FEASIBILITY OF MEASURING MICROSTRUCTURAL FEATURES OF SYSTEMS WITH INTERMEDIATE EXCHANGE AND SUB-CELLULAR COMPARTMENTALIZATION USING DIFFUSION MRI

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

Introduction and Background. In diffusion MRI, the measured signal attenuation is proportional to residual spin phase incoherence due to spin motion in the direction of applied diffusion gradients, and depends implicitly on the geometry of the substrate. The Gaussian assumption of diffusion tensor 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 much better adept to distinguish particular microstructural features. For certain simple geometries the solution to diffusion equation is analytic [2,3] which can be readily exploited in modelling of signals in tissues approximated by finite combinations of simple geometric elements. Further, mathematical models can incorporate a variety of parameters related to diverse microstructural features, such as: cell density and radii, cell-membrane permeability, or intrinsic diffusivities [4-6]. Multicompartment models of the diffusion signal reflect that from neuronal tissues composed of cells and extracellular space [4-6]. These kinds of models provide new potential for measuring microstructure features that may prove valuable biomarkers of different pathological mechanisms. We examine multi-compartmental systems where the intra-cellular architecture and exchange between the compartments are considered. We build an analytic model that can explain cell characteristic sizes, including the nuclear size, as well as the cell-membrane permeability, the features that are suggested to be related to different tissue pathologies. For example, the nuclear-to-cell ratio is a proven marker of the tumour malignancy grade [7], while the increase in water permeability has been detected for cells of some pathological tissues [8]. Using this model, an optimized imaging design [9,10] to measure the relevant microstructure features is delivered. Using Markov Chain Monte-Carlo (MCMC) simulations, we test the feasibility of estimating the proposed model parameters, for technical settings adapted to small animal imaging. We are particularly interested in the cell sub-compartment sizes, cell density, and cell-membrane permeability.

Methods. For the purposes of this study, the basic pulsed-gradient spin-echo (PGSE) imaging protocol is assumed [11]. *Tissue Geometry* The intracellular (IC) space consists of spherical cells of the same radii, packed uniformly inside a homogeneous substrate. All the cell nuclei are of the same radii, and are centered at cell centers. Cell-membranes and nuclear membranes are semi-permeable. We use spherical cells to avoid the extra complication of anisotropy, since the primary aim is to evaluate the ability to recover microstructure features when IC space is compartmentalized. *Diffusion Model from Tissue Geometry* Tissue geometry implies three distinct compartments to diffusion: semi-permeable cytoplasmic IC (ICC) and nuclear IC (ICN), and a macroscopically homogeneous and isotropic extracellular (EC) compartment. Semi-permeable membranes imply exchange of diffusing spins between the ICC and ICN, and ICC and EC compartments, on the intermediate time scale (see Fig.1). We follow the modifications of Chapman-Kolmogoroff equations [12] to define the first order differential equations describing the temporal evolution of the macroscopic magnetizations in the three compartments of this locally inhomogeneous system. For this macroscopic model, the ADC of IC sub-compartments is calculated assuming non-permeable membranes, and the permeability effects are modelled by coupling the differential equations via spin-exchange terms between the compartments (in the equations and initial conditions) [5,6,10,12]. For each macroscopic magnetization, dephasing due to the diffusion inside the corresponding compartment is modelled as a linear function of the corresponding ADC. The ADC of the EC compartment is approximated by its intrinsic diffusivity d_E. The ADC of the ICN compartment resulted from the diffusion signal equation of the restricted spherical domain [2,3], of radius R, and intrinsic diffusivity d_N, under the assumption of Gaussian phase distribution (GPD). The ADC of the ICC compartment (of intrinsic diffusivity d_C) resulted from the diffusion signal equation of the restricted spherical shell domain [13], also under the GPD assumption. Using the theory presented in [13], we finalize the signal derivation for the case of the spherical layers of general thickness (as a complement to the presented approximation for the thin layers), and calculate the necessary signal weighting to conform to the PGSE protocol [10]. To reduce the number of parameters, we assume, in the first approximation that $d_N = d_E$. We also account for T2 relaxivities, assuming equal relaxivities in ICN and EC compartments, different from the ICC relaxivity. *Macroscopic Signal Equations*:

$$\dot{M}_N = -(\gamma G\delta)^2 ADC_N M_N - r_N M_N - k_N M_N + p_{CN} k_C M_C$$
$$\dot{M}_C = -(\gamma G\delta)^2 ADC_C M_C - r_C M_C - k_C M_C + k_N M_N + k_E M_E$$
$$\dot{M}_E = -(\gamma G\delta)^2 d_E M_E - r_E M_E - k_E M_E + p_{CE} k_C M_C$$

$$f_N k_N + f_E k_E = f_C k_C \qquad p_{CN} + p_{CE} = 1 \qquad p_{CN}/p_{CE} = 1/(1 + \tfrac{l}{R})^2$$

M_i, f_i, ADC_i, r_i, k_i stand for the macroscopic magnetization, volume fraction, ADC, relaxivity and exchange factor for the indexed compartment, i, respectively; γ is the gyromagnetic ratio of H^1-proton, G and δ, the gradient strength and duration; p_{CN} and p_{CE} represent the probabilities for a molecule exiting the ICC compartment to enter either the ICN or EC compartment. We split the system for two different time intervals, similar to [6]: 1) from 0 to Δ (diffusion gradient separation time), and 2) from Δ to $\Delta+\delta$ (assuming the echo time: TE=$\Delta+\delta$). In the first period both diffusion and relaxation terms are present, while in the second there is no diffusion term. The final signal is given as the sum of the fixed-point solutions for magnetizations in all three compartments.

Experiments and Results. *Protocol Optimization* [9] The dependent variables were set at: f_E=0.2, d_N=d_E=3·10^{-5}cm²s^{-1}, d_C=10^{-5}cm²s^{-1}, r_N=r_E=10s^{-1}, and r_C=20s^{-1}; P=0 or 10^{-3}cms^{-1} (to conform to negligible and moderate permeability, respectively), and (R,l)={(2,3),(3,2)μm}, for two different ICN-to-cell volume ratios. The normalized noise variance was σ=0.02. Maximum allowed gradient strength was 0.8 T/m, and the number of measurements was 16. *MCMC Simulations* We run MCMC simulations using the optimized protocols to understand how well the parameter settings can be recovered by fitting to the synthetic measurements. We run different experiments for P=0 or 10^{-3}cms^{-1}, in order to test the estimation accuracy for negligible and moderate permeability. Likewise, two different settings R and l were tested: (R,l)={(2,3),(3,2)}μm, simulating two different ICN to cell volume ratios: 6.4%, related to normal cell geometry; and 21.6%, associated with malignant cells [7]. For all other parameters, we assume the same true values as for optimization. The relaxivities are assumed known. The noise on the data is Rician (σ=0.02), and the initial parameter values equal to their respective optimization setting. The histograms from the MCMC are shown in Fig. 2. Also, to stress the difficulty in parameter estimation in models with exchange, we show the results (Fig. 3) of the experiments for the same model and with all parameters kept the same, but assuming no exchange between the compartments. With this model, we obtain the accurate estimates even with protocols with 10 times weaker maximum gradient strength (G_{max}=80mT/m).

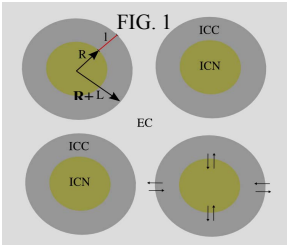

FIG. 2

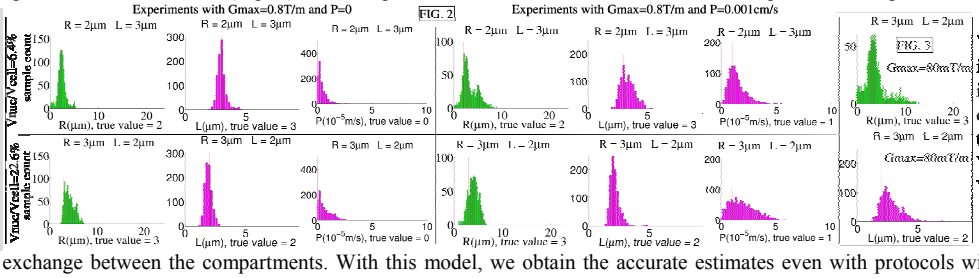

FIG. 3

Vertical red bars in Figs. 2 and 3 indicate the positions of model parameters' true values.
Vnuc: nuclear volume
Vcell: cell volume

Conclusion. We proposed a three-compartment analytic tissue model with spin-exchange. The simulation results demonstrate the accuracy of estimating the parameters with both negligible and moderate membrane permeability, and thus suggest the sensitivity to accurately detect the change of particular parameters, e.g., the change of cell-characteristic sizes and membrane permeability. The evidence relating the latter to pathological tissue alterations promotes the potential of the proposed model to provide new microstructural biomarkers.

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