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Historical Perspective

Recollections about our 1996 JMR paper on diffusion anisotropy

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ABSTRACT

We provide scientific background information and personal accounts relating to our publication of "Microstructural and Physiological Features of Tissues Elucidated by Quantitative-Diffusion-Tensor MRI" in the Journal of Magnetic Resonance B. This paper provided a framework for measuring and mapping intrinsic features of diffusion anisotropy obtained from diffusion tensor MRI (DTI) data.

It is a great honor and privilege to have been invited to describe the background and circumstances surrounding the publication of our 1996 paper, "Microstructural and Physiological Features of Tissues Elucidated by Quantitative-Diffusion-Tensor MRI" in the *Journal of Magnetic Resonance B*. As authors, we derive a great deal of satisfaction knowing that this paper had a significant impact on the development of diffusion tensor MRI (DTI) and it biological and clinical applications. We remember 1995–1996 as a very exciting and creative period in which we were actively investigating ways of improving DTI to make it a robust and useful clinical tool.

In 1995, DTI was still in an early stage of development. Only a handful of groups were using it; most others appeared to view it as a mathematical/physical curiosity rather than a potentially useful scientific and clinical imaging method. Several research groups had previously tried to characterize features of diffusion anisotropy in the brain and in other soft tissues, but had not proposed measures of diffusion anisotropy that were *intrinsic* to the tissue.

Carlo recognized that for DTI to be clinically useful, we needed to generate scalar parameters with which biologists and MDs could characterize diffusion anisotropy reliably in the brain. He noticed that background RF noise in the diffusion weighted MRIs (DWIs) could significantly bias a particular DTI measure of diffusion anisotropy that Peter had proposed earlier—the ratio of the largest and smallest eigenvalues (or principal diffusivities) of the diffusion tensor. Noise tended to increase the numerator and decrease the denominator, making this ratio much larger than its true value in the absence of noise. Carlo discovered that the ratio of eigenvalues was particularly vulnerable to this bias because the eigenvalues needed to be sorted in order of decreasing magnitude to compute this measure, effectively creating a spurious, noise-induced separation between the distribution of the largest and smallest eigenvalues. Carlo further investigated this effect using Monte Carlo simulations and he anticipated that indices of diffusion anisotropy that do not require eigenvalue sorting would have been less susceptible to bias.

In earlier work with Denis LeBihan and James Mattiello, Peter had already introduced the idea of using "scalar invariants" of the diffusion tensor, like the trace, as useful parameters or features of diffusion in DTI. These had the advantage that their value was unaffected by a rotation of the laboratory coordinate frame, and additionally, were independent of the order in which one assigned the eigenvalues. Anisotropy measures derived from scalar invariants indeed represented a very promising solution to the problem.

The main goal of this paper was to identify or generate a family of tensor-derived scalar anisotropy measures that would provide new useful intrinsic tissue "stains" and be relatively noise immune.

From a continuum mechanics perspective, a good starting point for studying anisotropic features of the diffusion tensor was its deviation tensor (or deviatoric). In the theory of elasticity, one frequently separates the stress tensor into a part that causes only changes in a material's shape (the deviatoric) and a part that only results in a change in its size or volume (the isotropic part). Peter's thinking was that if we study the properties of the deviatoric we might be able to use it to derive scalar invariant quantities that characterize diffusion anisotropy. The most obvious course of action then was to find the magnitude of the anisotropic part of the diffusion tensor. Finding the magnitude of a tensor is analogous to finding the magnitude of a vector—in this case, one takes the tensor dot product of the deviatoric of the diffusion tensor with itself. A little algebra showed that this quantity was proportional to the sum of the squares of the deviations between each of the eigenvalues of the diffusion tensor and the mean of the three eigenvalues.

However, when Carlo used this mean-squared deviation to investigate living cat brain, monkey brain, and human brain, he found that the regions that had the highest anisotropic part were ventricles containing cerebrospinal fluid (CSF), which one would

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have presumed to be isotropic. The reason for this was that the water diffusivity in these CSF compartments was about three times higher than water in brain parenchyma (like gray matter and white matter) and flow and other pulsation effects made CSF in the ventricles appear anisotropic. Happily, white matter still appeared much more anisotropic than grey matter in these maps. Carlo proposed that the way to address this problem was to normalize the magnitude of the deviatoric of the diffusion tensor in a self-consistent way so that it would become a feature of the shape of the diffusion displacement profile rather than being affected by its magnitude. Peter worked on this idea and proposed a few different normalization factors, most of which are included in the paper. The scalar measure of diffusion anisotropy that has become most widely adopted is the Fractional Anisotropy or FA. This quantity represents the magnitude of the anisotropic part of the diffusion tensor divided by the magnitude of the entire diffusion tensor, appropriately scaled so that this quantity only assumes values between 0 (representing no anisotropy) and 1 (representing complete anisotropy). While CSF might have the highest absolute diffusion anisotropy in the brain, when it was scaled to the overall "size" or magnitude of the entire diffusion tensor there, the FA would appear low. Other anisotropy measures we proposed and considered were the Relative Anisotropy or RA, which was like a coefficient of variation of the three eigenvalues.

A striking features in this paper is the uniformity of the Trace of the diffusion tensor plotted within a slice of living cat brain in Fig. 2, and the clear identification and delineation of white matter pathways in a map of the FA in this same cat brain slice shown in Fig. 3.

The isotropic and anisotropic parts of the diffusion tensor described so far only pertained to a diffusion tensor in a particular voxel. However, from diffusion ellipsoid maps it was clear that the anisotropic part of the diffusion tensor *field* also was rich in information about tissue structure and organization over a larger length scale. For instance, in Fig. 1b it was clear that the spatial pattern of diffusion ellipsoids implied long-range white matter fiber structure. It was straightforward to begin studying these intervoxel features of diffusion anisotropy using the same tensor dot product framework we employed in studying anisotropic diffusion within a single voxel. What resulted were a family of intervoxel diffusion anisotropy measures. A point we tried to make here is that one can construct different intervoxel measures that are sensitive to the size, shape, or orientation of neighboring diffusion ellipsoids.

This paper represented a true collaboration between the authors in which the whole was greater than the sum of its parts. Carlo, a neurologist by training, and Peter, formally schooled in fluid and continuum mechanics, had already been working together since 1993 developing and applying of DTI. In this paper, we were able to construct and demonstrate a framework needed to characterize and map features of anisotropic diffusion using DTI data.

Regarding the publication of this paper, there was no doubt that we should submit our manuscript to the *Journal of Magnetic Resonance B*, the preeminent journal in MR physics. We felt that subsequent medical applications would be published in journals like *Magnetic Resonance in Medicine*, where they would reach a clinically and biologically oriented readership.