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White matter microstructure from nonparametric axon diameter distribution mapping

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Abstract

We report the development of a double diffusion encoding (DDE) MRI method to estimate and map the axon diameter distribution (ADD) within an imaging volume. A variety of biological processes, ranging from development to disease and trauma, may lead to changes in the ADD in the central and peripheral nervous systems. Unlike previously proposed methods, this ADD experimental design and estimation framework employs a more general, nonparametric approach, without *a priori* assumptions about the underlying form of the ADD, making it suitable to analyze abnormal tissue. In the current study, this framework was used on an *ex vivo* ferret spinal cord, while emphasizing the way in which the ADD can be weighted by either the number or the volume of the axons. The different weightings, which result in different spatial contrasts, were considered throughout this work. DDE data were analyzed to derive spatially resolved maps of average axon diameter, ADD variance, and extra-axonal volume fraction, along with a novel sub-micron restricted structures map. The morphological information contained in these maps was then used to segment white matter into distinct domains by using a proposed k-means clustering algorithm with spatial contiguity and left–right symmetry constraints, resulting in identifiable white matter tracks. The method was validated by comparing histological measures to the estimated ADDs using a quantitative similarity metric, resulting in good agreement. With further acquisition acceleration and experimental parameters adjustments, this ADD estimation framework could be first used preclinically, and eventually clinically, enabling a wide range of neuroimaging applications for improved understanding of neurodegenerative pathologies and assessing microstructural changes resulting from trauma.

Keywords: MRI, double diffusion encoding, double pulsed field gradient, axon diameter distribution, pore size distribution, nonparametric, empirical, average axon diameter

1. Introduction

The axon diameter distribution (ADD) is a key microstructural feature in the peripheral and central nervous systems. Conduction velocity scales with axon diameter (Tasaki et al., 1943; Waxman et al., 1995) and therefore provides an important functional marker that reflects information transmission in the nervous system. Conventional neuroanatomical methods applied to postmortem human or animal tissue have provided evidence that the ADD changes in neurological conditions such as amyotrophic lateral sclerosis (ALS) (Cluskey and Ramsden, 2001) and multiple sclerosis (MS) (Trapp et al., 1998; Evangelou et al., 2001; Lovas et al., 2000). In addition, several pathologies, including autism (Hughes, 2007), dyslexia (Njiokiktjien et al., 1994), schizophrenia (Randall, 1983), and even alcoholism (Livy and Elberger, 2008), have been associated with changes in the distribution of axon size. Changes in the number of axons and their diameters also take place throughout normal development accompanying the period of dynamic behavioral, cognitive, and emotional changes in childhood and adolescence (Yakovlev, 1967; Pfefferbaum et al., 1994; Gregg et al., 2007; Barnea-Goraly et al., 2005; Schlaug et al., 2009).

The biological significance of axon caliber is not limited to development or well-defined pathologies. Central nervous system neurites exhibit a beaded axonal morphology following mechanical, chemical, or metabolic insults (Ochs et al., 1997; Roediger and Armati, 2003). Beading is also seen in the peripheral nervous system when nerves are incrementally stretched and rapidly fixed by freeze-substitution or cold fixation (Ochs and Jersild, 1987). Recently, this mechanism of axonal beading was proposed to explain both the reduction in the mean apparent diffusion coefficient (ADC) during traumatic brain injury (TBI) and cerebral ischemia, and its re-elevation observed during recovery (Budde and Frank, 2010). Diffusion tensor imaging (DTI)-derived parameters, including fractional anisotropy (FA), while sensitive to these changes in axonal dimensions, do not provide information about specific microstructural or morphological changes or about their biophysical basis. Assuming it is well-defined in the presence of beading, the ADD would directly reveal these underlying microstructural changes resulting from TBI or ischemia.

A common way to measure the ADD is by using optical or electron microscopy on fixed specimens. Measurement of post-

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