Time-dependent diffusion and kurtosis as a probe of tissue structure

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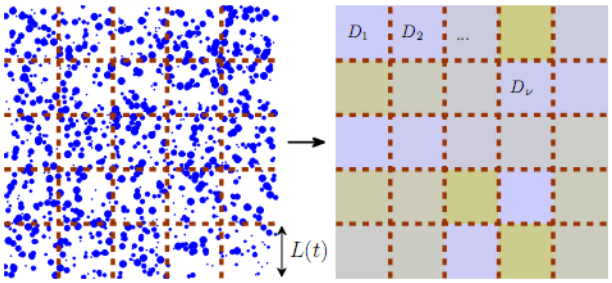
Introduction: Diffusion coefficient in tissues is known to depend on the diffusion time t. The particularly strong time dependence $D(t)$ has been demonstrated in cartilage [1], packed red blood cells [2], gray matter [3], and tongue and heart muscles [4]. There exist two regimes for the time-dependence of $D(t)$. The short-time limit may be used to characterize individual restrictions (e.g. surface area of pore walls) [5,2]. However, it often requires prohibitively short times, especially for clinical DWI. Here we focus on the opposite, *long-time limit* of $D(t)$, and argue that this limit probes the degree of the structural order in a medium (tissue).

Results: At long t, the molecules travel across multiple structural features (e.g. membranes, cells with different local diffusivities). At this point, the spatial fluctuations of the tissue microstructure become essential, and the DWI signal becomes sensitive to whether the microarchitecture is regular (periodic) or random, and to the degree of such randomness. The effect of structural fluctuations on $D(t)$ can be elucidated by the following coarse-graining procedure in which the tissue is being gradually homogenized over the diffusion length $L(t)\sim t^{1/2}$ increasing with t.

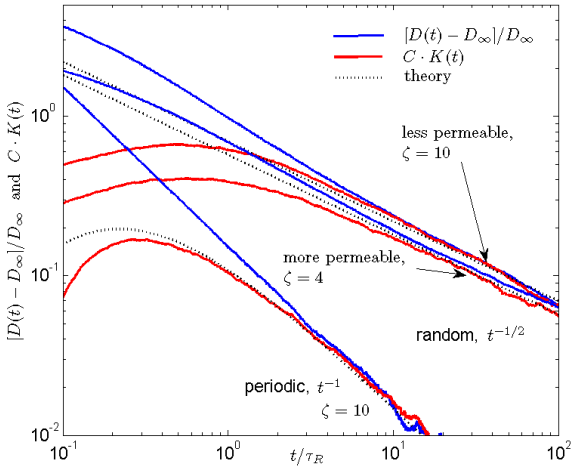
Here we outline our qualitative picture, which is backed by a rigorous derivation, for any permeable medium. For a given time t, the diffusion length $L(t)$ effectively splits a sample into domains of size $L(t)$ (see the top Figure), assigning a coarse-grained diffusion coefficient D_v to each domain (labeled by v=1,2,…). The values D_v are not all the same due to structural fluctuations. The "instantaneous" diffusivity $D(t)$ measured by DWI is then the ensemble average over the domains, $D(t) \equiv \langle D_v \rangle|_{L(t)}$. Remarkably, this quantity can be expressed via the variance $\langle(\delta D_v)^2\rangle$ of the domain diffusivities, and the tortuosity limit $D_\infty \equiv D(t)|_{t\to\infty}$:



$$\frac{D(t)-D_\infty}{D_\infty} \equiv \frac{1}{d}\times\frac{\langle(\delta D_v)^2\rangle|_{L(t)}}{D_\infty{}^2} \equiv C\cdot K(t) \qquad (1)$$

in d spatial dimensions. In the last equation we used the fact that the variance $\langle(\delta D_v)^2\rangle$ is also proportional to the diffusional kurtosis $K(t)$ [6] at the current time scale t. Indeed, t serves as an initial time scale for the coarse-grained medium, for which the short-time kurtosis limit [6] applies.

Our result (1) is very general and applies for *any permeable medium*, e.g. for any tissue with permeable membranes. It is asymptotically exact when the right-hand side is a small correction, which is always valid for sufficiently long t. Indeed, as $L(t)\sim t^{1/2}$ increases, the width of the distribution of the values $\{D_v\}$, caused by the presence of structural fluctuations, decreases with time due to the gradually improving self-averaging. This explains why *the genuine diffusion coefficient $D(t)$ cannot grow with t*, and any ADC increase is either a sign of magnetic heterogeneity or an artifact. Hence, the structural fluctuations determine the t-dependence of the diffusivity at long t via the scaling of the variance $\langle(\delta D_v)^2\rangle$ with the diffusion length $L(t)$.



In particular, the decrease in equation (1) is $D(t) - D_\infty \sim K(t) \sim 1/t^{1/2}$ for any random placement of flat permeable barriers with Poissonian fluctuations [7], and $D(t) - D_\infty \sim K(t) \sim 1/t$ for any periodic arrangement in any dimension (no fluctuations), generalizing [8]. The factor C in equation (1) depends on the statistics of the fluctuations and spatial dimensionality d. For d=1, we find C=1/2 for any Poissonian disorder (random barriers, randomly varying local diffusivity, etc) *irrespective of the microscopic details* such as barrier permeability, disorder correlation length etc. For the periodic case, C depends on the microscopic details. For identical periodic barriers in d=1, C=1/6.

Our results are confirmed in the bottom Figure by the one-dimensional Monte Carlo simulations of diffusion restricted by identical barriers with a fixed mean density n, arranged either in a periodic or in a random fashion. The power law exponent both for $D(t)$–D_∞ and $K(t)$ changes from -1/2 to -1 as the system becomes ordered. Time is in the units of the residence time τ_R=1/(2κn) in a typical interval between successive barriers, and the dimensionless parameter ζ=nD_0/κ [7] is a measure of barrier permeability κ, with D_0 the unrestricted diffusion coefficient. We observe that, as $t >> \tau_R$, equation (1) becomes asymptotically valid irrespective of the microscopic details (e.g. change in κ).

Discussion: The time-dependence of the diffusivity and kurtosis can be used to probe long range tissue architecture, and to determine how ordered or disordered it becomes at increasing length scales. The deviation of $K(\infty)$ from zero, when equation (1) does not apply, points at the fraction of water confined within cells with impermeable membranes; in that case, our relation applies separately to the contribution(s) of the unrestricted compartment(s). In particular, our exact results in d=1 for the factor C, together with the exact prefactor A in $D(t)$–D_∞=$At^{-1/2}$, can allow one to determine structural irregularities along fibrous tissues, such as the parameters of neuritic beading or axonal varicosities, from the t-dependent DWI.

Conclusions: In this work, we showed that: (i) the way $D(t)$ approaches its terminal value D_∞ is determined by how homogeneous the sample gradually becomes after being coarse-grained over an increasing set of diffusion lengths $L(t)$; (ii) both $D(t) - D_\infty$ and the time-dependent diffusional kurtosis $K(t)$ approach zero in the same way, equation (1), if water molecules can travel everywhere in a sample (permeable restrictions). Our results agree with Monte Carlo simulations in one dimension, and can be applied to characterize structural tissue composition over large diffusion lengths.

[1] Burstein *et al*, J Orth Res 11 (1993) 465. [2] Latour *et al*, PNAS 91 (1994) 1229. [3] Does *et al*, MRM 49 (2003) 206. [4] Kim *et al*, MRM 54 (2005) 1387. [5] Mitra *et al*, Phys Rev Lett 68 (1992) 3555. [6] Jensen *et al*, MRM 53 (2005) 1432. [7] Novikov *et al*, http://arxiv.org/abs/1004.2701. [8] Sukstanskii *et al*, JMR 170 (2004) 56.