Published in final edited form as:

J Magn Reson. 2014 August ; 245: 58–62. doi:10.1016/j.jmr.2014.05.010.

Heteronuclear refocusing by nonlinear phase and amplitude modulation on a single transmitter channel

Jay Moore^{a,c,1}, Raul D. Colon^{a,b,1}, Sasidhar Tadanki^a, and Kevin W. Waddell^{a,b,c,*}

^aVanderbilt University Institute of Imaging Science, Vanderbilt University, Nashville, TN 37232-2310, United States

^bDepartment of Physics and Astronomy, Vanderbilt University, Nashville, TN 37232-2310, United States

^cDepartment of Radiology and Radiological Sciences, Vanderbilt University, Nashville, TN 37232-2310, United States

Abstract

The application of low magnetic fields to heteronuclear NMR has expanded recently alongside the emergence of methods for achieving near unity polarization of spin ensembles, independent of magnetic field strength. The parahydrogen induced hyperpolarization methods in particular, often use a hybrid arrangement where a high field spectrometer is used to detect or image polarized molecules that have been conjured on a separate, dedicated polarizer instrument operating at fields in the mT regime where yields are higher. For controlling polarizer chemistry, spare TTL channels of portable NMR spectrometers can be used to pulse program reaction timings in synchrony with heteronuclear RF transformations. The use of a spectrometer as a portable polarizer control module has the advantage of allowing detection *in situ*, simplifying the process of optimizing polarization yields prior to *in vivo* experimental trials. Suitable heteronuclear spectrometers compatible with this application are becoming more common, but are still sparsely available in comparison to a large existing infrastructure of single channel NMR consoles. To determine if one of these single channel spectrometers could be used for heteronuclear NMR, the feasibility of rotating a pair of heteronuclear spins (¹³C and ¹H) at 12 mT was investigated in this study. Nonlinear phase and amplitude modulated waveforms designed to simultaneously refocus magnetization at 128 kHz (¹³C) and 510 kHz (¹H) were generated numerically with optimal control. Although precise quantitative comparisons were not attempted due to limitations of the experimental setup, signals refocused at heteronuclear frequencies with this PANORAMIC approach (Precession And Nutation for Observing Rotation At Multiple Intervals about the Carrier) yielded amplitudes comparable to signals which were refocused using traditional block pulses on heteronuclear channels. Using this PANORAMIC approach to heteronuclear NMR at low field would reduce expense as well as hardware complexity and bulk, weighed against the caveat that elaborate pulses are required. More work will be necessary to test this method on the

© 2014 Published by Elsevier Inc.

*Corresponding author at: Vanderbilt University Institute of Imaging Science, Vanderbilt University, 1161 21st Avenue South, Medical Center North, AAA-3110, Nashville, TN 37232-2310, United States. Fax: +1 (615)322 0734. kevin.waddell@vanderbilt.edu (K.W. Waddell).

¹JM and RDC contributed equally to this work

targeted application of parahydrogen induced hyperpolarization as well as to quantify efficiency, but upon further development we anticipate that this method may offer a viable ‘software’ approach to heteronuclear manipulations of spins at low magnetic fields.

Keywords

Single channel spectrometer; Low field NMR; Parahydrogen induced polarization; Phase modulation; Amplitude modulation; Broadband NMR; Transmitter multiplexing; PANORAMIC; Optimal control

1. Introduction

The feasibility and use of low magnetic fields for heteronuclear NMR has been expanding recently in part due to the emergence and development of varied techniques for achieving spin polarization levels well beyond the usual field-dependent Boltzmann distribution. Where applicable, these so-called hyperpolarization techniques reduce the penalty for detecting NMR signals with compact magnets, and consequently are helping to stimulate interest in a range of applications that require portable spectrometer systems [1]. In some cases such as those based on parahydrogen for example [2], low fields are preferred to attain optimal polarization yields [3–6]. Consequently, biomedical applications of parahydrogen induced hyperpolarization techniques in particular, have tended towards a hybrid setup where a high-field spectrometer is used to detect molecules that have been polarized separately, on a dedicated instrument operating in the mT regime or lower where yields are optimized [7,8].

When a sufficiently large array of pulse-programmable TTL lines are accessible, the low-field spectrometer of these hybrid experimental setups can also provide a convenient and portable polarizer control platform. Although portable spectrometer consoles equipped for heteronuclear NMR in the sub MHz regime are now becoming more common, they are still rather sparse compared to the analogous single channel spectrometers which have already found relatively widespread application in an array of bulk liquid and relaxation experiments. These single channel consoles are not immediately useful for parahydrogen experiments though, because thus formed, pulsed transformation of the parahydrogen singlet-states into net magnetization requires that the protons of parahydrogen be rotated in addition to coupled heteronuclei [3–5].

With this application of low field parahydrogen hyperpolarization as motivation, we became interested in extending the range of an existing portable single-channel spectrometer so as to enable heteronuclear spectroscopy. The objective in this stage of the project was to determine basic feasibility – can nonlinear phase and amplitude modulation be used to efficiently rotate relevant heteronuclear spins at fields in the mT regime using a single channel spectrometer?

The need to rotate spins simultaneously at heteronuclear frequencies with a single channel has clearly been motivated here by a specialized application. The need to simultaneously rotate spins at multiple frequency bands however, has a dense historical context in NMR that

underscores the general relevance of pursuing pulse sequence solutions to applications involving magnetic spins. More than 40 years ago for example, Tomlinson and Hill first reported using Fourier synthesis to solve a homonuclear problem related to that addressed here – to selectively rotate spins occurring at multiple frequency bands [9]. A series of methods still in active use today were developed shortly thereafter, that enabled the selected frequency bands of multiple-banded homonuclear responses to be tuned based on varying interpulse delays [10], applying linear phase ramps [11,12], or combinations thereof [13]. Generating frequency responses at large offsets to the carrier by rapidly modulating phase has also been used in solids.

Whereas in liquids, the ability to selectively rotate proximal slivers of frequencies is often desirable, solid-state spins are often spread over large frequency bands by dipole or quadrupolar coupling. Diminished selectivity is ideal in that case, and to achieve this effect rapid modulation of phase has frequently been employed (e.g. [14–18]). These examples represent but a few selected out of a large and growing list of how NMR spectroscopists have leveraged phase and amplitude modulation to fine tune or extend the reach of their spectrometers.

This project is positioned within the general realm of more selectively addressing spins per unit investment in hardware, but presented distinct challenges related to the frequency separations (382 kHz) in conjunction with the applied field strength available (<75 uT). To circumnavigate these challenges, nonlinear phase and amplitude modulated waveforms were developed numerically for simultaneously refocusing ^{13}C and ^1H at 12 mT using a fixed, central carrier frequency. In turn, these waveforms were transmitted to a dual-tuned ($^{13}\text{C}/^1\text{H}$) probe, and the resulting signals were observed with a broadband T/R switch [19]. Further work will be necessary to more fully establish the range of applicability and limitations of this approach, but the results of this feasibility study support further development and use of these PANORAMIC waves (Precession And Nutation for Observing Rotation At Multiple Intervals about the Carrier) as a streamlined and inexpensive alternative for refocusing heteronuclear spins at low fields with a single transmitter channel. Future work will be aimed at generalizing the approach towards application in parahydrogen based hyperpolarization experiments requiring polarization transfer in coupled spins systems.

2. Methods

2.1. Waveform design

PANORAMIC waveforms were designed numerically with optimal control using methods similar to those reported by Skinner et al. [20,21]. Initial amplitudes and phases of the composite waveform were seeded randomly and set to zero, respectively. Iterative adjustments to the amplitude and phase modulations were determined via differences in the physical paths associated with: (1) the forward radio frequency (RF) induced propagation of the magnetization $M^F(t)$ from the initial state M_0 , and (2) the propagation of the magnetization $M^R(t)$ due to the time-reversed RF waveform starting with the target magnetization state M^T [22]. The difference in these two spatial trajectories, $\omega(t)$, was

quantified by the vector cross product of the magnetization vector at each time point in the composite RF waveform such that

$$\Delta\omega(t) = M^F(t) \times M^R(t). \quad (1)$$

The composite pulse for the next computational iteration was then determined by

$$\Delta\tilde{A}(t) = \lambda |\Delta\omega(t)|, \quad (2)$$

with $\tilde{A}(t)$ representing the complex waveform consisting of a magnitude component, $A(t)$, and a phase component, $\phi(t)$. In our implementation of this procedure, the parameter, λ , was determined by least-squares minimization to maximize improvement in the cost function for a given iteration. A relaxation-free form of the Bloch equations was used to calculate the magnetization trajectories $M^F(t)$ and $M^R(t)$ [23].

The average scalar product formed between the targeted magnetization state and the magnetization state resulting from a given RF modulation (phase and amplitude) was used to construct a generic cost function, $\delta(A)$. This cost function was calculated in 20 Hz bands centered at both heteronuclear frequencies, then summed to form an average scalar product across the entirety of both passbands. Thus the cost function δ can be described algebraically as

$$\delta(A) = \frac{1}{m} \sum_{i=1}^m \left(1 - M_i^F(T_f) \cdot M_i^T \right) + \frac{1}{n} \sum_{j=1}^n \left(1 - M_j^F(t_f) \cdot M_j^T \right) \quad (3)$$

where t_f represents the end-time of the RF transmission and the indices i and j indicate the step number through the lower (^{13}C) and upper (^1H) frequency bands, respectively. To refocus over a frequency range large compared to the static field in homogeneity, design passbands were set to 2 kHz and computed in 20 Hz intervals ($m = n = 100$ steps). Homogeneities in the transmitted RF field intensity were neglected due to the relatively small volumes and large wavelengths under consideration [20,21]. Phase reversals (refocusing) of transverse magnetization within the design passbands of PANORAMIC waveforms were enforced by specifying $M_0 = (M_x, M_y, M_z) = (+\sqrt{2}, +\sqrt{2}, 0)$ and $M^T = (M_x, M_y, M_z) = (+\sqrt{2}, -\sqrt{2}, 0)$ across each of the two 2 kHz bands located at offsets of ± 191 kHz relative to the carrier at 319 kHz [13]. The PANORAMIC waveform resulting from this procedure consisted of 1500 subpulses sampled in 2.1 μs steps, for a total composite pulse duration of 3.15 ms. Phases were allowed to roam over the transverse plane while amplitudes ranged between 0 μT and 75 μT (Fig. 1).

2.2. Experimental

NMR signals were refocused at the Larmor precession frequencies of carbon-13 (128 kHz) and protons (510 kHz) at a field of 12 mT. A portable spectrometer equipped with a broadband transmit/receive switch covering approximately 100–600 kHz (Magritek, NZ),

was used to transmit PANORAMIC waves to a single input probe dual tuned to 128 and 510 kHz. Static magnetic fields were generated by a custom solenoidal electromagnet (4 layer, 3.5" ID, 3.75" OD, 11 AWG square wire, 22" bore length) driven by a programmable power supply operated in constant current mode (model PM 2813 Fluke, Holland, Netherlands). Carbon-13 spins were not measured directly due to expense – ^{13}C spins at 12 mT were instead emulated by protons at a field decreased by the gyromagnetic ratio (~ 3 mT). The ^{13}C magnetic field was generated with a current of 1.30 amps, while the proton field at 12 mT was generated with 5.25 amps. RF pulses were synthesized with a portable low field spectrometer (model KEA, Magritek, NZ) and routed to a 250W low frequency pulsed amplifier (model BT00250-AlphaA Tomco Technologies, Adelaide, Australia). All experiments were conducted with a single port probe circuit which was simultaneously tuned and matched to 128 and 510 kHz [19]. Experimental spectra were acquired from a CuSO_4 sample contained in a 2.54 cm-diameter plastic sphere using a spin-echo sequence with TR/TE equal to 500/8 ms. For PANORAMIC trials, refocusing pulses were applied at the mean of the ^{13}C and ^1H resonance frequencies (319 kHz). For comparison experiments, 180° block-shaped pulses were applied on resonance at each frequency separately.

3. Results and discussion

This study assessed the feasibility of performing multinuclear NMR at low fields by transmitting nonlinear phase and amplitude modulated waveforms from a single transmitter channel. The waveforms for accomplishing this were developed numerically using optimal control to achieve a design objective of simultaneous refocusing at the Larmor frequencies of both carbon-13 (128 kHz) and protons (510 kHz) at a field of 12 mT. The resulting PANO-RAMIC waveform was tested experimentally on a portable spectrometer setup using a single port, dual-resonant probe circuit and a broadband duplexer covering approximately 100–600 kHz.

The PANORAMIC refocusing waveform developed for this feasibility study consisted of 1500 subpulses with amplitudes ranging from 0 to 75 μT , and phases from $-\pi$ to $+\pi$ radians (Fig. 1). Maximum design amplitudes were limited by probe efficiency and constrained to 75 μT or less to avoid hardware damage due to reflected power at the edges of the spectrometer duplexer. Conspicuous clipping is evident from Fig. 1 (top trace, amplitude) at the maximum amplitude constraint of 75 μT . The presence of these amplitude plateaus suggests that shorter waveforms could likely be designed with the optimal control optimization used here [20–22] by increasing the maximum applied field amplitude.

The evolution of M_x and M_y during application of the PANO-RAMIC waveform is illustrated for three frequency components located at the edges and center of the ^{13}C band at 128 kHz and the ^1H band at 510 kHz (Fig. 2). In accord with the intended refocusing operation, amplitudes of M_x and M_y were initially both set at $+\sqrt{2}$, and over the course of the pulse, M_y is inverted while M_x returns to the initial state. The full pulse profiles shown in Fig. 3 illustrate that the refocusing operation is approximately uniform across the 2 kHz design passband. Frequency bands flanking the passband were not constrained in the optimization, and it is noted that transition bands of this particular pulse were somewhat jagged. These wing frequencies were not constrained outside of the targeted bands so that

computational burden would be reduced, with the expectation that any deleterious impacts would be mitigated experimentally through the combined impact of probe circuit response and the relatively broad design passband (2 kHz) relative to the static magnetic field in homogeneities (on the order of hundreds of Hz). Experimental line shapes lend credence to this approach as they varied smoothly within the design bands of the targeted frequencies.

Efficiency of this PANORAMIC refocusing waveform was estimated by comparison to traditional block pulse analogs in spin-echo experiments (Fig. 4). A systematic comparison was unfortunately not possible at this stage because driving the probe circuit to produce 75 μ T caused damage to the spectrometer duplexer. To move around this problem, further studies will evaluate lower power pulses and improved probe circuit efficiency or designs. At the ^{13}C band (128 kHz), where the design amplitude was reached, signal amplitudes were within experimental error with respect to (on resonant) block pulses. At high field (510 kHz) where the applied field design requirement was not reached, PANORAMIC refocusing amplitudes were reduced to approximately 85% of those achieved with on-resonant block pulses. Other than improving the pulses and hardware to be respectively matched and optimal, design criteria such as pulse length could also be expected to impact theoretical efficiency and be leveraged to potentially reduce relaxation effects and improve pulse performance.

In summary, results were promising in the case where the magnitude of the applied field reached the design field (low field, 128 kHz), counter weighted in the context of unknown but potentially lower efficiency measured in terms of relative refocusing amplitudes at high-field. To apply this method to heteronuclear systems outside of the basic models examined here, it will be necessary to rigorously account for differential probe responses at each frequency. A couple methods seem plausible for this purpose: (1) using a single wave designed to account for the differential responses of the probe, and (2) use of two independent waves that could interleaved. For the latter, waves would be designed to create single side-band responses, and to balance differential coil effects, the amplitude of the individual waves would be scaled accordingly. These approaches could be used interactively, and in addition it may also be possible to construct single waves with sufficient insensitivity to B_1 to account for differential probe channel effects.

Finally, while heteronuclear refocusing at large offsets from the carrier seems feasible from this pilot study, considerable work will be needed to translate the approach to the targeted application of parahydrogen induced hyperpolarization. The design algorithms will need to be transformed from Bloch equations to a quantum mechanical treatment for example, which will undoubtedly increase computational burden considerably. It may also be necessary to account for relaxation effects to improve performance. Solutions to these challenges will likely be nontrivial but are not without literature precedent [24,25]. It should be noted that during the completion of this study, a second channel became available commercially for our spectrometer. While the availability of commercial hardware decreases the attractiveness of this approach, new applications in parahydrogen hyperpolarization have also emerged recently that would benefit from a third channel [26], which is not yet available commercially.

4. Conclusions

The purpose of this study was to evaluate the feasibility and efficiency of using nonlinear phase and amplitude modulated pulses as a streamlined approach to perform heteronuclear NMR at low fields. Emerging applications of parahydrogen induced hyperpolarization to biomedicine are more efficient at low fields where protons are strongly coupled, but multinuclear NMR spectrometers are not yet widely available to operate in this field regime. Although further studies will be necessary to better characterize the efficiency of these PANORAMIC waveforms, the use of nonlinear phase and amplitude modulation does appear feasible for multiplexing in low field NMR applications. Therefore with further development, we anticipate that this approach could provide a streamlined and inexpensive method of preparing spins at multinuclear Larmor precession frequencies at low magnetic fields, with a particular utility towards parahydrogen induced hyperpolarization.

Acknowledgments

We thank Craig Eccles and Andrew Coy for help with implementing phase and amplitude modulation on the Magritek KEA. RDC was supported by NIH Grant R25 CA136440, JM by NIH training Grant 5T32 EB001628-09 and KWW by a pilot Grant ICMIC 5P50 CA128323-03 and R21 GM107947-01.

References

1. Blumich B, Casanova F, Appelt S. NMR at low magnetic fields. *Chem Phys Lett.* 2009; 477:231–240.
2. Bowers CR, Weitekamp DP. Para-hydrogen and synthesis allow dramatically enhanced nuclear alignment. *J Am Chem Soc.* 1987; 109:5541–5542.
3. Cai C, Coffey AM, Shchepin RV, Chekmenev EY, Waddell KW. Efficient transformation of parahydrogen spin order into heteronuclear magnetization. *J Phys Chem B.* 2013; 117:1219–1224. [PubMed: 23214962]
4. Goldman M, Johannesson H, Axelsson O, Karlsson M. Hyperpolarization of ^{13}C through order transfer from parahydrogen: a new contrast agent for MRI. *Magn Reson Imaging.* 2005; 23:153–157. [PubMed: 15833606]
5. Kadlecsek S, Emami K, Ishii M, Rizi R. Optimal transfer of spin-order between a singlet nuclear pair and a heteronucleus. *J Magn Reson.* 2011; 205:9–13. [PubMed: 20427216]
6. Waddell KW, Coffey AM, Chekmenev EY. In situ detection of PHIP at 48 mT: demonstration using a centrally controlled polarizer. *J Am Chem Soc.* 2011; 133:97–101. [PubMed: 21141960]
7. Golman K, Axelsson O, Johannesson H, Mansson S, Olofsson C, Petersson JS. Parahydrogen-induced polarization in imaging: subsecond C-13 angiography. *Magn Reson Med.* 2001; 46:1–5. [PubMed: 11443703]
8. Zacharias NM, Chan HR, Sailasuta N, Ross BD, Bhattacharya P. Real-time molecular imaging of tricarboxylic acid cycle metabolism in vivo by hyperpolarized 1- ^{13}C diethyl succinate. *J Am Chem Soc.* 2012; 134:934–943. [PubMed: 22146049]
9. Tomlinso BL, Hill HDW. Fourier synthesized excitation of nuclear magnetic-resonance with application to homonuclear decoupling and solvent line suppression. *J Chem Phys.* 1973; 59:1775–1784.
10. Morris GA, Freeman R. Selective excitation in fourier-transform nuclear magnetic-resonance. *J Magn Reson.* 1978; 29:433–462.
11. Kupce E, Freeman R. Polychromatic selective pulses. *J Magn Reson Ser A.* 1993; 102:122–126.
12. Patt SL. Single-frequency-shifted and multiple-frequency-shifted laminar pulses. *J Magn Reson.* 1992; 96:94–102.
13. Geen H, Wu XL, Xu P, Friedrich J, Freeman R. Selective excitation at 2 arbitrary frequencies – the double-dante sequence. *J Magn Reson.* 1989; 81:646–652.

14. Baum J, Tycko R, Pines A. Broad-band population-inversion by phase modulated pulses. *J Chem Phys.* 1983; 79:4643–4644.
15. Tycko R, Pines A. Iterative schemes for broad-band and narrow-band population-inversion in NMR. *Chem Phys Lett.* 1984; 111:462–467.
16. Tycko R, Schneider E, Pines A. Broad-band population-inversion in solid-state NMR. *J Chem Phys.* 1984; 81:680–688.
17. Baum J, Tycko R, Pines A. Broad-band and adiabatic inversion of a 2-level system by phase-modulated pulses. *Phys Rev A.* 1985; 32:3435–3447. [PubMed: 9896511]
18. Baum J, Tycko R, Pines A. Spatially selective NMR with broad-band radiofrequency pulses. *Chem Phys.* 1986; 105:7–14.
19. Tadanki S, Colon RD, Moore J, Waddell KW. Double tuning a single input probe for heteronuclear NMR spectroscopy at low field. *J Magn Reson.* 2012
20. Skinner TE, Reiss TO, Luy B, Khaneja N, Glaser SJ. Application of optimal control theory to the design of broadband excitation pulses for high-resolution NMR. *J Magn Reson.* 2003; 163:8–15. [PubMed: 12852902]
21. Skinner TE, Reiss TO, Luy B, Khaneja N, Glaser SJ. Reducing the duration of broadband excitation pulses using optimal control with limited RF amplitude. *J Magn Reson.* 2004; 167:68–74. [PubMed: 14987600]
22. Conolly S, Nishimura D, Macovski A. Optimal-control solutions to the magnetic-resonance selective excitation problem. *IEEE Trans Med Imaging.* 1986; 5:106–115. [PubMed: 18243994]
23. Bendall MR, Pegg DT. Theoretical description of depth pulse sequences, on and off resonance, including improvements and extensions thereof. *Magn Reson Med.* 1985; 2:91–113. [PubMed: 3831687]
24. Khaneja N, Reiss T, Kehlet C, Schulte-Herbruggen T, Glaser SJ. Optimal control of coupled spin dynamics: design of NMR pulse sequences by gradient ascent algorithms. *J Magn Reson.* 2005; 172:296–305. [PubMed: 15649756]
25. Khaneja N, Reiss T, Luy B, Glaser SJ. Optimal control of spin dynamics in the presence of relaxation. *J Magn Reson.* 2003; 162:311–319. [PubMed: 12810014]
26. Shchepin RV, Coffey AM, Waddell KW, Chekmenev EY. PASADENA hyperpolarized C-13 phospholactate. *J Am Chem Soc.* 2012; 134:3957–3960. [PubMed: 22352377]

Fig. 1.

Amplitude (top) and phase (bottom) modulated PANORAMIC waveforms. These waveforms are comprised of 1500 subpulses sampled at $2.1 \mu\text{s}$ dwell times for a total composite pulse duration of 3.2 ms. When applied at a carrier frequency of 319 kHz in a static magnetic field of 12 mT, these waveforms enable ^{13}C (128 kHz) and ^1H (510 kHz) magnetization to be simultaneously refocused. Amplitude clipping at $75 \mu\text{T}$ reflects an optimization constraint enforced to limit the power reflected to the duplexer.

Fig. 2.

Simulated time evolution of magnetization components M_x (top) and M_y (bottom) during execution of the RF waveform for three frequencies within the targeted 2 kHz lower band (left column) and upper band (right column). This figure illustrates how three frequency components in each refocusing band evolve in time and converge to the final state where phase is reversed relative to the initial state. Phase reversal was enforced by conservation of M_x and reversal of M_y . Frequencies are specified relative to a central carrier positioned at 319 kHz.

Fig. 3.

Simulated magnetization profiles centered at the ^{13}C resonance (-191 kHz, left column) and the ^1H resonance ($+191$ kHz, right column) of M_x (top), M_y (middle) and M_T (bottom) relative to a central carrier at 319 kHz. Dotted lines denote the initial conditions of the optimization, with the magnitude of M_T equal to 1 and the phase at 45° . The combination of M_x and M_T conservation along with M_y reversal imply refocusing within the targeted 2 kHz frequency bands. The 2 kHz refocusing band was chosen to be large compared to the static field in homogeneity.

Fig. 4.

Wide-angle NMR spectroscopy at low field with phase and amplitude modulated (PANORAMIC) waveforms. PANORAMIC waveforms were transmitted at a carrier frequency of 319 kHz, and these spectra represent magnetization that has been refocused at 128 kHz (−191 kHz, left) and 510 kHz (+191 kHz, right). Both spectra were acquired from protons in aqueous CuSO_4 with a spectral width of 500 kHz (zoomed regions shown). Current applied to the electromagnet was decreased in order to generate a field of 3 mT to mimic the Larmor precession frequency of ${}^{13}\text{C}$ at 12 mT.