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Concise derivation of oscillating-gradient-derived ADC

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ABSTRACT

The apparent diffusion coefficient (ADC) is analyzed for the case of oscillating diffusion-sensitizing gradients in the high-frequency regime. We provide a concise derivation of the analytical expression for the ADC for an arbitrary number of gradient oscillations N and initial phase φ. It is demonstrated that an ultimate goal – to determine the surface-to-volume ratio (S/V) from MR measurements by using oscillating gradients – can be achieved with *cosine*-type gradients ($\varphi = 0$) for an arbitrary N. However, to determine S/V employing gradients with $\varphi \neq 0$ (including the *sine*-type gradients) and arbitrary N additionally requires prior knowledge of the time-dependent diffusion coefficient $D(t)$. The latter is rarely known *a priori* but can be estimated under certain limiting conditions: (i) in the short time regime, when the *total* diffusion time of the measurements, t, is smaller than the characteristic diffusion time of the microstructural system of interest, an analytical expression for $D(t)$ is available (Mitra's expression) and this allows S/V to be determined in the short time regime with *sine*-type gradients; (ii) in the important case of purely *restricted* diffusion, $D(t) \to 0$ at sufficiently long time, the signal becomes independent of φ and behaves as for the *cosine*-type gradients, thus, allowing determination of S/V.

1. Introduction

Diffusion MRI studies of short length microstructural scales provide a powerful tool for examination of porous media and biological systems. However, such measurements are predicated on acquiring an MR "diffusion signal" having sufficient dynamic range in the short diffusion-time regime, i.e., sufficient signal-to-noise at sufficiently high diffusion-encoding (i.e., high b-values). Achieving high b-values in the short time regime is a challenging technical problem. A promising approach to the short time limit is to apply high frequency oscillating gradients (OG). Most often, the gradient oscillation pattern is simply sinusoidal or cosinusoidal. Oscillating gradient diffusion experiments are increasingly being used for studying short length microstructural scales, e.g., [1–16]. In particular, OG are used for calculating the surface-to-volume ratio (S/V) from the measured apparent diffusion coefficient (ADC).

The ADC, herein identified by the symbol $\tilde{D}(t)$, is defined in the standard way [17],

$$\tilde{D}(t) = -\frac{1}{b} \cdot \ln\left(\frac{S(t)}{S_0}\right), \tag{1}$$

where $S(t)$ is the MR signal at diffusion time t, S_0 is the signal in the absence of diffusion-sensitizing gradients and b is the b-value. In general, the ADC, $\tilde{D}(t)$, depends not only on the diffusion time of the measurements, t, but on the time evolution of the diffusion sensitizing gradient as well. For experiments with gradients oscillating at frequency ω, t can be effectively substituted (at least, in some cases) by the period of a *single* gradient oscillation $T = 2\pi/\omega$. The oscillation period T can, in principal, be chosen to be "short enough" by using a high oscillation frequency. Likewise, the b-value is proportional to the number of oscillations N and can, in principal, be made "high enough" to achieve sufficiently high diffusion-encoding. (As noted earlier, achieving such experimental conditions in practice can be very challenging, a subject beyond the scope of this manuscript.)

In a previous publication [18], one of us (AS) derived analytical expressions for $\tilde{D}(t)$ in the case of an oscillating diffusion-sensitizing gradient,

$$g(t) = g_0 \cdot \cos(\omega t - \varphi), \tag{2}$$

as a function of ω, the total number of oscillations N, and the initial gradient phase φ in the "high-frequency regime", Eq. (3):

$$\tilde{D}(t = 2\pi N/\omega) = D_0 \cdot \left[1 - \frac{c(\varphi, N)}{d} \cdot \left(\frac{S}{V}\right) \cdot \sqrt{\frac{D_0}{\omega}}\right],$$
$$\omega \gg t_D^{-1} = D_0 \cdot \left(\frac{S}{d\,V}\right)^2. \tag{3}$$

Here D_0 is the free diffusion coefficient, (S/V) is the surface-to-volume ratio of the microstructural system of interest, d is the

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system's dimensionality, t_D is the characteristic diffusion time, and the coefficient $c(\varphi, N)$ is given by

$$c(\varphi,N) = \frac{32\pi N^{3/2}\sin^2\varphi + 12\pi N\cdot \mathrm{C}(2N^{1/2}) + 3(3+4\sin^2\varphi)\cdot \mathrm{S}(2N^{1/2})}{6\sqrt{2}\pi N(1+2\sin^2\varphi)}, \quad (4)$$

where C(x) and S(x) are the Fresnel functions [19]. The particular cases of the *cosine*- and *sine*-type gradients correspond to $\varphi = 0$ and $\varphi = \pi/2$, respectively. The limiting value of $c(0, N \to \infty) = 1/\sqrt{2}$ coincides with the result obtained in [20] in the framework of the frequency domain approach.

Note that, as per Eq. (3), the high frequency regime is defined as $\omega \gg t_D^{-1}$ and t_D is a function of D_0, S/V, and d. Considering the diffusion of water at 37 °C ($D_0 \sim 3\ \mu\mathrm{m}^2/\mathrm{ms}$) in idealized spherical volumes of radii 0.5, 1, 5, 10, and 50 μm, the characteristic diffusion times are about 0.08, 0.33, 8.3, 33, and 833 ms, respectively. Accepting $\omega \sim 10 \cdot t_D^{-1}$ as the lower limit to the high frequency regime, then the high frequency regime is achieved when $f = \omega/2\pi > 20000, 5000, 200, 50$, and 2 Hz, respectively.

The divergence of the coefficient $c(\varphi \neq 0, N)$ at large N imposes a restriction on the oscillation number N, namely, Eqs. (3) and (4) are valid only under the condition $c(\varphi \neq 0, N)/\Omega^{1/2} \ll 1$, where $\Omega = \omega t_D$ is the dimensionless frequency. In particular, for any φ not too close to 0 (including the *sine*-type gradient), these equations are valid when the number of oscillations N does not exceed the parameter Ω: $N < \Omega$, or, put another way, when the *total* duration of the diffusion-sensitizing waveform $t = N \cdot 2\pi/\omega$ is smaller than the characteristic time t_D. This brief Communication provides a simple and straightforward derivation of the expression for the ADC, $\tilde{D}(t)$, that is valid for an arbitrary relationship between the parameters N and Ω. Further, it is shown that, under certain conditions, measurement of $\tilde{D}(t)$, thus estimation of Ω and hence t_D, given knowledge of ω, allows determination of S/V.

2. Derivation of ADC

In the Gaussian phase approximation, which is valid at sufficiently low b-values, (e.g., [17,21]) the time-dependent ADC, $\tilde{D}(t)$, can be expressed in terms of the mean square displacement $L(t) = \langle(\delta x)^2\rangle_t$ [22]

$$b \cdot \tilde{D}(t) = -\frac{\gamma^2}{2}\int_0^t d\tau_1 \int_0^{\tau_1} d\tau_2\, g(\tau_1)g(\tau_2)\cdot L(\tau_1 - \tau_2), \quad (5)$$

where $t = 2\pi N/\omega$ is the total time of the gradient waveform duration, γ is the gyromagnetic ratio of the nuclide of interest, and b is the b-value. For the oscillating gradient waveform in Eq. (2), the latter is given by [3]:

$$b = N \cdot b_0 \cdot (1 + 2\sin^2\varphi), \quad b_0 = (\gamma g_0)^2 \cdot \frac{\pi}{\omega^3}. \quad (6)$$

Introducing a new variable $\tau = \tau_1 - \tau_2$ in the internal integral and changing the order of integration, Eq. (5) can be rewritten as

$$b \cdot \tilde{D}(t) = -\frac{\gamma^2}{2}\int_0^t d\tau\, L(\tau)\int_\tau^t d\tau_1\, g(\tau_1)\cdot g(\tau - \tau_1). \quad (7)$$

For the gradient waveform given in Eq. (2), the internal integral can be readily calculated:

$$b \cdot \tilde{D}(t) = -\frac{(\gamma g_0)^2}{4\omega}\int_0^t d\tau\, L(\tau)\, u(t,\tau)$$
$$u(t,\tau) = \omega\cdot(t-\tau)\cdot\cos\omega\tau - \cos 2\varphi\cdot\sin\omega\tau. \quad (8)$$

Integrating the integral in Eq. (8) by parts yields,

$$b \cdot \tilde{D}(t) = \frac{(\gamma g_0)^2}{2\omega^2}\cdot\sin^2\varphi\cdot L(t) + \frac{(\gamma g_0)^2}{2\omega^2}\cdot\int_0^t d\tau\,\frac{\partial L(\tau)}{\partial\tau}\,w(t,\tau)$$
$$w(t,\tau) = \omega\cdot(t-\tau)\cdot\sin\omega\tau - 2\sin^2\varphi\cdot\cos\omega\tau. \quad (9)$$

Note that the quantity $\partial L(\tau)/\partial\tau$ in the integrand has the meaning of an *instantaneous* diffusion coefficient (i.e., the diffusion coefficient determined at a given instant in "diffusion time").

To proceed further requires specifying an expression for the mean square displacement, or for the *effective* time-dependent diffusion coefficient $D(t)$ defined as

$$D(t) = \frac{L(t)}{2dt}. \quad (10)$$

In [18], we used the well-known short time expansion for $D(t)$ derived by Mitra [23]:

$$D(t) = D_0\cdot\left[1 - \frac{4}{3\pi^{1/2}}\cdot(t/t_D)^{1/2}\right], \quad t \ll t_D. \quad (11)$$

Combining Eqs. (10) and (11) yields an expression for $L(t)$. Substituting this in both the $L(t)$ terms in Eq. (9) and calculating the integral in the second term yields the previously obtained results as in Eqs. (3) and (4).

Importantly, the divergence at large N ($\sim N^{1/2}$) of the ADC in this approximation comes from the first (integrated) term in Eq. (9). The second (non-integrated) term remains finite: with N increasing, it converges to its limiting value rather fast. Such a fast convergence justifies using the short-time expansion of $D(t)$ in this term. Thus, substituting the expression for $L(t)$ derived by combining Eqs. (10) and (11) only in the second term in Eq. (9) and integrating yields the following expression for the ADC:

$$\tilde{D}(t) = \frac{1}{1+2\sin^2\varphi}\cdot\left\{[D_0 + 2\sin^2\varphi\cdot D(t)] - D_0\cdot\frac{4\pi N\cdot\mathrm{C}(2N^{1/2}) + (3+4\sin^2\varphi)\cdot\mathrm{S}(2N^{1/2})}{2\pi N\cdot(2\Omega)^{1/2}}\right\}. \quad (12)$$

We note that this result, which is valid without restriction on the number of gradient oscillations N, can be also derived in the framework of a less compact, alternative approach based on Fourier domain analysis [24].

Eq. (12) relates the free diffusion coefficient D_0, the effective diffusion coefficient $D(t)$, the ADC, i.e., $\tilde{D}(t)$, and the parameter Ω. Hence, in the general case ($\varphi \neq 0$, arbitrary N), even with known D_0, Eq. (12) does not allow the estimation of Ω (and, consequently, S/V) from MR measurements with oscillating gradients without prior knowledge of $D(t)$, which is rarely known *a priori* but can be estimated under certain limiting conditions.

3. Discussion

As the Fresnel functions tend to ½ at large arguments, the ADC converges to

$$\tilde{D}(t) = \frac{D_0}{1+2\sin^2\varphi}\cdot\left(1 - \frac{1}{(2\Omega)^{1/2}}\right) + \frac{2\sin^2\varphi}{1+2\sin^2\varphi}\cdot D(t), \quad N \gg 1. \quad (13)$$

In any purely *restricted* geometry, at sufficiently long time, $t \gg t_D$, the mean squared displacement, $L(t)$, becomes a constant depending on system geometry, consequently the effective diffusion coefficient $D(t) \to 0$ as [25]

$$D(t) \approx \eta\cdot R^2/t \sim 1/N, \quad (14)$$