An approximate analytical formula for the long time apparent diffusion coefficient

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Introduction

Diffusion MRI gives a measure of the average distance travelled by water molecules in a certain medium and can give useful information on cellular structure and structural change when the medium is biological tissue (see review [1]). In particular, a useful feature would be to infer from DMRI measurements changes in the cellular volume fraction occurring upon various physiologic or pathologic conditions. We give in two and three dimensions an approximate analytical formula for the long time apparent diffusion coefficient (ADC) of the diffusion MRI signal attenuation typically obtained with clinical scanners. From the long time ADC measurements before and after cell swelling, we are able to use the analytical formula to accurately and robustly estimate the change in the cellular volume fraction.

Theory

Given the intrinsic diffusion coefficient D, permeability κ, intra-cellular volume fraction v^i, and surface to volume ratio S/V, we propose an approximate analytical formula for the long time ADC, more precisely, for the steady-state value, ADC_∞, in the limit as the diffusion time goes to infinity. We define the ADC in the following way: $\log\Psi(b) = -ADC * b + O(b^2)$, where ψ is the total signal attenuation and the b value is $b = \|\vec{q}\|^2 \int_0^t (\int_s^u f(s)ds)^2\, du$ for the diffusion gradient with profile $f(t)$ and gradient strength $\vec{g} = \vec{q}/\gamma$, where γ is the gyro-magnetic ratio. This ADC can be measured from signals obtained only at low b-values. Now we give the approximate formulae in two and three dimensions for the steady-state value of the ADC. The formulae are obtained by generalizing the results for disks and spheres [2,3] and they are $D_{2D}^A \equiv D\frac{1+\xi(1-v^i)/2}{1+\xi(1+v^i)/2}, dim = 2$ and $D_{3D}^A \equiv D\frac{1+2\xi(1-v^i)/3}{1+\xi(2/3+1/3v^i)}, dim = 3$, where $\xi = \frac{DS/V}{\kappa dim}$. In the limit case v^i=1, the corresponding results are known (see [4]). The formulae we present above are more general in that v^i can be any value between 0 and 1. We show if D, S/V and κ can be obtained, we can robustly use the formulae to estimate change in the cellular volume fraction v^i.

Results and discussion

First we simulated DMRI signals for the PGSE sequence with δ=10 ms and Δ=50 ms by numerically solving the two compartment Bloch-Torrey partial differential equation on a sample consisting of periodically placed cubes in three dimensions (Fig 1), with the distance between cube centers being 10 μm. We simulated the DMRI signal with an intrinsic diffusion coefficient D = 2.8e-3 μm²/μs. In Table 1, we show the computed ADC for two different volume fractions, v^i = 0.73 and v^i = 0.93 (surface to volume ratio S/V=0.67μm^{-1} and 0.62μm^{-1}, respectively) at different permeabilities κ. Because at the higher volume fraction, the ADC has not reached its steady-state value even at diffusion time δ+Δ=60 ms, we also included the steady-state value ADC_∞ computed from the theory of homogenization. We see that the simulated ADC is very close to ADC_∞ for v^i = 0.73 at diffusion time δ+Δ=60 ms, but for v^i = 0.93 and lower permeability, the steady-state value still has not been reached. Comparing both the simulated ADC and ADC_∞ with the analytical formula in 3 dimensions, D_{3D}^A, we see the agreement is good. Finally, we used the exact values of D, S/V and κ and the simulated ADC at δ=10 ms and Δ=50 ms to invert the analytical formula for the volume fraction. We see the estimated v^i is very accurate at low permeabilities and less good at high permeabilities. Fortunately, the error in the estimate of v^i occurs in the same direction for both volume fractions (in this case, an under-estimate), so that when we subtract the two estimated volume fractions, we are able to obtain a very good estimate of the **change** in the volume fraction, the true value of which is Δv=0.2. Our estimated Δv is between 0.16 and 0.19 for all the permeabilities tested.

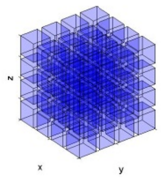

Fig 1. Periodic lattice of cubic cells

κ (μm/μs)	Simulated ADC (μm²/μs) δ=10 ms, Δ=50 ms		ADC_∞ (homogenization)		Analytical formula D_{3D}^A		Invert ADC for v^i		Invert 2 ADCs for Δv^i
	v^i=0.73	v^i=0.93	v^i=0.73	v^i=0.93	v^i=0.73	v^i=0.93	v^i=0.73	v^i=0.93	
5e-4	1.76e-3	1.54e-3	1.75e-3	1.53e-3	1.61e-3	1.39e-3	0.63	0.82	+0.19
1e-4	1.04e-3	7.18e-4	1.01e-3	6.78e-4	8.93e-4	5.43e-4	0.66	0.83	+0.17
5e-5	8.42e-4	5.05e-4	8.11e-4	4.54e-4	7.38e-4	3.58e-4	0.68	0.85	+0.17
1e-6	6.17e-4	2.74e-4	6.04e-4	2.13e-4	5.95e-4	1.87e-4	0.72	0.88	+0.16
5e-6	5.79e-4	2.37e-4	5.74e-4	1.77e-4	5.75e-4	1.63e-4	0.73	0.89	+0.16

In Figure 2, we plot the family of solutions (v^i,S/V) giving D_{3D}^A in the range of 5e-4 to 1.5e-3 μm²/μs, which is consistent with experimental findings. In Fig2a we show the solution curves for intrinsic diffusion coefficient D = 2.8e-3 μm²/μs and κ= 1e-4μm/μs. In Fig 2b we show the analogous curves for D = 2.8e-3 μm²/μs and κ= 1e-5μm/μs. Suppose the experimentally measured ADC is 1e-3 μm²/μs, looking at the Fig 2a, where κ= 1e-4μm/μs, we see that S/V is in the range [0.2,0.4] μm^{-1}, otherwise, the corresponding volume fraction v^i will be too low to be physically realistic (less than 0.7). Assuming convex-shaped cells, the range of the S/V ratio means that the average radius of the cells is 3/(S/V), i.e., in the range [7.5, 15] μm. In Fig 2b, where κ= 1e-5μm/μs, we see that the S/V will have to be less than 0.1 μm^{-1} to obtain a corresponding volume fraction v^i of at least 70%. But an S/V ratio of 0.1 μm^{-1} is very low, meaning the average radius of the cells is 3/(S/V) = 30 μm, which is too large. In Fig 2c and 2d, we show the family of solutions (v^i,S/V) giving a D_{3D}^A **drop** of between 5% and 75%, when going from v^i to 100 percent intra-cellular volume fraction for κ= 1e-4μm/μs and κ= 1e-5μm/μs, respectively. We have defined this drop as $D_{3D}^A\, drop = 1 - \frac{D_{3D}^A(v^i_{swell=100\%})}{D_{3D}^A(v^i)}$. We see that given a fixed v^i, cells swelling to 100% volume fraction causes a higher ADC drop when S/V is higher (equivalently, when the cells are smaller). For a given amount of cell swelling, the ADC drop is also higher when κ is smaller.

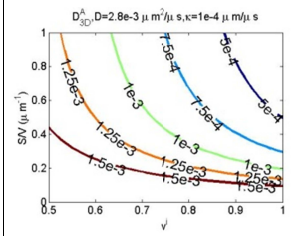

Fig 2a. ADC level curves, D = 2.8e-3 μm²/μs and κ= 1e-4μm/μs

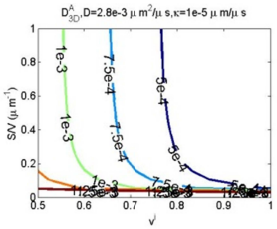

Fig 2b. ADC level curves, D = 2.8e-3 μm²/μs and κ= 1e-5μm/μs.

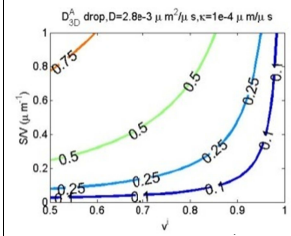

Fig 2c. ADC drop from v^i to 100%, D = 2.8e-3 μm²/μs and κ= 1e-4μm/μs

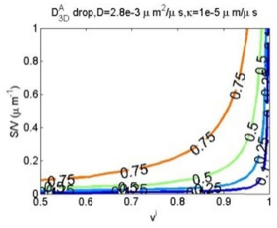

Fig 2d. ADC drop from v^i to 100%, D = 2.8e-3 μm²/μs and κ= 1e-5μm/μs

References [1] LeBihan 2007 Phys Med Bio 52. [2] Torquato et al 1995, Phys. Rev. Lett. 75: 4067. [3] Graham et al 2003 J. Heat Transfer 125:389—393. [4] Novikov et al 2011, Nat Phys 7:508—514.