clinical and chemical applications of this work have been reviewed by Radda et al.[19], although the significance of the former is too early to asses, with the most significant work, perhaps, being the studies of metabolite change in babies that had suffered brain asphyxia at birth[20]. Studies of tumours in general may have limited diagnostic value, but could be of value in monitoring response to therapy[21] and ^{1}H spectroscopy may be of value in monitoring lactate and other compounds, such as phenylalanine in PKU[22].

Fluorine spectroscopy is as yet little developed, but it is of interest in the examination of chemotherapeutic drugs such as 5-Fluorouracil[23]. Sodium is more useful from an imaging point of view and *in vivo*, work on carbon is in the earliest stages.

7 Conclusions

In vivo specroscopy is an exciting field of study—but one for which the clinical utility remains to be evaluated. In this respect it differs very substantially from magnetic resonance imaging where clinical progress has been relatively rapid. To put the matter in perspective, the two topics have been studied for very similar periods of time, so emphasising the greater difficulty and subtlety of *in vivo* spectroscopy.

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