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Effect of impermeable boundaries on diffusion-attenuated MR signal

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Abstract

The nonlinear dependence between the logarithm of the diffusion weighted signal, $\ln S$, and the b-value, b, has often been interpreted as a manifestation of two physically distinct compartments, resulting in a biexponential form of the signal. This model fits to experimental data, however, has failed to yield realistic compartment sizes, severely jeopardizing the use of DWI to infer structural information on a cellular level. It has been hypothesized that the biexponential behavior can be attributed to the effect of confining boundaries that restrict diffusion in individual physical compartments. This interpretation is based on the analysis of diffusion in the presence of impermeable interfaces for short diffusion times such that the layer in which diffusion is affected by the boundary is thin as compared with the dimensions of the whole compartment. This model system is analyzed from the point of view of the cumulant expansion of the diffusion-weighted signal that results in a Taylor expansion of $\ln S$ in powers of b. Termination of this expansion to a polynomial form provides an excellent accuracy for small b-factors, but the series diverges for large b. The convergence of the series is studied, yielding a large range of b-values in which the absolute error of terminating the series at the second term remains smaller than 1% relative to the signal magnitude without diffusion weighting. With this accuracy, the signal in the studied model can be described as $\ln S \approx -A \cdot bD + B \cdot (bD)^2$, where the parameters A and B can be expressed in terms of correlation functions of molecular velocity. Fitting of these parameters to the exact signal is more stable than for the three parameters of the biexponential function. This description fails for large b, for which the cumulant expansion diverges. The signal at even larger b-values is proportional to $1/b$, $1/b^{3/2}$, and $1/b^2$ in one-, two-, and three-dimensional systems, respectively.
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1. Introduction

Numerous studies, see, e.g., [1,2] and references therein, give evidence that the normalized diffusion-weighted signal from a single voxel can be described as a weighted sum of two exponential functions

$$S = (1 - w)\exp(-bD_1) + w\exp(-bD_2), \quad (1)$$

where b is the b-value, D_1 and D_2 are two apparent diffusion coefficients, hereafter $D_1 > D_2$ for the definiteness, and w is the volume fraction of the slow-diffusion compartment. The signal in Eq. (1) is commonly termed the biexponential diffusion.

This form of the signal would be exact for samples consisting of two compartments without exchange. The experimentally observed weight of the compartment with slow diffusion is about 20–30% [1,3]. The latter fact presents a serious problem concerning a straightforward interpretation of these compartments as e.g., the intracellular and the extracellular volumes with the slow and the fast diffusion, respectively, since the weight of the intracellular compartment is typically 80% [2,4,5].

A more elaborate model with an exchange term between compartments [6] (the Kärger–Andresko equation) results in a very reasonable signal behavior with time dependence of the apparent diffusion coefficients, but it fails to resolve

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the problem of unrealistically small size of the compartment with slow diffusion [6]. Latour et al. [7] obtained the apparent diffusion coefficient for long times in tissue consisting of densely packed cells, taking into account the finite cell size and permeability of membranes. However, the accuracy of the developed approximation of effective medium remains unclear. The authors did not address the nonlinear dependence between $\ln S$ and the b-factor.

Schwarcz et al. [8] seemingly ruled out the possibility to interpret the biexponential diffusion in relation to the presence of an intracellular compartment. They showed that the biexponential signal decay is observed in the cold-injured mouse brain, where the membranes are disintegrated. The same was shown to be the case for centrifuged red blood cells, having disintegrated membranes. Independence of the weights of two compartments on the actual volume fraction of cells was recently demonstrated by Ababneh and colleagues [9] by a comparison of endemic and normal muscle tissue in a rat model.

These results are in agreement with another interpretation of the biexponential diffusion proposed by Sukstanskii and colleagues [10–12]. They related the "hidden" compartment with slow diffusion to the layers of water adjacent to impermeable or partially permeable membranes which are abundant in biological tissue. This idea is based on a simple model of diffusion with a coefficient D in a slab restricted by two impermeable parallel boundaries. For short times, t, such that the diffusion length, $(Dt)^{1/2}$ is shorter that the slab thickness, L, the apparent diffusion coefficient D_2 does not depend on L and $D_1 \approx D$. The weight, w, of the compartment with low diffusivity scales as $(Dt)^{1/2}/L$.

This model may serve as a basic building block in explaining the behavior of the apparent diffusion coefficient at short times, providing a relation between the signal and the specific surface, σ, (the surface to volume ratio) in porous media [13–15]. In this case the diffusion length should be shorter than the typical pore size. The volume with reduced diffusivity has the weight of the order of $(Dt)^{1/2}\sigma$.

This volume fraction remains small within the validity range of the model, and the problem of unphysiological predictions therefore persists. Nonetheless, it is theoretically attractive by its explanation of the signal being biexponential, and by its impressive accuracy in fitting the expression Eq. (1) to the exact signal [11].

In this paper, we advocate an alternative approach to describe the nonlinear dependence between the logarithm of the diffusion-weighted signal and the b-factor. We refrain from building models of diffusion at the cellular level, adverting instead to an ab initio property of diffusion-weighted signal which is expressed by the following expansion in powers of b:

$$\ln S = -A \cdot bD + B \cdot (bD)^2 + C \cdot (bD)^3 + \cdots, \qquad (2)$$

where D is the diffusion coefficient for free diffusion. It is reasonable to define the apparent diffusion coefficient as the slope of $-\ln(S)$ at $b = 0$. According to this definition, the coefficient A accounts for the time dependence of the apparent diffusion coefficient, $D_{\mathrm{app}} = AD$. In homogeneous media $A = 1$, while B, C, and all higher coefficients turn to zero. The expansion in Eq. (2) follows from an expansion of S in powers of the applied gradient, which is a particular case of the cumulant expansion as discussed below. We shall loosely apply the same term "cumulant expansion" to Eq. (2) in the context of the present paper.

The cumulant expansion, Eq. (2), is in fact a Taylor expansion. Terminating this series provides for a good approximation to the signal when bD is small. This results in a polynomial dependence between $\ln S$ and bD, which diverges after a certain bD-value. Including more terms helps to increase the accuracy only for small bD. For large values, the series diverges. In this case the signal takes a form that cannot be approximated by the exponential of a polynomial and the series in Eq. (2) cannot be applied. The cross-over between the domains of small and large bD can be termed the radius of convergence, following the reason explained below.

To serve as a practical approximation, this radius must be sufficiently large to incorporate measurements with typical experimental b-values. We address this issue using the basic model of diffusion near an impermeable wall in line with a number of previous studies, [11,12,16,17]. The possible applications and restrictions of this basic model is discussed in Section 3. We focus on the simplest measurement sequence with narrow gradient pulses that is used in the q-space imaging and determine the coefficients in Eq. (2). It turns out that the cumulant expansion converges for realistic b-values achievable in human scanners and $\sqrt{Dt} \ll L$. For example, terminating expansion Eq. (2) at the second term for $\sqrt{Dt} = 0.01L$ results in an absolute error which increases with bD and reaches 0.1% of the signal in the absence of diffusion weighting at $bD = 2$. This absolute error remains smaller than 1% for $b < 8$ ms/μm^2. This means that experimental data obtained with b-factors $b < 2$ ms/μm^2, which is typical for human scanners, can be fitted with the two first terms of the expansion in Eq. (2). Such a description involves only two parameters, one of which is the apparent diffusion coefficient D_{app} while the other describes the curvature of the dependence between $\ln S$ and b. A further advantage is that the cumulant expansion of the signal enables to trace the relation between these parameters on one hand and the pulse sequence used as well as the structure of the media investigated, on the other. The latter is represented by the correlation functions of molecular velocity (the cumulants) that may take a rather complicated form. The cumulant expansion of the signal has been discussed in earlier MR studies, e.g., [16,18–21]. We comment on some of these works in Section 3.

The paper is organized as follows: in the next section, we discuss shortly the cumulant expansion of the signal, that gives rise to Eq. (2). The coefficients in Eq. (2) are calculated for the diffusion between impermeable walls in the approximation of narrow gradient pulses. The discussion following in Section 3 focuses on the convergence range

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