

Inferring millisecond-scale functional connectivity from tissue microstructure

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Target audience: MR scientists and neuroscientists interested in functional and structural brain connectivity; neuroradiologists;

Introduction: Quantifying voxel-averaged descriptors of cytoarchitecture and tissue microstructure, such as average axon diameters (AAD) or axon diameter distributions (ADD), using diffusion MRI can provide valuable information about the functional organization of normal and pathological nervous tissue (1). Nevertheless, measuring AADs across the whole brain is complicated by orientational effects of the local microanatomy. In this study we apply a recently proposed MRI technique for measuring the mean apparent propagator (MAP) to provide the zero-displacement probability of the diffusion propagator projected along the axes of the local anatomical reference frame defined by the diffusion tensor (2). From the MAP-MRI derived return-to-axis probability (RTAP) we estimate AADs, quantify their variations along white matter fibers, and discuss the feasibility of inferring average conduction velocities (ACVs) along these pathways. We propose a new measure we call the Mean Latency Matrix for quantifying whole-brain functional connectivity at a millisecond-scale, based on the non-invasive quantitation of microstructure with MAP-MRI.

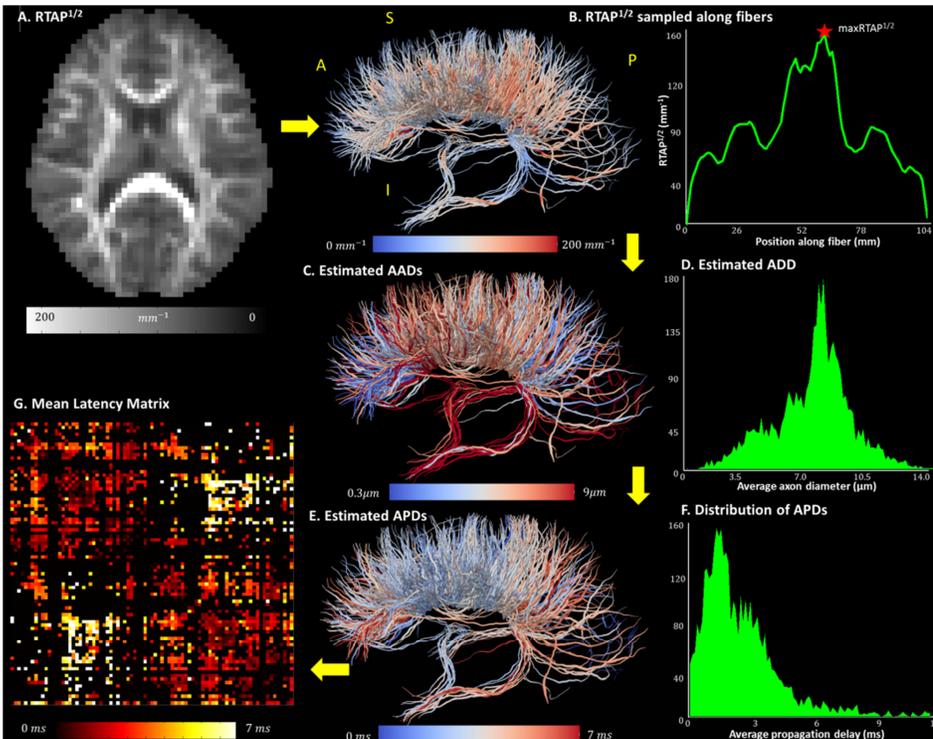


Figure 1: A. Axial RTAP^{1/2} image; B. Variation of RTAP^{1/2} (sagittal view) along interhemispheric fibers (left) and profile of RTAP^{1/2} along a fiber (right); C. AADs estimated using the maxRTAP^{1/2} along the fiber. D. ADD computed by binning all AADs for the entire brain (the multimodal distribution suggests different groups of axons). E. Estimated APDs for the fibers in C. F. Distribution of APDs for the whole brain. G. Mean Latency Matrix derived from whole brain APD measurements using 81 GM ROIs from Freesurfer.

incoherence, residual contributions from extracellular space, biased MR signal weighting from larger caliber axons, and membrane permeability/exchange. By quantifying the maximum RTAP along individual fibers, we can identify regions where these factors are minimized and the RTAP-based AAD estimate is reliable and physically meaningful: $AAD=2(\pi \max_{\text{fib}} RTAP)^{-1/2}$. Assuming constant AAD and g-ratio along the fiber, and a linear relation $ACV[\text{mm}/\text{ms}]=5.5AAD[\mu\text{m}]$ for myelinated axon populations (6), we can infer average action potential propagation delays ($APD=L/ACV$, with L =fiber length) along specific pathways and construct the Mean Latency Matrix (MLM).

Results and Discussion: As expected, the largest RTAP values were found in regions with high fiber coherence, such as the corpus callosum (Fig.1A). Fig.1D quantifies the whole-brain distribution of AAD as a histogram. From the average conduction delays (Fig.1E) the MLM was constructed using the Freesurfer anatomic segmentation scheme with 81 GM ROIs (Fig.1G). Variations of AAD in the corpus callosum and throughout the brain are consistent with previous studies (7). Apart from the aforementioned factors, potential errors in the RTAP-based AAD estimation could also be attributed to other cellular restrictions outside the axon. These contributions would also likely overestimate the AAD, and implicitly underestimate the average propagation delay. Therefore the resulting MLM can be treated as a lower limit for the millisecond-scale functional connectivity in the brain.

Conclusion: Our results suggest that it is possible to non-invasively infer information about the functional organization of the human brain from microstructural measurements using MAP-MRI. The proposed Mean Latency Matrix describes brain function at a millisecond-scale and could provide valuable neuropathological and functional information complementary to fMRI. Along with conventional measures of cognitive performance, they could help better understand and characterize complex neurological pathologies such as autism, depression or schizophrenia.

References: 1. Assaf et al., MRM 2008;59:1347-54; 2. Özarslan et al., Neuroimage 2013;78:16-32; 3. Dale et al., Neuroimage 1999;9:179-94; 4. Pierpaoli et al., ISMRM 2010;#1597; 5. Tournier et al., Neuroimage 2007;35:1459-72; 6. Waxman & Bennett, Nature 1972;238:217-9; 7. Aboitiz et al., Brain Res. 1992;598:143-53;

Theory and Methods: We scanned three healthy volunteers on a 3T MRI scanner using spin-echo diffusion-weighted EPI with full brain coverage, 3mm slice thickness, imaging matrix size 70x70, field-of-view 21x21cm², SENSE factor of 2, and TE/TR=94/5800ms. For each subject, 600 DWIs were acquired with multiple orientations sampling the sphere for each of the 6 b-values ($b_{\text{max}}=6,000 \text{ s}/\text{mm}^2$). The diffusion gradient pulse width and separation were $\delta=34\text{ms}$ and $\Delta=41\text{ms}$, respectively and $G_{\text{max}}=4.93\text{G}/\text{cm}$, resulting in an effective $q_{\text{max}}=0.45\mu\text{m}^{-1}$. A 1mm³ MP-RAGE scan acquired in the same session was used as an anatomical template for image registration and gray matter (GM) region-of-interest (ROI) segmentation using Freesurfer (3). After motion and eddy current correction of all DWIs (4), probabilistic fiber tractography (5) was performed to visualize and quantify the connectivity between GM ROIs, and MAP-MRI was applied to measure the propagator and its RTAP. Given the diameter of human axons ($\sim 5\mu\text{m}$) and the water diffusivity in the brain ($\sim 1.8\text{mm}^2/\text{ms}$) we expect water molecules to fully sample each axon during the 41ms diffusion time of our clinical experiment. Under these conditions, in regions of highly coherent fiber populations the RTAP can be related to the mean cross-sectional area of the cylindrical pore, which determines the AAD (2). However, in the RTAP-based calculation of the AAD, overestimations can occur due to: fiber