How to Tickle Spins with a Fourier Transform NMR Spectrometer

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Dedicated to Ray Freeman and Wes Anderson, inventors of spin tickling in 1962 and recipients of the 2012 Russell Varian Prize

In the long bygone days of continuous-wave nuclear magnetic resonance (NMR) spectroscopy, a selected transition within a multiplet of a high-resolution spectrum could be irradiated by a highly selective continuous-wave (CW) radio-frequency (rf) field with a very weak amplitude $\omega_0/2\pi \leq J$. This causes splittings of connected transitions, allowing one to map the connectivities of all transitions within the energy-level diagram of the spin system. Such “tickling” experiments stimulated the invention of two-dimensional spectroscopy, but seem to have been forgotten for nearly 50 years. We show that tickling can readily be achieved in homonuclear systems with Fourier transform spectrometers by applying short pulses in the intervals between the sampling points. Extensions to heteronuclear systems are even more straightforward since they can be carried out using very weak CW rf fields.

1. Introduction

It is now half a century ago that Wes Anderson and Ray Freeman, then both at Varian Associates in Palo Alto, California, published two seminal papers about theoretical and experimental aspects of double resonance in high-resolution nuclear magnetic resonance (NMR).[1] This was before the introduction of Fourier transform (FT) NMR,[2] when the signal was measured by continuously sweeping the carrier and receiver frequencies (or the main magnetic field) in the manner of “slow passage”. In double resonance 1 experiments, a second radio-frequency (rf) field is applied to characterize the energy levels of the spin systems. If the amplitude $\gamma B_2/(2\pi) = \omega_2/(2\pi)$ of the second rf field is equal or greater than the spin coupling constant $J$, a collapse of the multiplets onto the underlying chemical shifts can be observed, a phenomenon that has come to be known as decoupling.[3] If the rf amplitude $\gamma B_2/(2\pi) = \omega_2/(2\pi)$ is smaller than the spin coupling constant $J$ but larger than the line width,[10] all transitions that have an energy level in common with the irradiated transition split into doublets. If the irradiation coincides exactly with the frequency of a single transition, and if all couplings are smaller than the chemical shift differences, all connected transitions split into symmetrical doublets with equal intensities, with a splitting equal to the amplitude of the second rf field. This phenomenon has later come to be known as “spin tickling”. The increased complexity, which appears to achieve the opposite effect as decoupling, offers a means to study connectivities of transitions in a spin system.

A tickling spectrum helps to discriminate between two possible types of connected transitions.[5] If the energy levels that are not shared differ by $\Delta n = \pm 2$ as shown in Figure 1, that is, if they span a double-quantum (DQ) transition, the connected transitions are called progressive (see the red transitions in the energy-level diagram of Figure 1a). On the other hand, if these energy levels differ by $\Delta n = 0$, they span a zero-quantum (ZQ) transition and are called regressive (blue transitions in Figure 1a). In the latter case, the splitting induced by tickling is usually well resolved, but in the case of progressively connected transitions, the lines are broader and the splitting is often hard to resolve, so that the two types can easily be distinguished. Freeman and Anderson explained the splitting of the lines by a partial admixture of allowed single-quantum (SQ) transitions and forbidden (ZQ or DQ) transitions. Both become equally allowed at exact resonance.[6] The broadening in the progressive case can be attributed to the fact that DQ transitions are more sensitive than ZQ transitions to the inhomogeneity of the static magnetic field $B_0$.

To illustrate this effect, a $J$-coupled two-spin system $\mathcal{I}_S$ was investigated by numerical simulations using the SIMPSON program.[7] The chemical shifts were set at $\Omega_{	ext{i}}/(2\pi) = 5\text{ Hz}$ and $\Omega_{	ext{j}}/(2\pi) = 405\text{ Hz}$, respectively, with a scalar coupling $J = 10\text{ Hz}$. The lowest-frequency line of the spin doublet at
\( \Omega/(2\pi) - J/2 = 0 \) Hz was irradiated with an average rf field strength \( \langle \omega_c \rangle/(2\pi) = 1 \) Hz. To simulate the inhomogeneity of the \( B_0 \) field, both rf carrier and receiver frequencies were shifted in 21 steps of 0.1 Hz from \(-1.0\) to \(+1.0\) Hz around the resonance condition. Relaxation was not taken into account. Figure 2 shows the spectral lines of the off-resonance spin \( S \). A few selected spectra with offsets of \(-1.0, -0.5, 0.0, 0.5,\) and \(1.0 \) Hz are shown in Figures 2a–e. The intensities are always symmetrical with respect to the chemical shift of spin 5. The 1 Hz splittings in the on-resonance spectrum in Figure 1c are equal to the amplitude of the ticking field. The sum of all 21 spectra is plotted in Figure 2f. This nicely reproduces the experimental pattern of the broad progressively connected peaks and narrow regressively connected peaks. The differential broadening originates from the distinct slopes of the individual peaks across Figures 2a–e.

Spin tickling is a convenient method to assign spectral transitions to the energy levels, and thus to reconstruct the entire energy-level diagram. The approach could be applied to other forms of spectroscopy, not just to magnetic resonance. A similar splitting of lines in vibrational spectroscopy was explained by Fermi in 1931[8] and is known today as Fermi resonance in infrared and Raman spectroscopy.[9,10] In modern NMR, continuous-wave (CW) experiments have been almost fully replaced by pulsed experiments. To study connectivities, two-dimensional correlation spectroscopy (COSY)\(^{[9]}\) has become popular. If the second pulse has a small flip angle (e.g. in COSY-45) one can readily determine the relative signs of \( J \) couplings from inspection of the multiplet structures.\(^{[11,12]}\) The combination of FT NMR and tickling was discussed (in German) by F. Günther in 1971,[11] but this was largely overlooked. In his calculations, Günther showed that tickling not only broadens the inhomogeneous line widths in a manner that depends on the connectivity, but the natural homogeneous line widths are also broadened in a differential manner. Such relaxation effects are reminiscent of the recently discovered long-lived coherences.[12] Wokaun and Ernst described a two-dimensional (2D) experiment where tickling is applied to multiple-quantum coherences in the evolution interval \( t_1 \), while the signal is observed in Fourier mode in the detection interval \( t_2 \).

\(^1\) The volume numbering of the Annalen der Physik was modified in 2010. The original reference of Günther’s publication (as cited by Ernst et al.) is: Annalen der Physik, 7. Folge, Band 27, Heft 4, 1971, S. 396–408. Note that the year of publication has changed from 1971 to 1972!
2. Results and Discussion

Today, tickling does not play a significant role in NMR spectroscopy, but there appear to be no obstacles to its renaissance. Recently, we developed a method dubbed window-acquired spin tailoring experiment (WASTE)\(^\text{[14]}\) that allows one to eliminate the effects of a manifold of homonuclear scalar couplings by alternating the sampling of the free induction decay with brief rf pulses. This is closely related to the time-shared method suggested by Jesson et al., who also mention spin tickling.\(^\text{[15]}\) If rf pulses and signal acquisition alternate, the effect of the second rf field can be described by an average Hamiltonian.\(^\text{[16]}\) By using a similar time-shared sequence, but with a much weaker rf field, tickling experiments can be readily carried out. Thus, double resonance tickling and decoupling experiments can both be transferred from CW to FT NMR.\(^\text{[1,17]}\)

For the sake of illustration, consider the pair of weakly coupled protons in 2,3-dibromothiophene dissolved in [D\(_6\)]-dimethyl sulfoxide (DMSO). This AX-system has a homonuclear scalar coupling of \(J_{AX} = 5.8\) Hz and a chemical shift difference \((\Delta \nu_A - \Delta \nu_X)/(2\pi) = 305\) Hz at 500 MHz (see Figure 1 a). Figure 1 b shows the tickling spectrum obtained when an rf field with an average amplitude of \((\omega_i)/(2\pi) = 1\) Hz is set on the left-most resonance 1, as evidenced by the interference pattern. The neighboring line 2 remains unperturbed. This confirms that these two transitions do not share any common energy level, as expected for parallel transitions. The left-hand peak 3 of the other doublet splits into two narrow lines, while the right-hand peak 4 is broadened. The transition 3 is regressesively connected, while 4 is progressively connected to transition 1. All of this is consistent with the energy-level diagram in Figure 1.

In a three-spin system, an unambiguous assignment of transitions to the energy-level diagram by simple inspection of the multiplets is no longer possible. We considered 2,3-dibromopropionic acid, the same molecule as Freeman and Anderson\(^\text{[18]}\) chose to tickle. This molecule gave rise to a strongly coupled ABC-system in the 60 MHz spectrometer used for their original paper, but now appears as an ABX-system at 500 MHz. Figure 3 a shows a normal one-dimensional (1D) spectrum. For simplicity, we kept the same numbering of the spectral lines. In a three-spin system, the energy diagram can be represented by a cube where the 12 transitions correspond to the 12 edges, with four parallel transitions for each spin, which correspond to the doublet-of-doublets of each spin. Figure 3 b shows a tickling spectrum obtained by irradiating the left-most resonance C4 with an average amplitude of \((\omega_i)/(2\pi) = 1.5\) Hz, showing the usual beat pattern. It can be seen that none of the three other C transitions are affected, since they are all parallel to C4. There are two pairs of connected transitions. A1 and B1 are both split into broad doublets since they are progressively connected, while A2 and one of the overlapping lines B2 or B3 are split into narrow doublets because of their regressive connectivities. The remaining lines A3, A4, B2 or B3, and B4 are not affected since they are not connected to C4. A single experiment is not sufficient to determine all connectivities. For a full analysis, we refer to the original work of Freeman and Anderson.\(^\text{[18]}\)

In analogy to our homonuclear decoupling experiments,\(^\text{[14]}\) the tickling field was generated by a sequence of \(n\) short pulses, each with a typical duration of \(\tau_p = 1\) \(\mu\)s, inserted in the \(n\) dwell times. If the latter have a duration of \(\Delta t = 50\) \(\mu\)s as required for a spectral width of 20 kHz, this corresponds to a duty cycle of 2% (see Figure 4). The peak rf amplitude of each tickling pulse was \(\omega_i/(2\pi) = 50\) Hz, resulting in an average amplitude of \((\omega_i)/(2\pi) = 1\) Hz that satisfies the tickling condition \((\omega_i)/(2\pi) \leq J\).
Since homonuclear tickling and decoupling can be achieved with the same pulse sequence, there is no need to introduce yet another acronym, and we prefer to stick to WASTE\cite{14} and replace the original “T” for tailoring by “T” for tickling. We are not aware of any experimental demonstration of homonuclear spin tickling since the introduction of Fourier spectroscopy.

In heteronuclear spin systems, tickling can be readily carried out on Fourier transform spectrometers, since one can apply a weak CW field to one nucleus while observing the other in Fourier mode. Thus, one can observe a splitting of \(^{13}\text{C}\) lines in a phosphine when some connected \(^{31}\text{P}\) transitions are irradiated.\cite{14} The heteronuclear version of tickling is actually quite easy to implement, since it is sufficient to apply a weak CW field to one of the transitions of the heteronucleus during acquisition (but not before the rf pulse to avoid inducing nuclear Overhauser effects). For illustration, we tickled the heteronuclear \(^{1}\text{H}\)-\(^{13}\text{C}\) two-spin system in \(^{13}\text{C}\)-enriched formate in \(^2\text{H}_2\text{O}\). Heteronuclear decoupling with a weak CW irradiation with \(\omega_0/(2\pi)\) = 1 Hz was applied with the rf carrier set on the left line of the proton doublet while the \(^{13}\text{C}\) signal was acquired. Figure 5 a shows the normal \(^{13}\text{C}\) doublet, split by the heteronuclear \(J\) coupling of 195 Hz. Figure 5 b shows a \(^{13}\text{C}\)(\(^{1}\text{H}\))-tickling spectrum. Both carbon lines are split by 1 Hz. Note the differential broadening, with narrow lines to the left and broad lines to the right. Figure 5 c and d show similar experiments with stronger tickling fields with \(\omega_0/(2\pi)\) = 5 and 33 Hz. In such heteronuclear systems, higher rf amplitudes can be employed than in homonuclear proton systems, since the tickling condition \(\omega_0/(2\pi)\) \(\leq J\) = 195 Hz is less restrictive. Nevertheless, the differential line broadening is most visible when the tickling fields are weak, which facilitates the identification of different types of connectivities, as can be seen in Figure 5 b.

The variation of the tickling-field amplitude in Figure 5 b–d demonstrates that tickling can also be used to calibrate weak rf fields.

3. Conclusions

Can Fourier tickling be useful in modern NMR? Since it requires only one-dimensional experiments, tickling is a quick approach to characterize the progressive or regressive connectivity of particular resonances, probably faster than selective or soft COSY.\cite{19} Another application might be the elimination of degeneracies in NMR spectra. In 1976, Courtieu et al. separated singlet and triplet lines in an AX$_2$ system by combining tickling with a partially oriented medium.\cite{20} Besides, we like dusting off the spider webs that have covered spin tickling over the last half century to expose this brilliant idea to the bright light of Fourier NMR.

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