An optimal control approach to design entire relaxation dispersion experiments

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ABSTRACT

A general approach is introduced to optimize experiments for the analysis of spin systems in the presence of chemical exchange. Rather than optimizing individual pulse sequence elements, such as refocusing pulses, entire relaxation dispersion sequences are optimized in the form of a single shaped pulse. This is achieved by defining a performance index that is only based on the remaining signal after the relaxation dispersion sequence for a range of exchange, relaxation, offset, and rf inhomogeneity parameters. The approach is demonstrated by optimizing energy-limited broadband relaxation dispersion sequences that closely approach the overall effect of ideal CPMG sequences. As illustrated both theoretically and experimentally, significant improvements are found compared to standard amplitude or energy-limited CPMG sequences.

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1. Introduction

Kinetic, thermodynamic and structural information of chemical exchange processes on the time scale of µs to ms can be obtained using relaxation dispersion (RD) experiments [1–7]. The standard approach to measure relaxation dispersion data is based on Carr-Purcell-Meiboom-Gill (CPMG) sequences [8–11] with different CPMG frequencies v_{CPMG}, which are applied in a given time period to measure effective transverse relaxation rates. Likewise one can use rotating frame relaxation dispersion to measure relaxation dispersion curves with different spin-lock amplitudes v_{SL} [12–14].

In the following, we focus on CPMG-type relaxation dispersion experiments. In the ideal case, CPMG sequences consist of hard 180° pulses with infinitely large pulse amplitude and negligible duration. However in practice, the ideal CPMG relaxation dispersion curves cannot be closely matched due to experimental constraints, such as limited pulse amplitude (due to hardware constraints) and limited total pulse energy (in order to limit rf heating effects). As a consequence, the approximation of the ideal case only works for a limited range of CPMG frequencies and for a limited offset range [15,16]. In addition, the resulting relaxation dispersion data can be further distorted due to experimental imperfections such as rf inhomogeneity. Conventional approaches to improve CPMG sequences have focused on the development of

improved refocusing pulses [17–19], replacing simple rectangular pulses by optimized composite or shaped pulses [20–23]. Although this *bottom-up* approach can provide individual pulses with improved refocusing properties, it also increases the pulse durations, making it even more difficult to approach high CPMG frequencies in RD experiments. In addition, the offset-dependent spin trajectories during these pulses significantly complicate the analysis of the exchange-dependent contribution to transverse relaxation rates. Additional approaches to improve the performance of CPMG sequences include the use of phase cycles [24–27] and magnetic field gradients [28].

Here, we explore a radically different *top-down* approach and consider the possibility to optimize the entire RD pulse sequence rather than its individual building blocks. This allows us to focus on the desired outcome (the measurement of exchange-dependent relaxation parameters) and provides new degrees of freedom in pulse sequence optimizations. It may be helpful to take a step back and consider the following conventional assumptions that perhaps can be thrown overboard. Does an optimal RD sequence really need to consist of a series of 180° pulses? Does an optimal RD sequence need to have a simple periodic structure? Does an optimal RD sequence need to have delays?

In order to address these questions, we use concepts of optimal control theory (OCT), which has been demonstrated to allow spectroscopists to optimize thousands of pulse-sequence parameters [29]. Analytical [30–32] and numerical [33–35] OCT approaches have been used to optimize experiments in nuclear magnetic

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resonance [36,37], electron paramagnetic resonance [38,39] spectroscopy and magnetic resonance imaging [40–45]. These general methods make it possible to include experimental constraints such as limited pulse amplitudes, limited average pulse power or limited total pulse energy, and the effects of pulse transients, rf inhomogeneity, offsets, relaxation [46] and radiation damping [47] can be taken into account. Optimal control theory was successfully applied to the design of band-selective and broadband individual excitation, inversion and refocusing pulses [21,23,48] but also to design cooperative pulses that compensate each other's imperfections [49,50] and even entire decoupling sequences [51–54]. In fact, the problem of broadband heteronuclear decoupling has a number of similarities with the problem to design optimal RD sequences and both applications can be based on ideal CPMG sequences. Until quite recently it was assumed that the best decoupling sequences consist of (composite or shaped) inversion pulses that are periodically repeated up to a systematic permutation of pulse elements and pulse phases in cycles and super cycles [24,55]. However, the optimization of entire decoupling sequences did not show such a structure and not only provided significantly improved pulse sequence performance but also new ways to tailor the offset-dependence of the effective coupling constants [52]. In contrast to decoupling sequences, in typical applications of RD sequences the signal is only acquired at the end of the sequence, whereas in heteronuclear decoupling experiments it is also acquired during the decoupling sequence.

Only recently OCT methods have been extended to NMR problems involving chemical exchange processes, and the efficiency of chemical exchange saturation transfer (CEST) experiments was optimized, resulting in a novel family of simple triangular-shaped saturation pulses [44].

In this article, we develop an approach that allows us to treat the optimization of entire RD pulse sequences as an optimal control problem. Initially, it was neither clear if such a formulation is possible nor if such an approach is able to provide significant advantages compared to conventional CPMG sequences. Therefore, in this pilot study we focus on simple model systems to explore the potential of this approach. We will restrict the discussion to the simple case of two-site exchange of uncoupled spins 1/2 and explore the possibility of using efficient optimal-control based numerical optimizations to design pulse sequences with RD properties that approach the RD properties of ideal CPMG sequences.

We refer to this new class of pulse sequences as ORECA (Optimized Relaxation Experiments for Chemical exchange Analysis). We optimized, analyzed and compared ORECA sequences to conventional CPMG sequences both in simulations and in experiments using small-molecule model systems.

2. Theory

2.1. Simulation of chemical exchange

In order to efficiently simulate exchange processes in the presence of rf pulses, it is convenient to use extended homogeneous Bloch equations [44,56,57]. The seven-dimensional homogeneous state vector $\overrightarrow{\rho}$ of a spin in two different chemical states A and B with individual Bloch vectors $\overrightarrow{M}^A = (M_x^A \; M_y^A \; M_z^A)^\top$ and $\overrightarrow{M}^B = (M_x^B \; M_y^B \; M_z^B)^\top$ can be written as

$$\overrightarrow{\rho} = (1 \; M_x^A \; M_y^A \; M_z^A \; M_x^B \; M_y^B \; M_z^B)^\top. \tag{1}$$

In the presence of exchange between the chemical states A and B

$$A \underset{k_{BA}}{\overset{k_{AB}}{\rightleftharpoons}} B$$
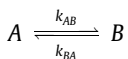
(where k_{AB} is the conversion rate from state A to B and k_{BA} the conversion rate from state B to A), the equation of motion is

$$\overrightarrow{\dot{\rho}} = (\Gamma + K)\overrightarrow{\rho} \tag{2}$$

with

$$\Gamma(t) = \begin{pmatrix} 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & -\frac{1}{T_2^A} & -\omega_A & \omega_y(t) & 0 & 0 & 0 \\ 0 & \omega_A & -\frac{1}{T_2^A} & -\omega_x(t) & 0 & 0 & 0 \\ \frac{p_A}{T_1^A} & -\omega_y(t) & \omega_x(t) & -\frac{1}{T_1^A} & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & -\frac{1}{T_2^B} & -\omega_B & \omega_y(t) \\ 0 & 0 & 0 & 0 & \omega_B & -\frac{1}{T_2^B} & -\omega_x(t) \\ \frac{p_B}{T_1^B} & 0 & 0 & 0 & -\omega_y(t) & \omega_x(t) & -\frac{1}{T_1^B} \end{pmatrix} \tag{3}$$

and

$$K = \begin{pmatrix} 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & -k_{AB} & 0 & 0 & k_{BA} & 0 & 0 \\ 0 & 0 & -k_{AB} & 0 & 0 & k_{BA} & 0 \\ 0 & 0 & 0 & -k_{AB} & 0 & 0 & k_{BA} \\ 0 & k_{AB} & 0 & 0 & -k_{BA} & 0 & 0 \\ 0 & 0 & k_{AB} & 0 & 0 & -k_{BA} & 0 \\ 0 & 0 & 0 & k_{AB} & 0 & 0 & -k_{BA} \end{pmatrix}, \tag{4}$$

where $\omega_A = 2\pi\nu_A$ and $\omega_B = 2\pi\nu_B$ represent the offset frequencies, T_1^A and T_1^B are the longitudinal relaxation times, T_2^A and T_2^B the transverse relaxation times, and p_A and p_B the populations of the chemical states A and B, respectively. $\omega_x(t) = 2\pi\nu_x(t)$ and $\omega_y(t) = 2\pi\nu_y(t)$ are the time-dependent amplitudes of the x and y components of the rf field.

In the following, we consider pulse sequences of duration T consisting of N time slices of equal duration $\Delta t = T/N$, during each of which the rf amplitudes are constant. During the j-th time slice, the rf amplitudes are $\nu_x(t) = \nu_{j,x}$ and $\nu_y(t) = \nu_{j,y}$ and the super operator representing the effects of offsets, pulses and relaxation is denoted $\Gamma(t) = \Gamma_j$. By applying an excitation pulse to the spin system at thermal equilibrium, the spins are flipped to the x axis and the initial state

$$\overrightarrow{\rho}(0) = (1 \; p_A \; 0 \; 0 \; p_B \; 0 \; 0)^\top \tag{5}$$

is prepared. At the end of the pulse sequence, the state is

$$\overrightarrow{\rho}(T) = P_{tot} \; \overrightarrow{\rho}(0), \tag{6}$$

where the total time-evolution operator P_{tot} of the sequence is given by [56]

$$P_{tot} = P_N P_{N-1} \cdots P_j \cdots P_2 P_1 \tag{7}$$

with

$$P_j = \exp\{(\Gamma_j + K)\Delta t\}. \tag{8}$$

2.2. Pulse sequence energy

In the following, it will be important to compare the total energy of different pulse sequences. Therefore, here we briefly review the general definition of pulse energy and how it is related to commonly used quantities for the special case of CPMG sequences.

In general, a pulse sequence consists of a time-dependent rf irradiation with amplitude $\nu_{rf}(t) = \gamma B_1(t)/(2\pi)$ and phase $\varphi_{rf}(t)$,