Spin-Noise-Detected Two-Dimensional Nuclear Magnetic Resonance at Triple Sensitivity

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Experimental Procedures

As mentioned in the main text, we modified the implementation of spin noise acquisition of previous publications\(^1\)–\(^3\) to avoid a hardware dependent artifact, which had been absent in our previous experiments. The artifact is generated, if one-dimensional spin noise spectra are recorded, noise block by noise block, while activating and deactivating the receiver channel for each block. The way one-dimensional spin noise spectra are processed is as follows: All the noise blocks are Fourier transformed individually to give power spectra and are co-added after that (see Figure S1).

The artifact was first observed on newer hardware using a preamplifier with active transmit/receive switching as an apparent dependence of the spin noise line shape on the duration of the original noise blocks, which cannot be explained by a change in resolution or signal-to-noise, as shown in Figure S5. The spectra shown were obtained on a 500 MHz Bruker Avance III instrument with an ambient temperature probe and a low noise preamplifier. In addition, a continuous phase shifter (ARRA, DN2448A)\(^4\) was placed between the probe and the preamplifier and adjusted to give a pure negative absorptive spin noise signal\(^5\)–\(^7\). We note that this adjustment is not a requirement for the occurrence of the artifact. In Figure S5 one can observe that a positive contribution to the line shape exists for noise blocks acquired early after the start of the acquisition. Under these circumstances the spin noise signal is negative (i.e. less than thermal circuit noise), while the artifact contribution is always has positive power. This additional signal is not observed when adding the phase sensitive noise blocks, as it has random phase.

The pulse sequence programming for the modified acquisition scheme for ctsnHMOC is shown as Figure S2 and that of ctsnHMBC is shown in Figure S3. Figure S4 depicts the automation script used for intermediate shimming in long spin noise acquisitions.
**Figure S2.** Pulse program (tested with TopsSpin 3.5pl5) of a ctsnHMQC experiment avoiding T/R switching artifacts.
include <De.incl>
#include <Avance.incl>

\textbf{Figure S3.} Pulse program (tested with TopsSpin 3.5pl5) of a ctsnHMBC experiment avoiding T/R switching artifacts.
int start = 2, end = 10, i = 0;

for(i=start;i<=end;i++){
    WRA(i);
    expno = i;
    SETCURDATA
    ZG
    CPR_exec("topshim tunea", WAIT_TERM); }

QUIT

Figure S4. AU script (tested with TopSpin 3.5pl5) for recording multiple experiments with shimming in between.

Assessment of Switching Artifacts

As can be seen in Figure S5, the time-dependent component is strongest for sub-blocks taken from the beginning of each noise block and it decays within 7–20 ms (probe and sample dependent). This effect has been traced back to the activation of the transmit/receive (T/R) switch in the preamplifier.[5] The impedance change caused by the T/R switching apparently acts like a minute random pulse excitation. The strength and persistence of this effect is highly dependent on the probe and the type of preamplifier. It was found to be independent of the carrier frequency.

Figure S5. Five 500 MHz $^1$H spin noise spectra of a sample of 90% H$_2$O / 10% D$_2$O. The sub-blocks were extracted from the original noise blocks as indicated in Fig. S1 and processed accordingly. The original noise blocks consisted of 4096 data points, which were recorded over a period of 80 ms and then divided into 5 equally spaced overlapping blocks of 1024 data points (corresponding to 20 ms) as visualized in Fig. S1. Spectra A to E were obtained from the equidistant 1024 data point contiguous sub-blocks corresponding to delay times of 0 ms to 64 ms after the start of the original block. The proton spin noise signal of H$_2$O is the negative peak at 4.7 ppm. The positive signals centered at 5.5 ppm are artifacts originating outside the spectrometer, most likely from a nearby TV station. The carrier frequency was set to 3.5 ppm.
For one-dimensional experiments this can be trivially accomplished by extending each noise block to the hardware maximum and discarding the noise recorded within 5×T₂ from the start of acquisition. For two-dimensional spin-noise-detected NMR spectra, where the acquisition of multiple non-contiguous individual noise blocks is required, the pulse programs have to be rewritten to prevent engaging the T/R switch. In Figure S6 we show a pulse program for a csnHMBC experiment, programmed such that the T/R switch is only activated once at the beginning of each burst of DBU-acquisition blocks. After the T/R switch is engaged, there is an additional delay of 20 ms, to allow for the artifact to decay. In order to avoid this potential source of interference in spin-noise-detected experiments, the programming of spin noise acquisition schemes was modified. Instead of activating the T/R switch for each noise block (Figure S6, upper panel), the switch remains in the receive state continuously (in practice, until the hardware buffer is full, Figure S6, lower panel).

![Figure S6](image)

Figure S6. The upper scheme shows the approach to transmit/receiver switch control used in previous experiments. Before each FID or noise block the switch is opened and after the acquisition the switch is closed again. The engagement of the switch however may cause a small pulse-like event at the beginning of the noise block, which shows up as an always positive distortion of the spin noise line shape, as shown in Fig. S2. This effect is only noticeable in spin noise experiments, due to the low amplitude of the phenomenon. Therefore, multiple FIDs or noise blocks are acquired with the switch continuously in the receive state, as shown in the lower scheme. This circumvents the problem if a delay Δ of duration 5T₂ is inserted after the T/R switch is activated.

On the spectrometer systems we used here (Bruker Avance III) with the software version used (Topspin 3.5pl5), implementing acquisition as shown in the pulse program of Figure S6 requires one to set the “acquisition mode” to “analog” (i.e. disable the real time digital signal processor) to avoid digital filtering artifacts to occur when multiple noise blocks are concatenated. As a consequence of this “analogue” acquisition mode, the acquired signals contain a direct current offset, that may drift over the course of an experiment (20 h), and which may lead to a visible center artifact in the final spectrum. To mitigate this interference, the individual noise blocks are linearly offset corrected, i.e. their average is subtracted from each data point. There is one caveat with this approach: any genuine NMR signal at the center will be removed as well. The data presented here in this Supplementary Information were recorded on a Bruker 500 MHz Avance III spectrometer, equipped with a BBI probe. On our Bruker 700 MHz Avance III spectrometer with a TCI triple resonance cryoprobe, the effect is weaker and decays faster, but still might be problematic for spin noise experiments. In spin-noise-detected experiments using repetitive T/R switching with the acquisition and cross-correlation processing scheme outlined in the main text or applying the original acquisition scheme the effect of the T/R switching artifact with is an increase of the uncorrelated noise as compared to the correlated spin noise signal, owed to the fact the T/R switch artifacts are not correlated between subsequently recorded noise blocks.

Spin Noise vs. Circuit Noise

While we have used the terms “pure spin noise” and “absorbed circuit noise” in previous work, the distinction between spin noise and circuit noise may be misleading and is not as clear-cut as it might seem, in particular on high-Q probes. Due to the strong coupling between the RF-circuit and the spins, one observes a collective phenomenon. The major source of noise not originating from the nuclear spins in our setup is the preamplifier noise, which has been extensively covered in our recent paper. As explained there, preamplifier noise causes line shape changes in the spin noise signals and, most importantly, quantitatively explains the frequency shifts in the tuning curves observed previously. We assured that there was no additional source of noise in the experimental setup used here, as the spin noise response is not affected by changing the cabling between the cold (77 K) pre-amplifier and the “warm” (ambient temperature) pre-amplifier including replacement of the RF-pulse cable by 50 Ohm terminators.

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Supporting Information

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Author Contributions

Experiments were performed with equal contributions by S.G., C.K., and V.V.R.; S.G. and M.B. handled the programming and data analysis; the manuscript was written by S.G., M.B. and N.M., N.M. and C.K. acquired the funding.