

# An Optimal Pulse Sequence for Parahydrogen-Induced Polarization of Heteronuclei

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**Introduction:** Parahydrogen, the nuclear singlet state of H<sub>2</sub>, is extremely long-lived and is straightforward to create. Following a hydrogenation of an unsaturated precursor molecule, this high degree of nuclear spin order can be transferred to polarization of a nearby heteronucleus, resulting in detectable spectra of reaction intermediates or greatly increased MRI/MRS signals. Field cycling or NMR pulse-based methods<sup>[1-2]</sup> have previously been proposed and implemented to achieve this transfer. In this abstract, we introduce an optimized pulse sequence which maximizes final heteronuclear polarization and minimizes the effect of T<sub>2</sub>-like decoherence and pulse imperfections. A closed form solution for pulses and delays simplifies sequence design.

**Method:** We restrict our treatment to cases in which nuclear interactions other than those between the para protons and the heteronucleus can be ignored. This is achieved in practice by locally substituting <sup>2</sup>H for <sup>1</sup>H in the precursor molecule. The rapidly reoriented molecule in solution is then described by a Zeeman energy for each nucleus and a scalar coupling between each pair of nuclei (terms representing large energy separations, e.g. *S<sub>1</sub>I<sub>2</sub>*, are greatly suppressed and have therefore been omitted):

$$\frac{H}{\hbar} = \omega_p(S_{1z} + S_{2z}) + \omega_c I_z + 2\pi(J_{12}S_1 \cdot S_2 + J_{1c}I_z S_{1z} + J_{2c}I_z S_{2z}) \quad \text{eq. 1}$$

Post-hydrogenation evolution then begins from the density matrix of eq. 2.

$$\rho(0) = \frac{1}{8} - \frac{S_1 \cdot S_2}{2} \quad \text{eq. 2}$$

In solving the Schrödinger equation, it is convenient to expand  $\rho(t)$  in terms of the sixty-four orthogonal matrices

$$\rho_{pqr} = I_p \otimes S_{1,q} \otimes S_{2,r}$$

in which the indices take values of o, x, y, and z, and  $S_o = I_o = \frac{1}{2} \times$  the unit operator. In this

basis, the initial state is  $\rho_{ooo} - \rho_{ozz} - \rho_{oxx} - \rho_{oyy}$ , and the time evolution consists of four terms:

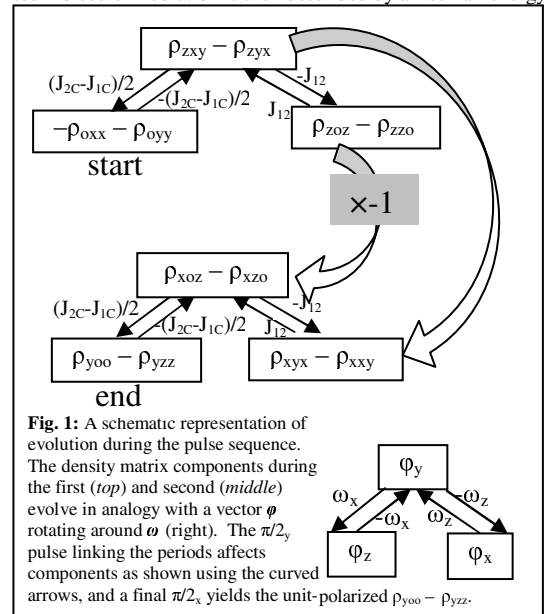
$$\rho(t) = c_0(\rho_{ooo} - \rho_{ozz}) + c_1(t)(-\rho_{oxx} - \rho_{oyy}) + c_2(t)(\rho_{xyx} - \rho_{zyx}) + c_3(t)(\rho_{zox} - \rho_{zox}) \quad \text{eq. 3}$$

The coefficients evolve according to the differential equations

$$\dot{c}_0 = 0, \quad \dot{c}_1 = \pi(J_{1c} - J_{2c})c_2, \quad \dot{c}_2 = -\pi(J_{1c} - J_{2c})c_1 - 2\pi J_{12}c_3, \quad \dot{c}_3 = 2\pi J_{12}c_2 \quad \text{eq. 4}$$

with the initial conditions  $c_1=1, c_2=c_3=0$ . We may control the evolution through selective application of heteronuclear inversion pulses, which invert  $c_2$  and  $c_3$ , but leave  $c_1$  unchanged.

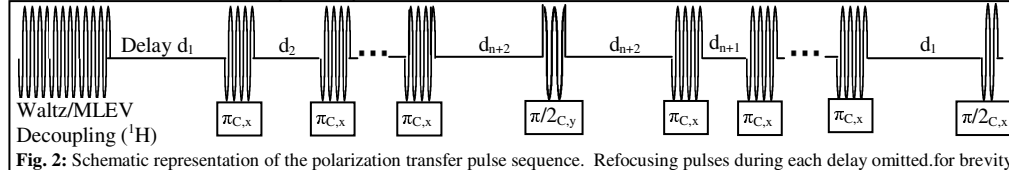
As was noted in ref. [2], the equations governing the evolution of the latter three coefficients are identical to those describing the motion of a unit vector originating along the +z axis and precessing around the vector  $\hat{\omega} = \pi(J_{2c} - J_{1c})\hat{x} + 2\pi J_{12}\hat{z}$ . (shown pictorially in fig. 1, bottom right). It is always possible to use this strategy to eliminate  $c_1$  and end this evolution with  $c_2=c_3$ . If we then put the heteronucleus into the transverse plane, evolution proceeds according to an identical set of differential equations (figure 1, middle), and a symmetric set of inversion pulses and delays will lead to the state  $\rho_{yoo} - \rho_{yzz}$ . A final  $\pi/2$  rotation leaves the heteronucleus with unity polarization.



**Fig. 1:** A schematic representation of evolution during the pulse sequence. The density matrix components during the first (top) and second (middle) evolve in analogy with a vector  $\phi$  rotating around  $\omega$  (right). The  $\pi/2_y$  pulse linking the periods affects components as shown using the curved arrows, and a final  $\pi/2_x$  yields the unit-polarized  $\rho_{yoo} - \rho_{yzz}$ .

## Results and Discussion:

The full “polarization transfer” pulse sequence is then as shown below:



**Fig. 2:** Schematic representation of the polarization transfer pulse sequence. Refocusing pulses during each delay omitted for brevity.

In this scheme, the decoupling pulse train delays evolution to synchronize molecules hydrogenated at different times. The subsequent pulses are all at the heteronuclear frequency with the specified rotation angle and axis. Optimal delays are calculated as below.

Let  $\delta = J_{1c} - J_{2c}$ ,  $\theta = \tan^{-1}(\delta/2J_{12})$ , and  $\omega = \sqrt{J_{12}^2 + \delta^2}/4$ . In the formulas below, choose the lowest  $n$  such that  $d_{n+1}$  is real, and  $d_{1...n} = \pi/\omega$ .

$$\text{If } \theta \geq \tan^{-1}(\sqrt{2}), d_{n+1} = \frac{1}{\omega} \cos^{-1} \left( -\frac{\cos([2n+1]\theta) \cos(2\theta) + (-1)^n \sin \theta / \sqrt{2}}{\sin(2\theta) \sin([2n+1]\theta)} \right), d_{n+2} = \frac{1}{\omega} \cos^{-1} \left( \frac{(-1)^n \sqrt{2} \{ \cos([2n+1]\theta) + 2 \sin([2n+1]\theta) \sin(\theta) \sin(\alpha_{n+1}) \} + \sin(\theta) \cos(2\theta)}{2 \sin(\theta) (1 + \cos^2(\theta))} \right)$$

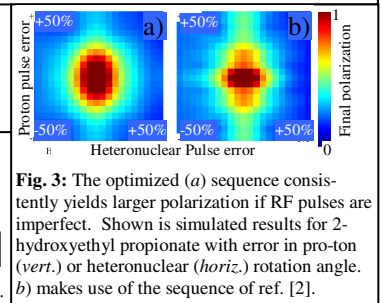
$$\text{If } \theta < \tan^{-1}(\sqrt{2}), d_{n+1} = \frac{1}{\omega} \cos^{-1} \left( -\frac{\cos([2n+1]\theta) \cos(2\theta) - \sin(\theta) / \sqrt{2}}{\sin(2\theta) \sin([2n+1]\theta)} \right), d_{n+2} = \frac{\pi}{\omega} + \frac{1}{\omega} \sin^{-1} \left( \frac{\sqrt{2} \{ -\cos([2n+1]\theta) + \sin([2n+1]\theta) \sin(2\theta) \cos(\theta) \sin(\alpha_{n+1}) \} + \sin(\theta) \cos(2\theta)}{\sin(2\theta) (1 + \cos^2(\theta))} \right)$$

This sequence is optimal in the sense that the total evolution time is minimized, thereby minimizing T<sub>2</sub>-like decoherence during the sequence (a negligibly shorter solution can be found which does not lend itself to closed-form expression). In addition, the effect of pulse imperfections is minimized both by limiting the number of pulses and as a result of the symmetry of the sequence (see fig. 3).

**Conclusion:** We have presented a closed-form expression for the sequence of pulses which optimizes final polarization of a heteronucleus derived from a para proton pair in a three-spin system. Only under unexpected circumstances (e.g., drastically differing decoherence rates among density matrix components) will this sequence be substantially sub-optimal.

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[1] Haake, Natterer and Bargon, *J. Am. Chem. Soc.*, **118** (36), 8688-8691, 1996 [2] Goldman, Jóhannesson, Axelsson and Karlsson, *Comptes Rendus Chimie*, **9** (3-4), 357-363 (2006).



**Fig. 3:** The optimized (a) sequence consistently yields larger polarization if RF pulses are imperfect. Shown is simulated results for 2-hydroxyethyl propionate with error in proton (vert.) or heteronuclear (horiz.) rotation angle. (b) makes use of the sequence of ref. [2].