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Localized, Gradient-reversed Ultrafast Z-spectroscopy in vivo at 7T

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Abstract

Purpose—To collect ultrafast z-spectra in vivo in situations where voxel homogeneity cannot be assured.

Theory—Saturating in the presence of a gradient encodes the frequency offset spatially across a voxel. This encoding can be resolved by applying a similar gradient during readout. Acquiring additional scans with the gradient polarity reversed effectively mirrors the spatial locations of the frequency offsets so that the same physical location of a positive offset in the original scan will contribute a negative offset in the gradient-reversed scan.

Methods—Gradient-reversed ultrafast z-spectroscopy (GRUFZS) was implemented and tested in a modified, localized PRESS sequence at 7T. Lysine phantoms were scanned at various concentrations and compared with conventionally-acquired z-spectra. Scans were acquired in vivo in human brain in homogeneous and inhomogeneous voxels with the ultrafast direction cycled between r , p , and s . Results were compared to those from a similar conventional z-spectroscopy PRESS-based sequence.

Results—Asymmetry spectra from GRUFZS are more consistent and reliable than those without gradient reversal and are comparable to those from conventional z-spectroscopy. GRUFZS offers significant acceleration in data acquisition compared to traditional CEST methods with high spectral resolution and showed higher relative SNR efficiency.

Conclusion—GRUFZS offers a method of collecting ultrafast z-spectra in voxels with the inhomogeneity often found in vivo.

Keywords

GRUFZS; ultrafast z-spectroscopy; CEST; brain; high field; glutamate

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Introduction

Chemical exchange saturation transfer (CEST) has become a popular technique to generate MR contrast based on solution metabolite content (1, 2). CEST contrast is generated by selectively saturating at the frequency of a labile proton group, allowing those saturated protons to exchange with unsaturated protons in the bulk water pool and measuring the subsequent reduction in water signal. Due to the many exchange events happening during prolonged saturation, sensitivity can be orders of magnitude greater than direct observation of the labile protons with MRS (3, 4).

Complicating biological factors such as magnetization transfer (MT) between bound water and the free water pool and direct saturation (DS) of the water protons necessitate an additional acquisition at a symmetric offset with respect to the labile proton group. The CEST signal is then proportional to the difference between the signals at the symmetric offset frequencies. This is referred to as asymmetry analysis (2) and can be represented as

$$MTR_{asym} = \frac{M_{sat}(-\Delta f) - M_{sat}(\Delta f)}{M_{ctrl}}, \quad [1]$$

where M_{ctrl} is control signal used for normalization and can be magnetization without saturation M_0 , magnetization far away from water $M_{sat}(> 20\text{ppm}) = M_0$, or the magnetization at the negative offset frequency $M_{sat}(-f)$ (5).

Furthermore, experimental factors like B_0 field inhomogeneity result in off resonance effects that can obscure the actual exchange signal, so a range of saturation frequencies is often obtained. A plot of saturation as a function of offset frequency is known as a z-spectrum (6), and z-spectrum fitting may be able to more accurately quantify the CEST effect than the simple asymmetry analysis in Eq. [1] (7). Collecting a highly resolved z-spectrum is time consuming even for a single voxel, since CEST scans usually require long TR to allow T1 recovery between saturations and to reduce average SAR.

By playing a gradient with the saturation pulse train, the offset frequencies can be encoded spatially and read out in a single scan. This idea was applied to measure MT (8) and is similar to “ultrafast” multidimensional NMR in which spatial locations are used to encode indirect evolution times (9). More recently, ultrafast z-spectroscopy (UFZS) has been used to measure CEST contrast in vitro both unlocalized (10) and slice localized (11), and it has been shown in vivo with single voxel localization (12). In each case though, the methods require a highly uniform volume over the ultrafast direction in terms of the CEST signal produced.

Here, we present an extension to the UFZS sequence that makes it more robust to voxel inhomogeneity by acquiring an additional scan with the gradient polarity reversed. Reversing the gradient polarity also reverses the direction of frequency offsets relative to isocenter. Positive frequency offset locations with one gradient polarity become negative frequency offsets with the opposite polarity. Asymmetry analysis can then be performed using positive and negative frequency offsets from the same spatial location, as opposed to

previous methods where positive and negative frequency offsets came from opposite sides of the saturated volume. We refer to this sequence as gradient-reversed ultrafast z-spectroscopy or GRUFZS.

GRUFZS is shown in multiple voxel locations in the human brain at 7T with saturation power tailored to measure the exchange of the amine protons of the excitatory neurotransmitter glutamate (4), one of many endogenous metabolites that can be potentially analyzed using this method.

Theory

In conventional z-spectroscopy, a nonlocalized saturation pulse is applied at a given offset frequency, after which, the bulk water magnetization is measured. The full z-spectrum is obtained by sequentially stepping through an adequate range of offsets. Overall scan time is highly dependent on the desired spectral resolution and range since only a single offset frequency is acquired per scan. This is true whether or not the acquisition itself is localized.

Ultrafast z-spectroscopy (UFZS) allows the collection of the full range of frequency offsets in a single acquisition by playing a gradient simultaneously with the saturation pulse, effectively localizing it. The presence of a gradient alters the field along that axis, causing the spins to precess at different frequencies. In particular, a spin at a location r from isocenter will experience saturation at a frequency

$$f(r) = f_s - \Omega - \gamma G_s r, \quad [2]$$

where f_s is the frequency of the saturation pulse, Ω is the chemical shift off resonance, G_s is the magnitude of the saturation gradient in the r direction, and γ is the gyromagnetic ratio divided by 2π . In order to resolve this spatially-dependent offset encoding, a similar (not necessarily identical) gradient must be applied during readout, and the resulting fid or echo must be Fourier transformed to give the z-spectrum.

Although Eq. [2] represents continuous encoding along the r direction, the acquired data is always read out at discrete points with a spectral resolution given by

$$\Delta f = \frac{BW_{ro}}{N_{pts}}, \quad [3]$$

where BW_{ro} is the readout bandwidth, and N_{pts} is the number of points in the fid or echo. The readout bandwidth along with the readout gradient G_{ro} set the field of view (FOV) according to

$$FOV = \frac{BW_{ro}}{\gamma G_{ro}}. \quad [4]$$

The readout field of view is distinct from the volume of interest (*VOI*) which is the spatial extent of excited frequencies and is determined by the slice profile in the PRESS sequence. The CEST bandwidth BW_c gives the range of excited frequencies and is proportional to the saturation gradient and the *VOI*,

$$BW_c = \gamma G_s VOI. \quad [5]$$

Practically speaking, the gradient-encoded saturation and subsequent readout can be thought of as physically separating the positive offset frequencies from the negatives, where the spatial separation increases with the amount of off resonance. This can be problematic when asymmetry analysis is performed if the voxel is not homogeneous in both proton density (PD) and CEST response.

Previous UFZS implementations (8, 10, 11, 12) deal with PD differences across the volume by recording a second, reference scan without saturation. The resulting z-spectrum has the same PD profile and can be divided out from the CEST-dependent z-spectrum. However, this normalization is limited to correcting for PD differences only, which can be acceptable for in vitro studies where rounded test tubes are filled with homogeneous solution. For in vivo studies, though, rarely can a voxel with inhomogeneous PD be expected to produce a homogeneous CEST signal.

In order to partially compensate for more general errors in asymmetry analysis due to the spatial separation of the positive and negative frequency offsets, we propose the acquisition of additional scans with the saturation and readout gradient polarities each reversed. The additional scans have the same gradient amplitudes and therefore cover the same z-spectrum with the same resolution. The difference is that voxel side originally associated with the negative offsets is now associated with the positive offsets and vice versa. In postprocessing, two mixed z-spectra can be produced. One consists of the positive offsets from the original z-spectrum combined with the negative offsets from gradient-reversed spectra, and the other consists of the negative offsets from the original spectrum and the positive offsets from the gradient-reversed spectrum. Figure 1 illustrates this principle with Bloch-simulated spectra of a 2 pool exchange system (13). A linear proton density was imposed spatially to distinguish the two sides of the voxel for illustrative purposes, but it should be noted that this specific type of inhomogeneity actually can be corrected for using a scan without saturation.

The field due to the applied gradient is zero at isocenter. However, it is usually desirable to have the on-resonance, zero frequency saturation at the voxel center. This is accomplished by shifting the center frequency of the saturation pulse according to Eq. [2],

$$0 = f_s - \gamma G_s x_0, \quad [6]$$

where x_0 is the voxel center position (12). The readout digital sampling frequency f_{ro} must be shifted as well for 0 Hz to appear in the center of the z-spectrum,

$$0 = f_{ro} - \gamma G_{ro} x_0. \quad [7]$$

The center frequency shifts are opposite for the positive and negative gradient polarities as illustrated in Supporting Fig. S1.

Methods

Pulse sequence

The pulse sequence is a modified version of PRESS (14) in which saturation is applied concurrently with a gradient before three plane localization. Saturation used Hanning-filtered rectangular pulses. Excitation used a hard, nonselective 90° pulse, while localization used three identical slice-selective sinc refocusing pulses. This was done so that there would be no slice profile differences in any of the three directions, but a more traditional PRESS localization could be used instead. To keep the refocusing pulse durations short and their bandwidths high, a flip angle of 160° was used instead of the usual 180° . Matched spoilers around each pulse ensured the dephasing of any parasitic fids. A gradient echo readout was started at the top of the final spin echo. The echo was created asymmetrically in the readout, with the goal of forming the echo as early as possible during the readout to minimize $T2^*$ decay while still ensuring that the echo was sampled in its entirety. The GRUFZS pulse sequence is shown in Fig. 2 for the case in which the z-spectrum is encoded in the r direction. An alternative version of the sequence in which the gradient echo is timed to coincide with the final spin echo produced by the localization is shown in Supporting Fig. S2.

In addition to specifying the z-spectral axis, BW_{ro} and voxel size are user-determined along with an oversampling factor n_{os} that relates the CEST bandwidth to the prescribed readout bandwidth,

$$BW_c = \frac{BW_{ro}}{n_{os}}. \quad [8]$$

BW_c was fixed to ± 1500 Hz (± 5 ppm) for each voxel. From BW_c and voxel size, the saturation gradient strength G_s was calculated using Eq. [5] and was 3.52 mT/m for a 2 cm size voxel. G_{ro} was set to the same amplitude as G_s for convenience. A large oversampling factor ($n_{os} = 10$) was used to ensure adequate sampling of the gradient echo.

For comparison purposes, a similar single voxel spectroscopy sequence was used to collect z-spectra in the conventional manner of stepping through offset frequencies.

Phantom Studies

Lysine solutions with 100 mM, 50 mM, and 0 mM were prepared at a pH of 4 and scanned on a Siemens Magnetom 7T whole body scanner equipped with a 32-channel receive/transmit head coil. Ten scans were collected with the ultrafast gradients applied in each of

the r , p , and s directions. Acquisition parameters were as follows: TR = 15 s, TE = 30 ms, echo formed at 20% of the readout duration, voxel size $2 \times 2 \times 2 \text{ cm}^3$, 10x oversampling collecting 4096 spectral points. Saturation parameters were peak $B_1 = 100 \text{ Hz}$, total saturation duration of 1 s, individual pulses 98 ms with 2 ms dead time between pulses. Ten conventional z-spectra were also acquired with identical saturation parameters and 51 offset frequencies spaced 0.2 ppm apart.

A 10 mM solution of monosodium glutamate was also prepared and scanned with a custom built small solenoid coil with the following acquisition parameters: TR = 15 s, TE = 30 ms, echo formed at 20% of the readout duration, voxel size was $15 \times 15 \times 15 \text{ mm}^3$, 2 averages. Ultrafast gradients were applied in the r direction only. Peak B_1 amplitude and saturation duration were varied to measure CEST response. These results are presented in Supporting Fig. S3.

Human Subject Studies

Six healthy volunteers were scanned using a Siemens Magnetom 7T whole-body scanner equipped with a 32-channel head coil. Target voxels were identified in the gray matter (GM) of the prefrontal cortex (PFC) and thalamus, as well as in the anterior cortical white matter (WM) using an initial 3D MP-RAGE (15) scan. The WM voxels were chosen to be largely homogeneous with little partial voluming, while the GM voxels had considerable partial voluming visible on the localized image. Center frequency, shim, and reference transmitter voltage were adjusted manually. Scans used a TR/TE of 8000/30 ms with 4096 total collected points and a 10x oversampled spectral window with the echo forming at 5% of the readout duration. Peak B_1 amplitude was 220 Hz with 800 ms saturation. Voxel size was $15 \times 15 \times 15 \text{ mm}^3$, and four averages were acquired. Saturation and readout gradient pairs were applied in each spatial direction. Conventional z-spectra were acquired with identical saturation parameters and 51 offset frequencies (0.2 ppm step size). All scans were conducted under an approved Institutional Review Board protocol of the University of Pennsylvania. Written, informed consent was obtained from all participants prior to being scanned.

For an additional volunteer, 10 GRUFZS scans and three conventional scans were collected in succession from the same white matter voxel to test reproducibility. Parameters were the same as above except that in the ultrafast scans, a single average was collected, the voxel volume was increased to $20 \times 20 \times 20 \text{ mm}^3$, and only one ultrafast gradient direction was collected. In the conventional scans, the step size was increased to 0.3 ppm, and 33 offset frequencies were collected.

Data Processing

Conventional z-spectroscopy—Raw data was exported from the scanner and processed offline in Matlab (Mathworks, Natick, MA). For each offset frequency, coil combination was performed on the absolute magnitude of the first time point. (We have also processed conventional spectra by Fourier transforming the fid, phase correcting the individual coils, summing, and fitting a Lorentzian to the water peak, but we found no significant difference compared to the simpler method we used.) The acquired z-spectrum was interpolated to 0.05

ppm resolution using cubic splines and smoothed with a three point moving average filter. Since no reference scan was collected, the z-spectrum was scaled to a maximum of 100%.

GRUFZS—The raw, time domain data from each coil was combined after phase correction and filtered using a binary threshold at the noise level since the readout was much longer than the actual echo duration. The filtered data was then Fourier transformed to the spatial/z-spectral domain. At this point, off resonance can be corrected by setting the minimum of the saturated z-spectra to 0 Hz. However, with proper frequency adjustment before scanning, we found that this step is often not necessary unless repeated measurements are taken. Each z-spectrum with on resonance saturation was normalized by the corresponding reference one. The reference scan can either be acquired with no saturation or with saturation far away from resonance ($> 20\text{ppm}$). Empirically, we have found better stability with the latter method in terms of scaling and SNR. To match scaling with the conventional z-spectrum, the maximum value of the normalized spectra was scaled to 100%, and the spectra were smoothed with a moving average filter. Mixed z-spectra were created by taking the positive frequency offsets from one spectrum and combining it with the negative frequency offsets of the reversed-polarity spectrum as described visually in Fig. 1. If a reference offset is collected in the conventional spectrum for scaling and the scaling between the reference and on resonance ultrafast scans is the same, no additional scaling or normalization is needed when taking the asymmetry.

Results

Phantom

Figure 3 shows a comparison of repeated scans with GRUFZS and conventional z-spectroscopy. The mean z-spectra are shown for each concentration with both acquisitions (ultrafast direction s for GRUFZS). Shading shows the standard deviations of the z-spectra at each frequency point. The standard deviations are very low away from the DS for both scans. The higher variation of the conventional z-spectroscopy around the DS is due to field drift during the prolonged scan time. Table 1 shows the signals and standard deviations at the lysine exchange peak for those scans along with scans collected with the ultrafast direction in the r and p . The signals are all within 1% on the normalized z-spectra. While the SNR of conventional z-spectroscopy is higher as expected, the relative SNR efficiency found by dividing the SNR by the square root of the acquisition time and normalizing to the conventional z-spectroscopy shows that the ultrafast scans are about twice as efficient on average. Supporting Fig. S4 shows the additional GRUFZS z-spectra with r and p ultrafast gradient directions along with a UFZS reconstruction (ultrafast direction r) that does not recombine the acquired z-spectra. For a uniform phantom, the choice of ultrafast direction is unimportant, and z-spectral recombination is not necessary.

Human brain

Figure 4 shows spectra from scans in the cortical white matter of two volunteers. In the first volunteer, the positive and negative UFZS produced qualitatively similar asymmetry curves with the negative curve being shifted downward (Fig. 4a), resulting in a large difference (over 10% at 3 ppm) depending on the choice of gradient polarity. Recombining the “left”

and “right” z-spectra results in nearly identical asymmetry curves (Fig. 4b) and a much better match to the conventionally-acquired z-spectrum (Fig. 4c). In the second volunteer, the positive and negative UFZS produced vastly different asymmetry curves that are obviously unusable (Fig. 4d) before recombination (Fig. 4e). Again, the “left” and “right” z-spectra closely match each other and the conventional z-spectrum from the same voxel (Fig. 4f).

For voxels with large gray and white matter partial voluming, the left and right z-spectra have clearly different direct saturation effects as shown in Fig. 5a,d. When the asymmetry is calculated, the difference in DS widths results in artifactually high values that can be either positive or negative. If the spectra are recombined (Fig. 5b,e), the asymmetry in the DS is mainly accounted for, and the calculated asymmetry can reasonably be ascribed to chemical exchange. Conventional z-spectra are an average over all the components in the entire volume, which can be clearly seen in Fig. 5c where the DS width appears to have two distinct components.

Generally speaking, the asymmetry curves from the acquired positive and negative z-spectra often straddle zero, making their individual values unreliable. The recombined z-spectra, on the other hand, continually result in positive MTR_{asym} values that are usually within 2% of each other. Additional examples are given in Supporting Figs. S5 and S6. Supporting Figure S7 shows the acquired and recombined z-spectra from a relatively homogeneous voxel with the ultrafast gradient direction varied, indicating the stability of the method.

Figure 6 shows the results of repeated GRUFZS and conventional z-spectroscopy scans on the same voxel. In this case, the variation in the conventional scans is larger, and the mean spectrum is noisier than GRUFZS. Each GRUFZS spectrum was acquired in 32 s (4 scans), while each conventional spectrum required 4 min 24 s (33 scans), suggesting that the noisier conventional spectrum is likely the result of motion artifacts.

Discussion

There are numerous factors that can affect the measured MTR_{asym} besides metabolite concentrations. External factors such as B_0 or B_1 inhomogeneity should be relatively unimportant for setups using clinical hardware over a single voxel volume. Inhomogeneities as a result of partial voluming are often significant though for typical voxel sizes and are averaged out in a conventionally-acquired z-spectrum. Proton density differences across the voxel affect the amplitude of signal and can be corrected by the previously described methods using an unsaturated (or off resonance) scan since they appear in both scans. However, differences in T2 or susceptibility cause changes in the saturated z-spectrum but not in the reference scan and cannot be corrected that way.

The readout bandwidth BW_{ro} and number of points N_{pts} were used to calculate the spectral resolution in Eq. [3]. As previously mentioned, f represents a discrete approximation to continuous encoding. However, the frequency spread is increased because of T2* decay during readout. At 7T, we have found that the gradient echo amplitude dies out after about 10 ms and can be represented by a few hundred points only. Therefore, the actual spectral

resolution of the ultrafast scans is less than predicted by Eq. [3] but is at least as good as that of a conventionally acquired z-spectrum which uses fewer points and still requires significant interpolation.

Even with the addition of two extra scans to the previous UFZ approaches, GRUFZS still offers a significant time reduction compared to conventional z-spectroscopy. For the in vivo experiments in this study, the GRUFZS data collection used four (or one) averages and required 16 (or four) acquisitions for a 0.03 ppm digital spectral resolution. Conventional z-spectroscopy at that resolution with a single average would over 300 acquisitions and take 20 times longer. The effective resolution in vivo in this study was closer to 0.2 - 0.3 ppm which would require between 30 - 50 acquisitions for conventional z-spectroscopy with a single average. In that case, GRUFZS still offers at least 2× acceleration, while for the single average scans in Fig. 6, the acceleration is at least 8×. Since the scan time for conventional z-spectroscopy is proportional to the spectral resolution, the relative acceleration of GRUFZS increases in situations where the achievable resolution is greater or in situations where averaging is not required.

To obtain a single asymmetry spectrum or MTR_{asym} value for the voxel, the “left” and “right” asymmetry spectra can be averaged. It should be noted that averaging these values calculated from the two mixed z-spectra is exactly the same as averaging the values calculated from the two acquired z-spectra without mixing when the normalization uses M_0 in Eq. [1]. If negative frequency offset normalization is used, these averages are not identical since $\frac{M_n(\Delta f)}{M_n(-\Delta f)} + \frac{M_p(\Delta f)}{M_p(-\Delta f)} \neq \frac{M_p(\Delta f)}{M_n(-\Delta f)} + \frac{M_n(\Delta f)}{M_p(-\Delta f)}$, but they are still similar. Even if M_0 normalization is used, the mixed z-spectra provide a nice consistency check of the overall voxel homogeneity and should be used. If the two MTR_{asym} values are too far apart, the voxel is too inhomogeneous to be accurately represented by a single value anyway.

An alternative to averaging the mixed z-spectra is to think about them as being from two half voxels, one from the left half of the full voxel and one from the right half. The mixed z-spectra can then be kept separate, and MTR_{asym} values can be calculated for the two smaller adjacent voxels. This can be particularly useful when examining a suspicious lesion. In such cases, a voxel inside the lesion is typically compared to a voxel outside. By placing a larger volume of interest centered on the interface between the lesion and normal tissue, these two voxels can be recorded simultaneously, provided that ultrafast gradient direction is the same as the tissue interface direction. Choosing the wrong gradient direction for the ultrafast saturation/readout would result in mixed z-spectra that each represent an average of the two tissue types. Differences in these half voxels contribute to most of the residual differences between the “left” and “right” mixed z-spectra when the voxels are inhomogeneous.

In a hypothetical situation where the localized voxel is composed of two otherwise uniform tissue types that are separated exactly in the center, GRUFZS will result in perfect reconstruction of z-spectra for each side with half voxel resolution when the ultrafast direction is chosen perpendicular to the tissue interface. Alternatively, if the voxel variation is in a direction perpendicular to the ultrafast gradient direction, GRUFZS theoretically would reconstruct identical spectra that represent whole voxel averages. For any other tissue distribution, voxel inhomogeneity still can cause differences in the mixed z-spectra, and it

should always be the operator's goal to choose a region that is as homogeneous as possible or orient the voxel such that the ultrafast direction is perpendicular to the tissue interface. Nevertheless, using gradient-reversed acquisitions would still be more robust than other UFZS methods, while conventional single voxel z-spectroscopy is always limited to being a weighted average over partial volumes.

If MTR_{asym} is calculated using the negative frequency offset for normalization in Eq. [1] and the desired offset is directly sampled during readout, no additional reference scans are needed to compensate for PD, and the overall scan time can be further reduced to $2 \times TR$. This is identical in scanning efficiency to previous UFZS sequences which require a reference scan to compensate for PD differences no matter how MTR_{asym} is calculated. Similarly, if dynamic changes in CEST contrast are being measured (16), reference scans only need to be acquired once. Nevertheless, the method is most robust to experimental errors when all four scans are collected and still offers subminute temporal resolution even with long TR.

GRUFZS was included here with a modified PRESS sequence, but it can be added to any single voxel spectroscopy sequence, such as STEAM (17), LASER (18), or semi-LASER (19). While each of those sequences can be particularly advantageous for high field spectroscopy, most of their benefits, such as less T2 signal decay and reduced chemical shift displacement error, are not as important in z-spectroscopy.

As with any ultrafast method, there is an SNR penalty associated with the effective reduction in volume for each offset. However, phantom data in Table 1 suggests that UFZS has better scanning efficiency compared to conventional z-spectroscopy when the fully-processed spectra are compared. The averaging required in GRUFZS varies depending on the voxel and scan parameters, though Figure 6 does show highly reproducible spectra acquired with a single average. Even in situations where the amount of averaging required makes the overall scan time comparable to a conventionally-acquired z-spectrum, there are still advantages to collecting an entire spectrum in a single shot. Artifacts such as motion or field drift that result in a shift of the center frequency can be corrected in an ultrafast acquisition by placing the minimum value of the spectrum on resonance at 0 ppm. Such a correction cannot readily be applied in conventional z-spectroscopy.

Ultrafast z-spectrum acquisition has recently been applied to acquire images of full z-spectra in phantoms with PARACEST agents (20). In this case, multiple physical slices are saturated at different offsets simultaneously and read out as part of a multislice imaging technique. There are numerous other challenges to ultrafast CEST imaging in vivo, but in principle, the idea of gradient polarity reversal could still be applied to compensate for inhomogeneity in the slice direction.

Conclusion

We have presented a method to acquire ultrafast z-spectra in vivo that requires only an additional scan with the gradient polarity reversed, sacrificing some acquisition speed for increased tolerance of voxel inhomogeneity. This improved tolerance to inhomogeneity is

evident in the asymmetry curves of the mixed z-spectra compared to the originally acquired ones. Quantitative CEST values of glutamate are similar to those acquired with a conventional single voxel-based z-spectroscopy sequence. This method offers a fast, robust way to record full z-spectra in vivo.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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1.

Illustration of GRUFZS z-spectra acquisition and processing using a 2 pool model. **(a)** z-spectrum acquired with a positive saturation gradient, **(b)** same z-spectrum as (a) with the frequency axis reversed, **(c)** z-spectrum acquired with a negative saturation gradient, **(d)** conventional z-spectrum acquired without a gradient, **(e)** mixed, “right” z-spectrum constructed from the right half of (b) and the left half of (c), **(f)** mixed, “left” z-spectrum constructed from the left half of (b) and the right half of (c). Note that the CEST exchange dip appears at the same frequency in each spectrum. Blue axes indicate the spatial positions of the offsets in the ultrafast z-spectra. Red and green dashed arrows show the mixing of the positive (b) and negative (c) spectra to form the “right” (e) and “left” (f) mixed z-spectra. A linear proton density gradient was imposed across the voxel dimension to aid in the visualization.

2.
GRUFZS pulse sequence. Dashed lines indicate the gradient polarity reversal of the saturation gradient, readout gradient, and readout gradient prephaser. Saturation used a train of Hanning-filtered rectangular pulses. The gradient echo is formed asymmetrically during readout.

3.

Mean z-spectra with MTR_{asym} for GRUFZS (solid line) with ultrafast direction s and conventional z-spectroscopy (individual points) collected in lysine phantoms (Red = 100 mM, Green = 50 mM, Blue = 0 mM). The scans match up well except for some effects of field drift at around 0 ppm associated with the longer scan times in the 0 mM conventional spectra.

4. z-spectra from relatively homogenous white matter voxels in two healthy volunteers. **(a)** Acquired z-spectra with positive (red) and negative (blue) ultrafast gradients in first volunteer. **(b)** Recombined z-spectra showing the “left” (green) and “right” (orange) z-spectra from (a) as well as a conventionally-acquired z-spectrum (black) from the same voxel. **(c)** Acquired z-spectra in second volunteer. **(d)** Recombined z-spectra from (c) along with conventional z-spectrum.

5.

z-spectra from inhomogeneous voxels with large partial voluming of gray/white matter in two healthy volunteers. **(a)** Acquired z-spectra with positive (red) and negative (blue) ultrafast gradients in first volunteer. **(b)** Recombined z-spectra showing the “left” (green) and “right” (orange) recombined z-spectra from (a) and a conventionally-acquired z-spectrum (black) from the same voxel. **(c)** Acquired z-spectra in second volunteer. **(d)** Recombined z-spectra from (c) and conventional z-spectrum.

6. Reproducibility of **(a)** GRUFZS and **(b)** conventional single voxel z-spectroscopy. The solid lines show the average of 10 GRUFZS and 3 conventional z-spectra from an identical voxel, while the shading shows the standard deviations. Each GRUFZS z-spectra had only one average but did average over the two recombined z-spectra.

Table 1

Comparison of the number of acquisitions (N_{acq}), mean signal amplitude (S), noise (σ), signal-noise-ratio ($SNR = S/\sigma$), standard deviation (SD), coefficient of variation ($CV = 100\ SD/S$), and SNR efficiency ($SNR_e = SNR / \sqrt{N_{acq}}$) for lysine phantom data with 50 mM and 100 mM concentration. S and SD were calculated at the offset of the lysine exchange peak at 2.9 ppm in the asymmetry spectra. σ was calculated as the standard deviation over the range from 1-4 ppm in the 0 mM scans. This range was chosen to avoid any DS artifacts or any edge effects in the slice profile. r , p , s subscripts indicate the ultrafast gradient direction.

	Conv		GRUFZS	
	N_{acq}	51	4	
0 mM	σ	0.13	0.20	
	S	10.62	10.66	
	SNR	80.5	52.3	
50 mM	SNR_e	11.3	26.1	
	SD	0.23	0.36	
	CV	2.14	3.41	
100 mM	S	22.91	22.68	
	SNR	173.6	111.1	
	SNR_e	24.3	55.6	
	SD	0.27	0.33	
	CV	1.17	1.46	