Diffusion MRI of Brain Connectivity and Microstructure: The Reality, the Hype, and the Hope

Peter J. Basser, Ph.D.
National Institute of Child Health & Human Development (NICHD)
National Institutes of Health (NIH)
Bethesda, MD 20892-5772 USA

Despite the fact that the first diffusion weighted MRIs (DWIs) were presented in 1984, problems in quantitation, validation, and interpretation of DWI data still persist. These present hardships to overcome as well as opportunities for creative solutions.

What is a "diffusion coefficient" or "diffusion tensor" in living tissue, anyway?
While the measurement of the self-diffusivity in an NMR tube represents a "gold standard", in complex media particularly in living tissue, water "diffusivity" ceases to have a clear meaning or definition. The apparent diffusion coefficient (ADC) and apparent diffusion tensor (ADT) concepts were introduced to answer the question: "What would the equivalent diffusion coefficient be if the displacement distribution were Gaussian?" The actual MR measurement is of the mean squared displacement not the diffusion coefficient, which offers improved prospects for discovering microstructural features over the ADC or ADT measurements.

What is the utility of physical model systems and *in vitro* tissues in DWI?
Physical models that have well defined structure, composition, and architectural organization can provide useful experimental systems with which to interrogate analytical or computational models of diffusion. *In vitro* tissue specimens represent the next level of complex biophysical models. For instance, fixed brain tissue, which can be analyzed independently using a variety of histological and optical methods, presents an excellent substrate to test mathematical theories of diffusion.

What can be learned from mathematical models of ordered and disordered media?
Mathematical models of diffusion in well-defined model systems are useful in two ways. They can provide a direct relationship between the observed or measured MR signal and microstructural characteristics of neural tissue, and they can be used to infer or estimate these microstructural quantities from real MR data. Recently, quantities like the axon diameter distribution have been measured from diffusion MRI experiments using this approach. Another promising use of mathematical models is in describing multiple-scattering experiments that provide higher-order correlations between microstructure and morphology and the measured MR signal.

What artifacts confound DWI measurements?
Temporal artifacts can cause lack of consistency and reproducibility in DWI data owing to different physiological processes occurring over a large range of timescales. Small-scale tissue motion, cardiac pulsation, respiratory motion, and even vasomotion all can contribute to changing the position of a block of tissue within the imaging volume over the course of a DWI acquisition. Generally, physiological motion has a deleterious effect on DWI data when

corresponding voxels in different DWIs do not contain the same tissue block. However, if motion is not coherent, it can produce signal loss in DWIs that manifests itself as diffusion.

Other MRI acquisition artifacts further distort or degrade DWI data. These include eddy-currents, improper gradient and RF calibration, and an inhomogeneous B0 field. Specific problems associated with DW echo-planar imaging (EPI), the most common method for acquiring DWIs, is signal dropout and distortion due to susceptibility differences within tissue.

Post-processing artifacts can further contaminate DWI measurements. Questions that are still being asked are: How can the best estimate of the diffusion tensor or other DT-derived quantities be obtained? What noise model is most appropriate for DWI data? How do we undo or coregister image distortion effects caused in living tissue? How can we remedy the problem of partial volume in which two or more distinct tissue types may occupy an individual voxels? What parametric statistical model is appropriate to characterize uncertainty in DWI-derived quantities and what manifold does it reside in?

How prone to errors are high-b or high-q methods as compared to DTI?
In considering methods based on more complex or general diffusion models than DTI, such as QSI, DSI, and HARDI based-methods, all of the previously noted errors and artifacts arise, but to a greater extent. While DTI is performed in the "linear" regime of the decay of the log of the MR signal, where the effective SNR of each DWI is high, in high-b or high-q DWI acquisitions, SNR is so low that it is often difficult to distinguish well-defined neural structures from background noise. Generally HARDI acquisitions require more DWIs than DTI so the likelihood is lower of finding the same tissue in the same physiological state and orientation/position in the same voxel. Spatial distortions are also more pronounced in high-b or high-q DWI since larger gradients are applied, inducing more serious eddy current distortion.

What are the prospects for using DWI to establish "connectivity" or function?
First, we have to define "connectivity". If we mean functional connectivity, DWI data alone cannot provide this information. However, if we are interested in intermediate or long-range anatomical connectivity mediated by large white matter pathways, DWI data can significantly inform this task. The purported fiber direction as given by the eigenvector associated with the largest eigenvalue provides a good estimate of white matter fiber direction in coherent pathways. In regions where the fiber orientational distribution is not described by a delta-function, more sophisticated methods, possibly with the inclusion of other *a priori* information could be used to constrain possible fiber pathways. We should always keep realistic expectations, being mindful that voxel sizes are still on the order of thousands of microns while axon diameters are on the order of microns, so under current SNR and imaging constraints, sufficient microscopic resolution is not available to follow individual axons in the brain.

What are the prospects for using DWI as an fMRI method?
LeBihan et al. recently proposed that DWI data provides a functional MRI signal that potentially has higher temporal resolution than the BOLD fMRI signal. The jury is still out about whether this application of DWI is viable and whether the DWI signal itself has a time-varying component that is more closely related to neural excitation than conventional fMRI methods are.

What are the prospects for obtaining new and useful microstructural features of neural tissue? The uses of DWI data to extract detailed microstructural features of tissues at the sub-voxel and even microscopic level continue to grow with improved hardware and better models. Although model dependent, these approaches may provide new features that should be of use in assessing development, degeneration, disease, and aging.

What are the prospects for clinical applications of DWI? The clinical outlook for the use of DWI data is excellent, with new applications like "whole body MRI" being developed. Caution is required if we plan to use DWI data to diagnose individuals suffering from psychiatric disorders, like schizophrenia or cognitive deficits, like dyslexia. More work is required to develop the DWI post-processing pipeline, particularly the development of rigorous statistical methods for determining the significance of differences between DWI-derived parameters in groups of subjects. Currently many studies are able to detect differences in populations in the aggregate, but are unable to detect individual variations on a case-by-case or patient-by-patient basis. Whether these reported differences in group studies are real or artifactual is worthy of further investigation.

Summary

DTI is becoming a mature MRI method, resulting in increased compartmentalization of tasks (e.g., DWI hardware and acquisition, tensor estimation, graphical representation of tensor data, statistics and group analysis) and the concomitant proliferation of black-box methods for performing each of these activities. Doing quantitative DWI can be tedious at times. However, ensuring the quantitative character of the displacement or diffusion measurements and the integrity of the pre- and post-processing data acquisition and analysis "pipeline" is the only way to assure the relevance and credibility of this data to the neuroscience and clinical communities. We should remain optimistic about being able to resolve ongoing problems in DWI data acquisition, data processing and analysis to extract connectivity and microstructural information about neural tissue. To paraphrase the wise tortoise in *Aesop*'s famous fable, "Slow and steady wins the race."