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Achieving high resolution and optimizing sensitivity in spatial frequency encoding NMR spectroscopy: from theory to practice†

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A detailed analysis of NMR spectra acquired based on spatial frequency encoding is presented. A theoretical model to simulate gradient encoded pulses is developed in order to describe the spatial properties of the NMR signals that are locally created throughout the sample. The key features that affect the efficiency of the slice selection process during excitation as well as refocusing pulses are investigated on a model ABX spin system, both theoretically and experimentally. It is shown that the sensitivity and resolution of the pure shift and *J*-edited experiments based on a spatial frequency encoding can be optimized to a point where high-resolution techniques based on a spatial frequency encoding approach show optimal performance compared to other methods.

Introduction

Considerable progress has been achieved over the last few years in mastering the key events and actors involved in chemical reactions. These advances were made possible – notably – by the major breakthroughs made in observing and describing them, leading to a deeper understanding of ever-more complex molecular structures, dynamics and reactivities. On this account, nuclear magnetic resonance (NMR) spectroscopy has been proved to be a tool of choice for probing molecular systems over very wide spatial and time ranges.^{1,2} Of particular importance is its suitability for providing computational chemistry methods with several physical measurements of the system under study. These observables are used either as parameters of the computer simulation, or as structural/dynamic constraints to select the most realistic computational results. In most of the cases outlined above, a key milestone to combine efficiently NMR with theoretical chemistry is of course the ability to record high-resolution NMR spectra for the analyzed sample. It has long been shown that proton nuclei can constitute informative, abundant and sensitive probes of

the local structure and dynamics in very diverse systems. Unfortunately, in several cases that are of prime interest nowadays, the resolution of ¹H spectra is often dramatically limited by the high number of homonuclear couplings, and the low chemical shift dispersion.

Several methods have been introduced in the last decade to overcome the resolution issues raised in ¹H NMR. Some of the most outstanding achievements reported in this field are based on the concept of Spatial Frequency Encoding (SFE).^{3–5} The idea is to perform at the same time a selective excitation, decoupling, or recoupling of different spin nuclei in different regions of the NMR sample. The last few years have witnessed a generation of original experiments that have paved the way to spectacular achievements. Among these, it was first shown that broadband homonuclear decoupling sequences based on spatial frequency encoding can be performed efficiently, even during a direct acquisition scheme, to produce δ -resolved (also known as a pure shift) spectra in which each proton signal appears as a singlet.^{5–8} Considerable developments have also been focused on the measurement of scalar or residual dipolar couplings, with the implementation of *J*-edited experiments whose unique analytical content is closely linked to the properties of the spatial frequency encoding process.^{9–16}

However, to date there has been no theoretical study that allows for describing the local spin dynamics occurring throughout the NMR sample during these pulse sequences, although the number of novel experiments implementing SFE techniques is continuously increasing. In this paper, we report the simulations of SFE experiments with two aims. On the one hand, simulations are the only way to describe the spatial

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variations of the encoded NMR signal that contributes to the properties of the overall spectrum. We remind that these variations cannot be probed experimentally since the receiver coil detects the overall change in the magnetic flux created by the sample, which makes the development of such a theoretical tool a key step toward understanding and optimizing pulse sequences relying on a spatial frequency encoding. On the other hand, the ability to simulate NMR spectra is nowadays often required in modern chemistry to fit them with the considered theoretical model and extract accurately structural or dynamic insights of the studied molecule.

In this context, we present a theoretical formalism to describe the gradient encoded irradiation schemes used to generate a spatial frequency encoding. We address the complex relationship between the spatial and spectral resolution, and its influence on the properties of the slice selection process that is operated throughout the sample. Finally, the resulting simulation tool is exploited to describe the optimization of resolution and sensitivity in two popular correlation spectra implementing routine gradient encoded spin evolutions (pure shift and J -edited).

Theory

In this section, a formalism to predict the main features of the NMR spectrum resulting from a spatially encoded excitation is presented. We remind that the concept of spatial frequency encoding is based on the simultaneous use of a selective shaped pulse and a magnetic field gradient. To address this question, the signal arising from a single encoded pulse experiment applied to 3-hydroxy-4,4,4-trichlorobutyric β -lactone **1** has been simulated. Beyond its structural simplicity, this compound

constitutes a good model spin system because proton spins H^A and H^B show close chemical shifts and are thus strongly coupled ($\Delta\nu_{AB}/J_{AB} \sim 4.4$ at 14.1 T), which allows for addressing some selectivity issues of spectroscopic methods based on a spatial frequency encoding (the single encoded pulse sequence and the structure of **1** are available in the ESI†). Attention must be paid to the definition of the spin Hamiltonian that governs the evolution of the spin system over different steps of this pulse sequence. First, the action of a pulsed field gradient is modeled by dividing the NMR sample into thin virtual slices (Fig. 1a) within which molecules undergo a position dependent – static – magnetic field $B(z)$:

$$B(z) = B_0 + G_z \cdot z \quad (1)$$

G_z is the strength of the pulsed field gradient taken here along the z axis, and z is the molecular position in the sample along this axis. This approach has been shown to provide a convenient way of simulating the action of pulsed field gradients, for instance for coherence selection purposes.¹⁷ Then, during a low power rf field applied together with the pulsed magnetic field gradient, the evolution of the local density operator $\rho(z,t)$ describing the state of the spin system is calculated by solving in each slice the corresponding Liouville–Von Neumann equation:

$$\frac{d}{dt}\rho(z,t) = -i[H(z,t), \rho(z,t)] \quad (2)$$

where $H(z,t)$ is the time- and position-dependent Hamiltonian that accounts for all the spin interactions – mainly the chemical shift, the scalar couplings, and the interaction with the radio-frequency (rf) field – acting on $\rho(z,t)$. Unless otherwise specified, in the following we neglect relaxation effects.

Fig. 1 (a) Schematic representation of the spatial frequency encoding performed during the single gradient encoded shaped pulse experiment. The receiver coil is represented in orange in order to materialize the total height of the sample that is detected. The z gradient coils are pictured in red. Yellow arrows symbolize the magnetic field gradient. (b) Proton spins H^A , H^B and H^X from the model compound 3-hydroxy-4,4,4-trichlorobutyric β -lactone **1** have different resonance frequencies and are thus excited in different cross-sections due to the spatial frequency encoding, giving rise to localized spin evolutions. In (c) the overall free induction decay detected by the receiver coil is the sum of these local NMR signals.

In the case of an amplitude modulated pulse, the corresponding Hamiltonian $H_{\text{rf}}(z,t)$, expressed in the reference frame rotating at the transmitter frequency reads:

$$H_{\text{rf}}(z,t) = \Delta\omega(z)I_z + \omega_1(t)\{I_x \cos \phi + I_y \sin \phi\} \quad (3)$$

where $\omega_1(t) = -\gamma_I B_1^{\text{rf}}(t)$ and ϕ are the angular nutation frequency and the phase of the resonant component of the oscillating field $B_1^{\text{rf}}(t)$, respectively. γ_I is the gyromagnetic ratio of the considered nuclear spin. The offset $\Delta\omega(z)$ is calculated between the Larmor frequency $\omega_0(z)$ of the spin I in the considered slice, and the transmitter frequency ω_{rf} :

$$\Delta\omega(z) = \omega_0(z) - \omega_{\text{rf}} = \gamma_I \{B_0 + G_z z\} \{1 - \sigma_I\} - \omega_{\text{rf}} \quad (4)$$

where σ_I is the chemical shielding of the spin I . After the gradient encoded excitation pulse (*i.e.* during acquisition), the main magnetic field (B_0) is again considered to be homogeneous, and the spin Hamiltonian incorporates only the ^1H chemical shift and scalar coupling interactions (Fig. 1b). The overall signal that is detected by the receiver coil is then the sum of the free induction decays originating from each virtual slice throughout the sample (Fig. 1c). In the following, all simulations and experiments were performed at 14.1 T ($\nu_{\text{H}} = 600.13$ MHz)

Simulation of spatial frequency encoded pulses

Excitation step

The action of a gradient encoded E-Burp2 pulse of duration 60 ms on the model system 1 has been simulated for each position z in the virtual sample. The E-Burp2 shape has been shown to provide experimental encoded spectra of good quality on a wide range of samples.^{9,10,13,18,19} The magnetization corresponding to a single coherence term from each proton has been evaluated in each virtual slice at the end of this excitation step. Fig. 2 shows the spatial distribution of these magnetizations for H^X and H^A . For H^X , a region is easily distinguishable, along which the transverse magnetization is spin-locked by the rf field (Fig. 2a). We note that this region is encoded around the position z_X that satisfies the relationship:

$$\nu^X = \frac{\gamma_{\text{H}}}{2\pi} \cdot \{B_0 + G_z \cdot z_X\} \{1 - \sigma_X\} \quad (5)$$

where ν^X is the Larmor frequency of H^X in the absence of a pulsed field gradient. Outside of this region, the amplitude of the magnetization is significantly weaker, and no phase coherence is remaining. Similarly, H^A magnetization is encoded in a restricted region around ν^A , but a distortion of the phase distribution is observed (Fig. 2b). This can be explained by the fact that in the region encoded between ν^A and ν^B , the selective pulse of bandwidth ~ 82 Hz²⁰ irradiates simultaneously H^A and H^B whose chemical shift difference is only ~ 75 Hz, which suggests that a coherence transfer is performed between these coupled spin nuclei. We note that this spatial selection issue is absent for H^X whose chemical shift difference with H^A and H^B is higher than 765 Hz.

Fig. 2 The spatial variation of the magnetization calculated at the end of a gradient encoded excitation pulse is represented with 2 viewing angles inside the NMR tube, for $A_\alpha B_\alpha X_+$ (a) and $A_+ B_\alpha X_\alpha$ (b) coherences. An E-Burp2 pulse of duration 60 ms was used for the selective irradiation. The virtual sample was divided into 401 slices of equal height around each region of interest, to which a position dependent magnetic field value was assigned.

We have further calculated, for each virtual slice building up the simulated sample, the free induction decay originating from the excitation of all the single quantum coherences that make up the spin-state of H^X on the one hand, and H^A on the other hand. The sub-spectra calculated at different positions along the encoding gradient axis are shown together with their amplitude profile in Fig. 3. Similar to what could be observed for a single coherence, the simulation highlights a restricted ensemble of virtual slices within which pure absorption spectra can be obtained. Again, outside this region, strong distortions affect the phase of the resulting spectra whose amplitude decreases rapidly, as it is underlined by the evolution of the amplitude profiles. This allows for addressing accurately one fundamental issue in gradient frequency encoding techniques, about defining the slice selection that is operated by the gradient and the selective pulse. This concept materializes here into the shape of the amplitude profiles, which demarcate the restricted volumes contributing quantitatively to the overall signal.

The sum of the sub-spectra generated in each virtual slice, and notably those within this quantitative volume, yields the signal that is detected for H^X , in agreement with what has

Fig. 3 The amplitude profile evaluated on the first point of the local NMR signal calculated for H^X (a) and H^A (b) is displayed in cylindrical coordinates within the NMR tube (left). The 1H spectra simulated for H^X and H^A in a selection of virtual slices distributed along the z axis (right). For each sub-spectrum, the difference between the offset of the local rf field and the resonance frequency of H^X (respectively H^A) is indicated. The SFE gradient was modeled by dividing each region of interest into 401 virtual slices.

already been described experimentally (Fig. 3a).^{6,9} It should be noted that the spatial distribution of the phase of the sub-spectra around ν^X is antisymmetric, whereas for H^A an asymmetry is observed, as it is illustrated for instance for sub-spectra calculated for opposite offsets of +48 Hz and -48 Hz with respect to ν^X and ν^A respectively (Fig. 3a and b). The amplitude profile around ν^A also reflects this asymmetry that is due to the spatial selection issue described above. We observe that the sum of the sub-spectra encoded in this cross-section where a spatial resolution issue is raised leads to a signal with a distorted lineshape for H^A . Furthermore, the spatial distribution of sub-spectra is displayed as a pseudo-2D map in Fig. 4.

The standard 1H spectrum is displayed along the NMR tube to illustrate the spatial frequency encoding. It is apparent that each signal from H^A , H^B , or H^X is selectively encoded in a restricted cross-section of the sample, which is the cornerstone

Fig. 4 The amplitude profile of the NMR signal represented in cylindrical coordinates (left). The spatial distribution of virtual proton spectra is reported in a pseudo-2D plot where the vertical axis refers to the position z in the NMR sample (right). Blue and red contours are positive and negative, respectively. The SFE gradient was modeled by dividing the sample into 1201 virtual slices.

of spatial frequency encoding. We remark however that for the E-Burp2 pulse of 60 ms implemented here, a spatial resolution issue is observed. Indeed, the two cross-sections within which H^A and H^B are encoded overlap with each other as it can be monitored on the amplitude profile depicted within the NMR tube. This result illustrates the difficulty to trigger selective evolutions involving protons with close resonance frequencies such as H^A and H^B .

We can now calculate the NMR spectrum that is yielded by the whole NMR sample. It is the sum of the local spectra calculated over all the virtual slices constituting the sample (Fig. 5a – this spectrum is also shown above the pseudo-2D map in Fig. 4a).

The general lineshape of this encoded 1H spectrum reflects the effect of the overlap of the encoded cross-sections. In

Fig. 5 The simulated (a and b) and experimental (c and d) spatial frequency encoded and standard (broadband) 1H spectra of **1**. An E-Burp2 pulse of duration 60 ms was used for the gradient-encoded excitation step. For **1**, scalar couplings are $J^{A-B} = -17.06$ Hz, $J^{A-X} = 3.72$ Hz, and $J^{B-X} = 5.75$ Hz. The SFE gradient was modeled by dividing the sample into 201 virtual slices.

particular, for H^A and H^B the intensities of the transitions in their respective multiplet do not follow the expected “roof” effect that is classically observed for ABX spin systems (Fig. 5b), since the opposite effect is observed. This simulation is coherent with its experimental counterpart recorded on **1**. The unusual lineshape that is observed for the experimental encoded spectrum is also clearly reproduced by the simulation (Fig. 5c), while the standard simulated ^1H spectrum mimics faithfully the second order effect observed experimentally between H^A and H^B (Fig. 5d). We note that the analysis of the symmetry of the amplitude profiles such as those presented in Fig. 3 and 4 constitutes a useful tool for predicting potential distortions of the overall NMR spectrum, although the knowledge of the phase distribution would of course also be required to analyse lineshapes in detail. In the following, the above-presented theoretical tools will be used to describe the evolution of resolution and sensitivity in the general frame of a gradient encoded pulse sequence, and discuss strategies that can be implemented to optimize them.

Optimizing spatial resolution and sensitivity

The spatial resolution issue raised above can be solved in different ways. A first approach is to increase the duration of the shaped pulse to act locally on spin coherences with better selectivity. We have studied the influence of the spectral selectivity of the excitation pulse on the slice selection process by simulating a series of gradient encoded E-Burp2 pulses whose duration varied between 20 ms and 120 ms. The spectral width that is encoded by the magnetic field gradient along the sample corresponds in general to the spectrum of the analyzed compound. It has rather been set here to 3772.6 Hz, which is equivalent to 6.3 ppm at 14.1 T, in order to provide a more realistic estimation of typical levels of sensitivity that can be reached using SFE techniques. The resulting amplitude profiles are shown in Fig. 6. As expected, we observe that the longer the

duration, the lower the height of the cross-sections within which each proton spin is encoded, as it can be monitored easily for H^X . For 20 ms, the pulse is not selective enough, and is thus exciting both H^A and H^B in the same region, which produces a signal with abnormally higher amplitude (Fig. 6a). Conversely, the quality of the slice selection process is higher at 120 ms, and spatially resolved cross-sections are obtained for each proton spin (Fig. 6f).

Attention must be paid to the fact that the improvement of the spatial resolution is accompanied by a loss of sensitivity, as suggested by the evolution of the height and the radius of the amplitude profiles. To quantify this loss, we have calculated for H^X the ratio between the integration of the signal resulting from an excitation with (I_{encoded}^X) and without encoding (I_{ref}^X). This sensitivity ratio ranges from 6.7 to 0.7% for pulse durations varying from 20 to 120 ms (Fig. 7 – corresponding

Fig. 7 The simulated (blue circles) and experimental (red circles) sensitivity ratios determined on H^X for a gradient encoded E-Burp2 pulse are plotted as functions of the pulse duration. The model curve corresponding to the ideal behaviour proposed by Pell and Keeler is plotted as a blue dashed line. The adapted model curve incorporating transverse relaxation is plotted as a red dashed line.

Fig. 6 The amplitude profiles calculated at the end of a gradient encoded excitation step on the model spin system **1**, for an E-Burp2 pulse of duration (a) 20 ms, (b) 40 ms, (c) 60 ms, (d) 80 ms, (e) 100 ms and (f) 120 ms. The SFE gradient was modeled by dividing the sample into 1201 virtual slices.

simulated spectra are shown in the ESI†). These values are coherent with the evolution of the sensitivity that is predicted by Pell and Keeler for a gradient encoding process.²¹ Sensitivity ratios were also measured experimentally on **1**, using an identical shaped pulse and an encoded spectral width. As expected, the experimental sensitivity curve slightly differs from simulation, due to the relaxation process occurring during the encoded pulse.^{22,23} The loss of sensitivity induced by relaxation for H^X is only 13% at 60 ms although H^X has a rather short T_2 (430 ms), which is known to be an unfavourable case (details about the modelling of the sensitivity curves are available in the ESI†).

We note that this ideal behaviour described by Pell and Keeler is not valid for H^A and H^B because the spatial selectivity issue described above induces slight deviations. We remark that the price to pay to achieve a spatially resolved slice selection in a sample containing coupled spins with close chemical shifts is a loss in sensitivity that can be significant, as it has already been observed experimentally. Another interesting feature that can be evaluated is the “height” of the slices that are selected in the NMR sample. For a routine detected sample height of 1.65 cm, with an encoded spectrum of width 3773 Hz (~ 6.3 ppm at 14.1 T) and a selective E-Burp2 pulse of duration 60 ms ($\Omega_B \sim 87$ Hz), this corresponds to physically encoded cross-sections of about 381 μm .

Different strategies have been described in the literature to overcome the sensitivity penalty imposed by the spatial frequency encoding. Among these, Zangger *et al.* have shown that fast-pulsing techniques can be implemented to increase the signal-to-noise ratio per unit time, by changing after each scan the offset of the encoded pulse in order to encode a different spatial region where magnetization is at thermal equilibrium.⁷ Another approach has also been introduced by Lokesh *et al.*, which is based on a polarization sharing technique to transfer each encoded slice polarization from protons that were not affected by the local selective pulse to selectively excited protons, leading to a faster data acquisition without long inter-scan delay.²⁴ Another solution consists in encoding the same proton site simultaneously in several slices located at different positions along the sample. In this spirit, Jeannerat and Cotte have recently introduced a non-equidistantly modulated Zangger–Sterk element that allows for selecting non-equidistant irradiation sites for the same proton, hence enhancing sensitivity by an order of magnitude without generating too many artifacts.²⁵ The latter concept has also been implemented successfully for performing ^{13}C broadband homonuclear decoupling in heteronuclear ^{13}C – ^1H correlation spectra.^{26,27}

Here we focus on the optimization of the selectivity of the encoded selective pulse itself, whose implementation in the frame of strategies presented above will need to be studied in further depth. From our results, it appears that a key step toward optimizing experiments based on a spatial frequency encoding is to find a compromise between the spatial resolution of the slice selection process, and the loss in sensitivity that is inherent to it. In the following, we study how this can be achieved by optimizing the properties of the refocusing pulses implemented in standard gradient encoded 2D experiments.

From excitation to refocusing pulse

In this section, the choice of the shaped pulse used to perform a gradient encoded irradiation is discussed. A wide variety of band-selective pulses is now available on modern spectrometers, whose amplitude and phase modulations have been optimized for specific purposes.^{28–32} In the field of SFE techniques, Burp (Band-selective Uniform-Response Pure-phase),³³ Gaussian and Snob (Selective excitation for Biochemical applications)³⁴ pulses have been frequently chosen for an implementation with a pulsed magnetic field gradient in order to yield gradient encoded excitation or refocusing of spin coherences. No comparison of their performances has been reported however to date. The spatial properties of Burp, Gaussian and Snob pulses have been studied for gradient encoded excitation and refocusing purposes. An excitation step was first simulated, starting from nuclear magnetization at equilibrium, with an E-Burp2 pulse of duration 60 ms on the one hand, and an E-Snob 270° pulse of 20 ms on the other hand. The duration of the E-Snob pulse was set so that both pulses have the same spectral bandwidth. Fig. 8a and b show the magnetization of the $A_2B_2X_4$ coherence of H^X at the end of the encoded excitation step, for E-Burp2 and E-Snob shapes, respectively (the complete simulation results including the Gaussian shape are available in the ESI†). Similar to the

Fig. 8 The spatial variation of the magnetization calculated at the end of gradient encoded (a) E-Burp2 90° and (b) E-Snob 270° for the $A_2B_2X_4$ coherence of H^X . The resulting calculated (c and d) and experimental (e and f) gradient encoded ^1H spectra of the model spin system **1**. The SFE gradient was modeled by dividing the sample into 401 virtual slices.

E-Burp2 pulse, the gradient encoded E-Snob pulse leads to the selective excitation of H^X in a cross-section located around ν^X . For the latter shape however, the phase of the magnetization is strongly modulated. Such a modulation is expected to lead to a partial cancellation of the overall signal. As a consequence of this phase modulation issue, the intensity of the simulated spectrum is significantly weaker for the E-Snob pulse than for E-Burp2 (Fig. 8c and d). This difference in sensitivity is also observed experimentally (Fig. 8e and f). The intensity of the experimental spectrum acquired with the E-Snob pulse is even weaker than expected in the simulation, which suggests that the rf field inhomogeneity has a more detrimental effect on this latter shape.

Such simulation-based study of the spatial properties of gradient encoded irradiations can be generalized to the optimization of all the parameters involved in the implementation of any encoded pulse.

In this spirit, the action of a gradient encoded refocusing step was simulated using Re-Burp and R-snob pulses (Fig. 9). The initial state of the spin system was defined as a transverse magnetization on H^X taken along the y axis. During these simulations, this magnetization is expected to undergo a π rotation around the x axis in the cross-section where H^X is encoded. The spatial properties of the gradient encoded refocusing pulses were found to be different from those of the excitation pulses based on the same family of amplitude and phase modulations. Indeed, a region where the resulting refocused magnetization is clearly spin-locked is observed for both shapes (Fig. 9a and b). Notably, the phase is kept constant in this restricted region for the R-snob encoded pulse. It is interesting to note that as expected from the spectral bandwidth of each refocusing pulse, the height of the encoded region where the phase coherence is achieved is approximately the same height for Re-Burp and R-snob shapes. We also note that the phase coherence within the encoded cross-section is better for the refocusing step than for the excitation step. This explains that gradient encoded refocusing pulses are sometimes implemented

after a hard $\pi/2$ pulse to perform an effective slice selective excitation. In this latter case however, further coherence selection may be required to remove unwanted signals created by the hard pulse.

This study of the spatial properties of selective pulses upon spatial frequency encoding was carried out on other popular selective pulses, and notably those implementing a Gaussian shape (the resulting phase distributions and amplitude profiles are shown in the ESI†). In particular, E-Snob pulses are found to be less suitable for performing a spatial frequency encoded excitation with satisfying phase coherence. By contrast, the Gaussian shape is rather robust regarding its implementation in a gradient encoded irradiation scheme, both for excitation (for a 270° angle) and refocusing purposes. For this latter shape however, it is known that artifacts may appear due to the profile edges of its spectral bandwidth when a high selectivity is required, as illustrated in the ESI† for protons H^A and H^B . These results are coherent with the experimental settings that are reported in the literature about the choice of the shapes implemented for gradient encoded irradiations. In the following, good spatial properties of refocusing pulses will be exploited to improve the quality of the spatial frequency encoding in 2D pulse sequences, and notably to optimize their resolution without sacrificing too much of sensitivity.

Slice selection processes in 2D experiments

The theoretical formalism presented above opens the way to a more general study of the different pulse sequences that are routinely implemented in the field of gradient encoded NMR to trigger selective spin echoes that are the core of the targeted resolution enhancements. This section is dedicated to the analysis of the evolution of the slice selection process over δ -resolved and J -edited experiments, which are built on the two most popular refocusing blocks.

δ -Resolved refocusing blocks

The basic δ -resolved (or pure shift) block is made of a gradient encoded soft π pulse followed by a hard π pulse in the middle of an evolution delay t_1 . These pulses allow for refocusing every homonuclear scalar or residual dipolar coupling involving each encoded proton, hence giving rise to a pure evolution of their chemical shifts during t_1 . This refocusing block that is also known as the Zangger–Sterk element has been implemented successfully in several correlation experiments, and notably in a direct acquisition scheme, to generate a pure shift ^1H spectrum along the spectral dimension of interest.³⁵ As a case study, the spatial resolution of the δ -resolved refocusing block has been addressed in the frame of a broadband ω_1 -decoupled experiment (Fig. 10a).⁶ In this sequence, a z gradient filter is used to obtain pure absorption spectra.¹⁸ The effect of this latter gradient has been simulated in the same manner as for the encoding gradient, by evaluating its contribution to the resulting position-dependent magnetic field in each virtual slice. The

Fig. 9 The spatial variation of the magnetization calculated at the end of gradient encoded (a) Re-Burp 180° and (b) R-snob 180° pulses, for the $A_2B_2X_4$ coherence of H^X . Pulse durations of 60 and 20 ms were used for Burp and Snob pulses respectively. The SFE gradient was modeled by dividing the sample into 401 virtual slices.

Fig. 10 (a) The broadband ω_1 -decoupled pulse sequence. On the proton channel, black and white ellipsoidal shapes correspond to $\pi/2$ and π shaped pulses respectively. On the pulsed field gradient channel, white rectangular bars refer to rectangular-shaped z field gradients, and open ellipsoidal shapes to sine-shaped z field gradients. The amplitude profiles calculated (b) after an E-Burp2 pulse of 60 ms (step 1), (c) after a δ -resolved block implemented with a Re-Burp pulse of 60 ms (for $t_1 = 0$ s – step 2), and (d) after a z -filter, using an E-Burp2 pulse of duration 60 ms (step 3). In (e), the same profile as in (c) calculated for a δ -resolved block implementing a Re-Burp pulse of duration 120 ms. The SFE gradient was modeled by dividing the sample into 1201 virtual slices.

evolution of the magnetization throughout the sample has first been evaluated at key moments in the pulse sequence. Fig. 10b–e show the evolution of the slice selection process during the δ -resolved pulse sequence (the spatial distribution of the magnetization corresponding to one single coherence from H^A is provided in the ESI†). It appears that each encoded pulse has an effect on the height of the slices selected throughout the pulse sequence. Notably, the refocusing block contributes to select narrower slices within the regions initially encoded by the excitation step (Fig. 10b and c). As a result, two distinct cross-sections can be observed at ν^A and ν^B , respectively, which suggests that the spatial resolution issue between H^A and H^B has been partially solved.

This enhanced spatial resolution suggests that it is possible to refine the slice selection process initially induced by the excitation step to achieve a more efficient homonuclear decoupling. This property is due to the better phase coherence achieved by the encoded refocusing pulses within each selected slice, as suggested in Fig. 9. We note that the z -filter also contributes to make these encoded cross-sections narrower (Fig. 10d). It should be highlighted that the overall shape of the encoded cross-sections during this pulse sequence is not cylindrical, and reflects the complexity of the action of the chosen shaped pulse on the phase and the amplitude of the localized NMR signal.

Moreover, the analysis of the slice selection process induced at the end of the δ -resolved block by using an encoded refocusing pulse of 120 ms shows that narrower slices are encoded due to the higher selectivity of this pulse (Fig. 10e). We observe however that the spatial resolution issue in the region around ν^A and ν^B is surprisingly still present, and that the amplitude in these cross-sections is weaker. This suggests that the duration, and thus the selectivity of the encoded pulses need to be adequately chosen in order to optimize both the spatial resolution and the sensitivity of the pulse sequence, especially in the challenging case of the homonuclear decoupling of strongly coupled proton spins, which can be easily monitored using this kind of simulation.

In light of these observations, a 2D ω_1 -homodecoupled spectrum was simulated on 1, and its experimental counterpart was recorded with the same experimental settings. We remind that most of the pure shift methods that have been developed to date have shown difficulties in decoupling H^A and H^B because they are strongly coupled. Burp pulses of duration 60 ms were implemented in order to optimize both the resolution and the sensitivity of the encoded refocusing block. The number of points in each time domain was set so as to allow for a reasonable calculation time on a single computer, and also for corresponding to the typical resolution that is routinely achieved in a ^1H - ^1H 2D correlation experiment, where the digital resolution in the indirect domain is in principle lower. As expected, the resulting spectra show only diagonal signals, with a multiplet structure in the direct domain, and a singlet structure in the – pure shift – indirect domain (Fig. 11). Overall, we observe that the simulated spectrum reproduces faithfully the experimental spectrum. In particular, it can be seen from the projections of these spectra that the proton sites H^A and H^B were properly decoupled, and that the only artifacts that are detectable result from classical truncation effects along the indirect domain.

In conclusion for this section, it is possible to monitor the evolution of the slice selection process that is performed throughout gradient encoded δ -resolved spin evolutions by using the theoretical formalism introduced in this paper, and to predict the quality of the resulting 2D spectrum so as to optimize key features of the sequence such as the selectivity of the encoded excitation and refocusing pulses.

From broadband homonuclear decoupling to 1D pure shift NMR spectra

The use of spatial frequency encoding techniques to perform broadband homonuclear decoupling on protons has first been considered as a promising way of rapidly and easily characterizing a sample from a 1D spectrum offering high resolution and, where possible, high sensitivity. Several methods have thus been developed in the past to record 1D pure shift ^1H spectra.³⁶ One of the first approaches to obtain such data, and actually one of the most robust and general, consists in performing the projection of the rows of a J -resolved spectrum that has previously been adequately tilted.³⁷ Similarly, it is straightforward to generate a pure shift spectrum by calculating

Fig. 11 Experimental (a) and calculated (b) 2D ω_1 -homodecoupled spectra of **1** obtained with Burp pulses of 60 ms, with 512 points in the indirect domain. The spectral width encoded by the encoding pulsed field gradient was 3773 Hz (6.29 ppm). For the simulated spectrum, only the virtual slices around positions encoded at ν^A , ν^B and ν^X were computed. It was checked that the resulting spectrum is similar to the one obtained by computing the whole virtual sample when a reduced swept width of 450 Hz (resp. 330 Hz) is considered around ν^A and ν^B (resp. ν^X). The resulting simulated spectrum was calculated in ~ 7 days.

the projection of the columns of a 2D broadband ω_1 -decoupled spectrum (Fig. 12). Ideally, the observed linewidth of the resulting spectra is only limited in the latter case by the number of points acquired in the indirect domain, and the line broadening arising from the projection step. Unfortunately, such approaches are time consuming because a multi-dimensional dataset needs to be recorded to reconstruct the desired 1D spectrum. The Zangger–Sterk element whose implementation

Fig. 12 (a) The standard ^1H spectrum recorded on **1**, and the pure shift spectra obtained from the projections of the columns of 2D homonuclear ω_1 -decoupled spectra recorded with (a) a Re-Burp pulse of 60 ms and (b) a R-snob pulse of 20 ms in the gradient encoded refocusing block, respectively. The projections were calculated from 2D maps recorded with 1024 points and zero filling up to 2048 points in the indirect domain. The relative intensities are indicated for each pure shift spectrum.

is discussed above is therefore at the root of a series of developments aimed at providing chemists with 1D pure shift NMR spectra of their sample within a reasonable experimental time. Among these, pseudo-2D experiments have first been introduced to shorten the acquisition time by recording data chunks whose duration is short enough to neglect the evolution of scalar couplings. The overall free induction decay is then reconstructed by combining the chunks acquired for successive values of the indirect evolution delay incorporated in the Zangger–Sterk element.⁶ In this method that has also been extended to the implementation of pseudo-3D experiments to generate a pure shift spectrum in the “direct” domain of a 2D map, the Zangger–Sterk element can be optimized according to the key features highlighted in the previous section. In particular, it is apparent from the pure shift spectra shown below that R-snob pulses show slightly less good performance than Re-Burp pulses, both in terms of decoupling efficiency for H^A and H^B and of artifacts (Fig. 12b and c).

More recently, Zangger *et al.* introduced a method for acquiring real time pure shift ^1H spectra.³ In this approach, the Zangger–Sterk element is implemented in a windowed acquisition scheme to perform instant homonuclear decoupling between the successive data chunks acquired in real time. The insertion of selective pulses within the acquisition scheme has been shown to induce relaxation between successive chunks, which contributes to broaden the lines of the resulting spectrum. In this particular case, it was demonstrated that Burp pulses are less suitable for performing instant homonuclear decoupling because they require longer irradiation delays to obtain the same spectral selectivity, and thus induce excessive relaxation that contributes (i) to a loss in sensitivity of the resulting windowed acquisition scheme and (ii) to create

discontinuities in the reconstructed NMR signal. In this context, Snob pulses have been preferred for real time homonuclear decoupling purposes. Furthermore, it was shown that the discontinuities of the resulting NMR signal arising from its reconstruction from the successive data chunks yields artifacts on the resulting spectrum. Specific developments have thus been implemented in order to minimize line broadening as well as spectral artifact issues on real time pure shift spectra, which are out of the scope of the optimizations of spatial frequency encoding techniques discussed in this work.³⁸ Notably, it was shown that the performance of the Zangger–Sterk element incorporating a R-snob pulse can be greatly improved by using strong pulsed field gradients of equal strength.

To summarize, the theoretical formalism presented here allows for describing and optimizing the main features of the acquisition of 1D pure shift spectra based on the implementation of the Zangger–Sterk element in a pseudo-2D acquisition scheme. This applies more generally to any gradient encoded pulse sequence where pure shift spin evolutions are triggered during an indirect evolution delay, either to perform spectral

aliasing by reducing the spectral window,²⁵ or to combine them with other selected interactions to generate fully tailored correlation spectra.¹⁰ However, the same conclusion cannot be made in the frame of real time pure shift NMR, where Burp pulses have been shown to induce sensitivity losses as well as a significant line broadening due to the relaxation occurring during their application. Nevertheless, we note that the choice to implement shaped pulses with comparable spectral selectivity has already been proposed by Helge Meyer and Zangger as a way of acquiring data of optimized quality in the field of real time broadband homonuclear decoupling. Indeed, they propose to use a combination of an E-Burp2 pulse of 60 ms for excitation, with a Gaussian pulse of 20 ms for decoupling as a routine experimental setting for recording real time pure shift 1D spectra, which corresponds to the conditions discussed here in terms of spectral selectivity.³⁹ Other experimental settings have also been reported in the literature, in which a gradient encoded excitation pulse that is more selective than the encoded refocusing pulse is implemented. In this latter case, the selective excitation pulse is used to avoid artifacts appearing in the regions of the sample where the application of the shaped 180° pulse produces flip angles other than 180°, which is a problem for instance when Gaussian pulses are used for refocusing purposes.⁴⁰

J-edited refocusing blocks

Another significant achievement introduced in recent years in the field of high-resolution NMR is the acquisition of *J*-edited spectra. It consists in combining the kind of resolution enhancement made available by SERF experiments in the field of *J*-resolved spectroscopy, with the spectral edition generated by a spatial frequency encoding process. The resulting encoded

Fig. 13 (a) The G-SERF pulse sequence. (b) The experimental 2D G-SERF spectrum recorded on the model ABX spin system **1**, with 128 increments in t_1 . The offset of the non-encoded refocusing pulses was set so as to edit the coupling network involving H^X . The projection above the direct dimension of each 2D map is the sum of the rows. The spectral width encoded by the encoding pulsed field gradient was 3773 Hz (6.29 ppm). (c) An expansion of the region where the couplings involving H^X are edited.

Fig. 14 The amplitude profiles calculated for a G-SERF experiment set to edit the coupling network involving H^A (a) after a gradient encoded E-Burp2 pulse of 60 ms (step 1 in Fig. 13a), (b) after the *J*-edited block implementing a Re-Burp pulse of 60 ms (for $t_1 = 0$ s – step 2), and (c) after the z-filter composed of a time reversal E-Burp2 pulse and an E-Burp2 pulse of 60 ms (step 3). In (d) the same distribution as in (b) has been calculated for a *J*-edited block implementing Re-Burp pulses of duration 120 ms. The SFE gradient was modeled by dividing the sample into 1201 virtual slices.

Fig. 15 The experimental (a) and calculated (b) 2D G-SERF spectra of the model ABX spin system set to edit the coupling network involving H^A . The projection above the direct dimension of each 2D map is the sum of the rows. Both data were obtained with 64 increments in t_1 . The spectral width encoded by the encoding pulsed field gradient was 3773 Hz (6.29 ppm). For the simulated spectrum, the whole virtual sample was computed. The resulting simulated spectrum was calculated in ~ 5 days.

refocusing block allows for triggering local selective spin echoes in the course of which only the coupling between a selected proton and one of its coupling partners can evolve. In the resulting spectrum, a fully resolved edition of the coupling network around this selected proton spin is thus made available. In addition, each coupling can be straightforwardly assigned to the right coupling partner.⁹ The spatial properties of this gradient encoded selective refocusing block have been evaluated in the framework of a G-SERF pulse sequence (Fig. 13a).

The experimental G-SERF spectrum shown in Fig. 13 was recorded so as to edit the coupling network involving H^X in **1**, using Burp pulses of 60 ms for both the excitation and refocusing steps, as discussed above. As expected two multiplets are observed at the chemical shifts of the coupling partners H^A and H^B whose splitting in the J -resolved dimension allows for accurately measuring the strength of their scalar coupling with H^X (Fig. 13b). The resolution achieved in the indirect domain allows for verifying that these multiplets show almost no artifact, which highlights the quality of the spatial frequency encoding process (Fig. 13c).

A specific advantage of the G-SERF experiment is the simplicity of its implementation, since one only has to change the offset of the non-encoded refocusing pulses to edit the coupling network of another proton nucleus. In this spirit, this offset has been switched to ν^A to probe the coupling network of H^A . The evolution of the slice selection process has been computed after each step of this G-SERF experiment prior to studying the resulting spectrum (Fig. 14). As for the δ -resolved block, we observe that the action of both the selective refocusing block and the z-filter leads to successive thinning of the cross-sections that are encoded for each proton site (Fig. 14a–c). The impact of the selectivity of the encoded refocusing pulse on the quality of the slice selection process has also been studied for this refocusing

Fig. 16 The expansions of the experimental (exp. – a–d) and simulated (sim. – e–h) 2D G-SERF spectra of **1** implemented with Re-Burp and R-snob refocusing pulses, taken around ν^X (a, b, e and f) and ν^B (c, d, g and h). The sum of the columns is displayed along the indirect dimension for each expanded area.

block (Fig. 14d). We observe that implementing a Re-Burp pulse of 120 ms results in an asymmetric amplitude profile for the cross-section encoded at ν^B . This allows for predicting that using a too selective encoded pulse would yield a signal at ν^B that is not only distorted, but also weaker.

A G-SERF experiment was thus implemented using selective Burp pulses of duration 60 ms, and its experimental counterpart was recorded using identical settings. Fig. 15 shows the experimental and simulated J -edited spectra that were generated to edit the coupling network of H^A .

Only 64 increments were acquired in t_1 , due to the length of the corresponding computational time needed to simulate this 2D experiment. In both spectra doublets with splittings J^{A-X} and J^{A-B} appear at ν^X and ν^B respectively. The cross-section encoded at ν^A does not yield any informative multiplet but only a dephased signal arising from the spatial resolution issue, as it was described elsewhere.¹¹ Zero-frequency artifacts were observed for H^X on both experimental and simulated spectra (Fig. 16a, b, e and f), which were identified as mainly arising from a truncation effect in the indirect time domain. Overall, similar lineshapes are found in the simulation and in the experiment, for each correlation (Fig. 16a, c, e and g). The slight differences that are visible between experimental and calculated lineshapes are mainly due to residual shim imperfections in the experiment on the one hand, and the difficulty to adjust the apodization parameters in the simulation on the other hand. The same study was carried on with R-snob refocusing pulses in order to evaluate the ability of this shape to undergo a spatial frequency encoding in the frame of J -edited spectroscopy. An E-Burp2 pulse was preferred to the E-snob shape for the excitation step as bad performance was observed with the latter.

The resulting correlations are strongly degraded compared to the Re-Burp shape (Fig. 16b, d, f and h). Notably, the linewidths are found to be broader, which arise from a less efficient control of the phase by Snob pulses throughout the encoded sample. In particular, for the signal encoded at ν^B both the experimental and simulated data confirm that the R-snob shape does not allow for generating a correlation of sufficient quality.

To conclude this part, the gradient encoded selective refocusing block that is typically implemented in J -edited techniques has the same property as the pure shift block of refining the slice selection process initially created during the preparation step. This allows for implementing shorter selective pulses, as it was demonstrated here with Burp pulses of 60 ms, and thus to optimize the sensitivity of the resulting experiment.

Conclusions

In this paper, we have presented the first theoretical and experimental analysis of the key features that drive resolution and sensitivity in high-resolution NMR methods based on the concept of spatial frequency encoding. A theoretical formalism, based on the modeling of selective pulses encoded by a magnetic field gradient, was introduced to study the slice

selection process underlying the acquisition of pure shift and J -edited NMR spectra, which are some of the most significant methodological developments introduced in the field of high-resolution NMR over the last few decades. The visualization of encoded signals throughout the NMR sample has shown to be a useful tool for deciphering the influence of experimental parameters such as the shape and the selectivity of the encoded irradiation scheme, and more generally for addressing spatial resolution issues raised by the implementation of gradient encoded refocusing blocks. Firstly, we have shown that Burp shapes are more suitable for spatial frequency encoding than Snob or to a lesser degree Gaussian shapes, because of a better coherence of the phase distribution achieved throughout each encoded cross-section. We note that the Gaussian shape shows however rather good performance, both for excitation and refocusing purposes, when it is implemented in a gradient encoded pulse sequence, and that Snob pulses have been shown elsewhere to give better performance in the framework of real time 1D pure shift NMR spectroscopy to date.

Secondly, we have found that pure shift and J -edited refocusing blocks allow for refining the slice selection process during the pulse sequence in which they are implemented, due to a better spatial resolution along with a better phase coherence of gradient encoded refocusing pulses. These key features were exploited to obtain 2D pure shift and J -edited spectra of good quality with shorter Burp pulses, which allowed for optimizing their sensitivity by limiting losses due to relaxation during refocusing of blocks on the one hand, and increasing the height of the encoded slices for each signal on the other hand. These results were obtained on a model spin system involving strongly coupled protons with close chemical shifts, which corresponds to the most challenging case for methods based on SFE.

These results shed new light on the recent achievements that have been reported in the field of high-resolution NMR.⁴¹ Two approaches have been claimed to provide a general method for extracting individual chemical shifts and/or scalar or dipolar couplings from crowded ^1H spectra. On the one hand, several pulse sequences based on the SFE technique explored in the present work have been developed for such purposes, with a particular emphasis on improving their sensitivity and the quality of the resulting spectra.^{7,8,14,25,35,36,38,42,43} As an illustration, the push-G-SERF experiment¹³ that allows for probing the coupling network involving a selected proton site is composed of the J -edited and pure shift blocks. The optimizations highlighted in this paper can thus be exploited straightforwardly to improve its resolution and sensitivity. On the other hand, the PSYCHE method takes advantage of a refocusing block implementing Chirp pulses with a low flip angle to act selectively on the fraction of the proton sites that are selected by this gradient encoded frequency-swept pulse, and trigger a pure shift or J -resolved spin evolutions.^{4,5,44–47} For instance, a PSYCHELIC experiment⁴⁸ has been recently introduced, which allows in principle for recording the same correlation spectra as G-SERF or push-GSERF experiments. This experiment shows however a rather low sensitivity (typically $\sim 2\%$ of a standard ^1H spectrum) as well as it produces several artifacts as

soon as coupled protons with close chemical shifts are probed. The present work paves the way for the rational optimization of the SFE method to a point where the observed performance is at least equivalent to that of the PSYCHE method. In particular, the deeper understanding of the local spin dynamics that takes place during the slice selection process allowed for obtaining high-resolution data for a second order spin system, without sacrificing too much sensitivity.

To conclude, high resolution NMR methods based on a spatial frequency encoding offer a collection of robust and easy-to-implement experiments that have first provided a unique access to the chemical shifts and homonuclear couplings in molecules showing very crowded ^1H spectra. The simulation presented in this paper will constitute an interesting basis for designing useful tools for chemists and spectroscopists implementing these methods, both for optimizing the conditions of their analysis, and for extracting a rich analytical content, even in difficult cases where strongly coupled systems yield unconventional lineshapes.

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