Diffusion Anisotropy Corrections for Vessel Size and Microvessel Density Imaging

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Introduction: The underlying theory for the closely related MRI techniques of vessel size imaging (VSI) [1-3] and microvessel density imaging (MDI) [4-6] is based on the work of Kiselev and Posse [7-8]. This theory, however, treats water diffusion as being isotropic. As a consequence, applying the standard VSI and MDI formulae to white matter regions, where diffusion can be highly anisotropic, may result in significant errors for MRI estimates of the vessel size and microvessel density indices. Here we explicitly calculate corrections for the VSI and MDI formulae that incorporate the effects of diffusion anisotropy. These may be particularly relevant for the application VSI and MDI to the assessment of angiogenesis in white matter tumors.

Theory: A key parameter measured for VSI and MDI is the quantity $Q \equiv \Delta R2/(\Delta R2^*)^{2/3}$, where the relaxation rate shifts $\Delta R2$ and $\Delta R2^*$ are, respectively, the single spin echo and gradient echo transverse relaxation rate increases caused by a sufficiently high dose of an intravascular paramagnetic contrast agent [4-6]. For anisotropic diffusion, the fundamental connection between Q and the microvasculature is

$$Q = b \cdot k_1 \cdot k_2 \cdot \left(\overline{D} N\right)^{1/3}, \tag{1}$$

where $\overline{D}$ is the mean diffusivity, N is the microvessel density, and $b = 1.6781$. As described in Refs. 4-6, the parameter k_1 depends on the distribution of microvessel radii according to

$$k_1 = \left\langle R^{4/3} \right\rangle \Big/ \left\langle R^2 \right\rangle^{2/3}, \tag{2}$$

where the angle brackets indicate ensemble averages of the microvessel radius R raised to the indicated powers. The main new result of this work is the correction factor, k_2, for diffusion anisotropy given by

$$k_2 = \frac{0.1077}{\overline{D}^{1/3}} \int_0^{\pi} d\theta \int_0^{2\pi} d\phi \, \sin^{7/3}\theta \cdot \left[W(\theta,\phi)\right]^{1/6} \cdot P_{1/3}\left(\frac{D'(\theta,\phi)}{\sqrt{W(\theta,\phi)}}\right), \tag{3}$$

where $P_{1/3}$ indicates a Legendre function of the first kind,

$$D'(\theta,\phi) \equiv \frac{1}{2}\left[D_{x'x'}(\theta,\phi) + D_{y'y'}(\theta,\phi)\right], \qquad \text{and} \qquad W(\theta,\phi) \equiv D_{x'x'}(\theta,\phi) D_{y'y'}(\theta,\phi) - \left[D_{x'y'}(\theta,\phi)\right]^2. \tag{4}$$

In Eq. (4), $D_{x'x'}$, $D_{y'y'}$, and $D_{x'y'}$ represent components of the diffusion tensor in a reference frame rotated by spherical angles of θ and ϕ relative to a (magnet) frame of reference for which the z-axis is parallel to main magnetic field. More explicitly, we have

$$\begin{aligned}
D_{x'x'}(\theta,\phi) &= \cos^2\theta\left(D_{xx}\cos^2\phi + 2D_{xy}\cos\phi\sin\phi + D_{yy}\sin^2\phi\right) + D_{zz}\sin^2\theta - 2\cos\theta\sin\theta(D_{xz}\cos\phi + D_{yz}\sin\phi), \\
D_{x'y'}(\theta,\phi) &= D_{xy}\cos\theta(2\cos^2\phi - 1) - \cos\theta\cos\phi\sin\phi\left(D_{xx} - D_{yy}\right) + \sin\theta(D_{xz}\sin\phi - D_{yz}\cos\phi), \\
D_{y'y'}(\theta,\phi) &= D_{xx}\sin^2\phi - 2D_{xy}\cos\phi\sin\phi + D_{yy}\cos^2\phi,
\end{aligned} \tag{5}$$

with (D_{xx}, D_{yy}, D_{zz}, D_{xy}, D_{xz}, D_{yz}) being the components of the diffusion tensor in the magnet frame. Thus, given the magnet frame diffusion tensor, one can use Eq. (3) to calculate k_2, typically by performing the integrals numerically. For isotropic diffusion, one may easily verify that $k_2 = 1$, and Eq. (1) then reduces to the standard form [4-6]. The derivation of Eq. (3) employed the idealizations of randomly oriented, cylindrical microvessels and of no correlation between vessel orientation and vessel radius. The effect of diffusion anisotropy on Q arises only through the diffusion dependence of $\Delta R2$, since within our model assumptions $\Delta R2^*$ is insensitive to diffusion.

Once Q has been determined, the vessel size and microvessel density indices are then found from

$$R_U = \left(\frac{f\overline{D}b^3k_2^3}{2\pi Q^3}\right)^{1/2}, \quad N_L = \frac{Q^3}{\overline{D}b^3k_2^3}, \quad \text{and} \quad N_U = \frac{Q}{bk_2}\left(\frac{f^2}{4\pi^2\overline{D}R_L^4}\right)^{1/3}, \tag{6}$$

where f is the blood volume fraction, R_U and R_L represent upper and lower bounds on the mean vessel radius, and N_U and N_L represent upper and lower bounds on the microvessel density. These are generalizations of the formulae given in Ref. 6, with the effect of diffusion anisotropy included through the parameter k_2. The parameter f (needed for R_U and N_U) and the parameter R_L (needed for N_U) are estimated independently of the measurement of Q (for example by dynamic contrast enhanced MRI for f and a priori histological knowledge for R_L). It should be emphasized that, while R_U, N_L and N_U formally represent upper or lower bounds, in practice they may often provide plausible estimates for the mean vessel radius and the mean microvessel density [1-6].

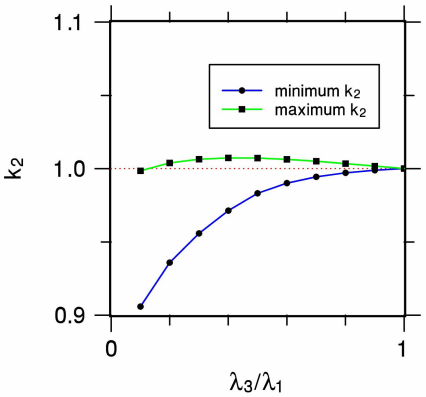

Figure 1. Minimum and maximum values for anisotropic diffusion correction factor k_2 as a function of the ratio, λ_3/λ_1, of the smallest and largest diffusion tensor eigenvalues. For a given value of λ_3/λ_1, the k_2 values were optimized for all possible diffusion tensor orientations and values for the intermediate diffusion tensor eigenvalue, λ_2. For isotropic diffusion, $k_2 = 1$.

Results: In order to investigate the range of allowed departures from unity of the anisotropic diffusion correction factor k_2, we used Eq. (3) to find the minimum and maximum k_2 values for fixed ratios of the smallest diffusion tensor eigenvalue (λ_3) to the largest eigenvalue (λ_1). These were optimized for all possible values of the intermediate eigenvalue ratio (λ_2/λ_1) and for all possible orientations of the diffusion tensor relative to the magnet frame. Only the eigenvalue ratios are specified, as k_2 is unaffected by an overall rescaling of the diffusion tensor. Figure 1 shows the minimum and maximum k_2 values for eigenvalue ratios varying from 0.1 to 1.0, which covers the range of physical interest for white matter [9]. The global maximum of k_2 is 1.007, which occurs for $\lambda_3/\lambda_1 = \lambda_2/\lambda_1 = 0.445$, and is less than 1% above the value for isotropic diffusion. For the range of eigenvalue ratios considered, the minimum k_2 was found to be 0.906 for $\lambda_3/\lambda_1 = \lambda_2/\lambda_1 = 0.1$. By combining these results with Eq. (6), we then find that neglecting diffusion anisotropy can lead, for R_U, N_L and N_U, to underestimates of up to 14%, 2%, and 1%, respectively, and to overestimates of up to 1%, 34%, and 10%.

Discussion: Diffusion anisotropy can significantly affect parameter estimates for VSI and MDI. If the diffusion tensor is known, then corrections to the standard VSI and MDI expressions can be calculated directly from Eqs. (3) and (6). Therefore the use of diffusion tensor imaging in conjunction with VSI and MDI is recommended when studying white matter regions. However in most cases, the errors caused by neglecting diffusion anisotropy will be small to moderate and the uncorrected formulae may still yield fair approximations.

References: 1. Tropres I, et al. MRM 2001; 45:397. **2.** Tropres I, et al. MRM 2004; 51:533. **3.** Kiselev VG, et al. MRM 2005; 55:553. **4.** Jensen JH & Chandra R, et al. MRM 2000; 44:224. **5.** Wu EX, et al. NMR Biomed 2004; 17:507. **6.** Jensen JH, et al. MRM 2006; 56:1145. **7.** Kiselev VG & Posse S. Phys Rev Lett 1998; 32:749. **8.** Kiselev VG & Posse S. MRM 1999; 41:499. **9.** Pierpaoli C & Basser PJ. MRM 1996; 36:893.