Denis Le Bihan, M.D., Ph.D., has achieved international recognition for his outstanding contributions to the development of innovative MRI methods, in particular diffusion MRI. His focus has been on applying these methods to areas of scientific and clinical importance. He completed his training in medicine and physics in Paris before moving to the United States in 1987. He worked as a Research Section Chief in the Clinical Center at NIH, Bethesda, Maryland, USA, and as a Clinical Associate Professor of Radiology at Georgetown University, Washington, DC, USA. In 1994, he accepted a post at the Service Hospitalier Frédéric Joliot of the French Atomic Energy Commission, in Orsay, France, an internationally recognized MRI and PET facility. In 2000, he was appointed director of the Federative Research Institute of Functional Neuroimaging (Orsay/Paris, France). In 2007, Denis Le Bihan founded NeuroSpin, a new Institute of the CEA aimed at developing and using ultra high field magnetic resonance to understand the brain, from mouse to man. He also holds Visiting Professor positions at Kyoto University (Graduate School of Medicine), the Kyoto Prefectural Faculty of Medicine, and the National Institutes of Physical Sciences in Okazaki, Japan.

Denis Le Bihan belongs to several professional societies. Commensurate with his prolific research, he has authored or co-authored over 400 articles, book chapters, and review articles in the fields of MRI, imaging, neuroscience, and radiology. For his contributions, in 2001, he was awarded the Gold Medal of the International Society for Magnetic Resonance in Medicine. He is also the 2002 recipient of the Lounsbery Award from the National Academy of Sciences (USA) and French Academy of Sciences, and the corecipient of the Louis D. Award of the Institut de France in 2003. Le Bihan also received the prestigious Honda Prize (2012), the Louis Jeantet Foundation Award (2014), and gave the Lauterbur lecture at the 2014 ISMRM meeting. He is a full member of the French Academy of Sciences, the Academy of Technologies, the Academy of Pharmacy, and a corresponding member of the National Academy of Medicine.

Diffusion MRI past and future: an overview

Dear readers and colleagues,

I am very pleased that Siemens Healthineers has chosen to include diffusion and IVIM MRI among the themes being covered by this issue of MAGNETOM Flash and extremely honored to have been invited to write this editorial.

Diffusion MRI has been extraordinarily successful over the past 30 years (over 1,290,000 entries in Google Scholar for "diffusion MRI" as of April 2018). Its main clinical domain of application has been neurological disorders, particularly the management of acute stroke patients. However, it has also rapidly become a standard for the investigation of brain white matter, as Diffusion Tensor Imaging (DTI) can reveal abnormalities in white matter fiber structure in neurological or psychiatric disorders. DTI and its variants have also made it possible to obtain stunning 3D color maps of brain connectivity. Besides their obvious clinical and research potential, these maps now feature in anatomical textbooks on brain white matter (which has become very colorful thanks to diffusion MRI), and the subject of works of art. For the past few years, these brain connection maps, obtained from Siemens Healthineers MRI scanners, have even been printed on the card keys ISMRM participants receive when checking into their hotels during the annual meetings (I have a whole collection!). This is a real mark of recognition!

A virtual biopsy

Diffusion MRI was conceived in 1984 with an inspirational goal: To use a noninvasive technique to provide information on tissue at the microscopic level, while MR images remain at a macroscopic (millimetric) resolution, in other words, a kind of virtual, noninvasive biopsy. Beyond the invention of diffusion MRI, this goal has driven, and is still driving, my efforts, and those of many teams around the world, to develop and apply this powerful concept to biomedical research and clinical practice. Diffusion MRI involves investigating the diffusion of water molecules in tissue (the diffusion of other molecular moieties can also be studied using MR diffusion spectroscopy). One way of looking at the method is to think of the water molecules as spies probing the tissue for us on a microscopic scale, providing an imprint onto the diffusion MRI signal of what they have 'seen' during their Brownian motion driven displacements: fibers, macromolecules, cell membranes, all the obstacles that prevented them from diffusing freely. Of course, it is important to bear in mind that this microscopic information is averaged out within each voxel, although it is still possible to obtain information on the degree of homogeneity or heterogeneity of the diffusion process within each voxel. This concept, inferring information on tissue microstructure in images with a macroscopic resolution has proved extremely useful in clinical practice, providing exquisite contrast not readily available with other imaging modalities, including MRI, without the need for contrast agents. For instance, brain cell swelling occurring right at the onset of ischemia (due to cytotoxic edema) is only revealed by diffusion MRI, well before any detectable changes in T1 or T2 may be cached. In the 1990s, for the first time, this discovery by Michael Moseley's team allowed the objective diagnosis of stroke at the acute phase and the development of thrombolytic agents. This completely changed our views on the management of acute stroke patients, improving the clinical outcome of many patients worldwide.

However, diffusion MRI is also increasingly being used with great success outside the brain to investigate a broad variety of illnesses, especially cancer, whether breast, prostate, or liver, as reported in the article by Petralia et al. in this issue of MAGNETOM Flash. It is perhaps not so well known that my experience of diffusion MRI also started in the liver. Back in the early 1980s (I was then a medical resident in neurosurgery and radiology, and a Ph.D. student in nuclear and elementary particles physics), I was asked whether MRI could differentiate liver tumors from angiomas. At the time, MRI contrast media were not clinically available. I quickly came back with a vague idea that, perhaps, a molecular diffusion measurement would result in low values in solid tumors, due to molecular movement 'restriction', while diffusion would be slightly enhanced in flowing blood. Based on Stejskal and Tanner's pioneering NMR work in the 1960's, I thought that specific diffusion coding could be accomplished using magnetic gradient pulses, but there was a problem with integrating these pulses into those used in the MRI sequence for spatial encoding. This may seem trivial, but in fact, it was a major hurdle. Some colleagues remarked at that time that it was not even possible to obtain images of diffusion *in vivo* and that my first (I)SMRM presentation in 1985 was nothing more than a collection of artifacts. I had to gather all my courage to continue. The innovative element of my approach was that it proposed *localizing* the diffusion measurements, that is obtaining *maps* of the diffusion coefficients in tissue. This had never been done before, especially in vivo, with any technique. I was very excited and, in a matter of weeks "diffusion MRI", as we know it, was born, implemented, and validated. In my first diffusion MRI papers (published in Radiology and the

journal of the French Academy of Sciences, *Comptes rendus*) I introduced the "b factor" to quantify the degree of diffusion weighting (as TE is for T2) from the gradient pulses magnitude and duration with the presence of cross-terms between diffusion and the multiple imaging gradient pulses (which were of course not taken into account by Stejskal and Tanner), the ADC concept, IVIM (IntraVoxel Incoherent Motion), and all the conceptual and technical ingredients that still ensure the success of diffusion MRI.

There were, indeed, many technical issues that still needed to be resolved, and the first trials conducted in the liver at 0.5T were very disappointing. The method never really worked, mainly because of huge motion artifacts due to respiration (we had to wait until 1999 when Professor Yamada and his team in Japan published a landmark paper proving that my idea of differentiating between angiomas and liver tumors was not misguided). First, the signal-to-noise ratio was very low. Second, gradient hardware rarely enabled us to reach strengths beyond 8 or 10 mT/m (at the price of very large eddy current artifacts) and the limit for the *b* values was around 100 or 200 mm/s². Third, there was no EPI, just conventional 2D FT spin-echo sequences. The acquisition times necessary for diffusion encoding were very long (close to 10 minutes per *b* value) and, as respiratory gating was not yet available either, motion artifacts caused by body movement were atrocious. So, I gave up, and quickly switched to the brain, which was my own area of expertise after all. I scanned my own brain and that of some of my colleagues before investigating patients. It worked beautifully and resulted in a great achievement: Diffusion MRI was established.

Strong gradient hardware makes all the difference

It took some time for diffusion MRI to come into clinical use, as it was without doubt a very innovative and "out of the box" concept for the time. Today, however, diffusion MRI has become a cornerstone of modern medical imaging. The method became clinically relevant in the 1990s when it was coupled to EPI (Echo-Planar Imaging), which reduced motion artifacts and acquisition times dramatically. EPI requires strong gradient hardware and in light of its potential for the management of acute stroke patients, MRI manufacturers built on diffusion EPI to provide robust and efficient technical solutions for the healthcare sector. Undeniably, the field of diffusion MRI has evolved considerably over the last 30 years, benefiting especially from improvements in gradient hardware, which is without doubt the most important component of efficient encoding of microscopic diffusion movements. Siemens Healthineers teams must be highly commended for their outstanding Connectome Gradient systems. This type of hardware enables gradient strengths of 100 or even 300 mT/m and *b* values higher than 20 000 s/mm² are within reach. Back in the 1980s, I could not never have imagined that the *b* values would increase 100-fold in 30 years (sadly, the *b* value is not a stock on the market).

This race toward larger gradient strength is not at all anecdotal. First, technically, it allows shorter TEs to be used for any given *b* value. This, in turn, increases the signal-to-noise ratio, which is of particular interest for tissue with short T2, such as body tissue, especially when going to high field (as shown at 7T in the spinal cord by Massire et al. in this issue of MAGNETOM Flash). More importantly, however, it allows us to reach higher *b* values. But why is this important for clinical needs? Diffusion driven displacements of water molecules are encoded in the MRI signal through variations of the magnetic field in space caused by magnetic field gradient pulses. The overall effect of diffusion in the presence of gradient pulses is a signal attenuation and the MRI signal becomes 'diffusion-weighted'. The signal attenuation is more pronounced when using large *b* values. As diffusion-weighted images also depend on other parameters, such as T1 and T2, we often calculate the ADC (Apparent Diffusion Coefficient) which depends solely on diffusion. The ADC is obtained from images acquired using only 2 different *b* values. When diffusion is free (no obstacles to water molecules), the ADC does not depend on the *b* values, so the choice of *b* values is just to provide the best ADC accuracy for an expected range of ADC values given the presence of noise. For instance, in the brain, the theoretically optimal pair of *b* values is 0 and 1000 s/mm², while in most body tissue 0 and 600 or 800 s/mm² would probably be the preferred values. Since this is what makes the diffusion MRI contrast so sensitive to tissue features), in most tissue, diffusion fortunately becomes non-Gaussian due to the many obstacles hindering water diffusion. As a result, the amount of diffusion-driven signal attenuation decreases when the *b* value increases. In other words, the ADC value decreases when high *b* values are used, whether in the brain or the body. In short, the higher the *b* values, the more sensitive the diffusion images are to tissue microstructure features. A consequence of non-Gaussian diffusion is that, in order to make meaningful comparisons across literature or across sites in the case of multicenter studies, it is important to report which *b* values have been used to acquire data.

Tractography also greatly benefits from high *b* values. In some tissue, notably brain white matter, but also heart/muscle fibers, diffusion is 'anisotropic', strongly depending on the direction of the gradient pulses used to provide diffusion sensitivity. Proper handling of anisotropic

diffusion requires the diffusion tensor imaging (DTI) method which we introduced with Peter Basser in the early 1990s. In conjunction with algorithms connecting voxels based on their individual diffusion features, DTI and its variants have served as the basis for brain white matter tractography since it was introduced. Switching to high *b* values decreases the contribution of non-axonal water diffusion to the diffusion MRI signal, allowing higher specificity and resolution in fiber delineation.

In fact, it is important to report not only the *b* values, but also the precise timing of the gradient pulses (which determines the 'diffusion time') used for diffusion encoding, as different time profiles could lead to different diffusion effects even with the same *b* value. This is due to the fact that there is a higher chance of water molecules interacting with tissue microscopic features when long rather than short diffusion times are used. Thus, comparing ADC values obtained with the same *b* values but using short and long diffusion times provides us with additional information on the tissue microstructure. In the brain, the NODDI and CHARMED models, for instance, exploit this time dependence to differentiate cellular components (cell body, dendrites) or evaluate their size (the axonal diameter, for example). Short diffusion times require very powerful gradients to ensure they can reach sufficiently high *b* values. To do this, in practice, diffusion gradient pulses are made to oscillate rapidly and the Pulsed Gradient Spin-Echo sequence (PGSE) becomes an Oscillating Gradient Spin-Echo sequence[1] (OGSE). To date, access to OGSE has been the privilege of researchers working with preclinical MRI scanners equipped with extremely powerful gradient systems (reaching 1 or even 2 T/m). Now, with Siemens Healthineers advanced MAGNETOM Prisma MRI scanners, OGSE has become available to clinicians as well as to their patients. Comparing ADC values at short and long diffusion times could reveal differences between tissue in terms of cellularity and membrane permeability to water (linked to aquaporin receptors expression, for instance). This has huge potential in oncology for diagnosing and staging malignant lesions or monitoring treatment efficacy.

Beyond image acquisition: The expanding world of data processing and artificial intelligence

At the other end of the *b* value spectrum there is an offshoot of diffusion MRI which should not be overlooked: IVIM[2] (IntraVoxel Incoherent Motion) MRI. Flow of blood water in randomly oriented capillaries (at voxel level) mimics a random walk (pseudodiffusion) which results in a pseudodiffusion effect when using diffusion MRI. The effect is seen at very low *b* values only because the pseudodiffusion coefficient, D*, associated with blood flow, is higher than the water diffusion coefficient. True diffusion and pseudodiffusion can thus be separated using dedicated algorithms. The idea of using diffusion MRI to obtain images of perfusion has been regarded controversial, but also ground-breaking, and IVIM MRI is enjoying a spectacular renaissance in the assessment of tissue perfusion in clinical practice, especially in the field of cancer imaging (as reported in the article by Granata et al. in this issue of MAGNETOM Flash). A key feature of IVIM diffusion MRI is that it does not involve contrast agents. This means that it could serve as an interesting alternative to contrast-enhanced perfusion MRI in certain patients with contraindications for contrast agents, such as those with renal failure at risk of Nephrogenic Systemic Fibrosis (NSF) or those requiring multiple MRI examinations, since gadolinium might accumulate in brain tissue. It is important to keep in mind, though, that IVIM MRI is a somewhat challenging method because separating perfusion and diffusion requires high signal-to-noise ratios.

"Postprocessing is a very important step enabling us to fully exploit the benefits of the method and access the wealth of information it provides."

It is undeniable that, with the availability of versatile MRI hardware and sequences, important progress has been made in our understanding of the diffusion processes at play in tissue, resulting in increasingly sophisticated models. Diffusion is a genuine physical process that occurs naturally in tissue, as opposed to T1 or T2 which are only defined in the MRI context. Postprocessing is, thus, a very important step enabling us to fully exploit the benefits of the method and access the wealth of information it

[1] Some of the concepts and information presented in this paper are based on research and are not commercially available.

[2] WIP, the product is currently under development and is not for sale in the US and in other countries. Its future availability cannot be ensured.

"This information is likely to prove be extremely useful when it comes to providing our patients with individual or personalized diagnostic strategies in the era of precision medicine."

provides; information that is not easily visible on raw diffusion-weighted images, or even the 'simple' ADC. During the postprocessing phase, signals from images are combined using algorithms and evaluated using mathematical and physical diffusion models. These models, such as the popular Kurtosis model, are designed to handle non-Gaussian diffusion. Finally, model outputs are transformed into a series of parametric maps, showing the means, but also heterogeneity, of parameters across tissue and organs. Once these diffusion related parameters have been estimated, it is also possible to generate a posteriori virtual diffusion-weighted images mimicking contrast, which can be obtained at any *b* value. Post-processing is obviously the cornerstone of tractography, providing 3D maps of brain connections from DTI images, but also information on axon fiber diameter or orientation coherence. Another important objective of postprocessing software is to 'clean' raw data, realigning images affected by organ motion, correcting geometric distortions induced by gradient pulses, or extracting meaningful signals from background noise. In summary, postprocessing is the key to fully exploiting the benefits of IVIM and diffusion MRI.

Model sophistication, however, should not be an obstacle to clinical application. Diffusion MRI must remain user-friendly and provide clinicians with the information they need to assess their patients' illnesses. For instance, instead of analyzing several parameters separately, such as IVIM, ADC, or kurtosis, which are not easy to interpret, software could digest this overwhelming information and provide semi-automatic analysis of lesions (through indices or scores) including diagnosis or lesion stage. Final decisions, would, of course, be made by clinicians. This is where artificial intelligence comes in to play in the field of diffusion MRI. For instance, each parameter might have a given threshold to differentiate benign and malignant tissue. Those parameters could be combined to give a summary diagnostic score based on the number of parameters supporting malignancy. Score maps can be generated providing diagnosis, but also showing which areas of lesions are likely to be most malignant thus suggesting the best locations for biopsies. An alternative method, using the Bayesian approach, is to weight each parameter value with population-based statistics to provide an overall probability for each tissue type (e.g., malignant versus benign or malignancy types). Another approach is to calculate a signature index from the 'proximity' or resemblance of the diffusion MRI signal profile of a examined tissue (information obtained using a set of limited key *b* values and/or diffusion times selected for their higher sensitivity to underlying tissue microstructure) to a database or library of 'signature' signal profiles. The profiles in the database are acquired from a reference cohort of patients with established malignant and benign tissue in a given organ, or even simulated using complex models. With this 'signature index', highly accurate diagnosis or tissue staging can be readily and automatically obtained without having to calculate any model parameter. This signature can also be adjusted to reveal more specific features, for instance to provide an estimation of radiogenomic biomarkers, such as the presence or absence of hormone receptors Her2 and PgR in breast cancer lesions. This information is likely to prove be extremely useful when it comes to providing our patients with individual or personalized diagnostic strategies in the era of precision medicine.

A promising future

In yet another application, voxels exhibiting high IVIM pseudodiffusion from fast flow can also be flagged and then connected using algorithms, similar to those used for tractography, to generate a completely new kind of IVIM based angiogram without the need for contrast agents. It is important to acknowledge that there is a wealth of information concealed in the diffusion MRI signal, so it is really up to our imagination to devise new ideas, methods, or algorithms to make the most of this treasure trove. For instance, the extreme sensitivity of diffusion MRI to minute changes in cell size (e.g., swelling) makes diffusion MRI a completely new approach for functional MRI, as neural activation is associated with cell swelling, a much more direct connection than with BOLD fMRI which relies on the neurovascular coupling principle. Moreover, considering that diffusion MRI is inextricably linked to tissue micro-structure, it should come as no surprise that diffusion MRI can also provide information on tissue elasticity. Indeed, diffusion features, especially through the synthetic indices

presented above, have been successfully quantitatively converted into tissue shear stiffness (in kPa) with extraordinary accuracy in the liver, and without the need for the vibration devices or phase sensitive MR sequences used with conventional MR Elastography (MRE). Research is currently being conducted to examine the possibility of using virtual MRE performed through diffusion MRI in staging liver fibrosis. Ironically, I now find myself involved in trials of diffusion MRI in the liver, the same place I was in more than 30 years ago, but this time with much greater success and using a totally unexpected twist in the method, far beyond my wildest dreams at the time (as far as diffusion MRI is concerned, at least). Moreover, the intravoxel phase dispersion resulting from propagating shear waves induced by mechanical vibrations can be emulated, and transformed into virtual elastograms through the IVIM effect, for any organ and for any combination of vibration frequency or amplitude. This is something that is not easy to achieve with conventional MRE hardware and has produced new and exciting contrast, as we have discovered, to our surprise, in the liver, the breast, and the brain.

From its conception, it took about 10 years for diffusion MRI to enter the routine clinical field in hospitals, a further 10 years from the first DTI papers to the start of generalized usage of tractography in the brain, and perhaps another 20 years for IVIM to be used clinically to evaluate perfusion in the body. Diffusion MRI is clearly a mind opener. Molecular diffusion has a 'life' of its own and remains a powerful, genuinely multidisciplinary concept at our fingertips with which we can investigate cell physiology, tissue structure, and ultimately life. After all, all biological processes require molecules to interact, for DNA replication, protein transcription, protein and enzyme activity, cross-membrane transport, and much more. However, for molecules to interact, they must first meet, and diffusion is the universal process that nature and evolution have capitalized upon for this purpose. In a sense, diffusion rates set life's speed limit, just as the speed of light sets the limit in the physical world. Diffusion MRI has a bright future ahead and will keep Siemens Healthineers teams busy for years to come, integrating those very promising innovations into their MRI scanners for the benefit of healthcare professionals and patients alike.

The statements by Siemens' customers presented here are based on results that were achieved in the customer's unique setting. Since there is no 'typical' hospital and many variables exist (e.g., hospital size, case mix, level of IT adoption), there can be no guarantee that other customers will achieve the same results.