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Diagonal and off-diagonal components of the self-diffusion tensor: their relation to and estimation from the NMR spin-echo signal

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Purpose: We derive an equation relating diagonal and off-diagonal elements of the apparent self-diffusion tensor, $\underline{D}$, to echo intensity in pulsed-gradient, spin-echo experiments. With it we design pulse sequences to estimate all components of $\underline{D}$. This procedure is validated by diffusion NMR spectroscopy and imaging of isotropic and anisotropic media. We suggest that errors are made in ignoring off-diagonal elements of $\underline{D}$ in anisotropic diffusion experiments.

Principles: In isotropic media (e.g. water), a scalar self-diffusivity, D, is the constant of proportionality between the gradient in concentration of spin-labeled protons, ∇C, and their flux, J; i.e., $J = -D\,\nabla C$. Analogously, in anisotropic media (e.g. skeletal muscle or brain white matter), a symmetric second-order apparent self-diffusion tensor, $\underline{D}$, relates ∇C and J; i.e., $J = -\underline{D}\,\nabla C$. Diagonal elements of $\underline{D}$ scale fluxes and concentration gradients in the same direction, while off-diagonal elements couple fluxes and concentration gradients in orthogonal directions. The importance of these off-diagonal elements has not been appreciated, nor have they ever been measured.

Theory: Following Stejskal [1], magnetic field gradients and their integrals are defined as:

$$G(t) = (G_x(t), G_y(t), G_z(t))^T;\ F(t) = \int_0^t G(t')\,dt'. \quad (1)$$

The echo attenuation by diffusion, A(TE)/A(0), is [1]:

$$\ln\left(\frac{A(TE)}{A(0)}\right) = -\gamma^2 \int_0^{TE} \left(F(t')-2\xi(t')f\right)^T \underline{D} \left(F(t')-2\xi(t')f\right)dt' \quad (2)$$

where γ is the proton gyromagnetic ratio; $\xi(t')$ is the Heaviside function, $H(t'-TE/2)$; and $f = F(TE/2)$. When $\underline{D}$ is independent of time, Eq. (2) reduces to:

$$\ln\left(\frac{A(TE)}{A(0)}\right) = -\sum_{i=1}^{3}\sum_{j=1}^{3} b_{ij} D_{ij}\,, \quad (3)$$

where the b_{ij} that are analogs to scalar b-factors [2], are calculated numerically or analytically for each sequence using Eq. (2). The b matrix is not necessarily symmetric.

Eq. (3) linearly relates the logarithm of the signal attenuation and each component of $\underline{D}$. We use multivariate linear regression (with weighted variances) to estimate optimally all components of $\underline{D}$ from measured echo intensities that are produced by field gradients applied in different directions.

Materials and Methods: Diffusion spectroscopy and imaging of water and pork loin samples were performed with a surface coil in a 4.7 T Spectrometer-Imager (GE Omega). Pulsed-gradient spin-echo sequences, incorporating symmetric trapezoidal gradient pulses (TR=15 s; TE=40 ms; pulse duration=4.0 ms; rise time=0.2 ms; pulse separation=22.5 ms), were applied in seven non-colinear directions: $(G_x, G_y, G_z) = \{(0,0,1), (0,1,0), (0,0,1), (1,0,1), (1,1,0), (0,1,1), \text{and } (1,1,1)\}$. In each direction, three trials were performed in which gradient strength was increased from 1 to 14 or 15 G/cm in 1-G/cm increments. The total number of acquisitions, N, was either 294 or 315.

Results: For water, the estimated $\underline{D}^{iso} \pm$ S.E. (ρ^2 = 0.999998; N = 315) at 14.0°C is:

$$\underline{D}^{iso} = (1.687 \pm 0.0020) \times 10^{-5} \begin{vmatrix} 1 & 0 & 0 \\ 0 & 1 & 0 \\ 0 & 0 & 1 \end{vmatrix} \frac{cm^2}{sec}\,. \quad (4)$$

The estimated $\underline{D}^{0°} \pm$ S.E. (cm^2/sec) for a pork loin sample at 14.5°C, whose grain was oriented nearly parallel to the x axis, (ρ^2 = 0.999999; N = 294) is:

$$\underline{D}^{0°} = \left(\begin{vmatrix} 10.137 & 0.365 & -0.530 \\ 0.365 & 9.401 & 0.203 \\ -0.530 & 0.203 & 8.840 \end{vmatrix} \pm \begin{vmatrix} 0.008 & 0.007 & 0.006 \\ 0.007 & 0.008 & 0.006 \\ 0.006 & 0.006 & 0.008 \end{vmatrix} \right) 10^{-6}\,. \quad (5)$$

The estimated $\underline{D}^{41°} \pm$ S.E. (cm^2/sec) for the same pork loin sample at 15.0°C, rotated 41° off the x axis in the x-z plane, (ρ^2 = 0.999999; N = 294) is:

$$\underline{D}^{41°} = \left(\begin{vmatrix} 9.188 & -0.099 & -0.618 \\ -0.099 & 9.346 & 0.038 \\ -0.618 & 0.038 & 9.694 \end{vmatrix} \pm \begin{vmatrix} 0.009 & 0.007 & 0.007 \\ 0.007 & 0.009 & 0.007 \\ 0.007 & 0.007 & 0.009 \end{vmatrix} \right) 10^{-6}\,. \quad (6)$$

Discussion/Conclusion: The control experiment validates the method to estimate $\underline{D}$. Statistically significant differences among diagonal components of $\underline{D}$ demonstrate diffusion anisotropy in the pork loin sample. Small S.E. and $\rho^2 \approx 1$ show the multivariate linear model (Eq. (3)) fits the data faithfully; $\underline{D}$ is estimated with high significance.

In anisotropic diffusion, off-diagonal components of $\underline{D}$ vanish only when the "fiber" and "laboratory" frames of reference are coincident [3] - a condition which is rarely verifiable or satisfied. So, diagonal and (non-vanishing) off-diagonal elements of both b and $\underline{D}$ are assumed to affect the measured echo attenuation. As a corollary, at least six experiments are generally required to estimate six independent components of $\underline{D}$ in order to infer microscopic displacements of protons or tissue microstructure [3]. Omitting off-diagonal components of $\underline{D}$ in describing diffusion in anisotropic media also precludes determination of fiber orientation [3].

References:

1. Stejskal, E. O., *J. Chem. Phys.* **43**, 3597, 1965.
2. LeBihan, D., *Magn. Res. Quart.* **7**, 1, 1991.
3. Basser, P. J., et al, submitted SMRM, 1992.