Spatial encoding strategies for ultrafast multidimensional nuclear magnetic resonance

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Multidimensional spectroscopy plays a central role in contemporary magnetic resonance. A general feature of multidimensional NMR is its inherent multiscan nature, stemming from the methodology’s reliance on a series of independent acquisitions to sample the spins’ evolutions throughout the indirect time domains. Contrasting this traditional feature, an acquisition scheme has recently been reported that enables the collection of complete of multidimensional NMR data sets within one single scan. Provided that the signals to be observed are sufficiently strong, this new “ultrafast” protocol can thus shorten the acquisition times of multidimensional NMR experiments by several orders of magnitude. This new methodology operates by departing from temporal encoding principles used since the advent of Fourier-transform NMR, replacing them with a spatial encoding of the spin interactions. Spatial encoding operates in turn on the basis of novel radiofrequency irradiation and magnetic field gradient waveform manipulations, designed so as to impart on the sample a coherent spin magnetization pattern that reflects the internal interactions to be measured. Given the central role played by this new kind of spectroscopic-oriented manipulations in ultrafast NMR, we devote this review to surveying different variants that have hitherto been proposed for their implementation. These include both discrete and continuous versions, real- and constant-time implementations, as well as amplitude- and phase-modulated alternatives. The principles underlying these various spatial encoding approaches are treated, their operation is graphically illustrated as well as formally derived within suitable theoretical frameworks, and an in-depth comparison of their line shape characteristics is discussed. © 2008 American Institute of Physics.

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I. INTRODUCTION

Few branches of spectroscopy match in either breadth or depth the impact achieved by multidimensional nuclear magnetic resonance (nD NMR).\textsuperscript{1,2} Originating as an extension of Fourier-transform pulsed NMR,\textsuperscript{3,4} the advent of multidimensional experiments—and the emergence of two-dimensional (2D) NMR, in particular—transformed NMR from an analytical technique geared toward the analysis of an important but confined class of organic molecules, into one of the cornerstones of modern chemical, biochemical, and medical researches. Indeed the last three decades have witnessed a growing number of nD NMR applications to materials, to solid biomolecules, to structural determinations of proteins and nucleic acids in their native solution state, to the screening of structure-activity relationships involving therapeutic drugs, and as tools to study metabolism and diagnose disease.\textsuperscript{5–8} In spite of the hundreds of multidimensional NMR experiments that are needed to carry out all these very different types of analyses, one main protocol underlies them all. For the case of 2D NMR this is the basic Jeener–Ernst scheme,\textsuperscript{9,10}

\begin{equation}
\text{Preparation – Evolution}(t_1) – \text{Mixing – Acquisition}(t_2),
\end{equation}

leading to the acquisition of a two-dimensional time-domain signal,

\begin{equation}
S(t_1,t_2) = \int d\Omega_2 \left[ \int d\Omega_1 l(\Omega_1,\Omega_2) e^{i\Omega_1 t_1} e^{-i\Omega_2 t_2} \right] e^{i\Omega_2 t_2} e^{-i\Omega_1 t_1}.
\end{equation}

From this signal, correlations between the indirect- and direct-domain NMR frequencies $\Omega_1, \Omega_2$ affecting spins in a sample can be extracted following a discrete version of the Fourier transform (FT),

\begin{equation}
I(\nu_1,\nu_2) \approx \sum_{t_2} \sum_{t_1} S(t_1,t_2) e^{-i\nu_1 t_1} e^{-i\nu_2 t_2}.
\end{equation}

In spite of the similar formal roles suggested by this equation for the variables $(t_1,t_2)$ toward extracting a 2D $I(\Omega_1,\Omega_2)$ NMR spectrum, these two “times” actually possess two very different origins. $t_2$ is a digitization time, of the kind that defines the acquisitions in one-dimensional (1D) NMR experiments. The spins’ behavior along this so-called direct domain can therefore be characterized by the FT of data digitized throughout a single-scan experiment. The remaining time-domain axis, by contrast, is sampled by the Jeener–Ernst paradigm in a parametric fashion. In other
words, an evolution delay $t_1$ within the pulse sequence is incremented throughout a series of $N_1$ independent experiments, in steps of duration $\Delta t_1$ [Fig. 1(a)]. This in turn means that, in spite of the unambiguous gains resulting from increasing NMR’s dimensionality beyond 1D, one fundamental drawback also becomes associated with this kind of acquisitions: as each point to be sampled along the indirect time-domain constitutes an independent acquisition, nD NMR will demand tens or hundreds of transients in order to adequately sample the $t_1$ domain—even if the signal-to-noise ratio is acceptable within a single scan. Such complication is built-in in the 2D scheme illustrated by Eq. (1), and gets exponentially compounded when porting these principles to higher nD NMR acquisitions.

Driven by this complication, and stimulated in all likelihood by continuous improvements in the sensitivity and resolution afforded by the NMR hardware, recent years have witnessed a number of efforts geared at shortening the durations that are required to collect multidimensional NMR data sets. Among these proposals counts an “ultrafast” alternative, capable of completing multidimensional NMR acquisitions within a single transient. Lying at the core of this approach is a departure from the traditional encoding used to monitor the indirect-domain frequencies as a function of time parameters. Instead spins are allowed to impart their indirect-domain evolution effects along an ancillary, inhomogeneous frequency distribution lying under the experimentalist’s control, so as to originate site-specific patterns of spin coherences/magnetizations within the sample’s volume. At a subsequent acquisition stage, these ancillary inhomogeneities are once again invoked in order to periodically unravel the information encoded by the spin patterns as a function of a direct-domain acquisition time. Following a suitable processing, involving, in general, only one numerical FT, the resulting data can then provide the desired multidimensional correlation. It should be noted that by contrast to alternatives that had been previously proposed for collecting specific 2D NMR spectra based on “walk in time domain” concepts related to echo-planar imaging, the ultrafast experiment just summarized is general and makes no special demand on the kind of correlations $I(\Omega_1, \Omega_2)$ that are to be established.

It follows from this brief summary that a key component in the implementation of single-scan nD spectroscopy lies in the encoding of the indirect-domain NMR interactions to be measured along ancillary, frequency-broadened domains. Out of the potential options available to achieve such goal there is one that stands out in generality, and which involves encoding the indirect-domain spin evolutions to be measured along a spatial axis. Such pattern, in turn, can be created using standard modern NMR hardware by the application of magnetic field gradients $G$ endowing spins at different positions with inequivalent resonance frequencies, acting in conjunction with frequency-selective radiofrequency (rf) pulses that manipulate the spins. In view of the novelty and flexibility of the ensuing spatial encoding proposal, we have chosen its in-depth description as the goal of the present article.

II. SPATIAL ENCODING AND THE COLLECTION OF 2D NMR SPECTRA WITHIN A SINGLE SCAN

The main aim of spatial encoding is to translate the indirect-domain evolution characterizing a 2D NMR acquisition from its traditional temporal dependence into a spatial dependence—for instance, along a longitudinal $z$ sample direction. In other words, instead of having a particular chemical site of shift $\Omega_1$ imparting a uniform phase $\phi(t_1) = \Omega_1 t_1$ to spin coherences throughout the sample, and then having $t_1$ incremented throughout a series of independent experiments, we seek to impart an analogous encoding but along a spatial axis:

$$\phi(z) = C(\Omega_1(z - z_0)),$$

with $C$ and $z_0$ two parameters under the experimentalist’s control. Moreover, we seek to impart this pattern over the complete sample length $L$, utilizing pulse sequences that can be concluded within a single scan. Equation (4) amounts to creating a “winding” of the spin coherences [Fig. 1(b)]; a pattern analogous to the one that would arise if a magnetic field gradient $G = \partial B_Z / \partial z$ would have been applied along the $z$ direction for a given time $\tau$, but which instead of being defined by a known winding pitch $\gamma G \tau$ that is uniform for all sites in the sample, is now given by a site-dependent topology. In fact, we seek to have this pattern dictated by an unknown interaction $\Omega_1$, which is the observable that we are attempting to measure. The rationale for creating such pattern is that its creation opens in turn the possibility of reading out the full 2D $I(\Omega_1, \Omega_2)$ correlation spectrum within a single scan.

![FIG. 1. (Color online) (a) Traditional approach to measure a NMR spectrum based on monitoring the spins’ $\Omega_1$ frequencies evolving as a function of a $t_1$ time parameter. (b) Spatial encoding approach discussed in this work whereby the same $\Omega_1$ interactions are exploited to impart an a priori unknown pattern of the coherences along a sample $z$ direction—equivalent to creating a winding of the magnetization. In either case the resulting evolution needs to be Fourier analyzed to extract the spectral information sought; in (a) this is done numerically while in (b) this is done analogically as depicted in Fig. 2.](Image 125x625 to 485x742)
scan. Indeed, when used to replace the traditional indirect-domain evolution period of a 2D NMR experiment, the winding generated by the spatial encoding procedure in Fig. 1(b) will be preserved throughout the mixing process and will consequently become the starting state of the \( t_2 \) acquisition. Because of the collective nature of the NMR detection process, this pattern will lead to no observable macroscopic signal when considering the sample as a whole. If, however, detection is implemented while subjecting the spins to an acquisition gradient \( G_a \), the spiral of magnetizations represented by Eq. (4) will be unwound. And the moment when this \( \Omega_1 \)-dependent unwinding becomes complete will be readily observable, as only at its juncture will spin packets located at different positions throughout the sample cease their destructive interference and lead to a macroscopic overall signal (Fig. 2). This in turn implies that the spatial encoding of the spin interactions and its subsequent gradient-assisted readout provides a way to monitor the \( I(\Omega_1) \) spectrum of all the indirect domain \( \Omega_1 \) evolution frequencies that were present in the sample; not by Fourier analysis of an evolving \( t_1 \)-dependent coherence as in usual time-domain spectroscopy, but rather via the timings observed for the various site-specific echoes that will be created by interfering spins located throughout the sample.

To further visualize how a gradient-driven acquisition acting on spatially encoded patterns can generate an indirect-domain NMR spectrum, consider an initial state given by a pattern \( M(z) = \sum_{\Omega_1} |I(\Omega_1)/L| \exp[ic\Omega_1(z-z_0)] \) that has somehow been imparted to every voxel \( z \) throughout a uniform sample of length \( L \), for every possible \( \Omega_1 \) site. The application of an additional common acquisition phase \( \phi_G(t) = \gamma_d |G_a(t')| dt' = \gamma_c G_a t = k z \), like the one arising from a constant field gradient, will then yield a signal

\[
f(k) \approx \sum_{\Omega_1} |I(\Omega_1)/L| \int_L \exp[iC\Omega_1(z-z_0)] \exp(ikz) dz \\
= \sum_{\Omega_1} I(\Omega_1) \exp[-ic\Omega_1 z_0] \delta[C\Omega_1 + k].
\]

Apart from the presence of a potential \( \exp[-ic\Omega_1 z_0] \) first-order phase distortion and for the need of a \( \nu_1 \leftrightarrow -k/C \) re-definition of the frequency axis from wavenumber units, this signal is entirely equivalent to the standard \( I(\nu_1) = \sum_{\Omega_1} |I(\Omega_1)/\delta(\Omega_1 - \nu_1) \) spectrum that could be expected to arise from the Jeener–Ernst scheme along the indirect domain. Further analogies and distinctions between conventional and spatially encoded indirect-domain line shapes are discussed in Sec. IV for a variety of cases.

Having translated in such manner the readout portion of indirect-domain NMR into a gradient-driven process opens up an opportunity for extracting the full information available in a 2D NMR spectrum within a single scan. One of the main features that brings about this possibility is the fact that, unlike a conventional time-domain readout which needs to proceed over a relatively long period of time in order to properly characterize the spin evolution frequencies, the gradient-driven readout of the indirect-domain frequencies represented by Eq. (5) can be concluded very quickly. How short the time \( T_{a_{max}} \) over which the \( G_a \) readout gradient needs to be applied is going to be, follows from the fact that the product of these quantities—\( k_{max} = \gamma_c G_a T_{a_{max}} \)—needs to equate the maximum spectral window \( SW_1 \) to be explored, scaled by the spatiotemporal \( C \) coefficient. As further derived below this coefficient is usually given by the ratio between the maximum \( T_{a_{max}} \) time used to impart the spatial encoding and the sample length \( L \). An optimized acquisition will therefore require \( k_{max} = SW_1 T_{a_{max}} \), which in turn predicts a readout time \( T_{a_{max}} = SW_1 C G_a / \gamma_c G_a L \). As typical NMR acquisition parameters can be set to make the latter ratio \( 0.01 \) (for instance, in high resolution liquids \({}^1H\) NMR one would have \( SW_1 = 2.5 \text{ kHz}, \gamma_c = 4.257 \text{ G/cm}, G_a = 30 \text{ G/cm}, \) and \( L = 2 \text{ cm} \)), \( T_{a_{max}} \)’s duration will generally be in the hundreds of microseconds; much shorter than the typical \( T_2 \) decay. The second important feature that allows one to complete the 2D acquisition within a single scan is the fact that such \( G_a \)-driven readout is a process that can be done and undone numerous times over the course of the data acquisition. Indeed, as this process takes a short time and is driven by a gradient amplifier, its effects can be echoed simply by reversing the currents generating the gradient following a time \( T_{a_{max}} \). This in turn enables the repetitive monitoring of the \( f(k/\nu_1) \) indirect-domain spectrum as a function of an acquisition time \( t_2 \), as schematized by the oscillating-gradient approach depicted in Fig. 3(a). The result of this oscillation is a mixed...
frequency/time-domain $S(k/v_1,t_2)$ interferogram, from which the 2D NMR spectrum being sought can be retrieved by 1D Fourier analysis along $t_2$. This process may require a data rearrangement [Fig. 3(b)], and different alternatives to it have actually been devised.21–23 Yet overall the principles just summarized offer the most general approach to concluding a 2D NMR experiment within a single scan, and hence on them we focus throughout the rest of this discussion.

III. STRATEGIES CAPABLE OF IMPARTING A SPECTROSCOPIC SPATIAL ENCODING

The preceding section evidences the central role played by spatial encoding toward the acquisition of single-scan 2D NMR spectra. Indeed it showed that by translating the conventional indirect-domain $t_1$ incrementation into a spatial kind of pattern, the possibility arises to read out the spectral information using an oscillating acquisition gradient and thereby to complete the 2D acquisition within a single scan. An appealing feature of the approach just summarized is its retention of the main central features of 2D NMR, including a comparable scope of generality in terms of the correlations that it can establish. Even from a practical standpoint several commonalities with conventional 2D NMR will remain, particularly in what concerns all the preparation and mixing processes. On the other hand it is also clear that the evolution and the detection stages will be substantially altered. Particularly significant will be the new demands imposed by the experiment on the indirect-domain evolution, which needs to morph from what is normally a free precession onto some kind of dependence on position $z$. As mentioned, a natural way of imposing such $z\rightarrow t_1$ connection is with the aid of a magnetic field gradient $\partial B_0/\partial z = G_z$, endowing different positions within the sample with different resonance frequencies. In combination with such encoding gradient one can then design frequency-selective rf pulse sequences that—either by sequential excitation, inversion, or storage of the spin coherences—address particular positions (voxels) at predetermined times. Important to remember upon designing such combined $G_z/rf$ manipulations for spectroscopic studies is the demand to buildup solely linear $\Omega z$-dependent phases, as this constitutes the only sort of dependence that can be subsequently refocused by the $G_z$ acquisition gradient. Another important criterion is to maximize the internal $\Omega z$ contribution to the overall evolution, as it will be this spectroscopic information that will eventually be sought; this, in turn, implies maximizing the value of the $C$ coefficient for a given encoding time $t_1^{\text{max}}$. This section surveys a number of different sequences that have been proposed to achieve this new kind of spin manipulation, focusing on both their physical basis as well as their mathematical description.

A. Discrete spatial encoding of the NMR interactions

Conventional 2D NMR monitors the spins’ evolution along the indirect-domain via $N_1$ independent experiments characterized by individual delay increments $\{n \cdot \Delta t_1\}_{n=0}^{N_1}$. This discretized time-domain encoding scheme can be translated in a one-to-one fashion into spatial terms by subdividing the sample’s length $L$ into $N_1$ discrete voxels, each of them endowed with an indirect evolution time $n \cdot \Delta t_1$. One possible way to implement such approach within a single scan is illustrated in Fig. 4.15 This sequence incorporates a train of “soft” frequency-shifted rf pulses, acting in synchrony with a rectangular $\pm G_z$ gradient oscillation. As each of these pulses is selective it will only affect a limited band- width $\Delta f$, or a $\Delta z = \Delta f / \gamma_z G_z$ voxel size when factoring in the $G_z$-derived spatial broadening effects. Moreover, as each of these pulses is generated with its own individual $O_z$ frequency offset, it can be used to affect “its” voxel in a time- and phase-specific manner. Finally, there is the $+/-$ gradient oscillation, which implies that all these specific spatial manipulations can be carried out repeatedly while averaging to zero the gradient’s long-term encoding effects. As a result of these various features a number of relationships between spatial position and evolution time can be achieved, including
the imprint of a spatial pattern where spins have accrued phases that stem mostly from the internal frequencies to be measured.

To derive the physical characteristics of such a pattern, we begin by noting that the relation between the centers \( \{ z_n \}_{n=1}^{N_1} \) of the \( N_1 \) voxels, affected by each of these discrete pulses and the offsets \( \{ O_n \}_{n=1}^{N_1} \), used to center the corresponding rf irradiation pulse train, will be given by

\[
\Omega_1 + \gamma_e G_e z_n = O_n. \tag{6}
\]

As usual \( \Omega_1 \) is the internal parameter we are attempting to measure, and all frequencies are defined with respect to some rotating-frame reference value. One can then impart on each of these voxels a linear spatial encoding by incrementing the separation between rf pulses within the train by a constant delay \( \Delta t_1 \), while at the same time incrementing their respective frequency offsets according to \( O_n = (n-N_1/2) \Delta O \). To further analyze the effects that such pulse train will have on the evolution of the spins it becomes necessary to define the actual kind of nutation imparted by the rf pulses. For instance, the rf train could be used to trigger (or to conclude) the spins’ evolution, in which case they would lead to so-called real-time NMR experiments. Or it could be tuned to impart \( \pi \) inversions that echo the spins’ net \( t_1 \) evolution, leading to “constant-time” experiments. Both concepts parallel similar approaches in conventional 2D NMR, yet differ of course by the spatial nature that they now adopt. In order to evaluate the spins’ behavior in these two classes of experiments and obtain explicit expressions for the phases that spins will accrue in each case as a function of position, we shall begin by using an approximation whereby voxels are considered as fixed magnetization elements that get excited or refocused as soon as they feel the effects of the corresponding rf pulses. Under this assumption, the phases evolved by voxels as a function of time will be

\[
\phi_{RT}(t, z_n) = z_0 + n \cdot \Delta z
\]

\[
= \begin{cases} 
0, & 0 \leq t \leq n \cdot \Delta t_1 \\
\int_0^t [\Omega_1 + \gamma_e G_e(t') z_n] \, dt', & n \cdot \Delta t_1 \leq t,
\end{cases}
\]

(7a)

for the real-time excitation case, and

\[
\phi_{CT}(t, z_n) = z_0 + n \cdot \Delta z = \begin{cases} 
\int_0^t [\Omega_1 + \gamma_e G_e(t') z_n] \, dt', & 0 \leq t \leq n \cdot \Delta t_1 \\
- \phi_{CT}(n \Delta t_1, z_n) + \int_{n \Delta t_1}^t [\Omega_1 + \gamma_e G_e(t') z_n] \, dt', & n \cdot \Delta t_1 \leq t,
\end{cases}
\]

(7b)

for the constant-time one. Taking into account that the \( +G_e \leftrightarrow -G_e \) oscillations executed throughout each cycle cancel away the net gradient effect (Fig. 4), one can substitute \( t = N_1 \cdot \Delta t_1 = t_1^{\text{max}} \) and derive overall indirect evolution phases for each experiment as

\[
\phi_{RT}(t_1^{\text{max}}, z_n) = (N_1 - n) \Omega_1 \Delta t_1 = C_{RT}(n - N_1) \Omega_1 \Delta z, \tag{8a}
\]

\[
\phi_{CT}(t_1^{\text{max}}, z_n) = (N_1 - 2n) \Omega_1 \Delta t_1 = C_{CT}(n - N_1/2) \Omega_1 \Delta z. \tag{8b}
\]

As desired both experiments yield evolution phases that are proportional to \( n \Delta z \sim z_n \), with spatiotemporal encoding coefficients \( C_{RT} = \Delta t_1/\Delta z = t_1^{\text{max}}/L \), \( C_{CT} = 2t_1^{\text{max}}/L \). The fact that the \( C \) coefficient in the constant-time experiment doubles its real-time counterpart for equal sample lengths and total encoding times means that the former will lead to shift-driven spatial windings that are twice as “tight” as the latter. This
doubling of the efficiency parallels similar effects observed in conventional 2D NMR acquisitions. Other considerations affecting real-versus constant-time acquisitions, including relaxation and line shape effects, are analyzed below.

### B. Continuous spatial encoding of the NMR interactions

The spatial encoding just described maps a finite number of $N_1$ evolution times, onto corresponding voxels. Such implementation follows from the scheme of conventional time-domain NMR, and thereby presents a number of appealing features. Yet it also involves a number of potential drawbacks, including stringent demands on the NMR hardware as well as the potential appearance of “ghost peaks”, echoes appearing at folded-over positions as a result of the encoding discreteness (cf. Sec. IV). Unlike the parametric incrementation used in conventional 2D NMR, however, spatial encoding employs a continuous physical variable for monitoring the indirect domain. One could therefore envision an approach whereby both $\Delta z$ and $\Delta t_1$ are made infinitesimally small while their ratio $C$ is maintained as in the discrete case, leading in essence to a continuous realization of the linear $\Omega_1$ encoding. Achieving such goal calls into play the use of rf pulses involving a continuous sweep of their frequency offsets. To analyze the effects that such frequency-chirped rf could have on the spins in the presence of a gradient $G_z$, a resonance criterion similar to that used for the discrete case [Eq. (6)] will be assumed. According to this premise, spins at a specific position $z$ will be affected whenever the rf time-dependent offset $O(t)$ matches the voxel’s resonance frequency,

$$\Omega_1 + \gamma G_z, z = O(t).$$  \hspace{1cm} (9)

In order to make the evolution arising from $\Omega_1$ linearly dependent on position as required by the spatial encoding scheme, this relation suggests sweeping the rf offset $O$ linearly in time; i.e., make $O(t) = O_0 + R t$, where $O_0$ is an initial frequency value and $R$ is the offset sweeping rate. Triggering, storing, or echoing the $\Omega_1$ effects in this fashion should thus bring about the desired $\Omega_1 \propto z$ form of encoding. At the same time, however, executing this continuous $t \propto z$ manipulation while in the presence of a constant $\gamma G_z$ frequency inhomogeneity will bring about an additional phase contribution that is quadratic in space. It is necessary to somehow cancel out this gradient-driven source of $z^2$ encoding, in order to read out the spatially encoded spectroscopic information. Since the advent of the ultrafast 2D NMR proposal a number of methodologies have been put forward, that manage to refocus away these undesired quadratic components while retaining in their phases a linear spatial encoding of the internal interactions. These sequences share in common the presence of at least two sets of spin manipulations, involving continuously chirped rf pulses acting under the effect of different $G_z, G_z'$ gradients. Yet they differ in the overall aims of their encoding, with alternative approaches being proposed to achieve continuous real-time or continuous constant-time spatial encodings of the spin interactions. Moreover in the real-time encoding case, variants have also been demonstrated depending on whether one is interested in achieving an amplitude-modulated or a phase-modulated indirect-domain encoding. While common physical frameworks and common terminologies can be used to understand the various resulting approaches, their resulting features will naturally be different. We devote the remainder of this paragraph to deriving the modus operandi of these various continuous schemes, leaving for the next section an analysis of the spectral features arising in each case.

#### 1. Real-time amplitude-modulated spatial encoding

A common class of 2D NMR spectroscopy pulse sequences begins and concludes their $t_1$ periods with a pair of $\pi/2$ pulses, thereby monitoring their indirect evolution frequencies via amplitude modulations introduced onto longitudinal spin states.\(^2\)\(^{24}\) Whereas traditional 2D NMR does so by varying the indirect-domain period separating the $\pi/2$ pulses by multiples of $\Delta t_1$, ultrafast techniques employ a scheme whereby amplitude modulation is imparted as a function of a continuous position variable $z$. In order to achieve such kind of spatial encoding it suffices to replace the conventional hard $\pi/2$ pulses, by a pair of chirped $\pi/2$ pulses acting during the course of a $+G_z/-G_z$ bipolar gradient waveform.\(^2\)\(^3\) To visualize how this scheme manages to impair the desired evolution, it is instructive to divide the overall process into two periods, associated with the effects of the first and second $\pi/2$ chirps, respectively (Fig. 5). The first of these periods entails the spins’ excitation, and we shall assumed for it that [following Eq. (9)] spins at a particular position $z$ will not evolve until the offset of the chirped pulse reaches their resonance frequency, and will evolve free from all rf effects thereafter. (Numerical simulations evidence that though simple, this model entails a very good description of the actual events.\(^2\)\(^6\)) Mathematically, the phase accrued by spins at a specific position $z$ during the course of this excitation process will then be given by

![Image](image_url)
\[
\phi_{\text{exc}}(t,z) = \begin{cases} 
0, & 0 \leq t \leq t_a(z) \\
\varphi_d(t_a(z)) + \int_{t_a(z)}^{t} \left[ \Omega_1 + \gamma_z G_z \right] dt', & t_a(z) \leq t
\end{cases}
\]

Here \(t_a(z)\) represents the time elapsed between the beginning of the chirped pulse and the time when the rf offset reaches the \(z\)-dependent resonance frequency, and \(\varphi_d\) is the total phase accumulated by the frequency-swept rf until the rotation of these spins. As illustrated on the lower cartoons of Fig. 5, this phase acts as the reference with respect to which spins at different positions will precess. Therefore, although its absolute value is not defined, its relative position ends up being passed onto the phase of the various spin coherences and hence is important. Using the various definitions given earlier these two parameters can be calculated as

\[
\varphi_d(t) = \int_{0}^{t} O(t') dt' = O_i \cdot t + \frac{1}{2} R \cdot t^2
\]

and

\[
t_a(z) = \frac{\Omega_1 + \gamma_z G_z - O_i}{R}.
\]

As reminder \(R\) is here the rate of the rf’s offset sweep, which we assume to extend over a symmetric range \(O_i = -\gamma_z G_z L/2 \rightarrow O_i = +\gamma_z G_z L/2\) and last a time \(t_{\text{max}} = \frac{L}{2} / R\). (Sweeps not centered around zero can always be considered symmetric with a redefined \(\Omega_1\) off-resonance value, while periods such as gradient switching times that are not executed under the presence of a rf will for simplicity be ignored.) With these various definitions, the explicit expression for the total phase accumulated by the spins as a function of position at the conclusion of the excitation becomes

\[
\phi_{\text{exc}}(t, z) = \left( \Omega_1 + \gamma_z G_z \right) \cdot t_{\text{max}}^2 - \frac{(\Omega_1 + \gamma_z G_z - O_i)^2}{2R}.
\]

Notice here the foretold presence of a quadratic \(z^2\) term that will prevent the refocusing of the sample magnetization by the action of a \(G_z\) gradient. Notice as well that the application of this single gradient prevents one to discriminate between the \(\Omega_1\) contribution arising from the shift to be measured, and a \(\gamma_z G_z\) imaging-type contribution that is not actually being sought.

The second sequence element involved takes care of these two complications. It entails a rf-driven storage of the spins’ coherences, and its treatment mirrors closely a reversal of what has occurred during the excitation period. Indeed during its course spins can be assumed to have evolved freely until the instant when the rf offset matches their resonance frequencies, at which point a component of the spin coherence becomes stored along the longitudinal axis of the Bloch sphere and all evolution ceases. To derive the final pattern created by this second chirp one should keep in mind that (i) spins begin this storage stage after having accumulated an initial \(\phi_{\text{exc}}(t_{\text{max}}^2, z)\) evolution phase, and (ii) that the encoding gradient over this second storage period will now be reversed from \(+G_z\) to \(-G_z\). Hence the phase function characterizing the amplitude modulation will become

\[
\phi_{\text{store}}(t, z) = \phi_{\text{exc}}(t_{\text{max}}^2, z) + (\Omega_1 - \gamma_z G_z) \cdot t.
\]

Attention should also be paid to the fact that in a storage process like the one under consideration, it is only the component perpendicular to the rf field that gets preserved in a longitudinal state (Fig. 5, bottom right). Thus, denoting \(t \rightarrow O = (\Omega_1 - \gamma_z G_z - O_i)/R\) as the time at which the storage rf offset \(O\) reaches the on-resonance condition of those spins at a position \(z\), one can express the state of the spins preserved along the longitudinal axis as

\[
\rho(z) \approx \cos \left[ \phi_{\text{store}}(t \rightarrow O, z) - \varphi_d(t \rightarrow O) \right].
\]

Substituting Eqs. (11)–(14) into Eq. (15) and carrying out some mathematical simplifications yield

\[
\rho(z) \approx \cos \left[ \Omega_1 \cdot t_{\text{max}}^2 \left( \frac{1 - z}{L/2} \right) \right]
\]

\[
\approx \cos \left[ \frac{t_{\text{max}}^2}{L} \cdot \Omega_1 \cdot \left( \frac{z - L/2}{L/2} \right) \right].
\]

As desired, this spin state reflects an encoding that is linearly dependent with respect to both \(\Omega_1\) and the \(z\) coordinate. The resulting spatiotemporal coefficient \(C = dt/dz = t_{\text{max}}^2 / L\) is analogous to that obtained in the discrete excitation case [Eq. (8a)], and so is the first-order \(C \Omega_1 (L/2)\) phase distortion affecting the peaks. In terms of gradient demands, however, this continuous encoding strategy turns out to be much less taxing than its discrete counterpart. Overall, the “trick” involved in achieving such spatial encoding without utilizing numerous gradient oscillations lies in relying on two rf-driven manipulations, identical to one another but executed under a reversal of their respective encoding gradient. This made the first slice to be excited also the last one to be stored (and vice versa), thereby canceling out the quadratic gradient effects while allowing the chemical shift evolution to keep on adding up coherently.

2. Variants of the real-time amplitude-modulated encoding

The case just treated presents one out of several strategies that can be devised for achieving a continuous spatial encoding. And although providing an efficient encoding option the pattern represented by Eq. (16) also presents a number of drawbacks, including the aforementioned presence of first-order phase distortions, that may complicate the retrieval of phased, purely-absorptive line shapes (as discussed...
in further detail below). The present paragraph summarizes a couple of strategies, capable of dealing with this kind of problem.

A naive solution to “symmetrize” to excitation profile would suggest reversing the sense of sweep for the first and second chirped pulses just described. A careful analysis of such scheme, however, reveals that not only will then quadratic \( z^2 \) term not vanish—it will become the dominant feature generated by the two rf chirps. It is possible to deal with this problem, preserving the chemical shift information while eliminating the undesired quadratic phase terms, by introducing an additional hard \( \pi \) pulse refocusing in between the two reversed chirps (Fig. 6). Under this hitherto unpublished sequence, the spin evolution until the action of the storage pulse will be given by a modified version of Eq. (14), which now becomes

\[
\phi_{\text{store}}(t,z) = -\phi_{\text{exc}}(t,\pi/2),z + (\Omega_1 - \gamma_c G_z z) \cdot t.
\]

Because of the reversed sense of the storage pulse sweep, also the time at which the storage rf offset reaches its on-resonance condition will be changed, becoming \( t(z) = (\Omega_1 - \gamma_c G_z z + O_1)/(-R) \). With these provisions at hand, a similar analysis to the one reported above reveals the storage of a final longitudinal state

\[
\rho_{f}(z) \sim \cos \left( \frac{\max L}{L} \left( \Omega_1 + \frac{\gamma_c G_z L}{2} \right) z \right).
\]

This entails once again a linear spatiotemporal pattern of \( \Omega_1 \), characterized by a \( C = \gamma_c G_z / L \) encoding efficiency. Two main differences \emph{vis-a-vis} the pattern in Eq. (16), however, involve (i) the fact that the spatial encoding has no \( z_0 \) displacement component and is thereby symmetric as desired, and (ii) the presence of an artificial \( \gamma_c G_z L/2 \) offset effect which, being defined entirely by externally controlled parameters, can be fully compensated without compromising the information being sought (for instance, by introducing an additional purging gradient, which is a common procedure to shift the indirect-domain axis in ultrafast 2D NMR implementations).

A central characteristic shared by the two amplitude-modulated approaches that have so far been described is their actual encoding of \emph{two} opposing spatial patterns. Indeed the cosine form that modulates the final longitudinal \( \rho_{f}(z) \) state, arising in either one of these cases, comprises two superimposed coherence transfer pathways entailing frequencies \( \pm \Omega_1 \). In traditional 2D NMR, signals from these two phasors can be distinguished in a variety of ways.\textsuperscript{2} In the spatial encoding case, the analog FT imposed by the \( k \) wavenumber [Eq. (5)] implies that, in general, only one of these windings will be decoded by the acquisition gradient (particularly if one is looking for an unambiguous positioning of the peak). Neither one of the continuous encoding schemes that were hitherto described took into consideration, the presence of these two complex conjugate winding patterns, and the ensuing nonquadrature detection of only one of them. It turns out, however, that this feature can be exploited for improving the efficiency of the spatial encoding, while simultaneously alleviating the undesirable effects arising from the asymmetric \( z_0 = L/2 \) choice. This forms the underlying basis of a “symmetric sweep” spatial encoding approach to ultrafast 2D NMR,\textsuperscript{27} whose principles are characterized in Fig. 7. To visualize this approach consider a situation where the upper and lower halves of the sample are treated independently throughout both the excitation and storage periods; assume as well that on each of these portions spatial encodings of opposing signs are applied, and that this is so done that the \( z = 0 \) coordinate corresponds with a null \( t_1 \) evolution time. Under such conditions the longitudinal state created for any given site at the conclusion of these processes will become

\[
\rho_{f}(z) \sim \begin{cases} 
\cos[C \cdot \Omega_1 \cdot z], & 0 \leq z \leq \frac{L}{2} \\
\cos[-C \cdot \Omega_1 \cdot z], & -\frac{L}{2} \leq z \leq 0.
\end{cases}
\]

At first glance this discontinuous phase expression appears problematic, given ultrafast NMR’s demand for a continuous, linear functionality for creating its constructive interference phenomena. On the other hand the cosine modulations bring about the presence of two opposing spatial windings within each half of the sample, counteracting the discontinuity in Eq. (19) and enabling the exploitation of the full sample length \( L \) toward the formation of uniform \( G_z \)-driven echoes. In terms of implementing such scheme, one can influence the two sample halves simultaneously by modulating the rf with pairs of symmetrically swept offset. These in turn should be chosen so as to excite the sample from the edges toward its center during the first stage of the spatial encoding and to store spin coherences from the center toward the...
edges in the second stage. These manipulations can be physically generated by a vector sum of two rf pulses, each of which addresses only half a sample with time-dependent offsets. During the initial excitation stage these offsets will be given by the superposition of

\[ O_s(t) = \begin{cases} O_1 + R \cdot t \\ -O_1 - R \cdot t, \end{cases} \tag{20} \]

where \( R = \gamma_G C_s (L/2) / t_i^{2(\pi)} \) and \( O_i = -\gamma_G C_s L / 2 \). As a result, the time at which the rf excites the spins as a function of their \( z \) position becomes a two-valued function,

\[ t_s(z) = \begin{cases} \frac{\Omega_1 + \gamma_G C_s z - O_i}{R}, & -\frac{L}{2} \leq z \leq 0 \\ \frac{\Omega_1 + \gamma_G C_s z + O_i}{-R}, & 0 \leq z \leq \frac{L}{2}. \end{cases} \tag{21} \]

In the second, storage portion of the experiment, the manipulating rf is once again built by superimposing two central frequencies varying now as a function of time as

\[ O(t) = \begin{cases} R \cdot t \\ -R \cdot t. \end{cases} \tag{22} \]

Given that this manipulation is imparted under the presence of a gradient \(-G_e\), the space-dependent storage of the spin coherences will then happen at times,

\[ t_s(z) = \begin{cases} \frac{\Omega_1 - \gamma_G C_s z}{R}, & -\frac{L}{2} \leq z \leq 0 \\ \frac{\Omega_1 - \gamma_G C_s z}{-R}, & 0 \leq z \leq \frac{L}{2}. \end{cases} \tag{23} \]

On the basis of these relations and following an analysis similar to the one carried out previously [Eqs. (11)–(14)], one can derive the spatiotemporal profile that will characterize the spin coherence,

\[ \rho(z) \sim \cos[C \cdot \Omega_1 \cdot z], \quad -\frac{L}{2} \leq z \leq \frac{L}{2}, \tag{24} \]

This is a uniform winding structure similar to that encountered in the single-sweep case [Eq. (16)]—except for two important features. The first one is an improved efficiency in the spatiotemporal encoding, resulting from the addressing of two sample positions at any given time. Indeed such addressing implies that the total evolution imparted by the excitation and storage chirped rf pulses over a time \( t_i^{\text{max}} \) needed to encode an \( L/2 \) spatial dimension instead of a length \( L \). The spatiotemporal coefficient consequently becomes \( C = dt / dz = (t_i^{\text{max}} / (L/2)) = 2t_i^{\text{max}} / L \), improving by a factor of 2 what was afforded by Eqs. (8a), (16), or (18). Second, the longitudinal state that is stored by these center-symmetric sweeps becomes free from the first-order \( \Omega_1 L / 2 \) phase distortion, and is also symmetrically affected vis-à-vis \( z_0 = 0 \) by potential relaxation losses. The benefits of these two features for retrieving undistorted spectral line shapes will be further analyzed in Sec. IV.

**3. Real-time phase-modulated encoding**

The previous paragraphs presented options capable of delivering a continuous, amplitude-modulated spatial encoding. Certain methodologies such as COSY or \( J \)-spectroscopy, however, are designed so as to keep the spin coherences in a transverse evolving state throughout the \( t_1 \) mixing, and \( t_2 \) periods.\(^{21,24}\) A storage procedure is therefore not suitable for this kind of sequences, which demand a phase rather than an amplitude-modulation of the spins. On considering the utilization of chirped pulses toward a spatial phase modulation, it is worth recalling that—as discussed within the context of Eq. (13)—a single chirp exciting spins throughout the sample will impose a linear phase modulation of the chemical shift with position, but also generates a quadratic phase term that needs to be canceled for a proper encoding. Whereas this term was handled before by a second storage process, phase modulation requires that the undesired term be eliminated while preserving the transverse nature of the spin coherence. One way of achieving this consists of applying a \( \pi \) rather than a \( \pi/2 \) sweep, during the course of the second gradient period.\(^{28,29}\) This second rf sweep will then “flip” spins at different times for different \( z \) positions throughout the sample, imposing a quadratic phase term of its own that can be used to counteract the quadratic effects of the first rf sweep, while preserving a net chemical shift or \( J \)-coupling evolution. There is ample freedom for choosing the \( G_e^{(\pi)} \) gradient strength that should accompany this \( \pi \)-driven inversion, as a suitable \( R^{(\pi)} \) rf sweep rate can, in

**FIG. 8.** (Color) Idem as in Fig. 5 but for a pulse scheme capable of imparting a phase-modulated spatial encoding of the spins interactions, based on the use of a progressive \( \pi/2 \) excitation followed by a progressive \( \pi \) refocusing. The timings and gradient strengths of these two sweeps need to be set so as to eliminate the gradient-derived quadratic dephasing terms [cf. Eqs. (25)–(27)]—the result is a continuous encoding incorporating a real-time \( \Omega_1 \) evolution.

**FIG. 9.** (Color) Idem as in Fig. 8 but for a pulse scheme that imparts a constant-instantaneous real-time \( \Omega_1 \) evolution. The sequence uses identical chirped rf pulses whose amplitudes are set to impart \( \pi \) nutations by making them approximately two to three times stronger than their swept \( \pi/2 \) counterparts; as a result of this reliance on \( \pi \) pulses, the no-evolution voxel is once again \( z_0 = 0 \).
general, always be found to compensate the initial, excitation-imposed quadratic dephasing. For practical purposes we focus here on the strategy illustrated in Fig. 8, whereby the second gradient is chosen opposite to the one used in the initial spin excitation: \( G_e^{(\pi)} = -G_e \). Then, following guidelines similar to those previously expounded and keeping in mind that a \( \pi \)-flip reverses a magnetization’s relative phase with respect to the instantaneous \( \varphi_{rf} \) the overall phase modulation imparted on the spins as a function of their position and of time can be written as

\[
\phi_{\text{PM}}(t, z) = \begin{cases} 
\phi_{\text{exc}}(t^{(\pi/2)}, z) + (\Omega_1 - \gamma_e G_e z) t, & 0 \leq t \leq t_{\text{e}}(z) \\
\phi_{\text{rf}}(t_{\text{e}}(z)) + [\phi_{\text{rf}}(t_{\text{e}}(z)) - \phi_{\text{PM}}(t_{\text{e}}(z), z)] + (\Omega_1 - \gamma_e G_e z)(t - t_{\text{e}}(z)) & t_{\text{e}}(z) \leq t
\end{cases}
\]

These transmitter phases, impact times, etc., are as in Eqs. (11)–(14), with the provision that we now allowed for different sweeping rates \( R^{(\pi/2)} \), \( R^{(\pi)} \) for each corresponding pulse. Substituting these definitions into Eq. (25) and evaluating this expression at the conclusion of the \( \pi \) chirp pulse (i.e., for \( t = t^{(\pi/2)} \)) provides the overall evolution phase as a function of position:

\[
\phi_{\text{PM}}(t^{(\pi)}, z) = \frac{\left(\Omega_1 + \gamma_e G_e z - O_1 \right)^2}{2R^{(\pi/2)}} - \frac{\left(\Omega_1 - \gamma_e G_e z - O_1 \right)^2}{R^{(\pi)}} - (\Omega_1 + \gamma_e G_e z) \cdot t^{(\pi/2)} + (\Omega_1 - \gamma_e G_e z) \cdot t^{(\pi)}.
\]

(26)

Here \( \phi_{\text{exc}}(t^{(\pi/2)}, z) \) is the phase accumulated following the initial excitation period [Eq. (13)], and \( \phi_{\text{rf}}(t_{\text{e}}(z)) \) denotes the instantaneous rotating-frame phase subtended by the rf field at a time \( t_{\text{e}}(z) \) when spin coherence undergo their \( \pi \) flip. These transmitter phases, impact times, etc., are as in Eqs. (11)–(14), with the provision that we now allowed for different sweeping rates \( R^{(\pi/2)} \), \( R^{(\pi)} \) for each corresponding pulse. Substituting these definitions into Eq. (25) and evaluating this expression at the conclusion of the \( \pi \) chirp pulse (i.e., for \( t = t^{(\pi/2)} \)) provides the overall evolution phase as a function of position:

\[
\phi_{\text{PM}}(t^{(\pi)}, z) = \frac{\left(\Omega_1 + \gamma_e G_e z - O_1 \right)^2}{2R^{(\pi/2)}} - \frac{\left(\Omega_1 - \gamma_e G_e z - O_1 \right)^2}{R^{(\pi)}} - (\Omega_1 + \gamma_e G_e z) \cdot t^{(\pi/2)} + (\Omega_1 - \gamma_e G_e z) \cdot t^{(\pi)}.
\]

(26)

\( \phi_{\text{PM}} \) possesses quadratic terms still depending on both the excitation and the refocusing characteristics, yet given the extra freedom now available from the use of two different pulses such undesirable terms can be eliminated by imposing \( R^{(\pi)} = 2R^{(\pi/2)} \). When considering a fixed sample length and the choice \( G_e^{(\pi/2)} = -C^{(\pi)} = G_e \), that we have made, this relation between the two sweeping rates is equivalent to setting

\[
l^{(\pi)} = \frac{1}{2}l^{(\pi/2)},
\]

(27)

under this constraint Eq. (26) simplifies into

\[
\phi_{\text{PM}}(t^{(\pi)}, z) = \frac{4}{3} \frac{t_{\text{e}}^{(\pi)}}{L} \left( z - \frac{L}{4} \right) \Omega_1 - \gamma_e G_e l^{(\pi)} z.
\]

(28)

This expression, defining the phase of a purely transverse coherence on which one can apply nonstoring mixing protocols, possesses the desired kind of spatial encoding with \( C = (4/3)t_{\text{e}}^{\text{max}} / L \); this is slightly larger than the efficiency obtained in the original \( \pi/2-\pi/2 \) scheme [Eq. (16)]. It also displays a first-order phase distorting term, as well as a \( \gamma_e G_e l^{(\pi)} \) offset which being \textit{a priori} known can be accounted for by a suitable ancillary pulsed gradient.

4. Constant-time phase-modulated encoding

A final class of continuous spatial encoding scheme deserving to be addressed concerns the use of constant-time (CT) sequences. A main characteristic of these protocols is the fixed duration of their indirect-domain evolution periods, regardless of the varying extents \( t_1 \) over which the interactions are allowed to exercise their encoding. As already mentioned, this can be achieved by allowing spins to evolve as transverse coherences throughout the entire indirect domain, while controlling their effective degree of \( t_1 \) encoding by means of an incremented refocusing pulse. When considering the extension of analogous schemes to continuous spatially encoded versions, it is clearly necessary to depart from the progressive excitation afforded by chirped \( \pi/2 \) pulses and replace them with an encoding that (just as in conventional 2D CT NMR schemes) commences with a hard \( \pi/2 \) pulse. To impart the desired \( \Omega_1 t \) evolution while remaining free from undesired quadratic components one can then invoke pairs of frequency-swept refocusing \( \pi \) pulses, acting in conjunction with gradients of different magnitudes over suitably chosen times. For concreteness we consider here the scheme shown in Fig. 9, employing two identical \( \pi \)-chirps acting in combination with a \( \pm G_e \) bipolar gradient. Following the arguments and notations introduced in the preceding paragraphs; these two identical rf rotations will impart spatially dependent evolution phases

\[
\phi_{\text{exc}}^*(t, z) = \begin{cases} 
(\Omega_1 + \gamma_e G_e z) t, & 0 \leq t \leq t_{\text{e}}(z) \\
\phi_{\text{rf}}[t_{\text{e}}(z)] + [\phi_{\text{rf}}[t_{\text{e}}(z)] - \phi_{\text{exc}}^*(t_{\text{e}}(z), z)] + (\Omega_1 + \gamma_e G_e z)(t - t_{\text{e}}(z)) & t_{\text{e}}(z) \leq t
\end{cases}
\]

(29)
when considering the effects of the first pulse, and a subsequent
\[
\phi_{\text{enc}}^{-1}(t, z) = \begin{cases} 
\phi_{\text{enc}}^{-1}(t, z) + (\Omega_1 - \gamma_G z) t, & 0 \leq t \leq t_\ell(z) \\
\varphi_{\text{ft}}(t_\ell(z)) + [\varphi_{\text{ft}}(t_\ell(z)) - \phi_{\text{enc}}^{-1}(t_\ell(z), z)] + (\Omega_1 - \gamma_G z)(t - t_\ell(z)), & t_\ell(z) \leq t \leq t^\pi.
\end{cases}
\] (30)

4. SPATIALLY ENCODED VERSUS CONVENTIONAL 2D NMR: LINE SHAPE CONSIDERATIONS

The spatial encoding patterns summarized above end up defining many of the spectral characteristics observed in ultrafast 2D NMR experiments. As alluded to earlier the line shapes observed in this kind of experiments share several commonalities with their conventional 2D NMR analogues; certain principles used to manipulate the frequency-domain peak shapes in conventional time-domain NMR also find parallels in spatially encoded experiments. To better appreciate the differences and similarities between the line shapes arising from the two methods it is helpful to recall that, in general, peaks arising in 1D FT NMR will be centered at the modulation frequency $\Omega_1$ and show a point spread function given by the support characteristics of the time-domain signal. For instance, when dealing with the usual exponential decay effects arising from $T_2$ relaxation, a Lorentzian line shape made up by a sum of absorptive and dispersive components
\[
I(\nu) \propto FT\{[\Omega_1(t - t_0)] \cdot \exp(-t/T_2)\} = \exp(i\Omega_1 t_0) [A(\nu - \Omega_1) + i \cdot D(\nu - \Omega_1)],
\] (32)
will follow.\textsuperscript{2} Improved resolution in 1D NMR is then sought by generating a purely-absorptive description of the spectrum; i.e., by placing the narrower $A(\nu - \Omega_1)$ line shape into the real component of the complex $I(\nu)$ function, and making this the sole display. If necessary, a first-order phase correction accounting for potential $t_0 \neq 0$ effects is also used in this process. In 2D NMR spectroscopy this problem gets aggravated by the fact that a full $(t_1, t_2)$ modulation by two decaying exponentials yields a 2D point spread function,\textsuperscript{2,24,31}
\[
I(v_1, v_2) \propto [A(v_1 - \Omega_1) + i \cdot D(v_1 - \Omega_1)] \cdot [A(v_2 - \Omega_2) + i \cdot D(v_2 - \Omega_2)].
\] (33)

No amount of phasing will then succeed in getting rid of the dispersive components in either the real or imaginary channels of $I(v_1, v_2)$, and a mix of $A(v_1 - \Omega_1)A(v_2 - \Omega_2)$, $D(v_1 - \Omega_1)D(v_2 - \Omega_2)$, $A(v_1 - \Omega_1)D(v_2 - \Omega_2)$, and $D(v_1 - \Omega_1)A(v_2 - \Omega_2)$ functions will characterize each spectral peak.\textsuperscript{2,23} Sequence-specific alternatives, however, can be devised for “symmetrizing” the support underlying the $t_1$ or $t_2$ evolutions, thereby eliminating (after proper phasing) the corresponding dispersive components. An example of this is given by amplitude-modulated sequences, where the indirect evolution arises as $\cos(\Omega_1 t_1)$ rather than as an exp($i\Omega_1 t_1$) phase modulation. A real FT can then be used to retrieve purely-absorptive $A(v_1 - \Omega_1)A(v_2 - \Omega_2)$ 2D line shapes even if at the expense of quadrature $v_1$ detection. Alternatively, the acquisition of two phase-shifted scans enables one to achieve a similar goal, while introducing a sign discrimination along $v_1$.\textsuperscript{24,32}

Many of these considerations keep on holding for ultrafast 2D NMR, despite its reliance on a single FT. To appreciate why we revert to Eq. (5) and expand it by noting that since a numerical FT is involved along $t_2$ (preceded if wished by weighting and zero filling and followed by phase correction), the spectral point spread function for any given peak in these experiments will be given by
\[
S(k/v_1, v_2) = f(k/v_1) \cdot [A(v_2 - \Omega_2) + i \cdot D(v_2 - \Omega_2)].
\] (34)
The single-site direct-domain line shape on this expression’s right-hand side will be properly characterized over a spectral bandwidth $SW_z = (2T_{\text{sa}})^{-1}$ or $(T_{\text{sa}})^{-1}$ [depending on whether uses a regular or an interfered FT along $t_2$ (Refs. 15 and 22)] and it will discern peaks with a resolution given by $t_{\text{max}}^{\text{enc}} = 2N_2 T_{\text{sa}}$. The $f(k/v_1)$ echo shapes on the other hand will be given by
\[
f(k/v_1) = \frac{I(\Omega_1, \Omega_2)}{L} \times \int_{-L/2}^{L/2} dz [\text{Enc}(C\Omega_1(z - z_0)\text{Decay}(z, T_2))e^{ikz},
\] (35)
where we have extended Eq. (5) by making Enc any of the amplitude- or phase-modulated expressions derived in the preceding section for the different encoding modes, and De-
cussed in Sec. III A, at whose conclusion an example, the discrete real-time spatial encoding case dis-
tual modulation will then be imposed arises from considering
pential encoding patterns of this type allow one to retrieve echo
sidered by including a storage-based mixing process.

The fact that sequences associated
line distortions arising in these peaks for each individual
This FT will lead to peaks centered at \( k = +C\Omega_1 \) and

where the sum stresses the discrete nature of the encoding

\begin{equation}
    f(k/v) = \left[ \frac{I(\Omega_1)}{N_1} \right] \sum_{n=1}^{N_1} \exp \left[ C(i\Omega_1 - \frac{1}{T_2})(z_n - z_{N_1}) \right] \exp(ikz_n),
\end{equation}

where the sum stresses the discrete nature of the encoding

\begin{equation}
    f(k/v) = \left[ \frac{I(\Omega_1)}{L} \right] \int_{-L/2}^{L/2} dz \cos \left[ C\Omega_1 \left( z - \frac{L}{2} \right) \right] \\
    \times \exp \left[ -C \left( z - \frac{L}{2} / T_2 \right) \right] \exp(ikz).
\end{equation}

This FT will lead to peaks centered at \( k = +C\Omega_1 \) and

\begin{equation}
    f(+k/v) = \left[ \frac{I(\Omega_1)}{L} \right] \int_{-L}^{L} dz \exp(i(C\Omega_1 + k)z) \\
    \times \exp[-C |z/T_2],
\end{equation}

\begin{equation}
    f(-k/v) = \left[ \frac{I(\Omega_1)}{L} \right] \int_{-L}^{0} dz \exp(i(C\Omega_1 + k)z) \\
    \times \exp[-C |z/T_2].
\end{equation}

Given the limits of integration appearing in these equations, it is clear that the resulting line shapes are complex conjugate of each other. Summing these two echoes together will thereby free the signals from their dispersive indirect-domain components; this is equivalent to having imposed a \( z=0 \) symmetry to the spatial decay profile caused by \( T_2 \) relaxation. A summary and demonstration of how this procedure adds the two spatially encoded pathways to retrieve purely-absorptive 2D line shapes is shown in Fig. 10. It may be worth adding that the same procedure can be applied in the discrete case if the phase-modulated spatial encoding treated above is modified to an amplitude-modulated form; for instance, by including a storage-based mixing process.

Alternatives to this postprocessing method that are also capable to deliver purely-absorptive line shapes arise if em-

This kind of folding phenomena will be absent when relying on any of the continuous spatial encoding modes discussed above, thereby simplifying considerably the spectral appearance. For instance, when considering the real-time amplitude modulated scheme arising from the use of two chirped \( \pi/2 \) pulses (Sec. III B 1), the observable indirect-domin peak shape will be described by

This FT will lead to peaks centered at \( k = +C\Omega_1 \) and

\begin{equation}
    f(k/v) = \left[ \frac{I(\Omega_1)}{L} \right] \int_{-L/2}^{L/2} dz \cos \left[ C\Omega_1 \left( z - \frac{L}{2} \right) \right] \\
    \times \exp \left[ -C \left( z - \frac{L}{2} / T_2 \right) \right] \exp(ikz).
\end{equation}

This FT will lead to peaks centered at \( k = +C\Omega_1 \) and

\begin{equation}
    f(+k/v) = \left[ \frac{I(\Omega_1)}{L} \right] \int_{-L}^{L} dz \exp(i(C\Omega_1 + k)z) \\
    \times \exp[-C |z/T_2],
\end{equation}

\begin{equation}
    f(-k/v) = \left[ \frac{I(\Omega_1)}{L} \right] \int_{-L}^{0} dz \exp(i(C\Omega_1 + k)z) \\
    \times \exp[-C |z/T_2].
\end{equation}

Given the limits of integration appearing in these equations, it is clear that the resulting line shapes are complex conjugate of each other. Summing these two echoes together will thereby free the signals from their dispersive indirect-domain components; this is equivalent to having imposed a \( z=0 \) symmetry to the spatial decay profile caused by \( T_2 \) relaxation. A summary and demonstration of how this procedure adds the two spatially encoded pathways to retrieve purely-absorptive 2D line shapes is shown in Fig. 10. It may be worth adding that the same procedure can be applied in the discrete case if the phase-modulated spatial encoding treated above is modified to an amplitude-modulated form; for instance, by including a storage-based mixing process.

Alternatives to this postprocessing method that are also capable to deliver purely-absorptive line shapes arise if em-

This kind of folding phenomena will be absent when relying on any of the continuous spatial encoding modes
its inherent nature will affect opposite ends of the sample in an equal manner. The second of the symmetric methodologies proposed based on excitation and storage rf pulses with opposite sweep directions (Fig. 6) achieves a similar symmetrization effect, as in it the sample edges that are excited first and last will also be stored first and last, respectively. This allocates to each voxel the same net duration of transverse evolution; the spatial dependence of the $T_2$-driven decay thus becomes uniform throughout $L$, no dispersive components will characterize the $f(k/\nu_1)$ functions, and the retrieval of purely-absorptive 2D line shapes becomes possible.

Also in parallel to what is observed in conventional 2D NMR, purely-absorptive 2D line shapes will not be amenable from the real-time phase-modulated kind of experiments introduced in Sec. III B 3. Indeed the encoding depicted in Fig. 8 makes the transverse evolution time experienced by spins at different voxels spatially dependent, thereby imparting a $T_2$-decay profile that is, in general, asymmetric with respect to $z=0$. This, in combination with the phase modulation, leads to dispersive components in the $f(k/\nu_1)$ peaks and to mixed phase line shapes for the full 2D function. One possible way to deal with this problem could involve relying on echoes or pseudoechoes along $t_2$; when this is not possible one might consider adopting a similar strategy as suggested above and rely on the use of magnetization storages and on discriminated $+k$ and $-k$ signal acquisitions—at the expense, however, of the main advantages afforded by phase over amplitude schemes. On the other hand and by contrast to these real-time sequence problems, the constant-time phase-modulation procedure introduced in Sec. III B 4 provides real, purely-absorptive line shapes in a fully built-in manner. The first of these features results from the fact that given the $\pi$-pulses involved, the no-encoding point corresponds to the $z_0=0$ position. While the lack of dispersive components in $f(k/\nu_1)$ reflects the fact that since all spins end up spending the same indirect-evolution times in their transverse states, their spatial encoding profile is uniform. Thereby the $f(k/\nu_1)$ point spread function approaches a purely-absorptive sinc function, even if its amplitude may be attenuated by the effects of a relaxation which has now acted on all voxels over a time $t_1^{\text{max}}$.

V. CONCLUSIONS AND PERSPECTIVES

The spatial encoding process lies at the heart of the single-scan 2D NMR experiment in liquids. Performing this encoding requires in turn a new kind of spin manipulation, based on the combined application of frequency-modulated rf pulses and of oscillating field gradients. In spite of constituting a relatively novel procedure, many different implementations of spatial encoding have already been put forward; as with most NMR manipulations of this kind, it is likely that further pulse schemes for spatial encoding will continue to arise in the future. In the meantime the present manuscript attempted to review the main features associated with the spatially encoding alternatives that have hitherto been proposed. Main objectives of this survey included an explanation of the physics underlying the implementation of such experiments, their mathematical description, as well as
analyzing the kind of spectral line shapes that can be expected from each method. Toward this end a formalism based on the coherent effects imparted by gradients and swept rf pulses was put forward and used to derive the amplitude and phase modulations imparted on the spins by the different schemes. Then, in combination with traditional $T_2$ decay function arguments, the point spread functions associated with such schemes could be derived. There are certainly additional features that are specific to each spatial encoding mode and which, while not hereby reviewed with the depth that they deserve, may also condition the final appearance of the 2D spectra. These include analyses of the rf and gradient-strength requirements posed by the sequences, considerations of how diffusion and motional effects affect the final line shapes, and a more detailed description of how all these factors combine to define the relative sensitivity merits of each sequence. It would also be interesting to compare these liquid-phase encoding features, against solid-state NMR alternatives such as orientational encoding. The treatment of the 2D spectra. These include analyses of the rf and gradient-strength requirements posed by the sequences, considerations of how diffusion and motional effects affect the final line shapes, and a more detailed description of how all these factors combine to define the relative sensitivity merits of each sequence. It would also be interesting to compare these liquid-phase encoding features, against solid-state NMR alternatives such as orientational encoding. The treatment of these various practical and important aspects, which in many instances are driven by noncoherent processes and sometimes require heuristic approaches, are deferred to a future expanded discussion.

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