Permeability and surface area of cell membranes from the DWI signal

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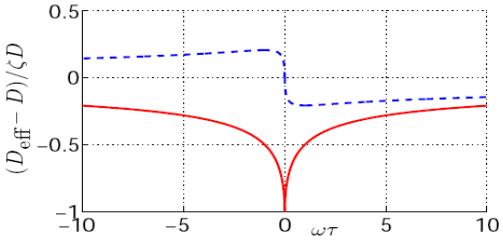
Introduction: Diffusion of water in living tissues is strongly restricted on the length scale of cell sizes, ~10 μm. The consequence of such a restriction is a ubiquitous non-Gaussian shape of the diffusion-weighted imaging (DWI) signal, $\log S(b) = -bD + (K/6)(bD)^2 + \ldots$, where $b=q^2t$. In particular, the probability distribution function for water molecules is characterized by a noticeable kurtosis K [1]; however, the microscopic origins of this non-Gaussian diffusion are not understood. The restrictions can potentially originate from two sources. The first is the difference in bulk diffusivity D between the extra- and intra-cellular compartments. The second is the finite permeability of cell membranes. Here we demonstrate that the presence of membranes alone leads to non-Gaussian diffusion, and suggest a model to determine cell permeability from the DWI signal.

Model: We consider diffusion restricted by flat, infinitely thin membranes with permeability κ, randomly embedded in a medium with uniform diffusivity D, so that there is no diffusivity difference between intra- and extra-cellular compartments. We obtain the Green's function for diffusion in such a random environment, by borrowing methods of disorder-averaging from condensed matter physics [2]. Since the general expression for the signal is complicated we do not quote it here in full, and only outline its main features relevant to DWI measurements. In particular, we find that after averaging over positions and orientations of membranes, the effective diffusivity $D_{\text{eff}}(\omega)$ acquires frequency dependence,

$$D_{\text{eff}}(\omega) = D\left(1 - \frac{\zeta}{1 - i\sqrt{i\omega\tau}}\right), \quad \zeta = \frac{S\ell}{Vd}.$$

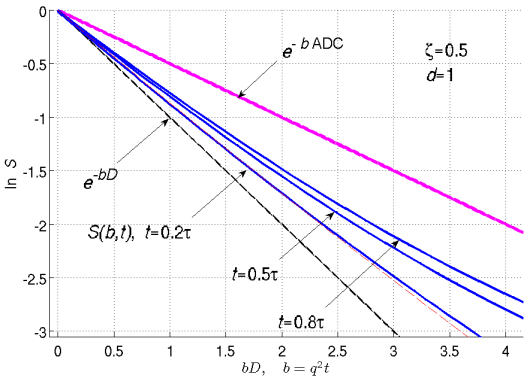
Here S/V is the ratio of surface area of all membranes to the voxel volume, d is the number of spatial dimensions (d=3 for gray matter, d=2 for diffusion across fibers in white matter), $\ell = D/(2\kappa)$ is the effective "thickness" associated with a membrane (such that a membrane disappears when its permeability is infinite), ζ is the permeability-dependent "volume fraction" of membranes, and $\tau = \ell^2/D$. The above result is exact for $\omega\tau \gg 1$, and is valid at long times, $\omega\tau \ll 1$, as long as the effective volume fraction is small, $\zeta \ll 1$ (i.e. for sufficiently permeable membranes). In the latter limit, the apparent diffusion coefficient $\text{ADC}=D_{\text{eff}}(\omega=0)\approx D(1-\zeta)$.

Results: The dispersive contribution $D_{\text{eff}}(\omega)-D$ to the diffusivity, shown in the top figure, has a characteristic square-root singularity (solid line is real part and dashed line is imaginary part). The real part, corresponding to the velocity autocorrelation function, can be accessed by applying oscillating gradients [3] and indeed looks similar to the measured $D(\omega)$, ref [3]. The evidently non-Gaussian shape of the DWI signal, as demonstrated in the bottom figure, corresponds to time-dependent diffusivity $D(t)$ and kurtosis $K(t)$, which, for $t \ll \tau$, are given by



$$D(t) \equiv \frac{\langle x^2(t)\rangle}{2t} \simeq D\left[1 - \frac{S}{Vd}\left(\frac{4\sqrt{Dt}}{3\sqrt{\pi}} - \kappa t\right)\right],$$

$$K(t) \equiv \frac{\langle x^4(t)\rangle}{\langle x^2(t)\rangle^2} - 3 \simeq \frac{S}{V}\beta_d\left[\frac{8\sqrt{Dt}}{5\sqrt{\pi}} - 2\kappa t\right]$$



Here $\beta_d = \langle\cos^4\theta\rangle = 1, 3/8, 1/5$ in dimensions d=1, 2, 3 correspondingly. The result for $D(t)$ agrees with [4]; the result for $K(t)$ is new. For d=1 it also follows from the exact solution for periodic membranes [5] at short times.

Discussion: From our solution, it follows that the manifestly non-Gaussian shape of the DWI signal can originate solely due to the presence of cell membranes, with no diffusivity difference between the intra- and extra-cellular compartments. Practically, cell membrane permeabilities range from κ~1-100 μm/s, corresponding to ℓ ranging from a few to hundreds of microns. Measuring either $D_{\text{eff}}(\omega)$, or $D(t)$ and $K(t)$, is suggested as a means to experimentally determine cell membrane permeability from the DWI signal. Correlating permeability with tissue physiology may lead to novel contrast between healthy and diseased tissues. Such a contrast could be especially revealing in stroke for which permeability changes may play a key role [6].

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