A study on the validity of the tortuosity approximation for extracellular diffusion using Monte Carlo simulations

H. M. Fonteijn[1], M. G. Hall[1], and D. C. Alexander[1]

[1]Department of Computer Science, Centre for Medical Imaging and Computing, London, United Kingdom

Introduction

In this abstract we will study whether common assumptions used to model extracellular diffusion in biological tissue are valid using Monte Carlo simulations. Diffusion in biological tissues is a process which is affected by the compartment in which the diffusing molecules are situated. More specifically, water molecules are either located within cells, which to a large extent restrict their diffusion, or in the space between cells in which their diffusion is hindered but not ultimately restricted. Most studies in diffusion-weighted MRI have focused on modeling the intracellular compartment correctly, because interesting microstructural parameters, such as cell size, can be learned from these models. However, to estimate these parameters, a model for extracellular diffusion must be estimated as well, as the diffusion-weighted signal contains contributions from both compartments. Moreover, extracellular diffusion is an interesting phenomenon in itself, since it plays an important role in the communication between cells and is important for drug distribution techniques [1].

Models for extracellular diffusion have generally been based on two assumptions: 1. diffusion is approximately Gaussian in all directions when the diffusion time is relatively long. 2. The free diffusion coefficient of the extracellular department and the measured diffusion coefficient are related through the volume fraction of the intracellular compartment and are not related to the precise distribution of cell sizes. The aim of this abstract is to test these assumptions, using Monte Carlo simulations of realistic models of white matter.

Theory

In MR diffusion imaging, extracellular diffusion is normally assumed to be Gaussian. Although the water molecules are hindered in their movement by cell structures, they are able to move around these obstacles and potentially spread through the whole extracellular space given enough time. Therefore diffusion can be described as approximately Gaussian, where the apparent diffusion coefficient is reduced with respect to the free diffusion coefficient. This reduction factor is called the tortuosity factor λ_x for a direction x and is defined as: $\lambda_x^2 = D_E/ADC_x$, where D_E is the free extracellular diffusion coefficient and ADC_x is the measured apparent diffusion coefficient in the direction x. Szafer et al. [2] have derived expressions for λ_x for randomly placed parallel cylinders, which only depend on only the intracellular volume fraction f and not on the size distribution of the cylinders: $(1/\lambda_x)^2 = 1 - f$. If this model is valid, the diffusion weighted signal should decay mono-exponentially provided the diffusion time is long enough and the relationship between the tortuosity factor and the volume fraction of the substrate should be linear as detailed above.

Methods

White matter is modeled as a collection of non-abutting cylinders with distributed radii. These radii are distributed according to the gamma distribution which is controlled by two parameters. These control in turn the mean cylinder radius and its variance. These cylinders are repeatedly randomly placed into the substrate until the maximum volume fraction for this substrate is reached. We have generated substrates containing 200 cylinders, while varying the mean radius size between 0.5 and 7 μm and the standard devaviation between 0.4 and 1 μm. This resulted in volume fractions which ranged between 0.55 and 0.86. For each of these substrates we have used Monte Carlo simulations [3] to synthesize diffusion-weighted measurements in the following way: 100000 spins are allowed to step through the substrate in a random fashion. To be able to study extracellular diffusion only, all spins are initially positioned outside of the cylinders, which have impermeable boundaries. When a spins reaches such a boundary it will bounce off symmetrically. The diffusion-weighted signal can now be calculated for any set of DW parameters by calculating the accumulated phase of each spin, given the gradient strength G, gradient duration δ, and spacing between the gradients Δ. We have simulated the signals using 6 DW directions, of which five were perpendicular and one was parallel to the direction of the cylinders. We have used the following range of DW parameters: δ = 20 ms, G = [0.01, 0.02, 0.03, 0.04, 0.06, 0.07, 0.08, 0.10, 0.14, 0.18, 0.22] T/m and Δ = [25, 30, 40, 80, 120] ms. The free diffusion coefficient of the extracellular compartment was set to $2 \cdot 10^{-9}$ m^2/s. No noise was added to the measurements.

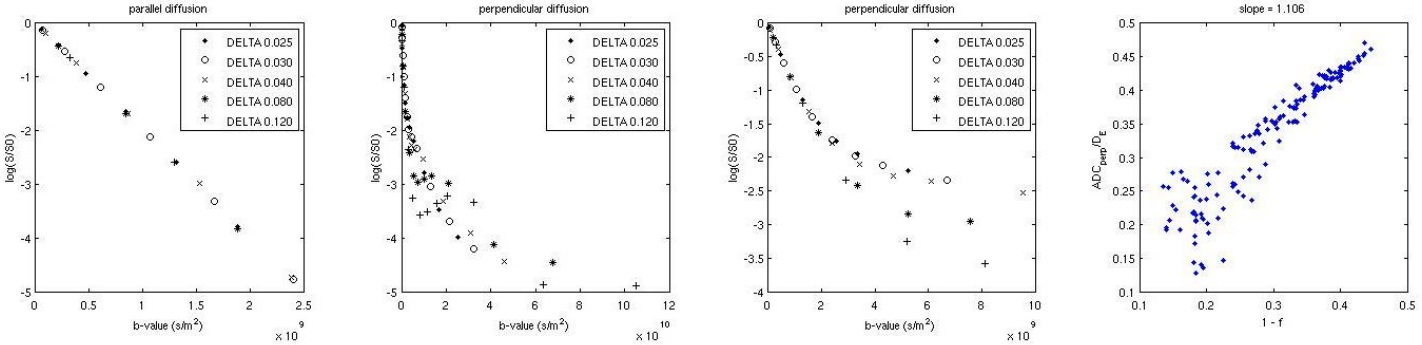

Figure 1. The diffusion-weighted signal in the parallel and perpendicular direction.

Figure 2. Relationship between perpendicular diffusion and volume fraction

Results

Figure 1 shows the signal decay curves b-value for a representative substrate. We ignore signals below e^{-5} for which the simulations become numerically unstable. The signal in the parallel direction displays a mono-exponential decay and its apparent diffusion coefficient is equal to the free diffusion coefficient. In the perpendicular direction a more complicated pattern arises. Below b = 2000 s/mm^2 the signal decays mono-exponentially with a reduced diffusion coefficient for all Δ's. After this point the diffusion coefficient is further reduced and more reduced for low Δ's than for high Δ's.. This is probably caused by the signal becoming more strongly weighted towards smaller diffusion lengths which causes the restriction between the cylinders to become more pronounced. This pattern is consistent over all substrates. Figure 2 plots the relationship between tortuosity and volume fraction. We have calculated the perpendicular diffusion coefficient in the mono-exponential regims for all substrates. The relationship from Szafer et al. predicts a line with slope 1. Although the overall slope is very close to one, in the biological relevant range of volume fractions 1 – f = [0.1 – 0.3], the curve shows a considerable spread. This indicates that perpendicular diffusion varies between substrates with different radii distributions but with similar intracellular volume fractions.

Conclusions

In this paper we have shown that perpendicular extracellular diffusion is only Gaussian for a limited range of b-values and that perpendicular diffusion is strongly influenced by the separation of the gradients and thus by the diffusion time. The relationship between perpendicular diffusion and volume fraction proposed by Szafer et al. holds approximately, although the spread in the biologically relevant parameter range leads us to conclude that perpendicular diffusion is also significantly dependent on the cell size distribution. Future work will be aimed at disentangling the contribution of Δ to this relationship.

References: [1] Bobo, R.H., et al. PNAS 1994, **91**: p. 2076-2080. [2] Szafer, A. Et al., MRM 1995, **33**: 697-712. [3] Hall, M.G., and Alexander, D.C. 2008 Proc CDMRI workshop at MICCAI