Dependence of Apparent Diffusion Coefficient on Cellular Structure

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Introduction

With typical MR measurements performed on the time scale of hundreds of ms, the diffusion length for water molecules corresponds to a few micrometers. This scale is commensurate with the dimensions of many cell species, suggesting a possibility to investigate the cellular characteristics using the diffusion weighted (DW) imaging. The main limitation of this promising method is a lack of understanding of the biophysical characteristics that affect the DW signal. This limitation, typical for any ill-posed inverse problem, comes from the observation that acquiring the MR signal over a voxel is equivalent to performing a statistical averaging of tissue properties over a macroscopic scale. In this case one hopes that the DW signal, at best, contains the information about certain average microscopic properties of the tissue. However, even this hypothesis has to be justified, and this is the subject of the present work. Here we examine how sensitive can the apparent diffusion coefficient (ADC) be as a probe of tissue properties down to the cellular level.

Method of Analysis

Assuming self-averaging tissue properties over a voxel size, one is bound to describe the tissue in terms of its statistical characteristics. In particular, here we assume that the diffusion coefficient $D=D_0+D_1(\boldsymbol{x})$ possesses a position-dependent component $D_1(\boldsymbol{x})$. If dominated by the cellular structure, $D_1(\boldsymbol{x})$ and its correlation functions vary on the scale of the cell size. The advantage of such a description is in its wide generality, with a possibility to include, e.g., cells with permeable membranes, or just about any other tissue inhomogeneities that affect the local diffusivity. Our aim is to investigate how sensitive is the measured DW signal $S(t)$ acquired over a macroscopic volume V to the *correlation functions* of $D_1(\boldsymbol{x})$. We employ the relationship between the macroscopic signal $S(t)$ and the solution ψ of the Bloch -- Torrey equation that contains the structure-dependent term:

$$\left(\frac{\partial}{\partial t}-D_0\nabla^2\right)\psi(\boldsymbol{x},\boldsymbol{x}_0,t)=\delta(\boldsymbol{x}-\boldsymbol{x}_0)\delta(t)+\left(\nabla D_1(\boldsymbol{x})\nabla-i\boldsymbol{g}\boldsymbol{x}\right)\psi(\boldsymbol{x},\boldsymbol{x}_0,t) \qquad [1]$$

and

$$S(t)=\frac{1}{V}\int\psi(\boldsymbol{x},\boldsymbol{x}_0,t)d^3\boldsymbol{x}d^3\boldsymbol{x}_0 \quad . \qquad [2]$$

Here ψ is the complex-valued density of transverse magnetization of a spin packet excited at a point $\boldsymbol{x}_0$ of three-dimensional space, and $\boldsymbol{g}$ is the diffusion-weighting gradient. The refocusing pulse in the spin-echo measurement is further accounted for by conjugating the previously acquired magnetization. The last term of Eq. [1] can be treated as a perturbation resulting in a series in the powers of $D_1(\boldsymbol{x})$ and $\boldsymbol{g}$. By definition, only the terms proportional to $\boldsymbol{g}^2$ should be taken into account for the determination of the ADC. In contrast, all powers of $D_1(\boldsymbol{x})$ should be included in order to describe realistic tissues with strong variations of the local diffusivity. This yields a formal series, containing all the correlation functions of the structure $D_1(\boldsymbol{x})$ that appear after performing the averaging in Eq. [2]. This series is best analyzed using a graphic representation of the resulted lengthy chains of convolutions of $D_1(\boldsymbol{x})$ with the unperturbed solution ψ_0 of Eq. [1] (corresponding to $D=D_0$ and $\boldsymbol{g}=0$). Examples of such diagrams are shown in Fig.1 – 2 for the terms of the fourth order in $D_1(\boldsymbol{x})$. Here ψ_0 is represented by the straight-line segments in-between vertices. The vertical bar indicates the refocusing pulse applied at a particular time moment. The blob with n legs in diagrams represents the connected n-point correlation function of $D_1(\boldsymbol{x})$ (the n^{th} cumulant). Calculations simplify when performed in the frequency - wave number representation (ω-$\boldsymbol{k}$ space), in which $\psi_0=(-i\omega+D_0\boldsymbol{k}^2)^{-1}$ for $\boldsymbol{x}_0=0$. The filled half-circles at the vertices stand for the factors $\boldsymbol{k}$ arising as the argument of the attached ψ_0 due to the differentiation associated with the term containing $D_1(\boldsymbol{x})$, Eq. [1]. The external legs have $\boldsymbol{k}=0$ due to the spatial integrations in Eq. [2], and the corresponding wave vector circulating around each loop is being integrated over.

In this language, dependence on the structure is studied by analyzing the integrals such as those illustrated in Fig.1 – 3.

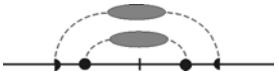
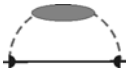
Fig. 1 

Fig. 2 

Fig. 3 

Results

Our analysis shows that each order in $D_1(\boldsymbol{x})$ in general gives both *local* and *non-local* contributions to the ADC. The local part, such as the one from the lowest order term (Fig. 3), $\delta D_{ADC}^{loc}=-\frac{1}{3D_0}\int\frac{d^3\boldsymbol{k}}{(2\pi)^3}\Gamma_2(\boldsymbol{k})=-\frac{\langle D_1^2\rangle}{3D_0}$, originates from the dispersion of the local diffusivity independently at each point in space, and is formally determined by the correlation functions at coinciding spatial points. This part (postulated in the compartment-based models) does not depend on the spatial structure of the diffusivity.

Higher orders in $D_1(\boldsymbol{x})$, however, give also non-local contributions that are sensitive to the particular angular and spatial dependence of the correlation functions $\Gamma_n(\boldsymbol{k})$ on the scale on which they vary appreciably, i.e. the cell size in our prime example. This part of the ADC is sensitive to the tissue structure and goes beyond the results of the compartment-based models. Note that the origin of the non-locality comes from diffusion in three dimensions. In one spatial dimension, all contributions to ADC would be local. This qualitative difference between one- and higher dimensions is similar to that observed in the resistance of one- and multi-dimensional conductors.

Discussion

The present analysis reveals the following picture of how the DW signal originates. The difference between the ADC and the average D_0 is accumulated on the length scale on which the correlation functions Γ_n decay, whereas for longer times the diffusion is that of the effective medium with the accumulated ADC (i.e. diffusion over larger scales does not change the ADC any further). The resultant ADC has both local (structure-independent) and non-local, or non-universal (structure-dependent) contributions. This non-universality can be either a curse or a virtue: It rationalizes the observed strong biological variability of the ADC measurement outcomes, giving structure-dependent corrections to the oversimplified predictions of compartment-based models. On the other hand, the structure sensitivity gives a possibility, at least in principle, to quantify the tissue characteristics well beyond the spatial limits on resolution if a careful interpretation of the DW measurements is employed, with a focus on the non-local part that is sensitive to the cellular structure. We note that the non-universality of ADC is similar to the shape-sensitivity found by present authors in the transverse relaxation due to susceptibility contrast (1). This non-universality justifies using the ADC as a probe of microscopic tissue structure.

(1) VG Kiselev and DS Novikov. Transverse NMR relaxation as a probe of mesoscopic structure. Phys. Rev. Lett. 89 (2002) 278101.