Effects of mesoscopic susceptibility and transverse relaxation on diffusion NMR

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ARTICLE INFO

ABSTRACT

Measuring molecular diffusion is based on the spatial encoding of spin-carrying molecules using external Larmor frequency gradients. Intrinsic variations of the Larmor frequency and of the local relaxation rate, commonly present in structurally complex samples, interfere with the external gradients, confounding the NMR-measured diffusion propagator. Here we consider, analytically and numerically, the effects of the mesoscopic magnetic structure (local susceptibility and transverse relaxation rate) on the NMR-measured "apparent" diffusion coefficient (ADC). We show that in the fast diffusion regime, when molecules spread past the correlation length of the magnetic structure, the deviation of ADC from the genuine diffusion coefficient increases as a power law of diffusion time. The effect of mesoscopically varying transverse relaxation rate is sequence-independent and always leads to the decrease of ADC with time, whereas the effect sign for the mesoscopic Larmor frequency variations depends on the presence of refocussing pulses in the diffusion sequence. We connect this unexpectedly diverging with time ADC discrepancy to the spatial statistics of the mesoscopic magnetic structure. Our results establish a novel kind of NMR contrast tied to the microstructural complexity, and can be applied to discern the mesoscopic effects of hindrances to molecular diffusion, susceptibility variations, and varying local relaxation rate, on the measured diffusion propagator. In particular, we numerically show that the susceptibility effect of a microvascular network is sufficient to explain the observed ADC decrease due to superparamagnetic iron-oxide contrast injection in monkeys.

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1. Introduction

The diffusion-weighted NMR [1] or MRI [2] (dMRI) does not measure diffusion *per se*. Rather, this technique measures the relaxation of the transverse spin magnetization in the presence of an externally applied pulsed Larmor frequency gradient. In the absence of magnetic structure, and for the short gradient pulses, this signal relaxation happens to coincide with the Fourier transform $G_{t,\mathbf{q}}$ of the diffusion propagator averaged over a sample or an imaging voxel [1,2].

Naturally, the dMRI outcome will be confounded by the presence of intrinsic magnetic field gradients at the mesoscopic scale, which can be induced, e.g., by the heterogeneous magnetic susceptibility [3,4]. In a conventional picture [3–7], the mesoscopic gradients, $\mathbf{g}_{\mathrm{meso}}$, create "hot spots", where the applied diffusion gradient, $\mathbf{g}$, is maximally compensated by the internal ones. The dMRI signal acquired over a macroscopic volume is *increased* relative to the

case of $\mathbf{g}_{\mathrm{meso}} \equiv 0$ due to the averaging of a convex function (the exponential) over the distribution of $\mathbf{g}_{\mathrm{meso}}$ within the sample — a consequence of Jensen's inequality.[1] Qualitatively, the signal's increase due to the "hot spots" prevails over its decrease due to the areas where the internal and external gradients are aligned. To the leading order, the signal's increase comes from the coupling between internal and external gradients via the so-called cross-terms $\sim \mathbf{q} \cdot \mathbf{q}_{\mathrm{meso}}$, where $\mathbf{q}$ and $\mathbf{q}_{\mathrm{meso}}$ are the time integrals of $\mathbf{g}$ and $\mathbf{g}_{\mathrm{meso}}$, respectively. Equivalently, the signal's increase results in the reduced "apparent" diffusion coefficient (ADC), $D^{\mathrm{app}} \leqslant D$, relative to the genuine molecular diffusivity D, as established experimentally in the 1990s [3,4], and utilized recently [5,6].

The intuitive picture of "hot spots" implies that their size is much larger than a typical molecular displacement $\sqrt{Dt}$ during

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[1] For any convex function $\phi(X)$ of a random variable X, its mean $\langle \phi(X) \rangle \geqslant \phi(\langle X \rangle)$, with the averaging $\langle \ldots \rangle$ taken over the distribution of X. This statement is actually a generalization of the original 1906 result by Jensen [8]. It was re-derived and popularized by R. P. Feynman in the practically important case of averaging an exponential function over the paths or over the statistical configurations [9].

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the measurement (slow diffusion, or static dephasing), i.e., that the diffusion time $t \ll t_c$, where $t_c \sim l_c^2/D$ is the time to diffuse across the correlation length l_c of the spatially varying Larmor frequency profile $\Omega(\mathbf{r})$. Assuming a locally constant internal gradient $\mathbf{g}_{\mathrm{meso}} = \nabla\Omega(\mathbf{r}_0)$ for each spin, the choice in sequence timings in the twice-refocussed spin echo (2SE) [10] can be made to cancel the interference terms completely [11]. However, as time t increases, the local field ceases to be idealized just by its value $\Omega(\mathbf{r}_0)$ and the linear term $\nabla\Omega(\mathbf{r}_0) \cdot (\mathbf{r} - \mathbf{r}_0)$; the higher-order terms in this expansion, effectively sampled by the diffusing spins, should break the 2SE cancellation. This results in a smaller than for the spin echo (SE), but numerically observable ADC decrease, as it was shown using Monte Carlo simulations of diffusion in the presence of the randomly oriented, infinitely long cylinders [12].

In this work, the time-dependent corrections to $D^{\mathrm{app}}(t)$ due to $\Omega(\mathbf{r})$ are considered for all t, analytically and numerically. The genuine molecular diffusion is assumed to be Gaussian for simplicity, $D(t) = \mathrm{const}$; this will help us to focus solely on the ADC corrections induced by $\Omega(\mathbf{r})$. As we argue, the crucial feature of the fast diffusion (diffusion narrowing regime), $t \gtrsim t_c$, is that the mesoscopic effects generally become inherent to dMRI measurements and cannot be fully removed by the choice of the pulse sequence. Their effect and *sign* depends on the sequence. Specifically, in the diffusion narrowing regime, we establish the following:

(i) For the sequence with narrow *bipolar* gradient pulses, where the gradient changes polarity and no refocussing pulses are present, ADC *increases*:

$$D^{\mathrm{app}}(t) \simeq D + \mathrm{const} \cdot (t/t_c)^{2-d/2}, \quad t \gg t_c \qquad (1)$$

with const > 0, for the case of short-range disorder in $\Omega(\mathbf{r})$ in d spatial dimensions. The dimensionality d is effective: for example, random infinitely-long cylindrical structures embedded in three-dimensional space correspond to $d = 2$, cf. Ref. [13]. Generally, $d/2$ is directly analogous to the dynamical exponent ϑ relating the spatial dimensionality d and the structural exponent p; here, the structure is magnetic, and the exponent p is defined via the low-k behavior [13] of the corresponding power spectrum of magnetic structure. Note that a genuine diffusion coefficient $D(t)$ in a structurally complex medium cannot increase with time [13]. The ADC increase with t and the corresponding signal attenuation relative to $\Omega(\mathbf{r}) \equiv 0$, are both signatures of dMRI being fundamentally a transverse relaxation measurement, with the relaxation rate increasing when the internal gradients are not refocused.

(ii) For all considered SE-type sequences, $D^{\mathrm{app}} \leqslant D$ for all t, where the diverging at $t \to \infty$ time-dependent correction is of the power-law form (1) with the sequence-dependent const < 0.

(iii) The effect of *spatially varying relaxation rate* $R_2(\mathbf{r})$ on ADC is qualitatively similar to that of SE-based dMRI in the presence of $\Omega(\mathbf{r}): D^{\mathrm{app}}(t)$ correction has the form (1) with const < 0. In contrast to $\Omega(\mathbf{r})$, the effect of $R_2(\mathbf{r})$ is *sequence-independent*, i.e., it is identical for bipolar and SE-based sequences.

Translating our results to biological tissues, we note that Eq. (1) applies separately to each tissue "compartment" (spin population). As diffusion in different compartments may have different effective dimensionality d, and may even experience different kinds of disorder in $\Omega(\mathbf{r})$ and $R_2(\mathbf{r})$, their contributions will generally come with different scaling laws (1). The overall ADC is a weighted average of the compartmental ADCs, with the weights determined by non-monoexponential tranverse relaxation for each spin population.

In what follows, we first describe the qualitative physical picture of the mesoscopic transverse relaxation and of the interfer-

ence effects, from which the scaling law (1) follows (Section 2). Then, in Section 3, we derive the result (1) for the ideal (narrow-pulse) bipolar sequence up to $\mathcal{O}\left(\Omega^2(\mathbf{r})\right)$, by extending the effective medium formalism [13–17] onto the interference problem, and in Section 4 we validate our analytical calculations with Monte Carlo simulations. Next, in Section 5, we consider an application of our results to the observation of the ADC decrease due to superparamagnetic iron-oxide contrast injection in monkeys [18].

2. Qualitative picture and estimates

In this Section, we first quickly get to the ADC correction, Eq. (7) below, using the cumulant expansion, which will be a bit technical, since the effect only emerges in the 4th-order term. We then discuss the physical picture of coarse-graining that underpins formal expressions, and enables order-of-magnitude estimates such as Eq. (1).

2.1. ADC correction from the cumulant expansion

After an excitation at $t = 0$, each spin acquires a precession phase

$$\varphi(t) = \int_0^t \mathrm{d}t' \, \Omega(\mathbf{r}_{t'}) + \int_0^t \mathrm{d}t' \, \mathbf{g}(t') \cdot \mathbf{r}_{t'} \qquad (2)$$

while traveling along its Brownian path[2] $\mathbf{r}_t$. This phase has two contributions: from the Larmor frequency offset $\Omega(\mathbf{r})$, and from the diffusion encoding, which in the narrow-pulse limit becomes $-\mathbf{q} \cdot (\mathbf{r}_t - \mathbf{r}_0)$, where the gradient $\mathbf{g}(t) = \mathrm{d}\mathbf{q}(t)/\mathrm{d}t$. The net signal is the average of $e^{-i\varphi(t)}$ over the Brownian paths and over the initial positions $\mathbf{r}_0$ (i.e., over the medium). This average can be represented as a cumulant expansion[3] [19,20]

$$S = \langle e^{-i\varphi(t)} \rangle = e^{-\langle\varphi^2(t)\rangle_c/2! + i\langle\varphi^3(t)\rangle_c/3! + \langle\varphi^4(t)\rangle_c/4! + \cdots} \qquad (3)$$

where $\langle\varphi\rangle \equiv 0$ as we can set sample (voxel) average $\overline{\Omega} = \langle\Omega(\mathbf{r})\rangle \equiv 0$ without the loss of generality, and due to the fact that the diffusion gradients are balanced.

For performing the averaging in Eq. (3), it is necessary to work with the cross-products of the two terms in Eq. (2) that can be correlated in the general case, for example, if $\Omega(\mathbf{r})$ is induced by magnetized inclusions that also hinder diffusion. The odd-order terms in $\mathbf{r}$ vanish regardless of Ω. This follows from the time-reversal symmetry of the Brownian motion: for any diffusion path there is the same one run in the opposite direction, which reverses the sign of $\mathbf{r}(t)$. By the detailed balance, the probability of these two opposite paths are equal for any pair of connected spatial points, which nulls their total contribution.

Accordingly, the lowest-order term, the variance

$$\langle\varphi^2(t)\rangle = \int_0^t \mathrm{d}t'\mathrm{d}t'' \langle\Omega(\mathbf{r}_{t'})\Omega(\mathbf{r}_{t''})\rangle_{\mathrm{paths};\,\Omega(\mathbf{r})} + q_i q_j \langle\delta x_i \delta x_j\rangle$$

has two separate contributions: the first one determines the lowest-order transverse relaxation, discussed below, and the second one is just a familiar diffusion weighting for the basic measurement with the bipolar narrow pulses, $\langle\delta x_i \delta x_j\rangle = 2D_{ij}t$, which for isotropic media yields $q_i q_j \langle\delta x_i \delta x_j\rangle = 2Dq^2 t$. Note that the components of the position vector $\mathbf{r}$ are denoted as x_i.

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[2] We use the notation $\mathbf{r}_t$ in place of $\mathbf{r}(t)$ for the readability.
[3] The cumulants generalize the relation between the variance and the second moment: The nth-order cumulant is the nth-order moment with the subtracted trivial products of the lower-order cumulants.