Z-Spectrum Fitting for CEST Contrast Computation in *In Vivo* Myocardium Tissue

Anup Singh[1], Mohammad Haris[1], Kejia Cai[1], Feliks Kogan[1], Walter RT Witschey[1,2], Gerald A Zsido[2], Jeremy McGarvey[2], Ravi PR Nanga[1], Francisco Contijoch[3], James J Pilla[4], Joseph H Gorman[2], Victor A Ferrari[5], Hari Hariharan[1], Robert C Gorman[2], and Ravinder Reddy[1]

[1]*CMROI, Department of Radiology, University of Pennsylvania, Philadelphia, Pennsylvania, United States,* [2]*Department of Surgery, University of Pennsylvania, Philadelphia, Pennsylvania, United States,* [3]*Bioengineering, University of Pennsylvania, Philadelphia, Pennsylvania, United States,* [4]*Department of Radiology, University of Pennsylvania, Philadelphia, Pennsylvania, United States,* [5]*Department of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania, United States*

INTRODUCTION: Chemical-exchange-saturation-transfer (CEST) technique is used for mapping molecular changes *in vivo* (1, 2, 3). We have recently shown that myocardial tissue data shows a promising CEST effect (4). Based upon our experimental data, CEST contrast obtained by asymmetry analysis (2, 3) is challenging *in vivo* due to respiratory and left ventricular wall motion and fluctuations of B_0 during CEST imaging. To address this issue we adopted an approach to fit z-spectral data with Lorentzian functions corresponding to direct saturation (DS), magnetization transfer (MT) and CEST components using either linear or probabilistic combination (5). We demonstrated the performance of these approaches in both *ex vivo* and *in vivo* myocardium.

MATERIALS AND METHODS: ***CEST MRI:*** All MRI experiments were performed on a 3T whole-body MRI scanner (Siemens Healthcare; Erlangen, Germany) using a previously described CEST sequence (3). CEST data was acquired using, a 250ms saturation pulse duration with B_{1rms} of 155Hz.

Ex vivo data: Normal lamb left ventricular (LV) myocardial tissue samples (n=3, < 24 hrs post-mortem) were submersed in the PBS (pH 7.0) and MRI was performed at 37°C. CEST data over a Δω range of -15 to +15 ppm were acquired. In addition, a base image without saturation (S_0), WASSR and B_1 map data were also acquired. The sequence parameters were: slice thickness = 10 mm, GRE flip angle=10°, GRE readout TR/TE=5.6/2.7 ms, FOV =100×100 mm^2, matrix size =128×128, and one saturation pulse and 64 segments acquired every 10s.

In vivo data: Healthy normal (N=2) and post-infarction (N=1, 8 week) Yorkshire swine were used in this study. All image acquisitions were performed during end-expiration and diastolic stasis with dual-physiologic gating. The CEST saturation pulse was delivered such that image acquisition was in diastolic phase (~200ms after the QRS complex) with a 3s inter-shot period to provide a delay for restoration of longitudinal magnetization.. CEST data were acquired over a Δω range of -6 to +6 ppm in 0.25ppm steps. In addition, a base image without saturation (S_0) and B_1 map data were also acquired. The sequence parameters were: slice thickness = 5mm, GRE readout TR/TE=5.2/2.5ms, FOV =243×300mm^2, matrix size =208×256. Total scan time was ~1 hour. CEST asymmetry (CESTasy) contrast was computed as described previously (3).

$$f(x) = 100*(1-LS(x)) \quad [1]$$

Where $LS(x) = \sum_{i=1}^{N} L(x, A(i), W(i), C(i))$

and $L(x, A, W, C) = A \times \frac{\left(\frac{W^2}{4.0}\right)}{\left(\frac{W^2}{4.0}\right)+(x-C)^2}$

A =amplitude, W=width, C =center of Lorentzian, x =offset frequency.

***Fitting function and procedure*:** In the current study, we fit two types of functions to z-spectra data, a linear combination of Lorentzians (LS) as given by the Eq. [1] and a probabilistic combination of Lorentzians (LPC) as described previously (5). As such multiple metabolites having labile protons (-OH(~1ppm), -NH_2(~1.8-3ppm) and –NH(3.5ppm)) can contribute to CEST effect in myocardium tissue; however, by using appropriate saturation parameters individual contributions can be highlighted or suppressed. Saturation parameters used in current study were chosen to highlight amine protons contrast and suppress –NH protons based contrast. Moreover, -OH protons contribution to CEST should also be minimal at 3T due to their fast exchange rate (~1000Hz). Since –NH_2 protons of creatine exhibits significant CEST contrast (~1.8ppm) and myocardial tissue contains a high concentration (~15 mM) of creatine and because of this we assumed only single CEST component centered at 1.8 ppm. Here we used a nonlinear constrained fitting approach. First, the method was tested on CEST data of *ex vivo* myocardium tissue acquired over frequency range of [-15, 15] ppm. The parameters (Mean+(3SD)) of *ex vivo* data fitting were used to guide upper bound constraints for *in vivo* data fitting. The mean CEST(%) was computed for an ROI drawn on tissue only.

Constraints on Fit			**LS Fitting**			**LPC Fitting**		
	LB	UB	FitPar	CI_L	CI_H	FitPar	CI_L	CI_H
Width (ppm)	1.0	10	4.18	4.04	4.32	4.81	4.70	4.91
Amp	0.30	1.0	0.59	0.58	0.61	0.92	0.92	0.93
Center(ppm)	-1.0	1.0	-0.03	-0.08	0.03	0.05	0.02	0.07
Width (ppm)	20	200	66.1	57.7	74.5	66.40	59.7	73.0
Amp	0.001	0.50	0.26	0.25	0.27	0.25	0.25	0.26
Center (ppm)	-3	0	-0.56	-1.08	-0.03	-0.42	-0.84	0.01
Width (ppm)	1.0	10	6.24	5.00	7.47	3.98	3.36	4.60
Amp	0.001	0.50	0.10	0.07	0.12	0.24	0.20	0.28

Table-1: Comparison of LS and LPS model fitting of z-spectra of a voxel in ex vivo tissue. LB: Lower bound, UB: Upper bound, CI: 95% confidence interval in fitted parameters (FitPar).

RESULTS AND DISCUSSIONS: Both LS and LPC models fit well to *ex vivo* myocardium data (Table-1 and Fig.1). The CEST contrast computed using LS fitting was comparable to the CEST obtained using asymmetry analysis in ex vivo myocardium tissue **(Fig. 2).** CEST contrast using LPC fitting was much higher compared to asymmetry and LS. PBS in phantom showed negligible CEST contrast in all approaches. CEST component is broad and CEST contrast computation using fitting involves no asymmetry and this seems to result in CEST contrast that is immune to B_0-fluctuations of ~[-0.2, 0.2] ppm. **Fig. 3** shows the CEST maps obtained using LS and LPC for a swine myocardium with an infarct. It is evident that there is a decrease in CEST effect in myocardium infarct tissue compared to healthy tissue in both models. CEST map using LPC model seems to show overall higher CEST contrast and lower contrast between infarct and normal myocardium tissue compared to LS model. This is under investigation. In conclusion, CEST contrast computation based upon z-spectra fitting mitigates B_0 inhomogeneity artifacts, particularly due to fluctuating B_0, and enables the CEST contrast computation in *in vivo* myocardium data. Moreover, there is no need to acquire WASSR or B_0 data for field inhomogeneity correction as the center of water resonance is one of the parameter in fitting function. Further in vivo studies are in progress.

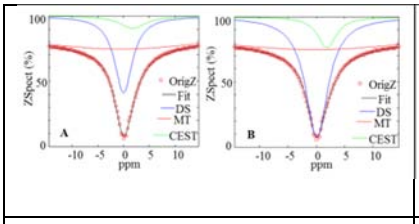

Fig.1: Fitting of z-spectra along with fitted components in a voxel in *ex vivo* tissue using LS model (A) and LPC model (B).

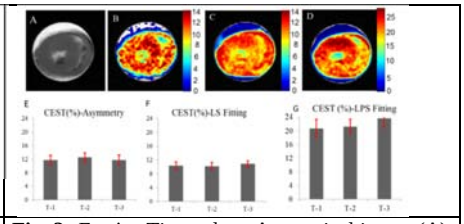

Fig. 2: *Ex vivo* Tissue data: Anatomical image (A). Color overlaid CESTasy (B) and CEST-LS(C), CEST-LPS (D) maps. (E, F, G) represents bar plots of CESTasy and CEST based upon LS and LPC model fitting in three tissues.

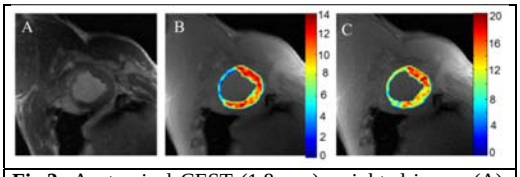

Fig.3: Anatomical CEST (1.8ppm) weighted image (A), myocardium CEST map overlaid on base image obtained using LS fitting (B) and LPC fitting (C) *in vivo* animal.

REFERENCES: [1] K.M. Ward, et al, JMR-2000. [2] J. Zhou, et al, Nat Med-2003. [3] K. Cai, et al, Nat Med-2011. [4] M. Haris, et al, ISMRM-2011. [5] M. Zaiss, et al, JMR-2011.

Acknowledgement: This project was supported by the National Institute of Biomedical Imaging and Bioengineering of the NIH through Grant Number P41-EB015893. Partial support was also provided by a grant from Translational Biomedical Imaging Center of Institute for Translational Medicine and Applied Therapeutics.