Theoretical background of optimal control calculations and rescaling property

In this section, we briefly outline the necessary theory for the calculations used in our study. Besides spin dynamics, we summarize the optimal control procedures used to design new pulse sequences to facilitate the discussion and to adapt optimal control experiments to a range of MAS frequencies.

We base our analysis on the irreducible spherical tensor formalism which is convenient to describe rotations of spherical tensor operators (51). The total NMR Hamiltonian can be split into an internal part, $H_{\text{int}}$, which includes the chemical shielding, dipolar and J-coupling interactions (possibly also the quadrupolar interaction), and an external part, $H_{\text{RF}}$, describing the influence of radiofrequency (rf) irradiation. The calculations are conducted in the reference frame which rotates around the axis given by the direction of an external static magnetic field with a frequency equal to the Larmor frequency of the spins. In addition, the secular approximation is assumed, and the Hamiltonians can be written as

$$H(t) = H_{\text{int}}(t) + H_{\text{RF}}(t)$$

$$H_{\text{RF}}(t) = \sum_l \omega_{l,x}^{\text{RF}}(t) I_{l,x} + \omega_{l,y}^{\text{RF}}(t) I_{l,y}$$

$$H_{\text{int}}(t) = \sum_{\lambda} A_{0,0}^{\lambda,\text{LAB}} T_{\lambda}^{\text{iso}} + \sum_{\lambda} T_{\lambda}^{\text{aniso}} \sum_{r=-2}^{+2} \omega_{(r)}^{\lambda} e^{-i r \omega_{\text{RF}} t}$$

$$\omega_{(r)}^{\lambda} = \sum_{p,q=-2}^{+2} A_{2,p}^{\lambda,\text{PAS}} D_{p,q}^{(2)}(\Omega_{\text{PAS}}^{\text{CRY}}, \Omega_{\text{PAS}}^{\text{ROT}}) D_{q,r}^{(2)}(\Omega_{\text{PAS}}^{\text{ROT}}, \Omega_{\text{PAS}}^{\text{LAB}})$$

The rf Hamiltonian $H_{\text{RF}}(t)$ involves external manipulations in terms of rf irradiation. In Eq. 2, it is expressed as a sum over $x$- and $y$-phase contributions for the involved spins (or spin species) through the functions $\omega_{l,x}^{\text{RF}}(t)$ and $\omega_{l,y}^{\text{RF}}(t)$. These functions constitute the actual rf pulse sequence and are optimized in the optimal control procedure.

The internal Hamiltonian $H_{\text{int}}(t)$ in Eq. 3 is split into the time independent isotropic part, and the time dependent anisotropic part expressed as a Fourier series with the interaction amplitudes $\omega_{(r)}^{\lambda}$ defined in Eq. 4. The symbol $A_{l,q}^{\lambda,\text{PAS}}$ denotes the component $q$ of the rank-$l$ spatial tensor corresponding to the interaction $\lambda$, and is expressed in the principal axis system (PAS) (51). $A_{l,q}^{\lambda,\text{PAS}}$ is transformed via the crystal-fixed frame (CRY) and the rotor-fixed frame (ROT) into the laboratory frame (LAB) using rank-2 Wigner coefficients $D_{p,q}^{(2)}(\Omega)$, using the Euler angles $\Omega_{\text{PAS}}^{\text{CRY}}$, $\Omega_{\text{PAS}}^{\text{ROT}}$, and $\Omega_{\text{ROT}}^{\text{LAB}}$ which describe the relative orientations of these reference systems. For powder samples, the distribution of crystallite orientations is reflected in the distribution of the Euler angles $\Omega_{\text{ROT}}^{\text{CRY}}$. The MAS condition implies that the transformation from ROT to LAB is time dependent and can be expanded using $\Omega_{\text{ROT}}^{\text{LAB}}(t) = (\omega_{R} t, \beta_{RL}, 0)$, where $\omega_{R}$ denotes the angular frequency of the rotor, and $\beta_{RL}$ is the magic angle ($\beta_{RL} = \text{atan} \sqrt{2}$). The terms $T_{\lambda}^{\text{iso}}$ and $T_{\lambda}^{\text{aniso}}$ represent spin operators of isotropic and anisotropic parts of the respective interactions (51).
For numerical calculations, the time dependence of the Hamiltonian is approximated by assuming a piecewise constant function, which can be obtained by sampling the total Hamiltonian at times $t_k$ separated by intervals $\Delta t$, $t_k = k\Delta t$, $k = 0, 1, \ldots N$. A convenient choice of $\Delta t$ is based on the MAS frequency, $\Delta t = (1/M) \cdot (2\pi/\omega_R)$, where $M$ is the number of time steps within one rotor period, as it allows to keep synchronization with the sample rotation (52-54). The spin dynamics of an NMR experiment can then be expressed in terms of the density matrix operator, $\rho(t)$, evolving under the influence of the propagators $U_k(t_{k-1}, t_k)$ extending the evolution by the time interval $\Delta t$. At the end of the pulse sequence, $T = N\Delta t$, we have

$$\rho(T) = U_N \cdots U_2 U_1 \rho(0) U_1^\dagger U_2^\dagger \cdots U_N^\dagger$$

We set up a numerical optimization protocol to find the series of rf amplitudes $\omega_{i,a}(t_k)$ that constitute the total pulse sequence and provide the maximal transfer efficiency for a desired magnetization transfer process. The optimal control algorithm GRAPE (19) was implemented in the software package SIMPSON (41, 46, 47) to achieve this goal. Typically, a state-to-state transfer of magnetization from one nucleus to another represented by the initial state $\rho(0)$ and the final state $F$ at time $t = T$ is optimized using the target function

$$\Phi = \sum_i \omega_i \Phi_i$$

$$\Phi_i = Tr \{F^\dagger U(0,T) \rho(0) U(0,T)^\dagger \}$$

Optimal control theory provides easy access to the first derivative of the objective function $\Phi_i$ and allows to optimize tens of thousands of variables – rf pulse amplitudes and phases – at once. The summation over $i$ in Eq. 7 reflects the fact that the calculation is performed for a particular set of parameters like the orientation of one crystallite within a powder sample. Because the pulse sequence is required to work for all possible crystallite orientations, independent calculations are repeated for a representative set of orientations. The total target function is a sum weighted by the relative contributions $\omega_i$ of each orientation. Additionally, specific experimental conditions such as the distribution of chemical shifts or the rf field inhomogeneity distribution within the sample can be covered as well. Eq. 7 allows to introduce these conditions easily by increasing the sum.

We show below that tm-SPICE sequences can be adapted for a different MAS frequency $\omega_R^{\text{new}}$ according to the following protocol. Using a scaling factor

$$\xi = \omega_R^{\text{new}} / \omega_R^{\text{opt}}$$

the new pulse shape is obtained by adjusting

1. length of the shape: $T_{\text{new}} = T / \xi$
2. rf amplitudes of the shape: $\omega_{i,\text{new}} = \omega_{i,\text{opt}} \cdot \xi$
We define new time steps as $t'_k = k \Delta t'$, where $\Delta t' = (1/M) \cdot (2\pi/\omega^{\text{new}}_R)$ and $k = 1, \ldots, N$. At the time $t'_k$, the rotor attains the same orientation as during the time $t_k$ defined previously with the frequency $\omega^{\text{opt}}_R$, as it is schematically depicted in Figure S-1. We also have $\Delta t' = \Delta t / \xi$, thus the rf pulses are again synchronized with the sample rotation.

![Figure S-1](image)

**Figure S-1.** Representation of the time steps used in the numerical simulation of a MAS experiment. The length of each circle represents one rotor period, the red color indicates the nominal MAS frequency. When the frequency is larger, the rotor period is shorter, and it corresponds to the inner circle. The relative phase of the rotor is the same at times $t_k$.

The central argument, that optimal control sequences can be adjusted to different MAS frequencies and keep their efficiency, is based on the fact that the propagators $U_k$, Eq. 6, remain the same upon a change of the MAS frequency. The exponent contains the terms $H_{\text{int}}(t_k)\Delta t$ and $H_{\text{RF}}(t_k)\Delta t$. By rescaling the rf amplitudes $\omega^{\text{RF}}_R(t)$, $\omega^{\text{RF}}_S(t)$ with the factor $\xi$, the new rf Hamiltonian $H'_\text{RF}(t'_k)$ satisfies $H'_\text{RF}(t'_k)\Delta t' = H_{\text{RF}}(t_k)\Delta t$, ensuring that this part of the propagator exponent is identical – the effect of the pulses is unchanged, the same effective angle is achieved. In case of the term $H_{\text{int}}(t_k)\Delta t$, the situation is more complex. By rescaling the time increments, we ensure the same sampling of the time modulations of the interactions, $H_{\text{int}}(t'_k) = H_{\text{int}}(t_k)$. However, the resulting propagators $U_k$ are different since $\Delta t' \neq \Delta t$. We note that we designed our pulse sequence to work equally well for all possible crystallite orientations, i.e., different conditions in Eq. 7. This powder distribution, which is imposed by the Euler angles $\Omega_{\text{CRY}}$, leads to a distribution of the effective interaction amplitudes, Eq. 4. If we assume that only a dipole-dipole interaction contributes, the effective amplitudes $d_{\text{eff}}$ for different crystallite orientations will be within the interval $[0, d_{\text{max}}]$ and they will be modulated by sample rotation as depicted in Figure S-2. Similarly, the ratio $\Delta t' / \Delta t$ can be regarded as a scaling factor of the effective interaction amplitudes.
Figure S-2. Dependence of the effective dipolar coupling $d_{\text{eff}}$ on crystallite orientation and on sample rotation, evaluated using Equations 3 and 4, $d_{\text{eff}}(t) = \sum_{r=-2}^{+2} \omega_{(r)}^2 e^{-\imath \omega_{(r)} t}$. Different curves correspond to different crystallite angles $\phi_{\text{CRY}}^{\text{ROT}}$ with values indicated at each curve. The horizontal axis represents time as a fraction of one rotor period. At different crystallites, the effective coupling is scaled by an amount depending on the orientation of the inter-nuclear vector with respect to the rotor axis (i.e., angle $\phi_{\text{CRY}}^{\text{ROT}}$) and it is periodically modulated in time as the sample rotates. The initial phase of these modulations depends on the crystallite angle $\phi_{\text{CRY}}^{\text{ROT}}$. This phase can be absorbed into the rotor phase.

After rescaling, the propagator $U_k$ will be thus identical to another original propagator corresponding to a different crystallite orientation. This is true for $1/\xi < 1$, i.e., for transformation to higher MAS frequencies. When going to $\omega_R^{\text{new}} < \omega_R^{\text{opt}}$, propagators with $d_{\text{eff}} > d_{\text{max}}$ will not find their counterparts in the original set, which will lead to a decreased performance of the pulse sequence. When several anisotropic interactions are present, with different orientations of their principal axis systems, the internal Hamiltonian $H_{\text{int}}$ evaluated for a particular crystallite orientation might not simply be a scaled version of $H_{\text{int}}$ taken at a different orientation. Thus, a decreased performance should be expected.

Optimal control sequences are typically optimized to include robustness towards a distribution of the isotropic (time independent) interactions like chemical shifts. As a result, the variation in evolution under time independent interactions is compensated by design.
In this section, we provide details on the spatial distribution of the rf fields used in our study. We assumed a solenoidal coil with the length of 7.9 mm, diameter of 3.9 mm, and with 7 turns, which represents the typical coil used in the 3.2 mm MAS probes (Bruker) (12). The magnetic field of the coil was calculated using a semi-analytical model introduced by Engelke (55). It was then converted to the rf field amplitudes and phases presented in Figure S-3 as described in (12).

**Figure S-3.** Illustration of the rf field distribution in a 3.2mm MAS rotor. (A) Definition of coordinates and sample volume elements used in optimal control calculations with compensation of rf field inhomogeneities. (B) Cross-sections through the sample, \((z, r)\) plane for \(\theta=[90^\circ,270^\circ]\), showing the distribution of rf amplitudes and phases. The amplitude at the coil edges \((z=3.9 \text{ mm})\) reaches only 50% of the amplitude in the center of the coil, while the phase can vary up to \(\pm 30^\circ\). When the sample rotates, molecules experience periodical modulations of the rf field due to spatial inhomogeneity as it is depicted in (C) for \(r=1.5 \text{ mm}\).
Calculation of tm-SPICE pulse sequences

The optimization protocol used to generate tm-SPICE pulse sequences was published in Reference (15) and the main features are repeated here for convenience.

To account for the 3D distribution of rf fields in optimal control calculations, the sample volume was divided into elements distributed along the coil axis (7 values to digitize the $z$-coordinate) in the different cylindrical layers (3 values of the $r$-coordinate) and over the azimuthal angle $q$ (6 values). The actual values of the $x$ and $y$ components of the rf field are provided in the Supplementary Information of Ref. (15) (Tables S-1, S-2 and S-3). To save computation time, the calculation results corresponding to the $z$-coordinates -0.85 mm and -1.71 mm were assumed to be identical to $z=0.85$ mm and 1.71 mm, respectively. Under MAS conditions, sample rotation induces periodical changes of the azimuthal angle $q$ which modulates the applied rf pulses. The calculations are repeated independently for different positions within the sample volume – values of $z$ and $r$, and for initial rotor phases $\theta_0$.

The input script for our optimal control calculation is provided further below in this Supplementary Materials as well as the spin system parameters. For generating the tm-SPICE-16.5 sequences, the following parameters were assumed:

- proton Larmor frequency: 850MHz
- MAS frequency: 16.5 kHz
- shaped pulse duration: 60 rotor periods
- number of elements in the shapes: 1500
- crystal file: ZCW3_144 (the crystal file was adapted from data provided by M.H. Levitt)
- spin system: using 4-nuclei sets defined below

The optimization was divided into 3 levels of complexity.

**Level 1** – an ideal rf field as well as perfect on-resonance conditions were assumed, pulse sequence initiated by random numbers.

**Level 2** – spatial distribution of rf fields as described above is included while keeping on-resonance conditions. The pulse sequence is initiated by the result of the previous level

**Level 3** – a spread of chemical shifts is included, digitized using 3 values for the amide nitrogen (-13.4, 0, +13.4 ppm) and using 5 values for the alpha carbon (-12.5, -6.25, 0, +6.25, +12.5 ppm). The range of chemical shifts of the carbonyl carbon was digitized using 3 values (-7.5, 0, +7.5 ppm).

In the final level of the optimization, the calculation was performed on 224 CPUs in parallel and was stopped after 380 optimal control iterations, which took approximately 6 days.

The sequences generated for the numerical survey of the maximal achievable transfer efficiency for the NCA experiment (Figure 2 of the main text) used 2-nuclei spin systems and Level 2 of complexity defined above (no distribution of chemical shifts). Independent runs were used to generate optimal control pulse sequences for each contact time. Calculations were initialized with random values and the algorithm was stopped after 1500 iterations or earlier. This was sufficient to reach high transfer efficiencies. The change of the target function was smaller than 0.001 in the final iterations. Wall times of these calculations were significantly shorter thanks to the smaller spin system and avoiding averaging over chemical shift distributions.
Comparison and parametrization of ramp and adiabatic cross-polarization between $^{15}$N and $^{13}$C

In this section, we provide details on the numerical study in which we determined the maximal achievable transfer efficiency under conditions reflecting a realistic experimental situation. The results are presented in Figure 2 in the main text.

Ramp-CP

The linear ramp is applied on the $^{13}$C channel. In the calculation, the following parameters were optimized for each contact time:

1. $\omega_N$ – rf amplitude on the $^{15}$N channel, range $\omega_N \in [1,50]$ kHz
2. $\omega_C$ – maximal rf amplitude on the $^{13}$C channel, range $\omega_C \in [1,50]$ kHz
3. $x$ – linear ramp percentage, range $x \in [50,95]$ %

Adiabatic-CP

The waveform of a tangential shape of length $T$ is given by the following equation

$$\omega_C(t) = \omega_C \left\{1 + a \tan \left( \frac{2t}{T} - 1 \right) \arctan \left( \frac{T}{a} \right) \right\}$$

In the experiment, the tangential shape was applied on the $^{13}$C channel. In the calculation, the following parameters were optimized for each contact time:

1. $\omega_N$ – rf amplitude on the $^{15}$N channel, range $\omega_N \in [1,50]$ kHz
2. $\omega_C$ – average RF amplitude on the $^{13}$C channel, range $\omega_C \in [1,50]$ kHz
3. $r$ – range of tangential sweep, RF amplitude grows from $(1 - r)\omega_C$ up to $(1 + r)\omega_C$, range $r \in [0.001, 0.999]\,$
4. $a$ – shape factor of the tangent curve, range $a \in [0.005, 0.5]$

![Figure S-4](image_url)

**Figure S-4.** Definition of parameters used to characterize linear rf ramp (left) and adiabatic tangential pulse shape (right) used in the cross-polarization experiment.

Comparison of shapes

When inspecting the maximal possible transfer in the NCA experiment performed at a MAS frequency of 16.5 kHz (Figure 2 of the main text), we found that the linear rf ramp and the adiabatic tangential pulse shape CP yield the same transfer efficiency. As shown in Figure S-5, their waveforms are quite similar. The linear ramp approximates the tangential shape in its middle part. The minute discrepancies at the beginning and at the end of the tangential shape do not yield significant improvements. Figure S-5 shows how the rf amplitude is swept through the Hartmann-Hahn condition for contact times of 2.42 ms (40 rotor periods), 4.24 ms (70 rotor periods), and 6.06 ms (100 rotor periods). The curves represent the difference between the rf amplitudes applied on the $^{15}$N and the $^{13}$C channels. This difference should be equal to 16.5 kHz, which corresponds to the MAS frequency. Due to rf inhomogeneity, the difference of mean rf amplitudes is, however, larger for all cases.
Figure S-5. Comparison of linear rf ramp (red) and adiabatic tangential pulse shape (blue) sweeps in the cross-polarization experiment. The parameters $\{x, \omega_C, \omega_N\}$ and $\{r, a, \omega_C, \omega_N\}$ were optimized individually for contact times 2.42 ms (40 rotor periods), 4.24 ms (70 rotor periods), and 6.06 ms (100 rotor periods) assuming MAS frequency of 16.5 kHz (dashed grey line), spatial rf field inhomogeneity, and NCA transfer conditions.
Cross-polarization between amide $^1$H-$^{15}$N spins

Figure S-6. (A) Top curve – best achievable transfer efficiencies estimated by numerical optimizations of ramp-CP (linear rf ramp 70-100% applied on the $^1$H channel). Pulse sequence parameters were optimized for each contact time independently. In the calculations, the assumed dipolar coupling and CSA parameters correspond to a $^1$H-$^{15}$N spin pair that interacts with a dipolar coupling constant of 10 kHz. The sample is rotated with a MAS frequency of 16.5 kHz, assuming a static magnetic field strength of 700 MHz. (B) Illustration of the spatial distribution of the magnetization transfer efficiency for a ramp-CP optimized for a duration of 6 rotor periods (about 0.36 ms). The large dipolar coupling constant leads to improved robustness towards rf inhomogeneities. Efficient transfer is achieved in a larger volume as compared to the $^{15}$N-$^{13}$C case.
Cross-polarization between $^{15}$N and $^{13}$C$\alpha$ or $^{13}$C' – mapping recoupling conditions

Here we present the results of numerical calibration of the linear rf ramp CP experiment applied to the NCA and NCO transfers. Figure S-7 complements similar data presented in the main text, Figure 5A.
Figure S-7. Transfer efficiencies calculated for NCA and NCO ramp-CP experiments. The calculations were performed over a wide range of rf amplitudes and for MAS frequencies of 13-19.5 kHz indicated in the graph titles. A linear ramp 90-100 % was applied on the $^{13}$C channel using the contact times indicated in the graph titles. Calculations assumed a magnetic field of 16.5 T (corresponding to a $^1$H Larmor frequency of 700 MHz), and a realistic 3D distribution of the rf fields generated by the solenoid coil. The maps can be used to identify appropriate rf parameters for the experiment.
Effect of proton decoupling on transfer efficiency as a function of MAS frequency

Experimentally, we observe a decrease of the signal intensities with increasing MAS frequencies, see Figure 6 of the main text. Using numerical simulations, we explain this by the effect of insufficient proton decoupling during the NCA/NCO transfer.

The spin systems, consisting of 8 nuclei and involving 4 heteroatoms and 4 nearby protons, were derived from the f-MLF structure (PDB entry 1Q7O) focusing on the leucine residue and are depicted in Figure S-8. The tm-SPICE-16.5 pulse sequence was used and rescaled to the corresponding MAS frequency while a fixed amplitude (continuous wave) rf irradiation was applied on the proton channel. For the sake of computation time, the spatial rf inhomogeneity was approximated by a corresponding distribution along the coil axis while rotational modulations were ignored for all 3 rf channels.

![Figure S-8. Definition of the spin systems used to evaluate the influence of insufficient proton decoupling on the NCA/NCO transfer efficiency.](image)

Figure S-9 demonstrates how the NCA/NCO transfer efficiency depends on the proton rf amplitude at different MAS frequencies. Sufficient proton decoupling is achieved using 200 kHz rf amplitude which is out of reach for a typical 3.2 mm MAS probe. At the same time, we observe decreasing performance of the tm-SPICE-16.5 sequence for increasing MAS frequency when the proton rf amplitude is fixed at 85 kHz (used in the experiment). In particular, the numerically predicted NCA transfer efficiency drops by 55% when the MAS frequency is increased from 13 to 19.5 kHz and in the case of the NCO transfer the efficiency decreases by 30%. Table S-1 provides a direct comparison of the relative experimental spectral intensities (integral of all three Cα peaks) with the numerically predicted transfer efficiencies calculated at different MAS frequencies (still assuming 85 kHz proton decoupling used for all MAS frequencies). We observe a fairly good agreement.
Figure S-9. Transfer efficiency in the NCA (left) and NCO (right) tm-SPICE-16.5 experiments as a function of rf amplitude of the continuous-wave proton (\textsuperscript{1}H) decoupling, calculated for MAS frequencies of 13, 16.5 and 19.5 kHz.

Table S-1. Relative intensities of the NCA transfer of the tm-SPICE-16.5 sequence as a function of MAS frequency. Simulation accounts for insufficient proton decoupling.

|        | 13 kHz | 15 kHz | 16.5 kHz | 18 kHz | 19.5 kHz |
|--------|--------|--------|----------|--------|----------|
| experiment | 1.00   | 0.93   | 0.84     | 0.72   | 0.55     |
| simulation | 1.00   | 0.86   | 0.71     | 0.58   | 0.45     |
Spin-system parameters used in numerical simulations – SIMPSON convention

Simulations of $^1$H-$^{15}$N transfer

spinsys {
  channels 1H 15N
  nuclei  1H 15N
  shift 1  0p 7.7p 0.65 37.47 84.54 134.52
  shift 2  0p 99p 0.19 103.01 -141.57 65.13
  dipole 1 2 10000.0 0 142.20 -142.56
  jcoupling 1 2 -92 0 0 0 0 0
}

Simulations of NCA transfer using 2 spins, $^{15}$N-$^{13}$C\(\alpha\)

spinsys {
  channels 15N 13C
  nuclei  15N 13C
  shift 1  0p  99p 0.19 103.01 -141.57 65.13
  shift 2  0p -20p 0.43 -81.06 37.80 37.44
  dipole 1 2 1019.18 0 63.76 113.83
  jcoupling 1 2 -11 0 0 0 0 0
}

Simulations of NCO transfer using 2 spins, $^{15}$N-$^{13}$C'\(\)

spinsys {
  channels 15N 13C
  nuclei  15N 13C
  shift 1  0p  99p 0.19 103.01 -141.57 65.13
  shift 2  0p -76p 0.90 100.87 -127.27 -131.30
  dipole 1 2 1349.5 0 72.69 -27.59
  jcoupling 1 2 -15 0 0 0 0 0
}

Optimizations of tm-SPICE NCA transfer using 4 spins, $^{13}$C'-$^{15}$N-$^{13}$C\(\alpha\)-$^{13}$C\(\beta\)

spinsys {
  channels 15N 13C
  nuclei  15N 13C 13C 13C
  shift 1  0p  99p 0.19 103.01 -141.57 65.13
  shift 2  0p -20p 0.43 -81.06 37.80 37.44
  shift 3 118.4p -76p 0.90 -150.38 89.66 -24.46
  shift 4 -16.1p -20p 0.43 -81.06 37.80 37.44
  dipole 1 2 1019.1 0 63.76 113.83
  dipole 1 3 224.7 0 92.27 88.65
  dipole 1 4 207.8 0 75.88 149.71
  dipole 2 3 -2153.9 0 61.21 -115.71
}
dipole 2 4 -2119.0 0 88.50 -0.56
dipole 3 4 -476.3 0 105.97 29.37

jcoupling 1 2 -11 0 0 0 0
jcoupling 2 3  55 0 0 0 0
jcoupling 2 4  35 0 0 0 0
}

Optimizations of tm-SPICE NCO transfer using 4 spins, $^{13}$Cα-$^{13}$C'.$^{15}$N-$^{13}$Cα

spinsys {
  channels 15N 13C
  nuclei   15N 13C 13C 13C
  
  shift 1 0p 99p 0.19 103.01 -141.57 65.13
  shift 2 0p -76p 0.90 100.87 -127.26 -131.30
  shift 3 -120.2p -20p 0.43 -81.06 37.80 37.44
  shift 4 -115.4p -20p 0.43 -81.06 37.80 37.44
  dipole 1 2 1349.4 0 72.69 -27.58
  dipole 2 4 -537.0 0 95.86 -47.18
  dipole 2 3 -2219.0 0 124.05 -71.46
  dipole 1 4 1019.1 0 63.76 113.83
  dipole 1 3 231.2 0 101.03 -49.47
  dipole 3 4 -144.8 0 106.93 -55.43
  jcoupling 1 2 -15 0 0 0 0
  jcoupling 1 3 7 0 0 0 0
  jcoupling 1 4 -11 0 0 0 0
  jcoupling 2 3 55 0 0 0 0
}

Simulation of proton decoupling influence on tm-SPICE NCA transfer using 8 spins

spinsys {
  channels 15N 13C 1H
  nuclei  15N 13C 13C 13C 1H 1H 1H 1H
  
  shift 1 0p 99p 0.19 103.01 -141.57 65.13
  shift 2 0p -20p 0.43 -81.06 37.80 37.44
  shift 3 115.4p -76p 0.90 100.87 -127.26 -131.30
  shift 4  -16.1p -10p 0.3 0 0 0
  # for 1H shifts, water is assumed on resonance
  shift 5 4.6p 7.7p 0.65 37.46 84.53 134.52
  shift 6 -0.17p  8p 0.5 0 0 0
  shift 7  -2.56p  6p 0.5 0 0 0
  shift 8  -2.56p  6p 0.5 0 0 0
  dipole 1 2 1019.1 0 63.76 113.83
  dipole 1 3 1349.4 0 72.69 -27.58
  dipole 1 4 207.87 0 75.88 149.71
  dipole 1 5 12853.5 0 142.19 -142.55
  dipole 1 6 1395.7 0 35.97 98.51
  dipole 1 7 590.5 0 99.04 150.58
Simulation of proton decoupling influence on tm-SPICE NCO transfer using 8 spins

spinsys {
    channels 15N 13C 1H
    nuclei 15N 13C 13C 13C 1H 1H 1H 1H

    shift 1 0p 99p 0.19 103.01 -141.57 65.13
    shift 2 0p -76p 0.90 100.87 -127.26 -131.30
    shift 3 -120.2p -20p 0.43 -81.06 67.80 -37.44
    shift 4 -115.4p -20p 0.43 -81.06 37.80 37.44

    # for 1H shifts, water is assumed on resonance
    shift 5 4.6p 7.7p 0.65 37.46 37.80 37.44 37.44
    shift 6 -0.17p 8p 0.5 0 0
    shift 7 -0.22p 8p 0.5 0 0
    shift 8 -2.56p 6p 0.5 0 0 0

    dipole 1 2 1349.4 0 72.69 -27.58
    dipole 1 3 231.2 0 101.03 -49.47
    dipole 1 4 1019.1 0 63.76 113.83
    dipole 1 5 12853.5 0 37.80 37.44
    dipole 1 6 1395.7 0 144.02 -81.48
    dipole 1 7 778.4 0 73.69 104.86
dipole 1 8 692.4 0 39.65 169.51
dipole 2 3 -2219.0 0 124.05 -71.46
dipole 2 4 -537.0 0 95.86 -47.18
dipole 2 5 -3868.5 0 53.97 -7.70
dipole 2 6 -1844.2 0 120.13 -54.00
dipole 2 7 -3202.3 0 58.85 74.08
dipole 2 8 -2017.8 0 13.85 -151.78

dipole 3 4 -144.8 0 106.94 -55.43
dipole 3 5 -2050.6 0 82.42 -35.14
dipole 3 6 -467.3 0 121.86 -60.31
dipole 3 7 -23949.7 0 76.67 31.86

dipole 3 8 -3107.8 0 43.46 -94.80

dipole 4 5 -3268.9 0 47.63 91.66

dipole 4 6 -23712.0 0 161.48 -178.00

dipole 4 7 -501.3 0 70.01 108.00

dipole 4 8 -587.9 0 44.75 145.41

dipole 5 6 -4853.5 0 146.92 -100.83

dipole 5 7 -10678.5 0 88.10 -60.75

dipole 5 8 -8257.1 0 120.14 1.73

dipole 6 7 -1497.2 0 123.30 -77.25

dipole 6 8 -1452.9 0 147.35 -39.59

dipole 7 8 -6782.3 0 60.08 -116.72

jcoupling 1 2 -15 0 0 0 0 0
jcoupling 1 3 7 0 0 0 0 0
jcoupling 1 4 -11 0 0 0 0 0
jcoupling 2 3 55 0 0 0 0 0
jcoupling 1 5 -92 0 0 0 0 0
jcoupling 3 7 140 0 0 0 0 0
jcoupling 4 6 140 0 0 0 0 0
}
}
Typical SIMPSON input files

The SIMPSON program that can account for rotation-modulated rf inhomogeneities is available from the web www.optimal-nmr.net. It is still under development and this feature requires a specific setup of the simulation which is not described in the previous SIMPSON papers. In particular, the time step of discretization of a shaped pulse must be smaller than 1/6 of the rotor period. The files containing the parametrization of the rf fields (coil_inhom.dat), as well as the following input files, can be obtained from the web www.optimal-nmr.net or on request from Z.T.

Calculation of transfer efficiency maps – ramp-CP

source NCA.spinsys
# or any other text-file containing spinsys section

par {
    method     direct dsysv
    crystal_file zcw3_144
    gamma_angles 1
    rfmap     coil_inhom.dat
    start_operator       I1x
    detect_operator      I2x
    proton_frequency     700e6
    sw                   1e6/100
    np                   1
    num_cores 28
    # this is to run on HPC, adjust to your computer’s number of cores
}

proc pulseq {} {
    global par shN shC

    maxdt $par(maxdt)
    pulse_shaped_rotormodulated $par(dur) $shN $shC
    acq
}

proc main {} {
    global par shN shC

    if {[llength $::argv] != 3} {
        puts stderr "Usage: simpson $par(name).in <MAS kHz> <dur us>
        exit
    }
    set mas [lindex $::argv 1]
    set par(spin_rate) [expr $mas*1000]
    set par(dur) [lindex $::argv 2]
    set par(maxdt) [expr 1.0e6/$par(spin_rate)/16]
    set Nelem 1000

    set fn [open $par(name)_$mas\_dur\_$par(dur)_results.txt w]
    puts $fn " rfN(const)  rfC(ramp 90-100)  eff "

    for {set rfC 5000} {$rfC<=60000} {incr rfC 1000} {
set par(rfC) [expr $rfC*1.0]
set shC [shape_create $Nelem -ampl {$par(rfC)*(0.9+0.1*(0-1)/$Nelem)}]
for {set rfN 5000} {$rfN<=55000} {incr rfN 250} {
    set par(rfN) [expr $rfN*1.0]
    set shN [shape_create $Nelem -ampl $par(rfN)]
    set f [fsimpson]
    set vals [findex $f 1 -re]
    funload $f
    puts $fn "[format "%.10f" $par(rfN)] [format "%.10f" $par(rfC)] $vals"
    free_shape $shN
} free_shape $shC
flush $fn
}

Calculation of tm-SPICE-16.5 sequence

# ZERO QUANTUM transfer, little RF energy penalty and hard RF limits

source NCACoCCB.spinsys
# or any other text-file containing spinsys section

par {
    num_cores 1
    # this calculation is distributed over multiple cores using MPI protocol
    method   direct dsyev
    crystal_file zcw3_144.cry
    gamma_angles 1
    spin_rate  16500
    start_operator  I1x
    detect_operator I2x
    proton_frequency 850e6
    sw  1e6

    variable Nspins 4
    variable recalc pow(2,2-Nspins)
    # define number of spins and calculate normalization factor
    oc_method CG
    oc_grad_level 2
    oc_var_save_proc rfstore
    conjugate_fid false
    # optimal control related parameters
}

# procedure to store rf shape(s) during oc_optimize and to monitor convergence
proc rfstore {} {
    global par rfsh1 rfsh2 optname itercount fout tfcomponents
    incr itercount $par(oc_var_save_iter)
    save_shape $rfsh1 $optname\_N_temp_$itercount.dat
save_shape $rfsh2 $optname\_C_temp\_$itercount.dat
puts $fout "Iter $itercount : $tfcomponents"
flush $fout
}

# pulse sequence when ignoring rf temporal modulations
proc pulseq_OC {} {
    global par rfsh1 rfsh2
    maxdt $par(maxdt)
    reset
    pulse_shaped $par(duration) $rfsh1 $rfsh2
    oc_acq_hermit
}

# pulse sequence which includes rf temporal modulations
proc pulseq_OC_rotmod {} {
    global par rfsh1 rfsh2
    maxdt $par(maxdt)
    reset
    pulse_shaped_rotormodulated $par(duration) $rfsh1 $rfsh2
    oc_acq_hermit
}

# optimal control target function
proc target_function {} {
    global par rfsh1 rfsh2
    set par(np) 1
    set f [fsimpson]
    set Res [expr [findex $f 1 -re]*$par(recalc) ]
    funload $f
    set pen1 [expr $par(lamN)*[shape_energy $rfsh1 $par(duration)]]
    set pen2 [expr $par(lamC)*[shape_energy $rfsh2 $par(duration)]]
    set Res [expr $Res - $pen1 - $pen2]
    return [format "%.20f" $Res]
}

# optimal control gradients, hidden variable $par(_phivals_) contains
# target_function value calculated along
proc gradient {} {
    global par rfsh1 rfsh2  tfcomponents
    # FID length with gradients is 2channels x number-of-elements-in-shape
    set par(np) [expr 2*$par(Norig) ]
    # looping over offset profiles is done in averaging_file (if defined)
    set f [fsimpson]
    fscale $f -scale $par(recalc)
    oc_grad_add_energy_penalty $f $rfsh1 -$par(lamN) $rfsh2 -$par(lamC)
    set pen1 [expr $par(lamN)*[shape_energy $rfsh1 $par(duration)]]
    set pen2 [expr $par(lamC)*[shape_energy $rfsh2 $par(duration)]]
    set tfcomponents [list [expr $par(_phivals_)*$par(recalc)] $pen1 $pen2 ]
    return $f
}
# generates list of control-point numbers distributed over +/-SW/2 range
proc get_lims {SWH cp} {
    if { $cp <= 1} {
        set Res 0
    } else {
        set step [expr double($SWH)/($cp-1)]
        set Res {} 
        for {set i 0} {$i < $cp} {incr i} {
            set shft [expr double($SWH)/2.0-$i*$step]
            lappend Res $shft
        }
        return $Res
    }
}

# preparing averaging file (over isotropic shifts)
proc prepare_ave {vals1 vals2 filename} {
    set fd [open $filename w]
    puts $fd "shift_1_iso shift_2_iso weight"
    set w [expr 1.0 / ([llength $vals1] * [llength $vals2]) ]
    foreach a $vals1 {
        foreach b $vals2 {
            puts $fd "[format "%8.2f" $a]p [format "%8.2f" $b]p [format "%12.8f" $w]"
        }
    }
    close $fd
}

proc main {} {
    global par rfsh1 rfsh2 limsC limsN optname itercount fout tfcomponents
    set number_of_rotor_periods 60
    set taur [expr 1.0e6/$par(spin_rate)]
    set par(duration) [expr $number_of_rotor_periods*$taur]
    set pulses_per_period 25
    set par(Norig) [expr $number_of_rotor_periods*$pulses_per_period]
    set tfcomponents [list 0.0 0.0 0.0]
    set par(lamN) 3e-11
    set par(lamC) 1e-11
    set par(maxdt) 3
    set par(levN) 35000
    set par(levC) 35000

    # level 1
    set rfsh1 [rand_shape 5000 $par(Norig) [expr int($number_of_rotor_periods/2)]]
    set rfsh2 [rand_shape 5000 $par(Norig) [expr int($number_of_rotor_periods/2)]]
    set optname shape_lev1
    set fout [open $optname\_output.txt w]
    set par(oc_var_save_iter) 30
    set par(pulse_sequence) pulseq_OC
    set itercount 0
    set par(oc_max_iter) 150
    set tfopt [oc_optimize $rfsh1 -max $par(levN) $rfsh2 -max $par(levC)]
    save_shape $rfsh1 $optname\_final_N.dat
save_shape $rfsh2 $optname\_final_C.dat
close $fout

# level 2
set optname shape_lev2
set fout [open $optname\_output.txt w]
set par(rfmap) coil_inhom.dat
# adds rf modulations in, need to change pulse sequence as well
set par(pulse_sequence) pulseq_OC_rotmod
set itercount 0
set par(oc_var_save_iter) 5
set par(oc_max_iter) 500
set tfopt [oc_optimize $rfsh1 -max $par(levN) $rfsh2 -max $par(levC)]
save_shape $rfsh1 $optname\_final_N.dat
save_shape $rfsh2 $optname\_final_C.dat
close $fout

# level 3
set optname shape_lev3
set fout [open $optname\_output.txt a]
# add averaging over distribution of chemical shifts by defining averaging_file
set limsN [get_lims 26.8 3]
set limsC [get_lims 25 5]
set par(averaging_file) $par(name).ave
prepare_ave $limsN $limsC $par(averaging_file)
set itercount 0
set par(oc_var_save_iter) 5
set par(oc_max_iter) 500
set tfopt [oc_optimize $rfsh1 -max $par(levN) $rfsh2 -max $par(levC)]
save_shape $rfsh1 $optname\_final_N.dat
save_shape $rfsh2 $optname\_final_C.dat
close $fout

free_all_shapes
}
We provide data files of the tm-SPICE-16.5 and tm-SPICE-20 NCA and NCO experiments in the Bruker wave format which can be directly used on the Bruker NMR spectrometers. These files can be downloaded from the publisher website or from www.optimal-nmr.net.

**Data S1.** tmSPICE-MAS16.5kHz-NCA.zip - tm-SPICE shaped pulses for the NCA experiment optimized for the MAS frequency of 16.5 kHz and the duration of 60 rotor periods. Maximal rf amplitude set to 35 kHz on both channels, mean rf amplitude is 10/15 kHz on the $^{13}$C/$^{15}$N channels.

**Data S2.** tmSPICE-MAS16.5kHz-NCO.zip - tm-SPICE shaped pulses for the NCO experiment optimized for the MAS frequency of 16.5 kHz and the duration of 60 rotor periods. Maximal rf amplitude set to 35 kHz on both channels, mean rf amplitude is 10/15 kHz on the $^{13}$C/$^{15}$N channels.

**Data S3.** tmSPICE-MAS20kHz-NCA.zip - tm-SPICE shaped pulses for the NCA experiment optimized for the MAS frequency of 20 kHz and the duration of 70 rotor periods. Maximal rf amplitude set to 40 kHz on both channels, mean rf amplitude is 10 kHz on the both $^{13}$C/$^{15}$N channels.

**Data S4.** tmSPICE-MAS20kHz-NCO.zip - tm-SPICE shaped pulses for the NCO experiment optimized for the MAS frequency of 20 kHz and the duration of 70 rotor periods. Maximal rf amplitude set to 40 kHz on both channels, mean rf amplitude is 10 kHz on the both $^{13}$C/$^{15}$N channels.

**Figure S-10.** Transfer efficiency of tm-SPICE-16.5 NCA/NCO experiments calculated over a range of chemical shift offsets. In both cases, a flat profile is obtained over the desired region.
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