A Simulation Framework for Diffusion Weighted MRI in Digitalized Neurons: extracting cytoarchitectural parameters using a new theoretical model for diffusion

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Introduction: Despite diffusion weighted MRI (DW-MRI) being firmly established as clinical modality, the understanding of its biophysical foundation remains incomplete. Furthermore, being sensitive to diffusion barriers and restrictions on a micrometer scale, the potential of DW-MRI for in vivo measurements of cytoarchitectural parameters is still not fully realized. In order to succeed with this goal one needs an appropriate model and a reliable way of testing and validating it. The criteria on which such a model should be judged include its biophysical justification, its ability to describe experimental data parsimoniously, and independent validation from other modalities. Computer simulations can be a valuable tool to assist in the development of new models, since they allow individual aspects and assumptions of candidate models to be tested independently [1]. Here we present a simulation framework capable of simulating the signal decay in a narrow pulse Stejskal-Tanner spin echo experiment for arbitrary geometries including entire digital neurons, and as an example application, we use it to test a promising new model with the potential of determining mean dendrite radii.

Theory: In order to simulate the signal decay due to diffusion inside structures bounded by impermeable barriers it is necessary to keep track of the transverse magnetization $M_+ = M_x + iM_y$ over time, and one way of doing this is to use the Bloch-Torrey equation with Neumann boundary conditions. Neglecting T2 relaxation, this equation reduces to the diffusion equation in the time interval Δ between the two gradient pulses in a spin echo Stejskal-Tanner experiment. Thus, if we assume the narrow pulse approximation to be satisfied, the temporal evolution of M_+ can be simulated by applying the gradients instantaneously and then solve the diffusion equation in the intervening time. There are several ways of solving the diffusion equation numerically; in this work, a simple forward time centered space finite difference method has been chosen [2]. This method is based on a discretization of space and time such that spatial locations are restricted to grid points and advances in time are made stepwise. In this discretization, the diffusion equation becomes an algebraic equation linking the magnetization at a given grid point and time step to the magnetization at the same grid point and its six nearest neighbours at the previous time step. Reflecting boundary conditions are implemented by a slight local modification of the algebraic equation excluding grid points outside the structure. The simulation framework consists of two programs, one that handles the position and neighbor information of all the grid points inside the structure and another one that does the actual simulation based on the output from the first. This division is crucial in terms of memory use and execution time. To model the signal decay for a neuron, we use a recently proposed model for diffusion in brain tissue [3], where the neuron is imagined as being comprised of a distribution $f(\theta,\varphi)$ of long cylinders. The signal decay for each of these cylinders is then approximated by the expression $E(\mathbf{q},\Delta) = (2J_1(2\pi Rq\sin\theta)/2\pi Rq\sin\theta)^2 \exp(-4\pi^2 D\Delta q^2\cos^2\theta)$ [7]; here J_1 is the Bessel function of order 1, R is the cylinder radius, D is the diffusion constant, Δ is the diffusion time (intergradient spacing), and θ is the angle between the gradients and the cylinder axis. This is an extension of the model presented in [3], such that the transverse part of the diffusion in the cylinder is described exactly in the long time limit $D\Delta >> R^2$. Since the diffusion length is relatively large compared to the average diameter of a dendrite for normal experimental diffusion times, this approximation is quite good. By integrating the product of these two functions (*E* and *f*) over the sphere and making a second order ($l = 2$) expansion of $f(\theta,\varphi)$ in spherical harmonics $Y_{lm}(\theta,\varphi)$ we end up with

$$E(\mathbf{q},\Delta) = 2\pi E_0 \sum_{l=0,2}^{l}\sum_{m=-l} G_l(q,\Delta) f_{lm} Y_{lm}(\theta_q,\varphi_q), \quad G_0(q,\Delta) = \sum_{n=0}^{\infty} \frac{4(-1)^n (2\pi qR)^{2n}}{(n+1)!(n+2)!} {}_1F_1(\tfrac{1}{2},\tfrac{3}{2}+n,-4\pi^2 D\Delta q^2), \tag{1}$$

where E_0 is the signal at $|\mathbf{q}| \equiv q = 0$, f_{lm} are the expansion coefficients, (θ_q,φ_q) are the spherical polar angles of $\mathbf{q}$, and ${}_1F_1(a,b,z)$ is the confluent hypergeometric function. The expression for G_2 has the same structure as G_0 and is omitted here for brevity. Since $f(\theta,\varphi)$ is a real function the coefficients are constrained by $f_{lm}^* = (-1)^m f_{l-m}$ giving Eq. 1 a total of 8 free parameters.

Materials and methods: The digital neuron part of the simulation framework is based on the SWC format [4], which specifies the neuron in terms of a large collection of truncated cones. So far we have worked with digital versions of pyramidal neurons from the pre-frontal cortex of Macaque monkeys, obtained with kind permission from [5]; see Fig. 1 for an example. The simulations were carried out on a state-of-the-art grid computer consisting of 23 machines each with Intel 2.8 GHz Xeon dual processors. For a typical neuron simulation with 10^7 grid points, a grid spacing of 0.075 µm, 10^4 time steps and 96 gradients, the execution time ranged from 5 to 6 hours. In each simulation we used $D = 1\mu m^2/ms$, $\Delta = 5ms$ and 96 gradients with a magnitude ranging from 0.15 to 0.4 μm^{-1} in a total of 8 steps using 12 directions from a 12 point spherical 5 design for each [6]. These data sets were then fitted to the model in Eq. 1 using nonlinear least squares, in order to evaluate average dendrite radius and bulk diffusivity.

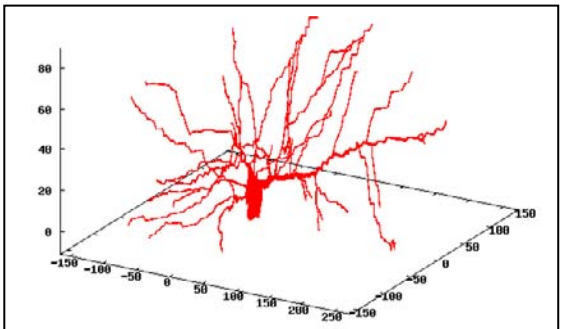

Fig. 1: An example of a digital pyramidal neuron obtained from [5].

Results: The simulation framework has been tested against various simple geometries including cylinders, spheres, boxes, parallel planes and unbounded space, and in each case excellent agreement with the analytical solutions (see e.g. [7]) was achieved. Furthermore, simulations with four different digital neurons has resulted in good agreement with Eq. 1, see Table 1 for details; here $\langle R\rangle$ is the volume weighted average radius of the truncated cones, whereas R_{sim} and D_{sim} is the radius and diffusion constant determined from the fit to the simulation data. There is a small tendency to overestimate the radius, and underestimate *D*.

	$\langle R\rangle$ / µm	R_{sim} / µm	D_{sim} / µm²/ms
Neuron 1	0.53	0.55 ± 0.05	0.91 ± 1.4
Neuron 2	0.43	0.63 ± 0.05	0.96 ± 1.4
Neuron 3	0.58	0.71 ± 0.06	0.91 ± 1.6
Neuron 4	0.63	0.72 ± 0.05	2.0 ± 7.6

Table 1: Fitting results for the simulation data of four different macaque pyramidal neurons.

Discussion and conclusion: We have presented a simulation framework with great potential as a testing ground for new diffusion models as well as a way of finding optimal parameter values for existing models. Furthermore a promising new model with the potential of obtaining average dendrite radii was fitted to the simulation data with relatively good agreement. The small discrepancy in the estimation of dendrite radius is presumably caused by the large soma radius which is not included in the calculation of $\langle R\rangle$, and curvature of the dendrites may also influence this estimate. These results provide strong support to the idea of describing diffusion in neurons in terms of collections of long cylinders, an approach used also in [3]. Such a model and the extension presented here may be used in the analysis of high-resolution diffusion data, which is the focus of our current efforts.

References: [1] S.N. Hwang et al, *Magn. Reson. Med.* **50** 373-382; [2] C.A.J. Fletcher, Computational techniques for fluid dynamics, vol. 1; [3] S.N. Jespersen et al., *appearing in NeuroImage*; [4] Cannon et al., *J. Neurosci. Methods* **84** 49-54; [5] The Computational Neurobiology and Imaging Center, Mt. Sinai School of Medicine; [6] R.H. Hardian et al. *Discrete Comput. Geom.* **15** 429-441; [7] P.T. Callaghan *J. Magn. Reson.* **113** 53-59.