Mapping the Parameter Space of a T2 Dependent Diffusion Model in Brain Tissue

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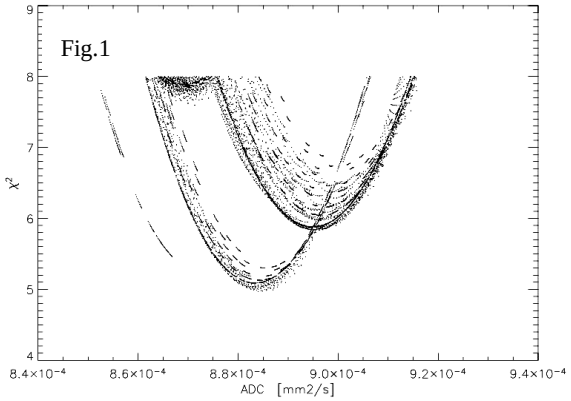
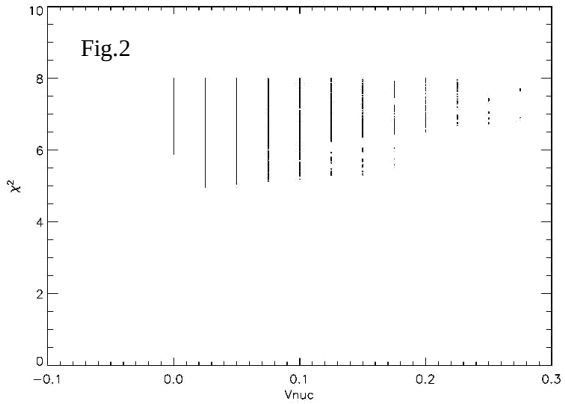
INTRODUCTION: A deeper understanding of water-diffusion in tissue is crucial for the further development and application of Diffusion Weighted MRI especially in the detection of acute cerebral ischemia where a reduction of the ADC of up to 40-50% has been found in several studies. The underlying cellular mechanisms responsible for the ADC change is still uncertain because many factors contribute to the average diffusion weighted signal obtained from all cellular compartments, influenced by e.g. the individual diffusion coefficients and transverse relaxation times, the possible restriction effects of the cell membranes and water exchange between these compartments.

To elucidate these mechanisms mathematical simulations of diffusional processes in biological tissue has been employed in a number of studies (1-3). The studies have produced realistic ADC reduction in the prediction of the cell swelling, but the absolute values of ADC, cellular fractions and tortuosity deviate from that measured experimentally or known from physiology. These studies have assumed a negligible influence of T2 relaxation in the models, however, dependency on echo time has been examined (4-5) using human erythrocytes. A recent model (6) incorporates T2 relaxation. The novel finding of this study on human gray matter was that when allowing for T2 heterogeneity of the intracellular and the extra cellular compartment, cellular fractions, extra cellular tortuosity and ADC were in accordance with physiological facts, other methods (7-8) and experimental findings. The results indicated (based on the assumption of slow exchange) that there are large T2 differences between the compartments. However there is inconsistency between the large T2 heterogeneity predicted by the model and the observed T2 relaxation from experiments. The study suggested the inclusion of an additional intracellular compartment with intermediate T2 relaxation to explain this inconsistency. This could explain the observed multi component diffusion and the lack of observed multiple T2 compartments in many studies. The finding of large diffusion and T2 heterogeneities between cytoplasm and nucleus in single neurons (9) supports this theory. We therefore hypothesize that by including heterogeneity of the diffusion and T2 in cytoplasm, nucleus and the extra cellular compartment in a model of gray matter it can produce solutions in accordance with experimental findings and results from well established methods. A novel approach of completely mapping the entire parameter space of this model was chosen.

METHODS: An analytical model very similar to that of (3) with inclusion of T2 relaxation (6) rates for cytoplasm, nucleus as well as the extra-cellular space was used. The three compartments are also assumed to have individual volume fractions, cell geometries and exchange rates. To maximize knowledge output and learning from this kind of model we performed discrete mapping of the whole parameter space assuming slow exchange ($k=1.0\ s^{-1}$) by putting the simulations in a loop structure and fitting to experimental data. Experimental gray matter data was obtained in healthy volunteers using diffusion weighted PGSE EPI with b-factors 0 - 4500 s/mm2 and Δ/TE=35.5/77.6 ms. A χ^2 threshold of 8.0 was applied to reduce the number of solutions in the analysis.

RESULTS: The simulation takes approximately 60 days on a high end work station running Linux. Analysis of our preliminary data (all





combinations for T_{2E} = 100 ms (lowest value), as well as combinations for 5 other values of T_{2E} - giving a total of 20% of the parameter-space) showed a distinct minimum in χ^2 for ADC (see Figure 1, 58581 data points). As an example the χ^2 dependence of the nucleus volume fraction is shown in Figure 2.The cellular fractions and diffusion coefficients with minimum χ^2 are shown in the table. T2 values remain to be analyzed due to the incompleteness of the dataset at the time of submission. Tortousity, λ, and ADC(b=966 s/mm^2) have been calculated from the preliminary data.

	Vcyt	Vnuc	Ve	Dcyt [mm^2/s]	Dnuc [mm^2/s]	De[mm^2/s]	λ	ADC [mm^2/s]
Parameter value at minimal χ^2	0.70	0.05	0.25	0.0001 – 0.0006	0.0017	0.0022	1.26	8.84×10^{-4}

DISCUSSION: By allowing for T2 heterogeneity in a three-compartment model of diffusion in gray matter consisting of nucleus, cytoplasm and an extra-cellular space we have found solutions with volume fractions, tortuosity and overall ADC highly matching those obtained from MR experiments and other modalities. This supports the assumption that gray matter should be treated as a three compartment system with individual properties of relaxation and diffusion for each compartment. The analysis of the complete dataset will provide valuable information of this type of models ability to reproduce experimentally determined values.

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