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

Dmitry S. Novikov1, Marco Reisert1, and Valerij G. Kiselev2

1Radiology, NYU School of Medicine, New York, NY, United States, 2Radiology, University Medical Center Freiburg, Germany

Introduction: Diffusion measurements are confounded by the presence of microscopic magnetic field gradients induced by a heterogeneous magnetic susceptibility $\chi(r)$ 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 $t << t_D$, where $t_D$ is the time to diffuse across the characteristic length scale on which the susceptibility profile $\chi(r)$ varies in space.

Results: Here, the opposite situation of the fast diffusion, $t >> t_D$, 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 $t/t_D >> 1$, 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 $\chi(r)$, 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 $\Omega(r)$ found by the convolution of $\chi(r)$ 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 $\rho = 3.5 \mu m$ in Fig. 1, and $t_D = \rho^2/D_0$, $D_0 = 1 \mu m^2/\text{ms}$. Explicit analytical expressions for the ADC are obtained up to the order $\alpha^2$. 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 $T_s = 90$ 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, $\delta R_2$, and the ADC change $\delta(ADC)$, is given by $\delta S/S = -t \cdot \delta R_2 - b \cdot \delta(ADC)$. For the twice refocused SE, the $\delta R_2$ and $\delta(ADC)$ 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 $T_s$ in the geometry of Fig. 1 for $\delta \Omega t_D = 5$, corresponding to native deoxygenation. The dip for $T_s < 5$ms is the artifact of finite lattice step. The predicted ADC change is ~5% at $T_s = 90$ ms in both hypercapnia and DfMRI.