Published in final edited form as:

Med Image Anal. 2016 August ; 32: 173–183. doi:10.1016/j.media.2016.03.009.

Spatially-Constrained Probability Distribution Model of Incoherent Motion (SPIM) for Abdominal Diffusion-Weighted MRI

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Abstract

Quantitative diffusion-weighted MR imaging (DW-MRI) of the body enables characterization of the tissue microenvironment by measuring variations in the mobility of water molecules. The diffusion signal decay model parameters are increasingly used to evaluate various diseases of abdominal organs such as the liver and spleen. However, previous signal decay models (i.e., mono-exponential, bi-exponential intra-voxel incoherent motion (IVIM) and stretched exponential models) only provide insight into the average of the distribution of the signal decay rather than explicitly describe the entire range of diffusion scales. In this work, we propose a probability distribution model of incoherent motion that uses a mixture of Gamma distributions to fully characterize the multi-scale nature of diffusion within a voxel. Further, we improve the robustness of the distribution parameter estimates by integrating spatial homogeneity prior into the probability distribution model of incoherent motion (SPIM) and by using the fusion bootstrap solver (FBM) to estimate the model parameters. We evaluated the improvement in quantitative DW-MRI analysis achieved with the SPIM model in terms of accuracy, precision and reproducibility of parameter estimation in both simulated data and in 68 abdominal *in-vivo* DW-MRIs. Our results show that the SPIM model not only substantially reduced parameter estimation errors by up to 26%; it also significantly improved the robustness of the parameter estimates (paired Students t-test, $p < 0.0001$) by reducing the coefficient of variation (CV) of estimated parameters compared to those produced by previous models. In addition, the SPIM model improves the parameter estimates reproducibility for both intra- (up to 47%) and inter-session (up to 30%) estimates compared to those generated by previous models. Thus, the SPIM model has the potential to improve accuracy, precision and robustness of quantitative abdominal DW-MRI analysis for clinical applications.

Graphical abstract

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Keywords

Diffusion-weighted MRI; abdomen; liver; spleen; probability distribution model; spatial homogeneity prior; model fitting; Markov Random Field

1. Introduction

Quantitative abdominal DW-MRI enables characterization of the tissue microenvironment by measuring variations in the mobility of water molecules (Murphy et al., 2014; Chow et al., 2012; Yoon et al., 2014). These variations typically develop in response to cellularity, cell membrane integrity, and to the compartment in which water molecules are located (intravascular, extracellular, or intracellular spaces) (Chavhan et al., 2014).

The commonly used mono-exponential signal decay model features a single decay rate parameter known as the “apparent diffusion coefficient” (ADC). The ADC is a robust summary measure of the diffusion of water molecules within a voxel. ADC parameter maps have been useful for identifying regions with restricted diffusion, such as tumor areas, or inflamed bowel loops in Crohn’s disease (Koh and Collins, 2007; Jang et al., 2014; Oto et al., 2011).

Diffusion of water molecules in biological tissues occurs, however, at multiple scales. In addition to the brownian motion of water molecules impacting the DW-MRI signal at the mid b-value range (200–1000 s/mm^2) (Freiman et al., 2012), motion of molecules in micro-capillaries also affects the DWMRI signal decay at the low b-value range (0–200 s/mm^2) (Lemke et al., 2010). Moreover, both slow and fast diffusion occur over a broad range of length and time scales due to widely varying cell structures (Yablonskiy et al., 2003), vessel sizes and flow rates (Henkelman et al., 1994). As a result, the ADC parameter, which encapsulates the entire range of diffusion scales into a single parameter, may not be sufficient to fully characterize the various diffusion scales.

The bi-exponential intra- voxel incoherent motion (IVIM) model introduced by Le Bihan et al. (1988) enable the characterization of the multiple diffusion scales by providing two point-estimates—one for the slow diffusion range and one for the fast diffusion range. Additional advanced models such as kurtosis and stretched exponential models (Bennett et al., 2003; Anderson et al., 2014) aimed to describe the remaining part of distribution by representing the heterogeneity of the diffusion components which is not well-described, however, by the bi-exponential model.

Several studies have demonstrated the potential of characterizing diffusion at different scales in clinical applications, including 1) treatment response monitoring in abdominal and pelvic tumors (Orton et al., 2015); 2) subtyping of renal tumors (Gaing et al., 2015); 3) renal dysfunction assessment (Ichikawa et al., 2013); 4) classifying the severity of liver fibrosis (Chung et al., 2014); and 5) assessing active inflammation in small bowel Crohn's disease (Freiman et al., 2013b) among others.

These studies were limited, however, to point-estimates of fast and slow diffusion as given by the bi-exponential model rather than by explicitly utilizing a full characterization of the distribution of diffusion scales that attenuate the DW-MRI signal.

In this work we introduce a generalized probability distribution model of incoherent motion (PIM) for abdominal DW-MRI that explicitly describes the full range of diffusion scales by a two-component mixture model of probability density functions (PDFs) – one representing slow diffusion, and the other representing fast diffusion. The variance in these PDFs represents the heterogeneities of the diffusion components within a voxel (See Fig. 1 (a)).

Obtaining reliable parameter map estimates of the PIM model for different diffusion scales that are suitable for clinical application is very challenging due to the inherent quality of the abdominal DW-MRI data (Andreou et al., 2013). To offset this limitation, we impose a spatial homogeneity constraint on the probability distribution model of incoherent motion to improve estimation reliability. Our spatially-constrained PIM model (SPIM) of DW-MRI signal decay uses the spatial homogeneity prior, previously proposed by Freiman et al. (2013c,a) for reliable estimation of the IVIM point estimates of fast and slow diffusion. We used the fusion bootstrap moves algorithm (Freiman et al., 2013c) to obtain reliable estimates of the distribution parameters by converting the continuous optimization problem into a sequence of binary optimization problems and solving for all voxels simultaneously, rather than solving for each voxel independently.

This paper is organized as follows: We first formulate the proposed spatially-constrained probability distribution model of diffusion-related signal decay. We then demonstrate the efficacy of this approach by comparing our model to the IVIM and to the previously proposed spatially-constrained IVIM (SCIM) model (Freiman et al., 2013c) in simulated and *in-vivo* experiments on clinical DW-MRI images. We present results from *in-vivo* DW-MRI data from normal abdominal organs in 68 DW-MRI scans from 24 subjects with longitudinal images. For each model, we report and compare normative values of parameters in liver and spleen regions. Finally, we compute and compare the precision, accuracy and reproducibility of parameter estimation in the abdomen achieved with the various models described in this paper.

2. Theory

2.1. Single Exponential Decay Model

The single exponential decay model represents the DW-MRI signal attenuation in each voxel v measured at b-value = b_j in the form of

$$S_{v,i} = S_0 \exp(-b_i(ADC_v)), \quad (1)$$

where ADC_v is the apparent diffusion coefficient that encapsulates the different scales of diffusion.

2.2. Bi-exponential Intra-voxel Incoherent Motion Model (IVIM)

The intra-voxel incoherent motion (IVIM) model introduced by Le Bihan et al. (1988) is a bi-exponential signal decay model that represents the twocomponent signal attenuation in each voxel v measured at b -value = b_i in the form of

$$S_{v,i} = S_{0,v} (f_v \exp(-b_i(D_v^* + D_v)) + (1 - f_v) \exp(-b_i(D_v))), \quad (2)$$

where D_v is the signal decay rate parameter for slow diffusion, and D_v^* is the signal decay rate parameter for fast diffusion. The IVIM model also has a single fraction parameter (f_v) representing the respective fractional contribution of fast diffusion component to the DW-MRI signal decay.

2.3. Probability distribution model of Incoherent Motion (PIM)

In this work, we represent the probability distribution of diffusion in each voxel v with a two-component mixture model $p_v(D)$ of two PDFs, one for fast diffusion (micro-capillary perfusion) and the other for slow diffusion:

$$p_v(D) = f_v p_{1,v}(D) + (1 - f_v) p_{2,v}(D), \quad (3)$$

where D is the random variable representing diffusion with distribution $p(D)$, the weights $f_v \in [0, 1]$ and $1 - f_v$ represent the volume fraction of fast and slow diffusion distribution in voxel v , respectively. $p_{1,v}$ and $p_{2,v}$ are the probability distribution of fast and slow diffusion, respectively.

We use a gamma distribution to describe each diffusion component because of its positive support ($D > 0$) that better matches to the range of diffusion scales which cannot have a negative value. Each diffusion probability density function ($p_{k_j, \theta_j}(D)$, where $j = 1..2$) is therefore defined as:

$$p_{v,k_j, \theta_j}(D) = \frac{D^{k_j-1}}{\Gamma(k_j) \theta_j^{k_j}} \exp(-D/\theta_j), \quad (4)$$

where $\Gamma(k_j)$ is the Gamma function, k_j is the shape parameter and θ_j is the scale parameter. (See Fig. 1 (c)).

Fig. 1 (a) illustrates the relationship between our generalized PIM model and the previously proposed bi-exponential IVIM model of the DW-MRI signal decay. In effect, the PIM model becomes equivalent to the bi-exponential IVIM model, when $p(D)$ is a mixture of two Dirac Delta functions with zero variance. The PIM model also becomes equivalent to the commonly used mono-exponential diffusion model with the decay rate parameter ADC, when the weight of one of components is set to 0.

We formulate the diffusion signal ($S_{v,i}$) (Fig. 1 (b)) for each voxel v measured at b-value b_i as the integral of the PDF $p_v(D)$ of diffusion within a voxel:

$$S_{v,i} = S_{o_v} \int_{-\infty}^{\infty} p_v(D) \exp(-b_i D) dD. \quad (5)$$

The integral in this equation is the Laplace transform of $p_v(D)$. Using the analytical expression of the Laplace transform of gamma distribution for each gamma in $p_v(D)$, we obtain

$$S_{v,i} = S_{o_v} (f_v \exp(-k_{1,v} \log(1 + b_i \theta_{1,v})) + (1 - f_v) (\exp(-k_{2,v} \log(1 + b_i \theta_{2,v}))). \quad (6)$$

We estimate the parameters ($\alpha_v = \{S_o \times f, S_o \times (1 - f), \theta_1, k_1, \theta_2, k_2\}$) of the model at each voxel v by solving a maximum likelihood estimation problem given by

$$\hat{\alpha}_v = \arg \max_{\alpha_v} p(S_v | \alpha_v) = \prod_{i=1}^N p(S_{v,i} | \alpha_v). \quad (7)$$

The measured signal in DW-MRI ($M_{v,i}$) is a sum of the signal component ($S_{v,i}$) and the noise component. We approximate the non-central χ -distributed noise of parallel MRI acquisition (Dietrich et al., 2008) with a Gaussian distribution. Taking the negative log of the maximum likelihood estimator; we obtain the following non-linear least-squares minimization problem:

$$\hat{\alpha}_v = \arg \min_{\alpha_v} \sum_{i=1}^N (M_{v,i} - S_{v,i})^2 \quad (8)$$

where $S_{v,i}$ is given by Eqn. 6.

The special structure of our cost function allows us to use the variable projection optimization algorithm by O'Leary and Rust (2013) which separates the optimization problem into linear and nonlinear parts to obtain more accurate parameter estimation. Rearranging of $S_{v,i}$ in the form of

$$S_{v,i} = \sum_{j=1}^2 c_{v,j} \Phi_j(\theta_j, k_j), \quad (9)$$

we obtain the least squares problem of the form $\sum_{i=1}^N \left(M_{v,i} - \sum_{j=1}^2 c_{v,j} \Phi_j(\theta_j, k_j) \right)^2$ where $c_{v,1} = S_{0v} \times f_v$, $c_{v,2} = S_{0v} \times (1 - f_v)$ are the linear parameters and θ_j, k_j are the nonlinear parameters.

We first solve for the nonlinear parameters by eliminating the linear parameters from the optimization problem. Next, given the value of non-linear parameters, we solve for the linear parameters using linear least squares minimization. This results in more accurate parameter estimates compared to those obtained solely with nonlinear optimization.

2.4. Spatially-constrained Probability distribution model of Incoherent Motion (SPIM)

2.4.1. Integrating the spatial homogeneity prior—Obtaining reliable parameter estimates for the PIM model can be very challenging due to the low signal-to-noise ratio (SNR) of the measured DW-MRI signals. We improve the reliability of the parameter estimates by further integrating a spatial homogeneity prior model as proposed in Freiman et al. (2013c) into our formulation. We estimate the model parameters for all voxels simultaneously rather than estimating the model parameters for each voxel using the least-squares optimization independently. Specifically, we estimate the model parameters by maximizing a posterior distribution given by the product of likelihood and spatial homogeneity prior terms:

$$\hat{\alpha} = \arg \max_{\alpha} p(\alpha|S) \propto p(S|\alpha)p(\alpha). \quad (10)$$

The posterior distribution can be decomposed into a product form using a continuous-valued Markov Random Fields (MRF) formulation given by

$$p(S|\alpha)p(\alpha) \propto \prod_v p(S_v|\alpha_v) \prod_{v_p \sim v_q} p(\alpha_{v_p}, \alpha_{v_q}) \quad (11)$$

where each spatial prior term $p(\alpha_{v_p}, \alpha_{v_q})$ is defined over a neighborhood ($v_p \sim v_q$) around voxel v_p . The likelihood term $p(S_v|\alpha_v)$, defined in Eqn 6 to 8, represents the probability of voxel v to have DW-MRI signal S_v given the signal model parameters α_v . Taking the negative log of Eq. 11, we obtain the following minimization problem:

$$\hat{\alpha} = \arg \min_{\alpha} \sum_v \phi(S_v; \alpha_v) + \sum_{v_p \sim v_q} \psi(\alpha_{v_p}, \alpha_{v_q}) \quad (12)$$

where $\varphi(\mathcal{S}_v; \alpha_v) = -\log p(\mathcal{S}_v | \alpha_v)$ is the negative data likelihood term and $\psi(\alpha_{v_p}, \alpha_{v_q}) = -\log p(\alpha_{v_p}, \alpha_{v_q})$ is the spatial homogeneity term defined using the L1 norm as follows:

$$\psi(\alpha_{v_p}, \alpha_{v_q}) = \gamma \|W(\alpha_{v_p} - \alpha_{v_q})\|_1 \quad (13)$$

where $\gamma \geq 0$ is a weight that determines the amount of spatial homogeneity, and W is a diagonal weighting matrix that accounts for the different scales of the parameters in α_v .

2.4.2. Optimization using fusion bootstrap moves solver—We use the fusion bootstrap moves solver Freiman et al. (2013c) to solve the high dimensionality energy minimization problem for parameter estimation as follows. At each iteration, a model-based bootstrap algorithm (Davidson and Flachaire, 2008) first generates a proposal that consists of signal for each voxel and b-value using the residuals between measured signal and current signal model from the previous iteration. The parameters of the proposal signal are then estimated independently for each voxel by solving Equation 9 as described in Section 2.3. Finally, a binary graph cut solver (Lempitsky et al., 2010) that minimizes the energy function in Equation 12 is used to fuse the current parameter estimates (α^0) with the new proposed parameter estimates (α^*) into a new estimate of parameters (α^{fused}) that better fit the observed DW-MRI signal while imposing spatial homogeneity constraints. Table 1 describes the steps involved in the parameter estimation algorithm. We initialized the parameters with the values estimated using the IVIM model.

2.4.3. Selection of hyper-parameters of the SPIM Model—The SPIM model includes three hyper-parameters: 1) the standard deviation of the signal noise; 2) the weight of the spatial homogeneity prior γ ; and 3) the parameter weighting matrix W . We estimate the standard deviation of the signal noise from a background region for each scan located in the corner of a b=0 image. The weight of the spatial homogeneity prior was determined experimentally and set to 0.003 as described in Section 3.1. To determine W , we assessed the scale difference in mean values of the SPIM parameters using the value of the IVIM parameters reported in the literature for the liver and spleen. The SPIM parameters were calculated from the values of IVIM parameters as explained in Section 3.1. We then set the rescaling matrix W diagonal to $\{1, .1, 1e-6, 10, 1e-7, 1\}$ to provide equal weight to each one of the SPIM model parameters $\{S_o \times f_v, S_o \times (1 - f_v), \theta_1, k_1, \theta_2, k_2\}$, respectively. We used these hyper-parameter values for the SPIM model in all of our experiments in this manuscript.

When estimating the SPIM model parameters, we used a 2D Markov Random Field (MRF) formulation instead of a 3D MRF for spatial regularization due to the anisotropic nature of voxels in DW-MRI images in the axial direction (i.e., $1.97 \times 1.97 \times 5.5\text{mm}^3$). The neighborhood size was selected to be 3×3 using the Markov property of the MRF theory. The optimization was performed over the entire image jointly. It is also possible, however, to use a 3D MRF formulation for parameter estimation.

2.4.4. Spatially-constrained IVIM (SCIM) Model—The spatially constrained IVIM model was introduced by Freiman et al. (2013c). We refer the readers to this paper for the

detailed description of the SCIM model. In our experiments, we used the hyper-parameters reported in Freiman et al. (2013c) for the SCIM model.

3. Experimental Methodology

3.1. Accuracy of SPIM model parameter estimates using simulated data

We assessed the accuracy and precision of parameter estimates produced by the proposed SPIM model in comparison to those produced by using the ADC (Koh and Collins, 2007), the IVIM (Le Bihan et al., 1988) and the SCIM (Freiman et al., 2013c) models using synthetic data. We generated synthetic images from *in-vivo* abdominal images to achieve structures that are similar to real abdominal diffusion images as follows: We first estimated fast and slow diffusion parametric maps from *in-vivo* DW-MRI data using the IVIM model. We then clustered each set of parametric maps (D , D^* , f) to obtain six clustered regions of abdominal structures and calculated the mean value of the parametric maps. Table 2 summarizes the mean values of IVIM parameters for each region l , from one to six. Next, we converted these IVIM parameters to SPIM parameters, assuming the mean of the gamma distributions are D and D^* and their mixing proportion is f . We set the standard deviation of the distributions to 0.1 for D and 1 for D^* . We set S_o to 200 for all regions. The parameters of two-component mixture of gamma distributions for each region l were

$$\alpha^l = \{S_o^l \times f^l, S_o^l \times (1 - f^l), \theta_D^l, k_D^l, \theta_{D^*}^l, k_{D^*}^l\}.$$

We simulated the diffusion signal for each voxel in region l at b-value b_i by sampling points from the corresponding mixture of gamma distributions and by integrating the samples using Eqn. 5. We used a set of 7 b-values (0, 50, 100, 200, 400, 600, 800 s/mm^2) that is similar to the clinical data used in the rest of our experiments. Last, we added noise sampled from a Rician distribution with values ranging from 2 to 8 to achieve an SNR between 65 ($200/2 \times 0.65$) and 16.25 ($200/8 \times 0.65$) for the chosen signal value of $S_o = 200$ at b-value = 0 mm^2 .

Fig. 2 shows a representative example of the clustered parameter maps (e); the probability mixture models of diffusion for the different regions (d); and the simulated DW-MRI images generated from the clustered maps (a–c).

We estimated the model parameters from the simulated DW-MRI data using the proposed SPIM model, the ADC, the IVIM, and the SCIM models. We assessed the accuracy of the parameter estimates produced by each model by calculating the Root Mean Squared Error (RMSE) of the estimated parameters for each region. We also analyzed the RMSE specifically for finer-scale regions (e.g., blood vessels within the liver, the cortex of kidney and the outer boundary of spleen) so that we could assess the influence of the spatial homogeneity prior on the estimation accuracy in these structures as well as optimize the spatial homogeneity prior weight by examining its influence on the RMSE. In addition, we characterized the precision of the parameter estimates of various models by calculating the standard deviation of absolute error of the estimates.

3.2. Precision of SPIM model parameter estimates from in-vivo DW-MRI experiments

We analyzed the improvement achieved in the precision of parameter estimation by using the SPIM model compared to that of the IVIM and the SCIM models using *in-vivo* DW-MRI experiments.

We acquired 68 abdominal DW-MRI datasets with multiple acquisitions from 5 healthy volunteers and 24 patients with normal radiological findings in the liver and the spleen using a 1.5T MRI scanner (Magnetom Avanto, Siemens Medical Solutions, Erlangen, Germany) with an 8-channel, bodymatrix receive coil. Free-breathing, single-shot echo-planar imaging was performed using the following parameters: repetition time/echo time (TR/TE) = 7500/77 ms; SPAIR fat suppression; matrix size = 192×156; field of view = 300×260 mm; number of excitations = 1; slice thickness/gap = 5 mm/0mm; 40 axial slices; 7 b-values=0, 50, 100, 200, 400, 600, 800 s/mm². We used a six-directional gradient scheme to acquire 6 successive images at each nonzero b-value. We also acquired three repeated images at b-value=0. The overall acquisition time was 5.5 min.

Assuming isotropic diffusion, we generated higher SNR diffusion trace-weighted images at each non-zero b-value using geometric averaging of the images acquired in six diffusion sensitization directions (Mulkern et al., 2001). To generate b-value=0 image, we computed the geometric average of the three repeated images at b-value=0. We estimated the diffusion parameters using 7 high SNR b-value images computed using 39 (1 × 3 + 6 × 6) acquired image volumes.

We quantified the uncertainty of parameter estimation using the wild-bootstrap analysis (Freiman et al., 2011) on all *in-vivo* DW-MRI datasets as follows: First, we generated multiple sets of the diffusion signal for each b-value from the estimated signal model using the bootstrap resampling strategy. Next, we estimated the diffusion model parameters (D, D*, f) using different models: 1) the IVIM model; 2) the SCIM; and 3) the proposed SPIM model for each set of generated DW-MRI signal at multiple b-values. Last, we calculated for each model the percentage of coefficient of variation (CV%=standard deviation/mean × 100) of the parameter estimates at each voxel. This measure indicates to what degree parameter estimates may vary over multiple bootstrap resampling repetitions. The smaller the CV% value, the more precise the parameter estimation. We performed multiple comparison tests to compare the CV% obtained using IVIM, SCIM and SPIM models, respectively. This analysis was performed in two circular regions of interest (ROI) of 5mm radius which were manually annotated in the liver and the spleen, respectively. We also calculated the average model parameters over these ROIs for each model. Figure 3 depicts representative dataset with the manually annotated ROIs used for the analysis.

3.3. Reproducibility of SPIM model parameter estimates over longitudinal inter- and intra-session in-vivo DW-MRI experiments

In this experiment, we analyzed both the intra- and inter-session reproducibility of the SPIM model parameter estimates compared to those of IVIM and the SCIM models. We used the healthy patient data described in Sec. 3.2 to determine the reproducibility of intra-session parameter estimates. We repeated the DW-MRI acquisition for the healthy volunteers

[6,4,4,3,3] times, respectively, within the same session. We determined the reproducibility of the inter-session longitudinal parameter estimates by retrospectively analyzing the longitudinal clinical DW-MRI data-sets of 24 patients acquired between 01/2011 and 06/2014. We selected 24 patients (10 female/14 male; ages range, 9-19) that were imaged at least two times. The second imaging session took place 6-24 months after the first session. Radiological findings in the livers and the spleens of the study subjects were normal.

We assessed the reproducibility of parameter estimates using the three different models as follows: We first placed a region of interest (ROI) in corresponding areas of the liver and spleen on each longitudinal scan, aided by anatomical landmarks. We estimated the model parameters using the IVIM model, the spatially-constrained SCIM model, and the proposed SPIM model. We then calculated the percentage of coefficient of variation of each parameter over time for each voxel in the ROIs. Last, we computed a mean CV% for each parameter representing the liver and the spleen regions of interest. This measure indicates to what degree parameter estimates may vary over different scans acquired at different time points, either within the same session or in different sessions.

4. Experimental Results

4.1. Accuracy of SPIM model parameter estimates using simulated data

Figure 4 presents the reference parameter maps of simulated data and the parametric maps estimated using the proposed SPIM, the SCIM, the IVIM and the ADC models. Figure 5 illustrates the respective accuracy of each model in estimating the parameters for the entire image by means of the percentage of the RMSE and the standard deviation of the absolute value error between the reference and estimated parameters as a function of the noise level. Specifically, the RMSE of parameter estimates obtained with the proposed SPIM model were 23%, 26%, and 12% lower for D, D*, and f parameters, respectively, compared to those obtained using the IVIM model. Compared to the SCIM model, the mean parameter estimation errors of SPIM were 4%, 6% and 3% lower for D, D*, and f parameters, respectively.

Figure 6 presents the effect of the spatial smoothness parameter γ on the parameter estimation accuracy in the finer scale structures. Our results show that setting γ 's value to the range of 0.0001 to 0.003 yield better accuracy than setting γ value to 0.01 or above. We therefore set the γ parameter to 0.003 in the remainder of the experiments reported in this work. Our results also show that the proposed SPIM model improved the accuracy of parameter estimates for finer scale structures compared to those of IVIM and SCIM models, respectively. Specifically, the mean parameter estimation errors obtained when using the proposed SPIM model were 15%, 20%, and 2% lower for D, D*, and f parameters, respectively, than the estimation errors obtained for those parameters when using the IVIM model. Compared to SCIM, parameter estimation errors were reduced by 8% for D, 4% for D*, but by less than 2%, for the f parameter.

4.2. Precision of SPIM model parameter estimates from in-vivo DW-MRI experiments

Figure 7 presents bar-plots of the CV% of parameter estimates over multiple bootstrap resampling repetitions for the IVIM, the SCIM and the SPIM models, respectively. The CV% of parameter estimates obtained by the IVIM model were 20% for D; 84% for D*; and 39% for the f parameter in the liver; and 15% for D; 118% for D*; and 70% for the f parameter determined in the spleen. While the CV% of parameter estimates obtained by the SPIM model were 6% for D; 17% for D*; and 8% for the f parameter in the liver and 5% for D; 23% for D*; and 17% for the f parameter in the spleen; the CV%'s of the SPIM parameter estimates were lower for all parameters compared to those of both the IVIM and the SCIM models. The improvements in CV% were statistically significant (multiple-comparison test, $p < 0.0001$).

Figure 8 shows representative parametric maps obtained using all four models. The SPIM parametric maps are visually of better visual quality than those of the IVIM model, especially the perfusion (D*) and perfusion fraction (f) maps. Fine scale structures such as vascular regions at the cortex of the kidneys and at the outer boundary of spleen can be identified by their high perfusion fraction values in the f parameter maps.

Table 4.2 summarizes the mean values of the parameters for the liver and spleen computed using the IVIM, the SCIM and the SPIM models, respectively. The ADC model parameter value reported in the last row shows that the ADC parameter deviated largely from the D parameter values of the IVIM, the SCIM and the SPIM models, respectively. This is due to the presence of a fast diffusion component that is not considered by the mono exponential ADC model. The differences in the mean values of parameters estimated using the SPIM model compared to both the IVIM and SCIM models were statistically significant (multi-comparison test, $p < 0.05$).

4.3. Reproducibility of SPIM model parameter estimates over longitudinal inter- and intra-session in-vivo DW-MRI experiments

Figure 9 shows the bar plot of intra-session CV% with error bars showing the variations over the 5 study volunteers. IVIM parameters had intra-session mean CV% of 22 ± 11 , 76 ± 33 and 34 ± 19 , while SPIM parameters had lower mean CV% values of 14 ± 7 , 29 ± 12 and 23 ± 12 for D, D* and f, respectively, in the liver. The improvement in CV% was statistically significant (paired student t-test, $p < 0.01$) for all parameters in the liver and for the D* and f parameters in the spleen.

Figure 10 shows the bar plot of inter-session CV% calculations for both liver and spleen computed over 24 patients. IVIM parameters had an interscan mean CV% of 23 ± 25 , 75 ± 43 and 46 ± 37 , while SPIM parameters had lower mean CV% values of 16 ± 14 , 45 ± 34 and 32 ± 21 for D, D* and f, respectively, over 24 patients in the liver. The improvement in the CV% was statistically significant (paired student t-test, $p < 0.01$) for all parameters in the liver and for D* and f parameters in the spleen.

5. Conclusions and Discussion

Quantitative DW-MRI is becoming increasingly important for various clinical applications in abdomen. Diffusion of water molecules in biological tissues occurs at multiple scales and has mainly two components: 1) fast diffusion, which is associated primarily with the motion of molecules in micro-capillaries; and 2) slow diffusion, which is associated with the Brownian motion of the water molecules. Currently available models represent the entire range of diffusion scales using one or two diffusion parameters. Unfortunately, these approaches do not fully characterize the multi-scale nature of diffusion.

In this work, we propose a spatially constrained probability distribution model of incoherent motion (SPIM) to fully characterize the entire range of diffusion scales within each voxel. The SPIM model represents the heterogeneous diffusion of water molecules in a voxel with a two-component mixture of Gamma PDFs that separately capture slow and fast diffusion.

Robust estimation of DW-MRI signal decay model parameters is challenging due to the inherently low SNR of the DW-MRI data. Previous approaches for achieving robust estimation by SNR increase, included averaging the DW-MRI signal over repeated acquisitions or over large regions. However, these approaches required either increased scan time which is not practical in most clinical settings, or reduced sensitivity to heterogeneous regions such as necrotic and viable parts of tumors.

The effectiveness of using a spatial homogeneity prior within a Markov Random Field framework to increase SNR and improve outcome in various low-level computer-vision applications have been first shown in a seminal paper by Geman and Geman (1984). Building on that work, Black and Rangarajan (1996) and others also showed that accounting for spatial homogeneity where it is present not only reduces noise effects, but also enforces appropriate boundaries between homogeneous regions when these boundaries are present. Encouraged by these earlier experiments, we have introduced a spatial homogeneity prior in a MRF framework to achieve robust parameter estimates of the probabilistic DW-MRI signal decay.

Our simulation experiments show that the SPIM model improves both the accuracy and precision of the DW-MRI signal decay model parameter estimates as well as the visual quality of the parametric maps. We compared our SPIM model results to those obtained with the previously applied mono-exponential signal decay model, the bi-exponential IVIM and the SCIM models. Specifically, SPIM achieved a 26% reduction in RMSE compared to the IVIM, and a 6% reduction in RMSE compared to the SCIM for the entire image. Moreover, SPIM achieved a 20% reduction in RMSE compared to the IVIM and a 4% reduction in RMSE compared to the SCIM for fine-scale structures, such as vascular regions in liver, spleen and kidney.

Our *in-vivo* experiments show that while ADC parameter maps, which are utilized in current practice, resulted in good visual quality; they failed to quantify the entire range of diffusion scales using a single parameter. Moreover, they failed to generate quantitative ADC values that are close to true slow diffusion values (Table 4.2, Fig. 4 and 8), due to the presence of the fast-diffusion. Thus, the full range of diffusion scales must be considered in quantitative

DW-MRI analysis for clinical applications such as staging disease and monitoring treatment response-to-therapy in cancer or in Crohns disease.

Compared to the bi-exponential IVIM and the SCIM models, our SPIM model increased the precision of the parameter estimates of DW-MRI signal by reducing the CV% of parameter estimates, especially for the fast diffusion component (D^*) (84% (IVIM) vs. 17% (SPIM) in the liver and 118% (IVIM) vs. 23% (SPIM) in the spleen). In addition, our results show that both the intra- and inter-scan longitudinal reproducibility of the diffusion signal decay model parameters estimated using the SPIM model improved significantly compared to both the IVIM and the SCIM models. Of particular note, the CV% of the fast diffusion parameter decreased by 47% for the intra-session estimate, and by 30% for the inter-session estimates when using the SPIM model compared to the IVIM model in the liver. These results demonstrate the potential role of fully characterizing the entire range of diffusion scales using the SPIM model in clinical applications for quantitative DW-MRI.

Our study had several limitations: First, this work was limited to a technical analysis of the performance of the SPIM model in simulated experiments, and in 68 *in-vivo* DW-MRI datasets from 29 subjects with radiologically normal abdominal organs. For assessing the clinical utility of the proposed model, a large clinical study to evaluate the quantitative markers estimated using the proposed SPIM model is required. Second, the study population was limited by the number and age of the subjects. Our DW-MRI analysis of the proposed model was restricted to 68 *in-vivo* DW-MRI datasets from 24 patients and 5 healthy volunteers. In this study, the average values of the estimated quantitative parameters were reported in this limited population. Third, the DW-MRI protocol for acquiring the study data was limited to the clinical protocol used at our institution. Therefore, the images were acquired with a fixed set of b-values for data from the 29 subjects used in this study. The effect of b-value selection (i.e., their value and number of b-values used) on the performance of parameter estimation should be evaluated for the SPIM model, as demonstrated by Lemke et al. Lemke et al. (2011) for the IVIM model. Furthermore, the effect of acquiring low b-value data ($0 < b < 50 \text{ s/mm}^2$) should be investigated using the SPIM model (especially for the liver), as suggested by Cohen et al. Cohen et al. (2014) in their study of IVIM. Fourth, a free-breathing acquisition scheme, prone to the confounding effects of motion due to respiration was employed in our study. Previous work compared free-breathing acquisition to respiratory-triggered acquisition schemes and found that parameter estimates were similar, but a free-breathing acquisition was preferable due to shorter scan times. Future work should analyze the impact of retrospective or prospective motion compensation techniques on the performance of parameter estimation.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This work is supported by the National Institute of Diabetes & Digestive & Kidney Diseases of the NIH under award R01DK100404 and by the Translational Research Program at Boston Childrens Hospital. The content is

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Highlights

- A novel probability distribution model of diffusion (PIM) for abdominal DW-MRI
- Accounts for heterogeneity and multi-scale nature of diffusion in a voxel
- A spatial constrained version of PIM (SPIM) for robust parameter estimation
- Solved with variable projection optimization and fusion bootstrap moves solver.
- Increased precision and reproducibility of parameter estimates from in-vivo DW-MRI

Figure 1.

(a) Comparison of probability density functions (PDFs) modeling fast (D^*) and slow diffusion (D) components, respectively. IVIM uses Dirac Delta PDFs, proposed SPIM model uses a mixture of gamma PDFs. (b) Diffusion signal of a voxel in liver at different b-values and fitted models using SPIM and IVIM, respectively. (c) Gamma PDF for different values of shape parameter k_i and scale parameter.

Figure 2. Simulated images at b-values 100 (a), 400 (b) and 800 (c); (d) shows PDF of diffusion for 6 regions. Each PDF is a two component mixture of gamma distributions

Figure 3.
Example slice showing the ROIs used to analyze parameter estimation performance. Regions of interest were drawn manually in the liver and spleen for each scan.

Figure 4.

Simulated data used in the accuracy evaluation experiment. The first row depicts the reference parametric maps (D, D*, and f). The second, third and fourth rows show parametric maps calculated using the IVIM model, the SCIM model, the proposed SPIM model, and the ADC model respectively. For all measures, the proposed SPIM model produced parametric maps that are more similar to reference maps than those produced with the IVIM model, especially, for the fast diffusion maps. However, the ADC model parametric map values deviated significantly from the true D parametric map values.

Figure 5.

Accuracy and precision of the incoherent motion parameter estimates on the entire image from the simulated data: The top and bottom plots depict the relative RMSE and the standard deviation of the absolute valued errors, respectively. The proposed SPIM model improved both the accuracy and precision of parameter estimates compared to the IVIM model for all SNR values. The SPIM model reduced the relative RMSE by 6% for D^* , 4% for D and 3% for the f parameter compared to the SCIM model.

Figure 6.

Accuracy and precision of the incoherent motion parameter estimates in finer-scale structures using the simulated data: Top and bottom plots depict the overall relative RMSE and the absolute valued error standard deviation, respectively. The effect of spatial smoothness parameter γ on the performance is also presented. Setting γ value in the range of 0.0001 to 0.003 is better than setting it in the range of $\gamma = 0.01$. The proposed SPIM model reduced the relative RMSE and the absolute valued error STD for all parameters compared to the IVIM model, and in D and D* parameters compared to the SCIM model.

Figure 7.

Bar plot of CV% of multiple bootstrap parameter estimates computed on 68 scans from 29 subjects. The improvements in CV% when using the SPIM model were statistically significant (multiple-comparison test, $p < 0.0001$).

Figure 8.

Representative parametric maps. Rows one to four show parameter maps estimated for a slice using the IVIM, the SCIM, the SPIM and the ADC models, respectively. Visual improvement in parameter estimates are observed, in particular, in fast diffusion (D^*) and in the fraction of fast diffusion (f) parametric maps. The ADC model parametric map values deviated significantly from the slow diffusion parametric map values generated by the IVIM, the SCIM and the SPIM models.

Figure 9.

Intra-session coefficient of variation percentage (CV%) of the D, D* and f parameters, respectively computed using IVIM, SCIM and SPIM models in the liver (left) and spleen (right) of 5 healthy volunteers. In the liver, a pair-wise student t-test showed that differences in CV% were statistically significant for all parameters using the SPIM model compared to both the IVIM and SCIM models; and in the spleen, the CV% of the D* and f parameters showed a statistically significant difference using SPIM compared to both IVIM, and SCIM models.

Figure 10.

Longitudinal reproducibility measured by inter-session coefficient of variation percentage (CV%) of D, D* and f parameters, respectively computed using the IVIM, SCIM and SPIM models in the liver (left) and spleen (right) of 24 patients. In the liver, a pair-wise student t-test showed that differences in CV% were statistically significant for all parameters using the SPIM model compared to both the IVIM and SCIM models. In the spleen, the CV% of the D* and f parameters had a statistically significant difference using SPIM compared to IVIM, and the D* parameter had a statistically significant difference compared to SCIM.

Table 1

The fusion bootstrap moves algorithm for the SPIM model parameter estimation

Input:	$m_{v,i}$ measured signal at voxel v at b-value b_i
Output:	α_v : final parameter values at voxel v after k^{th} iteration
Initialization:	$\alpha_v \leftarrow \alpha_v^0$ parameter values at iteration 0 estimated for each voxel v independently using Eqn. 9.
Step 1.	Model based bootstrap resampling: (Davidson and Flachaire, 2008; Freiman et al., 2011) $s_{v,i} \leftarrow$ signal for model parameters α_v at each b_i 1) Compute residuals: $\varepsilon_{v,i} = m_{v,i} - s_{v,i}$ 2) Compute proposed signal $s_{v,i}^* : s_{v,i}^* = m_{v,i} + t_{v,i} \varepsilon_{v,i}$ where $t_{v,i}$ is a two-valued Rademacher distributed r.v. with $p(t_{v,i} = 1) = 0.5$, $p(t_{v,i} = -1) = 0.5$.
Step 2.	Estimate proposed parameter values (α_v^*) from $s_{v,i}^*$ for each voxel v independently (Eqn. 9).
Step 3.	Fusion of current (α_v) and proposed parameters (α_v^*) for all voxels simultaneously: (Freiman et al., 2013c) by solving the MRF formulation in Eq. 12 using a binary graph cut solver to obtain new fused parameter values: ($\alpha_v \leftarrow \alpha_v^{fused}$) Go back to Step 1 until convergence.

Table 2

Mean values of the parameters of clustered regions one to six are shown in units of $\mu m^2/ms$ for D and D*.

	l=1	l=2	l=3	l=4	l=5	l=6
D_l	0.8	1.3	1.8	1.1	2.8	1.1
D_l^*	21	17	27	24	10	37
f_l	0.18	0.26	0.49	0.47	0.22	0.38

Table 3

Comparison of mean and standard deviation of parameters estimated using the IVIM, the SCIM and the SPIM models for liver (L) and spleen (S) regions. The values are in units of $\mu m^2/ms$.

	IVIM		SCIM		SPIM		p-value		p-value	
		mean $\pm$ std		mean $\pm$ std		mean $\pm$ std	IVIM-SCIM	IVIM-SPIM	SCIM-SPIM	
L	D	0.99 $\pm$ 0.25		1.00 $\pm$ 0.22		0.96 $\pm$ 0.18	0.47	< 0.001	< 0.001	
	D*	63.84 $\pm$ 59.18		48.94 $\pm$ 47.62		33.92 $\pm$ 22.01	< 0.001	< 0.001	< 0.001	
	f	0.26 $\pm$ 0.16		0.26 $\pm$ 0.15		0.27 $\pm$ 0.15	0.49	< 0.001	< 0.001	
S	D	0.71 $\pm$ 0.16		0.68 $\pm$ 0.16		0.67 $\pm$ 0.16	< 0.001	< 0.001	0.02	
	D*	41.92 $\pm$ 38.47		35.49 $\pm$ 10.09		29.79 $\pm$ 6.11	< 0.001	< 0.001	< 0.001	
	f	0.11 $\pm$ 0.13		0.12 $\pm$ 0.12		0.13 $\pm$ 0.14	< 0.001	< 0.001	0.008	
ADC										
L	D	1.22 $\pm$ 0.28								
	S	0.80 $\pm$ 0.15								