

Multi-band Frequency Encoding Method for Metabolic Imaging with Hyperpolarized [1-¹³C]Pyruvate

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Introduction- Hyperpolarized ¹³C MRI requires rapid sampling of spatial and chemical shift information. Prior approaches include MRSI methods such as CSI (1), EPSI (2), and spiral CSI (3), as well as "imaging" approaches like multi-echo methods (4), and interleaved frequency-specific excitation (5). We have developed a fast new "imaging"-type approach that leverages the large chemical shifts between hyperpolarized ¹³C resonances for multi-band frequency encoding (FE) of a single echo for both localization and spectral separation, allowing metabolic imaging with comparable or faster speeds than prior fast MRSI approaches, while avoiding the complexity of fast MRSI acquisition schemes involving rapidly switching gradients and/or non-Cartesian k-space trajectories, and their associated reconstruction steps, without sacrificing readout efficiency. This new imaging technique was tested in phantoms and then through *in vivo* investigations to image hyperpolarized [1-¹³C]pyruvate and its metabolic products in normal and transgenic murine models of prostate cancer.

Theory- In spectroscopic imaging, spin frequency ω is modulated by a gradient (i.e.

along \hat{x}) and chemical shift: $\omega_i(x,t) = \gamma(\delta_i B_0 + G(t) \cdot x)$, where γ is the gyromagnetic ratio, δ_i is the chemical shift of species *i*, B_0 is main magnetic field strength, G is gradient strength and x is spin position. In this technique (Fig. 1, top), the readout gradient amplitude is set so that the minimum chemical shift separation among species exceeds the gradient field difference across the FOV, whereby unique modulation occurs for all species at all locations. Following Fourier transformation, metabolite images appear side-by-side in separate bands (Fig. 1, bottom). The images are shifted to their proper locations based on known chemical shift differences. While G is usually maximized in order to minimize distortion (also, to maximize speed), in this method it is typically much lower than maximum. However, the readout filter is set wider than the conventional imaging setting-- minimum value = $(\delta_{\max} - \delta_{\min} + \Delta\delta_{\min})\gamma B_0$. The maximum FE bandwidth per pixel is $\gamma\Delta\delta_{\min}B_0/N$ (N = # of pixels), also equal to the inverse of the minimum full readout time, determining the minimum TE and TR (and scan time). B_0 misregistration (i.e. in mm per ppm offset) scales with $FOV/\Delta\delta_{\min}B_0$. Applicability to ¹H imaging would be limited by low bandwidth. For example, in ¹H MRSI of the brain, choline and creatine are separated by just 0.2 ppm, while ¹³C-pyruvate and alanine are separated by 5.7 ppm. Therefore, misregistration is ~28x smaller for ¹³C vs. ¹H in this comparison (e.g. for a 2.4-cm FOV, misregistration due to 0.5 ppm inhomogeneity, a typical maximum value, is 60 mm for ¹H vs. just 2.1 mm for ¹³C), and imaging is also ~7x faster. Linewidth blurring should be minimal for most ¹³C compounds of interest, vs ¹H fat.

Methods- Pyruvate metabolism was imaged in one normal mouse and two transgenic mice with prostate cancer (transgenic adenocarcinoma of the mouse prostate, or TRAMP) (6), in a 3T GE clinical scanner with a quadrature T/R dual-tuned ¹H/¹³C RF coil. Each sample (24 μ L) of 99% [1-¹³C]pyruvate mixed with trityl radical OX063 (GE Healthcare, Oslo, Norway) was loaded into the 3.35T magnet of the HyperSense polarizer, where it was cooled to 1.3 K and irradiated for ~1 hr, and then rapidly dissolved in a heated solution of 4.6 mL TRIS/NaOH buffer, resulting in a ~80 mM solution of pH ~7.5. Mice were injected with a 350 μ L bolus over 12 sec, followed by a 150 μ L saline flush. Eight axial slices (prostate→liver) were acquired @ 35 sec post-injection, with a multi-slice spoiled gradient echo acquisition. *In vivo* chemical shifts were determined from previously acquired MRS data. Nominal spatial resolution was 3mm in-plane by 5mm slice (0.045 cm³). The other parameters were: TE/TR= 26ms/58ms, $\tau_{\text{read}}= 44$ ms with $G_{\text{read}}= 0.072$ G/cm, readout bandwidth= 0.74 kHz, FOV= 2.4 cm (AP, frequency) x 4.8 cm, acquisition matrix= 32 x 16, scan time= 7.4 sec. Flip angle was increased over phase encoding steps by $\theta(n) = \arctan(\sin(\theta(n+1)))$, with last pulse 90° (7). Transmit gain was calibrated with an enriched [¹³C]lactate syringe. The RF pulse bandwidth for the animal experiments was 1250 Hz (centered on pyruvate), resulting in shifted transmit profiles for alanine (~0.7mm) and lactate (~1.6mm), corrected in post-processing. Contamination from pyruvate hydrate was reduced by estimation of a minimum hydrate signal (5% x pyruvate, based on previous MRS studies), and subtraction from the appropriate locations in the alanine and lactate bands. Interpolated color images were overlaid onto T₂-weighted ¹H FSE images.

Results- Shifting metabolite sub-images according to their previously measured *in vivo* chemical shifts resulted in good registration of all images. For each metabolite, exactly the same shift was applied across all slices in all data sets. Both transgenic prostate cancer mice had T2-weighted signal changes in the anatomic region just surrounding and superior to the urethra, which is the site of early tumor development in the TRAMP model. The mean tumor lactate-to-pyruvate ratios in both mice, 1.32 for one mouse with a large periurethral gross tumor ($d_{\max}= 1.5$ cm), and 0.64 for the other mouse with a smaller tumor region ($d_{\max}= 1.0$ cm), were elevated over the prostatic region of the normal mouse (0.49).

Discussion- Applicability of identical shifts to all data was expected due to the fact that very consistent chemical shifts have been observed in prior *in vivo* MRSI studies. If misregistration were increased in a different application or experimental conditions of poor shim, misregistration could also be corrected based on a B_0 map. Performance (i.e. in terms of resolution, speed, and misregistration) is increased by larger minimum chemical shift separation. Imaging of pH using hyperpolarized [¹³C]bicarbonate could also benefit (36 ppm separation) (8). Similarly for pyruvate, if only pyruvate and lactate measurements were needed, more advanced RF methods such as multi-band excitation of pyruvate and lactate alone (9) could be utilized to localize just these components, for improved performance.

Ref. - 1. Golman et al. *PNAS*. 2003. 2. Cunningham et al. *JMR*. 2007. 3. Mayer et al. *JMR*. 2010. 4. Leupold et al. *MAGMA*. 2009. 5. Lau et al. *MRM*. 2010. 6. Greenberg NM et al. *PNAS*. 1995. 7. Zhao et al. *JMRB*. 1996. 8. Gallagher et al. *Nature*. 2008. 9. Larson et al. *JMR*. 2008.

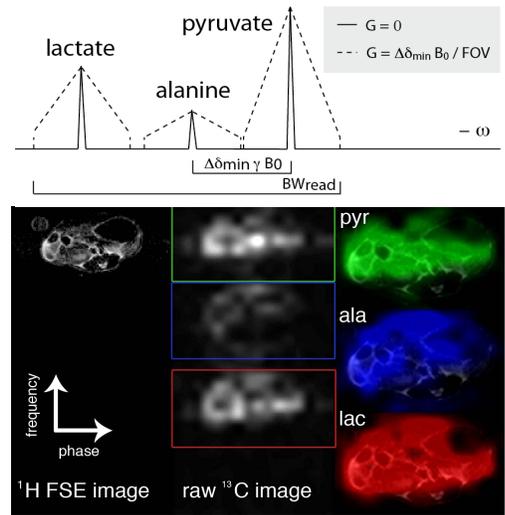


Figure 1 – Formation of metabolite images by multi-band frequency encoding method.

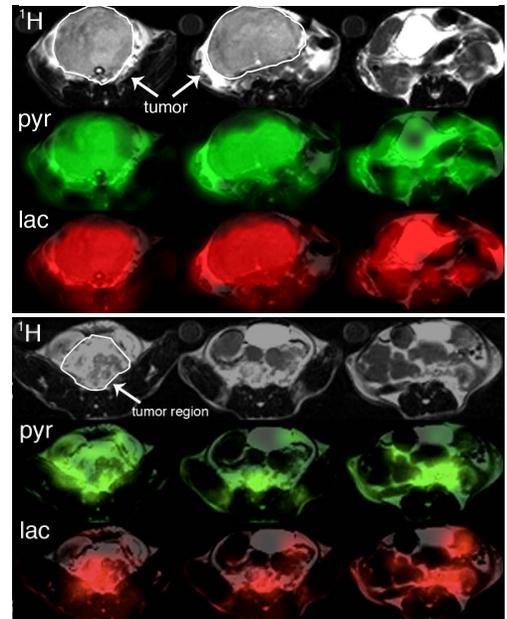


Figure 2- Metabolite distributions in TRAMP mice imaged using multi-band FE