1. Introduction

Two- and higher-dimensional experiments have revolutionized the field of nuclear magnetic resonance (NMR). Traditionally the desired coherence pathway for these experiments is selected by phase cycling. However, phase cycling requires a minimum number of repetitions of the experiment to be effective. For samples that produce a good signal-to-noise spectrum in a single scan this makes the experimental time unnecessarily long. In 1978 Maudsley et al. discovered that coherence selection can be achieved using magnetic field gradients [1]. This is based on the fact that each coherence order responds differently to a gradient. Later, in 1990, Hurd showed that this technique can be applied to two-dimensional experiments [2]. For these gradient-filtered experiments only a single scan is needed and they are less sensitive to phase errors.

Instead of using pulsed-field gradients ($B_0$) one can also use $B_1$ gradients, as was first demonstrated in 1985 by Counsell et al. [3], who used the inhomogeneity of their RF field to perform one-dimensional multiple quantum filtering. The main advantage of this method is that it can be performed with any NMR probe, a special probe and amplifier to create pulsed-field gradients are not needed.

After the paper by Counsell et al. only a dozen articles have been published on the use of $B_1$ gradients, nearly all in the 90's and mostly by two teams of researchers: The team of Mutzenhardt, Brondeau and Canet [4–7] have shown that a single-turn coil can be used to create a quasi-uniform $B_1$ gradient and that this can be used, in combination with a homogeneous RF coil, to select coherence pathways. The team of Laukien, Maas and Cory [8–11] designed a special quadrupolar RF coil that creates a spatially dependent phase and showed that this can be used for coherence selection.

It has been demonstrated that these $B_1$ gradient methods can be used for one-dimensional multiple quantum filtering [3,12,6], solvent suppression [12,5], Correlation Spectroscopy (COSY) [4,9,6,7], Double-Quantum-Filtered COSY (DQF-COSY) [10,5], Nuclear Overhauser Effect Spectroscopy (NOESY) [13,14], Total Correlation Spectroscopy (TOCSY) [14] and Heteronuclear Single-Quantum Coherence (HSQC) [11,15], as is summarized in a review article by Canet [16].

In this work we propose to use soft off-resonance pulses employing a tapered stripline [17] for coherence selection. The tapered stripline produces a well-defined uniform $B_1$ gradient along the direction of the main magnetic field ($z$-axis), which obeys $\frac{dB_1}{dz}$ = constant. This is unlike most other approaches to produce $B_1$ gradients used before. Another difference with previous work is that we make use of off-resonance pulses instead of composite $z$-pulses to select coherences. In this way it is no longer necessary to use both a homogeneous and an inhomogeneous RF coil, a single RF gradient coil is sufficient to perform the experiment with good sensitivity and resolution. We demonstrate this for a magnitude-mode $^1$H COSY and a phase sensitive $^1$H DQF-COSY.
2. Experimental

2.1. Tapered stripline

The tapered stripline chip used in the experiments is shown in Fig. 1a. The stripline was created on a 500 µm thick fused silica wafer using photolithography, magnetron sputtering and electroplating. The length of the taper is 15 mm. The width of the taper varies from 5 mm to 1 mm [17]. The stripline is oriented parallel to the main magnetic field. The NMR sample is contained in a fused silica capillary (Polymer microtechnologies) with an outer diameter of 360 µm and an inner diameter of 250 µm. The position of the capillary on the stripline is shown in Fig. 1b. The detected volume of the tapered stripline is 0.5 µL, which is indicated in red.1 The capillary can either be filled completely with sample or as a plug in proton-free FC-40 (fluorinert), shown in blue in Fig. 1b. The stripline detector is suitable for creating well defined B1 gradients. The detector shown in Fig. 1a is designed for a linear B1 profile. The simulated RF field created by a stripline detector is shown in Fig. 2. At the narrow side of the taper the magnetic field created in the capillary is 0.46 mT A⁻¹ with a gradient of 23 mT A⁻¹ m⁻¹. The sensitivity of the sample on the taper is directly proportional to the B1 field strength (reciprocity principle). The sensitivity of the complete 15 mm of sample is 1.0 × 10⁵ spins per √Hz. When a hard (rectangular shaped) RF pulse is applied using a tapered stripline the magnetization will nutate over a position dependent flip angle. Thus the magnetization will dephase in the xy-plane when a pulse is applied along the y direction in the rotating frame. This is unlike PFG (B0) pulses, which dephase the magnetization in the xy-plane. To obtain dephasing in the xy-plane we propose the use of shaped OFF-resonance B1 field gradient (OFFBEAT) pulses. When a RF pulse is applied off-resonance the magnetization will precess around the effective field in the rotating frame as is shown in Fig. 3a. The effective field at any given position z on the tapered stripline is the vector sum of B1(z) and Boffset = -γBg(z)h, where h is the difference between the RF carrier frequency and the resonance frequency of the spins. The magnetization precesses around the effective field with a frequency:

\[ \omega_{\text{eff}}(z) = -\gamma B_{\text{eff}}(z) = -\gamma \sqrt{B_1(z)^2 + \Delta B_{\text{offset}}} \]

When a pulse is applied in the presence of a B1 gradient the phase evolution of the magnetization will be a function of the position along the tapered stripline (z). To obtain dephasing in the xy-plane while leaving the z magnetization undisturbed the pulse is shaped. The pulse profile of such a shaped pulse is shown in Fig. 3c. The resonance offset frequency during the pulse is constant and the B1 amplitude profile is sine shaped. The strength of the effective field at a given position on the stripline B_{eff}(z) is shown by the blue curve in the top figure of Fig. 3c. The direction of the effective field parametrized by the angle θ between B_{eff}(z) and the z direction is shown in the bottom figure of Fig. 3c. At the start of the pulse θ is 0 (B_{eff}(z) = 0) and thus B_{eff} = B_{offset}, which is directed along z. Then B_{eff}(z) increases, which means B_{eff} will tilt away from z until θ = 50° depending on the offset and B1 amplitude. Secondly the size of B_{eff} is position dependent as B1(z) is position dependent. At the end of the pulse θ returns to 0, because the RF amplitude is ramped back to 0. The trajectory of the magnetization during a pulse with a maximum RF field of 150 kHz and an offset of 100 kHz is shown in Fig. 3e. When the magnetization is initially directed along z (Fig. 3e, top) the magnetization will stay aligned with B_{eff}. This means it will return to z at the end of the pulse. If the magnetization is initially directed along x (Fig. 3e, bottom) the magnetization will keep precessing in a plane perpendicular to B_{eff}. The angular frequency in the plane is determined by the size of B_{eff}, which is position dependent. At the end of the pulse the plane perpendicular to B_{eff} coincides with the xy-plane if the angle variation of B_{eff} is adiabatic. This means the magnetization will have acquired a position dependent phase in the xy-plane at the end of the pulse. The dephasing in the xy-plane is similar to that resulting from a PFG pulse, as shown in Fig. 4b. Unlike PFG pulses the spatial encoding created by OFFBEAT pulses is isotope selective. A PFG pulse dephases the transverse magnetization of all isotopes by their gyromagnetic ratio. An OFFBEAT pulse on the other hand dephases the transverse magnetization of only the single isotope that is irradiated by the RF and leaves the (transverse) magnetization of other isotopes undisturbed. To create dephasing with a phase which is approximately linear in z the RF field strength should be larger than the offset frequency (B1 > B_{offset}), see Fig. 3d.

2.2. Coherence selection

The selection of a particular coherence pathway in a 2D-NMR experiment can be performed using pulsed-field gradients by selective refocusing of the desired pathway. During a pulse sequence N PFG pulses are applied. Each of these pulses creates a spatially dependent phase:

\[ \Phi_n(z) = -\gamma_p s_n B_{y,n}(z) \tau_n \]

where \( s_n \) is the coherence order, \( s_o \) is the shape factor of the pulse, \( B_{y,n}(z) \) is the strength of the field at position z and \( \tau_n \) is the duration of the pulse. Only coherence pathways for which

\[ \sum_{n=1}^{N} \Phi_n(z) = 0 \]

are refocussed and can be observed. In this way a coherence pathway can be selected by using the appropriate magnitude and/or duration of the gradient pulses. For example in a COSY sequence two identical gradient pulses can be used to select the +1 → -1 coherence pathway since

\[ -s_1 \gamma_{B_{y,1}}(z) \tau_1 + s_2 \gamma_{B_{y,2}}(z) \tau_2 = 0 \]

when the amplitude, duration and shape of the two gradients are equal.

Such a pulse sequence is shown in Fig. 5a. This COSY pulse sequence can easily be modified to use offset B1 gradient pulses instead, as is shown in Fig. 5b.

2.3. Frequency swept pulses

When phase sensitive spectra are required the PFG pulses are often used in combination with refocussing echoes to prevent phase distortions in the spectra. These phase distortions are due to the finite duration of the gradient pulses. The advantage of B1 gradient pulses is that during the RF pulse the evolution due to for example chemical shift is (to a large extent) suppressed. When two spins have a slightly different resonant frequency they will have a different B1 offset. Their small frequency difference \( \Delta B_{\text{offset}} \) will change B_{eff} by

\[ \Delta B_{\text{eff}} = \Delta B_{\text{offset}} \cdot \cos(\theta) \]

where \( \theta \) is the angle between the effective field B_{eff} and the z axis. This means the phase distortions in B1 gradient pulse experiments can be minimized by having \( \theta \) close to 90° during the main part of the pulse. For the fixed frequency OFFBEAT pulses large B1 field strengths \( B_1 > B_{\text{offset}} \) are required to bring \( \theta \) close to 90°. For phase sensitive pulse sequences we propose the use of adiabatic frequency sweeps to be able to tilt the effective field over larger angles.

1 For interpretation of color in Figs. 1 and 3, the reader is referred to the web version of this article.
Unlike PFG pulses, where homonuclear interactions are not included, are suppressed. This is the on-resonance part of the chirped OFFBEAT pulse all interactions, dephasing (besides the spatially encoded dephasing) occurs. During the central part of the swept pulse the amplitude is increased while the frequency offset decreases. During the central part of the sweep pulse the offset frequency is near 0 and thus the effective field vector equals the RF field vector \( B_1 \). As long as \( B_1 \) is large compared to the chemical shift differences between the spins the final phase will be independent of the shift differences. This means no refocusing echoes are required when using chirped OFFBEAT pulses since no additional dephasing (besides the spatially encoded dephasing) occurs. During the on-resonance part of the chirped OFFBEAT pulse all interactions, including the homonuclear interaction, are suppressed. This is unlike PFG echo pulses, where homonuclear interactions are not refocused by the echos.

Such an adiabatic swept OFFBEAT pulse is shown in Fig. 6. This pulse is similar to an adiabatic full passage except for the offset frequency which is reversed during the second half of the pulse. The resulting spatial encoding created by such a pulse is comparable to that of a fixed frequency OFFBEAT pulse. During the first part of the pulse the amplitude is increased while the frequency offset decreases. The central part of the sweep pulse the offset frequency is near 0 and thus the effective field vector equals the RF field vector \( B_1 \). As long as \( B_1 \) is large compared to the chemical shift differences between the spins the final phase will be independent of the shift differences. This means no refocusing echoes are required when using chirped OFFBEAT pulses since no additional dephasing (besides the spatially encoded dephasing) occurs. During the on-resonance part of the chirped OFFBEAT pulse all interactions, including the homonuclear interaction, are suppressed. This is unlike PFG echo pulses, where homonuclear interactions are not refocused by the echos.

2.4. Results

Three types of \(^1\)H COSY experiments were performed on a sample of 1-propanol (Sigma-Aldrich). The experiments were performed using a Varian 400 MHz NMR spectrometer. The stripline was used in a probe with an unloaded Q of 75. The highest RF field strength of all pulses was 180 kHz at the narrow part of the stripline. The hard pulses in the pulse sequence (rectangular shaped) are also created using the tapered stripline. For the hard pulses a pulse width of 1.5 \( \mu \)s was used, which corresponds to a 90° pulse at the narrow part of the stripline. Spins at other positions experience a smaller flip angle. At the wide part of the stripline this pulse corresponds to a 22.5° flip angle. Hard pulses applied using a \( B_1 \) gradient coil thus result in a lower efficiency of the pulse sequence. For example the efficiency of a ‘90° pulse’ using the tapered stripline is approximately 85% compared to ideal excitation. This effect becomes more severe for pulse sequences with a large number of hard pulses, because of the cumulative effect of the pulses. The efficiency of the pulse sequence can be restored, however, by replacing the hard pulses by \( B_1 \)-independent rotation (BIR) pulses [18, 19]. For example when BIR-4 pulses are used in the COSY pulse sequence the signal amplitude increases by 18%. First a basic COSY experiment was performed with an 8 step phase cycle on a sample of 1-propanol. The resulting spectrum is shown in Fig. 7a. A minimum of 4 phase cycle steps is required to select the desired coherence pathway. The FWHM linewidth on this prototype stripline is 8 Hz. The second experiment, shown in Fig. 7b, is the basic COSY where the phase cycle is omitted. Without phase cycling the positive and negative frequency components cannot be distinguished in the indirect dimension, this results in mirrored peaks. Finally the experiment depicted in Fig. 5b was performed using the OFFBEAT pulses to select the coherence pathway (Fig. 5b). The OFFBEAT pulses have a frequency offset of 100 kHz and a duration of 200 \( \mu \)s. As described earlier, the OFFBEAT pulses have a sine shaped amplitude profile, with a maximum equal to that of the square excitation and conversion pulses. The resulting spectrum is shown in Fig. 7c. The mirrored peaks are now almost completely suppressed by the offset \( B_1 \) gradient pulses. There are small residual signals visible just above the noise (see the supplementary for spectra with low contour levels). These are most likely caused by the contact planes of the stripline chip which create no RF gradient but do detect a minor NMR signal.

Unlike PFG pulses the offset \( B_1 \) gradient pulses cannot be varied in amplitude to select a coherence pathway, because a change in the RF field strength will change the z dependence of \( B_{\text{eff}} \) as can be seen in Fig. 3d. However, the duration of the OFFBEAT pulses can still be used to select a coherence pathway since the phase evolution is linear in time. For example in a double-quantum filtered (DQF) COSY pulse sequence the pathway selection can be performed by using the pulse sequence shown in Fig. 8. In this sequence the OFFBEAT pulses have a 4:3:10 pulsewidth ratio [20]. This selects the \(+1 \rightarrow +2 \rightarrow +1\) coherence pathway. Fig. 9b shows the result of a traditional DQF-COSY experiment of 1-propanol using an 8 step phase cycle. The spectrum was recorded
phase sensitive using the TPPI method, which requires double the number of increments to obtain the phase information in the indirect dimension. Fig. 9a shows the spectrum when only a single scan per increment is recorded. Frequency discrimination is still possible because of TPPI, but the diagonal peaks are much larger than expected and their lineshape is distorted.

For comparison a DQF-COSY spectrum with pulsed-field gradients was recorded of 1-propanol in deuterated chloroform on a 500 MHz Bruker spectrometer. The DQF-COSY spectra have been recorded without refocussing pulses, shown in Fig. 9c, and with refocussing pulses, which is shown in Fig. 9d. The PFG pulse sequences are given in the supplementary. The duration of the pulsed-field gradients was 400 \( \mu \)s, 300 \( \mu \)s and 1000 \( \mu \)s. The peaks in Fig. 9c are of comparable intensity to the those of Fig. 9d, but the phase of the peaks is distorted.

In Fig. 9e the DQF-COSY experiment was performed with OFFBEAT pulses in a single scan as shown in Fig. 8. The phase information for this experiment was obtained using the echo/antiecho method. In PFG coherence selected experiments the echo/antiecho method is performed by using a PFG pulse with negative amplitude. An OFFBEAT pulse with “negative amplitude” can be created by using a pulse with a negative offset with respect to the first pulse.
The resonance frequency of the spins. As can be seen from Fig. 3a, a pulse with a negative $B_{\text{offset}}$ makes the spins precess around an effective field vector which makes an angle $\theta_{\text{0}} = 180^\circ / C_\text{14} / C_\text{0}$ with the main magnetic field. This creates a 'time-reversed' spatial encoding of the magnetization and can thus be used to perform echo/antiecho acquisition.

The three OFFBEAT pulses had a duration of 400 µs, 300 µs and 1000 µs. In this experiment no phase cycling was used. The intensity of the cross peaks is similar to that of the experiment with the full phase cycle, yet the phase is slightly distorted. This phase distortion is caused by the differences in resonance frequency of the spins. As discussed, during the OFFBEAT pulse the size of $B_{\text{offset}}$ depends on the individual resonance frequencies of the different spins in the sample, which results in a different effective field $B_{\text{eff}}$ and thus a different overall phase at the end of the pulse. The phase issue also occurs when pulsed-field gradients are used for coherence selection, because differences in $B_{\text{off}}$ are also present during $B_0$ gradient pulses. In this case refocusing echos are required to remove the effects of the evolution during the gradient pulse. Such an echo pulse refocuses the evolution of all interactions except for homonuclear interactions.

In Section 2.3 we introduced an alternative OFFBEAT pulse for phase sensitive experiments. The chirped OFFBEAT pulses suppress the (chemical shift) evolution, which removes phase distortions without the need for refocussing pulses. A DQF-COSY experiment using this kind of chirped OFFBEAT pulses is shown in Fig. 9f. This spectrum is similar to the one with fixed frequency OFFBEAT.
pulses except now all the peaks have the correct phase. The chirped OFFBEAT pulses are preferred over the fixed frequency OFFBEAT pulses in particular when recording phase sensitive 2D data.

3. Conclusions

Using a tapered stripline probe it is possible to combine $B_1$ gradients, high sensitivity and good resolution using a single resonant structure. We have developed a novel method where offset $B_1$ gradient pulses are used to perform coherence selection in 2D-NMR. Besides the tapered stripline, no additional hardware is required to perform this type of coherence selection. The main advantage of OFFBEAT pulses over other $B_1$ gradient methods is the ease of implementation, because of the similarity with PFG-selected pulse sequences. An experiment which uses pulsed-field gradients for coherence selection can be converted to a $B_1$ gradient experiment by simply replacing all the PFG pulses by soft off-resonance pulses of appropriate length. This means no new pulse sequences need to be developed to be able to use offset $B_1$ gradient pulses for coherence selection.

During an OFFBEAT pulse the magnetization precesses around the effective field $B_{\text{eff}}$. The angle $\theta$ between the effective field and the $z$-axis changes adiabatically, which results in a phase encoding in the $xy$-plane at the end of the pulse. The control over the angle $\theta$ can be increased by using frequency swept pulses. This way the effective field can be brought all the way to the $xy$-plane ($\theta = 90^\circ$). In this case effects like chemical shift evolution are suppressed during the pulse. This means refocusing echos like those used in PFG selected sequences are not required, which could improve sensitivity for fast relaxing systems. The RF pulses also suppress homonuclear couplings, which cannot be done using PFG methods combined with refocusing echos. This effect might be of interest in strongly coupled systems.

The $B_1$ gradient of the OFFBEAT pulses consisted of RF field strengths ranging from 45 kHz to 180 kHz at an offset frequency of 100 kHz. From Fig. 4b it can be seen that such a pulse does not result in a linear spatial encoding. For coherence selection a linear encoding is not required as long as the position dependent phase of the unwanted coherences average out over the length of the stripline at the end of the pulse sequence. If needed, the
Stripline geometry can easily be designed such that the phase encoding becomes strictly linear for a given offset and $B_1$ field. The second requirement is that the coherence pathway of interest should be selected by changing the pulse length of the OFFBEAT pulses while keeping the amplitude constant. This is unlike PFG coherence selection where it is common to vary the amplitude of the gradient pulses. When adiabatic frequency swept OFFBEAT pulses are used for coherence selection the pathway can be selected by varying either the pulse length or the pulse amplitude.

The $B_1$ gradient coherence selection is well suited for situations where Eddy currents prevent the rapid switching of strong $B_0$ field gradients. The OFFBEAT pulses can also be of interest when combined with surface coils, such as in MRI or when single sided magnets are used. The tapered stripline design is a simple and cheap alternative to create a well defined $B_1$ gradient. Since the tapered stripline uses a capillary to contain the sample it is possible to combine the coherence selection method with in-line NMR experiments [21].
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Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.jmr.2017.11.004.

References


