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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, \( \mathbf{D} \), to echo intensity in pulsed-gradient, spin-echo experiments. With it we design pulse sequences to estimate all components of \( \mathbf{D} \). 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 \( \mathbf{D} \) 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, \( \mathbf{v} \), and their flux, \( \mathbf{j} \); i.e., \( \mathbf{j} = -D \mathbf{v} \). Analogously, in anisotropic media (e.g. skeletal muscle or brain white matter), a symmetric second-order apparent self-diffusion tensor, \( \mathbf{D} \), relates \( \mathbf{v} \) and \( \mathbf{j} \); i.e., \( \mathbf{j} = -\mathbf{D} \mathbf{v} \). Diagonal elements of \( \mathbf{D} \) 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:

\[
G(t) = (G_x(t), G_y(t), G_z(t))' \quad \text{and} \quad F(t) = \int_0^t G(t') \, dt'.
\]  

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

\[
\ln \frac{A(TE)}{A(0)} = -\gamma^2 \int_0^t (F(t') - 2\xi(t')f(t'))^T \mathbf{D} (F(t') - 2\xi(t')f(t')) \, dt' \tag{2}
\]

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

\[
\ln \frac{A(TE)}{A(0)} = -\sum_{i=1}^{3} \sum_{j=1}^{3} b_{ij} D_{ij},
\]  

where the \( b_{ij} \) that are analogous 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 \( \mathbf{D} \). We use multivariate linear regression (with weighted variances) to estimate optimally all components of \( \mathbf{D} \) 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), 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 \( D^{iso} \pm \text{S.E.} \) (\( \rho^2 = 0.999998; N = 315 \)) at 14.0°C is:

\[
D^{iso} = (1.687 \pm 0.0020) \times 10^{-5} \, \text{cm}^2/\text{sec}. \tag{4}
\]

The estimated \( D^{0} \pm \text{S.E.} \) (cm²/sec) for a pork loin sample at 14.5°C, whose grain was oriented nearly parallel to the x axis, (\( \rho^2 = 0.999999; N = 294 \)) is:

\[
D^{0} = \begin{pmatrix}
10.137 & 0.356 & -0.530 \\
0.365 & 9.401 & 0.203 \\
-0.530 & 0.203 & 8.840
\end{pmatrix} \pm \begin{pmatrix}
0.008 & 0.007 & 0.006 \\
0.007 & 0.008 & 0.006 \\
0.006 & 0.006 & 0.008
\end{pmatrix} \times 10^{-6}. \tag{5}
\]

The estimated \( D^{45} \pm \text{S.E.} \) (cm²/sec) for the same pork loin sample at 15.0°C, rotated 45° off the x axis in the x-z plane, (\( \rho^2 = 0.999999; N = 294 \)) is:

\[
D^{45} = \begin{pmatrix}
9.188 & -0.099 & -0.618 \\
-0.099 & 9.346 & 0.038 \\
-0.618 & 0.038 & 9.694
\end{pmatrix} \pm \begin{pmatrix}
0.009 & 0.007 & 0.007 \\
0.007 & 0.009 & 0.007 \\
0.007 & 0.007 & 0.009
\end{pmatrix} \times 10^{-6}. \tag{6}
\]

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

In anisotropic diffusion, off-diagonal components of \( \mathbf{D} \) 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 \( \mathbf{D} \) are assumed to affect the measured echo attenuation. As a corollary, at least six experiments are generally required to estimate six independent components of \( \mathbf{D} \) in order to infer microscopic displacements of protons or tissue microstructure [3]. Omitting off-diagonal components of \( \mathbf{D} \) in describing diffusion in anisotropic media also precludes determination of fiber orientation [3].

References: