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A Post-processing Framework for Localized 2D MR Spectroscopy in Vivo

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Purpose: We propose a post-processing framework for localized two-dimensional (2D) magnetic resonance spectroscopy (MRS) in vivo.

Methods: Our framework consists of corrections on eddy current and subject motion along with the framework used in conventional analytical 2D nuclear magnetic resonance (NMR) spectroscopy. In the eddy current correction, the phases of the free induction decays (FIDs) of the metabolite $^1$H are corrected along the $t_2$ direction by the phase of the FID of water $^1$H. The corrected FIDs are Fourier transformed along the $t_2$ direction, and interferograms of $F(t_1, \omega_2)$ are calculated. In the motion correction, the zero-order phase of the N-acetyl aspartate (NAA) singlet peak for each $t_1$ axis is corrected after correction of frequency drift.

We applied this framework in phantom and human brain measurements in a 4.7T whole-body MR system. Two-dimensional data were collected by the localized 2D constant-time correlation spectroscopy (CT-COSY) sequence. We used a phantom containing a brain metabolite mixture of NAA, creatine (Cr), glutamate (Glu), glutamine (Gln) and $\gamma$-amino butyric acid (GABA). We demonstrated the eddy current correction procedure in the phantom experiments and the subject motion correction in human measurements.

Results: Though asymmetric patterns of the singlets of NAA and Cr were shown around the peak along the $F_2$ direction in the reconstructed phantom spectra without eddy current correction, symmetric patterns arose after the correction. The $t_1$ noise caused by those singlets was found in the human brain spectra without motion correction. The $t_1$ noise was sufficiently suppressed by the motion correction.

Conclusion: Our proposed post-processing framework for localized 2D MRS can improve the quality of in vivo 2D spectra and may allow improved quantitation and robustness of in vivo 2D spectroscopy.

Keywords: two-dimensional $^1$H MR spectroscopy, in vivo, human brain, eddy current, motion

Introduction

Multidimensional nuclear magnetic resonance (NMR) spectroscopy is indispensable for structural studies of proteins or nucleic acids. This method can reveal connectivity and distance between spins by various kinds of spin information associated with chemical shifts and couplings. Recently, localized versions of sequences of two-dimensional (2D) $^1$H spectroscopy have been developed, and 2D spectra of human brains have been reported. Because one of the important roles of in vivo 2D magnetic resonance spectroscopy (MRS) is the high resolution of resonances, constant time (CT) methods that can decouple spins along $F_1$ are promising. Though glutamate (Glu), $\gamma$-amino butyric acid (GABA), and glutamine (Gln) are heavily overlapped in one-dimensional (1D) $^1$H spectra as a result of small chemical shift differences and spin couplings, those resonances can be resolved in spectra obtained by a CT-correlation spectroscopy (COSY) sequence and in those obtained by CT-point resolved spectroscopy (PRESS) at 4.7T.
These new technologies of 2D MRS are also in demand for in vivo MRS fields.

In analytical NMR spectroscopy, various post-processing methods for obtaining 2D spectra have been developed. In addition to these methods, special tools are required for in vivo 2D MRS. The first is a correction method for spectral distortion by the eddy current induced by gradient pulses for localization. The second is a correction for subject motion that causes t1 noise running parallel to the F1 axis caused by a strong peak on the 2D spectra. Although a post-processing framework including these correction methods is required for in vivo 2D MRS, it has not been discussed in the literature.

In this work, we propose a post-processing procedure for in vivo 2D MRS and demonstrate the efficiency of 2D 1H spectra of the human brain.

Materials and Methods

Figure 1 shows a proposed framework for in vivo 2D MRS, which consists of 3 correction methods for in vivo spectra and the conventional reconstruction methods of applying window functions and zero filling. After 2D MRS signals are accumulated and the 2D time domain (TD) dataset S(t1, t2) is stored on a computer, eddy current correction is applied along the t2 direction. The window function is then applied to increase the signal-to-noise ratio, and zero filling is done along the t2 direction. Next, S(t1, t2) is generated, a 1D Fourier transformation (FT) is applied along the t2 direction, and the interferogram that is a series of 1D spectra F(t2, ω2) is calculated. Then, a motion correction, consisting of frequency drift and zero-order phase corrections, is applied for each 1D spectrum of ω2. Finally, a window function is applied and zero filling is done along the t1 direction. After the one-dimensional FT of t1, we can obtain a 2D spectrum F(ω1, ω2). In the following, we explain 2 methods for correcting artifacts resulting from eddy current and subject motion.

Eddy current correction

The magnetic fields induced by eddy currents that come from gradient pulses distort the 2D spectra. We explain the correction method here for the case of spectra obtained by the localized 2D CT-COSY sequence shown in Fig. 2.4

This sequence consists of the water and outer volume suppression (OVS) modules and the localized CT-COSY module. The localized CT-COSY module consists of the 90° pulse for preparation for the first slice localization, the 180° pulse for refocusing and inversion for the second slice, and the 90° pulse for mixing of the third slice.

In the CT-COSY module, the delay between the
first preparation and the third mixing pulse is kept constant during the entire measurement. The temporal position of the 180° pulse with the slice and crusher gradient pulses is shifted for each t₁ increment. These pulses are indicated as crosshatched areas in Fig. 2. The temporal positions of the other pulses are fixed. The number of t₁ increments is defined as n_i. Thus, n_i free induction decays (FIDs) modulated by t₁, are collected along the t₂ direction. The 2D time domain dataset of metabolite signals, S(t₁, t₂), is accumulated after the scan. As the ¹H chemical shift is refocused by the 180° pulse in the CT-COSY module, the generated chemical shift evolution depends on the t₁ increment. In contrast, J_HH evolution is kept constant because J_HH is not affected by this 180° pulse. After reconstruction, the 2D spectra are decoupled along the F₂ direction.

The temporal positions of gradient pulses other than those shown as crosshatched areas are identical during the entire measurement in this sequence. Because the effects of eddy currents caused by those non-shifted gradients to all FIDs on S(t₁, t₂) are the same, those eddy currents distort peaks only along the F₂ direction. The following eddy current correction method for 1D spectra can be used to correct those effects.

Upon the appearance of an eddy current, the water ¹H signal, S_water, at resonance is described as:

\[ S_{\text{water}}(t) = A_{\text{water}}(t) e^{i\phi_{\text{eddy}}(t)}, \]

where \( A_{\text{water}}(t) \) is the amplitude of the water signal and \( \phi_{\text{eddy}}(t) \) is the phase induced by the eddy current. The ¹H signal of the metabolite S_metabolite(t) is also described as:

\[ S_{\text{metabolite}}(t) = A_{\text{metabolite}}(t) e^{i(\omega t + \phi_{\text{eddy}}(t))}, \]

where \( A_{\text{metabolite}}(t) \) is the amplitude of the metabolite signal and \( \omega \) is the resonant frequency of the metabolite. Because \( \phi_{\text{eddy}}(t) \) corresponds to the phase of the water signal from Eq. [1], we can eliminate \( \phi_{\text{eddy}}(t) \) from Eq. [2], and the phase induced by the eddy current can be corrected for the ¹H signal of metabolites. To correct the eddy current of the 2D dataset of S(t₁, t₂) along t₂, the FID of water, ¹H S_water(t₁ = 0, t₂), is acquired by the localized 2D CT-COSY sequence without water suppression with the value of t₁ set to zero.

The effects of t₁-dependent eddy currents caused by crosshatched gradient pulses in Fig. 2 can be classified into 2 types. The first is a t₁-dependent phase shift of each FID, which causes artifacts along the F₁ direction (t₁ noise). In our method, this phase shift is corrected with the motion correction. The second effect is the peak distortion along the F₂ direction in the same manner as described above, but with t₁ modulation. To correct those distortions, the entire dataset for water ¹H signals, S_water(t₁, t₂), should be accumulated apart from the collection of the data for metabolite signals, S(t₁, t₂). However, this measurement is time-consuming. Instead, we correct the entire dataset of S(t₁, t₂) using the FID of S_water(t₁ = 0, t₂) in our method. We did phantom experiments to validate this correction method.

**Motion correction**

The subject’s motion shifts the position of the voxel and causes B₀ shifts. This affects the 2D spectrum along both the F₁ and F₂ axes. This motion causes a frequency shift along the F₂ axis because the resolution in the frequency domain is a few Hz in ¹H MRS. This effect can be corrected by the frequency drift correction.

In the t₁ direction, the subject’s motion causes rotation of the magnetization vector in the voxel, and the zero-order phase is added to the FID signal at each t₁. Because this phase varies randomly for n_i FIDs, t₁ noise arises along the F₁ direction after the 2D FT. In our method, this artifact is corrected as follows. First, the dataset, S_n(t₁, t₂) in the t₁ − t₂ domain after eddy current correction, is Fourier transformed along the t₂ direction, and n_i separate interferograms F(t₁, \( \omega_2 \)) in the t₁ − F₂ domain are calculated. Second, the phase of the resonance for the singlet of N-acetyl aspartate (NAA), at 2.01 ppm, \( \phi_{\text{NAA}}(t₁) \), is calculated at each t₁. Next, the zero-order phase correction is performed for each F₂ spectrum using \( \phi_{\text{NAA}}(t₁) \) to remove the zero-order phase changes. Finally, the corrected dataset is Fourier transformed along the t₁ direction, and the 2D spectrum, without motion effects, can be obtained. This zero-order phase correction can also correct for changes in phase due to the t₁-dependent eddy currents mentioned earlier.

**Experimental**

We performed phantom experiments and volunteer measurements using a 4.7T INOVA whole-body MR system (Agilent, Palo Alto, CA, USA) with a quadrature volume transverse electromagnetic (TEM) coil of 130-mm diameter for both transmission and reception.

In the phantom experiments, we used a phantom containing a brain metabolite mixture consisting of 10 mM of NAA, 8 mM of creatine (Cr), 9 mM of Glu, 3 mM of Gln, and 2 mM of GABA. We placed a 200-mL bottle containing this solution in a water bath containing 0.9% dissolved sodium chloride (NaCl) to mimic the in vivo load. We first obtained the 2D TD dataset of localized CT-COSY signals...
inside a voxel of $25 \times 25 \times 25$ mm$^3$ within the bottle. Next, we applied our proposed post-processing framework, without the zero-phase correction for minimizing motion artifacts, to this 2D TD dataset and obtained 2D CT-COSY spectra. For comparison, we also performed our framework without the eddy current and the zero-phase corrections to the same dataset.

Volunteer measurements were performed after obtaining informed consent following the protocol approved by the internal review board at the National Institute for Environmental Studies. We selected a volume of interest (VOI) of $30 \times 30 \times 30$ mm$^3$ in a parieto-occipital region on a scout image. First, a line width of roughly 10 Hz on the $^1$H spectrum was achieved by FASTMAP shimming. After radio frequency (RF) power adjustments, water signal was measured for the eddy current correction. Then, localized CT-COSY signals were acquired with a measurement time of 20 min. Next, we applied our framework to the 2D TD dataset and obtained the CT-COSY spectra. For comparison, we also performed our framework without motion correction to the same dataset.

In all CT-COSY measurements, we used a simultaneous quadrature detection to acquire 512 complex data points in $t_2$ (number of points $n_p = 1024$) with 150 increments in $t_1$ (number of $t_1$ increments $n_i = 150$). The spectral width for $F_1$ was 1 kHz, and that for $F_2$ was 2 kHz. The constant time delay was $T_{ct}$ of 110 ms, with TR of 3 s. In the human brain measurements, a Gaussian window function, described as $\exp \left[ -((t-gfs)/gf)^2 \right]$, was applied in both the $t_1$ and $t_2$ directions. The parameter values recorded were $gf = 0.15$ s along the $t_2$ direction and $gf_1 = 0.1$ s, shifted by $gfs_1 = 0.075$ s along the $t_1$ direction. In the phantom experiments, the Gaussian window function was applied in the $t_2$ direction and the sine-bell window function, described as $\sin \left( \frac{\pi t}{2sb} \right)$, was applied in the $t_1$ direction. The parameter values used were $gf = 0.15$ s along the $t_2$ direction and $sb_1 = 0.075$ s along the $t_1$ direction.

Results

Figure 3 shows the 2D CT-COSY spectra of the phantom without (a) and with (b) eddy current correction. The spectra are displayed in a magnitude mode. In the spectrum without eddy current correction, the peaks are distorted, and asymmetric patterns appear around the peak along the $F_2$ direction. These features are shown in 3 single peaks of NAA at 2.01 ppm, Cr at 3.02 ppm, and Cr at 3.91 ppm. In contrast, peak patterns are corrected and symmetric patterns arise in the spectrum with the eddy current correction (b). To evaluate this asymmetry of the peak shape caused by the eddy current, we defined a ratio of the left half width to the

**Fig. 3.** Spectra of a phantom containing brain metabolite mixtures at 4.7T obtained by the localized two-dimensional (2D) constant-time correlation spectroscopy (CT-COSY) sequence. Before the eddy current correction, 3 singlet peaks of N-acetyl aspartate (NAA) and creatine (Cr) show a distorted pattern along the $F_2$ direction and asymmetric patterns about the peak (a). After the correction, these distortions disappear, and symmetric patterns arise (b). We measured the right width of $"a"$ and the left width of $"b"$ at 1% of the peak height of the NAA singlet and calculated a ratio of $"b/(a+b)"$ to evaluate this asymmetry (c). When a peak shape is symmetric, this ratio is 0.5. Whereas this ratio was 0.648 on spectrum (a) without the eddy current correction, it was 0.483 on spectrum (b) with that correction.
full width as shown in Fig. 3c. We measured the right width of "a" and the left width of "b" at 1% of the peak height of the NAA singlet and calculated a ratio of "b/(a+b)". When a peak shape is symmetric, this ratio of b/(a+b) is 0.5. Whereas this ratio was 0.648 on the spectrum (a) without eddy current correction, it was 0.483 on that (b) with correction. These results show that the 1D water $^1$H signal, $S_{water}(t_1=0, t_2)$, is sufficient for eddy current correction.

Figure 4 shows an expanded area around the singlet of NAA at 2.01 ppm on the interferogram of $F(t_1, \omega_2)$ of a human brain after a 1D FT along the $t_2$ direction. Figure 4a shows the interferogram reconstructed without motion correction in the magnitude mode. The peaks of NAA are shifted along the $F_2$ direction. The embedded red line traces the peak of this NAA singlet (a).

After frequency shift correction, the peaks were aligned (Fig. 4b). On the real part of the interferogram of $F(t_1, \omega_2)$, after the frequency shift correction shown in Fig. 4d, the phases of the NAA singlet peaks were found to vary along the $t_1$ direction. In the scanning of the CT-COSY signals, the resonant frequency of the NAA singlet is not tuned to the central frequency. Instead, the chemical shift evolution adds these phase changes. Because this evolution has a linear dependence in the $F_2$ direction, the zero-order phase correction does not remove the chemical shift evolution. Figure 4c shows the phase change curve of the NAA singlet in the interferograms of $F(t_1, \omega_2)$ before (black line) and after (red line) the phase correction for $t_1$. Figure 4a also shows the curve before the zero-order phase correction as a white line.

Figure 4e shows the real part of the interferogram after the zero-order phase correction. Phases of the NAA singlet peaks along the $t_1$ direction were corrected to roughly the same phase.

Figure 5 shows the 2D spectrum of the human brain after a 2D FT without motion corrections (a) and the spectrum reconstructed with motion corrections (b). These spectra were applied with eddy current correction. Two singlet peaks of NAA at 2.01 ppm and Cr at 3.0 ppm caused $t_1$ noise on the original spectrum (a). Because the peak height of NAA is 1.7 times higher than that of Cr, $t_1$ noise caused by NAA is more conspicuous. After motion corrections, the NAA singlet peaks were aligned and the $t_1$ noise was reduced. The second curve is obtained after the correction (red line). The peak positions of the NAA singlet are shown as red lines, and the phase change of that peak before the phase correction is shown as a white line in Fig. 4a. A white arrow shows the time of $t_1$ when the largest peak shifts and phase changes occurred.

**Fig. 4.** Interferogram of a series of N-acetyl aspartate (NAA) singlet peaks in $^1$H spectra of a human brain at each $t_1$ increment. The vertical axis is frequency, $F_2$, and the horizontal axis is time, $t_1$. After a one-dimensional (1D) Fourier transformation (FT) along the $t_2$ direction of the two-dimensional (2D) time domain data, $S(t_1, t_2)$, collected by the localized 2D constant-time correlation spectroscopy (CT-COSY) sequence, this interferogram is calculated. The cases before motion correction (a) and after frequency drift correction (b) are shown in magnitude mode. Absorption spectra are shown after drift correction (d) and after zero-order phase correction (e). Two curves of the phase change of the NAA singlet peak are also shown (e). The first is the curve before the zero-order phase correction (black line). The second is that obtained after the correction (red line). The peak position of the NAA singlet is shown as a red line, and the phase change of that peak before the phase correction is shown as a white line in Fig. 4a. A white arrow shows the time of $t_1$ when the largest peak shifts and phase changes occurred.
corrections, $t_1$ noise was sufficiently diminished (b). To evaluate the effect of this motion correction, we calculated the ratio of the area of $t_1$ noise to the white noise area before (a) and after (b) motion correction. The area of $t_1$ noise was shown as the area enclosed by broken lines in Fig. 5. As a result, the ratio decreased by 37.7% after motion correction.

**Discussion**

We developed a post-processing framework for localized 2D MRS that adds corrections of eddy current and motion to the conventional post-processing procedures for 2D NMR spectroscopy. The effects due to the eddy current in the localized 2D MRS can be corrected using the 2D dataset of the $^1$H water phase. We evaluated the effects caused by gradient pulses in phantom experiments. Distorted peak patterns along the $F_2$ direction were shown in the localized 2D CT-COSY spectra of the phantom containing brain metabolite mixtures (Fig. 3a). After correcting the phase data of water $^1$H for one FID, $S(t_1=0,t_2)$, a symmetric peak pattern along the $F_2$ direction was obtained (Fig. 3b). This implies that the FID of water $^1$H is sufficient for eddy current correction in our measurement. This sufficiency of one FID may depend on the scanner condition of a small amount of residual eddy current or on pulse sequences. Because it is time-consuming to collect the entire dataset of water $^1$H signals, $S_{\text{water}}(t_1,t_2)$, for eddy current correction, we should evaluate the correction with one FID in the phantom experiment.

In the localized CT-COSY sequence shown in Fig. 2, the temporal position of the slice gradient and the crusher gradient 180° pulses are shifted at each $t_1$ increment. These gradients cause the eddy currents to vary at each $t_1$ increment. The slice and the crusher gradient pulses for the third mixing pulse are closest to the start of the data acquisition along the $t_2$ direction. The eddy current caused by these gradients for the third pulse most strongly affects the $^1$H metabolite signal. In contrast, the effect of the $t_1$-dependent eddy current is small. In addition, there is no $t_1$ noise in the original spectrum in Fig. 3b. This means that the $t_1$-dependent eddy current is small. Thus, the FID of $t_1=0$ is sufficient for eddy current correction in the 2D MRS.

For motion correction, the $t_1$ noise induced by the phase changes that vary with $t_1$ are sufficiently suppressed, and the peak shift along the $F_2$ direction caused by the $B_0$ shift from subject motion is corrected. We found the peak shift of the NAA singlet along the $F_2$ direction nearly synchronized with the phase change of that peak (Fig. 4a). Whereas the value of the peak shift is at most 6 Hz, the phase change is around 60° at 50th order in $t_1$ (white arrow, Fig. 4a). In the localized CT-COSY sequence shown in Fig. 2, the delay between the third mixing pulse and the start of data acquisition...
along the $t_2$ direction was roughly 5 ms. During this delay, the magnetization precesses approximately $360^\circ/6$ Hz x 5 ms, which is $\sim 10^\circ$ smaller than the 60° associated with the phase change of the NAA singlet. This shows that the phase change occurs during the $t_1$ period. When the subject moves during the $t_1$ period, $B_0$ in the VOI is varied, and the phase of the magnetization changes. This causes $t_1$ noise in the 2D spectrum. This $B_0$ shift also causes the peak shift along the $F_2$ direction. Thus, the subject’s motion during the $t_1$ period is one reason for the synchronization between the peak shift and the phase change of the NAA singlet.

Weak $t_1$ noise remains in the 2D spectrum after motion correction in Fig. 5b. After phase correction of the NAA singlet, most of the phase values equal zero (Fig. 4c). This may be due to an overcorrection, given that noise causes phase errors. This overcorrection is a likely reason for the remaining $t_1$ noise. Our developed motion correction cannot reduce $t_1$ noise caused by the changing magnitude of signals. This may be another reason for the residual $t_1$ noise. We may reduce that residual $t_1$ noise through analysis of the source of the residual noise by measuring the magnitude and phase of $t_1$ noise.

Conclusion

We have proposed a post-processing framework for an in vivo localized 2D MRS sequence. This framework adds corrections of eddy current and subject motion to the conventional reconstruction methods for 2D NMR. We demonstrated that the eddy current correction yields a spectrum without $F_2$ distortion, and the motion corrections allow us to obtain the spectrum with lower $t_1$ noise in the case of localized 2D CT-COSY. Artifacts caused by eddy current and subject motion may also occur in the case of other localized 2D MRS sequences, and we believe our framework can be applied for the subject’s spectra collected by these sequences. Our framework may allow improved quantitation and robustness of in vivo 2D spectroscopy.

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