

Shift-driven modulations of spin-echo signals

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Since the pioneering works of Carr-Purcell and Meiboom-Gill [Carr HY, Purcell EM (1954) *Phys Rev* 94:630; Meiboom S, Gill D (1958) *Rev Sci Instrum* 29:688], trains of π -pulses have featured amongst the main tools of quantum control. Echo trains find widespread use in nuclear magnetic resonance spectroscopy (NMR) and imaging (MRI), thanks to their ability to free the evolution of a spin-1/2 from several sources of decoherence. Spin echoes have also been researched in dynamic decoupling scenarios, for prolonging the lifetimes of quantum states or coherences. Inspired by this search we introduce a family of spin-echo sequences, which can still detect site-specific interactions like the chemical shift. This is achieved thanks to the presence of weak environmental fluctuations of common occurrence in high-field NMR—such as homonuclear spin-spin couplings or chemical/biochemical exchanges. Both intuitive and rigorous derivations of the resulting “selective dynamical recoupling” sequences are provided. Applications of these novel experiments are given for a variety of NMR scenarios including determinations of shift effects under inhomogeneities overwhelming individual chemical identities, and model-free characterizations of chemically exchanging partners.

chemical exchange | dynamic decoupling | magnetic field inhomogeneity | magnetic resonance | quantum control

The unprecedented scope of applications achieved by contemporary magnetic resonance reflects the degree of control that can be imparted on the spins' evolution. Using judicious combinations of multiple-pulse sequences one can tailor Hamiltonians that highlight a variety of interactions. When coupled to the long-lived coherences typical of spin-1/2 nuclei, this enables probing matter over a broad range of conditions and scenarios—from nanomaterials to rocks under the oceans; from proteins to human metabolism and disease (1–4). Besides its wide scope of applications, NMR awakes constant interest as a benchmark for other fields of physics; in particular, the quantum information community has adopted a number of NMR paradigms as tools of its own (5–16). The most prominent example among these is the spin-echo sequence, proposed over half a century ago for removing inhomogeneous broadenings (17–19). When extrapolated to trains of π -pulses spaced by a constant delay (Fig. 1A), the resulting CPMG sequences eventually became associated to a long list of landmark measurements including T_2 determinations, structural-oriented experiments, diffusion measurements, *ex situ* investigations in inhomogeneous fields, kinetic chemical and biophysical determinations, spin decoupling, and single scan MRI (1–4). Overall, the extremely wide range of useful measurements that this single sequence enabled is truly remarkable.

Further CPMG generalizations have been proposed in recent years, aimed at improving the dynamical decoupling (DD) between a spin and its surroundings (5–9). In cases where environmental fluctuations are dominated by low-frequency components having a sharp cutoff, minimal decoherence was shown to arise when the modulation $h(t)$ imposed by the pulsing on the spin-bath interactions (Fig. 1B) departs from a single, constant value (10–16). Motivated by these findings, this work seeks the design of sequences that can highlight desirable site-specific molecular features, given certain a priori known features about

the fluctuations. We find that variations in the canonical CPMG timing enable interactions proportional to σ_z , such as chemical shifts, to impart a temporal modulation that one would assume beyond the reach of sequences fulfilling $\int_0^{TE} h(t') dt' = 0 - TE$ being the total echo time. This is a highly unusual effect, since a common aim of all these sequences is to *cancel out* evolutions proportional to the σ_z terms. Still, as shown below, the presence of infrequent fluctuations in a spin's environment can reintroduce a net Hamiltonian proportional to σ_z , whose effects can be detected with the aid of suitably designed sequences. Although we illustrate this fluctuation-driven recoupling for an NMR scenario where the interactions sought are given by chemical shifts, the application of these new sequences extends to a wider range of phenomena including spin-diffusion in coherently manipulated solid-state spin devices, motion-related phenomena in MRI, hyperfine couplings in solid-state assemblies, barrier fluctuations in Josephson junctions, or optical intermittency in photoluminescence experiments.

Theoretical Description of Selective Dynamical Recoupling

Despite the $\int_0^{TE} h(t') dt' = 0$ refocusing condition associated with DD, oscillations in the signals can still arise from these sequences if the targeted spin is subject to infrequent jumps in its evolution frequency. In quantum control parlance this would amount to allowing for a strong fluctuation of the qubit while under the action of dynamical decoupling. In NMR one would describe this as the reintroduction of chemical shifts even under the action of CPMG, owing to environment-driven offset changes. To visualize how this can lead to periodic σ_z -driven modulations consider a spin-echo train composed of N segments, each of duration $2\tau_i$ with a π -pulse in its center. Assume also that, to first order, the targeted spin executes on average a single spectral jump during the spin-echo train—from $-\omega_o$ to $+\omega_o$. Since each control π -pulse imposes a sign change of the evolution phase, the train's overall effect amounts to a square-wave modulation of the spin's dynamic phase; this is thus refocused for all segments, except for the one where the spectral jump has occurred (Fig. 1B). The net dispersion accumulated by the ensemble due to the $\xi(t)$ stochastic jump function, can then be computed by integrating the dynamic evolution phasor $\langle \exp(i\Delta\Phi) \rangle$ over a single $2\tau_i$ oscillation, and integrating this over all N segments comprising the π -pulse train. The signal contribution arising due to the fluctuations over TE will be

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herences or magnetizations between sites. The execution of a spin-echo train, however, can reactivate such transfers; in the slow-pulsing regime $(\omega_i - \omega_k)\tau \gg 1$ this will only happen with a low efficiency on the order of $\sim TE \cdot J_{ik}^2 / (\omega_i - \omega_k)$, consistent with the demands involved in the derivation of Eqs. 1–3. Relying on average Hamiltonian theory (27) to compute the final modulation expected from the sequence in Fig. 1E (SI Text, Supplement A), one reaches a first-order expression for the normalized amplitude that SDR will yield for an i -spin that is J -coupled to a k -spin:

$$\langle I_+ \rangle = \cos \left\{ \pi J \cdot TE - \frac{\pi J}{\omega_o} [(N-1) \sin(\omega_o x) + \sin(\omega_o (TE - x(N-1)))] \right\} \quad [4]$$

Besides an overall J -modulation that is constant for a fixed TE value, this expression is similar to that given in Eq. 3—with $\omega_o = (\omega_i - \omega_k)/2$ now denoting the frequency separation between sites. Notice that given the weak, exchange-like effects driven by the J -couplings, the addition of a third qubit leads to an analogous term modulated with a different ω_o -value. Fig. 2 summarizes the resulting modulations for a number of typical J -coupled scenarios including two isolated spins, the same system under the effect of sizable field inhomogeneities that preclude the measurement of individual resonance offsets, and a number of multispin systems. Shown together with the experiments are predictions arising from Eq. 4, as well as the results of numerical simulations where the full pulse sequence was propagated on

the basis of input parameters. Notice that, given the a priori known values of shifts and J -couplings, no fittings are actually involved in these comparisons. The main feature common to all these results is a clear modulation of the signals, defined solely by chemical shift differences that can be read out by Fourier transforms of the ensuing amplitude modulations. Notice that these modulations reveal spectral offsets among the coupled neighbors with high resolution even under gross inhomogeneous broadenings, and that the complexity of these patterns simply grows linearly with the number of distinct sites. Also worth stressing are the differences between these modulations and the evolution of zero-quantum states [which would also evolve as a function of frequency differences (29, 30)], or between them and experiments dominated by effective isotropic J Hamiltonians arising when applying windowless trains of π -pulses (31, 32).

Another mechanism capable of introducing the fluctuations required by SDR, is chemical exchange. In NMR this could involve tautomerisms, binding dynamics, or spin-diffusion. For the simplest scenario, involving a chemical exchange taking place at a rate κ that is slow in the NMR timescale between equally populated states, the formalism presented in SI Text, Supplement B predicts that the sequence in Fig. 1E will modulate the normalized resonance amplitudes as

$$\langle I_+ \rangle = 1 - \kappa \cdot TE + \frac{\kappa}{\omega_o} [(N-1) \sin(\omega_o x) + \sin(\omega_o (TE - x(N-1)))] \quad [5]$$

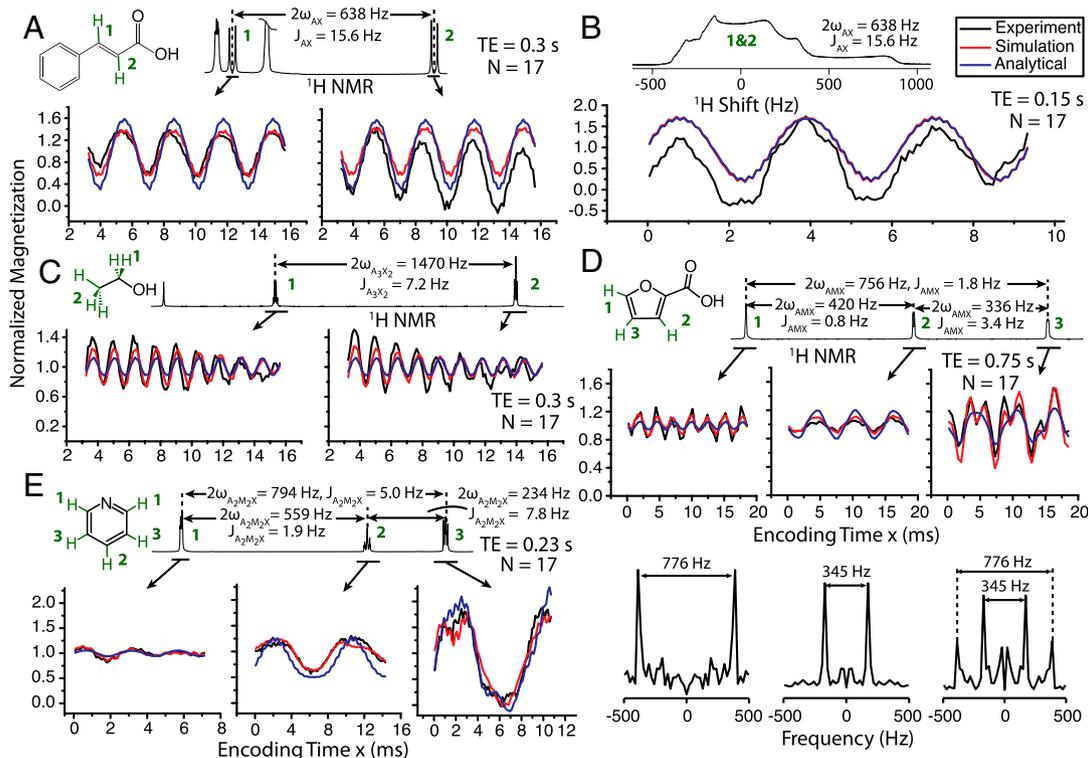


Fig. 2. Behavior observed for the illustrated compounds upon implementing the SDR sequence in Fig. 1E, as mediated by homonuclear ^1H - ^1H couplings, for the indicated parameters. Experiments (black traces) are compared against simulations (red) resulting from SpinEvolution (28) computations using the indicated parameters, and analytical curves (blue) arise from the two-site modulation predicted by Eq. 4. (A) x -dependence observed for the isolated olefinic proton pair of Cinnamic acid at high-resolution. (B) Idem but for the Cinnamic acid placed in a grossly inhomogeneous magnetic field (shimming coils off), illustrating SDR's ability to retrieve high resolution shift modulations even though it relies on fully refocused π -pulse trains. (C) Idem as (A) but for the two chemically distinct sites of ethanol/ D_2O —a five-proton system. (D) Behavior displayed by the three chemically distinct protons of Furoic acid in D_2O —an AMX spin system at this field—highlighting the dual modulations at $\omega_o = (\omega_A - \omega_M)/2$ and $\omega_o = (\omega_M - \omega_X)/2$ frequencies shown by site 3 arising upon Fourier transforming its baseline-corrected modulation curve. (E) SDR modulations for Pyridine, a site that like (D) possesses three chemically distinct proton sites but by contrast to it is characterized by five magnetically inequivalent spins. All x -dependent curves are shown normalized to a value of one.

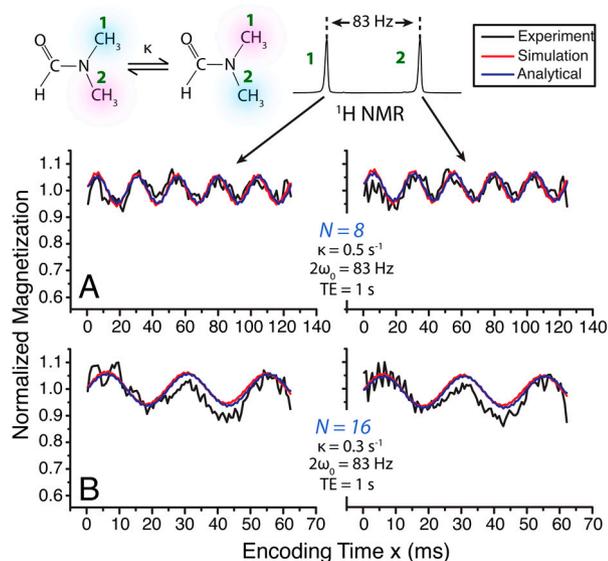


Fig. 3. Idem as illustrated in Fig. 2, but for a case where the indicated two-site chemical exchange process drives the fluctuation $\xi(t)$. Data were collected on 10% dimethylformamide (shown) in CCl_4 at 67 ± 0.25 (A) and 64 ± 0.25 °C (B) for a total TE of 1 sec. Simulations were done with SpinEvolution (28), and the analytical curves correspond to Eq. 5 for the indicated parameters.

where $\omega_o = (\omega_i - \omega_j)/2$ is now the half-difference between the sites interconverted by the dynamics. As illustrated in Fig. 3, these differences are again clearly visible in the modulations displayed by each of the exchanging partners. Also shown are the effects that changing the number N of π -pulses will have in the apparent modulation imparted by for a fixed overall TE. There is once again a remarkable agreement between the experimental results and these parameter-free fits. *SI Text, Supplement B* extends this two-site exchange to more complex networks and to unequally populated situations; these results reveal once again a desirable

superposition of single-frequency modulations such as those noted in Fig. 2.

The oscillatory modulations in Fig. 2 and 3 only evidence some of the instances where these recoupling sequences could be exploited. SDR can open a number of valuable NMR applications, including determinations of chemical shifts among J -coupled partners under challenging in vivo or *ex situ* conditions, or the definition of the precession frequencies of exchanging partners even when one of them is not clearly visible. Additional instances where these phenomena could be exploited include cross-relaxation transfers, and monitoring molecular diffusion in the presence of field gradients. In some of these instances the information being sought could also become amenable by modeling the signal's decay (2, 3). Still, the analysis of periodic, parameter-free modulations like those introduced in this work, make the measurement process much more robust. It is also evident that cross-fertilizations are possible between spin manipulations like those hereby introduced, and other state-of-the-art control strategies within the quantum information field. Examples of these to NMR, MRI, and other spectroscopic applications, will be presented in upcoming studies.

Materials and Methods

All experiments in this study were collected at 600 MHz using a Varian VNMR5® spectrometer and a 5 mm HCN inverse probe. Sequences based on the schemes shown in Figs. 1 A, D, and E were written; in all cases ^1H $\pi/2$ pulses were 8 μs and an XY-4 (33) supercycle was used over the course of the π -pulse train. Data were processed and analyzed offline; typical acquisition conditions included two phase-alternated scans, 20 sec recycle delays, and 2 sec acquisition times.

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Supporting Information

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SI Text

Supplementary Material A: Selective Dynamical Recoupling Driven by a High-Field J-Coupling. Assuming a system made up by two spin-1/2 qubits with zero average chemical shifts and a coupling among them, the total Hamiltonian of concern is (1)

$$H_t = \begin{pmatrix} \pi J/2 & 0 & 0 & 0 \\ 0 & \omega_o - \pi J/2 & \pi J & 0 \\ 0 & \pi J & -\omega_o - \pi J/2 & 0 \\ 0 & 0 & 0 & \pi J/2 \end{pmatrix}$$

where ω_o is the semidifference between the two-spins' chemical shifts and J is the spin-spin coupling. Focusing only on the zero-quantum subspace containing the off-diagonal elements, we have:

$$H_{\text{zero}} = \begin{pmatrix} \omega_o - \pi J/2 & \pi J \\ \pi J & -\omega_o - \pi J/2 \end{pmatrix}.$$

In a toggling reference frame (2) and over a cyclic RF perturbation of the form $\tau - \pi - 2\tau - \pi - \tau$ where ideal pulses are assumed, this Hamiltonian becomes

$$H_{\text{zero}}' = \begin{pmatrix} h(t) \cdot \omega_o - \pi J/2 & \pi J \\ \pi J & -h(t) \cdot \omega_o - \pi J/2 \end{pmatrix}$$

where the $h(t)$ square-wave modulation introduced in Fig. 1, is a function that assumes a value of 1 for $0 < t < \tau$ and $3\tau < t < 4\tau$, and a value of -1 for $\tau < t < 3\tau$. It is possible to transform to an interaction frame where the chemical shift terms are accounted for using the following evolution operator

$$U_{CS} = \begin{pmatrix} \exp[-i\omega_o\phi(t)] & 0 \\ 0 & \exp[i\omega_o\phi(t)] \end{pmatrix}$$

where $\phi(t) = \int_0^t h(t') dt'$. This leaves a Hamiltonian

$$H_{\text{zero}}''(t) = \begin{pmatrix} -\pi J/2 & \pi J \exp[2i\omega_o\phi(t)] \\ \pi J \exp[-2i\omega_o\phi(t)] & -\pi J/2 \end{pmatrix},$$

$$U_t = \begin{pmatrix} \exp(i\frac{\pi J t}{2}) & 0 & 0 & 0 \\ 0 & \cos(\pi J k t) \exp(-i\frac{\pi J t}{2}) & i \sin(\pi J k t) \exp(-i\frac{\pi J t}{2}) & 0 \\ 0 & i \sin(\pi J k t) \exp(-i\frac{\pi J t}{2}) & \cos(\pi J k t) \exp(-i\frac{\pi J t}{2}) & 0 \\ 0 & 0 & 0 & \exp(i\frac{\pi J t}{2}) \end{pmatrix}$$

If $\rho_0 = I_{1x} + I_{2x}$ then the observable response will be $\langle I_{1+} \rangle = \text{Tr}\{U_t^{-1}(I_{1x} + I_{2x})U_t \cdot I_{1+}\}$; an expression leading to $\langle I_{1+} \rangle \propto \cos[\pi J t(1-k)]$. Such result agrees with that reported by Allerhand (3) and, more recently, by Kowalewski and coworkers (4).

To calculate from this derivation the observable NMR signal at the conclusion of an SDR sequence like that introduced in Fig. 1E, two propagators need to be considered: one for which the expression for k utilizes $\tau = x/2$ and $t = (N-1)x$, and another for which $t = TE - x(N-1)$ and $\tau = TE/2 - x(N-1)/2$ (TE being the overall time of the π -pulse train and N the number of pulses applied during this train). As these

whose average to zero order is given by

$$\bar{H} = \frac{1}{T_c} \int_0^{T_c} H_{\text{zero}}''(t) dt$$

This average Hamiltonian can be found by breaking up the RF cycle into parts and calculating each element of the Hamiltonian matrix individually. For instance the following integrals:

yield the 1,2 matrix element of interest

$$\begin{aligned} \bar{h}_{1,2} &= \frac{\pi J}{4\tau} \int_0^\tau dt [2 \exp(2i\omega_o t) + 2 \exp(-2i\omega_o t)] \\ &= \frac{\pi J}{\tau} \int_0^\tau dt \cos(2\omega_o t) = \frac{\pi J}{2\omega_o \tau} \sin(2\omega_o \tau). \end{aligned}$$

Likewise, the remainder of the average zero-quantum Hamiltonian

$$\bar{H} = \begin{pmatrix} -\pi J/2 & \pi J k \\ \pi J k & -\pi J/2 \end{pmatrix}$$

follows, where $k = \text{sinc}(2\omega_o \tau)$. As the toggling frame's final reference position coincides at the conclusion of each cycle with the original reference frame, it is unnecessary to transform back to the latter—all propagations will be carried out stroboscopically and at the end of such cycles. Returning back to the full 4×4 two-spin Hilbert space, the problem can then be cast as a need to diagonalize the average Hamiltonian:

$$\bar{H}_t = \begin{pmatrix} \pi J/2 & 0 & 0 & 0 \\ 0 & -\pi J/2 & \pi J k & 0 \\ 0 & \pi J k & -\pi J/2 & 0 \\ 0 & 0 & 0 & \pi J/2 \end{pmatrix},$$

which leads to the corresponding propagator

propagators commute, the overall evolution becomes $\langle I_{1+} \rangle = \text{Tr}\{U_2^{-1}U_1^{-1}(I_{1x} + I_{2x})U_1U_2 \cdot I_{1+}\}$ with $U_1 = U_t(t = x(N-1), \tau = x)$ and $U_2 = U_t(t = TE - x(N-1), \tau = t/2)$. This leads to

$$\begin{aligned} \langle I_{1+} \rangle &= \cos \left\{ \pi J \cdot TE - \frac{\pi J}{\omega_o} [(N-1) \sin(\omega_o x) \right. \\ &\quad \left. + \sin(\omega_o (TE - x(N-1)))] \right\} \end{aligned}$$

which is Eq. 4 in the paper and was used as the "analytical" prediction in Fig. 2.

Supplementary Material B: Selective Dynamical Recoupling Driven by Chemical Exchange. We next look at a spin-1/2 system that can exchange its environment at a rate κ , among two equally populated states possessing chemical shifts $\pm\omega_o$. As before, this ensemble will be subject to a sequence composed of $1 \leq i \leq N$ segments of duration $2\tau_i$ each, possessing an echoing π -pulse in their center and timed such that $\sum_{i=1}^N \tau_i = TE/2$. Because of this pulsing a spin's phase will be refocused at the conclusion of each segment regardless of its environment—this, as long as no exchange has occurred during that segment. On the other hand, should a single exchange event happen during a segment i , the normalized magnetization amplitude would become

$$\langle I_+^i \rangle = \langle e^{i\Delta\Phi} \rangle_{+\omega_o \leftrightarrow -\omega_o}^{2\tau_i} = \frac{\sin(2\omega_o\tau_i)}{2\omega_o\tau_i}$$

For the slow, infrequent exchange regime where rates $\kappa < TE^{-1}$ that will here be assumed, the probability that such a single exchange has happened during a segment i is $\mathcal{P}_i(1) = \kappa 2\tau_i$. The probability that one single exchange has happened throughout the π -pulse train is then $\mathcal{P}(1) = \sum_{i=1}^N \mathcal{P}_i(1) = \kappa TE$, and the possibility of two or more spectral changes will be disregarded as too unlikely. This means that the probability of having a spin undergoing zero exchanges becomes $\mathcal{P}(0) = 1 - \kappa TE$; as in this latter, exchange-free case, the π -pulse train will entirely refocus the phases of the qubits, the resulting amplitude $\langle I_+ \rangle$ observed at the conclusion of the SDR train can be approximated as

$$\langle I_+ \rangle = \sum_{j=1}^{\infty} P(j) \langle I_{+,j} \rangle \approx P(0) \cdot 1 + \sum_{i=1}^N P_i(1) \langle I_+^i \rangle$$

From here one can find the first-order approximation to the resonance amplitude:

$$\langle I_+ \rangle \approx 1 - \kappa \cdot TE + \frac{\kappa}{\omega_o} \sum_{i=1}^N \sin(2\omega_o\tau_i),$$

which is the expression used to derive Eq. 5 in the main text.

It is interesting to reflect on three additional aspects of this scenario. A first issue to remark is that the $\langle I_+ \rangle$ equation just derived remains valid in cases where the two states are not equally populated, provided one takes $\kappa = 2(\kappa_{1 \rightarrow 2} + \kappa_{2 \rightarrow 1}) \text{Pop}_1 \text{Pop}_2$, where Pop_i is the population of state i and $\kappa_{i \rightarrow j}$ is the exchange rate between states i and j . As illustrated in Fig. S1 even in such cases chemical shift modulations can be measured on the major component's peak, that reveals the nature of its less-abundant exchange partner.

Also interesting to investigate is what would be the optimal pulse arrangement for minimizing the exchange-induced decay effects; i.e., the τ_i 's that minimize the dynamics-induced decoherence that the "noise" (i.e., the exchange) imparts on the qubit (i.e., the NMR amplitude). Given a number N of segments spanning a total echo time TE , one can use Euler-Lagrange methods to maximize such signal amplitude. Two domains result from these constraints. One arises when the average $\bar{\tau} = \frac{TE}{2N}$ is such that

$\bar{\tau} \cdot \omega_o < \frac{\pi}{2} \Delta \bar{\tau} < \frac{\pi}{2}$. In this case the optimal solution to minimize the effect of the noise is a CPMG sequence where all τ_i are set equal to the average $\bar{\tau}$. This is to be expected, as for small ω_o 's only linear frequency terms remain in the signal's amplitude and the problem reverts to the canonical DD domain. This contrasts with a second possible scenario, where the average $\bar{\tau}$ is such that $\bar{\tau} \cdot \omega_o > \frac{\pi}{2}$. In such cases, minimizing the signal's decay requires choosing the τ_i 's in such a way as to set all $\sin(2\omega_o\tau_i)$ terms in Eq. 1 equal to 1. This can be achieved by setting the durations of certain segments to $\tau_j = \frac{(\frac{\pi}{2} + 2\pi m + 2\pi)}{\omega_o} > \bar{\tau}$ and the rest to $\tau_i = \frac{(\frac{\pi}{2} + 2\pi m + 2\pi)}{\Delta} > \bar{\tau}$, and by selecting the size of each group in such a way so as to keep the average τ as desired. Choosing in such fashion the sequence's timing according to ω_o , is something that has no parallel in any of the hitherto proposed DD methods.

A final interesting issue to consider concerns an exchange scenario where the dynamics can connect several $1 \leq k \leq M_{\text{ex}}$ sites, each with population P_k and frequency ω_k , by a series of $\{\kappa_{k \rightarrow i}\}_{i \neq k}$ exchange rates. Like before we assume that this system is subject to N segments of duration $2\tau_i$ such that $2 \sum_{i=1}^N \tau_i = TE$, with an echo pulse in the middle of each segment and the infrequent jump condition $\kappa_{k \rightarrow i} \cdot TE \approx 1$ still valid. At the end of each segment the spins' evolution phases will be refocused unless there has been a state exchange during that segment. One can then calculate the average dephasing accumulated throughout the system and all segments, as

$$\langle I_+ \rangle = \sum_{i=1}^{M_{\text{ex}}} P_i \left(1 - TE \sum_{k \neq i}^{M_{\text{ex}}} \kappa_{i \rightarrow k} \right)$$

Contribution of non-exchanged k 's

$$+ \sum_{i=1}^{M_{\text{ex}}} \sum_{k \neq i}^N \sum_{n=1}^N (P_i 2\kappa_{i \rightarrow k} \tau_n) \langle e^{i\Delta\Phi} \rangle_{\omega_i \leftrightarrow \omega_k}^{2\tau_n}$$

Contribution of all $i \rightarrow k$ exchanges

The microscopic detailed balance condition $P_k \kappa_{k \rightarrow i} = P_i \kappa_{i \rightarrow k}$ leads to:

$$\langle I_+ \rangle \approx 1 - TE \sum_{k=1}^{M_{\text{ex}}} P_i \kappa_{i \rightarrow k} + 2 \sum_{i=1}^{M_{\text{ex}}} \frac{P_i \kappa_{i \rightarrow k}}{\omega_i - \omega_k} \sum_{n=1}^N \sin[(\omega_i - \omega_k) \tau_n],$$

which is very similar to the result obtained earlier, only summed over all the possible site exchanges. On the basis of this modulation it follows that the behavior arising from site k from a SDR sequence like the one implemented in Fig. 3, leads to

$$\langle I_+^k \rangle \approx 1 - TE \sum_{i=1}^{M_{\text{ex}}} P_i \kappa_{i \rightarrow k} + 2 \sum_{i=1}^{M_{\text{ex}}} \frac{(N-1) P_i \kappa_{i \rightarrow k}}{\omega_i - \omega_k} \sin[(\omega_i - \omega_k)x]$$

This is once again a linear superposition, now involving *all* frequency differences connected by the exchange.

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