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Two pulse recoupling

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ABSTRACT

The paper describes a family of novel recoupling pulse sequences in magic angle spinning (MAS) solid state NMR, called two pulse recoupling. These pulse sequences can be employed for both homonuclear and heteronuclear recoupling experiments and are robust to dispersion in chemical shifts and rf-inhomogeneity. The homonuclear pulse sequence consists of a building block $(\pi)_{\phi}(\pi)_{-\phi}$ where $\phi = \frac{\pi}{4n}$, and n is number of blocks in a rotor period. The recoupling block is made robust to rf-inhomogeneity by extending it to $(\pi)_{\phi}(\pi)_{-\phi}(\pi)_{\pi+\phi}(\pi)_{\pi-\phi}$. The heteronuclear recoupling pulse sequence consists of a building block $(\pi)_{\phi_1}(\pi)_{-\phi_1}$ and $(\pi)_{\phi_2}(\pi)_{-\phi_2}$ on channel I and S, where $\phi_1 = \frac{3\pi}{8n}, \phi_2 = \frac{\pi}{8n}$ and n is number of blocks in a rotor period. The recoupling block is made robust to rf-inhomogeneity by extending it to $(\pi)_{\phi_1}(\pi)_{-\phi_1}(\pi)_{\pi+\phi_1}(\pi)_{\pi-\phi_1}$ and $(\pi)_{\phi_2}(\pi)_{-\phi_2}(\pi)_{\pi+\phi_2}(\pi)_{\pi-\phi_2}$ on two channels respectively. The recoupling pulse sequences mix the z magnetization. Experimental quantification of this method is shown for $^{13}C_{\alpha}$-^{13}CO homonuclear recoupling in a sample of Glycine and ^{15}N-$^{13}C_{\alpha}$ heteronuclear recoupling in Alanine. Application of this method is demonstrated on a sample of tripeptide N-formyl-[U-^{13}C,^{15}N]-Met-Leu-Phe-OH (MLF). Compared to R-sequences (Levitt, 2002), these sequences are more robust to rf-inhomogeneity and give better sensitivity, as shown in Fig. 3.

1. Introduction

Nuclear magnetic resonance (NMR) spectroscopy opens up the possibility of studying insoluble protein structures such as membrane proteins, fibrils, and extracellular matrix proteins which are difficult to analyze using conventional atomic-resolution structure determination methods, including liquid-state NMR and X-ray crystallography [1–6]. Recoupling pulse sequences that enable transfer of magnetization between coupled spins is the workhorse of all these experiments, either as a means to obtain structural information (e.g., internuclear distances) or as a means to improve resolution as building blocks in multiple-dimensional correlation experiments. The present paper describes some new methodology development for design of recoupling pulse sequences and demonstration of their use in correlation experiments.

To put this work in proper context, and motivate the proposed new methodology, we look at development of dipolar recoupling. The work of Tycko [7–9] on **DRAMA** initiated homonuclear dipolar recoupling methods in solids. This was followed by methods like **Rotational Resonance** [10,11] and **RFDR** [12]. Later came gamma encoded recoupling in **HORROR** [13], and its adiabatic version **DREAM** [14]. Further developments include, **DRAWS** [15] and **MELODRAMA** [16]. Subsequently, there was development of **C7** [17], **POSTC7** [19], **SPC5** [18] and **CMR7** [20]. Recently Levitt [24] and co-workers have further developed symmetry based pulse sequences. Some new work in recoupling includes, **CMRR** [28,29], phase alternating recoupling [25] and most recently **TPR** and **FPR** recoupling [21,22]. If we study sequences like **C7**, **POSTC7**, **SPC5**, **CMR7**, **Symmetry sequences**, **CMRR** and **TPR** and **FPR** recoupling, we find they have a common design principle. A strong rf-field is used to eliminate chemical shifts and make the sequence broadband. Furthermore, this strong rf-field is used to demodulate a second oscillating field which performs recoupling. The second oscillating field comes about by principled phase changes in these sequences. To add to this family, we propose in this paper, a new two phase modulated recoupling, we call **TOPR**. The sequence is interesting from simplicity of its design for broadband recoupling and robustness to rf-inhomogeneity. Compared to symmetry based R-sequences, [24] these sequences are more robust to rf-inhomogeneity and give better sensitivity, as shown in Fig. 3. Furthermore, **TOPR** adds to our repertoire of recoupling sequences and to our understanding of recoupling which is fundamental to solid state NMR.

The paper is organized as follows. In Section 2, we describe **TOPR**, a novel approach to homonuclear recoupling that recouple

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dipolar coupled spins under Magic angle spinning (MAS) experiments. **TOPR** experiments are broadband and robust to rf-inhomogeneity. This work extends recently developed techniques for broadband homonuclear recoupling as reported in the [21,25,26,28–30]. In Section 3, we describe these methods in the context of heteronuclear experiments. In the context of heteronuclear spins, the recoupling is achieved by matching the syncronized phases on the two rf-channels (analogous to Hartmann-Hahn matching of the rf-power commonly seen in heteronuclear recoupling experiments [31]). Section 4 describes experimental verification of the proposed techniques. We conclude in Section 5 by comparing **TOPR** with state of the art pulse sequences.

2. TOPR in homonuclear spins

Consider two homonuclear spins, I and S, under magic angle spinning condition [13]. In a rotating frame, rotating with both the spins at their common Larmor frequency, the Hamiltonian of the spin system takes the form

$$H(t) = \omega_I(t)I_z + \omega_S(t)S_z + \omega_{IS}(t)(3I_zS_z - I\cdot S) + 2\pi A(t) \times (\cos\phi(t)F_x + \sin\phi(t)F_y), \quad (1)$$

where the operator $F_x = I_x + S_x$, and $\omega_I(t)$ and $\omega_S(t)$ represent the chemical shift for the spins I and S respectively and $\omega_{IS}(t)$ represents the time varying couplings between the spins under magic-angle spinning. These interactions may be expressed as a Fourier series,

$$\omega_\lambda(t) = \sum_{m=-2}^{2} \omega_\lambda^m \exp(im\omega_r t), \quad (2)$$

where ω_r is the spinning frequency (in angular units), while the coefficients ω_λ $(\lambda = I, S, IS)$ reflect the dependence on the physical parameters like the isotropic chemical shift, anisotropic chemical shift, the dipole-dipole coupling constant and through this the internuclear distance [6].

The term $I\cdot S$ in (1), commutes with the rf-field Hamiltonian, and in the absence of the chemical shifts, it averages to zero under MAS.

Consider the pulse sequence, made of building block

$$(\pi)_\phi(\pi)_{-\phi},$$

with n such blocks in a rotor period and $\phi = \frac{\pi}{4n}$. This means amplitude A of pulses is $2\pi A = C = n\omega_r$ and phase $\phi(t)$ alternates between $\phi = \frac{\pi}{4n}$ and $-\phi$ every $\frac{\tau_c}{2} = \frac{\pi}{C}$ units of time as shown in Fig. 1, where τ_c is duration of building block. We can think of phase as starting from zero and jumping to value ϕ at $t = 0$ and then jumping to $-\phi$ at $t = \frac{\tau_c}{2}$ and then returning to 0 at $t = \tau_c$ and this cycle continues as shown in Fig. 1A.

Over one building block, the rate of change of phase $\dot\phi$ takes the form,

$$\dot\phi(t) = \frac{C\pi}{4n}[\delta(Ct) - \delta(Ct-\pi) + \delta(Ct-2\pi)], \quad (3)$$

where $\delta(t)$ is a delta function $(\int_0^t f(\tau)\delta(\tau)d\tau = \int_{-t}^0 f(\tau)\delta(\tau)d\tau = \frac{1}{2}\int_{-t}^t f(\tau)\delta(\tau)d\tau = f(0)$ for $t > 0$). See Fig. 1B.

In the modulation frame of the phase $\phi(t)$, the rf-field Hamiltonian takes the form

$$H^{rf}(t) = CF_x - \dot\phi F_z, \quad (4)$$

where C is in the angular frequency units and we choose $C \gg \omega_I(t), \omega_S(t), \omega_{IS}(t), \omega_r$. In the interaction frame of the irradiation along x axis, with the strength C, the chemical shifts of the spins are averaged out. The rf-field Hamiltonian of the spin system transforms to

$$H_I^{rf}(t) = -\underbrace{\frac{C\pi}{4n}(\delta(Ct) - \delta(Ct-\pi) + \delta(Ct-2\pi))}_{\dot\phi(t)}(F_z\cos(Ct) + F_y \times \sin(Ct)), \quad (5)$$

which accumulates an integral only when delta function peaks at $Ct = 0, Ct = \pi$ and $Ct = 2\pi$. The net rf rotation generated by $H_I^{rf}(t)$ is therefore $-\frac{\pi}{n}F_z$, which corresponds to a phase advance of $\frac{\pi}{4n}$ at $Ct = 0$ and $Ct = 2\pi$ and phase decrement of $\frac{\pi}{2n}$ at $Ct = \pi$ (a negative phase decrement is multiplied by $\cos(\pi)$, which makes it a positive accumulation). See Fig. 1C. A net rotation of $\frac{\pi}{n}$ in time $\tau_c = \frac{\tau_r}{n}$ corresponds to a net effective field of $\frac{\omega_r}{2}$ along $-z$ direction. This field recouples, as field of strength $\frac{\omega_r}{2}$ is a recoupling field.

As an example, if we choose $C = 6\omega_r$, with $n = 6$, **TOPR** takes the form

$$(\pi)_{7.5^\circ}(\pi)_{-7.5^\circ}.$$

When pulse amplitude has inhomogeneity, such that rf-field strength instead of C is $C(1+\epsilon)$, then, in the modulation frame of the phase $\phi(t)$, the rf-field Hamiltonian takes the form

$$H^{rf}(t) = C(1+\epsilon)F_x - \dot\phi F_z. \quad (6)$$

In the interaction frame of the irradiation along x axis, with the strength C, the rf-field Hamiltonian of the spin system transforms to

$$H_{I_a}^{rf}(t) = \epsilon CF_x - \underbrace{\frac{C\pi}{4n}(\delta(Ct) - \delta(Ct-\pi) + \delta(Ct-2\pi))}_{\dot\phi(t)}(F_z\cos(Ct) + F_y\sin(Ct)), \quad (7)$$

which has an additional factor of ϵCF_x coming from rf-inhomogeneity, which over a building block, accumulates to first order an evolution $\epsilon 2\pi F_x - \frac{\pi}{n}F_z$, which for an inhomogeneity of $\epsilon = .05$ and $n = 6$, corresponds to an evolution $\frac{\pi}{10}F_x - \frac{\pi}{6}F_z$. Presence of additional factor $\frac{\pi}{10}F_x$, limits the transfer efficiency. This inhomogeneity factor can be canceled by following this building block with a building block of amplitude $-C$ (adding 180° to all phases).

In the interaction frame of the irradiation along x axis, with the strength $-C$, the rf-field Hamiltonian of the spin system transforms to

$$H_{I_b}^{rf}(t) = -\epsilon CF_x - \underbrace{\frac{C\pi}{4n}(\delta(Ct) - \delta(Ct-\pi) + \delta(Ct-2\pi))}_{\dot\phi(t)} \times (F_z\cos(Ct) - F_y\sin(Ct)), \quad (8)$$

Which accumulates an integral only when delta function peaks at $Ct = 0, 2\pi$ and $Ct = \pi$. The net rf rotation is therefore $-\frac{\pi}{n}F_z - \epsilon 2\pi F_x$. The $-\epsilon CF_x$ in $H_{I_b}^{rf}$ cancels ϵCF_x in $H_{I_a}^{rf}$ to first order.

The $-C$ amplitude may be implemented with a two pulse element (for $n = 6$)

$$(\pi)_{187.5^\circ}(\pi)_{172.5^\circ}.$$

The total compensated pulse sequence takes the form

$$(\pi)_{7.5^\circ}(\pi)_{-7.5^\circ}(\pi)_{187.5^\circ}(\pi)_{172.5^\circ}.$$

We have calculated $\int_0^{\tau_c} H_{I_a}^{rf}(t)dt$ and $\int_0^{\tau_c} H_{I_b}^{rf}(t)dt$, which are first order contributions to generated rotation by time varying Hamiltonian $H_{I_a}^{rf}(t)$ and $H_{I_b}^{rf}(t)$. We can calculate the second order terms, by writing evolution of $H_{I_a}^{rf}(t)$ and $H_{I_b}^{rf}(t)$ as,