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Local volume fraction distributions of axons, astrocytes, and myelin in deep subcortical white matter

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ABSTRACT

This study aims to statistically describe histologically stained white matter brain sections to subsequently inform and validate diffusion MRI techniques. For the first time, we characterise volume fraction distributions of three of the main structures in deep subcortical white matter (axons, astrocytes, and myelinated axons) in a representative cohort of an ageing population for which well-characterized neuropathology data is available. We analysed a set of samples from 90 subjects of the Cognitive Function and Ageing Study (CFAS), stratified into three groups of 30 subjects each, in relation to the presence of age-associated deep subcortical lesions. This provides volume fraction distributions in different scenarios relevant to brain diffusion MRI in dementia. We also assess statistically significant differences found between these groups. In agreement with previous literature, our results indicate that white matter lesions are related with a decrease in the myelinated axons fraction and an increase in astrocytic fraction, while no statistically significant changes occur in axonal mean fraction. In addition, we introduced a framework to quantify volume fraction distributions from 2D immunohistochemistry images, which is validated against *in silico* simulations. Since a trade-off between precision and resolution emerged, we also performed an assessment of the optimal scale for computing such distributions.

Introduction

Brain tissue microstructural damage can result from neurodegenerative diseases such as amyotrophic lateral sclerosis, Parkinson's disease, and Alzheimer's disease (Stoessl, 2012; Tur et al., 2016; Pearson et al., 1985). These conditions produce gradual deterioration or even death of neurons with concomitant alterations in brain structure and function. Devising imaging techniques capable of characterising brain tissue microstructure *in vivo* is topical within neuroimaging. Key information about brain microstructure is provided by the volumetric densities of the different white matter (WM) structures (Horsfield and Jones, 2002). This knowledge might be valuable not only for research but also for its potential to help in developing early stage diagnosis of neurodegenerative diseases. The aim of this paper is to characterise the local volume fraction distribution of axons, astrocytes, and myelinated axons in deep white matter for different populations. These are important stereological parameters, but their distribution has not been previously identified.

Age-associated cerebral white matter lesions can be sub-classified into those within deep white matter (DWM) of the *centrum semiovale* (deep subcortical lesion, DSCL) and those close to the angles of the lateral ventricles (periventricular lesion, PVL). Each has its own clinical relevance (Park et al., 2011), but both are thought to be the consequence of small vessel-related vascular pathology such as vascular dementia. This work focus on DSCLs, which are associated with loss of myelin components (Wharton et al., 2015) and astrogliosis (Simpson et al., 2007, 2010). To this purpose, various subjects belonging to groups that represent healthy and diseased conditions were imaged. We analyse immunohistochemically stained sections of three populations of DWM samples: Control (no DSCLs were present in the subject), Lesion (the sample presented DSCLs), and Normal Appearing White Matter (NAWM, the subject presented DSCLs but not in the sampled tissue).

Tens of thousands of structures such as axons, coexist in 1 mm^3 of brain tissue (Azevedo et al., 2009). Their arrangement varies between different subjects and also with the presence of disease. The information obtained from histological analysis has the potential to help in the description and understanding of healthy tissue, and also in a diverse

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range of conditions including multiple sclerosis (Peterson et al., 2001; Trapp et al., 1998), schizophrenia (Colon, 1972), and Alzheimer's disease (Stark et al., 2005). Volume fraction maps of the main white matter structures can further inform and validate magnetic resonance imaging (MRI) techniques. Prior distributions on the microstructural parameters of biophysical models can be generated from this kind of information.

MRI has become a clinical standard to diagnose brain diseases among other conditions in several body organs (Hollingworth et al., 2000). It has a spatial resolution considerably lower than histology. While MRI voxels are in the order of the millimetres, light microscopy can resolve structures smaller than a micron. While microscopy can discern individual structures, MRI can only detect the aggregate signal of the distribution of components within a voxel. However, MRI has the advantage of being a non-invasive imaging technique that can be used *in vivo*. Due to the limited resolution that can be achieved with MR scanners, a modality that has gained popularity is diffusion MRI (dMRI) (Assaf, 2008). Diffusion weighted images (DWIs) are sensitised to displacements in water molecules along pre-determined directions. By measuring across multiple orientations and processing the set of signals, this technique enables the extraction of information about the underlying tissue architecture within a voxel. A wide range of analysis methods have been developed in the dMRI literature to extract different information from the DWIs (Basser et al., 1994; Assaf and Cohen, 1999; Tournier et al., 2004; Jensen et al., 2005). Among them, a number of biophysical tissue models (Assaf et al., 2004; Jespersen et al., 2007; Alexander et al., 2010; Fieremans et al., 2011; Zhang et al., 2012; Jelescu et al., 2015; Reisert et al., 2017; Veraart et al., 2017) have been proposed that aim to describe degeneration processes with higher sensitivity and specificity than previous attempts to characterise tissue microstructure with Diffusion Tensor Imaging (DTI) or similar phenomenological models.

As in any other physical problem involving a model, the accuracy of the results relies on how representative the model is for the phenomenon under study (see recent review (Novikov et al., 2016)). The validation of dMRI biophysical models is generally hindered by the complexity and unavailability of the ground truth. Some of the prominent dMRI biophysical models make unrealistic assumptions and hence renders the results of these models dubious (Lampinen et al., 2017). In addition, in absence of additional information, the precise estimation of the model parameters requires a huge amount of measurements. This is where the characterisation of V_V distributions, or more generally information derived from histology, can play a key role. This information has the potential to improve the performance of existing tissue models and help in the validation of new ones. For example, Clayden et al. (2016) showed that by introducing structured prior information on model parameters, the accuracy in the estimation is improved. The interpretation of parameters from several existing dMRI techniques such as DTI or biophysical models has been previously validated using histological sections (*cf.* (Chenevert et al., 2000; Assaf et al., 2008; Jespersen et al., 2010; Xu et al., 2014; Sepehrband et al., 2015; Szczepankiewicz et al., 2016)). Additionally, combined analyses of histology and dMRI have been performed to further understand the development of certain diseases and the healthy brain (Budde and Frank, 2012; Kolasinski et al., 2012; Khan et al., 2016; Mollink et al., 2017). Information from histology can also help developing realistic *in silico* biomimetic phantoms of brain tissue (Cook et al., 2006; Beltrachini et al., 2015). Phantoms provide controlled ground truth that can test different dMRI acquisition schemes and post-processing methods.

Local volume fractions depend on the scale of the windows of observation. Previous works have only considered the global average V_V of white matter structures for the whole brain or over complete regions (Tang et al., 1997; Xu et al., 2014; Sepehrband et al., 2015). There is little information on which scale should be considered for computing local volumetric density maps. As in other imaging fields, there is a trade-off here between precision and resolution (Chen et al., 2000; Kale et al., 2009). The choice of a small scale can lead to imprecise estimates due to the comparable size of the structures and the averaging window. Larger scales yield stable density estimates, but at the price of losing microstructural detail and hence be uninformative. To define a convenient scale of analysis, we computed the standard error in volume fraction estimates for windows of observation of various scales, together with the significant differences found between adjacent windows. In order to characterise different populations, we required histology data from a large cohort of subjects. The best option for this was immunohistochemistry. However, this modality produces slices with non-negligible thickness in comparison with the structures of interest. Thus, to recover the volume fraction from area fraction measures, we had to adapt and develop new stereological methods. These methods are an interesting additional contribution in themselves.

This paper addresses first the challenge of analysing the appropriate scale for computing local V_V values. Second, the development of a method for an automatic computation of the V_V intra-subject distributions from thin histology sections. Finally, this paper tackles the computation of local V_V probability distribution functions in different populations of deep white matter.

Material and methods

Tissue sample selection

The tissue samples for this work came from the Cognitive Function and Ageing Study (CFAS) neuropathology cohort (Brayne et al., 2006; Cognitive Function and Ageing Studies (CFAS) Collaboration, 2017). Brains were removed with the consent of the next of kin and with multicentre research ethics committee approval, according to standard CFAS protocols (Fernando et al., 2004). Brains were removed within 60 h of death, one cerebral hemisphere was fixed in buffered formaldehyde and sliced into 10 mm thick coronal slices. These slices were: 1) immediately anterior to the temporal stem (anterior), 2) at the level of the pulvinar (middle), and 3) at the posterior most limit of the occipital horn of the lateral ventricle (posterior). These slices were scanned using T_1 and T_2 weighted MRI (details available in (Fernando et al., 2004)). The MR images were rated by three experienced observers (blind to clinical status) and given a score for DSCLs using a modified Scheltens' scale (Scheltens et al., 1993). Following this scoring, the coronal slices were stored in formalin until required for this study (at least four weeks). From every subject one block of approximately $20mm \times 20mm \times 10mm$ was sampled from one of the slices. Blocks were allocated in three groups: Control, NAWM, and Lesion. Control blocks were taken from cases where all three levels were scored as 0 on this scale or where only one slice had a score of a maximum of 1. Lesion blocks were taken from regions with a Scheltens' score of 4 or greater. NAWM blocks were taken from lesion free regions of deep white matter in which a DSCL of score 3 or greater was present elsewhere.

To decide the total number of samples for the study, we performed a pilot study using five samples for each group. We required that the standard error of the mean V_V for every group needed to be below 0.5% for all structures. This resulted in the need of at least 25 samples from each group. To guarantee our requirement, we decided to run the complete experiment with 30 samples per group. Table 1 presents the main information of the selected patient cohort. Additionally, a baseline demographic analysis was performed to assess significant differences in the position of the samples or the sex of the subjects between the groups. No

Table 1
Patient cohort details: Number of samples per group (N), age of death (mean and standard deviation), sex (M = Male, F=Female), and level (A = Anterior, M = Middle, P=Posterior).

Tissue	N	Age [y-o]	Sex	Level
Control	30	85 ± 8	13M-17F	9A-17M-4P
NAWM	30	86 ± 6	14M-16F	10A-16M-4P
Lesion	30	87 ± 7	12M-18F	12A-14M-4P

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