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The physical basis of diffusion-weighted MRI

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Abstract

Diffusion-weighted (DW) magnetic resonance imaging (MRI) is the only technique that permits a non-invasive in vivo assessment of water molecular diffusion, which reflects tissue configuration at a microscopic level. Therefore, this technique appears to be particularly useful in monitoring brain abnormalities. However, the quantitative measurement of diffusion is not without problems, which may limit the widespread use of diffusion-weighted MRI. In this report, the phenomenon of diffusion is described, together with its effect on the nuclear magnetic resonance signal. The concepts of diffusion anisotropy and diffusion tensor are also introduced, and the technical and hardware requirements are discussed.

Keywords: Diffusion; Motion; Gradient pulses; Tensor; Anisotropy

1. Introduction

Diffusion-weighted (DW) magnetic resonance imaging (MRI) is a relatively new MRI technique that permits the measurement of water self-diffusivity and, as a consequence of the interactions between water molecules and obstacles that hinder their motion, gives information about the size, orientation, and shape of cellular brain structures in vivo. The basic principles of diffusion and its assessment of MRI are summarised here. For general reviews on diffusion, see Refs. [1–3].

2. Background

Diffusion phenomena are the consequence of a microscopic random motion, known as Brownian motion. As an effect of molecular thermal energy, every particle in a fluid is moving and is jostled and struck by other molecules. With every hit, a particle changes direction randomly, so that, over time, its path can be described as a random walk. In non-uniform systems (where there is a gradient in the concentration of a diffusing fluid), diffusion results in a macroscopic flux of the fluid, which can be observed and measured. Conversely, when the concentration is stable, diffusion can only be described statistically, i.e. by measuring the probability that a molecule travels a given distance in a given time. Such a probability has a Gaussian distribution, with zero mean (since the probability of moving in one direction or in the opposite direction is the same) and a variance proportional to time, according to the Einstein equation:

$$\langle r^2 \rangle = 2NDt,$$

where t is time, N is the "dimensionality" of the space over which diffusion distances are measured, and D is the diffusion coefficient. D characterizes the mobility of molecules in a given fluid at a given temperature. MRI measurements of diffusion indirectly measure the displacements of diffusing molecules in one dimension; therefore, the value of N for MRI measurements is one.

3. Diffusion and MRI

Diffusion can be measured in vivo by MRI, by exploiting the natural sensitivity of MR to motion. In the presence of a magnetic field gradient, spins accumulate different phase shifts due to their diffusional motion, resulting in a reduced MR signal intensity. In practice, these effects are extremely small, and very difficult to measure. However, sensitivity to motion can be increased by adding strong

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magnetic field gradient pulses to a pulse sequence. A simple pulse sequence, which permits accurate measurements, consists of a spin–echo sequence with two additional gradient pulses positioned around the refocusing pulse [4]. During the first gradient pulse, spins sitting at different positions in the magnet bore experience different magnetic fields. As a consequence, they accumulate different phase shifts. However, if the spins remain stationary, the phase accumulated during the second gradient pulse is the same as the phase accumulated during the first one and, since the first phase shift is reversed by the 180° pulse, the net phase shift is zero. Consider now what happens to a group of diffusing spins, moving randomly. As consequence of their motion, the spins do not experience the same gradient field during the two pulses. At the time of the echo, the phase shifts will be randomly distributed, resulting in an imperfect refocusing of the spin–echo, leading to signal attenuation. Such attenuation is proportional to the diffusion coefficient.

4. Diffusion in biological tissues

In a simple, bulk liquid, molecules are free to diffuse in any direction, with the diffusion distances increasing in proportion to the square root of time, and increasing indefinitely. Conversely, if the diffusion is limited by a container, when the molecules reach the boundaries, they are reflected. In this situation, the diffusion distance increases linearly with the square root of time only for short diffusion times, and reaches a plateau at longer times. In biological tissues, barriers are constituted by membranes and organelles that are generally partially permeable, leading to an intermediate situation, where the diffusion distance increases in proportion to the square root of time (for long diffusion times); but now, the diffusion distances are smaller than for a free fluid, and are governed as much by the membrane permeability as by the diffusion coefficient of the fluid. As a consequence, the diffusion coefficient measured in vivo by MRI is always lower then that of free water [5]. Moreover, the diffusion coefficient measured by MRI is the result of all the so-called intra-voxel incoherent motion, not only of diffusion. Therefore, the diffusion coefficient measured by MRI is termed the apparent diffusion coefficient (ADC) [6].

5. Measurement of diffusion

The signal intensity in a diffusion-weighted spin–echo sequence also depends on transverse relaxation. When measuring diffusion, long TEs are needed in order to achieve an adequate diffusion-related signal attenuation, and therefore, DW images are also heavily T_2-weighted. If, in addition to the diffusion-weighted image, a T_2-weighted image is collected (at the same echo time, but without diffusion-weighted), it can be used to remove this confounding effect, according to the following:

$$\mathrm{ADC} = -(1/b)\log(S_1/S_0),$$

where S_1 is the signal intensity of the diffusion-weighted image, S_0 is the signal intensity of the non-diffusion-weighted image, and b is a factor that depends on the strength and the duration of the diffusion-encoding gradient pulses. If applied on a voxel-by-voxel basis, this formula allows ADC maps to be computed.

The gradient b factor above, which determines the degree of signal attenuation due to diffusion, is given by the expression below:

$$b = \gamma^2 G^2 \delta^2 (\Delta - \delta/3).$$

γ is the gyromagnetic ratio; G is the strength of the gradient used to encode diffusion; δ is the duration of a gradient pulse; and Δ is the time between the leading edges of the pair of pulses.

In order achieve significant, measurable signal attenuation when the diffusion-encoding gradients are applied, either the pulses must be strong or the gradient must be applied for a long time. In the latter case, this can lead to extended echo times, which consequently determines poor signal-to-noise ratio in the resulting images. A much more satisfactory arrangement is to apply strong gradient pulses; however, this places strong demands on the magnetic field gradient hardware so that DW imaging is often the technique that determines the gradient strength performance required of an MRI scanner.

Because, in DW imaging, we are deliberately sensitizing the MR image to microscopic diffusional motion, this leads to a high sensitivity to other forms of motion, such as brain pulsation or patient movement. This high sensitivity means that conventional spin–echo imaging sequences are prone to very severe motion artefacts, making DW conventional imaging generally unsuccessful in the clinical environment. Single-shot echo-planar imaging (EPI) effectively freezes motion, and is not prone to the motion-related problems of conventional imaging. Therefore, recent clinical use of DW imaging has been almost exclusively performed with EPI image acquisition. Good EPI capability should be considered the other important prerequisite for a system that will be used for DW imaging.

6. Diffusion anisotropy

In many biological tissues, particularly those that have a regular, ordered microstructure, the diffusion coefficient depends on the direction along which it is measured. MRI can only measure diffusion along one direction at time, and thus different directionally dependent components must be measured separately. While being a potential source of

information at a microscopic level, this diffusion anisotropy may give difficulties when trying to interpret DW images. With diffusion weighting applied in a single direction, a bright region may due either to a focal abnormality or to the particular alignment of tissue structures in that region. In the brain, gray matter and cerebro-spinal fluid are isotropic, at least on a voxel scale, while white matter is strongly anisotropic [7,8]. The most plausible explanation for this phenomenon is that oriented structures, such as axons and axonal transport, myelin sheath and filamentous cytoskeleton, hinder diffusion of water [9]. Under these circumstances, a scalar index, such as the ADC, does not provide a complete, valid description of the diffusion phenomenon.

7. The diffusion tensor

In analogy with other anisotropic phenomena, such as conductivity and elasticity, a full characterisation of diffusion can be obtained in terms of a tensor [10]. This is a 3×3 matrix of numbers that describes diffusion in three dimensions. The on-diagonal elements of the tensor represent the mobility rates in each direction, while the off-diagonal elements account for the correlation existing between orthogonal directions. A helpful aid to visualizing the diffusion tensor is given by the diffusion ellipsoid [11].

Since the diffusion tensor is symmetric, only six elements are independent. As a consequence, at least six measurements in non-collinear directions plus a T_2-weighted measurement are needed to estimate the tensor. The trace of the tensor, equal to the sum of the on-diagonal elements, is a rotationally invariant measure of diffusion. One-third of the trace is often referred to as the mean diffusivity, and constitutes a directionally averaged diffusion coefficient that can also be obtained by averaging the ADC measured in three orthogonal directions, without estimating the full tensor. However, from the tensor, further information can be extracted. For each voxel, it is possible to derive the local fibre frame, i.e. the intrinsic fibre directions. In this frame, one axis is aligned with the direction of fastest diffusion, the second (orthogonal) axis is aligned with the direction in which diffusion is fastest in the plane perpendicular to the principal diffusion direction, and the third axis is orthogonal to the other two. The principal direction of diffusivity thus also represents the white matter axonal fibre orientation. It is possible to display this information about the directionality of diffusion through colour-coded maps, and in other ways [12,13]. An interesting novel application consists of following fibre trajectories, reconstructing anatomical structures [14].

From the tensor, the degree of diffusion anisotropy in each voxel is also available. It is reasonable to presume that pathological conditions that alter microstructure also affect the anisotropy of diffusion, as reported by several authors [15–17]. Images of anisotropy show a marked contrast between white matter and the virtually isotropic gray matter and cerebro-spinal fluid. The degree of anisotropy is highly variable in white matter, ranging from a maximum in regions characterized by a strongly ordered parallel fibre arrangement, to much lower values in anisotropic regions where fibres have incoherent orientations, or where fibre bundles cross.

8. Conclusion

Diffusion tensor MRI is one of the most interesting non-conventional MRI techniques available today. It has been applied to several pathologies of the central nervous system that are believed to affect tissue microstructure, and has the potential to elucidate many characteristics of tissue microstructure inaccessible by other techniques. Hardware demands, and signal-to-noise requirements are still the main constraints that limit the application of DT-MRI in a routine clinical setting.

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