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Evaluation of the dependence of CEST-EPI measurement on repetition time, RF irradiation duty cycle and imaging flip angle for enhanced pH sensitivity

Phillip Zhe Sun^{1,*}, Jie Lu¹, Yin Wu², Gang Xiao^{3,4}, and Renhua Wu^{4,*}

¹Athinoula A. Martinos Center for Biomedical Imaging, Department of Radiology, Massachusetts General Hospital and Harvard Medical School, Charlestown, MA, USA

²Paul C. Lauterbur Research Center for Biomedical Imaging, Shenzhen Key Laboratory for MRI, Shenzhen Institutes of Advanced Technology, Chinese Academy of Sciences, Shenzhen, China

³Department of Math and Applied Mathematics, Hanshan Normal University, Chaozhou, China

⁴Department of Radiology, 2nd Affiliated Hospital of Shantou University Medical College, China

Abstract

Chemical exchange saturation transfer (CEST) is an MRI contrast mechanism that can detect dilute CEST agents and microenvironmental properties, with a host of promising applications. Experimental measurement of the CEST effect is complex, and depends on not only CEST agent concentration and exchange rate, but also experimental parameters such as RF irradiation amplitude and scheme. Although echo planar imaging (EPI) has been increasingly used for CEST MRI, the relationship between CEST effect and repetition time (TR), RF irradiation duty cycle (DC) and EPI flip angle () has not been fully evaluated and optimized to enhance CEST MRI sensitivity. In addition, our study evaluated gradient echo CEST-EPI by quantifying the CEST effect and its signal-to-noise ratio per unit time (SNR_{put}) as functions of TR, duty cycle and . We found that CEST effect increased with TR and duty cycle but decreased with . Importantly, we found that SNR_{put} peaked at intermediate TRs of about twice the T_1 and , at approximately 75°, and increased with RF duty cycle. The simulation results were validated using a dual-pH creatine-gel CEST phantom. In summary, our study provides a useful framework for optimizing CEST MRI experiments.

Keywords

Chemical Exchange Saturation Transfer (CEST); Magnetic Resonance Imaging (MRI)

1. Introduction

Chemical exchange saturation transfer (CEST) MRI is a relatively new technique that enables detection of dilute labile proton groups and microenvironmental properties. Given the broad range of potential applications for CEST MRI (Ward *et al.*, 2000; Zhou *et al.*, 2003; Zhang *et al.*, 2003; Aime *et al.*, 2005a; Jones *et al.*, 2006; Sun *et al.*, 2007c; Sherry and Woods, 2008), several exogenous CEST agents have been or are being developed to image local pH, lactate and enzyme activity (Aime *et al.*, 2002; van Zijl *et al.*, 2007; Longo

*Corresponding author: Dr. Phillip Zhe Sun (pzhesun@nmr.mgh.harvard.edu) or Dr. Renhua Wu (rhwu@stu.edu.cn), Athinoula A. Martinos Center for Biomedical Imaging, Department of Radiology, MGH and Harvard Medical School, Rm 2301, 149 13th Street, Charlestown, MA 02129, Phone: 617-726-4060, Fax: 617-726-7422.

et al., 2011; Li *et al.*, 2011; Chan *et al.*, 2013). A specialized form of CEST MRI, amide proton transfer (APT) imaging has been applied to study conditions such as stroke, multiple sclerosis (MS), and tumor, as well as to examine cartilage and assess liver and renal function (Salhotra *et al.*, 2008; Mougin *et al.*, 2010; Sun *et al.*, 2011b; Shah *et al.*, 2011; Zhou *et al.*, 2011; Ling *et al.*, 2008; Sun *et al.*, 2012; Dula *et al.*, 2012; Cai *et al.*, 2012). Despite the many benefits of this technique, the experimental optimization of CEST MRI is complex (Sun *et al.*, 2007b; Jin *et al.*, 2012; Wu *et al.*, 2012). Whereas a large RF power level is efficient for saturating labile protons to generate CEST effect, a strong off-resonance RF level may directly saturate the bulk water signal, and therefore reduce the CEST effect (Ward *et al.*, 2000). The effect of RF power level on CEST measurement can be empirically described by an RF spillover factor, which facilitates experimental optimization (Baguet and Roby, 1997; Sun *et al.*, 2005; Sun, 2012). To date, the effects of experimental parameters such as repetition time (TR), RF irradiation duty cycle and imaging flip angle on CEST measurement have not been systematically evaluated.

CEST imaging has been conventionally described by steady state solutions that assume long relaxation and saturation durations (Woessner *et al.*, 2005; Sun *et al.*, 2007a; Sun, 2010; Li *et al.*, 2008). However, more recent studies have used a moderate TR to reduce the scan time, making in vivo applications feasible. Therefore, it is necessary to elucidate the relationship between experimental parameters and CEST measurements (Sun *et al.*, 2008; Sun *et al.*, 2011c; Zu *et al.*, 2011; Sun *et al.*, 2011a). As the analytical solutions that describe the transient CEST measurements are somewhat cumbersome (Murase and Tanki, 2011; Jin *et al.*, 2012; Zaiss and Bachert, 2013), we numerically simulated the magnitude of CEST effect and signal-to-noise ratio per unit time (SNR_{put}) to evaluate the effects of experimental parameters on CEST measurement. We simulated the widely used CEST echo planar imaging (EPI) signal as a function of TR, RF saturation duty cycle, and imaging flip angle, and calculated both CEST effect and SNR_{put} . We validated the simulation results in a creatine-gel CEST phantom. By characterizing the CEST-EPI sequence our study provides new insights to optimize CEST MRI.

2. Materials and Methods

Numerical Simulation

We used the Matlab 7.4 software suite (Mathworks, Natick MA) to simulate CEST effect. Specifically, we used Bloch-McConnell equations to simulate two-site chemical exchange, assuming a representative labile proton chemical shift of 2 ppm for a typical RF irradiation power of 0.75 μT , with concentration and exchange rates of 1:500 and 150 s^{-1} , respectively. We assumed T_1 (T_{1w}) and T_2 (T_{2w}) were 2 s and 100 ms, respectively, for bulk water, and 1 s and 15 ms for labile protons. Fig. 1a shows a typical CEST-EPI sequence, where TR is equal to the sum of the delay time (T_d), saturation time (T_s) and acquisition time (T_a) (i.e., $\text{TR} = T_d + T_s + T_a$). For a typical CEST-EPI sequence, which applies an RF irradiation on the order of multiple T_1 , T_a is significantly shorter than both T_d and T_s . Therefore, $\text{TR} \approx T_d + T_s$, and the RF irradiation duty cycle is represented by $T_s/(T_d+T_s)$. The magnetization evolution was simulated piecewise (Fig. 1 b). The equilibrium magnetizations (M_{eq}) for the bulk water and CEST pools were used as the initial states, and we simulated the magnetization evolution following the CEST-EPI sequence. Since for moderate flip angles and TRs, bulk water magnetization approaches its steady state after two to three TRs, we assumed that the steady state CEST measurement could be obtained after five dummy scans. The signal was calculated as $I = M_w * \sin(\)$, and the CEST ratio (CESTR) was calculated using asymmetry analysis, specifically, by the equation

$$\text{CESTR} = (I_{\text{ref}} - I_{\text{label}}) / I_0 \quad (1)$$

where I_{ref} and I_{label} are the reference and label scans, and I_0 is the control scan (i.e., $B_1 = 0$). RF irradiation was applied at the labile proton frequency (i.e., ω_s) for the label scan, while for the reference scan, RF irradiation was applied at an offset opposite the labile proton frequency around the bulk water resonance (i.e., $-\omega_s$). To calculate SNR_{put} , we assumed the standard deviation of the noise to be 1% the equilibrium magnetization. Rician noise was generated and superimposed on simulated I_{ref} , I_{label} and I_0 signals. The SNR_{put} was calculated as

$$\text{SNR}_{\text{put}} = \frac{\text{CESTR}}{\text{S.D.} \cdot \sqrt{\text{TR} \cdot \text{NSA}}} \quad (2)$$

where S.D. is the standard deviation of noise and NSA is the number of signal averages; this calculation is similar to the CNR efficiency defined by Danagouliau et al. (Danagouliau et al., 2012). We simulated both CESTR and SNR_{put} as a function of TR, RF duty cycle and α . Briefly,

1. TR (Fig. 2). TR was varied from 0.5 to 4 times of T_{1w} in 32 steps for three representative T_1 of 1.5, 2 and 3 s, assuming an RF duty cycle of 0.5 and $\alpha = 60^\circ$.
2. RF duty cycle (Fig. 3). We varied RF duty cycle from 0.2 to 0.8 in 32 steps. We assumed $\text{TR} = 2 \cdot T_1$ for three representative T_1 of 1.5, 2 and 3 s, and $\alpha = 60^\circ$.
3. Imaging flip angle (Fig. 4). We varied α from 10° to 90° in 32 steps, and assumed $\text{TR} = 2 \cdot T_1$ for three representative T_1 of 1.5, 2 and 3 s (RF duty cycle = 0.5).

Phantom

We prepared a dual-pH phantom of creatine and low gelling point agarose (Sun and Sorensen, 2008; Mouglin *et al.*, 2010). Briefly, we first added 2% agarose to phosphate-buffered saline (PBS) solution doped with a trace amount of $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$ (Sigma Aldrich, St Louis, MO). Copper sulfate was added to modulate T_1 , while the agarose gel concentration controls T_2 . The mixture was microwave-heated and immersed in a water bath at 46.5°C (Cole-Parmer, Vernon Hills, IL). We then added creatine to a concentration of 50 mM, which has been shown to generate measurable CEST effect. To create in the phantom compartments of different pH we titrated the pH of the creatine-gel solution to 5.8 and 6.5 (EuTech Instrument, Singapore); the solution was transferred into two concentric tubes and sealed.

MRI

Images were acquired using a 4.7 Tesla small-bore scanner (Bruker Biospec, Billerica, MA). We used single-shot single-slice gradient echo EPI sequence (slice thickness = 10 mm, field of view (FOV) = 76×76 mm, bandwidth = 200 kHz) with image matrix of 64 by 64 and echo time (TE) of 15 ms; the control, reference and label images were averaged twice each (NSA = 2). Because we expected steady state to be reasonably obtained after two repetitions for moderate TR, we used two dummy scans. We imaged creatine amine labile protons at 6.6 ppm (1.9 ppm from bulk water resonance), applying continuous wave block pulse irradiation at ± 1.9 ppm (± 380 Hz at 4.7 T, $B_1 = 0.75$ μT). The RF saturation time was varied according to TR and RF duty cycle ($T_s = \text{TR} \cdot \text{duty cycle}$), which, along with α , we serially varied. Specifically, for each TR of 2, 4, 6, 8 or 10 s, the RF duty cycle was varied at increments of 0.10, from 0.2 to 0.8, while the imaging flip angle was varied by 15° increments, from 15° to 90° , for each TR and RF duty cycle. We also acquired Z-spectra ranging from -3 to 3 ppm at intervals of 0.25 ppm (TR = 6.5 s, $T_s = 3$ s and $B_1 = 0.75$ μT). In addition, T_1 and T_2 maps were obtained with inversion recovery (using seven inversion

intervals (TI) ranging from 0.25 to 5 s, recovery time (T_r)/TE = 6500/28 ms), and fast RF-enforced steady state spin echo (SE) EPI (TR = 6.5 s, TE = 30, 60 and 90 ms) (Cheung *et al.*, 2012).

Data Processing

T_1 and T_2 were obtained using least squares fitting of the signal as functions of inversion time ($I = I_0[1 - (1 - \alpha)e^{-TI/T_1}]$), where α is the inversion efficiency, and TE ($I = I_0e^{-TE/T_2}$), respectively. CESTR was calculated by asymmetry analysis at 1.9 ppm. Because the phantom was well shimmed with B_0 inhomogeneity of -1.3 ± 2.0 Hz (mean $\pm$ S.D.), B_0 inhomogeneity correction was not required. The contrast to noise ratio per unit time (CNR_{put}) between pH compartments was calculated as follows:

$$CNR_{put} = \frac{CESTR|_{pH=6.5} - CESTR|_{pH=5.8}}{\sqrt{(\sigma_{pH=6.5}^2 + \sigma_{pH=5.8}^2) / 2} \cdot \sqrt{TR \cdot NSA}} \quad (3)$$

where CESTR and σ represent the mean CESTR and its standard deviation for each pH compartment. We used the mean standard deviation of the two compartments to estimate the

background noise in Eq. 3 (i.e. $\sigma = \sqrt{(\sigma_{pH=6.5}^2 + \sigma_{pH=5.8}^2) / 2}$). For the case of homogeneous background noise, we have $\sigma_{pH=5.8} = \sigma_{pH=6.5}$.

3. Results

As Fig. 2 illustrates, we characterized the simulated TR dependence of CEST MRI. Fig. 2a shows Z-spectra for three representative TRs of 1, 2 and 4 times of T_1 , using typical values of T_1 , RF duty cycle and imaging flip angle ($T_1 = 2$ s, RF duty cycle = 0.5, flip angle = 60°). As Fig. 2b shows, the normalized signal intensity (i.e., I/I_{eq}) for control, reference and saturated magnetizations increases with TR; I_{eq} is the equilibrium signal at infinite TR. The

steady-state water signal, expressed by the equation $I_0 = \frac{(1 - e^{-TR/T_1}) \cdot \sin \alpha}{1 - \cos \alpha \cdot e^{-TR/T_1}} I_{eq}$, decreases at short TR, reducing the water signal; hence signal reduction as a result of CEST effect is also mitigated. The reference signal is less than that in the control scan because of direct RF saturation. Fig. 2c shows that CESTR generally scales with T_1 (i.e.,

$CESTR \propto \frac{f_s \cdot k_{sw}}{R_{1w} + f_s \cdot k_{sw}}$, where R_{1w} is the longitudinal relaxation rate, and f_s and k_{sw} are the labile proton concentration and exchange rate, respectively). As we varied T_1 from 1.5 to 3 s, in 16 steps, we found that the optimal TR for SNR_{put} was 1.9 ± 0.1 times T_1 (Fig. 2d). This is because CESTR approaches its steady state approximately monoexponentially in the case of slow chemical exchange (i.e., $1 - e^{-(R_{1w} + f_s \cdot k_{sw}) \cdot T_s}$); the slope of CESTR decreases with T_s and increases with T_1 (i.e., $(R_{1w} + f_s \cdot k_{sw})e^{-(R_{1w} + f_s \cdot k_{sw}) \cdot T_s}$). It is important to note that the effect of T_1 on SNR_{put} is significantly less than that of CESTR. The decrease of SNR_{put} at long TR indicates that the CEST-EPI sequence is not efficient for scans with exceedingly long TR.

Fig. 3 shows the simulated RF duty cycle dependence of CEST MRI. For a representative TR (i.e., $2 T_1$), the Z-spectral signal decreases with RF duty cycle, indicating signal loss due to persistent RF irradiation, particularly for the label signal (Fig. 3a). Fig. 3b shows that the steady state signal is independent on RF duty cycle for a given TR, while both the reference and saturated signals decrease with RF irradiation time. As noted, CESTR scales with T_1 , which approaches its steady state approximately at the rate of $(1 - \exp^{-(R_{1w} + f_s \cdot k_{sw}) \cdot T_s})$,

and thus increases with both T_1 and RF duty cycle (Fig. 3c). Therefore, for a given TR, SNR_{put} increases with RF duty cycle due to its higher CESTR (Fig. 3d).

Fig. 4 simulates how the CESTR varies with the imaging flip angle. Fig. 4a shows Z-spectra for three flip angles of 30° , 60° and 90° . The signal is modulated by $\sin(\alpha)$, which increases with flip angle (Fig. 4b). Interestingly, Fig. 4c shows that the CESTR decreases with RF flip angle. This suggests that signal readout competes with relaxation recovery and CEST effect (Sun *et al.*, 2011a). Specifically, a small imaging flip angle has less effect on the steady state CESTR. However, for large flip angles, the Z-magnetization is severely attenuated, and the steady state magnetization must recover from this attenuation. While the recovery of label signal is governed by both relaxation and CEST processes the reference and control scans are determined mainly by relaxation alone. This difference causes the label signal to approach steady state faster than in the reference and control scans, resulting in decreased CESTR at large flip angles. In addition, SNR_{put} initially increases with RF flip angle but peaks before 90° (Fig. 4d). Whereas CESTR peaks at small flip angles (Fig. 4c), the image intensity and, hence, SNR are low at small flip angles because the acquired signal is proportional to $\sin(\alpha)$. We repeated the simulation assuming T_1 in a range of 1.5 to 3 s in 16 steps, and found the optimal flip angle to be $75 \pm 3^\circ$. This suggests that the RF flip angle must be carefully optimized in order to balance CESTR and SNR_{put} .

Fig. 5 shows a representative CEST asymmetry map and Z-spectra from the tissue-like CEST phantom ($B_1=0.75 \mu T$). Higher pH is associated with great signal attenuation at 1.9 ppm of the Z-spectrum, as a result of faster chemical exchange. The respective CESTR values for the pH compartments of 5.8 and 6.5 were $5.0 \pm 0.6\%$ and $12.0 \pm 0.5\%$. By comparison, the two pH compartments showed little difference in T_1 and T_2 . T_1 was 2.43 ± 0.04 (mean $\pm$ SD) and 2.44 ± 0.04 s, while T_2 was 52.5 ± 1.1 and 50.8 ± 0.9 ms in the compartments of pH 5.8 and 6.5, respectively. We analyzed CEST MRI contrast for the two pH compartments ($CESTR = CESTR_{pH=6.5} - CESTR_{pH=5.8}$) and CNR_{put} as a function of TR, RF duty cycle and α (Fig. 6). Specifically, we found that CESTR decreases with flip angle, consistent with the simulation (Fig. 4c). Given the total irradiation time scales with both TR and RF duty cycle, CESTR increases consistently with both RF duty cycle and TR due to prolonged RF irradiation (Fig. 6a). We found that CNR_{put} initially increased with flip angle and TR, then peaked and decreased for very high flip angle and TR. Specifically, CNR_{put} peaked at TR of 5.1 ± 1.6 s (i.e. $TR/T_1 = 2.1 \pm 0.7$) and flip angle of $77.1 \pm 5.7^\circ$ (Fig. 6b). These results agreed very well with the numerical simulation.

4. DISCUSSION

This study showed that CESTR increases with TR and duty cycle but decreases with α . Because CNR is an index to evaluate the CEST signal difference between regions of interest, we also investigated CNR. By calculating CNR per unit time we can compare the quality of the CEST images acquired within a given time period. We found that SNR_{put} peaked at an intermediate TR, about twice the T_1 , and increased with RF duty cycle. CESTR consistently decreased with imaging flip angle, while SNR_{put} peaked at an intermediate imaging flip angle. This shows that the relationship between TR, α and CEST MRI differs from the well-known Ernst angle relationship.

EPI readout has become increasingly used in CEST imaging due to its spatiotemporal resolution (Zhou *et al.*, 2003; Scheidegger *et al.*, 2011; Jin *et al.*, 2011; Zu *et al.*, 2012; Jones *et al.*, 2012). The fast EPI acquisition enables CEST-EPI with long RF irradiation but still reasonable scan time, such that pseudo-steady state CEST measurement can be obtained. By using asymmetry analysis, the signal in the label scan is normalized by the signal of the control scan; the T_2 -induced signal decay does not affect the magnitude of CESTR. We also

simulated Rician noise, and estimated CEST SNR with simulated noise for I_{ref} , I_{label} and I_0 . If we assume identical background Gaussian noise () in the control, reference and label images, and there is no co-variance, the SNR for CEST images could be derived with error

propagation (i.e. $\text{SNR}_{\text{CESTR}} = \frac{\text{CESTR}}{\sqrt{2 + \text{CESTR}^2}} \text{SNR}_{I_0}$), where SNR_{I_0} is SNR of the control image. In addition, the $\text{SNR}_{\text{CESTR}}$ formula agreed well with numerical simulated SNR ($R^2 > 0.99$) for TR, RF duty cycle and flip angle dependence (data not shown). Importantly, the derivation shows that $\text{SNR}_{\text{CESTR}}$ is proportional to SNR_{I_0} . Because SNR_{I_0} decays with echo time following T_2 relaxation, it is necessary to minimize the echo time in order to achieve higher sensitivity (Sun *et al.*, 2013). In addition, CEST MRI using spin echo EPI acquisition is less susceptible to image distortion in the presence of minor field inhomogeneity compared to gradient echo EPI. However, the refocusing pulse in the standard spin echo sequence makes it less efficient than the gradient echo sequence when a short TR is used. This can be addressed by incorporating an additional flip back pulse after EPI to realign the inverted longitudinal magnetization with the magnetic field, for which our conclusions are applicable. Alternative image readout schemes such as gradient echo, rapid acquisition with relaxation enhancement (RARE), fast low angle shot (FLASH) and steady-state free precession (FISP) have been explored in the literature (Dixon *et al.*, 2010; Longo *et al.*, 2011; Shah *et al.*, 2011; Desmond and Stanis, 2012; Sheth *et al.*, 2012). However, systematic comparison of different image readout schemes, in terms of the magnitude of CESTR, SNR, image susceptibility to distortion and across field strength is complicated and beyond the scope of this current work.

Our study validated the numerical simulation results with in vitro experiments. Such in vitro CEST MRI applications have been explored as a platform for developing innovative CEST applications, to which the findings of our current study could be directly applied (Aime *et al.*, 2005b; McMahon *et al.*, 2008; Chan *et al.*, 2013). Our in vitro multi-dimensional acquisition (i.e., with variable TR, duty cycle and imaging flip angle) took approximately 6 hours. Since the typical magnitude of in vivo APT effect is significantly less than that of the engineered CEST phantom, the scan time that would be required to reproduce our results in vivo will be exceedingly long. In addition, in vivo APT/CEST image is heterogeneous and confounded by magnetization transfer (MT) effects (Sun *et al.*, 2007b; Desmond and Stanis, 2012; Lee *et al.*, 2012), and because the in vivo MTR is slightly asymmetric, calculation of the CEST asymmetry analysis may induce a negative shift (Hua *et al.*, 2007; Ling *et al.*, 2008). This may be addressed with other techniques such as Lorentzian line fitting and chemical exchange rotation transfer (CERT), which are beyond the scope of our current work (Zaiss *et al.*, 2011; Zu *et al.*, 2012).

5. CONCLUSION

Our study elucidated the relationship between CEST measurement and experimental parameters including TR, RF duty cycle and imaging flip angle. The results showed that for CEST agents undergoing slow and intermediate chemical exchange, CESTR increases with TR and RF duty cycle but decreases with the imaging flip angle. In addition, SNR efficiency increases with RF duty cycle, and peaks at intermediate TR and imaging flip angle. Our results hold important potential to help guide CEST experimental optimization and quantification.

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APPENDIX

We derived SNR for CEST MRI following the error propagation theory. CEST effect is often measured using MTR asymmetry, which is equivalent to CESTR for a simple 2-pool exchange model, expressed by

$$\text{CESTR} = \frac{I_{\text{ref}} - I_{\text{label}}}{I_0} \quad (\text{A.1})$$

We can also calculate that the partial derivatives of CESTR with respect to I_{ref} , I_{label} and I_0 are

$$\left(\frac{\partial \text{CESTR}}{\partial I_{\text{ref}}} \right)^2 = \left(\frac{\partial \text{CESTR}}{\partial I_{\text{label}}} \right)^2 = \left(\frac{1}{I_0} \right)^2 \quad (\text{A.2.a})$$

$$\left(\frac{\partial \text{CESTR}}{\partial I_0} \right)^2 = \left(\frac{I_{\text{ref}} - I_{\text{label}}}{I_0^2} \right)^2. \quad (\text{A.2.b})$$

Hence, the standard deviation of CESTR can be obtained as

$$\begin{aligned} \sigma_{\text{CESTR}}^2 &\approx \left(\frac{\partial \text{CESTR}}{\partial I_{\text{ref}}} \right)^2 \sigma_{\text{ref}}^2 \\ &+ \left(\frac{\partial \text{CESTR}}{\partial I_{\text{label}}} \right)^2 \sigma_{\text{label}}^2 + \left(\frac{\partial \text{CESTR}}{\partial I_0} \right)^2 \sigma_0^2 \approx \frac{\sigma_{\text{ref}}^2}{I_0^2} \\ &+ \frac{\sigma_{\text{label}}^2}{I_0^2} \\ &+ \left(\frac{I_{\text{ref}} - I_{\text{label}}}{I_0^2} \right)^2 \sigma_0^2 \approx \frac{1}{I_0^2} \left(\sigma_{\text{ref}}^2 + \sigma_{\text{label}}^2 + \left(\frac{I_{\text{ref}} - I_{\text{label}}}{I_0} \right)^2 \sigma_0^2 \right) \end{aligned} \quad (\text{A.3})$$

If we assume that noise characteristics of the control, reference, and label signals are identical (i.e., $\sigma_{\text{ref}} = \sigma_{\text{label}} = \sigma_0$), the standard deviation of CESTR can be simplified as

$$\sigma_{\text{CESTR}}^2 \approx \frac{1}{I_0^2} \left(\sigma_{\text{ref}}^2 + \sigma_{\text{label}}^2 + \left(\frac{I_{\text{ref}} - I_{\text{label}}}{I_0} \right)^2 \sigma_0^2 \right) \approx (2 + \text{CESTR}^2) \frac{\sigma_0^2}{I_0^2} \quad (\text{A.4})$$

Therefore, CESTR SNR can be derived as

$$\text{SNR}_{\text{CESTR}} = \frac{\text{CESTR}}{\sigma_{\text{CESTR}}} \approx \frac{\text{CESTR}}{\sqrt{2 + \text{CESTR}^2}} \cdot \text{SNR}_{I_0} \quad (\text{A.5})$$

where SNR_{I_0} is SNR of the control signal (i.e., $B_1=0$). For a typical dilute CEST agent with slow and intermediate exchange rate, $\text{CESTR}^2/2 \ll 1$, and $\text{SNR}_{\text{CESTR}}$ can be approximated by

$$\text{SNR}_{\text{CESTR}} \approx \frac{\text{CESTR}}{\sqrt{2}} \cdot \text{SNR}_{I_0} \quad (\text{A.6})$$

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Fig. 2.

Simulated TR dependence of CEST MRI (2 ppm at 4.7 Tesla, $B_1 = 0.75 \mu T$). a) CEST Z-spectral intensity vs. TR. b) The steady state magnetizations for control (I_0), reference (I_{ref}) and label scans (I_{label}), normalized by the equilibrium signal (I_{eq}) obtainable under infinite TR. c) CESTR versus TR and T_1 . d) The SNR per unit time (SNR_{put}) versus TR.

Fig. 3. Simulated RF duty cycle dependence of CEST MRI (2 ppm at 4.7 Tesla, $B_1 = 0.75 \mu T$). a) CEST Z-spectra vs. RF duty cycle. b) The normalized steady state I_0 , I_{ref} and I_{label} versus RF duty cycle. c) CESTR increases with RF duty cycle and T_1 . d) SNR_{put} increases with RF duty cycle and T_1 .

Fig. 4. Simulated imaging flip angle (α) dependence of CEST MRI (2 ppm at 4.7 Tesla, $B_1 = 0.75$ μ T). a) CEST Z-spectra vs. flip angle, with the control signal (I_0) shown in gray lines. b) I_0 , I_{ref} and I_{label} as a function of the imaging flip angle. c) CESTR decreases with flip angle and increases with T_1 . d) SNR_{put} increases with T_1 but peaks at an intermediate imaging flip angle.

Fig. 5. Experimental measurement of pH-weighted CEST MRI at 4.7 Tesla ($TR=6.5$ s, $T_s=3$ s and $B_1=0.75$ μ T). The Z-spectra show pH-specific CEST effect at 1.9 ppm from bulk water resonance, as confirmed by the CESTR map calculated by asymmetry analysis.

Fig. 6.

Experimental evaluation of TR, RF duty cycle (DC) and flip angle (α) dependence of CEST MRI. a) The dependence of pH-sensitive CEST contrast as functions of TR, flip angle and RF duty cycle. b) CNR_{put} as functions of TR, flip angle and RF duty cycle.