Weighted linear least squares estimation of diffusion MRI parameters: Strengths, limitations, and pitfalls

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Purpose: Linear least squares estimators are widely used in diffusion MRI for the estimation of diffusion parameters. Although adding proper weights is necessary to increase the precision of these linear estimators, there is no consensus on how to practically define them. In this study, the impact of the commonly used weighting strategies on the accuracy and precision of linear diffusion parameter estimators is evaluated and compared with the nonlinear least squares estimation approach.

Methods: Simulation and real data experiments were done to study the performance of the weighted linear least squares estimators with weights defined by (a) the squares of the respective noisy diffusion-weighted signals; and (b) the squares of the predicted signals, which are reconstructed from a previous estimate of the diffusion model parameters.

Results: The negative effect of weighting strategy (a) on the accuracy of the estimator was surprisingly high. Multi-step weighting strategies yield better performance and, in some cases, even outperformed the nonlinear least squares estimator.

Conclusion: If proper weighting strategies are applied, the weighted linear least squares approach shows high performance characteristics in terms of accuracy/precision and may even be preferred over nonlinear estimation methods.

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Introduction

Diffusion magnetic resonance imaging (dMRI) is currently the only method for the in vivo and non-invasive quantification of water diffusion in biological tissue (Le Bihan and Johansen-Berg, 2012). Several diffusion models have been proposed to obtain quantitative diffusion measures, which could provide novel information on the structural and organizational features of biological tissues, the brain white matter (WM) in particular. Typical examples of such diffusion models are diffusion tensor imaging (DTI; Basser et al., 1994a) and diffusion kurtosis imaging (DKI; Jensen et al., 2005; Veraart et al., 2011a). Both diffusion models have in common that they can be linearized by the natural log-transformation for computing the model parameters. Despite the overwhelming literature on advanced diffusion (kurtosis) tensor estimation (e.g., Andersson, 2008; Jones and Basser, 2004; Koay et al., 2009; Kristoffersen, 2007, 2011; Landman et al., 2007a; Veraart et al., 2011b, 2012), the class of linear least squares (LLS) estimators is still widely used in diffusion MRI due to its low computational cost and ease of use.

It is well recognized that the variance of a log-transformed diffusion-weighted (DW) signal depends on the signal itself (Basser et al., 1994b; Koay et al., 2006; Salvador et al., 2005). Given the signal-dependency of their variances, a set of log-transformed DW signals is heteroscedastic. Consequently, a weighted linear least squares (WLLS) approach with well-defined weights, i.e. the inverse of the log-transformed signals’ variances, is expected to provide more precise diffusion parameter estimates, at least, compared to its unweighted linear alternative. Indeed, Optimal performance of the linear estimators can only be achieved if the variance of the log-transformed MR signals is known. Salvador et al. (2005) showed that this variance is a function of the noise-free signal if the magnitude MR data is Rice distributed. Obviously, the noise-free signals are not known and, as such, the weight terms need to be estimated. Different ways to approximate the theoretically optimal weights have been suggested (Koay et al., 2006; Basser et al., 1994b; Salvador et al., 2005) and adopted by the community. A consensus on how to use the WLLS in practice has thus not been reached yet. Moreover, information on the weighting is often omitted in scientific reports or software documentation. In this study, we will evaluate the impact of the different weighting strategies on the performance of the linear diffusion parameter estimators. Additionally, we will compare the linear estimators to their nonlinear alternative (Koay et al., 2006) in terms of accuracy and precision. By doing so, we aim to obtain...
more insight in the strengths, limitations, and potential pitfalls of the simple, yet elegant, class of linear estimators.

Materials and methods

Diffusion models

The natural logarithm of the DW MR signal, $S$, can be expanded in powers of the wave number $g$ in a zero-centered neighborhood (Kiselev, 2010). This expansion is known as the cumulant expansion, with DTI and DKI being the three-dimensional generalization of the second and fourth order cumulant expansion, respectively (Basser et al., 1994a; Lu et al., 2006). The expansion is generally expressed in terms of the diffusion sensitizing gradient strength ($\beta$) and its direction ($g$):

$$\ln S(b, g) = \ln S(0) - b \sum_{ij} g_i g_j D_{ij} + \frac{b^2}{6} \left( \sum_{ij} D_{ij} \right)^2 \sum_{ijkl} g_ig_ig_ig_k W_{ijkl}.$$  \hspace{1cm} (1)

In Eq. (1), $S(0)$ is the non-DW signal, $D = \{D_{ij} : i, j = 1, ..., 3\}$ the (apparent) diffusion tensor, and $W = \{W_{ijkl} : i, j, k, l = 1, ..., 3\}$ the (apparent) kurtosis tensor. Because both tensors are fully symmetric, $D$ and $W$ have 6 and 15 degrees of freedom, respectively.

Tensor estimation

Consider a set of independently Rice distributed DW images $\tilde{S} = \{\tilde{S}(b, g_i) : i = 1, ..., N\}$. The natural logarithm of $\tilde{S}$ can be modeled as (Basser et al., 1994b):

$$y = X\beta + \epsilon$$  \hspace{1cm} (2)

with $y = \left[ \ln \tilde{S}(b_1, g_1), ..., \ln \tilde{S}(b_N, g_N) \right]^T$ and $X$ is the design matrix of all diffusion gradient directions and strengths, which directly relates to the $b$-matrix (Mattiello et al., 1997). Furthermore, $\epsilon$ denotes the column vector of independent error terms and $\beta$ is the diffusion model’s parameter vector, including all independent tensor elements and the noise-free non-DW signal. Obviously, $N$ must be greater than or equal to the number of model parameters. Interestingly, Salvador et al. (2005) showed $\epsilon$ to have expectation zero if the signal-to-noise ratio (SNR) of the DW images exceeds two (see Appendix A and Fig. 1(a)). Under that condition, the linear least squares (LLS) estimator of $\beta$:

$$\hat{\beta} = (X^T X)^{-1}X^T y.$$  \hspace{1cm} (3)

is unbiased. However, Salvador et al. (2005) also showed that the variance of $\epsilon$ depends on the respective noise-free signals (see Fig. 1(b)):

$$\text{var}(\epsilon) = \left[ \frac{\sigma^2}{S^2(b_1, g_1)}, ..., \frac{\sigma^2}{S^2(b_N, g_N)} \right].$$  \hspace{1cm} (4)

with $S(b, g) = \{S(b_i, g) : i = 1, ..., N\}$ the noise-free DW signals and $\sigma$ the noise level. The best linear unbiased estimator (BLUE) of $\beta$, i.e. the estimator with the highest precision within the class of unbiased linear estimators, can thus only be designed by including weights that equal the (scaled) reciprocal of the variance of the corresponding error terms (Eq. (4)):

$$\hat{\beta} = (X^T WX)^{-1}X^T Wy.$$  \hspace{1cm} (5)

Obviously, the noise-free DW signals are not known and, as such, the weight matrix $W$ needs to be estimated. Two suggested approaches are:

(a) WLLS: $\hat{W} = \text{diag}\left(\tilde{S}^2(b, g)\right)$, the weights are the squares of the respective noisy DW signals (Basser et al., 1994b; Koay et al., 2006);

(b) WLLS2: $\hat{W} = \text{diag}\left(\exp\{2X\hat{\beta}\text{LSS}\}\right)$, the weights are the preliminary estimates of $S^2(b, g)$, predicted by the LLS estimate of $\beta$ (Salvador et al., 2005).

The subindices of WLLS indicate that (a) and (b) are single-step and dual-step strategies, respectively. The estimation of $W$ can iteratively be improved (Salvador et al., 2005). The weight matrix for the $n$th iteration is given by the predicted DW signals from the previous estimate of the diffusion model parameters $\beta_{n-1}$:

$$\hat{W}_n = \text{diag}\left(\exp\{2X\beta_{n-1}\}\right).$$  \hspace{1cm} (7)

This iterative WLLS can be initialized by (a) or (b), which will be referred to as IWLLS1 and IWLLS2, respectively.
Simulation experiments

Monte Carlo simulations (50,000 trials) were performed to evaluate the performance of the different strategies in the estimation of fractional anisotropy (FA), mean diffusivity (MD) and mean kurtosis (MK). In addition to the linear estimators described in Section 2.2, the ordinary nonlinear least squares (NLS; Koay et al., 2006) estimator, initialized by a guess through WLLS2, was evaluated. Throughout all experiments, FA and MD were estimated with the DTI model, whereas the MK was estimated with the DKI model.

Simulation experiment 1

The accuracy and the precision of the different estimators were evaluated as a function of the SNR of the Rice distributed signals. The SNR is here defined as the ratio between the non-DW signal and the noise level (cf. Jones and Basser, 2004). For the DTI model, the MD and FA were set to $0.8 \times 10^{-3}$ mm$^2$/s and 0.85, respectively. The $b$-value was 1000 s/mm$^2$, and 60 gradient directions – isotropically distributed over a unit sphere using Coulomb’s law of repulsion (Jones et al., 1999) – were used. We included five non-DW signals. For the DKI simulations, additional DW signals with $b = 2500$ s/mm$^2$ were sampled along the same 60 directions. The MK was defined as 1.05, which is in agreement with values typically observed in the corpus callosum of the healthy human brain (Lätt et al., 2012). Noisy synthetic data were obtained by adding zero-mean complex Gaussian noise to the noise-free DW signals, which were calculated from the ground truth tensors using Eq. (1). The absolute value of the resulting complex noisy signals was taken afterwards to obtain their magnitudes.

Simulation experiment 2

We evaluated the influence of the number of gradient directions per $b$-value shell on the accuracy of WLLS. Unlike the initial simulation experiment, the SNR was kept constant at the level of 20, whereas the number of gradient direction per shell varied from 6 to 120 for DTI and from 15 to 120 for DKI.

Simulation experiment 3

The effect of increasing the number of iterations $n$ on the iterative WLLS approaches was evaluated. Now, the SNR was kept constant at the level of 20, whereas $n$ varied from one to ten.

Simulation experiment 4

Rice distributed simulation data sets, representing the whole human brain white matter, rather than a single voxel, were used for comparing the accuracy, precision and mean squared error (MSE) of the diffusion parameters obtained by the different least squares estimators. The simulated data sets were constructed as follows. First, ground truth tensors were obtained by voxel-wise fitting the DKI model to a real data set (see Section 2.4: Data set 1). Second, a set of noise-free DW signals was reconstructed from these diffusion tensors using the DTI and DKI models for the DTI and DKI analyses, respectively. Gradient directions and $b$-values were in agreement with the single-voxel experiments. Third, 5000 sets of noisy DW signals with a uniform SNR of 20 were generated by adding 5000 realizations of complex Gaussian noise to the noise-free DW signals. From each set, the diffusion tensors were estimated. From the 5000 trials, the accuracy and precision of the different estimators were evaluated.

Real data experiments

The following DW data sets of different healthy volunteers were acquired:

- **Data set 1**: A first DW data set was collected on a 3 T Philips Achieva MR scanner, using an 8-channel receiver head coil. Diffusion sensitizing was applied along 60 isotropically distributed gradient directions with $b = 1200$ s/mm$^2$ as well as $b = 2500$ s/mm$^2$. Additionally, one image without diffusion sensitization was acquired. Other imaging parameters were: TR/TE: 10,265/107 ms; in-plane resolution: $1.75 \times 1.75$ mm$^2$; NEX: 1; slice thickness: 2 mm; axial slices: 120; and parallel imaging: mSENSE with acceleration factor 2.

- **Data set 2**: A second DW data set was acquired on a 1.5 T Siemens MR system using a single receiver coil (Leemans et al., 2006). A gradient configuration with 60 isotropically distributed gradient directions with $b = 700$ s/mm$^2$ was used. 10 non-DW images were additionally acquired. Other acquisition parameters were as follows: TR/TE: 8300/108 ms; in-plane resolution: $2 \times 2$ mm$^2$; NEX: 1; slice thickness: 2.5 mm; axial slices: 60.

- **Data set 3**: A third DW data set was acquired on a Siemens Trio (3 T) MR scanner, using a 12-channel receiver head coil. Diffusion weighting was applied along 60 isotropically distributed gradient directions with $b = 1000$ s/mm$^2$ as well as $b = 2500$ s/mm$^2$. Additionally, 10 non-DW images were acquired. Other imaging parameters were: TR/TE: 6100/118 ms, in-plane resolution: $2.5 \times 2.5$ mm$^2$; NEX: 1; slice thickness: 2.5 mm; axial slices: 40; and parallel imaging: mSENSE with acceleration factor 2.

The DW data were corrected for motion and eddy currents, including signal modulation and $b$-matrix rotation (Leemans and Jones, 2009; Leemans et al., 2009). Next, if the diffusion protocol met the minimal DKI requirements (Lu et al., 2006), a DKI analysis was performed in addition to a DTI analysis. During the DTI analyses, all high $b$-valued, i.e. $b > 1500$ mm$^3$/s, DW images were excluded. Since data set 2 has only one nonzero $b$-value shell, a DKI analysis was not possible. FA and MD maps were calculated from the DTI analysis with the optimal DKI analysis also providing a MK map. The percentage differences in the estimation of the diffusion parameters of the different estimators, compared to a bronze standard were calculated. As a bronze standard, we adopted the previously proposed parameter estimation framework, consisting of the estimation of a (spatially varying) noise map and an accurate parameter estimator, i.e. the conditional least squares (CLS) estimator, which properly accounts for the Rice distribution of all acquired DW data samples (Veraart et al., 2012).

Results

Simulation experiments

Simulation experiment 1

In Fig. 2, the different estimators are compared in terms of accuracy, precision, and MSE as a function of SNR $^{-1}$. The FA, MD, and MK values – calculated from the average model parameters to exclude nonlinear effects such as eigenvalue repulsion (Pierpaoli and Basser, 1996) – strongly vary across the different estimators (see Figs. 2(a–c)). Generally, the NLS estimator shows a large difference to the reference values, compared to the unweighted and weighted linear approaches. However, note that non-optimal weighting strongly reduces the accuracy of the estimator. The practical WLLS approaches, i.e. WLLS$_1$ and WLLS$_2$, show a lower accuracy than the LLS and BLUE. Remarkably, the drop in accuracy is especially large for the WLLS$_1$. While the accuracy of the WLLS$_2$ is only slightly lower than BLUE, the WLLS$_2$ performs even worse than the NLS in terms of accuracy. At very low SNR e.g., due to the use of high $b$-values, all least squares estimators are inherently biased. In terms of precision (see Figs. 2(d–f)), all weighted linear estimators outperform the unweighted alternative. The LLS has low performance in terms of MSE because of the low precision, whereas the high MSE of the WLLS$_2$ results from its low accuracy (see Figs. 2(g,h)). For the MSE in the estimation of MK (see Fig. 2(i)), the low accuracy of the NLS and the WLLS$_1$ is strongly counterbalanced by their high precision. Therefore, both estimators have a relatively low MSE. Simulations beyond these single-voxel experiments are needed to avoid overinterpretation of that observation (see Section 3.1.4).
In general, the differences between the estimators diminish with increasing SNR.

Simulation experiment 2
In Fig. 3, the influence of the number of gradient directions per b-value shell on the accuracy of the different estimators is shown. The accuracy of the WLLS2 increases steadily with increasing number of gradient directions due to the increasing precision of the LLS estimator or, as such, the increasing precision of the predicted DW signals. By contrast, with a low number of gradient directions, the difference between the WLLS1 and the WLLS2 in terms of accuracy vanishes due to the reduced performance of the WLLS2.

Simulation experiment 3
In Fig. 4, the effect of iterations on the performance of the (I)WLLS estimators is shown. The graphs indicate that after a few iterations, both IWLLS estimators already closely approximate the performance of the BLUE, in terms of accuracy, precision, and MSE. The effect of the initial weighting matrix already vanishes for \( n > 1 \). Same findings are observed for all diffusion metrics.

Simulation experiment 4
In Fig. 5, scatter plots show the relationship between the accuracy, precision and MSE in the estimation of the diffusion model parameters of WLLS1 and WLLS2 against that of LLS. Each point in the scatter plot corresponds to a single voxel of the simulated data set. In Fig. 6, WLLS1 and WLLS2 are compared to NLS, whereas in Fig. 7, IWLLS1 and IWLLS2 are compared to their non-iterated counterparts. First, on average, the WLLS1 has a significantly large bias in the estimation of the diffusion model parameters, compared to the LLS, WLLS2, IWLLS1,2 \( (n = 5) \), and NLS. Indeed, WLLS1 significantly underestimates FA and MD. The underestimation is significantly larger than the...
Fig. 3. Simulation experiment 2: FA, MD, and MK calculated from the averaged model parameters are shown as a function of the number of gradient directions per b-value shell for the different least squares estimators.

Fig. 4. Simulation experiment 3: FA, MD, and MK calculated from the average model parameters (a–c), the standard deviation of the estimated diffusion parameters (d–f), and MSE in the estimation of FA, MD, and MK (g–i) are shown as a function of the number of iterations (n) for the different least squares estimators.
underestimation of FA and MD observed for the NLS. The NLS, on its turn, is significantly outperformed by the multi-step WLLS approaches and the LLS in terms of accuracy in the estimation of the diffusion tensor. Moreover, the one-sample Wilcoxon signed rank test demonstrated that LLS, WLLS2, and IWLLS1,2 are not significantly biased. For MK, similar conclusion can be drawn. However, this time, all least squares estimators show a significant overestimation of the MK. Again, LLS, WLLS2, and WLLS1,2 show significantly higher accuracy compared to NLS and, especially, WLLS1. Second, in terms of precision, LLS is significantly outperformed by all of its weighted alternatives as theoretically expected. In general, NLS showed higher precision in the estimation of all diffusion parameters than the WLLS approaches. However, in the estimation of MD and MK, the WLLS1 showed the highest precision. Third, on average, WLLS1 showed the highest MSE in the estimation of MD and MK in comparison to all other estimators. The estimator with the least average MSE in the estimation of MD was the WLLS2. For MK, WLLS2 was significantly outperformed by NLS, which compensated its low accuracy by its high precision. The NLS also showed the least MSE in the estimation of FA. The MSE in the estimation of FA, MD and MK was significantly lower for WLLS2 in comparison to IWLLS2, whereas IWLLS1 had always significantly lower MSE than its non-iterated alternative. During these simulations, statistical significance \( p < 0.01 \) was always shown with a paired Wilcoxon signed rank test.

Fig. 5. Simulation experiment 4: Scatter plots show the relationship between the bias, standard deviation and MSE in the estimation of the diffusion model parameters of WLLS1 and WLLS2 against that of LLS. Red circles: Initial weights of the WLLS approaches are the squares of the respective noisy DW signals — green dots: Initial weights are the predicted signal from an estimate of the diffusion model parameters, obtained with the unweighted LLS estimator. The blue lines are unit-slope-lines.
In Figs. 8, 9, and 10, the percentage differences in the estimation of FA, MD, and MK of the different estimators, compared to the *bronze standard*, are shown for a single slice of data sets 1, 2, and 3, respectively. For each data set, an axial slice composed out of white matter, (deep) gray matter, and cerebrospinal fluid was selected to represent the anatomy of the human brain. The *bronze standard* maps are shown for anatomical reference (left columns). In general, the results are in line with the simulation results. Indeed, the WLLS1 and the NLS significantly underestimate the diffusion tensor model parameters in both gray matter and white matter. However, it must be noted that for data set 1, a minimal, though significant, overestimation of MD was observed. This observation might indicate a slight underestimation of the spatially varying noise levels in the *bronze standard*. Unsurprisingly, for all estimators, the overestimation of MK is significant due to the low SNR of the high-b-valued DW images. Again, the overestimation is significantly larger for the WLLS1, compared to all others. The NLS showed significantly higher error in the estimation of MK than the LLS, WLLS1, and IWLLS1,2. The paired Wilcoxon signed rank test was always applied to evaluate the pairwise difference between

**Real data experiments**

In Figs. 8, 9, and 10, the percentage differences in the estimation of FA, MD, and MK of the different estimators, compared to the *bronze standard*, are shown for a single slice of data sets 1, 2, and 3, respectively. For each data set, an axial slice composed out of white matter, (deep) gray matter, and cerebrospinal fluid was selected to represent the anatomy of the human brain. The *bronze standard* maps are shown for anatomical reference (left columns). In general, the results are in line with the simulation results. Indeed, the WLLS1 and the NLS significantly underestimate the diffusion tensor model parameters in both gray matter and white matter.
two estimators. The statistical tests included all white and/or gray matter voxels.

**Discussion**

The DTI and DKI models have in common that they can be structured into a linear regression form depending on the natural logarithm of the DW MR signals. The unknown model parameters can be estimated with a LLS estimator, or its weighted variants. Those estimators are widely used in DTI and DKI studies, because they come with several strengths. First, the (weighted) LLS estimators have a closed-form solution. Therefore, unlike iterative nonlinear strategies, the linear estimators are computationally efficient and not prone to getting stuck in a local optimum. Second, the linear estimators are potentially very accurate, especially compared to the NLS estimator (Salvador et al., 2005). Under conditions that are discussed below, the linear estimators are even unbiased due to the zero expectation of the error term in the log-Rice framework. Third, the high accuracy is not at the expense of the ease of use. Indeed, unlike many advanced diffusion parameter estimators, e.g., the maximum likelihood (ML) estimator, the linear estimators don't require the knowledge of the noise parameter (Veraart et al., 2012). The estimation of the noise parameter is not only
challenging, it also reduces the precision of the diffusion parameter estimator. Unfortunately, those advantages go hand in hand with some limitations and potential pitfalls. Some of them are to the best of our knowledge still unrecognized.

The unbiasedness of the linear estimators, even under inequality of variances, is subject to two conditions: the SNR of the DW signals should not be too low (>2) and the DW data are assumed to be Rice distributed before the log-transformation. Those conditions might not be fulfilled because of the use of high b-values or high spatial resolution, magnitude image operations prior to model fitting (Rohde et al., 2004; Veraart et al., 2012), or the use of some parallel MR imaging techniques (Aja-Fernández and Tristán-Vega, 2012; Aja-Fernández et al., 2011). Indeed, our simulation and real data experiments confirmed that systematic errors in the calculation of quantitative parameters of clinical interest such as FA, MD, and MK will appear by lowering the SNR. The bias becomes even more prominent for multichannel and/or accelerated MRI reconstruction techniques that generate non-Rice distributed data (e.g., GRAPPA (Griswold et al., 2002) or homodyne partial Fourier reconstruction (Noll et al., 1991; Tristán-Vega et al., 2012; Veraart et al., 2012)). Furthermore, the accuracy of the linear estimators drops by applying operations such as motion correction and smoothing on the magnitude DW data as these might change the native data distribution (Veraart et al., 2012). The mathematical reasoning of Salvador et al. (2005) then no longer holds. However, although motion and eddy current distortion correction was applied prior to tensor fitting in our real data study, the linear approaches still outperformed the NLS estimator in terms of accuracy.

Fig. 8. Real data set 1: The percentage differences between the FA, MD, and MK estimates for the least squares estimators and the bronze standard, i.e. an accurate diffusion parameter estimation framework, which accounts for the Rice data statistics. The bronze standard diffusion parameter maps are shown for anatomical reference (left column).

Fig. 9. Real data set 2: The percentage differences between the FA, MD, and MK estimates for the least squares estimators and the bronze standard.
The linearization of both diffusion models comes with the cost of a reduced precision of the diffusion parameter estimators. The cost, however, can be limited by accounting for the heteroscedasticity of the log-transformed data. The variances of the log-transformed Rice-distributed magnitude MR signals must be known in order to design a WLLS estimator with optimal precision and accuracy. Unfortunately, the variances depend on the unknown noise-free DW signals (Salvador et al., 2005). Therefore, the best linear unbiased estimator (BLUE), i.e. the unbiased linear estimator with the highest precision, does not exist in practice. Nevertheless, we showed that optimal linear performance can be well approximated by a WLLS estimator for which the weight terms are estimated from noisy data with SNR > 2. The approximation improves by drawing more DW samples or by iteratively updating the estimate of the weight matrix. In practice, only a few iterations are needed for convergence.

Already in the early days of DTI, Basser et al. (1994b) stated that the weights for the WLLS can simply be the squares of the respective noisy DW signals (cf. WLLS1). More than a decade later, the statement was repeated by Koay et al. (2006). Many widely used software packages (e.g., ExploreDTI v4.8.2 (Leemans et al., 2009), FSL v5.0.1 (Jenkinson et al., 2012), Tortoise v1.3.1 (Pieper et al., 2010)) and, as such, numerous researchers working in the field of dMRI, adopted the approach. In the meantime, Salvador et al. (2005) proposed alternative, multi-step weighting schemes. In those approaches, the weights are the squares of the predicted signals, which are reconstructed from a previous estimate of the diffusion model parameters, obtained with the unweighted LLS estimator (cf. WLLS2) or a previous iteration of the WLLS estimator (cf. IWLLS). The latter strategy was adopted by software packages such as Camino (Cook et al., 2006) and Slicer v4.2.1 (Pieper et al., 2006). So, nowadays, different weighting strategies are commonly used in a daily practice. This lack of unity not only obstructs multi-center research, but it might also lead to misleading conclusions or irreproducible results. Indeed, we showed in this work that the performance of the WLLS strongly depends on the selected weight terms. More specifically, ill-chosen weights strongly reduce the accuracy of the linear estimator. Simulation and real data experiments indicated that the strategy proposed by Basser et al. (1994a) (WLLS1) is the least favorable weighting strategy. Therefore, we suggest always opting for multi-step weighting strategies.

In this study, we only reported results for the most widely used diffusion and kurtosis metrics, i.e. FA, MD, and MK. Nevertheless, similar conclusions can be drawn for the other tensor-derived metrics to a greater or lesser degree depending on the directionality of the SNR (Jones and Basser, 2004). Unlike quantitative metrics such as axial and radial diffusivity, or axial and radial kurtosis, the first eigenvector of the diffusion tensor is not subject to the Rician noise bias due to the symmetry of the tensor.

If the number of DW samples and the SNR are low, then the DW signals predicted from the LLS estimates may show high variance. A weight matrix estimated with low precision might lower the accuracy of the WLLS2 estimator. Increasing the number of DW samples thus not only improves the precision of the WLLS2 estimator, it also improves its accuracy. The latter does not hold for the WLLS1. Recently, it has been suggested to use non-linear tensor estimators rather than its linear alternatives (Jones et al., 2012). Our results, however, indicate the non-triviality in choosing between multi-step WLLS and NLS strategies for estimating dMRI parameters. Indeed, the decision depends on the number of DW signals (see Fig. 3), the parameter of interest (see Fig. 6 and Landman et al., 2007b), and – possibly – the actual data distribution. However, further study is needed to extensively showcase the strengths, limitations, and pitfalls of the different diffusion estimators in case of non-Rice data distributions.

**Conclusion**

Within the wealth of different diffusion parameter estimators, the WLLS estimator stands out by its simplicity and elegance. To date, no consensus has been reached on how to use the estimator in practice. In this work, it has been shown that the accuracy of the WLLS estimator strongly depends on the selected weight terms. A comparison of the most common weighting strategies indicated that the squares of the noisy DW signals should not be used if one is interested in designing a linear estimator with the highest achievable accuracy. However, if multi-step weighting strategies are applied, the weighted linear least squares estimator shows high performance characteristics in terms of accuracy/precision and may even be preferred over nonlinear estimation methods.
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Conflicts of Interest

The authors declare no conflicts of interest.

Appendix A

The bias of the weighted linear least squares estimator, defined in Eq. (5), is given by

$$\text{bias}(\hat{\beta}) = \mathbb{E}[\hat{\beta}] - \beta_0 = \mathbb{E}\left[(X'WX)^{-1}X'W\varepsilon\right]. \quad (8)$$

Under the assumption of a deterministic design matrix ($X$) and weight matrix ($W$), the estimator will be unbiased if the error term ($\varepsilon$) has zero expectation. Salvador et al. (2005) derived an analytical expression for the expectation value of the error term, given that the linearized diffusion model is fitted to the natural logarithm of Rice distributed diffusion-weighted measurements ($m$). The probability distribution function (PDF) of an arbitrary Rice distributed variable $m$ is given by Sijbers et al. (1998):

$$f_m(m|\mu_0, \sigma^2) = \frac{m}{\sigma^2} \exp\left(-\frac{m^2 + \mu_0^2}{2\sigma^2}\right) I_0\left(\frac{m\mu_0}{\sigma^2}\right), \quad (9)$$

with $\mu_0$ the noise-free signal, $\sigma^2$ the noise variance, and $I_0$ the zeroth order modified Bessel function of the first kind. The PDF of the log-transformed variable $m' = \ln(m)$ can be determined by substituting $m$ in Eq. (9) by $m'$:

$$f_m(m'|m_0, \sigma^2) = \frac{1}{\sigma^2} \exp\left(-\frac{e^m + \mu_0^2}{2\sigma^2}\right) I_0\left(e^m\mu_0/\sigma^2\right). \quad (10)$$

The expectation value of $m'$ is given by:

$$\mathbb{E}[m'] = \int_{-\infty}^{\infty} m f_m(m'|m_0, \sigma^2)dm' = \frac{1}{\sqrt{2\pi}} \int_{-\infty}^{\infty} \frac{1}{\sigma^2} e^m dt + \ln(m_0), \quad (11)$$

with $\mathbb{E}[\varepsilon] = \frac{m_0}{\sqrt{2}}$. If the error term $\varepsilon$ is defined as $m' - \ln(m_0)$, then its expectation value can immediately be derived:

$$\mathbb{E}[\varepsilon] = \mathbb{E}[m' - \ln(m_0)] = \frac{1}{\sqrt{2\pi}} \int_{-\infty}^{\infty} \frac{1}{\sigma^2} e^m dt + \ln(m_0) - \ln(m_0) = \frac{1}{\sqrt{2\pi}} \int_{-\infty}^{\infty} \frac{1}{\sigma^2} e^m dt. \quad (12)$$

In Fig. 1(a), $\mathbb{E}[\varepsilon]$ is shown for different SNR values. It can be seen that for SNR > 2, the error term is zero-centered. The potentially high accuracy of the (weighted) linear least squares estimators originates in this observation. However, often the weight matrix is not deterministic. If so, correlations between the weight terms and the unweighted error terms will introduce a bias.

References


