Spatial Localization in NMR Spectroscopy in Vivo

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SUMMARY

Spatial localization techniques are necessary for in vivo NMR spectroscopy involving heterogeneous organisms. Localization by surface coil NMR detection alone is generally inadequate for deep-lying organs due to contaminating signals from intervening surface tissues. However, localization to preselected planar volumes can be accomplished using a single selective excitation pulse in the presence of a pulsed magnetic field gradient, yielding depth-resolved surface coil spectra (DRESS). Within selected planes, DRESS are spatially restricted by the surface coil sensitivity profiles to disk-shaped volumes whose radii increase with depth, notwithstanding variations in the NMR signal density distribution. Nevertheless, DRESS is a simple and versatile localization procedure that is readily adaptable to spectral relaxation time measurements by adding inversion or spin-echo refocusing pulses or to in vivo solvent-suppressed spectroscopy of proton ('H) metabolites using a combination of chemical-selective RF pulses. Also, the spatial information gathering efficiency of the technique can be improved to provide simultaneous acquisition of spectra from multiple volumes by interleaving excitation of adjacent planes within the normal relaxation recovery period. The spatial selectivity can be improved by adding additional selective excitation spin-echo refocusing pulses to achieve full, three-dimensional point resolved spectroscopy (PRESS) in a single excitation sequence. Alternatively, for samples with short spin-spin relaxation times, DRESS can be combined with other localization schemes, such as image-selected in vivo spectroscopy (ISIS), to provide complete gradient controlled three-dimensional localization with a reduced number of sequence cycles.

LOCALIZATION STRATEGIES

The great promise of in vivo NMR spectroscopy lies in its ability to provide chemical information about physiologic function, its perturbation by disease, and its restoration to health via therapy. Although proton ('H) NMR spectra from living cells were reported as early as 1955 and natural abundance phosphorus (31P) spectra were acquired from blood cells nearly two decades later, human in vivo NMR spectroscopy was not practical until the advent of larger bore superconducting magnet systems capable of accommodating the human limbs, the head, and the body only in the last few years. Since human experimentation demanded safe, noninvasive protocols involving intact anatomy, and the body was much larger than the homogeneous volumes that were suitable for spectroscopy within the magnet bore, small circular flat NMR coils positioned on the surface of the body were crucial in providing the first access to spatially localized 31P NMR spectra.

Unfortunately, surface coil localization has one major problem: its high sensitivity to surface tissue results in significant contamination of the NMR signals from important deeper lying organs of significant interest such as the brain, the liver, and the heart. The effect is illustrated in Figure 1, which shows 1H surface coil NMR
images acquired from a single-turn, 6.5 cm diameter surface coil located on the head above the temple. A $^1$H NMR spectroscopy experiment employing such a coil would collect a total integrated signal composed of approximately equal contributions from the brain and bone marrow, the scalp, and surface musculature (Fig. 1A). Although the proportion of signal derived from brain can be improved somewhat by increasing the NMR flip-angle beyond $\pi/2$ at the surface (Fig. 1B), substantial surface tissue contributions are clearly inevitable.

To address this problem and to improve the control and definition of spatially localized regions for spectroscopic analysis, a battery of spatial localization schemes have been proposed and demonstrated as summarized in TABLE 1. These techniques employ either radio frequency (RF), static, or time-dependent magnetic field gradients to restrict data acquisition to single or multiple selected volumes. They can be combined with either surface detection coils or whole volume detection coils analogous to those used in conventional $^1$H NMR imaging, depending on the desired depth of the selected volume relative to the surface. At shallow sample depths, surface coils provide dramatic advantages in signal-to-noise ratio over volume coils because they are closer to the signal-generating nuclei and remote from a large fraction of the sample that contributes only noise. The dependence of the signal-to-noise ratio of a 6.5 cm diameter $^{31}$P NMR surface coil at 25.7 MHz as a function of depth in the head along the coil axis is shown in FIGURE 2: for depths less than about 5.5 cm the surface coil performance is superior to that of a 27 cm–diameter 30 cm–long cylindrical $^{31}$P head coil, assuming that the principal noise source is the sample rather than the coil in both cases.

LOCALIZATION WITH DRESS

Our approach to the elimination of surface tissue contamination in surface coil spectroscopy is to apply an imaging type selective excitation $\pi/2$ NMR pulse in the

(a) $\sim$90° surface pulse  (b) $B_1$ increased 2.5-fold

FIGURE 1. $^1$H NMR images recorded at 64 MHz using a 6.5 cm diameter surface coil located on the human head above the temple. The surface coil was used as both transmitter and receiver with a 2 sec pulse repetition to reduce $^1$H T1 relaxation effects. The imaging plane is perpendicular to the plane of the surface coil, which was located at the bottom of the images. In (a), the integrated signal from brain (top) constitutes only 54% of the total signal. This fraction increased to 72% in (b) upon increasing the RF field amplitude 2.5-fold. Dark rings in (b) correspond to the RF field contours of the surface coil at points in the sample that experience integral multiples of a $\pi$ pulse.
**TABLE 1. Methods of Spatially Localizing $^{31}$P and $^1$H Metabolite NMR Spectra**

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<thead>
<tr>
<th>Type</th>
<th>Description/Acronym</th>
<th>Reference</th>
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<tr>
<td>RF gradient</td>
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<td>Static gradients</td>
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<td>Time-dependent gradient</td>
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The presence of a pulsed magnetic field gradient directed coaxial to the surface coil in a simple, single pulse sequence known as depth-resolved surface coil spectroscopy (DRESS), as depicted in Figure 3. The combination of the narrow bandwidth (Gaussian or sinc function modulated) selective excitation pulse and the magnetic field gradient excites a flat plane of nuclei parallel to the plane of the surface coil. The location of the plane relative to the center of the gradient field is $y_i = 2nf_i/\gamma G_x$, where $f_i$ is the frequency of the excitation pulse, $\gamma$ is the gyromagnetic ratio of the observed nucleus, and $G_x$ is the strength of the gradient applied during the RF pulse. $f_i$ can be varied automatically to select planes at different depths $y_i$ relative to the surface coil simply by offsetting the NMR frequency of the selective excitation pulse provided under computer control in a high-field imaging/spectroscopy system with a single sideband transmitter. The slice thickness is $\delta y = 2\pi \delta f/\gamma G_x$, where $\delta f$ is the spectral width of the selective excitation pulse.
The extent of the sensitive volume in the two orthogonal directions parallel to the selected plane in DRESS is determined by the surface coil sensitivity profile, which in turn depends upon the diameter of the surface coil and the distance of the coil from the sensitive plane. The shape of the sensitive volume as a function of depth is thus the same as that of a surface coil at the intersection of its sensitivity profile and the selected plane, as shown in Figure 4 for a uniform RF excitation field. The sensitive volume is approximately disk shaped, at least up to the useful depth of about one diameter of the surface coil (Fig. 2), but the diameter of this sensitive disk increases with depth. However, the true size of the selected sensitive volume is not determined by the full-width-half-maximum of the sensitivity profiles (Fig. 4), but rather by the relative contributions of the integrated signal from the sensitive disk and that from the surrounding tissues. The radius of the sensitive disk that represents 50% of the total integrated signal in the selected plane is plotted against depth (in coil radii) in Figure 5, assuming a uniform NMR signal density extending infinitely in the selected DRESS plane.

Of course, in real in vivo applications of DRESS as well as virtually all other localization schemes that employ relatively coarse volume selection to compensate for the poor sensitivity of $^3$P and $^1$H metabolites, the assumption of a homogeneous signal...
density across the selected volume is often not even approximately true and the real density distribution is usually unknown. Consequently, the shape and size of actual selected volumes can vary dramatically from idealized profiles computed assuming uniform signal distributions. As an example, consider a series of $^{31}$P DRESS spectra from a dog myocardium acquired as a function of depth with a 6.5 cm diameter surface coil before and after occlusion of a coronary artery (FIG. 6). Postmortem staining of this heart revealed a 14 g endocardial infarction, consistent with the total depletion of high energy metabolites (phosphocreatine and adenosine triphosphate) apparent in the deepest postocclusion spectrum. This spectrum therefore represents a $^{31}$P NMR-visible tissue volume of about 14 cm$^3$ at most. However, the computed tissue volume representing 50% of the total signal at this depth according to FIGURE 5 is about 80 cm$^3$, if we divide by a factor of about 2 because the surface coil was used for both transmission and reception in this experiment. Clearly, and fortuitously for heart studies, a large fraction of the sensitive volume here is occupied by tissues such as adipose, lung, and moving blood in the ventricle that contribute negligible detectable $^{13}$P NMR signals to the observed spectrum.

**DRESS NMR EXPERIMENTS**

Simplicity is a key, perhaps unequaled, advantage of the DRESS technique relative to other current spectral localization schemes. This simplicity translates into a versatility of applications employing both conventional NMR pulse sequences, or even incorporating elements of the other localization techniques (TABLE 1) to improve the spatial resolution or enable volume coil detection as opposed to surface coil detection.

**FIGURE 3.** Depth-resolved surface coil spectroscopy (DRESS) pulse sequence. A sinc function-modulated $\pi/2$ RF pulse selects a plane parallel to the surface coil when applied in conjunction with a magnetic field gradient ($G_y = dB_y/\text{dy}$, where $B_y$ is the main magnetic field) directed coaxial to the coil. Data are acquired (NMR) commencing as the nuclei are rephased slightly before the cessation of the negative $G_y$ rephasing lobe.
Such applications are permissible because the entire spatial localization procedure is completed with just a single application of the sequence and because the sequence perturbs the nuclear magnetization from only the selected volume, leaving the NMR signal in all of the remaining space undisturbed. Thus, spatially localized spectral spin lattice ($T_1$) or spin spin ($T_2$) NMR relaxation times can be measured by incorporating a conventional square $\pi$ NMR pulse either at time $\tau$ prior to the plane-selective $\pi/2$ pulse of Figure 3, or at time $\tau$ after the $\pi/2$ pulse, respectively. The sequence is repeated with different $\tau$ values and the amplitude of each resonance fitted to $S = S_0 \cdot [1 - 2 \exp (-\tau/T_1)]$ or $S = S_0 \exp (-\tau/T_2)$ to yield the individual $T_1$ and $T_2$ values in the usual fashion.

Similarly, the DRESS sequence is amenable to solvent suppression techniques, which are pivotal to the in vivo detection of millimolar level metabolites, such as lactate in $^1$H NMR spectra, that are otherwise dominated by water protons at concentrations of around 100 molar.¹⁴,¹⁵ A series of four water suppression pulse sequences incorporating DRESS localization are shown in Figure 7. In (a) and (b), a long duration, sinc function modulated, $\pi/2$ selective excitation RF pulse of spectral linewidth comparable to and centered on that of the water resonance in the frequency domain, is applied prior to DRESS selection in the absence of any applied field

![Perspective plots of the NMR sensitivity profile](image)

**FIGURE 4.** Perspective plots of the NMR sensitivity profile of a circular coil of radius $a$ at depths of 0.25 radii (a), 0.5 radii (b), 1.0 radii (c), and 2.0 radii (d).⁶ The coil is oriented parallel to the $x$-$z$ plane with axis at the origin and scales in radii. The vertical axis is proportional to the signal-to-noise ratio depicted in Figure 2. The plots are computed from equations for the field transverse to the main field, $B_0$, given by Smythe (Static and Dynamic Electricity. 3rd edit. 1968. McGraw-Hill. New York.) assuming a uniform RF excitation field, and represent the shapes of the sensitive volume in the selected DRESS planes. (Courtesy J. F. Schenck.)
FIGURE 5. The radius of the sensitive volume, assumed circular, representing 50% of the total integrated signal in DRESS selected planes lying parallel to the surface coil as a function of depth along the coil axis. All dimensions are in coil radii. The curve was obtained by iteratively integrating the sensitivity profile until it represented 50% of the total integral at that depth. (Courtesy W. A. Edelstein.)

gradients. Following DRESS selection, all of the nuclei in a selected plane parallel to the surface coil are excited but the H$_2$O protons have received a net $\pi$ nutation rendering them, in principle, unobservable. In practice, the amplitude of the H$_2$O-selective pulse is adjusted for maximum annihilation of the H$_2$O resonance during data acquisition. The water-suppressed spectrum is then either detected immediately following the slice-selective pulse (Fig. 7(a)) or refocused to a spin echo using a subsequent $\pi$ pulse applied at time $\tau$ later (Fig. 7(b)). The latter sequence provides additional attenuation of tissue $^1$H resonances that exhibit shorter $T_2$ values than the metabolites of interest. Furthermore, if the echo-producing $\pi$ pulse of Figure 7(b) is also a chemical-selective pulse that refocuses only the resonances of interest, the water suppression will be further enhanced.

Discrimination against H$_2$O signals on the basis of relaxation times is extended in the sequence shown in Figure 7(c), wherein the chemical selective pulse is abandoned to be replaced by an initial $\pi$ inversion pulse applied at time $\tau_{null}$ preceding the slice selective $\pi/2$ pulse. $\tau_{null}$ is adjusted to eliminate the H$_2$O resonance at $\tau_{null} \approx 0.69\ T_1$ (H$_2$O), where $T_1$ (H$_2$O) is the water spin-lattice relaxation time. The sequence shown in Figure 7(d) is a reduction of that in Figure 7(b), in which the initial $\pi/2$ excitation pulse is a chemical-selective pulse tailored to select only the metabolically useful portion of the $^1$H spectrum and exclude the H$_2$O resonance. Slice selection is subsequently performed by the $\pi$ refocusing pulse applied in the presence of the gradient. In all cases, data are best averaged from two applications of the sequences repeated with the phase of the $\pi/2$ excitation pulse alternated to remove unwanted spurious signals generated by the other RF pulses.

FIGURE 8 shows an example of a normal human brain $^1$H NMR spectrum acquired
FIGURE 6. $^{31}$P NMR surface coil spectra recorded noninvasively in vivo at 0.5 intervals through the anterior myocardium of a dog before (A), and 50 min to 70 min after occlusion of the left anterior descending coronary artery (B) using DRESS.$^{13}$ Postocclusion spectra at 5.5 cm depth show essentially complete depletion of phosphocreatine (PCr) and adenosine triphosphate, and the appearance of a large inorganic phosphate (P_i) resonance. Less depletion is evident at 5.0 cm and essentially no postocclusion spectral changes are apparent at 4.5 cm. Postmortem staining of the excised heart revealed a 14 g endocardial infarction. Data acquisition periods were 11 ± 1 min per spectrum cardiac gated with a 1.1 ± 0.1 sec pulse-sequence repetition period. Depths are nominally relative to the surface with a 1 cm slice thickness.

in 2 sec at a depth of 5 cm with the water-suppressed DRESS sequence of Figure 7(b). A 3-cm diameter surface coil was used to localize to the volume shown in the image. N-acetyl aspartate, phosphorylcholine, and creatine resonances are evident at around 5–10 mM concentrations, but any lactate resonance at 1.3 ppm is sufficiently small as to be obscured by lipid -CH2- resonances, as might be expected in a healthy brain.

ADVANCED LOCALIZATION SEQUENCES

Adaptations of DRESS that improve its spatial data-gathering efficiency include slice-interleaved DRESS (SLIT DRESS), which enables acquisition of spectra from multiple sensitive disks at different depths in essentially the same time as required for a single DRESS volume acquisition.$^{16}$ The idea is to interleave excitation of $n$ different slices during the period $\tau$, normally allotted for spin-lattice relaxation recovery in the first excited slice. Thus the DRESS sequence of Figure 3 is repeated $n$ times faster at intervals of $\tau, n$, sequentially advancing the NMR offset frequency $f_i$ to a new depth at
each application. To minimize partial saturation effects due to partially overlapping slice profiles, it is prudent to order the offset frequencies nonconsecutively. FIGURE 9 shows a series of six $^3$P SLIT DRESS spectra as a function of depth in the human liver at 1-cm intervals. The spectra were acquired in a total averaging time of 10 min with $\tau_r = 2$ sec.

Improving the spatial selectivity of DRESS beyond that achieved by surface coil detection in the selected planes parallel to the surface coil (Fig. 4), can be accomplished by adding two echo-producing, spatially selective $\pi$ pulses at times $\tau$ and $3\tau$ following the plane-selective $\pi/2$ pulse, as shown in FIGURE 10. Each $\pi$ pulse is applied in the presence of a gradient magnetic field pulse directed along each of the two remaining orthogonal axes that are directed parallel to the selected plane, thereby producing two spin echoes. The first spin echo derives from a sensitive line lying at the intersection of the two orthogonal planes selected by the $\pi/2$ pulse and the first $\pi$ pulse. The second spin echo derives from a sensitive point lying at the intersection of the planes selected by all three pulses, and is collected. The gradient pulses are asymmetric

![FIGURE 7. Timing diagrams for the gradient ($G_y$) and the NMR pulses (RF) for four methods of performing solvent suppressed DRESS. Selective pulses are depicted as sinc-function modulated envelopes: they are chemical selective when applied in the absence of a gradient pulse and spatially selective when applied in the presence of a gradient pulse. A negative $G_y$ lobe is not required in (d) if the $\pi$ RF pulse is symmetrically located with respect to the positive $G_y$ pulse. $\tau$ is the time between $\pi/2$ and $\pi$ RF pulses, $\tau_{null}$ is the time between $\pi$ and $\pi/2$ pulses, and sample is the data acquisition period.](image-url)
FIGURE 8. H$_2$O-suppressed $^1$H spectrum (left) acquired from a 5-cm deep sensitive disk in the normal human brain imaged at right. The DRESS sequence shown in FIG. 7(b) was used to obtain the spectrum in 2.0 sec. The lactate -CH$_3$ resonance, located at 1.3 ppm is not discernible here (PCho/PCr/Cr, phosphorylcholine and total creatine pool; AA, amino acids including aspartyl, glutamate, and glutamine groups; -CH$_2$-, lipid resonance).
FIGURE 9. In vivo $^{31}$P slice interleaved DRESS (SLIT DRESS) spectra obtained with a 6.5-cm diameter surface coil located on the human chest above the liver. Depths nominally relative to the surface are indicated. Negligible phosphocreatine (PCr) at depths ≥2 cm is consistent with liver metabolism. The complete spectral series was recorded in 10 min with a 2 sec sequence repetition period (PM, phosphomonoesters; P, inorganic phosphate; PD, phosphodiesters; γ-, α-, β-ATP, γ-, α- and β phosphates of adenosine triphosphate).
with respect to nuclei that are not selectively rephased by $\pi$ pulses. Therefore NMR signals excited outside the sensitive point rapidly dephase.

The advantages of this point-resolved spectroscopy (PRESS) technique are that it yields sharply defined volumes localized in all three dimensions in a single application of the pulse sequence, and that it provides automated control of the sensitive volume size and location independent of the size of the detection coil. In fact, surface detection coils are no longer necessary. Its main disadvantage is that the spectral components of interest must possess sufficiently long $T_2$ values to ensure a detectable NMR spin-echo signal at time $4\tau$ following initial excitation. This is probably unacceptable for in vivo $^{31}$P NMR since the $T_2$ of adenosine triphosphate is only about 10 msec, but $^1$H NMR spectroscopy of lactate and other metabolites or tumor lipids should be accessible.

For spectral components with short $T_2$ values, and $^{31}$P metabolites in particular, relocating the spatially selective $\pi$ pulses prior to the $\pi/2$ pulse is a viable approach to three-dimensional volume localization with pulsed gradients analogous to the above PRESS technique. However, complete volume localization is no longer possible with a single application of the sequence because there is no way of discriminating between inverted and noninverted signal contributions in one free induction decay following the

![Gradient pulse, RF pulse, and NMR signal timing diagram for a point-resolved spectroscopy (PRESS) technique employing DRESS plane localization and two spin echoes.](image)

Gradients along the three orthogonal axes, denoted $G_x$, $G_y$, and $G_z$, are applied in the presence of each of the RF pulses to achieve three-dimensional localization of NMR signals persisting to the second spin echo. All NMR pulses are selective and depicted here as sinc function–modulated envelopes. Negative rephasing lobes are unnecessary following the $G_x$ and $G_y$ gradient pulses if these are symmetric with respect to the $\pi$ pulses. The gradient pulses will also dephase previously excited signals, which are not rephased by the selected $\pi$ pulses. The sequence generates two spin echoes and one free induction decay (fid).
\(\pi/2\) pulse. Thus, in the original version of this technique, termed ISIS for image-selected \textit{in vivo} spectroscopy, all three orthogonal gradients are sequentially pulsed prior to a nonselective \(\pi/2\) pulse, and the selective \(\pi\) inversion pulses are either applied or not applied according to the cycle number in Table 2. The \(\gamma\)-selective excitation and data acquisition is performed as for DRESS (Fig. 3) but the resultant signals are added or subtracted as indicated in Table 2. Selective \(\pi\) pulses are depicted as sinc function envelopes, but improved designs are available.

A potential problem of the ISIS approach in regions subject to large physiologic movement such as in the heart, is that motions which occur before the total sequence cycle is completed could introduce substantial volume localization artifacts. A similar problem was encountered in cardiac NMR imaging with an early line-scan technique employing selective inversion. It is aggravated here by the use of a nonselective \(\pi/2\) pulse that excites all accessible nuclei in the sample. Such a situation might thus be ameliorated by combining DRESS-selective excitation on the \(\pi/2\) pulse for one-dimensional localization, with the ISIS technique in the other two dimensions. This combined strategy would reduce the amount of excited signal present at any point in time by the ratio of the DRESS slice thickness to the sample dimension, that is, by roughly an order of magnitude, and halve the duration of the ISIS sequence cycle to \(2^2 = 4\) sequence applications. Its main disadvantage relative to conventional ISIS is the

\begin{table}
\begin{center}
\begin{tabular}{llll}
\hline
Sequence Number & \text{z-Selective Pulse} & \text{x-Selective Pulse} & \text{Contribution to Total Spectrum} \\
\hline
1 & off & off & +1 \\
2 & on & off & -1 \\
3 & off & on & -1 \\
4 & on & on & +1 \\
\hline
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\end{table}

FIGURE 11. RF and gradient pulse timing diagram for combined DRESS/ISIS\(^{20}\) sequence (CRISIS). The sequence is repeated four times with the three orthogonal gradient pulses \(G_z\), \(G_x\), and \(G_y\) applied as shown. However, in each application, the \(z\)-selective and \(x\)-selective \(\pi\) pulses are either applied or not applied according to the cycle number in Table 2. The \(\gamma\)-selective excitation and data acquisition is performed as for DRESS (Fig. 3) but the resultant signals are added or subtracted as indicated in Table 2. Selective \(\pi\) pulses are depicted as sinc function envelopes, but improved designs are available.\(^{22}\)
small delay of a few milliseconds required for gradient rephasing following the $\pi/2$ pulse in the DRESS sequence (Fig. 3), during which time some signal might be lost through $T_2$ decay. In the spirit of pun acronyms in NMR, we might call the combined resolved ISIS sequence, CRISIS. This modified sequence is depicted in Figure 11, and the condensed sequence cycle is shown in Table 2: sensitive point/volume resolution is obtained by adding and subtracting the resultant signals according to the signs in the last column. Selective inversion pulses that use both amplitude and phase modulation can also be employed.

CONCLUSION

DRESS offers a practical means of acquiring spatially localized spectra in vivo that can be easily incorporated into a variety of conventional NMR experiments or included as an element of other localization procedures. Its main problems are the poorer spatial localization achieved in directions orthogonal to the slice selective gradient, and possible signal loss incurred during the delay following selective excitation required to refocus the NMR signal. In combination with $^1$H NMR imaging as a means of locating pathologies or other regions of interest, $^{31}$P DRESS studies in brain and heart patients are currently underway to evaluate its clinical utility.

ACKNOWLEDGMENTS

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REFERENCES


DISCUSSION OF THE PAPER

D. I. HOULT: I’ve got compound thoughts for you. You’ve not addressed several problems. The problem of the eddy currents, the problem with the final technique, the rather poor way in which selective 180 degree pulses for refocusing work, can you just address them?

P. A. BOTTOMLEY: Well, we never really had an eddy current problem with DRESS. Perhaps one of the reasons for this is that we used imaging gradient coils of
around 0.6 meters or 0.7 meters diameter—much smaller than the 1 meter magnet bore diameter. This means that the gradients do not couple significantly with the magnet structure. A second point is that the bore of the magnet was made of fiberglass so the first metal that the gradient fields hit is cold aluminum, which has a long decay constant. When we actually perform the DRESS experiment we shim on the DRESS sequence and use just the standard static magnet shims to offset any eddy-current effects. The final answer is that we're now even trying to reduce the eddy currents that we do get. This is being done, as was shown in Montreal (SMRM) by Peter Roemer—and Peter Mansfield is doing it as well—by placing shields between the magnetic field gradient coils and the magnet to eliminate any interactions of the coils with the magnet. But I think these problems are really not all that major. The second problem of the poor refocusing ability of the selective 180° pulse, I think that you will probably come up with solutions that will enable us to do that better.