Singular behavior of time-dependent diffusion in a fiber bundle geometry due to a disordered packing

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Introduction: How important is disorder in the packing geometry of an axonal fiber bundle from the standpoint of a diffusion measurement? Here we show that the randomness in fiber arrangement in a bundle crucially affects diffusion in the extra-axonal space, which can have implications for both pulse-gradient[1] and oscillating gradient methods[2] of characterizing white matter fiber integrity. Specifically, we focus on the time-dependence of the diffusion coefficient, $D(t)$, in the extra-axonal space by diffusion measurements in a phantom made of randomly packed parallel aligned impermeable fibers and Monte-Carlo simulations. We show that $D(t)$ transverse to a fiber bundle has a *logarithmic singularity* at long diffusion times,

$$D(t) \equiv \frac{\langle x^2\rangle}{2t} \simeq D_\infty + c\ln\left(\frac{t}{t0}\right)/t, \quad t \gg t_0. \qquad (1)$$

This singularity is a consequence of *short-range disorder* in the fiber packing. As axons are ~1μm in diameter, almost any measurement is in long-time limit, and hence the above singularity may significantly affect the interpretation of time-dependent diffusion-based methods of evaluating fiber integrity, as described below.

Methods: *Theory.* As recently shown[3], the power law exponent ϑ describing the approach of the tortuosity limit D_∞ can yield information about the type of disorder in a system. This exponent appears both in the *instantaneous* diffusion coefficient $D_{inst}(t)$, and in OGSE $\mathcal{D}(\omega)$

$$D_{inst}(t) \equiv \frac{1}{2}\frac{\partial}{\partial t}\langle x^2\rangle = D_\infty + a t^{-\vartheta} + \cdots \quad \Leftrightarrow \quad \mathcal{D}(\omega) = D_\infty + b|\omega|^{\vartheta} + \cdots \qquad (2)$$

In two dimensions, $\vartheta = 1$ for the most commonplace random packing characterized by short-ranged disorder in fiber placement[3]. The integration[3,4,5] of $D_{inst}(t)$ up to t and dividing by t yields the $\ln t/t$ behavior of $D(t)$ in Eq. (1) above. Conversely, for any more ordered arrangement (e.g. periodic), $\vartheta > 1$, yielding $D(t) \sim D_\infty + c/t$. Hence, in a $D(t)$ measurement, *the effect of disorder is in the extra* $\ln t$ *factor.*

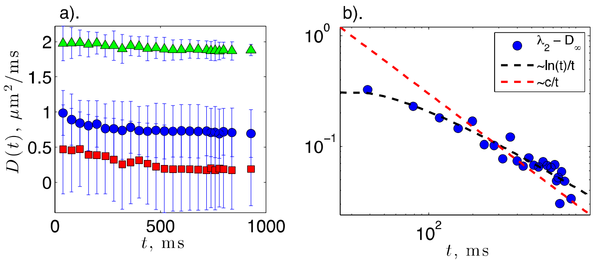

Figure 1: **a**) Diffusion tensor eigenvalues $\lambda_1 > \lambda_2 > \lambda_3$ measured in the phantom, as function of diffusion time *t*. **b**) Taking $D(t)=\lambda_2$, we fit it to Eq (1), and show the difference $D(t)$-D_∞ in log-log scale. The systematic slope change relative to the $1/t$ fit is a hallmark of logarithmic singularity.

Phantom Construction. The diffusion phantom for this study was constructed with approximately 195,000 Dyneema® fibers tightly held together with a shrinking tube measuring 8 cm long. The fibers are 17±2.6 μm in diameter, ultrahydrophobic and impermeable to water. The fiber bundle was suspended in a 1.5 L plastic bottle filled with a distilled water solution of 0.09% w/v NaCl to reduce B_1 field inhomogeneities.

MRI Measurements. Imaging was performed at 15°C on a 7T Siemens clinical MRI scanner using a 28 channel knee coil. DTI was carried out using a STEAM sequence which allows for long diffusion times while minimizing echo attenuation caused by T2 relaxation. Twenty five measurements were performed at b values of 0 and 500 in 20 directions, each with TE of 57 ms and TM ranging from 10ms to 1000 ms, corresponding to diffusion times, *t,* of 38.5 ms to 1028.5 ms. Three slices of resolution 3 mm × 3mm × 10 mm were used. The fiber bundle was placed parallel to the B_0 field to eliminate the possibility of internal field inhomogeneities.

Results: The DTI eigenvalues are plotted *vs t* in Fig. 1a. We focus on the second eigenvalue, $D(t) = \lambda_2$. Fig. 1b shows a plot of $D(t)-D_\infty$ vs t on a log-log scale, along with a fit of $D(t)-D_\infty$ to $c\ln(t/t_0)/t$ (black dashed line) and a fit to c/t (red dashed line), showing clearly that the c/t fit is insufficient to properly describe the data. Fig. 2a and b show the same $D(t)$ data plotted with respect to $1/t$ and $\ln(t/t_0)/(t/t_0)$, respectively. In Fig. 2a, a slight curve can be seen in the data indicating the logarithmic singularity. Fig. 2b shows that the bend is removed when plotted with respect to $\ln(t/t_0)/(t/t_0)$, $t_0 = 11$ms. Fig. 2c and d show Monte Carlo simulation data using a free diffusion coefficient of 2 μm^2/s, and fiber size distribution centered around 17 μm, with $t_0 = 7.3$ms, in agreement with experiment.

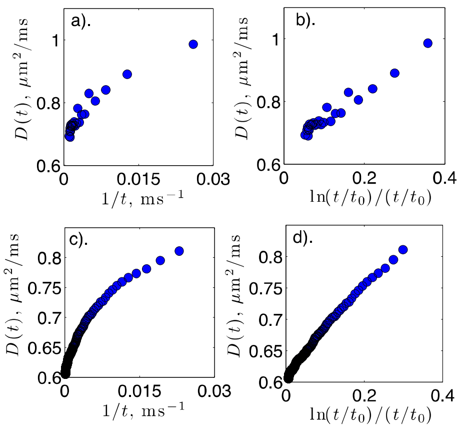

Figure 2: a) This singularity is also manifest in the "bend" in $D(t)$ vs. $1/t$ using $\lambda_2(t)$ from Fig.1. **b)** The logarithmic "bend" straightens up when $D(t)$ is replotted with respect to $\ln(t/t_0)/t$. **c) and d)** The same as for a and b, but with MC simulated data.

Discussion: *Implication for PGSE:* The diffusion restricted inside axons, giving the $1/t$ contribution, is used[1] to probe internal diameter distribution. However, as we have shown, the t-dependence in the extra-axonal space is more relevant, as $\ln(t)/t$ eventually exceeds $1/t$ in long-t limit. Hence, modeling the disorder in extra-axonal space is essential for interpreting such measurements.

Implication for OGSE: The non-analytic $\ln(t)/t$ in $D(t)$ translates into linear behavior in $|\omega|$ (a sharp kink in $D(\omega)$ for near $\omega = 0$). Indeed, such sharp non-parabolic behavior is clearly seen is recent OGSE measurements in brain [Fig 6 of ref 6], which may indicate 2-dimensional disorder in extracellular space. For ordered arrangements, or for confined diffusion (e.g. inside axons), the $1/t$ behavior in $D(t)$ translates into ω^2 in $D(\omega)$.[2,4,7] This parabolic behavior will be less relevant than $|\omega|$ at small ω and the effect of packing disorder will again dominate over that of confined water.

Conclusions: The logarithmic singularity in two-dimensional diffusion has been demonstrated for a first time as a hallmark of disordered packing geometries. This singularity dominates the time-dependence of diffusion across axonal fiber bundles and should be included in any quantification scheme for adequate fiber characterization.

References: **1.** Assaf, Y *et.al. MRM* 59 1347 (2008). **2**. Gore, J *et.al. NMR Biomed.* 23 745 (2010) **3.** Novikov, DS *et al.* preprint http://arxiv.org/abs/1210.3014 (2012). **4.** Novikov DS & Kiselev VG, NMR Biomed 23, 682 (2010). **5.** Novikov DS & Kiselev VG, JMR 210, 141 (2011). **6.** Portnoy, S *et.al. MRM* doi:10.1002/mrm.24325 (2012). **7.** Stepišnik, J *et.al. MRI* 25 517 (2007)