The extracellular diffusion weighted signal predicts axon diameter distribution parameters

H. M. Fonteijn[1], M. G. Hall[1], and D. C. Alexander[1]
[1]Computer Science, Centre for Medical Image Computing, London, United Kingdom

Introduction

In this abstract we show that the diffusion-weighted (DW) signal from the extracellular space can be used to estimate white matter microstructure parameters, such as axon diameter distribution and volume fraction. A key challenge in Diffusion-Weighted Imaging (DWI) is to estimate more specific features of tissue microstructure than existing methods such as Diffusion Tensor Imaging provide. For example, model-based approaches [1, 2, 3] show some success in recovering axon density and diameter in white matter. White matter models typically separate the intra and extra-axonal water populations and assume that only the intra-axonal signal is sensitive to the distribution of axon diameters. In this abstract, we show that in fact the extracellular signal is highly sensitive to the axon diameter distribution for typical diffusion times. This finding motivates the future development of new models to exploit this sensitivity and thus provide better estimates of the axon diameter distribution and other microstructural parameters.

Theory

Biophysical models of human brain white matter generally consist of an intracellular and an extracellular compartment. Diffusion in the intracellular space is modeled as being restricted and is parameterized by the axon diameter, amongst other parameters. Diffusion in the extracellular compartments is hindered by the presence of the cells and the dispersion becomes Gaussian in the long diffusion time limit. This hindrance is characterized by the tortuosity factor λ and is defined as the ratio of the extracellular diffusion coefficient (ADC) and the free diffusion coefficient (D_{free}): $\lambda^2 = D_{free}/ADC$. Both Szafer et al. [4] and Sen and Basser [5] derive models for the long-time limit where the tortuosity factor depends only on the intracellular volume fraction and is independent of the axon diameter distribution. However, in typical measurements from white matter, the long diffusion time limit does not hold. We use Monte Carlo simulations of diffusion to simulate the DW signal of the extracellular compartment in a large number of substrates that mimic human brain white matter. We use diffusion times that range from values typically used in DWI to values that will satisfy the long diffusion time limit. Because there are no analytical models available that models the extracellular DW signal for all diffusion times, we estimate a nonparametric model relating the DW signals of all substrates to their microstructure parameters using Gaussian Process Regression (GPR) [6].

Methods

Monte Carlo Simulations

White matter is modeled as a collection of non-abutting cylinders with radii which are distributed according to the gamma distribution, as in [3,7]. We generate 1000 substrates, each containing 200 cylinders with each combination of mean radius in {0.5, 1, 2, 5} μm and standard deviation in {0.1, 0.2, 0.5, 1, 2} μm. The volume fractions vary between 0.53 and 0.87. We allow no exchange between compartments. For each of these substrates we use Monte Carlo simulations [7] to synthesize diffusion-weighted signal. We simulate the signals using 2 DW directions, 1 in the parallel and 1 in the perpendicular direction to the cylinders. We use all possible combinations of the following set of DW parameters: δ = {8, 20} ms, G = {0.002, 0.005, 0.01, 0.02, 0.04, 0.06, 0.08, 0.10, 0.2, 0.4, 0.8, 1.0} T/m and Δ = {25, 100, 200, 1000} ms. The free diffusion coefficient of the extracellular compartment is set to 2×10^{-9} m^2/s. No noise is added, because the focus in this abstract is on whether there is any empirical relationship between extracellular diffusion and microstructure parameters.

Gaussian Process Regression

We perform GPR on the diffusion-weighted signals of all the substrates, using 80% of the substrates as training data, using publicly available GPR software [8] to perform model comparison on the neighborhood of interpolation and subsequent regression. The results show GPR-based prediction on the remaining 20% of the substrates (the test data).

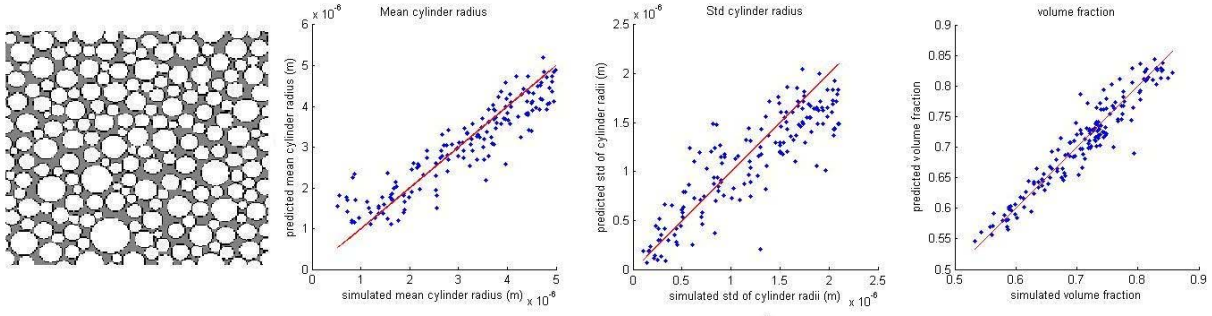

Figure 1. Results of the Monte Carlo simulations and the GPR-based estimation of substrate parameters. a: Example of a substrate. b: Predicted substrate parameters from the diffusion-weighted signals of the test substrates against the simulated substrate parameters. The red lines correspond to the limit of perfect prediction.

Results

Figure 1 shows the results of our Monte Carlo diffusion simulation experiment. In figure 1b we show the predicted microstructure parameters against their simulated values. This shows clearly that the axon diameter distribution parameters and the intracellular volume fraction all can be estimated from the extracellular diffusion-weighted signal alone. The mapping between DW signal and the microstructure parameters is not perfect as can be seen from the spread around the ideal prediction curve. It is important to stress here that this spread is not caused by any experimental noise but is purely a result of the statistical relationship between the DW-parameters and the microstructure parameters. This might be due to the number of substrates used in this abstract, which could be too low to perfectly sample the relationship between DW signal and substrate parameters, or to a genuine ambiguity in the relation between the extracellular DW signal and cell size parameters.

Conclusions

In this abstract we construct a nonparametric model for the extracellular DW signal by combining Monte Carlo simulations of diffusion and GPR. The application of GPR to this problem is to our knowledge the first demonstration that Monte Carlo simulations can be used to determine microstructure parameters. It is moreover the first demonstration of the fact that cell size parameters can be estimated from the extracellular DW signal alone. Because the extracellular DW signal can never be measured in isolation we will extend the work in this abstract to substrates to simulations of the DW signal of both compartment together and we will investigate whether our approach is more accurate than existing analytical models.

References: [1] Stanisz G.J. et al. MRM 1997, **37**: 103-111. [2] Assaf Y. et al. MRM 2008 **59**: 1347-1354. [3] Alexander, D.C., MRM 2008, **60**: 439-448 [4] Szafer, A. et al., MRM 1995, **33**: 697-712. [5] Sen, P.N. and Basser, P.J., Biophys. J. 2005 **89**: 2927-2938 [6] Gaussian Processes for Machine Learning, Rasmussen C.E. and Williams, C. MIT Press 2006. [7] Hall, M.G., and Alexander, D.C. IEEE TMI 2009, **28**: 1354-1364. [8] http://www.gaussianprocess.org/gpml/code/matlab/doc/regression.html