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Low-power homonuclear dipolar recoupling in solid-state NMR developed using optimal control theory

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Abstract

Novel low-power pulse sequences for homonuclear dipolar recoupling in biological solid-state NMR spectroscopy are presented. The pulse sequences are developed numerically using the Simpson simulation program in combination with optimal control procedures. The quality criteria for the experiment optimizations are the achievement of the highest possible sensitivity for powder samples under typical experimental inhomogeneous radio-frequency (rf) field conditions, while keeping the rf field strength sufficiently low to prevent undesirable sample heating in biological applications. The new dipolar recoupling methods are demonstrated numerically and experimentally by double-quantum filtration magic-angle spinning NMR experiments for which sensitivity gains approaching a factor of 2 is observed.

1. Introduction

In the past few years, solid-state NMR spectroscopy has progressed significantly towards structural analysis of biological macromolecules [1–4]. This development is based on many years effort on the construction of the required methodology in the form of advanced instrumentation and pulse sequences for re- and decoupling of anisotropic nuclear spin interactions. Recent applications concern structure determination of proteins up to about 100 residues [5–11]. These results are very encouraging and may promote the breakthrough of solid-state NMR for structural analysis of 'insoluble' protein systems such as membrane proteins, fibrils/amyloids, and protein aggregates. Such proteins can not easily be brought into well-defined large crystals as needed for X-ray diffraction or into solution with fast molecular tumbling as needed for liquid-state NMR.

Recoupling of the structurally important dipole–dipole coupling in magic-angle spinning (MAS) experiments can be conducted by using γ-encoded pulse sequences such as HORROR [12], C7 [13], and numerous variants of these experiments [14–19]. The HORROR experiment benefits from the use of rf irradiation with low power, but suffers from high dependence on isotropic and anisotropic chemical shielding. Furthermore, it is quite sensitive to rf inhomogeneity. The more compensated C7-type experiments solve some of these problems, however, at the expense of dramatically increasing the power of the required rf irradiation and significantly longer times for the accomplishment of the most efficient coherence transfer. The high rf power requirements may pose impossible demands to the solid-state NMR instrumentation, in particular if efficient

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decoupling of the dipolar interactions from protons is required under high-speed MAS conditions [14,20]. In addition, strong rf may heat the sample and in worst case destroy it. We note that the sample heating problem can be reduced by using probes with resonators [21,22] instead of the commonly used solenoids.

In this Letter, we demonstrate that optimal control theory in combination with numerical simulations is a versatile tool for the design of dipolar recoupling methods coping with some of these problems. It is shown that it is possible to design pulse sequences which at the same time only consume low rf power and solve common problems induced by rf inhomogeneities and the need for recoupling experiments with well-defined excitation band-widths for typical coherence transfers in biological solid-state NMR. The goal is to develop low-power sequences with shorter coherence transfer time than adiabatic recoupling experiments [23] so that the combination with fast spinning becomes easier and losses due to relaxation can be reduced.

2. Design of dipolar recoupling experiments by optimal control

Optimal control theory [24,25] has found widespread application in economy and engineering, e.g., for optimization of the outcome of investments under specific conditions. More recently, the same tool has found successful application for the design of NMR experiments, as demonstrated in the areas of magnetic resonance imaging [26], liquid-state NMR [27–31], and solid-state NMR [32]. Addressing solid-state NMR, the major challenges to an efficient optimization protocol are the presence of anisotropic nuclear spin interactions, sample spinning, and often significant rf inhomogeneity. The combined effect from these is exceedingly difficult to handle purely by analytical means. This motivates our use of optimal control procedures [33] in combination with numerical simulation programs [34] as recently demonstrated successfully in the context of heteronuclear dipolar recoupling [32]. In this Letter, the target will be low-power recoupling of homonuclear dipole–dipole interactions under high-speed MAS conditions.

In the Zeeman interaction frame, the Hamiltonian for a simple homonuclear spin-pair system may be written as

$$H(t) = H_{\mathrm{int}}(t) + H_{\mathrm{rf}}(t) \tag{1}$$

with the high-field truncated internal and rf field Hamiltonians expressed as

$$H_{\mathrm{int}}(t) = \omega_A(t)I_{Az} + \omega_B(t)I_{Bz} + \omega_D(t)(3I_{Az}I_{Bz} - I_A\cdot I_B), \tag{2}$$

$$H_{\mathrm{rf}}(t) = \omega^x_{\mathrm{rf}}(t)I_x + \omega^y_{\mathrm{rf}}(t)I_y, \tag{3}$$

where A and B denote the two spins, $I_q = I_{Aq} + I_{Bq}$, $\omega_\lambda(t) = \sum_{m=-2}^{2}\omega_\lambda^{(m)}\mathrm{e}^{\mathrm{i}m\omega_r t}$ the chemical shift ($\lambda = A$ or B) and dipolar coupling ($\lambda = D$) frequencies (the Fourier components $\omega_\lambda^{(m)}$ can be found in [34]), ω_r the sample spinning frequency, and ω^x_{rf} and ω^y_{rf} the x and y components of the rf field amplitude.

The time evolution of the density operator from its initial state $\rho(0)$ to its value at time $T = t_N$ may be described as

$$\rho(t_N) = U_N\ldots U_2U_1\rho(0)U_1^\dagger U_2^\dagger\ldots U_N^\dagger \tag{4}$$

with the instantaneous propagator expressed as

$$U_j = \exp\{-\mathrm{i}\int_{t_j}^{t_{j+1}}(H_{\mathrm{int}}(t) + \omega^x_{\mathrm{rf},j}I_x + \omega^y_{\mathrm{rf},j}I_y)\,\mathrm{d}t\}, \tag{5}$$

where we for simplicity digitized the time evolution into N steps over each of which the x- and y-phase rf field components are kept constant.

For a given desired final spin state C, we can maximize the overall transfer efficiency $\mathrm{Tr}\{\rho(T)C^\dagger\}$ by systematically changing the rf field amplitudes according to

$$\omega^q_{\mathrm{rf},j} \to \omega^q_{\mathrm{rf},j} + \epsilon\mathrm{Tr}\{\mathrm{i}\Delta t_j[I_q,\rho(t_j)]\lambda(t_j)\}, \tag{6}$$

where $q = x$ or y, ϵ is a small real number, $\Delta t_j = t_{j+1} - t_j$, and

$$\lambda(t_j) = U^\dagger_{j+1}\ldots U^\dagger_N C U_N\ldots U_{j+1} \tag{7}$$

as described by Khaneja et al. [33]. By implementing the forward (Eq. (4)) and backward (Eq. (7)) calculation of the density operator along with a conjugated gradient optimization procedure to optimize the transfer efficiency (Eq. (6)) into the open-source Simpson program [34], it is possible to establish an efficient and highly flexible tool for automated design of optimal pulse sequences for any coherence/polarization transfer relevant for solid-state NMR applications.

Based on our experience with existing homonuclear dipolar recoupling experiments, we can specify a set of quality criteria for the design of optimal control recoupling experiments: (i) high coherence transfer efficiency, ideally between 73% and 100% being the ideal measures for γ-encoded [12] and adiabatic [23] transfer schemes, respectively, (ii) fast coherence transfer and definitely shorter pulse sequences than typically used for adiabatic transfer, (iii) low consumption of rf power to access high MAS frequencies while enabling efficient ^{1}H decoupling and lower the problems with sample heating, (iv) band-selective transfer over a well-specified chemical shift range, and (v) robustness towards non-idealities such as rf inhomogeneity. All of these qualities are of relevance for biological solid-state NMR.