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Communication: Partial polarization transfer for single-scan spectroscopy and imaging

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A method is presented to partially transfer nuclear spin polarization from one isotope S to another isotope I by the way of heteronuclear spin couplings, while minimizing the loss of spin order to other degrees of freedom. The desired I spin polarization to be detected is a design parameter, while the sequence of pulses at the two Larmor frequencies is optimized to store the greatest unused S spin longitudinal polarization for subsequent use. The unitary evolution for the case of $I_N S$ spin systems illustrates the potentially ideal efficiency of this strategy, which is of particular interest when the spin-lattice relaxation time of S greatly exceeds that of I. Explicit timing and pulses are tabulated for the cases for which $M \leq 10$ partial transfers each result in equal final polarization of $1/M$ or more compared to the final I polarization expected in a single transfer for $N = 1$, 2, or 3 I spins. Advantages for the ratiometric study of reacting molecules and hyperpolarized initial conditions are outlined. © *2011 American Institute of Physics*. [doi:10.1063/1.3652965]

The methods of nuclear magnetic resonance (NMR) and magnetic resonance imaging (MRI) are uniquely informative for chemically specific kinetics and imaging, but are typically limited by a poor signal-to-noise ratio. Greater applicability is being enabled by methods for generating liquid samples of molecules with spin polarization of order 10^{-1} at sites with spin-lattice relaxation times of tens of seconds,[1–5] an enhancement of 10^4–10^5 over ambient temperature experiments on samples initially at equilibrium in typical high magnetic fields. The opportunity is to maximize the information content obtained from each introduction of such hyperpolarized molecules to a system of interest.

In the most common current practice,[3–8] a series of small angle pulses is used, rather than a single $\pi/2$ pulse, in order to obtain signal transients at multiple time points over a total duration limited by spin-lattice relaxation. Within this constraint, signals may be elicited at intervals chosen to optimize time resolution, sensitivity to changing concentrations, or synchronization with other phenomena such as physiological cycles. Importantly, multiple sampling at successive times allows ratiometric comparisons free of the relatively large amplitude fluctuations associated with the imperfect reproducibility of non-equilibrium polarization processes, the molecular delivery, and the state of the (living) target system.

Hyperpolarized signals are typically generated on insensitive spin 1/2 heteronuclei such as ^{13}C or ^{15}N, which are preferred for their longer relaxation times and often superior chemical specificity. Longer relaxation time allows time to transfer the highly polarized molecules from the polarizer to the system of interest and to allow time for chemical dynamics with minimum polarization loss. Nuclei with lower gyromagnetic ratios tend to have longer spin-lattice relaxation times, so the most desirable targets from the point of view of long spin lifetimes are also the least desirable from the point of view of sensitivity. The gyromagnetic ratio enters linearly in both the magnitude of the detected magnetic moment and through the proportionality of inductive signals to Larmor frequency, offsetting the gains from hyperpolarization in comparison to detection on more sensitive nuclei.

Transferring the polarization to protons[9–11] recovers this lost sensitivity[12–15] and, for the purposes of MRI, additionally allows obtaining a given spatial resolution with practical pulsed field gradient power. When N equivalent protons I couple to the heteronucleus S, this transfer is efficiently produced by the refocused insensitive nucleus enhanced by polarization transfer (INEPT) sequence[9–11] in the "reverse" direction as shown in Fig. 1(a). This strategy has previously been extended to hyperpolarized samples[12,13,15] in which the pulse sequence was designed to optimally polarize the target protons at the expense of fully depleting the heteronuclear hyperpolarization in the interrogated ensemble of molecules. This restricts the time series on such an ensemble to a single measurement of the state of the S spins with the possibility of observing that derived spin order with multiple small angle I pulses within a time comparable to the much shorter proton relaxation time. In the special case of a system with uniform chemical composition (e.g., a solution in a NMR tube), a longer time course may be generated by spatially selecting different voxels for probing a reaction with complete S to I transfer at different times.[15]

A desirable feature for more effective use of the polarization available in a single pool of hyperpolarized molecules is a process that allows partial transfer to protons while preserving most of the spin order on the original heteronucleus in any ensemble of interrogated spins. This would allow for a greater range of experiments, for instance, acquiring multiple time points for MRI of chemical dynamics in a spatially

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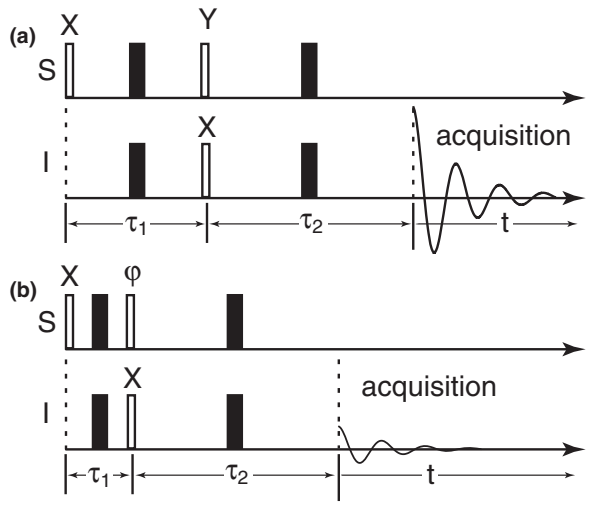

FIG. 1. Pulse sequence schematics for (a) INEPT and (b) HINDER. Filled rectangles represent π pulses and empty rectangles represent $\pi/2$ pulses in the sequence. The first evolution period τ_1 and relative phase of the second $\pi/2$ pulse on S in HINDER are optimized to leave the desired amount of polarization on S for subsequent experiments.

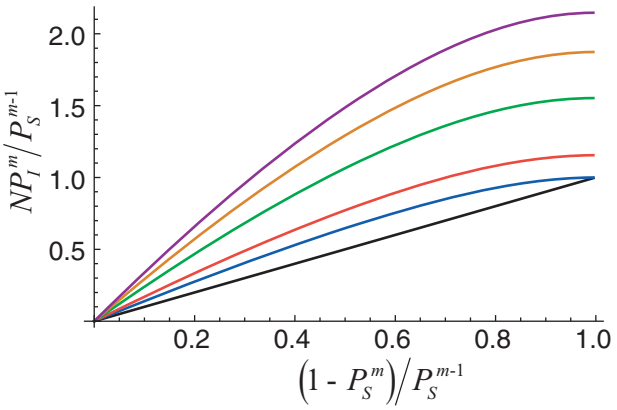

FIG. 2. Optimized spin order obtainable on N spins I as a function of the preselected fraction of S polarization used. The curves are for, from bottom to top, $N = 1, 2, 3, 6, 9, 12$.

non-uniform system. This can be achieved if it is possible to detect a fraction of the chemically exchanging polarization on sensitive protons I of product formed or precursor depleted, while continuing to accumulate reaction product under the protection of the slower S spin-lattice relaxation rate.

Here, we detail such a method[16] in which a *h*yperpolarized *i*nsensitive *n*ucleus *d*elivers *e*nhancement *r*epeatedly (HINDER). It is well known that for INEPT, the two $\pi/2$ pulses on S must have a 90° phase offset in order to fully transfer polarization to I. A 0° relative phase would lead to scrambling of the existing polarization into unwanted operators. However, when τ_1 is shortened from the value prescribed by INEPT, this second $\pi/2$ pulse serves to return some polarization to the z axis. With this degree of freedom, it is possible to divide the spin order between the two useful paths, becoming final I or S polarization, using the phase of a single pulse. These paths can be simultaneously optimized, by choosing a relative phase of the two S pulses between 0° and 90° and tuning τ_1 for a given system to minimize unwanted operators, yielding the HINDER sequence in Fig. 1(b). The sequence is repeated with the updated optimum variables for each of M desired transfers and observations as I spin transients.

When this pulse sequence is used on an $I_N S$ spin system for a series of M transfers, the polarization left on S after the mth ($1 \le m \le M$) transfer P_S^m is

$$P_S^m(\tau_1) = P_S^{m-1}\cos^N(J_{IS}\tau_1/2)\cos\phi, \tag{1}$$

where J_{IS} is the scalar coupling between S and I in radians per second. The total signal NP_I^m available for detection on I after the mth transfer is

$$NP_I^m(\tau_1,\tau_2) = P_S^{m-1}N\sin(J_{IS}\tau_1/2) \times \cos^{N-1}(J_{IS}\tau_1/2)\sin(J_{IS}\tau_2/2)\sin\phi. \tag{2}$$

This signal is optimized with respect to τ_2 when

$$\tau_2 = \pi/J_{IS}, \tag{3}$$

giving the mth signal

$$NP_I^m(\tau_1) = P_S^{m-1}N\sin(J_{IS}\tau_1/2)\cos^{N-1}(J_{IS}\tau_1/2)\sin\phi. \tag{4}$$

To choose the HINDER parameters, first specify the fraction $(1 - P_S^m)/P_S^{m-1}$ to be transferred to I according to Eq. (1), which then constrains the optimization of Eq. (4). Alternatively, the final I polarization given by Eq. (4) may be specified, constraining the optimization of Eq. (1). These points of view lead to the same optimum values of ϕ and τ_1 and the results of such an optimization are shown in Fig. 2.

The transfer efficiency $e_m = NP_I^m/(1 - P_S^m)$ for each repetition varies with the fraction of S polarization transferred for $N > 1$, as seen from Fig. 2. Note that the asymptotic value for small fractions$(1 - P_S^m)$ is $e_m = \sqrt{N}$, exceeding the efficiency of optimized INEPT and leading to the interesting observation that the summation of the I spin signal over m can also exceed the signal from optimized INEPT. This does not violate constraints of unitary time evolution, since this treatment of the overall HINDER process assumes I spin relaxation after each transfer and is thus non-unitary. This sum of signals is shown in Fig. 3 in the limit that both relaxation during the transfers and subsequent S spin-lattice relaxation are negligible, while all other spin orders either decay or are destroyed between transfers. To the extent that other relaxation processes will affect the transfer, they will need to be accounted for in a fully optimized sequence. Such optimization in the presence of relaxation has already been applied to INEPT.[17]

In utilizing this sequence in an experiment, it is repeated multiple times with an appropriate progression of parameters. Here, we illustrate the strategy for which (a) each partial transfer results in the same proton polarization and (b) the entire polarization initially available on S is eventually transferred to I for detection. The excess proton spin order on I, as well as any that is in the form of heteronuclear product operators, will be assumed to be fully dissipated by spin relaxation prior to the next HINDER transfer, an approximation that is accurate when the I spin relaxation times are much shorter than the S spin-lattice relaxation time. The fractional transfers may be determined by a recursive method starting with the final repetition $m = M$ and working backward. This final

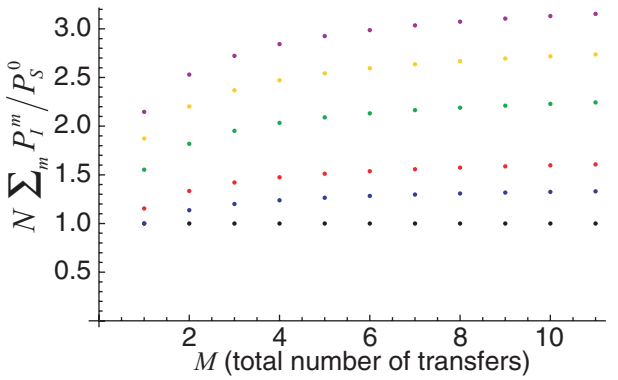

FIG. 3. Total signal delivered to N spins I when transferred in M equivalent partial transfers for, from bottom to top, $N = 1, 2, 3, 6, 9, 12$.

step should use all of the remaining polarization, so is equivalent to INEPT ($\phi = 90°$). Each prior step is then determined in turn such that the polarization generated on I is equal to that found for the next step when scaled by the polarization left on S, i.e., $P_I^m = P_I^{m+1} P_S^m$. Parameters for such a sequence for some commonly occurring cases are displayed in Table I. Since the desired signal originates on the heteronucleus, background signals can easily be reduced by presaturation of the protons prior to the HINDER sequence.

The sequence timings are calculated for the scalar couplings of a specific grouping, so the method presented is most readily optimized in experiments in which the fate of a single molecular species over time is examined. This is the case in experiments where the hyperpolarized molecule provides contrast to highlight specific areas,[18,19] such as vascular imaging. This is also the case when a specific molecule generated from the hyperpolarized molecule is of interest, as in the imaging of plaques where the bound molecule is the interesting species[12,20] or in cases where the information of interest is the changing concentration or distribution of a particular metabolite. In cases of metabolite mapping where more than one of the daughter molecules of the hyperpolarized species is of interest, this technique will also work efficiently when the daughter molecules fortuitously require similar parameters for the polarization transfer. Otherwise, the relative concentrations of species as shown by the magnitude of the peaks will be distorted by the inconsistent polarization transfer within the differing molecules. However, this distortion is consistent and calculable. In these cases, the situation may be improved by similar adaptation of a variation of INEPT[21] meant to be less dependent on the specific coupling constants in the molecule.

TABLE I. Values determined for ϕ and $J_{IS}\tau_1$ that will yield a series of $M \leq 10$ partial transfers, starting at $m = 1$ as determined by selecting M, and continuing to $m = M$. These transfers give equivalent final proton enhancement in the case that T_1^{-1} on the heteronucleus is negligible and the order besides S_z decays or is destroyed prior to subsequent transfers.

	$N = 1$		$N = 2$		$N = 3$	
m	ϕ (°)	$J_{IS}\tau_1$	ϕ (°)	$J_{IS}\tau_1$	ϕ (°)	$J_{IS}\tau_1$
$M-9$	18.435	0.644	18.050	0.442	17.980	0.358
$M-8$	19.471	0.680	19.033	0.465	18.956	0.377
$M-7$	20.705	0.723	20.199	0.493	20.112	0.400
$M-6$	22.208	0.775	21.614	0.527	21.515	0.426
$M-5$	24.095	0.841	23.382	0.569	23.268	0.460
$M-4$	26.565	0.927	25.681	0.623	25.549	0.503
$M-3$	30	1.047	28.855	0.696	28.698	0.562
$M-2$	35.264	1.231	33.680	0.806	33.492	0.648
$M-1$	45	1.571	42.558	0.997	42.353	0.799
M	90	3.142	90	1.571	90	1.231

The strategy used in the construction of this sequence could be applied to other order transfer sequences, possibly also leading to improvements over the usual methods. The recognition herein of the possibility and advantages of such an efficient partial polarization sequence, together with known (numerical and analytical) strategies for optimizing a pulse sequence for a particular final state, comprises a design strategy enabling other such sequences. The starting point for such a design strategy could be other sequences for spin order transfer between groups of like or unlike spins.

A number of modifications applicable to INEPT have been shown to improve the sequence under certain circumstances and are applicable to HINDER. One such improvement is the use of a refocus period[10] incorporated into the sequence, which may be further optimized taking relaxation into account.[17] Phase cycling may be used to suppress unwanted signal from equilibrium polarization.[22] When phase cycling is undesirable, pulsed field gradients[23,24] provide a good alternative for selecting specific magnetization for detection and destroying undesirable coherences. When there are additional, inequivalent protons, selective recoupling[14,15] will help direct the polarization to the intended protons. The chemical shift range of heteronuclei may require the application of more broadband inversion pulses.[25]

There are potential applications for this partial transfer in non-hyperpolarized systems studied by NMR and MRI. A number of experiments prepare the spin order into a non-equilibrium state, allow some interesting dynamics to proceed, and finally convert that state to transverse magnetization for readout. The HINDER approach enables experiments in which long-lived Zeeman polarization, prepared once, is probed at multiple times. This would represent the time savings and improved time resolution over the conventional method when there is sufficient signal. Furthermore, it achieves signal-to-noise advantages associated with the ability to compare the ratio of successive measurements resulting from the same initial reservoir of spin order, regardless of whether that order results from an equilibrium or non-equilibrium process.

A method by which a specific fraction of polarization may be transferred from a heteronucleus to coupled equivalent protons for more sensitive detection while the majority of the polarization is placed back on the heteronucleus for later utilization has been detailed. The HINDER strategy enables high sensitivity ratiometric single scan dynamics for molecules in diverse and complex reaction environments, including *in vivo*.

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