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SliceMap: An Algorithm for Automated Brain Region Annotation

Barbier M¹, Bottelbergs A², Nuydens R², Ebneth A² and De Vos WH^{1,3,*}

¹Laboratory of Cell Biology & Histology, Department of Veterinary Sciences, University of Antwerp, Universiteitsplein 1, 2610 Wilrijk, Belgium, ²Department of Neuroscience, Janssen Research and Development, Turnhoutseweg 30, 2340 Beerse, Belgium, ³Department of Molecular Biotechnology, Ghent University, Coupure Links 653, 9000 Ghent, Belgium.

*To whom correspondence should be addressed.

Abstract

Summary: Many neurodegenerative disorders, such as Alzheimer's Disease, pertain to or spread from specific sites of the brain. Hence, accurate disease staging or therapy assessment in transgenic model mice demands automated analysis of selected brain regions. To address this need, we have developed an algorithm, termed SliceMap, that enables contextual quantification by mapping anatomical information onto microtome-cut brain slices. For every newly acquired high-resolution image of a brain slice, the algorithm performs a coarse coagulating-based registration to a library of pre-annotated reference slices. A subset of optimally matching reference slices is then used for refined, elastic registration. Morphotextural metrics are used to measure registration performance and to automatically detect poorly cut slices. We have implemented our method as a plugin for FIJI image analysis freeware, and we have used it to regionally quantify tau pathology in brain slices from a tauopathy (P301S) mouse model. By enabling region-based quantification, our method contributes to a more accurate assessment of neurodegenerative disease development.

Availability: The method is available as a plugin for FIJI from <https://github.com/mbarbie1/SliceMap/>, along with an example dataset and user instructions.

Contact: Winnok.DeVos@UAntwerpen.be

Supplementary information: Supplementary data are available at *Bioinformatics* online.

1 Introduction

Brain tissue slices are commonly used in neurobiological research for analyzing pathological features in an anatomically defined manner. However, as yet, brain region-specific analysis is mainly performed by manual delineation. With image acquisition gaining throughput, automated annotation and quantification is highly needed. Two major strategies exist for automatically defining tissue regions, namely those that solely use the image content, *e.g.*, texture information (machine learning) (Kim, et al., 2014), or those that align new images to similar, pre-annotated ones (registration) (Oliveira and Tavares, 2014). In registration, the use of multiple references improves the accuracy of the resulting annotation, albeit at the expense of computation time (Aljabar, et al., 2009). To reduce the computational cost of multi-atlas approaches, subset selection and group-wise approaches can be introduced (Wang, et al., 2010). Brain mapping and atlas generating methods based on image registration have been developed (Qu and Peng, 2015; Wu, et al., 2011), but these are tailored to specific datasets such as MRI, or their use requires advanced computer science skills. We have now developed a data-driven and easy-to-use method, termed SliceMap, that enables mapping of anatomically defined regions onto microtome-cut brain slices. It is based on a combination of coarse pre-registration steps and fine elastic registration using a library of pre-annotated reference slices.

2 Methods

The plugin consists of a user-interface for facile and consistent manual annotation of brain tissue slices to build or expand a reference image library, and the actual algorithm for automated annotation of new sample images. The automated region mapping algorithm consists of three steps, namely (a) Subset selection; (b) Elastic registration; and (c) Region transformation (Fig. 1). The first step (a) aims at selecting a subset of reference

slices that correspond best to the sample image. This reduces the number of reference templates (and the associated computational load) and it lowers noise caused by suboptimal references. To achieve this, the sample image is combined with the reference image library into one single, downsampled stack (binned 8 times). This complete stack is first subjected to a rigid transformation (P_j) so as to align the most prominent image features, determined by Harris corner detection (Harris, 1988) at a pre-defined scale (5% of the average image width). Next, a group-wise registration (G_j) of the brain slices is performed by means of an adapted cone-alignment method (Learned-Miller, 2006) that allows rigid and mirror transformations. Among the complete set of registered reference slices, a user-defined number (5-10) is selected that shows the highest similarity (measured by the Pearson correlation coefficient) with the sample image. In the next step (b), the subset of reference slices is elastically registered to the sample image, whereby smaller discrepancies in shape between the sample and the references of the subset are removed. The elastic registration is done using BunwarpJ (Arganda-Carreras, et al., 2006) in a landmark-guided manner. Landmarks are obtained using one of three automated interest point detection methods (Harris, A-KAZE, or SIFT features) (Alcantarilla, et al., 2013; Harris, 1988; Lowe, 2004). The optimal method identifies a maximum number of matching interest points between sample and reference. This results in a transformation E_j . Thus, the sample and references slice j are related by the following total transformation: $T_j = E_j G_j P_j$. Since the brain regions of reference slices have been annotated, every region of reference slice j is automatically mapped to the sample image using the back-transformation T_j^{-1} . Finally, (c) the back-transformed regions are interpolated to the actual sample image size. Median region outlines are plotted along with a confidence interval ($\pm$ standard deviation). Prior to the registration procedure, brain slices are also segmented as a whole so as to extract global morphotextural features. The latter can be used to classify brain slices (e.g., using PCA) and identify aberrant (e.g., poorly cut) slices (Suppl. Section S1).

Fig. 1. SliceMap workflow. The algorithm performs a subset selection within a pre-annotated reference library (a), elastic registration of the best matching images (b) and finally region mapping onto the sample image by back-transformation (c) (see the text for details).

3 Results

To assess the accuracy of our approach, we generated manually annotated reference regions for 60 mouse DAPI- (cell nuclei) and NeuN- (neuronal marker) counterstained brain slices. Subsequently, we applied SliceMap using a leave-one-out approach, i.e., using all slices except for one as reference, and the omitted one as sample slice. Next, we compared the resulting regions with the manually annotated ones by calculating the relative overlap between regions A and B in terms of a Dice index: $S = |A \cap B| / |A \cup B|$. On average, a Dice index of $\sim 90\%$ was obtained (Fig. 2A, Suppl. Section S2). As proof of concept, we implemented SliceMap in the PerkinElmer Columbus® high-throughput environment, to quantify hyperphosphorylated tau (stained with AT8 antibody) load in microtome-cut slices from a P301S mouse. The tau load was expressed as relative number of AT8-positive cells per region (Fig. 2B; Suppl. Section S6).

Fig. 2. SliceMap in practice. a) Annotation performance expressed as Dice index between manual and automated region segmentations ($n=60$); b) Region-based quantification of

AT8-positive cells in P301S mouse brain slice (BS=Brain stem, CB=Cerebellum, MB=Mid-brain, TH=Thalamus, HC=Hippocampus, CX=Cortex).

4 Conclusions

We have conceived an algorithm for automatic brain region definition in large images from fluorescently labeled mouse brain sections. We have used this approach in a longitudinal study to map tau distribution during pathology progression. Our method contributes to a more accurate assessment of neurodegenerative brain disease development in mouse models, and may also improve the evaluation of the therapeutic efficiency of lead compounds in preclinical studies.

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Conflict of Interest: AB, RN, and AE are employees of Janssen Pharmaceutical Companies of Johnson & Johnson. This does not alter their adherence to the journal's policies on sharing of data and source code.

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