Susceptibility-induced increase in apparent diffusion coefficient

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Introduction: Diffusion measurements are confounded by the presence of microscopic magnetic field gradients induced by heterogeneous magnetic susceptibility $\chi(\mathbf{r})$ which often varies on the cellular scale [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 effect of such an interference is a net increase of the DWI signal, with the apparent diffusion coefficient (ADC) 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 $t \ll t_c$, where t_c is the time to diffuse across the correlation length of the spatially variable susceptibility profile $\chi(\mathbf{r})$.

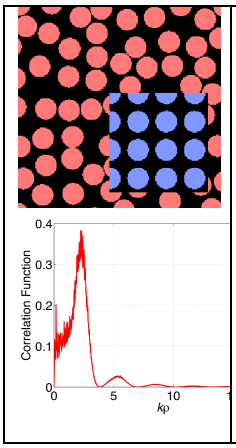
In this study, the opposite situation of the *fast diffusion*, $t \gg t_c$, is considered theoretically for the first time. We find the following:

1. Remarkably, *the effect is opposite*: **Spatially varying magnetic susceptibility in the fast diffusion regime results in an increase of the ADC**. This increase turns out to be especially strong, enhanced by the factor $t/t_c \gg 1$, when the microscopic magnetic field is induced by effectively two-dimensional objects, such as the smallest blood vessels.
2. The effect of the spatially varying relaxation rate $R_2(\mathbf{r})$ reciprocates that of the varying $\chi(\mathbf{r})$. That is, for $t \ll t_c$, the ADC is overestimated, and for $t \gg t_c$, the ADC is underestimated, as compared with the genuine diffusivity (see Figures).
3. As $\chi(\mathbf{r})$ and $R_2(\mathbf{r})$ affect the ADC in opposite directions, they may completely compensate each other, leading to ADC=D_0, if $\chi(\mathbf{r})$ and $R_2(\mathbf{r})$ follow the same spatial profile, $\chi(\mathbf{r}) = cR_2(\mathbf{r})$ with a certain ratio c, e.g. when induced by added contrast agent.

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] and with the transverse relaxation rate $R_2(\mathbf{r})$. We assume unrestricted Gaussian diffusion for simplicity. The signal averaged over a large volume is calculated in the effective medium framework [3,4]. The ADC corresponds to narrow gradient pulses. The magnitude of the effect is determined by the parameter $\alpha^2 = \langle\Omega^2\rangle\, t_c^2 - \langle(\delta R_2)^2\rangle\, t_c^2$, where $\delta R_2 = R_2(\mathbf{r}) - \langle R_2\rangle$, and $\langle\ldots\rangle$ stands for volume averaging. Explicit analytical expressions for the ADC are obtained for $\alpha \ll 1$. All results are verified with Monte Carlo simulations of spins performing random walk on a 4096^2 two-dimensional lattice with round "objects" in which χ and/or R_2 differ from that of the black background (Fig.1). We focus on the varying $\chi(\mathbf{r})$ first, and then briefly outline results for $R_2(\mathbf{r})$.

Results: The central quantity characterizing the medium is the two-point Larmor frequency correlation function $\Gamma_\Omega(\mathbf{r}) = \langle\Omega(\mathbf{r})\Omega(0)\rangle$. We work with its Fourier transform $\Gamma_\Omega(k) \sim \Gamma_\chi(k)$ proportional [3] to that of $\langle\chi(\mathbf{r})\chi(0)\rangle$, Fig.2. The peak in $\Gamma_\Omega(k)$ signifies the short-range order due to dense packing of the objects, while the nonzero value of $\Gamma_\Omega(k)$ at small k reflects long-range *fluctuations* in their positions. The latter value, $\Gamma(0)$, is shown to determine the behavior of the ADC for long diffusion times, $t \gg t_c$. In particular, its nonzero value results in a steady increase in the ADC proportional to the diffusion time t (Fig.3). Physically, this means that the ADC increase at long times is determined by the spatial fluctuations of the Larmor frequency at increasing length scales. In our perturbative calculation, the smallness of α results in a small rate of the ADC increase, but given a sufficiently long diffusion time, the effect on the ADC becomes notably large, ~100%. The essential role of $\Gamma(0)$ is confirmed with simulations for regularly arranged objects (Figs.1,3, blue), for which $\Gamma(0)=0$, and the anomalous increase in the ADC disappears, while the overall effect of increase in ADC for $t \gg t_c$ is still present. Simulations for large α qualitatively agree with this picture. The effect of the spatially variable $R_2(\mathbf{r})$ differs from that considered above by the known factor c and *an overall sign*. In particular, it can compensate for the variable magnetic susceptibility if both are present.

Discussion: It is well recognized that diffusion probes tissue microstructure. This study for the first time demonstrates that the *apparent* diffusion coefficient, being sensitive to structural fluctuations, also possesses such a potential. An estimate of the effect of the capillaries with the native deoxygenation gives the ADC increase by ~1% for T_E=70 ms. Hence, hypercapnia would lead to a decrease in the ADC, i.e. to a signal increase. Effect of **the same sign** and order of magnitude was observed in brain [5]. Likewise, neuronal activation would result in an increase in DWI signal by about ~1%, in apparent agreement with the so-called diffusion fMRI results [6].



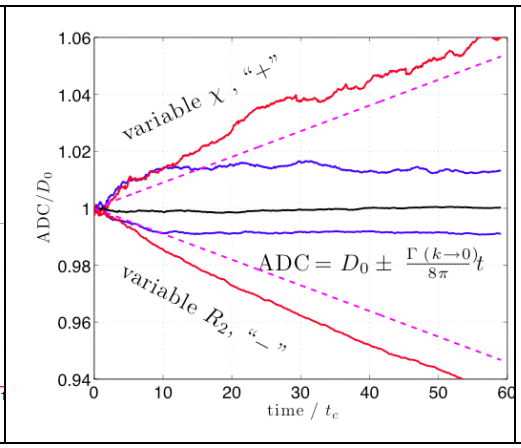


Fig.1 (top left): Portions of random and regular media.
Fig.2 (bottom left): Correlator $\Gamma(k)$ of the above shape in the k space for the random medium, with $\Gamma(0) \approx 0.1$.
The corresponding $\Gamma(k)$ for the periodic medium is a set of Bragg peaks, with $\Gamma(0) \equiv 0$ (not shown).
Fig.3: ADC vs. diffusion time t for α=0.32. Red lines: Effect of variable magnetic susceptibility (ADC > D_0) and of matching variable relaxation rate (ADC < D_0) for the random medium. Magenta: Theory for $t \gg t_c$ given by the expression in Figure. Blue: ADC for the periodic medium. Black: genuine simulated diffusivity D_0 without the confounding effects.

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