A Stretched-Exponential Model of Distributed Diffusion Rates in Brain

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Synopsis: A stretched-exponential model of water diffusion was developed to account for the non-exponential signal-attenuation commonly observed in diffusion-weighted experiments in cerebral cortex. The stretched-exponential model makes no assumptions about the number of sub-voxel proton pools. One derives from it a statistical measure of the continuous sub-voxel distribution of diffusion coefficients. Fits of the stretched-exponential model to data from the cerebral cortex in rats were significantly better in 85% of voxels compared to bi-exponential fits. Whole-brain maps showed high contrast in sub-cortical structures, suggesting this model as a new technique for diffusion-related contrast.

Introduction: Experience with diffusion-weighted imaging shows data to be consistent with a multi-compartmental theory of water diffusion (1). The source of this non-exponential behavior is a topic of debate, because cerebral cortex is characterized by microscopic tissue heterogeneity. The common problem of assigning the source of non-exponential decay terms to water pools in cerebral cortex was approached with a general statistical method in this work, with the goal of obtaining a measure of this sub-voxel heterogeneity and a measure of the local distribution of diffusion coefficients. Understanding the effects of sub-voxel heterogeneity in diffusion would be valuable in non-invasive assessment of disease processes in the brain such as cancer (2). The stretched exponential function (3) was developed to describe this decay as being composed of a continuous distribution of sources that diffuse at different rates, with no assumptions made about the number of participating sources. The model assumes there is a continuous distribution of intra-voxel diffusion coefficients **D**. The signal attenuation $\mathbf{S/S_0}$ under the stretched-exponential model takes the form: $\mathbf{f=S/S_0 = exp\{-(b\times DDC)^{\alpha}\}}$, **[Eq.1],** where the b-value is determined by the imaging gradients in a spin-echo diffusion- weighted imaging (DWI) pulse sequence. The parameter α measures the homogeneity in the intra-voxel distribution of D. When α approaches 1, the distributed diffusion coefficient (DDC) approaches D, which is the standard "ADC" in the case of mono-exponential signal attenuation. Fig. 1 shows that DDC determines the point at which the signal attenuation curves, resulting from signal decays with different α values, are equal. (Arrows indicate decreasing α from 1.0 in increments of 0.2). If b×DDC<1, higher values of α result in reduced signal attenuation. At high values of b×DDC, signal attenuation increases when α increases. If b×DDC = 1, DDC is the ADC calculated at that b-value. The partial derivative of the stretched-exponential function f=S/S0 with respect to α is shown in Fig. 2. It is notable that f is most sensitive to changes in α when b×DDC is either greater or less than one. The sensitivity of f to α depends on the range of α, being maximally sensitive if α=1. The value $E(D^n)$ is the n^{th} moment of the distribution of D, (not to be confused with DDC), and can be calculated by integrating D^n **exp** $\{-(b\times DDC)^{\alpha}\}$ over all D to yield:

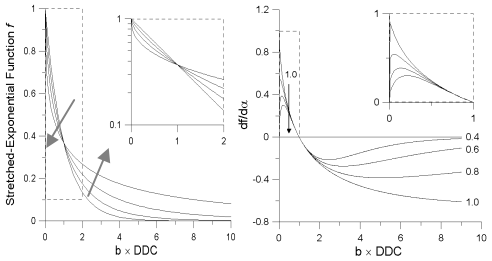

Fig.1: *Stretched exponential function f.* **Fig.2:** *df/dα*

$\mathbf{E(D^n) = (DDC/\alpha)(\Gamma(n/\alpha)/\Gamma(n))}$. **[Eq. 2].** The significance of the first three moments with regard to the intra-voxel distribution of D is most readily understood: $E(D^1)$ is the average value of the distribution, $E(D^2)$ describes the number of diffusion coefficients lying to either side of the average value and $E(D^3)$ describes the extent to which the contributing components lie to one side of the average. The gamma-function is defined as Γ in Eq.2.

There are therefore five useful parameters that characterize intra-voxel diffusion with this model: α, DDC, and the first three moments of the distribution of D. All of these parameters are obtained in a fit of the stretched exponential function to the data. The goal of this work was to determine whether the stretched-exponential model was well fit to signal attenuation curves from voxels taken from the cerebral cortex. We also explored the possibility of image contrast with the stretched-exponential model of diffusion using maps of α, DDC, and the first three moments of the intra-voxel distribution of D.

Materials and Methods: Six healthy male Sprague-Dawley rats were imaged. The rats were anesthetized using urethane (1.2 g/kg), with 0.1 ml booster injections as needed, and were immobilized with a fiberglass bite bar. A Stejskal-Tanner pulse sequence was applied in a Bruker Biospec 3T scanner using a 64x64 matrix, FOV of 6.4 cm, axial slice thickness of 1.0mm, and TE of 43 ms. A surface RF coil was used to obtain sufficient SNR in the imaged region. The b-value was varied from 0 to 6500 s/mm^2 in increments of 500 s/mm^2, with a diffusion time of 27 ms, and b- values were randomly chosen in the read-gradient direction. Two averages were obtained with each b-value. The data was fit with the stretched-exponential model (Eq.1) on a voxel-wise basis, using a nonlinear least-squares method developed for AFNI. An ROI was drawn to cover the cortical ribbon, as shown in Fig. 3. To determine if the stretched-exponential was as well fit to the cortical data as was the common bi-exponential model, we fitted the bi-exponential model to the data as well. The sum-of-squared residuals (SSR) was calculated for each fit, and a likelihood ratio was computed based on the likelihood function of each model. If the log likelihood ratio (Ls/Lb) was positive, the stretched-exponential model was considered better fit to the data.

Results: The mean value of SSR of the stretched-exponential fit of the data (0.043) was less than that of bi-exponential fit (0.045). The likelihood ratio between the stretched- and bi-exponential fits for 2552 voxels (six rats) is shown in histogram form in Fig. 4. 85% of signal attenuation curves were better fit with the stretched-exponential model than with the bi-exponential model. While α maps show some distinction between cortical gray matter and white matter, (with regions of mostly cortical gray matter having higher α values), the most prominent contrast occurs in the DDC and $E(D^n)$ maps. DDC maps had high contrast between the corpus callosum and surrounding brain, but other sub-cortical structure was particularly visible in maps of D^3, suggesting that these regions contained off-center intra-voxel distributions of D.

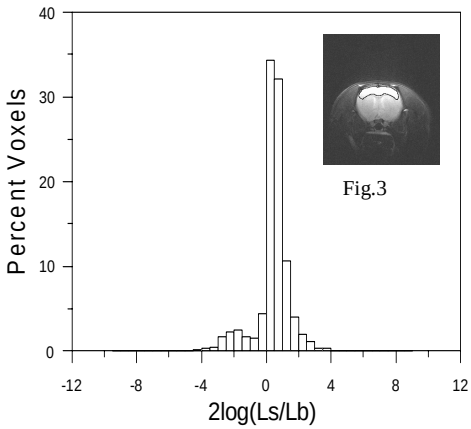

Fig.4: *Likelihood ratio between stretched- and bi-exponential fits to rat cortex.*

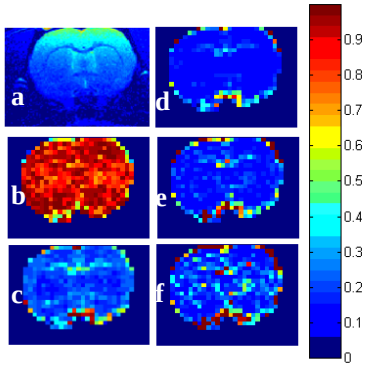

Fig.5: *Maps of stretched-exponential parameters: a. T1-weighted anatomical image, b. α, c. DDC, and d., e., and f. are the first three moments of D.*

Conclusions: The stretched-exponential model was shown to be significantly better fit than the common bi-exponential model to data from voxels taken from cerebral cortex. In practice, one would prefer the stretched exponential model if no information about the number of diffusing components exists, because it does not assume the number of compartments present. Whole-brain maps revealed contrast between structures and surrounding brain that were different for each parameter, suggesting their combined use in fully characterizing heterogeneous sub-voxel diffusion.

References:

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