

## SUPPORTING INFORMATION FOR

### Ultrafast double-quantum NMR spectroscopy with optimized sensitivity for the analysis of mixtures

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## THEORY: propagation of the density matrix

Consider three spins  $I = 1/2$ : A, M and X, with spin X coupled to spins A and M. The propagation of the density matrix is computed with the product operator formalism, ignoring relaxation and diffusion effects. The proposed description assumes an instantaneous rotation provided by the chirp pulse. While, for a given value of the position  $z$ , each spin in principle has a different rotation time during the chirp pulse, the modulation caused by the resulting small delays is found to be negligible<sup>1</sup>; in the following calculation, we assume that all spins for a given  $z$  are flipped simultaneously.

In the case of weak couplings, the free precession Hamiltonian ( $H_{FP}$ ) is given by:

$$H_{FP} = \Omega_A A_z + \Omega_M M_z + \Omega_X X_z + 2\pi J_{AX} A_z X_z + 2\pi J_{MX} M_z X_z \quad (\text{S1})$$

Where  $\Omega_i$  is the chemical shift offset of spin  $i$ , and  $J_{ij}$  is the scalar coupling constant between spins  $i$  and  $j$ .

In the high-temperature approximation, the density operator is:

$$\sigma(0)^- = A_z + M_z + X_z \quad (\text{S2})$$

After the preparation period (i.e. the double-quantum build-up), the density matrix becomes:

$$\sigma(2\Delta)^+ = \left\{ \begin{array}{l} \frac{1}{4i} \cdot \sin(2\pi J_{AX}\Delta) \cdot [1 + \cos(2\pi J_{MX}\Delta)] \cdot 2A^- X^- \\ + \frac{1}{4i} \cdot \sin(2\pi J_{MX}\Delta) \cdot [1 + \cos(2\pi J_{AX}\Delta)] \cdot 2M^- X^- \\ + \frac{1}{4} \cdot \sin(2\pi J_{AX}\Delta) \cdot \sin(2\pi J_{MX}\Delta) \cdot 4A^- M^- X_z \end{array} \right\} \quad (\text{S3})$$

Given the CTP  $\{0 \rightarrow \pm 1 \rightarrow -2 \rightarrow +2 \rightarrow -2 \rightarrow -1\}$ , only the evolution of the terms whose coherence order is -2 is relevant.

Right before the final mixing pulse, following the spatial encoding step, we have:

$$\sigma(2\Delta + TE + t_{mix})^- = \left\{ \begin{array}{l} \frac{1}{4i} \cdot \sin(2\pi J_{AX}\Delta) \cdot [1 + \cos(2\pi J_{MX}\Delta)] \cdot [\cos \alpha_{MX} \cdot 2A^- X^- + i \sin \alpha_{MX} \cdot 4A^- M_z X^-] \cdot e^{iCz(\Omega_A + \Omega_X)} \\ + \frac{1}{4i} \cdot \sin(2\pi J_{MX}\Delta) \cdot [1 + \cos(2\pi J_{AX}\Delta)] \cdot [\cos \alpha_{AX} \cdot 2M^- X^- + i \sin \alpha_{AX} \cdot 4A_z M^- X^-] \cdot e^{iCz(\Omega_M + \Omega_X)} \\ + \frac{1}{4} \cdot \sin(2\pi J_{AX}\Delta) \cdot \sin(2\pi J_{MX}\Delta) \cdot (\cos \alpha_{AX} \cos \alpha_{MX} - \sin \alpha_{AX} \sin \alpha_{MX}) \cdot 4A^- M^- X_z \cdot e^{iCz(\Omega_A + \Omega_M)} \end{array} \right\} \quad (\text{S4})$$

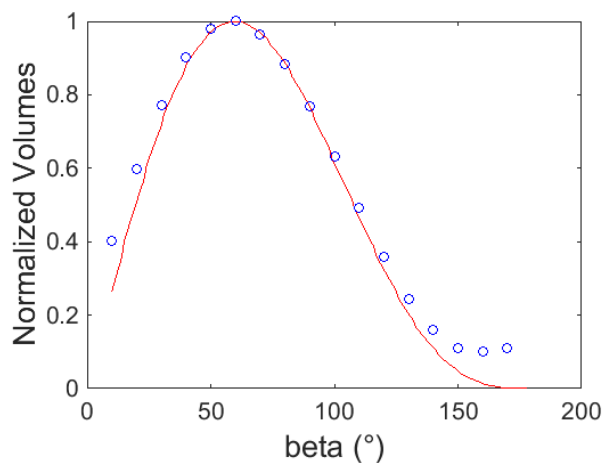
Where:  $\alpha_{AX} = \pi J_{AX}(TE + t_{mix})$  and  $\alpha_{MX} = \pi J_{MX}(TE + t_{mix})$ .

After the action of the mixing pulse, the observable terms of the density operator become:

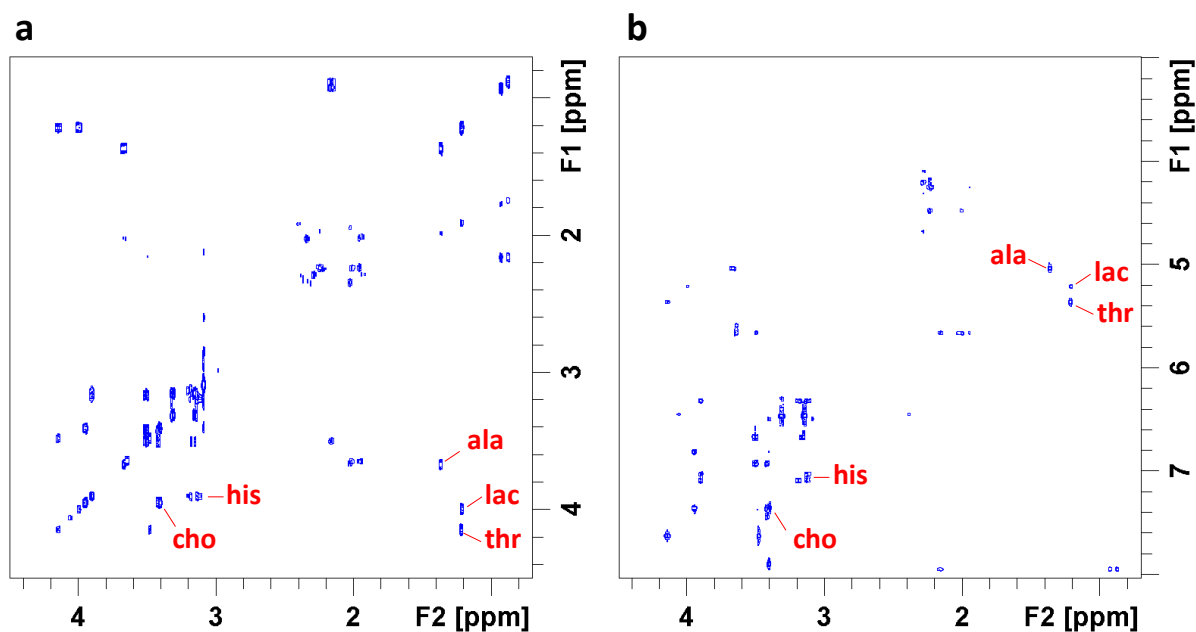
$$\begin{aligned} & \sigma(2\Delta + TE + t_{mix})^+ \\ &= \left\{ \begin{array}{l} -\frac{1}{4} \sin(2\pi J_{AX}\Delta) \cdot [1 + \cos(2\pi J_{MX}\Delta)] \cdot \cos(\beta/2)^2 \cdot \sin \beta \cdot [\cos \alpha_{MX} (2A^- X_z + 2A_z X^-) + i \sin \alpha_{MX} \cdot \cos \beta \cdot 4A_z M_z X^-] \cdot e^{iCz(\Omega_A + \Omega_X)} \\ -\frac{1}{4} \sin(2\pi J_{MX}\Delta) \cdot [1 + \cos(2\pi J_{AX}\Delta)] \cdot \cos(\beta/2)^2 \cdot \sin \beta \cdot [\cos \alpha_{AX} (2M^- X_z + 2M_z X^-) + i \sin \alpha_{AX} \cdot \cos \beta \cdot 4A_z M_z X^-] \cdot e^{iCz(\Omega_M + \Omega_X)} \\ -\frac{1}{8i} \sin(2\pi J_{AX}\Delta) \cdot \sin(2\pi J_{MX}\Delta) \cdot \sin(\beta)^3 \cdot (\cos \alpha_{AX} \cos \alpha_{MX} - \sin \alpha_{AX} \sin \alpha_{MX}) \cdot 4A_z M_z X^- \cdot e^{iCz(\Omega_A + \Omega_M)} \end{array} \right\} \quad (\text{S5}) \end{aligned}$$

Thanks to the density matrix established at the beginning of the detection, that is,  $t_2 = 0$ , the analytical expression of  $\beta$  and J-modulations of the peak located at  $[\Omega_A; \Omega_A + \Omega_X]$  is:

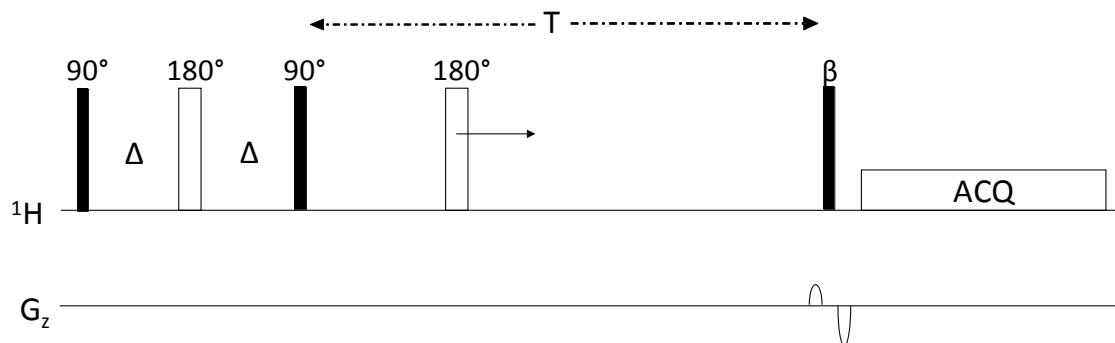
$$S_{A;AX} \propto \cos(\beta/2)^2 \sin \beta \cos(\pi J_{MX}T) \quad (\text{S6})$$



**Figure S1.** Theoretical (solid line) and simulated (circles)  $\beta$ -modulation for an AMX spin system where spin M is coupled to spins A and X.  $\beta$ -modulation is studied for the peak located at  $[\Omega_A; \Omega_A + \Omega_X]$ . The curves are normalized to their maximum.



**Figure S2.** Conventional “constant-time” COSY (a) and “constant-time” DQS (b) spectra of a metabolite mixture, recorded on a 700 MHz spectrometer equipped with a cryoprobe. The DQS experiment uses a double-quantum buildup delay  $\Delta = 35.7$  ms. As the indirect spectral width is larger for DQS vs COSY experiments, the two experiments are compared with identical numbers of points per Hertz in the indirect dimension. It results in a longer experiment time for DQS vs COSY (16 min vs 10 min).



**Figure S3.** Conventional “constant-time” DQS pulse sequence ( $\Delta = 1/4 \cdot J_{H-H}$ ). The amplitude ratio for the coherence-selection gradients is 1:-2.

1. Gouilleux, B.; Rouger, L.; Charrier, B.; Kuprov, I.; Akoka, S.; Dumez, J.-N.; Giraudeau, P., Understanding J-Modulation during Spatial Encoding for Sensitivity-Optimized Ultrafast NMR Spectroscopy. *ChemPhysChem* **2015**, *16* (14), 3093-3100.