Splitting one dimension into four: progressing from diffusion distributions into diffusion tensor distributions

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Introduction: To this date, relaxation-diffusion correlation studies have relied on the Stejskal-Tanner experiment [1] where the signal is encoded for diffusion using a pair of collinear gradient pulses. Diffusion-encoding along a single direction convolves the contributions of isotropic and anisotropic diffusivities into a single 1D distribution of effective diffusivities, thus preventing the unambiguous quantification of microscopic environments within heterogeneous anisotropic materials. To overcome this difficulty, we translated data acquisition and processing schemes from multidimensional solid-state NMR into the field of diffusion NMR [2-4], and devised a new framework wherein microscopic heterogeneity is resolved with 4D diffusion tensor **D** distributions rather than 1D scalar diffusion distributions. Here, we demonstrate our novel framework with an MRI protocol that quantifies the microscopic heterogeneity of the living human brain in a 5D space of R_2 and axisymmetric **D**.

Methods: Data was acquired at multiple echo-times and axisymmetric diffusion-encoding tensors, parameterized by four independent dimensions: size, orientation, and normalized anisotropy. This yields 5D datasets that are converted to spatially resolved 5D R_2-**D** nonparametric distributions using an unconstrained Monte Carlo approach. Different acquisition protocols were tested on healthy volunteers using a custom spin-echo diffusion-weighted EPI sequence. The shortest protocol resulted in a scan time of 15 min.

Results and discussion: Pure component voxels containing either white matter WM, gray matter GM, or cerebrospinal fluid CSF give rise to clearly distinctive R_2-**D** distributions that accurately capture the main microscopic features of the various tissues (CSF: high isotropic diffusivity D_{iso}, low normalized diffusion anisotropy D_Δ, low R_2; WM: low D_{iso}, high D_Δ, high R_2; GM: low D_{iso}, low D_Δ, high R_2). As shown in Fig. 1, voxels comprising mixtures of GM, WM, and GM are characterized by multimodal distributions wherein the contributions from distinct tissue environments can be easily discerned. The rich information contained within the voxel-wise R_2-**D** distributions is visualized as sets of statistical parameter maps, or arrays of smooth Orientation Distribution Functions.

Conclusion: We demonstrate a protocol to resolve broad 1D diffusion distributions into four distinct dimensions of D_{iso}, D_Δ, and diffusion tensor orientation. In the context of *in vivo* brain studies, 5D R_2-**D** distributions can separate and characterize sub-voxel tissue environments without assumptions on the number or properties of the individual environments. Good quality data can be acquired within a scan time of 15 min, meaning that the proposed protocol displays great potential for clinical studies dealing with tissue heterogeneity (*e.g.* tumor infiltration in healthy tissue).

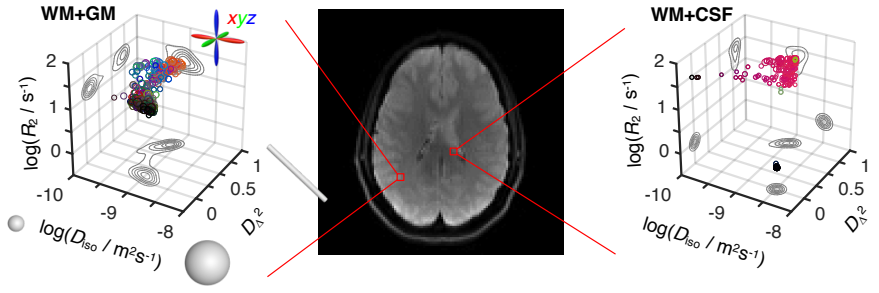

Fig.1: 5D R_2-**D** distributions shown as logarithmic plots of the isotropic diffusivity D_{iso}, squared normalized diffusion anisotropy D_Δ^2, and R_2, with circle area proportional to the weight of the corresponding $P(R_2,\mathbf{D})$ coordinates. Here, we display the distribution from two voxels; one containing a mixture of white matter WM and gray matter GM, and another containing both WM and cerebrospinal fluid CSF.

References: [1] Stejskal, J. Chem. Phys. (1965). [2] de Almeida Martins, Phys. Rev. Lett. (2016). [3] de Almeida Martins, Sci. Rep. (2018). [4] Topgaard, NMR Biomed. (2019).