Model-based estimation of microstructure parameters from diffusion MRI data in a substrate with microscopic anisotropy and a distribution of pore sizes

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Target Audience Biophysical modellers, diffusion MRI researchers

Introduction Non-invasive estimation of cell size and shape is a key challenge in diffusion MRI with potential applications in cancer imaging to discern differences in tumour microsctructure and grey matter imaging to discriminate cytoarchitectures. [1, 2] used the difference between parallel and perpendicular gradients in double pulsed field gradient (dPFG) acquisitions to derive a rotationally invariant index of microscopic anisotropy (μFA), while [3] used a single-shot diffusion trace sequence to arrive at a similar metric. Such measures of μFA, lack a quantitative interpretation, because they intrinsically depend on sequence parameters and are not invariant to size distribution. This issue is illustrated in Fig 2 for an ensemble of randomly oriented finite cylinders with Gamma distributed radii, where the same μFA value can correspond to different microstructure parameters. Previously, angular dPFG measurements have been used to estimate pore size in an ensemble of identical pores with either low eccentricity (spheres) or very high eccentricity (infinite cylinders) [4]. Here we demonstrate in simulation the feasibility of using a model-based approach to provide more quantitative information on compartment shape that is invariant to size distribution, motivating further work to devise practical sequences and protocols enabling such measurements in practice.

Fig.1: Randomly oriented finite cylinders with Gamma distributed radii – GFAC

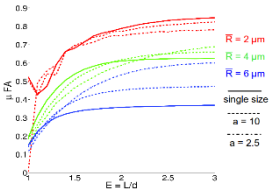


Fig.2: μFA simulation for GFAC as a function of the ratio between cylinder length and diameter. Protocol from [1]: δ = 5ms, Δ = tm =50 ms, G = 500mT/m., SNR = 50.

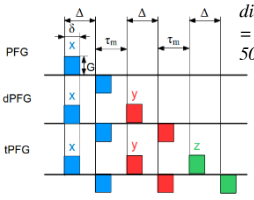


Fig.3: Diffusion sequences used for model-fitting approach

Purpose: In this work we estimate microstructure parameters such as pore size and elongation using a model which accounts for size distribution. We hypothesize that standard single PFG measurements cannot support the estimation of such parameters, but double PFG measurements can, while adding a third encoding for isotropic sensitivity, as in [4], may further enhance sensitivity.

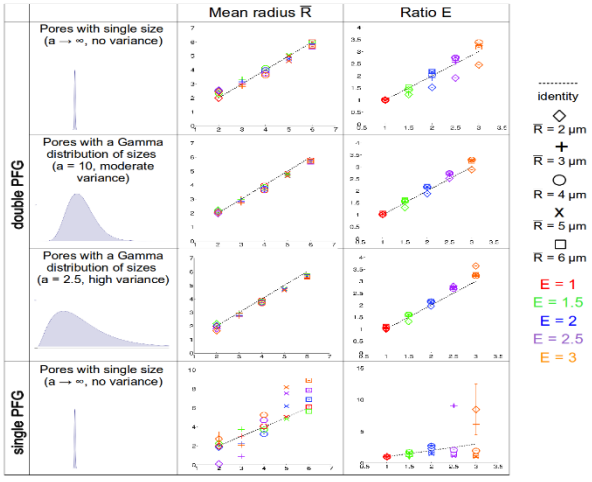
Methods Tissue model: The model we consider here is macroscopically isotropic, composed of randomly oriented finite cylinders with a Gamma distribution of radii (Gamma finite astro-cylinders GFAC), as illustrated in Fig 1. The model parameters are the intrinsic diffusivity D, which we set equal to *2E-9* s/m^2, mean cylinder radius $\bar{R}$=*{2, 3, 4, 5, 6}* um, the ratio between the length and the diameter of the cylinder E = *{1, 1.5, 2, 2.5, 3}* and the shape parameter of the Gamma distribution a = *{2.5, 10, ∞}*. Diffusion sequences: We investigate single, double and triple PFG protocols as shown in Fig. 3. For each sequence we construct a protocol with a wide range of diffusion parameters as follows: δ = *{5,10 …,25}*ms, $\Delta = \delta$+*{5, 10, 20, 30, 40}* ms, *tm* = Δ and G = *{25, 50, 75, 100, 300, 500}*mT/m. Data synthesis: We synthesised diffusion data using MISST toolbox which implements a matrix formalism extended for gradients with varying orientation [5,6] and added 10 instances of Rician noise with SNR of 50. Diffusion model: Iterative model fitting requires fast evaluation of the signal from the parameters which excludes the matrix method in MISST, so we derive Gaussian Phase Distribution approximations for each of the pulse sequences in Fig. 3, which allows a faster signal evaluation. We calculate the signal for each individual cylinder and then numerically integrate over orientation and size distribution: $S = \int_{\vec{u}}\int_R S(\vec{u}, R)$ where $S(\vec{u}, R) = S_{\perp,\vec{u}} S_{\parallel,\vec{u}}$ with

$$\ln(S_{\perp,\vec{u}}) = \frac{\gamma^2}{2}\sum_n B_{cyl,n}\int_0^{TE} dt_1 \int_0^{TE} dt_2 \exp\left(-\lambda_{cyl,n} D(t_2 - t_1)\right) G_{\perp,\vec{u}}(t_1) G_{\perp,\vec{u}}(t_2) \cos\left(G_{\perp,\vec{u}}(t_1), G_{\perp,\vec{u}}(t_2)\right) \text{ and}$$

$$\ln(S_{\parallel,\vec{u}}) = \frac{\gamma^2}{2}\sum_n B_{plane,n}\int_0^{TE} dt_1 \int_0^{TE} dt_2 \exp\left(-\lambda_{plane,n} D(t_2 - t_1)\right) G_{\parallel,\vec{u}}(t_1) G_{\parallel,\vec{u}}(t_2) \cos\left(G_{\parallel,\vec{u}}(t_1), G_{\parallel,\vec{u}}(t_2)\right);$$

γ is the gyromagnetic ratio, B_n and λ_n are geometry related factors for cylindrical and planar restriction [7] and $G_\perp$ and $G_\parallel$ are the perpendicular and parallel components of the diffusion gradient to the cylinder axis for the given orientation. For numerical integration, we used 10 samples from the Gamma distribution and 50 isotropic orientations on a sphere. Parameter estimation: For each combination of model parameters, we fit the GFAC model in a two-step fitting procedure: grid search and gradient descent. In this preliminary work, the diffusion constant is fixed to its correct value.

Results. Figure 4, rows 1-3, illustrate the microstructure parameters ($\bar{R}$ and E) estimated with GFAC model and double PFG protocol as a function of the ground truth values used in the simulation for three different diffusion substrates. (Shape parameter a was fitted as well, but not shown for simplicity.) The different symbols represent data sets with different mean radii and the ratio of length to diameter is colour coded. The data points in the two columns correspond. The standard deviation over the 10 instances of noise with SNR = 50 is small and contained in the size of the marker. For triple PFG the results are very similar to those from double PFG (data not shown), with the largest differences between the parameter estimates and ground truth values occurring for small pores with $\bar{R}$ =2 *um,* that do not produce enough diffusion weighting for the weak gradients and are more affected by noise. For the substrate with single sized pores, triple PFG provides better estimates for $\bar{R}$ =2 *um*, possibly due to the increased diffusion weighting. Larger errors also occur for higher ratios of length to diameter, some cases in which the cylinder length is larger than the root mean square displacements given by the chosen diffusivity value and diffusion time. Nevertheless, the largest differences do not exceed 30% of the ground truth values. The microstructure parameter estimates are accurate for double and triple PFG, while single PFG cannot recover the ground truth parameters, which is illustrated in Fig 4, row 4 for an ensemble of single sized pores.



Discussion: This work shows for the first time the feasibility of estimating explicit microstructure parameters in a substrate with macroscopic isotropy but microscopic anisotropy using a model-based technique which accounts for pore size distribution. The model makes various simplifying assumptions that future work can consider relaxing: the ratio of cylinder length to diameter is fixed within each substrate; there is no extracellular signal or exchange; the pore orientation distribution is isotropic. For example, this technique can be extended to a rotationally invariant framework by modelling the orientation of the pores (eg. using a Watson distribution [8]). A comprehensive diffusion protocol was chosen in order to have sensitivity over the wide range of parameters chosen in the simulation. However, in practice, this protocol is not achievable for several reasons: the gradient strengths are hard to achieve and the time required to acquire the data is too large. Adaptations of the sequences we use here, for example to use stimulated rather than spin echoes and/or replacing the rectangular gradients with oscillating gradients, should help to maintain a wide range of sensitivity in practical situations. Moreover, if there is prior knowledge of the system, then the diffusion protocol can be substantially shortened using numerical optimisation [9].

References: [1] Jespersen et al, NMRBiomed 2013,[2] Lawrentz et al JMR 2010, [3] Lasic et al Front Phys 2014, [4] Shemesh et al, NMRBiomed 2012, [5] Codd and Callaghan JMR 1999, [6] Drobnjak et al, JMR 2011, [7] Stepisnik, Physica B 1981, [8] Zhang et al NI 2011, [9] Alexander et al MRM 2008