Investigating spatial variances in MR using molecular information from MALDI imaging mass spectrometry

T. K. Sinha[1], Z. Yang[2], W. M. Hardesty[3], and J. C. Gore[4]

[1]Radiology and Radiological Sciences, Vanderbilt University, Nashville, Tennessee, United States, [2]Chemical and Physical Biology, Vanderbilt University, Nashville, Tennessee, United States, [3]Biochemistry, Vanderbilt University, Nashville, Tennessee, United States, [4]Institute of Imaging Science, Vanderbilt University, Nashville, Tennessee, United States

Introduction.

MR relaxation phenomena are determined by a variety of factors reflecting tissue composition and structure. There is considerable potential value in understanding how specific factors within tissue influence the observed MR signal. In an accompanying abstract, we show how, at high spatial resolution, we can resolve spatial fluctuations in tissue NMR properties that contribute to the variance within a single tissue but which do not average out when integrating multiple acquisitions. The MR signal for a single tissue is then given as:

$$S_i = S + \Delta_p + \Delta_{acq} \quad (1)$$

where, S_i is the signal intensity at a voxel, S is the mean signal intensity for a type of tissue, Δ_p is the spatial variance of the signal intensity for a given tissue, and Δ_{acq} represents additive noise. The incorporation of the tissue specific spatial variance (i.e. microscopic variations in tissue composition) accounts for the observed behavior of apparent SNR as a function of number of acquisitions.

We here describe an extension of these investigations to evaluate the relationship of spatially varying tissue NMR properties to underlying variations in tissue protein content by incorporating matrix assisted laser desorption/ionization imaging mass spectrometry (MALDI IMS) to probe the molecular spatial variance. We have reported our development of a method to accurately co-register MALDI IMS images and MR data, and have demonstrated that the molecular distributions observed via MALDI IMS correlate well with corresponding quantitative measures observed via MR [1]. Here we investigate the correspondence of the spatial variance of the MR signal within tissue to the spatial variance of its proteomic profile. We hypothesize that the two measures will be spatially correlated, and will therefore allow us to investigate the degree to which MR relaxation is affected by specific variations in molecular composition.

Methods.

The spatial variances of MR and MALDI IMS measurements were examined in fresh tissues from normal animals (C57BL/6). In a first study, liver was excised and submerged in a 10 mm Eppendorf centrifuge tube. M_0, T_1, and T_2 measures were calculated from nine T_{2w} images acquired via a spin echo sequence (TR = {4000, 1000, 620} msec, TE = {46, 33, 20} msec, matrix 256x128x9, FOV 25.6x9.8x0.5 mm, NEX=10) by non-linearly fitting to the following expression:

$$S = M_0(1-e^{(-T_R/T_1)})(e^{(-T_E/T_2)}). \quad (2)$$

The sample was then frozen and sectioned for MALDI IMS acquisition using preparation techniques described in [1] and collected on a Bruker Autoflex imaging mass spectrometer. The resulting MALDI image was 28x58 with 200 micron in-plane resolution.

Results and Discussion

Figure 1 shows the spatial variations of protein contents and T1 measurements in the same piece of tissue. The MALDI map was generated by integrating the total ion current at each position, yielding a measure of total molecular content at that location. The mass spectrum shown in the image was generated by averaging the spectra at all pixel, and demonstrates the variety of molecular information acquired by MALDI IMS. The T_1 map has been scaled by the measured total water content, M_0, and demonstrates similar spatial variance. From a simple two-component fast exchange model of relaxation, we expect:

$$R_1 = \alpha R_{1b} + (1-\alpha)R_{1f}, \quad (3)$$

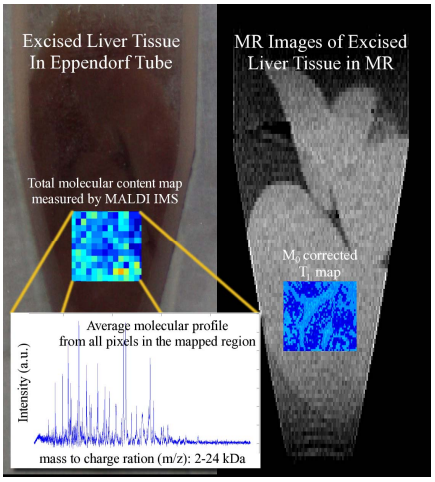
where R_1 is $1/T_1$, R_{1b} and R_{1f} describe 'bound" (or rapidly relaxing protons associated with macromolecules) and "free" water R_1 values respectively, and α is the "bound" water fraction. In addition, we assume:

$$\alpha = h*m_p / (h*m_p + M_0), \quad (4)$$

where h is a proportionality constant describing the hydration of macromolecules, m_p is the total mass of hydrated proteins, and M_0 is the mass of free water. With realistic assumptions, expression (3) can be reduced to:

$$R_1 - R_{1f} = k\,(m_p/M_0), \quad (5)$$

where k is a proportionality constant. This expression was used to compute the distribution of relaxation rates corrected for variations in water content.



The methods described in [1] can be used to accurately co-register these data to analyze correlations in their spatial variances. Figure 1 shows that there are significant variations in both protein signatures and NMR parameters that can be measured at similar spatial resolutions.

Conclusion

We demonstrate a novel method to explore the influence of the proteomic content in tissue on observed MR relaxation rates. We hypothesize that these investigations will yield a more complete and accurate understanding of how the spatial heterogeneity of tissue composition contribute to measurements made by MR imaging.

Acknowledgements: NIH-NIBIB R01-EB000214, R01-CA109106, T32-ED001628

References

[1] Sinha, T.K., et al. 3D MALDI imaging mass spectrometry integration with *in vivo* MRI. Nature: Methods. *In Press.*