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Intravoxel incoherent motion MRI in neurological and cerebrovascular diseases☆

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ABSTRACT

Intravoxel Incoherent Motion (IVIM) is a recently rediscovered noninvasive magnetic resonance imaging (MRI) method based on diffusion-weighted imaging. It enables the separation of the intravoxel signal into diffusion due to Brownian motion and perfusion-related contributions and provides important information on microperfusion in the tissue and therefore it is a promising tool for applications in neurological and neurovascular diseases. This review focuses on the basic principles and outputs of IVIM and details it major applications in the brain, such as stroke, tumor, and cerebral small vessel disease. A bi-exponential model that considers two different compartments, namely capillaries, and medium-sized vessels, has been frequently used for the description of the IVIM signal and may be important in those clinical applications cited before. Moreover, the combination of IVIM and arterial spin labeling MRI enables the estimation of water permeability across the blood-brain barrier (BBB), suggesting a potential imaging biomarker for disrupted-BBB diseases.

1. Introduction

Perfusion refers to the passage of blood delivering nutrients and oxygen to the tissue in the capillary bed (Krogh, 1922). It is an important mechanism of the brain metabolism and plays a crucial role in its normal operation. It is directly involved with regulatory mechanisms (e.g. autoregulation of blood flow, vascular reactivity, and hyperemia) that once unregulated result in cerebral disorders (Hall and Guyton, 2011), such as stroke, dementia and cognitive deficits.

In the brain, perfusion is classically quantified as cerebral blood flow (CBF) which consists of blood volume per unit of brain tissue per unit of time, usually given in mL/100 g/min (Le Bihan, 1992). However, other metrics can be estimated depending on the imaging method. Among several methods, intravoxel incoherent motion (IVIM) estimates brain perfusion based on magnetic resonance imaging (MRI) (Le Bihan et al., 1986). Other approaches are also based on MRI, nuclear medicine and optics (Obrig, 2014; Wintermark et al., 2005).

MRI-based perfusion methods include dynamic contrast enhancement (DCE), dynamic susceptibility contrast (DSC), arterial spin labeling (ASL) (Wintermark et al., 2005), and IVIM. The former two techniques are based on the concept of a bolus of blood volume transiting through the tissue. DCE provides information about K_{trans} (volumetric transfer constant between blood plasma and extracellular extravascular space (EES)) (Sourbron and Buckley, 2013b), permeability-surface area product, and cerebral blood volume (CBV) (Heye et al., 2016; Paldino and Barboriak, 2009). However, the latter is not usually assessed. DSC, the best choice for brain evaluation in clinical settings, provides a relative measurement of CBV, mean transit time (MTT), time to peak (TTP) and an estimation of CBF. ASL is a noninvasive alternative that assesses perfusion through quantification of CBF, which takes advantage of the hydrogen in the arterial blood as an endogenous tracer (Detre et al., 1992; Ferre et al., 2013; Williams et al., 1992).

In the late 1980's, Le Bihan designed IVIM, another approach that measures perfusion-related parameters using MRI noninvasively (Le Bihan et al., 1986). Multiple diffusion-weighted images (DWI) were acquired varying the diffusion gradient weighting. The amplitude of the resulted signal decays exponentially as the diffusion weighting increases. This decay is fitted to a theoretical model to separate diffusion and perfusion contributions of the signal (Le Bihan et al., 1988). A detailed explanation is provided is section 2.

Initially, IVIM drew interest for applications in liver and kidney. Several studies proved its usefulness (Hu et al., 2017; Li et al., 2017; Luciani et al., 2008; Meeus et al., 2018; Yamada et al., 1999). Despite having been initially tested for cerebral imaging, due to its high fractional anisotropy, the existence of several other established imaging methods, and the lack of a consensus about the best fitting method to adjust the signal to a physiological model, IVIM was not very well explored a priori. However, a better physiological description of IVIM

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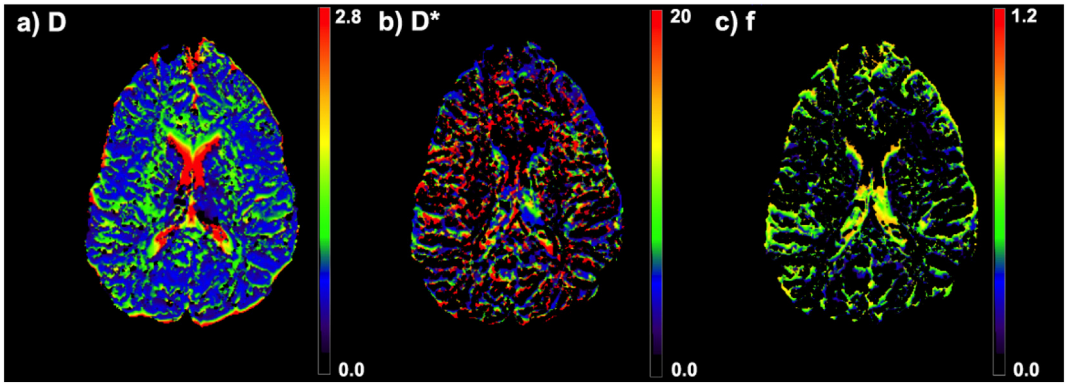

Fig. 1. Examples of D, f and D* maps.

signal and emergence of optimized fitting approaches have increased the application of IVIM in the brain over the past years.

This review provides an overview of the IVIM technique and addresses its main applications in the brain and future directions regarding its use for the study and evaluation of neurological and neurovascular diseases. The combination of IVIM with ASL and their complementarity are also discussed.

2. Theoretical considerations

2.1. The concept of the IVIM signal

Water molecules in a fluid exhibit microscopic random translational motion, called Brownian motion (Einstein, 1956), which results in molecular diffusion. The mean square distance traveled by a molecule is proportional to time and diffusion coefficient D. The latter coefficient depends on diffusing molecules, fluid viscosity, and temperature. At the capillary bed, besides the free water diffusion, the water molecules also flow (Budinger et al., 1985), due to the blood flow. Therefore, in the vascular compartment, the molecular diffusion path is limited by the vessel wall and influenced by the fluid viscosity and blood flow, which results in another diffusion contribution, modulated by a different coefficient, D*, one order of magnitude greater than coefficient D and first described by Le Bihan in 1986 (Le Bihan et al., 1986).

Restrictions imposed on diffusion motion (Tanner and Stejskal, 1968) are measured by MR experiments through the application of magnetic field gradients and result in diffusion-weighted images (Carr and Purcell, 1954; Hahn, 1950). After the use of those gradients, the MR signal decays exponentially according to the diffusion coefficient and the b-value, introduced by Stejskal and Tanner in 1965 (Stejskal and Tanner, 1965) and refers to the weighting of the diffusion pulse sequence. The b-value, expressed in s/mm^2, depends on the diffusion gradient waveform, the time duration of the gradients and the interval between them, according to the following equations:

$$b = (2\pi)^2 \int_0^{TE} \overrightarrow{K_{(t)}} * \overrightarrow{K_{(t)}} dt \tag{1}$$

$$\overrightarrow{K_{(t)}} = \frac{\gamma}{2\pi} \int_0^t \vec{G}_{(t')} dt' \tag{2}$$

where γ is the gyromagnetic ratio, G is the diffusion gradient magnitude in mT/m and t is the time duration of the application of the gradient pulse.

If the signal is measured in a pure solution, where the only source of motion is Brownian due to thermal diffusion, the MR signal can be expressed by a single exponential equation:

$$\frac{S(b)}{S_0} = e^{-bD} \tag{3}$$

where S(b) represents the signal acquired at a specific b-value and S_0 is the signal with no application of diffusion gradients.

When the signal comes from a biological tissue, some factors reduce the diffusion motion, such that it decays according to a different diffusion coefficient, called apparent diffusion coefficient (ADC) (Le Bihan et al., 1986) which is the sum of contribution of all diffusion coefficients related the resulting motion. Under such a condition, diffusion MR signal can be expressed by:

$$\frac{S(b)}{S_0} = e^{-bADC} \tag{4}$$

which is the representation of the diffusion mono-exponential model.

Several components account for the total ADC under biological conditions. However, in comparison to contributions of thermal diffusion and flowing effects, other sources can be neglected, and the signal can be modeled through a bi-exponential model (Eq. (5)), in which each exponential amplitude depends on the blood volume perfusion fraction (f) in a way the sum of those amplitudes must be one.

$$\frac{S(b)}{S_0} = fe^{-bD^*} + (1-f)e^{-bD} \tag{5}$$

Eq. (5) describes the IVIM signal where D is the diffusion coefficient of free water, D* is the pseudo-diffusion coefficient, f is the perfusion fraction and b is the b-value. The idea beyond the IVIM method is to separate those contributions through the mapping of D, D* and f (Fig. 1). Each map contributes with different information, which, combined, helps the understanding of the water movement. Perfusion fraction f represents the volume of blood flowing into the capillary, whose water movement has the contribution of the blood flow and the diffusion motion within a single voxel. All such motions are summarized into pseudo-diffusion coefficient D*. Thus, with the parameters f and D*, IVIM provides the perfusion contribution to the MR signal. Although D* maps are noisier than the others (Fig. 1b), studies in the literature have shown their utility, as discussed in section 2.1. The omission of D* maps might result in the loss of useful information. On the other hand, D is the pure water diffusion coefficient and represents a voxel diffusion contribution to the signal in the extra-vascular pool.

Since D* is one order of magnitude higher than D, the exponential decay with the pseudo-diffusion coefficient vanishes faster, and its contribution to the total signal is distinguishable only at low b-values. At higher b-values, the contribution of the exponential with D models the signal. Multiple b-values are necessary to estimate from which b-value there is only diffusion contribution and consequently to estimate D, D* and f precisely (Fig. 2). Le Bihan proposed acquisition with only three b-values, which are theoretically enough for the obtaining of IVIM outputs. However, more points are necessary especially for the brain due to noise contamination and low D/f ratio, i. e., 0.5%, in comparison to 3.5% in the liver, for example (Le Bihan, 2017). Such a small percentage of perfusion contribution requires oversampling of low b-