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Invariant and Orthonormal Scalar Measures Derived from Magnetic Resonance Diffusion Tensor Imaging

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A diffusion tensor is a mathematical construct used to describe water diffusion in complicated biological structures. It describes a process which occurs in all directions simultaneously. It is difficult to comprehend or graphically display the information in the diffusion tensor. This paper describes a coordinate system approach for producing scalar measures which characterize key aspects of the diffusion tensor. The eigenvalues of the diffusion tensor are introduced as the three elements of a point in a Cartesian coordinate system. The Cartesian coordinates are then expressed in cylindrical and spherical coordinates. The orthonormal coordinates of the spherical system are particularly useful scalar measures of attributes of the diffusion tensor: One coordinate contains all the information about the overall magnitude of diffusion. Another contains all of the anisotropy information. The third coordinate contains all of the information about skewness. No information is lost when transforming the original eigenvalues to spherical coordinates. © 1999 Academic Press

Key Words: **diffusion tensor imaging; magnetic resonance imaging; anisotropy; diffusion; skewness.**

INTRODUCTION

The rate of water diffusion in complex three-dimensional biological tissues is not the same in all directions. Therefore, this process cannot be fully characterized by a simple scalar. A tensor is a mathematical construct which can be used to describe diffusion in complex media. A tensor describes a process which occurs in all directions simultaneously, with possibly different magnitudes in each direction. However, it may be difficult to comprehend or graphically display all the information contained in the diffusion tensor. It is often necessary to extract information about some aspect of the tensor which is found to be useful. When applied to medical imaging, this problem is compounded because information about regional diffusion is obtained by measuring the diffusion tensor in many voxels. It is not possible to produce a single image which conveys all of the information contained in the diffusion tensor. It is necessary to extract scalar measures from the diffusion tensor which represent useful characteristics of the tensor. These measures can be tabulated and easily compared. Parametric images of these scalar values can be produced.

There are many aspects of the diffusion tensor which have been shown to be interesting and informative. Four of these basic characteristics follow. (1) The overall magnitude of diffusion. (2) The degree that the rate of diffusion is dissimilar in different orthogonal directions. This is referred to as the degree of diffusion anisotropy. (3) The degree that the rate of diffusion in two of three orthogonal directions differs from the rate of diffusion in the third direction, i.e., how symmetrically the diffusion is distributed in orthogonal directions. This is referred to as skewness. (4) Information about the relative magnitudes of the eigenvalues, i.e., the largest, intermediate, and smallest eigenvalues. This is referred to as the eigenvalue order. It should be noted that the measured diffusion tensor represents an average value over a voxel. On a microscopic scale the diffusion will always be anisotropic. However, the measured diffusion tensor will demonstrate anisotropy only if the cell structures are ordered on the scale of the voxel.

The magnitude measure should have units of rate of diffusion. The anisotropy and skewness measures should be unitless so that they are independent of scale.

The mathematical notation for the diffusion tensor is an array of nine elements, with the diagonal elements corresponding to the rate of diffusion in different directions and the off-diagonal elements describing the degree of correlation between the diffusion measured along the various axes.

$$D = \begin{bmatrix} a_{11} & a_{12} & a_{13} \\ a_{21} & a_{22} & a_{23} \\ a_{31} & a_{32} & a_{33} \end{bmatrix} \quad [1]$$

In biological systems the rate of diffusion is the same in directly opposing directions. This results in a symmetric tensor with $a_{ij} = a_{ji}$. Therefore, there are only six unique elements in the diffusion tensor. This paper describes a method for extracting useful scalar information from the tensor.

A first step to extracting scalar information from the diffusion tensor is to dissect it into two parts, each having comple-

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mentary information. Diagonalization of the tensor separates it into component eigen*values* and eigen*vectors* (*1*, *2*).

$$D = \begin{bmatrix} V_1 & V_2 & V_3 \end{bmatrix} \begin{bmatrix} \lambda_1 & 0 & 0 \\ 0 & \lambda_2 & 0 \\ 0 & 0 & \lambda_3 \end{bmatrix} \begin{bmatrix} V_1 & V_2 & V_3 \end{bmatrix}^{-1} \quad [2]$$

The eigenvectors, V_1, V_2, and V_3, are column vectors which describe the orientation of the primary diffusivity in space relative to an external frame of reference. These unitless vectors define an orthonormal basis for a preferred coordinate system for the diffusion tensor. The eigenvalues of a diagonalized tensor are the three elements along the principal diagonal of the tensor, λ_1, λ_2, and λ_3. The eigenvalues each have the units of diffusivity, usually mm^2/s. Each eigenvalue corresponds to an eigenvector and together they specify the magnitude of diffusivity in each of three orthogonal directions in space relative to an external frame of reference. However, the positions in which the eigenvalues appear along the principal diagonal of the tensor depend on the original frame of reference. The positions do not correspond to the relative magnitudes of the eigenvalues. Thus the process of mathematical diagonalization separates the diffusion tensor into two component parts: The eigenvectors are unitless and contain all of the information about the spatial orientation of the diffusion relative to an external frame of reference. The eigenvalues have the units of diffusivity and carry all of the information about the magnitude of diffusion, with no information about direction (other than the fact that the three eigenvalues describe diffusion in orthogonal directions). The eigenvectors will not be considered further in this paper.

A diffusion tensor describing a biological system has three real positive eigenvalues. This set of three eigenvalues can be considered to be coordinates of a point in three-dimensional Euclidean space. Because the eigenvalues are all positive, the allowed position of the point they describe in space is restricted to one-eighth of three-dimensional space. This allowable subset of three dimensional space will be referred to as *eigenvalue space.* A coordinate system other than the rectangular Cartesian coordinate system of the original eigenvalues can be imposed on this eigenvalue space. A desirable requirement for any new coordinate system, such as a cylindrical or spherical coordinate system, is that the component basis elements are orthogonal. This eliminates colinearity among the coordinates so that each coordinate supplies unique, complementary, and independent information about each point in space. A point in eigenvalue space, which is a subset of three-dimensional space, requires exactly three coordinates in an orthogonal system for its unique specification.

None of the information which can be conveyed by the original three eigenvalues is altered by adopting a new coordinate system for eigenvalues space. Any parameter or measure which can be expressed as a function of the original three eigenvalues can also be expressed as a function of the coordinates in any new coordinate system.

There are six possible permutations of the order of the eigenvalues. Each permutation defines a point in eigenvalue space. Thus eigenvalue space can be divided into six regions, each corresponding to a permutation of the order of the eigenvalues. Sets of eigenvalues in which two or three are identical lie at the boundaries between these regions. The region corresponding to the ordering (λ_{max}, λ_{int}, λ_{min}) will be referred to as ordered eigenvalue space where λ_{max}, λ_{int}, and λ_{min} refer to the largest, intermediate, and smallest eigenvalues, respectively. This definition refers to the true values of the eigenvalue; the influence of measurement error is not a factor in this formulation.

THE COORDINATE SYSTEMS

A scalar measure is a scalar valued function of the eigenvalues of the diffusion tensor which conveys information about the tensor, such as an anisotropy measure. The value of an invariant measure does not depend on the frame of reference of the measurement (*1*). An invariant measure is unchanged for any of the six cyclic permutations of the order of the three eigenvalues. The information about eigenvalue order allows differentiation of the six permutations of the eigenvalues. It is this information that is lost during a transformation from eigenvalue space to ordered eigenvalues space.

The first coordinate system to be discussed will be the rectangular Cartesian coordinate system. A modification of this system will involve ordering the eigenvalues by magnitude. Next the axes of the original Cartesian coordinate system will be rotated to create the rotated Cartesian coordinate system. The particular axes rotation which is chosen is a key element to the subsequent coordinate systems. This orientation of the axes will be maintained and a circular cylindrical coordinate system will be imposed. Then, again maintaining the same orientation of the rotated axes, a spherical coordinate system will be defined. Finally, the measure of the polar angle will be separated into a skewness measure and an indicator of the specific permutation of the order of the eigenvalues. The three parameters of the spherical system will be shown to be in a particularly useful form: magnitude, anisotropy, and skewness, respectively. It will be shown that the three parameters of the spherical coordinate system which correspond to magnitude, anisotropy, and skewness have invariant forms so that their values are independent of the frame of reference. Moreover, these three measures are mutually orthogonal so that they contain independent and complementary information about the eigenvalues.

Rectangular Cartesian coordinate system. In this coordinate system, the position of a point, $\underset{\sim}{P}_c$, in eigenvalue space is specified by the eigenvalues themselves,

$$\underline{P}_c(\lambda_1, \lambda_2, \lambda_3) = \begin{bmatrix} \lambda_1 \\ \lambda_2 \\ \lambda_3 \end{bmatrix}. \quad [3]$$

The component elements, λ_1, λ_2, and λ_3, of the Cartesian system are by definition orthogonal. But, in general, the elements of the Cartesian coordinate system are not invariant since, in general,

$$\begin{bmatrix} \lambda_1 \\ \lambda_2 \\ \lambda_3 \end{bmatrix} \neq \begin{bmatrix} \lambda_2 \\ \lambda_1 \\ \lambda_3 \end{bmatrix}. \quad [4]$$

Each element of the vector $\underline{P}_c$ has the units of diffusivity.

Cartesian coordinate system with ordered eigenvalues. In this coordinate system, the position of a point in eigenvalue space is specified by the eigenvalues ordered by magnitude

$$\underline{P}_{\text{ordered}}(\lambda_1, \lambda_2, \lambda_3) = \begin{bmatrix} \lambda_{max} \\ \lambda_{int} \\ \lambda_{min} \end{bmatrix}, \quad [5]$$

where λ_{max}, λ_{int}, and λ_{min} denote the maximum, intermediate, and minimum values of the eigenvalues.

This is not a true coordinate system, since it maps six points from eigenvalue space onto one point in ordered eigenvalue space. The six points which map onto ordered eigenvalue space are the points defined by the six possible permutations of the eigenvalue order. However, the $\underline{P}_{\text{ordered}}$ transformation is invariant.

Rotated Cartesian coordinate system. The axes of the original (not ordered) Cartesian coordinate system can be rotated by taking linear combinations of the eigenvalues. The rotation matrix must have orthogonal basis vectors in order for the new coordinate system to have orthogonal axes. If the rotation matrix is orthonormal (the orthogonal basis vectors are of unit length) there is no resultant dilation or contraction of eigenvalue space. If an orthonormal transform is used, the resulting measures maintain units of diffusivity.

$$\underline{P}_{\text{rotated}}(\lambda_1, \lambda_2, \lambda_3) = \begin{bmatrix} u_{11} & u_{12} & u_{13} \\ u_{21} & u_{22} & u_{23} \\ u_{31} & u_{32} & u_{33} \end{bmatrix} \begin{bmatrix} \lambda_1 \\ \lambda_2 \\ \lambda_3 \end{bmatrix} \quad [6]$$

A particularly useful orthonormal rotation matrix is one which places the new z axis along the eigenvalue triple identity line, $\lambda_1 = \lambda_2 = \lambda_3$, with the positive z axis in the direction of the positive eigenvalues. When diffusion is isotropic, the same in all directions, the diffusion eigenvalues lie along this triple identity line.

$$\underline{P}_r(\lambda_1, \lambda_2, \lambda_3) = \begin{bmatrix} \frac{-2}{\sqrt{6}} & \frac{1}{\sqrt{6}} & \frac{1}{\sqrt{6}} \\ 0 & \frac{-1}{\sqrt{2}} & \frac{1}{\sqrt{2}} \\ \frac{1}{\sqrt{3}} & \frac{1}{\sqrt{3}} & \frac{1}{\sqrt{3}} \end{bmatrix} \begin{bmatrix} \lambda_1 \\ \lambda_2 \\ \lambda_3 \end{bmatrix} = \begin{bmatrix} x \\ y \\ z \end{bmatrix}, \quad [7]$$

where $x, y, z > 0$.

The eigenvalue triple identity line is an obvious line of symmetry in eigenvalue space since any measure applied to any point along the line of triple identity will automatically be invariant.

The coordinates x, y, and z all have units of diffusivity. The subscript r in $\underline{P}_r$ denotes the particular rotation of the axes where the z axis is along the triple identity line. In this system the x axis is arbitrarily chosen to be in the $\lambda_2 = \lambda_3$ plane with the positive x axis in the direction where $\lambda_1 < \lambda_2$. The positive y axis is in the plane $\lambda_1 = (\lambda_2 + \lambda_3)/2$ with the positive y direction where $\lambda_2 < \lambda_3$. As shown in Eqs. [7] and [8], z is invariant, whereas x and y are not invariant measures. The parameter z is closely related to the well-known measures D_{bar} (*3*) and trace (*1, 2, 4*).

$$z = \frac{(\lambda_1 + \lambda_2 + \lambda_3)}{\sqrt{3}} = \lambda_{\text{bar}}\sqrt{3} = D_{\text{bar}}\sqrt{3} = \frac{\text{trace}(D)}{\sqrt{3}}, \quad [8]$$

where D is the diffusion tensor and λ_{bar} is the mean of the three eigenvalues. D_{bar} and trace are defined as in Refs. (*1–4*).

The six points in eigenvalue space corresponding to the six permutations of the order of the eigenvalues, when defined in terms of rotated Cartesian coordinate system, all have the same z value. The points defined by the six permutations of the eigenvalues display an interesting symmetry in the x–y plane (orthogonal to the z axis). These six points all lie the same distance from the origin in the x–y plane. This radial symmetry of the eigenvalue permutations is utilized in the circular cylindrical coordinate system described below. The six points defined by the six permutations of the eigenvalues can be considered to be three sets of two points; each set is symmetrically placed about one of the three lines defined by the intersection of the x, y plane and the planes: $\lambda_1 = \lambda_2$, $\lambda_2 = \lambda_3$, and $\lambda_3 = \lambda_1$; see Fig. 1.

The $\underline{P}_r$ system is similar to a set of measures proposed by Conturo *et al.* (*3*). Conturo *et al.* applied their transformation only to ordered eigenvalues. Their axes of the major and minor elements of anisotropy, η and ε, are colinear with the x and y axes, respectively. However, transformation from the Cartesian coordinate system to the η, ε, λ_{bar} system is not performed with an orthonormal matrix so there is a distortion of distances in space, $\eta = -x/\sqrt{6}$, $\varepsilon = -y/\sqrt{2}$, $\lambda_{\text{bar}} = z/\sqrt{3}$, when $\lambda_1 < \lambda_2 < \lambda_3$.

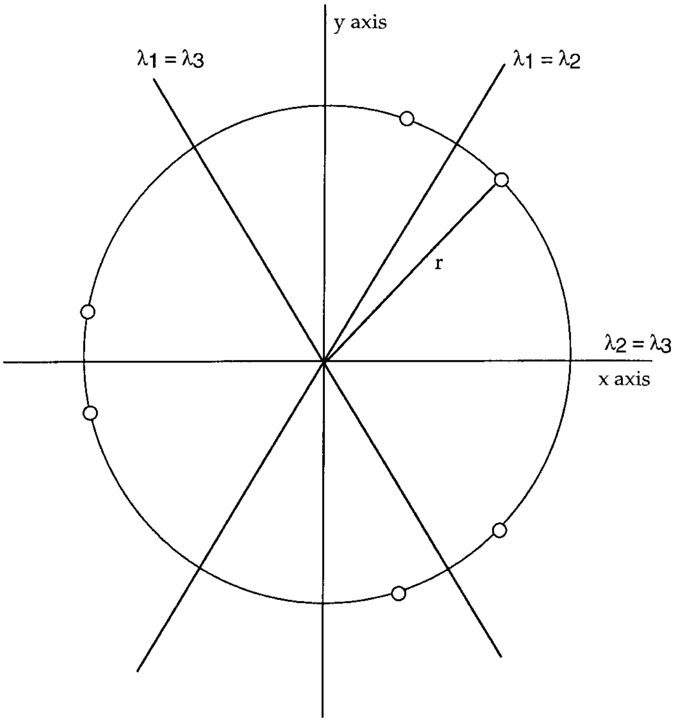

FIG. 1. The x–y plane of the rotated Cartesian coordinate system showing the projection of points defined by the six permutations of the eigenvalue order. These points all lie in at a distance r from the origin.

Circular cylindrical coordinate system. This system is a modification of the $\underline{P}_r$ system, Eq. [7]. The z axis is the same as in the $\underline{P}_r$ system. The other two coordinates, r and ϕ, of $\underline{P}_{cyl}$ are the coordinates x and y of $\underline{P}_4$ written in polar coordinate form. λ_{bar} denotes the mean of the eigenvalues, $r \geq 0$, and $0 \leq \phi < 2\pi$.

$$\underline{P}_{cyl}(\lambda_1, \lambda_2, \lambda_3) = \begin{bmatrix} r \\ \phi \\ z \end{bmatrix} \quad [9]$$

$$r(\lambda_1, \lambda_2, \lambda_3) = \sqrt{x^2 + y^2} = \sqrt{(\lambda_1 - \lambda_{bar})^2 + (\lambda_2 - \lambda_{bar})^2 + (\lambda_3 - \lambda_{bar})^2} \quad [10]$$

The value of the polar angle measure, ϕ, must be defined to account for the specific quadrant of the x–y plane where the eigenvalue point lies.

Case I, Quadrant I: $x > 0$ and $y > 0$.

$$\phi(\lambda_1, \lambda_2, \lambda_3) = \mathrm{ArcTan}\left[\frac{y}{x}\right] = \mathrm{ArcTan}\left[\frac{\sqrt{3}\,(\lambda_2 - \lambda_3)}{2\lambda_1 - \lambda_2 - \lambda_3}\right] \quad [11]$$

Case II, Quadrants II and III: $x < 0$.

$$\phi(\lambda_1, \lambda_2, \lambda_3) = \pi + \mathrm{ArcTan}\left[\frac{\sqrt{3}\,(\lambda_2 - \lambda_3)}{2\lambda_1 - \lambda_2 - \lambda_3}\right] \quad [12]$$

Case III, Quadrant IV: $x > 0$ and $y < 0$.

$$\phi(\lambda_1, \lambda_2, \lambda_3) = 2\pi + \mathrm{ArcTan}\left[\frac{\sqrt{3}\,(\lambda_2 - \lambda_3)}{2\lambda_1 - \lambda_2 - \lambda_3}\right] \quad [13]$$

As in the $\underline{P}_4$ system, z is invariant. Equation [10] demonstrates that the new parameter r is also invariant. r has the same units as the eigenvalues. r is proportional to the standard deviation of the eigenvalues (*2*).

$$\mathrm{sd}(\lambda_1, \lambda_2, \lambda_3) = \frac{\sqrt{(\lambda_1 - \lambda_{bar})^2 + (\lambda_2 - \lambda_{bar})^2 + (\lambda_3 - \lambda_{bar})^2}}{\sqrt{2}} = \frac{r}{\sqrt{2}}, \quad [14]$$

where sd is the standard deviation of the eigenvalues.

The polar angle measure, ϕ, is unitless but not invariant. The zero point of ϕ is chosen to be the x axis, where $\lambda_2 = \lambda_3$, in the direction that $\lambda_1 < \lambda_2$. ϕ ranges from 0 to 2π.

An invariant measure, which represents the coefficient of variation of the diffusion eigenvalues (*2*), is (Appendix A)

$$cv(\lambda_1, \lambda_2, \lambda_3) = \frac{\sqrt{3}}{\sqrt{2}}\frac{r}{z} = \frac{\sqrt{(\lambda_1 - \lambda_{bar})^2 + (\lambda_2 - \lambda_{bar})^2 + (\lambda_3 - \lambda_{bar})^2}}{\sqrt{2}\,\lambda_{bar}}. \quad [15]$$

cv is unitless. It is related to measures commonly used to express the degree of eigenvalue anisotropy (see Appendix A): A_σ (*3*), RA (relative anisotropy) (*2, 4*), and FA (fractional anisotropy) (*2, 4*). However, cv is not orthogonal to z (or D_{bar} or trace). Thus, the values of cv and z are neither independent nor complementary (see Discussion).

Spherical coordinate system. This coordinate system is composed of one radial measure, ρ, and two unitless angle measures, θ and ϕ. The polar angle measure ϕ is identical to

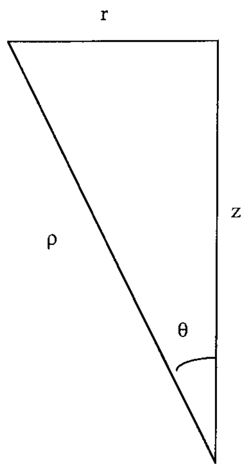

FIG. 2. A point in the x–z plane. Tan $\theta = r/z$ and cos $\theta = z/\rho$.

the polar angle measure ϕ in the circular cylindrical coordinate system:

$$\underline{P}_s(\lambda_1, \lambda_2, \lambda_3) = \begin{bmatrix} \theta \\ \phi \\ \rho \end{bmatrix} \quad [16]$$

$$\rho(\lambda_1, \lambda_2, \lambda_3) = \sqrt{\lambda_1^2 + \lambda_2^2 + \lambda_3^2} \quad [17]$$

$$\theta(\lambda_1, \lambda_2, \lambda_3) = \text{ArcCos}\left[\frac{(\lambda_1 + \lambda_2 + \lambda_3)}{\sqrt{3}\ \sqrt{\lambda_1^2 + \lambda_2^2 + \lambda_3^2}}\right] = \text{ArcCos}\left[\frac{z}{\rho}\right] = \text{ArcTan}\left[\frac{r}{z}\right] \quad [18]$$

(see Fig. 2).

$$\phi(\lambda_1, \lambda_2, \lambda_3) = \text{quadrant modification} + \text{ArcTan}\left[\frac{\sqrt{3}\ (\lambda_2 - \lambda_3)}{2\lambda_1 - \lambda_2 - \lambda_3}\right], \quad [19]$$

where $\rho > 0$, $0 \le \theta < \text{ArcCos}(\sqrt{3}/3) = 0.96$ Rad $= 54.74°$, and $0 \le \phi < 2\pi$. The quadrant modification for ϕ was detailed in Eqs. [11–13].

ρ is invariant and has the units of diffusivity. It is a measure of the total magnitude of diffusion (*4*). θ is invariant and unitless. It is related to the coefficient of variation of the eigenvalues (Appendix A) and is thus a measure of their relative dispersion. ϕ is unitless but not invariant. It is a mixed measure of the skewness of the diffusion eigenvalues and an indicator of the permutation of the order of the eigenvalues (discussed below). The zero point of θ is chosen to coincide with the eigenvalue triple identity line. The zero point of ϕ is again chosen to coincide with the plane $\lambda_2 = \lambda_3$ in the direction that $\lambda_1 < \lambda_2$.

The skewness measure, s, and permutation indicator, p. The measure of the polar angle, ϕ, can be divided into two components. The first component is s, a skewness measure. The second component is p, an indicator of the order of the eigenvalues.

The indicator measure, p, can be defined as (Fig. 3)

$$\begin{aligned} p &= 1 \quad \text{for } 0 \le \phi < \pi/3 \\ p &= 2 \quad \text{for } \pi/3 \le \phi < 2\pi/3 \\ p &= 3 \quad \text{for } 2\pi/3 \le \phi < \pi \\ p &= 4 \quad \text{for } \pi \le \phi < 4\pi/3 \\ p &= 5 \quad \text{for } 4\pi/3 \le \phi < 5\pi/3 \\ p &= 6 \quad \text{for } 5\pi/3 \le \phi < 2\pi. \end{aligned} \quad [20]$$

p is an indicator of the permutation of the eigenvalue order. An equivalent definition of p is

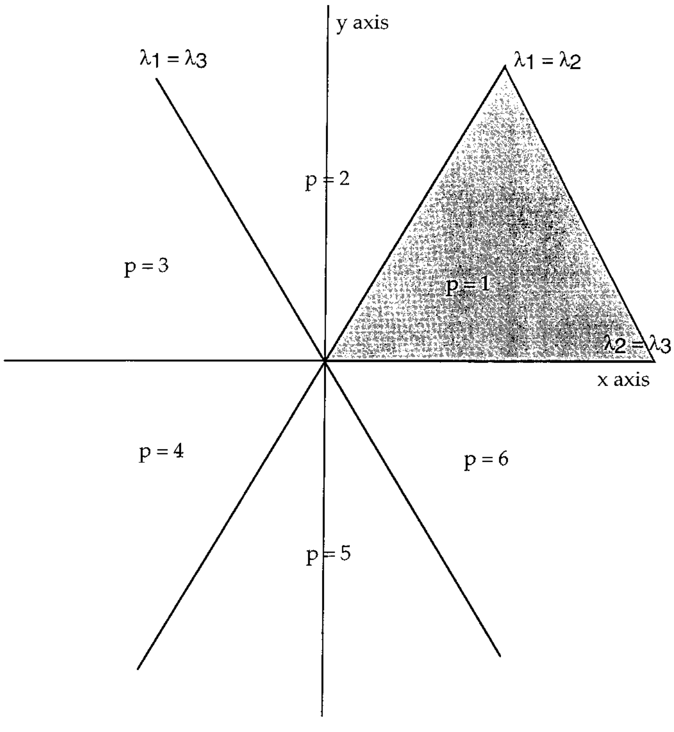

FIG. 3. The x–y plane. The lines indicate the intersection of the x–y plane with the $\lambda_1 = \lambda_2$, $\lambda_2 = \lambda_3$, and $\lambda_3 = \lambda_1$ planes, respectively. The regions corresponding to different permutations of the eigenvalue order are indicated. The region where $p = 1$ corresponds to the projection of ordered eigenvalue space onto the x–y plane.

$$p = 1 \quad \text{for } \lambda_1 < \lambda_2 \le \lambda_3$$
$$p = 2 \quad \text{for } \lambda_2 \le \lambda_1 < \lambda_3$$
$$p = 3 \quad \text{for } \lambda_2 < \lambda_3 \le \lambda_1$$
$$p = 4 \quad \text{for } \lambda_3 \le \lambda_2 < \lambda_1$$
$$p = 5 \quad \text{for } \lambda_3 < \lambda_1 \le \lambda_2$$
$$p = 6 \quad \text{for } \lambda_1 \le \lambda_3 < \lambda_2. \qquad [21]$$

The skewness measure, s, can be defined as

$$\text{when } p = 1 \quad s = \phi$$
$$\text{when } p = 2 \quad s = (2\pi/3) - \phi$$
$$\text{when } p = 3 \quad s = \phi - (2\pi/3)$$
$$\text{when } p = 4 \quad s = (4\pi/3) - \phi$$
$$\text{when } p = 5 \quad s = \phi - (4\pi/3)$$
$$\text{when } p = 6 \quad s = 2\pi - \phi. \qquad [22]$$

The skewness parameter, s, can equivalently be defined by using ordered eigenvalues,

$$s(\lambda_1, \lambda_2, \lambda_3) = \text{ArcTan}\left[\frac{\sqrt{3}\,(\lambda_{\text{int}} - \lambda_{\text{max}})}{2\lambda_{\text{min}} - \lambda_{\text{int}} - \lambda_{\text{max}}}\right]. \qquad [23]$$

In other words, s equals ϕ when the eigenvalues lie in ordered eigenvalue space, $p = 1$. s is a mapping of ϕ onto a restricted range [0, $\pi/3$]. As with ordering the eigenvalues according to their magnitudes, s is invariant. A third method of calculating s without the use of logical operators or the need to order the eigenvalues is given in Appendix C; see Eq. [C7].

Many other skewness measures are possible. The necessary and sufficient requirements for a skewness measure are that, first, it is a function of ϕ only (not ρ or θ), second, it is a periodic function of ϕ with period $2\pi/3$, third, it is monotonic over each half of its period and, fourth, it is symmetric about the midpoint of its period (see Fig. 4).

SUMMARY OF THE TRANSFORMATIONS

The three eigenvalues of the diffusion tensor define a point in a Cartesian coordinate system. This point can be uniquely expressed in other coordinate systems. The spherical coordinate system is particularly useful since its orthogonal coordinates, ρ, θ, and ϕ, separate the information about diffusion magnitude, relative eigenvalue dispersion, and skewness, respectively. The parameter ϕ also contains information about the ordering of the eigenvalues. These two components of ϕ can be separated as the measures p and s. The three measures ρ, θ, and s are invariant, independent, and mutually orthogonal.

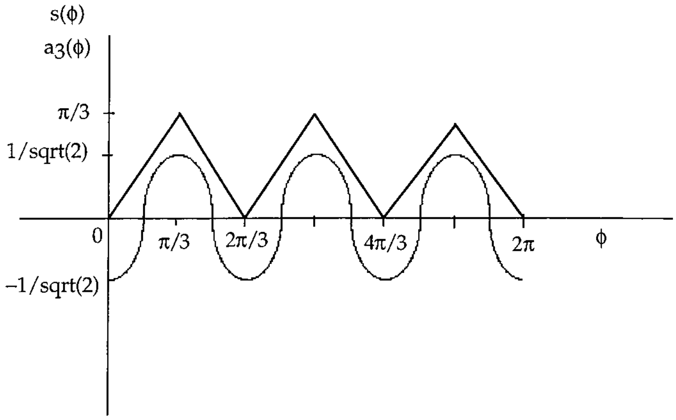

FIG. 4. Graphs of skewness measures s (sawtooth function) and a_3 (smooth function, see Appendix 3). Both satisfy the criteria for skewness measures as defined in the text.

OTHER VARIATIONS

It is not necessary to use the eigenvalues as the fundamental unit for the Cartesian coordinate system. One alternative would be to use the square root of the eigenvalues. This choice is motivated by the Einstein equation which relates the root mean square diffusion distance to the square root of the diffusion coefficient (*2*, *5*),

$$K = \begin{bmatrix} \kappa_1 \\ \kappa_2 \\ \kappa_3 \end{bmatrix} = \sqrt{\Lambda} = \begin{bmatrix} \sqrt{\lambda_1} \\ \sqrt{\lambda_2} \\ \sqrt{\lambda_3} \end{bmatrix}. \qquad [24]$$

To the degree that the Einstein equation holds true for diffusion in the complex tissue environment, the elements of K are related to the average distance traveled by the molecules in the different directions. A diffusion ellipsoid has been used to characterize the diffusion tensor (*2*). The elements of K are the lengths of the principal axes of the diffusion ellipsoid.

Using the spherical coordinate system, the K values become

$$\rho(\kappa_1, \kappa_2, \kappa_3) = \sqrt{\kappa_1^2 + \kappa_2^2 + \kappa_3^2} = \sqrt{\lambda_1 + \lambda_2 + \lambda_3} \qquad [25]$$

$$\rho(\kappa_1, \kappa_2, \kappa_3) = \sqrt{3D_{\text{bar}}} = \sqrt{\text{trace}(D)} \qquad [26]$$

$$\theta(\kappa_1, \kappa_2, \kappa_3) = \text{ArcCos}\left[\frac{(\kappa_1 + \kappa_2 + \kappa_3)}{\sqrt{3}\sqrt{\kappa_1^2 + \kappa_2^2 + \kappa_3^2}}\right] = \text{ArcCos}\left[\frac{(\kappa_1 + \kappa_2 + \kappa_3)}{\sqrt{3}\sqrt{\lambda_1 + \lambda_2 + \lambda_3}}\right]. \qquad [27]$$

A constant value of $\rho(\kappa_1, \kappa_2, \kappa_3)$ for a volume of brain tissue can be interpreted as a constant total average pathlength of diffusion, with pathlength in the root mean square sense.

DISCUSSION

In the present derivation, the orthogonal coordinates of the spherical system are shown to be particularly useful scalar measures of the diffusion tensor: One coordinate contains all the information about the overall magnitude of diffusion. Another contains all of the information about relative eigenvalue dispersion. The third coordinate contains all of the information about skewness. Because these coordinates are orthogonal they represent independent and distinct attributes of the diffusion tensor. Moreover, no information is lost when transforming from the original three eigenvalues to the coordinates of the spherical system. The measures of diffusion magnitude, relative dispersion, and skewness are all invariant to the frame of reference in which measurement of the diffusion tensor is performed.

The parameter ρ represents the total magnitude of diffusion. It is the distance in eigenvalue space from the origin to the point defined by the eigenvalues. It is the only parameter in the spherical system with units of diffusivity. ρ is an extension of the apparent diffusion coefficient (*1*) applied to isotropic diffusion; in the isotropic diffusion case ρ equals the apparent diffusion coefficient.

z or a function of z is a measure of the magnitude of the isotropic part of total diffusion (*4*). z does not contain all of the information about total diffusion magnitude. r has units of diffusivity and contains the information about the absolute dispersion of the eigenvalues. Since z depends on both ρ and θ, z (and thus any function of z) can also be thought of as a mixed measure containing both magnitude and relative eigenvalue dispersion information. This can be seen by the relationship

$$z = \rho \cos(\theta). \qquad [28]$$

In the case of isotropic diffusion $z = \rho$ (since $\theta = 0$).

Heretofore the term "anisotropy" has not been strictly or absolutely defined other than in the sense that it literally means "not isotropic." The parameters z, r, and ϕ (or s) of the circular cylindrical coordinate system demonstrate that two parameters are necessary to describe the eigenvalue information which is not isotropic (not contained in z), in this case r and ϕ. *No single scalar parameter can be constructed which reflects all of the information about anisotropy which is contained in the eigenvalues.* The parameter r is the distance in eigenvalue space from the eigenvalue point to the line of isotropic diffusion. Since r is related to the standard deviation of the eigenvalue, it measures the dispersion of the eigenvalues. Taken literally, the term anisotropy encompasses two attributes of the eigenvalues: eigenvalue dispersion and eigenvalue skewness. The parameter r is similar to many of the "anisotropy" measures proposed in the literature (*2, 3*). However, it has the units of diffusivity and thus is not invariant to scale.

In the spherical coordinate system there is no parameter which describes isotropic diffusion. However, ρ describes the magnitude of total diffusion. The other two parameters, θ and ϕ (or s), reflect the eigenvalue information which is "not total diffusion." θ is scale invariant and closely related to the coefficient of variation of the eigenvalues. It is more correct to refer to θ as a measure of *relative* eigenvalue dispersion rather than anisotropy. Allowing for this slight discrepancy in terminology, θ will herein be referred to as a measure of anisotropy because it is closely related to previously described "anisotropy" measures (*2, 3*) and it contains the information from the eigenvalues which is currently referred to as "anisotropy" instead of relative eigenvalue dispersion (RED). This usage of the term anisotropy separates skewness from anisotropy (RED).

Other "anisotropy" measures have been proposed in the literature, in particular, RA, FA, A_σ, and the volume ratio (VR) (*2, 3*). Appendices A and B derive mathematical expressions relating these measures to the parameters of the present spherical coordinate system. It is shown in Appendix A that RA, FA, and A_σ are functions of θ only and thus are pure anisotropy (RED) measures. They all contain identical information about the eigenvalues.

The volume ratio, VR, however, is shown in Appendix B to be a function of both θ and ϕ. In particular the form of the relationship of VR to ϕ is that of a skewness measure. Therefore, VR is a mixed measure containing contributions from both skewness and anisotropy (RED).

An advantage of θ over the other anisotropy (RED) measures is that differences in θ have a ready interpretation. A set of eigenvalues with an anisotropy of 2θ is twice as anisotropic as one with a measure of θ. This is because the rate of change of θ is uniform throughout its range. This sort of relationship does not hold for RA, FA, or A_σ. All three coordinates ρ, θ, and ϕ (or s) have this property of being uniform metrics over their range.

θ is orthogonal to ρ. It is not orthogonal to z (or trace or D_{bar}). Therefore, there is a degree of colinearity between z and θ, i.e., these measures do not give complementary information. r is orthogonal to z but r would not be a preferred choice for a second measure to complement z since it's value is dependent on scale, i.e., sets of eigenvalues which differ only by a scale factor would have different values of r. Normalizing r to eliminate the scale factor, (i.e., r/z) yields a measure proportional to the coefficient of variation of the eigenvalues which is a function of θ (Appendix A).

The measure of polar angle, ϕ, contains information about both the order of the eigenvalues and the skewness of the three eigenvalues. In Appendix C it is shown that a previously proposed skewness measure (*3*) can be expressed as a function of ϕ. The skewness measure, s, is invariant. It is orthogonal to ρ and θ. It is also orthogonal to z and r. s also has the property of being a uniform metric, i.e., a set of eigenvalues with a skewness value of $2s$ has twice the skew as one with a value of s. Like z, r, ρ, θ, and ϕ, the skewness measure, s, can be calculated without ordering the eigenvalues according to their magnitude; see Eq. [C7]. This avoids bias that might be introduced as a result of ordering the eigenvalues (*6*). However, the effect of measurement error on the values of all of the measures discussed in this paper must be assessed.

CONCLUSIONS

Using a spherical coordinate system approach, new invariant scalar measures for attributes of the diffusion tensor eigenvalues have been derived. These measures have the unique property of being mutually orthogonal. Therefore, unlike other measures, the information contained in these measures is totally independent and complementary, there is no colinearity between measures. Also, use of the coordinates of the spherical coordinate system as scalar measures utilizes all of the information from the original eigenvalues. Any other measure which can be derived from the original eigenvalues can also be derived from the measures of the spherical coordinate system.

APPENDIX A

Theorem. The relationship between the two measures θ and cv is

$$cv = \frac{\sqrt{3}}{\sqrt{2}} \tan\theta. \qquad [A1]$$

Proof. By definition, the coefficient of variation, cv, equals

$$cv(\lambda_1, \lambda_2, \lambda_3) = \frac{\text{standard deviation}}{\text{mean}} = \frac{\sqrt{(\lambda_1 - \lambda_{\text{bar}})^2 + (\lambda_2 - \lambda_{\text{bar}})^2 + (\lambda_3 - \lambda_{\text{bar}})^2}}{\sqrt{2}\,\lambda_{\text{bar}}}. \qquad [A2]$$

The standard deviation was defined in Eq. [14] and the mean was defined in Eq. [8]. z and r are defined in Eqs. [8] and [10]. Substituting these expressions into Eq. [A2] and simplifying yields

$$cv = \frac{\sqrt{3}}{\sqrt{2}} \frac{r}{z} = \frac{\sqrt{3}}{\sqrt{2}} \tan\theta. \qquad [A3]$$

r, z, and ρ form two sides and the hypotenuse of a right triangle, respectively; see Fig. 2.

Corollaries.

$$(1) \quad \text{RA} = \tan\theta \qquad [A4]$$

$$(2) \quad \text{FA} = \sin\theta \qquad [A5]$$

$$(3) \quad A_\sigma = \frac{\tan\theta}{\sqrt{2}}. \qquad [A6]$$

Proof of Corollary (1). The relative anisotropy (*2, 4*) is a function of θ,

$$\text{RA}(\lambda_1, \lambda_2, \lambda_3) = \frac{1}{\sqrt{3}} \frac{\sqrt{(\lambda_1 - \lambda_{\text{bar}})^2 + (\lambda_2 - \lambda_{\text{bar}})^2 + (\lambda_3 - \lambda_{\text{bar}})^2}}{\lambda_{\text{bar}}}. \qquad [A7]$$

It is immediately evident from Eqs. [A2] and [A1] that

$$\text{RA} = \frac{\sqrt{2}}{\sqrt{3}} cv = \tan(\theta). \qquad [A8]$$

Proof of Corollary (2). The fractional anisotropy (*2, 4*) is also a function of θ,

$$\text{FA}(\lambda_1, \lambda_2, \lambda_3) = \frac{\sqrt{3}}{\sqrt{2}} \frac{\sqrt{(\lambda_1 - \lambda_{\text{bar}})^2 + (\lambda_2 - \lambda_{\text{bar}})^2 + (\lambda_3 - \lambda_{\text{bar}})^2}}{\sqrt{\lambda_1^2 + \lambda_2^2 + \lambda_3^2}}. \qquad [A9]$$

Substituting Eqs. [A7], [10], and [17] and then substituting Eq. [A9] (noting that $z/\rho = \cos\theta$),

$$\text{FA} = \frac{\sqrt{3}}{\sqrt{2}} \frac{z}{\rho} \text{RA} = \frac{\sqrt{3}}{\sqrt{2}} \cos\theta \tan\theta = \frac{\sqrt{3}}{\sqrt{2}} \sin\theta. \qquad [A10]$$

Proof of Corollary (3). A_σ is a function of θ. It is defined as (*3*)

$$A_\sigma(\lambda_1, \lambda_2, \lambda_3) = \frac{1}{\sqrt{6}} \frac{\sqrt{(\lambda_1 - \lambda_{\text{bar}})^2 + (\lambda_2 - \lambda_{\text{bar}})^2 + (\lambda_3 - \lambda_{\text{bar}})^2}}{\lambda_{\text{bar}}}. \qquad [A11]$$

Using Corollary (1), Eq. [A6],

$$A_\sigma = \frac{\tan\theta}{\sqrt{2}}. \qquad [A12]$$

APPENDIX B

Theorem. The volume ratio is a mixed measure containing contributions from both anisotropy (RED) and skewness.

Proof. The volume ratio is defined as (*2*, *6*)

$$\mathrm{VR}(\lambda_1,\ \lambda_2,\ \lambda_3) = \frac{\lambda_1\ \lambda_2\ \lambda_3}{\left[\dfrac{\lambda_1 + \lambda_2 + \lambda_3}{3}\right]^3}. \qquad [B1]$$

Using Eq. [7] and the fact that the inverse of the rotation matrix is equal to its transpose,

$$\begin{bmatrix}\lambda_1\\ \lambda_2\\ \lambda_3\end{bmatrix} = \begin{bmatrix}\dfrac{-2}{\sqrt{6}} & 0 & \dfrac{1}{\sqrt{3}}\\ \dfrac{1}{\sqrt{6}} & \dfrac{-1}{\sqrt{2}} & \dfrac{1}{\sqrt{3}}\\ \dfrac{1}{\sqrt{6}} & \dfrac{1}{\sqrt{2}} & \dfrac{1}{\sqrt{3}}\end{bmatrix}\begin{bmatrix}x\\ y\\ z\end{bmatrix}. \qquad [B2]$$

In the *cylindrical coordinate system,*

$$x = r \cos \phi \qquad [B3]$$

$$y = r \sin \phi. \qquad [B4]$$

Substituting Eqs. [B2], [B3], and [B4] into Eq. [B1] yields

$$\mathrm{VR}(r,\ \phi,\ z) = 1 - \frac{3\ r^2}{2\ z^2} - \frac{r^3 \cos(3\phi)}{z^3\sqrt{2}}. \qquad [B5]$$

This derivation demonstrates that in the cylindrical coordinate system, the volume ratio depends on all three parameters, r, ϕ, and z. The ϕ dependence satisfies the criteria for a skewness measure defined in the text.

In the *spherical coordinate system,*

$$\tan \theta = \frac{r}{z}. \qquad [B6]$$

Substituting this into Eq. [B5] yields

$$\mathrm{VR}(\rho,\ \phi,\ \theta) = 1 - \frac{3}{2}\tan^2 \theta - \frac{\cos(3\phi)}{\sqrt{2}}\tan^3 \theta. \qquad [B7]$$

This derivation demonstrates that in the spherical coordinate system, the volume ratio is independent of the diffusion magnitude measure, ρ. However, it is a mixed measure containing information about anisotropy (RED) and skewness as shown by its dependence on θ and ϕ, respectively.

Substituting Eq. [A8] into Eq. [B7] yields

$$\mathrm{VR}(\rho,\ \phi,\ cv) = 1 - (cv)^2 - \frac{2}{3\sqrt{3}}\cos(3\phi)(cv)^3. \qquad [B8]$$

This expression relates the volume ratio to the coefficient of variation. The dependence of VR on ϕ remains because it is a mixed measure of anisotropy (RED) and skewness.

APPENDIX C

Theorem. The relationship between the two measures a_3 (*7*) and ϕ is

$$a_3 = -\frac{\cos[3\phi]}{\sqrt{2}}. \qquad [C1]$$

Proof. The moment index of skewness, a_3, is defined as (*7*)

$$a_3 = \frac{m_3}{d^3}. \qquad [C2]$$

The third moment of the distribution, m_3, is (*3*)

$$m_3(\lambda_1,\ \lambda_2,\ \lambda_3) = \frac{(\lambda_1 - \lambda_{\mathrm{bar}})^3 + (\lambda_2 - \lambda_{\mathrm{bar}})^3 + (\lambda_3 - \lambda_{\mathrm{bar}})^3}{3} \qquad [C3]$$

and

$$d(\lambda_1,\ \lambda_2,\ \lambda_3) = \sqrt{m_2} = \sqrt{\frac{(\lambda_1 - \lambda_{\mathrm{bar}})^2 + (\lambda_2 - \lambda_{\mathrm{bar}})^2 + (\lambda_3 - \lambda_{\mathrm{bar}})^2}{3}}. \qquad [C4]$$

λ_{bar} is the mean of the three eigenvalues as defined as in Eq. [8]. a_3 is an invariant measure of skewness.

ϕ is the mixed skewness measure and indicator of eigenvalue order in both the cylindrical and the spherical coordinate systems. Consider the three eigenvalues in the cylindrical coordinate system. Using the results of De Moivre's theorem from complex analysis along with Eq. [10] yields

$$m_3(r,\ \phi,\ z) = -\frac{r^3 \cos[3\phi]}{3\sqrt{6}} \qquad [C5]$$

and

$$d(r, \phi, z) = \frac{r}{\sqrt{3}}. \qquad [C6]$$

Equations [C5] and [C6] lead directly to Eq. [C1], the desired result. The relationship satisfies the criteria for a skewness measure as defined in the text. Figure 4 compares the values of the skewness measures $a_3(\phi)$ and $s(\phi)$.

These results yield a method of calculating s without the use of logical operations or the need to explicitly order the eigenvalues:

$$s = \frac{\mathrm{ArcCos}[-a_3\ \sqrt{2}]}{3}. \qquad [C7]$$

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