

Surface-to-volume ratio with oscillating gradients

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Introduction: The universal short-time behavior [1] of the diffusion coefficient in d spatial dimensions, Eq.(1), allows one to determine the surface-to-volume ratio S/V of restrictions in porous materials [2, 3] and in biological tissues [4]. However, the direct measurement of $D(t)$ with pulse field gradient (PFG) diffusion-weighted NMR at millisecond time scales is often technically challenging, especially *in vivo*. A more convenient way to get into the short-time limit is by applying the oscillating gradient (OG) method [5], where the diffusion weighting is effectively accumulated over many periods of oscillation. A variant of this technique requires a constant diffusion gradient, with the temporal modulation achieved by applying periodic refocusing radiofrequency pulses of the CPMG type [5, 6].

$$D(t) \equiv D_0 \left(1 - \frac{4}{3d\sqrt{\pi}} \cdot \frac{S}{V} \sqrt{D_0 t} \right), \quad D_0 \equiv D|_{t=0}, \quad (1) \quad D_{OG}(\omega) \equiv D_0 \left(1 - C_d \frac{S}{V} \sqrt{\frac{D_0}{\omega}} \right), \quad \omega \rightarrow \infty. \quad (2)$$

In view of applying the oscillating techniques [5, 6], an immediate question is, What is the counterpart of Eq. (1)? As $t \sim 1/\omega$, where ω is the gradient oscillation frequency, the $t^{1/2}$ term in Eq. (1) must transform in the frequency domain to $\sim \omega^{-1/2}$, cf. Eq.(2). Quite remarkably, the prefactor C_d in this expression has never been explicitly derived, except for the case of a finite number of CPMG echoes in $d=1$ dimension [7, 8]. Furthermore, there exists a discrepancy between its numerical value provided by different groups [9-12].

In this work, we find the prefactor C_d *exactly* both for the OG and CPMG cases [Eqs. (6) and (7) below] in the limit of a large number $N \gg 1$ of oscillations, which 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. (7)], thereby justifying the view of the CPMG method as being basically equivalent to the OG, and validate the approximate numerical values found in Ref. [9] for the CPMG and of Ref. [10] for the OG. To derive our result, we utilize the recently established one-to-one correspondence between the PFG and OG diffusivities using the effective-medium description of diffusion in disordered materials [13,14].

Methods: We begin with the known approximation to the diffusion-weighted signal, S , for weak gradients [15, 16]:

$$-\ln S(T) \equiv \frac{1}{2} \int_0^T dt_1 dt_2 q(t_1) \langle v(t_1) v(t_2) \rangle q(t_2) \equiv \frac{1}{2} \int \frac{d\omega}{2\pi} q_{-\omega} \langle v_{-\omega} v_{\omega} \rangle q_{\omega}, \quad q_{\omega} = \int_0^T dt e^{i\omega t} q(t), \quad \text{where} \quad q(t) = \gamma \int_0^t dt' g(t'). \quad (3)$$

The signal depends on the gradient wave form $g(t)$ with total duration T (here γ is the gyromagnetic ratio). In Eq.(3), we went from the time to the frequency representation, which in this context proves especially convenient. The power spectrum $\langle v_{-\omega} v_{\omega} \rangle$ of molecular velocity is just the Fourier transform of the autocorrelation function $\langle v(t_1) v(t_2) \rangle$ with respect to the time interval $t_1 - t_2$. The OG diffusivity (2) is then $D_{OG}(\omega) = \frac{1}{2} \langle v_{-\omega} v_{\omega} \rangle$ [5,6,15]. The key problem is to find $\langle v_{-\omega} v_{\omega} \rangle$ for the system in which the time-dependent PFG diffusion coefficient has the form (1) due to restrictions.

In Ref. [14], we derived a general relation that connects $\langle v_{-\omega} v_{\omega} \rangle$ and the PFG diffusivity $D(t)$ for *any* medium. This relation involves the following fundamental object, the complex-valued *dispersive diffusivity* $D(\omega)$, which is a retarded response function relating the Fourier harmonic $\mathbf{J}(\omega, \mathbf{r}) = -D(\omega) \cdot \partial_r \Psi(\omega, \mathbf{r})$ of the current $\mathbf{J}(t, \mathbf{r})$ of diffusing particles to the corresponding frequency harmonic of a lump of particle density $\Psi(t, \mathbf{r})$. The diffusivity $D(\omega)$ enters the generalized diffusion equation $-i\omega \Psi(\omega, \mathbf{r}) = D(\omega) \partial_r^2 \Psi(\omega, \mathbf{r})$, whose solution yields $\langle x^2 \rangle / 2t \equiv D(t)$, the PFG diffusivity. It is given by

$$D(\omega) = D_0 + \int_0^{\infty} dt e^{i\omega t} \partial_t^2 [tD(t)]. \quad (4)$$

We show that its real part $\text{Re } D(\omega) = \frac{1}{2} \langle v_{-\omega} v_{\omega} \rangle \equiv D_{OG}(\omega)$ [14]. This links the diffusive response $D(\omega)$ to the OG attenuation with $N \gg 1$ oscillations.

Results: Substituting the second term of Eq. (1) into Eq. (4), we find the universal high frequency limit (5) of the dispersive diffusivity. This can be also derived from the $\omega \rightarrow \infty$ limit of $D(\omega)$ found in Ref. [13]. Taking the real part of Eq. (5) we arrive at our main result, Eq.(6), in d dimensions.

$$D(\omega) \equiv D_0 \left(1 - \frac{e^{i\pi/4}}{d} \frac{S}{V} \sqrt{\frac{D_0}{\omega}} \right), \quad \omega \rightarrow \infty. \quad (5) \quad \text{Re } D(\omega) \equiv D_0 \left(1 - C_d \frac{S}{V} \sqrt{\frac{D_0}{\omega}} \right), \quad C_d = \frac{1}{d\sqrt{2}} \quad (6) \quad \tilde{C}_d \approx 0.99351277 C_d. \quad (7)$$

The above value of C_d contradicts the calculation reported in Refs. [11, 12], where the corresponding prefactor is about six times greater than our C_3 . Numerical simulations of Ref. [10] reproduce the above results within 3% accuracy. For CPMG in a constant gradient, with the OG frequency $\omega = \pi/\tau$, where 2τ is the interval between successive echoes, the corresponding coefficient is given by Eq.(7). The approximate numerical limit (Ref. [9]) of the calculation [7, 8] for the finite number of pulses performed in the time domain agrees well with the exact value (7).

Discussion: Our approach shows that the exact prefactor C_d , Eq. (6) [and its CPMG modification (7)], of the high-frequency limit, is as universal and independent of the system's geometry as is the corresponding coefficient $4/3d\sqrt{\pi}$ in the original t -dependent result (1), due to the equivalence of the t and ω representations. The generality of this derivation underscores the utility of the dispersive diffusivity $D(\omega)$. We also note that in general, the concept of the effective diffusion time [17] is defined only as an order-of-magnitude estimate, $t \sim 1/\omega$. Indeed, the relations between $D(\omega)$ and $D(t)$, such as Eq.(4), are nonlocal integral relations in time or in frequency [14, 13], i.e. to determine $D(\omega)$ one needs to know $D(t)$ for all t , and vice-versa. The knowledge of $D(\omega)$ allows one to calculate the effect of restrictions for an arbitrary gradient wave form $g(t)$ using the Fourier representation (3). In particular, one can substitute into Eq.(3) the Fourier transform q_{ω} obtained from $g(t)$ defined as a numerical table in magnet's software.

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