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Real-time simultaneous shim and motion measurement and correction in glycoCEST MRI using Double Volumetric Navigators (DvNavs)

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Abstract

Purpose—Chemical Exchange Saturation Transfer (CEST) MRI allows for indirect detection of molecules with exchangeable protons, measured as a reduction in water signal due to continuous transfer of saturated protons. CEST requires saturation pulses on the order of a second, as well as repeated acquisitions at different offset frequencies. The resulting extended scan time makes CEST susceptible to subject motion, which introduces field inhomogeneity, shifting offset frequencies and causing distortions in CEST spectra that resemble true CEST effects. This is a particular problem for molecules that resonate close to water, such as hydroxyl group in glycogen. To address this, a technique for real-time measurement and correction of motion and field inhomogeneity is proposed.

Methods—A CEST sequence was modified to include Double volumetric Navigators (DvNavs) for real-time simultaneous motion and shim correction. Phantom tests were conducted to investigate the effects of motion and shim changes on CEST quantification, and to validate the accuracy of DvNav motion and shim estimates. To evaluate DvNav shim and motion correction in vivo, acquisitions including five experimental conditions were performed in the calf muscle of two volunteers.

Results—Phantom data show that DvNav-CEST accurately estimates frequency and linear gradient changes due to motion and corrects resulting image distortions. In addition, DvNav-CEST improves CEST quantification in vivo in the presence of motion.

Conclusion—The proposed technique allows for real-time simultaneous motion and shim correction with no additional scanning time, enabling accurate CEST quantification even in the presence of motion and field inhomogeneity.

Keywords

Chemical Exchange Saturation Transfer (CEST); glycogen; Double volumetric Navigator (DvNav); motion correction; B0 correction

Introduction

Magnetic resonance spectroscopy (MRS) allows for direct detection and quantification of different endogenous metabolites containing ^1H . However, in vivo measurement of certain metabolites remains challenging due to their low concentrations. In 2000, Ward and Balaban (1) demonstrated that molecules can be detected indirectly through the chemical exchange of protons from preselected labile groups with free water. This technique is known as Chemical Exchange Saturation Transfer (CEST) MRI.

Since hydrogen nuclei bound to metabolites and those in free water possess different chemical shifts, chemical exchange processes can be probed by selectively exciting the bound hydrogen nuclei and detecting the attenuated MR signal in the water pool. CEST typically involves exchange of protons from amides ($-\text{NH}$), termed Amide Proton Transfer (APT) (2), amines ($-\text{NH}_2$) and hydroxyls ($-\text{OH}$). Transfer of amine protons is involved in the quantification of glutamate (Glu-CEST), γ -aminobutyric acid (GABA) (3) and creatine (Cr-CEST), and transfer of hydroxyl protons in measuring glucose (Gluco-CEST), myo-inositol (MICEST), as well as glycosaminoglycan content (GagCEST) in cartilage (4). The feasibility of detecting glycogen using CEST (glycoCEST) from hydroxyl protons ($-\text{OH}$) was demonstrated previously in vitro and in vivo in animal studies of the liver at 4.7 T (5).

In the ideal CEST experiment, quantification is achieved by measuring the reduction of the water signal due to saturation transfer (S_{sat}) relative to the corresponding unsaturated image (S_0). However, there are several factors that complicate CEST measurements. These include magnetization transfer (MT) between semi-solid macromolecules and water, and direct water saturation (DS) (6–8). These effects reduce the attenuated water signal and should be eliminated for reliable quantification of CEST.

To mitigate the effects of MT and DS, and isolate the effects of chemical exchange, instead of comparing only the signal reduction caused when saturating a specific spectral location ($+\omega$ with respect to water) to that without saturation, the CEST effect is assessed by subtracting the labeled signal ($S_{\text{sat}}(+\omega)$) from the reference signal acquired after applying a saturation pulse at the opposite spectral location ($S_{\text{sat}}(-\omega)$) (9). This assumes that the MT and DS effects are symmetrical about the water frequency. The most commonly utilized CEST metric, the Magnetization Transfer Ratio (MTR_{asym}) at $+\omega$, is defined as:

$$\text{MTR}_{\text{asym}} = \frac{(S_{\text{sat}}(-\Delta\omega) - S_{\text{sat}}(+\Delta\omega))}{S_0}$$

where $S_{\text{sat}}(+\omega)$ and $S_{\text{sat}}(-\omega)$ are the measured signals with RF saturation at $+\omega$ and $-\omega$, respectively, and S_0 is the signal measurement without RF saturation (2,9–11).

Although it is difficult to absolutely quantify the CEST effect, the relative magnitude can be

described using MTR_{asym} . While MTR_{asym} is the most widely used metric to quantify CEST effects, it is contaminated by asymmetry of MT in the frequency range close to the water resonance (12). Therefore, instead of comparing the saturated water signals at a pair of offsets, CEST is quantified by comparing the saturated water signals over a range of offsets. Furthermore, in the presence of severe B0 inhomogeneity, the labeled and reference scans will no longer be symmetric about the true water resonance of the spin system (13,14) resulting in a B0 inhomogeneity-dependent MTR offset that may cause errors in CEST quantification.

Since CEST acquisitions are repeated at different spectral offsets to adequately sample the CEST spectrum (Z-spectrum) for each voxel, the acquisition will be long when using traditional imaging readouts. This causes CEST MRI to be sensitive to motion and B0 inhomogeneity. To decrease the overall acquisition time, rapid MRI acquisition techniques such as Rapid Acquisition with Relaxation Enhancement (RARE) (15), Echo Planar Imaging (16,17), True Fast Imaging with Steady State Free Precession (FISP) (18), Gradient and Spin Echo (GRASE)(14), Variably-accelerated Sensitivity Encoding (vSENSE) (19), keyhole (20), as well as optimized spiral-centric-reordered GRE approaches (21) have been adapted for CEST. Fast imaging techniques, however, cannot eliminate motion between the different offset frequency acquisitions. If there is a mismatch between the corresponding voxels due to subject motion, the acquired Z-spectrum will not be accurate and high signal variations (peaks or dips) that resemble those expected from the metabolites of interest may be introduced in the curve (22). The effect of motion in CEST MRI is almost unexplored. The few studies that examine motion correction in CEST MRI are based either on rigid image registration (23) or retrospective time domain analysis (24).

During a prolonged CEST scan, several sources can alter the homogeneity of the static shim prepared by the MRI scanner. These include subject motion (25), breathing (26), heating of the iron plates in the shim trays by eddy currents and mechanical vibrations (27,28). This can severely impact the accuracy of the CEST measurement. For example, at 3T, a shift of just 100 Hz in the central frequency may cause the amine ($-NH_2$) group to be saturated instead of the $-OH$ group in glycogen. While shim changes before the start of the scan can be corrected by the scanner's automatic shimming or by manual shim optimization, standard techniques cannot correct shim changes that occur during the scan. Given that the endogenous CEST contrast is only a few percent, accurate quantification requires correction of field inhomogeneity-induced measurement errors.

To date, shim has been corrected retrospectively in CEST imaging using a pre-acquired B0 map (8,29), or by fitting the CEST spectrum to a higher-order polynomial (2,10). In the first method, the local B0 shift at each voxel is determined from separately acquired gradient-echo phase images or using Water Saturation Shift Referencing (WASSR). WASSR uses a weak saturation pulse to measure the direct water saturation at each voxel (8). Assuming that maximal saturation occurs when the saturation offset equals the B0 shift, the offset in the acquired CEST data is corrected, effectively moving the center of the Z-spectrum for each voxel back to 0 Hz. Alternatively, CEST spectra are fitted to a polynomial, where the minimum is deemed to be the reference frequency and each voxel's CEST spectrum is shifted accordingly (2,10). These techniques, which rely on sampling the minimum of the

CEST spectrum in sufficient detail, are only applicable when the spectrum is symmetric and the water peak is sharp, or if the CEST agents' exchangeable protons are sufficiently far from water that small errors in B0 correction do not cause problems (i.e. MTC and DS effects are small). It is worth noting that these methods cannot detect and remove errors that occur due to motion and dynamic changes in field inhomogeneity between different frequency offsets.

In contrast, navigator methods are able to detect B0 changes throughout the scan and correct these in real time by adjusting both zeroth- and higher-order shims. Navigators can also correct for motion during the scan by updating the slice positions and gradient coordinate system (30–32), and are advantageous for CEST over hardware-based motion detection methods (33–35) in that they can be inserted into unused time during the imaging sequence and require no additional hardware. To accurately measure motion and shim changes, navigator images require a consistent contrast independent of the CEST contrast. Volumetric imaging navigators have been used previously for prospective motion and shim correction in diffusion tensor imaging (36), single voxel spectroscopy (37) and chemical shift imaging (38). A similar approach based on dual-echo Prospective Motion correction (PROMO) has also been reported to correct for motion in single voxel spectroscopy (39).

The current work presents a method for real-time simultaneous measurement and correction of motion and field inhomogeneity, in terms of frequency (zeroth-order) and linear (first-order) shim gradients, in CEST MRI using ultrafast double volumetric navigators (DvNavs).

Methods

CEST-EPI pulse sequence

The CEST MRI pulse sequence consists of three blocks (Fig. 1a): relaxation, saturation and image acquisition. A long recovery period ensures sufficient magnetization (Mz) prior to excitation. The relaxation period is followed by RF saturation and comprises either a long continuous-wave RF pulse or a train of short pulses. The current implementation uses a long continuous-wave pulse. For image acquisition, we use 2D gradient echo single-shot EPI. These three blocks are repeated for saturation pulses with chemical shifts ranging from -3 to 3 ppm relative to water in increments of 0.15 ppm.

Volumetric navigated (vNav) CEST-EPI for prospective motion correction

The volumetric navigator (vNav) was previously implemented in DTI (32), single voxel spectroscopy (37), chemical shift imaging (38), MEGA-SPECIAL (40) and morphometry (31). The vNav uses multi-shot EPI with three-dimensional encoding. A single complete slice of k-space is collected with a Cartesian sampling scheme after each excitation. The full navigator consists of a stack of k-space slices collected across multiple excitations.

Since the relaxation period in the CEST sequence occupies a significant portion of the repetition time (TR), the vNav was inserted into this block, immediately before the saturation block (Fig. 1b). This ensures that all CEST measurements are affected equally. A small flip angle (2°) further ensures minimal impact on the CEST contrast. vNav sequence parameters are echo time (TE) 6 ms, repetition time (TR_{vNav}) 11 ms, bandwidth 4882 Hz/px,

6/8 slice partial Fourier, turbo factor 32, acquisition matrix $32 \times 32 \times 32$, resolution $8 \times 8 \times 8 \text{ mm}^3$, and FOV 256 mm; duration 264 ms.

For pose estimation, each 3D navigator magnitude image is compared to a reference, selected to be the first navigator after the dummy scans. Prospective Acquisition CorrEction (PACE) (41), performed immediately after the navigator acquisition, computes translation and rotation parameters relative to the reference. Motion estimates are sent to the sequence and slice position and orientation are updated for subsequent CEST and vNav acquisitions. The complete navigator block, including computation and transmission of the motion estimates back to the sequence, requires 344 ms and fits into the CEST relaxation period without requiring any additional time.

Double vNav (DvNav) CEST-EPI for prospective motion and shim correction

For simultaneous shim and motion correction, the navigator sequence was modified to acquire a pair of navigators (double vNavs) with different echo times ($TE_1/TE_2 = 4.8/7.0 \text{ ms}$). The 2.2 ms difference in TE is chosen so that fat and water are in phase at 3T. The partitions of the two navigators are acquired in an interleaved fashion as shown in Figure 1c. Due to the longer TE₂, the TR of the navigator had to be increased to 13 ms, increasing the total acquisition time for the pair of navigators to 624 ms. All other parameters are as for vNav-CEST.

The sequence protocol was enabled to run with three options: the standard CEST sequence (CEST), DvNav-CEST with only prospective motion correction, and DvNav-CEST with prospective motion and shim correction.

The magnitude and phase images of both navigators (vNav1 and vNav2) are generated after acquisition. Pose estimation is performed in real-time using successive vNav1 images and shim correction using successive navigator pairs. Each vNav1 image is co-registered to the reference using PACE and motion estimates are sent back to the sequence.

A 3D field map is computed by complex division of the vNav1 and vNav2 phase images. Voxels with low signal-to-noise ratio (SNR) are excluded using a mask created from the vNav1 magnitude image. Phase unwrapping is performed online using Phase Region Expanding Labeller for Unwrapping Discrete Estimates (PRELUDE) (42). Motion parameters calculated from vNav1 are used to reorient the field map to the current position. Since DvNav-CEST effectively consists of two interleaved sequences with different FOVs, two frequency (f_s) and first order shim (linear shim gradients G_x , G_y and G_z) estimates are calculated online, one for the selected CEST FOV and one for the DvNav FOV. The shim estimate for the DvNav is calculated using an unweighted least squares regression (37). For CEST, the shim estimate within the plane uses a weighted least squares regression, where the weighting of each navigator voxel is according to its intersection with the CEST FOV, while the through-plane (slice direction) shim is set equal to that of the DvNav. Shim parameters for CEST and DvNav are sent to the sequence.

First, slice position and orientation are corrected for both CEST and DvNav, followed by adjustment of the linear shim gradients for both sequences. Frequency correction involves

recalculating the frequency and the phase of the RF and ADC pulses for both the vNav and CEST sequences. Although higher order shim terms can be calculated from the field map, only the linear terms can be applied in real time by the hardware. Using 6/8 partial Fourier in the slice direction, the total time required for the DvNav block (including communication time) is about 704 ms, which is short enough to fit inside the CEST relaxation time without requiring any additional imaging time. Therefore, any motion and accompanying field changes are corrected immediately after the navigator block so that the CEST offset is corrected in the very next measurement. Since the first measurement in the CEST acquisition will not be shim corrected, two reference measurements (images without saturation) are acquired. This ensures that shim-corrected data are available for all CEST offsets, including the reference. To avoid interaction with the DvNav, the standard frequency offset correction for the Siemens platform based on the non-phase-encoded echoes embedded into each EPI readout was disabled during DvNav-CEST acquisitions. Figure 2 shows a flow diagram of the DvNav-CEST sequence.

MRI Data acquisition and scanning protocols

All scans were performed on a Skyra 3 T (Siemens, Erlangen, Germany) according to protocols that had been approved by the Human Research Ethics Committee of the Faculty of Health Sciences, University of Cape Town. Sequences were tested on water, pineapple, and bovine liver glycogen (Type IX G0885, CAS Number: 9005 79 2, Sigma, Aldrich) phantoms, and in vivo on the calf muscle of two volunteers using a 15-channel Tx/Rx knee coil. vNav parameters were as described earlier. The CEST parameters for both in vitro and in vivo acquisitions were: TR 2000 ms (including the navigator time), TE 21 ms, 1 average, single slice, slice thickness 5 mm, 64×64 acquisition matrix and FOV of 220 mm. Each CEST acquisition included two reference measurements and 41 CEST offsets between -3 and 3 ppm (relative to free water) in increments of 0.15 ppm with an optimized rectangular RF saturation pulse of duration 700 ms and amplitude $1.5 \mu\text{T}$; total CEST acquisition time 86 seconds. Matlab was used to process the images and generate CEST and MTRasym curves. For all acquisitions, glycogen concentrations were determined by integrating the MTRasym curve across the region where glycogen resonates ($0.5 - 1.5$ ppm downfield of water) (5).

1. Assessing the effect of the vNavs on CEST and vice versa—First, we investigated the effect of the navigator on CEST saturation and acquisition efficiency, as well as the effect of the CEST saturation pulse on the navigator signal. To this end, a pineapple was scanned twice, once using the standard CEST sequence and again using DvNav-CEST, both without motion. We examined how the navigator signal intensity varied for different CEST offsets and compared the CEST and MTRasym curves for the two acquisitions.

2. Assessing the effect of motion and B0 inhomogeneity on CEST quantification—The effect of motion on CEST data was examined by scanning a pineapple using the standard CEST sequence both without (NoMo) and with (Mo) motion. A motion stick was used to introduce pose changes during the “with motion” acquisition.

The MTRasym curves were integrated from 0 to 3 ppm downfield of water to compare effects on quantification.

The effect of B0 inhomogeneity was assessed by scanning a 50mM bovine glycogen phantom with saturation pulses applied at -1, 0 and 1 ppm while intentionally manipulating the zero- and first order shims. After the baseline acquisition, the acquisition was repeated with the central frequency manually adjusted by ± 32 Hz, ± 64 Hz, ± 96 Hz, ± 128 Hz, and ± 160 Hz from its nominal value (equivalent to ± 0.25 ppm, ± 0.5 ppm, ± 0.75 ppm, ± 1 ppm, and ± 1.25 ppm at 3T). Next, the linear shim gradient values were manually adjusted simultaneously in G_x , G_y and G_z by ± 5 μ T/m, ± 10 μ T/m and ± 20 μ T/m. The MTRasym values in a $35 \times 35 \times 5$ mm³ ROI at 1 ppm downfield of water were compared for the different acquisitions.

3. Performance of the DvNavs in estimating and correcting zero- and first-order shim changes—To assess the ability of the DvNavs to accurately detect and correct zero- and first-order shim changes, the central frequency and linear gradients were manually adjusted for successive DvNav-CEST acquisitions. First a baseline acquisition was performed on the standard MRI water phantom with the scanner's initial system settings. The acquisition was then repeated with the system frequency adjusted by 32 Hz, 64 Hz, 96 Hz, 128 Hz, and 160 Hz, respectively. These frequency shifts (0.25 – 1.25 ppm in steps of 0.25 ppm) were selected to assess the ability of the DvNav to correct frequency changes of the same order as the chemical shift of the glycogen hydroxyl group. Next, the acquisition was repeated with the gradient values changed by 10 μ T/m in G_x only, both G_x and G_y , and finally G_x , G_y , G_z together. DvNav shim correction was applied to all acquisitions. Since shim correction is only applied from the second measurement, we compared, for each acquisition, the first uncorrected CEST reference image to the second shim-corrected reference image. In addition, shim estimates computed by the DvNavs were compared to known adjustments.

4. In vivo validation—To investigate the benefits of real-time simultaneous motion and shim correction on CEST data in the presence of subject motion in vivo, five acquisitions were performed on the calf muscle, targeting the middle of the gastrocnemius, in each of two healthy adult male volunteers: two DvNav-CEST acquisitions without motion (NoMo) – one without correction (-NoCo) and one with both motion and shim correction (-AllCo); and three acquisitions with motion (Mo) – one without correction (-NoCo), one with motion correction only (-MoCo), and the last with both motion and shim correction (-AllCo). Before the scan session, participants were instructed to lie still unless prompted to move. For acquisitions with motion, subjects were instructed to change their position slightly and slowly twice to the left and twice to the right (for volunteer one), and four times progressively to the left (for volunteer two) at equal intervals during the CEST acquisition. Prior to each CEST acquisition the scanner's shim was manually optimized. All the measurements were acquired in the transverse plane and the center slice of the navigator was aligned to the CEST slice.

Results

1. Assessing the effect of the vNavs on CEST and vice versa

Figure 3 demonstrates the effect of the navigator and CEST sequences on each other. The navigator curve (blue) shows the normalized signal intensity in a $35 \times 35 \times 5 \text{ mm}^3$ ROI on the pineapple as a function of different CEST offsets. The green and red lines are CEST and MTRasym curves for the CEST and DvNav-CEST acquisitions, respectively. The black dotted curve indicates the difference between the CEST curves acquired with and without the navigator.

2. Assessing the effect of motion and B0 inhomogeneity on CEST quantification

Figure 4 shows how motion (red curve) during the acquisition causes artifacts (evident here at 1.3 ppm and 1.8 ppm) that resemble the features expected in a CEST curve, as well as inaccurate CEST estimates (38.8% in the presence of motion compared to 23.3% in the absence of motion).

Figure 5a shows the MTRasym value at 1 ppm downfield of water for a 50mM glycogen phantom for various manual frequency adjustments both downfield and upfield of the scanner central frequency. The MTRasym value at 0 ppm was acquired without any change to the system frequency. MTRasym values to the left of 0 ppm are from acquisitions where the system frequency was manually increased in 32 Hz intervals (approximately 0.25 ppm at 3T) and those on the right from acquisitions where it was manually decreased in 32 Hz (−0.25 ppm) intervals. Figure 5b shows the effect of linear gradient (Gx, Gy, Gz) changes on MTRasym values at 1 ppm.

3. Performance of the DvNavs in estimating and correcting zero- and first-order shim changes

Figure 6 shows geometric distortions and voxel shifts in the CEST reference images of a water phantom after manual adjustment of the system frequency and linear gradient values. For each acquisition, the top row shows the first CEST reference image (before shim correction), and the bottom row, the second reference image acquired after shim correction by the DvNavs. Frequency shifts cause the image to shift in the phase encoding direction (Fig. 6a), while gradient changes cause geometric distortions (Fig. 6b). Figure 6c demonstrates how a frequency shift of −128 Hz introduces a Nyquist N/2 ghost in the CEST reference image that is minimized after frequency correction by the DvNavs.

Figure 7 shows good agreement between shim estimates computed by the DvNavs and known adjustments. Across all frequency shifts, the mean absolute estimation error was $0.23 \pm 0.15 \text{ Hz}$, with a maximum error of 0.45 Hz for a 32 Hz frequency change (Fig. 7a). Additionally, we found that changes in the linear shim terms also caused global frequency changes, which could be correctly detected by the DvNav (Fig. 7b). Each manual adjustment was performed after first resetting both the system frequency and linear-gradients to their optimal (“well shimmed”) values.

4. In vivo validation

Figure 8 shows the translation, rotation and shim parameters estimated by the DvNav for in vivo scans of one volunteer. In the corrected cases, the image FOV and shim are immediately adjusted when a change in position is detected. The coordinates of the current acquisition (including the vNav) and shim are adjusted by the previously detected translation, rotation and shim parameters, respectively. This causes measured parameters in the prospectively-corrected case to resemble the derivative of these parameters in the non-corrected case.

Figure 9 shows the CEST and MTRasym curves from a $35 \times 35 \times 5 \text{ mm}^3$ ROI for the NoMo-NoCo, NoMo-AllCo, Mo-NoCo, Mo-MoCo and Mo-AllCo acquisitions of one volunteer. The uncorrected and incompletely corrected acquisitions with motion result in corrupted MTRasym curves. Table 1 compares the integral of the MTRasym curve between 0.5 and 1.5 ppm downfield of water, and peak values at 1 ppm, for the different acquisitions in each of the volunteers. Motion without correction or motion correction only result in inaccurate CEST quantification.

Discussion

Although CEST MRI has emerged as a promising technique to detect molecules present in concentrations in the nanomolar to millimolar range, accurate analysis and quantification using remains challenging. Since the CEST spectrum is generated from multiple acquisitions with different saturation frequencies, it is prone to subject motion and heating of the iron shim coils due to eddy currents or mechanical vibrations, both of which can lead to significant fluctuation in the B0 field (27,28,43). Even after automatic shimming at the beginning of every acquisition, field homogeneity may change between measurements due to many unavoidable factors (36). The dependence of CEST on the chemical shift of endogenous molecules makes it especially sensitive to B0 field inhomogeneity. This is exacerbated in glycoCEST where the resonance frequency of hydroxyl protons is very close to the water resonance (8). Effective shim correction is therefore essential for accurate quantification, particularly at 3T.

Current CEST B0 correction methods rely on data post-processing and require either a separate field map acquisition or multiple acquisitions with a fine frequency interval to correct the shift in the CEST spectrum caused by zero-order shim changes (8,29). Motion correction is performed retrospectively via rigid (23) or nonrigid (44) registration of CEST offset-images. However, the CEST signal attenuation caused by geometric distortion due to gradient field variation cannot be corrected in this way. To our knowledge, no previous study has examined the effects of both motion and shim on CEST data analysis and quantification.

We have implemented fast double volumetric navigators in the CEST sequence to measure and correct shim changes and motion for each CEST frequency offset measurement. For each offset measurement, the motion and shim parameters are calculated and the FOV, frequency and gradient currents are updated for subsequent navigator and CEST measurements in real-time. This improves on existing correction methods by incorporating

prospective correction, as well as the ability to report and correct changes in field inhomogeneity between different frequency offset measurements.

Placing the navigator immediately before the RF saturation pulse of the parent sequence is intended to minimize the signal saturation from the CEST sequence on the navigator. Accordingly, we observe a relatively stable navigator signal across the offset scans, with only a slight signal drop observed close to the water frequency, due to the residual saturation effect from the preceding CEST (Fig. 3). The stable signal intensity over successive navigator images allows for accurate registration and motion estimation, whereas methods that attempt to correct for motion by registering CEST offset images (45,46) must address the challenge of registering images with varying contrast. Similarly, the small mean difference between CEST curves generated from acquisitions with and without the navigator confirms that the navigator's 2^0 flip-angle RF excitation is sufficiently low not to affect CEST saturation.

Although it is difficult to absolutely quantify glycogen levels, relative quantification is possible using the MTRasym integral. For example, exercise-induced glycogen depletion can be examined using MTRasym measured before and after exercise, provided that all other conditions are identical between scans. However, a small change in intensity due to motion and B0 variation may alter the MTRasym integral between 0 and 3 ppm downfield of water by up to 60% of its true value (Fig. 4). Given the low MRI signal of endogenous molecules, even a small change in MTRasym has a large effect on data interpretation, and artifacts may resemble a metabolite of interest.

Our phantom results demonstrate the sensitivity of MTRasym values to slight zero-order shim changes. As the frequency of the saturation pulse shifts away from the expected glycogen resonance, saturation of glycogen protons decreases and hence also the indirect saturation of the water signal due to proton transfer. Changes in linear gradients also affect MTRasym, possibly due to intensity variation resulting from geometric distortion and phase encoding shifts. The pattern of artefactual changes in MTRasym as a function of shim variation is not deterministic but Figure 5 demonstrates the substantial effect of small variations in zero- and first-order shim.

The CEST-DvNav sequence accurately detects, measures and corrects the change in B0 following manual adjustment of the scanner system frequency (zero-order shim) and the linear gradients (first-order shim). A change in zero-order shim results in a shift of the volume image in the phase encoding direction, and a visible phase wraparound (Nyquist N/2 ghost) artifact, especially for larger zero-order shim changes (Fig. 6). This causes misregistration of voxels from consecutive offset volumes, in addition to a shift in offset frequency in the CEST-spectrum. These artifacts, as well as geometric distortions and intensity variations caused by varying linear shim gradients (particularly apparent when more than one shim term is adjusted) are corrected by the DvNav. Since variation in B0 can result in misinterpretation during voxel-wise CEST analysis, for accuracy it is important that B0 be corrected in each CEST offset volume acquisition.

In our in vivo test, the relatively stable zero- and first-order shims are distorted directly after pose changes during acquisitions with motion but no correction (Fig. 8). Without correction, the frequency increases/decreases as pose changes with respect to the initial frequency and returns towards its initial value upon return to the initial pose. Both pose changes and shim distortions are corrected when shim and motion correction are applied using the DvNav-CEST sequence (Fig. 8: Mo-AllCo). Due to motion, a gradient change of about 5 $\mu\text{T/m}$ (uncorrected case) and 4 $\mu\text{T/m}$ (corrected case peak to peak) occurred in G_x (excluding the initial shim offsets), which is a significant amount to alter the CEST effect (as demonstrated in Fig. 5).

Although a single vNav can correct a subject's pose change, it cannot correct the resultant offset shifts in the CEST-spectrum and yields corrupted CEST and MTRasym curves (Mo-MoCo). In contrast, motion and shim corrected (AllCo) CEST-spectra and MTRasym curves both without and with motion are in good agreement with the NoMo-NoCo baseline scan (Fig. 9). While the MTRasym integral and peak values between 0.5 and 1.5 ppm downfield of water for both volunteers are substantially reduced in scans with motion and either no correction (Mo-NoCo) or motion correction only (Mo-MoCo), values are similar for scans without motion (NoMo) – both with and without correction) and for scans with motion and both shim and motion correction (Mo-AllCo). This highlights the importance of correcting both motion and shim to achieve accurate CEST quantification in the presence of motion.

Recent similar work has included volumetric navigators to correct for motion in glutamine CEST at 7T (47). However, motion correction was only effective for motion less than 0.7mm/0.7-degrees. By contrast the PACE estimation method used here is potentially effective for translations/rotations of up to 20mm/8-degrees (41). We have demonstrated effective motion correction for up to 7mm translation and 1.5-degrees rotation. While the B0 field was corrected retrospectively in (47) using the dual echo of the CEST sequence, and receiver sensitivity using the vNav intensity, the current implementation corrects B0 prospectively in real-time without additional scanning time.

Very few studies have attempted glycoCEST in humans at 3T as motion of organs, and B0 spatial inhomogeneity and temporal changes present a challenge to quantification. One study has demonstrated liver glycogen reduction after fasting (48). Another has shown that muscle glycogen can be assessed at 3T with proper frequency correction using the WASSR method (8). The DvNav-based prospective frequency and first order shim measurement and correction presented here could improve accuracy of muscle glycogen CEST measurements. Even with minimal motion, the proposed method would correct any drift in the scanner center frequency that occurs during the CEST acquisition (49).

A limitation of this work is that reproducibility of the CEST measurements obtained with the DvNav sequence was not evaluated. This will be addressed in future work. We also did not quantify the incremental benefit of linear shim correction above frequency correction alone.

Conclusion

Given that endogenous CEST imaging contrasts are only a few percent, even small errors significantly impact CEST data analysis and quantification. Field inhomogeneity is unavoidable and may occur during a scan due to heating of the shim iron, subject motion and other factors. We have presented a technique that accurately detects, measures and corrects changes in the B0 field using double volumetric navigators (DvNavs). Our method was shown to decrease the effects of subject motion and field inhomogeneity by simultaneously correcting for both in real-time with no additional scanning time. Phantom and in vivo test results show improved CEST quantification in the presence of motion and field variations. Although the method was demonstrated for glycogen, which is more sensitive to field inhomogeneity than other metabolites due to its resonance being close to that of water, it can be extended to other metabolites detectable with CEST-MRI.

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Figure 1:

(a) Standard CEST-EPI sequence blocks; t_{sat} and B_s are, respectively, the duration and amplitude of the saturation pulse. (b) vNav-CEST with the volumetric navigator (vNav) inserted for prospective motion correction. (c) DvNav-CEST with a pair of volumetric navigators (DvNavs) inserted for real-time motion and shim correction. Individual partitions (P) of the pair of navigators are acquired in an interleaved fashion. $v\text{Nav}P_i$, $v\text{Nav}1P_i$ and $v\text{Nav}2P_i$ are the i^{th} partitions of $v\text{Nav}$, $v\text{Nav}1$ and $v\text{Nav}2$, respectively; k is the total number of partitions.

Figure 2:

Flow diagram showing how the DvNav sequence (orange blocks) is integrated into the CEST acquisition (purple blocks) to perform real-time motion and shim correction. Shim correction is applied to all CEST measurements except the first one. N = total number of CEST measurements.

Figure 3:

A plot showing how the navigator signal intensity (blue) in a pineapple phantom varies for different CEST offsets, as well as a comparison of CEST and MTRAsym curves obtained from the standard CEST (green) and DvNav-CEST (red) acquisitions, respectively. The black dotted curve indicates the difference between the CEST curves acquired with and without the navigator.

Figure 4:

CEST and MTRasym curves for a pineapple phantom in the absence (blue) and presence (red) of motion. The peaks and dips in the MTRasym and CEST curves correspond to measurements when the pineapple was intentionally moved. The MTRasym curve was integrated between 0 and 3 ppm to compare CEST quantification.

Figure 5:

MTRasym at 1 ppm as a function of (a) zero-order (F) shim change, and (b) first-order shim change (G_x , G_y , G_z) for a 50mM glycogen phantom. The value at 0 (circled) is without any manual adjustment and represents the true MTRasym value at 1ppm downfield of water.

Figure 6: CEST reference images of a water phantom following (a) Zero-order and (b) first-order shim changes. In each case, the top row shows the reference image acquired after manually changing the shim, and the second row the image acquired following shim correction by the DvNavs. (c) Illustration of the Nyquist N/2 ghost that is introduced by a -128 Hz frequency shift, and correction of the artifact by shim correction.

Figure 7:

Comparison of (a) zero- and (b) first-order shim changes computed by the DvNavs to known adjustments. The bottom plot also shows the effect of first-order shim changes on system frequency.

Figure 8:

DvNav motion and shim estimates for NoMo-NoCo, NoMo-AllCo, Mo-NoCo, Mo-MoCo and Mo-AllCo acquisitions in one volunteer. The corrected plots demonstrate how the DvNav-CEST sequence adjusts the image FOV and shim parameters to correct for changes that occur due to motion. Top: Translation (mm), Middle: Rotation (degrees) and Bottom rows: Shim (zero-order and first-order). (NoMo = no motion, Mo = motion, NoCo = no correction, MoCo = motion correction only, AllCo = both shim and motion correction).

Figure 9:

CEST spectra and MTRasym curves acquired in the calf muscle in one volunteer. **Top row:** (left) no motion and no correction (NoMo-NoCo); (right) no motion but with both shim and motion correction applied (NoMo-AllCo). **Bottom row:** (left to right) motion but no correction (Mo-NoCo), motion and motion correction only (Mo-MoCo), and motion and both shim and motion correction (Mo-AllCo).

Table 1:

Summary of MTRasym peak values at 1ppm and integrals between 0.5 – 1.5 ppm downfield of water for two volunteers during NoMo-NoCo, NoMo-AllCo, Mo-NoCo, Mo-MoCo and Mo-AllCo acquisitions.

Scans	Volunteer 1		Volunteer 2	
	MTRasym peak (1ppm)	MTRasym integral (0.5 – 1.5 ppm)	MTRasym peak (1ppm)	MTRasym integral (0.5 – 1.5 ppm)
NoMo-NoCo	11.34	32.62	11.90	38.66
NoMo-AllCo	12.14	34.21	14.64	41.80
Mo-NoCo	8.36	28.25	5.04	11.36
Mo-MoCo	1.94	12.42	5.35	15.37
Mo-AllCo	10.08	29.56	13.99	40.63