



Editorial: Assessing Cellular Microstructure in Biological Tissues Using *in vivo* Diffusion-Weighted Magnetic Resonance

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Editorial on the Research Topic

Assessing Cellular Microstructure in Biological Tissues Using *in vivo* Diffusion-Weighted Magnetic Resonance

Since the seminal works of Stejskal and Tanner in the 1960s [1], the study of molecular self-diffusion by diffusion-weighted (DW) nuclear magnetic resonance (NMR) has emerged as a dynamic and rich research field. Initially introduced as a tool to measure diffusion in materials and to estimate microstructural properties of materials by modeling deviations from free diffusion caused by microstructural barriers [2], DW-NMR was soon proposed as a tool to characterize cellular microstructure in biological tissues [3]. It was then quite a natural—although challenging—step to endow magnetic resonance imaging (MRI) with diffusion-weighting capabilities to map water diffusion *in vivo* [4], which almost immediately revolutionized the diagnosis of brain ischemic stroke [5–7]. This partial historical account of the early days highlights the different “flavors” still characterizing our research field at the interface of physics, chemistry, biology, computer science, and medical imaging: a unique blend of powerful concepts and theories, cutting-edge methodological, and technical innovations, ideally leading to highly-relevant biological insights or clinical applications.

Various approaches, each with their own strengths and weaknesses, have been developed over the years to probe microstructure with ever higher degrees of sensitivity and specificity. The goal of this Research Topic was to gather experts in various acquisition and modeling strategies and show how these approaches can yield unique and complementary information about cellular microstructure. In parallel to the topics discussed here, other developments are also driving *in vivo* DW-NMR forward. Important examples are the ever increasing field strength and gradient performance of MRI scanners, boosting signal-to-noise, and enabling larger and better temporally resolved diffusion-weighting, respectively [8, 9]. However, these technical innovations also come with new difficulties or limitations, e.g., increased tissue heating, decreased transverse relaxation times, increased sensitivity to motion and field fluctuations, decreased field homogeneity and increased geometrical distortions at high fields [10, 11], and increased peripheral nerve stimulation by powerful gradients [9]. The drawbacks resulting from these technical innovations are partially offset by parallel developments in coil and pulse sequence technology. Such technical innovations and solutions are not discussed in this Research Topic.

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Many fundamental questions remain open about the relationships existing between the diffusion-weighted signal and its derived diffusion metrics on one hand, and the underlying microstructural features on the other hand. Approximately half of the papers of this research topic aim at addressing such fundamental questions, using different approaches.

Some rely primarily on theoretical considerations. Özarşlan et al. revisit the q^{-1} decay in narrow fibers, taking curvature into account. The problem is examined in three distinct temporal regimes of the Stejskal-Tanner pulse-field gradient experiment. For smaller cells, the q^{-1} decay of the orientationally-averaged signal is only predicted for straight fibers. This decay is more general for cells with longer projections, but fades away for curvy structures as gradient pulse duration increases. The authors stress that the q^{-1} decay could represent an intermediate range, as the true asymptotic behavior is governed by a steeper attenuation. Laun et al. tackle another kind of diffusion experiments, where the time-dependence of the apparent diffusion coefficient (ADC) is measured. In the short diffusion time (t_d) regime, the ADC is known to decrease as the square root of t_d multiplied by the surface to volume ratio (S/V). The next term in the expansion is proportional to t_d multiplied by a factor depending on permeability and curvature. Laun et al. show that this term is identically zero for oscillating gradients, meaning that permeability and curvature cannot be easily measured with these sequences, while S/V term may be easier to quantify than with pulsed-field gradients. Ozarşlan et al. present a new perspective for the representation of restricted diffusion that is highly suitable for diffusion experiments performed with commonly available gradient hardware, for example on clinical scanners. Diffusion experiments under such conditions are typically performed with long gradient pulses, thus blurring the information necessary for the characterization of the restricting pore. The approach presented here assumes that diffusion occurs in an effective quadratic potential landscape, thus resulting in a linear (Hookean) dependence of the stochastic effective force on the center-of-mass position. The implications that this approach may have on the interpretation of diffusion experiments performed with long diffusion gradients are discussed, together with possible extensions of this theoretical framework to potential landscapes other than quadratic.

Theoretical analysis typically relies on idealized assumptions for mathematical tractability, and therefore struggle to evaluate the quantitative impact of complex structural features in realistic acquisition conditions. In that case, numerical simulations may help. Ginsburger et al. describe simulations in synthetic white matter mimicking axonal bundles (Ginsburger et al.), with a small set of parameters controlling the level of tissue complexity and disorder. Their results show that angular dispersion and most importantly axonal beading have non-negligible effects on extracellular diffusion which may be measured using DW-MRI clinical protocols with oscillating gradients.

A major limitation of both theoretical analysis and numerical simulation may be the insufficient knowledge about the precise nature or magnitude of some features potentially affecting diffusion (such as the properties and detailed distribution of membranes or the existence of molecular pools with

different relaxation times), thus precluding solid theoretical or numerical approaches. In such situations, we must rely on experiments for gaining further fundamental insights about what diffusion measurements reflect. Shemesh investigates the microstructural correlates of fractional anisotropy (FA) and microscopic FA (μ FA) using high resolution double-diffusion encoding (DDE) and double oscillating gradient diffusion encoding (DODE) experiments in fixed spinal cords. The results indicate that μ FA(DODE) mostly depend on axon sizes and myelin water fraction, whereas μ FA(DDE), FA(DODE), and FA(DDE) correlate to a much lesser extent with those cellular features. This is promising for future interpretations of these metrics in health and disease. Valette et al. recapitulate how intracellular metabolite diffusion has been measured in the brain, using DW-NMR spectroscopy *in vivo*, from $t_d < 1$ ms to $t_d > 1$ sec, and how the picture emerges that metabolites are not confined into subcellular compartments, but are instead diffusing in long fibers with some long-range complexity. Some possible future directions to extend the range of diffusion times, and what information about cell structure can be gleaned, are also discussed. As a final illustration of how well-thought experiments may yield fundamental insight, Lemberskiy et al. exploit data obtained in the prostate at multiple t_d and echo times to select and combine two different models, which allows disentangling the cellular compartment (exhibiting shorter relaxation time T2 and associated with diffusion through extended disorder) from the lumen (exhibiting longer T2 and associated with the short-time S/V limit). Beyond fundamental understanding, data modeling allows extracting lumen diameter, fiber diameter and membrane permeability, with possible application to non-invasive diagnosis and staging of prostate cancer with MRI.

The potential relevance for applications of DW-NMR *in vivo* certainly underlies all works in our field, even those aiming at gaining fundamental knowledge, but some works more directly aim toward applications in animals or humans. Such more “application-driven” papers, either describing optimized methods to measure biologically/clinically relevant parameters, or evaluating the value of these methods under various conditions (e.g., in disease), represent approximately another half of this research topic.

Hansen and Jespersen review fast kurtosis imaging protocols, which are capable of estimating the mean, axial and radial kurtosis (i.e., deviations from Gaussian diffusion when q is varied at constant t_d) with only a few diffusion directions. The review describes the theoretical foundations for these methods, technical and practical considerations, and potential applications mostly related to peripheral nerve or white matter microstructure. In a similar vein, Jelescu and Budde review popular models of diffusion in white matter to extract parameters such as axonal orientation dispersion, axon diameter, and extracellular volume fraction, from the q -dependence at constant t_d . Assumptions and required data are detailed for each model, before examining how these models can be validated using numerical simulations, phantoms, or *ex vivo* microscopy. Zeng et al. consider the fitting quality of multi-exponential signal expressions to diffusion data from white matter in healthy volunteers. Specifically, they propose to describe water diffusion in white matter in terms

of a modified tri-exponential expression; a biexponential plus a “dot” compartment, i.e., a water pool having zero diffusivity. The latter component is interpreted as restricted diffusion, and the modified tri-exponential is found to have lower corrected Akaike criterion than both free tri-exponential and biexponential signal representations in several white matter ROIs.

Mériaux et al. present an original method which, unlike other papers of this research topic, does not assess diffusion by gradient-induced diffusion-weighting, but by dynamically acquiring concentration maps of contrast agents as they diffuse through the extracellular space (as more traditionally performed with optical imaging) to evaluate the ADC and tortuosity in the extracellular space. One original point of their approach is that the agent is delivered to the brain after i.v. injection and ultrasound-induced blood-brain barrier opening, avoiding invasive intracerebral injection. This technique may be useful to characterize the alterations of extracellular space diffusion properties in pathologies such as Alzheimer’s disease, and also to predict drug biodistribution.

Some methods may prove particularly relevant for specific pathologies, such as tumors. Reynaud starts by reviewing the fundamentals of time-dependent diffusion in the short-time regime and near the tortuosity limit. The main three geometrical models (IMPULSED, POMACE, VERDICT) implemented so far to describe tumor cells as spheres are then reviewed, and their applications for estimating tumor intra- and extracellular volume fraction and cell size is then presented and discussed. Budde et al. present an optimization of pulse sequences for imaging of spinal cord injury. The authors consider orientationally invariant DDE, filter probe DDE and filter probe single-diffusion encoding (SDE), in which the idea of a filter probe is basically to suppress extra-axonal water with a diffusion gradient perpendicular to

the cord. They find that filter probe SDE coupled with reduced field-of-view excitation is the best protocol with highest signal-to-noise ratio and with high sensitivity to injury, without contamination from edema and cerebrospinal fluid. This is demonstrated with simulations, and *in vivo* rat and human spinal cord imaging. Finally, one important clinical use of MRI is in assessing tissue damage and prospective recovery in ischemic stroke. Question remains as to what are the most meaningful diffusion metrics in ischemic stroke, that is, those that most sensitively reflect microstructural characteristics of tissue affected by ischemia. Galazzo et al. consider a set of indices obtained from the Simple Harmonic Oscillator Based Reconstruction and Estimation (SHORE). Assessment of quantities associated with the SHORE formalism are investigated in a tract-based fashion in white matter and region-of-interest analysis in gray matter in patients and controls, providing insight into the potential benefits of adopting the SHORE model and some of its metrics in the clinic.

In conclusion, this research topic illustrates the multifaceted nature of cellular microstructure assessment using DW-NMR. While no particular method can grasp the full complexity of cellular microstructure, each of them can shed light on different aspects and find specific applications. In the long term, some approaches will certainly prove more insightful or useful than others. For now, the present collection of works pays tribute to the vitality and diversity of our research field.

AUTHOR CONTRIBUTIONS

JV drafted the first version of the editorial. IR and SJ revised the first draft and made contributions about papers they edited.

REFERENCES

- Stejskal EÖ, Tanner JE. Spin diffusion measurements: spin echoes in the presence of a time-dependent field gradient. *J Chem Phys.* (1965) **42**:288. doi: 10.1063/1.1695690
- Tanner JE, Stejskal EO. Restricted self-diffusion of protons in colloidal systems by pulsed-gradient spin-echo method. *J Chem Phys.* (1968) **49**:1768. doi: 10.1063/1.1670306
- Tanner JE. Self diffusion of water in frog muscle. *Biophys J.* (1979) **28**:107–16. doi: 10.1016/S0006-3495(79)85162-0
- Lebihan D, Breton E, Lallemand D, Grenier P, Cabanis E, Lavaljeantet M. Mr imaging of intravoxel incoherent motions - application to diffusion and perfusion in neurologic disorders. *Radiology.* (1986) **161**:401–7. doi: 10.1148/radiology.161.2.3763909
- Le Bihan D, Breton E, Lallemand D, Aubin ML, Vignaud J, Lavaljeantet M. Separation of diffusion and perfusion in intravoxel incoherent motion MR imaging. *Radiology.* (1988) **168**:497–505. doi: 10.1148/radiology.168.2.3393671
- Moseley ME, Kucharczyk J, Mintorovitch J, Cohen Y, Kurhanewicz J, Derugin N, et al. Diffusion-weighted MR imaging of acute stroke: correlation with T2-weighted and magnetic susceptibility-enhanced MR imaging in cats. *AJNR Am J Neuroradiol.* (1990) **11**:423–9.
- Warach S, Chien D, Li W, Ronthal M, Edelman RR. Fast magnetic resonance diffusion-weighted imaging of acute human stroke. *Neurology.* (1992) **42**:1717–23.
- Le Bihan D, Schild T. Human brain MRI at 500MHz, scientific perspectives and technological challenges. *Superconduct Sci Technol.* (2017) **30**:033003. doi: 10.1088/1361-6668/30/3/033003
- Jones DK, Alexander DC, Bowtell R, Cercignani M, Dell’Acqua F, McHugh DJ, et al. Microstructural imaging of the human brain with a ‘super-scanner’: 10 key advantages of ultra-strong gradients for diffusion MRI. *Neuroimage.* (2018) **182**:8–38. doi: 10.1016/j.neuroimage.2018.05.047
- Moser E, Stahlberg F, Ladd ME, Trattnig S. 7-T MR—from research to clinical applications? *NMR Biomed.* (2012) **25**:695–716. doi: 10.1002/nbm.1794
- Ladd ME, Bachert P, Meyerspeer M, Moser E, Nagel AM, Norris DG, et al. Pros and cons of ultra-high-field MRI/MRS for human application. *Prog Nucl Magn Reson Spectrosc.* (2018) **109**:1–50. doi: 10.1016/j.pnmrs.2018.06.001

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