



Chemical Exchange Rate Study by NMR CPMG Method

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Abstract

Analysis of the NMR CPMG method is presented that enables direct sampling of the spectral-density function of the chemical exchange processes. The approach is demonstrated on a solution of sucrose in water. The result confirms that the method can provide insight into the details of the dynamics of molecular conformations beyond a single-parameter description by an exchange rate. The results of the method are not limited to a single exchange process but can be of advantage if a large and potentially unknown number of exchange processes is contributing to the dynamics of a spin system.

1 Introduction

Various nuclear magnetic resonance (NMR) methods, which manipulate spins to convey information about their environment, i.e., the structure and dynamics of matter, are used in chemistry, physics, material science, biology, and medicine. In NMR studies of liquid dynamics in the sub-MHz frequency range and at high temperatures, we assume that the rapid molecular motion on the pico- or nanosecond time scale completely cancels out both near- and long-range spin dipole–dipole interactions and first-order quadrupole interactions [4], if not taking into account their effect on the spin-relaxation times. However, we cannot neglect interactions of spins with electrons in molecular orbitals, i.e., the chemical shift of spectral lines, nor the indirect dipolar interaction between spins in different molecular conformations mediated by electrons of molecular orbitals, i.e., the line splitting by J -coupling. In liquids, direct couplings are usually averaged out, but we also have to take into account the effects of molecular and chemical dynamics causing fluctuations

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in interactions of spins with magnetic fields induced through electron orbitals. Particularly useful for the study of correlation functions of these fluctuations is the Carr–Purcell–Meiboom–Gill sequence (CPMG) [6, 16] with a train of π radio-frequency pulses. The sequence was originally introduced to provide reliable spin-relaxation measurements by eliminating the spin echo attenuation effect created by the spin motion in an inhomogeneous magnetic field of unshimmed magnets. Later on, it turned out that the modulated gradient spin echo (MGSE) method [5, 18], which combines CPMG with an inhomogeneous magnetic field, characterized by the magnetic field gradient (MFG), provides a direct insight into the spectrum of the molecular velocity auto-correlation. This spectrum is the key dynamic quantity of molecular translational motion and contains details about the underlying nature of molecular interactions. While interpreting the method, we commonly assume that the effect of a strong MFG dominates over all other interactions. But in the case of measurements in weak MFG [19], which can be generated by magnetic impurities or weak magnetic susceptibility mismatch at the interface, these interactions must be taken into account.

In this paper, we consider a rather unexplored phenomenon related to interactions associated with fluctuations in molecular conformations, which leads to the temperature dependence of high-resolution NMR spectrum of liquids. This phenomenon was initially explained by random motion among various molecular spatial orientations [9] and later as a nuclear exchange between states in different molecules or intra-molecular conformations. Now, it is in NMR commonly considered as the chemical exchange, which refers to processes in which the fluctuation of molecular conformation affects NMR parameters (chemical shift, scalar coupling, dipolar coupling, relaxation rate). Measuring chemical exchange with NMR has become a powerful tool of following molecular kinetics in solutions, either by measuring splitting and broadening of lines in NMR spectroscopy [3] or by measuring the spin echo decay [11]. The two-dimensional NMR EXSY experiment is used to analyze systems undergoing slow and intermediate exchange processes that occur prior to the coalescence of spectral lines and have a rate of exchange lower than the difference in Larmor frequencies between the two states. On the other hand, CPMG echo train decay allows us to study the dynamics of chemical exchange in an extended rate range on both sides of the coalescence condition, as the spectral line shape analysis becomes inaccurate at both rate extremes. In this paper, we present a description of the CPMG spin echo method of chemical exchange measurements.

2 Spin Echo in Liquids

Thermally induced molecular and chemical dynamics cause spin parameter fluctuations, which are usually analyzed in a quasi-classical manner using the Bloch–Torrey equation [21] for NMR diffusion measurements and the Bloch–McConnell equation [15] for chemical exchange. Such an approach cannot reveal details that can only be obtained within the framework of frequency domain derivation. Similar to how the frequency domain treatment of the MGSE method reveals the possibility of studying the molecular translational dynamics in an inhomogeneous magnetic field, it also

provides insight into the correlation function of chemical exchange in the case of transfer between molecular isomers [1, 10]. Since the theoretical analysis of this method is not essential for understanding the measurement results and their analysis, we have included its brief discussion in the Appendix.

Let us consider spins that experience Larmor precession frequency shifts $\Delta\omega$ due to molecular dynamics. The shifts can be caused by molecular translation in MFG: $\Delta\omega = \gamma\mathbf{G} \cdot \mathbf{r}$. Another mechanism is chemical exchange which involves the fluctuation of molecular conformation by the making and breaking of chemical bonds. Both, chemical shifts and J -couplings can change when exchange process takes place. In the case of exchange between two states A and B, the changes are discrete: $\Delta\omega = \gamma B_0(\delta_A - \delta_B)$ or $\Delta\omega = \frac{2\pi}{h}J_{IS}$. The changes between the two states are random and to the first order described by the appropriate rate constant k or spin–lattice relaxation time constant T_1 . The phase of a spin in an ensemble in the frame rotating with the Larmor frequency of one of the states is given by

$$\theta = \int_0^t \Delta\omega(t')dt'. \quad (1)$$

The time dependence of frequency shifts is governed by two processes. One is random jumping between the states described by a step function $k(t)$ alternating between 0 and $\Delta\omega$ as shown in Fig. 1 (top), the other is an effective change in the frequency sign at the moment a π pulse is applied. This can be described by a function $b(t) = (-1)^{n_\pi(t)}$, which is shown for the first few pulses of a CPMG sequence in Fig. 1 (middle). Here, $n_\pi(t)$ is the number of π pulses applied up to the time t . The effect of RF pulses on effective frequency can be described quantum mechanically as shown in Appendix.

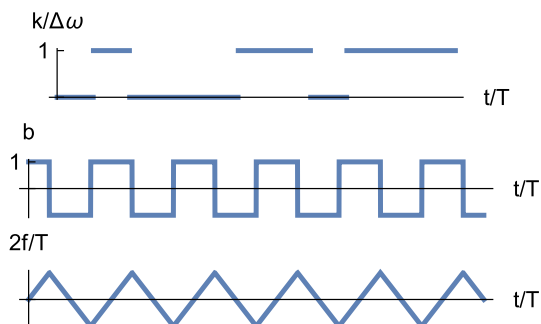
With these definitions, the frequency shift can be expressed as

$$\Delta\omega(t) = b(t)k(t). \quad (2)$$

The next step in evaluating the echo attenuation factor is to integrate the phase per parts:

$$\theta = \int_0^t \xi(t')f(t')dt'. \quad (3)$$

Fig. 1 The function describing the chemical state of a spin, randomly hopping between the two states (top), step function describing the change of effective frequency sign of the CPMG sequence (middle), and the integrated phase factor of the CPMG sequence (bottom)



Here, we have taken into account, that we are interested in the result at the time of a spin echo, when $f(t) = \int_0^t b(t') dt' = 0$, and we have defined a new variable $\xi = \dot{k}$. $f(t)$ of the first few pulses of a CPMG sequence is shown in Fig. 1 (bottom). Next, we sum the contributions of all spins in the ensemble to get the signal:

$$E = E_0 \sum_i e^{i\theta_i}. \quad (4)$$

The frequency shift is a stochastic variable and can be calculated for an ensemble exchanging between the two states with an appropriate ensemble average:

$$E = E_0 \langle e^{i\theta} \rangle. \quad (5)$$

It is straightforward to extend the problem to several ensembles exchanging between several states or indeed experiencing continuous change as in the case of self-diffusion in a MFG, e.g., [5, 18]. We can express the attenuation of the spin echo ($\beta = \ln(E_0/E)$) in the Gaussian approximation, if we evaluate the average in Eq. 5 with cumulant expansion and truncate it at the second term:

$$\beta(t) = \int_0^t dt' \int_0^{t'} dt'' \langle \xi(t') \xi(t'') \rangle_c f(t') f(t'') + \dots \quad (6)$$

In the next step, we express the time domain exchange auto-correlation function and RF-train factor $f(t)$ with their respective spectra:

$$\kappa(\omega) = \int_0^\infty \langle \xi(t) \xi(0') \rangle_c e^{i\omega t} dt \quad (7)$$

and

$$f(\omega, t) = \int_0^t f(t') e^{i\omega t'} dt' \quad (8)$$

and arrive at the expression for the spin echo peak attenuation according to Eq. 18:

$$\beta(NT) = \frac{1}{\pi} \int_0^\infty \kappa(\omega) |f(\omega, NT)|^2 d\omega. \quad (9)$$

The spectrum of the CPMG pulse sequence

$$|f(\omega, NT)|^2 = \frac{8 \sin^4 \left(\frac{\omega T}{4} \right) \sec^2 \left(\frac{\omega T}{2} \right) (1 - (-1)^N \cos(\omega NT))}{\omega^4}, \quad (10)$$

depends on the consecutive order of the echo N and time interval T between successive π pulses.

The reasoning behind the representation described in the previous paragraph is demonstrated in Fig. 2. The dashed line in Fig. 2 shows an example of chemical exchange spectrum $\kappa(\omega)$ with several distinct features such as its zero low-frequency value, typical peak, and its width. Superposed on this spectrum are

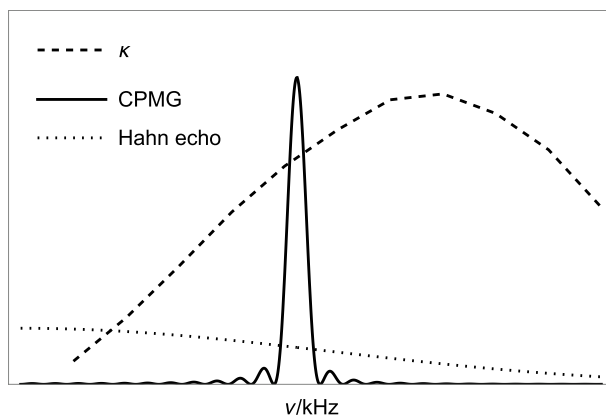


Fig. 2 The CPMG sequence spectrum with $N = 10$ and the Hahn echo spectrum with $N = 1$ shown as $|f(\omega, NT)|^2/N^{4/3}$ presented together with the predicted spectrum $\kappa(\omega)$

the spectra of a CPMG sequence (solid line) and a Hahn echo sequence (dotted line), which is the sequence with a single π -RF pulse. The spectra of the two RF sequences are calculated according to Eq. 10. The rate of the chemical exchange presented in the figure is such that the peak of the CPMG sequence spectrum is narrow compared to the chemical exchange spectral peak and thus the CPMG sequence acts as a natural exchange spectrum sampling function and no prior knowledge or model of the spectrum is needed for it to be measured. On the other side, the Hahn sequence spectrum is wide and not in the range of the main chemical exchange spectrum features. For the presented $\kappa(\omega)$, the signal attenuation is stronger when measured with the CPMG sequence than with the Hahn sequence. From this figure, we can understand how in the case of a slower chemical exchange rate, as the wide spectral lobe of $\kappa(\omega)$ narrows, and shifts towards lower frequencies, the lobe falls inside the spectral domain of the Hahn sequence, and outside the sensitive domain of the CPMG sequence. This reduces the spin echo attenuation measured with the CPMG sequence. With a very fast exchange rate, $\kappa(\omega)$ peak shifts to higher frequencies, completely out of the frequency domains of both RF sequences, which reduces the spin echo attenuation in both cases. This is commonly referred to as the NMR motion narrowing phenomenon.

Assuming that the frequency variation of $\kappa(\omega)$ is negligible inside the interval of the CPMG sequence spectral peak, which is determined by $1/NT$, we can approximate

$$|f(\omega, NT)|^2 = \frac{4NT}{\pi\omega_m^2} \delta(\omega - \omega_m) + \dots \quad (11)$$

with a peak at modulation frequency $\omega_m = \pi/T$. With this approximation, it is easy to get the contribution of the spin echo attenuation as

$$\beta(NT) = \frac{8}{\pi^2 \omega_m^2} \kappa(\omega_m) NT + NT/T_2. \quad (12)$$

This derivation shows that the decay of the CPMG spin echo train is directly proportional to the chemical exchange spectrum at the value of the spin phase modulation frequency. Therefore, $\kappa(\omega)$ is measured by changing the repetition time T of the π pulses. In this way the spectrum $|f(\omega, NT)|^2$ samples through the frequency range of $\kappa(\omega)$ to provide its frequency dependence through the decay rates of spin echo peaks.

However, we must note that this method might not provide the chemical exchange spectrum between just two molecular conformations. The echo attenuation can result from several exchange processes. In addition, we must not forget that the chemical shifts of all homonuclear spins in the molecule are refocused in the spin echo. Thus, the measured spectrum is the sum of many chemical exchange processes, with contributions that can only be distinguished by frequency analysis of the signals, i.e., by the high-resolution measurement of the NMR spectrum, where the area under the spectral lines gives us information about the spectrum of the chemical exchange.

3 Experiment

The measurements were carried out at room temperature of 21 °C using a Tecmag spectrometer with a 100 MHz (2.35 Tesla) horizontal bore superconductive magnet equipped with a homemade 5 mm i.d. pick-up coil. The sample was a 15 mm long, horizontal cylindrical cell with 5 mm o.d. filled with a 0.1 g/mL (10% w/v) mass concentration sucrose water solution. The complete echo train duration was set to 1000 ms and a series of 60 CPMG sequences with varying T was recorded, starting with 100 pulses up to 6000 pulses. The minimal number of pulses corresponds to $T = 10$ ms or $\omega_m = 314$ s⁻¹ and the maximal number to $T = 0.167$ ms or $\omega_m = 18.8$ kHz. Nominal RF power corresponded to 4.1 μ s long π pulse. The repetition time was set to 10 s. The train of echoes was fit to Eq. 12.

4 Results and Discussion

Echo trains for several different total numbers are shown in Fig. 3. A trend of decreasing relaxivity with increasing CPMG modulation frequency is clear. Two components corresponding to hydroxyl protons residing in water and in sucrose can be discerned in the echo train. Only the slowly decaying water signal was taken into consideration.

According to Eq. 12 a train with a given T and thus $\omega_m = \pi/T$ exhibits echo attenuation $\log(E) \propto -R_2^* t$ where $t = NT$ is the time of successive echoes and the

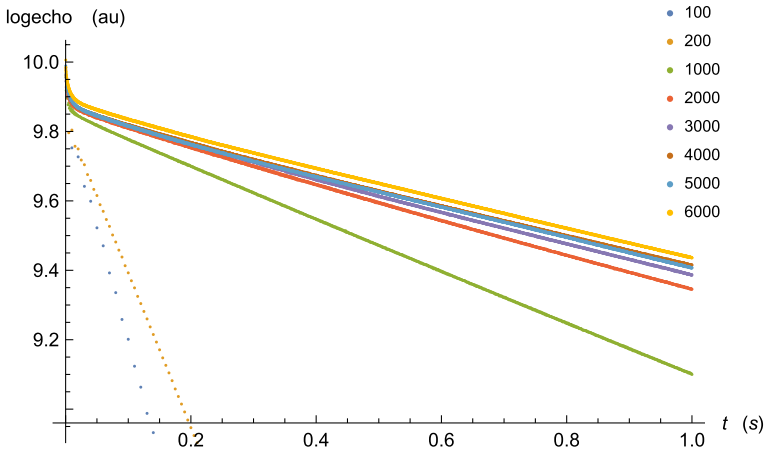


Fig. 3 Echo trains for several different modulation frequencies in 10% w/v sucrose measured by CPMG method. The slope of the graphs is the relaxation rate. Graphs show double exponential decay. The fast-decaying component belongs to protons of sucrose or water bound to it and was not considered in the analysis. Drop in relaxivity is clearly observed as the frequency of RF pulses is increased

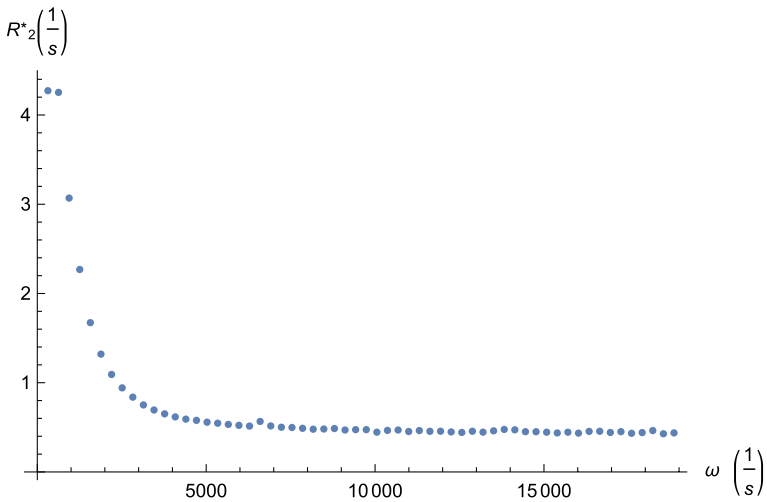


Fig. 4 Relaxivity of water in sucrose solution measured by the CPMG echo train shown as a function of the CPMG modulation frequency

transverse relaxivity $R_2^* = R_2 + \frac{8}{\pi^2 \omega_m^2} \kappa(\omega_m)$ is given by the transverse relaxation time $R_2 = 1/T_2$ and the chemical exchange spectrum $\kappa(\omega_m)$. Figure 4 shows the

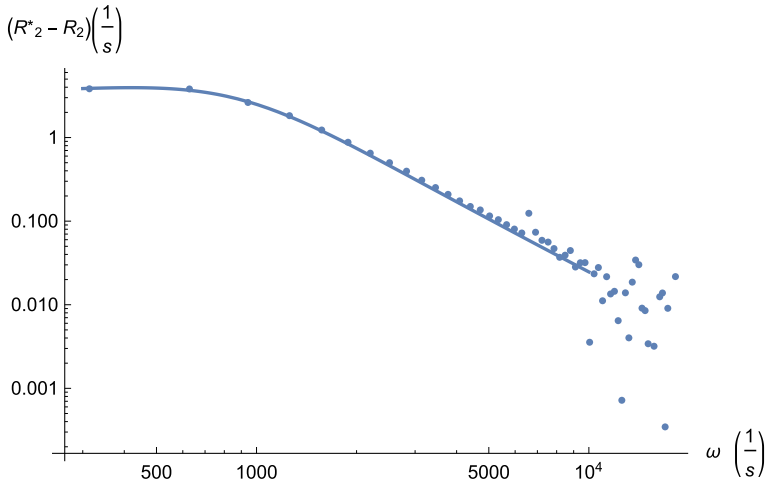


Fig. 5 Fit to the relaxivity residue given by model in Eq. 13 shown in a log–log scale

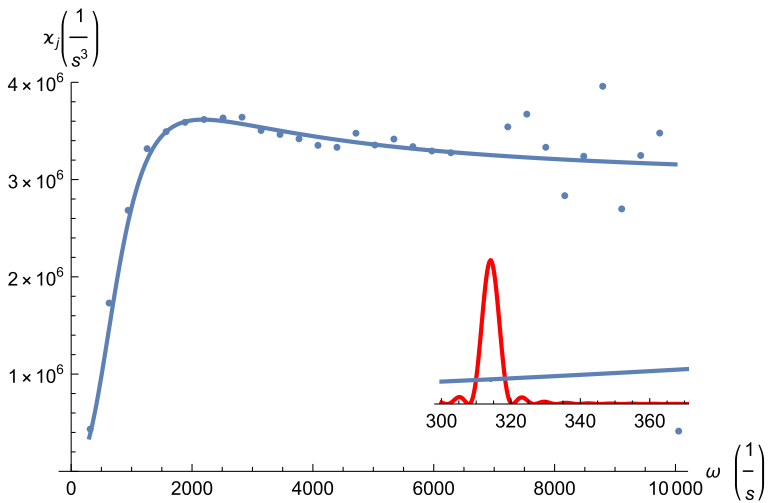


Fig. 6 Spectra of the chemical exchange rate in 10% w/v sucrose by the CPMG method. The inset shows an overlay of the spectrum sampling function $f(\omega, NT)$ in the case of the lowest modulation frequency, as the peak of the function is at its widest. It clearly shows the validity of the assumption, that frequency variation of the exchange spectrum is negligible in the interval of the spectral peak width of the CPMG sequence

measurements of R_2^* as a function of modulation frequency where it can be seen how the relaxivity levels off at high frequencies to the value $R_2 = 1/T_2 = 0.44 \text{ s}^{-1}$.

With these data, a fit can provide information on $\kappa(\omega)$, as shown in Fig. 5. Best fit gives the spectrum of chemical exchange fluctuation shown in Fig. 6 as

$$\kappa(\omega) = \frac{\alpha\pi^2\Gamma^2\omega^2}{8((\omega - \Omega)^2 + \Gamma^2)}, \quad (13)$$

where $\alpha = 3.95 \text{ s}^{-1}$, $\Omega = 420 \text{ s}^{-1}$ and $\Gamma = 760 \text{ s}^{-1}$. The spectrum fitting parameters are intricately related to frequency shift between different exchange sites and the exchange rate.

5 Conclusion

Proton NMR relaxation rates were measured in an aqueous solution of sucrose. CPMG pulse sequences with various RF-pulse rates were used for the measurement of relaxation rates. Comparable results of previous measurements [2] show that the values of relaxation rate increase as the concentration of the sugar is increased. The results were discussed on the basis of the molecular association between sugar and water molecules through hydrogen bonding. However, the shape of the spectrum reported here strongly deviates from the expected one, when $\omega^2\kappa(\omega)$ should have a Lorentzian shape in the case of chemical exchange determined only by the rate parameter k_{AB} , i.e., with only one exchange time τ_{ex} . It indicates much more complex dynamics of molecular conformations in the process of chemical exchange.

The experiment confirms the usefulness of the CPMG sequence to obtain information about chemical processes, such as chemical exchange, in liquids. The decay of the peak of the CPMG spin echoes, which gives the effective spin-relaxation time, is directly proportional to the value of the spectrum of the chemical exchange rate at the spin phase modulation frequency determined by the frequency of the CPMG π pulses. The method provides insight into the details of the dynamics of molecular conformations, which may also include chemical exchange with several molecules.

Appendix

Here, a detailed analysis of the CPMG echo train attenuation using the quantum mechanical concept is given. In NMR in liquids, the spins interact with the strong external uniform magnetic field aligned in the direction of z -axis causing the spin Larmor precession with frequency $\omega_0 = \gamma B_{z0}$. If B_{z0} is much larger than any other magnetic field in the sample, spin dynamics can be described with a Hamiltonian abbreviated for non-concomitant terms [20] as

$$\mathcal{H} = - \sum_{ij} [\omega_0 + \omega_{ij}(t)] \mathcal{I}_{zi} + \mathcal{H}_J(t) + \mathcal{H}_{rf}(t) + \mathcal{H}_L, \quad (14)$$

where i refers to a molecule in the sample and j to a spin in a molecule. Different spins experience different chemical environments and thus exhibit different precession frequencies. The deviation from the Larmor frequency $\omega_{ij}(t) = \omega_{C_{sij}}(t) + \gamma \mathbf{G} \cdot \mathbf{r}_{ij}(t) + \frac{2\pi}{h} \sum_h J_{ijh}(t) \mathcal{S}_{zh}$ contains the effects of chemical

shifts, translation of spins in the gradient field and heteronuclear J -coupling with the spins \mathcal{S}_{ij} . Homonuclear J -coupling is described in $\mathcal{H}_J(t)$. Interaction of spins with the RF field can be described as $\mathcal{H}_{rf}(t) = \mathcal{H}_{\pi/2}^x(t) + \mathcal{H}_{cpmg}^y(t)$. This Hamiltonian includes the initial excitation with the $\pi/2$ pulse that excites the magnetization in the transverse direction along the y -axis followed, after an intermediate interval $T/2$, by a series of π pulses applied at intervals T . This term can be written as $\mathcal{H}_{cpmg}^y(t) = -2\omega_\pi(t) \cos(\omega_0 t) \sum_i \mathcal{I}_{y_i}$, where $2\omega_\pi(t)/\gamma$ denotes the amplitude of the π pulses. Each π pulse rotates the magnetization around the y -axis by 180 degrees. The last part of the Hamiltonian, \mathcal{H}_L , includes all other molecular interactions, including the magnetization relaxation [13].

Complex spin dynamics under the influence of a sequence of RF pulses and different magnetic fields modulated by molecular dynamics can be solved using the Feynman operator calculus [7, 8], in which the Hamiltonian is transformed into successive interaction representations. Various interaction representations, including the transformation to a frame rotating with ω_0 and to a switching frame defined by $\mathcal{H}_{cpmg}^y(t)$ [5, 18] gives the effective Hamiltonian, with detailed derivation in [19].

If we consider isotropic fluid, then the indirect dipolar interaction tensor can be replaced by a scalar. And if we assume weakly coupled spins, and the differences in chemical shifts much larger than the J -splitting, then the fluctuation of the molecular conformations dominates the effects of the J -coupling fluctuation in the spin dephasing. Under these assumptions, we obtain an effective Hamiltonian that enables the calculation of the spin echo along the y direction in the first approximation as

$$\begin{aligned}
 E(t) &= \hbar\gamma \frac{d}{dt} \sum_{ij} \text{Tr} \rho_r(t) \mathcal{I}_{y_{ij}} \\
 &\approx \sum_{ij} \text{Tr} \mathcal{I}_{y_{ij}}^2 J_{s_{ij}}(t)^{n_j} e^{-i\Delta\omega_{ij}(t)f(t)} \left\langle e^{i \int_0^t \xi_{ij}(t')f(t')dt'} \right\rangle,
 \end{aligned} \tag{15}$$

by assuming uniform sensitivity of the detection coils [17]. We see that the signal oscillates with the frequency $\Delta\omega_{ij}$, which is also modulated by the factor $J_{s_{ij}}(t)^{n_j}$, as a result of the J -coupling and depends on the number of magnetically equivalent spins n_j with the spin number s . Fluctuations, due to chemical exchange and molecular motion in an inhomogeneous magnetic field, contain the time average of the factor, in which the spin phase is equal to the integral of the product of the function $f(t)$ defined by the π pulse sequence, and the frequency shift fluctuation rate $\xi_{ij}(t) = \frac{d}{dt} \Delta\omega_{ij}(t)$. If the fluctuation rate $\xi_{ij}(t)$ can be considered a random variable, the average in Eq. 15 can be expanded into a cumulant series. The series truncated after the first two terms is called the Gaussian approximation and is commonly considered a sufficient approximation for various physical processes [5, 14, 18]. In general, the sufficiency of the Gaussian approximation is determined by the condition $\Delta\omega\tau < 1$, where τ is the correlation time of the physical process, but by using phase

modulation of the spins with the CPMG sequence, the correlation time is replaced by the interval between CPMG RF pulses T , which allows for an external manipulation of the series convergence. In this approximation, the echoes at the moments of spin phase refocusing $t = NT$, i.e., at echo peaks when $f(NT) = 0$, are given by

$$E(NT) \approx \sum_{ij} J_{sij}(NT)^{n_j} e^{-\int_0^{NT} \int_0^t \langle \xi_{ij}(t) \xi_{ij}(t') \rangle_c f(t') f(t) dt' dt} \quad (16)$$

Since the auto-correlation function of the fluctuating term can be substituted according to Wiener–Khinchine theorem [12] by the spectrum of the term

$$\langle \xi_j(t) \xi_j(t') \rangle_c = \frac{1}{\pi} \int_0^\infty \kappa_j(\omega) e^{i\omega(t-t')} d\omega, \quad (17)$$

the attenuation of spin echo peaks can be written as

$$\beta_j(NT) = \frac{1}{\pi} \int_0^\infty \kappa_j(\omega) |f(\omega, NT)|^2 d\omega. \quad (18)$$

Here, $\kappa_j(\omega)$ can contain the spectra of all fluctuations: chemical shift, spin motion in the gradient field, and the J -coupling of hetero-nuclear spins. In the experimental results, we are focused only on the chemical shift fluctuation due to chemical kinetics in the exchange of hydrogen between molecules.

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Declarations

Conflict of Interest No conflicts.

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Consent to Participate Not applicable.

Consent for Publication Approved by the employing institutions.

Code Availability Not applicable.

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