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Portable, Low-cost NMR with Laser-Lathe Lithography Produced Microcoils

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Nuclear Magnetic Resonance (NMR) is unsurpassed in its ability to non-destructively probe chemical identity. Portable, low-cost NMR sensors would enable on-site identification of potentially hazardous substances, as well as the study of samples in a variety of industrial applications. Recent developments in RF microcoil construction (i.e. coils much smaller than the standard 5 mm NMR RF coils), have dramatically increased NMR sensitivity and decreased the limits-of-detection (LOD). We are using advances in laser pantographic microfabrication techniques, unique to LLNL, to produce RF microcoils for field deployable, high sensitivity NMR-based detectors. This same fabrication technique can be used to produce imaging coils for MRI as well as for standard hardware shimming or "ex-situ" shimming of field inhomogeneities typically associated with inexpensive magnets.

This paper describes a portable NMR system based on a laser-fabricated microcoil and homebuilt probe design. For testing this probe, we used a hand-held 2 kg Halbach magnet that can fit into the palm of a hand, and an RF probe with laser-fabricated microcoils. The focus of the paper is on the evaluation of the microcoils, RF probe, and first generation gradient coils. The setup of this system, initial results, sensitivity measurements, and future plans are discussed. The results, even though preliminary, are promising and provide the foundation for developing a portable, inexpensive NMR system for chemical analysis. Such a system will be ideal for chemical identification of trace substances on site.

1. Introduction

The need for portable chemical analysis of suspect analytes in the field, including signatures from production of chemical and biological weapon agents, drugs, explosives, toxins, and poisons is well established. Demand for portable analysis equipment is growing in the defense and intelligence communities and, as a result, a number of field deployable analytical methods are being developed, including mass spectrometric- and infrared-based systems. Still, unambiguous identification of suspect reagents can be difficult because of the dilute concentrations of suspect analytes as well as the typically large background signals from complex mixtures. The unambiguous assignment of molecular signatures to scheduled compounds can be compromised in mass spectrometry by derivitization steps or unexpected chemistry in the high temperatures present in gas chromatographic columns. Nuclear Magnetic Resonance (NMR), however, offers a non-destructive, reagentless analytical method for the identification of suspect analytes. NMR is one of the more important techniques for quantitative analysis [1–3], in no small part because it provides the inherently quantitative spectrum with unique structural information encoded in the chemical shifts and coupling constants without the need for precise matching to signature libraries.

Unfortunately, commercial systems are not well suited for portable NMR platforms due to the inherent lack of sensitivity of standard NMR receiver coils and the bulky size of the associated superconducting magnet. During recent years several groups have been working towards portable NMR systems. Portable NMR systems offer several advantages over conventional NMR, such as scanning in the field, access to immovable, arbitrary-sized objects, lower cost, and increased robustness. Existing unilateral sensors are now being used routinely to perform NMR imaging and relaxation measurements. Despite the strongly inhomogeneous fields, devices such as the NMR MOUSE [4–9], and other unilateral or inside-out sensors [10–16] are being used for applications ranging from materials (e.g. mechanical properties of polymers, fat content of dairy products) and tissue evaluation [17–25] to flow measurements [26,27], art preservation [28,29] and oil well logging [30,31]. However, the spatial inhomogeneity of the static magnetic field has precluded the use of such devices for high-resolution spectroscopy.

During the past few years ex-situ methodologies have been developed to obtain high-resolution NMR spectra in the presence of field inhomogeneities, typical of MOUSE-type instruments [32,33], ex-situ shimming [34] and hardware shimming [35] have been used to acquire high-resolution spectra in single-sided systems. The open-sided field geometry, as well as the inherently low static field of such systems, result in a decreased sensitivity relative to laboratory NMR systems.

Microcoils are now used to increase the sensitivity of NMR spectra for mass limited samples [36–42] because the reduced RF coil diameter leads to an increase in the sensitivity of the coil itself [36,37,41,43]. Thus, for mass limited samples, one can obtain a significant increase in signal-to-noise (SNR). Olson et al. [37] have even reported limits of detection to the order of pico-moles. Others use planar microcoils that are made in two-dimensions for NMR experiments, but these systems still lack sensitivity because flat coils are inherently less sensitive than RF coils surrounding the sample. Most solenoidal microcoils are hand-wound with insulated copper wire around a capillary [37,43–47]. Hand-wound

coils, however, are difficult to manufacture reproducibly and are not amenable to design optimization and customization. Rogers et al. [39,40] were the first to employ microfabrication techniques (based on a wet-resist transfer method) to manufacture RF coils with variable design parameters. This technique uses photolithographic fabrication of an elastomeric stamp with a series of evenly spaced raised lines. This stamp is then coated with resist or ink, which is transferred to a titanium-silver coated capillary tube by rolling it across a wet line at a specific angle. This process yields RF microcoils that show an increase in SNR in a standard NMR experiment.

We have reported previously on the fabrication of complex design MR microcoils by a 3-dimensional laser direct-write lithographic technique [48]. This technique is used on a variety of micro-devices, including micro-catheters and electrical contacts to diamond anvil cells [49]. We have used this strategy to produce microcoils on the order of 100 μm in diameter. While the properties of our coils are very similar to those described by Sillerud et al. via the focused ion beam lathe for microcoil fabrication [50], we have the ability to control to a larger extent the fabrication process and therefore are able to achieve more desirable characteristics (e.g. thicker deposition corresponds to lower direct current resistance), as well as complex shapes. Our fabrication process and electrical characterization of these microcoils are discussed elsewhere [48,51].

A portable NMR system based on microcoil technology has numerous advantages. First, the sensitivity of the system increases as the sample volume decreases (a conventional system using a 5 mm diameter RF coil can detect 10^{17} spins while 100 μm coils can detect 10^{12} spins [44]). Second, the power needed to efficiently excite nuclei decreases by orders of magnitude, reducing the need for large RF amplifiers [52]. Third, the need for the large regions of field homogeneity produced by superconducting magnets is eliminated due to the drastic decrease in sample volume, thus permitting the use of small permanent magnets (NdFeB magnets can produce fields of 2 Tesla in a 1 kg package). At 2 Tesla, the proton Larmor Frequency is 85 MHz, which is quite acceptable for the identification of low molecular weight compounds, considering that 90 MHz was the frequency of the standard laboratory-size NMR in the 1980's.

The small portable, permanent magnets, such as Halbach- and barrel-based, U-shaped, and dipoles, are unfortunately characterized by complex magnetic field profiles requiring field compensation via pole shaping, magnetic shims or shim coils. Their small size further requires a large amount of RF circuitry to be fit in a restricted space. The design and construction of such coils is ill-suited to typical construction methods, but becomes feasible with LLNLs unique microfabrication methods [48]. In a similar fashion, this lithography method affords the integrated design and manufacture of combined receiver, shim, and gradient coils, as well as flow and multiplex capabilities in a compact package. These unique advantages of LLNL lithographic fabrication allow the production of a high resolution, high sensitivity, and portable NMR spectrometer to be realized.

2. Setup of a portable system

The goal of our research is to produce a compact, inexpensive NMR system for on-site chemical analysis of compounds. For such a system to materialize, there are several parameters that need to be optimized; including the RF probe characteristics, the magnet,

and the spectrometer. There are several companies now producing inexpensive spectrometers for frequencies applicable to permanent magnet based sensors.

The spectrometer we used for the experiments reported in this paper is a custom made spectrometer from Tecmag Inc, which has a frequency range of 0.002-100 MHz. The technical specifications are available from the manufacturer [53]. Briefly, the instrument includes an RF pulse programmer, digital receiver, waveform generators for shim control and imaging, and signal-averaging capabilities. The system is controlled via a laptop computer with NTNMR software for instrument control and data processing. Already commercially available systems, such as the Tecmag LapNMR or Magritek Kea [53,54], can perform the tasks necessary for our experiments. In addition, other groups are starting to produce inexpensive, homemade or custom-built controllers for NMR experiments [55,56].

Advances in portable, inexpensive permanent magnet design and construction are making promising steps towards the development of low-cost devices for use in portable, and on-site sensing and analysis of suspect samples. Permanent magnet design optimization and construction is now a task undertaken by several groups and companies. Despite the general focus in this area, a commercial permanent magnet with high field homogeneity has not yet been produced; however, this is an on-going field. For this study, we have employed a magnet with a Halbach [57] design based upon an eight element internal dipolar flux [58] and a resulting 2 Tesla permanent field. The magnet was purchased off-the-self from Magnetic Solutions, ltd., and weighs less than 2 kg. It has 9 cm diameter, 7 cm height and easily fits into the palm of a hand. Alternatives to Halbach designs for field optimization have been described in various references [58–62].

A schematic of the current generation microcoil NMR tabletop system is shown in Fig. 1. A compact Tecmag spectrometer, a small permanent magnet, and an RF probe with laser-lathe lithographically produced microcoils were used. A picture of the Halbach magnet and RF probe with a 360 μm outer diameter microcoil on a translation stage, which is used to map out the magnetic field of the Halbach magnet, are shown in Fig. 2. The RF microcoil has an inductance of 76 nH and direct current resistance of 1.8 Ohms. The probe is made from a transmission line probe design and achieved a forward to reflected power of 20-to-1. The measured Q factor is 28.15, while the predicted value from ($Q = \omega L/R$) is 22. The magnet is fixed and the position of the probe can be adjusted manually. ^{1}H NMR spectra were taken at 0.1 mm increments in all three directions (x,y,z). The linewidths of the ^{1}H NMR spectra were subsequently evaluated. The resulting field map (Fig. 3) and the 3D offset from the central frequency (83.69 MHz) as a function of 3D space is shown to have a linear dependence on the x direction, and linear and quadratic dependence in y and z, y being the direction of the field. The 3D fit is given by [1]:

$$\gamma \Delta B_0(x, y, z) = 25.5 - 0.7646x + 0.0866y + 0.2636z + 0.0191y^2 - 0.0051z^2 \quad (1)$$

The spatial dependence of the field was not symmetric along the direction of the field, y, which is contrary to what we expected from the magnet design. This could be due to manufacturing inconsistencies of the permanent blocks used for the construction of the magnet.

[1]The unit of space is in increments in translation stage (1/25 inches) and the offset units in kHz (offset from the central frequency that was chosen, 83.69 MHz).

We have used the LLNL laser-lathe lithography system to fabricate microcoils with 1 mm, 360 μm, and 100 μm outer diameters. Our first RF microcoil probe was made with a circuit board. A schematic of the probe is shown in Fig. 4A. Since the bore of the 2 T magnet is 0.8 cm in diameter, the circuit board RF microcoil probe fit very tightly in the magnet to obtain field maps of the magnet and was not versatile enough to find the region of maximum homogeneity. Fig. 4B compares spectra from our first generation, circuit board RF microcoil probe with a 1 mm and 360 μm RF coil with a lab-based 500 MHz Bruker Advance instrument with a 360 μm RF coil surrounding a sample of water. The resolution of the lab-based 360 μm probe is 0.1 ppm in the 500 MHz superconducting magnet. Originally, the resolution of the portable RF microcoil on a circuit board probe was approximately 64.4 ppm with a 1 mm micrcoil and approximately 27 ppm with a 360 μm microcoil.

Our current RF microcoil probe uses a 360 μm coil and is based on a transmission line design [2]. Our RF microcoil probe is extremely compact and is 0.2 cm in diameter, a fraction of the bore of the magnet. The behavior of the RF probe was evaluated at various power values, as summarized in Table 1. The 90^0 pulse widths range from 0.21 μs with 391 Watts of power to 6.3 μs for 0.02 Watts of power. A typical nutation curve for our current RF microcoil probe in the handheld 2 T magnet, is shown in Fig. 5. These measurements demonstrate the robust characteristics of the microcoils; they are able to withstand high RF powers, yet are also capable of commercial probe 90-degree pulse times with only 20 mW of power.

3. Preliminary Results

An NMR spectrum was taken with a single pulse-observe experiment in the most homogeneous region of the field (i.e. the sweet spot) after the field profiles were mapped, as described in the previous section. This region is not in the geometrical center of the magnet, but offset by 3 mm along the y-axis. A fluorinated compound, Fluorinert (FC-43), was used to demonstrate a spectral resolution of 17 ppm, while in separate experiments signal was obtained for proton and phosphorous by retuning of the probe. Fig. 6 shows the Fourier transform of the acquired ^{19}F NMR signal from the sweet spot using a 360 μm microcoil with an inner diameter of 320 μm. The fluorine spectrum clearly shows two resolved peaks, where the amount of liquid inside the 360 μm microcoil was approximately 80 nL. This data was taken at a field of frequency of 78.89 MHz, with 64 averages, a 1 second delay time, and a pulse width of 0.35 microseconds. Thus, the total time of acquisition was 30 minutes. The signal-to-noise ratio (SNR) (in the Fourier Transfer Mode) was 32, much lower by comparison to that reported by Sillerud et al. for a single scan [50].

The low SNR is mainly related to the much lower resolution in our magnet by comparison to the larger NEOMAX magnet which was used by Sillerud et al. [2]; however our magnet is portable. Additionally the low SNR is attributed to grounding problems between the magnet and the probe and other noise factors inherent to the large-opening

[2]The resolution in the 30 cm cube 1 T NEOMAX magnet is 0.056 ppm. For the equivalent resolution we have estimated an SNR of 1200 for a single scan, which is larger than the SNR reported by Sillerud et al., i.e. 137.

Magnetic Solutions magnet. [3] Optimization of the RF microcoil geometry and characteristics, according to the findings reported in [51], and probe design, as well as testing of a variety of magnets is underway.

4. Microcoil Sensitivity Analysis

The NMR sensitivity, as reflected by the SNR, is dependent on the nuclear precession frequency, the sample volume, concentration, and natural abundance of the nuclei in question, the magnitude of the RF field induced for a current unit, as well as the noise [52,38]. Because of the latter dependence, the RF coil and probe circuitry properties are important parameters to be optimized in designing a robust NMR system. To compensate for the volume reduction in NMR measurements of small samples, high RF strengths are desirable, especially when use of higher static fields is not feasible. Pre-concentration of the sample and high filling factors are also desirable. The noise is dependent on the resistance of the coil, which in turn depends on the diameter of surface of the wire, thus fine control of the properties of the microcoil is advantageous. We have shown that we can fabricate coils of various thicknesses, winding, number of turns, pitch, and therefore have the ability to control the inductance and resistance of the coil, and detailed evaluations of the Laser-Lathe lithography based fabricated coils is presented elsewhere [51].

Of course the SNR increases with the number of acquisitions and therefore the total acquisition time (t_{acq}). Thus, to measure the NMR sensitivity (S) with a particular RF coil, one must take into account the sample concentration (C) or mass and the total experiment time. Also, a number of interest is the limit of detection (nLOD), i.e. the approximate concentration or mass of a sample needed to obtain a desired SNR:

$$S_C = \frac{SNR}{C \cdot t_{acq}^{1/2}} \quad and \quad nLOD_C = \frac{3}{S_C} \tag{2}$$

The performance of NMR probes and RF micro-coils under different analytical situations can be compared with these above criteria [44].

To test the sensitivity of two laser-lathe microcoils (diameters of 1 mm and 360 μm), a ^{1}H transmission line probe for an 11.5 T (500 MHz) Bruker magnet was built. Photos of the transmission line flow probe are shown in Fig. 7. For ^{1}H NMR sensitivity on LLNLs RF microcoils, we used a 1% ethyl alcohol solution in D_2O. The molarity of the solution was 165 mM. The 1 mm coil was constructed with an outer diameter of 1 mm, an inner diameter of 0.7 mm, 25 turns, 3 mm length, and 3 μm thick copper. The 360 μm was constructed with an outer diameter of 360 μm, an inner diameter of 320 μm, 25 turns, 1 mm length, and copper thickness of 10 μm. In Table 2 the S_C, S_M [4] , $nLOD_C$, and $nLOD_M$ for LLNLs laser-lathe RF microcoils of two different diameters, 1 mm and 360 μm, are compared with previously reported NMR RF coils, including a Varian 5 mm, Nalorac SMIDG, and a hand wound microcoil of diameter 850 μm [44]. In order to fairly compare the limits of detection of our microcoils in 500 MHz to those done

[3]The gap in this magnet is 1 cm. The problem is more apparent in a 1 T magnet by Magnetic Solutions with a 2 cm opening that we have tested. These results are not included here.

[4]the S_M and $nLOD_M$ can be obtained from the same equations as S_C and $nLOD_C$ by substituting the concentration with moles of sample

in the 600 MHz, to what would be expected from all coils at 2 T (85.1 MHz) we have extrapolated, assuming that the 2 T field has the same order of homogeneity, according to $B_0^{7/4}$. While the S_C is smaller for the LLNL microcoils, the S_M is higher and the LOD_M is also dramatically improved, showing that portable NMR is indeed a real possibility for small sample sizes.

5. Gradient and shim coil fabrication

The Laser-lathe system has produced coils of various geometries, and we used this technique to build coils for conventional shimming or for the application of shim pulses as described in reference [33]. A set of gradient coils was designed and built for the initial tests. This was a modified Maxwell pair producing a gradient in the y-direction (Fig. 8A), which is the direction of the main field. The coils were placed so that they surround the microcoil probe (Fig. 8B). Fig. 8C shows a schematic of the gradient coil and the simulated field produced by the coil in the center of the gradient along the coil length for an xy slice, as indicated in the schematic. The field produced by the gradient coils has a linear dependence along y over the sample region and is constant along the x and z directions (z is not shown). The coil resistance was 1.5 Ω and for the initial tests a Techron LVC 2016 linear amplifier was used to drive current through the coil. An applied current of 0.1 Amp was enough to completely spoil the signal, corresponding to a value of 8% of the amplifier capabilities. Changing the gradient strength results in changes in the spectrum lineshape (Fig. 8D). When the sample was offset from the "sweet spot", the gradients acted as shims, with a resulting improvement in linewidth from 200 ppm to 20 ppm. Application of shim currents while the sample is at the sweet spot did not yield any linewidth improvements, therefore higher order shims or shim pulse corrections are necessary. This work is currently under investigation and will be the subject of a subsequent publication.

6. Conclusions

The sustainability of a portable NMR system for chemical analysis of samples in the field is within reach. However, critical developments remain necessary: smaller control system electronics, lower power requirements, sensitivity and resolution enhancements. RF transmitter and receiver components in single boards have been developed from several companies [5] and advances in wireless communications have the potential of assisting in further miniaturization of the control electronics. For our initial system we used an off-the-self Halbach magnet. Permanent magnet manufacturing companies,[6] however, are making progress and several approaches toward smaller, higher field strength and quality systems seem to offer promising alternatives.

The use of microcoils to study small amounts of samples is well established. We have previously presented a microcoil fabrication scheme [48]. We have studied the properties of the microcoils as a function of winding spacing, width, and thickness of the loops, allowing for choice of most desirable characteristics, i.e. maximum quality factor and minimum

[5] e.g. Tecmag Inc, Quantum Magnetics/GE Security, Magritek, Topspin
[6] e.g. Aster Enterprises, NEOMAX

resistance give higher SNR, though that work is outside the scope of this publication and is published separately [51]. For a 360 μm outer diameter coil of 76 nH inductance and 1.8 Ω resistance, we built an RF probe and accomplished modest resolution using only 0.02 Watts of RF power, which gave a 90-degree pulse width of 6.7 μs. While using higher homogeneity permanent magnets is an option we are hoping to have, to improve the resolution and sensitivity we next plan to use smaller microcoils, with a goal of a diameter of 100-260 μm, and lengths of 1 and 2 mm.

We have shown that the microcoil fabrication lab can produce complex three dimensional shapes and we have produced field gradient and field shim coils to improve the field quality of the permanent magnet. While these coils are clearly effective at creating significant field perturbations with small amounts of current, the quadratic and higher order spatial dependence of the Halbach-type or other portable systems will require higher order shim coils. It is also feasible to use the present coils for effective shimming based on the series of ex-situ methodologies developed in the Pines lab [56], where by special pulse sequences (e.g. combinations of frequency and amplitude modulated RF pulses and amplitude modulated gradients) are used to impart spatially dependent phase corrections. Higher homogeneity will also improve the sensitivity of our experiments. In addition standard NMR approaches for sensitivity enhancement (e.g. CPMG train) as well as sample pre-concentration is an area we are currently undertaking.

7. Acknowledgements

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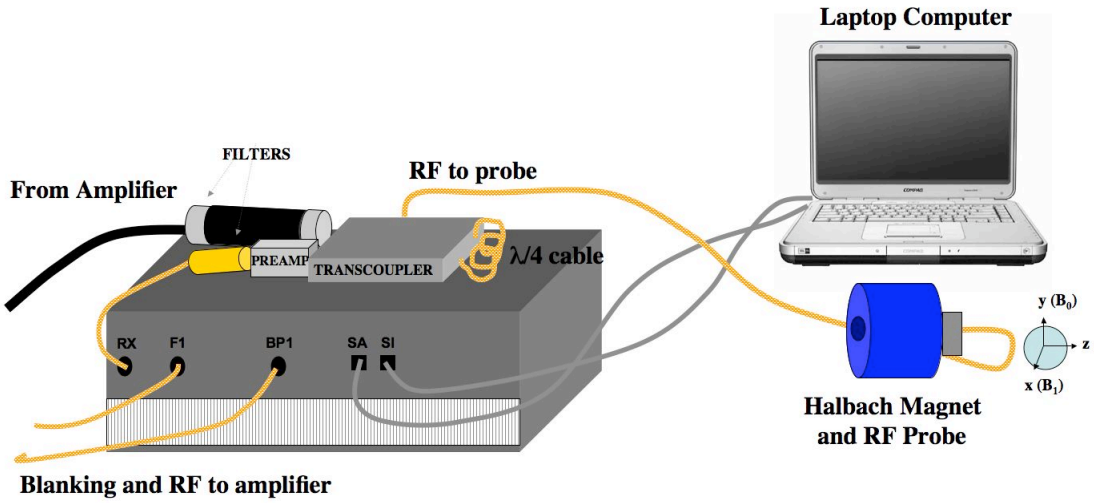

Figure 1. Schematic of our table-top laser-lathe lithographically microcoil NMR setup, which consists of a Tecmag spectrometer for control, a small Halbach magnet, and an RF probe with a 360 μm micrcoils.

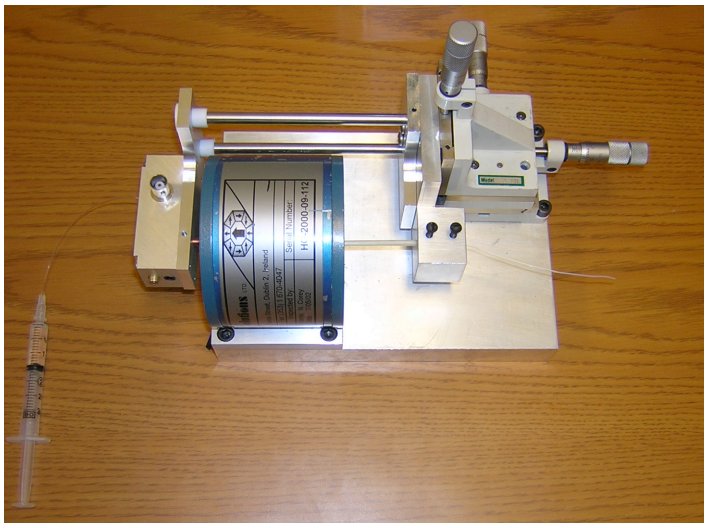

Figure 2. An actual picture of the Halbach magnet and RF probe with a 360 μm microcoil on a translation stage, which is used to map out the magnetic field of the Halbach magnet.

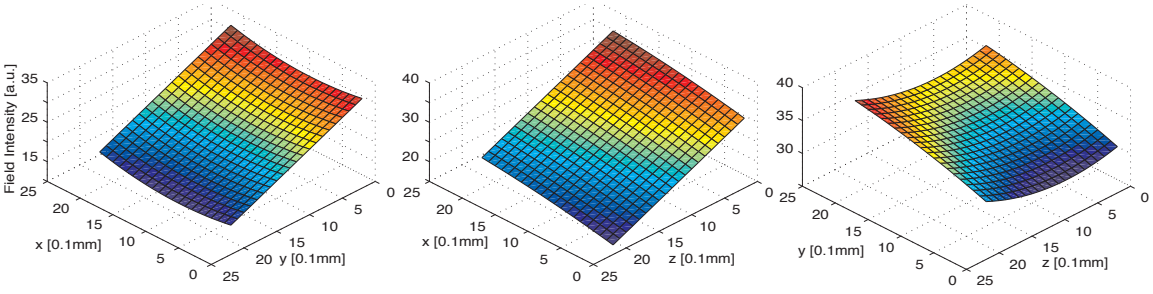

Figure 3. 2D surface plots of the static field in the Halbach magnet.

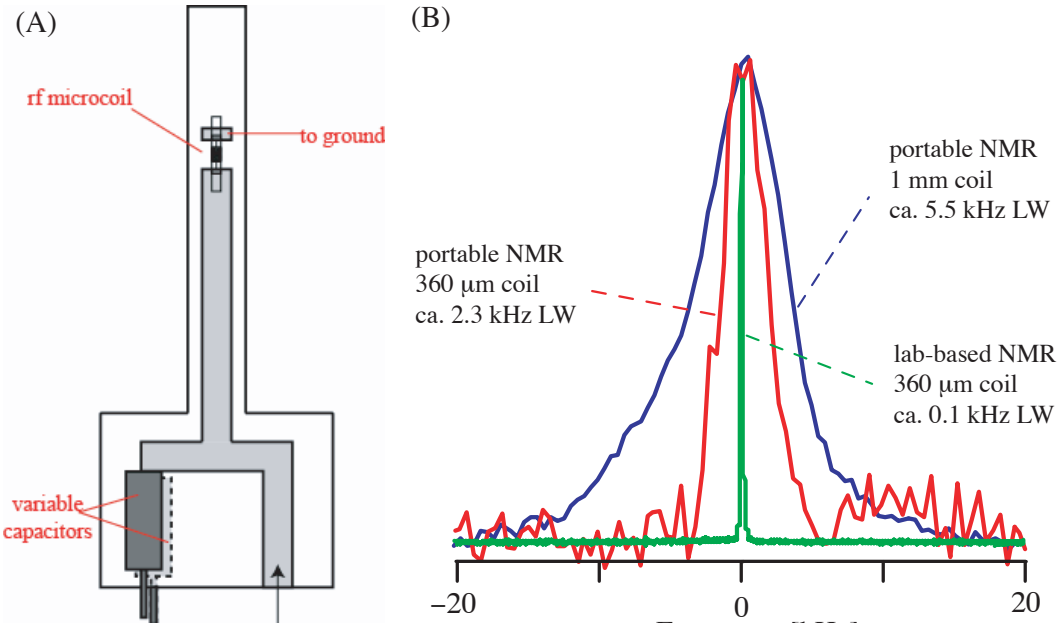

Figure 4. (A) A Schematic of our first generation micrcoil probe made with a circuit board. (B) NMR spectra taken from a homebuilt probe with a 360 μm RF microcoil for our 500 MHz system, a homebuilt probe made from a circuit board with a 1mm and 360 μm RF microcoil for our portable 2T Halbach magnet.

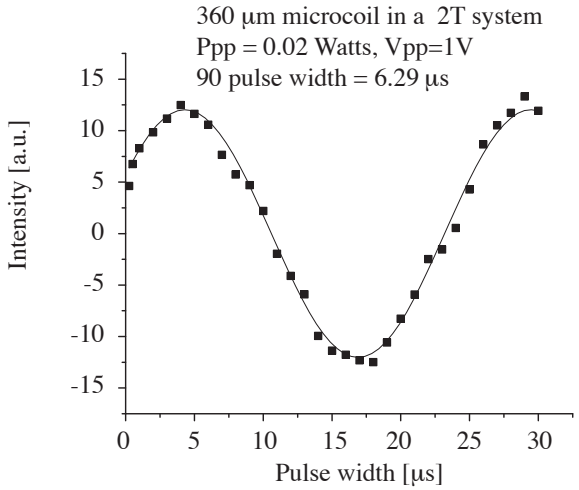

Figure 5. Nutation curve of the portable RF probe with 360 μm OD microcoil for 0.02 Watts of power.

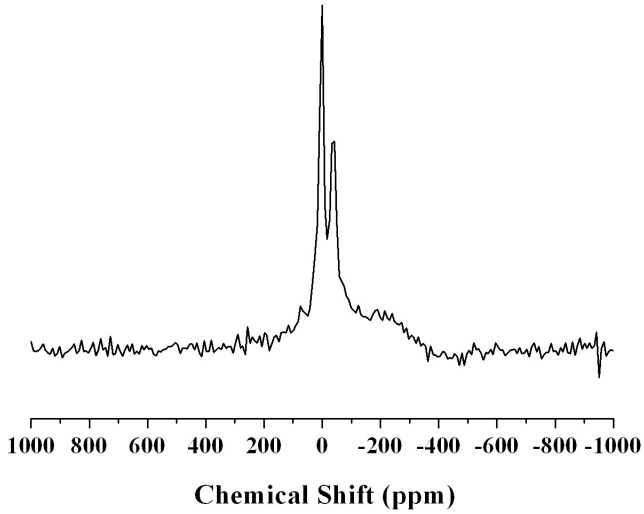

Figure 6. ^{19}F spectrum in the optimal sweet spot of the magnet. The resolution is 17 ppm.

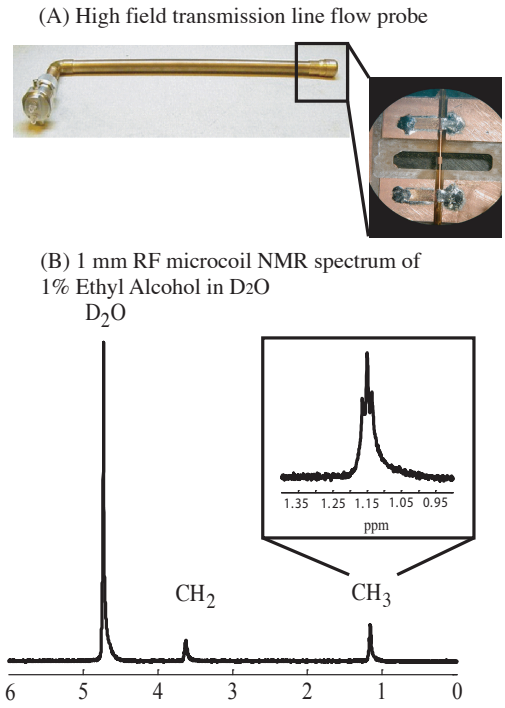

Figure 7. Double resonance, transmission line flow probe for 500 MHz NMR spectrometer. The photo on the right is a close up image of the end of the probe, including the flow system, RF connection, and fine tuning capacitor.

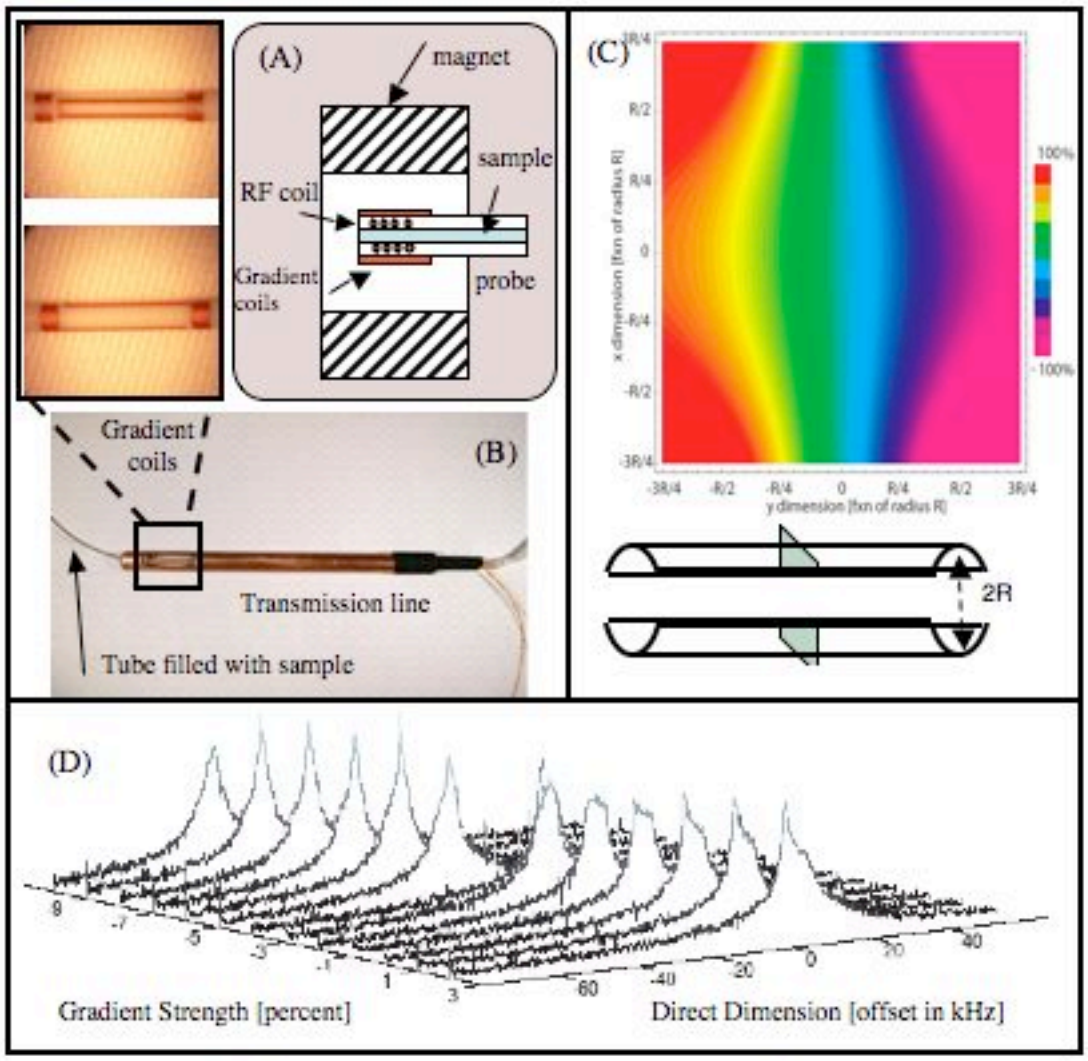

Figure 8. (A) Photographs of the Gradient coils and schematic of the probe and magnet. (B) Photograph of the assembled probehead (RF and gradient coils, sample tube). (C) The simulated field produced by the gradient coils is assumed to be linear along the y direction and constant on x and z. Here an xy slice of the y component is shown. The field strength is in arbitrary units as a percentage of the total field produced by the coil. The position of the slice is shown in the schematic of the coil to the right. (D) Applying different gradient strengths, we see changes in the lineshape. The results here show that for an offset from the sweet spot we actually are shimming the field as indicated by the fact that we have a better lineshape in the presence of the gradient. Here the gradient strengths are shown as percentages, with 10% corresponding to 200 mV or 0.13 Amps of current.

Power (W)	Voltage (V)	90^0 pulse width (μs)
319	126	0.21
151	87	0.34
29	38	0.70
5	16	2.80
0.02	1	6.29

Table 1
Power consumption of the portable NMR microcoil system is shown above

Figure of Merit (units: C in mM, V in μL, t_{acq} in s)	Varian 5 mm (600 MHz)	Nalorac SMIDG (600 MHz)	HW microcoil 850 μm (500 MHz)	LLNL's microcoil 1 mm (500 MHz)	LLNL's microcoil 360 μm (500 MHz)
t_{acq}	4.1	4.1	4.1	10	10
Volume	222	38.3	0.62	1.15	0.08
C	2.26	21.8	–*	165	165
SNR	136	193	–*	452.35	15.82
$S_C(@85.1MHz)$	0.98	0.14	0.03	0.009	$3.16\ 10^{-4}$
$S_M(@85.1MHz)$	4.39	10.49	50.15	98.50	489.47
$nLOD_C(@85.1MHz)$	3.05	21.05	97.6	332.59	9512
$nLOD_M(@85.1MHz)$	671	292.9	61.01	31.04	6.21

Table 2
Data for LLNLs 1 mm RF microcoil, LLNLs 360 μm RF microcoil, and HW 850 μm microcoil were collected with a 500 MHz spectrometer. Data for Varian 5 mm and Nalorac SMIDG were collected with a 600 MHz spectrometer. Varian 5 mm, Nalorac SMIDG, and HW microcoil 850 μm were done elsewhere [44]. Data for all coils were normalized to 85.1 MHz, according to $B_0^{7/4}$.

* These values were not reported in the original reference.

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