Ultrafast NMR Diffusion Measurements Exploiting Chirp Spin Echoes

Short title: Ultrafast diffusion measurements

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Abstract

Standard diffusion NMR measurements require the repetition of the experiment multiple times with varying gradient strength or diffusion delay. This makes the experiment time-consuming and restricts the use of hyperpolarized substances to boost sensitivity. We propose a novel single-scan diffusion experiment, which is based on spatial encoding of two-dimensional data, employing the spin-echoes created by two successive adiabatic frequency-swept chirp π pulses. The experiment is called ultrafast pulsed-field-gradient spin-echo (UF-PGSE). We present a rigorous derivation of the echo amplitude in the UF-PGSE experiment, justifying the theoretical basis of the method. The theory reveals also that the standard analysis of experimental data leads to a diffusion coefficient value overestimated by a few per cent. Although the overestimation is of the order of experimental error and thus insignificant in many practical applications, we propose that it can be compensated by a bipolar gradient version of the experiment, UF-BP-PGSE, or by corresponding stimulated-echo experiment, UF-BP-PGSTE. The latter also removes the effect of uniform background gradients. The experiments offer significant prospects for monitoring fast processes in real-time as well as for increasing the sensitivity of experiments by several orders of magnitude by nuclear spin hyperpolarization. Furthermore, they can be applied as basic blocks in various ultrafast multidimensional Laplace NMR experiments.

Key words: NMR, diffusion, ultrafast, single-scan, spatial encoding

Introduction

NMR spectroscopy is one of the very few methods for measuring self-diffusion of molecules without tracers.[1] Apart from the self-diffusion coefficients of bulk liquids or gases, the diffusion measurements reveal details about the structure of materials, since the boundaries of materials restrict the diffusion of fluids, and this is reflected in the measured apparent diffusion coefficients as well as diffusion decay curves.[2-4] Therefore, diffusion NMR is broadly exploited in the characterization of various materials, such as porous media,[5-9] wood,[10-13] paintings,[14] food,[15] emulsions,[16] ionic liquids,[17] liquid crystals, lipid membranes,[18] biological tissues[19] and oil.[20]

NMR diffusion measurements exploit spin echoes and field-gradients, which make the magnetic field linearly dependent on position. In the pulsed-field-gradient spin-echo (PGSE) NMR experiment,[21] the π pulse in the center of the sequence inverts the phase of spins gained during the first gradient pulse. Consequently, the effects of two gradient pulses are cancelled out, if the spins are stationary. The refocused spin coherences generate an echo signal at the end of the sequence. However, if the spins change their position due to diffusion during the delay between the two gradient pulses, the refocusing is incomplete and the echo signal is weakened. The change of the amplitude of the echo as a function of gradient strength or diffusion delay reveal the diffusion coefficient of a fluid.

Pulsed-field-gradient stimulated-echo (PGSTE) method[22] is a variant of the PGSE method, in which the magnetization is stored in the longitudinal direction during the diffusion delay. This lowers the sensitivity by the factor of 2 because only one component of the transverse magnetization is stored. However, if the T_1 relaxation time is much longer than T_2,

which is commonly true for fluids in porous materials, signal in the PGSTE experiment is stronger than in the PGSE, because in the former experiment magnetization is stored in the longitudinal direction most of the time.

Background gradients present in the sample affect also the echo amplitude in the diffusion experiments, hampering the analysis. Fortunately the effect of uniform background gradients can be cancelled out by using bipolar gradients, with a π pulse in between them, in the PGSTE experiment (BP-PGSTE experiment).[23]

The determination of diffusion coefficients by NMR requires that the diffusion experiment is repeated several times with varying gradient strength or diffusion delay, making it very time-consuming. This prevents monitoring fast processes in real-time. In addition, this makes the use of nuclear spin hyperpolarization techniques, including dynamic nuclear polarization (DNP),[24] parahydrogen-induced polarization (PHIP),[25] signal amplification by reverse exchange (SABRE)[26] and spin-exchange optical pumping (SEOP),[27] that otherwise would allow one to increase the sensitivity of experiments by several orders of magnitude, very difficult, because, for example, preparation of hyperpolarization by DNP typically takes from tens of minutes to hours, and it is very difficult to reproduce exactly the same degree of polarization for each repetition.

Thrippleton *et al*[28] proposed a single-scan technique for the measurement of diffusion coefficients. It is based on similar spatial encoding of diffusion data that has been exploited in single-scan T_1 measurements[29,30] and in ultrafast multidimensional NMR spectroscopy.[31-33] An adiabatic frequency-swept chirp π pulse is applied simultaneously with the gradient pulse in a PGSTE-type experiment, inverting the phase of spin coherences in different sample layers at

different times. Consequently, the effective length of the gradient pulses becomes linearly dependent on position, and the magnetization profile along the gradient direction is equivalent to the echo amplitude decay curve in the conventional experiment. Several other single-shot diffusion measurements has been proposed as well in the literature, based on the small tipping angle pulses and a train of diffusion gradients.[34-37]

Based on the method of Thrippleton *et al*,[28] we recently introduced a single-scan D-T_2 correlation experiment,[38] reducing the experiment time by one to three orders of magnitude. We demonstrated that the single-scan approach allows the use of hyperpolarized substances (as in ultrafast 2D NMR spectroscopy),[39] even with low-sensitivity nuclei, such as ^{13}C, which are extremely useful in the studies of relatively slow biological processes.[40] We have classified this experiment, along with the single-scan T_1-T_2 correlation experiment,[41] its low-field single-sided magnet variant[42] and a broad range of other envisioned single-scan relaxation and diffusion experiments, under the concept of ultrafast multidimensional Laplace NMR.

In addition to hard pulses, also adiabatic frequency-swept pulses have been exploited in creation of spin echoes in order to excite a broader range of frequencies.[43-46] A single frequency-swept π pulse replacing the hard π pulse in a spin echo sequence does not refocus the magnetization because both the phase and the refocusing time of the pulse is dependent on the frequency offset. Some composite pulses have been proposed to eliminate the additional phase factor caused by a single frequency-swept pulse.[47-49] A double spin-echo sequence, in which the phase factor caused by the first frequency-swept π pulse is compensated by a second identical pulse, has been introduced as well.[50] Furthermore, chirp pulses with linear frequency sweep have been employed for both excitation and refocusing to produce spin-echoes.[44,45,51-53]

In this article, we introduce a novel PGSE-type single-scan diffusion experiment, which employs the spin-echoes created by two successive chirp π pulses. We demonstrate that this sequence removes some artefacts visible in the single-scan PGSTE experiment, since it does not destroy one component of magnetization as the single-scan PGSTE experiment inherently does. We present a thorough theoretical analysis verifying the principles of the single-scan PGSE experiments and revealing that the experiments result in slightly overestimated values of diffusion coefficients. Furthermore, we introduce bipolar gradient versions of the single-scan PGSE and PGSTE experiments compensating for the overestimation, and, in the latter case, removing the effect of uniform background gradients.

Theory

The pulse sequence of ultrafast, single-scan PGSE (UF-PGSE) experiment is shown in Fig. 1a. Frequency-swept chirp π pulses, *i.e.* pulses with their frequency increasing linearly with time, are applied simultaneously with the first half of diffusion gradient pulses. The bandwidth of the pulse is matched with the range of the Larmor frequencies (spread by the diffusion gradient) in the sensitive region of the radio frequency (RF) coil. The frequency of the chirp pulse matches the Larmor frequency of spins on the top of the sensitive region at the end of the chirp pulse, and therefore the spins are refocused in the center of the gradient pulse; hence, effectively, they do not feel the gradient at all. The spins on the bottom, in turn, are refocused right in the beginning of the gradient pulse, and they feel the full gradient length. The effective length of the gradient is linearly dependent on the position, and the profile of the transverse magnetization at the end of the sequence is equivalent of the echo amplitude curve measured as a function of gradient

strength in the conventional PGSE experiment. The magnetization profile along the *z*-axis is obtained by using a read gradient as in a standard MRI experiment. Contrary to conventional PGSE experiment, there is no hard π pulse in the sequence, but, instead the two identical chirp π pulses produce a spin echo at the end of the sequence.

We present a rigorous derivation of the echo amplitude as a function of the position *z* in the Supporting Information (SI). The derivation gives also an in-depth explanation for the basis of the method. The derivation is based on the assumption that the chirp pulse rotates the spins by 180° around the $\boldsymbol{B}_1$ vector instantaneously when the chirp frequency matches with the Larmor frequency of spins. This has turned out to be a good approximation.[33] The phase of the chirp pulse rotating spins at different sample layers is proportional to z^2 (see the definitions of the phases of the chirp pulse and spins in SI). If the pitch of the chirp phase spiral is much longer than the displacement of molecules during the diffusion delay Δ, the echo amplitude in the UF-PGSE experiment is

$$E(z) = \exp\left[-Db(z)\right] \ , \tag{1}$$

where *D* is the diffusion coefficient and

$$b(z) = \left[q(z)\right]^2\left[\Delta - \frac{\delta_{EFF}(z)}{3}\right] \tag{2}$$

(see SI). The wave vector $q(z)$ is

$$q(z) = \gamma G_{DIFF}\,\delta_{EFF}(z) \ , \tag{3}$$

where $\delta_{EFF}(z)$ is the effective length of diffusion gradient pulse, being linearly dependent on position:

$$\delta_{EFF}(z) = t_{CHIRP}\left(1 - \frac{\gamma G_{DIFF} z}{\pi \Delta \nu}\right). \qquad (4)$$

Here, γ is the gyromagnetic ratio, G_{DIFF} is the amplitude of diffusion gradient, and t_{CHIRP} and $\Delta\nu$ are the length and bandwidth of the chirp pulse, respectively. Consequently, the magnetization profile along the *z* axis corresponds to the echo amplitude curve measured as a function of G_{DIFF} in a conventional PGSE experiment. If the echo signal is measured in the presence of a read gradient (see Fig. 1a), the 1D MR image of the magnetization profile can be obtained by a Fourier transform of the signal along the wave vector *k* direction. The *z* axis of the profile can be converted into *b* axis using Equations 2-4.

If the change of the phase of the chirp pulse is not negligible, when a spin moves from its initial position z_0 to final position *z* during the Δ delay, the echo amplitude is

$$E(z) \approx \exp[-Db(z)]\exp\left[-\frac{\gamma^2 G_{DIFF}^2 t_{CHIRP} Dq(z) z \Delta}{2\pi^2 \Delta \nu}\right]\exp\left[-\frac{\gamma^4 G_{DIFF}^4 t_{CHIRP}^2 D z^2 \Delta}{16\pi^4 \Delta \nu^2}\right] \qquad (5)$$

(see SI). As compared to Eq. 1, the echo amplitude in Eq. 5 is weighted by two additional exponential terms, the arguments of which are not linearly proportional to *z*. Consequently, the magnetization profile along the *z* direction is not anymore exactly identical to the echo amplitude curve of the conventional experiment, and, if the data of ultrafast PGSE experiment is analyzed in a standard way by fitting on exponential function shown in Eq. 1 in the data points, the analysis results in slightly erroneous *D* value. Typically, the value is overestimated by 1-7% (see SI), which is quite small as compared to the accuracy of the diffusion measurement. Therefore, it is justified to ignore the additional terms in many applications. If the overestimation is a problem, then one can either use Eq. 5 in the data analysis or exploit the modified version of the sequence described below to compensate for the effect.

Bipolar gradient version of UF-PGSE experiment (UF-BP-PGSE) is shown in Fig. 1b. It includes two pairs of gradients with opposite polarity, and the chirp pulse corresponding to the negative gradient lobe is swept from high to low frequencies. The sequence eliminates the extra terms in Eq. 5, because, after applying the first two chirp pulses related to the bipolar diffusion encoding, the dependence of the phase of spins on the phase of chirp pulse is canceled out, and therefore, if the phase of the chirp pulses felt by spins after the diffusion delay is different, it does not have any effect on the echo amplitude profile. Hence, conventional exponential fit to UF-BP-PGSE echo amplitudes results in a correct *D* value.

The analysis of the echo amplitude profile of UF-PGSE experiment also holds true to UF-PGSTE experiment[28] shown in Fig. 1c. Also in this case the bipolar version of UF-PGSTE experiment (UF-BP-PGSTE), shown in Fig. 1d, eliminates the extra terms in Eq. 5. Contrary to UF-BP-PGSE, UF-BP-PGSTE experiment removes the effect of uniform background gradients as well, which is very important in many materials research applications. The echo amplitude in the UF-BP-PGSTE experiment is[1]

$$E(z) = \exp\left[-Db'(z)\right] \ , \tag{6}$$

where

$$b'(z) = \gamma^2 G_{DIFF}^2 \left[\delta_{EFF}(z)\right]^2 \left\{4\Delta' + 6\tau - 2\delta_{EFF}(z)/3\right\} \ . \tag{7}$$

Here, Δ’ is the delay between the second and third hard π/2 pulses and 2τ is the delay between the first and second hard π/2 pulses (see Fig. 1d).

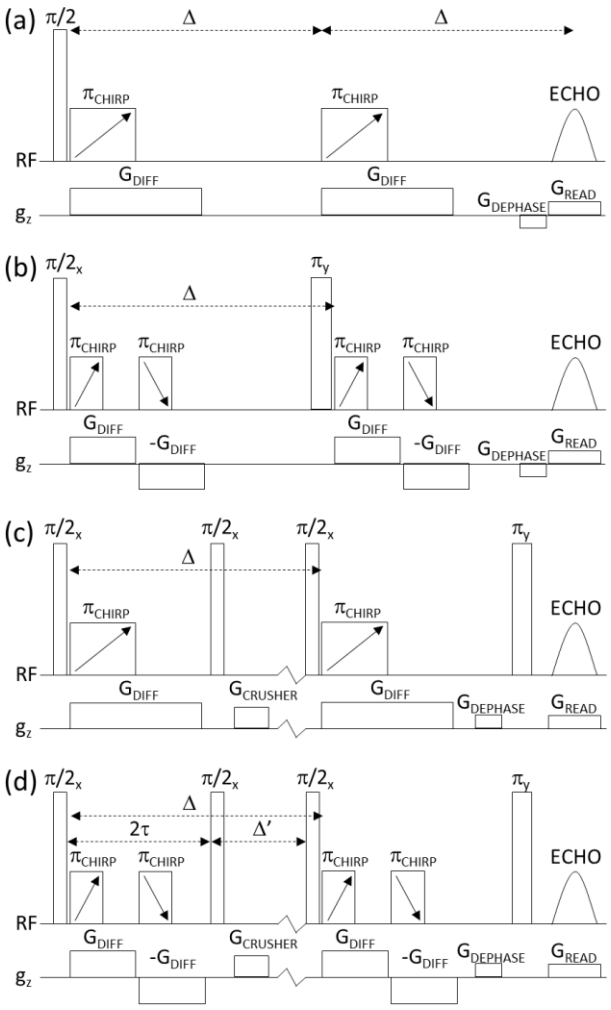

Figure 1. Pulse sequence of (a) ultrafast PGSE (UF-PGSE), (b) ultrafast PGSE with bipolar gradients (UF-BP-PGSE), (c) ultrafast PGSTE (UF-PGSTE) and (d) ultrafast PGSTE with bipolar gradients (UF-BP-PGSTE). Read gradients are applied at the end of the sequences in order to have an image of the profile of transverse magnetization along the *z* axis. In the UF-PGSTE and UF-BP-PGSTE experiments, an additional π pulse is applied at the end of the sequence in order to produce a spin-echo image of the encoded magnetization profile along the *z* direction. $G_{CRUSHER}$ removes the unwanted transverse magnetization during the diffusion delay in the PGSTE-type experiments.

Experimental

Diffusion in a 10 mm diameter water sample containing 20% of H_2O in D_2O was measured by both the UF as well as conventional methods in order to evaluate the accuracy of the proposed experiments. The sample was doped with $CuSO_4$ (0.1% $CuSO_4 \cdot 5H_2O$) in order to make relaxation time shorter. All experiments were performed with a Bruker Avance III 300 MHz spectrometer equipped with a Micro2.5 microimaging unit and a 10 mm birdcage RF coil. The measurement temperature was 25 °C. The T_1 relaxation time of the sample was measured with an inversion recovery experiment to be 270 ms. A relaxation delay of 2 s was used in all the experiments.

In the UF-PGSE (Fig. 1a) and UF-PGSTE (Fig. 1c) experiments the following experimental parameters were used: The duration and bandwidth of chirp pulse (10% "WURST"[54] smoothing in the pulse envelope) were 1.4 ms and 108490 Hz. The diffusion delay Δ was 80 ms. The strength of gradient G_{DIFF} was 0.22 T/m, and trapezoidal gradient shape was used, with the ramp time of 1 ms, plateau time of 2.8 ms (two times the length of chirp pulse) and gradient stabilization delay of 1 ms. The field of view of 3 cm was obtained by using a spectral width of 100 kHz and read gradient G_{READ} of 0.08 T/m, and 256 complex points per echo were collected. The experiment was performed with both 1 and 8 scans yielding experiment durations of 2 s and 16 s, respectively. In UF-PGSTE and UF-BP-PGSTE, a separate spin echo was created 20 ms after the principal stimulated echo with an additional hard π pulse. In the UF-BP-PGSE (Fig. 1b) and UF-BP-PGSTE (Fig. 1d) experiments the chirp pulse duration was 0.7 ms, and the diffusion gradient length was adjusted correspondingly. All other parameters were the same as in the corresponding experiments without bipolar pulses.

In the reference PGSE, PGSTE and BP-PGSTE experiments standard pulse programs were used with the following experimental parameters: The diffusion delay Δ and the length of the diffusion gradient pulse δ were 80 ms and 1 ms, respectively. The gradient strength was increased from 0.03 T/m to 0.6 T/m using 16 steps. The experiment time was 5 min 44s with 8 scans.

Results and Discussion

UF-PGSE magnetization profile of the water sample is shown in Fig. 2a. The diffusion decay curve is visible in the center of the profile, inside the range of frequencies swept by the chirp pulses. The spins outside that region are not refocused by the chirp pulses, and therefore, effectively, they are exposed to the full diffusion gradient, leading to signal amplitude close to zero. The signal amplitude close to the beginning and end of the chirp sweep region is significantly lowered because the adiabatic full-passage condition is not satisfied in the extremes. Therefore, a narrower range of data (about 80% of the full chirp sweep region) was selected for the determination of diffusion coefficient. The sensitivity profile of the coil causes its own weighting to the observed magnetization profile, but this was compensated by dividing the UF-PGSE profile by the 1D spin-echo image of the water sample (shown in Fig. 2a), measured with the same setup. The *z* axis of the profile was converted into *b* axis by using Eq. 2, and the data outside the fitting region was neglected.

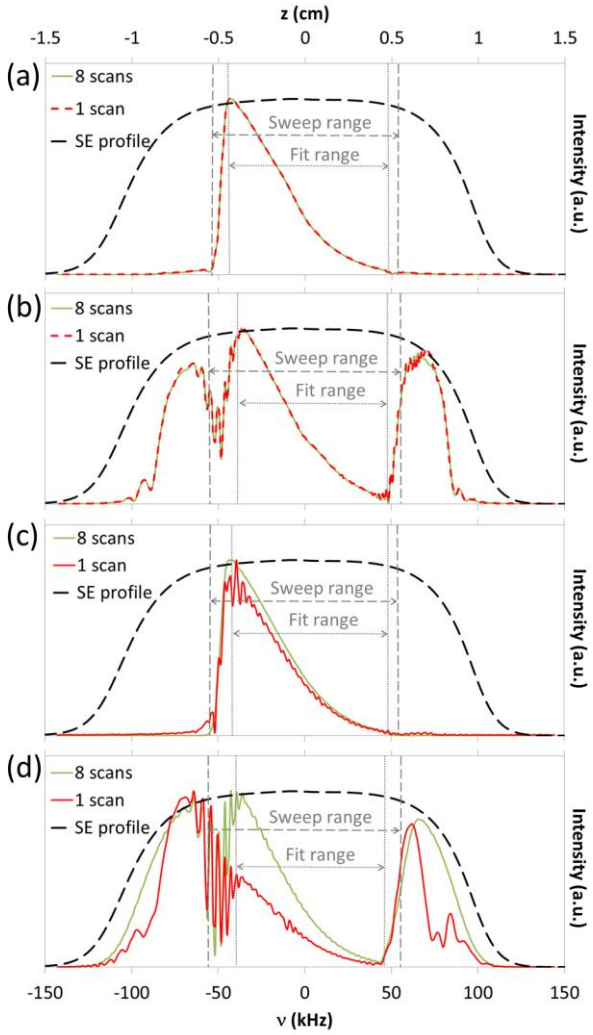

Figure 2. Magnetization profiles along the *z* axis in the water sample measured by (a) UF-PGSE, (b) UF-BP-PGSE, (c) UF-PGSTE and (d) UF-BP-PGSTE experiments, with either 1 or 8 scans. The profiles were normalized so that the maxima has the same value. The frequency range of the chirp pulse (sweep range) and the range of the data used in the determination of diffusion coefficient (fit range) are indicated in the figures. Spin-echo image of the sample (SE profile) used in the coil sensitivity profile correction is also shown in the image.

The fit of Eq. 1 to the data points (see Fig. 3) resulted in $D = (2.19 \pm 0.13) \cdot 10^{-9}$ m^2/s, where the error is determined from the variability of the observed D value when the experiment is repeated with varying experimental parameters. The average reference values given by standard PGSE, PSGTE and BP-PGSTE experiments is $(1.95 \pm 0.11) \cdot 10^{-9}$ m^2/s. Consequently, the UF-PGSE experiment seem to results in slightly overestimated value, although the overestimation is within the experimental error. Partially, the overestimation is a consequence of the fact that spins are feeling slightly different phase of the chirp pulse after they have changed their location during the diffusion delay, as described in Theory and SI; We produced theoretical data corresponding to the experimental parameters by using Eq. 5, and fit of Eq. 1 to the curve yielded the diffusion coefficient with $0.09 \cdot 10^{-9}$ m^2/s (5%) overestimation. The rest of the difference comes from the experimental error.

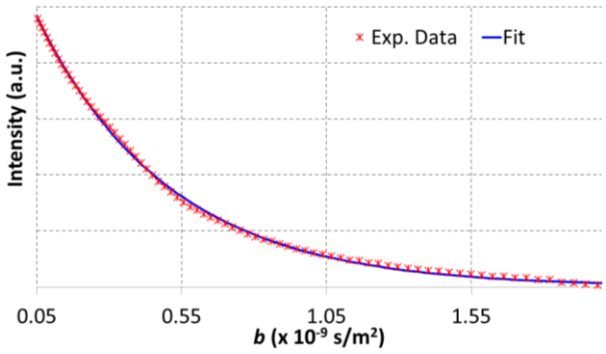

Figure 3. Coil sensitivity profile corrected experimental data of the UF-PGSE experiment in the fit range (see Figure 1) and fit of Equation 1 to data points.

Contrary to single-scan UF-PGSTE (see discussion below), single-scan UF-PGSE experiment resulted in artefact-free magnetization profile (apart from faint Gibbs ringing in the vicinity of the abrupt change in signal intensity close to the extremes of the chirp sweep region). This is extremely important for the application requiring fast monitoring or the use of hyperpolarized substances; acquisition of high-quality data does not require the repetition of the experiment.

The magnetization profiles of UF-BP-PGSE experiments are shown in Fig. 2b. Now the amplitude of signal is high outside the region swept by the chirp pulse, because the two consecutive gradients with opposite polarity result in zero net phase. The coil sensitivity correction and neglecting of data outside the chirp sweep region was performed in the similar manner as above. The fit of Eq. 1 to the data points resulted in smaller diffusion coefficient value, $(1.85\pm0.13)\cdot10^{-9}$ m^2/s, than in the case of UF-PGSE, and the value is in good agreement with the value obtained from the reference experiments within the experimental error. This implies that the use of bipolar gradients compensates the effect leading to overestimated *D* values in non-bipolar UF-PGSE experiments, as the theory predicts. Single-scan UF-BP-PGSE experiment resulted also an artefact-free magnetization profile, and the profile and diffusion coefficient are identical with the corresponding 8 scans experiment with a phase cycling.

The magnetization profile in the UF-PGSTE experiment, shown in Fig. 2c, is similar to the profile of the UF-PGSE experiment. The signal outside of the chirp sweep region is close to zero. However, in the single-scan experiment, the signal is oscillating quite much. Likely this arises from the fact that only one component of transverse magnetization is stored along the longitudinal direction during the diffusion delay and the second component is destroyed by the crusher gradient. Phase cycling removes the oscillation efficiently (four scans in enough, see

Table S3 in SI). In spite of the oscillation, the single-scan and 8 scans experiments results in equal D values, $(2.16\pm0.13)\cdot10^{-9}$ m^2/s, and therefore the single-scan experiment can be used for reliable analysis as well. The value is slightly overestimated due to the same reason as in the case of the UF-PGSE experiments. If experimental conditions allow (if T_2 is long enough), it is advisable to use UF-PGSE instead of UF-PGSTE in single-scan experiments in order to avoid the oscillation. In the multiple scan experiments, the quality of UF-PGSTE data is of the same level with the UF-PGSE.

Results of UF-BP-PGSTE experiments are shown in Fig. 2d. Similarly to UF-BP-PGSE, signal is strong outside the chirp sweep region. Signal oscillation inside the chirp sweep region is stronger than in other experiments, and the oscillation is also observed in the 8 scans experiment (see phase cycling in Table S4 in SI). It may arise from the fact that the spins at certain z position do not feel the chirp pulses at exactly identical time instances, when the polarity of the gradient pulse is changed, due to imperfections of gradient fields. The oscillations may lower slightly the accuracy of the analysis. Anyway, the data analysis results in diffusion coefficient value of $(2.12\pm0.13)\cdot10^{-9}$ m^2/s, which in agreement with the results of reference experiments within the experimental error. As explained in the theory part, UF-BP-PGSTE experiment removes the effects of both changing chirp phase at different sample layers and uniform background gradients.

One limitation of the proposed ultrafast experiments is that the frequency-swept refocusing π-pulse does not work perfectly immediately after it has been switched on. This limits the measurement of the echo amplitudes corresponding to very small and very large b values simultaneously in a single experiment, and consequently impacts the range of the diffusion

coefficients that can be detected. However, the typical moderate range of D of liquids falls well in the capacity of the experiments, as our recent ultrafast D-T_2 experiments, based on UF-PGSTE-type diffusion encoding, carried out with various solutions, including also multiple components show;[38] so far we have reported successful diffusion coefficient measurements in the range of $0.7\text{-}4.1\cdot10^{-9}$ m^2/s, but we have yet unpublished data showing that much broader range of diffusion coefficients can be detected.

Conclusions

An ultrafast diffusion experiment, UF-PGSE, exploiting spin-echoes formed by two adiabatic chirp π pulses, was introduced. The sequence shortens the experiment time by one to three orders of magnitude as compared to conventional PGSE experiment. Contrary to UF-PGSTE experiment,[28] UF-PGSE produces artifact-free data with a single-scan, providing significant prospects for monitoring fast processes in real time. Spatial encoding lowers the sensitivity of the experiment, typically by factor of four,[38] but signal-to-noise ratio per unit time may be increased, because multiple scans can be collected in the experiment time of the conventional experiment.[38,42] The single-scan approach also enables one to use hyperpolarized substances to boost the sensitivity by several orders of magnitude,[38] allowing the studies of samples with low concentration. A rigorous theoretical analysis of the echo amplitude in UF-PGSE and UF-PGSTE experiment justified the theoretical basis of the methods and revealed that the conventional exponential fit to the experimental data leads to diffusion coefficient values overestimated by a few per cent. Although this is insignificant (below the experimental error) in most of applications, alternative bipolar gradient versions of the sequences were introduced that

remove the overestimation. UF-BP-PGSTE experiment removes also the effect of uniform background gradients, which is important in materials applications.

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Supporting Information

Additional supporting information may be found in the online version of this article at the publisher's web site.

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