NMR IN BIOMEDICINE
NMR Biomed. 2002;**15**:431–434
Published online in Wiley InterScience (www.interscience.wiley.com). DOI:10.1002/nbm.798

Editorial

From the diffusion coefficient to the diffusion tensor

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Received 14 May 2001; Revised 20 August 2001; Accepted 17 December 2001

ABSTRACT: With diffusion tensor MRI one has access to the organization in space of tissue microstructural components. This outstanding potential adds, however, another layer of complexity to the diffusion MRI data acquisition and analysis processes. Over the last few years many articles have been published dealing with those matters. This special issue is thus timely to provide readers with the synthesis and the overall viewpoints from leading contributors to the field. Copyright © 2002 John Wiley & Sons, Ltd.

KEYWORDS: diffusion; MRI; diffusion tensor imaging (DTI); white matter; tractography; connectivity

INTRODUCTION

The number of articles in the literature dealing with diffusion MRI and MRS has been soaring during the last 10 years. Within this field, diffusion *tensor* MRI (DTI) is taking an increasingly important place. DTI is certainly not an easy concept, so this special issue of NMR in Biomedicine comes at the right time. Several key players in the field of DTI have been invited to review DTI concepts, discuss the current outstanding issues and to give overviews of potential applications.

The basic principles of 'plain' diffusion MRI were laid out in the mid 1980s (see for instance Le Bihan[1] for a review) by combining MRI pulse sequences with methods that had been previously developed to encode molecular diffusion effects through the use of pairs of magnetic field gradient pulses. The rapid adoption of diffusion MRI and its long-term potential both arise from the powerful principle that, during their random diffusion-driven displacements, molecules probe tissue structure at a microscopic scale well beyond the usual image resolution. During typical diffusion times of about 50–100 ms, water molecules (water is the most convenient molecular species to study with diffusion MRI, but some metabolites may be studied too with spectroscopy[2]) move in the brain on average over distances around 10–15 μm, bouncing into, crossing or interacting with many tissue components, such as cell membranes, fibers or macromolecules. The overall effect observed in a diffusion MRI image voxel reflects, on a statistical basis, the displacement distribution of the water molecules which are present within this voxel. The noninvasive observation of this displacement distribution *in vivo* may thus provide unique clues concerning the structure and geometric organization of tissues. The most successful application of diffusion MRI since the early 1990s has been acute brain ischemia (see Moseley,[3] Warach,[4] reviewed by Sotak[5] in this issue).

Furthermore, as diffusion is truly a three-dimensional process, molecular mobility in tissues is not necessarily the same in all directions. This diffusion anisotropy may result from the presence of obstacles that limit molecular movement in some directions. With the advent of diffusion MRI, anisotropy was also detected for the first time *in vivo* at the end of the 1980s in spinal cord and brain white matter.[6,7] Diffusion anisotropy in white matter roughly originates from its specific organization in bundles of more or less myelinated axonal fibers running in parallel: diffusion in the direction of the fibers is faster than in the perpendicular direction. However the relative contributions of the intraaxonal and extracellular spaces to the ADC, and the exact mechanism for the anisotropy are still not completely understood and remains the object of active research, as described by Beaulieu.[8] It was quickly apparent that this feature could be exploited to map out the orientation in space of the white matter tracks in the brain, assuming that the direction of the fastest diffusion would indicate the overall orientation of the fibers[9]. Work on diffusion anisotropy really took off with the introduction in the field of diffusion MRI of the more rigorous formalism of the diffusion tensor, by Basser *et al.*[10,11] With this formalism diffusion anisotropy effects

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could be fully extracted, characterized and exploited, providing even more exquisite details of tissue microstructure. Many studies have been published thereafter dealing with the optimization of the MRI sequences necessary to get access to the diffusion tensor, the processing and the display of DTI data,[12,13] and of course, potential applications. The most advanced application is certainly that of fiber tracking in the brain (reviewed by Mori *et al.*[14]), which, in combination with fMRI, might open a window on the important issue of connectivity. On the other hand, diffusion anisotropy has sometimes proven cumbersome when studying changes in apparent diffusion in pathologies such as stroke, leading to the suggestion of the use of the orientation-independent trace of the tensor for such applications.[15]

BRAIN CONNECTIVITY

The possibility of visualizing anatomical connections between different parts of the brain, non-invasively and on an individual basis, has opened a new era in the field of functional neuroimaging. Studies of neuronal connectivity are very important for interpreting functional MRI data and establishing how activated foci are linked together through networks. Basic DTI provides a mean for determining the overall orientation of white matter bundles in each voxel, assuming that only one direction is present or predominant in each voxel and that diffusivity is the highest along this direction. Several algorithms have been proposed and are still under development to infer continuity, 'connecting' subsequent voxels on the basis of their respective fiber orientation.[14,16,17] Attractive color maps showing 'virtual' fiber bundles across the brain, which can now be fairly easily produced, regularly make the cover page of imaging journals.

Still, these virtual bundles have not yet been quantitatively validated against actual anatomical data, even in animal models. In fact no such data exists, as there are no means to dissect entire fiber bundles. Fibers can be labeled and seen *in vitro* using the peroxidase approach, but only over a short range. The combination in animal models of DTI and fiber tracking using manganese as a contrast agent actively up-taken by neurons is thus a breakthrough, which will help validate DTI.[18] Also, group analysis, for instance using tools such as Voxel Based Morphometry could highlight common features and differences across subjects in a given population. This approach will certainly be useful, not only to assess the robustness of DTI, but also to establish atlases of the white matter bundles which are currently lacking.

There remain, however, important fundamental issues, which might ultimately invalidate the diffusion tensor approach. The 'one bundle–one orientation' assumption is acceptable for the main large tracts, but becomes unrealistic in regions where several fiber tracks with different orientations cross, diverge or converge. It can be shown that, in these situations, the basic tensor formalism fails. For instance, with two bundles crossing at a right angle in a voxel, the largest diffusivities are measured at 45° of the actual bundle directions. This is clearly a problem which requires serious improvements to the diffusion tensor model or the development of new strategies. Among such strategies the direct processing (by-passing the tensor calculation) of diffusion-weighted images acquired with a high angular resolution (diffusion sensitization along many directions) has proved successful,[19] although acquisition times are still long. One may also consider increasing image spatial resolution leading to a reduction in partial volume effect, because fewer fiber bundles will be present in smaller voxels. This is certainly true to some extent, but there will always be regions where fibers of different bundles travel together. This poses the question of the ultimate spatial resolution which can be achieved from diffusion MRI. Some degree of anisotropy must exist for the tracking algorithms to work and, so far, most algorithms stop short of the brain cortex where diffusion anisotropy is apparently strongly reduced. However, recent data at high resolution in animals[20] and humans[21] are showing gray matter structure. Although such data have to be viewed carefully, the fact that voxels in the cortex might have a predominant diffusion direction in the developing brain[20,21] seem reliable in view of existing knowledge about the formation of the cortex. This brings us to the exciting issue of the origin of diffusion anisotropy.

THE ORIGIN OF WATER DIFFUSION ANISOTROPY

Early reports simply assumed that intra-axonal water movement was more restricted perpendicularly to the axons than along them. However this effect probably accounts for only a limited part of the whole picture, as 'true' restriction patterns have not been observed for water diffusion in white matter *in vivo*. Extracellular water may also contribute to the anisotropy effect: perpendicularly to the fibers water molecules must diffuse along tortuous pathways around fibers, which 'slow' them down. The issue is then to distinguish the respective contributions of the extra- and intracellular compartments to the measured ADC. It is now clear that water diffusion measured in tissues, including brain white matter, cannot be described in terms of a simple linear relationship between the logarithm of the signal intensity and the b factor, as predicted for free diffusion. Biexponential fitting of the data has been proposed and is reviewed in this issue by Cohen and Assaf.[22] Results obtained by independent groups are quantitatively very similar and compatible with the existence of two water diffusion 'pools', one fast, the other slow, although other explanations have been suggested to explain this

nonlinearity. However the physical origin of these pools is still mysterious. The assignment of the fast and the slow diffusing pools to the extra- and the intracellular compartments, respectively, is tempting, but far from straightforward, as their 'physical' contributions to the ADC apparently do not match the expected 'biological' extra- and intracellular volume fractions (82.5 and 17.5%, respectively). This discrepancy can be mitigated by introducing relaxation and exchange effects, but the recent ISMRM Workshop on the 'Biophysical Issues of Diffusion MRI' held in March 2002 in Saint-Malo, France, has clearly revealed our lack of understanding on this topic.[23] Other compartments could be considered as well, for instance inside the cells, the axons or in the myelin.[8] Some progress is expected from diffusion studies of larger molecules or metabolites which are well compartmentalized. Another promising avenue is the possibility to look at actual molecular displacement distributions through *q*-space measurements.[22]

Although the exact mechanism for diffusion anisotropy is not well understood, it is clear that this anisotropy directly reflects the presence of spatially oriented structures in the tissue. The degree of anisotropy, as measured with the various anisotropy indices which have been proposed in the literature, is somewhat linked to the quality and the density of oriented structures in the tissue. When studying and interpreting these anisotropy data, limitations have to be kept in mind, especially the inevitable partial volume effects when using the coarse resolution available in clinical studies. Another important point to keep in mind is that all orientation-independent anisotropy indices in the literature are calculated from the same eigenvalues and thus are intrinsically related to each other.[24]

Any change in tissue orientation patterns inside the MRI voxel would probably result in a change in the degree of anisotropy. There is a growing body of literature supporting this assumption: many clinical studies carried out on patients with white matter diseases have shown the exquisite sensitivity of DTI to detect abnormalities at an early stage or to characterize them in terms of white matter fiber integrity (see Horsfield and Jones[25]). Furthermore, anisotropy measurements may highlight subtle anomalies in the organization of white matter tracks otherwise not visible with plain, anatomical MRI. The potential is enormous for patients with functional symptoms linked to dysconnectivity, for instance in the psychiatric population.[26]

Over the course of life white matter matures and declines. Effects of aging on white matter ordering can now be studied[27] and DTI has been proposed for monitoring the myelination process in babies and children.[21] Research on brain development has been exploding recently. Advances in neuroimaging have certainly contributed to this expansion, as data can now be obtained noninvasively in newborns or even before birth to study combined effects of genes and environment on brain development. Of particular interest is the observation with DTI that water diffusion anisotropy changes dramatically in the developing brain. Although water diffusion appears isotropic in the adult brain cortex to some extent, there is a short time window when anisotropy can definitely be found. This transient anisotropy effect probably reflects the migration and organization process of glial cells and neurons in the cortex layers.[20,21] For white matter during postnatal development, the degree of water diffusion anisotropy follows the myelination process, but the effect is small compared with the prenatal stage where large anisotropy is observed even before axons get myelinated.[8] The combined effects of the axon packing in the fiber bundles and the thickness of the myelin sheath on the degree of anisotropy have still to be detailed, but DTI already represents an outstanding tool for studying brain development, especially of the human brain.

DTI OUTSIDE THE BRAIN

Outside the brain, diffusion MRI and DTI have been more difficult to use successfully, because of the occurrence of strong respiratory motion artifacts in the body; in addition, the short T_2 values of body tissues require shorter *TE* than in the brain, and thus, leave less time for the diffusion gradient pulses. These obstacles, however, can sometimes be overcome with *ad hoc* MR sequences and hardware as demonstrated for spinal cord studies.[28] However body DTI has also great potential for muscle fiber orientation studies, in particular in the heart.[29] Myocardial DTI might provide data on heart contractility, a very important parameter, but obviously remains technically very challenging *in vivo* due to heart motion.[30] Other applications may be in the study of the structure of tumors.

CONCLUSION

In summary it is important to remember that diffusion imaging is a truly quantitative method which gives direct insight into the voxel-averaged microscopic physical properties of tissues (e.g. cell size and shape, geometric packing, etc.) through the observation of random translational molecular movement. Many theoretical and experimental analyses on the effect of restriction, membrane permeability, hindrance or tissue inhomogeneity have underlined how much care is necessary, however, in order to properly interpret DTI data and infer accurate information on microstructure and microdynamics of biological systems.

Despite these difficulties, it remains clear that even in its current stage DTI is the only approach available to track white matter fibers non-invasively in the human brain and to address anatomical connectivity. In combi-

nation with fMRI, which outlines activated cortical networks and may provide clues on functional connectivity, DTI should thus have a tremendous impact on brain function studies, from animal models to human neuroscience. It has also been suggested that diffusion MRI could provide a direct avenue to detect cortical activation.[31] DTI is also increasingly being used to demonstrate subtle connectivity anomalies in a variety of dysfunctions, such as cancer, dyslexia or diseases including multiple sclerosis and schizophrenia, and is currently becoming part of many routine clinical protocols. With the development of powerful improvements to DTI, such as diffusion spectroscopy of metabolites or *q*-space imaging, one may expect that the already flourishing field of diffusion imaging will continue to break new ground. We thus hope that this special issue of *NMR in Biomedicine* will attract new colleagues, so that they can share the level of excitement that this field has provided us for almost the last two decades.

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