A Robust, Modern Strategy for Treating Coherence Pathways in Unstable and Inhomogeneous Magnetic Resonance Experiments

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Over recent decades, motivated either by practicality or the need to tap into new types of measurements, the science of Magnetic Resonance has expanded into more adverse conditions: deliberately chosen lower frequencies, inhomogeneous fields, and/or time-variable fields. The extensive body of research involving NMR at higher and more homogeneous fields – i.e., highly optimized static magnetic fields, encourages the assumption that previous research has precluded the discovery of new techniques and perspectives relevant to the acquisition of one dimensional NMR data. However, Overhauser Dynamic Nuclear Polarization (ODNP) presents a case study that challenges this expectation and offers an interesting test-bed for further developments. For example, an interest in the nanoscale heterogeneities of hydration dynamics demand increasingly sophisticated and automated measurements deploying ODNP on a modular, open source instrument operating at 15 MHz. As part of this effort, ODNP requires the acquisition and automated processing of large quantities of one dimensional NMR spectra. The acquisition of this data can present various problems: in particular, unambiguous identification of signal in newly configured instruments presents a practical challenge, while field drift tends to remain an issue even in fully configured instruments, among other issues.

Recent advances in the capabilities of open-source libraries opened up the opportunity to address these issues at the fundamental level, by developing a specific schema that treats the phase cycle of a pulse as an explicit “phase domain” dimension that Fourier transforms into the “coherence domain.” In particular, a standardized protocol for organizing and visualizing the resulting data clearly presents all the information available from all coherence transfer pathways of a phase-cycled experiment, with intelligible results that don’t rely on preliminary phase corrections. It thus organizes and visualizes data in ways that more accurately reflect the rich physics of the underlying NMR experiments, and that more fully bear out the original fundamental concepts of coherence transfer pathways. It also enables development of a collection of algorithms that provide robust phasing, avoidance of baseline distortion, and the ability to lift relatively weak signals out of a noisy background through a signal-averaged mean-field correlation alignment algorithm. Both the schema for processing and visualizing the raw data, and the algorithms whose developments it guides are expected to be either directly applicable or easily extensible to other techniques facing similar challenges, particularly to other emerging forms of coherent spectroscopy that support pulse phase cycling.

I. Introduction

This manuscript focuses on a comprehensive, non-standard approach to processing and presenting data from the various coherence pathways accessed by a magnetic resonance experiment. This formalized approach – i.e., “schema” – significantly improves the speed with which spectroscopists can develop new types of experiments. When confronted with adverse experimental circumstances, this schema also guides the identification of data and the development of routines that improve the quality of that data. As the authors’ lab has developed an ODNP system, these methods serve here to improve the quality of ODNP data, with particular focus on mitigating the effects of inhomogeneity and time instability of the fields offered by conventional room temperature electromagnets.

Modern ODNP observes the cross-relaxation between carefully chosen electron spin label sites and the hydration water surrounding macromolecules. Despite the rapid, sub-nanosecond exchange of hydration water with bulk water, ODNP has the capability of measuring the variation in both the dynamics of hydration water molecules at different surface sites [1, 2], as well as the accessibility of a surface site to water [3, 4]. The spectroscopist can choose sites either at the surface of, or within the core of, macromolecules and macromolecular assemblies. Previous literature has advocated ODNP as a tool for analyzing the hydration layer for more than 12 years [5, 6]. Furthermore, the technique employs relatively low magnetic fields (typically 0.35 T), permitting dissemination in concert with cw ESR spectroscopy [1, 2] and extension to permanent magnet systems [5, 7, 8], making it an eminently customizable technique. Nonetheless, ODNP has not yet been widely adopted for studying the hydration layer, which we ascribe in part to the practical barriers imposed by the differences between ODNP and more traditional NMR methods.

ODNP studies conducted at higher resonance frequencies tend to sample intramolecular motions of the spin label [9], or even correlated motions [10] that obfuscate

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the translational dynamics that many studies seek to recover [11]. Thus, rather than seeking increasingly higher fields and resonance frequencies, Overhauser Dynamic Nuclear Polarization (ODNP) studies of dynamics actually demand relatively low fields and low resonance frequencies tuned to the translational dynamics of solvent molecules. Lower fields, of course, give rise to challenges with respect to spin polarization and signal amplitude in reference experiments. The integration of the Nuclear Magnetic Resonance (NMR) spectrometer with the ESR spectrometer and high power microwave amplifier also gives rise to a host of practical challenges. Furthermore, a full analysis of dynamics includes collection of both a series of measurements of spin polarization at different levels of microwave (ESR) excitation, as well as several inversion recovery sequences acquired under different conditions. Careful manual analysis of the resulting data generally demands a level of fastidiousness that is unreasonable given the quantity of data under consideration.

For particular sample configurations, one can achieve reasonable ODNP results with mostly commercial hardware [2, 11–14]. Most ODNP studies follow a strategy that employ standard approaches to phase cycling and where 90°-pulse FID experiments or, occasionally, standard CPMG experiments quantify the signal intensity. Recent studies have demonstrated spectral resolution without the need for added shim coils [8], as well as examples that implement a practicable shim stack [15]. More broadly, recent advances have been made toward making the NMR spectrometer simple, portable, and more closely based on off-the-shelf test and measurement equipment [16, 17]. Importantly, thus far, all such advances detail an engineering of the spectrometer device itself, rather than addressing a strategy to provide a finer level of control, applicable to all instruments, when visualizing and processing the data. This manuscript addresses the latter concern. Overall, the development of ODNP spectroscopy and other emerging magnetic resonance techniques mandates a new approach to conventional NMR. In order to attend to all the previously mentioned problems, this manuscript carefully reviews, then formalizes a schema that tweaks, how standard processing algorithms organize and present signal at the fundamental level.

In particular, this manuscript focuses on maximizing and manipulating the information available from phase-cycled magnetic resonance experiments. Of course, work on a formalized procedure for cycling the phases of pulses goes back decades [18–23] and such work introduced coherence transfer (CT) maps (also known as coherence transfer pathway diagrams) as a means to understand the multiple coherence transfer pathways existing in a phase cycled pulse sequence. However, traditional experiments select a single coherence pathway; as presented in more recent work on multiplex phase cycling [24] and multiplex-quadrature detection (MQD) [25], now-antiquated hardware motivated this choice. By simply forgoing the cycling of the receiver phase and separately storing the acquired transients, post-acquisition processing can select any of the CT pathways acquired during the experiment, as described in the early works that developed the theory of multiple quantum transfer [26] and phase cycling [23], and utilized in multidimensional solid state [27] and biomolecular NMR [28]. This work formalizes and builds on these earlier contributions by presenting a comprehensible display of all of the raw data available from a phase cycled experiment.

The DCCT map builds on these earlier contributions to provide a modern comprehensive analysis of signal phase and coherence pathways, and an associated coding strategy to organize and manipulate the data. While the authors expected the DCCT map schema to aid in the diagnosis of instrumentation issues, it also, surprisingly, aids in identifying signal acquired under more adverse experimental conditions, and proves especially useful in guiding the data acquisition and developing processing algorithms. It should benefit not only ODNP, but other magnetic resonance methods and, more generally, other forms of spectroscopy capable of accessing multiple different coherence pathways [29–31].

The paper is organized as follows: Sec. II covers the theoretical basis of this paper, with emphasis on data processing in Sec. II.1, which includes the mathematical basis of phase cycling (Sec. II.1.A), the rationalization for echo detection for accurate integrals (Sec. II.1.B) and phase corrections (Sec. II.1.C and II.1.D), along with the mathematics underlying the “signal averaged” alignment routine (Sec. II.1.E), and apodization (Sec. II.1.F), as well as a review of ODNP theory (Sec. II.2). Sec. III contains all relevant experimental details, including sample preparations (Sec. III.1) and details regarding home-built low field (Sec. III.2) and commercial high-field (Fig. 8) instrumentation, along with the custom python software which serves as a cornerstone of this work Sec. III.3. Sec. IV contains results, with the motivation and explanation of the DCCT map plotting style in Sec. IV.1 and IV.2, and with subsequent demonstrations on specific NMR experiments presented in Sec. IV.3. The DCCT schema for organizing and plotting the data then motivates and enables the algorithms in Sec. IV.4, which presents phasing (Sec. IV.4.A), alignment (Sec. IV.4.B), and apodization (Sec. IV.4.E) in the context of routine NMR experiments relevant to ODNP (Sec. IV.4.C and IV.4.F), including a uniquely low SNR case-scenario (Sec. IV.4.D), highlighting the prowess of this means of data handling and presentation. Sec. V and VI, place the schema in the broader context of the literature and forecast future applications.

In keeping with this, the Theory section (Sec. II) covers some mathematical considerations utilized during data processing. Since compact scripting comprises part of the results presented here, equations are referenced against an appendix (appendix A) that offers a glimpse at the corresponding code. The DCCT map and related techniques capitalize on modern object-oriented programming to lower the barrier for introducing multiple di-
mensions, tracking errors, etc. The Experimental section (Sec. III) briefly discusses the experimental setup and sample preparation. In (Sec. IV), the results presented here involve data processing that relies only on relatively few specialized hardware components of relatively low sophistication. Acquisition of short-time echoes yields the benefits of an EXORCYCLE [21] phase cycle and permits routine baseline-free spectral acquisition that simple calibration routines can easily phase correct and introduces a correlation-based frequency alignment in the presence of phase cycling at low SNR and apodization routines, demonstrated via data visualization/plotting techniques that form a central component of the new approach. The DCCT map proves particularly useful for time-variable magnetic fields present in many low-field and portable instruments and does guide advances along several fronts particularly relevant to quantitative Magnetic Resonance desired for ODNP spectroscopy. Taken together, these processing procedures prove extremely flexible and adaptable to the polarization transfer experiment (ε(p) curves) and to the inversion recovery experiments that are essential to recording data relevant to hydration dynamics. As explained in the discussion (Sec. V), these techniques enable a synergy between data acquisition and processing, which relies less on starting infrastructure and allows for sophistication in the processed results. Looking forward, the DCCT map and resulting signal optimization techniques will enable not only improvements in processing methodologies presented here, but also provide the framework for many future advances.

II. Theory

II.1. Data Processing

Several sections below utilize the notation

\[ c(\Delta x) = f(x) \ast g(x) \]

for the correlation function, such that:

\[ c(\Delta x) = \int_{-\infty}^{\infty} f^*(x)g(x + \Delta x)dx \]  

(1)

Aside from providing compactness, this notation emphasizes the fact that a Fourier domain multiplication (\( \hat{c}(\nu) = \hat{f}^*(\nu)\hat{g}(\nu) \)) significantly outperforms numerical differentiation of Eq. (1), so that processing code never calculates the latter.

II.1.1. Phase Cycling

Throughout, the software utilizes the standard relationship that [23]:

\[ s(\Delta p, t) = \frac{1}{\sqrt{n_\phi}} \sum_j \epsilon^{-i2\pi\Delta p \phi_j} s(\phi_j, t) \]  

(2)

where \( n_\phi \) gives the number of phase cycle steps and, following standard notation, \( \Delta p_j \) indicates the coherence change during pulse \( j \). The phase angle \( \phi_j \) has units of \([\text{cyc}] = [\text{rad}]/2\pi\), such that an \( x \) pulse has \( \phi = 0 \) [cyc] a \( y \) pulse has \( \phi = 0.25 \) [cyc], etc.; the resulting \( \Delta p_1 \) are then unitless. This manuscript employs the phrasing that Eq. (2) relates the “phase cycling domain” (\( \phi_j \)) to the Fourier conjugate “coherence transfer domain” (\( \Delta p_j \)).

When the pulse sequence cycles the phase of multiple pulses, the signal in the coherence transfer domain, \( s(\Delta p_1, \Delta p_2, \cdots, \Delta p_N, t) \), derived from an N-dimensional Fourier transform of the phase cycling domain signal, gives the component of the signal that changes by \( \Delta p \) during the first pulse, \( \Delta p_2 \) during the second pulse, etc. Thus, \( s(\Delta p_1, \Delta p_2, \cdots, \Delta p_N, t) \) includes the signal for all distinguishable coherence transfer pathways. The \( \Delta p \) dimensions are subject to standard Fourier aliasing, resulting from the Nyquist theorem—when a single coherence transfer pathway is selected, this aliasing collapses to the well-known rules laid out in the seminal phase cycling contribution from Bodenhausen, Kogler, and Ernst [23, 32].

II.1.2. Deriving Integrals from Echoes

ODNP relies on high-quality quantitative NMR. Inhomogeneous fields and low SNR conditions pose some obstacles toward routinely acquiring data with correct phasing that avoids baseline artefacts. Fortunately, echo-based signal acquisition not only refocuses inhomogeneities but also circumvents baseline problems by yielding distortion-free early time points of the FID [33], thus circumventing baseline problems and recovering signal typically lost to the pulse deadtime. It also reaps the benefits arising from EXORCYCLE phase cycling [21], and (as will be shown) permits straightforward automated approaches for signal phase correction. Typical 90° pulse and subsequent 180° pulse are advantageously short (\( \leq 10 \) ms) in an ODNP system, while \( T_2 \) times are long (hundreds of ms to s), garnering the above benefits virtually free of cost.

Phase correction routines (subsequently introduced) identify the origin of the time axis, \( t = 0 \): defined as the time point at which all the isochromats in the signal present the same phase [33, 34]. For an idealized (noise-free) echo, \( t = 0 \) corresponds to the peak of the echo. Echoes symmetric about \( t = 0 \) yield purely real Fourier transforms, but echoes generated in response to short echo times (which refocus shortly after the 180° pulse) can also be converted to FID’s via multiplication by an appropriate Heaviside function, \( h(t) \):

\[ s_{FID}(t) = s(t)h(t) = \begin{cases} 0 & t < 0 \\ \frac{1}{2}s(t) & t = 0 \\ s(t) & t > 0 \end{cases} \]  

(3)

Eq. (3) implies (1) adjustment of the origin of the time axis and (2) the discarding of signal before the point labeled as \( t = 0 \). The pySpecData Python library (developed in-house and used throughout here) facilitates these manipulations by maintaining the time coordinates of the signal and providing a compact notation that selects
and manipulates the signal based on its time coordinates (listing 1). Upon Fourier transformation, the pySpecData library also automatically (without additional lines of code) generates an appropriate axis of frequency coordinates and, for time axes that do not begin at \( t = 0 \), automatically multiplies in the frequency domain by the appropriate first-order phase shift.

The relatively simple treatment of short-time echoes contrasts with the behavior of FIDs arising in response to an isolated 90° pulse. Assuming the frequency-domain signal comprises a superposition of Lorentzians, beginning acquisition on a time axis (\( t' \)) at some time point \( t_d \) after the nominal center of the echo (s.t. \( t = t' + t_d \)) ideally results in

\[
\sum_j e^{2\pi \nu_j t - R_j t_d} h(t - t_d) = \sum_j e^{2\pi \nu_j t_d} e^{-R_j t_d} e^{2\pi \nu_j t' - R_j t'} h(t') \tag{4}
\]

- i.e., a frequency-dependent phase shift and a suppression of the signal determined by the relaxation rate, (arising from the first two exponential terms in Eq. (4) respectively), but an otherwise valid spectrum. However, as is well known, issues arise from either distortion of the initial FID datapoints [33] or from choosing a value of \( t_d \) that is a non-integer multiple of the dwell time [35, 36].

### II.1.C. Zeroth-Order Phase Correction

Very simple methods for calculating zeroth-order (frequency-independent) phase correction function very well when all datapoints are positive; however, both for inversion recovery curves and for ODNP enhancement curves, the sign of any given datapoint is unknown. Therefore, given a collection of complex datapoints assumed to be distributed primarily along the real axis of the complex plane and then rotated by some arbitrary constant (zeroth-order) phase, the principle axis of the matrix

\[
I_{ij} = \sum_{k=1}^{N} \left[ \begin{array}{c} |s(t_k)|^2 - \Re\{s(t_k)\}^2 - \Re\{s(t_k)\} \Im\{s(t_k)\} - \Im\{s(t_k)\}^2 \\ -\Re\{s(t_k)\} \Im\{s(t_k)\} - \Im\{s(t_k)\}^2 \end{array} \right]
\]

\[
= \sum_{k=1}^{N} \left[ \begin{array}{c} \Im\{s(t_k)\}^2 - \Re\{s(t_k)\} \Im\{s(t_k)\} - \Re\{s(t_k)\}^2 \\ -\Re\{s(t_k)\} \Im\{s(t_k)\} - \Re\{s(t_k)\}^2 \end{array} \right]
\]

(motivated by the formula for the inertia tensor) would provide the vector in the complex plane that the real axis had been rotated to. The zeroth order phase correction that corresponds to rotating this axis to align with the real axis performs well even when the datapoints have a variable sign.

### II.1.D. First-Order Phase Correction

One can determine the timing shift introduced by travel through the transmission lines, etc., by comparing the expected time between the end of the last pulse and the center of the echo:

\[
\tau_{	ext{echo}} \approx \tau + 2\varphi_0 / \pi \tag{6}
\]

to the actual/observed \( \tau_{	ext{echo}} \) [33, 37]. However, if the timescale of the inhomogeneous decay (\( T_2 \)) exceeds the required timing correction, the determination of the center maximum of the echo frequently proves less trivial than expected. In particular, the presence of noise complicates attempts to choose between the amplitude of time points near the peak of the echo, where the magnitude is relatively flat as a function of time. Furthermore, echoes resulting from experiments that invert some isochromats but not others (or from antiphase signal) will not necessarily present maximum amplitude at the center of the echo.

Three strategies yield more robust procedures for finding the echo center.

The first strategy exploits the Hermitian symmetry of echo-like signal by finding the value of \( \tau_{	ext{shift}} \) that minimizes the cost function

\[
C(\tau_{	ext{shift}}, R_2) = \int_0^{t_w} \left| e^{-i\varphi_0 + R_2(t - \tau_{	ext{shift}})} s(t - \tau_{	ext{shift}}) - e^{+i\varphi_0 - R_2(t - \tau_{	ext{shift}})} s^*(-(t - \tau_{	ext{shift}})) \right|^2 dt \tag{7}
\]

where \( R_2 \) accounts for the slight asymmetry of the echo due to the transverse relaxation; \( t_w \) gives a window that is as long as possible without becoming larger than the time between the start of acquisition and the echo; and \( \varphi_0 = \angle(s(\tau_{	ext{shift}})) \) is chosen to enforce the fact that the echo must be real at its center (\( \tau_{	ext{shift}} \)).

The second strategy considers a time-domain echo signal that decays smoothly to zero for large positive times as well as large negative times. The cross-correlation of this signal with its Hermitian conjugate can identify the relative offset at which the echo and its conjugate have the best overlap. Invoking established procedure for analogous calculations in the molecular dynamics literature [38], this strategy begins by zero-filling the signal, \( s(t) \), to twice its length. For a discrete signal with \( N \) datapoints, the resulting zero-filled signal \( s_{z\bar{f}}(t) \) (like all discrete signals treated by a discrete Fourier Transform) has a periodicity of \( 2N t_{dw} \), where \( t_{dw} \) gives the separation between datapoints in the time domain. For any real inhomogeneous broadening, the cost function

\[
c(\Delta t) = \frac{t_{dw}}{\Delta t + t_{dw}} \int_{-\Delta t}^{0} \left| e^{i\varphi_0} s^*(-t) - e^{-i\varphi_0} s(t + \Delta t) \right|^2 dt \tag{8}
\]

should drop to a minimum for the value of \( \Delta t / 2 \) corresponding to the center of the echo. In Eq. (8), the integral limits run only over times where the integrand
is non-zero and the term outside the integral normalizes by the number of integrated datapoints [39]; \( \varphi_0 \) signifies that the zeroth-order phasing of the signal remains unknown until determination of the echo center. Expansion of the absolute square, and extension of the limits to times where third term is zero yields

\[
c(\Delta t) = \int_{-\Delta t}^{\Delta t} \left| s^*(t) \right|^2 + |s(t + \Delta t)|^2 \] \ dt
\]

\[
-2 \int_0^{2Nt_{dw}} \left[ \Re \left[ e^{-i\varphi_0} s(t + \Delta t) s(t) \right] \right] \] \ dt
\]

while substitution of integration variables and utilization of the definition of the correlation symbol yields

\[
c(\Delta t) = 2 \int_0^{\Delta t} |s(t)|^2 \] \ dt
\]

\[
-2 \Re \left[ e^{-i\varphi_0} s^*(-t) * s(t) \right]
\]

Finally, note that the choice of \( \varphi_0 \) that will minimize the previous expression is simply the phase of \( s_{zf}(t) \) at the echo center. Therefore, the expression

\[
c'(\Delta t) = 2 \int_0^{\Delta t} |s(t)|^2 \] \ dt
\]

\[
-2 |s^*(-t) * s(t)|
\]

has a minimum at the same \( \Delta t \) as . The \( \Delta t \) at the minimum, \( \Delta t_{min} \) gives the time shift needed to align the echo center in the periodic \( s_{zf}(t) \) with the echo center in the hermitian conjugate \( s^*_{zf}(-t) \). Therefore \( \Delta t_{min}/2 \) identifies the location of the echo center in \( s_{zf}(t) \).

The third strategy relies on the fact that the integral of the absolute value of the absorptive component of a Lorentzian peak is smaller than the absolute value of the dispersive component. Previous literature has extensively employed this principle for first order phase correction of FIDs [40]. Applied to an FID sliced from the decaying end of a short-time echo, this principle translates to the fact that

\[
C(t_d) = \frac{\int \left| \Re \left[ e^{i2\pi\nu t_d} \int e^{-i2\pi\nu t} h(t - t_d) s(t) \] \ dt \right| \] \ dv
\]

\[
\int \left| \Im \left[ e^{i2\pi\nu t_d} \int e^{-i2\pi\nu t} h(t - t_d) s(t) \] \ dt \right| \] \ dv
\]

will have a local minimum for every \( t_d = n t_{dw} \), with \( t_{dw} \) being the dwell time and \( n \) an integer. This effect has been noted previously experimentally [35, 36] and can be rationalized by noting that the comb function representing the discrete sampling of the signal should be in register with \( t = 0 \) in order to avoid introducing low-frequency distortions to the signal. When a convincing case can be made for the simplicity of simple 90° pulse acquisition over echo-based acquisition, this last cost function can also cross-validate the timing of the FID against that of an echo function to ensure optimal phase correction of both.

\[ \text{II.1.E. Cross-Correlation} \]

Fluctuations of the field of permanent magnets and room-temperature electromagnets lead to slight shifts in the resonance frequencies of subsequent transients. Some previous methods for spectral alignment have relied on iterative Bayesian [41] and other statistical methods [42] while other methods rely on correlation of spectral fragments [43, 44]; however, these methods typically operate on the absolute value of the signal or well-phased signal. More recent studies have demonstrated the promise of cross-correlation of transients as a simple and robust technique to align NMR transients in the presence of a variable field [15]. As noted here, cross-correlation can explicitly deal with complex signals and can be clearly mathematically justified. Furthermore, a specific variant of cross-correlation can function even under circumstances where individual pairs of transients do not offer sufficient SNR for alignment.

Consider inspecting the signal from two transients in the frequency domain, \( S_j(\nu) \) and \( S_m(\nu) \), shifting \( S_j \) to the left by \( \Delta \nu_j \) to maximize the norm of the resulting signal \( |S_m(\nu) + S_j(\nu + \Delta \nu_j)|^2 \) - i.e., consider maximizing the expression:

\[
\int |S_m(\nu) + S_j(\nu + \Delta \nu_j)|^2 \] \ dv
\]

\[
= \int |S_m(\nu)|^2 \] \ dv
\]

\[
+ \int |S_j(\nu + \Delta \nu_j)|^2 \] \ dv
\]

\[
+ 2 \Re \left[ S_m^*(\nu) S_j(\nu + \Delta \nu_j) \] \ dv
\]

(13)

\( S_j \) and \( S_k \) are periodic because Fourier transformation of discretely sampled time domain signals generates periodic frequency domain signals. Therefore, not only the first term in Eq. (13), but also the second term, remains constant for all values of \( \Delta \nu_j \). Because of this, the problem of aligning the signals in the frequency domain to give maximum overlap corresponds mathematically exactly to the much simpler problem of finding the maximum of the real part of the correlation function \( (C(\nu_j)) \) in the third term, where

\[
C(\nu_j) = \int S_m^*(\nu) S_j(\nu + \Delta \nu_j) \] \ dv
\]

\[
= S_m(\nu) * S_j(\nu)
\]

(14)

where the second equality makes use of the * symbol to denote the correlation integral (Eq. (1)), and the FFT makes calculation trivial and fast. The difficulty in applying this mathematical truism to real data appears when considering noise and phase cycling.

First, consider that noisy transients lead to noisy correlation functions, and that the maximum of the signal
and the presence of noise together influence the position of the maximum of Eq. (13). Therefore, the generalization of Eq. (14) to the case of more than two transients involves not comparing adjacent transients, but considering the total overlap of all transients, and requires finding the maximum of the real part of:

$$C(\Delta \nu_1, \ldots, \Delta \nu_j, \ldots, \Delta \nu_J) = \sum_{m, j \neq j} \int S_m^*(\nu + \Delta \nu_m) S_j(\nu + \Delta \nu_j) d\nu$$

$$= S_m(\nu + \Delta \nu_m) * S_j(\nu)$$

(15)

to determine the corrective shift relevant to one transient (here \(j\)) in an experiment with \(J\) transients. Note that Eq. (15) depends on the shifts for all transients, simultaneously; thus, the \(\cdot\) indicate the presence of \(J\) arguments to the highly multi-dimensional function \(C\). One approach to optimizing \(C\) involves finding a "mean field"-type solution that finds the \(\Delta \nu_j\) to optimize \(C_{m.f.}(\Delta \nu_j)\) with the position of all other transients \((\Delta \nu_m)\) held constant. Thus, for a given dataset, the relationship:

$$C_{m.f.}(\Delta \nu_j) = \sum_m \Re \left[ S_m(\nu) * S_j(\nu) \right]$$

(16)

where the correlation resulting from \(*\) is a function of \(\Delta \nu_m\). This expression generates a single one dimensional curve for each transient (of subscript \(j\)), each of which yields a clear optimal \(\Delta \nu_j\). This solution requires iterating until the list of \(\Delta \nu_j \rightarrow \Delta \nu_m\) values remain consistent from one iteration to the next: typically 3-10 iterations. While requiring a more laborious computation by demanding calculation of all possible correlation functions between all possible transients (rather than merely, \(\epsilon.g.,\) adjacent transients in a time series), the sum in this expression actually involves a signal averaging of the correlation function and proves particularly important in the case where individual transients may have particularly low SNR. We therefore refer to Eq. (16) and its generalization to phase-cycled signal below as a "signal-averaged correlation function."

Aligning in the presence of a phase cycle also requires further consideration. Following the strategy advocated here, one can treat phase cycling as an added dimension and seek to optimize the portion of the (Frobenius) norm of the signal in the coherence domain that varies with the frequency

$$C(\Delta \nu_{1,1}, \ldots, \Delta \nu_{j,k}, \ldots, \Delta \nu_{J,K}; \Delta p_l) = \sum_l \int \left| \sum_{l=0}^\infty e^{-i2\pi l (\nu + \Delta \nu_{j,k})} \right|^2 d\nu$$

(17)

following the same strategy for an experiment with \(J\) scans cycled over \(K\) phases. Here, the sum over \(q\) spans all signal averaged transients (including \(j\)), while the sum over \(r\) spans all pulse phases (including \(k\)), as well as many others (indicated by the \(\cdots\) arguments), again leading to a highly multidimensional \(C\). As in the 1D case, one can optimize \(C\) by iteratively optimizing the individual mean field correlation functions:

$$C_{m.f.}(\Delta \nu_{j,k}) = \sum_n \Re \left\{ e^{-i2\pi \phi_k \Delta l} \sum_n e^{i2\pi \phi_n \Delta p_l} \right\}$$

(18)

After defining \(\Delta \phi_k = \phi_k - \phi_n\), rearranging the order of the Fourier transform, and taking advantage of the \(*\) symbol (now redefined to generate a function of \(\Delta \nu_{j,k}\)) this becomes

$$C_{m.f.}(\Delta \nu_{j,k}) = \sum_n \Re \left\{ \sum_{m,j} \left[ e^{-i2\pi \Delta \phi_k \Delta p_l} S_{j,k}(\nu, \Delta \phi_k + \phi_n) \right] \right\}$$

(19)

Note that the code which implements the innermost square brackets first introduces a new dimension \((\Delta \phi_k)\) along which the elements of the \(\phi_n\) dimension are cyclically permuted by \(n \Delta \phi_k/\phi_n\) and then FFTs along the new \(\Delta \phi_k\) dimension.

Importantly, since the signals are periodic, Plancherel’s theorem implies that different frequency shifts applied to different spectra along an indirect dimension cannot change the norm of the data. Therefore, unlike the case of frequency shifts \(\Delta \nu_{j,k}\) among transients that are signal averaged (the \(q, m, \text{or}\ j\) indeces) of Eq. (16) and Eq. (17)), differences between the frequency shifts along the phase cycling dimension (the \(r, n, \text{or}\ k\) indeces) cannot lead to optimization of Eqs. (15) to (17). Both the specifics of this effect and a work-around can be considered with the simplest possible example: signal acquired with two transients under a two-step phase cycle, exemplified in Fig. 1.

Specifically, consider an idealized signal:

$$s(\nu, \phi) = \left( \frac{1}{\sqrt{2}} \right) e^{i\phi} e^{-i2\pi (\nu - \nu_0) + R}$$

(20)

acquired in two transients for \(\phi = 0\) and \(\phi = \pi\) (\(i.e.,\) using a two-step phase cycle). Upon discrete Fourier transformation (dimension of length 2) along \(\phi\) into conjugate domain \(\Delta p\), the signal appears centered about \(\nu_0\) at \(\Delta p = +1\) (red lines in Fig. 1a) This signal has a norm of 1, before and after unitary Fourier transformation. No signal appears in the other coherence pathway \((\Delta p = 0;\)
FIG. 1. Simulated data demonstrating the expense of phase cycle data that is unaligned (e.g., that which undergoes field fluctuations during the experiment, as is often the case on low field systems). The transients of each step of the phase cycle in (a) are aligned, and the transients of each step of the phase cycle in (b) are offset by 7.5 Hz, simulating misaligned data. Red represents the desired coherence pathway \( \Delta p = +1 \) is red and blue represents the undesired pathway \( \Delta p = 0 \). The bolder lines show the mod square of the data to emphasize that the overall norm of the data remains preserved, whether the data is aligned or not, even though misalignment spreads signal intensity across a wider bandwidth in both the frequency (\( \nu \)) and coherence (\( \Delta p \)) domains.

blue lines in Fig. 1a). Next, in the case where field fluctuations shift one of the transients by \( \Delta \nu \gg R \), the signal must still have a norm of 1. However, now, one transient presents signal centered at \( \nu_0 \) and another at \( \nu_0 + \Delta \nu \). After Fourier transformation from \( \varphi \) to \( \Delta p \), the signal energy from both peaks (\( \nu_0 \) vs. \( \nu_0 + \Delta \nu \)) spreads equally across \( \Delta p = 0, 1 \), resulting in 4 peaks, each with norm 0.5, as shown in Fig. 1b.

Notably, in Fig. 1b, signal intensity “smears” out both along the frequency domain (\( \nu \)) and the coherence domain (\( \Delta p \)). This effect appears later, to less dramatic extent, in Fig. 14. A different signal metric – specifically a “masked norm”:

\[
N(\Delta \nu_{qr}) = \sum_l \int f_{\text{mask}}(\nu, \Delta p_l) \times \left| \sum_{q, r} e^{-i2\pi \varphi_r} S_{q,r}(\nu + \Delta \nu_{qr} + \varphi_r) \right|^2 d\nu
\]

(21)

where the new function \( f_{\text{mask}}(\nu, \Delta p_l) \) is the (real and positive) “mask” function provides an analog of Eq. (17). With appropriate choice of the mask function, the masked norm \( N(\Delta \nu_{qr}) \) will indeed only rise to a maximum for the choice of \( \Delta \nu_{qr} \) that aligns the transients. For example, consider a mask function that is uniform along \( \nu \) and significantly exceeds 0 along \( \nu \) only in a bandwidth of similar size to the linewidth. The solid blue line indicating the artefactual pathway \( \Delta p = 0 \) shows the presence of signal, in contrast to Fig. 1a, which has a mod square of 0.25 as indicated by the bolder blue line. In the example of Eq. (25) and Fig. 1, this choice of \( f_{\text{mask}} \) would lead to a masked norm for properly aligned signal (\( \sim 1 \)) approximately twice that of the masked norm for the unaligned signal (a contribution of \( \sim 0.25 \) for each value of \( \Delta p \) for a total of \( \sim 0.5 \)). Thus, attempting to optimize \( N(\Delta \nu_{qr}) \) for this choice of \( f_{\text{mask}} \) would result in aligned signal. A mask function that is uniform along \( \nu \) and only nonzero for \( \Delta p_l = +1 \) (the expected coherence pathway of Eq. (20)) would lead to a similar optimization, while masking along both \( \Delta p \) and \( \nu \) leads to a \( \sim 1 : 0.25 \) improvement here.

Thus, to align signal in the presence of phase cycling, one typically constructs a \( f_{\text{mask}}(\nu, \Delta p_l) \) that is nonzero along \( \nu \) only over a bandwidth slightly smaller than the (unaligned) signal and nonzero along \( \Delta p \) only for values of \( \Delta p_l \) where the signal or significant artifacts appear. Then, one iteratively optimizes the masked version of Eq. (19):

\[
C_{m, f.}(\Delta \nu_{j,k}) = \sum_n \mathbb{R} \left\{ \sum_{m \neq j} \left| s_m(\nu, \varphi_n) \right|^2 \ast \sum_l \left| e^{-i2\pi \Delta \varphi_k \Delta p_l} s_{j,k}(\nu, \Delta \varphi_k + \varphi_n) \right| \right\}
\]

(22)

II.1.F. Apodization

For various purposes, one wishes to determine a generic measure of linewidth, defined even for complicated line-shapes. The results here rely on a simple, robust method that observes how the signal energy (\( \int \left| s(t) \right|^2 dt \)) responds to apodization (in the time domain, equivalently filtration in the frequency domain). By assuming (correctly or not) that the signal follows a particular functional form, one can calculate a matched filter, and assign its width to the generic linewidth. For example, the energy \( E(\sigma) \) of a signal \( s(t) \) subject to apodization with a Gaussian of width \( \sigma \) is

\[
E(\sigma) = \int \left| s(t) e^{-t^2/2\sigma^2} \right|^2 dt
\]

(23)

Provided that \( s(t) \) is an ideal Gaussian, then apodization by a Gaussian of precisely the same linewidth (i.e., matched filter) produces a function whose energy is equivalent to the energy of the signal without apodization reduced by \( \frac{1}{\sqrt{2}} \).

For signal that is not an ideal Gaussian, \( S(t) \), one may still identify a Gaussian which matches the generic linewidth of the signal, according to
which identifies that \( \sigma_{\text{opt}} \) is the linewidth of a Gaussian function whose apodization with \( S(t) \) results in a new function whose energy is equal to the energy of \( S(t) \) reduced by \( \frac{1}{\sqrt{2}} \), as discussed above, thus finding a matched Gaussian filter for \( S(t) \).

Alternatively, the energy of a signal subject to apodization by a Lorentzian of width \( \sigma \) can be defined analogously to Eq. (23).

In the case of apodizing ideal Lorentzian signal by another Lorentzian of the same width, the energy of the resulting apodization would yield an energy reduction of \( \frac{1}{2} \), relative to the signal without apodization.

For signal that is not an ideal Lorentzian, \( S(t) \), a Lorentzian function may still be found which matches the generic linewidth of this signal, analogous to Eq. (24), but relying on a reduction of the original signal’s energy by \( \frac{1}{2} \) rather than \( \frac{1}{\sqrt{2}} \), thus finding a matched Lorentzian filter for \( S(t) \).

In these ways, we may easily identify either Gaussian or Lorentzian functions for apodization with widths, \( \sigma_{\text{opt}} \), that match the generic linewidth of signal which is neither ideally Gaussian nor ideally Lorentzian.

One may also choose to filter \( S(t) \) with approximately Gaussian lineshapes, otherwise known as a Lorentzian-to-Gaussian transformation,

\[
S'(t) = S(t) \frac{\exp(-2t^2/\sigma_{\text{opt}}^2)}{\exp(-|t|/\sigma_{\text{opt}})}
\]

with \( S'(t) \) representing the signal resulting from apodization.

Here Eq. (24) is evaluated for the width of a matched Lorentzian, \( \sigma_{\text{opt}} \), which is then used to construct the approximate Gaussian, relying on the relationship between the linewidth of a Gaussian (\( \sigma_g \)) and the linewidth of a Lorentzian (\( \sigma_L \)), such that \( \sigma_g \times \sigma_L = \frac{1}{\sqrt{2}} \).

Such a transformation allows for an improvement in lineshapes that further aids in signal processing, as discussed in Sec. IV.4.E.

II.2. ODNP

An ODNP experiment simultaneously excites ESR with \( \mu \)w radiation and detects NMR with rf. It distinguishes between the movement of water at two different time scales by measuring two different relaxivities, \( k_{\text{low}} \) and \( k_{\sigma} \) [M⁻¹s⁻¹], which respond to changes in motion at the NMR (here 15MHz) and ESR (9.8 GHz) timescales, respectively.

Some of the experiments reported here measure the signal intensity, \( I(p) \), as a function of microwave power, \( p \), where \( I(0) \) gives the thermally polarized (i.e. Boltzmann, non-hyperpolarized) signal intensity. The results follow the established convention [3] of defining the transferred polarization as \( \varepsilon(p) = I(0) - I(p)/I(0) \), so that

\[
\varepsilon(p) = \frac{k_\sigma s(p)C_{SL}}{R_1(p)} \left| \frac{\omega_e}{\omega_H} \right| \left( \frac{1}{\omega_e} - \frac{1}{\omega_H} \right).
\]

where \( s(p) \) is the electron spin saturation factor (averaged across all hyperfine transitions) as a function of microwave power, \( \omega_e \) [rad/s] is the Larmor frequency of the electron, \( \omega_H \) [rad/s] is the Larmor frequency of the \(^1\text{H}\) nucleus, and \( R_1(p) \) [s⁻¹] is the longitudinal relaxation rate of the \(^1\text{H}\) nuclei at a given microwave power, and where, e.g., \( |\omega_e/\omega_H| = 659.44 \pm 0.05 \) for 4-hydroxy TEMPO in aqueous solution.

Importantly, even mild variations in temperature can significantly change \( R_1(p) \), thus affecting the overall \( \varepsilon(p) \) [2]. For this reason, ODNP measurements of dynamics depend on efficient \( R_1(p) \) measurements to enable accurate quantification of the product of the cross-relaxativity (\( k_\sigma \)) and the saturation factor:

\[
k_\sigma s(p) = \frac{\varepsilon(p)R_1(p)C_{SL}}{\omega_H} \left| \frac{1}{\omega_e} - \frac{1}{\omega_H} \right|.
\]

Eq. (27) typically follows an asymptotic form, even when \( \varepsilon(p) \) does not [2, 45]. \( R_1(p) \) is found from inversion recovery experiments at different powers and finding the \( R_1 \) at each power by fitting each set of data to the equation

\[
0 = 1 - 2e^{-R_1v.d.}
\]

where \( v.d. \) represents the variable delays used in each inversion recovery experiment. Therefore, the typical procedure for ODNP entails collecting several individual NMR experiments: a series of FIDs, recorded at different microwave powers to obtain an enhancement (\( \varepsilon(p) \)) curve, and also several inversion recovery experiments, recorded at different microwave powers to obtain \( R_1(p) \).

III. Experimental

III.1. Sample Preparation

4-hydroxy TEMPO (Sigma-Aldrich) provided the spin label for most measurements.

For reverse micelles measurements, CTAB (0.186 g, 57 mM, Sigma-Aldrich) was dissolved in 8.39 mL of CCl₄, into which hexanol co-surfactant (0.460 g, 502 mM) was added.

After addition of 50\( \mu \)M TEMPO water (68 mg, 424 mM), yielding a molar ratio of H₂O:CTAB:hexanol 7.45:1:8.82, for a total H₂O:surfactant ratio of \( w_0 = 7.45 \), the sample was vortexed \( 2 \times 30 \) s, rested for 5 min at r.t., and loaded into a 0.6 x 0.8 mm capillary tube (Fiber Optic Center, New Bedford, MA, USA) that was flame-sealed at both ends.

For measurements in the solenoid probe, a 13 mM NiSO₄ (Fisher) solution was prepared in a 5 mm o.d. NMR tube.
III.2. Minimalistic and Modular Design

III.2.A. ODNP spectrometer

ODNP data was acquired on a modular NMR spectrometer operating in tandem with a Bridge12 microwave power source and the magnet of a Bruker E500 cw EPR with SuperX bridge. A home-built probe (4.8 µL sample volume, 17 mm length) integrates specifically with the Bruker Super High Sensitivity Probehead X-Band resonator (ER 4122 SHQE), and interfaces with a SpinCore RadioProcessor-G transceiver (TTL and rf waveform generator and rf digitizer) board by way of a home-built passive duplexer and standard LNA receiving chain, as well as a SpinCore rf amplifier powered by generic power supply electronics.

III.2.B. NMR spectrometer independent of microwave electronics

Some experiments that do not require high-power microwaves instead utilize a probe with a solenoid coil, rather than the typical hairpin loop employed in the ODNP experiments. The solenoid probe accommodates a sample size of 390 µL, allowing for better signal to noise. Notably, however, the larger sample size also leads to significantly larger field inhomogeneities. A simple off-the-shelf oscilloscope and arbitrary waveform generator assembled into a 15 MHz NMR spectrometer function in conjunction with the same duplexer electronics. An enclosed probe with a solenoid coil, placed into the electromagnet of the Bruker EPR system. This setup utilizes the GW-Instek AFG-2225 waveform generator, GW-Instek GDS-3254 oscilloscope with digital filtering, and an ENI 3100L RF amplifier.

Finally, the same solenoid probe and duplexer system functions in combination with the SpinCore transceiver board.

A high-field Bruker spectrometer AVANCE III HD spectrometer, equipped with a broadband room temperature SMART probe with Z-gradient, acquired the high-field NMR data. By default, phase cycling on a Bruker spectrometer results in selection of only a single coherence pathway. To implement the we present a robust template for saving all transients of a phase cycle in listing 2.

III.3. Software Strategy

The pySpecData library, developed in part for this work, plays a crucial role in the software strategy deployed here. Aside from storing data in an object-oriented format (with a structure not dissimilar to the xarray library [46]), pySpecData offers key advantages for spectroscopic data.

As a specifically relevant example, most of the methods presented here require treatment of the phase cycle as an additional dimension of the data, beyond the standard direct and indirect dimensions. Addition of multiple dimensions can introduce practical challenges involved with data handling. In particular, the need to keep track of the meaning of the multiple dimensions used to structure data at various points in the processing code can easily lead to unintelligible code. Therefore, practicable implementation of the methods advocated here relies on the pySpecData library’s implementation of modern object-oriented capabilities (especially class-based organization and operator overloading), which give each dimension a title (“label”) specified by a string, along with optional units and axis coordinates. The pySpecData library capitalizes on this information e.g. to automatically relabel axis coordinates and units during Fourier transformation, and to implement automatic dimensional alignment and creation. As another example, these feature streamline the computation of cost functions by vectorizing the resultant dataset along an easily introduced optimization parameter. Other benefits include (1) automatically (without additional lines of code) utilizing and manipulating the axis coordinate information in a natural way (e.g., Fourier transforming leads to adjusted axis, relabeling a time axis leads to a frequency-dependent phase shift upon Fourier transformation) (2) uniform storage and processing of data both from proprietary file formats and directly acquired from instruments and (3) automatic propagation of errors.

IV. Results

While advancing the ODNP methodology, the authors noted a need for a sweeping reevaluation of basic elements of NMR acquisition and data processing along several fronts. Such an evaluation should enable advances in ODNP and other emerging spectroscopic techniques. While various ad-hoc solutions have been developed over the years, this work focuses on addressing the lack of a consistent, modern, and well-explained schema (approach, plan, and organization) for presenting and optimally processing all the raw data acquired during an NMR experiment. This schema for data manipulation and visualization underwent iterative refinement until arriving at the results presented here. Conceptually, it integrates the benefits of three techniques: (1) domain coloring for visualizing complex phase [47], which removes the need for phase correction before data can be interpreted, (2) object-oriented capabilities that facilitate the treatment of new dimensions introduced to store all the information in a phase-cycled experiment, and (3) open-source libraries that aid in visualization.

In the following text, Sec. IV.1 first demonstrates how domain coloring can provide a compact representation of NMR signal phase. A visualization of standard mutation curve data provides a straightforward introduction to this non-standard plotting technique. Formal addition of “phase cycling dimensions” as additional dimensions in the NMR dataset yields a variety of benefits, starting with the rapid setup and optimization of the NMR experiment and instrumentation, in Fig. 4. Notably, a simultaneous presentation of all (distinguishable) coherence transfer pathways, which typically have different signal phases or timings, in a domain-colored format proves surprisingly useful. We refer to the resulting image as
a “domain colored coherence transfer (DCCT) map.” While traditional techniques involve throwing out at least some data (undesired coherence transfer (CT) pathways, the imaginary part of data, etc.), DCCT maps provide a comprehensive overview of all acquired data in one image, visualizing the relationship between signal in the desired coherence pathway and correctly separated artefacts, as well as signal improperly sorted into undesired CT pathways. The manuscript refers to these three contributions, respectively, as: “desired signal,” “artefacts” or “artefactual pathways,” (Sec. IV.3) and “phase cycling noise” (Sec. IV.3.C). In the results that follow, DCCT maps Sec. IV.3 enrich signal analysis to inform experimental design and the development of data-processing algorithmsSec. IV.4 without adding any additional time cost to a more traditionally-acquired NMR experiment.

IV.1. Display of Signal Phase

For simplicity, before considering the visualization of signal in the coherence transfer domain, this manuscript first considers the domain coloring concept. Domain coloring plots appear in other fields: e.g. in solid state physics studies, hue frequently represents directionality [48, 49], while even public-domain webpages not uncommonly illustrate phase with hue. Nonetheless, they remain under-exploited in MR data visualization.

A 390 µL sample inside a solenoid coil probe provides the signal for this section; as it exceeds the size of a typical ODNP or aqueous ESR sample, it experiences a much greater range of field inhomogeneity than results presented in subsequent sections. Fig. 2b illustrates the raw signal (no phasing corrections), from the appropriate CT pathway of an echo-based nutation curve (pulse sequence: \(\theta \rightarrow \tau \rightarrow -2\theta \rightarrow \text{acq.}\), with tip angle \(\theta\) increasing along the indirect dimension). Hue corresponds to the complex phase and value/intensity corresponds to the complex magnitude, as indicated in Fig. 2a.

Armed with this plotting technique, the spectroscopist can assess the success of an experiment at a glance, without requiring any phase or timing corrections. Fig. 2b (inset) shows all frequencies where the pulse excites signal while also clearly demonstrating the inversion of the signal as \(\theta\) passes through multiples of 180°. Information that may otherwise require a(n inverse) becomes available at a quick glance Fourier transform and separate plot to clearly demonstrate. For example, a time-shift appears in the frequency-domain plot as a “rainbow” color variation, and in the case of a spin echo, indicates that the origin of the time axis \((t = 0)\) does not properly align with the center of an echo. Here, simple inspection of Fig. 2b (inset) indicates 5 cycles \((10\pi \text{ rad})\) of phase rotation over a span of 5 kHz, corresponding to a time shift of 1 ms. Fig. 2c introduces this 1 ms timing/phase correction (achieved by shifting the time axis in the pySpecData processing code or, equivalently, applying the appropriate first-order phase shift in the frequency domain). As expected from an echo signal properly centered about \(t = 0\), Fig. 2c yields a purely absorptive, uniform phase.
FIG. 3. In (a) the complex magnitude of the pulse waveform (black) and signal (blue) for the echo coherence pathway, captured on an oscilloscope, with $t = 0$ set to the echo center. (Real part shown in fainter blue.) A comparison to the hermitian conjugate of the signal (red) clearly illustrates the time at which the signals diverge (indicated by the dashed black vertical line) of 35.7 μs. This figure also clearly demonstrates how, due to $T_2^*$ (inhomogeneous) decay, over the timescale of the deadtime the signal loses some 25% of its amplitude. In (b), the pulse length has been optimized following a mutation curve measurement and carrier frequency set on resonance, showing the echo pathway (blue), the residual FID pathway (green), and pathway which should not contain any signal (purple). Given the pulse length optimization and on resonance condition, the echo pathway is much more intense than the unwanted FID pathway.

This example demonstrates just one of many possible examples of the general result that domain coloring plots both quickly guide simple manual data processing of raw data, and also allow instant access to information (here, the time delay of the signal) in both domains (time and frequency), while other plotting strategies might make this information apparent in only one domain.

IV.2. Treatment of Phase Cycling

As demonstrated in this and the following subsections, the incorporation of many short dimensions corresponding to the cycling of individual pulses clearly indicates the effects of drifting fields, rf amplitude misset, resonance frequency offset effects, and pulse ringdown. It also yields a simple scheme for quantifying the signal to noise ratio.

With the increased practicality offered by object oriented programming in hand, the original conceptual approaches to phase cycling – pioneered by Wokaun, Bodenhausen, Ernst, and others – take in new meaning. These approaches incisively focus on the concept that the change in coherence order during a pulse (Δp) is, quite simply, the Fourier transform of the cycled pulse phase ($\varphi_i$, Eq. (2)) [23, 26, 50]. Thus, in addition to the traditional direct ($t_2$) and indirect dimensions, the processing code implements a schema that organizes data into one or more short (typically 2-4 elements long) dimensions, one for each pulse. Each of these can be in the “phase cycling domain” ($\varphi_i$ for pulse $i$) or the conjugate “coherence transfer domain” (Δp). Rather than effectively filtering and discarding these additional dimensions, as in more typical phase cycling procedures, libraries such as the pySpecData Python library provided by the authors can draw on modern open-source programming libraries and object-oriented programming both to facilitate implementation of these new dimensions and provide a function to automatically generate DCCT map plots. A central result presented here is that modern coding and instrumentation standards provide novel elements enabling facile treatment of the phase cycle as an additional (small) dimension, and the ability to visualize these dimensions with a DCCT map. Together, these offer a more comprehensive view of the underlying spin physics and its interaction with experimental imperfections.

The next several subsections therefore demonstrate the DCCT schema on several hardware systems, ranging from a “bare-bones” spectrometer, made from non-specialized equipment (Sec. IV.3.A), to a modular system with a specialized SpinCore transceiver (Sec. IV.3.B), to a standard commercial Bruker high-field system (Sec. IV.3.D).

IV.3. Domain Colored Coherence Transfer (DCCT) Schema

IV.3.A. Example: Phase-cycled NMR with Standard Test + Measurement Equipment

The DCCT schema enables rapid setup and diagnosis of a “bare bones” NMR instrument. Non-specialized test and measurement components can – in fact – acquire reasonable NMR signal. For example, an arbitrary function generator (GW-Instek AFG-2225) can operate as an rf source and a digital oscilloscope (GW-Instek GDS-3254) can operate as a digital to analog converter whose bandwidth (250 MHz) and sampling rate (5GSps) exceed that of an attached analog low-pass filter (MiniCircuits SLP-21.4+).

The resulting inexpensive, uncomplicated NMR spectrometer remains invaluable for diagnostic purposes: for example, when assembling a modular ODNP spectrometer.

Object-oriented Python code [51] controls both instruments via USB 2.0 communication. Despite the fact that a standard oscilloscope has no built-in phase-cycling capabilities, the software can trivially save separate tran-
sients acquired with different pulse phases, along with the pulse waveform as a phase reference. The object-oriented code implemented here frequency filters the results, digitally mixes down and phase references by comparison to the captured pulse waveform, and saves data in an HDF5 format. It stores the data immediately available from the acquired transients in a 3-dimensional array of data, with shape $n_{\varphi_1} \times n_{\varphi_2} \times n_{t_2}$, representing the function $s(\varphi_1, \varphi_2, t_2)$. Here $n_{\varphi_1}$ and $n_{\varphi_2}$ are the number of phase cycling steps for the two pulses, and $n_{t_2}$ is the number of time points along the direct dimension [52].

After 3-dimensional Fourier transformation (without zero filling, cf. appendix C for notes on normalization) along the $\varphi_1$, $\varphi_2$ and $t_2$ dimensions, the signal becomes:

$$\tilde{s}(\Delta p_1, \Delta p_2, \nu_2) = \int \int \int e^{-i2\pi(\nu t_2 + \Delta p_1 \varphi_1 + \Delta p_2 \varphi_2)} f_{\text{sampling}}(\varphi_1, \varphi_2, t_2) s(\varphi_1, \varphi_2, t_2) d\varphi_1 d\varphi_2 dt_2$$

(29)

where $\Delta p_j$ indicates the coherence change during pulse $j$, $\nu_2$ gives the offset frequency (in Hz) along the direct dimension, and $f_{\text{sampling}}$ gives the function representing the instrumental and/or digital filtering and discrete sampling of the otherwise continuous signal (e.g., $f_{\text{sampling}}$ can be a convolution of a Dirac comb function convolved with an FIR filter, multiplied by a Heaviside hat function spanning the acquisition length), and $\Delta p_j$ (the coherence level change) and $\varphi_j$ (the cycled pulse phase) are Fourier conjugates (Eqs. (2) and (29)).

As noted previously, developing new methods under adverse circumstances – such as new ODNP instrumentation or protocols – requires unambiguous identification of signal as well as quick insight into any potential issues with the setup. Equally important to this requirement as identifying the main signal, the DCCT map also displays the undesired signal in the artefactual coherence pathways, as well as any imperfections in the phase cycle itself, that may arise from instrumental errors. As a simple example, Fig. 4a presents the DCCT map that results for an initial attempt at finding signal with a spin echo pulse sequence (Fig. 4a), as well as an optimized attempt (Fig. 4b). In both Fig. 4a and Fig. 4b, the CT pathways $\Delta p_1 = +1$ and $\Delta p_2 = -2$ contain the unambiguously identified signal arising from the spin echo.

Most notably, Fig. 4a indicates that the majority of the polarization yields signal not as spin-echo, but in the pathway where the longer pulse (nominally the 180° pulse, or second pulse in the pulse sequence) of a standard spin echo experiment excites an FID ($p = -1$) directly from the polarization ($p = 0$). By identifying the pathways where the polarization has been utilized, the DCCT map indicates how to improve the experiment; in this simple example, by increasing the length of both pulses. At the same time, the rainbow banding in this time domain data, Fig. 4a also indicates that the resonance frequency differs significantly from the carrier frequency. Fig. 4b corrects both the 90-pulse time and the carrier frequency to yield an intense, single colored band in the desired CT pathway for the echo signal.

Finally, for completeness, note that artefacts due to pulse ringdown appear in the CT pathways $\Delta p_1 = 0, \Delta p_2 = -1$ and $\Delta p_1 = -1, \Delta p_2 = 0$, since the ringdown cycles with the same phase as the pulses, in the $\Delta p = -1$ pathway for the relevant pulse. This artefact overlays with simple (FID-like) excitation, and appears as regions of alternating signal (colored) and no signal (white), with the latter arising from times where the the oscillating high-intensity ringdown saturates the duplexer diodes and/or LNA.

The insight provided by the DCCT schema can, of course, be extended to other pulse sequences. For example, the DCCT map of the standard spin echo (Fig. 4b) highlights a high-intensity signal that may arise from instrumental errors. As a simple example, Fig. 4b presents the CT pathways $\Delta p_1 = 0, \Delta p_2 = -1$ and $\Delta p_1 = -1, \Delta p_2 = 0$, since the ringdown cycles with the same phase as the pulses, in the $\Delta p = -1$ pathway for the relevant pulse. This artefact overlays with simple (FID-like) excitation, and appears as regions of alternating signal (colored) and no signal (white), with the latter arising from times where the the oscillating high-intensity ringdown saturates the duplexer diodes and/or LNA.

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course, reduce to more traditional presentations. For example, after plotting Fig. 4 in the generically applicable DCCT format, extraction of a subset of the data in a customized plot yields Fig. 3b. Meanwhile, traditional NMR acquisition employing on-board signal averaging through a phase-cycled receiver would further reduce the available information, detecting and saving exclusively the signal from the desired echo CT pathway $\Delta p_1 = +1, \Delta p_2 = -2$ (the blue line in Fig. 4c); the resulting data would only indicate the presence or absence of signal. In this example, the complete overview of the acquired data via the DCCT, in Fig. 4a, allows the spectroscopist to instantly detect the misfit in the pulse lengths by noting a large portion of the signal present in the undesired (FID-like) CT pathway. In a positive sense, the DCCT map also clearly demonstrates that, despite the non-specialized instrumentation employed, the phase cycling of the pulses on the AFG and phase referencing of the oscilloscope does operate as expected, since it cleanly isolates the CT pathways. Furthermore, the sign associated with the phases can differ on different spectrometers from different manufacturers, as previously noted, [53, 54], and this would be observable in the DCCT map.

**IV.3.B. Example: Nutation Curve**

The instrument constructed from non-specialized test and measurement equipment did suffer from two drawbacks: first, a data size limitation, and, second, slow communication between programmed commands and actual execution on the hardware. For a spectrometer constructed from non-specialized components, higher-end test and measurement equipment with a larger storage memory could address the first limitation, as could a standard analog quadrature mixer and filter scheme, both of which were beyond the scope of this study. The second limitation may be overcome with test and measurement instruments providing USB 3.0 capabilities. However, in the subsequent results here, the more advanced (but still very component-based and modular) SpinCore RadioProcessorG replaces the AFG and oscilloscope to enable faster rates of data transfer to the computer, as well as the use of digital filtering and downsampling, which permit the distortion-less capture of longer signals.

The same spin echo nutation experiment from Fig. 2, offers more information when presented as a DCCT map. The full dataset comprises a 4 dimensional function, $s(t_p, \varphi_1, \varphi_2, t_2)$, where $n_{\varphi_1} \times n_{\varphi_2} \times n_{t_p} \times n_{t_2} = 2 \times 2 \times 100 \times 1024$, and after a 3D Fourier transform becomes $\tilde{s}(\tau_p, \Delta p_1, \Delta p_2, \nu_2)$.

**IV.3.C. Example: Field Instabilities and the Estimation of Noise**

Another example arises when considering field instabilities. The Bruker EPR system comes equipped with a system for generating a standard modulation field (typically varying with a period of 10 µs), and one practical concern of ODNP spectroscopy involves what influence this might have on the NMR signal (when the spectrom-
FIG. 6. Attaching vs. detaching the ESR modulation coil allows for a controlled test of 2 situations with different field stability, as shown for both the time domain ((a) and (b)) and frequency domain ((c) and (d)), respectively. Three notable effects include the variation of the average frequency, increased amplitude of signal in inactive coherence transfer pathways elements of the coherence dimension, and variation of the echo center. With the mod coil detached (d), the average signal value in the desired coherence pathway is $1.04 \times$ that with the mod coil attached (c), while the root mean squared amplitude of the noise in all other (i.e., inactive) coherence pathways decreases by a factor of $0.86 \times$. Therefore, while the signal amplitude remains roughly equivalent, detaching the mod coil leads to a noticeable decrease in artifacts linked to improper phase cycling (variation of static field’s magnitude or time dependence from one step of the phase cycle to the next).

First, as already noted, the phase (color) of the signal at $t = 0$. Notably, domain coloring helps to emphasize this variation. As expected, the signal remains more stable when the connector for the modulation coil is detached, as in Fig. 6b.

The echo signal responds to the increased field variation from the modulation coil in three specific ways. First, as already noted, the phase (color) of the signal at $t = 0$ varies more across consecutive scans. This inconsistency arises from the residual modulation field driving changes in the $B_0$ field strength before v.s. after the 180° pulse. Second, greater frequency variation of the individual transients contributing to the signal in Fig. 6c results in the more jagged appearance of the signal “bands” as compared to Fig. 6d. Notably, if the various scans were averaged together, this would yield a distorted lineshape with increased linewidth. Third, and perhaps most significantly, in both cases, the DCCT map shows noise/artefacts in the CT pathways other than the echo-

FIG. 7. Mean of the absolute value of inactive coherence pathways with modulation coil attached ((a)) and detached ((b)).

er is set to “standby” mode). While a specific practical interest related to ODNP motivates this measurement, it also, more importantly, helps to demonstrate general effects that can arise in the presence of unstable fields. The DCCT maps in Fig. 6 illustrate signal from a spin echo experiment comprising a complete 8-step phase cycle with 16 repeats, when the modulation cable is left attached to the cavity (Figs. 6a and 6c) v.s. when it is detached from the cavity (Figs. 6b and 6d).

The timing and phase of the echo in Figs. 6a and 6b vary from scan to scan, as evidenced by, respectively, left v.s. right translation of the echo position relative to the $x$-axis and change to the color of the signal at $t = 0$. Notably, domain coloring helps to emphasize this variation. As expected, the signal remains more stable when the connector for the modulation cable is detached, as in Fig. 6b.
like ($\Delta p_1 = +1$, $\Delta p_2 = -2$) and FID-like ($\Delta p_1 = 0$, $\Delta p_2 = -1$) pathways, concentrated within the signal bandwidth. No explanation based on the transitions between different coherence levels of the density matrix can rationalize the appearance of significant artefactual signal in these “inactive” CT pathways. Rather, since the phase cycle must be sorting signal into the wrong CT pathway, we refer to the noise-like artefacts that appear in the inactive pathways as “phase cycling noise.” The difference is subtle, but attachment of the modulation coil does lead to more intense spikes in the phase cycling noise, as can be quantified from the mean squared phase cycling noise amplitude (1.3× higher with modulation coil attached).

Clearly, ODNP should be acquired with the modulation coil detached under all cases. Under these conditions, the phase cycling noise notably minimizes at the echo center, but – due to slightly different resonance frequencies arising from slow electromagnet field drift – then slowly grows in amplitude as the phase of the signal for each step of the phase cycle evolves at a slightly different rate.

Finally, referring back to Fig. 2, because the phase cycling noise does contribute to uncertainty in the measurement of the integral, it provides an appropriate source for error bars on integrals that are derived from the data. For example, in this case, one can integrate the 16 scans separately and then take the standard deviation in order to estimate the noise of the integral: with the modulation cable attached, this procedure yields a standard deviation of 0.18193 (normalized against the average signal intensity), and with the modulation cable detached, we retrieve a standard deviation of 0.10213. The standard deviation of the signal in the inactive coherence channels, when subjected to the appropriate error propagation formulas, yields estimates for the standard deviations of 0.05319 and 0.05201 respectively. In contrast, taking the standard deviation of the signal 200 Hz off-resonance from the signal from within the active coherence pathway, subject to the same error propagation formula, (i.e., resembling a standard SNR estimating procedure) yields an under-estimate of the standard deviation – 0.036 and 0.042, respectively.

IV.3.D. Example: CPMG

As noted in other publications, ODNP can be acquired with a CPMG sequence [6, 8, 55]. An interesting result of the DCCT map technique arises when applied to a fully phase cycled CPMG: a four step phase cycle on a 90° excitation pulse, followed by a train of evenly spaced 180° pulses, phase cycled in concert. In contrast to the scheme presented here, some analysis schemes bin the results of the phase cycle into a “CP” component, where the phases of the 90° pulse aligns with the phase of the 180° pulses, and a “CPMG” component, with orthogonal phases. Since the DCCT map offers a new means for visualizing signal, it provides the opportunity to revisit the decay of CP components and persistence of CPMG components [56]. Briefly, as further explained in Fig. 11a, signal should alternate between $\Delta p_1 = +1$ and $\Delta p_1 = -1$; however, signal starts to “bleed” into the opposite $\Delta p_1$ value following pathways like those shown in Fig. 11b, ultimately yielding a constant signal for both values of $\Delta p_1$. This corresponds to the previously observed decay of the “CP” component [56], viewed from a new perspective.

Naively following the methodology laid out in Sec. IV.1, the processing software here can sort the data into a 4D dataset (a single-line command in pySpecData), with the signal given by the discretized function $s(\varphi_1, \varphi_2, \tau_{echo}, t_2)$ of shape $n_{\varphi_1} \times n_{\varphi_2} \times n_{\tau_{echo}} \times n_{t_2}$; where $t_2$ gives the points within each echo and $\tau_{echo}$ gives the center position of each echo. This can be Fourier transformed along the $\varphi_1$, $\varphi_2$, and $t_2$ dimensions to permit filtering by resonance frequency and coherence pathway.

The initial (nominal) 90° pulse changes the coherence order of the initial polarization by $\Delta p_1 = \pm 1$. Here, since the 180° pulses are phase cycled together, $\Delta p_2$ refers to the net change in coherence order due to all 180° pulses. Therefore, odd-numbered echoes harvest signal from the pathway that experiences $\Delta p = +1$ and $\Delta p_2 = -2$. In contrast, even-numbered echoes harvest signal from the pathway that experiences $\Delta p = -1$ and $\Delta p_2 = 0$.

Thus, the CPMG experiment particularly motivates an informed choice of phase cycling dimensions to simplify the analyses. Specifically, a coherence-domain dimension $\Delta p_1 + \Delta p_2$ only yields signal for $\Delta p_1 + \Delta p_2 = -1$, and serves to separate only instrumental artefacts or higher order coherences. A rearrangement of the expression $\Delta p_1 \varphi_1 + \Delta p_2 \varphi_2$ (the effect of phase cycling on the phase angle of the transients) yields

$$\Delta p_1 \varphi_1 + \Delta p_2 \varphi_2 = \Delta p_1 (\varphi_1 - \varphi_2) + (\Delta p_1 + \Delta p_2) \varphi_2,$$

and motivates rearranging the signal to the form $s(\varphi_1 - \varphi_2, \varphi_2, n_{\tau_2})$ whose (3D) Fourier transform is given by $s(\Delta p_1, \Delta p_1 + \Delta p_2, n_{\tau_2}, n_{t_2})$. By definition, the Fourier con-

![FIG. 8. CPMG data acquired on high-field (400 MHz) Bruker spectrometer for 64 180 pulses. After each 180 pulse, the signal alternates between $\Delta p_1 = 1$ and $\Delta p_2 = -1$ until eventually bleeding is observed (by around the 12th echo).](image)
FIG. 9. This figure illustrates, in detail, the application of the processing and visualization algorithms outlined here to the task of determining a high-quality result for an inversion recovery experiment, despite fluctuating fields and resulting imperfections in phase cycling. In (a), the raw data has not been Fourier transformed along the phase cycling dimension. This data already clearly shows a null followed by phase inversion along the indirect dimension. Fourier transformation of this data from the phase cycling to the coherence transfer pathway domain yields a DCCT map. Furthermore, the Hermitian symmetry cost function Eq. (7) determines the center of the spin echo, yielding a phase-corrected signal (b). The alignment routine aligns the frequency drift of the result to yield (c). Finally, after slicing out the FID in the time domain, following Eq. (3), (d) illustrates the real part of the signal, free of baseline distortion, with automatically chosen integration bounds delineated between the crosshatched areas. This signal now shows a significant improvement in the signal alignment indicated by the sharper edges and uniformity. In addition, inspection of the DCCT map will show much cleaner signal intensity in the inactive coherence transfer pathways.

FIG. 10. Here we show (a), the raw data Fourier transformed along both the phase cycling and direct dimension and (b), the same plot but after correction of the spectra to place the maximum of the echo at time 0. We next (c), show the data after using the Hermitian symmetry of echoes to center our signal at t=0, and lastly (d), after applying the correlation alignment procedure, which noticeably cleans up the inactive coherence transfer pathways. Notice, even with alignment, there is still some variation which leads to a loss of signal, to correct for this we also apply a zeroth-order phase correction of all the individual transients.
jugate of $\Delta p_1$, the $\phi_1 - \phi_2$ dimension, labels the “CP” v.s. “CPMG” components of the signal, which arise naturally from this analysis. Specifically, transients for which $\phi_1 - \phi_2 = 0$ cyc or $\frac{1}{2}$ cyc ($\pi$ rad) are the “CP” component and those for which $\phi_1 - \phi_2 = \frac{1}{4}$ cyc or $\frac{3}{4}$ cyc ($\frac{\pi}{2}$, $\frac{3\pi}{2}$ rad) are the “CPMG” component. The $\Delta p_1$ dimension disentangles the pathways that should give rise to the even v.s. odd echoes. Odd-numbered echoes (following 1, 3, etc., inversion pulses) should only present signal for $\Delta p_1 = +1$, since the expected/desired coherence pathway with $\Delta p_1 = +1$ (shown as green line in Fig. 11b) only reaches $p = -1$ for odd echoes. Analogously, even numbered echoes should only present signal for $\Delta p_1 = -1$ (shown as blue line in Fig. 11b). The observed signal shown in the DCCT map of Fig. 11a derives from the alternating green and blue lines along the $p = -1$ coherence level. In this scheme, as long as even v.s. odd echoes remain separated along $\Delta p_1$, any phase encoded between the excitation and first echo pulse would be properly preserved.

However, due to offset or misset effects, imperfect 180° pulses can store a small fraction of transverse magnetization along the $z$-axis for one or more echo periods and then re-excite it as observable magnetization. In Fig. 11b the signal cleanly separates into the desired coherence channels for the first few echoes. However, near the 8th echo, significant amounts of $\Delta p_1 = +1$ signal begins to appear in even-numbered echoes, as well as significant amounts of $\Delta p_1 = -1$ signal in odd-numbered echoes – i.e. the signal “bleeds” from the even echo pathway into the odd echo pathway, and vice versa.

Fig. 11b also demonstrates that signal that does not experience any initial encoding can be combined into a single decay by subtracting (adding with a phase out of 180°) of the $\Delta p_1 = -1$ signal from that of the $\Delta p_1 = +1$ signal. Indeed,

$$\frac{1}{2}(\tilde{s}(t_2, +1) - \tilde{s}(t_2, -1)) =$$

$$\sum_{n=0}^{4} e^{i2\omega \frac{n}{4}} s(t_2, \frac{n}{4})$$

$$\sum_{n=0}^{4} e^{-i2\omega \frac{n}{4}} s(t_2, \frac{n}{4}) =$$

$$\frac{1}{2}(s(t_2, 1) - s(t_2, 3))$$

where $s$ is a function of $t_2$ and $\phi_1 - \phi_2$ and $\tilde{s}$ a function of $t_2$ and $\Delta p_1$ (and which uses the identities $e^0 = e^\pi$ and $e^{i\pi} = -e^{i\pi}$ while $e^{i\frac{\pi}{2}} = -e^{i\frac{\pi}{2}}$ and $e^{-i\frac{\pi}{2}} = -e^{-i\frac{\pi}{2}}$) demonstrates this math is equivalent to adding the CPMG components ($\phi_1 - \phi_2 = \frac{1}{4}$ cyc) or subtracting the long-lived tails, which are 180° out of phase. In the case where field inhomogeneity is much smaller than the $B_1$ multiplied by the number of echoes ($\Delta \Omega \ll |B_1 n_{echo}|$), both CP and CPMG signals present a significant amplitude [56]. As has been observed previously, because only magnetization orthogonal to the direction of the pulse field in the rotating frame (e.g., $x$-magnetization subjected to a $y$-pulse) is stored along the $z$-axis, this affects only the CP transients of the phase cycle, and not the CPMG transients. Therefore, the “bleeding” observed here illustrates the approach to 0 of the CP-component [56] from a new perspective, and clearly indicates when quadrature phase information is not valid. The unanticipated storage of coherence along $z$ (the red line in Fig. 11b) that leads to “bleeding” of the signal into the incorrect pathway directly corresponds to oscillation and decay of the CP component ($\phi_1 - \phi_2 = \frac{1}{4}$ cyc) and loss of phase-sensitive information and demands application of alternate acquisition scheme [56].

The echo signal should alternate between two desired coherence pathways, as shown in Fig. 8 for a sample acquired in a high-resolution 400 MHz spectrometer. The small amount of signal in the $\Delta p_1 = 0$ channel likely arises from FID-like behavior of magnetization off of each 180° pulse, likely due to signal from sample regions near the edge of the coil’s active volume or with other $B_1$ inhomogeneity (and therefore misset). The clean separation of even and odd echoes indicates that the signal follows the expected coherence pathways and that the echo train could form a component of a longer pulse sequence that required a preparation period before the 180° train that encodes a phase, e.g. for an indirect dimension.
IV.4. Algorithms Motivated by DCCT

The following subsections introduce several realistic ODNP-related examples of how DCCT visualizes the transformation of the complete signal, from raw signal, through phasing and alignment, and ultimately to integration of the real part of the signal.

IV.4.A. Phasing of NMR Transients

In the field of quantitative NMR, various studies have treated the seemingly trivial, but ultimately pervasive and fundamentally linked issues of automated baseline correction and first-order phase correction [40, 57, 58]. The presence of shot-to-shot instabilities of the magnetic field and the desire for a seamless transition between 1D spectroscopy and stroboscopic (e.g. CPMG) acquisitions further complicate such attempts. As discussed in theory Sec. II.1.D, echo-based signals can simplify the timing/phase correction of the signal by removing the need to account for the distortion or loss of the very first points in the FID. Specifically, acquisition of echo-based signals replaces the potentially iterative phase and baseline correction with the problem of locating the center of the echo.

Fig. 6a highlights the fact that even when the temporal (left to right) variation of the echo intensity is subtle, the phase (color) of successive echoes varies noticeably. This encourages the use of the full complex signal – i.e. phase as well as magnitude – from as much of the echo as possible in order to identify the echo center.

In fact a simple algorithm that utilizes the phase information as well as the amplitude information of the echo can generate well-phased baseline-free signal from spin echoes. As a test case, a standard sample of water and 4-hydroxyTEMPO generated a series of signals as part of a progressive enhancement sequence. Eq. (7) calculates a cost that is minimized at the center of an echo signal with Hermitian symmetry. Fig. 12a displays this cost averaged across 28 indirect power steps × 8 phase cycled transients, at microwave powers ranging from 0 to 4 W. The cost function exhibits as well-defined minimum at ~10.6 ms.

Fig. 12b displays the signals that have been shifted in the time domain to place the \( t = 0 \) of the time axis at the minimum of this cost function, and all transients have been multiplied by the same zeroth order phase correction. The imaginary components of all scans cross zero at \( t = 0 \), despite the fact that all were acquired with different microwave powers. The residual calculated by subtracting the signal from its Hermitian transpose \((s^*(-t))\) barely rises above the level of noise, and likely arises only from slight relaxation and field drift effects. This means that the detected echo comprises a rising signal \((s_{rising}(t))\) for \( t < 0 \) and a free-induction decay \((s_{FID}(t))\) for \( t > 0 \), and \( s_{rising}(0) = s_{FID}(0) = \frac{1}{2}s(0)\); the two portions mirror each other (in the sense of hermitian symmetry, such that \( s(t) = s^*(-t)\)), Fig. 12a.

Furthermore, while under high-resolution (superconducting) conditions, one might expect a loss of signal due to \( T_2 \) decay, the results here show detection of echoes does not provide a decrease in signal amplitude relative to detection of FID signal, as a result of the refocusing of inhomogeneities, since, typically, \( T_2^* \parallel T_2 \).

An echo time of 3 ms is optimal to optimize the timing correction following Eq. (7), as it allows for deadtime and diode recovery delays which would otherwise affect the echo maximum. While the timing correction needed may be a conglomerate of various contributions, from delays to hardware triggering events, transmission line lengths, and amount of noise present, the system in the
authors’ lab typically requires a timing correction of 100-500 μs relative to the expected center of the echo ($t_{\text{echo}} = \tau + 2t_{\text{iso}}/\pi$ [33]).

Barring perturbations to the field, repeated experiments satisfactorily reproduce the echo location and enable signal averaging. Specifically, Eq. (7) typically yields a minimum at a consistent time, as shown in the data of Fig. 6 in Fig. 13.

### IV.4.B. Simple NMR Signal Alignment

Even with a reasonable effort to invoke a stable resonance frequency (as in Figs. 9a and 9b), significant phase cycling noise appears in the DCCT. One can hypothesize that the phase cycling noise arises from residual field fluctuations of the electromagnet. Fig. 14a is a clear example of such a fluctuation during an inversion recovery experiment, plots the DCCT of the signal from a simple spin echo with a short (1 ms) echo time on the 15 MHz electromagnet system. The amplitude of the phase cycling noise relative to the amplitude of the signal increases noticeably for times increasingly further away from the center of the echo. This effect matches the expected effect of slowly changing resonance (field) offset, which does not affect signal at the echo center, but does affect signals at times further from the echo center. Thus, an initial inspection implies that a significant portion of phase cycling noise results from field fluctuations.

To ascertain the extent to which the presumed drifting of the static magnetic field leads to phase cycling noise, iterative maximization of Eq. (16), (subjected to a Gaussian mask of width $\sigma = 1274$ and nonzero only for the coherence pathways $\Delta p_1 = 1$, $\Delta p_2 = -2$, and $\Delta p_1 = 0$, $\Delta p_2 = -1$) aligned the signal Fig. 22. This routine serves to mitigate the phase cycling noise, while also improving the resolution and sensitivity of any 1D signals averaged from multiple transients. Thus, signal alignment proves a viable means to address the experimental complications owed to randomly varying offset.

### IV.4.C. Example: Inversion Recovery

For example, Fig. 9 shows the data for an inversion recovery experiment at various stages of processing: first, the “raw” data, simply Fourier transformed along the phase cycling ($\varphi_1$, $\varphi_2$) and direct ($t_2$) dimensions (Fig. 9a). The majority of the signal appears in the correct coherence pathway, indicating that the majority of the equilibrium magnetization goes towards generating the signal of interest – as opposed to a situation where misset or inhomogeneities expend a significant portion of the signal on irrelevant coherence pathways. Without any phase correction, the figure illustrates an inversion in phase as the signal passes through the signal null ($M(\tau) = 0$ at $\tau = -T_1 \ln(\frac{1}{2})$). A quick glance at such a data display reveals the relative success or failure of a user’s choice of inter-pulse delays – especially those between the initial 180 DEG pulse and the second 90 DEG pulse – without the need for phase correction or for intensive data processing. These plots unambiguously indicate a successful inversion recovery experiment, with clear, solid colored regions of inverted phase (given that hue represents phase in these plots).

As before, the number of full color cycles that occur within a given frequency bandwidth (e.g., in Fig. 9b, 4 full color cycles / 100 Hz = 40 ms) indicate the approximate timing (first-order phase) correction required.

![Diagram](image-url)
while the Hermitian symmetry test enables an automated means to find and apply this correction. Shifting the zero of the time axis to the center of the echo [33], much of the first order phase error (which appears as a color grating) along the x-direction disappears (Fig. 9b). Finally, after alignment (Fig. 9c), the phase cycling noise reduces in intensity while the intensity of the signal increases slightly. During the alignment procedure here and in the following results, four features prove to be essential. First, the algorithm must perform any timing (first order phase) corrections before alignment, since signals of different phases do not align properly. Second, to allow for high resolution in the calculated $\nu_{\text{shift,max}}$, a significant zero-filling of the time domain precedes Fourier transformation back to the time domain. Furthermore, Eq. (16) requires a cross-correlation function for each transient cross-correlated against all others, which permits higher SNR than, e.g., calculating only cross-correlations for nearest-neighbor transients, as might be implied by Eq. (13). Finally, as noted in Sec. II, optimizing the masked energy/norm of the signal, rather than the full energy/norm of the signal, proves to be essential, along with adequate frequency resolution achieved by sufficient acquisition time (of at least 1 second).

**IV.4.D. Example: Reverse Micelles**

Typical ODNP studies rely on the fact that water comprises most of the sample, enabling employment of relatively small sample volumes ($\sim 4.8$ µL). Studying the water inside reverse micelles proves challenging, as the proton spectra present $\sim 1/30^{\text{th}}$ the SNR of aqueous samples. However, with longitudinal relaxation rates $R_1$ (e.g. $\sim 7.7$ s$^{-1}$) that are significantly faster than that of aqueous samples ($\sim 0.4$ s$^{-1}$), reverse micelles provide an opportunity for rapid signal averaging not otherwise possible in typical ODNP samples. In addressing this low SNR dilemma, previous reverse micelle studies used large probes and subsequently larger sample volumes [13], but to adequately minimize heating effects would require smaller volumes ($\leq 0.6$ mm sample radius) in typical ODNP setups [59]. Other ODNP measurements have employed larger sample volumes in studies of organic solvents [60], where the sample can extend into the electric field of the cavity with less substantially detrimental heating effects. Reverse Micelles (RMs) provide an intermediate case, where water comprises a fraction of the sample, resulting in significantly less signal to noise, while (based on changes to cavity $Q$) still presenting a significant concern w.r.t. sample heating. While individual transients have insufficient SNR to clearly identify signal, acquiring many transients can lead to broadening of the averaged signal in the presence of slow field drift, rendering characterization of thermal signal particularly problematic. Fig. 15 shows the DCCT map for thermally polarized NMR signal for a reverse micelle sample, before performing the correlation alignment. To compensate for the very low $^1$H content of this system, the pulse sequence cycles through the 8-step Hahn echo phase cycle 200 times, resulting in 1600 individual transients. The 1D plots in Fig. 15 (top) show the spectrum from one complete phase cycle (i.e. one scan, in red), as well as the average over all 200 scans (blue). The DCCT plot shows red signal in the expected coherence channel but is very faint. The 1D plots illustrate that signal is not observable from a single phase cycled scan of the 1600 scans (red) and faintly detectable upon averaging over all of these scans (blue). The DCCT plot allows separate display of scans, while also emphasizing the phase-coherent signal.

**FIG. 15.** A domain colored plot of signal from a reverse micelle sample before undergoing the correlation alignment. This map only shows the $\Delta p_2 = -2$ portion of the coherence domain for the second pulse, as the other CT pathways include only noise similar to the noise-only pathways shown here. The signal appears in red in the expected coherence channel but is very faint. The 1D plots illustrate that signal is not observable from a single phase cycled scan of the 1600 scans (red) and faintly detectable upon averaging over all of these scans (blue). The DCCT plot allows separate display of scans, while also emphasizing the phase-coherent signal.
FIG. 16. A domain colored plot of a reverse micelle sample (same as in 15) after undergoing the correlation alignment in Eq. (22). Signal concentrates into a bright red band in the appropriate coherence pathway. The 1D plots illustrate that signal is marginally observable from a single scan out of the 1600 scans (blue); this arises from alignment of the various transients in the phase cycle. An average taken over all scans significantly improves the signal amplitude (red), and does so with much greater efficiency when the signal has been previously aligned than in the absence of alignment.

significantly after averaging over all 200 cycles through the phase cycle (red). This signal exhibits a significantly reduced linewidth of ≈ 125 Hz. A component of Fig. 15 vs Fig. 16 demonstrates how the same correlation alignment permits the observation of thermal NMR signal for the RM case with higher SNR and better resolution than without. Even though the net signal energy, averaged across repeats, remains the same, aligning the signal improves the phase coherence of the signal from transient to transient and makes the signal much more visible not only in averaged signal, but also in the DCCT map. This is a striking and somewhat unexpected result.

IV.4.E. Lineshape Improvement and Choice of Integration Bounds

To filter out unneeded frequencies in a typical new experiment, the operator will display data in a frequency-domain DCCT plot, then slice out the portion of the frequency axis containing significant signal, thus filtering out off-resonance noise and reducing the memory footprint of the signal. The pySpecData library accepts slices given in frequency units (not requiring an array index) in a compact notation (listing 4) and automatically recalculates the new time axis (since the slicing operation increases the spacing between the time-domain datapoints).

Similarly, standard protocols require filtering out longer times, where the signal has decayed to zero. The $T_2^*$, in general, remains unknown due to the variable inhomogeneity of the electromagnet; and, in-fact, inhomogeneities frequently lead to sharp peaks in otherwise broad lineshapes that make the concept of $T_2^*$ somewhat of an oversimplification. Therefore, optimal signal acquisition encompasses relatively large $t_2$ values. Interestingly, standard error propagation formulae reveal that truncation of time domain signal has no effect on the error of an integral over a given bandwidth. [61]

Optimal processing of ODNP data requires apodiza-
FIG. 18. An inversion recovery dataset recorded for toluene 4.8 µL NMR signal after undergoing alignment procedure, before (a) and after (b) apodization routine.

FIG. 19. Correlation alignment improves the signal to noise of inversion recovery data, and reduces the imaginary component of the integral. The procedure described in the text automatically determines the integration limits and analyzes the inactive coherence transfer pathways to determine the error bars.

FIG. 20. The DCCT map provides both error bars (from the inactive coherence channels) and guidance for applying correlation alignment and baseline-free phasing routines that enable precise ODNP. In this illustration of the $E(p)$ curve for 150 µM hydroxytempo, subsequent (following Fig. 10) auto-integration of the NMR peaks determines the NMR signal intensity, denoted by circles, and accompanying error bars (from inactive coherence channels), with fits produced from Eq. (26). The blue circles, error bars, and fit are from phase corrected but unaligned NMR data. However, the green circles illustrate the specific benefit of correlation alignment that takes advantage of multi-transient averaging. Correlation alignment and the refinement of the integrations bounds that it allows improve the signal to noise of the ODNP enhancement curve, as well as its fit to the model.

phase

$$s_{err}(\tau) = \sum_{(\Delta p_1, \Delta p_2)} \int_{p_{low}}^{p_{high}} |s(\nu_2, \tau, \Delta p_1, \Delta p_2)|^2 d\nu_2$$

(32)
the alignment reduces the error bars. A better match of the data to the standard model Eq. (28) also supports
the conclusion that alignment reduces the noise.

In Fig. 20, a moderate, but more consistent with literature [2], increase in the observed enhancement is ob-
served after alignment along with an improvement in the
observed signal saturation at higher power, which is ex-
pected given the consideration of heating taken into the
data analysis.

V. Discussion

Thus the DCCT map serves as an excellent tool for
detecting signal for challenging $^1$H concentrations, which
might otherwise appear to be only noise. Following this
up with the correlation alignment presented here results
in a very clear improvement in the linewidth of the NMR
resonance as well as the SNR.

The results here advocate for a non-standard approach
to coherence pathways.

The DCCT schema as applied in these low field con-
ditions contains 5 features: (1) storage of all transients
acquired to long acquisition times (i.e. not phase cycling
the receiver and/or averaging on board), (2) multidimen-
sional organization of data via object-oriented code that
assists in usage and manipulation, (4) visualization of data in the DCCT map, and (5) echo-based detection enabling facile phase correction.

Notably, this manuscript demonstrates that domain
coloring combines synergistically with the simultaneous
presentation of multiple coherence transfer pathways. In
particular, domain coloring bypasses complexities when
different pathways have different phases or timings, en-
abling straightforward simultaneous visualization of CT
pathways. (5) a preference for echo-based detection, where sensible

This approach is not without historical precedent. Very early examples [23, 26, 50] explicitly Fourier trans-
form along a dimension where phases were cycled in a
procedure formalized as the “Phase Fourier Transform,”
though always within the context of multiple quantum
spectroscopy. Indeed, separately storing the transients to
perform this transformation has proven advantageous
in 2D multiquantum experiments, such as in multiplex
phase cycling [24] and MQD [25]. While undoubtedly
useful as a method for coherence selection, this technique
enrich signal analysis and inform experimental design and
improperly sorted into undesired pathways. DCCT maps
afford a comprehensive overview of all acquired data in one im-
age, at a very early stage of data processing, visualizing
the relationship between signal in the desired coherence
pathway, correctly separated artefacts, as well as signal
improperly sorted into undesired pathways. DCCT maps
enrich signal analysis and inform experimental design and
the development of data-processing algorithms, without
adding any additional time cost to a more traditionally-
acquired NMR experiment.

It is important to note that many modern laborato-
ries may informally use a methodology similar to some
subset of the DCCT schema to some extent, but the au-
thors are unaware of an extant formal description of this
very useful procedure in the literature, nor of a way of
visualizing the data in a convenient fashion. Essentially,
the data processing technology previously lagged behind
the established understanding of coherence pathways, re-
quiring researchers to skip over the detailed analysis of
correlation pathways that leads to better alignment and
better identification and selection of signal under adverse
circumstances, and straight to the selection of the de-
sired coherence pathway. Here, this is achieved easily
through the object-oriented treatment of the resulting
multi-dimensional data, and through robust multi-color
domain coloring plots. The success of these methods in
improving the practicability of the modular ODNP sys-
tem here indicate future successes in other fields of cus-
tomized NMR.

It is worth noting that typical current approaches to
NMR data acquisition and processing bear many histori-
cal artifacts that date back to the days of analog mixing,
as opposed to the digital filters that are typically used
today, as well as limited memory space requirements and
data transfer rates. In particular, the rather stringent
constraints of minimizing the size of temporarily-stored
The DCCT schema offers unique clarity into the role of phase cycling. In particular, it provides a means for visually representing several known, but important properties of phase cycling. For example, Plancherel’s theorem emphasizes that the noise from different transients in the phase cycle domain will spread equally across the coherence domain, yielding the same SNR benefit as (non phase-cycled) signal averaging. The low field studies in the results here typically benefit from the added SNR of additional phase cycling, but for more elaborate pulse sequences, implemented on high SNR systems, DCCT maps offer promise for choosing the most effective phase cycles [63]. Specifically, by since visualizing all the coherence pathways for a comprehensive pulse sequence they clearly show where artifacts occur and where they do not occur. Eliminating or reducing the size of phase cycling dimensions whose coherence domain shows only noise along one or more dimensions only decreases SNR in accordance with the square root of the reduced number of acquired transients. As a simple example, in Fig. 5, among the phase cycle of the first pulse under these specific circumstances would add noise of the $\Delta p_1 = \pm 1$, $\Delta p_2 = \pm 1$ pathway to that of the $\Delta p_1 = 0$, $\Delta p_2 = -1$ pathway and the noise of the $\Delta p_1 = 0$, $\Delta p_2 = 0$ pathway to the $\Delta p_1 = +1$, $\Delta p_2 = -2$. While this decreases the SNR by $\sqrt{2}$, the artefact remain separated (no significant DC artifacts at $\Delta p_1 = 0$, $\Delta p_2 = 0$ are present here), and the number of scans reduces by a factor of 2. In a more complicated example, the CPMG results Fig. 11a emphasize when a 4 step vs 2 step phase cycle of the excitation pulse proves useful. This study offers a more intuitive method of optimizing pulse sequences than previously proposed methods.

The results here also demonstrate that phase cycled echoes offer distinct advantages over standard 90° pulses when acquiring signal on a system, especially for the first time. Aside from offering a maximum signal intensity that is not sensitive to field inhomogeneity, echo signals are also cleanly isolated from any ringdown arising from the pulses because they cycle in phase differently than the pulse waveforms.

VI. Conclusion

The results presented here highlight the DCCT schema for presenting NMR data from phase cycled experiments as generally useful tool for displaying raw data in a meaningful format, with minimal manipulation after acquisition, for quickly identifying which coherence pathways utilize most of the initial polarization of the NMR experiment, and for optimizing signal in the midst of adverse conditions. The DCCT schema points out experimental errors which may otherwise be overlooked, serving to optimize the NMR signal acquired for emerging techniques, as well as to rapidly deploy new types experiments during the development of new MR methods; as demonstrated here for Overhauser Dynamic Nuclear Polarization. The general schema developed here should extend naturally to the task of optimizing the phase cycle in complex experiments, and towards efficiently visualizing and optimizing the data from multidimensional multiple quantum experiments. The authors anticipate the schema will apply directly to 2D Electron Spin Resonance (2D-ESR) and can adapt to accommodate other forms of coherent spectroscopy where phase cycling is possible; notably 2D-infrared spectroscopy [64–66]. Overall, the authors expect this work to represent the origin of a more comprehensive schema for visualizing, processing, and understanding coherently phase cycled spectroscopic data.

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Listing 2. Separately saved phase cycling in Bruker pulse program

```python
121 = 4
122 = 2
loopcounter num_ph
"num_ph = 121+122"
"120 = td1/num_ph"
"nbl = num_ph"

2 st0
; pulse programming elements
ippl = increment phase of first pulse
lo to 2 times 121

2 st1
; pulse programming elements
ippl = increment phase of second pulse
lo to 2 times 122

Acquisition with the digital oscilloscope requires digital demodulation and filtering, which typically takes the following form

Listing 3. Oscilloscope-based acquisition

```python

Listing 4. Frequency slicing

```python

Listing 5. Example of chunking data for DCCT

```python

A. Code Snippets

The FID is sliced from the echo by subtracting the delay between the start of acquisition and the center of the echo, \( t_{delay} \), from the original \( t_2 \) axis coordinates, then placing the axis in register (so that one of the axis coordinates occurs at exactly \( t_2 = 0 \)), slicing out only values \( t_2 > 0 \), and finally setting the first datapoint to 1/2 its original value.

Listing 1. FID slice

```python
s['t2'] = t_delay
s.register_axis('t2')
s=s['t2']:(0,None)
s['t2',0] *= 0.5
```

with oscilloscope() as g:
pulse = g.acquire_waveform(ch=1) # typically, split off and capture
s = g.acquire_waveform(ch=2) # signal after
duplexer
and LNA
pulse.ft('t', shift=True) # move the pulse
into
the frequency
domain
center_freq = abs(pulse['\nu']*(0,None))
.argmax('\nu') # estimate the
carrier frequency
from the max
s.ft('t', shift=True) # move the signal
into the time
domain
s = s['\nu']((center_freq+r[-10e3,10e3]))
# filter out a
10 kHz bandwidth
s.fft('t') # move s back to the time
domain
```

```
"center_freq = abs(pulse['\nu']*(0,None))")
.argmax('\nu') # estimate the
carrier frequency
from the max
s.ft('t', shift=True) # move the signal
into the time
domain
s = s['\nu']((center_freq+r[-10e3,10e3]))
# filter out a
10 kHz bandwidth
s.fft('t') # move s back to the time
domain
```

```
s['t2']:(-400,400)
```

```
s['t2']:(-400,400)
```

```
s['t2']:(-500,500)
```

```
s['t2']:(-400,400)
```

```
s['t2']:(-500,500)
```
B. Figures

C. Normalization of Fourier Transforms

Eq. (29) is appropriate for a continuous signal, normalized in the integral sense according to Plancherel’s theorem. If one rather treats $s'$ and $\tilde{s}'$ that are assumed to be modifications of the underlying continuous functions that have been discretized and made periodic following the standard convention of using multiplication by, and convolution with, Dirac comb functions, the equation must be modified in order to preserve the normalization of the underlying continuous signals, as follows:

$$\tilde{s}'(\Delta p_1, \Delta p_2, \nu_2) = \sqrt{\frac{\Delta \nu_2}{\Delta \varphi_1 \Delta \varphi_2 \Delta t_2}} \times \int \int \int e^{-i2\pi(\nu_2 + \Delta p_1 \varphi_1 + \Delta p_2 \varphi_2)} \times s'(\varphi_1, \varphi_2, t_2) d\varphi_1 d\varphi_2 dt_2 \quad (C1)$$

where $\Delta \varphi$ is the phase cycling increment as a fraction of a cycle ($2\pi$ rad), $\Delta \nu_2$ is the resolution of the frequency-domain signal and $\Delta t_2$ the dwell time. The discrete version of this integral is numerically equivalent to Eq. (2), so that the discretized data arrays have the same vector norm before and after the discretized analog of Eq. (C1).

D. Comparison of FID to Echo Amplitude

Fig. 23 compares the FID amplitude to that of a short-time echo.
FIG. 23. A comparison of FID v.s. short time echoes on the modular spectrometer that utilizes the SpinCore transceiver board. The difference in amplitude between the FID signal and short-time echoes is insignificant.