3D Co-Registration of MRI and Histology in a Mouse Model of Obesity and Non-Alcoholic Fatty Liver Disease

Eli Gibson[1,2], Lanette J Friesen-Waldner[2,3], Amanda M Hamilton[2], Emeline J Ribot[2], Trevor P Wade[2,3], Curtis N Wiens[4], Kundan Thind[2,3], Jacqueline K Harris[3], Nica M Borradaile[5], Charles A McKenzie[1,3], and Aaron D Ward[1,2]

[1]*Biomedical Engineering, University of Western Ontario, London, Ontario, Canada,* [2]*Robarts Research Institute, London, Ontario, Canada,* [3]*Medical Biophysics, University of Western Ontario, London, Ontario, Canada,* [4]*Physics and Astronomy, University of Western Ontario, London, Ontario, Canada,* [5]*Physiology and Pharmacology, University of Western Ontario, London, Ontario, Canada*

Target Audience: Investigators interested in validation of imaging in murine models via registration to histology.

Purpose: The rising incidence of obesity and metabolic syndrome has led to an emerging epidemic of liver diseases. Non-invasive quantification of the distribution of liver fat may support the diagnosis and monitoring of non-alcoholic fatty liver disease, the primary manifestation of metabolic syndrome in the liver. Validation of quantitative MRI for this purpose ideally uses accurate registration to an accepted reference standard, such as histology. Our purpose is to demonstrate the feasibility of accurate co-registration of in vivo 3D whole body water-only and fat-only images of mice to stained histological liver images.

Methods: Three 129/SVJ mice were fed a high fat diet (40% of calories from fat) for 3 months [1] to induce hepatic steatosis and obesity (protocol approved by the institution's Animal Use Subcommittee). *MRI*: Mice were anesthetised using isoflurane and placed in a custom-built ^{1}H bird cage coil in a 3T MRI (Discovery MR750, GE Healthcare, Waukesha, USA). MR images were acquired using 3D quantitative IDEAL with 0.5mm isotropic resolution [2]. *Whole Body 3D Colour Imaging:* Immediately following MRI, mice were euthanized and flash frozen in an embedding compound using liquid nitrogen. They were serially sectioned on an automated cryomicrotome (BioInVision, Cleveland, USA), during which high-resolution (17x17x40µm) block face, 3D optical images were acquired. *Stained Sections:* With a tape transfer system (Section-lab Co., Yokohama, Japan), three 20 µm-thick whole-mount histology sections were collected during the sectioning of one mouse. H&E-stained sections were digitized (0.5µm/pixel) on a TISSUEScope scanner (Huron Technologies, Waterloo, Canada). *Registration:* The 3 histology sections were interactively registered to the corresponding planes of the 3D optical image using a 2D thin-plate spline (TPS) transformation. The 3D optical images were interactively registered to fat and water MRI using a 3D TPS transformation. The target registration errors (TRE) were quantified (by cross-validation) as the post-registration Euclidean distances (2D TRE for the histology-optical image registration and 3D TRE for the optical-MRI registration) between homologous liver landmarks (e.g. vessel cross-sections and bifurcations).

Results: Fig. 1 shows a MR-histology co-registration, with only one of the three histology slices shown for visual clarity. The mouse was non-rigidly distorted between MR imaging and acquisition of histology sections; thus, each histology image corresponds to a curved surface in the MR image space (Fig. 1a). To illustrate the MR-histology correspondence, an oblique MR plane manually fit to this curved surface is shown without (Fig. 1b) and with (Fig. 1c) histology overlaid. The mean TRE were 0.1 mm (histology-optical registration; 57 landmark pairs), and 0.7 mm (optical-MR registration; 19 landmark pairs). Fig. 1, row 2 shows a tissue sub-region (rectangles in Fig. 1b-c) chosen for heterogeneity of histological appearance. Two corresponding regions are denoted on the MR fat (Fig. 1d) and histology (Fig. 1e) images. Full resolution histology images (Fig. 1f-g) show that the 'fat+' region has more fat globules than the 'fat-' region; these appear to correspond to high and low signal intensity in the MR fat images.

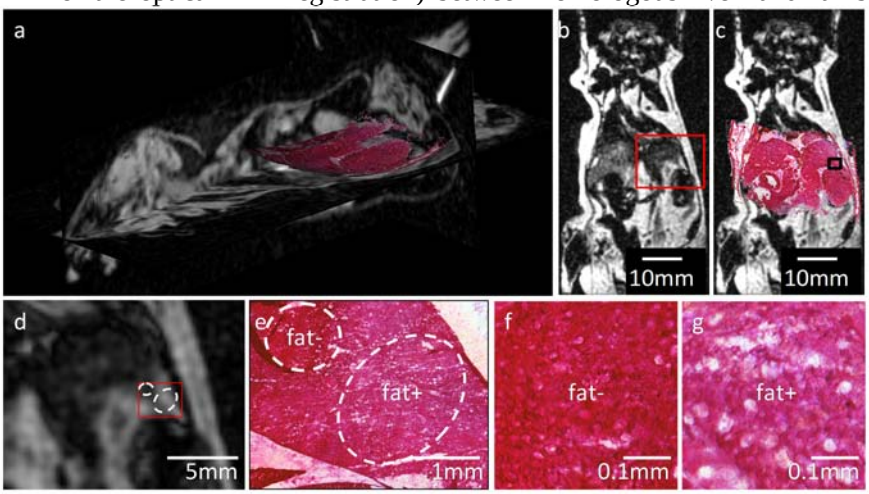

Figure 1: (a) 3D view of transformed histology within a 3-plane view of the water MRI. (b) Oblique planar slice from fat MRI manually fit to histology with box indicating liver region shown in d. (c) Image in b with histology overlaid; box indicates region with histological differences shown in e. (d) Part of the liver region from fat MRI; box indicates corresponding co-registered histology region shown in e. (e) Liver region with histological differences; 'fat+' and 'fat-' denote regions with more and fewer fat globules. (f,g) Samples from 'fat-' and 'fat+' regions, respectively, at full magnification (0.5µm/pixel).

Conclusions: This study has successfully co-registered MR images to volumetric optical images with mean TRE of 0.7 mm, and co-registered histology to volumetric optical images with mean TRE of 0.1 mm.

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References: [1] Syn *et al.* Liver Int 2009;29(8):1262. [2] Hines *et al.* Magn Reson Med 2010;254(1):119-128.