Hyperpolarized Laplace NMR

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Laplace nuclear magnetic resonance (NMR), dealing with NMR relaxation and diffusion experiments, reveals details of molecular motion and provides chemical resolution complementary to NMR spectra. Laplace NMR has witnessed a great progress in past decades due to the development of methodology and signal processing, and it has lots of extremely interesting applications in various fields, including chemistry, biochemistry, geology, archaeology, and medicine. The aim of this minireview is to give a pedagogically oriented overview of Laplace NMR. It does not provide a full literature review of the field, but, instead, it elucidate the benefits and features of Laplace NMR methods through few selected examples. The minireview describes also recent progress in multi-dimensional Laplace NMR and Laplace inversion methods. Furthermore, the potential of modern hyperpolarization methods as well as ultrafast approach to increase the sensitivity and time-efficiency of the Laplace NMR experiments is highlighted.

KEYWORDS
diffusion, hyperpolarization, Laplace NMR, relaxation, ultrafast

1 | FOURIER TRANSFORM NMR

Nuclear magnetic resonance (NMR) spectroscopy is one of the most versatile analytical techniques used in various disciplines ranging from chemistry to medicine and materials science. A simple NMR experiment begins with a hard $\pi/2$ excitation pulse, which excites all resonances of one type of nuclei (such as $^1$H nuclei) in a sample. Thereafter, an oscillating time-domain free induction decay (FID) signal is observed (see Figure 1a).

If there are nuclei resonating at various different frequencies, the shape of the FID signal may be very complex, and it is impossible to see which frequencies it includes. However, the mathematical operation called Fourier transform converts the time-domain FID signal into a frequency domain spectrum (see Figure 1a). The peaks in the spectrum reveal the resonance frequencies of nuclei, and additionally, they reflect the relative number of nuclei having a particular frequency in the sample. Because the resonance frequency of the nuclei is dependent on their local chemical environments, the spectrum is like a fingerprint of the molecule under investigation, and therefore, it can be used for identification of molecules.

2 | LAPLACE NMR

NMR is one of the very few methods for measuring molecular self-diffusion coefficient, $D$, without introducing an invasive tag, even inside opaque samples. Relaxation experiments, in turn, reveal the rates of recovery of the initially perturbed magnetization to the thermal...
equilibrium, mainly due to the random rotational motion of molecules.\[^1\] The $T_1$ relaxation time reflects the rate of recovery of the longitudinal (along the external field) magnetization to its equilibrium value, whereas the $T_2$ relaxation time deals with the rate of decay of the transverse component. Therefore, the relaxation and diffusion experiments provide detailed information about molecular motions. Furthermore, they may offer chemical resolution not available in traditional NMR spectra.

Similar FID signals are observed in relaxation and diffusion experiments as in the measurement of a basic NMR spectrum, although in some cases, it may be a full echo containing both increasing and decaying signal parts. The Fourier transform of the signal yields the spectrum. However, the intensity of the Fourier transformed signal is typically decaying (or, in some cases, increasing) exponentially with a certain measurement parameter. For example, Carr–Purcell–Meiboom–Gill (CPMG) experiment\[^5\] produces a train of spin echoes with exponentially decreasing amplitudes due to $T_2$ relaxation (see Figure 2a). On the other hand, when the inversion recovery (IR) experiment\[^6\] is repeated several times with a varying delay $\tau$ between the initial $\pi$ inversion and the following $\pi/2$ read pulses, an exponentially increasing data set is produced due to $T_1$ relaxation (Figure 2b). The pulsed-field-gradient spin-echo (PGSE) experiment,\[^7\] in turn, results in exponentially decaying data due to molecular diffusion, when the experiment is repeated with increasing gradient strength and the data are plotted as a function of parameter $b$ being proportional to the square of the gradient strength (Figure 2c). Note that a typical spectrometer software plots the diffusion data as a function of gradient strength, instead of its square, and in this case, a bell shape decaying signal is observed.

Normalized exponentially decaying signal $E$ observed in the relaxation and diffusion experiments can be represented by the following equation\[^3\]:

\[
E(t) = E_0 e^{-t/T_2}
\]

where $E_0$ is the initial signal amplitude, $t$ is the time, and $T_2$ is the relaxation time. The signal decays exponentially with time, and the rate of decay is given by $1/T_2$.
\[ E(t) = \exp(-tR). \] (1)

Here, \( t \) is the time and \( R \) is the relaxation rate \((1/T_2)\) in the case of \( T_2 \) relaxation experiments. In the case of diffusion experiments, \( t = b \), where \( b \) is a parameter proportional to the square of the area of the gradient pulse and the length of diffusion delay \( \Delta \). In PGSE experiment applied with rectangular gradient pulses (see Figure 2c), \( b = (\gamma g \delta^2)(\Delta - \delta/3) \), where \( \gamma \) is the gyromagnetic ratio, \( g \) is the amplitude of the gradient, and \( \delta \) is the gradient pulse length. Furthermore, \( R = D \) in the diffusion experiments, where \( D \) is the molecular self-diffusion coefficient.

If the spins have varying physical and chemical environments in the sample, they may be characterized by a distribution of relaxation times or diffusion coefficients, \( P(R) \). In this case, a multiexponential decay is observed, instead of the single exponential, and the signal is described by the following integral function:

\[ E(t) = \int P(R) \exp(-tR) dR. \] (2)

Equation 2 is identical to the definition of the Laplace transform, although in the general case, the parameter \( t \) is a complex number, but in this context, it is a real number. Therefore, the signal observed in the relaxation and diffusion experiments, \( E(t) \), is the Laplace transform of the relaxation time or diffusion coefficient distribution function \( P(R) \). Because of this common relationship, the relaxation and diffusion experiments can be classified under the same, compact concept: Laplace nuclear magnetic resonance (LNMR). However, it is good to be aware that not all relaxation or diffusion experiments result in exponentially decaying data: Different behavior may be observed, for example, in NOE and restricted diffusion experiments.\(^{[1, 3]}\) Because the relaxation time and diffusion coefficient distributions contain detailed information about dynamics of molecules as well as spin interactions, a general goal in the LNMR experiments is to extract \( P(R) \) from the measured signal \( E(t) \). How this could be done is the topic of the next section.

3 | LAPLACE INVERSION

According to Equation 2, the measured signal, \( E(t) \), in LNMR experiments is the Laplace transform of the relaxation time or diffusion coefficient distribution, \( P(R) \). Therefore, one might anticipate that \( P(R) \) could be resolved by the inverse Laplace transform (ILT; see Figure 1b), similarly to the Fourier transform NMR, in which the time domain signal is the inverse Fourier transform of the frequency domain signal, and the spectrum is extracted from the time domain signal by the Fourier transform. Indeed, there does exist an analytical form to the ILT of Equation 2.\(^{[3]}\) However, the ILT is an ill-posed problem; the Laplace transform belongs to a class of Fredholm integrals of the first kind, and there exists an infinite number of distributions \( P(R) \) that are consistent with an experimentally measured, noisy, and finite data set \( E(t) \).\(^{[18]}\) Luckily, it is possible to extract a good approximate of \( P(R) \) from the experimental data with the use of constraints and regulators,\(^{[3, 9-12]}\) and this process is often called the ILT, although, strictly speaking, it is only an approximate of the ILT. Alternatively, it called the inversion of Laplace transform or Laplace inversion. The last term is used in this article.

Before discussing more about the Laplace inversion, it is good to try to understand why the ILT is “an ill-posed problem,” that is, why it is difficult to extract the distribution of relaxation times or diffusion coefficients from the data obtained from Laplace NMR experiments. Examples of \( T_2 \) relaxation time distributions and corresponding Laplace NMR data of some hypothetical samples are shown in Figure 3. In Figure 3a, the sample is assumed to be characterized by a single \( T_2 \) value of 10 ms. Therefore, signal \( E(t) \) is represented by a single exponential decay, Equation 1. The old trick to check whether the signal really represents a single exponential decay or not is to plot natural logarithm of the signal, \( \ln(E) \), as a function of time. According to Equation 1,

\[ \ln(E) = -tR. \] (3)

Therefore, a straight line is seen in this plot in the case of single exponential decay, and the slope of the line is \(-R = -1/T_2\).

Figure 3b shows corresponding data for a sample characterized by two \( T_2 \) values, 10 and 100 ms, with equal amplitudes of the components. It is easy to see that signal \( E(t) \) includes more than one \( T_2 \) component, because the \( T_2 \) values deviate significantly, by the factor of 10. The plot of \( \ln(E) \) versus \( t \) deviates also significantly from a straight line, clearly demonstrating that the data represent a multieponential decay instead of the single exponential. The initial slope of the plot is equal to average value of \( R, R_{av} = (1/T_2)_{av} \), and the final slope is \(-1/T_2(\text{longest})\), where \( T_2(\text{longest}) \) is the longest \( T_2 \) relaxation time of the sample.

Figure 3c represents also a sample with two \( T_2 \) values (10 and 20 ms), but in this case, the values differ only by the factor of two. Because of the small difference, it is impossible to see, whether the measure \( E \) versus \( t \) data is single or double exponential. However, comparison of the \( \ln(E) \) versus \( t \) plot with the straight line fitted to the data (shown by blue dots in the figure) reveals a small
deviation of the signal from the linear behavior as an indication of two components. Because the deviation is very small, it is clear that the signal-to-noise ratio (SNR) in the Laplace NMR experiment has to be high in order to be able to detect components with small differences in $T_2$ or, in general, in $R$; the higher SNR, the better resolution.\[13\]

Figure 3 shows the data of the sample including three $T_2$ components (10, 50, and 300 ms) with equal amplitudes. It is clear from both $E$ versus $t$ and $\ln(E)$ versus $t$ plots that the data represent multiexponential decay, but it is very difficult to see exactly how many components are included.

In the case of multicomponent decay, the discretized signal in the LNMR experiment is

$$E(t) = \sum_k P(R_k) \exp(-t_i R_k) + \varepsilon_i,$$  \hspace{2cm} (4) 

where $\varepsilon_i$ represents noise. Therefore, in principle, the following least squares fitting provides means to perform an approximated Laplace inversion:

$$\min \left\{ \chi^2 = \sum_i \left[ E_i - \sum_{k=1}^{N_c} P(R_k) \exp(-t_i R_k) \right]^2 \right\}. \hspace{2cm} (5)$$

Here, $N_c$ is the number of relaxation or diffusion components and parameters $R_k$ are adjusted in the fitting procedure. However, often, the number of the components is unknown. In this case, one can begin the fitting with a single component ($N_c = 1$) and then increase the number of components one by one. Improved fit due to the increased number of components results in a decreased minimum value of $\chi^2$. Therefore, the process could be continued until the increase of $N_c$ does not result in significant decrease in $\chi^2$. However, it may be difficult...
to find an optimal number of components, and the fit may become unstable (e.g., strongly dependent on the initial values of the parameters) when the number of components is high.

Another issue related to the Laplace inversion is illustrated in Figure 4. Let us assume that the $T_2$ distribution contains nothing (Figure 4a), that is, we detect no signal in the LNMR experiment, but only noise, with $E(t)$ varying randomly around 0. Within the noise variation, almost equally good solution of the Laplace inversion is a distribution including pairs of peaks with $T_2$ values close to each other but with amplitudes of opposite signs (see Figure 4b and 4d). These components produce almost identical time domain signals but with opposite signs (see Figure 4c), and the signals are canceling each other out. Therefore, the resulting total signal $E(t)$ is almost equal to the signal observed in this hypothetical experiment. Based on this logic, it is easy to understand that there is an infinite number of distributions that are consistent with the experiment.

A relevant question, therefore, is how to make the fitting more stable? One solution is to use constraints.[9] The most obvious constraint is to assume that the relaxation time or diffusion coefficient distribution $P(R)$ includes only peaks with positive amplitudes. Often, this so-called nonnegative constraint is physically valid. However, it is good to be aware that, if cross-relaxation or exchange occur in the studied system, also negative peaks may appear.[12,14–16] Anyway, the nonnegative constraint prevents the appearance of the artificial pairs of positive and negative peaks illustrated in Figure 4. Therefore, it reduces significantly the number of wrong solutions consistent with the experimental data. Other constraints may include monotonic from peak, as well as unimodal or bimodal distributions.[17]

Often, the constraints are used together with regularization, such as Tikhonov regularization,[9] which makes also the Laplace inversion more stable. In this case, not only the sum of squares of residuals are minimized, as shown in Equation 5, but also the sum is minimized together with the sum of the squares of the amplitudes, first derivatives (slope) or second derivative (curvature) of the relaxation time or diffusion coefficient distribution function $P(R)$[17]:

$$
\min \left\{ \chi^2 = \sum_i \left[ E_i - \sum_{k=1}^{N_c} P_k \exp(-t_i R_k) \right]^2 + A \sum_{k=1}^{N_c} P_k^2 + S \sum_{k=1}^{N_c-1} (P_{k+1} - P_k)^2 + C \sum_{k=2}^{N_c-1} (P_k - 2P_{k+1} + P_{k+2})^2 \right\}
$$

Consequently, the regularization favors smooth distributions instead of distributions with very sharp peaks and wild oscillations, which is often physically justified. In Equation 6, $A$ is the coefficient for amplitude smoothing, $S$ for slope smoothing, and $C$ for curvature smoothing. Usually, only one type of smoothing is used at a time. An optimal value of the smoothing coefficient $A$, $S$, or $C$ should provide the best compromise between smoothing and accuracy of $P(R)$,[18] but finding such an optimal value is not completely unambiguous.

A drawback of the method is that, naturally, the smoothing tends to increase the width of intrinsically narrow peaks. Another, less expected drawback is that the method tends to split up intrinsically broad peaks into a series of narrow peaks.[17,19] Sometimes this phenomenon is called pearling. Large peaks may also affect the amplitudes and positions of adjacent smaller peaks, and spurious minor peaks may appear in the resulting distributions.[9] Therefore, it is important to be aware of the problems of the Laplace inversion, and one should critically evaluate the reliability of the results. For example, repetition of the LNMR experiment with slightly different experimental parameters may provide means to distinguish true peaks from artifacts. On the other hand, sometimes, the performance of Laplace inversion is underestimated: If the LNMR data have been measured with high SNR and proper experimental parameters, actually, the reliability and resolution of the resulting distribution may be quite good; for example, if SNR is 1,000, peaks of equal amplitude with relaxation times and/or diffusion coefficients differing by a factor of 1.5 can be resolved.[13] Naturally, SNR in most of LNMR experiments is lower than 1,000, leading to a lower resolution.

In addition to SNR, the number, range, and grid of the $t$ or $b$ domain data points affects the resolution of the relaxation time or diffusion coefficient distribution. In general, the more the data points, the higher the resolution. Furthermore, the broader the region covered, the broader the range of LNMR parameters probed. For example, $T_2$ values significantly shorter than the time of the first point observed in the CPMG experiment cannot be reliably detected, because the signals of these components have already been almost completely decayed before the data observation. In a typical Laplace inversion process, the range of the relaxation times or diffusion coefficients is selected in advance. In the case of relaxation experiments, the maximum range is roughly equal to the time range of the LNMR data, because longer or shorter relaxation time values cannot be reliably observed...
in the experiment. The maximum number of points in the grid of the relaxation time or diffusion coefficient distribution is equal to the number of points in the LNMR experimental data (otherwise, one would encounter an overfitting problem); therefore, the number of the experimental points has a direct effect on nominal resolution in the distribution. The resolution of the distribution can be improved also by “zooming in” to the region in which the relaxation time or diffusion coefficient components exist.

The so-called uniform-penalty smoothing may provide a satisfactory solution to the peak broadening and pearling issues. Furthermore, an algorithm based on Tikhonov regularization to perform the Laplace inversion without a nonnegativity constraint has also been proposed. In this case, a penalty is introduced for zero crossings of the relaxation time or diffusion coefficient distribution.

Prange and Song have developed an efficient Monte Carlo algorithm for assessing uncertainty of LNMR distributions. Without a regulator (but with the nonnegative constraint), they generated thousands of distributions being in agreement with the experimental data. Because there was no smoothing regulator, the distributions were very spiky. However, the mean distribution was smooth and similar to the regularized distribution. Statistical analysis of the distributions enabled them to determine the error bars of the distribution.

4 | EXAMPLES OF ONE-DIMENSIONAL LNMR STUDIES

There are a big number of excellent publications describing useful applications of LNMR. However, as the aim of this article is not to be a comprehensive review of literature, but, instead, a pedagogical perspective to the subject, only two examples of one-dimensional (1D) LNMR are given. Here, the concept of “one-dimensional” refers to LNMR experiments resulting in 1D LNMR data, that is, 1D distributions of relaxation times or diffusion coefficients. In some cases, the experiment itself may belong to the class of 2D NMR experiments, because, for example, the IR experiment (Figure 2b) has to be repeated many times with a varying evolution delay in order to collect appropriate LNMR data.

Figure 5a represents a $^1$H NMR spectrum of moisture in pine wood. The spectrum consists of only a single, broad peak, presenting very little information about the sample. However, the $T_2$ relaxation time distributions shown in Figure 5b reveal the existence of many different environments of the fluid molecules. The NMR spectrum of a crude oil sample, in turn, is too crowded to resolve chemical components, but the diffusion coefficient distribution shown in Figure 5c can be converted into an alkene length distribution (Figure 5d) based on the scaling laws of diffusion coefficients.

Previous examples demonstrate that LNMR can reveal various relaxation and diffusion components existing in the samples. Furthermore, LNMR may offer chemical
resolution not available in the traditional NMR spectra, which may be very useful in understanding the dynamics and structures of materials.

5 | MULTIDIMENSIONAL LNMR

Like in the conventional NMR spectroscopy, the resolution and information content of LNMR can be improved significantly by a multidimensional approach. Multidimensional LNMR experiments allow one to correlate relaxation times and/or diffusion coefficients. They also make it possible to investigate chemical exchange via relaxation or diffusion parameters. Traditionally, chemical exchange is investigated by exchange spectroscopy (EXSY) NMR method, which requires that the exchanging sites produce separate peaks in the NMR spectrum. However, multidimensional LNMR may provide exchange maps corresponding to the EXSY spectra even in the case when the exchanging sites are not resolved in the traditional spectra, providing that the sites have different relaxation times or diffusion coefficients.

As an example, the pulse sequence of two-dimensional $T_1-T_2$ relaxation correlation experiment is shown in Figure 6a. It includes the IR part (Figure 2b) for $T_1$ encoding, followed by the CPMG loop (Figure 2a) for $T_2$. The experiment has to be repeated many times with varying recovery delay $\tau_1$. Consequently, in this experiment, $\tau_1$ corresponds to the evolution period in the general scheme of two-dimensional NMR.
Figure 6b represents the pulse sequence of diffusion–
$T_2$ relaxation correlation ($D-T_2$) experiment. It comprises a pulsed-field-gradient stimulated-echo (PGSTE)\cite{27} part for diffusion encoding, followed by the CPMG loop. PGSTE is a variant of PGSE (Figure 2c) diffusion experiment, in which the magnetization is stored in the longitudinal direction during the diffusion delay $\Delta$ in order to avoid the fast decay of magnetization due to short $T_2$ relaxation time. In this sequence, the incremented evolution period is replaced by the incremented gradient amplitude, that is, the parameter $b$ is incremented instead of time.

Figure 6c, in turn, shows the pulse sequence of $T_2$–$T_2$ relaxation exchange experiment, including two CPMG loops separated by the mixing time $\tau_m$. The sequence enables one to correlate the $T_2$ relaxation times before and after the mixing time. If these values differ, it indicates that chemical exchange (or magnetization transfer) takes place between the sites characterized by the different $T_2$ times. The $T_2$–$T_2$ experiment is repeated many times with increasing number of 180° pulses in the initial CPMG loop, corresponding to the measurements of 2D data with incrementing the evolution time.

In addition to the LNMR experiments described above, there is a vast number of different kinds of two-dimensional or multidimensional LNMR experiments for correlating different relaxation or diffusion parameters as well as for studying chemical exchange.\cite{3,24} The selection of the most appropriate experiment is strongly dependent on the system at hand as well as the type of desired information. For example, if one aims to investigate chemical exchange, it depends on the sample whether the relaxation times or diffusion coefficients provide the best contrast between the exchanging sites. In addition to observe the desired information, one has to ensure that the potential unwanted coherences created during the course of an LNMR experiment are also suppressed using phase cycling or coherence selection gradients.\cite{4}

A general form of the signal observed in the 2D LNMR experiment is

$$E(t_1, t_2) = \int \int P(R_1, R_2) \exp(-t_1 R_1) \exp(-t_2 R_2) dR_1 dR_2.$$

This is a 2D counterpart of Equation 2. Here, subscripts 1 and 2 refer to the first (indirect) and second (direct) dimension, respectively. The determination of the distribution function $P(R_1, R_2)$ requires 2D Laplace inversion of the signal. However, the inversion is very slow due to the big sizes of matrixes of the digitized signal, distribution $P$, and exponential kernels. Song et al.\cite{10,11} accelerated the inversion significantly by data compression using independent singular value decompositions (SVD) of the exponential kernel matrixes as well as by using the nonnegativity constraint. After this algorithm development, 2D LNMR approach has entered routine use.

6 | EXAMPLES OF TWO-DIMENSIONAL LNMR STUDIES

Figure 7a shows an example of $T_1$–$T_2$ correlation map of moisture in wood.\cite{28} The map demonstrates that the 2D approach can improve the resolution of LNMR, because the moisture components, which overlap in 1D $T_1$ and $T_2$ distributions, are resolved in the 2D map. $T_1$–$T_2$ correlation experiments can also be exploited in the determination of $T_1/T_2$ ratio, which provides information about the molecular mechanisms of surface relaxation, particularly in porous materials.\cite{11}

A $T_2$–$T_2$ exchange map of water in a porous sandstone sample is shown in Figure 7b.\cite{29} In general, $T_2$ relaxation time of water (or any liquid) confined to a pore decreases with decreasing pore size,\cite{31} and therefore, in this case, the broad distribution of $T_2$ values in the map reflects the broad pore size distribution of the sample. The off-diagonal cross-peaks visible in the map reveal chemical exchange of water between pores with different sizes. The amplitudes of the cross peaks depend on the length of the mixing time. The measurement of $T_2$–$T_2$ exchange maps with varying mixing time provides means to quantify the exchange rate. Because the signals of water in the pores with different size overlap in the spectrum, chemical exchange cannot be monitored by the conventional EXSY method, but LNMR based methods, such as $T_2$–$T_2$ exchange experiment, make it feasible.

Figure 7c shows a $D-T_2$ correlation map of a halogen-free orthoborate-based ionic liquid.\cite{30} The map reveals two coexisting dynamic “phases” with significantly different diffusion coefficients. The component with the smaller $D$ was interpreted to arise from aggregates of anions and cations, and the other component from free anions and cations. The $D-T_2$ map enabled one to identify the $T_2$ values corresponding to the “phases.” This information was exploited in relaxation modeling to estimate the sizes of the aggregates. Furthermore, the knowledge of the $T_2$ values of the ”phases” made it possible to determine exchange rates between the two “phases” by $T_2$–$T_2$ exchange method (Figure 7d).

7 | HYPERPOLARIZED LNMR

Similarly to other NMR experiments, the sensitivity of LNMR can be improved by many orders of magnitude with the modern nuclear spin hyperpolarization techniques. For example, magnetic moment of electron is
about 660 times larger than that of proton, and therefore, thermal polarization of unpaired electrons is much larger than that of nuclei. When the sample is cooled down below 10 K at a magnetic field of a few Tesla, thermal polarization of electrons is close to 100%. In dissolution dynamic nuclear polarization (DNP) method,[32] the high electron polarization is transferred to nuclei by using microwave irradiation. Thereafter, the sample is dissolved rapidly and transferred to NMR spectrometer. In para-hydrogen-induced polarization [33] and signal amplification by reverse exchange (SABRE) [34] methods, para-hydrogen-enriched H₂ is prepared by cooling hydrogen gas in the presence of ortho-para conversion catalyst. Then, para-hydrogen is let to react with an unsaturated precursor or reversibly interact with a substrate in a metal complex in order to observe high nuclear spin polarization. Spin-exchange optical pumping of mixtures of alkali-metal vapors and noble gases can be used to hyper-polarize noble gases.[35]

In spite of this, hyperpolarization has not been broadly utilized in LNMR yet. However, it is anticipated that this will be a rapidly growing field in the near future.

Typically, hyperpolarization is created outside the NMR spectrometer, and the sample has to be rapidly transferred into the spectrometer before the hyperpolarization has decayed. Furthermore, one has to ensure that composition of the sample is desired after the transfer, and residual motion or convection does not cause artifacts to LNMR (especially diffusion) experiments. Reile et al.[36] exploited SABRE technique in diffusion-ordered spectroscopy (DOSY) analysis of low-micromolar mixtures. Figure 8a shows schematics of their experimental setup. Hyperpolarization was created by bubbling para-hydrogen through a catalyst-substrates solution. Thereafter, the solution was transported to NMR spectrometer by applying N₂ pressure. A stabilization delay of 5 s was required before the DOSY experiment in order damp liquid motions. The SABRE spectrum of the mixture including six substrate compounds is seen in Figure 8b. Corresponding DOSY spectrum is shown in Figure 8c. DOSY is basically a PGSE-type (Figure 2b) or PGSTE-type experiment with spectral resolution, and Laplace inversion or exponential fit is performed separately for each signal.[37]
Therefore, it results in a 2D spectrum in which in direct dimension corresponds to \( D \). The spectrum allows identification of molecules based on \( D \), and it can be used to estimate molecular sizes. Figure 8c shows that all the compounds of the mixture are resolved in the \( D \) direction regardless of small size difference between the molecules. The sensitivity enhancement provided by SABRE made at least 100-fold lower concentrations of substances detectable.

There are also many other publications, in which the sensitivity boost provided by hyperpolarization was exploited in diffusion measurements. For example, Moudrakovski et al\(^{38}\) studied diffusion of hyperpolarized xenon in mesoporous Vycor porous glass, using both PGSE and 1D MRI-based methods. Guillot et al\(^{39}\) utilized hyperpolarized \(^3\)He and CPMG with gradients to investigate diffusion in aerogel. Hyperpolarized xenon has also been exploited in the investigation of single-file diffusion effects in small channels, in which adsorbed Xe atoms cannot pass each other\(^{40-43}\). Chen and Hilty\(^{44}\) used DNP and small flip-angle PGSTE technique to study suppression of flow motion after the injection of hyperpolarized substance. Diffusion of hyperpolarized noble gases in lung has been shown to provide detailed information about the changes of alveolar structures, for example, due to emphysema\(^{45,46}\). So-called long-lived states increase significantly the lifetime of hyperpolarized magnetization, therefore opening the way to observe very slow diffusion and slow transport phenomena\(^{47,48}\).

Hyperpolarization has also been utilized in some 1D relaxation experiments. For example, Neudert et al\(^{49}\) combined DNP with fast-field-cycling \( T_1 \) relaxometry to investigate the paramagnetic nuclear spin relaxation of \(^{13}\)C in a benzene-\(^{13}\)C\(_6\)D\(_6\) solution of nitroxide radicals. Franck et al\(^{50}\), in turn, combined DNP with \( T_2 \) relaxometry and were able to selectively amplify the NMR signal of only one solvent population, which was in contact with a paramagnetic probe and occluded from a second solvent population. The method can be exploited, for example, to illuminate a dilute population of fluid within a porous medium.

8 | ULTRAFAST LAPLACE NMR

One limitation of two-dimensional and multidimensional as well as some 1D LNMR experiments is that the experiment has to be repeated many times (typically from tens to hundreds of times) with varying evolution delay or gradient strength in order to collect the multidimensional data (see Figure 9a). Before each repetition, one has to have a proper relaxation delay in order to wait for the
recovery of longitudinal magnetization. Therefore, the experiments are very time consuming. In fact, this is a general problem of multidimensional NMR.\cite{1}

There is also another problem related to the need for repetitions: If one desires to exploit nuclear spin hyperpolarization in the experiments in order to boost sensitivity, one should reproduce the hyperpolarization before each repetition. However, typically the polarization process is very time consuming; for example, in the case of dissolution DNP, it may take from tens of minutes to hours.\cite{32}

Furthermore, the polarization degree may vary significantly between the repetitions, messing the obtained data. Therefore, the combination of multidimensional NMR experiments with hyperpolarization is typically very difficult, although in some favorable cases, it is possible (see above).\cite{36}

Small flip angle experiments, which allow several excitations after a single hyperpolarization process, may offer remedy for this problem.\cite{51} However, here, we concentrate on another solution.

Both of the above-mentioned problems can be solved, if the multidimensional data are measured by a single scan. Frydman et al.\cite{52–54} introduced a technique called ultrafast NMR spectroscopy, which is based on spatial encoding of multidimensional data. In the method, various evolution times are encoded into the layers of the sample, as illustrated in Figure 9b. Thereafter, the data are read by using “read gradients” like in MRI. This strategy allows the measurement of 2D data in a single scan. The spatial encoding has been also exploited in 1D LNMR experiments,\cite{55–57} as well as in correlating $T_1$ relaxation or diffusion parameters with spectroscopic data.\cite{58–61}

Recently, it has been applied also in two-dimensional LNMR.\cite{13,62–64} This so-called ultrafast LNMR method shortens the experiment time by one to three orders of magnitude as compared with corresponding conventional LNMR experiments. On the other hand, the spatial encoding slightly lowers the sensitivity of the ultrafast LNMR experiment as compared with the conventional experiment.\cite{13,62} However, similarly to ultrafast NMR spectroscopy,\cite{65–67} ultrafast LNMR allows the use of nuclear spin hyperpolarization to increase the sensitivity of experiment, leading to the overall sensitivity enhancement of several orders of magnitude.\cite{13,60,64}

As an example, the pulse sequence of ultrafast $T_1$ – $T_2$ relaxation correlation experiment\cite{62} is shown in Figure 10a. It includes a single-scan IR\cite{55} part for $T_1$ encoding, followed by a CPMG loop for $T_2$. The sequence begins with simultaneous gradient pulse and frequency-swept chirp $\pi$ pulse. The gradient field makes the resonance frequency of spins to be linearly dependent on the position along the sample tube (the z direction). Because the frequency of the chirp pulse is linearly increasing with time, the spins at the bottom of the sample tube are inverted first and those at the top last (see Figure 10b).

Because the length of the gradient and chirp pulses is long, typically 1–3 times $T_1$, the spins inverted first at the bottom have recovered close to thermal equilibrium by the end of the pulses, and the magnetization profile along the z axis includes both positive and negative values (see Figure 10b). In fact, the profile is equivalent to the IR curve observed in the traditional IR experiment (see Figure 2b). This profile is read by applying the principles of MRI, by using the read gradient shown in Figure 10a. During the course of the CPMG loop, the profile is decayed by $T_2$ relaxation. Consequently, 2D data set corresponding to traditional $T_1$ – $T_2$ correlation experiment (see Figure 6a) is collected in a single scan. An example of ultrafast $T_1$ – $T_2$ correlation map of a double-tube sample including doped water with different relaxation times at different compartments is shown in Figure 10c. Both compartments produce well-resolved peaks to the map. The experiment time of the measurement was only 2 s, whereas the corresponding traditional experiment took 13 min.\cite{62}

Because of the layered spatial encoding, it is desirable to have a homogeneous sample in ultrafast LNMR experiments. However, small heterogeneities of the sample may be possible to compensate in postprocessing, in the same way as the coil sensitivity correction is done.\cite{13,62}

In principle, it might be also possible to perform the spatial encoding in a homogeneous voxel of a heterogeneous sample.

Ultrafast $T_1$ – $T_2$ and $D$ – $T_2$ experiments have been used for the determination of $T_2$ relaxation times and diffusion coefficients of liquids and gases, distinguishing physical environments of liquids and gases in porous materials.
and resolving alkenes with different chain lengths.\cite{13,62,64} Several hyperpolarization methods, including dissolution DNP, parahydrogen-induced polarization, and spin-exchange optical pumping\cite{13,64} have been combined with ultrafast LNMR to boost the experimental sensitivity. Ultrafast LNMR has been shown to be feasible also with low-field, single-sided NMR instruments\cite{68} with very inhomogeneous magnetic field.\cite{63} In fact, the field inhomogeneity is exploited in the spatial encoding. Hyperpolarized ultrafast LNMR may make even single-scan multidimensional experiments feasible with mobile instruments, which may revolutionize mobile chemical and medical NMR analysis. This trend is supported by the recent development of miniaturized, portable hyperpolarizers.\cite{69,70}

9 | CONCLUSIONS

LNMR has witnessed a great progress due to the development of multidimensional techniques, multidimensional Laplace inversion algorithms, hyperpolarization techniques, and ultrafast approach to measure multi-dimensional data. Therefore, the information content, sensitivity, and time efficiency of the method have extended significantly. The method has lots of extremely interesting applications in various fields including chemistry, biochemistry, geology, archaeology, and medicine. Low-field, mobile LNMR has a potential to bring advanced, low-cost chemical and medical NMR analysis broadly available outside the laboratories and even in developing countries.

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