Practical Use of Multiple-Quantum-Coherences in Spectral Editing and 2D NMR

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Introduction

Pulsed NMR detects rotating transverse magnetization that is associated with single quantum transitions in which the spin-quantum number changes by ±1. In a sample of non-interacting spins only transverse and longitudinal magnetization are present, of which longitudinal magnetization is undetectable. However, in a spin system composed of multiple scalar-coupled spins there are also other types of magnetization, which are typically referred to as coherences. Besides single-quantum-coherences (SQCs, i.e. regular transverse magnetization), a scalar-coupled two-spin system can also create zero and double quantum coherences, in which the spin-quantum number changes by 0 and ±2, respectively. Higher order coherences can be generated in larger multi-spin systems. The key difference between SQCs and other coherences is that only SQCs can generate a detectable signal in an NMR receiver coil. However, the other coherences can still be generated and manipulated; they just have to be converted back to detectable SQCs if their indirect effects are to be observed.

One of the desirable characteristics of MQCs is that uncoupled spins (e.g. water, creatine) cannot generate these coherences. This feature has been used to distinguish uncoupled from coupled spins through spectral editing. A feature specific for homonuclear ZQCs is that their evolution is insensitive to magnetic field inhomogeneity, which provides interesting opportunities for the detection of NMR signals in the presence of poor magnetic field homogeneity. The resonance frequency of DQCs is equal to the sum of the individual spin frequencies and has been used in 2D NMR and spectral editing.

Throughout this presentation the various coherences will be described with the product operator formalism (1). The product operator formalism is attractive as it provides a quantitative description of the experiment while still retaining a graphical depiction of the coherences involved. The primary example will be for a weakly-coupled homonuclear IS spin system as this reveals most of the various aspects of MQCs.

Preparation

The preparation part of a NMR pulse sequence is the collection of delays and RF pulses that convert longitudinal magnetization to MQCs. In scalar-coupled spin-systems MQCs are always created from a state of anti-phase coherence and requires at least two RF pulses. The simplest NMR sequence to create homonuclear anti-phase coherence is 90°(X) – TE/2 – 180°(X) – TE/2, i.e. a regular Hahn spin-echo in which the 90° and 180° pulses are applied along the +X axis of the rotating frame of reference. The 180° pulse refocuses chemical shifts and frequency offsets, but does not affect scalar coupling evolution. For a two-spin-system IS the density matrix at the top of the spin-echo is:

$$\sigma(TE) = (I_y + S_y)\cos(\pi JTE) - 2(I_xS_z + I_zS_x)\sin(\pi JTE) \quad [1]$$

where I_y and S_y represent in-phase coherence of spins I and S and $2I_xS_z$ and $2I_zS_x$ represents anti-phase coherence of spins I and S with respect to the other spin, respectively. When TE = 1/(2J), Eq [1] reduces to $\sigma(TE) = -2(I_xS_z + I_zS_x)$ and a state of pure anti-phase coherence has been created. The conversion to MQCs is achieved with a second 90° pulse applied along the X axis such that $\sigma(TE+) = 2(I_xS_y + I_yS_x)$, which represents a state of pure double-quantum coherence. This is an unusual situation that only happens for a homonuclear two-spin-system. For a heteronuclear two-spin-system, the described preparation sequence element will generate both zero- and double quantum coherences.

Evolution

If signal acquisition would start following the second 90° pulse, no signal would be detected. However, DQCs are nevertheless present in the transverse plane and will evolve under a number of effects, including chemical shifts, magnetic field gradients and offsets, but not scalar coupling. The density matrix at the end of the time period τ is equal to:

$$\sigma(TE+\tau) = 2(I_xS_y + I_yS_x)\cos(\omega_I\tau + \omega_S\tau) + 2(I_yS_y - I_xS_x)\sin(\omega_I\tau + \omega_S\tau) \quad [2]$$

It follows that DQCs evolve under the frequency sum ($\omega_I + \omega_S$). This also means that any applied frequency offset or phase shift is twice as strong for DQCs than for SQCs. Similarly, the application of a magnetic field gradient will dephase DQCs twice as fast as SQCs. This difference forms the basis to separate DQCs and SQCs by spectral editing. While the current example does not generate any net ZQCs, it can easily be shown that ZQCs evolve under the frequency difference ($\omega_I - \omega_S$), consequently making them insensitive to frequency offsets, magnetic field inhomogeneity and magnetic field gradients.

Acquisition

As MQCs are not directly detectable, their presence and evolution can only be revealed by converting them back to SQCs. This is achieved by a third 90° pulse which converts the density matrix to:

$$\sigma(TE+\tau) = 2(I_xS_z + I_zS_x)\cos(\omega_I\tau + \omega_S\tau) + 2(I_zS_z - I_xS_x)\sin(\omega_I\tau + \omega_S\tau) \quad [3]$$

The density matrix is composed of four distinct contributions. The term $2I_zS_z$ represents longitudinal scalar order and, similar to regular longitudinal magnetization I_z and S_z, is not NMR observable. The term $2I_xS_x$ represents MQCs which are also not NMR observable. The terms $2I_xS_z$ and $2I_zS_x$ represent anti-phase coherence which is NMR observable and can evolve into in-phase coherence under the influence of scalar coupling. The presence of MQCs have been transferred to the detectable SQCs as an amplitude modulation given by $\cos(\omega_I\tau + \omega_S\tau)$.

Spectral editing and 2D NMR

The basic pulse sequence 90°(X) – 1/(4J) – 180°(X) – 1/(4J) – 90°(X) – τ – 90°(X) – acquisition is readily converted into a single-shot spectral editing sequence by placing magnetic field gradients around the third 90° pulse. The first magnetic field gradient will dephase DQCs, whereas uncoupled spins reside along the longitudinal axis and are not dephased at all. Following the final excitation, the dephased SQCs can be rephased by a second magnetic field gradient of twice the area compared to the first gradient. The longitudinal magnetization of uncoupled spins was excited by the last 90° pulse and is thus dephased by the second magnetic field gradient. The combination of different coherences for uncoupled and scalar coupled spins and magnetic field gradients can thus achieve spectral editing in a single experiment. MQC-based spectral editing have been used for *in vivo* applications since the late 1980s for the selective detection of a number of compounds, including lactate, glucose and γ-aminobutyric acid (2-10).

By linearly incrementing the τ delay, the same pulse sequence can also be used to obtain a 2D NMR spectrum depicting the DQC frequencies along the indirect dimension. By omitting the 180° refocusing pulse and linearly incrementing the TE delay, the sequence is converted to the double-quantum-filtered (DQF) COSY 2D NMR method (11). This method gives essentially the same information as a regular COSY experiment, i.e. cross peaks between scalar-coupled spins, but has the added advantage that strong diagonal signals from uncoupled spins are removed. This allows a more reliable detection of small cross peaks close to the diagonal.

Conclusions

The unique features of multiple quantum coherences open up a wide range of interesting experiments that are simply not possible with regular magnetization. The different sensitivities of DQCs and SQCs towards magnetic field gradients provide a straightforward method to their separation. The indirect detection of MQCs by 2D NMR techniques can provide unique information regarding scalar-coupled networks and provides, in the case of ZQCs, a way to obtain high-resolution NMR spectra independent of the magnetic field homogeneity (12). Besides a theoretical treatment of the characteristics of MQCs, the presentation will focus on practical aspects involving MQCs with an emphasis on *in vivo* NMR applications.

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