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Pure shift ^1H NMR: what is next?

Laura Castañar*

Currently, pure shift nuclear magnetic resonance is an area of high interest. The aim of this contribution is to describe briefly how this technique has evolved, where it is now and what could be the next challenges in the amazing adventure of the development and application of pure shift nuclear magnetic resonance experiments. Copyright © 2016 John Wiley & Sons, Ltd.

Keywords: NMR spectroscopy; pure shift NMR; homonuclear decoupling; scalar coupling; high resolution; structure analysis

Introduction

Over the last few years, a high level of interest has emerged again in the development of new pure shift nuclear magnetic resonance (NMR) techniques – also called homonuclear broadband decoupling – which greatly improve the signal resolution of NMR spectra. Numerous new pure shift methods and a wide variety of their applications have been reported showing the high versatility and usefulness of this methodology.^[1–3] The aim of this contribution is to describe briefly how this technique has evolved, where it is now and what could be the next challenges in the amazing adventure of the development and application of pure shift NMR experiments.

Scalar couplings (J) are a key source of information to conduct structure analysis of molecules by using NMR, but they are also an unwelcome source of complications. Most ^1H NMR spectra suffer from low signal resolution and severe overlap due to the narrow range of ^1H chemical shifts (about 10 p.p.m.) and also due to the splitting of each signal arising from the proton–proton scalar coupling (J_{HH}). The main goal of pure shift techniques is to remove the effect of J_{HH} and in this way, collapse all multiplets into singlets, simplifying the spectrum and making its interpretation easier and faster. The advantages of obtaining pure shift ^1H NMR spectra can be observed in Fig. 1, which shows how the absence of J_{HH} couplings leads to a single line for each proton resonance. A huge improvement of the signal resolution and a reduction of the signal overlap, which facilitates and simplifies the analysis of complex regions, are observed.

Birth and Development of a Great Idea

The idea of a pure shift experiment is not new, and it was present in the NMR community since the early days of NMR. In 1963, Ernst and Primas wrote: 'For the practical spectroscopist it would be ideal if he could remove all the spin-spin couplings at the same time'.^[4] Over the last 50 years, several approaches have been proposed to overcome the problem of poor signal dispersion in ^1H NMR spectroscopy.

One of the first methods to achieve ^1H spectral simplification was based on the use of frequency-selective continuous-wave irradiation of a single signal during the acquisition period.^[5] However, this technique provides only a partial simplification of some signals and not broadband homodecoupling of the entire spectrum. The first method for obtaining a broadband homodecoupled

high-resolution ^1H NMR spectrum was proposed by Aue *et al.* in 1976, where a pure shift spectrum was extracted from the F_2 projection of a two-dimensional (2D) J -resolved absolute value spectrum.^[6] This method allows the extraction of pure chemical shift spectra by manipulation of the 2D data without conducting actual decoupling. Pure shift one-dimensional (1D) NMR spectra can also be obtained by decoupling in the indirect dimension in 2D spectra (like constant time evolution experiments^[7] and time reversal^[8]) or from the diagonal of the modified anti z-COSY experiment.^[9] An extensive review of all these methods can be found in Refs.^[1,2]

In order to decouple one set of spins (active spins) from all their neighbours (passive spins), they have to be selected and manipulated independently of other spins. The first method that was published based on this idea was proposed in 1982 by Garbow *et al.*, where active and passive spins are differently manipulated by using a bilinear rotation decoupling (BIRD) element (Fig. 2A) to differentiate protons bound to ^{13}C from those bound to ^{12}C .^[10] The BIRD element was used beside a hard ^1H 180° pulse at the centre of an incremented period t_1 (pseudo 2D acquisition). After Fourier transform, the first point of each free-induction decay (FID) with respect to t_1 – a broadband homodecoupled 1D spectrum – is obtained, where only protons bounded to ^{13}C (active spins) are observed. The combination of the hard 180° pulse and the BIRD block (which selectively inverts the active spins) has the dual effect of refocusing J_{HH} and allows evolution under the effect of the chemical shift. This combination is named 'J-refocusing element', and it is the most important element used in the design of the modern pure shift experiments (Fig. 2).

In 1997, Zangger and Sterk published a new pure shift method where the selective inversion of the active spins was performed by using the spatial encoded – also called 'slice selective' – concept (Fig. 2B).^[11] The spatial codification (or slice selection) is achieved by applying a selective ^1H 180° pulse simultaneously with a weak pulsed field gradient (PFG), and in combination with the hard 180° pulse, it is possible to selectively homodecouple different

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Figure 1. (A) Conventional and (B) pure shift ^1H NMR spectra for an estradiol sample in acetone- d_6 .

signals in different parts of the NMR tube. To obtain a 1D homonuclear broadband decoupled ^1H spectrum, the experiment is acquired in a 2D fashion (called interferogram acquisition) where the evolution time is incremented stepwise; in the middle of this delay, the J -refocusing element is applied (Fig. 3A). Unlike the previous experiment (where only the first point of each FID is used), here, the first data points of each FID are used and the timing of the pulse sequence is chosen to guarantee that the J_{HH} evolution is refocused at the centre of the first data chunk of each FID.^[12] Finally, post-processing is needed in order to extract the first chunk of each FID (chunking process) and arrange them together consecutively to reconstruct a new homodecoupled FID after which a conventional Fourier transformation will give a pure shift ^1H NMR spectrum.

In 2012, Lupulescu *et al.* described a new acquisition method where the J -refocusing element (using the BIRD block as a selective inversion element) is applied in real time during the acquisition in

order to obtain a single FID (Fig. 3B), during which the J_{HH} is periodically refocused.^[13] The great advantage of this approach is that, in contrast to the interferogram acquisition, there is no experiment time penalty and a higher sensitivity per unit time is obtained. Besides, this method does not require any special data post processing and is easily implementable in the direct dimension of standard 1D and multidimensional NMR experiments. Based on this experiment in 2013, Zangger and Meyer described a general approach to achieve single-shot pure shift spectra by using real-time acquisition and slice-selective spin selection.^[14]

Soon after, a homonuclear band-selective (HOBS) decoupling scheme (also known as **band-selective homodecoupling**) that uses real-time acquisition was proposed.^[15,16] In this approach, a band-selective pulse is applied as a selective inversion element (Fig. 2C) that selects a range of resonances which are not mutually coupled, and a pure shift spectrum containing only these signals is obtained. HOBS works very well for peptides and proteins – where the chemical shifts of active and passive spins appear in well-separated regions (e.g. the H_α or amide NH) – and also for mixtures of isomers. In contrast to slice-selective and BIRD real-time pure shift spectra, HOBS does not suffer from sensitivity loss, and even higher signal-to-noise ratio (SNR) – compared with a regular spectrum – is obtained due to the collapse of multiplets into singlets.

The most recent pure shift method was proposed in 2014 by Foroozandeh *et al.*, where two small flip angle swept-frequency pulses (chirp pulses) are used in the presence of a weak PFG to achieve the selective spin inversion (Fig. 2D).^[17] This new pure shift yielded by CHIRP excitation (PSYCHE) experiment allows the acquisition of broadband homodecoupled spectra with an acceptable level of sensitivity and is more tolerant of strong coupling than most of the other pure shift methods.

Where Are We?

Currently, all of the aforementioned pure shift methodologies have been successfully implemented in most of the conventional 1D

Figure 2. Basic J -refocusing element for suppressing the homonuclear coupling evolution consisting in a nonselective 180° pulse, followed by a selective spin inversion element. This selection can be achieved by using (A) a BIRD filter, (B) a slice-selective element, (C) a band-selective pulse or (D) the PSYCHE block.

Figure 3. General acquisition schemes used to obtain homodecoupled FID. (A) 2D acquisition mode interferogram method where the final homodecoupled FID is obtained after a reconstruction process where the initial chunks of each increment are arranged together. (B) Real-time acquisition mode where the acquisition element is repeated n times until collecting a complete FID.

and multidimensional NMR experiments. The resulting pure shift spectra have a wide range of potential applications, and their usefulness has already been demonstrated (an extensive review of all these methods can be found in Ref. [3]). However, no NMR experiment is perfect, and pure shift methods are no exception. Some of the problems/limitations of pure shift experiments will be presented in the following sections as well as some proposed solutions for their removal/reduction.

Sensitivity

One of the main costs to pay for obtaining a broadband homodecoupled spectrum is sensitivity. In general, low SNR is an unavoidable feature of most pure shift experiments. This is an inherent problem that comes with the use of selective inversion elements as a part of the J -refocusing scheme. Using the BIRD filter (Fig. 2A), only protons bounded to ^{13}C are selected, and then its sensitivity is just 1.1% of the SNR of a conventional ^1H spectrum due to the natural abundance of ^{13}C isotopomers. However, in the special case of heteronuclear correlation experiments where ^{13}C nuclei are already selected, the pure shift version using the BIRD element does not suffer any extra penalty in sensitivity.^[18]

In the slice-selective approach (Fig. 2B), each active spin is excited in a narrow region (slice) of the sample, and the detected amount of signal depends on the selectivity of the slice-selective excitation. The main consequence is that the SNR is drastically reduced compared with regular proton spectra. Several techniques have been proposed for increasing the sensitivity per unit time of these experiments by applying a multiple-frequency selective

pulse (multi-slice excitation methods) with equidistant^[19] or nonequidistant^[20] phase modulation. HOBS methodology (Fig. 2C) does not use the PFG applied simultaneously with the band selective pulse (no slice-selection); therefore, a spectrum with full sensitivity (and even higher due to multiplets collapsing) is obtained.

The sensitivity of the PSYCHE element (Fig. 2D) mainly depends on the flip angle of the chirp pulses used. The higher the flip angle, the higher the SNR but also the more spectral artefacts appear. Therefore, a compromise between sensitivity and spectral quality is needed. Typically, a flip angle value about 10–30° is used which leads to SNR levels between 3 and 20% compared with the conventional hard pulse. The sensitivity is still reduced compared with regular 1D spectra but is higher than most of the other interferogram pure shift methods, such as slice-selective or BIRD decoupling. A comparison of the sensitivity obtained with the selective inversion methods noted in the preceding text is summarized in Table 1.

As noted previously, the use of a selective inversion element in pure shift experiments plays a key role in the final spectrum sensitivity. Another factor that affects the SNR per unit time of these experiments is the acquisition mode used. With the interferogram method (Fig. 3A), an extra dimension has to be acquired to build

Table 1. Relative sensitivity of different selective inversion elements compared with the sensitivity obtained by using a hard pulse

BIRD	Slice-selective	Band-selective	PSYCHE
1.1%	0.5–10%	≥100%	3–20%

up the homodecoupled FID by concatenating the first data chunks extracted from each FID (2D acquisition mode). The direct consequence of using this method is that the experiment time required to obtain pure shift spectra is significantly longer compared with regular 1D experiments. In the real-time approach (Fig. 3B), the whole FID is acquired at once by interrupting the acquisition every 2τ to apply the J -refocusing block with BIRD, slice-selective or HOBS as a selective inversion element. It should be noted that the PSYCHE element – which affords the highest sensitivity to obtain broadband spectra – cannot be used in real-time acquisition mode because the distinction between active and passive spins is purely statistical. The real-time method leads to a large reduction in experiment time compared with the interferogram method where multiple data chunks are acquired in individual increments of a 2D experiment.

Combining the selective inversion elements and acquisition modes, spectra with different levels of sensitivity can be recorded. The experiment that offers the highest SNR per unit time is obtained by using the HOBS/~~band-selective homodecoupling~~ refocusing element and real-time acquisition mode where the same or even higher sensitivity than the conventional ^1H NMR spectrum is accomplished.^[15,16] However, the main limitation of this experiment is that only a pure shift spectrum of the selected band of frequencies is obtained (it is not broadband). In broadband homodecoupled NMR experiments, the price for signal simplification is a considerable penalty in sensitivity. Until now, the most general method for obtaining a broadband pure shift spectrum of an unknown sample with acceptable sensitivity and easy setup is the PSYCHE experiment, despite the fact that it uses the interferogram acquisition mode.^[17]

There is only one broadband pure shift experiment where no additional penalty is added by the decoupling scheme: 2D real-time BIRD-based ^1H – ^{13}C HSQC.^[18] This elegant method uses real-time BIRD decoupling where only protons attached to ^{13}C are decoupled. The penalty for only choosing ^{13}C -attached protons has already been paid during the INEPT block of the HSQC experiment. So, the sensitivity drawback of BIRD decoupling is already included in the HSQC experiment. Here, the decoupling actually leads to an increase in both sensitivity and resolution compared with a regular HSQC experiment. This experiment only fails for the geminal $^2J_{\text{HH}}$ between diastereotopic protons because the BIRD filter cannot differentiate between protons directly bonded to the same ^{13}C nucleus. In the final pure shift spectrum, the geminal interaction is retained and nonequivalent methylene proton signals are doublets. This limitation can be circumvented by using the constant-time BIRD^[21] or perfect BIRD^[22] elements to refocus the geminal coupling effects. However, these elements can only be used with the interferogram acquisition mode (pseudo three-dimensional experiment) where the SNR is reduced compared with the real-time version.

Sensitivity can be more problematic in multidimensional pure shift experiments, where high resolution is also needed in the indirect dimension. In order to keep a reasonable experiment time, pure shift methods have been combined with spectral aliasing^[23–25] and **nonuniform sampling**^[24,26,27] techniques. In the case of multidimensional ^1H – ^1H NMR spectroscopy, ultra-high-resolution pure shift spectra can be obtained with homodecoupled signals in both dimensions. This can be carried out by applying the J -refocusing block in both the direct and the indirect dimensions but comes with the cost of very long experiment times and very low sensitivity. To circumvent these limitations, several experiments have been proposed where only one dimension is homodecoupled – either

direct^[28] or indirect dimension^[29] – and covariance post-processing is applied in the other one.

Spectral quality

Most of the pure shift NMR experiments offer high-resolution spectra, but some factors can affect spectral quality such as the presence of strong coupling effects or the presence of chunking sidebands, among others.

Two spins are strongly coupled when the size of the coupling constant (J_{HH}) between them is in the same magnitude as the frequency difference ($\Delta\nu$) between them ($\Delta\nu \approx J_{\text{HH}}$). In standard, ^1H NMR spectrum strong coupling leads to a distortion of the signal amplitudes and positions. In general, all pure shift techniques work well for weakly coupled protons, but in the case of strongly coupled resonances, they lead to the appearance of artefacts that in some cases can complicate the spectrum. However, some of the available approaches are more tolerant to strong couplings and the adverse effects can be minimized. For example, the slice-selective approach performs very well with **strong** coupled systems if very selective pulses (narrow excitation bandwidth) are used for exciting each signal in a different slice. Nevertheless, the higher the selectivity is, the less sensitive the method becomes, and when selective pulses longer than about 20 ms are needed, only the interferogram acquisition method can be used. The BIRD approach works very well in most of the cases,^[30] but it fails when the ^{13}C satellites are strongly coupled. The PSYCHE approach is more robust with respect to strong coupling than most of the other pure shift methods. The combination of low-flip angle chirp pulses and PFGs allows coherence transfer pathways (CTPs) generated by strong coupling interactions to be diminished. Even better results are achieved when the PSYCHE J -refocusing element is combined with two extra chirp pulses in the **triple spin echo PSYCHE** experiment (Fig. 4).^[31]

The spectral quality of pure shift experiments can also be affected by the presence of ‘chunking’ sidebands, which are related with the piecewise acquisition method (‘chunking’) used in the interferogram (Fig. 3A) and real-time (Fig. 3B) experiments. In both acquisition modes, J_{HH} evolution is refocused at the centre of each

Figure 4. (A) Conventional, (B) PSYCHE and (C) **triple spin echo PSYCHE** ^1H NMR spectra for an estradiol sample in $\text{DMSO}-d_6$. Asterisks mark the residual strong coupling artefacts.

chunk, and the chunk duration ($t_{\text{chunk}} \equiv 1/SW_1 \equiv 2\tau$) is kept short enough to be sure that J -evolution remains small at the beginning and at the end of the chunk ($t_{\text{chunk}} \ll 1/J_{\text{HH}}$). The effect of this residual J -modulation is that the signal intensity is slightly less at the edges than in the centre of the chunk. After Fourier transformation, this periodic intensity decrease is converted into weak sidebands around each homodecoupled signal, which are spaced by frequency steps corresponding to the inverse of the chunk duration ($1/t_{\text{chunk}}$) and decay rapidly either side of the homodecoupled signal. In general, the shorter the chunk duration is, the cleaner the pure shift spectrum is as the deviation from exact J -refocusing is smaller. The intensity of the 'chunking' sidebands varies approximately as $(J_{\text{HH}} * t_{\text{chunk}})^2$, considering that the timing of the chunk is typically chosen about 10–20 ms; in most cases, their intensity is at the level of the ^{13}C satellites.

In real-time pure shift experiments (Fig. 3B), in addition to the small J -modulation at the edges of the chunk that leads to 'chunking sidebands', another effect is taking place: T_2 relaxation during the J -refocusing element applied between chunks. This extra transverse relaxation during the acquisition interruption leads to a step-like modulation in the FID (see FID in Fig. 3B), and after Fourier transformation, these periodic 'steps' are converted into weak artefacts, which are flanking the homodecoupled signal and are equally spaced at frequencies corresponding to the reciprocal value of the chunk duration (Fig. 5C). In general, the shorter the duration of the J -refocusing element, the lower the intensity of these artefacts. Recently, a method was proposed to 'reduce' the sidebands/artefacts in real-time experiments by varying the FID chunk lengths between individual scans.^[32] Because the position of the sidebands/artefacts depends on the chunk duration, this variation of the chunking time leads to a 'smearing out' of the sidebands/artefacts, and in the spectrum, their intensity is 'reduced' below the level of ^{13}C satellites.

When J -refocusing elements are used to obtain pure shift spectra, it is very important to choose the appropriate CTP to avoid unwanted magnetizations (those that have not been subjected to the J -refocusing) contributing to the final signal; otherwise, artefacts may be observed. These artefacts appear at the same frequency as the 'chunking' sidebands; however, they decay slowly either side of the decoupled signal. An effective CTP selection can be made by using PFGs, which should be placed either side of the hard 180° pulse and the selective inversion element of the J -refocusing block (Fig. 2) and can additionally be combined with a phase cycling of the pulses that provide the selective spin inversion (BIRD filter, selective pulse or chirp pulses).

The spectral quality of pure shift experiments not only depends on the presence of strong coupling effects or the presence of sidebands/artefacts and their intensity but is also determined by the resolution of the homodecoupled signals. The resolution of the signals in the interferogram approach is directly related with the number of increments in the indirect dimension. The homodecoupled FID is built by using the first data chunk of each increment, so the number of increments determines the number of chunks and the resolution of the final FID. In general, the higher the number of increments (number of chunks), the longer the FID and the better the signal resolution (narrower lines). Normally, about 16–32 increments in the indirect dimension are required to obtain a good compromise among signal resolution, spectral quality and experiment time.

The resolution of the homodecoupled signal in the real-time approach depends on (i) the resolution of the FID (as in the conventional ^1H NMR spectrum) and (ii) the extra T_2 relaxation during the J -refocusing element. As mentioned before, in real-time experiments, the J -refocusing element is inserted between successive data chunks during the acquisition. The resulting gaps are excised from the FID so that it is shorter (compared with the conventional one) and after Fourier transformation signals are slightly broadened. For molecules that relax rapidly (short T_2), relaxation decays between individual chunks of the FID are more severe and therefore shorter FIDs are recorded and broader signals are observed in the resulting pure shift spectrum. If the BIRD filter is used in real-time experiments, then the duration of the J -refocusing block is given by 2Δ [$\Delta = 1/(2 * J_{\text{CH}})$] which normally corresponds with values between 5 and 10 ms. If the slice-selective approach is used, then the duration of the J -refocusing element is determined by the selectivity of the 180° pulse, which is adjusted depending on the spin system being analysed. For systems where coupled signals are close in chemical shift, a longer (more selective) selective pulse has to be applied which leads to very long times between chunks, and because of that, broad signals and more intense artefacts are observed in the final pure shift spectrum. Recently, a new approach named Extended Acquisition Time NMR was proposed where the missing data point periods are not excised but instead are algorithmically reconstructed after acquisition.^[33] With this method, the full length of the FID is kept, avoiding artificial shortening of the FID, and so narrower linewidths are observed in the pure shift spectrum. In practice, the use of selective pulses longer than 15–20 ms is not recommended if spectra with good quality are desired. Then, in cases where relaxation is limited or when very high resolution is needed, interferogram methods give better resolution than real-time decoupling (Fig. 5).

Figure 5. Expanded region showing proton 2α from the equimolar enantiomeric mixture of (*R,S*)-1-aminoindan with 4.5 equivalents of Pirkel alcohol in CDCl_3 . Comparison of the spectral quality of (A) standard ^1H NMR, (B) interferogram slice-selective and (C) real-time slice-selective spectra. A 20-ms selective 180° Gaussian pulse was used in both pure shift spectra. Red arrows in (C) mark the artefacts observed in the real-time spectrum. Different linewidths are also observed in interferogram and real-time spectra.

What Could Be Next?

In the NMR community, an interesting discussion about what could be the next steps in pure shift NMR spectroscopy exists. Some scientists consider that it is difficult to achieve 'very' important improvements in terms of methodological development and that future work will be focused on their applications. My point of view – as a young and very novice researcher in this area – is closer to those scientists who think that the future of the pure shift NMR will be long and very exciting. Here, I would like to highlight some key points that I think we should keep in mind in the near future.

Methodology

The development of new strategies to improve pure shift experiments is a current area of great interest in NMR. Most of the new strategies are focused on increasing the sensitivity of these experiments and reducing the presence of sidebands/artefacts in the pure shift spectra. The main goal is to achieve broadband homodecoupled spectra without sacrificing sensitivity, with high spectral quality and in the same experiment time as the analogue conventional NMR experiments. However, this is not currently possible for most of the pure shift experiments, with the sole exception of real-time BIRD-HSQC^[18] which can be only applied to molecules with ^{13}C at natural abundance.

Sensitivity is the most demanding challenge in the development of novel pure shift experiments. In recent years, impressive improvements have been achieved. Nevertheless, the sensitivity of most pure shift methods to obtain broadband homodecoupled spectra (not in the case of the band-selective version) is still far away compared with the standard experiments. As mentioned before, the two main sources of sensitivity loss are the selective inversion element used in the J -refocusing block and the acquisition method. It would be ideal to be able to apply the J -refocusing block interleaved during the dwell time (real time mode), but at the moment, this is not possible because any homodecoupling scheme takes much longer than the dwell time. One of the greatest challenges in the near future is the design of improved J -refocusing methods that enhance absolute sensitivity and their robustness for a general and routine use.

On the other hand, strong coupling effects remain as one of the most difficult challenges to overcome. The effects of strongly coupled systems in homodecoupled spectra can be often circumvented by using BIRD^[30] or ~~triple spin echo~~ PSYCHE elements,^[31] but there is not a general method to deal with them in all possible cases. Regarding the 'chunking' sidebands in the interferogram experiments, it could be possible to reduce or remove them by using methods that have been already proposed with other aims. For example, the idea of 'reducing' the sidebands in real-time experiments by varying the FID chunk lengths^[32] could be used in the interferogram ones. Another possibility to remove the 'chunking' sidebands could be to construct an interferogram point-by-point (such as in Garbow's approach^[10]), avoiding any residual J -modulation, but at the cost of acquiring very long experiments with a high number of increments to achieve an acceptable resolution in the final homodecoupled FID. This last possibility could be explored in combination with the ~~nonuniform~~ sampling technique to speed up the acquisition.

A promising field that probably will be explored in the coming years is the use of post-processing methods to improve the existing

experimental homodecoupling techniques or even to create synthetic pure shift spectra. This approach becomes less time-consuming in terms of spectrometer time, could reduce sensitivity problems, and it could be possible to obtain pure shift spectra free from artefacts. Covariance processing is already used to obtain a semi-synthetic 2D ^1H - ^1H homonuclear double pure shift spectrum by using an F_1 or F_2 -homodecoupled spectrum and mapping the information extracted from the homodecoupled dimension onto the coupled one.^[28,29] Following this idea, a generalized indirect covariance post-processing was recently proposed to generate synthetic 2D homonuclear and heteronuclear pure shift spectra by using a ^1H - ^1H F_1 -homodecoupled spectrum (containing only diagonal peaks) as a reference.^[34,35]

Application

Pure shift NMR spectroscopy has demonstrated the ability to have a wide range of potential uses and applications when spectral simplification and high resolution are needed. The resulting pure shift spectra have been successfully applied to the structure analysis of small, medium and large-size molecules,^[26,36,37] for the study of enantiomeric,^[23,38,39] diastereomeric^[40] or complex mixtures^[24,27,41,42] and for the study of diffusion^[43–46] and dynamic processes,^[47] among others (an extensive review of all these applications can be found in Ref. [3]). An important practical application of the pure shift techniques is the determination of the magnitude and sign of scalar and residual dipolar coupling constants through the highly resolved and simplified pure shift spectra.^[21,22,25,48–55] Further promising applications are currently in their initial stage of development, such as the combination of pure shift with the dynamic nuclear polarization technique^[56] or the use of pure shift spectra to carry out quantitative studies in metabolomics.^[57] In the future, it could also be possible to explore the application of pure shift techniques to other nuclei (such as ^{19}F , ^{31}P or ^2H), in quality control processes, drug degradation studies and to monitor fast reactions, among others. Additionally, the use of pure chemical shift data also opens up new possibilities to carry out structure elucidation and verify molecular structures in an automatic way by using for example computer-assisted structure elucidation programs.^[58,59]

Improvements achieved in the past several years have led to pure shift experiments that can be easily processed – using an available post-processing code in the case of interferogram methods^[60] and a regular Fourier transformation in real-time methods – and even acquired in a single scan. The NMR community has performed a great job designing these experiments to ensure their usefulness for routine NMR users without tedious setup. Most of the pulse programs, parameter sets and data are available online, facilitating the implementation of this new methodology in all NMR facilities.

However, I think that it is time to do a special effort in divulging the huge utilities of all these new experiments to the whole scientific community, especially among those who use NMR spectroscopy as a fundamental tool for their research, such as synthetic chemists and biochemists. Because it makes no sense to develop dozens of new experiments if no one uses them. They have the problems and we can propose the solutions; it is the perfect combination!

The opinions expressed in this article are my personal point of view as a young and novice researcher in the NMR field. I really believe that our community is doing an excellent job and that we have an amazing future ahead of us.

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Special issue perspective

Pure shift ^1H NMR: what is next?

Laura Castañar

Currently, pure shift nuclear magnetic resonance is an area of high interest. The aim of this contribution is to describe briefly how this technique has evolved, where it is now and what could be the next challenges in the amazing adventure of the development and application of pure shift nuclear magnetic resonance experiments.

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