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Experimental considerations for fast kurtosis imaging

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Abstract

Purpose—The clinical use of kurtosis imaging is impeded by long acquisitions and post-processing. Recently, estimation of mean kurtosis tensor $\bar{W}$ and mean diffusivity ($\bar{D}$) was made possible from 13 distinct DWI acquisitions (the 1-3-9 protocol) with simple post-processing. Here, we analyze the effects of noise and nonideal diffusion encoding, and propose a new correction strategy. We also present a 1-9-9 protocol with increased robustness to experimental imperfections and minimal additional scan time. This refinement does not affect computation time and also provides a fast estimate of fractional anisotropy (FA).

Methods—1-3-9/1-9-9 data are acquired in rat and human brains, and estimates of $\bar{D}$, FA, $\bar{W}$ from human brains are compared to traditional estimates from an extensive DKI data set. Simulations are used to evaluate the influence of noise and diffusion encodings deviating from the scheme, and the performance of the correction strategy. Optimal b-values are determined from simulations and data.

Results—Accuracy and precision in $\bar{D}$ and $\bar{W}$ are comparable to nonlinear least squares estimation, and is improved with the 1-9-9 protocol. The compensation strategy vastly improves parameter estimation in non-ideal data.

Conclusion—The framework offers a robust and compact method for estimating several diffusion metrics. The protocol is easily implemented.

Keywords

Diffusion; kurtosis; higher-order tensors; orientational sampling; fractional anisotropy

Introduction

Diffusion weighted MRI (DWI) is uniquely sensitive to tissue pathology and is widely used to investigate tissue microstructure. Standard clinical DWI approximates the water diffusion

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profile by a Gaussian distribution (accurate for free diffusion), when estimating the apparent diffusivity $D(\hat{n})$ along a direction $\hat{n}$, or the full diffusion tensor D (1,2). In tissue however, diffusion is generally non-gaussian. Therefore, diffusion kurtosis imaging (DKI), which improves on DWI by including the leading deviation from Gaussianity, is an increasingly popular method for analysis of DWI data. Along each direction DKI obtains apparent kurtosis, $K(\hat{n})$ in addition to $D(\hat{n})$. When $K(\hat{n})$ is estimated along many directions, various metrics can be computed: mean kurtosis (MK), kurtosis anisotropy (3,4), fractional kurtosis anisotropy (5–7), and axial and radial kurtosis (3,8,9).

Numerous reports find DKI to be a valuable supplement to standard DWI. In stroked animals, MK improved infarct visualization over mean diffusivity $\bar{D}$ (10), and informed early assessment of stroke due to different time-course than $\bar{D}$ (11,12). In (13), histology supported DKI's enhanced sensitivity compared to DTI in detecting stroke-induced microstructural changes in gray matter (GM) and white matter (WM). Elevated MK was reported in stroke patients in (14–17). MK's reflection of cellular changes was also seen in traumatic brain injury (TBI) (18,19) with early increases in FA (fractional anisotropy) and MK. When $\bar{D}$ and FA had normalized, hyper-normal MK persisted and was associated with increased reactive astrogliosis identified by immunohistochemistry (c.f. review in (20)). MK may hold value for other neurological diseases, e.g. epilepsy (21), attention deficit hyperactivity disorder (22), chronic mild stress (23,24), gliomas (25,26), Parkinson's disease (27,28), multiple sclerosis (29), and for the study of brain maturation (30,31). In summary, the literature suggests that DKI is a sensitive, albeit unspecific, microstructural biomarker (32) of clinical value, improving sensitivity to microstructural features resolvable with MR microscopy (33–36).

Clinically, DWI is typically used alongside other MRI techniques leading to comprehensive examination protocols. A key challenge for DKI, therefore, is to collect the required data in a clinically feasible time - for acute MRI, mere minutes. Often, DKI data analysis estimates both the diffusion tensor, D , and the rank-4 kurtosis tensor, W , corresponding to a total of 22 free parameters. This requires a substantial amount of data: hence, a typical DKI protocol acquires 30 uniformly distributed directions at 3–6 b-values from 0–3 ms/ μm^2 (4,37). Thus, neither scan time nor computational load is negligible, limiting exploration and clinical use of DKI.

Recently, we formulated an apparent mean kurtosis with a direct relation to the diffusion signal and the kurtosis tensor (6,38). In this framework MK is the average over all directions of the kurtosis *tensor*, W , and we will refer to this MK variant as the mean (of the) kurtosis tensor, MKT, or $\bar{W}$. Our analysis of data from human and animal brain demonstrated strong similarity of $\bar{W}$ and MK, which was also reported in (7). We further showed that $\bar{W}$ is simply related to W through its trace. This allowed a rotationally invariant way of estimating $\bar{W}$ from 13 images: 1 at $b=0$, 3 at $b_1=1$ ms/ μm^2 and 9 at $b_2=2.5$ ms/ μm^2 acquired using well-defined directions. We termed this the 1-3-9 scheme. Recently, 1-3-9 estimates of diffusion and kurtosis lesion size and severity were found to agree very well with conventional DKI in acute stroke in rats (39). Recent clinical findings show the method's utility in glioma patients (40).

The 1-3-9 scheme rests on a number of approximations. These include exact realization of the prescribed directions and constant effective b-values over each shell, as well as the Gaussian description of diffusion at low b-value. Furthermore, with an estimation based on summation of a low number of log signals, there is a need to characterize the effects of Rician noise on bias and precision. Here we address all of these issues. Beginning with a determination of optimal b-values for fixed tissue and in vivo applications, we proceed by evaluating the influence of Rician noise on parameter estimation. Next, we consider errors in $\bar{W}$ and $\bar{D}$ originating from deviations in diffusion encoding from the prescribed b-values and directions. The nominal directions are typically unfulfilled in practice, e.g. due to interaction of imaging and diffusion gradients, so effective b-matrices deviate from the nominal ones in a directionally dependent manner. Even though this can be alleviated in principle, and b-matrices can be calculated accurately (even for advanced sequences (41,42)) hardware imperfections may still play a role so that actual encoding deviates from that prescribed by the protocol (43,44). The result is that the signal is probed on two “rugged b-shells”. Another source may be co-registration, necessitated by subject motion, requiring post hoc rotations of each volume’s b-matrix. We propose and demonstrate postprocessing methods to mitigate effects of b-matrix deviations on the accuracy of metric estimates. To circumvent the approximation of Gaussian diffusion, a strategy was employed already in (6) based on (45). Here the 1-3-9 protocol is extended so all nine directions are acquired at both non-zero b-values. This 1-9-9 method inherently estimates $\bar{D}$ without presuming the Gaussian approximation at the low b-value with the benefits shown in (46), and robustly estimates DKI parameters with better accuracy and precision. Moreover, the 1-9-9 scheme enables simultaneous estimation of FA in addition to $\bar{D}$ and $\bar{W}$ without fitting, and the entire diffusion tensor can be estimated with e.g. constrained linear least squares.

Theory

We first recapitulate the theoretical background of the 1-3-9 method leading naturally to the derivation of the 1-9-9 scheme. A method to compensate for b-matrix imperfections is then introduced based on the 1-9-9 scheme.

In the DKI formulation, the signal reads (8):

$$\log S(b, \hat{n}) = -bn_i n_j D_{ij} + \frac{b^2}{6} n_i n_j n_k n_l \bar{D}^2 W_{ijkl} + O(b^3) = -bD(\hat{n}) + \frac{b^2}{6} \bar{D}^2 W(\hat{n}) + O(b^3), \quad (1)$$

where b is the diffusion weighting applied along $\hat{n} = (n_x, n_y, n_z)$ and subscripts label Cartesian components (e.g. $i = x, y, z$). The kurtosis tensor W_{ijkl} is defined as in (8), $\bar{W}$ is its average over all directions (S_2 is the sphere):

$$\overline{W} = \frac{1}{4\pi} \int_{S_2} d\hat{n} W(\hat{n}) = \frac{1}{5} W_{ijkl} \mathbb{I}_{ijkl} = \frac{1}{5} (W_{xxxx} + W_{yyyy} + W_{zzzz} + 2W_{xxyy} + 2W_{xxzz} + 2W_{yyzz}) \equiv \frac{1}{5} \text{Tr}(W)$$

(2)

Here $\mathbb{I}$ is the fully symmetric isotropic tensor (47), and Tr is the trace. On this basis it was shown that $\overline{W}$ may be obtained from $W(\hat{n})$ along nine distinct directions, $\hat{n}^{(i)}$, $\hat{n}^{(i+)}$ and $\hat{n}^{(i-)}$ ($i=1,2,3$)(6,38):

$$\frac{1}{15} \left(\sum_{i=1}^3 \log S(b, \hat{n}^{(i)}) + 2 \sum_{i=1}^3 \log S(b, \hat{n}^{(i+)}) + 2 \sum_{i=1}^3 \log S(b, \hat{n}^{(i-)}) \right) = -b\overline{D} + \frac{1}{6} b^2 \overline{D}^2 \overline{W} \quad (3)$$

The nine directions are given explicitly as normalized vectors in the Supporting Materials (SM), (Supporting Table 1). In this manner the 1-3-9 method estimates $\overline{W}$ from one $b=0$ ms/ μm^2 image, three images at low $b_1 \sim 1$ ms/ μm^2 and the nine prescribed directions at $b_2 \sim 2.5$ ms/ μm^2 . Using three orthogonal b_1 directions also included in the b_2 shell allows a good estimation of $\overline{D}$ (45). Then Eq. (3) yields $\overline{W}$ from the nine directions acquired at b_2 . If instead all nine directions are acquired at b_1 and b_2 , one can use Eq. (3) to form a set of two equations with unknowns $\overline{D}$ and $\overline{W}$:

$$A_1 \equiv \frac{1}{15} \left(\sum_{i=1}^3 \log S(b_1, \hat{n}^{(i)}) + 2 \sum_{i=1}^3 \log S(b_1, \hat{n}^{(i+)}) + 2 \sum_{i=1}^3 \log S(b_1, \hat{n}^{(i-)}) \right) = -b_1 \overline{D} + \frac{1}{6} b_1^2 \overline{D}^2 \overline{W}$$

(4)

$$A_2 \equiv \frac{1}{15} \left(\sum_{i=1}^3 \log S(b_2, \hat{n}^{(i)}) + 2 \sum_{i=1}^3 \log S(b_2, \hat{n}^{(i+)}) + 2 \sum_{i=1}^3 \log S(b_2, \hat{n}^{(i-)}) \right) = -b_2 \overline{D} + \frac{1}{6} b_2^2 \overline{D}^2 \overline{W}$$

and obtain estimates for $\overline{D}$:

$$\overline{D}_{199} = (b_1^2 A_2 - b_2^2 A_1) / (b_1 b_2^2 - b_1^2 b_2) \quad (5)$$

and for $\overline{W}$:

$$\overline{W}_{199} = 6b_1 b_2 (A_1 b_2 - A_2 b_1) (b_1 - b_2) / (A_1 b_2^2 - A_2 b_1^2)^2 \quad (6)$$

Because the 1-9-9 method uses more data and accounts for the kurtosis at lower b-values, it could be expected to be more robust than 1-3-9. Eqs. (5) and (6) enable a straightforward numerical analysis of the dependence on b-values and SNR, and will be used to estimate optimal b-values (see Methods). Throughout SNR is calculated as the mean signal in a homogenous region in the object imaged divided by the standard deviation of the signal in a background region, corrected for Rayleigh distribution in a standard manner.

The 1-9-9 strategy yields $D(\hat{n})$ and $W(\hat{n})$ along nine directions, which is sufficient to estimate FA without fitting. The log-signal with diffusion weighting b along a direction $\hat{n}$ is:

$$\ln S(b, \hat{n}) = -bD(\hat{n}) + \frac{1}{6}b^2D(\hat{n})^2K(\hat{n}) \equiv L(\hat{n}, b) \quad (7)$$

where $W(\hat{n}_j) = K(\hat{n}_j)D(\hat{n}_j)^2/\bar{D}^2$. With measurements at two different b-values, b_1 and b_2 , we find

$$D(\hat{n}_j) = (b_1^2 L(\hat{n}_j, b_2) - b_2^2 L(\hat{n}_j, b_1)) / (b_1 b_2^2 - b_1^2 b_2) \quad (8)$$

and

$$W(\hat{n}_j) = 6 \frac{D(\hat{n}_j)^2}{\bar{D}^2} b_1 b_2 (L(\hat{n}_j, b_1) b_2 - L(\hat{n}_j, b_2) b_1) (b_1 - b_2) / (L(\hat{n}_j, b_1) b_2^2 - L(\hat{n}_j, b_2) b_1^2)^2 \quad (9)$$

The fractional anisotropy (FA) (48) is defined as:

$$FA = \sqrt{\frac{3}{2} \frac{(\lambda_1 - \bar{\lambda})^2 + (\lambda_2 - \bar{\lambda})^2 + (\lambda_3 - \bar{\lambda})^2}{\lambda_1^2 + \lambda_2^2 + \lambda_3^2}} = \sqrt{\frac{3}{2} \frac{\text{std}(\lambda)}{\text{rms}(\lambda)}} \quad (10)$$

where λ_i are eigenvalues of D, overbar denotes averaging, and std and rms abbreviate standard deviation and root mean square, respectively. An FA estimate is obtained from the variance (var) of $D(\hat{n})$ over the 9 sampling directions:

$$FA_{199} = \sqrt{\frac{3}{2} \frac{\text{var}(D(\hat{n}))}{\text{var}(D(\hat{n})) + 6/15 \bar{D}^2}}, \quad (11)$$

which is exact in the limit where the variance is over all directions on the sphere, and hence FA_{199} would approximate FA to arbitrary precision with increasingly complete sampling of the sphere. Setting $\bar{D} = \bar{D}_{199}$ from Eq. (5) keeps the method self-contained.

Alternatively, all elements D_{ij} of D can be estimated by the linear least squares solution of $D_{ij}n_i n_j = D(\hat{n})$ for all nine directions $\hat{n}_i$. This approach would provide all of the metrics from diffusion tensor imaging, but will not be considered in depth here. However, a comparison of the FA obtained with this method is included in the results section.

If the directions or b-values deviate from the nominal ones prescribed by the 1-9-9 protocol, the basic Eq. (3) does not hold. However, if we can find weights w_a ($a=1\dots9$) such that

$$\sum_{a=1}^9 w_a b_{ij}^a = \bar{b} \delta_{ij} / 3 \quad (12)$$

$$\sum_{a=1}^9 w_a b_{ij}^a b_{kl}^a = \bar{b}^2 \mathbb{I}_{ijkl} / 5$$

with $\bar{b}$ the shell-average of effective b-values and b_{ij}^a ($a = 1\dots9$) the experimental b-matrices, it is straightforward to establish the generalization of (3)

$$\sum_{a=1}^9 w_a \log S(b^a) = -\bar{b} \bar{D} + \frac{1}{6} \bar{b}^2 \bar{D}^2 \bar{W} \quad (13)$$

In practice, one cannot expect an exact solution to Eq. (12), so we approximate the weights by the least squares solution, i.e. choosing weights that minimize the squared difference between the left and right hand sides of Eq. (12). This optimization is performed independently for b_1 and b_2 . Since Eq. (12) is a linear system of 21 equations (one for each of the independent components of b_{ij} and $b_{ij}b_{kl}$) with 9 unknowns (w_a), the least squares solution is found effectively with standard linear routines.

Methods

Fixed rat brain data acquisition

A rat brain was fixed as in (10). Prior to imaging, one hemisphere was washed in PBS for 24 hours to improve signal by removing excess fixative. Data was acquired using a 9.4T MRI system (Bruker Biospin, Germany) equipped with a 15 mm quadrature coil using a standard DW spin echo sequence. 15 b-values (0–3 ms/ μm^2 in steps of 0.2 ms/ μm^2) were acquired along 33 gradient directions each. These directions were a combination of a 3-dimensional 24-point spherical 7-design (11) and the nine directions identified in (6). Imaging parameters were: TE=23.3 ms, TR=4 s, $\delta/\phi=4/14$ ms, 2 averages, SNR at $b=0 > 65$. Fifteen image slices were acquired at a resolution of $100 \mu\text{m} \times 100 \mu\text{m} \times 500 \mu\text{m}$.

Human MRI data

Human data was acquired in normal volunteers on a Siemens Trio 3T using a 32 channel head coil and a double spin echo DW EPI sequence. Separate data sets were acquired for b-

value optimization and for investigation of the fast parameter estimation method. Padding was used to avoid head motion during the acquisitions.

Data set A: b-value optimization

Data consisted of 1 $b=0$ image and 14 shells with 33 directions at b -values of 0.2–3.0 ms/ μm^2 . We employed the same 33 direction sampling scheme as in rat brain, except an additional 10 $b=0$ images were acquired for the analysis and to assess temporal stability of SNR. Image resolution was kept at 3 mm isotropic to provide optimal b -values relevant for typical acute imaging protocols. A total of 32 slices were acquired, with $\text{TR}=4300$ ms, $\text{TE}=103$ ms. The SNR was 51 at $b=0$ and varied approximately 5% in both GM and WM across 10 $b=0$ acquisitions.

Data protocol B: investigation of the fast protocols

Three subjects were scanned at a resolution of 2.5 mm isotropic. CSF suppression (FLAIR) was employed as recommended in (49). The DWI sampling was identical to data set A. Imaging parameters were $\text{TR} = 7200$ ms, $\text{TE} = 116$ ms, $\text{TI} = 2100$ ms, 19 consecutive slices, and all data had $\text{SNR} > 39$ at $b=0$. When showing data from protocol B we use the same subject throughout, but analysis results are reported based on whole-brain data from all three subjects.

Postprocessing

All data sets were evaluated visually for quality (artifacts and subject movement). Due to the padding around the subjects head, image registration was found to be unnecessary in all cases.

Data processing

Identical analysis was performed in human and rat brain data: Eq. (1) was fitted to the normalized data ($S(b)/S(b=0)$) from $b=0$ –3.0 ms/ μm^2 using non-linear (and unweighted) least squares fitting implemented in Matlab®. We have previously observed a low sensitivity to initial values, which were here the same for all voxels and chosen to be neutral (e.g. zero-valued Euler angles) or non-extreme physically relevant values. The fit yielded tensors $\bar{D}$ and $\bar{W}$ providing ground truth estimates of $\bar{D}$, FA, and $\bar{W}$ for comparison to the rapid protocols. A method relying on only nine encoding directions may be expected to perform differently in tissues displaying different degrees of anisotropy. Therefore, our analysis investigates performance in areas of low anisotropy (mostly GM) and high anisotropy (WM). The low anisotropy range was $0.1 < \text{FA} < 0.3$, corresponding to FA for GM in FLAIR data (50). The high anisotropy region was defined by $0.6 < \text{FA} < 1$ corresponding to regions of uniformly ordered WM. In the 1-9-9 analysis, we calculated the metrics using Eqs. (5), (6), (11) with b -values $b_1 = 1$ ms/ μm^2 and $b_2 = 2.4$ ms/ μm^2 .

b-value optimization

In mapping the optimal b -value pair, $\bar{D}_{199}$ and $\bar{W}_{199}$ was calculated from all combinations of b_1 and b_2 in data set A. Parameter estimates at each b -value pair were compared to true values and the absolute %-error on each parameter summed over the entire image plane. A

penalty term of 20 %-points was added for each pixel where no estimate was obtainable (producing NaNs or Infs in matlab) with the 1-9-9 method. This served as a way to take into account overall quality of the parameter map. This was performed on both human data set A and the fixed rat brain data.

Numerical optimization of b-values

For numerical estimation of optimal b-values we use numerically generated 1-9-9 signals: for each b_1, b_2 combination, the voxel signal S is computed using Eq. (7). We use as input DTI and DKI tensors obtained from the fit of Eq. (1) to the human data set. Subsequently Gaussian noise with an SNR=51 as in the experiments (data set A), was added to the real and imaginary channels, the modulus operation applied, and estimates of $\bar{D}$ and $\bar{W}$ obtained using Eqs. (5) and (6). This operation is repeated 500 times, and mean absolute error as well as variance over noise realizations is determined and averaged over 100 voxels selected randomly from brain tissue on a single slice. The entire procedure is repeated on a 60×60 grid of values of (b_1, b_2) .

Simulations of the robustness of the 1-3-9 and 1-9-9 methods to experimental inaccuracies

The ground truth tensors from one slice of a data set acquired with protocol B were used as input to the DKI model to generate 1-3-9 and 1-9-9 data sets with varying degrees of Rician noise and b-matrix perturbations.

In a first set of simulations, Rician noise propagation was investigated in one typical WM and one typical GM voxel. After generating the signal from the ground truth D and W , various levels of complex Gaussian noise was added before the modulus operation. Subsequently, the average accuracy and precision of diffusion and kurtosis metrics were assessed using 500 noise realizations. For comparison, estimation with nonlinear least squares (NLS) was also applied to signals generated from five b-values from 0 to $2.5 \mu\text{m}^2/\text{ms}$ and 30 directions.

In a second set of simulations, the consequences of imperfect diffusion encoding on the rapid diffusion and kurtosis estimates were investigated. 150 pixels were chosen randomly in each tissue type, and from the underlying ground truth tensors, 1-3-9/1-9-9 diffusion signal sets were generated with varying degrees of deviation from the ideal experiment. First, gradient directions alone were allowed to deviate from the nominal directions. A range of deviations from $0-10^\circ$ were simulated with 50 random phases for each direction and each deviation level. The absolute %-error from ground truth in 1-3-9 and 1-9-9 estimates was calculated for each realization and averaged over phases. The mean absolute error was then calculated over pixels. To address b-value errors, a similar simulation was performed with unperturbed directions and b-value deviations that varied randomly between the nine directions producing non-spherical ("rugged") b-value shells. Here, b-value deviation for each direction was coupled between the high and low b-value to mimic gradient hardware performance. Fifty realizations of each noise level was performed. We also evaluated the absolute %-error in the presence of both directional deviation and b-value variation. In all of these simulations, we also evaluated the efficiency of the weighted average method

described in the theory section in correcting non-ideal b-matrices. The correction scheme was implemented in Matlab using the function `lsqlin`.

Results

Investigation of optimal b-value combination

Simulation results of the sum of mean absolute error in estimates of $\bar{D}$ and $\bar{W}$ is shown in Fig. 1A. As expected, a high error ridge exists along the $b_1=b_2$ diagonal, but an extended region centred at (0.7,2.3) ms/ μm^2 has a sum of errors below 3%. The average variability (precision) in this region is about 10%, but this drops to about 4% when 10 outlier pixels are removed. The experimental b-value optimization spans a smaller b-value range and indicates the lower b-value to be larger than 1 ms/ μm^2 , but otherwise shows similar qualitative behaviors with some outliers present (Fig. 1B). The error maps suggest that many b-value combinations produce reasonable estimates. Evidently, $b_1 = 1$ ms/ μm^2 produces good estimates over an extended range of b_2 values, and this is also common choice for routine estimation of $\bar{D}$. Hence we use this value in the following, and recommend a b_2 larger than 2.4 ms/ μm^2 .

Comparing $\bar{W}$ from data set A to $\bar{W}_{139}$ and $\bar{W}_{199}$ at these optimal b-values shows the fast estimates to be virtually identical and with equally strong linear correlation to $\bar{W}$ (0.8 for both methods in data set A and 0.97 for both methods in the smoothed data used in (6)). We therefore recommend these b-values for both the 1-3-9 and the 1-9-9 methods. Optimization on fixed rat brain data yielded ideal b-values $b_1, b_2 = 0.8\text{--}1.0$ ms/ μm^2 , 2.4–2.6 ms/ μm^2 . Parameter estimates from a fit to the full rat brain data set are compared to 1-3-9 and 1-9-9 estimates at these b-values in Supporting materials Figs 1–3. The 20 %-point penalty for lost pixels used in our optimization was applied in only 1% of the pixels at the optimal b-value combination.

Robustness of parameter estimation

Figure 2 illustrates precision and accuracy in the fast protocol estimates of $\bar{D}$ and $\bar{W}$. Two sets of ground truth inputs are used: in the upper row (A, B), a typical WM voxel corresponding to $\bar{D} = 0.74$ $\mu\text{m}^2/\text{ms}$, $\bar{W} = 1.12$ FA=0.72, and in the lower row (C, D), a typical GM voxel with $\bar{D} = 0.86$ $\mu\text{m}^2/\text{ms}$, $\bar{W} = 0.5$ FA=0.04. Both estimates of $\bar{D}$ (A, C) have a low bias for all SNR values and perform quite comparably to NLS. Above an SNR of 20, $\bar{D}_{139}$ is relatively robust and typically deviates less than ~10%. However, $\bar{D}_{199}$ estimates are substantially more precise than the $\bar{D}_{139}$ estimates and remain below 5% for SNR > 20, and the NLS are even more precise. The performance in terms of bias and precision is relatively similar in GM and WM. Both fast estimates of $\bar{W}$ (B, D) tend to underestimate mean kurtosis, and the 1-3-9 scheme markedly more so than the 1-9-9 scheme, but in both cases this bias tends rapidly toward zero with increasing SNR: for 1-9-9, it is less than 5% when SNR is larger than 20. The bias of NLS is slightly larger than 1-9-9, and has an opposite sign. Regarding precision, the 1-9-9 scheme for kurtosis estimation is comparable to NLS and also vastly outperforms the 1-3-9 scheme with a precision better than 4% for WM when SNR>20. For low kurtosis values, such as in the GM voxel for the lower row of Fig. 2, the

relative precision becomes poorer, and drops below 5% for both NLS and 1-9-9 only when the SNR surpasses 40.

Figure 3 shows the effects of imperfect diffusion directions on the estimates of $\bar{D}$ and $\bar{W}$ in GM (panels A and B) and WM (C and D). As expected, the deviation from ideal estimates is a steadily increasing function of deviation in diffusion directions. However, the overall magnitude of the error in the estimations is quite small in all cases, except for a maximum of about 25%, attained in the case of 1-3-9 estimation of $\bar{W}$ in WM (Fig. 3D) for an angular deviation of about 10°. Note that the deviation of the 1-9-9 estimates are consistently well below the 1-3-9 estimates, indicating that the 1-9-9 scheme is more robust. Estimating $\bar{D}$ in GM (Fig. 3A) with either scheme is the least sensitive to imperfect directions, followed by $\bar{D}$ in WM (Fig. 3C), $\bar{W}$ in GM (Fig. 3B), and $\bar{W}$ in WM (Fig. 3D). The effects of applying the correction scheme are also shown for all parameters except $\bar{D}_{139}$ where the correction method does not apply as it requires two nine direction shells to be present for correction of the $\bar{D}$ estimate. For $\bar{D}_{199}$ the correction scheme reduces the estimation error to less than 1% in both GM and WM (Fig. 3A and C). As an extreme case, combining 1-9-9 with the compensation strategy improves estimation of $\bar{D}$ by a factor of 20 in WM (Fig. 3C), and the estimate of $\bar{W}$ by more than a factor of two in WM (Fig. 3D), compared to the 1-3-9 scheme without compensation. In the case of $\bar{W}$, the correction scheme is seen to improve the estimates in WM (Fig. 3D) but the effect is negligible or even negative in GM (Fig. 3B).

Figure 4 evaluates the influence of b-values varying across directions. Estimation errors monotonically increase to a maximum of about 20% for $\bar{W}$ in GM (Fig. 4B). This time, the deviations for $\bar{D}$ in GM (Fig. 4A) and WM (Fig. 4C) are the smallest, followed by $\bar{W}$ in WM (Fig. 4D), and maximum for $\bar{W}$ in GM (Fig. 4B). Again, the 1-9-9 scheme consistently outperforms the 1-3-9 scheme. The combination of 1-9-9 and the correction scheme improves estimation substantially, reaching a factor of >10 for $\bar{D}$ (Fig. 4A) and ~5 for $\bar{W}$ in GM (Fig. 4B). The compensation is most effective in the case of the 1-9-9 scheme, where the error drops below 4% in all cases. The graphs also demonstrate the positive effect of using the shell-average of the varying b-values in the 1-3-9 estimation of $\bar{D}$ (Fig. 4A and C). When both b-values and diffusion directions depart from the nominal values, the deviations in the estimates are conveniently shown as color maps with the b-value deviations and angular deviations indicated along the horizontal and vertical axis, respectively. Figures 5 and 6 show the effects on $\bar{W}_{139}$ and $\bar{W}_{199}$ in GM and WM, respectively. The top rows (A, B) show the uncorrected estimates and the bottom rows (C, D) show the effect of the correction scheme. In both tissues, one readily appreciates the increased robustness of the 1-9-9 protocol compared to the 1-3-9 protocol. Even so, the influence of imperfections in the diffusion encoding on the estimated metrics can be just over 14% in $\bar{W}_{139}$ in both GM and WM (Fig. 5A and 6A)). The most robust estimate is $\bar{W}_{199}$ in WM (Fig. 6B), which stays below 10%. In GM (Fig. 5), the influence of angular deviations is seen to be weaker than the influence of b-value deviations, which could be expected due to the more isotropic nature of GM. Indeed, the behavior is different in WM where angular deviations are more important than b-value deviations for $\bar{W}_{139}$ (Fig. 6A).

Panels C and D of Figs. 5 and 6 show the effect of applying the compensation scheme before estimation of $\bar{W}$. This generally decreases the estimation errors, with the most significant

effect on $\bar{W}_{199}$ in GM (Fig. 5B and D) where the maximum error is almost halved and the sensitivity to b-value deviation is reduced and for GM almost completely removed. Results from identical simulations based on the data from fixed rat brain are provided in SM (Supporting Figs 4–7). The same overall behavior is found.

Figure 7 is similar to Figs. 5 and 6, but considers in detail a high FA region in the corpus callosum (average FA = 0.8). Here the influence of b-value and direction errors are of almost equal strength (Fig. 7A) and quite significant. Even in this case, the compensation strategy manages to improve the estimates (Fig. 7B) and substantially increases the window with low error estimates.

Evaluation of the 1-9-9 method

Figure 8 compares ground truth values from protocol B to the 1-3-9 and 1-9-9 estimates of $\bar{D}$ (Fig. 8A–C) and $\bar{W}$ (Fig. 8D–F) in a representative slice. Note that the $\bar{D}_{199}$ map (Fig. 8C) is slightly more noisy than $\bar{D}$ (Fig. 8A), and $\bar{D}_{139}$ (Fig. 8B) noisier still. A similar tendency is noticeable in the $\bar{W}$ estimates. The scatter plots in Fig. 9 show the correlations between the estimates shown in Fig. 8. The linear correlation coefficients for $\bar{D}$ and $\bar{W}$ from 1-3-9 are 0.94 (Fig. 9A), 0.79 (Fig. 9C) and for 1-9-9, 0.96 (Fig. 9B) and 0.83 (Fig. 9D), confirming that the association to the full estimates are stronger with the 1-9-9 protocol. For whole brain the correlations for this subject for $\bar{D}$ and $\bar{W}$ from 1-3-9 are 0.84 and 0.71, and for 1-9-9, 0.86 and 0.75. Over all three subjects the whole brain correlations are: for $\bar{D}_{139}$ 0.84+/-0.02, for $\bar{D}_{199}$ 0.87+/-0.02, for $\bar{W}_{139}$ 0.67+/-0.04, and for $\bar{W}_{199}$ 0.72+/-0.03. The SM provides more information, including whole brain maps of full estimates, 1-3-9 estimates, and 1-9-9 estimates and their correlation in three subjects (Supporting Figs. 8,12,16 ($\bar{D}$) and 10,14,18 ($\bar{W}$), panels A–C in each).

The supplementary parameter maps show that all three estimations fail to produce credible parameter values in some pixels. In the subject shown throughout the manuscript we find that this loss is largest for the 1-3-9 method (5.2%), while the loss of pixels is significantly lower for the 1-9-9 method (3.5%), which is very similar to the loss seen in the fit (3%). All percentages are for whole brain. This trend is consistent in all three subjects.

Evaluation of the 1-9-9 estimate of FA

Figure 10 compares an FA map (Fig. 10A) to the FA₁₉₉ (Fig. 10B) map. The contrast is qualitatively quite similar in the two maps, but the FA₁₉₉ map presents as somewhat more noisy. Moreover, it tends to overestimate FA, especially in GM, resulting in less overall contrast. These observations are supported by the scatterplot shown in Fig. 10C, which nevertheless correspond to a linear correlation coefficient of 0.83 (0.81 for whole-brain for this subject and on average 0.77+/- 0.04 for whole brain across the three subjects). Using linear least squares to estimate D from the 1-9-9 data yields a slightly better estimate of FA with a correlation coefficient of 0.85 when compared to true FA (data not shown).

Discussion

We extended the 1-3-9 fast kurtosis imaging protocol (6) by acquiring all nine diffusion directions at both nonzero b-values. This 1-9-9 method allowed fast estimation of $\bar{D}$, FA, and

$\bar{W}$ from 19 DWIs. We compared the performance of the fast protocols to nonlinear least squares, and characterized the impact of a number of practical factors on the accuracy of 1-3-9 and 1-9-9 estimates, specifically departures of b-values and diffusion directions from nominal directions. These effects are unavoidable or even quite typical in experiments. We devised a practical and straightforward procedure to compensate for some of these imperfections, and performed a b-value optimization on both fixed rat brain and normal human brain.

We examined the b-value dependency of parameter fidelity using experimental data and numerical simulations. The data-based b-value optimization was performed on data where no registration or smoothing was employed. This is important for online reconstruction in acute settings where preprocessing is unfeasible. The analysis showed behavior in qualitative agreement with predictions by simulations using realistic noise characteristics and levels. The error was low over an extended b-value range, and a good b-value combination for the 1-9-9 scheme in vivo is $b_1 = 1 \text{ ms}/\mu\text{m}^2$ and $b_2 \approx 2.5 \text{ ms}/\mu\text{m}^2$, but also that precise selection of these two b-values was not critical. The selected minimum is a realistic choice considering gradient performance available on most systems, and enables a reasonably low TE and sufficient SNR. These values also agree with typical recommendations, so that $b_1 = 1 \text{ ms}/\mu\text{m}^2$ ensures $b\bar{D} \approx 1$ and $b_1^2 \bar{D}^2 \bar{W} \approx 1$ in most areas, while $b_2 = 2.5 \text{ ms}/\mu\text{m}^2$ corresponds to $b_2^2 \bar{D}^2 \bar{W} \approx 1$ in areas of low $\bar{W}$ (e.g. GM). The $\bar{W}$ estimates produced by the 1-3-9 and 1-9-9 methods at these b-values were found to be nearly identical, and so the b-value recommendation extends to the 1-3-9 method (11). Note that if a substantially different gradient profile (e.g. diffusion time) is used, the underlying “true” diffusion and kurtosis tensors may be different. This in turn will imply that the optimal b-values could be different. However, we believe this will have only a minor effect on our results due to the slow variation of the error as function of b-values, and since diffusion parameters are not likely to show a strong diffusion time dependence in the most commonly probed regimes.

In fixed rat brain an optimal b-value range of $b_1 = 0.8\text{--}1 \text{ ms}/\mu\text{m}^2$, $b_2 = 2.4\text{--}2.6 \text{ ms}/\mu\text{m}^2$ was found. Considering lower diffusivity in fixed tissue it was surprising to find similar optimal b-values. This might be due to the interplay of shorter restriction distances in fixed rat brain and differences in sequence timing between pre-clinical and clinical MR-systems. Further work is needed to elucidate this. In simulations of scheme robustness and effectiveness of the compensation strategy based on rat data, the same overall behavior was observed but effect sizes were different. This is not surprising considering the different characteristic structural length scales and measurement conditions available in microimaging experiments.

The 1-9-9 method was shown to offer improved robustness against non-optimal experimental conditions compared to the originally proposed 1-3-9 method (6). This was observed in numerical simulations of the effects of Rician noise, and of angular deviations in diffusion directions and b-value inaccuracies alone and in combination.

With Rician noise present, the accuracy and precision with ideal diffusion encoding was already quite high for both protocols, and the 199 protocol performed as good or better than the NLS estimation in terms of $\bar{W}$ estimation. This is remarkable as the NLS method

employed substantially more data and required advanced and time-consuming postprocessing. For $\bar{D}$ estimation, the NLS estimator was more precise, but the 1-9-9 $\bar{D}$ estimate is comparable to the NLS estimate in terms of bias.

The performance of all three estimation strategies applied will be affected by low SNR. This was also observed in our analysis where fewer pixels produced unrealistic $\bar{W}$ values (defined here as outside of the 0–4 range) in the b-value optimization based on lower resolution data (higher SNR) than in the evaluation of 1-9-9 based on the higher resolution (lower SNR) protocol B. In all cases the 1-9-9 estimation was more robust than 1-3-9 and had pixel loss close to or comparable to the loss seen in the fit. We again note that our analysis is performed on data where no preprocessing has been applied, and the examples should therefore be taken as a raw performance demonstration. The number of pixels lost in the analysis will possibly be reduced by preprocessing strategies. Our analysis of the improvements offered by the 1-9-9 strategy over 1-3-9 do not in general indicate improvements to be limited to particular brain regions, although a slight improvement in problematic deep structures is seen (SM Figs. 8 and 10, panels D–F).

In large studies, data preprocessing (image registration, eddy current compensation etc) is standard. Based on registration results from FSL (51) in seven patients with substantial head motion, we found that no image plane was rotated more than 3°. This is well within the region where the 1-9-9 method is stable to directional deviations and therefore in principle, the analysis could be performed on the registered data directly with estimation errors on the level of noise induced errors.

For more severe cases a compensation strategy using redistribution of directional weights in parameter calculation was demonstrated. Implementation of the correction scheme is straightforward when effective b-matrices are known. When only effective b-values are known, using shell-averaged b-values in the analysis already improves parameter estimates (only shown for $\bar{D}_{139}$). Although the deteriorating effects of inaccurate encoding were not large to begin with, the compensation strategy offered substantial relative improvement.

FA estimation was also demonstrated with the 1-9-9 protocol, and displayed high correlation with true FA, although a slight systematic overestimation was observed. This likely stems from the method's low number of diffusion directions compared to the recommendations for state-of-the-art diffusion tensor estimation (49). Nevertheless, when time is a concern, the FA_{199} estimate is a reasonable estimate, obtained in addition to robust estimates of $\bar{D}$ and $\bar{W}$. Even the full diffusion tensor, D , could be obtained with linear least squares, facilitating maps of radial and axial diffusivities, and direction encoded color (DEC) FA (52). To increase the robustness of these estimates, including FA, more directions could be acquired with an accompanying increase in scan time but negligible effect on postprocessing time.

Since the 1-9-9 method uses data from a standard diffusion sequence, it is readily implemented. It may be simpler to implement than the 1-3-9 method, since 1-9-9 requires the same encoding directions for both non-zero b-values, which most platforms assume when specifying gradient tables. Like 1-3-9, 1-9-9 post-processing does not require fitting procedures and all post-processing can therefore be implemented on the scanner. Both fast

methods have been implemented for Siemens systems with online post-processing by one of the authors (JF), and are available as c2p. In principle, both schemes could be incorporated in single shot multiecho sequences, with b-values and directions encoded in different echo pathways, c.f. the recent MEDITATE framework (53). Likewise, the correction strategy suggested here for nonideal diffusion weighting could also be useful for such sequences, as well as isotropic diffusion weighting schemes (54).

While recent advances in simultaneous multi-slice EPI (55) give access to 2–10 fold reduction of acquisition times, reconstruction is still time consuming on all but the newest generation of reconstruction computers. Our technique can easily, and without loss, be combined with simultaneous multi-slice EPI resulting in further acceleration. These gains in speed can be traded for SNR or higher resolution and allow for improved data quality through the use of e.g. cardiac gating, navigator echoes, CSF nulling, blip up/down EPI, and readout segmented EPI.

In conclusion, the 1-9-9 estimates of $\bar{D}$, FA, and $\bar{W}$ correlate strongly with their true values. Accuracy and precision is better than for 1-3-9 and comparable to advanced estimations based on larger data sets. Scanner implementations of 1-9-9 with online post-processing enable simultaneous, real-time estimation of the three metrics. This might be useful when scan time is a constraint, particularly in the acute setting.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Fig. 1.

Panel A (B) shows simulation results of the mean absolute error on estimation of $\bar{D}$ and $\bar{W}$ as function of b_1 and b_2 in the 1-9-9 scheme. Two outlier pixels dominating the mean were removed. In panel C, combined experimental error (absolute %-error) on estimates of $\bar{D}$ and $\bar{W}$ using the 1-9-9 protocol compared to the values from a fit to a large data set. The minimum error occurs at high values for b_2 but similar minima are present at lower b -values.

Fig. 2. Precision and bias for the fast estimates of 1-3-9 (red) and 1-9-9 (green) estimates of $\bar{D}$ (A,C) and $\bar{W}$ (B,D) quantified by standard deviation (filled area) and mean values (markers) over 500 noise realizations. For comparison, nonlinear least squares (blue) are shown also. The top row (A, B) corresponds to a WM voxel with ground truth values $\bar{D}=0.74 \mu\text{m}^2/\text{ms}$, $\bar{W}=1.12 \text{ FA}=0.72$, and in lower row (C, D) to a GM voxel with ground truth values $\bar{D}=0.86 \mu\text{m}^2/\text{ms}$, $\bar{W}=0.5 \text{ FA}=0.04$.

Fig. 3.

Comparison of robustness to angular inaccuracy in the 1-3-9 and 1-9-9 estimates of $\bar{D}$ and $\bar{W}$. The effect on $\bar{D}$ estimation in gray matter is shown in panel A and in white matter in panel C. The effect on $\bar{W}$ estimation in gray matter is shown in panel B and in white matter in panel D.

Fig. 4.

Evaluation of the effect of b-value deviations among true directions on parameter estimates. The graphs also show the effect of using the correction scheme in the estimation of $\bar{D}$ and $\bar{W}$ in gray (A and B, respectively) and white matter (C and D) as well as the effect of using the mean b-values in the estimation of $\bar{D}_{139}$ (A and C).

Fig. 5.

Simulation results from 75 random pixels of GM. The combined effect of rugged b-value shells and angular deviations in 1-3-9 (A) and 1-9-9 (B) are mapped. The bottom row shows the effect of using the correction scheme in 1-3-9 (C) and 1-9-9 (D). See the methods section for simulation details.

Fig. 6.

Simulation results from 75 random pixels of WM. The maps show the combined effect of rugged b-value shells and angular deviations in 1-3-9 (A) and 1-9-9 (B). The bottom row shows the effect of the correction scheme in 1-3-9 (C) and 1-9-9 (D). See the methods section for simulation details.

Fig. 7.

Correction example in high FA region (Corpus callosum, average FA in ROI=0.8). Panel A shows the effect without correction. In B the correction scheme is seen to extend the low error region to include even large deviations in both b and angles.

Fig. 8. Parameter maps of $\bar{D}$ (A) and $\bar{W}$ (D) obtained from tensor model fit to the full data set. The corresponding estimates obtained with the 1-3-9 method are seen in B and E, respectively. The 1-9-9 estimates are shown in C and F. Note that the 1-9-9 estimates generally appear less noisy. This is also seen in a similar comparison based on the rat brain data (see SM).

Fig. 9.

Scatterplots comparing the 1-3-9 and 1-9-9 estimates to the true parameter values. The plots correspond to the maps shown in fig 1. The insets in the $\bar{D}$ correlation plots (A and B) show the entire range of values, whereas the main graphs focus on the densest part of the data cloud. The linear correlation coefficients for $\bar{D}$ (A) and $\bar{W}$ (C) from 1-3-9 are 0.94, 0.76 and for 1-9-9 0.96 (B) and 0.81 (D). In each plot the red line is the identity line.

Fig. 10.

Figures of true FA (A), FA from the 1-9-9 method (B) and a scatterplot showing the correlation between the two (C). The red line is the identity line. The fast estimate is seen to generally overestimate FA. This effect is largest for low FA regions causing some loss of contrast in the FA map obtained by 1-9-9. The linear correlation coefficient is 0.83.