Apparent Diffusion Coefficient in Terms of Statistical Properties of Tissues

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Introduction

NMR measurements of water diffusion in living tissues can be used in principle to probe their cellular structure at the scale of several micrometers. However the way in which the cellular morphology is imprinted in the measured diffusion-weighted NMR signal, is currently poor understood. It remains unclear which microscopic properties are represented in the signal from macroscopic objects. Available theoretical models have been developed for examinations of porous media, in which diffusion is restricted by hard boundaries. Such models can reasonably describe the fiber bundles in brain white matter or diffusion of gas in the lungs, but their relevance for other tissues such as the brain gray matter is questionable. Here an alternative model is proposed, in which the tissue is treated as a soft matter. It is assumed that all space points are reachable for water molecules. The restriction of diffusion by membranes and cell organelles is described by a diffusion coefficient that varies in space. The only compromise made for the theoretical tractability of this model is an additional assumption that the magnitude of the variation of diffusion coefficient, D_1, is much smaller than its mean value, D_0: $D_1 \ll D_0$. It is not true in general. For example, the apparent diffusion in the brain gray matter is known to be about three fold reduced as compared with that in pure water. The advantage of the present assumption is that it allows one to find the effect of diffusion weighting in the form of a Taylor expansion in powers of D_1/D_0 thus providing a regular framework for expressing the signal in terms of the statistical properties of the medium studied. In some cases the explicitly found first terms of the series can catch essential properties of the whole sum. These reasons justify the development of the proposed model.
Below we address the following question: What is the apparent diffusion coefficient measured by the spin echo technique?

Theory

The following form of the Bloch – Torrey equation describes diffusion in the medium with the variable diffusion coefficient $D=D_0+D_1(r)$:

$$\frac{\partial \psi}{\partial t} = D_0 \nabla^2 \psi + \nabla \left(D_1(r) \nabla \psi \right) - igr\psi \quad . \qquad [1]$$

Here $\psi=\psi(r, r_0, t)$ is the magnetization density of a spin packet initially located at point r_0, D_0 is a constant equal to the mean value of diffusion coefficient, $D_1(r)$ is its variable component with zero mean, and g is the applied gradient of the Larmor frequency. The signal attenuation caused by the diffusion weighting, s, is given by $s=\int \psi(r, r_0, T_E) dr dr_0/V$, where V is the sample volume.
Generically, the signal can be expanded in even powers of g:

$$\ln s = -\frac{1}{12} D_{app} T_E^3 g^2 + C_4 g^4 + ... \quad . \qquad [2]$$

The first term provides a definition for the apparent diffusion coefficient, D_{app} that dominates the signal for relatively low diffusion weighting. Equation [1] is solved iteratively in g and D_1 and the result is averaged over realizations of the diffusion coefficient. The first nontrivial term has the order $g^2 D_1^2$ that yields

$$D_{app} = D_0 - \frac{1}{3D_0} \int_0^\infty \rho_2(p) h\left(\frac{1}{2} D_0 p^2 T_E \right) \frac{d^3 p}{(2\pi)^3} \quad , \text{ where } \quad h(z) = 1 - \frac{3}{z^2} + \frac{9}{2z^3} - \frac{6e^{-z}}{z^3} + \frac{3e^{-2z}}{2z^3} \quad . \qquad [3]$$

The function $\rho_2(p)$ is the Fourier transform of the correlation function of the diffusion coefficient, $\langle D_1(0) D_1(r) \rangle$.
The obtained result describes a transition between $D_{app}=D_0+O(T_E^{\nu})$ at short times to $D_{app}=D_0/\lambda$, at large times, where the short time exponent ν and the tortuosity λ are constants that characterize the medium. The exponent ν depends on the behavior of $\rho_2(p)$ at large p, or, equivalently, of $\langle D_1(0) D_1(r) \rangle$ at short r. If $\rho_2(p)$ decreased faster than p^{-5}, then $\nu=1$, and

$$D_{app} = D_0 + \frac{1}{8} T_E \nabla^2 \left\langle D_1(0) D_1(r \to 0) \right\rangle \quad . \qquad [4]$$

Here r should be set to zero after the derivative is taken.
The obtained correction is negative for the correlators that are smooth at $r=0$, for instance $\langle D_1(0) D_1(r) \rangle \sim \exp(-r^2/a^2)$. The exponent ν becomes fractional if $\rho_2(p)$ decreased slower than p^{-5}. For an exponentially decaying correlation, $\langle D_1(0) D_1(r) \rangle = \text{Const} \exp(-r/a)$, where a is the correlation length, $\nu=1/2$ and the short time dependence of D_{app} mimics an apparent value of the surface to volume ratio $(S/V)_{app}$ of restrictive boundaries if treated in the spirit of diffusion in porous media:

$$\left(\frac{S}{V} \right)_{app} = Const \frac{\left\langle D_1^2 \right\rangle}{a D_0^2} \quad . \qquad [5]$$

Here *Const* is known analytically and $\langle D_1^2 \rangle$ is the variation of the diffusion coefficient.
The long time asymptotic behavior is characterized by the tortuosity that is also defined by the short-distance value of the correlation function $\langle D_1^2 \rangle$:

$$\lambda = 1 + \frac{\left\langle D_1^2 \right\rangle}{3D_0^2} \quad . \qquad [6]$$

This conclusion might appear counterintuitive, since it states that the shortest (zero) length governs the large-time behavior of D_{app}. This is due to a strong sensitivity of result [3] to the shape of the correlation function. Its mathematical expression is a divergence of integral in [3] for uncorrelated D_1 for which $\rho_2(p)=\text{Const}$. Analysis shows that this feature persists in all orders of the expansion in D_1/D_0.

Discussion

The model of diffusion in tissues without impermeable boundaries can be treated within a well-established approach of perturbation theory. The tissue is specified statistically in terms of correlation functions of the diffusion coefficient. Note that the variable component of the diffusion coefficient, though limited in magnitude, may sharply change as a function of position to describe cells and their organelles. The present general analysis can be extended to study the multiexponential diffusion or can be specified to describe physiological models of interest such as cell swelling. The first steps along these lines are discussed in separate Abstracts.