High Acceleration 3D Compressed Sensing Hyperpolarized ^{13}C MRSI of a Transgenic Mouse Model of Liver Cancer

S. Hu[1,2], A. Balakrishnan[3], M. Lustig[4], P. E. Larson[1], R. Bok[1], J. Kurhanewicz[1,2], S. J. Nelson[1,2], J. M. Pauly[4], A. Goga[3], and D. B. Vigneron[1,2]

[1]Dept. of Radiology and Biomedical Imaging, University of California, San Francisco, CA, United States, [2]UCSF & UCB Joint Graduate Group in Bioengineering, San Francisco, CA, United States, [3]Dept. of Medicine, Division of Hematology/Oncology, University of California, San Francisco, CA, United States, [4]Dept. of Electrical Engineering, Stanford University, Stanford, CA, United States

Introduction: High polarization of nuclear spins in liquid state through hyperpolarized technology utilizing DNP has enabled the direct monitoring of ^{13}C metabolites *in vivo* at very high SNR [1]. Acquisition time limitations due to T1 decay of the hyperpolarized signal make accelerated imaging methods, such as compressed sensing, very attractive. Previously, we developed a 2-dimensional compressed sensing scheme to achieve 2-fold acceleration to obtain 2 times better spatial resolution without increasing scan time [2-3]. In this project, we developed new techniques and applications. We developed a x3.37 accelerated sequence to achieve 4 times better resolution in approximately the same scan time and acquired hyperpolarized spectra from a transgenic mouse model of liver cancer for the first time, observing elevated lactate and alanine in tumors in preliminary data. Subsequently, we extended our methodology further to achieve a x7.53 accelerated sequence, which we used in prostate cancer mouse studies to achieve a factor-of-4 resolution enhancement in approximately half the acquisition time. In addition, we validated the accelerated designs through simulations and phantom experiments.

Liver Cancer Model: We used Tet-o-MYC/LAP-tTA double transgenic mice [4-5] as our liver cancer animal model. Prominent features of this model are: 1) MYC human proto-oncogene overexpression only in the liver 2) on/off tumor regulation with doxycycline and 3) similarities to human disease, e.g. growth of tumors in nodules. We developed compressed sensing hyperpolarized ^{13}C MRSI with liver cancer in mind because high resolution and coverage are needed to isolate liver tumor nodules, which can be small compared to the FOV of the whole liver. The same holds true for eventual human studies where high coverage with good resolution is needed in the time of one breath-hold.

Pulse Sequence Design: Our new accelerated pulse sequences extend our previous designs [2-3] by employing both x and y gradient blips to achieve random undersampling in the spectral dimension and two spatial dimensions. The blips for the x3.37 design have an area of one phase encode step, allowing for random undersampling of 2x2 k_x-k_y blocks in the time of one phase encode (x3.37 acceleration achieved by acquiring a 16x16 matrix with 16 fully sampled central encodes and 60 encodes with x4 undersampling). In the x7.53 design, the blips range in area from one to three phase encode steps (Figure 1), allowing for random undersampling of 4x4 k_x-k_y blocks in the time of one phase encode. x7.53 acceleration was achieved by acquiring a 16x16 matrix in the time of 34 phase encodes (16 central encodes that were fully sampled, 6 encodes that randomly undersampled 8 k-space lines, and 12 encodes that randomly undersampled 16 k-space lines).

Methods: All experiments were performed on a General Electric EXCITE 3T (Waukesha, WI) MR scanner equipped with 40 mT/m, 150 mT/m/ms gradients and a broadband RF amplifier. For studies using a spherical ^{13}C phantom, the acquisition parameters were: 10 degree flip angle, TE = 140 ms, TR = 2 s, FOV = 8x8 cm, and 16x16 spatial resolution. The mouse experiment acquisition parameters were: variable flip angle, centric phase encoding order, TE = 140 ms, TR = 215 ms, and FOV = 4x4 cm. For the liver cancer mice, we used the x3.37 sequence, collecting 76 encodes from a 16x16 matrix. For the phantom and prostate cancer mice [6], we used the x7.53 sequence, collecting 34 encodes from a 16x16 matrix. The simulation validation used data created by thresholding the peaks from a phantom acquisition (to remove noise) and giving them Lorentzian lineshapes modeled with a T2* of 50 ms. For the *in vivo* experiments, we achieved ~20% liquid state polarization of [1-^{13}C]pyruvate (with 0.5 mM gadolinium) using a DNP polarizer. We injected ~350μL (~80 mM) over 12 seconds followed by a saline flush, with acquisitions starting 30 and 35 seconds from the time of injection for liver cancer mice and prostate cancer mice respectively. Custom built, dual-tuned ^{1}H/^{13}C transmit/receive coils were used for all phantom and animal experiments. The compressed sensing reconstruction software has been described previously [2-3,7]. We used the following reconstruction parameters: TV penalty = 0.0001, sparsifying transform (1D length-4 Daubechies wavelet transform along spectral dimension) weight = 0.0005.

Results: We collected x3.37 accelerated 3D-MRSI data from several control and MYC mice. Figure 2 shows representative data from slices through normal and cancerous liver. The normal slice in Figure 2 contains the right lobe of the liver (right side of anatomical image), and the cancer slice contains a large tumor. We observed dramatically elevated lactate/pyruvate and alanine/pyruvate ratios for the liver cancer mice. (Note: ratios were derived from integrated magnitude peak areas averaged over all normal liver voxels in the normal mice and all tumor voxels in the cancer mice.) For the MYC mouse shown in Figure 2, lac/pyr was 2.27, and ala/pyr was 1.27. The elevated alanine in the MYC mice is significant in that it is the first report of hyperpolarized alanine as a biomarker of disease. Figure 3 shows simulation and phantom validation of the more highly accelerated x7.53 accelerated sequence (similar results applying to the x3.37 sequence). The simulations show that, as expected, the x7.53 undersampled compressed sensing reconstructed data set matched the fully sampled data set extremely well. The error in the magnitude reconstruction was uniformly ~1/50 of the original signal throughout all the slices. The phantom experiments also showed excellent agreement between the accelerated and normal acquisitions. Finally, the *in vivo* data in Figure 3, which show a factor-of-4 resolution enhancement in approximately half the acquisition time, demonstrated good spectral quality and the preservation of small peaks.

Discussion: The compressed sensing methods developed in this project provided dramatic acceleration factors over prior hyperpolarized C-13 echo-planar MRSI studies. In the examples shown with the x3.37 and x7.53 sequences, the acceleration was used to enhance resolution and/or decrease acquisition time, but for human liver, which is much larger, it could be used to increase spatial coverage. In summary, this study demonstrates that compressed sensing methods can provide 7+ accelerated high-resolution hyperpolarized ^{13}C spectroscopic imaging, which greatly benefits the acquisition of high resolution metabolic images of preclinical cancer models and ultimately future human studies.

References: [1] Ardenkjaer-Larsen et al., Proc Natl Acad Sci USA 2003;100:10158-10163 [2] Hu et al., JMR 2008;192:258-264 [3] Hu et al., ISMRM 2008 #195 [4] Shachaf et al., Nature 2004;431:1112-1117 [5] Goga et al., Nature Med 2007;13:820-827 [6] Chen et al., MRM 2007;58:1099-1106 [7] Lustig et al., MRM 2007;58:1182-1195

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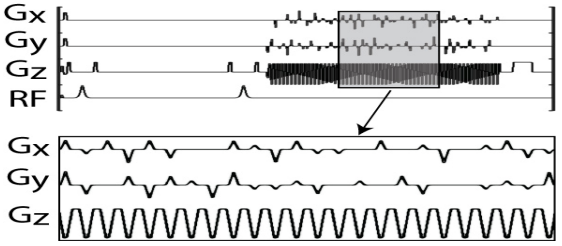

Figure 1: *Blipped compressed sensing pulse sequence where blip areas range from 1 to 3 phase encode steps, allowing for jumps between 4x4 adjacent k-space lines. The sequence used for the liver cancer mice was a similar design in which blips had an area of one phase encode increment, allowing for jumps between 2x2 adjacent k-space lines.*

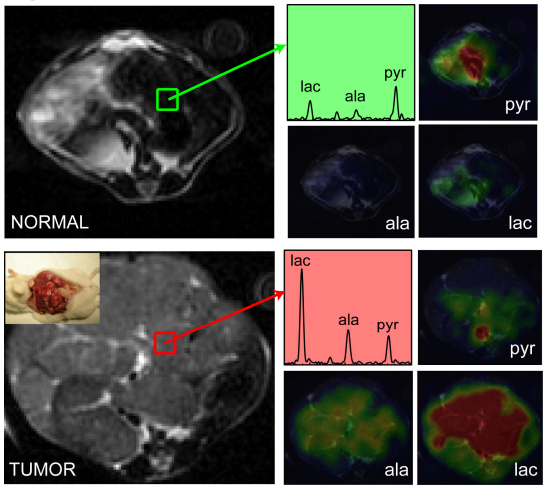

Figure 2: *Representative hyperpolarized spectroscopic data from normal and liver cancer mice. Individual spectra as well as metabolite color overlays are shown.*

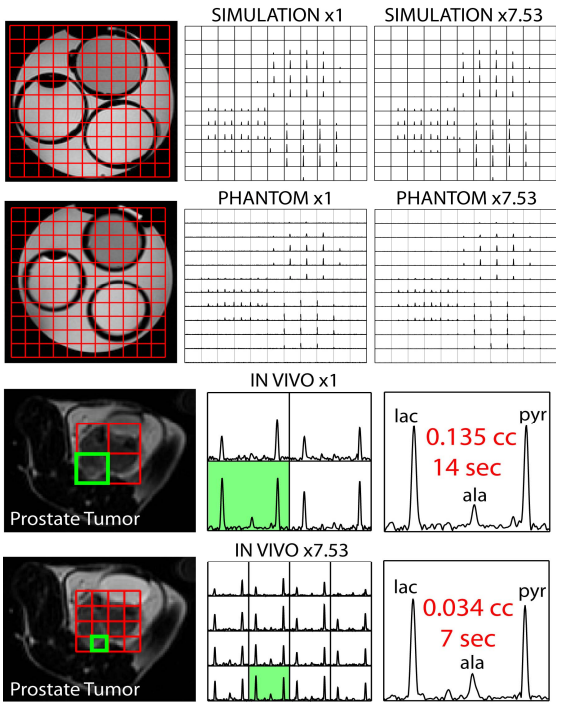

Figure 3: *Slices from simulation/phantom validation of the x7.53 sequence and an in vivo example from a prostate cancer mouse. The simulated and phantom grids show the central portions from the full 16x16.*