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Automatic anatomical labeling of the complete cerebral vasculature in mouse models

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ABSTRACT

Study of cerebral vascular structure broadens our understanding of underlying variations, such as pathologies that can lead to cerebrovascular disorders. The development of high resolution 3D imaging modalities has provided us with the raw material to study the blood vessels in small animals such as mice. However, the high complexity and 3D nature of the cerebral vasculature make comparison and analysis of the vessels difficult, time-consuming and laborious. Here we present a framework for automated segmentation and recognition of the cerebral vessels in high resolution 3D images that addresses this need. The vasculature is segmented by following vessel center lines starting from automatically generated seeds and the vascular structure is represented as a graph. Each vessel segment is represented as an edge in the graph and has local features such as length, diameter, and direction, and relational features representing the connectivity of the vessel segments. Using these features, each edge in the graph is automatically labeled with its anatomical name using a stochastic relaxation algorithm. We have validated our method on micro-CT images of C57Bl/6J mice. A leave-one-out test performed on the labeled data set demonstrated the recognition rate for all vessels including major named vessels and their minor branches to be >75%. This automatic segmentation and recognition methods facilitate the comparison of blood vessels in large populations of subjects and allow us to study cerebrovascular variations.

Introduction

The cerebrovasculature is a network of blood vessels including arteries, veins, sinuses, arterioles, venules and capillary beds, which supplies blood to the brain. The malfunction of this system can lead to morbidity and death. Many of the degenerative diseases such as Alzheimer's disease have been proposed to have an underlying vascular etiology (Bell and Zlokovic, 2009; de la Torre, 2004; de la Torre and Stefano, 2000). The characteristics of the cerebrovasculature may affect the probability of occurrence of such disorders. However, our understanding of the development, structuring and anatomical variations of the cerebrovascular system is limited. Phenotyping the cerebral vasculature and analyzing the vascular variations are essential for understanding genetic factors in the development, characteristics and diseases of the cerebrovasculature.

Due to the high variability of the cerebrovasculature, inter-subject comparison in a large number of subjects is required in order to characterize variations of the blood vessels. A method for studying and comparing cerebral anatomical structures is to generate an atlas and registering new subjects to it, in order to identify the corresponding structures in each individual. This approach has enabled a comparative study of cerebral structures across multiple subjects (see Dorr et al. (2008) for example). However, unlike neuroanatomical regions, where there is homology between different subjects, the differences between cerebral vasculature of any two subjects are so large that common registration methods fail to correct for such differences. These differences include the number of branches, size, curvature, and branching locations in the vascular network and can include the absence of a major artery (Beckmann, 2000; Kitagawa et al., 1998).

There is a rich literature on automatic methods of vascular segmentation (Babin et al., 2013; Caselles et al., 1997; Forkert et al., 2013; Frangi et al., 1998; Fridman et al., 2004; Krissian et al., 2000; Lorigo et al., 2001; Piccinelli et al., 2009; Qian et al., 2009; Shang et al., 2011; Sofka and Stewart, 2006). A review of different approaches of vessel segmentation can be found in Suri et al. (2002), Lesage et al. (2009). However, only a few automated methods for labeling vasculature have been investigated in the past. Graph matching algorithms have been employed to identify and label the vascular systems such as the airway trees (Tschirren et al., 2005) and the bronchial branches (Mori et al., 2000, 2009). In most of the early works such as the labeling of the bronchial branches, a knowledge-based algorithm based on fixed topological constraints on the bifurcations was used, which is likely to fail in the case of large variations from the reference such as missing vessels (Mori et al., 2000,

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2009). Tschirren et al. proposed an automated labeling of the airway trees where the branches are first segmented and skeletonized from the CT images and are represented by a directed acyclic graph (DAG) (Tschirren et al., 2005). A branch point matching algorithm is then performed in order to find corresponding major branches in different data sets. In order to perform automatic labeling, an average labeled tree is generated from manually labeled trees which represent the geometrical and topological features of the bifurcations. Labels are assigned to the target tree by matching it to the average labeled hierarchical tree using association graphs. In another approach, supervised machine learning algorithms were used to automatically identify and label the abdominal arteries (Mori et al., 2010). For each vessel branch, features including the direction, length and diameter are extracted and the main abdominal aorta is found by the largest diameter. A pair-wise labeling is then performed based on the local features of the branches. Despite the high recognition rate of these tree matching algorithms, their applications are limited by their dependence on the topology of hierarchical structures.

There has been only a few works investigating the labeling of the cerebral arteries. Maximum a posteriori probability (MAP) estimation was used to automatically label the circle of Willis (Bogunovic et al., 2013). In this approach, the arteries in the circle of Willis are segmented from the magnetic resonance angiography and are modeled as a rooted attributed graph. Local features, such as the radius and direction of the vessels, are computed for each bifurcation. Topological information is defined based on comparison with a reference labeled graph. The optimal labeling is formulated as a MAP. They labeled 11 bifurcations of the circle of Willis with 95% accuracy. In another approach, Bilgel et al. used a combination of random forests on local features of vessels with a belief propagation of vascular tree connectivity to label the anterior cerebral arteries in 3D time of flight MR angiography (TOF MRA) (Bilgel et al., 2013). The application of these methods has been demonstrated for a few cerebral arteries and may not generalize to the more complex graph of the complete cerebrovasculature. Specifically, the labeling method used by Bogunovic et al. (2013) is based on finding maximal cliques between the graph and a reference graph. Constructing a reference graph such as that constructed for the circle of Willis is an elegant approach for labeling sub-trees in the cerebrovasculature. However, the high variations in the branching of the cerebrovasculature make it very complicated to construct an encyclopedic reference graph for the complete cerebrovascular graph. To the best of our knowledge, no previous work has been published on the labeling of the complete cerebrovasculature.

The difficulty of high resolution imaging of cerebral vessels of laboratory animals such as mice, the high complexity of the cerebrovasculature and the density of vessels in the brain makes the study of this interesting anatomy challenging. As a result, there has been little detailed description of the whole cerebrovasculature of mice. A few reference works are the mouse cerebrovascular atlas by Dorr et al. (2007), and the description of the mouse cerebrovascular system detailed by Scremin and Holschneider (2011). Developing a framework to automatically recognize and label all the vessels in the mouse cerebrovascular system will enable the study of large populations in greater detail and can lead to a better understanding of the development, phenotypes and diseases of vasculature in the brain. In this paper, we detail the development of such a framework.

Methods

Our automatic segmentation and recognition of the vasculature consist of sub-processes as shown in the pipeline in Fig. 1. First, an ex vivo high resolution micro-CT image is acquired from the complete cerebrovascular system of the mouse brain filled with contrast agent. The details of preparation and imaging of the specimens can be found in Ghanavati et al. (2014). The images are then registered to a common space by manually selecting landmarks on the major vascular branches as described by Chugh et al. (2009). The common space used is the vascular atlas created by Dorr et al. (2007). The registered images are normalized so that the background and foreground intensity of all the subjects will be in a similar range. The original CT scans contain cerebral vessels as well as facial arteries and veins and upper jaw. Therefore, the brain in each scan is delineated manually using the CT-Analyser software (Bruker micro-CT, Belgium), so that final images only contain the cerebral blood vessels. Where an MRI scan has been acquired in addition to micro-CT, this step can be replaced by an automatic method using a brain mask constructed from the anatomical MRI and registered to the CT scan. Next, the cerebrovasculature is automatically segmented and is represented as a connected graph. Finally, each graph is automatically labeled using a reference set of labeled cerebrovasculatures (the training set) through a stochastic optimization scheme. In the following sections, we will describe the steps of the pipeline in detail.

Vascular segmentation

The first step in the automatic labeling of vasculature is to segment the vessels and to represent them as a graph. The vessel segmentation was fully automated. The method closely follows the tubular object extraction method of Fridman et al. (2004) and is detailed in Rennie et al. (2011). We have modified the method to eliminate the need for manual definition of seeds required for the initialization of the segmentation algorithm. The distance transform of a binarized version of the image is calculated and used to place an initial seed at the center of the largest

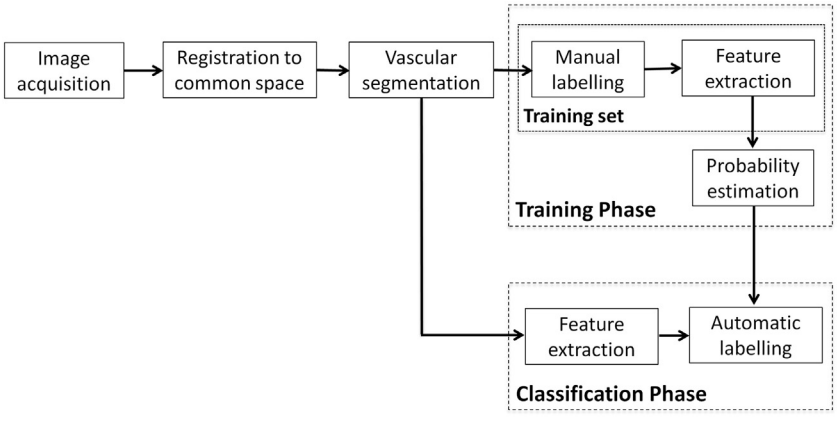

Fig. 1. The pipeline for the automatic segmentation and labeling of the cerebrovascular system.