Simplified RF spillover-corrected omega plot for simultaneous determination of labile proton ratio and exchange rate

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Introduction CEST MRI provides an exchange-dependent contrast mechanism that is sensitive to dilute CEST agents and microenvironment properties, and remains promising for a host of in vivo applications[1-8]. However, CEST MRI contrast is complex, depending on not only the labile proton concentration and exchange rate, but also on the experimental parameters such as the field strength and RF irradiation power. It has been shown that the CEST effect can be described as a multiplication of the simplistic CEST contrast, the labeling coefficient and the spillover factor[9,10]. The labeling coefficient quantifies the saturation efficiency of the exchangeable protons, while the spillover factor calculates the direct RF saturation of the bulk water signal, which competes with the CEST effect. Because the RF spillover factor shows very little variation with labile proton ratio and exchange rate, we postulated that the RF spillover factor can be estimated and compensated so that both the labile proton ratio and exchange rate can be determined from the proposed simplified qCEST analysis [11,12].

Materials and Methods Phantom: Creatine solution was added to trace gadolinium-doped phosphate buffered solution (PBS) at concentrations of 20, 40, 60, 80 and 100 mM; pH was titrated to 6.75. MRI: Single-slice, single-shot echo planar imaging (EPI) images were obtained from a 4.7 T small-bore MRI scanner. For the CEST MRI, 3-point CEST imaging was performed with continuous wave (CW) RF irradiation applied at ±1.875 ppm, in addition to a control scan. The RF power was varied from 1, 1.5, 2, 2.5 and 3 μT (TR/TS/TE=20s/10s/28 ms). In addition, T_1 (TR/TE =12,000/28 ms, NSA=2) and T_2 (TR=12,000 ms, NSA=2) were obtained using inversion recovery and spin echo MRI, respectively. All images were processed in Matlab.

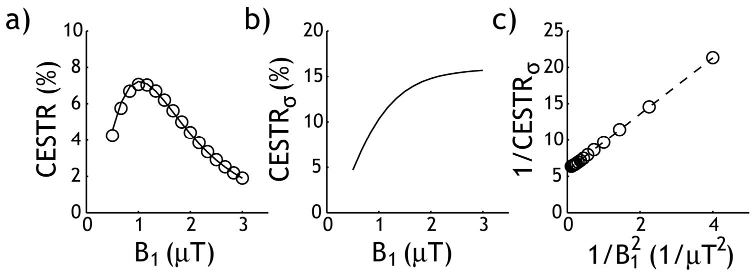

Fig. 1, The proposed spillover factor-corrected qCEST analysis. a) CESTR as a function of RF power level, which indicates non-negligible RF spillover effects. b) RF spillover effect-corrected CEST effect as a function of RF power level. c) The RF spillover effect-corrected omega plot, which can be described by linear regression, from which both labile proton ratio and exchange rate can be determined.

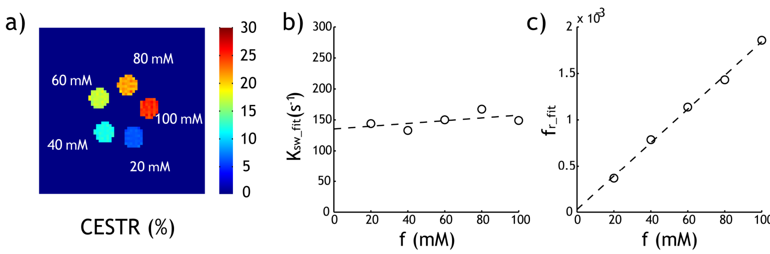

Fig. 2, Quantitative CEST MRI. a) CEST contrast is sensitive to agent concentration. b) The numerically solved labile proton exchange rate as a function of creatine concentration. c) The labile proton ratio as a function of creatine concentration.

Results and Discussion The CEST effect can be described by an empirical solution $CESTR=f_r \cdot k_{sw}/(R_{1w}+f_r \cdot k_{sw}) \cdot \alpha \cdot (1-\sigma)$, where α and σ are the labeling coefficient and spillover factor, respectively. Notably, the spillover factor shows relatively small dependence on the labile proton ratio and exchange rate. As such, the RF spillover effect can be reasonably estimated based on the RF irradiation amplitude, offset and relaxation constants, and the spillover factor-corrected CEST effect can be calculated as $CESTR|_\sigma = CESTR/(1-\sigma)$. Both the labile proton ratio and exchange rate can be determined from the linear regression fitting, being $f_r=R_{1w}/(k_{sw}*(C_0-1))$, and $k_{sw}=(sqrt(R_{2s}^2+4*C_1/(C_0-1)-R_{2s})/2$, respectively.

Fig. 1 evaluates the proposed qCEST analysis with simulated CEST results using a 2-pool Bloch-McConnell model. Fig. 1a shows RF power level-dependent CEST effect, with typical RF power level from 0.5 to 3 μT, assuming representative labile proton ratio and exchange rate of 1:2000 and 200 s^{-1}, respectively. Fig. 1 b shows the RF spillover correction can effectively compensate the loss of CEST effect at high RF power levels. Fig. 1 c shows the inverse spillover factor-corrected CEST effect as a function of $1/B_1^2$, (i.e. modified omega plot). Importantly, both the labile proton ratio and exchange rate can be determined from the slope and intercept of the linear regression, in good agreement with the simulated values.

Fig. 2 validates the proposed algorithm using a creatine CEST phantom. Specifically, Fig. 2a shows CEST MRI is sensitive to creatine concentration. Using the proposed simplified qCEST analysis, we found the exchange rate to be 149 ± 12 s^{-1} (Fig. 2b), and its correlation with the creatine concentration was insignificant (ρ =0.56, P=0.32). In comparison, the labile proton ratio was found to be 1:2723, 1:1271, 1:879, 1:698 and 1:538 (ρ=0.998, P<0.0001) for 20, 40, 60, 80 and 100 mM creatine concentration (Fig. 2c). It is important to point out that whereas the spillover factor was estimated assuming the same labile proton ratio and exchange rate (i.e. 1:1000 and 100 s^{-1}) for all creatine compartments, the numerically solved parameters correctly delineated and solved the labile proton exchange rate and ratio despite non-negligible RF spillover effects.

References 1) Ward et al. JMR 2000;143:79-87. 2) Zhang JACS 2005;127:17572-3. 3) Gilad et al. Nat Biotecholo 2007; 25:217-9. 4) Zhou et al. Nat Med. 2011;17:130-4. 5) Sun et al. JCBFM 2011;31:1743-50. 6) Shah et al. MRM 2011;65:432-7. 7) Longo et al MRM 2011;65:202-11. 8) Cai et al. Nat. Med. 2012;18:302-6. 9) McMahon et al MRM 2006;55:836-47. 10) Sun et al. JMR 2005;175:193-200. 11) Wu et al. CMMI 2012;7:384-89. 12) Dixon et al. MRM 2010:63:625-32.