Development of a Clinical Chemical Exchange Saturation Transfer MR fingerprinting (CEST-MRF) Pulse Sequence and Reconstruction for Brain Tumor Quantification

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ABSTRACT

Purpose: To develop a clinical chemical exchange saturation transfer magnetic resonance fingerprinting (CEST-MRF) pulse sequence and reconstruction method.

Methods: The CEST-MRF pulse sequence was modified to conform to hardware limits on clinical scanners while keeping scan time \( \leq 2 \) minutes. The measured data was reconstructed using a deep reconstruction network (DRONE) to yield the water relaxation and chemical exchange parameters. The feasibility of the 6 parameter DRONE reconstruction was tested in simulations in a digital brain phantom. A healthy subject was scanned with the CEST-MRF sequence and a conventional MRF sequence for comparison. The reproducibility was assessed via test-retest experiments and the concordance correlation coefficient (CCC) calculated for white matter (WM) and grey matter (GM). The clinical utility of CEST-MRF was demonstrated in a brain metastasis patient in comparison to standard clinical imaging sequences. The tumor was segmented into edema, solid core and necrotic core regions and the CEST-MRF values compared to the contra-lateral side.

Results: The 6 parameter DRONE reconstruction of the digital phantom yielded a mean absolute error of \( \leq 6\% \) for all parameters. The CEST-MRF parameters were in good agreement with those from a conventional MRF sequence and previous studies in the literature. The mean CCC for all 6 parameters was 0.79±0.02 in WM and 0.63±0.03 in GM. The CEST-MRF values in nearly all tumor regions were significantly different (p=0.001) from each other and the contra-lateral side.

Conclusion: The clinical CEST-MRF sequence provides a method for fast simultaneous quantification of multiple tissue parameters in pathologies.

Keywords: chemical exchange rate, pH, chemical exchange saturation transfer (CEST), magnetic resonance fingerprinting (MRF), deep learning, DRONE.
1. Introduction

Chemical Exchange Saturation Transfer (CEST) MRI uses frequency selective radiofrequency pulses to saturate the magnetization of labile protons on proteins and metabolites [1]. The saturated protons exchange with the unsaturated water protons and lead to a measurable reduction in the water MRI signal. The CEST contrast is attractive since it is sensitive to metabolite concentrations with higher spatial resolution (~1 mm) and shorter scan times (~5 min) than MR spectroscopy [2]. Moreover, the measured CEST signal depends, inter alia, on the chemical exchange rate, which is pH sensitive. Because many pathologies (e.g., cancer) are characterized by tissue hypoxia leading to an acidic microenvironment, pH is a potentially valuable metabolic biomarker [3]–[6]. In cancer imaging, the CEST contrast has been used to distinguish pseudoprogression and radiation necrosis from true progression in brain tumors [7]–[9], quantify tumor extracellular pH [3], [10], evaluate the grading and cellularity of gliomas [11] and monitor early effects of radiation therapy [12].

Although preclinical and early clinical CEST studies have demonstrated the potential utility of CEST methods for assessing disease pathologies, disease progression and therapeutic response, they have not been widely adopted for clinical use due to several challenges encountered in clinical translation. Specifically, the qualitative nature of the CEST contrast, the relatively long image acquisition times, and the complicated data processing have all hindered clinical translation. To overcome these challenges, MR fingerprinting (MRF) based CEST pulse sequence were recently introduced [13], [14] and demonstrated in the in vivo rat brain on a preclinical 4.7T scanner [15]. The CEST-MRF sequence has the following advantages over conventional CEST: tissue maps are fully quantitative, the acquisition time is short (less than 2 minutes) and the data analysis is greatly simplified because only a single resonance frequency offset is excited with saturation pulses of varying powers (instead of the full Z-spectrum) which also reduces the sensitivity to B0 variations. The accuracy of the tissue parameter maps was already validated in phantoms and compared to reference methods from the literature [16]–[19].

The diagnostic potential of CEST-MRF for pathologies is considerable since the resulting parametric maps reflect different biophysical processes, and their combination provides a comprehensive picture of complex pathologies, like brain tumors, where multiple parameters change simultaneously. However, to realize the clinical potential of CEST-MRF, the pulse sequence must be adapted to clinical scanners. This is challenging because preclinical scanners
have significantly different RF and gradient amplifier capabilities and limitations compared to clinical scanners. For example, patient imaging is bound by strict limits on specific absorption rate and peripheral nerve stimulation. These hardware and software differences require careful consideration when adapting a sequence for clinical use. An additional challenge inherent to CEST-MRF is the large number of tissue parameters quantified by the sequence. In conventional MRF, tissue quantification is achieved by pattern-matching the measured signal to a pre-computed database of signal magnetizations [20]. However, the exponential growth in dictionary size for multiple tissue parameters renders this approach impractical for CEST-MRF.

The aim of this work is to enable CEST-MRF scans of brain tumor patients by development of acquisition and quantification methods suitable for clinical scanners and workflow. To this end, we test the proposed methods in simulations and a healthy volunteer and demonstrate the clinical utility in a metastatic brain cancer patient.

2. Methods

2.1. Pulse sequence

Figure 1 shows the proposed pulse sequence for one point of the acquisition schedule. The following points of the acquisition schedule use the same pulse sequence but with different CEST saturation encoding. The initial pulse train saturates the solute protons and is composed of 160 non-selective, Gaussian-shaped, 16 ms sub-pulses applied with a 100% duty cycle for a total pulse train duration ($T_{sat}$) of 2560 ms. The saturation pulse train power ($B_{1\text{sat}}$) was varied according to a pre-determined schedule as described in section 2.1.1. The resonance frequency of the RF pulses was set to the chemical shift of the amide protons (3.5 ppm) in this study but protons of other moieties (amine, hydroxyl etc.) are easily probed by setting the resonance frequency to the appropriate chemical shift. The saturated protons chemically exchange with the unsaturated bulk water protons which leads to a reduction in the water signal which can be measured by excitation with an on-resonance RF pulse with flip angle (FA) set according to the MRF acquisition schedule. The magnetization is then sampled with an echo planar imaging (EPI) readout and the acquisition repeated, following a repetition delay (TR), for each point in the acquisition schedule.

2.1.1. MRF acquisition schedule
To ensure a differential signal evolution for different tissues and facilitate their quantification, the acquisition parameters must be varied for each schedule point. Although simultaneous variation of multiple acquisition parameters can improve discrimination and reduce acquisition times [21] the choice of a good schedule is a challenging problem [22], and will be explored in future studies. For simplicity, in this work B1sat was randomly varied for 30 schedule points with powers in the range 0-4µT (Supplementary Figure 1), which was found to yield accurate parameters in prior preclinical in vivo studies [15]. All other acquisition parameters (FA, TR, Tsat) were kept constant with FA set to 90°, TR set to 3500 ms and Tsat set to 2560 ms.

2.2. Tissue parameter quantification

In conventional MRF, tissue parameters are quantified by matching the measured signal to a pre-computed dictionary of signal magnetizations. Because of the large number of tissue parameters (dictionary dimensions) and the exponential growth of the dictionary, this approach is infeasible for CEST-MRF. We have previously demonstrated the use of a model-trained neural network named DRONE [23]–[27] to perform a functional mapping between the measured data and the underlying tissue parameters. In this work, we extended the DRONE approach to enable reconstruction of the high-dimensional CEST-MRF signals in a clinical setting. The benefits of DRONE include nearly instantaneous reconstruction time and elimination of the requirement for large patient-derived training datasets. The neural network used in this work was also trained on simulated data, as in the original DRONE method, but in this case training data was generated by solving the Bloch-McConnell equations for a 3 pool (water, solute, semi-solid) model.

The neural network was implemented in PyTorch [28] and consisted of a 30-node input layer (corresponding to the 30-point magnitude images acquired with the CEST-MRF sequence), four fully connected hidden layers with 300 nodes per layer and a 6-node output layer. The output layer corresponded to the six parameters measured by the CEST-MRF sequence consisting of water T1 relaxation (T1w), water T2 relaxation (T2w), amide exchange rate (ksw) and volume fraction (fs) and semi-solid exchange rate (kssw) and volume fraction (fss). A training dataset was generated by sampling the tissue parameter ranges using latin hypercube sampling [29] and simulating a CEST-MRF acquisition by solving the Bloch-McConnell equations. All signals were normalized with the l2-norm. The transmit field inhomogeneity (B1) was included in the training dictionary but not in the error calculation to induce the network to minimize the error in the other parameters.
instead. To accelerate the training set generation the CEST-MRF simulation was implemented on a Nvidia RTX2080 Ti GPU (Nvidia Corp. Santa Clara, CA) with 11GB of memory which enabled parallel processing of the training set entries. A fraction (20%) of the dataset was used as a validation set to assess the quality of network training with the remainder (80%) used for training. The network was trained for 4000 epochs with the Adam optimizer [30] using an l1-norm loss with a batch size of 1000 and an adaptive learning rate with weight decay of 1e-4. Zero-mean Gaussian noise with 1% standard deviation was added to the training dictionary to promote robust learning. Network training required approximately 3.5 hours on the GPU whereas quantification of the six parameter maps with the trained network required only ~100 ms for an image with 256×256 voxels.

| Tissue Parameter | Numerical simulations | In vivo studies |
|------------------|-----------------------|----------------|
| T1w (ms)         | [1, 2000]             | [400,3000]     |
| T2w (ms)         | [1, 200]              | [1, 2000]      |
| ksw (Hz)         | [1, 100]              | [1, 100]       |
| fs (%)           | [0, 0.91]             | [0, 2.27]      |
| kssw (Hz)        | [1, 100]              | [1, 50]        |
| fss (%)          | [0, 13.63]            | [1.81, 27.27]  |
| B1 (a.u.)        | 1                     | [0.5, 1.5]     |

2.3. Numerical simulations

The feasibility of DRONE reconstruction for six parameter maps was assessed in a custom modified Brainweb-based [31] digital phantom. The segmented grey matter (GM), white matter (WM) and cerebrospinal fluid (CSF) phantom maps were used to assign quantitative values for each tissue type and parameter (Supplementary Table 1). The digital phantom was used to simulate a CEST-MRF acquisition with the sequence and acquisition schedule described in section 2.1. The simulated data was reconstructed using a DRONE network trained with a training set of 400,000 entries sampled from the ranges shown in Table 1. The error between the reconstructed tissue
parameter and the reference values (Supplementary Table 1) was calculated as Error =
100×|Reference – Reconstructed|/Reference.

White Gaussian noise was added to the simulated data to study the effect of noise on the
reconstruction for varying levels of signal-to-noise ratio (SNR). The SNR was defined as
20·log₁₀(S/N) where S was the average white matter signal intensity for the acquisition and N was
the noise standard deviation. The SNR was varied from 20 to 80 dB in intervals of 5 dB [32] and
the data reconstructed with the same network for each SNR level. The normalized root-mean-
square (NRMSE) was used to calculate the error between the estimated and reference values for
the different SNR levels.

2.4. In vivo studies

All experiments were conducted on a 3T GE Signa Premier (GE Healthcare, Waukesha, WI)
with the built-in transmit body coil and a 48-channels head coil for reception.

2.4.1. Healthy volunteer subject

A healthy 34 years old female volunteer was recruited for this study and provided informed consent
in accordance with our institution’s IRB protocol. The subject was scanned with the CEST-MRF
sequence described in section 2.1 with the following image acquisition parameters: field of view
(FOV)= 280×280 mm², matrix size=256×256, in-plane resolution=1.1×1.1 mm², slice thickness=5
mm, echo time (TE) = 24 ms, partial Fourier, number of averages (NEX) = 1, TR = 3500 ms, FA
=90°, T_sat = 2560 ms, bandwidth = 250 kHz. The total scan time was 105 seconds. The measured
data was reconstructed with a DRONE network trained on 650,000 entries selected from the ranges
shown in Table 1. A B0 map was also acquired using a dual-echo gradient echo sequence to assess
the impact of B0 inhomogeneities on the CEST-MRF parameters.

2.4.1.1. In vivo reproducibility

The in vivo reproducibility of the CEST-MRF sequence was assessed by test-retest scanning. The
healthy volunteer was sequentially scanned twice with the CEST-MRF sequence and then removed
from the scanner. Following a 5 minutes delay, the subject was again placed in the scanner, re-
localized and scanned two more times with the CEST-MRF sequence. Data from each scan were
reconstructed with the trained DRONE network and segmented into GM and WM using the
reconstructed T2w map. Specifically, voxels with T2 values between 20 and 90 ms were assigned
to WM and those with T2 values between 90 and 200 ms assigned to GM. The same masks were then used to determine the GM and WM values for all other parameter maps. The Lin’s concordance correlation coefficient (CCC) [33] was calculated in the GM and WM of each tissue parameter as a measure of the reproducibility of each parameter.

2.4.1.2. Comparison with conventional MRF derived T1 and T2 maps

The water T1 and T2 relaxation maps obtained with CEST-MRF were compared to our previously validated optimized MRF-EPI sequence [23], [32]. The imaging parameters were kept the same as the CEST-MRF acquisition with the exception of the initial adiabatic inversion pulse with inversion time of 50 ms which is part of the sequence [20]. The acquired data were processed by a separate DRONE network and the total acquisition time for the optimized 50 point schedule was approximately 6 seconds per slice. The segmentation obtained in section 2.4.1.1 was used to calculate the reference mean±standard deviation T1 and T2 values in GM and WM.

2.4.2. Brain metastasis patient

A 60 years old male subject with brain metastasis from non-small-cell lung cancer previously treated with stereotactic radiosurgery (SRS) 6 months prior, was recruited for this study and gave informed IRB consent. To assess the response to SRS treatment, the patient was scanned per the consensus standardized brain tumor imaging protocol [34] and institutional standard-of-care that included T1-weighted sequences pre- and post-gadolinium (Gd) contrast injection, FLAIR, diffusion, and perfusion acquisitions. The proposed CEST-MRF was acquired prior to Gd injection using the same imaging parameters and tissue quantification as for the healthy volunteer scans (section 2.4.1) other than the resolution which was set to 1×1×3 mm³ to enable visualization of small lesions. The tumor was contoured into ROIs comprising a necrotic core, solid core and edema as well as a contra-lateral healthy region (Supplementary Figure 3) by one of the authors (RY), a trained neuroradiologist with 20 years of experience. Statistical significance of differences in the reconstructed tissue map values for each ROI was evaluated using a multi-comparison ANOVA test with Tukey HSD [35] with a significance level set at p=0.05.

3. Results

3.1. Numerical simulations
The DRONE reconstruction of the 6 tissue parameter maps in the simulated digital phantom is shown in Figure 2 for an high SNR simulation (80 dB) to isolate the intrinsic error in the DRONE reconstruction for the highly under-determined CEST-MRF data. Despite the high dimensionality of the data, the DRONE reconstruction accurately quantified the tissue maps yielding an error of less than 6% for all the parameters. The impact of SNR on the quantitative accuracy for each parameter is shown in Figure 3 on a log-log scale. As expected, increasing SNR reduced the NRMSE for all tissue parameters although the rate of improvement varied per parameter which is reflective of the intrinsic sensitivity of the sequence to the different parameters. As an example, the NRMSE at 60 dB was approximately 10% for fss but only 4% for T1w and T2w.

3.2. Healthy human volunteer

The quantitative CEST-MRF tissue parameter maps for the healthy human subject are shown in Figure 4. The mean and standard deviation of the grey and white matter values for each tissue parameter are listed in Table 2 along with the reference water T1 and T2 values obtained with the conventional MRF sequence. The B0 map and a violin plot [36] of the distribution of values are shown in Supplementary Figure 2. The mean B0 value across the slice was approximately 4 Hz but significantly higher (~60 Hz) near the frontal sinuses, as expected. The susceptibility differences near the sinuses and the EPI readout used gave rise to the geometrical distortions apparent in that region. The CEST-MRF parameters in that region, however, did not vary significantly compared to the rest of the slice.

| Tissue Type | T1w (ms) | T2w (ms) | ksw (Hz) | kssw (Hz) | fs (%) | fss (%) | Reference T1w (ms) | Reference T2w (ms) |
|-------------|----------|----------|----------|----------|--------|---------|-------------------|-------------------|
| **WM**      | 866.32±  | 77.80±   | 51.07±   | 25.74±   | 0.52±  | 8.96±   | 974.45±           | 74.40±            |
|             | 122.13   | 7.00     | 7.16     | 1.41     | 0.07   | 0.99    | 263.92            | 10.07             |
| **GM**      | 987.64±  | 105.37±  | 47.76±   | 21.27±   | 0.58±  | 7.08±   | 1368.20±          | 123.46±           |
|             | 187.96   | 12.87    | 10.36    | 2.35     | 0.11   | 1.43    | 373.91            | 30.32             |
### 3.2.1. In vivo reproducibility

The mean tissue parameter values for each of the 4 repeated scans are shown for GM and WM in Figure 6 and the corresponding CCC values are tabulated in Table 3. The repeated scans showed generally good reproducibility despite uncorrected registration errors induced by patient motion between scans. Because the GM maps are sparser than WM maps, they are more susceptible to misregistration caused by motion which was reflected in the generally lower CCC values. Switching to a 3D acquisition and co-registering the different volumes [37]–[39] to mitigate subject motion is expected to improve these results further.

| Tissue Parameter | GM CCC (CI) | WM CCC (CI) |
|------------------|------------|------------|
| T1w              | 0.603 [0.598,0.608] | 0.763 [0.760,0.766] |
| T2w              | 0.651 [0.646,0.655] | 0.775 [0.772,0.778] |
| ksw              | 0.630 [0.625,0.634] | 0.810 [0.807,0.812] |
| kssw             | 0.625 [0.620,0.629] | 0.807 [0.804,0.810] |
| fs               | 0.639 [0.634,0.643] | 0.779 [0.776,0.782] |
| fss              | 0.604 [0.599,0.610] | 0.812 [0.809,0.814] |

### 3.3. Brain metastasis patient

The CEST-MRF parameter maps for the cancer patient scans are shown in Figure 6 along with the T1-weighted (pre-, post-Gd), FLAIR, diffusion and perfusion scans from the standard brain protocol for comparison. Box and whiskers plots of the CEST-MRF tissue map values for each ROI are shown in Figure 7 with the median and first and third quartile ranges. The differences between the parameter values in the different ROIs for all tissue parameters were statistically significant (p=0.001) except for the edema and solid core ROIs in the ksw and kssw maps. There were notable trends in the parameter maps. The T1w and T2w in the tumor were both elevated in comparison to the contra-lateral tissue and particularly in the edema and necrotic region. In contrast, the amide exchange rate in the necrotic region was lower which is suggestive of a lower pH environment. The amide volume fraction was also reduced in the necrotic and edema regions.
4. Discussion

This is the first study to demonstrate the feasibility and utility of CEST-MRF in clinical cancer imaging. In addition to a short acquisition, the combination of CEST-MRF with DRONE enables nearly immediate parameter quantification at minimal computational cost, which would potentially allow for image evaluation at the scanner and facilitate clinical adoption.

4.1. Effect of schedule on quantitative parameters

The CEST-MRF signal depends on multiple acquisition parameters including the saturation pulses’ shape, duration and frequency, the excitation flip angle, saturation power, and others. The dependence on multiple parameters can be beneficial in improving the discrimination between signals from different tissues. The semi-solid pool, in particular, can benefit from inclusion of additional resonance frequency offsets in the schedule given the very broad linewidth of the MT pool which would improve kssw discrimination. For simplicity, in this work only the saturation power was varied using a random schedule that is unlikely to be optimal. The numerical phantom results (Figure 3) exemplify this since increasing the SNR reduced the NRMSE for all tissue parameters, as expected, but the rate of improvement varied by parameter. This reflects the intrinsic sensitivity of the sequence to each parameter which can be optimized by modifying the acquisition schedule. Indeed, work by our group and others has shown that simultaneously varying multiple acquisition parameters and optimizing the acquisition schedule can markedly improve tissue discrimination, reduce the sensitivity to noise and shorten the total scan time [22], [32], [40]–[42]. However, the optimization of CEST-MRF schedules is challenging because of the large number of parameters, hence high dimensionality of the optimization problem. To overcome this difficulty, we have previously introduced a deep learning schedule optimization approach for CEST-MRF optimization and demonstrated it on a preclinical scanner [21], [43]. This method can be readily adapted for the clinical CEST-MRF sequence described in this work and is expected to significantly improve the sensitivity to noise and the accuracy of the tissue map quantification. Future work will explore this idea.

4.2. Neural network reconstruction of high dimensional signals

While the original DRONE was only applied for T1 and T2 mapping [23], the method is capable of simultaneous estimation of a much larger set of parameters [24]–[27]. Nevertheless, there are
important challenges associated with reconstruction of high dimensional signals. First, for the network to correctly estimate the underlying tissue parameters, the training set must adequately cover the parameter space. Unfortunately, due to the “curse of dimensionality”, this requires large training datasets and consequently long processing time. To overcome this problem, we used a regular sampling of the parameter space and implemented the training dataset generation on a GPU to parallelize the processing. This enabled the use of a relatively small (650,000 entries) 7-dimensional dictionary comprising of the 6 tissue parameters and the instrumental parameter B1. Although the B1 was included in the training dictionary, to avoid the risk of the network converging to spurious solutions given the high dimensionality of the problem, B1 was excluded from the network output and the training error calculation. The network training therefore minimized errors in the tissue parameters alone while still accounting for the inevitable B1 variations in vivo. Since T1 estimation is biased by B1, the inclusion of B1 mitigates the T1 underestimation described in prior CEST-MRF studies [15]. Although B0 was not included in the network training, there was little variation in the tissue parameter values across the measured slice (Figure 4), despite significant susceptibility differences near the sinuses. This illustrates the intrinsic robustness to B0 inhomogeneity of the CEST-MRF pulse sequence combined with the DRONE reconstruction. However, more severe B0 inhomogeneity that may be encountered in future 3D whole brain studies may need to be addressed by including B0 in the training dictionary as was done for B1.

4.3. In vivo studies

There was generally good agreement between the tissue parameter values obtained with the CEST-MRF sequence and alternative methods. While there is a wide range of reported values in the literature, the mean WM T1w/T2w measured in this study (T1w/T2w=866.32±122.13 /77.80±7.00 ms) were similar to those reported by other groups [44] and within the standard deviation of the reference values from a conventional MRF sequence (T1w/T2w=974.45±263.92 / 74.40±10.07 ms). The mean GM T1w values were similar to prior MRF studies [45] but lower than those obtained with other methods [44]. Optimizing the schedule to improve the T1 discrimination (by additionally varying FA and TR, for instance) and refining the network’s B1 estimation may address this issue but further study is needed to confirm this. The mean amide exchange rates measured in this study (WM/GM=51.07±7.16 / 47.76±10.36 Hz) was similar to that measured in
the in vivo rat brain in our previous CEST-MRF study [15] as well as exchange rates measured with spectroscopic methods [19]. There was a clear delineation between GM and WM in the fss map which is to be expected given the high WM myelin content and the sensitivity of the semi-solid volume fraction to lipid content.

The test-retest experiments (Figure 5, Table 3) demonstrate good reproducibility of the CEST-MRF tissue maps. Further work is necessary to confirm the reproducibility, which is a critical feature for longitudinal studies or treatment response monitoring applications for this technology.

**4.4. Brain tumor studies**

In many tumors, changes to the tissue parameters occur simultaneously and can therefore confound the CEST signal. In contrast, the combination of the CEST-MRF maps allows separation of different contributors to the signal which can improve tumor characterization. The significantly different values between the drawn tumor ROIs (Figure 7) can improve tumor segmentation and may provide more specific tumor characterization. It should be noted that the lesion imaged in this work (Figure 6) is one that was previously irradiated which is sure to affect the CEST-MRF maps. This is also evident in the perfusion maps (Figure 6 K, L) which are suggestive of a treated tumor. Some features in the CEST-MRF maps, like the reduced amide volume fraction (fs) in the necrotic and edema regions, can be understood as resulting from disrupted protein synthesis in necrotic cells and diluted protein concentrations due to edema. Similarly, the reduced semi-solid volume fraction (fss) in the lesion can be a result of demyelination in that region or post-treatment effects. At present, the biological effects of radiation on the CEST-MRF tissue maps are not well understood and represent an additional confounding factor. Because of the intrinsic biological variability in tumors, prospective large-scale studies will be required to draw meaningful conclusions about relationships between the CEST-MRF maps and the associated tumor characteristics.

**4.5. Limitations and future work**

In the current version of the sequence, coverage is limited to a single slice which may be inadequate for tumors with large spatial extent. Incorporating simultaneous multi-slice and/or slice interleaving can resolve this issue without increasing the total scan length. An optimized ordering of the slice interleaving can also improve tissue discrimination as previously shown [46]. The WM
and GM tissue parameter values calculated in this study were obtained with a simple tissue segmentation based on the intrinsic differences in T2 values between WM and GM and may be affected by partial volume artifacts that can bias the mean. For example, while the mean GM fss value across the slice was 7.08±1.43% (Table 3), a manually drawn circular ROI in the GM yielded a value of 4.78±0.86%, which is similar to what was measured by other groups [47]. In future studies a pulse sequence specifically tuned for GM/WM segmentation can be added to the protocol and all volumes co-registered to that template prior to segmentation with more sophisticated algorithms [48].

The availability of a rapid and non-invasive method for imaging endogenous amide exchange rates and pH makes possible many different studies. One example is the imaging of the tumor’s response to oncolytic virotherapy, as our recent work demonstrated in a preclinical model [24]. Such studies will facilitate development of personalized therapies and can help improve treatment outcomes.

5. Conclusion

This work demonstrated the feasibility of a pulse sequence and a fast, deep learning-based parameter reconstruction algorithm for quantitative CEST-MRF imaging on a clinical scanner. The proposed CEST-MRF presented adequate reproducibility and quantitative results that are consistent with conventional qualitative MRI. CEST-MRF can be particularly beneficial in complex pathologies such as cancer.

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8. Figures

Figure 1: Clinical CEST-MRF pulse sequence shown for one schedule point. The magnetization is saturated with a Gaussian-shaped pulse train and exchanged with the water. The water signal is then excited and read out with an EPI k-space sampling. The saturation pulse train power ($B_{1}^{\text{sat}}$) and duration ($T_{\text{sat}}$) and the excitation pulse flip angle (FA) are varied according to the MRF acquisition schedule. For simplicity, only the saturation power was varied in this study.
Figure 2: DRONE reconstruction of 6 parameters in a digital phantom in comparison to the reference values for an SNR of 80 dB. Regions associated with the background, skull and scalp were set to zero. The error, calculated as $100 \times |\text{Reference} - \text{DRONE}|/\text{Reference}$, was less than 6% for all tissue maps.
Figure 3: Normalized root-mean-square error (NRMSE), on a log scale, of the DRONE reconstructed CEST-MRF maps in a digital brain phantom using a random schedule for varying levels of added white gaussian noise. Changes in SNR non-linearly affected the NRMSE of the different parameters illustrating the sensitivity of the sequence and schedule to each tissue parameter.
**Figure 4**: Reconstructed tissue parameter maps obtained from a healthy volunteer. (A) T1w, (B) T2w, (C) ksw, (D) kssw, (E) fs, and (F) fss. Note the elevated semi-solid volume fraction in the WM reflective of the higher myelin content in WM.

**Figure 5**: In vivo GM and WM tissue parameter values for the four CEST-MRF scans in the healthy volunteer. Scans 1 and 2 were acquired in the first session and scans 3 and 4 in the second session. Blue entries correspond to the left y-axis and red entries to the right y-axis with error bars omitted for clarity. (A) T1w and T2w, (B) ksw and kssw, (C) fs and fss. Note the good repeatability between scans. The concordance correlation coefficient for each parameter and tissue type is listed in Table 3.
Figure 6: In vivo CEST-MRF maps from the patient with brain metastasis and the corresponding images from a standard clinical protocol for comparison. Top: (A) T1w, (B) T2w, (C) ksw, (D) kssw, (E) fs, (F) fss, Bottom: (G) pre-Gd T1-weighted, (H) post-Gd T1-weighted, (I) ADC map, (J) FLAIR map, (K) perfusion map, (L) plasma volume map. The location of the lesion is marked by the green arrows. Note the marked differences in the tissue map values between the lesion and healthy tissues.

Figure 7: Box and whiskers plots of the reconstructed tissue maps values for the different ROIs. The distribution of the parameter values along with the median and the first and third quartile ranges are shown. (A) T1w, (B) T2w, (C) ksw, (D) kssw, (E) fs, (F) fss. The differences between the ROIs were all statistically significant (p=0.001) as determined by a multi-comparison ANOVA test with Tukey HSD except for the regions marked in the ksw and kssw plots.