Free-water DTI estimates from single b-value data might seem plausible but must be interpreted with care

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Purpose: Free-water elimination DTI (FWE-DTI) has been used widely to distinguish increases of free-water partial-volume effects from tissue’s diffusion in healthy aging and degenerative diseases. Because the FWE-DTI fitting is only well-posed for multishell acquisitions, a regularized gradient descent (RGD) method was proposed to enable application to single-shell data, more common in the clinic. However, the validity of the RGD method has been poorly assessed. This study aims to quantify the specificity of FWE-DTI procedures on single-shell and multishell data.

Methods: Different FWE-DTI fitting procedures were tested on an open-source in vivo diffusion data set and single-shell and multishell synthetic signals, including the RGD and standard nonlinear least-squares methods. Single-voxel simulations were carried out to compare initialization approaches. A multivoxel phantom simulation was performed to evaluate the effect of spatial regularization when comparing between methods. To test the algorithms’ specificity, phantoms with two different types of lesions were simulated: with altered mean diffusivity or with modified free water.

Results: Plausible parameter maps were obtained with RGD from single-shell in vivo data. The plausibility of these maps was shown to be determined by the initialization. Tests with simulated lesions inserted into the in vivo data revealed that the RGD approach cannot distinguish free water from tissue mean-diffusivity alterations, contrarily to the nonlinear least-squares algorithm.

Conclusion: The RGD FWE-DTI method has limited specificity; thus, its results from single-shell data should be carefully interpreted. When possible, multishell acquisitions and the nonlinear least-squares approach should be preferred instead.

KEYWORDS
free-water elimination DTI, nonlinear least-squares FWE-DTI, regularized gradient descent, single-shell data
1 | INTRODUCTION

Diffusion-weighted MRI (dwMRI) is a noninvasive imaging modality that is sensitive to microscopic tissue properties beyond the spatial resolution offered by current MRI scanners. The information captured by dwMRI is multidimensional, and its sensitivity to different diffusion properties depends on the acquisition parameters. For example, DTI can estimate diffusion anisotropy from dwMRI images acquired with different gradient directions for a single level of diffusion weighting and at least one unweighted image (ie, single-shell acquisition). Another technique, diffusion kurtosis imaging, allows estimating non-Gaussian diffusion properties from dwMRI images acquired with different nonzero contrast levels (ie, multishell acquisition). Although both are sensitive to tissue alterations undetected by conventional structural images, the derived metrics are not specific to concrete microstructural properties and are hard to interpret.

To improve specificity, microstructural models have been introduced to directly extract biophysical measures. However, assumptions and constraints are often required to minimize the number of parameters to be estimated. For instance, several studies used a simplified tissue model, with two compartments assigned to intracellular and extracellular media to estimate axonal water fraction and diameter. In FWE-DTI, a two-compartmental model is used to account for the arbitrary scanner intensity scaling (eg, due to receiver gain); $\nu$ is the volumetric tissue fraction; $\rho_0$ and $\rho_w$ are the tissue and water proton densities; $T_2$, and $T_2w$ are the tissue and FW transverse relaxation times; $D_i$ is the tissue’s apparent diffusion tensor; $D_w = 3 \text{ mm}^2 \text{ms}^{-1}$ is the constant diffusivity of isotropic FW at body temperature ($\geq 37^\circ$); $b$ is the diffusion weighting; and $\theta$ is the respective gradient direction (normalized column vector; $T$ denotes the transpose). This model assumes no water exchange between compartments and that both display Gaussian diffusion.

Because decoupling the volumetric tissue fraction $\nu$ from parameters $\rho_0$, $\rho_w$, $T_2$, and $T_2w$ require additional relaxation measurements, the effective tissue-water fraction is often defined as $f = \nu S_r/S_0$, where $S_0$ is the signal measured at b-value $b_0 = 0$ (ie, $S_0 = vS_r + (1 - v)S_w$); $S_r$ is the reference $b_0$ signal from voxels containing only gray-matter (GM) and white-matter (WM) tissues (assuming that tissue presents a single $T_2$ value, $S_r = \rho_0 \exp\left(-TE/T_2\right)$); and $S_w$ is the reference $b_0$ signal from voxels containing only FW ($S_w = \rho_w \exp\left(-TE/T_2w\right)$). Inserting $f$ into Equation 1, the FWE-DTI model can be rewritten as
\[ A(D_r, f) = f \exp (-bn^T D_r n) + (1 - f) \exp (-bdw), \]  
where \( A \) is the diffusion signal attenuation (ie, \( A = S / S_0 \)). From Equation 2, the effective FW fraction is defined as \( f_w = 1 - f \). The FWE-DTI fitting procedures estimate seven model parameters (ie, the six independent elements of the tissue’s diffusion tensor \( D_t \) and \( f \)). If \( \rho_r, \rho_w, T2_r, \) and \( T2_w \) are known, the effective fractions can be converted to volumetric fractions \( v = f s_w / \left( S_r + f \left( S_w - S_r \right) \right) \).

Despite its simplicity, Equation 2 is a two-compartmental model and has a flat fitting solution landscape (ie, similar residuals are observed for different \( D_r \) samples for any given \( f \in [0, 1] \) as shown in Refs. 28 and 29 so that choosing the most viable pair \( (D_r, f) \) is not straightforward). The tested DTI and FWE-DTI model fitting routines are described in the next sections and summarized in Table 1.

### 2.2 Regularized gradient descent fitting procedure

To fit the FWE-DTI model to single-shell data, previous studies proposed using RGD algorithms with careful parameter initializations. The different initialization procedures and the RGD algorithm are described in the next subsections.

#### 2.2.1 Parameter initialization

Three strategies were tested to initialize \( f \) in the RGD algorithm.

- **Initialization based on the \( T_2 \)-weighted images (S0-INI):**
  Assuming that regions with higher FW fraction present hyperintense \( T_2 \)-weighted signals (\( S_0 \)).

\[
 f_{s0} = 1 - \log \left( S_0 / S_r \right) / \log \left( S_w / S_r \right),
\]

where \( f_{s0} \) is the \( f \) estimate from S0-INI. Here, \( S_r \) and \( S_w \) can be estimated from regions of interest placed on deep WM or the ventricles. To avoid implausible estimates, \( f_{s0} \) values are constrained as follows:

\[
 \frac{\min \left( \hat{A} - \exp (-bd_{w}) \right)}{\max \left( \exp (-b\lambda_{\text{min}}) - \exp (-bd_{w}) \right)} \leq f_{s0} \leq \frac{\min \left( \hat{A} - \exp (-bd_{w}) \right)}{\max \left( \exp (-b\lambda_{\text{max}}) - \exp (-bd_{w}) \right)},
\]

Notably, although designed for single-shell acquisitions, all can be adapted to multishell data sets (vide infra).

### TABLE 1 Overview of the acronyms of the fitting procedures and variables used in this study

| DTI/FWE-DTI fitting procedures | Description |
|--------------------------------|-------------|
| DTI                            | Standard DTI was fitted using DIPY's weighted linear least squares (WLLS) \(^2,37\) |
| S0-INI                         | FWE-DTI model initial guess estimation based on S0 priors for water and tissue \(^19\) |
| MD-INI                         | FWE-DTI model initial guess estimation based on a healthy tissue's MD prior \(^31\) |
| HY-INI                         | FWE-DTI model initial guess estimation based on the log-linear interpolation between S0-INI and MD-INI estimates \(^31\) |
| RGD                            | FWE-DTI fitting procedure based on regularized gradient descent \(^19\) (this acronym will be used to discuss general aspects of this algorithm, independently of the used initialization) |
| RGD (S0)                       | RGD fitting based on the RGD algorithm initialized by the S0-INI estimator \(^31\) |
| RGD (MD)                       | RGD fitting based on the RGD algorithm initialized by the MD-INI estimator \(^31\) |
| RGD (HY)                       | RGD fitting based on the RGD algorithm initialized by the HY-INI estimator \(^31\) |
| NLS                            | FWE-DTI fitting using an NLS approach, initialized by an WLLS approach \(^25,29\) |
| NLS*                           | FWE-DTI fitting by the NLS approach, initialized with the HY-INI estimator |

**Acronyms of variables**

- \( A \), total diffusion signal attenuation; \( \hat{A} \), measured total diffusion signal attenuation; \( A_r \), tissue contribution to the diffusion signal attenuation; \( b \), diffusion weighting parameter; \( D_r \), tissue’s apparent diffusion tensor; \( D_w \), free water diffusion coefficient; \( f \), effective tissue water fraction; \( f_{s0}, f \) estimate from S0-INI; \( f_{\text{MD}}, f \) estimate from MD-INI; \( f_{\text{HY}}, f \) estimate from HY-INI; \( f_{\text{w}}, f \) effective free water fraction; \( FA \), total fractional anisotropy; \( FA_r \), fractional anisotropy of the tissue’s diffusion tensor; \( FW \), free water; \( MD \), mean diffusivity; \( MD_r \), mean diffusivity of the tissue’s diffusion tensor; \( MD_{\text{p0}} \), tissue’s MD prior used for the MD-INI estimator; \( S_r \), signal measured at b-value \( b = 0 \); \( S_w \), reference signal measured at b-value \( b = 0 \) from voxels containing only tissue (GM or WM); \( S_{\text{w,r}} \), reference signal measured at b-value \( b = 0 \) from voxels containing only \( FW \); \( T2_r \), tissue transverse relaxation time; \( T2_w \), free water transverse relaxation time; \( n \), diffusion gradient direction; \( v \), volumetric tissue fraction; \( \chi \), diffusion tensor independent elements (\( i = 1 \) to \( 6 \)); \( \alpha \), parameter that determines the relative weights on the log-interpolation for \( f_{\text{HY}} \) estimation; \( \rho_r \), tissue proton density; \( \rho_w \), free water proton density; \( \rho \), induced metric determinant that acts as a regularizer on RGD fitting procedure; \( \alpha \), hyperparameter for controlling the spatial smoothness of the estimated tensor field on RGD fitting procedure; \( F \), fidelity term for the RGD fitting procedure.
where $\hat{A}$ is the measured signal decay, and $\lambda_{\text{min}}$ and $\lambda_{\text{max}}$ are the minimum and maximum expected tissue diffusivities (0.1 and 2.5 $\mu$m$^2$ ms$^{-1}$, respectively$^{19}$). The equation was modified for compatibility with multishell data, and to correct for the swapped denominators in Pasternak et al.$^{19}$

Initialization based on a tissue’s mean diffusivity prior (MD-INI): To avoid relying on the non-quantitative $S_0$ images, $f$ estimates from MD-INI (here referred to as $f_{\text{MD}}$) can be computed based on a fixed prior for the tissue’s mean diffusivity (MD)$^{31}$:

$$f_{\text{MD}} = \frac{\exp(-bMD) - \exp(-bD_w)}{\exp(-bMD_{\text{ref}}) - \exp(-bD_w)},$$

(5)

where $MD$ is computed with standard DTI; $MD_{\text{ref}}$ is the tissue’s MD prior (set to 0.6 $\mu$m$^2$ ms$^{-1}$); and $b$ is the single-shell b-value. For multiple-shell acquisitions, one b-value is empirically selected (1 ms $\mu$m$^{-2}$ in our study), which provides sufficient contrast while minimizing non-Gaussian diffusion effects not considered by FWE-DTI.$^{19}$ Notably, voxels with higher MD values will present higher $f_{\text{MD}}$. Unlike $f_{\text{SO}}$, $f_{\text{MD}}$ is constrained by 0 and 1.

Hybrid initialization (HY-INI): To combine T$_2$-weighted and dwMRI information, a log-linear interpolation can be performed between $f_{\text{SO}}$ and $f_{\text{MD}}$ estimates as follows$^{31}$:

$$f_{\text{hy}} = f_{\text{SO}}^{1-\alpha} \times f_{\text{MD}}^{\alpha},$$

(6)

where $f_{\text{hy}}$ is the $f$ estimate from HY-INI, and $\alpha$ determines the relative weights. To assign a higher weight to $f_{\text{MD}}$ in regions with T$_2$-weighted signals closer to typical tissue intensities (ie, healthy tissue) and higher weights to $f_{\text{SO}}$ in hyperintense voxels (ie, edematous tissue), $\alpha$ is set to the initial, but unconstrained, tissue water fraction computed by Equation 3.$^{31}$

Initialization of tissue’s diffusion tensor: The tissue fraction initializations were used to estimate the normalized tissue’s signal attenuation $A_t = \left( \hat{A} - (1-f) \exp(-bD_w) \right) f$. For each initialization ($f_{\text{SO}}, f_{\text{MD}},$ and $f_{\text{hy}}$), an initial estimate of $D_t$ was obtained by fitting the standard DTI model to $A_t$.

### 2.2.2 Regularized gradient descent

We implemented an adapted version of the FWE-DTI fitting framework that constrains $D_t$ to be spatially smooth by introducing a regularization term into the minimization functional$^{19}$:

$$L(D_t,f) = \Omega \left\{ \frac{1}{2} \left( A(D_t,f) - \hat{A} \right)^2 + \omega \sqrt{\gamma(D_t)} \right\} d\Omega,$$

(7)

where $\Omega$ represents the image domain; $A(D_t,f)$ is the predicted signal attenuation given by Equation 2; $\hat{A}$ is the measured signal attenuation for a given direction; $\gamma(D_t)$ is the determinant of the induced metric, which acts as a regularizer; and $\omega$ is a hyperparameter for controlling the spatial smoothness of the estimated tensor field.$^{19}$ The metric tensor is computed from the spatial derivatives of $D_t$ and was chosen to be Euclidean to reduce computational burden.$^{27}$ These concepts are borrowed from differential geometry; application to diffusion tensors is further explained in Refs. 19 and 39, and the Euclidean metric implementation is described in Ref. 27.

Minimization of Equation 7 can be done with a gradient descent scheme, following the iteration rules provided in Refs. 19 and 27. Here, a small correction is proposed to the fidelity term $\Delta F^f$ in Ref. 19, obtained by differentiating the first term of Equation 7 with respect to each independent diffusion element $X_i$ (ie, ranges from 1 to 6) as follows:

$$\Delta F^f = \sum \left( A(D_t,f) - \hat{A} \right) f \exp\left(-bD_t \frac{\partial^2 D_t}{\partial X_i^2}\right).$$

(8)

Minimization of the second term in Equation 7 gives rise to the Laplace-Beltrami operator.$^{19,27}$ Differentiating Equation 7 with respect to $f$ gives the tissue-fraction increment:

$$\Delta f = \sum \left( A(D_t,f) - \hat{A} \right) \left( f \exp\left(-bD_t \frac{\partial^2 D_t}{\partial X_i^2}\right) - \exp\left(-bD_w\right) \right).$$

(9)

### 2.2.3 Dealing with voxels containing only FW

The FWE-DTI estimates are not well-defined for voxels containing only FW.$^{25,29}$ Because their signal is well-described by a single exponential with high isotropic diffusion (ie, $\sim 3 \mu$m$^2$ ms$^{-1}$), $D_t$ can erroneously be fitted with a diffusion tensor with a large trace and FW assigned any value between 0 and 1. To ensure a FW estimate close to 1, initial parameter estimates with high tissue MD can be re-adjusted to have $f = 0$ and $D_t$ assigned null elements. Tissue MD is classified as high if above 1.5 $\mu$m$^2$ ms$^{-1}$.$^{25,29}$ To avoid low-precision FWE-DTI estimates in regions with low tissue contributions, refined tissue MD and fractional anisotropy (FA) estimates are set to zero when the refined $f$ is below 0.3.$^{25,29}$

### 2.3 Standard least-squares fitting procedure

The FWE-DTI model has a unique $(D_t,f)$ solution when multishell data are available, providing a reference for regularized single-shell fitting procedures. A two-step minimization
based on a combination of standard weighted linear least-squares and nonlinear least-squares (NLS) routines was used as the reference multishell FWE-DTI fitting procedure.25,29

3 | METHODS

3.1 | Magnetic resonance imaging data

A dwMRI data set of a healthy volunteer acquired in a Siemens Prisma 3T scanner was used, including b-values 0.2, 0.4 ms μm⁻² (eight directions per shell, sampled twice) and 1, 2, 3 ms μm⁻² (90 directions per shell); an unweighted image was acquired every eighth or ninth volume. Other relevant imaging parameters: isotropic resolution = 2 mm, multiband factor = 3, TR = 3000 ms, TE = 74 ms, and flip angle = 72°. The data were taken from a public repository, having been acquired following the ethical approval from the institutional review board and with informed subject consent. This data set had been preprocessed to correct for eddy current distortions and motion using FSL40,41 and incorporated into DIPY. In addition, here this data set was corrected for variations in image intensity using “dwibiascorrect” from MRTrix3 (FSL-FAST option).42

These data were first used to provide a qualitative assessment of the different FWE-DTI estimates. For this, all dwMRI images acquired with b-values larger than 1 ms μm⁻² were removed to avoid non-Gaussian diffusion effects.25,29 Diffusion parameter maps were extracted and compared among (1) standard DTI model (DIPY’s weighted linear least-squares fitting37), (2) FWE-DTI model using the regularized gradient descent algorithm including only the data with b = 0 and 1 ms μm⁻² (RGD, single-shell), (3) FWE-DTI model using the regularized gradient descent algorithm on all b-values ≤ 1 ms μm⁻² data (RGD, multishell), and (4) FWE-DTI model using the standard nonlinear approach25,29 (NLS, multishell). For simplicity, the single-shell and multishell RGD algorithm for this first assessment was initialized with the HY-INI technique.31

3.2 | Simulations

Quantitative analyses to assess the robustness of different FWE-DTI fitting steps were first performed based on single-voxel and multivoxel synthetic phantoms. The dwMRI signals were numerically generated using Equation 1 with ρ and ρw set to typical proton density values (70% and 100%,43 TE set to 74 ms (as for the in vivo data set), and T2g and T2w set to 80ms and 500ms, typical 3T transverse relaxation times for tissue44 and CSF.45 Ground-truth tensors were simulated considering reference values for the Dᵢ’s eigenvalues, λ₁ᵢ = 1.6, λ₂ᵢ = 1.5 and λ₃ᵢ = 0.3 μm² ms⁻¹ (typical for WM46), corresponding to FAᵢ = 0.7 and MDᵢ = 0.8 μm² ms⁻¹. Synthetic signals were simulated using (Equation 1) and Rician noise added to achieve an SNR of 40 (reference S₀ SNR for FW voxels).

3.2.1 | Single-voxel simulations

To compare between initialization methods, simulations were repeated for Dᵢ with different MDᵢ ground-truth values (sampled between 0.1 and 1.6 μm² ms⁻¹). To maintain FAᵢ⁰ and the eigenvalues of Dᵢ, were computed by $\lambda_1^{gt} = c\lambda_1^{WM}$, $\lambda_2^{gt} = c\lambda_2^{WM}$, and $\lambda_3^{gt} = c\lambda_3^{WM}$, where $c = MD_i / MD_i^{WM}$. Simulations were repeated for different tissue-water fraction values f linearly spaced between 0 and 1, converted to volume fractions $\nu$ to generate the synthetic dwMRI signals using Equation 1. For each ground-truth (f, MDᵢ) pair, 100 different directions were considered for the principal orientation of $D_i$, and for each orientation, single-shell signals were generated along 32 gradient directions with $b = 1 ms μm⁻²$ and six $S_0$ images. Synthetic Rician noise was added for 100 noise instances and the initialization methods applied to each single-voxel signal. The median and interquartile ranges of the $f_w$, FAᵢ, and MDᵢ estimates were computed over the 100 repeated $D_i$ directions multiplied by 100 noise instances.

3.2.2 | Multivoxel phantom

Aimed to assess whether applying spatial regularization to the RGD algorithm improves the estimates of FWE-DTI in a best-case scenario (ie, phantom with a smooth $D_i$ field), a multivoxel phantom (21 × 21 × 21 voxels) of a cylindrical fiber (radius of 7 voxels) was designed, with flat ground-truth $D_i$. The fiber was contaminated with three levels of effective FW fraction $f_w = 0.1, 0.4$, and 0.7, increasing along the radial direction while kept constant along the axial direction. To compare the FWE-DTI with DIPY’s multishell fitting procedure (NLS25), simulations also considered a multishell data set with $b$-values of 0.5 and 1 ms μm⁻² (32 directions per shell), with six $S_0$ images. Standard DTI and the RGD procedure for the FWE-DTI model were applied to both data (RGD single-shell and multishell for short), while the NLS procedure was applied to the multishell data only. The estimated $f_w$, FAᵢ, and MDᵢ maps were visually assessed, and the medians of the initial (S₀-INI, MD-INI, and HY-INI) and optimized parameter estimates using the RGD procedure a were compared to the ground-truth values.

3.2.3 | In vivo data with simulated lesions

The aim was to evaluate the specificity of FWE-DTI parameter estimates (ie, whether these enable decoupling alterations to $D_i$ from changes in the degree of FW contamination). Two types
of synthetic lesions were inserted into a representative dwMRI brain data set: (1) lesions with altered FW content (FW lesion) and (2) lesions with modified MD, (MD lesion). Ground-truth FWE-DTI parameter maps were obtained by applying the gold-standard NLS technique. Lesions covering a spherical volume (radius of 14 mm) were placed in a WM region near the superior portion of the left internal capsule. The lesions were generated by modifying the $f_w$ ground truth inside the lesion mask to a single value in the range of 0.2 – 0.6 in steps of 0.1 (FW lesion) or by altering $MD$, to a value in the range of 0.4 – 1.2 $\mu m^2 ms^{-1}$ in steps of 0.2 $\mu m^2 ms^{-1}$ without changing the ground-truth $FA$, (as described for the single-voxel simulation). The ground-truth parameters were plugged into (Equation 1) to generate, for each lesion type and each value in the aforementioned range, single-shell and multishell data with the same number of directions and b-values as described for the multivoxel phantom. All non-diffusion parameters of the lesions were as for the synthetic phantoms. Standard DTI and RGD FWE-DTI (for the best performing initialization technique according to the phantom simulations) were applied to all single-shell and multishell data sets, while the NLS algorithm was applied only to the multishell data. The multishell data were also processed with a modified NLS algorithm using the best-performing single-shell initialization for a fairer comparison (NLS*; Table 1). The estimated scalar maps were compared with the ground-truth parameters to assess specificity.

For every run of the RGD routine, unless stated otherwise, the number of iterations was 200, the learning rate was 0.0005, and the spatial regularization operator was turned off halfway ($\omega = 1$ at iteration 0 and $\omega = 0$ at iteration 100) according to the recommendations in Ref. 19.

4 | RESULTS

Figure 1 shows the estimated scalar maps from a healthy human brain. The $f_w$ maps show values near one for all FWE-DTI fitting procedures in regions comprising the brain ventricles and surrounding the parenchyma (first row). The corresponding $MD$, values were always lower than obtained using standard DTI (second row). Both RGD single-shell and multishell procedures provided $MD$, maps with lower GM to WM contrast compared with NLS FWE-DTI. The FA maps look similar for all methods (third row), but the FWE-DTI estimates were higher than the DTI estimate, particularly for WM regions. Median and interquartile ranges of scalar estimates in WM and GM are presented in Table 2, using the masks shown in the Supporting Information Figure S2. Difference maps are shown in Supporting Information Figure S3.

The results obtained for the single-voxel simulations are presented in Figure 2. For a fixed ground-truth $MD_i = 0.6 \mu m^2 ms^{-1}$ and varying $f_w$ (first column), the initialization based on the MD-INI method (blue markers) shows the smallest deviations to the ground-truth line (in orange). When $f_w$ was fixed at 0.2, 0.5, or 0.8 and $MD$ deviated from 0.6 $\mu m^2 ms^{-1}$ (second, third, and fourth columns), the MD-INI and HY-INI (green) methods differed more from the ground-truth values. The performance of the S0-INI method (red markers) was invariant to the ground-truth $MD$ (second, third, and fourth columns), but its estimates present a constant bias.

Scalar maps estimated for the single-shell data set of the synthetic multivoxel phantom are presented on the left side of Figure 3. Although no spatial variation was simulated on $MD$, and FA ground-truth maps (first column), $f_w$ contamination
induced a spatial variation on the standard DTI FA and MD maps (second column). The FA, and $MD_i$ initial estimates obtained using the HY-INI method (third column) show a lower spatial dependence compared with DTI estimates. The fourth column shows the FWE-DTI estimates refined using the RGD (HY) single-shell algorithm, showing identical contrast to the initial estimates. The median and interquartile ranges of the FWE-DTI parameter errors computed from initial estimates (SO-INI, MD-INI, and HY-INI) and optimized RGD estimates - RGD (S0), RGD (MD), and RGD (HY)- are

|               | DTI single-shell | RGD (HY) single-shell | RGD (HY) multishell | NLS multishell |
|---------------|------------------|-----------------------|---------------------|----------------|
| **WM**        |                  |                       |                     |                |
| FW            | –                | 0.088 (0.045-0.132)   | 0.096 (0.060-0.133) | 0.107 (0.056-0.158) |
| $MD$ ($\mu m^2 s^{-1}$) | 0.688 (0.660-0.724) | 0.606 (0.580-0.631) | 0.599 (0.571-0.625) | 0.586 (0.528-0.644) |
| FA            | 0.488 (0.409-0.584) | 0.547 (0.463-0.655) | 0.556 (0.470-0.663) | 0.581 (0.486-0.688) |
| **GM**        |                  |                       |                     |                |
| FW            | –                | 0.155 (0.095-0.238)   | 0.141 (0.086-0.216) | 0.105 (0.002-0.203) |
| $MD$ ($\mu m^2 s^{-1}$) | 0.734 (0.684-0.804) | 0.587 (0.554-0.614) | 0.596 (0.555-0.630) | 0.635 (0.539-0.713) |
| FA            | 0.160 (0.118-0.228) | 0.216 (0.166-0.291) | 0.209 (0.159-0.284) | 0.192 (0.139-0.279) |

$^a$See Supporting Information section 1.2 for details on how these masks were obtained.
shown on the right side of Figure 3. The latter plots confirm that refined estimates present similar accuracy and precision to their initial estimates, with the HY-INI method resulting in smaller bias levels.

Figure 4 shows the analogous results for the multishell data set of the multivoxel phantom. Both HY-INI and RGD (HY) estimates present higher precision (lower interquartile ranges) than the NLS estimates, but lower accuracy (higher deviation between estimates' median and ground-truth values). The interquartile range for the refined RGD estimates are slightly lower than the initial estimates (right side of Figure 4).

The results for the synthetic lesions are presented in Figures 5 and 6 for the specific case in which the ground-truth $f_w$ was increased to 0.6 (FW lesion) or $MD$, increased to 1.1 $\mu$m$^2$ ms$^{-1}$ (MD lesion), respectively. All fitting routines were able to estimate the high $f_w$ increases in the FW lesion area (true positives indicated by the cyan arrows). Both the standard DTI and single-shell RGD erroneously estimated an increased MD (false positives indicated by red arrow) in the FW lesion. Moreover, this FWE-DTI technique removed the $MD$ contrast between GM and WM regions. For MD lesions (Figure 6), the single-shell and multishell RGD algorithms (third and fourth columns) erroneously estimated increased $f_w$ in the lesion (false positives indicated by the red arrow).

The slight increase in MD (second row) is, however, captured by the RGD particularly for the multishell data set. Both NLS runs detected increased MD in the lesion without overestimating FW or affecting FA. The NLS was specific to both lesion types, even when initialized with the single-shell HY-INI estimates (ie, NLS*, last column of Figures 5 and 6).

These results are quantitatively summarized in Figure 7, where the median and interquartile ranges for the lesion are shown for the HY-INI estimation, RGD (HY) single/multishell, and NLS* fits (red, blue, green, and cyan, respectively). Deviation of RGD quantities from the ground-truth median (gray line) and interquartile ranges (gray shadow area) are smaller for the FW lesion (first column) than for the MD lesion (second column). The NLS produces increased interquartile ranges (due to its lower precision); however, it produces median values that closely match the ground-truth values, confirming its higher accuracy. Similarly, Figure 8 summarizes the median and interquartile intervals of estimates from RGD (HY) and NLS* (green and blue, respectively) as a function of all tested ground-truth values (orange) for each lesion. The observations from Figure 7 also apply to the wide range of tested values shown in Figure 8, where for larger deviations of the ground-truth MD from the assumed prior of 0.6 $\mu$m$^2$ ms$^{-1}$ (third and fourth columns), increasingly inaccurate estimates were obtained with RGD (HY).
FIGURE 4  Results for the multishell data set of the multivoxel phantom. On the left side of the figure, the parametric maps of FW, FA, and MD estimates are shown for the GT values (first column), FWE-DTI hybrid initialization (second column), FWE-DTI RGD initialized using the hybrid method (third column), and the NLS FWE-DTI algorithm (fourth column). On the right side, the corresponding distributions are plotted for the initial estimates (S0-INI, MD-INI, and HY-INI) and refined estimates (RGD(S0), RGD(MD), and RGD(HY)) compared with the GT (orange). To enable an easier interpretation, the median and interquartile rates were computed inside the region with an intermediate GT FW value of 0.4 (similar conclusions could be drawn for the other GT FW values; results not shown)

FIGURE 5  Scalar maps estimated from in vivo data after introducing a simulated FW lesion. The ground truth (GT) is represented on the first column, while the remaining columns show the estimates obtained using standard DTI (second column), RGD(HY) FWE-DTI for single-shell and multishell data (third and fourth columns) and NLS FWE-DTI (sixth column). The NLS FWE-DTI* (fifth column) shares the same initialization method used in the RGD routine (HY-INI approach). The single-shell data was simulated along 32 directions with $b = 1$ ms $\mu$m$^{-2}$ (in addition to six $b$-value = 0 images); the multishell data was simulated with $b$-values of 0.5 ms $\mu$m$^{-2}$ and 1 ms $\mu$m$^{-2}$ (32 directions each, in addition to six $b$-value = 0 images)
DISCUSSION

The FWE-DTI model was designed to quantify the fraction of free diffusing water molecules in biological tissue.\textsuperscript{18,19} Despite being based on a simplistic two-compartmental model, several studies showed that FWE-DTI can be useful in eliminating confounding FW partial-volume effects from standard DTI metrics, particularly in subjects with varying...
degrees of tissue maturation or atrophy.\textsuperscript{20-22,30,31} The application of FWE-DTI to single-shell acquisitions remains, however, controversial. Although some studies showed that plausible FW fractions can be obtained using RGD algorithms,\textsuperscript{19,27,31} others argued that these maps are unreliable, as this model is degenerate for single-shell acquisitions.\textsuperscript{25,29} We aimed to address this controversy using representative in vivo data of a healthy human brain and synthetic signals with known ground-truth parameters.

### 5.1 Free-water elimination DTI provides plausible estimates

We confirm that plausible maps can be obtained from FWE-DTI by applying RGD algorithms to single-shell data sets; the FW fraction estimates obtained present the expected hyper-intensities in the cerebral ventricles and subarachnoid space and hypo-intensities in deep WM (Figure 1). Moreover, RGD estimates fitted to a healthy subject single-shell data set provides similar contrasts to well-posed standard FWE-DTI procedures fitted to multishell data sets. However, plausibility does not imply specificity (vide infra).

### 5.2 Initialization determines FWE-DTI plausibility

Single-shell FWE-DTI fitting procedures are based on two main steps: (1) fast parameter initialization and (2) refinement of initial estimates using RGD algorithms.

A common feature of initialization methods is that all resort to prior information. Particularly, the S0-INI method uses priors on the typical pure FW and tissue signals; the MD-INI method assumes a constant prior for $MD_t$, whereas the HY-INI method is just a log interpolation between the former techniques. Resorting to these priors, a well-posed solution for an initial FW fraction (one unknown) can be

![Figure 8](image-url)
obtained assuming that all other parameters are known: the water and tissue signals acquired with b-value = 0 for S0-INI (Equation 3), or \(MD_t\) for MD-INI (Equation 5).

Refining the estimates when using the RGD algorithm attempted to use spatial information to improve the accuracy and precision of FWE-DTI estimates. Our numerical single-voxel simulations revealed that the initialization methods provide FW estimates somewhat sensitive to changes to the ground-truth FW (Figure 2). Additionally, our synthetic multivoxel phantom simulation showed that the FWE-DTI estimates refined by the RGD algorithm match the initial estimates when only single-shell data are provided (Figure 3). Based on these findings, we show that the FWE-DTI initialization priors are the main determining factor for the plausibility of FWE-DTI single-shell estimates.

5.3 Comparison across FWE-DTI initialization methods

Because initialization methods determine the plausibility of FWE-DTI contrasts for single-shell data, it is crucial to compare their robustness. Three initialization strategies were explored. The FWE-DTI initialization matches its ground truth only under certain conditions. Particularly, the \(f_w\) estimates for MD-INI matches the ground-truth identity line only when the \(MD_t\) prior is identical to the ground-truth values of 0.6 \(\mu m^2 ms^{-1}\) (first panel of Figure 2), whereas \(MD_t\) estimates for S0-INI approach the ground truth for synthetic signals generated with low FW (sixth panel of Figure 2).

In previous studies by Parker et al. \(^{31}\) these initialization methods were also compared, reporting final estimates closely matching the simulation ground-truth values. However, the biases that can be induced when ground-truth parameters deviate from the assumed priors had been barely considered. Indeed, our study shows that signals generated with \(MD_t\) larger than 0.6 \(\mu m^2 ms^{-1}\) can substantially inflate the FW fraction estimates for the MD-INI, leading to underestimated \(MD_t\) and overestimated FA. Although less dependent on the ground-truth \(MD_t\), the \(f_w\) estimates from S0-INI present biases that depend on the ground-truth FW content. Regarding the HY-INI method, its estimates present an intermediate behavior, as it interpolates between the MD-INI and S0-INI-based estimates, resulting in biases that depend on both \(MD_t\) and \(f_w\) ground-truth values. As this method presented lower biases than the MD-INI method for the single-voxel simulations and the lowest errors for the synthetic phantom (Figure 3), it was used for producing Figures 5-7.

Although one might argue that initialization might be improved by adjusting the priors, constant priors cannot represent the expected biological variance of dwMRI signals. Indeed, even for healthy brain data, having a constant \(MD_t\) prior is inadequate for representing the variability of tissue’s effective diffusivities across GM and WM regions presenting different microstructural properties. Additionally, selecting reference values for the FW and tissue signals (\(S_r, S_w\)) may be inadequate to capture the spatial variation of the \(T_2\)-weighted images due to bias field inhomogeneities. Although performing image uniformity corrections does help, as shown in the Supporting Information Figure S1, the corrections cannot remove contrast differences due to the transmit \(B_1^+\) field. Moreover, it is unlikely that such complex spatial patterns can be properly captured by a trivial combination of MD-INI and S0-INI initializations (as the HY-INI method).

5.4 Assessment of FWE-DTI specificity

Given the expected heterogeneity of healthy tissue or pathological lesions, it is important to assess the robustness of FWE-DTI algorithms in simulations with ground-truth parameters representing the spatial variation of realistic dwMRI data sets. The specificity of FWE-DTI was explored on synthetic data sets generated based on the parameter estimates obtained for a representative in vivo human brain data set using the FWE-DTI gold-standard technique (NLS fitting designed particularly for multishell data set\(^{25,29}\)).

Although FWE-DTI techniques can provide plausible estimates from single-shell data, plausibility is not equivalent to validity. While the priors imposed by the initialization techniques appear to provide sensitivity to the high \(f_w\) fractions in brain cerebral ventricles and the subarachnoid space (Figure 1), the specificity of FWE-DTI can only be ensured if changes in \(f_w\) can be distinguished from changes of the effective tissue diffusivity \(MD_t\). To test for specificity, we assessed the performance of the different fitting algorithms on two different types of synthetic lesions. Our results show that, when a lesion is generated for an increase of the \(f_w\), the HY-INI technique and consequently the RGD (HY) algorithm correctly predict high \(f_w\) fractions on the lesion area (Figure 5). However, when a lesion with increased \(MD_t\) was simulated, single-shell techniques barely detected a change in \(MD_t\), and instead they erroneously predicted an increase in \(f_w\) (Figure 6); these conclusions are valid for the more general case shown in Figure 8. Our results therefore demonstrate that FWE-DTI specificity is not guaranteed for single-shell data.

5.5 Regularized descent algorithm in multishell data

While no advantage was observed for single-shell data sets, RGD appears to slightly improve the robustness of FW estimates. The measured FW fraction presented slightly increased precision on phantom simulations (Figure 4), and MD biases were suppressed on the MD lesion (Figure 5) when...
multishell acquisitions are considered. This result is consistent with RGD algorithms successfully converging to a more accurate solution only when multishell data are provided and when the FWE-DTI estimation becomes well-posed.

Interestingly, the refined RGD FWE-DTI estimates never reached the accuracy of standard NLS FWE-DTI fitting procedures (Figures 5-7). This might indicate that imposed spatial regularization might impede convergence to a global minimum. This contrasts with the performance of the NLS FWE-DTI algorithm, which recovered the specificity of the estimates even when initialized with the single-shell HY-INI method. Although not shown here, single-shell and multishell RGD algorithm results were robust to changes in the learning rate and number of iterations. These observations are in agreement with Parker et al., in which the authors noted that for data of 2 patients suffering from brain tumors, the estimates obtained with and without the RGD algorithm were similar. In our work, we show that the RGD algorithm might present some benefits regarding estimation precision.

5.6 Limitations and future work

The FWE-DTI fitting routines were only tested on data and simulations reconstructed from a single healthy subject. Although not shown here, our analysis was repeated for other data sets available in DIPY showing consistent results. Because all of our code implementations are openly available, the analysis can easily be reproduced for other open-access data like the Human Connectome project or the Biobank. Although we were able to demonstrate the limitations of the RGD algorithm using simplistic simulations, it will be of interest to reproduce the results on dwMRI data of real lesions or even on physical phantoms, as proposed by Farrher et al.

Tissue’s non-Gaussian diffusion effects due to the presence of multiple tissue compartments or due to the interaction between diffusing water molecules and boundaries were not considered. As we wanted to separately assess the pitfalls of using priors on FWE-DTI initialization and the pitfalls of using spatial regularization of the RGD algorithm, we did not include data for b-values higher than 1 ms μm⁻² (tissue non-Gaussian effects in FWE-DTI multishell fitting have been explored elsewhere). Analogously to other microstructural models (eg, Zhang et al), FWE-DTI fixes the isotropic FW diffusion at 37 °C; however, this prior may be inaccurate for CSF’s FW, due to the presence of metabolites, viscosity differences, or temperature variations). Exploring the accuracy of the FW prior is beyond the scope of this study, because having a fixed FW diffusivity is fundamental to ensure fitting stability. If this constant is released, FWE-DTI fitting will be undetermined even for multishell data, as the information provided by the diffusion-weighted decay is insufficient to disentangle the isotropic FW diffusivity from the FW volume fraction and the MD of water in biological tissues. In future studies, it will be of interest to assess how tissue non-Gaussian effects or inaccurate FW diffusivity priors can further compromise the specificity of FWE-DTI estimates on both single and multishell data sets.

Our main findings point to the need of moving from single-shell to multishell protocols for proper fitting of the FWE-DTI model. This study may also motivate the exploration of techniques that incorporate other sources of information. For instance, FW and tissue components may be decoupled from the signal’s TE dependence, as these components are expected to have different T₂ relaxation properties. The combined use of relaxometry (eg, T₂, T₂*, and T₁) and diffusion information might be facilitated by the rise of acquisition approaches such as ZEBRA, enabling simultaneous measurement of different diffusion weightings and TEs with varying sensitivity to T₂*. or the addition of inversion-recovery modules for T₁ measurement. These approaches may aid in better characterizing tissue compartments, while enabling us to assess the true fractions of different compartments.

6 CONCLUSIONS

We address the controversies behind the use of regularized gradient descent algorithms to fit the FWE-DTI model on single-shell and multishell in vivo and synthetic data sets. We show that these algorithms can provide plausible FW fraction maps on both single-shell and multishell data, due to the priors introduced following initialization. However, based solely on these priors, FWE-DTI estimates are not able to distinguish changes in FW content from changes in MD for single-shell data acquisitions; thus, we stress that results from single-shell FWE-DTI in previous and future studies should be interpreted with care.

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are openly available in ResearchWorks at the University of Washington at https://digital.lib.washington.edu/researchworks/handle/1773/33311, reference number 1773/33311. The code that supports the findings of this study is openly available in https://github.com/mvgolub/FW-DTI-Beltrami.

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**SUPPORTING INFORMATION**

Additional Supporting Information may be found online in the Supporting Information section.

**FIGURE S1** Impact of image-uniformity correction on initial guess maps. The columns from left to right in the left column show the maps obtained using initialization based on the T2-weighted images (S0-INI), a tissue’s mean diffusivity prior (MD-INI), and hybrid (HY-INI) approaches: the first two rows correspond to the free water (FW) and the third and fourth rows to the mean diffusivity (MD) maps obtained from either the uncorrected or corrected data. The right panel depicts the corresponding S0 image before (top) and after (bottom) uniformity correction. The red arrow indicates a region of hyperintensity that leads to reduced MD values when using the uncorrected data.

**FIGURE S2** Tissue segmentation masks used for quantitative evaluation of the parametric maps. From left to right: white matter (WM), gray matter (GM), and CSF.

**FIGURE S3** Difference maps of scalar MD and fractional anisotropy (FA) presented in Figure 1. The metrics from DTI were subtracted to those obtained with regularized gradient descent (RGD) (HY) single-shell and multishell and non-linear least squares (NLS) (multishell) (first, second, and third columns, respectively). Voxels with singularities (ie, FW > 0.7) were set to zero. Because FW elimination (FWE) DTI eliminates the isotropic diffusion contributions to the tissue’s tensor, the MD difference maps (first row) are mostly negative, whereas the FA difference maps (row) are positive (ie, the corrected tensor has increased anisotropy). Differences with higher magnitude appear at the brain border and at interfaces between tissue and CSF.