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Multimodal registration of high-resolution histology and ultra-high field MRI using BigBrain2 pipeline in the rat brain

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Introduction: Accurate co-registration of high-resolution histology data to multimodal MRI provides complementary benefits for validation of imaging biomarkers from healthy brain and its alterations. While BigBrain [1] and Julich-Brain atlas [2] provide multi-level probability maps for cell distribution and morphology, BigMac [3] extends these efforts to co-registration of multi-contrast microscopy to 7-T MRI. In this work, we report the development of a customized pipeline of BigBrain2 [4], applied to a rat model of traumatic brain injury (TBI), for co-registration of high-resolution, multiple contrast microscopy cut from coronal or horizontal sectional planes to the anatomical and diffusion MRI at various resolutions.

Methods: Our semi-automated pipeline for histology-MRI co-registration and volumetric reconstruction includes (a) automated, section-to-section alignment at cellular resolution; (b) affine registration to ex vivo structural and diffusion-weighted MRI maps; (c) iterated 2D and 3D linear and nonlinear transformations between stacked histology and reference MRI to account for translation, rotation, scaling, and shearing; and (d) optical balancing of the reconstructed histology volumes.

We tested this pipeline on the left hemisphere of four rats –one each of naïve, sham-operated, mild TBI (mTBI), and moderate TBI (moTBI) animals - from a larger dataset introduced in Table 1. Details of surgical procedures, lateral fluid percussion, and tissue processing are presented in [5]. We used the 11.7-T ex vivo MRI with T1-w and T2-w sequences (70-100 µm isotropic) and orientationally averaged diffusion image (150-µm isotropic) as the reference volume. We processed the Nissl- and myelin-stained sections to assess the cyto- and myeloarchitectonics. The stained sections were scanned at 136.9 nm/pixel in-plane, quality controlled, and downsampled to 10.95 µm. Histology photomicrographs and MRI images were masked, and the MRI volumes were re-oriented along the stacking axis of the corresponding histological object.

Results: Our customized pipeline was successful in volumetric reconstruction of Nissl- and myelin-stained histology at 10.95 µm in-plane resolution from anatomical and diffusion reference 11.7-T MRI volumes in both coronal and horizontal cutting planes. We ran experiments with section-to-section co-registration at anatomical extremes to evaluate the orientation of misaligned and broken histological pieces. Optical intensity balancing was also able to resolve staining imbalances.

Conclusions: The developed pipeline has the potential for facilitating multimodal data integration in preclinical and clinical studies. The ongoing work includes extracting anatomical landmarks from MRI and histological blocks for quantitative evaluation of linear and nonlinear transformations and section-to-section registrations.

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[4] Lepage C et al. 3D reconstruction of BigBrain2: Progress report on semi-automated repairs of histological sections. 8th BigBrain Workshop 2024.

[5] Molina IS et al. In vivo diffusion tensor imaging in acute and subacute phases of mild traumatic brain injury in rats. Eneuro. 2020 May 1;7(3).

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