Integrated Environment for High-Throughput MR Histology of the Developing Mouse

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Introduction

The growing interest in phenotyping genetically engineered mouse models calls for rapid screening methods. The non-destructive and multi-contrast aspects of magnetic resonance microscopy (MRM) make this modality an excellent candidate for this task. Strategies to increase the signal-to-noise-ratio (SNR) in specimens as small as 2 mm to 20 mm, and increase the resolution, without considerably increasing scan times need to be developed and routinely applicable. We report here methods to solve these problems with an integrated environment for high throughput studies. We have developed a standard MR atlas of the mouse embryo/fetus for those using this high-throughput environment, with selected sections labeled in all three planes, readily accessible to the public through the Mouse Biomedical Informatics Research Network (MBIRN) [1].

Methods

Embryonic day (E) 10.5 through 19.5 mice were collected and immersion-fixed in a mixture of fixative (Bouin's) and an MR stain (gadolinium chelate Gadoteridol, ProHance). The concentration was fixed (Bouin's:ProHance 20:1, v:v) and the duration of immersion varied as a function of embryo size (5 min–24 h). After imaging, the specimens were stored in a mixture of PBS and ProHance (200:1) to stabilize the staining [2]. Three-dimensional images were acquired at 9.4 T (400 MHz), with an isotropic resolution of 19.5 microns, in a scan time of 3 h 11 min. Partial Fourier acquisition was used in combination with segmented Fourier acquisition to extend dynamic range. Anatomical structures of E14.5-E18.5 were labeled in coronal, sagittal, and axial planes. MBAT (Mouse Brain Atlas Tool, MBIRN software) was used to display the labeled volumes in an interactive way and to allow multimodal data viewing.

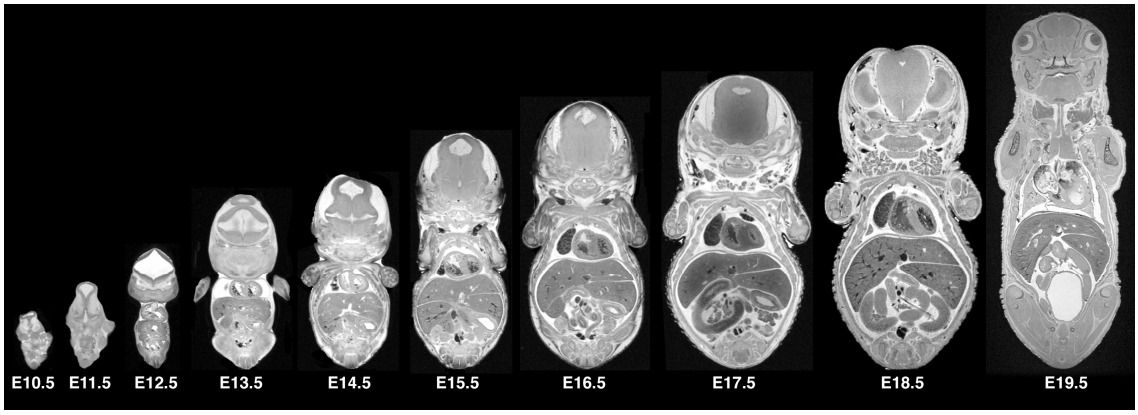

Figure 1: Representative mid-coronal slices of E10.5-E19.5 mice

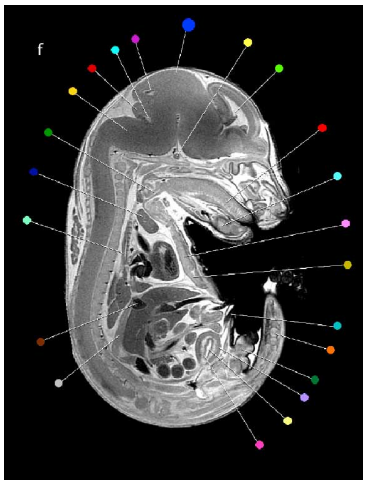

Figure 2: Example of a labeled mid-sagittal slice on MBAT

- roof of midbrain
- right lateral border of anterior pituitary gland (adenohypophysis)
- right lateral ventricle
- tongue mass
- right mandible
- sternum
- xiphisternum
- left umbilical artery
- vertebral body in mid-tail region
- genital tubercle
- muscular wall of bladder
- lumen (cavity) of bladder
- epithelial lining of bladder
- right crus of diaphragm
- proximal part of post-hepatic part of inferior vena cava
- lumen of trachea
- right lobe of thymus gland
- thyroid cartilage
- medulla oblongata
- cerebellum
- fourth ventricle (lateral part)
- caudal part of cerebral aqueduct

Results

Staining with an MR contrast agent resulted in T1s on the order of 50-90 ms and T2s on the order of 10-15 ms, which allowed rapid scan times and high SNRs of ~ 20:1 (Fig.1). Selected slices in all 3 planes were labeled and approximately 200 different structures were identified by MH Kaufman based on his histological Atlas of Mouse Development (1992) [3]. The labeled images are displayed in MBAT, enabling the user to browse through slices and identify structures by scrolling the mouse over a dot (Fig.2).

Conclusion

We have integrated a staining method and an acquisition strategy for fast high-resolution MR imaging of the mouse embryo. This work has set a platform for high-throughput studies for three-dimensional histology and phenotyping mouse models, which will be the focus of our future work.

References

1. MBIRN: Mouse Biomedical Informatics Research Network: http://www.nbirn.net
2. A Petiet, LW Hedlund, GA Johnson, Staining methods for magnetic resonance microscopy of the rat fetus, accepted for publication in JMRI, 2006.
3. MH Kaufman, The Atlas of Mouse Development, Elsevier Academic Press, 1992.