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Clean TOCSY transfer through residual dipolar couplings

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Abstract

The transfer efficiency of cross-relaxation compensated (Clean) TOCSY sequences is analyzed for applications to residual dipolar couplings. Surprisingly most conventional Clean TOCSY sequences are very inefficient for dipolar transfer. It is shown theoretically, that this is a general property of all phase-alternating mixing sequences, i.e., for such sequences the suppression of cross-relaxation excludes dipolar transfer in the spin-diffusion limit. A new family of clean dipolar TOCSY sequences is derived which provides excellent transfer efficiencies for a broad range of offset frequencies.

Keywords: Hartmann–Hahn transfer; Residual dipolar couplings; Dipolar mixing; TOCSY; Clean TOCSY; Cross-relaxation compensation

1. Introduction

During the mixing period of a homonuclear TOCSY experiment [1,2], coherent Hartmann–Hahn-type transfer can be accompanied by incoherent transfer via cross-relaxation [2,3]. This leads to unwanted interferences and ambiguities in TOCSY spectra of macromolecules. Fortunately, in the case of large molecules, the transverse, and longitudinal cross-relaxation rates have a different algebraic sign. This makes it possible to design Clean TOCSY sequences [2,4–9], which cancel cross-relaxation induced artifacts with the help of a compensation strategy [4]. Here, we analyze the dipolar transfer efficiency of conventional Clean TOCSY sequences, which were originally developed for broadband scalar transfer. Pulse sequences can effect clean transfer only for one unique magnetization component $I_{1\alpha} \rightarrow I_{2\alpha}$, e.g., $I_{1z} \rightarrow I_{2z}$ for TOWNY [9] and DIPSI-2rc [7] and $I_{1y} \rightarrow I_{2y}$ for Clean MLEV-17 [4]. For simplicity, we restrict the following discussion to the transfer of Cartesian magnetization components and assume that the spin system is in the spin-diffusion limit, where $\sigma_{\mathrm{ROE}} = -2\sigma_{\mathrm{NOE}}$. Surprisingly, it turns out that most existing Clean TOCSY sequences are dysfunctional for (residual) dipolar couplings. This failure can be rationalized by combining average Hamiltonian theory and the invariant trajectory approach. As a general result, we find that all phase-alternating TOCSY sequences such as DIPSI-2rc [7], or TOWNY [9] are incompatible with dipolar transfer in the spin-diffusion limit (here, we use the term "phase alternating" for sequences in which all pulses have the same phase, except for a possible sign change, e.g., $x, -x, \ldots$). This is a non-trivial result of the fact that, in the spin-diffusion limit, the ratio of the longitudinal and transverse cross-relaxation rate is −2, which is identical to the ratio of the pre-factors of the transverse ($I_{1x}I_{2x}$ or $I_{1y}I_{2y}$) and longitudinal ($I_{1z}I_{2z}$) bilinear operators in the dipolar coupling term (vide infra, Eq. (1)).

The theoretical results lead to a simple strategy to significantly enhance the dipolar transfer properties of conventional cross-relaxation compensated TOCSY sequences by using non-phase alternating super cycles.

2. Numerical simulations

We examined the dipolar transfer properties of well known cross-relaxation compensated (Clean) TOCSY sequences. Numerical simulations were carried out using an extended version of the program SIMONE [10]. For the simulations, we assumed a homonuclear spin system consisting of two spins 1/2 with either a dipolar coupling term

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$$\mathscr{H}_D = 2\pi D\left\{ -\tfrac{1}{2}I_{1x}I_{2x} - \tfrac{1}{2}I_{1y}I_{2y} + I_{1z}I_{2z}\right\} \quad (1)$$

or a scalar coupling term

$$\mathscr{H}_J = 2\pi J\left\{ I_{1x}I_{2x} + I_{1y}I_{2y} + I_{1z}I_{2z}\right\}. \quad (2)$$

In addition to the standard sequences Clean MLEV-17 [4], Clean CITY [6], DIPSI-2rc [7], and TOWNY [9], we also included a Clean CITY version (Clean CITY-M16) expanded by an MLEV-16 super cycle and a clean version of the MOCCA-M16 sequence [11,12] with $\Delta/d = 0.5$, where Δ is the delay between the 180° pulses of duration d [13]. The results of the simulations for Clean MLEV-17 are shown in Fig. 1 and for the sequences Clean CITY, Clean CITY-M16, DIPSI-2rc, TOWNY, and Clean MOCCA-M16 in Figs. 2–5. In Figs. 1A and 2A–E the on-resonance dipolar transfer functions $T^D_\alpha(\tau)$ [2] are shown for mixing times τ of up to 200 ms (coupling constants: $J = 0$ and $D = 20$ Hz). $T^D_\alpha(\tau)$ is the transfer function of the clean magnetization component $I_{1\alpha} \rightarrow I_{2\alpha}$, averaged over a Gaussian distribution of rf amplitudes with a full width of 10% at half height, to simulate the effects of rf inhomogeneity [2]. Figs. 1B and 3A–E show the two-dimensional offset dependence of the transfer efficiency $T^D_\alpha(\tau^D_{\text{opt}})$ of cross-relaxation compensated dipolar transfer as a function of the offset frequencies ν_1 and ν_2 of the spins I_1 and I_2. The optimal dipolar mixing times τ^D_{opt} for each pulse sequence in the on-resonance case are taken from Figs. 1A and 2A–E and are summarized in Table 1. Figs. 1C and 4A–E show the corresponding efficiency $T^J_\alpha(\tau^J_{\text{opt}})$ for scalar ($J = 10$ Hz, $D = 0$ Hz) transfer with $\tau^J_{\text{opt}} = 1/(2J) = 50$ ms. Figs. 1D and 5A–E show the quality factor $q^{\text{cr}}_\alpha(\nu_1, \nu_2)$, which reflects the effective cross-relaxation rate as a function of the offsets ν_1, and ν_2. The cross-relaxation quality factor $q^{\text{cr}}_\alpha(\nu_1, \nu_2)$ is defined by [2,3]

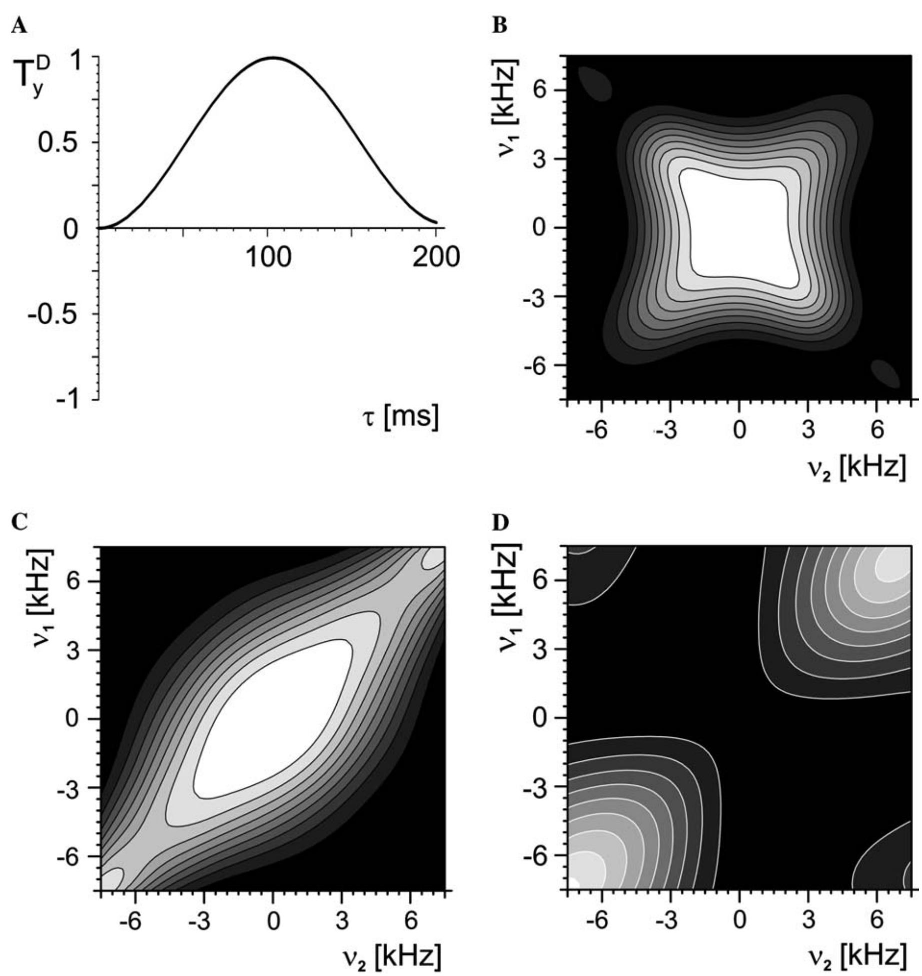

Fig. 1. Transfer properties of the Clean MLEV-17 sequence. (A) Time dependence of the on-resonance transfer efficiency $T^D_y(\tau)$ in the range $\tau = 0$–200 ms. (B) Offset dependence of the dipolar transfer efficiency $T^D_y(\tau^D_{\text{opt}})$ for $J = 0$ Hz and $D = 20$ Hz. (C) Offset dependence of the scalar transfer efficiency $T^J_y(\tau^J_{\text{opt}})$ for $J = 10$ Hz, and $D = 0$ Hz. (D) Offset dependence of the effective cross-relaxation quality factor $q^{\text{cr}}_y(\nu_1, \nu_2)$ (Eq. (3)). All numerical calculations were carried out with an extended version of the program SIMONE [10]. The effects of rf inhomogeneity were considered, assuming a Gaussian rf inhomogeneity distribution with a full width of 10% at half height. Contour lines (black if positive, white if negative) are shown for $\pm 0.1, \pm 0.2, \ldots, \pm 0.9$. Areas with the same value of $|T^{D,J}_y(\tau^{D,J}_{\text{opt}})|$ and $|q^{\text{cr}}_y|$, respectively, are filled with the same grey level, e.g., black for $|T^{D,J}_y(\tau^{D,J}_{\text{opt}})| \leqslant 0.1$.

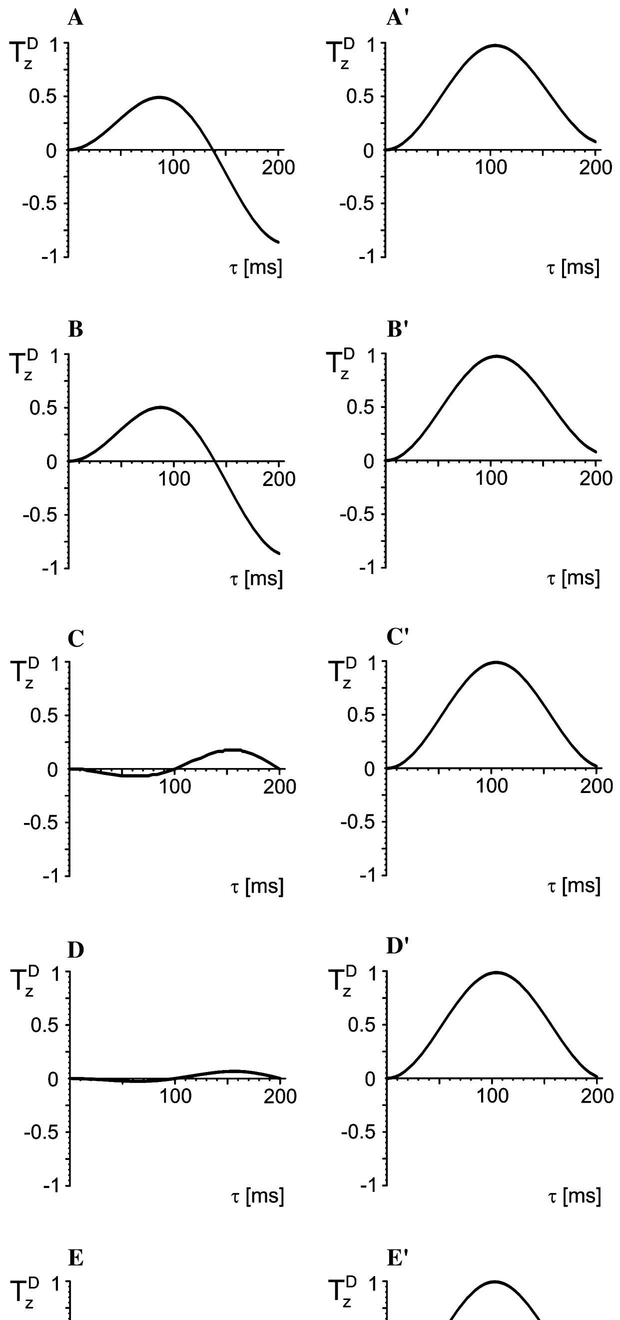

Fig. 2. Time dependence of the on-resonance dipolar transfer amplitude $T_z^D(\tau)$ in the range $\tau = 0$–200 ms for the sequences Clean CITY (A), Clean CITY-XY4 (A′), Clean CITY-M16 (B), Clean CITY-XY16 (B′), DIPSI-2rc (C), DIPSI-2rc-XY4 (C′), TOWNY (D), TOWNY-XY16 (D′), Clean MOCCA-16 (E), and Clean MOCCA-XY16 (E′). Coupling constants: $J = 0$ Hz and $D = 20$ Hz.

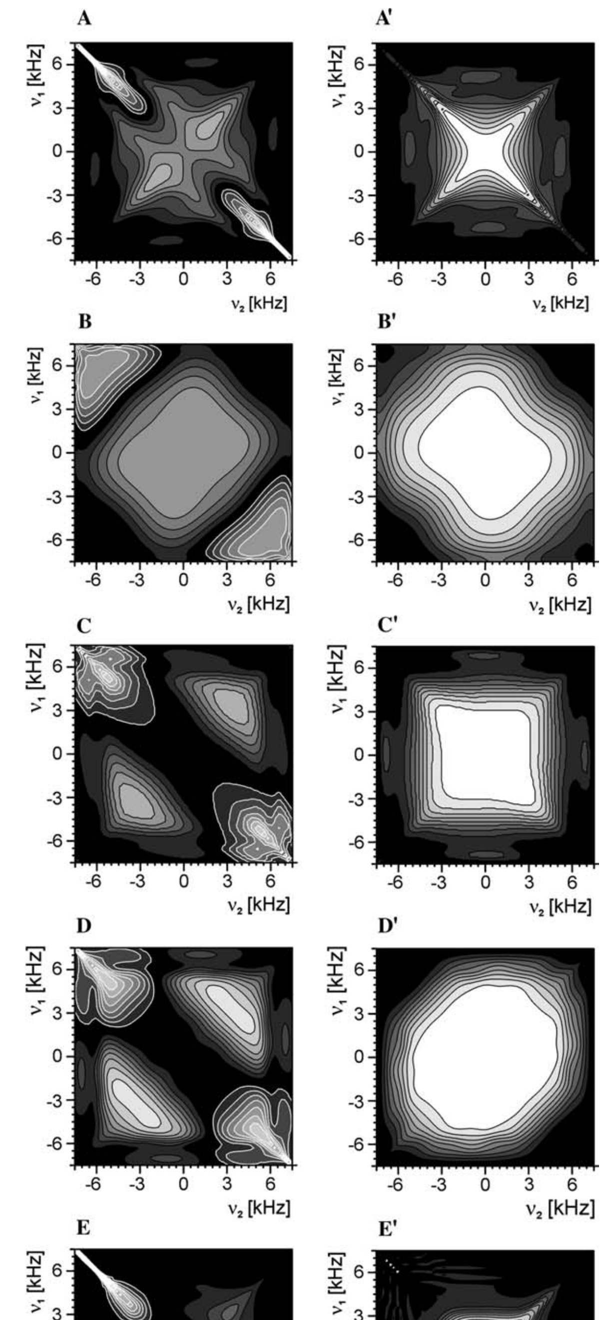

Fig. 3. Offset dependence of the dipolar transfer efficiency $T_z^D(\tau_{\mathrm{opt}}^D)$ for the sequences Clean CITY (A), Clean CITY-XY4 (A′), Clean CITY-M16 (B), Clean CITY-XY16 (B′), DIPSI-2rc (C), DIPSI-2rc-XY4 (C′), TOWNY (D), TOWNY-XY16 (D′), Clean MOCCA-16 (E), and Clean MOCCA-XY16 (E′). Coupling constants: $J = 0$ Hz and $D = 20$ Hz.

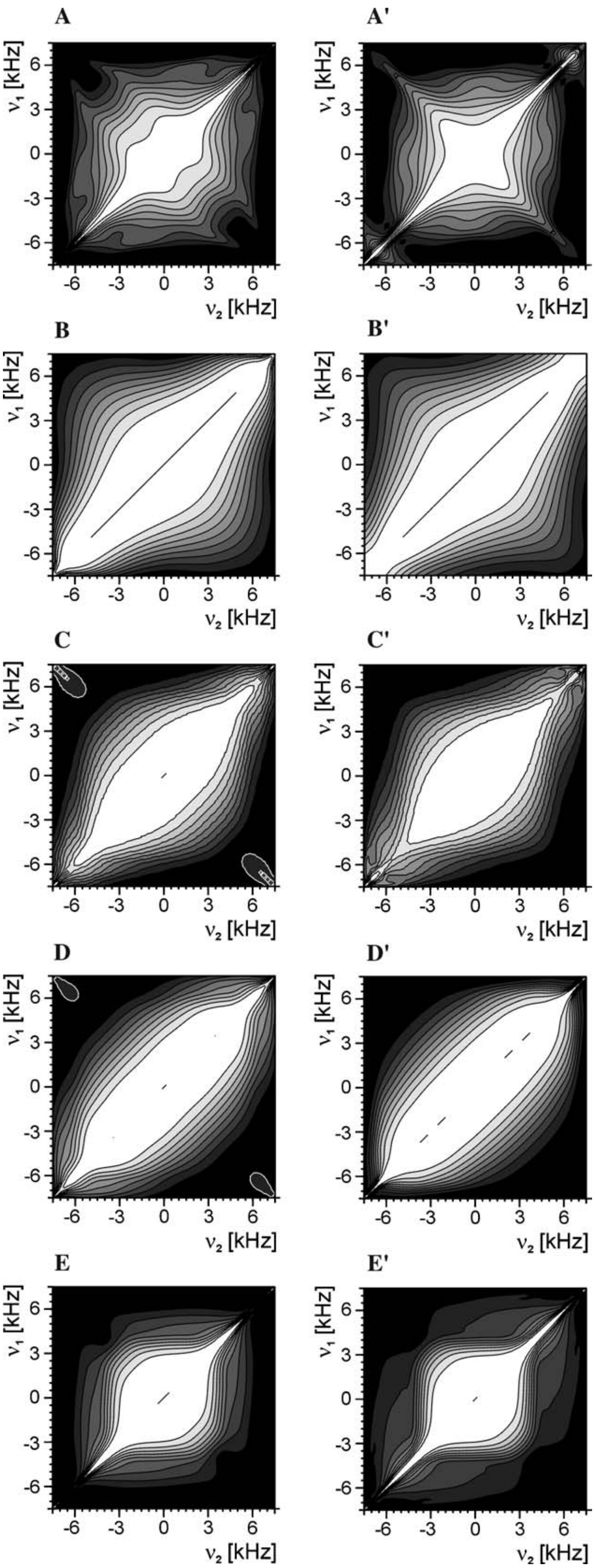

Fig. 4. Offset dependence of the scalar transfer efficiency $T_y^J(\tau_{opt}^J)$ for the sequences Clean CITY (A), Clean CITY-XY4 (A′), Clean CITY-M16 (B), Clean CITY-XY16 (B′), DIPSI-2rc (C), DIPSI-2rc-XY4 (C′), TOWNY (D), TOWNY-XY16 (D′), Clean MOCCA-M16 (E), and Clean MOCCA-XY16 (E′). Coupling constants: $J = 10\,\text{Hz}$ and $D = 0\,\text{Hz}$.

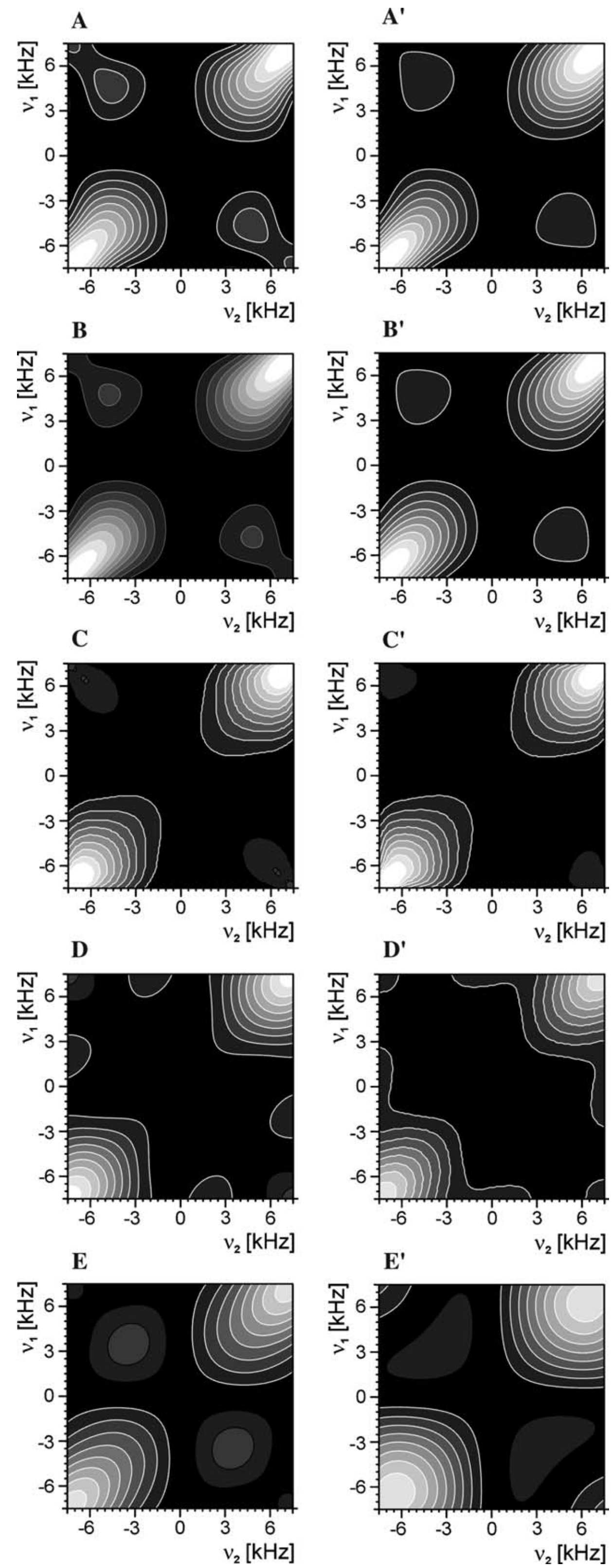

Fig. 5. Offset dependence of the effective cross-relaxation quality factor $q_y^{cr}(\nu_1, \nu_2)$ (Eq. (13)) for the sequences Clean CITY (A), Clean CITY-XY4 (A′), Clean CITY-M16 (B), Clean CITY-XY16 (B′), DIPSI-2rc (C), DIPSI-2rc-XY4 (C′), TOWNY (D), TOWNY-XY16 (D′), Clean MOCCA-M16 (E), and Clean MOCCA-XY16 (E′).

Table 1
Properties of Clean TOCSY sequences which are cross-relaxation-compensated in the spin-diffusion limit ($\sigma_{ROE}/\sigma_{NOE} = -2$)

Clean homonuclear Hartmann–Hahn mixing sequences							
Sequence (α)	Basic sequence R	Δ	Expansion	Bandwidth b (kHz)		Dipolar transfer	
				Scalar	Dipolar	τ^D_{opt}(ms)	$T^D_\alpha(\tau_{opt})$
Clean MLEV-17 (y)	$90^\circ_x \Delta\ 180^\circ_y \Delta\ 90^\circ_x$	90°	MLEV-16 + 60°_y	5.1	7.0	103	0.99
Clean CITY (z)	$\Delta\ 180^\circ_y\ 2\ \Delta\ 180^\circ_y\ \Delta\ 48^\circ_{-x}$ $276^\circ_x\ 48^\circ_{-x}\ \Delta\ 180^\circ_y\ 2\ \Delta\ 180^\circ_y\ \Delta$	48°	MLEV-4 (type A)	6.0	—	87	0.49
Clean CITY-M16 (z)	$\Delta\ 180^\circ_y\ 2\ \Delta\ 180^\circ_y\ \Delta\ 48^\circ_{-x}$ $276^\circ_x\ 48^\circ_{-x}\ \Delta\ 180^\circ_y\ 2\ \Delta\ 180^\circ_y\ \Delta$	48°	MLEV-16	8.4	4.2	87	0.50
DIPSI-2rc (z)	$180^\circ_x\ \Delta\ 140^\circ_x\ 320^\circ_{-x}$ $\Delta\ 90^\circ_{-x}\ 270^\circ_x\ \Delta\ 20^\circ_x$ $200^\circ_{-x}\ \Delta\ 85^\circ_{-x}\ 30^\circ_x\ 125^\circ_{-x}$ $\Delta\ 120^\circ_{-x}\ 300^\circ_x\ \Delta\ 75^\circ_x\ 255^\circ_{-x}$ $\Delta\ 10^\circ_{-x}\ 190^\circ_x\ \Delta\ 180^\circ_x\ \Delta$	144°	MLEV-4 (type B)	6.4	—	65	−0.07
TOWNY (z)	$15^\circ_x\ 75^\circ_{-x}\ 270^\circ_x\ 45^\circ_{-x}$	—	MLEV-16	5.8	—	65	−0.03
Clean MOCCA-M16 (z)	$\frac{\Delta}{2}\, 180^0_\varphi\, \frac{\Delta}{2}$	90°	MLEV-16	6.0	—	64	−0.03

The delay Δ is defined as the corresponding duration of a pulse with the given flip angle. The bandwidth b refers to the central offset region in which the transfer efficiency $|T^D_\alpha(\tau_{opt})|$ is $\geqslant 0.5$ for an average rf power $\nu^{rms}_{rf} = 10$ kHz. Super cycles: MLEV-4 (type A) = $RR\bar{R}\bar{R}$, MLEV-4 (type B) = $R\bar{R}\bar{R}R$, MLEV-16 = $RR\bar{R}\bar{R}\ \bar{R}RR\bar{R}\ R\bar{R}\bar{R}R\ \bar{R}\bar{R}RR$. Dipolar transfer: $J = 0$ Hz, $D = 20$ Hz; scalar transfer: $J = 10$ Hz, $D = 0$ Hz.

$$q^{cr}_\alpha(\nu_1, \nu_2) = \frac{\sigma^{Sequenz}_{eff}(\nu_1, \nu_2)}{\sigma_{NOE}} = w^{(12)}_l(\nu_1, \nu_2) - 2w^{(12)}_t(\nu_1, \nu_2). \tag{3}$$

Here, the ratio $\sigma_{ROE}/\sigma_{NOE}$ of the transverse and longitudinal cross-relaxation rates is assumed to be −2, corresponding to the spin-diffusion limit. The weight of the longitudinal cross-relaxation $w^{(12)}_l(\nu_1, \nu_2)$ and the weight of the transverse cross-relaxation $w^{(12)}_t(\nu_1, \nu_2)$ are calculated numerically for the clean invariant trajectories during the sequence (including super cycle) [2,3]. The range of possible values of the quality factor q^{cr}_α lies between −2 (pure ROE) and 1 (pure NOE) and should be close to zero for clean sequences.

The pulse sequence parameters and the results of the numerical simulations are summarized in Table 1, where all data refer to the transfer of the unique clean magnetization component $I_{1\alpha} \to I_{2\alpha}$ for each pulse sequence. The best dipolar transfer properties of the conventional Clean TOCSY sequences are found for Clean MLEV-17. For the on-resonance case, Clean MLEV-17 creates the following effective Hamiltonian:

$$\mathscr{H}^{Clean\ MLEV-17}_{D,eff} = 84.32(I_{1y} + I_{2y}) + 2\pi D\{-0.24 I_{1z}I_{2z} - 0.25 I_{1x}I_{2x} + 0.49 I_{1y}I_{2y}\}, \tag{4}$$

which was calculated numerically using the program SIMONE [10]. The effective dipolar coupling constant is scaled by a factor of approx. 0.5 (in addition to a permutation of the axis labels) [11]. As noted before [11], the dipolar scaling factor of Clean MLEV-17 is a factor of two larger than for the uncompensated MLEV-17 sequence [14].

The dipolar transfer efficiency of Clean CITY is very poor (see Fig. 3A). As shown in Table 1 (see also Figs. 4A and B) for Clean CITY, the extension of the super cycle from MLEV-4 to MLEV-16 leads a more than 40% increased bandwidth of scalar transfer. The dipolar transfer of Clean CITY-M16 is clearly improved compared to the standard Clean CITY sequence, but the maximum transfer efficiency is only about 50% (see Figs. 2A/B, 3A/B, and Table 1). The scalar bandwidths of the phase-alternating sequences DIPSI-2rc, TOWNY, and Clean MOCCA-M16 (see Figs. 4C–E) are similar or better than for Clean MLEV-17. However, these sequences effect very little dipolar transfer on resonance (see Figs. 2C–E). In fact, dipolar transfer is inefficient (Figs. 3C–E) in the entire central spectral region, where cross-relaxation is well suppressed (Figs. 5C–E).

For the on-resonance case, the numerically determined effective dipolar coupling Hamiltonians are:

$$\mathscr{H}^{DIPSI-2rc}_{D,eff} = 2\pi D\{0.49 I_{1z}I_{2z} - 0.50 I_{1x}I_{2x} - 0.01 I_{1y}I_{2y}\}, \tag{5}$$

$$\mathscr{H}^{TOWNY}_{D,eff} = \mathscr{H}^{MOCCA-M16}_{D,eff} = 2\pi D\{0.50 I_{1z}I_{2z} - 0.50 I_{1x}I_{2x}\}. \tag{6}$$

All three effective Hamiltonians have a bilinear x and y term with a pre-factor of about 0.5 while the term $I_{1y}I_{2y}$, which is also required for effective transfer of z magnetization [2], approaches zero. This observations suggest the general rule, that no dipolar transfer is possible with simultaneous suppression of cross-relaxation under phase alternating sequences such as DIPSI-2rc, TOWNY, and Clean MOCCA-M16. This hypothesis will be proven in the next section.

3. Theory

Without loss of generality, we consider a phase-alternating basis sequence R [2] of duration τ_b which consists only of pulses with phase $\phi = x$ or $-x$. For such a sequence, clean transfer $I_{1x} \rightarrow I_{2x}$ is impossible for the on-resonance case because I_{1x} and I_{2x} are transverse all the time (resulting in full ROE transfer). Hence, for the initial density operator at the time $\tau = 0$, we assume a linear combination of I_{1y} and I_{1z}:

$$\rho(0) = aI_{1y} + bI_{1z} \tag{7}$$

with $a^2 + b^2 = 1$. In the classical vector model, this density operator corresponds to the magnetization vector

$$\vec{M}(0) = \begin{pmatrix} 0 \\ a \\ b \end{pmatrix}. \tag{8}$$

For the on-resonance case $\nu_1 = \nu_2 = 0\,\mathrm{Hz}$, the effective cross-relaxation rate σ_{eff} for a phase-alternating sequence (relative to the full NOE rate) is given by

$$\frac{\sigma_{\mathrm{eff}}}{\sigma_{\mathrm{NOE}}} = a^2\left(3\overline{\sin^2\beta} - 2\right) + b^2\left(1 - 3\overline{\sin^2\beta}\right) + 6ab\overline{\sin\beta\cos\beta}, \tag{9}$$

where $\beta(t)$ is the accumulated angle between the instant magnetization vector $\vec{M}(t)$ and the initial vector direction $\vec{M}(0)$ (the bars over the expressions in Eq. (9) denote the time average over the duration τ_b).

On the other hand, the average dipolar coupling Hamiltonian of a phase-alternating sequence is given by

$$\overline{\mathscr{H}}_D = 2\pi D_{12}\Big\{ -\tfrac{1}{2}\left(3\overline{\sin^2\beta} - 2\right)I_{1z}I_{2z} - \tfrac{1}{2}I_xS_x - \tfrac{1}{2}\left(1 - 3\overline{\sin^2\beta}\right)I_{1y}I_{2y} + \tfrac{3}{2}\overline{\sin\beta\cos\beta}\left(I_{1y}I_{2z} + I_{1z}I_{2y}\right)\Big\}. \tag{10}$$

In practice, the basis sequence is expanded to make it cyclic. In the case of MLEV-type cycles or super cycles [15], which are used for conventional Clean TOCSY sequences and which are also purely phase-alternating, the term $\overline{\sin\beta\cos\beta}$ is averaged to zero. Hence, for such sequences the effective cross-relaxation rate (Eq. (9)) and the expression for the effective Hamiltonian simplify to:

$$\frac{\sigma_{\mathrm{eff}}}{\sigma_{\mathrm{NOE}}} = a^2\left(3\overline{\sin^2\beta} - 2\right) + b^2\left(1 - 3\overline{\sin^2\beta}\right) \tag{11}$$

and

$$\overline{\mathscr{H}}_D = 2\pi D\Big\{ -\tfrac{1}{2}\left(3\overline{\sin^2\beta} - 2\right)I_{1z}I_{2z} - \tfrac{1}{2}I_{1x}I_{2x} - \tfrac{1}{2}\left(1 - 3\overline{\sin^2\beta}\right)I_{1y}I_{2y}\Big\}. \tag{12}$$

For a cross-relaxation compensated sequence Eq. (11) must be zero, which implies

$$\overline{\sin^2\beta} = \tfrac{1}{3}\left(\frac{a^2}{2a^2 - 1} + 1\right). \tag{13}$$

Inserting Eq. (13) in Eq. (12) results in the following simplified expression for the average dipolar Hamiltonian of a clean, MLEV-type phase-cycled pulse sequence:

$$\overline{\mathscr{H}}_D = 2\pi D\Big\{ -\frac{1}{2}\left(\frac{a^2}{2a^2 - 1} - 1\right)I_{1z}I_{2z} - \tfrac{1}{2}I_{1x}I_{2x} + \frac{1}{2}\left(\frac{a^2}{2a^2 - 1}\right)I_{1y}I_{2y}\Big\}. \tag{14}$$

(Note that the norm of $\overline{\mathscr{H}}_D$ cannot exceed the norm of $\mathscr{H}_D$, restricting the experimentally accessible range of a.) Eq. (14) can be used to analyze the dipolar transfer properties of cross-relaxation compensated, phase-alternating TOCSY sequences. For the case of clean longitudinal transfer ($\alpha = z$), where $a = 0$ and $b = 1$, the average Hamiltonian is given by

$$\overline{\mathscr{H}}_D = 2\pi D\{\tfrac{1}{2}I_{1z}I_{2z} - \tfrac{1}{2}I_{1x}I_{2x}\}, \tag{15}$$

which corresponds to the numerically determined effective Hamiltonians in Eqs. (5) and (6). Hence, for clean z transfer only the term $I_{1x}I_{2x}$ is available in the effective Hamiltonian $\overline{\mathscr{H}}_D$ ($I_{1z}I_{2z}$ commutes with I_{1z}), which cannot effect any polarization transfer $I_{1z} \rightarrow I_{2z}$, explaining the unsatisfactory dipolar transfer properties found for the sequences TOWNY, DIPSI-2rc, and Clean MOCCA, described above.

Also for the case of clean y transfer ($\alpha = y$) where $a = 1$ and $b = 0$ the average Hamiltonian

$$\overline{\mathscr{H}}_D = 2\pi D_{12}\{-\tfrac{1}{2}I_{1x}I_{2x} + \tfrac{1}{2}I_{1y}I_{2y}\} \tag{16}$$

is missing a bilinear term ($I_{1z}I_{2z}$), which is required for dipolar transfer $I_{1y} \rightarrow I_{2y}$. Hence, for phase-alternating basis sequences expanded in MLEV-type cycles or super cycles, no clean dipolar TOCSY transfer $I_{1\alpha} \rightarrow I_{2\alpha}$ is possible for $\alpha = x$, y, or z.

4. New sequences

At first glance, the theoretical results seem to imply that it is necessary to optimize novel non-phase-alternating clean dipolar TOCSY sequences from scratch in order to improve the transfer properties of MLEV-17. However, the fact that in conventional Clean TOCSY sequences the cross-relaxation compensation is achieved already during the basis sequence R suggests that existing phase-alternating Clean TOCSY sequences can be significantly improved by simply replacing the phase-alternating MLEV-type super cycles by non-phase-alternating super cycles, such as XY16 [16,17]. The dipolar transfer properties of the resulting new family of cross-relaxation compensated TOCSY sequences is documented in Figs. 2A′–E′. The modified Clean TOCSY sequences show dramatically improved dipolar transfer efficiencies. At the same time their scalar transfer properties (cf. Figs. 3A′–E′) and the degree of cross-relaxation compensation (cf. Figs. 4A′–E′) are comparable or even improved compared to the conventional sequences. The pulse sequence parameters and numerical results of these

Table 2
Properties of modified Clean TOCSY sequences with super cycles XY4 = *XYXY* and XY-16 = *XYXY YXYX* $\bar{X}\bar{Y}\bar{X}\bar{Y}$ $\bar{Y}\bar{X}\bar{Y}\bar{X}$ [16,17]

New clean homonuclear Hartmann–Hahn mixing sequences							
Sequence (α)	Basic sequence R	Δ	Expansion	Bandwidth b (kHz)		Dipolar transfer	
				Scalar	Dipolar	τ^D_{opt}(ms)	$T^D_\alpha(\tau^D_{opt})$
Clean CITY-XY4 (z)	Δ $180°_y$ 2 Δ $180°_y$ Δ $48°_{-x}$ $276°_x$ $48°_{-x}$ Δ $180°_y$ 2 Δ $180°_y$ Δ	48°	XY-16	7.5	5.2	105	0.98
Clean CITY-XY16 (z)	Δ $180°_y$ 2 Δ $180°_y$ Δ $48°_{-x}$ $276°_x$ $48°_{-x}$ Δ $180°_y$ 2 Δ $180°_y$ Δ	48°	XY-16	8.6	7.4	106	0.97
DIPSI-2rc-XY4 (z)	$180°_x$ Δ $140°_x$ $320°_{-x}$ Δ $90°_{-x}$ $270°_x$ Δ $20°_x$ $200°_{-x}$ Δ $85°_{-x}$ $30°_x$ $125°_{-x}$ Δ $120°_{-x}$ $300°_x$ Δ $75°_x$ $255°_{-x}$ Δ $10°_{-x}$ $190°_x$ Δ $180°_x$ Δ	144°	XY-4	6.8	8.7	104	0.99
TOWNY-XY16 (z)	$15°_x$ $75°_{-x}$ $270°_x$ $45°_{-x}$	—	XY16	5.8	7.9	104	0.99
Clean MOCCA-XY16 (z)	$\frac{\Delta}{2}180^\circ_\varphi\frac{\Delta}{2}$	90°	XY-16	6.0	5.2	102	0.99

simulations are summarized in Table 2 (the transfer properties refer again to the unique clean transferred magnetization component $I_{1\alpha}$ for each sequence). For the sequences in Table 2, the dipolar scaling factor is approx. 0.5 for all sequences and the numerically determined effective Hamiltonians (on-resonance case) are given by:

$$\mathscr{H}_{D,\mathrm{eff}}^{\mathrm{Clean\ CITY-XY16}} = \mathscr{H}_{D,\mathrm{eff}}^{\mathrm{Clean\ MOCCA-XY16}} = 2\pi D\{0.50 I_{1z}I_{2z} - 0.25\boldsymbol{I_{1x}I_{2x}} - 0.25\boldsymbol{I_{1y}I_{2y}}\}, \tag{17}$$

$$\mathscr{H}_{D,\mathrm{eff}}^{\mathrm{DIPSI-2rcXY4}} = 2\pi D\{0.49 I_{1z}I_{2z} - 0.24\boldsymbol{I_{1x}I_{2x}} - 0.24\boldsymbol{I_{1y}I_{2y}}\}, \tag{18}$$

$$\mathscr{H}_{D,\mathrm{eff}}^{\mathrm{TOWNY}} = 2\pi D\{0.49 I_{1z}I_{2z} - 0.24\boldsymbol{I_{1x}I_{2x}} - 0.24\boldsymbol{I_{1y}I_{2y}} + 0.01(I_{1x}I_{2y} + I_{1y}I_{2x} + I_{1x}I_{2z} + I_{1z}I_{2x} + I_{1y}I_{2z} + I_{1z}I_{2y})\}. \tag{19}$$

As the basis sequence R is not cyclic, the substitution of a phase-alternating MLEV-type phase cycle by a XY-type phase cycle results in drastic changes in the average Hamiltonian of such sequences, leading to a scaling of both bilinear coupling terms ($I_{1x}I_{2x}$ and $I_{1y}I_{2y}$) required for polarization transfer $I_{1z} \rightarrow I_{2z}$. These coupling terms are printed in bold face type in Eqs. (17)–(19). Also for the Clean CITY sequences, the dipolar transfer properties are significantly improved by replacing the MLEV-type super cycle by the non-phase-alternating XY-16 super cycle.

5. Conclusion

The conventional phase-alternating Clean TOCSY sequences TOWNY, DIPSI-2rc, and Clean MOCCA-M16, which were originally developed for scalar coupled spin systems, are very inefficient for transfer through (residual) dipolar couplings. In fact, no dipolar transfer is possible on resonance in the spin-diffusion limit ($\sigma_{\mathrm{ROE}}/\sigma_{\mathrm{NOE}} = -2$). The presented theoretical results explain this observation and show that for all phase-alternating sequences expanded by a phase-alternating MLEV-type super cycle, it is impossible to effect clean dipolar x, y, or z transfer. Of the conventional sequences shown in Table 1, only Clean MLEV-17 effects efficient clean dipolar transfer. The Clean CITY sequences achieve in the case of dipolar transfer only 50% of the maximum possible transfer amplitude.

A potentially interesting application of the suppression of dipolar transfer in conventional phase-alternating Clean TOCSY sequences could be the experimental discrimination between cross-peaks resulting from scalar or residual dipolar couplings. However, it should be noted, that the effective dipolar coupling Hamiltonian (of Eq. (15)) only suppresses polarization transfer in a two-spin system, whereas in larger spin systems polarization transfer is still possible [18].

Substituting the phase-alternating MLEV-type super cycles by XY-type super cycles transforms the conventional TOWNY, DIPSI-2rc, and Clean MOCCA-M16 sequences into the non-phase-alternating sequences TOWNY-XY16, DIPSI-2rc-XY4, and Clean MOCCA-XY16 with broadband and efficient clean dipolar transfer. The dipolar transfer properties of the Clean CITY sequences are also significantly improved by using the XY-16 super cycle. In addition, the new modified sequences have an increased bandwidth of scalar transfer compared to the conventional versions. For clean dipolar transfer the DIPSI-2rc-XY4 sequence and the TOWNY-XY16 sequence have the largest bandwidth.

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