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Homonuclear decoupled proton NMR spectra in modest to severe inhomogeneous fields via distant dipolar interactions

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ABSTRACT

On the basis of distant dipolar interactions, two new pulse sequences were proposed to obtain homonuclear broadband-decoupled proton NMR spectra in modest to severe inhomogeneous fields with time efficient acquisitions. Theoretical expressions for signals were derived according to the distant dipolar field (DDF) treatment combined with the product operator formalism. The measurements under either moderate (~0.4 ppm) or severe (~7 ppm) field inhomogeneity in a 500 MHz spectrometer show that the new sequences are complementary to each other and provide an attractive way to eliminate the influences of field inhomogeneities on homonuclear decoupled proton spectra.

1. Introduction

Nuclear magnetic resonance (NMR) spectroscopy has been applied for identification and quantification of molecular structures in chemical and biological samples [1–3]. The resonance assignment of metabolites and quantification of their concentrations in the proton NMR spectra of biological samples are extremely meaningful for *in vivo* and *in vitro* studies [4,5]. However, in proton NMR spectra of complex systems, crowded resonances and line splittings due to scalar coupling between spins often hamper the resonance assignment and quantification. Decoupled proton NMR spectra containing only singlets for chemically distinct protons and free of the influence of scalar coupling is usually utilized to simplify crowded spectra and extract quantitative information. The decoupled spectroscopy also holds advantages in the enhancement of signal-to-noise ratio (SNR) and more accurate measurements of spin–lattice and spin–spin relaxation rates and diffusion coefficients [6]. Decoupling technique is also a common and powerful tool for ^{13}C NMR spectroscopy [7,8].

A number of techniques have been developed to obtain decoupled proton spectra. The first method was proposed by Aue et al. [9], which was based on the mechanism of 2D *J*-resolved spectroscopy. Improved versions of this method were subsequently proposed [10–13]. Based on *z*-COSY [14], the broadband-decoupled proton spectroscopy with pure absorption lineshape and correct peak integrals was proposed by Pell et al. [15]. Based on the constant time (CT) principle, the CT-PRESS method was put forward to allow the detection of *in vivo* proton spectra with effective homonuclear decoupling [16]. In addition, some data post-processing methods were established to obtain decoupled proton spectra [17–19]. All the existing decoupling approaches provide complementary strategies for simplifying spectra and eliminating peak overlap. However, most of these techniques are only feasible under homogeneous magnetic field and their spectral qualities are generally demolished by magnetic field inhomogeneity since it is often conventional single-quantum coherences (SQCs) that evolve in the evolution periods of these decoupled sequences. Although shimming techniques have been developed to remove field inhomogeneities, there are many circumstances where the magnetic field homogeneities are degraded due to variations in magnetic susceptibilities, and these inhomogeneities usually cannot be completely eliminated by conventional shimming methods.

The effect of distant dipolar field (DDF) has long been recognized [20,21]. The DDF is the source of intermolecular multiple-quantum coherences (iMQCs) which contain information of dipole–dipole coupled spins within the dipolar correlation distance [22,23]. The iMQC signals have been shown to be intrinsically insensitive to the field inhomogeneities and have been used to achieve high-resolution spectra in inhomogeneous fields [24–26]. In this study, two new pulse sequences, named DDF Decoupling-1 (DDF-D1) and DDF Decoupling-2 (DDF-D2), were proposed to obtain broadband-decoupled proton spectra in modest to severe inhomogeneous fields with high acquisition efficiency. The

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DDF-D1 sequence is more suitable for modest inhomogeneous fields since it is based on homonuclear distant dipolar interaction, while the DDF-D2 sequence is useful in severe inhomogeneous fields since it is based on heteronuclear distant dipolar interaction. In contrast to the aforementioned decoupled techniques [9–16], a fundamental requirement of the new approaches is that one component of the sample (e.g. solvent) contains a concentrated magnetization to generate a DDF.

2. Theories and methods

The DDF-D1 and DDF-D2 sequences are schematically shown in Fig. 1. In the DDF-D1, the first and third RF pulses are solvent-selective, while the second RF pulse is solute-selective. Three linear coherence selection gradients (CSGs) are applied along the z-direction to select the coherence transfer pathway $0 \rightarrow +1 \rightarrow +2 \rightarrow +1 \rightarrow -1$. The first CSG can greatly suppress the radiation damping effects during the t_1 period. The CT scheme [16] is utilized during the t_1 period to achieve J decoupling, in which the minimum value for the echo time Δ is $-t_1^{\max}/2$. Since solute and solvent spins are in the same channel and solvent-selective RF pulses are used for DDF, the maximum allowed field inhomogeneity is related to the difference between the chemical shifts of solvent and its nearest solute peak [27], suggesting that the application of this sequence is limited to small to modest inhomogeneous fields. For severe inhomogeneous fields, the DDF-D2 sequence was designed. In the DDF-D2, the solute and solute spins are excited in different RF transmit channels (^{1}H channel for solute spins and X channel for solvent spin), thus the solvent-selective RF pulses are unnecessary and the excitation of solvent spin is not disturbed by the overlap of solvent and solute peaks. Similarly, three CSGs are applied along the z-direction to select the same coherence transfer pathway. In addition, the foldover correction (FOC) scheme [28,29] is used to process the spectra from the two sequences to improve acquisition efficiency.

Theoretical expressions for signals resulting from the new sequences are derived according to the DDF treatment [30,31] combined with the product operator formalism. A similar derivation can be found in the previous study [32]. Without losing generality, we consider a homogeneous liquid mixture consisting of S and I components. S is an AX spin-1/2 system (including S_k and S_l spins with a scalar coupling constant J_{kl}) and I is an isolated spin-1/2 system. I (corresponding to solvent) is abundant and S (corresponding to solute) is either abundant or dilute. Assume that ω_m is the frequency offset of spin m ($m = I, S_k, S_l$) in the rotating frame in the absence of field inhomogeneity. For simplification, the effects of radiation damping, diffusion, relaxation, and intermolecular NOE are ignored. The magnetic field is assumed to be only inhomogeneous along the z-direction, and $\Delta B(z)$ is the field inhomogeneity at position z. When the DDF-D1 sequence is applied, the DDFs $B_d^I(z)$ and $B_d^S(z)$ experienced by the I and S spins at position z, respectively, can be expressed as

$$\begin{aligned} B_d^I(z) &= -\frac{\Delta_s}{\gamma\tau_d}\cos[\omega_I t_1 + \gamma\Delta B(z)t_1 + 1.7\gamma G\delta z], \\ B_d^S(z) &= \frac{2}{3}B_d^I(z) = -\frac{2\Delta_s}{3\gamma\tau_d}\cos[\omega_I t_1 + \gamma\Delta B(z)t_1 + 1.7\gamma G\delta z], \end{aligned} \quad (1)$$

where $\tau_d^I = (\gamma\mu_0 M_0^I)^{-1}$ is the dipolar demagnetizing time of I spins, in which γ is the gyromagnetic ratio for proton, μ_0 is vacuum magnetic permeability and M_0^I is the equilibrium magnetization per unit volume of I spin; G and δ are strength and duration of the first CSG, respectively; $\Delta_s = [3(\hat{\mathbf{s}}\cdot\hat{\mathbf{z}})^2 - 1]/2$, in which $\hat{\mathbf{s}}$ is the unit vector along the CSG direction, and $\hat{\mathbf{z}}$ is the unit vector along the direction of static magnetic field. Since the gradient field is oriented along the z-direction, i.e. $\hat{\mathbf{s}} = \hat{\mathbf{z}}$, we have $\Delta_s = 1$.

Under the effect of DDFs, the observable transverse magnetization is deduced to be (see Supplementary material for detail derivation)

$$\begin{aligned} M_+(t_1+t_2,z) = {} & \frac{M_0^I}{2i}\sum_{m=-\infty}^{\infty} i^m J_m(\xi_1) \\ & \times \left\{ e^{i[1.7(m+1)\gamma G\delta z + 2.4\gamma G\delta z + \omega_I t_2 + \gamma\Delta B(z)t_2 + (m+2)\omega_I t_1 + (m+2)\gamma\Delta B(z)t_1]} \right. \\ & \left. - e^{i[1.7(m-1)\gamma G\delta z + 2.4\gamma G\delta z + \omega_I t_2 + \gamma\Delta B(z)t_2 + m\omega_I t_1 + m\gamma\Delta B(z)t_1]} \right\} \\ & + \frac{iM_0^S\cos(2\pi J_{kl}\Delta)}{2}\left(e^{i\pi J_{kl}t_2} - e^{-i\pi J_{kl}t_2}\right)\sum_{m_1=-\infty}^{\infty} i^{m_1} J_{m_1}(\xi_2) \\ & \times e^{i[1.7(m_1+1)\gamma G\delta z + m_1\omega_I t_1 + \omega_{S_k}t_1 + \omega_{S_k}t_2 + \gamma\Delta B(z)t_2 + (m_1+1)\gamma\Delta B(z)t_1]}, \end{aligned} \quad (2)$$

where M_0^S is the equilibrium magnetization per unit volume of S spin, $J_m(\xi_1)$ and $J_{m_1}(\xi_2)$ are the Bessel functions [33] with integer orders m and m_1, respectively, and $\xi_1 = \gamma\mu_0 M_0^I(2\Delta + t_2)$ and $\xi_2 = \frac{2}{3}\xi_1$. In order to evaluate the detectable signals from the whole sample, an average of the complex magnetization over all z positions should be taken. If the sample size is much larger than the dipolar correlation distance $d_c = \pi/(\gamma G\delta)$, the spatial averaging across the sample causes the signals to vanish unless $1.7(m \pm 1) = -2.4$ for the first term (signals for I spin) and $m_1 = -1$ for the second term (signals for S_k spin) in Eq. (2), which are independent of the absolute position in the sample. Since no integer m satisfies the equation $1.7(m \pm 1) = -2.4$, the signals originated from I spin disappear during the period t_2. When $m_1 = -1$, the observable signals from S_k spin at the detection period is given as

$$\begin{aligned} M_+^{S_k}(t_1+t_2,z) = {} & \frac{-M_0^S\cos(2\pi J_{kl}\Delta)}{2} J_1\left(\frac{2}{3}\gamma\mu_0 M_0^I(2\Delta + t_2)\right) \\ & \times e^{-i(\omega_I - \omega_{S_k})t_1} e^{i[\omega_{S_k} \pm \pi J_{kl} + \gamma\Delta B(z)]t_2}. \end{aligned} \quad (3)$$

Eq. (3) provides a quantitative description for the signal from the DDF-D1 sequence. If ΔB is the width of the spatially dependent field inhomogeneity along B_0 direction, the signal is located at $(\omega_I - \omega_{S_k}, \omega_{S_k} \pm \pi J_{kl} + \gamma\Delta B)$. When the spectrometer reference frequency coincides with the resonance frequency of I spin in B_0 field, i.e. $\omega_I = 0$, the location becomes $(-\omega_{S_k}, \omega_{S_k} \pm \pi J_{kl} + \gamma\Delta B)$. It can be noticed that in the resulting 2D spectrum, the signals are free of field inhomogeneities and J couplings in the F1 dimension. All the peaks extend as streaks parallel to the F2 axis and row up along the anti-diagonal direction. A decoupled proton spectrum can be obtained by projecting the 2D spectrum onto the F1 dimension. All the chemical shifts of solutes in this decoupled spectrum are reversed, which does not satisfy the requirement of decoupled proton spectra. In addition, this approach requires a long time for data acquisition since sampling of the full range of solute chemical

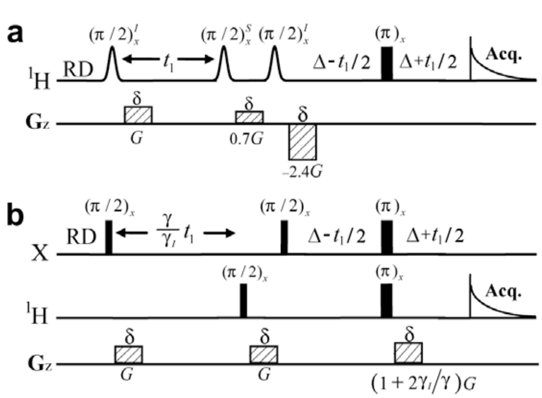

Fig. 1. Pulse sequences for decoupled proton spectra in inhomogeneous fields. (a) DDF-D1, and (b) DDF-D2. Related parameters are defined in the context.