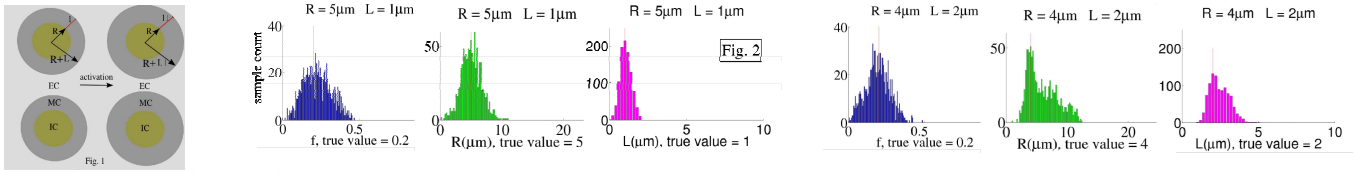
Measuring microstructural features related to neuronal activation using diffusion MRI and three-compartment diffusion models: a feasibility study

I. Kezele[1], D. C. Alexander[2], P. Batchelor[3], J-F. Mangin[1], D. Le Bihan[1], and C. Poupon[1]
[1]NeuroSpin, CEA, Gif-sur-Yvette, France, [2]University College, London, United Kingdom, [3]King's College, London, United Kingdom

Introduction and Background. *Diffusion Signal Modelling* In diffusion MRI, the measured signal attenuation is proportional to residual spin phase incoherence that results directly from the component of spin motion in the direction of applied diffusion gradients. Since the spin motion depends on the geometry of the substrate, the signal inherently encodes this dependence. The Gaussian assumption of diffusion tensor MRI (DT-MRI) [1] cannot capture all the complexity of Brownian motion of water molecules inside the tissue. Diffusion techniques that can work with non-Gaussian displacement profiles are therefore better adept to distinguish particular microstructural features. For certain simple geometries (e.g., parallel planes, spheres or cylinders), the solution to diffusion equation is analytic [2,3]. This can be readily exploited in modelling of signals in tissues approximated by combinations of finite numbers of simple geometric elements. In addition, mathematical models can incorporate a variety of parameters related to diverse microstructure features, such as: cell density and radii, cell-membrane permeability, intrinsic diffusivities, and transverse relaxation constants [4-6]. Multicompartment models of the diffusion signal reflect that from neuronal tissues composed of cells and extracellular space [4-6]. They provide new potential for measuring microstructural features. *Water and Neuronal Activation* Optical imaging studies suggest that the brain cell swelling is one of the physiological responses associated with neuronal activation [7]. It has been hypothesized that cortical cells swell as a consequence of water infiltration during activation. *Tissue and Diffusion Signal Model in Neuronal Activation* In [8] a simple tissue model to explain the diffusion signal changes accompanying the neuronal activation has been proposed. Three distinct tissue compartments were assumed: the extracellular (EC) compartment; membrane compartment (MC) that accounted for the cell membrane and the water trapped by the electrostatic forces of the membrane (and the associated cytoskeleton); and the intra-cellular (IC) compartment that accounted for the remaining cytoplasmic water. Cell swelling during activation is reflected in the MC compartment enlargement. A biphasic diffusion model was employed to explain the overall diffusion signal coming from all three tissue compartments: the first phase was related to the signal coming from the merged "free" water pool, i.e. the sum of the signals from the EC and IC compartments; the second phase was related to the signal coming from the "membrane-bound" water pool (MC). The MC enlargement during activation induces changes of the diffusion signal. *Goals of the Study* We propose a geometric model for the presumed tissue model, and an analytic diffusion signal model to explain the signal coming from the assumed geometry. An optimized imaging protocol for this model is delivered [9]. The accuracy to estimate the MC size before and during the activation, and thus the sensitivity of diffusion signal to changes in MC size during activation is tested using the optimized protocol.

Methods. For the purposes of this study, the basic pulsed-gradient spin-echo (PGSE) imaging protocol is assumed [10]. *Tissue Geometry* In this study, cells are spherical which implies the sphere as the unit block of the IC compartment, and the spherical layer as the unit block of the MC compartment (see Fig. 1). As in [8], the membranes are assumed of sufficiently low permeability, and for short enough measuring times they can be considered impermeable in practice. *Diffusion Model from Tissue Geometry* Tissue geometry implies three distinct compartments to diffusion: IC and MC and a macroscopically homogeneous and isotropic EC compartment. However, to conform to the biphasic model from [8], the intrinsic diffusivities for IC and EC compartments are assumed equal. Also, our model accounts for distinct T2 relaxivities for two different water phases [6] (i.e., the IC and EC compartment have the same relaxivity $r_C = r_E$ which is different from the relaxivity in MC space, r_M). For each compartment, the macroscopic magnetization dephasing due to the diffusion inside the corresponding compartment is modelled as a linear function of the ADC of that compartment. The ADC of the extracellular compartment is approximated by its intrinsic diffusivity d_E. The ADC of the IC (ADC_C) compartment resulted from the diffusion signal equation of the restricted spherical domain [2,3], of radius R, and intrinsic diffusivity $d_C = d_E$, under the assumption of Gaussian phase distribution (GPD). The ADC of the MC compartment, ADC_M, (of intrinsic diffusivity d_M) resulted from the diffusion signal equation of the restricted spherical shell domain [11], also under the GPD assumption. We accommodated the equations from [11] to the measurements using the PGSE protocol. The final signal equation is given by: $S(q)/S_0 = f_C \exp(-q^2 ADC_C t_D - r_C TE) + f_M \exp(-q^2 ADC_M t_D - r_M TE) + f_E \exp(-q^2 d_E t_D - r_E TE)$, $f_C + f_M + f_E = 1, f_M = ((R+l)^3/R^3 - 1)\cdot f_C$ (f_C, f_M, and f_E are volume fractions of IC, MC, and EC compartments, respectively; t_D is diffusion time; TE is echo-time; $q=\gamma\delta G/(2\pi)$, where γ is the H^1-proton gyromagnetic ratio, and δ and G are the diffusion gradient duration and strength.)
Protocol Optimization The aim is to find the set of best triples of the PGSE independent parameters: the gradient magnitude G, duration δ, and pulse separation Δ. The maximum gradient magnitude and number of measurements were 80mT/m and 16, respectively. The protocol optimization method is otherwise as in [9], although we allow the echo-time to vary between the measurements. The dependent model parameters are: EC volume fraction, $f_E = f$ =1- (overall cell density)), cytoplasmic radius R, MC layer thickness, l, intrinsic diffusivities $d_C = d_E$ and d_M, and the relaxation rates $r_C = r_E$ and r_M.

Experiments and Results. *Protocol Optimization* The dependent variables for optimization experiments were set at the following values: f_E=0.2, $d_C = d_E = 3\cdot10^{-5}$cm²s^{-1},



d_M=1·10^{-5}cm²s^{-1}, $r_C = r_E$=10s^{-1}, r_M=20s^{-1}. The nuclear radius and cytoplasmic layer thickness, were set at (R,l)={(5,1),(4,2)}μm to emulate the cell characteristic sizes before and during the activation (for a cell of average size). The normalized noise variance was σ=0.02 for all the tests. *Markov Chain Monte-Carlo (MCMC)* We synthesize data from the model to understand how the parameter settings can be recovered by fitting to the synthetic measurements. Since, in this study, we are particularly interested in seeing how well we can recover the cytoplasmic radius, R, and membrane-layer thickness, l, we change R and l over the experiments, while assuming the same true values for all other parameters, and sample the posterior distribution on each parameter using MCMC. We assume Rice noise on the data (σ=0.02), and the initial parameter values equal to their respective optimization setting. The relaxation rates $r_C = r_E$ and r_M are assumed known, and are fixed in MCMC tests. The estimates of all model parameters were accurate. The histograms of posterior samples of the most relevant microstructural features for this studies, f, R, and l are shown in Fig. 2 (vertical red bars mark the position of the true value for each parameter).

Discussion. We proposed a diffusion signal model to explain the neuronal tissue changes during activation as described in [8]. We extended the active imaging optimization framework for PGSE experimental design to accommodate this model. The MCMC tests performed with the optimized imaging protocol show that we are able to estimate accurately the assumed "before" and "during" the activation membrane-layer thickness, thus suggesting that we can also detect the changes of membrane-layer thickness due to activation. Hence, this model may prove quite valuable for testing the hypotheses in [8]. To perform the latter, future work will include experiments on real data.

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