Registration of MALDI mass spectrometry images and MR parametric maps for relaxomic analysis

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Introduction

There is considerable potential value in being able to correlate tissue relaxation properties obtained via quantitative MRI and the protein composition of tissue obtained via imaging mass spectrometry. We have termed the analysis of MR relaxation parameters and corresponding tissue proteomic information as "relaxomics". In principle, constituent macromolecule distribution of a given molecular weight can be obtained for each and every voxel within a slice of tissue via imaging matrix-assisted laser desorption/ionization mass spectrometry (MALDI-MS) at a spatial resolution comparable to that of high resolution MR images. In order to correlate and interpret such information, the data sets from each of these imaging modalities must be accurately aligned, or coregistered. We describe here the sample preparation techniques and computer algorithms developed to achieve accurate coregistrations. We demonstrate the application of these methods for the co-registration of MALDI-MS images of myelin base protein to MR images of the same section and provide preliminary measures of our registration accuracy.

Methods

The data used in this paper are from a single mouse brain. The mouse head was imaged using a 9.4T MRI system (Varian, Inc). The MR data acquired in this study included a 3D gradient-echo T1-weighted image (256x256x256, TR=25msec, TE=2.3msec, α=15˚, with an isotropic voxel resolution of 100x100x100µm), T1 parametric maps generated from multiple flip-angle gradient-echo multi-slice images (256x256x19, with a voxel resolution of 100x100x1000µm), and T2 maps generated from mutltiecho spin-echo images (256x256x19, with a voxel resolution of 100x100x1000µm). After MR data acquisition, the mouse was sacrificed, ex-sanguinated (with saline perfusion), decaptitated, and immediately frozen. The frozen head was incrementally sectioned into 20µm thick slices using a cryomacrocut (Leica, Inc.). For alternating slices, the exposed face of the ice-block was photographed using a high-resolution digital camera that was rigidly attached to the macrotome. The resulting images were concatenated to form a digital image volume of the mouse head; we term this volume the blockface image volume. To correct for variations in the position of the ice-block relative to the digital camera, a mutual information-based registration algorithm [1] was used between subsequent section images to align the tissue structures properly. The resulting blockface image volume of the mouse brain was (700x700x482, with a voxel resolution of 31x31x40µm).

Brain tissue sections of interest were collected during the sectioning process and mounted to plates for MALDI data acquisition. In this study, we limited MALDI acquisition to a single slice containing a portion of the corpus callosum and, therefore, a strong myelin signature in the MS image. Imaging mass spectrometry was carried out using an Ultraflex II MALDI/TOF system (Bruker, Inc.). An array of matrix spots, 200µm diameter, were deposited in a 43x38 array to completely cover the brain region and a mass spectrum was recorded from each spot. The spectra were condensed to an integrated scalar value of the signal intensities between 14243-14538 daltons, corresponding to the myelin base protein, which produced a 200x200µm ion image highlighting the distribution of myelin in the section of the mouse brain.

The process of registering the MALDI-MS ion image to the MR parametric images used sequential transformations through a number of intermediate spaces. The most significant imaging spaces in the registration process were the MS image space, blockface image space, and MR image space. Rigid-body registrations were used to traverse from the MS image space, through the blockface image space, into the MR images. The concatenated transformation provided a continuous mapping of any location in the MS image to its corresponding location in any MR parametric space. A fiducial registration method was used to transform MS image locations into their corresponding positions in the blockface image volume. The blockface image volume was then rigidly registered to the 3D anatomic MR image using a 6 degrees-of-freedom (translation and orientation) transformation computed with a mutual information registration algorithm. Since the parametric MR images were acquired during the same imaging session as the anatomic image volume, they were inherently registered to the anatomic images. Therefore, the concatenation of the fiducial registration from MS image space to blockface image volume space, and the rigid-body registration of blockface image volume space to MR space, provided the complete transformation from MS image space to MR parametric image space.

Results

Registration accuracies for each registration process were calculated as RMS distance measurements between corresponding fiducials or targets after registration. The target registration error in reconstructing the blockface volume was determined using two external target landmarks that were rigidly attached to the iceblock, and therefore should overlap perfectly after blockface reconstruction. The RMS target registration error for the blockface reconstruction was calculated to be 60.77µm. Fiducial registration error of the transformation between MS image and corresponding blockface volume slice was found to be 26.26µm using 3 fiducials. Finally, the accuracy of the rigid-body registration between MR image space and blockface volume space was determined by manually localizing corresponding structures in each modality. The RMS target registration error of 5 manually localized targets was 382.6µm.

Qualitative evidence of registration performance is visualized in Figures 1 and 2. Figure 1 demonstrates the effectiveness of the reconstruction registration. Features in the concatenated volume, prior to reconstruction, are not well resolved. However, after inter-slice registration, features in the orthogonal view planes are well-resolved and details of the mouse's anatomy are clearly visible. Figure 2 shows the result of the registration of MALDI MS image space to both blockface image volume space and MR image space. Myelin signatures from the MS image are color encoded to grayscale; the more white the pixel the larger the myelin signature in the underlying tissue.

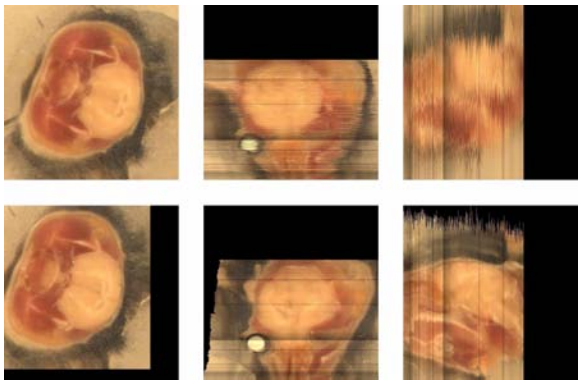

Figure 1: The top row shows orthogonal views of the raw blockface image volume, the bottow row shows the reconstructed volume using inter-slice registration. From left to right, the slice planes are: axial, coronal, sagittal.

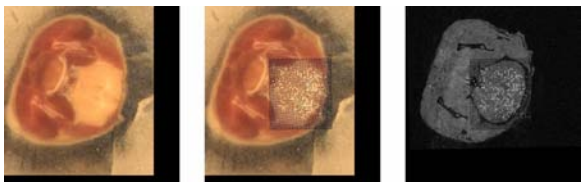

Figure 2: From left to right: tissue section image, MALDI MS image registered to section image, MALDI MS image registered to corresponding MR anatomic image. High myelin levels are shown as brighter pixels in the overlay images.

Conclusion

We demonstrate a complete method to align MR parametric information with tissue proteomic information as determined by MALDI mass spectrometry. Quantitative relaxomic analysis of various proteins is currently underway using the methods described in this abstract.

References

1. Maes, F., et al. Multimodality image registration by maximization of mutual information. IEEE: Trans. on. Med. Img. 1997; 16(2): 187-198.