Optimizing multislice acidoCEST MRI for assessments of extracellular pH in tumor and kidney tissues.

Edward A Randtke[1], Kyle Jones[1], Christy Howison[1], Julio Cárdenas-Rodríguez[1], and Mark D Pagel[1]
[1]*Biological and Medical Imaging, University of Arizona, Tucson, Arizona, United States*

Introduction: Studies of extracellular pH (pHe) in solid tumor models can show spatial heterogeneity, necessitating multislice imaging of the entire tumor volume. Also, longitudinal studies of tumor pHe require consistent analysis of the same tumor regions, which is facilitated by multislice imaging. CEST MRI methods that use exogenous agents require fast imaging methods, which are typically limited to single-slice imaging. To address this problem, we have applied the Phase-Offset MultiPlanar (POMP) Simultaneous MultiSlice (SMS) technique (1) to acidoCEST MRI that uses an exogenous agent (2). We have optimized the performance of the method to image mouse kidneys, and we have demonstrated the application of 3D acidoCEST MRI to evaluate a solid tumor in a model of mammary carcinoma.

Methods: A MCF7 tumor model was imaged using a CEST-FISP MRI sequence with CW saturation applied at 3 μT for 2 sec; RF spoiling to suppress motion artifacts; 2.7 ms TE and a 5.8 ms TR; 0.5x0.5 mm in-plane resolution with 0.5 mm slice thickness. This pulse sequence was modified to include a 3.75° flip angle excitation pulse that consists of a sum of 4 Hermite pulses that simultaneously excites four non-contiguous slices. This pulse sequence was repeated 5 times to acquire 20 contiguous slices. Three CEST spectra were acquired prior to injection, then a 200μL bolusof 300 mg. of Iodine/mL iopamidol was administered i.v., followed by a 200μL/hr infusion of iopamidol for 54 minutes, while 3 sets of multislice CEST MR images were acquired. A fourth multislice image set was acquired after the infusion ended. We also acquired multislice image sets with 1 mm and 2 mm isotropic voxel resolution prior to and during infusion.

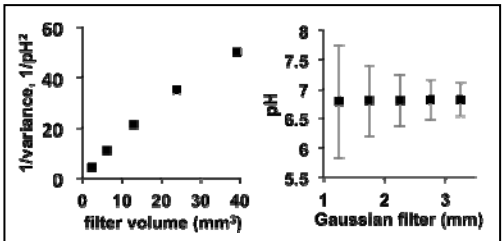

Figure 1: A) Gaussian filtering improved median precision of Bloch-McConnell fitting to CEST voxelwise spectra. B) Gaussian filtering improved median 95% confidence intervals(shown as error bars) forpH estimates.

Images were filtered with a 3D Gaussian filter prior to fitting to mitigate noise. The Bloch-McConnell equations (3) were fit to pixelwise CEST spectra generated from subtracting the average pre-injection image from the average post-injection image. The k_{ex} values of iopamidol were calibrated with pH using phantoms, so that pHe could be fit directly in our model.

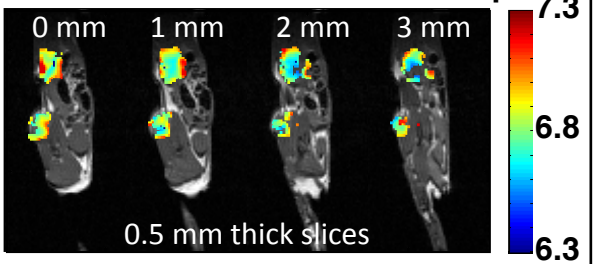

Figure 2: A pHe parametric map overlaid on RARE MR images. Only 4 of 20 slices are shown. Pixels with 95% CI > 0.5 pH units are pruned. Only pixels in the tumor and kidney were retained after this pruning.

Results: When processing kidney-imaging results, the fitting precision and precision of pH measurements scaled with the Gaussian filter size (Fig. 1). A Gaussian filter with a FWHM of 2.25 mm provided precise measurements while still retaining good spatial resolution, so that this Gaussian filter size was used for subsequent analyses.

The average tumor pHe was 7.00 pH units, with a decreasing pHe gradient from the core to the rim of the tumor in 3D (Fig. 2). The average kidney pHe was 6.83 pH units, with an increasing pHe gradient from the medulla to cortex as expected. For comparison, we observed an average pHe of 7.3 units in muscle tissue. The median 95% confidence interval (CI) for voxelwise pHe measurements was 0.43 pH units in kidney and 0.55 pH units in the tumor, which shows that the average pHe should be analyzed for the tissue or sub-tissue regions (rim vs. core, medulla vs. cortex) to offset this voxelwise variance. Also, voxels with a lower pHe had higher variance, because base-catalyzed chemical exchange of iopamidol is weaker under acidic conditions.

Discussion: These results show that 3D acidoCEST MRI is feasible; Gaussian filtering is critical for improving CEST MRI for voxelwise analysis; the pHe in tumor, kidney, and muscle tissues can be measured using Bloch-McConnell fitting of CEST spectra; although voxelwise pHe measurements have some variance, pHe analyses of tissue and sub-tissue regions have excellent precision.

1) Glover, et al., J Magn Reson Imag 1991
2) Chen, et al., Magn Reson Med 2014
3) Woessner, et al. Magn Reson Med 2005