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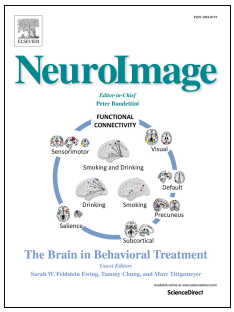

What dominates the time dependence of diffusion transverse to axons: Intra- or extra-axonal water?

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What dominates the time dependence of diffusion transverse to axons: Intra- or extra-axonal water?

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Abstract

Brownian motion of water molecules provides an essential length scale, the diffusion length, commensurate with cell dimensions in biological tissues. Measuring the diffusion coefficient as a function of diffusion time makes in vivo diffusion MRI uniquely sensitive to the cellular features about three orders of magnitude below imaging resolution. However, there is a longstanding debate, regarding which contribution — intra- or extra-cellular — is more relevant in the overall time-dependence of the MRI-derived diffusion metrics. Here we resolve this debate in the human brain white matter. By varying not just the diffusion time, but also the gradient pulse duration of a standard diffusion MRI sequence, we identify a functional form of the measured time-dependent diffusion coefficient transverse to white matter tracts in 10 healthy volunteers. This specific functional form is shown to originate from the extra-axonal space, and provides estimates of the fiber packing correlation length for axons in a bundle. Our results offer a metric for the outer axonal diameter, a promising candidate marker for demyelination in neurodegenerative diseases. From the methodological perspective, our analysis demonstrates how competing models, which describe different physics yet interpolate standard measurements equally well, can be distinguished based on their prediction for an independent "orthogonal" measurement.

Keywords: diffusion, white matter, microstructure, time dependence, model selection

1. Introduction

The ultimate promise of diffusion MRI (dMRI) (Jones, 2011), a technique that maps the diffusion propagator in each imaging voxel, is to become sensitive and specific to tissue features at the cellular level, orders of magnitude below the nominal imaging resolution. The foundation for this sensitivity is provided by the diffusion length, i.e. the rms displacement of water molecules, being of the order of a few μm, which is commensurate with cellular dimensions. By controlling the diffusion time, one can probe the time-dependent diffusive dynamics (Tanner, 1979; Mitra et al., 1992; Assaf and Basser, 2005; Assaf et al., 2008; Alexander et al., 2010; Novikov et al., 2014; Burcaw et al., 2015; Fieremans et al., 2016; Reynaud et al., 2016), and quantify the relevant cellular-level tissue structure indirectly, using biophysical modeling (Yablonskiy and Sukstanskii, 2010; Kiselev, 2017; Novikov et al., 2016a).

In most tissues, and in the human brain in particular, the dMRI signal generally originates from at least two "compartments" — intra- and extra-cellular spaces (Ackerman and Neil, 2010). Their distinct microgeometries provide different competing contributions to the overall non-Gaussian diffusion(Assaf and Basser, 2005; Alexander et al., 2010; Assaf et al., 2008; Fieremans et al., 2016; Burcaw et al., 2015). For any microstructural interpretation of MRI experiments, it is crucial to determine which contribution dominates at clinically feasible diffusion times, and which associated μm-level length scale can be in principle quantified.

Here we consider diffusion in human white matter (WM), transverse to major WM tracts. For the past decade, the focus of microstructural modeling has been on the intra-axonal compartment, where the nontrivial (fully restricted) diffusion was thereby related to the *inner* axonal diameters (Assaf and Basser, 2005; Assaf et al., 2008; Alexander et al., 2010), whereas the extra-axonal diffusion has been deemed trivial (Gaussian). This framework has served as the basis for a number of techniques (CHARMED (Assaf and Basser, 2005), AxCaliber (Assaf et al., 2008), ActiveAx (Alexander et al., 2010)) for axonal diameter mapping. Their outcomes were subsequently debated due to a notable (Innocenti et al., 2015), sometimes by an order-of-magnitude (Alexander et al., 2010), overestimation of human inner axonal diameters relative to their histological values of $\sim 1\,\mu$m (Aboitiz et al., 1992; Caminiti et al., 2009; Liewald et al., 2014; Tang and Nyengaard, 1997; Tang et al., 1997). This recently prompted an alternative suggestion (Fieremans et al., 2016; Burcaw et al., 2015) of the dominant role of non-Gaussian, time-dependent diffusion in the extra-axonal space, with the role of the intra-axonal space deemed trivial (negligible radial signal attenuation due to thin axons). Relevant parameters for the extra-axonal picture characterize the packing geometry in a bundle; e.g., the packing correlation length should give a measure of *outer* axonal diameters (Fieremans et al., 2016; Burcaw et al., 2015).

Since both alternatives have compelling arguments behind them and "fit the data well" (Alexander et al., 2010; Assaf et al.,

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