Susceptibility-induced increase of apparent diffusion coefficient: BOLD effect behind diffusion fMRI

Dmitry S. Novikov[1], Marco Reisert[2], and Valerij G. Kiselev[2]
[1]*Radiology, NYU School of Medicine, New York, NY, United States,* [2]*Radiology, University Medical Center Freiburg, Germany*

Introduction: Diffusion measurements are confounded by the presence of microscopic magnetic field gradients induced by a heterogeneous magnetic susceptibility $\chi(\mathbf{r})$ inherent to specific cell populations [1]. A simple picture [1,2] is that the microscopic gradients create "hot spots", where the applied DWI gradient is nearly cancelled by the microscopic ones. The result of such interference is a net increase of the DWI signal, with the apparent diffusion coefficient ADC$<D_0$ always smaller than the genuine (molecular) one, D_0, in agreement with early experiments [1]. The picture of "hot spots" presumes their size to be larger than the typical displacement of water molecules during the measurement (slow diffusion), i.e., that the diffusion time $t \ll t_D$, where t_D is the time to diffuse across the characteristic length scale on which the susceptibility profile $\chi(\mathbf{r})$ varies in space.

Results: Here, the opposite situation of the *fast diffusion*, $t \gg t_D$, is considered theoretically and numerically for the first time for a variety of diffusion sequences in the geometry of Fig. 1. We find:

1. ADC either over- or underestimates the genuine diffusivity D_0. **The sign of the deviation of ADC from D_0 depends on the pulse sequence** (Figs. 2-3). In particular, **ADC > D_0** when either no refocusing is used (diffusion pulses of opposite polarity), or for the twice refocused SE [3]. For the single refocusing pulse (e.g. PGSE), **ADC < D_0** in agreement with early experiments [1].
2. **Any deviation of ADC from D_0 grows with t**, Figs. 2-3, being effectively enhanced by the factor $t/t_D \gg 1$, when the microscopic magnetic field is induced by effectively two-dimensional objects (of any orientation), such as the capillary network, Fig. 1.
3. **The deviation of ADC from D_0 is inherently anisotropic:** For the statistically isotropic distribution of $\chi(\mathbf{r})$, the ADC tensor eigenvalues along x, y, z relate in proportion 5:5:11 due to the Larmor frequency anisotropy induced by B_0 field along z.
4. The deviation of ADC from D_0 is quantitatively sufficient to explain the relative signal change, increasing with the b-value, both in hypercapnia [4] and under neuronal activation (in the so-called diffusion fMRI experiments [5]), suggestive of the BOLD-related origins for these effects.

Methods: Our starting point is the microscopic Bloch-Torrey equation with the locally variable Larmor frequency offset $\Omega(\mathbf{r})$ found by the convolution of $\chi(\mathbf{r})$ with an elementary dipole field. We assume unrestricted Gaussian diffusion for simplicity. The signal averaged over a large volume is calculated in the effective medium framework [6,7]. Analytical calculations are shown in Fig. 2 for the narrow gradient pulses of opposite polarity, with straightforward generalizations onto other diffusion sequences. The magnitude of the effect is determined by the parameter $\alpha = \delta\Omega\, t_D$, where $\delta\Omega$ is a typical Larmor frequency shift, in our case taken on the surface of a vessel with radius ρ = 3.5 μm in Fig. 1, and $t_D = \rho^2/D_0$, D_0 = 1 μm^2/ms. Explicit analytical expressions for the ADC are obtained up to the order α^2. Numerical results in Figs. 2-3 are obtained using simulated paramagnetic microvasculature (Fig. 1) created by tracking a random walker moving with a significant inertia under periodic boundary conditions. This medium is isotropic by selection and is cast on a 256^3 lattice. The volume fraction of vessels is 2.2%. Monte Carlo simulations were performed with 1-20×10^6 spins accumulating phases during random hopping on the 256^3 lattice, with the applied gradients switching in time as prescribed by the diffusion sequences, e.g. [3].

Discussion: It is well recognized that diffusion probes tissue microstructure. This study for the first time demonstrates that the *apparent* diffusion coefficient possesses such a potential for probing the heterogeneous susceptibility. The decreased ADC$<D_0$ observed in early PGSE experiments [1] can be due to either the "hot spots" picture, or the present effect, Fig. 3. Conversely, an almost 5% *increase* in ADC relative to D_0 under native deoxygenation for T_E = 90 ms (Fig. 3) should occur if measured with twice refocused SE. Hence, hypercapnia would lead to a decrease in the ADC, i.e. to a signal increase. Effect of **the same sign and magnitude** was observed in brain [5]. Likewise, neuronal activation would result in an increase in signal by a few percent, suggesting that BOLD effect is sufficient for rationalizing the "diffusion fMRI" phenomenon [6]. The relative change in MRI signal due to both the change in dephasing, δR_2, and the ADC change δ(ADC), is given by $\delta S/S \approx -t\cdot\delta R_2 - b\cdot\delta(\mathrm{ADC})$. For the twice refocused SE, the δR_2 and δ(ADC) changes are of the same sign, enhancing the net signal change at finite b as compared to the BOLD effect in relaxation (b=0), in agreement with the results [4,5].

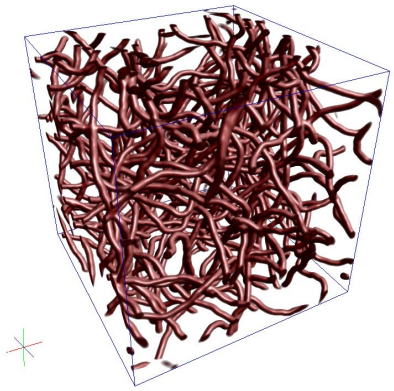

Fig. 1: Simulated microvasculature with periodic boundary conditions on 256^3 lattice

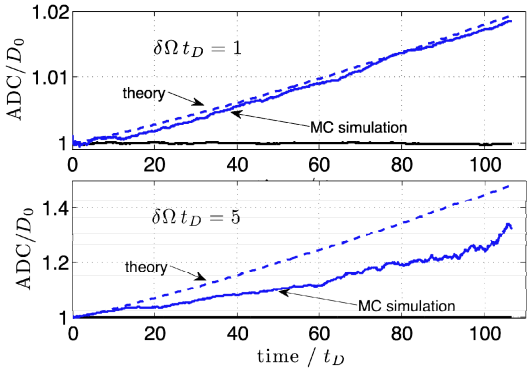

Fig. 2: ADC deviation calculated for narrow pulses, compared with MC simulations. **Top:** quantitative agreement in perturbative regime. **Bottom:** qualitative agreement, non-perturbative regime

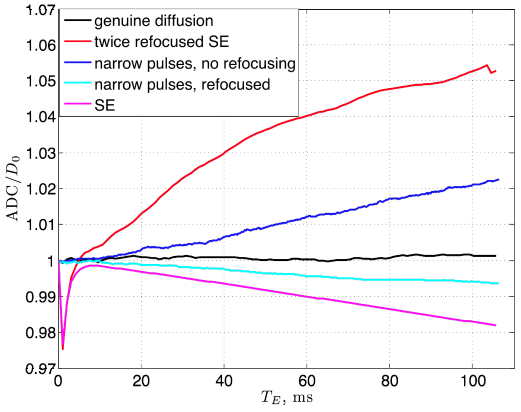

Fig. 3: ADC change depending on pulse sequence and T_E in the geometry of Fig. 1 for $\delta\Omega\, t_D = 5$, corresponding to native deoxygenation. The dip for T_E < 5ms is the artifact of finite lattice step. The predicted ADC change is ~5% at T_E = 90 ms in both hypercapnia and DfMRI.

[1] Does MD *et al.*, *MRM* 41 (1999) 236. [2] Kiselev VG, *JMR* 170 (2004) 228. [3] Reese TG *et al*, *MRM* 49 (2003) 177. [4] Miller KL *et al.*, *PNAS* 104 (2007) 20967. [5] LeBihan D *et al.*, *PNAS* 103 (2006) 8263. [6] Novikov DS, Kiselev VG, *JMR* 195 (2008) 33. [7] Novikov DS, Kiselev VG, *NMR Biomed* 23 (2010) 682.