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Local and global anisotropy - recent re-implementation of 2D ILT diffusion methods

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ABSTRACT

Multidimensional Inverse Laplace Transform (ILT) NMR methods have established themselves over the last two decades in material science, engineering, medical research and industry. Here we report on two variants of the two-dimensional (2D) Diffusion-Diffusion Correlation Spectroscopy (DDCOSY) which allows for the correlation of molecular displacements in different directions, thus sampling local mobility and confinement. The first variant aims to measure Fractional Anisotropy (FA) averaged over the whole sample which can be extracted from the DDCOSY results using a particular gradient orientation scheme. We demonstrate that this method returns averaged FA values which are consistent with DTI measurements. The second variant concerns a shortened version of the DDCOSY (sDDCOSY) experiment for which gradients in the two different directions are applied at the same time. This shortened DDCOSY version may proof indispensable for samples with short T_2 relaxation times.

1. Introduction

Fractional anisotropy (FA) [1] quantitatively characterises orientation dependence of molecular mobility. It is a single normalised number extracted from the diffusion tensor (DT), which is a three-dimensional (3D) Gaussian model of molecular diffusion [2,3]. In a material with internal structure, a spherical pore or compartment filled with fluid would return a FA value of zero due to isotropic diffusion. However, anisotropic diffusion (represented by an ellipsoidal shape of the DT) would be reflected by a FA value between zero and one. In biological tissues, complex interior fibre structures and cell alignments result in different FA values. For instance, it was shown that FA in breast cysts is three times smaller in comparison to the surrounding healthy tissues [4]; the changes of FA in the central nervous system due to fibre disorder can be indicators of abnormalities such as stroke [5]. Therefore, the determination of FA enables one to distinguish compartment shapes or identify pathological changes in biological tissues.

FA is usually measured through diffusion tensor imaging, DTI [6], thus the signal is spatially resolved into voxels upon image reconstruction. While this method is common in radiology, medical research and science, it is known to be sensitive to eddy current effects, off-resonance effects and signal-to-noise ratios (SNR) [7]. Furthermore, it has been shown that spacial resolution is not always required and sample averaged FA may be sufficient in order to study the post-natal development of mouse brain at various ages [8]. Spectroscopic methods may offer advantages over spatially resolved (DTI) methods in such cases since the the signal is not divided between voxels. A spectroscopic method probing local anisotropy was suggested as “Diffusion-Diffusion COrrelation SpectroscopY” (DDCOSY) [9]. It is based on two-dimensional (2D) correlation experiments providing easy access to the local anisotropy even when diffusion is isotropic on average over the whole sample. Early applications to biological tissues returned signatures of cell shapes in chive plants [10].

In this contribution we report on an approach which is based on DDCOSY while combined with the core idea of DTI. We will show that this new approach is able to return sample averaged FA values. To this end we will briefly summarise DTI and DDCOSY and provide proof of principle experiments on plant tissues. Furthermore, we will provide first indications that DDCOSY may be improved by applying diffusion sensitising magnetic field gradients at the same time, thus reducing the

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length of the pulse sequence by a factor of two.

2. Methodology

Anisotropic diffusion can be described by a tensor [11], which contains nine elements in the laboratory coordinate system:

$$\mathbf{D} = \begin{pmatrix} D_{xx} & D_{xy} & D_{xz} \\ D_{yx} & D_{yy} & D_{yz} \\ D_{zx} & D_{zy} & D_{zz} \end{pmatrix}, \tag{1}$$

whereby the subscripts denote the directions in the Cartesian coordinate system. D_{xx}, D_{yy} and D_{zz} are the diffusion coefficients along x-, y- and z-axis, respectively. D_{xy}, D_{yx}, D_{xz}, D_{zx}, D_{yz} and D_{zy} correspond to the degree of coupling between diffusion in the two indexed directions, and can be negative [12]. Since $\mathbf{D}$ is symmetric [13], only six uncorrelated elements of the DT need to be reconstructed. The values of those elements are dependent on the anisotropic structure as well as the sample orientation.

It is customary to extract FA's from diffusion tensors (acquired by DTI [6]) using eigenvectors and eigenvalues. In the meantime, it is possible to derive the FA directly from the non-diagonalised DT values:

$$\mathrm{FA} = \sqrt{1 - \frac{D_{xx}D_{yy} + D_{yy}D_{zz} + D_{xx}D_{zz} - D_{xy}^2 - D_{yz}^2 - D_{xz}^2}{D_{xx}^2 + D_{yy}^2 + D_{zz}^2 + 2D_{xy}^2 + 2D_{yz}^2 + 2D_{xz}^2}}. \tag{2}$$

FA = 0 only when the off-diagonal elements are zero and the diagonal elements are identical. This means that molecular diffusion is isotropic at least macroscopically.

DDCOSY is a double pulsed-gradient-spin-echo (PGSE) technique that allows one to observe local structures without imaging encoding [9,14]. This technique is capable of correlating molecular displacements utilising successive time intervals, thus acquiring a 2D dataset holding the signature of local diffusional anisotropy. The NMR signal intensity M in DDCOSY is a function of the so-called wave vector or q-vector [15]. More specifically, two vectors $\mathbf{q}_1$ and $\mathbf{q}_2$ are applied successively and incremented independently, thus returning a 2D data set $M(\mathbf{q}_1, \mathbf{q}_2)$. Upon numerical inversion [16,17] (often referred to as two-dimensional Inverse Laplace Transform (2D-ILT)) a 2D distribution function $f(D_1^{app}, D_2^{app})$, holding the probability of the joint occurrence of apparent diffusivities $D_{1,2}^{app}$, can be extracted and displayed in a D-D correlation map. Spatial orientations in the two diffusion domains will be referred to a D_{ij}^{app} with $i, j = x, y, z$. This allows for the designation of apparent diffusivities along directions which are linear combinations of the laboratory coordinate system.

DTI and DDCOSY share the same mathematical model characterising diffusion anisotropy via the DT. Therefore, it is tempting to extract FA using an approach based on DDCOSY. In order to obtain the six uncorrelated elements of the bulk diffusion tensor (*i.e.* averaged over the sample volume), we propose to combine three independent DDCOSY experiments with gradient orientations as depicted in Fig. 1. While $\mathbf{q}_1$ is the gradient wave-vector along a main axis in the laboratory (Cartesian) system ($x-$, $y-$, or $z-$axis), $\mathbf{q}_2$ is the gradient wave-vector on the plane ($yz-$, $xz-$, or $xy-$plane) with an off-axis angle of θ. If the direction of the gradient pairs follows Fig. 1 (a) it follows that

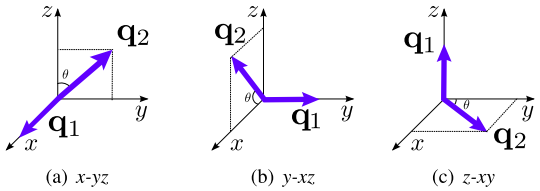

Fig. 1. Diagram for gradient directions in the three independent DDCOSY experiments. Diffusion gradient pairs ($\mathbf{q}_1$ and $\mathbf{q}_2$) applied along (a) [1, 0, 0] and [0, sin θ, cos θ]; (b) [0, 1, 0] and [cos θ, 0, sin θ]; (c) [0, 0, 1] and [sin θ, cos θ, 0], respectively.

$$D_1^{app} = D_{xx}, \tag{3}$$

while the apparent diffusion coefficient in the second dimension is

$$D_2^{app} = D_{yy}\cos^2\theta + D_{zz}\sin^2\theta + 2D_{yz}\cos\theta\sin\theta. \tag{4}$$

Similarly, one can work out that gradient directions in Fig. 1 (b) return apparent diffusion coefficients as

$D_1^{app} = D_{yy}$, and

$D_2^{app} = D_{xx}\cos^2\theta + D_{zz}\sin^2\theta + 2D_{xz}\cos\theta\sin\theta$;

and Fig. 1 (c) gives:

$D_1^{app} = D_{zz}$, and

$D_2^{app} = D_{xx}\cos^2\theta + D_{yy}\sin^2\theta + 2D_{xy}\cos\theta\sin\theta$.

Consequently, in all three DDCOSY experiments, only one diagonal matrix element D_{ii} contributes to the signal decay in the first dimension. However, signal decay in the second dimension includes one off-diagonal element D_{ij} ($i \neq j$) besides the remaining two other diagonal elements. A convenient choice for θ is $\pi/4$ such that the apparent diffusion coefficient in the second dimension can be calculated as:

$$D_2^{app} \equiv D_{ij}^{app} = \frac{D_{ii}}{2} + \frac{D_{ij}}{2} + D_{ij} \tag{5}$$

If the system is macroscopically isotropic, then we have $D_{ij} = 0$, and $D_{ii} = D_{jj}$, thus $D_2^{app} = D_{ii} = D_{jj} \neq 0$.

In order to make DDCOSY more suitable for samples with short T_2 it was suggested to apply the two independent gradient pairs at the same time in an experiment called “short DDCOSY” (sDDCOSY) [18]. This reduces the structure of the pulse sequence to a Stejskal-Tanner experiment [19], thus expressing its echo decay as

$$M(\mathbf{q}) = M_0\exp\{-\mathbf{q}^T\mathbf{D}\mathbf{q}\Delta\}, \tag{6}$$

where $\mathbf{q} = \mathbf{q}_1 + \mathbf{q}_2$. Expanding the expression in the exponent returns terms proportional to $\mathbf{q}_1^2$ and $\mathbf{q}_2^2$ which also appear in the DDCOSY experiment. However, additional cross terms proportional to $\mathbf{q}_1^T\mathbf{D}\mathbf{q}_2$ and $\mathbf{q}_2^T\mathbf{D}\mathbf{q}_1$ are also present. Their influence can be compensated by executing the experiment twice while inverting one of the two gradient pairs. While this has no effect for the quadratic terms it inverts the sign of the cross terms which therefore cancel when the two experimental runs are multiplied with each other.

3. Experimental

Experiments were performed on a Bruker Avance 400 MHz NMR spectrometer equipped with a Bruker Micro2.5 micro-imaging system. The maximum gradient value was 1.45 T/m. All experiments were carried out at ambient temperature.

As a widely used phantom in diffusion anisotropy experiments [20,21], a carrot was used for the measurement of the sample averaged FA. DDCOSY experiments using the pulse sequence in Fig. 2 with the proposed three gradient orientation schemes shown in Fig. 1 were used in triplicate. In order to achieve a pronounced influence of the tissue

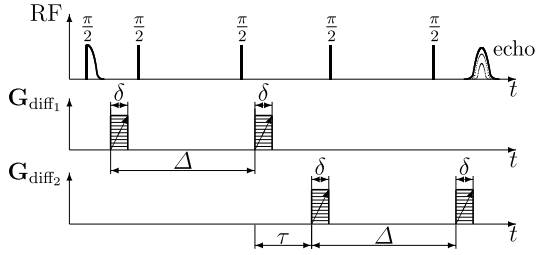

Fig. 2. DDCOSY pulse sequence [9,10]. RF stands for radio frequency pulses and received signal. $\mathbf{G}_{\mathrm{diff}}$ is the diffusion gradient where the subscripts 1 and 2 represent two diffusion gradient directions.