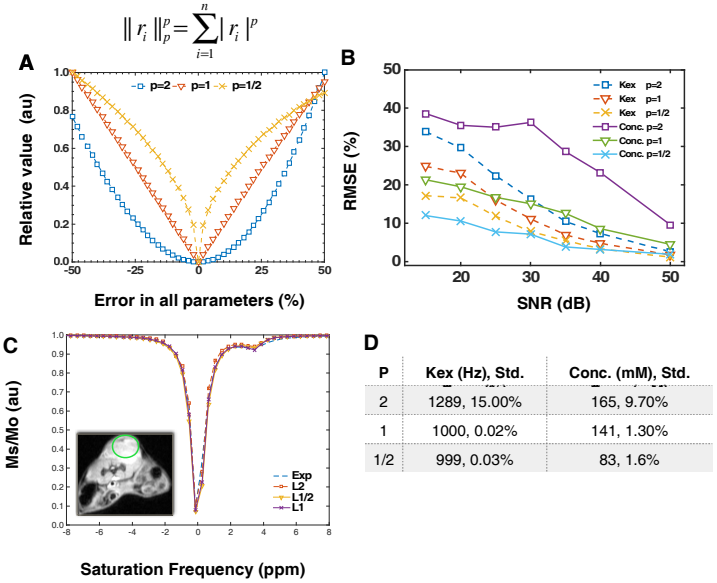
A robust method to estimate CEST MRI parametric maps in vivo: Simultaneous quantification of concentration and exchange rate by minimizing the Lp norm

Julio Cárdenas-Rodríguez[1] and Mark D. Pagel[1]
[1]*Biomedical Engineering, University of Arizona, Tucson, AZ, United States*

Introduction

Chemical Exchange saturation transfer (CEST) MRI has proven to be sensitive to the concentration of metabolites, extracellular pH, enzymatic activity, and gene expression. The contrast in CEST MRI is a complex function of the concentration (M_{os}) and exchange rate (k_{ex}) of the exchangeable pool(s), and experimental parameters (saturation time, power, and magnetic field). The Bloch-McConnell equations provide a means to estimate all the properties of an exchangeable pool based on the CEST MRI signal using non-linear regression [1-2]. However, it is not feasible to perform such regression *in vivo* to construct CEST parametric maps using standard least square curve fitting (LSQ) methods. The LSQ method has three major flaws that prevent its application on a voxel-by-voxel basis: 1) Poor performance under low signal-to-noise-ratio, 2) Its estimates are highly dependent on the initial guess provided by the researcher, 3) Several solutions are equivalent under the LSQ minimizer (Figure 1A). In this study we propose to analyze the CEST by applying regression algorithms that minimize the absolute deviation (L_1 norm) and the absolute squared root ($L_{1/2}$ norm) of the curve fitting residuals. We also compared computationally and experimentally these two minimizers to the standard LSQ (L_2 norm).



P	Kex (Hz), Std.	Conc. (mM), Std.
2	1289, 15.00%	165, 9.70%
1	1000, 0.02%	141, 1.30%
1/2	999, 0.03%	83, 1.6%

Figure 1. Comparison of three methods to do non-linear regression to the Bloch-Mcconnell Equations. **A)** Formulas and behavior of each minister as function of the error in all parameters in a 2-pool model. When p=2 multiple solution are near optimal. **B)** Root-mean squared errors in the estimated Kex and conc. as a function of signal-to-noise-ratio. Noise was added to a simulated to 2-pool model and each algorithm was used to estimate Kex and Conc. This process was repeated a thousand times for each noise level. **C)** Experimental CEST spectra. The green circle show approx. the ROI used for the curve fitting. **D)** Standard errors in the estimated Kex and Conc using the data from Panel C. The residual for each minimizer were bootstrapped 1000 times with the experimental CEST to obtain these errors.

Methods.

Simulations. The endogenous CEST effect was simulated under several conditions by solving a homogenous version of the Bloch-McConnell equations for two pools. These synthetic data were used to study the effect of signal-to-noise ratio, initial guess, and saturation power on the accuracy and precision of each regression algorithm. Parameters previously reported were used [1]. Animal Model. Five female SCID mice were injected subcutaneously with $10x10^6$ MDA-231 breast cancer cells in the right flank. Tumors were allowed to grow to an average volume of 250 mm^3 before initiating **CEST MRI studies**. All animals were imaged on 7T on a Bruker Biospec while maintaining their temperature at 37°C. MRI: A CEST-FISP pulse sequence (1.0 T, 3 sec, CW) with 101 saturation frequencies (+10 to -10 ppm) was used to acquire a CEST image in 5.05 min. **Experimental Curve Fitting**. The residuals for each regression method were bootstrapped 500 times with the original CEST spectrum to estimate the confidence of the estimated M_{os} and Kex. **Results**: Due to space constraints only representative results are presented. Simulations. *1)* Only the L_1 and $L_{1/2}$ norm methods can estimate M_{os} and Kex at moderate SNR (Figure 1B). *2)* Only the $L_{1/2}$ norm method can estimate M_{os} and Kex when the initial guess in the parameters is systematically erroneous (data not shown). Experimental. *1)* All methods predict the same CEST spectrum, but the parameters obtained by L_2 min. are different. 2) The L_2 min method (LSQ) is not a robust estimator of M_{os} and Kex (Table 1). **Discussion/Conclusion**: The standard LSQ curve fitting method is not a robust method to estimate the concentration and exchange rate of a CEST pool simultaneously. The minimization of the L_1 or $L_{1/2}$ norm of the residuals are proposed as suitable alternatives.

References: 1) Murase K. et al. Magn. Reson. Img. 2011, 126–131. 2) Woesnner et al. Mag. Res. Med, 2005, 790–799