Predicting Optimal Properties of CEST MRI Agents under Practical Experimental Conditions

P. Z. Sun[1], G. Liu[2,3], J. Zhou[2,3], P. van Zijl[2,3], and M. T. McMahon[2,3]

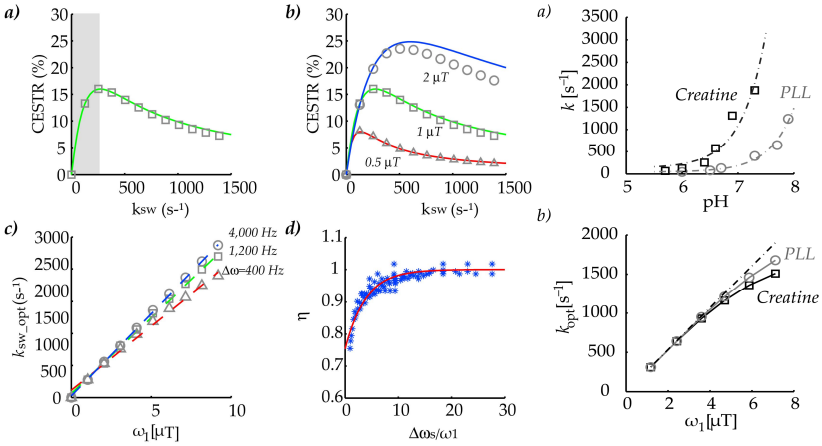
[1]Department of Radiology, Harvard Medical School, Athinoula A. Martinos Center for Biomedical Imaging, Charlestown, MA, United States, [2]Russell H. Morgan Department of Radiology & Radiological Science, Johns Hopkins University School of Medicine, Baltimore, MD, [3]F. M. Kirby Center for functional Brain Imaging, Kennedy Krieger Institute, Baltimore, MD, United States

Introduction Chemical exchange saturation transfer (CEST) MRI provides a sensitivity enhancement mechanism that allows measurement of microenvironment properties such as pH and temperature through dilute labile protons [1-3]. Because CEST contrast often increases with chemical exchange rate, a common strategy to improve CEST MRI sensitivity is to design PARACEST and LIPOCEST agents that have fast exchange groups [4-6]. Recently libraries of these agents have been produced with different shifts for the exchangeable protons / water molecules ($\Delta\omega$). It has been suggested the optimal exchange rate is about equal to the RF irradiation power, however, this does not take into account the direct RF saturation effects and especially for diamagnetic agents this should depend on $\Delta\omega$. In this study, we investigated the optimal exchange rate using both analytical and numerical solutions, and further validated these experimentally for two of the main exchangeable groups found in proteins amide (NH) and guanidyl NH_2 (gNH_2). We have demonstrated that by normalizing the exchange rate and chemical offset by the RF irradiation power, the optimal exchange rate can be predicted using a stretched exponential function. In summary, our results predicting optimal properties under practical experimental conditions may help guide the rational design of CEST agents.

Methods Numerical simulations were conducted using MATLAB 7.4, with labile proton content assumed to be 1:800, and longitudinal relaxation times for water and labile protons being 1.5s and 1s, while the transverse times were 60 ms and 10 ms, similar to in vivo parameters [7]. The chemical exchange rate, RF irradiation power, and labile proton offset were varied from 0 to 2,500 s^{-1}, 0 to 10 μT and 400 to 4,000 Hz, respectively. The prediction of optimal exchange rate as a function of irradiation RF power and chemical offset was obtained using a representative chemical offset of 1,000 Hz, and the RF power was varied from 1 to 10 μT. In addition, Poly-L-lysine (PLL, 10mg / ml) and Creatine (3mg / ml) solutions were used to test the derived relationship. Specifically, CEST MRI of solution phantoms was performed at 500 MHz with a series of RF powers (50- 300 Hz), whose pHs have been titrated to produce a broad range of chemical exchange rates. The optimal exchange rate (k_{opt}) for a given RF power was obtained by fitting the CEST ratio (CESTR) as a function of exchange rate.

Results and discussion The CEST MRI contrast was modeled using a 2-pool exchange model. Fig. 1a shows the empirical solution of CESTR as a function of exchange rate for a B_1 of 1 μT, in good agreement with numerical simulations. CESTR initially increases with exchange rate, but for very high exchange rates, CESTR decreases. This is due to insufficient saturation of fast exchange protons using a limited RF power. It is important to note that the empirical solution is only an approximation of CEST MRI contrast, and is susceptible to non-negligible errors for intermediate RF powers (Fig. 1b). The optimal exchange rate (k_{opt}) is shown to be proportional to RF power (Fig. 1c), as expected. However, it is necessary to note that k_{opt} also depends on the chemical offset: for the same RF power, k_{opt} decreases with chemical offset as the contrast is subject to reduction from larger RF spillover effects. In fact, k_{opt} can be described using a stretched exponential function as $k_{opt} = C_1\left(1 - C_2 \cdot e^{-C_3 \cdot \Delta\omega_s / 2\pi\gamma B_1}\right) \cdot 2\pi\gamma B_1$.

For a representative chemical offset of 1,000 Hz, C_1, C_2 and C_3 were found to be 1, 0.25 and 0.26, respectively. The fact that C_1 is equal to 1 suggests that our solution is consistent with the simplistic conclusion that ignores spillover effects (i.e., □□ / □$_1$>10). However, k_{opt}, in general, is attenuated from the simplistic relationship, which can be predicted using the proposed empirical formula. In addition, the derived solution was tested experimentally. Two compounds with different chemical shifts for their exchangeable protons were titrated to produce chemical exchange rates varing from 30Hz to >1500Hz . The optimal exchanges rate for PLL and Creatine were plotted as a function of RF power, with the dashed line showing the simplistic linear relationship (Fig. 2b). It shows that although the experimentally measured k_{opt} is about equal to RF power below 3 μT, it is significantly attenuated at high RF powers, as we have predicted. Moreover, because the NH protons in PLL (3.6 ppm from bulk water) are 1.6ppm further away than the gNH_2 protons in Creatine, the k_{opt} for PLL is consistently higher for any given RF power. In summary, our study established an empirical formula for predicting the optimal CEST agents' properties under practical experimental conditions (field strength, RF power etc.), and may help guide future rational design of CEST agents.



References: 1)Ward & Balaban MRM2000; 44:799-802. 2)Zhou et al. Nat Med 2003; 9:1120-6.3)Zhang et al. JACS 2005:127;17572-3. 4)Aime et al. MRM2002:47(4): 639-648. 5)Zhang et al. JACS 2001;123;1517-8. 6) McMahon et al. MRM2006; 55(4):836-47. 7) SunPZ et al. JMR2005;175:193-200.