Title: Geometry Processing of Conventionally Produced Mouse Brain Slice Images

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PII: S0165-0270(18)30111-0
DOI: https://doi.org/doi:10.1016/j.jneumeth.2018.04.008
Reference: NSM 7983

To appear in: *Journal of Neuroscience Methods*

Received date: 12-1-2018
Revised date: 10-4-2018
Accepted date: 13-4-2018

Please cite this article as: Nitin Agarwal, Xiangmin Xu, M. Gopi, Geometry Processing of Conventionally Produced Mouse Brain Slice Images, *<![CDATA[Journal of Neuroscience Methods]]>* (2018), https://doi.org/10.1016/j.jneumeth.2018.04.008

Geometry Processing of Conventionally Produced Mouse Brain Slice Images

Abstract—*Background:* Brain mapping research in most neuroanatomical laboratories relies on conventional processing techniques, which often introduce histological artifacts such as tissue tears and tissue loss.
New Method: In this paper we present techniques and algorithms for automatic registration and 3D reconstruction of conventionally produced mouse brain slices in a standardized atlas space. This is achieved first by constructing a virtual 3D mouse brain model from annotated slices of Allen Reference Atlas (ARA). Virtual re-slicing of the reconstructed model generates ARA-based slice images corresponding to the microscopic images of histological brain sections. These image pairs are aligned using a geometric approach through contour images. Histological artifacts in the microscopic images are detected and removed using Constrained Delaunay Triangulation before performing global alignment. Finally, non-linear registration is performed by solving Laplace's equation with Dirichlet boundary conditions.
Results: Our methods provide significant improvements over previously reported registration techniques for the tested slices in 3D space, especially on slices with significant histological artifacts. Further, as one of the application we count the number of neurons in various anatomical regions using a dataset of 51 microscopic slices from a single mouse brain.
Comparison with Existing Method(s): To the best of our knowledge the presented work is the first that automatically registers both clean as well as highly damaged high-resolutions histological slices of mouse brain to a 3D annotated reference atlas space.
Conclusions: This work represents a significant contribution to this subfield of neuroscience as it provides tools to neuroanatomist for analyzing and processing histological data.

Index Terms—Histological Artifacts, Image Registration, Image Processing, 3D Visualization, Mouse Brain.

1 Introduction

Understanding the brain connectome or the wiring diagram of the brain is essential to understand how the brain circuits work [48, 29]. However, obtaining the wiring diagram of the human brain is extremely difficult as it is large and contains billions of neurons forming complex interconnecting networks. Obtaining the connectome of even a simple roundworm such as C. elegan, which consists of only 302 neurons took many years [51]. Only recently, with the advances in both computing power and optical imaging techniques, it has now become feasible to obtain the connectome of more complex brains. A salient example of this is the ongoing efforts in mapping the connections in Drosophila's brain which has nearly 100,000 neurons [10]. Over the past decade, neuroscience researchers have started studying the mouse brains due to their physiological and genetic similarity to humans, the ease with which their genomes can be manipulated, and the ability to train mice to perform behavioural tasks relevant to human cognitive processes.

There are two steps in processing mouse brains. The first step comprises of sample preparation, imaging, and collection of histological slice data, while the second step consists of analyzing this histological data for measurement and quantification of labeled neurons, studying gene expression patterns, connectome exploration, etc. In most neuroanatomical laboratories, both these steps are largely performed manually [2, 45]. Manual sample preparation, although offers great flexibility especially in restaining of slices, slicing at arbitrary intervals etc., introduces many slice-specific histological artifacts such as tissue tears, folds, and missing regions. The second step, manual analysis of histological slices, is tedious, incomplete, and introduces various subjective errors. There is very little advantage to do the analysis, measurement, and visualization of histological slices manually.

It is advantageous to allow manual sample preparation, if required, and automate the second step, namely the post processing of histological slice data. However, the artifacts introduced during manual sample preparation makes many post-processing operations such as automatic alignment and 3D reconstruction extremely challenging [52, 1]. Another challenge in processing these conventionally produced slices is that a variety of sample preparation and staining procedures like In-Situ Hybridization (ISH), histology, etc., result in brain slices having different intensity profiles making comparisons with the reference atlas images extremely difficult (Fig. 1). In this paper, we present algorithms and techniques to address this challenging task of automating the post-processing of mouse brain slices including those that are produced by conventional techniques.

In order to understand the wiring diagram of a mouse brain, it is crucial to visualize and explore the connectome data in a standardized brain space or a reference atlas. There exists many mouse brain reference atlases, each constructed using different procedures [38, 14, 47]. Among these, the Allen Reference Atlas (ARA) [14] has been widely used in neuroanatomy laboratories around the world. ARA is being continuously updated and so far it has delineated approximately 738 mouse brain anatomical regions. ARA consists of two reference atlases (coronal and saggital reference atlas) created by slicing the mouse brain in different directions. The coronal reference atlas consists of 132 sections evenly spaced at 100 μm whereas the saggital reference altas consists of 21 sections spaced at 200 μm. Each of these reference