Quantification of white matter fiber orientation at tumor margins with diffusion tensor invariant gradients

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Introduction: Neurosurgical planning of tumor resection seeks to minimize damage to healthy tissue during surgery. Diffusion tensor imaging (DTI) may help to resolve how the tumor has affected nearby white matter pathways, and to discriminate between fibers extending into the tumor, versus those deflected around it. Fiber orientation is usually modeled by the tensor principal eigenvector $\mathbf{e}_1$, enabling qualitative tumor assessment with $\mathbf{e}_1$ colormaps [2] and tractography [3,4]. Tumors can also affect scalar-valued functions called invariants, such as Trace (3 times mean diffusivity or "ADC") and Fractional Anisotropy (FA) [1]. Invariants enable quantitative tumor assessment through metrics such as the Tumor Infiltration Index [5]. We seek to unify these approaches by measuring *spatial gradients* of invariants: vectors that estimate the surface orientation of the tumor, and that can be quantitatively compared with fiber orientation. We propose two metrics: *Diffusion angle* Da to quantify the angle between the fiber direction and the tumor boundary, and *Diffusion fraction* Df to quantify the fraction of diffusion across the tumor boundary.

Theory: To the extent that changes in invariants like Trace and FA highlight tissue affected by a tumor, the gradients of the invariants (vectors pointing in the direction of fastest increase) may indicate the surface orientation of the affected tissue boundary. The relationship between the tumor and surrounding fibers can then be quantified by the angle between the invariant gradient and $\mathbf{e}_1$. For example, where the Trace gradient is parallel to $\mathbf{e}_1$, the fibers are going directly into and out of edema (in which trace is elevated [5]); where perpendicular, fibers are going around edema. Similar reasoning applies to the gradient of FA, since pathology can lower FA [5]. For invariant X (e.g. Trace or FA) we define *Diffusion Angle along X* as $\mathrm{Da}(\mathrm{X}) \equiv 1 - 2\cos^{-1}(|\mathbf{e}_1 \cdot \widehat{\nabla}\mathrm{X}|)/\pi$, where $\widehat{\nabla}\mathrm{X} \equiv \nabla\mathrm{X}/|\nabla\mathrm{X}|$ is the normalized gradient of X. Anisotropy mode [6] near tumors can be more planar than linear [7], making $\mathbf{e}_1$ numerically unstable. Avoiding eigensystem computation, we also define *Diffusion Fraction along X* as $\mathrm{Df}(\mathrm{X}) \equiv \widehat{\nabla}\mathrm{X}^{\mathrm{T}}\mathbf{D}\widehat{\nabla}\mathrm{X}/\mathrm{Tr}$, the fraction of diffusion along the X gradient relative to the Trace (which by invariance is the sum of tensor $\mathbf{D}$ eigenvalues). Da(X) and Df(X) vary between zero and one as diffusion lies entirely perpendicular to or parallel to the gradient of X, respectively. Invariant gradients are calculated by applying the differentiation chain rule to the gradient $\nabla_{\mathbf{p}}\mathbf{D}$ of tensor $\mathbf{D}$ with respect to position $\mathbf{p}$ [8] and the tensor-valued gradient $\nabla_{\mathbf{D}}\mathrm{X}$ of invariant X with respect to tensor $\mathbf{D}$ [6]: $\nabla\mathrm{X} \equiv \nabla_{\mathbf{p}}\mathrm{X} = \nabla_{\mathbf{D}}\mathrm{X} \cdot \nabla_{\mathbf{p}}\mathbf{D}$. Figure 1 illustrates the hypothetical behavior of Da(Tr) and Da(FA) around edema and a tumor.

Methods: Echo-planar images were acquired on a General Electric (Milwaukee, WI) 3T Signa scanner with Excite 12.0; using an 8-channel head coil and ASSET; matrix=128x128; FOV=25.6cm; Phase FOV=1.0; slice thickness=2.6mm; B value=1000s/mm^2; 31 DWI gradients and 5 baseline T2 images; voxel size=2x2x2.6mm^3. Diffusion tensors were estimated by linear least squares fitting on the image logarithms [1]. Polygonal invariant isosurfaces were extracted from tensor volumes upsampled to 0.5x0.5x0.5mm^3 by spline interpolation [8], the 2nd-order continuity of which enables analytical measurement of Da and Df at isosurface mesh nodes. Tractography used 4th-order Runge-Kutta integration of $\mathbf{e}_1$, 0.5mm step size, terminated at Cl=0.13 [9]. Calculations and renderings used locally developed software.

Results: We first demonstrate the metrics by measuring them on a structure where prior anatomical knowledge implies a particular pattern of variation: the cortical white/gray matter interface. Figure 2 illustrates a stereotypical gyrus. Given the millimeter-scale resolution of clinical imaging, Da(FA) and Df(FA) should be high on the gyral ridge (where many axons project perpendicular to the interface), but low on the sulcul banks (where some axons turn and project, but more continue underneath). Figure 3 shows measurements in a healthy control of Da(FA) and Df(FA), colormapped onto an FA=0.2 isosurface that approximates the white/gray matter interface, with a viewpoint centered on the left central sulcus. As expected, Da(FA) and Df(FA) are consistently highest along the gyral ridges (outlined). Our preliminary evaluation of the metrics for neurosurgical planning uses a Grade II oligodendroglioma case shown with standard slice displays in Figure 4; note raised Trace and lowered FA at tumor (arrow 1). Figures 5 and 6 depict invariant isosurfaces (same colormaps as Fig 3) that roughly model the tumor extent, and are clipped (manually) well outside the tumor extent for visual clarity. The FA=0.22 isosurface in Figure 5A is cut by the same FA slice as in Fig 4. The high Da(FA) values (Fig 5A arrow) are where in Figure 4 (arrow 2) white matter FA appears reduced by the tumor, and few areas elsewhere on the FA isosurface (Fig 5B) show high Da(FA) not associated with a sulcus. Consistent with this, the tractography in Figure 5C enters the tumor interior from the high Da(FA) location, but otherwise stays largely tangential. Figure 6 colormaps Df(Tr) onto a Trace=0.0028mm^2/s isosurface of the same location. The red spot on the posterior end of the edematous region (Fig 6A arrow) highlights a higher fraction of diffusion across the surface than tangential to it, consistent with where tracts enter the edematous region in Figure 6B.

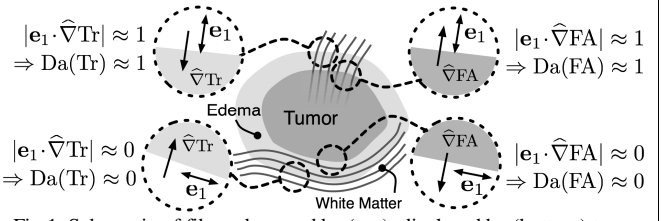

Fig 1. Schematic of fibers damaged by (top), displaced by (bottom) tumor

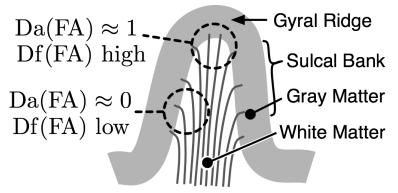

Fig 2. Expected Da(FA),Df(FA) along gyrus

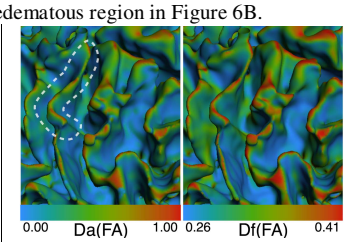

Fig 3. Da(FA),Df(FA) on FA isosurface

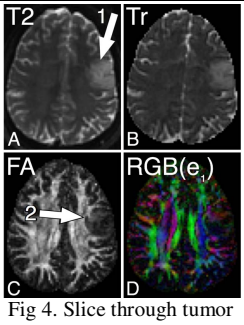

Fig 4. Slice through tumor

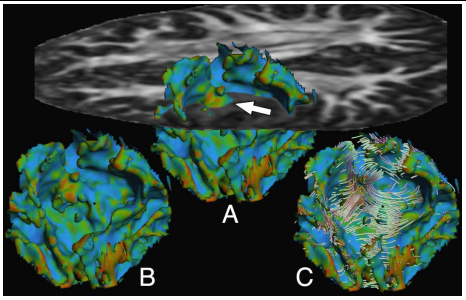

Fig 5. Da(FA) on FA isosurface (with tracts, C)

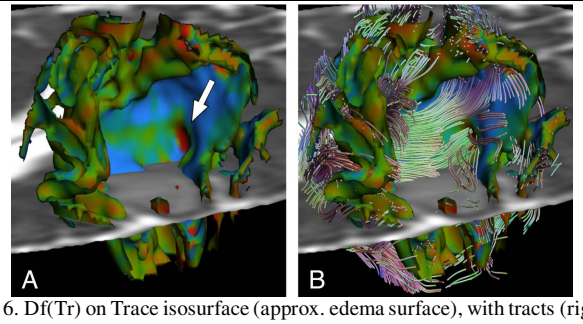

Fig 6. Df(Tr) on Trace isosurface (approx. edema surface), with tracts (right)

Discussion: Our initial results suggest the proposed metrics Da and Df can differentiate fibers coursing directly into a tumor from those deflected around it. This may simplify and improve the surgical planning task of identifying critical white matter tracts from that of spatial reasoning about complex 3-D tractography renderings to the visual inspection of metrics colormapped onto slices or surfaces. More generally, further study of Da and Df in healthy well-understood cerebral structures (as in Figure 3) may help strengthen inferences made about axonal micro-architecture from clinical DTI scans with comparatively low-resolution [1,10].

Acknowledgements: Supported by NIH T32-EB002177, P41-RR13218, R01-MH074794, R01-MH050740, U41-RR019703, and the Brain Science Foundation.

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