Using MRI to Build a 3D Reference Atlas of the Mouse Brain from Histology Images

P. A. Yushkevich[1], B. B. Avants[1], P. D. Burstein[1], H. Zhang[1], L. Ng[2], M. Hawrylycz[2], J. C. Gee[1]

[1]Department of Radiology, University of Pennsylvania, Philadelphia, PA, United States, [2]Allen Institute for Brain Science, Seattle, WA, United States

Introduction

The problem of reconstructing a 3D volume from a sequence of histological slices frequently arises in studies that involve animals. We argue that 3D reconstruction from slices requires both a fine-scale alignment of neighboring slices, which can be achieved using histology data alone, as well as a coarse-scale alignment of the reconstructed 3D volume to a reference model of anatomy, which should be supplied by MRI or another 3D imaging modality. Neither the fine-scale nor the coarse-scale alignment is sufficient by itself: naïve slice-to-slice registration does not guarantee proper alignment of far-away slices and results in gross shearing and twisting in the reconstructed volume; histology-to-MRI registration can recover the 3D shape of the anatomy at a gross level, but results in poor matches between adjacent slices. However, by combining these two approaches, we generate a reconstruction that is accurate at the coarse and fine levels simultaneously. Our methods and results using mouse brain data are presented below.

Methods and Results

Data Sets. The histology dataset contains 525 high resolution (0.95 μm) color images of Nissl counterstained coronal slices of the mouse brain acquired with 25μm spacing. Figure 1 shows one of these images. The reference MRI data set is an average of 30 in vivo MRI scans of 10 mice with the same genetic makeup as the mouse in the histology dataset. The reference MRI, shown in Figure 2a, has the resolution of 12.9 μm. The data was collected as a part of a large ongoing study that involves mapping gene activation at the cellular level in the mouse brain.

Fine-Scale Alignment. A simple way to reconstruct a 3D volume is to align each slice with the next slice in the sequence using rigid registration, to choose the first slice as a reference, to concatenate the transforms resulting from registration into transforms that align a given slice into the reference slice and to reconstruct the volume by applying these transforms. However, since histological data typically includes a large number of slices with torn or missing tissue, large misalignment errors are bound to occur and to propagate during reconstruction. This error propagation results in large scale shearing and twisting of the reconstructed anatomy. To avoid error propagation, we introduce a technique where the sequence of registrations that aligns a given slice with the reference slice can bypass some of the intermediate slices if these slices can not be accurately registered with their neighbors. We implement this technique by constructing a graph whose vertices represent the slices and whose edges connect each slice to 10 of its nearest neighbors. For each pair of slices connected by an edge, a rigid registration is performed and the resulting transform and value of the image match function are recorded. Each edge is assigned a weight, which is the product of the image match value and a penalty term that increases exponentially with the number of slices in the original sequence that are "skipped" by the edge. To find a sequence of transforms that map a given slice to the reference slice, we compute the shortest path in this graph using Dijkstra's algorithm. This sequence represents a tradeoff between including too many bad registrations and skipping too many slices. The tradeoff is modulated using the exponent of the penalty term. Under this scheme, slices that register poorly to their neighbors do not affect the registration of other slices and error propagation is reduced dramatically. Figure 2b shows the results of aligning histology slices with this technique.

Coarse-Scale Alignment. To recover the gross shape of the mouse brain, we register the histology slices with cross-sections of the reference MRI. We first use 3D rigid registration to align the MRI volume with the histology volume reconstructed in the previous step. By reconstructing the transformed MRI in the image space of the histology volume, create a set of 525 parallel cross-sections through the MRI. We rigidly register each histology slice to the corresponding cross-section and reconstruct a 3D volume, shown in Figure 2c. The shape of the reconstructed brain roughly matches the shape of the brain in MRI, but the alignment between neighboring slices is poor because multi-modality registration is less accurate than the histology-to-histology registration. If we consider the sequence of histology-to-MRI transforms as a combination of some smooth function that deforms the histology volume into the true brain shape plus some unbiased uncorrelated noise, then we can recover a coarse approximation of this function by filtering away the noise. We do this by applying a Gaussian smoothing kernel to the translation and rotation parameters of the transforms, resulting in a smooth sequence of transforms. When applied to the slices in the reconstructed histology volume, these transforms generate a new volume which is accurate both in terms of global shape and slice-to-slice alignment. This result is shown in Figure 2d.

Registration Technique. We use AIR software to perform all registrations [1]. To increase the accuracy of the registration, we automatically segment the brain in the histology images using level set and mathematical morphology techniques and use the segmentations to mask away background and debris in the images (Figure 1).

Discussion and Conclusions

We have presented a reconstruction technique that produces histological volumes that are accurate at the local level and true to the overall shape of the imaged anatomy. In the process of building a 3D atlas of the mouse brain, we intend to augment our current technique with non-parametric registration, which would help correct for tearing and other artifacts. Gene mapping presents the challenge of applying this technique to stains other than the Nissl solution, which contain less structural information.

References

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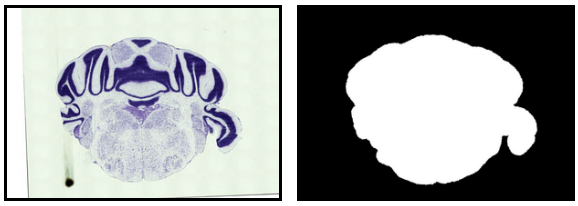

Figure 1. A sample histology slice (left), a binary mask computed using level set segmentation (right).

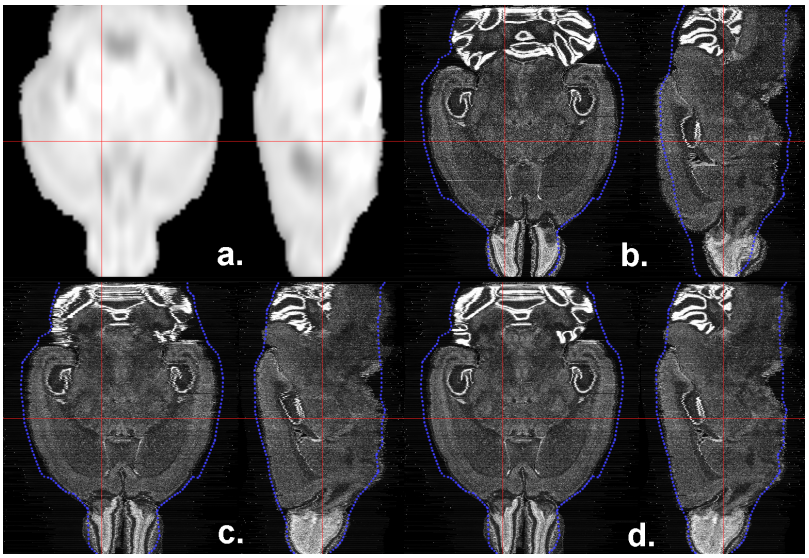

Figure 2. Four data sets involved in the reconstruction. **a.** Axial and sagittal cross-sections of the reference MRI data set. **b.** Reconstruction of the brain volume from histology slices using fine-scale alignment. Histology images were converted to grayscale and inverted; the outline of the brain from MRI is shown as a dashed blue curve. **c.** Coarse scale histology-to-MRI registration result. **d.** Final result obtained by smoothing the histology-to-MRI transforms.