Noise Detected NMR Spectroscopy

Kousik Chandra[1,2]

Abstract | Spin noise phenomenon was predicted way back in 1946. However, experimental investigations regarding spin noise became possible only recently with major technological improvements in NMR hardware. These experiments have several potential novel applications and also demand refinements in the existing theoretical framework to explain the phenomenon. Elegance of noise spectroscopy in gathering information about the properties of a system lies in the fact that it does not require external perturbation, and the system remains in thermal equilibrium. Spin noise is intrinsic magnetic fluctuations, and both longitudinal and transverse components have been detected independently in many systems. Detection of fluctuating longitudinal magnetization leads to field of Magnetic Resonance Force Microscopy (MRFM) that can efficiently probe very few spins even down to the level of single spin utilizing ultrasensitive cantilevers. Transverse component of spin noise, which can simultaneously monitor different resonances over a given frequency range enabling one to distinguish between different chemical environments, has also received considerable attention, and found many novel applications. These experiments demand a detailed understanding of the underlying spin noise phenomenon in order to perform perturbation-free magnetic resonance and widen the highly promising application area. Detailed investigations of noise magnetization have been performed recently using force microscopy on equilibrium ensemble of paramagnetic alkali atoms. It was observed that random fluctuations generate spontaneous spin coherences which has similar characteristics as generated by macroscopic magnetization of polarized ensemble in terms of precession and relaxation properties. Several other intrinsic properties like g-factors, isotope-abundance ratios, hyperfine splitting, spin coherence lifetimes etc. also have been achieved without having to excite the sample. In contrast to MRFM-approaches, detection of transverse spin noise also offers novel applications, attracting considerable attention. This has unique advantage as different resonances over a given frequency range enable one to distinguish between different chemical environments. Since these noise signatures scale inversely with sample size, these approaches lead to the possibility of non-perturbative magnetic resonance of small systems down to nano-scale. In this review, these different approaches will be highlighted with main emphasis on transverse spin noise investigations.

REVIEWS

[1]Johannes Kepler University, Linz 4040, Austria.

[2]NMR Research Centre, Indian Institute of Science, Bangalore 560012, India.

kousik.chandra@jku.at, kchandra@sif.iisc.ernet.in

1 Introduction

Experimental observation of nuclear magnetic resonance in water was first performed by Felix Bloch in 1946.[1] The external magnetic field was held constant along the Z axis, while an oscillating magnetic field was applied along the x-axis. As the frequency of oscillating magnetic field approached the Larmour frequency, the nuclear polarization was detected as an induced voltage in a pick-up coil kept parallel to y-axis. In the next pioneering paper, Bloch predicted that even in the absence of static magnetic field, a sample of N spins, each carrying a magnetic moment μ, would induce tiny voltage fluctuations proportional to $N^{1/2}\mu$ in a surrounding coil because of statistical incomplete cancellation.[1] Later Hoult et al. gave a classical picture of this temperature independent magnetization, which is caused by the Brownian motion of the rotating frame magnetization.[2] The bulk equilibrium nuclear magnetic moment vector performs a stochastic trajectory very close to the z axis. Upon mapping the projection of this vector on xy plane of the rotating frame, it follows a Rayleigh distribution with time with correlation time of T_2, the transverse relaxation time, and this induces a voltage at the Larmor frequency with randomly varying amplitude and phase in the receiving coil. Sleator et al.[3,4] achieved the first experimental observation of this temperature independent nuclear spin noise by detecting a weak nuclear quadrupole resonance noise at 30 MHz arising from ^{35}Cl nuclei in $NaClO_3$ sample. The sample was placed in an inductor of LCR circuit and detection was achieved using a super conducting quantum interference device (SQUID) maintained at liquid-^{4}He temperature (1.5 K).[3] The presence of the sample was found to modify the Lorentzian shape of the noise-power spectrum. In order to explain the phenomenon, concept of enhancement of spontaneous emission by Purcell that relies coupling to cavity modes, was used along with Nyquist theorem, Einstein's equation, and modified form of Bloch's equations. As spontaneous emission rate at radiofrequency from nuclear magnetic moment is low (~10^{-27} sec^{-1} in free space), the dipole system was coupled to the cavity modes of circuit with high Q factor (7320) employing SQUID principle, which leads to a large enhancement (~10^{11}) in the emission rate. Utilizing low noise temperature of SQUID detector along with signal averaging techniques, it was possible to detect the spin noise power of the sample, which is 5–10% of the Johnson–Nyquist noise power P_N generated in the same bandwidth ($P_N = 4k_B T\Delta\gamma$, where k_B is the Boltzmann constant). Later, groups of Ernst and McCoy[5] and Gueron

and Leroy[6] independently were able to detect nuclear spin noise spectra at room temperature. The measurements were done with conventional rf probes of lower Q factors (300 and 115) than the SQUID, which had been implemented during the earlier experiments by Sleator et al.[3,4] Ernst and McCoy achieved a higher signal-to-noise ratio in room temperature experiments employing NMR spectrometer with high sensitivity and resolution for liquid sample that has low Johnson–Nyquist noise (line width $\Delta\gamma = 0.2$ Hz). These factors compensate low Q factor. McCoy and Ernst followed the concept given by Sleator et al.[4] in describing the origin of the spin noise, and also assessed the role of radiation damping. Gueron et al. too described the spin system by model equivalent to coupled electrical resonator, and achieved a straightforward derivation of radiation damping along with spin noise effects.[6] However, recently, Hoult et al.[2,7] extensively studied the quantum mechanical origin of free induction decay including spin noise, and determined the conditions for the detection of spin noise while minimizing radiation damping effects. Generally, spontaneous emission, either coherent or random, are believed to be responsible for the voltage induced, in the case of either free induction decay or spin noise. This emission is enhanced by the Q-factor of the receiving coil. In the absence of any other known mechanism, this concept got established. Later, a series of experiments were carried out to provide evidences that only spontaneous emission is not the origin of either the FID or the spin noise voltage. After observation of spin noise in coils devoid of high Q-factor, the explanation that high Q-factor is responsible for spontaneous emission coupled with radiation field amplification, becomes questionable. Classical electromagnetic theory implies that when a random voltage due to spin noise is present in an open-circuit coil, the amplification factor in the radiation density in the coil derived by Bloembergen and Pound[8] becomes very low and cannot be detected. Hoult et al.[7] devised an experiment where spin noise was observed in the same manner as free induction decay with a high input impedance preamplifier connected directly to a receiving coil in form of an open circuit. At the time of explaining origin of spin noise and free induction decay, previous approaches taken by Slater et al.,[4] Ernst et al.,[5] and Gureon et al.[6] were expanded in light of well established Fluctuation dissipation theorem, which is a standard way of approaching the calculation of any noise phenomenon. Here, certain characteristics of stochastic processes were emphasized as mentioned by Helstrom.[9] According to this, whenever

a mechanism converts coherent energy in heat, that same mechanism manifests a randomly fluctuating force while the system is in thermal equilibrium. The spectral density of the induced force is proportional to the same constant, as it determines the rate of conversion of work into heat. Hence, an application of voltage to a coil causes a current to flow that current produces a near magnetic B_1 field, which causes the NMR active spins to absorb energy and subsequently be turned into heat. During this time a random electromagnetic fluctuation is induced in the coil by the same near magnetic field by means of Faraday induction. Thus, Hoult et al.,[7] with help of the Fluctuation Dissipation theorem, proved that spin noise is a near-field phenomenon. All the previous results were in agreement as the magnetic field B_1 field used in continues wave saturation experiment were near field. Spectral density function of the induced electromagnetic field measured as spin noise was identical to the previously mentioned model of enhanced spin emission coupled with cavity modes. Earlier spin noise was restricted to be relevant for conceptual understanding only, and practical importance for conventional NMR was considered unlikely as at that time it could only be detected for extremely strong resonance lines. Intrinsic properties like spontaneous emission and the coupling of the spins to the cavity modes of the receiver could be explained in details as suggested by Sleator et al.[4] Further measurement of spin noise can determine resonant frequency and line-width for specific samples whose longitudinal relaxation rate is too high and conventional techniques fail. In recent years, spin noise is found to have profound implementation in wide spread areas ranging from MRI (Magentic resonance imaging), to bio-molecular NMR, and solid state NMR.

Spin noise is clearly the deciding factor for sample size in lower scale and has lot more opportunities compared to conventional NMR. This is best illustrated by the following example. In a 0.8 ml liquid sample of 2 mM ^{13}C labeled organic compound, there are 10^{18} target spins considering carbon of interest per molecule. At room temperature and at 125 Mhz, if single-quantum ^{13}C NMR desired, sample's magnetization (M) can be calculated using the Curie law

$$M = (Nh\gamma/4\pi) * \tan h(h\gamma B/4\pi k_B T)$$

N is spin density (10^{18}), T is temperature, γ is magnetogyric ratio and B is static field. The polarization can be approximated at high temperature to ($h\gamma B/4\pi k_B T$). In this case, polarization is 10^{-5}. As the sample contains total 10^{18} spins and the equilibrium polarization is 10^{-5}, sample magnetization detectable becomes of 10^{13} spins. Being the gyromagnetic ratio ½, the situation implies that each magnetic moment has close to equal probability of possessing either +1 or −1 nuclear moment to the magnetization while polarization is much less than unity. According to Bloch's prediction, the uncertainty in initial magnetization is proportional to $\sqrt{N}$, which will derive spin noise. In this case, spin noise magnetization comes from 10^9 spins, which is only 0.01% of equilibrium magnetization. This is the reason that spin-noise was restricted to limited applications in NMR as the current detection schemes are applicable to sample of 10^{16} or higher number of spins. In this regime, equilibrium polarization dominates noise polarization. However, the situation is completely reversed for low spin numbers. Considering a case of 10^5 spins (~nm nl sample), equilibrium magnetization at room temperature at 125 MHz field corresponds to that of only one spin on average as polarization is still 10^{-5}. However, the noise magnetization comes from ~316 spins, which is more than 300 times larger than equilibrium magnetization even in the case of no instrument noise.

In this direction lot of effort is on currently, which aim at coupling optical spectroscopy and NMR. The principle is somewhat related to principle of Magnetic Force Resonance Microscopy (MRFM). In MRFM, ideas of Magnetic Resonance Imaging (MRI) and Atomic Force Microscopy (AFM) are jointly implemented.[10–14] MRI/NMR spectroscopy measures nuclear magnetic moments present in a sample, placed in a strong static magnetic field to produce a Zeeman splitting between nuclear spin states. The energy difference is measured in the perpendicular plane by radio-frequency irradiation with matching frequency. In classical point of view, net magnetic moment of sample changes its orientation and comes in the perpendicular plane and induces a tiny voltage in the receiving coil. The signal is amplified and is proportional to the number of nuclear spins. The net magnetic fields produced are small which makes NMR/MRI less sensitive compared to optical ones. MRFM attempts to improve sensitivity by mechanically detecting the magnetic forces produced by nuclear moments. Here a cantilever is used to sense magnetic forces arising between nuclear spins of the sample and ferromagnetic material of the tip, which act as nano-magnet. As the tip comes close to the sample, nuclear spins generate a small force on the cantilever. The spins are then repeatedly flipped using techniques of conventional NMR by flipping the direction of static field, which results in

generation of an oscillating magnetic force acting on the cantilever. The cantilever's mechanical oscillations are measured using beam deflection detector. The electronic signal emerged is proportional to the cantilever oscillation amplitude and the number of nuclear spins excited in the thin slice of the sample volume. This gives rises to spatial resolution as varying the radiofrequency alters the slice thickness as a function of position, and thus imaging becomes possible. Scanning the sample in various directions by varying resonant region, a complete spatial map of spin density can be achieved. Compared to the inductive coil approach, MRFM sensitivity increases as device and sample dimensions are reduced.[15–19] MRFM devices are cryogenically cooled, as in the low sample regime; Brownian motion is the primary source of noise. This makes MRFM a challenging experimental technique since low temperature and vacuum is a pre-requisite. Although remarkable NMR and MRI measurements at low spin number, even down to a level of detection of single electron have been achieved,[20–22] drastic sample condition limits the generality of the approach. The field is on-going and the sensitivity gain in current MRFM is 10^7 times better than the first report already.[19]

Meanwhile several new approaches are evolving based on coupling of other techniques, keeping the samples magnetic interaction with the probe intact. One very recently proposed technique utilizes a single Nitrogen-Vacancy (NV) center in diamond as atomic size magnetic field sensor, and widens the application potential as it works under ambient conditions. This NV center is a defect in the lattice of the diamond, consisting of nitrogen atom and adjacent vacancy. The spin state can be polarized and read out optically as it emerges red fluorescent glow, which can vary on the nature of electrons spinning in nitrogen-vacancy centre. This enables the single NV center to be used as nanoscale magnetic field sensor, which can detect magnetic field in nanotesla range[23–25] corresponding to the field of a single nuclear spin at a distance of a few nanometers.[26] Detection of single ^{13}C nuclear spins as well as[27–29] proton (^1H) nuclear spins in small sample has been achieved.[30] The sample size can go as low as $(5\ nm)^3$.[31]

Recently, Smith et al.[32] showed measured spin noise effect to perform perturbation-free magnetic resonance. In their experiment, off-resonant Faraday rotation was used passively to detect spin noise from an equilibrium ensemble of paramagnetic alkali atoms (Rb). The random fluctuations of the spin system generated spontaneous spin coherences. The frequency of

precession and characteristic relaxation timescale remain same as induced by the macroscopic magnetization of a perturbed polarized sample. Many fundamental properties like g-factors, nuclear spin, isotope abundance ratios, hyperfine splitting, nuclear moments and spin coherence lifetimes were obtained from correlation spectra of the spin noise. Since all these parameters were obtained without perturbation of the system by any means away from thermal equilibrium and these noise signatures scale inversely with interaction volume, it could lead to towards magnetic resonance of small and delicate systems, which is non-invasive and non-perturbative in nature. So the common perception about utility of noise in experimental measurements is changing, since many fundamental noise sources contain valuable information about the system itself. Inherent voltage fluctuations represented as Johnson noise, allow one to measure the temperature.

In addition to recent developments in the field of transverse nuclear spin noise from both theoretical and application aspect, much effort has been attempted on the transverse nuclear spin noise, which is directly connected to NMR and MRI. Seminal contributions came from Müller, Jerschow and Desvaux in this direction. Novel applications appeared in the field of MRI, where imaging was achieved without the requirement of any external electromagnetic irradiation in radio frequency range.[33] Only spontaneous spin noise from the sample was acquired as data in a coupled, highly tuned rf circuit. The major advantage was no requirement of rf irradiation and temperature independence as spin noise signals are inherent property of the spin ensemble, and hence the requirement of population differences between the nuclear spin states were avoided. Although these spin noise signals were weak, highly sensitive commercially available NMR spectrometers, equipped with a cryogenically cooled probe,[34,35] made the detection possible. In a typical 'cryo-probe', the rf coil and the preamplifier unit are cooled to ≥30 K and ≥77 K respectively, reducing Johnson Nyquist noise contribution, while keeping the sample at ambient temperature. Spin noise signals have a random phase, and hence novel accumulation and processing protocols were developed for image reconstruction. Although the application of magnetic field gradients is required to obtain spatial encoding, no rf pulses or irradiation were used and fast switching of magnetic field gradient were also not required. This approach solves a long withstanding problem in MRI of deposition of applied rf power in form various pulses like excitation pulses, refocusing pulses or

decoupling pulses in sample as a result of resistive losses.[36] A direct consequence is heating due to thermogenic properties of the electromagnetic and various other effects of rf irradiation on living cells or tissue,[37,38] which leads to establishment of strict safety regulations for medical applications of MRI,[11,39] restricting applied rf power limit to control the energy deposition in patients and medical staff. This is the reason MRI at higher magnetic fields, which is suited for higher sensitivity and resolution, cannot be used for safety concerns as the amount of rf power deposition in sample increases rapidly as second power of the rf field strength which varies linearly with magnetic field strength. This spin noise imaging removes the rf power deposition factor and is extremely useful for very delicate sample like forensic and explosives.

Since nuclear spin noise is correlated by nonlinear coupling between bulk magnetization and the coil through radiation damping,[40] hyperpolarized sample was used to enhance the radiation damping factor, which leads readily observable nuclear spin noise spectra. This observed spin noise additionally allows determination of longitudinal (T_1) and transverse (T_2^*) self-relaxation times, which would otherwise be biased as rf pulses in classical detection schemes, since this would destroy the hyper-polarization. Also, since radiation damping is solely dependent on the coil specifications and spin concentration, use of this dilute hyperpolarized sample leads to access to various new applications in spectral and dynamics characterization involving low spin number in NMR and MRI. In combination with hyperpolarization, use of microcoils leads to sensitivity enhancement of about two orders of magnitude for spin noise spectra. Using this combination, spin-noise spectrum of a solution containing 8 mML^{-1} ^{129}Xe was obtained, corresponding to a noise detection of about $4*10^{16}$ spins, which is below the detection limit at thermal equilibrium by conventional NMR. Implementation of 50 mm diameter solenoid,[41] this spin concentration limit comes to a threshold of about $7*10^{11}$ hyperpolarized spins, which is remarkably below the sensitivity limit of the classical pulse scheme. Since noise detection is primarily dependent on radiation damping contribution, this is more efficient for small samples in a magnetic field independent manner.

Recently, systematic investigations of line shapes in proton nuclear spin-noise spectra were done for assessment of the fundamental properties of spin-noise by group Muller et al.[42] It was found that line-shape depends on various factors including resonance circuit characteristics, total number of spins, transverse relaxation, inhomogeneous broadening and radiation damping etc. After recording a ^{1}H spin-noise power spectrum of a solution of 80% iso-propanol in DMSO, dispersive-like line-shape was observed, which was most dominant in CH_3-region. Baseline is determined by the thermal circuit noise power. Additionally, relative integrated peak areas were not consistent with the number of nuclei as maintained in conventional pulse NMR. The amplitude of ^{13}C-satellites of the methyl groups was much higher than expected natural isotope abundance. Formulation of McCoy and Ernst[5] was adapted to explain the data. According to this, spin-noise signal can be a negative deviation or 'dip' from the otherwise flat baseline, if the tuning frequency of the rf circuit (ω_c) was equal or close to the Larmor frequency. Although most of the features could be explained satisfactorily, some discrepancies remain unsolved. Experimentally, spin-noise signal showed large tuning dependency. At a considerable offset, the spin-noise spectrum showed a symmetrical dip and this was termed as Spin-Noise Tuning Optimum (SNTO), which varies considerably between different probes. SNTO is independent of the sample properties such as polarity and temperature.

The non-linearity of spin-noise signal amplitudes was studied at various concentrations to probe the effect of number of spins. Base line is positively offset due to the thermal/Johnson noise background of entire electronics circuit, a negative peak or dip in a spin noise spectrum represents less noise situation and a positive peak or bump means more noise situation than thermal noise level. Non-linearity of the spin noise power spectrum is most apparent at high spin concentrations where the effect inverts its sign. By simulating according to McCoy and Ernst,[5] the influence of the spin numbers, radiation damping rate, sample and circuit temperature were assessed successfully. Simulation concluded that for appearance of a dip in the spin-noise spectrum at equilibrium depends on the radiation damping rate, transverse relaxation rate and ratio between sample temperature and circuit temperature. For a room-temperature probe, this temperature ratio is unity and hence there should always dip will arise under SNTO conditions. However for cryogenic probe, circuits are kept at very low temperature while the sample is kept room temperature. Here the relative amount of the temperature ratio, transverse relaxation time and radiation damping rate determines whether there will dip or bump and both the features will appear together. This was observed experimentally also. Room temperature

probe displays dip for all signals whether for cryogenic probe both bump and dip were observed, and dip was observed for the most intense signals from the methyl groups as this satisfied the condition for a dip spectrum due to the high proton density. Simulations also explained correctly the effect of T_2, which is mediated by decrease in the negative broad component and an increase of the positive component as T_2 is decreased. When T_2^* is very small than radiation damping rate, spin-noise power becomes linearly dependent on spin concentration. Earlier observation by McCoy and Ernst,[5] in which saturation of NMR signal prior to the acquisition of noise spectrum removed the negative component was attributed to the increase in spin temperature, and similar transitional behavior for cryogenic probes was also accounted for. Small frequency shifts were observed for samples with narrow lines, and this shift is also dependent on extent of tuning offset and total amount of sample polarization. Although for exact SNTO conditions, for an ideal probe, no concentration dependent frequency shift should be observed. However in reality, non-ideal nature of rf-circuit makes a substantial difference in the zero frequency shift tuning position and the spin-noise dip and complexity of the situation increases. The strong appearance of ^{13}C-satellites was attributed to strong radiation damping rate, which leads to a non-linear distortion of line-shapes and results in reduction of central peak intensity. Though qualitative explanation were obtained for the spin-noise spectra by the formulation of McCoy and Ernst,[5] some asymmetries due to frequency shift in the spin-noise spectra remain elusive, and these discrepancies between theory and experiments were attributed to non-ideality of probe rf-circuits. Till date, this is the most systematic investigation concerning the detailed features of spin noise spectra and this again corroborates the fact that detection of small signals are much easier by spin-noise measurement by virtue of strong appearance of ^{13}C-satellites compared to main signal.

Spin-noise phenomena are very useful for testing rf-probes for performance optimizations. The earlier mentioned spin-noise tuning optimum depends on circuit tuning characteristics and the electronic component properties, and has to be determined for each probe individually, which leads to optimum signal receiving condition. Marion and Desvaux[43] used this property as an alternative tuning strategy for NMR. Muller et al.[44] reported a ~50% increase of the Signal-to-Noise Ratio (SNR) for an aqueous sample under SNTO conditions. The increase in SNR was found to be due to the main increase in signal, keeping noise level largely unaltered as tuning position changes. This was recently shown to be extremely useful for achieving sensitivity enhancement by spin-noise aided tuning for various multidimensional bio-molecular NMR experiments. An enhancements in the range of 7–22% was achieved for various basic triple resonance experiments like HNCO, HNCA, CBCACONH etc.,[44] which are a prerequisite for any resonance assignment and structure determination for macromolecules. The gain in sensitivity could lead to time savings of up to 49%. For these experiments, over a considerable temperature range (~5–50°C), which is typical bio-molecular samples, SNTO largely remains unaffected. Since ionic strengths, conductivities of buffers are known to affect probe tuning, matching and pulse performance[45–47] signal enhancement at the SNTO, are expected change with salt concentration as well. It is worthwhile to mention that high salt concentrations in biological samples decrease the sensitivity significantly, particularly in case of cryogenically cooled probes. It was noted that in absence of salt in the sample, a noise gain ~25% was attainable with SNTO. With addition of 100 mM NaCl salt, signal-to-noise gain ~20% was achieved. Although spin-noise tuning optimum frequency was shifted ~100 kHz away from the transmission optimum, which increases pulse-width nominally, there was substantial gain in signal-to-noise ratio for all recorded multidimensional spectra. The tuning offsets for SNTO for ^{1}H detected experiments are probe specific and optimization the tuning offset, which is pretty straightforward as no additional change is required in existing hardware, under specific conditions, by merely observing the spin noise signal from solvent, can considerably decrease the acquisition time for bio-molecular NMR experiments owing to sensitivity enhancement.

Demonstration ^{1}H-NMR spin noise signals from solid samples were done recently under static and magic-angle spinning conditions. The earlier work considering the origin of characteristic spin noise signals in terms of line shape, noise level and tuning dependence remain same as observed in case of liquid state NMR.[42] When experiments were performed in static situation in high-resolution cryogenically cooled probe, noise signal showed a bump, which indicates dominance of pure spin-noise compared to absorbed circuit noise[48] as short transverse relaxation times competently quench radiation damping. The spin noise line shape in case of magic angle spinning depends on tuning, and also substantially on the matching adjustment and the preamplifier. Significant de-matching, though, could lead to the

SNTO. The spin-noise tuning optimum offsets are not influenced significantly by the sample properties for solid. It was observed that spin-noise tuning optimum is nearly identical for liquid H_2O and solid adamantane. This leads to the conclusion that determination of spin noise tuning offset only once for a particular probe/preamplifier pair is sufficient for its best performance. At spin-noise tuning optimum conditions, the signal in the case magic angle spinning spectra can be improved ~20–30% compared to conventional tuning conditions. This implication was recently reported by Rossini et al.[49] for improvement in nuclear quadrupole resonance spectra of ^{75}As and ^{35}Cl. Recently, spin noise in ^{1}H NMR of liquid water samples were detected that was hyperpolarized by dynamic nuclear polarization, which increase noise amplitudes owing to an enhanced coupling with the reception circuit. This dynamic nuclear polarization approach can lead to enhancement up to ~1000 for conventional ^{1}H NMR samples, as well as is routinely employed to hyperpolarize dilute ^{13}C or ^{15}N spins in metabolites. The main conclusion was that the dynamic nuclear polarization leads to the enhanced of noise signals as demonstrated by recording power spectra from very low-concentrated samples, which is pre-enhanced by dynamic nuclear polarization. The main reason is that polarization enhancement results in an increased coupling of the fluctuating signals with the rf-circuit, manifesting increase in the sample noise. Since at microscopic levels, it is exceedingly difficult to delineate the radiation-damping phenomenon, noise originating purely from rf-circuit and spin ensemble respectively, as the former two are present in any measurement process,[50] this dynamic nuclear polarization approach is utilized in understanding the underlying fundamental physics as this can detect pure spin noise characteristics. Moreover, recently, spin noise was detected for nuclei other than ^{1}H.[51]

The situation described clearly indicates the immense potentiality of spin noise NMR in less sample concentration regimes, which can be as low as ~10^7 spins. NMR measurement of sample containing 10^9–10^{12} spins can widen the horizon of application side as molecular monolayers, and other surface species can be probed in this scale. This leads to the development of magnetic resonance force microscopy—an emerging field now. When MRFM is not dependent on field gradient in the sample volume is based upon principal called Better Observation of Magnetization, Enhanced Resolution, and No Gradient (BOOMERANG),[11] which is the most used method of acquiring data. Unlike longitudinal component, developments

of spin noise NMR, which deals with transverse component, is adequate for probing at the micron scale, and can be extremely beneficial in virtually all kinds of problems in materials science, catalysis, and biochemistry, which provide sufficient motivation. Although there have been remarkable development in MRFM, it is far from being a commercially routine method, as the need for exhaustive set-up is required and has limited application potential. With improvement of NMR detection schemes, spin noise NMR, however, can lead to a situation in the context of very high sensitivity, where structures of large biological macromolecules can be obtained at microlitre and nanomolar level in physiological condition, which can be of pivotal importance. Hence, multidimensional spin noise NMR becomes extremely important from both theoretical understanding (the nature of various interactions, i.e. coupling, chemical shift etc, present in the system) and application wise.

In the present context, multidimensional spin noise NMR was reported as a proof of principle recently.[52] Since fluctuating transverse spin-noise has random phase, noise blocks have zero expectation value due to cancellations. Only averaging over the signal magnitude or power has been used for signal accumulation, which was done by Fourier-transforming and adding the power spectra of noise blocks. The aforementioned procedure is equivalent to taking Fourier-transform of the autocorrelation or Fourier-transform followed by autocorrelation as described by the Wiener-Khintchine Theorem (WKT). These procedures can be used to get rid of random phases, which are characteristic of noise signals. The basic scheme for two-dimensional Fourier-transform spin-noise NMR is shown in Figure 1.

The acquisition and processing is based on 'correlated observations narrow quantum uncertainty enhancing spectroscopic transients' (CONQUEST) principle[53] used previously in BOOMERANG procedure. Like conventional 2D NMR method, a delay is implemented between two pulses, which gets incremented during successive repetitions. The inherent spin magnetization, which survives the evolution period, is measured. In CONQUEST, a second period of driving is inserted before the first pulse, which is before the incremented delay. The fluctuations in magnetization before and after the pulse-evolution-pulse sandwich are cross-correlated and resultant fid provides direct dimension, while the indirect dimension is the incremental delay. Two noise blocks, (t_0) and (t_2) are recorded in similar fashion as in CONQUEST scheme. Between the two noise blocks an
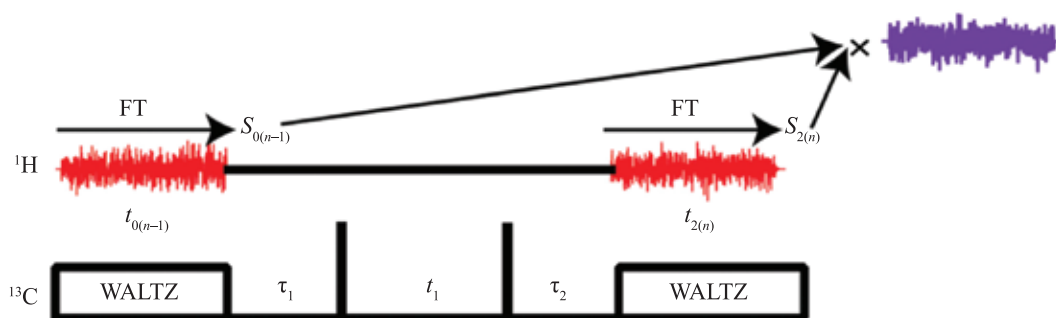
Figure 1: Acquisition scheme for spin-noise-HMQC(snHMQC). The basic scheme contains an evolution time t_1 sandwiched between mixing periods (τ_1 and τ_2) and two noise acquisition periods (t_0 and t_2). In the acquisition period, noise blocks (t_0) and (t_2) are acquired.

evolution period (t_1) is inserted as usual in multi-dimensional NMR, sandwiched by two mixing periods. Cross-correlating noise blocks (t_0) with (t_2) either in frequency domain or time-domain yields a fid for each t_1 value, like a conventional two-dimensional time domain NMR data set that can be processed in the usual manner by Fourier-transformation. A critical factor is that the cross-correlation has to be done prior to signal averaging to nullify the random phase contribution. The ^{1}H spin-noise detected HMQC experiment is shown in Fig. 1, correlates spin-noise detected ^{1}H chemical shifts with heteronuclear multiple-quantum coherence, and requires no rf-pulses on the ^{1}H channel. During the first acquisition period t_0 a ^{1}H noise block is recorded with decoupling still on in ^{13}C channel, and only chemical shift of ^{1}H spin noise is encoded with random phase. After the end of the first acquisition period, decoupling is turned off. The surviving coherences, which are exceedingly small that arises from the incomplete cancellation of spin-noise transverse components, start evolving under heteronuclear coupling constant. After the end of the τ_1 (1/2J) period, anti-phase magnetization is generated. The subsequent 90° hard pulse on ^{13}C channel generates super-position of double-quantum and zero-quantum coherences, which get frequency labeled during t_1. The second 90° pulse generates observable single quantum coherence of ^{1}H-spins, which is anti-phase. After the second τ_1 delay this is refocused to in-phase transverse magnetization. Since pulse is absent in ^{1}H channel, various random phase contributions arise, namely from spin-noise and noise other than spin-noise originating during the pulse sequence. Among all these, spin-noise signal undergoes laws of coherence as explained before. The desired signals can be filtered out from the data in two measurement blocks for each t_1 by calculating the correlation function either in time

domain or frequency domain, which is equivalent according to WKT. In this case, first Fourier-transform was performed for individual noise blocks (S_0 and S_2 respectively), and then multiplied with the complex conjugate to generate the correlation function. This results in various cross-terms containing random phase contributions. Only one single term contains square of random amplitude that represents correlated signals and increases linearly with the number of co-added cross-correlated data blocks; all other uncorrelated terms grow with square root with number of data blocks. So signal averaging results in building of this correlated signal over the uncorrelated ones. Total duration of the first acquisition block, the pulse sequence and the second acquisition block should be less than transverse relaxation time in order to correlation to be obtained. A further Fourier-transform with respect to t_1 gives the correlation peaks of interest and generates two dimensional spectra. Heteronuclear cross-peaks are obtained at frequency ($\Omega_{1H} \pm \Omega_{13C}, \Omega_{1H}$). Using this scheme, spin-noise detected two-dimensional HMQC (snHMQC) spectrum of 99% ^{13}C enriched glucose in ^{2}H$_2$O. Since, correlated signal is inherently weak, 6000 experimental data were co-added. It is worthwhile to mention that, since there is no effect of ^{1}H longitudinal relaxation time T_1, repetition interval of spin-noise detected experiments can be as low as allowed by hardwire configuration and acquisition schemes can be very fast. Still signal-to-noise per unit time is very low compared to pulse excitation spectra, as cor-related noise contribution is very less compared to uncorrelated noise and requires high amount signal averaging. As mentioned earlier, in low spin number regime, this noise magnetization exceeds equilibrium magnetization observed by conventional NMR by several orders, and in such cases, only this type of acquisition scheme will work.

Spin-noise NMR is thus, gaining importance as it has the power to take NMR at nano scale. The recently proposed noise-correlation principle can open up possibilities of large range of multi-dimensional magnetic resonance experiments to be acquired in similar fashion. Existing coherence transfer pulse sequences can be converted accordingly. With concurrent developments in the sensitivity improvement, all these approaches can lead to potential application at nano-scale (10^8 nuclear spins). To enhance the sensitivity, some application of refocusing rf-pulses are possible on observed channel at this scale, as coherence generated will be less than equilibrium-polarization governed by Coorie law. All these features make spin noise detected magnetic resonance techniques demanding and continue to attract detailed attention for future developments to probe at nano-scale.

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Dr. Kousik Chandra 1981. M.Sc. (2004) in Chemistry from Banaras Hindu University, Varanasi and Ph.D. (2011) from Tata Institute of Fundamental Research, Mumbai. Had postdoctoral experience at Indian Institute of Science (2011–2012) and Johannes Kepler University, Austria with Lize Meitner Fellowship (2012–2014). Currently at Indian Institute of Science as DST INSPIRE Faculty. Research interests include development of nuclear magnetic resonance methodologies for various applications which include function and dynamics of macromolecules and noise spectroscopy.