Pulsed CEST for the quantification of pH

K. L. Desmond[1], and G. J. Stanisz[1,2]
[1]Medical Biophysics, University of Toronto, Toronto, Ontario, Canada, [2]Imaging Research, Sunnybrook Health Sciences Centre, Toronto, Ontario, Canada

Introduction: pH figures prominently in much pathology, since it changes when hypoxic conditions disrupt the natural metabolism pathway causing a shift towards anaerobic respiration. Changes in pH have been observed by several different imaging modalities[1], including by phosphorus MRI and with MRI contrast agents including PARACEST[2]. There is a drive towards developing the ability to image pH without the introduction of exogenous contrast agents and with more widely available proton MRI[3]. Towards this purpose, amide proton transfer experiments (a subset of chemical exchange saturation transfer (CEST) experiments) have successfully demonstrated the dependence of hydrogen exchange on the local hydrogen ion concentration to create pH-weighted images of ischemia[4, 5] and cancer[6]. However, *in vivo*, in the presence of structured semi-solid macromolecules which are dominated by magnetization transfer (MT) effects, the relationship between the observed CEST-related contrast and pH becomes complicated[7] due to the overlapping of the amide resonance with that of bulk water. Previously it has been shown that the pulsed CEST method can consistently measure CEST parameters, such as exchange rate, in the presence of an MT component[8]. In this abstract it is shown in a phantom experiment that pulsed CEST can be used to quantitatively measure proton exchange rate indicative of the underlying pH of the solution.

Method: A series of phantoms was constructed with 1M ammonium chloride (NH_4Cl) with pH modified by the addition of a 10mM citric acid buffer for pH in increments of 0.25 from 5 to 6. Phantoms were measured at 3T (GE MR750, Milwaukee, WI) with pulsed CEST, consisting of the addition of a hanning-windowed, gaussian-shaped saturation pulse to a stock spoiled gradient echo sequence[9]. Saturation pulse duration was 106 ms, saturation pulse angle was twice repeated with values 500° and 1000°, repetition time 200 ms, echo time 4 ms, range of saturation offset frequencies linearly spaced from -800 to 800 Hz, with a reference image at 200kHz used for normalization. An *a priori* measurement of T1, required by the fitting algorithm, was obtained via an inversion recovery experiment with the inversion time, TI, ranging from 50 to 2000 ms and a TR of 3000 ms. A two-compartment model of the Bloch equations in the presence of exchange was applied to obtain a global fit for the following parameters: M_{0c} (relative concentration of protons associated with the CEST pool), $T2_a$ and $T2_c$ (T2 of water and CEST pool respectively), R_c (1/T1 of the CEST pool) and Δ_{0c} (the frequency offset between the CEST pool and the free water pool). R_{cest} (rate of chemical exchange between the CEST and free water pools), was allowed to vary in the fit for each phantom.

Results and Discussion:

Figure 1:

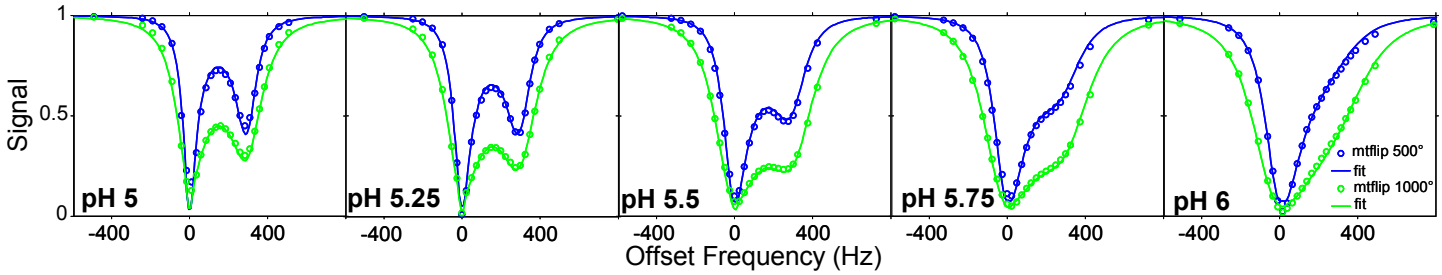

Figure 2:

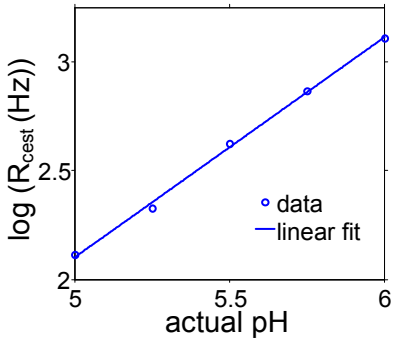

Figure 1 shows the fitted CEST data for each pH, for both saturation pulse flip angles. The results of the global fit to the CEST model for each of the five phantoms are as follows: $T2_a$ = 185 ms, R_c = 3.62 Hz, M_{0c}/M_{0a} = 0.13, $T2_c$ = 15 ms, Δ_{0c} = 293Hz. The fitted results for R_{cest} for each phantom are shown as a function of actual pH in the semi-log plot in Figure 2. A linear fit was applied to obtain the following relationship between the exchange rate and pH: $pH = (\log(R_{cest}) + 2.95)/1.01$. These results lay the groundwork for quantitative determination of pH *in vivo* with a pulsed CEST experiment measuring amide proton transfer.

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