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EDITORIAL

Are we ready to image the incoherent molecular motion in our minds?

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The increasing radiological awareness about intravoxel incoherent motion imaging (IVIM) is reflected in this month's issue of *Neuroradiology*. Hauser et al. [1] following hard on the heels of previous work [2] contribute substantially to the accumulating evidence for the utility of IVIM in tissue characterization. Several studies in abdominal imaging, where the theoretical principles of IVIM are verified in vivo in a satisfactory way [3], spearheaded the translation of IVIM into clinical applications after some time of hibernation.

In human tissue, diffusion-weighted imaging (DWI) detects the molecular motion, which includes the molecular diffusion of water as well as the blood microcirculation in the capillary network. The cardinal DWI-derived parameter, apparent diffusion coefficient, has been adapted over time to investigate the tissue-of-interest but is dependent on the choice of *b* values and is endowed with a lumped and nonspecific character. The separation of pure diffusion from flow-related molecules motion demands complex models to describe the signal decay in DWI after application of increasing "motion probing" gradient intensities. The parameters *D* (tissue diffusivity or pure diffusion coefficient), *D** (pseudo-diffusion coefficient or perfusion-related incoherent microcirculation coefficient), and *f* (microvascular volume or perfusion fraction), which were dubbed by Le Bihan et al. [4] as the hallmarks of IVIM-sensitized DWI, seem to adequately resolve the perfusion (microcirculation or net flow) from the true diffusion given a sufficient *b* value sampling and a biexponential curve fit analysis.

Almost simultaneous to the premier presentation of the IVIM technique, considerable skepticism was voiced concerning the suitability of *f*, *D**, and *fD** to measure perfusion in the "classical" sense of the term [5]. The debate remains ongoing and probably will not be terminated since it all seems to be a matter of definition. Actually, the rather loosely used term perfusion implies the efficiency of blood to saturate the tissue with oxygen and nutrients as well as to desaturate it from waste products. The monitoring of exogenous tracers (gadolinium compounds) by MRI provides the well-known blood flow parameter, which is conceptually related to perfusion. Diverse applied models rely on several assumptions that oversimplify the physiological background, resulting in an apparently meaningful determination of blood volume, which is not perfusion or blood flow. In contrast, IVIM devotees, by measuring the phase effects of flowing blood (endogenous marker), provide new insights into the capillary microcirculation, which may be conceptually related to "classical" perfusion under several assumptions about capillary network structure, too [6, 7]. Remarkably, the cellular shape/structuring may cause pseudo-perfusion like "guided flow" (for example in the kidney medulla or in the white brain matter). The apparent "overestimation" of perfusion fraction *f* compared to dynamic contrast-enhanced MR perfusion is inevitably influenced by the choice of motion-probing gradient directions versus the directionality of the neurons in the white matter. The bottom line is that the terms should be meticulously chosen to avoid confusing imprecision that only serve to please our ears. Thus, before any further work clarifies these issues, it would be advisable to denominate *f* strictly as fractional volume of capillary flow instead of perfusion fraction.

Whether IVIM launch means that "the end is nigh" for the contrast-enhanced perfusion-weighted MRI, the answer is probably not. The compartmental water exchange in the DWI experiments is not adequately captured due to the short evolution time (≈100 ms) compared to the dynamic contrast-enhanced MRI, which tracks the intra- and extravascular as

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well as the exchange dynamics of the contrast agent over longer time acquisitions. Since perfusion connotes not only vascularity but also extravasation of blood products, contrast-enhanced perfusion-weighted MRI has a distinct biophysical sensitivity, which cannot be easily abolished. It would be more useful to exploit the interconnections between these two techniques and provide original insights to the tissue perfusion imaging.

Ischemic stroke imaging appears to be the most appealing candidate for IVIM-modeled DWI due to the alleged visualization of the "most-wanted" tissue-at-risk with preserved blood flow and restricted water diffusion which results from energy breakdown. Indeed, from a theoretical point of view and free from conceptual bias with perfusion, the *D* and *D** coefficients in ischemic stroke might be superior to the perfusion–diffusion mismatch principle because they allow us to monitor the untangled changes in cellular volume and extracellular space as well as the shift of balance between the fast and the slow diffusion water pools in the tissue [8]. As water and cell swelling are strongly associated with neuronal activation, it is reasonable to think that IVIM bears a tremendous potential to shed light on the early pathophysiology of ischemia.

IVIM-DWI in acute stroke and within the thrombolysis time frame might identify salvageable brain regions. The preliminary evidence suggests that *f* is indeed lower in infarcted tissue [9] but the measurements of the flow-related parameters are notoriously affected by the fitting process (full vs. asymptotic fitting) and thus, it is expected that any mismatch map should be qualitatively rather than quantitatively appreciated. The strong dependence of the *f* deviations on the signal-to-noise ratio (SNR) is another inherent drawback and systematic errors in *f* estimation appear even at moderate SNR and are exacerbated during the full-fitting process [10, 11]. Specifically, the full-fitting procedure may overestimate *f* due to the inherent behavior of nonlinear least squares fitting in the presence of substantial noise contribution. In full fitting, the mean value of the retrieved *f* increases systematically when the SNR decreases, being almost 200 % higher than the expected value, while asymptotic fitting under the same circumstances results in a simulated mean that is only 14 % lower than the expected value [10]. This drawback of the full biexponential fitting may be less pronounced in well-vascularized high-grade gliomas, which, similar to gray matter, have an inherently satisfactory SNR. Interactions between the imaging gradients and Stejskal–Tanner gradients could also modify the effective *b* value, especially the lower ones. Last but not least, a sufficient number (10–16) and an optimal distribution of the applied *b* values is mandatory for reliable parameter estimation [11, 12].

Whether long DWI acquisitions under these preconditions may be implemented in the clinical setting of acute stroke and outperform the short-lasting and robust combination of dynamic susceptibility contrast-enhanced (DSC) imaging with conventional DWI acquisition is questionable. While tertiary and university hospitals will be tempted to use IVIM-modeled DWI in acute stroke, they will soon face the next shortcoming of the method in neuroimaging, namely the contaminating effect of cerebrospinal fluid (CSF), which due to its rapid decay with increasing *b* value leads to an overestimation of *f*. It will be difficult to translate information garnered in the CSF-filled sulci or in the periventricular white matter back into the mismatch map. Concerning the advantageous visualization of collateral vessels, compensating for impaired perfusion, and microvasculature in the vicinity of CSF spaces by DSC imaging, *f* maps may have to rectify the irritating constant linear flow of CSF by inversion or flow-compensated gradient pulses as well as higher acquisition matrices [13, 14]. This is possible but not always feasible or meaningful, since CSF suppression in the areas with rapid flow is usually incomplete, the normal brain parenchyma signal is also considerably attenuated, the slice thickness has to be suitably increased, partial volume effects are unpreventable, and cardiac gating may be necessary.

However, these considerations are not all doom and gloom. Undoubtedly, the mileage of IVIM-modeled DWI in neuroradiology will be estimated from the tumor characterization and the utility of *D*, *D**, and *f* parameters as surrogate tumor biomarkers, i.e., for WHO grading. This potential was underscored in the seminal work of Le Bihan et al. in mid-1980s [14] but received virtually no attention until recently when Cho et al. succeeded in generating IVIM-sensitive parametric maps in a complex flow phantom assimilating the tumor buildup [15]. Within this paradigm, IVIM parameters may help to differentiate the true vasogenic edema from diffusively infiltrating tumor in the vicinity of the gliomas. CSF partial volume contamination may be partly overcome by referring to the anatomic images for the exact topography of the lesion. Though IVIM may act as complementary and not "stand-alone" modality for tumor differentiation, given the remarkable efficiency of other functional and physiologic MRI modalities, it is of major interest, as introduced in the paper of Hauser et al. [1], to monitor the intra-treatment alterations in *D*, *D**, and *f*. This might provide tremendous advances in our understanding of the molecular response of brain cancer in the different clinical and experimental therapy regimens. It is legitimate to assume IVIM parameters as potential prognostic factors, as monitoring tools, and/or as complementary methods for differentiating tumor recurrence from therapeutic effects. However, we have to be very cautious with the interpretation of *f* in tumor follow-up since prolonged T2 of the tissue, not uncommon under therapy, may lead to increasingly lower *f* estimates with the latter being aggravated by longer TE or pronounced difference in T2 between the capillary

blood and tissue. Finally, an interesting facet of the IVIM-sensitized DWI would be to act as a "splice" in the strife between the interstitial fluid pressure and the capillary blood flow. These counteracting processes are responsible for the drug delivery in tissue and the potential utility of noninvasive IVIM metrics as surrogate marker for IFP measurements is intriguing and was recently investigated in animals [16].

Novel applications of IVIM-labeled diffusion metrics, which will provide much food for thought in the future, are the diffusion-weighted functional MRI (fMRI) and the diffusion-weighted arterial spin labeling (ASL) [8, 17]. Brain activation (small) signal changes, due to cell swelling and the associated water-phase transitions, accompany the change from the resting to the activated conditions. These changes can be tracked by IVIM-DWI and demonstrate that the diffusion response after stimulation precedes the blood oxygenation level-dependent response both at onset and offset with comparable amplitude. Therefore, under appropriate SNR conditions, diffusion fMRI will also unravel the physiology of cell activation at this level. In case of diffusion ASL, the arterial blood volume may also be quantified if we assume that arterial blood is the major source of the pseudo-diffusion component in ASL measurements with IVIM-sensitive gradients.

For the clinical implementation of IVIM-DWI, the choice of the post-processing method seems crucial. Since the acquisition of multiple *b* values is markedly motion-sensitive, the curve fitting on a voxel-by-voxel basis may be rather poor, though voxel-based analysis is desired for an adequate mapping of tissue heterogeneity. Current standard methods pursued to overcome such weaknesses by averaging the parameter values in large ROIs and setting in an arbitrary way nonphysiological or meaningless (i.e., negative) values to zero since they are likely to result either from noise, turbulent CSF, or biexponential fitting of voxels with monoexponential signal decay. A further indispensable step is to examine the reproducibility and the repeatability of the method. Such measurements in the brain and abdominal imaging are scarce, mostly due to the demand for sufficiently high-quality images acquisition [18]. The next formal action is to test the sensitivity of the method for quantifying the fluctuation of capillary blood flow during induced vasoconstriction or vasodilatation [19, 20].

In conclusion, this commentary is insufficient to accommodate all potential dimensions and viewpoints in the emerging applications of IVIM-related DWI analysis. Its main intention is solely to echo to our readers the exceptional potential of this method in neuroimaging that will fuel the future research endeavors.

Conflict of interest I declare that I have no conflict of interest.

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