Isotropic and Anisotropic Measures of Anomalous Diffusion in Chronic Stroke Subjects

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Target Audience Those interested in new tools to probe neural tissue complexity, degeneration, and plasticity by exploiting anomalous diffusion.

Purpose In this study, we make use of anomalous diffusion measures in chronic stroke patients to better characterize tissue complexity in the left hemisphere, local to the necrotic region, which often results in language deficits[1]. To our knowledge, this is the first report to demonstrate application of the Continuous Time Random Walk (CTRW) theory and Entropy to model *in vivo* anomalous diffusion measurements in neurodegenerative subjects. In conventional diffusion MRI (DWI) studies, the signal decay is modeled as $exp(-bD)$, where D is the diffusion coefficient and b is the pulse sequence controlled parameter. Typically, the b-value chosen for the experiment is ~1,000 s/mm^2, in which the signal decay is reasonably mono-exponential, even for restricted and tortuous white matter (WM) and gray matter (GM) regions of interest (ROI). However, anomalous diffusion, which deviates from the mono-exponential model at b-values > 1000 s/mm^2, has been reported in several DWI studies of neural tissue[2-4]. An approach to capture the features of anomalous diffusion is the (CTRW) theory which relaxes *a priori* assumptions regarding the governing statistics to encapsulate both Gaussian and non-Gaussian diffusion processes[5].

Methods In the CTRW framework, the characteristic function (i.e., Fourier transform of the diffusion propagator) is described by the Mittag-Leffler function (MLF), which through the fractional order stretching exponent, α, is able to capture diffusion decay processes that are anomalous to indicate sub-diffusion when $\alpha < 1$; however, when $\alpha = 1$, the MLF returns to a mono-exponential decay to indicate Gaussian diffusion[4]. Furthermore, using Entropy, H, we are able to quantify the 'information' in the characteristic function in order to distinguish the 'complexity' of WM, GM, and lesion ROIs[4]. Two end-stage chronic stroke subjects were scanned on a 3T Siemens Trio system. DW SE-EPI experiments were performed with the following parameters: TE = 102 ms, TR = 6 s, Δ = 41.2 ms, δ = 40.6 ms, b-values = 0, 500, 1000, 3000, 4000 s/mm^2, 12 non-collinear diffusion weighted directions, NA = 3, in-plane resolution = 2x2 mm, slice thickness = 4 mm, 20 slices, scan time ~ 12 min. Using custom Matlab code, the data were fit on a voxelwise basis to the MLF and computed the entropy, H, of the signal decays. D, α, and H were each fit to tensor constructs to produce isotropic (mean of eigenvalues in Fig. 1) and anisotropic (values along a specific eigenvector in Fig. 2) parameter maps. The direction encoded color (DEC) maps in Fig. 2, show the orientation of the eigenvectors associated with maximal diffusivity (D along primary eigenvector), maximal sub-diffusion (α along the tertiary eigenvector), and maximal complexity (H along primary eigenvector).

Results ROIs were selected in the longitudinal fasciculus affected by the lesion and the contralateral WM tract for numerical comparisons shown in Tables 1 and 2. In Fig. 1 (left column), the isotropic D maps show the chronic stroke region has unrestricted diffusion (~3x10^{-3} mm^2/s) as brain tissue has been replaced with CSF, however WM / GM contrast is not visible. In Fig. 1 (middle column), the isotropic α maps show the lesion as Gaussian ($\alpha \sim 1$), but also differences in anomalous sub-diffusion between GM and WM in which the WM is more sub-diffusive, or anomalous, than the GM. In the region of the stroke in subject 1 (top row) there is a thin ribbon of tissue that has a reduced mean D (~2.1x10^{-3} mm^2/s) from the CSF (~3.0x10^{-3} mm^2/s), but with α values (~0.92) similar to contralateral GM ($\alpha \sim 0.90$). In subject 2 (bottom row) there are two islands of reduced mean D (~1.4x10^{-3} mm^2/s) from the CSF (~3.0x10^{-3} mm^2/s), but with α values (~0.71) comparable to contralateral WM (~0.73). In Fig. 1 (right column), the isotropic H maps demonstrate GM/WM entropy differences, with WM having more information content. In both patients, the suspect region appears with lower entropy, or information, compared to GM or WM. In Fig. 2 (left column), the fractional anisotropy (FA) of D demonstrates the longitudinal fasciculus in the left hemisphere which appears as a connected, albeit diminished, tract (FA ~ 0.14). However, in Fig. 2 (middle column) the FA of α indicates a complete loss (FA ~ 0.03) in the principal direction for sub-diffusion along this tract, appearing disconnected which is confirmed by reduced FA of H (FA ~ 0.05), Fig. 2 (right column).

Discussion A great deal of effort has been spent recently to identify white matter tracts using Diffusion Tensor Imaging (DTI) and higher order diffusion models[3]. These methods attempt to identify crossing and intersecting fibers to create more accurate descriptions of WM connectivity. Utilizing the information provided by anomalous diffusion in high b-value acquisitions, it is possible to characterize the quality of the WM connectivity in brain tissue. For example, in this study, FA(D) indicates the longitudinal fasciculus remains connected, however, the complementary anisotropic information provided by α and H suggest the tissue microstructure is severely compromised, perhaps due to neurodegenerative processes or cell death. Finally, the isotropic measures of α and H produce results in which WM, GM, and lesion contrast are visible in one image, which is not apparent with the classical measure of mean D.

Conclusion We have demonstrated, to our knowledge, the first use of the CTRW and entropy measures to characterize anomalous diffusion in a chronic stroke population, which represents the end-stage decay of brain tissue. The output from this pilot study is to apply these same anomalous diffusion measurements in the (early stage) acute stroke patient cohort to identify tissue that is at increased risk of cell death which results in language deficits. Furthermore, as the stroke patients undergo treatment and therapy, D, α, and H will be utilized synergistically to identify evidence of brain plasticity.

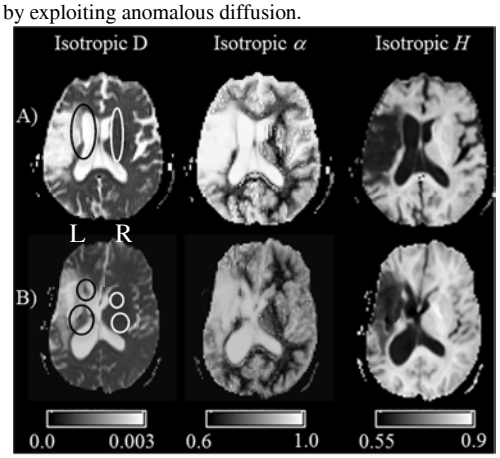

Fig. 1: ROIs and Isotropic parameter maps of the mean estimations of D (mm^2/s), α, and H for A) stroke subject 1 and B) stroke subject 2.

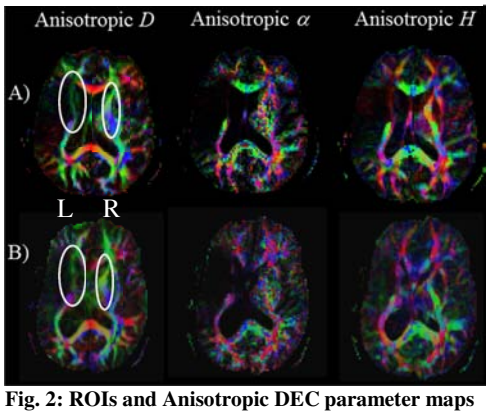

Fig. 2: ROIs and Anisotropic DEC parameter maps modulated by the FA estimations for D, α, and H for A) stroke subject 1 and B) stroke subject 2.

Table 1: Isotropic parameters for WM ROIs circled in Fig. 1 A) stroke subject 1 and B) stroke subject 2.

	Mean D (x10^{-3} mm^2/s)	Mean α	Mean H
A) L	2.1±0.1	0.92 ± 0.01	0.65 ± 0.01
R	0.7± 0.2	0.65 ± 0.04	0.83 ± 0.01
B) L	1.4 ± 0.3	0.71 ± 0.03	0.81 ± 0.02
R	0.8 ± 0.1	0.73 ± 0.03	0.82± 0.01

Table 2: Anisotropic parameters for WM ROIs in Fig. 2 A) stroke subject 1 and B) stroke subject 2.

	FA D	FA α	FA H
A) L	0.14±0.04	0.03 ± 0.02	0.04 ± 0.01
R	0.64± 0.14	0.42 ± 0.15	0.17 ± 0.04
B) L	0.17 ± 0.06	0.02 ± 0.01	0.05 ± 0.01
R	0.40 ± 0.12	0.36 ± 0.13	0.09 ± 0.01

References [1] Thompson et al. Neuropsychologia 2010. [2] De Santis S, et al. Magn Reson Med 2011. [3] Ozarslan E, et al. Neuroimage 2012. [4] Ingo C, et al. Magn Reson Med 2013. [5] Metzler R & Klafter J. Phys Rep 2000.