

THE RELATION BETWEEN DISTRIBUTION OF EFFECTIVE DIFFUSIVITY AND MULTI-EXPONENTIAL MODELS IN A VARYING MICROSTRUCTURE: A MONTE CARLO STUDY

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Introduction: The non-monoexponential DWI decay at high b-values has been attributed to the multiplicity of water diffusion rates, which may provide the information about the water compartmentation. The common way to compute the diffusion rates is through the multi-exponential analysis. The bi-exponential model [1] assumes two diffusion rates. The distributed exponential model [2] makes no assumption about the number of diffusion rates, and can be empirically described by the stretched exponential model (α -DWI) [3]. The parameter α has been theoretically derived from physical models of anomalous diffusion [4]. Those models have a few parameters, and have been shown to correlate with the pathology [5-7]. However, the link between the fitted parameters and biophysical mechanisms remains unclear. The multi-exponential relation is also phenomenological [8,9], because each diffusion rate is no longer associated with a mono-exponential decay when diffusion time is long (>30 ms in a clinical DWI). In this study, the distribution of 'effective' water diffusivity in a simulated cell structure (Fig. 1) was calculated using Monte Carlo simulation [10]. DWI experiments were simulated [11], and the DWI signals were fitted by the bi-exponential and α -DWI models. We studied how the fitted parameters: Dfast, Dslow, Vfast (fraction of Dfast) of the bi-exponential fit, and DDC, α of the α -DWI, tracked the distribution of effective diffusivity when the microstructures were changed. This may give insights into the relationship between the phenomenological fitting models and the tissue structure.

Method: A random walk model and Monte Carlo simulation were implemented in C. Given a diffusion time, 5000 spins were initially placed in a 2-D space at random, and took successive random steps at a rate: 40,000 steps/per sec. The experiment was repeated 2000 times with 'the same' initial locations for all spins. The effective diffusivity of each spin was then calculated through its mean square displacement over the repeated experiments. All the spins diffusing in a 2-D space thus generated a distribution of effective diffusivity. At long diffusion time (86 ms), a single narrow peak was expected for free diffusion with $D = 1.0 \times 10^{-3} \text{ mm}^2/\text{s}$ (fig. 2a), whereas there was a spread of effective diffusivity in the presence of intra/extracellular compartments with $D_m/D_{out} = 1.0/2.5 \times 10^{-3} \text{ mm}^2/\text{s}$ [12] (fig. 2b-2d). Other parameters of simulations were: cell volume fraction: 0.65, mean cell diameter: 10 μm , cell membrane permeability (defined in [12]): 0.01 mm/s, FOV: 250 μm^2 . DWI signals were simulated by the phase accrual of 60,000 random walkers. Parameters of the simulated PGSE sequence: G_{max} : 40 mT/m and $\delta/\Delta = 40/46 \text{ ms}$. The b-value was set to be 0-6000 in increments of 500 s/mm^2 by changing the gradient strength G. The Levenberg-Marquardt algorithm was applied in the data fitting using Matlab (Mathworks, Inc.). The residual sum of squares (RSS) was used for fitting accuracy assessment. The correlation between parameters was measured by the correlation coefficient with significance level: $p < 0.05$.

Results: The distribution of effective diffusivity varied distinctly with the simulated biophysical changes (Fig. 2b-2d). The corresponding results of model fitting are given in fig. 3b-3d. While the bi-exponential model, with one more parameter, fit the data more accurately than the α -DWI (fig. 3a), both models achieved reasonable accuracy (RSS of the bi-exponential model: $5.61 \pm 2.62 \times 10^{-5}$, RSS of the α -DWI: $1.74 \pm 0.50 \times 10^{-3}$). **The bi-exponential fit:** When cell radius increased, the increased mean diffusivity was correlated with an increase in Dfast, Dslow, and Vfast ($p < 0.05$) (fig. 2b, 3b). When cell volume fraction increased, there was a shift in the fast diffusion components (fig. 2c). This was reflected by the larger variations of Dfast: $2.61 \times 10^{-4} \text{ mm}^2/\text{s}$, compared with the variation of Dslow: $2.35 \times 10^{-5} \text{ mm}^2/\text{s}$ (fig. 2c, 3c). However, Vfast was uncorrelated with cell volume fraction ($p = 0.10$). When membrane permeability increased, a shift in slow diffusion components was observed (fig. 2d). This was reflected by an increase in Vfast and the larger variation of Dslow: $1.09 \times 10^{-4} \text{ mm}^2/\text{s}$, compared with the variation of Dfast: $4.36 \times 10^{-5} \text{ mm}^2/\text{s}$ (fig. 2d, 3d). **The α -DWI fit:** DDC was correlated with the mean effective diffusivity ($p < 0.05$) (fig. 2b-2d, 3b-3d). The 'diffusion heterogeneity' measured by α was correlated with the standard deviation (STD) of effective diffusivity ($p < 0.05$), increased by a decrease in cell volume fraction and in membrane permeability (fig. 2c-2d, 3c-3d). The measured diffusion heterogeneity increased with a decrease in cell radius, where the variation of STD was small ($5.12 \times 10^{-5} \text{ mm}^2/\text{s}$) and the mean effective diffusivity decreased (fig. 2b, 3b). In summary, when cell radius became larger, the increased mean effective diffusivity was correlated with an increase in Dfast, Dslow, Vfast, and DDC. The increased cell volume fraction, leading to the decreased STD of effective diffusivity, was specifically reflected by a decrease in Dfast, the difference: Dfast - Dslow, and in the measured diffusion heterogeneity. The increased membrane permeability, leading to the decreased STD of effective diffusivity, was specifically reflected by an increase in Dslow and Vfast, and a decrease in 'Dfast - Dslow' and in the measured diffusion heterogeneity.

Discussion: Our results suggest that the direct correlation of the bi-exponential fit with the biophysical changes should be cautious, because Vfast was found to be uncorrelated with the simulated changes in cell volume fraction. We also found that the diffusion heterogeneity measured by α , correlated with the spread of effective diffusivity, may increase with the restricted diffusion when cell radius reduced. In conclusion, our simulation demonstrated that the phenomenological models tracked the changes of the mean effective diffusivity and the overlap/spread of multiple diffusion components, which are specific to the changes in biophysical mechanisms. This may help to pin down the pathological mechanisms reflected by the phenomenological models.

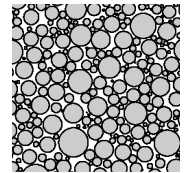


Figure 1: Simulated 2-D intra/extracellular compartments (gray/white color) ($200 \times 200 \mu\text{m}^2$).

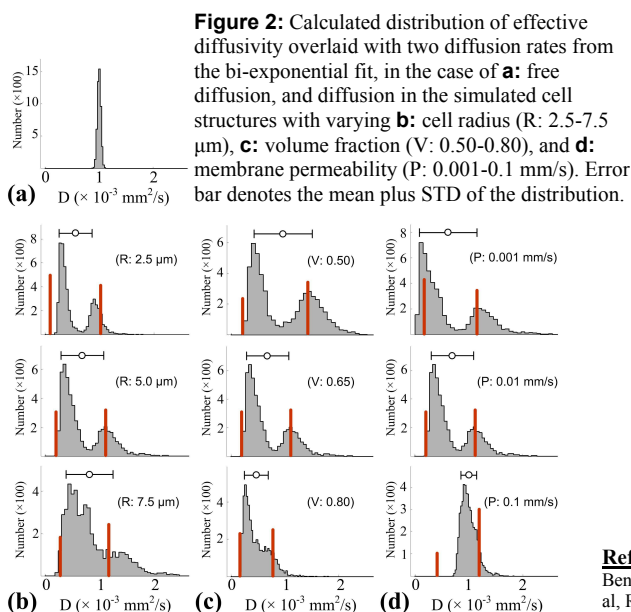
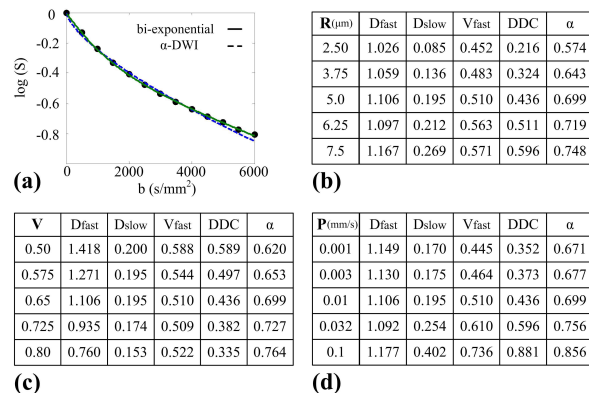


Figure 3: **a**: An example of model fits to the simulated DWI signals from the cell parameters given in Method session. **b-d**: The fitted parameters of the bi-exponential fit (Dfast, Dslow, Vfast) and α -DWI (DDC, α), when **b**: cell radius (R), **c**: cell volume fraction (V), and **d**: membrane permeability (P) were changed. (Unit of diffusivity: $\times 10^{-3} \text{ mm}^2/\text{s}$)



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