



Communication

Surface-to-volume ratio with oscillating gradients

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ABSTRACT

Restrictions to diffusion result in the dispersion of the bulk diffusion coefficient. We derive the exact universal high-frequency behavior of the diffusion coefficient in terms of the surface-to-volume ratio of the restrictions. This frequency dependence can be applied to quantify structure of complex samples with NMR using oscillating field gradients and static-gradient CPMG. We also demonstrate the inter-relations between different equivalent diffusion metrics, and describe how to calculate the effect of restrictions for arbitrary gradient waveforms.

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1. Introduction

The universal short-time behavior [1] of the diffusion coefficient

$$D(t) \simeq D_0 \left(1 - \frac{4}{3d\sqrt{\pi}} \cdot \frac{S}{V} \sqrt{D_0 t} \right), \quad D_0 \equiv D|_{t=0}, \quad (1)$$

allows one to determine the surface-to-volume ratio S/V of restrictions in porous materials [2,3] and in biological tissues [4]. Here D_0 is the unrestricted diffusion coefficient, and d is the effective spatial dimensionality, with the factor $1/d$ arising from the orientational average of the restrictions assuming their statistically isotropic distribution [1].

While Eq. (1) has been instrumental in characterizing restrictions in a variety of media, the direct measurement of $D(t)$ with pulse field gradient (PFG) diffusion-weighted NMR at millisecond time scales is often technically challenging, especially in the *in vivo* applications.

A promising way to get into the short-time limit is to apply the oscillating gradient (OG) method [5], where the diffusion weighting is effectively accumulated over many periods of oscillation. In this way, the time scale for the diffusivity (the oscillation period) can be much shorter than the total acquisition time thus enabling practical measurements. A variant of this technique requires a constant diffusion gradient, where the temporal modulation is achieved by applying periodic radiofrequency pulses of the CPMG type [5–7].

In view of applying the oscillating techniques [5–7], an immediate question is, what exactly should one substitute for the diffusion time t in Eq. (1)? As $t \sim 1/\omega$, where ω is the gradient oscillation angular frequency, the right-hand side of Eq. (1) must transform in the frequency domain to

$$D_0 \left(1 - C_d \frac{S}{V} \sqrt{\frac{D_0}{\omega}} \right), \quad \omega \rightarrow \infty.$$

Quite remarkably, the prefactor C_d in this expression has never been explicitly derived for the OG case. The existing analytical results are concerned with a finite number of echoes [8–13]. Furthermore, there exists a discrepancy between the numerical values of C_d provided by different groups [13–17].

In this work, we find the prefactor C_d *exactly* both for the OG and CPMG cases (Eqs. (10) and (12) below) in the limit of a large number of oscillations. This limit is practically applicable for high oscillation frequencies in accord with the requirement of short diffusion time for the validity of Eq. (1). We show that the exact prefactor values for the infinite OG and CPMG trains differ by less than 1% from each other (Eq. (12)), thereby justifying the view of the CPMG method as being basically equivalent to the OG, and validate the approximate numerical values found in Ref. [14] for the CPMG and in Ref. [15] for the OG. To derive our result, we utilize the recently established equivalence between the PFG and OG diffusivities using the effective-medium description of diffusion in disordered materials [18,19].

Here, as in Ref. [1], we do not take into account the confounding effects of heterogeneous magnetic susceptibility or relaxation. These effects generally make the interpretation of the diffusion-weighted measurements challenging [13,20–22]. For the shortest

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times, they are less relevant; in particular, the effect of the surface relaxation at the pore walls can be factored out [13]. However, the confounding effects can accumulate over the total acquisition time of many oscillations, significantly modifying the apparent S/V ratio.

2. Methods

In this section we outline the relations between the second cumulant of the diffusion-weighted signal and the diffusion characteristics relevant for the PFG and OG measurements, valid for any statistically isotropic disordered medium. In Section 3 we will apply these relations to the problem in question.

2.1. The second cumulant

We begin with the Gaussian phase approximation [23,24] to the diffusion-weighted signal, S ,

$$-\ln S(T) \simeq \frac{1}{2} \int_0^T dt_1 dt_2 q(t_1) \langle v(t_1) v(t_2) \rangle q(t_2), \tag{2}$$

which amounts to keeping the second-order term of the cumulant expansion [25]. The signal depends on the total duration T of the gradient train $g(t)$, and is a functional of the diffusion-weighting $q(t) = \gamma \int_0^t dt' g(t')$, with γ the gyromagnetic ratio. The diffusion is characterized by the autocorrelation function $\langle v(t_1) v(t_2) \rangle$ of molecular velocity, an even function of $t_1 - t_2$ in stationary media. As we assumed isotropic diffusion from the outset, v here is the velocity component along the fixed direction of the applied gradient. For uniform media, $\langle v(t_1) v(t_2) \rangle = 2D_0 \delta(t_1 - t_2)$, leading to the standard expression $-\ln S = bD_0$ with $b = \int_0^T q^2(t) dt$.

Here we will utilize an equivalent, and often more convenient way to represent Eq. (2), in terms of Fourier transformed quantities, such as $q_\omega = \int_0^T dt e^{i\omega t} q(t)$:

$$-\ln S(T) \simeq \frac{1}{2} \int \frac{d\omega}{2\pi} q_{-\omega} \langle v_{-\omega} v_\omega \rangle q_\omega. \tag{3}$$

The velocity autocorrelator in the frequency representation is defined as $\langle v_{-\omega} v_\omega \rangle \equiv \int_{-\infty}^{\infty} d\tau e^{i\omega\tau} \langle v(t_0 + \tau) v(t_0) \rangle$ independent of t_0 due to time translation invariance. The representation (3) underscores that, knowing the correlator $\langle v_{-\omega} v_\omega \rangle$, one can evaluate the diffusion-weighted signal (2) for any gradient waveform $g(t)$. Conversely, by selecting a particular form of $q(t)$ according to its Fourier

representation q_ω , one effectively allocates a larger or a smaller weight to particular Fourier harmonics $\langle v_{-\omega} v_\omega \rangle$ contributing to the measured signal (3).

There are two advantages of working in the frequency representation (3). From the practical standpoint, a single integral in ω is simpler than a double integral in t . This reduction is due to the time translation invariance not explicitly utilized in Eq. (2). From the fundamental standpoint, $\langle v_{-\omega} v_\omega \rangle$ is directly related to the dispersive diffusivity $\mathcal{D}(\omega)$ discussed below.

2.2. The dispersive diffusivity

As outlined in detail in Ref. [19], the dispersive diffusivity $\mathcal{D}(\omega)$ is a retarded response function relating the temporal Fourier component $\mathbf{J}_{\omega, \mathbf{r}} = -\mathcal{D}(\omega) \nabla_{\mathbf{r}} \Psi_{\omega, \mathbf{r}}$ of the current $\mathbf{J}(t, \mathbf{r})$ of diffusing particles to that of a lump of particle density $\Psi(t, \mathbf{r})$. This makes $\mathcal{D}(\omega)$ a central object in the effective medium description of diffusion in disordered media, as it defines the disorder-averaged diffusion equation

$$-i\omega \Psi_{\omega, \mathbf{r}} = \mathcal{D}(\omega) \nabla_{\mathbf{r}}^2 \Psi_{\omega, \mathbf{r}} + \mathcal{C}(\nabla_{\mathbf{r}}^4 \Psi_{\omega, \mathbf{r}})$$

which incorporates the characteristics of the restrictions that can be quantified with a bulk measurement. At the same time, $\mathcal{D}(\omega) = \int_0^\infty dt e^{i\omega t} \mathcal{D}(t)$ is the Fourier transform of the retarded velocity autocorrelator $\mathcal{D}(t) \equiv \theta(t) \langle v(t) v(0) \rangle$, with $\theta(t)$ a unit step function, cf. Fig. 1 and Ref. [19]. Therefore,

$$\langle v_{-\omega} v_\omega \rangle \equiv 2\text{Re} \mathcal{D}(\omega).$$

As a result, the knowledge of $\mathcal{D}(\omega)$ allows one to find the second cumulant contribution to the signal attenuation for any pulse sequence $g(t)$ via Eq. (3):

$$-\ln S(T) \simeq \int \frac{d\omega}{2\pi} q_{-\omega} \mathcal{D}(\omega) q_\omega. \tag{4}$$

Here, only $\text{Re} \mathcal{D}(\omega)$ contributes, as $\text{Im} \mathcal{D}(\omega)$, odd in ω , yields zero after being integrated with an even function $|q_\omega|^2$. $\text{Im} \mathcal{D}(\omega)$ does not contain additional information as it can be restored using the Kramers–Kronig relations [26]. As we show below, it may be useful to work with the analytic function $\mathcal{D}(\omega)$ rather than with its real part.

The dispersive diffusivity can be obtained exactly from the narrow-pulse PFG diffusion coefficient $D(t) \equiv \langle x^2 \rangle / 2t$ via

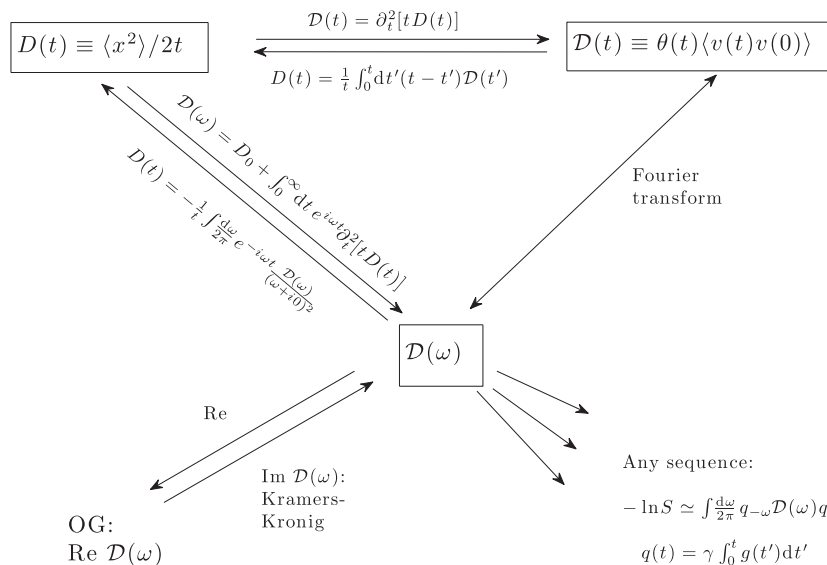


Fig. 1. General relations between the three diffusion metrics: $\mathcal{D}(\omega)$, $\mathcal{D}(t)$ and $D(t)$, and the signal attenuation.

$$\mathcal{D}(\omega) = D_0 + \int_0^\infty dt e^{i\omega t} \partial_t^2 [tD(t)], \quad (5)$$

where $D_0 \equiv D(t)|_{t=0}$ (cf. Eq. (D3) in Appendix D of Ref. [19]). The three diffusion metrics: the dispersive diffusivity $\mathcal{D}(\omega)$; the retarded velocity autocorrelator $\mathcal{D}(t)$; and the time-dependent diffusion coefficient $D(t)$ contain the same amount of information about restrictions, and thus can be expressed via each other [19], as illustrated schematically in Fig. 1.

2.3. Oscillating gradients

A comprehensive diffusion-weighted measurement must provide a way to obtain the diffusivity $\mathcal{D}(\omega)$, or the correlator $\langle v_{-\omega} v_{\omega} \rangle$, for all ω . From this point of view, the OG method, with $g(t) = g_0 \cos \omega_0 t$, is the easiest one to interpret, as in the limit of the large number $N = \omega_0 T / 2\pi \gg 1$ of oscillations,

$$q_\omega = \frac{i\pi\gamma g_0}{\omega_0} [\delta(\omega - \omega_0) - \delta(\omega + \omega_0)]$$

effectively selects the ω_0 component $\langle v_{-\omega_0} v_{\omega_0} \rangle$, so that

$$-\ln S(T)|_{g(t)=g_0 \cos \omega_0 t} \simeq \frac{(\gamma g_0)^2 T}{2\omega_0^2} \cdot \text{Re} \mathcal{D}(\omega_0). \quad (6)$$

Here we used $\delta(\omega)|_{\omega=0} = T/2\pi$ from the Fourier representation of $\delta(\omega)$. As a result, it is $\text{Re} \mathcal{D}(\omega)$ that is measured via the OG techniques [19]. In the above equation, the attenuation over each oscillation period is accumulated, such that the signal $S = \exp(-b \cdot \text{Re} \mathcal{D}(\omega_0))$ with $b = Nb_1$, $b_1 \equiv \pi(\gamma g_0)^2 / \omega_0^3$. For the dispersive $\mathcal{D}(\omega)$, the b -value alone does not define the measurement: the same value, achieved with different oscillation frequencies ω_0 , will yield different results for S .

Remarkably, the signal S is also sensitive to the initial phase φ of the oscillation $g_\varphi(t) = g_0 \cos(\omega_0 t - \varphi)$, yielding

$$-\ln S(T)|_{g_\varphi(t)} \simeq \frac{(\gamma g_0)^2 T}{\omega_0^2} \cdot \left[\frac{1}{2} \text{Re} \mathcal{D}(\omega_0) + \sin^2 \varphi \cdot D(T) \right], \quad (7)$$

where $D(T) \simeq D_\infty \equiv \mathcal{D}(\omega)|_{\omega=0} = D(t)|_{t \rightarrow \infty}$ practically is the tortuosity asymptote, since the latter is typically reached over the sufficiently long total measurement time T . Physically, the initial phase φ leads to the admixture of the PFG attenuation over the time T due to the nonzero value of $q_\omega|_{\omega \rightarrow 0} \propto \sin \varphi$, cf. Ref. [27] for $\varphi = \frac{\pi}{2}$.

Eq. (6), as well as its more general counterpart (7), link the diffusive response function $\mathcal{D}(\omega)$ of any medium to the OG attenuation with $N \gg 1$ oscillations.

The above relations reduce the original problem to finding the diffusivity $\mathcal{D}(\omega)$ for the system in which the PFG diffusion coefficient is given by Eq. (1). It can be done either by solving the problem [1] in the ω -representation, or from a Fourier transform of the retarded velocity autocorrelator $\mathcal{D}(t)$, or directly from the time-dependent diffusion coefficient $D(t)$ such as the one in Eq. (1), measured by ideal narrow-pulse PFG, via Eq. (5).

3. Results

3.1. Dispersive diffusivity at high frequencies

Below we find the high frequency limit of $\mathcal{D}(\omega)$ corresponding to Eq. (1) in three different ways, in order to demonstrate the inter-relations between the above diffusion metrics (Fig. 1): (i) directly from Eq. (1) using Eq. (5); (ii) from the recent result for the diffusivity restricted by membranes [18] derived in the frequency representation from the very beginning; and (iii) from the velocity autocorrelator $\mathcal{D}(t)$ near a flat impermeable wall [28,29].

(i) The most direct way to obtain $\mathcal{D}(\omega)$ is to use the exact relation (5). In general, this relation allows one to find $\mathcal{D}(\omega)$ for all ω knowing $D(t)$ for all t . However, it can be also utilized to relate *each term* of the expansion of $D(t)$ for short or for long t to the corresponding term of the expansion of $\mathcal{D}(\omega)$ for high or for low ω , respectively. Such expansions in the (fractional) powers of t or $1/t$ usually have finite (or even zero) convergence radius, hence their frequency counterparts should be used within the corresponding bounds. With all that in mind, we substitute the second term of Eq. (1) into Eq. (5). Reducing the Fourier integral to the Gamma-function by rotating the integration contour $\omega t = e^{i\pi/2} u$, $\int_0^\infty dt e^{i\omega t} t^{-1/2} = e^{i\pi/4} \omega^{-1/2} \Gamma(\frac{1}{2}) = e^{i\pi/4} \sqrt{\pi/\omega}$, we find the universal high frequency limit of the dispersive diffusivity

$$\mathcal{D}(\omega) \simeq D_0 \left(1 - \frac{e^{i\pi/4}}{d} \frac{S}{V} \sqrt{\frac{D_0}{\omega}} \right), \quad \omega \rightarrow \infty, \quad (8)$$

which directly leads to our main result (10) below.

Eq. (8) is the exact universal high-frequency limit of the dispersive diffusivity in the presence of restrictions, valid in the limit in which Eq. (1) applies. Further corrections in the inverse powers of ω will contain information about the permeability and curvature of the barriers, as well as the spatial correlations between them [18].

(ii) In recent Ref. [18], the problem of diffusion restricted by flat permeable membranes was considered in the frequency representation. At high frequencies, this solution is completely equivalent to that of Mitra et al. [1], as in the latter work the impermeable pore walls are approximated by locally flat randomly oriented planes as long as the diffusion length is much smaller than the curvature radius of the walls. Eq. (8) then follows from the $\omega \rightarrow \infty$ limit of $\mathcal{D}(\omega)$ found in Ref. [18], keeping only the $\mathcal{O}(\omega^{-1/2})$ term.

(iii) Finally, in Refs. [28,29] the correction $\delta \mathcal{D}(t)$ to the one-dimensional velocity autocorrelator $\theta(t) \langle u(t) u(0) \rangle$ in an impermeable box of size L was expressed as the mean

$$\delta \mathcal{D}(t) = \frac{1}{L} \int_0^L \hat{v}(t) G(x_t, x_\epsilon; t) \hat{v}(0) dx_0 dx_\epsilon dx_t dx_{t+\epsilon},$$

where $\epsilon \rightarrow 0$, $G(x_2, x_1; t)$ is the exact diffusion propagator, and the velocity operator $\hat{v}(t) \equiv [(x_{t+\epsilon} - x_t)/\epsilon] G(x_{t+\epsilon}, x_t; \epsilon) \rightarrow -2D_0 \delta'(x_{t+\epsilon} - x_t)$. Indeed, when integrated with any smooth function $f(x)$, \hat{v} gives

$$\lim_{\epsilon \rightarrow 0} \int_0^L dx dx_0 \frac{x - x_0}{\epsilon} G(x, x_0; \epsilon) f(x) = -2D_0 \int_0^L dx dx_0 f(x) \delta'(x - x_0) = D_0 [f(L) - f(0)]$$

since G at short times becomes Gaussian, $G \rightarrow G_0(x - x_0; \epsilon) \rightarrow \delta(x - x_0)$, with $\frac{x-x_0}{\epsilon} G_0 = -2D_0 \partial_x G_0$. Hence

$$\delta \mathcal{D}(t)|_{t>0} = -\frac{2}{L} D_0^2 G(0, 0, t) = -\frac{S}{V} \frac{D_0^2}{\sqrt{\pi D_0 t}}$$

for $L \gg \sqrt{D_0 t}$, where $2/L \equiv S/V$. In the last expression we used the mirror image result for the propagator $G(x, x_0; t) = G_0(x - x_0; t) + G_0(x + x_0; t)$ near a wall. Averaging over the orientations in d dimensions leads to

$$\mathcal{D}(t) = D_0 \theta(t) \left(\delta(t) - \frac{1}{d\sqrt{\pi}} \frac{S}{V} \frac{\sqrt{D_0}}{\sqrt{t}} \right). \quad (9)$$

Eq. (8) is indeed the Fourier transform of this expression (here the first term should be understood as $\lim_{\eta \rightarrow +0} \delta(t - \eta)$, as explained in Appendix D of Ref. [19]). This derivation completes the “triangle” of inter-relations in Fig. 1.

3.2. Oscillating gradients

Taking the real part of Eq. (8) we arrive at our main result,

$$\operatorname{Re} \mathcal{D}(\omega) \simeq D_0 \left(1 - C_d \frac{S}{V} \sqrt{\frac{D_0}{\omega}} \right), \quad C_d = \frac{1}{d\sqrt{2}} \quad (10)$$

in d dimensions. Note that, for the phase-shifted OG sequence, Eq. (10) defines only the first term in Eq. (7), whereas the second term, $\propto D(T)$, depends on the particular system geometry over large spatial scales $\sim \sqrt{D(T)T}$.

The above value of C_d contradicts the calculation reported in Refs. [16,17], where the corresponding prefactor $1.11 \cdot \frac{4}{\pi} \approx 1.41$ (presumably for the three-dimensional case) is about six times greater than our C_3 .

In Ref. [15], the above result for $d=3$ was represented in the form $4c/(9\sqrt{\pi}) \cdot (S/V) \sqrt{D_0 \Delta_{\text{eff}}}$, where $\Delta_{\text{eff}} = 1/(4f) = \pi/(2\omega)$ was called the effective diffusion time [30], and the correction factor $c \approx 0.73$ was evaluated numerically. The exact value is $c = 3/4$ according to Eq. (10), which indicates a 3% deviation in the numerical approximation found in Ref. [15].

3.3. CPMG in a constant gradient

A closely related measurement technique is the CPMG train in the presence of a constant gradient [5–7]. Let the interval between successive echoes be 2τ , with the rf pulses applied at $t = \tau, 3\tau, 5\tau, \dots$ (cf. notation of Ref. [14]). This is equivalent to the box-shaped oscillating gradients $g(t)$ alternating between the values $\pm g_0$ with the frequency $\omega_0 = 2\pi/4\tau$, with 4τ being the OG period. The Fourier decomposition of this effective square gradient waveform

$$g(t) = \frac{4g_0}{\pi} \sum_{k=0}^{\infty} (-)^k \frac{\cos \omega_k t}{2k+1}, \quad \omega_k = (2k+1)\omega_0.$$

The corresponding $q(t)$ has the Fourier decomposition

$$q_\omega = \frac{4\gamma g_0}{i\omega_0} \sum_{k=0}^{\infty} \frac{(-)^k}{(2k+1)^2} [\delta(\omega + \omega_k) - \delta(\omega - \omega_k)].$$

Substituting it into Eq. (4), we find the signal accumulated over a large measurement interval $T = 2n\tau$, $n \gg 1$:

$$-\ln S(T) = \frac{8(\gamma g_0)^2 T}{\pi^2 \omega_0^2} \sum_{k=0}^{\infty} \frac{1}{(2k+1)^4} \operatorname{Re} \mathcal{D}(\omega_k).$$

Using the above expression (10), find

$$-\ln S(T) = \frac{\pi^2 (\gamma g_0)^2 D_0 T}{12 \omega_0^2} \left(1 - \tilde{C}_d \frac{S}{V} \sqrt{\frac{D_0}{\omega_0}} \right), \quad (11)$$

where

$$\tilde{C}_d = C_d \cdot \frac{s_{9/2}}{s_4} \approx 0.99351277 C_d. \quad (12)$$

Here $s_\nu = \sum_{k=0}^{\infty} (2k+1)^{-\nu} = (1-2^{-\nu})\zeta(\nu)$, where $\zeta(\nu)$ is the Riemann ζ -function. In particular, $s_4 = \pi^4/96$.

The $1/\sqrt{\omega_0}$ term in the exact result (11) can be written as $-\tilde{C}_d \sqrt{2/\pi} S \sqrt{D_0 \tau}/V \approx -0.186843 S \sqrt{D_0 \tau}/V$. The numerical prefactor here agrees well with the approximate numerical limit, -0.19 (Ref. [14]), of the calculation for the finite number of pulses performed in the time domain [10,11].

4. Discussion

Our approach shows that the exact prefactor C_d , Eq. (10) (and its CPMG modification (12)), is as universal and independent on the

system geometry, as is the corresponding coefficient $4/3d\sqrt{\pi}$ in the original result (1). The simplicity and generality of this derivation underscores the utility of the dispersive diffusivity $\mathcal{D}(\omega)$. Keeping the diffusivity complex-valued simplifies calculations in many contexts [18,19]; taking its real part or relating $\mathcal{D}(\omega)$ to $D(t)$ is best left for the very last step.

We also note that in general, the concept of the effective diffusion time for the OG protocols [9,30] is well defined only as an order-of-magnitude estimate, $t \sim 1/\omega$. Indeed, the relations between $\mathcal{D}(\omega)$ and $D(t)$ are nonlocal integral relations in time or in frequency [18,19], i.e. to determine $\mathcal{D}(\omega)$ one needs to know $D(t)$ for all t , and vice-versa, to determine $D(t)$ one needs to know $\mathcal{D}(\omega)$ for all ω . For the particular short-time limit (1), it was possible to relate the $1/\sqrt{\omega}$ term in the expansion of $\mathcal{D}(\omega)$ to the corresponding \sqrt{t} term in $D(t)$, which may prompt one to define some effective diffusion time $t_{\text{eff}} = \beta/\omega$ so that the relative changes in Eqs. (1) and (10) are the same (this happens for $\beta = 9\pi/32$). However, this exact proportionality relation generally does not hold for all ω , i.e. one cannot define some constant β such that $\operatorname{Re} \mathcal{D}(\omega) = D(t)|_{t=\beta/\omega}$ for all t . Instead, one has to use the exact integral relations [19] between these quantities.

The effect of restrictions can be calculated for arbitrary gradient waveform using Eqs. (4) and (10) or their time-domain counterparts. In particular, one can use a gradient waveform defined as a numerical table in magnet's software.

5. Conclusions

In this work we used the equivalence between the description of restricted diffusion in time and frequency domains, to find the exact high-frequency behavior for the frequency-dependent diffusivity in disordered media with restrictions, accessible with the oscillating gradient and static-gradient CPMG protocols. Our results will allow one to determine the surface-to-volume ratio of restrictions using the measurement techniques naturally suitable for the shortest time scales. We also demonstrated how the effective medium approach unifies and relates to each other different diffusion metrics, such as the velocity autocorrelator and the time- and frequency-dependent diffusion coefficients.

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References

- [1] P.P. Mitra, P.N. Sen, L.M. Schwartz, P. Le Doussal, Diffusion propagator as a probe of the structure of porous media, Phys. Rev. Lett. 68 (1992) 3555–3558.
- [2] L.L. Latour, P.P. Mitra, R.L. Kleinberg, C.H. Sotak, Time-dependent diffusion coefficient of fluids in porous media as a probe of surface-to-volume ratio, J. Magn. Reson. Ser. A 101 (1993) 342–346.
- [3] R.W. Mair, G.P. Wong, D. Hoffmann, M.D. Hürlimann, S. Patz, L.M. Schwartz, R.L. Walsworth, Probing porous media with gas diffusion NMR, Phys. Rev. Lett. 83 (1999) 3324.
- [4] L.L. Latour, K. Svoboda, P.P. Mitra, C.H. Sotak, Time-dependent diffusion of water in a biological model system, Proc. Natl. Acad. Sci. USA 91 (1994) 1229.
- [5] J. Stepišnik, Analysis of NMR self-diffusion measurements by a density matrix calculation, Physica B 104 (1981) 350–364.
- [6] P.T. Callaghan, J. Stepišnik, Frequency-domain analysis of spin motion using modulated gradient NMR, J. Magn. Reson. A 117 (1995) 118.
- [7] P.T. Callaghan, J. Stepišnik, Generalised Analysis of Motion Using Magnetic Field Gradients, Advances in Magnetic and Optical Resonance, vol. 19, Academic Press, New York, 1996, pp. 324–397.
- [8] T.M. de Swiet, P.N. Sen, Decay of nuclear magnetization by bounded diffusion in a constant field gradient, J. Chem. Phys. 100 (1994) 5597–5604.
- [9] E.J. Fordham, P.P. Mitra, L.L. Latour, Diffusion times in multiple-pulse PFG diffusion measurements in porous media, J. Magn. Reson. A 121 (1996) 187–192.

- [10] P.N. Sen, A. André, S. Axelrod, Spin echoes of nuclear magnetization diffusing in a constant magnetic field gradient and in a restricted geometry, *J. Chem. Phys.* 111 (1999) 6548.
- [11] S. Axelrod, P.N. Sen, Nuclear magnetic resonance spin echoes for restricted diffusion in an inhomogeneous field: methods and asymptotic regimes, *J. Chem. Phys.* 114 (2001) 6878.
- [12] L.J. Zielinski, P.N. Sen, Restricted diffusion in grossly inhomogeneous fields, *J. Magn. Reson.* 164 (2003) 145–153.
- [13] L.J. Zielinski, Effect of internal gradients in the nuclear magnetic resonance measurement of the surface-to-volume ratio, *J. Chem. Phys.* 121 (2004) 352.
- [14] L.J. Zielinski, M.D. Hürlimann, Probing short length scales with restricted diffusion in a static gradient using the CPMG sequence, *J. Magn. Reson.* 172 (2005) 161–167.
- [15] J. Xu, J. Xie, J. Jourquin, D.C. Colvin, M.D. Does, V. Quaranta, J.C. Gore, The influence of cell cycle phase on ADC in synchronized cells detected using temporal diffusion spectroscopy, *Magn. Reson. Med.*, in press, doi:10.1002/mrm.22704.
- [16] J. Stepišnik, A. Mohorič, A. Duh, Diffusion and flow in a porous structure by the gradient spin echo spectral analysis, *Physica B* 307 (2001) 158–168.
- [17] J. Stepišnik, S. Lasič, A. Mohorič, I. Serša, A. Sepe, Velocity autocorrelation spectra of fluid in porous media measured by the CPMG sequence and constant magnetic field gradient, *Magn. Reson. Imaging* 25 (2007) 517–520.
- [18] D.S. Novikov, E. Fieremans, J.H. Jensen, J.A. Helpert, Random walks with barriers, *Nature Phys.* (2011), doi:10.1038/nphys1936.
- [19] D.S. Novikov, V.G. Kiselev, Effective medium theory of a diffusion-weighted signal, *NMR Biomed.* 23 (2010) 682–697.
- [20] R.P. Kennan, J. Zhong, J.C. Gore, On the relative importance of paramagnetic relaxation and diffusion-mediated susceptibility losses in tissues, *Magn. Reson. Med.* 22 (1991) 197–203.
- [21] M.D. Does, J. Zhong, J.C. Gore, In vivo measurement of ADC change due to intravascular susceptibility variation, *Magn. Reson. Med.* 41 (1999) 236–240.
- [22] V.G. Kiselev, Effect of magnetic field gradients induced by microvasculature on NMR measurements of molecular self-diffusion in biological tissues, *J. Magn. Reson.* 170 (2004) 228–235.
- [23] P.T. Callaghan, *Principles of Nuclear Magnetic Resonance Microscopy*, Oxford University Press Inc., New York, 1991.
- [24] V.G. Kiselev, The Cumulant Expansion: An Overarching Mathematical Framework for Understanding Diffusion NMR, in: D. Jones (Ed.), *Diffusion MRI: Theory, Methods and Applications*, Oxford University Press, 2010.
- [25] N.G. van Kampen, *Stochastic Processes in Physics and Chemistry*, Elsevier Science BV, 1997.
- [26] L.D. Landau, E.M. Lifshitz, *Statistical Physics. Pt. 1*, Pergamon Press, Oxford, 1969.
- [27] M.D. Does, E.C. Parsons, J.C. Gore, Oscillating gradient measurements of water diffusion in normal and globally ischemic rat brain, *Magn. Reson. Med.* 49 (2003) 206–215.
- [28] A.F. Fröhlich, V.G. Kiselev, Effect of impermeable interfaces on apparent diffusion coefficient in heterogeneous media, *Appl. Magn. Reson.* 29 (2005) 123–137.
- [29] A.F. Fröhlich, S.N. Jespersen, L. Østergaard, V.G. Kiselev, The effect of impermeable boundaries of arbitrary geometry on the apparent diffusion coefficient, *J. Magn. Reson.* 194 (2008) 128–135.
- [30] E.C. Parsons, M.D. Does, J.C. Gore, Temporal diffusion spectroscopy: theory and implementation in restricted systems using oscillating gradients, *Magn. Reson. Med.* 55 (2006) 75–84.