The Problem with Peanuts

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Introduction: In the q-space NMR experiment the measured signal, $E(\mathbf{q})$, is the 3-D Fourier transform of the displacement probability distribution $p(\mathbf{R},\Delta)$ (1). When the direction of $\mathbf{q}$ is held fixed but its magnitude is varied, i.e. $\mathbf{q} = q\hat{\mathbf{r}}$, then $E(\mathbf{q})$ is the Fourier transform of the *marginal* displacement probability distribution, obtained by projecting $p(\mathbf{R},\Delta)$ onto $\hat{\mathbf{r}}$, a result which follows directly from the Fourier Slice Theorem. This projection process creates confusion when $E(\mathbf{q})$ data is used to infer microscopic-scale molecular displacements and complicates the definition and meaning of the apparent diffusion coefficient (ADC).

Macroscopic ADC Measurements: Following Callaghan (1), we consider a simple 2-D (or 3-D cylindrically-symmetric) anisotropic diffusion process in which we write the measured *apparent* mean-squared displacement, $< R^2 >$, in terms of the principal diffusivities in the parallel and perpendicular directions, $D_\parallel$ and $D_\perp$, obtained by projecting the diffusion tensor, $\mathbf{D}$, along the unit-vector specified by $\hat{\mathbf{r}} = (\cos(\theta),\sin(\theta))^T$ (see Eq.(1)). Here $\mathbf{D}$ is expressed in the principal coordinate frame, $\mathbf{\Delta}$ is the diffusion time, and θ is the angle between $\hat{\mathbf{r}}$ and the eigenvector associated with $D_\parallel$. If the ADC is defined as $< R^2 > / (2\Delta)$, then we obtain the now familiar peanut shaped profile of ADC(θ) predicted by Eq. (2).

$$\left\langle R^2 \right\rangle(\theta) = 2\left(D_\parallel \cos^2(\theta) + D_\perp \sin^2(\theta)\right)\Delta \quad (1); \qquad ADC(\theta) = D_\parallel \cos^2(\theta) + D_\perp \sin^2(\theta) \qquad (2)$$

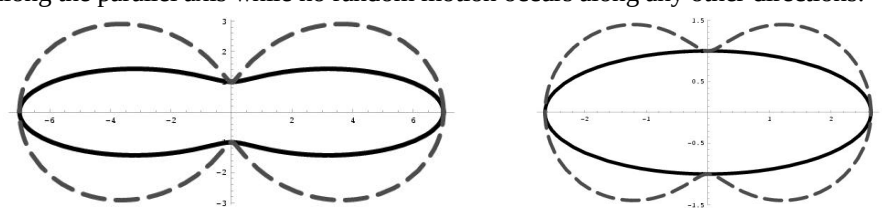
Microscopic Brownian Probabilistic Picture: Consider $p(\mathbf{R},\Delta)$ obtained by following spin-labeled molecules in the same anisotropic medium. For the same anisotropic diffusion process, $p(\mathbf{R},\Delta)$ is:

$$p(\mathbf{R}\,|\,\Delta) = \frac{1}{4\pi\Delta\sqrt{|\mathbf{D}|}}\, e^{-\frac{\mathbf{R}^{\mathrm{T}}\mathbf{D}^{-1}\mathbf{R}}{4\Delta}} = \frac{1}{4\pi\Delta\sqrt{D_\parallel D_\perp}}\, e^{-\frac{R^2}{4\Delta}\left(\frac{\cos^2(\theta)}{D_\parallel}+\frac{\sin^2(\theta)}{D_\perp}\right)} \quad (3); \qquad p(R\,|\,\Delta) = A(\Delta)\, e^{-\frac{R^2}{4D_e(\theta)\Delta}} \quad (4)$$

where $\mathbf{R}$ is expressed in the polar coordinates, (R, θ). Note, for each direction, $p(\mathbf{R},\Delta)$ can be expressed as a 1-D diffusion process along $\mathbf{R}$ as in Eq. (4). Equating terms dependent on θ in Eq. (3) and (4), we can define a 1-D diffusion coefficient, $D_e(\theta)$:

$$D_e(\theta) = \frac{D_\parallel D_\perp}{D_\perp \cos^2(\theta) + D_\parallel \sin^2(\theta)} \quad (5); \qquad \lim_{D_\perp \to 0} D_e(\theta) = \begin{Bmatrix} 0 & \theta \neq 0 \\ D_\parallel & \theta = 0 \end{Bmatrix} \quad (6); \qquad ADC(\theta) = D_\parallel \cos^2(\theta) \qquad (7)$$

In the limit in which $D_\parallel$ is finite and $D_\perp = 0$, approximating a nematic liquid crystal, we obtain Eq. (6), in which diffusion occurs only along the parallel axis while no random motion occurs along any other directions.



a) b)

Figure 1. (a) Polar plot of $D_e(\theta)$ (solid line) and ADC(θ) (dashed line) for a case $D_\parallel/D_\perp$=7; (b) RMS displacement of the diffusing particles as a function of θ, based on the Brownian model, Eq.5, (solid line) and ADC model, Eq.2, (dashed line).

Discussion: The 1-D limit for the microscopic diffusivity obtained in Eq. (6) should be compared to Eq. (7)—the corresponding limiting case for the ADC. Clearly, Eq. (6) predicts an ADC profile that is peanut-shaped when there is uniform, 1-D anisotropic diffusion. Although there is molecular diffusion only along the parallel direction, it *appears* that diffusion occurs in *all* directions, except along $\theta = 90°$. More important, qualitatively similar behavior is also predicted for ADC(θ) obtained for restricted tubes, such as those describing water diffusion in white matter and for other restricted geometries.

The disparity between the molecular scale and ADC profiles arises because the Einstein equation is used to relate the *apparent* mean-squared displacement to the ADC, as in Eq.(1) above. However, by projecting $p(\mathbf{R},\Delta)$ along the direction of the diffusion gradient, all diffusive motion having a component of the displacement in that direction will be observed. Therefore, one measures *apparent* displacements in virtually all directions, even when there is diffusion only along one.

Conclusions: If one uses the familiar Einstein equation to define the ADC as the *apparent* mean-squared displacement divided by twice the diffusion time, as in (2), then this ADC will not be consistent with the microscopic diffusivity measured in various paradigmatic anisotropic media. Moreover, directionally dependent ADC measurements, ADC(θ), will generally not reflect the true microscopic diffusion profile, obscuring the underlying microstructure of a material or tissue.

1. Callaghan PT. Principles of nuclear magnetic resonance microscopy. Oxford: Oxford University Press; 1991.
2. Tanner JE. Transient diffusion in system partitioned by permeable barriers. Application to NMR measurements with a pulsed field gradient. Journal of Chemical Physics 1978;69(4):1748-1754.