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Double tuning a single input probe for heteronuclear NMR spectroscopy at low field

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Abstract

Applications of PASADENA in biomedicine are continuing to emerge due to recent demonstrations that hyperpolarized metabolic substrates and the corresponding reaction products persist sufficiently long to be detected *in vivo*. Biomedical applications of PASADENA typically differ from their basic science counterparts in that the polarization endowed by addition of parahydrogen is usually transferred from nascent protons to coupled storage nuclei for subsequent detection on a higher field imaging instrument. These pre-imaging preparations usually take place at low field, but commercial spectrometers capable of heteronuclear pulsed NMR at frequencies in the range of 100 kHz to 1 MHz are scarce though, in comparison to single channel consoles in that field regime. Reported here is a probe circuit that can be used in conjunction with a phase and amplitude modulation scheme we have developed called PANORAMIC (Precession And Nutation for Observing Rotations At Multiple Intervals about the Carrier), that expands a single channel console capability to double or generally multiple resonance with minimal hardware modifications. The demands of this application are geared towards uniform preparation, and since the hyperpolarized molecules are being detected externally at high field, detection sensitivity is secondary to applied field uniformity over a large reaction volume to accommodate heterogeneous chemistry of gas molecules at a liquid interface. The probe circuit was therefore configured with a large (40 mL) Helmholtz sample coil for uniformity, and double-tuned to the Larmor precession frequencies of ¹³C/¹H (128/510 kHz) within a custom solenoidal electromagnet at a static field of 12 mT. Traditional (on-resonant) as well as PANORAMIC NMR signals with signal to noise ratios of approximately 75 have been routinely acquired with this probe and spectrometer setup from 1024 repetitions on the high frequency channel. The proton excitation pulse width was 240 μs at 6.31 W, compared to a carbon-13 pulse width of 220 μs at 2.51 W. When PANORAMIC refocusing waveforms were transmitted at a carrier frequency of 319 kHz, integrated signal intensities from a spin-echo sequence at both proton (510 kHz) and carbon-13 (128 kHz)

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frequencies were within experimental error to block pulse analogs transmitted on resonance. We anticipate that this probe circuit design could be extended to higher and lower frequencies, and that when used in conjunction with PANORAMIC phase and amplitude modulated arrays, will enable low field imaging consoles to serve as multinuclear consoles.

Keywords

Single channel spectrometer; Low field NMR; Parahydrogen induced polarization; Dual resonant probe circuit; Double tuned; Single input; PANORAMIC; Phase and amplitude modulation; PASADENA; Hyperpolarization

1. Introduction

Methods for polarizing nuclear spins far above the temperature dependent Boltzmann levels (hyperpolarizing) have been drawing increased attention recently, due to their strategic ability to generate metabolic contrast in biological tissue on a time-scale of seconds. The most commercially developed of these technologies, dynamic nuclear polarization (DNP) [1-3], has been shown to be capable of detecting, grading, and monitoring response to therapy in tumors [4-6]. Newer and less well-developed technologies that achieve polarization via parahydrogen [7,8], offer similar levels of enhancement to DNP at reduced complexity and cost. It follows that the biomedical application of parahydrogen hyperpolarization appears poised to continue growing as its requisite equipment, methods, and precursors become more widely available.

Aside from variations in Faraday induction and relaxation properties, DNP approaches the theoretical limits of NMR sensitivity approximately independent of magnetic field strength. Polarization is obtained on long-lived nuclei at low temperatures (~2 K) with DNP, and the associated contrast agents are subsequently warmed rapidly to biological temperatures prior to injection *in vivo*. In contrast, parahydrogen polarization is obtained at the catalytic hydrogenation temperature, although polarization transfer to a coupled heteronucleus (with long T_1) is necessary to extend polarization lifetimes for the subsequent voyage *in vivo*. Aside from cases where the transfer step is induced by field cycling, the biomedical parahydrogen experiment is therefore inherently heteronuclear. In addition, the efficiency of this process is field dependent and generally increases towards zero field in the strong coupling regime of protons. It turns out that spectrometers for performing multinuclear NMR at low fields are somewhat scarce though, whereas comparable single channel imaging consoles are relatively abundant. During recent construction of a PASADENA polarizer, we were motivated to extend the capabilities of our existing single channel console to enable these double resonance (heteronuclear polarization transfer) experiments without incurring significant additional expenses to add a transmitter channel. By using pulse design methods based on optimal control akin to those published recently for constructing broadband pulses for use at high field [9], we found that phase and amplitude modulation could be used to access heteronuclear (^{13}C , ^1H) frequencies at a static field of 12 mT. These waveforms were transmitted at the central frequency (319 kHz at 12 mT) of ^1H and ^{13}C to generate simultaneous rotations at heteronuclear frequencies. We refer to these as PANORAMIC experiments (Precession And Nutation for Observing Rotations At Multiple

Intervals about the Carrier), because of the expanded field of field, and they appear to offer a viable and minimally invasive technique for doing heteronuclear low field NMR with a single phase and amplitude modulated transmitter channel.

Presented here is a single input, double-tuned probe circuit required for transmitting these PANORAMIC waveforms, that in turn will enable double resonant NMR to be performed on a single transmit channel. The probe dplexes a single resonant mode to simultaneously produce tuned and matched responses of carbon- 13 and protons in a static field of 12 mT (128 and 510 kHz). Transmitting PANORAMIC refocusing waveforms at 319 kHz to the 40 mL Helmholtz sample coil of this probe circuit yielded integrated spin-echo signal intensities at 128 and 510 kHz that were within experimental error to the block pulse analogs transmitted on resonance. We anticipate that this probe circuit will be useful for performing heteronuclear hyperpolarization experiments at low fields with single channel consoles when used in conjunction with specially tailored PANORAMIC waveforms.

2. Materials and methods

2.1. Probe circuit

A single resonant circuit (Fig. 1a) with sample coil inductance L_s , tuning capacitance C_t , and matching capacitance C_m were converted to a single-input, dual resonant coil by replacing C_t with a complex impedance network (Fig. 1b), Z_T , and by replacing the matching capacitor, C_m , with complex impedance network Z_M (Fig. 1c) [10]. The parallel resonant circuit (trap) formed by C_t and L_t , created an open circuit to isolate the high frequency channel (510 kHz):

$$\omega_{hf}^2 = (C_t \cdot L_t)^{-1} \quad (1)$$

C_{thf} was then chosen to satisfy the high frequency tuning condition with L_s :

$$C_{thf} = (L_s \cdot (\omega_{hf})^2)^{-1} \quad (2)$$

The impedance presented by the parallel resonant circuit is inductive below its resonant frequency, and C_{thf} was therefore chosen so that the equivalent impedance of C_{thf} , the trap circuit, and C_{tlf} were equivalent to the impedance required to satisfy the low frequency tuning condition. Inductance was estimated at 214 μ H using an LCR meter (model E5071C, Agilent, Santa Clara, CA). To account for changes in sample coil and trap circuit inductances inside the electromagnet, all inductors inside the bore were characterized as single port networks for the required frequency range. This was done by calibrating a single port S -parameter response using a network analyzer (model E5071C, Agilent, Santa Clara, CA). The main advantage with this procedure was that S -parameter responses captured both the deviations from ideal performance and the accumulated nonlinear interactions with surroundings. The data was then imported into CST design studio circuit simulator (version 2012.00 CST AG, Germany) to calculate the other component values.

2.2. Experimental

The probe circuit was tested on a custom spectrometer setup based around a low field console (model KEA, Magritek, New Zealand). A solenoidal electromagnet (4 layer, 3.5" ID, 3.75" OD, 11 AWG square wire, 22" bore length) was powered by a programmable power supply operated in constant current mode (model PM 2813, Fluke, Holland, Netherlands) with 1.30 and 5.25 amps to generate 3 and 12 mT fields, respectively. Radiofrequency pulses were amplified by a 250W low frequency pulsed amplifier (model BT00250-AlphaA, Tomco Technologies, Adelaide, Australia). Proton spectra were acquired at 128 kHz (carbon-13 channel) and 510 kHz (proton channel) from an aqueous copper(II) sulfate solution, using a spin-echo with echo-time and recycle delay equal to 8 ms and 400 ms, respectively.

3. Results and discussion

The purpose of this study was to design and construct a probe circuit for performing heteronuclear NMR experiments at low field with a single channel console. This probe was developed to be used in conjunction with PANORAMIC waveforms to expand the reach of a single channel console to enable simultaneous and phase coherent rotations at heteronuclear frequencies with a centrally placed, constant carrier frequency. The single probe input was diplexed with pole insertion for simultaneous tuning and matching at the Larmor precession frequencies of both ^{13}C (128 kHz) and ^1H (510 kHz). The probe has proven to be useful and predictable for both PANORAMIC and traditional single channel experiments, and yields signal to noise ratios of approximately 75 in 1024 repetitions with either traditional on-resonant or PANORAMIC acquisitions (high field).

A single resonant circuit (Fig. 1a) with sample coil inductance L_S , tuning capacitance C_T , and matching capacitance C_M can be converted to a single-input, dual resonant coil by replacing C_T with a complex impedance network (Fig. 1b), Z_T , and by replacing the matching capacitor, C_M , with complex impedance network Z_M (Fig. 1c) [10]. When used with the component values listed in Table 1, the resulting probe circuit (Fig. 1c) exhibits impedance matched resonances at both 128 and 510 kHz, and an additional minor resonance at approximately 220 kHz (Fig. 2). This additional peak in the probe circuit frequency sweep was predicted by simulation, and appeared to permit some innocuous noise to be picked up outside the frequencies of interest at an offset of approximately +100 kHz relative to carbon-13.

Single input, double-tuned probe circuits tuned to Larmor precession frequencies less than one Megahertz do not appear in the literature, but two higher field circuits may be viable alternatives to the circuit design presented here [11,12]. Hu and coworkers previously double-tuned a single channel by coupling tank circuits [11], a technique that is also discussed in Section 6.3 of Ref. [13]. Their probe exhibited excellent matching at both 26.08 (^{27}Al) and 28.92 MHz (^{65}Cu) with one matching capacitor. Another possibility for double tuning a single input is the foster-type circuit reported by Kan and coworkers [12]. This probe circuit was designed for proton and phosphorous-31 NMR at a field strength of 2 T, with resonant modes at 35 and 85 MHz. In this case, a parallel resonant circuit was inserted with component values chosen to enable sample coil tuning at both frequencies with a single

capacitor. In both of these alternative circuits, simultaneous tuning and matching was not theoretically accounted for. In practice, both of these comparison circuits appeared to match at the frequencies of interest suggesting that the design was well suited to the applications. The design constraints of our application and setup motivated a circuit with more flexibility and robustness. For example, iterative tuning and matching might be expected with less complicated circuits but this is not compatible for our applications where variable nonmagnetic capacitors with high Q -factors are not readily available. There is no guarantee that matched resonances could be found at each frequency or for other sets of frequencies that other applications may warrant as well, with simpler alternative designs. In summary, due to a combination of unknown potential peculiarities in the much lower fields of interest (12 mT) than were present in the literature, and to enable maximum flexibility for translation to additional nearby (low) fields as application warrants, we preferred the capability of independently matching on each channel from the outset and developed a circuit specifically tailored to our application.

The relative design efficiency of this circuit was biased to the low frequency channel in order to compensate for the inherently reduced sensitivity at 128 versus 510 kHz. The Q -factor at 128 and 510 kHz was 13.9 and 36.1, respectively and reflected losses on resonance were estimated to be less than one percent. We observed from the single port S -parameter file of the saddle shaped sample coil (see Section 2.1), that the resistive components at 128 kHz and 510 kHz were approximately 4.5 Ω and 18 Ω , respectively. With the LCR meter at 100 kHz, the main coil resistance is reduced to 3.15 Ω and in agreement with the S -parameter file value. Similarly the other two inductors in the circuit also have resistances which are frequency dependent, and based on these observations, the Q -factor was not expected to scale with the square root of frequency. Proton and carbon-13 excitation pulse widths were 240 and 220 μ s, at 6.31 and 2.51 W input powers respectively, and in qualitative accord with the initial design efficiency specifications. For reference, this circuit enabled acquisition of traditional (on-resonant) spin-echoes on the high frequency channel with signal to noise ratios of approximately 75 from 1024 repetitions (Fig. 3). In Fig. 3, note that in order to increase sensitivity (or reduce sample expense), proton spectra were acquired at the carbon-13 Larmor frequency by reducing the static field strength to approximately 3 mT. In this implementation, the sample coil is used to apply uniform rotations to the initial parahydrogen singlet-state spin ensembles. In addition, since the PASADENA preparation involves a chemical reaction at the interface of a gas and a liquid, a large sample coil was needed to optimize reaction volume. Both of these design constraints (large and homogeneous volume) were accommodated in our custom static solenoid electromagnet by using a Helmholtz saddle pair. A solenoidal sample coil would have enabled greater efficiency, reduced B1 uniformity, and the orthogonal orientation would have significantly reduced reaction surface area.

The overall purpose of this study was to develop a probe circuit for performing heteronuclear NMR with PANORAMIC waveforms using a single channel console. The ultimate goal of these experiments is to develop a pulsed PASADENA polarizer that operates on a single channel. This application is well-suited to applications of PASADENA to biomedicine, because samples are preferentially prepared at low field and detected on

high field imaging consoles. Single channel consoles with phase and amplitude modulated channels are abundant for low field imaging, and this circuit used in conjunction with PANORAMIC reduces the cost of building a PASADENA polarizer. We tested the efficiency of PANORAMIC with respect to traditional on-resonant NMR acquisitions at each frequency and found that spin-echoes formed from PANORAMIC refocusing waveforms transmitted at 319 kHz were comparable to integrated signals when compared to block pulse analogs transmitted on resonance at 128 and 510 kHz (Fig. 4). Work is currently underway to evaluate other PANORAMIC waveforms designed for excitation and inversion for example, in order to get both a more comprehensive overview of performance and viability of the technique overall, as well as to complete the pulsed toolset that would fully enable a single channel spectrometer to be multiplexed at these fields. We anticipate that this probe circuit will extend to frequencies bracketed about those presented here in the sub MHz regime, and that when used in conjunction with phase and amplitude modulation on a single channel will provide a viable approach for extending the reach of low field imaging consoles to serve as multinuclear consoles.

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Fig. 1.

Single input probe circuit diagram. (a) Basic parallel resonant circuit, (b) parallel resonant circuit with capacitors and inductors replaced by complex tuning and matching networks, (c) the complete implementation of the single input, double tuned coil circuit. Subscript symbols refer to: inductor (L), capacitor (C), sample coil (s), tuning (t), matching (m), complex tuning network (T), complex matching network (M), trap circuit (trap), high frequency (hf), and low frequency (lf).

Fig. 2. Reflected power as a function of frequency for the single input probe circuit tuned to 510 and 128 kHz (circuit diagram, Fig. 1c).

Fig. 3.

Experimental spectra acquired with a spin-echo at 128 kHz (lower trace) and 510 kHz (upper trace), corresponding respectively to carbon-13 and proton Larmor precession frequencies at 12 mT. At both frequencies, 1024 transients were signal averaged using a spin-echo with an 8 ms echo-time and a recycle delay of 400 ms, from a 125 mL aqueous solution of copper(II) sulfate. The proton channel pulse width was 240 μ s at an applied power of 6.31 W, while the carbon-13 channel values were 220 μ s and 2.51 W.

Fig. 4. PANORAMIC proton spectrum acquired at 12 mT. 1024 transients were signal averaged from a 125 mL aqueous solution of copper(II) sulfate to obtain this spectrum using the single input, dual tuned circuit (see Fig. 1c for diagram). The PANORAMIC waveform was transmitted at 319 kHz (−191 kHz carrier offset) to efficiently refocus transverse magnetization in a spin-echo acquisition.

Table 1

Component values used to tune and match the single input probe circuit (Fig. 1c) to 128 and 510 kHz (corresponding to ^{13}C and ^1H at 12 mT).

Component	Value
L_s	214.6 μH , resistance = 3.15 Ω
L_t	150.5 μH , resistance = 2.45 Ω
L_m	131.2 μH , resistance = 2.20 Ω
C_t	590 pF
C_{thf}	188 pF
C_{lhf}	4390 pF
C'_{mlf}	575 pF
C_{mhf}	748 pF
C_{mlf}	4600 pF

Inductor (L) subscripts refer to sample (s), tuning (t), and matching (m). Capacitor (C) subscripts refer to tuning (t), high frequency tuning (thf), low frequency (lf), matching (m), and high field matching (mhf).