Cell size, intracellular volume fraction and membrane permeability weighted imaging: a Monte Carlo study

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Target audience: Those interested in increased specificity of diffusion-weighted (DW) MRI to changes in microstructural properties of tissues, particularly for application to clinical imaging.

Purpose: DW-MR images are sensitive to tissue alterations (for example in stroke or cancer) but have low specificity, as it is difficult to relate signal changes to specific changes in microstructural tissue properties. Here we show how DW-MRI scans can have their signals weighted to give sensitivity to changes in different tissue properties, potentially allowing users to emphasise one property (e.g. cell radius, R, intracellular volume fraction, f_i, or membrane permeability, κ), in a manner analogous to the weighting schemes used to create T_1- or T_2-weighted images. This may provide a practical way to interpret DW signals in terms of microstructural alterations, without directly estimating tissue properties using signal modelling methods. We use Monte Carlo diffusion simulations to investigate how different DW-MRI scan parameters (gradient strength, G, separation, Δ, and duration, δ) can be used to maximise sensitivity to changes in different microstructural properties.

Methods: ***Simulations:*** Water diffusion was simulated using a 3D random walk with spatial and temporal resolutions of 0.655 μm and 0.0357 ms, respectively, in a model tissue environment of monodisperse spheres, designed to mimic cancer cells. Separate simulations were performed for all combinations of the following microstructural properties of the model tissue: R={7,10,15,20,30} μm, f_i={0.16,0.31,0.49,0.62,0.71} and κ={0,0.013,0.023,0.057,0.092} μm/ms; for all simulations the intra- and extra-cellular diffusion coefficients were 2 μm^2/ms. For each of these 125 environments, pulsed gradient spin-echo (PGSE) signals, S, were synthesised for the following pulse sequence parameter combinations: G={0,5…80} mT/m, Δ={30,40…110} ms and δ=10 ms. All simulations were performed with Camino[1,2]. ***Sensitivity analysis:*** Synthesised signals were then used to calculate the sensitivity to microstructural changes by calculating the rate of change of signal with respect to the different tissue properties, e.g. $\Delta S/\Delta f_i$. Average sensitivities to changes in each tissue property were then calculated by taking the mean of these individual sensitivities; this was done for each $\{R,f_i,\kappa\}$ combination separately, giving, for example, 25 mean sensitivities to changes in f_i (one mean for each combination of R and κ). Finally, an overall mean sensitivity for each tissue property was calculated by averaging the above mean sensitivities over all combinations of the other two tissue properties. These overall mean sensitivities were then plotted as a function of G and Δ, to see how weighting towards changes in different microstructural properties is affected by the choice of pulse sequence parameters.

Results and discussion: ***Simulations:*** Example synthetic signals are shown in Fig. 1, where S is plotted as a function of G and Δ (circles), for R=10 μm, f_i=0.49 and κ=0,0.023 μm/ms (left, right). For the impermeable cells (κ=0 μm/ms), simulated signals are compared with an analytic expression (dashed lines) combining intracellular restricted diffusion within a sphere[3] and hindered extracellular diffusion[4]; there is good agreement between the simulated and analytic signals. ***Sensitivity analysis:*** Before calculating overall mean sensitivities, analysis showed that sensitivity to given microstructural changes depends on the other tissue properties. An example of this is shown in Fig. 2, where the sensitivity to a change in f_i from 0.49 to 0.31 for cells with R=15 μm is plotted as a function of G and Δ, for different κ. Sensitivity to the change in f_i is seen to decrease with increasing κ; indicating that whichever scan parameters are used, a change in f_i will yield a smaller signal change for more permeable cells. Because information about f_i stems from the spins' interactions with the cell membranes, as the membranes' influence decreases (that is, as κ increases), a reduction in sensitivity to changes in f_i is to be expected. This shows that for tissues with different properties (which, in general, are unknown), the same microstructural change produces different changes in the diffusion signal. However, Fig. 3 plots the overall mean sensitivity to changes in R, f_i and κ as a function of G and Δ. Averaging over all combinations of tissue properties shows that sensitivity to change in R is maximised by using a sequence with high G and low Δ (G≈80 mT/m, Δ≈40 ms), demonstrating that this combination provides optimum *cell-size-weighted DWI*. Conversely, greatest sensitivity to change in f_i is found at a lower G and higher Δ (G≈30 mT/m, Δ≈100 ms), providing optimum *intracellular-volume-fraction-weighted DWI*. Higher Δ also increases sensitivity to change in κ; though it is greatest at a slightly higher G (G≈50 mT/m) than f_i, providing optimum *cell-permeability-weighted DWI*. In analogy to conventional signal weighting, there is for all $\{G,\Delta\}$ combinations a mixed dependence on R, f_i and κ; but different pulse sequences can be used to maximise sensitivity to changes in each microstructural property.

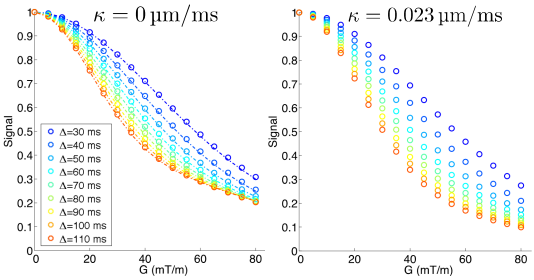

Fig. 1. Simulated $S(G,\Delta)$ (circles) for R = 10 μm, f_i = 0.49 and κ = 0, 0.023 μm/ms. Analytic expression (dashed lines) also plotted for impermeable cells (left).

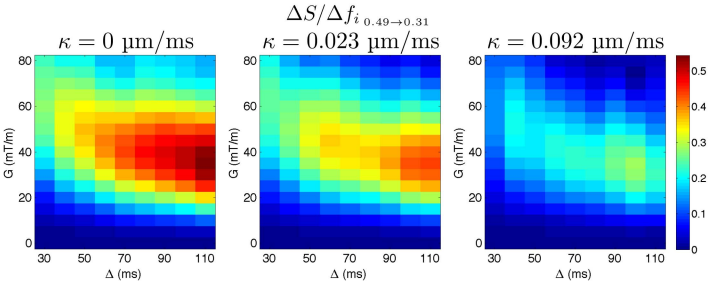

Fig. 2. Sensitivity to a change in f_i from 0.49 to 0.31, for R = 15 μm and κ increasing from left to right, plotted as a function of G and Δ.

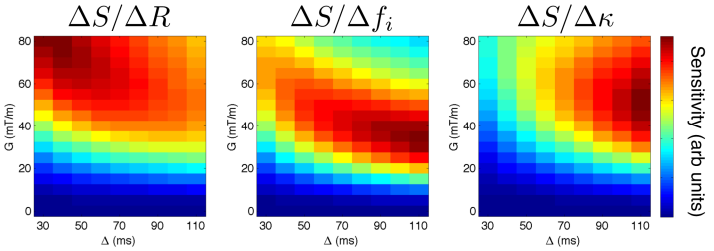

Fig. 3. Overall mean sensitivity for R, f_i and κ (left, middle, right), plotted as a function of G and Δ.

Conclusion: While sensitivity to a given microstructural change depends on the other tissue properties, the overall mean sensitivities suggest that different pulse sequences can be used to obtain images which are weighted by changes in cell size, intracellular volume fraction and membrane permeability.

References: [1] Cook et al. ISMRM 2006;14:2759. [2] Hall and Alexander. IEEE Trans Med Imaging 2009;28:1354–1364. [3] Murday and Cotts. J Chem Phys 1968;48:4938–4945. [4] Price et al. Biophys J 1998;74:2259–2271.

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