Low-Pass Filter Effect of Finite Gradient Duration on Time-Dependent Diffusion in the Human Brain

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Purpose: **To determine brain microstructural parameters from time dependent diffusion in a clinical setting.** Time dependence of the diffusion coefficient, $D(t)$, observed with both oscillating[1,2] and pulse-gradient[2,3] methods, reflects tissue complexity[4] on a μm scale. In particular, $D(t)$ can provide novel biophysical contrast by revealing the strength and the correlation length of the restrictions to diffusion.[4] Here we show that this information can be recovered even when the duration δ of diffusion gradient pulses is not infinitely narrow, and design the framework to extract these parameters from a realistic clinically measured $D(t, \delta)$. Technically, $D(t, \delta)$ can be viewed as the low-pass filtered "ideal" $D(t)$. We apply this framework to human brain DTI measurements[3] along white matter tracts, and find that the predicted δ-dependence agrees with experiment without any adjustable parameters, and furthermore obtain the correlation length l_c that matches the distance between varicosities found along axons.[5]

Methods: **Theory.** Recently, it was shown that the way the instantaneous diffusion coefficient $D_{\rm inst}(t) = D_\infty + A/t^\vartheta$ approaches its bulk value D_∞ is characterized by the dynamical exponent ϑ related to the disorder class and the spatial dimensionality.[4] The effect of finite δ can be evaluated via a low-pass filter[6] $F(\omega)=16(\sin(\omega t/2)/\omega)^2(\sin(\omega\delta/2)/\omega)^2$ applied to the velocity autocorrelation function $D(\omega)$ in the frequency domain. The convolution of $D_{\rm inst}$ with F, performed via rotating the integration contour in the complex plane of ω, gives $D(t,\delta) = D_\infty - \frac{A\vartheta}{\delta^2(t-\delta/3)}[-2f(t) + f(t-\delta) - 2f(\delta) + f(t+\delta)]$, where $f(t) = -\frac{1}{\pi}\Gamma(-\vartheta)\Gamma(\vartheta-3)\sin(\pi\vartheta)\,t^{3-\vartheta}$, and Γ is Euler's Γ-function, for all possible values of ϑ. We observe that for $0<\vartheta<1$, the asymptotic A/t^ϑ dependence is indeed recovered for $t \gg \delta$; for $\vartheta=1$, the log singularity[7] $\ln(t/t_c)/t$ changes to $\ln(t/\delta)/t$, thereby masking out any correlation length l_c below $\sim(D_\infty\,\delta)^{1/2}$ (the effect of the low-pass filter); and for $1<\vartheta<2$, the exponent ϑ manifests itself in the $1/\delta^{(\vartheta-1)}$ dependence *on the filter width*, rather than in the $1/t^\vartheta$ dependence on diffusion time. We then apply our general result to $D_{||}(t, \delta)$ measured[3] parallel to major axonal tracts, for which the exponent ϑ = ½ would reflect short range disorder of restrictions in a one-dimensional geometry.[4] For ϑ=½, the finite-δ measurement would yield

ROI	D_∞(μm²/ms)	A(μm²/ms½)	$l_c^{||}$(μm)	R^2
FA > 0.3	0.987±0.016	1.16±0.13	4.15±0.47	0.9175
FA > 0.4	1.009±0.017	1.37±0.14	4.82±0.50	0.9304
FA > 0.5	1.056±0.019	1.58±0.17	5.44±0.58	0.9262
FA > 0.6	1.119±0.023	1.77±0.21	5.93±0.70	0.9117

Table 1. Parameters of $D_{||}(t, \delta)$ obtained using eq [1] fit to data from scan 1 (with fixed δ = 20 ms).

$$D_{||}(t,\delta) = D_\infty + \frac{8A}{15\delta^2\left(t-\frac{\delta}{3}\right)}\left[-2t^{\frac{5}{2}} + (t-\delta)^{\frac{5}{2}} - 2\delta^{\frac{5}{2}} + (t+\delta)^{\frac{5}{2}}\right] \quad \textbf{[1]}$$

$$\cong D_\infty + \frac{2A}{\sqrt{t}}\left[1 + O\left(\sqrt{\delta/t}\right)\right], \qquad \text{for } t \gg \delta. \quad \textbf{[2]}$$

Additionally, we estimate the disorder correlation length $l_c^{||} = 2A\sqrt{\pi/D_\infty}$ as the average distance between restrictions along axons.

MRI. Diffusion measurements were performed on five healthy subjects (4 males, 1 female, 25-41 years old) using a 3T Siemens Tim Trio with a 32 channel head coil.[3] The stimulated echo DTI sequence provided by the vendor (WIP 511E) was used to perform two different scans for each subject. For both scans, we acquired five b=0 images and b=500 s/mm² images along 20 directions with isotropic resolution of (2.7 mm)³ and a FOV of (221 mm)². In scan 1, we measured $D_{||}(t, \delta)$ with varied t and a fixed δ: t = 55-600 ms, δ = 20 ms, TE = 100 ms, TR = 7000-10200 ms; in scan 2, we fixed t = 100 ms and varied δ = 10, 20, and 37 ms, with TE/TR = 100/7000 ms. To observe the influence of increasing fiber alignments, a series of ROIs were created based on four minimum FA thresholds ranging from 0.3 to 0.6. The ROIs for a representative subject are shown in **Fig. 1A**.

Results and Discussion: Using data in scan 1, we observe that $D_{||}(t, \delta)$ decreases with t, asymptotically consistent with the limit [2], dashed lines in **Fig. 1B**. However, the **systematic bend** in the curves, pronounced at short $t \sim \delta$ (large $1/\sqrt{t}$), reveals the filter effect, captured well via eq [1]. Corresponding fit parameters are shown in **Table 1**, where the estimated values of $l_c^{||}$ increase with fiber alignment. This increase, as well as the $l_c^{||}$ values, are consistent with the 3–6μm spacing between axonal varicosities,[5] whose projection along the tract direction should increase with FA. Varicosities become more pronounced in stroke[8] and in traumatic brain injury,[9] providing potential diagnostic value to the correlation length $l_c^{||}$ and the strength A of restrictions. To further illuminate the δ-dependence, **we predicted scan 2 results** based on parameters from scan 1 (**Table 1**), capturing the systematic decrease of $D_{||}(t, \delta)$ with increasing δ (solid lines versus data in **Fig. 1C**). This was done without any adjustable parameters, as the filter properties are known, and tissue properties have been found in scan 1.

Conclusion: The consistency between scans 1 and 2 underscores the validity of the long-time $D(t)$ framework,[4] the presence of short-range disorder along axons captured by the exponent ϑ=½, and the low-pass filter effect on $D(t)$ by finite-duration pulses. Regardless of the finite δ, we are still able to evaluate microstructural parameters, such as correlation length $l_c^{||}$ and the strength A of restrictions along axons, using time-dependence of the clinically measured diffusion coefficient $D(t, \delta)$. Future work will focus on optimizing acquisition protocols to explore the feasibility of potential clinical applications in stroke, TBI, and neurodegenerative diseases.

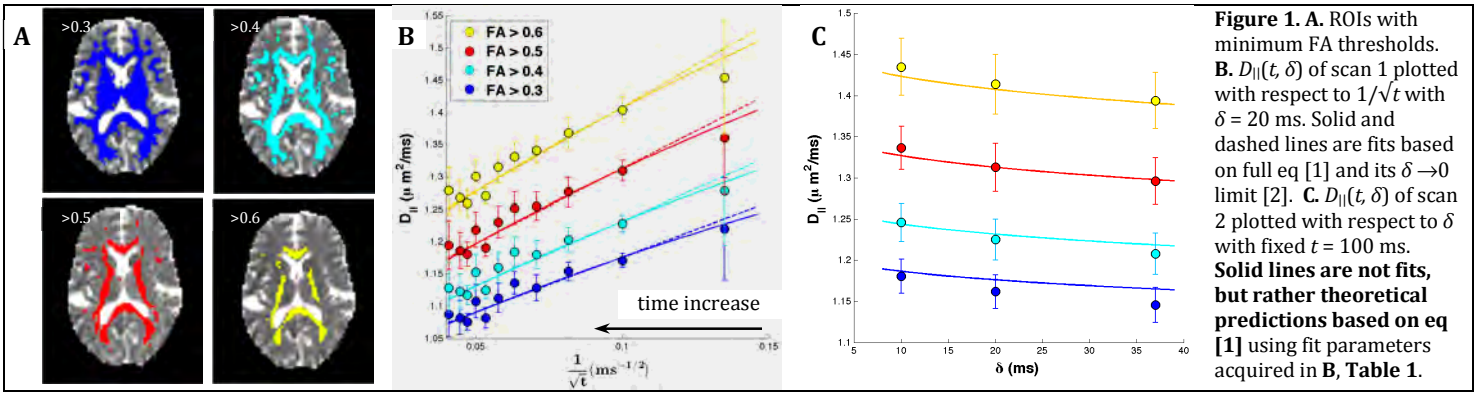

Figure 1. A. ROIs with minimum FA thresholds. **B.** $D_{||}(t, \delta)$ of scan 1 plotted with respect to $1/\sqrt{t}$ with δ = 20 ms. Solid and dashed lines are fits based on full eq [1] and its $\delta \to 0$ limit [2]. **C.** $D_{||}(t, \delta)$ of scan 2 plotted with respect to δ with fixed t = 100 ms. **Solid lines are not fits, but rather theoretical predictions based on eq [1]** using fit parameters acquired in **B**, **Table 1**.

References: 1. Does, *et al. MRM* 49, 206 (2003). 2. Baron, Beaulieu. *MRM* 72, 726 (2014) 3. Burcaw, *et al.* Proc ISMRM 22, 4434 (2014); submitted, *NI* (2014). 4. Novikov, *et al. PNAS* 111, 5088 (2014). 5. Shepherd, *et al. PNAS* 99, 6340 (2002) 6. Callaghan, *Principles of NMR Microscopy,* Oxford (1994). 7. Burcaw, et al. Proc ISMRM 21, 495 (2013). 8. Li, Murphy. *J Neurosci* 28, 11970 (2008) 9. Tang, *et al. Exp Neurol* 223, 364 (2012). Work supported by NIH R01 NS088040.