Optimal Properties of Chemical Exchange Saturation Transfer (CEST) Contrast Agents

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INTRODUCTION

Chemical exchange saturation transfer (CEST) imaging provides a unique sensitivity enhancement mechanism through the saturation exchange between labile solute protons and bulk water protons [1]. Because CEST contrast usually increases with the chemical exchange rate, a common strategy to improve CEST sensitivity is to design agents with rapidly exchanging protons. To efficiently label such protons, a RF irradiation pulse of high power is required, which, depending of the chemical shift difference with water, may directly saturate the bulk water (RF spillover). In order to retain the advantage of fast exchange while suppressing non-specific spillover effects and avoid venturing into the NMR fast-exchange regime, the chemical shifts of fast exchange protons in CEST agents are often shifted away from water using paramagnetic metals (PARACEST) [2,3]. With the goal of applying CEST/PARACEST agents to in vivo imaging, there are a few experimental limitations; among them is the specific absorption rate (SAR), which limits the maximal applicable RF power. In this study, we modeled the CEST process using a 2-pool model, and investigated the optimal exchange rates using both analytical and numerical solutions.

MATERIALS AND METHODS

Numerical simulation was conducted using custom code in MATLAB (Mathworks, Natick MA). The ratio of labile protons to bulk water protons simulated was 1:2,000 (55mM), and longitudinal relaxation times used for water and labile protons were 1.5s and 0.77s respectively, while the transverse times were 60ms and 33ms. The optimal irradiation power was derived using Eq. [22] of Ref (4), and the maximum CEST contrast was calculated by substituting the obtained optimal irradiation power into Eq. [1] of Ref (4). In addition, for a given RF power, the CEST contrast for a wide range of exchange rates were numerically simulated, and the exchange rate at which the CEST contrast was maximal was taken as the optimal exchange rate. All experiments were performed at 500 MHz (Avance, Bruker). The pH of PLL phantoms were adjusted to 6, 6.5, 6.7, 7.3, 7.7 and 7.9, and the APTR were measured with RF powers of 50, 75, 100, 150, 200 and 250 Hz. The optimal exchange rates were obtained by fitting the measured APTR vs. exchange rates for the maximal APTR. Due to the fact that the maximal RF power used was 250 Hz, only three optimal exchange rates (pH=6, 6.5 and 6.7) were obtained.

RESULTS & DISCUSSION

The maximal proton transfer ratio (PTR) can be obtained by an empirical solution that accounts for the maximal theoretical PTR (PTR_{max}), labeling coefficient (L) and the spillover factor (σ) as $PTR=PTR_{max} * L * (1-\sigma)$. Fig. 1a shows that with optimal irradiation RF powers, the maximal obtainable PTR could be obtained at the highest offset and exchange rates. Such results were expected, as these regions are of the most efficient saturation transfer with the least spillover effects. However, it is worthwhile to note the optimal irradiation power also increased with the offset and exchange rates significantly up to 20 μT (Fig. 1b). On the other hand, when applying CW RF pulse to indirectly saturate bulk water protons, it takes about the timescale of the longitudinal relaxation time of bulk water (~T1w) in order to transfer significant amount of saturation for detection. However, the RF energy deposition of such a long labeling pulse will be enormous and may be beyond the SAR limit. As the maximal RF power is likely to be a limiting factor for the PARACEST imaging, we simulated the optimal exchange rate for a given maximal RF power as shown in Fig. 2a, with the red and blue line representing the analytical solution and Woessner's prediction, respectively[6]. This study shows that for low to intermediate RF powers (<10μT), the optimal exchange rates obey a simple relationship with RF power ($k=2\pi\gamma B_1$), similar as Woessner's conclusion[6]. In addition, the experimental results from McMahon et al. were analyzed and it confirmed the derived relationship[5] (Fig. 2b).

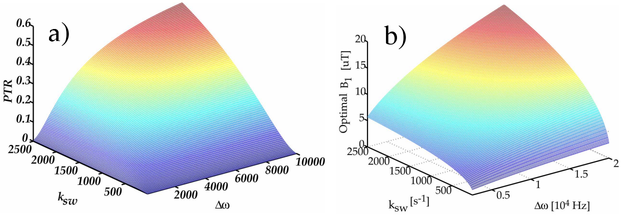

Fig. 1, a) PTR versus chemical offset and exchange rate. It shows that the maximal PTR contrast can be obtained at high offset and fast chemical exchange. B) The optimal RF power required to obtain the maximal PTR. In order to take advantage of fast exchange protons, the required RF field is extremely high, ~15-20 μT.

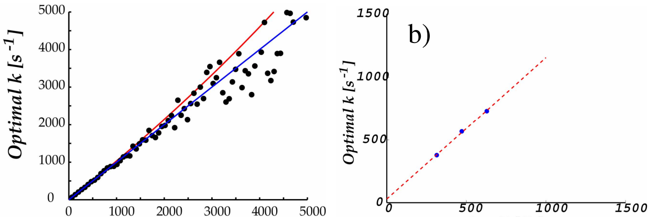

Fig. 2, a) Numerically simulated optimal exchange rates (black dots) versus analytical prediction (red line) and Woessner's solution (blue line). B) Experimental derived optimal k versus the irradiation power, and it agreed with the derived relationship very well.

In addition, our results indicates that if the RF power is the limiting factor for fast exchange CEST/PARACEST agents, it may be advantageous to perform CEST imaging at lower fields as for the same SAR limit, the maximal RF power is higher at low field (i.e., 1.5T vs. 3 T).

REFERENCES

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