Anisotropically Weighted MRI

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The intensity of an isotropically weighted MR image is proportional to a rotationally invariant measure of bulk diffusion, Trace($\underline{D}$) (where $\underline{D}$ is the effective diffusion tensor). Such images can be acquired from as few as two diffusion-weighted images (DWIs). Analogously, the intensity of an anisotropically weighted MR image is proportional to a rotationally invariant measure of diffusion anisotropy derived from $\underline{D}$, such as the variance of the principal diffusivities of $\underline{D}$. By using linear algebra, we show that to produce an anisotropically weighted MR image requires acquiring at least seven DWIs, which is also the minimum number of DWIs sufficient to estimate the entire diffusion tensor, as well as the T_2-weighted amplitude image, $A(\underline{b} = \underline{0})$, in each voxel. A general mathematical framework for constructing isotropically weighted and anisotropically weighted MR images is also provided.

Key words: diffusion; anisotropy; teusor; MRI.

INTRODUCTION

The trace of the diffusion tensor, Trace($\underline{D}$), is a physically and biologically informative MRI parameter (1). Trace($\underline{D}$) is proportional to the orientationally averaged diffusivity (2) and is thus independent of tissue fiber orientation and, more generally, of the laboratory coordinate system in which the components of the diffusion tensor are measured (1). To date, its clinical utility derives from its ability to demarcate ischemic regions in acute stroke (3). When one is interested in measuring changes of water diffusion in tissues, a map of an intrinsic parameter such as Trace($\underline{D}$) (1) is preferable to a map of an apparent diffusion coefficient (4), in which the contrast in white matter depends on both the local diffusivity of water as well as the orientation of the nerve fiber tracts.

The first reported measurements of Trace($\underline{D}$) were obtained by (a) acquiring diffusion-weighted images (DWIs) with diffusion gradients applied in a multiplicity of directions and amplitudes, (b) using a model of anisotropic diffusion in tissues to estimate an apparent or effective diffusion tensor $\underline{D}$ in each voxel from these DWIs, and (c) calculating Trace($\underline{D}$) in each voxel from $\underline{D}$ (1). Recently, however, "single-shot" isotropically weighted sequences have been developed, which produce an image in which the intensity is proportional to Trace($\underline{D}$) (5–7). Their potential benefit is that a smaller number of DWIs and postprocessing steps are required to produce an image in which the intensity is proportional to Trace($\underline{D}$) than the seven DWIs required to acquire the entire diffusion tensor in diffusion tensor MRI. However, intrinsically, isotropically weighted imaging sequences provide no information about diffusion anisotropy.

BACKGROUND

Whether one is performing diffusion tensor MRI or developing isotropically or anisotropically weighted pulse sequences, the following relationship between the echo attenuation and the apparent or effective diffusion tensor (8) provides a constraint that must be satisfied:

$$\ln\left(\frac{A(\underline{b})}{A(\underline{b}=\underline{0})}\right) = -\sum_{i=1}^{3}\sum_{j=1}^{3} b_{ij}\,D_{ij} = -\,\mathrm{Trace}(\underline{b}\;\underline{D})$$

$$= -\,(b_{xx}\,D_{xx} + 2\;b_{xy}\,D_{xy} + 2\;b_{xz}\,D_{xz} + b_{yy}\,D_{yy} + 2\;b_{yz}\,D_{yz} + b_{zz}\,D_{zz}) \qquad [1]$$

Above, b_{ij} is the component of the ith row and jth column of the symmetric b matrix, $\underline{b}$; D_{ij} is the corresponding component of the symmetric effective diffusion tensor, A($\underline{b}$) is the echo intensity for a gradient sequence with b matrix, $\underline{b}$; and A($\underline{b} = \underline{0}$) is the echo intensity for a gradient sequence in which the $\underline{b}$ is the zero matrix, $\underline{0}$. The b matrix used in Eq. [1] is calculated from the pulse gradient sequence as described elsewhere (8, 9).

Wong *et al.* (5–7) produced an isotropically weighted MR image by prescribing a pulsed gradient sequence in which the resulting b matrix is proportional to the identity matrix, $\underline{I}$, the diagonal elements of which are all equal and the off-diagonal elements of which all vanish.[1] Thus, the b matrix is of the form:

$$b_{ij} = \alpha\;\delta_{ij} \text{ or } \underline{b} = \alpha\;\underline{I} \qquad [2]$$

(where α is a constant and δ_{ij} is the Kronecker delta). Then, by substituting Eq. [2] into Eq. [1]; we see that

$$\ln\left(\frac{A(\underline{b})}{A(\underline{b}=\underline{0})}\right) = -\,\alpha(D_{xx} + D_{yy} + D_{zz}) = -\,\alpha\;\mathrm{Trace}(\underline{D}) \qquad [3]$$

The logarithm of the echo attenuation is directly proportional to Trace($\underline{D}$). In general, to produce such an image requires obtaining at least two DWIs, one without diffusion weighting, $A(\underline{b} = \underline{0})$, and another with "isotropic weighting", i.e., $A(\underline{b} = \alpha\underline{I})$.

It is reasonable to ask whether one can also construct an *an*isotropically weighted MRI, i.e., one in which the intensity is proportional to a quantitative measure of diffusion *anisotropy*, also by using a small number of DWIs. This question is particularly timely because of the

[1] An additional constraint is that each of the phases (k vectors) is refocused at the echo, i.e., $\mathbf{k}(2\,\tau) = \mathbf{0}$.

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increasing number of *in vivo* studies indicating that the degree of diffusion anisotropy is potentially informative, such as in the detection of Wallerian degeneration and organized gliosis in humans (10), in the identification of Pelizaeus-Merzbacher disease (11), in the "aging" of lesions in clinical stroke studies (12), in identifying microstructural changes in schizophrenia (13), and in observing changes in fiber tract organization in the brains of kittens (14) and neonates (15) and in the spinal cord of transgenic mice (16).

Herein we provide a method to construct an anisotropically weighted MRI, determine the fewest DWIs required to construct such an image, and consider the relative merits of diffusion tensor MRI and anisotropically weighted MRI.

ADMISSIBLE MEASURES OF DIFFUSION ANISOTROPY

Before developing anisotropically weighted MRI sequences, one must first identify parameters that are admissible quantitative measures of diffusion anisotropy, i.e., they are (a) physically meaningful or informative and (b) rotation and translation invariant (17). Although Trace($\underline{D}$) is sufficient to characterize isotropic diffusion, there are numerous admissible measures with which to characterize different features of anisotropic diffusion. Below we briefly describe a few to show explicitly how they are functionally related to $\underline{D}$. Their definitions and uses are described elsewhere (17, 18).

Whereas Trace($\underline{D}$) is proportional to the first moment or mean of the distribution of eigenvalues of $\underline{D}$ in a voxel, useful anisotropy measures proposed recently depend on the second or higher moments of this distribution (e.g., its variance and skewness). These measures have been derived from $\underline{D}$ by using the explicit requirements that (a) they are scalar invariant quantities and (b) they measure a characteristic of the anisotropic part or deviatoric of the diffusion tensor, $\underline{\Delta}$ (17), where

$$\underline{\Delta} = \underline{D} - \langle D \rangle \, \underline{I} \quad [4]$$

and

$$\langle D \rangle = \frac{\text{Trace}(\underline{D})}{3} \quad [5]$$

One quantity that possesses these properties is the "double-dot product" (19) of the deviatoric tensor with itself, $\underline{\Delta} : \underline{\Delta}$ (17), which can also be written as Trace($\underline{\Delta}^2$), where

$$\text{Trace}(\underline{\Delta}^2) = \text{Trace}(\underline{D}^2) - 3\langle D \rangle^2 = \frac{2}{3}(D_{xx}^{\;2} + D_{yy}^{\;2} + D_{zz}^{\;2}) - \frac{2}{3}(D_{xx}D_{yy} + D_{yy}D_{zz} + D_{zz}D_{xx}) + 2D_{xy}^{\;2} + 2D_{xz}^{\;2} + 2D_{yz}^{\;2} \quad [6]$$

It was shown that Trace($\underline{\Delta}^2$) is a scalar measure of the degree to which the diffusion tensor deviates from isotropy (in a mean-squared sense) and that it is proportional to the second moment or sample variance of the principal diffusivities of the diffusion tensor (17). It is important to note that Trace($\underline{\Delta}^2$) is a quadratic function of the elements of $\underline{D}$.

Another quantity that can be used to characterize diffusion anisotropy is the third moment of the eigenvalues of $\underline{D}$. This quantity can be written as Trace($\underline{\Delta}^3$), which is a cubic function of the elements of the diffusion tensor.

In general, admissible quantitative measures of diffusion anisotropy to date are functionally related to second and higher moments of the eigenvalues of the diffusion tensor in each voxel, which can be represented by second or higher-order polynomial functions of the elements of $\underline{D}$.

Comparison of Isotropic and Anisotropic Diffusion Weighting

While a single scalar quantity, Trace($\underline{D}$), which is a *linear* function of only the three diagonal elements of the diffusion tensor, is sufficient to characterize isotropic diffusion in a voxel, polynomial (or more complicated nonlinear) functions of all of the elements of the diffusion tensor are required to describe diffusion anisotropy quantitatively within a voxel. Moreover, although Eq. [1] establishes a simple, linear relationship between the Log of the DWI intensity and the six independent elements of the diffusion tensor (whose six independent coefficients must be specified in order to produce an isotropically weighted DWI), it does not suggest a simple linear relationship between the Log of the DWI intensities and any quadratic or cubic functions of the diffusion tensor (e.g., given in Eq. [6]) that would furnish a suitable anisotropy measure.

THEORETICAL RESULTS AND DISCUSSION

Since $\underline{D}$ in Eq. [1] has six independent elements, at least six ratio images (i.e., log(A($\underline{b}$)/A($\underline{b} = \underline{0}$))) are required to solve for each element (8). No manipulations (e.g., raising Eq. [1] to different powers) will reduce that number. However, information about diffusion anisotropy is embodied in the deviatoric tensor, $\underline{\Delta}$, in Eq. [4], so it may be possible to reduce the number of DWIs required to represent the information contained in it. We will show that this is not possible by using linear algebraic reasoning.

The question of whether one can construct an anisotropically weighted image can be reduced to the question of whether one can use Eq. [1] to generate an image from a set of DWIs in which the intensity is proportional to an admissible quantitative diffusion anisotropy measure. Examining Eq. [6] together with Eq. [1] suggests an approach to solving this problem. First, square Eq. [1]:

$$\left(\ln\left(\frac{A(\underline{b})}{A(\underline{b} = \underline{0})}\right)\right)^2 = b_{xx}^{\;2}\, D_{xx}^{\;2} + 4b_{xx}\, b_{xy}\, D_{xx}\, D_{xy} + \ldots + b_{zz}^{\;2}\, D_{zz}^{\;2} \quad [7]$$

It is helpful now to introduce two column vectors, $\mathbf{D}$, a six-element vector containing the six independent diffusion tensor coefficients,

$$\mathbf{D} = \{D_{xx}, D_{yy}, D_{zz}, D_{xy}, D_{xz}, D_{yz}\}^T \quad [8a]$$

and $\mathbf{b}$, a six-element vector containing the six corresponding b matrix coefficients

$$\mathbf{b} = \{b_{xx}, b_{yy}, b_{zz}, b_{xy}, b_{xz}, b_{yz}\}^T \quad [8b]$$

where the superscript "T" indicates the transpose operation. We see that the right side of Eq. [7] is a linear combination of 21 (= 6 + 5 + 4 + 3 + 2 + 1) independent quadratic terms containing products of elements of the diffusion tensor, some of which appear in Eq. [6] and some of which do not. In general, the product of the ratio images, $\log(A(\underline{b}^i)/A(\underline{b} = \underline{0}))$ and $\log(A(\underline{b}^j)/A(\underline{b} = \underline{0}))$ (where $\underline{b}^i$ and $\underline{b}^j$ denote b matrices of the ith and jth DWIs) produces the same independent quadratic terms (as in Eq. [7] above). Accordingly, the b vector associated with the ith DW ratio image is also written as a six-element column vector $\mathbf{b}^i$

$$\mathbf{b}^i = \{b_{xx}{}^i, b_{yy}{}^i, b_{zz}{}^i, b_{xy}{}^i, b_{xz}{}^i, b_{yz}{}^i\}^T \quad [9]$$

just as we have written the elements of the diffusion tensor above in Eq. [8a]. For Eq. [9] and onward, superscripts of $\underline{a}$, $\mathbf{b}$, $\underline{b}$, and $\underline{Q}$ will denote indices rather than exponents. The outer products of the vectors $\mathbf{b}^i$ and $\mathbf{b}^j$ are 6×6 matrices, denoted by $\underline{Q}^{ij}$ (for quadratic anisotropy measures):

$$\underline{Q}^{ij} = \mathbf{b}^i\, \mathbf{b}^{jT} \quad [10]$$

For $n + 1$ DWIs, (n DWIs with nonzero weighting, and one DWI with zero weighting), the most general linear combination of the ratio images that is quadratic in the elements of the diffusion tensor is:

$$\mathbf{D}^T\left(\sum_{i=1}^{n}\sum_{j=1}^{n} a^{ij}\, \underline{Q}^{ij}\right)\mathbf{D} \quad [11]$$

where a is an $n \times n$ matrix with as yet undetermined constants. Each quadratic anisotropy measure can also be written as a quadratic form in terms of the same quadratic terms obtained from the diffusion tensor:

$$\mathbf{D}^T\underline{R}\mathbf{D} \quad [12]$$

where $\underline{R}$ is a symmetric matrix of coefficients, which are easily determined from the particular expression of the quadratic anisotropy measure. For example, for the anisotropy measure Trace($\underline{\Delta}^2$) :

$$\underline{R}_{\Delta} = \begin{Bmatrix} 2/3 & -1/3 & -1/3 & 0 & 0 & 0 \\ -1/3 & 2/3 & -1/3 & 0 & 0 & 0 \\ -1/3 & -1/3 & 2/3 & 0 & 0 & 0 \\ 0 & 0 & 0 & 2 & 0 & 0 \\ 0 & 0 & 0 & 0 & 2 & 0 \\ 0 & 0 & 0 & 0 & 0 & 2 \end{Bmatrix} \quad [13]$$

Therefore, to make an anisotropically weighted image, we require that

$$\mathbf{D}^T\left(\sum_{i=1}^{n}\sum_{j=1}^{n} a^{ij}\mathbf{Q}^{ij} - c\,\underline{\mathbf{R}}\right)\mathbf{D} = 0 \quad [14]$$

for any $\mathbf{D}$. Therefore, the quantity in parentheses must equal the zero matrix, or

$$\sum_{i=1}^{n}\sum_{j=1}^{n} a^{ij}\mathbf{Q}^{ij} = \underline{\mathbf{P}}^n \text{ where } \underline{\mathbf{P}}^n = c\underline{\mathbf{R}} \quad [15]$$

The equation above still contains some ambiguities of scale. The scalar c can be subsumed in the coefficients a^{ij}. Likewise, the vectors $\mathbf{b}$ that produce the Q matrices can be scaled arbitrarily, with the scale factors also subsumed in the coefficients a^{ij}. Hence, without loss of generality, we can normalize each $\mathbf{b}^i$, restricting it to five degrees of freedom (DOFs) rather than six. (After a solution has been found, the $\mathbf{b}^i$ can be rescaled.)

Since $\underline{R}$ is a symmetric 6×6 matrix, it contains 21 independent entries, each of which is to be matched by a sum of terms linear in the as and quadratic in the $\mathbf{b}$s, i.e., 21 equations in several unknown as and $\mathbf{b}$s. A physical requirement placed on each 3×3 b matrix is that it be non-negative definite; otherwise, we could always find a coordinate transformation in which an increase in diffusion weighting would produce an increase (not a decrease) in the measured echo amplitude. One implication of this condition is that each of the diagonal elements of $\underline{b}$, b_{xx}, b_{yy}, and b_{zz} is non-negative. One further restriction placed on a is that it is symmetric, i.e., $a^{ij} = a^{ji}$. The number of independent coefficients a^{ij} for n diffusion-weighted ratio images is given by $n(n + 1)/2$, yielding the following apparent DOFs:

No. of DWIs	No. of ratios images	Apparent No. of DOFs from b	$\underline{a}$	total
2	1	5	1	6
3	2	10	3	13
4	3	15	6	21
5	4	20	10	30
6	5	25	15	40
7	6	30	21	51

[16]

Referring to Eq. [16] above, it is tempting to speculate that only three diffusion-weighted ratio images or four DWIs could provide 21 total DOFs, which would be sufficient to solve the 21 equations. Therefore, one might suspect that only four DWIs would be sufficient to construct an anisotropically weighted MRI. However, we will now show below that at least six linearly independent ratio images or seven DWIs are required.

The particular R matrix we use is given above in Eq. [13]. This is a rank-5 matrix. It has one zero eigenvalue corresponding to the eigenvector $[1,1,1,0,0,0]^T$ that spans the null space of $\underline{R}$. The form of Q^{ij} implies that each of its rows is proportional to $\mathbf{b}^i$ and each of its columns is proportional to $\mathbf{b}^j$. Therefore, each Q^{ij} matrix is of rank 1, because all of its rows (and columns) lie in the same direction.

If there were one ratio image, there would be only one Q^{ij}, namely Q^{11}, and only one coefficient, a^{11} so that the equation to solve would reduce to:

$$\underline{P}^1 = \underline{R} \text{ where } \underline{P}^1 = a^{11}\, Q^{11} \quad [17]$$

We know that this equation has no solution because $\underline{P}^1$ has a lower rank than $\underline{R}$, and matrices whose ranks differ cannot be equal. With the addition of a second independent image, the equation is more complex:

$$\underline{P}^2 = \underline{R} \text{ where } \underline{P}^2 = a^{11}\, Q^{11} + a^{12}(Q^{12} + Q^{21}) + a^{22}\, Q^{22} \quad [18]$$

There are now three terms in $\underline{P}^2$, but one can see by the form of Q that the rows of $\underline{P}^2$ are all linear combinations of $\mathbf{b}^1$ and $\mathbf{b}^2$, and hence, $\underline{P}^2$ is only of rank 2, not rank 5. Likewise, with the addition of a third independent DWI, $\underline{P}^3$ has six terms, but is only of rank 3, so there is no hope of finding a solution for an image weighted by Trace($\underline{\Delta}^2$) using only three ratio images. To complete the thought, n linearly independent ratio images produce a $\underline{P}^n$ of (at most) rank n, up to a maximum of rank 6. Since $\underline{R}$ is of rank 5, at least five ratio images or six DWIs are necessary.

What remains is to show that even five ratio images is not sufficient. The matrix $\underline{R}$ is of order 6, rank 5, and nullity 1. The rows of $\underline{R}$ span only five of the six dimensions available to them. The null space (the space not spanned by the rows of $\underline{R}$) is one-dimensional. Moreover, any six-vector in the row space of $\underline{R}$ must be orthogonal to $[1,1,1,0,0,0]^T$, the vector that spans the null space of $\underline{R}$. For five ratio images to form a basis for the row space of $\underline{R}$, all five of the corresponding $\mathbf{b}^i$ that form the basis of $\underline{P}^5$ must also be orthogonal to the null space of $\underline{R}$. The rank-5 matrices, $\underline{R}$ and $\underline{P}^5$, cannot be equal unless their null spaces coincide. So the problem reduces to finding five such vectors that are perpendicular to $[1,1,1,0,0,0]^T$. But recall that the first three elements of any admissible $\mathbf{b}^i$ are non-negative (except for the trivial image that is reserved for scaling and is not included in this proof). So, at least one of the first three elements must be positive. Therefore, it is impossible to find five (or even one) $\mathbf{b}^i$ orthogonal to $[1,1,1,0,0,0]^T$. Therefore, any solution requires at least six ratio images or a total of seven DWIs.

Viewed in another way, by referring to Eq. [2], we can decompose $\underline{D}$ into its isotropic and anisotropic parts, as in Eqs. [5] and [4], and substitute these definitions into Eq. [1]:

$$\ln\left(\frac{A(\underline{b})}{A(\underline{b} = \underline{0})}\right) = -\,\mathrm{Trace}(\underline{b}\,\underline{D}) = -\,\mathrm{Trace}(\underline{b}(\langle D\rangle \underline{I} + \underline{\Delta})) \quad [19]$$

$$= -\underbrace{\mathrm{Trace}(\underline{b})\langle D\rangle}_{\text{isotropic weighting}} - \underbrace{\mathrm{Trace}(\underline{b}\,\underline{\Delta})}_{\text{anisotropic weighting}}$$

Because, by construction, $\underline{b}$ is a positive semidefinite matrix, Trace($\underline{b}$) is positive. Moreover, the mean diffusivity must be positive (i.e., $\langle D\rangle > 0$). Therefore, according to the equation above, all DWIs must possess some diffusion attenuation ascribable to $\underline{D}$ (i.e., some isotropic weighting). Generally, while it is possible to sensitize the DWI exclusively to the isotropic part of $\underline{D}$ without also producing some attenuation caused by anisotropic diffusion, it is impossible to sensitize the DWI exclusively to the anisotropic part of $\underline{D}$ without also producing some attenuation caused by isotropic diffusion.

So far, we have shown that six ratio images (or seven DWIs) are required to satisfy the condition of anisotropic weighting, Eq. [15], when $\underline{R}$ is full-rank, or when $\underline{R}$ has the one-dimensional null space:

$$\mathbf{R}_0 = [1, 1, 1, 0, 0, 0]^T \quad [20]$$

Still, one could imagine choosing $\underline{R}$ with a null space other than $\mathbf{R}_0$, or with more null dimensions (so that $\underline{R}$ spans fewer dimensions). However, one cannot do this without diminishing the generality of the weighting. The vector $\mathbf{R}_0$ holds a special place in that it represents pure isotropic weighting. That is $1/3\ \mathbf{R}_0^T\, \mathbf{D}\, \mathbf{R}_0$ is the isotropic part of $\mathbf{D}$ (i.e., the projection of $\mathbf{D}$ onto the null space $\mathbf{R}_0$), whereas $\mathbf{D} - 1/3\ \mathbf{R}_0^T\, \mathbf{D}\, \mathbf{R}_0$ is the anisotropic part of $\mathbf{D}$ (i.e., the projection of $\mathbf{D}$ onto the range space of $\underline{R}$). It is easily demonstrated that $\mathbf{D}$ spans all six dimensions, which means that $\underline{\Delta}$ spans a five-dimensional subspace that is orthogonal to $\mathbf{R}_0$. A null space that would overlap this five-dimensional subspace would reduce some of the required degrees of freedom. Thus, the null space spanned by $\mathbf{R}_0$ is the only one that permits the complete characterization of diffusion anisotropy.

Our demonstration is now complete. Using $\underline{\Delta}$ rather than $\underline{D}$ does not allow one to economize on the number of DWIs required to characterize diffusion anisotropy, unless one can justify ignoring certain dimensions, e.g., by assuming symmetry, which we discuss below. In the process, we have also developed a general framework for considering both isotropically and anisotropically weighted MRIs. We see that a DWI in which $\mathbf{b}$ lies entirely in the null space of $\underline{R}$, i.e., $\mathbf{b} = [1,1,1,0,0,0]^T$, results in an isotropically weighted image. This is the same requirement used by Wong *et al.* (6) (see Eq. [2]) to produce such an image. Moreover, any six linearly independent $\mathbf{b}^i$ that span the range and null space of $\underline{R}$ can be used to produce an anisotropically weighted image. Finally, this linear algebraic formulation highlights the orthogonality or complementarity of the information required to characterize the isotropic and anisotropic contributions to diffusion.

Interestingly, our results are not dependent on the details of the experimental design (e.g., the gradient magnitudes, directions, timing parameters, etc.). Almost any choice of six ratio images yields a set of as that satisfies Eq. [15]. An obvious exception is a linearly dependent set of $\mathbf{b}^i$, e.g., in which at least two DWIs have diffusion gradient vectors that are collinear and thus provide redundant directional information. Any set of 21 linear equations in 21 as can be solved analytically. However, one could choose the gradient strengths and directions (b

matrices) of these images to minimize the effect of measurement error, e.g., by minimizing the condition number of the 21 linear equations.

To produce a single image in which the contrast is proportional to a quadratic anisotropy measure, we must satisfy 21 independent equations simultaneously, one for each independent component or direction.[2] When imaging gradients contribute negligibly to the b matrix, then $\underline{b}$ can be factored as follows:

$$\underline{b} = \nu^2 \, \mathbf{G} \, \mathbf{G}^T \quad [21]$$

where $\mathbf{G}$ is the column vector of peak diffusion gradient values and ν is a constant (8). In this case, only three elements of the b matrix are independent, b_{xx}, b_{yy}, and b_{zz}. Therefore, it is algebraically impossible to satisfy 21 independent equations required to specify the contrast of a computed anisotropically weighted image with fewer than seven DWIs. One might have suspected that if imaging gradients do contribute significantly to the attenuation of each echo, that each b matrix might contribute more than three DOFs, and thus, fewer than seven images might be sufficient to obtain an anisotropically weighted image. However, because of intrinsic algebraic properties of the b matrix and the form of the quadratic scalar invariant anisotropy measures, we have shown that this is not the case.

Is it reasonable to try to design specialized pulse sequences exclusively to construct an anisotropically weighted MRI? Our findings here suggest that the answer is "No." We have seen that seven DWIs are required to provide enough independent information to calculate a new image in which the contrast is a useful quadratic, rotationally invariant measure of diffusion anisotropy. However, this is the same number of DWIs required to calculate each element of the diffusion tensor analytically, as well as the T_2-weighted signal $A(\underline{b} = \underline{0})$ (8). It is clearly preferable to determine $\underline{D}$ directly from a set of seven DWIs, since with it one is able to calculate the tensor's three eigenvectors and eigenvalues, its Trace, and other invariant quantities, along with information about diffusion anisotropy *per se*. Moreover, if we are interested in displaying anisotropy measures other than one for which the b matrices were determined, we would have to recalculate a new set of a coefficients for each measure. Finally, anisotropically weighted sequences would provide no estimates of uncertainty of the diffusion anisotropy measure itself. This is not the case with conventional diffusion tensor imaging using more than seven DWIs, which is intrinsically a statistical technique.

One could speculate that the number of ratio images required to produce an anisotropically weighted image would be reduced by assuming cylindrical or spherical symmetry *a priori*. In general, there is a significant risk in doing so. *In vivo* diffusion tensor MRI studies of monkey (20) and of human brains (21) produced many voxels that did not satisfy either hypothesis. Although the assumption of cylindrical symmetry of the diffusion tensor should reduce the number of ratio images required to characterize anisotropy from six to four, and the assumption of spherical symmetry should further reduce the number from four to one, one should not apply these assumptions *a priori*. Instead, it is preferable to establish the degree of symmetry *a posteriori* (e.g., by hypothesis testing) (22).

[2] *N.B.* To use Eq. [1] to estimate a cubic function of the diffusion tensor elements is more complicated but proceeds in the same way.

CONCLUSIONS

By exploiting properties of the b matrix and by using linear algebraic reasoning, we show that the minimum number of DWIs required to produce an anisotropically weighted MRI is seven for the simplest admissible diffusion anisotropy measures. Clearly, "single-shot" anisotropically weighted MRI is an impossibility. These findings are quite general, since they do not require specifying the functional form of the b matrix or the pulsed-gradient sequence used to produce it. Seven is also the minimum number of DWIs required to determine the entire diffusion tensor, $\underline{D}$, as well as the T_2-weighted amplitude image, $A(\underline{b} = \underline{0})$ in each voxel (8), from which one can compute Trace($\underline{D}$), the principal diffusivities, and the principal directions (which are not readily calculated from a series of specialized anisotropically weighted imaging sequences). Now, when we generate maps of admissible measures of diffusion anisotropy using seven DWIs, it is with the knowledge that we are being as efficient as possible.

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